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To our patients, whose courage, suffering, and triumphs have instructed us;

To our teachers, from whom we learned that true wisdom is found at the intersection of knowledge and values;

To our trainees, who will demonstrate that the best way to predict the future of cancer care is to invent it;

To the universities where we have worked and continue to work—institutions that are committed to generation, conservation, and dissemination of knowledge about the causes, prevention, and treatment of human disease and disability; and

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Preface: The Past and Future of *Principles and Practice of Radiation Oncology*

It was probably 2002 when I flew from the Raleigh-Durham airport in North Carolina to the Philadelphia airport. I took a taxi cab (remember those?) to the neighborhood of Independence Hall. It was where the Declaration of Independence was crafted and adopted and the Liberty Bell then resided. I walked south of the national historic landmark into a conference room at the Independence Square home offices of the venerable medical publishing house, J.B. Lippincott. I was being brought on-board to join Carlos Perez and Luther Brady as one of the senior editors of *Principles and Practice of Radiation Oncology*. Our task was to create the fourth edition.

I was seated at a table with Drs Perez and Brady. We were joined by Stuart Freeman, managing editor and representing J.B. Lippincott. As "the new kid on the block" I thought it best to sit quietly and "learn the ropes."

"Do you want to know how I came to create this book in 1987?," Luther Brady asked me earnestly. By his expression, it seemed clear that he had a story to tell and intended to tell it.

"Yes, sir, certainly," I replied.

Carlos Perez cut him off. "Oh no, Luther," he said. "Edward does NOT want to hear THAT story."

Luther Brady sat back in his chair, looking somewhat deflated. I learned several key lessons: (1) There was only one person I would ever meet who had the authority to tell Luther Brady "no." (2) That person was the courtly and dignified Carlos Perez. (3) If Luther Brady wanted to tell a story, there was no one, including Dr Perez, who was, in the long run, going to stop him.

The meeting to prepare the fourth edition continued for about another hour and it was time for a break. Mr Freeman and Dr Perez left the room. A

nanosecond after they left, Luther Brady turned to me.

"Let me tell you the story of how I came to create this book," he said.

"Yes, sir, certainly," I once again replied.

"Years ago," he began, "I sat down with Phil Rubin [the Chair of Radiation Oncology at the University of Rochester] to discuss the need for a definitive textbook to succeed Gilbert Fletcher's *Textbook of Radiotherapy*. I had asked Fletcher if he planned on a new edition and he told me the current edition of his book had no need for improvement. We also discussed the need for a definitive dedicated radiation oncology scholarly journal. We agreed that both needed to be created. What we couldn't agree upon was who would take charge of which project."

I had the feeling that Dr Brady had wanted to be the founding editor-in-chief of the radiation oncology journal. I knew that, in fact, he had been the founding editor-in-chief of the *American Journal of Clinical Oncology*, but I said nothing and urged him to continue his tale.

"Well," he resumed, "we flipped a coin and Phil got the journal and I got the book. That's why Phil was the founding editor of the *International Journal of Radiation Oncology Biology Physics*, generally called the red journal, and I created this book!"

As a part-time historian, I would like to have independent verification of this coin flip story from an objective third party, but I don't have it. Whether it is the founding story of this textbook or the founding myth, I am unable to say. Whichever it is, the book you hold in your hands, which emerged from that coin flip, may be rightly referred to as "The Bible of Radiation Oncology," "The *New York Times* of Radiation Oncology," or, as I often hear, "The Book." I have come to be one of the stewards of the edifice created by Drs Perez and Brady. I have taken that responsibility seriously.

Drs Perez and Brady asked Rupert Schmidt-Ullrich to join the team of senior editors for the fourth edition. Unfortunately, Rupert passed away before we could prepare the fifth edition. David Wazer joined as an associate editor for the fifth edition in 2008 and moved up to join me as a senior editor for the sixth and subsequent editions. Drs Perez and Brady continued to actively work on the book until Dr Brady's death as the seventh edition was being prepared for publication in 2018 and Dr Perez's death as we were collecting chapters for the eight edition. Since it takes

about 2 years to prepare each edition, Dr Perez devoted 39 years to this book; Dr Brady devoted 33 years; I have devoted 22 years to four editions so far; and David Wazer has devoted 18 years to three editions so far. Those are big numbers.

From the first edition of the *Principles and Practice of Radiation Oncology* in 1987 to this eighth edition being published in 2025, we have clocked 38 years, approximately 13,300 pages of printed text, many tens of thousands of pages of typed and computer printed text, and an immeasurable number of meetings, phone calls, letters, e-mails, faxes, and text messages to produce these eight editions. Many things have changed and others have stayed the same.

What has stayed the same? For 38 years, radiation therapy has remained a major component of the curative and palliative therapy of cancer and plays a major role in the management of many benign diseases. Patients with cancer are generally best managed by a combined modality approach that requires the participation of a well-informed, well-trained, and well-equipped radiation oncologist and medical physicist collaborating with a radiation oncology team. The radiation oncologist must be capable of taking a detailed medical history; performing a thorough and accurate physical examination of the patient; assessing and integrating the information from diagnostic imaging, from gross and microscopic pathology—incorporating a growing list of chemical and molecular markers that guide therapy and predict outcome—and from clinical chemistry; and formulating and implementing a treatment plan that is cognizant of the wishes of the patient and realistic in its goals.

For this book, in particular, what has also stayed the same since 1987 is the vision and participation of the editorial team. Having such stability in the editorial team is exceptional in the history of textbook publishing. As we note in our acknowledgments, we remember and mourn those who contributed to previous editions of this book but are no longer with us: Ruth Aultman, Jonathan Pine, Rupert Schmidt-Ullrich, Carlos Perez, and Luther Brady.

What has changed? There has been an explosion of knowledge concerning the molecular biology of cancer and tumor physiology. Concepts that were unknown in the 1980s are now considered fundamental building blocks of knowledge concerning cancer. As it concerns the

technology of this specialty, when the first edition of this book was published, some radiation oncology residents were training, in part, on orthovoltage units; cobalt-60 machines remained in widespread use; simulation using diagnostic radiographs still vied with clinical setups of treatment fields using surface anatomy; and many radiation oncologists carried slide rules, protractors, right angle drafting triangles, and rulers to calculate and map radiation dose distributions. Now, elaborate linear accelerators with multileaf collimators, particle machines, intensity-modulated and/or image-guided radiation therapy, complex brachytherapy devices, dose painting, image fusion, metabolic imaging, and increasingly powerful computers that support the preceding list of technologies have become the norm in the developed world. (And, unfortunately, the paucity of even the most minimal radiation therapy services remains the norm in many parts of the economically less-developed world, and economic and racial disparities persist in cancer care and outcomes in the economically developed world.) In some diseases, the diagnostic and staging workup has changed profoundly in the past quarter of a century—for example, the role of staging laparotomy in Hodgkin disease. In other diseases, the role of radiotherapy in treatment has shifted dramatically, as demonstrated by the decline in the role or frequency of use of radiation therapy in the management of retinoblastoma, Burkitt lymphoma, and Wilms tumor, following balloon angioplasty and stenting for coronary artery disease, and AIDS-associated malignancies. There have been significant changes in the patterns of use of radiation therapy for breast and prostate cancer, brain metastases, and non–central nervous system oligometastases.

The editors have striven to be cognizant of change by constantly adding and pruning chapters to document the current state of knowledge of cancer biology, medical radiation physics, dosimetry, cancer epidemiology, clinical radiation oncology, and radiation oncology economics, education, ethics, and policy. Particular attention has been devoted to an attractive and usable design of the printed version of this book and the new electronic versions. We have taken care to have this book evolve with the times. We have simultaneously striven to be true to the core mission of being “the book of record” for clinical care, providing the data that justify treatment recommendations as well as comprehensive illustrations and references in radiation oncology. We take this responsibility very seriously.

We have been gratified by the public reception of this book. Sales of the fifth edition rose dramatically compared to the fourth edition—an atypical pattern in the medical book business. Sales of the sixth and seventh editions remain high. It is, we like to believe, evidence that the pact wordlessly exchanged between the editors, the chapter authors, and our readers is being honored by all parties.

The editors sincerely hope that this eighth edition of *Principles and Practice of Radiation Oncology* will continue to advance the understanding of the causes, prevention, and treatment of human cancer. We pray that this new edition will contribute to the cure of some malignancies, the amelioration of suffering for many patients and their families, the relief of pain, and the ultimate triumph of human knowledge over cancer.

I began this preface with stories that included the fact that Drs Perez and Brady worked on this book until they died. Dr Wazer and I hope to have many fruitful years to continue working on the ninth edition and its successors. We have both decided, however, that prudent responsibility for this international treasure of a book includes both having a long-term succession plan for its leadership and increasing the diversity of the editorial team. We have, therefore, invited Drs Baumann, Blitzblau, and Esiashvili to join the team as associate editors for the eighth edition and begin "learning the ropes," as I did back in that Philadelphia conference room over 20 years ago.

Immediately following this preface, the reader will find a page of acknowledgments from all five senior and associate editors. I will, however, take the prerogative as the author of this preface to particularly acknowledge David Wazer. David has negotiated the personalities and politics of editorship and publishing with a calm hand, a steady gaze, and a mission-driven focus. He has done all of this while being a busy clinician, journal editor, and academic leader. He has also done all of this while dealing with the curve balls that life often throws you. Both David and I can testify that "Getting old isn't for sissies." I have been blessed to have him as a partner in creating this book for the last 18 years.

Edward C. Halperin, MD, MA
September 7, 2024
Valhalla, New York, USA

Acknowledgments

When I joined the editorial leadership team of *Principles and Practice of Radiation Oncology*, for the preparation of the fourth edition, which was published in 2003, my secretary was Ms Ruth Aultman. Ms Aultman was a quiet, hardworking, church-going woman who suffered much hardship in her life. She and I worked side-by-side when I was on the faculty at Duke University, department chair and vice dean at Duke, and dean of the School of Medicine at the University of Louisville—about 25 years in all. She was responsible for a great deal of the work on this book up through 2012 when she passed away. I remain grateful for her loyalty and kind, reliable presence.

Since 2012, when I became chancellor/CEO of New York Medical College, I have benefited from the assistance in my office of the college's chief-of-staff Vilma Bordonaro and executive assistant Ashley McCarrick. The director of the college's library, Marie Ascher, and her staff have fulfilled endless requests for references and intra-library loans. I express my appreciation to all three.

The publisher's representatives over the years have included Stuart Freeman, Joseph Cho, Anne Malcom, Ariel S. Winter, and Sean Hanrahan. I am grateful for their hard work. Jonathan Pine served as our publisher's supervising editor for the fifth and sixth editions of this book. Jonathan was an endearing person: kind and possessed of a gentle sense of humor. The editors did not know of his long-standing diagnosis of lymphoma until what was perceived by us as his unexpected death in 2013. An obituary in *The Baltimore Sun* quoted one of Mr Pine's friends, who called him the "perfect gentleman. He had manners you don't see anymore, and he also had his first job. He was a rarity for this generation."

I was taught that in the decalogue "Honor thy father and thy mother" encompassed honoring one's teachers. In that spirit, I acknowledge my teachers of radiation oncology: James J. Fisher at Yale; Leonard Prosnitz at

Yale and Duke; Rita M. Linggood and Noah C. Choi at the Massachusetts General Hospital; J. Robert Cassady at Boston Children's Hospital; C. Norman Coleman at Stanford; and, most importantly, Herman D. Suit at the Massachusetts General Hospital.

My wife, Sharon Halperin, and our three daughters, three sons-in-law, and six grandchildren have patiently endured the house being filled with piles of references and manuscripts and my consumption of reams of printer paper and ink cartridges. Without their love and support, neither the eighth edition nor the previous four editions would have been produced.

We are grateful for the scholarly, meticulous, and thorough work of the contributors to this volume. Through eight editions, this book has become the "book of record" for the specialty of radiation oncology. It has achieved that distinction through the hard work of the individual chapter authors.

The staff of Wolters Kluwer have professionally seen this work through from planning to distribution. We are in their debt.

We express our gratitude to our patients and their families for trusting us to be part of their cancer care team and inspiring our research. Our fellow faculty members, residents, medical students, and interdisciplinary cancer care teams have supported our work, providing consistent intellectual stimulation, valuable suggestions, and materials that have contributed to our knowledge and, consequently, to this book. We are grateful to the many librarians of our respective institutions who have come to our aid in finding the necessary books and articles to support the preparation of this book.

We thank our mentors throughout our training and careers, generously giving of their time and wisdom to help us grow as people, physicians, and radiation oncologists.

Dr Esiashvili thanks her two daughters, who have always had a deep appreciation for her work. "I firmly believe it helped them become empathetic and kind human beings."

Dr Blitzblau thanks her wonderful family for their unwavering support and encouragement throughout her career and in the making of this book. "I could not do it without you."

Dr Baumann expresses his "gratitude to my patients who place their trust in me, to my partners for their support, and to my mentors and trainees who have helped me to learn and improve as a clinician and human being. I want

to express my sincere love and gratitude to my wife and children who are such a wonderful blessing in my life, and to my parents who gave me the gift of opportunity and the support and love I needed to pursue my dreams. I am very lucky to have such wonderful family, friends, and colleagues. I am eternally grateful."

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David E. Wazer, MD, FASTRO
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Contents

Volume I
The Scientific, Technological, Economic, and Ethical Basis of Radiation Oncology

Contributors
Preface: The Past and Future of Principles and Practice of Radiation Oncology
Acknowledgments

SECTION I Overview and Basic Science of Radiation Oncology

1. **The Discipline of Radiation Oncology**
   Edward C. Halperin

PART A: Cancer Biology

2. **Molecular Cancer and Radiation Biology**
   Michael Baumann, Ina Kurth, Nils Cordes, Cristina Conde Lopez, Mechthild Krause, and Annett Linge
3. **Biologic Basics of Radiation Oncology**
   Gopika SenthilKumar, Buck E. Rogers, Francisco Reynoso, Julie Schwarz, and Carmen Bergom
4. **Molecular Pathophysiology of Tumors**
   John D. Martin, Dan G. Duda, and Rakesh K. Jain
5. **Precision Medicine as Applied to Radiation Oncology**
   Jeffrey C. Buchsbaum and Pataje G. S. Prasanna

PART B: Medical Radiation Physics and Dosimetry

6. **Principles of Radiation Physics and Dosimetry**
   James A. Purdy, Geoffrey D. Hugo, and Hania A. Al-Hallaq
7. **Patient Positioning Methods: Immobilization, Stabilization, and Monitoring**

Tianjun Ma, Kujtim Latifi, Bruce Libby, Joshua Evans, and Stanley H. Benedict

8. **Photon External-Beam Dosimetry and Two-Dimensional Radiation Treatment Planning**
James A. Purdy, Geoffrey D. Hugo, and Hania A. Al-Hallaq

9. **Electron-Beam Therapy Dosimetry, Treatment Planning, and Techniques**
Angélica Pérez-Andújar and Eric E. Klein

10. **Conformal and Intensity-Modulated Radiation Therapy Physics: Treatment Planning and Techniques, and Clinical Applications**
James A. Purdy, Geoffrey D. Hugo, and Hania A. Al-Hallaq

11. **Physics and Dosimetry of Proton Therapy**
Brian Winey

SECTION II **Techniques, Modalities, and Modifiers in Radiation Oncology**

12. **Late Effects, QUANTEC, and HyTEC**
John P. Kirkpatrick, Michael T. Milano, Jimm Grimm, Louis S. Constine, Zeljko Vujaskovic, and Lawrence B. Marks

13. **Quality Assurance and Error Avoidance in Radiation Therapy**
Wesley J. Talcott, Kelly Paradis, Eric Ford, and Suzanne Evans

14. **Methodology of Clinical Trials**
Ethan B. Ludmir, Ruitao Lin, Abigail T. Berman, Clifton D. Fuller, and Charles R. Thomas, Jr

15. **Stem Cell Transplantation and Radiation Therapy Techniques**
Christopher R. Kelsey, Jeffrey W.C. Wong, Pranalee Patel, Mitchell E. Horwitz, Qiuwen Wu, and Sarah Jo Stephens

16. **Stereotactic Irradiation of Tumors of the Central Nervous System**
Trey C. Mullikin, John C. Flickinger, and Paul W. Sperduto

17. **Stereotactic Irradiation of Tumors Outside the Central Nervous System and Oligometastases**
Ambrosia J. Simmons, Brian D. Kavanagh, and Robert D. Timmerman

18. **High-Dose, Ultra-High Dose Rate (FLASH), and Spatially Fractionated Radiotherapy**
Robert J. Griffin, Yolanda Prezado, and Nina A. Mayr

19. **Intraoperative Radiotherapy**
William Sperduto, Jonathan B. Ashman, and Safia K. Ahmed

20. **Particle Therapy: Protons, Heavy Ions, and Neutrons**
Nancy P. Mendenhall and Perry B. Johnson

21. **Physics and Radiobiology of Brachytherapy**
Zhe (Jay) Chen, Jeffrey F. Williamson, David J. Brenner, Emily Draeger, and Mark J. Rivard

22. **Clinical Applications of Brachytherapy: Low Dose Rate and Pulsed Dose Rate**
Aspazia Spyrou, Sophie Otter, Caroline Holloway, Phillip M. Devlin, and Alexandra J. Stewart

23. **The Physics and Dosimetry of High-Dose Rate Brachytherapy**
Bruce Thomadsen, Eric N. Carver, and Mark J. Rivard

24. **Clinical Aspects and Applications of High-Dose-Rate Brachytherapy**
Mustafa Al-Balushi, Ivan Buzurovic, Phillip M. Devlin, Peter Orio, and Martin T. King

25. **Beyond the Beam: Radiopharmaceutical Therapy**
Freddy E. Escorcia, Ravi B. Patel, Teresa Fisher, and Katherine A. Vallis

26. **Radiation Therapy and the Immune System**
Ahsen Ahmed, Charles X. Wang, Michael Gough, and Arta M. Monjazeb

27. **Hyperthermia**
Mark Hurwitz, Mark Dewhirst, and Johannes Crezee

28. **Reirradiation**
Carsten Nieder and Anthony E. Dragun

29. **Chemical Modifiers of Radiation Response**
Yvonne Marie Mowery, Ashlyn G. Rickard, and David M. Brizel

30. **Oncologic Imaging and Oncologic Anatomy**
Edina Wang, Pooja Karukonda, Christopher R. Kelsey, Bryan O'Sullivan-Murphy, Travis Henry, and Junzo P. Chino

31. **Basic Concepts of Chemotherapy and Irradiation Interaction**
Sean C. All, D. Nathan Kim, and Christopher D. Willey

32. **Artificial Intelligence and Data Science as Applied to Radiation Oncology**
Tafadzwa L. Chaunzwa, Danielle S. Bitterman, Christian Guthier, Carl F. Haugg, Benjamin H. Kann, and Raymond H. Mak

SECTION III Policy, Economics, Education, Ethics, and Technology Assessment

33. **Technology Assessment, Outcome Analysis Research, Comparative Effectiveness, and Evidence-Based Radiation Oncology**
James B. Yu and Ronald C. Chen

34. **Global Radiation Oncology**
Timothy P. Hanna, Melinda Mushonga, Fabio Ynoe de Moraes, and C. Norman Coleman

35. **Radiation Oncology Undergraduate, Graduate, and Continuing Medical Education**
Eulanca Y. Liu and Ann C. Raldow

36. **Ethics, Professional Values, and Legal Considerations in Radiation Oncology**
Austin J. Sim and Brian D. Kavanagh

37. **Health Economics and Health Policy**
P. Travis Courtney, Ann C. Raldow, Eric M. Chang, and Michael L. Steinberg

38. **Economic, Gender, and Racial Disparity in Radiation Oncology**
Erica Fleming-Hall and Shearwood McClelland III

Volume II
The Clinical Practice of Radiation Oncology

SECTION IV Clinical Radiation Oncology

PART A: Skin

39. **Skin**
William M. Mendenhall, Anthony A. Mancuso, Peter T. Dziegielewski, and Christiana Shaw

PART B: Central Nervous System

40. **Primary Intracranial Neoplasms**
Vinai Gondi, Qian S. Zhang, Michael A. Vogelbaum, Yazmin Odia, and Minesh P. Mehta

41. **Fractionated Radiation Therapy and Stereotactic Radiosurgery for Pituitary Adenomas**
Chloe Dumot, Georgios Mantziaris, Salem M. Tos, and Jason P. Sheehan

42. **Primary Base of Skull Tumors**
Mark W. McDonald

43. **Spinal Canal Tumors**
Nikhil Rammohan, Clifford G. Robinson, Jeff M. Michalski, and Jiayi Huang

PART C: Head and Neck

44. **Adult Tumors of the Eye and Orbit**
Shervin Tabrizi and Helen A. Shih

45. **Ear**
Geoffrey Sedor, Luqman Dad, and Tony J. C. Wang

46. **Locally Advanced Squamous Carcinoma of the Head and Neck**
Jessica W. Lee, Jessica L. Geiger, and David M. Brizel

47. **Nasopharynx**
Fan Yang, Benjamin H. Lok, Jonathan E. Leeman, and Nancy Y. Lee

48. **Cancer of the Nasal Cavity and Paranasal Sinuses**
Steven J. Frank, Anesa Ahamad, and Carlos A. Perez

49. **Salivary Glands**
Neil Panjwani, Pattana Wangaryattawanich, Brittany Barber, Lauren Shih, Christina P. Rodriguez, and Upendra Parvathaneni

50. **Oral Cavity**
Irini Yacoub and Nancy Y. Lee

51. **Oropharynx**
Pooja Karukonda, Joseph K. Salama, and Yvonne Marie Mowery

52. **Hypopharynx**
Matthew E. Witek, Jonathan P. Giurintano, Nitika Tripathi, and Paul M. Harari

53. **Laryngeal Cancer**
William M. Mendenhall, Anthony A. Mancuso, Rui P. Fernandes, and Peter T. Dziegielewski

54. **Unusual Nonepithelial Tumors of the Head and Neck**
Adam L. Holtzman and Daniel M. Trifiletti

55. **Neck Cancer, Including Carcinoma of Unknown Primary**
William M. Mendenhall, Anthony A. Mancuso, Robert J. Amdur, Rui P. Fernandes, and Peter T. Dziegielewski

56. **Thyroid Cancer**
Robert J. Amdur and Roi Dagan

PART D: **Thorax**

57. **Lung Cancer**
John Kang, Michael T. Milano, Marco Schwarz, Rafael Santana-Davila, Ramesh Rengan, and Jing Zeng

58. **Mediastinum and Trachea**
Florence K. Keane, Annemarie Shepherd, Christopher S. Nabel, Ravi A. Chandra, Anneyuko Saito, Gregory A. Russo, Clifton D. Fuller, and Charles R. Thomas, Jr

59. **Esophageal Cancer**
Brian G. Czito and Christopher G. Willett

60. **Tumors of the Heart, Pericardium, and Great Vessels**
Aviva Berkowitz

PART E: Breast

61. **Breast Cancer: Stage Tis**
Alfredo I. Urdaneta, Todd Adams, David E. Wazer, and Douglas W. Arthur

62. **Breast Cancer: Early Stage**
Nisha Ohri, Sharad Goyal, Thomas Buchholz, and Bruce G. Haffty

63. **Breast Cancer: Locally Advanced and Locally Recurrent**
Christin A. Knowlton, Nancy Chan, Serena Wong, Meena S. Moran, and Jennifer R. Bellon

PART F: Gastrointestinal

64. **Stomach Cancer**
Brian G. Czito and Christopher G. Willett

65. **Pancreatic Cancer**
Christopher G. Willett and Brian G. Czito

66. **Cancer of the Liver and Hepatobiliary Tract**
Jia-Shing Wu, Huei-Chuang Yeh, and Andrew T. Huang

67. **Cancer of the Colon and Rectum**
Christine E. Eyler, Manisha Palta, Brian G. Czito, and Christopher G. Willett

68. **Anal Cancer**
Paul Riviere and James D. Murphy

PART G: Urinary Tract

69. **Cancer of the Kidney, Renal Pelvis, and Ureter**
Hiram A. Gay and Jeff M. Michalski

70. **Adjuvant and Neoadjuvant Radiation Therapy for Locally Advanced Bladder Cancer**
Brian C. Baumann and Mohamed S. Zaghloul

71. **Bladder Cancer**
Sophia C. Kamran, Brian C. Baumann, and Jason A. Efstathiou

PART H: Male Genitourinary

72. **Low-Risk Prostate Cancer**
Hiram A. Gay and Bridget F. Koontz

73. **Management of Intermediate- and High-Risk Prostate Cancer**
Quaovi H. Sodji and Mack Roach III

74. **Testicular Cancer**
Gerard C. Morton

75. **Cancer of the Penis and Male Urethra**
Vivek Verma and Hiram A. Gay

PART I: **Gynecologic**

76. **Cancer of the Uterine Cervix**
Yosef Landman-Gigi, Darien Colson-Fearon, Akila N. Viswanathan

77. **Endometrial Cancer**
Benjamin W. Fischer-Valuck and Yuan James Rao

78. **Ovarian and Fallopian Tube Cancer**
Christopher Weil

79. **Vaginal Cancer**
Joanne W. Jang and Akila N. Viswanathan

80. **Female Urethral**
Benjamin D. Hopkins and Tony Y. Eng

81. **Carcinoma of the Vulva**
Diandra N. Ayala-Peacock, Mary Katherine Anastasio, and Junzo P. Chino

PART J: **Adrenal and Retroperitoneal Tumors**

82. **Retroperitoneum**
Meng Xu-Welliver, Eric D. Miller, Joel L. Mayerson, Brian A. Van Tine, and Jeffrey C. Buchsbaum

83. **Adrenal Cancer**
Filip T. Troicki

PART K: **Lymphoma and Hematologic Tumors**

84. **Hodgkin Lymphoma**
Bradford S. Hoppe, Omran Saifi, and Richard T. Hoppe

85. **Non-Hodgkin Lymphomas**
Christopher R. Kelsey, Edina Wang, Alex J. Gooding, and Leonard R. Prosnitz

86. **Primary Cutaneous Lymphomas**
Tarsheen K. Sethi, Youn H. Kim, Lynn D. Wilson, and Richard T. Hoppe

87. **Leukemia**
Timothy J. Robinson, Kenneth B. Roberts, Scott Huntington, Jessica M. Stempel, and Nikolai Podoltsev

88. **Plasma Cell Neoplasms: Multiple Myeloma and Solitary Plasmacytomas**
Belinda A. Campbell, Sarah A. Milgrom, Andrea Lo, Amit Khot, Richard Bakst, and Joseph Mikhael

PART L: **Soft Tissue**

89. **Soft Tissue Sarcoma (Excluding Retroperitoneum)**
Kilian E. Salerno and Elizabeth H. Baldini

PART M: **Pediatric**

90. **Central Nervous System Tumors in Children**
Kevin X. Liu, Hesham Elhalawani, and Daphne A. Haas-Kogan

91. **Wilms Tumor**
John A. Kalapurakal and Arnold C. Paulino

92. **Neuroblastoma**
Christine E. Hill-Kayser and Mark Gaze

93. **Rhabdomyosarcoma**
Michael D. Young and Dana L. Casey

94. **Nonrhabdomyosarcoma Soft Tissue Sarcoma in Children**
Leslie Chang, Erin McCammack, Dana L. Casey, Susan Hiniker, Colette J. Shen, and Stephanie A. Terezakis

95. **Osteosarcoma and Other Primary Tumors of Bone**
Safia K. Ahmed and Nadia N. I. Laack

96. **Ewing Sarcoma**
Line Claude, Akmal Safwat, Raquel Davila Fajardo, Marija Kacar, Matthew Krasin, and Daniel Indelicato

97. **Lymphomas in Children, Adolescents, and Young Adults**
Sarah A. Milgrom, James E. Bates, Matthew D. Hall, Jamie E. Flerlage, Sharon M. Castellino, and Louis S. Constine

98. **Retinoblastoma**
Beate Timmermann and John T. Lucas, Jr

99. Rare Tumors in Children
Cheng-Chia Wu and Matthew Krasin

PART N: **Benign Diseases**

100. Nonmalignant Diseases
Simon A. Brown, Jerry J. Jaboin, Tony Y. Eng, Jose Bazan, and Charles R. Thomas, Jr

SECTION V **Palliative and Supportive Care**

101. Palliation of Brain Metastases
Hua-Ren R. Cherng, Mark Mishra, Roy A. Patchell, William F. Regine, and Young Kwok

102. Palliation of Vertebral and Spinal Cord Metastases
Emily MacDuffie and Joshua Jones

103. Palliation of Bone Metastases
Alexander A. Harris, Michael Kharouta, Chirag Modi, and William F. Hartsell

104. Palliation of Visceral Recurrences and Metastases and Treatment of Oligometastatic Disease
Alexander A. Harris, Michael Kharouta, Chirag Modi, and William F. Hartsell

105. Cancer Pain: Assessment and Management
Ellen Kim and Tracy A. Balboni

106. Palliative and Supportive Care
Ellen Kim and Tracy A. Balboni

107. Management of Radiation Side Effects
Shirin Sioshansi, Gavin Jones, and Paul Rava

Index I-1

SECTION I

Overview and Basic Science of Radiation Oncology

CHAPTER 1

The Discipline of Radiation Oncology

Edward C. Halperin

WHAT IS RADIATION ONCOLOGY?

Radiation oncology is a discipline of human medicine concerned with the generation, conservation, and dissemination of knowledge concerning the causes, prevention, and treatment of cancer and other diseases. The discipline requires special expertise in the therapeutic applications of ionizing radiation (Box 1.1). As a discipline that exists at the juncture of physics and biology, radiation oncology addresses the therapeutic uses of either ionizing radiation alone or in combination with other treatment modalities, such as cytotoxic chemotherapy and biologic and immunologic and cellular therapies, surgery, radiosensitizing and radioprotective drugs, oxygen, and heat. Furthermore, radiation oncology is concerned with the investigation of the fundamental principles of cancer biology; the physical, chemical, and biologic interaction of radiation with normal and malignant tissue; and the physical basis of therapeutic radiation. As a learned profession, radiation oncology is concerned with clinical care, scientific research, and the education of professionals within the discipline.

Box 1.1

The Etymology of *Radiate*

The defining verb of the discipline of radiation oncology, *radiate*, is derived from the Latin verb *radiatus. Radiatus* is the participial stem. Some dictionaries cite the origin of the word *radiate* as being from other tenses of the verb such as the present infinitive *radiarae* or the first-person singular present indicative *radio*. Radiate is defined as “to spread from the common center” or “to diverge or spread from the common point” or “to issue and raise.” Radiate shares a common root and related meanings with other English words, such as *ray*, *radius*, and *radial*. The verb *radiate* is more distantly related to other words. For example, if one proceeds along the ray from the political center to the extreme, then one is called *radical*.

The verb *irradiate* means “to direct rays upon” or “to cause rays to fall upon something.” In Latin, the prefix *in* conveys the meaning of in, within, on, upon, or against. When the prefix *in* is used with the word that begins with the letter *r*, the letter *r* is substituted for the letter *n* in the prefix to assimilate the initial sound of the verb. Thus, the verb that indicates the placement of water within or on the ground changed from *inrigate* to *irrigate*. Similarly, *inradiate* was changed to *irradiate*.

An object may be said to radiate something or to emit a ray. For example, “The block of cobalt 60 radiates gamma rays.” The verb that indicates directing rays on or into an object is *irradiate*. An example of proper usage would be “I recommend that we irradiate the tumor to a total dose of 45 Gy.” Incorrect usage would be “I think the primary tumor should be radiated to a dose of 45 Gy.”[1]

Radiation therapy is a clinical modality dealing with the use of ionizing radiation in the treatment of patients with malignant neoplasias (and occasionally benign diseases). The aim of radiation therapy is to deliver a precisely measured radiation dose to a defined tumor volume with as minimal damage as possible to surrounding healthy tissue, resulting in the eradication of the tumor, high quality of life, and prolongation of survival or palliation of symptoms at a reasonable cost. In addition to curative efforts, radiation therapy plays a major role in cancer management in the effective palliation or prevention of symptoms of the disease: Pain can be alleviated, luminal patency can be restored, skeletal integrity can be preserved, and organ function can be reestablished with minimal morbidity.[2]

WHAT IS A RADIATION ONCOLOGIST?

Franz J. Buschke (1902-1983) posed and answered the question “What is a radiotherapist?”

> When the patient is under our care we take full and exclusive responsibility, exactly as does the surgeon who takes care of a patient with cancer . . . . During the course of treatment, we ourselves direct any additional medication that may be necessary . . . and are ready to be called in an emergency at any time.[3] (Reproduced with permission from Buschke F. Editorial: what is a radiotherapist? *Radiology*. 1962;79(2):319-321. Copyright © 1962 Radiological Society of North America.)

Eli Glatstein (1938-2019) and Leonard Prosnitz rank ordered the priorities of a radiation oncologist as follows: “You are a general physician first, a general oncologist second, and a radiation oncologist third - and you need to keep them in that order” (Figure 1.1).

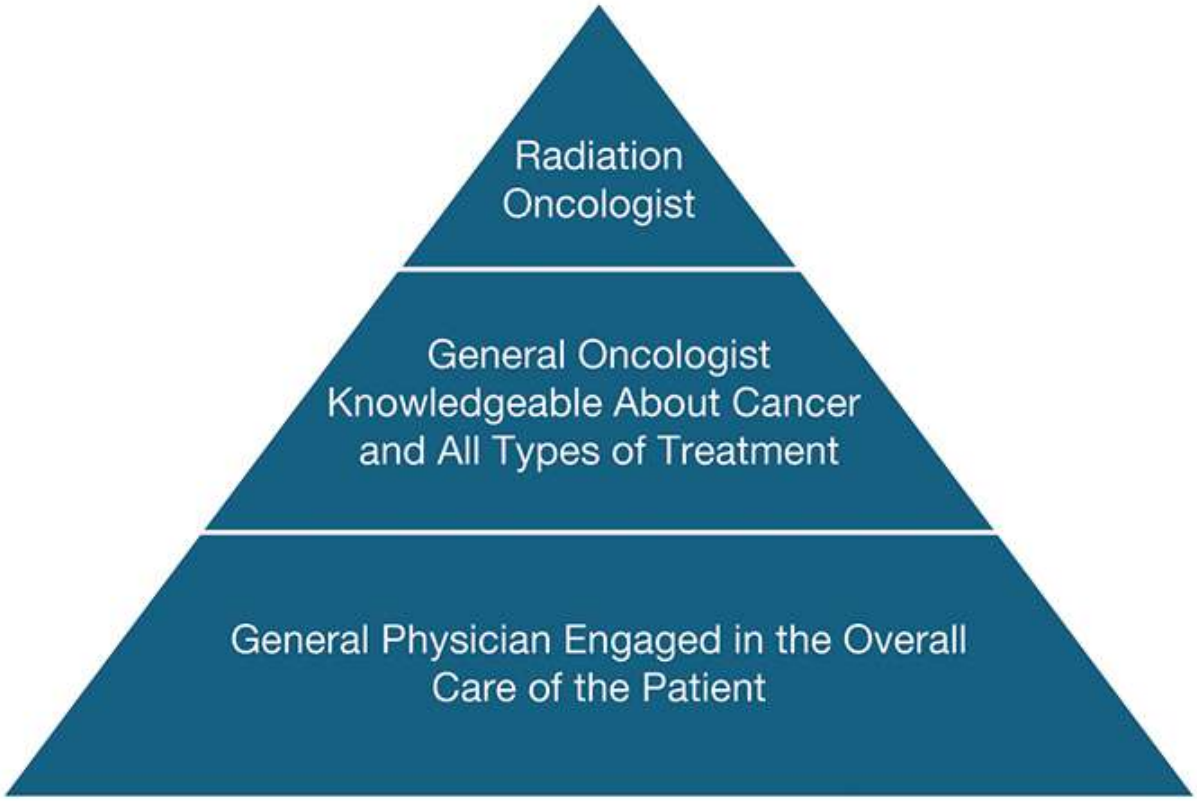


FIGURE 1.1 Eli Glatstein and Leonard Prosnitz have proposed a pyramidal definition of a radiation oncologist. Built upon the solid base of general medical knowledge resides a broad knowledge of oncology. The specialized knowledge of radiation oncology, in turn, sits upon that second base.

Morton Kligerman (1917-2006) tackled the topic in his 1982 American Society for Radiation Oncology (ASTRO) Gold Medal Address. Kligerman criticized the departure of the specialty from the ideals articulated by Buschke, Glatstein, and Prosnitz.

> I would like to suggest that the radiotherapy community bears the major responsibility for the loss of [respect for] our traditional role, largely because we have given up the general medical care of patients under our management, There is a growing unwillingness on our part to participate in many of the activities normally associated with primary care physicians . . . it is on the [hospital] floor where the radiation therapist meets medical students, interns, and other house officers . . . . The failure to admit patients on our own services . . . is the self-recognition that the radiation therapist has not kept up with primary patient care. Secondly . . . [it is often because] the radiation therapist is unwilling to spend the time and be inconvenienced by the requirements of in-patient care.[4] (Used with permission of Elsevier Science & Technology Journals from Kligerman MM. Gold medal acceptance speech: comprehensive patient care in radiation therapy practice. *Int J Radiat Oncol Biol Phys*. 1983;9(7):1091-1092; permission conveyed through Copyright Clearance Center.)

Buschke, Glatstein, Prosnitz, and Kligerman are all making the same fundamental points: A radiation oncologist is a physician who strives to understand the causes, prevention, and treatment of human cancer with special expertise in the use of

ionizing radiation. Most importantly, the radiation oncologist is a physician who cares for the whole patient and provides that care in the clinic and on the hospital wards. The radiation oncologist performs a complete medical history and physical examination, reviews the pertinent laboratory and imaging data relevant to the patient, and offers an opinion on the optimum treatment plan with special expertise in the use of radiation therapy.

If this IS what a radiation oncologist is, then what IS NOT a radiation oncologist? The radiation oncologist is not the button pusher in the basement. They are not a physician who says, "If the patient can't come downstairs from their hospital bed to my clinic, then I can't treat them - so I don't made inpatient rounds." They are not the type of doctor who says, "I don't need to do a medical history and physical, I can tell what I need to do by looking at the CT and/or MRI." They are most emphatically not the type of doctor who refuses to deal with the complications of radiation therapy, refuses to see patients on nights and weekends, refuses to evaluate patients in the emergency department, and refuses to provide inpatient care.[5]

In Galatians 6:7, we read: "For whatsoever a man soweth, that shall he also reap." If a radiation oncologist acts like a technician in the basement and declines to act like a full-fledged member of the medical team, then their fellow physicians will treat them that way and the radiation oncologist will only have themselves to blame.

It is the goal of the eighth edition of this textbook to provide radiation oncologists with the tools they need to practice their specialty commensurate with the ideals described earlier. It is the goal of this chapter to provide an overview of this branch of medicine. In particular, the author hopes that this overview will be of value to medical students and residents experiencing their first significant contact with radiation oncology.

A CANCER BIOLOGY PRIMER

What Is Cancer?

If the medical discipline of radiation oncology primarily concerns itself with the causes, prevention, and treatment of human cancer, then it seems logical that we must begin an introduction to this discipline by answering the fundamental question, "What is cancer?"

For many years, it has been the habit of the author to ask medical students beginning a clinical elective on the radiation oncology service or new radiation oncology residents beginning their training, "How do you define the word *cancer*?" For someone beginning the study of cancer, this would seem to be the most fundamental question to answer at the outset. The question is most often met by a blank stare. Faced with the likelihood that, like these trainees, many of my readers

have not grappled with this question, it seems worthy of some consideration in these pages.

James Ewing, early in his magisterial 1919 textbook *Neoplastic Diseases*, grapples with this question. He begins with the statement, "A tumor is an autonomous growth of tissue." He then succinctly reviews the views of his era.

> v. Rindfleisch says briefly, "A tumor is a localized degenerative excess of growth." Ziegler defines a tumor as a new growth of tissue, which apparently originates and grows spontaneously, possesses an atypical structure, does not subserve the uses of the organism, and reaches no definite termination of its growth. According to Birch-Hirschfeld, tumors are progressive new growths of tissue arising spontaneously from cells of its own, and separated from normal tissue both in morphology and in function. Ribbert states that tumors are new growth of tissue, self-centered, largely or wholly uncontrolled by the organism which supplies their nutrition, and a structure never entirely normal, and reaching no definite termination of growth.[6]

Ewing, who is profiled elsewhere in this chapter, spends many pages in the four editions of *Neoplastic Diseases* trying to present a succinct definition. He settles on "a tumor is an autonomous new growth of tissue" while citing the attempts of others. He writes, " Adami accepts White's descriptive definition: 'A tumor proper is a mass of cells, tissues or organs resembling those normally present, but arranged atypically. It grows at the expense of the organism without at the same time subservient any useful function.'"[7]

The National Cancer Institute (NCI) Dictionary of Cancer Terms offers the following definition: Cancer is "a term for diseases in which abnormal cells divide without control and can invade nearby tissues. Cancer cells can also spread to other parts of the body through the blood and lymph systems."[8]

If you were to line up a series of dictionaries and pathology textbooks on your desk, and open each to the proffered definition of cancer, you will find phrases such as "an uncontrolled division of abnormal cells . . .," "a malignant tumor of potentially unlimited growth that expands locally by invasion and systemically by metastasis . . .," and "an abnormal growth of cells which tend to proliferate in an uncontrolled way and, in some cases, to metastasize (spread)."

No matter what definition one chooses, there will always be exceptions. The best is the enemy of good, as Voltaire reminded us, and the lack of a perfect definition should not dissuade us from finding a good, working, reasonable definition.

A modern definition of cancer is "a disease of cell proliferation, it is heritable in that it is conveyed by a cell to its daughter cells; in which cells do not respect the usual constraints on their growth of space and time. It is characterized by invasion and metastases" (Figure 1.2).

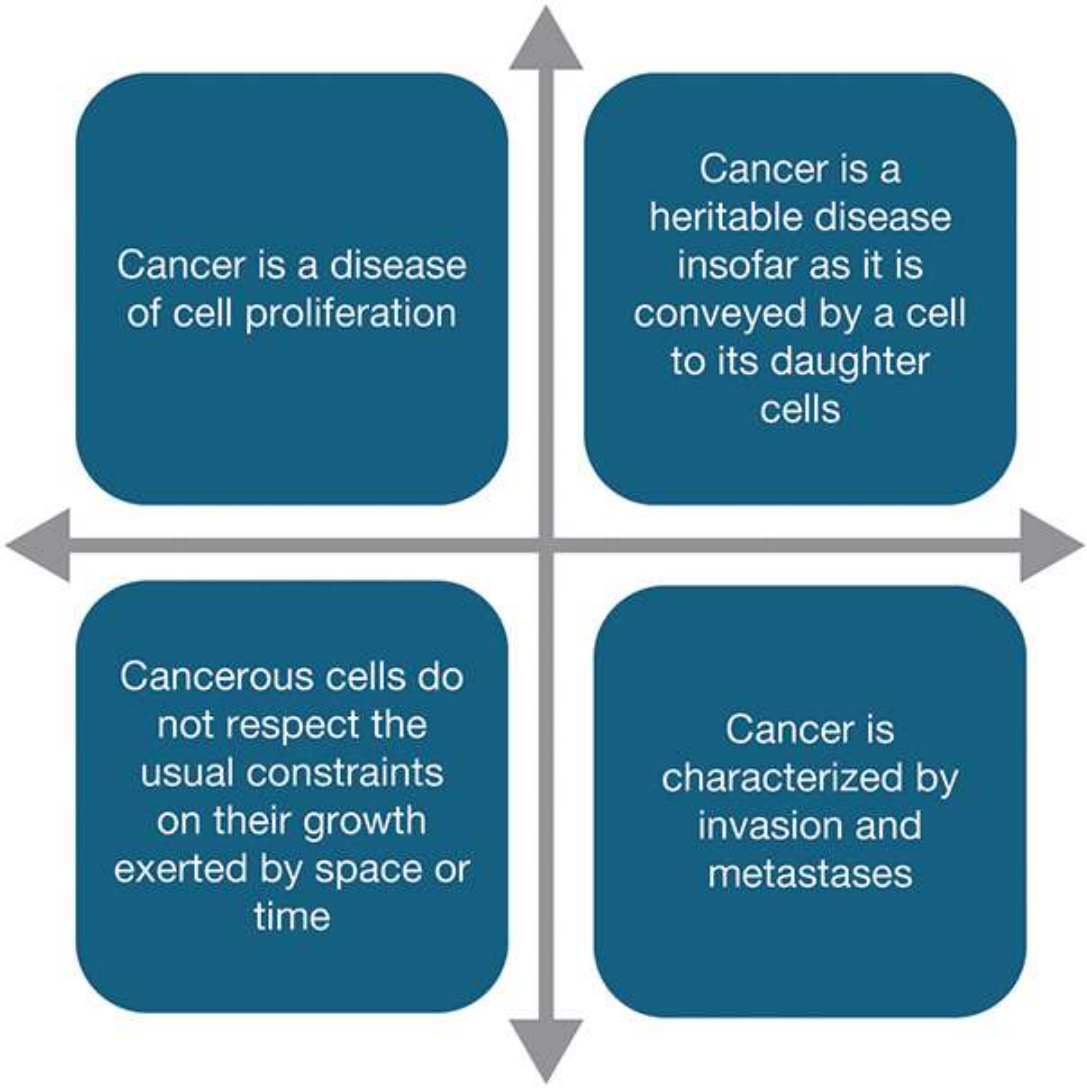


FIGURE 1.2 The four components of the definition of cancer.

Let us unpack this definition and strive to understand its full meaning.

- "a disease of cell proliferation"

  The fundamental essence of cancer is that it is a problem of cell multiplication.

- "conveyed by a cell to its daughter cells"

  When a cancerous cell divides, both of its daughter cells are also cancerous. The cancerous nature of a cell is passed with the parent genetic material to the daughter cells.

- "cells do not respect the usual constraints on their growth of space and time"

  Normal cell growth is constrained. If you cut yourself, then fibroblasts begin to proliferate to heal the wound. They grow and grow and then a cellular switch

turns the growth off (except in keloid formation). Similarly, in embryonic development, our cells proliferate to grow organs; at some point, however, the growth stops. Cancer cells do not stop growing when they bump up against adjacent cells (contact inhibition) or according to some internal time clock. Their growth is not constrained. Contact inhibition is not a characteristic of cancer cells. Furthermore, cancer cells generally have cell cycle times faster than normal tissue.

- "characterized by invasion and metastases"

  As Ewing wrote, "Growth is infiltrative, single cells or cell groups pushing their way through and destroying adjacent tissues". Cancers tend to invade surrounding tissue. Most have the ability to disseminate cells into the blood, lymph, cerebrospinal fluid, and/or pleural and peritoneal cavities where they will eventually come to rest, invade, and proliferate in different tissues from whence they began.

In contrast to cancerous tumors, benign tumors do not invade adjacent tissues. When benign tumors are fully removed, they usually do not grow back nor do metastases appear elsewhere in the body, in contrast to cancerous tumors. Nonetheless, in certain situations, benign tumors can be life-threatening—such as in the brain.

In what ways are cancer cells different from normal cells? Here is a partial list, stated in very broad strokes:

- Normal cells typically rely on the receipt of growth signals to proliferate. A typical signal of this type would be hormonal. In contrast, cancerous cells grow due to intrinsic properties possessed within; such as growth-promoting genes.
- Cancer cells have the ability to ignore growth-inhibiting messages.
- Cancer cells are able to avoid programmed cell death (apoptosis).
- Normal cells stop growing when they abut other cells (contact inhibition), cancer cells generally do not.
- Cancer cells invade surrounding tissues, normal cells do not.
- Cancer cells can produce chemical signals to draw blood vessels toward themselves. Creating a ready supply of nutrients and oxygen promotes further growth. Indeed, some cancer cells have alternative pathways for nutrition, and they derive energy in ways normal cells cannot.
- In contrast to normal cells, cancer cells can detach, travel via the blood or lymph or cerebrospinal fluid or in the pleural or peritoneal cavities, reattach, and develop as a new colony, called a metastasis.

- While the immune system patrols the body and destroys damaged or abnormal cells, cancer cells often have the ability to avoid the assault of the immune system and, sometimes, even manipulate the immune system to aid cellular proliferation.
- Cancer cells often have multiple copies of chromosomes and/or duplications and deletions of chromosomes. It is common for cancer cells to have a very high nuclear to cytoplasm ratio, compared to normal cells. This makes sense for a cell that devotes itself so profoundly to proliferating.

Genes and the Biology of Cancer

The infectious nature of some cancers was demonstrated by Francis Peyton Rous (1879-1970) in a 1910 experiment showing that defined, submicroscopic, filterable agents (viruses) isolated from a chicken sarcoma could induce new sarcomas in healthy chickens. Rous and his work languished in obscurity before being rediscovered and recognized with the Nobel Prize in Physiology or Medicine in 1966 (Figure 1.3).[9] In his Nobel Lecture, "The Challenge to Man of the Neoplastic Cell," Rous considered the possible existence of growth-promoting genes—what he called oncogens and what are now called oncogenes.

FIGURE 1.3 Peyton Rous won the Nobel Prize in 1966 for experiments he began in 1910. He demonstrated that a sarcoma could be transmitted from one chicken to another via a very small carcinogenic agent—a virus. A. Rous as a young investigator. B. At the time of the receipt of the Nobel Prize. (Courtesy of Rockefeller Archives Center.)

Tumors destroy man in a unique and appalling way, as the flesh of his own flesh that has somehow been rendered proliferative, rampant, predatory, and ungovernable. They are the most concrete and formidable of human maladies, yet despite more than 70 years of experimental study, they remain the least understood. This is the more remarkable because they can be evoked at will for scrutiny by any one of a myriad chemical and physical means, which are left behind as tumors grow. These had acted merely as initiation. Few situations are more exasperating to the inquirer than to watch a tiny nodule form on a rabbit's skin at a spot from which the chemical agent inducing it has long since been gone and to follow the nodule as it grows, and only too often becomes a destructive epidermal cancer. What can be the reason for these happenings?

> Every tumor is made up of cells that have been so singularly changed as to no longer obey the fundamental law whereby the cellular constituents of an organism exist in harmony and act together to maintain it. Instead the changed cells multiply at its expense and inflict damage that can be mortal. We term the lawless cells neoplastic because they form new tissue, and the growth itself is a neoplasm; but on looking into medical dictionaries, hoping for more information, we are told, in effect, that *neoplastic*

means “of or pertaining to a neoplasm,” and turning to *neoplasm* learn that it is “a growth which consists of neoplastic cells.” Ignorance could scarcely be more stark.

The chemical and physical initiators ordinarily are called *carcinogens*; but this is a misleading term because they induce not only the malignant epithelial growths known as carcinomas but also other neoplasms of widely various kinds.... the less often used term oncogenes will be used, meaning “thereby capable of producing a tumor.” It hews precisely to the fact. . . .

What can be the nature of the generality of neoplastic changes, the reason for their persistence; for their irreversibility; and for the discontinuous, steplike alterations that they frequently undergo? A favorite explanation has been that oncogenes cause alterations in the genes of the body—somatic mutations as these are termed. But numerous facts, when taken together, decisively exclude this supposition.[10] (Peyton Rous—Nobel Lecture. The Challenge to Man of the Neoplastic Cell. NobelPrize.org. From Nobel Lectures, Physiology or Medicine 1963-1970, Elsevier Publishing Company, Amsterdam, 1972. Copyright © The Nobel Foundation 1966.)

Rous, it turned out, was wrong about oncogenes. Theodor Boveri[256] was right. In 1914, he used his studies of normal mitosis in sea urchins and worms as a platform for suggesting that cancer might be caused by the abnormal gain or loss of chromosomes and their function. In a 1929 English translation of his 1926 book, *The Origin of Malignant Tumors*, Boveri wrote:

The unlimited tendency to rapid proliferation in malignant tumor cells [could result] from a permanent predominance of the chromosomes that promote division. . . . Another possibility [to explain cancer] is the presence of definite chromosomes which inhibit division. . . . Cells of tumors with unlimited growth would arise if those “inhibiting chromosomes” were eliminated . . . [since] each kind of chromosome is represented twice in the normal cell, the depression of only one of these two might pass unnoticed.[11]

Boveri predicted that the genetic abnormalities leading to the development of cancer are of two sorts: growth-promoting genes and growth-suppressing genes. If the growth-promoting genes are excessive in number or activity, they lead to cell proliferation. If, however, the growth-suppressing genes are defective in amount or activity, they fail to halt cell proliferation and lead to unbridled cell replication (Figure 1.4). These growth-promoting genes are called *oncogenes*. The growth-suppressing genes are called *tumor suppressor genes*.

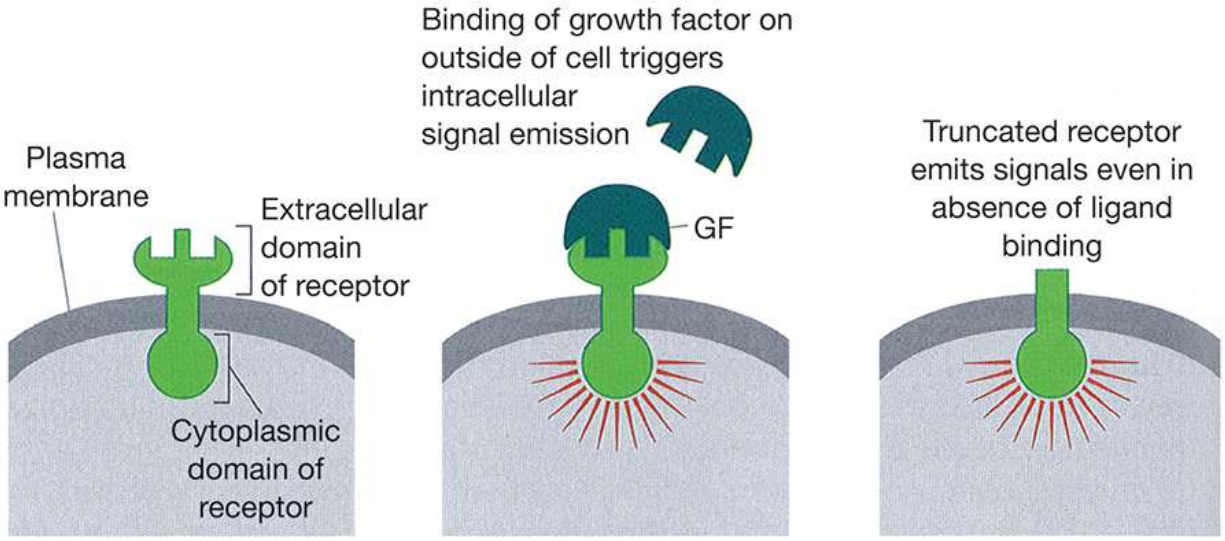


FIGURE 1.4 Oncogenes can act in multiple ways. One method is for a growth factor receptor, which ordinarily is only active when it binds to a ligand, to become active all the time, even in the absence of a growth factor binding to it. This is called "being constitutively active" and is the result of an oncogenic mutation. (From Weinberg RA. *The Biology of Cancer*. Garland Science; 2007. Copyright © 2007 by Garland Science, Taylor & Francis Group. Used by permission of W. W. Norton & Company.)

We may think of oncogenes and tumor suppressor genes as analogous to the accelerator pedal and the brake pedal of an automobile. The car can move forward when it is idling with the transmission in drive either by pushing on the accelerator pedal, by taking pressure off the brake pedal, or by doing both simultaneously. Similarly, cell growth and proliferation, leading to cancer, can occur either by the activity of the oncogenes or by the inactivity of the suppressor genes.

There are clearly a wide variety of physiologic conditions that call for the effective use of growth-promoting and growth-suppressing genes. There must be a mechanism to cause the fetus to grow and then, at the appropriate time, to restrain growth. There must be a way of causing fibroblasts to proliferate to heal a wound and then, at the appropriate time, halt the fibroblasts (except in the case of keloid formation). Uncontrolled cell growth, or cancer, may be thought of as a set of physiologic controls of cell growth gone awry.

Oncogenes

The experiments that initially identified oncogenes were based largely on transformed retroviruses in transplantable tumors in chickens, mice, and rats.[12] Oncogenes were described as the genetic material carried by RNA tumor viruses that resulted in rapid malignant transformation of target cells.[13,14] The name oncogene was given to virus-encoded single genes that either alone or in combination with other genes induced a transformed phenotype in affected cells.[15,16]

The word oncogene derives from the Greek *onkos*, a “mass” or “tumor.” Many oncogenes are those found in retroviruses. However, not all cellular genes capable of transforming cells have been identified within the genome of known retroviruses. It is accepted that an oncogene is a gene capable of contributing directly to the conversion of a normal cell to a tumorigenic one and that a proto-oncogene is a cellular gene convertible to an oncogene by various molecular mechanisms: sequence mutations, gene amplification, chromosomal translocation, viral transduction, and insertional mutagenesis. In general, these perturbations result in two net effects: altered regulation or augmented expression of an oncogene through mutation or rearrangement of the nucleotide sequences that constitute signals for control of transcription, messenger RNA processing, and stability via insertion of a strong foreign promoter or by increased gene dosage and altered biochemical function or ectopic expression of a protein product as a result of a mutation or translocation within the protein-coding region of the oncogene. Proto-oncogene products are involved in the regulation of normal cellular growth and differentiation.

A large number of viral oncogenes have been identified. In addition, oncogenes have been identified that are not associated with RNA tumor viruses but are recognized either by their activity in transformation or by their association with chromosome translocations.[17] In a study of tumors in chickens using DNA probing techniques, it was found that sequences homologous to the oncogene region of the virus were present in the DNA of all tissues of virus-free chickens. The normal cellular sequences are proto-oncogenes. The oncogene carried by a virus is referred to as *v-onc*, whereas the proto-oncogene is referred to as *c-onc*. In the normal cell, the expression of proto-oncogene is well controlled and appears to play a role in the growth and development of the organism. The function of some of these genes has been determined, whereas for others, a close association between cell proliferation and gene expression has been established.

Stimulation of a nonmalignant cell into a proliferative state often depends on an external signal, which is received by a receptor on the cell membrane and transferred through the membrane into the cytoplasm and ultimately to the nucleus where DNA synthesis is initiated. Proto-oncogenes have been found to function at each step of this pathway. The *erb*-B oncogene is homologous to the gene encoding for the cell membrane receptor of epidermal growth factor (EGF). The interaction of EGF with this receptor reduces the proliferation of epidermal cells, such as breast epithelium.

Strong evidence suggests that malignancy induction may be associated with genetic changes in the cell. Examples of this are the finding of specific chromosomal abnormalities in malignant cells, association of tumor development with DNA-damaging agents such as ionizing irradiation and chemical carcinogens, and increasing incidence of cancer in hereditary diseases such as xeroderma pigmentosum. It is recognized that oncogenes are normal cellular genes that may

contribute to the development of the malignant cell if their expression is altered through mutation, translocation, amplification, or some other mechanism. Evidence suggests that several genetic changes are needed to produce a cancer cell, and oncogene studies support this concept.

Chromosome translocations occur at a high frequency in some types of tumors, suggesting that they may play a role in their development. Examples of translocations are the t(9;22) Philadelphia chromosome in chronic myelogenous leukemia (CML), the t(15;17) in promyelocytic leukemia, and several translocations involving chromosome 8 seen in lymphatic malignancies. Common sites of translocations in malignant cells are frequently near an oncogene. Those translocations such as the t(9;22) in CML can result in the formation of a new protein that is intimately involved in the tumorigenic transformation of the cell. In the CML example, the *ber*-gene is translocated next to the *abl*-oncogene, forming the new *bcr-abl* gene. The proteinaceous product of this newly formed gene is a hyperactive protein kinase that provides permanent growth signals to the cell.

Role of Proto-Oncogenes in Normal and Transformed Cells

Proto-oncogenes are genes with oncogenic potential, and because they are apparently present in all animals, some kind of activation of proto-oncogenes is likely to be associated with the initiation and progression of neoplasia. Activated oncogenes are detected in a large percentage of human tumors, suggesting a prominent role of these genes in their development; the association between activated oncogenes and neoplastic diseases must have some kind of specificity for both the oncogene and the tumor.

Proto-oncogenes can be activated by genetic changes that affect either protein expression or structure. As succinctly stated by Weinberg:

> The somatic mutations that caused proto-oncogene activation could be divided into two categories—those that caused changes in the structure of encoded proteins and those that led to elevated, deregulated expression of these proteins. Mutations affecting structure included the point mutations affecting *ras* proto-oncogenes and the chromosomal translocations that yielded hybrid genes such as bcr–abl. Elevated expression could be achieved in human tumors through gene amplification or chromosomal translocations, such as those that place the *myc* gene under the control of immunoglobulin enhancer sequences. . . .
>
> Gene amplification occurs through preferential replication of a segment (the amplicon) of chromosomal DNA. The result may be repeating end-to-end linear arrays of the segment, which appear as homogeneously staining regions (HSRs) of a chromosome when viewed under the light microscope. Alternatively, the region carrying the amplified segment may break away from the chromosome and can be seen as small, independently replicating, extra-chromosomal particles (double minutes). Gene amplification does not always result in overexpression of the gene. . . .[18] (From Weinberg RA. *The Biology of Cancer*. Garland Science; 2007. Copyright © 2007 by Garland Science, Taylor & Francis Group. Used by permission of W. W. Norton & Company.)

A variety of structural changes in proteins can also lead to oncogene activation. Examples include alterations in the structure of growth factor receptors (such as the EGF receptor [EGFR]) and translocations that fuse two distinct reading frames to yield a hybrid protein (such as *bcr-abl*). Both types of alterations deregulate the proteins, causing them to emit growth-promoting signals in a strong, unremitting manner.

Oncogene protein products can be grouped into several classes depending on their location and reactivity: nuclear, cytoplasmic, and membrane protein kinases; cytoplasmic guanosine triphosphate–binding proteins; growth factors; and others. The protein products of the proto-oncogenes *src*, *abl*, and *ras* are cytoplasmic in location. The proto-oncogene products of *myc*, *fos*, *ski*, and *myb* are nuclear in location and are believed to play an important role in the control of cell division. The expression of these genes may be responsible for the entry of the cell into DNA synthesis. Growth factors are proteins that act at the cell surface to stimulate cell growth.

Current evidence suggests that *ras* oncogenes contribute to both initiation and progression of human neoplasia. The incidence of proto-oncogene amplifications in biopsy specimens from tumors, although highly variable, is usually low. However, there may be a tendency toward association of amplification of specific proto-oncogenes and particular types of tumors. Amplifications of the c-*erb*-B-2/*neu* proto-oncogene (also referred to as *her*-2) may be involved in the etiology of human breast, salivary gland, and ovarian cancers and might serve as a useful prognostic marker for these malignancies.[19] The *erb*-B-2/*neu* locus is amplified in 30% of primary breast carcinomas and that amplification is associated with a worse prognosis.[20-21]

Amplification of another proto-oncogene, C-*myc*, occurs mainly in adenocarcinomas, squamous cell carcinomas, and sarcomas, but not in hematologic malignancies, whereas N-*myc* amplification occurs most frequently in neuroblastomas and occasionally in retinoblastomas and a few small cell lung carcinomas.

Tumor Suppressor Genes

The concept that a gene product could inhibit or suppress the proliferation of cells in a tumor was derived from experiments using somatic cell genetics.[22] Different chromosomes from normal human cells carry tumor suppression genes that are able to block tumor formation by the cancer cell. The cancer cells must sustain mutation in both alleles of these genes to develop the ability to produce tumors.[23,24]

These somatic cell genetic experiments relied on cell fusion. In the first type of experiment, a cancerous cell that was able to form a tumor in an animal was fused

with a normal cell. The hybrid cell no longer produced tumors in animals. One could conclude that there was an element in the normal cell that was able to suppress the tumorigenic potential of the cancerous cell. It was found that, on occasion, one of the hybrid cell lines produced by the fusion of cancerous and normal cells was tumorigenic. Why? These malignant cell lines were missing genetic material supplied by the normal parent cells. Further investigation identified the presence of tumor-suppressing genes from the normal parent. Eventually, several specific tumor suppressor genes were identified and named.[383,384]

The next important part of the story of tumor suppressor genes comes from studies of the ocular tumor of infancy—retinoblastoma. Retinoblastoma can be either unilateral and unifocal or bilateral and multifocal. The disease also can be heritable or nonheritable based on the presence of a positive family history. Alfred Knudson[25] (1922-2016) noted that heritable retinoblastoma was more often bilateral and multifocal and occurred in younger children rather than nonheritable unilateral retinoblastoma, which occurred in older children (Figures 1.5 and 1.6). Knudson postulated that there was a gene that renders children susceptible to retinoblastoma. Patients with early-onset bilateral, multifocal disease inherit one defective copy of this gene and one normal allele. With a very high frequency, mutations develop in the normal allele, and children develop the tumor. However, patients with nonheritable retinoblastoma inherit two normal alleles. Only if two independent mutations develop in the same gene, completely obliterating the function of that gene, will a cancer arise.

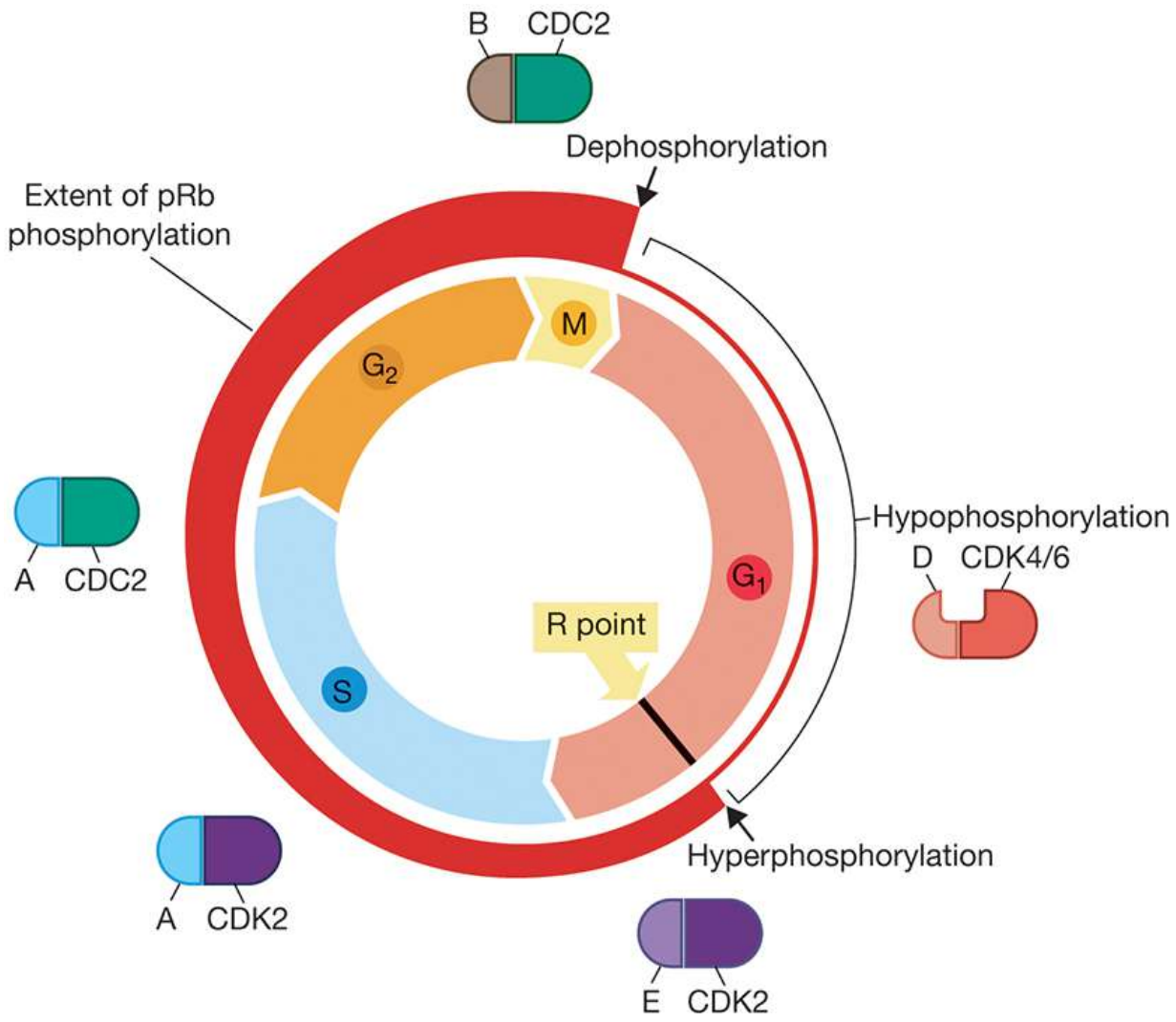


FIGURE 1.5 The phosphorylation of the retinoblastoma gene product protein, depicted as the red circle, helps to control the cell cycle. As the cell moves from M to G1, the protein is unphosphorylated; as the cell progresses through G1, the protein is hypophosphorylated; and after passing the R point (the restriction point), it is hyperphosphorylated. This process of phosphorylation is controlled by cyclins. (From Weinberg RA. *The Biology of Cancer*. Garland Science; 2007. Copyright © 2007 by Garland Science, Taylor & Francis Group. Used by permission of W. W. Norton & Company.)

FIGURE 1.6 Alfred Knudson (1922-2016) received a BS degree from the California Institute of Technology (Caltech) in 1944, an MD from Columbia in 1947, and a PhD from the California Institute of Technology in 1956. He served in the Navy during World War II and in the Army during the Korean War. In 1971, he published his "two-hit" hypothesis for the etiology of some forms of cancer. We now know this to be the result of the disabling of a tumor suppressor gene.[26] (Photo courtesy of Fox Chase Cancer Center Archives, Philadelphia, PA.)

Knudson concluded that it requires two genetic injuries in two alleles to produce retinoblastoma. This is called the "Knudson two-hit" hypothesis. The hypothesis predicts that if only one of the two gene copies remains active, there is sufficient growth suppression activity to keep the cell normal. Only if both copies are inactivated is there sufficient loss of genetic activity to allow unbridled cell proliferation. The retinoblastoma gene, *Rb*, was isolated on the long arm of chromosome 13. Because the short arm of chromosomes is abbreviated as p and the long arm as q, the deletion of the *Rb* gene is abbreviated as 13q-.[26]

How could one find tumor suppressor genes when their existence was most apparent by their absence? Robert Weinberg explains:

The dominantly acting oncogenes, in stark contrast, could be detected far more readily through their presence in a retrovirus genome, through the transfection-focus assay, or through their presence in a chromosomal segment that repeatedly undergoes gene amplification in a number of independently arising tumors. . . .

A more general strategy was required that did not depend on the chance observation of interstitial chromosomal deletions or the presence of a known gene . . . that, through good fortune, lay near a tumor suppressor gene on a chromosome. Both of these conditions greatly facilitated the isolation of the Rb gene. In general, however, the searches for most tumor suppressor genes were not favored by such strokes of good luck.[27] (From Weinberg RA. *The Biology of Cancer*. Garland Science; 2007. Copyright © 2007 by Garland Science, Taylor & Francis Group. Used by permission of W. W. Norton & Company.)

The tendency of tumor suppressor genes to undergo loss of heterozygosity (LOH) during tumor development provided cancer researchers with a novel genetic strategy for tracking them down. Because the chromosomal region flanking a tumor suppressor gene seemed to undergo LOH together with the tumor suppressor gene itself, one might be able to detect the existence of a still-uncloned tumor suppressor gene simply from the fact that an anonymous genetic marker lying nearby on the chromosome repeatedly undergoes LOH during the development of a specific type of human tumor.

The use of more powerful mapping techniques allowed geneticists to plant polymorphic markers more densely along the genetic maps of each chromosomal arm. Within a given chromosomal arm, some markers were found to undergo LOH far more frequently than others. Clearly, the closer these markers were to a sought-after tumor gene (ie, the tighter the genetic linkage), the higher the probability that such markers would undergo LOH together with the tumor suppressor gene. Conversely, markers located further away on a chromosomal arm were less likely to undergo LOH together with the tumor suppressor gene. Genetic analyses of DNAs prepared from various types of human tumors have revealed a large number of chromosomal regions that frequently suffer LOH. A subset of these regions have yielded to the attacks of the gene cloners, resulting in the isolation of many tumor suppressor genes.[28]

A number of distinctions separate the oncogenes from the tumor suppressor genes. It is almost certain that, in most human cancers, there is a multistep pathway to tumor development, which involves the accumulation of mutations in a series of oncogenes and suppressor genes.[29]

Many tumor suppressor genes have been cloned. The suppressor p53 gene resides in 20 kb of DNA located in chromosome 17p13.1. The gene is a nuclear phosphoprotein composed of 393 amino acid residues in humans.[30] p53 mutations have been detected in a wide variety of malignant human tumors. The *p53* gene

encompasses 16 to 20 kb of DNA on the short arm of human chromosome 17. Loss of normal p53 function is associated with cell transformation in vitro and the development of neoplasms in vivo. Abrogation of the normal p53 pathway is a common feature in human cancers, and it appears to be critical in the pathogenesis and progression of these tumors.[31] In some cases, candidate tumor suppressor genes have been identified based on an association between loss or inactivation and tumor development, with the causal connection being only inferred.

Cell Cycle Control

The cell cycle, which consists of four phases (G1, S, G2, and M), regulates the duplication of genetic information and the distribution of duplicated chromosomes to daughter cells. The phrases "cell cycle control" and "cell cycle clock" are used to describe the cell's molecular circuits operating in the nucleus that process and integrate afferent signals and decide if the cell will actively proliferate or remain quiescent. If the "go/no-go" decision is to "go" into proliferation, the circuitry is engaged to launch the biochemical changes necessary to allow the cell to double its contents and divide into two daughter cells. Key providers of the afferent information are tyrosine kinase receptors, G-protein coupled receptors, transforming growth factor-β (TGF-β) receptors, integrins, and the cell's nutritional status.

The Nobel Prize in Physiology or Medicine for 2001 was awarded to Leland H. Hartwell, R. Timothy Hunt, and Sir Paul M. Nurse for their discoveries regarding the control of the cell cycle. The Nobel presentation speech by Professor Anders Zetterberg succinctly describes the important controls of cell replication elucidated by these three scientists:

Cell division is a fundamental process of life. All living organisms on earth are descended from an ancestral cell that appeared about 3 billion years ago, and which has undergone an unbroken series of cell divisions since then. Each human being also began life as one single cell—a cell that divided repeatedly to give rise to all one hundred thousand billion cells that we consist of. . . . Every second millions of cells divide in our body.

The cycle of events that a cell completes from one division to the next is called the cell cycle. During the cell cycle the cell grows in size, duplicates its hereditary material—that is, it copies the DNA molecules in the chromosomes—and divides into two daughter cells.

This year's Nobel Laureates have discovered the key regulators of the cell cycle—cyclin dependent kinase (CDK) and cyclin. Together these two components form an enzyme, in which CDK is comparable to a "molecular engine" that drives the cell through the cell cycle by altering the structure and function of other proteins in the cell. Cyclin is the main switch that turns the "CDK engine" on and off. This cell-

cycle engine operates in the same way in such widely disparate organisms as yeast cells, plants, animals, and humans.

How were the key regulators CDK and cyclin discovered? Lee Hartwell realized the great potential of genetic methods for cell cycle studies. He chose baker's yeast as a model organism. In the microscope, he could identify genetically altered cells—mutated cells—that stopped in the cell cycle when they were cultured at an elevated temperature. Using this method Hartwell discovered, in the early 1970s, dozens of genes specific to the cell division cycle, which he named *CDC* genes. One of these genes, *CDC28*, controls the initiation of each cell cycle, the "start" function. Hartwell also formulated the concept of "checkpoints," which ensure that cell cycle events occur in the correct order. Checkpoints are comparable to the program in a washing machine that checks if one step has been properly completed before the next can start. Checkpoint defects are considered to be one of the reasons behind the transformation of normal cells into cancer cells.

Paul Nurse also used the genetic approach in his cell-cycle studies but in a different kind of yeast. In the late 1970s and early 1980s he discovered the gene *CDC2*, which could be mutated in two different ways. Either the cells did not divide, or they divided too early. From this he correctly concluded that *CDC2* controls cell division. He later discovered that *CDC2* not only controls cell division, the final event of the cell cycle; it also has a key regulatory function for the whole cell cycle, including that described for *CDC28* in baker's yeast. This key function was shown to be that of CDK in the cell-cycle engine. By moving human genes into yeast cells, in 1987 Nurse isolated a human *CDC2* gene. This human *CDC2* gene functioned perfectly in yeast cells. Thus, the CDK function in the cell-cycle engine had been conserved through more than 1 billion years of evolution—from yeast to man.

Tim Hunt discovered the other key component of the cell-cycle engine, the protein cyclin, which regulates the function of the CDK molecule. Working with sea urchin eggs as a model organism, in 1982 he discovered a specific protein that increased in amount before cell division but disappeared abruptly when the cells divided. Because of these cyclic variations, he named the protein cyclin. These experiments not only led to the discovery of cyclin, but also demonstrated the existence of periodic protein degradation in the cell cycle—a fundamental control mechanism. Hunt also showed the existence of cyclins in other, unrelated species. Thus cyclins, like CDK, had been conserved during evolution.[32] (Zetterberg A. Award ceremony speech. The Nobel Prize in Physiology or Medicine 2001. NobelPrize.org. https://www.nobelprize.org/prizes/medicine/2001/ceremony-speech/. Copyright © The Nobel Foundation 2001.)

Since the structure of the DNA molecule—the double helix—was discovered, we have a molecular explanation of how a gene can make a copy of itself. With the

discoveries of CDK and cyclin, we are now beginning to understand, at the molecular level, how the cell can make a copy of itself.

To ensure that the daughter cells possess a full complement of genetic information, checkpoints exist to ensure fidelity of DNA duplication and accuracy of chromosome segregation.[48] Checkpoint pauses permit editing and repair of genetic information so that each daughter cell receives a full complement of genetic information identical to the parent cell. In some cells, there are checkpoints for initiation of mitosis. Mutation of the checkpoint genes allows the cell to enter mitosis after x-irradiation.[33] For example, the *rad-9* is a G2/M checkpoint gene which responds to two different types of signals.[34] Experimental observations suggest that the *p53* gene, shown to be a transcriptional activator,[35] may be critical for G1 checkpoint control. *p53* has been shown to induce transcription of *p21*, which, in turn, inhibits the association of CDK 4,6 with proliferating cell nuclear antigen and cyclin D. As a consequence, the retinoblastoma protein cannot be phosphorylated and stays in complex with the transcription factor E2F, effectively blocking the transcription of cell cycle–promoting proteins and causing a cell cycle arrest.

Checkpoints are signal transduction systems that must receive a signal, amplify it, and transmit it to other components that regulate the cell cycle. Double-strand DNA breaks, unexcised ultraviolet light–induced dimers in DNA, and centromeres not engaged by the spindle are potential signals.[36,37] Checkpoints ensure the fidelity of genomic replication and segregation. Biologically significant levels of spontaneous damage require checkpoint control for cells to maintain a high fidelity of chromosome transmission. Therefore, restoration of compromised checkpoints could slow cancer cell evolution even in the absence of exogenous sources of DNA damage.[266] Many signal transduction systems, including checkpoint controls, exhibit adaptation; that is, in the presence of a constant stimulus, the response diminishes with time. As a consequence, the cell may proceed through the cell cycle, although the original perturbation has not been removed or cannot be repaired. Checkpoint activation may induce a variety of cell responses, including cell death. The checkpoint controlling entry into S phase in mammalian cells includes *p53*. One function under the control of this pathway is apoptosis. Restoration of defective checkpoints could restore the apoptotic response of cancer cells and increase their sensitivity to DNA-damaging agents. It may be possible to achieve specificity for certain types of cancer cells because not all cells respond to the same apoptotic signals.[38-44]

Growth Factors and Signal Transduction

Transmission of biochemical signals to the cellular nucleus leads to altered expression of a wide variety of genes involved in microgenic and differentiation responses. A number of growth factors exert their effects through receptors possessing intrinsic protein tyrosine kinase activity. On activation, these receptors phosphorylate both themselves and other intracellular proteins on the amino acid tyrosine. Among the receptors for growth factors are EGF, platelet-derived growth factor, insulin, nerve growth factor, and macrophage colony–stimulatory factor. The mitogenic signaling pathway activated by protein tyrosine kinase receptors involves the activation of *ras* proteins. *Ras* undergoes conformational change and interacts with additional downstream targets. A protein kinase cascade is activated, which conveys the growth factor–initiated signal to the nucleus via the *raf*, *mek*, *map* kinase, and other proteins.

Telomeres

Human chromosomes are linear. At each end of the chromosome are structures known as telomeres, from the Greek *telo* for "end" and *mere* for "structure." Telomeres are composed of specialized DNA and DNA-binding proteins. As chromosomes are replicated, telomeres shorten each time during the process of cell division. Continued cycles of cell division result in shortened telomeres. The telomeres, for example, in the fibroblasts of older adults are shorter than those in children. Normal human cells senesce when the telomeres shorten to a critical length.

Stem cells and cancer cells must maintain their telomere lengths to prevent senescence. Two mechanisms of telomere maintenance have been identified: expression of the telomerase enzyme and the recombination of telomeres.

The telomere hypothesis states that critical telomere shortening prevents somatic cells from dividing. In contrast, the maintenance of telomere length allows cancer cells to continue to divide. An increasing body of experimental evidence supports the telomere hypothesis and its association with cancer.

The capacity of cells to respond to ionizing radiation is determined by multiple factors. There are a variety of syndromes associated with molecular defects that are characterized by clinical radiosensitivity, including ataxia, telangiectasia, Nijmegen breakage syndrome, and ataxia telangiectasia–like disorder. These syndromes all have defective telomere maintenance in common. It has been hypothesized, therefore, that the radiosensitivity phenotype and the telomere dysfunction phenotype may be linked. A variety of experimental models suggest that telomere maintenance and radiosensitivity are associated and that this may offer the opportunity for a therapeutic target.

Apoptosis

Apoptosis or programmed cell death, a phenomenon distinct from necrosis, was described in 1972 by Kerr et al.[45] Apoptosis is programmed by specific signals in the cell that cause an endonuclease to cleave DNA at internucleosomal sites.

Apoptosis is detected by histologic evaluation of membrane blebbing and chromatin condensation, by flow cytometry using fluorescent nucleotides and terminal transferase to detect fragmented DNA, by detecting apoptotic cells that are usually very small with characteristic profiles of right-angle and forward light scattering, or by using DNA fluorochrome to detect a decrease in fluorescence as small DNA fragments diffuse from the cell that is undergoing apoptosis. An early change in apoptosis, the flip-flop of the phospholipid phosphatidylserine (PS) from the inner to the outer leaflet of the bilayer membrane, also can be detected using a fluorescently labeled annexin V protein that has a high binding affinity to PS. Several oncogenes, cytokines, and growth factors have been reported to play a role in promoting or reducing radiation-induced apoptosis.[46,47]

Most radiation-induced cell lethality (loss of reproductive integrity) for dividing cells appears to be caused by mitotic-linked death, resulting in the loss of genetic information as cells with chromosomal aberrations divide. Apoptosis, frequently seen within 4 to 6 hours after irradiation, occurs spontaneously and is enhanced by radiation as observed in vivo in the intestinal crypt and salivary and lacrimal glands with nondividing cells and nondividing lymphocytes. Apoptotic cells are eliminated rapidly in vivo, making it difficult to quantify. In contrast, this cell death mechanism is easy to quantify in vitro because apoptotic cells persist in culture for many hours. However, cell division of nonapoptotic cells complicates quantification. In cell lines susceptible to apoptosis, this process sometimes occurs early before cells enter mitosis or later after the cells divide. Late apoptosis may be associated with mitotically linked death and, in fact, may be triggered by chromosomal aberrations. Apoptosis may be quite important for clinically relevant doses of fractionated irradiation, even if it causes a relatively small reduction in clonogenic survival. However, this requires that cells be recruited into the apoptotic susceptible fraction after each dose fraction.

It appears that with the progression of certain tumors, spontaneous and therapy-related apoptosis occurs less frequently. The apoptotic response to irradiation can be modified by cytokines to protect normal tissues or to induce tumor cell killing.[48,49] Tumor necrosis factor increases apoptosis after irradiation in some tumors while protecting the hematopoietic compartment, possibly by blocking apoptosis. Irradiation prevents extensive cellular proliferation by increasing differentiation in both tumors and normal tissues. Also, irradiation appears to increase the aging of normal cells. Another mechanism of reversible loss of proliferative capacity induced

by irradiation is necrosis, which occurs with high doses of radiation and is a major mechanism seen with large-dose fractions such as in stereotactic irradiation.

The Biology of Metastasis

The prefix *meta* is of Greek origin and is defined as "after," "beyond," or "over." It is used to denote change or transformation. The word *stasis* means "stand" or "stationary." Thus, when the two words are combined to form *metastasis*, the new word is used to represent a change in the location of a disease or its manifestations. It also means the transfer of a disease from one organ or body part to another organ or body part not directly connected. The oncologist uses the term *metastasis* to refer to the manifestation of malignancy that arises from the primary growth but is now in a secondary site.

It is clear that the pattern of metastatic spread of cancer is not random.[50] The distribution of some secondary tumor deposits can be explained on mechanistic grounds (ie, that the tumor cells are shed into the bloodstream and lodge in the first narrow capillary network that they encounter downstream). This would explain, for example, why the liver is the most common site for secondary tumors in patients with primary cancer within the catchment area of the hepatic portal vein, such as gastrointestinal malignancies. Similarly, the lung would be a favored site in patients with primary tumor spilling into the systemic veins. There can be no doubt that vascular drainage patterns influence the distribution of secondary tumor deposits from some types of primary cancer.

It is also clear, however, that the distribution of some metastatic tumors cannot be explained solely by patterns of encountering and lodging in the nearest narrow capillary bed. This is called "metastatic tropism": Carcinomas form detectable metastases in only a limited subset of possible distant organ sites. The seminal paper addressing the problem of metastatic tropism was by Stephen Paget (1855-1926) (Figure 1.7). Paget was the fourth and youngest son of the famous British physician Sir James Paget (1814-1899). James Paget was one of the founders of modern pathology and is the namesake of Paget disease. Stephen Paget worked as an assistant surgeon at the West London and Metropolitan Hospitals in England. Later in life, he devoted himself to public health issues and became a highly regarded biographer and essayist.[51] Writing in *The Lancet* on March 23, 1889, on "The distribution of secondary growth in cancer of the breast," Paget wondered:

FIGURE 1.7 Stephen Paget (1855-1926) (Image courtesy of the U.S. National Library of Medicine.).

> The question ought to be asked, and if possible answered: "What is it that decides what organs shall suffer in a case of disseminated cancer?" If the remote organs in such a case are all alike passive and, so to speak, helpless—all equally ready to receive and nourish any particle of the primary growth which may "slip through the lungs," and so be brought to them—then the distribution of cancer throughout the body must be a matter of chance. But if we can trace any sort of rule or sequence in the distribution of cancer, any relation between the character of the primary growth and the situation of the secondary growths derived from it, then the remote organs cannot be altogether passive or indifferent as regards embolism. . . . Every single cancer cell must be regarded as an organism, alive and capable of development. When a plant goes to seed, its seeds are carried in all directions; but they can only live and grow if they fall on congenial soil.[52]

Paget observed, in a large number of autopsies of women with breast cancer, that the lymph nodes, liver, lung, bone, and brain commonly were involved. However, he found that the kidney and spleen rarely were involved despite receiving a significant amount of blood flow. He was struck by the discrepancy between the relative blood supplies and the relative frequencies of metastatic tumors in various organs. From his data, Paget expounded his "seed and soil hypothesis." He argued that metastasis required both a willing seed (intrinsic cellular factors) and hospitable soil (host organ). There must be intrinsic cellular factors that lead to a satisfactory interaction between the tumor cell and the host organ, resulting in successful metastasis. In contemporary terms, we understand this to mean that the tumor cell must have favorable adhesion molecules, and the host organ must be accepting receptors on its endothelial cells, which results in appropriate sites for the circulating tumor cells to bind, migrate into the organ, and subsequently grow, or, perhaps, that tumor cells promote upregulation of adhesion receptors in specific stromal cells.

As they grow, tumors almost certainly release large numbers of malignant cells into the blood and lymphatics continuously. It is clear, however, that the mere presence of tumor cells in the bloodstream does not always lead to the formation of distant metastases. A. J. Salisbury of the Brompton Hospital in London is credited as being one of the first to emphasize that the metastatic process is highly inefficient. The overwhelming majority of malignant cells released in the blood die.[282] They are battered in the circulation, assaulted by the immune system, and fail to reproduce. Metastasis formation is an inefficient process. Fidler and colleagues[53-56] injected melanoma cells into the peripheral vein of a mouse whose DNA had been labeled with radioactive iodine. They found that, shortly after the injection, most of the injected cells rested in the lung (ie, the nearest narrow capillary bed). Most of the tumor cells, however, went on to die in the lung. Only a few live cells continued to circulate. Within a day, only 1% of the injected cells were alive, and after 2 weeks, no known metastasis could be seen in the lungs. Only 0.1% of the cells originally

injected were still alive.[57] Blood-borne metastasis must be a highly selective process. Only a very small proportion of malignant cells that enter into the bloodstream are able to survive and grow.

The fact that only a small fraction of a tumor's cells can successfully form metastatic colonies implies that the survivors are, indeed, specially adapted cells. One might think of them in evolutionary terms. These successfully metastasizing cells must represent the survival of the fittest: the most hardy, most resilient, and most able to fend off the body's attempt to kill them. Isaiah J. Fidler performed an experiment with B16 melanoma cells in mice wherein he injected them into a peripheral vein, harvested the ones that grew in the lungs, grew them in a tissue culture environment, and repeated the process over and over and showed that he could create increasingly efficient cancers, which became better and better of metastasizing to the lung. He showed that they truly were "the fittest" when they came to metastatic potential.

A long period of tumor growth leads to progressive changes in a tumor's structure, blood supply, oxygenation status, antigenic characteristics, doubling rate, growth properties, and metastatic potential. Several investigators have performed variations of the following experiment: Unselected tumor cell suspensions were divided into two parts. One part was injected intravenously into a group of mice. The other part was subdivided into separate cultures. From each culture, a single tumor cell was isolated and grown to produce a large number of different clones, that is, cells with identical genetic composition. Then, these clones were injected into groups of mice.[58]

If the metastatic potential of tumor cells was homogeneous, then you would expect that the number and location of tumor colonies in the injected mice would be similar in the mice receiving the unselected tumor cell suspensions and the mice receiving the cloned lines. If different cloned subpopulations gave rise to widely different numbers of colonies compared to the uncloned cells, it would indicate that the tumor was heterogeneous—that the tumor contained cells with a variety of metastatic potential. The result was that there were widely different numbers of metastatic colonies. This implies the intrinsic heterogeneity of metastatic potential in a growing tumor.

As Stephen Paget suggested, there really is a tendency for particular types of primary tumors to preferentially metastasize to particular organs. Can we show, experimentally, that this is true and that it really is not about "the nearest, narrowest capillary bed trapping the tumor cells"? Garth L. Nicholson and Isaiah J. Fidler took highly metastatic melanoma cells, serially passed so that they were quite efficient at metastasizing to the lungs, and injected some into the tail vein of mice where the first narrow capillary bed they would encounter was the lung and, in other animals, they injected the cells into the left ventricle, just beyond the lungs, where they would

be more likely to be disseminated throughout the body. Initially, the animals who had cells injected into the tail vein had far more tumor cells in the lungs. One day after injection, there was no difference in the number of cells in the lungs, irrespective of the site injection. After 2 weeks, the same number of lung tumors were found for the two sites of injection. Tumor cells destined to form metastases in a particular organ appear capable of detaching from their first home and recirculating until they come to rest at their preferred site of ultimate metastases.[59]

The three major pathways of metastasis are as follows:

- Across body cavities such as the peritoneal cavity or within the cerebrospinal fluid. This is the way, for example, that medulloblastoma disseminates via the leptomeninges or that ovarian tumors form on the peritoneal surface of the intestine.
- Via the lymphatic system. Axillary masses following breast cancer, which are easily palpable, would be a common example of lymphatic metastases.
- Hematogenously, usually via veins rather than arteries. The spread of a limb sarcoma to the lungs would be an example.

The molecular mechanism of tumor metastasis is a multistep process involving many tumor cells—host-cell interactions as well as cell-matrix associations.[60,61] This process is sometimes called the invasion-metastasis cascade. The crucial processes are as follows:

- Tumor cell adhesion to other tumor cells at the site of the primary malignancy, host cells, or components of the extracellular matrix
- Proteolysis of the extracellular matrix during invasion
- Tumor cell motility through the extracellular matrix to reach the vascular or lymphatic endothelium
- Intravasation into the lumina of blood vessels or lymphatics— this is facilitated by molecular changes that promote the ability of carcinoma cells to cross the pericytes and endothelial cell barriers
- Embolism into the lymphatic system and/or the blood circulation
- Tumor cell survival despite both the mechanical trauma endured by the cell in transit in the vascular system and the body's immunologic assault directed against the circulating tumor cell (insofar as most tumor cells have a diameter of 20-30 μm and capillaries have a diameter of ~8 μm; most tumor cells in circulation are probably quickly trapped in capillary beds)
- Adherence to the endothelium when the tumor cell comes to rest at the metastatic site in the secondary organ

- Dissolution of the cell-cell junction and the basement membrane of the blood vessel or lymphatic into the organ parenchyma
- Survival in the new host organ microenvironment and interaction with that new microenvironment in the host organ to permit growth of the tumor deposit
- Tumor cell proliferation in the new organ and angiogenesis to achieve metastatic colonization

Only if all of these steps can be negotiated successfully can the tumor cell ultimately "set up shop" as a metastatic focus (Figure 1.8). The fact that only a small fraction of tumor cells survive and successfully establish a metastasis would suggest that the ultimately successful cells must be quite unusual. It would be reasonable to believe that they represent a subpopulation of tumor cells that are endowed with particular characteristics that make for successful metastasis. As the population of tumor cells evolves, it is likely that aggressive subpopulations, having diverse properties, will arise and that their frequency in the population will increase under selective pressure of the host immune defenses. This will lead, ultimately, to the emergence of cells with enhanced malignancy.[62] Many people believe that tumor cells evolve via a Darwinian selection—a concept we referred to earlier in this section of the chapter as "survival of the fittest." Genetic variation continuously occurs in the tumor population and clones with a survival advantage become overrepresented. These cells have "metastasis virulence genes" enabling their spread. The successful metastatic cells will possess characteristics of neoplastic transformation—the ability to turn on an angiogenic switch, an invasive phenotype, and the capacity to evade the immune response—as well as favorable cell adhesion and motility characteristics.[63,64]

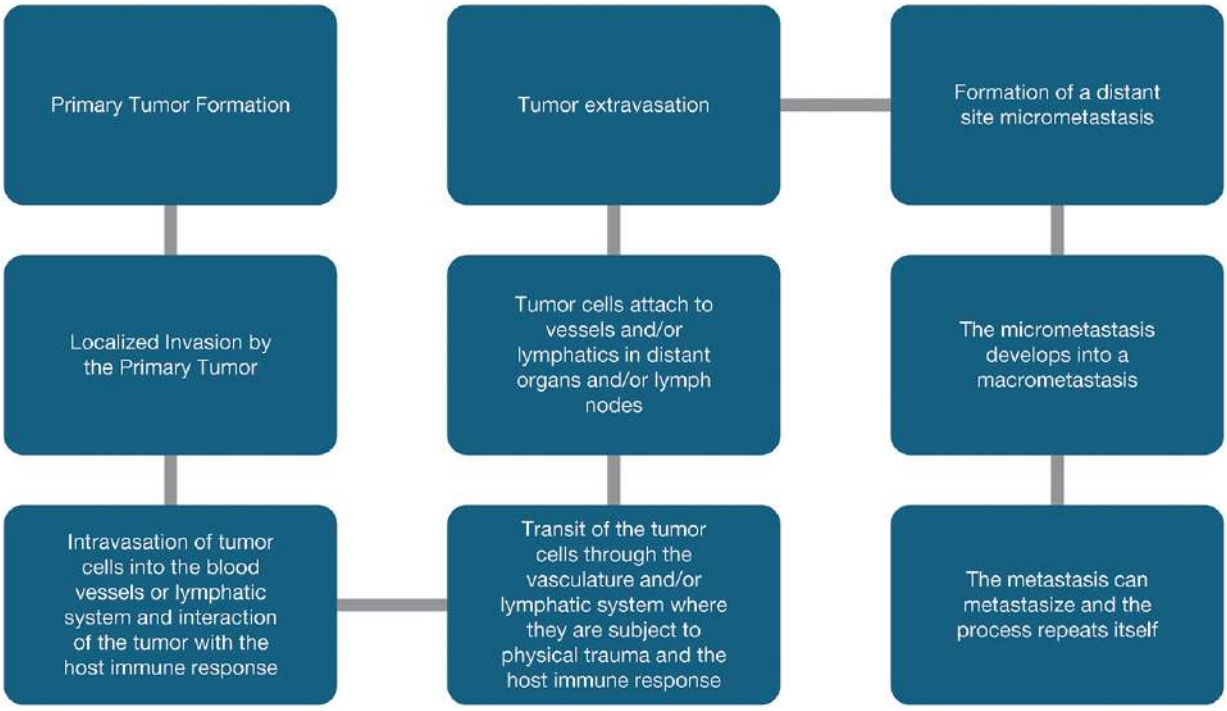


FIGURE 1.8 The development of metastasis is a multistep process that is highly inefficient. In order to form a metastasis, the tumor must breach the basement membrane and enter either a blood vessel or a lymphatic, travel through the bloodstream or the lymphatics, and not be destroyed either by attack of the immune system or mechanical trauma, adhere to the endothelium at a distant anatomic site, invade the organ parenchyma, draw a blood supply into the metastatic deposit, and colonize the new organ.

Metastatic progress involves not only the tumor's cells but also those cells' ability to recruit the aid of stromal cells. As tumors progress, the stroma becomes increasingly "reactive"—akin to the tissue of wound healing or chronic inflammation.

The Molecular Biology of the Metastatic Phenotype and Angiogenesis

Tumor progression is the acquisition of permanent, irreversible, qualitative changes in one or more characteristics of neoplasm that ultimately will lead to the tumor becoming more autonomous and malignant.[65] A genetic analysis of the stages of tumor progression has led to the formulation of the multistep theory of tumorigenesis. The multistep theory involves activation of oncogenes, inactivation of tumor suppression genes, and identification of many tumor-associated molecules. The metastatic phenotype appears to require cells to have the additive effect of positive modulators (oncogenes) as well as the loss of negative effectors (tumor suppressor genes, invasion and metastasis suppressor genes). Thus, the molecular biology of a metastatic cell is clearly a multistep process of diversification and clonal selection for aggressive cells.

The mutated *ras* oncogene sequences, when transfected into mouse embryo–derived fibroblasts (NIH 3T3 cells), cause those transfected cells to produce numerous metastases. This finding has been confirmed in both fibroblasts and epithelial cells of human and rodent origin. A number of other metastasis-associated genes have been described. These include NM23-1 and stomelysm-3 (ST-3). NM23-1 has features similar to a transcription factor and may play a role not only in *c-myc* expression but also in the response of cells to TGF-β. ST-3 is a member of the matrix proteinase family.[66]

It would be far too simplistic to conclude that the metastatic phenotype arises only from genetic alterations associated with the acquisition of aggressive tumorigenicity. Cells clearly can be transformed by oncogene transfection, but not all cells acquire a metastatic phenotype after this oncogene transfection. Simply stated, we must bear in mind that there is a separation between the genetic changes that drive tumorigenicity and the metastatic phenotype. Invasion and metastasis will require the activation of additional effector genes or loss of suppressor local inhibitors above those genetic changes required for uncontrolled growth alone.

The successful development of a metastatic focus requires new blood vessel growth. There are angiogenesis promoters and inhibitors that may be modified or removed during the tumor- induced angiogenic response. Tumor angiogenesis in the nascent metastasis is a tightly regulated process in a delicate balance between the proangiogenic and antiangiogenic factors.[66]

Angiogenesis and Tumor Cell Invasion into Blood Vessels

The success of the growth of a tumor is, in part, governed by a complex interplay between the tumor cells and the surrounding normal tissue. A dramatic example of this interplay is the process of tumor angiogenesis (also called tumor neovascularization).

The growth of the tumor depends on the tumor's access to nutrients and oxygen as well as its ability to eliminate metabolic waste and carbon dioxide. In very small tumors, these requirements are addressed by diffusion. As the tumor enlarges, however, diffusion is inadequate. The growing tumor requires direct access to the circulatory system.

Tumor access to the circulatory system is secured through angiogenesis, through which the tumor cells encourage the ingrowth of capillaries and larger vessels from the adjacent normal tissue. The tumor cells recruit these vessels through the release of angiogenic factors. These cause the proliferation of endothelial growth factor and, almost certainly, tissue growth factor-β. The generation of tumor vessels is the result of a delicate balance between angiogenesis-promoting factors and angiogenesis-

inhibiting factors. These factors have now provided a growing body of therapeutic targets in the treatment of cancer.

Some authorities encourage us to think about the tumor as a structure composed of varied compartments, including the actual clonogenic cells, a connective structure, and the blood vessels. Utilizing this way of thinking about tumors, we envision cancer treatment as striking at different components of the tumor (ie, antiangiogenesis agents directed against the vasculature and anticlonogenic agents directed against proliferating cells). Experimental evidence suggests that, in certain tumor systems, the combination of radiation and antiangiogenic agents is a fruitful way of treating cancer. We may expect to see an increasing body of evidence for the use of combinations of radiation, chemotherapy, hormonal therapy, and antiangiogenesis agents in the coming years.

The "father of angiogenesis" was a pediatric surgeon, Judah Folkman (1933-2008) (Figure 1.9). While he was not the first person to notice that tumors needed blood vessels to grow, his detailed investigation into why tumors draw blood vessels to themselves and how to inhibit that process was groundbreaking. Folkman published a controversial theory that is now widely accepted: Targeting angiogenesis may potentially arrest cancer. The author of this chapter distinctly recalls Dr Folkman presenting his research, when the author was a resident, at the invitation of the chair of radiation oncology at the Massachusetts General Hospital, Dr Herman Suit, in 1980 to 1983. Folkman's work created a frenzy in 1998 when a front-page article in *The New York Times* reported how two drugs he had developed had eradicated tumors in mice. The article quoted Dr James Watson, a Nobel laureate who shared the prize with Francis Crick for the discovery of the structure of DNA, as saying, "Judah is going to cure cancer in two years (Box 1.2)."[67]

FIGURE 1.9 Judah Folkman (1933-2008).

Box 1.2

Antiangiogenesis Therapy of Cancer

Tumor vessels are fundamentally different from normal blood vessels insofar as they are usually irregular and disorganized. In vessels that are leaky, hemorrhagic, or torturous or in those containing poorly oxygenated blood that may flow backward and forward in the same vessel, tumor vasculature may provide an interesting therapeutic target. The general public and the scientific community have recently experienced a wave of considerable excitement associated with the possibility that antiangiogenesis agents may be employed clinically to disrupt tumor angiogenesis. This form of therapy may complement existing cancer treatments. Vascular endothelial growth factor (VEGF) is a key element in the stimulation of angiogenesis. VEGF binds to a receptor on endothelial cells (VEGFR), which stimulates tyrosine kinase activity, which, in turn, stimulates downstream signaling and activation of endothelial cells. The drugs in the therapeutic pipeline may be categorized as follows:

- Anti-VEGF agents: Some drugs prevent the binding of VEGF to its receptors. *Bevacizumab (Avastin)* is a monoclonal antibody that binds to VEGF, prevents it binding to VEGFR, and

inhibits VEGFR activation. It is being utilized in the therapy of a variety of human malignancies.

- Anti-VEGFR agents: Several receptors bind to VEGF: VEGFR1, VEGFR2, NRP-1, and NRP-2. VEGR2 is thought to mediate most of the angiogenic properties of VEGF and is expressed at high levels on the endothelial cells of tumor vasculature. Several monoclonal antibodies are under investigation in animal models to target the VEGFR.
- Receptor tyrosine kinase inhibitors: An antiangiogenesis strategy is to target the downstream activity of the binding of the VEGFR by inhibition of tyrosine kinase activity. The following drugs, now in human clinical trials, fall into this category: cediranib or recentin (AZD2171), pazopanib, BIBF 1120, sorafenib, and sunitinib (SU11248).

The hallmark of an invasive cancer is its ability to disrupt the epithelial basement membrane and the presence of cancer cells in the stromal compartment. It makes sense, therefore, that two broad classes of molecules have been implicated repeatedly in contributing to the metastatic ability: Cell-cell adhesion molecules and motility molecules play a crucial role in the development of metastatic potential.[68] The ability of tumor cells to adhere to other tumor cells, cells of the host, or components of the extracellular matrix affects multiple components of the metastatic cascade. These interactions depend on several classes of molecules expressed on the cell surface. Cadherins are calcium-dependent molecules that mediate homophilic cell-cell adherence. Integrins are heterodimeric transmemory proteins that are formed by the noncovalent association of α- and β-subunits. The binding of the extracellular matrix ligands to integrins is known to initiate similar transduction pathways. These pathways lead to cell proliferation, differentiation, migration, or cell death. Selectins act through a terminal calcium-dependent lexon domain. They are prominently involved in heterotypic cell-cell adhesion between blood cells and endothelial cells.[69]

Tumor adherence to the extracellular matrix and cell motility is the next crucial component of the metastatic cascade. Tumor cells are able to attach to a specific lipoprotein of the extracellular matrix, such as fibronectin, collagen, and laminin. These adherences are formed either through integrin or through nonintegrin cell surface receptors. CD44 is a crucial transmembrane glycoprotein with a large echo domain and a single cytoplasm domain. CD44 is involved in cell adhesion to hyaluronan[70].

The potentially metastatic cell must overcome a series of tissue barriers. These include the basement membrane and connective tissue. These must be traversed by the tumor cells during the metastatic process. Five classes of naturally occurring proteinases have been associated with aggressive tumor cells and implicated in metastases. These include members of the gene family of matrix metalloproteinases. These enzymes, each of which is secreted by a proenzyme that subsequently requires activation, may be divided into three general subclasses: interstitial collagenase, type

4 collagenase (gelatinases), and stromelysins. Once having dissolved barriers, active tumor cell motility is required for the penetration of the basement membrane and the interstitial stoma. Successful migration of metastatic cells requires the transition of propulsive force from the extracellular matrix to the cytoskeleton. Tumor cells exhibit amoeboid movement, which is characterized by pseudopod extension. For the protrusion and retraction of pseudopods, the network of intracellular polymerized cross-linked filaments must be disassembled and then reassembled.[71,72]

THE COMMON FORMS OF ADULT AND PEDIATRIC CANCER

We have now defined the word cancer, discussed its characteristics and pathophysiology, and been introduced to the biology of cancer metastases. Now we are ready to review the most common forms of cancer in adults and children.

Our first problem to resolve is that there is more than one way to define "common" in the context of "common forms of cancer." We could list the most common forms of cancer by counting the "incidence" during a year. "Incidence" means the number of newly diagnosed cases in a year. We could list the most common forms of cancer by counting the number of deaths from each type of cancer during the year. We could also list the most common forms of cancer by counting the "prevalence" during a year. "Prevalence" means the number of people alive with a particular form of cancer (Box 1.3).

Box 1.3

A Call to Arms

An Institute on Cancer meeting was conducted at the University of Wisconsin in Madison in 1936. Among the prominent scientists in attendance were James Ewing, professor of oncology at Cornell University Medical College, after whom Ewing sarcoma is named; Gioacchino Failla, the famous radiation physicist of the Memorial Hospital for Cancer and Allied Diseases of New York; and Henri Coutard, pioneer radiation therapist of the Curie Institute of Paris. Glenn Frank, president of the University of Wisconsin, addressed the scientists on the first day of the meeting. Seventy-five years later, Frank's opening address remains a moving call to arms for basic science, translational, and clinical researchers, physicists, and clinicians.

> "Down the ages, cancer has been the most hideously persistent and the most persistently hideous enemy of mankind, the suffering it lays upon men intolerably horrible, its toll of life progressively devastating, its blows falling so often just when men have reached the years of ripest usefulness to family and state. But not all these tragic consequences together are the worse evil wrought by cancer. For every *body* that is *killed* by the *fact* of cancer, multiplied thousands of *minds* are *unnerved* by the *fear* of cancer. What cancer, as an unsolved mystery, does to the morale of millions who may never know its ravages is incalculable. This is an incidence of cancer that cannot be reached by the physician's medicaments, the surgeon's knife, or any organized advice

against panic. Nothing but the actual conquest of cancer itself will remove this sword that today hangs over every head. I can remember, as a boy in rural Missouri, that death from cancer was rarely mentioned and then only with bated breath. I realize now that this reaction was born of a feeling of utter helplessness and awe in the presence of a mysterious enemy. That almost primitive reaction to cancer has happily vanished. We have not penetrated the mystery, but, thanks to you and your colleagues the world over, we have made notable rents in the veil surrounding the mystery. The world is determined to conquer this thing that steals upon men like a thief in the night and without warning strikes down the strong and weak alike. By one thing alone can this conquest come, and that is by the tireless, painstaking, and self-sacrificing genius of scientists who, like yourselves, go to their laboratory tables as to an altar and sink their lives in the great adventure of emancipating mankind from the fact and fear of this plague. Surely, if anywhere in the secular activities of men, there is a spark of divinity in lives so dedicated!"[73]

These three ways of counting the number of cancer cases will give varying answers to the question, "What are the most common forms of cancer?" For example, the mortality rate of lung cancer in adults is very high. The mortality rate of prostate cancer in adults is very low. If you measure mortality from cancer, lung cancer will rank higher than prostate cancer. If you measure prevalence, the reverse is the case. Some will argue that this fact manifests itself politically. There are a great many prostate and breast cancer survivors in the United States who vote and express their wishes to their elected representatives to fund research for these diseases. Most patients with lung cancer die and do not, therefore, constitute a voting bloc to advocate for research in lung cancer.

Basal and squamous cell carcinomas of the skin are so common, so often curable, and so often treated in the offices of dermatologists and surgeons that they are not reported in the lists of common adult cancers. The most common forms of adult cancer are listed by incidence and mortality, for the United States, in Table 1.1. Trends in cancer incidence and mortality are shown in Figure 1.10. The most common forms of childhood cancer are listed by incidence in Table 1.2.

TABLE 1.1 ESTIMATED NEW CANCER CASES AND DEATHS, UNITED STATES, 2024

	Estimated New Cases	Estimated Deaths
All sites	2,001,140	611,720
Oral cavity and pharynx	54,450	12,230
Digestive system	353,820	174,320
Respiratory system	252,950	130,450
Bones and joints	3,970	2,050
Soft tissue (including the heart)	13,590	5,200

	Estimated New Cases	Estimated Deaths
Skin (excluding	108,270	13,120
Breast	313,510	42,780
Genital system	427,800	70,100
Urinary system	169,360	32,350
Eye and orbit	3,320	560
Brain and other nervous system	25,400	18,760
Endocrine system	48,010	3,300
Lymphoma	89,190	21,050
Myeloma	35,780	12,540
Leukemia	62,770	23,670
Other and unspecified primary sites	34,950	49,240

Data from Siegel RL, Gioquinto, AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin*. 2024;74(1):12-49.

TABLE 1.2 INCIDENCE RATES, CASE DISTRIBUTION, AND 5-YEAR RELATIVE SURVIVAL BY AGE AND INTERNATIONAL CLASSIFICATION OF CHILDHOOD CANCER (ICCC), TYPE, BIRTH-19 YEARS, UNITED STATES

	Birth-14 y			15-19 y		
	Incidence/Million	Distribution %	Survival %	Incidence/Million	Distribution %	Survival %
All ICCC groups (malignant only)	171	92	85	238	86	87
Leukemias	53	28	88	35	13	77
Lymphomas	22	12	95	52	19	94
CNS	47	25	75	60	22	77
Neuroblastomas	11	6	82	11	<1	82
Retinoblastomas	4	2	96	<0.1	<1	–
Wilms/other renal	8	4	93	0.3	<1	–
Liver	3	2	80	1.4	<1	56
Malignant bone	8	4	73	15	5	70
Rhabdomyosarcoma	5	3	67	4	1	54
Germ cell/gonadal	6	3	93	27	10	94
Thyroid	4	2	99	33	12	>99
Malignant melanoma	2	1	94	8	3	97

CNS, central nervous system.
Modified from Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin*. 2024;74(1):12-49. Reprinted by permission of John Wiley & Sons.

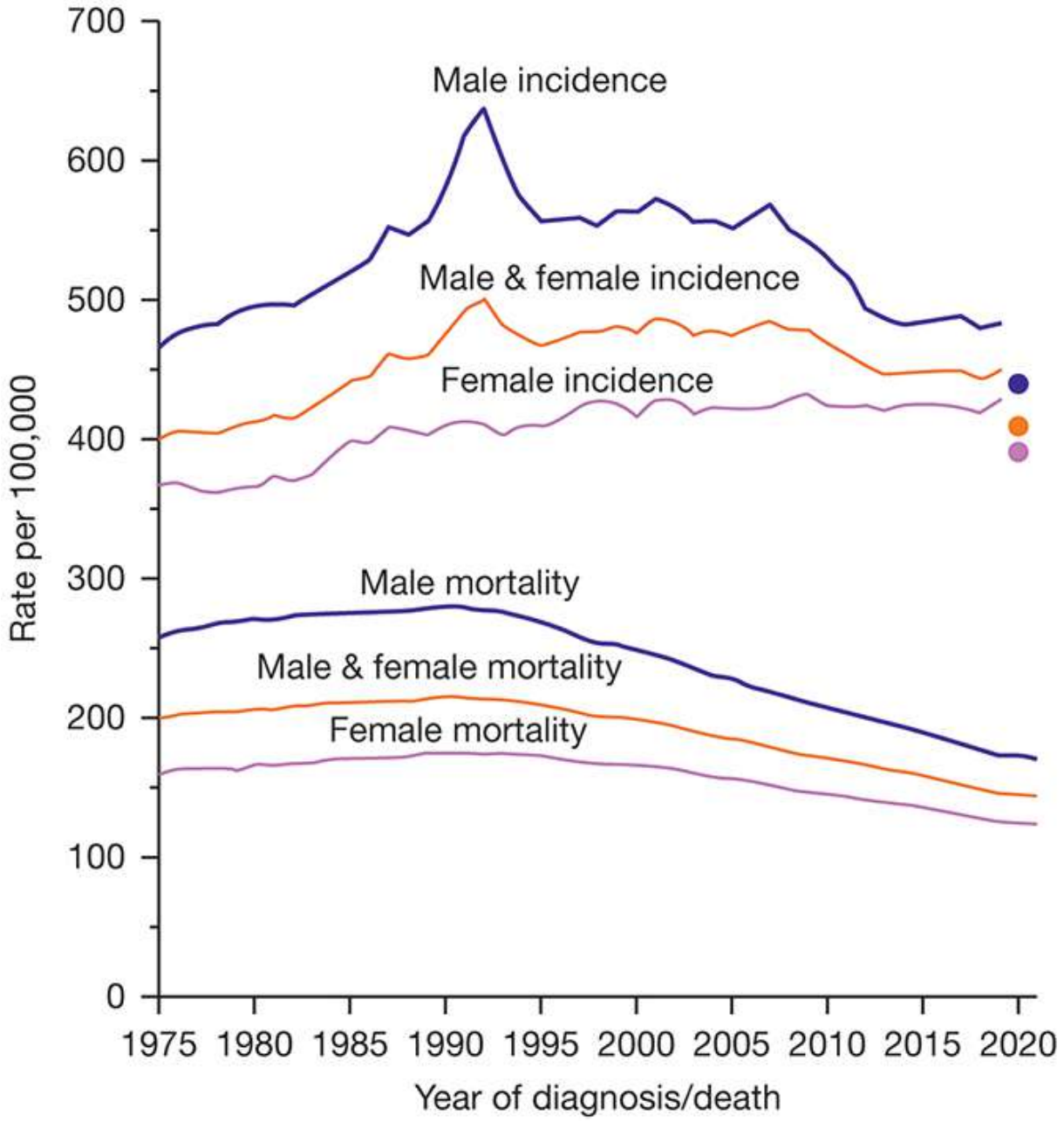


FIGURE 1.10 Trends in cancer incidence (1975-2020) and mortality (1975-2021) rates for selected cancers by sex, United States. Rates are age adjusted to the 2000 U.S. standard population and adjusted for delays in reporting. (From Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin*. 2024;74[1]:12-49. Reprinted by permission of John Wiley & Sons.)

As you examine Tables 1.1 and 1.2, you will note that there is almost nothing in common. The major problems of adult cancer are cancers of the lung, breast, gastrointestinal tract, head and neck, prostate, bladder, cervix, and uterus. In contrast, the major forms of childhood cancer are brain tumors, leukemias, lymphomas, and a series of interesting but rare tumors: Wilms tumor, rhabdomyosarcoma and nonrhabdomyosarcoma, soft tissue sarcomas, Ewing sarcoma, neuroblastoma, and retinoblastoma. Why?

The short answer is that adults get cancer in places where their bodies meet the environment. Children do not. Adults douse their bodies with carcinogens via excessive sun exposure, tobacco use, chewing betel nuts, drinking alcohol, having a diet with too little fiber and too much fat, sexual practices that transmit carcinogenic viruses, and occupational exposures. These repetitive carcinogenic insults produce an array of activated oncogenes and failed tumor suppressor genes, which result in malignancies. Children, in contrast, do not smoke too much, drink too much alcohol, or engage in unsafe sex. They get cancers because of intrinsic genetic problems leading to malignancies rather than inducing genetic changes by exogenous carcinogens.

In adults, therefore, cancer is a largely preventable disease. Epidemiologic studies have identified the causative agents for a significant proportion of adult cancers. Approximately 30% to 35% of cases of cancer in the United States are associated with tobacco use.[74] Another 30% to 35% of cases are associated with excessive dietary fat and obesity. Approximately 5% of cancer is related to alcohol use. Another 5% is associated with exposure to viral agents.[75] Among the other causative factors of cancer, each responsible for a small percentage of malignancies, are occupational exposures, a family history of cancer, environmental pollution, ionizing and ultraviolet irradiation, prescription drugs, and medical procedures (Tables 1.3 and 1.4).[76-81]

TABLE 1.3 QUANTITATIVE ESTIMATES OF AVOIDABLE RISKS OF CANCER IN THE UNITED STATES, 1981: THE CLASSIC STUDY BY DOLL AND PETO

Diet	35%
Tobacco	30%
Infection	7%
Reproductive and sexual behavior	4%
Occupation	4%
Alcohol	3%
UV light	3%
Pollution	2%

Diet	35%
Food additives	1%
Industrial products	1%
Medicines	1%

UV, ultraviolet.
Data from Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst*. 1981;66(6):1191-1308.

TABLE 1.4 CAUSES OF CANCER WORLD CANCER REPORT, INTERNATIONAL AGENCY FOR RESEARCH ON CANCER, 2008

Smoking	32%
Diet	30%
Infection	15%
Genetics	5%
Occupation	5%
Alcohol	3%
Pollution	3%
Radiation	3%
Other	4%

Data from Boyle P, Levin B, eds. *World Cancer Report 2008*. IARC Press; 2008.

CANCER PREVENTION

There are two general approaches to cancer prevention. They are referred to as *primary prevention strategies* and *secondary prevention strategies*. A primary preventive strategy may be invoked when there is an explicit and indisputable behavior that should be avoided or adopted because of its association with a predictable and certain reduction in cancer risk for an individual. A secondary prevention is distinguished from primary prevention in that it is an intervention focused on altering the natural history of a disease and thus avoiding disease-related adverse outcomes.[82] The most commonly used secondary prevention strategy is broad based or targeted population screening.

The principal primary prevention strategies are directed against cancers that have been associated with certain behaviors. They begin with the avoidance of tobacco. Tobacco is the single largest preventable cause of death in the Western world today. Tobacco use, either in the form of cigarette, pipe, or cigar smoking or the use of snuff or chewing tobacco, is strongly associated with carcinoma of the lung, larynx, pharynx, oral cavity, and esophagus. Tobacco also appears to be an important

contributing factor in cancer of the pancreas, bladder, kidney, stomach, colon, and uterine cervix. In addition to its role in the etiology of cancer, tobacco also is associated with coronary heart disease, chronic lung disease, stroke, and other maladies.[83]

Chewing betel nuts has long been known to be a cause of head and neck cancer in the less economically developed world. With immigration to the economically developed world, cancers associated with betel nut chewing are increasingly being seen in these counties as well. The combination of tobacco use, betel nut chewing, and alcohol consumption creates a lethal Ven diagram where all three intersect to produce a very high incidence of head and neck cancer.

We have come to understand the role of diet, excessive fat consumption, and obesity in the etiology of cancer.[84] Studies suggest a direct correlation between average dietary fat intake in various countries and the incidence of breast cancer. Classic studies have shown that the incidence of stomach cancer among the Japanese decreases when Japanese individuals migrate to Hawaii. Second-generation Japanese residents of Hawaii have an incidence of stomach cancer equivalent to that of the White population.[85] Clearly, a healthier diet could reduce the incidence of cancer.[86]

Excessive alcohol consumption also is associated with cancer. Alcohol consumption is particularly harmful among cigarette smokers. It appears that smoking acts as an initiator, producing injurious mutations, and alcohol acts as a promoter of cancers of the oral cavity, oropharynx, pharynx, larynx, and esophagus.

A variety of occupational exposures also are associated with specific cancers, including cancer in asbestos miners and workers, various forms of cancer in workers in the chemical industry, and radiation-associated cancers in uranium miners. An obvious preventive strategy is to minimize or eliminate such harmful exposures in the workplace.

In recent years, scientists have become increasingly aware of various genetic syndromes associated with the etiology of cancer, including the multiple endocrine neoplasia syndromes and their association with medullary cancer of the thyroid, susceptibility genes that increase the risk of colon cancer, and the association of the *BRCA1* and *BRCA2* genes with carcinoma of the breast and ovary. For some of these genetic susceptibility traits, the best that the physician can offer is close follow-up. There are certain situations where the avoidance of a potentially lethal cancer may lead an individual to consider prophylactic surgery.

An exciting development in cancer prevention is the development of a vaccine capable of reducing, by about 70%, the incidence of human papillomavirus–associated cervical cancer. The U.S. Food and Drug Administration (FDA) approved this vaccine for clinical use in 2006. This vaccine, along with the use of routine Pap testing, has the potential to make invasive cervical cancer a rare event, although

adoption of the vaccine has been hindered by the false claim that it is associated with the encouragement of sexual relations in the young.

Cancer screening is the most frequently considered secondary preventive strategy. A cancer screening procedure should lead to the early detection of an asymptomatic or unrecognized disease by the application of simple, inexpensive tests or examinations in a targeted population. For cancer screening to be appropriate and successful, several criteria should be met, including:

1. The cancer for which one is screening should have a substantial morbidity and/or mortality rate that warrants the screening procedure.
2. The cancer for which one is screening should have a sufficiently high prevalence in a detectable, preclinical state to warrant screening.
3. Once the cancer is detected by a screening procedure, there should be an effective treatment related to early detection. This criterion is quite important because there is little value in screening for an untreatable malignancy.
4. The screening test should have a high sensitivity and specificity.
5. The screening test should be of low cost such that the expense of screening a large population would be more than offset by the reduced cost to society of treating early rather than advanced malignancy.
6. Individuals screened should suffer little inconvenience and discomfort.

There is no perfect screening test. Those tests currently used generally meet most, but not all, of the aforementioned criteria.

There are several examples of currently used screening tests. For breast cancer, these include self-examination, examination by a trained health practitioner, and mammography, augmented, when appropriate, by ultrasound and magnetic resonance imaging (MRI). The value of these tests in various populations of women is a long-standing debate. Every few years, in the United States, organizations issue new, and sometimes conflicting, advice on which women need routine screening mammography, when they need it, and how often they need it.

In screening for colorectal cancer, the tools available to the clinician include testing for fecal occult blood, sigmoidoscopy, colonoscopy, barium enema studies, the developing field of virtual colonoscopy, stool DNA testing, and fecal immunochemical testing. There is a general consensus that in the appropriate aged population screening colonoscopy is worthwhile.

Among the most controversial areas for cancer screening is the role of screening in the detection of early prostate cancer. There was rapid general acceptance of the use of physical examination and prostate-specific antigen (PSA) testing to ascertain the presence of early prostate cancer. On further consideration, however, many investigators fear that we have, as a society, successfully identified large numbers of

men who would never have been diagnosed with symptomatic prostate cancer in their remaining lifetime or required treatment. The appropriate role of screening for prostate cancer has generated as much controversy as the debate over mammography in breast cancer. A considerable amount of anxiety has been generated in asymptomatic men compulsively watching their PSA levels. The U.S. oncology community has engaged in a very public debate over a 2012 recommendation of the U.S. Preventive Services Task Force ("USPSTF") to rescind a recommendation in favor of the widespread use of PSA for screening. The task force report in 2012 advised that healthy men should no longer receive the PSA blood test to screen for prostate cancer because the test does not save lives overall and often leads to more tests and treatments that needlessly cause pain, impotence, and incontinence in many.

The draft recommendation was based on the results of five clinical trials and had the potential to substantially change the care given to men aged 50 years and above. There are 44 million such men in the United States, and 33 million of them have already had a PSA test—sometimes without their knowledge—during routine physicals. As further evidence became available, the USPSTF revised its recommendations and, in 2018, recommended that men between 55 and 69 years discuss with the doctor the risks and benefits of PSA screening and make a decision based on personal values and risk factors. The USPTF does not recommend screening for men aged 70 years and above. Recent studies suggest that the use of PSA, Kallikrein panel, and MRI may be better at detecting high-grade prostate cancer.[87]

It is likely that, in the future, efforts will be expended to identify that subset of men with biologic markers suggesting that they might benefit from PSA screening and, if diagnosed, treatment compared to those who are "best left alone."

Far less controversial, however, has been the use of the Pap test for early detection of carcinoma of the cervix. Where properly used, the test appears to have resulted in a decrease in mortality from this malignancy.

Cancer chemoprevention is defined as a pharmacologic intervention with specific nutrients or other chemicals intended to suppress or reverse carcinogenesis and to prevent the development of invasive cancer. Trials involving chemopreventive therapy require large numbers of individuals who are at high risk for malignancy because of family history, carcinogenic exposure, or the presence of a mutated gene. The ideal chemopreventive agent would have minimal side effects because it would be given to a considerable number of people, none of whom have cancer. Chemoprevention trials differ from other types of cancer prevention studies and from therapeutic studies in important ways. The participants are healthy volunteers, and one seeks to measure a reduction in morbidity and mortality in the long run. Chemoprevention trials are, by definition, large. There are strict enrollment criteria

that reflect the group of interest. These studies are often long term and expensive. To date, the best studied agents in human preventive trials are retinoids (the natural derivatives and synthetic analogs of vitamin A) and one member of the carotenoid class, β-carotene. The results are mixed.[88]

INTRODUCTORY RADIOBIOLOGY

The Concept of Dose in Radiation Therapy

The concept of "dose" is fundamental to medical therapeutics. The dictionary definitions of "dose" include "a quantity of a medicine or drug taken or recommended to be taken at a particular time" ("Johnny took his dose of cough medicine."); "an amount of ionizing radiation received or absorbed either at one time or over a specified period of time" ("Johnny received a dose of 50 Gray of radiation in five weeks."); or "a quantity of something analogous to medicine", ("Let's give Johnny a dose of his own medicine. That will teach him not to misbehave.")

Radiation therapy was administered to human patients well before there were any standardized concepts of radiation dose. The early radiation oncologists learned that the production of a skin reaction to ionizing radiation depended on four physical factors:

- The **voltage** of the x-ray tube, which was originally measured by the number of inches of spark gap
- The **current** flowing through the x-ray tube, which was measured in milliamperes
- The **focal skin distance** measured in the distance to the patient's skin
- The **time** duration for the administration of the radiation therapy

It was recognized that the first, second, and fourth factors increased the amount of radiation administered but that the third factor reduced the dose because the dose fell off as the square of the distance.

While the relative importance of the four factors was not well understood for many years, the general formula employed was

$$\text{Dosage} = \frac{(\text{milliamperes}) \times (\text{spark gap})^2 \times \text{time}}{(\text{focal skin distance})}$$

Chemical reactions began to be used to estimate the dose in radiation therapy around 1900. Holzknecht developed a "chemoradiometer." Reported in 1902, this device consisted of small discs of KCl and Na_2CO_3, which became discolored when irradiated. The degree of discoloration was associated with dose[89] (Figure 1.11). In 1904, Sabourand and Noire described a "radiometer" where small pastilles of compressed barium plastinocyanide varied in color from bright green to deep orange based on the dose of radiotherapy.[90] By correlating the dose with the effects on the patient, one could infer a "minimum skin erythema dose," for example.

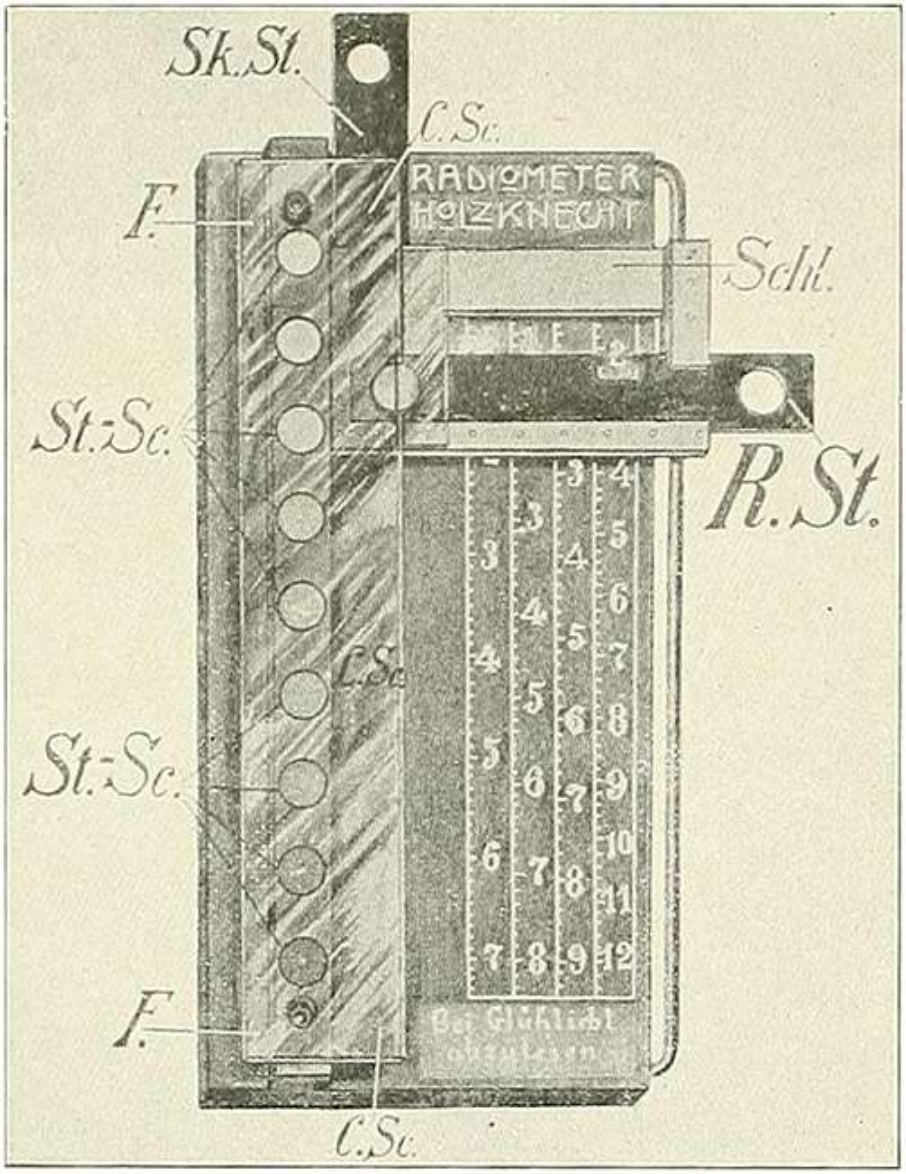


FIGURE 1.11 This is a Holznecht Radiometer as illustrated in I. Seth Hirsch's 1920 textbook *The Principles and Practice of Roentegenological Technique*. The pastille exposed to an unknown dose of radiation exposure is matched to the tint of a standard tint of a known radiation dose exposure (C. Sc. = reddish brown color band, under which was a semicircular piece of screen, carried on Sk.St. is placed; R.St. holds the exposed pastille with the unknown dose exposure; R.St. slides on Schl. until both semicircles form a circle of the same color.) The scale is read on the notch of R.St. The other scales are for pastille pieces, which have slightly different initial tints. (Reading Room 2020/Alamy Stock Photo.)

Over time, radiation therapy came to be reported in a unit called a "Roentgen" or "R." It was defined as "the amount of radiation producing one electrostatic unit of positive or negative ionic charge in one cubic centimeter under standardized conditions." This was replaced by a "rad" or "radiation absorbed dose" or "r." It was defined as *a unit of absorbed dose of ionizing radiation equal to an energy of 100*

ergs per gram of irradiated material. The rad was succeeded by the centigray or cGy. A centigray is 0.01 of a Gray (Gy), and the Gray is defined as the absorption of 1 J of energy from ionizing radiation by 1 kg of matter. A Roentgen, obviously, was named in honor of the discoverer of the x-ray: Wilhelm Conrad Roentgen. The Gray was named in honor of Louis Henry Gray, a pioneer in the measurement of radiation and its effects on living tissue.

In modern practice, a typical description of external beam radiation therapy (EBRT) dose might be "the patient received 2 Gy per day, five days per week, to a total dose of 60 Gy in six weeks." An example of a description of brachytherapy dose is that "the patient received a dose of 4 Gy to a depth 2 millimeters below the vaginal surface, five days per week via a radioactive implant, for a total dose of 28 Gy in seven brachytherapy sessions."

DNA Damage by Ionizing Radiation

The biologic effects of ionizing radiation are largely the result of DNA damage, which is caused directly by ionization within the DNA molecule or indirectly from the action of chemical radicals formed as a result of local ionization in water. The general forms of DNA damage are base damage, DNA-protein cross-links, single-strand breaks, double-strand breaks, and complex combinations of all of these.[91]

Normal mammalian cells repair a significant proportion of radiation-induced DNA damage. Long-term biologic consequences are the result of those injuries, which are irreparable or misrepaired. The cell will attempt to repair DNA injury induced by radiation via several pathways. Key genes are involved in repair of double-strand DNA breaks.

There is some evidence that clustered local damage to DNA, such as a double-strand break accompanied by additional breaks, base damage, or DNA-protein cross-links, is especially difficult for cells to repair. Even lesions that are potentially repairable may be repaired incorrectly (misrepaired) if lesions are accumulating very rapidly because of high-dose rate (HDR) radiation or if the cell enters M phase and attempts DNA synthesis while repair is in progress. Conversely, radiation, which is given at a low-dose rate (LDR) or is highly fractionated, provides an opportunity for repair of radiation-induced lesions and recovery from injury. DNA damage that is not repaired may cause cell death, prevent cell division, or permanently give rise to heritable lesions, such as point mutations, small and large deletions and translocations of DNA sequences, and a wide variety of DNA aberrations.[92],[93]

Effects of Irradiation on Cells

The radiation-induced lesion most detrimental to cell survival involves damage to the DNA. This may result in either mitotic cell death or apoptosis. If the cell

survives and repairs the damage, it may achieve a normal status. If there is misrepair, it may be associated with permanent mutations and induction of carcinogenesis. The physical interaction of ionizing radiation with the molecular infrastructure of the cell results in chemical reactions that occur within 10^{-18} to 10^{-3} seconds[94] (Figure 1.12). Absorption of the photon energy destabilizes the target molecule, resulting in molecular breaks or release of energetic electrons and secondary energy-attenuated photons, which may interact with other cellular molecules, leading to a chain reaction that produces a variety of short-lived ions and chemically unstable free radicals. The most common radicals are produced from the radiolysis of cellular water and include hydroxyl radicals (•OH), hydrated electrons (e_{aq}), hydrogen atoms ($H^{\bullet}$), and hydrogen peroxide (H_2O_2). Free radicals are extremely unstable and interact nearly instantaneously with neighboring molecules to produce chemically stable lesions. This process can be modified by free radical scavengers or by oxygen, which has opposing effects on the number of stable lesions and the level of cellular radiosensitivity. However, if all factors remain constant, the permanent damage is linear with dose. Experiments in which the cell nucleus and the cytoplasm were selectively irradiated show that the dose required in the cytoplasm to kill a cell is larger than doses required in the nucleus.[95],[96] It is generally accepted that most target molecules for radiation-induced cell killing are located in the nucleus and involve damage to the DNA.[97] However, other targets such as the cell membrane and the membrane of mitochondria have been proposed as the origin of apoptotic cascades that follow irradiation also contributing to cell death (Figure 1.13).

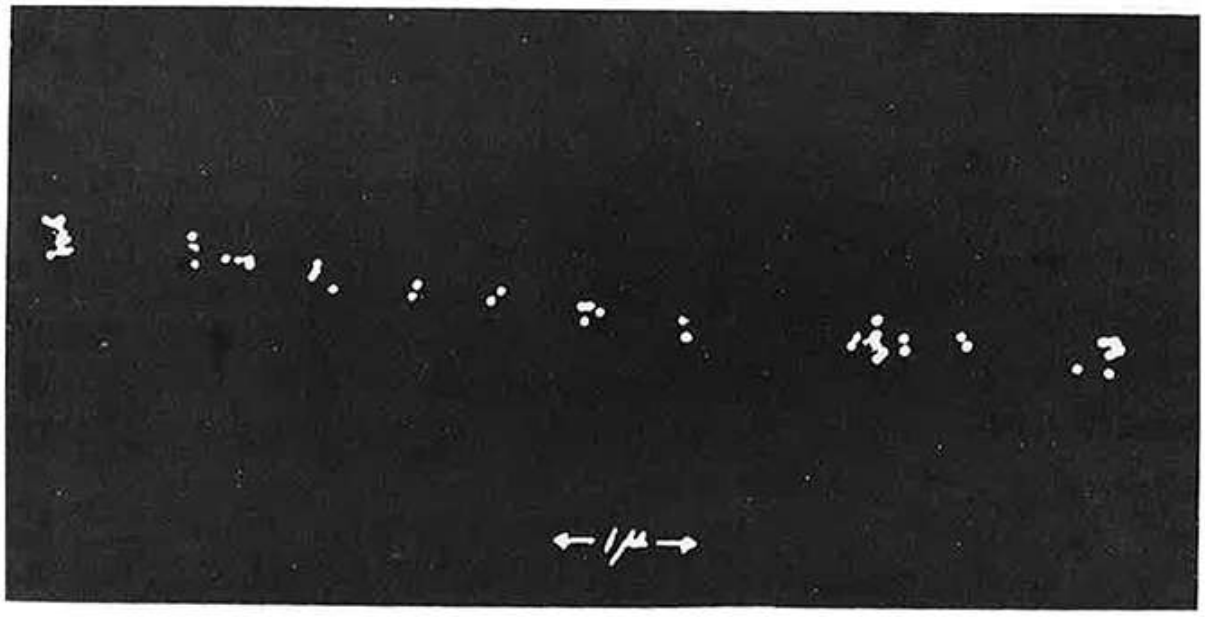


FIGURE 1.12 This cloud chamber photograph of a fast electron illustrates that ionization occurs in clusters. (Reprinted from Bacq ZM, Alexander P. *Fundamentals of Radiobiology*. 2nd ed. Pergamon Press; 1961. Copyright © 1961 Elsevier. With permission.)

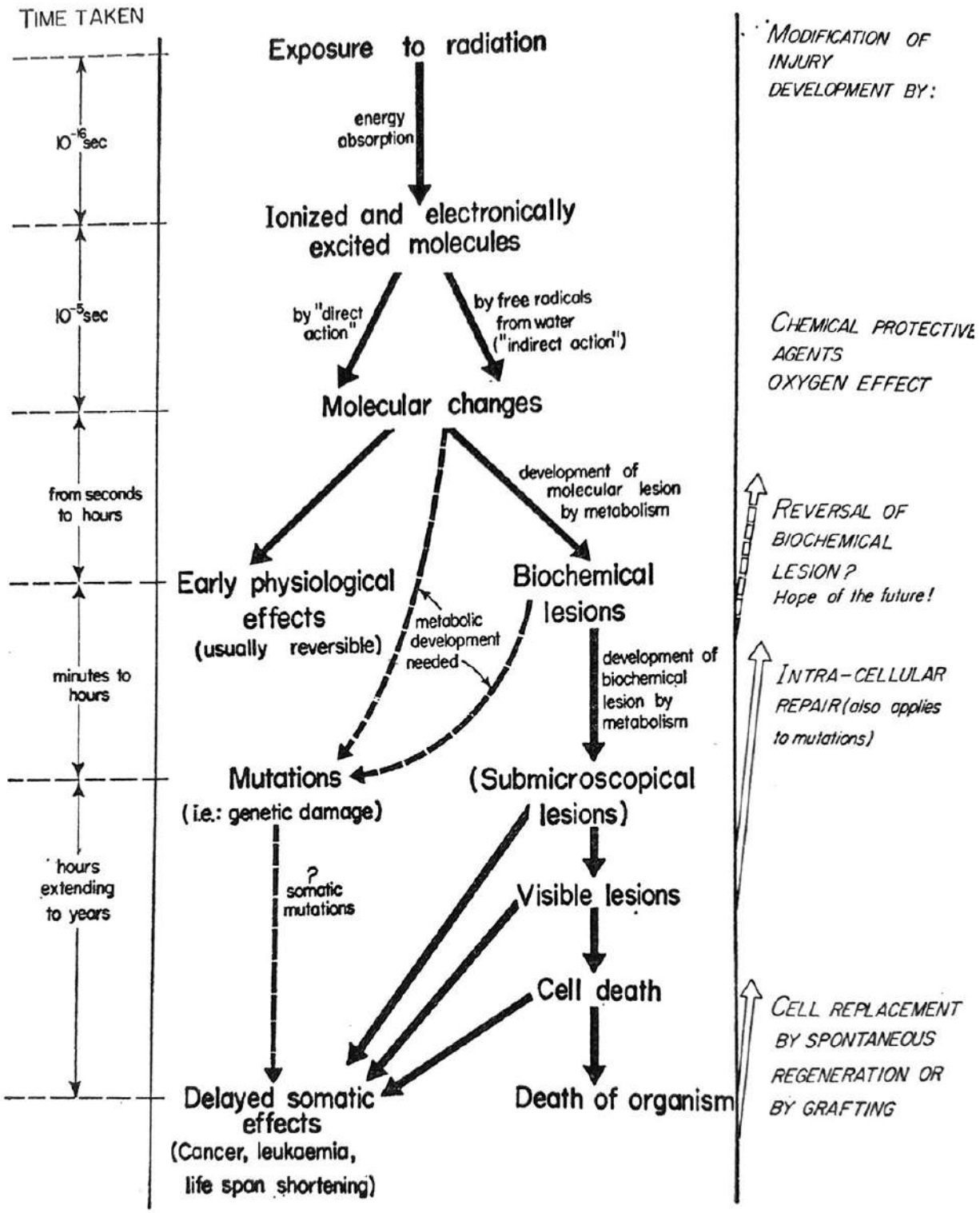


FIGURE 1.13 In their 1961 *Fundamentals of Radiobiology*, second edition, Z. M. Bacq and Peter Alexander managed, in a single diagram, to describe the stepwise development of ionizing radiation's injury to a cell and an organism. Our knowledge has grown, but the principles described by Bacq and Alexander over 60 years ago remains the same. (Reprinted from Bacq ZM, Alexander P. *Fundamentals of Radiobiology*. 2nd ed. Pergamon Press; 1961. Copyright © 1961 Elsevier. With permission.)

In many cells, radiation-induced lethality is not instantaneous because cells continue to function and even undergo several divisions before final mitotic death occurs. Noncycling lymphocytes, thymocytes, and hematopoietic cells were shown to undergo an interphase cell death without progressing through the mitotic phase of the cell cycle.[98] Two patterns of morphologic changes are associated with cell death in mammalian cells. Cell necrosis, which is degenerative, is the most usual type of cell damage. Necrotic cell death results from collapse of cellular metabolism and depletion of its adenosine triphosphate storage. The final events of necrosis involve membrane rupture, loss of lysosomal enzymes, degradation of nuclear chromatin, and karyolysis. The other process of radiation-induced cell death is apoptosis. Programmed cell death, or apoptosis, is a physiologic process that involves a series of characteristic, genetically controlled steps. These include chromatin condensation and segmentation, fragmentation of the nucleus into apoptotic bodies, cell shrinkage, and loss of cellular contact with neighboring cells. Apoptosis culminates in the engulfment of the cell by neighboring cells, such as macrophages, without a concomitant inflammatory response. Apoptosis occurs spontaneously in various solid tumors and contributes to the balance between tumor cell gain and cell loss.[99]

Within minutes after irradiation, signal transduction pathways mediated by protein kinase C and tyrosine kinase are stimulated. Genes and enzymes involved in genetic control of radiation damage repair are activated, stress genes are induced, and growth factors and cytokines that modulate response of mammalian cells to ionizing radiation are activated. Radiation-induced stimulation is probably critical to induction of many genes and proteins, including early response genes, which, in turn, activate other genes, including those for tumor necrosis factor, fibroblast growth factor, and TGF. In addition, new proteins, such as tissue plasminogen activator, are synthesized. This cascade of gene activation and transcription and protein synthesis is related to key cellular functions that the cell invokes in an attempt to survive a dose of radiation.[100-109]

Modifiers of Radiation Response

Several approaches have been used to enhance the therapeutic ratio in radiation therapy:

1. *Physical modifiers of low linear energy transfer (LET) radiations*. Intensity-modulated proton therapy (IMPT), photon therapy, EBRT, intensity-modulated radiation therapy (IMRT), three-dimensional (3D) treatment planning, respiratory-gated radiation therapy, improvements in anatomic and functional imaging, the increasing power of computer hardware and software, and treatment machine improvements have led to better photon, electron, and proton dose distributions; less side scatter; less differential absorption in the bone and

normal tissues; and, with charged heavy particles, selective energy deposition at specific depths.

2. *High LET radiations*. Tumor hypoxia and cells residing in relatively resistant phases of the mitotic cycle are less likely to cause unsatisfactory clinical results with neutrons, pi mesons, and heavy ions than with standard radiation doses delivered with low LET beams. The risk of adverse normal tissue reactions with high LET radiation, however, is significant.[110]
3. *Hyperbaric oxygen or tourniquet techniques*. These techniques involve the use of increased oxygen tension to improve the effects of irradiation on the tumor or the use of a tourniquet to produce severe hypoxia in the surrounding normal tissues so that higher irradiation doses can be delivered.[104] Theoretically, these approaches yield better tumor control without damaging normal tissues. Interest in the tourniquet technique waned years ago. Some investigators continue to evaluate hyperbaric oxygen. The logistics are formidable, and clinical trials have been inconclusive.[111-114]
4. *Hypoxic and other radiosensitizers*. Compounds with electron affinity, from the nitroimidazole group, theoretically produce free radicals in a manner similar to that of oxygen, selectively sensitizing hypoxic cells to radiation. Misonidazole (RO-07–0582) was evaluated in numerous clinical trials by the RTOG, with no evidence of clinical efficacy; however, in the Danish Head and Neck Cancer trial, there was a highly significant survival benefit in the subgroup of patients with pharynx tumors.[108,109] There are other radiosensitizers under study.[115-117]
5. *Perfluorocarbons*. These agents are administered in emulsion (they are insoluble in water) in sufficient concentrations coupled with inhalation of 95% to 100% oxygen to enhance oxygen transport and release in the presence of low oxygen tension. Their potential application in the treatment of patients with cancer was evaluated.[118,119] Interest in the technique waned.
6. *Cytotoxic agents*. Actinomycin D, doxorubicin, 5-fluorouracil, cyclophosphamide, taxanes, cisplatin, methotrexate, bleomycin, and others have been shown to interact with radiation in several forms to maximize tumor cell killing.[120-126]
7. *EGFR*. EGFR, a member of the ErbB family of receptor tyrosine kinases, is activated in several epithelial cancers. Radiotherapy increases the expression of EGRF in cancer cells, and blockade of EGFR signaling can sensitize cells to radiation. Cetuximab is a chimeric monoclonal antibody that targets EGFR. The drug appears to improve locoregional tumor control and survival in locally advanced squamous cell carcinoma of the head and neck.[127,128]

8. *Radioprotectors*. Sulfhydryl-containing compounds, such as cystine and cysteamine, have been used in animals to protect normal tissues against irradiation. Amifostine (WR-2721), a thiophosphate derivative of cysteamine, has been shown to selectively protect normal tissues, including the bone marrow, salivary glands, and intestinal mucosa, in animals, with little effect on tumor response to irradiation. Amifostine undergoes dephosphorylation by cellular-bound alkaline phosphatase to an active metabolite, WR-1065. This alkaline phosphatase–dependent activation is thought to contribute to selective normal tissue protection because of a higher concentration of alkaline phosphatase in normal tissue. Cytoprotection is believed to be the result of the elimination of free radicals. The compound was widely investigated in phase II and III clinical trials. It is used to reduce the incidence of neutropenia-related fever and infection from drugs like cyclophosphamide and cisplatin and for the reduction of xerostomia in patients with head and neck cancer undergoing radiotherapy. A meta-analysis has shown that amifostine does not reduce overall or progression-free survival in patients treated with radiotherapy or chemoradiotherapy—arguing against amifostine protecting tumor tissue.[129-132]
9. *Hyperthermia*. Heat at temperatures of more than 42.5 °C kills cells by itself or enhances the effects of irradiation and numerous cytotoxic agents. Heat selectively kills cells that are chronically hypoxic, acidotic, and nutritionally deficient—characteristics shared by tumor cells in comparison with the better oxygenated and better nourished normal cells. Furthermore, heat preferentially kills cells in the S phase of the proliferative cycle, which are known to be relatively resistant to irradiation.[133] This topic is addressed in Chapter 27.
10. *FLASH*. Ultra HDR radiation therapy appears to create a favorable therapeutic ratio for sparing normal tissue. The mechanism of action is unclear but may involve tissue depletion of oxygen, vascular effects, immune effects, and/or microdosimetric effects.[134]

Radiosensitivity and Radiocurability

In 1906, Bergonié and Tribondeau[135] formulated a law relating radiosensitivity to reproductive capacity of cells, based on their experiments on rat testis in which they were able to destroy the germinal cells while the interstitial tissue and Sertoli syncytium remained unimpaired. They wrote that "x-rays are more effective on cells which have a greater reproductive activity; the effectiveness is greater on those cells which have a longer dividing future ahead. . . . From this law, it is easy to understand that roentgen radiation destroys tumors without destroying healthy tissues." Fletcher[136] and del Regato[137] felt that this observation, which was interpreted to indicate that radiosensitivity of tumors was linked to that of the mother

organ, did much harm to clinical radiation therapy, leading to the erroneous concept that undifferentiated tumors with mitotic activity were radiosensitive and that more differentiated tumors were radioresistant.

In 1914, Schwarz[138,139] introduced the concept of fractionation by postulating that it was inefficient to deliver the total radiation dose in one treatment because cells were in different states of radiosensitivity and because there was a better chance that multiple exposures could hit the cells in a radiosensitive phase (eg, mitosis). Fractionation was assumed to create a favorable therapeutic ratio because the tolerance of normal tissues increased relative to that of tumors and because malignant cells had a greater reproductive capacity and were, therefore, more likely to be in a radiosensitive phase.

Based on these and other observations, the term *radiocurability* was coined. It refers to the eradication of tumor at the primary or regional site and reflects a direct effect of the irradiation producing logarithmic cell killing; this does not necessarily equate with the patient's cure from cancer. In contrast, *radiosensitivity* is a measure of tumor-radiation response, thus describing the degree and speed of regression during and immediately after radiotherapy. However, for some malignant tumors, no significant correlation exists between the responsiveness of a tumor to irradiation and its radiocurability.

At least four explanations have been considered that could either alone or in combination account for the different radiosensitivities of tumors[140-142]:

1. *Hypoxia*. To explain the spectrum of clinical radioresponsiveness on this basis, it is likely that the less responsive tumors either have a high hypoxic fraction, have failed to reoxygenate during fractionated treatment, or both.[143] Direct oxygen electrode measurements have shown that human cervical cancer, breast cancer, and squamous cell cancers have mean oxygen pressures below those of the surrounding tissue.[144,145] Despite a wide range of values, the oxygen pressure in tumors tends to decrease with increasing tumor size.[146] Although it is not possible to prove that hypoxia is unimportant in conventional radiation therapy, some doubts about its importance have been expressed based on the limited success of neutron therapy or hypoxic cell radiosensitizers.[147-149] Hypoxia can act as an important determinant of selecting tumor cells of a more malignant phenotype that is likely to adversely affect treatment outcome.
2. *Proportion of clonogenic cells*. Proliferating cells are more radiosensitive and have a greater turnover (cell loss) rate. Tumor regression during irradiation may be proportional to the total number of proliferating cells (growth fraction) or the proliferative rate, which may accelerate for certain tumor cells as a result of adaptive processes (accelerated repopulation) during fractionated irradiation.

3. *Inherent radiosensitivity of tumor cells*. Fertil and Malaise[150] and Deacon et al[151] established a positive correlation between the steepness of the initial slope of the oxic cell survival curve for human tumor cells and their response to radiation. The magnitude of differences between cell lines at low doses is sufficient to explain the range of curability observed clinically. Steel and Peacock[152] analyzed human tumor radiosensitivity in light of existing concepts of cell killing based on the linear quadratic (LQ) equation. However, despite encouraging correlations in some studies, these radiobiologic parameters have not been accepted for routine clinical use.
4. *Repair of radiation damage*. Repair of sublethal damage (SLD; split-dose effect) is observed in almost all tumor cell lines.[153-157] Potentially lethal damage (PLD) repair after a single dose varies considerably from one cell line to another and has been reported by Weichselbaum and Little[158] to correlate with clinical radiocurability, with less curable tumors showing the greatest degree of PLD recovery. These repair parameters have not been confirmed in larger clinical experiences to justify their use as predictors of radiotherapy outcomes.

By the 1970s to 1980s, it was observed that there was a correlation between the clinical or pathologic response of a tumor after the completion of irradiation with the ultimate probability of local tumor control.[159] For this analysis to be valid, it was necessary to compare patients with the same initial stage because, in general, more advanced lesions have a greater probability of tumor persistence at the completion of radiation therapy and local recurrence may be more frequent. Barkley and Fletcher[160] reported 82% tumor control in 88 patients with tumors of the oropharynx that had regressed completely at the end of therapy, in contrast to 41% in 237 patients with persistent tumors at the completion of therapy. Sobel et al[161] concluded that local tumor control in head and neck carcinomas could be predicted with the greatest accuracy and consistency 1 to 3 months after the completion of radiotherapy. They noted that the prediction was 80% accurate in favorable tumors (T1 and T2) but decreased to 50% to 60% in more advanced primary lesions; complete tumor clearance was a more accurate predictor of tumor control. This was confirmed for the radiotherapeutic management of N2 (>3 cm) neck disease, where complete clinical resolution of tumor within 8 weeks of completion of irradiation correlated with a less than 90% freedom from neck failures.[162] Modern studies are based on pathologic confirmation of complete tumor response or positron emission tomography (PET) scan response. They show similar results. Depending upon the type of tumor and its stage, there is a debate as to when to get the post-radiotherapy PET scan.

Tumor Radiosensitivity and Predictive Assays

Since the inception of the use of ionizing radiation, many investigators have categorized the response of tumors according to their sensitivity to irradiation. Wetterer[163] in 1913 characterized tumor radiosensitivity based on histologic types, and Paterson[164] divided tumors into three groups: radiosensitive, intermediate, and radioresistant. The first category included germ cell tumors and what were called reticuloses (leukemia and lymphoma); the second included squamous cell and adenocarcinomas; and the third group included soft tissue and bone sarcomas and melanomas. However, depending on the variation in proliferative rates and cell loss, end points for response assessment may vary substantially, as has been pointed out for malignant melanoma.[165]

Attempts have been made to predict the response of tumors to radiation depending on several parameters, such as the assay proposed by Glucksmann[166] consisting of differential cell counts of mitotic, resting, and degenerating cells in biopsy samples from the growing edge of the tumor before and after initiation of radiotherapy. It is generally accepted that tumors contain mixed cell populations of stem cells with differing sensitivity to antineoplastic agents and that therapy can be selected for resistant cell populations or, in the case of certain cytotoxic agents, to induce cellular resistance.[167] Peters et al[168,169] described a predictive assay to assess tumor response in vitro and the difficulties in predicting the probability of tumor control by irradiation in a given patient.

Unfortunately, despite promising correlations between radiosensitivity in vitro and radioresponsiveness of normal tissues and tumors,[170] sufficiently powered predictive assays have not been identified. Given the inherent intertumor variability of predictive parameters, such as SF_2[171,172] or T_{pot},[173,174] and the genetic profile of tumor cells, a single predictive assay is unlikely to carry sufficient predictive power. The incorporation of multiple radiobiologic tumor cell parameters (eg, markers for radiosensitivity and proliferation potential) into tumor control probability (TCP) (see later in this chapter) models appears more promising but awaits broader validation in clinical trials.[175]

Probability of Tumor Control

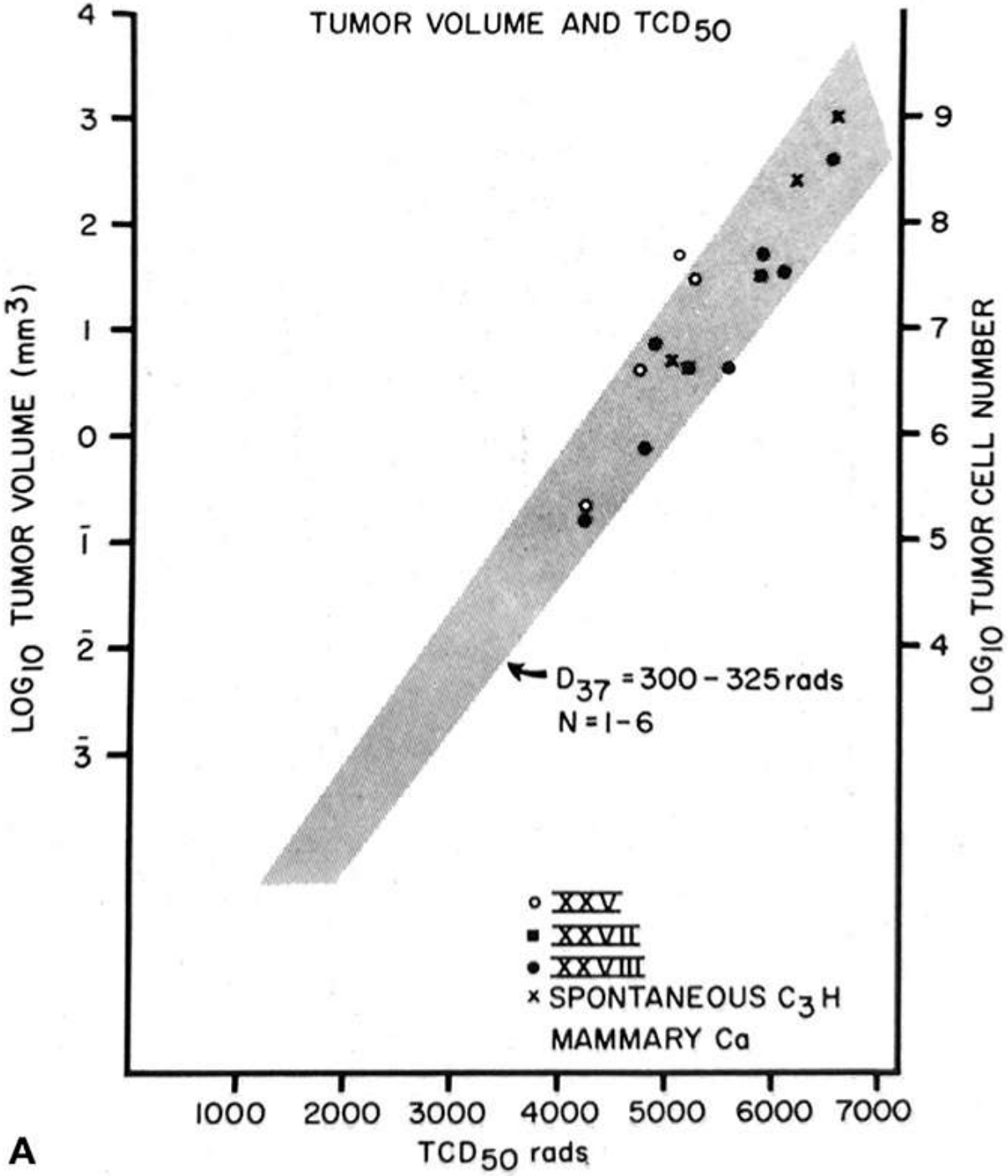
For many histologic types of cancer, higher radiation doses produce better tumor control. Numerous dose-response curves for a variety of tumors have been published. The first dose-response data were reported for skin cancer by Miescher[176] in 1934; 10 years later, Strandqvist[177] published a dose-response curve for skin cancer. The Strandqvist plots were refined by von Essen,[178,179] who demonstrated from a large skin carcinoma experience that the slopes for 97% tumor control and 3% skin necrosis differed and permitted, through appropriate fractionation schedules also considering the volume of disease, a dissociation of the two endpoints. As

Fletcher[170] pointed out, meaningful dose-response curves can be generated only when a group of homogeneous tumors is given a range of radiation doses, indicating that tumor control is a probabilistic event. For every increment of radiation dose, a certain fraction of cells will be killed; therefore, the total number of surviving clonogenic cells will be proportional to the initial number present and the fraction killed with each dose[180,181] (Table 1.5). Thus, various levels of irradiation will yield different probabilities of tumor control, depending on the extent of the lesion (number of clonogenic cells present) (Box 1.4). For subclinical disease in squamous cell carcinoma of the upper respiratory tract, doses of 45 to 50 Gy will result in disease control in more than 90% of patients.[182,183] Subclinical disease has been referred to as deposits of tumor cells that are too small to be detected clinically and even microscopically but, if left untreated, subsequently may evolve to clinically apparent tumor.[184,185] It must be emphasized that microscopic evidence of tumor, such as at the surgical margin, should not be regarded as a subclinical disease; cell aggregates $10^5/cm^3$ or larger are required for the pathologist to detect them. Therefore, these volumes must receive higher doses of irradiation, in the range of 60 to 65 Gy, in 6 to 7 weeks for epithelial tumors (Figure 1.14). This distinction of disease extent is reemphasized by clinical results, demonstrating the need for irradiating patients with likely subclinical carcinoma to postoperative doses near 60 Gy[186] (Figure 1.15).

TABLE 1.5 VARIOUS LEVELS OF IRRADIATION WILL YIELD DIFFERENT PROBABILITIES OF TUMOR CONTROL, DEPENDING ON THE SIZE OF THE LESION

Cumulative Dose (Gy)	Initial Cell Number	Probability of Survival	Remaining Cell Number
2	1,000,000,000	×0.5 =	500,000,000
4	500,000,000	×0.5 =	250,000,000
6	250,000,000	×0.5 =	125,000,000
8	125,000,000	×0.5 =	62,500,000
10	67,500,000	×0.5 =	31,250,000
12	33,750,000	×0.5 =	15,625,000
14	15,625,000	×0.5 =	7,812,500
16	7,823,500	×0.5 =	3,906,250
18	3,906,250	×0.5 =	1,953,125
20	1,953,125	×0.5 =	976,562
22	976,562	×0.5 =	488,281
24	488,281	×0.5 =	244,140
26	244,140	×0.5 =	122,070

Cumulative Dose (Gy)	Initial Cell Number	Probability of Survival	Remaining Cell Number
28	122,070	×0.5 =	61,035
30	61,035	×0.5 =	30,517
32	30,517	×0.5 =	15,258
34	15,258	×0.5 =	7,629
36	7,629	×0.5 =	3,814
38	3,814	×0.5 =	1,907
40	1,907	×0.5 =	953
42	953	×0.5 =	476
44	476	×0.5 =	238
46	238	×0.5 =	119
48	119	×0.5 =	59
50	59	×0.5 =	29
52	29	×0.5 =	15
54	15	×0.5 =	7
56	7	×0.5 =	4
58	4	×0.5 =	2
60	2	×0.5 =	1
62	1	×0.5 =	<1


TUMOR VOLUME AND TCD50
LOG10 TUMOR VOLUME (mm3)
LOG10 TUMOR CELL NUMBER
4
3
2
1
0
-1
-2
-3
9
8
7
6
5
4
D37 = 300 - 325 rads
N = 1-6
XXV
XXVII
XXVIII
SPONTANEOUS C3H MAMMARY Ca
1000
2000
3000
4000
5000
6000
7000
TCD50 rads

A

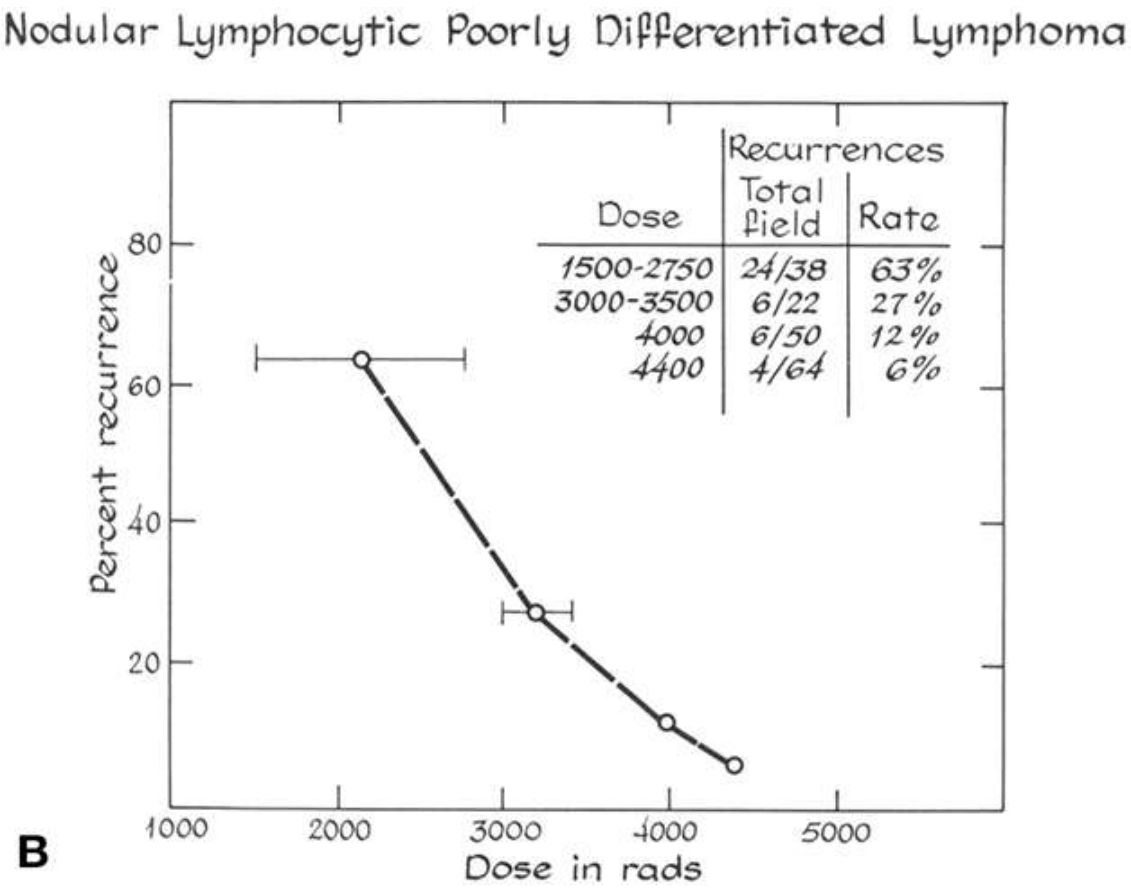


FIGURE 1.14 As a physical, rather than a chemical, modality of cancer treatment, radiation therapy is in a unique position to correlate *dose* with treatment outcomes. If a radiation oncologist says they administered 40 Gy to a tumor, they actually did. The dose of radiation administered is not affected by factors that influence chemotherapy dose to a tumor cell: blood flow, interstitial tumor pressure, membrane transport, and/or speed of the body's excretion or metabolism of the drug. Here are two examples of radiation dose-response relationships: A. The dose that yields a local control in 50% of irradiated tumors (TCD_{50}) in 16 experimental animal dose-response curve studies shows tumor control as a function of dose and tumor volume. (Reprinted with permission from HD Suit. Radiation biology: a basis for radiotherapy. In: Fletcher GH, ed. *Textbook of Radiotherapy*. Lea & Febiger; 1966:77.) B. This is an example of a classic clinical radiation dose-response relationship for local control of a solid tumor. Zvi Fuks and Henry Kaplan, in 1973, analyzed the local recurrence rate after initial radiotherapy in 198 patients with nodular and diffuse non-Hodgkin lymphoma. In this example, Figure 2 from their paper, they plot the probability of tumor recurrence on the y-axis for nodular poorly differentiated non-Hodgkin lymphoma. On the *x*-axis, they show the dose of external beam radiotherapy. This is an example of an attempt to correlate tumor histology, radiation dose, and local control for the purpose of identifying the recommended treatment dose. (Used with permission of Radiological Society of North America from Fuks Z, Kaplan HS. Recurrence rates following radiation therapy of nodular and diffuse malignant lymphomas. *Radiology*. 1973;108(3):675-684; permission conveyed through Copyright Clearance Center.)

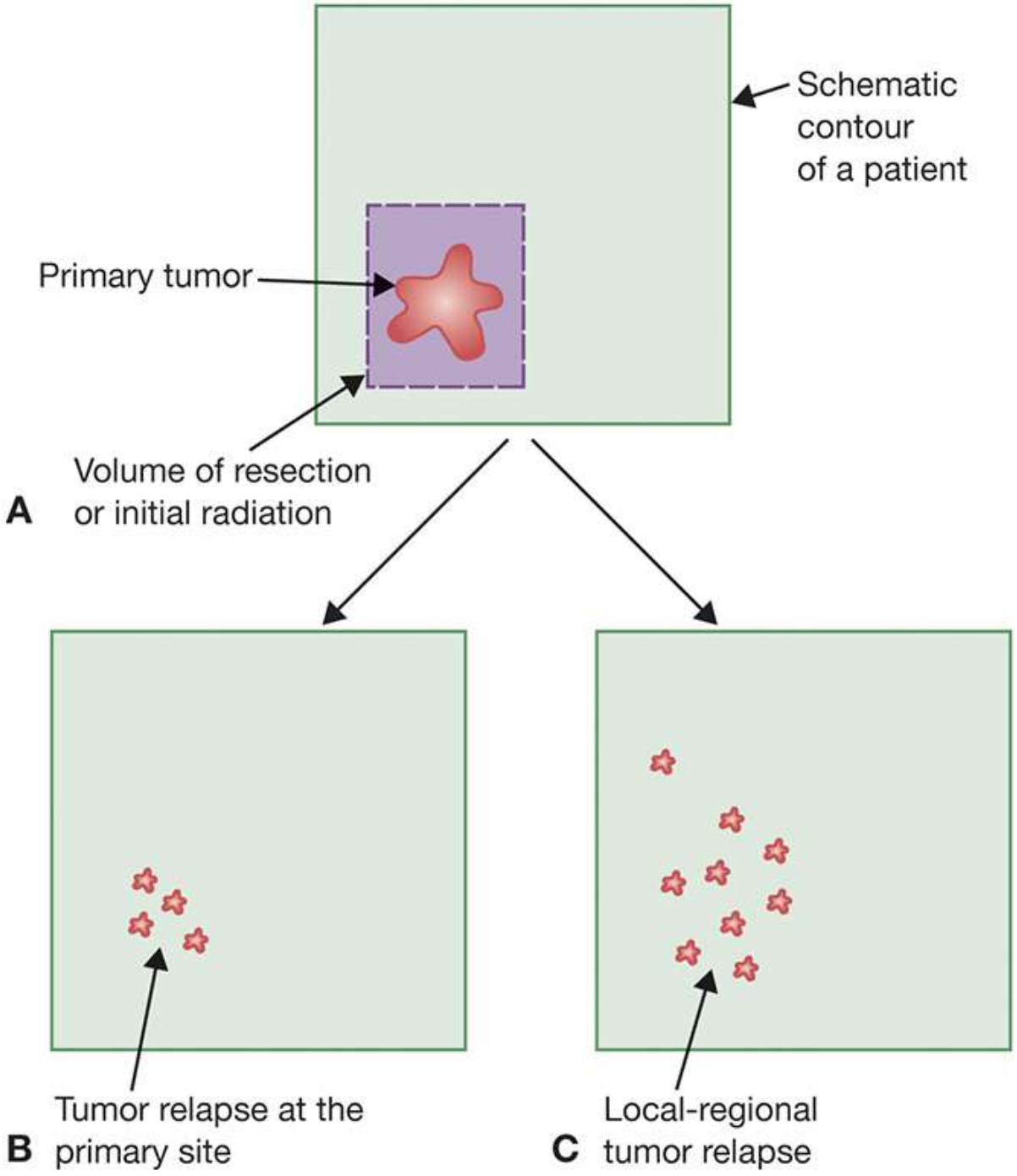


FIGURE 1.15 A. A pattern of failure analysis is useful to improve the treatment of malignancies. B. If the tumor after surgery and/or radiotherapy tends to relapse at the primary site within the volume treated, it would suggest that the local therapy is insufficiently intense. C. If, however, there is a locoregional tumor relapse, it would suggest that the initial surgery or radiotherapy field size is insufficient to cover the microscopic extension of disease that has the potential to be controlled. A pattern of failure as shown in panel C is not, by itself, sufficient to make the case for extended-field radiation. One must have a pattern of failure such as that which is seen in panel C and also be able to show that intervention with large field irradiation can alter that pattern in a favorable manner.

Box 1.4

Logarithmic Cell Kill

Among the simplest exercises a radiation oncologist–in-training can undertake is the creation of a table of logarithmic cell kill. At first, such an exercise seems trivial. The effort expended on this somewhat tedious exercise will, however, be repaid many times over.

Let us assume that we have a tumor that follows a typical cell survival curve. These tumor cells have a 50% probability of cell survival after a radiation dose of 2 Gy. If we assume, for the purpose of this exercise, that there are no changes in the probability of cell kill wrought by changes in tumor oxygenation, pH, or other factors during the course of treatment; that there is no accelerated repopulation; and that only the simplest conditions apply (ie, that there is 50% kill for each dose), then we can create a table showing the number of cells killed and the number of cells remaining after each dose (Table 1.5).

Let us assume that we begin with a relatively small tumor (ie, a spherical tumor a bit >1 cm in diameter containing, say, 10^9 cells). At each dose of 2 Gy, 50% of the cells are killed. Thus, after the first dose, 500 million cells are killed and 500 million cells remain. At each successive dose, 50% of the cells are killed. Therefore, by the end of the course of radiation, very few cells are killed with each individual dose.

One can see, from going through the exercise, that even for a very small tumor, the number of initial cells is very large and the marginal killing of the absolute number of cells, with the last few doses, is small. It is not surprising, therefore, that for a tumor of average radiation sensitivity, quite a high dose of radiation is required.

Obviously, the exercise would change if we were to use a different radiation dose per fraction, producing a different probability of survival, or if the intrinsic radiosensitivity of the tumor cell line were different and the probability of survival were different.

Based on Suit HD. Radiation biology: a basis for radiotherapy. In: Fletcher GH, ed. *Textbook of Radiotherapy*. Lea & Febiger; 1966.

For clinically palpable head and neck tumors, doses of 65 (for T1) to 75 to 80 Gy or higher (for T4 tumors) are required at 2 Gy/day using five fractions weekly. This dose range and probability of tumor control have been documented for squamous cell carcinoma and adenocarcinoma.[187-189] Even with preoperative irradiation, the dose effect on the probability of tumor control can be documented.

Baclesse[190] introduced the concept of different doses of irradiation for various portions of the tumor. The higher dose administered through small portals to residual disease is called a *boost*, which is delivered in an effort to achieve the same probability of tumor control as for subclinical aggregates.[191] One consequence of the concepts discussed earlier is the use of portals that are progressively reduced in size. This *shrinking-field* technique administers higher radiation doses to the entire gross tumor where more clonogenic cells (including hypoxic cells) reside, relative to lower doses to tissues in the immediate proximity of the clinically apparent (gross)

tumor. The tissues making up the "tumor margin" contain a lower number of tumor clonogens that are better oxygenated (see Figure 1.16).

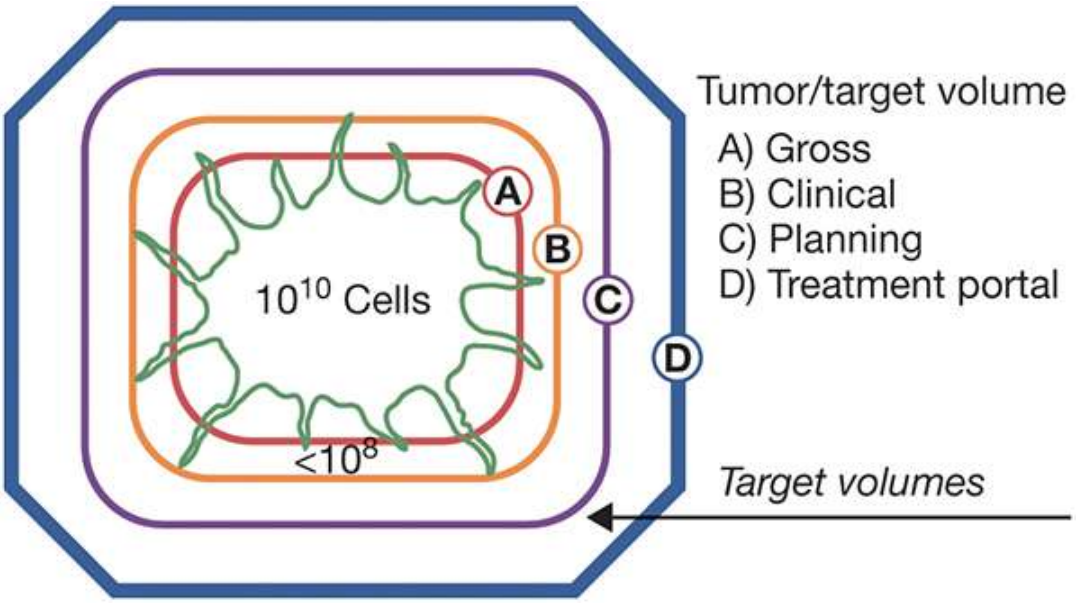


FIGURE 1.16 Schematic representation of "volumes" in radiation therapy. The treatment portal volume includes the tumor volume, potential areas of local and regional microscopic disease around the tumor, and a margin of surrounding normal tissue. (Modified with permission from Perez CA, Purdy JA. Rationale for treatment planning in radiation therapy. In: Levitt SH, Khan FM, Potish RA, eds. *Levitt and Tapley's Technological Basis of Radiation Therapy: Practical Clinical Applications*. 2nd ed. Lea & Febiger; 1992.)

The Impact of Local Tumor Control on Survival

Systemic chemotherapy, immunotherapy, and molecularly targeted therapy have been emphasized as therapies that could improve survival of cancer through control of systemic metastatic disease. The effect of locoregional tumor control on patient survival has also been emphasized repeatedly.[192] Clinical experiences and randomized trials demonstrate for cancers with high metastatic potential, such as breast, prostate, and lung, that improved locoregional control by radiotherapy with or without chemotherapy enhances overall survival. This has revived the interest in locoregional radiotherapy as a survival-prolonging treatment modality, also confirming earlier clinical experiences in patients with carcinoma of the lung, prostate, and uterine cervix.

Because of the emphasis on control of systemic disease, assessment of the importance of locoregional tumor control in patients with malignant tumors has been relatively underemphasized. In a large proportion of patients with cancer seen in the United States, locoregional recurrence is just as prevalent (69% of patients dying

with locoregional disease) as distant metastases. A large proportion of patients (50%) have both locoregional recurrence and distant metastases.

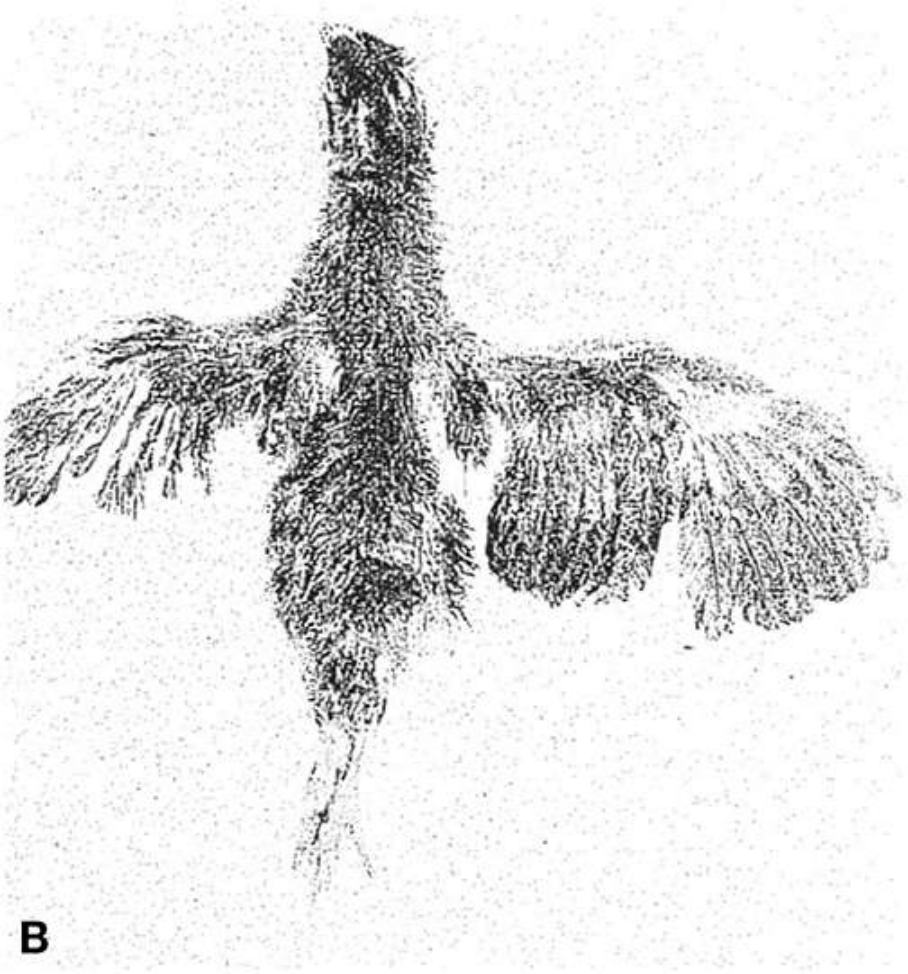
Clinical data demonstrate that tumor persistence after initial therapy does, because of tumor progression, carry as poor a prognosis as treatment of a more advanced cancer. In addition, radiotherapy has been shown, for tumors with high metastatic potential such as breast, prostate, and lung, to prolong overall survival if higher radiation doses are delivered and achieve improved local control rates.[193]

RADIATION THERAPY AND THE RISK OF INJURY TO NORMAL TISSUE

In 1936, Herman Holthusen (Figure 1.17) published a landmark paper in *Strahlentherapie*.[194] He described uncomplicated tumor control on the one hand and normal tissue injury on the other hand. Holthusen observed that the dose-response relationship for both tumor control and normal tissue injury had a sigmoidal shape. At very low doses, there was little or no effect. At very high doses, both tumor control and normal tissue injury probabilities plateau. At intermediate doses, the slope of the curve is steep, and there is a marked dose-response relationship (Figure 1.18).

FIGURE 1.17 Hermann Holthusen (1886-1971).

A



B

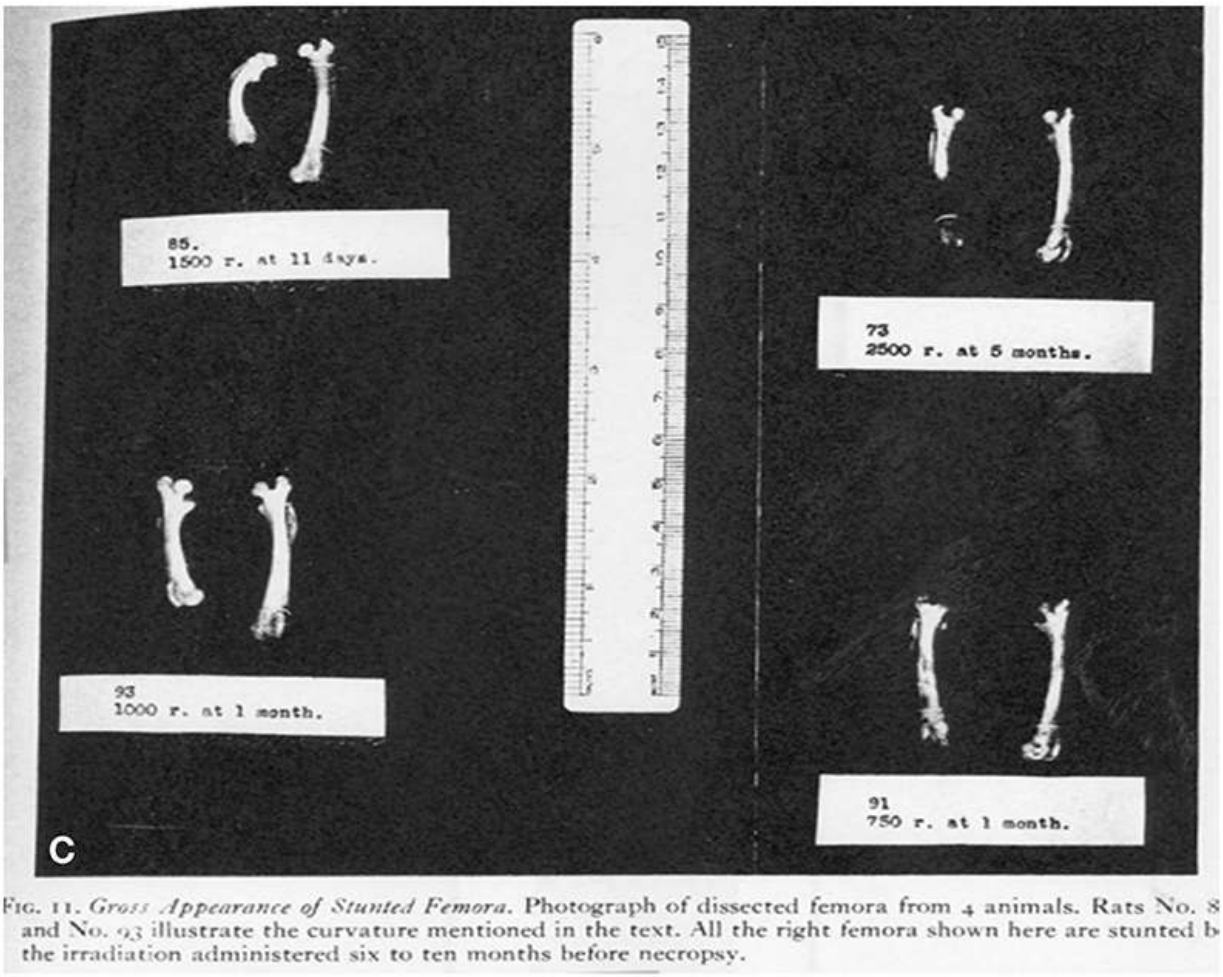


FIG. 11. *Gross Appearance of Stunted Femora.* Photograph of dissected femora from 4 animals. Rats No. 8 and No. 93 illustrate the curvature mentioned in the text. All the right femora shown here are stunted b the irradiation administered six to ten months before necropsy.

FIGURE 1.18 Radiation oncologists quickly ascertained that radiation could cause normal tissue injury. If there ever were examples of "one picture is worth a thousand words," they would include this demonstration by (A) Georg Perthes. B. In 1903, Perthes published this dramatic picture showing the ability of radiation to arrest tissue growth. He observed stunting of the growth of a chicken's wing exposed to radiation while a chick. (A, B. From Perthes G. Über den Einfluss der Röntgenstrahlen auf epitheliale Gebilde. *Arch Kiln Chir*. 1903.). (C) A graphic demonstration of femoral bone growth arrest in albino rats following a single dose of 750, 1,000, 1,500, or 2,500 Roentgen at 1 month of age by Charles Hinkel, MD, Med Sc D, and reported in 1942. (C. From Hinkel CL. The effect of roentgen rays upon the growing long bones of albino rats. I. Quantitative studies of the growth limitation following irradiation. *Am J Roentgenol Radium Ther Nucl Med*. 1942;47:439-457, Figure 11. Reprinted with permission from the *American Journal of Roentgenology*.)

The radiation oncologist seeks to find a "sweet spot" where there is a high probability of tumor control and a low risk of normal tissue injury (Figures 1.19-1.23). This "sweet spot" only exists if there is a separation between the two sigmoidal-shaped curves.

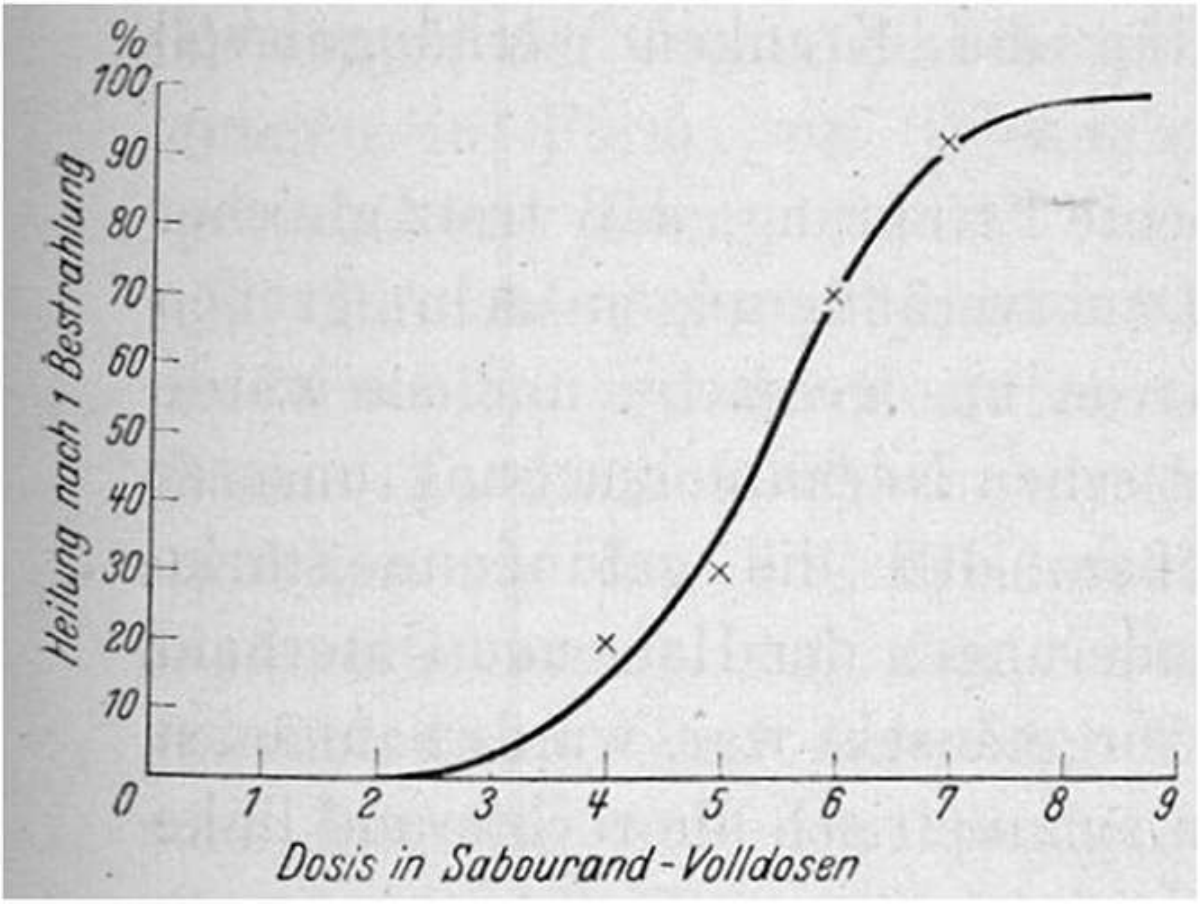


FIGURE 1.19 This is figure 1 from Holthusen's 1936 paper. The dose of radiation is indicated on the *x*-axis in Sabourand units. The concept of Sabourand units was described earlier in this chapter in the section on the origin of the concept of dose in radiation therapy. The *y*-axis shows the percentage cure rate of a tumor with a single fraction of radiation therapy. The curve is sigmoidally shaped. (Used with permission of Springer Nature BV from Holthusen H. Erfahrungen über die Vertraglichkeitsgrenze fur Röntgenstrahlen und deren Nutzanwendung zur Verhütung von Schäden. *Strahlentherapie*. 1936;57:254-269, Figure 1; permission conveyed through Copyright Clearance Center.)

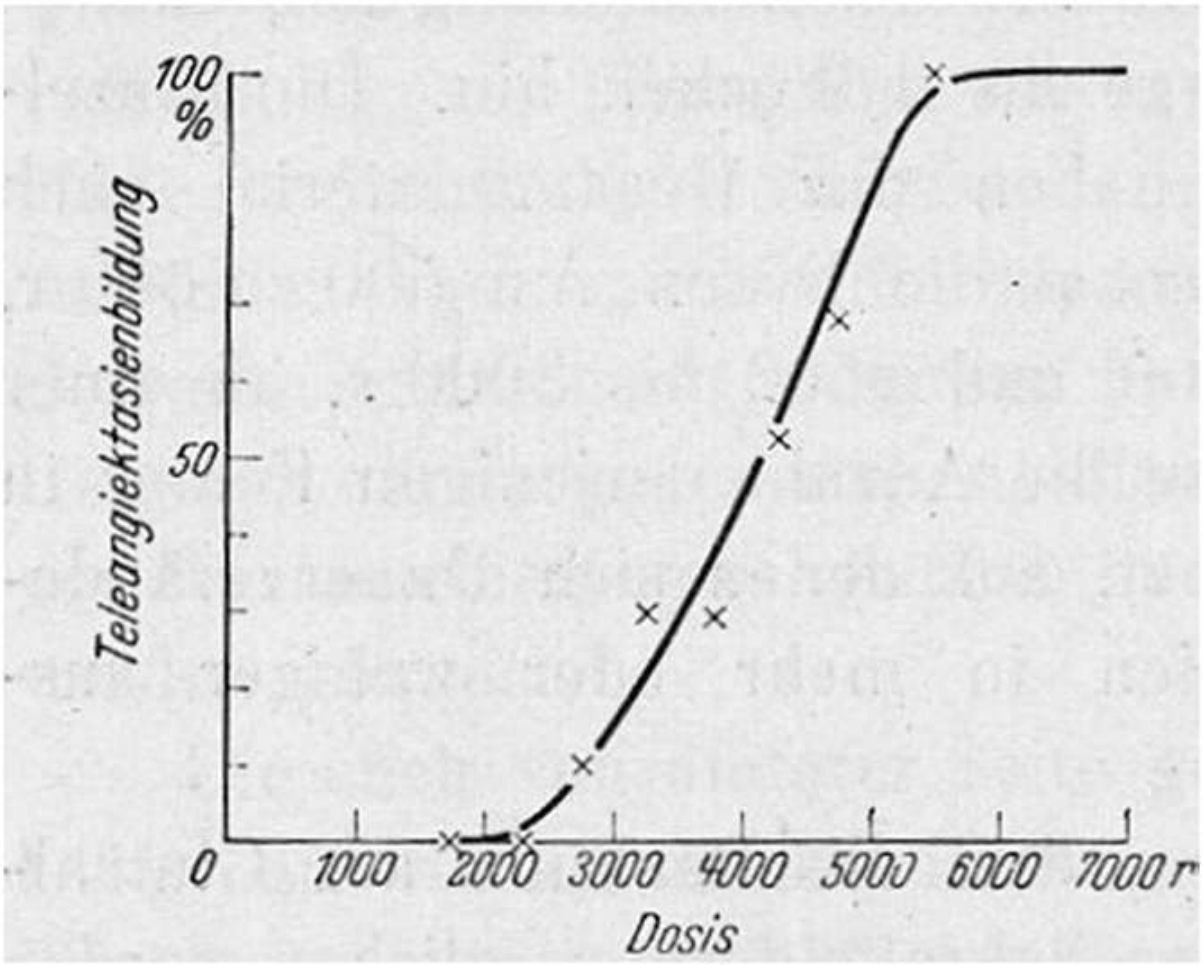


FIGURE 1.20 This is figure 3 from Holthusen's 1936 paper. The dose of radiation is shown on the *x*-axis. The probability of telangiectasis on the y-axis. Once again we see a sigmoidal-shaped curve. (Used with permission of Springer Nature BV from Holthusen H. Erfahrungen über die Vertraglichkeitsgrenze fur Röntgenstrahlen und deren Nutzanwendung zur Verhütung von Schäden. *Strahlentherapie*. 1936;57:254-269, Figure 3; permission conveyed through Copyright Clearance Center.)

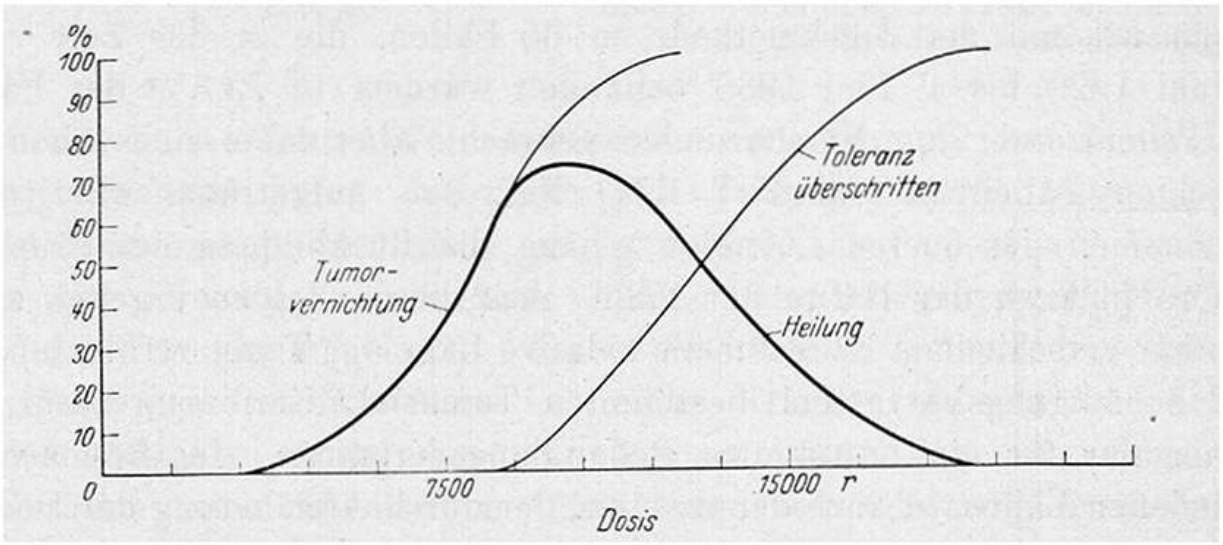


FIGURE 1.21 This is figure 6 from Holthusen's 1936 paper. The *x*-axis represents dose of radiation. The *y*-axis represents efficacy. The sigmoidal curve on the left depicts tumor destruction. The sigmoidal curve on the right shows the probably of normal tissue injury (he labeled it "tolerance exceeded"). The bell-shaped curve with the dark line is "cure rate" by which he meant tumor control in the absence of complications. If the treating radiation oncologist can find the right dose, then they will maximize the chance of cure while avoiding undesired effects on normal tissue. (Used with permission of Springer Nature BV from Holthusen H. Erfahrungen über die Vertraglichkeitsgrenze fur Röntgenstrahlen und deren Nutzanwendung zur Verhütung von Schäden. *Strahlentherapie*. 1936;57:254-269, Figure 6; permission conveyed through Copyright Clearance Center.)

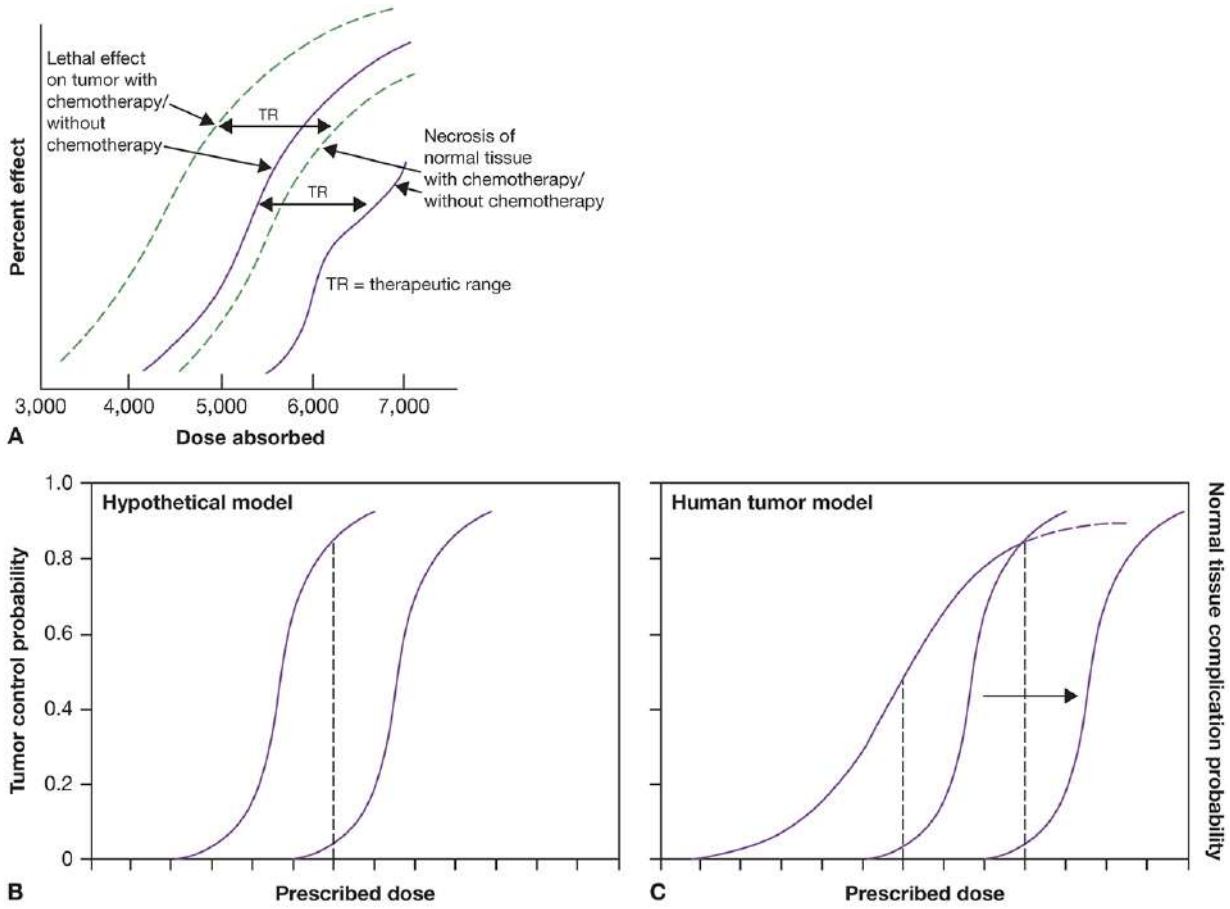


FIGURE 1.22 A. Building upon the work of Holthusen theoretical curves are shown for tumor control and complications as a function of radiation dose with and without chemotherapy. *TR* is the therapeutic ratio, or the difference between tumor control and complication frequency. (Reprinted from Perez CA, Thomas PRM. Radiation therapy: basic concepts and clinical implications. In: Sutow WW, Fernbach DJ, Vietti TJ, eds. *Clinical Pediatric Oncology*. 3rd ed. CV Mosby; 1984:167-209. Copyright © 1984 Elsevier. With permission.) B. Hypothetical dose-response curves for tumor control and normal tissue injury. Because the tumor control and the normal tissue complication curves are approximately parallel in shape and are sufficiently separated, the dose levels necessary to cure a high percentage of patients can be administered without producing excessive normal tissue damage (indicated by the vertical dotted line). C. Human tumor model. The slope of the tumor control curve is less steep than the normal tissue-complication curve; thus, for an acceptable level of normal tissue injury, the probability of tumor control is decreased compared to the hypothetical model. Because of the volume effect, reducing the volume of normal tissues shifts the curve to the higher dose region, thereby effectively increasing the separation of the dose-response curves. Consequently, a higher dose can be given to the tumor, improving the probability of tumor control without increasing the probability of normal tissue injury. (B, C. Reprinted with permission from Leibel SA, Fuks Z, Zelefsky MJ, et al. Intensity-modulated radiotherapy. *Cancer J*. 2002;8[2]:164-176.)

FIGURE 1.23 In the absence of the knowledge of the late adverse effects of radiation and of the principles of radiation protection, many pioneering radiologists and radiation oncologists suffered injuries. These are the hands of Dr Mihran Krikor Kassabian (1870-1910) of Philadelphia, photographed in 1903 and showing severe late radiation dermatitis from exposures that began in 1899. Kassabian developed skin cancer that metastasized. He died at age 39. (From Kassabian MK. *Röntgen Rays and Electro-Therapeutics, with Chapters on Radium and Phototherapy*. J.B. Lippincott; 1907.)

Holthusen's curves are among the most famous in radiation oncology. They have been recreated innumerable times by investigators in the approximately 90 years since they were first published—often without giving credit to Holthusen. They repay careful study today.

Improved definitions of TCP and normal tissue complication probability (NTCP)[195] imply that there is an optimal radiation dose that produces a maximum tumor control with a minimum (reasonably acceptable) frequency of complications, also called treatment sequelae. The farther the TCP and NTCP curves diverge, the

more favorable the therapeutic ratio. The therapeutic ratio or therapeutic gain factor (TGF) of a given regimen could be expressed as a ratio: The higher the TGF, the more efficient a particular therapy. Such a quantitative expression could be used to compare different therapeutic strategies. Mendelsohn[196] expressed this concept in terms of "uncomplicated tumor ablation."

The selection of a dose must weigh the probability of major complications for any potential enhancement of tumor control. Models for decision-making, using Bayesian theory, incorporate values assigned to positive or negative outcomes. Positive outcome is considered tumor cure without complication, whereas negative outcomes include tumor cure with significant complications or tumor recurrence with or without complications (Figures 1.24 and 1.25).

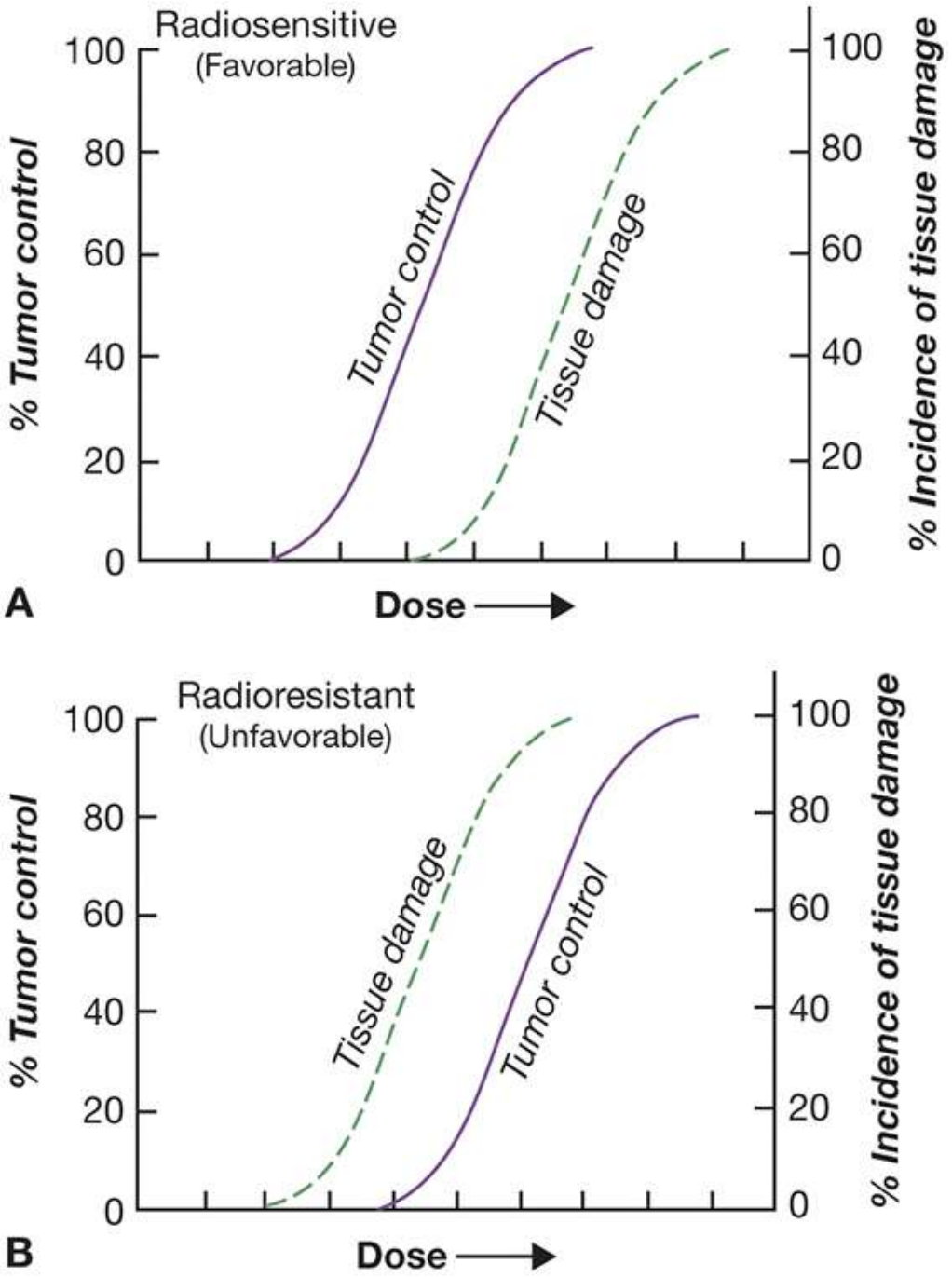
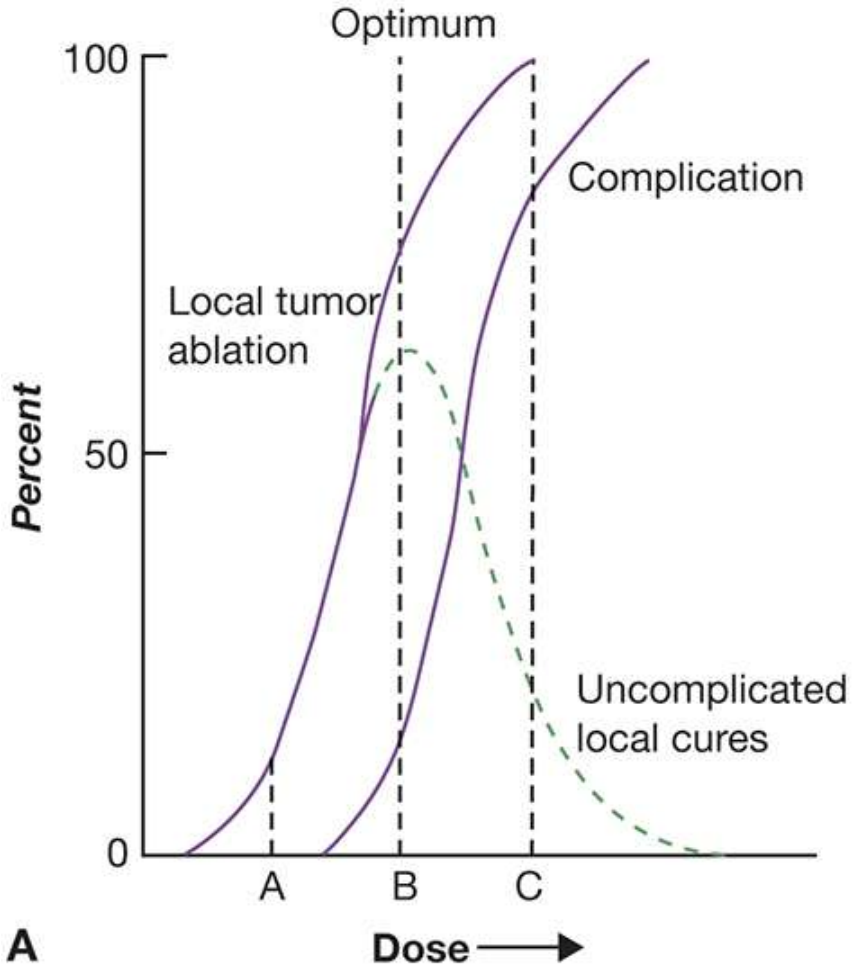


FIGURE 1.24 Different therapeutic ratios exist in different clinical circumstances depending on the radiosensitivity (dose-response curves) for the tumor versus critical normal tissue in the treatment field. A. Favorable. B. Unfavorable. (Reprinted from Rubin P. *Clinical Oncology: A Multidisciplinary Approach for Physicians and Students*. 7th ed. W.B. Saunders; 1993. Copyright © 1993 Elsevier. With permission.)


Optimum
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A
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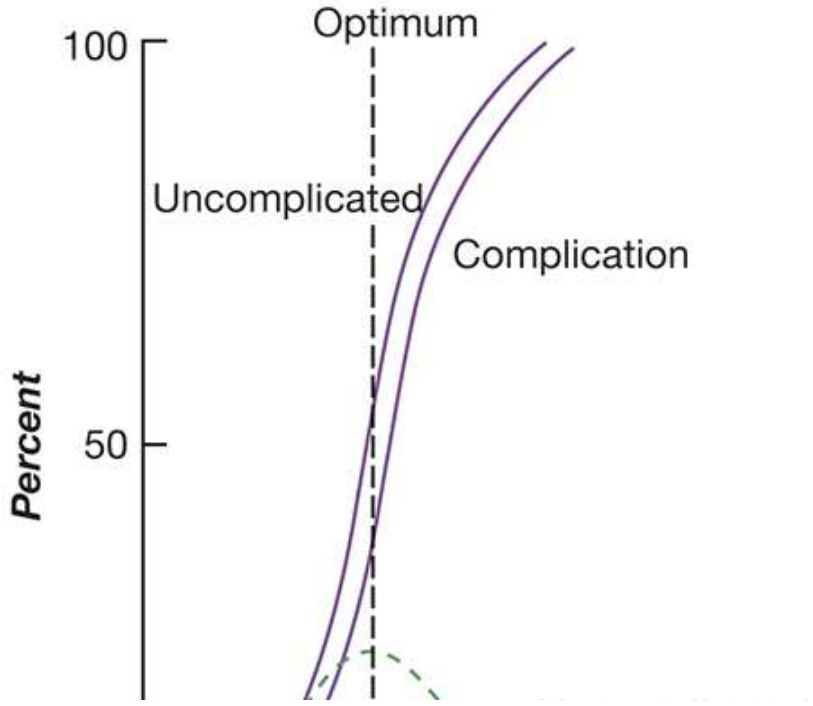
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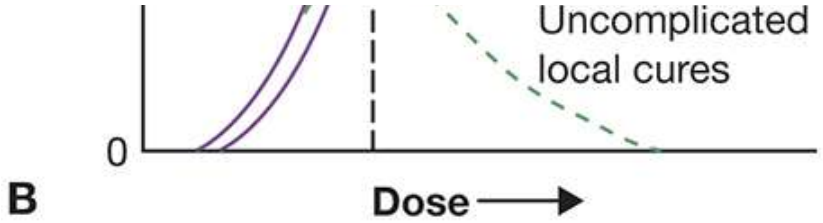


FIGURE 1.25 Treatment outcomes. Uncomplicated curves (dashed line) are the desired results of treatment. This is illustrated as a function of the therapeutic ratio; that is, the greater the separation of the tumor control curve and the normal tissue-complication curve, the greater the number of uncomplicated cures that will result. The letters *A*, *B*, and *C* represent three different dose levels, which, if chosen, would lead to three different outcomes: *A* would result in few tumor cures but no complications; *C* would lead to complete cure in many cases, but virtually all patients would suffer complications. The optimal choice in this group of dose levels is *B*, which would result in the greatest number of cured patients without complications. (From Mendelsohn ML. The biology of dose-limiting tissues. In: *Time and Dose Relationships in Radiation Biology as Applied to Radiotherapy*. Brookhaven National Laboratory; 1969:154-173. Brookhaven National Laboratory (BNL) Report 5023 (C-57). Courtesy of Brookhaven National Laboratory.)

THE ORIGINS OF CLINICAL RADIATION THERAPY

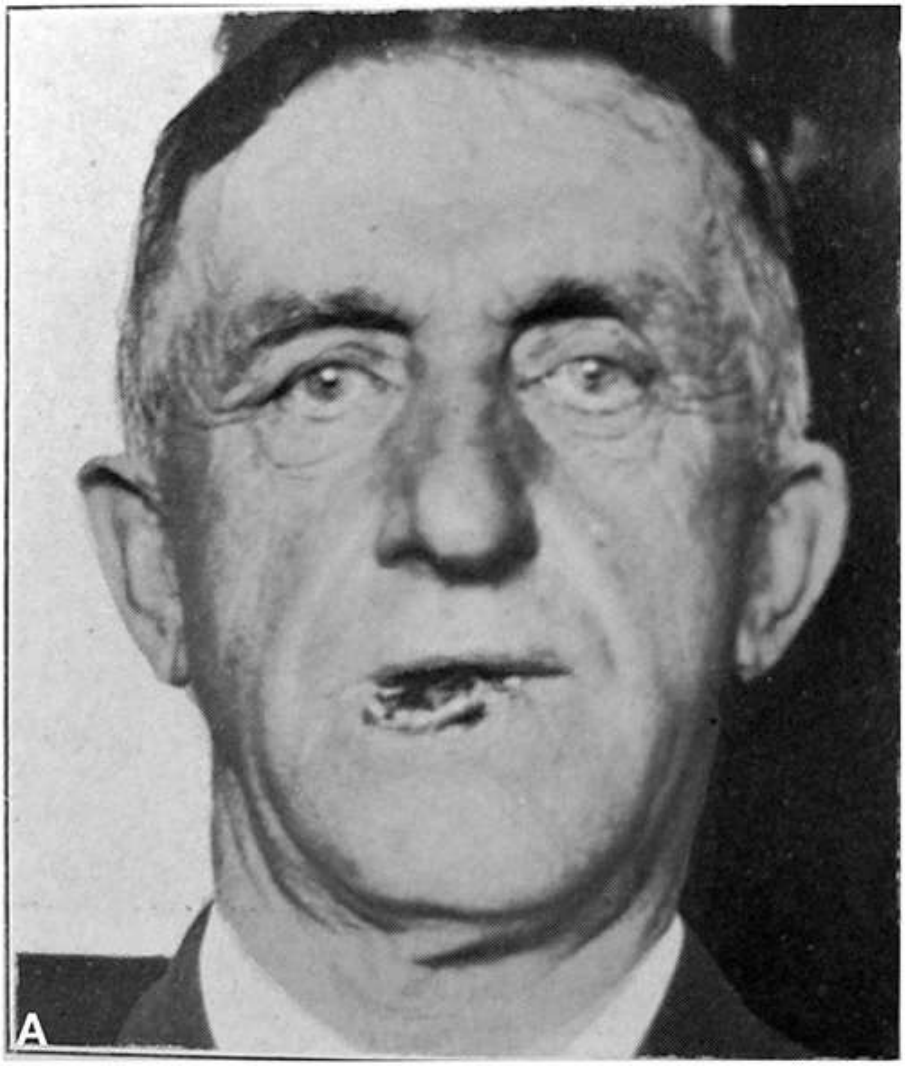
EBRT quickly showed itself to be a useful form of cancer treatment. Only 8 years after Röntgen's discovery, Dr Charles L. Leonard, in 1903, observed that:

> in spite of the most diligent study, there is nothing known of the etiology and histology of malignant disease that aids its treatment. Its development and fatal termination cannot be retarded, if the diseased tissue be permitted to remain in the body. Total extirpation by surgical intervention has been the only chance of cure.[197]

Leonard, however, discerned some promise in a new form of treatment.

> The results obtained by the use of the Röntgen rays seems to . . . have demonstrated their power to alter the character of malignant cells, to prevent their spread and development, and to produce retrograde changes that result in fatty and cystic degeneration or absorption, and often terminate in a restoration of the affected part to a nearly normal state. . . . The Röntgen treatment applied as a palliative in many hopeless, operatively impossible cases, has resulted frequently in cures that, if not permanent, have at least restored the patient to health and given months and even years of usefulness. . . . The results so far obtained are, therefore, very encouraging. An agent has been found which has a greater influence in retarding the growth of malignant tumors than any heretofore known. Many remarkable and apparently permanent cures have been obtained.[198]

Although it is controversial, most likely Leopold Freund was the first to report, in 1897, the use of ionizing radiation to "cure" a large nevus pigmentosus on the back of a young girl. Unfortunately, she later developed skin ulceration and scars.[199] Another pioneer in the therapeutic use of x-rays was Victor Despeignes who, in 1896, published on the treatment of a 52-year-old man who had an advanced stomach tumor (likely a lymphoma), with "considerable improvement in the condition of the patient"[200] (Figure 1.26).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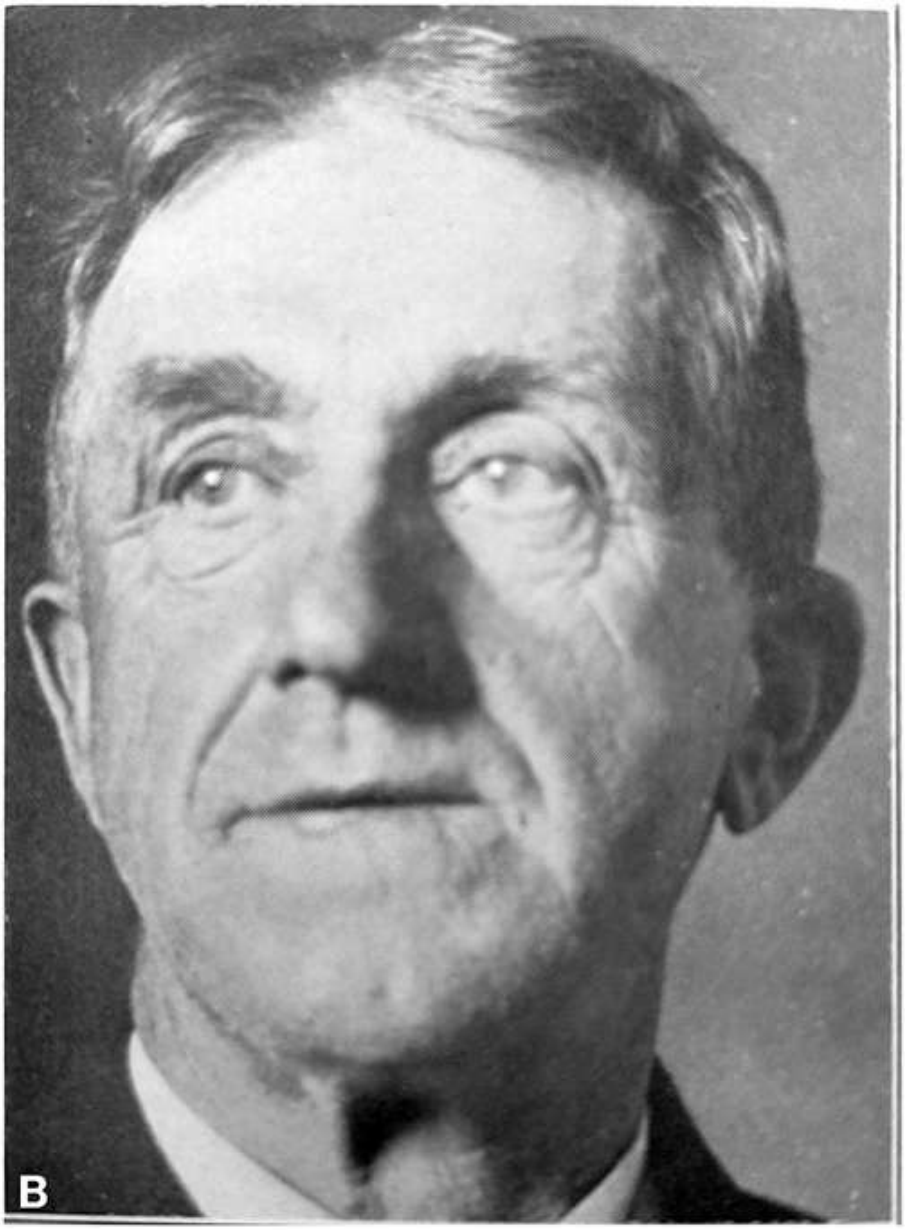
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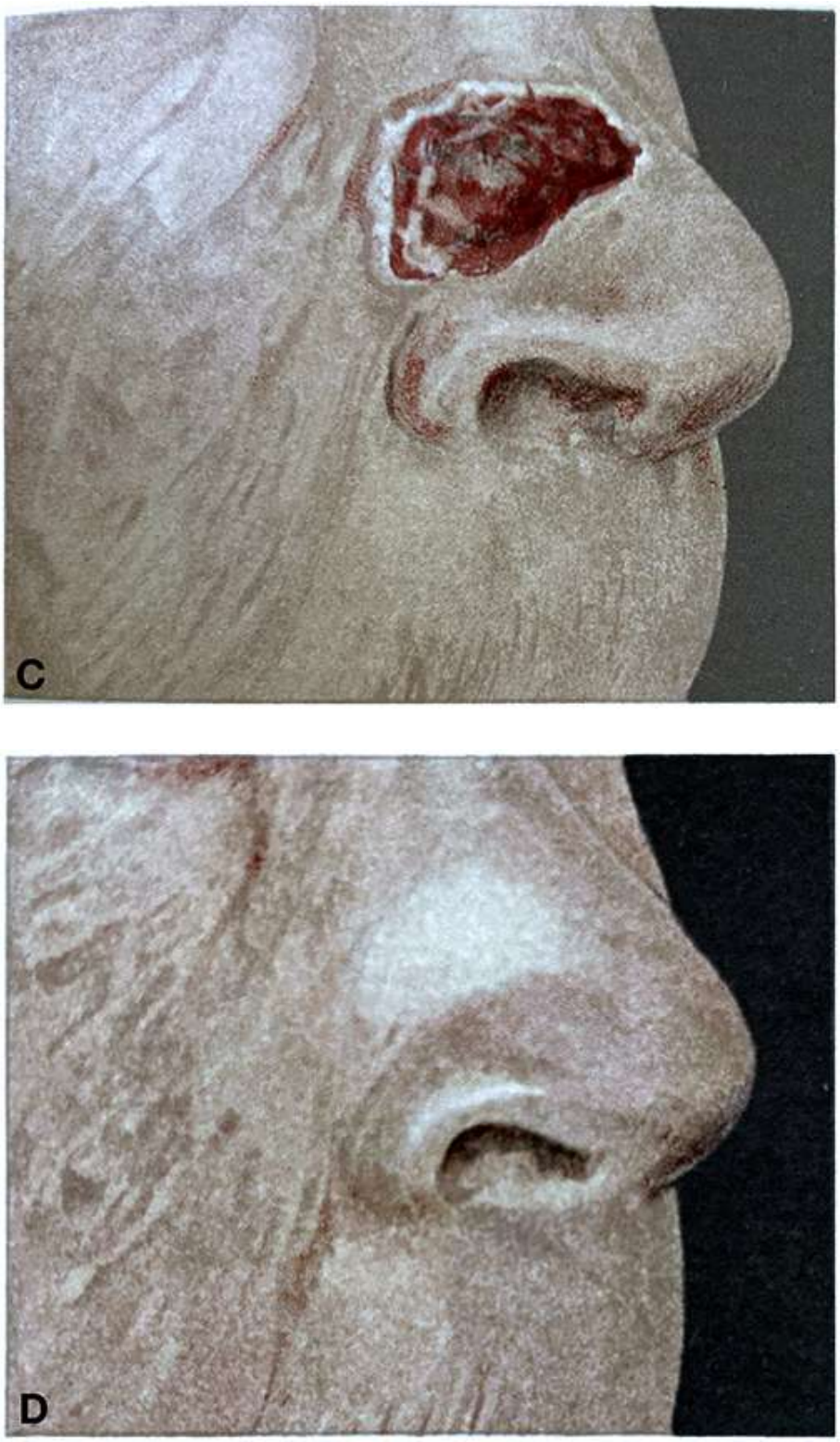

FIGURE 1.26 A and B. The pioneers of radiation therapy reported promising results. In 1918, Dr Albert F. Tyler of Nebraska reported the case of a 42-year-old male with carcinoma of the lower lip, recurrent after treatment with a caustic paste and surgery. After 19 fractions of radiotherapy administered over a 4-month period, he was alive and well 3.5 years after therapy, and “the lip is as pliable as it was before

the growth occurred" (A, B. Reproduced from Tyler AF. *Roentgenotherapy*. CV Mosby Company; 1918.) C and D. Similar dramatic results were demonstrated in 1910 with radiation therapy for a skin cancer of the nose by Dr Wickham and Degrais of Paris (C,D. Reproduced from Wickham L, Degrais P. *Radiumtherapie*. Verlag von Julius Springer; 1910.)

At the International Congress of Oncology in Paris in 1922, Coutard[201] and Hautant presented evidence that advanced laryngeal cancer could be cured without disastrous, treatment-induced sequelae. By 1934, Coutard[202] had developed a protracted, fractionated scheme that remains the basis for current radiation therapy, and, in 1933, Paterson[203] published results on the classification of tumors in relation to radiosensitivity.

The use of brachytherapy, starting with radium-226 (^{226}Ra) needles and tubes, is useful in the treatment of malignant tumors in many anatomic locations. Isotopes such as cesium, iridium-192 (^{192}Ir), iodine-125 (^{125}I), and palladium-103 (^{103}Pd) were generated from nuclear reactors, and the use of afterloading techniques, including remote afterloading devices and high dose rate (HDR) brachytherapy, has contributed to this important treatment modality. With time, ionizing radiation became more precise; high energy photons, electrons, protons, neutrons, and carbon ions became available for treatment; and treatment planning and delivery became more accurate and reproducible. Advances in computer and electronic technology fostered the development of more sophisticated treatment planning and delivery techniques, leading to the development and eventually broad implementation of 3D conformal radiation therapy (3DCRT) and IMRT.

The Planning and Conduct of a Course of Radiation Therapy

When a physician proposes administering radiation therapy to a patient, six fundamental questions must be answered. Once these questions have been answered, an appropriate first step has been taken toward the development of a comprehensive justification and plan for the conduct of a course of radiation therapy. The six questions are as follows:

1. What is the *indication* for radiation therapy?
2. What is the *goal* of radiation therapy?
3. What is the treatment *volume*?
4. What is the treatment *technique*?
5. What is the treatment *dose* and *fractionation*?
6. What is the radiation *tolerance* of surrounding normal tissues?

The *indication* for radiation therapy is that body of data that can be brought to bear showing that radiation therapy would be efficacious for the patient's condition.

Such data might exist in the form of retrospective single-institution reviews of the specific malignancy, which provide evidence favoring the role of radiotherapy. Phase I and II studies demonstrating safety and possible efficacy could be invoked to justify a course of radiation therapy. For many physicians, the gold standard, however, is a prospective, randomized, phase III trial that demonstrates the value of radiation therapy and a meta-analysis of multiple trials confirming its benefit. There remains a role for sound personal clinical experience. Although there is increasing reliance on published trials, and special deference is given to double-blind, prospective, randomized phase III trials, it is still appropriate for a physician to rely firmly on their clinical experience in the context of an intimate knowledge of the patient's problems. A sound scientific basis and an extensive knowledge of clinical research augment the essential nature of the physician-patient relationship, but they do not substitute for it.

Radiation therapy can be justified either because it improves local tumor control, ameliorates a specific symptom, improves the quality of life, or increases the probability of cure. Any data used to justify a course of radiation therapy must have a clearly defined end point, appropriate data analysis, and accepted statistical methodology. It is incumbent on the radiation oncologist to know how to critically evaluate the scientific literature and synthesize it in the best interest of the patient.

There are two possible *goals* of radiation therapy. *Curative* radiation therapy is used for the purpose of curing the patient where one is willing to engender a small risk of significant side effects in return for the possibility of cure. An example is the use of radiation therapy for the treatment of early-stage breast cancer. In return for a high probability of cure, one is willing to engender a very small risk of pneumonitis. *Palliative* radiation therapy is designed to ameliorate a specific symptom such as pain, obstruction, or bleeding (Figure 1.27). When palliative radiation therapy is used in the context of an incurable malignancy, one is not willing to engender a significant risk of side effects to achieve a palliative goal. Thus, if one wishes to relieve pain from lung cancer metastatic to a bone, one would pick a dose and technique of radiation therapy sufficient to relieve pain but not enough to run a risk of radiation osteonecrosis.

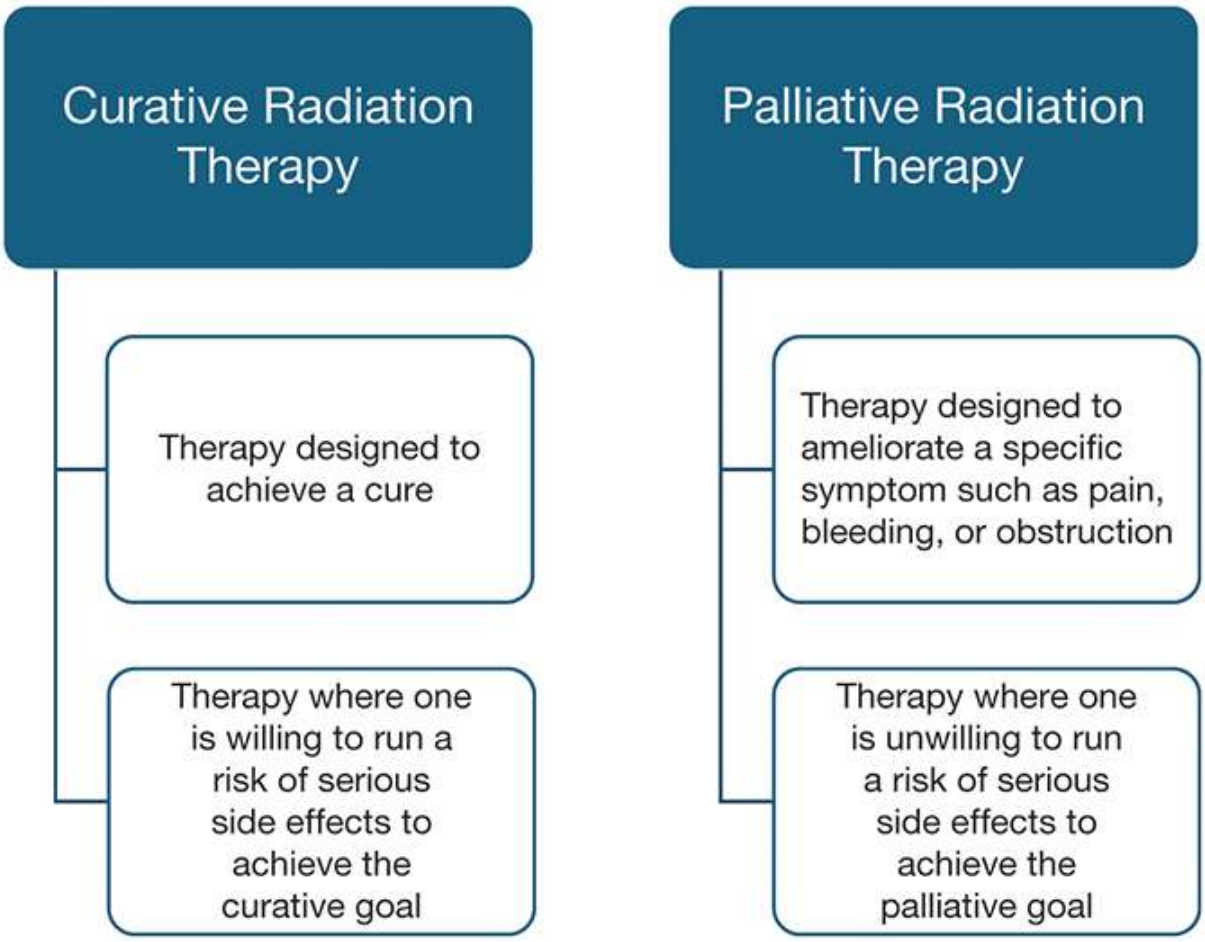

FIGURE 1.27 The *goal* of a course of radiation therapy may be *curative* or *palliative*.

The questions of *indication* and *goal* are generic. They should be answered irrespective of the modality of therapy being used for the treatment of malignancy. It is reasonable to ask for indications and goal if one is planning on using chemotherapy, surgery, cellular therapy, immunotherapy, hyperthermia, biologic therapy, or radiation therapy.

Oncologists are often better at formulating indications for curative than for palliative therapy. It is not good palliative medicine to make the patient ill from therapy in order to make asymptomatic metastatic masses smaller. In palliative cancer treatment, one must treat the patient and their symptoms and not treat the mass devoid of its context.

The next three of the six major questions, *volume*, *dose*, and *technique*, are not generic—they are specific to the discipline of radiation oncology. First, the radiation oncologist must consider *volume*. What is the appropriate volume of tissue that needs to be irradiated for the purpose of achieving the desired curative or palliative goal in the context of the justification? Does one need to treat strictly the visualized

or palpable tumor mass? Is it also appropriate to treat the mass and surrounding lymphatic drainage? Does one have to worry about the routes of spread of microscopic disease? All of these are crucial questions in formulating a plan for a course of radiation therapy. If radiation oncologists only needed to treat visible or palpable masses, then radiation oncology would be more of a physics exercise than the practice of human medicine. Understanding a cancer's routes of spread and the radiation tolerance of organs surrounding the cancer requires honed clinical judgment.

An example of the problem of volume in the radiation therapy of cancer is medulloblastoma, a tumor that arises in the posterior fossa of the human brain. If, however, one is treated with resection alone, patients almost uniformly relapse both locally and by leptomeningeal dissemination via the cerebrospinal fluid. Thus, the treatment volume for radiation therapy of medulloblastoma, in children older than 3 years, is the area within the posterior fossa wherein the tumor arises and the entire craniospinal axis. Another example of the problem of treatment volume would be in head and neck cancer. Many of these tumors, by physical examination and by diagnostic imaging, appear to be localized at their site of origin. For many of these squamous cell cancers, there is, however, a high incidence of dissemination to the lymph nodes of the neck. Thus, the appropriate radiation therapy treatment volume would include both the primary tumor site and the neck.

The next question that the radiation oncologist must face is what is the appropriate *technique*.

Radiation oncologists, in general, have two techniques at their disposal. The first, *teletherapy*, has a similar etymology to telephone, telegraph, and telepathy. It refers to the projection of radiation through space. Teletherapy is administered with external beam sources such as a cobalt-60 (^{60}Co) machine or a linear accelerator. If one elects to treat a patient with teletherapy, one must derive appropriate external beam treatment plans. These plans include considerations such as whether the patient should be treated with photons, electrons, neutrons, carbon ions, or protons; with parallel-opposed fields, four fields, or multiple oblique fields; with IMRT or IMPT; with or without respiratory gating; with or without compensators; and the like. There has been an explosion of interest in techniques of teletherapy related to improvements in sophisticated diagnostic imaging and the rapidly increasing power of computers to allow manipulation of vast amounts of data.

Brachytherapy is the other important technique of radiation therapy. The word brachytherapy shares an etymology with words such as brachycephaly and brachydactyly. It refers to short or slow therapy (ie, a radioactive implant). There are several broad categories of brachytherapy: *interstitial* brachytherapy, *intracavitary* brachytherapy, and *mold* therapy. Interstitial brachytherapy refers to the placement of radioactive sources directly into tissue. An example might be the implantation of

the tumor bed for breast cancer or soft tissue sarcoma. Intracavitary radiotherapy refers to the placement of a radioactive source in a body cavity such as sources placed within the nasopharynx or against and through the cervical os. Mold brachytherapy refers to the placement of radioactive sources on the skin surface, such as treatment utilized for a superficial malignancy on the back of the hand. If brachytherapy is used, the radiation oncologist must determine the appropriate isotope and whether that isotope is to be delivered by an afterloading technique or by a direct radioactive application (a hot implant).

Once the radiation oncologist has determined the appropriate treatment volume and the treatment technique(s), they must determine the appropriate radiation *dose*. Radiation dose selection is a complex issue. One must determine the correct number of *fractions* of radiation per day, the correct dose per fraction, and the proposed total dose of irradiation. Furthermore, in certain situations, the dose rate (ie, the number of cGy per minute) matters, such as in total-body irradiation (TBI) for bone marrow transplantation and in brachytherapy. FLASH radiotherapy (FLASHRT) uses ultra HDRs. Decisions concerning dose will, in part, be driven by decisions concerning treatment volume and technique. Paramount in the physician's mind will be the goal of treatment. The physician must determine what the correct dose is to achieve the proposed curative or palliative goal. In broad terms, the radiation oncologist must consider what is known about the dose-response relationship for tumor control in a particular clinical situation. This subject, addressed in detail earlier in this chapter, concerns the probability of tumor control within a radiation therapy field as a function of the dose administered.

Finally, the radiation oncologist must consider normal tissue *tolerance*. In general terms, the probability of acute and late ill effects of radiation is a function of total dose and dose per fraction. Ultimately, the prescription of a dose requires the radiation oncologist to engage in a balancing act between a sufficient dose of radiation to achieve the desired treatment goal and not giving so much dose as to engender an unacceptable risk of side effects.

The fundamental questions of radiation therapy are not for the physician alone. A patient has the right to be apprised of the physician's views on these questions, probability of tumor control (and cure, if possible), and sequelae. This information should be presented to the patient in an appropriate intellectual, social, and cultural context (ie, in a manner in which the patient can understand) and translated skillfully into the patient's preferred language if necessary so that the patient becomes a full partner in their care. The signing of an informed consent document by the patient is the norm, but a signed document does not substitute for a proper doctor-patient conversation.

TREATMENT PLANNING IN RADIATION THERAPY

Treatment Volume

Tumor cell killing by ionizing radiation is an exponential function of dose. The dose required for a certain level of TCP (or local control) is proportional to the logarithm of the number of clonogenic cells in the tumor. Subclinical extensions of tumor (also called microscopic disease or disease below the level of ready clinical detection) should be controlled, in general, by a lower dose of radiation than is required for a palpable tumor mass. Microscopic tumor extensions may be less likely than bulky tumors to contain hypoxic cells. This also means that they may be more readily controlled by radiation.

Insofar as the dose tolerated by normal tissue is inversely related to the volume of normal tissue irradiated, delivering a uniform physical dose of radiation requires that one choose between the risks of marginal recurrence around small volumes of high dose, central recurrences in large volumes of low dose, or excessive normal tissue damage and large volumes of high dose. We may conclude that different doses of radiation are required for a given probability of tumor control, depending on the type and initial number of clonogenic cells present.

A shrinking-field technique is a rational approach to the problem of heterogeneous tumor distribution (Figure 1.28). Withers and Taylor[204] have argued that "in the ideal case, the doses would be graded to provide a homogeneous TCP throughout the treatment volume rather than a homogeneous physical dose distribution." We are entering an era of "dose painting" where a heterogeneous dose will be layered on a tumor as determined by sophisticated imaging tools.[205] The radiation oncologist delivers varying radiation doses to certain portions of the tumor (periphery vs central portion or metabolically active vs inactive on computed tomography [CT]/PET) or may vary the dose in cases in which gross tumor has been surgically removed.

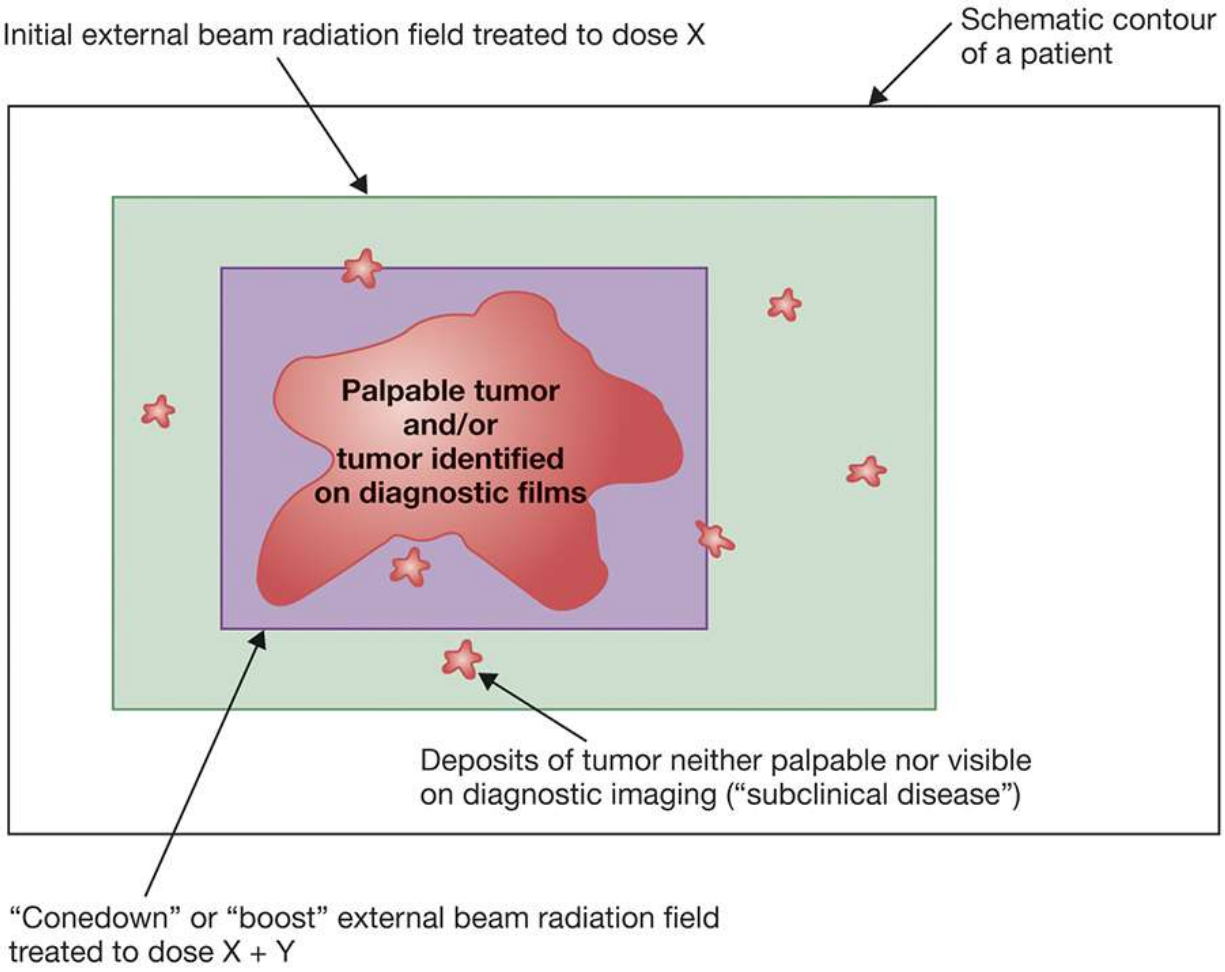

FIGURE 1.28 Cell killing by ionizing radiation is an exponential function of dose. It follows that the dose required for a certain level of tumor control probability (TCP) is directly proportional to the logarithm of the number of clonogenic cells in the tumor deposit. It would be reasonable to expect that subclinical extensions of disease could be controlled by a lower dose of irradiation than what is required for a bulky palpable tumor mass. It has been argued by some researchers that microscopic tumor extensions are less likely to contain hypoxic foci that will minimize the requirement for reoxygenation for their control—but this is controversial. Insofar as the dose tolerated by a tissue is inversely related to the volume of tissue irradiated, delivering a uniform physical dose requires that one choose between the risk of marginal recurrences around small volumes of high dose, central occurrences in large volumes of low dose, or excessive normal tissue damage in large volumes of high dose. A reasonable approach is to use a shrinking-field technique in which one delivers an initial external beam field that is treated to dose X and then "cones down" to a smaller field to treat to dose X + Y. In the ideal case, doses are graded to provide a homogeneous TCP throughout the treatment volume rather than a homogeneous physical dose distribution. (Based on a concept articulated by Withers HR, Peters LJ. Biologic aspects of radiotherapy. In: Fletcher GH, ed. *Textbook of Radiotherapy*. 3rd ed. Lea & Febiger; 1980:142.)

The International Commission on Radiation Units and Measurements (ICRU) Report 50 has recommended definitions of terms and concepts for radiation therapy treatment volumes and margins[206]:

- The gross tumor volume (GTV) denotes demonstrable tumor. It includes all known gross disease including abnormally enlarged regional lymph nodes. In the determination of GTV, it is important to use the appropriate imaging modality and physical examination to give the maximum dimension of what is considered potential gross disease.
- The clinical target volume (CTV) denotes the GTV and subclinical disease (ie, volumes of tissue with suspected tumor).
- The planning target volume (PTV) denotes the CTV and includes margins for geometric uncertainties. One also should account for variation in treatment setup and other anatomic motion during treatment, such as respiration.

Because the PTV does not account for treatment machine characteristics, the actual treated volume is that volume enclosed by an isodose surface that is selected and specified by the radiation oncologist as being appropriate to achieve the goal of treatment. It is impossible to design a radiation therapy treatment plan that limits the prescribed dose to the PTV only. Some tissues en route to the target or near the target also will be irradiated to the same dose as the target. The treated volume is, therefore, almost always larger than the PTV and usually has a somewhat simpler shape.

- The irradiated volume is that volume of tissue that receives a dose considered significant in relationship to tissue tolerance. This would include tissues in the exit region of unopposed photon, electron, or neutron beams or in the penumbra region of a beam.
- The planning organ at risk (OAR) volume refers to the definition of margins around OARs for injury by radiation. For example, one might define a 0.5-cm margin around the optic chiasm to avoid the risk of blindness.

Uncertainties

There are, inevitably, uncertainties in the planning and delivery of a course of radiation therapy. These were well characterized by the esteemed dosimetrist Gunilla Bentel[207,208] (1936-2000), to whom I am grateful for the following discussion. Ms. Bentel's biography will be found near the end of the chapter.

Uncertainties are divided into two general categories. First, there are uncertainties related to the delivery of dose, such as inhomogeneities in the beam, problems related to dose calculations, variables in the output of treatment machines, instability of the beam monitoring technique, and problems related to beam flatness. Spatial uncertainties in the delivery of radiation therapy may be divided into those related to mechanical inaccuracies in the equipment and those related to the patient.

Mechanical Uncertainties

- *Field-size settings*. There can be errors related either to mechanical dials or to digital settings in which the field-size set on the machine is not precisely the same as that delivered.
- *Rotational settings*. Mechanical or digital settings that display the degree of angulation of the gantry or the collimator may be in error.
- *Cross hairs*. Wires in the linear accelerator designed to show the central axis or the field edges may become displaced.
- *Isocenter*. Deviations in the position of the isocenter may occur as a result of sagging of the gantry head.
- *Light beam congruence*. The light beam within the treatment machine may be in error. These misalignments may be caused by small shifts in the mirror or the light bulb.
- *Alignment systems*. The laser beam systems used for alignment may be in error.[209] They may not intersect exactly at the isocenter, they may not be perpendicular, and some systems may display relatively thick lines allowing for errors in judgment.
- *Couch top*. There can be differences in sag between radiation treatment couches. In addition, there may be differences in sag between the simulator couch, the CT couch used for 3D or IMRT planning, and the accelerator couch. Sometimes, in the treatment room, a tennis racket–type insert is used. Over time, couch tops can become tilted from side to side or from end to end.
- *Beam-shaping blocks or collimators*. At institutions that are still using blocks rather than a multileaf collimator (MLC), there may be errors in constructing the blocks related to user error or because the cutting wire becomes too hot or is moved too fast around a corner when the Styrofoam mold is cut. If MLCs are used, there may be errors in alignment.

Patient-Related Uncertainties

- *Target delineation*. No matter how sophisticated the computerized treatment planning system, it will be to no avail if the physician is uncertain about where the tumor is located. The inherent problems related to PET, MRI, CT, and our ability to make correlations between anatomic and functional imaging and the location of tumor may result in difficulty determining the extent of tumor as well as in transferring anatomic information from imaging studies to the 3D or IMRT treatment planning system.

- *Organ motion*. Organ motion can occur from respiration, heartbeat, or changes in the size or shape of an organ as a function of digestive or excretory function (ie, changes in the size and position of the stomach, intestines, bladder, and rectum and, in the last case, its influence on prostate position).
- *Skin marks or marks on a stabilization device*. Skin marks can shift relative to deeper tissues. This can change as a result of alterations in patient weight, patient positioning, or the use of steroids during a course of radiation therapy. A particular problem is related to the width of setup lines drawn by therapists on the patient's skin. The thickness of the point of the marking pen used can produce variation in the width of the lines drawn. When this is accompanied by variation in the position of the light fields in relationship to the lines, it can cause uncertainty in treatment delivery. Marks drawn on a stabilization device may cease to match deeper tissues.
- *Repositioning*. Day-to-day problems in reproducing the position may occur.
- *Patient motion*. Some patients simply will not hold still during radiation therapy. Whether this is related to the patient being anxious, in pain, demented, or subject to a neurologic disorder, it can lead to uncertainties in radiation therapy treatment delivery.

Immobilization and Spacing

The magnitude of uncertainties in radiation therapy treatment delivery varies. Furthermore, some uncertainties may be additive and some may cancel each other out. The net effect, on any given day, can be quite variable.

To irradiate a tumor while minimizing the radiation dose to uninvolved normal tissue, control of patient movement must be precise and absolute. Sophisticated tumor localization, 3D treatment planning, radiosurgery, and/or IMRT or IMPT will be of no use if the patient is not holding still. Often, positioning and mobilization can be the weakest link in the chain of treatment planning.[210] Quality radiotherapy demands that a daily setup accuracy of a few millimeters be ensured.

Mechanical immobilization of the awake radiotherapy patient is an adjunct to patient education and psychological preparation of the patient. Although not a substitute for education and psychological preparation, mechanical aids can greatly facilitate accurate treatment. The ideal mechanical aid for patient positioning will achieve the following goals[211]:

1. The patient must be comfortable and secure. There must be no danger of falling. The patient should not become claustrophobic.
2. The device must satisfy the radiotherapy treatment plan regarding patient position for correct geographic irradiation.

3. The setup should be quick and easy for the radiation therapist.
4. The body part treated should be rendered immobile.
5. Position of the body part should be reproducible for daily treatment.
6. Construction of the device should be reasonably quick. It should not be difficult to train therapists, dosimetrists, and physicians in the construction procedure.
7. The stabilization device should not adversely affect beam buildup and backscatter characteristics.
8. This system should be economical.
9. If anesthesia is being used, the device must not interfere with the establishment of a secure airway, intravenous access, or the use of monitoring equipment.

A variety of immobilization devices meet these stated criteria to varying degrees. There is no perfect system. Techniques will vary among institutions. It is reasonable to expect, however, that the radiation oncologist should be knowledgeable in several techniques that can be brought to bear as the situation demands.

There are a variety of stabilization devices. These include commercially available accessories such as plastic headholders and sponges; bite blocks; thermoplastics; plaster of Paris; vacuum-molded thermoplastics; polyurethane foams; vacuum bags; intrarectal balloons to stabilize the prostate and rectal wall during prostate radiotherapy or injectable absorbable material, respiratory-gated radiotherapy, and therapy while breath holding to minimize respiratory excursion; and mechanical devices to compensate for patient movement by compensatory couch movement, collimator leaf movement, or robotic arms to move the linear accelerator.

Accuracy of external beam placement was typically assessed periodically with portal (localization) films. It is now far more common to use online imaging verification (electronic portal imaging) devices or online CT, fluoroscopy CT/PET, MRI, or ultrasound.[212,213] Portal localization errors may be systematic or occur at random. Online electronic portal imaging has been used to document inter- or intratreatment portal displacement.

Clinical evidence supports the benefit of stabilization devices in reducing patient motion. Marks et al[214,215] demonstrated, by systematic use of verification films, a high frequency of localization errors in patients irradiated for head and neck cancer or malignant lymphomas. These errors were corrected with improved patient immobilization; with the use of a bite block in patients with head and neck tumors, localization errors were reduced from 16% to 1%[49] (Table 1.6). The use of 3DCRT and IMRT, as well as the emphasis on stereotactic body radiosurgery, has led to several excellent contributions to the literature assessing the value of stabilization devices. Such devices are particularly important in the treatment of lung, liver, and paraspinal tumors. Often, these devices include a combination of a thermoplastic

body cast, vacuum pillow, arm and leg support, wooden backing and/or sides, or a carbon plate. It has been demonstrated that such devices can achieve setup errors and deviations in the 1- to 3-mm range.[216,217] Some institutions rely on vacuum-molded plastic shells. These devices, similarly, will achieve displacements on the order of 1 to 3 mm.[218]

TABLE 1.6 THE IMPACT OF STABILIZATION DEVICES ON EXTERNAL BEAM SETUP REPRODUCIBILITY

	Number of Position Adjustments per Number of Times Tested (%)	*P*
Hodgkin disease (*n* = 56)[a]		
Short cradle stabilization device	48/237 (20)	.009
Whole-torso cradle stabilization device	21/213 (10)	—
Head and neck cancer (*n* = 71)[b]		
Three casting strip stabilization device	55/307 (18)	.23
Customized mask device	40/291 (14)	—
Lung cancer (*n* = 60)[c]		
No stabilization device	17/119 (14)	.139
Cradle	14/171 (8)	—

[a]Bentel GC, Marks LB, Krishnamurthy R, et al. Comparison of two repositioning devices used during radiation therapy for Hodgkin's disease. *Int J Radiat Oncol Biol Phys.* 1997;38(4):791-795.

[b]Bentel GC, Marks LB, Hendren K, et al. Comparison of two head and neck immobilization systems. *Int J Radiat Oncol Biol Phys*. 1997;38(4):867-873.

[c]Bentel GC, Marks LB, Krishnamurthy R. Impact of cradle immobilization on setup reproducibility during external beam radiation therapy for lung cancer. *Int J Radiat Oncol Biol Phys*. 1997;38(4):527-531.

In a randomized trial from the Karolinska University Hospital in Stockholm, Sweden, patients with head and neck cancer were randomly assigned to be stabilized with a thermoplastic head mask or a thermoplastic head and shoulder mask. Reproducibility was assessed by comparing port films in these 3D planned patients with simulator films. This was done twice during treatment and by comparing the actual treatment table positions weekly. Patient tolerance and skin reactions were also assessed. A total of 241 patients were evaluated. There were no statistically significant differences between the head mask stabilization device or the head and shoulder mask stabilization device in terms of reproducibility. It was of note, however, that patients with the thermoplastic mask extending over the head and

shoulders experienced significantly more claustrophobic reactions and greater skin reactions. This study has been criticized for its reliance on thermoplastic devices rather than the vacuum-formed clear polyethylene masks.[219]

Because different stabilization devices are utilized in different clinical situations, there is no simple way to know which is the best stabilization device. An excellent comparative study done at the Northeast Proton Therapy Center analyzed the length for which there is a 95% probability that the total displacement will be smaller as a result of intrafractional patient motion. It is reasonable to expect that customized closely fitting molds should achieve intrafractional stabilization of 2 to 7 mm, with the best stabilization being obtained in precision treatment of the brain utilizing a rigid halo and bite block (Table 1.7).[220]

TABLE 1.7 INTRAFRACTIONAL PATIENT MOTION AS A FUNCTION OF THE IMMOBILIZATION DEVICE

Immobilization Device	Patient Motion (mm)
Alpha cradle	5.0
Beanbag	6.8
Head Aquaplast	3.6
Duncan headrest	7.0
Modified Gill-Thomas-Cosman frame	1.8
Prone craniospinal head support	3.0
Head Aquaplast with bite block	2.9
Wing board	5.9

Based on an analysis of >10,000 fields, there is a 95% chance that the change in patient position between the initial patient setup and the position before the next treatment field setup will be less than the measurement shown.

Modified from Engelsman M, Rosenthal SJ, Michaud SL, et al. Intra and interfractional patient motion for a variety of immobilization devices. *Med Phys*. 2005;32(11):3468-3474. Copyright © 2005 American Association of Physicists in Medicine. Reprinted by permission of John Wiley & Sons, Inc.

We may expect further benefits from research on stabilization. For example, injectable material in the rectal wall has been shown to decrease reduce the risk of rectal injury during prostate radiotherapy.

The best radio protector of normal tissue is not to irradiate it. An intraoral bite block can be fabricated by a dentist with dental mold material, or with mold material or a bottle cork and tongue depressors in the radiation oncology department. However, it is made, the goal is to push the tongue away from a prepared radiation beam above it. During intraoperative radiotherapy in the abdomen, packing may be used to push normal tissue away from the radiotherapy beam.

Respiratory-Dampened, Respiratory-Gated, and Respiration-Synchronized Radiotherapy

The movement associated with respiration affects the position of multiple organs. If the radiation oncologist wishes to administer highly conformal fractionated or single-fraction treatment(s) to tumors of the liver, lung, pancreas, kidney, retroperitoneum, thoracic wall, mediastinal region, and adjacent structures, it will be necessary to either account for respiration-induced movement by putting a larger margin around the tumor or use an intervention to reduce this movement (Table 1.8).

TABLE 1.8 AVERAGE DIAPHRAGM MOTION DURING ACTIVE BREATHING CONTROL (ABC) (MEAN, RANGE)

By Fluoroscopy at Simulation	By Fluoroscopy During Treatment	Beam's-Eye View During Treatment
1.4 mm (0-3.4 mm)	1.2 mm (0.4-2.5 mm)	0.5 mm (0-4.2 mm)

From Dawson LA, Brock KK, Kazanjian S, et al. The reproducibility of organ position using active breathing control (ABC) during liver radiotherapy. *Int J Rad Oncol Biol Phys*. 2001;51:1410-1421; Eccles C, Brock KK, Bissonnette JP, Hawkins M, Dawson LA. Reproducibility of liver position using active breathing coordinates for liver cancer radiotherapy. *Int J Rad Oncol Biol Phys*. 2006; 64(3):751-759; and Wang JW, Sharpe MB, Jaffray DA, et al. The use of active breathing control (ABC) to reduce margin for breathing motion. *Int J Rad Oncol Biol Phys*. 1999;44:911-919.

One method for limiting respiratory motion during radiotherapy is the *abdominal compression method*. This involves placing a plate or some other restrictive device above or around the abdomen and chest, sometimes in association with supplemental oxygen, in an effort to minimize the amount of diaphragmatic motion during radiotherapy.[221,222] This is also referred to as *respiratory-dampened radiotherapy*.[223] Many patients can be trained to modify their respiratory excursion by use of feedback by showing their respiration graphed on a video screen. Another technique involves general anesthesia and high-frequency jet ventilation to minimize diaphragm motion during liver radiosurgery.[224]

Respiratory-gated radiotherapy involves turning the beam on only during portions of the respiratory cycle. Some techniques call for the patient to hold their breath during the irradiation.[225]

THE QUANTITATION OF TREATMENT TOXICITY

Normal Tissue Effects

A variety of normal tissue changes are induced by ionizing radiation, depending on the total dose, fractionation schedule (daily dose and overall treatment time), and volume treated. These factors are closely interrelated. We discussed the work of Hermann Holthusen (1886-1971) earlier in this chapter. He created a diagram, which

represented the hoped-for relationship between radiation dose and tumor control and radiation dose and normal tissue injury. Holthusen "maintained that the margin of safety between effective tumor dose and safe tissue tolerance was dependent on volume of tissue irradiated and fractionation of the total dose . . . tolerance could be increased by fractionation."[226,227]

It has been postulated that for many normal tissues, the radiation dose necessary to produce a particular sequela increases as the irradiated fraction of volume of the organ decreases. This concept was demonstrated for skin by Paterson,[228] who plotted doses delivered with orthovoltage x-rays that would produce moist desquamation (Figure 1.29). The same phenomenon later was reported for supervoltage irradiation of other organs[229] and for brachytherapy (Figure 1.30).

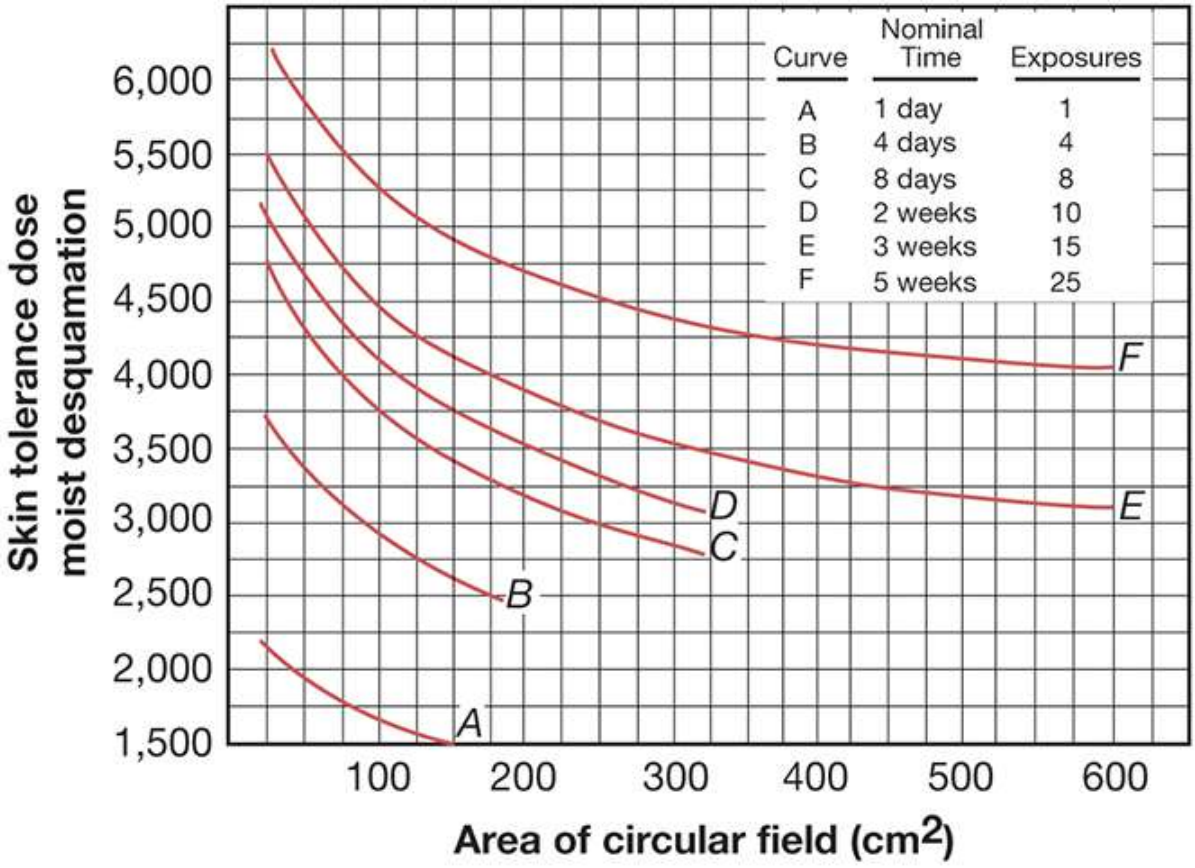

FIGURE 1.29 Graph showing the relationship between dose and size of area irradiated (healthy skin in an "average" site) to produce moist desquamation for various overall treatment times (daily irradiation at about 50 R/min for each exposure with radiation of half-value layer 1.5 mm Cu). (Reprinted with permission from Paterson R. *The Treatment of Malignant Disease by Radium and X-rays*. Williams & Wilkins; 1949:39.)

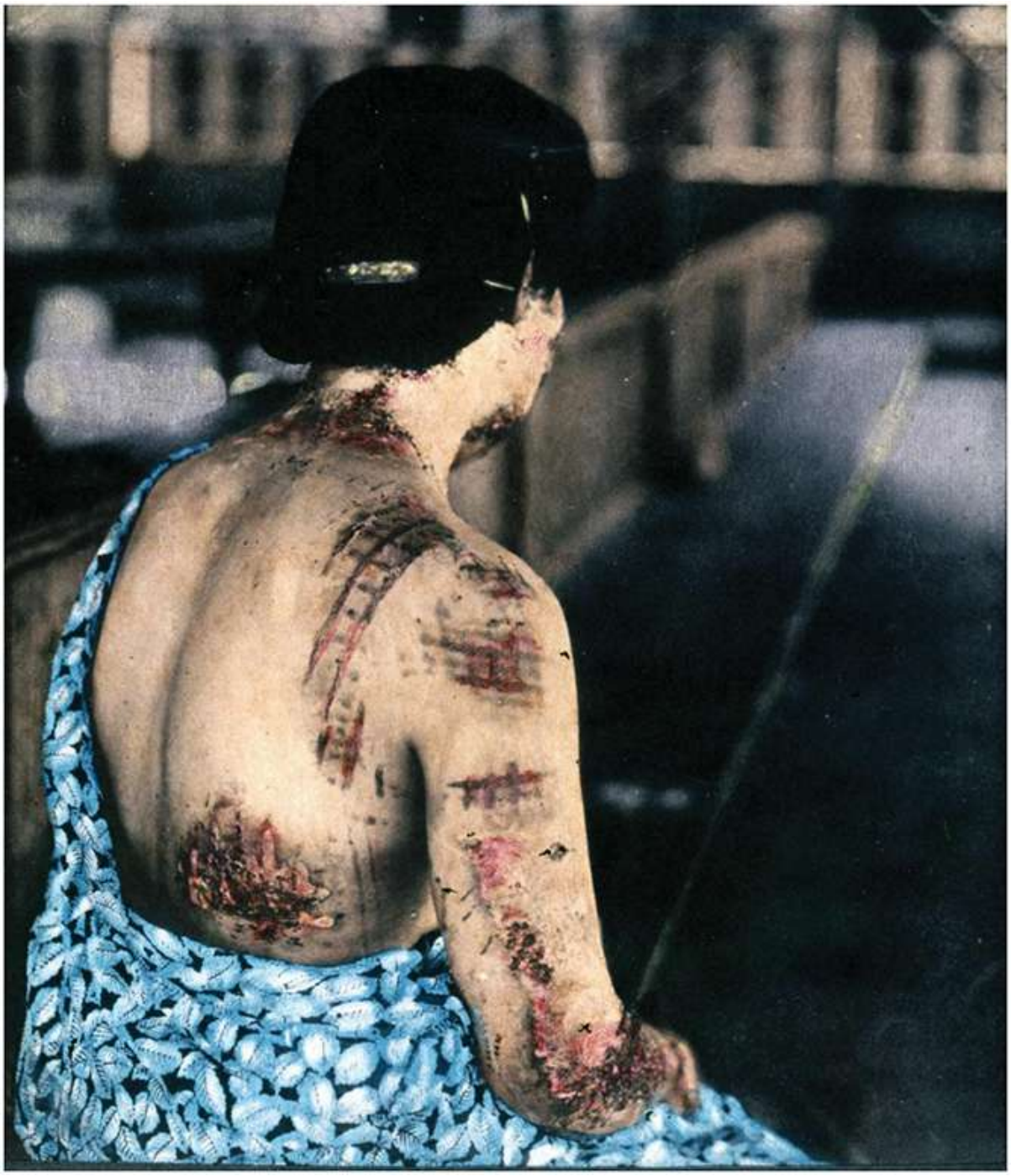

FIGURE 1.30 The Joint Commission for the Investigation of Effects of the Atomic Bomb in Japan issued detailed reports of their findings. This illustration demonstrates acute injury from the thermal effects of the blast. The victim's skin was burned in a pattern produced by the colors in her kimono. The darker colors more readily absorbed the heat of the thermal blast and burned the skin more than the lighter colors. The photograph was taken about nine days after the bombing of Hiroshima. (National Archives and Records Administration.)

Higher tolerance doses (TDs) than initially reported have been observed for a variety of organs,[230-234] as a result of conformal irradiation. This stresses the importance of updating tolerance information in light of more precise treatment planning and delivery of irradiation and more accurate evaluation and recording of sequelae. Examples are radiation dose escalation studies using CRT delivery techniques.

In studying late radiation effects, it is useful to think of organs, which are made up of multiple functional subunits (FSUs) that are arranged serially or in parallel.[235,236] For serially structured organs, such as gastrointestinal tract or spinal cord, damage to one portion of the organ may render the entire organ dysfunctional. In contrast, in organs with parallel structure, like a kidney, FSU damage may not impair the entire organ function because the remaining FSUs operate independently from the damaged group, and clinical injury occurs only when a critical volume of the organ (or proportion of FSUs) is damaged and the surviving FSUs are unable to maintain organ function. Therefore, the sensitivity of an organ depends on the number of FSUs. Marks and others[237,238] have discussed the importance of organ structure in determining late radiation effects and pointed out that conventional dose-volume histograms (DVHs) and NTCP models are frequently inadequate because they ignore functional and structural heterogeneities. Such considerations will be particularly important for partial irradiation of the lung, liver, and kidney to doses that approach the tolerance of the organs' functional units. Variations in FSUs and functional reserve in a patient population may produce NTCP dose-response curves, the widths of which are comparable with those observed clinically.[239,240]

Structural alterations without anatomic or functional impairment may be noted, whereas in other instances, substantial injuries with tissue destruction, severe dysfunction, or even death may occur. Normal tissues have a substantial capacity to recover from sublethal or PLD induced by radiation (at tolerable dose levels). Injury to normal tissues may be caused by the radiation effect on the microvasculature or the support tissues (stromal or parenchymal cells).

Rubin et al[241-243] indicated the usefulness of assigning a certain percentage of risk of complication, depending on the dose of the radiation. The minimal TD is defined as $TD_{5/5}$, which represents the dose of radiation that could cause no more than a 5% severe complication rate within 5 years after treatment. (Some authors use the equivalent terms "tissue tolerance dose," or $TTD_{5/5}$. Both the $TD_{5/5}$ and the $TTD_{5/5}$ are based on treatment at 2 Gy per fraction, five fractions per week.) A complication risk rate for severe injury of 5% in most curative clinical situations is generally viewed as acceptable. Moderate sequelae are noted in varying proportions (10%-25% of patients), depending on the dose of irradiation given and the OARs.

Chronologically, the effects of irradiation are subdivided into acute (first 3 months) and late effects (>3 months after irradiation), according to the NCI Common Toxicity Criteria. The gross manifestations depend on the kinetic properties of the cells (slow or rapid renewal) and the total radiation dose given.[244]

Early applications of time-dose considerations were applied by Baclesse[245,246] based on observations by Coutard[247] that various degrees of mucositis and moist desquamation were repaired by reepithelialization of the mucosa and skin from the periphery of the irradiated field and from cells surviving in the center of the field. Protracted fractionation schedules for carcinoma of the breast with lower daily doses over 10 to 12 weeks were successful in avoiding acute moist desquamation,[248] but the higher radiation doses caused severe tissue damage in a large number of patients.[249]

No correlation has been established between the incidence and severity of acute reactions and the occurrence of late effects. Withers et al[250] compiled data depicting isoeffect lines for acute or late effects in several organs. The slopes for late reactions were steeper than for acute effects, and there was a lack of correlation between the doses producing similar severities of acute or late effects.[251,252] This may result from the difference in the slopes of cell survival curves for acute or late-reacting.[253]

Combining irradiation with surgery or cytotoxic drugs frequently modifies the tolerance of normal tissues to a given dose of irradiation, which may necessitate adjustments in treatment planning and dose prescription. The lack of correlation between acute and late-reacting tissues represents one rationale for combining radiotherapy with chemotherapy.

There is a critical need to accurately assess and record the morbidity of treatment because this, in addition to therapeutic efficacy, is a crucial parameter in the evaluation of new regimens and the selection of therapy for an individual patient. Multiple schemata have been developed, although a complete consensus has not been reached as to ideal grading scores. Toxicity grading systems for various organs were developed by RTOG and the European Organisation for Research and Treatment of Cancer (EORTC). Overgaard and Bartelink[254] stressed the importance of proper recording of morbidity in clinical radiation oncology, with quantification of the normal tissue effects and description of the treatment-related factors correlating with morbidity.

The evolution of radiation treatment planning and delivery, with innovative techniques (3DCRT, IMRT, IMPT image-guided radiation therapy, image-guided brachytherapy) allowing for better definition of target and sensitive structure volumes and more precise quantitation of dose, has introduced more complexity into the evaluation of radiation effects on OARs.[255] Journal articles and books have been devoted to the “Quantitative Analysis of Normal Tissue Effects in the Clinic” (QUANTEC), which provided an updated review of knowledge in this area and

practical guidance on toxicity risks and attempted to identify future research to elucidate radiation effects in normal tissues and organs. The QUANTEC program has continued its efforts and is reviewed in Chapter 12.

ADVERSE NORMAL TISSUE EFFECTS OF RADIATION THERAPY

The Pathology and Pathophysiology of Radiation Fibrosis in Normal Tissue Uninvolved With Tumor

We are in debt to the pathologist Shields Warren (1898-1980) of the New England Deaconess Hospital and New England Baptist Hospital for meticulous and detailed descriptions of the pathology of ionizing radiation, particularly from the atomic bombings of Japan (Figures 1.30-1.32). He described the light microscopic appearance of late radiation fibrosis of the subcutaneous tissues. In heavily irradiated tissues the fibrocytes become functionally and structurally abnormal. The elastic tissue may increase while losing its fine lamellar arrangements. Sometimes irradiated elastic tissue degenerates. Collagen increases "and loses its fibrillar structure, becoming hyalinized." With high doses of radiation "necrosis of collagen will occur. A number of fibrocytes become large and irregular with giant and distorted nuclei resembling those seen in tumor giant cells, although not in themselves neoplastic."[256]

FIGURE 1.31 Total-body irradiation from a nuclear explosion will cause injuries, which have been categorized as the CNS syndrome, GI syndrome, and bone marrow syndrome. The physical manifestations of total-body irradiation exposure on the hair, gastrointestinal tract, and bone marrow are illustrated in this photograph. This 21-year-old soldier was in a wooden house within 1 kilometer of the hypocenter of the Hiroshima explosion. He suffered lacerations on his back and abdomen from the explosion. Twelve days after the blast his hair fell out. Twenty-three days after the blast his gums bled. Purple subcutaneous hemorrhage spots appeared and 25 days after the blast he developed a fever. This was followed by throat pain, which prevented him from drinking. Continuous gum bleeding began. Purple spots spread over the face and upper body. He lost consciousness 27 days after the blast and died on the 28th day after the blast. (National Archives and Records Administration.)

A

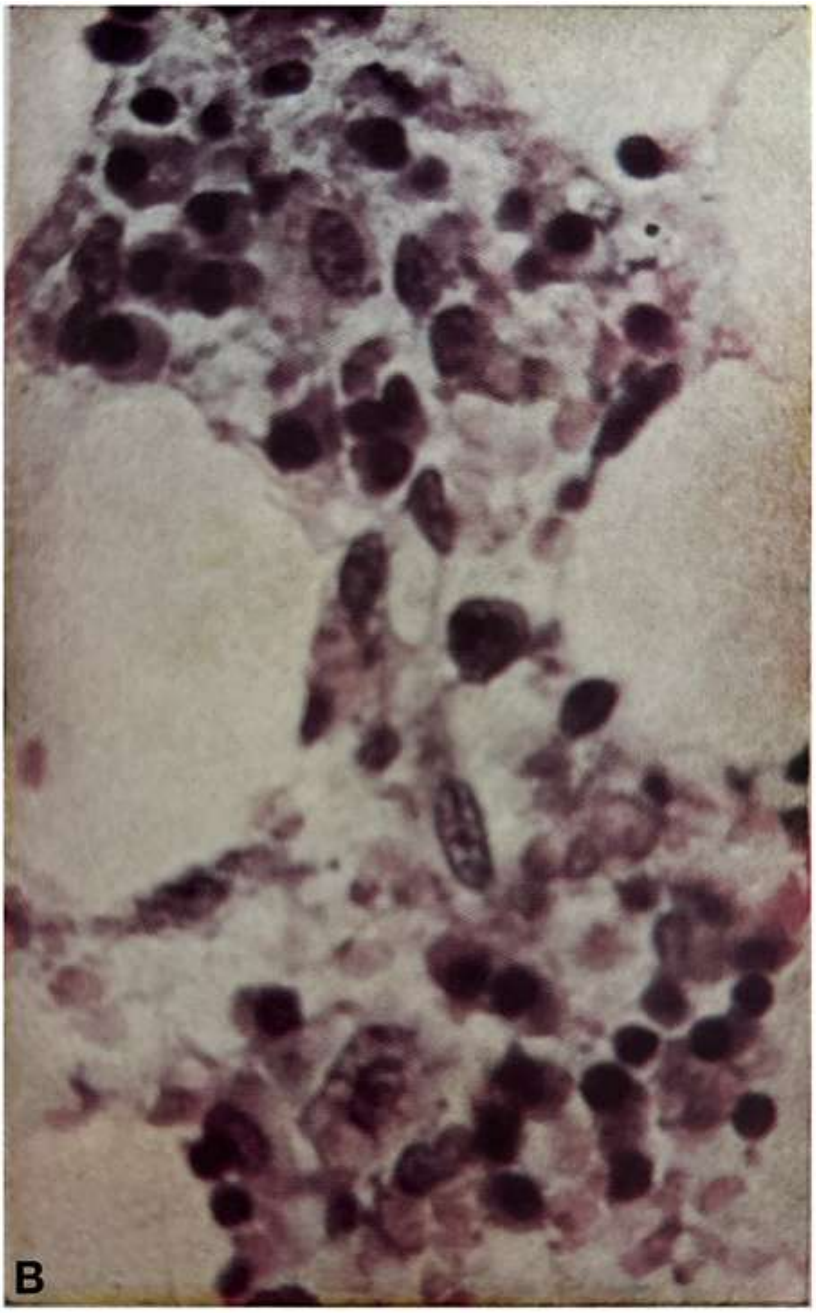

FIGURE 1.32 A 39-year-old male died 6 days after the atomic bombing. He was about 1,000 years from the hypocenter. A. The femur has red gelatinous and gray-red cellular marrow in the upper portion of the shaft but only gelatinous and yellow fatly marrow distally. B. In the microscopic image, there is no normal hematopoietic tissue. There are reticulum cells, plasmacytoid elements, and some large intermediate cells between the two. There is reticulum cell erythrophagocytosis (650×). (Reproduced, with permission from Oughterson AW, Warren S. *Medical Effects of the Atomic in Japan*. McGraw-Hill; 1956.)

With our modern understanding of molecular and cellular biology, we may characterize the development of late radiation injury to normal tissue as a process

launched by the direct and indirect damage of DNA through the generation of reactive oxygen species and free radicals. In normal tissue, what follows is a cascade of chemical signals and cellular responses that produce radiation fibrosis[257], including:

- Radiation induces inflammatory, epithelial, and mesenchymal cells to secrete TGF-β. In response to TGF-β, fibroblasts convert into matrix-synthesizing myofibroblasts. The myofibroblasts secrete collagen, proteoglycans, and fibronectin. This results in avascularity of tissues and their thickening, stiffness, scarring, atrophy, and loss of function. The effects of TGF-β are widespread. Matrix metalloproteinases 2 and 9 are downregulated, while fibroblast growth factor, tumor necrosis factor, EGF, and interleukin-1 are upregulated.
- Radiation damages the vascular endothelium. Platelet aggregation and coagulation occur, and vessels are narrowed or obliterated. Normal tissue hypoxia ensues.
- Radiation causes activation of the Janus kinase and signal transducer and transcription proteins along with nuclear factor κ light-chain enhancer of activated B-cell pathways. As a result, pro-inflammatory cytokines and growth factors are released.[258]

Radiation-Induced Second Primary Malignant Tumors

Patients cured of cancer have a significant probability of developing other cancers. Many publications have documented the frequency of second malignant neoplasms, associated with radiation therapy, in cancer survivors.[250] Several principles characterize radiation-induced cancers:

1. A wide variety of histologic types of cancers can be induced by radiation therapy. The current state of knowledge does not allow us to distinguish these tumors, morphologically, from "naturally" occurring cancers. In the future, it may be possible to identify specific genetic changes associated with radiation-induced malignancy. This future technology, termed *molecular forensics*, may, ultimately, affect our understanding of attributable risk of radiation-induced malignancies.[259,260]
2. The dose incidence curve for carcinogenesis generally rises more steeply with high LET radiation doses than with low LET doses, especially at LDRs (Figure 1.33).[253] In a liver cancer model in mice, neutron irradiation produces a greater incidence of hepatomas than γ irradiation.[261] Low LET radiation becomes less effective at carcinogenesis per cGy as the dose falls. High LET radiation, however, does not.[262,263]

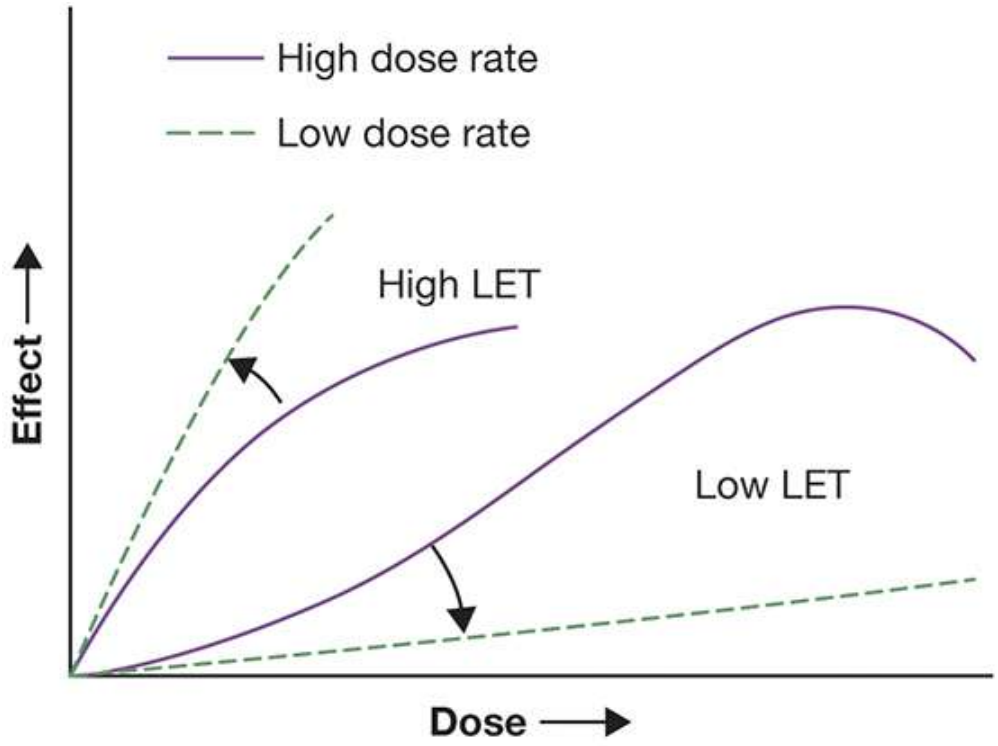

FIGURE 1.33 Dose-response curves for incidence of tumors in relation to dose and dose rate of high linear energy transfer (LET) and low LET irradiation. (Reprinted with permission from Upton AC. Biological aspects of radiation carcinogenesis. In: Boice JD, Fraumeni JF, eds. *Radiation Carcinogenesis: Epidemiology and Biological Significance*. Raven Press; 1984:9.)

3. Earlier in the history of radiation oncology, when one compared the frequency of second malignant neoplasms over time, it appeared that orthovoltage radiation therapy was more likely to be carcinogenic than megavoltage therapy. This may have been a dose-related phenomenon insofar as orthovoltage irradiation gave a higher dose to bone. It was also possible that the longer term follow-up available for survivors of orthovoltage irradiation, somewhat artifactually, leads to a higher reported incidence of tumors.
4. The sensitivity of tissues to radiation-induced malignancies is not uniform. Current evidence indicates that the thyroid gland and the breast are sensitive to cancer induction at relatively low doses of radiation; lymphoid tissue, lung, and liver require moderate doses; and bone requires the highest dose. It also seems likely that the relationship between dose and response may vary according to the type of induced tumor. One can estimate the cancer risk from radiation either per unit dose measured in Gy or per unit dose equivalent measured in sievert. When one measures in sieverts, a quality factor (Q) is used to take account of the varying biologic effectiveness of the different forms of radiation. For example, for a conventional γ-ray or x-ray, $Q = 1$. For neutron irradiation, $Q = 20$. A review of the available literature indicates that the lifetime cancer mortality risk

for a working population of both sexes is 0.008 per Sv for high doses and 0.004 per Sv for low doses.[264] The cancer mortality risk for the general population after whole-body exposure is 0.0001 to 0.0004 per cGy per person.

5. One of the most puzzling aspects of radiation-induced cancer concerns the issue of the relation of low radiation dose to carcinogenesis. Most of the data we have concern relatively high doses. Much of the public debate, however, concerns exposure to relatively low doses. Because we have few exact data regarding low doses, extrapolation is, for the most part, used to predict risk at low doses. This can be a particularly vexing problem in litigation where a plaintiff sues for an alleged radiation-induced malignancy following relatively low-dose exposure to radiation.
6. Any assessment of the radiation dose-response curve for the production of second malignant neoplasms has to take into account the fact that neoplasms also can be induced by agents other than radiation. These include chemotherapy, environmental exposures, and hereditary disposition.
7. Because the risk of radiation-induced carcinogenesis is very small, a large denominator of irradiated patients followed for a long period with thorough follow-up would be necessary to calculate risk with any reliability.
8. Latent periods for the production of a radiation-induced tumor vary according to the type of induced tumor. One type of latency is exemplified by the risk of leukemia in survivors of the atomic bombing. This consisted of an early pulse of increased risk followed by a gradual decline to baseline levels. The second pattern of occurrence, more typical of solid tumors, is an increase in the relative risk of second malignant neoplasms over many years that remains constant over time thereafter. It is important to remember, therefore, that the duration of follow-up for any study population is very likely to influence the frequency of tumors seen.
9. Age is a critical factor in determining radiation risk. In children, second cancers would be more likely to occur in tissues undergoing rapid proliferation, such as the bone and thyroid tissue.[265,266]

There are several classically cited episodes of human radiation carcinogenesis, including:

1. Individuals who were treated with radiation for ankylosing spondylitis suffered from an increase in leukemia. Mortality from colon cancer, which is associated with spondylitis through a common association with ulcerative colitis, was increased in irradiated patients. Mortality for patients with cancers other than leukemia or colon cancer also rose.[267]

2. Diagnostic x-rays of the abdomen and pelvis taken of a pregnant woman to ascertain the size of the pelvic outlet before delivery were associated with an increased risk of malignancy in the offspring.
3. Thomas Edison's assistant died of radiation-induced cancer from experiments conducted shortly after the discovery of the x-ray (Figure 1.52).
4. A large number of immigrants entered the State of Israel following its founding in 1948. X-ray epilation was used to treat tinea capitis. There was an increased incidence of brain and nervous system tumors (1.8 excess risk per 10,000 persons per year) in 10,834 children irradiated for tinea capitis compared with the same number of nonirradiated matched controls and 5,392 siblings. There were 12 malignant brain tumors in the irradiated patients versus five and one suspected in nonirradiated people. The average dose received was 4 Gy in 5 consecutive days. Irradiation doses of 1 to 2 Gy significantly increased the risk of neurologic tumors.[268]
5. The United States dropped atomic bombs on Hiroshima and Nagasaki in Japan in August 1945. Radiation-related risks among bomb survivors show that the incidence of leukemia rose. The increased risk appeared 1 to 3 years after the bombing and peaked at 6 to 7 years. In solid tumors, excess tumor risk was manifest only after exposed individuals reached the age at which the cancer was normally prone to develop.
6. Uranium miners suffered an increase in lung cancer as a result of inhalation of radon gas. Workers who painted luminous radium dials on watch faces developed bone sarcomas because of the habit of shaping the paintbrush in the mouth and ingesting bone-seeking radium.[269]
7. In the past, thorotrast was used as a contrast medium in diagnostic radiology. This material is a colloidal suspension of the α-emitter thorium dioxide. The compound was associated with the late development of angiosarcoma.
8. Canadian studies of women with tuberculosis who were fluoroscoped repeatedly for monitoring of an induced pneumothorax demonstrated an increased incidence of breast cancer.
9. The Chernobyl Nuclear Power Plant accident of April 26, 1986, is associated with an increased risk of thyroid cancer in Belarus and Ukraine.

An important review of radiation-induced sarcomas was published by Cahan et al[270] in 1948. Cahan et al's criteria, which were used to define a radiation-induced sarcoma, have wide applicability and are used, by some investigators, as the standard for demonstration of any alleged radiation-induced malignancy. The Cahan criteria are as follows:

a. A radiation-induced malignancy must have arisen in an irradiated field.
b. A sufficient latent period, preferably longer than 4 years, must have elapsed between the initial irradiation and the alleged induced malignancy.
c. The treated tumor must have been biopsied. The alleged induced tumor must have been biopsied. The two tumors must be of different histologies.
d. The tissue in which the alleged induced tumor arose must have been normal (ie, metabolically and genetically normal) prior to radiation exposure.

THE BASIC CONCEPTS OF CLINICAL RADIATION THERAPY

Dose-Time Factors

Dose-time considerations constitute complex relationships that express the interdependence of total dose, time, and number of fractions in the production of a biologic effect within a given tissue volume. This phenomenon, from a radiobiologic viewpoint, is closely related to the four Rs of ionizing radiation:

1. *Repair* of sublethal damage (SLD), repaired within hours under normal circumstances, and potentially lethal damage (PLD), which can be modified by post-irradiation conditions.
2. *Repopulation* of cells between fractions
3. *Redistribution* of cells throughout the cell cycle (partially, the result of radiation-induced synchrony secondary to transient arrest at cell cycle checkpoints and cell cycle–dependent cell killing)
4. *Reoxygenation* occurring during repeated radiation exposures

The advantages of dose fractionation include the following:

1. Reduction in the number of hypoxic cells occurs through cell killing and reoxygenation. There is increased oxygenation in the tumor after irradiation, whereas changes in normal tissue oxygen are slight or nonexistent.[271]
2. Reduction in the absolute number of clonogenic tumor cells by the preceding fractions with the killing of the better oxygenated cells. Assuming a constant supply of oxygen, fewer cancer cells will have access to an increased amount of oxygen.
3. Blood vessels compressed by a growing cancer are decompressed secondary to tumor regression, thus permitting better oxygenation despite the constant diffusion distance of oxygen in tissue near 200 μm.
4. Fractionation exploits the difference in recovery rate between normal, acute, and late-reacting tissues and tumors. Radiation-induced redistribution of cells within

the cell cycle tends to sensitize rapidly proliferating cells as they move into the more sensitive phases of the cell cycle.

5. The acute normal tissue toxicity of single radiation doses can be decreased with fractionation. Thus, patients' tolerance of radiotherapy will improve with fractionated irradiation.

In general, fractionated irradiation will spare acute reactions because of compensatory proliferation in the epithelium of the skin or the mucosa, acceleration of which can be measured experimentally 2 or 3 weeks after initiation of therapy, but most likely starts with initiation of irradiation.[272-275] However, a prolonged course of therapy with small daily fractions will decrease early acute reactions, but not necessarily prevent serious late damage to normal tissues. This approach also promotes accelerated repopulation and permits the growth of rapidly proliferating tumors. A major research effort in clinical radiobiology is and will be devoted to the optimization of dose-time fractionation schedules for various tumors that are individualized depending on cell kinetic characteristics, molecular biology, and clinical observations.[276,277] Fowler[278] published theoretic considerations based on a series of assumptions of the values used in the LQ equation with a time factor in which he attempted to predict the optimal dose fractionation schedules for tumors with various cell doubling times. He concluded that optimal overall times depend primarily on the doubling time of the tumor cells and intrinsic radiosensitivity, α (assumed to be proportional to α/β). Short overall treatment times are required for tumors with a low α/β ratio or fast proliferation. For median potential doubling times of 5 days and intermediate radiosensitivity, overall times of 2.5 to 4 weeks would be optimal. More slowly proliferating tumors, he argued, should be treated with longer overall times (Figure 1.34). Clinical studies, however, support relatively short overall treatment times in several common solid malignancies, in contrast to Fowler's conclusions. In vitro techniques to assess tumor radiosensitivity in biopsy specimens ultimately may be helpful as predictive assays.

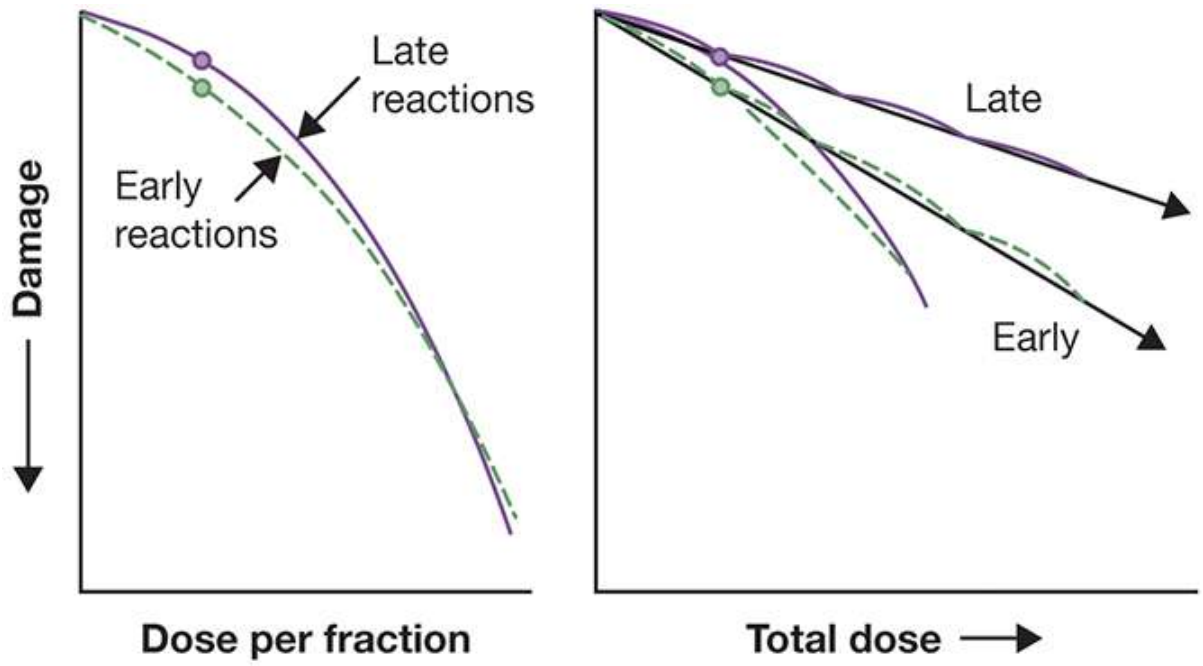

FIGURE 1.34 Difference in cell survival curves for acute and late radiation effects with single or multifractionated doses of irradiation. (Used with permission of Elsevier Science & Technology Journals from Fowler JF. Fractionation and therapeutic gain. In: Steel GG, Adams GE, Peckham MJ, eds. *The Biological Basis of Radiotherapy*. 2nd ed. Elsevier Science; 1983:181-194; permission conveyed through Copyright Clearance Center.)

Altered Fractionation

Without a solid biologic basis and out of empiricism and convenience, the "standard fractionation" for radiation therapy has evolved into five fractions weekly. Other fractionation schedules have been proposed that deliver a single fraction, multiple fractions daily, fractions 3 days a week, six fractions weekly, or use a hyperfractionation split-course regimen (Figure 1.35). Based on the narrow window between improvements in tumor control and enhanced normal tissue toxicities,[279] any altered fractionation schedule is potentially harmful and must be approached with caution. However, the improved quality of clinical trials by national study groups and by individual institutions has generated a growing body of clinical outcome data that, together with improved biologic modeling, allows relatively accurate predictions of clinical outcomes based on relative biologic effectiveness (RBE) calculations[280] (Table 1.9).

TABLE 1.9 COMPARISON OF VARIOUS FRACTIONATION SCHEDULES

	Conventional	Split-Course	Accelerated Fractionation	Hyperfractionation
Indication, in tumors, of	Average	Average or slow	Rapid	Slow (with large cell loss factors)

	Conventional	Split-Course	Accelerated Fractionation	Hyperfractionation
growth rate				
Normal tissue effects, acute	Standard	Standard or greater	Greater	Standard or greater
Normal tissue effects, late	Standard	Greater	Standard (if complete repair of sublethal damage occurs) or greater	Lower
Advantages	—	Shorter actual treatment time (fewer fractions)	Destroys more tumor cells; prevents tumor cell repopulation; less overall treatment time	Lower OER with small doses; spares late damage; allows reoxygenation; allows stem cell repopulation
Disadvantages	—	May permit tumor repopulation	—	More fractions

OER, oxygen enhancement ratio.

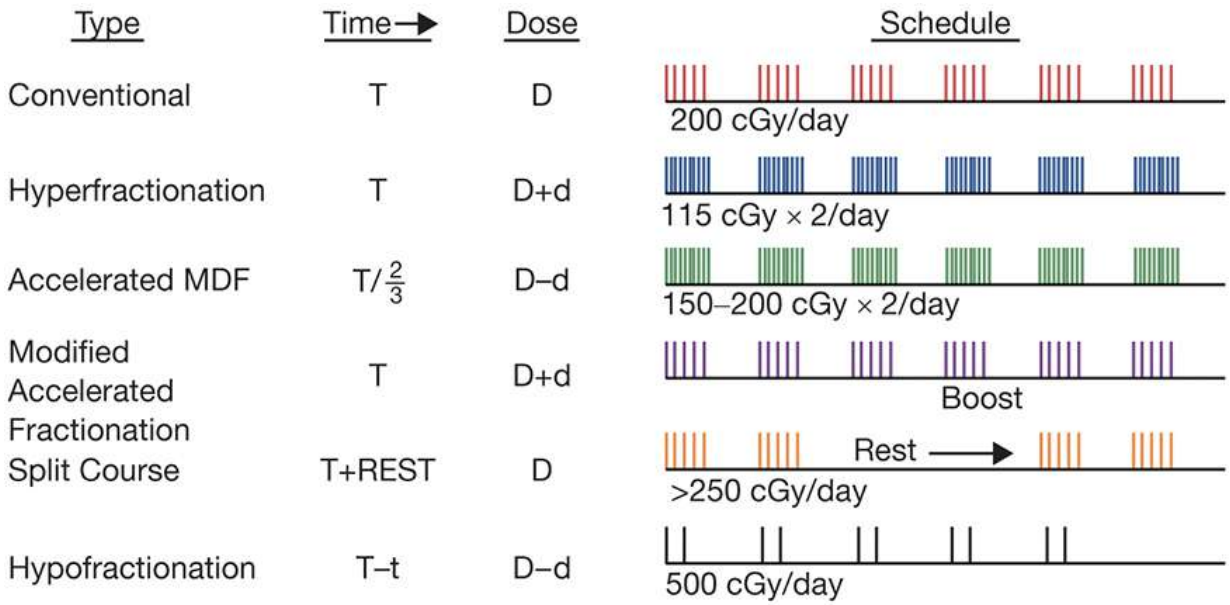

FIGURE 1.35 Various types of fractionation used in radiation therapy.

Multiple daily fractions are likely to be more effective in rapidly growing tumors with a high growth fraction. Normal tissues behave as actively proliferating cells for expression of acute reactions but as slowly proliferating cells in the manifestation of late injury.[281,282] As suggested by several biologic studies,[283] clinical trial results conducted by EORTC and RTOG demonstrated that a minimum of 6 hours of

interfraction interval should be allowed when multiple daily fractions are used to allow maximum repair of normal tissues. This is supported by reduced complication rates in patients irradiated for carcinoma of the lung and a highly uniform cohort of patients with tonsillar squamous cell carcinomas.[284]

Accelerated fractionation aims at shortening the overall treatment time. Schedules may use larger than standard size fractions 5 times weekly or more than five fractions per week of 2 Gy. In addition, multiple fractions of radiation may be given daily exclusively or in combination with standard fractions of 2 Gy. Some reduction in the total dose delivered may have to be used for fractions greater than 2 Gy for normal tissue sparing. These schedules may be preferable with hypoxic cell sensitizers or other chemical modifiers of radiation response that require the presence of a high concentration of the compound in the tumor at the time of the radiation exposure.

With hyperfractionation, a larger number of smaller than conventional dose fractions are given daily; the total daily dose is usually 10% to 20% greater than with standard fractionation; the total period of time is minimally changed; and the total dose needs to be escalated to achieve tumor toxicity similar to that of standard fractionation. The aim of hyperfractionation is to achieve the same incidence of late effects on normal tissue as observed with a comparable conventional regimen while increasing the probability of tumor control through dose escalation.[285]

Accelerated Repopulation

Withers and Taylor[286] described experimental observations documenting accelerated repopulation of tumor cells during fractionated radiotherapy and provided convincing evidence that this phenomenon occurs in clinical situations. Although Withers and Taylor's analyses suggested that accelerated repopulation occurs preferentially after the fourth week of radiotherapy, reanalysis of the same data by Bentzen[287] and Thames et al[288] and independent derivations by Fowler[289] suggested that repopulation starts early during fractionated irradiation. The latter is supported by experimental data of Schmidt-Ullrich et al,[290] showing that molecular processes of accelerated repopulation, mediated through radiation-induced receptor activation and cellular growth stimulation, occur after a single radiation exposure of 2 Gy. The effectiveness of a course of fractionated irradiation depends in part on the killing by individual fractions as well as on the rate of proliferation of surviving cells between irradiation fractions (Figures 1.36-1.38). Neoadjuvant chemotherapy also may lead to increased proliferation of surviving tumor cells after partial regression of the lesion, which could result in decreased cell killing by subsequent fractionated irradiation.

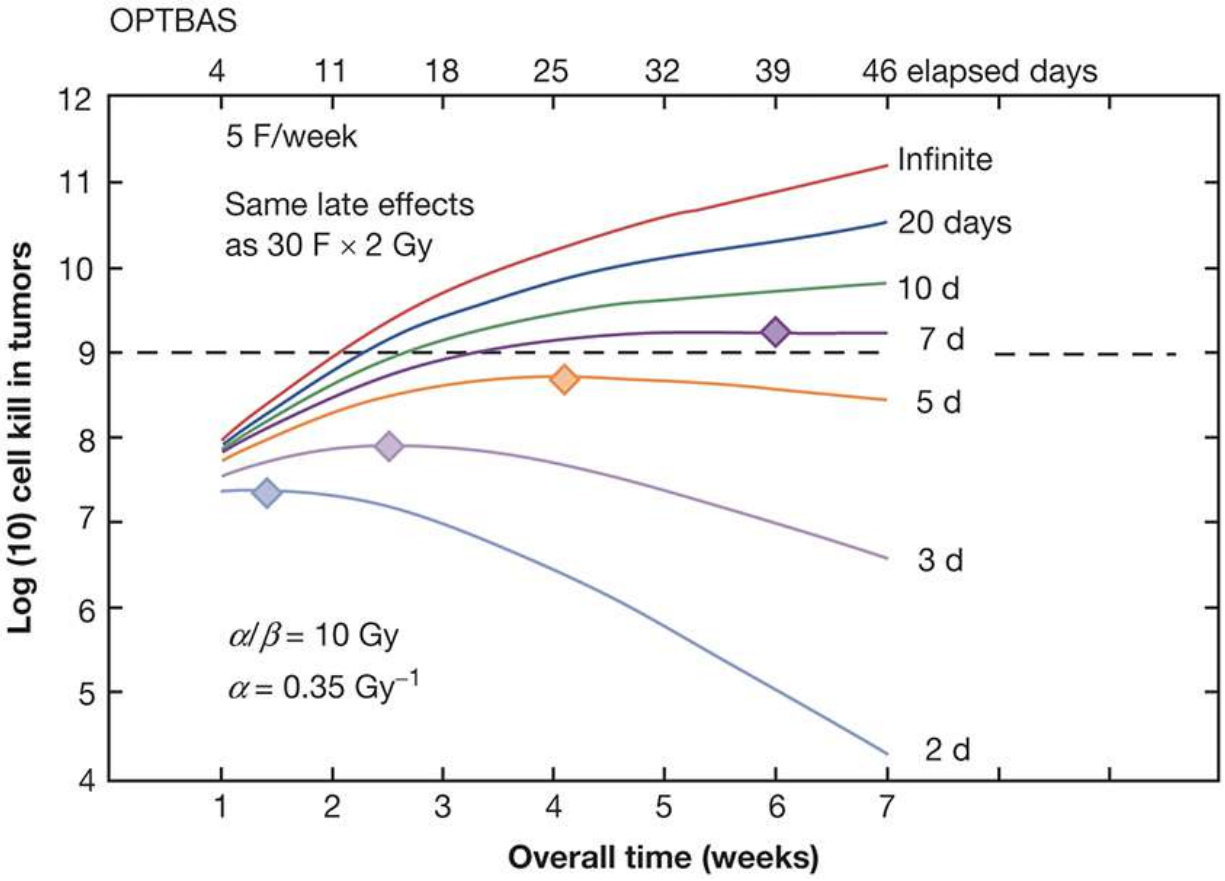

FIGURE 1.36 Log cell kill in tumors as a function of overall time, for schedules using five fractions per week to a total dose that gives the same late effects as 30 fractions of 2 Gy (assuming α/β = 3 Gy for late effects). Each curve is for the stated proliferation doubling time (average over the overall time). The diamond-shaped symbols show the maximum cell kill for that doubling time, at the optimum overall time for that number of fractions per week. If there is no diamond, the optimum overall time is >7 weeks. The dotted line is drawn arbitrarily at 9 logs of cell kill. (Reprinted from Fowler JF. How worthwhile are short schedules in radiotherapy? A series of exploratory calculations. *Radiother Oncol*. 1990;18[2]:165-181. Copyright © 1990 Elsevier Ireland Ltd. With permission.)

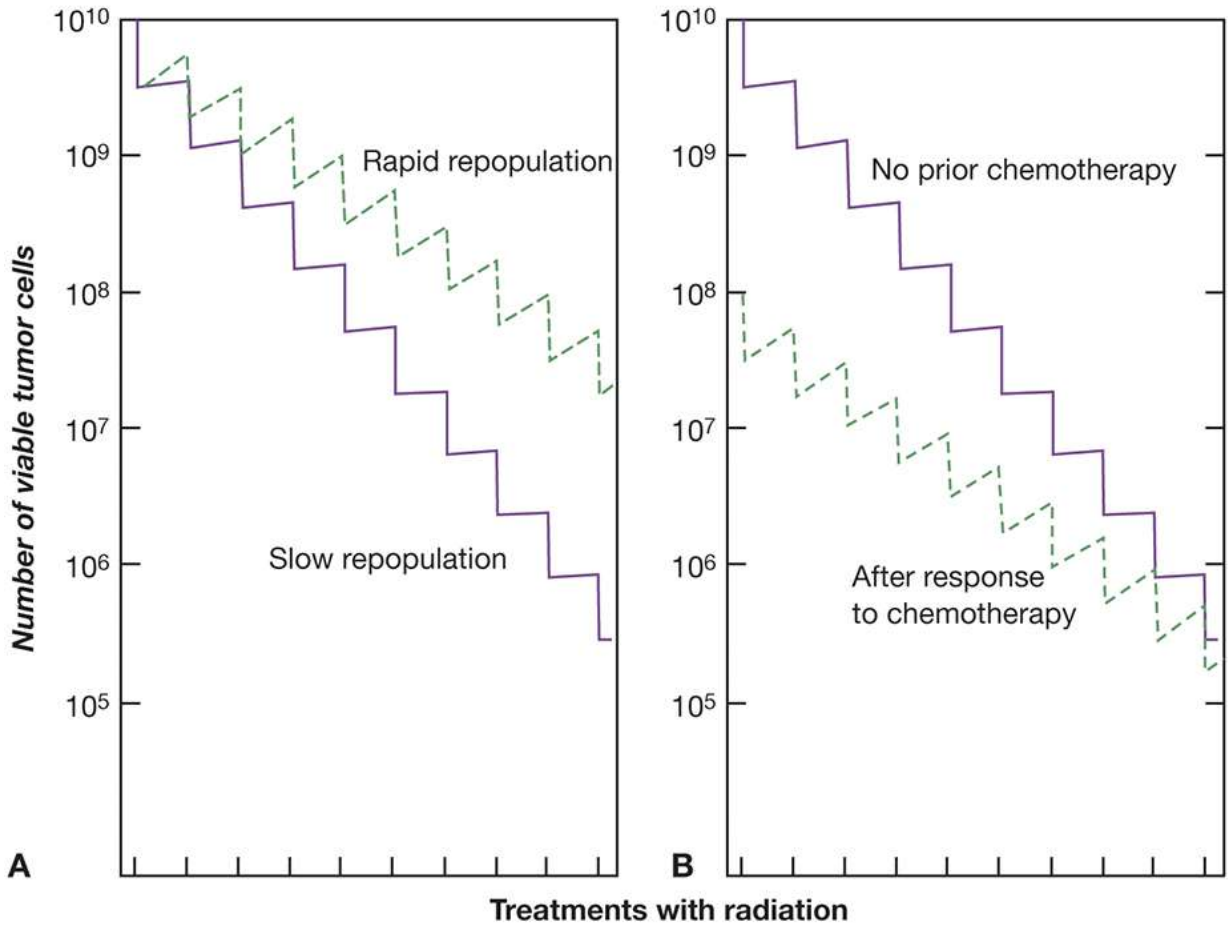

FIGURE 1.37 A. Schematic diagram indicating that cell survival during a course of fractionated irradiation depends not only on the proportion of cells killed with each dose (equal for the two curves shown) but also on the rate of proliferation of surviving cells between dose fractions, which differs for the two curves. (Reprinted from Tannock IF. Combined modality treatment with radiotherapy and chemotherapy. *Radiother Oncol*. 1989;16[2]:83-101. Copyright © 1989 Elsevier Ireland Ltd. With permission.) B. Hypothetical diagram to illustrate the number of surviving cells in a tumor during treatment with irradiation alone (solid line) or during radiation therapy delivered to a tumor that has responded to chemotherapy (ie, cell number reduced to 1% at the start of irradiation) but where proliferation has been stimulated (dashed line). Note that cell survival is similar after fractionated irradiation, despite the initial response to drugs. (Reprinted from Tannock IF. Combined modality treatment with radiotherapy and chemotherapy. *Radiother Oncol*. 1989;16[2]:83-101. Copyright © 1989 Elsevier Ireland Ltd. With permission.)

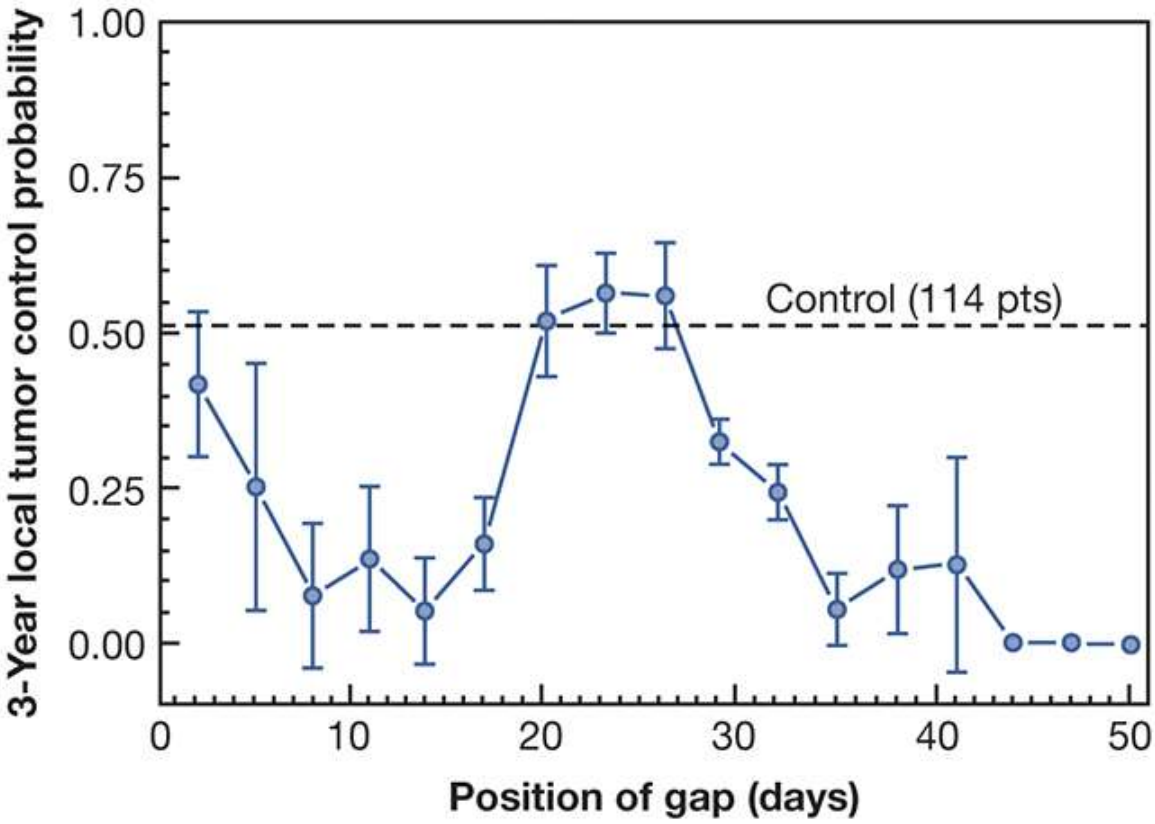

FIGURE 1.38 Dependence of tumor control probability (TCP) on the position of a single-treatment gap in 533 patients. Gap duration ranged from 3 to 20 days. Position of a gap is defined by its starting point. Each point shows the TCP averaged over 3 consecutive days (±SD). (Reprinted from Skladowski K, Law MG, Maciejewski B, Steel GG. Planned and unplanned gaps in radiotherapy: the importance of gap position and gap duration. *Radiother Oncol*. 1994;30[2]:109-120. Copyright © 1994 Elsevier Ireland Ltd. With permission.)

Isoeffect Graphs

To express an equal biologic effect produced by various fractionation schedules, isoeffect lines have been generated. Kronig and Friedrich[291] first published the observation that a specific physical dose of irradiation is less biologically effective if given in multiple fractions, which embodies the original concept of recovery between fractions. Later, MacComb and Quimby[292] and Reisner[293] established the rate of recovery in experimentally produced skin reactions in patients.

In 1944, Strandqvist[294] published a monograph describing the results of treatment of 280 patients with skin cancer (squamous cell and basal cell carcinoma); most tumors were treated within 14 and 29 days, and only one was treated within 45 days. An isoeffect line was drawn, with a slope of 0.22. He fitted the recovery factors of MacComb and Quimby and Reisner using an extrapolated value of 0.35 per day as the time for a single dose. He also produced a graph for various degrees of radiation reaction on the skin, ranging from erythema to necrosis (Figure 1.39). It should be

emphasized that in these curves, the vertical coordinate represents the total dose given, and the abscissa represents the total duration in days after the first irradiation. However, some authors have plotted similar graphs representing the number of fractions in the horizontal coordinate. It is critical to identify these two parameters because one could deliver 60 Gy in 6 weeks in 30 fractions given 5 times weekly or the same dose delivered in 18 fractions given 3 times weekly. The effects on normal tissues certainly would be different. von Essen,[295] using the Strandqvist data as well as his own, pointed out the importance of the volume irradiated when isoeffect parameters are studied and generated a 3D display of these data.

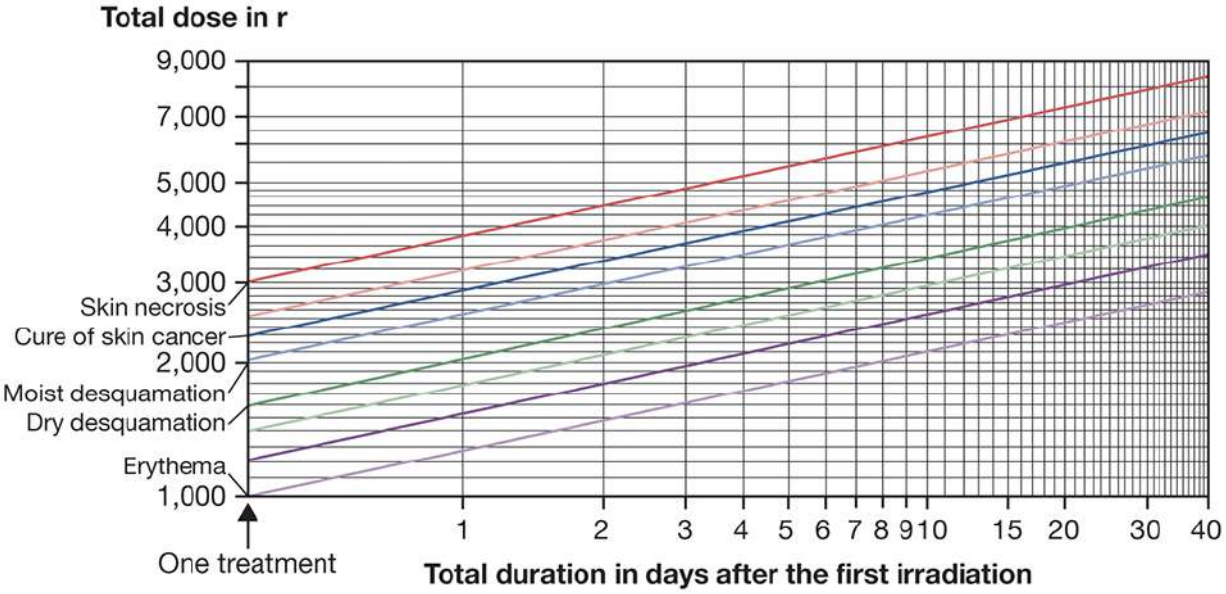

FIGURE 1.39 Strandqvist's curves on log paper.[177] The slope of the curves (0.22) is the same for the tumoricidal dose for squamous cell carcinoma for various degrees of skin reactions. (From Strandqvist M. Studien iiber die kumulative Wirkung der Rontgenstrahlen bei Fraktionierung. Erfahrungen aus dem Radiumhemmet an 280 Haut- und Lippenkarzinomen. *Acta Radiol*. 1944;55[suppl]:1-300. Copyright © 1944 SAGE Publications. Reprinted by permission of SAGE Publications.)

Dutreix et al[296] published observations on the influence of fraction size in patients with cancer of the lung, on whom one of the supraclavicular areas received a single exposure and the other area received two exposures separated by 6 hours. They noticed that two fractions of 1 Gy produced the same skin reaction as one fraction of 2 Gy. As the fraction size increased, however, it took a higher dose in the two-fraction schedule to produce the same reaction as with the single-fraction schedule. With mucositis of the faucial arch used as an end point, researchers at MD Anderson Cancer Center observed that 10 Gy per week given in five fractions of 2 Gy is equivalent to 11 Gy given in 10 fractions, twice a day, separated by 3 hours.[297]

The slopes for reactions for various normal tissues differ, as do slopes of tumor curability and normal tissue late effects. In general, the slope for tumor curability is less steep than that for normal tissue reactions. Isoeffect lines for various squamous cell carcinomas of the head and neck, different stages, have slopes varying from 0.33 to 0.38.[298,299] Furthermore, as stated earlier, tolerance of normal tissues is strongly related to the volume irradiated. Whereas 60 Gy could be given safely in 5 weeks for a small glottic tumor with a 5-cm by 4-cm portal, the same dose delivered in the same period for a supraglottic carcinoma, with a larger portal covering the entire larynx, would result in more severe acute and late sequelae[300] (Box 1.5).

Box 1.5

Nominal Standard Dose and Time-Dose Factor

The nominal standard dose (NSD) concept is of historic interest. For 20 years, NSD was used frequently to express equivalency of clinical doses of irradiation based on human skin tolerance and curability of squamous cell carcinoma. Cohen[374] pointed out that the regression coefficient for squamous cell carcinoma was different from that of normal skin (0.24). In 1969, Ellis[375] suggested that if one number could be used to represent the dose of irradiation that reached normal tissue tolerance, this would be advantageous in comparing different techniques. This figure should represent the normal connective tissue tolerance because this was, in his thinking, the limiting factor in most tumor therapies.

The unit for NSD expression was the *ret*. It could never be assumed that the NSD value represented a “single equivalent dose” because the isoeffect time calculated by Ellis used data from 4 to 30 fractions. Another flaw of the NSD calculation was that it did not allow for the effect of variations in volume treated or for interruptions of therapy (split-course therapy). Orton[380] estimated that NSD calculations were misused about 50% of the time by unaware clinicians comparing different radiation therapy regimens. The NSD formula did not predict isoeffect in pig skin irradiation using two to five fractions per week. Moreover, early reactions did not predict the magnitude of late damage when dose fractionation was altered from conventional daily schedules.

In 1973, Orton and Ellis[376] (*Br J Radiol*. 1973;46:529-537) published a simplification of the NSD concept more applicable to clinical radiation therapy, stating that when a treatment did not result in normal connective tissue tolerance, treatment effectiveness should be described in terms of partial tolerance. Although there was no definite basis for the application of the time-dose factor (TDF) concept to clinical radiation therapy, equivalency of various dose schedules is sought constantly. For split-course regimens, the TDF values (in units of ret) were used by adding the TDF value for each of the partial tolerance factors corresponding to each component of the treatment and correcting for the decay of the first part of the treatment TDF.

In 1974, Orton[377] (*Radiology*. 1975;46:526-537) defined TDF values for continuous irradiation that could be used with temporary or permanent brachytherapy implants, using various isotopes. A standard radium therapy regimen of 60 Gy in 168 hours was used for comparison with other equivalent techniques. This was equivalent to 1,800 ret of fractionated external irradiation.

Linear Quadratic Equation (α/β Ratio)

Formulations based on dose survival models have been proposed to evaluate the biologic equivalence of various doses and fractionation schedules. These assumptions are based on an LQ survival curve represented by the following equation:

$$\log_e S = \alpha D + \beta D^2,$$

in which α represents the *linear* (ie, first-order dose-dependent) component of cell killing and β represents the *quadratic* (ie, second-order dose-dependent) component of cell killing. Thus, β represents the more reparable (over a few hours) component of cell damage. The dose at which the two components of cell killing are equal constitutes the α/β ratio (Table 1.10).

TABLE 1.10 RATIO OF LINEAR (*A*) TO QUADRATIC (*B*) TERMS FROM MULTIFRACTION EXPERIMENTS AND CLINICAL DATA

	α/β Ratio (Gy)	
Tissue	**Experimental**	**Clinical**
Early Reactions		
Skin/subcutaneous tissues	9-12	5-10
Jejunum	6-10	2.2-8
Colon	10-11	—
Testis	12-13	—
Callus	9-10	—
Late Reactions		
Spinal cord	1.0-4.9	3.3
Kidney	1.5-2.4	—
Lung	2.4-6.3	4.2-4.7
Bladder	3.1-7.0	3.4-4.5

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In a study of 17 human tumor cell lines, Steel and Peacock[301] observed that the average surviving fraction at 2 Gy is 0.44 from the α component and 0.88 from the β component. The β effect at that dose level appears to be similar in radiosensitive and radioresistant tumors; thus, among radiosensitive tumors in which the survival from the α component is below 0.3, the β effect makes a very small contribution to overall

radiosensitivity in the lower dose region. The overall effect of many small fractions is to amplify the dominance of the α component. The β effect is unimportant because repair will be almost complete. In the more radiocurable tumors, cell killing by the α component represents the predominant fraction of tumor cell killing (Figure 1.40).

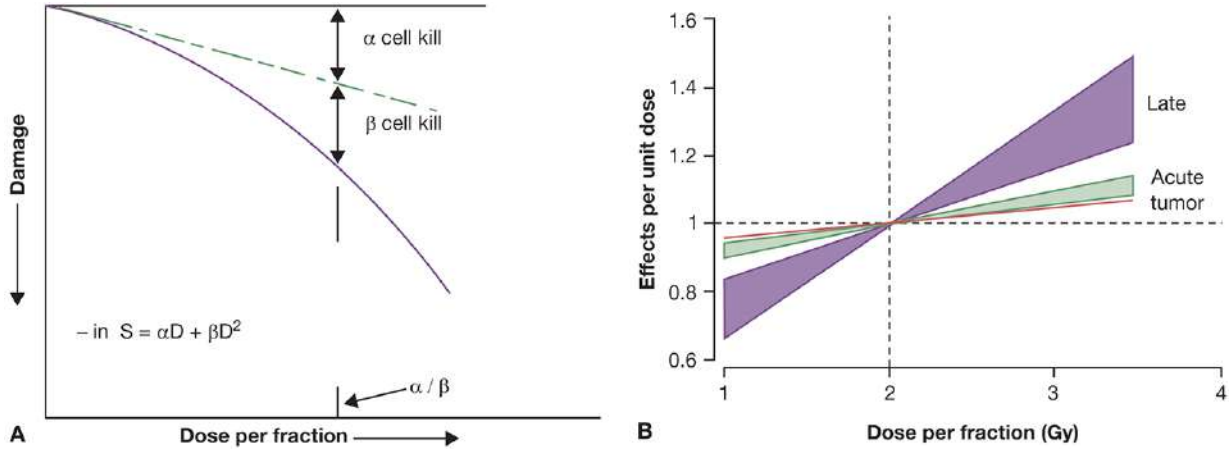


FIGURE 1.40 A: At a dose equal to the *α/β* ratio, the log cell kill because of the α-process (nonreparable) is equal to that because of the β-process (reparable injury); *α/β* is thus a measure of how soon the survival curve begins to bend over significantly. The *α/β* ratio for late effects on normal tissue generates a "curvier curve" than the *α/β* ratio for radiation's effects on acutely reacting normal tissue and tumor cells. Thus, the relative effect of dose per fraction is higher for late-responding tissues than for acutely responding tissues. In particular, for the central nervous system, high dose per fraction radiation therapy is associated with an increased risk of late effects. An *α/β* ratio of 2 to 3 commonly is used in calculations of radiation effects on late-reacting tissue, whereas a ratio of 10 is used more commonly for acute-responding tissues or tumor. (Used with permission of Elsevier Science & Technology Journals from Fowler JF. Fractionation and therapeutic gain. In: Steel GG, Adams GE, Peckham MJ, eds. *The Biological Basis of Radiotherapy*. 2nd ed. Elsevier Science; 1983:181-194; permission conveyed through Copyright Clearance Center.) B. A schematic representation of biologic data relating dose per fraction to effect on tumors, early-reacting, and late-reacting normal tissues. (Reprinted from Saunders MI. Programming of radiotherapy in the treatment of non-small-cell lung cancer—a way to advance care. *Lancet Oncol*. 2001;2[7]:401-408. Copyright © 2001 Elsevier. With permission.)

The shape of the dose survival curve with photons differs for acutely and slowly responding normal tissues. This difference in shape is not observed with neutrons. The severity of late effects changes more rapidly with a variation in the size of dose per fraction when a total dose is selected to yield equivalent acute effects. With a decreasing size of dose per fraction, the total dose required to achieve a certain isoeffect increases more for late-responding tissues than for acutely responding tissues. Thus, in hyperfractionated regimens, the tolerable dose would be increased more for late effects than for acute effects. Conversely, if large doses per fraction are used, the total dose required to achieve isoeffects in late-responding tissues would be reduced more for late effects than for acute effects. In general, tumors and acutely

reacting tissues have a high α/β ratio (8-15 Gy), whereas tissues involved in late effects have a low α/β ratio (1-5 Gy).

The values for α and β can be obtained from graphs in which the reciprocal of the total dose (Gy^{-1}) and the dose per fraction (Gy) are plotted. A straight line is obtained. The intercept of this line with the zero dose-per-fraction axis is proportional to α and equal to $\alpha/\ln S$, wherein S is the natural logarithm of survival. The slope is proportional to β and equal to $\beta/\ln S$.

The algebraic functions to derive the straight line from the reciprocal total dose per fraction plot are as follows: Tumor cell survival following n fractions, each of dose d:

$$S = (e^{-\alpha d} - \beta d^2)n$$
$$-\ln S = n\,(\alpha d + \beta d^2)$$
$$-\ln S = \alpha\, nd + \beta n d^2$$
$$-\ln S = nd\,(\alpha + \beta d)$$

Dividing both sides by total dose nd, we have

$$\frac{-\ln S}{nd} = \alpha + \beta d$$

Intercept Slope

Withers et al[302] proposed a method for using these survival curve parameters for calculating the change in total dose necessary to achieve an equal response in tissue when the dose per fraction is varied, using the α/β ratios. This calculation accounts only for the effect of repair of cellular injury. The isoeffect curves vary for different tissues. A biologically equivalent dose (BED) can be obtained using following formula:

$$\text{BED} = \frac{\ln S}{\alpha}$$
$$\text{BED} = nd\left[1 + d/(\alpha/\beta)\right]$$

If one wishes to compare two treatment regimens, the following formula can be used:

$$\frac{Dr}{Dx} = \frac{\alpha/\beta + dx}{\alpha/\beta + dr}$$

in which Dr is the known total dose (reference dose), Dx is the new total dose (with different fractionation schedule), dr is the known fractionation (reference), and dx is the new fractionation schedule.

Let us consider an example of the use of this formula (with some reservations). Suppose 50 Gy in 25 fractions is delivered to yield a given biologic effect. If one assumes that the subcutaneous tissue is the limiting parameter (late reaction), it is desirable to know what the total dose to be administered will be using 4-Gy fractions. Assume α/β for late fibrosis equals 2 Gy.

Using the above formula:

$$Dx = \frac{Dr\ (\alpha\ /\ \beta + dr)}{\alpha/\beta + dr}$$

Thus,

$$Dx = 50\ Gy \left(\frac{5 + 2}{5 + 4}\right) = 39\ Gy$$

The basic LQ equation addresses the inactivation of a homogeneous population of cells. One should be wary, however, of accepting the basic equation as being complete. Because it is likely that accelerated repopulation of tumor clonogens occurs during the course of radiotherapy, and that cell cycle redistribution and reoxygenation also occur, we should consider how these factors can be accounted for in the formula.[303,304]

Repopulation may be accounted for, in broad approximation, by describing the number of clonogens (N) at time t as being related to the initial number of clonogens (No).

Then,

$N = \mathrm{No}^{e\lambda t}$

The parameter λ determines the speed of cell repopulation and is given by

$$\lambda = \frac{\log e^2}{T_{\text{pot}}} = \frac{0.693}{T_{\text{pot}}}$$

where T_{pot} is the effective doubling time of cells in the tumor. If we ignore spontaneous cell loss, then T_{pot} is approximately the same as the measurable in vitro doubling time of tumor cells. Reported values of T_{pot} are 2 to 25 days with a median value of approximately 5 days. For late-responding tissues, T_{pot} is so large that λ is effectively zero.

Incorporating the allowance for tumor proliferation, with t representing time, the LQ equation becomes

$$\text{BED} = nd\left(1 + \frac{d}{\alpha/\beta}\right) - \frac{0.693t}{\alpha T_{\text{pot}}}$$

Let us assume an α/β for an acutely reacting tissue, such as a tumor, of 10, and an α of 0.3 with a T_{pot} of 5. The BED of 70 Gy of 2 Gy/fraction, five fractions per week, in 46 days, is

$\text{BED} = 70(1 + 0.2) = 84\ \text{Gy}_{10}$.

Now let us add the correction for tumor repopulation during the course of treatment:

$$\text{BED} = 70\left(1 + \frac{2}{10}\right) - \frac{0.693t}{0.3} \times \frac{46}{5}$$

$$\text{BED} = 84 - 21 = 63\ \text{Gy}_{10}.$$

The decrease in clonogens by radiotherapy is attenuated, in part, by the repopulation of the surviving clonogens (Figures 1.41 and 1.42).

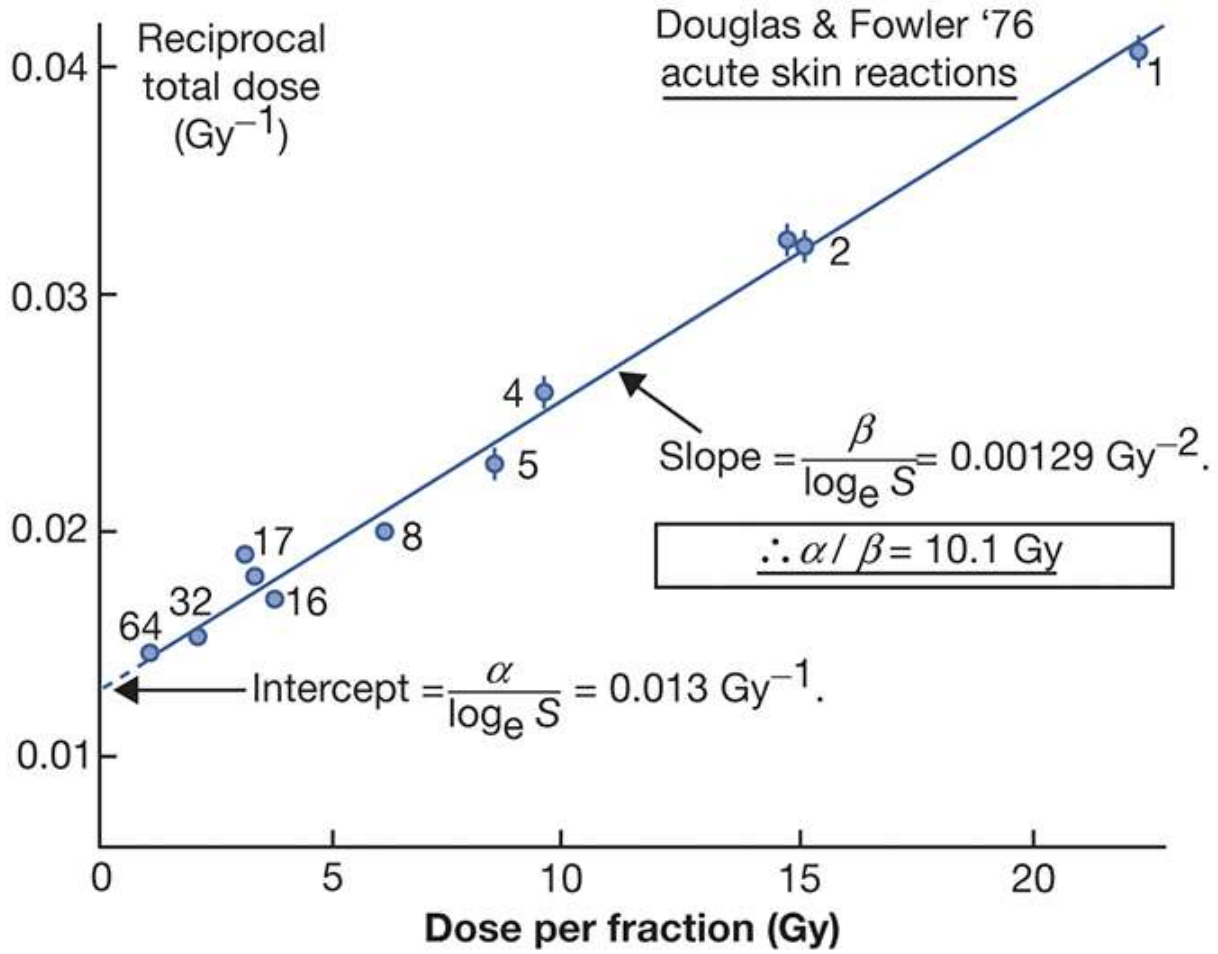


FIGURE 1.41 Values of α and β. If the reciprocal of the total dose (for several multifraction schedules) is plotted against dose per fraction, a straight line will be obtained. The intercept of this line with the zero dose-per-fraction axis is proportional to α (α/ln S). The slope is proportional to β (β/ln S). The α/β ratio is readily determined. For absolute values of α and β, the clonogenic assay is necessary for the end point. (Used with permission of Elsevier Science & Technology Journals from Fowler JF. Fractionation and therapeutic gain. In: Steel GG, Adams GE, Peckham MJ, eds. *The Biological Basis of Radiotherapy*. 2nd ed. Elsevier Science; 1983:181-194; permission conveyed through Copyright Clearance Center.)

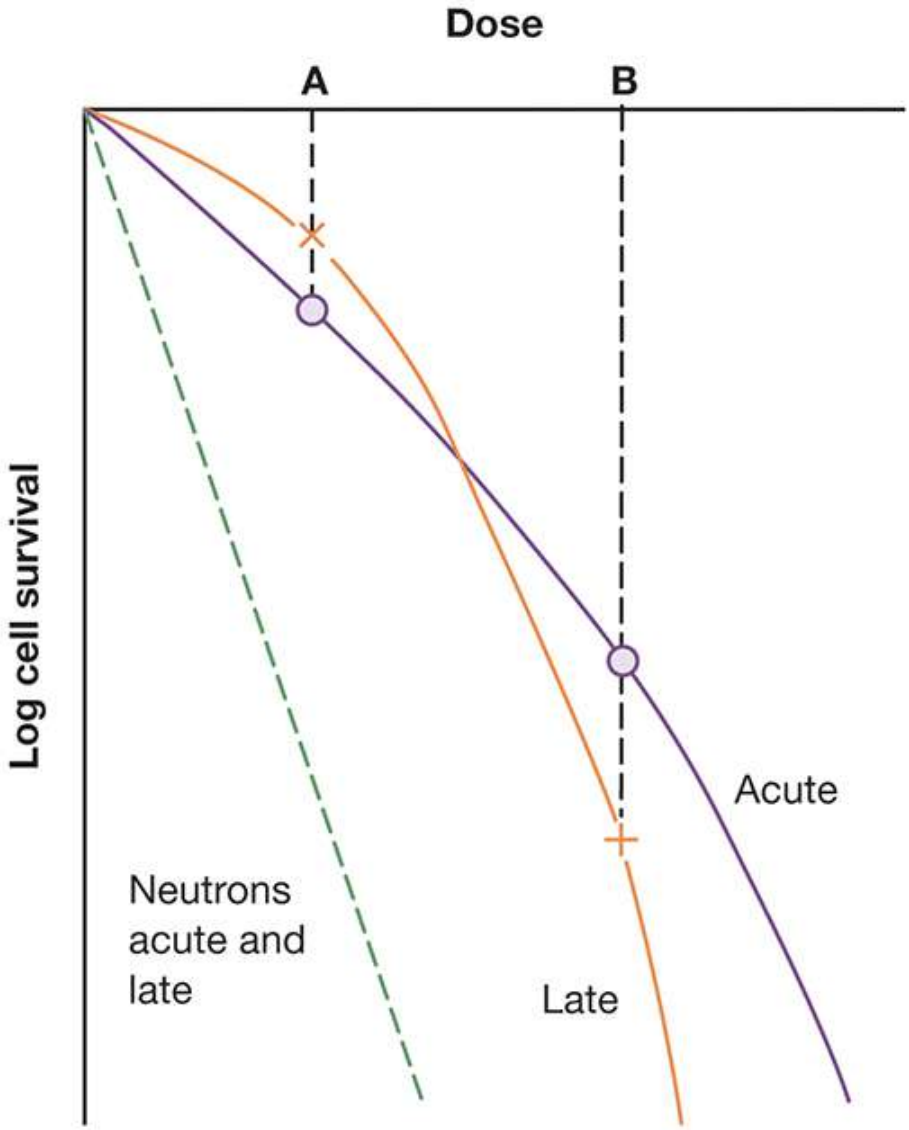


FIGURE 1.42 Hypothetical survival curves for the target cells for acute and late effects in normal tissues exposed to x-rays or neutrons. The α/β ratio in the equation for surviving fractions (SF = $e^{-\alpha D+\beta D_2}$) is higher for late effects than for acute effects in x-irradiated tissues, resulting in a greater rate of change in effect in late-responding tissues with a change in dose. At dose A, survival of target cells is higher in late effects than in acute effect tissues, whereas at dose B, the reverse is true. Therefore, increasing the dose per fraction from A to B results in a relatively greater increase in late rather than acute injury. In the case of neutrons, the α/β ratio is low, with no detectable influence on the quadratic function ($e\beta D \pm D_2$) over the first two decades of reduction in cell survival, implying that accumulation of sublethal injury plays a negligible role in cell killing by doses of neutrons of clinical interest. At these doses, the relative biologic effectiveness is higher for late effects than it is for acute effects. (Reprinted from Withers HR, Thames HD Jr, Peters LJ. Biological bases for high RBE values for late effects of neutron irradiation. *Int J Radiat Oncol Biol Phys*. 1982;8[12]:2071-2076. Copyright © 1982 Elsevier. With permission.)

In the LQ equation, redistribution in the cell cycle and reoxygenation may be modeled by a single term called *resensitization*. Immediately after a dose of

radiation, the average radiosensitivity of the cell population falls and then gradually returns to greater sensitivity. In contrast to tumor proliferation, resensitization probably increases as overall treatment time increases. Not enough is known about resensitization's clinical importance to make it useful to incorporate a numeric value for it in the LQ formula.

The LQ model can be used to construct a biologically oriented dose distribution algorithm for clinical radiation therapy.[305,306] A physical dose distribution can be translated to a BED using published biologic parameters. It may help clinicians to optimize treatment plans, and the technique may be used for outcome analysis in clinical research when the biologic parameters and the assumptions can be validated.

Brachytherapy and the Radiobiologic Dose Rate Effect

An interesting letter to the editor appeared in *Nature* on August 6, 1903.[307,308] The author, Alexander Graham Bell (1847-1922), is best known for his role in the invention of the telephone (Figure 1.43).

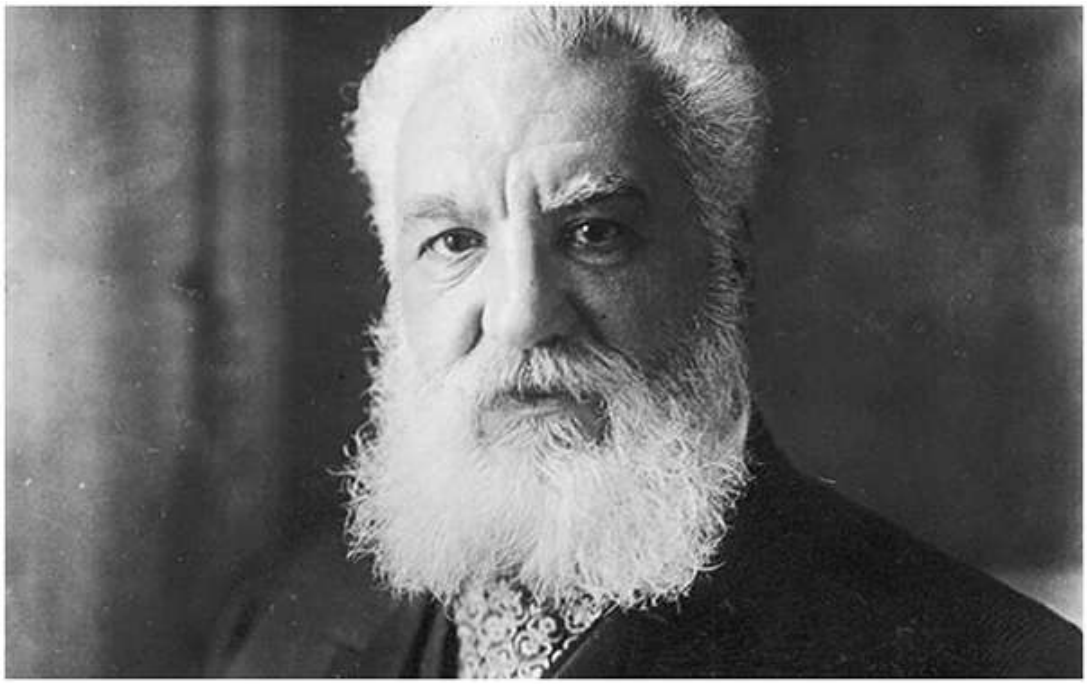


FIGURE 1.43 Alexander Graham Bell (1847-1922).

It has occurred to me that perhaps you would care to publish the enclosed letters, and thus start some one experimenting with the radium rays in the manner suggested. Dr. Sowers is a distinguished physician of Washington, D.C., now spending a portion of his summer vacation in Baddeck, Nova Scotia.

Alexander Graham Bell.

Beddeck, N.S., July 21

Dr. Z.T. Sowers,

1707 Massachusetts Avenue,

Washington, D.C.

Dear Dr. Sowers,

I understand from you that the Röntgen x-rays, and the rays emitted by radium, have been found to have a marked curative effect upon external cancers, but that the effects upon deep seated cancers have not thus far proved satisfactory.

It has occurred to me that one reason for the unsatisfactory nature of these latter experiments arises from the fact that the rays have been applied externally, thus having to pass through healthy tissues of various depths in order to reach the cancerous matter.

The Crooke's tube from which the Röntgen rays are emitted is, of course, too bulky to be admitted into the middle of a mass of cancer, but there is no reason why a tiny fragment of radium sealed up in a fine glass tube should not be inserted into the very heart of the cancer, thus acting directly upon the diseased material. Would it not be worth while making experiments along this line?

Yours sincerely,

(Signed) Alexander Graham Bell

Baddeck, N. S., July 21.

Dr. A. Graham Bell,

Baddeck, N. S.

Dear Dr. Bell,

> The suggestion which you make in regard to the application of the radium rays to the substance of deep seated cancer I regard as very valuable. If such experiments should be made, I have no doubt they would prove successful in many cases where we now have failures.
>
> Yours sincerely,
>
> (Signed) Z. T. Sowers, MD
>
> Baddeck, N. S., July 21.

The recipient of Bell's letter was the distinguished Washington D.C. physician, Zachariah Turner Sowers, MD (1845-1919), vacationing in Nova Scotia.

This form of radiotherapy is referred to as *brachytherapy* or *endocurietherapy*. The prefix *brachy*, from the Greek, means short, slow, or short range. The suffix therapy is derived from *therapeaia*, also Greek, meaning care or service to the sick. Some physicians use the alternative term *endocurietherapy*. The prefix *endo*, also from the Greek, means "within."

There are several ways we can describe the forms of brachytherapy. First, we can subdivide brachytherapy into a classification system based upon the physical placement of the radioactive sources. Thus, (1) *interstitial brachytherapy* is the placement of the radioactive sources directly into the tumor of the tumor bed. Implanting radioactive seeds into the prostate would be an example of this form of treatment. (2) *Intracavitary brachytherapy* is the placement of the radioactive sources inside a body cavity and up against a tumor-bearing structure. The placement of tandem and ovoids for the treatment of carcinoma of the cervix or of a radioactive source–bearing catheter inside the nasopharynx are examples of this form of brachytherapy. Finally, (3) *mold brachytherapy* is the placement of radioactive sources upon the skin surface bearing a tumor. The use, for example, of radioactive sources embedded in a glove worn upon the hand for a period of time to treat a tumor of the dorsum of the hand, while preserving the function of the ligaments controlling the fingers, is an example of this form of treatment.

Another way we can subdivide the forms of brachytherapy is by the duration of the treatment. A (1) *temporary brachytherapy* application resides in the tumor, body cavity, or adjacent to the tumor for a finite period of time before it is removed. Tandem and ovoid placement for carcinoma of the cervix is typically a temporary brachytherapy application. A (2) *permanent brachytherapy* application is placed permanently and, over time, the radioactive source decays. Injecting radioactive Au-198 seeds into a bronchogenic carcinoma for palliation of bronchial obstruction by tumor is an example of a permanent implant.

Yet, a third way we can think about the forms of brachytherapy is by the speed with which the radiation is administered in cGy/min. Three types are generally described. (1) *low dose rate (LDR) brachytherapy* typically administers its dose over a period of days. For example, administering 1,000 cGy/day to point A in a Cs-137 tandem and ovoid application would be a classic example of LDR brachytherapy. (2) *high dose rate (HDR) brachytherapy* delivers the dose in a few minutes. The use of a robot referred to as a remote HDR remote afterloader to pump high-activity Ir-192 into and out of a series of Teflon catheters in the tumor bed for the postoperative treatment of a high-risk soft tissue sarcoma is an illustration of HDR brachytherapy. Finally, there is a so-called (3) *intermittent HDR brachytherapy* or *pulsed-dose rate brachytherapy*. This usually refers to fractionating the HDR brachytherapy several times during the day, but the term is used by some physicians to refer to once per day or once every other day insertion of the HDR sources in the Teflon catheters. In either situation, an HDR remote afterloader machine is used.

When LDR brachytherapy is used for cancer treatment, we must give due consideration to its particular radiobiologic effects. We can think of LDR brachytherapy as the ultimate form of fractionation, being equivalent to an infinite number of small fractions with no interfraction intervals devoid of irradiation. What are the implications of this infinite fractionation on tumor cell killing and normal tissue tolerance?

The first point to consider is that much of the value of brachytherapy has less to do with biology than it has to do with physics. Brachytherapy is typically highly localized irradiation. The radiation beam in EBRT comes “from the outside in” and passes through normal tissue on its way to the tumor volume and, in the case of uncharged beams like photons and neutrons, passes through normal tissue on its way back out of the body after passing through the tumor. In contrast, the radiation beams in brachytherapy come “from the inside out” and are generally within or directly upon the tumor with the dose falling off rapidly as the square of the distance as one moves away from the radioactive source(s). Long before computer modeling of external beam irradiation and MLCs for external beam treatment, brachytherapy was, to some extent, the first form of “dose painting” or “IMRT.” The ability to confine the radiation dose to a small area with brachytherapy, with the avoidance of exposing large areas of normal tissue, allows the treating clinician to safely give doses sometimes unimaginable with external beam treatment.

Perhaps, the ultimate clinical example of the volume effect of brachytherapy is the treatment of choroidal melanoma or retinoblastoma with a I-125 or Ir-192 or Co-60 or Ruthenium plaque sewn to the choroid and overlaying the tumor bed. In some cases, 40,000 to 70,000 cGy will be administered to a small area of the outer surface of the choroid with an acceptable long-term ill effect on normal tissue profile. This is only possible by the use of highly localized brachytherapy. This had led some

wags to observe that “this isn’t really radiotherapy as we know it. It is nuclear warfare.”

It is also worth remembering that the dose in the tumor volume created by brachytherapy is often highly heterogeneous. In the treatment of carcinoma of the cervix, for example, generations of radiation oncologists have prescribed and described the dose administered to “point A” and “point B,” both located lateral to the cervix. Radiation dose, however, falls off as the square of the distance. Therefore, the dose at the surface of the tumor-containing cervix from a Cs-137 tandem and ovoid application is much higher and more tumoricidal than the dose at point A.

I have treated vaginal embryonal rhabdomyosarcoma in very young girls with intracavitary pulsed HDR brachytherapy and custom-built lead shields to both push uninvolved normal tissue away from the brachytherapy catheters and partially shield this tissue with lead. It is difficult to imagine achieving more exquisitely conformal radiation dose distributions by any means other than brachytherapy.

The second point to consider is the fundamental series of effects of LDR on cell death. We can think of the radiation damage to mammalian cells as divisible into (1) lethal, irreversible, and irreparable lethal damage; (2) PLD whose injurious effects can be either exacerbated or ameliorated by the postirradiation environmental conditions of the irradiated cells; and (3) SLD, which, under normal circumstances, can be repaired unless additional SLD is heaped upon existing damage and converts it to lethal damage. Here is a simple way to think about SLD mathematically. Assume that A% of cells are killed by dose X of external beam irradiation. If you take dose X and split it into two equal fractions, then each fraction is $X/2$. Now, instead of giving all of the radiotherapy dose X at once, give $X/2$ today and the remaining $X/2$ tomorrow. What will happen? Instead of A% of cells dying as a result of radiation, $A\% - B\%$ will die. The improvement in the probability of cell survival, represented by B, is repaired SLD.

Let us turn our attention to PLD. By definition, PLD is influenced by the conditions the cells find themselves in after being irradiated. Let us assume we do something to the cells, which prevents them from moving forward in the cell cycle. We might achieve this by lowering the ambient temperature or allowing the cells to be packed in closely so that density inhibition of growth occurs or by using a culture media, which starves the cells of nutrients. If we keep the cells from moving forward in the cell cycle, then we will inhibit the ability of radiation-induced DNA injury to manifest itself by causing cell death when the cells try to divide. Cell survival will rise compared to allowing the cells to vigorously march through the cell cycle into M phase. This diminution in cell mortality represents PLD.[309]

With LDR, several things happen simultaneously, which influence cell killing. The relative importance of these factors will vary based on the specifics of whether

you are thinking about normal tissue tolerance to radiotherapy or the tumor type, the tumor's growth environment, and, for normal or tumor tissue, the dose rate (Figure 1.44). The factors are as follows:

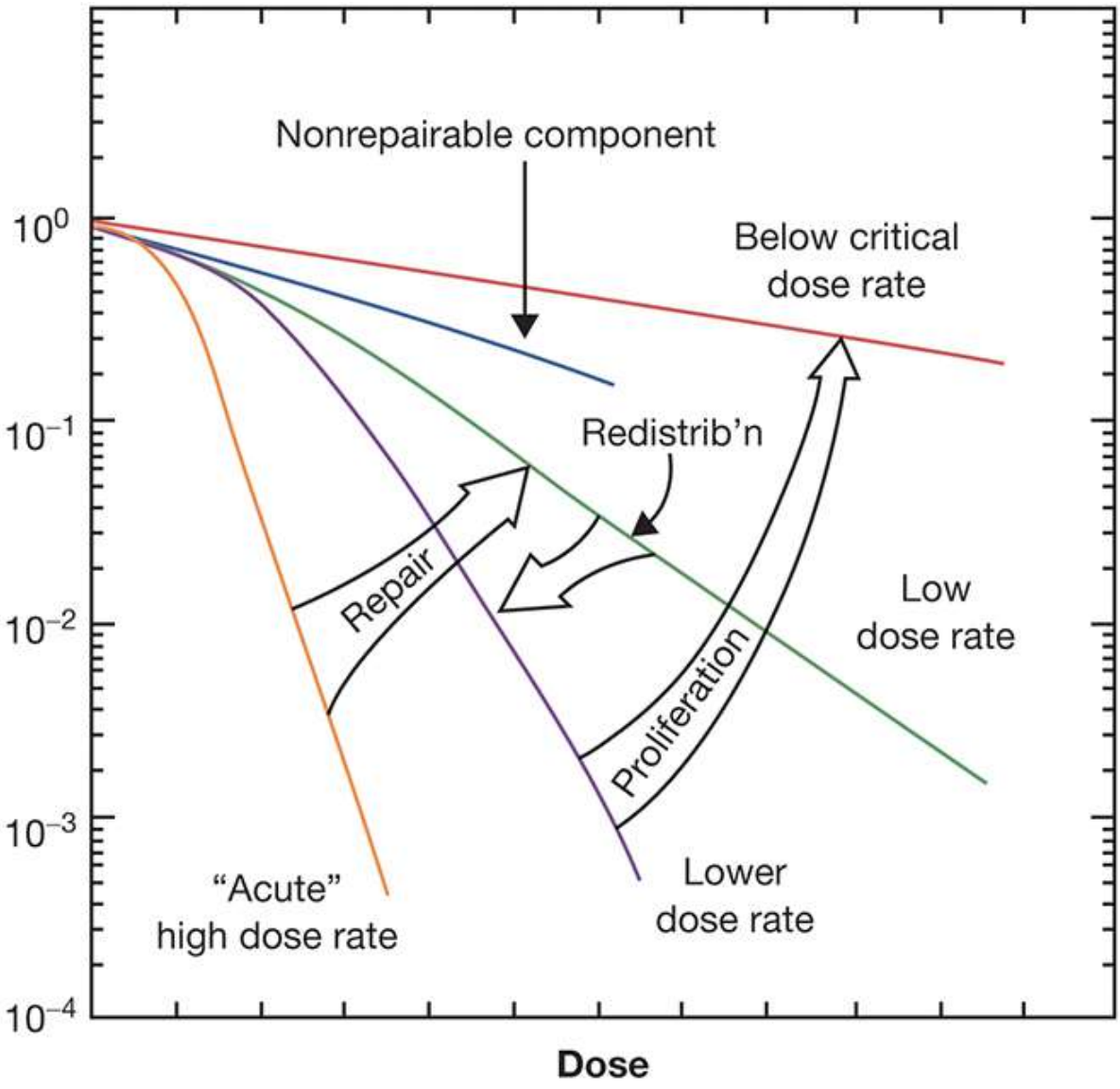


FIGURE 1.44 The dose rate effect as a result of repair of sublethal damage, redistribution in the cycle, and cell proliferation. The dose-response curve for acute exposures is characterized by a broad initial shoulder. As the dose rate is reduced, the survival curve becomes progressively shallower as more and more sublethal damage is repaired, but cells are "frozen" in their positions in the cycle and do not progress. As the dose rate is lowered further and for a limited range of dose rates, the survival curve steepens again because cells can progress through the cycle to pile up at a block in G2, a radiosensitive phase, but still cannot divide. A further lowering of dose rate allows cells to escape the G2 block and divide; cell proliferation then may occur during the protracted exposure, and survival curves become shallower as cell birth from mitosis offsets cell killing from the irradiation. (Based on the ideas of Dr. Joel Bedford, and from Hall EJ. *Radiobiology for the Radiologist*. 4th ed. J.B. Lippincott; 1994.)

(a) *Repair*: As the dose rate slows, some cells will endeavor to repair the radiation injury as it occurs. The cell's ability to survive may gain the upper hand if the dose rate is low enough, and the cell's intrinsic radiation repair functions can handle the injury as it occurs. Imagine you are sitting in a rowboat in the middle of a lake and the boat springs a pinhole-sized leak. If the rate of the water entering your boat is slow enough, you can bail the boat fast enough to get yourself back to shore. If the rate of the water entering the boat becomes too fast, you and your boat are going to find yourselves seated on the bottom of the lake. The size of the hole in your boat is analogous to the rate of induction of radiation injury by brachytherapy.

(b) *Repopulation*: Some cells will be killed by the radiation. For those that survive, they no longer have to compete with their adjacent newly dead neighbor for oxygen and other nutrients. They will start to grow faster and, to varying extents depending upon the type of tissue or tumor, repopulate the neighborhood with new cells.

(c) *Reoxygenation*: Oxygen is the most powerful radiosensitizer. To the extent that LDR kills cells, the "neighborhood effect" as described in (b) also applies to oxygen. The continuous reoxygenation will render the remaining cells, which have survived the initial onslaught of radiation more sensitive to subsequent radiation injury.

(d) *Reassortment*: As a general principle, reassortment refers to the progression of cells through the cell cycle during the interval between split doses. To the extent that cells move into the more radiosensitive phases of the cell cycle, they are more likely to be killed by radiotherapy. To the extent that they move into less radiosensitive phases of the cell cycle, they are more likely to be spared. There is a paradoxical form of reassortment, which occurs in some cell lines during LDR. It is called the "inverse dose rate effect." When the inverse dose rate effect occurs, cells march through the cell cycle but become arrested in G2. G2 is a highly radiosensitive phase of the cell cycle, and the cells are more likely to be mowed down by radiation.[310]

Let us put all these factors together and think about what the net effect will be of LDR.

To the extent that cells repair SLD more effectively, then the lower the dose rate, the better the cell survival. The magnitude of the effect will be dependent upon the efficacy and speed of SLD repair in an individual cell line.

To the extent that cells are redistributed into a more sensitive phase of the cell cycle, then the lower the dose rate, the worse the survival unless the dose rate is so low that the cells progress right on through into more resistant phases of the cell cycle. Then, their survival will rise.

To the extent that cells become better oxygenated as a result of LDR, then the worse the cell survival.

On net, from most mammalian cell lines, LDR produces a decrease in cell killing via a "flattening" of the cell survival curve and a "loss of the survival curve shoulder."[311]

Brachytherapy is often a highly effective treatment for solid tumors as a result of its conformal dose distribution and radiobiologic effects on killing tumor cells and sparing normal tissue (Figure 1.45). Brachytherapy requires technical expertise, patience, access to a procedure room or operating room, and due attention to radiation safety and radiation protection. Catheters and seeds can be misplaced, and there are risks of bleeding and infection. Practice makes perfect, and, unfortunately, many radiation therapy treatment centers do not do brachytherapy procedures frequently enough to develop local expertise and confidence with the techniques. It is not surprising that in the United States, inadequate brachytherapy experience is a common citation against radiation oncology residency programs. I am reminded of the words of wisdom of one of my beloved professors at the Massachusetts General Hospital in the early 1980s, Leonidas Harisiadis: "Brachytherapy is a highly effective form of treatment, but doing it can be a pain in the neck."

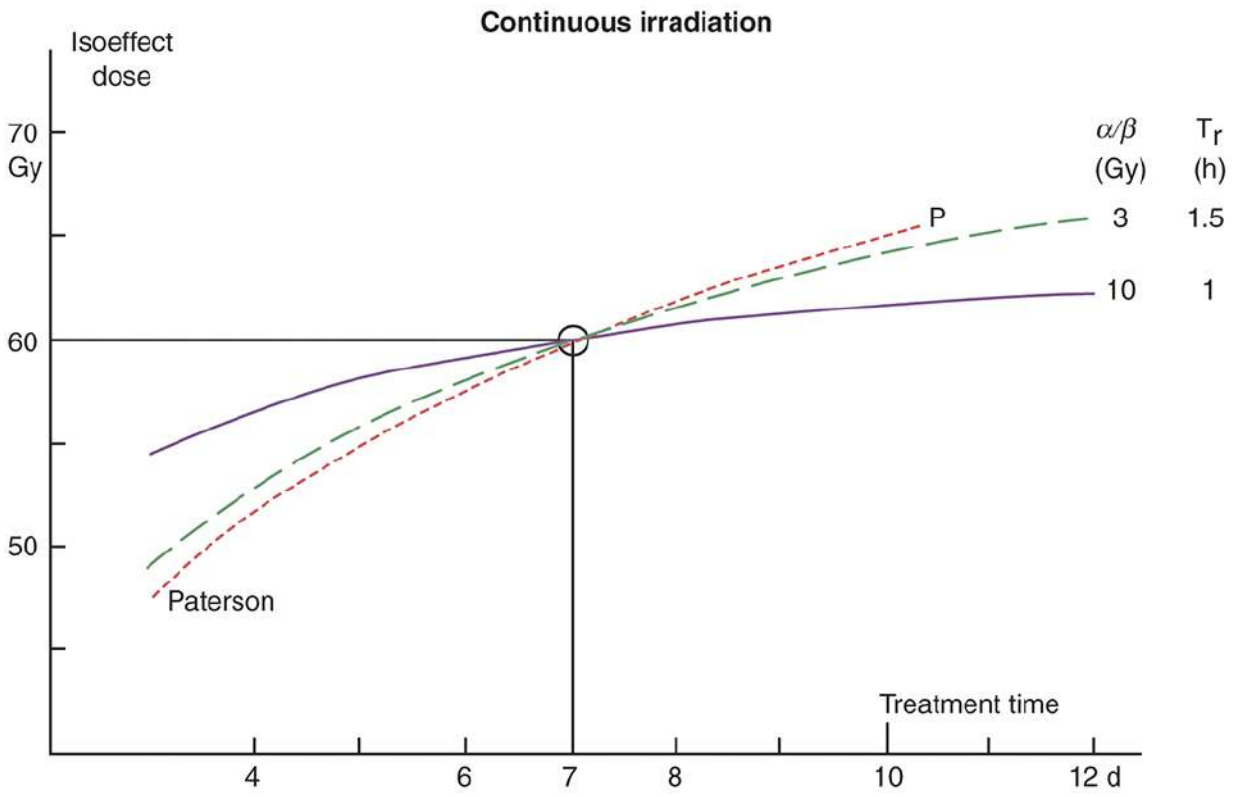


FIGURE 1.45 Low-dose rate irradiation. Isoeffect dose equivalent to 60 Gy in 7 days. Two sets of parameters have been considered for the computation, which would presumably correspond to skin and mucosa early reactions and to the effect on the epithelioma (α/β = 10 Gy, T_r = 1 hour) and to late reactions (α/β = 3 Gy, T_r = 1.5 hour). (Reprinted from Dutreix J. Expression of the dose rate effect in clinical curietherapy. *Radiother Oncol*. 1989;15[1]:25-37. Copyright © 1989 Elsevier Ireland Ltd. With permission.)

With the advent of moderate-dose rate and HDR remote control afterloading devices, increased emphasis has been placed on the biologic effects of dose rate. Many in vitro and in vivo experimental observations indicate variations in cell killing and repair of SLD or PLD with varying dose rates. The so-called dose rate effect is most dramatic between 1 cGy/min and 1 Gy/min.[312] The biologic effect achieved by a given irradiation dose decreases as the dose rate diminishes, chiefly as a result of the increase in cell repair that occurs during continuous prolonged irradiation, because cell proliferation is virtually negligible in the range of treatment times used in LDR brachytherapy.[313]

In some experiments, a bending of the cell survival curve at very LDRs has been noted, instead of the expected exponential result, possibly because of cell redistribution or a decline in the repair capacity with large doses.[314] At a very LDR, because the cell killing is caused only by direct lethal events that are considered independent of the dose rate, cell repair is also negligible. The induction of sublethal injury is relatively slow compared with the rate of repair, and cell killing, by

accumulation of sublethal injury, remains minimal. Variation of the isoeffect dose occurs mainly in the range of medium-dose rates (1-10 Gy/hour), and it vanishes at very HDRs because the cell repair is negligible during the short treatment time.[315]

The dose rate effect in clinical brachytherapy was described initially by Paterson and reiterated by Ellis and Orton.[315-321] The historic isoeffect curve showed a significant increase in dose when time was increased from 2 to 7 days. However, the validity of Paterson's curve was questioned by Pierquin et al,[322] who used the same dose of 70 Gy with treatment times ranging from 3 to 8 days for the treatment of head and neck tumors with Ir-192 implants and did not observe any difference in the control rate or incidence of necrosis. The agreement with Paterson's curve is acceptable when the α/β value equals 3 Gy and repair half-time (T_r) equals 1.5 hours, but the curve is shallower when α/β equals 10 Gy and T_r equals 1 hour. One should expect Paterson's curve to correspond to late reactions and to overestimate the variation for early reactions and control of squamous cell carcinoma.

Several important concepts should be considered regarding the clinical relevance of brachytherapy dose rate:

1. At ultra-high doses and instantaneous dose rates (ie, 10 Gy pulsed in nanoseconds), the rapid deposition of energy consumes oxygen too quickly for diffusion to maintain an adequate level of oxygenation, and dose-response curves are characteristic of hypoxia. The disparate effect of radiation on tumor versus normal tissue lessens. It is thought by some that FLASHRT exploits this phenomenon to achieve relative sparing of normal tissue. Others question this mechanism of action.
2. Based on laboratory data, it may be possible to design schedules with a pulse width of several minutes and a pulse interval of about 1 hour to achieve cell killing equivalent to that obtained with a continuous 30 Gy in 60 hours (0.5 Gy/hour).
3. Using the LQ equation, it is possible to estimate the equivalency of HDR and LDR exposures with a variety of fractionation schedules (remembering that a lower number of fractions may result in enhanced late effects).

Special consideration should be given to the effect of HDR brachytherapy on normal tissues. The tumor dose must be decreased 30% to 50% in comparison with that delivered with conventional LDR brachytherapy.[323,324] (For further discussion, see Chapters 22-24.)

In the past, there was some interest in continuous LDR irradiation with external cobalt units.[203] Pierquin et al[325] used a modified cobalt unit with a small industrial source (activity 45 Ci). Radiation was delivered at 1 to 1.39 Gy/hour to administer

daily tumor doses of 8 to 10 Gy in 7 to 8 hours. A minimum of five treatments was given per week, although occasionally weekends and holidays caused schedule modifications. Patients were given short rest periods every 1 or 2 hours. Tumor doses of approximately 63 Gy were delivered in 8 to 11 fractions, with the volume reduced to 8 by 10 cm^2 after 45 Gy. Nineteen patients with advanced tumors of the mouth and pharynx were treated; 15 had no evidence of tumor 3 months after treatment. Only three patients developed recurrences. Of the 19 patients, 2 developed moist desquamation and 6 developed dry desquamation; the others had only erythema. No significant late effects on the skin or the subcutaneous tissues were noted; 16 of 19 patients developed severe mucositis. Seven patients developed necrosis, six in large areas of the oral cavity and pharynx and, in several instances, at the tumor site.

The Target Theory of Radiobiology and How It Has Shaped Our Understanding of the Cell Survival Curve

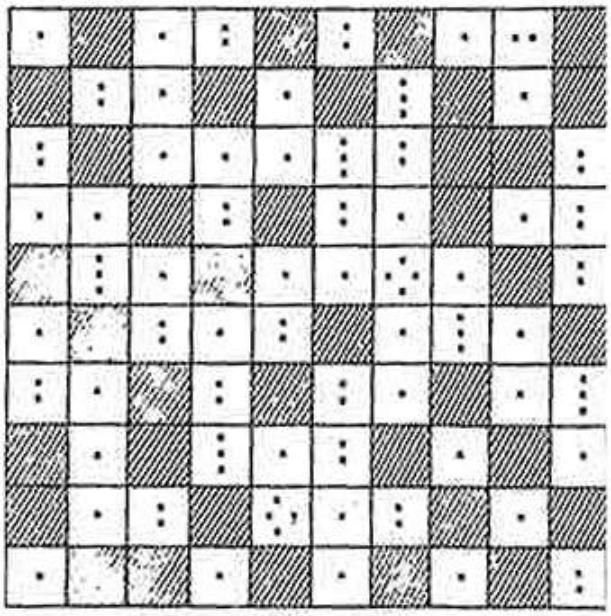
We hold a dart in our hand and toss it at the dart board. What is our goal? To hit the target; to make a "bull's eye." We go to a pistol range and, similarly, aim at the target. We try to "hit the target," whether it is a series of concentric circles or a paper outline of a man. A hunter stalks their prey in the woods with a rifle or a bow and arrow. They, similarly, want to cause a lethal injury and "bag the game."

A dart, a bullet, and an arrow are all physical modalities, not chemical, either used to inflict injury or death or show a person's ability to shoot straight and true. It is not much of a leap to envision how the early students of ionizing radiation's ability to kill cells envisioned that the physical modality of radiation would kill cells by hitting a target. Because many of these original investigators came from the world of physics, they sought to reduce the description of radiation's killing effect on viruses, bacteria, and cells to a series of mathematical equations, which described the cell survival curve. Furthermore, the empirical data, which were derived from radiation survival curves from the exposure of viruses and bacteria, could be fit to these equations.

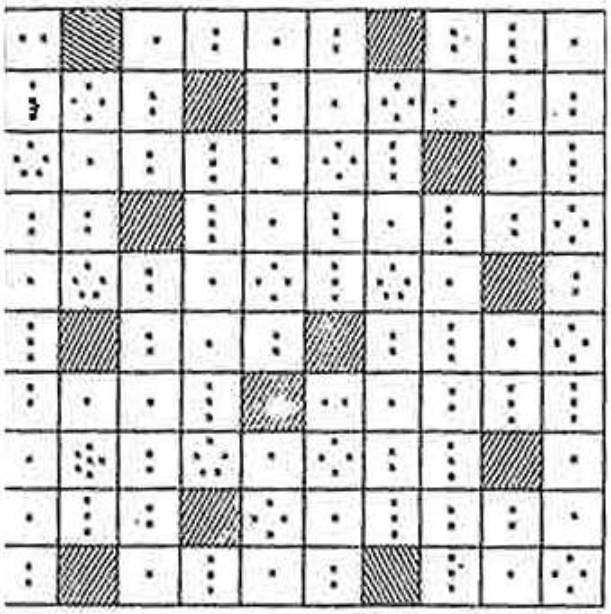
The target theory is based on the concept that the biologic end product of cell death is related to the initial physical events, which occur upon irradiation. The fundamental principle of target theory is that inactivation of the target inside a cell or a bacteria or a virus results in its death.[326] The target is considered a unit of biologic function. The theory implies that the exact site where an ionizing event occurs, such as a double-strand DNA break, is the place where the primary ionizations responsible for that event occurred. Radiation-induced cell death can occur, in simplest terms, when there is a single hit of sufficient power to inactivate a single target and that target is sufficiently important that, when inactivated, the cell dies.

This is called the single-hit/single-target model. One can also envision that some cells might not die unless multiple targets are inactivated. This is called the multiple-hit/multiple-target model. All manner of variations might be imagined, such as a stubborn single target that required repetitive assaults to be inactivated (multiple hit/single target).[327,328]

With low LET radiation, ionizations occur in clusters and sporadically along the path traveled by the particle. The radiation survival of most bacteria and viruses is a constant exponential function of dose. To kill them, it would seem to require inactivation of at least one target per bacteria or virus. At this point, however, we need to rethink our metaphor of the dart, the bullet, or the arrow. Darts, bullets, or arrows are very consciously and with great intent aimed at a specific target. Radiation beams, however, while they are aimed at tumors, are not aimed at individual cells, and they certainly are not aimed with any knowledge of where, at any moment, the important target is located. The target, the DNA, is moving within the cell. This brings us to a crucial point: The deposition of ionizations from radiation and the production of radiochemical injury to the cell are random events[329,330] (Figure 1.46).



$\lambda = 1$



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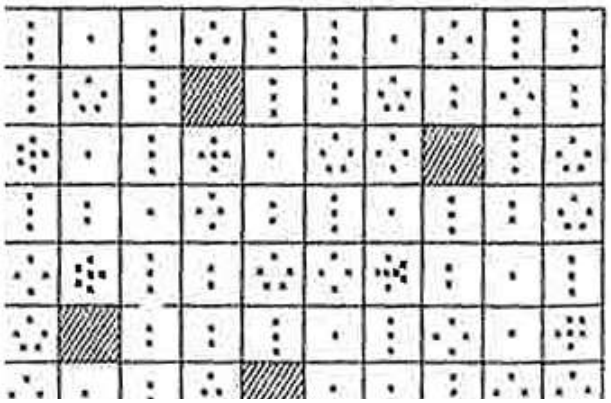


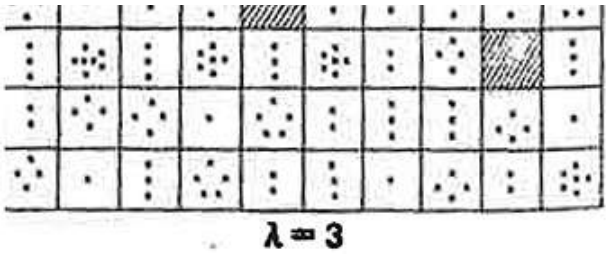


FIGURE 1.46 Let us assume that there are 100 equally sized tumor cells. Any individual cell will be killed if a crucial single target is hit at least once. This is a single-hit/single-target model. Assume we fire a radiation beam capable of producing 100 lethal hits/ionizations at the 100 cells in the upper panel, and the deposition of ionizations occurs along the beam bath in clusters and randomly. Any individual cell's target is struck 0 to 4 times with lethal ionizations. Any cell's target, which is struck at least once, is killed. Sixty-three cells die. Thirty-seven survive. The probability of any one cell surviving the onslaught is 37%, which is e^{-1}. In the next panel, in the middle, we fire a radiation beam capable of producing 200 lethal hits/ionizations at the same 100 cells. The targets of some cells are completely missed. Others are hit up to 6 times. Eighty seven cells die. Thirteen survive. Thirteen is 37% × 37% or e^{-2}. In the lowest panel, we fire a radiation beam capable of producing 300 lethal hits/ionizations at the same 100 cells. How many cells survive? 37% × 37% × 37% or e^{-3} = 5 cells or 5% of the 100. The mathematical result of this random deposition of ionizing energy, which is part of target theory, helps us understand the derivation of the equations, which gives mathematical representation to the cell survival curve, and helps define the concept of D_0. (Reprinted with permission from Withers HR, Peters LJ. Biological aspects of radiotherapy. In: Fletcher GH, ed. *Textbook of Radiotherapy*. 3rd ed. Lea & Febiger; 1980:103-180.)

Unlike the straight-line survival curves of many bacteria and viruses, when you plot the cell survival curve of most mammalian cells on a semilog plot, you see a "shoulder" in the low-dose region indicative of a decreased efficiency of cell killing and then a straight or "exponential" component of the curve.

If we think about a strand of DNA as containing some regions that are essential to maintain the reproductive ability of the cell, then these regions are the specific targets for radiation damage. As we have pointed out, straight survival curves are usually found for the inactivation of bacteria and viruses and some very sensitive normal and malignant human cells, for the radiation response to low LET radiation at very LDRs and the response to high LET radiation.

We described how the dose D_0 is that dose of radiation, which gives an average of one hit per target and reduces the probability of cell survival from 1 to 0.37 or e^{-1}. Using Poisson statistics, and understanding that the probability of the next hit occurring in any given cell is small, then the probability of a given cell surviving is the same as the probability that a cell suffers zero hits = $\exp(-D/D_0)$. (For a brief description of the Poisson distribution, see Box 1.6.) We could also look at the situation, mathematically, this way[330,331]:

Box 1.6

How the Poisson Distribution Helps Us Understand the Equations for the Radiation Cell Survival Curve

The Poisson distribution is named after the French mathematician Siméon Denis Poisson (1781-1840). A Poisson distribution expresses the probability of a given number of events occurring in a fixed interval of time and/or space if these events occur with a known average rate and independently of the time since the last event.

Let us think of some examples in order to understand this concept. Assume that a person receives an average of 50 text messages on their personal electronic device (cell phone or pad) every day from a very wide variety of sources. If the receipt of any particular email message does not affect the probability of getting the next email message, then some days the person will get 49 emails, some days they will get 51, some days they will get 100, and if enough time elapses, then there will be a day when they get zero. While the average number of emails that arrive per day is 50, on any particular day, the number of emails received will vary. Most days, the number of emails will cluster close to the number 50, but there will be a wide variation.

We can think of the deposition of ionizing events in cells and inactivating targets as following a Poisson distribution. If you look back at the panel at the top of Figure 1.46, the average number of hits per cells is 1, but the actual number of hits per cell varies from 0 to 4. If you plot the number of hits per cell, they will follow a Poisson distribution. Most cells will have one hit, but they will be a wide variation.

A Poisson distribution is not the same as a normal distribution (sometimes called a “bell-shaped curve”), although, at first glance, they look somewhat similar. These two statistical concepts come from two different principles. A Poisson distribution is one example for discrete probability distribution, whereas normal belongs to the idea of a continuous probability distribution.

If there is one target per cell, then the probability of that cell surviving (S) an average of one hit per cell for a large number of cells is

$$P(1) = S = e^{-1}$$

If we gave a dose, which caused an average of two hits per cell, for a large number of cells, then the probability of any individual cell surviving is

$$P(2) = S = e^{-2}$$

If we gave a dose, which caused an average of X hits per cell, for a large number of cells, then the probability of any individual cell surviving is

$$P(X) = S = e^{-X}$$

Because the typical radiation cell survival curve for normal and malignant mammalian cells has a "shoulder" and then an exponential component, it can be fit to a multitarget model. The initial slope of the curve, D_1, is the result of single-hit killing and has a slope, which represents the dose that is required to reduce the number of surviving cells from 100% to 37%. The final slope of the curve is the dose that is required to reduce survival from 0.1 to 0.037 or from 0.01 to 0.0037.

We can represent this "two-sloped" curve in the multitarget model by

$$P(\mathrm{X}) = S = 1 - (1 - \mathrm{e}^{-xD})^n$$

S is the probability of survival, D is the dose that causes a mean of hit per cell, X is the number of hits per cells, and N is the number of targets that must be hit in an individual cell to cause cell death.

If we use the term D_0 for the slope of the exponential part of the curve, then

$$S = [1 - (1 - \mathrm{e}^{-D/D_0})^n]^m$$

In this equation, S is the probability of survival; D is the dose of radiation administered; D_0 is the dose that causes a mean of one hit per cell; N is the heterodiploid number so that 1 is haploid, 2 is diploid, and 3 is triploid; and m is the number of targets that must be hit in an individual cell to cause cell death.

For a diploid cell with an average of one target per cell, the equation becomes

$$S = 1 - (1 - \mathrm{e}^{-D/D_0})^2$$

Although there may or may not be discrete and identifiable target areas within DNA, the multitarget model does a pretty good job of predicting many cell survival curves, and the concepts of DQ, D_0, and n are understandable tools in describing radiation sensitivity. There are radiation cell survival curves, which are not well represented by the target model, and the LQ theory was developed to be a more general concept.

RELEVANCE OF RADIOBIOLOGIC CONCEPTS IN CLINICAL RADIATION THERAPY

Radiation and Cancer Biology's Contributions to the Clinical Practice of Radiation Oncology

Generations of radiation oncologists have grappled with the question of radiation and cancer biology's contribution to the clinical practice of radiation oncology. The question was posed and addressed in two classic lectures: first by Stanford's Henry

S. Kaplan[332] in his 1970 Failla Lecture to the Radiation Research Society and then by Harvard's Herman D. Suit[333-335] in his 1983 Failla Lecture. (There are brief biographies of Suit and Kaplan at the end of this chapter.) Treading on the ground prepared for us by Kaplan and Suit, we will reconsider the question in the context of the explosion of knowledge concerning the molecular and cellular basis of cancer.

One can look at the history of cancer biology's contribution to the clinical practice of radiation oncology in terms of two debates: *empiricism versus research-based radiation oncology* and *biology versus physics*.

Empiricism Versus Research-Based Radiation Oncology

Empiricism harkens to the views of David Hume (1711-1776) and other British philosophers of the 17th and 18th centuries and their distrust of the power of unaided reason. In the philosopher's view of empiricism, the best contact between one's understanding of knowledge and the world is not the point at which a mathematical proof crystallizes, but the point at which you see and touch a familiar object. Their paradigm was knowledge by sensory experience rather than by reason alone.[336-338]

Empirical radiation oncologists rely on accumulated clinical experience, also known as "what has worked in the past." They are suspicious of therapies based on theories and laboratory research and feel safest when treading the pathway of tested experience. One can find very strong signs of empiricism in the radiation oncology literature: case reports, single-institution retrospective clinical series, and a marked concern with retrospective clinical analyses of radiation therapy that mine clinical experience to aid the selection of radiation treatment volume, dose, and treatment techniques.

There can be no doubt that the development of radiation oncology has been extensively based on empiricism. We must note, however, that radiation biologists worked closely with the early radiation oncologists. It would be erroneous to suggest that the early history of radiation oncology was completely devoid of reliance on radiation biology.

The theme of hostility to empiricism and support for finding a firm basis for clinical radiation oncology in radiation and cancer biology research is easily identified in the development of the specialty. "Some people do the same thing wrong for 30 years and then call it accumulated clinical experience," said one critic; or it has been said, "If radiation oncologists were put in charge of the war against polio in 1945, they certainly would have perfected the iron lung by now." Our growing knowledge of the genome, proteomics, secondary messengers, and solid tumor biology and the identification of new molecular targets for drugs, immunotherapies, cellular therapies, angiogenesis, oxygenation, and cell cycle

control are changing the present and future of medicine. If clinical radiation oncologists have a future, these individuals say, then they must actively participate in the investigation of the molecular and cellular basis of cancer and in translational research.

Physics Versus Biology

One may also formulate the debate over the role of basic biology in clinical radiation oncology as a pull and tug between physics and biology. Medical radiation physics has dominated the thinking of clinical radiation oncologists. Among the major achievements of this discipline are the following:

- The identification and characterization of physical units of radiation dose
- Significant changes in photon and electron radiation therapy apparatus (initially, kilovoltage and later 60Co, high-energy linear accelerators, the Gamma Knife [Elekta Corp.], and the CyberKnife [Accuray])
- The development of 3D treatment planning for the identification of tumor volume and characterization of irradiated normal tissue
- IMRT and IMPT for improved conformality of treatment beams
- Particle therapy, including neutrons, protons, pions, and stripped nuclei
- Improved stabilization devices to aid the reproducibility of treatment
- Advances in brachytherapy technology, including new isotopes, the afterloading technique, and remote HDR machines
- The apparatus for intraoperative radiation therapy (IORT)
- Equipment for heat deposition in tumors leading to the clinical applications of hyperthermia

At present, a considerable effort in clinical radiation oncology is focused on the tools and techniques provided to the physician by the physicist. Radiation oncology meetings are dominated by discussions of proton therapy, IMRT, radiosurgery/conformal radiation FLASH, and innovations in equipment. Many of these techniques offer better radiation dose distributions, which, one hopes, will lead to an increase in local control of tumors and a decrease in normal tissue toxicity. At present, a better dose distribution is the solution physics offers to the problems of oxygenation, monitoring of tumor blood flow, tumor pH, secondary messengers, tumor suppressor genes, oncogenes, the biology of metastasis, normal tissue radioprotectors, and tumor radiosensitizers. Could it be that “if all you have is a hammer, then everything looks like a nail”?

What has cancer biology ever done for the clinical radiation oncologist? It is, we think, a generally fair question, although it might be characterized as somewhat

narcissistic, along the lines of "what have you done for me lately?" Among the areas one should consider on the list of laboratory contributions to the clinic are the following:

- As early as 1906, Bergonié and Tribondeau[339] enunciated a series of famous laws of radiosensitivity. This was followed by the work of the French investigators Regaud and Ferroux,[340] who demonstrated that whereas a single dose of radiation to the testes always produced maximal damage to the scrotal skin, fractionated exposure spared the skin but destroyed spermatogenesis. They speculated that this same technique of fractionation might be differentially advantageous in the treatment of tumors. This led to Coutard's[341] studies that culminated in the fractionated EBRT techniques of today.
- The identification of the relationship between radiation dose and cell kill led to the characterization of the radiation cell survival curve. This contributed to our understanding of radiation therapy dose and fractionation and, consequently, to our knowledge of radiation repair. This development placed our grasp of radiation fractionation on sound footing and led to investigations of alternative fractionation schemes. This has contributed to improved tumor control as well as the limitation of normal tissue toxicity. Ultimately, the radiation cell survival curve also provided the underpinnings for our views of elements of the dose-response relationship for tumor control and normal tissue toxicity.
- In 1909, Schwarz[342] demonstrated that compression of the skin to diminish capillary blood flow reduces the severity of cutaneous radiation reactions. This may have been the first demonstration of the "oxygen effect." L. H. Gray[343] pointed out the relevance of the "oxygen effect" to radiation oncology by identifying the fact that human neoplasms contain a significant subpopulation of hypoxic cells.[344] A series of important developments have driven home the centrality of hypoxia to our understanding of radiation's effects on tumors. Histopathologic studies and invasive measurements of intratumoral partial oxygen pressure have shown that many human tumors contain regions with low oxygen tension.[345] We now believe that there are at least two different mechanisms, called *diffusion-limited* and *perfusion-limited* hypoxia, behind this observation. Some have called these *permanent* and *transient* hypoxia.[346] Diffusion-limited hypoxia results from inadequate angiogenesis, whereas perfusion-limited hypoxia is associated with intermittent closure of tumor vessels, leading to acute hypoxic conditions for tumor cells downstream from the obstruction. In addition, we now understand how hypoxia activates genes and may produce tumor differentiation and increase a tumor's metastatic potential. Clinical studies have associated the prognostic value of hemoglobin level with tumor local control.[347] The characterization of the hypoxia problem has led to a

variety of largely unsuccessful strategies to overcome it. One has been to have the patient breathe high oxygen content gas mixtures or to irradiate patients in hyperbaric oxygen chambers. Another option involves the use of oxygen-mimetic chemicals. Other treatment strategies include blood transfusions or the specific use of hypoxic-specific cytotoxins, such as mitomycin C.

- There has been considerable growth in our understanding of cell proliferation, the cell cycle, and cell repair mechanisms. We now understand that cells are more sensitive to radiation in M phase and more sensitive to hyperthermia in S phase. Our understanding of the differential sensitivity of cells to radiation during the cell cycle helps provide a rational basis for the use of radiation and chemotherapy.
- As an extension of the knowledge associated with the radiation cell survival curve, clinicians obviously need to have a good understanding of the radiation dose and response for both normal and malignant tissues. The development of research involving the lethal dose of 50% (LD50), local control rates, and normal tissue toxicity in animal models has led to an improved understanding of the radiation dose-response relationship. Correlates of this understanding have included the use of the progressive shrinking-field technique, IORT, and brachytherapy as a "boost" and the use of increasingly conformal beams associated with our improved understanding of how radiation dose should be associated with tumor volume and dose painting. One expects, in the future, to see increasing work in intentional dose heterogeneity as a technique for improving local control.

In his 1983 Failla Lecture, Herman Suit[348] considered the evolution of the principles of clinical radiation therapy. He prepared a table in which he attempted to articulate the principles of radiation therapy invoked in the United States in 1956 and 1982. This is reproduced in the first two columns of Table 1.11. The author of this chapter has added a third column identifying the appropriate principles for 2026. One can see, by scanning across the table, the significant changes that have taken place in our discipline. It is clear that the future holds a role both for empiricism and for research-based radiation oncology as well as a role for improvements in physics and biology. Through cooperation and constructive dialogue, all may contribute to the future of cancer care.

TABLE 1.11 PRINCIPLES OF RADIATION ONCOLOGY DERIVED FROM THE INITIAL WORK OF SUIT

1956	1982	2026
1. Aim for uniform dose throughout	1. Use shrinking-field technique (ie, a	1. Moderate, conform, and "paint" the external beam or brachytherapy dose distribution in

1956	1982	2026
the treatment volume. Treatment volume is constant for entire treatment (ie, no shrinking field).	nonuniform dose distribution related to number of tumor cells).	accordance with the viable tumor cell distribution and minimize injury to normal tissue.
2. Initial large treatment volume is carried to tolerance.	2. Dose to the initial volume is usually less than tolerance. Only the final treatment volume is carried to tolerance dose level.	2. Dose to the initial volume is less than tolerance and may be moderated because of the specific host and treatment factors affecting tolerance.
3. No special emphasis to push dose to higher levels for larger tumors	3. Dose aim is planned on the basis of tumor size or estimated tumor cell number. a. Maximum doses (with higher risk of morbidity) for large tumors b. Modest well-tolerated dose levels for subclinical disease c. For combination of radiation and surgery, use less than radical dose level.	3. Dose aim is planned on the basis of tumor size, estimated tumor cell number, extent and completeness of surgical resection, biologic and genetic and imaging predictors of tumor aggressiveness, and response to induction chemotherapy. a. Maximum doses (with higher risk of morbidity) for large and more aggressive tumors b. Modest well-tolerated dose levels for subclinical disease c. For combinations of radiation and surgery, chemotherapy, and/or biologic therapy, one might use less than radical dose level in certain situations. d. For combinations of external beam radiation therapy and brachytherapy or radiation therapy and hyperthermia, the dose of each modality is modified as a function of the other modalities used.
4. Little priority given to planned combinations of radiation and surgery.	4. Major emphasis on planned combinations of radiation and surgery	4. Major emphasis on planned combinations of radiation, surgery, chemotherapy, hormonal therapy, and biologic therapy
5. Treatment fields are square or rectangular.	5. Secondary collimation is utilized on virtually all fields to reduce irradiation of tissues not suspected of involvement by tumor.	5. Multileaf collimators and intensity modulation and/or use of electrons, protons, or charged nuclei are used in an attempt to improve conformality of the radiation and reduce irradiation of tissue not suspected of being involved with tumor. Radiation dose distribution is based on sophisticated imaging technologies.

1956	1982	2026
6. Radiation alone is the general rule.	6. Multidisciplinary approach accepted as most effective for most tumor problems	6. The radiation oncologist is expected to be trained in and make use of genetics, biomarkers, and conventional pathology for tumor subtyping and grading; anatomic and molecular staging; diagnostic imaging; and the therapeutic role of chemotherapy, hormonal therapy, biologic therapy, and surgical therapy.
7. Results of treatment described almost exclusively in terms of absolute survival at a fixed period (eg, 5 y).	7. Results analyzed on the basis of detailed assessment of causes of failure (eg, local persistence or regrowth, local complication, marginal miss, regional spread, distant metastases, intercurrent disease)	7. The phase III randomized prospective trial the gold standards for clinical decision-making. Decisions based on properly planned and conducted cancer trials concerning radiation therapy dose, volume, and technique are most appropriate. It is expected that evidence-based medicine will guide clinical decision-making. If such trials are not available or are inadequate, then phase II trials or retrospective reviews involving survival, local control, patterns of failure, and multivariate analysis of outcome are often useful. The future will depend on and meta-analyses are research in cancer biology and medical physics being brought to the clinic.

It is essential that radiation oncologists remain current with scientific findings that will be critical in the development of improved therapeutic strategies. Approaches that alter the cell's surface membrane, receptors, secondary messengers, or nuclear contents may overcome cellular radiation resistance. By exploiting cellular mechanisms related to apoptosis, it may be possible to kill cells with irradiation by inducing changes other than unrepaired DNA damage. With an understanding of the tumor microenvironment and techniques such as complementary DNA microarrays, as well as an understanding of how growth factors may alter cellular processes, innovative bioinformatics and improved combined modality strategies may emerge. The ability to genetically sequence tumors will provide information beyond the era when biologic effects were attributed to a single gene. A better understanding of hypoxia may improve clinical outcome with antihypoxia strategies, including hypoxic cell radiosensitizers and hypoxic cytotoxic agents. Cyclins and growth factors may be useful as clinical radiation modifiers. Pharmacogenomics may inform how we prescribe drugs.

There is a critical need to balance the investment in technical aspects of radiation therapy with concepts and innovative approaches derived from a better understanding of cancer biology. These scientific developments will greatly alter the way in which we practice our discipline

IMPORTANCE OF TREATMENT PLANNING IN RADIATION THERAPY

The predicted consequences of radiation therapy are based on the precision with which the dose and the irradiated volume are defined. An imprecise treatment system could lead to a high incidence of normal tissue injury with a low probability of tumor control.[349] Decreasing irradiation doses to avoid complications will further reduce the probability of achieving tumor control if such action is based on the wrong assumption that the tumor control/complication ratio is related only to radiation dose levels. The ICRU recommends a ±5% accuracy for dose delivery computations.[350,351] However, every effort should be made to develop accurate dose calculation algorithms, including methods to correct for inhomogeneities in tissue density and the shape of the patient's body, and to develop practical treatment planning capabilities to obtain the highest possible dose optimization in the irradiated volume (tumor and normal tissues). There are benefits of reducing the treatment volume in an effort to deliver higher doses of irradiation. This may improve the quality of tumor control without excessively irradiating surrounding normal tissues, thereby decreasing treatment-related morbidity.

Various steps can be taken to decrease toxicity in normal tissues, including precise treatment planning and irradiation techniques, selectively decreased volume receiving higher doses dictated by estimated cell burden, and maneuvers to exclude sensitive organs from the irradiated volume. With the emphasis on organ preservation, treatment planning is critical to achieve maximum TCP and satisfactory cosmetic results.

Optimal dose distribution in EBRT may be achieved by a combination of multiple stationary beams or by moving beam therapy, such as in arc or full rotational techniques or IMRT or IMPT. In addition, the optimal dose distribution in many tumors requires access to more than one modality or beam energy particle type. A combination of external beams and brachytherapy may also be required, depending on the location of the tumor.

Three-Dimensional Treatment Planning

Computer technology creates accurate and timely computation, display of 3D radiation dose distributions, and dose-volume histograms (DVHs).[352,353] These developments have stimulated sophisticated 3D treatment planning systems, which yield relevant information in the evaluation of tumor extent, definition of target volume, delineation of normal tissues, virtual simulation of therapy, generation of digitally reconstructed radiographs, design of treatment portals including the use of MLCs and aids (eg, compensators, blocks), calculation of 3D dose distributions and dose optimization, and critical evaluation of the treatment plan.[354,355]

With advanced computerized and display technologies, contiguous CT and/or MRI and/or PET slices are used to define anatomic structures and target volumes. External radiation beams of any possible orientation are simulated. A significant feature of these systems is the so-called beam's-eye view, in which patient contours are viewed as if the observer's eye is placed at the source of radiation looking out along the axis of the radiation beam.[356] These systems allow simulation of the geometric setup; evaluation of the plan for dose optimization still is made on the merits of volumetric dose distributions.

Quantitative treatment planning evaluation is crucial in the selection of the best portals and radiation beams to deliver an optimal dose to the tumor with relative sparing of normal tissues. The ICRU Report 50 and its supplement G2 define 3D volumes for the prescription and reporting of EBRT.[357] The concepts of PTV and CTV were defined earlier in this chapter.

The DVH is useful as a means of dose display, particularly in assessing several treatment plan dose distributions.[358] A DVH provides a complete summary of the entire 3D dose matrix, showing the amount of target volume or critical structure receiving more than a specified dose level. Because a DVH does not provide spatial dose information, it cannot replace the other methods of dose display; it can only complement them.

Models for optimization of 3D dose distribution using biologic models of tumor and normal tissue responses correlated with physical radiation doses have been described.[359,360]

Intensity-Modulated Radiation Therapy and Intensity-Modulated Proton Therapy

An approach to 3D treatment planning and conformal therapy optimizes the delivery of irradiation to irregularly shaped volumes through a process of complex inverse (or forward) treatment planning and dynamic delivery of irradiation that results in modulated fluence of photon or proton beam profiles and a more conformal dose to the target volume(s), with enhanced sparing of surrounding normal tissues.[361,362]

Treatment planning begins with the determination of the GTV and the CTV, and an estimate of where the tumor may spread. CT, MRI, and fluorodeoxyglucose PET imaging along with image fusion have enhanced the possibilities for determining the target more accurately. The PTV accounts for inaccuracies in positioning patients and organ motion.

In "forward" planning, software calculates the dose distribution, displays it with a 3D anatomic model, and provides analytical and graphical metrics for assessing the adequacy of tumor treatment and normal tissue avoidance. The physician decides if

the plan is acceptable. If not, an alteration is made in the beam arrangement, and the process is repeated.[363]

Computerized optimization techniques have led to "inverse" planning. Goals of an acceptable treatment plan are delineated, and the inverse planning algorithm searches through many thousands of possibilities to find a plan that best satisfies the goals. In IMRT, the beams are broken up into "beamlets" (on the order of 0.5 by 0.5 or 1 by 1 cm^2) that can each have a different intensity. IMRT or IMPT may improve the ability to treat with a high radiation dose while minimizing dose to nearby critical structures.

There are a variety of forms in which IMRT can be administered:

1. A linear accelerator and MLC, with a variety of beam configurations at various angles, may be used; the MLC determines the portal shape of each of the portals. Photon-modulated fluency may be obtained (a step-and-shoot method). Analogous techniques may be used with protons.
2. Dynamic computer-controlled IMRT is delivered when the configuration of the beams outlined with the MLC is changing at the same time that the gantry or the accelerator is changing positions around the patient.
3. In helical TomoTherapy, the photon fan beam continually rotates around the patient as the couch transports the patient longitudinally through the ring gantry. The verification processes for helical TomoTherapy are enabled by the use of the ring gantry; the geometry of a CT scanner allows tomographic processes to be reliably performed. Dose reconstruction is a key process of tomography; the treatment detector sinogram computes the actual dose deposited in the patient. The length of the beam is 40 cm at the central axis and has a width that can vary between 0.5 and 5 cm. The lengths of the MLC in helical tomography are temporarily modulated or binary in the sense that they are rapidly driven either in or out by air system actuators rather than beam slowly pushed by motors driving lead screws as in the conventional MLC.
4. The robotic IMRT system consists of a miniaturized 6-MV photon linear accelerator mounted on a highly mobile arm and a set of ceiling-mounted x-ray cameras to provide near real-time information on patient position and target exposure during treatment.

The majority of the IMRT systems use 6-MV x-rays, but energies of 8 to 10 MV may be more desirable in some anatomic sites (to decrease skin and superficial subcutaneous tissue dose). Higher energies will increase neutron contamination of the therapeutic beam(s). The dose distribution and field-shaping parameters are based on inverse 3D planning using a specially defined minimal dose to target and dose constraints for surrounding normal tissues.[364,365] Inverse planning starts with an

ideal dose distribution and finds through trial and error or multiple iterations (simulated annealing) the beam characteristics (fluence profiles) and then produces the best approximation to the ideal dose defined in a 3D array of dose voxels organized in a stack of 2D arrays.[366]

A back-projection technique through careful choice of filters, beam placement, and shaping of the portals conforms the irradiation dose to the shape of the tumor, minimizing dose to critical adjacent structures. When this technique is used, it is critical to adhere to basic concepts of treatment planning and evaluation of the pathobiology of malignant disease. Well-designed treatment plans based on radiographic imaging (CT, MRI, or PET), which, in most instances demonstrates gross disease, are necessary to minimize the risk of missing or underirradiating adjacent microscopic or subclinical tumor.

Given the added time and labor involved in IMRT, numerous issues require study:

1. Can the tumor be localized with sufficient accuracy to take advantage of the improved dose localization?
2. Treatment plans that produce a rapid drop in dose between the edge of the tumor and the normal tissue require more exact patient positioning; otherwise, there is a high risk of underdosing the tumor or overdosing normal tissue.
3. Some IMRT plans treat the center of the tumor with a very high dose to achieve an acceptable dose at the edge. This may not be optimal.
4. Many IMRT techniques spread a low dose over a larger volume or normal tissue. This may increase the risk of secondary malignancies years later.

Four Truisms Regarding Radiation Oncology or Four Debatable Points of View?

Herman Suit asserted the existence of four truisms related to randomized trials and proton beam radiation therapy.[367,368] The definition of "truism" is "a statement that is obviously true" or, perhaps, a statement which is self-evident. Suit's truisms, while derived regarding whether randomized prospective clinical trials are necessary for proton beam therapy, might be reviewed as having general applicability to the specialty. Suit argued that randomized prospective clinical trials to ascertain the alleged benefits of highly conformal proton beam therapy were unnecessary. Protons, he felt, were intuitively obviously better.

The four truisms are:

(1) There is no benefit to any patient for any radiation of normal tissue not suspected of involvement by tumor.

(2) Complications of radiation therapy never occur in unirradiated tissues.

(3) Ascertaining whether a smaller treatment volume of normal tissue being exposed to radiation is superior is not a medical research question.

(4) Experimentation only investigates the magnitude of gain for a superior radiation therapy dose distribution or its cost—it does not ascertain the necessity of seeking that gain.

Following Suit's logic, we can claim two benefits attributed to proton beam radiation therapy for some forms of childhood cancer: (a) either the ability to reduce radiation dose to tissues uninvolved with tumor in some cases and/or (b) the potential to escalate the dose to the tumor in some cases.

Suit's truisms are articulate, but are they all self-evident, particularly for adult tumors? Each alleged truism may be critiqued.

> "There is no benefit to any patient for any radiation of normal tissue not suspected of involvement by tumor."

"Suspected" is an imprecise term in this context. In many patients, we make a probabilistic assessment of whether tissue is involved by tumor. Then, based on that assessment, we decide if the risks of irradiating that tissue warrant the potential benefit. Should the patient's neck be irradiated, when we can neither palpate any involved cervical lymph nodes or image any, in squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, nasopharynx, or larynx? Should the internal mammary or paraclavicular lymph nodes be irradiated in a patient with infiltrating ductal carcinoma of the breast? How much "suspicion" or normal tissue involvement by tumor is required to derive a potential benefit by subjecting it to radiation therapy?

"Complications of radiation therapy never occur in unirradiated tissues."

We know that we can find evidence of cells reacting to pulmonary radiation therapy in the unirradiated lung. Infections promoted by the immunosuppression produced by radiation therapy can occur in tissues distant from those irradiated.

> "Ascertaining whether a smaller treatment volume of normal tissue being exposed to radiation is superior is not a medical research question. Experimentation only investigates the magnitude of gain for a superior radiation therapy dose distribution or its cost—it does not ascertain the necessity of seeking that gain."

These are the most controversial of the alleged truisms. First of all, in many cases, we do not have the clinical tools to ascertain the presence of any benefit to a smaller radiation therapy treatment volume. Yes, highly conformal radiation therapy to a 65-year-old with glioblastoma multiforme (GBM) will expose less normal tissue to radiation than less conformal treatment. We have no ability to measure any alleged benefit of a 20-Gy isodose line administered over 6 weeks to the nondominant

hemisphere of the brain in this GBM patient with less conformal treatment compared to, say, a 10-Gy isodose line over 6 weeks with more conformal treatment. Second of all, and most importantly, the world of medicine is full of examples of concepts that did not warrant randomized prospective studies because the answer was self-evident. Then someone did the randomized study and showed that the self-evidently true answer was wrong.

HEAVY PARTICLE BEAMS

One can imagine two possible mechanisms by which one could improve on therapeutic x-rays with an alternative particle. First, the alternative particle could have energy deposition characteristics that lead to a superior dose distribution. A beam, conceivably, could have more skin sparing than x-rays, better stopping characteristics, and/or less side scatter. This might allow a more conformal therapy. Second, the alternative particle could have advantageous radiobiologic properties. It might be more toxic than x-rays to hypoxic cells or cells in the late S phase of the mitotic cell cycle. Such a particle would have, perhaps, a lower oxygen enhancement ratio (OER) and a higher RBE than x-rays. These two possible mechanisms of improving on x-rays are not mutually exclusive. A particle could have both superior physical dose distribution and radiobiologic properties.

The effort to identify improved alternatives to x-rays has focused on the group of particles called hadrons. These are particles constituted of strongly interacting particles called quarks and gluons. The hadrons include the mesons and the baryons. The latter include protons, neutrons, negative pions, and the nuclei of heavier atoms, such as He^{2} (helium), C^{6} (carbon), O^{8} (oxygen), Ne^{10} (neon), and Ar^{18} (argon). All of these forms of radiation are distinguished from x-rays and electrons by their greater masses. These alternative radiation modalities are relatively difficult to produce, are expensive, and are considerably more difficult to control.

Proton, heavy ion, and hadron beams have attracted radiation oncologists because they offer interesting and potentially beneficial dose distribution characteristics. Radiobiologically, their properties are not significantly different from x-rays. When a heavy particle beam traverses tissue, the dose is deposited in an approximately constant rate. The rate of energy loss (also called the “stopping power”) of a heavy charged particle is proportional to the square of the particle charge and inversely proportional to the square of its velocity. As a proton or heavy ion slows down, its rate of energy loss increases and so does the ionization or absorbed dose to the tissue. Near the end of the proton’s range, the deposition of energy rises very sharply before dropping to almost zero. This peaking of dose near the end of the particle range is called the Bragg peak. As a result of the Bragg peak effect and minimal scattering, the proton offers the potential advantage and the ability to concentrate

dose inside and immediately adjacent to the tumor volume and minimize dose to surrounding normal tissues. There are multiple proton treatment facilities operational and under construction throughout the world.

For a thorough discussion of proton and neutron radiation, as well as a consideration of pi meson therapy and charged nuclei therapy such as helium ions and neon ions, the reader is referred to Chapters 11 and 20 of this volume.

BORON NEUTRON CAPTURE THERAPY: AN IDEA WHOSE TIME HAS NOT YET COME

The fundamental concept of boron neutron capture therapy (BNCT) is the production of high LET particles ($^{7}Li^{3+}$ and $^{4}He^{2+}$) when one "tags" or "labels" a tumor cell with a compound having a large cross section capable of capturing a "slow" (thermal) neutron. After the compound captures the neutron, it goes into an excited state. The excited fission of the ^{9}B nucleus will release energy, which drives the heavy ion products over short distances comparable to the dimensions of one cell. A 0.48-MeV photon is also produced in 94% of the fission events. This is useful for monitoring the reaction but is of little consequence for cell killing.

The neutron has a mass of 0.782 MeV, more than that of the proton. Neutrons were identified in 1932 by Chadwick[369] at Cambridge University's Cavendish Laboratory. Subsequently, Fermi[370] discovered that neutrons react most efficiently with a number of elements after they are slowed by passage through a hydrogen-rich substance such as paraffin. Chadwick and Goldhaber,[371] Taylor and Goldhaber,[372] and Burcham and Goldhaber[373] showed that slow neutron bombardment of specific stable isotopes of boron, lithium, and nitrogen yields charged particle tracts in photographic plates. The tracts from boron's interaction with neutrons were short and straight and were consistent with the formation of two particles traveling in opposite trajectories. In photographic gelatin, their average travel distance was 7.6 μm. The boron neutron capture process is highly localized. In principle, one could kill a tumor cell containing boron while sparing an adjacent normal cell that does not contain boron (Box 1.7).

Box 1.7

Terms Pertinent to Neutron Capture Therapy

Epithermal neutrons: Energetic neutrons pass through an intermediate energy range on the way to becoming slow or thermal neutrons. This intermediate energy range is called epithermal.
Fast neutrons: Fast neutrons are highly energetic and travel quickly.

Moderation: Neutrons generated from the fission process or from particle bombardment of materials have significant energy. They lose that energy by colliding with atoms in their environment and create energetic recoil atoms. After a sufficient number of collisions, the neutrons lose essentially all of their energy and become thermal. This process of energy loss is called moderation. The material that provides the atoms the fast neutrons collide with is called a moderator. Water is the usual moderator.

Slow neutrons: Slow neutrons have little energy. They also are referred to as thermal neutrons because they have the same average kinetic energy as gas molecules in their environment.

Thermalize: Epithermal neutron beams, as they penetrate tissue, become additionally moderated. This is called becoming thermalized.

Based upon Yanch JC, Shefer RE, Busse PM. Boron neutron capture therapy. In: Fletcher GH, ed. *Sci Med.* 1999;January/February:18-27.

The complete chemical reaction is as follows:

$^{10}B + {}^{1}n \rightarrow {}^{7}Li + {}^{4}He + \gamma + 2.4$ MeV.

The attraction of BNCT, for many clinicians, was the notion of the "magic bullet." The idea that one could specifically label tumor cells with a compound with an enlarged cross-sectional area, not label surrounding normal tissue, and therefore, deposit radiation only in the tumor is most attractive. Unfortunately, reality is far different from the ideal.

Fast neutrons differ from x-rays in the mode of their interaction with tissue. Whereas x-ray photons interact with the orbital electrons of atoms via the Compton or photoelectric process and set fast electrons in motion, neutrons interact with the nuclei of the atoms of the absorbing tissue. Neutrons put fast recoil protons, α-particles, and heavier nuclear fragments in motion. At energies above about 6 MeV, inelastic scattering by neutrons takes place.[374] A neutron may interact, for example, with a carbon or an oxygen nucleus to produce α-particles. These led to nuclear fragments called spallation products.

The LET is considerably higher for neutrons than for x-rays. Because the LET of neutron radiation is higher, the slope of the cell survival curve becomes steeper and the size of the initial shoulder gets smaller. This produces a beam with a lower OER than x-rays—neutrons are considerably more toxic to hypoxic cells than x-rays. Also, neutrons are more toxic to cells in phases of the cell cycle that are relatively radioresistant to x-rays. Thus, the RBE of neutrons is higher than x-rays.[378]

In 1936, Locher[379] published a theoretical account of the possible biologic effects and therapeutic possibilities of boron neutron capture.

> The possibility of destroying or weakening cancerous cells is by the general or selective absorption of neutrons by themselves, and particularly there is the possibility of introducing small quantities of neutron absorbers into the regions where it is desired to liberate ionizing energy. A simple illustration

> would be the injection of a soluble nontoxic compound of boron, lithium, or gold into a superficial cancer followed by bombardment with slow neutrons. (Locher GL. Biologic effects and therapeutic possibilities of neutrons. *Am J Roentgenol*. 1936;36:1-13.)

In 1950, Conger and Giles[380] from Oakridge National Laboratories reported that the trace amounts of boron normally present in lily bulbs were responsible for most of the radiation changes in the plants following exposure to slow neutrons. This demonstrated the biologic fact clearly and led William H. Sweet[381] and others to see if the normal brain could exclude enough boron and if tumor tissue could take up enough boron to produce an appropriate therapeutic ratio.

Sweet began work at the Brookhaven National Laboratory in New York with a 20-MW nuclear reactor in 1950.[382] He initially treated 10 patients with glioblastoma multiforme who had undergone gross total resection of their tumors at the Massachusetts General Hospital in Boston. Sweet described the initial clinical work:

> A portion of the shielding atop the reactor was removed to permit placing the lateral aspect of the patient's intact scalp and skull at the specially designed portal. To prevent scalp damage, we tied off the external carotid arteries and covered the entire scalp with tight elastic bandages in an attempt to prevent boron-containing blood from entering the scalp. These tactics, however, did not prevent the development of several large radiation erosions of the scalp. Five patients received a single radiation dose and the remaining 5 were given the treatment in 2 to 4 fractions. Although there were no life threatening complications of therapy, all of the patients died from 6 to 21 weeks after the first session of neutron capture therapy, which was usually the case in the 1950s for glioblastoma patients treated by any means. Postmortem studies done in 6 of the patients showed abundant viable tumor. Their painful scalp lesions together with the inadequacy of the radiation dose lead us to attempt to deliver the thermal neutron beam directly to the grossly normal but microscopically tumor-infiltrated brain. The Rockefeller Foundation made this approach possible with a $500,000 gift to the Massachusetts Institute of Technology to provide additional features to a nuclear reactor that was then being constructed. Included was a surgical operating room immediately beneath the reactor core. This permitted us to turn down the scalp, bone, and dural flap used in the prior removal of gross tumor. At reopening the cerebrospinal fluid replacing tumor was also drained away to give maximally unimpeded access of the thermal neutrons through sterile air to the tumor-infiltrated brain.[383] (Reprinted by permission from Springer: Sweet WH. Early history of development of boron neutron capture therapy of tumors. *J Neurooncol*. 1997;33(1-2):19-26. Copyright © 1997 Kluwer Academic Publishers.)

Sweet treated 18 patients at the Massachusetts Institute of Technology. They died from 10 days to 11.5 months after radiation. In every patient, the cause of death was cerebral, and extensive irradiation necrosis of the brain was induced in nine cases. In two cases, only recurrent tumor was seen, and in one patient, there was extensive radiation necrosis and tumor.

Some of the initial work with BNCT was highly controversial and, decades later, led to investigations concerning the nature of informed consent for these human experiments. President William J. Clinton created, by executive order, a commission to study the ethics of Cold War–era medical experimentation using radiation. One of the collateral effects of this commission's report was that Sweet and his colleagues

were sued for malpractice 40 years after the BNCT experiments. Although the plaintiffs were awarded substantial damages at trial, the decision was eventually overturned on appeal.[384]

Lack of progress in BNCT may be attributed to two factors: inadequate tumor specificity of the boron compounds used to localize in the tumor and poor penetration into tissue of the thermal neutrons. In addition, the thermal and antithermal neutron beams produced by nuclear reactors have considerable contamination with γ-rays and fast neutrons. These can cause normal tissue damage even in the absence of boron concentration in tissues. In addition, there are a number of compounds in normal tissue that can interact with thermal neutrons and have capture events of their own, producing biologic damage even to non–boron-containing tissue.

The development of suitable boron-carrying agents remains a stumbling block to clinical programs. The ideal agent will be nontoxic, will have a high tumor-to-normal tissue ratio, and will have a high absolute boron concentration.

Investigations of improved ways of delivering thermal neutrons have centered on two areas: the use of nuclear reactors and useful alternatives to reactors.

The most intense way to generate a neutron beam is with a nuclear reactor. Despite the high neutron intensities available from these reactors, it is widely recognized that alternative neutron sources will be necessary for BNCT to be performed. First of all, there are few suitable nuclear reactors in operation. A patient would have to travel a long distance for treatment. Second, nuclear reactors, for political and social reasons, are not likely to be sited near major population centers in the future. A major reactor facility located far from a population center would have to be provided with its own clinical infrastructure The target patient population would not be large enough to support the operation of more than a few medical reactors. Therefore, some investigators have been pursuing nonreactive sources of thermal and epithermal neutrons with a sufficiently high flux to be used for BNCT.[385-387]

An alternative to the reactor would be a neutron source from radioactive decay such as californium-252 (^{252}Cf). However, the production of a neutron beam with sufficient intensity for BNCT would require more than the entire present annual supply of ^{252}Cf. Another alternative source is a particle accelerator. Accelerator-based neutron beams are created when light ions such as protons or deuterons are accelerated in an electric field and are made to bombard target materials.

GRID THERAPY, BYSTANDER EFFECTS, ABSCOPAL EFFECTS, RADIATION-ENHANCED ANTIGEN PRESENTATION, AND DANGER-ASSOCIATED MOLECULAR PATTERNS

Early in radiotherapy's history, some clinicians tried to improve normal tissue sparing, particularly the skin, by creating a shielding block that resembled a checkerboard. Imagine a radiation beam striking a checkerboard in which the black squares are lead and the white squares are open. This would permit radiation to travel through the open squares, while the black squares would shield the patient, the patient's normal tissue, and the tumor from radiation. If a single-photon field was used to deliver the grid pattern of radiation, there would be a dose distribution of peaks and valleys across the normal tissue and the tumor because of penumbra and side scatter. A radiation dose, which is delivered to a contiguous region, induces greater damage than the same dose fractionated in space. This concept is generally called *GRID radiation therapy*. It can now be performed with TomoTherapy, MLCs, and/or a proton beam. In three dimensions, the GRID or "checkerboard" is probably better thought of as a honeycomb.

Spatially fractionated radiotherapy causes irradiated tumor cells to engage in cell-to-cell signaling. Neighboring unirradiated cancer cells are clearly affected. One observes cells undergoing a stress response, activation of repair enzymes, and antioxidant gene expression. It is as if the irradiated cells are sending a "mayday . . . mayday . . . I am under attack" message to neighboring cells. Furthermore, in some experimental models, the irradiated cells provoke an immune response, which can kill irradiated and unirradiated cells. It appears that the radiation causes the emission of antigens and cell signals, which activate an immune reaction. The phenomena of the irradiated cells have an effect upon neighboring unirradiated calls, called "the bystander effect."[388]

The *abscopal effect* is a phenomenon where the localized treatment of a tumor causes not only a shrinking of the treated tumor but also a shrinking of tumors outside the scope of the localized treatment. Imagine, for example, an experimental mouse with a tumor implanted in the left thigh and a tumor of the same histology implanted in the right thigh. If a highly localized external radiation beam were directed against the tumor of the left thigh and it regressed and, in addition, the unirradiated tumor of the right thigh regressed, then the behavior of the tumor of the right thigh is called an abscopal effect. In a 1953 paper in the *British Journal of Radiology*, R.H. Mole proposed the term "abscopal" ("ab," away from; "scopus," target) to refer to radiation's effects "at a distance from the irradiated volume but within the same organism."[389]

A current active area of research addresses the idea that irradiation may augment the immunogenicity of tumors and accentuate the cytotoxic effects of radiotherapy both on the irradiated tumor and on distant tumors—a form of the abscopal effect. In combination with immunotherapeutic agents, an irradiated tumor might be able to act as an autologous in situ tumor vaccine. The mechanism of action might involve radiation-enhanced antigen presentation, damage-associated molecular patterns, or

danger-associated molecular patterns, by which host molecules initiate and perpetuate a noninfectious inflammatory response, immunomodulation of tumor cell surface molecules, and the modulation of cellular infiltrates in the tumor microenvironment.[390,391]

FLASH THERAPY

FLASH radiotherapy (FLASHRT) is defined as the ultrafast delivery of therapeutic radiation at dose rates several orders of magnitude greater than those used in conventional radiation therapy. If a typical linear accelerator delivers its dose at 0.5 to 5 Gy/min, FLASHRT treats at a rate on the order of 40 Gy/s.

Why? The leading theory is that ultrafast delivery of radiation therapy depletes tissue of oxygen and causes transient hypoxia. (There is far from uniform acceptance of this theory.) This exerts a protective effect on oxic normal tissue by rendering it hypoxic. In contrast, tumors have significant anoxic and hypoxic components, FLASHRT eliminates the differential oxygen effect between normal tissue and tumor and, therefore, allows the delivery of high doses of radiation therapy with a relatively protective effect on normal tissue.

If this story sounds vaguely familiar to older radiation oncologists, it is because it is familiar and almost 60 years old. In 1968, Herman Suit and Robert Lindberg described this idea succinctly. A possible explanation of the radioresistance of sarcomas of bone and soft tissue is the presence of hypoxic and radioresistant cells. If one could eliminate the pO_2 differential between tumor and normal tissue, then it might be possible to achieve increased effectiveness of radiation therapy without increasing the risk of normal tissue injury. "A simple, direct, and relatively effective way of essentially eliminating tissue pO_2 differentials between and tumor of an extremity and the surrounding normal tissue would be to apply a tourniquet to the upper thigh or arm and thereby prevent accession of oxygen-containing blood to the part."[392]

The clinical results of the tourniquet technique of radiotherapy were unsatisfactory, but the principle articulated is the same biologic explanation offered for the normal tissue–sparing effect of FLASHRT: eliminating the discrepancy between the oxygen status of normal tissue and tumor.

In 1959, Dewey and Boag found that the radiosensitization achieved by irradiating bacteria in 1% oxygen compared to 100% nitrogen was eliminated by using ultra HDRs compared to conventional dose rates.[393] Beginning with these experiments, the oxygen depletion hypothesis of FLASHRT was developed.

There are alternative theories regarding the mechanism of action of FLASHRT, including induction of an immune response, vascular changes, and/or microdosimetric effects.

FLASHRT and its early clinical results are addressed in Chapter 18.

THE CARE AND PROTECTION OF THE RADIATION ONCOLOGY PATIENT

The Process of Care in Radiation Oncology

The "process of care" in radiation oncology refers to a conceptual framework for ensuring the appropriateness, quality, and safety of all patients treated with radiation for therapy. Each of the aspects of the process of care in radiation oncology requires knowledge and training in the natural history of cancer and certain benign diseases, radiobiology, medical physics, and radiation safety that can only be achieved by board certification in radiation oncology (or equivalent training) to synthesize and integrate the necessary knowledge base to safely and completely deliver care. This high level of training and board certification applies as a recommendation for all of the specialists on the radiation oncology team. The medical therapeutic application of ionizing radiation is irreversible, may cause significant morbidity, and is potentially lethal. The use of ionizing radiation in medical treatment, therefore, requires direct or personal physician management, as the leader of the clinical team, as well as input from various other essential coworkers.

The radiation oncology process of care can be separated into categories:

- Patient evaluation
- Preparing for treatment
- Therapeutic simulation
- Treatment planning
- Pretreatment quality assurance (QA) and plan verification
- Radiation treatment delivery
- Radiation treatment management
- Follow-up care management

A course of radiation therapy is composed of a series of distinct activities of varying complexity and is a function of the individual patient situation. All components of care involve intense cognitive medical evaluation, interpretation, management, and decision-making by the radiation oncologist and other members of the clinical team. Each time a procedure is approved and reported, its level of effort/complexity should be appropriately documented in the patient record.

The clinical team, led by the radiation oncologist, provides the medical services associated with the process of care. Other team members involved in the patient's planning and treatment regimen include the medical physicist, dosimetrist, radiation therapist, and nursing staff. Many of the procedures within each phase of care will

be carried to completion before the patient's care is taken to the next phase. Others will occur and recur during the course of treatment, and they are by necessity repeated during treatment because of patient tolerance, changes in tumor size, need for boost fields or port size changes, or protection of normal tissue, or as required by other clinical circumstances (ie, certain procedures may need to occur multiple times during the treatment course). Each phase of care involves medical evaluation, interpretation, management, and decision-making by the radiation oncologist as well as other team members.

Patient Evaluation

Patient evaluation is a service provided by a physician to either recommend care for a specific condition or problem or determine whether to accept responsibility for the ongoing management of the patient's entire care or for the care of a specific condition or problem. The physician as part of this process will review the pertinent imaging and pathologic studies, the patient's complaints, and physical findings. Nowadays far too many radiation oncologists seem to act as if the patient evaluation starts and ends with a review of the CT, CT/PET, or MRI. "The good physician treats the disease"; Sir William Osler said, "The great physician treats the patient who has the disease."[394] Cancer occurs in the context of the patient's general medical condition, family, culture, means of employment, home, and aspirations. All of these must be considered along with the anatomic location of the tumor and normal tissue. This initial visit can also be used for patient counseling, coordinating care, and making recommendations about other aspects of oncologic management or staging.

Preparing for Treatment

The selection of a comfortable and appropriate patient position for treatment is an important part of the simulation process. The selected position should consider the location of the target and the anticipated orientation of the treatment beams. Appropriate immobilization devices provide comfort, support, and reproducibility. Immobilization of the patient in a comfortable position for treatment might involve the construction or selection of certain treatment devices for helping the patient remain in position during treatment. This step must consider the potential treatment planning considerations so that the treatment aids do not restrict the treatment techniques.

Simulation is the process of determining critical information about the patient's geometry, to permit safe and reproducible treatments on a megavoltage machine. Simulation for external beam radiation treatment is always image based. Simulation procedures have shifted away from the direct use of the treatment beam to using diagnostic x-rays, CT, PET/CT, or MRI. In general, this part of the overall process of

care determines the relationship between the position of the target or targets and the surrounding critical structures. When a simulator of conventional design is used that mimics the geometry of the treatment unit, when direct simulation is performed on the treatment machine, or if a CT or MRI simulator is used, this relationship is sometimes determined indirectly through observation of skeletal anatomy that can act as a surrogate for the target position. A CT or MRI simulator can include the ability to produce volumetric data in addition to 2D images.

The preparation for external beam treatment can also depend on other imaging modalities that are directly or indirectly introduced in the simulation process. MRI, ultrasound, and/or PET are frequently used, and treatment planning systems that include image registration capabilities allow combining of information from other imaging modalities with the standard CT data set obtained during simulation in appropriate situations. It is now possible to produce image data sets that quantify the motion of structures and targets because of respiration, cardiac motion, and physiologic changes in the body.

For most brachytherapy, treatment preparation is similar to the procedure described earlier for EBRT. The simulation process is also image based. Multiple imaging modalities may be important for some brachytherapy procedures, and these studies can be obtained as part of the preplanning imaging process. For clinical situations where therapy is delivered by unencapsulated radionuclides, a separate and distinct treatment planning process is necessary because of its multidisciplinary execution.[395]

Clinical treatment planning is a comprehensive, cognitive team effort performed under the direction of the radiation oncologist for each patient undergoing radiation treatment. The radiation oncologist is responsible for understanding the natural history of the patient's disease, knowing the extent of the disease relative to the adjacent normal anatomic structure, and integrating the patient's overall medical condition and associated comorbidities. A detailed understanding of the integration of chemotherapeutic and surgical treatment modalities with radiation therapy is also essential.

The skills of the trained and appropriately credentialed dosimetrist relate to the efficient and effective use of the complex treatment planning system hardware and software. This individual must also understand the clinical aspects of radiation oncology in order to interact with the radiation oncologist during the planning process. The role of the medical physicist is to guarantee proper functioning of the hardware and software used for the planning process, consult with the radiation oncologist and dosimetrist, check the accuracy of the selected treatment plan, and perform measurements and other checks aimed at ensuring accurate delivery of the plan.

For either EBRT or brachytherapy, treatment planning starts with a complete, formally documented, and approved directive. Details including total dose to all targets and OARs, fractionation, treatment modality, energy, time constraints, normal tissue constraints, and all other aspects of the radiation prescription in a written or electronic format must be provided by the radiation oncologist prior to the start of treatment planning. In some cases, this prescription can require modification based on the results of the treatment planning process.

Clinical treatment planning for either EBRT or brachytherapy is an important step in preparing for radiation oncology treatment. This planning includes the following components: determining the disease-bearing areas based on the imaging studies and pathology information, identifying the type (brachytherapy, external photon, or electron or proton beam) and method of radiation treatment delivery, specifying areas to be treated, and specifying the dose and dose fractionation. In developing the clinical treatment plan, the radiation oncologist may use information obtained from the patient's clinical evaluation as well as any additional tests, studies, and procedures that are necessary to complete treatment planning. Studies ordered as part of clinical treatment planning may or may not be associated with studies necessary for staging the cancer and may be needed to obtain specific information to accomplish the clinical treatment plan. Review of imaging studies and laboratory tests must be performed to determine treatment volume and critical structures in close proximity to the treatment area.

At various steps in the treatment planning process, the radiation oncologist is presented with one or more treatment plans for review and selection. This process is often iterative and requires additional treatment planning. The radiation oncologist is responsible for selecting and formally approving the plan to be used for treatment.

The QA steps taken after the completion of treatment planning and before the start of treatment are critical for guaranteeing patient safety. In the past, treatment verification consisted of field aperture imaging using radiographic film. These images were referred to as portal images or port films. With the introduction of IMRT or IMPT, imaging of individual apertures is no longer practical. However, the traditional method of verifying the plan isocenter position using "beam's-eye" imaging is often used for 3DCRT, IMRT, and IMPT. For IMRT, this important QA technique is not considered to be sufficient to guarantee patient safety. In addition to this isocenter check procedure, for IMRT and other complex delivery techniques that use inverse treatment planning, patient-specific QA measurements are also required.

Radiation Treatment Delivery

The physician is responsible for verification and documentation of the accuracy of treatment delivery as related to treatment planning and setup procedures. Image

guidance radiation therapy (IGRT) may be performed to ensure accurate targeting of precise radiation beams. IGRT requires a target that is expected to move from day to day and can be reliably identified by the selected imaging modality. The physician is responsible for the supervision and review of these images and prescribing necessary positional shifts to ensure the therapy delivered conforms to the originally planned dosimetric constraints. Similarly, the management of organ motion during treatment delivery is the responsibility of the treating physician.

Radiation Treatment Management

Radiation treatment management encompasses the radiation oncologist's overall management of the course of treatment and care for the patient as well as checks and approvals provided by other members of the radiation therapy team that are necessary at various points in the process. For the radiation oncologist, radiation treatment management requires and includes a minimum of one examination per week of the patient for medical evaluation and management. The professional services furnished during treatment management typically include the following:

- Review of portal images in a format appropriate to the technique of radiotherapy delivery
- Review of dosimetry, dose delivery, and treatment parameters
- Review of patient treatment setup
- Patient evaluation visit

Not all of these elements of treatment management are required for all patients for each week of management (except for the patient evaluation visit) because the clinical course of care may differ due to variations in treatment modality and individual patient requirements. Examinations and evaluations may be required more often than once weekly.

Follow-Up Care

Continued follow-up care of patients who have completed radiation therapy is necessary to manage acute and chronic morbidity resulting from treatment as well as to monitor the patient for tumor recurrence.

In the team approach to cancer care, the role of the radiation oncologist in follow-up is debatable. Traditionalists will say that "you irradiated the patient. You know more about radiotherapy effects than any other member of the team. You must follow the patient for the rest of their lives." Others say that "see the patient once or twice for follow-up and then return them to the care of their primary care physician, or surgeon, or medical oncologist" or "see the patient once per year." Unfortunately,

one also hears “you make money treating patients, not doing follow-up visits. Minimize them.”—a despicable point of view. Patients with cancer require follow-up. If the radiation oncologist does not do it themselves, then they must ensure that it is done by a competent health care provider.

Telemedicine and Remote Practice

With the worldwide shutdown that occurred in 2020 to 2022 due to the COVID-19 pandemic, many medical practices adopted telemedicine visits. Using readily available computer video technology, the patient and the physician can see each other and speak. Even some elements of a physical examination can be done via telemedicine including remote auscultation of the heart and lungs using an electronic stethoscope plugged into the computer or an electrocardiogram. One cannot, of course, palpate and measure the size and feel the consistency of a lymph node by telemedicine, do a pelvic examination for carcinoma of the cervix, or examine a patient’s prostate for the presence or absence of a nodule.

Radiation oncologists adopted telemedicine for follow-up visits during the pandemic. They were far from perfect, but they served a purpose in reducing the risk of the spread of COVID-19. Multidisciplinary tumor boards are relatively easy to conduct using online meeting software—pathologists can show their slides, and diagnostic radiologists can show their images. Professional meetings can be conducted online. Scientific papers can be presented and discussed. Indeed, some physicians found that they prefer online scientific and professional meetings: no drives to the airport, no delayed flights, no checking into and out of hotels, and minimizing time away from the family.

We now here widespread vaccination. Recognizing the convenience of telemedicine (The patient does not have to leave the house. The doctor can work from home.), there will continue to be a role for this technique postpandemic.

Radiation oncologists have observed that some medical specialties have adopted a work-from-home ethos. To various levels, some of the subspecialties among diagnostic radiologists, psychiatrists, and dermatologists are practicing medicine from workstations at home. Indeed, in some parts of the United States, employers are hard-pressed to find diagnostic radiologists who are willing to set foot in the hospital anymore.

What about radiation oncologists? Is it possible to use telemedicine to replicate the treating radiation oncologist walking in and out of the treatment room, checking the position of the stabilization device, looking at the alignment of the laser beams for patient positioning, looking at the projection of the light field on the patient, giving the patient a comforting word or pat on the arm, and looking at the QA portal images on the screen remotely? Is it possible to use telemedicine to stage most forms

of human cancer using a physical examination to assess the size, location, and mobility of the primary tumor and the presence or absence of involved lymph nodes; to check the function of the cranial nerves, sensation in response to tuning forks or pinpricks, or reflex response to a reflex hammer; or to look at the eye grounds, the tympanic membranes, or palpate internal organs or view them with a fiberoptic scope remotely? Even if it is possible, is it equivalent? At present, it is neither possible nor equivalent.

Furthermore, medicine is fundamentally a social activity that takes place between two people. Any seasoned clinician will tell you that there is therapeutic value to touching your patients and showing them that you care.

At the time the author is writing these words, he thinks that "remote, practice-from-home" radiation oncology has a limited role. First, there are some patients who live so far away from a radiation oncology facility that telemedicine serves a very real benefit by providing initial consultative services to the on-site physician that otherwise could not be delivered. Similarly, telemedicine may be of benefit to incarcerated patients at a distance from the radiation oncologist. Initial advice may be given without the risks attendant to moving a prisoner out of prison and transporting them great distances. Second, multidisciplinary tumor conferences seem to work well using computer technology and spare doctors from long hours on the highway driving in order to attend an 8 am conference at a distance from their home or their primary practice site. Third, some departmental conferences can be conducted by use of group meeting computer video technology. Finally, as long as the department is properly staffed on site, allowing some staff members to have a "hybrid model" of work (ie, 1 or 2 days out of 5 at home, 3 or 4 days out of 5 in the clinic), where the days at home are devoted to sitting at the computer or desk making sure all clinical charting is up to date, insurance forms are completed, protocol paperwork is done, and manuscripts are being written will have a role in the modern radiation oncology department.

Artificial Intelligence

If you take a long view of the history of medicine, there is always something that "is going to transform medicine." A partial list of these "transforming inventions / technologies / discoveries" over the past 200 years might include "the invention of the stethoscope is going to transform medicine (1816) . . . the discovery of anesthesia is going to transform medicine (1842-1846) . . . the discovery of antisepsis is going to transform medicine (1865-1867) . . . the discovery of penicillin is going to transform medicine (1928) . . . heart transplantation is going to transform medicine (1967) . . . the invention of commercially viable CT scan is going to transform medicine (1967-1971). . . ." To be added to the list, it is being widely

asserted as this book is being written, that "artificial intelligence is going to transform medicine."

Artificial intelligence (AI) is a branch of computer science that concerns itself with the development of computer software and computers that mimic human cognitive functions such as learning and problem-solving (Box 1.8).

Box 1.8

The Language of Artificial Intelligence

Artificial Intelligence is a term used to describe computer systems that are able to perform tasks that normally require human intelligence. Examples include visual perception, speech recognition, decision-making, translation between languages, and writing. Machine learning is a form of artificial intelligence.

Machine learning enables computers to learn from a dataset without being programmed with explicit rules. There are three general forms of machine learning: supervised, unsupervised, and reinforcement.

Supervised machine learning uses algorithms which are trained to learn from accurate, ground truth data.

Unsupervised machine learning does not require algorithms to rely on labeled input data. Instead the computer examines datasets independently and identifies patterns passed upon similarities and differences.

Reinforcement machine learning uses algorithms that are not explicitly trained but, instead, learn from the consequences of interactions with their environment. On an assembly line, for example, this technique is used to train a robot to navigate from picking up a part in a bin, carrying it to the assembly line, and placing it in the correct location while not bumping into anything and performing the task with speed and accuracy.

Machine learning can be performed with *artificial neural networks*. Artificial neural networks are a type of machine learning which uses computational platforms modeled on neuronal circuitry. It makes use of interconnected elements called artificial neurons, also called nodes, to process information. The two general types of artificial neural networks are convolutional and generative adversarial.

Convolutional neural networks provide local connectivity between neurons of adjacent layers. These connections exploit spatially local correlations to allow the network to learn features on a global and local scale. This should make the network more robust to subtle variations in inputs.

General adversarial networks use two trained networks simultaneously, serving different purposes to train algorithms.

Chapter 32 of this book is devoted to AI in radiation oncology. We will, therefore, only briefly mention a few of its potential applications.

- Compilation of a large number of patient variables, such as physical findings, laboratory tests, and imaging findings to suggest a diagnosis, predicts a clinical

outcome or prioritizes a clinical work list to decrease the time to diagnosis and treatment.

- Reviewing diagnostic images or pathology slides, identifying abnormalities, and suggesting diagnoses
- Decreasing the levels of required radiation, contrast dosage, and scanning time in diagnostic radiology
- Generation of medical reports, patient communications, patient appointment schedules, staffing assignments, clinical bills, assigning *ICD-10* codes to patient charts, and addressing payment claim denials
- Search Engines to explore databases to aid research

While the promise of AI in radiation oncology is enormous, so are its dangers. These dangers in part include leakage or misuse of medical data, biases built into AI models, erroneous algorithms, invention of nonexistent but plausible-sounding references for publications, exam-taking and term-paper-writing for medical students, and black box treatment models wherein the underlying reasoning is opaque. While AI is capable of doing many things well and quickly, we do not know if AI actually improves patient outcomes. It is for these reasons that many thought leaders in the field think AI should be subject to the same level of regulatory scrutiny and approval that are currently in place for drug and medical devices.

The Radiation Oncology Team

The radiation oncology team ensures every patient undergoing radiation treatment receives the appropriate level of medical, emotional, and psychological care before, during, and after treatment, through a collaborative multidisciplinary approach.

The radiation oncology team consists of, but is not limited to, radiation oncologists, physicists, dosimetrists, oncology nurses, and radiation therapists. The process of care in radiation oncology involves close collaboration of a team of qualified professionals. On-site or consultation services can be provided by nonphysician providers, including nurse practitioners, clinical nurse specialists, advanced practice nurses and physician assistants (PAs), dentists, clinical social workers, psychologists/psychiatrists, nutritionists, speech pathologists, physical therapists, occupational therapists, genetic counselors, integrative medicine specialists, and pastoral care providers.

Board certification is the primary consideration for establishing proper qualifications and training for any professional working in radiation oncology. The relevant professional societies will establish the eligibility requirements to sit for a board exam. This may include education and training requirements, such as a

clinical residency. In addition, in some jurisdictions, professionals must meet additional requirements for obtaining appropriate licensure.

The applications, technologies, and methods of radiation oncology continue to expand and develop. Lifelong learning is vital to ensure incorporation of new knowledge into clinical practice. Therefore, each member of the interdisciplinary radiation oncology team should participate in available Continuing Education and Maintenance of Certification programs. Each facility should have a policy regarding orientation, competency, credentialing, and periodic competency evaluations of all team members.

Staffing Requirements

Starting in 1986, the Intersociety Council for Radiation Oncology published a set of guidelines in a small pamphlet titled "Radiation Oncology in Integrated Cancer Management," often referred to as the "Blue Book."[396] This was updated several times.[397] The document offered guidelines for staffing requirements and equipment utilization.

The American College of Radiology (ACR) provides data on average staffing levels.[398] The staffing needs of each facility are unique based on the patient mix and complexity of the services offered. The patient load, number of machines, and satellite clinics and affiliated treatment centers will influence the demand on management and clinical staff. The minimum personnel requirements for a radiation oncology facility specify the need for one medical director (radiation oncologist), chief medical physicist, and department manager per program[399] (Table 1.12).

TABLE 1.12 AVERAGE STAFFING LEVELS FOR RADIATION ONCOLOGIST, MEDICAL PHYSICIST, DOSIMETRIST, AND RADIATION THERAPY TECHNOLOGIST

Clinical FTE[a]	Approximate Maximum # of Patients Treated per FTE per Year
Radiation oncologist	212
Physicist	258
Dosimetrist	254
Therapist	85
Treatment machine	300[b]
Therapists/treatment machine	3.1

These data vary by the type of practice, assignment of staff duties, complexity of patients seen, and the age and pathologies of the patients seen.

FTE, full-time equivalent.

[a]It is recommended that a minimum of two qualified individuals be present for any external beam patient treatment.

[b]Each treatment machine is assumed to be operational for 9 hours a day.
Derived from American College of Radiology. Accreditations support Katie Albus. Personnel: Radiation Oncology. Revised February 8, 2022. Accessed July 15, 2023. accrediationssupport.acr.org

QUALITY AND SAFETY

Quality and safety are important topics in radiotherapy.[400] The issue of patient safety for radiation therapy and diagnostic imaging has been pulled to the forefront by press reports and associated congressional hearings. A number of misadministrations described in a series of *New York Times* articles triggered increased interest in improved patient safety in radiation oncology.[401,402] These articles highlighted some of the risks inherent to advanced radiation therapy treatment planning and delivery systems and techniques. Many new patient safety initiatives, meetings, and other efforts have been organized to address the need to continue to enhance the safety of patients undergoing radiation therapy.

Safety and quality are different but related concepts. Safety generally relates to preventing errors that can have major therapeutic implications (eg, treatment of the wrong patient, treatment with the wrong plan, incorrect placement of a block or wedge, failure to correctly transfer electronic data between the various computer systems). In contrast, quality often relates more to somewhat subjective issues such as ensuring that the defined volumes, doses, beams, and so forth are clinically appropriate and that the treatment is delivered as prescribed within acceptable clinical tolerance limits. To reconcile these concepts, beginning in 2011, the ASTRO sponsored the Intersociety Council to review and update previously published guidelines concerning the role of radiation oncology in integrated cancer management. Every facet of patient evaluation, treatment planning, and treatment delivery was described with the specific goal of maximizing patient safety.[403-406] The process of care, the roles and responsibilities of staff, staff training and maintenance of competency, requirements for facilities and equipment, and the management of QA were formally recognized as inextricably linked to the provision of safe, efficient, and effective radiation therapy. These ASTRO initiatives have involved cooperation with other organizations, including the American Association of Physicists in Medicine, the American Brachytherapy Society, the ACR, the American College of Radiation Oncology, the American Board of Radiology, the American Society of Radiation Technologists, and the Society of Radiation Oncology Administrators.

Modern radiation therapy is complex and rapidly evolving. The safe delivery of radiation therapy requires the concerted and coordinated efforts of many individuals with varied responsibilities. Thus, all team members need to work together to create a *safe*, *high-quality*, and *efficient* clinical environment and workflow.

QA in radiation oncology is a set of processes and procedures designed to improve the practice of radiation therapy by confirming that radiation therapy will be or was administered appropriately and safely and documented properly. The overall goal of a QA process is the delivery of high-quality radiation oncology treatment to all patients. Note that QA is an all-encompassing term that is often used to describe some or all of the different elements involved in quality management (QM) and a culture of safety. Cost and value are important in determining the quality of care. To prove that technology adds value to patients, patient-reported outcomes should be included.

A radiation oncology facility must satisfy numerous requirements:

- A department must provide adequate clinic space, exam rooms and equipment, patient waiting and changing space, convenient patient parking, treatment rooms, simulation and imaging space, brachytherapy source preparation and storage space, dosimetry/treatment planning rooms, office space for professional staff, and medical physics laboratory and equipment storage space. The extent of facilities should be appropriate for the volume of patients seen and treated.
- Treatment rooms must be carefully designed for radiation shielding, environmental conditions, adequate storage space for spare parts, testing and dosimetry equipment, and patient access and safety (Figure 1.47).

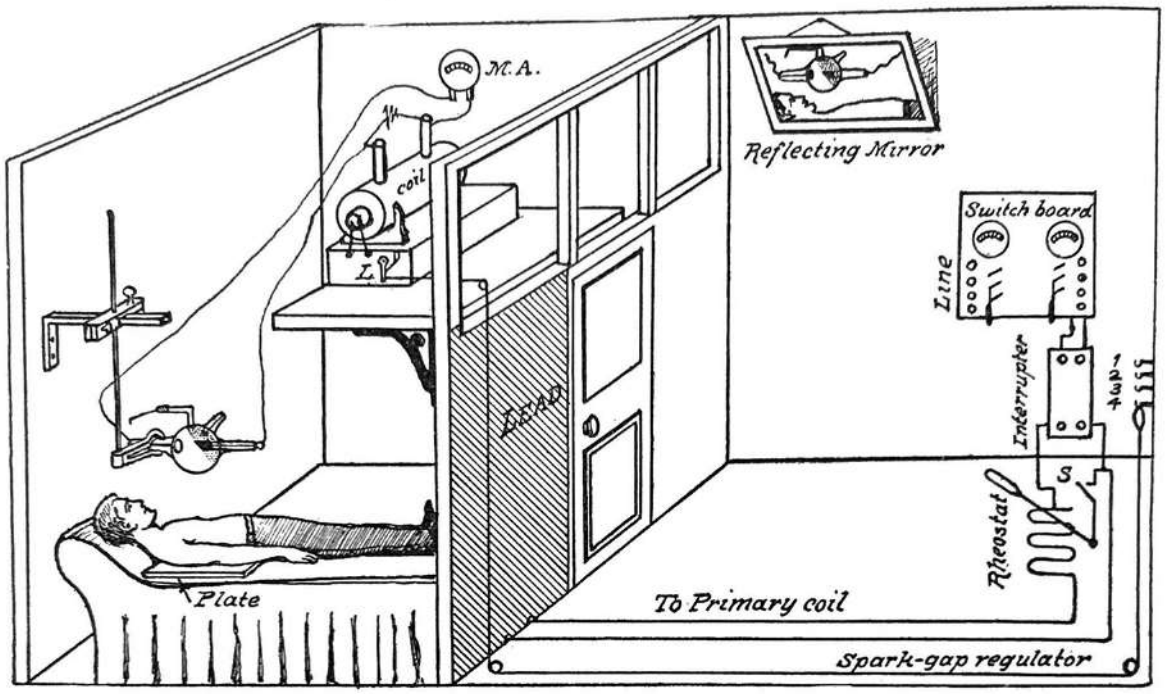


FIGURE 1.47 This diagnostic radiology and radiation therapy treatment room, designed by Dr M.K. Kassabian of Philadelphia and published in his 1907 textbook, exhibits several elements still familiar to a modern radiation oncologists: lead shielding, remote operation of the radiation equipment and a mirror to observe the patient around a barrier. (From Kassabian MK. *Röntgen Rays and Electro-Therapeutics, with Chapters on Radium and Phototherapy*. J.B. Lippincott; 1907.)

- There must be access to CT, MRI, and PET imaging for treatment planning.
- Rooms used for brachytherapy procedures require special attention to the specific radiation protection requirements associated with the particular brachytherapy modalities to be used. If the brachytherapy procedures warrant it, a brachytherapy suite should be available, including patient waiting space, procedure rooms, recovery rooms, and brachytherapy source preparation and storage areas.
- Each department must have electronic access to the hospital or clinic information system for medical records and picture archiving and communication.

The following specific capabilities and methods for various aspects of the radiotherapy process are considered essential:

- Calibration of treatment machines, CT and MRI scanners, treatment planning systems, and brachytherapy sources is to be carefully accomplished according to the appropriate protocols described by scientific/professional organizations.
- A safety program designed to monitor patient safety, avoid radiation incidents, and prevent errors in the treatment process should be in place and subject to periodic review and update.

- A system for documenting radiotherapy treatment and other aspects of the patient's medical care should be rigorous and be subject to periodic review and update.
- High-quality and comprehensive treatment planning, using 3D computerized treatment planning for dose calculations, imaging, and other aspects of the planning process
- A comprehensive QA program
- Radiation monitoring of simulators and treatment machines. A system to carefully control and monitor all radioactive sources in accordance with the requirements of regulatory agencies
- A program for maintenance and repair of equipment
- Staff training that is comprehensive, ongoing, and well documented
- A well-developed process for continuous peer review. This should include a mechanism for peer review of the entire department and its procedures as well as for individual clinical care decisions.
- Access to pathology, diagnostic radiology, medical oncology, surgical oncology, and other physician and nonphysician specialists involved in the multidisciplinary care and follow-up of the patient
- Each department must implement careful and well-described policies and procedures for every aspect of patient care, for QA of the patient care process, for staff behavior, and for any issues that may impact the safety of patients and/or staff. Each specific treatment modality (eg, IMRT, IGRT, IMPT, stereotactic body radiation therapy [SBRT]) should have detailed documentation of its treatment planning and delivery process including a description of the roles and responsibilities of each team member in that procedure, QA checklists, and a plan for continuous quality improvement and safety.

One of the most crucial activities in a quality radiation oncology department is the organized review and monitoring of all aspects of safety, errors, and outcome. Creating a "culture of safety" depends on guidance, direction, and financial support from the leadership of the institution and of the radiotherapy department, on individual effort by every member of the department, and on organized support for quality and safety at every level in the institution.

Each department should have a department-wide review committee that monitors specific quality metrics, including near misses and errors in treatment, diagnosis, patient care, or other procedural problems that might lead to errors. This committee should organize the collection and analysis of such events, work to identify potential problems in devices or processes, and then try to mitigate these problems by

modifying processes or adding new checks or actions to minimize the likelihood of further problems. Radiation oncology departments should hold regularly scheduled rounds to review patient morbidity and mortality, dose discrepancies, and any incident reports that involved an accident or injury to a patient. Morbidity and mortality monitoring includes unusual or severe complications of treatment, unexpected deaths, or unplanned interruptions of treatment. Staff included should represent all the team members, including radiation oncologists, nurses, physicists, dosimetrists, therapists, and administrators.

Equipment and Device Quality Management

Radiation therapy is employed for the treatment of a broad spectrum of diseases. The delivery of radiation therapy relies on computer-controlled treatment machines, interconnected imaging, delivery and planning systems, and complex ancillary devices. Any new radiotherapy system should go through the following processes as it is prepared for clinical use:

- Each system should be carefully specified before acquisition, purchase, or development, including design, expectations, capabilities, tolerances, hazards, necessary training, usability, and technical specifications.
- To prevent data communication errors and clinical efficiency issues, each system must be interoperable and connectable with other systems in the clinic.
- Acceptance testing must be performed to document that the new system satisfies the specifications. Often, the acceptance criteria and/or testing methods should be documented as part of the specification for the system.
- Clinical commissioning includes all the activities that must be performed to understand, document, characterize, and prove that a given system is ready to be used clinically. Standard operating procedures, training, and hazard analysis should be part of the commissioning process.
- Each new system, device, and process must be formally released for clinical use after clinical commissioning has been completed.

Clinical use of a device, system, or process must involve the creation and application of a safety- and quality-oriented program designed to ensure that the machine or device is functioning in accordance with accepted standards:

- QM is defined as the overall program to organize the oversight of the use of any system or process in radiation oncology. The QM program should include hazard analysis, quality control (QC), QA, training and documentation, and ongoing quality improvement efforts.

- Hazard analysis is the active evaluation of the potential for failures that will cause incorrect results or harm to the patient and should be performed for any new system.
- QC checks on the data that are input into a decision or process and is designed to prevent the propagation of error.
- QA is the typical shorthand term for the entire QM program and addresses quality checks that confirm that a given process is reasonable and generates appropriate results. QA checks, along with QC, are essential parts of the QM process for most devices and systems, as they can check the output of potentially very complicated decisions or actions performed by the system.
- Training of staff in goals, methods, results, operation, and evaluation of the quality of the output is important for the proper use of any system.

Patient-Related Quality Management

Within the complex and many-step process with which radiotherapy patients are treated, patient-specific issues must be carefully and comprehensively analyzed, documented, and verified. Each radiation oncology facility, regardless of its location or size, must appropriately manage and adhere to high-quality standards of practice for general medical issues, including:

- Drug allergies
- Medication reconciliation
- Do-not-resuscitate codes
- Cleanliness and efforts to reduce infection
- Patient confidentiality and security of protected health information

Modern oncology patient care very often involves multiple modalities and requires the review and discussion of experts in various oncology-related disciplines. It is critical that the management of most cancers be addressed by the appropriate mix of disciplines. Regular presentation of these cases to a multidisciplinary tumor board is the standard of care and should be performed for most cancer cases to determine the appropriate combination (and coordination) of therapies for each individual case.

The details of the patient care process in radiation oncology vary from institution to institution. However, maintenance of the safety and quality of the radiotherapy process for most patients requires that a number of procedures be performed, including:

- A new patient conference that consists of a brief presentation of the details of each patient's history and physical examination, disease status, and plan for therapy to the other departmental physicians and staff involved in patient care is used as an initial peer review for the basic treatment decisions and plan.
- The physician must obtain a clear, accurate, and detailed description of the patient's chief complaint and pertinent history in conjunction with an appropriate physical examination as part of the decision process for radiation therapy.
- Most patients who receive radiation therapy should receive a CT, PET/CT, or MRI-based simulation.
- After treatment planning is complete, the physician and members of the planning team should review the plan at a conference and verify that it satisfies the clinical requirements and prescription(s) from the physician and that it can be carried out accurately.
- On-treatment visits of the patient by the physician are essential for continuity of care and monitoring of tumor response and normal tissue toxicity. Typically, this occurs every five daily fractions, but some situations may require more frequent visits.
- Patient chart rounds are an important peer-review procedure used involving weekly review of all patients under treatment by the radiotherapy team, including physicians, therapists, nurses, dosimetrists, and physicists.
- Follow-up visits are a critical component of care for the radiotherapy patient. The frequency of follow-up visits and if they are done by the radiation oncologist or another physician will vary in accordance with the type of cancer, stage, degree of tumor response, normal tissue reactions, and other factors.
- Documentation is required of all the relevant details of patient care. Maintenance and continuous improvement of the quality and accessibility of the treatment record are essential.

The overall performance status of the patient prior to treatment should be recorded. Assessment of tumor response and normal tissue toxicity should occur both during and after treatment. Clinical assessment of patient response is a valuable independent check on the success of the overall QM system as unexpected outcomes may identify issues related to technique or equipment performance.

External Beam Quality Assurance

Nearly all external beam treatment requires the following steps, each of which must be carefully confirmed as part of the patient-specific QA process: determination of patient setup position and immobilization; cross-sectional imaging (CT, PET/CT, or

MRI simulation); creation of the anatomic model (contouring); specification of the treatment intent; creation of the planning directive and treatment prescription by the physician; computerized treatment planning and dose calculation; monitor unit calculation and/or IMRT or IMPT leaf sequencing; plan and (electronic chart) preparation; plan evaluation; download to treatment management system; patient-specific QA as typically performed for IMRT, IMPT, stereotactic radiosurgery (SRS), or SBRT; patient setup and delivery; plan verification checks; plan adaptation and modifications; chart checks; and more.[388]

Brachytherapy Quality Assurance

The QA process for brachytherapy is similar to that of external beam and involves several components that must be confirmed as part of the patient-specific QA management: treatment planning; treatment delivery systems; applicator commissioning and periodic checks; cross-sectional imaging (often with CT simulation); specification of the treatment intent, planning directive, and treatment prescription by the physician; plan preparation; plan evaluation; download to the electrical medical record; plan verification checks; plan modifications; and chart checks.[407-413]

COMBINATION OF THERAPEUTIC MODALITIES

Management of the Patient With Cancer

The optimal care of patients with cancer is a multidisciplinary effort that may combine multiple disciplines: surgery, radiation therapy, chemotherapy, and biologic or immunotherapy. Many professionals, including physicians, physicists, laboratory scientists, nurses, rehabilitation staff, sociologists, and social workers, are intimately involved. Pathologists, radiologists, clinical laboratory physicians, and immunologists are integral members of the team. Biology, biochemistry, and pharmacology have contributed greatly to the advancement of methods used to evaluate and treat patients with cancer (eg, biomarkers, cell kinetic indicators, oncogenes).

The radiation oncologist, must assess all conditions relative to the patient and the tumor under consideration for treatment and systematically review the need for diagnostic and staging procedures as well as the best therapeutic strategy. This is well illustrated by treatment algorithms or "decision trees."[414] In several instances, a clear relationship existed between compliance with guidelines for diagnostic or therapeutic procedures (best current management consensus) and therapy outcome, as defined by survival, recurrence patterns, or complications of treatment.

Emphasis on screening and early diagnosis of cancer, as well as improvements in therapeutic strategies, has had a significant positive impact on the survival of patients with cancer. In the United States, results of the Surveillance, Epidemiology, and End Results program have shown a small but steady improvement in survival for a variety of tumor sites. The relative survival of patients with cancer at various times after diagnosis has improved substantially since 1960.

How Radiation Therapy Was Perceived to Be Different From Surgery in the Treatment of Cancer

At the beginning of his 1929 textbook *Radium Treatment of Cancer*, the legendary British surgeon and pioneering radiation oncologist Sir Stanford Cade carefully lays out the evolution of oncologic thinking.[415] Changing from "to cut is to cure," Cade developed a more holistic view of the roles of surgery and radiation therapy in cancer treatment. (For a biographical note on Sir Stanford Cade, the reader is referred to the last section of this chapter.)

> Until recently the principle underlying the treatment of cancer was the elimination of the growth by excision with knife or diathermy. The vital question for each case was: "Is it removable?" The answer varied with the site of the growth, the skill and courage of the surgeon, the general condition of the patient, and the presence of recognizable metastasis. Even in its widest sense the measure of operability depended on the question: "Is the lesion removable?" and not on the question: "Is the removal of the lesion going to cure the patient?" In the last ten years rapid progress of radium therapy has changed the concept of operability, and for the disappearance of the cancerous lesion it is no longer imperative to rely entirely upon the scalpel . . . no patient, however "inoperable," should remain untreated . . . . The combination of the biological factor of selectivity with the power of penetration of gamma rays gives the possibility of treating lesions which are irremovable either because of their situation or because of the involvement of important structures. Further, radium therapy abolishes or at least minimizes, operative mortality and mutilation. It enlarges the field of "treatable" cases beyond the limits imposed on purely operative surgery.[416]

We now practice medicine in an age in which the concepts articulated by Cade almost 100 years ago have been extended to the use of preoperative, intraoperative, and postoperative radiation therapy and, in some cases, definitive irradiation in lieu of definitive surgery. What has not changed is the principle articulated by Cade: The core issue is what provides the patient with the best chance of cure or palliation of cancer with the preservation, where possible, of organ function.

Irradiation and Surgery

The rationale for *preoperative radiation therapy* relates to its potential ability to eradicate subclinical or microscopic disease beyond the margins of the surgical resection, to diminish tumor implantation by decreasing the number of viable cells within the operative field, to sterilize lymph node metastases outside the operative

field, to decrease the potential for dissemination of clonogenic tumor cells that might produce distant metastases, and to increase the possibility of resectability. The disadvantages of preoperative irradiation are that it may interfere with normal healing of the tissues affected by the radiation, it delays surgery, and it may disrupt surgical staging of the tumor and/or the expression of histologic or immunohistochemical prognostic factors.

The rationale for *postoperative irradiation* is based on the fact that it is possible to eliminate subclinical foci of tumor cells in the tumor bed (including lymph node metastases). By delivering higher doses to the volume of high-risk or known residual disease than can be achieved with preoperative irradiation, a greater tumor control may be obtained. The potential disadvantages of postoperative irradiation are related to the delay in the initiation of radiation therapy until wound healing is completed. Theoretic and experimental evidence suggests that the radiation effect may be impaired by vascular changes produced in the tumor bed by surgery.

Irradiation and Drug Therapy

Tumor or *normal tissue enhancement* describes any increase in effect greater than that observed with either cytotoxic chemotherapy, biologic therapy, immunotherapy, or irradiation alone.[399] Agents used in chemoirradiation include those with cytotoxic activity against the tumor, which may show additive, subadditive, or supra-additive effects, such as 5-fluorouracil or mitomycin C in anal carcinoma; agents with minimal or no significant activity against a specific tumor, which may, however, enhance the irradiation effect; radiation hypoxic cell cytotoxins or bioreductive agents; and radioprotectors.

Chemotherapy alone or combined with irradiation may be used in many settings.[417,418] *Primary chemotherapy* is used as part of the primary lesion treatment (even if later followed by other local therapy) and when the primary tumor response to the initial treatment is the key identifier of systemic effects. *Adjuvant chemotherapy* is used as an adjunct to other local modalities as part of the initial curative treatment. The term *neoadjuvant chemotherapy* is used when this modality is used in the initial treatment of patients with localized tumors, before surgery or irradiation.

The effects of combined radiation therapy-chemotherapy can be independent, additive, or interactive. Chemotherapy and irradiation can be administered sequentially or concomitantly. Sequencing of treatment at the appropriate time is significantly related to the residual tumor cell burden at the point of introduction of each new treatment program.

Administration of chemotherapy before irradiation may produce cell killing and reduce the number of cells to be eliminated by irradiation. The use of chemotherapy

concurrently with radiation therapy has a strong rationale because it could interact with the local treatment (additive and even supra-additive action) and also could affect subclinical disease early in treatment. However, the combination of modalities may enhance normal tissue toxicity. When agents with added toxicity are used, lower tumor control may result because the added morbidity requires lowering the doses of the effective agents or prolonging overall irradiation treatment time. When fatal toxicity from chemotherapy occurs, it is possible that in some patients the clinical researcher will fail to record a tumor response that could have been observed had they survived.

Biologic Considerations in Combinations of Drug Therapy and Radiation

Many experimental animal studies have shown therapeutic benefits from a combination of irradiation and drugs, but most are phenomenologic. Therapeutic benefit requires differential properties on tumor and normal tissues, which may be exploited for therapeutic gain, including genetic instability of tumors compared with normal tissues, differences in cell proliferation (particularly cell repopulation during fractionated radiation therapy), and environmental factors such as hypoxia and acidity (which are usually confined to tumors). There are variations in sensitivity or resistance to irradiation or drugs. The mechanisms for resistance to these agents may be shared in some tumors and different in other tumors. Resistance to anticancer drugs may have implications for resistance to radiation therapy; many drug mechanisms for resistance are multifactorial, such as in cisplatin, in which this phenomenon may be the result of decreased drug uptake, increased repair of DNA, increased expression of sulfhydryl compounds such as glutathione and metallothionein, and increased expression of glutathione-*S*-transferase. Combined treatment with radiation and drugs might result in an improved therapeutic index if mechanisms of resistance are independent.

Oxygen, pH, and nutrient supply can play an important role in the combined effects of chemotherapy and irradiation on tumor cells.[419] Hypoxic cells are less radiosensitive and chemosensitive to many drugs, and chronic hypoxia can alter cell cycle age distribution and proliferation rate—both important modifiers of cellular response to ionizing radiation and drugs. In addition, chronic hypoxia can affect cellular ability to repair radiation- and drug-induced DNA damage. Bioreductive drugs such as mitomycin C are activated to toxic species under hypoxic conditions. DNA repair, cell cycle age distribution, and the activity and stability of some chemotherapeutic drugs may be pH dependent; thus, this factor plays a role in the sensitivity of cells to irradiation and cytotoxic agents.

Hypoxic conditions may lead to the amplification of genes. Under hypoxic conditions, hypoxia-inducible factor-1 (HIF-1) occurs, levels rise, and functional HIF-1 transcription factor complexes induce angiogenesis, erythrocytopoiesis, glycolysis, and glucose transport into cells—all techniques to allow the cell to survive hypoxia. HIF-1 induces the genes encoding vascular endothelial growth factor (VEGF), platelet-derived growth factor, and TGF.[420] Some cytokines such as tumor necrosis factor-α or interleukin[421] and growth factors such as platelet-derived and fibroblast growth factors are seen in malignant and normal human cells after irradiation.[422] These cytokines and growth factors enhance the cytotoxic effects of irradiation and chemotherapy in tumor cells or offer radioprotection in normal cells.[423]

Possible molecular or cellular mechanisms of interaction of chemotherapy and irradiation include the following:

1. Modification of the slope of the dose-response curves, as has been shown with actinomycin D, cisplatin, doxorubicin, mitomycin C, 5-fluorouracil, and other agents
2. Decreased accumulation or inhibition of repair of SLD, as induced by actinomycin D, cisplatin, bleomycin, hydroxyurea, and nitrosoureas.[424,425] Doxorubicin and other DNA intercalators decrease the shoulder widths but do not decrease the slope or suppress the repair of lethal damage in in vitro studies.[426]
3. Inhibition of repair of PLD, as has been shown with actinomycin D, doxorubicin, and cisplatin[427]
4. Perturbation of cell kinetics, for example, after treatment with hydroxyurea, which kills cells in the S phase, when cells may become partially synchronized and blocked at the G1/S phase of the cell cycle. If irradiation is delivered during this sensitive phase, as the cells subsequently emerge from the block, an enhanced cytotoxic effect may be expected.
5. Selective cytotoxicity and radiosensitization of hypoxic cells, which have been reported with mitomycin C and cisplatin[428]
6. Inhibition of cell repopulation
7. Decrease in tumor bulk leading to improved blood supply, reoxygenation, and cell cycle recruitment, resulting in increased radiosensitivity and chemosensitivity

A possible danger in the administration of cytotoxic drugs before radiation therapy is accelerated cell proliferation or repopulation. Because some tumor regression is induced by the cytotoxic agent (drugs or irradiation), the distance

between the tumor cells, and decreases in adjacent functional capillaries, this may induce tumor cell proliferation so that higher doses of irradiation would be required to produce a given tumor control. This may occur because, during radiation therapy, tumor cells surviving neoadjuvant chemotherapy may be stimulated to repopulate at a faster rate. Because of this effect, the initial advantage in cell killing by drugs is lost, and the survival curves for fractionated radiation therapy may come together or even cross over. Although this mechanism is hypothetical, it suggests caution in the use of induction chemotherapy and explains why an initial tumor response may not necessarily translate to a therapeutic advantage with combined modality treatment given in this manner. For example, three courses of induction chemotherapy might reduce tumor cell numbers from 10^{10} to 10^{8} (from 10 to about 0.1 g), which is considered a complete clinical tumor regression. Even a pathologic complete response has limited long-term implications; a complete pathologic regression is consistent with the presence of about 10^{6} tumor cells per gram, a substantial biologic cell burden (Figure 1.48).

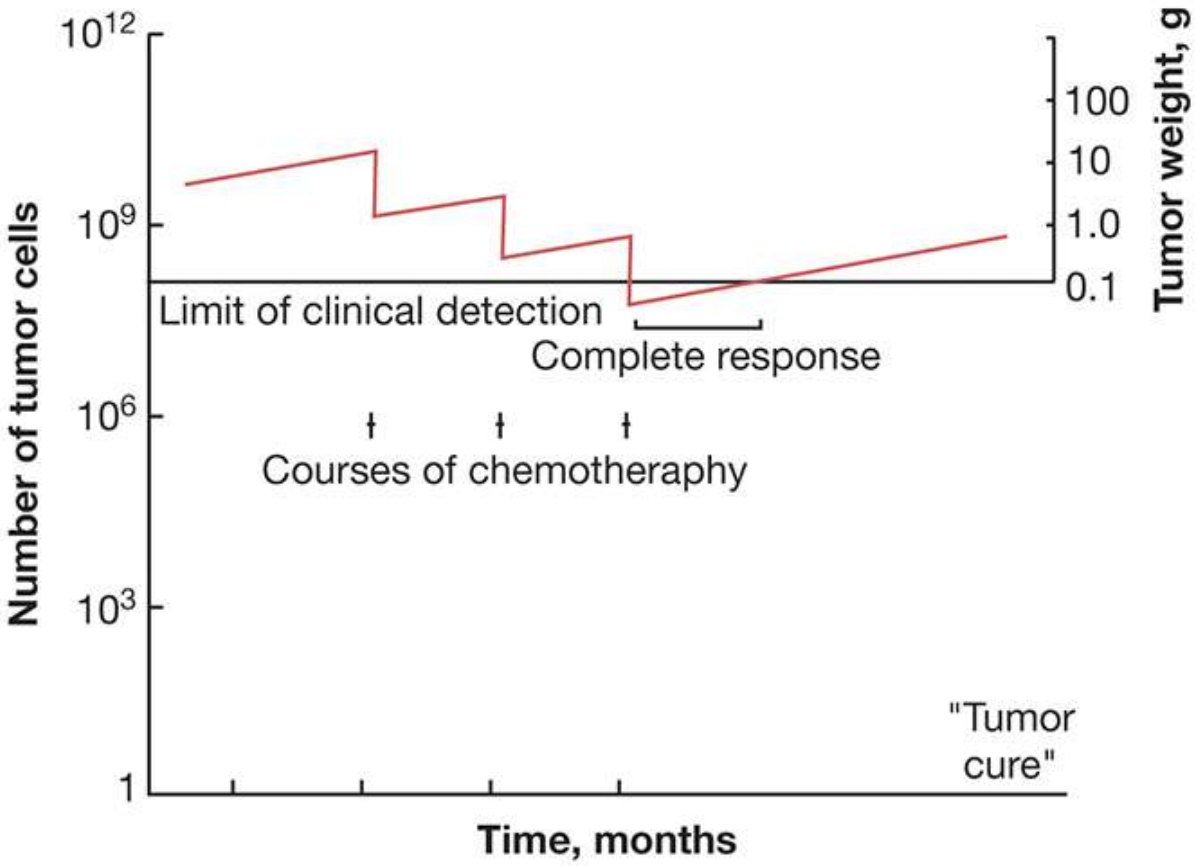


FIGURE 1.48 Relationship between clinical remission and cure. A 10-g tumor containing 10^{10} cells is treated with three courses of chemotherapy, each of which kills 90% of the tumor cells present. After three courses, the number of viable tumor cells is $<10^{8}$ (<0.1 g), and the patient is judged to be in clinical and radiologic complete remission. Note that this is a small step toward tumor cure. Moreover, additional chemotherapy may not be helpful if drug-resistant cells have been selected after three courses of chemotherapy. (Reprinted from Tannock IF. Combined modality treatment with radiotherapy and chemotherapy. *Radiother Oncol*. 1989;16[2]:83-101. Copyright © 1989 Elsevier Ireland Ltd. With permission.)

Integrated Multimodality Cancer Management and Organ Preservation

Combined treatment modalities are frequently used to improve tumor control and patient survival. Steel and Peckham[429] postulated the biologic basis of cancer therapy as spatial cooperation, in which an agent is active against tumor cells spatially missed by another agent, addition of antitumor effects by two or more agents, and nonoverlapping toxicity and protection of normal tissues. Large primary tumors or metastatic lymph nodes must be removed surgically or treated with definitive radiation therapy. Regional microextensions are eliminated effectively by irradiation without the anatomic and at times physiologic deficit produced by equivalent medical surgery. Chemotherapy is applied mainly to control disseminated subclinical disease, although in some diseases in clearly has an effect on primary tumors.

Organ preservation is being vigorously promoted because it enhances the quality of life and psychoemotional feelings of patients if it can be combined with excellent tumor control and survival. In some types and stages of head and neck tumors, breast cancer, gastrointestinal malignancies, genitourinary tumors, soft tissue sarcomas, and pediatric tumors, studies have shown that less radical surgical procedures combined with chemotherapy and radiation therapy yield the same local tumor control at the primary site and survival as did radical procedures. Advances in reconstructive surgery have greatly improved our ability to repair defects of radical surgery.

Clinical Trials

These studies have been classified as phase I (toxicity), phase II (dose/efficacy), and phase III (efficacy and toxicity of a new drug compared with an established standard). Randomized phase III clinical trials and meta-analyses of those trials are the two most accepted sources of scientific information in evidence-based medicine. These randomized clinical studies, with sometimes complicated treatment schemas, large numbers of patients, defined end points, and rigorous statistical testing, which are increasingly required by the U.S. FDA to document the efficacy and safety of new drugs (and, I believe I should add, should be required for medical devices), are logistically difficult and expensive to conduct. Cooperative clinical trial groups have been a major contributor, to clinical investigation centered on the application of ionizing radiations, either alone or combined with other treatment modalities to improve the management of patients with cancer. It is the responsibility of practicing radiation oncologists in academic and community centers to be active contributors, with both scientific input and encouragement of their patients to participate in many of these trials.

THE PRACTICE OF RADIATION ONCOLOGY

The Three A's of Being a Successful Consulting Radiation Oncologist

For the most part, radiation oncologists are consulting physicians. Patients do not enter the front door of the health care system via the radiation oncologist's office. Instead, they first see their primary care physician, pulmonologist, surgeon, obstetrician-gynecologist, adult or pediatric medical oncologist, urologist, or neurosurgeon. A diagnosis is made. A referral request brings the radiation oncologist into the management of the patient.

Many years ago, the author of this chapter was given sound advice as to how to succeed as a consulting physician. It was to follow "the three A's": *availability*,

affability, and *ability*. It was not enough to follow "the three A's," it was important to remember that they need to be observed precisely in the stated order.

Availability: Come when the referring physician calls. When taking care of a patient with cancer, the referring physician does not want to be told that it is hard to get an appointment, that the radiation oncologist is "very busy," or that there will be a delay in seeing the patient. The referring physician wants the patient checked-off of their "to do" list and moved onto the radiation oncologist's "to do" list. If you want to succeed as a radiation oncologist, be readily available.

Affability: No referring physician wants to deal with a grumpy radiation oncologist. They do not want to hear how busy you are, how behind you are in your tasks, or why you would rather not be bothered with yet another "uninteresting" referral. They want to have a radiation oncologist on the team who is a cheerful, cooperative, and businesslike professional.

Ability: After you make yourself available and are affable, then you need to know, clinically, what you are doing. But you will never get to show your clinical ability if you are not available and affable.

Go to Their Office

Eugene Anson Stead Jr., MD (1908-2005) was Dean of the Emory University School of Medicine and later Chair of the Department of Medicine at Duke University School of Medicine. A master clinician, teacher, and cardiovascular researcher, he is perhaps best known today as the founder of the profession of physical assistant (PA). He taught the author a valuable lesson that has proven its worth during a career in clinical radiation oncology.

Stead taught that one should avoid requesting meetings in your own office. When you go to someone else's workspace, he would say, you are sending the nonverbal message that they are very important and, therefore, you have chosen to stop what you are doing to go seek them out. In contrast, when you ask people to come see you or if you interrupt them with a phone call, you are sending the nonverbal message that you are important and the other person must arrange their day to suit your needs.

Some radiation oncologists read diagnostic imaging reports on the electronic medical record and/or look at the images on their computer. They read pathology reports on the computer. What they should do, whenever possible, is walk over to the diagnostic radiology reading room to review the images with the radiologist and walk to the pathology department to review the slides with the pathologist. A great deal more information about the case can be gleaned in this manner, questions may be posed, and new insights obtained. In addition, the radiation oncologist is demonstrating, to the pathologist and radiologist, their importance in the oncology

team and the respect in which they are held. Similar behavior is appropriate when discussing the case with the referring physician or doctors you elect to consult.

Rosen's Rules Applied to Radiation Oncology

When the author of this chapter was a rising second-year medical student, he was assigned to a summer clinical rotation at the Berkshire Medical Center in Pittsfield, Massachusetts. At that hospital, he was, for part of the summer, under the supervision of internal medicine resident Clifford Rosen, MD. Rosen would go on to have a distinguished career and become the director of clinical and translational research and a senior scientist at Maine Medical Center's Research Institute. He is a professor of medicine at Tufts University School of Medicine. Rosen is the founder and former director of the Maine Center for Osteoporosis Research and Education. He was the first Editor-in-Chief of the *Journal of Clinical Densitometry*, is the current Editor-in-Chief of *The Primer in Metabolic Bone Diseases*, and is an associate editor for *New England Journal of Medicine*. He has close to 400 peer-reviewed publications.

Clifford Rosen taught me "Rosen's Rules of Clinical Medicine." I have used them to advantage in my career, such as:

1. Clinically, if what you are doing is working, keep doing it.
2. Clinically, if what you are doing is not working, stop doing it.
3. If you are not sure what to do clinically, do not do anything lest you make the patient worse.

When I was a medical student, I did not fully appreciate both the wisdom and the errors intrinsic to these three rules. It may seen obvious, as indicated by rules 1 and 2, that a course of treatment that is producing a favorable response should be continued and one that is not ought to be abandoned. One must remember the dictum, however, that "some doctors do the same thing wrong for 40 years and call that 'decades of clinical experience.'" As Hippocrates taught, clinical experience is, sometimes, delusive. As a profession, radiation oncologists certainly cured small children with retinoblastoma with EBRT. Orbital malformations and second malignant neoplasms occurring decades later taught us, however, that we could do a better job for these children.

In my experience as a radiation oncologist, the most valuable rule has been number 3. An inability to figure out what else to try for a patient's treatment is not an indication for radiation therapy.

MALPRACTICE AND RADIATION ONCOLOGY

A plaintiff initiates a radiation oncology malpractice lawsuit by filing papers with the court claiming that they were harmed by the radiation oncologist and is entitled to legal redress. The claim of malpractice must be set out in the plaintiff's prima facie case. This will include a statement of the facts and legal theories that establish that the plaintiff believes they are legally entitled to enforceable claims against the physician.

There are four essential elements to a prima facie case of medical malpractice: *establishment of duty*, *breach*, *causation*, and *damages*. To demonstrate medical malpractice, a plaintiff-patient must show that the radiation oncologist had a duty to provide nonnegligent care to the patient, that the provider breached that duty by providing negligent care, and that this breech caused the patient injury or damage.[430-433]

To establish a *duty*, the plaintiff must have facts that demonstrate a legal relationship between the radiation oncologist and the patient. It is a basic rule of Anglo American law that there is no duty to another person unless there is a legally recognized relationship with that person. The plaintiff-patient must demonstrate the existence of a physician-patient relationship.[434]

To establish a *breach*, the patient-plaintiff must demonstrate facts that illustrate the radiation oncologist breached the legal duties implied in the physician-patient relationship or duties that would be generally imposed on members of society. The plaintiff must establish that the appropriate standard of care was violated. Although, in theory, the establishment of the standard of care and the breach of that standard are legally separate, in reality, unless there is a factual question about what the radiation oncologist actually did, the proof of the standard of care would also demonstrate the defendant's breach. Most commonly, in law, the definition of *standard of care* is how similarly qualified radiation oncologists would have managed the patient's care under the same or similar circumstances. In 2024, the American Law Institute proposed a new standard for medical malpractice, where "reasonable medical care is the care, skill, and knowledge regarded as competent among similar medical providers in the same or similar circumstances."[435] In most medical malpractice cases, both the standard of care and the breach are established through the testimony of expert witnesses.

Negligence is "the omission to do something which a reasonable man guided by those ordinary considerations which ordinarily regulate human affairs would do, or the doing of something which a reasonable and prudent man would not do." The person claiming malpractice is asserting that they are owed a duty by the defendant physician and that violation of that duty by the physician caused injury. The court will make a determination concerning the propriety or impropriety of the defendant physician's performance on the basis of "the reasonable man" had they been in the same situation as the individual being judged. Negligence may derive from the

physician's lack of training or experience or from their carelessness or inadvertence[436] (Box 1.9).

Box 1.9

The New York Times Investigates Radiation Therapy

Radiation therapy practice was severely shaken when *The New York Times* published an article on June 21, 2009, titled "At V.A. Hospital, a Rogue Cancer Unit" and a second article on January 23, 2010, titled "Radiation Offers New Cures, and Ways to Do Harm." Both were authored by Walt Bogdanich.[401,402]

The first article described allegations that the prostate brachytherapy program at the Philadelphia V.A. Medical Center was "a rogue cancer unit at the hospital, one that operated with virtually no outside scrutiny and botched 92 of 116 cancer treatments over a span of more than six years—and then kept quiet about it. . . ." There were allegations of repetitive misplacement of prostate brachytherapy seeds, changing of treatment plans to cover up alleged errors, lack of peer review and quality assurance procedures, and the development of severe complications in patients.

The second article focused on the death of a 43-year-old man who had been irradiated at St Vincent's Hospital in Manhattan for a tongue carcinoma and a 32-year-old female with breast cancer treated at the State University of New York Downstate Medical Center. In the former case, the multileaf collimator was left fully open during IMRT. In the latter case, a wedge was left out of the linear accelerator. Both patients were overdosed, and the patient with tongue cancer died of radiation injuries. Bogdanich explores the causes of the errors: possible software malfunctions, human error, and lack of QA and safety check procedures. Furthermore, the reporter raised the question of whether governmental oversight was sufficient to ensure the safety of clinical radiation therapy.

The articles made the safety of radiation therapy a national concern and produced considerable soul searching in the medical physics and clinical radiation therapy communities. Error-reduction programs seek to understand what can go wrong in radiation therapy, what can be done to prevent errors, how much can be done to engineer procedures to prevent machine and human error, and what types of oversight are necessary to minimize error. We must never forget the Hippocratic admonishment *primum non nocere:* "First do no harm."

To understand the concept of an expert witness, we must consider the legal doctrines of the *school of practice*, the *locality rule*, and the concept of the *qualifications of an expert*.[441],[442] The legal doctrine of the school of practice is designed to deal with the historic problem of the competing interests of physicians. Physicians generally do not want to testify against their colleagues, but they are often tempted to try to run their competitors out of business. Allopathic physicians were happy to label homeopathic physicians as quacks, and many medical doctors would be happy to dispute the competence of a chiropractor. To deal with the problem, the courts use the legal doctrine of the *school of practice* in which they refuse to allow physician experts to question a different school based on philosophic

or psychological beliefs.[443] The school of practice rule is now generally used to differentiate physicians in the self-designated specialties. (We use the term *self-designated* because few state licensing boards recognize specialties or limit physicians' rights to practice the specialties in which they have been trained.)

The *locality rule* refers to the concept that a physician's competence should be determined by comparison with other physicians in the community or in similar neighboring communities.[444] However, with the development of national standards for the practice of radiation oncology, there is no justification for rules that shelter substandard medical decision-making by using an excuse that it is the norm for a given community. A radiation oncologist, for example, could not be held at fault for failing to treat a patient with an unusual or exotic technology if that technology were not available in their local community. However, physicians are required to inform the patients of the limitations of the available facilities and recommend prompt transfer if indicated. Failure to refer patients when a provider lacks the experience to appropriately treat may create malpractice liability. Furthermore, if a radiation oncologist does not give a patient information about the potential result associated with not seeing a subspecialist able to use a specific technology, then the initial radiation oncologist may be held liable. Physicians must recognize when a particular medical problem is beyond their capacity for diagnosis or treatment. They are responsible for obtaining timely and adequate consultations when indicated and for referring the patient to an appropriate specialist or facility whenever the requirements for the appropriate or specialized care cannot be satisfied at the available facilities. The continued expansion of knowledge in radiation oncology and the increasingly specialized training of physicians make it essential that the radiation oncologist be able to recognize any limitations in their capabilities or ability to treat a given patient with what is perceived to be standard of care. Failure to obtain an appropriate consultation or make an appropriate referral may denote negligence.[445-447]

Qualified experts sometimes disagree as to the standard of care. When alternative schools of thought exist, the physician defendant is entitled to be judged by the tenants of the school they follow. In such states, this is called the *minority practice doctrine*. With this doctrine, also called the *respectable minority rule*, the physician may show that although the course of therapy followed was not the same as other practitioners would have followed, it was one that was accepted by a respectable minority group of practitioners.[448]

A problem that is increasingly facing physicians in the United States has been the pressure radiation oncologists face from their employers or from insurance companies to conform their proposed care to a predetermined regimen. Despite legislative initiatives to hold such organizations accountable, the radiation oncologist will, for the most part, carry a significant portion of the risk of liability in cases

where the patient asserts that they were unable to obtain the most accurate and appropriate diagnostic and therapeutic measures. It is essential that the radiation oncologist come to their own conclusions about the standard of care, irrespective of any pressures applied by an employer or an insurance company. In litigation, the radiation oncologist's best defense against a claim of malpractice is if they can demonstrate action only in the interest of the patient, regardless of any financial consideration or bureaucratic restraint imposed by an insurance company, a health maintenance organization (HMO), a health care system or any other financial consideration. If a conflict arises between the radiation oncologist's recommendations for the best course of treatment and the level of care authorized by their employer, or insurance company, or an HMO, the physician must give the best care to the patient even if it means they will not ultimately be compensated.[449]

Radiation oncologists will, on occasion, be called on to serve as expert witnesses in malpractice cases. Physicians, trained to give opinions, may find the give and take of the courtroom off-putting. For an expert witness, the foremost qualifications are effective presentation and teaching ability. The radiation oncologist, serving as an expert witness, must educate the attorneys, judge, and jury. Once there is a perception of understanding, the radiation oncologist may be able to convince the judge and jury that they can make an independent decision that their testimony is correct.

Both the plaintiff's attorney and the defense attorney will retain expert witnesses who will be persuaded to "take sides." The expert witness will be asked to swear, under oath, what influence the radiation dose, volume, or technique had on the risk of an ill effect of radiation therapy on normal tissue or alleged failure to control the tumor. This expert witness system troubles many physicians who feel that they can bring a dispassionate and scientific view to such cases and come to a reasonable conclusion about whether malpractice occurred outside the process of litigation.[450] Whatever the wishes of the physician, a trial is an adversarial process. The physician as an expert witness is advised, therefore, to state their opinion about the case frankly and not attempt to predict or handicap how a trial will turn out. They should do their best to provide an opinion and then step aside to let a system, in which they have little expertise, run its course in the hands of the attorneys and judge. Although often frustrating and distressing, the physicians will find themselves out of their league if they attempt to act as attorney or judge.

Each physician must make a determination as to whether they feel comfortable participating as an expert witness. Some radiation oncologists accept employment as expert witnesses in both plaintiffs' actions and in defense. Some only choose to participate as expert witnesses for the defendant physicians or simply wash their hands of the matter and will have nothing to do with the process. The lure of money is strong and serving as an expert witness can be lucrative. There are physicians who

became well-paid professional expert witnesses and companies that broker their services. Each physician must, however, determine for themself whether the financial compensation for serving as an expert witness outweighs the considerable effort and troubling aspects of the process.

It is important that radiation oncologists understand that the concept in malpractice law of *res ipsa loquitur*,[451] roughly translated as "the thing speaks for itself," is used to deal with cases in which the actual negligent act may not be proved, but it is clear that the injury was caused by negligence. In law, this doctrine was first recognized in the case of a man who was injured when a barrel rolled out of a second-story window of a warehouse. The defense attorney argued that the plaintiff did not know what events preceded the barrel rolling out of the window, and, therefore, it could not be proven that an employee of the warehouse was negligent. The plaintiff, however, countered that barrels do not normally fall out of second-story warehouse windows. The simple fact that the barrel fell from the window and caused an injury "spoke for itself" and demonstrated that someone must have been negligent.

In medical malpractice law, *res ipsa loquitur* is used to shift the burden of proof to the defendant's position regarding causation. *Res ipsa loquitur* can be invoked if the patient suffers an injury that is not an expected complication of medical care, the injury does not normally occur unless someone has been negligent, and the defendant was responsible for the patient's well-being at the time of the injury. Examples in which this concept has been invoked include the dislocation of a patient's shoulder while aligning it for a chest x-ray, knocking out a patient's tooth while the patient was under anesthesia for a tonsillectomy, nerve injury because of a hypodermic injection, leaving a sponge in the abdomen during an operation, or fracturing a patient's jaw while extracting a tooth.[452]

An *intentional tort* is an action that can result in harm to the plaintiff. The classic intentional tort in medical malpractice law is forcing unwanted medical care on a patient. Even if care clearly would benefit a patient, if that care were refused and the radiation oncologist had no state mandate to force care on the patient, but did so anyway, the patient might sue for intentional tort. The most common intentional tort is *battery*. The legal standard for a battery is "an intentional unconsented touching."[453]

Battery is not the same, in law, as *assault*. Assault is the act of putting a person in fear of bodily harm. Most battery claims against physicians are based on real attacks. However, battery claims can also be created by the circumstances of the medical treatment. The legal standard of care is that male health care providers do not examine female patients without a female attendant present. Although the standard frequently is ignored, it should not be. An attorney representing a plaintiff-patient may attempt to demonstrate that allowing an unattended examination of a female

patient by a male radiation oncologist is concrete evidence that, at the very least, the physician has very poor judgment.

Of particular concern to radiation oncologists, in the realm of malpractice, is the concept of *loss of chance*. This is usually evoked in circumstances where physicians failed to diagnose a terminal illness. The loss of chance stems from the failure to diagnose in time for the patient to have a chance of cure. Not all states recognize this standard. In those states that do, however, the patient must show that the loss of chance is statistically significant.[454]

It is generally viewed that any patient injured by exposure to a defective x-ray machine will be compensated as a matter of law.[455] If, however, the radiation oncologist did not know or could not have reasonably been expected to know that a machine was defective, they will generally not be held liable if they used the machine properly.[456] Radiation oncologists are bound by the usual standards of skill, knowledge, and appropriate diligence that apply to the specialists within the field.

If a patient is hypersensitive to radiation therapy, and in the absence of any reasonable way to predict this, the radiation oncologist will not be expected to predict or prevent it.[457-459] There is, however, the possibility that the plaintiff's attorney will invoke *res ipsa loquitur* in certain circumstances.[460] For example, in a patient who received radiation therapy for a benign condition and suffered a severe radiation cutaneous reaction that required bilateral amputation, the radiation oncologist was found to be negligent.[461] In the employment of diagnostic radiation, minimal exposure is involved, and it is not expected that a skin reaction will be produced. Thus, if a skin reaction does ensue, many courts would infer negligence.[462] If a part of the body is unintentionally irradiated and injured, liability will generally follow. For example, a patient who is undergoing radiation therapy to the head and neck was compensated when he suffered severe injury to the arms.[463] A patient given radiation therapy to the ear suffered reaction of the head, face, and neck. Liability was also imposed.[464] It is reasonable to expect that patients give informed consent for radiation therapy and will accept a certain risk of ill effects. This does not mean that the patient assumes a risk of negligent care.[465,466]

In a case where a patient with carcinoma of the rectum was given radiation therapy at a dose above that recognized as proper and suffered severe ill effects, the radiation oncologist offered a defense that such dosage had been given in accordance with the recommendation of a recently delivered scientific paper. The court rejected this claim. In the court's view, this was not a generally accepted course or program of therapy, and the patient's specific consent to the variance in therapy had not been obtained.[467]

One must be particularly cautious in dealing with a woman of childbearing age concerning the possibility of pregnancy before exposing her to radiation therapy. Because the fetus might be injured, producing birth defects or necessitating an

abortion, the patient has a right to refuse or at least should be given the full chance of providing informed consent.[468] Some departments require a negative pregnancy test on the chart before irradiating any woman of childbearing age.

One must also be wary of injury through other forms of negligence involving radiation therapy. Injuries of this type include allowing the patient to fall, unstrapped, off the couch of a treatment machine as it is being moved into the correct position, being struck by equipment from a treatment machine or a simulator, being shocked or burned, or being permitted to come in contact with high tension electrical wires.

There are some data concerning the types of malpractice claims brought in radiation oncology. From 1975 through 1994, a total of 18,860 malpractice suits were brought in Cook County, Illinois, naming at least one codefendant physician; 8% named a radiation oncologist as one of the defendants. The number of suits directed against radiation oncologists fell sharply in Cook County after 1982. At that time, allegations that thyroid cancer in adults developed from tonsillar irradiation administered in childhood for benign disease halted when such suits proved unsuccessful. The most common complaints initiating radiation oncology suits in recent years relate to:

(a) Alleged complications of radiation therapy
(b) Alleged administration of radiation therapy for inappropriate indications
(c) Alleged inappropriate withholding of radiation therapy[469]

An interesting survey of 107 radiation oncology lawsuits conducted by the Fletcher Society found that 59% of the plaintiff patients were female. The four most common organ sites involved in the suits were gynecologic (17%), breast (16%), head and neck (14%), and urologic (12%). The actuarial probability of a radiation oncologist remaining free of a lawsuit after 30 years in practice was 35%.[470]

From 1985 to 2007, I reviewed 20 cases of alleged malpractice involving radiation oncology in the capacity of an expert reviewer employed by an attorney—almost always for the defense. When there was sufficient information to determine the intent of treatment, it was always curative rather than palliative. A few themes emerged from an analysis of the primary complaints of the plaintiffs. In 6 of the 20 cases, the plaintiff alleged that a delay in diagnosis by someone other than the radiation oncologist adversely affected the prognosis and/or increased the risk of adverse late effects of radiotherapy. In 4 of the 20 cases, the plaintiff alleged a breach of the standard of care caused radionecrosis, cognitive injury, or second malignant neoplasm induction. In two cases, the plaintiff alleged that the treating radiation oncologist should have obtained a second surgical pathology or cytology opinion and that failure to do so resulted in unnecessary ill effects of treatment.[471]

The National Association for Insurance Commissioners conducted an extensive study of medical liability claims and insurance indemnity. It was published yearly between 1977 and 1980. The final report was based on data collected from over 70,000 medical liability claims arising from over 62,000 alleged injuries or incidences that were closed with payments to the plaintiffs by insurers. These data show that 4% of paid claims were related to EBRT.[472]

Marshall et al reviewed 362 closed malpractice claims filed against radiation oncologists collected by a U.S. liability trade association from 2003 to 2012. Of the 362 claims, 102 (28%) were paid, totaling $38 million or an average of $372,468/paid claim. The most common alleged error leading to a paid claim was improper performance of radiation therapy (18%). Examples include misplaced prostate brachytherapy seeds causing rectal toxicity, or forgetting a spinal cord block and causing radiation myelitis. Errors in diagnosis accounted for 12% of paid claims. Examples include failure to diagnose a new tumor on a follow-up imaging study, stimulating a patient for prostate radiotherapy and not recognizing the presence of a colon cancer, or failure to diagnose appendicitis or an aortic aneurysm.

Death-related claims had a lower average payment and lower percentage of paid claims than claims for radiation injury. Why? It may be more difficult to blame a radiation oncologist for the death of a patient with cancer than for radiation toxicity in a living patient.[473]

Prabhu et al used an online legal database to retrospectively study radiation oncology medical malpractice cases from 1985 to 2015. Thirty-two cases were analyzed. In only 23% was the radiation oncologist the sole defendant. In the remainder of the cases, two or more specialists were named as defendants. The most common reasons for litigation were allegations of excessive radiation (34%), failure to refer or order appropriate tests (28%), death of the patient (22%), failure to treat (19%), and failure to diagnose in a timely manner (16%). The jury verdicts were for the doctor(s) 53% of the time, the plaintiff(s) 34% of the time, and 13% of the cases were settled without a verdict. The mean settlement was $1.5 million. The mean award for the plaintiff, if they won the case, was $4.7 million.[474]

Marshall et al performed a retrospective analysis of 1,517 closed malpractice claims filed between 1985 and 2012 by a nationwide medical liability trade association involving radiation oncology. Only 22.5% of closed claims resulted in indemnity payments ranking radiation oncology as 18 out of 22 specialties in the percentage of closed claims paid. The highest was obstetrics-gynecology at 34.2%, and the lowest was gastroenterology at 18.1%. The average indemnity payment per claim is $276,972, the fifth highest of the 22 specialties. The highest were neurology and neurosurgery; the lowest was dermatology. About 2.4% of U.S. radiation oncologists had a closed claim and 0.68% a paid claim.[475]

Brachytherapy as the origin of a malpractice action poses particular problems for the radiation oncologist. Brachytherapy procedures are relatively rare. Therefore, expertise is often limited and the individual experience of the practicing radiation oncologist may be minimal. The existence of postimplant films, which document the location of the radioactive material, can be used to challenge the quality of the implant procedure. Brachytherapy complications can take years to occur and, because brachytherapy is often employed in the treatment of carcinoma of the prostate, cervix, and uterus, the development of fistulas in long-term survivors can be the cause of a malpractice action.

Radiation oncologists conduct their practice with the assistance of others: physicists, dosimetrists, nurses, and therapists. It is necessary, therefore, for radiation oncologists to understand *vicarious liability*. In general, employers are responsible for the actions of their employees. This is called *respondent superior*—also called the master-servant relationship.[476] The fundamental issue that determines whether a person is legally treated as an employee is the extent to which the person hiring the worker may control the details of that work. Nurses, PAs, radiation therapists, and other physician extenders are professionals, but in most states in which they are licensed, they generally have a limited license. The extent to which they make medical decisions is determined by state law, but they usually must work under the supervision of a practicing physician. The physician's license, however, is unlimited. The physician, for example, may perform nursing tasks without violating nursing practice laws. Injury caused by extenders may, ultimately, lead to a malpractice claim against the physician. Physician liability for the actions of hospital employees is particularly problematic for radiation oncologists. Many radiation oncologists practice in hospital-based clinics. In general, the *doctrine of the borrowed-servant* or the *captain of the ship doctrine* states that all actions of hospital employees are attributable to the patient's attending physician. Under such a doctrine, the radiation oncologist may be found liable for the actions of a nurse, dosimetrist, or radiation therapist who the physician can neither hire, fire, nor otherwise directly control.[477]

When radiation oncologists are directors of clinical services, they also should be aware of the fact that they may be vicariously liable for the behavior of employees if they tolerate inappropriate activity or do not properly screen employees for dangerous tendencies. If, for example, a therapist has assaulted persons in the past and the radiation oncologist was negligent in discovering this, the radiation oncologist could be held liable under the theory of negligent hiring. The radiation oncologist also could be held liable for negligent retention if there were complaints about the behavior of the therapist and the physician failed to act on them.[478]

The captain of the ship doctrine means that physicians may have responsibility for the mistakes of their radiation therapy technologists, dosimetrists, physicists, nurses,

and fellow practicing physicians allegedly under their supervision or control. It is, therefore, incumbent upon the responsible radiation oncologist to take care in staff selection, training, and supervision. There is a risk in delegating such matters to an office manager. Ultimately, the physician must maintain an active role in ascertaining that they can fully trust the person selected to assist in all aspects of patient care. This means that the radiation oncologist must protect against allegations of sexual misconduct or abuse, alcohol or drug impairment, or mental illness potentially affecting patient care; because the physician is ultimately liable for the care given to a patient, the radiation oncologist must play an active role in ongoing training and professional development of their staff.

If an accident or allegation of misconduct occurs, the radiation oncologist must have a thorough, efficient, and adequate means of investigation of the matter and, if necessary, discipline or dismissal. Adequate employment records must be maintained (Box 1.10).

Box 1.10

Systematic Radiation Therapy Overdose and Underdose: Events in the United Kingdom

In the United Kingdom, it was discovered in 1998 at Exeter that 207 patients were given a radiation dose >25% than that generally deemed appropriate for the treatment of breast cancer. Some patients had more marked radiation reactions than appropriate. When this became known, adverse publicity appeared in the press. At Stafford, ~1,000 patients received ~25% underdosing over a 20-year period. An investigation concluded that in ~500 patients, there was a real possibility that underdosage may have affected the outcome of treatment and, in a small number of patients, produced a cancer recurrence higher rate than that expected.[479-481]

The causes of these two incidents were analyzed in great detail and may have been related to inadequate medical physics staffing. A Royal College of Radiologists survey showed that radiation oncologists in many UK radiotherapy departments were seeing ≥600 new patients per year as compared to the usual 250 to 300 patients seen in France, Germany, and the United States.

One of the most vexing problems now facing the practicing radiation oncologist is the matter of substance and alcohol abuse in the workplace and the potential criminal records of employees. Some practices are instituting mandatory preemployment screening for alcohol and drug abuse and criminal background checks. These issues, however, are extremely complicated. There is a growing list of which drugs should be tested for, no consensus for when the testing should occur, who should be evaluated for a potential criminal background, which positive

criminal background checks merit a decision not to employ an individual or to dismiss the person, under what circumstances a person can be felt to have paid their debt to society in a way that allows the individual to practice in a health care environment, and to what extent a radiation oncologist can be held liable for failure to exercise due caution in this process. Obtaining sound advice from experts in personnel relations and legal counsel is advisable.[482]

It is well recognized that no radiation oncologist can be available at all times and in all circumstances. A physician may arrange, during their absence for vacation or ill health, for practice coverage by another physician. When one radiation oncologist "covers" for another, there are risks to patient safety, and possible susceptibility to malpractice claims, if clinical care "falls through the cracks."[483] To minimize the risk of malpractice claims, the following guidelines should be followed:

- When you are away from your practice, you should select a covering radiation oncologist who possesses knowledge and skill at least equal to yours.
- Inform and obtain consent from those patients who will be affected.
- Apprise your covering physician of any important clinical information pertaining to patients that they will see in your absence.
- The covering physician is expected to do more than just "fill in." They must apply the same degree of medical skill and care as the regular radiation oncologist.
- When the regular radiation oncologist returns, they should receive a report of any noteworthy patient care events, laboratory tests or diagnostic imaging results that deserve follow-up, and any other "loose ends."[484]

It cannot be overemphasized that well-maintained, either electronic or paper and ink, medical records are crucial to a satisfactory legal defense in malpractice claims in radiation oncology. In law, the concept of *spoliation* refers to the destruction of evidence of significance or a meaningful alteration of a document. In medical malpractice cases, this would refer to the absence or disappearance of medical records. One radiation oncologist wisely counseled: Now and then look over an old chart, see if you can trace all of your steps in making decisions and executing treatments. Would this chart be sufficient to defend yourself against a malpractice claim?[485]

The Nature of Grievances, Malpractice Claims, and Insurance Disputes in Radiation Oncology

Dissatisfied patients might ignore their physician's advice or seek a new physician. Assertive patients may confront their physician. It is also commonplace for patients

to discuss their complaints about physicians with friends and relatives.

Patients whose dissatisfaction prompts formal action have several options. These include bringing a malpractice claim and seeking redress in courts. Other options include filing a complaint with a government medical board; filing a complaint with the "patient relations office" of a hospital or group practice; directing a complaint to a hospital's chief of medical staff or credentials office; or submitting a grievance to the local, state, district, or national medical society. Why do some dissatisfied patients do nothing and others take formal action?[486] The general nature of patient grievances against physicians, has been evaluated by several authors.[487,488] Complaints fall into several broad categories:

- Alleged failure of physicians to fulfill the patient's expectations for examination and treatment (ie, inadequate therapy, failure to obtain informed consent prior to a procedure, inadequate physical examination, or lack of prompt attention following hospitalization)
- Alleged failure to make a prompt diagnosis
- Alleged rude or discourteous behavior
- Alleged unacceptable practice behavior, such as producing excessive pain or practicing outside an area of expertise
- Alleged inappropriate behavior related to billings and collections
- Alleged physician's use of alcohol or drugs
- Alleged sexual misconduct
- Alleged errors in prescribing
- Alleged insurance fraud

Formal complaints, including malpractice suits, represent only the tip of the iceberg of patient dissatisfaction. Patients far more often deal with their dissatisfaction by complaining to family and friends or switching doctors than by submitting a written complaint. A study by the Harvard Medical Practice Study Group, for example, found that less than 2% of patients who had adverse events because of medical malpractice ever filed malpractice claims.[489]

Few complaints turn into malpractice claims, a fraction of these claims go to trial, and a fraction of those end up in a finding for the plaintiff. Patients pursue medical malpractice claims for a variety of reasons. The four most common include an attempt to hold the offending caregiver accountable, to seek a more complete or satisfying explanation for the adverse event, to stop similar events from occurring to other patients, and to obtain financial compensation[490,491] (Box 1.11).

Box 1.11

The RAGE Campaign

In 1991, a group of women formed an organization in the United Kingdom called RAGE (Radiation in Action Group Exposure). A patient developed brachial plexus damage following surgery and radiotherapy for breast cancer. The patient wrote a letter to several newspapers describing these events and criticizing the medical and legal processes. This produced an outpouring of concern from other patients who claimed to have suffered from the same side effects. RAGE called for significant changes in the use of radiotherapy for the treatment of breast cancer.[374] The group successfully applied to the legal aid board for funds to undertake research toward a group legal action and, in 1995, constituted a group of plaintiffs in a malpractice case. Publicity associated with the litigation prompted the Royal College of Radiology to establish a multidisciplinary working party that made recommendations to ensure that patients with symptoms that might be due to radiation-associated brachial plexus injury had access to a network of health care professionals and cancer centers with the necessary skills for diagnosis, functional assessment, and treatment. The case highlighted the risks of high dose per fraction radiation therapy used in the 1970s and 1980s. When the case eventually came to judgment, Justice Ebsworth concluded that there was no negligence and costs were directed against the plaintiffs. The justice commented that "it was unfortunate that litigation in terms of medical negligence was felt to be the only mechanism available," particularly in view of the fact that the cost of litigation exceeded £4 million. The case is instructive on several grounds:

1. The ill effects of radiation therapy may take a long time to become manifest.
2. Communication with patients concerning the causes and treatment of an injury is crucial.
3. The cost of litigation is high, would hope that in the future society can derive alternative mechanisms to costly malpractice actions to allow patients to understand how and why injuries occur and prevent future occurrences.[437-440]

A disagreement between a patient and their radiation oncologist may cause the patient to have diminished trust in the physician, to be dissatisfied with the clinical results, to change physicians or health plans, to file a complaint, or to undertake litigation. For physicians, however, disagreements with patients may result in frustration, anger, a feeling of loss of control, and career dissatisfaction.

In 2010, California law required that radiation oncologists disclose wrong site of treatment, treatment of the wrong patient, and dose variance of 20% or more of the total prescribed dose to the patient and the Department of Public Health.[492] Mandatory disclosure of medical errors, either by law or institutional policy, is becoming increasingly popular. There is, of course, considerable judgment involved in what kind of error warrants disclosure. Few would argue that a major discrepancy in the dose administered versus the one prescribed would warrant disclosure. Not placing the bolus for 1 fraction out of 30, for example, probably has no significant influence on patient outcome.

When a medical error is discovered, prompt action needs to be taken in regard to disclosure. This topic is eloquently addressed by Evans and Decker.[493] We articulate some basic principles of the response.

- Your first obligation is to be certain that the care of the patient is receiving full attention, including any medical care that may be necessary as a result of the medical error.
- Notify your institution's office of risk management about the error. This will set in motion the implementation of the appropriate institutional policies and procedures. (And if your institution does not have an office of risk management with written policies, it should.)
- After carefully preparing, in advance, what you want to tell the patient and their family and how you want to present the information, do so in a quiet place, without distractions, in an unhurried fashion, with clear and understandable explanations and plenty of time to hear and answer questions. Do follow-up meetings as indicated.
- Make sure that all documentation of what happened and what was reported to the patient is meticulously prepared and recorded.
- Complete any required reports to government agencies.
- Learn from medical errors. A departmental conference designed to understand "What happened? Why it happened? How it can be prevented from happening again?" is an important part of a radiation oncology department's QA process.

The Vanderbilt University Medical Center's Center for Patient and Professional Advocacy database was used to ascertain the number and types of unsolicited patient complaints that were leveled by patients against radiation, medical, and surgical oncologists up until 2018.[494] Radiation oncologists engendered fewer complaints per doctor (1.28) than medical oncologists (3.81) or surgical oncologists (6.89). In an ordinal regression model, academic radiation oncologists and radiation oncologists who graduated from a medical school outside the United States seemed to provoke more complaints. For radiation oncologists, the most common source of the complaint was dissatisfaction with the quality of care and treatment, complaints about communication, complaints about the doctor's accessibility, and concern for the patient's welfare.

It is important to document your explanation of the risks and benefits of radiation therapy and to obtain the patient's written authorization to proceed, with a full understanding of those risks. In discussing any procedure or treatment with the patient or their guardian, the radiation oncologist should endeavor to explain all of the risks in sufficient detail to permit the patient to make a well-educated decision. Written informed consent should be obtained. But simply having the patient sign a

standard form is not the end of the matter. The forms need to be easily understood and written in clear language. It is unwise for a physician to adopt standard printed forms without giving them proper scrutiny. Radiation oncologists must also be sure that the consent form is properly filled out. If, for example, there are blanks for explanations of particular risks involved for the procedure, they should be properly filled in.[495]

It is essential that radiation oncologists use fundamental communication skills to avoid grievances and malpractice claims, understand the patient's worries and concerns, express empathy, actively discuss care options, negotiate differences of opinion, and allow time for adequate conversation. The challenge for radiation oncologists is to recognize patients' unfulfilled expectations and to engage patients in a discussion with the goal of identifying and avoiding dissatisfaction while building a trusting therapeutic relationship.[496]

Insurance disputes involving radiation oncology typically centered on one or more of the following questions: Is the recommended course of radiotherapy covered under the patient's insurance contract? Is the proposed treatment standard of care or experimental? Is the proposed course of treatment likely to be more beneficial than alternatives? What are the supporting references from the medical literature underpinning the doctor or the insurance company's decisions?

I was asked, between 1995 and 2007, to review 69 radiation oncology insurance disputes. Overwhelmingly, these disputes were about a radiation oncologist's desire to employ and bill for the use of an expensive technique of external beam radiotherapy and the insurance company's response that the technology was not standard of care. Examples include Gamma Knife or Cyber Knife treatment of metastatic corner or proton therapy for prostate cancer or vestibular schwannoma or IMRT for localized breast cancer.[497]

Health Insurance Portability and Accountability Act

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) resulted in changes in the area of health care fraud and abuse. HIPAA created new criminal offenses and brought civil remedies while strengthening existing ones. More important for the practicing radiation oncologist, however, HIPAA is part of a larger political initiative in which health care fraud and abuse became a top law enforcement priority. Large numbers of civil investigations have been brought regarding alleged abuses of Medicare and Medicaid. Many physicians and organizations have been excluded from federally funded health care programs, and there have been criminal convictions and the collection of large criminal fines.

Risk Management in Radiation Oncology

In an era of increasing litigation and, unfortunately, a growth in adversarial situations between physicians and patients, it is critical for the radiation oncologist and staff to make every effort to decrease professional liability risks.

The origins of medical malpractice suits include[498]:

- Medical accidents that may not be adequately understood by the patient or explained by the treating physician
- Less than successful or unexpected adverse results of treatment
- Poor results from previous treatment elsewhere and ill-advised comments by other physicians or health care personnel
- Rejection of a plan of therapy without appropriate documentation that the physician has advised the patient of the consequences of declining treatment. Some physicians document this discussion in the chart and send a certified letter advising the patient of the consequences of rejection of treatment.
- Complaint of experimentation when the patient has not been appropriately informed of the nature of the therapy to be administered
- An angry patient who may find this a way to vent anger or frustration about any events surrounding treatment, including lack of communication, discourteous treatment by the physician or staff, or the amount of the medical bill

The best prevention against a lawsuit is good rapport with the patient and relatives, effective communication and QA programs, and clear and accurate documentation of all procedures, discussions, and events that take place before, during, and after treatment.

After appropriate clinical assessment, the histologic diagnosis of the patient must be confirmed at the treating institution; this often includes a review of outside pathologic slides. The rationale of therapy and any changes in the treatment plan should be duly explained and documented in the record. All procedures performed on the patient should be recorded in the chart, including details of daily treatments, such as the use of special treatment aids (ie, bight blocks, testicular shields, eye shields, immobilization devices), and any problems related to equipment operation. All treatment parameters and calculations should be accurately recorded and verified by a physicist or dosimetrist, in addition to the radiation oncologist. We should remember that, as liability attorneys say, “If it is not recorded on the chart, we may assume it never happened.”

The physician and staff may help in their own professional liability defense in case a lawsuit occurs. It is extremely important for the physician to understand and, at an appropriate time, identify early warning signs of an impending malpractice suit. The physician should promptly contact their attorney, risk management office, and insurance carrier.

The physician should prepare an incident report in anticipation of potential litigation, describing the potential liability, including dates when events took place and actors and witnesses to be identified by name, affiliation, and status. Incident reports are confidential information between the physician and the attorney, risk manager, or insurance carrier. The report should be prepared while the facts are still fresh so that documentation will be optimal.

Clear and well-kept records with notes documenting every discussion and procedure that is performed on the patient should help in case of a lawsuit. A full discussion with the patient and relatives regarding planned therapy, particularly side effects of irradiation, and a well-documented informed consent form are valuable in risk management.

Informed Consent

The need to obtain informed consent for treatment is based on the patient's right to self-determination and the fiduciary relationship between the patient and physician.[499] The law requires that the treating physician adequately apprise every patient of the nature of the disease requiring treatment, recommended course of therapy and details regarding it, alternative treatments available, benefits of recommended treatment, and all minor and major risks (acute and late effects) associated with the recommended therapy (Table 1.13). If the plan of therapy is modified, this should be discussed with the patient, and, if warranted, a second informed consent may be required. It is advisable to discuss the informed consent contents in the presence of a witness and have that person sign an informed consent form or the chart verifying that the information was discussed with the patient.

TABLE 1.13 POSSIBLE SPECIFIC SEQUELAE OF THERAPY DISCUSSED IN INFORMED CONSENT

Anatomic Site	Acute Sequelae	Late Sequelae
Brain	Earache, headache, dizziness, hair loss, erythema	Hearing loss Damage to middle or inner ear Pituitary gland dysfunction Cataract formation Brain necrosis
Head and neck	Odynophagia, dysphagia, hoarseness, xerostomia, dysgeusia, weight loss	Subcutaneous fibrosis, skin ulceration, necrosis Thyroid dysfunction Persistent hoarseness, dysphonia, xerostomia, dysgeusia Cartilage necrosis Osteoradionecrosis of mandible Delayed wound healing, fistulae Dental decay

Anatomic Site	Acute Sequelae	Late Sequelae
		Damage to middle and inner ear Apical pulmonary fibrosis Rare: myelopathy
Lung and mediastinum or esophagus	Odynophagia, dysphagia, hoarseness, cough Pneumonitis Carditis	Progressive fibrosis of lung, dyspnea, chronic cough Esophageal stricture Rare: chronic pericarditis, myelopathy
Breast or chest wall	Odynophagia, dysphagia, hoarseness, cough Pneumonitis (asymptomatic) Carditis Cytopenia	Fibrosis, retraction of breast Lung fibrosis Arm edema Chronic endocarditis, myocardial infarction Rare: osteonecrosis of ribs
Abdomen or pelvis	Nausea, vomiting Abdominal pain, diarrhea Urinary frequency, dysuria, nocturia Cytopenia	Proctitis, sigmoiditis Rectal or sigmoid stricture Colonic perforation or obstruction Contracted bladder, urinary incontinence, hematuria (chronic cystitis) Vesicovaginal fistula Rectovaginal fistula Leg edema Scrotal edema, sexual impotency Vaginal retraction or scarring Sterilization Sexual impotence Damage to liver or kidneys
Extremities	Erythema, dry/moist desquamation	Subcutaneous fibrosis Ankylosis, edema Bone/soft tissue necrosis

Informed consent is a process, *not a form*. A consent form documents and codifies the process but does not substitute for clear and appropriate provision of information to the patient with adequate time for questions, answers, and free discussion and exchange. Ultimately, the competent adult patient or a legal representative must agree to the treatment and give approval. For unemancipated minors or legally incompetent adults, informed consent must be signed by the parents, adult brothers or sisters, or a responsible near relative or legal guardian. For incompetent adults, spouses may be allowed by the state to sign. Emancipated minors may provide their own consent. It is extremely important for the radiation oncologist and the staff to spend as much time as is needed to ensure that the patient and, if necessary, relatives understand all aspects of the radiation therapy, particularly the specific description of the various potential deleterious effects of this modality.[500] Many physicians indicate which situations may require surgery to treat a complication and, specifically, when

a gastrostomy, colostomy, ileal bladder, or other organ-substituting operation may be necessary to correct sequelae of therapy.

The radiation oncologist is always balancing a full disclosure of risks and options without overwhelming the patient with data and causing distress. It is reasonable to expect the patient to come away from a meeting with the treating radiation oncologist with a general realistic hope regarding the proposed course of treatment and honest understanding of the side effects and a sense of trust for the physician and the organization. Good documentation is crucial, and, if a malpractice action were to occur, liability may hinge on who said what to whom at what point of the treatment process. Absent, incomplete, or lost records will reflect extremely poorly on the radiation oncologist.[501]

It must be stressed that in dealing with children or mentally incompetent adults, a thorough discussion of the plan of therapy and sequelae should be held with the parents, relatives, or legal guardian of the patient. Also, they must sign the informed consent.

Although, in case of a lawsuit, having a properly executed informed consent form in the record is helpful, more important is the incontrovertible documentation in the chart of the pertinent discussion held with the patient. Radiation oncologists should also be aware of court decisions that place a greater burden on the physician to disclose statistical life expectancy information to critically ill patients as part of the informed consent and as an affirmation of patient-centered decision-making (regarding treatment) in the context of a physician-patient relationship based on trust.[502]

BIOGRAPHICAL SKETCHES OF SOME IMPORTANT EUROPEAN AND NORTH AMERICAN FIGURES IN THE HISTORY OF RADIATION ONCOLOGY

Radiation oncologists of the modern era stand upon the shoulders of their predecessors. The following biographical sketches, presented in order of their subject's year of birth, is a partial representation of the European and North American giants of the specialty. The author has taken the liberty of adding some personal recollections of those individuals he had met.

Wilhelm Conrad Röntgen (1845-1923)

On March 27, 1845, in Lennep, Germany, a son, Wilhelm Conrad, was born to Friedrich Conrad Röntgen and his wife, Charlotte Constanze (Figure 1.49). Röntgen's father was a textile merchant. When Wilhelm was 3, the family moved from Prussia to Apeldoorn in the Netherlands, about 100 miles to the northwest, where Wilhelm's maternal grandparents lived. Wilhelm enrolled in the Utrecht

Technical School in 1862. A fellow student caricatured a teacher on the fire screen of the schoolroom. The schoolmaster demanded the name of the unflattering artist, but Wilhelm refused to betray his classmate and was expelled. There was a risk that his education would come to an end after this episode. Fortunately, the Polytechnical School in Zurich, Switzerland, accepted students based on stiff entrance examinations. The black mark of expulsion was no impediment. Röntgen began classes in 1865 and received his diploma in mechanical engineering in 1868.[503-505]

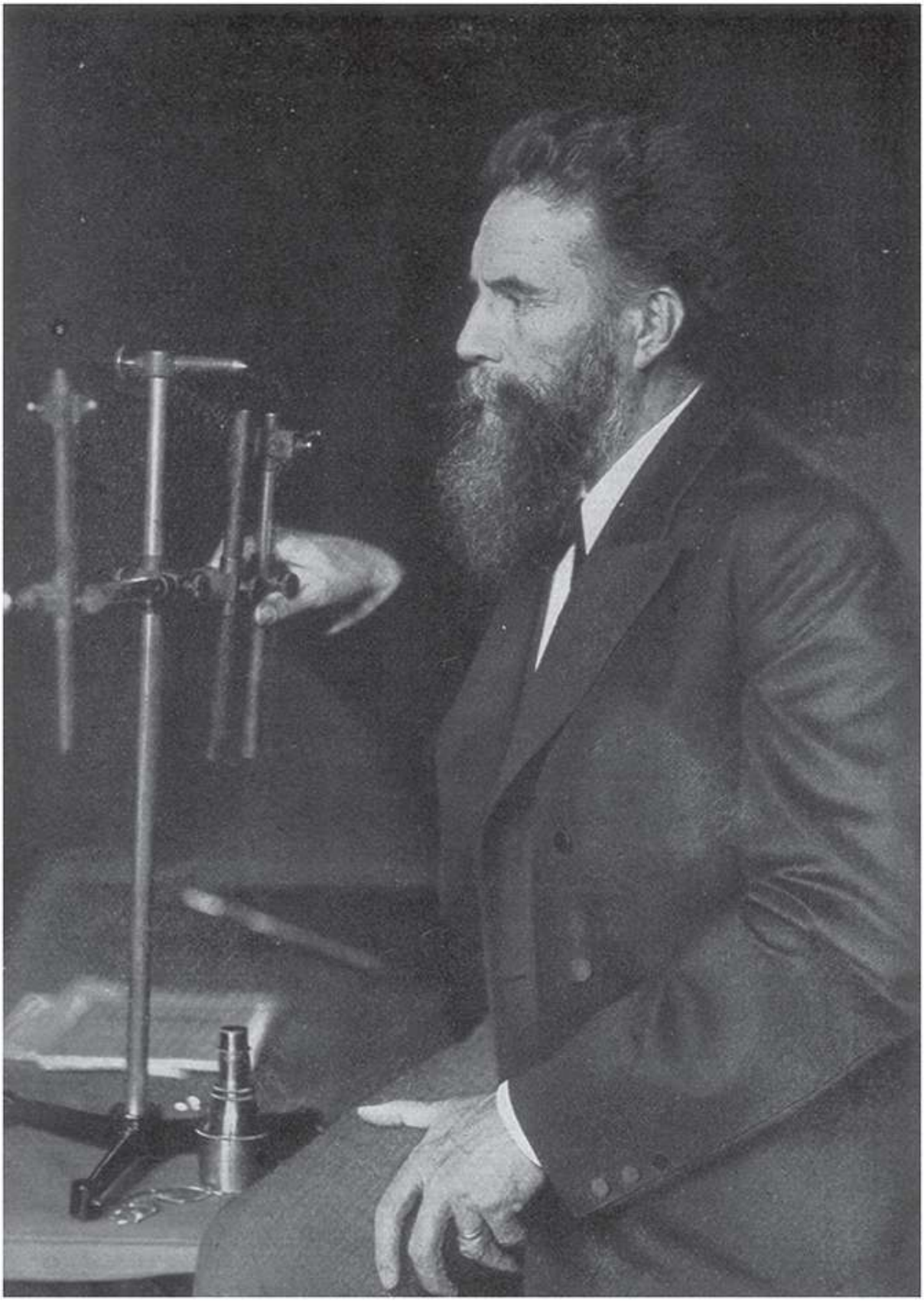


FIGURE 1.49 Wilhelm Conrad von Röntgen. He is shown in this photograph with physics instruments. (From Glasser O. *Wilhelm Conrad Röntgen and the Early History of the Roentgen Rays*. Charles C. Thomas; 1934.From Glasser O. *Wilhelm Conrad Röntgen and the Early History of the Roentgen Rays*. Charles C. Thomas; 1934.)

Röntgen's considerable skill in designing and constructing precision instruments for measuring physical phenomena attracted the attention of Dr August Kundt, a theoretical physicist. Röntgen became Kundt's assistant at the University of Zurich. When Kundt moved, in turn, to the University of Würzburg and then to the University of Strasbourg, Röntgen followed. In 1879, Röntgen struck out on his own as a professor at the University of Giessen.

In 1888, Röntgen accepted a professorship of theoretical physics at the University of Würzburg (Figure 1.50). On November 8, 1895, Röntgen saw the effects of an unusual phenomenon while doing laboratory experiments. He presented his results to the president of the Physical Society at Würzburg on December 28, 1895[506,507] (Figure 1.51).

FIGURE 1.50 Photograph of the Physical Institute of the University of Würzburg from 1896. Professor Röntgen and his wife lived on the top floor. On the left side of the upper story can be seen the conservatory, of which Röntgen and his wife were particularly fond. (Photograph by G. Glock, Würzburg, 1896.)

FIGURE 1.51 A print of one of the first of Rontgen's x-ray images. It shows the left hand of Rontgen's wife, Anna Bertha Ludwig. The wedding ring can be clearly seen. The image was presented to Professor Ludwig Zehnder of the Physik Institut, University of Freiburg, on January 1, 1896. (A similar image exists which is said to have been made on December 22, 1895 and was sent by Rontgen to the Vienne physicist F. Exner. The original plate of that image is in what was called the Deutsche Museum, Munich, and is now the Deutsches Rontgen Museum, Munich.)

There are many accounts of Röntgen's discovery. Among the multitude of reporters who rushed to interview Röntgen was H. J. W. Dam, an Englishman who

was a correspondent for the Canadian *McClure's Magazine*. Dam had a letter of introduction but, like all other reporters, when he arrived in Würzburg, he was turned away. Dam, however, was persistent and wrote a letter in French to Röntgen insisting upon an interview. "You are very difficult, much more difficult than Berthelot, Pasteur, Dewar, and other men of science about whose discoveries I have written." Apparently taken by Dam's audacity and, perhaps, willing to have a sensible article written by a knowledgeable reporter, Röntgen granted Dam an exclusive interview.

Dam's lead story in the April 1896 *McClure*'s is generally regarded as an accurate depiction.[508] Dam told his readers that "in all the history of scientific discovery there has never been, perhaps, so general, rapid, and dramatic an effect wrought on the scientific centers of Europe as has followed, in the past four weeks, upon an announcement made to the Wurzburg Physio-Medical Society, at their December meeting, by Professor William Konrad Röntgen, professor of physics at the Royal University of Würzburg . . . . Röntgen's own report arrived, so cool, so business-like, and so truly scientific in character, that it left no doubt either of the truth or of the great importance of the preceding [newspaper] reports."[509]

Dam, who was able to converse with Röntgen in English, French, and German, conducted an on-site interview in Röntgen's laboratories and had him describe the circumstances related to the discovery. Dam's charming description, excerpted here, gives an excellent insight into Röntgen the man and the nature of his scientific inquiry.

> "Now, Professor," said I, "will you tell me the history of the discovery?"
>
> "There is no history," he said. "I have been for a long time interested in the problems of the cathode rays from a vacuum tube as studied by Hertz and Lenard. I had followed theirs and other researches with great interest, and determined as soon as I had time to make some researches of my own. This time I found at the close of last October. I had been at work for some days when I discovered something new."
>
> "What was the date?"
>
> "The eighth of November."
>
> "And what was the discovery?"
>
> "I was working with a Crookes' tube covered with a shield of black cardboard. A piece of barium platino- cyanide paper lay on the bench there. I had been passing a current through the tube and I noticed a peculiar black line across the paper."
>
> "What of that?"
>
> "The effect was one which could only be produced, in ordinary parlance, by the passage of light. No light could come from the tube, because the shield which covered it was impervious to any light known, even that of the electric arc."
>
> "And what did you think?"
>
> "I did not think; I investigated. I assumed that the effect must have come from the tube, since its character indicated that it could come from nowhere else. I tested it. In a few minutes there was no doubt about it. Rays were coming from the tube which had a luminescent effect on the paper. I tried it successfully at greater and greater distances, even at two metres. It seemed at first a new kind of invisible light. It was clearly something new, something unrecorded."
>
> "Is it light?"

"No."

"Is it electricity?"

"Not in any known form."

"What is it?"

"I don't know. Having discovered the existence of a new kind of rays, I of course began to investigate what they would do. It soon appeared from the tests that the rays had penetrative power to a degree hitherto unknown. They penetrated paper, wood and cloth with ease, and the thickness of the substance made no perceptible difference within reasonable limits. The rays passed through all the metals tested with the facility varying, roughly speaking, with the density of the metal. These phenomena I have discussed carefully in my report to the Würzburg Society and you will find all the technical results therein stated. Since the rays had this great penetrative power, it seemed natural that they should penetrate flesh, and so it proved in photographing the hand I showed you."

A detailed discussion of the characteristics of his rays the professor considered unprofitable and unnecessary. He believes, though, that these mysterious radiations are not light, because their behavior is essentially different from that of light ways, even those light rays that are themselves invisible. The Röntgen rays cannot be reflected by reflecting surfaces, concentrated by lenses, or refracted or diffracted. They produce photographic action on a sensitive film, but their action is weak as yet, and herein lies the first important field of their development. The professor's exposures were comparatively long—an average of 15 minutes in easily penetrable media, and half an hour or more in photographing the bones of the hand. Concerning vacuum tubes, he said that he preferred the Hittorf, because it had the most perfect vacuum, the highest degree of air exhaustion being the consummation most desirable. In answer to the question, "What of the future?" he said:

"I am not a prophet, and I am opposed to prophesying. I am pursuing my investigations, and as fast as my results are verified I shall make them public."

"Do you think the rays can be so modified as to photograph the organs of the human body?"

In answer he took up the photograph of the box of weights. "Here are already modifications," he said, indicating the various degrees of shadow produced by the aluminum, platinum, and brass weights, the brass hinges, and even the metallic stamped lettering on the cover of the box, which was faintly perceptible.

"But, Professor Neusser has already announced that the photographing of the various organs is possible."

"We shall see what we shall see," he said; "we have the start now; the developments will follow in time."

"You know the apparatus for introducing the electric light into the stomach?

"Yes."

"Do you think that this electric light will become a vacuum tube for photographing, from the stomach, any part of the abdomen or thorax?"

The idea of swallowing a Crookes tube, and sending a high frequency current down into one's stomach, seemed to him exceedingly funny. "When I have done it, I will tell you," he said, smiling, resolute in abiding by results.

"There is much to do, and I am busy, very busy," he said in conclusion. He extended his hand in farewell, his eye already wandering toward his work in the inside room. And his visitor promptly left him; the words, "I am busy," said in all sincerity, seeming to describe in a single phrase the essence of his character and the watchword of a very unusual man.[510]

Kaiser Wilhelm II invited Röntgen to the imperial court at Potsdam in January 1896, shortly after the scientist had mailed out reprints to prominent physicists. Röntgen demonstrated his findings and was decorated with the Prussian Order of the Crown, Second Class. On January 23, he gave a lecture to the Würzburg Physical-Medical Society and was startled and overwhelmed by the cheers of the audience. At

the end of the talk, Röntgen invited Albert von Kölliker, one of Germany's most distinguished anatomists, to come to the podium and have his hand x-rayed. When the audience saw the bones of his hand, it erupted in thunderous applause. This was one of Röntgen's last formal lectures on x-rays. He became flustered before large groups and, when lecturing to small groups of students, was generally regarded as lusterless and dull.

Röntgen received the Nobel Prize in Physics in 1901 from the Swedish king. He thanked him but gave no speech. He willed the prize money to the University of Würzburg.[511] In the presentation speech, the president of the Royal Swedish Academy of Sciences, C. T. Odhner, commented on the enormous potential of Röntgen's discovery for diagnosis and therapy:

> The Academy awarded the Nobel Prize in Physics to Wilhelm Conrad Röntgen, Professor in the University of Wurzburg, for the discovery with which his name is linked for all time: the discovery of the so-called Röntgen rays, or, as he himself called them, x-rays. These are, as we know, a new form of energy and have received the name "rays" on account of their property of propagating themselves in straight lines as light does. The actual constitution of this radiation of energy is still unknown. Several of its characteristic properties, however, have been discovered first by Röntgen himself and then by other physicists who have directed their research into this field. And there is no doubt that much success will be gained in physical science when this strange energy form is sufficiently investigated and its wide field has been thoroughly explored. Let us remind ourselves of one of the properties that has been found in Röntgen rays—the basis of the extensive use of x-rays in medical practice. Many bodies, just as they allow light to pass through them in varying degrees, behave likewise with x-rays but with the difference that some that are totally impenetrable to light can be penetrated easily by x-rays, whereas other bodies stop them. Thus, for example, metals are impenetrable to them; wood, leather, cardboard, and other materials are penetrable as are the muscular tissues of animal organisms. Now, when a foreign body impenetrable to x-rays (eg, a bullet or a needle) has entered these tissues, its location can be determined by illuminating the appropriate part of the body with x-rays and taking a shadowgraph of it on a photographic plate, whereupon the impenetrable body is detected immediately. The importance of this for practical surgery and how many operations have been made possible and facilitated by it is well known to all. If we add that in many cases severe skin diseases (eg, lupus) have been treated successfully with Röntgen rays, we can say at once that Röntgen's discovery already has brought so much benefit to mankind that to reward it with the Nobel Prize fulfills the intention of the testator to a very high degree[512] (Figures 1.52 and 1.53).

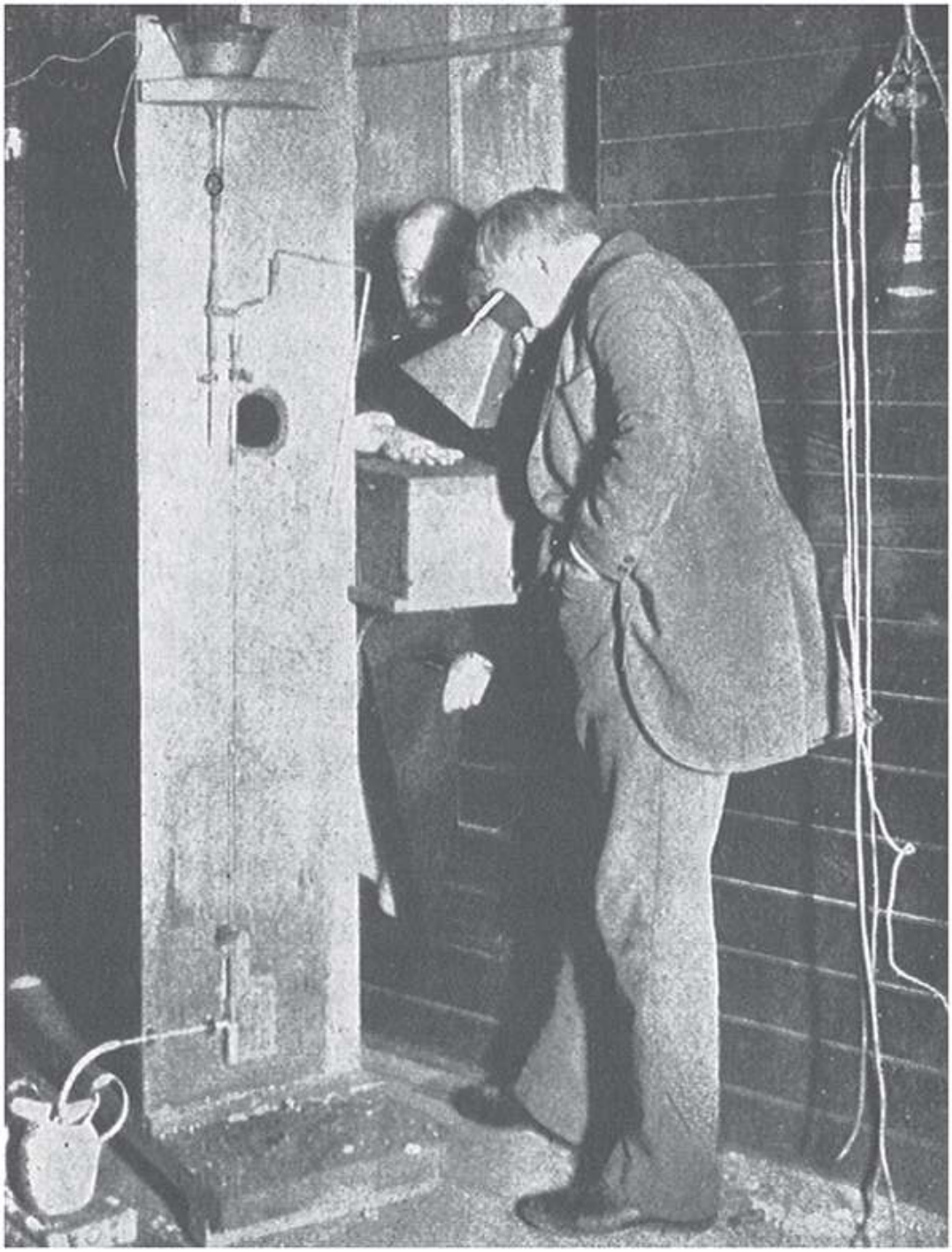


FIGURE 1.52 Thomas A. Edison experimenting with x-rays with no radiation protection. Edison's assistant, Clarence Dally, died of radiation-induced cancer. By 1903, Edison told a reporter for the *New York World*, "Don't talk to me about x-rays. I am afraid of them. I am afraid of radium and polonium too and I don't want to monkey with them." (Thomas Edison National Historical Park, U.S. National Park Service, 1896.)

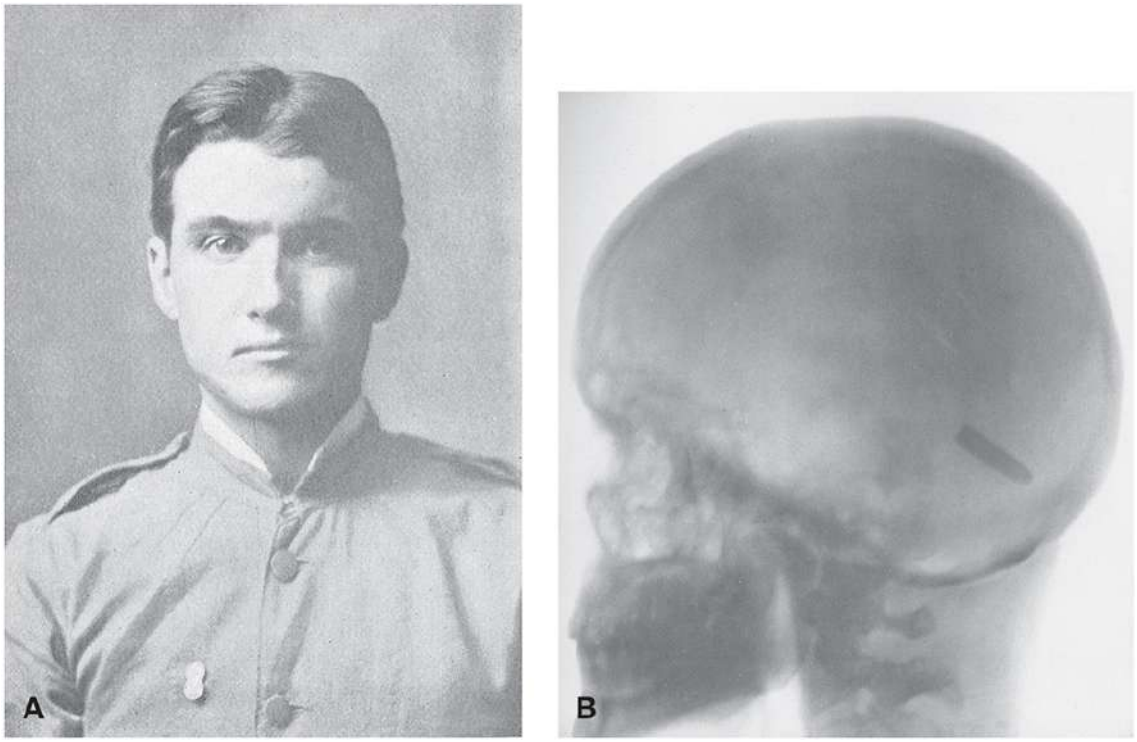


FIGURE 1.53 A and B. Private John Gretzer, Jr, Company D, First Nebraska Volunteers, U.S. Army injury, wounded above his left eye at long range in combat at Mariboa, Philippines. Five months after the injury, he returned to duty in the military mail service. Diagnostic x-ray units were utilized by the U.S. Army Medical Department in the 1898 war with Spain and the Philippine insurrection—within 4 years of the discovery of the x-ray. (From Borden WC, Sternberg GM. *The Use of the Röntgen Ray by the Medical Department of the United States Army in the War with Spain (1898)*. Government Printing Office; 1900.)

Antoine Henri Becquerel (1852-1908)

Antoine Henri Becquerel was born in Paris in 1852 into a family of scientists (Figure 1.54). His father was a professor of applied physics who had conducted research on solar radiation and phosphorescence. His grandfather was the inventor of an electrolytic method of extracting metals from ores.

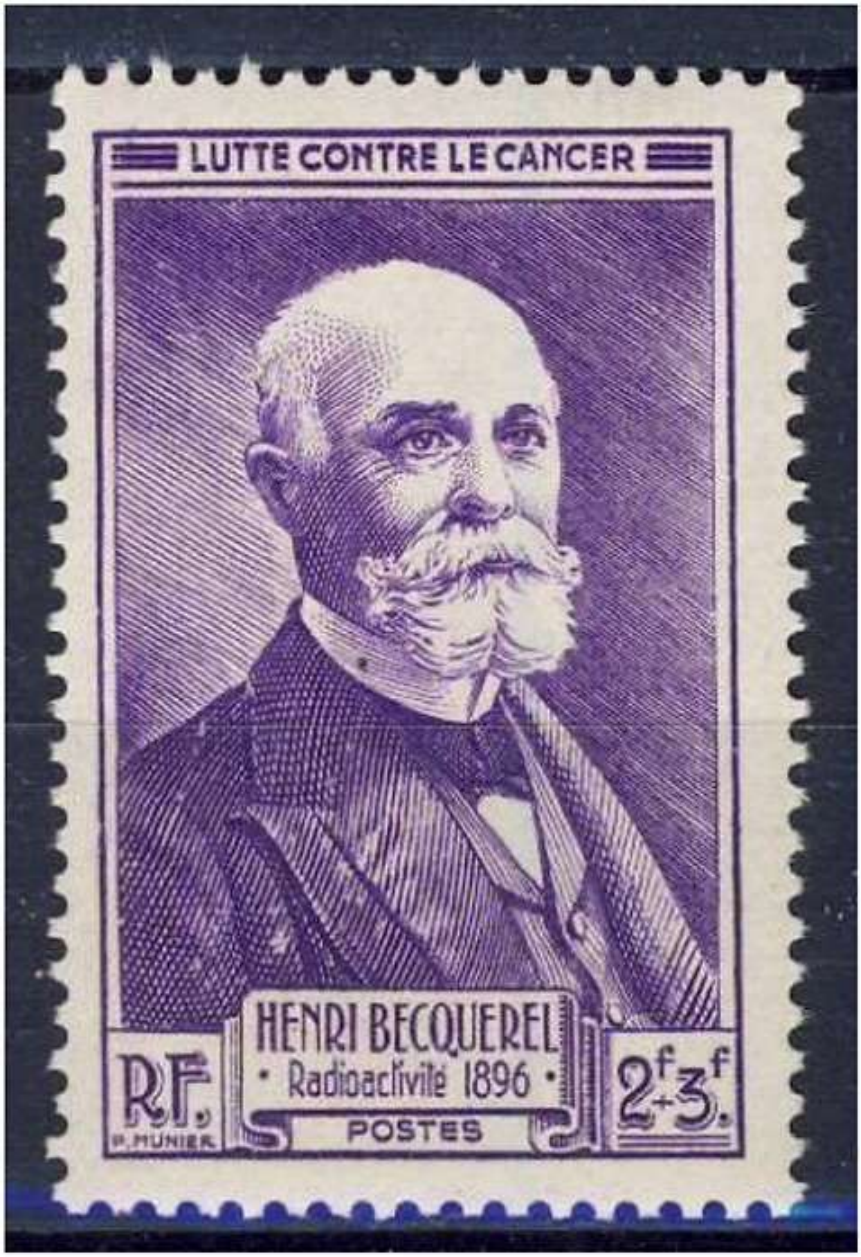


FIGURE 1.54 Henri Becquevel (1852-1908) honored on a French postage stamp.

Becquerel's early scientific work concerned the plane polarization of light, phosphorescence, terrestrial magnetism, and the absorption of light by crystals. Becquerel first heard of Röntgen's discovery in January 1896 at a meeting of the French Academy of Science. He wondered if there was a connection between phosphorescence and x-rays. He had inherited, from his father, a supply of uranium salts, which phosphoresced upon exposure to light.

Becquerel thought that the phosphorescent uranium salts might absorb sunlight and, in turn, reemit the energy as x-rays. He placed crystals of the uranium salts on

top of photographic plates wrapped in opaque black paper. After placing the experimental setup in the sun, he developed the plates and saw an outline of the crystals. When he placed coins and other metal objects between the crystals and the plates, he could produce outlines of the shapes of the metal objects. These initial experiments seemed to confirm his suspicions.

When he encountered several overcast days in February 1896, Becquerel put his uranium crystals and photographic plates in a drawer. On March 1, he opened the drawer and developed the plates. It is not clear why he did this. Nonetheless, he saw a clear image of the crystals on the plates. He had demonstrated that the uranium crystals were emitting x-rays on their own and had discovered spontaneous radioactivity (Figure 1.55).

FIGURE 1.55 In 1915, Dr Sinclair Tousey of New York City, after describing how Henri Becquerel, Marie Curie, and Pierre Curie, suffered painless skin ulcers after carrying a radium tube in a shirt pocket, reported that he reproduced the event by self-experimentation. He exposed his own forearm to contact with radium in a sealed glass tube and caused radiation dermatitis. (From Tousey S. *Medical Electricity: Rontgen Rays and Radium with a Practical Chapter on Phototherapy*. 2nd ed. W.B. Saunders; 1915.)

Becquerel subsequently showed that the radioactive emissions from uranium could ionize gases and be deflected by electric or magnetic fields.[513-515]

Half of the 1903 Nobel Prize in Physics was awarded to Becquerel. The other half was given to Pierre and Marie Curie.[516]

Pierre Curie (1859-1906) and Marie Sklodowska Curie (1867-1934)

Marya Sklodowska was born in Warsaw on November 7, 1867. The youngest of four sisters and a brother, she lived under Russian rule in partitioned Poland. At 17, she left home to work as a governess to the daughters of the supervisor of a large sugar beet factory northeast of Warsaw in order to save enough money to attend university. In 1891, Sklodowska enrolled at the Faculte des Sciences at the Sorbonne in Paris—one of just 23 women in a student body of about 1800. She completed degrees in mathematics and physics and in 1893 was hired by the Society for the Encouragement of National Industry to study the magnetic properties of steel. While in the process of securing additional laboratory space, she was introduced to Pierre Curie.

Curie was the son of a physician who had worked in the laboratory of Louis Pierre Gratiolet (1815-1865), who described the occipital visual pathways. Pierre Curie's doctoral thesis, "Magnetic Properties of Bodies at Diverse Temperatures," evaluated changes in magnetic properties of materials heated to high temperatures. He found that the magnetic properties of a substance change at a very specific temperature. This temperature is called the "Curie point" and is of great importance in studying plate tectonics, understanding extraterrestrial magnetic fields, and measuring the chemical contents of liquids. Curie also found that when crystals were pressed along their axis of symmetry, they produced an electric charge. This phenomenon is called "piezoelectricity," from the Greek word *piezin*, meaning "to squeeze," and is of importance in the operation of quartz watches, ink-jet printers, autofocus cameras, and medical ultrasound.

Marya Sklodowska (now using the French form of her first name, "Marie") and Pierre Curie wed on July 26, 1895 (Figure 1.56).

FIGURE 1.56 Marie Curie honored on a Swedish postage stamp.

For her doctoral thesis, Marie chose to investigate Becquerel's rays. She found that the intensity of the rays was affected neither by external conditions nor by any chemical process—they were an atomic property of the element. Marie observed that "it was obvious that a new science was in the course of development . . . . I coined the word *radioactivity*."[517]

After confirming Becquerel's observations, Marie and Pierre Curie in 1898 published a paper entitled "Sur une substance fortement nouvelle radio-active, continue dans la pechblende" ("On a new, strongly radio-active substance contained in pitchblende"). The new radioactive substance was called polonium (named in honor of Poland). In late 1898, while working on polonium, they noticed another substance, chemically akin to barium and more radioactive than polonium. Demarçay found specific spectral characteristics of this new element, which was called radium (from the Latin word for "ray"). The Curies declined to patent their

findings because, in Pierre's words, "it would be contrary to the scientific spirit." In 1903-1904, radium-226 began to be used in the treatment of patients with skin and uterine cancer.[518] On June 25, 1903, Marie defended her thesis "Researches on Radioactive Substances" and became the first woman in France to receive a doctorate. Later that year, the Curies and Becquerel shared the Nobel Prize in Physics.

On April 19, 1905, Pierre Curie was killed while crossing the Rue Dauphine near the Seine—run down by a horse-drawn carriage carrying 13,000 pounds of military equipment. Marie returned to work and described the radioactive decay series of polonium. In 1911, she became the first person to win the Nobel Prize twice, this time in chemistry.

When France entered World War I, Marie Curie assembled hospital and mobile x-ray units for the care of the wounded. The mobile units were dubbed "petites Curies."[519] In March 1912, a glass tube containing 20 mg of radium was declared the international radium standard after comparison with a similar standard prepared in Vienna. The radioactivity unit was called Curie and defined as the emanation in equilibrium with 1 g of radium. In 1975, the International Commission on Radiation Units and Measurements replaced the Curie with the Becquerel (1 Curie = 3.7×10^{10} Bq). Marie Curie died on July 4, 1934, from the consequences of radiation exposure.

James Ewing (1866-1943)

For much of the 20th century, if a person was selected by the editors of *Time* magazine to appear on the weekly newsmagazine's cover, it was a mark of distinction. Individuals on the cover of the magazine were "newsmakers": important, notable, and worthy of your attention. The January 12, 1931, issue of *Time* portrayed a dignified pathologist in a drawing. "Cancer Man Ewing": The "weapons" referred to in the caption were dedicated cancer institutions. "He wants six $10,000,000 weapons" (Figure 1.57).

FIGURE 1.57 James Ewing (1866-1943).

James Ewing, born in Pittsburgh in 1866, was the son of Thomas Ewing who began his career as a teacher and began the study of law at age 36. He became a judge in the Court of Common Pleas in Pittsburgh, an elder of the Presbyterian

Church, and was viewed as a leading local citizen. Ewing's mother, Julia, graduated in the first class of Mt. Holyoke College and was a teacher.[520,521]

Ewing's personal life was marked by a series of illnesses and tragedies. He developed osteomyelitis of the femur when he was 14 and was bedridden for 2 years, his wife died after less than 3 years of marriage from toxemia of pregnancy, he suffered from tic douloureux and was operated on by Harvey Cushing, a urinary calculus developed later in life, and he ultimately died of bladder cancer. It was said of him that adversity, suffering, disappointment, and sorrow left their mark on him not in the form of bitterness or disillusionment but in increasing sensibleness for the misfortune of others. "His sympathy and kindliness became almost legendary during his lifetime and the very legend of his benignity impressed itself on his character. . . . That this benignity was not of the mere sentimental variety was shown by his intolerance of sham, hypocrisy, and mental laziness, which led him to be an unsparing critic."[522]

Ewing received his undergraduate education at Amherst College and was in the first class of the College of Physicians and Surgeons of New York that graduated after the institution had become affiliated with Columbia University.[523]

In 1899, Ewing was appointed the first professor of pathology at Cornell Medical College and held that position for 33 years. Ewing began to focus his interest on cancer when Mrs Collis P. Huntington (c.1851-1924) established the C.P. Huntington Fund for Cancer Research in 1902. The thrice-married Mrs Huntington was the heiress to a railway and industrial fortune and was said, by some, to be "the richest woman in America." Income from the fund was expended for cancer research at Cornell Medical College under Ewing's direction. Ewing's early studies focused on lymphosarcoma of dogs. (Many other U.S. institutions benefited from the philanthropic support of C.P. Huntington and his wife including the Collis P. Huntington Memorial Hospital in Boston, the site of important early work in radiation therapy. After the closure of this hospital, some of its radiation therapy equipment was moved to the Massachusetts General Hospital.)

In 1919, after a decade of work, Ewing published the first of four editions of *Neoplastic Diseases*, the definitive reference of its time on tumor pathology. Unlike the multiauthored oncology books of today, including the one you are holding in your hands, *Neoplastic Diseases* was solely Ewing's work with greater than 450 illustrations and 49 chapters (Figure 1.58). He wrote in the preface to the first edition:

NEOPLASTIC DISEASES

A TEXT-BOOK ON TUMORS

By

JAMES EWING, A. M., M. D., Sc. D.

Professor of Pathology at Cornell University Medical College
New York City

WITH 479 ILLUSTRATIONS

PHILADELPHIA AND LONDON

W. B. SAUNDERS COMPANY

1919

FIGURE 1.58 The title page of the first edition of Ewing's outstanding textbook.

> Up to a very recent time it has been the prevailing impression that tumors fall into a limited number of grand classes in which the forms occurring in the several organs are so nearly related as to be virtually identical. Hence the practical physician or surgeon has been content without regard to the organ involved, and on this theory to treat the members of each class alike . . . . I believe that this point of view has greatly retarded the progress of the knowledge of tumors, and it has been the writer's effort to combat such a conception, so far as present knowledge permits.[524]

In 1920, Ewing reported to the New York Pathological Society that he had observed a malignant tumor of the bone, most frequently arising in teenagers, and "composed of broad sheets of small polyhedral cells with pale cytoplasm, small hyperchromatic nuclei, well-defined cell borders, and complete absence of intercellular material." He considered the tumor to be an "endothelioma of bone" arising from blood vessels. In a second report, he called the tumor an "endothelial myeloma." Ewing commented on the tumor's marked radiosensitivity, its tendency to invade soft tissues, and its ability to metastasize to lymph nodes.[525,526]

Ewing was quick to recognize the potential of radiation therapy for cancer treatment. He called it "the first rational treatment of cancer ever devised."[527] Ewing revisited radiation therapy many times in his publications:

"From the most unexpected source, experimental physics, a new and powerful weapon has been brought into play."[528,529]

"Radiation therapy, by demanding a detailed knowledge of the symptoms, clinical course and pathology of tumors, has introduced a new era in the study of cancer."[530]

"Cancer research has entered a . . . fruitful era of therapeutics and more intelligent descriptive study . . . . The developments of radiotherapy have opened a new biology of tumors, have stimulated new lines of research and suggested new concepts . . . many new facts and principles of tumor growth have been brought to light."[531,532]

Ewing conducted experimental work on cancer, vigorously worked to secure the funding for the establishment of New York's Memorial Hospital for Cancer and Allied Diseases (now called Memorial Sloan Kettering Cancer Center), investigated the role of radium in the treatment of cancer and worked to establish the production of radium in the United States, wrote four editions of the *Neoplastic Diseases*, and helped found the American Society for the Control of Cancer (now called the American Cancer Society) in 1913 and served on the organization's governing board for more than 30 years.[533]

Ewing viewed an organized war on cancer as a societal imperative and that success would be slow and incremental:

> It is a growing conviction that to know cancer in man, one must study the disease most carefully in the human subject. Personally, I do not look for any startling advances or sensational discoveries, since it is much more likely that a steady reduction in the mortality from cancer will come chiefly from a large number of separate factors, of which the most significant appear to be increased control of the conditions leading to cancer, more general recognition of the preliminary stages of the disease, early diagnosis, and treatment of the established disease. From the consideration of these various functions of the modern cancer research hospital, I think that it must be evident that such an institution not only can justify its existence, but fill a very urgent need without which progress of cancer research would be handicapped and much relief that might early be extended to cancer victims would be unavailable. Nor is there any doubt that the function of supporting such an institution is properly exercised by the State, which support should be continuous and liberal.[534] (Reprinted from del Regato JA. James Ewing. *Int J Radiat Oncol Biol Phys*. 1977;2(1-2):185-198. Copyright © 1977 Elsevier. With permission.)

At the age of 76, Ewing fractured his right femur. The fracture site showed metastatic bladder carcinoma. He died of bladder cancer in 1943.

Claudius Regaud (1870-1940)

Claudius Regaud attended medical school at the University of Lyon, France. His research demonstrated that the formation of new blood vessels in malignant tumors was not accompanied by a proliferation of lymphatics, but rather their progressive obliteration.

In 1904, Jean Bergonié (1857-1925) and Louis Tribondeau began studies on the irradiation of mouse testis. They verified the production of azoospermia after a latent period. Histologic studies showed seminal tubules with preserved Sertoli cells and mature sperm cells in the epididymis. Regaud also began studying the effects of radiation on the testis. Regaud and his collaborators identified the increased radiosensitivity of cells in mitosis. It also appeared that the less differentiated the cells, the more radiosensitive they were. Bergonié and Tribondeau had articulated a "law" of radiosensitivity: "The effects of irradiation on the cells are more intense the greater their reproductive activity, the longer their mitotic phases, and the less their morphology and functions are established."[535]

Regaud's work on the development of brachytherapy and radiobiology was interrupted by his service as a French military physician during World War I. After the war, he resumed his work and found that fractionated radiation therapy was better able to sterilize the testes of an experimental animal, with acceptable normal tissue tolerance, than single fractions. He became convinced that fractionated radiotherapy was the superior way to treat human malignant tumors and popularized the principles of fractionated treatment that continue to this day.[536]

Ernest Rutherford (1871-1937)

Many essential aspects of our understanding of atomic structure can be directly or indirectly attributed to the work of Ernest Rutherford (Figure 1.59). Rutherford's supervisor discovered the electron, Rutherford discovered the proton, and Rutherford predicted the existence of the neutron and his student discovered it. In the words of one of his biographers, the radiation oncologist Juan A. del Regato, "He became the outstanding atomic physicist of his time: amid a constellation of brilliant protagonists, he was second to none; in an era of rapidly developing, new revolutionary concepts, his own prevailed."[537]

New Zealand
Lord Rutherford
1871-1937
1c

New Zealand
Lord Rutherford
1871-1937
$^{14}_{7}N + ^{4}_{2}He \rightarrow ^{17}_{8}O + ^{1}_{1}H$
7c

A

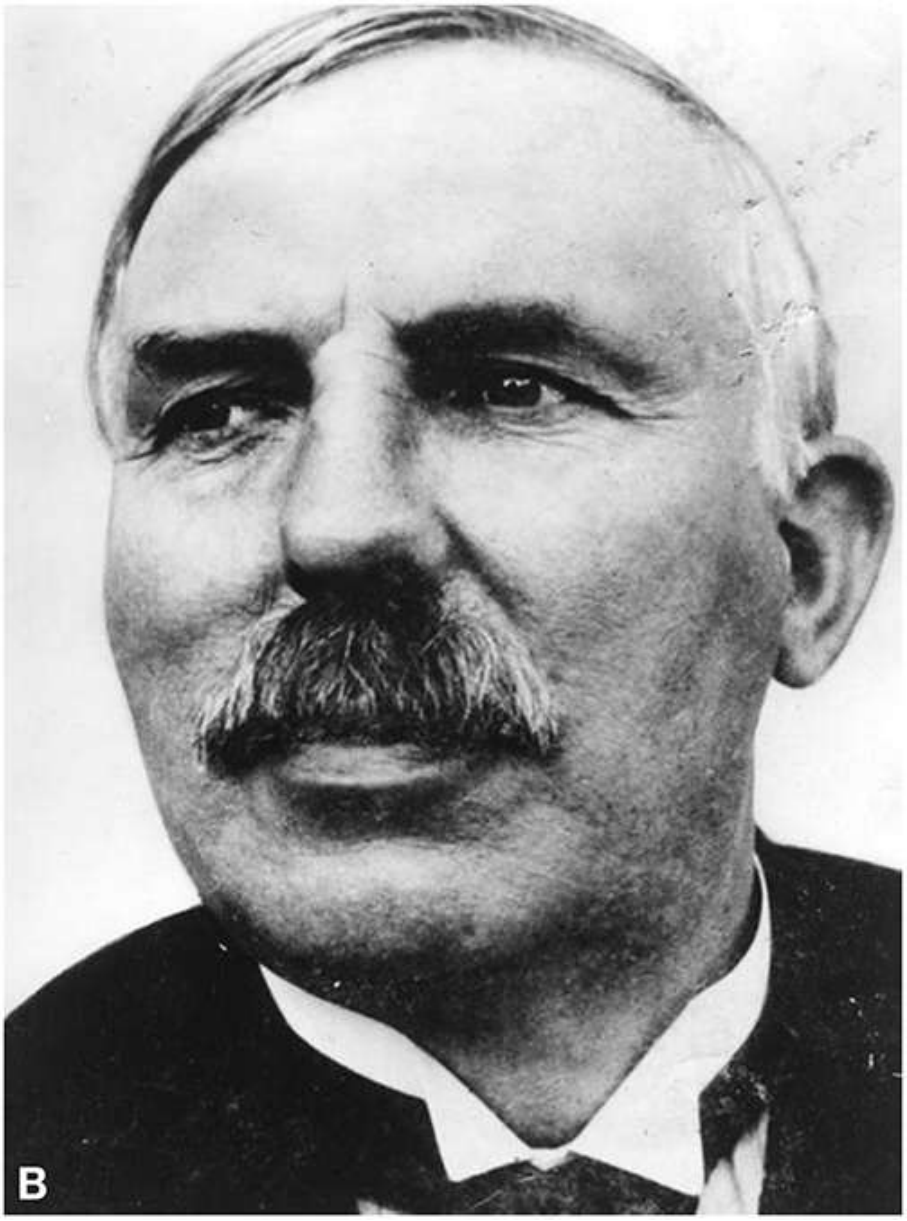


FIGURE 1.59 A. Ernest Rutherford (19761-1937) honored on a New Zealand postage stamp (Birley, Oswald Hornby Joseph (Sir), 1880-1952. Birley, Oswald Hornby Joseph, 1880-1952 :[Lord Rutherford of Nelson] 1934. Ref: G-826-2. Alexander Turnbull Library, Wellington, New Zealand. https://natlib.govt.nz/records/22645763. Courtesy of New Zealand Post). B. Ernest Rutherford (AIP Emilio Segrè Visual Archives, W. F. Meggers Gallery of Nobel Laureates Collection).

Born in New Zealand, Ernest Rutherford received his BA and MS degrees at Canterbury College, Christchurch, New Zealand, received a scholarship to continue his studies at Cambridge University in England, and began work in the Cavendish Laboratories under the supervision of Professor Sir J. J. Thomson (1856-1940), discoverer of the electron and recipient of the 1906 Nobel Prize in Physics for his work on the conduction of electricity in gases. Within a few weeks of Rutherford's

arrival in England, Röntgen's discovery of the x-ray became known. Thomson and Rutherford soon demonstrated the ability of x-rays to produce ionization in gases.

In 1898, Rutherford accepted the professorship of physics at Montreal's McGill University. It was at McGill that he identified and named α- and β-radiation and also described the concept of radioactive half-life. In collaboration with the chemist Frederick Soddy (1877-1956), he developed a disintegration theory of radioactivity in which chemically different elements undergo a series of changes with decreasing radioactivity at each step. Most radioactive elements, they concluded, are the product of this successive decay.[538]

In his 1904 Bakerian Lecture, he laid out a broad and prescient view of radioactivity. In 1907, Rutherford became professor of physics at Victorian University of Manchester, England. He demonstrated that α-particles were helium atoms. The next year, he was awarded the Nobel Prize in Chemistry for "investigations into the disintegration of elements and the chemistry of radioactive substances."

Rutherford collaborated with Hans Wilhelm Geiger (1882-1945) and invented what is generally called the Geiger counter or scintillation counter to identify radioactivity. Working in Rutherford's laboratory, Geiger and Sir Ernest Marsden (1889-1970) observed that α-particles that were streamed into a thin metal foil were sometimes scattered at very wide angles. Rutherford reasoned that this was the result of the α-particles encountering an atomic particle of large size. The atom, he concluded, had a central, large, positively charged portion surrounded by negatively charged electrons.

After World War I ended, Rutherford returned to Cambridge University to succeed Thomson as professor and director of the Cavendish Laboratory. Rutherford proved that the hydrogen nucleus is present in other nuclei. He could show that hydrogen nuclei were produced as a product of the impact of α-particles on nitrogen gas. The majority of air consists of nitrogen. When α-particles passed through air, scintillation detectors showed the signatures of typical hydrogen nuclei as a product. When alphas were fired into pure nitrogen gas, the effect was larger. Rutherford determined that hydrogen could have come only from nitrogen, and therefore, nitrogen must contain hydrogen nuclei. One hydrogen nucleus was being knocked off by the impact of the α-particle, producing oxygen-17. $^{14}N + \alpha \rightarrow {}^{17}O + p$.

Insofar as the hydrogen nucleus is present in all other nuclei as an elementary particle, Rutherford decided to give the hydrogen nucleus a special name as a particle, since he suspected that hydrogen, the lightest element, contained only one of these particles. He named this new fundamental building block of the nucleus the *proton*, after the neuter singular of the Greek word for "first."

After the experiments of Walther Wilhelm Georg Franz Bothe (1891-1957) and Herbert Becker who, when they bombarded boron and beryllium with α-particles,

found that they produced a beam more penetrating than γ rays, and in the work of the Joliot-Curies (described in the next section) and Sir James Chadwick (1891-1974), the neutron was identified. Rutherford had predicted its existence in 1923. Chadwick was the 1935 Nobel Laureate in Physics. Bothe shared the 1954 Nobel Prize in Physics for his role in the description of wave-particle duality.

Irene (1897-1956) and Frederic Joliot-Curie (1900-1958)

In 1924, Marie Curie interviewed Frederic Joliot for a position in her laboratory. Joliot had a recommendation from the famed physicist Paul Langevin (1872-1946). Marie Curie's daughter Irene also worked in the laboratory. Romance blossomed and Frederic and Irene were married in 1926 (Figure 1.60). The two worked together in the laboratory.[539] A reporter for *Time* magazine wrote:

FIGURE 1.60 Irene and Frederic Joliot-Curie honored on a French postage stamp.

> Husband and wife work like one person with two heads, four hands, 20 fingers. "We compare notes," says M. Joliot, "and exchange our thoughts so constantly that we honestly don't know which of us is the first to have an original idea. Don't you agree, ma chere?"[540]

Toward the end of 1931, the Joliot-Curies were studying the effects of α-particle irradiation of elements such as boron and beryllium. These metals gave off

secondary radiations more penetrating than the γ rays of radium. Interposing substances containing hydrogen in the beam, such as paraffin or cellophane, increased the intensity of secondary radiation. The couple considered these secondary radiations to be high-energy x-rays that knocked out protons from the atomic nucleus of hydrogenated substances. In England, James Chadwick conducted similar experiments with superior equipment. Remembering that Ernest Rutherford had predicted the probable existence of a nuclear chargeless particle, Chadwick correctly deduced that the secondary radiations were this chargeless particle, the neutron. Frederic Joliot-Curie admitted that he had not read Rutherford's Bakerian Lecture where he had predicted the existence of this particle and said the credit for the discovery ought go to Chadwick.

In 1934, Irene and Frederic Joliot-Curie, by bombarding aluminum targets with α-particles, transformed a naturally stable element into radioactive phosphorus. Additional radioactive isotopes were produced by the irradiation of fluorine, sodium, and other metals. The induction of "artificial radioactivity" created the field of nuclear medicine—but Frederic always insisted that the so-called artificial radioactivity was identical with natural radioactivity. In 1935, they learned that they had been awarded the Nobel Prize in Physics for their work. Husband and wife divided the Nobel Lecture between them. Frederic predicted that researchers would find ways of exploiting progressive transmutations of elements by irradiation such that "veritable chemical chain reactions" would be produced—intimating the creation of self-sustaining nuclear fission chain reactions. In 1936, Irene Joliot-Curie was appointed by the Socialist President of France Léon Blum as under-secretary of state for scientific research.

Frederic Joliot realized the possibility of atomic release of large amounts of energy and the potential of this for warfare. He pursued experiments designed to establish that a sustained chain reaction could be produced through nuclear fission leading to the production of vast amounts of energy.

Joliot might have been the first to achieve a sustained nuclear chain reaction had not the German invasion of France and the capture of Paris intervened. Frederic Joliot-Curie and his scientific collaborators spirited their stock of heavy water and uranium out of France just ahead of the Germans. The Joliot-Curies hid their scientific papers on nuclear fission in a vault. Frederic joined the French Resistance, whereas Irene, her health in decline, moved to the French Alps with the couple's daughter. Eventually, mother and daughter crossed over to Switzerland in 1944. One wonders what would have been different in the history of science if the couple had taken the opportunity to escape to England in 1940 and continue their work. They would, perhaps, have played an even greater role in the development of nuclear weapons and atomic energy.

The work of Joliot-Curie was invoked in the famous letter Albert Einstein signed sent to President Franklin D. Roosevelt on August 2, 1939. The letter, written by the Hungarian American physicist Leo Szilard, was designed to spur American action to assure that the United States would acquire nuclear weapons before Nazi Germany.

> Some recent work by E. Fermi and L. Szilard, which has been communicated to me in manuscript, leads me to expect that the element uranium may be turned into a new and important source of energy in the immediate future. Certain aspects of the situation which has arisen seem to call for watchfulness and if necessary, quick action on the part of the Administration. I believe therefore that it is my duty to bring to your attention the following facts and recommendations.
>
> In the course of the last four months it has been made probable through the work of Joliot in France as well as Fermi and Szilard in America—that it may be possible to set up a nuclear chain reaction in a large mass of uranium, by which vast amounts of power and large quantities of new radium-like elements would be generated. Now it appears almost certain that this could be achieved in the immediate future.
>
> This new phenomenon would also lead to the construction of bombs, and it is conceivable—though much less certain—that extremely powerful bombs of this type may thus be constructed. A single bomb of this type, carried by boat and exploded in a port, might very well destroy the whole port together with some of the surrounding territory.
>
> In view of this situation you may think it desirable to have some permanent contact maintained between the Administration and the group of physicists working on chain reactions in America.
>
> I understand that Germany has actually stopped the sale of uranium from the Czechoslovakian mines which she has taken over. That she should have taken such early action might perhaps be understood on the ground that the son of the German Under-Secretary of State, von Weizsacker, is attached to the Kaiser Wilhelm Institute in Berlin, where some of the American work on uranium is now being repeated.[541]

After the war, France created a civilian atomic energy authority. Frederic was appointed head of the Commisariate de l”Energie Atomique, the French Atomic Energy Commission. In 1946, he was promoted to Commandeur de la Legion d’Honneur and was awarded the Croix de Guerre for heroism during the Nazi occupation of France. A member of the French Communist Party, Joliot was dismissed as high commissioner for atomic energy in 1950 because of his political views.

Irene Joliot-Curie died of acute leukemia in 1956. Frederic Joliot-Curie died in 1958.

Edith Hinkley Quimby (1891-1982)

Edith Smaw Hinkley Quimby graduated from Whitman College in Washington with a bachelor's degree in mathematics and physics. After a brief period teaching high school in Oregon, she received an MS degree from the University of California. In 1919, she became an assistant physicist under Gioacchino Failla at the Memorial Hospital for Cancer and Allied Diseases in New York. In 1942, she moved, with Failla, to the Center for Radiological Research at Columbia University where she remained for the rest of her career (Figure 1.61).

A

FIGURE 1.61 A. Edith Quimby (1891-1982) (From the Center for the American History of Radiology, courtesy of American Institute of Physics (AIP) Emilio Segrè Visual Archives). B. Edith Quimby with equipment at the Presbyterian Hospital at Columbia-Presbyterian Medical Center, 1955 (AIP Emilio Segrè Visual Archives, Physics Today Collection).

When Quimby began work as a medical radiation physicist in 1919, the field was in a primitive state. "Major engineering developments were required to attain reproducibility, reliability, and safety in the operation of [radiation-emitting] sources, physical quantities and their units had to be defined to permit measurement, instruments to perform these measurement needed to be invented . . . Quimby was principally responsible for confronting the . . . problems that arose when patients were exposed to ionizing radiation . . . [including devising] means to achieve optimal irradiation conditions, including the use of multiple fields [for external beam irradiation and for radioactive implants] . . . the most effective placement of sources . . . [For external beam irradiation she helped develop the use] "of filters, bolus, wedges."[542] She trained more than 1,000 physicians in the fundamentals of radiation physics. She also made fundamental contributions to the physics of nuclear medicine.

Generations of radiation oncologists, including the author of this chapter, learned the distinction between the Patterson- Parker (Manchester) system for a radioactive implant and the Quimby System. The Patterson-Parker system was designed to deliver a uniform dose within the target volume by the nonuniform distribution of the radioactive sources. Sources with more source strength were concentrated in the periphery of the tumor target volume. In contrast, the Quimby system is based upon the uniform distribution of source strength, with the radiation dose in the target center being higher than the dose in the periphery. Radiation doses at specific points were obtained by consulting "Quimby Tables." For points equidistant from the implant plane of a single-plane implant, the dose rate is higher near the center.

Quimby was the recipient of the Janeway Medal of the American Radium Society and Gold Medals of the ACR and the Radiological Society of North America.[543,544]

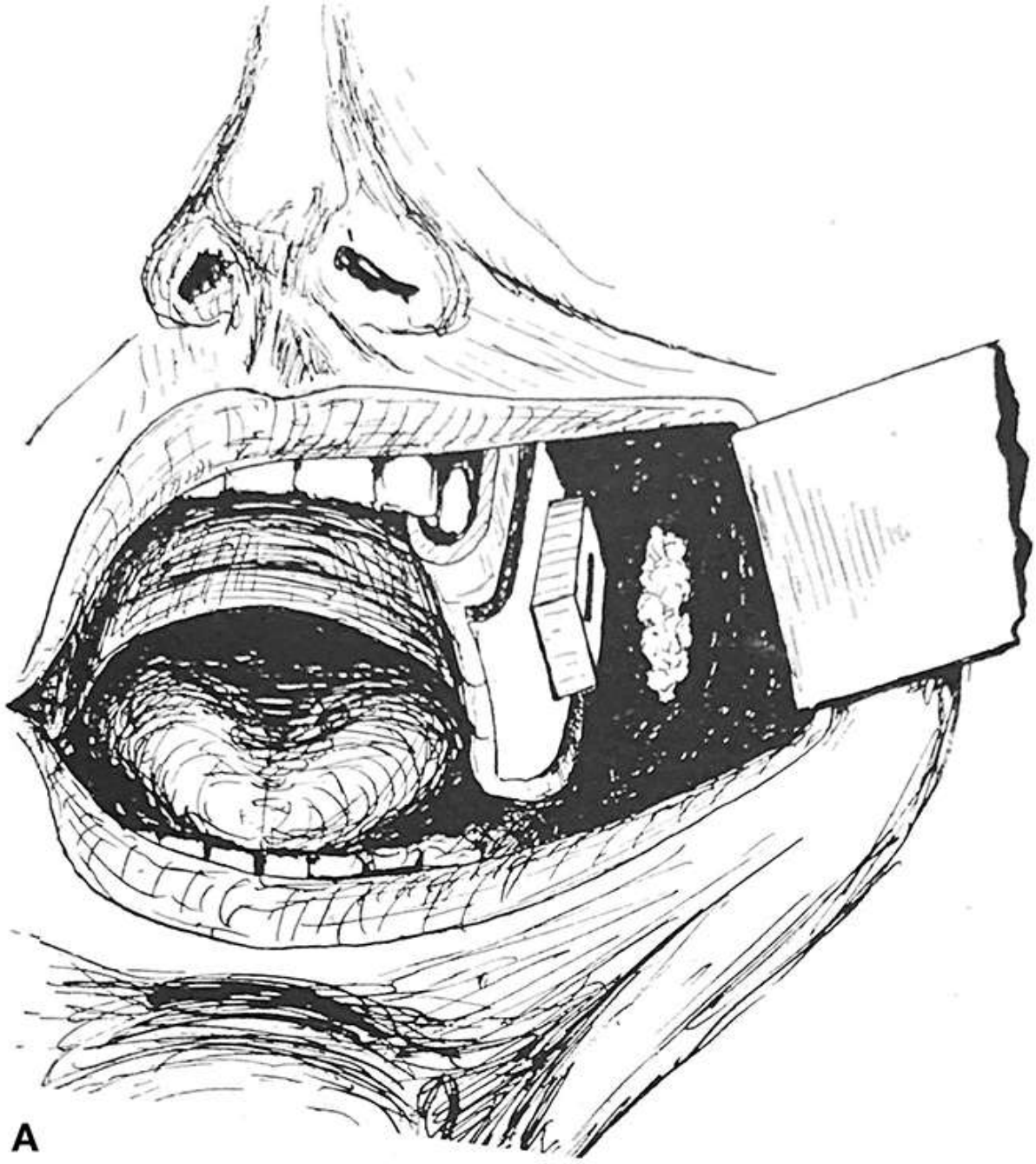
Quimby's husband, Shirley Leon Quimby (1893-1986), was also a professor of physics at Columbia University. He pioneered the use of quartz crystals to make precise measurement of the elastic qualities of solids. He was also an accomplished amateur magician.

Stanford Cade (1895-1973)

Saloman Kadinsky was born in a part of the Czar's Russian Empire, which is now part of Latvia. His father was Jewish and a diamond dealer. Salomon was sent to school in Antwerp, Belgium, in 1903. In 1913, he began medical school at the University of Brussels. With the onset of World War I, he served in the Belgian army in the doomed attempt to thwart the German invasion. Evacuated to Great Britain, he was unable to enlist in the British army because of an insufficient knowledge of English. He was permitted to sit for his admissions examinations in French and was admitted to King's College, London, to begin medical school. He completed his clinical studies at Westminster Medical School. He qualified with MRCS LRCP in 1917.[545]

He became a British citizen in 1920 and legally changed his name to Stanford Cade in 1924. After training as a surgeon, he spent his career at the Westminster Hospital, the Mount Vernon Hospital, and The Radium Institute.

Cade obtained a supply of radium in Paris in 1924 and became an expert in medical radiation physics, radiation biology, and brachytherapy. He generated a vast clinical experience, kept careful records of his results, was an early proponent of multidisciplinary cancer management, and published the important text *Malignant Disease and Its Treatment by Radium*. His creativity in the brachytherapy treatment of a wide variety of malignancies is astonishing (Figure 1.62). He was also an early proponent of supervoltage EBRT over orthovoltage.[546]



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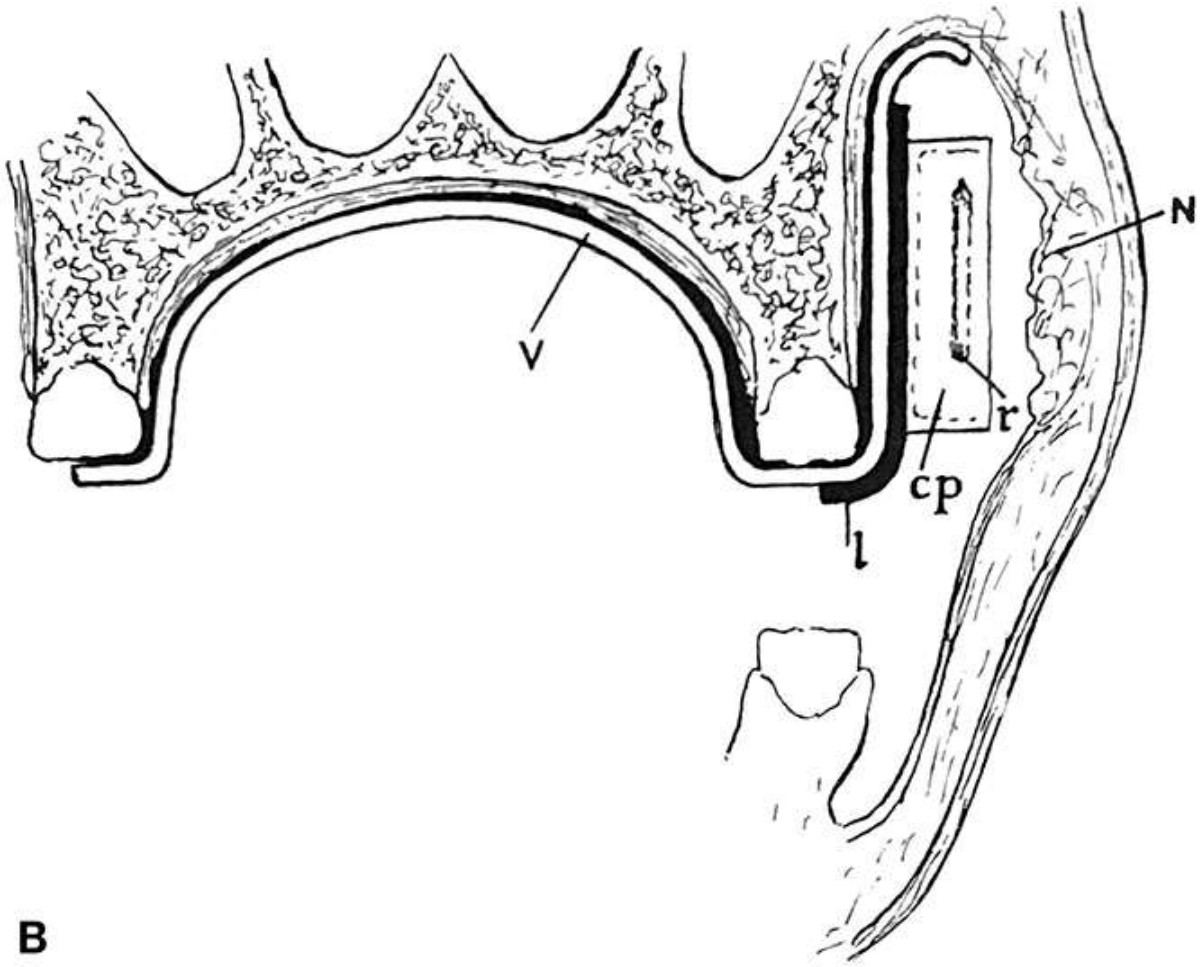

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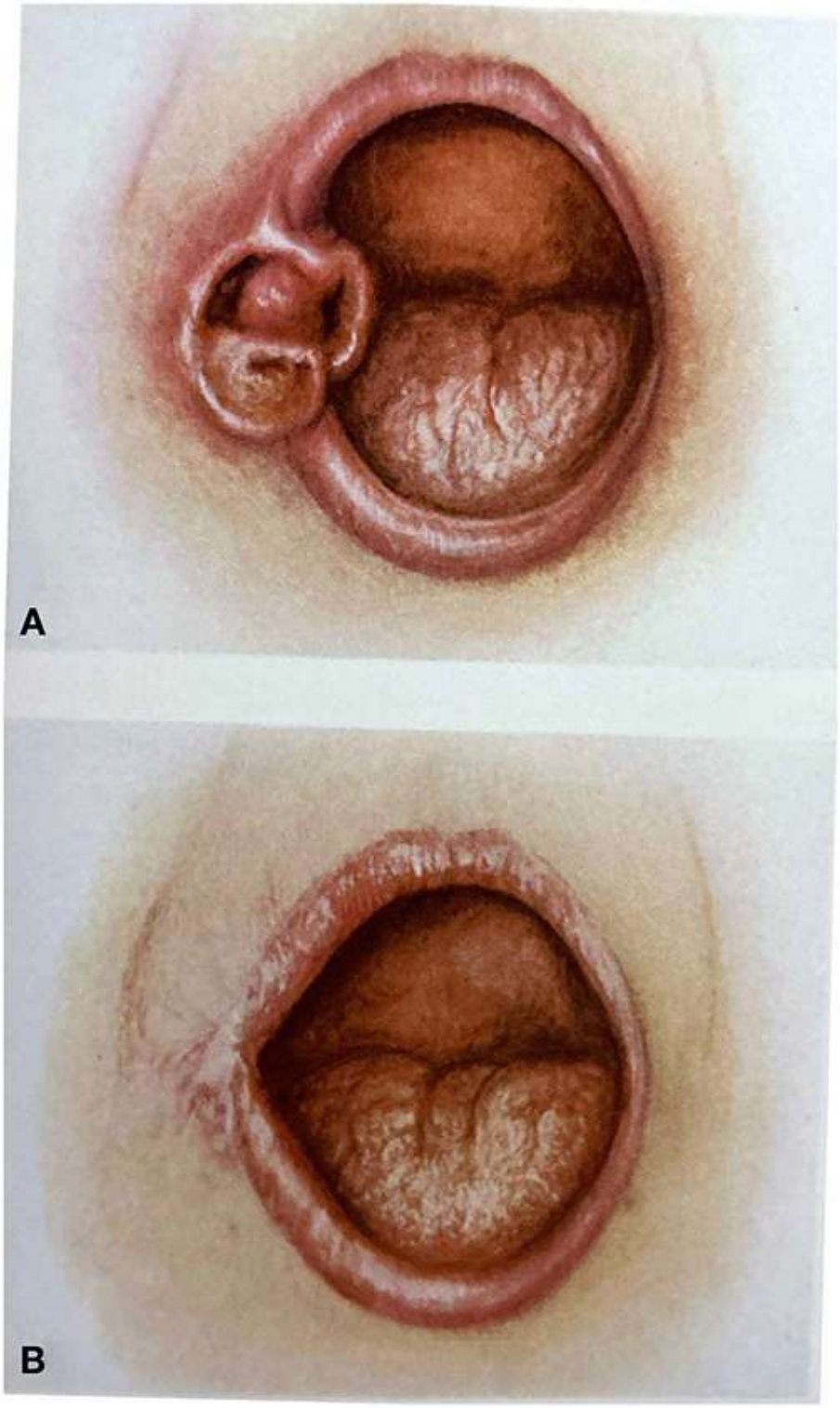

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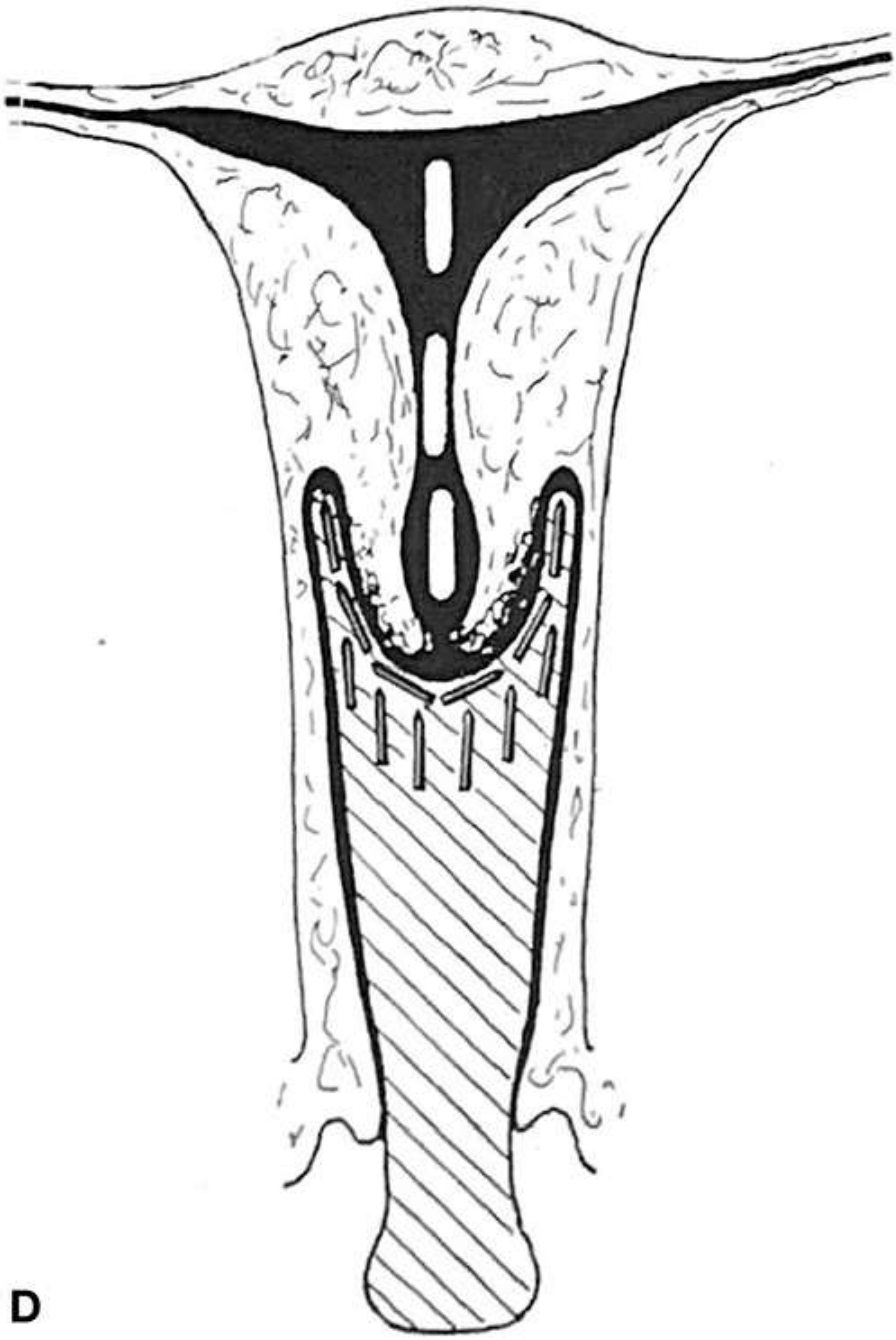

FIGURE 1.62 The erudition of Sir Stanford Cade and his extensive knowledge of oncology and medical radiation physics are demonstrable in these examples from his 1929 textbook *Radium Treatment of Cancer.* (This work is in the public domain.) A. An intrabuccal apparatus was used to treat squamous cell carcinoma of the buccal mucosa. The apparatus is lined with lead and carries a small box containing radium. The box keeps the tumor, and the alveolar margins a proper distance from the radium. B. The same device shown in A is illustrated in cross section wherein v represents vulcanite, l is lead, cp is Columbia paste, and N is the neoplasm. (Reproduced from Cade S. *Radium Treatment of Cancer*. J. & A. Churchill; 1929.) C. This colored plate shows an excellent response to the radium treatment of squamous cell carcinoma of the lip. A is before treatment and B is after. D. This is a highly creative design for the use of brachytherapy in the treatment of carcinoma of the cervix. There are three tubes of radium in the cervical canal and uterus inside a rubber tube. (For clarity, the rubber tube

is not shown in the drawing.) A wax mold containing radium is in the vaginal canal and the radium is placed to irradiate the cervix and the fornices. One can well imagine how this would create what we know would consider a desirable “pear-shaped dose distribution” from modern-day cesium-137 brachytherapy or the use of a remote high-dose rate afterloading machine.

Cade served with distinction in the medical corps of the Royal Air Force in World War II. His modifications of airplane cockpit design substantially reduced pilot death and injury. For his service, he was knighted and named an Honorary Air Commodore, a distinction he shared at that time with only one other person, Sir Winston Churchill.[547]

Among Cade’s many contributions to cancer therapy and radiation therapy, a particular interesting one was his 1955 clinical review of his experience with osteosarcoma.[548] This paper contains a well-known and oft-misquoted description of the high mortality rate of this childhood tumor in the era prior to chemotherapy.

> [The] relentlessness of the disease, its lack of control by accepted therapeutic measures . . . has led to a sense of despondency among surgeons and occasionally cynicism amongst radiotherapists. Thirty years ago a celebrated surgeon of international repute summarised a scientific meeting on “Bone Sarcoma” with the sentence: “If you do not operate they die, if you operate they die just the same – gentleman, this meeting should be concluded with prayers.” And 20 years later a radiotherapist in a discussion on the same topic suggested that for all the good radiotherapy does in bone sarcoma, the surgeon might just as well send the amputated limbs to be irradiated.[549]

Cade concluded that if high-dose supravoltage irradiation was given, that in many cases the tumor would respond locally. One could then wait for 6 to 12 months and see if distant metastases appeared. If they did not, then one would have reason to think that local control alone might lead to cure and consider definitive surgery. This plan of therapy was called “The Cade Technique.”

James Ralston Kennedy Paterson (1897-1981)

After service as an officer in the British army in World War I, Ralston Paterson received an MD, ChB from the Royal Infirmary of Edinburgh in 1923, a DMRE (Diploma in Medical Radiology and Electrology) from Cambridge in 1925, and a MD from Edinburgh in 1927. He did brief stints at the Mayo Clinic and the University of Chicago in the United States, and in private practice in Toronto.

He was appointed radiotherapy director of the Holt Radium Institute and Christie Hospital in Manchester in 1931 where he would remain for the rest of his career.

In collaboration with the medical physicist Herbert Myers Parker (1910-1984), Patterson developed a series of rules for the homogeneous irradiation of a given surface area and, later, by a similar system for interstitial radioactive implants. (See the note on Edith Hinkley Quimby earlier in this section of the chapter to compare the Patterson-Parker system with the Quimby system.)

Under Patterson's leadership, the Holt Radium Institute became a leading center for radiation therapy where generations of physicians trained. Treatments were standardized, and most courses of external beam radiation therapy took 3 weeks. Patients were stabilized for the treatment in plaster casts. The use of points A and B for brachytherapy for carcinoma of the cervix was developed. In 1947, he published a widely used and admired textbook *The Treatment of Malignant Disease by Radium and X-Rays: Being a Practice of Radiotherapy*. Medical textbooks rarely employ the phrase "being a practice of" nowadays. It referred to a text that "told you how to do it" rather than reviewing and commenting upon the array of medical literature from multiple authors and institutions.[550]

Ralston Patterson was married to Dr Edith Isabel Patterson (1900-1995), a radiation biologist and pediatric radiation oncologist.

Shields Warren (1898-1980)

Shields Warren was an outstanding pathologist of radiation injury. Born in Cambridge, Massachusetts, he received an AB from Boston University, MD from Harvard University, and spent his academic career at Harvard Medical School's affiliates the New England Deaconess Hospital, New England Baptist Hospital, and Pondville State Hospital.[551] His book *Medical Effects of the Atomic Bomb in Japan* (1956)[552] and his small monograph *The Pathology of Ionizing Radiation* (1961)[553] can both still be read today, with profit, by the interested student to learn about the acute and late effects of ionizing radiation.

Gilbert H. Fletcher (1911-1982)

As I sit at my desk writing, I can turn to my right and see, on my bookshelf, Gilbert Fletcher's *Textbook of Radiotherapy*. During my residency in the 1980s, this textbook, along with Moss and Brand's *Therapeutic Radiology*, and Ralston Paterson's text (described in the biographical note about Paterson), were the most widely used English-language textbooks—but unquestionably Fletcher's book was the most often relied upon. Fletcher's chapter authors were largely drawn from his home institution, the MD Anderson Cancer Center of Houston, Texas. The book was peppered with photographs illustrating specific cases. It was long on practical advice and short on theory, but it was indispensable.

Fletcher was among the first to develop practical cobalt-60 teletherapy units and high-voltage linear accelerators. He had particular interests in the treatment of head and neck and gynecologic cancers and coauthored a large number of papers related to determining the proper radiation dose, volume of treatment, and technique.[554]

Fletcher was raised in France and Belgium, the son of an American father and a French mother. His undergraduate and medical degrees were from the University of

Brussels. As World War II raged in Europe, his American passport, because of his father's citizenship, got him out of harm's way and into the United States. His postgraduate training was at New York Hospital, and he served in the Army Medical Corps. By 1949, he was the first full-time radiologist at the newly founded MD Anderson Cancer Center. He chaired the radiation oncology department until 1981.[555]

He was a short, bald, energetic man with a thick French accent and strongly held and often strongly expressed opinions (Figure 1.63).

FIGURE 1.63 Gilbert H. Fletcher (1911-1982), far left and the first cobalt-60 unit; the design and installation owed much to Drs Leonard Grimmett, Robert Shalck, and R. Lee Clark.

M. Vera Peters (1911-1993)

Mildred Vera Peters (known throughout her career as Vera) was born and raised on a farm in Ontario, Canada, and received her elementary education in a one-room schoolhouse. After high school, she enrolled in the Faculty of Medicine of the University of Toronto and graduated in the class of 1934. During medical school, she met her future husband. Peters' mother had been treated at the Radiotherapy

Institute of the Toronto General Hospital by Dr Gordon Richards but died while her daughter was still in medical school.

Dr Peters, after a 1-year internship at St John's Hospital, a women's surgical hospital in Toronto, joined Richards as a trainee—although there was no formal residency program in radiotherapy. A 400-kV treatment unit was installed at Toronto General Hospital in 1937, the same year Dr Peters was appointed to the hospital's full-time staff as a junior assistant radiotherapist. She became one of the first female physicians to have a clinical appointment at a Toronto teaching hospital.

Peters can be justly credited for two major contributions to modern radiotherapy. We will consider, first, her role in the development of curative treatment for Hodgkin disease. In 1947, Richards stopped Peters in the hallway at the Toronto Radiotherapy Institute and in his characteristically formal way said, "Dr. Peters, how would you like to review our experience with Hodgkin's disease? All the textbooks say it is a fatal disease, but we seem to be seeing patients who are cured." In response, Peters carefully reviewed the Toronto clinical experience, working at night at home on records and files at her kitchen table while balancing her career, her marriage, and the care of her children.[556]

Richards died in 1949 before Peters completed her study. By 1950, Peters published the first of a series of landmark papers in which she described a three-level staging system for Hodgkin disease and observed the prognostic importance of constitutional symptoms.[521] The current staging system of Hodgkin disease is based on the foundation laid by Peters. She also reported superior survival rates to those previously described and observed that irradiation of involved lymph nodes along with the inclusion of adjacent nodal groups in the radiotherapy fields improved survival in early-stage disease. Peters also identified factors which predicted findings in staging laparotomy and the value of lymphangiography. She persisted in reporting her findings and advocating for the curability of Hodgkin disease in spite of denigrating treatment by prominent male radiation oncologists.

Peters was also one of the pioneers in the development of techniques for the conservative management of early-stage breast cancer. She began to study a cohort of women who were treated with lumpectomy and radiation therapy in contrast to the prevailing wisdom favoring modified radical mastectomy. The patients Peters studied had received limited surgery and radiation because of advanced age, poor general medical condition, the patients' refusal to accept their surgeon's advice to have radical surgery and, instead, insisting upon breast conservation, or the views of a limited number of surgeons favoring more conservative treatment. Peters observed that cancer-specific survival rates in these women seemed no different than those treated with radical surgery.[557] In 1967, Peters published a paper in *Journal of the American Medical Association* titled "Wedge resection and irradiation: an effective treatment in early breast cancer."[558] She also began giving lectures arguing that for

patients with stage I and early-stage II breast cancer, lumpectomy and radiotherapy were as effective as radical surgery. She continued to publish and lecture on the topic until her retirement in the mid-1970s. The rise of the women's movement and its associated contribution to the insistence of women to have a say in their treatment, and not be subservient to the dictates of a largely male-dominated medical profession, helped promote Peters' views. Large-scale randomized prospective clinical trials ultimately validated her initial observations (Figure 1.64).

FIGURE 1.64 Vera Peters (1911-1993) honored on a Canadian postage stamp and first day cover.

N. Harold E. Johns (1915-1998) and Sylvia Ferchuck (1927-2012)

When the author of this chapter was a resident in radiation oncology at the Massachusetts General Hospital in the early 1980s, Professor Harold E. Johns of the University of Saskatchewan was invited to serve as visiting professor by the chief of medical physics, Professor Edward R. Epp. Epp and Johns had coauthored one of the seminal papers in medical radiation physics of the 20th century in 1951: the report of the development of a cobalt-60 machine for external beam radiation therapy.[559]

A fellow resident asked Johns what he thought was the greatest discovery in the therapy of cancer in the 20th century up to that point. "Cobalt 60," he replied. "Think about the amount of press that is devoted to the use of MOPP chemotherapy for Hodgkin disease. Hodgkin disease is a rare disease. In contrast, Cobalt 60 machines are used to treat a large variety of malignancies including deep seated

common tumors like, for example, carcinoma of the cervix. Cobalt 60 has impacted far more patients than chemotherapy."

With cobalt-60 supplied by the Canadian nuclear reactor at Chalk River, Ontario, Johns designed an elegant, simple, reliable machine that contained a block of cobalt-60 surrounded by a lead box. A rotating wheel inside the box moved the cobalt-60 so that it was over a hole in the box and allowed the escape of 1.17- and 1.33-MeV γ-ray beams. By this means, the machine was "on." When the wheel continued to rotate so that the cobalt-60 was encased by the lead box, the beam was "off." Meticulous depth dose measurements were performed on the machine by Sylvia Ferchuck[560] (Figure 1.65).

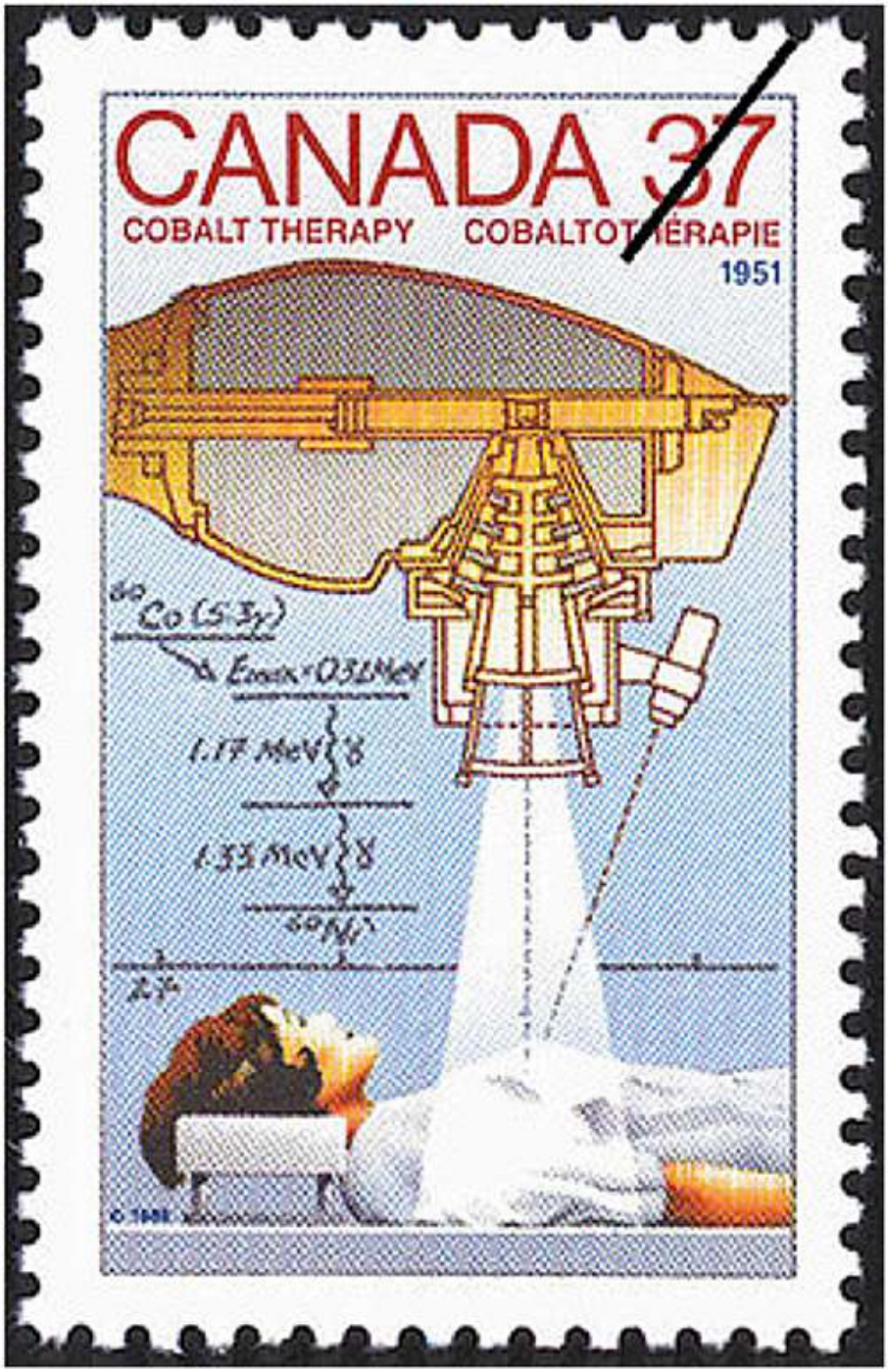

FIGURE 1.65 A 1988 series of Canadian postage stamps honors scientific and technological achievements by Canadians. The stamp portrayed honors the 1951 invention of the cobalt-60 teletherapy machine.

Henry S. Kaplan (1918-1984)

Henry S. Kaplan received a BS from the University of Chicago, MD from Rush Medical College, and an MS in radiology from the University of Minnesota. After 2

years as an instructor at Yale, he became the chair of radiology at Stanford University in 1948 where he remained for the rest of his career.

Kaplan's major contributions to radiation oncology include his role in the development of a medical linear accelerator with Ginzton and Hansen. It was put into use in 1954 and changed the nature of radiation oncology profoundly; he identified the viral causation of murine leukemia; and with his collaborator and medical oncologist Saul Rosenberg, he conducted a series of important clinical trials to improve the treatment of Hodgkin disease. Therapy adapted to the stage of the disease, where staging including lymphangiography and staging laparotomy, became the norm and remained so for several decades.[561,562]

Kaplan has been described as sometimes difficult to work with, combative, and acerbic. I never experienced such behavior. I first met Dr Kaplan in 1978 when I was a fourth-year medical student interviewing for a radiation oncology residency. He had me sit next to him while he reviewed port films for the patients with Hodgkin disease receiving radiotherapy and explained the reason behind a junction block over the spinal cord. When I was in his office for the formal residency interview, I commented on the large number of honors and awards on the wall.

"What's the one over there?," I asked.

"The French Legion of Honor (Ordre national de la Legion d'honneur)," he replied. There was, of course, no follow-up to a statement like that!

I was an internal medicine intern at Stanford from 1979 to 1980 where we saw many cases of acute myelocytic leukemia after curative therapy for Hodgkin disease. In 1983, as a chief resident of the Massachusetts General Hospital, I presented my data on the use of total lymphoid irradiation (TLI) as an immunosuppressive agent for solid organ transplantation in monkeys. Because there were other speakers on the program discussing TLI for the treatment of multiple sclerosis, rheumatoid arthritis, and for bone marrow transplantation, Dr Kaplan was in attendance. During a break in the meeting, I went to sit near the conference center pool and found myself next to Dr Kaplan. We discovered that we were both lifetime readers of *The New Yorker* and spent hours discussing which articles he liked and which I liked.

Maurice Tubiana (1920-2013)

Born and raised in French Algeria, Tubiana left for Paris to study medicine. When his studies were interrupted by World War II and the anti-Semitic policies of the Vichy government, he fought with the Free French Forces in North Africa, Italy, and France. He was named *Chevalier de la Legion d'Honneur* and received the *Croix de Guerre*.

Tubiana received doctoral degrees in medicine in 1945 and physics in 1947. In 1952, he joined the Institut Gustave Roussy in Villejuif. Author and coauthor of

more than 350 publications, he is remembered for pioneering the use of megavoltage units in radiotherapy, development of standards for the treatment of lymphoma and thyroid cancer, QA standards, and the development of computerized dosimetry and computerized medical records. He played a major role in public health reform in France and smoking prevention laws.[563]

I recall having dinner with Dr Tubiana in the early 1980s. My memories are of a dignified gentleman with a philosophical bent of mind.

Luther W. Brady (1925-2018)

At his death, an obituary referred to Luther W. Brady as a "venerable Philadelphia physician . . . recognized as one of the world's foremost experts on radiation oncology and who has served as chairman of the Department of Radiation and Nuclear Medicine at Hahnemann Medical College of Pennsylvania and Graduate Hospital."[564] At the time of his death, he was in his 55th year on the staff of Hahnemann University Hospital. His name is attached to a cancer center in Philadelphia, an endowed professorship at George Washington University where he was a triple graduate (AA, BA, MD), an art gallery at that university, a curatorship at the Philadelphia Museum of Art, and endowed professorships at the Wills Eye Hospital and Hahnemann Medical College before it transitioned to be part of Drexel University. His name, of course, also sits on the masthead of this textbook.

Brady was born in Rocky Mount, North Carolina. After graduating from medical school, he served as an intern at the Thomas Jefferson Medical College Hospital in Philadelphia and during the Korean War trained in nuclear medicine at the U.S. Naval Hospital in Bethesda, Maryland. After leaving the Navy, he resumed his training in radiology and radiation oncology at Thomas Jefferson and the Hospital of the University of Pennsylvania. After a stint at Columbia University in New York, he returned to Philadelphia where he became a medical and cultural institution as a physician and patron of the visual arts and music. He served on the board of directors of the Opera Company of Philadelphia, the Philadelphia Museum of Art, Philadelphia's Settlement Music School, the Curtis Institute of Music, and the Santa Fe, New Mexico, opera.[565,567]

Brady's medical contributions included the development of iodine-125 plaque therapy for choroidal melanoma, multiple publications regarding tumors of the eye and orbit, and a long list of publications concerning radioimmunotherapy, and cancers of the breast, lung, cervix, and lymphatics. Later in life, he developed an interest in radiosurgery.

Luther Brady was a master of organized radiation oncology. He served as president of at least eight different national radiation oncology organizations, founded and edited journals, and chaired multiple committees. Generations of

radiation oncologists went through their oral certification board examinations under his supervision.

Brady had exceptional diction, an eye for fine art and home furnishings, and a taste for fine food and wine. He could be withering in dissecting the foibles of others and could trade stories and gossip with the best. In working on this textbook, one only argued with him about the quality of the paper and the depiction of the illustrations at one's peril.

Seymour H. Levitt MD (1928-2017)

Born in Chicago, Levitt received a BA and MD degrees from the University of Colorado. After an internship at the Philadelphia General Hospital and service in the U.S. Army, he did his residency in radiology at the University of California, San Francisco. After stops at several institutions, he became chair of the Department of Therapeutic Radiology at the University of Minnesota where he remained for the rest of his career.[568]

Levitt made significant contributions to the treatment of Hodgkin disease and breast cancer. A textbook he co-edited with Tapley, Kahn, Perez, Purdy, Vijayakumar, and Poortman, *The Technological Basis of Radiation Therapy* went through four editions. It was an important contribution to improvements in the technical administration of radiation therapy.

Levitt was responsible for training a large number of radiation oncologists and served as a leader of multiple radiation oncology organizations.

Carl Mansfield (1918-2018)

Born in Philadelphia and a graduate of Howard University School of Medicine, Carl Mansfield successively served as professor and chair of radiation oncology at the University of Kansas, Thomas Jefferson University, and the University of Maryland. His research focused on the treatment of breast cancer. He was very active in multiple professional societies, and he has the distinction of being the first Black person to be president of a major U.S. radiation oncology organization, the American Radium Society.[569]

He was a dignified presence at national professional meetings.

Herman D. Suit (1929-2022)

Herman D. Suit was born in Waco, Texas, and attended the University of Houston and the Baylor College of Medicine in Houston.

As a young man, he directly observed racial discrimination, found he was not in agreement with the prevailing Texas attitudes favoring bigotry, and became and

remained a staunch advocate for inclusiveness throughout his life. He also showed no interest in religion and its ritualistic trappings. Regarding these two topics, he would write as an adult, "All humans are one species and are near identical genetically. . . . Time is absolutely equalitarian. There is not and has not been an unnatural event in this universe. Luck is the dominant factor in an individual's success in life. At birth, the infant has zero choice of genes, parents, siblings, relatives, era, and site of birth."[570]

After medical school, he trained under Dr Frank Ellis at the University of Oxford where he received a DPhil for his studies on the effects of radiation on the cellularity of human bone marrow. Upon his return to the United States, after a brief period at the NCI, he returned to Houston for a position at the MD Anderson Cancer Center where the radiation oncology department was chaired by Gilbert Fletcher, MD, whose life and career was described earlier in this chapter.

Suit worked at the MD Anderson Cancer Center from 1959 to 1970 when he was named professor and chair of radiation medicine at the Harvard Medical School at the Massachusetts General Hospital. He had chosen the name "radiation medicine" rather than "radiation therapy" or "radiation oncology" to be more inclusive and to recognize the myriad roles of ionizing radiation in diagnosis and therapy.

Suit's contributions to the field of radiation oncology were extensive. At their core, they were based in a profound belief in laboratory science, the application of scientific principles to clinical medicine, rigorous experimentation, thoughtfulness, and a belief in identifying talented individuals wherever in the world he encountered them and bringing them to the Massachusetts General Hospital to work, study, and do science.

A partial list of his major accomplishments, in approximate chronological order, would include a fuller understanding of the role of hypoxia in tumor resistance to radiation therapy, authoring the chapter on radiobiology in the early editions of Fletcher's *Textbook of Radiotherapy*, which gave generations of radiation oncologist their first taste of the biologic basis of their medical specialty, creating a world-class mouse colony for the conduct of research, invention of what would be called the Fletcher-Suit Apparatus for the afterloading brachytherapy treatment of carcinoma of the cervix, establishing the ability to obtain local tumor control with improved functional results of nonrhabdomyosarcoma soft tissue sarcoma through the skillful combined used of surgery and radiotherapy, developing techniques of 3D tumor and normal tissue radiation treatment planning with the physicist Michael Goitein, and the development of proton beam external beam radiation therapy as an established treatment modality.[571,572]

Suit was the president of the Radiation Research Society and the American Society for Therapeutic Radiology and Oncology (ASTRO). He was the recipient of multiple awards and medals. His wife, Joan Suit, was a noted bacterial geneticist.

Suit was a tall, thin man. He was careful-of-speech, extraordinarily polite, and with a fondness for garish neckties. He had exacting standards, and it was hard, when one was one of his subordinates, to ever "measure up." He also inspired fierce loyalty among his trainees—including me (Figure 1.66).

FIGURE 1.66 Herman D. Suit (1929-2022) and the author of this chapter, Edward C. Halperin. The picture was taken circa 2006.

Gunilla Bentel (1936-2000)

Gunilla Bentel was an international leader in the application of practical innovations to improve the accuracy of the planning and delivery of radiation therapy. Born in Sweden, Gunilla was formally trained as a nurse/radiation therapist, but spent most of her career functioning as a dosimetrist and physicist at Duke University in Durham North Carolina. She was a superb clinician who had a knack to develop practical solutions to real clinical problems. Her major contributions were in the areas of treatment planning, dose calculation, patient setup, and immobilization, and she authored three textbooks on these topics (packed with helpful illustrations), which were the mainstay for students in our field for decades. She was active in the clinic, often working closely with her physician colleagues, assessing patients, and their technical challenges, together. She was a founding member of the American Association of Medical Dosimetrists (in 1975) and served as editor of *Medical Dosimetry*. Through her books, her leadership, and other activities, Gunilla helped to

improve the quality of care for patients around the world. Lawrence B. Marks, MD, University of North Carolina—Chapel Hill (Figure 1.67).

FIGURE 1.67 Gunilla Bentel.

James J. Fischer (1936-2012)

I knew him as a tall, owlish-looking man with a droll sense of humor and a penchant for sports cars and dining out. I also heard Herman Suit refer to him as "the smartest radiation oncologist" he knew. Now, a decade after his death, few radiation oncologists have heard of J. J. Fischer. This is because, in part, he had little interest in organizational radiation oncology or publishing textbooks. To my knowledge, he never held any office in national professional organizations.

Fisher received a BS in biophysics from Yale and an MD and PhD from Harvard. He used nuclear magnetic resonance to study enzyme complexes and published important findings in *Nature* in 1963. He returned to Yale for residency training and served as professor and chair of the department for a remarkable 30 years: 1972-2002. His best known published papers focused on targeting hypoxic tumor cells with hypoxia-activated prodrugs and improved oxygen-carrying drugs like Fluosol. He also wrote prescient papers, 50 years ago, on the potential for computers in radiation oncology and mathematical modeling of the benefits of combined chemoradiotherapy.[573]

Fischer authored a murder mystery titled *Runner's Blood*, which centers around long-distance running, oxygen transport, and partially takes place in a thinly disguised fictional version of Yale's Department of Radiation Oncology. He was an avid cyclist and runner.

As an example of Dr Fischer's dry sense of humor, when I was a fourth-year Yale medical student, I requested a letter of reference for my applications for radiation

oncology residency training. Everywhere I went for an interview, I observed distinguished department chairs chuckling as they read the letter. Eventually, I got to see it. Dr Fischer advised that I had played softball while at medical school, was a weak hitter, not aggressive on the basepaths, and had a weak throwing arm but, perhaps, with coaching I might improve. When I discovered what he had done, I asked him why.

"You were cute," he replied. "You asked for a letter-of- reference with solemnity, as if you were applying for a residency in internal medicine with large numbers of entering residents in each program. You asked for a letter so I gave you one. This is a small field, young man, and everyone knows everyone. Now that you are back from your interviews tell me where you want to go and I'll make a phone call."

Carlos Perez (1934-2023)

Carlos A. Perez was born in Pereira, Columbia. He earned his medical degree from the University of Antioquia School of Medicine in Medellin, Columbia, in 1960. After residency training in Colombia, he came to Washington University School of Medicine for a residency in radiation oncology at that institution's Mallinckrodt Institute of Radiology (MIR). He completed his fellowship at what was them known as MD Anderson Hospital and Tumor Institute in Houston, before returning to St Louis to join the Washington University faculty in 1964. He became director of MIR in 1976. When radiation oncology became a separate academic department at Washington University in 2001, he was the inaugural department chair.

Perez's contributions to radiation oncology were primarily in gynecologic cancers and tumors of the breast, prostate, and lung. Along with Luther Brady, whose profile appears in this chapter, he founded the textbook you are now reading. Perez received the ASTRO's Gold Medal Award in 1992; the ACR's Gold Medal Award in 1997; the Society's Janeway Gold Medal in 2003; and the Marie Curie Medal from the Groupe Europèen de Curiethèrapie—European Society for Therapeutic Radiology and Oncology Brachytherapy Society in 2012. He was the president of ASTRO, a trustee of the American Board of Radiology, a member of the National Board of the American Cancer Society. His name appears as an author/coauthor on more than 370 scientific articles and more than 40 book chapters.[574,575]

Dr Perez was a courtly, dignified, and gracious gentleman with an extraordinary work ethic. He was always impeccably dressed and groomed. He continued to work on chapters for the edition of the book you are now reading up until the time of his death (Figure 1.68).

FIGURE 1.68 The team responsible for the fourth edition of this textbook from left to right. Jonathan W. Pine, Carlos M. Piecz, Luther W. Brady, Edward C. Halperin, Rupert Schmidt-Ullrich. This photograph was taken in approximately 2003. Jonathan Pine was a kind and gentle individual who represented the publishing company in the preparation of several editions of this textbook. Drs Brady, Schmidt-Ullrich, and Perez were very different in temperament. Brady could alternate between withering criticism and effusive charm. Schmidt-Ullrich was serious and strong-willed. Perez was unfailingly gracious and able to defuse editorial meetings becoming tense because of Dr Brady's temper. All of the senior editors of the first to seventh editions of this book are the subjects of biographical sketches in this chapter except for Dr David Wazer and the author of this chapter who are carrying on the duties of our predecessors and mindful of our roles as stewards of this book.

Rupert Schmidt-Ullrich (1943-2004)

Rupert Schmidt-Ullrich completed his medical studies at the University of Heidelberg in 1970. He then became a research fellow at the Max Planck Institute for Immunobiology in Freiburg, Germany. This was followed by an appointment as a research fellow and a subsequent appointment to the faculty in the Division of Cancer and Radiation Biology at Tufts-New England Medical Center. From 1978 to 1981, he completed his radiation oncology residency at Tufts. According to my co-senior editor of this textbook, Dr Schmidt-Ullrich "remains, to my knowledge, the first and only resident ever to complete his residency while simultaneously being awarded two RO-1 research grants and earning the rank of associate professor in the

same department. He achieved the rank of full professor within 3 years of completing his residency."

In 1988, Schmidt-Ullrich moved to the Virginia Commonwealth University in Richmond where he became professor and chairman of the Department of Radiation Oncology. He was an authority in the molecular mechanisms that underpin radiotherapy. He investigated altered fractionation for the treatment of head and neck cancer. He was instrumental in the development of IMRT. He discovered the molecular mechanisms by which tumor cells adapt to radiotherapy through accelerated repopulation and helped establish the discipline of "genetic radiation therapy."[576]

He was a cultured man, an exacting scientist, and very brave. He carried on with his work in the face of colorectal cancer and never disclosed his illness to me. I only learned of it when he died.

C. Norman Coleman (1945-2024)

C. Norman Coleman received his undergraduate degree from the University of Vermont and an MD from Yale. He trained in internal medicine at the University of California San Francisco, medical oncology at the NCI, and in radiation oncology under the direction of Henry S. Kaplan at Stanford University. After a period of time on the Stanford faculty, he was named the Alvin T. and Viola D. Fuller American Cancer Society Professor and Chair of the Harvard Joint Center for Radiation Therapy. He then moved to the National Institutes of Health (NIH) and NCI as the director of the Radiation Oncology Sciences Program, chief of the Radiation Oncology Branch in the NIH Clinical Center, and associate director of the Radiation Research Program, which administered NCI's grants in radiation research. He was the was the founder of the International Cancer Expert Corps, a nonprofit he created to provide mentorship to cancer professionals in low- and middle-income countries and in regions with indigenous populations in upper income countries. He became an expert in dealing with nuclear catastrophes and participated in the response to the Fukushima Daiichi disaster in 2011 (Figure 1.69).

FIGURE 1.69 C. Norman Coleman, MD (1945-2024). (Bill Branson/National Cancer Institute.)

Former NCI director Richard Klausner wrote of Coleman.

Norm had four characteristics that made him outstanding:

First was his dedications to patients, both his and those around the world who could not access places like NCI and doctors like Norm

Second, he was a curious, generous, and dedicated scientist who wanted to push the boundaries of our understanding about how radiation interacted with biology.

Third, he was the ultimate mensch, a delight to work with, to be with and a selfless colleague where the outcome of work vastly superseded the credit he sought or expected—always crediting instead the colleagues he felt lucky to be among.

Fourth, he was an engaged citizen and physician of the world, from international partnerships such as the All-Ireland Cancer Consortium to the King Hussein Medical Center to his work post 9/11 and after Fukushima.

Finally, Norm was just a delight to spend time with—fun, funny, a valuable thought partner who always brightened a conversation with generosity, listening, and humor.[577]

The author of this chapter first met Dr Coleman when he was an attending radiation oncologist at Stanford and the author was an internal medicine intern. They kept in touch over the subsequent decades, and I can confirm Dr Klausner's impressions. He was a remarkable individual.

Jay S. Loeffler (1955-2023)

Jay S. Loeffler attend Williams College and medical school at Brown University. He completed his radiation oncology training at the Harvard Joint Center for Radiation Therapy, where he served as chief resident. He began his academic career at the Brigham and Women's Hospital and Dana-Farber Cancer Institute, where he focused on neuro-oncology and became the founding director of the Brain Tumor Center.

In 1996, he was recruited to the Massachusetts General Hospital to be the director of the Francis Burr Proton Therapy Center. He later was the Herman and Joan Suit Professor of Radiation Oncology and Professor of Neurosurgery at Harvard Medical School. For 20 years, he served as Chairperson of Radiation Oncology at Massachusetts General Hospital.

The author and coauthor of more than 400 publications and co-editor of nine cancer textbooks, Dr Loeffler helped develop stereotactic radiosurgery for central nervous system tumors and stereotactic body radiation therapy for malignancies throughout the body. He was elected to the National Academy of Medicine[578-580] (Figure 1.70).

FIGURE 1.70 Jay Loeffler, MD (1955-2023).

A. William Blackstock Jr (1963-2023)

Blackstock was born in Eden, North Carolina; received a scholarship to attend Wake Forest University and then went on to medical school at East Carolina University School of Medicine. He completed a radiation oncology residency at the University of North Carolina Chapel Hill.

His initial work focused on gemcitabine radiation sensitization for pancreatic cancer.

He eventually returned to Wake Forest University School of Medicine where he rose through the ranks to become professor and then chair of the Department of Radiation Oncology. His clinical focus was on the treatment of gastrointestinal and thoracic malignancies. He helped establish a role for PET in the prognostic assessment of the treatment response of esophageal cancer.

Dr Blackstock played an active role in clinical cooperative group studies, and, along with Dr Mansfield who was profiled early in this chapter, he was among the

first Black physicians to chair an academic radiation oncology department[581,582] (Figure 1.71).

FIGURE 1.71 A. William Blackstock, MD (1962-2023).

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PART A

Cancer Biology

CHAPTER 2

Molecular Cancer and Radiation Biology

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Over the past several decades, molecular cancer research has become a rapidly growing branch of the biomedical sciences. Many advances in our understanding of cancer are closely related to innovations in biotechnology, such as gene editing techniques to modify the specific gene of interest, experimental maneuvers to manipulate temporal and spatial gene expression, the utilization of high-throughput methods to study the entire genome and proteome of cancer cells, and a vastly growing methodology to specifically interfere with signal transduction. Due to the rapidly expanding knowledge in molecular cancer and radiation biology, this chapter can only provide an introductory overview on selected topics.

Cell biology approaches contribute to modern radiobiology and help to better understand the effects of ionizing radiation on cells, tumors, and normal tissues. Knowledge in molecular cancer biology is important for clinical decision-making in oncology and the development of novel biology-driven strategies in the multidisciplinary clinical environment.[1-4] *Molecular pathology* of tumors increasingly supplements classic histopathology and immunohistochemistry, thereby providing the basis for improved treatment stratification in oncology.[5-7] *Molecular pathophysiology* describes mechanisms leading to a characteristic microenvironment of tumors or that eventually manifest radiation sequelae in normal tissues.[8] *Molecular imaging* has become important not only for staging but also for

biologic characterization of tumors and for determination of target volumes in radiation oncology, including approaches such as dose painting.[9-12] *Molecular targeting* in radiotherapy may either increase the tumor response or protect normal tissues, thereby enhancing the therapeutic gain of the treatment.[13-17]

Radiotherapy appears to be particularly promising to integrate molecular targeting approaches.[15,17] First, the radiobiologic mechanisms of the response of tumors and normal tissues to radiotherapy are well characterized, and the molecular pathways involved in these responses are increasingly known. Second, similar to conventional chemotherapeutic drugs, the novel drugs developed are not necessarily curative by themselves. In contrast, radiotherapy in itself is extremely efficient in eradicating cancer stem cells (CSCs), and recurrences often occur from only one or a few surviving CSCs.[18-20] Thus, even if novel drugs have only the potential to kill a limited number of CSCs, this might be sufficient to increase local control when combined with radiotherapy. The same argument applies when these drugs increase the radiosensitivity of tumor cells or when normal tissues are specifically protected. Third, in contrast to systemic chemotherapy, radiotherapy can be modulated in dose, time, and space. This allows individual tailoring of the effects of combined treatments in consideration of the spatial distribution of CSC burden as well as with consideration of normal tissues. Preclinical data and early clinical results corroborate these arguments[18,19,21-26] and support further translational research on biologically enhanced radiotherapy.

THE HALLMARKS OF CANCER

During carcinogenesis, neoplastic cells are gaining several biologic capabilities, which enable tumor growth and metastatic dissemination. Molecular biology of cancer can be summarized by a simplified concept based on a small number of underlying principles. In their seminal articles, Hanahan and Weinberg described these principles, which are being shared by most human tumor types, as the eight core *hallmarks of cancer*, as well as four *emerging hallmarks* and two *enabling characteristics* facilitating tumor promotion.[27-29] The hallmarks describe molecular and cellular characteristics such as specific genetic and epigenetic alterations as well as

modifications in key oncogenes and tumor suppressor genes that elicit neoplastic malignant transformation and tumor evolution, whereas the enabling characteristics (genome instability and tumor-promoting inflammation) are rather consequences of the aberrant tumor state that provide the tumor with functional means for further development.[29]

Sustaining Proliferative Signaling

Mitogenic signals from growth factors, cytokines, extracellular matrix, and cell-cell adhesion molecules are transferred into the cell by different classes of transmembrane receptors.[27,28] Malignant cells acquire the capability to escape from the tightly regulated dependence on extracellular growth signals. The molecular mechanisms include overexpression of growth factors as well as growth factor receptors (autocrine and paracrine stimulation), receptor mutations leading to constitutive receptor activation without ligand binding, and molecular aberrations in the intracellular signal transduction pathways.[27,28]

Evading Growth Suppressors

Normal cell division is tightly regulated by stimulatory and inhibitory growth signals. Growth signaling involves interaction of diffusible growth factors or cytokines with transmembrane receptors, as well as regulation of growth by components of the extracellular matrix and by cell-cell interactions. Once a resting cell receives a sufficient growth stimulus, it enters the cell cycle by passing the restriction point and four distinct phases of cytokinesis and mitogenesis: gap-1 (G1), DNA synthesis (S), gap-2 (G2), and mitosis (M).[30] The passage through the restriction point and the entry into S and M (G1/S and G2/M checkpoints) are governed by several proto-oncogenes and tumor suppressor genes such as *TP53* and *RB1* encoding for p53 and the retinoblastoma protein (pRb), respectively (Figure 2.1).[27,28,31,32] Inactivation of tumor suppressor genes by genetic mutations or epigenetic mechanisms will ultimately lead to sustained cell proliferation.[27,33-35]

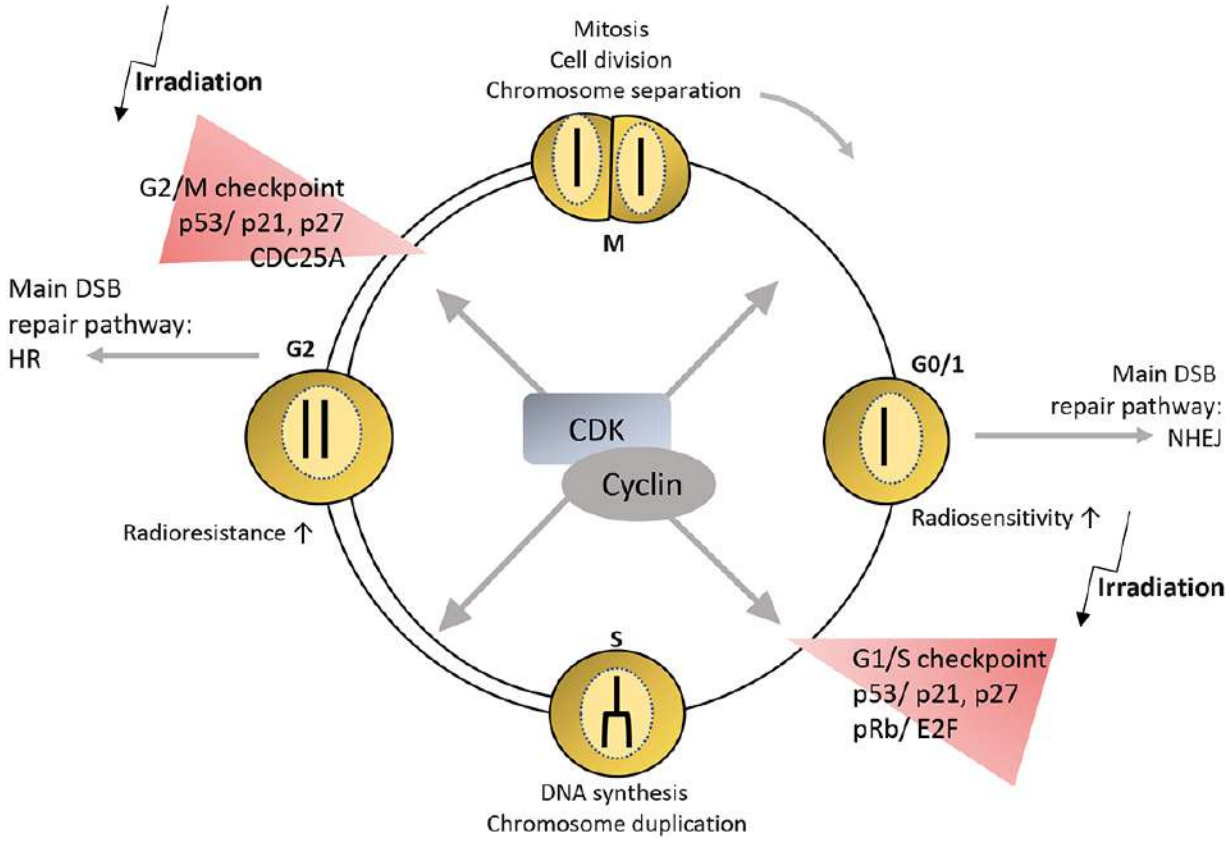

FIGURE 2.1 Cell cycle and checkpoints. The cell cycle is the backbone process that facilitates duplication of the DNA and cell division in order to generate two daughter cells. The distinct phases of the cell cycle are differently susceptible to irradiation damage. The highest radiation sensitivity is in early S and late G2/M phase. The cell cycle checkpoints in gap 1 (G1) and gap 2 phase ensure that the cell is ready for DNA synthesis (S phase) or mitosis (M). If the DNA is damaged the cell stops cycling and either the damage will get repaired and the cell continues with the cycle or the cell undergoes apoptosis and dies. Many types of cancer arise from mutations that lead to checkpoint misregulation or skipping of those. Cell cycle progression is governed by various cyclins and cyclin-dependent kinase (CDK). Different cyclin-CDK complexes determine targeted downstream proteins that, for example, promote DNA replication and degrade S-phase inhibitors.

Activating Invasion and Metastasis

Locoregional and distant spread of tumor cells requires detachment from the primary tumor, invasion into surrounding tissues, intravasation into blood or lymphatic vessels, anoikis resistance, adhesion to endothelial cells at distant sites, extravasation, and eventually colonization in distant organs.[28,36] The acquired capability of cancer cells to grow invasively and to metastasize is associated with multiple genetic and biochemical alterations of the cell-cell and cell-matrix interactions.[27,28] Tissue invasion and

metastasis require, at different steps, contrary capabilities—for example, detachment from the primary tumor versus adhesion at the metastatic site—suggesting that rapid adaptations, genetic instability, and clonal selection play an important role.[36] Primary tumors, by, for example, releasing membrane vesicles containing signaling molecules into the bloodstream, are also capable of remodeling the vasculature in distant organs, thereby creating organotropic pre-metastatic niches that enhance the ability of circulating metastatic cells to colonize these organs.[37,38] Also the intratumoral microenvironment of the primary tumor plays a key role; for example, hypoxia is described as one possible activator of metastasis.[39] To effectively metastasize, several critical steps are necessary, which involve epithelial to mesenchymal transition, extracellular matrix modulation, intravasation, circulation, extravasation, homing, forming the pre-metastatic niche for organotropic colonization, and mesenchymal to epithelial transition.[40,41]

Enabling Replicative Immortality

Loss of growth control and resistance to cell death are not sufficient for the development of macroscopic tumors. Normal cells have the capacity for a finite number of cell divisions, which results in a limited replicative potential. Thereafter cells either stop proliferating and enter the process of senescence, which is a viable but nonproliferative state, or they die.[28,42] During tumorigenesis, some premalignant cells become immortal by circumventing senescence, that is, by acquiring a capability of limitless replicative potential.[27,28] Of importance, malignant tumors consist of heterogeneous populations differing in their replicative potential. While most cancer cells have a limited replicative potential, a small subpopulation (ie, CSCs) have an infinite replicative capacity and the capability to reconstitute the tumor.[43] Thus, this subpopulation represents the target for curative cancer therapy, that is, all of these stem cells have to be inactivated by therapy or by host-related mechanisms to achieve cure.[18] It remains to be clarified whether CSCs represent distinct tumor cell subpopulations or whether they can switch between different stages in response to stress or environmental conditions.[44-46]

The molecular mechanisms underlying the escape from senescence and other modes of cell death include loss of tumor suppressor proteins such as p53 and pRb as well as telomere maintenance.[28] Telomeres are chromatin segments located at the ends of the chromosomes that protect these regions from recombination and degradation.[47] As telomeres are incompletely replicated, they become progressively shorter during cell divisions, subsequently resulting in loss of chromosomal protection, which in turn triggers senescence. Cancer cells generally have shorter telomeres than normal cells but are able to perpetuate their replicative potential by expressing telomerase, a complex including DNA polymerase, which reconstitutes the telomeres.[47]

Inducing or Accessing Vasculature

To grow beyond microscopically sized cell aggregates of around 1 mm, tumors depend on angiogenesis. Proliferating cells require appropriate oxygen and nutrient supply, which is physiologically limited to a distance of 100 to 200 μm from the next blood vessel. Therefore, malignant cells must induce and sustain their own vascular system to form tumors and metastases.[48] The process of the *angiogenic switch* during tumorigenesis (ie, the transition from the avascular phase to the vascular stage) is governed by different molecular changes in tumor cells and in cells of the surrounding stroma.[27,28,49] The major event of the angiogenic switch is that proangiogenic factors—mostly growth factors such as vascular endothelial growth factors (VEGFs), fibroblast growth factors, and platelet-derived growth factors (PDGFs)—outbalance antiangiogenic factors, such as thrombospondin (*TSP-1*), *angiostatin*, and *endostatin*. Hypoxia promotes tumor angiogenesis via the hypoxia-inducible factor 1, which transcriptionally regulates many angiogenic molecules.[50,51]

Resisting Cell Death

Under physiologic conditions, tissue homeostasis results from the balance of cell division and cell loss. This balance is disturbed in most tumors by an increased cell division rate due to the molecular mechanisms previously described and by a reduced rate of cell death, such as by apoptosis and senescence[27,28,52,53] (Table 2.1).

TABLE 2.1 TYPES OF RADIATION-INDUCED CELL DEATH AND THEIR CHARACTERISTICS

Type of Cell Death	Important Morphologic Characteristics	Important Molecular Mechanisms
Mitotic catastrophe	During or after mitosis, missegregation of chromosomes, cell fusion, micronuclei, giant cell formation	Lethal chromosome damage, caspase independent
Apoptosis	Chromatin condensation, nuclear fragmentation, blebbing of cell membrane	Damage to DNA, and/or membranes, and/or alterations of intracellular signaling, caspase dependent (intrinsic pathway via caspase 9)
Senescence	Metabolically active but nondividing, functionally differentiated cells	Damage to DNA and/or alterations of intracellular signaling, generally p53-dependent terminal growth arrest, increased senescence-associated β-galactosidase
Autophagy	Partial chromatin condensation, cell membrane blebbing, increased number of autophagic vesicles	Protein degradation characterized by double-membrane vesicles in the cytoplasm, possibly related to DNA protein kinase activity
Necroptosis	Early plasma membrane permeabilization, translucent cytosol, swollen mitochondria	Damage to DNA, and/or membranes, and/or alterations of intracellular signaling, caspase independent
Necrosis	Increased vacuolation, swelling of organelles and cells, rupture of cell membranes, formation of necrotic mass	Unregulated traumatic cell destruction; after irradiation as consequence of, for example, mitotic catastrophe or vascular damage

Deregulating and Reprogramming Cellular Metabolism

The sustained cell proliferation of cancer cells requires modifications and adjustments to and reprogramming of their energy metabolism.[28] Because deciphering the metabolome of cancer cells is still in its infancy, it is generally understood that all known metabolic pathways are altered and reprogrammed to provide a survival advantage.[54,55] Across the entire metabolome, cellular functions related to oxygen, pH, and glycolysis are the most intensively studied. Under aerobic conditions, normal cells use oxygen and pyruvate, which are split into carbon dioxide and water inside the

mitochondria to produce energy in the form of adenosine triphosphate. Under anaerobic conditions, cells rely solely on glycolysis—the breakdown of glucose into pyruvate. Cancer cells were shown to favor enhanced glycolysis for energy production, also under aerobic conditions, and this has been termed *aerobic glycolysis* or *Warburg effect*.[28,56-58] Glutamine and lactate have also been shown to serve as metabolic fuel in cancer cells.[59-61]

Avoiding Immune Destruction

During the development of cancer, antitumor responses represent a barrier that must be overcome. It has been shown that many types of tumors use different strategies to evade immune destruction. Tumor cells change such that surface expression of antigens renders them invisible to cytotoxic T cells or secrete immune inhibitory proteins.[62]

Tumor-Promoting Inflammation

Immune cell infiltration can be seen in most neoplastic tissues, but to a varying extent.[63] Inflammation has been shown to be involved in a number of hallmark capabilities by supplying growth and survival factors, proangiogenic factors, and extracellular matrix-modifying enzymes.[28,64-66] Furthermore, inflammation can drive the progression of cancers from incipient neoplasias.[28,66] The release of reactive oxygen species (ROS) by cells of the immune system can also have a mutagenic effect on surrounding cells.[28,65] However, the immune system is also capable of evoking an antitumor response.[67]

Genome Instability and Mutation

Genomic alterations or modifications of neoplastic cells are largely necessary to acquire the hallmarks outlined earlier. During tumor progression, not only mutations and epigenetic modifications but also nonmutational gene expression changes are leading to the accumulation of more favorable genotypes and clonal expansion of cells.[28] The identification of driver mutations leading to malignant progression is important also in terms of therapeutic targeting. For the detection of epigenomic changes,

more comprehensive analyses such as histone modifications and DNA methylation are necessary.[28,68]

Upcoming Hallmarks and Enabling Characteristics

Unlocking phenotypic plasticity can be achieved through several processes: (1) Through dedifferentiation, cancer cells can acquire the capability to revert to cellular states that are similar to that of progenitor cells. This has already been described for different entities such as colon cancer and malignant melanoma.[29,69-72] (2) Cells that are following the differentiation process may escape on the way, that is, maintaining in a not fully differentiated state, and thus serve as progenitors, leading to tumor progression as discovered in acute promyelocytic leukemia, melanoma, and others.[29,73,74] Thereby, cancer cells can also go into dormancy and escape into protective niches before eventually proliferating.[29] (3) Transdifferentiation may occur, during which cells switch between different development pathways, which may help to gain additional hallmark capabilities. An example is the development of adenosquamous esophageal cancer instead of squamous cell cancer that would be expected when cells arise from its original squamous epithelium.[29,70]

Nonmutational epigenetic reprogramming has been understood to be independent from changes in gene expression that are solely epigenetically regulated.[29] This form of epigenetic reprogramming is well known and needed in embryonic development, differentiation, and organogenesis.[29,75-77] However, during tumor development and progression, also microenvironmental mechanisms such as hypoxia-induced changes in the methylome are leading to reprogramming. Also, the deprivation of nutrients has been shown to cause inflammatory responses at transcriptional and translational level in tumor cells.[29,78] Epithelial to mesenchymal transition is another well-known example for microenvironmental-induced changes thus enhancing tumor growth in solid tumors.[29,79] Moreover, epigenetic heterogeneity has been linked with heterogeneous phenotypic states, as discovered through modern technologies.[29,80,81] Finally, the tumor microenvironment (TME) is also capable of recruiting and epigenetically modifying endothelial cells, cancer-associated fibroblasts, innate immune cells, and others through physical and soluble factors.[29,82]

Polymorphic microbiomes were shown to have an impact in cancer phenotypes. Especially bacteria have been identified that can positively or negatively affect the whole process of malignant transformation including development of cancer, malignant progression, and therapy response.[29,83,84] To date, the most important and best investigated microbiome is the gut microbiome, also because of its impact on the development of colon cancer. Studies have shown that the microbiome can have cancer-protective or cancer-promoting effects, which is due to a particular subset of bacteria.[29,85] Bacterial toxins and other secreted molecules can negatively impact the colon cells by promoting mutagenesis, by causing DNA damage with insufficient DNA repair, and others.[29,86] In addition, bacteria have been shown to enhance epithelial cell proliferation, which in turn may lead to an increasing number of neoplastic cells. In addition, bacteria are also capable of producing so-called immunomodulatory factors that lead to the activation of various chemokines and cytokines, which in turn affect both the number and characteristics of immune cells within the colonic epithelium, its associated stroma, and the draining lymphatic tissue,[29] but they may also be able to cross the epithelia and their connecting tight junctions and make their way into the stroma, which in turn activates the innate and adaptive immune systems, potentially leading to tumor-promoting inflammation and also determining response or nonresponse to various types of immunotherapy.[29,83,87-89] Interestingly, some (solid) tumor entities were also shown to be populated by a distinct microbiome that together with the gut microbiome affects the immune phenotype and, more importantly, also survival.[29,90]

Cellular senescence, more specifically the activation of a senescence-associated phenotype, may lead to the stimulation of tumor progression by affecting several processes such as proliferative signaling, induction of angiogenesis, and invasion and metastases.[29,91,92] Especially transitory senescence, where senescent cells can resume with cell proliferation and become a full tumor cell again, has been shown to be an important issue in the development of resistance to anticancer therapy.[29,93] Besides the senescence-associated phenotype, cancer-associated fibroblasts in the TME can also undergo senescence and thereby enhance malignant progression.[29,94,95]

PRINCIPLES OF MOLECULAR CANCER BIOLOGY

Carcinogenesis describes the transformation of normal cells into cancer cells and the subsequent development of a tumor. This is a multistep process that includes accumulating changes on the cellular, genetic, and epigenetic level and is characterized by abnormal cellular proliferation. However, these changes can differ between tumor cells within the same tumor leading to intratumoral heterogeneity but also between patients causing intertumoral heterogeneity.

Genetic cancer factors include somatic mutation, deletion, insertion, gene amplification, chromosomal instability and rearrangements, chromothripsis, loss of heterozygosity, and translocation. More than 700 cancer driver genes have been described up to date[96] that contribute to the above-described hallmark traits in cancer evolution and therapy resistance. A curated list of evidence-based driver genes can be found within the Cancer Gene Census of the Catalogue of Somatic Mutations in Cancer.[97]

Chromothripsis is a massive catastrophic single mutational event that is thought to occur at the onset of tumorigenesis and results in massive chromosomal rearrangements leading to loss of tumor suppressor function and activation of oncogenes, loss of cell cycle checkpoint regulation, and impaired DNA repair.[98] Recent pan-cancer studies revealed an average prevalence of 30% across all cancer types with a frequency above 50% in certain cancer entities.[99,100]

Epigenetic regulation of cancer, that is, a genomic mechanism that reversibly modifies gene expression without altering DNA sequences,[101] is less well defined, yet, and includes, for example, silencing of tumor suppressor genes by promoter hypermethylation, histone modifications, transcription of these modifications, chromatin remodeling, and the effects of transcription.[102] Chromatin remodeling and the effects of noncoding RNA such as microRNA expression are important epigenetic mechanisms in tumorigenesis.[33,35,103]

Environmental factors such as chemical agents, radiation and errors in DNA replication, infection with oncogenic viruses, as well as chronic inflammation caused by other infectious agents can also contribute to the development of human cancer (eg, human papillomaviruses in cervical or head and neck cancer, hepatitis B viruses in hepatocellular carcinoma, and

human immunodeficiency viruses in Kaposi sarcoma, bovine meat and milk factors, small episomal DNA molecules).[104-106] The hostile micromilieu in solid tumors, particularly hypoxia, further promotes progressive genomic alterations and clonal selection.[107,108] The potential role of the microbiome in cancer development, metastasis, and treatment response via secreted or modulated metabolites is increasingly recognized. Consequently, cells gain advantage in proliferation and survival, which eventually results in malignant transformation, a prerequisite for the development of cancer and metastatic spread.

Conceptually, three classes of cancer genes can be distinguished. First, *oncogenes* are activated in cancer cells by genomic alterations (vide supra) resulting in a gain of function. Typical oncogene functions are stimulation of cell proliferation (eg, by activation of Ras) and increase in cell survival (eg, by activation of phosphoinositide 3-kinase [PI3K]/Akt signaling). Disorders in the second class of cancer genes, *tumor suppressor genes*, which normally slow down cell division and instruct cells to die at the right time, cause loss of function and allow cells to grow out of control, leading to cancer. The third class of cancer genes are *DNA repair genes*, which help to repair DNA damage or trigger cell death if they can't repair the damage. While some cancers can be attributed to single genetic alterations, most sporadic solid tumors exhibit a wide range of disorders in numerous cancer genes. Simplified mathematical modeling of the increasing incidence of common cancers as a function of age suggests that four to seven somatic gene alterations are required for carcinogenesis.[109,110] A typical example for multistep tumorigenesis is the adenoma-carcinoma sequence in colorectal cancer.[111]

Inherited cancer predisposition can be divided into the rare group of inherited cancer syndromes and familial cancers (strong predisposition) and the more frequent group of predisposition without evident family clustering (weak predisposition).[112] The first group includes syndromes caused by germline mutations affecting DNA repair, genomic stability, and cell cycle control, for example, the tumor suppressor gene *TP53* (Li-Fraumeni syndrome), nucleotide excision repair genes (xeroderma pigmentosum), *ATM* (ataxia telangiectasia mutated), DNA mismatch repair genes (hereditary nonpolyposis colorectal cancer), and *BRCA 1/2* (familial breast cancer). An example of a familial cancer syndrome related to oncogene

activation is neurofibromatosis type 1, in which the mutated *NF1* gene results in activation of the Ras oncogene.[112] Germline mutations causing inactivation of the cell-cell adhesion molecule E-cadherin can be found, for example, in familial diffuse gastric carcinoma.[113] An ongoing debate is the question of how close the risk of cancer depends on the number of normal stem cell divisions in contrast to the influence of environmental factors.[114,115] Approximately 70% to 90% of cancers are believed to be related to environmental exposures.[116] This issue is highly relevant for public health considerations as it points to the "bad luck" hypothesis versus a cancer risk importantly effected by external influences. As a general note, more investigations into early precancerous lesions are key for a better understanding of tumorigenesis, the relative importance of intrinsic or external risk factors, as well as the rationale behind the development of potential interventions and preventive strategies. Current molecular knowledge of these processes is often extrapolated from observations made at much later stages of tumor progression, which may obscure and bias our understanding of the initial events.[117-119]

MOLECULAR RADIATION BIOLOGY

Biologic Consequences of Irradiation

The effects of ionizing radiation on cellular target molecules may lead to various functional consequences. These functional effects can be broadly categorized into cell death, repair, cell cycle effects, altered gene expression, modification of signal transduction, mutagenesis, and genomic instability (Figure 2.2). These categories are not exclusive.

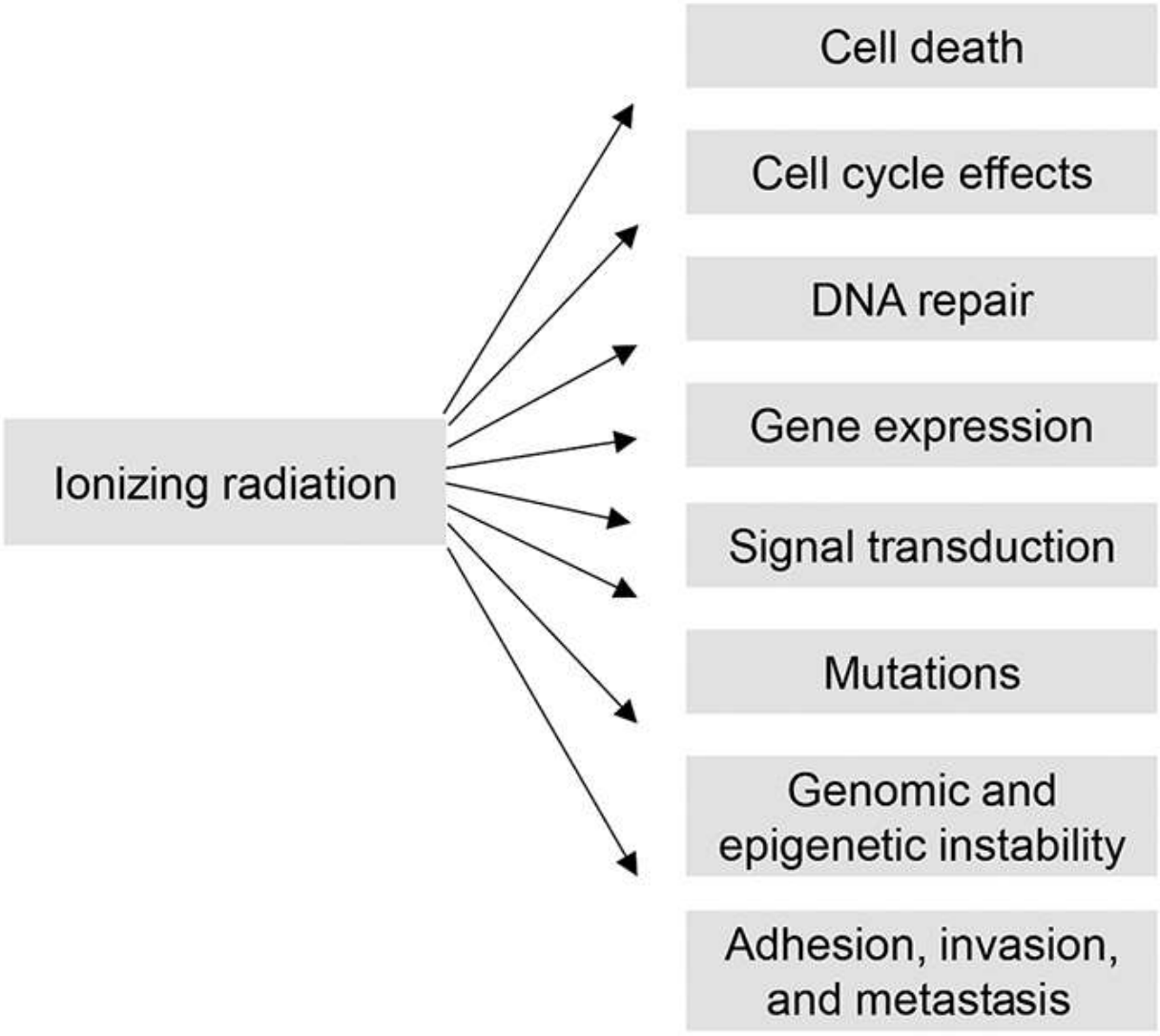

FIGURE 2.2 Illustration of cellular effects on ionizing radiation.

Cell Death

Among the functional consequences of ionizing radiation, cell death is the most important one for radiation oncology. Cells can die in several ways[120] —by apoptosis, mitotic catastrophe, senescence, necrosis, necroptosis, ferroptosis, disulfidptosis, pyroptosis, and autophagy (Figure 2.3 and Table 2.1). Most important for the cell killing effect of radiotherapy of solid tumors is the *mitotic catastrophe*, which is caused by lethal chromosome damage.[121] After irradiation, cells can pass through one or few mitotic cycles before missegregation of chromosomes or cell fusion leads to the loss of their replicative potential (or clonogenicity). Often micronuclei,

containing nonrepaired chromosome fragments, can be detected. Those micronuclei, and hence essential genetic information, will be lost during the following cell cycle, which results in cell death. Frequent multinucleate giant cells reflect a radiation-induced failure of cytoplasmatic separation on cell division.

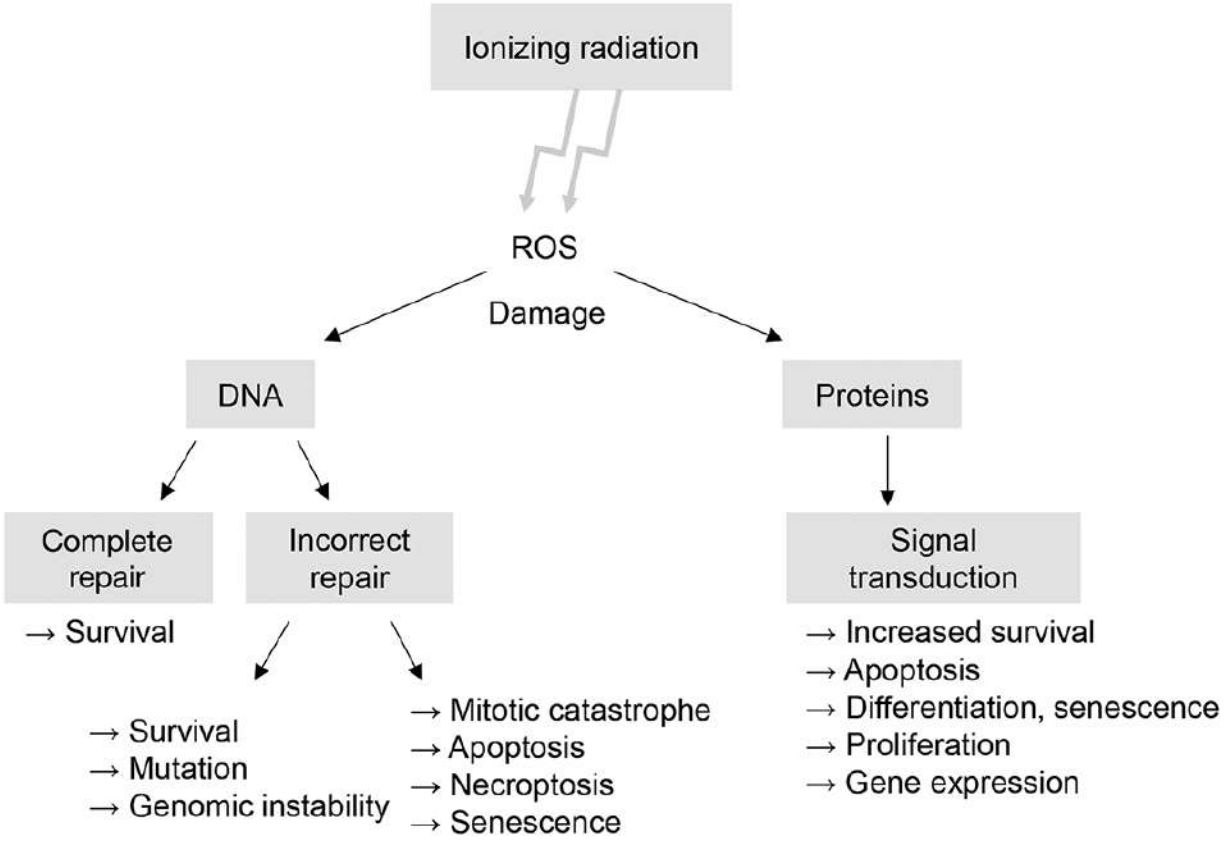

FIGURE 2.3 Simplified illustration of cellular reactive oxygen species (ROS) effects. The generation of ROS causes DNA and non-DNA damage and results in different cellular effects.

Neoplastic hematopoietic or lymphatic cells often die from radiation-induced *apoptosis* via the intrinsic, caspase 9-dependent pathway or pyroptosis.[122] Two different forms of radiation-induced apoptosis can be distinguished—early or premitotic versus late or postmitotic apoptosis.[123] Early apoptosis is p53 dependent, occurs within a few hours after irradiation before the cells enter mitosis, and is primarily a consequence of DNA damage. Early apoptosis represents a distinct mode of radiation-induced cell death. In contrast, secondary apoptosis occurs after mitosis and

is one of several possible manifestations of radiation-induced lethal chromosome aberrations and DNA damage. In most cancers, apoptosis appears not to be the main mechanism of radiation-induced cell death.[124]

Radiation-induced *senescence* plays an important role in the development of normal tissue damage—for example, fibrosis[125]—but occurs also in response to nonlethal stress in tumor cells.[126] Cells survive and are metabolically active but lose their replicative potential. *Necrosis* is an unregulated process of cell destruction by the release of intracellular components. This is usually the consequence of pathophysiologic conditions such as ischemia and inflammation.[120] It is well known that tumors often show massive necrosis after neoadjuvant radiotherapy or radiochemotherapy, which in some tumors correlates with improved prognosis.[127,128] It is likely that this radiation-induced necrosis is explained by several factors, including mitotic catastrophe of tumor cells and the effects of irradiation on tumor vessels leading to changes in the TME, which consequently cause cell death.

Necroptosis, the prototype of regulated necrosis, is a caspase-independent form of programmed cell death (PD) and kills apoptosis-deficient cells. It is stimulated by death receptor ligands of the tumor necrosis factor (TNF) receptor subfamily such as TNF-α, CD95 ligand, or tumor necrosis factor–related apoptosis-inducing ligand, but also by other receptors such as ectodermal dysplasia receptor.[129] Necroptosis can also be induced by other stress-inducing factors such as ionizing radiation, DNA-damaging agents as well as ROS.[130] Experimental data show that knockout of necroptotic genes leads to significantly enhanced radiosensitivity and reduces tumor formation in mice.[131] Other reported forms of regulated necrosis are ferroptosis, oxytosis, ETosis, NETosis, cyclophilin D–mediated regulated necrosis, parthanatos, pyroptosis, and pyronecrosis.[130]

Ferroptosis is a form of iron-dependent regulated cell death/necroptosis caused by ROS-induced lipid peroxidation by radiotherapy. Increased ferroptosis after radiotherapy correlates with improved patient survival.[132] Increased expression of cellular inhibitors of ferroptosis, such as SLC7A11 that protects cancer cells from oxidative stress, may contribute to radioresistance and provides a promising target for inhibitors.

Disulfidptosis is caused by extensive toxic levels of intracellular cystine and other disulfide molecules.[133] Moderate expression of SLC7A11, the

cystine transporter, seems to protect tumor cells from oxidative stress leading to therapy resistance, whereas overexpression leads to increased amounts of cystine in the tumor cell that cannot be reduced to cysteine via nicotinamide adenine dinucleotide phosphate.

Autophagy is a form of nonapoptotic and nonnecrotic cell death that is related to lysosomal degradation of proteins and cell organelles that are then utilized for the production of new cells.[120] This mode of PD is triggered by growth factor withdrawal, differentiation, and developmental stimuli. Although the molecular regulation is not completely understood, data suggest an ambiguous role of autophagy in radiotherapy response with evidence for cytoprotective and cytotoxic effects.[134] A high rate of autophagy contributes to radiation resistance, and autophagy is regulated through different hypoxia-dependent pathways, thereby cellular homeostasis and survival during metabolic stress.[134-136]

Target Molecules of Radiation Damage

Nuclear DNA, lipids, and proteins are considered as the three main target molecules of radiation-induced cell death or damage. Radiation effects may occur as direct ionizations in an organic molecule or indirectly via free radical processes. As cells consist mostly of water, most ionizations produced by irradiation occur in water molecules. Within only 10^{-10} seconds, radiolysis of water leads to, among other entities, e^{-}_{aq}, $H^{\cdot}$, and $OH^{\cdot}$. About 60% to 70% of cellular DNA damage produced by ionizing radiation is caused by OH.[137] The radiation-induced ROS undergo further reactions—for example, production of H_2O_2 from two hydroxyl radicals. Aerobes have evolved antioxidant defenses to protect themselves against the oxygen-derived species generated in vivo or from external sources. These defenses include enzymes (eg, superoxide dismutases, catalase, and glutathione peroxidase [GPX]), low-molecular-mass agents (eg, α-tocopherol and ascorbic acid), and proteins that bind metal ions in forms unable to catalyze the generation of free radicals. The oxygen molecule has a high affinity to free radicals, which may give rise to further cascades of radical production and thereby to the fixation of free radical damage to important macromolecules of the cell (eg, DNA). This is one explanation of the

oxygen effect of radiation damage, that is, the fact that well-oxygenated cells are more radiosensitive than hypoxic cells.[138,139]

By far the most important target for the biologic effects of ionizing radiation is the DNA (Figure 2.3). For example, irradiation of the cytoplasm of cells with short-range α-particles only leads to cell kill at very high doses, whereas 1,000-fold lower doses to the nucleus are sufficient to kill the cell.[140] Radioactive isotopes with short-range emission effectively kill cells when incorporated into the DNA but not when predominantly incorporated in cell membranes.[141] Modification of radiation-induced cell kill by different measures, including hypoxia, high linear energy transfer radiation, or hyperthermia is linked closely with a change in the induction and repair of DNA double-strand breaks (DSBs). Exposure of cells to about 1 Gy causes approximately 3,500 DNA injuries, 1,500 to 2,500 of which are damaged bases, 1,000 single-strand breaks (SSBs), 40 DSBs, and an estimated 100 to 200 local multiple-damaged sites, where one or several DSBs occur in close proximity to SSBs and base damage.[142] Most radiation-induced DNA damage is recognized and very efficiently repaired by the cell (*vide infra*). Importantly, it also has to be considered that different types of radiation treatment can cause different extent of damage to the DNA in a tumor cell. In contrast to photon therapy, particle therapy causes more severe DNA damage.[143,144]

Besides effects on DNA, ionizing radiation also evokes biologically important responses on proteins (eg, transmembrane receptors) and on lipids (eg, ceramides) (Figure 2.3). Radiation-induced activation of receptors will be discussed later in this chapter. Lipids are a critical buffer against ROS, maintaining lipid redox homeostasis and thereby ensuring cell survival.[145] The susceptibility of tumor cells to radiation-induced damage via lipid peroxidation depends on the ROS scavenging system involving glutathione and GPX4.[146] Radiation-induced lipid peroxidation triggers ferroptosis (*vide supra*).[147] Interestingly, FLASH irradiation, that is, ultra-high-dose-rate radiation, inhibits lipid peroxidation in liposomes and micelles, which may partly explain the FLASH effect of preserving normal tissue.[148]

Recognition of Radiation-Induced DNA Damage

The DNA damage response (DDR) to DNA DSBs and replication stress is orchestrated by the kinases ATM[149] and ataxia telangiectasia and Rad3-related (ATR)[127] signaling cascades (Figure 2.4).[150,151] In response to DNA damage ATM and ATR phosphorylate thousands of downstream effectors. ATM activation requires the highly conserved Mre11-Rad50-Nbs1 (MRN) complex and other factors at sites of DNA breaks.[152] Oxidation of ATM activates the kinase independently of the MRN complex.[153] In addition to proper activation of downstream DNA repair proteins, histone H2AX molecules need to be phosphorylated in the vicinity of the DSB. Phosphorylated H2AX, termed γH2AX, is therefore frequently used as surrogate marker for DSBs. All of these proteins assemble at the site of the breaks and presumably control the choice of one of several repair pathways. ATM is involved in the regulation of multiple cell cycle checkpoints (G1/S, S, G2/M) following DNA damage, thereby slowing cell cycle progression to allow for proper repair.[154] ATM, ATR, and DNA-dependent protein kinase catalytic subunit (DNA-PK_{CS}) phosphorylate p53 and a number of proteins involved in cell cycle delay, apoptosis, and induction of DNA repair. ATR appears to be important for sensing ultraviolet-related and other types of bulky lesions, as well as damage that induces a replication block, while ATM seems to be the sensor for DSB induced by ionizing radiation.[150]

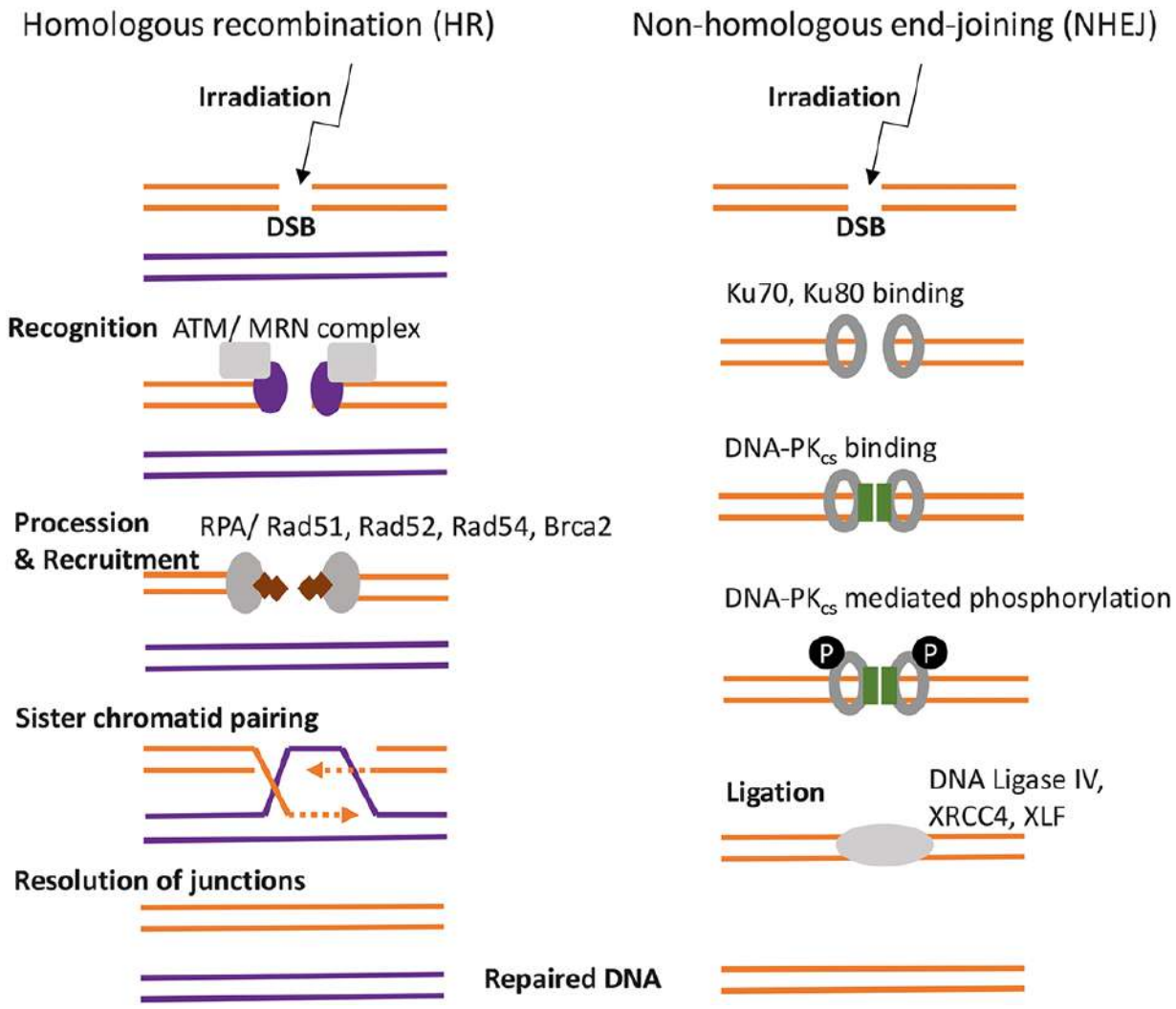

FIGURE 2.4 Main DNA double-strand break damage repair mechanisms. The more error-prone nonhomologous end-joining (NHEJ) is active throughout the whole cell cycle. For homologous recombination (HR) an identical DNA strand is necessary and used as template for precise repair.

DNA Repair

Genome integrity is essential to the survival of cells and organisms. It is estimated that about 10^4 DNA lesions occur in a single human cell every day.[155] Most of the damage is caused by endogenous sources such as oxygen free radicals, replicative errors, and spontaneous deaminations. To cope with the plethora of continuous damage, a repair system was developed during evolution that also acts on external challenges such as radiation or chemical DNA damage. To enable repair of massive DNA damage, the cells stop proliferation. This may prevent replication or segregation of damaged

genetic material. If repair is not possible, the cells either die or, in case of survival, may propagate mutated DNA (see Figure 2.4). When the DNA replication machinery meets damaged DNA, replication may continue despite the damage by translesion synthesis, which requires DNA polymerase with low fidelity. Different mechanisms are involved in DNA repair.[150,156]

Base Excision Repair

Base damages and SSB are the most frequent types of DNA damage after irradiation.[157,158] The mechanism of base excision repair (BER) is responsible for the repair of various kinds of base damage (abasic sites, oxidized bases, deaminated bases, and alkylated bases) and SSB. The major BER pathway is the short-patch pathway, which involves excision of only one base. SSBs are primarily recognized by the enzymes poly(ADP-ribose) polymerase (PARP)1 and PARP2.[151]

DSB Repair

Radiation-induced DSBs are, despite their relatively low induction frequency (40 Gy per cell), biologically much more important as they pose a higher threat to genome integrity than base damage and SSB and are far more difficult to repair.[151] There are two major pathways—homologous recombination (HR) and nonhomologous end-joining (NHEJ)—to repair DSB (Figure 2.5).[159,160]

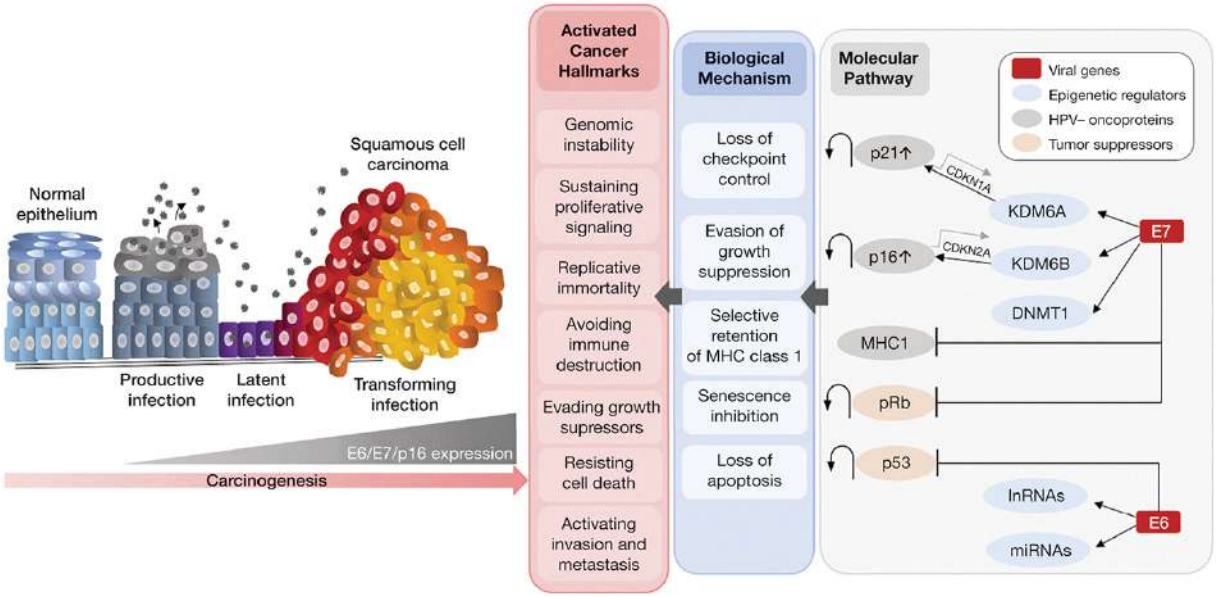

FIGURE 2.5 Human papillomavirus (HPV) infection and activation. Left: Microtraumas allow the entrance of HPVs to the epithelial basal cell layer. This is followed by the coordinate expression of different viral genes. E6/E7 causes viral genome amplification and shedding of the newly produced viral particles. Persistent expression can lead to malignant dysplasia once the HPV infection has established and evaded from immune recognition. Malignant transformation is characterized by loss of differentiation, high E6/E7 level, and no viral replication. Right: Mechanism of E6/E7-mediated addiction: The expression of the viral genes E6 and E7 inhibits the expression of the tumor suppressor genes p53 and pRP, respectively. E6-triggered inhibition of the tumor suppressor p53 leads to loss of apoptosis control and with this to uncontrolled growth of squamous carcinoma cells. The E7 oncoprotein inactivates pRb, which prevents oncogene-induced senescence. The epigenetic reprogramming via the E7-KDM6A/B axis leads to induction of p16 (used as histologic biomarker for HPV infection) and p21, resulting in loss of cell cycle control and avoidance of lethal replication stress. The intracellular mechanisms driven by HPV oncogenes are cancer hallmark–enabling processes.[299] E6 induces additional epigenetic regulators such as long noncoding RNAs and microRNAs that further contribute to HPV-driven tumor evolution and maintenance.

HR is a slow, high-fidelity repair pathway. Regions of DNA homology—usually the sister chromatid—are used as the template. During HR, activated ATM recruits endonucleases that process broken ends, which ultimately creates single-stranded 3′ ends. For the processing, the MRN complex is required. In concert with BRCA1, BRCA2, and Rad51 paralogues (XRCC-2, XRCC-3, Rad51B, Rad51C, Rad51D, Rad52, Rad54), the Rad51 protein binds to single-stranded DNA with the aid of replication protein A and searches for a homologous sequence on the sister

chromatid template. On strand invasion, Rad51 enables the formation of a temporary triple helix. Once the complementary strands have paired, the 3′ end of the damaged DNA will be elongated by DNA polymerase beyond the position of the former DSB. When the 3′ single strand of the second end of the DSB also invades the structure, a quadruple helix is formed called a *Holliday junction*, which can be extended in both directions. After the gap has been safely bridged (usually about 50 base pairs will be copied), the Holliday junction is resolved, and the remaining nicks are sealed by a DNA ligase.[161,162]

NHEJ is a fast pathway often referred to as error-prone repair pathway that rejoins DNA ends without needing a repair template, usually after removal of a limited number of base pairs.[163] Most (~80%) radiation-induced DSBs outside of S phase are repaired by NHEJ independently of ATM. NHEJ is initiated by the Ku70/Ku80 heterodimer, which binds to DNA ends and recruits the DNA-PK_{CS}. DNA-PK_{CS} can phosphorylate a variety of repair proteins such as Ku, x-ray cross-complementation protein 4 (XRCC-4), Artemis, p53, or replication protein A. However, only the autophosphorylation has been identified as being essential for repair. Artemis, in concert with DNA-PK_{CS}, trims the DSB ends for subsequent processing. After release of DNA-PK_{CS} from the DNA, the end will be bridged by the complex of ligase IV/XRCC-4/XRCC-4-like factor (XLF), which also performs the final ligation step. It has been observed that NHEJ can, to some extent, occur in the absence of several core proteins. This gave rise to the idea of a backup pathway that only operates when the DNA-PK-dependent NHEJ fails.[164] Besides the genuine repair proteins, the tumor suppressor p53 is involved in controlling the repair. p53 appears to suppress both HR and NHEJ in case an error-free repair is not possible and thereby reduces the mutagenic effect of radiation.[165]

Chromatin organization has also been shown to impact DSB induction and repair.[166-169] Chromatin is organized as euchromatin and heterochromatin, representing loose and condensed DNA areas, respectively. While DSBs in euchromatin are easily accessible for repair proteins, DSBs in heterochromatic DNA regions need to be moved to less condensed areas for efficient repair.[167,169]

Radiation-Induced Cell Cycle Delay

It has long been recognized that radiation-induced DNA damage is associated with delay in the cell cycle, which has been interpreted as allowing additional time for the cells to repair. Radiation-induced DSBs are key signals leading to arrest in the cell cycle at various stages in G1, S, and G2/M phase. Spindle assembly checkpoints arrest in the mitotic phase upon damage. Furthermore, DSBs can be found in all cell cycle phases, suggesting incomplete repair before entering the next phase. For example, tracking of radiation-induced γ H2AX foci, representing DSBs, revealed transfer of DSBs induced in the G1 cell cycle phase to daughter cells.[170]

G1 Phase

The G1 cell cycle checkpoint prevents damaged DNA from being replicated and is the best understood checkpoint in mammalian cells.[171] Radiation-induced G1 phase cell cycle arrest is regulated by p53 (see Figure 2.1). Loss of p53 function, which is found in most tumors, leads to a lack of G1-phase arrest. These cells only exert a dose-dependent block in the G2 and M phases of the cell cycle. Central to the G1 checkpoint is the accumulation and activation of the p53 protein, which is controlled by the ATM and ATR kinases. These kinases, together with DNA-PK, are activated by and recruited to radiation-induced DNA lesions. Physiologically, p53 expression levels are low due to interaction with its negative regulator MDM2, which targets p53 for nuclear export and proteasome- mediated degradation in the cytoplasm.[172] Following radiation-induced DNA damage, ATM activates the downstream cell cycle checkpoint kinase Chk2 by phosphorylation, leading to p53 phosphorylation and finally resulting in p53 accumulation. Moreover, ATM exerts p53 stability and thereby prevents p53 nuclear export to the cytoplasm for degradation. p53 target genes include several genes that are involved in the DDR (eg, *MDM2, GADD45A, CDKN1*). Accumulation of the cyclin-dependent kinase inhibitor $p21^{Cip1}$ blocks G1/S-phase progression by binding to the cyclin E/cdk2 complex, reducing cdk2 activity, which has an important function in the phosphorylation of retinoblastoma protein pRb.[173] Loss of pRb function is often found in malignant cells and leads to an uncontrolled G1/S transition, genomic instability, and loss of differentiation.

S Phase

After irradiation, the rate of DNA synthesis is decreased via ATM- and NBS1-dependent pathways.[174] Radiation-induced DNA damage activates ATM for Thr68 phosphorylation of Chk2.[175] Activated Chk2 targets CDC25A phosphatase for ubiquitination. As a result, Cdk2/cyclin E and Cdk2/cyclin A complexes remain inactive, which prevents completion of DNA synthesis and G2 entry. Alternatively, radiation-activated ATM phosphorylates several downstream substrates, including BRCA1, NBS1, and SMC1.[175,176] ATR phosphorylates the cell cycle checkpoint kinase Chk1. Subsequently, Chk1 phosphorylates CDC25A, which results in cytoplasmic sequestration and thereby inhibition of S-G2 transition.[177]

G2/M Phase

In contrast to the G1 checkpoint, all mammalian cells, normal or transformed, undergo cell cycle arrest in G2 after radiation-induced damage.[178] The G2 cell cycle checkpoint is the essential final determinant allowing cells to divide. The entry into mitosis is regulated by the activity of the cyclin- dependent kinase Cdk1[179] (see Figure 2.1). Phosphorylation of Cdk1 blocks cell entry into G2. These phosphorylations are removed by the phosphatase CDC25C. After irradiation, ATR and ATM activate the downstream checkpoint kinases Chk1 and Chk2, which phosphorylate CDC25C.[180] This results in binding of 14-3-3 proteins. The CDC25C/14-3-3 protein complex is translocated into the cytoplasm for sequestration. As a consequence of this CDC25C degradation, Cdk1 remains phosphorylated, thereby preventing entry into mitosis. ATM appears to be more dominant at the early stage of G2/M checkpoint activation, whereas ATR seems to contribute mainly to sustained checkpoint events.[181] G2/M arrest prevents cells from entering mitosis in the presence of DSBs.[182]

Molecular Targets for Radiotherapy

Molecularly targeted anticancer drugs specifically interfere with signaling pathways that keep tumor cells alive, thereby affecting the “hallmarks of cancer” mechanisms inside a tumor cell. Most clinically used anticancer agents are not developed for use in radiotherapy. A major challenge is to define the optimal dose, timing, and drug distribution for combination

therapies and to evaluate and utilize synergistic potentials between the drugs and irradiation. Therapeutic success is highly dependent on proper patient stratification and the ability to predict the response potential of a given combination.[4] Tumor cells respond to radiation by altering the expression or downstream signaling of the desired target molecule. The effect of a targeted drug in combination with radiotherapy is highly dependent not only on the expression but also on the alterations of the target molecule under irradiation. Different radiation qualities, such as photons versus particles, may trigger different molecular signaling pathways. With increasing molecular investigations and novel sequencing techniques, many putative targets have emerged. However, druggability is not always given, and some other considerations have to be taken into account. Not all differentially expressed genes, pathways, and mutations are necessarily critical for cancer progression and maintenance but instead represent so-called passenger mutations and only coincide within the particular cancer; they do not reflect the actual driving force of malignancy, which, as described above, is often due to three driver mutations.[183] This does not facilitate the selection of potential targets and patient stratification. Cell surface–associated proteins such as serine/threonine/tyrosine kinases, growth factor receptors, G protein–coupled receptors, and receptor ligands are classical druggable targets. Intracellular molecular targets that do not function as an enzyme, but are loss-of-function targets, such as tumor suppressors, are not directly druggable. Transcription factors are also considered undruggable, but recent advances in understanding the regulation of transcription factors such as c-Myc, YAP/TAZ, and β-catenin are emerging and may lead to useful drug approaches.[184]

RTK

Receptor tyrosine kinases (RTKs) represent a group of transmembrane receptors consisting, if complete, of an extracellular ligand-binding domain, a transmembrane part, and an intracellular catalytic domain with tyrosine kinase activity.[185] RTKs are central to cell growth and survival, hence most cancers rely on their activity.[186] Upon ligand binding and receptor homo- or heterodimerization, the protein kinase is subsequently activated, resulting in phosphorylation of tyrosine residues of the receptor itself

(autophosphorylation) or target proteins. Depending on the cellular context, this triggers an intracellular signaling cascade that eventually leads to proliferation, survival, differentiation, and migration. Among the known human RTKs are the epidermal growth factor receptors (EGFRs), the PDGF receptors, the VEGF receptors (VEGFRs), the fibroblast growth factor receptors, the ephrin receptors, and tyrosine kinase receptor. RTK dysregulation is implicated in many cancers, driven by their overexpression, activating mutations, oncogenic fusions, and ligand dysregulation, making them attractive targets for molecular drugs.[186]

EGFRs

The *EGFR family* consists of four distinct members (EGFR/ErbB-1, HER2/ErbB-2, HER3/ErbB-3, and HER4/ErbB-4) that are dimerized after ligand binding to the extracellular domain.[187,188] The receptor ligands, such as epidermal growth factor (EGF), tumor growth factor alpha (TGF-α), and neuregulin-1, as well as their cognate receptors, are abundantly expressed in a large variety of human cancers, including lung, breast, head and neck, and gliomas, and have been related to poor prognosis. The EGFR is being activated through its natural ligands such as EGF, TGF-α, or amphiregulin and can be transactivated by cell adhesion molecules such as integrins or immunoglobulin-like receptors.[189] In addition, ionizing radiation is able to stimulate EGFR.[190] Radiation doses of 1 to 2 Gy activate the EGFR and its downstream signaling cascades with similar efficiency as physiologic EGF concentrations of 0.1 to 1 nM. EGFR signaling via Ras-Raf-MAPK after irradiation has been implicated in increased proliferation,[191] which corresponds to observations that EGFR overexpression is associated with repopulation during fractionated irradiation.[192-194] In addition, EGFR-dependent signaling via PI3K/Akt has been associated with increased cellular survival and cell cycle progression.[195,196] Monoclonal antibodies and tyrosine kinase inhibitors against the EGFR have been investigated in the past 20 years without showing clinical superiority over cisplatin-based combined radiotherapy (summarized by Krishnamurthy et al[197]). A direct comparison in unselected patients with head and neck squamous cell carcinoma (HNSCC) even revealed a lower locoregional control rate after cetuximab versus cisplatinum.[198] Preclinically, EGFR amplification status in

combination with gene expression profiling has been shown to have predictive potential, suggesting that appropriate patient stratification is necessary to guide anti-EGFR therapy.[199] In addition, a combined approach of molecularly radiolabeled anti-EGFR antibodies plus radiotherapy may have the potential to improve curative outcomes.[200] As also shown preclinically, EGFR tyrosine kinase inhibitors may be able to offset the negative impact of KRAS mutations on local tumor control after radiotherapy.[201] The heterogeneity of the results suggests the need to improve patient selection and preclinical testing of combined modality drugs.

PI3K/AKT/mTOR and the Ras-Raf-MEK-ERK Pathway

Inhibitors of the PI3K/AKT/mTOR and the Ras-Raf-MEK-ERK pathways aim to target important signal transduction routes within RTK signaling. Constitutive activation of the mammalian target of rapamycin (mTOR) is a key PI3K/AKT signaling molecule that contributes to radioresistance. Dual PI3K/AKT/mTOR inhibitors are currently under investigation and have shown promising therapy improvement for patients with non–small cell lung cancer (NSCLC) with Ras mutations.[202]

The *Ras proteins* (H-Ras, K-Ras4A, K-Ras4B, and N-Ras) are GTPases and are attached in their active state (GTP bound) to the inner surface of the cell membrane. The Ras proto- oncogene, predominantly K-Ras, is mutated in about one-third of human cancers. Activating mutations are frequent in adenocarcinomas of the pancreas (up to 90%), colorectum (about 50%), and the lung (about 30%).[203] The processing and membrane attachment of the functional Ras are governed by farnesyltransferases, which are the molecular target for specific pharmaceutical inhibitors of activated Ras.[204] Activated Ras has an effect on various downstream molecules, including *PI3K*.[205] Signaling mediator molecules of PI3K include phosphoinositide-dependent kinase 1, Akt, protein kinase C, and subsequently the nuclear transcription factor nuclear factor kappa B (NF-κB). The cellular responses on activation of the PI3K pathway are cell type specific and include changes in gene expression, cell cycle progression, survival, and apoptosis. The tumor suppressor protein *PTEN* negatively regulates the PI3K/Akt pathway. Akt overexpression or hyperactivity and PTEN mutations are

found in numerous human malignancies.[206] Therefore, Ras proteins and their signaling pathways represent attractive targets for combined radiotherapy treatment. To date, most Ras-Raf-MEK-ERK inhibitors have only been tested as monotherapies and warrant further investigation in combination with radiotherapy.

VEGFR-Mediated Signaling

For neoangiogenesis the VEGF plays an important role in cancer therapy as there is almost no angiogenesis in adults except in growing tumors. Transmembrane receptors for VEGF and related ligands include VEGFR-1 (Flt-1), VEGFR-2 (KDR/Flk-1), VEGFR-3 (Flt-4), neuropilin-1, and neuropilin-2.[207] Upregulated VEGFR expression has been found after ionizing irradiation.[208,209] Besides normalizing the tumor micromilieu,[210] inhibition of radiation-induced VEGF/VEGFR signaling represents the rationale for combining anti-VEGF strategies with radiotherapy. First clinical trials combining anti- angiogenic drugs with radiotherapy are awaiting randomized phase III results. A summary of the clinical progress can be found in Hamming et al and Goedegebuure et al.[211,212]

Immune Checkpoints

Immune therapy today uses predominantly checkpoint blockade, targeting the PD protein 1 (PD-1)/PD ligand 1 (PD-L1) and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4). This immune checkpoint blockade (ICB) relies on the abundance and activity of immune effector cells within the TME.[149] For tumor infiltration, immune cells require a normal vasculature (see earlier). Radiotherapy has the potential to reprogram non-immune "cold" TMEs into immunoreactive "hot" tumors, thereby facilitating ICB and in parallel promoting neoantigen expression on the tumor cell surface.[213] Radiotherapy- induced DNA damage can induce the cytoplasmic DNA–sensing cyclic guanosine monophosphate–adenosine monophosphate synthase (cGAS)-stimulator of interferon genes (STING) pathway, which induces type I interferon production and inflammatory cytokine secretion necessary for T-cell infiltration into the TME.[214,215] Radiotherapy combined with ICB has been shown to enhance so-called abscopal effects (ie, response of tumor deposits not directly exposed to radiation) in numerous

clinical and preclinical studies.[216] The immunologic effects of different types of radiation are currently poorly understood. ICB concentrations, fractionation schemes, and radiotherapy doses as well as the optimal sequence of ICB and fractionated radiotherapy are currently being investigated for combined ICB-radiotherapy optimization.

Wnt Signaling

Wnt proteins are diffusible growth factors that bind to specific surface receptors (Frizzled) and trigger distinct intracellular pathways leading to cell growth.[217] Wnt signaling involves the tumor suppressor protein adenomatous polyposis coli (APC) and regulates by phosphorylation the steady-state levels of cytosolic β-catenin. An increased level of β-catenin facilitates its transit into the nucleus, activation of transcription factors, and subsequently transcription of β-catenin target genes, including *MYC*, *JUN*, *CCND1*, and *ALDH1A1*.[218,219] The aberrant activation of Wnt signaling caused by mutations in the β-catenin and *APC* genes are typical findings in colon cancer and melanoma but also have been identified in a large variety of other human cancers. Wnt/β-catenin signaling has been shown to play an important role in tumorigenesis, CSC self-renewal and differentiation, and radioresistance, making it a promising target for cancer therapy.[220]

Integrin-Mediated Signaling

Crosstalk between tumor cells and tumor stroma has emerged as an important determinant for tumor response to radiation and as a potential target for novel therapeutic combinations. Interactions between cells and extracellular matrix proteins are facilitated mainly by the integrin family of cell adhesion molecules.[221] Resistance-promoting effects by integrin-mediated adhesion to extracellular matrix were found in cell lines from solid tumors of the lung,[222,223] breast,[224] liver,[225] colon,[226] pancreas,[227-229] ovary,[230] prostate,[231] brain,[232] and leukemia cells.[233] Certain integrins seem to communicate increased radiation and drug resistance, which is cooperatively influenced by RTKs like EGFR.[234,235] For example, α5β1 integrin, the “classic” fibronectin receptor, acts as a major antagonist of cell death induced by doxorubicin or melphalan in multiple myeloma,[236] by paclitaxel in breast cancer or small cell cancer and NSCLC,[237,238] or by

cisplatin or mitomycin C in NSCLC.[237] Additional studies underscored the important role of β1 integrins in promoting resistance against ionizing radiation.[239,240] In addition to regulating cell survival, cell-matrix interactions affect radiation-induced cell cycle arrest, that is, adhesion of cells to matrix proteins prolongs the G1 and G2 cell cycle blockage in parallel with enhanced activation of DNA repair pathways involving the checkpoint kinases Chk1, Chk2, Cdk1, p53, and diverse cyclins.[237,241-243] Following radiation exposure, the expression of several integrin subunits, including β1, β3, α5, and αv, is upregulated in human skin and lung fibroblasts,[227] endothelial cells, and keratinocytes,[244] as well as in tumor cells of the colon,[226] hematopoietic cells,[245] prostate,[246] lung,[247] brain,[248] and melanomas.[227] Generally, integrin-mediated adhesion to matrix proteins confers chemoresistance and radioresistance.[233,234,249,250] Integrin antagonists and monoclonal antibodies are currently under clinical investigation (summarized by Li et al).[251]

Transcription Factors

Transcription factors bind to the DNA and activate the expression of specific genes. Oncogenic transcription factors are overactive in most human cancers and contribute to the autonomy of growth signaling. Key dysregulated transcriptional programs in cancer cells and how they are altered upon radiotherapy provide opportunities for therapeutic intervention.[252] Transcription factors as such are not druggable at present (see earlier).

Cancer Stem Cells

Malignant tumors are composed of genetically and phenotypically heterogeneous cells in various differentiation states. Within this pool, CSCs are considered the major cell population responsible for tumor initiation, growth, and relapse as well as for metastasis formation and therapy resistance.[253] Evidence shows that CSCs, which constitute a rather small fraction of the tumor mass, are often stunningly resistant to cytotoxic therapies as compared to the bulk tumor cells.[254] This is one of the reasons why the reduction of tumor mass is not an adequate measure of therapy success.[18] The identification of CSC populations within a tumor represents a

promising strategy for prognosis, prediction, and also targeting of aggressive tumors (also see section “Molecular Stratification Toward Personalized Radiotherapy”). However, identification and targeting of CSC is challenged by the high inter- and intratumoral diversity of different putative stem cell populations and CSC plasticity during cancer evolution and treatment. The CSC phenotype does not describe a static subpopulation but rather a highly dynamic intrinsic property of a tumor cell. This means that the CSC pool might be reestablished by non-CSC tumor mass cells and cancer therapy can only be effective when eradicating both tumor mass and CSC simultaneously.[255]

Targeting the signaling axes of CSC alone and in combination with cytotoxic drugs and/or radiotherapy is one approach. For example, simultaneous application of radiotherapy and putatively targeting the CSCs using a monoclonal antibody to the CSC marker CD44 (specifically targeting CD44v6) showed significant higher tumor control rates compared to radiotherapy alone in vitro.[256] CSC signaling pathways often shared with normal stem cells include Notch, Hedgehog, and Wnt/β-catenin signaling.[257] Activated Wnt/β-catenin signaling, for instance, is one of the key pathways during embryonic development and is described for carcinogenesis, epithelial to mesenchymal transition, and radiation resistance, such as summarized by Yang et al.[220] The first clinical phase I trial in patients with previously treated metastatic or untreated tumors applying the Wnt signaling inhibitor ipafricept (FZD8-Fc, *OMP-54F28*) showed safety and resulted in stable disease in some of the patients analyzed but could not lead to partial or complete remission.[258] Another phase I trial investigated the combination of ipafricept with cytotoxic drugs (gemcitabine and nab-paclitaxel) in patients with previously untreated advanced pancreatic cancer, which improved therapy outcome. However, this combined therapy approach was also associated with increased toxicity.[259] In both trials, the expression of Wnt signaling genes as well as CSC genes was downregulated after therapy in comparison to their pretreatment expression.[258,259] Another promising example for CSC signaling pathway targeting is the monoclonal antibody demcizumab, which inhibits the Notch signaling pathway by preventing DLL4-mediated Notch signaling, and has been tested in combination with carboplatin and pemetrexed in metastatic nonsquamous NSCLC.[260] While again, at least grade 3 toxicity was

observed in the majority of patients because of the combined treatment approach, a high response rate was observed.[260] Many other combinations are being tested in early clinical trials, for example, as recently summarized by Philchenkov and Dubrovska.[261] Both preclinical and clinical trials studying combined treatment of these novel agents with radiotherapy are awaited.

Metastatic spread is caused by disseminated tumor cells with CSC characteristics that leave the primary tumor and settle and grow at distant hostile places in the body. The transport phase of those cells, then called circulating tumor cells (CTCs), through the blood system represents another attractive diagnostic and therapeutic target. However, there is still no standard definition of those CTCs. To date, the magnetic bead–mediated CellSearch system is the only U.S. Food and Drug Administration (FDA)-approved method for the enrichment of epithelial cell adhesion molecule (EpCAM) expressing CTCs. Within the context of clinical studies, but with no FDA approval yet, the RareCyte liquid biopsy platform is being used, which is based on the identification of nucleated cells, which express EpCAM and cytokeratin, but lack CD45.[262] Counts of EpCAM-positive cells show significant prognostic relevance for patients with breast and prostate cancer.[263-265] Further biomarkers for the identification of CTCs are under investigation in different tumor entities. Also, methods for CTC enrichment are evolving, such as patient-derived CSC/3D cultures, that are being accumulated from the patient's tumor cell culture. This method also formed the basis for a randomized clinical trial in patients with recurrent glioblastoma, where successful enrichment was based on increased positivity in CD44, CD24, and CD133 cells.[266] Patients receiving a selected chemotherapy based on the CSC assay showed very promising results, with a prolonged overall survival.[266]

Several CSC-directed therapies are being tested in phase I/II clinical trials. For the implementation in the clinics, this requires not only the development of appropriate, standardized methods for CSC-specific analyses for screening and to measure CSC response, but also selection of appropriate CSC-based clinical endpoints such as locoregional tumor control.[261]

The CSC niche as a tumor-supporting microenvironment resembles another potential target for anti-CSC therapies. The niche maintains and

sustains CSCs and orchestrates their fate decisions via extracellular matrix molecules, cell-to-cell contacts, pH value, vascularization, hypoxia, etc, that may induce, for instance, stem cell–related signaling cascades.[39] Thereby the niche also provides a protective microenvironment for CSCs, for example, hypoxia can induce quiescence of the cells.[45] Thus, the cells escape chemotherapy, which mainly attacks rapidly proliferating cells. However, the extracellular matrix molecules and their cognate receptors on the CSC surface represent further potential druggable targets. One example is the c-Met protein, which can be targeted by the multitargeted inhibitors cabozantinib or crizotinib.[267,268] The CSC metabolism, in part intrinsically regulated, also depends on the microenvironment and the given nutrition supply, comprising a targetable CSC feature. One example is a hypoxic microenvironment. Preclinical studies showed that application of the hypoxic cell sensitizer nimorazole prior to radiotherapy can lead to higher local control rates in a subset of HNSCC compared to radiotherapy alone,[269,270] but selection of patients requires further biomarkers.[269,271] Safety of nimorazole has been shown in the clinical setting.[272]

Epigenetics

A variety of epigenetic mechanisms contribute to tumor heterogeneity and to the initiation and maintenance of CSC traits. Per definition, epigenetics defines stable heritable changes in gene expression that are not caused by changes in the underlying DNA sequence.[35] Chromatin and histone modifications and DNA methylation are epigenetic key mechanisms that are influenced by cancer risk factors such as chronic inflammation, aging, and environmental changes including radiation. Replication of DNA methylation is highly error prone, and it is contemplated that not only genomic but also epigenetic instability drives tumorigenesis and heterogeneity.[68,273,274] Epigenetic alterations can silence or activate genes and thereby offer tumor cells two possible choices to rapidly evolve under therapy pressure, which can lead to therapy resistance and tumor relapse.[35] Epigenetic therapeutics can reverse those epigenetic changes and resensitize tumor cells. Epigenetic drugs such as enhancer of zeste homolog 2 (EZH2), isocitrate dehydrogenase (IDH), and bromodomain and extra-terminal inhibitors are currently under investigation in clinical trials.[275,276] IDH1

mutations lead to DNA and histone hypermethylation. The IDH1 R132 mutation is of particular interest because it can also act as a so-called neoantigen (*vide infra*). Peptide vaccines that capture this mutated region are currently under development and testing.[277] Epigenetic changes such as the IDH1 R132 mutation can directly affect tumor immune evasion because DNA hypermethylation and promoter methylation can regulate the expression of cancer antigens and foster the evolvement of neoantigens. Therefore, epigenetic inhibitors also play an important role in immunotargeting. How the epigenetic machinery is affected by radiotherapy is not yet fully understood, so few clinical trials are currently being conducted that combine epigenetic targeting with radiotherapy. (Note: The histone phosphorylation γH2AX mentioned earlier is the best-known epigenetic modification following radiotherapy, which is rapidly reversed within a few days.) Another well-known epigenetic example is promoter methylation of the O6-methylguanine DNA methyltransferase (MGMT) gene, a DNA mismatch repair gene, which results in suppressed MGMT enzyme activity and increased sensitivity of glioblastoma to temozolomide.[278]

Antitumor Immunity

Mutagenesis as well as genomic and epigenomic instability in the tumor can lead to the expression of tumor-specific mutant proteins (neoantigens) that are not present on normal cells.[279] Neoantigens are short peptides presented by major histocompatibility complexes on the tumor cell surface and thereby become recognizable to T cells as foreign antigen. Those neoantigens resemble attractive immune targets with minimal risk of autoimmunity and immune tolerance, because of their exclusive presentation on the surface of tumor cells. Also, virus antigens can be released by tumors with a viral etiology (eg, human papillomavirus [HPV]-caused cancers of the cervix and the oropharynx). However, neoantigens arise in most cases from unique mutations, which complicates identification and needs individualized targeted immunotherapy. Current advancements in proteomics, genomics, and sequencing coupled with epitope prediction algorithms are speeding up the future development of such therapy approaches. Immune checkpoint inhibitors targeting CTLA-4 and PD-1

were shown to provide clinical benefit in melanoma,[280] NSCLC, and others.[281] In recent years, clinical studies have been investigating them not only in second-line therapy or later but also—often in combination with cytotoxic drugs—in first-line therapy such as in patients with recurrent or metastatic cervical cancer[282] or HNSCC.[283] Recently, a randomized, double-blind, phase III clinical trial in patients with locally advanced cervical cancer has shown, that the addition of pembrolizumab to primary radiochemotherapy leads to significantly improved progression-free survival (*clinicaltrials.gov*, NCT04221945).[284] However, this combined therapy is associated with an increasing severity of therapy-related side effects and thus requires optimal patient selection in the future.

Also, cell-based therapies, including engineered bispecific T cells and chimeric antigen receptor T cells have been shown to be therapeutically active in several cancers, including leukemia.[285,286]

Radiation therapy has been increasingly shown to cause systemic activation and local expansion of CD8+ T cells in preclinical as well as clinical studies, which is due to the cell surface localization of many tumor-associated antigens as well as presentation of neoantigens.[287] The combination of radiotherapy and immune checkpoint inhibitors has not only been shown to be tolerable in clinical studies but may also suggest a radiotherapy-enhanced response rate to immunotherapy in some but not all tumor entities.[288-290] More clinical studies assessing the combinational effect of radiotherapy plus immunotherapy and biomarkers for appropriate patient selection are needed.

Human Papillomavirus

Oncogenic viruses such as HPV are contributing to carcinogenesis and are driving malignant progression. Papillomaviruses are small, nonenveloped, double-stranded circular DNA viruses. More than 200 HPV genotypes have been identified, including low-risk and high-risk subtypes.[291] Especially the high-risk subtypes HPV16 and HPV18 are known to cause a variety of carcinomas such as cervical cancer, oropharyngeal cancer, and anal cancer. While traditional risk factors like tobacco use have been declining in recent years, a noteworthy upward trend in the incidence of HPV-driven cancers has emerged. The most effective approach to address this rising trend is to

prevent HPV infection. Vaccination programs for youth are being implemented worldwide to address this pressing issue.[292,293]

In contrast to most viral infections, where virions are produced directly in the target cell, the syntheses of new HPV virions occurs only after the target cell has undergone mitosis, followed by differentiation of one of its daughter cell.[294] HPV infects proliferating cells in the basal layer of stratified squamous epithelia following microtrauma, and leads to the establishment of the HPV genome as extrachromosomal elements or episomes. Since HPV genomes lack the necessary replication machinery, they rely on the host's DNA replication machinery to replicate viral DNA.[295] During early infection, the virus remains relatively inactive but prevents the cell from entering a resting phase (G0). After undergoing differentiation, virus-infected cells remain active in the cell cycle. In the suprabasal layers, some cells are still able to reenter the S phase in order to replicate HPV genomes and synthesize virions. When the epithelial cells reach the outer layer, the HPV virions are released.[294]

HPV infection triggers an immune response, but the virus has evolved sophisticated mechanisms to evade immune clearance, including interference with antigen processing and presentation. Despite these evasion mechanisms, HPV-specific immune responses can occur in HPV-driven cancers, which suggests that the immune system can still recognize and respond to HPV infection.[296] The presence of an HPV-specific immune response is a strong prognostic marker for patients with HPV-driven cancer, with significantly improved disease-specific survival in those with detectable HPV-specific T cells.[297,298] This highlights the role of the immune system in controlling HPV-driven cancer growth and metastasis.

HPV carcinogenesis is driven by two key viral oncoproteins, E6 and E7, which inactivate two important cellular tumor suppressor proteins—p53 and pRb, respectively. This inactivation is a fundamental step in the development of HPV-associated cancers, since it disrupts the normal control of cell cycle progression, leading to uncontrolled proliferation and malignant transformation of the affected tissue.[299,300] While increased E6 and E7 expression is associated with viral DNA integration into the host genome, carcinogenesis has also been observed in cases lacking integration, where the presence of viral episomes was identified.[301]

The E6 oncoprotein targets and degrades p53, a critical regulator of cell cycle arrest and apoptosis. The loss of the tumor suppressor gene *p53* leads to defective control at the G1/S and G2/M checkpoints and subsequently to uncontrolled cell cycle progression.[302] The HPV E7 oncoprotein binds to proteins of the pRb and targets them for degradation. The degradation of Rb proteins removes the inhibitory effect of Rb on E2 transcription factors inducing the expression of genes involved in S-phase progression, initiating the cell cycle.[303] The inactivation of the pRb pathway by E7 also disrupts the normal negative feedback loop that controls the expression of the tumor suppressor protein p16. Normally, the Rb-E2F pathway suppresses the transcription of the *CDKN2A* gene, which encodes for p16. However, when the pRb pathway is inactivated, p16 expression is no longer suppressed, leading to its overexpression, which is then detected histologically by p16-positive staining of the tumor cells[304] (see Figure 2.5).

In addition to its direct interaction with Rb, HPV infection can also trigger epigenetic changes that further contribute to Rb inactivation.[305] For instance, HPV can induce the expression of lysine demethylases, such as KDM6A and KDM6B, which remove repressive methyl groups from histone H3K9. This histone modification, known as H3K9 demethylation, can promote the recruitment of transcription factors to Rb-controlled promoters, leading to the activation of E2F-dependent genes and Rb inactivation.[306,307] HPV infection also affects the expression of microRNAs and other noncoding RNAs, which can further alter gene expression and contribute to carcinogenesis.[308]

The heterogeneity of HPV-driven cancers, resulting from a wide range of factors such as the level of HPV protein transcripts, the integration or episomal state of HPV DNA, the anatomic location of the cancer, or the immune response, can have a significant impact on both the prognosis and treatment of patients with HPV-driven cancer.[300] HPV-driven HNSCC is more radiosensitive than non–HPV-driven carcinoma, which is due to their cell cycle dysregulation (*vide supra*) including impaired DNA DSB repair capacity.[309]

This heterogeneity highlights the complexity of HPV-driven cancers and the importance of considering these factors when determining treatment options for patients.

Radiation-Induced Gene Expression

Radiation may significantly modify gene expression.[310] Many of the transcriptionally activated proteins have been shown to be centrally involved in the pathogenesis of radiation damage or to modulate the effect of radiation on tumor cells. Early responses may occur within hours after irradiation and involve mostly transcription factors such as the proto-oncogenes *JUN*, *FOS*, *JUNB*, and early growth response gene 1 (*EGR1*).[149] Sustained activation of early radiation response genes such as NF-κB may contribute to late radiation damage.[311] Other examples of radiation-induced genes that may occur early and/or late after irradiation include TGF-β, TNF-α, basic fibroblast growth factor, PDGF, interleukin 1 (IL-1), and EGFR.[312-314]

Gene expression and DNA-binding activity of *NF-κ B* are induced soon after ionizing radiation.[315] NF-κB is a sequence-specific DNA-binding protein complex that binds to DNA as a dimer. According to its multiple functions, NF-κB can also be activated by a variety of agents, for example, membrane receptors such as TNF receptor or Toll-like receptors and oxidative stress. Radiation-induced activation of NF-κB is mediated by IκB kinase (IKK).[316] This response does not depend on a nuclear signal, as it also occurs in enucleated cells.[317] However, it has been shown that ATM is required for chronic activation of the transcription factor NF-κB.[318] NF-κB acts in an antiapoptotic way and mediates radioresistance.[319]

Radiation exposure induces immediate and sustained *TGF-β1* gene expression, as well as activation of this cytokine.[320] On transcriptional activation TGF-β is produced as an inactive latent form and secreted. Latent TGF-β is stored in the extracellular matrix and proteolytically activated in irradiated tissues.[321] Active TGF-β1 binds and activates the TGF-β1 type I receptor, resulting in TGF-β1-dependent gene expression, inducing, for example, p21, p27, collagen, and tissue inhibitor of metalloproteinase (TIMP).[15,322] This is most likely responsible for the cellular effects of TGF-β, such as modulation of proliferation, differentiation, and radiation sensitivity of fibroblasts, and for the biochemical events (eg, collagen deposition, characteristic of radiation-induced fibrosis). In addition, TGF-β secreted by tumor cells on irradiation contributes to the development of radiation-induced fibrosis.[323] Intervention of TGF-β-mediated effects (eg, by

TGF-β1-neutralizing antibodies and superoxide dismutase) offers a promising strategy to prevent radiation-induced fibrosis. Moreover, a recent preclinical study showed that combined inhibition of TGF-β and PDGF with small molecules is a promising approach in diminishing radiation-induced lung toxicity.[324] Aside from fibrosis, TGF-β has been demonstrated to reduce latency, promote aggressive tumor growth, and increase estrogen receptor–negative breast cancers.[325] Moreover, the radiosensitivity of cancer cells can be enhanced by TGF-β-directed treatments.[326,327]

TNF-α belongs to the group of proinflammatory cytokines involved in radiation-induced normal tissue damage, such as pneumonitis and lung fibrosis. Immediately after irradiation, TNF-α is transcriptionally upregulated and released by the bronchiolar epithelium. TNF-α enhances phagocytosis and cytotoxicity by neutrophilic granulocytes and modulates the expression of other cytokines such as IL-1 and IL-6.[328] Experimental data show that also tumor lines, particularly pediatric sarcomas, may produce large quantities of bioactive TNF-α after irradiation, which is of potential importance for tumor response and for normal tissue reactions after radiotherapy.[329]

Tracking of genetic changes during and after ionizing radiation will further elucidate the molecular and basic impact of how cancer and normal cells respond to radiation and may serve as predictors for therapy response.

Genome Instability and Mutation

Cells may survive radiation despite unrepaired or misrepaired DNA damage, that is, with mutations or chromosomal aberrations. These may remain silent or result in radiation-related secondary primary cancers or, as germline mutations, cause hereditary disease.[330-332] In addition to directly induced mutations, radiation may induce a heritable, genome-wide process of instability (ie, genomic instability) that leads to an enhanced frequency of genetic changes occurring among the progeny of the original irradiated cell, which is transmissible over many generations of cell replication.[333] Whereas most mutations induced directly by radiation involve loss of large parts of the tested gene, leading to a loss of heterozygosity, most mutations resulting from radiation-induced genomic instability involve point mutations and small deletions.[333,334] While some studies, particularly on

thyroid cancer in children after the Chernobyl fallout, suggest a nonrandom pattern of chromosomal damage, generally no fingerprint alterations have been identified that would unequivocally indicate radiation-induced cancer.[332]

Molecular Stratification Toward Personalized Radiotherapy

The treatment decision for patients with malignant tumors is clinically based on anatomic location and histopathologic features. To verify the anatomic extent of the disease, the tumor, node, metastases classification has been introduced, which considers the size of the primary tumor, the regional lymphatic spread (lymph node metastases) as well as distant metastases. The cell type and histopathologic features are being assessed based on the World Health Organization classification. With recent advances in molecular pathology, implementation of DNA or RNA sequencing of cancer and normal tissue genomes, single-cell analysis, and biologic imaging techniques, a better understanding of the tumor and radiation biology is being gained and is leading toward molecular subclassification of tumors and, thus, to molecular stratification of patients along with clinically established biomarkers.

In patients with HNSCC and specifically in those with oropharyngeal carcinomas, the HPV infection status has been found to be associated with improved therapy response and prognosis. Preclinical studies showed that HPV infection leads to increased radiosensitivity in HNSCC cell lines.[309,335] Retrospective and prospective clinical studies including patients with HNSCC who received radio(chemo)therapy revealed that the HPV status is a strong independent parameter for locoregional tumor control, disease-specific survival, and overall survival.[336,337] After postoperative radiochemotherapy, patients with HPV-positive HNSCC showed an excellent locoregional control of nearly 100%,[338] suggesting that these patients may benefit from de-escalation therapy, such as by reducing the radiation dose. A number of clinical studies on radiation dose de-escalation in the postoperative treatment of HPV-driven oropharyngeal squamous cell carcinoma (OPSCC) has been set up in the past (*clinicaltrials.gov*, NCT03396718).[339-341] The first of the abovementioned clinical studies, conducted in patients with HPV-driven OPSCC who are undergoing

surgery, have been finished and showed that this is safe and reduces radiation-induced side effects while achieving high tumor control probability.[339,341]

Patients with HPV-negative tumors who received postoperative radio(chemo)therapy could be further stratified by CSC marker expression as well as tumor hypoxia, which is in line with radiobiologic knowledge. Patients with HPV-negative, low-hypoxic, and low CSC marker–expressing tumors also showed a superior locoregional control, while patients with hypoxic, CSC marker–overexpressing tumors showed a poor locoregional control and might benefit from intensified therapy regimes.[342] In contrast to the patients receiving postoperative radiochemotherapy, where only a few remaining tumor cells may have been left, the tumor volume is an important parameter for patients who are undergoing primary radiochemotherapy. The tumor volume is associated with the CSC number and is therefore important for local control. CSC marker expression reflecting CSC density varies widely between different tumors and can further enhance the powerful predictor tumor volume. Also patients receiving primary radiochemotherapy could be stratified for their risk of locoregional failure based on their HPV status, tumor hypoxia, and CSC marker expression levels within the tumors.[343] DNA methylome–based analyses of tumor hypoxia further improved the identification of patients with HPV-negative HNSCC who are on high risk for developing locoregional recurrences after postoperative or primary radiochemotherapy.[344,345] Also, several biomarker panels have been developed that may help to identify patients with radiosensitive and/or radioresistant HNSCC, such as that of the Radiation Oncology Group of the German Cancer Consortium (DKTK-ROG).[346-351] Overall, these studies highlight the potential for refined patient stratification for specific treatment intensification or de-escalation based on molecular biology. For the application of biomarkers for patient stratification in the clinics, the selection of the “most suitable” biomarker panel still remains a challenge.

An important issue in research on biomarkers for radiotherapy is that parameters reflecting tumor response may change during treatment. For example, hypoxic tumors may reoxygenate during treatment, and it has been demonstrated that this is associated with improved local control compared to tumors with residual hypoxia.[352,353] Therefore, more extensive

investigations into biomarker dynamics, by imaging, repeat tumor biopsies, or liquid biopsies, are underway in several (pre-)clinical studies to further improve their predictive value.

The identification of predictive biomarkers for the development of normal tissue toxicity in the individual patient is also a relevant issue in terms of personalized radiotherapy. It is well recognized that the degree of radiation-related toxicity varies between patients, which may be partly due to genotypic variation. The study of germline genotypic variations and the large clinical variability associated with the response to radiotherapy is termed *radiogenomics*.[354] The overall aim of radiogenomics is to identify patients with common genetic variants who are particularly likely to develop normal tissue toxicity following radiotherapy. A meta-analysis of genome-wide association studies in prostate cancer identified two single-nucleotide polymorphisms (SNPs), which are associated with late toxicity following radiotherapy in patients with prostate cancer: rs17599026 on 5q31.2 with urinary frequency and rs7720298 on 5p15.2 with decreased urine stream.[355] Also for patients with breast cancer, a recent multicenter study identified several SNPs that are associated with radiation-induced late toxicity such as induration, breast lymph edema as well as arm lymph edema, underlining the evidence of the association of SNPs with respective toxicity endpoints.[356]

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CHAPTER 3

Biologic Basics of Radiation Oncology

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Ionizing radiation therapy (RT) involves the utilization of high-energy electromagnetic waves or particles that interact with tissue atoms or molecules with enough energy to eject one or more orbital electrons. This ionization can generate reactive oxygen species (ROS) and overall contribute to damage to a wide array of cellular compartments and membranes. DNA is the primary cellular target of ionizing radiation. Radiation can cause direct damage to DNA or indirectly damage DNA and other structures by the radiolysis of water molecules and subsequent formation of ROS. The effect and type of damage inflicted depend on factors such as radiation quality, dosage, and time available for repair. Additionally, radiation exposure can detrimentally affect both DNA repair mechanisms and antioxidant defense mechanisms such as glutathione, superoxide dismutase, and catalase. DNA damage accumulation can impair cell cycle progression, and oxidative stress can contribute to organelle damage. These collectively lead to the activation of cell death mechanisms. Beyond the cellular level, the overall tumor microenvironment (ie, blood vessels, immune landscape) is also altered by radiation exposure. This chapter details the biologic basics of RT and sheds light on how the physics of RT influences both tumor and normal tissue damage versus repair.

BIOPHYSICS OF TISSUE DAMAGE FROM RADIATION

The interaction between radiation and tissues varies significantly between uncharged particle radiation (eg, x-rays, γ-rays, neutrons) and charged particle radiation (eg, α and β particles, protons, carbon ions). Uncharged particles may go through tissue with no interactions at all or may deposit their energy in a few large interactions. For massive uncharged particles

like neutrons, these interactions are directly with the nuclei via neutron capture (thermal neutrons) or elastic and inelastic scattering (intermediate and fast neutrons). For massless uncharged particles like x-rays and γ-rays, these interactions are with outer electrons (the Compton effect) or less commonly with inner electrons (the photoelectric effect), producing secondary electrons that damage DNA. In comparison, charged particles interact with electrons and the nucleus of almost every atom it passes due to Coulombic forces.

The mechanistic differences in how radiation interacts with matter influence tissue penetration and the density of energy deposition in radiation tracks of any given RT. Linear energy transfer (LET) describes the rate of energy deposition of charged particles released during radiation exposure and has deep implications for the type of DNA damage produced. The secondary electrons produced by x-rays and γ-rays have low-LET values (0.3-2 keV/μm).[1,2] LET is inversely proportional to the square of the particle's energy; therefore, as charged particles lose energy penetrating tissues, LET increases and the particle deposits a large portion of its energy at the end of its track, producing a peak of dose deposition (ie, Bragg peak). This explains why protons have high-LET values (10 keV/μm)[1,2] at the end of their tracks when compared to that of secondary electrons produced by x-rays and γ-rays, but have relatively low LET at high energies (>100 MeV) upon entry. LET is also proportional to the particle's mass, so heavier charged particles like carbon ions (10-100 keV/μm) and α particles (114 keV/μm) have the highest LET at the end of their tracks of any particles used clinically. These differences in LET are important given that they impact the extent and mechanism of tissue damage.[3] Low-LET radiation requires about 1,000 ionization tracks to deposit 1 Gy in a hypothetical 8 μm cell, while high LET requires only about four tracks. The density of ionization events in each of these tracks is much lower with low-LET radiation, and thus less energy is deposited over the distance of a track, which limits the complexity of tissue damage. High-LET radiation creates more dense energy deposition sites along its tracks, concentrating the damage to a smaller volume of tissue.

The principal contributor to cellular damage and death following radiation is DNA damage. High-LET RTs cause more direct and complex DNA strand breaks that contribute to cell death. Low-LET radiation causes

damage primarily (>70%) through indirect, oxidative stress that stems from the ionization of water within cells. These interactions result in the formation of highly reactive species such as hydroxyl radicals (·OH), through a process known as radiolysis. Hydroxyl radicals are extremely potent ROS and can cause significant cellular damage by modifying DNA, proteins, and lipids. Radiation also disrupts mitochondrial integrity and increases ROS production via leakage of electrons from the electron transport chain; these electrons react with molecular oxygen to produce superoxide ions ($O_2 \cdot^-$). Superoxide ions are highly reactive and contribute to DNA damage and are also broken down into other damaging ROS species such as hydrogen peroxide (H_2O_2) by superoxide dismutase enzymes. ROS not only contributes to direct cellular damage but also can damage the tumor parenchyma, especially the blood vessels,[4,5] and increase immune cell recruitment into the tumor microenvironment.[5] Catalase breaks down H_2O_2 into water and oxygen to help mitigate the harmful effects of radiation-induced ROS generation. Another key antioxidant defense mechanism includes the glutathione peroxidase/reductase system.[5] However, radiation itself can damage antioxidant enzymes, and damaged DNA prevents the replenishment of antioxidant enzyme levels; these effects amplify ROS-induced DNA damage. Of note, ROS induce base modifications, including 8-oxoguanine, that are typically repaired by alternate DNA repair pathways (ie, base excision repair) instead of repair pathways classically utilized to repair DNA double-stranded breaks (non-homologous end joining [NHEJ] and homologous recombination [HR]; see next section as well as Chapters 2 for further details on DNA repair pathways).[3,6,7]

Complex or Clustered DNA Damage and Repair Mechanisms

Differences in the type and severity of DNA damage determine the DNA repair pathways activated within cells (Figure 3.1). It is estimated that low-LET radiation results in about 50% to 70% single-strand, base, or isolated double-strand damage and 30% to 50% complex or clustered double-strand breaks (DSBs; termed “multiply damaged sites”).[8,9] Single-base, non-DNA helix–distorting lesions are resolved through base excision repair while bulky helix-distorting damages are repaired through nucleotide excision

repair. Single-strand breaks (SSBs) are repaired through base repair pathways, as well as through single-strand base repair. DSBs can be repaired using either the more accurate, but slower, S/G2-phase-restricted HR, which uses sister chromatids as a template, or the error-prone, non-cell cycle–restricted, more rapid NHEJ (see DNA repair mechanisms detailed in Chapters 2). Importantly, nearly 50,000 to 100,000 spontaneous DNA lesions per day (most commonly single strand or base damage) are generated within cells from naturally occurring oxidative stress or DNA replication errors within the body, and approximately 50 DSBs are said to occur per cell cycle within mammalian cells. As such, these DNA repair mechanisms are well conserved within cells, although they are most optimized for resolving *isolated* lesions. These mechanisms are less efficient in resolving locally multiply damaged sites in DNA, which are defined as having two or more damage sites within 1 to 2 turns of the DNA helix (ie, within 10-20 base pairs). These clustered DNA lesions are comprised of not only double-stranded DNA breaks but also oxidative stress–induced base damage.[8,10]

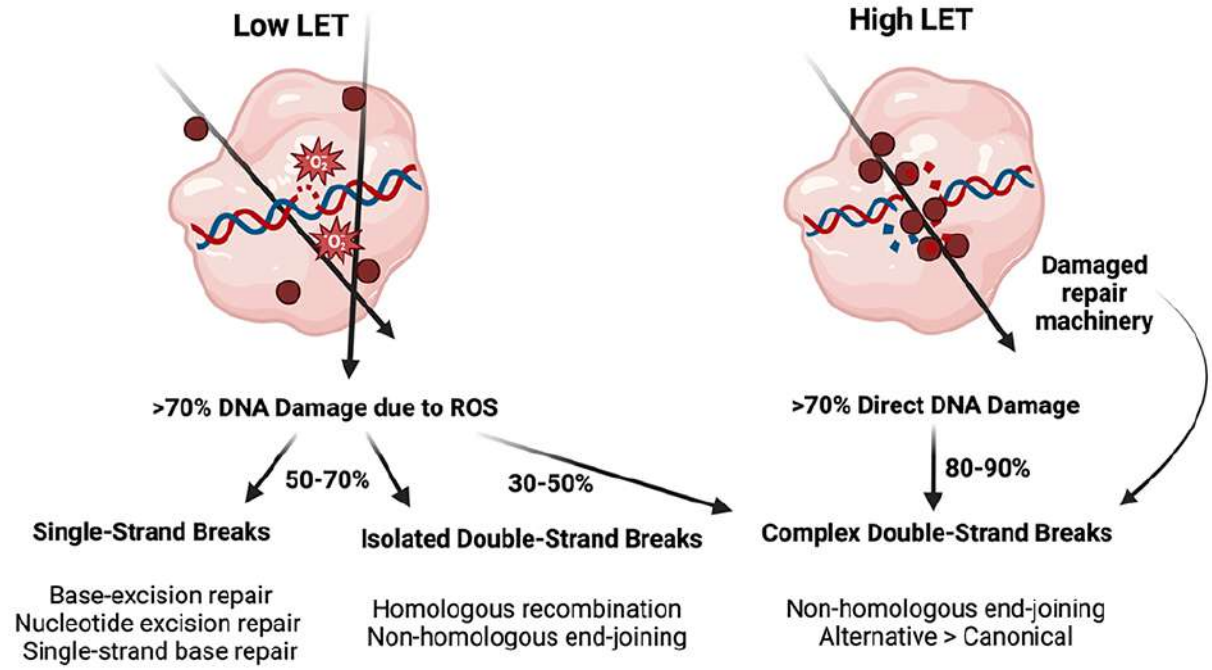

FIGURE 3.1 Differences in DNA strand damage and repair mechanisms activated by low versus high linear energy transfer radiation. (Created in BioRender: Bergom C. BioRender. 2025. https://BioRender.com/e74k396.)

As LET increases so does the percent of complex DNA damage created. It is estimated that proton beams can induce nearly 80% clustered lesions while α particles generate >90%.[11] Unlike the previously described repair mechanisms for isolated single-stranded, double-stranded, and base damage, it is well established that the efficiency of repair is reduced for complex lesions.[12,13] Numerous studies show a persistence of complex DNA damage for days to weeks following radiation exposure,[14-16] while low-LET-induced DSBs are commonly resolved in less than 24 hours.[3] Damage to DNA repair machinery is also reported with high-LET radiation, which contributes to the persistence of DNA damage that ultimately leads to chromatin fragmentation[17] and catastrophic genetic rearrangement.[3] It should be noted that the generation of complex lesions is thought to reflect the mechanism of DNA damage and repair induced by high versus low LET rather than the amount of energy deposited, since the extent of complex damage is greater with low-energy high-LET proton exposure compared to high-energy low-LET x-rays.[18] In line with these findings, a combination of low- and high-LET radiation has synergistic effects on cellular damage, likely due to the impaired repair machinery from high-LET radiation that sensitizes cells to further DNA damage from low-LET radiation.[19]

The DNA repair pathways are detailed in Chapters 2. In essence, DNA damage is detected by specialized “sensor” molecules that upon recognizing the damage initiate the activation of “transducer” protein kinase cascades. These stimulate the downstream effectors involved in the DNA damage response (DDR). One of these key kinase cascades is initiated by the ataxia telangiectasia mutated (ATM) protein, the deficiency of which results in heightened radiosensitivity and manifests as a complex human syndrome (ataxia telangiectasia). Another important kinase pathway is initiated by ATR (ataxia telangiectasia and Rad3-related), which identifies and rectifies stalled DNA replication complexes at the sites of DNA damage. The ATR pathway is primarily activated in response to SSBs. The third important kinase cascade involves DNA-dependent protein kinase (DNA-PK), which is a crucial component in the NHEJ pathway, which facilitates the repair of DSBs in DNA.

Early phases of DNA repair are marked by ionizing radiation–induced foci (IRIF), which congregate at DNA DSBs to signal the initiation of the DDR. The complexity and quantity of IRIF are sophisticated, varyingly

dependent upon factors such as the chromatin state where the DSB has occurred (ie, euchromatin is more easily accessed by DDR compared to heterochromatin) and the specific phase of the cell cycle during irradiation. In early stages of the IRIF event, the histone 2A subtype H2AX is phosphorylated by one of several phosphatidylinositol 3-kinase–related protein kinases, which include ATM, DNA-PK, and ATR. This phosphorylation results in the formation of γ-H2AX molecules that latch onto DSBs spanning several megabases along the neighboring chromatin, a phenomenon that can be conveniently identified via antibody tagging. This methodology, owing to its high sensitivity, has gained popularity as a go-to method for tracking DSB formation and repair processes.[20,21] The phosphorylated histone establishes interaction platforms for IRIF, facilitating the recruitment of repair and checkpoint molecules, subsequently activating further kinase-dependent pathways that pave the way for a coordinated downstream DDR response.

The exact cellular machinery that can contribute to repair of *clustered* DNA damage has yet to be fully elucidated; however, studies highlight complex activation of numerous DNA repair pathways—mainly alternative NHEJ. Alternative NHEJ, also called microhomology-mediated end joining, is the process by which short homologous sequences at the breakpoints of DNA are used to align DNA strands for ligation; this process is even more error-prone than NHEJ. Inhibition of poly(ADP-ribose) polymerase-1 (PARP-1), a protein that is critical for shifting cells from canonical to alternative NHEJ, further radiosensitizes cells to high-LET radiation.[22] Of note, these inhibitors are known to sensitize tissues to RT in general. However, it is postulated that its effects on alternative NHEJ may allow PARP inhibitors to more effectively sensitize cells to high-LET RT. Studies also suggest that the short fragments of DNA overhangs generated from complex lesions result in the inhibition of enzymes responsible for canonical, but not alternative, NHEJ, an effect that can also push cells toward HR during the G2 phase.[23] The presence of SSBs activates ATR pathways.[24] Interestingly, the DNA-PK catalytic subunit, a key complex involved in canonical NHEJ (see Chapters 2), is also thought to more specifically regulate the delayed repair of complex DNA damage compared to isolated SSBs.[19,25] Although the mechanisms contributing to DNA repair

are complex and influenced by the type of DNA damage, inhibition of DDR machinery has emerged as a key radiosensitization strategy.[26]

Oxygen and the Severity of DNA Damage

The presence of oxygen has critical effects on the severity of DNA damage. Oxygen interacts with damaged DNA free radicals to form DNA peroxides, which are stable and difficult for cells to repair. As such, these DNA peroxides effectively "fix" the cellular DNA damage. On the contrary, cells can more effectively repair DNA damage in hypoxic conditions through the interaction between DNA free radicals and H^+ ions from nonprotein sulfhydryl compounds; this contributes to tumor radioresistance.[27]

Figure 3.2 highlights the relationship between the partial pressure of oxygen and the relative radiosensitivity of tumors. The ratio of radiation dose needed in hypoxic conditions to oxic conditions is defined as the oxygen enhancement ratio, which ranges from 2 to 3 in normal tissues and with low-LET radiation treatment of tumors.[28] With high-LET radiation, this ratio is closer to 1, which signifies that a similar dose is needed in both conditions and the effectiveness of radiation treatment is less affected by oxygen presence. This makes high-LET radiation more suitable, in theory, for treating hypoxic tumors.

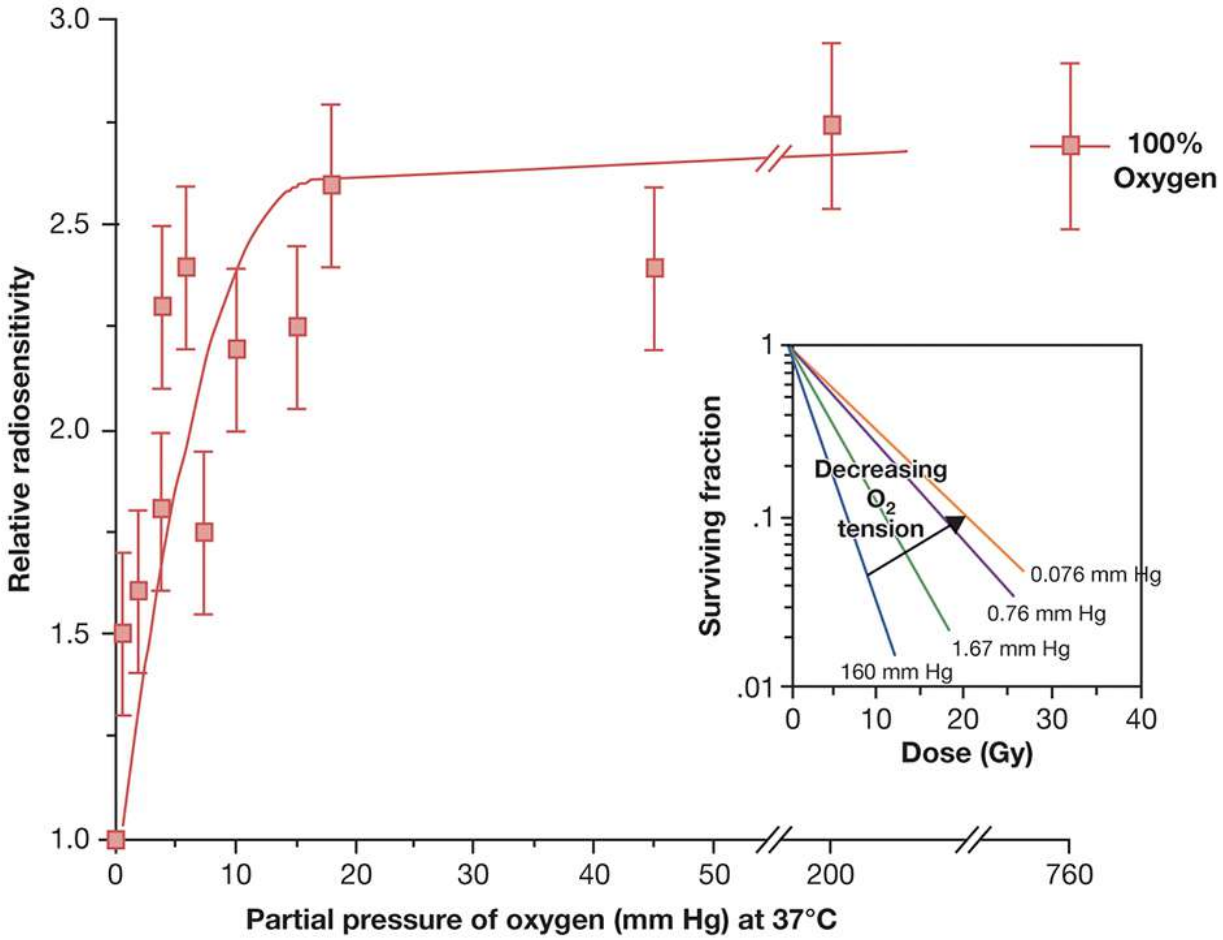

FIGURE 3.2 Curve relating cellular radiation sensitivity to partial pressure of oxygen at the time of irradiation. Data were obtained by scoring anaphase aberrations in Ehrlich ascites tumor cells, although similar curves have been obtained for killing of bacteria. About 50% of the total sensitization by oxygen is seen at a partial pressure of approximately 4 mm Hg at 37 °C. The inset shows survival curves for different levels of oxygenation.

This phenomenon extends beyond tumor control, as studies report a more severe reduction in coronary arterial radiosensitivity to low-LET radiation compared to high-LET radiation with hypoxic conditions,[29] which has critical implications for radiation-induced heart disease as well as brachytherapy for preventing restenosis after percutaneous coronary stent implantation.[30]

Cell Death Mechanisms

The ultimate goal of RT for cancer is to induce tumor cell death. The primary cell death pathway that is activated can differ based on radiation

type (eg, high vs low LET), the dose and fractionation scheme utilized, coadministration of chemo- or immune therapies, the tumor microenvironment, and cellular mutation profiles.

Apoptosis is a form of programmed cell death that can be activated through an intrinsic cellular pathway or extrinsic signaling. This form of cell death involves the shrinking of cells, chromatin condensation and DNA fragmentation, and subsequent formation of apoptotic bodies that are cleared by neighboring and immune cells. Importantly, apoptotic bodies maintain plasma membrane integrity that limits inflammation. Intrinsic apoptosis is driven by the activation of proapoptotic Bcl-2 family proteins (Bax and Bak) as a result of unrepairable DNA damage and/or endoplasmic/mitochondrial damage. Bax and Bak then trigger mitochondrial membrane permeabilization, which releases cytochrome C. Cytochrome C then activates caspase-9, which activates the effector caspases 3 and 7. These caspases cleave critical cellular proteins, including those in the cytoskeleton, nuclear lamin, and DNA repair pathways, leading to programmed cell death. Extrinsic apoptosis is primarily driven by extracellular activation of death receptors (eg, Fas and tumor necrosis factor receptor 1), which then activate caspase-8. Caspase-8 then activates the effector caspases 3 and 7.[31,32] Certain solid cancers such as colon, glioblastomas, and pancreatic tumors are known to often be more resistant to apoptosis due to overexpression of antiapoptotic proteins (Bcl-2 and Bcl-xl) or mutations in the p53 tumor suppressor protein, a key regulator of the intrinsic apoptosis pathway.[33] On the contrary, lymphomas and leukemias are often much more sensitive to apoptosis.

Mitotic catastrophe is the most common contributor to cell death following radiation exposure, and it occurs due to severe DNA damage that interferes with proper mitosis. Morphologically, these cells show multi- and macro-nucleation due to chromosomal mis-segregation, as well as areas of micronucleation due to acentric chromosomes.[34] Cells can die following mitotic catastrophe (ie, mitotic cell death) through activation of intrinsic apoptosis or entering a state of non-replication called cellular senescence (described further). Notably, these catastrophes are key players in initiating neoplastic changes and progression and as such are important mechanistically in driving secondary cancers. It is suspected that high-LET radiation increases susceptibility to mitotic catastrophe compared to low-

LET radiation given the extent of unrepairable clustered DNA damage that occurs with high-LET radiation.

Necrosis is a form of disorganized, unregulated cell death that results from severe tissue injury, and it is characterized by cell swelling, release of lysosomal enzymes, and loss of membrane integrity. The cells eventually rupture and trigger an inflammatory response. This form of cell death is more prominent with high-LET radiation, although can be seen with both low- and high-LET radiation. Necrosis is seen after a number of types of pathologic tissue injuries. After radiation, necrosis can occur from direct damage or by secondary immune responses triggered after radiation. Necrosis can be triggered by the opening of mitochondrial permeability transition pores (MPTs) following oxidative stress–dependent destabilization of mitochondrial membranes (ie, MPT-driven necrosis).

Necroptosis is a form of regulated cell death triggered by death receptor activation (eg, tumor necrosis factor family, interferon, and toll-like receptors) in response to both intra- and extracellular perturbations. These receptors initiate the formation of a necrosome complex comprised of receptor-interacting protein kinase 1 and 3 (RIPK1, 3).[34] This subsequently activates mixed-lineage kinase domain–like pseudokinase (MLKL), which is primarily responsible for the disruption of the plasma membrane and eventual cellular rupture. Notably, cells with increased caspase-8 are able to cleave and inactivate RIPK1 and 3, which prioritizes apoptotic cell death and prevents necroptosis.[35] Higher doses of radiation can decrease caspase-8 to push cells toward necroptosis-dependent cell death.[31] This pathway in general is thought to be highly immunogenic and increases the recruitment of immune cells that can promote antitumor responses (discussed in more detail in later sections).

Parthanatos is a form of cell death driven by the prolonged hyperactivation of PARP-1, which as previously described plays a key role in alternative NHEJ and is seen in cells with high levels of clustered DNA damage, severe alkylation of DNA, excess oxidative stress, and/or hypoxia.[31] Overactivation of PARP-1 consumes cellular NAD^+ stores to produce PARPs. Not only does this trigger a bioenergetic crisis from the loss of adenosine triphosphate (ATP) formation, but these polymers activate apoptosis-inducing factor (AIF) that translocates to the nucleus to trigger DNA fragmentation and chromatin condensation.[34]

Ferroptosis is a form of regulated cell death initiated by iron- and ROS-dependent lipid peroxidation. It is characterized by mitochondrial contraction and reduction in or loss of mitochondrial cristae. Specifically, radiation-induced oxidative stress consumes the antioxidant glutathione and increases expression of ACSL4, an enzyme that metabolizes lipids and plays a key role in upregulating membrane lipid peroxidation.[36,37] Radiation-induced ferroptosis has important implications not only in cancer cell death and the development of antitumor immunity, but also in normal tissue damage, including injury of the skin, lungs, and intestine.[37]

Autophagy is a regulated cellular recycling machinery defined by the engulfment of damaged cellular material by autophagosomes that then fuse with lysosomes to degrade the material.[38] This process is upregulated in response to radiation, and studies show that excessive upregulation in autophagy can lead to cell death and enhance radiosensitivity.[39] Notably, basal levels of autophagy can help maintain cellular homeostasis by clearing damaged proteins and organelles in response to radiation.[40] As such, the interplay between radiation and autophagic cell death is complex and dependent on both the extent of radiation-induced damage and level of cellular autophagic activation.

Lysoptosis is a highly evolutionarily conserved form of cell death, and the hallmark of lysoptosis is the leakage of cathepsin proteases from lysosomes triggered by increased permeabilization of lysosomal membranes.[41] This pathway is inhibited by cysteine protease inhibitors that are known to be upregulated in cancers (eg, cervical cancer), and inhibition of these proteases has been shown to radiosensitize cancer cells by upregulating lysoptosis.[42]

Methuosis is a cell death pathway that primarily occurs in cancers with activating H-Ras or K-Ras mutations, although there is some level of methuosis that can be triggered in response to radiation in cancers that do not contain H- or K-Ras mutations.[43] Morphologically, the dying cells exhibit large, fused, fluid-filled vacuoles formed through macropinocytosis. These vacuoles displace the cytoplasm, and eventually cells lose plasma membrane integrity and the resulting phenotype resembles necrotic cell death.[44]

Senescence is a state of irreversible, non-replicative cell cycle arrest that can be upregulated due to both aging- and stress-related pathways, such as

radiation-induced DNA damage and subsequent cell cycle dysregulation. Cellular senescence is commonly triggered from sublethal, sustained radiation exposure while higher doses/high-LET radiation triggers more apoptosis compared to senescence.[43,45] Morphologically, senescent cells are enlarged, resistant to apoptosis, and secrete proinflammatory molecules (commonly defined as the senescent-associated secretory phenotype [SASP]). This SASP can trigger neighboring cell damage and recruit immune cells, further augmenting antitumor effects in the initial stages.[46,47] However, the presence of senescence cells chronically can break down extracellular matrices to promote tumor invasion and metastasis, suppress immune cells, and become resistant to future therapies. As such, newer evidence suggests that the use of senolytics to remove senescent cells may allow for the beneficial antitumor initial stages of post-RT effects, while preventing the chronic detrimental effects.[46,47] Importantly, the SASP-related processes also contribute to damage and senescence activation within the surrounding tissues that increase the risk for cardiovascular disease,[48] pulmonary fibrosis,[49] bone damage,[50] and other chronic pathologies. Whether senolytic strategies can prevent these effects is currently unclear.

Inflammation and Radiation

Inflammation following RT has been linked to DNA damage and oxidative stress, as well as activation of nonapoptotic cell damage/death pathways—mainly necrosis, senescence, and mitotic catastrophe. Evidence shows that mitotic catastrophe following DNA DSBs can activate the cytoplasmic nucleic acid sensors: stimulator of interferon genes cyclic GMP-AMP synthase (STING-cGAS).[51] STING-cGAS pathway subsequently activates nuclear factor-κB and upregulates interferon gamma (IFNγ) signaling as well as other cytokine cascades to promote inflammation[52-54]; importantly, these pathways are seen in many cell types within the tumor microenvironment.[26] In addition to the release of cytokines, radiation increases major histocompatibility complex I expression, which allows for neoantigen presentation and subsequent recruitment of $CD8^+$ T cells. Following RT, tumor cells also release damage- associated molecular patterns (DAMPs) (eg, ATP, calreticulin, high mobility group box 1), which

allow for cross-presentation by dendritic cells in the tumor microenvironment and activation of phagocytic tumor clearance.[26,55] Recent studies critically link the persistence of DNA damage with the extent of inflammation, as inhibition of DDR machinery further enhances IFNγ signaling, release of cytokines, and neoantigen presentation by tumor cells. This is commonly described as turning a tumor "hot" and allows for tumor cell killing by immune cells such as natural killer cells and $CD8^+$ T cells.[26]

Interestingly, local tumor radiation has rarely been associated with shrinkage of metastatic tumors, outside of the treatment field an effect termed the "abscopal effect." This effect is linked to the migration of antigen-presenting dendritic cells from the tumor microenvironment to lymph nodes, where they can activate tumor-specific $CD8^+$ T cells.[56] These activated T cells then target metastatic tumors. The abscopal effect can be exacerbated in models that combine RT with immune checkpoint inhibitors,[57] and enhancing this effect robustly in patients with cancer with combined radiation and immunotherapy is a focus of a number of investigations.

The effect of radiation on antitumor immunity can be complex. Studies show that ablative RT can promote antitumor inflammatory responses; however, paradoxically some studies also report increases in immunosuppressive myeloid-derived suppressor cells and regulatory T cells in the tumor microenvironment following RT.[58,59] The balance between antitumor immunogenicity versus immunosuppression is likely influenced by the varying sensitivities of immune cells as well as the vasculature to radiation damage, which greatly influences the tumor microenvironment.[58] Activated and regulatory T cells are more radioresistant, while B cells are highly radiosensitive. Macrophages and dendritic cells are relatively radioresistant; however, following high-dose radiation, dendritic cells have impaired ability to activate T cells.[58,60] Fractionated dosing is less cytotoxic to the vasculature, and low-dose fractionations (0.5-2 Gy) of radiation in fact may normalize dysfunctional vessels within the tumor stroma.[61] On the contrary, ablative doses can severely damage the vasculature and promote killing of tumors. Despite these benefits, areas of hypoxia promote radioresistance.[58] As such, when selecting appropriate RT doses and regimens, one needs to consider the complex impact they have on the inflammatory milieu and tumor microenvironment.

NORMAL TISSUE RESPONSES TO RADIATION INJURY

Kinetics of Tissue Injury versus Regeneration

The rate of cell cycle turnover greatly influences normal tissue responses to RT, as well as damage from RT. In general, tissues with high turnover, such as the small intestine, hair follicles, and lymphoid tissues, have more early damage from RT given the importance of DNA integrity for cell cycle progression. This principle is one of the primary drivers of tumor death from radiation, but this effect in normal tissues can lead to many radiation-induced side effects.

The ability of a tissue to regenerate also influences the extent and prolongation of damage from RT. In homeostatic states, the rate of cell production and loss are balanced, and the cell loss factor ϕ, which is the fraction of newly produced cells that die or stop dividing, is equal to 1. During tissue regeneration and in solid tumors, ϕ is typically less than 1. Tumors with a low ϕ are more radioresistant. ϕ can also change with tumor size, with increasing values with increasing tumor size. After radiation therapy, some rapidly regenerating normal tissues have ϕ closer to 0, while additional tissues—such as skin—may have reduced ϕ to approximately 0.5 and regenerate more slowly, and other tissues such as seminiferous epithelium have little change in ϕ. As such, cell counts (eg, sperm) remain reduced for months to years following RT, and this is in direct proportion to the number of cells depleted during therapy.

The rate of cellular turnover influences the temporal changes in tissues after radiation. Platelet and white blood cell counts decrease most quickly after radiation to the bone marrow, which is related to their rapid turnover rate and in comparison to later and more minimal decreases in red blood cells due to their long turnover rate (~115 days).[62]

Functional Subunits and Radiation Tolerance

The ability of any given tissue to regenerate is influenced by the availability of surviving clonogenic cells that can divide and repopulate into mature cells capable of maintaining normal organ function. Unlike tumors where a few surviving cells can regrow into a tumor, many organs are organized into functional subunits (FSUs) that can be linked in series or parallel. These units can sometimes be defined anatomically (eg, nephrons in kidney or

lobules in the liver); however, this is not always the case (eg, the spinal cord).

In series organs (eg, spinal cord, esophagus), the FSUs are arranged end to end, and each subunit critically influences the broader organ function. As such, damage to one FSU can contribute to whole organ dysfunction. In addition, in series organs, each FSU is limited to the availability of surviving cells within that FSU to repopulate and regenerate that FSU; thus, if the FSUs are smaller and contain lower number of clonogens, then a lower dose of radiation can sufficiently kill all the cells. For example, if radiation damages a segment of the spinal cord, it disrupts signal transmission across the whole cord. This greatly limits how much radiation organs can tolerate. This principle also affects tumors as they act as one FSU. Larger tumors require greater doses of radiation than many small tumors to avoid any surviving clonogen at each tumor location that can repopulate the tissue.

On the contrary, parallel tissues such as the kidneys, lungs, and the liver have independent FSUs that can continue maintaining organ function even if a portion of the FSUs is damaged. Other tissues such as the skin/mucosa and gut epithelium have poorly defined/no defined FSUs and as such there are no physical barriers that prevent cell migration. Thus, if one area of these tissues is greatly impacted, clonogens from other FSUs can migrate and repopulate that area. Even within these tissues, the number of available clonogenic cells influences the radiation dose tolerance and subsequent tissue effects. For instance, hair follicles contain a smaller number of melanocytes than the epidermis, thus hair follicles get depigmented from lower radiation doses compared to the epidermis.

Volume Effect

The tolerance dose of any given tissue can be defined as the dose necessary to produce a complication beyond an acceptable threshold of symptomology. This dose depends on the volume of tissue irradiated (ie, volume effect). The tolerance dose is influenced by the number of FSUs irradiated (n) and the probability of the loss of one FSU (p). As such, the probability (P) of complications can be quantified using:

$$P = 1 - (1 - p)n$$

This equation is illustrated in Figure 3.3, which shows that radiation exposure of a greater number of FSUs (left curves) shifts the probability curve to the left and makes it steeper; that is, complications are more likely to be seen with lower radiation doses, and with each subsequent dose increase a greater likelihood of complication rates is seen. In serial tissues, this produces a binary phenotype whereby above a certain tolerance dose threshold, significant loss of organ function is seen. Below this threshold, the organ functions normally. On the contrary, in parallel tissue or in serial tissues with only one FSU irradiated, the probability of a complication rises relatively slowly with higher dose (the rightmost curve in Figure 3.3). As such, these tissues exhibit a graded response to increasing doses of radiation, rather than a binary response, after reaching a threshold of tissue volume radiation. This threshold is dependent on the functional reserve capacity of a given organ. The lungs and kidney only need approximately 30% of their total organ volume for adequate, physiologic functioning. As such, they are tolerant to higher doses of radiation administered to smaller areas, despite being highly sensitive to radiation-induced damage with whole organ irradiation.

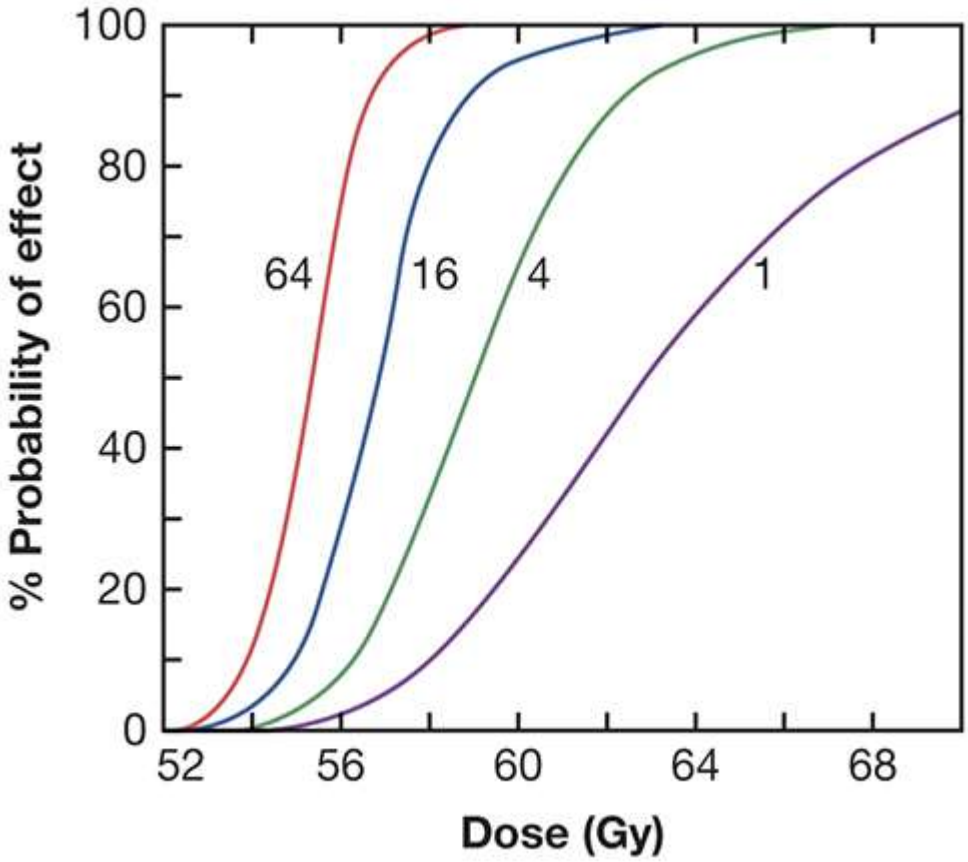

FIGURE 3.3 Curves illustrating how the probability of producing a complication increases with increases in the number of serially arranged FSUs included in the treatment volume. The curves were positioned by assuming that 58 Gy in 2-Gy fractions sterilized 10% of FSUs and that for a series of 2-Gy fractions, the effective D_0 for the target cells was 4 Gy. The curves are shifted to the left and are steeper with increase in number of FSUs exposed; however, this effect becomes less obvious once large numbers of subunits are involved. FSU, functional subunit. (Reprinted from Withers HR, Taylor JM, Maciejewski B. Treatment volume and tissue tolerance. *Int J Radiat Oncol Biol Phys*. 1988;14[4]:751-759. Copyright © 1988 Elsevier. With permission.)

The skin/mucosa shows an interesting phenomenon clinically, whereby at low levels of injury, they can heal from migrating clonogens throughout the volume of irradiation and thus do not exhibit the same volume effect described earlier. However, symptomatically, a smaller area of injury (eg, ulceration) is better tolerated by patients than a larger area, and the latter can also have longer healing times and increased risk for infection. As such, in these tissues the volume effect clinically is based on the tolerability of injury rather than the probability or severity of injury.

Latency of Tissue Effects from Radiation

The time taken for normal tissues to express radiation-induced injury is termed "latency," and based on acute, subacute, or late response to radiation, the symptomology from radiation can vary.[63] An acute response to radiation is defined as occurring during treatment or within days to weeks after treatment and is seen in tissue with a rapid turnover of cells: mucosa of oropharynx and esophagus, bone marrow, gastrointestinal epithelium, and skin. These tissues commonly have a well-defined stem cell population; however, the acute effect symptoms develop when the stem cell population is damaged and cannot replace the cells that are lost from fast turnover/radiation damage.[63] Eventually the remaining stem cells proliferate, allowing for repair of the tissue. A subacute response, sometimes called a consequential effect, is seen in the period of months from RT. These effects can be due to the persistence of acute effects,[63] often stemming from not having enough undamaged stem cells available for tissue restoration. Examples include spinal cord demyelination (Lhermitte syndrome) and pneumonitis. The severity of both acute and subacute effects worsens with increasing doses. A late response to radiation commonly occurs months to years after treatment and is seen in tissues with the slowest turnover rate: heart, lungs, kidneys, liver, and central nervous system organs. Notably, despite being late response tissues, acute inflammatory or edematous changes can result in the presentation of acute timelines as well. The pathophysiology of late effects has many overlapping mechanisms to wound healing: radiation-induced inflammation and vascular damage promote leakage of cytokines, fibrin, and subsequent collagen deposition and tissue scarring (ie, fibrosis).[64] Late effects are also more sensitive to fractionated treatments compared to acute/subacute effects. Secondary malignancies are also considered late effects of RT.

The latency of tissues also influences how long it takes for cells to regenerate and repair radiation-induced damage. Figure 3.4 shows the days after the initial dose of radiation when the repopulation of cells can be seen. This figure highlights that in acute-responding tissues, repopulation of cells can be seen even within 24 hours due to the rapid loss of cells. On the contrary, this effect is not seen for months in late-responding tissues. There are also major differences in the tissue turnover kinetics between mice and

humans, with humans having slower kinetics. These need to be accounted for when translating findings across species.

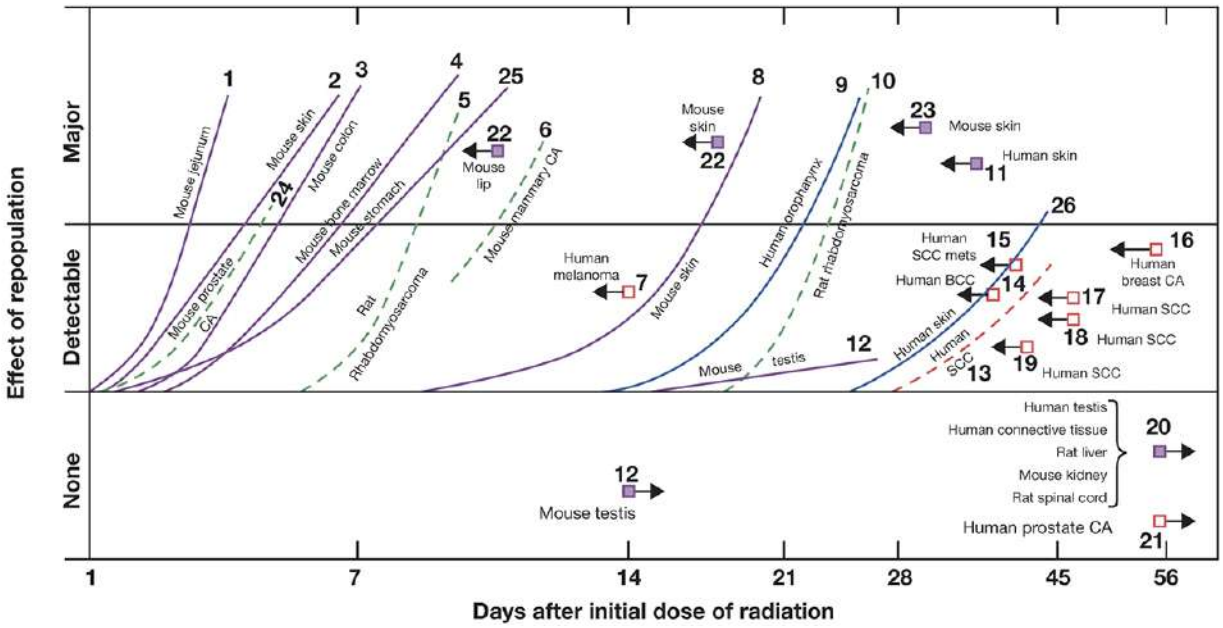

FIGURE 3.4 Representation of the approximate kinetics of regeneration of irradiated normal tissues (solid lines, solid symbols) and tumors (dashed lines, open symbols). Curves are based on measurements or estimates of regeneration; symbols denote times at which an effect of regeneration has already appeared (left-pointing arrow) or has not yet appeared (right-pointing arrow). The logarithmic abscissa is for convenience of presentation only and has no biologic rationale. In general, the human data are displaced to the right of experimental animal data, reflecting a slower initiation of repopulation. Because human tissues proliferate more slowly than do their rodent counterparts, they were exposed to protracted dose regimens, and less-sensitive end points were used to detect onset of repopulation in humans. Numbers on the curve and symbols refer to different sources of data. These come from many sources. (Further details are in the previous editions of this book.)

Skin and Connective Tissue

Erythema/dermatitis, desquamation (eg, scaling or peeling), pruritus, and hypersensitivity are common acute manifestations of radiation effects in the skin/connective tissue. While these commonly resolve throughout the course of the treatment, some patients can present with painful moist desquamation following high doses of radiation; this is due to the complete loss of basal stem cell populations and any healing requires migration of cells. These changes, especially dermatitis, can persistent over weeks to months (subacute) or show discoloration during the healing process (eg,

hypo- or hyperpigmentation). Late effects on the skin include pigmentation changes, telangiectasias, fibrosis, and/or atrophy. Connective tissue fibrosis can cause pain and affect mobility, and if it impairs lymphatic drainage, it can lead to lymphedema as well. The most concerning late skin effects include skin necrosis and chronic nonhealing wounds.[65]

Head and Neck

Acute manifestations after head and neck radiation commonly present as skin/soft tissue reactions like those noted earlier, as well as mucosal ulceration or infection. Fibrotic changes during the healing process as well as persistent mucositis are subacute manifestations within the mucosa. Such symptoms, when severe, might necessitate a feeding tube. Chronically, patients can have dental infections/caries and xerostomia (from salivary gland radiation) and osteoradionecrosis of the jaw, which can worsen quality of life and dental health.[66,67] These late effects are one of the primary reasons for recommending removal of damaged or unhealthy teeth prior to treatment in areas of high radiation exposure and emphasizing oral hygiene throughout treatment.

Central Nervous System

Acute symptoms from central nervous system radiation stem from local edema. Symptoms include fatigue, nausea, vomiting, loss of appetite, headaches, and rarely acute encephalopathy. Subacute effects include the persistence of fatigue, neurocognitive defects, and acute transient myelopathy of the spinal cord (Lhermitte syndrome) resulting from demyelination. Late effects can range from cavernous hemangioma formation[68] and cognitive/memory impairment[69] to progressive myelopathy, which can result in complete paraplegia when severe.[70]

Cardiovascular System

Acute cardiac symptoms include pericarditis, pericardial effusion, and vascular dysfunction. Late effects include the development of coronary artery disease from vascular damage and heart failure/cardiomyopathy from fibrotic and inflammatory changes,[71,72] which can contribute to morbidity and mortality in patients with breast cancer, lung cancer, and lymphomas

undergoing thoracic radiation with incidental heart exposure. Within the broader vascular system, acute radiation-induced damage can lead to thrombus. Chronically, the veins are less radiosensitive than arteries, and radiation can contribute to arteriolar senescence and atherosclerosis development chronically.[73] Notably, lung damage from radiation can greatly influence cardiovascular function, and vice versa. As such, studies aimed at differentiating the damage in the two organ systems need to be designed carefully to isolate lung radiation versus cardiac radiation.[74]

Lungs

Subacute effects include pneumonitis and fibrosis, which can progress into chronic fibrotic changes leading to restrictive lung disease that can limit respiratory function (late effects).[75] The persistence of inflammatory cascades within the lungs as well as general wound healing processes contribute to the late fibrotic changes in the lung.[76] Given that the lung FSUs (lobules) are organized in parallel, the volume of lung irradiated greatly influences the extent of functional limitations.

Gastrointestinal System

The acute effects of gastrointestinal system irradiation result from damage to the rapidly dividing cells throughout the system.[77] These effects include difficulty swallowing due to damage to the mucosal layer of the esophagus, nausea/vomiting from damage to the columnar epithelium of the stomach (which contains mucin-containing cells), as well as damage to the precursor cells that replenish the epithelium, diarrhea from damage to the intestinal epithelium, stem cells located in the crypts of Lieberkuhn, and the villus structures. Ulcerations can also be seen throughout the system. Late effects in the esophagus are driven by muscular layer necrosis and thickening of the epithelial layers, which impair swallowing. Within the stomach and intestine, late effects include fibrosis and ischemia resulting from atrophy of the supplying vasculature and potentially bowel obstruction.[78-80]

Tissue Tolerance to Retreatment

Tissue tolerance to retreatment is higher in early-responding tissues (eg, intestinal crypt cells, epithelial cells, hemopoietic cells) since they usually

recover well from the initial treatment. On the contrary, late-responding tissues can tolerate lower doses (eg, spinal cord) during retreatment since they do not recover well from the initial treatment. As such, the limiting factor in the decision for retreatment is late effects.[81] Additionally, whether the initial treatment was below or above the tolerance level of a given organ also influences the safety of retreatment. In tissues where the tolerance was not exceeded during the initial treatment, retreatment may be safe, while this is not typically the case if the tolerance was exceeded— especially in serially organized tissues. For example, Figure 3.5 shows how initial doses of radiation (priming dose) to the spinal cord in a variety of animal models influence the remembered dose of the tissue. The higher the remembered dose, the lower the tissue tolerance to re-irradiation.[82-84] The tissue tolerance to retreatment also decreases with decreasing times between treatment, likely due to the lower recovery of tissue from the initial damage.

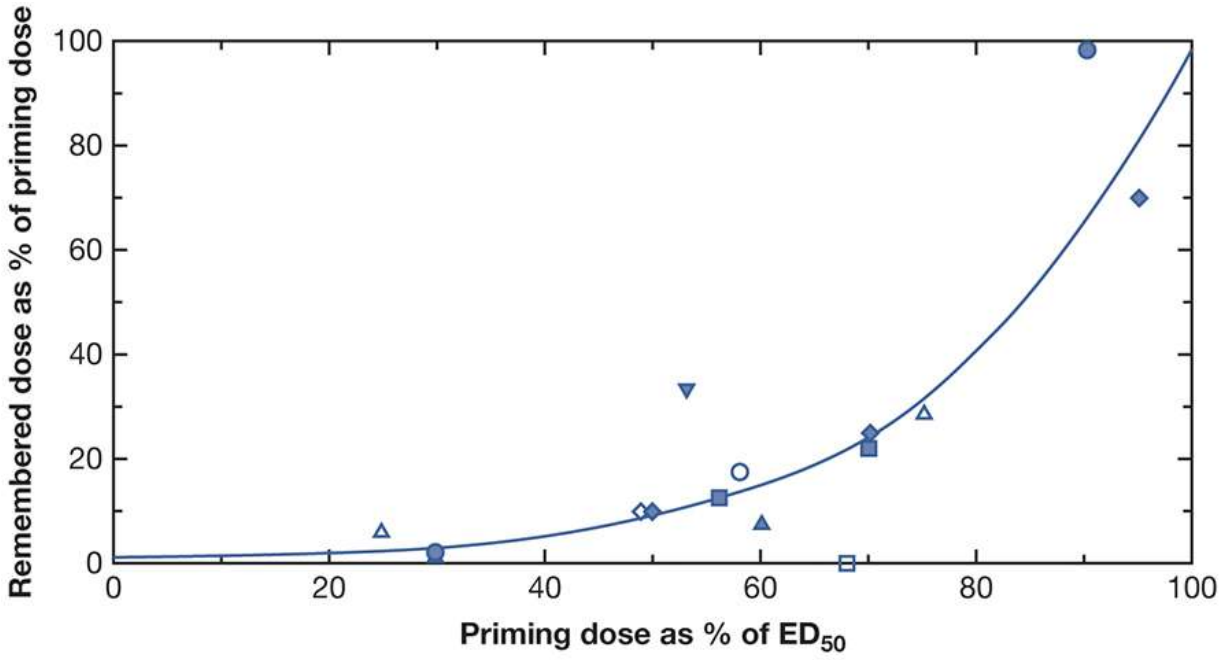

FIGURE 3.5 The dependence of remembered dose on size of priming dose (as a percentage of ED_{50}) is shown for a variety of animal species at long periods (6 months to 2 years) after the initial radiation treatment: O, adult rhesus monkey; Δ, 12-week-old rat([49]); ◊, 1-day-old guinea pig; •, young adult mouse; filled ▲, 8-week-old guinea pig; filled ▼, 8-week-old guinea pig; filled ■, 3-week-old weanling rat; ♦, young adult rat. (Reprinted from Mason KA, Withers HR, Chiang CS. Late effects of radiation on the lumbar spinal cord of guinea pigs: re-treatment tolerance. *Int J Radiat Oncol Biol Phys*. 1993;26[4]:643-648. Copyright © 1993 Elsevier. With permission.)

The injury from further damage in tissues where its tolerance for recovery has been exceeded is not only specific to re-irradiation but also to other trauma or stressors. For example, in patients with a high level of spinal cord dysfunction and late effects, hyperthermia can induce myelitis. In patients with significant chronic effects from head and neck radiation, the trauma of dental procedures can be enough to induce necrosis of the mandible.

Prediction of Normal Tissue Toxicities

The high level of patient-to-patient variation in normal tissue toxicity from RT has been extensively documented, and it is suggested that up to 90% of this variation can be explained by patient-specific factors such as genetics, lifestyle, comorbidities, and other factors beyond dose and fractionation.[85] For instance, numerous studies show that patients with cardiovascular disease risk factors are at higher risk for adverse cardiac events following thoracic RT.[72,86]

Recent advances in genomic sequencing can allow for the development of more precise risk prediction strategies that assess patient-specific genetic variations to (1) predict those who will be at high risk for specific normal tissue toxicities and (2) predict which therapies may be beneficial in preventing toxicities in specific populations.[87] For example, studies show that small nucleotide polymorphisms (SNPs) in the follicle-stimulating hormone gene can increase the risk for erectile dysfunction in patients receiving RT for prostate cancer.[88,89] Another study showed that SNPs within genes that regulate DDRs can predict the risk for acute toxicity following head and neck RT.[90] The large prospective REQUITE cohort study, which included more than 1,600 patients with breast cancer in the United States and Europe, identified eight specific SNPs associated with chronic late effects on breast tissue (eg, lymphedema, nipple retraction).[91] For the various late effects that the researchers measured, the top genomic risk loci ranged from those encoding adhesion proteins to transcription factors that have crucial roles in embryonic development.[91] The variability in genes associated with different toxicities suggests that unique genetic predispositions determine risk for various toxicities. Notably, analysis of the REQUITE study also showed that polygenic predisposition to cancers

(breast, prostate, or lung) did not increase the risk for late normal tissue effects, highlighting that SNPs associated with cancer risk may be distinct from those associated with RT-induced toxicity,[92] that is, those at high risk for normal tissue toxicity may not necessarily also be at high risk for secondary malignancies.

Therapeutic Use of Normal Tissue Radiation

While RT is commonly associated with cancer treatment, it has a broader range of therapeutic applications. For instance, RT, specifically high-dose stereotactic body RT, is currently being evaluated for noninvasive treatment of refractory ventricular tachycardia.[93,94] While radiation of the vasculature and heart can be associated with dysfunction, radiation can cause changes in inflammatory pathways, and the ROS produced by radiation has been shown to upregulate stress protection pathways in some preclinical models. This protection can trigger a "preconditioning" effect that has been shown to protect kidney,[95] brain,[96] and heart[97] tissue from ischemic injury. Radiation can also cause changes in other pathways that in some situations may be favorable to reduce symptoms, such as alterations in cell surface proteins that may contribute to reductions in ventricular tachycardiac events.[98] Additionally, by altering different pathways, intravascular brachytherapy has been used after angioplasties to reduce the risk of vascular restenosis.[99]

Outside the cardiovascular system, RT can decrease the recurrence of keloids[100] following surgical removal and can prevent the formation of heterotopic ossification (abnormal bone growth in soft tissues) following surgeries such as joint replacements.[101] RT has also been examined to minimize symptoms in osteoarthritis.[102] These varied therapeutic uses of RT take advantage of advances in technology that allow for targeted and more precise delivery of radiation.

TUMOR RESPONSE TO RADIATION THERAPY

The tumor response to radiation is influenced by the heterogeneity of cell populations, the capacity for DNA repair, the extent of apoptosis/senescence upregulation, the organization and oxygenation of the tumors, and the intrinsic turnover rate of the cancer cells. Similar to normal tissue, tumors

with higher turnover rates exhibit greater cell death from radiation, analogous to acute effects. The tumors with lower turnover rates are more radioresistant and have slower regression rates, analogous to late effects.

Tumor growth rate is also influenced by growth fraction (GF), tumor doubling time, and the tumor's cell loss factor (ϕ). GF represents the proportion of proliferating tumor cells (P) to quiescent tumor cells (Q), and can be represented as:

$$\mathrm{GF} = P/(P + Q)$$

The level of quiescent cells is determined by the proportion of stem cells (generally quiescent) as well as the extent of hypoxia in the tumor. For most solid tumors, the GF is approximated to be 30% to 50% in animals, highlighting the heterogeneity of cell proliferation within a tumor. The doubling time (T_D) of a tumor is determined by the GF and the time required to go through one cell cycle (T_C) and can be defined as:

$$T_D = T_C / \mathrm{GF}$$

Tumor doubling times can range from 4 to 34 days for a wide range of tumors, and the doubling time is mainly influenced by the fraction of cells that are in the S phase (labeling index [LI]) at any given time. This can be modeled as:

$$T_D = \lambda T_s / \mathrm{LI}$$

T_S represents the time spent in the S phase with a cell distribution correction factor λ to account for the uneven distribution of cells throughout the cell cycle; this value is usually between 0.67 and 1.00. T_S is thought to be relatively similar across most cells, and as such increased proportion of cells in the S phase primarily results in a lower doubling time. The tumor's cell loss factors, with $\phi < 1$ representing tumor growth and $\phi > 1$ representing tumor regression, can be defined based on the predicted doubling time (T_D) and actual doubling time (T_{Da}) calculated based on measurements of tumor diameter:

$$\phi = 1 - T_D / T_{Da}$$

This, in essence, estimates the level of cell loss while accounting for the rate of new cell production/doubling and the growth rate of the tumor.

In general, tumors that have a high ϕ regress quickly following RT and this is independent of their pretreatment tumor growth rate or fraction. In tumors with a low ϕ, rapid postradiation tumor regression can also be seen if the tumor has a high GF and rate of new cell production (ie, doubling time).

Mammalian Survival Curves and the Random Nature of Cell Killing

Survival curves for tumor cells are usually plotted as dose (x-axis, linear scale) versus surviving tumor fraction (y-axis, log scale), and this curve differs based on the LET. Low-LET radiation is characterized by sparse ionization events and at lower doses the surviving fraction shows an exponential relationship with increasing doses; this is represented as a straight line on this log-linear plot. The curve then bends for a range of doses and turns into a straight line at higher doses as these sparse ionization events compound with multiple hits creating more damage. On the contrary, the curve remains a straight line across dose ranges with high-LET radiation due to more dense ionization events generating more complex DNA damage and is steeper compared to low-LET radiation curves, suggesting that cell survival decreases exponentially with increasing doses of high-LET radiation.[103,104]

This survival relationship can be described using numerous mathematical models. The initial model proposed was the multitarget model, which models the surviving fraction in relation to dose based on an initial slope (D_1) that represents a single-hit killing event while the final slope (D_0) represents damage from multiple hits. The width of the initial shoulder (D_q) is the dose range of single-hit killing events. This dose-response relationship is modeled in Figure 3.6 and is based on the dose required to decrease the fraction of surviving cells to 37% of the previous value. Given the linear nature of the second component of the curve on a logarithmic scale, the dose required to decrease cell survival to 37% of the prior value

remains the same across all survival levels (ie, to kill 63% of existing cells $\rightarrow 1 - e^{-1}$).

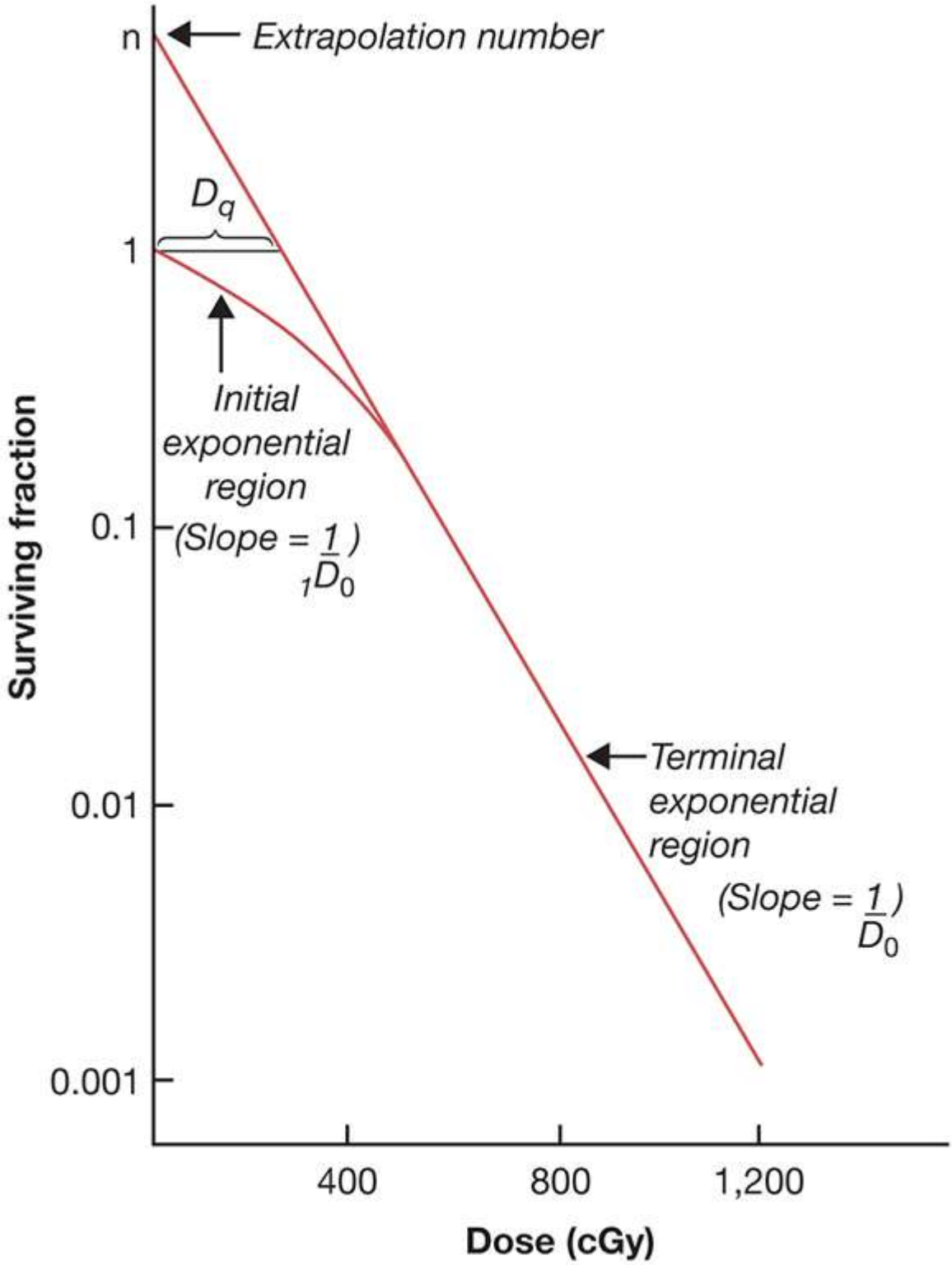

FIGURE 3.6 A TC survival curve for mammalian cells is characterized by a "shoulder" followed by a terminal exponential region, the slope of which is defined by a D_0 value (slope = $1/D_0$). The position of the curve on the radiation dose axis can be fixed by the intercepts of the terminal exponential region extrapolated back to the zero-dose axis (n) or to the

100% survival level (D_q): *n* is termed the extrapolation number, and D_q the quasi-threshold dose. Although *n* and D_q are parameters that define the width of the shoulder on the survival curve, they do not indicate its shape, which is of prime importance in RT. The survival curve shoulder can be considered to consist of an initial exponential region (the slope of which is defined by JDQ), followed by a downward-bending segment that merges asymptotically into the final exponential region of the survival curve. (Reprinted with permission from Withers HR, Peters LJ. Biological aspects of radiotherapy. In: Fletcher GH, ed. *Textbook of Radiotherapy*. 3rd ed. Lea & Febiger; 1980:103-180.)

The basis of this relationship is shown in Figure 3.7, which in essence shows that if 100 cells are irradiated, there is approximately a 37% (ie, e^{-1}) probability that any one of the cells will not be hit when 100 hits are delivered randomly. An additional 100 hits (200 total) would result in a 13.7% ($e^{-2} = 0.37 \times 0.37$) likelihood of survival (no hits).

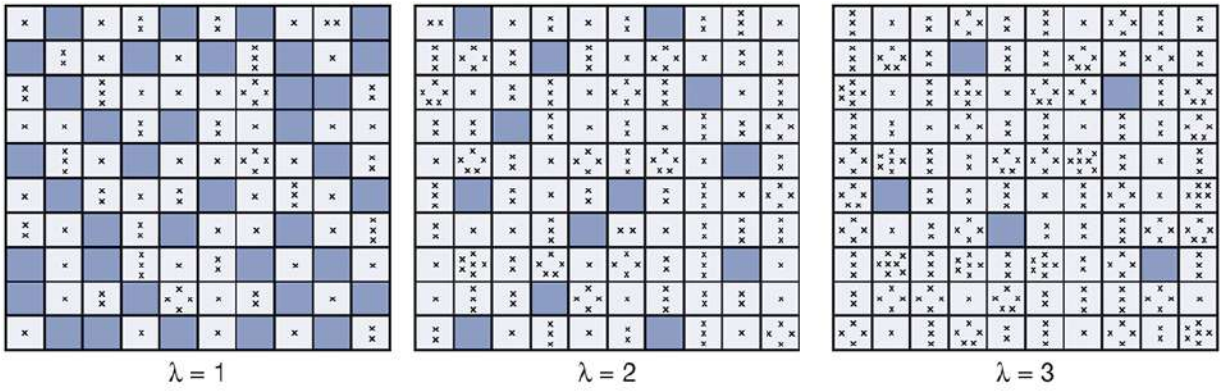

FIGURE 3.7 Random distribution in 100 equal-sized "targets" of 100, 200, or 300 "hits." The probability that any one of the 100 targets will not be struck when 100 hits are delivered randomly is e^{-1}, or 37%. The same probability of survival applies for each equal increment in the number of hits: 200 hits would result in a probability of survival of e^{-2}, or 0.37 × 0.37. Even after 300 hits are delivered, there is still a chance of e^{-3} = 5% that any one target will survive. This proportionate, or geometric, decrement in survival rate may be plotted as a straight line on semilogarithmic coordinates. (Reprinted with permission from Withers HR, Peters LJ. Biological aspects of radiotherapy. In: Fletcher GH, ed. *Textbook of Radiotherapy*. 3rd ed. Lea & Febiger; 1980:103-180.)

The most widely accepted mathematical model for describing cell survival curves is the linear quadratic (LQ) model, which assumes there are two components of damage that result in cell killing. The first is linearly associated with radiation dose (*D*) and modeled using the coefficient α and the second is proportional to the square of radiation dose modeled using the

coefficient β. Using these coefficients, the fraction of cells surviving (S) a dose of D is modeled as:

$$S = e^{-\alpha D - \beta D2}$$

The first component, $e^{-\alpha D}$, describes the injury from a single radiation hit and thus has a linear effect on cell survival in a log-linear plot. The $e^{-\beta D2}$ describes injury from multiple or cumulative hits and shows a continuously bending relationship between dose and cell survival (Figure 3.8).

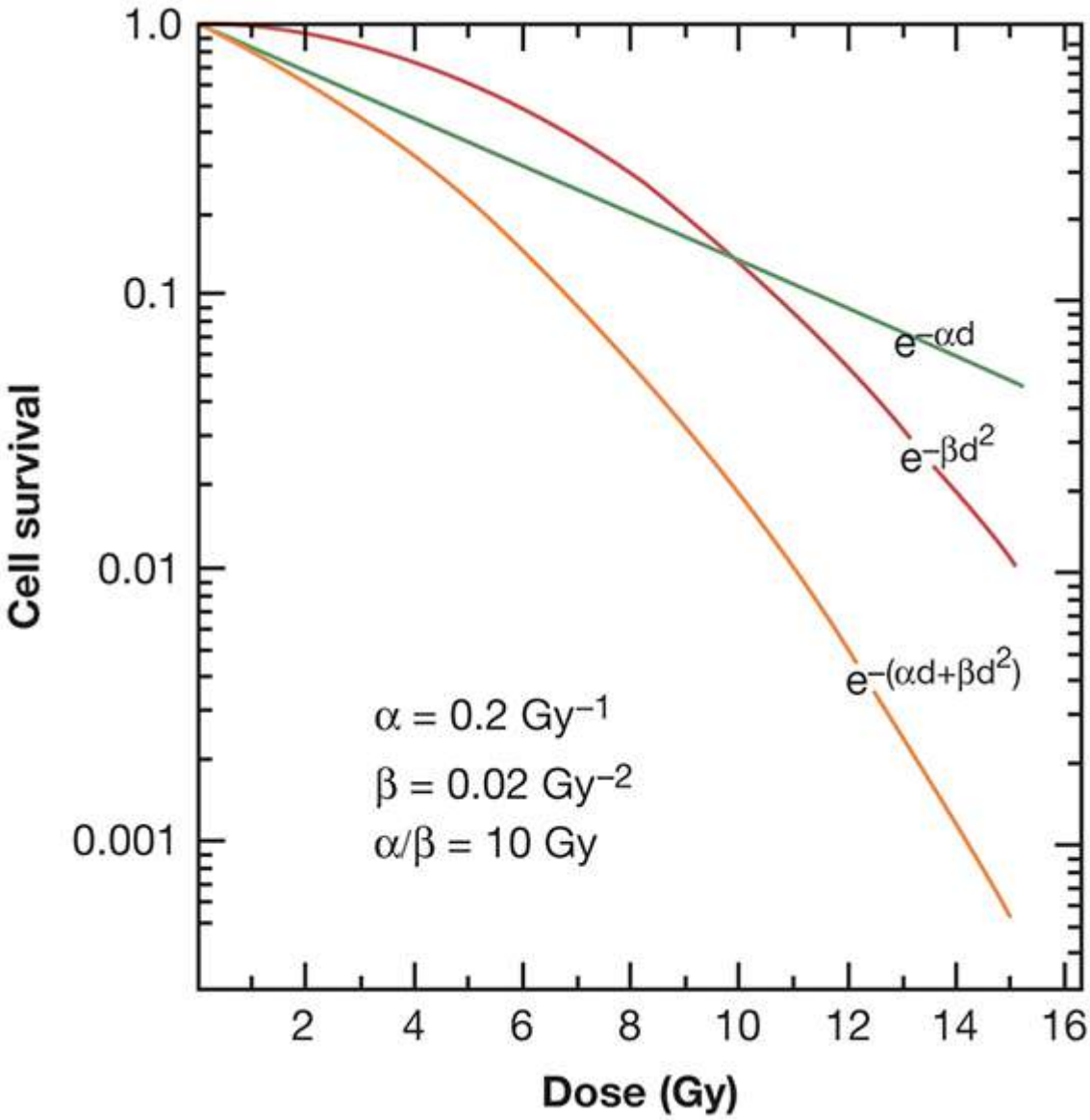

FIGURE 3.8 Model dose-survival curves for mammalian cells showing that the experimentally determined curve for acute exposures (lowest curve) is the product of two mechanisms: single-hit injury described by an exponential curve ($e^{-\alpha d}$), and multihit, or cumulative, injury described by a continuously bending curve related by a coefficient, β, to the square of the dose. At doses of clinical relevance, cell death from the single-hit mechanism predominates. The rate at which the survival curve bends from an initial, essentially exponential region depends on the ratio (α/β) of the coefficients for single-hit and multihit killing: the lower the value, the sooner and more steeply the curve bends. The value of α/β is the dose at which single- and multihit mechanisms contribute equally to cell killing. In these curves, α/β = 10 Gy, which is a value characteristic of acutely responding tissues. Target cells in late-responding normal tissues are characterized by low α/β values; hence their survival curves are curvier. The flexure dose, D_f, is the dose at which deviation from the initial exponential part of the curve is difficult to detect and, for available biologic assay systems, is about one-tenth of α/β. When doses in a multifraction regimen are less than D_f,

further dose fractionation does not produce detectable "sparing" (because cell killing is essentially all the result of single-hit events, the lesions potentially contributing to multievent killing being completely repaired during the fractionation intervals). The lower the α/β value, the lower the dose at which multihit mechanisms cause cell death, the lower the value of D_f, and the lower the dose per fraction below which a sparing effect of dose fractionation is lost. The curve for single-hit killing ($e^{-\alpha d}$) can be measured experimentally using very small dose fractions or a continuous low-dose-rate exposure; however, the curves for multihit killing ($e^{-\beta D2}$) can be determined only indirectly from a knowledge of the other two curves.

The dose range when the curve stays linear as well as the extent of bending beyond the initial linear component can be described by the ratio of the two coefficients α/β, known as the α/β ratio. Mathematically, the actual value of α/β describes the dose at which both mechanisms (single hit and cumulative/multihit) contribute equally to cell death. As such, a lower value is interpreted as needing a lower dose to induce a multihit mechanism of cell killing.

Biologically, the ratio of these coefficients is linked to the acute versus late response of tissues. The tissues with higher α/β are usually more acute-responding, and most tumors fall within this category as well. However, some tumors such as melanomas, liposarcomas, prostate tumors, soft tissue sarcomas, and breast tumors can have lower α/β ratios. The α/β ratio is lower in late-responding tissues and thus their survival curves start bending at lower doses and are steeper; at low doses, this results in lower cell killing compared to acute effects as shown in Figure 3.9. At higher doses, however, a greater level of cell death compared to acute tissues is seen with each subsequent dose escalation. Table 3.1 shows the α/β values for various early- and late-responding tissues. It illustrates that the α/β values for early-responding tissues are close to 10 Gy, while they are closer to 2 Gy for late-responding tissues.

TABLE 3.1 *A/B* VALUES

Early-Responding Tissues	α/β (Gy)	Late-Responding Tissues	α/β (Gy)
Skin (desquamation)	9.4-21.0	Spinal cord (paresis)	1.6-5
Skin—pig (desquamation)		Cervical	2-3.4
Time ≤16 d	8.7	Lumbar	4-5
Time >16 d	0.9	Brain (LD_{50}/10 mo)	2.1

Early-Responding Tissues	α/β (Gy)	Late-Responding Tissues	α/β (Gy)
Lip mucosa (desquamation)	7.9	Kidney (multiple endpoints)	0.4-5
Jejunal mucosa (clones)	7-13	Lung (pneumonitis)	1.6-4.5
Tongue mucosa (ulceration)	11.6	Lung (fibrosis)	2.3
Colonic mucosa (clones)	7-8.5	Heart failure	3.7
Hair follicles (epilation)		Liver (clones)	2.5
Anagen	7.5	Bladder (frequency)	7.2
Telogen	5.5	Bladder (contraction)	5.8-11.0
Testis (clones)	13.9	Bowel (stricture/perforation)	3.5-5
Spleen (clones)	8.9	Bowel (fistula/obstruction)	10.7
Bone marrow (clones)	9.0	Bowel (rectal stenosis, <5 d)	6.2
Melanocytes (depigmentation)	6.5	Bowel (rectal stenosis, >5 d)	1.1
Tumors (cure)		Dermal contraction	1.5-3.5
Experimental tumors	10-35	Dermal wound healing	2.5
Most human tumors	6-25	Eye cataracts	1.2
Human prostate cancer	1.5	Bone (human fracture)	2.2
		Cartilage and submucosa	1-4.9
		Total body irradiation (LD_{50}/1 y)	5.1

These values represent a synthesis from many sources. Individual values are means from one study. Where a range is given, it represents mean values from multiple studies.

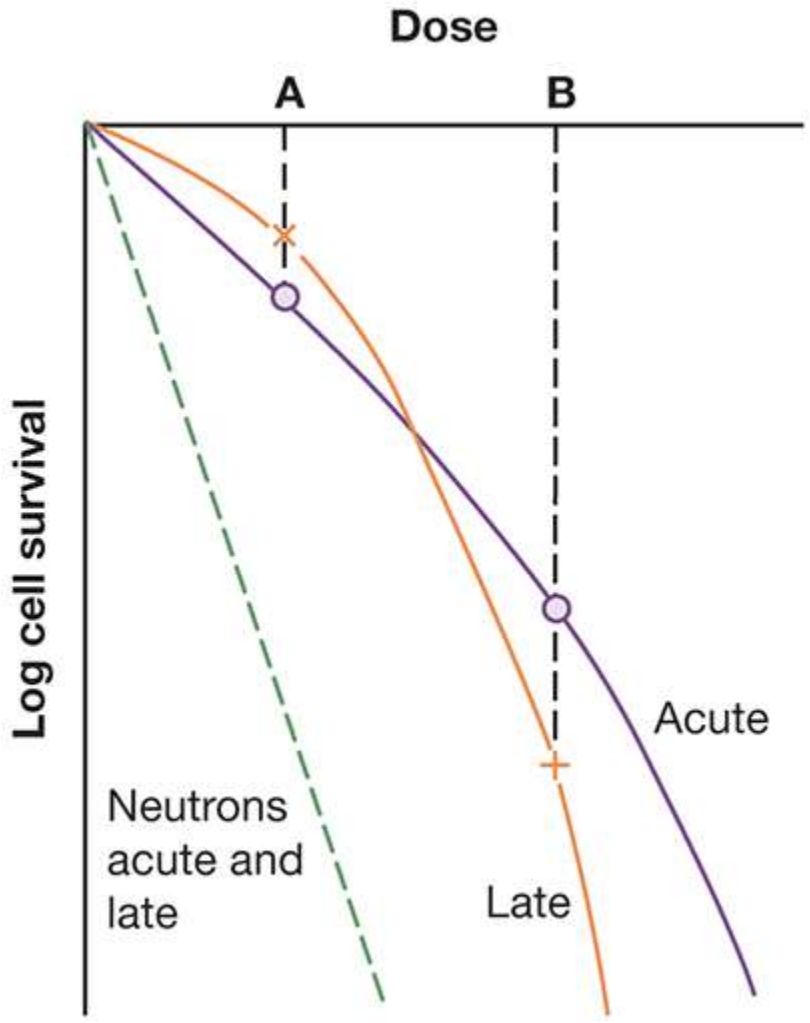

FIGURE 3.9 Hypothetical survival curves for the target cells for acute and late effects in normal tissues exposed to x-rays or neutrons. The α/β ratio is lower for late effects than for acute effects in x-irradiated tissues, resulting in a greater change in effect in late-responding tissues with change in dose. At dose A, survival of target cells is higher in late-effect than in acute-effect tissues; at dose B, the reverse is true. Increasing the dose per fraction from A to B results in a relatively greater increase in late than acute injury. For neutrons, the α/β ratio is high, with no detectable influence of the quadratic function (βd^2) over the first two decades of reduction in cell survival, implying that accumulation of sublethal injury plays a negligible role in cell killing by doses of neutrons of clinical interest. (Reprinted from Withers HR, Thames HD Jr, Peters LJ. Biological bases for high RBE values for late effects of neutron irradiation. *Int J Radiat Oncol Biol Phys*. 1982;8[12]:2071-2076. Copyright © 1982 Elsevier. With permission.)

The LQ model also explains differences in response to fractionated treatment of early- versus late-responding tissues. With each treatment fraction, the shoulder of the dose-response curve gets repeated. Acute-

responding tissues, with higher α/β values and a steeper dose-response relationship, are less sensitive to dose fractionation. On the contrary, the late-responding tissues with more curved relationships and lower α/β values are greatly influenced by changes in the fractionation pattern. Figure 3.10 illustrates this by showing the isoeffect of various tissues. This graph portrays the relationship between the total dose of radiation and the dose per fraction needed to achieve the same biologic effect. The curve typically slopes down since increasing the dose per fraction reduces the total dose needed to achieve the same effect. This is due to the greater cumulative cell-killing effect with larger individual doses per fraction. This curve for late effects in normal tissue is steeper compared to acute effects, due to lower tolerance to large individual doses within late-responding tissues. Figure 3.11 shows the relationship between dose per fraction and the total dose represented as the ratio of 2 Gy fractions. This graph shows that with a reduction in the dose per fraction, the isoeffect dose increases more rapidly in late-responding tissues. The biologic effective dose (BED) can be calculated accounting for the fractionation using the equation:

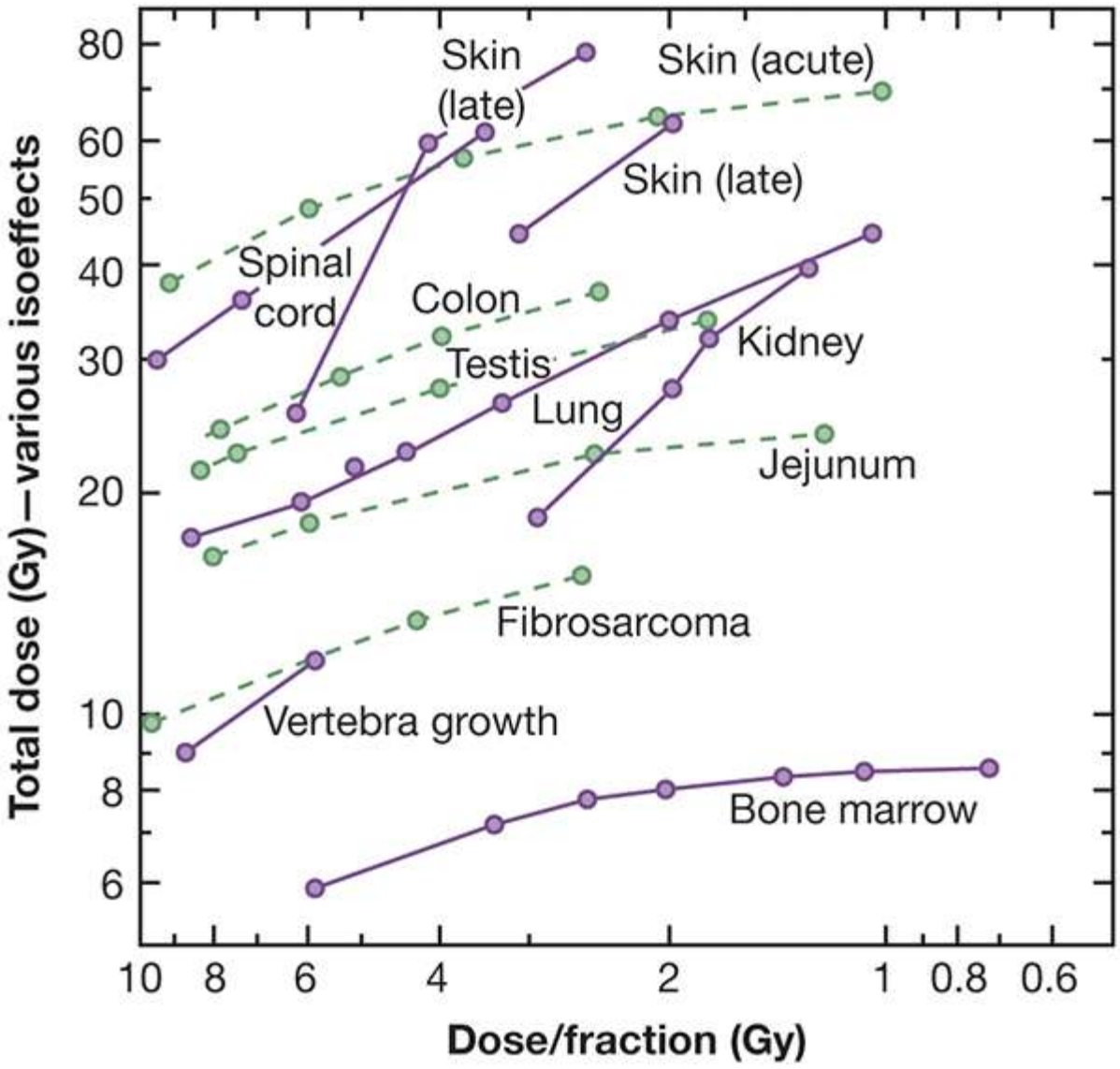

FIGURE 3.10 Isoeffect curves in which the total dose necessary for a certain effect in various tissues is plotted as a function of dose per fraction (late effects, solid lines; acute effects, broken lines). Data were selected to exclude an influence on the total dose of regeneration during the multifraction experiments. The isodoses for late effects increase more rapidly with decrease in dose per fraction than is the case for acute effects. (From Withers HR. Biologic basis for altered fractionation schemes. *Cancer*. 1985;55[9 suppl]:2086-2095. Copyright © 1985 American Cancer Society. Reprinted by permission of John Wiley & Sons, Inc.)

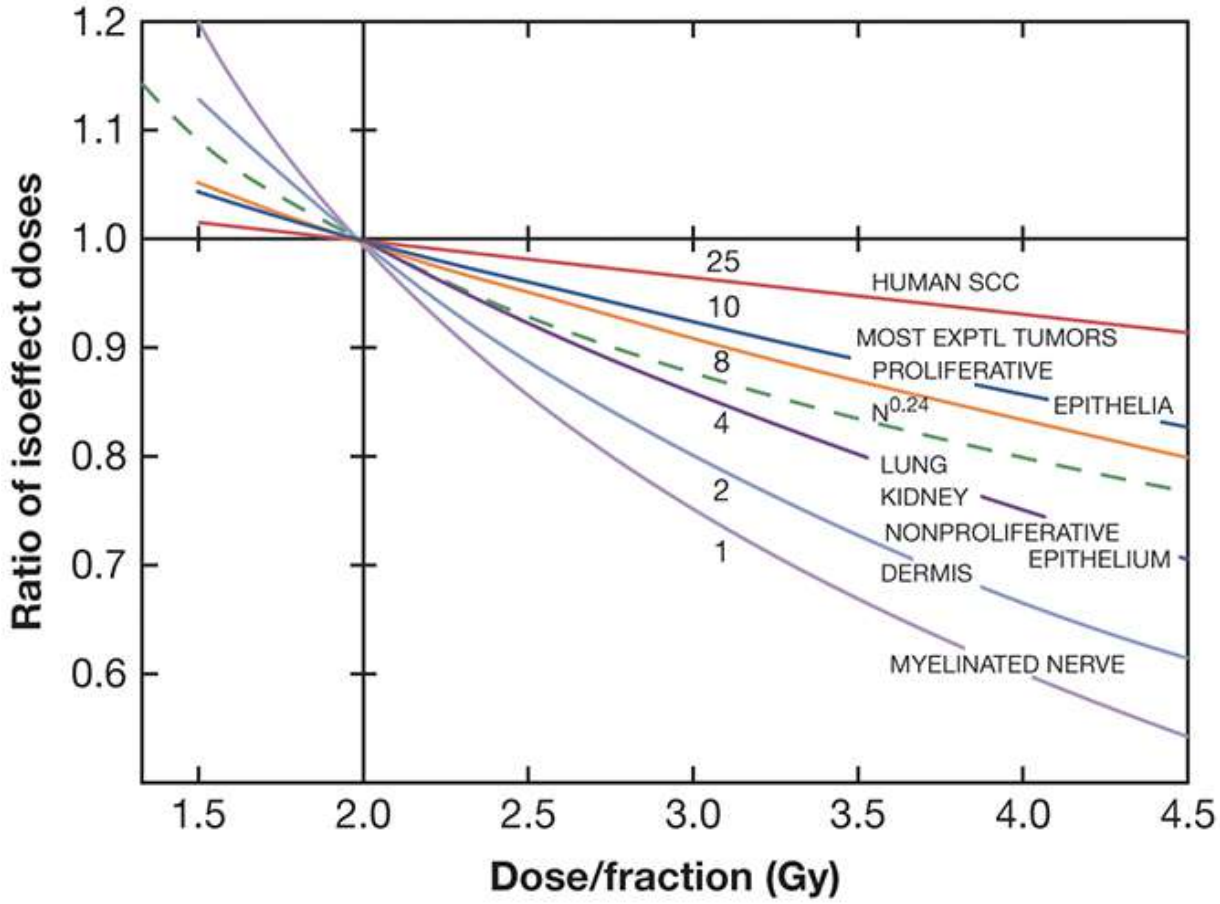

FIGURE 3.11 Isoeffect curves relating total dose to dose per fraction, with total dose being expressed as a ratio of that necessary in 2-Gy fractions (ie, the $LQED_{2Gy}$). α/β ratios (in Gy) are shown on the curves. Although the α/β ratios are not yet established accurately or even precisely for most normal tissues, especially late-responding ones (Table 2.2), the likely order of fractionation sensitivities is as shown. The broken line traces the change in dose, as it would have been predicted by a factor $N^{0.24}$ in the NSD formula. Phenomena other than repair of sublethal injury, specifically repopulation, are not accounted for by these curves. (From Withers HR. Failla memorial lecture. Contrarian concepts in the progress of radiotherapy. *Radiat Res*. 1989;119[3]:395-412. Copyright ©2024 Radiation Research Society.)

$$\mathrm{BED} = \frac{nd}{1 + \dfrac{d}{\alpha/\beta}}$$

This equation is based on the LQ model, and the n represents the number of fractions of dose d.[105]

Tumor Control Probability

The likelihood of successfully controlling a tumor is directly linked to the increasing amounts of radiation administered and subsequently the higher proportion of tumor cells that do not survive. This hinges on the ability to eliminate the final clonogen, which could be the cell capable of regenerating the entire tumor. Hence, the achievement of tumor control happens quite suddenly. When visualizing the relationship between tumor control probability (TCP) and the dosage of radiation, a unique pattern emerges. For a certain range of dosages, there appears to be no noticeable response. However, once a specific threshold is crossed, there's a swift rise in the TCP, culminating in a hypothetical 100% control rate when all tumor cells are killed. This progression closely follows a sigmoidal pattern with a low initial slope, increasing the slope to an inflection point, and leveling off as it approaches 100%. Furthermore, if the radiation treatment manages to diminish cell survival to the point where there is just one clonogen left in each tumor on average, the cure rate would be 37%. This probability of tumor control can be modeled using the equation:

$$\mathrm{TCP} = e^{-Sn}{}_0$$

In this equation, n_0 is the initial number of tumor cells and S is the surviving fraction of clonogens per tumor. Thus, if the average number of surviving clonogens is 1, the TCP is 37%.

It is often advantageous to use the dose required to kill 90% of the population, D_{10}, to calculate TCP where D_{10} is defined as:

$$D_{10} = \ln 10 \times D_0 = 2.3 \times D_0$$

Therefore, if a tumor has 10^{10} initial clonogens, and on average there is 1 clonogen remaining (ie, TCP = 37%), the tumor will have been treated with $10 \times D_0$. If the D_0 in this example is 3 Gy, then D_{10} is 6.9 Gy and the total dose required to achieve 37% TCP is 69 Gy. If one additional D_{10} is given with a total dose of 75.9 Gy, then there is only 0.1 clonogen surviving on average and TCP increases to 90%. This sensitive behavior of TCP is due to the sigmoidal shape of the function requiring careful consideration of

radiation dose. This relationship is modeled in Figure 3.12, which further shows that as the tumor size increases, the dose needed for tumor control also increases.

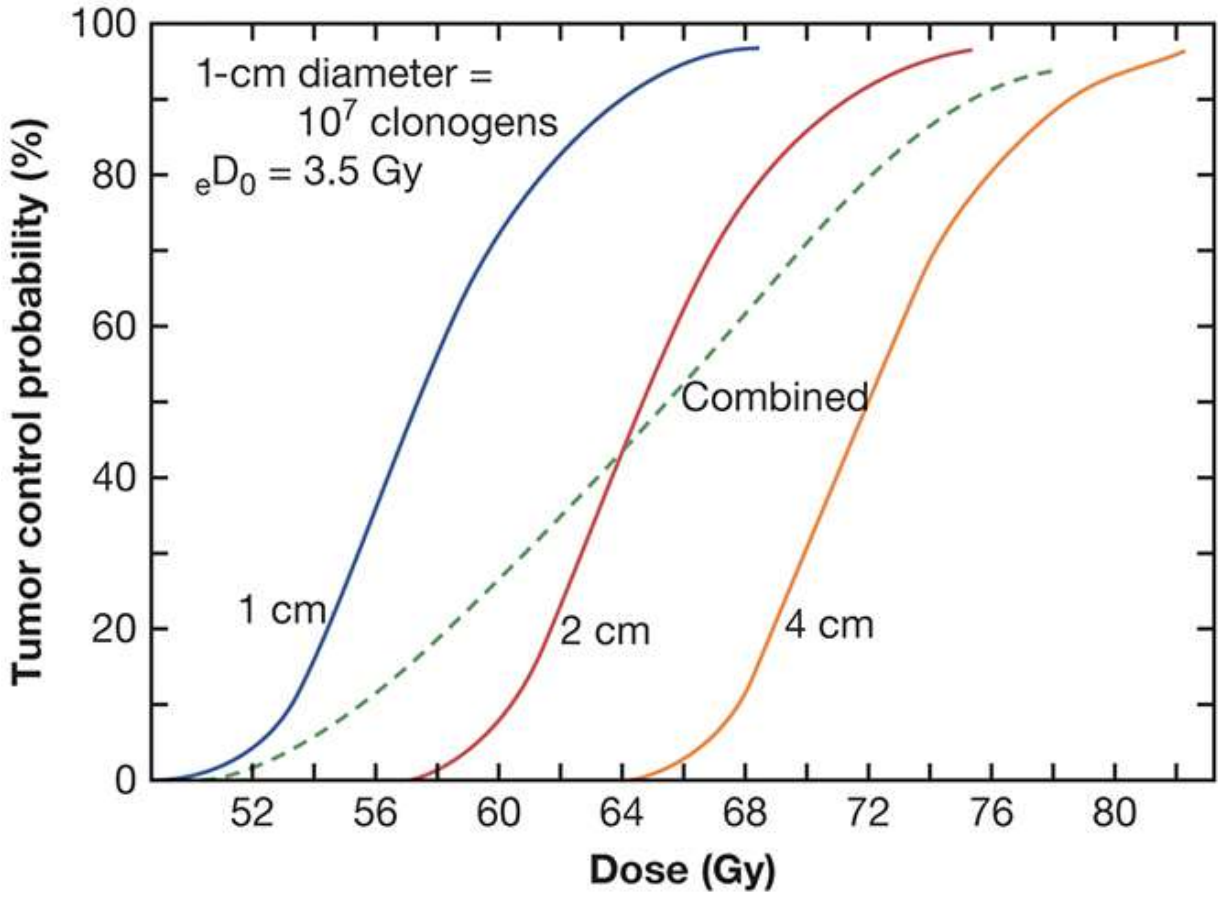

FIGURE 3.12 Theoretic tumor control probability (TCP) curves for three sizes of spherical tumors (solid lines) and one that would result from a study incorporating into the dose-response analysis all three tumor sizes in equal proportions (broken line). They were calculated on the assumptions that the dose was given in 2-Gy fractions, that the $_eD_0$ value for 2 Gy/fraction was 3.5 Gy, and that a 1-cm diameter spherical tumor contained 10 clonogens. As tumor volume increases, so does the dose required for a certain probability of control. The cell number increases by 8 times and 64 times as the spherical tumor increases from 1 cm diameter to 2 and 4 cm, respectively. An exponential increase in clonogen number is related to a linear increase in dose for an isoeffect. Heterogeneity of even one factor, initial clonogen number, causes the TCP curve to be shallower (broken line). Retrospective clinical studies incorporate a large number of causes for heterogeneity of response.

This same relationship can be applied to normal tissues as well, generating a dose-response relationship curve for tumors versus normal

tissues. If the tumor is more sensitive to radiation than the normal tissue, then the tumor's dose-response curve will be shifted more to the left than the tissue's curve (Figure 3.13); this would be clinically favorable. On the contrary, if the likelihood of controlling the tumor falls to the right of the risk of damaging normal tissue, it implies a high risk of complications. In such cases, other treatments, like surgery or chemotherapy, might need to be considered if possible.

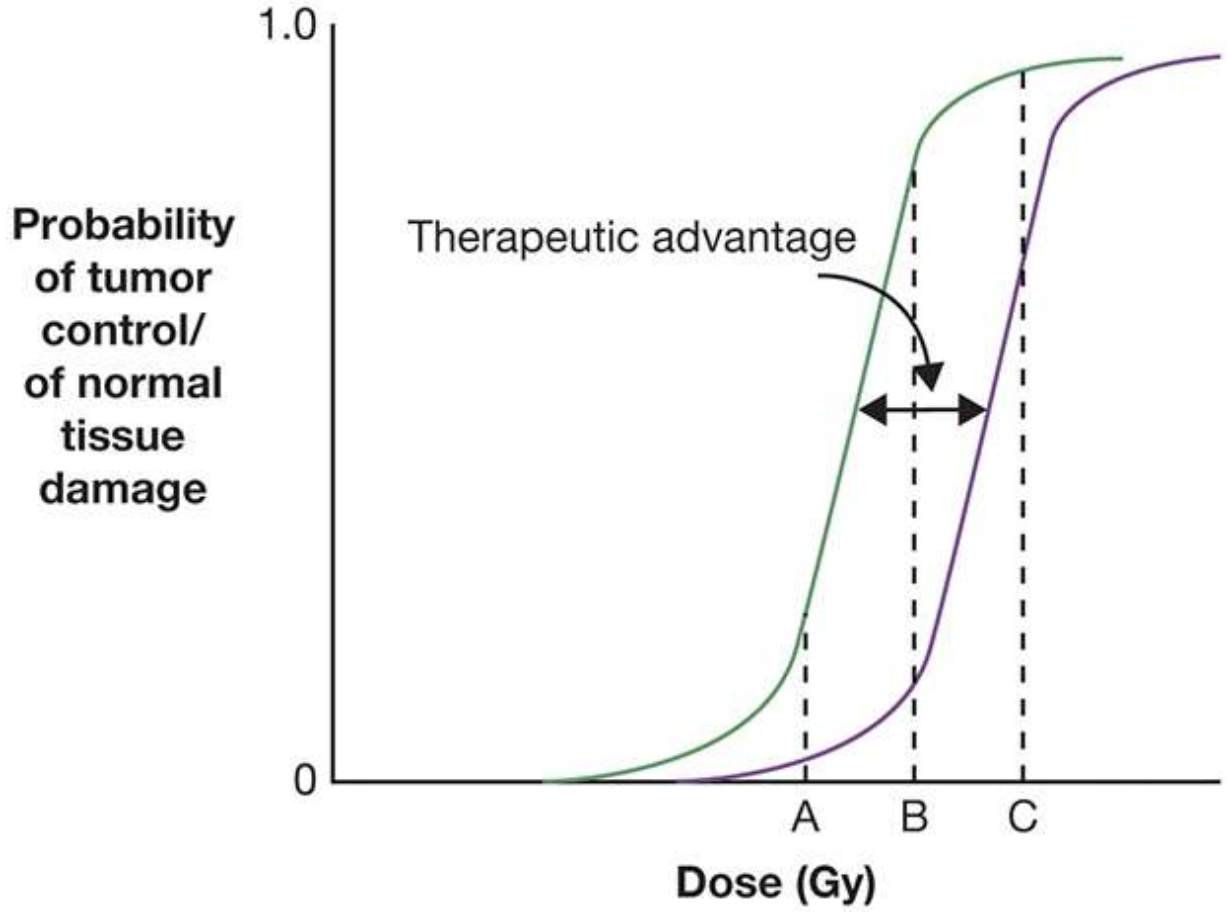

FIGURE 3.13 Theoretical curves showing the probability of tumor control and normal tissue complications. Both curves have a threshold and are log sigmoid in nature. The art of radiotherapy is to increase the distance between these two curves, that is, to derive a therapeutic benefit. If the normal tissue damage curve is to the left of that for tumor control probability (TCP), tumor control is unlikely without unacceptable normal tissue complications.

The Rs of Radiobiology

The *four classical Rs of radiobiology* are repair, reoxygenation, repopulation, and redistribution. These Rs are fundamental principles that explain why fractionated radiotherapy (dividing the total dose of radiation into multiple smaller doses over time) is effective in killing cancer cells. In recent years, two new Rs have been introduced: radiosensitivity and reactivation of antitumor immune responses.

Repair

Repair refers to the ability of cells to repair DNA damage following radiation exposure. The rate and degree to which normal tissue and tumor cells repair their DNA damage influence the effectiveness of RT. The ideal treatment regimen will allow for normal tissues to repair their DNA, while impairing repair mechanisms within cancer cells. Tumors frequently have defects or mutations in their DNA repair machinery. As such, fractionation of radiation treatment can allow for DNA repair within normal tissue, with more limited efficacy of repair in tumor cells. The accumulation of DNA damage within tumor cells with repeated radiation doses ultimately promotes cell death.

The extent of repair is influenced by whether the damage from radiation treatment is lethal or sublethal. Lethal damage is unrepairable and irreversible, while sublethal damage can be repaired unless additional doses are administered to collectively cause lethal damage. This phenomenon is illustrated in Figure 3.14, which shows that a same dose split over time will allow for greater cell survival compared to administering the total dose at one time; this is due to the ability of cells to repair between treatments. In line with this principle, increasing the time between each dose allows for more time for repair and thus increases the surviving fraction. The LET of the radiation administered can alter this relationship due to the higher complexity of DNA damage of high-LET radiation (ie, complex DSB vs isolated DSB and SSB). Damage from low-LET radiation is therefore easier to repair, and increasing the time between fractions can help promote tissue repair. On the contrary, the damage from RT is more pronounced for high-LET radiation given the complexity of DNA damage as well as known damage to the DNA repair machinery (see previous sections of this

chapter). This leads to more irreversible lethal damage, and greater time between doses might be needed to repair the sublethal damage.

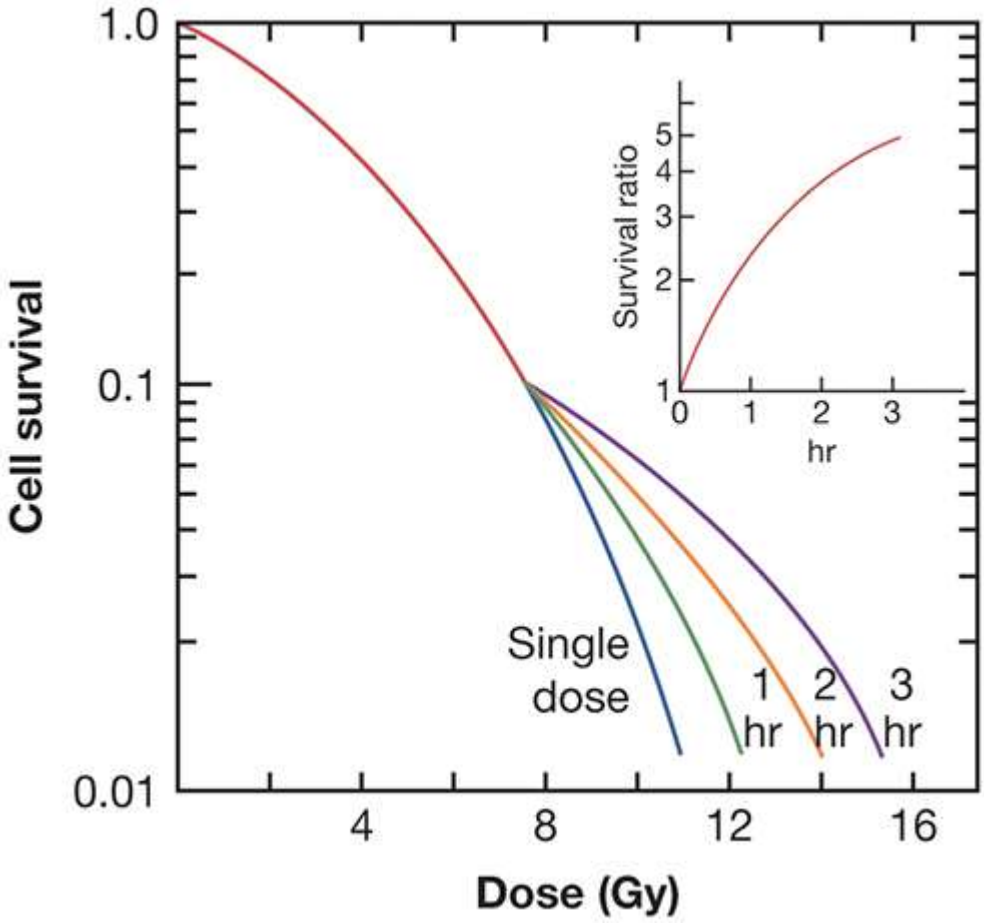

FIGURE 3.14 Recovery curves of the type first described by Elkind and Sutton.[77] The repair of sublethal injury begins immediately and can be measured in terms of survival ratio (inset) *or* the increment in dose to achieve isosurvival. (Reprinted by permission from *Nature:* Elkind MM, Sutton H. X-ray damage and recovery in mammalian cells in culture. *Nature*. 1959;184:1293-1295. Copyright © 1959 Springer Nature.)

The dose-rate effect is another principle of radiobiology primarily influenced by the extent of sublethal damage repair. Dose rate is the amount of radiation delivered per unit time, and a low-dose-rate (LDR) regimen is delivered throughout a more extended period. One example of this is with LDR brachytherapy. LDR treatments enhance the ability of normal tissues to repair sublethal damage. On the contrary, high-dose-rate (HDR) radiation regimens may limit the time available for repairing sublethal damage. As

shown in Figure 3.15, fractionated delivery repeats the “shoulder” of the LQ survival curve, illustrating the ability to repair sublethal damage due to the time between radiation fractions. LDR irradiation achieves the same effect and can be considered as infinitesimally small fractions yielding a shallower cell survival curve with no visible shoulder. Conversely, HDRs lead to less time available to repair sublethal damage, resulting in a steeper curve than LDR. As the dose rate is reduced, the curve shows a shallower relationship due to the higher repair of sublethal damage.

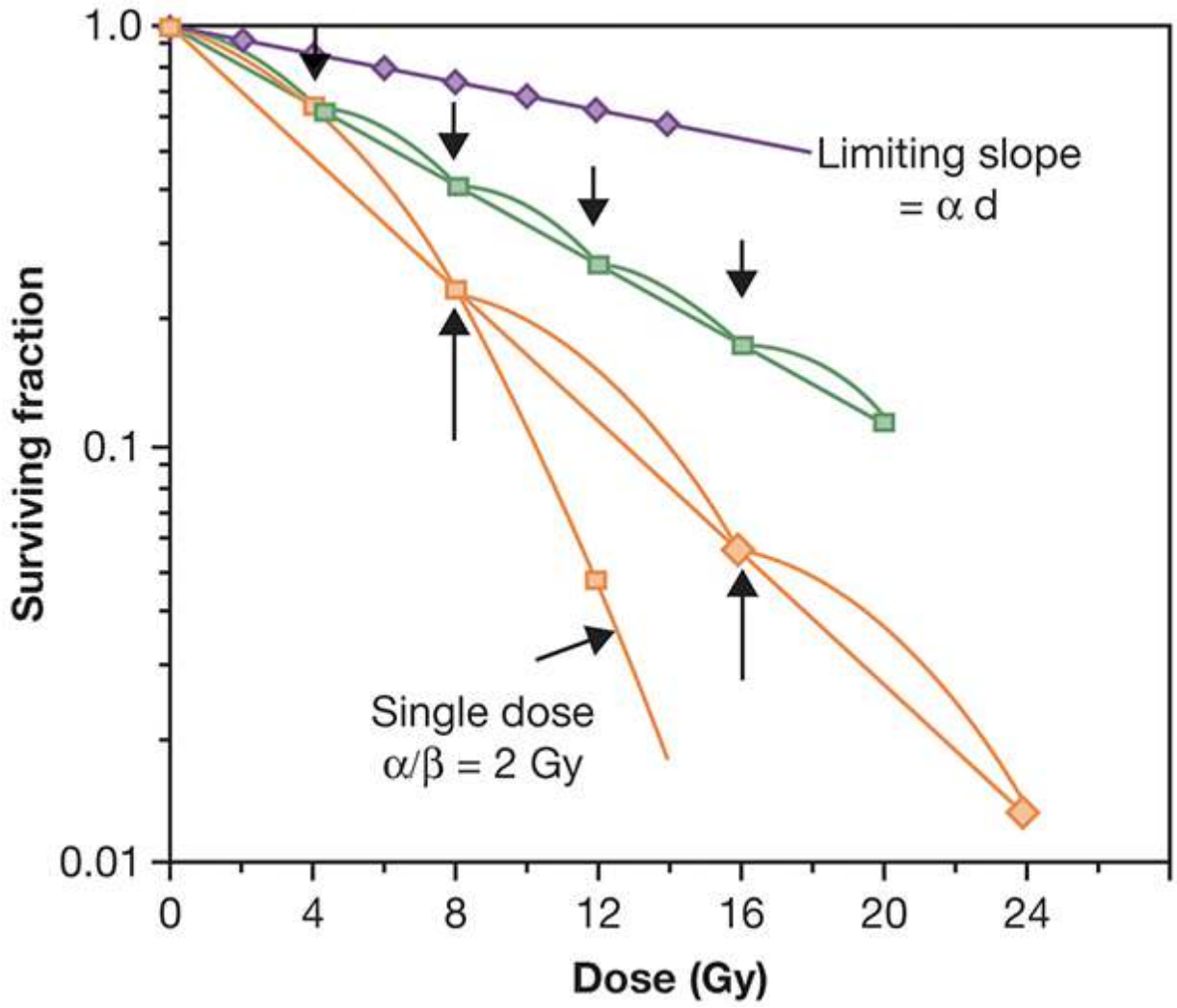

FIGURE 3.15 Multifraction dose-survival curves compared with a single-dose curve. Effective survival curves for multifraction regimens that produce an equal (proportionate) decrement in survival from each dose are linear, with shallower slopes than the single-dose curve at the same dose. Slopes of the multifraction curves become less steep with a decrease in fraction size until the dose per fraction is so low that multihit killing contributes negligibly and the slope is the limiting one determined by single-hit killing (and ${}_eD_0$ = 1/cr). The dose per fraction below which the effective survival curve becomes no shallower is a function of the curviness of the single-dose survival curve and is lower than the α/β value.

Reoxygenation

There is great heterogeneity in the level of oxygenation within solid tumors, given the abnormal and aberrant blood supply commonly seen within tumors. As previously discussed, oxygen helps stabilize DNA damage and limits the cell's ability to repair DNA. As such, during each radiation treatment, the well-oxygenated radiosensitive tumor cells are preferentially

killed. The clearance of these cells allows for more oxygen to become available to other previously hypoxic areas of the tumor. This process of making the formerly hypoxic cells more susceptible to radiation-induced DNA damage is termed "reoxygenation." Importantly, "reoxygenation" commonly occurs between doses of radiation treatment and is one of the primary reasons for delivering radiation treatment in small, fractionated doses. The importance of oxygen in RT-induced cell killing has sparked interest in strategies that help increase tumor oxygenation. These include hyperbaric oxygen therapy,[106] as well as treatment with nanoparticles carrying oxygen-producing molecules.[107,108]

Redistribution

The cell cycle is broken down into multiple phases: G1 (post- mitotic), S (DNA synthesis), G2 (pre-mitotic), and M (mitosis). Cells in the G2 and M phases are more radiosensitive while those in the late S phase are most resistant to radiation (Figure 3.16). As such, during radiation treatment, the cells in the M and G2 phases are preferentially killed. Fractionating the doses allows for multiple opportunities for cells to "redistribute" to the more radiosensitive cell cycle phases during treatment. This phenomenon also is another important reason for fractionating treatment. Of note, certain tumor cells can be slow-cycling or enter a senescent stage where they do not progress through the cell cycle phases; this can promote radioresistance.

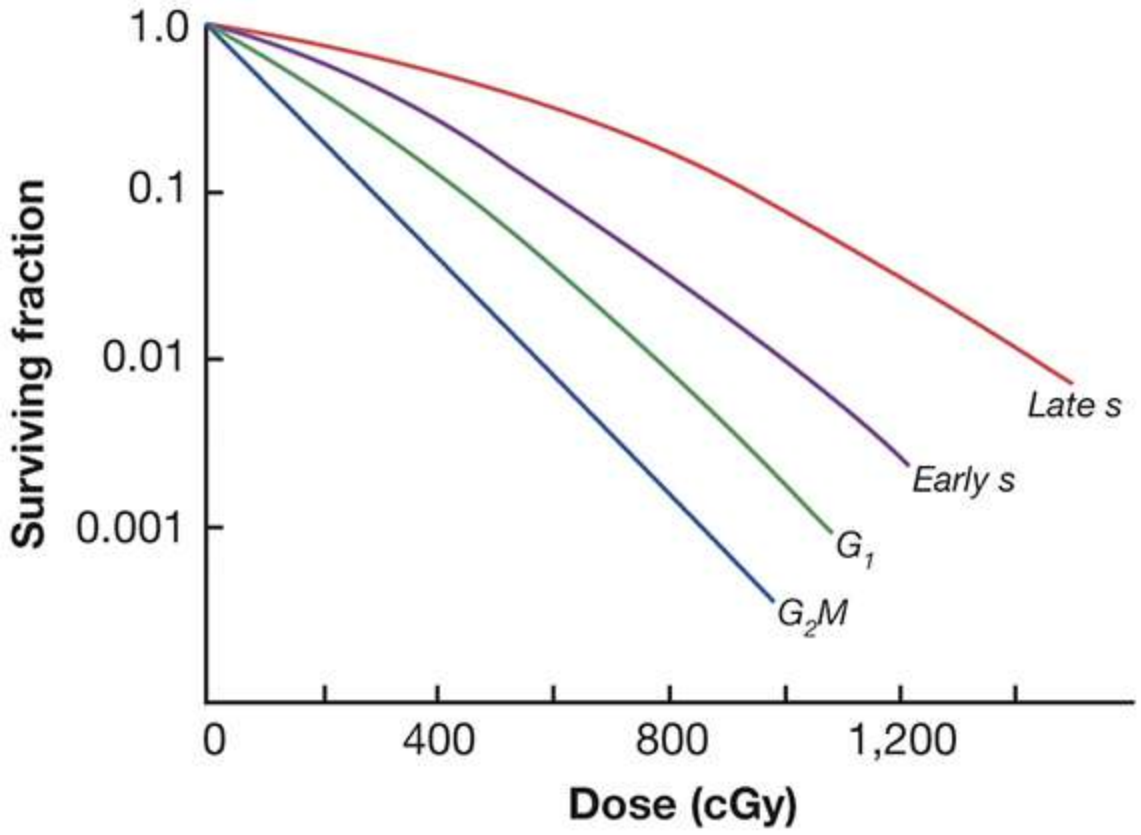

FIGURE 3.16 Radiation dose-survival curves for one line of mammalian cells (V79 Chinese hamster) synchronized in four positions in the division cycle. Significant differences occur in the survival of cells at different ages, with the differences relative to absolute survival being greatest at lower doses. The survival ratio between late S and G_2M cells after 2 Gy is approximately 5. (Reprinted with permission from Withers HR, Peters LJ. Biological aspects of radiotherapy. In: Fletcher GH, ed. *Textbook of Radiotherapy*. 3rd ed. Lea & Febiger; 1980:103-180.)

Cell cycle redistribution is one of the primary influencers of the "reverse dose-rate effect," whereby reducing the dose rate can allow for cells to more efficiently cycle through the cell cycle and thus increase the likelihood that they are in the more radiosensitive phase during radiation administration. On the contrary, with HDRs, cells can enter a senescent state or have sufficient damage to the DNA to prevent quick progression through the cell cycle.

Repopulation

Following radiation exposure, cellular repopulation can occur in normal tissues and tumors. Most cancer cells have a higher rate of cell division and

act similarly to acute-responding tissues. In cancer cells after cytotoxic therapy, the surviving cells (clonogens) can increase their rate of division to repopulate the tumor, termed “accelerated repopulation.” Figure 3.17 shows an example of a rat rhabdomyosarcoma’s exponential repopulation of the surviving clonogens within days after radiation treatment.[109] In this figure, the repopulation of surviving clonogens can be appreciated even when the overall tumor seems to be regressing. This phenomenon is known as accelerated repopulation, and if the surviving tumor cells are able to divide faster than the speed of radiation-induced cell killing, the tumor grows back over time. This is especially relevant during long treatment regimens (eg, over several weeks).

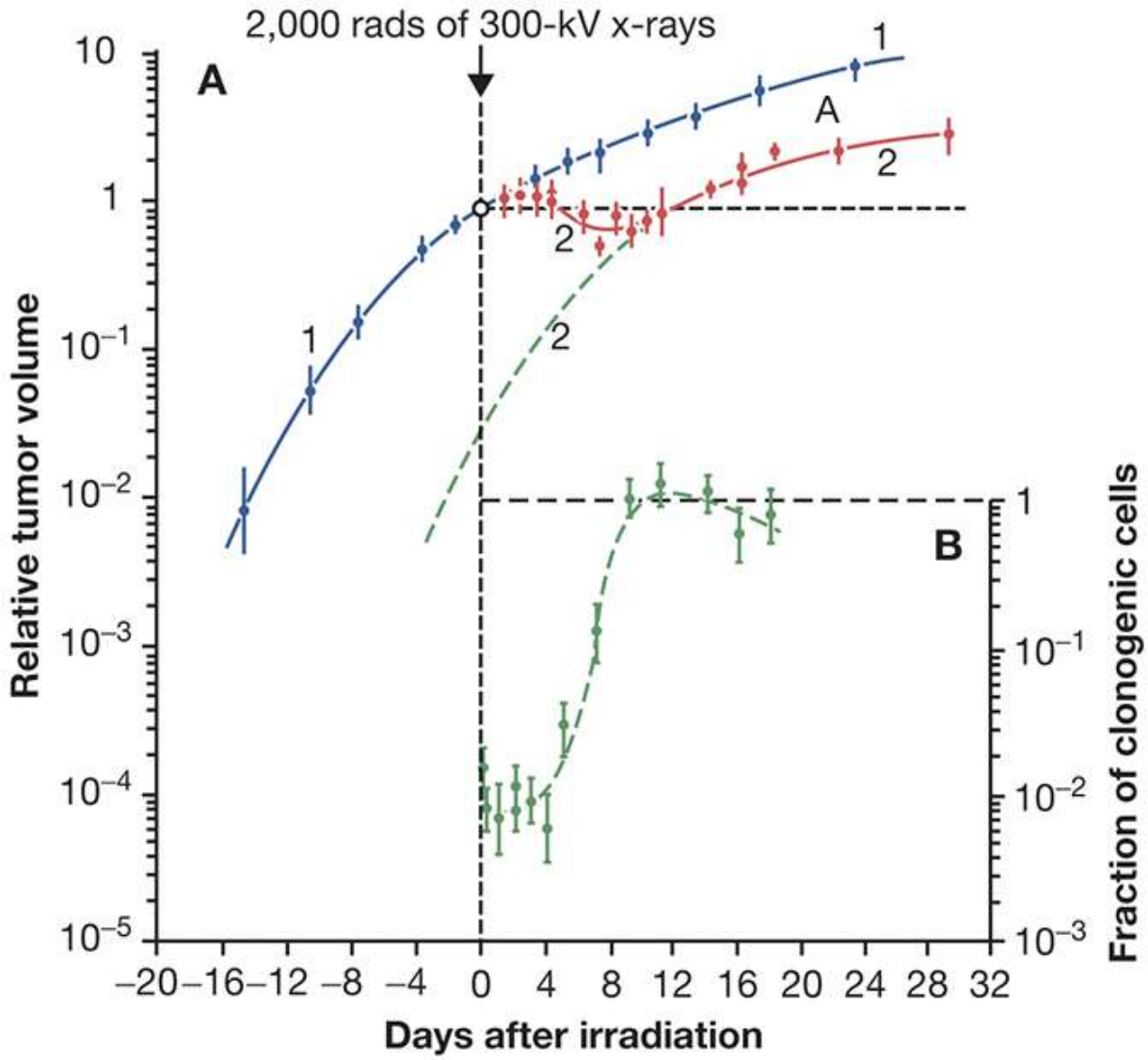

FIGURE 3.17 A. Growth curves for a rat rhabdomyosarcoma and its constituent clonogenic cells after a dose that reduced survival to 1%. The upper curve (1) shows unperturbed growth of tumors; the middle curve (2) shows regression and regrowth of tumors irradiated on day 0 with a dose that reduced cell survival to 1%; the lower curve (B) traces the repopulation of the tumor by surviving clonogens. Exponential regrowth of the surviving clonogenic cells occurs, whereas the gross tumor is regressing. (Reprinted from Hermens AF, Barendsen GW. Changes of cell proliferation characteristics in a rat rhabdomyosarcoma before and after x-irradiation. *Eur J Cancer*. 1969;5[2]:173-189. Copyright © 1969 Elsevier. With permission.)

To conceptualize the significance of accelerated repopulation during treatment, consider this: a 2- to 3-fold increase in the number of surviving clonogenic cells can enhance the tumor burden to an amount comparable to advancing the tumor's T-stage by one level.

One potential strategy to counteract repopulation is to use a technique called accelerated fractionation. This involves delivering the same total dose of radiation over a shorter time period, and sometimes delivering more than one fraction per day. While this strategy aims to complete radiation treatment before substantial repopulation can occur, it's important to balance this effect against the other Rs of radiobiology—which require time between treatments. Shortening the overall treatment time may limit the opportunity for healthy cells to repair, and for tumor cells to redistribute and reoxygenate. Notably, late-responding tissues are not affected by such treatment time changes given that they are not influenced by the extent of repopulation.

Radiosensitivity

The susceptibility to RT-induced DNA damage varies across tumor types, and it is based on the dose and fractionation regimen used; this understanding led to the proposal of "radiosensitivity" as the fifth R of radiobiology.[110] Relative radiosensitivity can be defined generally based on tumor types. For instance, hematologic-origin cancers and lymphomas are more radiosensitive while melanomas and sarcomas are more radioresistant. In addition, cellular-level genetic changes, alterations in signaling pathways, and availability of cancer stem cells within the tumor can all influence the relative radiosensitivity of a tumor. These cellular-level factors have led to the study of more targeted radiosensitization pathways for various cancers—for example, targeting the fibroblast growth factor receptor pathway to radiosensitize head and neck cancer and lung cancer,[20,111] suppressing autophagy to radiosensitize breast cancers,[112] and impairing DNA repair to radiosensitize prostate cancer.[113]

Reactivation of Antitumor Immune Response

As described in earlier sections, radiation significantly alters the immune cell milieu of the tumor microenvironment, and these changes can either promote or impair tumor cell killing. Importantly, the dose and fractionation regimen utilized greatly influence whether RT has a pro- or antitumor promoting effect; preclinical studies show that there is a threshold of dose/fractionation that increases antitumor immune responses while higher

doses can actually decrease tumor immunogenicity.[51] These thresholds have yet to be evaluated and established in humans with various cancers. Immunomodulators also show great promise as combination therapies with RT have been suggested to improve patient survival.[114] These observations have led to the recent proposal of reactivation of antitumor immune response as the sixth R of radiobiology.[115]

MODIFICATION OF DOSE FRACTIONATION PATTERNS

Conventional fractionated RT routines delivering around 2 Gy/day for 5 days a week were developed more than 50 years ago with the aim of limiting late effects by exploiting the differential response of tumors and normal tissues. The typically high α/β ratios of rapidly proliferating tissues like tumors make them more susceptible to radiation damage than tissues with lower α/β ratios like most normal tissues. This difference in α/β ratios is mostly evident in the initial shoulder of cell survival curves with low α/β ratio cells showing a large shoulder and high α/β ratio cells showing a much steeper curve. At a low dose of 2 Gy, the difference in cell survival is not as evident, but by repeating these 2 Gy fractions there is a large difference in cell survival at larger cumulative doses.

Early clinical data that supported conventional fractionation have been obtained with 2D radiotherapy techniques that irradiated the tumor volume along with larger volumes of normal tissues in close proximity. Modern RT techniques can deliver much more conformal dose distributions that limit the dose and volume of normal tissues receiving radiation, thereby decreasing late effects. Therefore, while conventional fractionation has proven effective for many situations, this delivery strategy is not universally ideal at maximizing the therapeutic ratio in all clinical scenarios.

In particular, this regimen might not be suitable for all medical scenarios, especially when dealing with extremely fast-growing tumors, and in tumors with heterogeneous α/β ratios that result in the accumulation of radioresistant cells with low α/β ratios.[116,117] The development of radioresistance following delivery of standard fractionated radiation regimens has been linked to improved DNA damage repair mechanisms in surviving clonogens, the high prevalence of radioresistant cancer stem cells within the tumor, and a higher redistribution of cells into the radioresistant

cell cycle phase.[118-120] These changes represent mechanisms that overcome the classical 4Rs of radiobiology that assist in tumor radiosensitization. Alternate fractionation regimens can help overcome radioresistance, improve targeting of tumors with low α/β ratios, and alter the delivered BED to tumors and normal tissues in order to maximize the therapeutic ratio.

Hypofractionation

Conventional dose fractionation might not be the best approach for low α/β ratio tumors that are late responding like most normal tissues. In fact, a low α/β ratio nulls the benefits of multifractionated, low-dose conventional fractionation regimens. Instead, hypofractionation could offer more therapeutic benefits administering larger doses of radiation in fewer sessions, which allows for the delivery of more substantial doses in each fraction while reducing the overall number of treatments. This strategy capitalizes on the fact that tumors with a lower α/β ratio are more sensitive to larger doses given in fewer fractions delivering a higher BED. However, clinicians often approach high-dose fractions with caution given that these large doses have historically been linked to vascular injuries, prolonged inflammation, and severe delayed side effects that could significantly impair a patient's quality of life and life span. However, technological and methodologic advancements allow for high-accuracy dose delivery to smaller well-defined targets that can tackle some of these biologic drawbacks. The safe delivery of large radiation doses and resulting high BED characteristic of hypofractionation and stereotactic body radiotherapy (SBRT) requires a high level of confidence in the accuracy of the entire treatment delivery process. This is accomplished by integrating modern imaging, simulation, treatment planning, and delivery techniques into all phases of the treatment process.

High single-dose RT regimens typical in stereotactic radiosurgery (SRS) or SBRT were pioneered in the late 1960s to target deep-seated brain lesions using single-dose treatments. These lesions required the use of stereotactic techniques to precisely locate lesions by using a well-defined three-dimensional coordinate system without the availability of modern image-guided techniques. This innovative approach paved the way for

Gamma Knife, a radiation tool designed for precise targeting of small brain lesions using 192 radiation beams emitted by radioactive Co-60 and collimated to deliver a single heavily focused dose of radiation.

The success of SRS pioneered by Leksell forms the basis of hypofractionation. SBRT has evolved into a highly effective treatment in controlling early-stage primary and oligometastatic cancer at locations throughout the abdominopelvic and thoracic cavities, as well as spinal and paraspinal sites; these treatments can now be delivered on linear accelerators. SBRT is used for select patients with primary or metastatic disease, with excellent local recurrence outcomes. The majority of patients treated with SBRT suffer from lung, liver, and/or spinal tumors, which also are common sites of oligometastatic disease. Eligibility for SBRT is typically limited to well-circumscribed tumors with a maximum cross-sectional diameter of up to 5 to 7 cm in order to limit the total volume of normal tissues receiving high doses.

Mounting evidence suggests that SBRT has remarkable efficacy in early-stage non–small cell lung cancer patients who are not candidates for surgery and its potential utility against limited metastatic disease.[121,122] The doses administered through stereotactic ablative radiotherapy are often adjusted based on the tumor's position, especially for tumors centrally located in the lung due to the presence of critical mediastinal structures. While the lung can tolerate the loss of function in small areas because of its ample residual functionality, not all tissues offer such flexibility. Therefore, the location and size of the treatment area are primary considerations in SBRT.

An illustrative example of hypofractionation comes from a study on SBRT for low- to intermediate-risk prostate cancer. This study revealed that delivering 36.25 Gy over four to five sessions led to prostate-specific antigen relapse-free survival rates on par with other standard treatments. Fraction sizes close to 8 Gy are particularly interesting, not just because they align well with the LQ model's parameters, but also due to their potential therapeutic advantages.[123] By optimizing dose distributions with intensity-modulated radiation therapy, fewer normal tissues are exposed to high radiation doses. Even if the total dose to the body might be higher, the rapid high-dose falloff outside the tumor can create a beneficial environment. In addition, it can result in gradients of immune mediators like cytokines and chemokines, which may boost the body's immune

response against the tumor.[124] Such doses might also send stronger "danger" signals, boosting tumor immunity and having a positive distant effect, which helps target smaller metastatic tumors (see the discussion about the abscopal effect in the prior section).

Hyperfractionation

Hyperfractionation involves delivering smaller radiation doses than the standard dose per fraction. The foundational principle behind this technique is to take advantage of the differential responses between the late-responding normal tissues and the acute-responding tumors when exposed to certain doses. By utilizing this difference, the treatment seeks to maximize tumor control while minimizing damage to the surrounding healthy tissues. The scheduling for hyperfractionation is also unique. While it can be performed by treating patients once a day for 6 or 7 days a week, the more common approach is to deliver two fractions per day for 5 days a week, with an intrafraction interval of no less than 6 hours.

Tumors that proliferate slowly and have a low α/β ratio might not benefit as significantly from hyperfractionation, making the approach more suited for acute-responding tumors. For late-responding tissues such as fibrovascular tissues, a 2 Gy/day fraction can be substituted with two fractions of about 1.2 Gy each. On the other hand, acute-responding tissues and tumors respond better to a fraction of about 1.05 Gy. This results in a therapeutic differential of 1.2/1.05, which translates to a 14% therapeutic benefit. Despite the tumor control benefits, it is important to note that there is a trade-off in the form of increased acute toxicity.

Several studies have been conducted to understand the benefits of hyperfractionation over conventional RT. A meta-analysis of randomized trials, mostly centered on cancers of the oropharynx and larynx, demonstrated the advantages of hyperfractionated RT. Even when some trials included a reduction in the total radiation dose, the hyperfractionated approach resulted in an 8% 5-year survival benefit.[125] It should be noted that clinically, hyperfractionation has not gained much use. This may in part be due to challenges in scheduling the twice-daily treatments.

LDR continuous irradiation, often seen in LDR brachytherapy, shares the biologic benefits of hyperfractionation. LDR brachytherapy involves

implantation of radioactive material into or close to the tumor. This method can delay proliferative cells in their cell cycle, especially in the late G2 phase, which can sensitize proliferative tissues and tumors without harming late-responding normal tissues. It ensures a high likelihood of sterilizing areas close to the radioactive sources and minimizes the volume of normal tissue exposed to high doses due to the rapid falloff of dose outside the treated area, providing what is known as a double advantage. However, the misplacement of seeds can create "cold spots" within the target volume, potentially reducing tumor control. Prolonged implantation of certain radioisotopes may expose normal tissues to high doses. Comparatively, HDR brachytherapy offers logistic benefits and increased safety for medical staff, along with the possibility of moving some normal tissues away from the high-dose field.

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CHAPTER 4

Molecular Pathophysiology of Tumors

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Radiotherapy (RT) is widely used for treating various cancer types. While RT has long been used, incorporating it in regimens involving the newest therapies remains a challenge. RT kills individual cancer cells by interfering with the biology of their proliferation. However, the efficacy of and resistance to RT are dependent on the pathophysiology of the tumor microenvironment (TME; Figure 4.1), which is made up of nonmalignant components. In addition, the efficacy of and resistance to the most commonly used cancer medicines, including chemotherapy, targeted therapy, and immunotherapy, depend on how RT alters the pathophysiology of the TME.

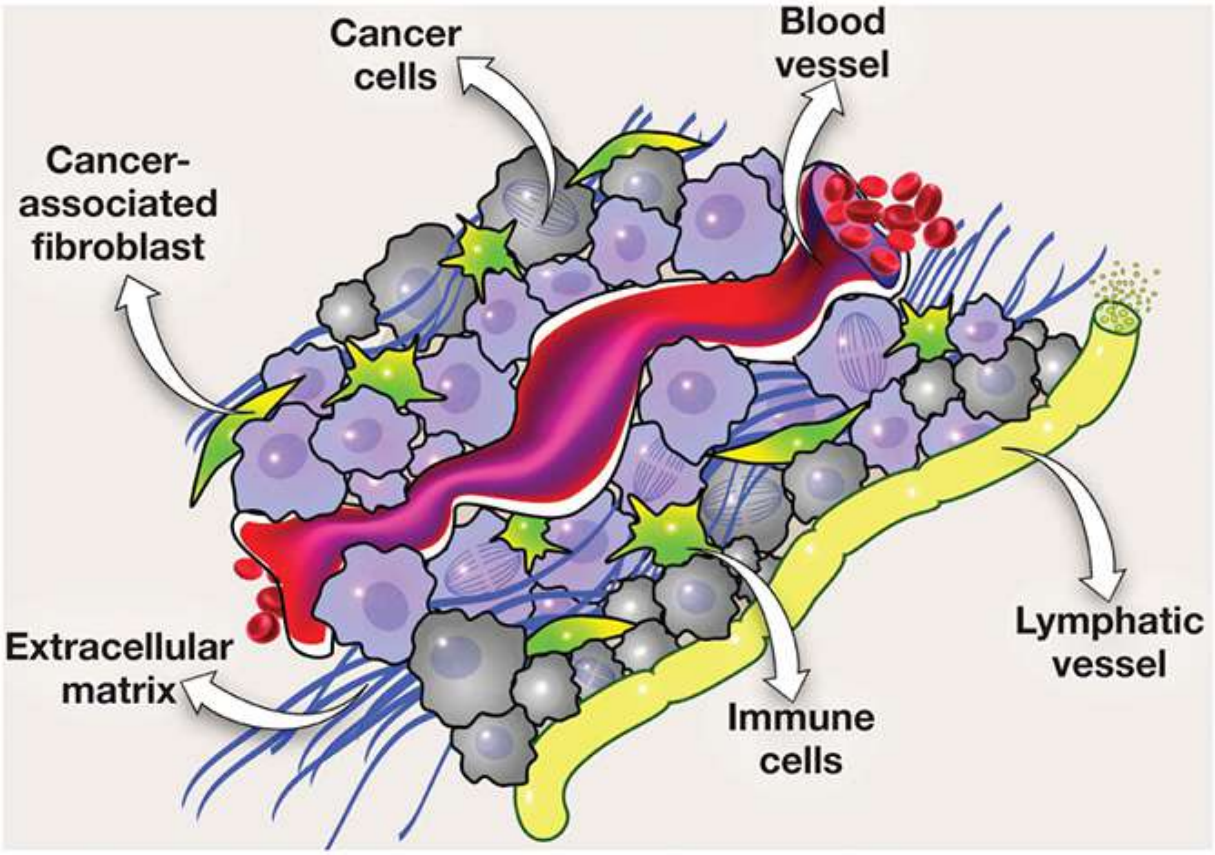

FIGURE 4.1 Solid tumors comprise cancer cells and stroma, produced abnormally through dysregulated angiogenesis, desmoplasia, and inflammation. Cancer cells recruit nonmalignant stromal cells, including fibroblasts, immune cells, blood, and lymphatic vascular cells, and promote extracellular matrix deposition. The result is a pathologic molecular, metabolic, and physical microenvironment that promotes tumor progression while resisting therapy and host immune response. (Used with permission of Annual Reviews: from Martin JD, Seano G, Jain RK. Normalizing function of tumor vessels: progress, opportunities and challenges. *Annu Rev Physiol*. 2019;81:505-534; permission conveyed through Copyright Clearance Center.)

Researchers have long appreciated that resistance to RT is fueled by subphysiologic oxygen concentration—hypoxia— within tumors.[1] However, we and others have worked to test the hypothesis that hypoxia is both a cause and effect of the molecular pathophysiology of tumors. Furthermore, we propose that RT be employed to reduce hypoxia toward sensitizing tumors to other therapies. In addition, alleviation of hypoxia can effectively sensitize a tumor for RT alone and with other treatments.

To increase the efficacy and overcome resistance to RT in patients, radiation oncology researchers must strive to understand the interplay

between RT, TME, and other therapies. This chapter describes how RT works and how the TME mediates its efficacy. It explains how RT affects other cancer therapies and how the TME inhibits these actions, as well as how RT can affect TME. How to modulate the TME to increase RT efficacy and overcome resistance and how to optimally combine these therapies are also explored.

HYPOXIA

Hypoxia is a hallmark of the TME. Several processes cause hypoxia in the TME. First, the abnormal growth (angiogenesis) and structure of vessels[2,3] make tumor vessels leaky and tortuous. Second, fibrosis (desmoplasia)[4] contributes to the compression of tumor blood vessels, which makes blood flow slower or not at all. Finally, immune cells (inflammation)[5-7] make vessels even leakier than angiogenic factors alone. Biomarkers related to these processes and hypoxia are negative prognostic biomarkers in many types of cancer, thereby underscoring their importance.[1] Thus, strategies that reverse these processes make TME more like a "normal" organ and prevent hypoxia have demonstrated benefits in some cancers when combined with RT or other cytotoxic therapies.[1,2,4,8-15]

Several strategies exist to "normalize" the TME toward alleviating hypoxia and increasing cytotoxic treatment efficacy. Tumor blood vessel leakiness and tortuosity are normalized with antiangiogenic therapies (AATs). Compression of tumor blood vessels is reversed by cancer-associated fibroblast (CAF)/extracellular matrix (ECM) normalization through CAF reprogramming by the administration of mechanotherapeutics.[16] Besides alleviating hypoxia, immunosuppression is reversed by administering immunotherapeutics, particularly immune checkpoint blockade (ICB), to normalize the activity of immune cells and blood vessel leakiness.[1] In this chapter, we describe these normalization strategies in the context of RT. We explore how RT primes the TME for other therapies and vice versa. We consider the various combinations of these therapies one by one. Finally, we survey some of the challenges of translating the results of preclinical studies of these drug combinations into clinical practice.

Hypoxia Mediates Treatment Response and Resistance

Blood vessels supply nutrients for cancer cells to expand. Paradoxically, cancer cells make blood flow inefficient by making vessel walls leaky through signaling and physically compressing the vessels.[17] Cancer cells produce angiogenic factors that produce vessels that never become mature.[2] Cell proliferation generates forces applied throughout the TME as compressive solid stresses. Cancer cell signaling stimulates CAF-mediated production and maintenance of ECM, which stores and transmits solid stresses.[4] Immature vessels are hyperpermeable with irregular morphology.[18] Solid stresses compress vessels, resulting in a reduced area through which blood flows. While in normal organs blood vessel permeability is consistent, and there is no compression, in tumors, these characteristics are heterogeneous and can differ between tumor types, stages, and locations within a tumor and between primary tumors and metastases in the same host.[1,19,20]

Healthy cells depend on nutrients to survive and proliferate, while cancer cells can survive in nutrient-sparse situations. Therefore, low oxygen concentrations (hypoxia) resulting from the dysfunctional tumor vasculature are a survival advantage for malignant cells. In addition, hypoxia in the TME reduces immune surveillance. Also, hypoxia promotes resistance to radiation, chemotherapy, and immunotherapy through various mechanisms. These factors provide a physiologic basis for findings demonstrating that the oxygen level in the TME is a validated prognostic biomarker and an emerging candidate biomarker of response.[1]

Hypoxia Promotes Malignant Disease Progression

Hypoxia makes cancer progress faster through several mechanisms. First, hypoxia exerts selection pressure because only particular cancer cells can survive the apoptotic cues induced by low oxygen.[21,22] Second, hypoxia inhibits tumor-suppressive genes, thereby permitting the proliferation of cancer cells.[23] Third, hypoxia promotes the production of immune-suppressive cytokines.[4] Fourth, hypoxia promotes invasive cancer cell phenotypes. Specifically, it stimulates cancer stem cells[24] and epithelial-to-mesenchymal transition phenotypes.[25] Fifth, hypoxia promotes some steps of the metastatic cascade, which is the process of cancer cells spreading

from the primary tumor throughout the host. For example, hypoxia promotes the production of promigratory and ECM-degrading factors that facilitate cancer cells to invade out of the primary tumor, intravasate into tumor blood vessels, and, from there, circulate throughout the host toward colonizing distant organs.[26,27]

Hypoxia Promotes Anticancer Treatment Resistance

Hypoxia is a cause of resistance to RT, most types of chemotherapy, and immunotherapy reducing these drugs' efficacy through multiple mechanisms. Here, we describe how hypoxia affects the efficacy of anticancer treatment modalities.

Radiotherapy

Ionizing radiation causes damage to mitochondria. The damage produces reactive oxygen species (ROS), which damage DNA, resulting in cell death. Unfortunately, RT induces less DNA damage in hypoxia.[28] Hypoxia stabilizes hypoxia-inducible factor 1 (HIF1). HIF1 induces glycolysis and accumulation of NADPH. Glycolysis induces lactate accumulation, which upregulates HIF1 to complete a feedback cycle.[29] Meanwhile, NADPH scavenges ROS, which are required for cell damage.[30]

Chemotherapy

Oxygen relies on functional tumor blood vessels to reach cancer cells; so does chemotherapy, both small molecules and nanoforumlations.[31] Unfortunately, these vessels are immature and inefficient. The drug concentration in a tumor lesion correlates with the lesion's volume reduction in patients.[32,33] If the delivery of oxygen is limited to a tumor, then it is likely that chemotherapy delivery is similarly restricted and that the efficacy of chemotherapy is weakened. So, hypoxia is likely correlated to chemotherapy resistance. Also, many chemotherapies are less potent in hypoxia. Along these lines, weak-base chemotherapies are neutralized by acidity, another metabolic characteristic of a hypoxic TME.[1] Therefore, hypoxia indicates that chemotherapy cannot reach tumors in sufficient concentrations and its presence reduces most chemotherapies' efficacy.

Immunotherapy

ICBs have revolutionized the treatment of many solid tumors. However, they are effective in less than 20% of patients with cancer,[34] and many develop severe immune-related adverse events.[35] Hypoxia mediates resistance to ICBs through several mechanisms.[6,36,37]

First, hypoxia recruits immunosuppressive cells. For example, hypoxia promotes the expression of chemokines that recruit regulatory T (Treg) cells.[38] These cells are immunosuppressive because they induce the immune system to tolerate cancer cells, which enables survival and proliferation.[38-40] Second, hypoxia stimulates proangiogenic and immunosuppressive signaling. Specifically, hypoxia promotes the expression of the angiogenic and immunosuppressive factor vascular endothelial growth factor (VEGF). Besides promoting the growth of immature tumor vessels, which leads to hypoxia, VEGF has immunosuppressive functions. For example, VEGF reduces the recognition of cancer cells by the immune system by inhibiting dendritic cell (DC) maturation.[41] With VEGF signaling, DCs do not present cancer cell antigens to other immune cells so that they can recognize cancer cells for elimination. Also, angiogenic signaling reduces the ability of leukocytes to attach to the tumor vessel wall toward migrating into the tumor parenchyma.[37],[42] Beyond angiogenic signaling, hypoxia affects the activities of leukocytes, which migrate slower in hypoxic tissues.[43,44] Hypoxia also reduces the functions of leukocytes. Specifically, hypoxia recruits immunosuppressive cells that block antitumor immune cells from recognizing and killing cancer cells.[38,45] Third, hypoxia signaling induces immunosuppression. Hypoxia and its signaling upregulate immune checkpoints on antitumor immune cells and checkpoint ligands on cells throughout the TME to halt the activities of T cells.[46-50] Similarly, acidity impairs antitumor immune cells' ability to kill cancer cells.[51] Fourth, hypoxia and immunosuppression are both related to low blood perfusion. Trafficking immune cells must enter lymph nodes and subsequently traverse tumor blood vessels to reach cancer cells.[52,53] In hypoxic areas of tumors where perfusion is low, immune cell infiltration also is low.[54] Accordingly, increase in perfusion is correlated with response to ICB in preclinical murine models.[55] Therefore, hypoxia affects the efficacy of immunotherapy through multiple mechanisms.

Hypoxia as a Prognostic Biomarker

Beyond affecting response to treatment, hypoxia plays a role in tumor progression. Many clinical studies have supported and validated the notion that hypoxia causes tumor progression and treatment resistance because hypoxia is an independent prognostic biomarker of poor outcome in many cancer types.[1,14,21] In an apparent contradiction with hypoxia as a negative prognostic biomarker, for decades, researchers observed that angiogenesis and a high degree of tissue vascularization are required for tumor growth.[2] Specifically, the density of blood vessels in tumor regions of intense new vessel formation[56] is validated broadly as an independent and prognostic biomarker of worse response.[1] Thus, neovascularization is required for tumor growth, while the lack of oxygen, which depends on blood vessels, also predicts faster disease progression.

Key Determinants of Hypoxia

Hypoxia is a biomarker of worse outcomes for patients with cancer, as is high vascularity.[1] This is paradoxical because oxygen is delivered to tumors through blood vessels, so assuming that higher vascularity results in more oxygen is reasonable but incorrect. To address this conundrum, in 2001, we proposed that the judicious use of angiogenesis inhibitors, which block new vessel formation, could improve vascular function and thus improve oxygenation.[8,9] In other words, the normalization hypothesis posits that an excess of immature blood vessels reduces oxygen delivery. In this section, we describe the vascular abnormalities caused by TME and how angiogenesis, desmoplasia, and inflammation cause them (Figure 4.2).

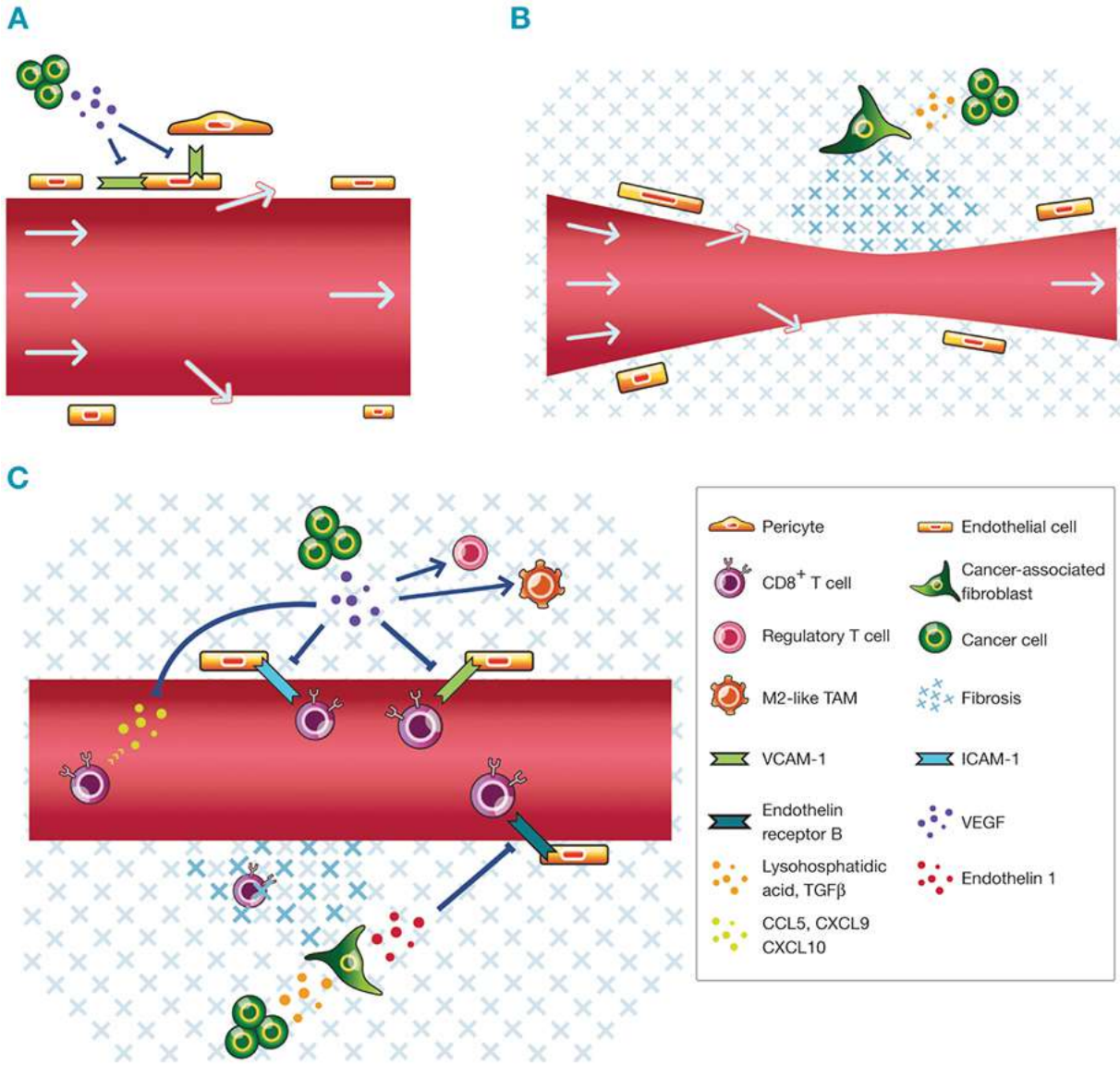

FIGURE 4.2 Tumors promote angiogenesis, desmoplasia, and immunosuppression, thereby inhibiting blood flow, oxygen delivery, and immune cell infiltration. A. Simplified depiction of leaky tumor blood vessels and relevant cells. Cancer cells secrete angiogenic factors, including vascular endothelial growth factor (VEGF), that reduce the expression of vascular stabilizing molecules, such as vascular adhesion molecule 1 (VCAM-1), which mediates the interaction of endothelial cells with themselves and perivascular cells in mature vessels. Plasma and blood-borne molecules (arrows) flow out of pores in the vessel wall, impairing blood flow. B. Simplified depiction of a compressed tumor blood vessel and pertinent cells. Cancer cells activate cancer-associated fibroblasts through various signals, including transforming growth factor-β (TGF-β). This activation leads to more fibrosis, which mediates the transfer of compressive physical force from the rapidly expanding cancer cell population onto blood vessels. Blood flow is reduced with compression. C. Simplified depiction of immunosuppression and pertinent cells. Cancer cells secrete VEGF and TGF-β among other factors that affect angiogenesis and fibrosis. VEGF recruits regulatory T cells and polarizes tumor-associated macrophages (TAMs) toward M2-like immunosuppressive

phenotypes. Further, VEGF blocks the recruitment and transmigration of $CD8^+$ T cells by interfering with VCAM-1 and intercellular adhesion molecule 1 (ICAM-1). In addition, TGF-β signaling increases fibrosis, physically impedes the migration of $CD8^+$ T cells, and inhibits their vascular transmigration through endothelin 1 signaling through the endothelin receptor type B. (Reprinted from Melo V, Bremer E, Martin JD. Towards immunotherapy-induced normalization of the tumor microenvironment. *Front Cell Dev Biol*. 2022;10:908389. http://creativecommons.org/licenses/by/4.0/)

Vascular Abnormalities

Structure

Tumor endothelial cells (ECs), which line the vessel wall, have an abnormal phenotype. In blood vessels of healthy organs, ECs are aligned with blood flow and attached tightly. Tumor ECs are misaligned with the flow. They are loosely connected and often protrude from either side of the vessel wall.[3,57] Similar to ECs in normal organs, tumor ECs have vesiculo-vacuolar organelles (VVOs), which connect the intravascular and extravascular areas. Their presence is increased with VEGF.[2,58,59] Perivascular cells provide structural support, filling gaps between ECs.[3] These cells send quiescence signals to ECs and separate from ECs during angiogenesis.[60] Tumor perivascular cells are less contractile, compromising their influence over vessel function.[61] In vessels in healthy organs, there is a vascular basement membrane (BM) that provides structural support for both ECs and pericytes. In tumor vessels, the BM is heterogeneous, thick in some sections, and absent in others.[62] Therefore, tumor vessels' components and structure are abnormal.[2,11,18]

Pathologic angiogenesis dictates that the blood vessels within a single tumor are more heterogeneous in their characteristics than in normal organs.[63] Vessels branch in an ordered hierarchy of arteries, arterioles, capillaries, venules, and veins in normal organs. In tumors, blood vessels do not display these phenotypes. They are often saccular with irregular branching.[64] The characteristics of single vessels can even vary substantially over their length.[64-66] Some tumor vessels have a large, dilated diameter. Others are tortuous rather than straight.[67,68] Solid stress leads to vessels collapsing shut with buckling.[69-71] As a result of angiogenesis and solid stress, only some tumor regions have perfusion while others have low or

none. In certain cases, tissue volumes on the order of cubic millimeters lack perfusion, while in normal tissues, vessels are only 100 to 200 μm apart.[66]

Function

As tumor vessels undergo angiogenesis and ECs detach from each other and pericytes, they become leaky[3] (Figure 4.2A). In addition, VVOs may cause leakiness.[58,59] As plasma leaks from vessels, the fluid pressure difference across the vessel wall is reduced, and fluid transport into tumors slows.[67,72] After plasma leaks, the red blood cell density increases so viscosity increases.[73] Also, leaky vessels upstream have lesser pressure such that the intravascular pressure gradient, which is the driving force of intravascular blood flow, is reduced.[74] Tumor ECs and pericytes cannot control flow, which is transient in speed and direction. Tumor vessels that collapsed lack blood flow.[75] Compressed vessels have reduced flow rates because of smaller luminal cross-sectional area.[65,74] One upstream collapsed vessel could eliminate flow to several downstream vessels.[64,71,75] Thus, the function of tumor blood vessels is characterized by spatial and temporal variations in flow.[76,77]

Causes of Vascular Abnormalities

Angiogenesis. One century ago, scientists noted that the vasculature is associated with tumor growth.[78] Afterward, the development of transparent window techniques enabled more insights.[79-82] In 1968, scientists suggested that tumors produce an "angiogenic" substance that initiates neovascularization.[83,84] In 1971, Folkman hypothesized that blocking angiogenesis reduces tumor growth and metastasis.[85] In 1978, researchers observed that angiogenesis occurs during neoplastic transformation—and, thus, the hypothesis that antiangiogenesis could be used to prevent cancer was put forth.[86] Decades later, in 2004, bevacizumab was the first antiangiogenic agent (AAT) approved for cancer treatment. An antibody specific to VEGF increased survival when added to standard chemotherapy in patients with metastatic colorectal cancer.[87] Today, more than a dozen AAT are approved for various types of cancer in combination with various treatments, including seven with ICBs.[1]

Angiogenesis is regulated by the balance of proangiogenic and antiangiogenic factors.[9] In normal physiology, this balance is in equilibrium spatially and the "angiogenic switch" is "off." A transient increase in proangiogenic molecules turns the "angiogenic switch" "on" during physiologic angiogenesis (eg, during embryonic development, wound healing, and formation of the corpus luteum). During tumor initiation and progression, the increase in tumor-derived proangiogenic molecules tips this balance permanently, and blood vessels form haphazardly to support the growing tumor mass. In "sprouting" angiogenesis, BM and other ECM are digested; ECs divest of pericytes, migrate and proliferate into a sprout; a lumen forms through canalization; branches form through confluence and anastomoses of sprouts enabling perfusion; and the newly formed vessels invest in BM and pericytes.[3] Tumor vessels remain immature, without typical differentiation into arterioles, capillaries, and venules.[3,18,82,88]

Besides sprouting angiogenesis, there are at least five mechanisms of neovascularization described in tumors: vessel co-option,[89,90] intussusception,[91] vasculogenesis,[3,92] vascular mimicry,[93] and cancer cell to EC transdifferentiation.[2] During vessel co-option, tumor cells migrate and proliferate surrounding vessels, forming "perivascular" cuffs. These cuffs grow past the diffusion distance limit of oxygen and other nutrients. Furthermore, they can collapse vessels as they generate solid stresses.[90] During intussusception, a vessel enlarges in response to angiogenic factors from cancer cells, and a tissue column grows in the expanded vessel lumen to separate the lumen into a vessel branch point.[91,94-96] During tumor vasculogenesis, endothelial precursor cells (EPCs)—originating from bone marrow niches and circulating in the peripheral blood circulation—can also promote neovascularization.[92,97,98] EPCs of non–bone marrow origin are recruited from adjacent tissues and/or circulation.[99,100] During vascular mimicry, the luminal surface of vessels may be lined by cancer cells.[93] Finally, trans-differentiated cancer cells[101] or cancer stem-like cells[3,102-104] can compose a fraction of ECs in tumor vessels. Thus, "vasculogenesis" describes neovascularization induced by cancer stem cell integration into the vasculature.[105] Parsing the relative contribution of these processes to tumor neovascularization could lead to better drugs to ameliorate pathologic angiogenesis.[105],[106]

Desmoplasia. Other components of the TME include CAFs and the ECM, which CAFs produce and maintain, giving a physical structure to tumors. Cancer cells stimulate desmoplasia, the growth of fibrotic tissue and ECM, through fibroblasts. Depending on the tumor type and its differentiation stage, malignant cells may be distributed throughout the ECM as individual cells (eg, lymphomas, melanomas) or clumps or nests (eg, carcinomas). In poorly differentiated carcinoma, the cancer cells are loosely packed in clumps, whereas in well-differentiated carcinoma, the cells are connected with intercellular junctions and tightly packed in a nest enveloped by a BM. Nearby host cells such as fibroblasts migrate from the adjacent connective tissue or the primary tumor to the metastatic site.[107]

Desmoplasia also is dysregulated in tumors. Cancer cells signal to fibroblasts through proteins (eg, transforming growth factor-β or TGF-β), transcriptional factors, interleukins, matrix metalloproteinases, and ROS.[108] Hypoxia induces fibroblasts to produce and maintain ECM through connective tissue growth factor, TGF-β, and Sonic hedgehog signaling.[109,110] Once activated by cancer cells or hypoxia, CAFs greatly differentiate, contract, proliferate, and generate ECM components. The proliferation and contraction of CAFs generate physical forces stored in and transmitted by the dense ECM. As a result, solid stress levels are elevated, and blood and lymphatic vessels are compressed[71,74] (Figure 4.2B). In turn, tumors' interstitial fluid pressure (IFP) is elevated because fluid drainage is reduced through the collapsed lymphatics.[71] Fluid is also trapped in dense ECM, thereby raising IFP.[20] Thus, therapies modulating desmoplasia reduce both solid stress and IFP. Given the effects on the mechanical TME, these therapies are called mechanotherapeutics.[16] Nonetheless, agents altering fibrotic pathways such as TGF-β also affect other components of TME, including immune cells and ECs.[111]

Desmoplasia exacerbates reduced blood flow in tumors by increasing solid stress and IFP. Reduced blood flow leads to hypoxia-induced disease progression. Independent of the effects on blood vessels, solid stress promotes disease progression by making cancer cells more invasive[112] and tumor-adjacent tissue more malignant.[113] Desmoplasia promotes angiogenesis and immunosuppression through signaling, as certain CAFs produce angiogenic molecules[114] and inflammatory cytokines[115,116] (Figure 4.2C). Thus, desmoplasia promotes disease progression.[117]

Microenvironment Normalization Alleviates Hypoxia and Overcomes Resistance to Various Treatments

Vascular Normalization

Microvascular density (MVD) in vascularized areas within tumors[56] and hypoxia[14,21] are independent biomarkers predictive of worse treatment response in most cancer types.[1] While vessels deliver oxygen, dense vessels and low oxygen concentrations predict shorter survival. In 2001, to resolve this paradox, we postulated that the judicious use of AAT, which usually reduces MVD, increases vascular function, and reduces hypoxia.[8] Results from subsequent clinical studies have demonstrated that vascular normalization does occur with judicious use of AAT.[2],[4,11,12] Furthermore, patients with tumors having increased vessel function and reduced hypoxia after AAT have better outcomes.[1,4,12,14] These clinical results confirm that reduced hypoxia post-AAT slows disease progression and overcomes treatment resistance. Changes in hypoxia should be investigated as a predictive biomarker of response.

Passive vessel normalization is the pruning of immature vessels (their leakiness shown in Figure 4.3A), resulting in the remaining vessels being mature. The remaining vessels are more efficient, but the MVD might not be sufficient to supply the entire tumor volume. Active vessel normalization is the fortification of immature vessels with perivascular cells, which makes them more mature (Figure 4.3B). The vessels are on average more efficient, and the MVD is more likely to be sufficient to supply the entire tumor volume. Data from clinical trials, in agreement with preclinical data,[118-120] demonstrate that vascular normalization occurs after administration of an appropriate dose of AAT that avoids too much vessel pruning.[1,2,4,11,12] Along these lines, there is clinical evidence that active rather than passive normalization is associated with improved response to chemotherapy.[121]

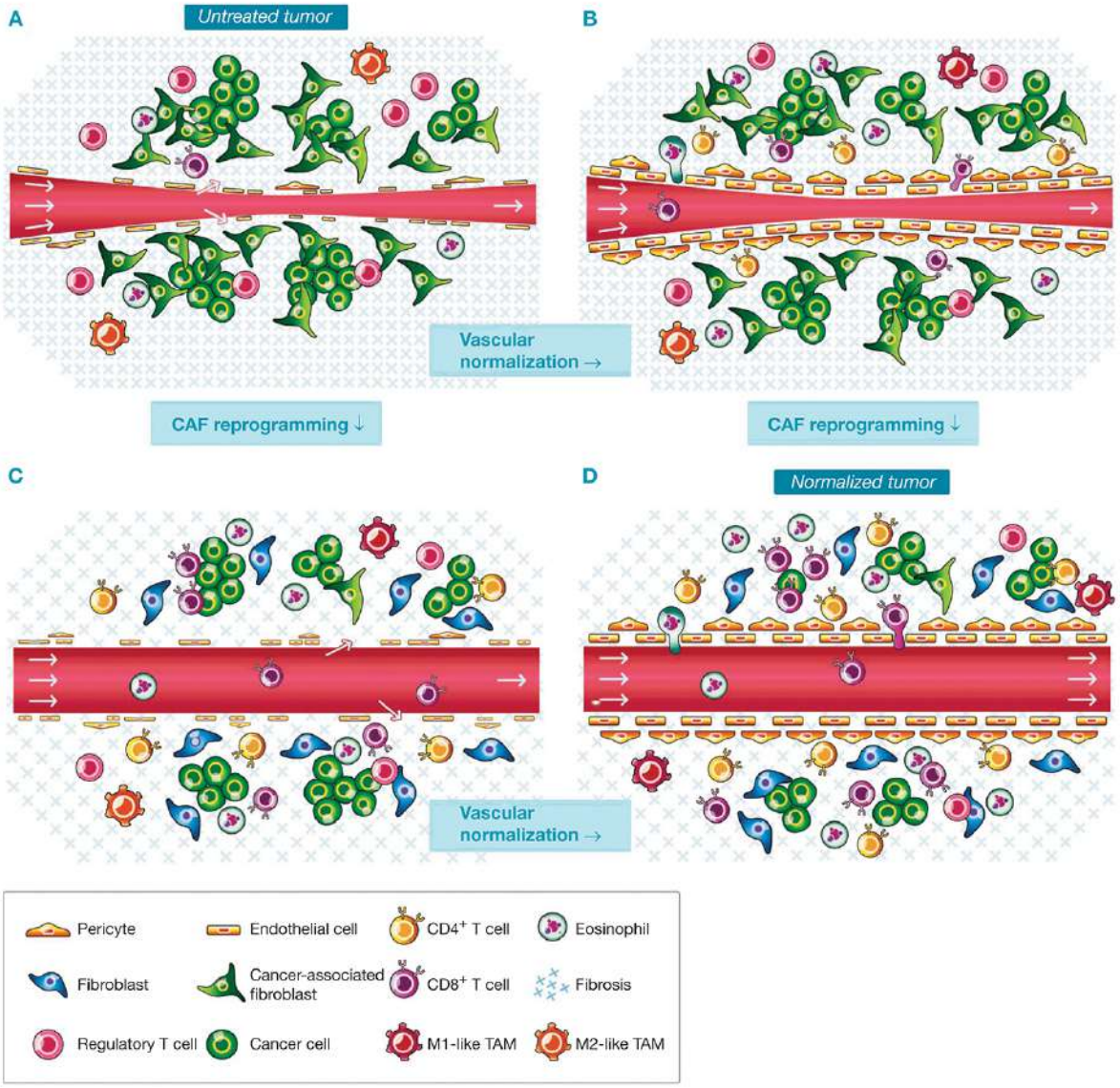

FIGURE 4.3 Vascular normalization and cancer-associated fibroblast reprogramming alleviate hypoxia toward promoting antitumor immunity. A. Depiction of a cross-sectional view of a single blood vessel in an untreated tumor. A pinch point in the blood vessel (red tube) and the inconsistent fortification of the endothelial cell layer with pericytes impair blood flow (gray arrows). The tumor has excessive immunosuppressive cancer-associated fibroblasts (CAFs), fibrosis, and $CD4^+CD25^+FOXP3^+$ regulatory T cells (T_{regs}), and reduced infiltration by $CD8^+$ and other subsets of $CD4^+$ T cells. B. Depiction of a cross-sectional view of a single blood vessel in a tumor treated with vascular-normalizing therapy. With treatment, the balance of pro- and antiangiogenic factors shifts such that endothelial cells are aligned and fortified with pericytes. Still, blood vessels remain compressed by mechanical stress. Immune trafficking and transmigration occur more efficiently. In addition, the immunosuppressive cells are reduced because of inhibited angiogenic and hypoxia signaling. Normalization by immune checkpoint inhibitors could depend on the accumulation of activated eosinophils. C. Depiction of a cross-sectional view of a single blood vessel in a

tumor treated with therapy that induces CAF reprogramming. With treatment, CAFs shift to quiescent fibroblasts and produce and maintain lower levels of fibrosis. These effects reverse vessel compression. Trafficking immune cells flow through tumors and migrate the interstitial space efficiently with less immunosuppressive CAF and hypoxia signaling. Also, the lack of fibrosis, particularly collagen, results in less physical migration restriction. D. A depiction of a cross-sectional view of a single blood vessel in a tumor treated with a combination of vascular-normalizing and CAF reprogramming therapy. Immune cells efficiently traffic to tumors, transmigrate, and migrate to clusters of cancer cells. (Reprinted from Melo V, Bremer E, Martin JD. Towards immunotherapy-induced normalization of the tumor microenvironment. *Front Cell Dev Biol*. 2022;10:908389. http://creativecommons.org/licenses/by/4.0/)

Hypoxia as a Potential Biomarker of Response to Vascular Normalization

Data from hypothesis-generating clinical trials indicate that patients with tumors that after AAT have increased tumor vessel function (eg, improved perfusion, increased vessel maturity, and less hypoxia) derive the most benefit.[1,4,12,14] For example, cediranib, an oral pan-VEGFR tyrosine kinase inhibitor (TKI), normalizes tumor vessel structure and reduces leakiness in patients with recurrent glioblastoma (GBM), as seen in preclinical studies.[122,123] More so, progression-free survival and overall survival (OS) were associated with the relative degree of normalization as quantified by a set of biomarkers characterizing vessel structure and function.[124] This correlation was confirmed subsequently, as cediranib-increased perfusion and oxygenation correlate with survival of patients with GBM.[125-127] Similarly, in patients with breast cancer, correlations between normalization and outcome have been observed using nintedanib,[128] eribulin,[129] and bevacizumab.[129-132] In addition, patients with non–small-cell lung cancer (NSCLC) treated with bevacizumab who had increased tumor blood perfusion had improved OS.[133] These findings indicated that normalization is a potential predictive physiologic biomarker of response that must be validated prospectively.

Stromal Normalization

Reducing fibrosis through “stromal” or “CAF/ECM normalization” can complement vessel normalization and is best embodied by reprogramming CAFs to a quiescent phenotype[75,134-137] (shown in transition from Figure 4.3A to C). Although vessel normalization enhances the function of

immature tumor vessels, it cannot affect collapsed vessels. Reprogramming of CAFs normalizes their phenotype and function, thereby reducing their production and maintenance of ECM.[75,134-136] Accordingly, ECM levels are lower after reprogramming CAFs. Either by "normalizing" CAFs and ECM through CAF reprogramming or by destroying CAFs/ECM, the fluid and solid stress is reduced toward normal levels.[71,74,138] Unfortunately, therapeutically killing CAFs and/or digesting ECM induces tumor progression and immunosuppression.[1] Therapies that reprogram CAFs are called mechanotherapeutics,[16] even though, in some cases, they might have effects on stromal cells besides CAFs, as well. CAF reprogramming decompresses vessels, thereby increasing perfusion and delivering oxygen and drugs.

Combined Vascular and Stromal Normalization

Normalizing vessels and reprogramming CAFs, either independently or in combination, are TME normalization and improve vascular function, thereby alleviating hypoxia and treatment resistance[1] (Figure 4.3D). Still, the best way of combining AAT with mechanotherapies is unclear and likely will depend on the context.[139-141] First, the state of the vessels matters. In tumors with leaky and compressed vessels, the combination of AAT and mechanotherapeutics will be most effective.[139] Second, in tumors with a lesser density of perfused vessels, mechanotherapeutics should precede AAT. Large doses of AAT can excessively prune vessels, causing hypoxia and resistance.[4,12] In contrast, preclinical data indicate that mechanotherapeutics restore blood flow to small, immature vessels.[120] As a result, there are more immature vessels on which subsequent AAT could act. Clinical data from hypothesis-generating trials support this notion as tumors with more vessels with open-lumen pre-AAT are associated with improved response to AAT and chemoradiation.[121] In patients with GBM, imaging studies revealed that angiotensin system inhibitors (ASIs), which decompress tumor blood vessels[75] and have unrelated effects on other stromal cells,[111] increased the amount of perfused vessels.[142] Retrospective studies indicate that ASIs alone or combined with other therapies increase the survival of patients.[36,143-146] By increasing perfusion, mechanotherapeutics counteract AAT-induced pruning. Third, AAT

preceding mechanotherapeutics is beneficial in certain cases. AAT can induce CAF activation and ECM deposition. So, administering mechanotherapies after AAT could reduce this AAT-induced treatment resistance.[147-149] Thus, combination normalization strategies are better suited for tumors with certain vascular characteristics, and the order could matter.

Tumor Microenvironment Normalization for Immunotherapy

TME normalization improves immunotherapy.[6,58,58,58] Immunotherapy can be radiosensitizing,[150] and RT primes tumors for immunotherapy. One example of this interaction is the abscopal effect.[151] Given the role immunotherapy could play in RT regimens, understanding how to combine TME normalization and immunotherapy is necessary to develop radiosensitizing strategies. For immunotherapy to be effective, the steps of cancer-immunity cycle must continue (Figure 4.4, outer ring). The characteristics of the TME determine where in the cycle is the "set point" or the current step of resistance to immunotherapies.[152] We hypothesized that TME normalization overcomes the resistance of each set point (Figure 4.4, inner ring).[36] These seven set points can be classified into three TME phenotypes.

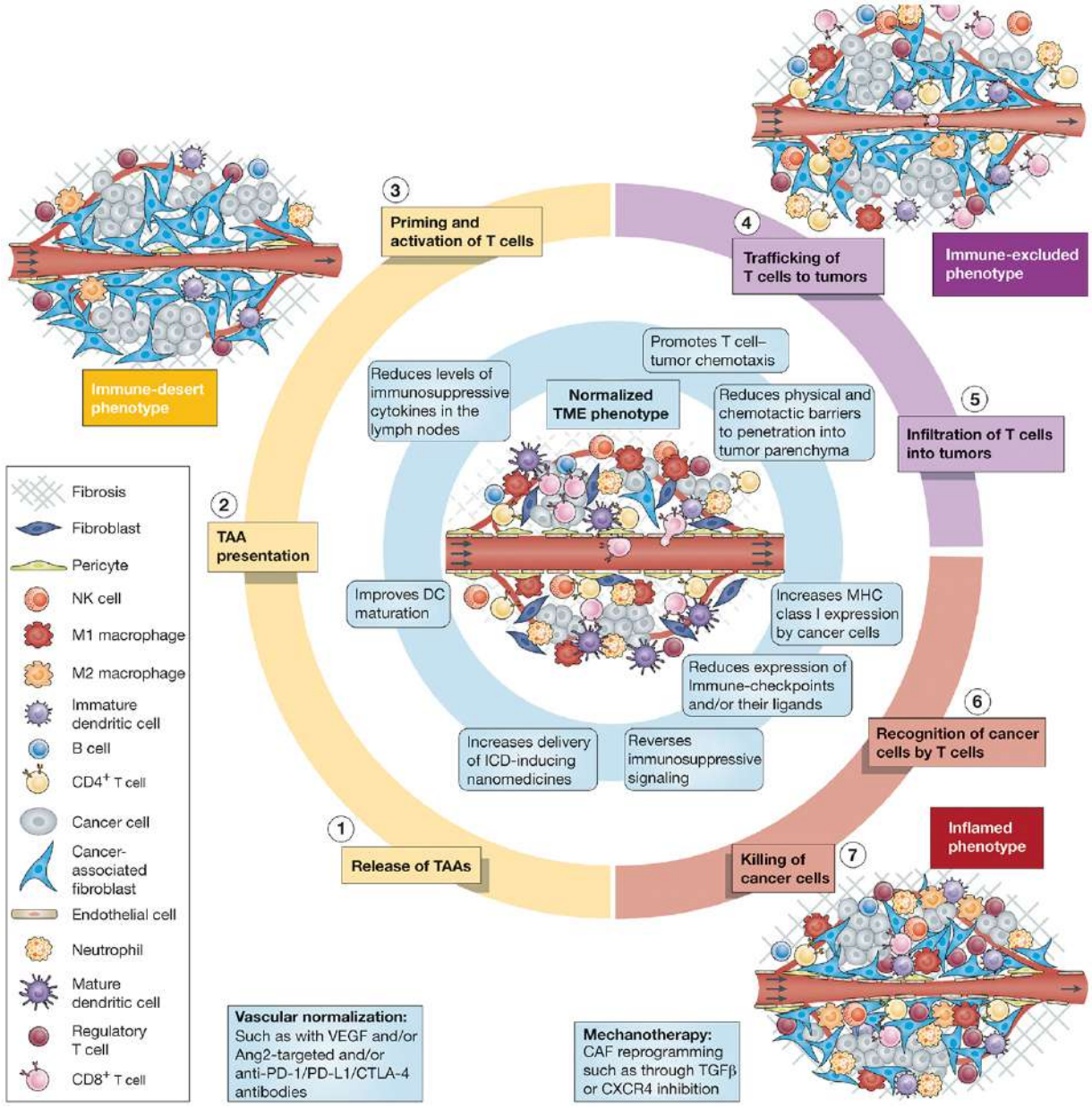

FIGURE 4.4 Cancer-immune TME phenotypes define the set points that predict sensitivity to immunotherapy,[152] while TME normalization perpetuates the cancer-immunity cycle.[36] TME normalization (blue inner circle) pushes the cycle through the various set points. In the immune-desert phenotype (yellow), the TME with sparse immune cells is immunosuppressed. The immune system allows malignant cell expansion because often it does not recognize antigens, tolerates the antigens if it does recognize them, and/or eventually fails to prime cytotoxic T cells. Hypoxia affects these steps in the cycle. In the immune-excluded phenotype (purple), the stroma restricts immune cell infiltration such that immune cells are retained in the tumor periphery and/or stroma. The TME characteristics that distinguish immune exclusion also reduce the delivery of various radiosensitizers and/or oxygen. In the inflamed phenotype (red), pro-inflammatory cytokines stimulate the relatively large amounts of immune cells migrating through the parenchyma. However,

inhibitory factors often induced by hypoxia reduce antitumor immunity. The structure and function of vessels may be normalized by inhibiting angiogenic factors and/or immune checkpoint molecules. Meanwhile, normalization of CAFs and/or the ECM could decompress vessels collapsed by solid stress. These two strategies work independently or as a combination to improve perfusion, oxygen delivery, and drug distribution. Strategies that cause excessive vessel, CAF, and/or ECM depletion could induce disease progression. Immune checkpoint blockade therapies such as anti-programmed cell death protein 1 (PD-1) or PD ligand 1 (PD-L1) antibodies induce blood vessel maturation in some tumor types, thereby protecting them from excessive pruning by antiangiogenic agents, which affect immature vessels. Blocking TME-normalizing signaling pathways such as those activated by vascular endothelial growth factor, angiopoietin 2, CXCL12/CXCR4, and TGF-β can also alleviate immunosuppression through additional mechanisms. Thus, combining these therapies that inhibit some of these pathways with radiosensitizers and immunotherapies could synergize. In conclusion, TME normalization strategies tailored to the immune TME phenotype of a tumor could enhance response rates and duration of responses to radiosensitizing immunotherapies. CTLA-4, cytotoxic T-lymphocyte protein 4; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1, programmed cell death 1 ligand 1; TAA, tumor-associated antigen; TME, tumor microenvironment. (Reprinted by permission from *Nature*: Martin JD, Cabral H, Stylianopoulos T, Jain RK. Improving cancer immunotherapy using nanomedicines: progress, opportunities and challenges. *Nat Rev Clin Oncol*. 2020;17[4]:251-266. Copyright © 2020 Springer Nature.)

Cancer-Immune Tumor Microenvironment Phenotypes

Of the three cancer-immune TME phenotypes, the immune desert is most resistant to immunotherapies.[153] This phenotype lacks antitumor immune cells, antigen presentation, and T-cell priming (Figure 4.4, light orange). Because angiogenesis and hypoxia promote the immune-desert phenotype, TME normalization could progress the tumor through the cycle (Figure 4.4, blue) into the immune-excluded phenotype (Figure 4.4, purple). One way that angiogenesis promotes the immune-desert phenotype is through VEGF expression, which reduces DC maturation, thereby interfering with antigen presentation.[41] Hypoxia enables immune tolerance by inducing chemokine expression that recruits protumor Treg cells.[38,39]

Less resistant than the immune-desert, immune-excluded tumors (Figure 4.4, purple) feature immune cells in the tumor periphery and/or stroma, but in not parenchyma.[152] The transition of these excluded immune cells is reduced by abnormal vessels and excessive fibrosis. Indeed, excessive levels of TGF-β, ECM, and CAFs characterize this phenotype.[135,136,154] Cancers resistant to ICBs tend to have a TME defined as “an immune desert” (Figure 4.4, red) because of the absence of intratumoral T cells.[153,154]

Besides the physiologic effects, the signaling that causes desmoplasia, solid stress, and vessel compression could also directly impair immune cells' cancer cell killing. CAFs secrete chemokines including TGF-β and stromal cell–derived factor 1α (SDF-1α), which hamper the transit of cytotoxic T lymphocytes (CTLs) to the tumor parenchyma.[135,136,154] Also, TGF-β promotes the maturation of naïve T cells into cells with a Treg phenotype.[39] Furthermore, excessive desmoplasia physically obstructs CTL migration.[155] Angiogenesis signaling also causes immune exclusion by reducing the expression of adhesion factors on vessel walls, thereby limiting CTL adhesion.[37,42,156] T-cell migration is reduced in hypoxic tumor regions.[43,44] Dysregulated angiogenesis and excessive desmoplasia cause hypoxia, and both the signaling and physiologic consequences of these processes limit the transit of CTLs.

The inflamed phenotype (Figure 4.4, red) is most sensitive to treatment, as it features T cells in the parenchyma and pro- inflammatory cytokines. Their presence indicates there was a previous antitumor immune response.[152] Accordingly, the densely accumulated T cells have T-cell receptors (TCRs) against tumor-associated antigens. As a result, stimulating these cells with ICB is likely to produce an antitumor effect.[154] Nonetheless, this phenotype also has immunosuppression mediated by angiogenesis, desmoplasia, and hypoxia such that TME normalization could further stimulate antitumor immunity. For example, VEGF signaling recruits immunosuppressive cells, such as Treg cells, myeloid-derived suppressor cells (MDSCs), and M2-like tumor-associated macrophages (TAMs).[45] In addition, hypoxia and CAFs increase the recruitment of Treg cells.[38,116] As there was already an immune response in inflamed tumors, immune checkpoints are expressed, reducing immune cell activity. Furthermore, VEGF upregulates various immune checkpoints on T cells.[46-48] Along these lines, hypoxia through HIF-1α does the same on MDSCs, TAMs, DCs, and cancer cells.[49,50] Acidity,[51] CAFs,[116] and collagen density[157] impair the cytotoxic activity of CTLs, even if they are already in the parenchyma.

While angiogenesis restricts cancer-immunity cycle, inflamed immune cells promote pathologic angiogenesis.[7,55,158,159] Thus, there is a vicious cycle of abnormal vasculature and protumor immunosuppression. To stop this cycle, we propose normalization of the TME to alleviate hypoxia[1,14] and increase immune cell density and antitumor function.[1,4,6] Given its role

throughout the entire cycle, this approach could be useful in the many patients with primary tumors and metastases with heterogeneous cancer-immunity phenotypes.[32,33,160,161]

Tumor Microenvironment Normalization Through Inhibition of Immunosuppressive Signaling Pathways

Normal, physiologic levels of tumor perfusion and oxygenation facilitate progression through the cancer-immunity cycle (Figure 4.4, inner ring).[55] Besides physiologic effects, blocking vascular "abnormalizing" pathways such as VEGF and ANG-2 and fibrosis pathways such as TGF-β and SDF-1α/CXCR4 promote antitumor immunity by blocking immunosuppressive signaling.[36,37,162] Preclinical studies show that vascular normalization enhances the antitumor efficacy of ICB,[156,163,164] whole cancer cell vaccines,[118] and adoptive cell therapy.[165,166] These studies are consistent with the success of combined AAT with ICB in patients. Indeed, phase III trials demonstrated the combination of the anti-VEGF antibody bevacizumab with the ICB atezolizumab and the chemotherapy paclitaxel in patients with metastatic nonsquamous NSCLC.[167] Similarly, the small-molecule VEGFR1-3 inhibitor axitinib with either ICB of avelumab[168] or pembrolizumab[169] succeeded in patients with advanced-stage renal cell carcinoma. In reverse, ICBs induce immune cells to normalize vessels in preclinical models.[55,159,164] Thus, combining vascular normalization with ICB could promote a cycle of efficient vasculature, alleviating hypoxia toward stimulating antitumor immunity.[1,58,58,58,58]

Mechanotherapeutics are in clinical trials with ICB. Mechanotherapeutics, such as angiotensin receptor blockers (ARBs) like losartan, that interfere with certain pathways, such as TGF-β signaling, in CAFs[75,135,144,170] could increase the efficacy of immunotherapies through various mechanisms including alleviating stresses in the TME.[171] TGF-β signaling affects many aspects of cancer immunosuppression.[154,171,172] TGF-β signaling inhibition increases the expression of adhesion molecules (such as intercellular adhesion molecule 1 [ICAM-1] or vascular cell adhesion molecule 1 [VCAM-1]) on tumor blood vessels so that leukocytes may better bind tumor vessels and penetrate into tumors.[6] In addition, TGF-β signaling inhibition promotes abscopal effects induced by RT.[173]

TGF-β associates with poor responses to ICB in patients with cancer.[154] Data from hypothesis-generating clinical trials support the notion that ARBs may improve outcomes with immunotherapeutics. In patients with pancreatic ductal adenocarcinoma (PDAC), gene expression associated with T-cell activation was enhanced with losartan treatment.[174] Retrospective analyses largely indicate that patients fare better when taking ARBs long-term versus those without long-term ARB use.[36,144] Adding losartan to chemoradiation reduces proinvasion and immunosuppression-related genes.[175] These various mechanisms provided a rationale for the clinical trial in patients with locally advanced PDAC receiving losartan in combination with nivolumab, FOLFIRINOX, and stereotactic body RT (NCT03563248). Unfortunately, losartan alone or without nivolumab did not show a benefit in increasing resection rates.[176] This failure could be related to variability in decisions to resect. Whether and how the clinical investigation of losartan will continue as PDAC therapy is currently unclear, but it is noteworthy to mention that losartan has shown the potential to improve ICB response and morbidity in preclinical GBM models.[177]

Immunotherapy-Induced Vascular Normalization

ICBs are part of the standard of care for most types of solid tumors, but they benefit a much smaller proportion of patients with cancer.[34] Even in responding cancer types, most patients do not experience a response to ICB-based therapies. To address this inherent resistance, which is mediated by immunosuppression, hypoxia, angiogenesis, and fibrosis in the TME, translational oncology researchers are investigating ICB therapy–based combination strategies with other immunotherapies and vascular-normalizing therapies,[37] CAF reprogramming, and nanomedicine.[36,178] Besides the role of antiangiogenic and CAF reprogramming therapies in TME normalization, researchers recently worked to understand the role of ICB in TME normalization.[140,179] These findings indicate that elucidating how immunotherapies normalize the TME could result in more effective combination regimens.

Recent studies produced data indicating that ICB alone can normalize blood vessels, particularly in tumors that responded to the treatment.[55] In

ICB-responsive murine models, immunotherapy led to vascular normalization and enhanced perfusion.[55] These effects were dependent on $CD8^+$ T cells and IFNγ production reversed.[55] As effective ICB therapy is thought to depend on $CD8^+$ T-cell accumulation and interferon γ (IFNγ) production, these findings support the notion that ICB-induced increased perfusion could be a potential biomarker of response to ICB treatment.[55]

Mechanisms of Immunotherapy-Induced Vascular Normalization

IFNγ and $CD8^+$ T cells are required for antitumor immunity.[180] High level of IFNγ induces apoptosis of cancer cells.[181] Lower levels of IFNγ induce cancer cell stemness, which facilitates metastatic progression.[181] In addition, IFNγ has non–immune-mediated antiangiogenic properties[182] that are IFNγ level dependent.[158] Specifically, high levels of IFNγ, independently of cancer cells, induce vascular regression and eliminate blood flow to tumors.[183] This effect is similar to that of AAT at high doses and distinct to vascular normalization.[4,14] Lower levels of IFNγ could induce vascular normalization. Indeed, IFNγ upregulates ICAM-1,[184] which mediates adhesion between ECs and leukocytes, and VCAM-1,[185] which promotes adhesion between pairs of ECs and ECs and leukocytes or mural cells. IFNγ might also normalize vessels through TAMs. Specifically, through IFNγ, $CD8^+$ T cells polarize TAMs to an antiangiogenic, antitumor M1-like phenotype.[186] ICB treatment, TAM polarization, adoptive cell transfer, and experimental models of inducible IFNγ all induce antiangiogenic effects to a different extent, which could result from the varying concentrations of IFNγ.[158] Thus, the extent of vascular normalization is mediated by IFNγ and must be elucidated in various tumor types and immunotherapies.

Studies from patients with various types of tumors underscore the host and tumor type dependence of the effect of IFNγ on vascular normalization. Patients with ICB-responding GBM had reduced vascular permeability, indicative of vascular normalization.[187] Interestingly, this effect occurred 6 months after ICB treatment initiation. In mice, the effect is induced more rapidly. Also, this effect occurred after a short period of increased vascular permeability, which has been observed in murine models.[177] These results reveal discrepancies between the kinetics of these ICB-induced vascular permeability changes between murine breast and brain tumors and between

patients and mice. To better determine the kinetics of a potential vascular normalization window, vascular permeability must be studied longitudinally before and shortly after ICB treatment initiation.[188] Further discrepancies exist. For example, in patients, vascular regression associated with ischemic tumor necrosis after vaccination or ICB immunotherapies was observed in responding melanoma and ovarian tumors.[189] These conflicting results highlight areas of future study.

The type of cells that produce IFNγ depends on the context. When interventions are administered before tumors grow, the experiment models the clinical "preventive" setting before cancer diagnosis. In such studies, knockout models indicated that T-cell subsets induce opposing angiogenic effects. Specifically, $CD8^+$ T cells promoted angiogenesis through EC proliferation. In contrast, $CD4^+$ T cells promoted vascular normalization through pericyte recruitment, reducing hypoxia.[159] Consistent with previous angiogenesis studies in early tumor development,[190] these studies suggest that in early stages, $CD4^+$ T cells and IFNγ promote vessel fortification through pericyte recruitment.[159,188]

ICB administered in the "interventional" setting normalized the breast tumor vasculature in an IFNγ-dependent manner. This conclusion was reached based on studies of abrogated ICB-induced normalization through IFNγ receptor knockout and IFNγ neutralization studies.[55] T-cell depletion studies in wild-type mice revealed that ICB-induced normalization and increased perfusion revealed a dependence on $CD8^+$, but not $CD4^+$, T cells.[55] Thus, $CD4^+$ T cells promote vessel maturation early in tumor development, while in the treatment setting with ICBs, $CD8^+$ T cells normalize blood vessels. The latter conclusion is supported by observations that adoptive transfer therapy of T cells contributes to normalized vascular morphology.[191]

Besides $CD8^+$ T cells and IFNγ, ICB-induced normalization also depends on the cross talk between eosinophils and $CD8^+$ T cells. The cross talk initiates a positive feedback loop of vascular normalization and antitumor immunity.[192] In addition, activated eosinophils in the TME, through IFNγ, skew TAMs to an antiangiogenic M1-like phenotype and an increased expression of VCAM-1. As a result, there is increased adhesion of eosinophils and T lymphocytes (among other cells) to the endothelium, transmigration, and infiltration. Accumulated T cells can then further

promote vascular normalization and TAM polarization. Another factor promoting tumor-specific effector T-cell trafficking are interferon-induced chemoattractants produced by activated eosinophils.[192] Supporting these preclinical findings, increased eosinophil and lymphocyte counts after ICB correlated with increased survival of patients.[193] Thus, ICB promotes a positive feedback loop of $CD8^+$ T cells and activated eosinophils, which normalizes vessels through IFNγ and TAM polarization and results in increased eosinophil and lymphocyte adhesion and accumulation (Figure 4.5A).

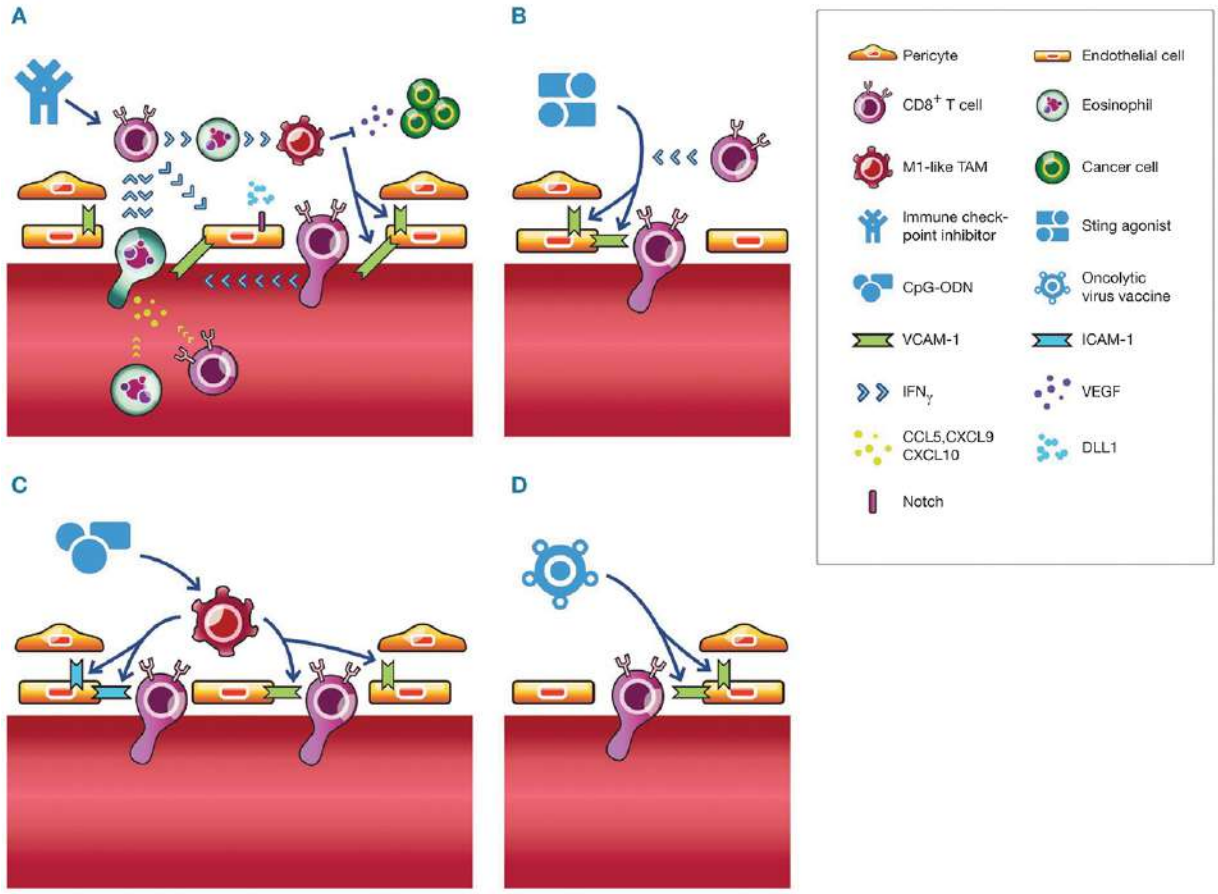

FIGURE 4.5 Vascular normalization induced by various immunotherapies through distinct mechanisms. A. Immune checkpoint blockers (ICBs) activate $CD8^+$ T cells, which secrete IFNγ and interact with activated eosinophils to induce M1-like tumor-associated macrophage (TAM) phenotypes. The TAM polarization reduces vascular endothelial growth factor signaling and increases vascular cell adhesion molecule 1 (VCAM-1) expression, leading to infiltration of $CD8^+$ T cells and activated eosinophils. The latter secretes chemokines (ie, CCL5, CXCL9, and CXCL10) that promote lymphocyte trafficking. For this mechanism, activated eosinophil accumulation precedes and is required for enhanced $CD8^+$ T-cell homing to normalized tumors. This process is a positive feedback loop of vascular normalization and antitumor immunity. In addition, DLL1-Notch signaling promotes $CD8^+$ T-cell activation and IFNγ production, further reinforcing this positive feedback loop for long-term vascular normalization. B. STING agonists increase levels of antiangiogenic factors, thereby increasing pericyte coverage and T-cell infiltration through increased VCAM-1 expression. C. CpG-ODN acts on TAMs and promotes an M1-like phenotype, leading to upregulation of intercellular adhesion molecule 1 (ICAM-1) and VCAM-1. In some but not all cases, depletion of regulatory T cells similarly increases ICAM-1 and VCAM-1 expression. D. Oncolytic vaccines prune vessels and increase VCAM-1 expression through poorly understood mechanisms. (Reprinted from Melo V, Bremer E, Martin JD. Towards immunotherapy-induced normalization of the tumor microenvironment. *Front Cell Dev Biol*. 2022;10:908389. http://creativecommons.org/licenses/by/4.0/)

The role of the ligand Delta-like canonical Notch ligand 1 (DLL1) in vascular normalization mediated by activated $CD8^+$ T cells[194] supports this positive feedback cycle hypothesis.[195] DLL1 levels are inversely correlated with circulating VEGF. The latter occurs in hosts bearing tumors with high levels of angiogenesis.[194] Circulating VEGF, through reduction of DLL1-Notch signaling in bone marrow precursors, reduces T-cell activation and antitumor immunity.[194] Overexpressing DLL1 in cancer cells induced long-term vascular normalization by overcoming circulating VEGF-induced DLL1-Notch signaling inhibition.[195] As in other studies, normalization occurred in ICB responders and required IFNγ production and $CD8^+$ T-cell accumulation.[195] These results support the notion that immune cells induce long-term vascular normalization by interfering with angiogenic and immunosuppressive signaling, thereby increasing the antitumor effect of ICB (Figure 4.5A).

Immunotherapy-Induced Vascular Normalization Beyond Immune Checkpoint Blockade

The findings that immunotherapies beyond ICB have normalizing effects support the observations of the role of immune cells in vascular normalization. STING agonist offers one example. In mice bearing melanoma, low-dose local administration led to the expression of antiangiogenic factors, leading to EC pericyte coverage and expression of VCAM-1.[196] This effect was mediated by STING activation of DCs rather than cancer cells.[196] STING agonism promoted the formation of normalized vessels and tertiary lymphoid structures, leading to increased T-cell infiltration.[196] Beyond melanoma, researchers explored STING agonism in breast, lung, and colorectal cancer models.[197] While confirming the findings in melanoma, these studies clarified several additional findings of STING agonist–induced vascular normalization. First, STING agonism of nonhematopoietic stromal cells, particularly ECs, mediates normalization.[197] Second, normalization depends on $CD8^+$ T cells and IFNγ, not TAMs.[197] Thus, similar to ICBs, STING agonists induce vascular normalization through $CD8^+$ T cells and IFNγ (Figure 4.5B).

Oligodeoxynucleotides with cytosine-guanine (CpG-ODN) motifs normalize vessels. CpG-ODN stimulates TAMs, which upregulate ICAM-1

and VCAM-1 in ECs.[198] After treatment, adoptively transferred immune cells extravasate and infiltrate tumors more efficiently (Figure 4.5C). CpG-ODN has not succeeded in the clinic, likely due to its local administration. Another potential cause of resistance could be the TME of distant metastatic lesions, which could present barriers to administration even if local treatment in the primary tumor induces a systemic abscopal effect.[36] The effects of depletion of T_{regs} can be similar to those of CpG-ODN treatment, as they both upregulate ICAM-1 and VCAM-1.[199] Other observed markers of normalization induced by the depletion of T_{regs} are reduced vessel diameter and increased perfusion.[199] In most cases, depletion of T_{regs} induces antitumor immunity. In PDACs, T_{regs} deplete fibroblasts, which promotes tumor growth and immunosuppression.[200] Thus, the effect of T_{reg} depletion varies by tumor type.

Oncolytic viruses also promote markers of normalization. Indeed, they reduce vascular density transiently while increasing VCAM-1 gene expression.[201] However, the mechanism and whether hypoxia is alleviated is unclear (Figure 4.5D). Considering the results when testing therapies other than ICB, we can generate hypotheses. Whereas ICB and STING agonists act through T cells and IFNγ, oligonucleotide therapies act through TAMs, increasing the expression of adhesion molecules. How to combine these immunotherapies for enhanced vascular normalization and antitumor efficacy remains untested.

Combined Antiangiogenic Therapy and Immunotherapy

AATs and ICB have disparate effects on vascular regression and normalization, so there could be potential to combine them. One observed mechanism of synergy involves passive vessel normalization, in which immature blood vessels are destroyed while the mature vessels remain. The other observations involved active vessel normalization, where pericytes are recruited to existing vessels. In the former, AAT recruits $CD8^+$ T cells, resulting in increased IFNγ, which upregulates immune checkpoints that can be neutralized by ICB.[156] This case involved passive normalization, as the combined AAT of VEGF and angiopoietin 2 inhibition induced vascular regression and necrosis, yet the vessels remained covered with pericytes.[156] In contrast, another study found evidence of active vessel normalization.

The researchers found that VEGF inhibition and ICB were complimentary in forming high endothelial venules, which are blood vessels supporting the interaction of T cells with antigen-presenting cells in tertiary lymphoid structures or lymph nodes.[163] While the researchers overserved regression of half of the vasculature, they also found the distinct contributions of AAT and ICB to vessel pruning and fortification.[163] Blocking VEGF induced vascular regression and fortification, but its combination with ICB led to increased pericyte coverage without additional regression.[163] Therefore, ICB induced active normalization through myeloid cells in the TME.[163] In the setting of tumor relapse from AAT monotherapy, the combination of AAT and ICB was necessary to reduce vessel density, which underscores the lack of redundancy of these therapies in their antiangiogenic properties.[163] A key takeaway of these studies is that ICB has stronger effects on vessel fortification than regression. A key challenge will be to determine whether the vascular regression induced by the combination is necessary for the efficacy, and if not, then to determine how best to combine AAT and ICB to alleviate hypoxia and promote antitumor immunity.

The findings in a series of reports on hepatocellular carcinoma (HCC) demonstrate the role of the organ environment and type of TME when combining AAT and ICB with respect to vascular normalization. The AAT sorafenib causes vascular regression, hypoxia, and resistance through activating SDF-1α/CXCR4 pathway.[149] In many tumor types, blocking CXCR4 reduces immunosuppression and fibrosis and increases T-cell infiltration.[136] In HCC, blocking CXCR4 alleviates immunosuppressive cell recruitment and angiogenesis after sorafenib treatment.[149] Then, combining ICB with AAT and CXCR4 inhibition ameliorates these resistance mechanisms further by increasing the amount of IFNγ and $CD8^+$ T cells in the tumor center, indicating further normalization of the TME.[149] A follow-up study in HCC investigated further, as ICB enhanced vessel normalization when combined with an anti-VEGFR2 antibody compared to AAT using multitargeted TKIs.[164] In HCC, the contribution of AAT and ICB to vascular normalization was mediated by $CD4^+$ T cells. AAT induced EC expression of immune checkpoints (programmed cell death 1 ligand 1 and programmed cell death protein 1) in an IFNγ-dependent manner and in $CD4^+$ T cells, which could be neutralized by ICB.[164] With further fortification by ICB treatment (Figure 4.6A), vessels resisted vascular

regression, even at higher doses of anti-VEGFR2 antibody.[164] Given the sensitivity of vascular normalization to AAT dose, ICB-induced resistance to regression makes finding an acceptable dose of AAT easier.[4] Indeed, when the AAT sorafenib follows ICB in HCC, the density of fortified blood vessels increases in a $CD8^+$ T-cell–dependent manner (Figure 4.6B), while sorafenib alone induces vascular regression.[202] Thus, ICB fortifies vessels, thereby preventing regression induced by AAT. In a study that supports these findings but with a differing order of treatment, administering vessel-fortifying AAT before oncolytic vaccine therapy avoided vascular regression and improved efficacy.[203] Nonetheless, the combination of ICB and AAT often induces vascular regression caused by high levels of IFNγ or high doses of AAT. In one case, high doses of the small-molecule tyrosine kinase anti-VEGFR inhibitor regorafenib combined with ICB induced vascular regression in HCC.[204,205] In conclusion, combinations of AAT and ICB or other immunotherapies should be tested in an agent- and tumor-specific manner to identify schedules that maximize vessel fortification while minimizing vascular regression to promote antitumor immunity optimally.

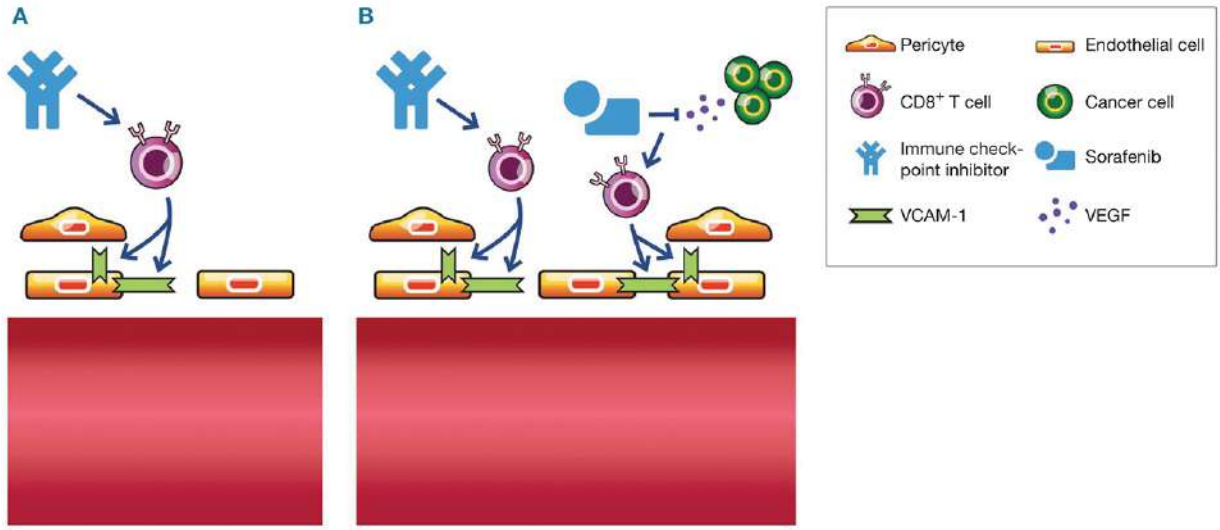

FIGURE 4.6 Immune checkpoint blockade (ICB) preceding antiangiogenic therapies (eg, sorafenib) promotes vascular normalization by protecting against vessel pruning in hepatocellular carcinoma. A. ICB monotherapy fortifies vessels by increasing the interaction between endothelial cells and perivascular cells through vascular cell adhesion molecule 1 (VCAM-1) upregulation in a $CD8^+$ T-cell–dependent manner. B. Sorafenib following ICB increases the density of tumor blood vessels fortified by pericytes and the antitumor efficacy in a $CD8^+$ T-cell–dependent manner. In contrast, sorafenib monotherapy causes vascular pruning and does not slow tumor growth. Thus, vascular-fortifying ICB alters the effect of subsequent antiangiogenic therapy from vessel regression to vascular normalization. (Reprinted from Melo V, Bremer E, Martin JD. Towards immunotherapy-induced normalization of the tumor microenvironment. *Front Cell Dev Biol*. 2022;10:908389. http://creativecommons.org/licenses/by/4.0/)

The studies in HCC support the notion of a positive feedback loop of vascular normalization and antitumor immunity induced by AAT and immunotherapy. Moreover, when dosed judiciously, the AAT regorafenib induces vascular normalization and the expression of CXCL10 in HCC cells. This chemokine binds to its receptor CXCR3 on infiltrating T lymphocytes, thereby resulting in increased trafficking into these tumors.[204] As more T cells enter the tumor, vascular normalization is further promoted.

Other immunotherapies besides ICB, when combined with AAT, can support vascular normalization and induce CAF reprogramming. An anti-CD40 antibody is one such immunotherapy. Interfering with CD40 promotes DC maturation, antigen presentation, and priming of T cells. Administration of the antibody to genetically engineered mouse models of colorectal cancer in combination with anti-VEGF and anti-angiopoietin 2

therapy fortified blood vessels.[206] This combination of AATs induced CAF reprogramming effects, which were increased by treatment with an anti-CD40 antibody.[206] While the antitumor efficacy depended on angiogenic (ie, angiopoietin 2) signaling and on T-cell infiltration, vascular normalization and CAF reprogramming were T-cell independent.[206] In this study, the tumors were well perfused before treatment. This raises the hypothesis that the increased antitumor activity results from increased T-cell trafficking and infiltration because of increased vessel maturity as well as increased T-cell migration resulting from reduced fibrosis.[206] These studies demonstrate that immunotherapies can promote vascular normalization and CAF reprogramming in combination with AAT, and the resulting increase in antitumor efficacy can occur through mechanisms independent of alleviated hypoxia.

NORMALIZING THE MOLECULAR PATHOLOGY OF TUMORS FOR RADIATION WITH COMBINATION THERAPY REGIMENS

RT is a local treatment. In certain cases, patients with fewer metastases in spatially defined sites may also have these oligometastases directly treated by RT, which may prolong OS. By treating oligometastases, which are limited in number and susceptible to local treatment, the fraction of patients who can benefit from RT can be expanded.[207-209] Unfortunately, even in this relatively easy-to-treat setting, the TME impairs the efficacy of RT. Priming tumors for RT could benefit patients with oligometastases, thereby increasing the fraction of patients with localized cancer that can be cured therapies to prime tumors likely must be systemically administered so that they can also induce antitumor efficacy against nonirradiated lesions. We put forth the following rationale. First, these systemically administered priming agents will act on nonirradiated lesions. Second, these priming agents can act on distant lesions to render them amenable to abscopal effects initially induced by RT treatment against the accessible lesion. This could occur by enabling antitumor immune cells to infiltrate distant lesions better. Third, these systemic priming agents can increase the abscopal effects by sensitizing the accessible lesion to RT by aiding immunogenic cell death (ICD) and antigen presentation. Here we describe strategies for

RT priming by nanomedicine-, TME normalization-, chemotherapy-, and/or immunotherapy-based radiosensitizers.

Combination With Nano-Radiosensitizers

High atomic number metals are radiosensitizers. Irradiation causes the atoms in high atomic number metals to undergo inner shell ionization and emit electrons, which damage cancer cells directly or indirectly by ROS production.[210] Researchers developed nanomedicines containing high atomic number metals that enhance the efficacy of RT at lower doses.[210] Nanomedicines administered systemically accumulate in tumors through the enhanced permeability and retention effect.[36,67,211-213] Nanomedicines with more toxicity are administered with an intratumoral injection in superficially located tumors. Given their inability to diffuse in the dense ECM of tumors, intratumorally injected nanomedicines are retained more than locally administered small molecules.[210] The European Medicines Agency (EMA) approved intratumoral injections of NBTXR3 hafnium oxide nanoparticles. These particles increase the RT abscopal effect in locally advanced soft tissue sarcomas.[214] Particles like these are especially important for immunotherapy regimens because they can increase the RT dose with the tumor while limiting the dose applied to healthy immune cells systemically. This is important because the efficacy of RT combined with immunotherapy is inversely correlated to the RT dose to healthy immune cells.[215]

Other nanomedicines that could prime tumors for RT include those encapsulating chemotherapies and/or TME-normalizing drugs.[36,137,216] Nano-based chemotherapy can prime tumors for RT more effectively than small-molecule chemotherapy for several reasons.[36] First, nanomedicines lessen and/or alter toxicity profiles compared to small molecules.[217,218] Second, nano-based chemotherapy normalizes the TME, similarly to metronomic chemotherapy, because nanocarriers have long blood circulation.[219,220] The presence of chemotherapy in the circulation either with metronomic small-molecule chemotherapy or with long circulating nanomedicine limits the proliferation of ECs, resulting in an antiangiogenic effect. Similarly, the constant supply of chemotherapy alleviates solid stress by steadily eliminating proliferating cancer cells, thereby decompressing vessels. Thus,

nano-based chemotherapy can act as an AAT, a mechanotherapeutic and a cytotoxic chemotherapy that induces ICD.

Mechanotherapeutic strategies often rely on drugs repurposed from other diseases to cancer, reprograming CAFs to a quiescent phenotype. The resulting lack of desmoplasia alleviates stresses, decompresses vessels, restores perfusion, and reduces hypoxia. Some mechanotherapeutic drugs also directly shift immune cells toward antitumor immunity.[111] These small-molecule repurposed drugs can benefit from a reformulation as a nanomedicine because the nanoformulation alters the pharmacokinetics, thereby reducing the normal systemic effects of these drugs while increasing their tumor accumulation.[36] For example, ARBs, used to treat hypertension, did not reduce blood pressure but had increased TME-normalizing effects when formulated as nanomedicine.[135] Still, it is unclear if these nanoformulations will be more effective in the clinic than the relatively inexpensive, generic, and repurposed TME-normalizing drugs.

Combination With Tumor Microenvironment Normalization

RT requires oxygen to kill cancer cells efficiently, and TME normalization increases oxygen levels in tumors. Accordingly, TME-normalizing therapies may prime tumors for RT by alleviating hypoxia.[4,125,221] In preclinical tumor models, AAT transiently normalizes vessels, providing a window of reduced hypoxia during which RT is effective.[221] In patients, AAT is administered with radiation increased tumor oxygenation after AAT is associated with survival.[125] In locally advanced PDAC, losartan potentiated tumor shrinkage by chemoradiation in some patients, thereby enabling more tumor resections.[222] Separately, TME normalization could enhance RT-induced abscopal effects on distant lesions by stimulating the distribution and phenotype of antitumor immune cells. Specifically, VEGF and TGF-β signaling pathways are immunosuppressive and pose barriers to immune cell transit to and within the TME.[173] Thus, TME normalization could enhance progression through the cancer-immunity cycle initiated by RT, which induces ICD, causing the release of tumor-associated antigens (see Figure 4.4).

Combination With Chemotherapy

Certain cytotoxic nanomedicines induce vascular and stromal normalization.[216] There are hypothesized mechanisms for additive and synergistic benefits when combining systemic chemotherapy and RT. For additive benefits, systemic chemotherapy can act against distant metastases that local RT cannot affect apart from inducing a systemic antitumor immune response. In addition, chemotherapy and RT might cooperate synergistically through at least five potential mechanisms.[223] First, certain chemotherapies that incorporate themselves into the structure of DNA enhance radiation damage. These drugs include halogenated pyrimidines and cisplatin, which, through different mechanisms, interact with DNA to enhance RT.[224] Second, although some cancer cells repair themselves after sublethal doses of RT, certain chemotherapies (eg, halogenated pyrimidines, nucleoside analogs, and cisplatin) inhibit this self-repair capacity. This effect of certain chemotherapies could be most important in fractionated RT, because lower sublethal doses are used.[225,226] Third, certain chemotherapies pause cancer cells into a proliferative, radiosensitive phase, while other chemotherapies can be combined to eliminate radioresistant cells that are in a nonproliferative phase. Taxanes arrest cells in proliferation,[227-229] while nucleoside analogs kill nonproliferative cancer cells.[226] Fourth, chemotherapies can reduce hypoxia. For example, paclitaxel increases tumor oxygenation through two mechanisms.[228] It decompresses vessels, thereby increasing blood flow. It also kills cancer cells, thereby reducing oxygen consumption. Alternatively, certain chemotherapies activate in hypoxia, thereby selectively killing hypoxic cells, so that RT can act on normoxic cancer cells.[226] Fifth, chemotherapies combined with fractionated RT stop the repopulation of cancer cells, which improves the efficacy of the subsequent fraction of RT.[223] The main downside of this combination is that chemotherapy could increase the toxicity of RT to normal tissues.

While the mechanisms of combination for small-molecule chemotherapy we described involve the chemotherapy priming the tumor for RT, cytotoxic nanomedicines might be best used after RT. Preclinical studies indicate that RT increases the penetration of nanomedicines by normalizing the TME and modulating immune cells.[230,231] TME normalization by RT depends on the dose and varies across tumor type.[232] Another approach involves developing nanomedicines with ligands targeting P-selectin, which better accumulate in

the tumor after RT-induced expression of P-selectin.[233] Whether these approaches will translate to patients remains unanswered.

Combination With Immunotherapy

Immunotherapy normalizes the TME and ameliorates hypoxia in certain cases.[6] Thus, in settings where immunotherapy enhances oxygen delivery, it could prime tumors for RT.[150] Alternatively, RT can prime the TME to improve the efficacy of subsequent immunotherapy through several mechanisms. First, RT normalizes the TME and ameliorates hypoxia in certain cases.[230,232,234] RT affects hypoxia through conflicting mechanisms. Radiation kills normoxic cancer cells, thereby increasing the fraction of hypoxic cells. In contrast, the killing of cancer cells, whether normoxic or hypoxic, reduces solid stress,[71] thereby ameliorating hypoxia by increasing supply and reducing consumption.[235] Also, fewer cells mean lesser levels of proangiogenic factors. Furthermore, RT directly kills proliferating ECs, so RT could have a large antiangiogenic effect that excessively prunes tumor vessels and ultimately results in regrowth of the vasculature.[105] In this case, testing that RT is not inducing hypoxia through excessive pruning is necessary. Reduced solid stress caused by cancer cell killing by RT decompresses lymphatic vessels.[71] As a result, RT alleviates IFP transiently. This can increase the accumulation of macromolecules and nanomedicines if administered during this window.[230,234]

The abscopal effect is the induction of ICD in one or more lesions, which can induce a systemic immune response against distant metastases[236-240] in part by expanding the circulating effector T cells.[241] ICD expands the diversity of the TCR repertoire.[242] Radiation dose and fractionation affect the abscopal effects. Fractionated RT induces ICD.[243,244] High-dose RT may limit immunogenicity because of the enzymatic digestion of cytosolic DNA, which eliminates one mechanism of immune recognition.[245] More research is needed to determine the dose dependency in various tumor types. EMA-approved NBTXR3 with RT stimulates an antitumor immune response in patients,[246] underscoring the applicability of this approach.

Treatment With Three or Four Modalities

There is potential to combine these various agents that prime tumors for RT treatment. Nano-based high atomic number metal radiosensitizers administered systemically or locally could have increased intratumor distribution if administered after TME normalization.[36,211] Vascular normalization increases the systemic delivery of smaller nanomedicines.[119,217,247] Mechanotherapeutics increase the penetration of systemically administered[75,220,248] and locally administered nanomedicines of all sizes.[170,249] Increased RT and/or chemotherapy payload delivery to cancer cells could increase ICD. Antitumor T cells sometimes normalize the vasculature, so immunotherapy and TME normalization combinations could better alleviate hypoxia toward potentiating RT. Through multiple mechanisms and combinations, TME normalization could increase the tumor infiltration of antitumor T cells, further reducing hypoxia.

Various immunotherapies benefit from TME normalization,[6,37] which can overcome each barrier posed by the cancer-immunity cycle.[36] TME normalization could increase chemotherapy and/or RT induction of ICD for subsequent immunotherapy. Also, TME normalization could reduce immunosuppressive cytokines in the tumor and the draining lymph nodes. T cells traffic through the circulatory system, infiltrate tumors, and migrate into the parenchyma. Although tumor signals reduce chemotaxis of T cells,[250] vascular normalization polarizes TAMs into an M1-like antitumor phenotype secreting chemokines-binding T cells[251] and induces T cells to express receptors to further enable chemotaxis.[48] T cells then must penetrate from tumor blood vessels to cancer cells. Vascular normalization could increase T-cell infiltration and activity[118] by increasing the number of perfused vessels, thereby reducing the distance T cells must migrate to cancer cells.[118,135,136] T cells[252] and natural killer cells[253] both are inhibited by low levels of adhesion molecules on the vessel wall. By inducing maturation, vascular normalization can increase T-cell adhesion and penetration.[48,165,254] Finally, vascular normalization improves T-cell recognition of cancer cells through at least two mechanisms. First, it reduces the hypoxia-induced shedding of major histocompatibility complex type I (MHC-I) molecules.[255] Second, it increases the expression of MHC-I molecules by limiting nitric oxide[255] and VEGF levels.[48] Indeed, vascular normalization improves antigen-specific T-cell migration.[48]

CHALLENGES

Rigorous Preclinical Models

Genetically engineered mouse models (GEMMs) reflect the natural occurrence of cancer as they form tumors without implantation and have mutations related to clinical disease. In many cases, GEMMs better recapitulate the physiology of the TME, such as hypoperfusion in PDAC.[256] Cell lines isolated from GEMMs, grown in mice by inoculating as a cell suspension or transplanting as a solid chunk into recipient mice, can recapitulate hypoperfusion.[75] A significant advantage of solid passage is that cancer cells are introduced along with their co-opted TME. During cancer initiation, mutations occur in single cells gradually and affect the physiology of the TME in the earliest stages of malignant transformation.[17] In contrast, the modifications in GEMMs are present before the TME is co-opted. There is a similar benefit when implanting tumor spheroids.[257]

Orthotopic models also recapitulate the TME.[258] Unfortunately, ectopic subcutaneous models have different TME properties than orthotopic ones of the same cell line.[19,20,256] Another critical decision is the selection of murine syngeneic versus human xenograft models for testing. The latter models form tumors with human cancer cells, and murine host cells are co-opted in the TME. Thus, investigating TME modulation is suboptimal in these models, especially given the importance of the immune system in current standard-of-care therapeutic regimens.[207] Still, there are experimental uses for mixing human and murine cells in a tumor model. For example, there is a model used with human stromal cells and murine cancer cells implanted into immunocompromised mice, and the human cells can be depleted selectively with diphtheria toxin to isolate the effects of specific cells in the TME.[70,71,107]

Using standard operating procedures when employing preclinical models for testing would better help determine the optimal combinations of drugs. Comparing data across studies is confounded by suboptimal experimental design, execution, and reporting.[259] TME-normalizing therapies should be tested with the standard of care, often chemoradiation.[260] Appropriate primary end points should be selected before initiating the study.[260]

Treatment Time Windows

TME normalization might lose its effectiveness with extended treatment. Tumors develop resistance through alternative signaling pathways.[2] Excessive doses and/or durations of TME normalization treatment deplete the stroma-inducing treatment resistance.[118,221] One main problem is the depletion by AAT of too many immature vessels, which exacerbates rather than alleviates hypoxia. AAT does not deplete mature vessels. Prioritizing AAT strategies that fortify vessels by reinvesting them of pericytes and reprograming CAFs toward quiescence addresses the problem of a limited time window of TME normalization.[1]

Identifying the TME normalization window would enable the optimal administration timing of RT and/or chemotherapy toward inducing ICD. However, the optimal timing of immunotherapy after ICD-inducing chemotherapy and/or RT is still being determined. Furthermore, whether these cytotoxic therapies should be continued during ICB treatment is still being determined. The answers to these questions differ for nano- and macromolecule-based therapies, which have long circulation times.

Imaging Biomarkers

Imaging predictive biomarkers of response to RT[261] and TME-normalizing strategies would help identify patients with susceptible tumors and aid in optimizing the timing of combination treatments. We hypothesize that hypoxia is a critical biomarker of treatment resistance and response. High oxygen levels result in better responses to RT. Thus, periods of high oxygenation in tumors could predict patient response to RT and optimal treatment windows.

Many therapies that can be combined with RT are nanomedicines or macromolecules. These drugs could have heterogeneous distribution in various metastases within patients and spatially within a single tumor.[36] Imaging of probes similar in size to nanomedicines and macromolecules that emit positron emission tomography or magnetic resonance imaging signals has heterogeneous distribution in solid tumors in patients.[32,33] Advances in imaging with such probes could help investigate the TME,[262] including the effects of immunotherapies.[263] These probes enable the evaluation of the ability of TME-normalizing strategies to reduce the heterogeneity of drug distribution, which could serve as a predictive marker

of delivery and response. Current predictive biomarker strategies include state-of-the-art tumor histology techniques, flow cytometry/CyTOF, and RNA and DNA sequencing. These biomarkers provide limited information about the pathophysiology of the TME. Imaging of drug distribution would visualize dynamic events to complement or replace other biomarker methods. TME normalization and nanomedicine development could advance symbiotically with the information gleaned from such biomarkers.

PERSPECTIVES

More research is needed to effectively combine RT with various forms and combinations of TME normalization and immunotherapy. Such research includes identifying and validating predictive biomarkers and biomarkers of response. In addition, understanding the temporal windows of the various treatments will enable effective drug combinations with fewer toxicities. We hypothesize that alleviating hypoxia is the critical biomarker for TME normalization and RT.

Hypoxia is a validated negative prognostic biomarker, induces disease progression through multiple mechanisms, and promotes resistance to most treatment modalities. Inefficient tumor blood vessel function causes hypoxia. Pathologic angiogenesis and desmoplasia cause hypoperfusion, resulting in hypoxia, acidity, and immunosuppression. Here, we described how to normalize the TME by reversing these pathologies to potentiate RT efficacy. Furthermore, we describe how TME-normalizing strategies benefit ICB, which has revolutionized cancer treatment but is estimated to benefit only a minority of patients with cancer.[34] There is an urgent need for novel combination strategies for ICB to expand its use, so we highlighted the mutually beneficial combinations of RT with ICB. TME normalization can improve the efficacy of this combination. Nanotechnologies and chemotherapies can be integrated rationally to enhance effectiveness further and limit the toxicity of RT, immunotherapy, and TME-normalizing combination strategies.

Given the potential mechanisms of synergies of these cancer therapies, future research should elucidate how to optimally combine these drugs. Unfortunately, the benefit of preclinical studies can be limited by suboptimal model choices, inconsistent reporting and protocols, and a need

for proper controls and study endpoints. These errors limit researchers' ability to determine optimal treatment windows for each therapy, as has been done for TME normalization. One solution involves the use of imaging biomarkers. Recent improvements in the imaging of perfusion, oxygen, and drug delivery in tumors have enabled data collection, supporting the notion that these biomarkers are central to determining how to best combine RT with chemotherapy, immunotherapy, AATs, and mechanotherapeutics.

DISCLOSURES

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CHAPTER 5

Precision Medicine as Applied to Radiation Oncology

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When we were asked to write this chapter, reflecting on our previous contributions to the SMART radiotherapy chapter in the seventh edition of this textbook, we chose to make our intentions clear, that is, to link biology and physics. As stated in the previous versions, we anticipate that the radiobiology chapters will cover the essential aspects of molecular radiation therapy and the tumor microenvironment, the physics chapters will include critical elements of particle therapy, and the clinical chapters will cover the molecular characterization of tumors, the use of molecular and functional imaging, and the current studies with molecularly targeted agents for various diseases. This chapter presents a new view of precision radiation oncology that is dynamic and critical to the field with some futurist thinking. "Precision" generally means matching the treatment to the patient in more than a generic way as done in the past—be it biomarker-driven, location-driven, genetics-driven, or some combination of those. Precision has historically focused on the choices at the start of the treatment course—getting drug A or drug B. We will address and expand this in this chapter, a text that has undergone transformative change in this edition.

The goal of this chapter is to take a broad view of some of the emerging innovative concepts in the practice of oncology that are relevant to radiation therapy researchers and practitioners in the optimization of selection and treatment choice—starting with what is called "precision" or, to be more precise, perhaps solid estimation. However, multiple areas covered previously in this chapter in previous editions are now further developed elsewhere in the textbook: artificial intelligence (AI; Chapters 32), radiotherapy in underdeveloped countries (Chapters 34 and 37), radiopharmaceutical therapy (Chapters 25), radiation and the immune

system (Chapters 26), hadron therapy and boron neutron capture therapy (Chapters 20), training and education (Chapters 35), and normal tissue radiobiology (Chapters 107).

A first major point that remains unchanged and needs to be stated early and firmly is that perhaps now more than ever, radiation oncology needs to be at the center of the science of cancer care. Our clinical expertise transcends all diseases; our technology impacts the most expensive, high-technology, upper-income-country care but can also reach people in dire need of cancer care in lower- and middle-income countries (as noted, it is discussed in another chapter). While not always recognized as such, in the evolving era of "precision medicine," radiation is both "precision and accurate medicine" when one looks at radiation as a "drug" compared to other drugs. We can control the pharmacokinetics and pharmacodynamics of radiation by hitting specific physical targets and using doses and schedules designed to activate molecular, cellular, and tissue pathways.[1] The term "focused biology" was coined about 20 years ago,[2,3] and it is now becoming increasingly relevant in image-guided radiation therapy, particle therapy, immune modulation, hypofractionation, and molecular-targeted drug treatment. We will focus on this aspect of radiation oncology in this textbook edition and finish with some thoughts on optimizing the patient's path, not just selecting which path to start.

PRECISION REQUIRES SCIENCE-FOCUSED CLINICAL CARE BASED ON CANCER, MOLECULAR, CELLULAR, AND TISSUE BIOLOGY

Radiation as a Drug

A concept introduced in previous editions of this chapter is radiation as a drug and immune modifier. Luo et al[4] modified the "hallmarks of cancer" model of Hanahan and Weinberg[5] by targeting non-oncogene addiction in addition to oncogene addiction. Logically, the biochemical and metabolic machinery of the cell carries out the functions of the genes, be they normal or abnormal, so that the target of cancer therapy is to disrupt the turning on and off of genes directly and also to disrupt the metabolic and biochemical pathways that they activate. Non-oncogene pathways include the stress responses: metabolic, proteotoxic, mitotic, oxidative, deoxyribonucleic acid

(DNA) damage, and evading immune surveillance. Notably, all these pathways can be modulated by radiation. Appreciating this aspect of radiation biology is critical to understanding precision medicine in our field, and we are developing this further here.

The initial work by Tsai et al[6] showed that multi-fraction adaptive responses used ribonucleic acid (RNA) microarrays to study the effects of 10 Gy as a single dose or as multi-fractionated radiation, 2 Gy × 5, in three tumor cell lines—breast, prostate, and brain—in vitro and in vivo. Fractionation results in a substantially different gene expression pattern compared to a single dose, with immune response genes being significantly upregulated. Fractionated radiation made the cell lines somewhat more alike (one of the hypotheses tested), with a substantial difference between tumors treated in vivo and in vitro, which might reflect the effects of radiation and the presence of various cell types within a tumor.

Aryankalayil et al[7] studied the molecular changes in prostate cancer cells exposed to 10 Gy as a single dose or multiple fractions using 2 Gy × 5 (multiple fraction 2) and 1 Gy × 10 (multiple fraction 1). The gene profiles are markedly different between single dose and multiple fractions, and multiple fraction1 induces more changes than multiple fraction 2. Summarizing substantial work in this regard,[3,7-9] it has been observed that: (a) an inflection point occurs after six to seven 1 Gy doses, with immune response genes being a major pathway so that this multi-fraction adaptive response may be missed in schedules using only three to five fractions; (b) changes occur in microRNA, metabolomics, and protein expression, which are now being correlated; (c) 0.5 Gy × 10 will induce changes so that many tissues know they've been hit; (d) similar changes are seen in endothelial cells, including immune response genes; and (e) as a proof of principle, drugs targeting the AKT-mTOR pathway were effective after multiple fractions but not before, demonstrating that radiation could stimulate drug susceptibility. These studies indicate the potential unique use of radiation in the "focused biology" concept for molecular-targeted therapy and emphasize the importance of investigating the molecular phenotype in cells that survive radiation.

The Tumor Microenvironment

The efficacy of radiotherapy is in part determined by tumor microenvironmental factors, including, but not limited to, the extent of tumor oxygenation, the tumor pH, and the interaction of tumor cells with host stroma and inflammatory cells. Tumors contain areas of poor vascular perfusion, low pH, and oxygen, which may provide regions in which both the delivery and activity of cytotoxic therapies are attenuated and in which cancer stem–like cells (CSC) reside.[10,11] In addition, certain tumor environments may select far more aggressive or resistant tumor clonogens.[12] One factor that has received little clinical attention but may provide an avenue for future advances is the impact of mechanical force on the transformation, progression, and treatment response of cancer cells.[13] Similarly, signaling originating from the interaction of stromal components with integrins on cancer cells can influence tumor survival and provide targets for intervention.[14,15]

The tumor microenvironment changes during radiotherapy.[16] Fractionated radiotherapy results in reoxygenation of the tumor due to the elimination of well-oxygenated cells, thus increasing oxygen delivery to the previously hypoxic areas. Conversely, high-dose single fractions (over 13 Gy) have been shown to result in the destruction of both tumor cells and vascular endothelium.[17] How and under what circumstances radiation-induced vascular injury impacts tumor responses continues to be a topic of investigation and is relevant to the current use of large-fraction stereotactic radiosurgery or therapy.[18-21] Radiation also results in the release of tumor antigens, and this release is qualitatively and quantitatively modulated by fractionation schedules, as discussed in the immunotherapy chapter.

Tumor Hypoxia

The longest-studied example of tumor microenvironment effects on cancer cell radiation survival remains the impact of tumor oxygenation. Radiation under atmospheric oxygen conditions enhances killing by a factor of 2 to 3 compared to irradiation under anoxic conditions, which has been termed the oxygen enhancement ratio[22] (as reviewed by Horsman et al[16]). In the clinical setting, hypoxia affects outcomes after radiotherapy.[23,24] However, hypoxia has also been shown to be a poor prognostic factor after chemotherapy[25] and surgery.[26,27] These findings were attributed to chronic hypoxia, which was

studied under controlled oxygen concentrations in vitro or using electrodes or immunohistochemical staining to measure tissue oxygenation in vivo. Overcoming hypoxia by biochemical targeting of hypoxic regions in tumors has proven difficult to translate to the clinic.[28] Going forward, molecular targeting of hypoxic cells may prove more practicable and effective.[29] The approach of reducing tumor oxygen consumption may also be more effective than either targeting hypoxic cells or trying to increase tumor oxygen.[30] Recent advances in noninvasive tumor hypoxia imaging may also play a role in the future, allowing precise definition of hypoxic tumors and tumor subregions through imaging with positron emission tomography,[31] magnetic resonance imaging (MRI),[32-34] or electron paramagnetic resonance imaging (reviewed in Colliez et al[35]). The resolution of these imaging modalities will be critical.[36]

More recent studies have shown that acute fluctuations in tumor oxygenation ("transient" or "cycling" hypoxia) interspersed with periods of reoxygenation may be even more effective in promoting tumor survival and progression than chronic hypoxia.[37] A third type of hypoxia, termed "longitudinal hypoxia," has also been proposed, which occurs as a gradient along the length of tumor vessels.[38] Defining the relative contributions of these hypoxia mechanisms to radiobiologic responses is ongoing; however, all could likely contribute to resistance. Cycling hypoxia may complicate efforts to identify and target radiobiologically important hypoxic regions within tumors using approaches such as radiation dose painting to hypoxic tumor subregions.[39] Cycling hypoxia is more difficult to image using current methods, such as nitroimidazole markers, which are better suited to detecting chronic hypoxia. Developments in imaging hypoxia with MRI and electron paramagnetic resonance may facilitate real-time detection of transient hypoxia in the future.

Hypoxic Cell Sensitizers and Cytotoxins

Targeting hypoxic cells should improve outcomes in frequently hypoxic tumors. Nimorazole, a nitroimidazole hypoxic cell sensitizer, has shown promising results when used with radiotherapy in patients with hypoxic tumors.[40,41] However, testing and adoption of this drug in countries other than Denmark have been limited. The alternative approach of using hypoxic

cell cytotoxins has also been tested. Tirapazamine (TPZ, 3-amino-1,2,4-benzotriazine-1,4-dioxide) undergoes reduction under hypoxia to form a highly reactive radical that causes DNA damage, leading to cell killing.[42] Under normoxic conditions, the reduction of nitroimidazoles and TPZ is reversed, thus providing the specificity for hypoxic tissues.[43,44] Despite promising early results, phase III testing of TPZ in combination with chemoradiotherapy failed to demonstrate improvement in failure-free survival, time to locoregional failure, or quality of life among patients with head and neck cancers.[45] However, patients in this trial were not selected for tumor hypoxia, and other treatment concerns were subsequently raised.[46] Developing new-generation hypoxic cell cytotoxins with greater preclinical efficacy than TPZ is underway.[47] In future tests of hypoxia-targeting agents, selecting or stratifying patients based on their tumor oxygenation status will be crucial.[48]

The identification and selective treatment of hypoxic tumors may enhance the results of radiotherapy in the future. This approach will benefit from novel imaging methods to identify hypoxia and new-generation hypoxic cytotoxins and sensitizers. In addition, hypoxia has been recently shown to impart susceptibility to DNA damage response inhibitors, as it downregulates components of the homologous recombination (HR) DNA damage repair machinery.[49,50] Exploiting this finding in radiotherapy with poly ADP ribose polymerase or other HR inhibitors could effectively eliminate otherwise resistant hypoxic tumor cells. The history and possible paths forward in exploiting hypoxia as a clinical target with a focus on lung cancer were recently reviewed.[51]

Tumor Angiogenesis and Antiangiogenic Approaches

Normal angiogenesis is a highly regulated process involving endothelial cells with differing functions (tip, stalk, and phalanx cells) under tight regulation of oxygen sensors (prolyl- hydroxylase-2 [PHD-2]), growth and maturation factors (vascular endothelial growth factor [VEGF], angiopoietins), and transmembrane receptors (Notch family) (reviewed in Carmeliet et al[52]). Small changes or imbalances in the expression of these regulators can significantly impact vascular development and lead to the formation of abnormal tumor vessels that are inefficient in transporting

nutrients, oxygen, and metabolic wastes. Limited perfusion and convection also reduce the efficacy of chemotherapeutic delivery. Unlike tumor cells, vascular endothelial cells are genetically stable and thus an attractive target. Antiangiogenic agents reduce or cut off tumor vascular flow by selectively targeting tumor vessel growth by blocking VEGF signaling. Targeting the tumor vasculature was initially proposed by Judah Folkman.[53] It is now clear, however, that this approach is complicated because development, structure, and the potential for recovery of tumor vasculature after treatment are influenced by bone marrow–derived progenitor cells in addition to the tumor and other stromal elements.[54] In addition, where tumor cell–derived vascular channeling (vasculogenic mimicry) plays a role in tumor circulation, the effects of antiangiogenic strategies that target host vascular endothelial cells may be less effective.[55]

VEGF can be induced in response to radiation, and inhibition of VEGF can increase tumor control after radiation in preclinical models.[56] VEGF receptor inhibition reduces endothelial cell proliferation in vitro after irradiation and reduces microvessel density in irradiated tumors.[57] Clinical trials have suggested a potential benefit of combining radiation and antiangiogenic therapy in rectal cancer and sarcoma.[58,59] However, the toxicity of bevacizumab in combination with radiotherapy has been of concern in some tumors.[60]

Vascular normalization is a term coined to denote transient changes observed in tumor vessels after VEGF inhibition with a VEGF receptor-2 antibody.[60] Other antiangiogenic approaches have shown similar morphologic effects on tumor vasculature. Methylselenocysteine, which has antiangiogenic activity, has been shown to induce a more mature morphology in FaDu xenograft tumor vessels, accompanied by enhanced perfusion and a 4-fold increase in doxorubicin delivery to treated tumors.[61] Normalization is characterized by a reduction in the chaotic branching and tortuosity of tumor vessels and is accompanied by a decrease in tumor hypoxia and enhanced radiosensitivity. The effects of vascular normalization may also involve a reduction of tumor interstitial fluid pressure. High tumor interstitial fluid pressure has been shown to impact survival after irradiation and may also be influenced by the tumor stroma.[62] Tong et al[63] demonstrated that blocking VEGF signaling decreases interstitial fluid pressure in mouse tumor xenografts. Although the

normalization period offers an opportunity for improved response to radiation and chemotherapy, the period of normalization obtained with direct targeting of VEGF signaling in preclinical studies lasts less than a week, followed by vascular insufficiency. In addition, vascular normalization may not occur in all tumors and has not been observed in all studies (reviewed in Horsman and Siemann[64]). In the clinical setting, vascular normalization has been proposed as a predictive marker in patients undergoing cediranib (VEGF inhibitor) treatment for recurrent glioblastoma.[65] Elevated blood perfusion after cediranib treatment has recently been associated with increased survival in these patients.[66]

More durable normalization of tumor vasculature might be clinically achievable through growth factor or oncogenic signaling inhibition. Studies have shown changes in vascular morphology, function, and maturation accompanied by decreased tumor hypoxia after inhibition targeting epidermal growth factor (EGF) receptor, RAS, phosphoinositide (PI) 3-kinase, or AKT in human tumor xenografts and spontaneous mouse tumors that last up to 2 weeks.[67] Others have shown that blocking EGF signaling increased tumor uptake of cisplatin while enhancing vascular function and oxygenation seen in tumor xenografts.[68] Signaling inhibition in these studies decreased, but did not eliminate, VEGF production by tumors, which might account for the effects seen and their duration.

Other approaches to altering tumor vasculature are being investigated. Inhibition of $\alpha(v)\beta(3)/\alpha(v)\beta(5)$ integrin has been reported to cause effects similar to signaling inhibition on tumor vascular morphology.[69] Using another approach, investigators showed that shutting off NOS1 production in U87 glioblastoma tumors restored a nitric oxide gradient around the tumor vessels. This was accompanied by a normalized phenotype with less tortuous and more abundant vessels that had increased perivascular cell coverage.[70] Hypoxia in these tumors was reduced, and their response to radiation increased, as measured by relative tumor volume and survival endpoints. Modulation of host PHD-2 can affect tumor vascular structure and maturity.[71] Inhibitors of PHD-2, such as dimethyloxalyl glycine, might be developed for clinical application. More recently, the interaction between T cells and tumor vasculature has been studied in the context of immunotherapy. Interferon (IFN) β produced by T-helper type 1 cells has

been shown to promote vascular normalization, facilitating T-effector functions.[72]

Inhibition of Vasculogenesis

Vasculogenesis, unlike angiogenesis, recruits cells from distant sites, including the bone marrow, to participate in the formation of new blood vessels (reviewed in Patenaude et al[73]). The process is considered an essential contributor to the tumor vasculature, but the precise contribution of the different recruited cell types is still debatable.[54] The CD11b-positive, matrix metalloproteinase-9-expressing myeloid cells appear central to this process.[74] A neutralizing antibody to CD11b inhibited the recruitment of myeloid cells to tumors and prolonged radiation-induced regrowth delay. Additionally, mice with reduced CD11b expression showed enhanced xenograft radiosensitivity.[75] Stromal-derived factor-1 (SDF-1) and the chemokine receptor CXCR4 also contribute to the recruitment of endothelial cell precursors and could be targeted. Inhibition of the interaction of CXCR4/SDF-1 reduced bone marrow– derived progenitor cell recruitment into irradiated glioblastoma orthotopic xenografts and slowed tumor regrowth.[76] An inhibitor of CXCR4 activation by SDF-1, AMD3100 (plerixafor), is in clinical use for stem cell mobilization and could be quickly adopted. This drug has been shown to have promising effects in chemoradiotherapy for cervical cancer.[77]

Antivascular Therapy

Selectively destroying tumor vasculature with vascular disrupting agents (VDA) is an approach that seeks to kill tumors by shutting off their blood supplies (reviewed in McKeage and Baguley[78]). This approach, however, acts primarily on the tumor core and does not eradicate host vessels that border the tumor and are in proximity to normal host vasculature. Tumor cells at the host-tumor interface can remain viable after this treatment to repopulate the tumor. Furthermore, vascular disruption could generate areas of hypoxia that still contain viable tumor cells, thereby selecting for more resistant clones.[12] Combining VDA treatment with a cytotoxic modality could overcome this problem. The effects of VDAs, both alone and in combination with antiangiogenics, chemotherapy, radiation, or other

modalities, have been examined in several preclinical studies (reviewed by Horsman and Siemann[64]). VDAs are currently in phase II to III clinical trials alone or in combination with cytotoxic chemotherapies.[79]

Tumor Stroma and Extracellular Matrix

The tumor stromal compartment, including the extracellular matrix, host fibroblasts, and immune cells, contributes to tumor progression and survival.[80,81] In certain tumors, like pancreatic cancers, activation of quiescent stromal cells, known as stellate cells, to myofibroblast-like cells involved in extracellular matrix production contributes significantly to tumor progression.[82] Activated fibroblasts deposit collagens, leading to changes in stromal rigidity, which can impact both transformation and progression.[83] This mechanism of stromal-induced tumor promotion includes intercellular signaling initiation via integrins to pro-survival pathways, including PI 3-kinase.[84]

There are multiple points at which stromal changes can be inhibited, including inhibition of fibroblast or stellate cell activation by angiotensin-converting enzyme (ACE) inhibitors or other antifibrogenic compounds such as halofuginone.[85] This class of agents can also protect from normal tissue fibrosis and inhibit tumor growth factor (TGF)-β.[86,87] Signaling by the cytokine TGF-β strongly promotes fibrosis, both in response to tumor growth and in normal tissues in response to treatment with radiation. Direct inhibition of TGF-β in tumors can interrupt or mitigate desmoplasia and reduce tumor growth.[88] Angiotensin-II (Ang II) can promote stellate cell growth under pathologic conditions, and ACE inhibitors partially act by blocking Ang II.[89] Angiotensin-(1-7), an endogenous amino acid peptide antagonist of Ang II, has been shown to reduce TGF-β expression, block the proliferation of cancer-associated fibroblasts, and inhibit tumor growth.[90] Inhibition of Hedgehog pathway signaling is another approach tested in pancreatic cancer mouse models.[91] However, there is controversy surrounding the role of Hedgehog signaling in pancreatic and other cancers.[92]

Integrin binding and signaling have been identified as potential targets for cancer treatment, as these receptors are involved in tumor growth, angiogenesis, and therapy resistance.[93] Cilengitide is a pentapeptide mimic

of the RGD binding site that blocks $\alpha(v)\beta(3)$ and $\alpha(v)\beta(5)$ integrin binding to extracellular matrix components.[94] In addition to its antiangiogenic activity, it inhibits focal adhesion kinase signaling.[95] Cilengitide is well tolerated and has some antitumor activity as a single agent.[96] It has been shown to be active in combination with radiation in several, but not all, reports.[97-99] However, questions remain about potential normal tissue toxicity in combined modality treatment because integrin signaling is required for normal cell function and survival.[97] A phase III trial of cilengitide with temozolomide-radiotherapy for glioblastoma multiforme saw no unanticipated toxicities but failed to meet its endpoints.[100]

Targeting Stem Cells

The CSC model is currently used as a framework for understanding cancer proliferation, growth, and treatment resistance (reviewed in Bednar and Simeone[101]). CSCs are considered a subset of cells at the peak of a developmental chain within a tumor with the capacity for unlimited self-renewal and lineage plasticity.[102] These cells give rise to more differentiated daughter cells with less replicative and tumorigenic potential that comprise the bulk of the tumor cell population. The CSC may be more quiescent than the general population of cells in a tumor and relatively resistant to cytotoxic therapy.[103,104] Some studies have identified perivascular niches for these cells[105,106] and the conditions that promote their colonization and survival. Still, identifying both the stem cells and their niches in a disorganized and dynamic tumor environment remains challenging.[107] The perivascular niche, particularly the endothelial cells, may aid in tissue repair and promote tumor growth by secreting "angiocrine factors."[108] Targeting these factors could be an approach to cancer treatment. Disruption of the perivascular niche with VDAs or antiangiogenics might also reduce CSC numbers. The potential for CSCs as targets and biomarkers for radiotherapy has recently been reviewed by Krause et al.[109]

Recent work indicates a novel potential target within the tumor stroma, fibroblast activation protein, which has the potential to enhance innate antitumor immune responses. In a transgenic mouse model, the elimination (through genetic manipulation) of fibroblasts and pericytes expressing fibroblast activation protein enhanced antitumor immune responses.

Activation of tumor-infiltrating T cells and the resulting increase in IFN-γ and tumor necrosis factor-α (TNF-α) promoted the antitumor immune response in a transgenic mouse model.[110] A possible pharmacologic approach to eliminating these activated fibroblasts is inhibiting the matrix enzyme lysyl oxidase–like 2 (LOXL2). Inhibition of this enzyme using a monoclonal antibody decreased desmoplasia and both primary and metastatic tumor growth[111]; small-molecule inhibitors of this enzyme also exist. Targeting LOX, which has been shown to promote tumor growth in orthotopic and spontaneous mouse tumor models, might also inhibit tumor growth.[84]

FLASH Radiotherapy

Since the publication of the last edition, the most significant emerging area in the field has been the exploration of ultrahigh dose rate, or FLASH, radiotherapy, where a dose of 6 to 15 Gy is given at an ultrahigh dose rate of above 40 Gy/s (these parameters are not formally set and are considered variable based on context).[112-115] It has enormous promise in that it seems to offer the possibility of equal tumor control in the proper dose regime (rate, total dose, field number) and a likely significant sparing of normal tissue, seeming to range from moderate to 50% with an average based on a review of the literature and perhaps of 30% dose reduction to normal tissue. Many questions exist in the FLASH domain: dose rate that is needed, mechanism, interaction with other agents (drugs, etc), quality assurance and measurement, feasibility of use with more than one field per day, whether planning systems can optimize it, how variable the effect is from person to person and tissue to tissue in the same individual, whether a FLASH effect on day one can still happen on day *N* over fractionated therapy, whether tumors can survive, whether they are more or less resistant to further treatment than standard treatment, and whether there are any odd side effects with normal tissue.[116-118] This incomplete list goes beyond the scope of this chapter, but we'll approach just a few of these issues from the precision radiation therapy perspective with full knowledge that these are very early days in this emerging field and patient data really do not exist yet in this space, so our short commentary should be considered just some open

thoughts and discussion pending more data in the coming years in preclinical and ultimately clinical trials.[119,120]

In the context of precision medicine, the primary question for the field is whether the FLASH effect is observed in all patients, and if not in all patients, whether it can be modified to personalize to benefit from the flash effect, and whether there is a way to tell immediately if the normal tissue sparing is occurring so that potential injuries can be avoided.[121] This is crucial because the plan may require the FLASH effect to keep an organ at risk (OAR) under a tolerance constraint value. In a similar vein, some people are more likely to have serious late effects from FLASH radiotherapy that may not appear until months or years after treatment. This is of particular concern in patients where treatment with standard therapy is very much able to deliver quality care with minimal risk in the context of expected long survivorship, such as in a pediatric patient with Hodgkin disease. Finally, whether people adapt to FLASH therapy differently is a critical question and completely unknown at this point. To be fair, it is also not very well known for standard radiation therapy. In case they adapt differently and in a significant fashion, the interpretation of a FLASH plan, even if done with the most robust methods and fewest assumptions, may only reflect the first fraction or two of treatment as adaptation may make FLASH an invalid approach over multiple fractions.[118]

The major current potential limitation of FLASH is that the window where it is useful may be different from a clinically viable window for most patients. We avoid using large fraction size radiotherapy in many situations because it can cause increased toxicity to normal tissue. While FLASH promises to reduce that, it may not or only partially do that. Large fraction sizes are generally used palliatively or for stereotactic cases where we know exactly (we think) where the tumor is. When there is an unknown tumor margin involved, we have mostly normal tissue but some tumor tissue. If the FLASH effect works without question, this might be a very sensible approach for this sort of margin, but if it does not, large areas of normal tissue may be damaged, and this is just one example of a situation where large fractions may not work.[122,123] If we accept that not all situations are best managed by hypofractionated therapy, not knowing if FLASH can be used for 10- or 20-fraction courses matters a lot. Finally, we need to understand the mechanism of FLASH better to understand how to take

maximal advantage of it by setting up the patient to have the best FLASH outcome and how to potentially mitigate it in cases where it appears to be sparing tumor unexpectedly.[124,125] We have not even started to discuss if other agents work as expected with FLASH, such as traditional chemotherapy. Given these and other issues, what is certain about FLASH is that there is much to learn, and we are not close to calling it a standard-of-care therapy in 2024. Yet, it has enormous promise and must be studied carefully via clinical trials.[126] More tools are needed, but we are slowly moving toward randomized trials in this space, given the published road maps for doing so.[117,127]

Summary of Microenvironment

It is impossible to predict how radiotherapy will evolve in its utilization of knowledge regarding the tumor microenvironment and host-tumor interactions. What appears clear is that increasing emphasis will be placed on these factors. Targeting changes specific to the microenvironment has the advantage of being largely tumor-specific and potentially less toxic than cytocidal therapies. Future developments may allow for hypoxic tumor region dose painting. Alternatively, hypoxia-targeting drugs may finally reach clinical maturity. Inhibition of hypoxia in tumors may also arise from strategies that revert tumor vasculature to more normal morphology and function. This strategy has the added advantage of reducing hypoxia selection for aggressive tumor clones and enhancing chemotherapy delivery. The impact of the immune response on tumors and, in turn, the effects of different radiotherapeutic interventions on immunity are now being exploited with the explosion of trials combining checkpoint inhibitors and radiation (see the next section). Findings relating to the impact of host stromal elements on tumor cell radiation survival through direct intercellular signaling, autocrine stimulation, or mechanical force may also soon reveal new targets and interventions applicable to radiotherapy.

In addition to the host and tumor microenvironment, external environmental factors may also play a role in response to therapy. These have yet to be thoroughly evaluated or exploited. Temperature (hyperthermia) is well known to impact radiation response,[128-130] but its evaluation and clinical application, at least in the United States, have

continued to lag. Conversely, preclinical studies have shown that lower ambient temperatures can induce resistance to cytotoxic therapies[131] and influence tumor growth and immune responses.[132] The impact of time of day of treatment and the role of circadian clock proteins are other understudied areas that could be exploited.[133] Preclinical work points to the possibility that the clock proteins influence tumor radiosensitivity.[134] There are indications from clinical studies that both toxicity and treatment failure could be impacted by the time of irradiation, but the data are not yet conclusive.[135] At a minimum, further study of these factors could inform preclinical study conditions and perhaps enhance the translation and reproducibility of results. And, as pointed out, we don't yet have enough data on FLASH therapy to really know much about when and how to best use it with actual patients with real tumors in the context of current standard-of-care therapy regimens.

Combining agents that alter the tumor environment with radiotherapy requires robust preclinical data demonstrating at least additive effect and acceptable toxicities. Careful preclinical testing, including normal tissue response evaluation, may avoid subsequent problems in many instances. Having markers and imaging that detect the targets of interventions, such as hypoxia, cancer-associated fibroblasts, or immune infiltrating cells, which can be used to assess intervention-mediated changes in the environment, will be critical to fully exploiting this approach. Recent developments in the analysis of circulating tumor cells and cell-free DNA (cfDNA) may revolutionize treatment monitoring, as discussed later in this chapter.

Chapters 26 addresses the unique role of the immune system, a critical part of the tumor microenvironment, and is closely connected to the abovementioned topics.[3]

PRECISION MEDICINE REQUIRES A MULTIDIMENSIONAL APPROACH FOR MAXIMUM IMPACT

Dimension 1: Normal Tissue Injury Science

Radiation risk to humans stems from a variety of complex radiation exposure scenarios, which include therapeutic and diagnostic medical exposures, occupational exposures, radiation accidents, nuclear weapons detonation, and terrorist events. Radiation exposure can cause acute,

intermediate, late, and/or chronic injury. The severity of the injury is dependent on radiation type, dose and dose rate, and volume of the tissue irradiated in addition to an individual's inherent sensitivity to radiation. In addition, different normal organs and normal tissues respond to radiation exposure in differing ways, influenced by, among other factors, intrinsic sensitivity to radiation, functional architecture, cellular turnover rate, and differences in damage response.

Acute exposure to total-body ionizing radiation in the dose range of 0.5 to 30 Gy can result in acute radiation syndrome (ARS), which is divided into organ syndromes based on the dose and cause of mortality.[136] The sequence of manifestation of ARS from lower to higher doses is as follows: hematopoietic, gastrointestinal, dermatologic, cardiovascular, and neurologic. However, syndromes overlap. For example, damage to the gastrointestinal or dermatologic systems can impact the outcome of hematologic syndrome at sublethal doses. Bioindicators or biomarkers of radiation exposure, even in the lower dose range, can reflect a response by multiple organs, all of which sense and respond to the radiation.[137]

At radiation doses below 0.5 Gy, acute effects are not observed, but there is the probability of late effects such as cancer and hereditary effects.[138] The possibility of exposure of a large number of people to radiation following a nuclear incident has raised the public's concerns about the increase in the chances of developing radiation-induced cancers.[139] However, public perception and "fear of radiation" appear well beyond the actual risk. This fear was elevated due to the Fukushima disaster despite the lack of evidence for acute radiologic injury in the general population.[140] Quantifying the risk associated with low-level radiation exposures is problematic and uncertain because of the unresolved shape of the dose-response curve for radiation-induced cancer in the low-dose region.[141] For the purposes of radiation protection, it is assumed that there is a linear relationship between exposure and future cancer risk. A linear no-threshold model is used to assess risk at doses below 100 mSv, recognizing that epidemiologic information in this dose region cannot unambiguously support or refute the model assumptions.[142] However, data from the Radiation Effects Research Foundation in Japan seem to align more with a linear relationship between radiation dose and cancer risk.[143] Evidence is emerging on the possibility of additional late-developing effects on health following somewhat higher

doses, such as cardiovascular[144] and respiratory disease,[145] premature senescence,[146] and damage to endothelial cells.[147,148]

A multidimensional approach is necessary to address the complexity of the radiobiologic issues facing society across a wide range of energies, types, and doses. Various agencies of the U.S. government conduct and fund studies on radiation-induced normal tissue injury and develop medical countermeasures (MCMs) to mitigate many risks to individuals or populations associated with radiation exposures, addressing different dose ranges relevant to an agency's mission. Successful development of risk mitigation strategies requires a multidimensional approach with mechanistic scientific underpinnings to address the complex biologic variables. Ongoing research efforts among various government agencies related to radiation-induced normal tissue injury are summarized in Figure 5.1.

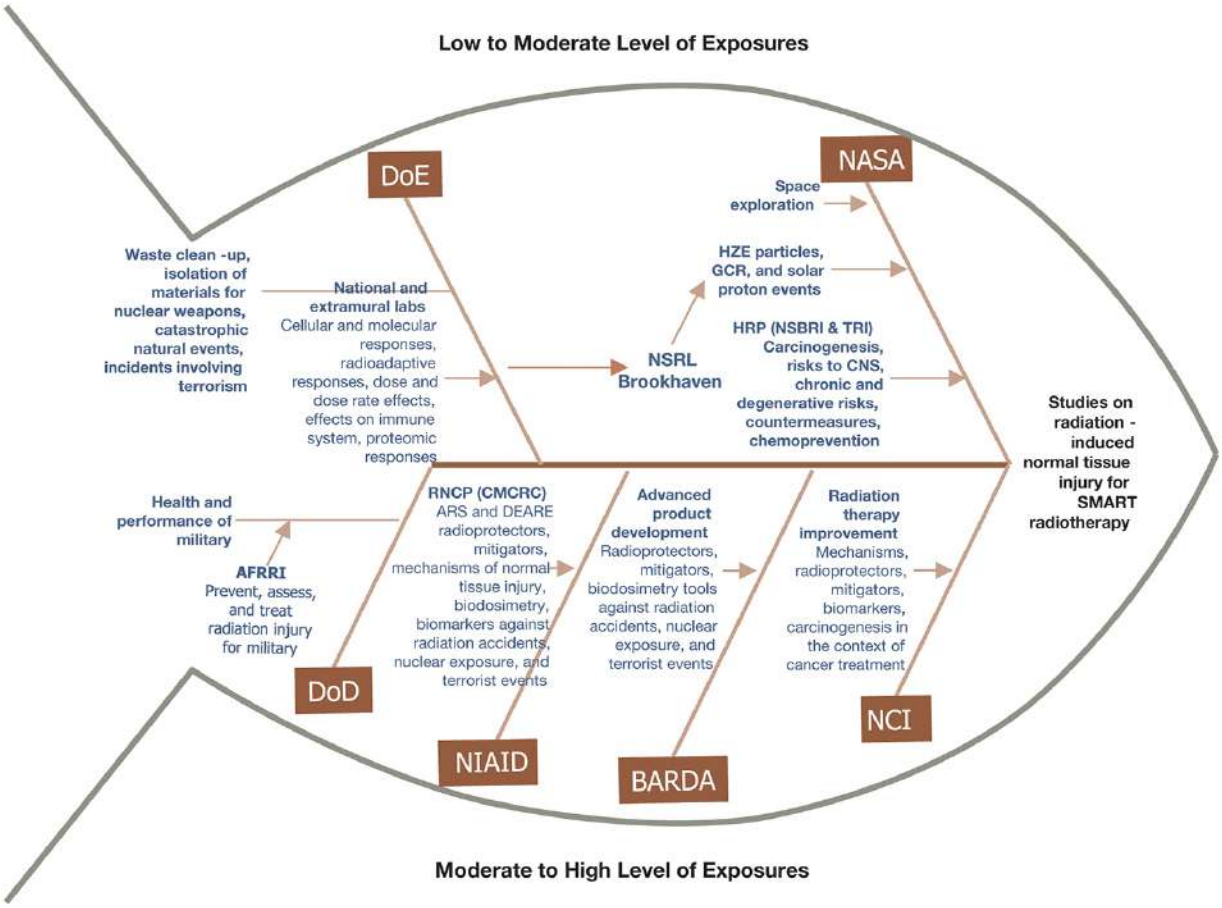

FIGURE 5.1 U.S. government research efforts among various government agencies related to radiation-induced normal tissue injury. AFRRI, Armed Forces Radiobiology Research Institute; ARS, acute radiation syndrome; BARDA, Biomedical Advanced Research and Development Authority; CMCRC, Center for Medical Countermeasures against Radiation Consortium; CNS, central nervous system; DEARE, delayed effects of acute radiation exposure; DoD, Department of Defense; DoE, Department of Energy; GCR, galactic cosmic rays; HRP, Human Research Program; HZE, High (H) Atomic number (Z) and Energy (E); NASA, National Aeronautics and Space Administration; NCI, National Cancer Institute; NIAID, National Institute of Allergy and Infectious Diseases; NSBRI, National Space Biomedical Research Institute; NSRL, National Space Radiation Laboratory; RNCP, Radiation and Nuclear Countermeasures Program; SMART, Societal focused, Molecularly aware, Altruistic, Research supportive, and wary of Technological solutions to biologic problems; TRI, Translational Research Institute (also known as the Translational Research Institute for Space Health [TRISH]).

The Department of Energy (DoE) under the Biological Systems Science Division studies radiation-related health risks from exposures to low levels of radiation. Exposures to low doses can occur in several scenarios, including (a) around nuclear power plants, (b) during isolation of materials for nuclear weapons and nuclear power production and waste cleanup, (c)

during medical diagnostic exposures, (d) during radiation terrorism incidents, etc.[149] The DoE's Low Dose radiation research program (poised to reopen with a promise of significant funding over a decade planned) is focused on cellular and molecular responses to doses relevant to workplace exposure limits, radio-adaptive responses, genetics of interindividual variation, low-dose and dose-rate effects, effects on the immune system, and epigenetic regulations.

The National Aeronautics and Space Administration (NASA)'s interest in radiation research focuses on space exploration, including earth orbits and, more recently, potential manned missions to Mars and beyond. The duration of the Mars mission necessitates understanding immediate health risks in the space radiation environment and long-term post-mission quality of life. The Human Research Program (HRP) was developed to refocus the space program in early 2004. NASA identified major risk categories attributable to space radiation, including carcinogenesis, risks to the central nervous system (CNS),[150] and chronic and degenerative tissue risks.[151] High-charge and high-energy ion components of galactic cosmic radiation can cause genetic mutations,[152] inflammation, and CNS structural damage and dysfunction.[153] The HRP is focused on understanding the possibility of reducing these health risks by developing countermeasures for acute exposures of greater than 1 Gy associated with large solar particle events and mitigators for lower-level exposures, particularly iron ions that will be encountered in the Mars mission. NASA's National Space Biomedical Research Institute conducts integrated biomedical research to support long-term human presence during space exploration and the enhancement of life on earth by applying these advances. The NASA Translational Research Institute was founded in 2016 to work in partnership with the HRP to translate cutting-edge terrestrial research into applications for space flight, focusing on human risk mitigation strategies for exploratory missions. Teaming up with the DoE's Office of Science, NASA has established the Space Radiation Laboratory (NSRL) at the Brookhaven National Laboratory. NSRL uses the Brookhaven ion beam facilities to enhance understanding of the link between radiation and cellular damage and also seeks approaches to limit the damage to healthy tissues by cosmic radiation in a simulated space radiation environment. NSRL uses beams of heavy ions extracted from Brookhaven's Booster accelerator to simulate cosmic

rays found in the space environment. NSRL has a beam line dedicated to radiobiology research. These studies are also relevant in particle therapy research for cancer treatment. Different but related is the International Space Station National Laboratory, which funds numerous studies on radiation effects in both human biology and manufacturing.

The Armed Forces Radiobiology Research Institute (AFRRI), within the Department of Defense, conducts basic and applied research to identify and develop measures to prevent, assess, and treat radiation injury to preserve and protect the health and performance of U.S. military personnel. The biodosimetry program has been developing rapid and precise methods to assess the severity of radiation injury as early as possible after the event to guide treatment decisions and aid in monitoring recovery from and the effectiveness of treatments for radiation injury.[154] AFRRI continues an intensive program on the identification and development of radiation countermeasures to be used by military and also civilian personnel.

The Department of Health and Human Services has two programs relating to normal tissue injury: (a) Medical Countermeasures against Radiological and Nuclear Threats at the National Institute of Allergy and Infectious Diseases and (b) the Public Health Emergency Medical Countermeasures Enterprise, which includes research and advanced development efforts in MCMs and biodosimetry including the Biomedical Advanced Research and Development Authority that deals with the full range of national security threats.[155] A key underlying principle of the entire radiologic or nuclear medical response program is that it is built on solid scientific underpinnings.[155] Research in normal tissue radiation biology received a substantial boost as the radiation biology community proactively responded to bringing the best science to help address the threat of radiologic and nuclear terrorism that became apparent following the September 11, 2001, terrorist attacks. Scientists from the academia and the government conceptualized a research plan that distinguished modifiers of normal tissue injury into three time phases: (a) protectors that are administered before radiation, (b) mitigators that are used following radiation exposure but before the damage has been fully manifest, and (c) treatment that is given for established radiation injury.[156] Some agents may function in more than one role. The radiologic or nuclear incident research plan includes the broad categories of (a) MCMs, which are drugs or

biologics developed as radiation mitigators, (b) biomarkers that can quantify an individual's radiation dose as a guide to treatment, and (c) agents that serve to reduce the exposure to internalized radionuclides by blocking uptake or enhancing excretion. The medical consequences of interest are those that result from a total-body exposure (or significant partial-body exposure) of a dose that can produce ARS.[137] A radiologic or nuclear incident will be a "no-notice" event, and for a large-scale nuclear incident, the requirement for an MCM is that it should be effective if started up to 24 hours after radiation.[157,158] A longer window of opportunity would be better given the chaos of the situation and that is part of the MCM development effort. What is not often appreciated is the concept of latency between exposure and clinical manifestation of radiation injury. To that end, there are two terms used to convey the concept: ARS and delayed effects of acute radiation exposure (DEARE). The development of the next generation of MCMs will exploit the evolving understanding of mechanisms by which radiation induces injury in normal tissue and its manifestation over time, from acute effects to DEARE to long-term late effects. The challenges in employing radioprotectors to reduce normal tissue injury during the course of radiotherapy are different. Here, a significant concern is the protection of the tumor itself, which would result in a compromised therapeutic benefit.

The National Cancer Institute (NCI)'s Radiation Research Program (RRP) has supported studies of normal tissue injury in radiation therapy for several decades. In the clinical context, a radioprotective drug might allow dose escalation to the tumor, leading to better tumor control or the same local control with less toxicity. Although many novel approaches of dose delivery to the tumor volume significantly reduce collateral normal tissue injury and improve the therapeutic ratio, the tumor's location within an organ of an inherent sensitivity to radiation and the dose needed to cure the tumor can still result in normal tissue injury.[156] Many patients still suffer adverse effects from radiotherapy, largely due to the biologic variables influencing treatment outcomes.[159,160] Improved survival results in increases in treatment-related adverse late effects, such as pulmonary fibrosis,[161] cognitive damage,[162] and secondary cancers, especially among children.[163] Prevention of these late occurring adverse effects warrants the development of countermeasures for enhancing posttreatment health-related quality of life (HRQOL) for cancer survivors.

Synergy among government agencies in supporting drugs to reduce radiation injury ensures our investments are rational, viable, sustainable, and cost-effective across a broad, multidimensional space so that precision can be applied to varied, critical situations. Academic and government research efforts can be leveraged by the NCI Small Business Innovation Research (SBIR) program through RRP initiatives to test promising radiologic countermeasures for clinical applicability so that such products gain "dual utility"—use in cancer treatment and also use for accidental or intentional civilian exposure. The development of dual utility agents will greatly reduce costs and risks of failure while enhancing the value of research.[164] The RRP-SBIR effort for advanced development of radiation-effect modulators serves as a model to reduce the risk for small businesses by providing government support.[165] Repurposed MCMs in the cancer treatment setting may help improve the treatment outcome by protecting normal tissue during treatment, reducing the acute adverse effects, or mitigating late effects, including therapy-induced secondary cancers, thus improving the HRQOL of patients.

A nuclear accident or terrorist incident could potentially expose a large number of people to low- to moderate doses of ionizing radiation and increase their lifetime cancer risk. There is an urgent need to develop low or nontoxic mitigators for this purpose. Current status, issues, and challenges regarding developing mitigators against radiation-induced cancers have been published.[166] These challenges include the long latency between exposure and cancer manifestation, limitations of animal models, potential side effects of the mitigator itself, the potential need for long-term use, the complexity of human trials to demonstrate its effectiveness, and statistical power constraints for measuring health risks (and reduction of health risks after mitigation) following relatively low radiation doses (<0.75 Gy). Nevertheless, progress in the understanding of the molecular mechanisms resulting in radiation injury, along with parallel progress in dose assessment technologies, makes this an opportune, if not critical, time to invest in research strategies that result in the development of agents to lower the risk of radiation-induced cancers for populations that survive a significant radiation exposure incident. Such mitigators will also be of immense value to counter late effects, including secondary cancers, after radiation therapy among cancer survivors.

Products that target the tumor promotion stage of a multistep carcinogenesis model, which involves initiation, promotion, and progression,[167] have primarily come from the field of chemoprevention. Modifiers of radiation-induced transformation in vitro systems include the following classes of compounds: (a) vitamins (or vitamin-like compounds), their precursors (eg, vitamin A, its precursor carotene and other carotenoids), and derivatives (eg, retinoids); (b) protease inhibitors (eg, the soybean-derived protease inhibitor, Bowman-Birk inhibitor); (c) hormones (eg, glucocorticoid hormones, testosterone, dihydrotestosterone); (d) modifiers of arachidonic acid metabolism (eicosanoids); (e) inhibitors of protein kinase C; and (f) antioxidants, including numerous products that scavenge free radicals.[166] Many cancer prevention products recognized by the Division of Cancer Prevention (DCP, NCI) also may be useful as mitigators of carcinogenesis after exposure to carcinogens, implying their potential to intervene in radiation-induced carcinogenesis at the promotion stage as exemplified by a curcumin study in which dietary administration significantly reduced the incidence of mammary tumors in rats.[168]

However, testing MCM drugs for use after radiation accidents for effectiveness, as well as mitigators to counter radiation-induced cancers, is challenging. The U.S. Food and Drug Administration (FDA)'s Animal Rule provides a regulatory framework for obtaining regulatory approval for MCMs. Previously, the FDA approved Neupogen (filgrastim), a granulocyte colony-stimulating factor, and Neulasta to counter radiation-induced neutropenia in a radiation emergency. The FDA recently approved a granulocyte-macrophage colony-stimulating factor growth factor supporting white blood cell production (Leukine) and a synthetic thrombopoietin receptor agonist, Nplate. Given the uncertain relationship between low-dose exposures and late effects, lack of suitable models, and early predictive biomarkers, regulatory challenges regarding mitigators have been even more significant.[166]

Dimension 2: Biomarkers

Clinical Application of Circulating Cell-Free Deoxyribonucleic Acid and Circulating Tumor Cell Deoxyribonucleic Acid to Assess Tumor Response and Evolution Under Treatment

One of the limiting factors slowing the integration of molecular therapies in the context of radiotherapy has been the relative lack of radiation biomarkers to monitor and predict clinical responses of both tumor and normal tissues, but this is changing rapidly. For monitoring tumor responses, the capacity to rapidly analyze cfDNA and circulating tumor DNA (ctDNA) promises to overcome this limitation. Analysis of free circulating DNA in plasma by droplet digital polymerase chain reaction (ddPCR) can reveal the presence of cancer in as little as 3 days compared to 4 weeks to obtain next-generation sequencing (NGS) results. In ddPCR, the purified plasma DNA is emulsified with oil into thousands of droplets containing at most one target DNA molecule that is PCR amplified, fluorescently labeled, and then read in an automated droplet flow cytometer. Each droplet is individually scored based on fluorescent intensity for the mutant or wild-type allele of a target locus.[169] This technology's high sensitivity and specificity have been demonstrated in a prospective study of non–small cell lung cancer.[170] The limitations of this test are that it is applicable only when the tumor sheds DNA into the bloodstream, it detects only known genotypes, it cannot detect rearrangements, and it is difficult to multiplex.

NGS can detect a broad range of targetable genomic alterations with 100% specificity. The sensitivity of this technique is equivalent to that of ddPCR.[171] When assessing for the presence of a driver or resistance-associated mutation, this technique applied to circulating DNA could avoid biopsy when results are positive. Still, sensitivity limitations mean that it cannot rule out mutation with a negative result. ctDNA analysis can also be used to monitor the evolution of a tumor under treatment. Novel methods have been and continue to be developed to use ctDNA analysis as a longitudinal diagnostic tool for patients with localized and metastatic cancers.[172-174] The mutation levels in patient plasma samples reflect the clonal hierarchy inferred from the sequencing of tumor biopsies. Serial changes in circulating levels of subclone-specific mutations correlate with different treatment responses between metastatic sites. A comparison of biopsy and plasma samples in individual patients with metastatic breast cancer demonstrates that ctDNA provides a dynamic sampling of somatic alterations that reflect the size and activity of distinct tumor subclones. Analysis of ctDNA also mirrors the clonal hierarchy determined by

multiregional tumor sequencing and tracks the variability of treatment responses by different metastases.

Identifying actionable somatic mutations, or alterations known to confer resistance to specific therapies and their relative circulating levels in pretreatment plasma samples, could inform an individualized choice of targeted treatments and represent a breakthrough for precision radiotherapy and cancer treatment.

The NGS-based approach of Cancer Personalized Profiling by Deep Sequencing (CAPP-Seq) for analysis of ctDNA enhances both the sensitivity and specificity of ctDNA detection and mutation analysis.[175] This method uses labeled DNA oligonucleotides (selectors) that target known DNA sequences mutated in the cancer of interest. The selector is applied to a tumor or circulating DNA to identify, by hybrid affinity capture, a patient's cancer-specific genetic aberrations (including driver mutations and rearrangements) and then used to quantitate their presence and change over time in circulating DNA. When combined with integrated digital error suppression, which eliminates most technical artifacts observed in cfDNA sequencing data,[176] CAPP-Seq can achieve the same sensitivity as the ddPCR technique. CAPP-Seq can achieve the equivalent or better sensitivity to ddPCR techniques (down to 4 in 10^5 cfDNA molecules) but can test a much wider number of sites on the genome. Epigenetic research has had a high impact in the radiation oncology space, with, for example, work in the prostate being of high impact and ongoing.[177,178]

These new minimally invasive genomic analysis techniques can monitor response, minimal residual disease, and give advanced warning of recurrence allowing for early changes in therapy. In the future, they may be adapted to early detection, allowing for early-stage radiotherapy treatment of currently intractable diseases such as pancreatic and CNS malignancies. An example of this is the demonstration of the sensitivity of ctDNA in cases of new melanoma brain metastases.[179] Biomarkers are not just blood-borne. Imaging tools and AI have made rapid strides in this space and will continue to accelerate.[180-182] These will be addressed in the AI chapter.

Dimension 3: Predictive Oncology Methods

The application of predictive biomarkers of radiation injury is another rapidly evolving area of research, with the potential to integrate with precision radiotherapy by (1) predicting individual differences in radiation sensitivity,[183] (2) predicting the severity of normal tissue injury among patients,[184] and (3) assessing and monitoring tumor response to radiation therapy.[185] A biomarker-based test that can predict the risks of developing severe radiotherapy-related complications will not only allow the delivery of alternative treatment modalities and the use of mitigators and protectors, but may also allow dose escalation to the tumor in less sensitive patients. This might improve the overall therapeutic benefit and outcomes among all patient cohorts. Various radiation biomarkers have already been explored or are currently under development at different technology readiness levels in the context of their potential application for individual dose assessment in accidental exposures to radiation or malevolent use of radiation.[186] However, the discovery, development, and validation of predictive biomarkers of radiation hypersensitivity are as challenging, if not more challenging, as radiation-effect modulators. This is due to the low prevalence of normal tissue complications in the clinic, a need for long-term studies for predicting late effects (eg, radiation-induced cognitive damage),[162] and the complexity related to the combination of chemotherapy with radiation as the standard of care for most tumors.

Mitigating the risk of radiation-induced cancers will require the use of three categories of biomarkers: (1) radiation dose assessment biomarkers (biodosimeters), (2) genomic health predictors, and (3) cancer surveillance biomarkers.[166] Diagnostic biomarkers for determining the radiation dose of individuals following accidental exposures or therapeutic exposures may also be useful in assigning risk to the exposed population for developing delayed health risks, including cancer. This would help identify “at-risk” individuals who may benefit from mitigators of late and/or enhanced cancer screening. In this context, well-established/validated cytogenetic assays, such as cytokinesis-block micronucleus assay[187] performed using peripheral blood lymphocytes for assessing “total genomic health risk,”[188] will be useful. There is also a need for using an enhanced cancer surveillance program for selected high-risk radiation-exposed cohorts, especially following a radiologic mass casualty. The Early Detection Research Network of the DCP at NCI, a laboratory consortium, focuses on

identifying, testing, and validating methods to noninvasively and accurately detect cancers at their earliest stages. Biomarker-based treatment decisions may eventually drive personalized medicine. Issues related to designing clinical trials with biomarkers have been discussed elsewhere.[189]

Several biomarker technologies are currently under development across government agencies and have been reviewed.[186] The biomarker and MCM development efforts complement one another. Concurrently, predictive biomarkers for radiation dose and genomic health will benefit commercial development and use of radiation risk mitigators, helping to understand the impact of nutrition, repurposed drugs, or other interventions.

In summary, Figure 5.1 provides a glimpse of ongoing multidimensional efforts in radiobiology related to radiation-induced normal tissue injury at various government agencies. These efforts over the past decades have significantly advanced our understanding of mechanisms of radiation injury to normal tissue and its manifestation in different cell renewal and organ systems, allowing the discovery and development of next-generation radiation countermeasures and biomarkers with foundational mechanistic radiobiology, which could be used to enhance precision radiotherapy. These issues and many others were addressed in a workshop on predictive oncology in radiation oncology held with NCI and DoE in 2021,[190] with the field exploding since then with a new focus on the digital twin, an area of research that has been of use in aerospace and engineering for decades but is only now being explored in the biomedical arena.[191] Radiation oncology lends itself to the use of digital twins in some ways because we are, as a field, comfortable with electronic models of our patients (eg, treatment plans). Adaptive radiotherapy is, in some ways, a digital twin approach as changes are incorporated during therapy to optimize dose delivery—with precision approaches ultimately allowing us to make better treatment plans for adapting and optimizing treatment courses.[192] The induction of targets via radiation delivery and what happens during the treatment course is being addressed with the NCI's U54 Radiation Oncology-Biology Integration Network consortium being established to collect the baseline data on what happens multidimensionally before, during, and after radiation therapy so that we can begin to create models and "twins" as a field to ultimately help our patients get the best therapy course as they evolve over the treatment course.[193,194]

Dimension 4: Different Types of Energy Delivery (Radiation and Other Things) Are Different Drugs

Particles Versus Photons: Two Different Drugs?

Particle therapy is, in many ways, a paradox in terms of precision radiotherapy. It is both very precise and not precise at all. It has the most complex infrastructure of the external beam modalities in terms of physics support and costs. As such, it is relatively uncommon in most countries and is often considered the most specialized form of radiation. It has been touted as having fewer side effects and is often considered the first choice when treating pediatric tumors.[195] It also may be the most problematic on multiple levels. It is, in some sectors, the most promoted form of radiation therapy, and yet it is the most immature form of radiotherapy.[196]

Particle therapy can be divided into two major categories: protons and the so-called "heavy ions," which typically include helium, carbon, and oxygen, among others (although these are often termed "light ions" in the physics literature because of their position on the periodic table), and neutrons are a separate subject that is addressed in other chapters. Unlike photons that are generated from electrons hitting a target or from radioactive decay from isotopes such as cobalt-60, charged particles must be accelerated to near the range of the speed of light to be effective. To achieve this, large machines employing large magnetic fields are used to accelerate particles. Typical devices to accomplish this include cyclotrons, synchrotrons, and other devices—areas of discussion in other chapters, so we only briefly mention them here. This section applies to both of these subgroups unless otherwise stated explicitly.

To explore the concept of precision particle radiotherapy, several interrelated domains that will likely change simultaneously will be presented in this section. While not exhaustive of all the possible changes to this type of radiation therapy, they are meant to reflect the overall trends in particle therapy broadly. What they have in common is that they are likely to reflect the decreasing cost of the devices and a crucial, newfound willingness to treat particles as imperfect and in need of rigorous study. These changes are all based on financial change and increasing translational knowledge.

Hopefully, the field will conduct and complete prospective randomized trials to better define and develop where particle therapy has clear advantages and is not only "less good" but perhaps "uniquely bad." This is something we have needed in the field for a long time—with published articles at one point debating if trials were needed, in this case, to evaluate protons because protons' superiority was supposedly obvious and not up for debate.[197] Many things have conspired to make that supposedly obvious truth less and less evident in the current space of using physical doses to prescribe proton therapy treatment. We really don't know if particles have unique long-term problems based on their biology compared to normal tissue.[198] We think they are likely better if used carefully by those with experience, but with relative biologic effectiveness higher than 1.1, how will 75 to 100 Gy equivalent doses affect normal tissues over time?[199] Conversely, if used poorly, they are, at best, likely to be far worse because it is far easier to dosimetrically miss a tumor with particles. Plans with photons and standard planning target volumes are generally more robust, making widespread use of particles without extensive expertise in the subtleties of their use a somewhat risky prospect moving forward for the field unless methods can be developed to make their use more robust and to contain the complexity in manageable planning interfaces.[200]

Trials and the development of new tools are needed to address these issues and will generate a host of data to be incorporated prospectively into the field. An honest evaluation of planning skills and time spent with the outcome will need to be performed. The risks particle therapy presents to the field due to biologically incomplete planning will be one of the forces that may drive the inclusion of AI into the planning process—to introduce more expertise into the treatment process. This goes beyond the rapid normalizing of auto-contouring. Over time, proper particle therapy will require advanced dose and robustness optimization tools that are accessible and easy to use as the number of users increases. Still, patients who benefit remain about the same. Beam selection will need to optimize (a) not only Bragg peak location but also (b) all areas of high linear energy transfer dose deposition, such as the penumbra of each field, perhaps of each spot, (c) inherent geometric motion statistics for site in three and four dimensions, and (d) specific tissue data based on voxel by voxel beam data and

situational awareness of other medical issues such as oxygenation of tissue, concurrent agent concentration, and prior tissue injury status.[199,201]

These changes in the domain of particle therapy are a component of the precision radiation therapy concept of radiation as a drug. Each particle will finally be seen and considered as a different drug. Trials will be designed in this way.[202] To date, we have allowed a mixture of photon and proton patients, use of two agents that may have vastly different activity based on the radiation type used, and looking at the results only after the fact will no longer be a viable trial design. Trials will need to be powered for each "drug" used. What each particle does to DNA and even the normal components of cells like the membranes, organelles, and proteins are vastly different and may yield opportunities for therapeutic index gain or cause just the opposite.[202] Each particle will be thought of as a new agent rather than just radiation therapy.[203] As such, agent mixes and even new agents designed to work specifically with our newly appreciated war chest of radiation "drugs" will allow further optimization of treatment and perhaps even cost savings. It might turn out that mixtures of particles of different types in specific sequences in time and space will be far superior to any monotherapy of particles or photons in use today, improving the precision of radiation therapy.

These new data are likely to shed light on the reality of particle therapy and allow it to reach the level of promise many have envisioned for it from the beginning. To do this, the resulting new set of biologic data will be the basis of a significant, global change in radiation oncology driven by particle therapy that affects all modalities: biologic treatment planning. The software methodologies discussed earlier will collapse to classical photons as the control state, like classical mechanics, is the default state of special relativity when one's velocity is far slower than the speed of light.[204] Plans for patients will move from physical energy dose prescription to this integrative form of a biologic dose prescription and OAR risk tolerance mapping model. Computer models incorporating libraries of biologic data will be invoked to do this work, adding situational precision. Imaging-based biomarkers will be used in real time to monitor biologic response to fit the models to an actual host response, adding path of treatment optimization—precision path radiation oncology. This new paradigm could be called adaptive biologic treatment planning.[205] Building the models in ways that

allow for real-time adjustment by incorporating biomarker data will be very labor-intensive. However, once built, what we do now with physical dose will seem extremely crude in comparison. This is perhaps the most accurate form of precision radiation therapy that is to come in the future. It will involve and allow for the use of all sorts of new agents and combinations of agents, their dynamic change, and the idea that radiation is very much biologically driven by the point in space and time it is being used, and rather than "a Gy is a Gy," it will be the new paradigm. Potentially critical to this new domain will be advancements in multiscalar, dynamic modeling —exemplified by the digital twin.[191,206]

Inexorably linked in time with more trials being performed will be a combination of decreasing cost of the devices, increasing availability of computing resources that can scale to these issues affordably, increasing numbers of particle treatment machines, more narrowly defined uses for radiation in general based on concurrent research expanding our biologic understanding, and likely decreased reimbursement. This is a metastable situation at best on several levels. The most profound level is the reality that everyone who wants one of these centers might be unable to support it with sufficient patient numbers where it is indicated to keep staff experts and bills paid. Financial uncertainty in radiation oncology is increasing, and these particle centers are likely to be the most uncertain financial component of any given center unless they are run with a "break-even at best" long-term business plan somehow supported by institutional commitment to the science involved despite risk of losses, the rare disease capacity, or development support.[207]

Light as a Drug

Photodynamic therapy (PDT), in which light interacts with chemical agents to deliver energy to tissue, is currently one of many prospective trials sponsored by several program project grants from the NCI and other support mechanisms. Areas of interest involve tumors of many regions, both from a definitive perspective in a postoperative and preventive setting. Additionally, some studies evaluate the interplay between the immune system and PDT usage.[208-210] PDT is under intense investigation, and its use may become more widespread if these trials define areas of significant

therapeutic benefit. This active milieu of trials will be the contemporary environment of PDT for the reader of this text during the active period of this edition.

Much of the work described in the last two editions[211] has progressed in terms of both molecular mechanistic understanding of how PDT works and of new light plus photo-agents that expand the use of the technology spatially.[212] These data will likely both inform the use of rationalized drug combinations with PDT, including checkpoint inhibitors,[209,213,214] and expand the spatial and temporal use of the methodology to new clinical indications.

Beyond this natural evolution of PDT, there have been exciting, promising developments in creating agents that interact with traditional ionizing radiation much like light does in PDT to make the range of action not just millimeters as in the case of light but centimeters.[215,216] This area may allow yet another way to use ionizing radiation with chemotherapy but with the agents being inert until radiated—that is, to be triggered with the radiation therapy like a mousetrap. This will move the scope of radiation therapy into a more diverse set of clinical situations as it further opens up the ability to spatially constrain side effects. Obviously, care will be needed to optimize this approach, given that radiation entry and exit doses may limit the ability to prevent damage to normal tissue in, at a minimum, entry dose regions. One could envision a mixture of old and new radiation modalities harnessing these new agents' potential.

The implications here are broad for radiation therapy departments globally. Orthovoltage optimization may become useful in this context again, as could the use of heavy ions at low doses. Suppose the agents can be designed to require a dosimetric threshold for action of, say, 0.25 Gy. In that case, one can imagine simple plans being able to address this with three-dimensional conformal radiotherapy at relatively low doses, opening up the possibility of routinely avoiding treating to normal tissue tolerance in the future. This would better enable retreatment and would lower costs to society overall. Given radiation's unique capacity to be spatially delivered, this approach has promise. The biodistribution of these agents, like any chemical, will impact the success of these methods radically.

Combinatory Therapies

Systemic administration of therapeutic agents for cancer treatment is a common practice. However, their presence in normal tissue is generally unfavorable as it could lead to adverse toxicities. The undue toxicity might be avoided if the therapeutic agents remained encapsulated or inactive until exposed to an extremal stimulus within the well-defiled volume. In addition, the time of activation could be adjusted so that the concentration of the therapeutic agents in the target volume reaches levels necessary for an effective treatment. The key criteria for achieving effective and safe treatment include minimal invasiveness of the external stimuli and quantitative control of localized therapeutic agent release or activation. Remote triggering mechanisms may include photodynamic, photothermal, photo-triggered chemotherapeutic release, ultrasound, electrothermal, magnetothermal, x-ray, particle beam, and radiofrequency. Examples of three combinatory strategies using nanoparticles are shown in Figure 5.2.

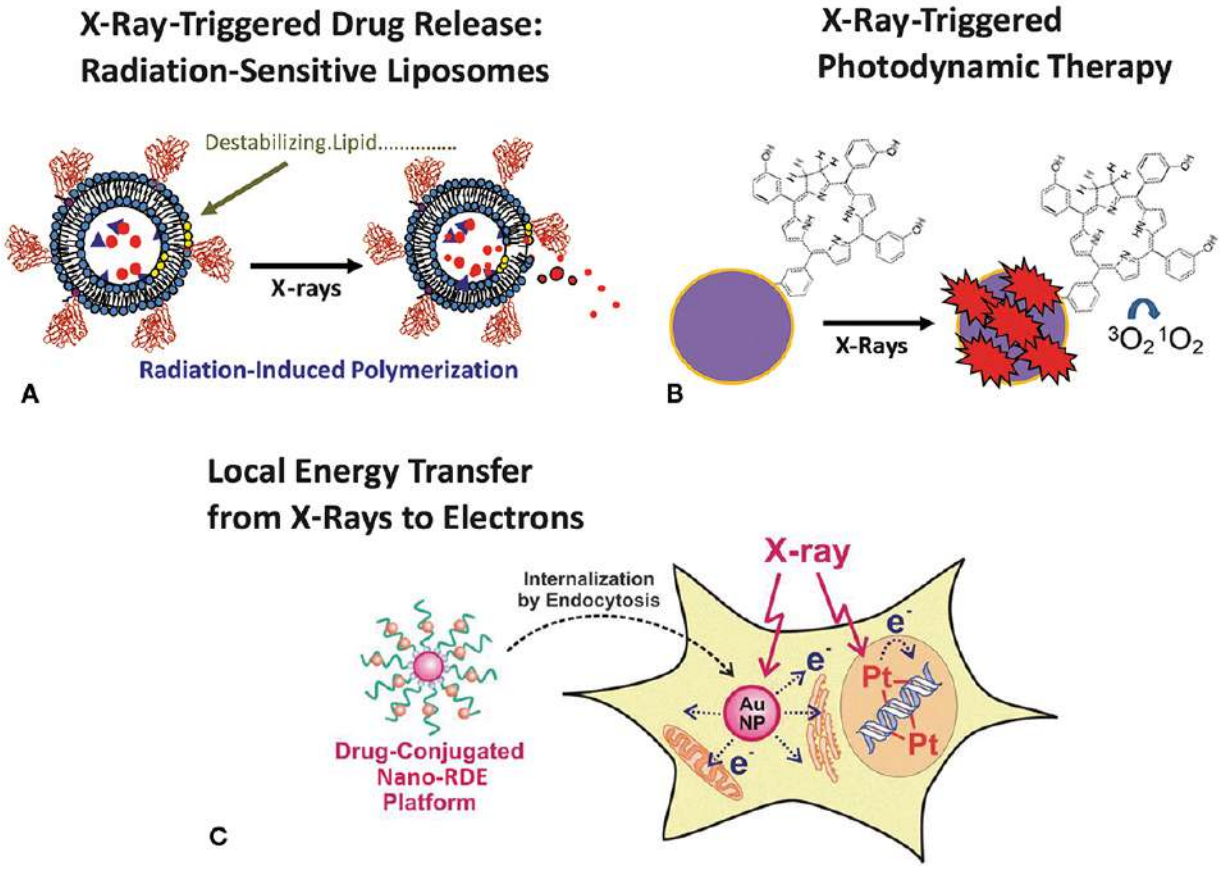

FIGURE 5.2 Examples of three combinatory strategies using nanoparticles. A and B. Radiation used to trigger liposomes and photodynamic therapy. C. Nanoparticles used to internalize drugs/molecules that enhance the effects of x-rays.

The use of radiation or ultrasound to activate or release therapeutic agents is an active research topic in many academic centers, and it has yielded fruitful results. The thermal release of drugs from liposomes has been a clinical practice for years. Other "smart" systems that might release drugs or induce a toxic effect in response to an externally controlled stimulus promise unique clinical benefits over conventional systems that release their cargo passively or are activated internally. In combination with radiotherapy, x-rays might be used to stimulate the local release of encapsulated drugs in tumor volume, or the combination of x-rays with nano scintillators producing light used in PDT would allow its extension to deep-seated tumors.

Even more novel, perhaps, is the use of combinations of radiation types, coined "blending," to take advantage of different biologies. The concept is not new, given combinations of brachytherapy with external beam therapy, but the differences may be more biologically advantageous in the case of photons mixed with protons, helium, carbons, and/or neutrons. Other combinations of energy delivery need to be tested perhaps further and seem to show promise, with radiation types including magnetic and electrical fields, different types of ultrasound including histotripsy, and new methods to deliver heat.[217]

Nanotechnology

Multifunctional nanoparticles allow simultaneous targeted delivery of diagnostic and therapeutic agents to the tumor tissue, giving rise to a new, fast-growing field of theranostics that combines the modalities of diagnosis and therapy.[218]

Gold Nanoparticles

Over the last two decades, radiation dose enhancement by high atomic number elements such as iodine has been explored for cancer radiotherapy.[219] As a small-molecule radiation dose enhancer (smRDE), iododeoxyuridine (IUdR) has been used due to its facile incorporation into cellular DNA.[219,220] The subsequent external irradiation of high-energy photons on the IUdR-containing target cells can trigger the secondary emission of photoelectric radiation (ie, Auger/secondary electron emission

or x-ray fluorescence).[221] The resulting triggered emission from smRDE can cleave the nuclear DNA double strands that can induce radio-sensitized cell death.[222] In this smRDE-mediated radiotherapy, several advantages have been demonstrated. The triggered emission from smRDEs generally decays in several millimeters, a typical length scale of a cell, so the resulting cytotoxicity is highly dependent on the cellular location of smRDEs. Therefore, only the smRDEs inside the target cells can deliver high toxicity upon radiation, but their off-target toxicity can be reduced to healthy cells.[223]

Although such smRDEs can improve radiotherapeutic efficacy with reduced side effects, safe and effective delivery of smRDE to target tissue remains one of the major drawbacks to clinical applications.[223] As iodine-attached tumor-targeting antibodies were used to improve their biodistribution, their targeting and therapeutic efficacies were not satisfied due to the rapid dehalogenation mechanism in DNA and the heterogeneity and limited expression of target receptors on cancer cells.[224] Furthermore, prolonged treatments with high dosages of iodine compounds should be avoided due to their toxic side effects on the host organs.

These limitations might be circumvented by developing a nano-encased RDE (nano-RDE) platform based on functionalizable polymer-modified nanoparticles. Nano-RDE platforms can demonstrate several advantages: First, the biodistribution of nano-RDE can be highly improved by the "enhanced permeation and retention" effect in solid tumor tissue, which allows for the selective accumulation of nano-RDE at diseased sites (passive targeting).[225,226] Second, a high amount of nano-RDE can be readily internalized in target cells by endocytic pathways, known as a completely different cellular internalization mechanism from small molecules.[227] In addition, the subsequent acidic endosomal environments can be used as a trigger for the pH-sensitive release of additional chemotherapeutic agents.[228]

In conventional chemotherapy, the rapid developments of multidrug-resistant characteristics in cancer cells cause a critical problem in clinical cancer treatments.[229] As such, it is evident that a combinational therapy is more effective than a single modality treatment. To this end, anticancer drug– conjugated nano-RDE could be a novel approach to achieve "precision combined modality therapy" as a multimodal delivery platform for both radio- and chemotherapy if susceptibility via biomarkers or other

means was evaluable. Gold nanoparticles (AuNPs) are one example of nanoparticles in this potential space.

AuNPs have been tested for improving chemotherapy[230] and radiotherapy.[231] The TNF-α-polyethylene glycol-colloidal AuNP, CYT-6091 (Citimmune, Gaithersburg, MD), has been shown to selectively traffic to tumor tissue. This agent was evaluated in a phase I trial and shown to selectively deliver TNF-α to tumors with reduced toxicity compared to recombinant human TNF-α alone.[232]

In addition to its properties as a nano-carrier, colloidal gold, being a high-*Z* element, may also increase the radiation dose explicitly delivered to the target cells. This system uses AuNPs as inorganic nanoRDEs for radiotherapy and as a delivery platform for chemotherapeutic agents. Due to the K-edge of gold at 80.7 keV, x-ray radiation with the energy level of Au K-edge can trigger the secondary emission of photoelectric radiation from AuNPs.[233,234] The resulting radiation can induce the degradation of target molecules by ionization and interact with surrounding water molecules to produce reactive oxygen species that can damage the target molecules.[235] As such, AuNP-sensitized degradations of plasmid DNA[236] and human proteins[237] upon x-ray radiation have been demonstrated in in vitro model systems. Additionally, when AuNP-containing tumor cells were irradiated, increased apoptotic cell death was detected due to the continuous stress on cytosolic organelles.[238] Furthermore, enhanced in vivo efficacy of AuNPs upon radiotherapy was also observed in human cancer-bearing mouse models.[231] However, these AuNPs have shown inferior pharmacokinetic results due partly to their limited surface functionality as bare colloidal particles.

AuNPs have been used in various biologic applications due to their biocompatibility and well-known surface chemistry. Using the known reactions, AuNPs can be readily modified with thiol-end-capped polymers[239] that can significantly alter the pharmacokinetics.[240,241] This functional polymer can be prepared by reversible addition-fragmentation chain-transfer radical polymerization, allowing for copolymerization of a wide range of monomers.[242]

As the gold K-edge is at 80.7 keV and the enhancement is optimal in the photoelectric-dominated x-ray spectrum, irradiation conditions could be optimized using monoenergetic x-rays. However, a significant enhancement

of the treatment efficacy might also be obtained in standard megavoltage x-ray beams.[243] To track the biodistribution of AuNPs, these can be easily activated with thermal neutrons prior to administration to emit 411 keV γ-rays, which can be detected by single-photon emission computed tomography. Recent work has confirmed that the enhancement of radiation dose is real from AuNPs.[244]

Liposomes

Another alternative approach would be using radiation as a trigger, releasing or activating drugs delivered to the tumor before irradiation. One option could provide radiosensitive liposomes. For decades, liposomes have been explored as viable carriers for targeting, imaging, and delivery of payloads of drugs.[245] Various triggering modalities such as local hyperthermia, pH-triggered, tissue-associated enzyme- and light-triggered drug release have been developed to date.[246] Among these, the electromagnetic radiation–triggered release of liposomal drugs appears promising and includes strategically designed phospholipid molecules to initiate a light- induced trigger. These liposomes are based on the principle of photo-polymerization of lipids,[247] photo-sensitization by membrane-anchored hydrophobic probes,[248,249] and/or photo-isomerization[250] of photo-reactive lipids. However, one major challenge to date has been the lack of adequate photon energy produced by the radiation source(s) and/or the inability of radiation to penetrate biologic tissues. However, this seems to be changing with the deployment of radiopharmaceuticals directly via liposomes.[251,252]

Radiation-Activated Photodynamic Therapy

PDT is increasingly recognized as an attractive and valuable tool in treating many diverse human diseases, including macular degeneration, dermatologic disorders, and oncology.[253] PDT utilizes photosensitizers that can be preferentially localized in malignant tissues. The interaction of the photosensitizer and light generates cytotoxic species, including singlet oxygen ($^1O_2$), free radicals, and peroxides, that attack key structural entities within the targeted cells. Those very toxic species are characterized by a short lifetime (<0.04 μs) and a short radius of action. Therefore, the

damaged area is essentially confined to tissue containing the photosensitizer and exposed to light.

Relative to current treatments, such as surgery, radiation therapy, and chemotherapy, PDT is also comparatively noninvasive, can be more accurately targeted, and is not subject to the total dose limitations associated with radiotherapy. In addition, the healing process typically results in little or no scarring.[254] Despite these advantages, PDT has yet to gain general clinical acceptance. The photosensitizers approved for routine PDT treatment absorb light in the visible spectral regions below 700 nm, thus preventing access to deeper residing tumors. As a result, even with the advent of more sophisticated light delivery systems, the clinical application of PDT is mostly limited to superficial solid tumors, endoscopically accessible regions, or skin lesions. Multiple new approaches in the photodynamic space are under investigation, with one example of a newer approach being akin to brachytherapy with the catheters delivering light at depth volumetrically.[255]

The combination of radiotherapy with PDT, exploiting the tissue penetration of ionizing x-ray radiation and the cell-level targeting of PDT, might provide a novel approach to overcome the problems with penetration depth and might help with the delivery and targeting of photosensitizing agents. It has been observed that some photosensitizers act as radiosensitizers under certain conditions. The combination of Photofrin, an FDA-approved photosensitizer, with radiation therapy significantly enhanced the cytotoxic and apoptotic death of cancer cells.[256,257] However, the molecular mechanism for this effect is still unknown.

There has been interest in developing a nanoparticle-based photosensitizer delivery system for a combination of PDT with radiation therapy. Chen and Zhang[258] used scintillating nanoparticles conjugated to photosensitizers; in response to irradiation with deeply penetrating x-rays, these nano scintillators would produce light capable of activating the attached photosensitizers, thereby producing toxic amounts of free radicals in any desired location of the body. These nanoparticles would overcome the limitations imposed on current PDT and expand its application to deeply located tumors. Multiple complex delivery methods are under investigation and may promise more active use of PDT for solid tumors.[255]

Several doped nanoparticles ($LaF_3:Ce^{3+}$, $LuF_3:Ce^{3+}$, $CaF_2:Mn^{2+}$, $CaF_2:Eu^{2+}$, $BaFBr:Eu^{2+}$) and semiconductor nanoparticles (ZnO, ZnS, and TiO_2) are potential light sources for use in a nanoparticle-PDT system. The emission spectra of these nanoparticles can be matched perfectly to the absorption spectra of Photofrin, fullerenes, and TiO_2 nanoparticles. For example, $BaFBr:Eu^{2+}:Mn^{2+}$ nanoparticles excited by x-ray have three emission bands, one peaking at approximately 400, 500, and 640 nm, respectively. The emission spectrum of these nanoparticles is well-matched to the absorption spectrum of hematoporphyrin. Another example is the x-ray luminescence spectrum of $LaF_3:Ce^{3+}$ nanoparticles with maximum emission at 350 nm, tailing to 500 nm. This emission spectrum matches the absorption spectra of most photosensitizers as well. The rationale for this approach is to combine the effects of PDT and radiation therapy while reducing toxicity.

A DYNAMIC, BIOLOGIC PRECISION MEDICINE FUTURE: FINAL THOUGHTS

This chapter focused on the complexity of integrating opportunities in biology with radiation oncology with the caveat that the only way forward, past where we are now, is a position of precision brought about by technology and physics, which is likely via biology.[116,201] Perhaps the crucial path forward for radiation oncology is the further development of the linkage between biology and physics that is elegant, robust, and based on kindness and trust to achieve the next accurate level of precision medical practice (along with other fields, we are not alone by any means)—via pragmatic trials, newly focused molecular small trials, and traditional trials where their design allows vast collection of data to later analyze in terms of dynamic biology. We are in the process phase where, in many ways, we need to pause and redefine the normal course of treatment from a granular biologic perspective because a lot is happening to patients during treatment that we have only recently been able to appreciate.[194] This pause and future similar biologic ground state reviews are setting up the field for a future of precision medicine that is far more robust and promising than that of today.[193]

The integration and interpretation of the presented data will allow accurate "precision." In this regard, we are in the infancy of the path toward a biologically optimized dose. Dynamic, multiscale modeling will be a core component of our processes to manage the added complexity. We have just begun to understand when to use imaging-focused adaptive radiation. Still, we need to incorporate the ever-changing tumor and host (normal tissue) biology with imaging. To do this, the digital twin approach is likely necessary to allow new "precision medicine" approaches for our patients.[191,206] If used as envisioned, the digital twin of a patient would be able to be developed to assess their risk of cancer, the response to therapy and likely toxicities, what agents to use for the best results both in the short term and the long term, how and when to modify their treatments as they move along a treatment course, how to follow them after therapy, and ultimately how their case can impact and help others in a FAIR (regarding data that is Findable, Accessible, Interoperable, and Reusable)[259] and equitable manner.[190]

We are approaching peak technology in terms of delivery of physical dose, where we achieve benefits via summations of marginal gains, and where our primary global challenge is not the advancement of technology but access to it. Improvements continue due to brilliant engineering and physics, but the improvements are often moderate, with the toughest of tumors showing little benefit from the technology (eg, glioblastoma). In some cases, machines can now cost, with custom building and additional staff, upward of half a billion dollars, and the results of trials have shown that a lack of insight into biology may have made such machines produce results that are inferior to standard, inexpensive therapy.[195,202]

That there is so much new material to discuss in this edition of this chapter is encouraging (resulting in the addition of multiple whole new chapters, too). There are improvements in the existing technology, including amalgamation of imaging and therapy to target the desired anatomic sites better. Particle therapy is understood to be much more than better dose distribution. Indeed, we must think of radiation in terms of the biologic changes it produces and how future inverse planning will include biologic events rather than just physical doses. The era of precision medicine is firmly upon us. It has already changed how cancer is diagnosed and classified and elucidated the remarkable heterogeneity in the cancer cells

before, during, and after treatment that makes targeting ever more challenging and exciting. As a result, trials are evolving to address the profound heterogeneity of precision medicine unearths, making for new challenges.[260] We are finally approaching a point in time where, just perhaps, the focal stress response induced by radiation and/or the other new technologies described in this chapter can help force tumor cells (or the normal tissue, or both) onto desired biologic paths where we have better agents and methods to then treat the tumor optimally—moving toward precision in terms of biologically forcing tumor treatment down a chosen, optimal path for the patient—dynamic, biologic precision medicine.[193,201]

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PART B

Medical Radiation Physics and Dosimetry

CHAPTER 6

Principles of Radiation Physics and Dosimetry

James A. Purdy, Geoffrey D. Hugo, and Hania A. Al-Hallaq

A solid foundation in the principles of radiation physics, dosimetry, and treatment planning is essential for the practice of modern-day radiation oncology. This chapter discusses the basic concepts in radiation physics, radiation therapy treatment machines, and the dosimetry parameters used for photon external beam treatment planning and dose/monitor unit calculation methods. As this textbook is aimed at practicing radiation oncologists and physician residents, these topics are not treated in the detail required for medical physicists. More details on these topics can be found in the medical physics textbooks listed in the references.[1-3]

ATOMIC AND NUCLEAR STRUCTURE

The *atom* may be thought of as consisting of a centrally located core, the *nucleus*, surrounded by small orbiting particles called *electrons*. The overall dimension of an atom is about 10^{-10} m, and the nucleus is about 10^{-14} m. An electron has a rest mass (m_e) of 9.109×10^{-31} kg and has a negative electrical charge equal to 1.602×10^{-19} coulomb (C). Most of the mass of the atom is contained in the nucleus, making it extremely dense (10^{15} kg/m^3). The nucleus is composed of two kinds of particles—*protons* and *neutrons*, known collectively as *nucleons*. A proton has a rest mass (m_p) of 1.673×10^{-27} kg and has a positive electrical charge equal in magnitude to the charge of the electron (1.602×10^{-19} C). Collectively, the protons

constitute the electrical charge of the nucleus. A neutron is slightly more massive than a proton ($m_n = 1.675 \times 10^{-27}$ kg) and has no electrical charge.

Units used to describe atomic processes include the *atomic mass unit* (amu) for mass, *nanometer* (nm) for distance, *electron volt* (eV) for energy, and *electronic charge* (*e*) for electrical charge. The amu is defined as one-twelfth the mass of a neutral carbon-12 atom. Thus, 1 amu = 1.660×10^{-27} kg. In terms of amu, a proton's rest mass is equal to 1.00727 amu, a neutron's rest mass is equal to 1.00866 amu, and an electron's rest mass is equal to 0.000548 amu. The electron volt (eV) is defined as the kinetic energy acquired by an electron accelerated through a potential difference (voltage) of 1 volt (V). One electron volt is equal to 1.6×10^{-19} joule (J) of energy. One writes 1,000 electron volts (keV) as 10^3 eV, and 1 million electron volts (MeV) as 10^6 eV. The nanometer is defined as equal to 10^{-9} m, and the electronic unit of charge is defined as equal to 1.602×10^{-19} C.

The planetary model of the atom is credited to Niels Bohr who embraced the revolutionary quantum concepts postulated by Max Planck and Albert Einstein.[4,5] Departing from classical physics, Bohr's model incorporated the newly emerging theory of quantized energy levels. He proposed that electrons orbit the nucleus in discrete, quantized energy states, or "shells," rather than in continuous paths as shown in Figure 6.1. This concept not only explained the stability of atoms but also elucidated the spectral lines observed in atomic spectra. Energy is released when an electron moves to an orbit closer to the nucleus, and energy is required to move an electron into a higher orbit. Historically, the shells are labeled, from innermost outward, by the letters *K*, *L*, *M*, and so forth. There are a maximum number of electrons that can be accommodated in each shell: 2 in the first shell, 8 in the second, 18 in the third, and so on. The maximum number of electrons allowed in each shell is given by $2n^2$, where *n* is an integer specific to each shell and is called the principal quantum number. By integrating the quantum theory with the planetary model, Bohr laid the foundation for a deeper understanding of the intricate nature of atoms and their behavior, marking a significant leap forward in the field of atomic physics.

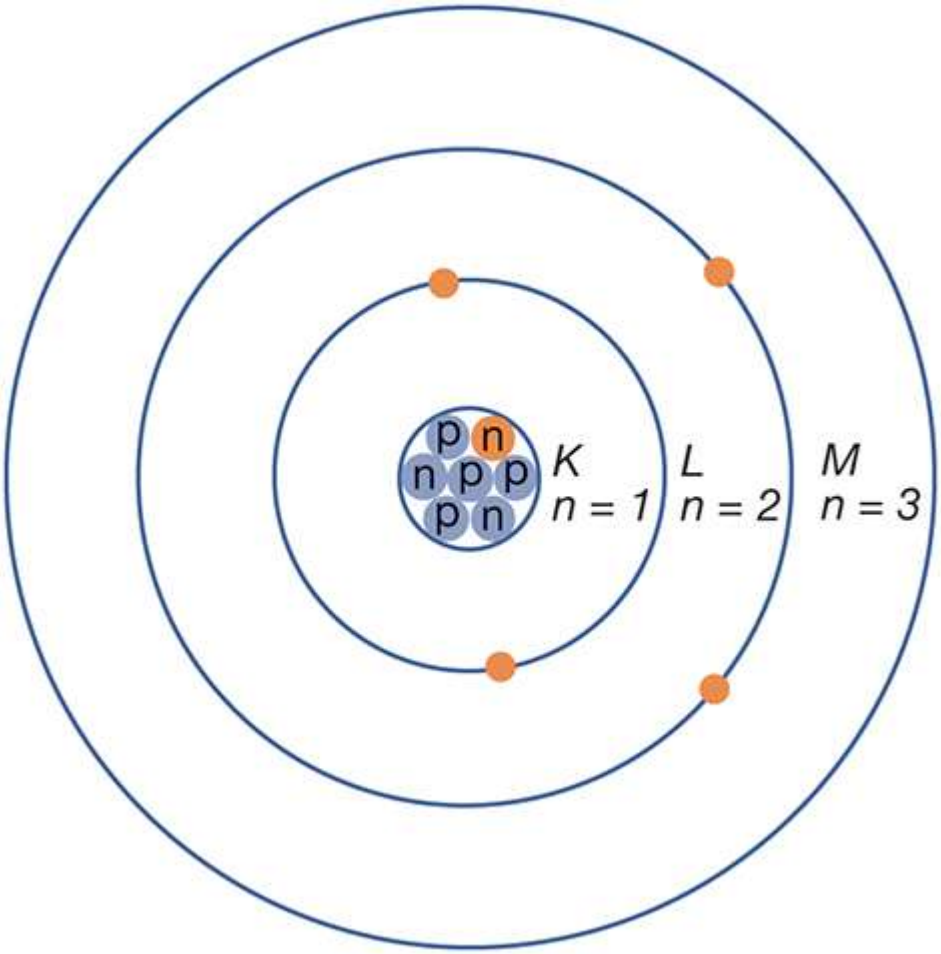

FIGURE 6.1 Schematic drawing of the Bohr model of the atom. The nucleus contains protons (p) and neutrons (n). Electrons revolve around the nucleus in specific orbits having discrete energy levels. By convention, the orbits (energy levels) are assigned either quantum numbers (n = 1, 2, 3, …) or letters (K, L, M,…).

Several other properties of the electron were also found to have discrete values specified by quantum numbers. These include the electron's angular momentum as it orbits the nucleus, denoted by quantum number l (l = 0, 1,…, n − 1); its spin about its axis, denoted by s ($s = \pm 1/2$); and its magnetic moment, denoted by m_l (m_l = 0, ±1,…, ±l). Thus, each electron in an atom has an associated set of quantum numbers (n, l, s, m_l). This is the basis of the Pauli exclusion principle, which states that no two electrons can have the same set of quantum numbers within a particular atom. As quantum theory continued to evolve, atomic physics replaced the early quantized orbiting electron model of Bohr with a more complex quantum mechanical

model of diffuse electron clouds that represent probability functions of the electron's position.[6]

In addition, modern physics research has discovered that protons and neutrons are not elementary particles and a new theory of matter (the Standard Model) is now in place (Figure 6.2).[7,8] As defined by the Standard Model, an *elementary particle* or *fundamental particle* is a subatomic particle that is not composed of other particles. Currently, the Standard Model recognizes 17 distinct particles. As a consequence of allowed characteristic combinations and antimatter, 61 elementary particles are embraced by the Standard Model. Note that in the earlier atom models consisting of electrons and nuclei containing protons and neutrons, only the electron is now considered an elementary particle, whereas a proton and a neutron contains three *quarks* each.[9] The experimental confirmations of the existence of quarks (1995) and the Higgs boson (2012) have provided strong credibility to the Standard Model. Physical properties of the particles most relevant to radiation therapy are listed in Table 6.1.

TABLE 6.1 PARTICLES OF INTEREST IN RADIATION THERAPY

Particle	Symbol	Charge	Mass
Photon	hν, γ	0	0
Electron	e, e^-, β^-	−1	0.000549 amu
Positron	e+, β+	+1	0.000549 amu
Proton	p, $^1_1$H	+1	1.007277 amu
Neutron	n, $^1_0$n	0	1.008665 amu
α-Particle	α, $^4_2$He++	+2	4.002604 amu
Neutrino	V	0	<1/2,000 m_0
Pi mesons	π+, π^-	+1, −1	273 m_0
	π°	0	264 m_0
Mu mesons	μ+, μ^-	+1, −1	207 m_0
K mesons	K+, K^-	+1, −1	967 m_0
	K^0	0	973 m_0

1 amu = 1.66043×10^{-27} kg. m_0, rest mass of an electron, 9.1091×10^{-31} kg.

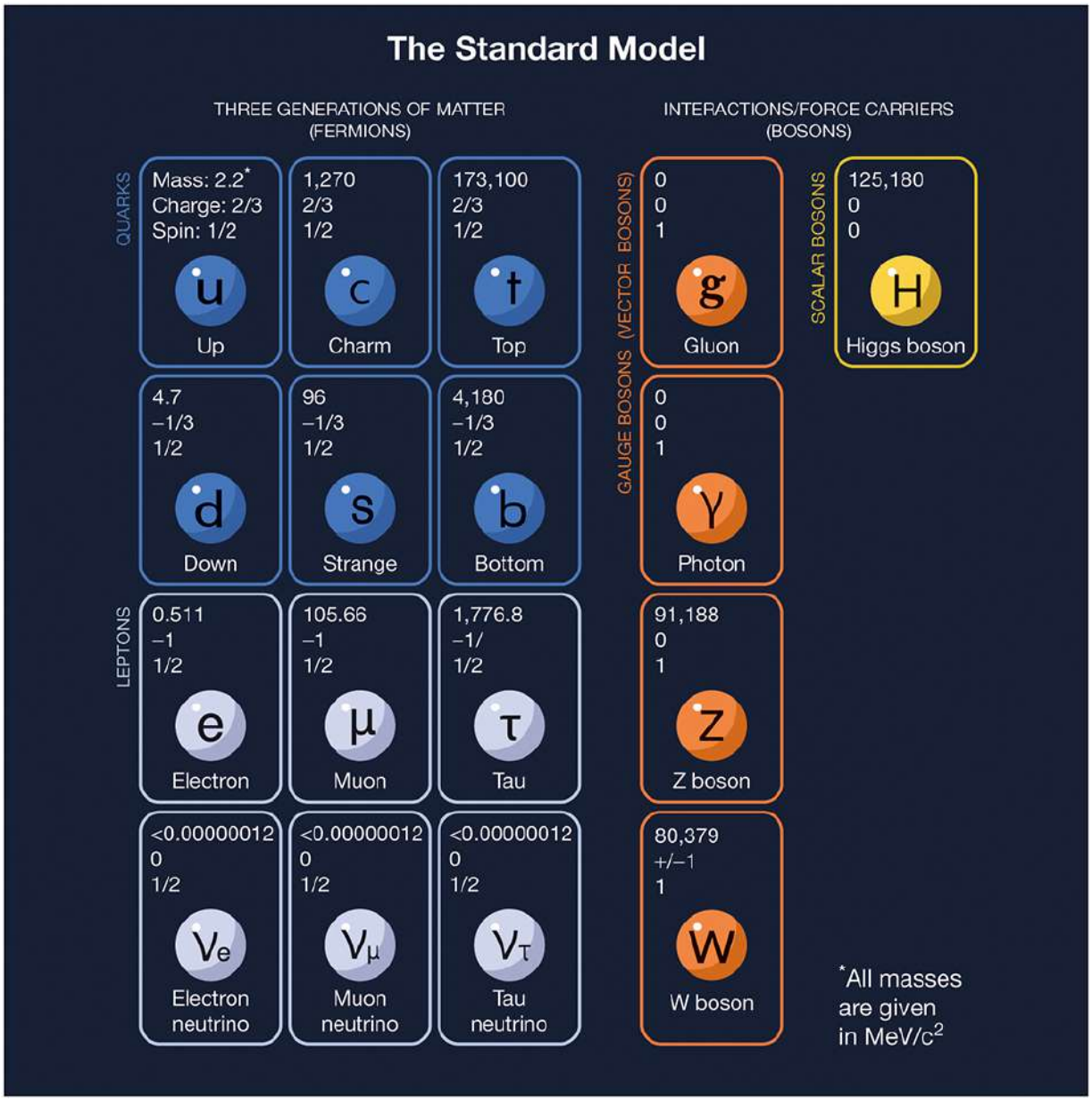

FIGURE 6.2 Schematic drawing showing the 17 fundamental particles of the Standard Model, grouped into four categories: quarks, leptons, gauge bosons, and scalar bosons. Quarks are the building blocks of protons and neutrons, while leptons are the building blocks of atoms. The quarks are further divided into three generations, each with two quarks. The leptons are also further divided into three generations, each with two leptons. A gauge boson is a force carrier that acts as the glue that holds fundamental particles together. The Higgs boson is the only known fundamental particle that is scalar, meaning it has no quantum spin. It is associated with the Higgs field, which gives mass to other fundamental particles like electrons and quarks.

The atom of an *element* is specified by its *atomic number*, denoted by the symbol Z, and its *mass number*, denoted by the symbol A. The atomic number is equal to the number of protons in the nucleus, and the mass number is equal to the number of nucleons (protons and neutrons) in the nucleus. Hence, A minus Z is equal to the number of neutrons, denoted by the symbol N, within the nucleus. In addition, each element has an associated chemical symbol (eg, Co for cobalt). When these definitions are used, the standard notation to specify an atom is ${}^{A}_{Z}\mathrm{X}$, as illustrated by ${}^{60}_{70}\mathrm{Co}$, which is a radioactive isotope of the element cobalt that has an atomic number of 27 (ie, 27 protons) and a mass number of 60 (ie, 60 nucleons, or 27 protons and 33 neutrons).

Isotopes of an element (eg, ${}^{58}_{27}\mathrm{Co}$, ${}^{59}_{27}\mathrm{Co}$, and ${}^{60}_{27}\mathrm{Co}$) have the same atomic number but different numbers of neutrons and therefore different mass numbers. Isotopes have the same chemical properties but have different physical properties. Atoms such as ${}^{60}_{27}\mathrm{Co}$ and ${}^{60}_{28}\mathrm{Ni}$, which have the same mass number but different numbers of protons and neutrons, are called *isobars*. Atoms such as ${}^{57}_{27}\mathrm{Co}$ and ${}^{56}_{26}\mathrm{Fe}$, which have the same number of neutrons but different atomic and mass numbers, are called *isotones*.

Every atom has a characteristic atomic mass A_{m} (sometimes referred to as atomic weight). The *gram atomic mass* of an isotope is the amount of isotope in grams that is numerically equal to the isotope's atomic mass. For example, 1 g atomic mass of carbon-12 is 12 g. One gram atomic mass contains 6.0228×10^{23} atoms, a constant that is called *Avogadro's number*

(N_A). Useful parameters that can be calculated using Avogadro number are as follows:

Number of atoms/gram = N_A / A_m
Number of electrons/gram = $(N_A Z)/A_m$
Number of grams /atom" = A_m / N_A

The closer the electrons are to the nucleus, the more tightly bound they are to the nucleus. This results from the attraction between the negatively charged electrons and the positively charged nucleus and is referred to as the *Coulomb* or *electrostatic force*. To move an electron from an inner shell to an outer shell (*excitation*) or to remove it completely from the atom (*ionization*), energy must be supplied. The energy required to remove an electron completely from an atom is called the *binding energy* for the electron. Binding energies are considered negative because energy must be supplied to remove the electron from its orbit. Atomic shells often are described in terms of binding energy, as shown in Figure 6.3 for the tungsten atom. The binding energies for the *K*, *L*, and *M* shells are −69,500, −11,000, and −2,500 eV, respectively. The electrons in the outermost shells are called *valence electrons* and have a binding energy of only a few electron volts because they are very loosely bound. These electrons determine the atom's chemical properties.

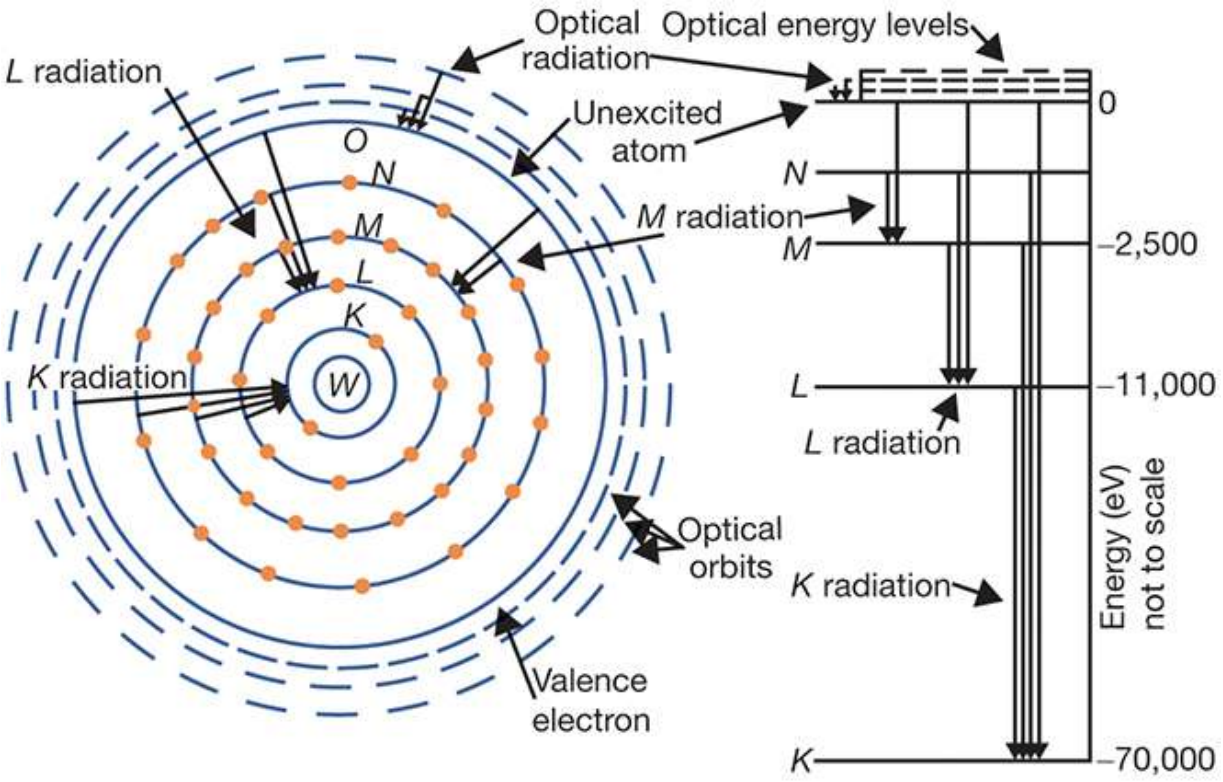

FIGURE 6.3 Schematic drawing of tungsten atom showing electron configuration and energy levels. (From Johns HE, Cunningham JR. *The Physics of Radiology*. 4th ed. Charles C Thomas; 1983:19. Courtesy of Charles C Thomas Publisher, Springfield, Illinois.)

ELECTROMAGNETIC RADIATION

Electromagnetic radiation can be represented by a varying electric and magnetic field that is conveniently described using a sine-wave model. The sine wave is characterized by two parameters: the *frequency*, represented by the Greek letter ν, and the *wavelength*, represented by the Greek letter λ. The wavelength is the distance from one crest of the sine wave to another; the frequency is the number of complete cycles or oscillations per second and is measured in *hertz* (Hz). The product of the frequency and wavelength is the speed with which the wave is propagated, which in a vacuum is the speed of light ($c = 3 \times 10^8$ m/s).

Electromagnetic radiation wavelengths extend from approximately 10^7 to 10^{-13} m. The frequencies associated with these radiations are approximately 10^1 to 10^{21} Hz. The electromagnetic spectrum shown in Figure 6.4 includes the radio and television bands; radar and microwaves; the infrared, visible, and ultraviolet regions; and x-rays and cosmic rays.

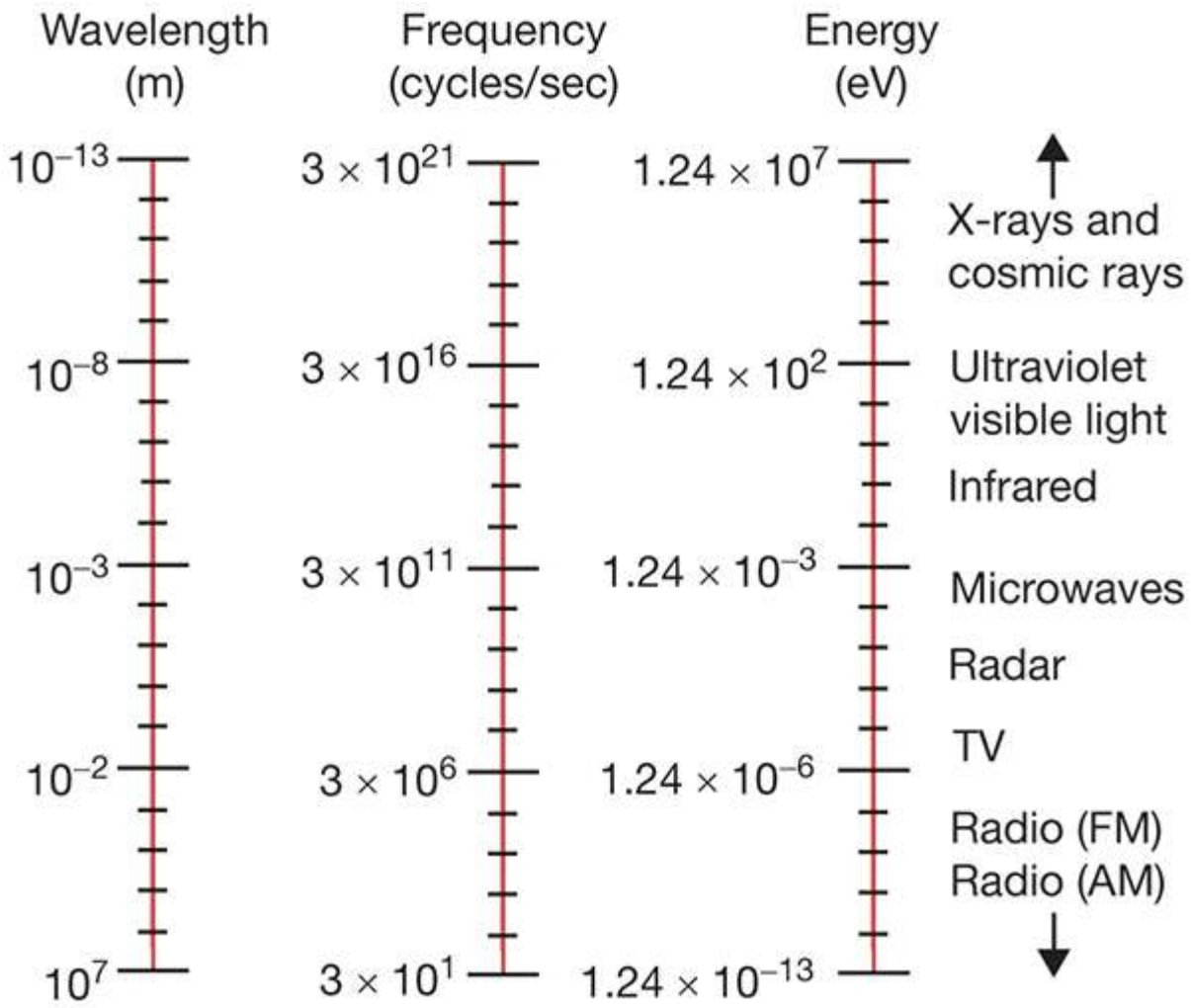

FIGURE 6.4 Electromagnetic spectrum extending over several orders of magnitude, with values of wavelength and frequency, and identifying values in some of the more common regions of the spectrum.

Quantum physics allows electromagnetic radiation to be represented as waves and also as particles, called *photons*. This is referred to as the *wave-particle duality of nature*. The photon energy is directly proportional to the classic wave frequency and is related to it through a constant of proportionality known as *Planck constant* (h), which has a numerical value of 6.625×10^{-34} J-sec. The relationship between energy, E, and frequency, v, is given by the following equation:

$$E = hv$$

The relationship between photon energy and photon wavelength is given by the following equation:

$$E = hc/\lambda$$

in which c is the speed of light in a vacuum. These relationships show that as the wavelength becomes shorter or the frequency becomes larger, the energy of the photon becomes greater.

X-RAYS

Wilhelm Conrad Röentgen discovered x-rays on November 8, 1895.[10] He observed that a paper screen coated with fluorescent material glowed when placed in the vicinity of a tube of gas at low pressure through which electricity was being passed. We now know that the x-rays were produced where the electron beam struck the anode. Energetic electrons that impinge on matter interact with either the orbital electrons or the nuclei of target atoms. The kinetic energy of the electrons then is converted into thermal energy or electromagnetic energy (in the form of x-rays).

The impinging electron's kinetic energy is converted into thermal energy through interaction with an outer shell electron of a target atom, which raises it to a higher energy level (referred to as *excitation*). The excited electron then returns to the normal energy level with the emission of low-energy electromagnetic radiation (*infrared*).

If the impinging electron's kinetic energy is high enough, the interaction can free an orbital electron (referred to as *ionization*), which then can result in the production of electromagnetic radiation (*characteristic x-rays*) when an outer orbital electron moves to the electron vacancy produced via ionization (Figure 6.5). The characteristic x-ray energy is equal to the difference in the binding energies of the two orbital electrons involved. Occasionally, this excess energy is transferred directly to another orbital electron, causing it to be emitted from the atom. Such electrons are called *Auger electrons*.

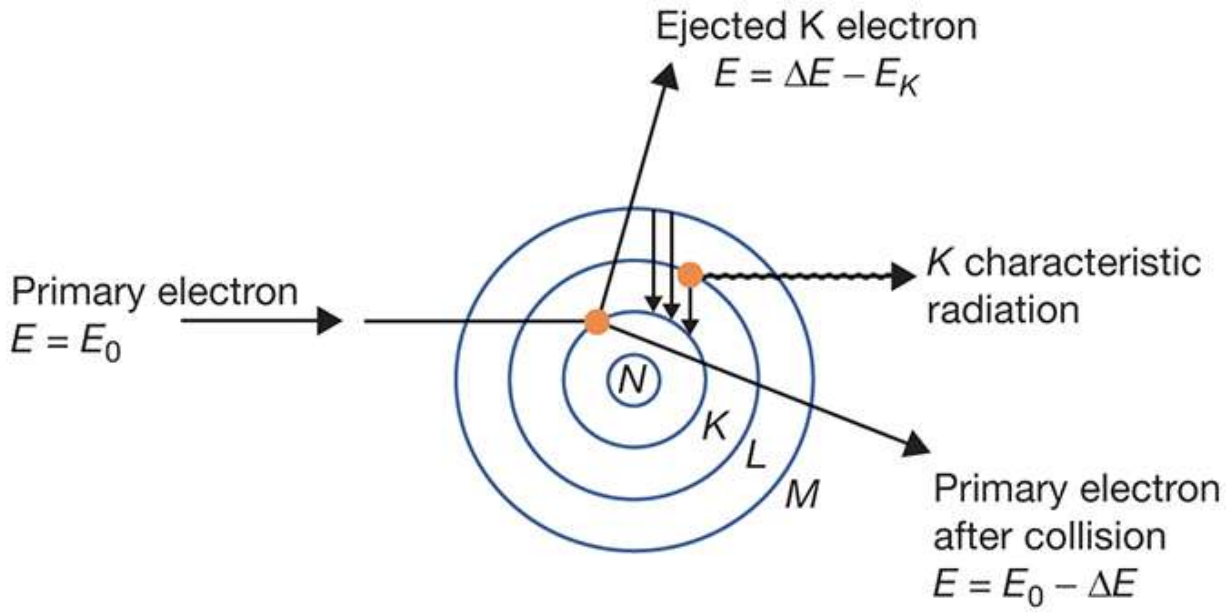

FIGURE 6.5 Schematic diagram illustrating characteristic x-ray production.

The impinging electron also can lose its kinetic energy via a process called *bremsstrahlung* (braking radiation), which occurs when the incident electron interacts with the electric field of the nucleus (rather than the orbiting electrons) and is deflected and loses energy. This loss of energy reappears in the form of an x-ray photon. The impinging electron can lose any amount of its kinetic energy in the bremsstrahlung process. Thus, the x-radiation produced via the bremsstrahlung process is characterized by having a continuous range of energy values, unlike characteristic x-rays, which have only discrete energy values. A bremsstrahlung spectrum (ie, a graph of x-ray intensity vs energy) is shown in Figure 6.6. Superimposed on the continuous bremsstrahlung x-ray spectrum are the characteristic x-rays. The maximum energy of a bremsstrahlung x-ray is numerically equal to the maximum energy of the incident electrons. The direction of emission of the bremsstrahlung x-ray depends on the energy of the incident electron, with higher-energy electrons producing more forward-directed x-rays.

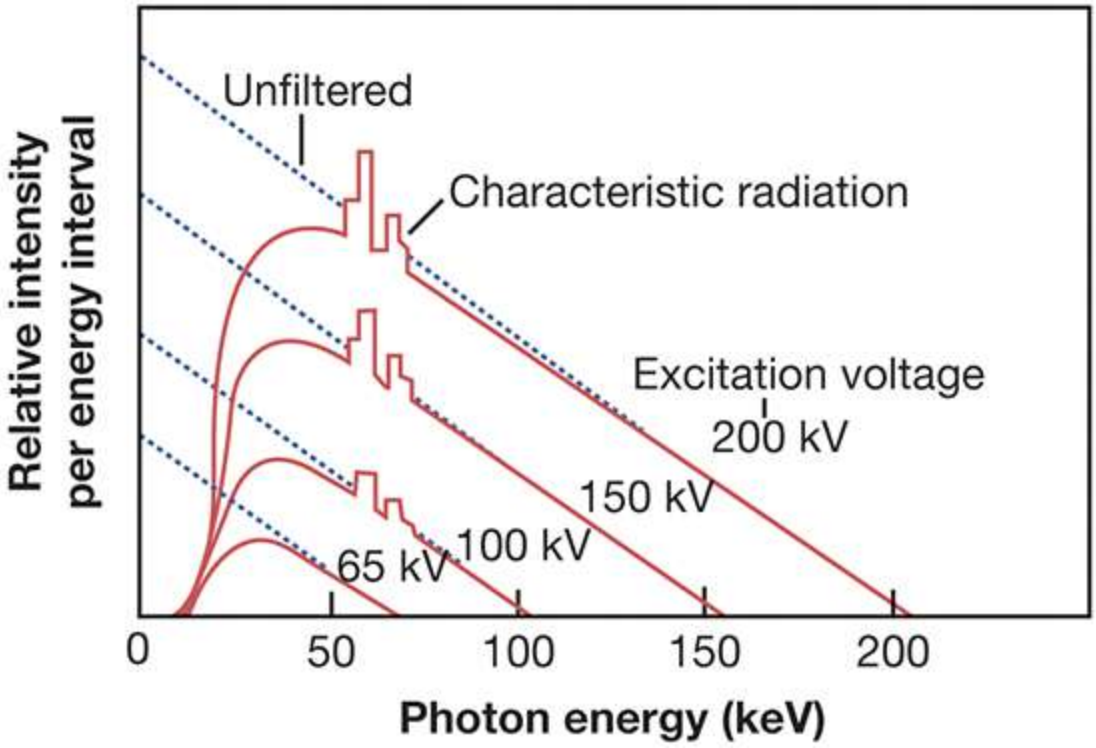

FIGURE 6.6 A bremsstrahlung x-ray spectrum calculated for a thick tungsten target extending from zero to the maximum energy of the electron. The dotted lines are for no filtration, and the solid curves are for a filtration of 1-mm aluminum. Note the superimposed characteristic x-ray emission spectrum. (From Johns HE, Cunningham JR. *The Physics of Radiology*. 4th ed. Charles C Thomas; 1983:271. Courtesy of Charles C Thomas Publisher, Springfield, Illinois.)

RADIOACTIVITY

In 1896, Henri Becquerel conducted experiments in which he wrapped a photographic plate in black paper to keep out the light and then placed pieces of various elements against the wrapped plate.[11] He discovered that the mineral pitchblende emitted x-rays. Other elements—such as thorium, actinium, and two new elements (polonium and radium) discovered by Pierre and Marie Curie[12]—also emitted x-rays. Further experiments showed that the radioactive elements emitted three types of radiation: *α-particles*, having a positive electrical charge; *β-particles*, having a negative charge; and high-energy *γ-rays*, having no charge at all. We now know that an *α*-particle is a helium nucleus, *β*-particles are electrons, and *γ*-rays are electromagnetic radiation that is similar to x-rays except that they originate from within the nucleus of the atom.

The radioactive decay processes are related to the forces involved. Huge electrostatic (Coulomb) forces of repulsion exist between the positively charged and closely spaced protons in a nucleus. However, a nuclear force of attraction (called the *strong nuclear force*) exists among the neutrons and protons, binding them together to form the nucleus. The strong nuclear force is much more complicated than the *electrostatic* (*Coulomb*) *force* and is still not completely understood. However, it is known that the strong nuclear force between nucleons depends on the distance between them and is effective only over a very short distance, whereas the electrostatic force decreases with the square of the distance. The strong nuclear force easily overcomes the repelling electrostatic force as long as the protons are very close together. However, for a large nucleus, the strong nuclear force binding the nucleons together may be weaker on opposite sides of the nucleus than the repelling electrostatic force. Therefore, a large nucleus is not as stable as a smaller nucleus.

Because neutrons interact through the attractive strong nuclear force and not the repelling electrostatic force, they can be considered stabilizing particles for the nucleus. For example, in light nuclei, only equal numbers of neutrons and protons are required, but in heavier nuclei, the number of neutrons must be about 1.5 times greater than the number of protons to counteract the repelling electrostatic forces of the protons. A nuclide having significantly more protons than neutrons is said to have an unfavorable *N*-to-*Z* ratio and thus undergoes *radioactive decay* to reach a stable configuration.

The *decay constant* of a radioactive nucleus is defined as the fraction of the total number of atoms that decay per unit of time and is denoted by the symbol λ. The decay process can be represented mathematically. If N_0 radioactive nuclei are initially present in a particular sample, the number of radioactive nuclei, N, remaining at a particular time, t, is given by the following equation:

$$N = N_0 e^{-\lambda t}$$

Activity, which describes the radioactivity of a sample and is denoted by the symbol A, is defined as the total number of disintegrations per unit of time and is given by the following relationship:

$$A = \frac{\Delta N}{\Delta t} = -\lambda N$$

This decay constant equation can be expressed in terms of activity:

$$A = A_0 e^{-\lambda t}$$

where A is the activity at time t and A_0 is the initial activity. The *curie* (Ci), a unit of activity, is equal to 3.7×10^{10} disintegrations per second, the approximate number of decays per second by 1 g of ^{226}Ra. The *becquerel* (Bq), the special name in the International System of Units (SI) for the measure of activity, is equal to one disintegration per second (Table 6.2).

TABLE 6.2 INTERNATIONAL SYSTEM OF UNITS (SI UNITS) FOR RADIATION THERAPY

Quantity	SI Unit (Special Name)	Non-SI Unit	Conversion Factor
Exposure	C kg^{-1}	roentgen (R)	1 C kg^{-1} ≈ 3,876 R
Absorbed dose, kerma	J kg^{-1} (gray [Gy])	rad	1 Gy = 100 rad
Dose equivalent	J kg^{-1} (sievert [Sv])	rem	1 Sv = 100 rem
Activity	s^{-1} (becquerel [Bq])	curie	1 Bq = 2.7 × 10^{-11} Ci

The *half-life* of a radioactive nuclide is the time required for the number of atoms in a particular sample to decrease by one-half. The half-life, $T_{1/2}$, is related to the decay constant by the following equation:

$$T_{1/2} = \frac{0.693}{\lambda}$$

The *average life,* T_a, of a radioactive nuclide is related to the decay constant and the half-life by the following equation:

$$T_{\mathrm{a}} = \frac{1}{\lambda} = 1.44 T_{1/2}$$

The average life represents the time period that a hypothetical source would need—if it retained its original activity for that time period and then suddenly decayed to zero activity—to produce the same number of disintegrations as produced over an infinite time period by the source if it decayed exponentially.

Gamma decay occurs when a nucleus undergoes a transition from a higher to a lower energy level. In this process, a high-energy photon, called a *γ-ray*, is emitted. These *γ*-rays are identical to the x-rays emitted by excited atoms, except that *γ*-rays originate from within the nucleus and x-rays originate from outside the nucleus. Half-lives for *γ* decay are usually very short, typically 10^{-15} second.

Closely related to *γ* decay is the process called *internal conversion*. Instead of emitting a *γ*-ray, the excess energy from the excited nucleus is transferred to an electron in one of the inner atomic shells, causing ejection of the electron from the atom with emission of characteristic x-rays. The probability of internal conversion occurring increases as the atomic number increases.

In *β decay*, a neutron within the nucleus is converted into a proton, and an electron and an *antineutrino* are emitted, or a proton is converted into a neutron, and a *positron* and a *neutrino* are emitted:

$$\beta^- \text{ decay: } n \rightarrow p + \beta^- + \bar{\nu}$$
$$\beta^+ \text{ decay: } p \rightarrow n + \beta^+ + \nu$$

The positron was discovered in cosmic ray experiments in 1932. It is a positively charged particle with the same mass and spin as the electron and is considered the antiparticle of the electron. The neutrino and its antiparticle, the *antineutrino*, are massless particles (or at least have only a very small mass) having no charge that carry opposite spins and account for the conservation of energy and continuous energy spectrum observed for *β* decay. Particle-antiparticle pairs interact by annihilating each other, converting all their mass into electromagnetic energy (two *γ*-ray photons,

each of 0.51 MeV). In β decay, the emitted particles may vary in the kinetic energy they possess, which is rarely >3 MeV. Half-lives for β decay are long compared with those for γ decay, varying from seconds to years. The forces responsible for the β decay processes are weak compared with both the *strong nuclear force* and the *electrostatic force* among the nucleons. Accordingly, the force responsible for β decay is referred to as the *weak nuclear force*.

Electron capture is an alternative to *positron decay*. In this process, an electron, usually in the *K* shell, is captured within the nucleus and combines with a proton to create a neutron. Electron capture most often is followed by γ decay to release any excess nuclear energy.

Alpha decay occurs in nuclides with atomic number >82 and where the ratio of neutrons to protons is low, thus resulting in the repulsive Coulomb force of the protons overcoming the attractive strong nuclear force. The emitted α-particle is a helium nucleus (two protons and two neutrons). The kinetic energy for a particular α decay is monoenergetic (ie, the transition may be to an excited energy state with subsequent γ emission) and often 4 to 5 MeV. Half-lives range from 10^{-3} to 10^{10} years. The radioactive decay of radium to radon is an example of α decay, where the Q term represents the total energy release in the transition (called *transition energy*). For example,

$$^{226}_{88}\mathrm{Ra} \rightarrow {}^{222}_{86}\mathrm{Rn} + {}^{4}_{2}\alpha + \gamma + Q$$

The most recent version of the periodic table of the elements shows a grouping of 118 elements. Only the first 92 occur naturally; the remaining ones have been produced artificially. In general, the elements with high atomic number tend to be radioactive; in fact, all but one of the elements with atomic number higher than 82 (lead) are radioactive; only Bi is stable.

The naturally occurring radioactive elements have been grouped into three radioactive series called the *uranium series*, the *actinium series*, and the *thorium series*, all of which terminate with a stable isotope of lead. The uranium series provides an example of radioactive nuclides undergoing

successive transformations through α and β decay in which the parent nuclide produces a radioactive product called the *daughter nuclide*.

When the half-life of the parent nuclide is longer than the half-life of the daughter nuclide, an equilibrium condition exists. When this occurs, the ratio of the activity of the daughter nuclide to the activity of the parent nuclide becomes constant, and the apparent decay rate of the daughter nuclide is controlled by the parent nuclide's decay rate. Two types of radioactive equilibrium conditions are defined: *transient equilibrium* and *secular equilibrium*. Transient equilibrium is established when the parent nuclide's half-life is not much greater than the daughter nuclide's half-life (Figure 6.7). In secular equilibrium, the half-life of the parent nuclide is much greater than that of the daughter nuclide (Figure 6.8). The two types of equilibrium are described mathematically by the following equations, in which A_P and A_D represent the activity of the parent and daughter nuclides, respectively:

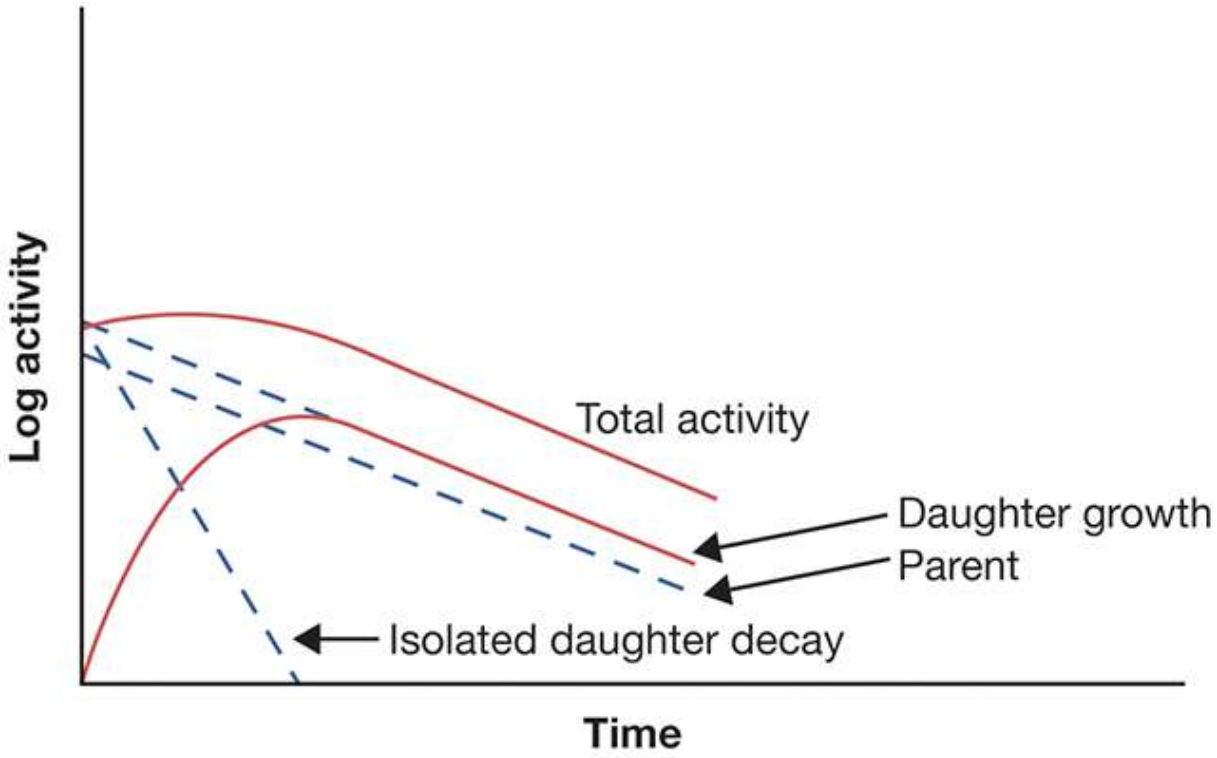

FIGURE 6.7 Transient equilibrium. Shown is a semilog plot of activity versus time for parent and daughter radionuclides illustrating conditions of transient equilibrium that may be achieved when the parent nuclide's half-life is not much greater than the half-life of the daughter nuclide. Once equilibrium is established, the daughter activity exceeds the parent activity, and both decay with the half-life of the parent.

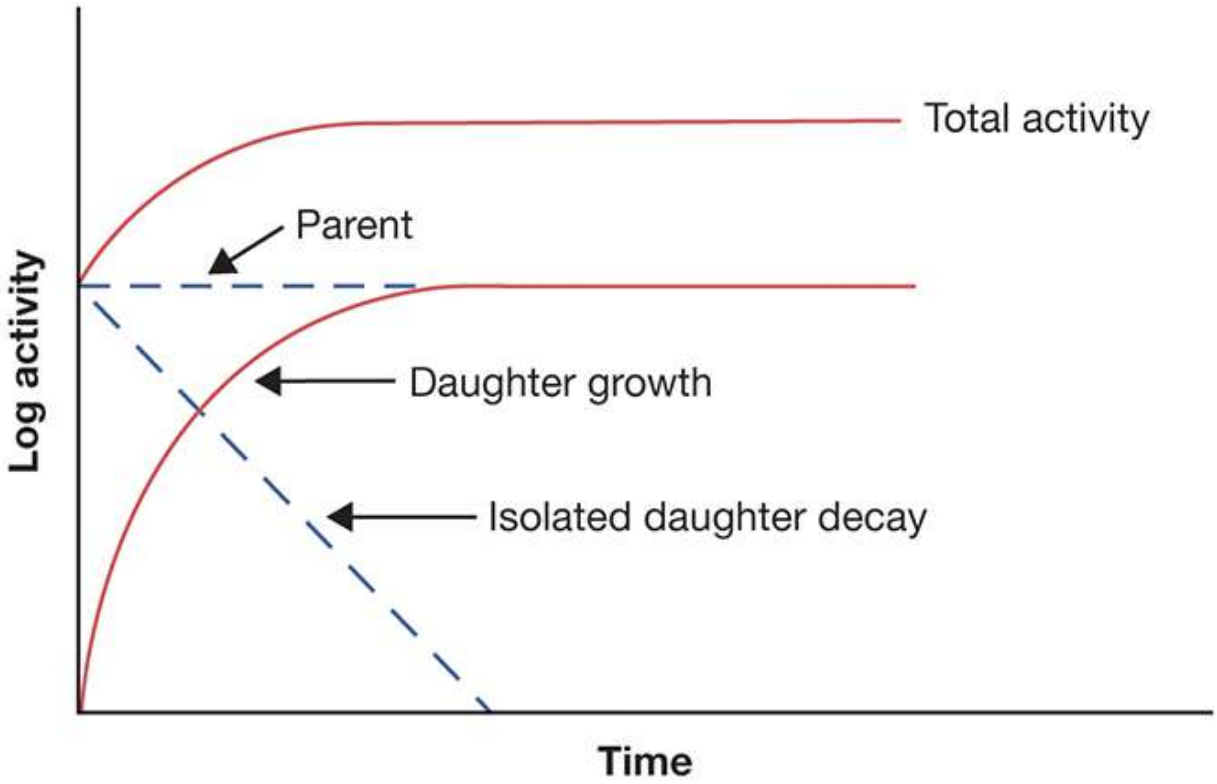

FIGURE 6.8 Secular equilibrium. Shown is a semilog plot of activity versus time for parent and daughter radionuclides illustrating conditions of secular equilibrium that may be achieved when the parent nuclide's half-life is much greater than the half-life of the daughter nuclide. Once secular equilibrium is established, activities of both parent and daughter are equal.

$$\text{Transient equilibrium: } \frac{A_D}{A_P} = \frac{\lambda_D}{\lambda_D - \lambda_P}$$

$$\text{Secular equilibrium: } A_D = A_P$$

INTERACTION OF PHOTONS WITH MATTER

As stated previously, x-rays and γ-rays may be considered as bundles of energy called *photons*. If an x-ray photon enters a thin layer of matter, it is possible that it will pass through without interaction, or it may interact (usually with the atomic electrons, but sometimes with the atomic nuclei) in one of five different ways (*coherent scattering*, *photoelectric effect*, *Compton scattering*, *pair production*, and *photodisintegration*). The probability that a photon will interact when it traverses through a given

thickness of material is the product of the individual interaction probabilities for each of these processes. The attenuation process can be described mathematically by the following equation:

$$N = N_0 e^{-\mu x}$$

where N_0 is the number of photons in the beam impinging on an absorber of thickness x, e is the base of the natural logarithms, and μ is the linear attenuation coefficient. The quantity μ is actually the sum of the individual attenuation coefficients for the five processes. Its numerical value depends on the energy of the photon and the type of attenuating material.

There are a variety of tabulated attenuation coefficients, including the *linear attenuation coefficient* (μ), the *mass attenuation coefficient* (μ/ρ), the *mass energy-transfer coefficient* (μ_t/ρ), and the *mass energy-absorption coefficient* (μ_{en}/ρ). Each type of coefficient is intended for use in the solution of different types of attenuation or energy-absorption problems; division by ρ, the physical density of the medium, makes the coefficient medium independent. Figure 6.9 shows the mass attenuation coefficient for lead and water as a function of incident photon energy. The discontinuities where the attenuation coefficient suddenly increases are called *absorption edges* and occur at photon energies just equal to the binding energy of a specific electron shell.

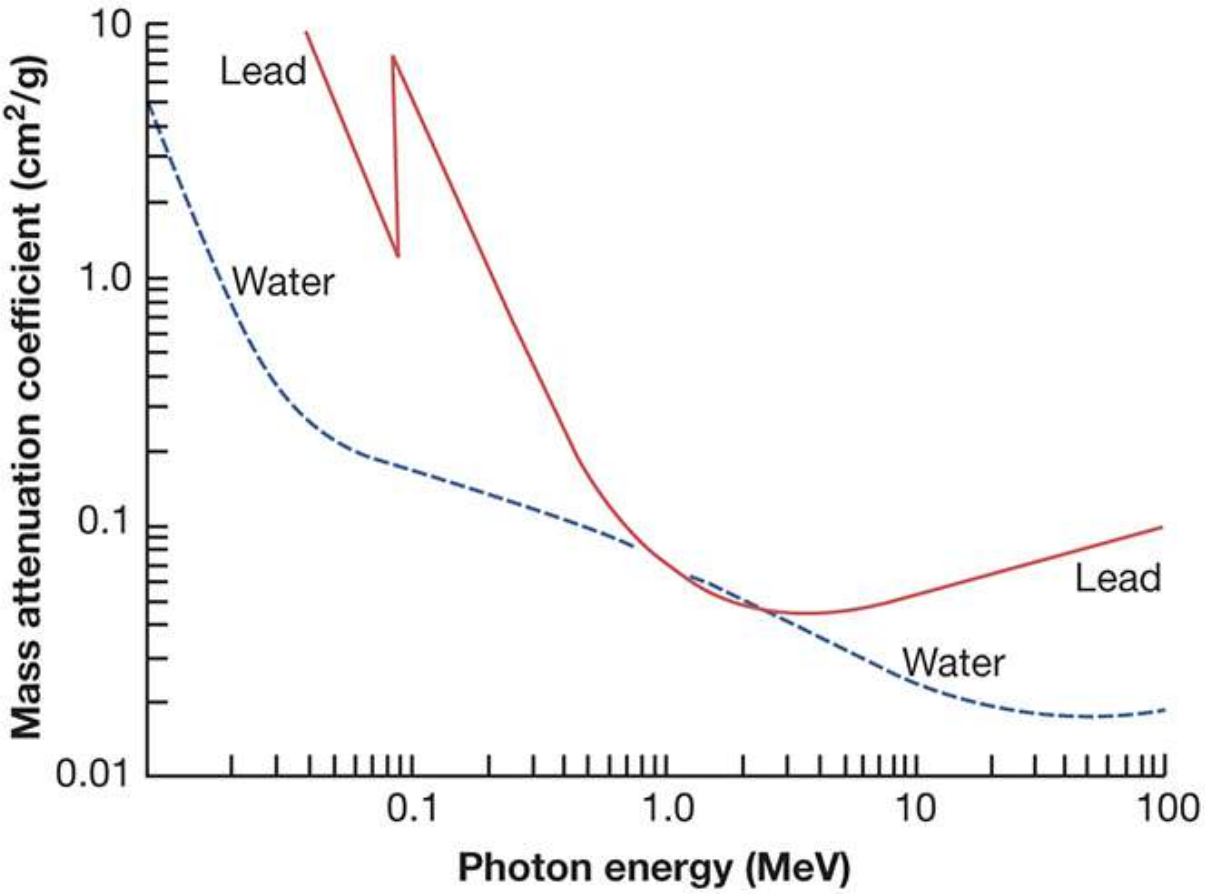

FIGURE 6.9 Mass attenuation coefficient for lead and water. Note sharp discontinuities, which are called *absorption edges*. (From Johns HE, Cunningham JR. *The Physics of Radiology*. 4th ed. Charles C Thomas; 1983:147. Courtesy of Charles C Thomas Publisher, Springfield, Illinois.)

The thickness of material that reduces the number of photons transmitted to one-half the incident number is termed the *half-value layer* (*HVL*). The HVL is related to the linear attenuation coefficient by the following equation:

$$\text{HVL} = \frac{0.693}{\mu}$$

This parameter is used to describe the *quality* or *penetrability* of the radiation and is discussed later in this chapter.

Coherent or Classical Scattering

If the photon energy is low enough that the quantum effects of the interaction are unimportant and the bound electron(s) can be regarded as essentially "free," the interaction corresponds to the "classical scattering" situation (called *coherent scattering*), in which the incident electrical field accelerates one or more orbital electrons and causes them to radiate. There are two types of coherent scattering: *Thomson scattering*, in which a single orbital electron is involved, and *Rayleigh scattering*, in which the orbital electrons act as a single group. In coherent scattering, no energy is transferred; only the direction of the incident photon is changed. The coherent mass attenuation coefficient is denoted by σ_{coh}/ρ.

Photoelectric Effect

In *photoelectric effect*, the total energy of the photon is transferred to an orbital electron, usually close to the nucleus, and the photon disappears. The electron then is ejected from the atom with an energy equal to the energy of the photon minus the binding energy of the electron (Figure 6.10). The direction in which the electron is emitted depends on the energy of the incident photon. For low-energy photons (eg, 50 keV), the photoelectron is ejected at a large angle with respect to the incoming photon's direction, increasing in the forward direction as the photon's energy increases. After ejection of the electron, the neutral atom becomes a positively charged ion with a vacancy in an inner shell that must be filled. The atom returns to a stable condition by filling the vacancy with a nearby, less tightly bound electron farther out from the nucleus, and characteristic x-rays or an Auger electron is emitted.

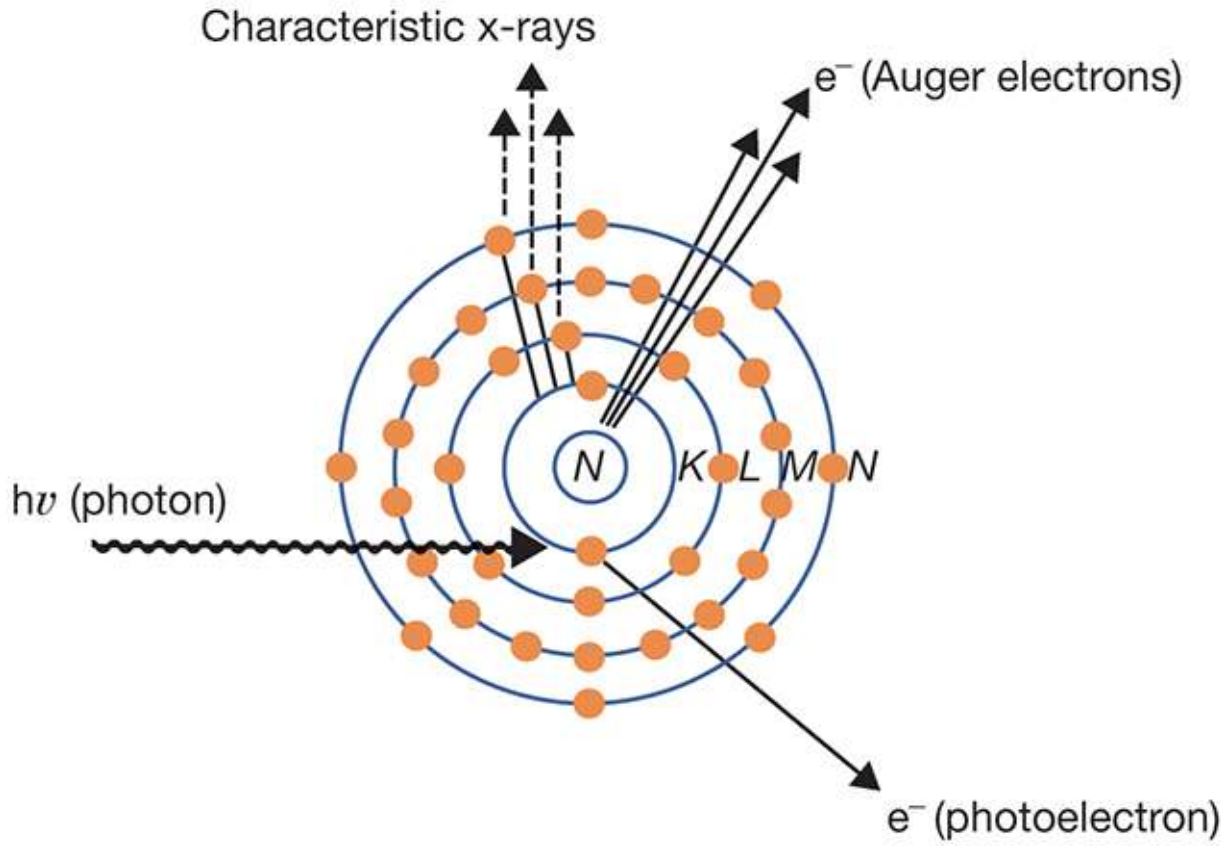

FIGURE 6.10 Photoelectric effect. In this type of photon interaction, the incident photon disappears, and an electron is ejected with kinetic energy equal to the incident photon's energy minus the binding energy of the electron. Characteristic x-rays and Auger electrons are emitted as the atom's electrons cascade to fill the vacancy created by the ejected electron.

The probability that a given photon will interact by means of the photoelectric process (denoted by τ/ρ) is a function of both the photon's energy and the atomic number of the target atom. For the process to occur, the incident photon must have energy greater than the binding energy of the involved orbital electron. In general, the probability per electron that a photon will undergo a photoelectric interaction is inversely proportional to the third power of the photon's energy and directly proportional to the third power of the atomic number of the target atom.

Compton Scattering

In *Compton scattering*, the incident photon interacts with a loosely bound orbital electron in which part of the photon's energy is transferred to the

electron as kinetic energy and the remaining energy is carried away by another photon (Figure 6.11). The binding energy of the electron is insignificant compared with the incident photon's energy and thus can be ignored. The energy of the Compton-scattered photon is equal to the difference between the energy of the incident photon and the energy transferred to the electron. If the incoming photon's energy is low (eg, 100 keV), very little energy is transferred to the electron. As the photon's energy increases, a greater proportion of the energy is transferred to the electron, so the scattered photon necessarily retains a smaller proportion of the incident energy. The photon may be scattered at any angle with respect to the direction of the incident photon, but the Compton electron is confined to angles between 0° and 90° with respect to the direction of the incident photon. If the incoming photon's energy is low, the distribution of the scattered photons is isotropic (equal in all directions). The scatter angles decrease for photons and electrons as the incident photon's energy increases (eg, at megavoltage [MV] photon energies, both are scattered predominantly in the forward direction).

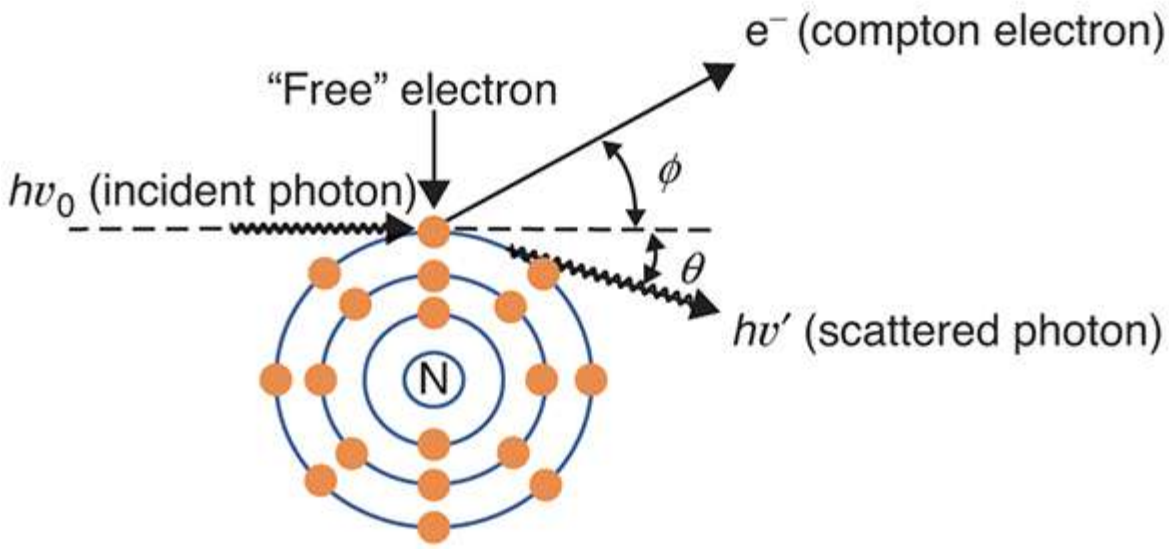

FIGURE 6.11 Compton effect. In this type of photon interaction, the incident photon interacts with one of the atom's outer electrons, and the energy is shared between the ejected electron and a scattered photon.

As a result of conservation of energy and momentum, the energies of the incident photon, $h\nu_0$; the scattered photon, $h\nu'$; and the scattered electron, E, are given by the following relationships:

$$E = h\nu_0 \frac{\alpha(1-\cos\theta)}{1+\alpha(1-\cos\theta)}$$

$$h\nu' = h\nu_0 \frac{1}{1+\alpha(1-\cos\theta)}$$

$$\cot(\varphi) = (1+\alpha)\tan(\theta/2)$$

where $\alpha = h\nu_0/m_0c^2$, and m_0c^2 is the rest energy of the electron (0.511 MeV). If $h\nu_0$ is expressed in MeV, then $\alpha = h\nu_0/0.511$.

The probability that a photon will interact with a target atom via the Compton process (σ_c/ρ) depends on the energy of the incoming photon, generally decreasing as the energy of the photon is increased. The probability of a Compton interaction is nearly independent of the atomic number of the absorber and is directly proportional to the number of electrons per gram.

Pair Production

Pair production (Figure 6.12) is possible only with photons having energies >1.02 MeV. When such an energetic photon approaches closely enough to the nucleus of the target atom, the incident photon energy may be converted directly into an electron-positron pair. Energy possessed by the photon in excess of 1.02 MeV appears as kinetic energy, which may be distributed in any proportion between the electron and the positron. When the positron comes to rest, it combines with an electron, and both particles then undergo mutual annihilation, with the appearance of two photons with energy of 0.511 MeV traveling in opposite directions. The probability of pair production (π/ρ) occurring increases rapidly with incident photon energy

above the 1.02 MeV threshold and is proportional to Z^2 per atom, Z per electron, and approximately Z per gram.

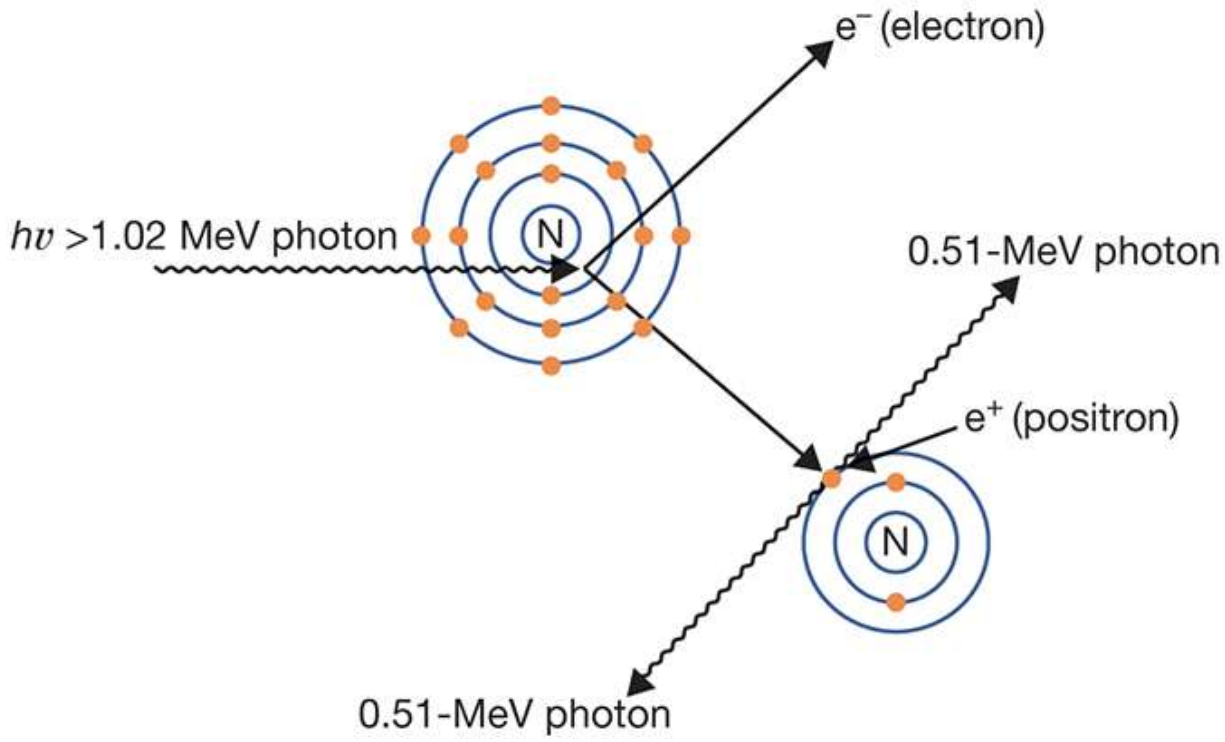

FIGURE 6.12 Pair production. In this type of photon interaction, the incident photon interacts with the electromagnetic field of the nucleus. The incident photon disappears, and two energetic electrons (a positron and a negatron) are produced. Two annihilation photons of energy 0.511 MeV then are produced when the positron interacts with its antiparticle, another electron.

Photodisintegration

In *photodisintegration*, a high-energy photon interacts with the nucleus of an atom, totally disrupting the nucleus, with the emission of one or more nucleons. It typically occurs at photon energies much higher than those encountered in radiation therapy. However, it is important to account for this in designing shielding around high-energy accelerators, as this interaction is a source of low-energy neutrons.

Relative Importance of Interaction Processes

Figure 6.13 illustrates the relative importance of the photoelectric, Compton, and pair-production processes—the three principal modes of interactions pertinent to radiation therapy—as a function of energy and atomic number of the absorber. For example, for an absorber with an atomic number approximately equal to that of tissue ($Z = 7$) and for monoenergetic photons, the photoelectric effect is the dominant interaction below about 30 keV. Above 30 keV, the Compton effect becomes dominant and remains so until approximately 24 MeV, at which point pair production becomes the dominant interaction. The total mass attenuation coefficient accounting for all the photon interactions discussed is given by the sum of the individual coefficients:

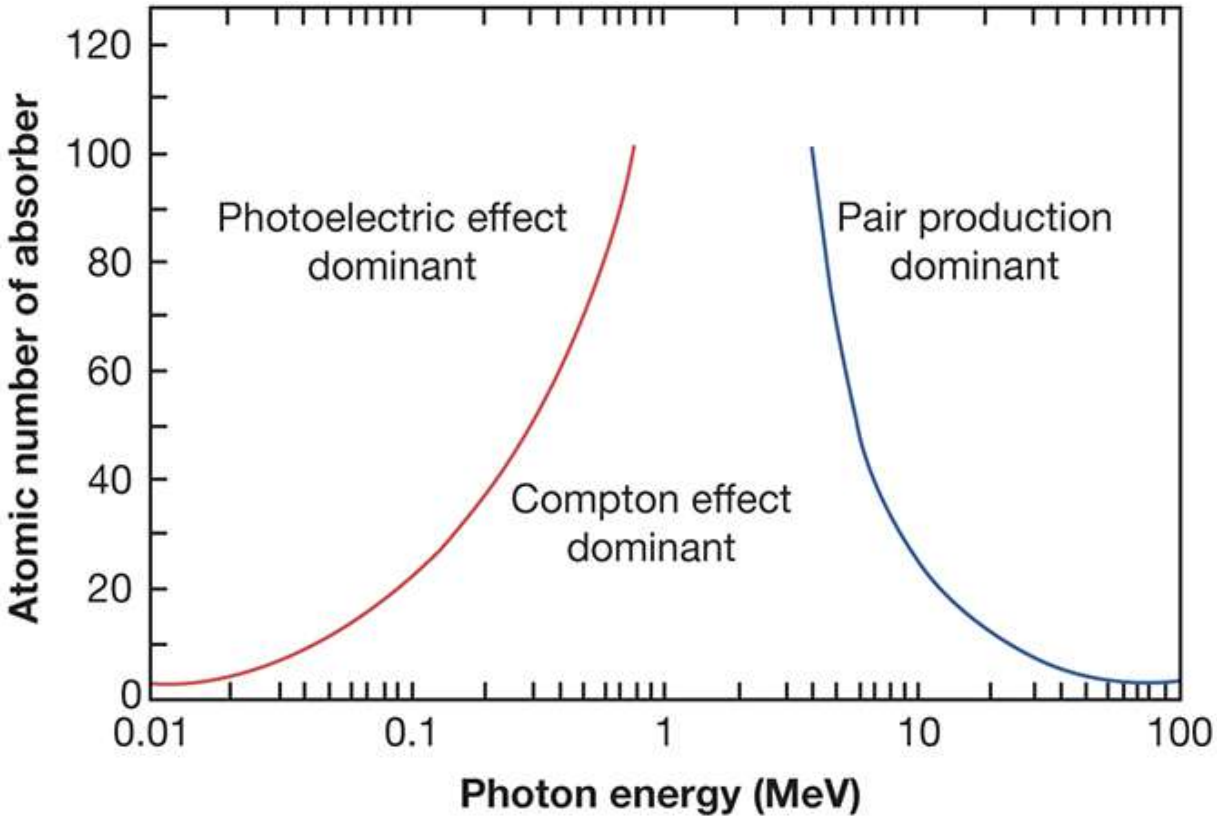

FIGURE 6.13 Relative importance of the three principal modes of interaction as a function of photon energy and atomic number of absorber. (Reprinted from Hendee WR, Ritenour ER. *Medical Imaging Physics*. 3rd ed. Mosby-Yearbook; 1992. Copyright © 1992 Elsevier. With permission.)

$$\mu_{en}/\rho = \sigma_{coh}/\rho + \tau/\rho + \sigma_{c}/\rho + \pi/\rho$$

INTERACTION OF PARTICLES WITH MATTER

Electrons

An electron loses its kinetic energy when traversing matter via interactions that can be either *elastic*, in which no kinetic energy is lost, or *inelastic*, in which some portion of the kinetic energy is changed into some other form of energy. The term *linear energy transfer (LET)* is used to describe how much energy an ionizing particle transfers to the material traversed per unit distance. Elastic collisions occur with either atomic electrons or atomic nuclei and are characterized by a change in direction of the incident electron with no loss of kinetic energy. Inelastic collisions can occur with atomic electrons, resulting in *ionizations* and *excitations* of atoms, or inelastic collisions with atomic nuclei, which result in the production of bremsstrahlung x-rays (*radiative losses*). In the case of ionization, it is possible for the ejected electron to acquire enough kinetic energy to cause additional ionizations of its own. These electrons are called *secondary electrons* or *Δ rays*, and they can go on to produce additional ionizations and excitations. The typical energy loss in tissue for a therapeutic electron beam, averaged over its entire range, is about 2 MeV/cm in water.

The complete description of the energy and depth of penetration of the moving electrons at any point in the medium is complicated by the fact that the electrons are very much lighter than the atomic nuclei. As a result, the electron can lose a very large fraction of its energy in a single process and thus can be deflected by very large angles. This means that even if the electron beam is monoenergetic when first impinging on a medium, there will be a large variation among all the moving electrons as to where in the medium each will stop. This is referred to as *range straggling*.

Protons and Heavier Ions

Protons traverse relatively straight paths through matter, slowing down continuously by interactions with atomic electrons and with atomic nuclei. This results in depth-dose characteristics that show an approximately constant absorbed dose value over most of the beam range until near the end of the proton's range, where a very sharp increase in dose occurs (called the *Bragg peak*), as shown in Figure 6.14. Dose at the peak is approximately 4 times the dose at the surface, and the distal width of the

peak is on the order of 1 cm, depending on beam energy and beam energy spread. Depth-dose characteristics customized for individual patients can be generated by superposition of multiple proton beams having different energies. This technique creates a *spread-out Bragg peak* that covers the target volume and decreases sharply to zero dose a few millimeters beyond the target. Protons are somewhat more effective biologically than photons, that is, a lower dose is required to cause the same biologic effect. This concept of *relative biological effectiveness (RBE)* of protons is defined as the dose of a reference radiation (typically ^{60}Co) divided by the proton dose to achieve the same biologic effect. Paganetti et al[13] have shown that proton RBE varies (≅10%) along the Bragg peak, particularly at the distal end where LET is high. Current clinical practice and International Commission on Radiation Units and Measurements (ICRU) recommendations[14] advocate that an overall RBE factor of 1.1 be applied.

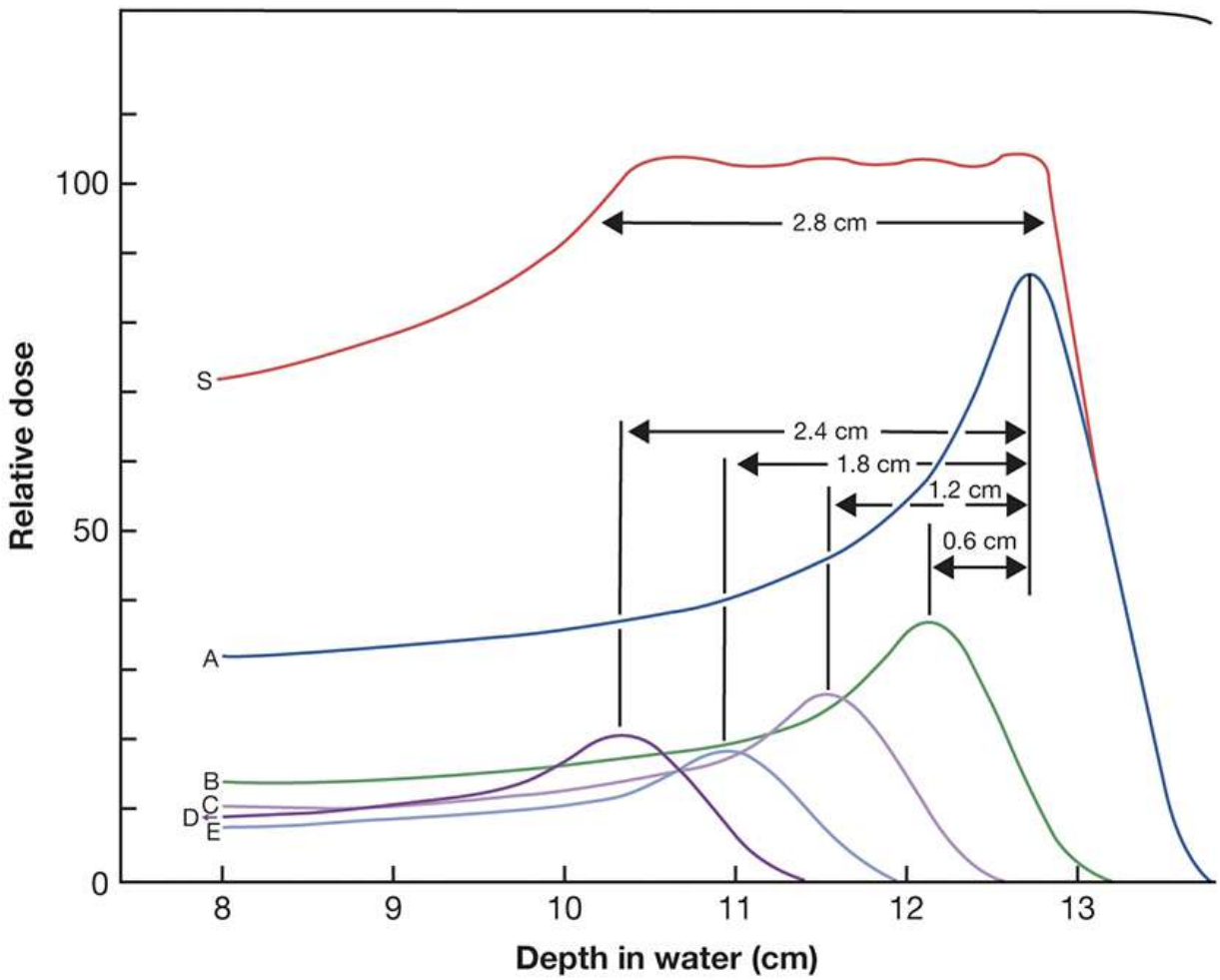

FIGURE 6.14 Drawing illustrating the way in which the Bragg peak for a proton beam can be spread out. Curve A is the depth-dose distribution for the primary beam of 160-MeV protons at the Harvard cyclotron. Beams of lower intensity and shorter range, as illustrated by curves B to E, can be added to give a composite curve, S, which results in a uniform dose of more than 2.8 cm. (Reprinted with permission from Hall *EJ. Radiobiology for the Radiologist*. 4th ed. J.B. Lippincott; 1994.)

Heavier ions, such as carbon, are also being used in modern radiation therapy at a few medical heavy-ion facilities in Europe and Asia.[15-17] Because of the greater mass of carbon ions, multiple scattering and range straggling are much less than protons, resulting in a sharper lateral and longitudinal edge. Also, because the LET in the peak of a carbon beam is larger than that of proton beams, the RBE is far greater for carbon ions.

Neutrons

Neutrons, like photons, are uncharged and thus are an indirectly ionizing radiation, which are exponentially attenuated by matter. The interactions are through processes that are primarily nuclear. They include elastic scattering with nuclei that make up the body's tissues (hydrogen, oxygen, carbon, nitrogen, etc). Neutron interactions result in recoil protons and charged nuclear fragments that have relatively low energy. The RBEs of these resultant particles are not fully known, thereby complicating the understanding of the relationship between clinical response and absorbed dose.

RADIATION THERAPY TREATMENT MACHINES

Kilovoltage Units

Before 1951, most radiation treatment units were kilovoltage x-ray machines capable of producing photon beams having only limited penetrability. Today, this type of machine is still used in some clinics for the treatment of skin cancer. In these machines, the electrons are accelerated by an electric field produced from a high voltage generated in a transformer that is applied directly between the filament (cathode) and the x-ray target (anode). A schematic diagram of a radiation therapy x-ray tube is shown in Figure 6.15. The potential difference (kVp) is variable on these machines, and metal filters can be added to absorb the lower-energy photons preferentially, changing the penetrability of the beam. The combination of variable kVp and different filtration provides the capability of generating multiple x-ray beams. The degree of penetrability is used to categorize the units as *contact*, *superficial*, and *orthovoltage* (deep-therapy) x-ray machines. A more detailed review of these type of treatment machines is provided by Biggs et al.[18]

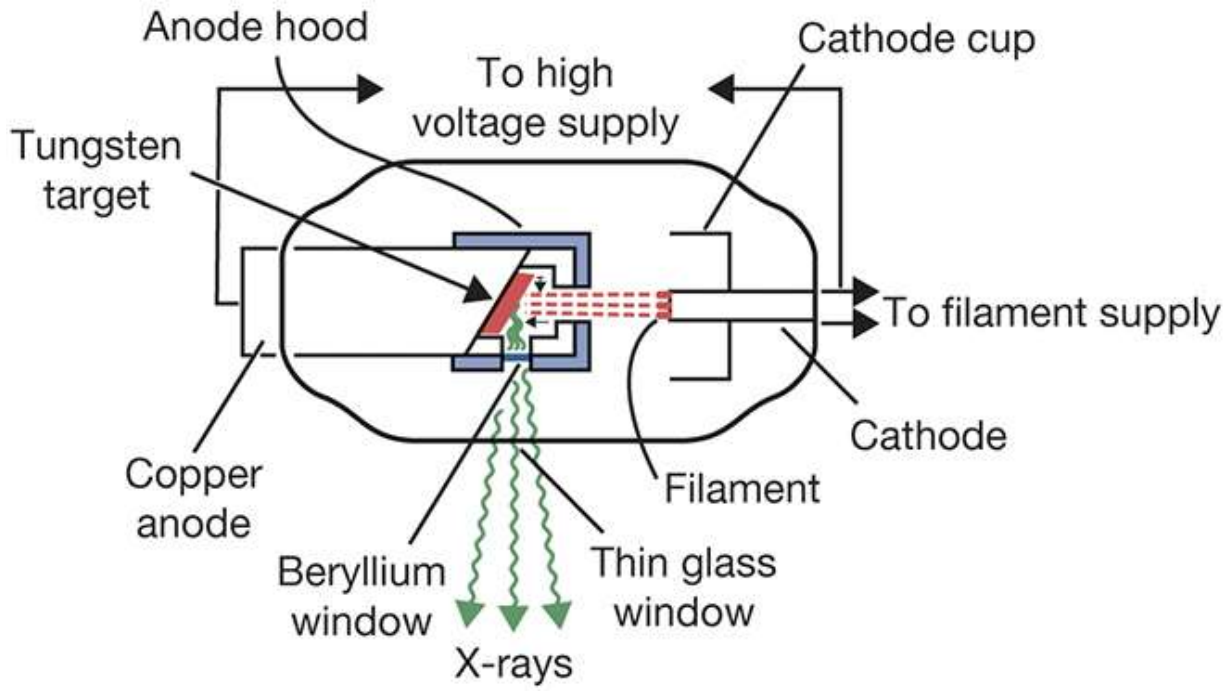

FIGURE 6.15 Schematic diagram of radiation therapy x-ray tube. (Reprinted with permission from Khan FM. *The Physics of Radiation Therapy*. 2nd ed. Williams & Wilkins; 1994.)

Contact Units

A contact x-ray machine typically operates at potentials of 40 to 50 kVp and at a tube current of 2 to 5 milliamperes (mA). Attached cones are used for a source-skin distance (SSD) of typically 2 cm or less. Filters of 0.5- to 1.0-mm aluminum are used to give a typical HVL of 0.6-mm aluminum. The x-ray tube is rod shaped with an extremely thin mica-beryllium window, having an inherent filtration of 0.03-mm-aluminum equivalence, and the radiation is emitted axially. The primary radiation therapy application of a contact x-ray unit is for endocavitary irradiation of selected small rectal carcinomas.[19]

Superficial Units

A superficial unit is an x-ray machine that operates at potentials of 50 to 150 kVp and 5 to 10 mA. Added thickness of filtration (1-mm Al to 1-mm Al + 0.25-mm Cu) produces HVLs of 1.0 to 8.0 mm of aluminum. Attached cones typically are used; lead masks are used to define irregular fields. The

SSD is typically 15 or 20 cm. These machines are used primarily to treat skin lesions.

Orthovoltage (Deep-Therapy) Units

Orthovoltage x-ray machines operate at potentials between 150 and 500 kV, with most operating between 200 and 300 kV, and with tube currents of 10 to 20 mA. HVLs of 1 to 4 mm of copper are common with the use of added filters, such as the *Thoraeus filter*, a combination of thin sheets of tin, copper, and aluminum arranged so that the highest atomic number sheet is always closest to the x-ray target, ensuring that the higher-energy characteristic x-rays are absorbed by the lower-*Z* metal. Treatment fields usually are defined using detachable cones. The SSD is typically 50 cm. Very few of these types of machines are still in clinical use.

Megavoltage Photon and Electron Beam Treatment Units

Radiation treatment machines that can produce beams 1 MV or greater have been designated as *MV therapy* machines. The *resonant transformer machine*, one of the first such treatment units, could generate x-rays between 300 kV and 2 MV.[20] Another early type of MV machine was the *Van de Graaff generator*, which operated at 1 to 2 MV. The *betatron*, first developed in 1941 by Kerst,[21] was adapted for use in radiation oncology and produced x-ray beams with energies of >40 MV. The *microtron*[22] and related *racetrack microtron*[23] combined the basic principles of the electron linear accelerator and cyclotron (both of which are discussed later in this chapter) and was one of the first intensity-modulated delivery systems. All of these machines are now obsolete and no longer in clinical use. Details on the history and development of these early accelerators used in radiation therapy can be found in the textbook by Karzmark et al.[24]

Cobalt-60 Teletherapy

The first *cobalt-60* (^{60}Co) *teletherapy* machine was loaded with its ^{60}Co source in August 1951 in the Saskatoon Cancer Clinic, Saskatoon, Canada, and the first patient was treated on November 8 of that year.[25,26] A very readable history of the development of the first ^{60}Co teletherapy machine in the United States is provided by Almond.[27] A technical review of ^{60}Co

teletherapy machines is provided by Glasgow.[28] The advantages of a ^{60}Co teletherapy machine are its relative constancy of beam output, predictability of decay because of a well-defined half-life, and lack of day-to-day small-output fluctuations typically found in electrical machines. Disadvantages include the need for source replacement approximately every 4 to 5 years, poor field flatness for large fields and large penumbra, and lower depth dose compared with high-energy photons generated by medical linear accelerators, which are discussed later. Isocentric units with source-to-axis distance (SAD) of 80 or 100 cm were designed with maximum field sizes of 40 × 40 cm at the machine isocenter for the 100-cm SAD machine. Source activities vary from about 5,000 to 13,000 Ci in 1.5- to 2.0-cm-diameter sources and yield exposure rates from 150 to 250 R/min at 1 m. The radiation consists of 1.17- and 1.33-MeV γ-rays having a $d_{1/2}$ in tissue (the depth at which the dose has been reduced to 50% of the maximum dose value) of about 10 cm.

Cobalt teletherapy machines became a mainstay for radiation therapy for nearly three decades but are rarely used in U.S. clinics today. Cobalt-based teletherapy machines do remain a valuable radiotherapy solution in developing countries, though there are several active programs to provide economic solutions that do not rely on radioactive materials.

Gamma Knife

Elekta *Gamma Knife* (Elekta AB, Stockholm, Sweden) is a dedicated stereotactic radiosurgical device that was developed in 1968 by Dr. Lars Leksell,[29] a Swedish neurosurgeon. This machine initially made it possible to deliver a single, large dose of highly conformal radiation (γ-rays) precisely to a number of intracranial sites using multiple fixed ^{60}Co sources aimed at a center point. As the field of cranial stereotactic radiosurgery evolved, Gamma Knife started offering solutions for fractionated treatments, named *stereotactic radiotherapy*. In stereotactic radiotherapy patients are treated with several fractions of highly conformal doses without use of ring frames and relying on thermoplastic masks for immobilization. The Gamma Knife traditionally consisted of three basic components—a spherical source housing/gantry, four collimator helmets, and a couch with electronic controls. The source housing (models U, B, and C) contains 201

^{60}Co sources distributed in a quasihemispherical arrangement. The γ-rays from each source converge to the *unit center point* (*UCP*), which is 40 cm away from each source. The UCP is analogous to the isocenter of a teletherapy machine and is the location where the target volume must be positioned during a treatment. This is accomplished by the three-axis coordinate system on the Leksell stereotactic frame. Each source has an activity of approximately 30 Ci when newly installed, and the 201 sources combined provide a dose rate of approximately 300 cGy/min at the UCP. Along the path to the UCP, the radiation beam from each source is collimated twice—once by a primary collimator and then by one of four secondary collimator helmets. For each helmet, 201 tungsten collimators define specified circular apertures (4, 8, 14, or 18 mm projected at the UCP). To conform the radiation dose to the shape of the target in the patient, various combinations of aperture diameters, aperture blocking (*plugging*), irradiation times, and head positions are used. A specific combination of these four parameters defines what is referred to as a *shot* in Gamma Knife terminology. Hundreds of thousands of patients have been treated using this type of treatment machine.

Since 2006, Elekta has introduced three new models of Gamma Knife, the Perfexion, Icon, and Esprit. The Perfexion model, which was a major change in design from the previous models, had several advanced features, including an enlarged internal patient cavity for extended access to peripheral cranial anatomy. Unlike the earlier models, the Perfexion moves the entire patient on the couch to each stereotactic x, y, and z coordinate. The collimation was also placed within the source housing part of the machine gantry, eliminating the external helmets. The sources are arranged radially and divided into eight moving sectors with 24 sources each. Each sector is independently selectable, thereby providing various sector combinations for aperture (collimation) size or blocking at each shot position during treatment. With the introduction of its associated Extend System accessory, the Perfexion has an increased reach to allow treatments to the upper cervical spine.

In 2015, Elekta introduced the Gamma Knife Icon (Figure 6.16), which added image-guided radiation therapy (IGRT) imaging capability. The Icon enables cone beam computed tomography (CBCT)-based patient localization capability and intrafraction patient monitoring with infrared

camera. CBCT isocenter is placed away from the cobalt sources isocenter, but the two isocenters are linked in software and hardware and the Icon provides workflows for patient localization, treatment evaluation, and adjustments when needed. In this sense the Icon offers modern IGRT capabilities in combination with cobalt radiotherapy. In 2022, Elekta introduced the Esprit model, which included more efficient and rapid planning, workflow improvement including remote review of plans, and a redesigned patient positioning system.

FIGURE 6.16 Elekta's Leksell Gamma Knife (Elekta AB, Stockholm, Sweden) is a dedicated stereotactic radiosurgery system developed in 1967 by Prof. Lars Leksell, a Swedish neurosurgeon, designed to noninvasively treat intracranial targets—such as brain tumors and lesions—with extreme precision. Shown is the most recent system, Elekta Esprit, which includes the option of frameless or frame-based workflows and stereotactic cone beam CT imaging technology. (Courtesy of Elekta.)

Linear Accelerators

The first microwave electron linear accelerator (8 MV) for medical use became operational in 1953 at the Radiation Research Center of the

Medical Research Council at Hammersmith Hospital in London.[30] The design for an isocentric gantry mount for the accelerator first was conceived by P. Howard-Flanders.[31] Shortly thereafter, Ginzton et al[32] at Stanford University developed a 6-MV isocentric medical linear accelerator (*linac*). The history of the development of this first medical linear accelerator in the United States is provided by Jacobs.[33] Since then, there have been continued advances in accelerator design and construction, and today, medical linear accelerators account for most of the operational MV treatment units in clinical use.[24,34]

Figure 6.17 is a block diagram of a high-energy, bent-beam medical linear accelerator showing the major components. The linac uses electromagnetic waves of frequencies in the *S-band* microwave region (2,856 megahertz [MHz]) to generate an electric field. The microwave radiation is propagated through a device called an *accelerator structure*, and the electrons injected into the structure are accelerated by the electric field in a straight line. The accelerator structure consists of a stack of cylindrical metal cavities having an axial hole through which the accelerated electrons pass. The accelerator structure's electric field produced by the microwaves can be either a *traveling wave* or *standing wave* design. In a traveling wave design, the electrons travel with the electric field as the field propagates through the structure with time, somewhat like a surfboarder riding the crest of an ocean wave. In a standing wave accelerator, the reflected microwave power is used to produce a standing wave electric field. In that case, the microwave power is coupled into the accelerator structure by side-coupling cavities rather than through the accelerator structure's axial cavity apertures.

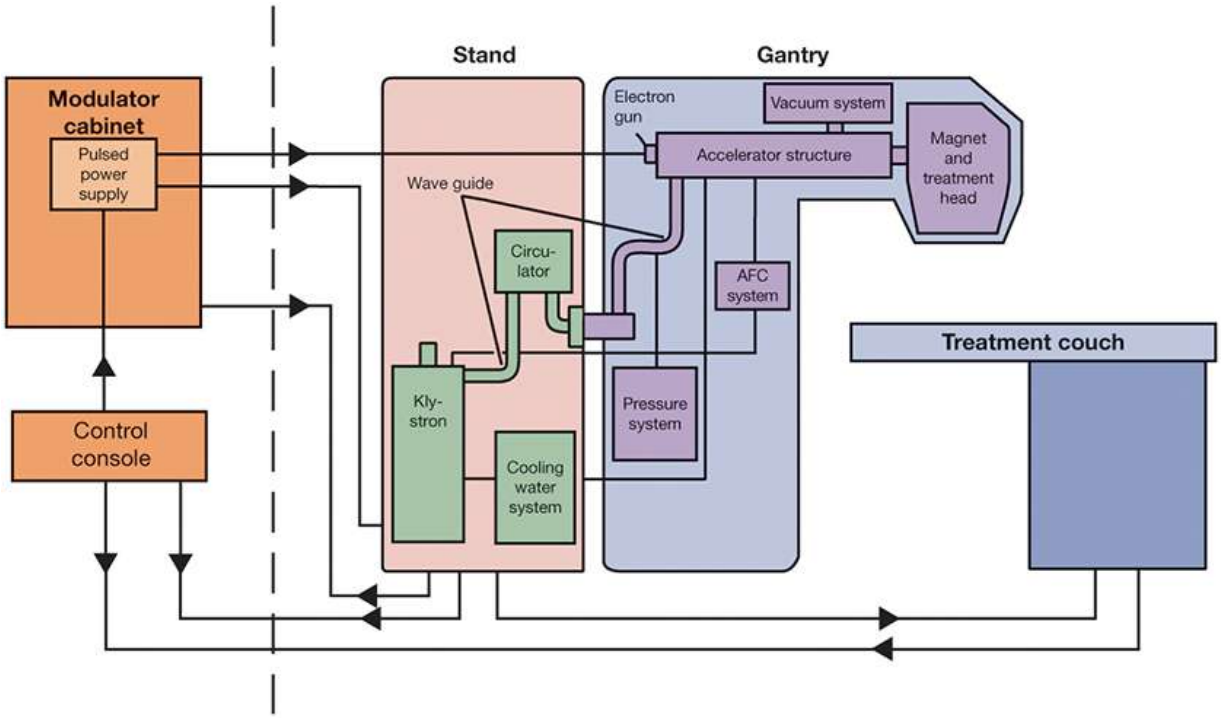

FIGURE 6.17 Schematic block diagram showing major components of a high-energy bent-beam medical linear accelerator. (Courtesy of Varian, Palo Alto, CA.)

The accelerator structure in low-energy (4-6 MV) linacs most often is mounted vertically in the treatment head collinear along with the components associated with producing, controlling, and monitoring the x-ray beam (Figure 6.18, left). High-energy (15-18 MV) linacs use a horizontally mounted accelerator structure with a beam-bending magnet system (Figure 6.18, right). Accelerator structure technology now makes multiple high-dose-rate photon beams of widely separated energies possible.

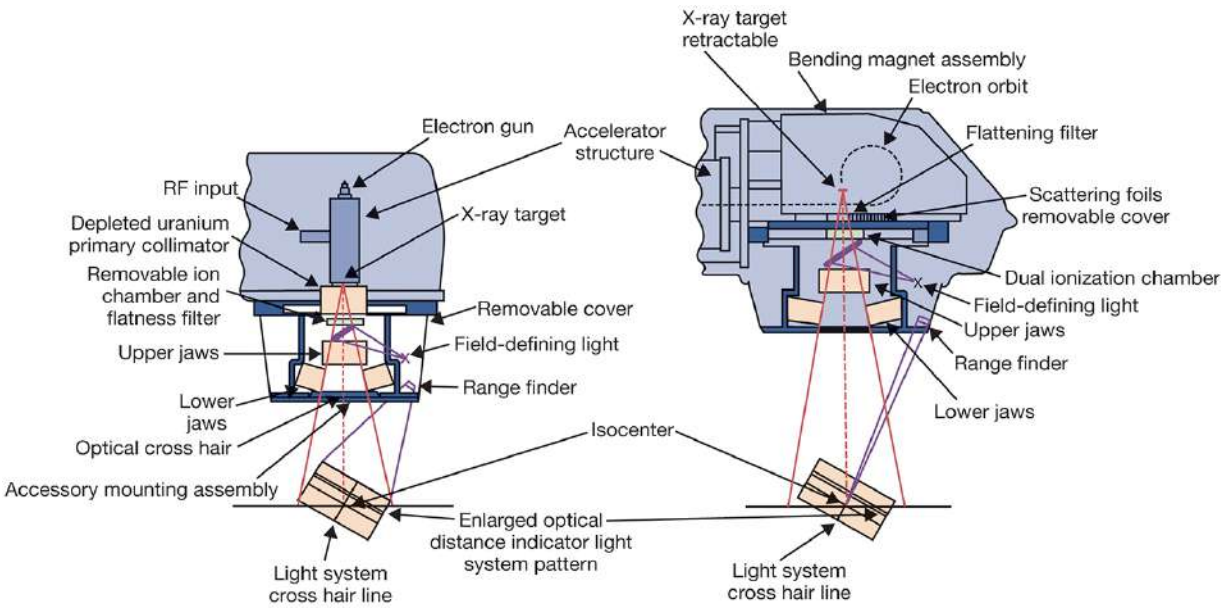

FIGURE 6.18 Schematic cutaway diagram of treatment heads for low-energy, straight-beam (left) and high-energy, bent-beam (right) medical linear accelerators. (Courtesy of Varian, Palo Alto, CA.)

Other important components of a linac are the modulator, microwave power sources, electron gun, and the beam-handling components. The modulator is the source of pulsed direct current (DC) power, needed for microwave power production. Pulsed DC power is also supplied to the *electron gun* (a hot-wire filament that serves as the source of the accelerated electrons). The electrons are bunched before acceleration by a device called a *buncher*. The electron beam thus consists of pulses of bunched electrons in the form of a narrow pencil beam. The magnetron serves as the source of microwaves and as a power amplifier. The *klystron* is a device used to amplify the microwave power that is generated from a separate microwave source (*radiofrequency driver*). The microwave power coming from the magnetron or klystron is transported to the accelerator structure by a metallic pipe called a *waveguide*. A device called the *circulator* is used to isolate the klystron/magnetron from the reflected microwave power.

Other important components in a linac are located in the treatment head. These include the *x-ray target*, *fixed primary collimator*, *scattering foils*, *flattening filter*, *monitor ion chamber, movable secondary collimator jaws and/or multileaf collimator* (MLC), *light field localizer*, and *optical distance indicator*. In addition, the treatment head contains a significant

amount of shielding material to minimize leakage radiation. A schematic diagram of all the treatment head subsystems for both x-ray and electron beams is shown in Figure 6.19.

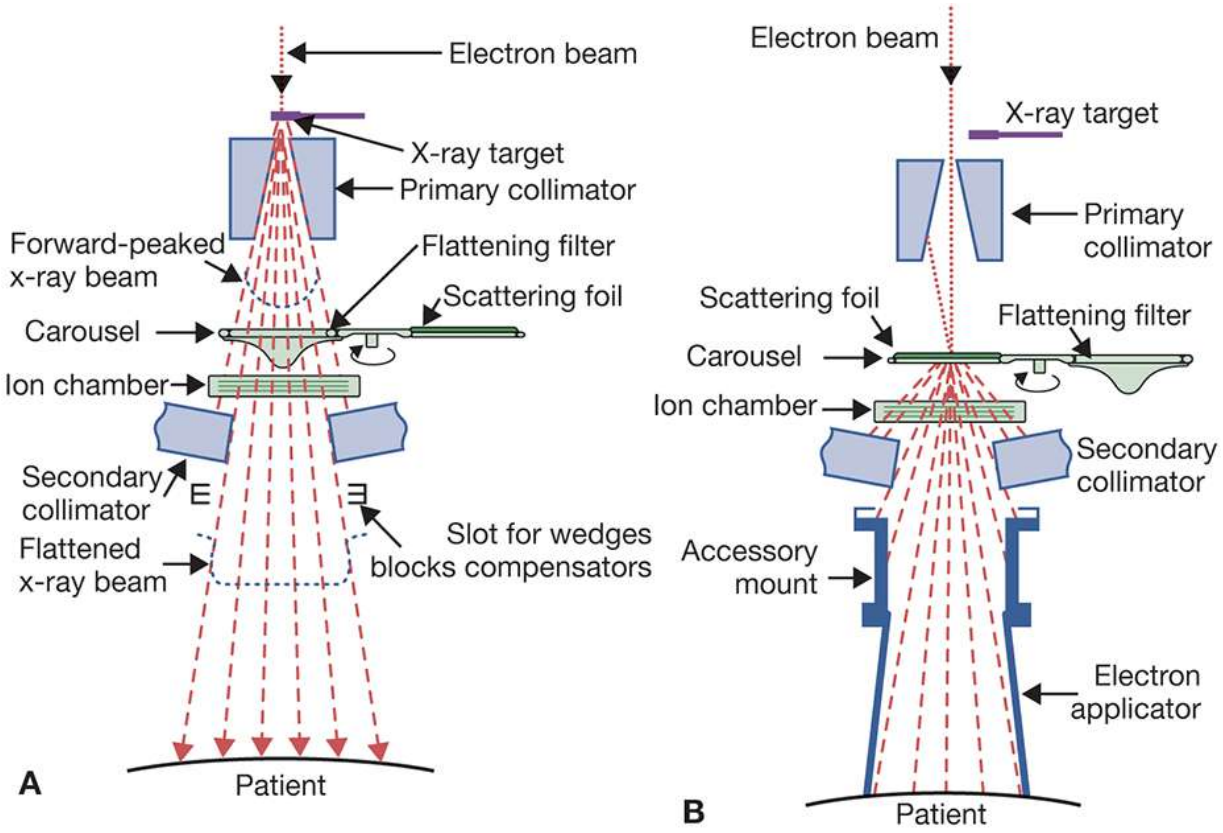

FIGURE 6.19 Schematic diagram of beam subsystems for x-ray beam (A) and electron beam therapy (B). (From Karzmark CJ, Morton RJ. *A Primer on Theory and Operation of Linear Accelerators in Radiation Therapy.* Department of Health and Human Services, Public Health Service, Food and *Drug* Administration, Bureau of Radiological Health; 1997.)

At the exit window of the accelerator structure, the high-energy electrons emerge as a pencil beam of about 2 to 3 mm in diameter. In a low-energy (4-6 MeV) linac, the accelerated electrons proceed in a straight line and strike an x-ray target when in photon mode, producing bremsstrahlung x-rays. In high-energy linacs, because the accelerator structure is much longer and is placed horizontally or at some angle with respect to the horizontal, the electrons must be bent through a suitable angle, usually 90° or 270° between the accelerator structure and the target. This is enabled by the beam

transport system, which consists of an *achromatic focusing and bending magnet*, as well as *steering* and *focusing coils*.

The *primary collimator* is a fixed collimator located just below the x-ray target and is used to collimate the x-ray beam in the direction of the patient treatment and reduces the leakage radiation from the x-ray source. The angular distribution of the bremsstrahlung x-rays produced by MV electrons incident on a target is forward peaked. To make the x-ray beam intensity uniform across the field, a conical metal *flattening filter* is inserted in the beam. Filters are constructed of lead, tungsten, uranium, steel, and aluminum (or some combination of these), depending on x-ray energy. The flattened x-ray beam then passes through a *monitor ionization chamber*. In most cases, this system consists of several transmission-type parallel-plate ionization chambers, which cover the entire beam. These ion chambers are used to monitor the field symmetry, dose rate, and integrated dose per monitor unit. In the 2010s, several linacs offering flattening filter-free beams were commercially introduced. Some of these systems provided only flattening filter-free beams, whereas some provided dual capability with and without flattening filters.

After passing through the monitor chamber, the beam can be further collimated by continuously and independently movable x-ray collimators consisting of two pairs of lead or tungsten jaws and/or an MLC system consisting of a large number of tungsten leaves arranged in an opposing configuration. Conventional linacs typically provided rectangular field sizes ranging from 0 cm to 40 × 40 cm at a distance of 100 cm. The field size can be defined by a *light localizer* and a *mirror assembly*. The introduction of independently movable collimators allowed simplified patient positioning and improved safety by avoiding overlapping field abutments without the necessity of using heavy beam-splitting blocks.[35] Independent jaw technology in conjunction with computer control of the dose rate can be used to create a wedge-shaped isodose pattern.[35]

Although the *MLC* systems (Figure 6.20) were initially developed to simplify beam shaping for 2D- and 3D-based conformal radiotherapy, their ultimate purpose excelled in *intensity-modulated radiation therapy* (*IMRT*) (discussed in Chapters 10), making them a prerequisite capability on all modern radiotherapy machines. The MLCs offered the ability to electronically and dynamically control beam shapes during treatment.

IMRT can be delivered in various combinations of MLC and gantry motions. With respect to MLC motion, IMRT can be delivered by (a) delivering multiple field segments (called *segmental MLC* or *step-and-shoot IMRT*) or (b) having the leaf pairs move across the field at a varying rate with the x-ray beam on (called *dynamic MLC* or *sliding window IMRT*).[36] With respect to gantry motion, the *volumetric modulated arc therapy* capability involves continuous gantry motion during delivery of typically coplanar beams,[37-39] while 4Pi delivery involves complex combinations of gantry, collimator, and couch rotations enabling highly conformal dose distributions with noncoplanar delivery.[40] Initial designs of MLCs relied on in-line opposing pairs of MLC leaves. Alternate MLC arrangements have been a long-standing topic of interest and double-focused and/or multilayer MLCs eventually became available. The double-focused MLCs offer improved penumbra compared to in-line MLCs by matching the leaf edge with the beam divergence across all field sizes. The in-line MLCs require a compromise of the beam penumbra as a function of the MLC position. The multilayer MLCs offer greater flexibility in field shape resolution, reduced leakage, greater speed, and simplification of operation. Recently, dual-stack MLCs have been introduced on O-ring accelerators, which are discussed later. Dual-stack MLCs offset one leaf bank by a half leaf width, effectively doubling the resolution of the MLC.[41] Additionally, the extra leaf bank provides sufficient attenuation that the secondary collimators can be eliminated.

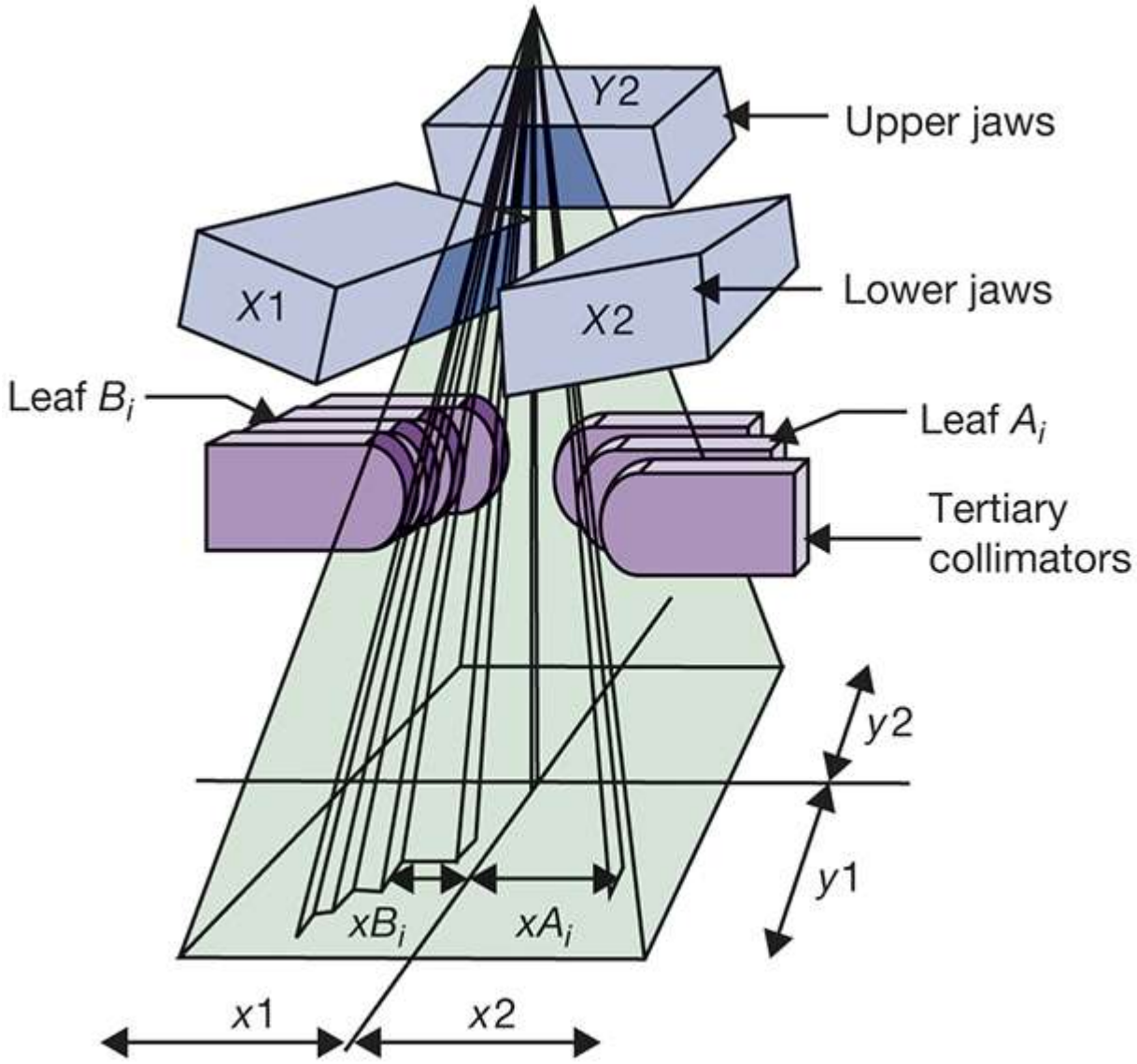

FIGURE 6.20 Schematic illustrating the geometry of a multileaf collimator for Varian linear accelerators. The *x*-direction is the field width across each leaf pair, and the *y*-direction is the field length. (Courtesy of Varian, Palo Alto, CA.)

In electron mode, the accelerator's beam current is reduced 1,000-fold and the x-ray target is retracted. An electron scattering foil is moved into place on the beam centerline so that the accelerated pencil electron beam strikes it to broaden the beam and produce a flat field across the treatment field. The scattering foil typically consists of dual lead foils. The thickness of the first foil ensures that most of the electrons are scattered with only a minimum of bremsstrahlung x-rays. The second foil is generally thicker in the central region and is used to flatten the beam across the field. The

bremsstrahlung produced appears as x-ray contamination of the electron beam and is usually less than 5% of the maximum dose. An *electron applicator* is mounted below the movable collimator jaws to provide the final field collimation.

Important new technical developments for improving external beam treatment planning and dose delivery for radiation therapy of cancer patients occurred in the late 1980s and early 1990s (see Chapters 10). Advances in medical imaging and computer hardware and software technologies led to the development of image-based 3D radiation treatment planning (3DRTP) systems and computer-controlled linacs having advanced delivery and treatment verification features. These advances were followed in the 1990s and 2000s with incorporation of volumetric imaging systems, either using the treatment beam or a standalone imaging source. The first commercial volumetric image-guided system was the tomotherapy system (see following section). Elekta integrated advanced imaging systems having kV *CBCT* capability on their C-arm linac (*Elekta Synergy*).[42,43] Such linacs are referred to as *IGRT* linacs (see Chapters 10). The Synergy IGRT system (referred to as XVI) consists of a retractable kilovolt x-ray source, an amorphous silicon flat-panel imager mounted on the linear accelerator perpendicular to the radiation beam direction, and a software module for processing the data and tools for registering the images (Figure 6.21). The XVI system provided planar, motion, and volumetric imaging capabilities. Registration software provided the ability to compare the daily patient setup image with the stored prescription computed tomography (CT)-planning image, after which table adjustments could be made prior to treating the patient. Other medical linac manufacturers also embraced the IGRT concept adding kV CBCT technology similar to the Synergy XVI, such as Varian Trilogy linac. Both Elekta and Varian have continued to improve their C-Arm IGRT linacs, the latest being the Elekta Harmony and Varian TrueBeam IGRT linacs. More detail about currently available IGRT systems is provided in the American Association of Physicists in Medicine (AAPM) Task Group Report 180.[44]

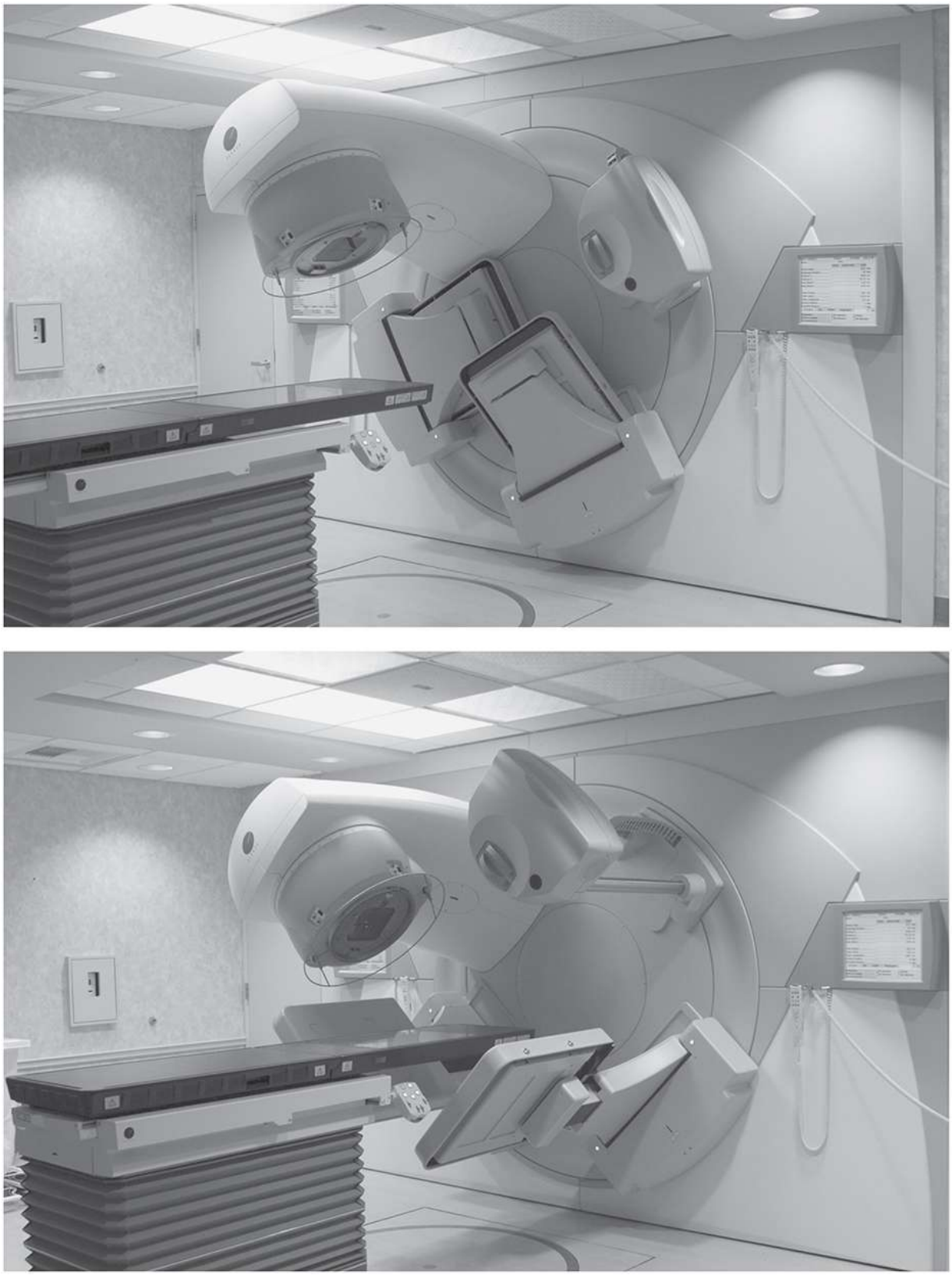

FIGURE 6.21 Elekta Synergy installed at the University of California Davis. The unit consists of a conventional multimodality medical linac with a retractable kilovolt x-ray

source, an amorphous silicon flat-panel imager mounted on the linear accelerator perpendicular to the radiation beam direction, and a software module (referred to as the XVI system). Top: The x-ray source, with the amorphous silicon flat panels retracted. Bottom: With the panels extended.

X-Ray-Guided O-Ring Linear Accelerators

Helical tomotherapy was first proposed by Mackie et al[45] and became commercially available as the TomoTherapy HI-ART system (Accuray, Madison, WI).[46] A short, in-line, 6-MV linac (Siemens Oncology Systems, Concord, CA) rotated on a ring gantry at a source-axis distance of 85 cm. This was one of the first IGRT systems, with CT-like detectors used to image the MV beam and generate a MVCT image. Figure 6.22 shows the unit installed at the University of California, Davis. The IMRT treatment is delivered while the patient-support couch is translated in the *y*-direction (toward the gantry) through the gantry bore in the same way as a helical CT study is conducted. Thus, in the patient's reference frame, the treatment beam is angled inward along a helix, with the midpoint of the fan beam passing through the center of the bore. Similar to helical CT, the treatment beam *pitch* is defined as the distance traveled by the couch per gantry rotation divided by the field width in the *y*-direction (typically between 0.2 and 0.5). The width of the beam in the y-direction is defined by a pair of jaws fixed for any patient treatment to one of three selectable values (1, 2.5, or 5 cm). Laterally, the treatment beam is modulated by a 64-leaf binary MLC, whose leaves transition rapidly between open and closed states. Each leaf has a projected width of 6.25 mm at the bore center, for a maximum possible open lateral field length of 40 cm. Intensity modulation is accomplished by varying the fraction of time different leaves are opened. The individual modulation pattern can change with angle (divided into exactly 51 projections over a full revolution). During the treatment, the gantry rotates at a constant velocity with a period ranging between 10 and 60 seconds/rotation. The extent to which a treatment beam projection is modulated is characterized through what is called the *modulation factor*, defined as the ratio of the maximum leaf open time to the average leaf open time for the projection. Pitch and maximum permissible modulation factor are new parameters that need to be specified by the treatment planner. Highly modulated treatments achieve greater conformality but inevitably

take longer to deliver. A helical MVCT image is acquired using the onboard xenon CT detector system and the 6-MV linac (detuned to 3.6 MV) with the leave fully opened when the patient-support couch is translated in the *y*-direction through the gantry bore. Registration software is provided to compare the daily patient setup image with the stored prescription CT planning image. More detail about currently available systems is provided in AAPM Task Group Report 306.[47]

FIGURE 6.22 TomoTherapy HI-ART system installed at the University of California Davis. A short, in-line 6-MV linac rotates on a ring gantry. Intensity-modulated radiation therapy treatment is delivered while the patient-support couch is translated through the gantry bore in the same way as a helical computed tomography study is conducted. The width of the beam in the patient-translated direction is defined by a pair of jaws that is fixed for any particular patient treatment, and laterally, the treatment beam is modulated by a 64-leaf binary multileaf collimator.

In 2017, Varian released the Halcyon system (Figure 6.23), an O-ring system with a straight-through 6-MV linac whose beam is collimated only by a dual-stack MLC[41] and was specifically designed to address challenges of deploying radiotherapy in low-resource settings. Some of the specific features include lower power consumption, a simpler installation process, easier serviceability, greatly simplified operation, and higher throughput than conventional machines. Halcyon is also designed to benefit from a treatment workflow that is purely IGRT based, whereby all treatments require MV image guidance and imaging dose is included in the treatment dose. The double-layer MLC is composed of offset 1-cm-wide leaves, which has been shown to provide significant dosimetric advantages.[41] In 2019, Varian released a second version that included a kV CBCT system. It is worth noting that all of the features that make this machine advantageous in emerging markets also make it attractive in developed settings. One pitfall is that the machine does not offer electron beam treatment capability. Another noteworthy point is that the system has an “O”-shaped design, as opposed to the conventional “C”-shaped design for Varian, Elekta, Siemens, etc, machines. This design joins a host of other advanced machines with “O” shape (Tomotherapy, ViewRay, and Elekta Unity) and potentially signals that this may become a more prevalent approach to radiotherapy patient treatments.

FIGURE 6.23 Varian Medical Systems' Halcyon introduced in 2017, which is specifically designed to provide highly efficient image-guided radiation therapy treatments. Note that the system does not offer electron beam treatment capability and has an "O"-shaped design, as opposed to the conventional "C"-shaped design used typically for other Varian and Elekta medical linacs.

Magnetic Resonance–Guided O-Ring Linear Accelerators

The ViewRay system (Figure 6.24), released in 2012, combines a 0.35-T split bore magnetic resonance imaging (MRI), which straddles a radiotherapy gantry housing three cobalt heads spaced 120° apart. Each head contains a nominal 15,000 Ci cobalt source mated to an MLC. The three sources contribute to the combined initial dose rate of approximately 600 cGy/min. The MRI scanner and radiotherapy gantry share a common isocenter enabling MR-based treatment localization as well as intrafractional treatment monitoring. The first MR-guided radiotherapy treatment occurred at Washington University in St. Louis on January 15, 2014. The clinical system relied exclusively on Monte Carlo–based dose calculation for treatments ranging from 2D-based radiation therapy to

IMRT. While ViewRay relies on cobalt sources, which inherently have a larger penumbra than linac-based systems (see further), the doubly focused MLCs offer superior collimation than those installed on contemporary linear accelerators, resulting in comparable treatment dose distributions between the two technologies.[48,49] In 2017, ViewRay released a linac version of the system that replaced the three cobalt units with a single 6-MV linac.

FIGURE 6.24 ViewRay system combines a 0.35-T split bore MRI with a radiotherapy gantry housing a single 6 MV linac with MLC for beam shaping and IMRT. The MRI scanner and

radiotherapy gantry shared a common isocenter enabling MR-based treatment localization as well as intrafractional treatment monitoring with MRI. IMRT, intensity-modulated radiation therapy; MLC, multileaf collimator; MRI, magnetic resonance imaging.

The initial ViewRay system also enabled a practical online adaptive radiotherapy workflow, during which patients could be imaged, a new plan generated, patient-specific quality assurance (QA) performed, and a treatment delivered, all within the same timeframe as conventional radiotherapy.[50,51] This also marked the initiation of the first practical online adaptive radiotherapy program, and Washington University treated the first online MR-guided adaptive radiotherapy treatment on September 8, 2014. This program quickly grew to include several hundred adaptive treatments within the first 2 years of operation.

In 2018, Elekta released the Unity system, an MR-guided system with a 7-MV linac and 1.5 T MRI unit.[52,53] The system uses an MLC with 7.1-mm-wide leaves and a single x-ray treatment head (Figure 6.25). Use of a diagnostic field strength enables use of standard sequences for both morphologic and functional (eg, diffusion-weighted) MRI. The Unity system is capable of on-table adaptation as described for the ViewRay system. Because the table cannot be moved laterally or vertically, plans for nonadaptive treatments can also be adapted to correct for patient setup variations instead of shifting the table.

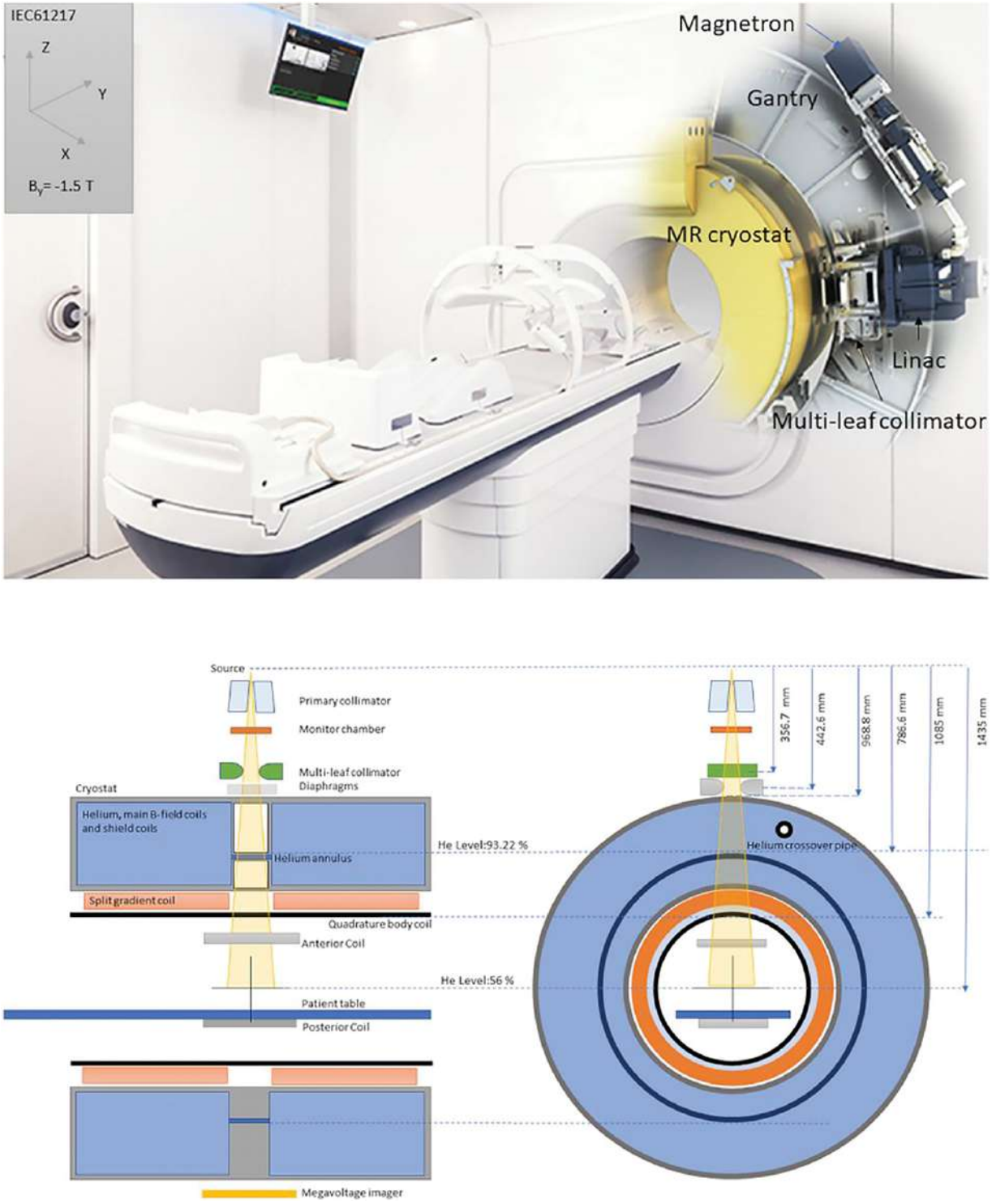

FIGURE 6.25 Elekta Unity MRI-guided linac, consisting of a 1.5-T MRI and 7-MV linac treatment head. MRI, magnetic resonance imaging. (Reprinted from Roberts DA, Sandin C, Vesanen PT, et al. Machine QA for the Elekta Unity system: a report from the Elekta MR-Linac consortium. *Med Phys*. 2021;48[5]:e67-e85. http://creativecommons.org/licenses/by/4.0/.)

Robotic Nonisocentric Treatment Systems

A small X-band (~10,000 MHz) linear accelerator mounted on an industrial robotic arm (Figure 6.26) was first developed for radiosurgery as the CyberKnife system.[54,55] The robotic arm provides the capability for aiming a narrowly collimated x-ray beam with any orientation relative to the target volume. The system uses two ceiling-mounted diagnostic x-ray sources and amorphous silicon image detectors mounted flush to the floor. The treatment is specified by the trajectory of the robot and by the number of monitor units delivered at each robotic orientation. During the patient's treatment, the CyberKnife system correlates live radiographic images with preoperative CT or MRI scans in real time to determine patient and tumor position repeatedly over the course of treatment.

FIGURE 6.26 CyberKnife robotic treatment system. This system is capable of non-isocentric treatment guided by ceiling-mounted stereoscopic x-ray units. (Reprinted from Ding C, Saw CB, Timmerman RD. Cyberknife stereotactic radiosurgery and radiation therapy treatment planning system. *Med Dosim*. 2018;43[2]:129-140. Copyright © 2018 American Association of Medical Dosimetrists. With permission.)

Proton, Heavy-Ion, and Neutron Beam Treatment Units

The first use of proton beams for radiation therapy is credited to Wilson,[56] who in 1946 pointed out the superior depth-dose characteristics provided by protons. Details on the history and development of proton beam radiation therapy (PBRT) machines are provided by Breuer and Smit[57] and DeLaney and Kooy.[58] PBRT is seeing increasing interest worldwide because its depth-dose characteristics show advantages over those of photon beams.[59]

In most existing or proposed proton and light-ion particle treatment facilities, either a *cyclotron* or a *synchrotron* is used to accelerate proton beams to sufficient energy (200-250 MeV) and beam intensity.

Cyclotron

The cyclotron (Figure 6.27) was invented by Ernest Lawrence of the University of California in 1929. It accelerates charged particles such as protons, deuterons, and light ions using a high-frequency, alternating voltage (potential difference) applied across two conducting D-shaped evacuated half-cylinders (Ds). A fixed magnetic field, perpendicular to the top of the two Ds, forces the charged particles to travel in a circular path. The charged particles accelerate only when passing through the gap between the two Ds. The beam spirals out to the edge of the container as the particle speeds increase. At this point, the particle speed approaches the speed of light. Proton beam energies of 200 to 250 MeV are considered adequate for most radiation therapy applications. Beam intensity from the accelerator must be adequate to overcome losses in the beam delivery system and provide tolerable treatment times.

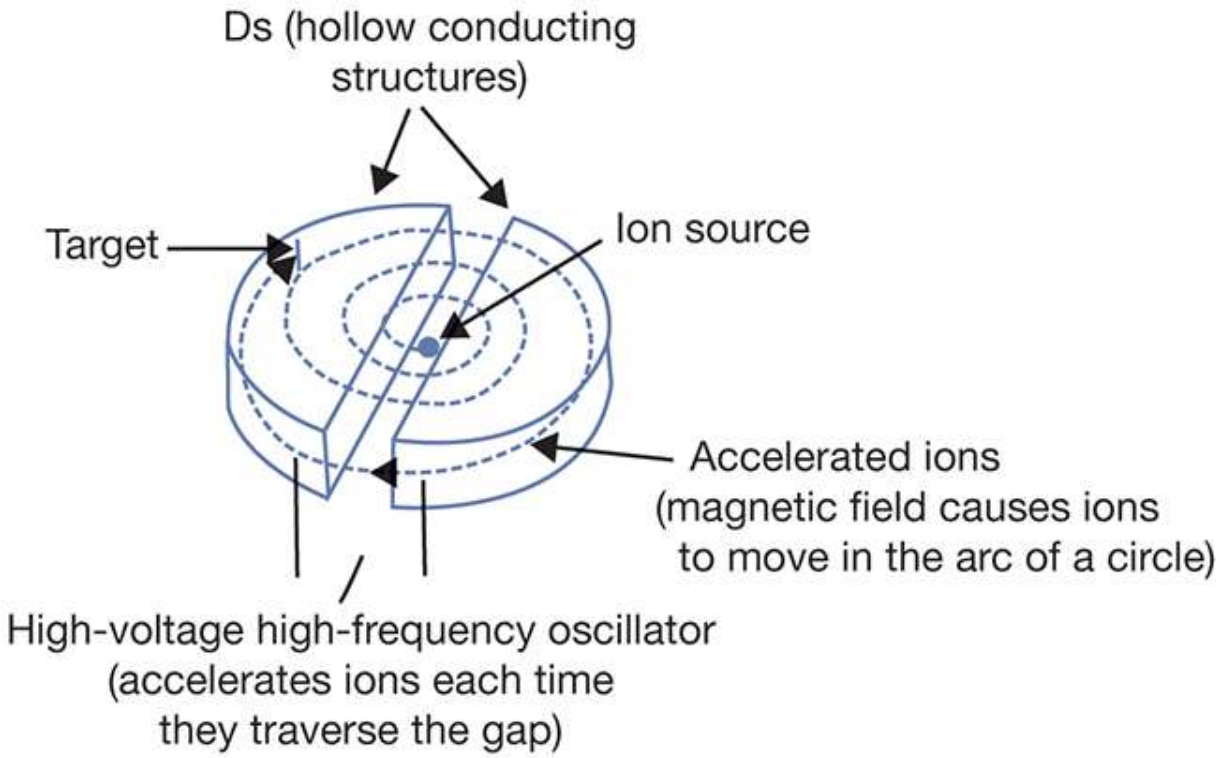

FIGURE 6.27 Schematic drawing showing principles of cyclotron operation. This machine is used for accelerating positive ions and is used clinically to produce proton and neutron beams. Metal half-disks (Ds) have an evacuated center through which the protons can travel. The protons are accelerated by an oscillating electric field operating between the half-disks. A magnetic field perpendicular to the plane of the half-disks confines the charged particles in the half-disks.

Synchrocyclotron and Synchrotron

A *synchrocyclotron* varies either the magnetic field or the frequency of the applied electric field; a *synchrotron* varies both. By increasing these parameters appropriately as the particles gain energy, one can hold their path constant as they are accelerated. This allows the vacuum container for the particles to be a large, thin torus. In reality, it is easier to use some straight sections and some bent sections using multiple bend magnets, thus creating the shape of a rounded-corner polygon. The proton beam facility at Loma Linda University Medical Center (Loma Linda, CA) uses this type of accelerator.[60]

The synchrotron has the advantage of simple energy variability, whereas the cyclotron produces continuous beams with a fixed energy and higher

beam intensity, making their design somewhat simpler. Beam-spreading mechanisms obtain suitable field sizes for radiation therapy by passive modulation (scattering foil) systems or by dynamic pencil-beam spot-scanning systems,[60] which allow dose conformation not only at the distal edge of the tumor but also at the proximal edge. Hall[61] pointed out that there is significant neutron leakage radiation for proton treatment machines that use a scattering foil and recommended moving to the pencil-beam scanning systems.

Proton and Heavy-Ion Treatment Machines

The initial clinical proton systems involved utilization of either physics research systems or commercial systems, which relied on multiroom solutions. Examples of early systems integrated with a hospital facility include multiroom proton centers at Clatterbridge Centre for Oncology, Loma Linda University Medical Center, and Massachusetts General Hospital. Currently, there are approximately 42 proton centers in the United States and 90 worldwide. Although the research systems enabled patient treatments, they did not allow broad-scale deployment of this technology. The commercial multiroom solutions enabled broader deployment of this technology, but the significant initial cost and the size of the operation limited deployment of this type of technology. Single-gantry proton systems reduced the overall cost of proton facility and offered a scale that was easier to deploy.

The first single-room proton solutions included the MEVION S250 Proton Therapy System (Mevion Medical Systems, Littleton, MA) shown in Figure 6.28 and IBA Proteus One (IBA, Louvain-La-Neuve, Belgium). The first Proteus One treatment occurred at Willis-Knighton Cancer Center in Shreveport, Louisiana, in September 2014, and the first Mevion S250 treatment occurred at Washington University in St. Louis, Missouri, in December 2014. This system uses a superconducting synchrocyclotron that is gantry mounted and incorporates image guidance and robotic patient positioning.

FIGURE 6.28 Single-room proton therapy system installed at Washington University. The system consists of a gantry-mounted 250-MeV synchrocyclotron specifically designed (uses

superconducting magnets) for proton therapy (with intensity-modulated proton therapy capabilities, high dose rate, high reliability, and easy maintenance). This photo shows the treatment room, including inner gantry and six-degree-of-freedom robotic couch. (Courtesy of Mevion Medical Systems., Littleton, MA.)

Several heavy-ion (carbon ion) radiation therapy facilities are now available in several centers in Asia and Europe,[15-17,59,62] and the first such facility in the United States will likely start construction in the next few years. Heavy-ion radiation therapy requires beams at much higher energies than proton therapy. For example, a proton beam of 150 MeV can penetrate 16 cm in water. To achieve the same penetration with carbon ions, energy of 3,000 MeV or 250 MeV/nucleon is needed. Synchrotrons are the only available sources for such high-energy ion beams, and they are large, complex machines requiring large facilities and similarly large capital expenditures.

Interest in heavy-ion radiation therapy is due primarily to its combination of two important physical advantages: its depth-dose characteristics and high LET in the Bragg peak region of the beam. For its depth characteristics, the ratio of the Bragg peak dose to the entrance region dose is even larger than for protons. In addition, there is a large increase in the radiation LET in the Bragg peak region of the beam. The combination of these two characteristics results in a potentially unique advantage of providing a high LET region that can be closely conformed to the target volume.

Neutron Therapy Treatment Machines

Modern neutron therapy machines use cyclotrons to accelerate protons or deuterons to energies of about 50 MeV to produce neutron beams with depth-dose characteristics equivalent to those of about 6-MV x-rays.[63] The p,Be (protons accelerated to strike a beryllium target) reaction is used most commonly because protons are much easier to bend around the gantry of an isocentric unit, and thus, the cyclotron can be much smaller and thus less expensive. The only exception is the superconducting cyclotron installed at Harper Hospital (Detroit, MI), which uses the d,Be (deuterons strike beryllium target) reaction.[64] With superconducting technology, the entire cyclotron is small enough to be rotated around the patient on isocentric

rings, thus eliminating the need for bending the deuteron beam around a rotating gantry. In addition, the neutron yield for the d,Be reaction is about 5 times that for the p,Be reaction. More details on the history and development of neutron beam therapy machines are provided in the review by Maughan and Yudelev.[65]

New and Evolving Treatment Machines

There are several other new treatment machine designs that show significant clinical promise.

Biologically Guided Radiotherapy

The functionality of positron emission tomography (PET) has been combined with that of a photon-producing linear accelerator in the RefleXion X1 (RefleXion Medical, Hayward, CA) (Figure 6.29). The goal is to use the PET emission signal as a tumor fiducial to guide radiotherapy in real time in a continuous feedback loop. To achieve this response with high speed while minimizing latency, several technologic innovations have been introduced including high rotational speed (60 rpm) and the design of high-speed MLCs that can move leaves at 100 MHz. The first clinical system was installed at Stanford University. More details about this technology can be found in the article by Shirvani et al.[66]

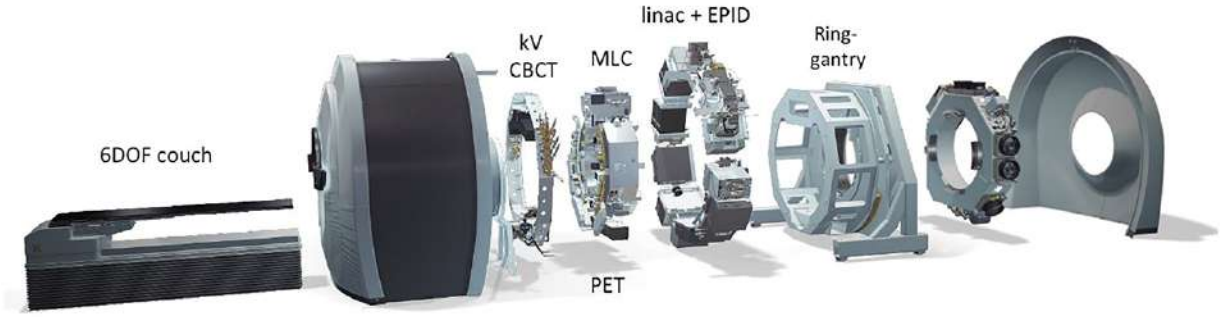

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FIGURE 6.29 A. The RefleXion X1 is designed with components that include kV CBCT, binary MLC, PET detectors, a compact 6 MV linac with MV imaging detectors, and a ring gantry, many of which function at high speeds with minimal latency in order to be capable of targeting a photon-based treatment along the detected paths of PET emission, thereby enabling the target to serve as its own real-time fiducial. B. The system in the treatment room including the six-degree-of-freedom couch. CBCT, cone beam computed tomography; MLC, multileaf collimator; PET, positron emission tomography. (Courtesy of RefleXion Medical. Copyright 2023.)

Very-High-Energy Electron Beams

Several investigators have also pointed out the utility of very-high-energy (VHE) electron beams (150-250 MeV).[67,68] Currently, only national and international laboratories are capable of producing such beams, but development is underway for a clinical system. The review article by Ronga et al provides more details about historical developments and the current status of VHE beams.[69]

Ultra-High-Dose-Rate Radiotherapy

Recent studies in animal models have demonstrated that treatment with ultra-high-dose rate radiotherapy, which is referred to as FLASH radiotherapy, may increase the therapeutic ratio due to normal tissue sparing.[70] For example, animal studies have demonstrated significant sparing of normal tissue in several organs.[71] Dose rates, which are on the order of 40 Gy/s, are much higher than can be produced by current clinical treatment machines. Thus, innovations in machine design are underway in order to facilitate the production of beams with FLASH capability for a variety of particle beams including electrons, photons, and protons[70] outside of large-scale beam lines such as synchrotrons. Access to such technology will enable investigators to probe the underlying biologic and immunologic mechanisms that are leading to the unexpected therapeutic advantage and facilitate the safe translation to clinical use.[72]

SIMULATORS

Conventional Simulator

Details on the development of the *radiation therapy simulator* and the selection, acceptance testing, and QA of conventional radiation therapy simulators are provided in the textbook by Van Dyk.[73] The conventional simulator mimics the functions and allowed motions of a therapy unit and uses a diagnostic x-ray tube to simulate the radiation properties of the treatment beam (Figure 6.30). A simulator allows the beam direction and the treatment fields to be determined to encompass the projection of the target volume. Radiographic visualization of internal structures in relation to external landmarks allows special shielding devices (Cerrobend blocks) to be constructed to help minimize the dose to normal critical structures. Gantry arms are rigid enough to support heavy shielding blocks and

simulated electron cones. Couch widths are similar to therapy-unit couch widths, and operating consoles feature digital displays of parameters and programmable settings for SAD, gantry angles, and field sizes. Older models of conventional simulators were equipped with an x-ray fluoroscopy system consisting of an image intensifier and video camera system to expedite field setup and beam angulations. Modern simulator design has replaced the image intensifier with amorphous silicon technology. The new imagers produce high spatial- and contrast-resolution images that approach film quality, facilitating the concept of filmless radiation oncology departments, and provide CBCT capability. Although this feature allows volumetric imaging on a conventional simulator, they have been nearly completely replaced with CT simulators.

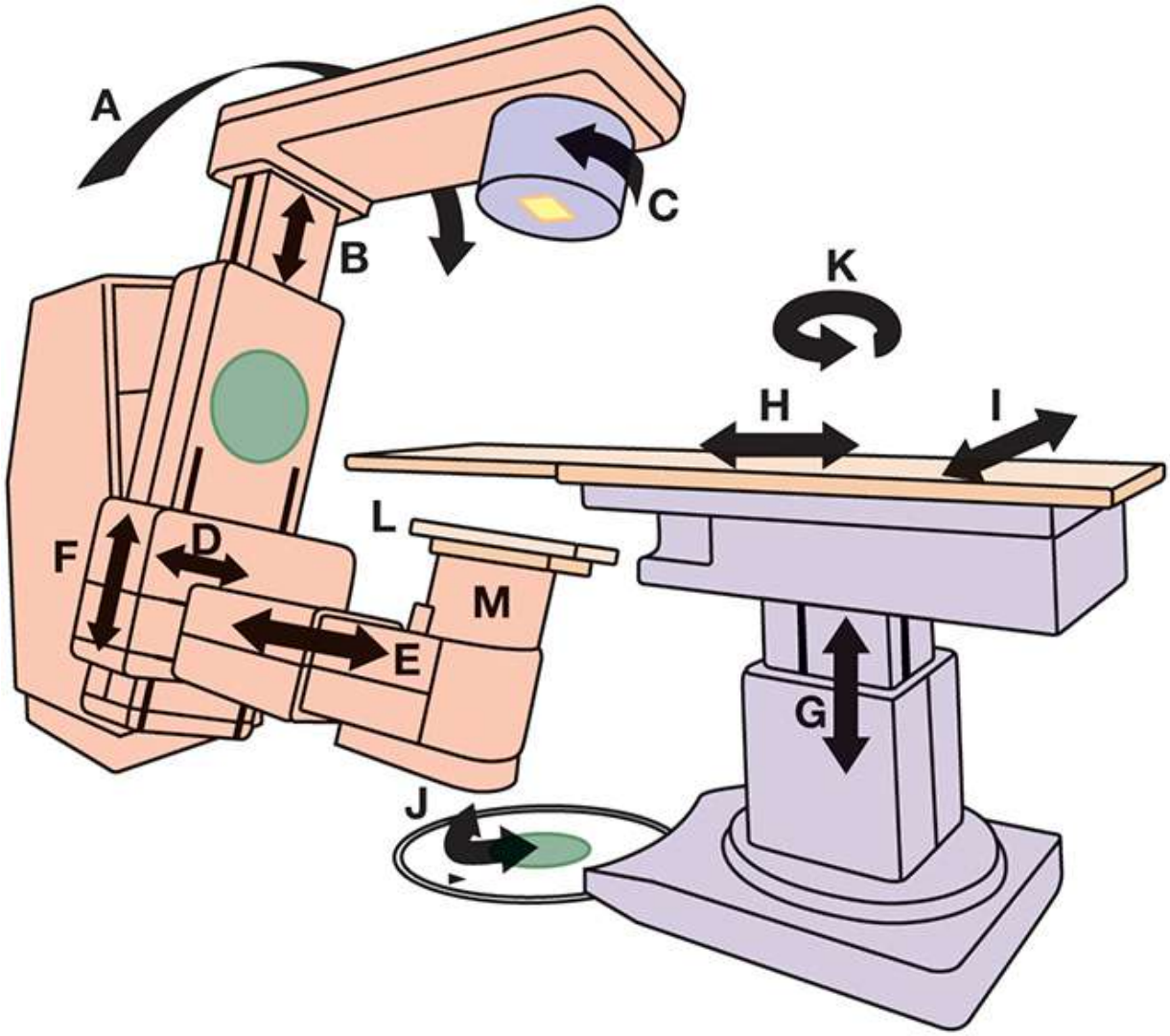


FIGURE 6.30 The basic components and motions of a radiation therapy simulator. A. Gantry rotation. B. Source-axis distance. C. Collimator rotation. D. Image intensifier (lateral). E. Image intensifier (longitudinal). F. Image intensifier (radial). G. Patient table (vertical). H. Patient table (longitudinal). I. Patient table (lateral). J. Patient table rotation about isocenter. K. Patient table rotation about pedestal. L. Film cassette. M. Image intensifier. Motions not shown include field-size delineation, radiation beam diaphragms, and source-tray distance. (From Van Dyk J, Mah K. Simulators and CT scanners. In: Williams JR, Thwaites DI, eds. *Radiotherapy Physics: In Practice*. Oxford Medical Publications; 1993:118. Reproduced with permission of the Oxford Publishing Limited through PLSclear.)

Computed Tomography Simulators

In the 1980s and early 1990s, research led to the integration of a diagnostic CT scanner with what was essentially a 3D treatment planning system, which led to the concept of *virtual simulation*.[74-76] Such a system is now

referred to as a *CT simulator* and consists of a CT scanner, a flat-tabletop patient position–alignment system, including an orthogonal laser system, and a digital interface (Digital Imaging and Communications in Medicine) to a planning system that is equipped with virtual simulation software (Figure 6.31). Modern CT simulation systems incorporate large-bore CT scanners especially designed for radiation oncology, with multislice capability, high-quality laser patient positioning/marking systems, and sophisticated virtual simulation software features. Conventional diagnostic CT scanners are typically equipped with 70-cm-diameter bore, whereas large-bore scanners have openings 80 to 90 cm in diameter. While the CT scanners used for CT simulation tend to be specifically designed for radiation oncology, there has been a steady adoption of technology developed for diagnostic purposes to CT simulators. Most of this technology concentrates on ever-evolving image reconstruction improvements as well as improvements in image acquisition technology. For example, iterative image reconstruction techniques and dual kV acquisition have found application in radiotherapy. Details of the virtual simulation process are discussed in some detail in Chapters 10. More details on CT simulation can be found in the review article by Van Dyk[73] and articles by Mutic et al.[77,78]

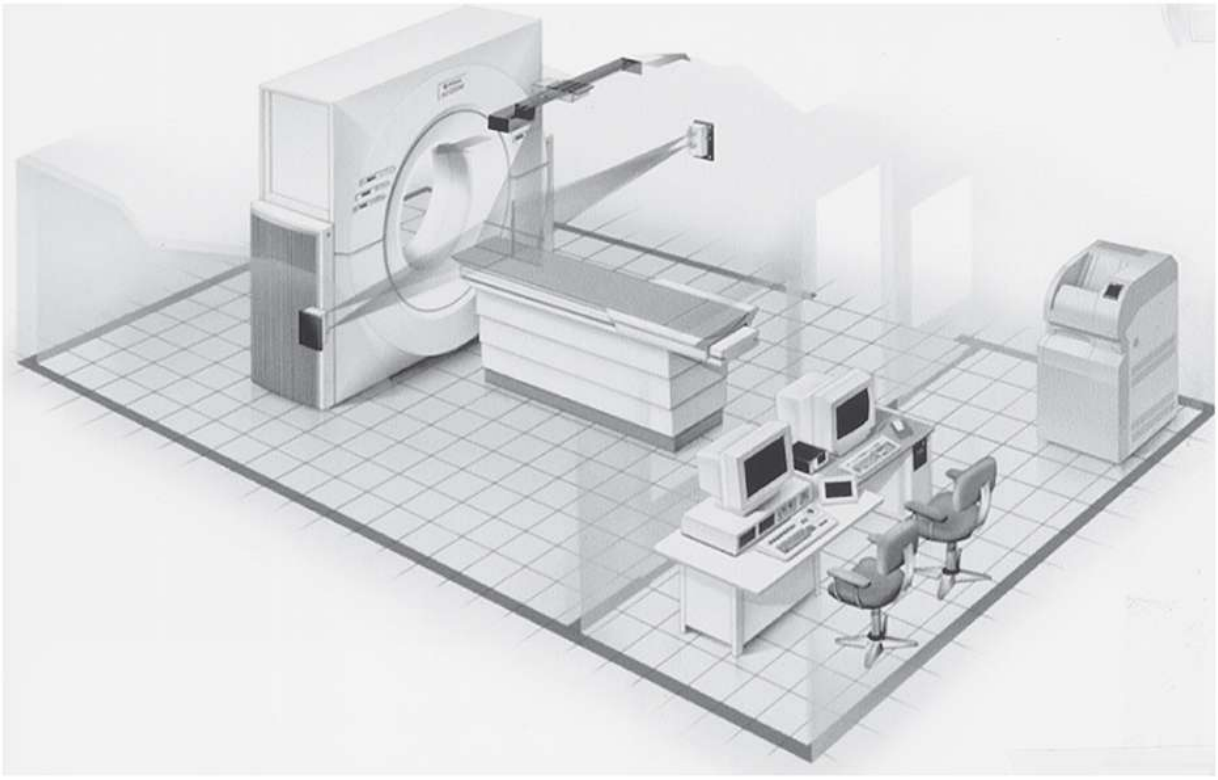


FIGURE 6.31 Typical computed tomography simulation suite showing the scanner, flat-tabletop, orthogonal laser system, virtual simulation workstation, and hardcopy output device.

New and Evolving Simulation Machines

PET/CT simulators and MR simulators have been available for radiotherapy purposes for a while. The adoption of this technology has been relatively modest and is somewhat limited by reimbursement practices and generally good access to these modalities through diagnostic radiology departments. Recent developments in radiotherapy treatment planning based on functional imaging and monitoring of response to therapy may increase the presence of MR- and PET-based simulators.[79,80] However, this will likely need to be facilitated by clinical evidence, which would result in modifications of reimbursement practices to allow broader use of multimodality scanners in radiotherapy departments.

QUALITY OF RADIATION

The penetrability of an x-ray beam, referred to as the *quality* of the beam, is completely specified by its spectral distribution curve (ie, the relative

intensities of photons of various energies), which is the result of fluctuations of tube potential, the bremsstrahlung radiation process, characteristic radiation, and multiple interactions of the incident electrons and the x-ray target. The distribution of the photon energies, including the peak photon energy, in the continuous spectrum is governed solely by the x-ray tube potential. However, the energy of the characteristic photons increases with increasing atomic number of the target element. All other factors being equal, the radiation intensity is proportional to the atomic number of the target element.

Spectral distribution of an x-ray beam can be modified by placing absorbing materials of various thicknesses (ie, filters) in the beam. In general, a filter removes relatively more low-energy photons than high-energy photons, although photons of all energies are removed to some extent. For radiation in the orthovoltage region (except for the absorption edge effect), the lower the energy of the photons, the larger is the total mass attenuation coefficient and therefore the greater is the likelihood that the photon will be absorbed. Thus, the beam emerges from the filter with a larger percentage of high-energy photons than it had on entering the filter. The beam has a greater penetration power and is said to have been "hardened" by the filter. The quality of an x-ray beam improves with increasing tube potential and with increasing thickness and atomic number of the filter.

A specification of beam quality based entirely on a spectral distribution is too cumbersome for radiation therapy. The usual method of specifying beam quality in superficial and orthovoltage therapy is to list the HVL and the accelerating potential. For MV beams, only the maximum energy of the electrons striking the x-ray target typically is used. The *homogeneity coefficient* denotes how homogeneous an x-ray beam is with respect to its photon energies. It is defined as the ratio of the first HVL to the second HVL. As the filtration is increased, the exposure rate decreases; therefore, there is a practical limit of filter thickness in orthovoltage therapy with a given combination of kilovolts, milliamperes, and treatment distance. In certain situations, it is convenient to express the quality of the x-ray beam in terms of an "equivalent energy," which can be derived from knowledge of the HVL. The type of x-ray beam that is used in radiation therapy is always heterogeneous; however, the x-ray beam can be considered to have

an *equivalent energy* of a monoenergetic x-ray beam that has a HVL equal to the measured HVL of the heterogeneous beam.

RADIATION EXPOSURE

In 1928, at the Second International Congress of Radiology, the ionization of air, called *exposure*, was adopted as the measurable effect of radiation of a photon beam.[81] As the beam passes through a material, it creates ion pairs via the ionization process. In air, these ion pairs have some mobility and can be collected by applying an electric field across the air. The number of ion pairs collected is a measure of the quantity of radiation passing through the air.

The *roentgen* (R), the unit for exposure, also was defined at the 1928 Congress. The definition has been modified slightly by subsequent congresses, but the basic concept remains the same. The roentgen is that amount of x- or γ-radiation that causes the associated corpuscular emission per 0.001293 g of air to produce, in air, ions carrying one electrostatic unit of charge of either sign. The value 0.001293 g is the mass of 1 cm^3 of air at 0 °C and 760 mm Hg pressure; "associated corpuscular emission" refers to the Compton and pair-production electrons set in motion by the interactions between the incident photons and the air molecules. By conversion of units, the roentgen can be expressed as follows:

$$1R = 2.58 \times 10^{-4}\ C/kg\ of\ air$$

With the advent of SI units, the roentgen no longer is used as a special name for a radiation unit, and the SI unit for exposure is Coulombs per kilogram (C/kg), which is equivalent to approximately 3,876 R (Table 6.2).

The condition of electronic equilibrium must exist for the definition of the roentgen to be satisfied (Figure 6.32). According to the definition, the electrons produced in a specified volume must spend all of their energies by ionization in air, and the total charge must be measured. However, because some electrons produced inside the specified volume create ion pairs outside the volume and some electrons produced outside the volume contribute ionization inside the specified volume, the gain and loss of ion pairs must be the same for the definition of the roentgen to be satisfied.

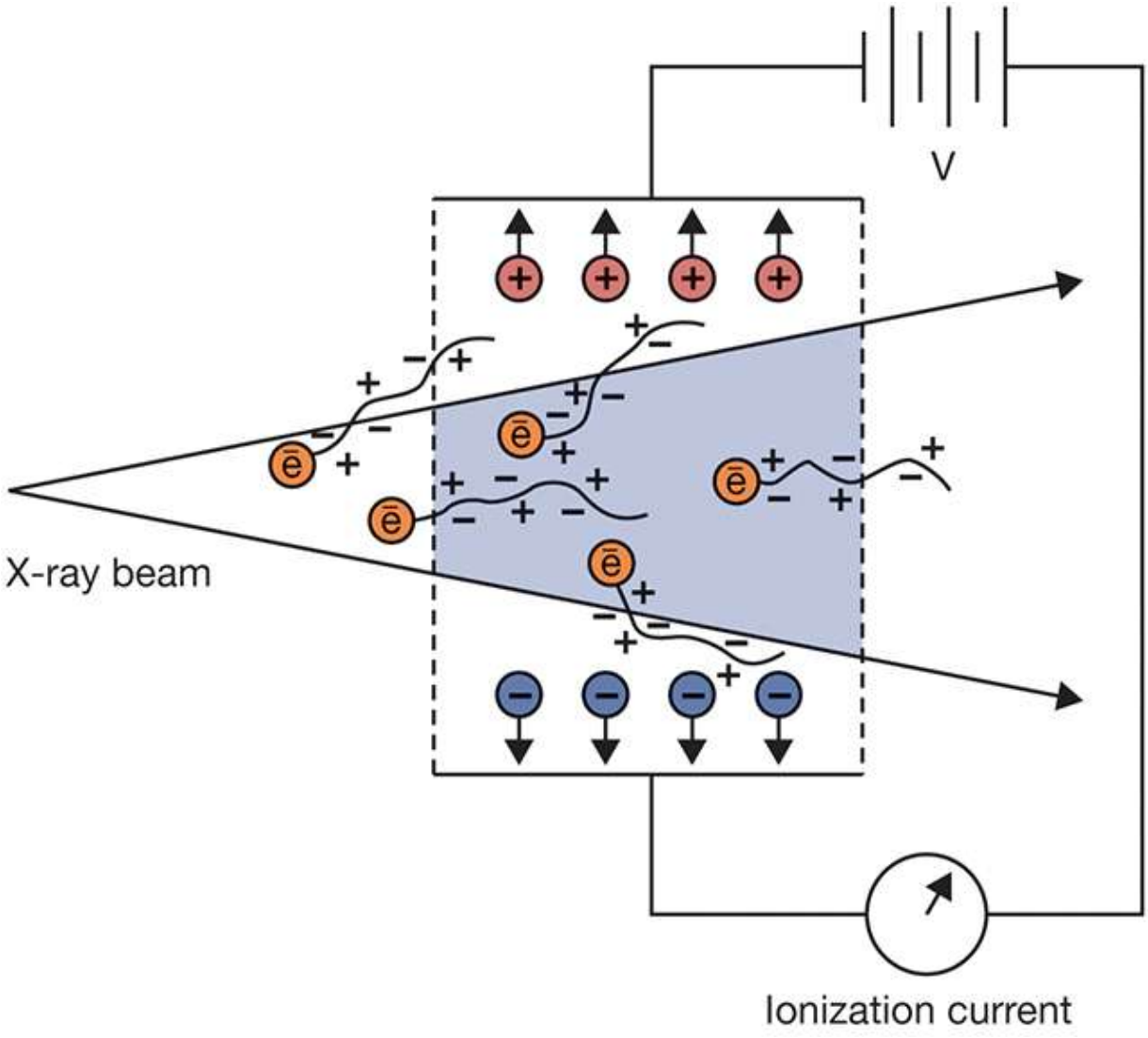


FIGURE 6.32 Schematic illustrating electronic equilibrium. (Reprinted with permission from Khan FM. *The Physics of Radiation Therapy*. 2nd ed. Williams & Wilkins; 1994.)

The free-air ionization chamber is used to measure exposure directly in roentgens.[1] It is designed to collect all the ions produced in a defined volume by the radiation beam and is used primarily by standards laboratories. Free-air chambers are bulky and too complicated to use for routine measurements. Instead, small ionization chambers called *thimble chambers* are typically used to measure exposure. The chamber measures the ionization produced, which is converted to exposure in roentgens by applying an exposure calibration factor, N_x, traceable to the National Institute of Standards and Technology (Gaithersburg, MD). Thimble

chambers are designed for use at specific energies; the thickness of the chamber wall is equal to the maximum electron range (electronic equilibrium established). If they are used at higher energies, at which the electron range is greater, an added wall thickness or *buildup cap* must be used.

To determine the exposure rate from an x-ray or γ-ray machine, an exposure-calibrated thimble chamber (with appropriate wall thickness) and connected to an *electrometer* is placed at the beam center, in air, at right angles to the beam's central axis and at the point where the exposure rate is to be specified. The field size for which the exposure rate is to be measured is set, and the radiation machine is turned on for a specified time, T, to achieve a reading, M, on the connected electrometer. The reading is corrected for *temperature and atmospheric pressure*, *timer error*, *stem effect*, and *ion-recombination effects*. The therapy machine exposure rate, X, is given in roentgens per minute by the following equation:

$$\dot{X} = \frac{M \cdot N_{\mathrm{x}} \cdot C_{\mathrm{tp}} \cdot C_{\mathrm{st}} \cdot C_{\mathrm{s}}}{T + \alpha}$$

where M is the raw ionization chamber reading, N_{x} is the exposure calibration factor obtained from a standards laboratory, C_{tp} is the temperature and pressure correction factor, C_{st} is the stem effect correction factor, C_{s} is the ion-recombination correction factor, T is timer (minutes) or monitor unit setting, and α is the timer error. The temperature-pressure correction factor C_{tp} is given by the following equation:

$$C_{\mathrm{tp}} = \left(\frac{t + 273.16}{295.16}\right)\left(\frac{760}{p}\right)$$

The timer error α is given by the following equation:

$$\frac{M_1}{T+\alpha} = \frac{M_2}{T+n\alpha}$$

where M_1 is the instrument reading for a single long exposure of T, M_2 is the instrument reading for n short exposures of total time T, and α is the timer error (monitor end effect for linacs) for a single exposure.[82]

Beyond 3 MeV, the roentgen cannot be measured accurately, and thus calibrations of radiation therapy machines at these higher energies are performed using an exposure-calibrated ionization chamber such as a Bragg-Gray cavity, and the ionization readings are converted to absorbed dose as discussed in the following section.

ABSORBED DOSE

In 1953 the ICRU introduced the concept of *absorbed dose* and defined its unit, the *rad*.[81] Before its definition can be presented, the reader must understand the concept of dose absorption. As a beam of radiation passes through an absorbing medium, it interacts with it in a two-stage process. The first step occurs when energy carried by the photons—the indirectly ionizing particles—is transformed into kinetic energy of high-speed electrons; the second step occurs as these electrons—the directly ionizing particles—are slowed down and deposit their energy in the medium.

Kerma, an acronym for "kinetic energy released in the medium," represents the transfer of energy from the photons to the directly ionizing particles (step 1). The subsequent transfer of energy from the directly ionizing particles to the medium (step 2) is represented by the absorbed dose and is defined in terms of the energy deposited by the radiation beam as it passes through the medium. The relationship between kerma and absorbed dose is illustrated in Figure 6.33.

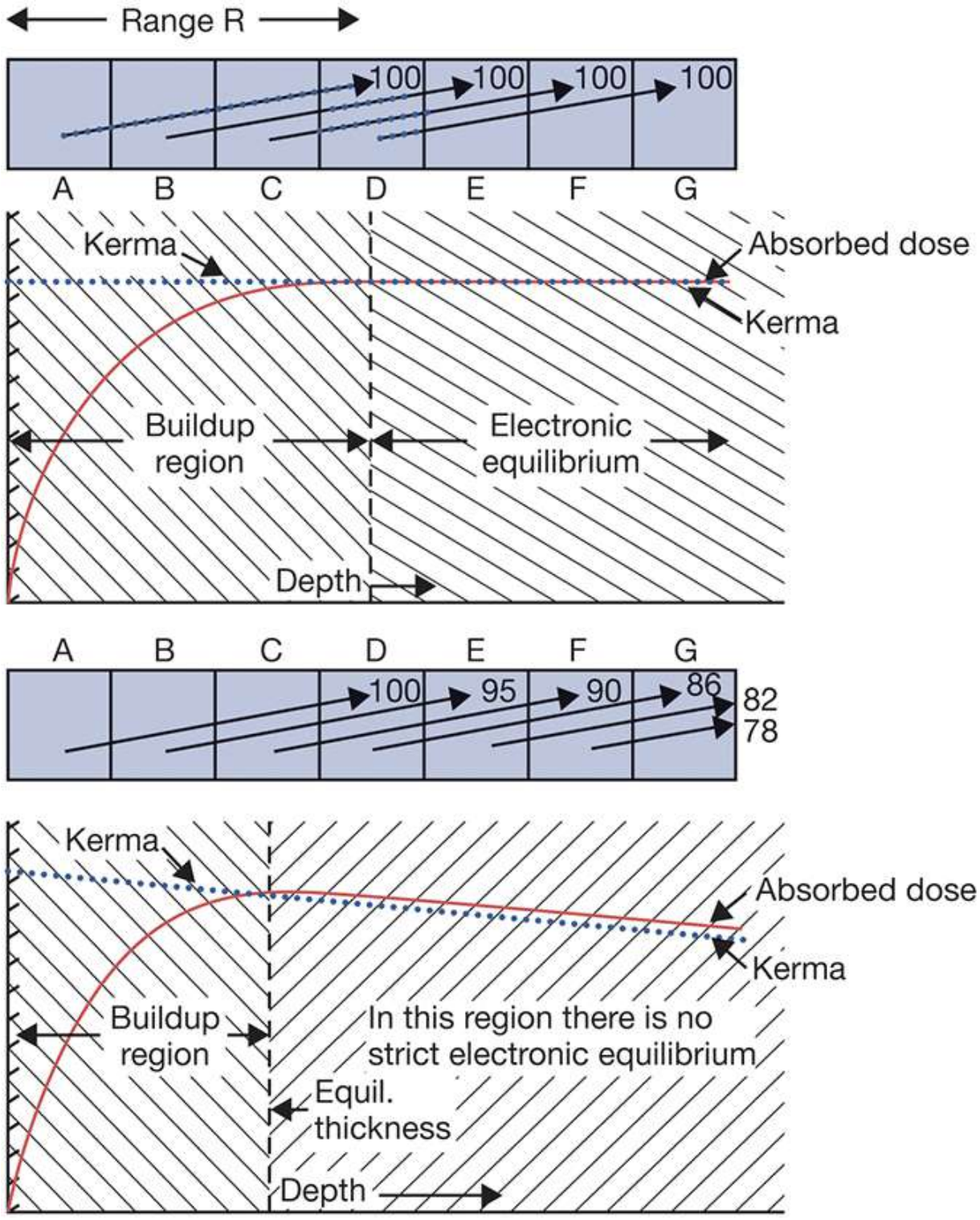


FIGURE 6.33 Graphs showing schematic relationship of kerma and absorbed dose. (From Johns HE, Cunningham JR. *The Physics of Radiology*. 4th ed. Charles C Thomas; 1983:222. Courtesy of Charles C Thomas Publisher, Springfield, Illinois.)

The *rad* represents the absorption of 0.01 J/kg of the absorbing material (1 rad = 0.01 J/kg). The rad now has been replaced with the SI unit for absorbed dose (1 J/kg) given the special name of *gray* (*Gy*) (Table 6.2). By conversion of units, the gray can be expressed as follows:

1 Gy = 1 J/kg= 100cGy = 100rad

Determination of Absorbed Dose

It is difficult to measure absorbed dose directly, but two direct methods—*calorimetry* and *Fricke dosimetry*—are available in some laboratories. Neither method is particularly practical nor widely used, and the reader is referred to the literature for more details.[83] Instead, a simpler, indirect method using an exposure-calibrated ionization chamber is used to determine absorbed dose.

Absorbed Dose Calculation From Exposure Measurement

For photon energies of ^{60}Co and lower, an ionization chamber having an exposure calibration factor assigned by an appropriate national calibration facility (eg, a dosimetry calibration laboratory accredited by the National Institute of Standards and Technology or the AAPM) can be used to measure exposure in air as described in the section "Radiation Exposure." Absorbed dose then can be calculated from the exposure as explained here. The energy deposited in a fixed mass of air from a known exposure can be calculated because it is known that an exposure of 1 R creates a finite number of ion pairs per unit mass of air (ie, 1.61×10^{15} ion pairs per kilogram of air) and that the mean energy required to create an ion pair in air (denoted by W) is equal to 33.97 eV per ion pair. When these values are used, the relationship between the exposure, X, and the dose to air, D_{air}, is given by the following expression:

$$D_{air}\,(\text{rad}) = 0.876\left(\frac{\text{rad}}{R}\right)\cdot X\,(R)$$

The *dose in free space*, D_{fs}, is defined as the dose at the center of a small mass of phantom-like material just large enough to provide electronic equilibrium (Figure 6.34) and can be derived from D_{air} using the ratio of the mass energy–absorption coefficients (u_{en}/ρ) and an attenuation correction factor, A_{eq}, that accounts for the photon attenuation in the small mass of phantom-like material:

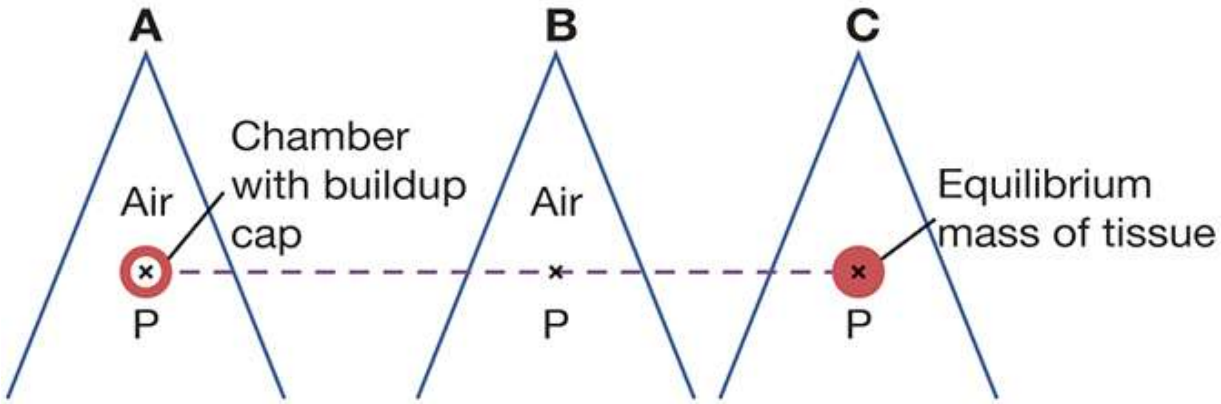


FIGURE 6.34 Schematic illustrating ionization measurement in air to determine dose in free space. (Reprinted with permission from Khan FM. *The Physics of Radiation Therapy*. 2nd ed. Williams & Wilkins; 1994.)

$$D_{fs} = \left[0.876 \frac{\mu_{en}\rho_{med}}{\mu_{en}\rho_{air}} \right] \cdot X \cdot A_{eq}$$

The term in brackets is called the *f-factor* or the *roentgen-to-rad conversion factor* and is represented as f_{med}, giving the dose in free space as follows:

$$D_{fs} = f_{med} \cdot X \cdot A_{eq}$$

Values of f_{med} are shown in Figure 6.35 over the energy range commonly used in radiation therapy. Notice that the *f*-factor is a function of the medium and the energy of the photon beam. Typical values of A_{eq} are 0.989 and 1.00 for ^{60}Co and 250-kV energies, respectively.

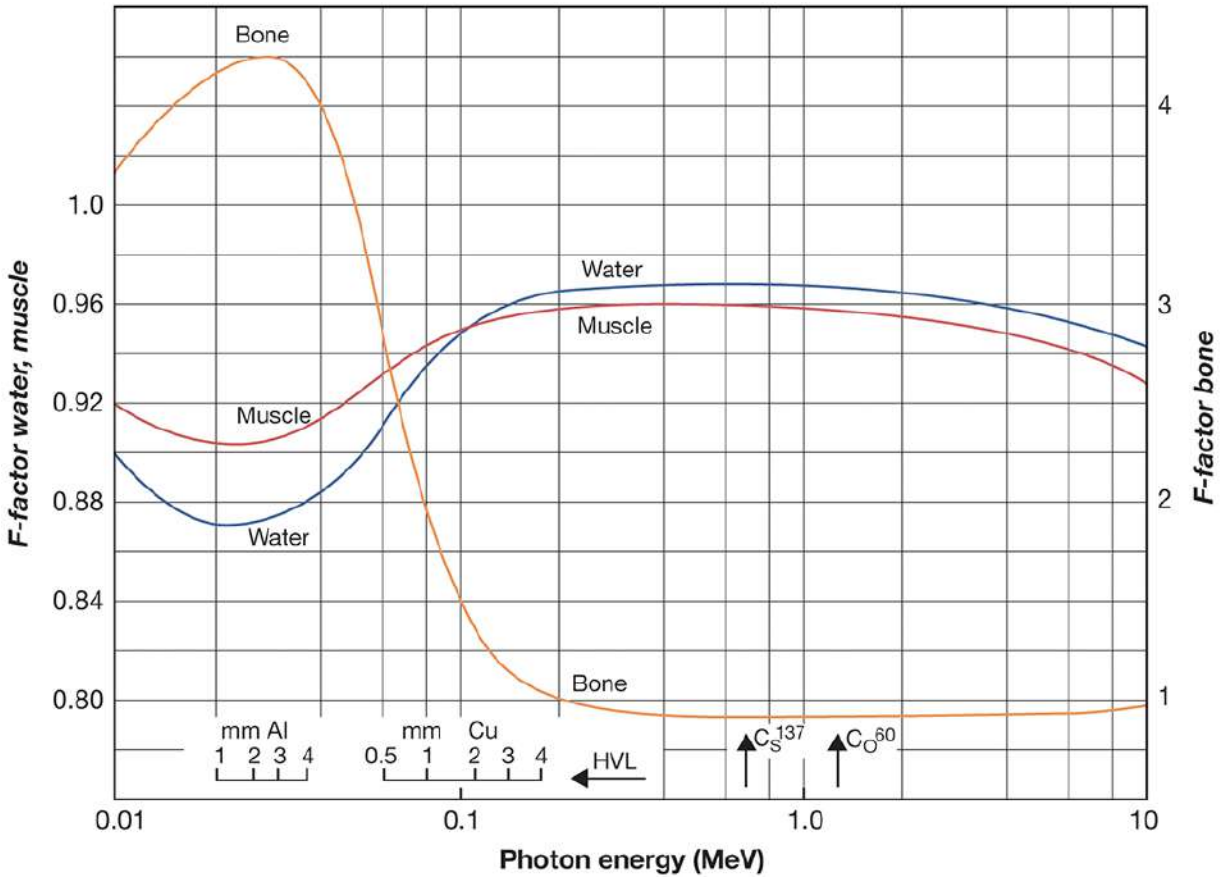


FIGURE 6.35 The roentgen-to-rad conversion factor for bone, muscle, and water as a function of photon energy. (From Johns HE, Cunningham JR. *The Physics of Radiology*. 4th ed. Charles C Thomas; 1983:287. Courtesy of Charles C Thomas Publisher, Springfield, Illinois.)

An in-air calibration procedure is performed as follows. The calibrated ion chamber (with wall thick enough to ensure electronic equilibrium) is placed in air with its sensitive volume on the central axis of the beam and its stem at right angles to the beam direction. The center of the chamber most often is placed at a distance from the source (or target) equal to the nominal SSD of the machine plus the buildup depth. A standard field size is set, usually 10 × 10 cm, using either movable collimators or the standard treatment applicator. An exposure is made for a known time or number of monitor units. The ionization chamber reading is converted to units of Gy/min at the depth of the maximum dose within a phantom, d_{med}, using the following equation:

$$\dot{D}_{\text{med}} = \frac{M \cdot N_{\text{x}} \cdot C_{\text{tp}} \cdot C_{\text{st}} \cdot C_{\text{s}} \cdot A_{\text{eq}} \cdot f_{\text{med}} \cdot \text{TAR}\left(d_{\text{max}}\right)}{T + \alpha}$$

where M, N_{x}, C_{tp}, C_{st}, C_{s}, A_{eq}, f_{med}, T, and α are used as defined earlier. The term TAR(d_{max}) represents the tissue-air ratio (TAR) at the depth of maximum dose (ie, the *backscatter* or *peakscatter factor*) and converts the dose in free space to the dose in a phantom at the depth of maximum dose. This parameter is discussed in more detail later. The preceding equation can be rewritten as follows:

$$\dot{D}_{\text{med}} = \dot{X} \cdot f_{\text{med}} \cdot A_{\text{eq}} \cdot \text{TAR}(d_{\text{max}})$$

and

$$\dot{D}_{\text{med}} = \dot{D}_{\text{fs}} \cdot \text{TAR}(d_{\text{max}})$$

This method is also valid when the measurements are made with the exposure-calibrated ion chamber embedded within a medium, such as a water phantom. In that case, the TAR(d_{max}) term is not included in the calculation, and the A_{eq} factor is replaced by a displacement factor, A_{m}. The numerical value of A_{m} is very close to that of A_{eq}, and for exposure measurements made within a water phantom, the dose rate is given by the following expression:

$$\dot{D}_{\text{med}} = \dot{X} \cdot f_{\text{med}} \cdot A_{\text{m}}$$

Absorbed Dose Calculation from Bragg-Gray Cavity Ionization Measurement

For energies above the level of ^{60}Co, exposure calibration factors are not available from the standards laboratories because of measurement limitations. In 1983, the AAPM introduced a protocol for the calibration of high-energy photon and electron beams that was based on *Bragg-Gray cavity theory* and allowed one to calculate dose directly from ion chamber

measurements in a medium for energies above the level of ^{60}Co.[84] The protocol updated physical parameters and procedures for calibration and measurement and accounted for the different phantom materials (eg, plastic and water) used for calibration and differences in ion chamber design and construction. The protocol introduced the *cavity-gas calibration factor*, N_{gas}, which is related to the ion chamber's ^{60}Co exposure calibration factor, N_x, and is used in conjunction with restricted stopping power ratios, $L- / \rho$, for the radiation beam in question to convert the ionization chamber reading to absorbed dose using the following expression:

$$D_{med} = M \cdot N_{gas} \cdot \left(\bar{L}/\rho\right)_{gas}^{med} \cdot P_{ion} \cdot P_{repl} \cdot P_{wall}$$

where M is the raw ionization chamber reading per monitor unit corrected for temperature and pressure, P_{ion} is the ion-recombination correction factor, P_{repl} is a correction factor for replacement of phantom material by the ionization chamber, and P_{wall} is a correction factor to account for ionization chamber wall composition.

In 1999, the AAPM published a new protocol (TG-51) for the calibration of high-energy photon and electron beams.[85] A practical implementation guideline was published in 2022.[86] This protocol uses ion chambers with absorbed-dose-to-water calibration factors, $N^{Co\text{-}60}_{D.W}$, which are traceable to national primary standards via the ^{60}Co standard. The absorbed dose to water D_W^Q at the point of measurement of the ion chamber placed under reference conditions is given by the following equation:

$$D_W^Q = M \cdot k_Q \cdot N_{D,W}^{Co\text{-}60}$$

where Q is the beam quality of the clinical beam, M is the fully corrected ion chamber reading, and k_Q is the *quality conversion factor* that converts

the calibration factor for a ^{60}Co beam to that for a beam of quality Q. An addendum to TG-51 was published in 2014 with updated quality conversion factor data.[87] The protocol is designed to be a simplification of the AAPM's TG-21 protocol in the sense that large tables of stopping power ratios and mass energy–absorption coefficients are no longer needed, and the user does not need to calculate any theoretical dosimetry factors.[88-90]

Other Dosimetry Methods

Thermoluminescent Dosimetry

Certain crystalline materials exhibit a phenomenon known as *thermoluminescence*. When a crystal capable of thermoluminescence is irradiated, a small portion of the energy absorbed is stored in the structure of the crystal lattice. If the material is heated, the energy is released in the form of visible light. Several thermoluminescent phosphors are available, but lithium fluoride, with an effective atomic number of 8.2, is the most commonly used.

The physical theory of thermoluminescent dosimetry (TLD) can be explained as follows. In the individual atom, electrons occupy discrete energy levels. However, in the crystal lattice, the electronic energy levels are perturbed by mutual interactions between atoms, giving rise to energy bands, so-called *allowed energy bands* and *forbidden energy bands*. Impurities in the crystal create energy traps in the forbidden bands, allowing metastable states to exist; for example, when the phosphor is irradiated, some of the electrons in the valence band (ground state) receive sufficient energy to be raised to the conduction band. If there is an instantaneous emission of light, the phenomenon is called *fluorescence*. If an electron in the trap requires energy to get out of the trap and return to the valence band, the emission of light is called *phosphorescence*. If the emission of light is slow at room temperature but can be sped up with heating, the process is called *thermoluminescence*.

Thermoluminescent dosimeters must be calibrated before they can be used for measuring an unknown dose. Because the response of the thermoluminescent material is affected by its radiation and thermal histories, the material must be annealed to remove residual effects. The standard preirradiation annealing procedure for lithium fluoride is 1 hour of

heating at 400 °C and 24 hours at 80 °C. More details can be found in the review article by DeWerd et al[91] and in AAPM Report TG-191.[92]

Optically Stimulated Luminescence Dosimetry

Optically stimulated luminescent dosimeters (OSLDs) are composed of carbon-doped aluminum oxide (Al_2O_3) with an effective atomic number of 11.28, and parallel TLDs in many ways. Not only are they passive dosimeters that are small in size but the underlying physical process for recording dose is also caused by charge trapping in electron-hole pairs, which can be read out by recombining the traps via optical rather than thermal stimulation. OSLDs also require a careful calibration process to account for dosimeter-specific sensitivity variations. Due to the efficiency of the overall readout workflow, which is on the order of minutes versus hours for TLDs, OSLDs have become the dominant method of in vivo patient dosimetry in many clinics. Some disadvantages include the fact that they are manufactured by a single vendor and require a light-proof encasing. More details can be found in AAPM Task Group Report 191.[92]

Film Dosimetry

When an x-ray film is exposed to ionizing radiation, the exposed silver bromide crystals form a latent image. In the film development process, the affected crystals cause a darkening of the film, and the unaffected crystals leave the film clear. The degree of blackening of the film is proportional to the energy absorbed and is measured by determining the optical density with a densitometer. The optical density is defined as follows:

$$\mathrm{OD} = \log(I_0/I_T)$$

where I_0 is the amount of light detected without the film in place and I_T is the amount of light detected with the film in place. For radiation dosimetry, the net optical density is obtained by subtracting the densitometric reading for the base fog (clear portion of the film) from the measured optical density. Most films are exposed to yield an optical density between 1.3 and 1.7 for optimal viewing.

A plot of net optical density as a function of radiation exposure or dose is called the *sensitometric curve* or the *Hurter-Driffield (H-D) curve*. If the curve is nonlinear, appropriate corrections must be applied to convert net optical density to absorbed dose.

The use of film is a relatively straightforward method of dosimetry for electron beams, but it must be done with extreme care in photon dosimetry. The problem is that the photoelectric effect depends on Z^3 ($Z_{silver} = 47$), and the film emulsion strongly absorbs radiation below 100 kV. A concise review of radiographic film dosimetry can be found in the article by Das.[93] Radiographic film has been replaced by radiochromic film in many countries where film processors have been discontinued in radiology departments following adoption of digital imaging.

Radiochromic Film Dosimetry

Radiochromic film consists of a thin (7-23 mm), radiosensitive, colorless leuco dye bonded to a 100-mm-thick Mylar base. Radiochromic films are colorless before irradiation and turn deep blue when irradiated without physical, chemical, or thermal processing. The film is approximately tissue equivalent, integrates simultaneously at all measurement points, and has a high spatial resolution (>1,200 lines/mm). It shows a stable, reproducible response if protected from ultraviolet light, unstable temperatures, and humidity. Because radiochromic dye is an aromatic hydrocarbon, like plastic scintillators, it has an energy response superior to that of diodes and comparable with TLD. Interest in radiochromic film as a quantitative dosimeter has been stimulated by the appearance of a 4-fold more sensitive film (model MD-55), which extends its response down to the 5-Gy level. More details on radiochromic film dosimetry are given in AAPM Report TG-235.[94]

Diode Dosimetry

Semiconductor diodes offer many advantages for clinical dosimetry, including high sensitivity, real-time readout, robustness, and independence of air pressure. Most semiconductor diodes are made from silicon, which is either *n* type (silicon doped with group V material, such as phosphorus) or *p*

type (silicon doped with group III material, such as boron). To form a diode detector, a *p*-*n* junction must be created.

The physical theory of semiconductor dosimetry can be explained as follows. During irradiation, electron-hole pairs are created both within and outside the depletion region in the body of the diode detector. The charge carriers are swept across the depletion region and collected rapidly under the action of the electric field that exists across it. In this way, a current is generated, flowing in the reverse direction to normal diode current flow, which can be measured and related to absorbed dose.

Dosimetry diodes are operated without an external reverse bias voltage and connected via cable to a simple electrometer. Details on their use for in vivo dosimetry are provided in AAPM Report 87.[95] Calibration of diodes typically is performed by comparison of readings against an ion chamber in a standard setup to establish a diode calibration factor for absorbed dose to water and the establishment of a series of correction factors to account for calibration differences when measurements are performed under various experimental conditions. Typical concerns are energy dependence, temperature sensitivity, directional dependence, and radiation damage. Each radiation therapy center should establish the responses of their diodes under the various conditions encountered and monitor them as the cumulative dose to the diodes' increases. Frequency of checks should be adjusted according to the frequency of use of the diodes and the variability encountered. More details on diode dosimetry are given in the article by Zhu and Saini.[96]

Metal Oxide Semiconductor–Field Effect Transistor Dosimetry

Metal oxide semiconductor–field effect transistors represent another example of a semiconductor dosimeter. Originally developed for space dosimetry, the operation is based on the buildup of charge in the silicon oxide transistor gate created by ionizing radiation. The reader is referred to the article by Cygler and Scalchi[97] for more details on this type of dosimeter.

Plastic Scintillation Dosimetry

In response to dose deposited by radiation, some plastic materials (eg, polystyrene) emit light that is linearly proportional to energy and independent of photon or electron energy above 125 keV. In the energy range where Compton interactions dominate, such plastic scintillators are also tissue equivalent. As a result, scintillating dosimeters require no correction factors when used for photon or electron beam dosimetry. The emitted light must first be collected by coupling the scintillator to an optical fiber and then quantified using a photomultiplier tube. Because optical fibers have an index of refraction that is higher than that in vacuum, Cherenkov light can be generated by electrons traveling faster than the speed of light. Such sources of optical noise degrade the light signal and must therefore be measured and removed using various strategies. Due to the direct relationship between light intensity and dose as well as the small size of a scintillation dosimeter (eg, 1 mm in diameter), it is well suited for small-field measurements, which are particularly challenging. The reader is referred to the article by Beaulieu and Beddar for more details on this dosimeter and its clinical applications.[98]

Polymer Gel Dosimetry

Gel dosimetry is based on quantifying the effects of radiation-induced chemical changes occurring within some volume of material filled with an aqueous gel matrix. The degree of chemical change in the gel is related to dose. The dose-dependent changes are determined by imaging techniques, including MRI, CT, and optical CT. Hence, gel dosimetry has the potential to provide full 3D dosimetry throughout the volume of the irradiated gel dosimeter.

For example, one form of this method exploits the radiation-induced free-radical chain polymerization of acrylic monomers dispersed in an aqueous gel. When irradiated, discrete, microscopic regions of cross-linked polymer are formed, the concentration of which is proportional to radiation dose. The water proton nuclear MR relaxation rates in the gel are strongly affected by local changes in the polymer molecular structure and dynamics; thus, the distribution of radiation dose may be visualized and quantified with high resolution using MRI. Because the polymer microparticles scatter

light, the dose distribution can also be visualized in the transparent gel as a dose-dependent 3D optical turbidity and read by optical CT.

Unfortunately, gel dosimetry, while having the potential for tissue-equivalent 3D dosimetry for almost three decades, has not come into common clinical use, as it has proven too difficult to use in the clinic setting.[99] Research continues in gel dosimetry, as there is clearly a need for a robust 3D high-resolution dosimetry system.[99,100] Recent publications indicate that these research efforts may result in viable clinical and commercial solutions.[101]

DOSIMETRY PARAMETERS

Percentage Depth Dose

Percentage depth dose (*PDD*) can be understood by reference to Figure 6.36. It is the ratio, expressed as a percentage, of the absorbed dose on the central axis at depth d to the absorbed dose at the reference point d_0. PDD is given by

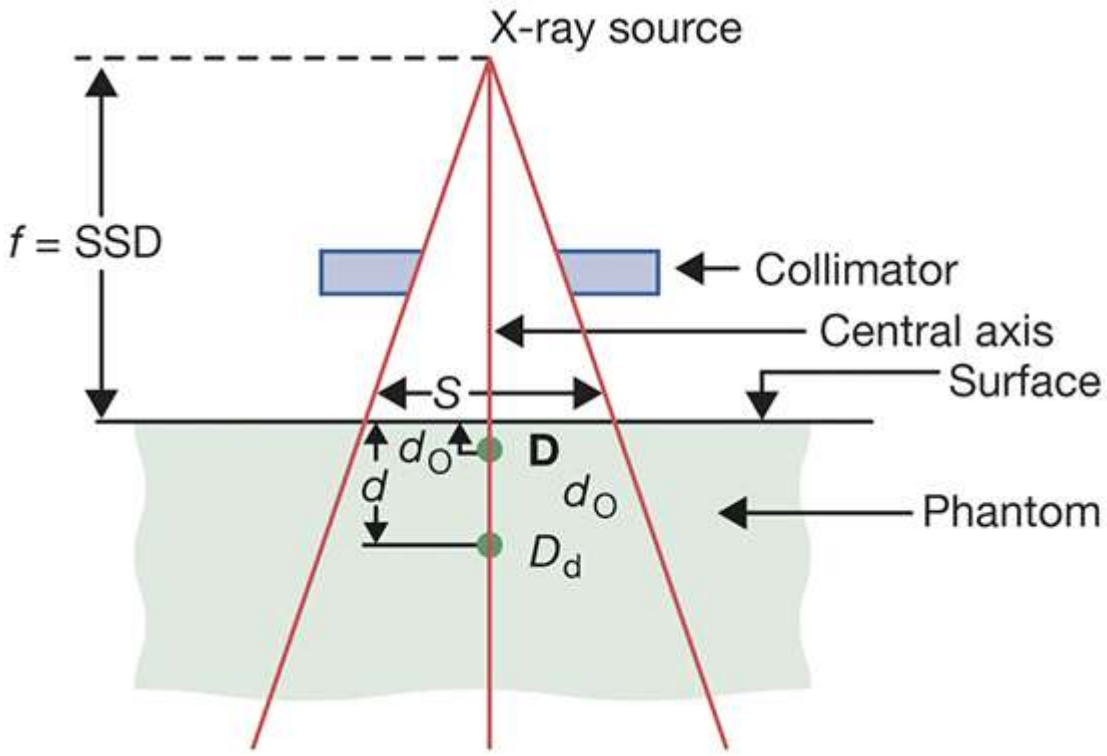


FIGURE 6.36 Schematic drawing illustrating definition of percentage depth dose, where d is any depth and d_0 is the reference depth, usually d_{max}.

$$\mathrm{PDD}\left(d, d_0, S, f, E\right) = \frac{D_d}{D_{d_0}} \times 100$$

The functional symbols have been inserted in the expression to make it clear that the PDD is affected by a number of parameters, including d, d_0, field dimension S, source-to-surface distance f, and radiation beam energy (or quality) E. S refers to the side length of a square beam at a specified reference depth. Nonsquare beams may be designated by their equivalent square. Field shape and added beam collimation also can affect the central axis depth-dose distribution. Photon-beam PDD increases with increasing energy, SSD, and field size. Figure 6.37 shows that the depth of the 50th percentile increases from approximately 14 cm for 4-MV x-rays to nearly 23 cm for 25-MV x-rays. The depth of the maximum dose varies from about 1 cm for 4-MV x-rays to >3.5 cm for 25-MV x-rays.

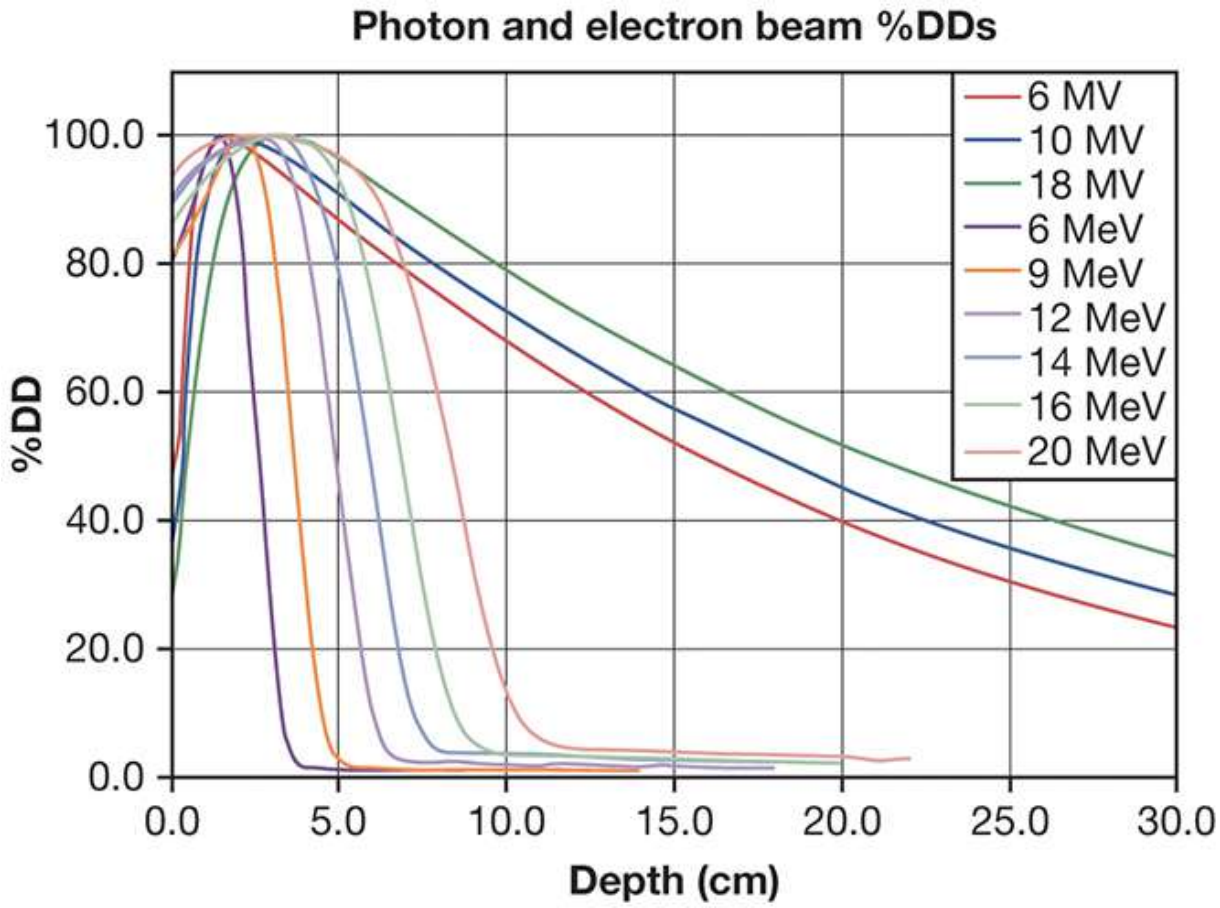


FIGURE 6.37 Examples of central axis percentage depth dose (DD) for megavoltage x-ray beams ranging from ^{60}Co to 18-MV x-rays and 6- to 20-MeV electron beams.

The PDD for one SSD is related to the PDD at a second SSD by the following equation:

$$\mathrm{PDD}\left(d, S, f_2\right) = \mathrm{PDD}\left(d, S, f_1\right)\left(\frac{f_1 + d}{f_2 d} \cdot \frac{f_2 + d_{\max}}{f_1 + d_{\max}}\right)^2$$

The term in brackets is called the *Mayneord F-factor*.[102]

Tissue-Air Ratio

TAR is defined as the ratio of the absorbed dose D_d at a given point in the phantom by the absorbed dose in free space, D_{fs}, that would be measured at the same point but in the absence of the phantom, if all other conditions of the irradiation (eg, collimator, distance from the source) are equal (Figure 6.38). The TAR is expressed as follows:

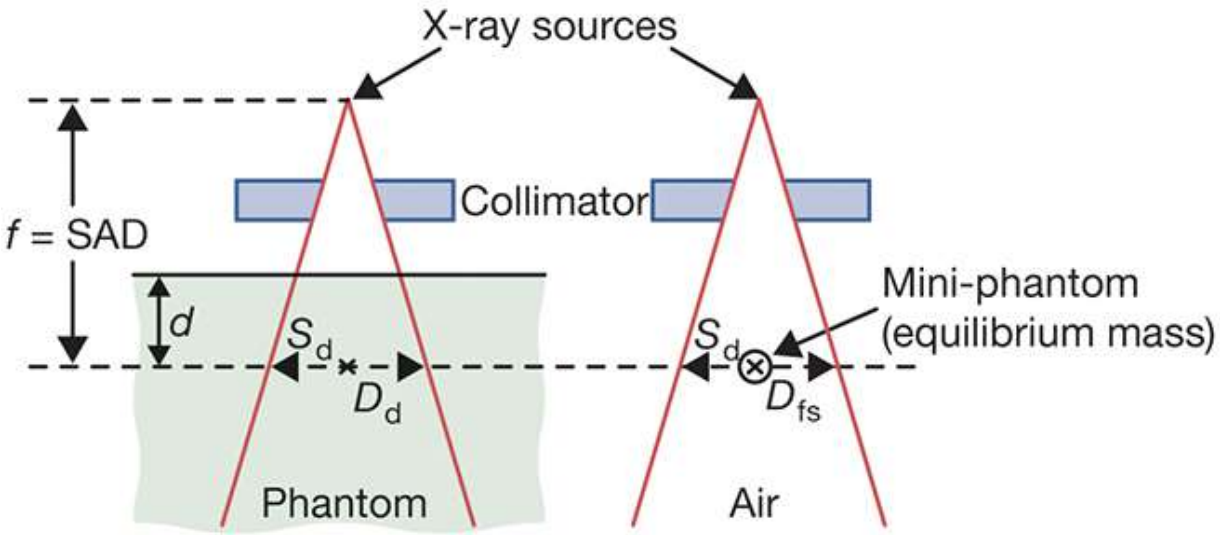


FIGURE 6.38 Schematic drawing illustrating the definition of tissue-air ratio, where *d* is the thickness of overlying material.

$$\mathrm{TAR}\left(d, S_d, E\right) = \frac{D_d}{D_{fs}}$$

where d is depth, E is radiation beam energy, and S_d is the beam dimension measured at depth d. TAR depends on depth, field size, and beam quality, but for all practical purposes, it is independent of the distance from the source.

The TAR at the depth of maximum dose is called the *peakscatter factor*. It is perhaps better known as the backscatter factor, but because of the finite depth d_0, this tends to be misleading. Figure 6.39 shows the peakscatter factors for various field sizes and beam qualities.

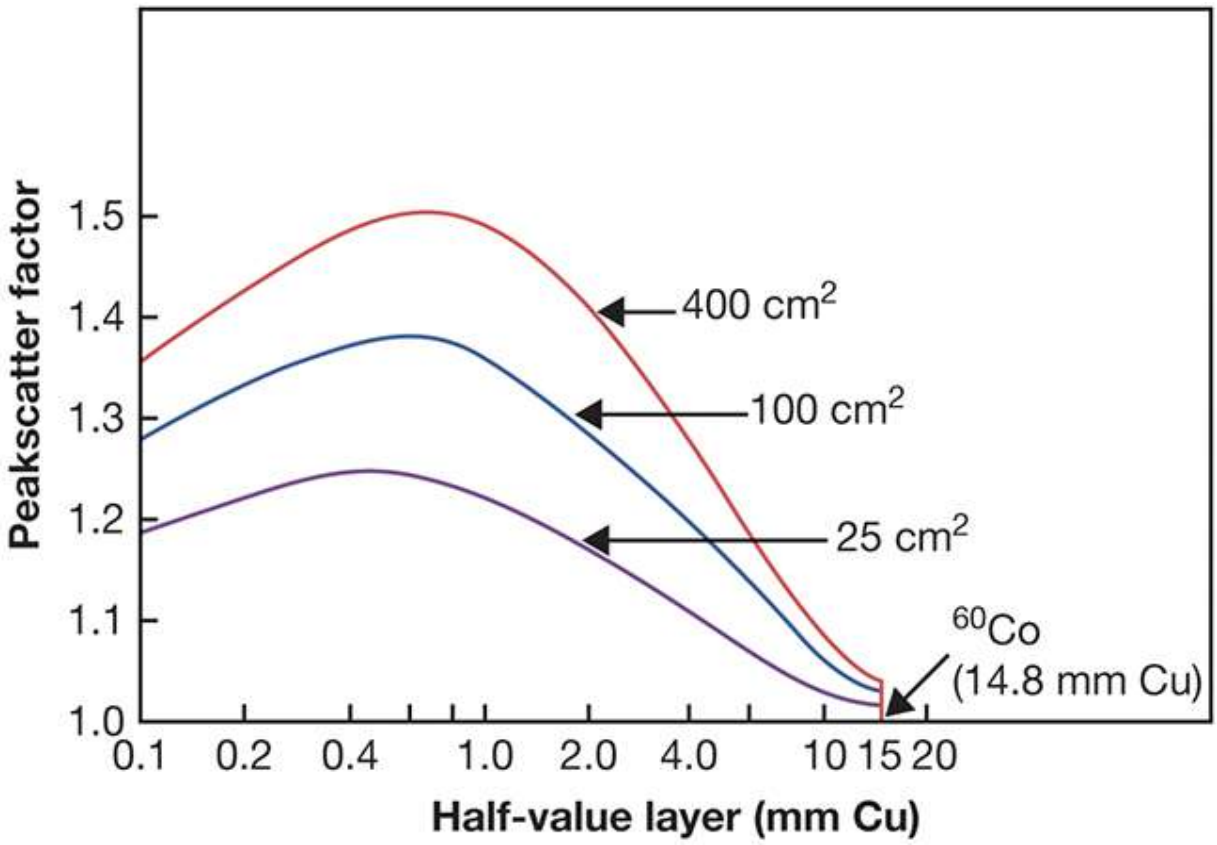


FIGURE 6.39 Variation of peakscatter factor with beam quality (half-value layer). (From Johns HE, Cunningham JR. *The Physics of Radiology*. 4th ed. Charles C Thomas; 1983:348. Courtesy of Charles C Thomas Publisher, Springfield, Illinois.)

Tissue-Phantom Ratio and Tissue-Maximum Ratio

The concepts of tissue-phantom ratio (TPR) and tissue-maximum ratio (TMR) were proposed for high-energy radiation as alternatives to TAR in response to arguments raised against the use of in-air measurement for a photon beam with a maximum energy >3 MeV.[103,104] As originally defined, TPR is given by the ratio of two doses:

$$\mathrm{TPR}\left(d, d_{\mathrm{r}}, S_{\mathrm{d}}, E\right) = \frac{D_{\mathrm{d}}}{D_{\mathrm{d_r}}}$$

where $D_{\mathrm{d_r}}$ is the dose at a specified point on the central axis in a phantom with a fixed reference depth, d_{r}, of tissue-equivalent material overlying the

point; D_d is the dose in the phantom at the same spatial point as before but with an arbitrary depth, d, of overlying material; and S_d is the beam width at the level of measurement (Figure 6.40). In each instance, the underlying material is sufficient to provide for full backscatter. There is no general agreement about the magnitude of the reference depth to be used for this quantity, particularly for high energies. The TPR is intended to be analogous to the TAR but has an advantage because the reference dose, D_{d_r}, is directly measurable over the entire range of x-rays and γ-rays in use, eliminating problems in obtaining a value for the dose in free space when the depth for electronic buildup is great.

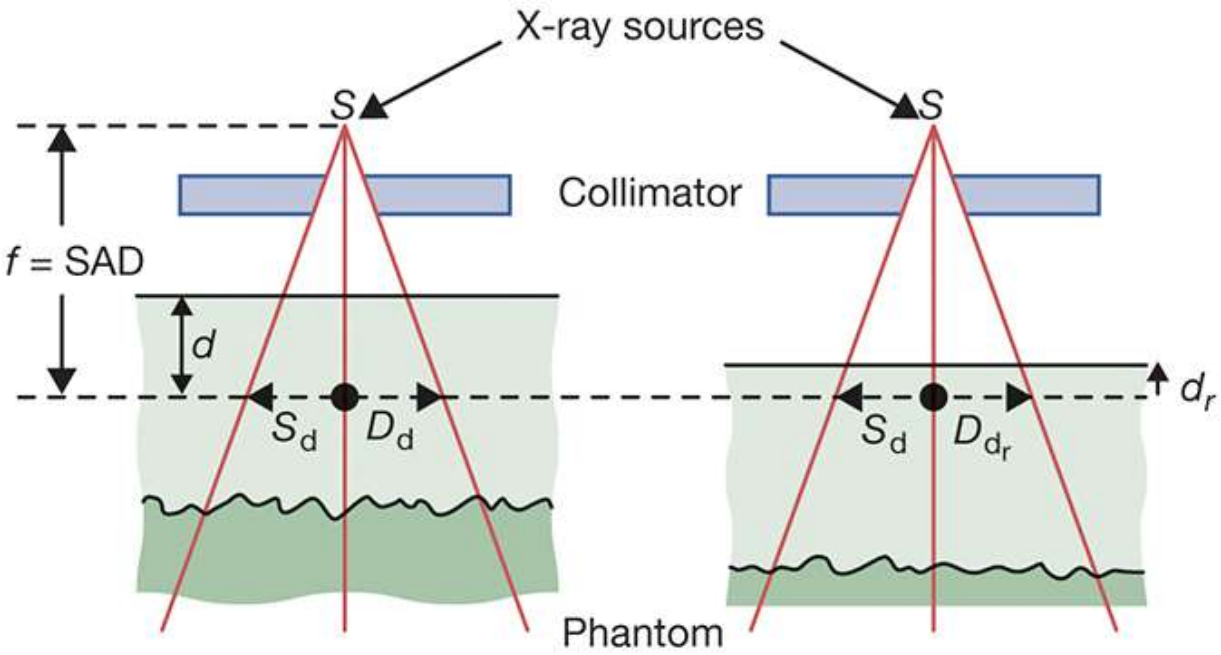


FIGURE 6.40 Schematic drawing illustrating the definition of tissue-phantom ratio and tissue-maximum ratio, where d is the thickness of overlying material and d_r is the reference thickness.

The original TMR definition is similar to the definition of TPR, except that the reference depth, d_r, is the depth of maximum dose. However, the depth of maximum dose for MV x-ray beams varies significantly with field size and also is a function of SSD. Thus, the definition of TMR creates a measurement problem because a variable d_r is required and the TMR

depends on SSD. A modification by Khan et al[105] proposed that the reference depth, d_r, must be equal to or greater than the largest depth of maximum dose.

Purdy[106] reported on the relationships between the central axis PDD and the TPR, TMR, and TAR. This work suggested that the degree to which the TPR and TMR are independent of distance from the radiation source depends largely on the linac's collimator/flattening filter scatter component of the beam.

Scatter-Air Ratio and Scatter-Maximum Ratio

The scatter-air ratio (SAR) can be thought of as the scatter component of the TAR.[107] It is defined as follows:

$$\mathrm{SAR}\,(d, S_d, E) = \mathrm{TAR}\,(d, S_d, E) = \mathrm{TAR}\,(d, 0, E)$$

SAR is the difference between the TAR for a field of finite area and the TAR for a zero-area field size. The zero-area TAR is a mathematical abstraction obtained by extrapolation of the TAR values measured for finite field sizes.

Similarly, the scatter-maximum ratio (SMR), the scatter component of the TMR, is defined as follows:

$$\mathrm{SMR}\left(d, S_d, E\right) = \mathrm{TMR}\left(d, S_d, E\right) \cdot \frac{S_p\left(S_d, E\right)}{S_p\left(S_0, E\right)} - \mathrm{TMR}\left(d, 0, E\right)$$

where S_p is a phantom scatter correction factor, which takes into account changes in scatter radiation originating in the phantom at the reference depth as the field size is changed.[105]

Output Factor

The output factor for a given field size is defined as the ratio of the dose rate at the depth of maximum dose for a given field size to that for the

reference field size (usually 10 × 10 cm) at its d_{max}. The output factor varies with field size (Figure 6.41) as a result of two distinct phenomena. As the collimator jaws are opened, the primary dose, D_p, at d_{max} on the central ray per monitor unit increases as a result of a larger number of primary x-ray photons scattered out of the flattening filter. In addition, the scatter dose, $D_s(d_{max}, r)$, at the measurement point per unit D_p increases as the scattering volume irradiated by primary photons increases with increasing collimated field size. These two components can vary independently of one another if nonstandard treatment distances or extensive secondary blocking is used.

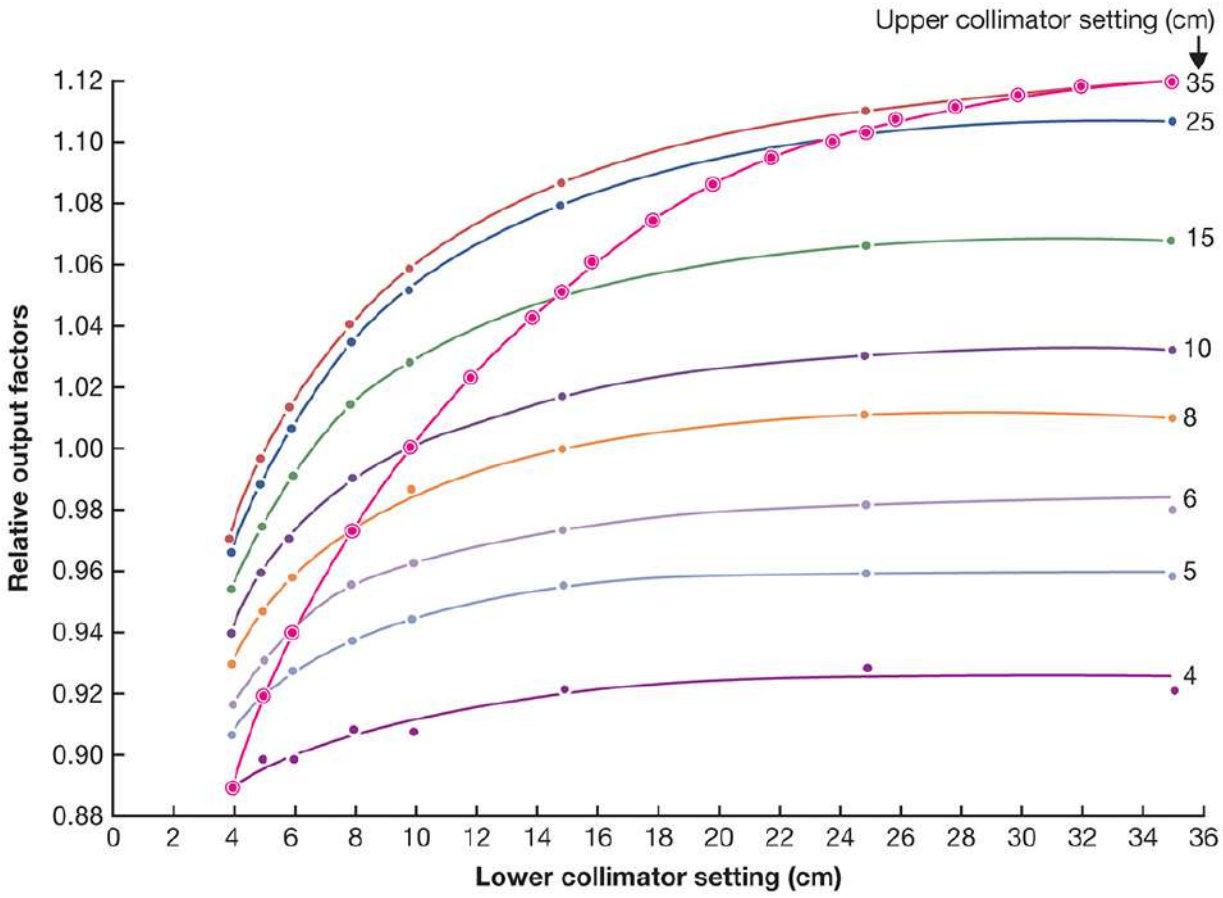


FIGURE 6.41 Example of output factor as a function of lower and upper collimator settings for a medical linear accelerator 18-MV x-ray beam.

Khan et al[105] described a method for separating the overall output factor, $S_{c,p}$, into two components. One is the collimator scatter factor, $S_c(r_c)$, which is a function only of the collimator opening, r_c, projected to the isocenter.

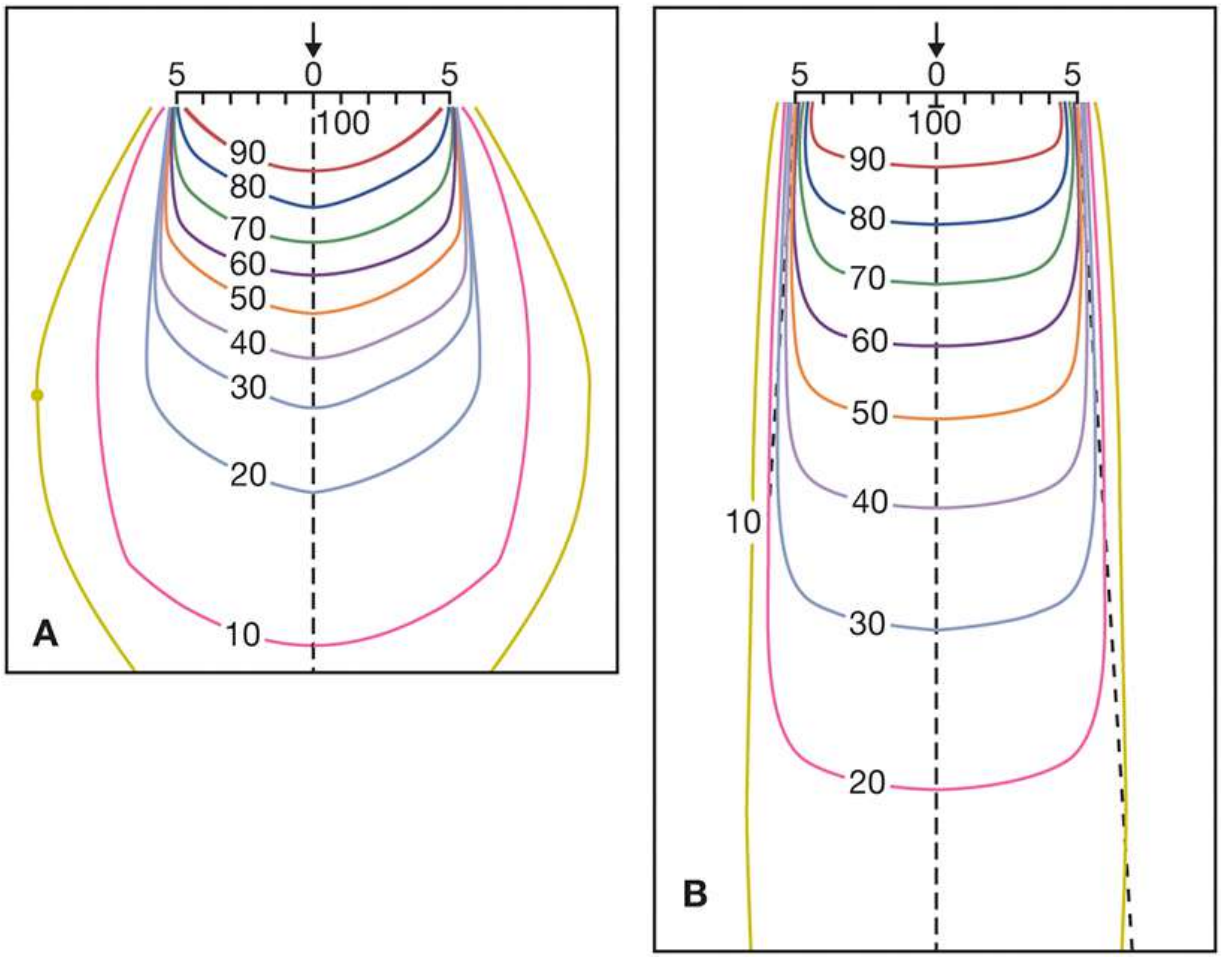
The other is the phantom scatter factor, $S_p(r)$, which is a function only of the cross-sectional area or effective field size, r, irradiated at the treatment distance. They demonstrate that

$$S_{c,p}(r) = S_c(r_c) \cdot (r)$$

In practice, the total and collimator scatter factors both are measured, and the phantom scatter factor is calculated using the relationship listed previously. $S_c(r_c)$ is measured in air using an ion chamber fitted with an equilibrium-thickness buildup cap and given by the ratio of the reading for the given collimator opening to the reading for a reference field (typically 10 × 10 cm) collimator opening. The overall output factor is measured in-phantom using the standard treatment distance and is given by the reading relative to that for a 10 × 10 cm field size. By carefully extrapolating this measured ratio to zero-field size, one obtains the zero-field-size phantom scatter factor, S_p (0). If a small ion chamber is positioned axially in the beam, it is possible to measure $S_{c,p}$ for field sizes as small as 1 × 1 cm. Because of the loss of lateral secondary electron equilibrium encountered near the edges of high-energy photon beams, S_p deviates significantly from unity. Consistent separation of primary and scatter dose components significantly improves the accuracy of dose predictions for irregular field calculations, especially near block edges and the resultant dose falloff resulting from lateral electron disequilibrium, and under blocks, overcoming many of the dose-modeling problems presented by use of extensive customized blocking.

Isodose Curves

An isodose curve represents points of equal dose. A set of these curves, normally given in 10% increments normalized to the dose at the reference depth, can be plotted on a chart (ie, isodose chart) to give a visual representation of the dose distribution in a single plane (Figure 6.42). Beam parameters, such as source size, flattening filter, field size, and SSD, play important roles in the shape of the isodose curve.


5
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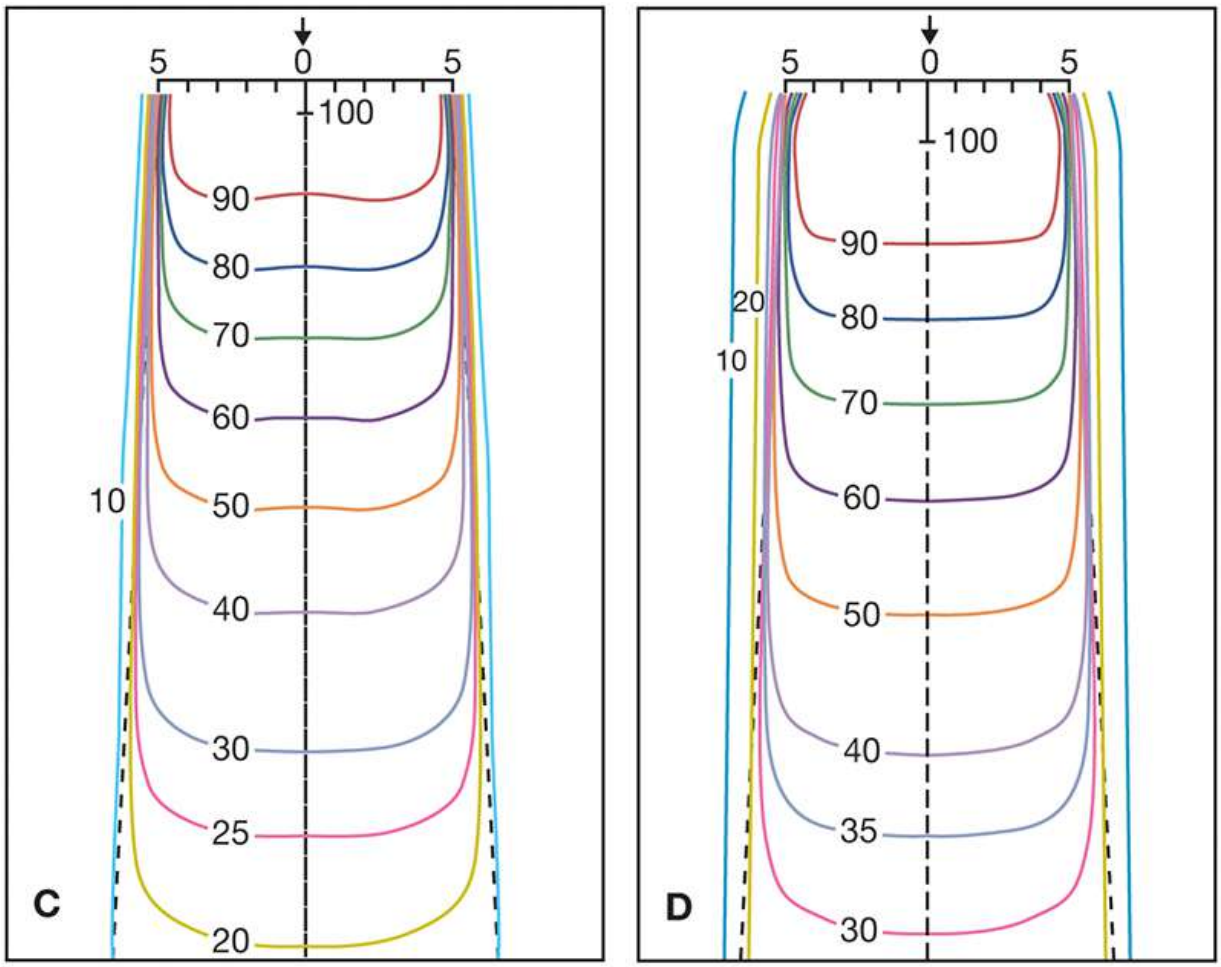
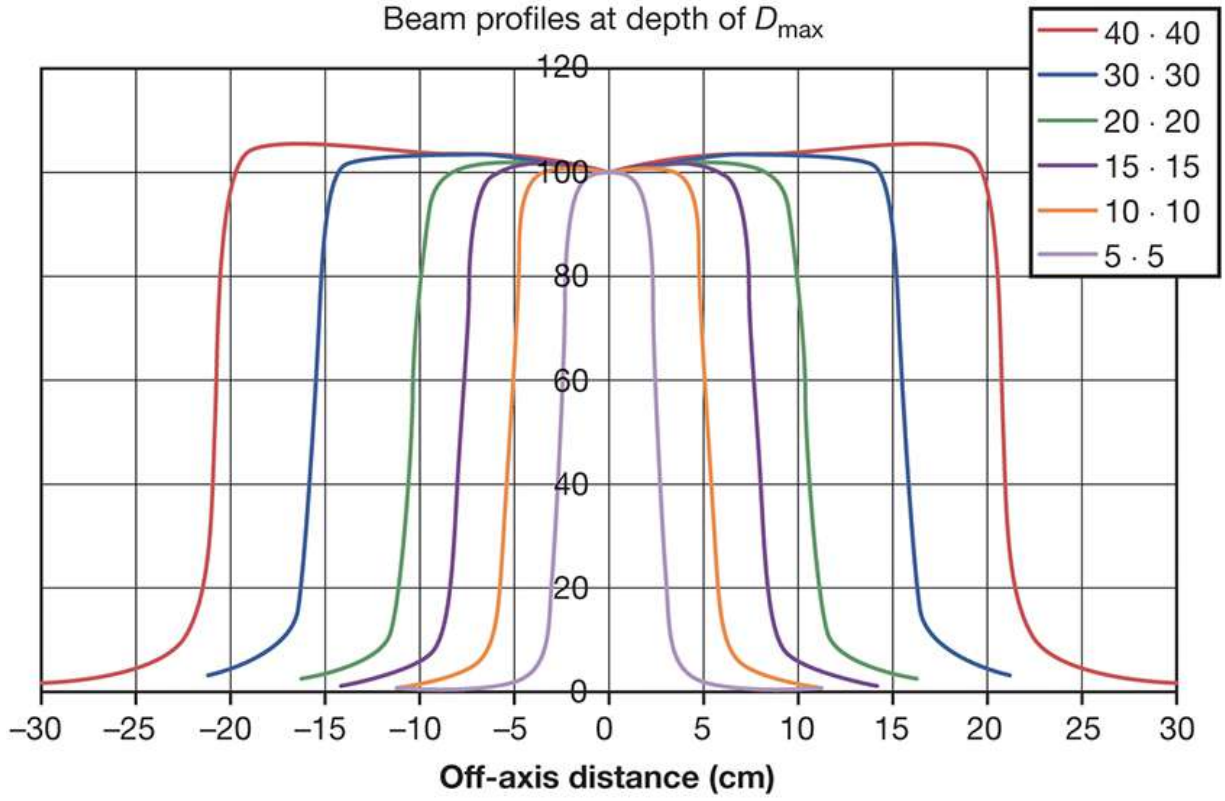


FIGURE 6.42 Isodose distributions for different quality radiations. A. 200 kVp, source-skin distance (SSD) = 50 cm, half-value layer (HVL) = 1 mm Cu, field size = 10 × 10 cm. B. 60Co, SSD = 80 cm, field size = 10 × 10 cm. C. 4-MV x-rays, SSD = 100 cm, field size = 10 × 10 cm. D. 10-MV x-rays, SSD = 100 cm, field size = 10 × 10 cm. (Reprinted with permission from Khan FM. *The Physics of Radiation Therapy*. 2nd ed. Williams & Wilkins; 1994.)

Dose Profiles

A dose profile is a representation of the dose in an irradiated volume as a function of spatial position along a single line. Dose profiles are particularly well suited to the description of field flatness and penumbra. The data most often are given as ratios of doses normalized to the dose on the central axis (Figure 6.43). The profiles, called *off-axis factor*s or *off-center ratio*s, may be measured in air (ie, with only a buildup cap) or in a phantom at selected depths. The in-air off-axis factor gives only the variation in primary beam

intensity; the in-phantom off-center ratio shows the added effect of phantom scatter.


Beam profiles at depth of D_{max}
40 · 40
30 · 30
20 · 20
15 · 15
10 · 10
5 · 5
120
100
80
60
40
20
0
–30 –25 –20 –15 –10 –5 0 5 10 15 20 25 30
Off-axis distance (cm)

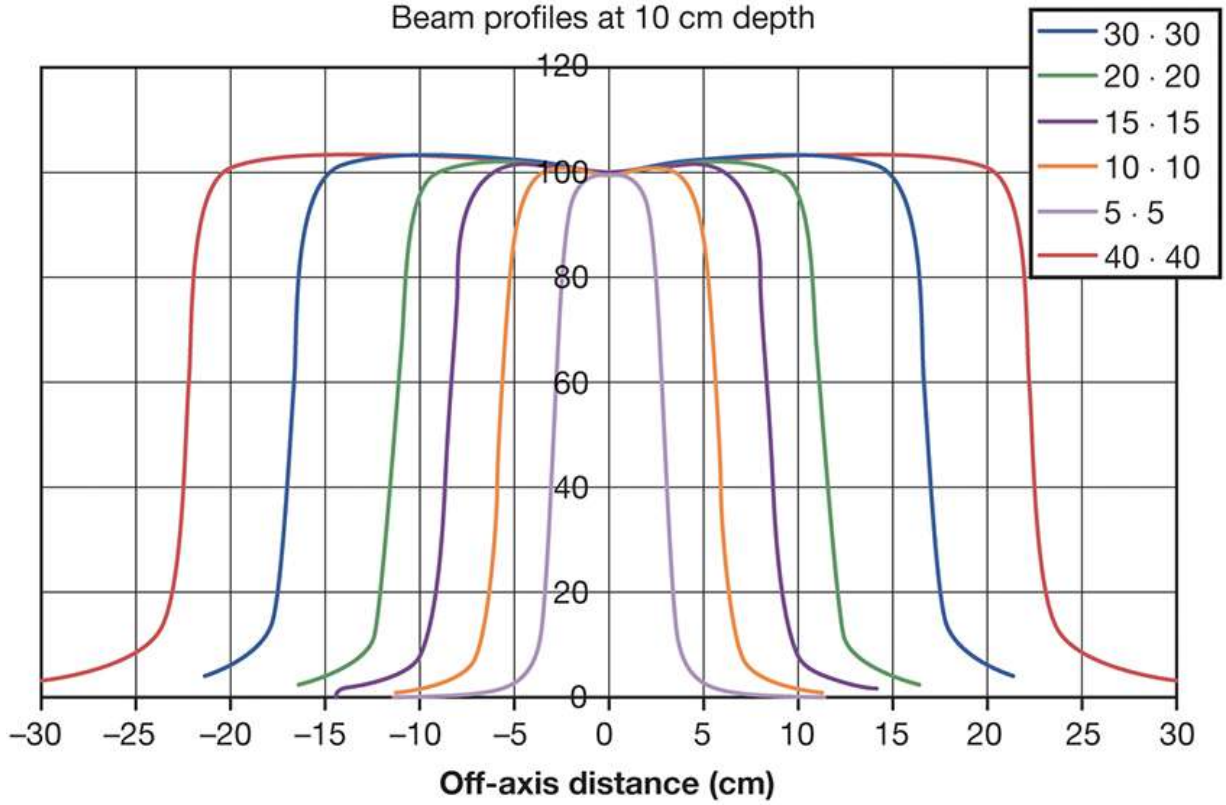

Beam profiles at 10 cm depth
30 · 30
20 · 20
15 · 15
10 · 10
5 · 5
40 · 40
120
100
80
60
40
20
0
–30 –25 –20 –15 –10 –5 0 5 10 15 20 25 30
Off-axis distance (cm)

FIGURE 6.43 Example of dose profiles for an 18-MV linear accelerator x-ray beam measured at depths of 3 and 10 cm.

Wedge Filter

Wedge filters, first introduced by Ellis and Miller,[108] have traditionally been physical wedges constructed of brass, steel, or lead. When placed in the beam they progressively decrease intensity across the field, causing the isodose distribution to have a planned asymmetry.

The wedge angle is defined as the angle the isodose curve subtends with a line perpendicular to the central axis at a specific depth and for a specified field size. Current practice is to use a depth of 10 cm. Past definitions were based on the 50th percentile isodose curve and, more recently, the 80th percentile isodose curve. The wedge angle is a function of field size and depth. The wedge factor is defined as the ratio of the dose measured in a tissue-equivalent phantom at the depth of maximum buildup on the central axis with the wedge in place to the dose at the same point with the wedge removed.

Wedge isodose curves can be normalized in different ways, as shown in Figure 6.44. The wedged isodose distribution on the left side of the figure has been normalized to 100% at d_{max} on the central axis with the wedge in place; on the right, the normalization is done without the wedge in place. Thus, it is imperative that the normalization and the use of the wedge factor should be clearly understood before wedges are used clinically.

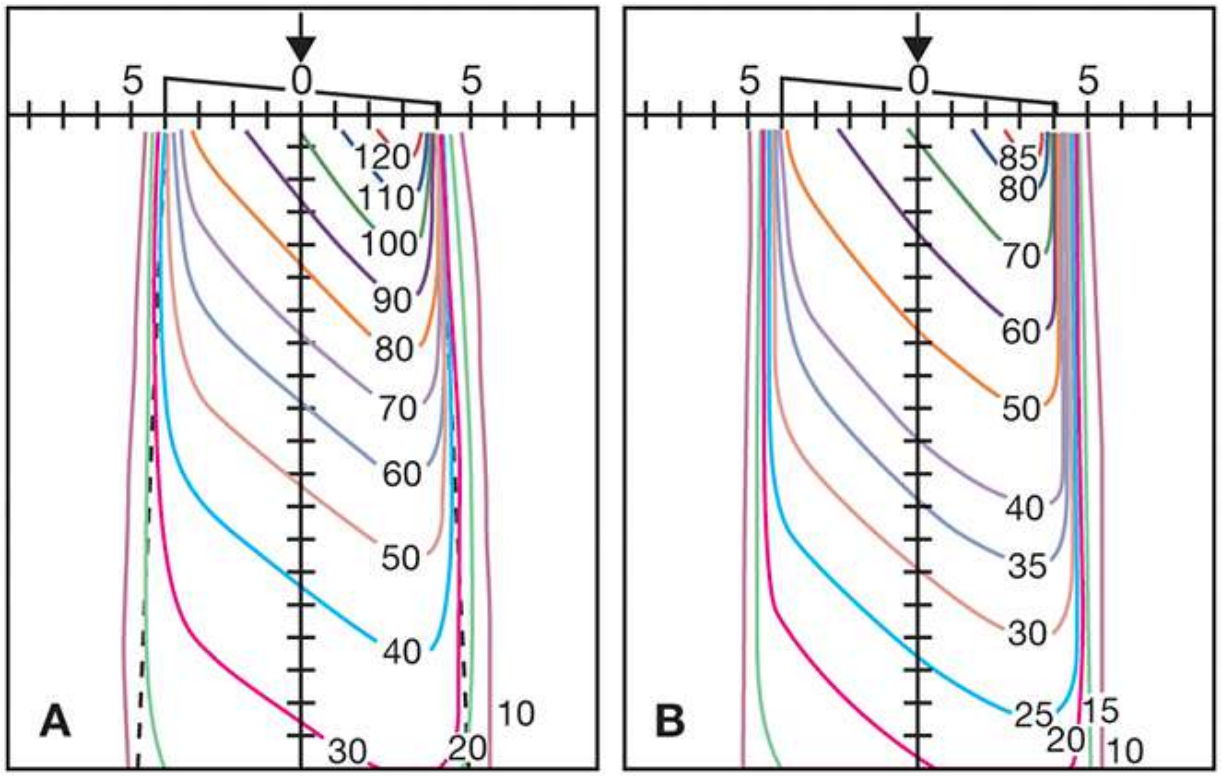


FIGURE 6.44 Isodose curves for a wedge filter. A. Normalized to D_{max}. B. Normalized to D_{max} without the wedge. ^{60}Co, wedge angle = 45°, field size = 8 × 10 cm, source-skin distance = 80 cm. (Reprinted with permission from Khan FM. *The Physics of Radiation Therapy*. 2nd ed. Williams & Wilkins; 1994.)

Beam hardening occurs when a wedge is inserted into the radiation beam. The PDD, therefore, can be considerably increased at depth. Differences in PDD of nearly 7% have been reported for a 4-MV x-ray, 60° wedge field, compared with the open field at a depth of 12 cm, and there have been reports of as much as a 3% difference between the 60° wedge field and the open field for a 25-MV x-ray beam.[109,110]

In many current machines, the physical wedge has been replaced by a dynamic or virtual wedge.[111,112] Based on similar principles as IMRT, one of the jaws or MLC banks is swept across the field while the beam is on. The velocity of the motion controls the steepness of the wedge angle. Details regarding QA for this technology are provided in AAPM Task Group Report 198.[111]

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CHAPTER 7

Patient Positioning Methods: Immobilization, Stabilization, and Monitoring

Tianjun Ma, Kujtim Latifi, Bruce Libby, Joshua Evans, and Stanley H. Benedict

OVERVIEW OF EXTERNAL BEAM IMMOBILIZATION AND STABILIZATION

Rationale for Patient Immobilization and Stabilization

The success or failure of a radiotherapy treatment hinges on the accuracy with which the radiation is delivered. There are many sources of uncertainty in the radiation therapy delivery process that can result in a geometric miss of the intended target volume, which will not only decrease the probability of tumor control but also increase the volume of normal tissue that is irradiated, thus increasing the probability of a treatment-related complication. Geometric uncertainties may be broadly classified as mechanical inaccuracies, localization inaccuracies, and positioning inaccuracies. Mechanical inaccuracies include the coincidence of the light and radiation fields, mechanical stability of the couch, laser alignment, and correspondence of the simulation and treatment isocenters. Localization uncertainty relates to the difficult nature of defining the location and extent of the target volume during both planning and treatment delivery. Patient positioning uncertainties relate to misalignment of the patient for treatment or dynamic movement of the target volume out of the treatment field. This chapter focuses on devices and techniques designed to minimize this last group: patient positioning uncertainties.

The goal of daily setup is to reproduce the patient's position at the time of simulation as best as possible; however, setup variations will inevitably occur, which is generally appreciated as a tangible problem and has earned considerable attention in the literature. In an early example, Dunscombe et al[1] assessed components of positioning accuracy in patients with head and neck (H&N) cancer and concluded that observed field placement errors were primarily attributable to patient motion. Patients may fidget from being uncomfortable or anxious during the treatment delivery. Furthermore, organs can move internally with respect to bony anatomy, skin marks, and other soft tissues because of normal and unavoidable physiologic processes such as breathing, swallowing, and peristalsis.

The focus of this chapter is on describing devices and methods for the immobilization and stabilization of patients undergoing radiotherapy, in which the goal is to reduce positioning uncertainties during each fraction (intrafraction error) and to increase the reproducibility of the patient setup for each fraction (interfraction error). In addition, immobilization devices can decrease the time needed for daily setup and target localization, thus increasing a clinic's throughput. Certain immobilization devices may also allow setup marks to be made directly on the device instead of the patient's skin, which can improve the patient's psychological well-being while under treatment, and some devices may even confer dosimetric advantages in treatment planning. The immobilization system should be lightweight for ease of setup and transport, yet strong and durable so that the device does not break during the patient's course of treatment. Furthermore, the device should be made of materials that minimally affect the megavoltage (MV) treatment beam and do not cause imaging artifacts that could impact three-dimensional (3D) visualization of the patient's anatomy for target identification or patient alignment.

The devices and techniques for patient immobilization and stabilization described in this chapter have been shown to improve interfraction setup reproducibility as well as reduce intrafraction uncertainties. The overall accuracy of any immobilization system, however, is dependent on the skill and patience of the personnel forming the device at the time of simulation and setting the patient up on the treatment table for each fraction. Adequate training should be provided for each immobilization system employed in a given clinic, and adequate time should be scheduled for proper patient setup and immobilization. Furthermore,

some patients will be more challenging to reproducibly align than others such as patients in pain and/or with mobility issues. A variety of devices and positions should be available for each treatment indication to help create a treatment position that maximizes both inter- and intrafraction reproducibility for each patient.

Surface imaging technologies for aiding in the initial setup and for real-time monitoring of the patient during treatment have experienced rapid clinical adoption over the last decade, and high-dose-rate (HDR) procedures and techniques have continued to evolve, supporting broad updates in these sections mentioned further. And exciting new technologies and modalities, including Cherenkov cameras for treatment monitoring and total body irradiation (TBI) with volumetric modulated arc therapy (VMAT), have motivated new sections to introduce these systems in the context of reducing patient positioning uncertainties.

Finally, it must be noted that in some cases, even the most robust techniques for patient immobilization and monitoring do not guarantee accurate daily localization of the tumor volume and should not be a substitute for image guidance when indicated. Tumors are well known to change position relative to other soft-tissue anatomy, the external surface, and bony anatomy. Thus, strategies for daily target localization, described elsewhere in this textbook, are also important and are intimately tied to patient immobilization.

Simple Immobilization Devices

Simple methods to reduce intrafraction positioning uncertainty because of patient motion have been in use for decades to ensure that the patient is comfortable. Figure 7.1 shows a variety of simple devices that can be used to enhance the patient's comfort. For patients treated in a supine position, a wedge or roll (A in Figure 7.1) underneath the knees can help to reduce stress on the lower back. For arm-down positioning, a ring for the patient to grip (D in Figure 7.1) can increase comfort. For lung and liver treatments, it may be preferable to position the patient with the arms above the head. In these cases, the arms may be supported under the shoulder by foam wedges (B in Figure 7.1) to help the patient attain a restful position. For some patients with H&N cancer, the patient's shoulders may block the inferior portion of lateral treatment fields. In this case, a simple strap (C in Figure 7.1) can be used to pull the shoulders down and out of the treatment fields. A headrest is almost always used with supine positioning to elevate the head and reduce strain on the neck. Standard sets of "Timo" and "Silverman" headrests (E in Figure 7.1) come in a variety of shapes, sizes, and materials. For those not adequately accommodated by the standard set of headrests, several manufacturers offer customizable head cushions that can be molded to the patient's head contour. All of these devices are relatively inexpensive and are often reusable if they can be covered and/or cleaned between uses.

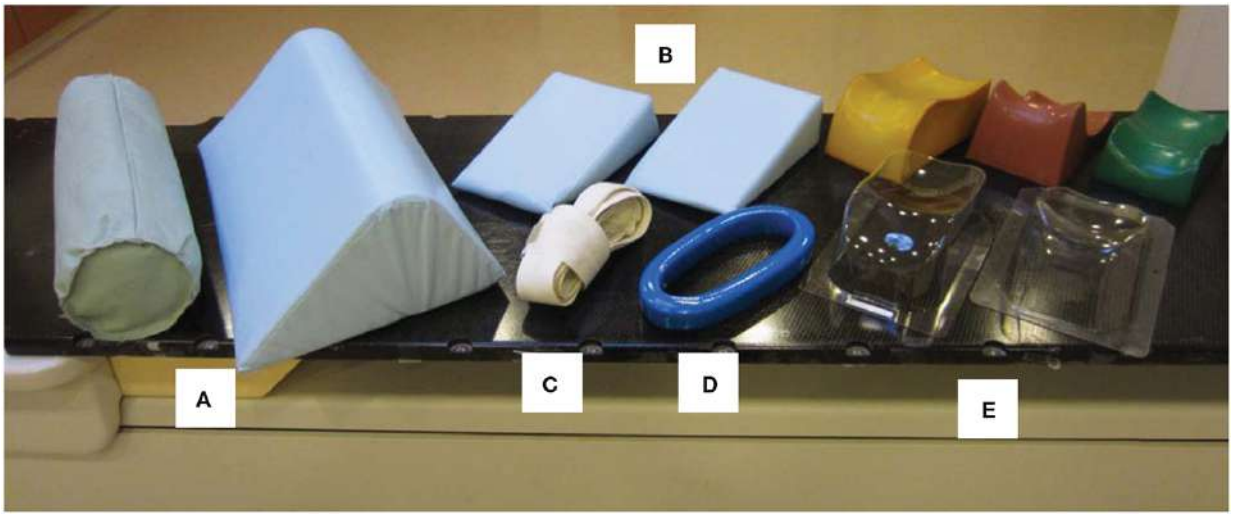


FIGURE 7.1 Simple devices are cost-effective and can reduce intrafraction positioning errors by increasing patient comfort. Shown here are rolls and wedges (A) that can be placed under the knees and wedges (B) to support the arms and shoulders. A simple strap can be used to suppress the shoulders in patients with head and neck cancer (C) and grip rings (D) for the patient to hold on to. Headrests are available in a wide range of shapes and sizes (E).

Immobilization Features of a Dedicated Radiation Oncology Computed Tomography Simulator

Simple devices incorporated during initial simulation can improve patient comfort and reduce intrafraction motion because of patient movement. However, they may not address day-to-day variations of overall patient setup and positioning accuracy. A major objective of a robust immobilization system is to reproduce the patient's anatomic geometry at the time of simulation for all subsequent treatment fractions. An example of a robust immobilization system to treat a patient with breast cancer is shown in Figure 7.2 to illustrate some of the desired features of a dedicated radiation oncology computed tomography (CT) simulator. With this immobilization system, the patient lies supine with an ergonomic wedge (E in Figure 7.2) under the knees. The arms are positioned above the head and out of the tangential treatment fields. A custom-formed, reusable vacuum-lock bag (C in Figure 7.2) helps to support the patient's arms, and a T-bar (B in Figure 7.2) may be used for the patient to grip. The angled baseboard (C in Figure 7.2) on which the vacuum-lock bag rests utilizes gravity to help the breasts fall into a more reproducible position and can be adjusted to minimize skin folds. Many of these devices provide indexing systems for the therapists to record the geometry used for each patient at the time of simulation. This example of a breast setup, where one or both arms may be positioned above the head, highlights the advantage of a wide-bore (eg, >85 cm diameter) CT scanner for radiation (B in Figure 7.2) oncology treatment simulation, as opposed to the more common 70 cm bore diameter, which may limit the options for positioning certain patients.

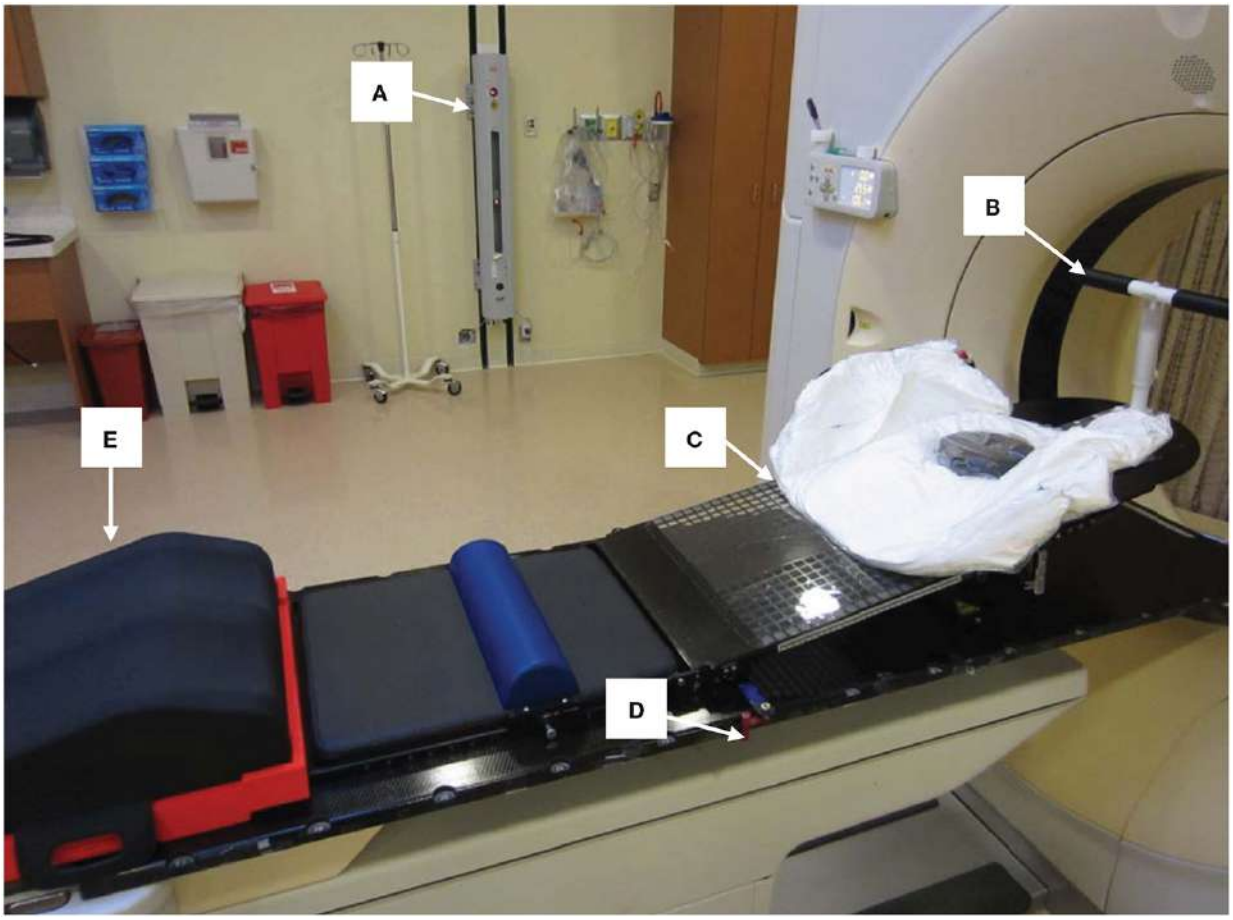


FIGURE 7.2 Displayed here is an immobilization system for a patient with breast cancer in the simulator suite at the University of Virginia. Some key features of a dedicated radiation oncology computed tomography (CT) simulator shown here include the following: A. An in-room laser system marks the reference point position. B. A wide-bore CT (85 cm diameter) allows more flexibility in patient positioning. A vacuum-lock mattress and a T-bar support the patient's arms above the head. C. An angled breast board can improve patient comfort and provide optimal positioning of the breast for radiotherapy. D. An indexed flat couch top overlay reproduces the geometry of the treatment table, with an indexing bar attaching the breast board to the flat couch top overlay. E. An ergonomic knee support can reduce stress on the lower back.

Flat couches are favored for radiation oncology treatments to accommodate a wide range of patient sizes, setup positions, and immobilization devices. Diagnostic CT scanners feature a curved couch for patient comfort; the geometry of a patient simulated on a curved diagnostic couch top will be challenging to reproduce on a flat treatment couch. Flat couch top inserts are offered by numerous vendors to reproduce the couch geometry of the treatment unit. An important feature of a couch top insert is the indexing system (D in Figure 7.2), which allows an assortment of immobilization devices to be rigidly affixed in concert to both the simulator and treatment tables with high accuracy. The indexing system improves the interfraction reproducibility of the patient setup and can also decrease the amount of time to set up a patient.

External marks placed on either the patient's skin or the immobilization devices are used for initial laser alignment on the treatment machine as a surrogate for the internal target anatomy. An in-room laser system in the CT simulator suite (A in Figure 7.2) is a necessary feature to provide external reference points that correlate to the internal reference point location. After the simulation CT scan is acquired, the isocenter is defined and the coordinates are transferred to the in-room laser system. The laser system and CT table are then moved to the defined setup point and external setup marks can be made, thus correlating the position of an internal setup point to the external markings.

HEAD AND NECK IMMOBILIZATION DEVICES

Thermoplastic Masks

Adequate immobilization is particularly critical in the treatment of H&N cancers as the target is frequently located in close proximity to critical structures. Thermoplastic masks have replaced traditional plaster casting methods in most clinics. Thermoplastic masks are heated to approximately 70 °C in a water bath or a dry heat oven. At this temperature, the thermoplastic material becomes malleable and can be stretched and shaped to conform to the patient's face, head, and neck. The patient's H&N region is supported by a simple preformed cushion, like those previously described and illustrated in Figure 7.1, or a custom-formed cushion may be made. The mask is connected to a base plate, which is attached to the couch via the indexing system. Setup marks can be made directly onto the thermoplastic mask, eliminating the need for unsightly marks to be placed on the patient's face for the duration of the treatment.

Early work with thermoplastic mask immobilization for H&N cancer by Bentel showcased the efficacy of the thermoplastic mask in comparison to the traditional plaster three-strip immobilization technique.[2] In terms of the rate of physician-requested shifts from port films, the thermoplastic mask had a frequency of 6.2% compared to 16.1% for the plaster casting method. However, this advantage was only observed when the mask was rigidly affixed to the couch, highlighting the importance of the couch indexing system.[2] Since then, numerous studies quantifying the accuracy of patient setup for H&N cancer have appeared in the literature. The bulk of these studies utilized two-dimensional (2D) portal imaging to quantify setup displacements, although studies utilizing 3D cone-beam CT (CBCT) data have become more common as this technology has recently gained widespread clinical adoption. Generally, systematic and random errors have been reported to have standard deviations ranging from 1 to 4 mm.[3-5] Based on a review of studies assessing setup errors using portal imaging, Hurkmans et al[4] suggest that random and systematic errors of 2 mm or less should be a practically achievable goal for patients with H&N cancer given current immobilization technology and methods.

Figure 7.3 illustrates the flexibility of patient positioning options with thermoplastic masks. Masks can encompass the head only or can extend inferiorly to cover the shoulders (Figure 7.3A, B). Gilbeau et al[3] compared the setup accuracy of the short and long thermoplastic masks in the treatment of H&N cancer. Portal images were acquired for isocenters placed at the level of the head, neck, and shoulders. Their results show similar setup accuracy with the long and short mask for the isocenters in the H&N. For isocenter placement at the shoulder level, the use of the long mask resulted in a random setup error of around 1.0 mm, which was significantly less ($P = .01$) than the 2.3 mm error of the short mask.[3] Thus, a long mask to immobilize the shoulders is recommended for patients receiving supraclavicular treatment in which the isocenter will be placed at the level of the shoulders.

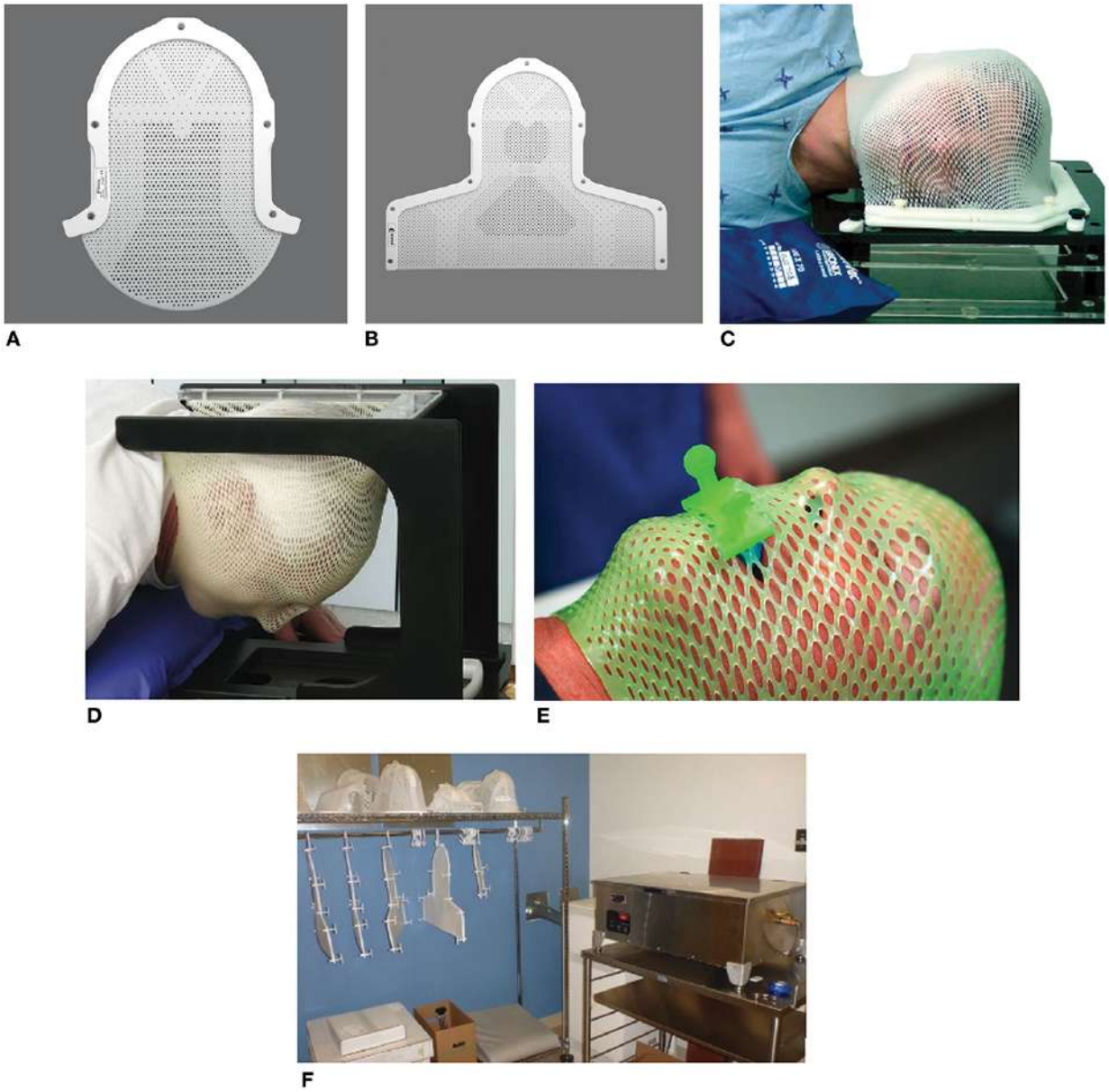


FIGURE 7.3 For treatment of targets in the head and neck, thermoplastic masks are routinely used for custom immobilization. A and B. Thermoplastic sheets are commercially available in short versions that cover only the head, as well as longer versions that extend over the patient's shoulders. C. They can also be used to treat patients in the prone and lateral positions. D. HeadStep Prone. E. BiteLok. F. Additional space is needed to accommodate the water bath used to warm the thermoplastic sheets. (A-C. Courtesy of Bionix. D. Courtesy of IT-V Medizintechnik GmbH. E. Courtesy of Klarity, and E. Taken at UVA by the author.)

Thermoplastic mask systems are available with a myriad of features including multilayer masks to increase rigidity and masks with cutouts for the patient's eyes to reduce anxiety and accommodate optically guided setup. They can also accommodate prone or lateral setups when these positions may be indicated (Figure 7.3C). Some commercially available base plates can be angled to allow for the patient to be set up with the neck in an extended or flexed position, which may be used to avoid critical structures such as the eyes. Neck extension can be used with prone positioning for craniospinal irradiation. For prone setup, a donut-shaped cushion supports the patient's face in the base plate and the thermoplastic mask is formed around the posterior aspect of the head to hold the patient's face in the donut. There is also a newer prone setup mask that can be archived through a board fixation accessory (Figure 7.3D). A potential disadvantage

of treatment with a flexed or extended neck position is the need for registration with different imaging modalities (eg, positron emission tomography [PET]-CT or magnetic resonance [MR]-CT) in which the PET or MR were not performed in the patient treatment position. Vendors have also developed H&N mask mouthpiece accessories such as Precise Bite from CQ-Medical and BiteLok from Klarity for accurately reproducing the position of the teeth and tongue, as illustrated in Figure 7.3E.

Every clinic must consider space limitations when selecting particular immobilization and stabilization systems. Thermoplastic H&N systems necessitate more equipment and thus more space in the simulation suite. The water bath or dry heat oven used to heat the thermoplastic sheets for the long H&N masks can be large (Figure 7.3F). It is recommended to consult with the hospital's infection control team to ensure water baths and dry heat ovens are properly cleaned and monitored since they are used for many patients. For clinics with insufficient space to house a large heating device, smaller devices are commercially available that will fit the short head-only masks. Furthermore, some commercially available base plates (eg, VersaBoard; Bionix Radiation Therapy, Toledo, OH) incorporate shoulder suppression systems, which consist of rigid plastic panels to push down on the shoulders. When a long thermoplastic mask is not indicated or not available, a base plate with shoulder suppression panels can help to keep the shoulders out of the beam path for lateral H&N beams (Figure 7.3A, B). In lieu of long thermoplastic masks or base plates with shoulder suppression panels, the patient can pull on a simple shoulder strap (C in Figure 7.1) to move the shoulders inferior and avoid unnecessary irradiation of the shoulders when opposed lateral beams are used to treat the neck.

Thermoplastic masks have been observed to shrink as they cool in the 24-hour period after formation, and this has been shown to lead to systematic setup errors if not taken into consideration.[6] Furthermore, a mask that has shrunk after the simulation process may be uncomfortable for the patient and may require a full resimulation. Bionix Radiation Therapy has attempted to address this problem with the Klarity Green and Blue line of thermoplastic material, which is designed to have reduced shrinkage coupled with increased rigidity. As with any immobilization system, the thermoplastic manufacturers' recommendations should be carefully followed, and adequate time should be allowed during simulation for the mask to harden properly while on the patient to minimize the effect of shrinkage.

Patients feeling claustrophobic may encounter difficulties in tolerating masks. One of the solutions is to use open face mask, which has been reported in the literature.[7] As a complementary feature, mouthpiece coupled with masks could help stabilize the location of the tongue.

Bite Blocks as an Alternative to Masks

Another alternative solution for patients with claustrophobia is the complete bite block systems that do not incorporate a mask. Elekta offers a flexible system that includes the option of using a bite block, the Fraxion, which is illustrated in Figure 7.4. A custom dental mold is formed to fit the patient's maxillary teeth, and a vacuum system creates suction between the mold and the hard palate. A custom cushion is placed under the patient's head, neck, and shoulders. The mouthpiece is attached to a carbon fiber frame, which is fixed to the treatment table's indexing system. The head is thus rigidly immobilized via the connection of the mouthpiece to the head frame. The carbon fiber design of the HeadFIX product allows for the use of in-room kilovoltage image guidance systems for target localization. The mold can be quickly released from the frame if the patient feels claustrophobic. Setup accuracy has been shown to be similar to thermoplastic masks, on the order of 1 to 3 mm.[8] These stand-alone bite block systems, however, require a high level of patient compliance and may not be suitable for patients with poor dentition or with edentulism. Bite blocks formed with a patient's false teeth are highly discouraged and may result in inaccurate setups or breakage of the patient's dentures. Custom-formed dental molds can also be incorporated in the conventional thermoplastic mask systems described earlier to provide an additional point of support for the patient. A custom bite block may also be formed with primary goals other than immobilization, for example, to separate the tongue from the roof of the mouth, which can be useful in treating sinus/nasal cavity tumors to decrease dose to the tongue and vice versa. Table 7.1 includes a top-level summary of the pros and cons of the available intracranial immobilization devices.

TABLE 7.1 INTRACRANIAL IMMOBILIZATION DEVICE SUMMARY

Device Name	Description	Pros	Cons	Typical Sites	Reusable?	Indexed?	Relative Cost
Timo and Silverman head rests	Foam and plastic head rests with various sizes for a range of body habitus	Inexpensive and reusable	Not custom formed	H&N, craniospinal, thoracic, abdominal, pretty much all supine patients	Yes	Some clip to baseplate, which is indexed to the couch; others do not clip to couch.	$
Custom-formed head rests	Vacuum-lock or water-activated custom-formed head rests	Custom formed to patient Some are reusable.	Added time to simulation process Some are not reusable.	H&N, craniospinal, thoracic, abdominal, Intracranial SRS	Some yes Some no	Can be molded around baseplate for reliable placement	$$
Thermoplastic masks	Thermoplastic mask material is warmed until pliable and then is stretched over the patient's face to create a customized device.	Accurate, custom-formed immobilization Can cut out treatment portals to reduce blousing	Potential for mask shrinkage Patient anxiety or claustrophobia Bolusing effect	H&N, craniospinal	No	Yes; clip to baseplate	$$
Elekta Fraxion	Relocatable bite block system designed for fractionated stereotactic and conventional radiotherapy	Noninvasive, relocatable Can be used with or without thermoplastic mask Allows for fractionated SRS High degree of patient setup accuracy	Requires operator skill to create custom maxillary dentition molds May not be the best option for patients with poor dentition	H&N, intracranial stereo and some extracranial SRS targets in neck	Frame = yes Bite block = no	Yes	$$$
Invasive, nonrelocatable stereotactic intracranial immobilization devices (eg, Leksell Stereotactic Coordinate Frame G)	Frame is attached to the patient's skull with four screws Used for single-fraction radiosurgery	Excellent accuracy in patient repositioning	Typically requires sedation Risk of infection and bleeding Patient discomfort Often not compatible with intrafraction monitoring	Intracranial	Frame = yes	Rigidly attached directly to treatment machine (Gamma Knife), table- or floor-mounted stand	$$$
Noninvasive, relocatable intracranial mask–based immobilization (eg, CQ-Medical Solstice,	Multiple thermoplastic shells or cushions molded to patient's head and face, which	Does not require placement of screws into the patient's skull Allows for fractionated	Thermoplastic mask may be undesirable in certain patients, such as those with claustrophobia or anxiety	Intracranial	Base frame = yes Thermoplastic masks/custom cushions = no	Attach to treatment table	$$$

Device Name	Description	Pros	Cons	Typical Sites	Reusable?	Indexed?	Relative Cost
BrainLab Cranial 4Pi)	are tightly secured in a clamshell design around the patient's head	SRS High degree of patient setup accuracy demonstrated with CBCT and intrafraction monitoring					

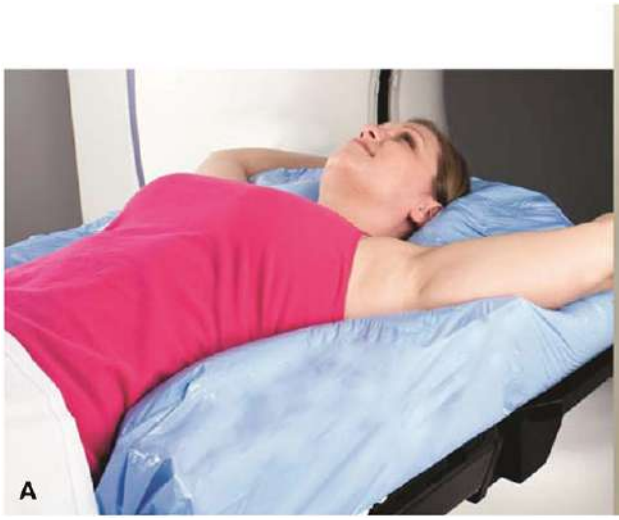
CBCT, cone-beam computed tomography; H&N, head and neck; SRS, stereotactic radiosurgery.

FIGURE 7.4 The Fraxion® is an example of a flexible system that offers a bite block system that can provide an alternative method for immobilizing head and neck patients who are not able to tolerate a thermoplastic mask due to anxiety or claustrophobia (Image courtesy from 3C-Medical Intelligence GmbH.)

BODY CONFORMAL IMMOBILIZATION DEVICES

Numerous commercial body conformal immobilization devices are available for a variety of treatment indications. One type of body conformal system uses a two-part foaming agent to form a permanent mold of the patient's body. One such system, the Alpha Cradle, is illustrated in Figure 7.5A, B. Forms are available for treatment of patients with a variety of disease sites, including the H&N, breast, thorax, abdomen, pelvis, and extremities. At the time of simulation, the appropriate body form is chosen and placed in a polyvinyl bag where the two-part chemical foaming agents are mixed together, initiating the chemical reaction that causes the foam to expand. The mixed foaming agent is distributed evenly throughout the body form and sealed inside the polyvinyl bag, and the patient is positioned inside the form as the foaming agent

expands and conforms to the patient's body contour. The foam continues to expand for approximately 10 to 15 minutes during which the therapists will need to vigilantly guide the foam around the patient to prevent the foam from escaping the bag and moving into locations of least resistance that may contribute little to immobilizing the patient. As with any immobilization device, adequate training is needed to form a high-quality customized patient mold and the manufacturer's instructions should be carefully followed. Chemical foaming agent systems generally require two therapists to form at the time of simulation, and the process can require approximately 30 minutes. Caution must be used to prevent chemicals coming in direct contact with skin as this may cause irritation.



A

B

C

FIGURE 7.5 Body conformal systems are used for treatment indications throughout the body. A and B. Two patients are shown in treatment position with the Alpha Cradle brand Patient Repositioning System, which uses a two-part foaming agent to create customized conformal body immobilization. C. Full-body vacuum-lock bag. D. Room used for storing vacuum-lock bags in the simulation suite at the University of Virginia. The simulation suite services multiple treatment machines at satellite locations. After simulation, the immobilization devices are transported to the satellite treatment sites via a courier service. (A and B. Images courtesy of Smithers Medical Products, Inc. Alpha Cradle™ is a registered trademark of Smithers Medical Products, Inc. C. Courtesy of CQ-Medical.)

Another class of body conformal systems, commonly referred to as "vacuum-lock bags," is comprised of an airtight bag filled with plastic mini-spheres. These bags are available in a variety of sizes to accommodate different treatment sites and patient positioning techniques. At the time of simulation, the bag is first conformed to the patient's body contour by pushing the mini-spheres to fill in around the patient. A vacuum pump is then connected to the bag and the air is evacuated from the bag, causing the plastic mini-spheres to lock together to rigidly retain the device's shape. During the evacuation, the therapists maneuver the mini-spheres within the immobilization device to provide optimal fit and stabilization of the patient's body contour. These vacuum-lock bags are made of a durable nylon material to resist tears or punctures and can be expected to retain their shape for 6 weeks or more. They are reusable and may require less time to generate a patient-specific mold than the expanding foam systems. Another advantage of the vacuum-lock bag is that if during the simulation process the device is found not to provide the intended level of immobilization or is found to be uncomfortable for the patient, it can be reinflated and remolded to achieve the desired shape as many times as necessary. Being reusable, the vacuum-lock systems do require a time commitment to clean and remove any setup marks prior to use with subsequent patients. Also, if a tear or puncture occurs during treatment, a new vacuum-lock bag would need to be formed and the simulation and treatment planning process may be repeated to deliver the remaining fractions. Each clinic is recommended to consider the benefits and drawbacks of each system and could consider utilizing both types of body conformal systems for different clinical scenarios.

As body conformal devices are used to treat a wide range of sites throughout the entire body, careful thought should be given to each specific case to ensure that the treatment site is properly immobilized, that the setup is reproducible from day to day, and that the patient is able to maintain the position for the duration of each fraction. An immobilization device that extends well beyond the treatment site to encompass adjacent anatomy can be more effective than a more local device that focuses only on the treatment region. Early work by Bentel et al[9] showed that for Hodgkin lymphoma a cradle that extends below the pelvis is more effective than a cradle that only includes the upper torso. Devices that extend around the patient also give the ability to make setup marks directly on the immobilization device for alignment. Aligning the beam to setup marks on the immobilization device can increase the daily setup reproducibility by reducing the reliance on skin marks, which can be especially troublesome for larger or older patients where the skin can be more mobile over the underlying anatomy. Marks can then be made on the patient to help align the patient within the immobilization device. Longer devices, for example, the full-body Vac-Lok from CQ-Medical shown in Figure 7.5C, also allow for longer setup marks to be made in the superior-inferior direction, which can help detect rotational setup errors.

As an early example of body conformal immobilization's efficacy, Bentel and colleagues at Duke University showed that immobilization with the Alpha Cradle expanding foam system reduced the frequency of physician-requested setup corrections based on portal images for a variety of treatment indications, including Hodgkin lymphoma and prostate, lung, and breast cancer.[9,10] It should be noted, however, that not all studies show a clear-cut advantage in setup accuracy with body conformal immobilization devices. For example, an early study by Song et al[11] showed no statistical advantage of using immobilization in the treatment of prostate cancer in terms of the number of deviations >5 mm as quantified on portal images. They did show that patients with bariatric needs tend to have larger setup errors, highlighting the fact that certain patient populations may be more difficult to set up than others.[11]

Hurkmans' assessment of setup accuracy based on portal imaging provides a good review of the early imaging-based immobilization assessment data up to 2001.[4] This work concludes that with appropriate setup, immobilization techniques, and portal imaging, systematic and random setup errors on the order of 2.5 to 3.5 mm should be achievable for treatments of the thorax, abdomen, and pelvis. The integration of CBCT units with treatment machines is an excellent tool for assessing setup accuracy and has proven to be highly valuable in studies comparing and evaluating various immobilization systems. CBCT has been especially helpful to study the setup accuracy of stereotactic immobilization devices, the subject of a later section in this chapter.

It should again be emphasized that the degree of interfraction setup accuracy achievable by a particular institution will depend on the skill and knowledge of the personnel involved in forming patient immobilization devices, setting up patients for daily treatments, making adjustments based on verification imaging, and the understanding of the limitations of each step of the process. Table 7.2 provides a top-level summary of the pros and cons of commonly available body conformal immobilization systems.

TABLE 7.2 EXTRACRANIAL IMMOBILIZATION DEVICE SUMMARY

Device Name	Description	Pros	Cons	Typical Sites	Reusable?	Indexed?	Relative Cost
Alpha Cradle	Expanding foam device custom-molded to patient body contour	Rigid immobilization for wide range of body sites	One time use One chance to achieve adequate and comfortable immobilization	Thorax, abdomen, pelvis, extremities	No	No	$$
Vacuum-lock bags	Nylon bag filled with plastic mini-spheres; upon evacuation, mini-spheres lock together to	Reusable Can quickly reinflate and re-form during simulation if necessary	Punctures, tears, or loss of vacuum may necessitate resimulation of the patient	Thorax, abdomen, pelvis, extremities	Yes	Some include indexing and, for those that do not, an indexing bar can be used	$$

Device Name	Description	Pros	Cons	Typical Sites	Reusable?	Indexed?	Relative Cost
	form a custom mold of the patient body contour.					to make indentations in the bottom of the bag for later setup with the indexing bar.	
Prone breast board	Prone breast board can improve dosimetry for patients with large, pendulous breasts.	Separates target tissue from chest wall to minimize skin folds and lung dose	May not be tolerated by all patients Poor visualization of treatment field alignment Not suitable for regional nodal irradiation	Breast	Yes	Yes	$$
Prone belly board	Prone board to help the small bowel fall out of the treatment fields	Displacement of bowel out of treatment field can reduce toxicity	May not be tolerated by all patients Variability in bowel sparing	Pelvis	Yes	Yes	$$
Modular stereotactic body immobilization systems	Indexed base board with a wide range of attachments for immobilization, localization, and motion management	Flexibility to treat variety of disease sites with SBRT Attachment of devices for abdominal compression, leg stabilization, etc	More room for storage More time for setup and indexing of attachments	Spine, lung, liver, abdomen, pelvis, neck	Yes	Yes	$$$

SBRT, stereotactic body radiation therapy.

Prone Positioning for Pelvic and Breast Treatments

The body conformal devices described earlier can help provide reproducible patient setup from day to day for a wide range of disease sites. The patient is most often positioned supine in these devices. For certain treatment indications, a prone setup may provide a dosimetric advantage. In pelvic and abdominal irradiation, the small bowel is an important organ at risk, and acute toxicity is correlated with the amount of small bowel that receives a high dose.[12] For patients receiving pelvic irradiation, a popular method is to use a belly board (Figure 7.6A) on which the patient lies prone with their stomach positioned over the cutout region. With the aid of gravity, the small bowel will fall into the board's cutout and can reduce the amount of bowel in the treatment fields. The use of a prone belly board has been demonstrated to reduce the volume of small bowel at all dose levels.[13-17] Even with intensity-modulated radiation therapy, the use of a belly board technique has been shown to further reduce the small bowel dose.[13,16,17]

A

B

FIGURE 7.6 Immobilization devices specifically designed for prone positioning. A. A prone belly board can be used in treating targets in the pelvis. Gravity assists small bowel migration out of the treatment fields, which can reduce treatment-related toxicity. B. A prone breast board can be advantageous for patients with large, pendulous breasts. The board features a cutout that is easily reversible for treatment of either breast. C. Prone breast board couch insert with right side breast opening from CQ-Medical, the setup shown was for CT simulation with gray risers below the couch insert. For actual treatment, the gray riser is not used. (A and B. Courtesy of Bionix.)

The magnitude of the small bowel reduction with prone belly board positioning can be highly patient dependent. Kim et al[13] correlated the amount of small bowel at the 50% isodose level with a patient's age, weight, and gender. For example, this work showed a larger amount of small bowel (total volume in milliliters) at the 50% isodose level for the subgroups of patients over 56 years old, female patients, and patients weighing <65 kg (143 lb). It must also be noted that some investigators have reported that the use of a belly board worsened the reproducibility of patient setup. For example, Martin et al[14] reported having to reposition the patient based on portal imaging 68% of the time with a prone belly board system, compared to 23% of the time with supine positioning. In contrast, Olofsen-van Acht et al[15] report similar setup reproducibility between prone positioning with a belly board and patients in the supine position. Each patient should be assessed at the time of simulation for the efficacy of the belly board method to displace the small bowel as intended, as well as the patient's ability to tolerate lying on the belly board itself. Kim et al[18] found nonsignificant dose differences in the bladder and small bowel between the prone and supine positions, but noted worse setup errors associated with the prone position, supporting the treatment of all preoperative patients with rectal cancer in the supine position with VMAT and CBCT image-guided radiation therapy (IGRT). Yang et al[19] reported that setup reproducibility in the supine position is better compared to prone position with belly board. And they observed potential dose reduction to the small bowel, in combination with affected target dose coverage.

Another site where prone positioning has been used is in the treatment of breast cancer. Figure 7.6B illustrates a patient positioned on a prone breast board offered by Bionix Radiation Therapy and Figure 7.6C shows the CQ prone breast couch insert solution. The patient is positioned on the cushioned platform with her face resting in a donut-shaped cushion. The patient can hold the hand posts to help improve reproducibility and comfort. The prone positioning is most efficacious for patients with large, pendulous breasts, although it may also be an effective option for patients with severe arthritis that may be unable to hold their arms over their head.[20] Patients with large breasts tend to have larger tissue separation, larger treatment volumes, worse surface irregularity, and an accentuated inframammary fold, which can cause these patients to have higher reported rates of toxicities such as high-grade dermatitis and fibrosis.[21]

The goal of prone positioning for breast treatment is to minimize the lateral tissue separation and thus improve dose homogeneity. Improved dose homogeneity may decrease the rate of late toxicities such as fibrosis—an undesirable cosmetic outcome, and decreased tissue separation can reduce the entrance dose

needed to provide target coverage at depth, which may decrease the overall hot spot for the treatment plan, particularly at the skin surface.[20] Improved dose homogeneity and decreased skin dose from prone positioning may also prove to be advantageous for hypofractionated breast regimens where larger doses per fraction are delivered. Five-year follow-up data from Stegman et al[20] have shown that the prone position offers comparable local control to traditional supine positioning for whole-breast irradiation, with lower levels of toxicity. With the breast hanging in the prone setup, it may also be possible to reduce the dose to other nearby normal tissues. The increased separation of the breast tissue from the chest wall has been shown to decrease the amount of irradiated lung in whole-breast irradiation.[22] Dose to the heart is more variable; for left breast patients, most heart doses (20-30 Gy levels) are decreased in the prone position, although some patients did exhibit higher heart doses when treated prone.[22]

It can be difficult to set up patients with large or pendulous breasts in a supine position because the breast can lie in a different position each day. In the supine position, a ring or tube can be used to keep the pendulous breast from folding over. With the aid of gravity, daily setup can be more reproducible with the breast hanging in the prone position. There are, however, potential disadvantages to the prone setup for patients with breast cancer, for example, reduced visibility of the breast for alignment purposes. Furthermore, the prone positioning may not be tolerable for patients who are elderly or have bariatric needs. And finally, the prone position may not be logistically suitable for patients requiring regional nodal irradiation as the prone position would severely limit visual alignment of an anterior supraclavicular field. Alternatively, immobilization bra could be an option for large or pendulous breast.[23,24]

Space Considerations

Whole-body expanding foam or vacuum-lock bag systems can provide excellent patient comfort and immobilization, but they are large devices that require storage space be considered. Adequate space is required to store each patient's custom-formed device for up to 6 weeks or more while a patient is under treatment. At the Emily Couric Clinical Cancer Center at the University of Virginia, a dedicated room next to the simulation suite and large closets in each treatment room are used for storing patient's body conformal immobilization devices (see Figure 7.5D). For clinics where one simulation suite is used to support multiple satellite clinics, the logistics of transporting the immobilization device must also be considered. At the University of Virginia, Virginia Commonwealth University, and Sanford Health, a courier service is used to transport large body conformal devices from the simulation site to satellite treatment facilities. Each clinic must assess space availability when deciding which systems to adopt in patient care.

DOSIMETRIC EFFECTS OF IMMOBILIZATION DEVICES

Any material placed between the patient and the radiation source can modify the dosimetric characteristics of the treatment beam. These materials, such as couch tops and immobilization devices, can have profound impact on patients, such as increasing skin dose, reducing tumor dose, or altering dose distribution. The American Association of Physicists in Medicine (AAPM) Task Group 176 has published an excellent report regarding the dosimetric effects of couch tops and immobilization devices including the basic physics rationale, a well-rounded literature review of relevant studies, and techniques that can be utilized to reduce and better model the dosimetric effects of these devices.[25]

Concerns regarding bolus effect have been reported for photon plans, resulting in clinically relevant skin toxicity due to the passage of beams through the couch top and immobilization devices.[25] Skin toxicity has been reported in the literature due to the failure to include the couch top and immobilization devices.[26-28] Hoppe et al[27] presented 7 out of 50 patients who experienced larger than grade 2 skin toxicity due to the lack of skin sparing from the immobilization device. An example is shown in Figure 7.7. And for inversely planned cases, even with the immobilization devices presented, skin can be contoured to lower its dose through the optimization process.[26]

FIGURE 7.7 Patient who developed grade 4 skin necrosis from stereotactic body radiation therapy. (Reprinted from Hoppe BS, Laser B, Kowalski AV, et al. Acute skin toxicity following stereotactic body radiation therapy for stage I non-small-cell lung cancer: who's at risk? *Int J Radiat Oncol Biol Phys*. 2008;72[5]:1283-1286. Copyright © 2008 Elsevier. With permission.)

Other than the observable skin effect, dose attenuation from couch top and immobilization devices is also a significant concern, which can result in tumor underdose and organs at risk overdose if not being taken care of. For photon plans, the average attenuation from couch tops is typically 2% to 5%, which can go up to 15% for certain parts of the couch top.[25] For proton beams, depending on the water equivalent thickness of the couch top or immobilization devices, the distal range of the particle beam will be shortened due to the material traversed if not incorporated into the calculation. This could, in theory, pull the dose completely away from the target to a shallower depth for small tumors and in the presence of thick attenuating materials.

It is recommended to incorporate couch tops and other immobilization devices (internal and external of the patient) and carefully verify the dimension and physical property of the material for accurate dose calculation.

STEREOTACTIC IMMOBILIZATION AND STABILIZATION

Introduction

Hypofractionated stereotactic techniques enable the radiation oncologist to deliver high-dose conformal radiation therapy with a sharp dose falloff to both intracranial and extracranial targets. Here, we describe stereotactic radiosurgery (SRS) as a single high-dose fraction to well-defined brain target(s), and stereotactic radiation therapy (SRT) as delivered over a small number (2-5) of high-dose fractions. Delivering a high dose to the target volume in only a few fractions increases the requirements for precise

delivery of the radiation. Advances in online image guidance have enabled the delivery of high-dose extracranial stereotactic treatments, and patient immobilization systems have evolved to help decrease interfractional variation in patient setup and intrafractional patient and target motion.

Intrafraction target motion occurs in lung and liver tumors because of normal physiologic processes such as respiration, and longer treatment times associated with high-dose SRT may increase the risk of intrafraction motion.[30] Numerous immobilization-based strategies to minimize this motion are discussed later in this section. In general, intrafraction error from patient movement within the device during treatment can be reduced by improving the comfort and stability of the immobilization system. As with all immobilization methods and devices, patients with poorer performance status may have worse interfractional setup reproducibility and more intrafraction motion within the immobilization device,[31] so patient- specific immobilization options may need to be considered.

Intracranial Immobilization Devices

Intracranial immobilization devices can generally be classified into two categories: invasive and noninvasive, which are reviewed in the following sections. Other important characteristics include if the device is relocatable or not, and what system is used to align the patient for treatment.

Invasive Cranial Immobilization

Invasive cranial immobilization devices enabled intracranial SRS treatments prior to the widespread adoption of in-room image guidance and are exemplified by rigid metal frames attached to posts and metal pins driven directly into the skull. The patient then undergoes imaging (CT, magnetic resonance imaging [MRI], or angiography, depending on device compatibility), a treatment plan is then developed, and at the time of treatment, the head frame is connected to either a floor-mounted stand or the treatment table to provide rigid cranial immobilization. The primary advantage of the invasive, frame-based, nonrelocatable stereotactic head frame is the rigid immobilization it provides, with accuracy generally reported on the order of <1 mm.[32]

For example, the Leksell Stereotactic Coordinate Frame G (Elekta, Stockholm, Sweden) (Figure 7.8) was shown in a phantom study on the gamma knife system using GafChromic film to achieve overall accuracy (mean ± standard deviation) of an MR-defined target to be 0.21 ± 0.32 mm and 0.15 ± 0.26 mm in the *x*- and *y*-axes, respectively, and 0.06 ± 0.09 mm and 0.04 ± 0.09 mm for a CT-based target.[32]

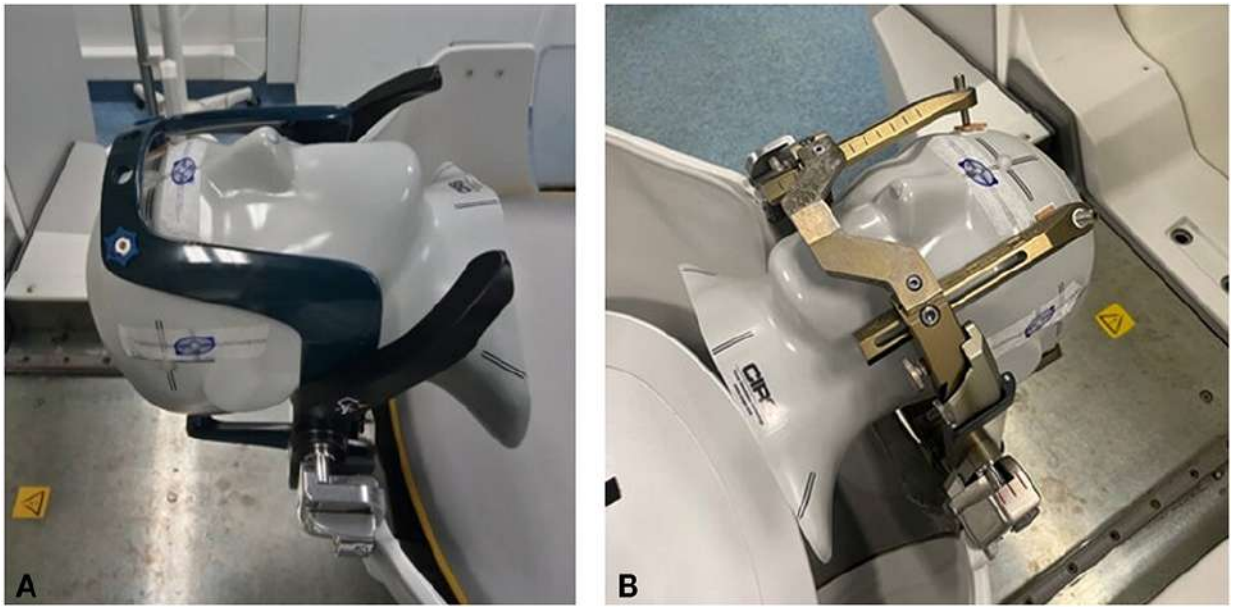


FIGURE 7.8 The Leksell® (A) Vantage Frame (B) G-Frame fixed to the head via screws. (From Vincent M, Michel-Amadry G, Nigoul JM, Beltaïfa Y, Régis J. Spatial accuracy of the stereotactic Leksell®Vantage™ head frame in comparison with the standard stereotactic Leksell®G frame for Gamma-Knife. *Biomed Phys Eng Express*. 2023;9[3]:035021. Copyright © Institute of Physics and Engineering in Medicine. Reproduced by permission of IOP Publishing. All rights reserved.)

A disadvantage of these invasive, nonrelocatable devices is that they are for the most part limited to single-fraction SRS, requiring frame placement, imaging, planning, quality assurance, and delivery to occur in the same day before the frame can be removed.

Noninvasive Cranial Immobilization

Invasive cranial immobilization devices have been successfully used for many years to deliver intracranial SRS, but these systems require placing of screws into the patient's head, which carries the risk of bleeding and infection and requires premedication and dedicated nursing support.[33] The compressed treatment planning time required for nonrelocatable systems may also be less desirable in certain scenarios. Numerous relocatable and noninvasive systems have been developed that can provide accurate and reproducible immobilization of the head without the use of screws driven into the skull and provide the flexibility to deliver multifraction SRT.

Frameless brain stereotactic immobilization systems aim to achieve sub-millimeter accuracy by minimizing both the initial setup difference between CT simulation and treatment sessions (interfraction uncertainty) and patient motion uncertainty during a treatment session (intrafraction error). Advanced thermoplastic mask systems specifically for brain stereo are designed to far exceed the performance of standard thermoplastic masks for conventionally fractionated treatments and often share a number of common features including custom immobilization of both the anterior and posterior aspects of the patient's head and some ability to "shim," that is, tighten or loosen the mask fit as needed for patient weight loss or swelling from steroids, respectively. Some systems, like the CQ-Medical Solstice System shown in Figure 7.9, include the ability to manually fine-tune rotations, in this case pitch. The radiation oncology field has leveraged the widespread adoption of in-room image guidance systems for patient positioning to increase our confidence in treating patients undergoing brain stereo with frameless thermoplastic mask systems by quantifying the stability that can be achieved when utilized appropriately.

FIGURE 7.9 The Solstice noninvasive mask system uses a rigid head cup to connect an open-faced thermoplastic mask. A patient-specific cushion is used to cradle the posterior head and neck. The open-faced mask design allows intrafraction monitoring and the rigid head cup includes a manual pitch adjustment, which can be used to perform pretreatment setup corrections or at CT simulation to optimize patient comfort and stability. (Courtesy of CQ-Medical.)

Early generations of frameless stereotactic brain masks have laid the foundation by confirming sub-millimeter intrafraction accuracy is achievable, for example, the BrainLab three-piece plastic mask system. Ali et al[34] evaluated the setup accuracy of the BrainLab mask system with the classic localizer box by acquiring verification onboard kilovolt images and reported mean shifts of 0.7 ± 2.0 mm, 1.6 ± 2.6 mm, and 0.1 ± 2.2 mm, respectively, in the *x*, *y*, and *z* dimensions. The random setup errors exhibited by standard deviations larger than 2 mm support the argument for daily pretreatment image guidance as opposed to relying solely on the localizer box.

The achievable intrafraction accuracy of open and full coverage mask systems for brain stereo has been confirmed with numerous studies utilizing pre- and post-CBCT imaging, for example, Ohira et al[35] compared two available systems used equally among 76 patients undergoing total brain stereo over 349 total treatments and reported similar sub-millimeter stability with both mask systems. An interesting analysis from Komiyama et al[36] assessed 89 patients undergoing brain stereo immobilized with the Encompass system by acquiring pre- and post-CBCT as well as MV images (anteroposterior [AP]/posteroanterior direction) at each couch angle before treating that beam. Using 2D-2D match data from the mid-treatment MV imaging, they convincingly show that on average, frameless brain stereo mask systems can provide sub-millimeter accuracy, although outliers with mid-treatment deviations >1 mm do happen. Building on lessons like these, many modern brain stereo mask systems offer an open face solution to support intrafraction patient monitoring in near real time, a topic treated in more detail in later sections. And finally, the recent expansion of commercially available systems to treat multiple brain met targets off-axis with a single isocenter should be noted to increase the importance of maintaining both sub- degree and sub-millimeter accuracy throughout treatment.

Extracranial Immobilization Devices

In 1995, Hamilton and colleagues from the University of Arizona published their preliminary clinical experience with linear accelerator–based SRS of the spine in five patients.[37] For immobilization, surgical clamps were secured directly to the spinous processes one to two vertebral levels above and below the target volume under local or general anesthesia, through a 2 cm incision. The spine was rigidly immobilized

by attaching the clamps to a frame consisting of a rigid box with two semicircular metal arches. After CT simulation and treatment planning, the patient and frame were transferred to a modified linear accelerator and setup according to stereotactic coordinates derived from the planning CT. While this highly invasive device was important in demonstrating the feasibility of extracranial stereotactic body radiation therapy (SBRT), modern immobilization systems for extracranial SBRT utilize noninvasive customizable devices like the previously described body conformal vacuum-lock bags, with added features and attachments to allow for more precise initial positioning and improved intrafraction stability.

One example of a modular immobilization system for extracranial SBRT includes the Alta platform from CQ-Medical depicted in Figure 7.10. SBRT-specific frames like these include indexing along the entire length of a lightweight carbon fiber platform allowing reproducible isocenter localization and for accessories to be attached. Attachment options typically include headrests, forehead restraints, upper arm supports, shoulder restraints, thigh and foot positioners, external fiducial arches, and abdominal compression devices. Newer platforms like the Alta are also designed to accommodate clam-shell-style mask systems for stereotactic brain treatments or angled breast boards.

FIGURE 7.10 The Alta platform is a modular immobilization system that can be used for many indications, including stereotactic body radiotherapy. A myriad of attachments are available to build a device customized to the needs of each patient. This particular setup uses an abdominal compression plate and a thigh arch for treating stereotactic targets in the lung. (Courtesy of CQ-Medical.)

Numerous investigators have assessed the reproducibility of these extracranial SBRT immobilization systems. Foster et al assessed pretreatment and mid-treatment CBCT data for 1,005 stereotactic treatment sessions, including lung, liver, prostate, and spine tumors, and reported interfraction setup errors of (mean ± standard deviation) 2.4 ± 3.8 mm in the AP direction and 1.3 ± 5.8 mm in the superoinferior (SI) direction, when using a dedicated stereotactic body immobilization system.[29] Purdie et al[30] evaluated the intrafraction positioning reproducibility by comparing pretreatment localization CT to a mid- or posttreatment CBCT with the Elekta Stereotactic Body Frame in 28 patients with lung SBRT. The mean 3D tumor position was within 2.2 ± 1.2 mm of the planned position when repeat imaging was performed within 34 minutes of target localization, and 5.3 ± 3 mm when performed more than 34 minutes after target localization ($P <$ .01). While this particular device is no longer commercially available, this study highlights the important consideration that longer treatment times can increase the intrafractional positioning error.

The Elekta BodyFIX is another example of a body conformal system with features specifically designed for SBRT. The distinguishing characteristic of the BodyFIX system is a thin clear plastic cover sheet that uses an active vacuum pump to create negative pressure providing additional immobilization of the patient. A study of 126 patients with lung SBRT used pre- and posttreatment CBCT to determine intrafractional stability of the BodyFIX system and reported the intrafractional variation of mean tumor position to be 2.7 ± 2.6 mm.[38]

Immobilization and Internal Motion Management

In addition to intrafraction error caused by patient movement within the immobilization device, internal target motion due to breathing must be accounted for in SBRT, particularly in the treatment of lung and liver tumors. The reports of AAPM Task Groups 76 and 101 address the management of respiratory motion in radiation therapy and present the results of a variety of studies showing that lung and liver targets exhibit a wide variation in motion amplitude during respiration.[39,40] While technology has continued to evolve since their publication, these reports are still highly regarded resources since the well-described mechanics of respiration and the risks of treating moving targets remain unchanged.

Numerous motion management strategies are available to account for and/or control internal target motion from respiration in radiotherapy, including abdominal compression, breath hold (BH), active breathing control, respiratory gating, and real-time tumor tracking. Brandner et al's review[41] provides an excellent overview of the risks and benefits associated with each motion management strategy for stereotactic treatment of lung and upper abdominal tumors.

Abdominal compression attachments are available with most modern stereotactic immobilization systems and are generally intended to physically limit a patient's respiratory amplitude. This technique is also referred to as forced shallow breathing. Abdominal compression devices typically consist of a plate attached to an arch that is indexed to a stereotactic body frame or the treatment couch. The plate is placed a few centimeters below the patient's xiphoid process and a screw is tightened until the desired amount of internal motion control is achieved. The screw is marked so that it can be reproducibly tightened for multiple fractions. This rigid plate is appropriate for lung targets since the treatment beams will not pass through the high-density arch and plate. For abdominal targets, inflatable compression belts are preferred as they are of lower density and thus affect the beams passing through it to a lesser extent.

Studies report varied results with the use of abdominal compression in reducing lung tumor motion amplitude. Bouilhol et al[42] studied lung tumor motion in 27 patients with lung SBRT using two four-dimensional (4D)CT scans at the time of simulation: with and without abdominal compression. As most practitioners would expect, abdominal compression reduced tumor motion for lower lobe lesions the most, with a modest average motion reduction of 3.5 mm. For upper lobe lesions, the average motion reduction was only 0.8 mm, and concerningly 5 of the 27 patients were observed to have increased motion with abdominal compression. Furthermore, the dosimetric gain of the compression on lung sparing in planning was shown to be minimal. Thus, a potential workflow for patients with lung SBRT could be to first assess target motion without abdominal compression, and then re-4DCT with abdominal compression added if motion is of a concerning magnitude.

The value of abdominal compression is clearer for abdominal targets like liver and pancreas. The mean amplitude for liver motion measured with fluoroscopy was shown to decrease from 40 mm with free breathing to 11 mm with the use of abdominal compression.[43] Another study showed that while abdominal compression reduced the SI and AP motion, an increased motion amplitude in the left-right dimension of 15% on average (maximum 1.6 mm) was observed,[44] indicating that compression may also be redistributing breathing motion.[39]

BH is another common technique that greatly changes the patient's natural respiratory pattern, so this topic will be discussed in the following section on optical surface imaging.

Respiratory gating and real-time tumor tracking are outside the scope of this chapter since they primarily rely on additional technology to treat the moving target in a subset of its observed motion range without modifying the patient's breathing in a fundamental way. Although not treated in detail here, clinics considering respiratory gating and/or real-time tumor tracking are referred to review AAPM recommendations due to the very real risk of missing the moving target due to intrafraction breathing changes leading to target displacement from isocenter, which have been observed to occur in as little as a few minutes while the patient is on the treatment table.[39,40,45,46]

REAL-TIME MONITORING OF PATIENT POSITIONING

Introduction to Intrafraction Monitoring with Surface-Guided Radiation Therapy

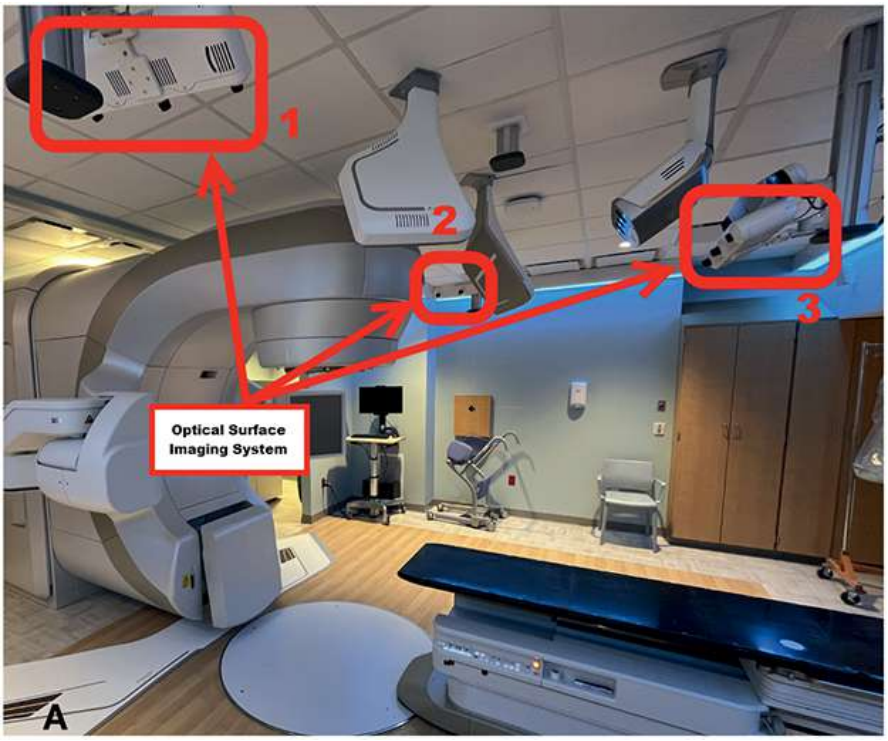
As established throughout this chapter, immobilization devices are crucial tools for the appropriate delivery of radiation treatments. They promote consistent setups throughout the course of radiotherapy and help patients hold their treatment position for the duration of each fraction. However, these systems have their limitations, and it cannot be assumed that the planned position is accurately replicated and maintained thanks to immobilization devices and pretreatment imaging alone. Moreover, these tools oftentimes must balance patient comfort with motion restriction. Hence, although immobilization devices conform to the patient and limit their mobility, patients can still move during treatment. This becomes progressively worrisome as margins are reduced and fraction doses escalate. Under these conditions, patient monitoring during treatment to detect undesired intrafraction motion becomes especially important.

Surface imaging systems can help facilitate patient setup and allow for intrafraction monitoring without the use of additional ionizing radiation, in what is known as surface-guided radiation therapy (SGRT). Optical surface guidance systems have become rapidly accepted in radiation oncology over the past decade due to sub-millimeter accuracy and sub-second feedback without any imaging dose. A system from BrainLab combines thermal and optical cameras to monitor patient's positions with sub-second temporal feedback paired with orthogonal in-room x-rays for periodic bony or fiducial imaging. Using Cherenkov radiation generated from the patient during beam-on is another interesting concept finding its way toward clinical utility.

Please note that while SGRT can be useful for initial positioning of any site, internal imaging must be performed when the target location might not properly correlate with the surface. Intrafraction monitoring with surface guidance systems can be used to detect external motion or even track breathing,[47] but this does not necessarily reflect the true target motion as not all internal involuntary movements will be revealed by the patient's surface. It is crucial to understand the technology, the information these systems provide, and their limitations to ensure they are used correctly and to their full potential. This section aims to give the reader a general overview of these systems, their characteristics, and some typical clinical uses, then finishes with two emerging technologies in radiation therapy monitoring.

Overview of Selected Optical Surface-Guided Radiation Therapy Systems

Optical imaging systems (Figure 7.11A) acquire a 3D map of the patient's surface in the treatment room and compare it to the patient's planned surface position, known as the reference surface. The reference surface is typically generated from the external CT contours and isocenter location from the Digital Imaging and Communications in Medicine (DICOM) files and is first used for initial patient in-room setup. A new reference surface can be captured at meaningful time points during the treatment, to create a re-zeroed patient surface reference for ongoing monitoring. For example, a reference surface captured shortly before, during, or after CBCT acquisition allows the team to verify, before applying the IGRT-indicated shifts, that the patient's surface has been stable during the time window needed for image matching, review, and approvals.



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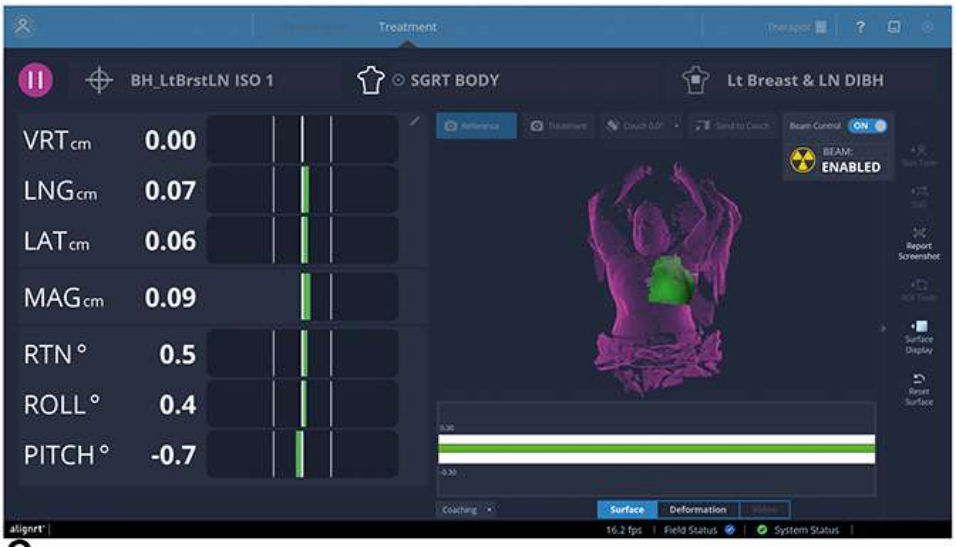


FIGURE 7.11 A. The optical surface imaging system consists of three ceiling-mounted camera pods to acquire a patient's surface in the treatment room. B. The system projects a visible pattern of light on the patient's surface to guide the therapists in aligning the patient to the reference surface. C. Monitors in the control and treatment rooms provide the therapists with real-time feedback about the current alignment of the patient's current and reference surfaces including rigid translations and rotations to help align the patient prior to treatment and track intrafraction surface motion during treatment.

The approach to obtain the real-time patient surface and its registration with the reference surface varies depending on the specific surface imaging system, although all provide six degrees-of-freedom (DoF) correction estimates to move the patient's observed surface closer to the chosen reference surface. Three main manufacturers of surface imaging equipment for radiotherapy are: Vision RT (London, UK) who manufactures the AlignRT system, C-RAD (Uppsala, Sweden) who manufactures the Sentinel and Catalyst systems, and LAP (Luneburg, Germany) who manufactures the LUNA 3D system. Each system uses a different approach in both physically acquiring the current surface and registering the acquired and reference surfaces. This list is not meant to be a comprehensive description of all available options but merely an introduction to a few examples that illustrate the current state of technology in optical surface imaging.

The C-RAD family of optical surface guidance systems includes Sentinel and Catalyst products. Sentinel is used at the CT simulator for respiratory tracking during 4DCTs and other gated scans, whereas the Catalyst family of systems is used for patient positioning and monitoring during treatment. The C-RAD Sentinel system comprises a sweeping visible red laser (635-690 nm wavelength) and a camera that captures the reflected light as the laser sweeps across the patient at discrete intervals to read their surfaces. It takes approximately 1 to 2 seconds to scan a length of 40 cm with a measurement reproducibility of 0.2 mm, and it detects respiratory signal with a frequency of 15 Hz. The C-RAD Catalyst system comprises one or three ceiling-mounted pods in the treatment room and facing the machine isocenter. In contrast with Sentinel, Catalyst uses light in the near-invisible violet range (405 nm), allowing the full patient surface to be read at once, instead of with discrete laser sweeps, which allows for scan speeds greater than 80 frames per second (fps). The position and motion detection accuracy is quoted as 1 mm for the standard system and 0.5 mm for the HD system. Details of the performance of these systems can be found in the literature.[48-50]

Vision RT offers a family of surface imaging systems that allow for patient positioning and monitoring during treatment (AlignRT), respiratory tracking at simulation for 4DCT acquisition (GateCT), and gating during treatment delivery (GateRT). AlignRT is typically a three-pod system mounted on the ceiling, with each pod containing two cameras and a projector that casts a red light speckle pattern on the patient. The stereoscopic cameras read the structured light projection pattern and reconstruct the patient's surface based on the deformation of the known pattern. The patient's current acquired surface is then rigidly registered to

the reference surface in the area defined by the user as the region of interest (ROI) (Figure 7.11B). The frame rate for this system depends on the size of the ROI and is typically at least 8 to 12 fps for thorax ROIs (Figure 7.11C). There is literature on its use in radiation therapy for all treatment sites, but especially in left-sided breast deep inspiration breath hold (DIBH) treatments[51-53] and SRS,[54-56] presented in more detail in later sections.

Thermal Imaging: BrainLab ExacTrac Dynamic System

The newer generation of BrainLab ExacTrac Dynamic, launched in 2020, comprises a kilovolt x-ray imaging system and a 4D thermal camera, which is made up of an optical surface tracking system and a thermal surface tracking system (Figure 7.12). Optical surface tracking systems, using the structured light scanning technique to determine the surface information, can struggle in tracking small, flat areas with little topographic variation. BrainLab claims the added thermal information integrates an additional dimension as depicted in Figure 7.13, allowing high patient positioning tracking accuracy compared to the surface-only option.[57]

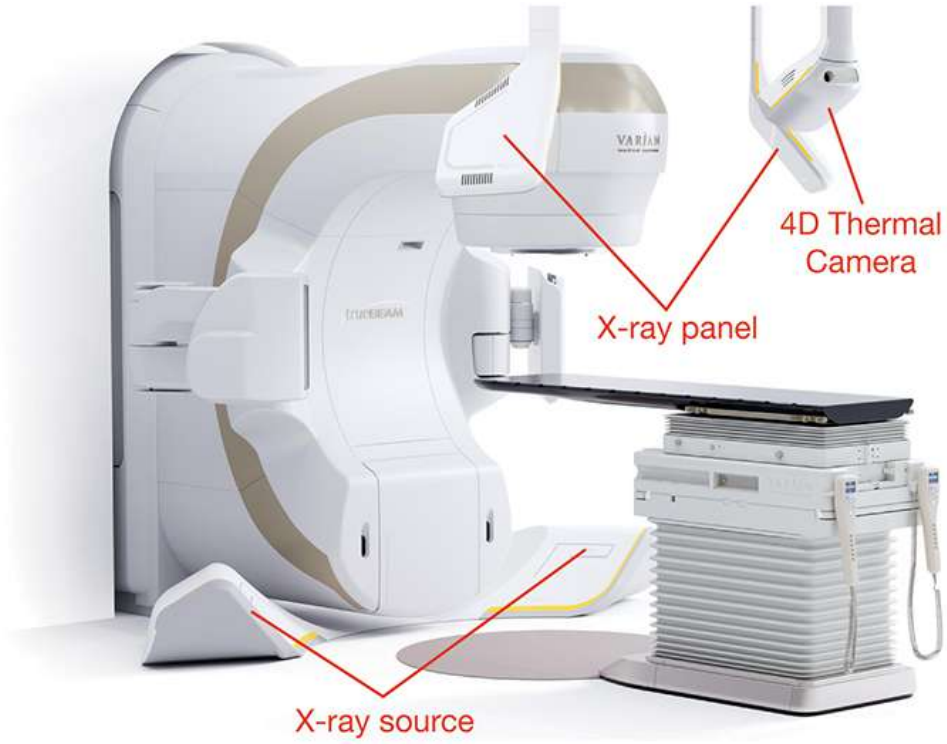


FIGURE 7.12 Room configuration for BrainLab ExacTrac Dynamic System. (Courtesy of Brainlab.)

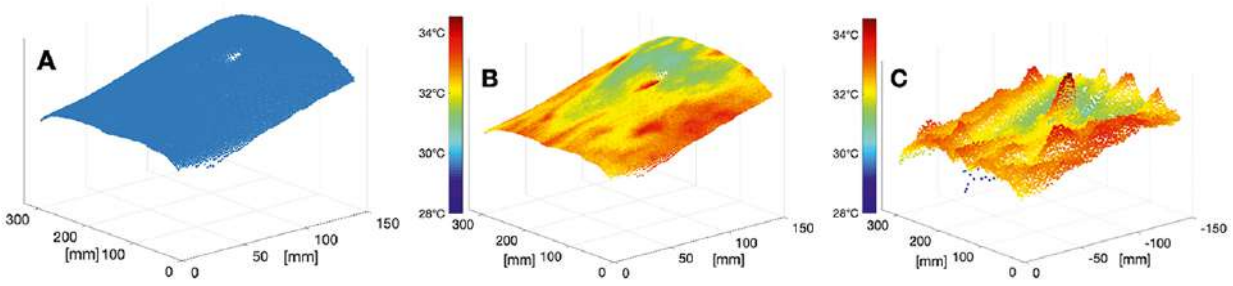


FIGURE 7.13 A. Preposition of the patient before treatment by matching the live three-dimensional (3D) surface with the reference contour. B. Combining the 3D and two-dimensional thermal data using the perspective-*n*-point algorithm to calculate a hybrid 3D/thermal matrix. C. Use of geometric and thermal data to match the reference data and the live surface. (Courtesy of BrainLab.)

Da Silva Mendes et al[58] concluded the ExacTrac Dynamic system is in close agreement (within 0.4 mm) with CBCT. Similar findings can be found by other authors.[59,60] Gutiérrez et al[61] published their verification study and stated with the help of both kilovolt x-ray and surface tracking that no margin is needed to compensate for intrafraction motion except for very small lesions (<0.1 mL). Additionally, BrainLab introduced ExacTrac Dynamic Surface in 2023, which consists of only the 4D thermal camera as their SGRT-only solution.

Current Clinical Applications

Initial Patient Setup

Current commercially available systems use a reference surface of the patient to guide therapists during initial in-room setup. The reference surface for daily alignment is generated from the CT planning data contours, acquired from a SGRT system at the time of simulation, or acquired during an earlier treatment fraction, typically following x-ray image-guided alignment.

As the patient's current surface is read and compared to the reference surface in near real time, six DoF shift information is displayed as three translations (vertical, longitudinal, lateral) and three rotations (yaw, roll, and pitch). Feedback about the deviation between the current surface and the reference surface is either projected on the patient's skin or shown on a screen, informing therapists what adjustments are needed to achieve the ideal match to the patient's reference surface. Once the desired external position has been achieved, anatomic alignment should be confirmed with internal image guidance techniques and a new reference surface acquired, if positioning adjustments are made.

Surface imaging systems give users the option to acquire a new reference surface with the optical cameras to guide patient alignment, and the pros and cons of acquiring a new reference surface should be considered in detail, for which the reader is referred to TG-302 (in particular table 6 of the reference).[62] The optical camera systems tend to capture a larger extent of the patient's external anatomy when compared to the DICOM reference from the CT. The purpose of updating the reference surface is 2-fold: (a) having a reference with extended external anatomy may facilitate setup for subsequent fractions, for example, of the elbows in arms-up positioning, and (b) re-baselining the reference position will allow for improved intrafraction monitoring sensitivity.

Although ideally the patient's external surface should exactly match the planning position every time, this is rarely the case in practice. If the patient's current position is found to be acceptable as confirmed with internal imaging, acquiring a new reference surface will zero out any residual surface offsets between the patient's approved treatment position and the original patient surface from the time of simulation. Hence, any change in the patient's surface ROI (ie, motion) throughout the fraction will become more obvious in the displayed shift values. This is even more important if the surface imaging system interfaces with the treatment machine to gate the beam. Removing the inherent shifts between the current approved treatment surface and the original reference will allow for tighter monitoring thresholds for any given

fraction and less beam interruptions from false large readings. It is important to note that for most commercial systems, the original reference surface based on the DICOM information remains available for selection throughout the course, giving the option to perform initial alignment with either an acquired reference surface or the DICOM CT sim surface at any time.

Surface imaging's usefulness in initial patient positioning is reflected in some clinic's decision to completely move away from permanent tattoos for initial setup marks on the patient's skin and instead rely entirely on the surface imaging system.

Surface imaging may be used for the initial positioning and monitoring of patients treated at any anatomic site; however, it has shown special utility for BH treatments for breast, lung stereo, and abdominal stereo as a surrogate for BH stability. It is also a highly valuable system for brain stereo because of the close correlation between the surface and the internal target position, sub-millimeter spatial accuracy, and near-real-time monitoring.

Deep Inspiration Breath Hold for Breast Radiotherapy

DIBH treatments for patients with left-sided breast cancer can provide cardiac sparing because the heart moves further away from the chest wall, and hence from the treatment volume, as the lungs inflate.[51] Surface imaging has emerged as a useful tool for voluntary DIBH treatments. The use of this technology can achieve reproducible patient setups and reasonably consistent distances between the heart and the chest wall during BHs, reliably minimizing cardiac side effects from radiotherapy.[51,62] When using SGRT for this purpose, the external surfaces from both a free-breathing and a DIBH scan are sent to the system. The patient is initially set up in-room to the free-breathing scan, and the BH reproducibility is checked with the DIBH DICOM CT sim reference surface, as recommended by TG-302 to help confirm BH reproducibility. An important point to describe clearly in the institutional workflow is which couch adjustments are allowed for initial setup and which are not. For example, adjusting the patient's vertical position with couch movement while in DIBH might mask BH reproducibility issues; if the BH was less deep than at CT sim, the couch vertical adjustment could bring the heart closer to the treatment beam than planned.

After the BH depth is confirmed in-room with SGRT, internal imaging such as CBCT should be acquired to calculate couch corrections and confirm target and heart position. Before applying the shifts, operators should have well-defined institutional workflows in place to confirm that the patient's BH level is consistent, then apply the shifts, and potentially capture a new reference. The choice of final reference surface used for confirming each BH's consistency prior to beam-on, with some systems allowing automatic BH using preset tolerances from the DIBH reference surface, typically is 3 to 5 mm.

Breath Hold for Body Stereo

BH for lung and abdomen stereo targets is commonly employed as it holds the promise of significantly reducing internal target volume (ITV) motion margins compared to free breathing. This promise does come with additional risk of geometric target miss that can be mitigated by understanding the subtleties of the BH maneuver, and the essential realization that BH-to-BH consistency is never guaranteed. In a survey of 87 clinics in Australia and New Zealand published in 2022, BH was reported in use at 41% of the clinics,[63] so it is relevant to outline how immobilization and monitoring can play roles in institutions creating and maintaining workflows to guide team members in this advanced procedure.

DIBH is commonly considered for lung stereo as it would naturally increase lung volume and thus confer improved lung sparing, although reports in the literature can provide a different perspective. Brandner et al's 2017 review[41] includes an excellent summary of literature on the topic of BH for body stereo and points to data that suggest that the end-exhale phase is often more reliable in reproducing the target's internal position. Lens et al[64] assessed abdominal organ velocity during both inhale- and exhale-BHs using cine MRI with 0.6-second time resolution and reported improved organ stability during exhale-BH, which is of interest for patients undergoing abdominal stereo. Wölfelschneider et al[65] shared their experience monitoring exhale-BH surface reproducibility for patients undergoing lung stereo, reporting that 15 of 20 patients showed end-exhale-BH surface reproducibility within 5 mm, showing exhale-BH could indeed be

potentially considered for select patients undergoing stereotactic procedures. The varying experiences with the efficacy of BH in radiotherapy reported in the literature hint at a bigger picture realization: that a workflow built around a single kind of BH (deep inspiration, normal inhalation, expiration, etc) may not be optimal or feasible for all patients undergoing stereotactic lung and abdomen procedures. Thus, when possible and practical, it is important to consider workflows that support patient-specific motion assessment and the application of meaningful motion management tools at the time of CT simulation.

Confirmation of BH-to-BH reproducibility at the time of treatment is another important point for body stereo workflows to consider. For example, at one author's institution (Sanford Health), three BH-CTs are acquired for three different BHs at the time of CT sim to provide an opportunity to assess BH-to-BH consistency and to generate a pseudo-ITV structure. For BH stereo treatment, each CBCT is consciously acquired with two to three independent BHs to allow some averaging of the internal target positioning on repeat BHs. This can increase confidence in the matching process that the BH-ITV is still adequate for the current treatment fraction.

Intracranial Stereotactic Radiosurgery

Patients with intracranial SRS can also benefit from SGRT setup and monitoring. Conventional masks used for frameless SRS are not suitable for SGRT because they cover the patient's entire face; SGRT technology requires uncovered skin for proper tracking. Open masks allow for immobilization of the patient while maintaining part of the face exposed for surface monitoring. Open mask immobilization in this scenario has the advantage of both allowing continuous tracking of the patient's surface directly, instead of monitoring infrared markers on the mask, and providing increased patient comfort. Several authors have published on the feasibility and accuracy of this technique, reporting the considerations necessary to achieve sub-millimeter accuracy for radiosurgery.[66,67] While initial positioning should always be confirmed with internal volumetric imaging to ensure the target alignment is within the tight planning margins, the use of surface imaging for these treatments allows for real-time monitoring of the patient without any additional ionizing radiation dose.

Emerging Technology for Monitoring

Ocular Tracking

A novel system of immobilization and tracking for uveal melanoma treatment is shown in Figure 7.14. The patient's head is immobilized in a thermoplastic mask, as is typical for H&N treatments, while the eye position was monitored in real time with an infrared camera. In this way the stereotactic treatment could be interrupted if the patient's eye position moved during the treatment.[68]

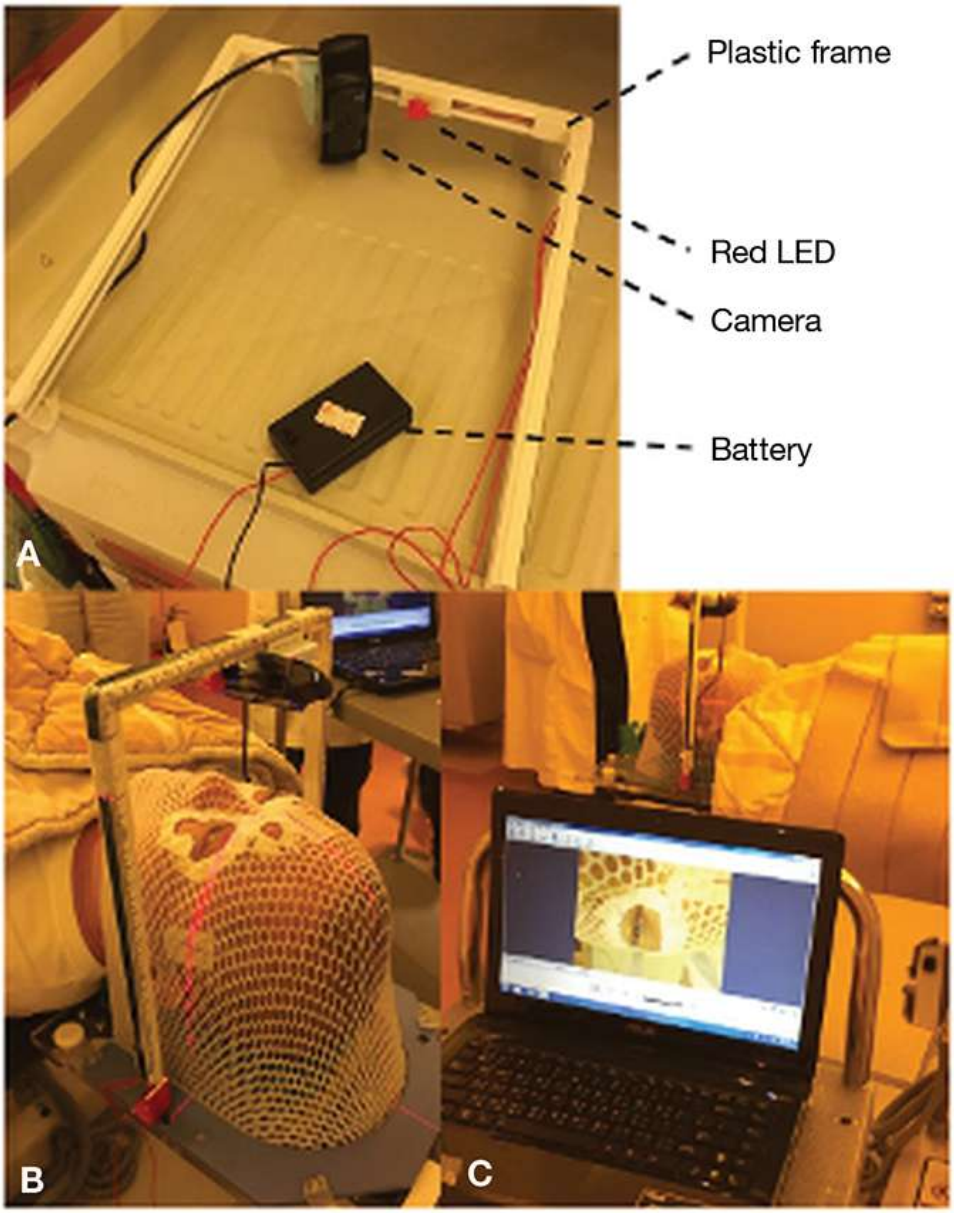


FIGURE 7.14 The noninvasive eye fixation device. A. The noninvasive eye fixation device consists of a plastic frame, a red light-emitting diode at the center, and a camera at the contralateral side. B. The device was customized and screwed on the thermoplastic head shell at the time of simulation. C. The eye position was monitored in real time and the eyeball was tracked with a camera. (Reprinted from Tsui MC, Chia-Hsien Cheng J, Lin CP. Stereotactic radiosurgery for medium and large uveal melanoma with a non-invasive eye immobilization device, a single institutional case series. *J Formos Med Assoc*. 2023;122[11]:1117-1124. Copyright © 2023 Formosan Medical Association. With permission.)

Cerenkov Radiation Camera Systems

Cerenkov radiation is a well-known phenomenon in which radiation is emitted when a charged particle, such as an electron, is traveling through a medium and its phase velocity is greater than the speed of light in that medium. It can be considered the equivalent of a "sonic boom." There has been growing work on the detection of Cerenkov radiation emitted from a patient's surface during radiation treatment; the clinical setup is demonstrated in Figure 7.15. Cerenkov imaging systems can be used in a variety of methods in radiation therapy. They can be used to confirm patient setup, to ensure that the patient radiation field does

not leak into unintended areas (such as the contralateral breast as shown in Figure 7.16), as well as a real-time dosimeter.

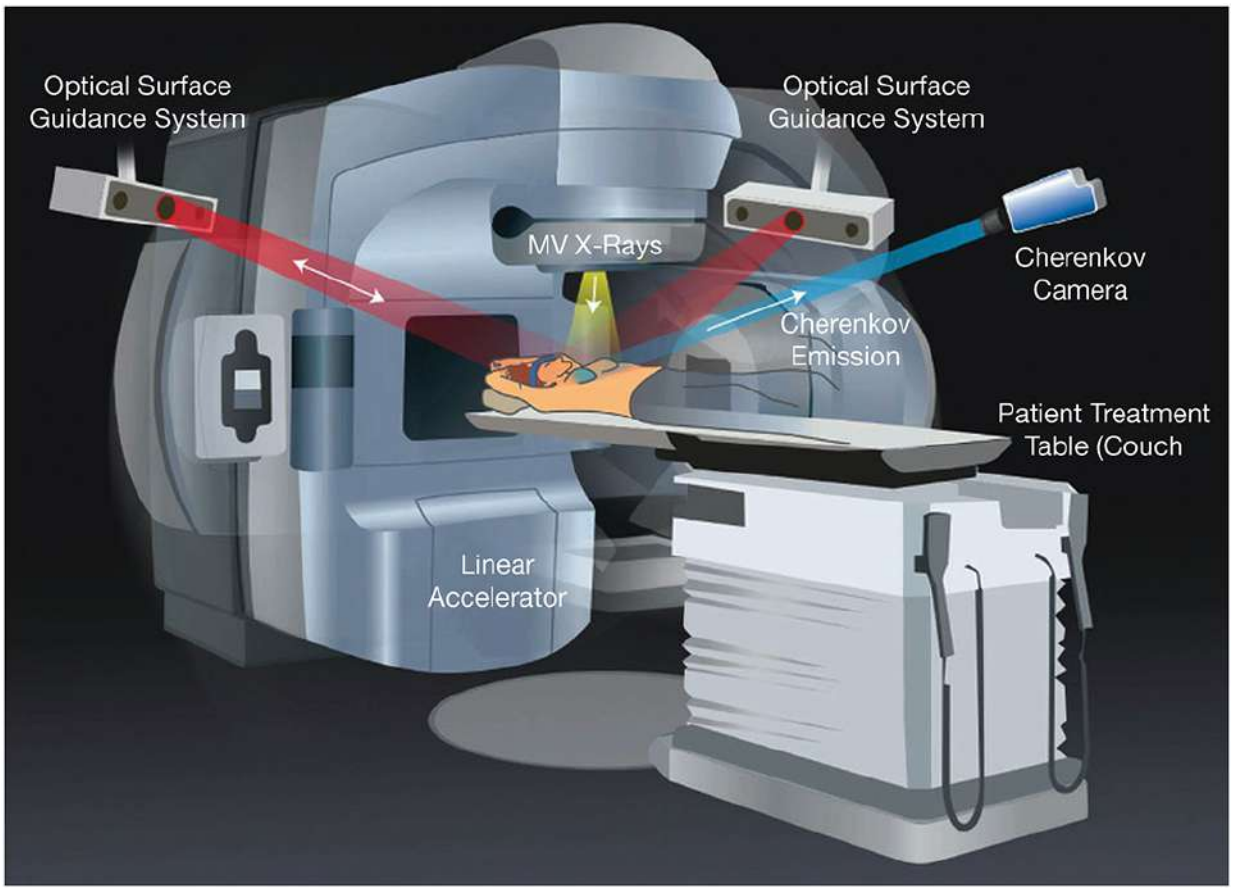


FIGURE 7.15 Room setup with Cherenkov cameras. (Reprinted from Hachadorian RL, Bruza P, Jermyn M, Gladstone DJ, Pogue BW, Jarvis LA. Imaging radiation dose in breast radiotherapy by x-ray CT calibration of Cherenkov light. *Nat Commun*. 2020;11[1]:2298. http://creativecommons.org/licenses/by/4.0/.)

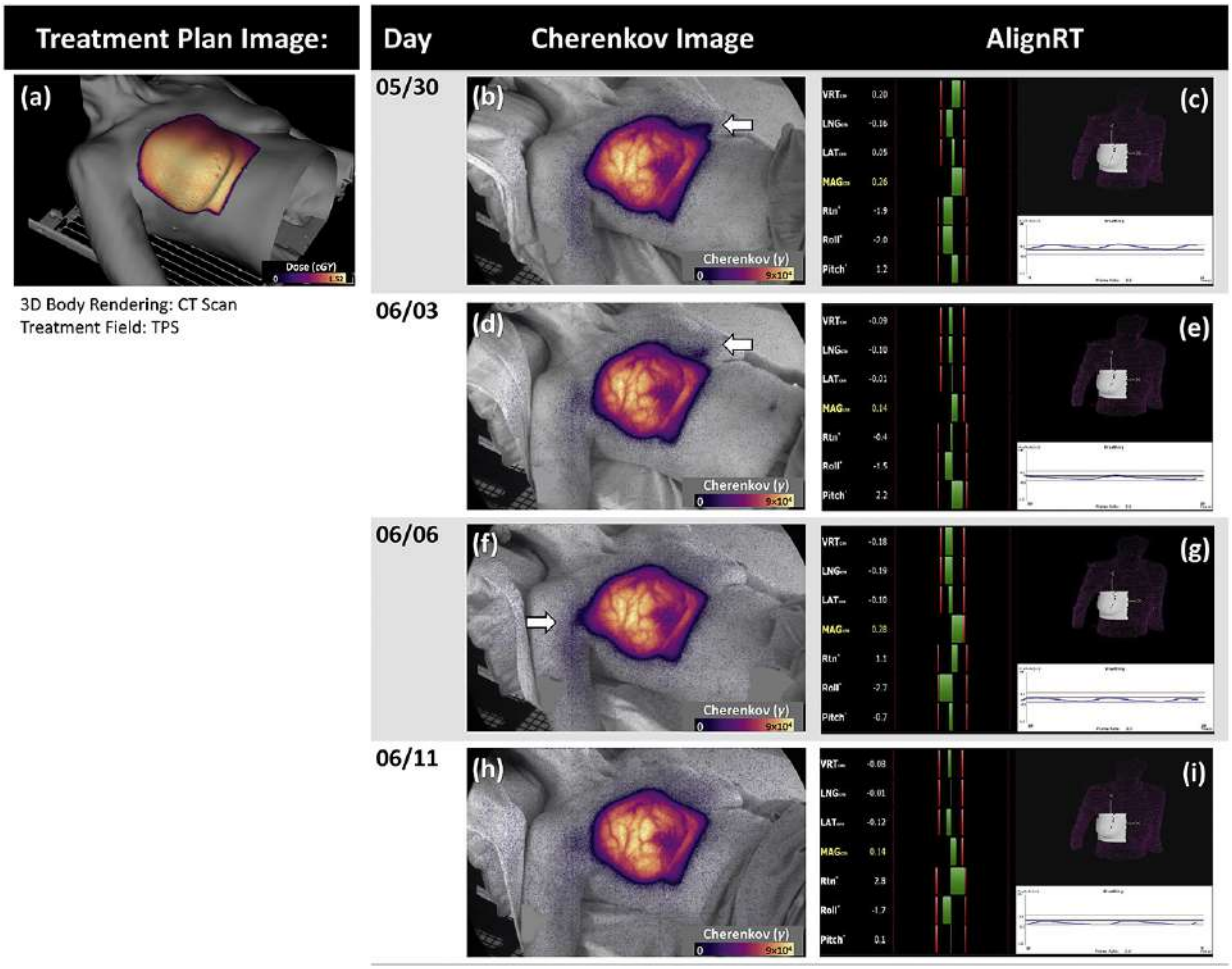


FIGURE 7.16 Cherenkov images for planning breast treatment. (Reprinted from Jarvis LA, Hachadorian RL, Jermyn M, et al. Initial clinical experience of Cherenkov imaging in external beam radiation therapy identifies opportunities to improve treatment delivery. *Int J Radiat Oncol Biol Phys*. 2021;109[5]:1627-1637. Copyright © 2020 Elsevier. With permission.)

BRACHYTHERAPY IMMOBILIZATION

Introduction

Immobilization in external beam treatments has been developed commercially over a period of decades, with many vendors and devices available, whereas immobilization for brachytherapy treatments has historically relied more on homemade devices. While there are some commercial devices, there are complicating factors for brachytherapy treatments that need to be considered. For external beam treatments, it is only the patient that needs to be immobilized because the treatment machine has fixed geometric positions with respect to the patient. In brachytherapy it is not just the patient that needs to be immobilized but also the brachytherapy applicator itself. In these treatments, the combination of small treatment margins and high dose gradients requires a high degree of immobilization, within 2 to 3 mm, to ensure patients are properly treated. A typical example of the combination of patient and applicator immobilization is shown in Figure 7.17.[69] The patient is immobilized in a mask while the skin applicator is placed next to the patient and held in a clamp.

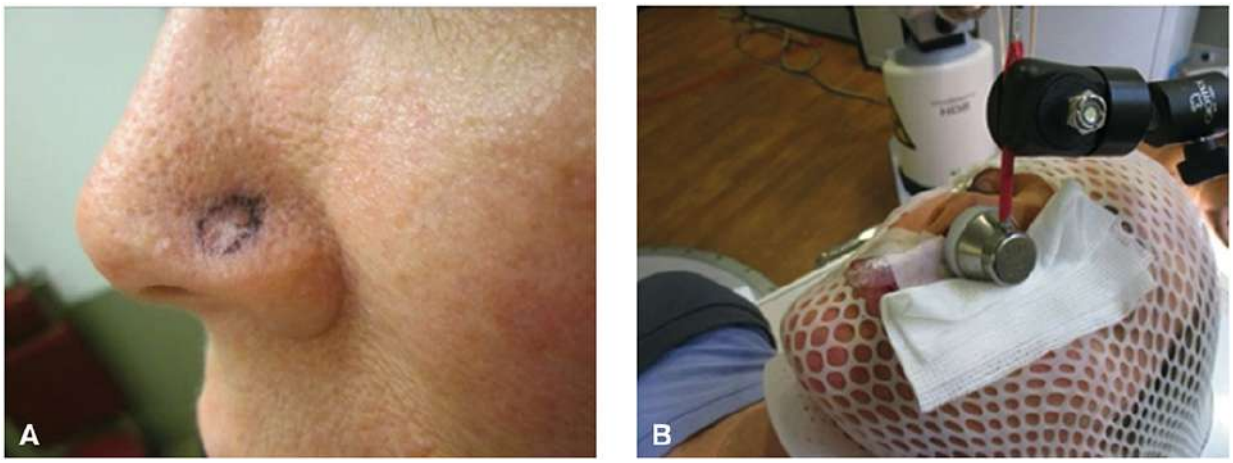
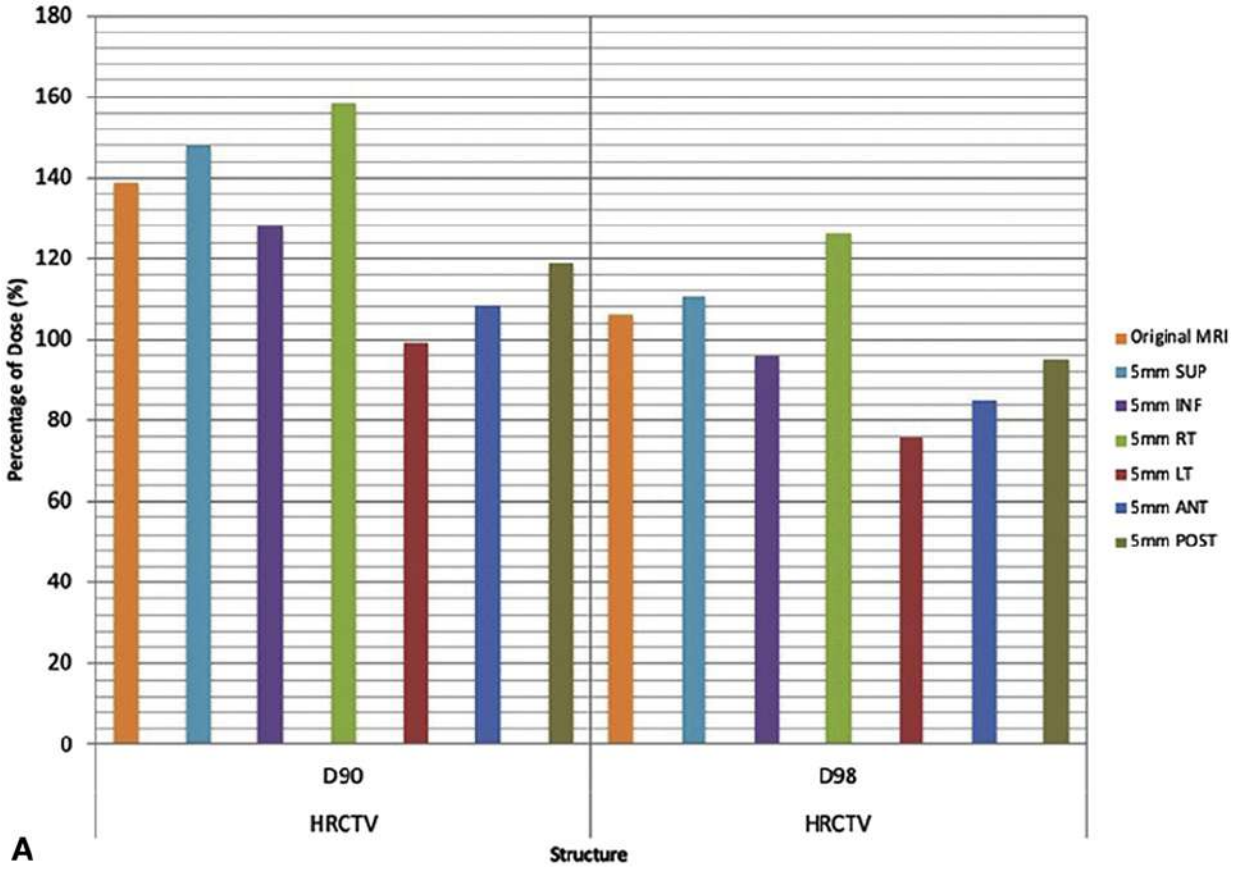


FIGURE 7.17 A. Keratinocyte carcinoma (KC) on the left nasal ala. B. KC treated using Leipzig applicator and articulated arm device. (Reprinted from Taylor JM, Dasgeb B, Liem S, et al. High-dose-rate brachytherapy for the treatment of basal and squamous cell carcinomas on sensitive areas of the face: a report of clinical outcomes and acute and subacute toxicities. *Adv Radiat Oncol*. 2020;6[2]:100616. With permission.)

Simple immobilization devices for vaginal cuff brachytherapy, such as straps or underwear, can be used to hold the cylindrical applicator in place. For these fractionated treatments it is necessary that the applicator is placed and immobilized in a reproducible way to minimize treatment variations, with rotation being a key component if utilizing multichannel cylinders.

For gynecologic treatments, it is necessary to immobilize the applicator to minimize unintended dosimetric coverage of both the target and organs at risk. This has been demonstrated in the work of Balsdon et al,[70] which analyzed the effect of a 5-mm displacement of the applicator in tandem and ovoid brachytherapy on target dose as shown in Figure 7.18. Similar results for critical structure doses are also shown.


180
160
140
120
100
80
60
40
20
0
Percentage of Dose (%)
D90
HRCTV
D98
HRCTV
Structure
Original MRI
5mm SUP
5mm INF
5mm RT
5mm LT
5mm ANT
5mm POST

A

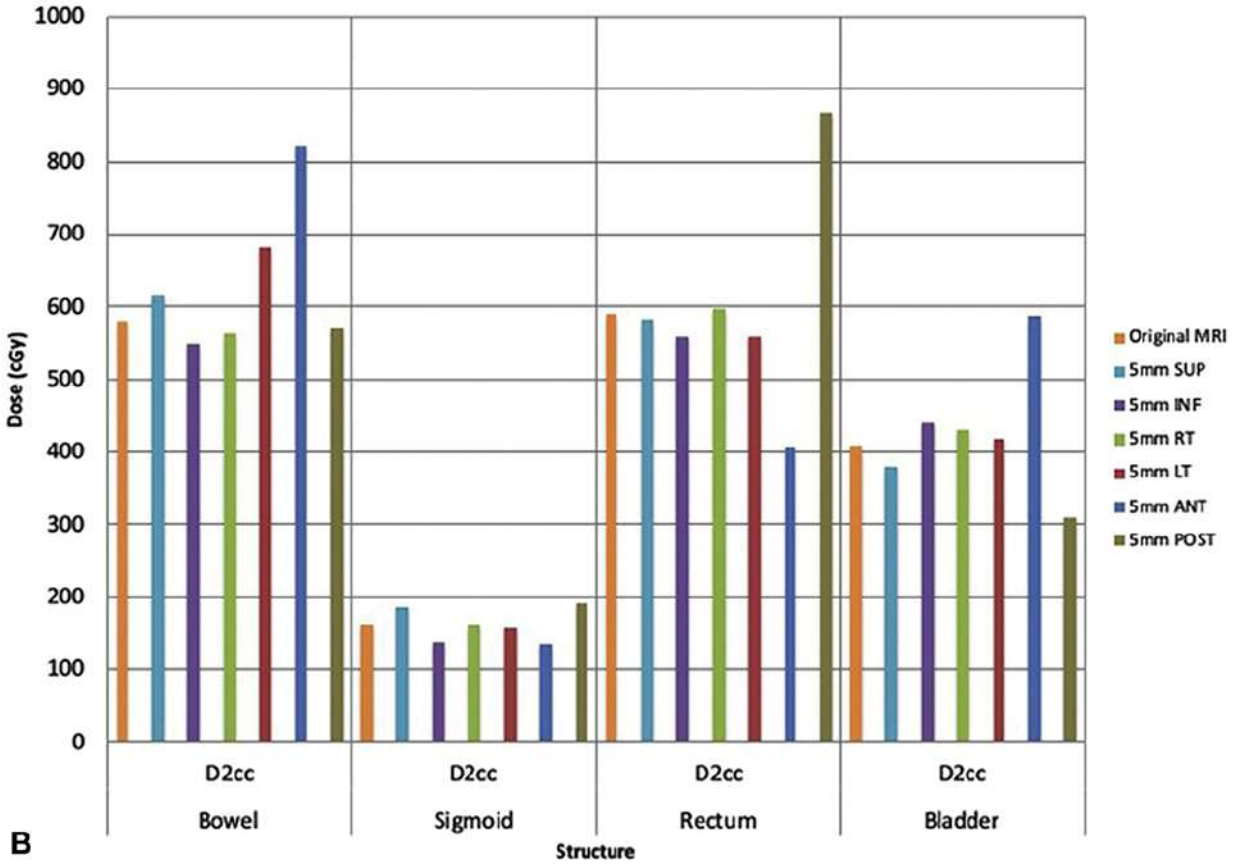


FIGURE 7.18 Effect of 5-mm shifts on percentage of dose to HRCTV D90 and D98 (A) organs at risk for D2 cc (B). (Reprinted from Balsdon A, Timotin E, Hunter R, Diamond K. Stability of intracavitary applicator placement for HDR brachytherapy of cervix cancer. *J Med Imaging Radiat Sci*. 2019;50[3]:441-448. Copyright © 2019 Canadian Association of Medical Radiation Technologists. With permission.)

Fan et al[71] described a belt system used to immobilize a tandem and ring applicator in cervical brachytherapy. This system is used in conjunction with an inflatable balloon to displace the rectum away from the applicator, reducing rectal toxicity. Alatus balloons have also been used to immobilize cervical applicators for patients spending the night in the hospital.[72]

Workflow in Brachytherapy

Prior to initiating a new brachytherapy program, an analysis should be done to determine the needs for patient transport and immobilization. For departments with dedicated brachytherapy suites in which applicator placement, imaging, and treatment all take place, patient transport and immobilization needs are less than those departments in which these activities take place in multiple locations. In this case, the patient and applicator need to be immobilized together to minimize motion during patient transport. A comparison of workflow in three different departments was published by Prisciandaro et al,[73] which has a useful description of all the tasks that need to be performed to ensure applicator and patient immobilization. These steps include proper suturing of the template to the patient, locking or gluing the needles to the template, having reference marks on the patient to ensure needles do not move in relation to the patient, and having methods to transport the patient.

For fractionated treatment, stability of the implant over the course of the treatment needs to be assessed. Typically, this is done by imaging the patient immediately prior to treatment to determine if applicators have shifted with respect to the patient's anatomy. This is usually a qualitative assessment, looking for only gross shifts that will require either minor adjustments of the applicator or, in the case of large changes,

replanning of the treatment. Karius et al[74] performed a retrospective analysis of implant stability in interstitial breast brachytherapy that is performed in nine treatments over the course of a week. Various causes of implant instability are shown in Figure 7.19.

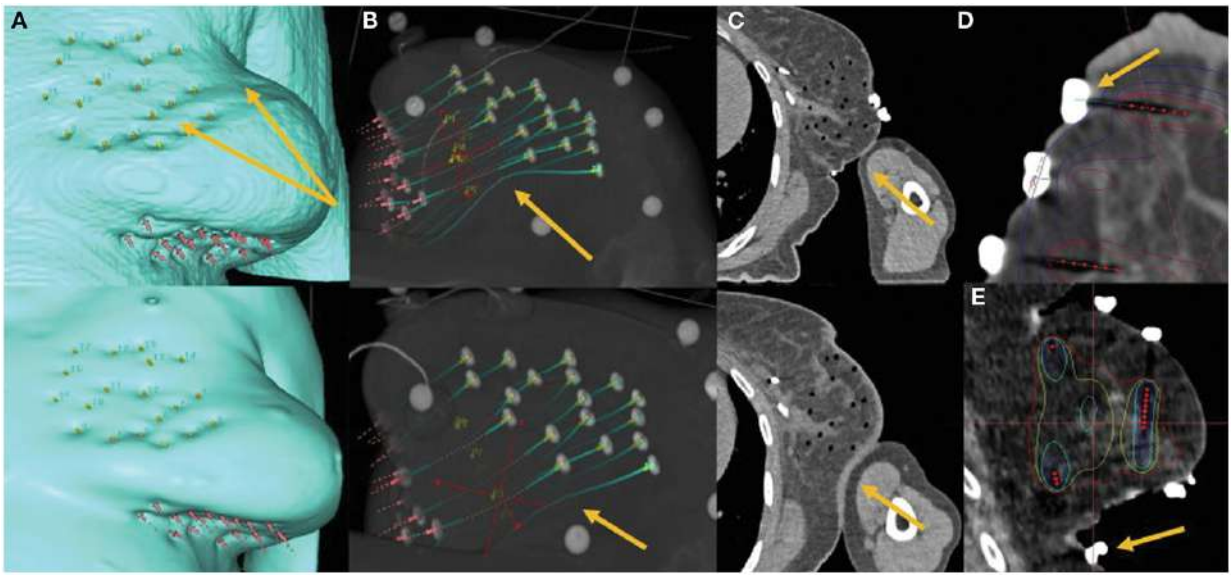


FIGURE 7.19 Causes for implant variations. Shown are the main causes for catheter changes. A. Skin contour of the breast from planning computed tomography (pCT; top) and control CT (cCT; bottom), where the breast was more contracted in the pCT (orange arrows). B. Implant reconstructed on the pCT (top) and cCT (bottom). One catheter (orange arrow) significantly changed its course in the tissue due to different muscle tension. C. Implant variation caused by different arm positioning (orange arrow). D. Slight indentation of the skin (orange arrow) due to a short-pulling of catheters, which resulted in a shortening of the button-to-button distance. E. Button shifted away from the skin (orange arrow), causing a change in the button-to-button distance. (Reprinted from Karius A, Szkitsak J, Strnad V, et al. On the implant stability in adaptive multi-catheter breast brachytherapy: establishment of a decision-tree for treatment re-planning. *Radiother Oncol*. 2023;183:109597. Copyright © 2023 Elsevier. With permission.)

Immobilization in genitourinary (prostate) brachytherapy was extensively discussed in the previous editions of this book and chapter. One advance has been the development of ultrasound-based treatment planning systems, such as Vitesse from Varian (Varian, Inc, Palo Alto, CA) or Oncura Prostate from Elekta. These new developments have allowed prostate brachytherapy to be performed without moving the patient from the brachytherapy suite to imaging. These solutions are used in conjunction with a tracked stepper, which connects the ultrasound to the treatment planning system and is a kind of Global Positioning System for the treatment. The planning system "knows" where the ultrasound is located in three dimensions, thus the needle positions can be monitored in real time along with the patient anatomy.

New Technologies

Three-Dimensional Printing in Brachytherapy

Over the last several years, various types of new technologies have come into clinical practice in brachytherapy. One of them is the development of 3D printed patient applicators. Rather than rely on commercial, one-size-fits-all solutions for clinical applications, 3D printing allows custom solutions that can be used for difficult cases, such as the nose, as shown in Figure 7.20.[75]

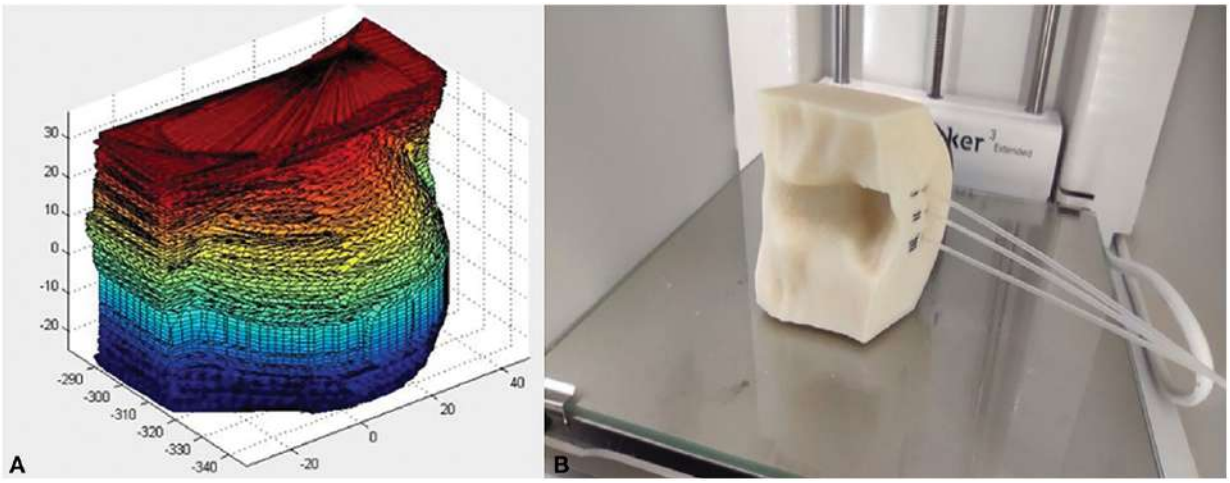


FIGURE 7.20 Applicator image (A) and printed applicator (B). (Reprinted from Membrive Conejo I, Pera Cegarra O, Foro Arnalot P, et al. Custom 3D-printed applicators for high dose-rate brachytherapy in skin cancer. *Brachytherapy*. 2021;20[6]:1257-1264. Copyright © 2021 American Brachytherapy Society. With permission.)

There are several different applications for 3D printing. In the simplest of these, an applicator can be created in which catheters are manually placed. More complex applicators can also be printed that incorporate both patient anatomy and catheter path optimization, as shown in Figure 7.21.[76]

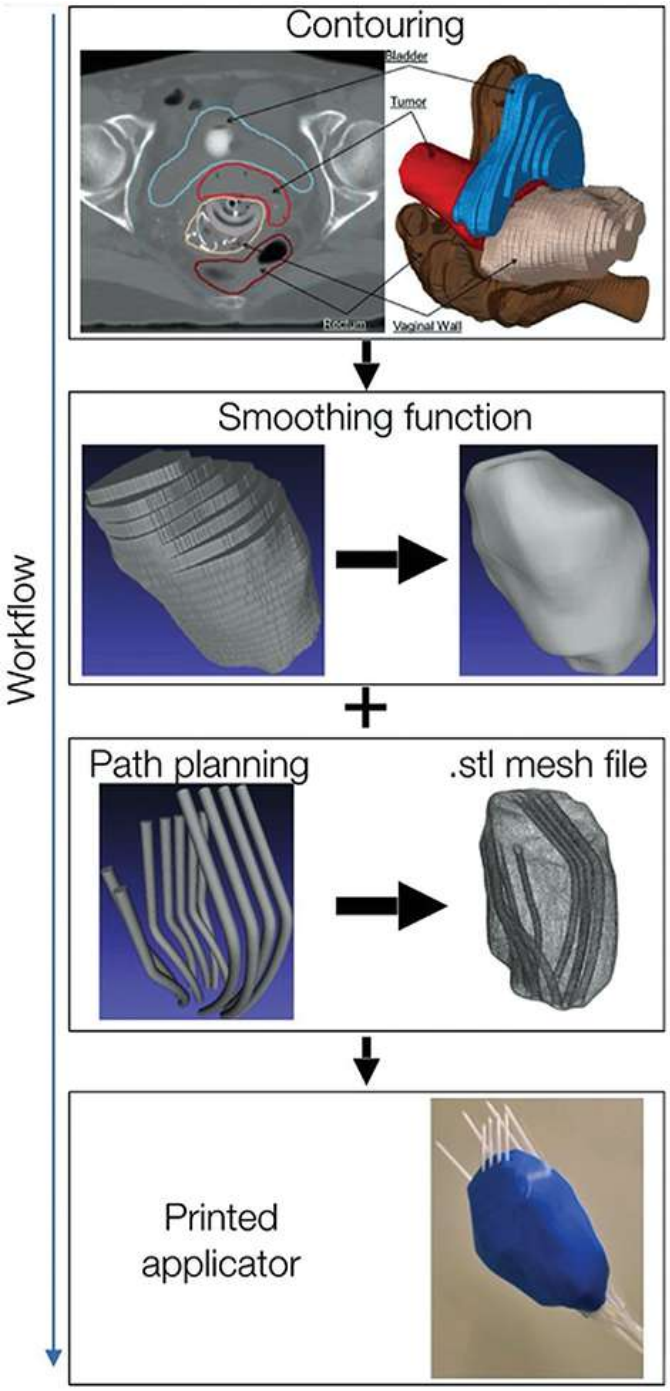


FIGURE 7.21 Example of a 3D printing workflow that incorporates both applicator shape and catheter path optimization. (Reprinted from Cunha JAM, Flynn R, Bélanger C, et al. Brachytherapy future directions. *Semin Radiat Oncol*. 2020;30[1]:94-106. Copyright © 2019 Elsevier. With permission.)

Electromagnetic Tracking

As discussed earlier, relatively small shifts in applicator, and thus source position, can lead to large changes in radiation dose distributions. Electromagnetic tracking technology, the equipment of which is shown in Figure 7.22,[76] has been shown to be capable of reconstructing catheter tips within 0.69 ± 0.29 mm in less

than 10 seconds. This compares favorably with the use of CT scanning in optimal conditions, which has been shown to provide catheter tip digitization accuracy on the order of 1.08 ± 0.67 mm.

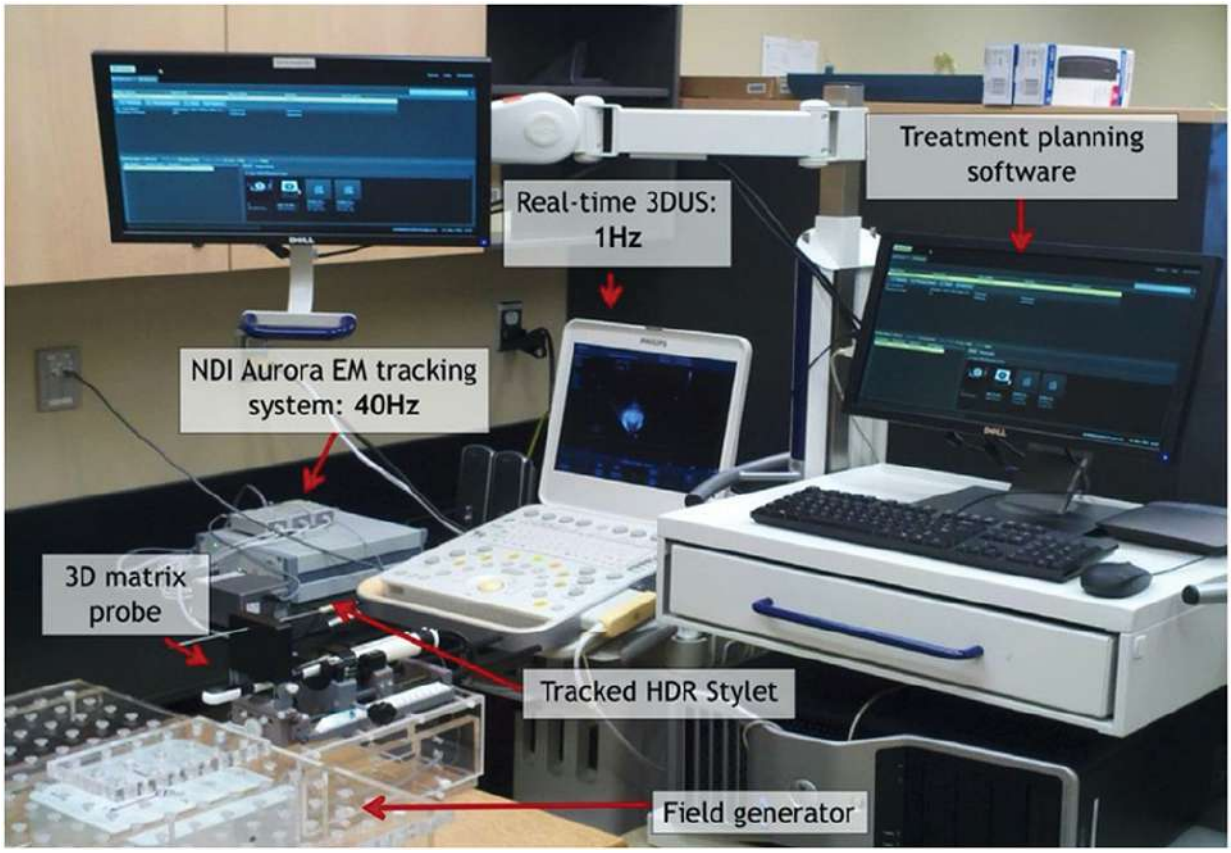


FIGURE 7.22 The components for an example electromagnetic tracking (EMT) system that may be used for brachytherapy. The system includes an ultrasound probe (3D matrix probe, Phillips), the EMT field generator and signal processor (Northern Digital Inc), and the treatment planning software. (Reprinted from Cunha JAM, Flynn R, Bélanger C, et al. Brachytherapy future directions. *Semin Radiat Oncol*. 2020;30[1]:94-106. Copyright © 2019 Elsevier. With permission.)

A recent clinical study has shown that the use of electromagnetic tracking for prostate brachytherapy treatments can be performed more rapidly with fewer interventions than the conventional ultrasound-based planning workflow.[77]

TOTAL BODY IRRADIATION IMMOBILIZATION

The setup for conventional TBI has been described in the AAPM Task Group 29.[78] Several devices are available for clinical programs that include conventional TBI with photons, generally utilized in preparation for bone marrow transplantation. These devices can also be designed to rotate and may also support total skin electron irradiation (TSEI) treatments for mycosis fungoides. Features of these systems generally include a beam spoiler, because a maximum dose at the skin entrance is preferred for TBI; systems for positioning partial lung blocks; and methods to keep the patient stable while standing for the treatments, which may take from 10 to 40 minutes, depending upon the treatment protocol. The major disadvantage for these systems is identifying storage in the treatment room since they are large and often take up vital space in the treatment area. It is important to note that these systems usually operate at a distance of several meters from the target, with the gantry at a horizontal angle (90° or 270°), so a large treatment vault is required. Figure 7.23 shows two representative TBI devices from Radiation Products Design, Inc. and Mick Radio-Nuclear Instruments, Inc. Features such as a bicycle seat, handgrips, and shoulder stabilizers are used

to help support the patient. Some photon TBI stands offer a harness that will provide an additional measure of security to prevent the patient from falling over in case the patient succumbs to fatigue and faints.

A

FIGURE 7.23 A stand is commonly used to help position patients for total body irradiation (TBI) with photons and electrons. A. Common features of TBI stands include hand grips and a seat to help support the patient. B. The harness used to prevent the patient from falling in the case of fatigue and/or fainting. (B. Courtesy of Radiation Products Design, Inc.)

Data suggest that higher dose TBI regimens can improve overall survival for some young patients with acute leukemia; however, total prescribed dose from conventional open-field TBI is limited by organs at risk receiving the prescribed dose as well.[79-84] Multiple isocenter VMAT for TBI has become a feasible option to improve dose homogeneity and conformality to the skeletal structure while reducing dose to the organs at risk, and whole-body immobilization is of paramount importance for accurate delivery. Multiple groups have described treatment planning for TBI using VMAT.[85-89] Typical prescriptions are 12 to 13.2 Gy delivered over 8 fractions BID 10. Multiple body conformal immobilization devices such as Vac-Lok, described in an earlier section, and thermoplastic masks are needed to immobilize the entire length of patients with VMAT TBI. An alternative immobilization method used at the Moffitt Cancer Center is described by Keit et al.[88]

Patient simulation for VMAT TBI is done in the supine position with arms on the sides. Patients are positioned on a long SBRT base plate shown in Figure 7.24 (Orfit Industries, NV, Belgium). Thermoplastic masks are added to the head, shoulders, chest, arms, abdomen, pelvis, and legs and locked onto the SBRT board to create a whole-body immobilization device. Patients then undergo CT simulation in the head-first supine (HFS) and feet-first supine (FFS) positions. The HFS scan is done from the head to the level of midthigh, the board is then rotated for the FFS scan from the toes to pelvis. Localization isocenters are placed near the base of the skull for the HFS scan and near ankles for the FFS scan. Additionally, to aid the treating therapists and ensure setup reproducibility, markings are placed on the immobilization system. A rotatable tabletop platform shown in Figure 7.25 and recently described by Losert et al[90] has the potential to make this process more efficient. This rotating platform can be used with either a specific SBRT board or multiple individual Vac-Lok and thermoplastic mask setups.

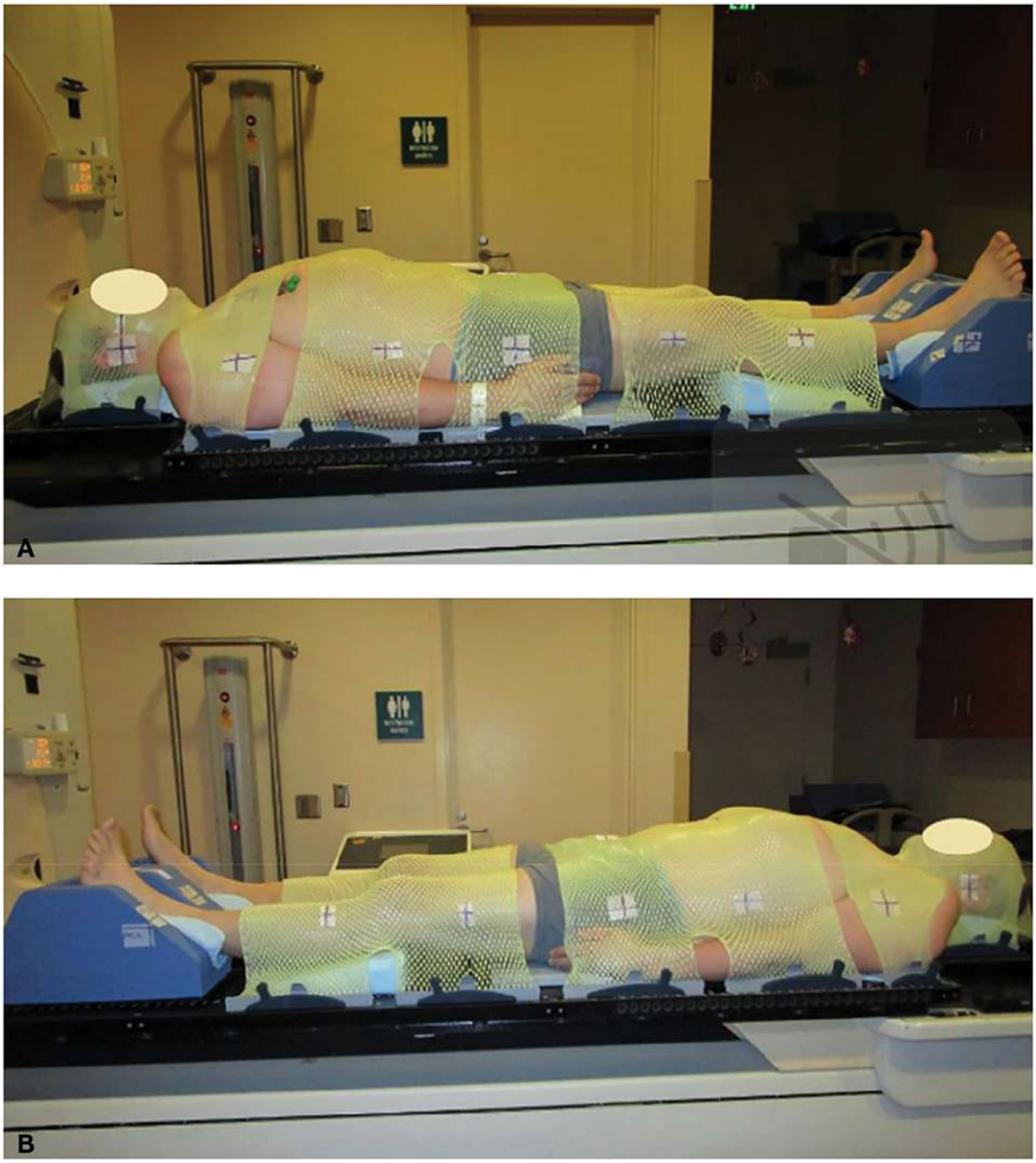


FIGURE 7.24 Example of a volumetric modulated arc therapy total body irradiation setup (A) and immobilization (B). (From Keit E, Liveringhouse C, Figura N, et al. Feasibility and toxicity of full-body volumetric modulated arc therapy technique for high-dose total body irradiation. *Technol Cancer Res Treat*. 2023;22:15330338231180779. Copyright © 2023 SAGE Publications. Reprinted by permission of SAGE Publications.)

FIGURE 7.25 Rotatable tabletop platform for volumetric modulated arc therapy total body irradiation.

Treatment planning for VMAT TBI requires the use of roughly six to eight isocenters, so patient stability over very long treatment times and multiple shifts and rotations is crucial. Four to five isocenters are placed on the HFS scan and two to three on the FFS scan depending on patient height. Isocenters are on the same plane spaced approximately 25 cm apart to ensure sufficient overlap between arcs with one to two arcs per isocenter. Treatment delivery for each isocenter is verified with image guidance using extended CBCT to expand the field of view. Depending on the complexity of the plan and patient size, the total treatment length may take an hour or more. Therefore, the quality of immobilization is very important for VMAT TBI.

TOTAL SKIN ELECTRON IRRADIATION IMMOBILIZATION

TSEI or total skin electron therapy is most often used to treat cutaneous T-cell lymphoma, a chronic progressive lymphoma including mycosis fungoides and Sézary syndrome.[91,92] The treatment utilizes very large electron fields to irradiate superficial skin lesions. Two widely used techniques for TSEI are six-dual-field technique (or Stanford technique) and rotational technique.[92-94] Similar to TBI, to apply these two techniques, the patient will be asked to remain in the standing position during the entire treatment, on a platform with bars to hold on to for immobilization and safety belts or a seat for patient support as previously shown in Figure 7.23. Classic patient positioning of both treatment techniques is demonstrated in Figure 7.26. Personalized shielding, such as for head, eyes, fingernails, and toenails, may be prescribed accordingly.

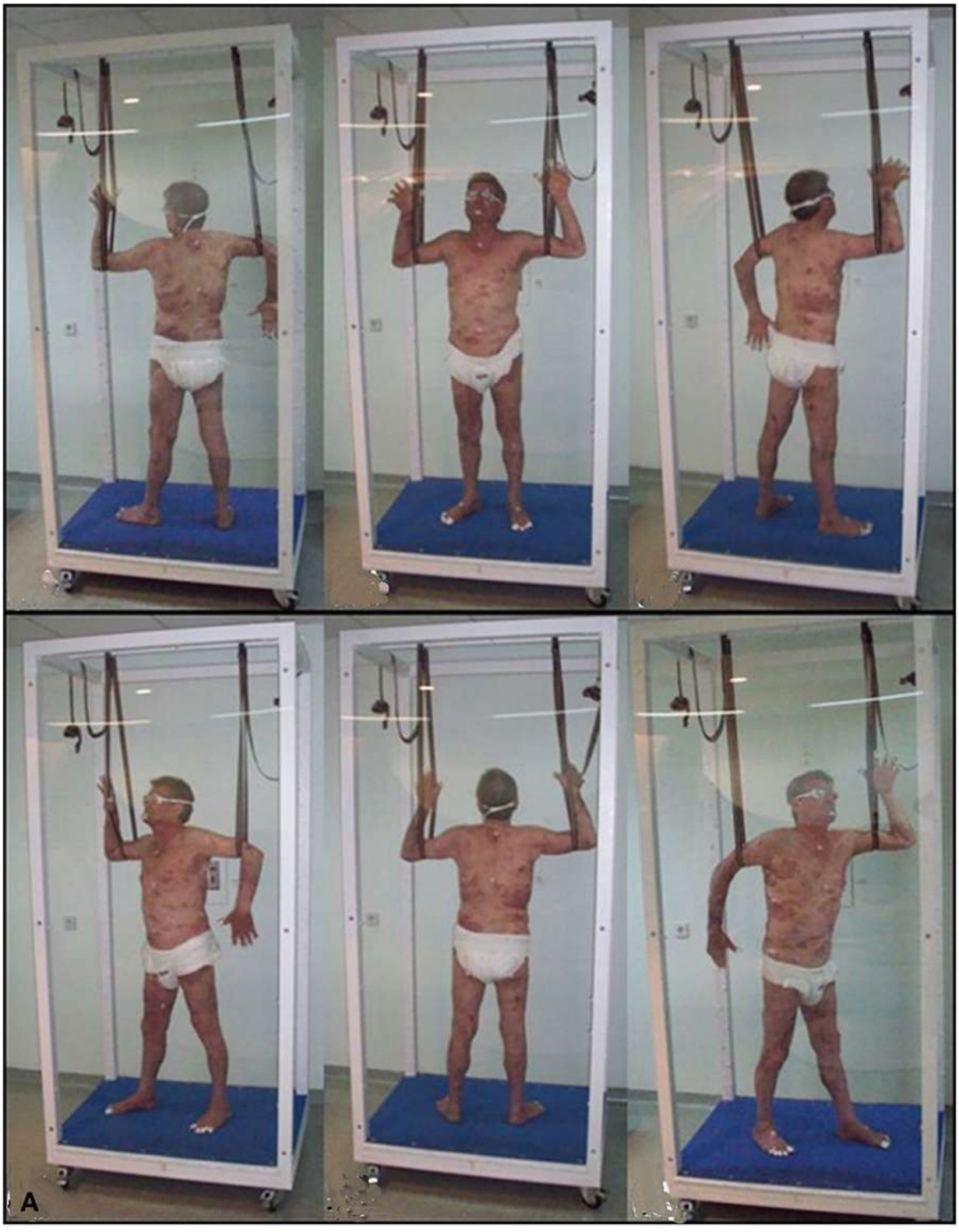

A

FIGURE 7.26 A. Example of six patient treatment positions for total skin electron irradiation. Top row: Left anterior oblique, anteroposterior, and right anterior oblique treatment positions. Bottom row: Left posterior oblique, posteroanterior, and right posterior oblique treatment positions. B. Example of a patient standing on the rotating platform with support of a hand grip above head. (A. Reprinted from Diamantopoulos S, Platoni K, Kouloulias V, et al. First treatment of mycosis fungoides by total skin electron beam (TSEB) therapy in Greece. *Rep Pract Oncol Radiother*. 2013;19[2]:114-119. Copyright © 2013 Greater Poland Cancer Centre. With permission.)

For nonstandard scenarios, such as for patients who are nonambulatory who may not tolerate prolonged treatment time, a lying-on-the-floor TSEI with proper immobilization setup can be an alternative option.[95,96] Pediatric patients may also require specific customization of the immobilization devices due to the significant anatomic difference from adults. Several customized TSEI techniques for pediatric patients have been reported.[97]

INTRAOPERATIVE RADIOTHERAPY

Intraoperative radiotherapy (IORT) is the delivery of a single, high-dose radiation treatment to the tumor bed during the surgical session. There are a variety of devices that are used to deliver the radiation, including brachytherapy, with temporally implanted applicators, the Zeiss Intrabeam device (Carl Zeiss Meditec AG, Germany), which uses 50 kV x-rays, or the Intraop Mobetron (Intraop Medical Corp,

Sunnyvale, CA), which uses 6, 9, or 12 MeV electrons. Not only are various devices used, but the radiation is delivered to many different treatment sites, including the breast,[98] pancreas,[99] rectum,[100] sarcoma,[101] and brain.[102] The Intrabeam device is shown in Figure 7.27A, with its articulating arm design to immobilize the applicator, while for Mobetron, a remote control can be used to maneuver and lock the gantry head after properly aligning with the applicator, as demonstrated in Figure 7.27B. An issue that arises during IORT is that patients are under anesthesia during the treatment, with the care team remotely monitoring both the patient and the treatment. Care must be taken to ensure that the patient does not move during the treatment. One method is to deepen the analgosedation and insert a laryngeal mask, so the patient breathes normally.

A

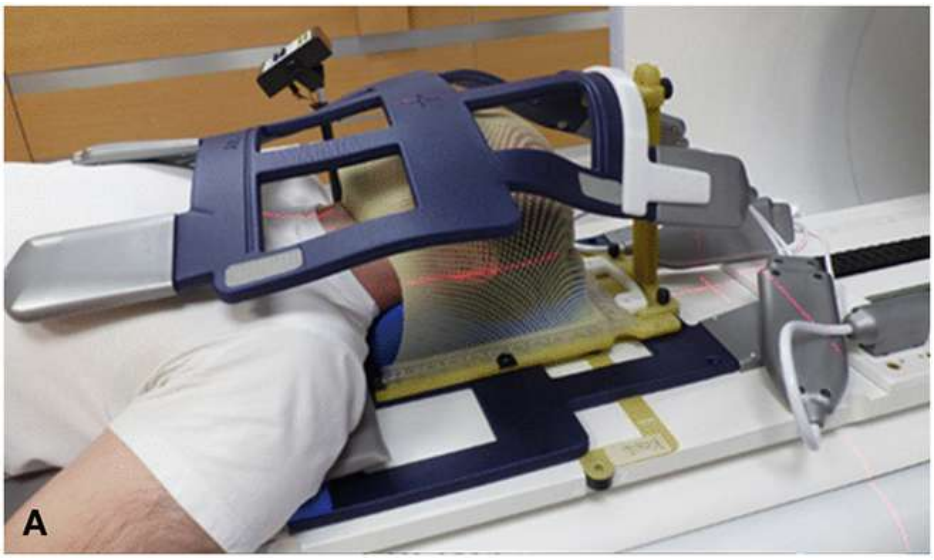
FIGURE 7.27 A. Intrabeam stand and x-ray source shown with spherical applicator attachment. The floor stand provides full flexibility of movement for the x-ray tube with millimeter precision in six dimensions. B. Mobetron soft docking illustration. The Mobetron head aligns with but does not contact the applicator. Alignment is facilitated by lasers in the Mobetron head, which are reflected by mirrors in the applicator collar to provide feedback on positioning. The applicator and collar are clamped to the surgical table. (A. Reprinted from Sethi A, Emami B, Small W Jr, Thomas TO. Intraoperative radiotherapy With INTRABEAM: technical and dosimetric considerations. *Front Oncol*. 2018;8:74. http://creativecommons.org/licenses/by/4.0/. B. Reprinted from Wootton LS, Meyer J, Kim E, Phillips M. Commissioning, clinical implementation, and performance of the Mobetron 2000 for intraoperative radiation therapy. *J Appl Clin Med Phys*. 2017;18[1]:230-242. http://creativecommons.org/licenses/by/4.0/.)

While IORT devices are normally placed visually, with the surgeon and the radiation oncologist conferring to decide on applicator size and placement, a novel method using ultrasound to provide image guidance to the applicator placement is being developed.[103] This will be especially useful for the treatment of thicker targets or those targets in which coupling the applicator directly to the tissue can be difficult. Ultrasound can provide real-time quantitative feedback on proper applicator placement to ensure the patient is treated according to the plan.

IMMOBILIZATION FOR ADVANCED AND EMERGING TECHNOLOGIES

Immobilization for Magnetic Resonance Linear Accelerator

The marriage of MRI and linear accelerator brought a lot of interest, especially due to improved soft-tissue contrast and real-time nonionizing radiation image guidance during treatment.[104,105] Immobilization devices and accessories for MR linear accelerator (MR-linac) have a lot of unique requirements compared to the conventional ones. The first and most important consideration is safety. A standard process for the safety check has been described in figure 1 of AAPM Task Group 334 Report.[106] Additionally, these devices and accessories need to pass the imaging artifact evaluation. Some other general immobilization considerations different from conventional radiotherapy are the limited bore size (usually 70 cm), restricted/limited couch movement, arm positioning, coil positioning, patient safety devices (such as hearing protection, emergency squeeze bulb or push-button alarm, communication devices), patient on-couch time, etc.[107,108] Immobilization examples of MR-linac-specific patient setup can be seen in literature,[107,109,110] with some examples shown in Figure 7.28. Generally, (1) patient is dressed in gown for MR safety requirement and lying flat on the treatment couch, (2) the coil placement will center around the target level and sandwiching the patient, and (3) a comfortable and stable arm position is usually recommended due to the length of the treatment time. The treatment time can vary significantly between patients depending on whether adaptive replanning is needed and how the adaptive procedure is performed.[111]


A

B

Elekta
Unity
C

D

FIGURE 7.28 Examples of immobilization devices and setup in MR-Linac settings. A and B. Head immobilization in MRIdia machine. C and D. Torso immobilization in a Unity machine. (Reprinted from Cuccia F, Alongi F, Belka C, et al. Patient positioning and immobilization procedures for hybrid MR-Linac systems. *Radiat Oncol*. 2021;16[1]:183. http://creativecommons.org/licenses/by/4.0/.)

Upright Radiation Therapy

Upright positioning devices are consistently being explored in particle radiation therapy for the past several decades.[112] Its unique treatment position enables another comfortable option when patients cannot tolerate classic supine or prone position.[113,114] Specifically, patients with certain clinical indications and palliative intent may find it difficult to lie down. Additionally, treatment couch weight limitation may prohibit traditional treatment position when dealing with patients with bariatric needs. It is also suggested that upright position can improve treatment delivery and potentially patient outcome for selected tumor sites.[112,113]

Various upright immobilization solutions have been described in the literature, from upright stabilization apparatus to versatile chair designs.[112,113] From those innovative ideas, there are several commercialized solutions, including products from P-Cure (P-Cure Ltd, Shilat Industrial Zone, Israel), BEC GmbH (Pfullingen, Germany), and Leo Cancer Care (Smallfield, Horley, Surrey, UK). Researchers are still actively developing prototypes.[115-118] One of the commercial solutions from Leo Cancer Care can be utilized for both photon and proton applications, depicted in Figure 7.29. In general, such a device usually consists of an adjustable backrest and seat to withhold the majority of the patient's weight plus additional accessories to hold the patient's head/torso and extremities. Depending on the patient's posture (leaned forward/leaned back/straight upright) and leg position, a leg support or shin rest may be chosen to further secure the patient.

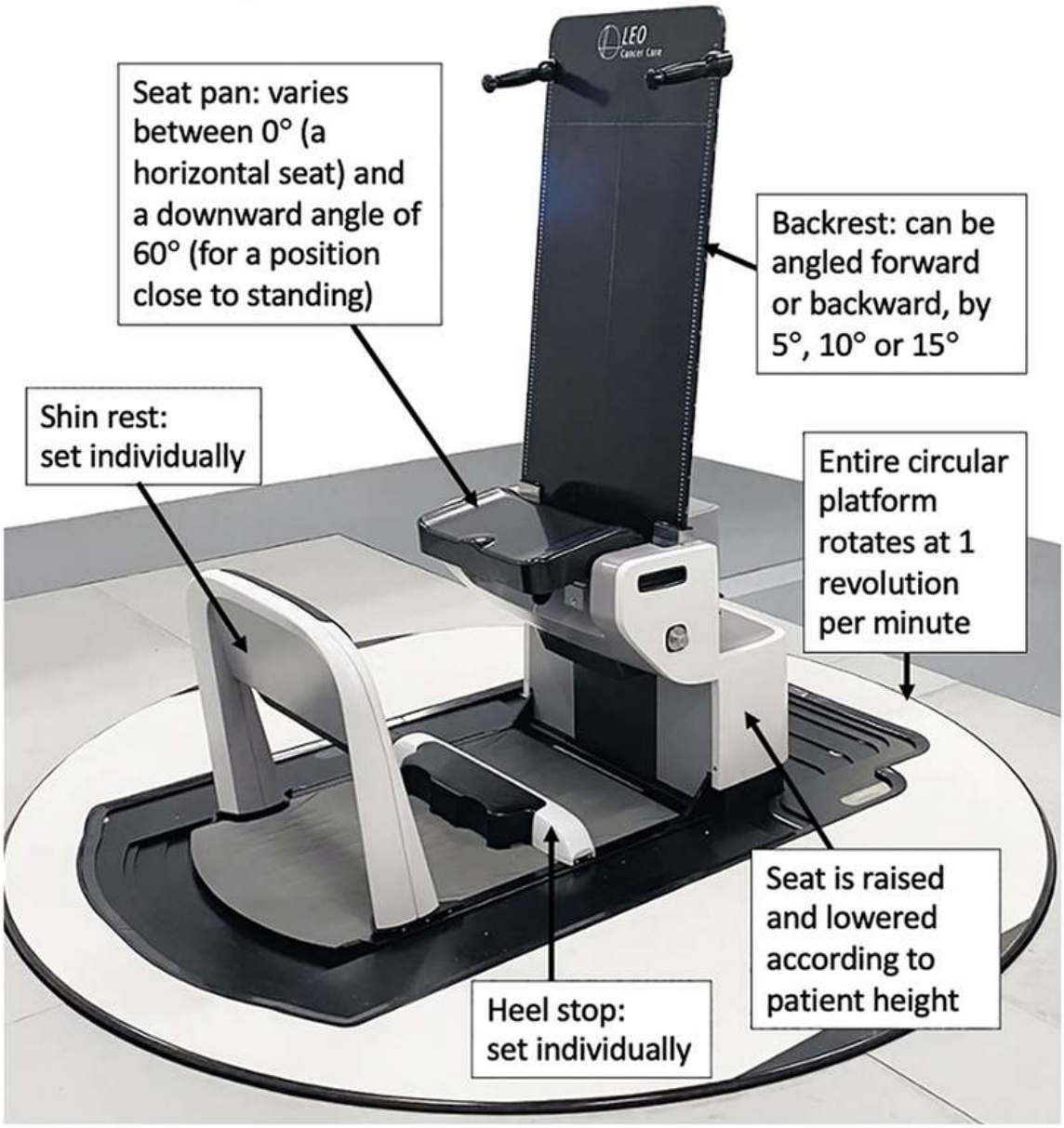


FIGURE 7.29 An upright patient positioner consists of seat pan, back rest, and shin rest. (Reprinted from Boisbouvier S, Underwood T, McNamara J, Probst H. Upright patient positioning for gantry-free breast radiotherapy: feasibility tests using a robotic chair and specialised bras. *Front Oncol*. 2023;13:1250678. http://creativecommons.org/licenses/by/4.0/.)

One of the difficulties in implementing upright treatment is the inability of acquiring upright simulation images such as CT or MRI with similar chair setup for radiation treatment planning purpose. Currently, vertical CT and MRI solutions exist but are not universally available in clinical practice. Vertical imaging system combined with upright immobilization solution can redefine the concept of upright radiation therapy in the future.

THE EVOLUTION OF PATIENT IMMOBILIZATION

Strategies to immobilize patients for radiotherapy have been developed since it was introduced as a treatment modality over 100 years ago. In this chapter, we have presented a wide array of simple devices that have continued to be used for decades, albeit with new designs and materials that make their use more

comfortable, convenient, and sanitary for the patient and the therapists. We have also presented highly specialized systems that may be used in the most sophisticated of radiation therapy treatment modalities that address specific needs of image guidance, highly conformal and high-dose stereotactic treatments, brachytherapy, intraoperative therapy, and other special procedures. Tables 7.1 and 7.2 have been included to provide a top-level summary of the pros and cons of the wide array of commercially available immobilization systems. Common themes in modern radiation therapy immobilization include striking a balance between patient comfort and stability, supporting effective and safe approaches for target localization during treatment, and supporting systems to verify the patient position prior to treatment using x-ray or allow monitoring with surface imaging. IGRT, immobilization, and monitoring are interlinked and should be considered together as part of the overall system to minimize patient alignment and stability uncertainties.

For brachytherapy, immobilization for both the patient and applicator has continued to be an important consideration for increasingly complex procedures, especially with the development of image-guided brachytherapy (IGBT), analogous to IGRT, in which the applicator is placed, simulation is performed, and the patient is treated with minimal motion of the patient or applicator. 3D printing has provided the ability for some clinics to design and fabricate patient-specific applicators, and electromagnetic tracking shows promise to increase the accuracy and efficiency of needle tip identification.

TBI has experienced renewed interest in dose escalation by using complex systems of immobilization to accurately translate and rotate between the multiple isocenter VMAT plan to conformally treat the skeletal structure.

CONCLUSION

Effective radiation treatment depends on both proper localization of the tumor and proper immobilization of the patient. As radiation therapy has evolved, so too have the strategies for immobilization of the patient. IGRT, including hypofractionated SBRT, as well as IGBT require that the patient be comfortably immobilized to ensure that the radiation is properly delivered to the tumor. Intrafraction monitoring has grown rapidly in clinical utility in recent years, due to the ability to monitor the patient in near real time without using ionizing radiation. This is especially necessary as the dose per fraction is increased, which could lead to serious complications should the normal tissue surrounding the tumor receive excessive dose because of poor localization and immobilization.

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CHAPTER 8

Photon External-Beam Dosimetry and Two-Dimensional Radiation Treatment Planning

James A. Purdy, Geoffrey D. Hugo, and Hania A. Al-Hallaq

When planning the treatment of a patient with cancer, the radiation oncologist is faced with the problem of prescribing a treatment regimen with a radiation dose that is large enough to potentially cure or control the disease but does not cause serious normal tissue complications. This task is a difficult one because tumor control and normal tissue effect responses for most disease sites are typically steep functions of radiation dose; that is, a small change in the dose delivered (±5%) can result in a dramatic change in the local response of the tissue (±20%).[1-3] Moreover, the prescribed curative doses are often, by necessity, very close to the doses tolerated by the normal tissues. Thus, for optimum treatment, the radiation dose must be planned and delivered with a high degree of precision.

One can readily compute the dose distribution resulting from photons, electrons, protons, or a mixture of these radiation beams impinging on a regularly shaped, flat surface, homogeneous unit-density phantom. However, the patient presents a much more complicated situation because of irregularly shaped topography and having tissues of varying densities and atomic composition (called *heterogeneities*). In addition, beam modifiers, such as wedges, compensating filters, or bolus, are sometimes inserted into the radiation beam, further complicating the calculation of the absorbed dose.

Two-dimensional radiation treatment planning (2DRTP) refers to a technique used to plan the delivery of radiation to a target area within a patient's body. It is an older and less sophisticated approach compared to modern three-dimensional radiation treatment planning (3DRTP), which is discussed in Chapters 10, but it is still widely used for simple treatment scenarios where a 2D calculation of the dose distribution is sufficient, or in

institutions with limited resources where advanced imaging modalities and/or 3DRTP systems are not available.

The 2DRTP approach emphasizes beam portal design on a simulator radiograph based on standardized beam arrangements applied to entire classes of comparable patients. For dose calculations, the patient's anatomy is simplified to a series of flat cross-sectional images, typically obtained from x-rays or computed tomography scans. These images represent slices of the patient's body, and the targeted area and surrounding critical normal tissues are contoured manually on each slice, often based on published consensus guidelines.[4] The treatment planner then designs radiation fields by selecting the appropriate beam angles and sizes based on the patient's anatomy. These fields are essentially 2D projections of the treatment beams onto each slice. The goal is to deliver a therapeutic dose to the tumor while minimizing the dose to nearby healthy tissues.

During the 2DRTP process, the planner uses basic dosimetric calculations to estimate the dose distribution within the patient based on the geometry of the radiation fields and the patient's anatomy. However, this approach generally does not consider the variations in tissue density and shape in the 3D, leading to less accurate dose calculations.

In this chapter, we review several aspects of photon external-beam 2DRTP and pertinent dosimetry, including methods used for dose/monitor unit (MU) calculations, crude correction for the effects of the patient's irregular surface and internal heterogeneities on the calculated photon dose distribution, isodose distributions for combined fields, field junctions, field shaping and design of treatment aids, and related clinical dosimetry issues.

DOSE CALCULATION METHODS

For purposes of discussion, it is convenient to characterize photon beam dose calculation methods as either *correction based* or *model based*.[5] In the former method, the dose at a given point is calculated using measured central-axis data, for example, percent depth dose (PDD), tissue-air ratios (TARs), tissue-maximum ratios (TMRs), tissue-phantom ratios (TPRs), and off-axis ratios (OARs). These quantities are measured under reference conditions (ie, in a homogeneous water phantom with a flat surface normal to the incident radiation beam at a standard distance from the x-ray source).

Hence, specific correction factors (CFs) are used in planning the treatment of real patients to account for varying patient surfaces, tissue heterogeneities, irregular field shapes, and any beam modifiers used.

In the model-based algorithms, the dose distribution is computed in a phantom or patient from more of a first-principles approach accounting for lateral transport of radiation, beam energy, geometry, beam modifiers, patient surface topography, and electron density distribution rather than correcting parameterized dose distributions measured in a water phantom. These models utilize convolution energy deposition kernels that describe the distribution of dose about a single primary photon interaction site and provide much more accurate results even for complex heterogeneous geometries. Both methods are discussed in the following sections, and more details on model-based photon dose calculation algorithms can be found in the references listed.[5,6] It should be noted that with the evolution of advanced computing methods, modern treatment planning systems generally do not rely on correction methods and are included here for historic reference rather than for practical treatment planning purposes. The correction-based models remain relevant for purposes of manual dose calculations and secondary/independent dose verification applications. However, many of the modern-day independent dose calculation programs include more sophisticated dose calculation algorithms.

Correction-Based Dose Calculation Methods

Using the notation of Khan et al[7] the dose at a point (D_P) at a depth d of overlying tissue on the central ray for an irregularly shaped field is given by

$$D_P = D_{ref} \cdot S_c\left(r_c\right) \cdot S_p\left(r_d\right) \cdot TF \cdot WF\left(\frac{SCD}{SAD}\right)^2 \cdot TMR\left(d, r_d\right)$$

where S_c denotes the *collimator scatter factor*; S_p is the *phantom scatter factor*; and TMR is the tissue-maximum ratio. TF and WF denote the tray and wedge factors, respectively, and are defined as the ratio of the central ray dose with the tray or wedge filter in place relative to the dose in the

open-beam geometry. The collimated field size is denoted by r_c and is usually described as the square field size equivalent to the rectangular collimator opening projected to the isocenter. The effective field size is denoted by r_d and is specified to the isocenter distance (SAD). The inverse-square law factor accounts for the difference in distances from the source to the point of dose calculation relative to the source to calibration point distance (SCD). Note that when isocentric calibration is used, this factor is unity. Also, note that collimator-defined field size is used for the lookup of the collimator scatter factor, S_c, whereas effective field size projected to the isocenter is used for the lookup of the TMR value and the phantom scatter factor, S_p. By separately accounting for the effect of collimator opening on the primary dose component and the influence of cross-sectional area of tissue irradiated, most of the difficulties in accurately calculating a dose in the presence of extensive blocking are overcome. Details on determining the effective field size for an irregularly shaped field, taking into account both the primary and scatter dose components, are discussed in a later section.

Correction for Varying Patient Topography (Air Gaps)

In the previous equation, it is assumed that the beam is normally incident on a unit-density uniform phantom. The following CF methods can be applied to the equation to account for the nonnormal beam incidence caused by the patient's varying surface.[8]

Air Gap Correction Factor: Ratio of Tissue-Air Ratio Method

In the ratio of TAR (RTAR) or TPR method, the surface (along a ray line) directly above point A (source-to-skin distance [SSD] = S′) is unaltered, so the primary component to the dose distribution at this point is unchanged (and the scatter component is also assumed to be unaltered) (see Figure 8.1). Thus, the dose at point A can be considered unaltered by patient shape. However, for point B, where there are considerable variations in the patient's topography, both the primary and scatter components of the radiation beam are altered. The CF may be determined using two TARs or TPRs as follows:

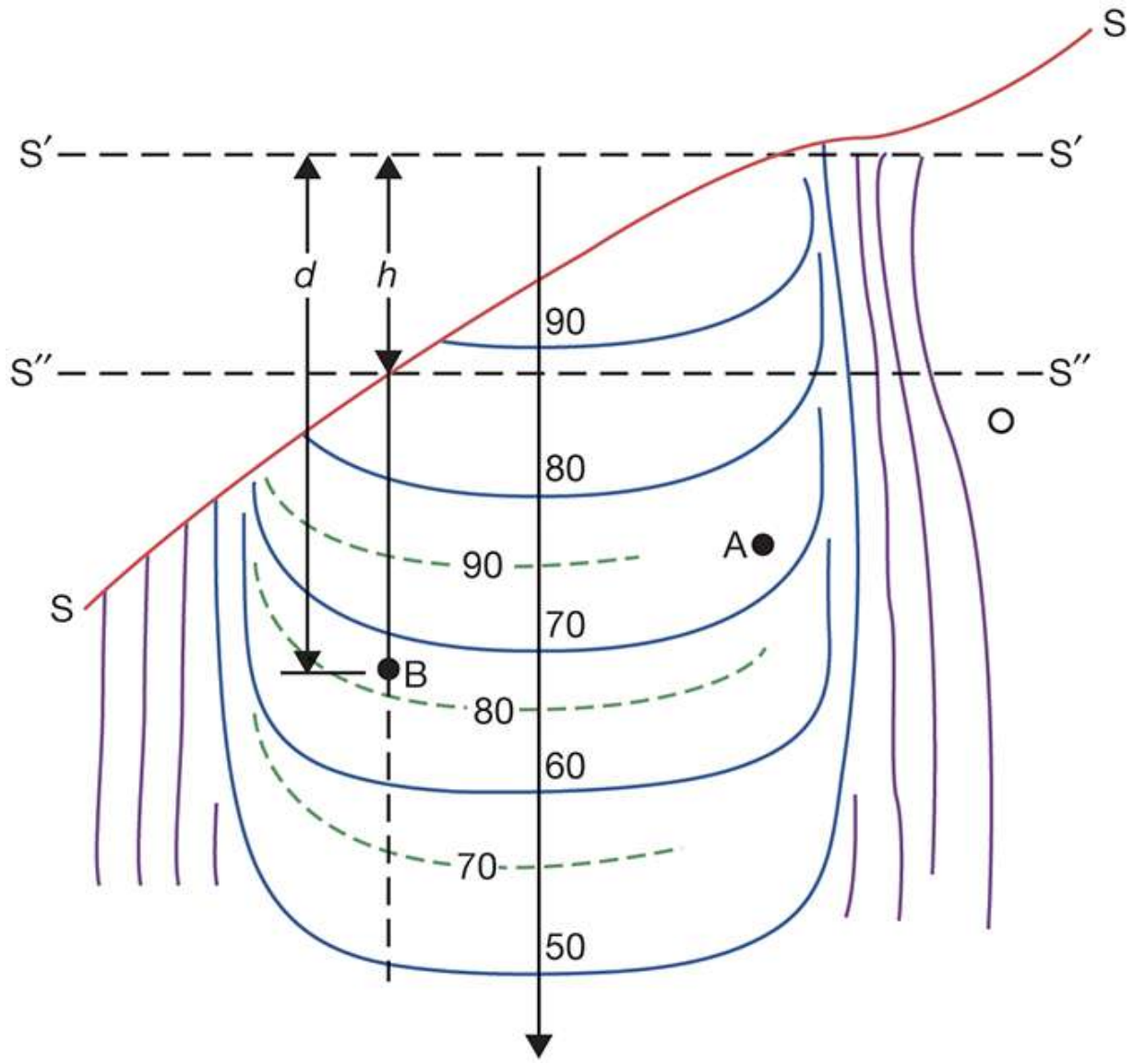


FIGURE 8.1 Schematic drawing illustrating tissue-air ratio and effective source-to-skin distance (SSD) methods for the correction of isodose curves under a sloping surface (solid lines for SSD = S′; dashed lines for SSD = S″). (From International Commission of Radiation Units and Measurements. Report 24: Determination of absorbed dose in a patient irradiated by beams of × or gamma rays in radiotherapy procedures. International Commission of Radiation Units and Measurements; 1976. Copyright © 1976 International Commission on Radiation Units and Measurements. Reprinted by permission of SAGE Publications.)

$$\mathrm{CF} = \frac{T\left(d-h, s_{\mathrm{d}}\right)}{T\left(d, s_{\mathrm{d}}\right)}$$

where h = air gap.

Air Gap Correction Factor: Effective Source-Skin Ratio Method

In the effective SSD method, the isodose chart to be used is placed on the patient's contour representation, positioning the central axis at the distance for which the curve was measured (Figure 8.1). It then is shifted down along the ray line for the length of the air gap, h, resulting in SSD = S″. The PDD value at point B is read and modified by an inverse-square calculation to account for the effective change in the peak dose. The CF can be expressed as follows:

$$\mathrm{CF} = \frac{P\left(d-h, d_0, S, f, E\right)}{P\left(d, d_0, S, f, E\right)} \cdot \left(\frac{f+d_0}{f+h+d_0}\right)^2$$

Correction for Tissue Heterogeneities

The following CF methods can be used to account for the tissue heterogeneities found within the patient.

Tissue Heterogeneities Correction Factor: Ratio of Tissue-Air Ratio Method

The RTAR method of correction for inhomogeneities is given by

$$\mathrm{CF} = \frac{T\left(d_{\mathrm{eff}}, S_d\right)}{T\left(d, S_d\right)}$$

where the numerator is the TAR for the equivalent water thickness, d_{eff}, and the denominator is the TAR for the actual thickness, d, of tissue between the point of calculation and the surface along a ray passing through the point. S_{d} is the dimension of the beam cross section at the depth of calculation. The RTAR method accounts for the field size and depth of calculation. It does

not account for the position of the point of calculation with respect to the heterogeneity. It also does not take into account the shape of the inhomogeneity; instead, it assumes that it extends the full width of the beam and has a constant thickness (ie, referred to as *slab geometry*).

Tissue Heterogeneities Correction Factor: Power Law Tissue-Air Ratio Method

The *power law TAR method* was proposed by Batho[9] and generalized by Young and Gaylord.[10] This method, sometimes called the *Batho method*, attempts to account for the nature of the inhomogeneity and its position relative to the point of calculation. However, it does not account for the extent or shape of the inhomogeneity. The CF for the point P is given by

$$\mathrm{CF} = \left(\frac{T(d_2, S_d)}{T(d_1, S_d)} \right)^{\rho_2 - 1}$$

where d_1 and d_2 refer to the distances from point P to the near and far side of the non–water-equivalent material, respectively; S_d is the beam dimension at the depth of P; and ρ_2 is the relative electron density of the inhomogeneity with respect to water.

Sontag and Cunningham[11] derived a more general form of this CF, which can be applied to a case in which the effective atomic number of the inhomogeneity is different from that of water and the point of interest lies within the inhomogeneity. The CF in this situation is given by

$$\mathrm{CF} = \frac{T(d_2, S_d)^{(\rho_b - 1)}}{T(d_1, S_d)^{(\rho_b - \rho_a)}} \times \frac{(\mu_{en} / \rho)_a}{(\mu_{en} / \rho)_b}$$

where r_a is the density of the material in which point P lies at a depth d below the surface and r_b is the density of an overlying material of thickness $(d_2 - d_1)$; and $(\mu_{en}/r)_a$ and $(\mu_{en}/r)_b$ are the mass energy absorption coefficients for the medium a and b, respectively.

Model-Based Dose Calculation Methods

Advanced 3D dose calculation algorithms, such as the convolution/superposition algorithm and Monte Carlo, have for many years now been the standard of practice.[5,6,12-14] These models provide accurate results even for complex heterogeneous geometries.

Convolution/Superposition Dose Calculation Algorithm

The convolution/superposition dose calculation algorithm is based on the following equation[5]:

$$D(\vec{r}) = \int\int\int\int T_E(\vec{S})\, h(E, \vec{r} - \vec{s})\, d^3s\, \mathrm{dE}$$

where D represents the dose at some point, T_E ($\vec{s}$) represents the total energy released by primary photon interactions per unit mass (or TERMA), and h (E, $\vec{r} - \vec{s}$) is the *point spread function* (also called *dose spread array, differential pencil beam*, and *energy deposition kernel*). The point spread function represents the fraction of the energy deposited (per unit volume) at a point that is subsequently transported to the calculation point. Hence, the DP is computed by integrating over all space the dose contributions from photons and electrons that are produced at all other points in the phantom or patient.

Ahnesjö et al[15] showed that the point spread function, h (E, $\vec{r} - \vec{s}$), changes only slightly as a function of energy and, thus, can be replaced by h (E, $\vec{r} - \vec{s}$) (defined as the average point spread function weighted by the

spectral components of the beam), reducing the basic convolution 4D integral to a 3D integral overall space. Point spread functions for monoenergetic photons are generally precomputed using Monte Carlo methods.[15] The energy dependence of the TERMA, T_E ($\vec{s}$), can be expressed by applying the inverse-square law and exponential attenuation to the photon fluence at the surface of the phantom or patient.

The 3D integral is typically evaluated in a two-step process. The first step takes into account the properties of the accelerator (including the finite source size, primary collimator, flattening filter, collimator jaws, multileaf collimators (MLCs), and any beam-modifying devices used for the treatment, such as wedges, alloy blocks, and compensating filters) to compute the energy fluence at the phantom or patient surface. The second step of the calculation takes into account the inverse-square law and exponential attenuation to this incident fluence to determine the TERMA, T_E ($\vec{s}$), at each point within the phantom or patient and convolve the result with the point spread function, h ($\vec{r} - \vec{s}$).

The convolution equation is strictly valid only for homogeneous media (ie, h ($\vec{s}$) must be spatially invariant). To account for the effects of tissue heterogeneities, all physical distances in the convolution integral are replaced with radiologic distances, that is, the physical distance multiplied by the average density along the line in question.[12,15] Hence, the convolution/superposition algorithm accounts for the effects of heterogeneities anywhere in the vicinity of the calculation point in 3D. In contrast, most CF-based dose calculation techniques require only a simple 1D evaluation of radiologic path length and can thus account for the effects of only those tissue heterogeneities that lie along a ray connecting the radiation source to the calculation point.

Several investigators have tested the convolution/superposition algorithm against measurements and Monte Carlo–generated data for complex phantom geometries including both homogeneous and heterogeneous phantoms and found that the convolution/superposition model gave accurate results, even in parts of the buildup region and penumbra.[16,17]

Dose Transport Methods

Dose transport calculations can be implemented either *deterministically* using linear Boltzmann transport equations (LBTEs) or *stochastically* using Monte Carlo.[18] Monte Carlo methods were introduced into treatment planning systems first but now both types of algorithms are available in clinical planning software.

Monte Carlo Method

Monte Carlo is, in principle, the only method capable of computing the dose distribution accurately for all situations encountered in radiation therapy, including being able to accurately predict the dose near interfaces of materials with very dissimilar atomic numbers, such as near-metal prostheses, or different densities such as tumors in lung tissue.[19] The Monte Carlo method uses the known cross sections for electron and photon interactions in matter and follows individual photons and the associated electrons set in motion through the entire heterogeneous phantom or patient. By calculating the trajectories and interactions of a very large number of photons and electrons, one can accurately model the dose distribution. Recently, Monte Carlo codes have been developed for radiotherapy treatment planning,[14,20] several of which have been implemented commercially. The reader is referred to the American Association of Physicists in Medicine (AAPM) Task Group (TG) 157 Report, which summarizes the commissioning and use of Monte Carlo for radiation therapy treatment planning.[21] The reader is also referred to the review article by Siebers et al for even more details on Monte Carlo calculation for external-beam radiation therapy.[19] More recently, Monte Carlo dose calculations have been extended to account for magnetic field effects on deposition of radiation dose for magnetic resonance (MR)-guided treatment machines.[22-24]

Linear Boltzmann Transport

LBTEs characterize the transport of radiation particles through a medium using physical principles, such as the interaction cross sections and conservation of energy. The flux of particles traversing a medium in a particular direction at a specific point of space can be quantified by tracking the addition of loss of particles due to scattering. In this regard, LBTE is

similar to Monte Carlo. But unlike Monte Carlo, the change in fluence is calculated in all directions for both photons and electrons, resulting in a set of simultaneous equations that can be solved to yield the composite fluence at any point in the medium, which, in turn, can be used to determine the absorbed dose at that point. As in Monte Carlo methods, approximations are utilized to ignore or simplify some interactions. More details about the equations, approximations used, and applicability to magnetic fields can be found in the review article by Bedford.[18] Currently, this algorithm has been implemented in the Eclipse treatment planning system (Acuros XB, Varian Medical Systems).[25]

Dose Calculation Algorithms and Tissue Heterogeneities

In 2004, the AAPM published Report 85 (TG 65) on tissue inhomogeneity corrections for megavoltage photon beams.[26] The task group recommended an accuracy goal for tissue heterogeneity corrections of 2% in order to achieve an overall 3% accuracy in dose delivery. The AAPM report recommended heterogeneity corrections be applied to plans and prescriptions, with the condition that the algorithm used for calculations be reviewed and rigorously tested by the medical physicist. A brief summary of the site-specific recommendations follows. For the head and neck region, a 1D path correction algorithm for point-dose estimations beyond mandible and ear cavities was thought to be reasonable. However, for soft tissue regions and volumes that are adjacent to these heterogeneities, superposition/convolution or Monte Carlo algorithms should be used. For the larynx, specifically, if the target volume is adjacent to the air cavity or if there is a severe case of disease in the anterior commissure, then either the superposition/convolution or Monte Carlo algorithms should be used. For the treatment of lung cancer, for interest points well beyond the lung interface, 1D path corrections were thought to be reasonable. However, accounting for doses at tumor-lung interfaces, the superposition/convolution or Monte Carlo algorithms should be used. Also, the report recommended that photon energies of 12 MV or less should be used for the treatment of lung cancer to minimize nonequilibrium conditions that exist with higher energies. For breast cancer treatment (particularly if the dose of interest of the target volume is considered to be chest wall), it is recommended that

calculations be performed with superposition/convolution or Monte Carlo. However, for simple intact breast planning, 1D algorithms were adequate. For the upper gastrointestinal tract, 1D corrections were adequate. However, one should be leery if barium contrast is used as it can erroneously impact the dose calculation because of its high Z. In terms of the pelvis and prostate, 1D corrections were quite reasonable, except in the presence of high-Z implanted hip prostheses. (Note that the dosimetric considerations for patients with hip prostheses undergoing pelvic irradiation are discussed in a later section.) The study by Frank et al[27] provides a clear method for safely transitioning clinical use from one based on planning that assumes a homogeneous unit-density patient to one using a heterogeneous patient model.

The Radiological Physics Center published the results of a study comparing measured results of irradiated lung phantoms having various geometries with dose calculations for similar conditions using commercial treatment planning systems. They found significant differences if algorithms less sophisticated than the superposition-/convolution-type algorithms were used.[28]

MONITOR UNIT CALCULATION METHODS

MU calculations refer to determining the linac MU setting per field to deliver the prescribed dose, taking into account the tumor depth, treatment distance, MLC setting or secondary blocking configuration, and primary collimator opening. This is accomplished by using the various dosimetric quantities described in the preceding chapter to relate the dose corresponding to an arbitrary set of treatment parameters to a normalization geometry where the output of the machine is specified in terms of cGy/MU. AAPM TG Report 71 differentiates between the reference geometry, where the output was calibrated, and the normalization geometry, where the output is specified.[29] While these may be consistent, it is also possible for a clinic to use a different normalization geometry than the calibration geometry. The normalization geometry including source-to-surface distance, field size, and depth of output specification is denoted by the symbols SSD_0, r_0, and d_0, respectively. For a fixed SSD normalization geometry,

$$MU = \frac{D}{D_0' * S_c(r_c) * S_p(r_d) * TPR(d, r_d) * WF(d, r_d, x) * TF * OAR(d, x) * \left(\frac{SSD_0 + d_0}{SPD}\right)^2}$$

Normal incidence and open-beam geometry (ie, absence of trays or any beam-modifying filters) are specified.

For treatment machines calibrated isocentrically, the point of MU specification is located at distance SAD rather than at distance SAD + d_{max} as stated previously. For isocentric calibration, $SSD_0 + d_0 = SAD$.

The linac is calibrated by adjusting the sensitivity of its internal monitor transmission ion chamber so that 1 MU equals D_0'cGy for the normalization geometry condition. Several reports providing more details on MU calculations and their verification are listed in the references.[29,30]

Monitor Unit Calculation for Fixed Fields

When the patient is to be treated isocentrically, the point of dose prescription is located at the isocenter, regardless of the target depth. Using the notation of Gibbons et al[29] the MU needed to deliver a prescribed tumor dose to the isocenter (D) for a depth d of overlying tissue on the central ray is given by

$$MU = \frac{D}{D_0' * S_c(r_c) * S_p(r_d) * TPR(d, r_d) * WF(d, r_d, x) * TF * \left(\frac{SSD_0 + d_0}{SAD}\right)^2}$$

where TF and WF denote the tray and wedge factors, respectively. They are defined as the ratio of the central ray dose with the tray or wedge filter in place relative to the dose in the open-beam geometry. The collimated field size is denoted by r_c and is usually described as the square field size equivalent to the rectangular collimator opening projected to the isocenter. The effective field size is denoted by r_d and is always specified to the isocenter distance (SAD). The inverse-square law factor accounts for the difference in distances from the source to the point of dose prescription relative to the point of MU specification. When isocentric calibration is used, this factor is unity. Note that collimator-defined field size is used for the lookup of the collimator scatter factor, S_c, whereas effective field size projected to the isocenter is used for the lookup of TPR and the phantom scatter factor, S_p. By separately accounting for the effect of collimator opening on the primary dose component and the influence of cross-sectional area of tissue irradiated, most of the difficulties in accurately delivering a dose in the presence of extensive blocking are overcome.

When a fixed distance between the target and entry skin surface (SSD) is used to treat the patient, a dose calculation formalism based on PDD is used rather than one based on isocentric dose ratios. When a dose D is to be delivered to depth d, MUs are given by

$$MU = \frac{\mathrm{D}*100\%}{D_0' * S_c(r_c) * S_p\left(r_{d_0}\right) * \mathrm{PDD}_N(d, r, \mathrm{SSD}) * \mathrm{WF}(d, r_d, x) * \mathrm{TF} * \mathrm{OAR}(d, x) * \left(\frac{\mathrm{SSD}_0 + d_0}{\mathrm{SSD} + d_0}\right)^2}$$

The field size (or its equivalent square) on the skin surface at the central axis is denoted by r and is used for the lookup of normalized PDD_N. The field size for S_p is r_{d0}, the field size at the patient surface. The collimated field size r_c at the isocenter must be used for the lookup of S_c. When an

extended treatment distance is used, the collimated field size at the isocenter differs significantly from that at the skin surface of the patient. Note that PDD is a function of SSD, depth, and effective field size. Collimator scatter factors measured at SAD are valid over a wide range of extended treatment distances.[7]

When this dose calculation formalism for highly extended treatment distances such as encountered in administering total-body irradiation is used, care must be taken to verify the validity of inverse-square law at these distances. It is recommended that such setups always be verified by ion chamber measurement at the extended distance. Because of the large scatter contribution to the effective primary dose originating from the flattening filter and other components in the treatment head, the virtual source of radiation may be as much as 2 cm proximal to the target of the accelerator.

All MU calculation formalisms require some means of estimating the square field size, *r*, that is equivalent, in terms of scattering characteristics, to an arbitrary rectangular field of width *a* and length *b*. Perhaps the most widely used rectangular equivalency principle is the "A/P" rule. It states that a square and a rectangle are equivalent if they have the same area/perimeter ratio; that is.

$$r = \frac{2(a \times b)}{(a + b)}$$

Another widely used approach to reducing rectangular estimates of effective field size to square field sizes is the equivalent square table published in the *British Journal of Radiology*.[31] Estimating the effective field size equivalent to an irregular field is best handled via irregular field calculations as discussed later in this chapter.[32,33]

Monitor Unit Calculations for Asymmetric X-Ray Collimators

Asymmetric x-ray collimators (also referred to as *independent jaws*) allow independent movement of an individual jaw and may be available for one jaw pair or both pairs. Because MU calculations and treatment planning

methods generally rely on symmetric jaw data, the dosimetric effects for asymmetric jaws must be fully documented before being implemented in the clinic. Several investigators have examined the effects of asymmetric jaws on PDD, collimator scatter, and isodose distributions.[34] MU calculations for asymmetric jaws are only slightly more complex than for symmetric jaws.[29] Typically, one simply applies an *OAR* or *off-center ratio (OCR)* CF that depends only on the distance from the machine's central axis to the center of the independently collimated open field.[35,36] PDD is only minimally affected, but the isodose curve shape can be altered and must be investigated for the particular treatment unit. Calculations for asymmetric wedge fields follow similar procedures by simply incorporating a wedge OAR or OCR.[37,38]

Monitor Unit Calculations for Multileaf Collimator

MLCs have nearly completely replaced conventional alloy field shaping for photon beams in most clinics around the world. Several investigators have examined the effects of the Varian MLC design (tertiary system) on PDD, collimator scatter, and isodose distributions, described in AAPM TG Report 72.[39] The effects due to field area shaped by this type of MLC on PDD and beam output parameters are similar to those resulting from Cerrobend field shaping. Thus, the dose/MU calculation methods discussed previously apply by simply using the equivalent area defined by the MLC. The collimator scatter factor and the dose in free space are determined using the x-ray collimator jaw settings, with an off-axis factor applied for any asymmetric jaw settings.

It should be noted, however, that for MLC systems that replace one of the collimating jaws, the MLC field shape can be a determining factor in selecting the appropriate output factor. For example, in the case of the Elekta linacs (Elekta AB, Crawley, United Kingdom), in which the lower jaws are replaced by the MLC system, the calculation takes into consideration the collective blocked area that is created by both the MLC leaves and the lower backup diaphragms. For an MLC system that replaces the upper jaw (eg, Siemens linac, Siemens Medical Solutions USA, Inc., Malvern, PA), the blocked area can be used for determining all the calculation parameters (mainly output, PDD, and scatter factor).

Hence, because of MLC design differences and the fact that vendors are continuing to modify/improve MLC designs, the authors caution that when a new linac is installed, the impact of the MLC on the institution's MU calculation procedure should be fully documented before clinical use. The reader is also encouraged to review AAPM TG Report 50, which provides more detail on various MLC types and discusses quality assurance (QA) and MU calculations.[39]

Monitor Unit Calculations for Irregular Fields

For large, irregularly shaped fields and at points off the central axis, it is necessary to take into account the off-axis change in intensity (relative to the central axis) of the beam, the variation of the SSD within the field of treatment, the influence of the primary collimator on the output factor, and the scatter contribution to the dose. Changes in the beam quality as a function of position in the radiation field also should be considered.[40,41]

The general method used for irregular field calculations consists of summation at each point of interest of the primary and scatter irradiation, with allowance for the off-axis change in intensity (off-axis factor) and SSD.[32,33] The MUs required to deliver a specified dose at an arbitrary point in an irregular field (Figure 8.2) can be calculated as follows:

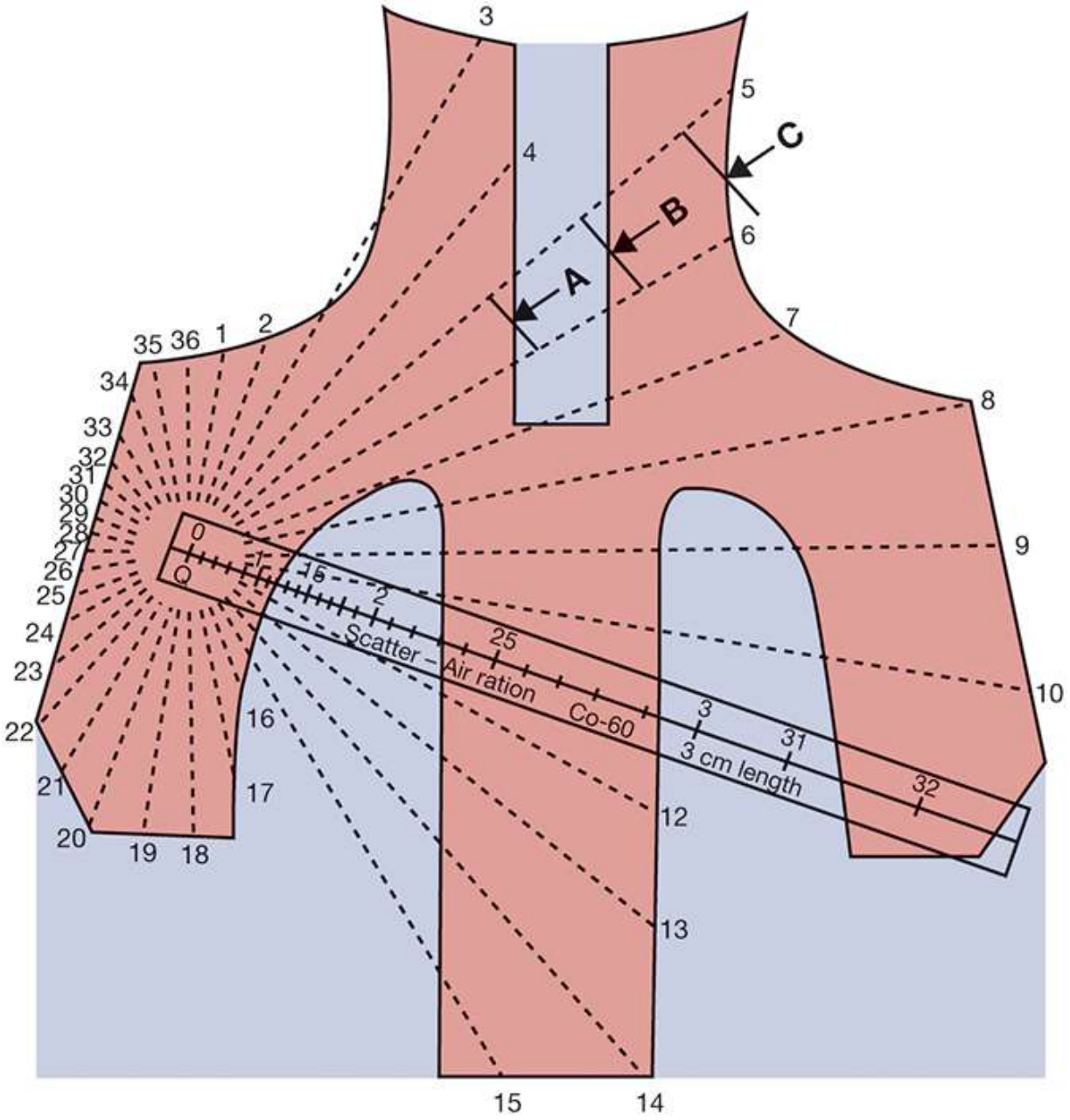


FIGURE 8.2 Outline of mantle field illustrating method of determining scatter-to-air ratio, used for irregular field dose calculations. (From Cundiff JH, Cunningham JR, Golden R, et al. A method for the calculation of dose in the radiation treatment of Hodgkin's disease. *Am J Roentgenol Radium Ther Nucl Med*. 1973;117[1]:30-44. Reprinted with permission from the American Journal of Roentgenology.)

$$MU = \frac{TD}{\left[TAR(d,0) + \overline{SAR}(d)\right] \cdot \dot{D}_{fs}\left(SSD + d_{max}, r_c\right) \cdot TF \cdot OAF\left(\frac{SSD + d_{max}}{SSD + g + d}\right)^2}$$

where the parameters used are

TAR (d,0) = zero-field size TAR at depth d

SAR (d) = average SAR for point in question at depth d determined using the Clarkson technique

D_{fs} = Gy/MU in a small mass of tissue, in-air, on the central axis at normal SSD + d_{max} for the collimated field size

SSD = nominal SSD for treatment constraints

d_{max} = depth of dose maximum

TF = blocking tray attenuation factor

g = vertical distance between skin surface over point in question and nominal SSD (beam vertical)

d = vertical depth, skin surface to point in question

OAF = in-air off-axis factor.

Computer implementations vary but typically include using the expanded field size at a depth for the SAR calculation, determining the off-axis factor using the distance from the central axis to the slant projection of the point of calculation to the SSD plane along a ray from the source and determining the zero-area TAR using the slant depth along a ray going from the source to the point of calculation. It is generally accepted that the off-axis factor should be multiplied by the sum of the zero-area TAR and the SAR as originally proposed.

Beam quality is a function of position in the field for beams generated by linear accelerators.[40,41] The TAR_0 may be expressed as a function of position in the beam so that changes in beam quality can be incorporated into calculations, and it can be related to the half-value layer (HVL) of water by the following equation:

$$\mathrm{TAR}\left(d,0,r\right)=e\left[\frac{-0.693\left(d-d_{\max}\right)}{\mathrm{HVL}\left(r\right)}\right]$$

where d is the depth of the point of reference, d_{max} is the depth of maximum dose, r is the radial distance from the central axis of the beam to the point of calculation, e is the base of the natural logarithm, and HVL*(r)* is the beam quality expressed as the HVL measured in water.

Monitor Unit Calculations for Intensity-Modulated and Rotational Therapy

The classic method for MU calculations for rotation therapy is given by the following equation:

$$\mathrm{MU}=\frac{\mathrm{ID}}{\mathrm{TAR}_{\mathrm{avg}}\cdot\dot{D}_{fs}\left(\frac{\mathrm{SCD}}{\mathrm{SAD}}\right)^{2}}$$

and the MU per degree setting is given by

$$\mathrm{MU/deg}=\frac{\text{monitor unit setting}}{\text{degrees of rotation}}$$

where the symbols have the previous meaning and $\mathrm{TAR}_{\mathrm{avg}}$ is an average TAR (averaged over radii [depth in the patient] at selected angular intervals, such as 10° or 20°).

Most recently, manufacturers of linacs and their associated planning systems have introduced features that provide rotational intensity-modulated radiation therapy (IMRT) capability[42] (eg, Elekta VMAT[43] and Varian RapidArc[44]), addressed in detail in Chapters 10. The linac-based

rotational IMRT concept was first proposed by Yu[45] and called *intensity-modulated arc therapy*, but planning software was not commercially available at that time. Rotational IMRT approaches on conventional linacs may provide even more conformal dose distributions delivered in a shorter treatment time, compared with *SMLC-IMRT (step and shoot)* or *DMLC-IMRT (dynamic)* approaches that use only a limited number of gantry directions. In addition, plan optimization is simpler because it eliminates the planner's iterative choices of beam number and direction. MU calculations for this more complex form of rotational therapy are generated via advanced treatment planning systems having this capability. All are techniques in which the MLC shape changes during a rotation therapy, and depending on the specific linac, other parameters, such as dose rate, may also change. This advanced type of treatment delivery is mainly checked via phantom measurements rather than manual calculations before the patient's treatment. AAPM TG 218[46] covers the role of such pretreatment, patient-specific QA measurements, and the use of electronic portal imaging devices for these measurements.

Secondary computer programs can also be used to perform independent dose calculations and MU as well as 3D dose calculations. It is apparent that the simple MU manual calculation methods described here are no longer adequate for the complex technologies in use today. Modern computer plans utilize dose weight points of interest, which classical MU calculation methods may not address; in addition, geometries that include the presence of heterogeneities, added tertiary devices such as MLCs and asymmetric jaws, and beam intensity modulation can all be problematic for manual check calculations. For example, when the dose weight point is within a small volume of mass surrounded by low-density tissue (eg, a coin lesion in lung) or one that is at the border of a chest wall and lung (as in a postmastectomy patient), MU calculations cannot easily be confirmed by simple hand-calculated MU methods, and one must rely on the planning system for calculations such as these, emphasizing the importance of fully testing such system prior to clinical use. Dedicated commercial software for MU verification is widely available; for example, RadCalc (LifeLine Software Inc, Austin, TX)[47,48] offers a variety of independent MU beam on-time calculations, including that for the Gamma Knife (software developed at Washington University and licensed to RadCalc).[49] Obviously, such

systems must be validated by the physics user prior to clinical use. AAPM TG 219 describes currently available MU verification software as well as recommendations for commissioning and use of such software.[50]

CLINICAL PHOTON BEAM DOSIMETRY

Percent Depth Dose and Single-Field Isodose Charts

The central-axis PDD expresses the penetrability of a radiation beam. Table 8.1 summarizes beam characteristics for x-ray and γ-ray beams typically used in radiation therapy and lists the depth at which the dose is maximum (100%) and the 10-cm depth PDD value. Representative PDD curves are shown in Figure 8.3 for conventional SSDs. As a rule of thumb, an 18-MV, 6-MV, and ^{60}Co photon beam loses approximately 2%, 3.5%, and 4.5% per centimeter, respectively, beyond the depth of maximum dose, d_{max} (values are for a 10- × 10-cm field, 100-cm SSD). There is no agreement as to what the single optimal x-ray beam energy is; instead, institutional bias or radiation oncologist training typically influences its selection, and it is usually treatment site specific. As pointed out in Chapters 6, most modern linacs are multimodality and provide a range of photon and electron beam energies ranging from 4 to 25 MV, with 6-, 10-, and 15-MV x-ray beams becoming the most common. It should be noted that in the case of IMRT, the impact of energy on the quality of the delivered radiation dose distribution is less compared to 2D and 3DCRT treatments and that all recent developments in radiotherapy use lower-energy beams exclusively (eg, CyberKnife, TomoTherapy, ViewRay, Halcyon).[51] The choice of high-energy beams in the era of predominantly IMRT delivery likely has a much larger effect on operational efficiency and facility design than on the quality of delivered radiation. Selection of treatment machines with the highest energy of 10 MV or less results in simplification of radiotherapy treatment rooms, typically allowing elimination of the maze and use of thinner and faster room entry doors. These shielding gains come from the elimination of shielding requirements for secondary neutron radiation.

TABLE 8.1 BEAM CHARACTERISTICS FOR PHOTON BEAM ENERGIES OF INTEREST IN RADIATION THERAPY

200 kVp, 2-mm Cu HVL, SSD = 50 cm

- Depth of maximum dose = surface
- Rapid falloff with depth due to (a) low energy and (b) short SSD
- Sharp beam edge due to small focal spot
- Significant dose outside beam boundaries due to Compton scattered radiation at low energies

^{60}CO, SSD = 80 cm

- Depth of maximum dose = 0.5 cm
- Increased penetration (10 cm PDD = 55%)
- Beam edge not as well defined—penumbra due to source size
- Dose outside beam low because most scattering is in the forward direction
- Isodose curvature increases as the field size increases

4-MV x-ray, SSD = 80 cm

- Depth of maximum dose = 1-1.2 cm
- Penetration slightly greater than cobalt (10 cm PDD = 61%)
- Penumbra smaller
- “Horns” (beam intensity off-axis) due to flattening filter design ≈14%

6-MV x-ray, SSD = 100 cm

- Depth of maximum dose = 1.5 cm
- Slightly more penetration than ^{60}Co and 4 MV (10 cm PDD = 67%)
- Small penumbra
- Horns (beam intensity off-axis) due to flattening filter design ≈9%

15- to 18-MV x-ray, SSD = 100 cm

- Depth of maximum dose = 3-3.5 cm
- Much greater penetration (10 cm PDD = 80%)
- Small penumbra
- Horns (beam intensity off-axis) due to flattening filter design ≈5%
- Exit dose often higher than entrance dose

HVL, half-value layer; PDD, percentage depth dose; SSD, source-to-skin distance.

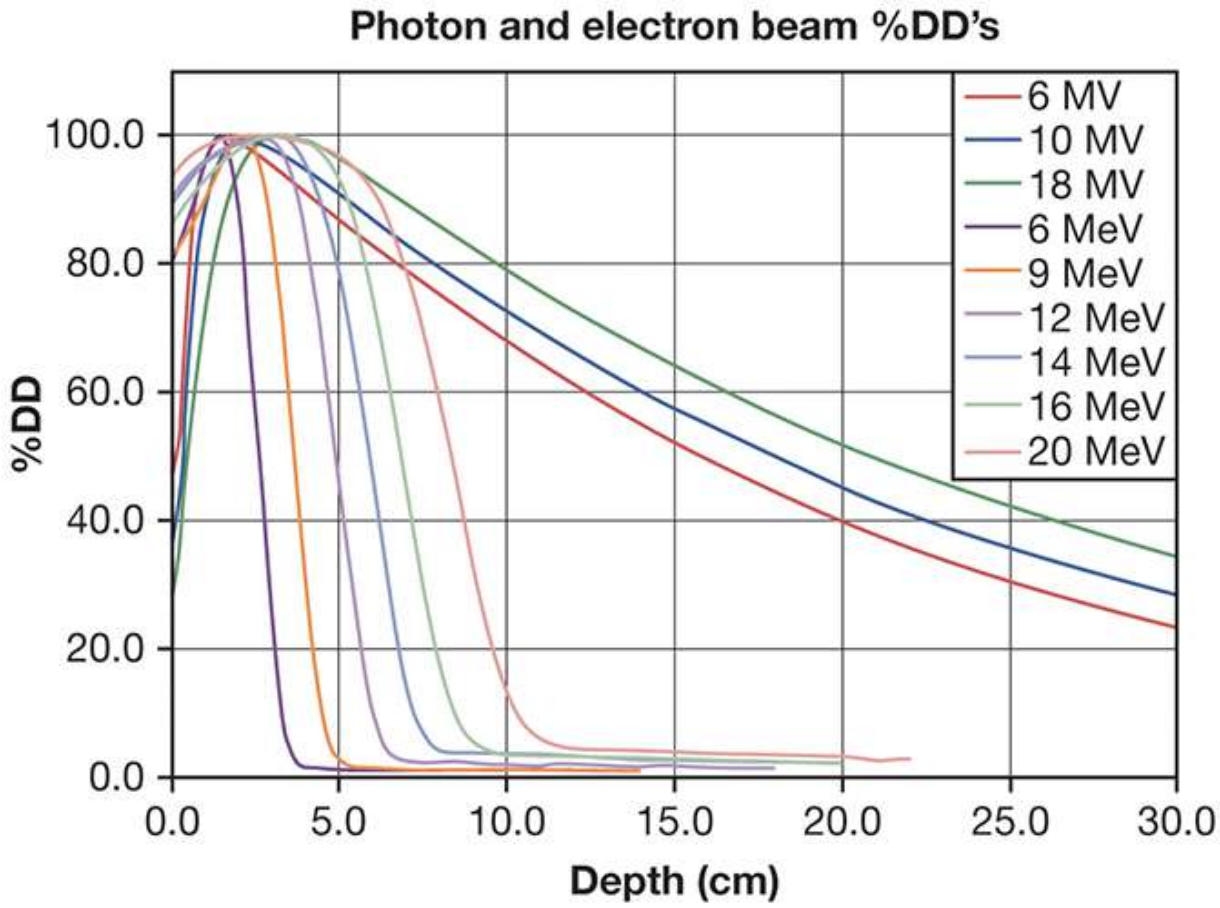


FIGURE 8.3 Typical photon and electron beam central-axis percentage depth-dose curves for a 10- × 10-cm beam for megavoltage beams ranging from ^{60}Co to 18-MV x-rays and 6- to 20-MeV electron beams.

Isodose charts provide much more information about the radiation beam characteristics than do central-axis PDD data alone. However, even isodose charts are limited in that they represent the dose distribution in only one plane (typically the one containing the beam's central axis) and are usually available only for square or rectangular fields. Isodose charts are usually measured in a water phantom with the radiation beam directed perpendicular to the phantom's flat surface. Isodose curves show the relative uniformity of the beams across the field at various depths and graphically depict the width of the beam's penumbra region. ^{60}Co teletherapy units exhibit a relatively large penumbra, and their isodose distributions are more rounded than those from linac x-ray beams. This is due to the relatively large source size (typically 1-2 cm in diameter vs only a few millimeters for linacs). Linac beam penumbra width does increase

slightly as a function of energy and if unfocused MLC leaves are used but is still much less than that for ^{60}Co units. The beam penumbra can be improved if focused MLCs are used. For example, the ViewRay's ^{60}Co could produce treatment plans equivalent in quality to that of modern linacs. This equivalence between ^{60}Co and linac plans was achieved through combining ^{60}Co with doubly focused MLCs on ViewRay.[52] This ability to improve the IMRT plan quality through MLC design will undoubtedly lead to further refinements in approaches to MLC design. ViewRay's double-layer doubly focused and Varian Halcyon's dual-layer MLCs are early indications of this possibility. In addition to the smaller penumbra, linac x-ray isodose distributions have relatively flat isodose curves at depth. However, at shallow depths, particularly at d_{max}, linac x-ray beams typically exhibit an increase in beam intensity away from the central axis; this beam characteristic is referred to as the dose profile *horns* and depends on flattening filter design. In general, each treatment unit has unique radiation beam characteristics, and thus, isodose distributions must be measured, or at least verified, for each specific treatment unit. Excellent dosimetric reproducibility between modern treatment machines has been observed, and there is now a trend toward verification of the expected beam dosimetry rather than attempting to fully characterize dosimetry for each machine.[53]

Another important point to understand is how the radiation field size is defined. The radiation field size dimensions refer to the distance perpendicular to the beam's direction of incidence that corresponds to the 50% isodose at the beam's edge. It is defined at the skin surface for SSD treatments and at the SAD for isocentric treatments.

Depth-Dose Buildup Region

When a photon beam strikes the tissue surface, electrons are set in motion, causing the dose to increase with depth until the maximum dose is achieved at depth d_{max}. As the energy of the photon beam increases, the thickness of the buildup region increases. The subcutaneous tissue-sparing effects of higher energy x-rays, combined with their great penetrability, make them well suited for treating deep lesions. In general, the dose to the surface and in the buildup region for megavoltage photon beams generally increases with increasing field size and with the insertion of blocking trays made of

plastic or other types of material in the beam (Figure 8.4). The blocking trays should be at least 20 cm above the skin surface because skin doses are significantly increased for lesser distances. Copper, lead, or lead glass filters beneath the blocking tray can be used to remove the undesired lower-energy electrons that contribute to skin dose, but this is nowadays rarely done routinely in the clinic.[54,55]

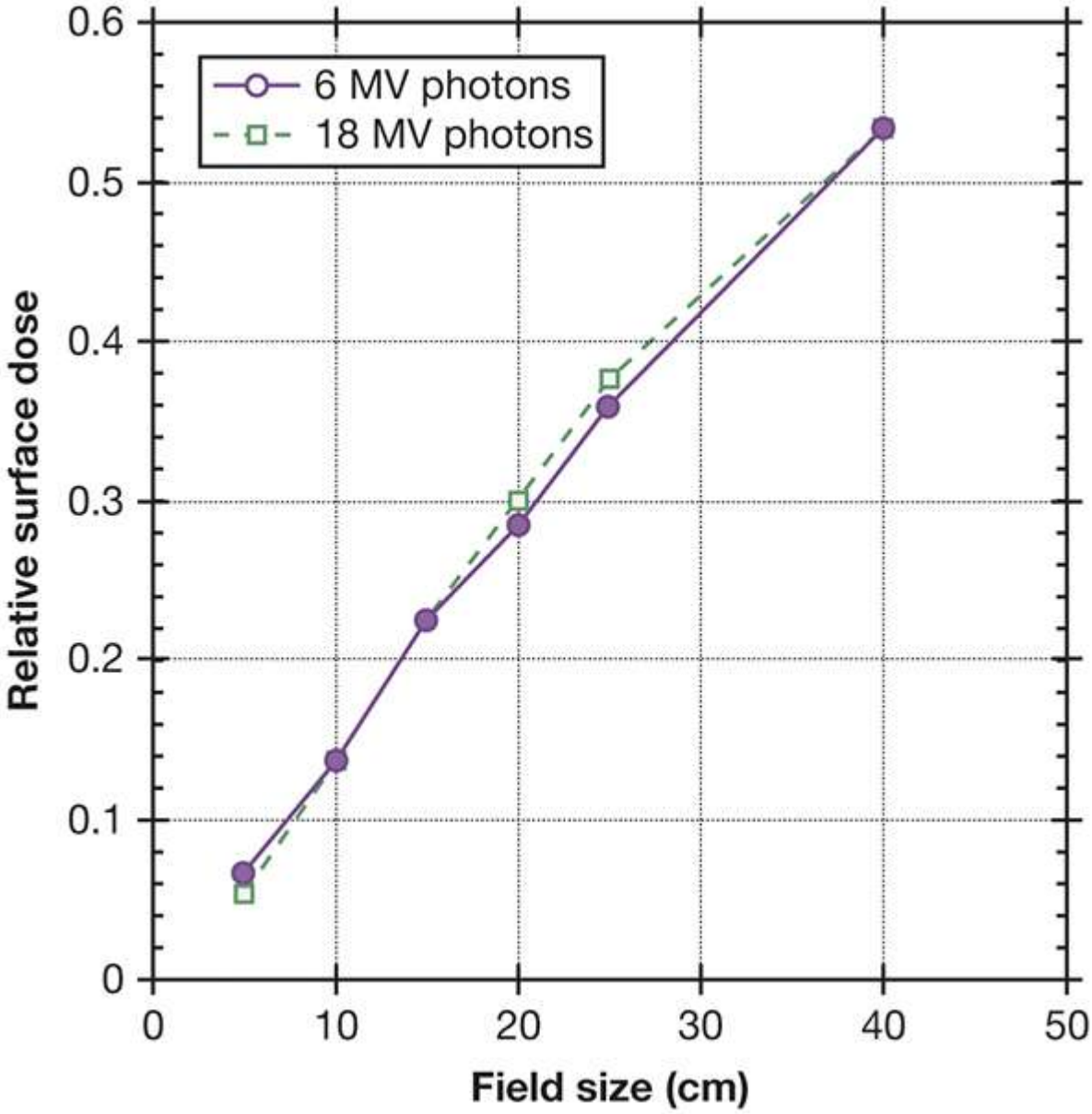


FIGURE 8.4 Relative surface dose versus field size with blocking tray in place for 6- and 18-MV photons. (Reprinted from Klein EE, Purdy JA. Entrance and exit dose regions for clinac-2100c. *Int J Radiat Oncol Biol Phys*. 1993;27[2]:429-435. Copyright © 1993 Elsevier. With permission.)

As the angle of the incident radiation beam becomes more oblique, the surface dose increases, and d_{max} moves toward the surface (Figure 8.5). This is primarily due to more secondary electrons' contribution from the media below the surface along the oblique path of the beam.[56]

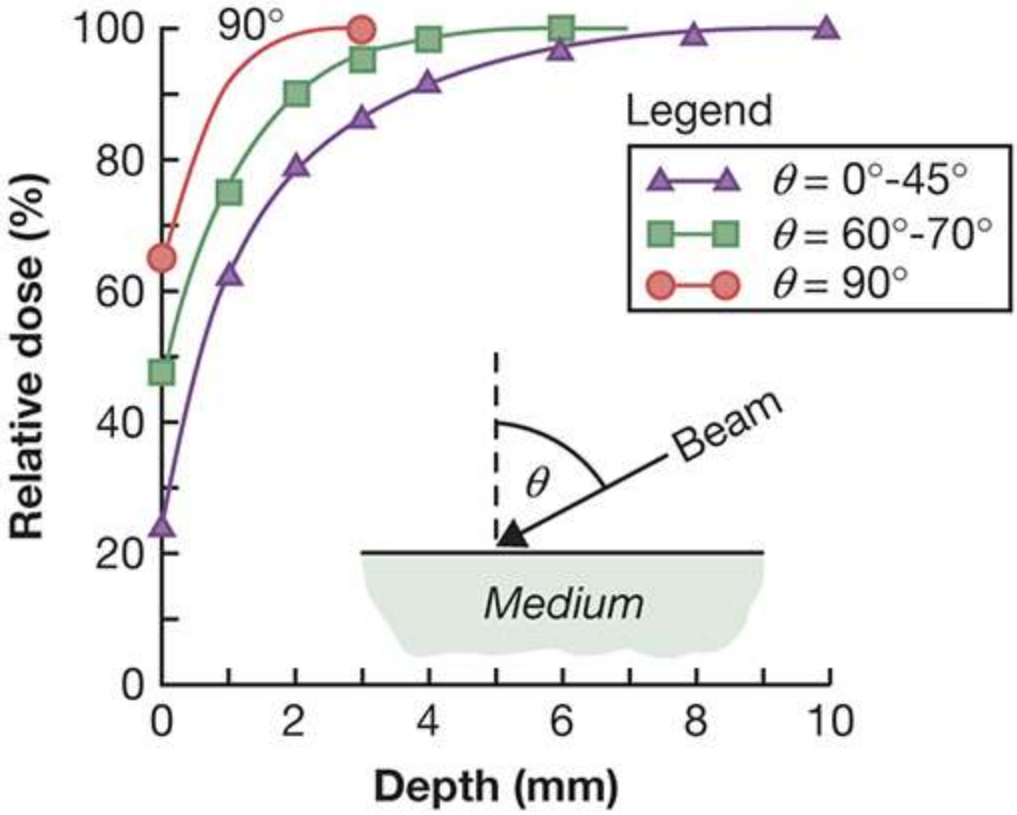
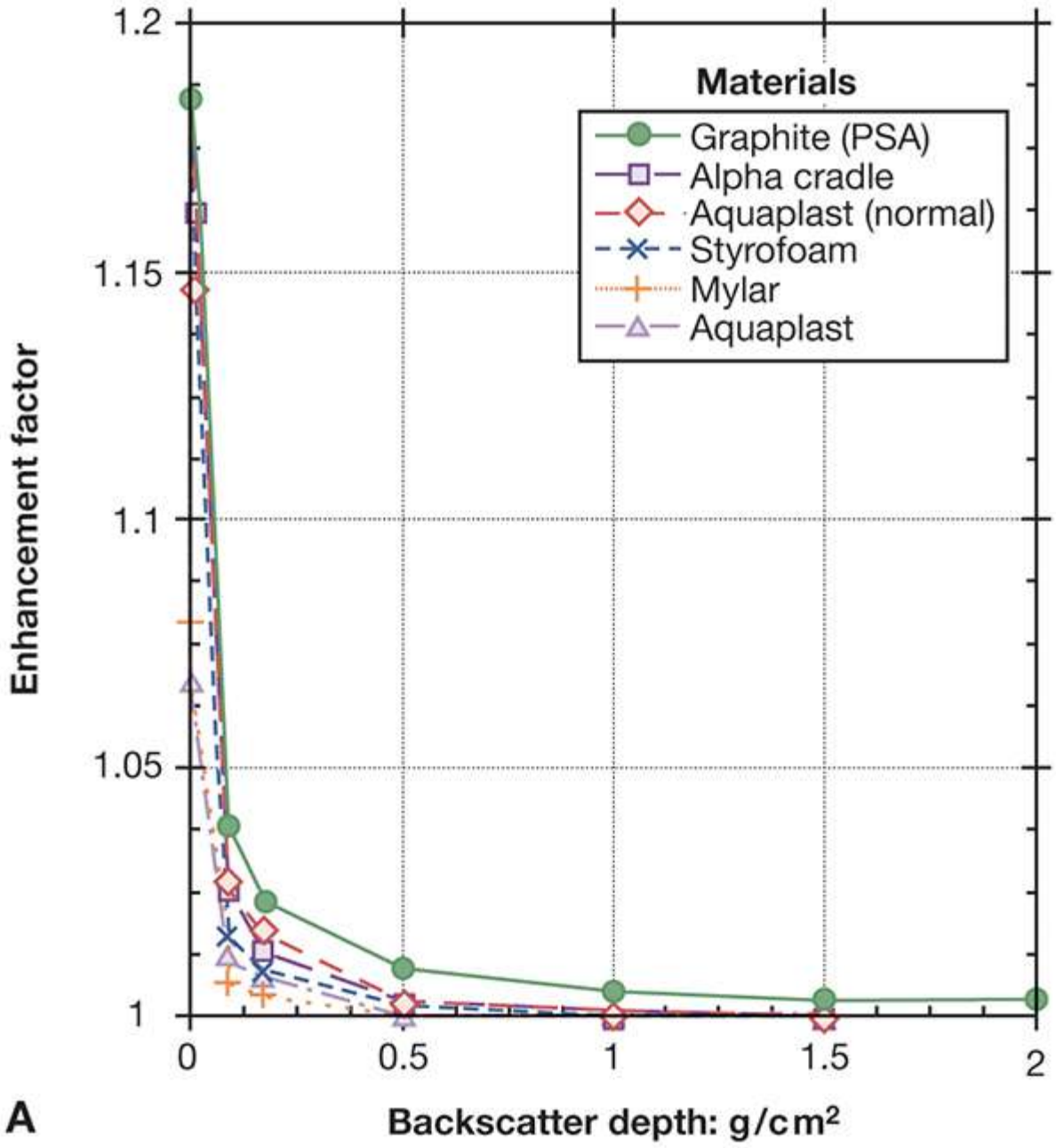


FIGURE 8.5 The variation of surface dose and depth of maximum dose as a function of the angle of incidence of the x-ray beam with the surface (4 MV, 10 × 10 cm^2).

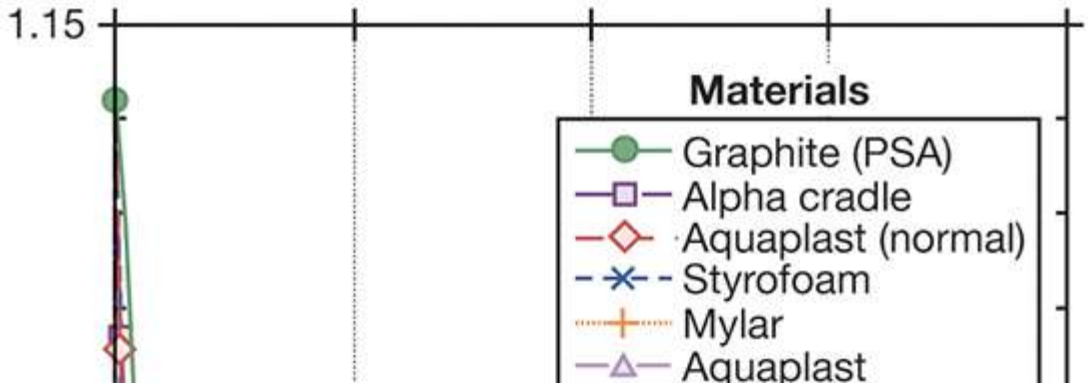
Depth-Dose/Exit Dose Region

The skin and superficial tissue on the side of the patient from which the beam exits receive a reduced dose if there is insufficient backscatter material present. The amount of dose reduction is a function of x-ray beam energy, field size, and the thickness of tissue that the beam has penetrated reaching the exit surface. For a 6-MV beam, a 15% reduction in dose with little dependency on field size has been reported,[54] and for 18-MV beams, an 11% reduction in exit dose was measured.[57] In general, the addition of a thickness of tissue-equivalent material on the exit side equivalent in

thickness to approximately two-thirds of the d_{max} depth is sufficient to provide full dose to the build-down region on the exit side. Figure 8.6 shows the effects of various backscattering media when placed directly behind the exit surface.


Materials
Graphite (PSA)
Alpha cradle
Aquaplast (normal)
Styrofoam
Mylar
Aquaplast
Enhancement factor
1.2
1.15
1.1
1.05
1
0
0.5
1
1.5
2
Backscatter depth: g/cm²

A


1.15
Materials
Graphite (PSA)
Alpha cradle
Aquaplast (normal)
Styrofoam
Mylar
Aquaplast

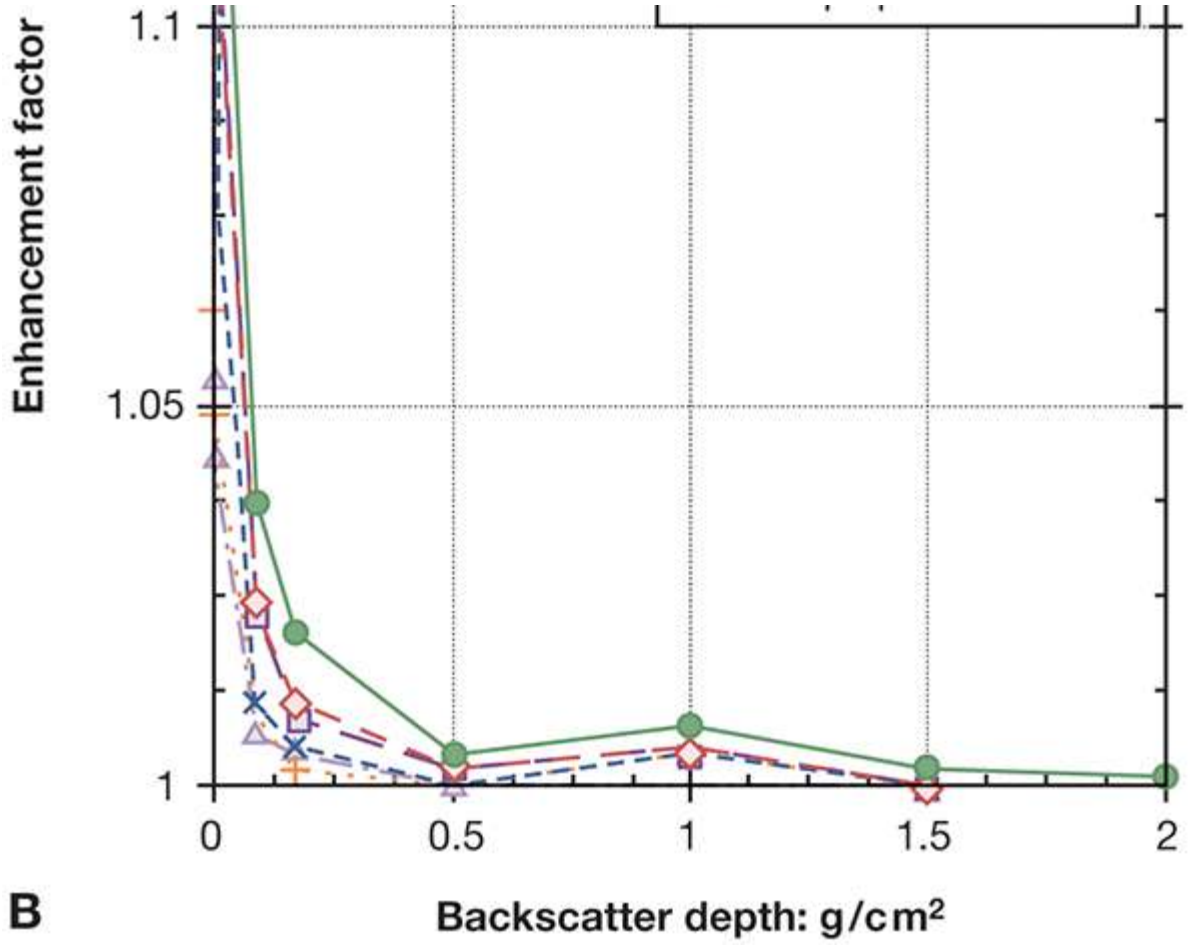


FIGURE 8.6 Enhancement of exit dose for (A) 6-MV and (B) 18-MV photons for a 15- × 15-cm field at 100-cm source-to-axis distance versus backscatter depth for various backscattering materials. (Reprinted from Klein EE, Purdy JA. Entrance and exit dose regions for clinac-2100c. *Int J Radiat Oncol Biol Phys*. 1993;27[2]:429-435. Copyright © 1993 Elsevier. With permission.)

Tissue Heterogeneities and Tissue Interface Dosimetry

The presence of tissue heterogeneities, such as air cavities, lungs, bony structures, and prostheses, can greatly impact the calculated dose distribution. The change in dose is due to the perturbation of the transport of primary and scattered photons and that of the secondary electrons set in motion from photon interactions. Depending on the energy of the photon beam and the shape, size, and constituents of the inhomogeneities, the resultant change in dose can be large.

Perturbation of photon transport is more noticeable for lower-energy beams. There is usually an increase in transmission, and therefore dose,

when the beam traverses a low-density inhomogeneity. The reverse applies when the inhomogeneity has a density higher than that of water. However, the change in dose is complicated by the concomitant decrease or increase in the scatter dose. For a modest lung thickness of 10 cm, there will be about a 15% increase in the dose to the lung for a ^{60}Co or 6-MV x-ray beam, but only about 5% for an 18-MV x-ray beam.[58]

When there is a net imbalance of electrons leaving and entering the region near an inhomogeneity (interfaces of different media), the condition of electron equilibrium is disrupted. The dose distribution in the patient in such transition zones depends on radiation field size (scatter influence), distance between interfaces (eg, air cavities), differences between physical densities and atomic number of the interfacing media, and the size and shape of the different media. Because electrons have finite travel, the resultant change in dose is usually local to the vicinity of the inhomogeneity but may be quite large. The effects are more noticeable for the higher photon energy beams because of the increased energy and range of the scattered electrons. Near the edge of the lungs and air cavities, the reduction in dose can be larger than 15%.[59]

For inhomogeneities with density larger than water, there will be an increase in dose locally due to the generation of more electrons. However, most dense inhomogeneities have atomic numbers higher than that of water so that the resultant dose perturbation is further compounded by the perturbation of the multiple Coulomb scattering of the electrons. Near the interface between a bony structure and water-like tissue, large hot and cold dose spots can be present. Several benchmark measurements have been reported for various geometries simulating clinical situations and are discussed briefly in the following sections.

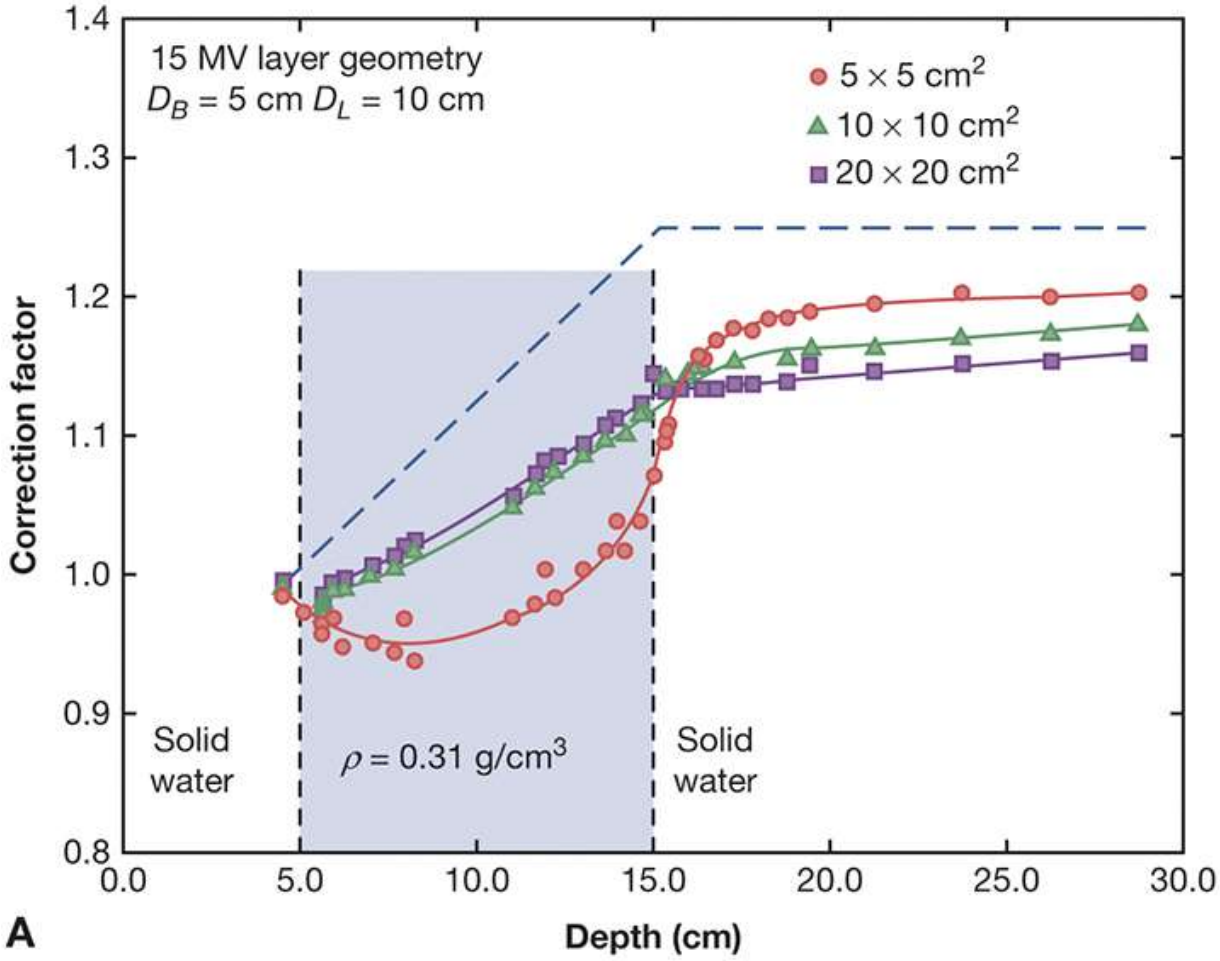
Air Cavities

Air cavities that appear in various locations of the body, most particularly in the head and neck region, pose a problem because of loss of equilibrium at the air-tissue boundaries internal to the patient. Epp et al[60] reported that for cobalt beams, a reduction in dose of approximately 12% was found for a typical larynx air cavity, which recovered within 5 mm in the new buildup region. The loss was due to a lack of forward scattered electrons. Epp et al[61]

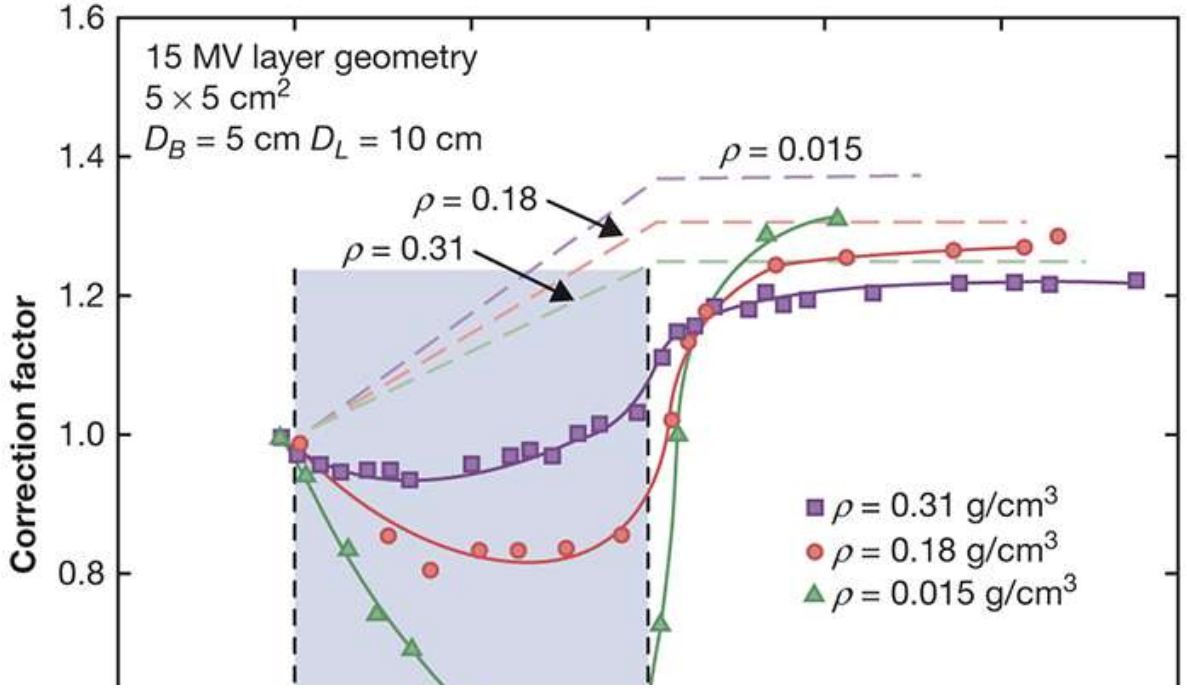
reported that for a 10-MV x-ray beam, a 14.5% loss was measured at the distal interface of the air cavity with a buildup curve that plateaued within 20 mm of the interface. Klein et al[62] measured distributions about air cavities for 4- and 15-MV x-ray beams in both the distal and proximal regions. The combined dose distribution in a parallel-opposed manner showed a 10% loss at the interfaces for both beam energies.

Lung Tissue

Although the problem of reestablishing equilibrium for lung interfaces is not as severe as with air cavities, a transition zone region at the lung-tissue interface still exists over the range of typical clinical photon beam energies. Rice et al measured responses within various simulated lung media for 4- and 15-MV x-rays using a parallel-plate ion chamber and a phantom constructed of solid water and simulated lung material (average lung material density, $\rho = 0.31$ g/cm^3; some additional measurements made with materials having densities of 0.015 and 0.18 g/cm^3).[63] Figure 8.7 shows the results in terms of measured CFs for the 15-MV beam. A considerable buildup curve was observed (10% change in CF) for small fields (5 × 5 cm^2) for the 15-MV beam, which began in the distal region of the lung and plateaued about 5 cm beyond the simulated lung interface.


15 MV layer geometry
D_B = 5 cm D_L = 10 cm
5 × 5 cm²
10 × 10 cm²
20 × 20 cm²
Solid water
ρ = 0.31 g/cm³
Solid water
Correction factor
Depth (cm)
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.0
5.0
10.0
15.0
20.0
25.0
30.0

A


15 MV layer geometry
5 × 5 cm²
D_B = 5 cm D_L = 10 cm
ρ = 0.015
ρ = 0.18
ρ = 0.31
ρ = 0.31 g/cm³
ρ = 0.18 g/cm³
ρ = 0.015 g/cm³
Correction factor
1.6
1.4
1.2
1.0
0.8

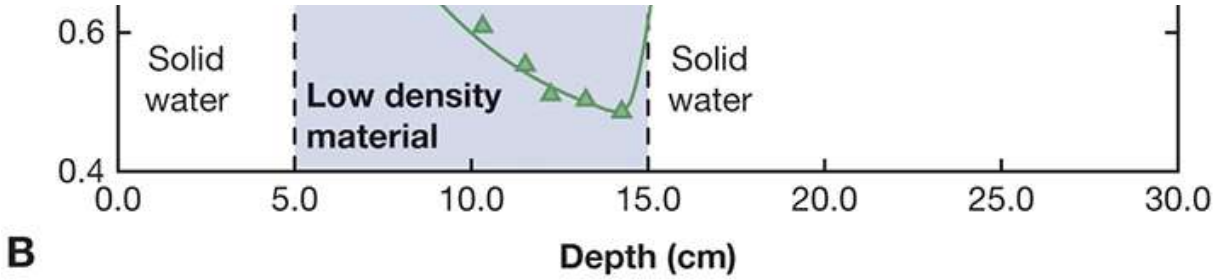


FIGURE 8.7 A. Dose correction factors as a function of depth for a transition zone geometry that simulates a lung-tissue interface for three different field sizes and a lung thickness of 10 cm for 15-MV x-rays. The modification to the primary dose only on the central axis (shown by the dashed curve) is independent of field size. B. Dose correction factors as a function of depth for a transition zone geometry that simulates a lung-tissue interface for three different densities, a 5- × 5-cm field and a lung thickness of 10 cm for 15-MV x-rays. The modification to the primary dose only on the central axis is shown by the dashed curve. (Reprinted from Rice RK, Mijnheer BJ, Chin LM. Benchmark measurements for lung dose corrections for x-ray beams. *Int J Radiat Oncol Biol Phys*. 1988;15[2]:399-409. Copyright © 1988 Elsevier. With permission.)

Bone-Soft Tissue Interfaces

Das et al[64] measured dose perturbation factors (DPFs) proximal and distal for simulated bone-tissue interface regions using a parallel-plate chamber for both 6- and 24-MV x-ray beams. They reported DPFs of 1.1 for the 6-MV beam and 1.07 for the 24-MV beam at the proximal interface. At the distal interface, a DPF of 1.07 was measured for the 24-MV beam, whereas the 6-MV beam exhibited a DPF of 0.95, resulting in a new buildup region in soft tissue. Note that both buildup and build-down regions dissipate within a few millimeters from the interfaces and the perturbations are independent of thickness and lateral extent of the bone or radiation field size.

Metal Prostheses

Das and associates measured DPFs following a 10.5-mm-thick stainless steel layer simulating a hip prosthesis geometry.[64] They reported a DPF of 1.19 for 24-MV photons, but only 1.03 for 6-MV photons; on the proximal side, they reported a DPF of 1.30 due to the backscattered electrons that was independent of energy, field size, or lateral extent of the steel. These interface effects dissipated within a few millimeters in polystyrene. Other

reports dealing with dosimetry perturbations due to metal objects are included in the references.[65,66]

Niroomand-Rad et al reported on dose perturbation effects at the tissue-titanium alloy implant interfaces in patients with head and neck cancer treated with 6- and 10-MV photon beams.[67] They found at the upper surface (toward the source) of the tissue-dental implant interface DPFs of 1.22 and 1.20 for the 6- and 10-MV photon beams, respectively. At the lower interface, dose reduction was approximately −13.5% and −9.5% for the 6- and 10-MV beams, respectively.

The most complete information currently available on hip prosthesis dosimetry is found in AAPM Report 81 (TG 63).[68] The report provides the current state of scientific understanding and clinical dosimetry in use for patients with high-Z hip prostheses undergoing radiation therapy. Beam arrangements that avoid the prosthesis should always be a first consideration. If this cannot be done, valuable information is available in Report 81, including values for different prostheses' electron density, approximate attenuation of the beam passing through the prosthesis, and possible dose increase to the hip bone. It should also be noted that some of the data provided and recommendations are also applicable to patients having other implanted high-Z prosthetic devices, such as pins and humeral head replacements.

Silicone-Soft Tissue Interfaces

Klein and Kuske reported on interface perturbations with silicone breast prostheses.[69] Such prostheses have a density like breast tissue but a different atomic number. They observed a 6% enhancement at the proximal interface and a 9% loss at the distal interface.

Wedge Filter Dosimetry

When a wedge filter is inserted into the beam, whether a physical wedge or a virtual wedge, the dose distribution is angled at some specified depth to some desired angle relative to the incident beam direction over the entire transverse dimension of the radiation beam (Figure 8.8). For cobalt units, the depth of the 50% isodose usually is selected for specification of the wedge angle, whereas for high-energy linacs, higher percentile isodose

curves, such as the 80% curve, or the isodose curves at a specific depth (10 cm) are used to define the wedge angle.

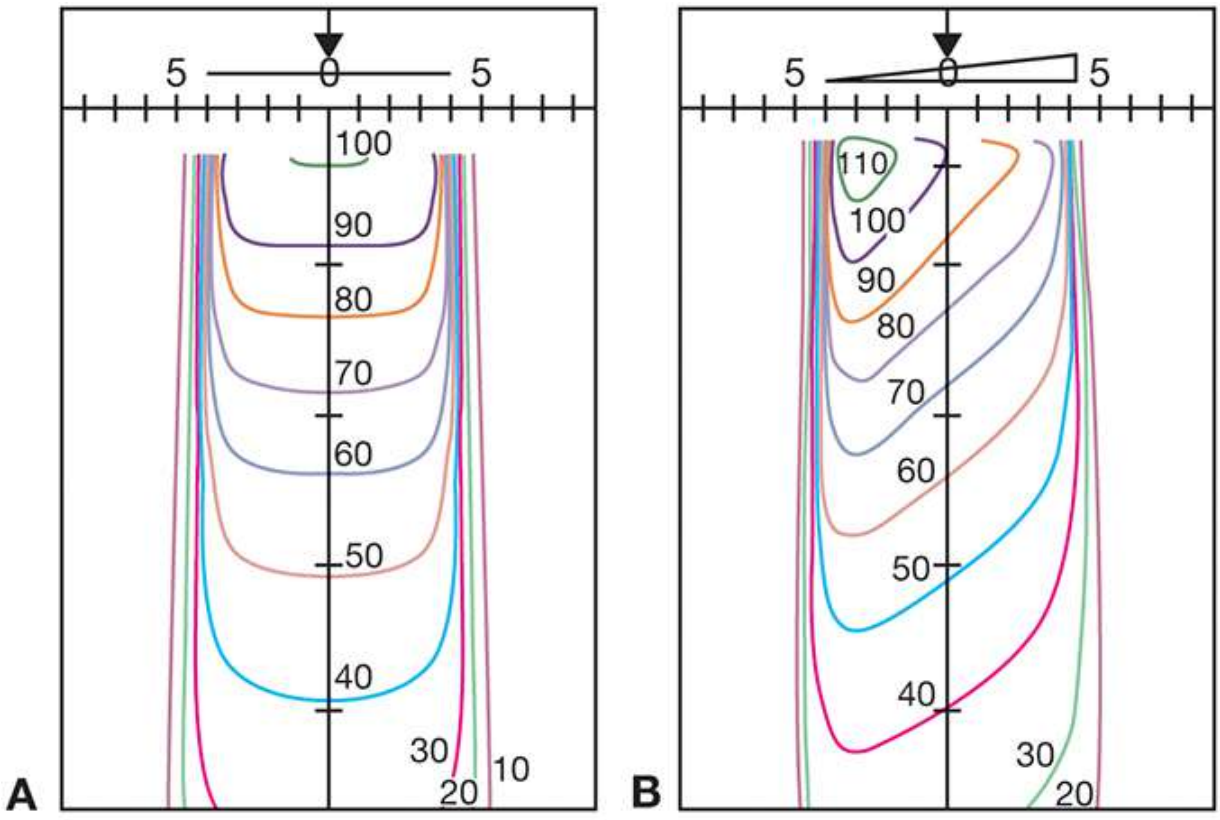


FIGURE 8.8 Isodose distributions for a 6-MV x-ray beam with an 8- × 8-cm field size. A. Open field. B. Field with a 45° wedge. (Reprinted with permission from Khan FM. *The Physics of Radiation Therapy*. 2nd ed. Williams & Wilkins; 1994.)

Linacs are typically equipped with multiple wedges that may be used with an allowed range of field sizes. Although linac wedges can be designed for any desired *wedge angle*, 15-, 30-, 45-, and 60° wedges are the most common.

Some linacs (Elekta AB, Sweden) feature a single wedge, referred to as a *universal wedge*, located in the treatment head, and the desired wedged dose distribution is obtained by the proper combination of wedged and unwedged treatment. A simple approximate model for combining open and wedged fields was first proposed by Tatcher,[70] in which the effective wedge angle q_E, resulting by the addition of a wedged and unwedged beam, is

equal to the nominal wedge angle q_W for the wedged beam, weighted by the fraction of wedged field B:

$$B = \theta_E / \theta_W$$

The Philips Medical Systems Division[71] proposed a slightly different method as follows:

$$B = \tan(\theta_E) / \tan(\theta_W)$$

Petti and Siddon[72] investigated both methods and showed that these are approximations of an exact theoretical solution, which is given by

$$B = f / ([\tan(\theta_E) / \tan(\theta_W)] + f - 1)$$

Most importantly, their investigations showed that Tatcher's approximation is good only for values of q_W <45° and thus is inadequate for accelerators such as Elekta, which use a 60° motorized universal wedge. They did show that for the field sizes studied (up to 20 × 20 cm^2), the Philips relationship was valid to within 3°.

The wedged isodose curves can be normalized in two different ways. In some older systems, the wedge dose distributions have the wedge factor (ie, the ratio of the measured central-axis dose rate with and without the wedge in place) incorporated into the wedged isodose distribution. More commonly, the wedge isodose curves are normalized to 100% at d_{max}, and a separate *wedge factor* is used to calculate the actual treatment MUs or time. McCullough et al[73] noted that wedge factors measured at d_{max} are usually accurate to within 2% for depths up to 10 cm but, at greater depths, can be inaccurate to 5% or more. The inclusion (or noninclusion) of the wedge factor is an extremely important point to understand because serious errors in dose delivered to the patient can occur if used improperly.

Sewchand et al[74] and Abrath and Purdy[75] pointed out that beam hardening results when a wedge is inserted into the radiation beam. The PDD, therefore, can be considerably increased at depth. Differences reported were nearly 7% for a 4-MV 60° wedge field PDD from the open field PDDs at

12-cm depth, and a 3% difference in depth-dose values between the wedge field and the open field for a 60° wedge using 25-MV x-rays was reported.

Modern computer-controlled medical linacs now have software features termed a *virtual wedge* that allow the user to create a wedge-shaped dose distribution by moving one collimator jaw across the field in conjunction with adjustment of the dose rate over the course of the daily single-field treatment.[76] This technology provides superior dose distributions and eliminates the previously mentioned beam hardening problem seen in physical wedges. This feature can deliver a greater number of wedge angles and over larger field sizes, including asymmetric field sizes (30 cm in the wedge direction, with 20 cm toward the wedge "heel" and 10 cm toward the wedge "toe"). The increased number of angles not only enhances planning options but also complicates commissioning and QA.[77] Unlike the physical wedge, beam hardening is not a consideration for the virtual wedge.

When the patient's treatment is planned, wedged fields are commonly arranged such that the angle between the beams, the *hinge angle (q)*, is related to the wedge angle (ϕ) by the following relationship (Figure 8.9):

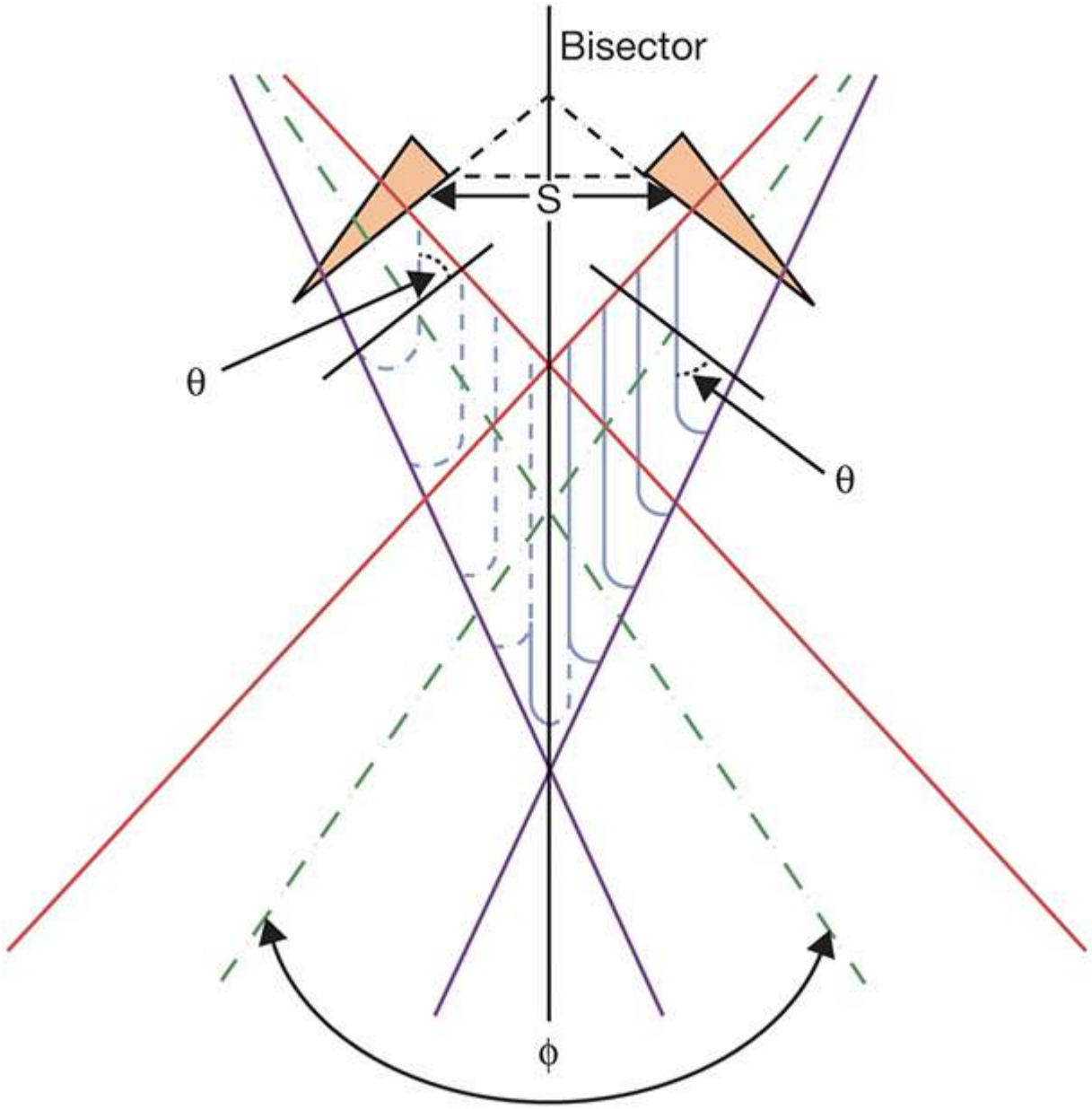


FIGURE 8.9 Parameters of the wedge beams: ϕ is the wedge angle, q is the hinge angle, and θ is separation. Isodose curves for each wedge field are parallel to the bisector. (Reprinted with permission from Khan FM. *The Physics of Radiation Therapy*. 2nd ed. Williams & Wilkins; 1994.)

$$\theta = 90° - \varphi / 2$$

For example, as shown in Figure 8.10, 45° wedge fields orthogonal to one another yield a uniform dose distribution.

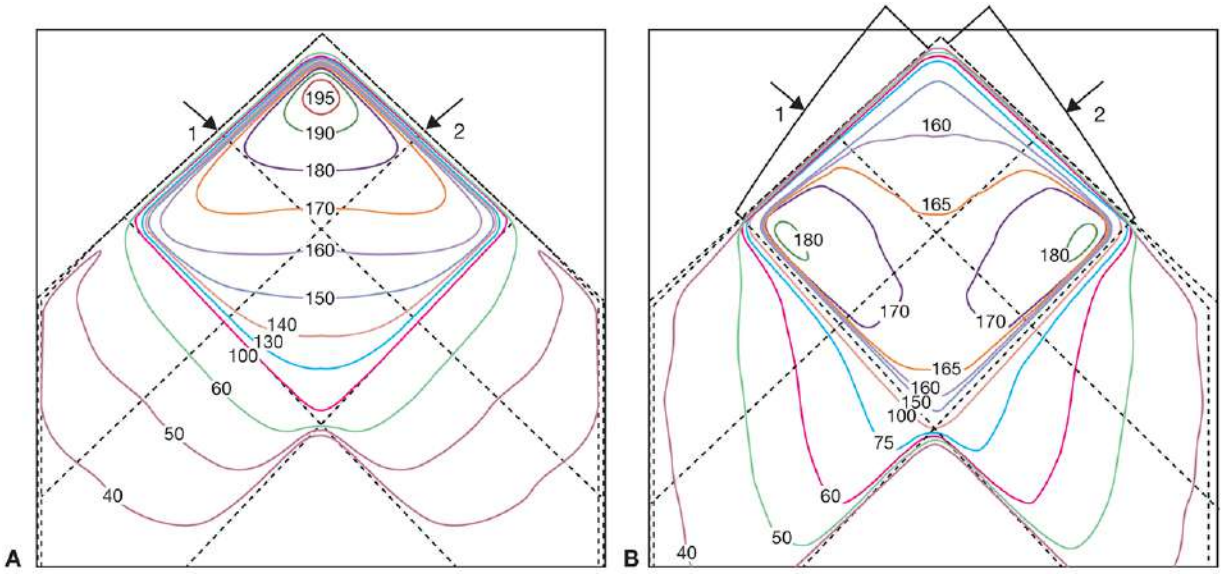


FIGURE 8.10 Isodose distribution for two angled beams. A. Without wedges. B. With wedges. Both: 4 MV; field size, 10 × 10 cm^2; source-to-skin distance, 100 cm; wedge angle, 45°. (Reprinted with permission from Khan FM. *The Physics of Radiation Therapy*. 2nd ed. Williams & Wilkins; 1994.)

TWO-DIMENSIONAL RADIATION TREATMENT PLANNING: COMBINATION OF TREATMENT FIELDS

Parallel-Opposed Fields

When only two unmodified x-ray beams are used in radiation therapy, they usually are parallel-opposed beams (ie, directed toward each other from opposite sides of the anatomic site with the central axes coinciding). Figure 8.11 presents the normalized relative axis dose profiles from parallel-opposed photon beams for a 10- × 10-cm field at an SSD of 100 cm and for patient diameters of 15 to 30 cm in 5-cm increments. The weight of a beam denotes a numeric value assigned to the beam at some normalization point. For SSD beams, the weight specifies the relative dose assigned to the beam at d_{max}, and for isocentric beams, at the isocenter. The beams shown are weighted 1 to 1 (ie, assigned equal value 100% at d_{max}), and the dose profiles have been normalized to the cumulative midline PDD.

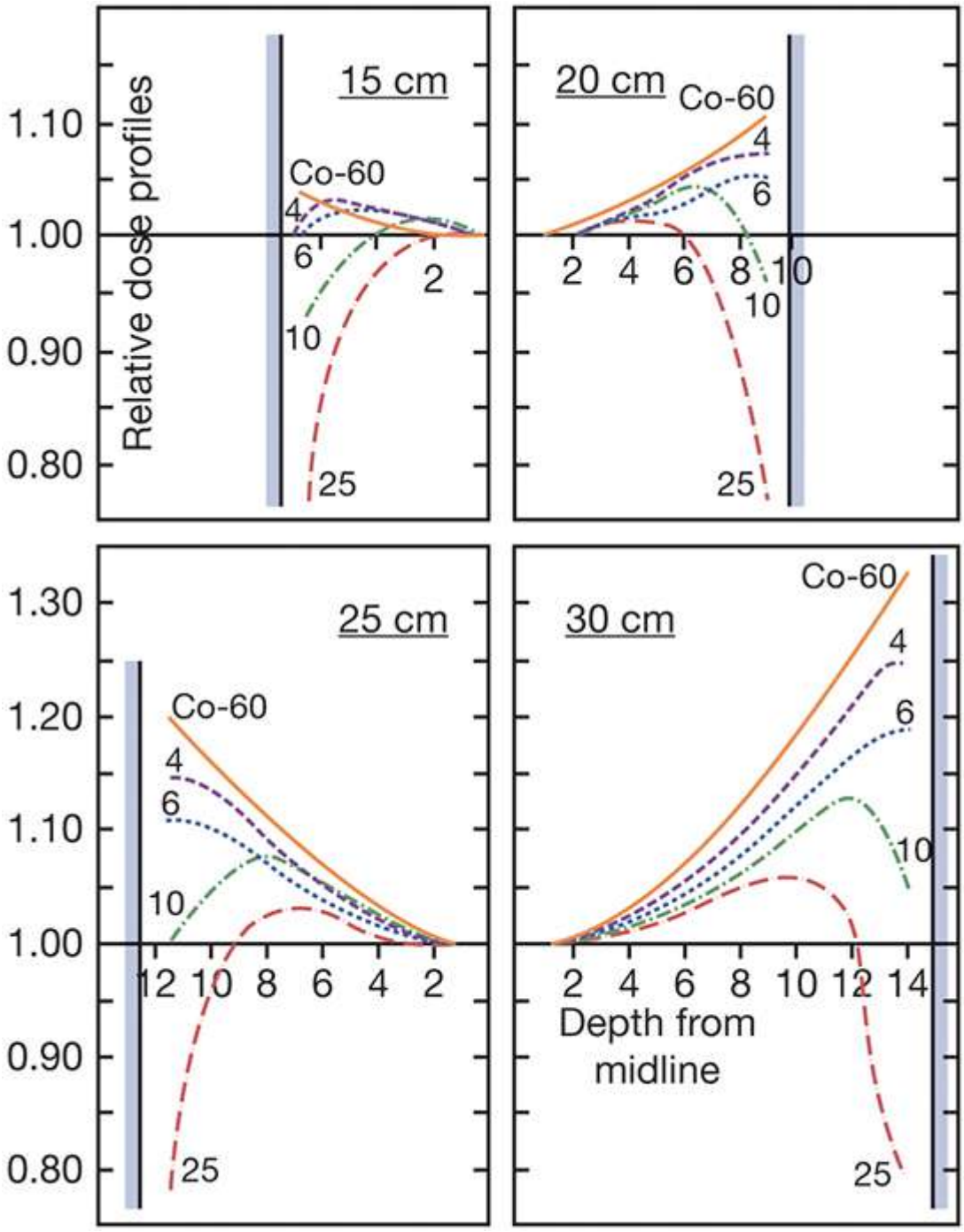


FIGURE 8.11 Relative central-axis dose profiles as a function of x-ray energy (^{60}Co or 4, 6, 10, and 25 MV) and patient thickness (15, 20, 25, and 30 cm). The parallel-opposed beams are equally weighted, and the profiles are normalized to unity at midline. Because of symmetry, only half of each profile is shown.

The maximum patient diameter easily treated with parallel-opposed beams for a midplane tumor requiring 50 Gy or less with low-energy

megavoltage beams is approximately 18 cm. For “thicker” patients, higher x-ray energies produce improved dose profiles with less dose variation along the central axis without resorting to more complex multibeam arrangements.

For some treatment sites, the underdosing achieved near the skin surface with very high-energy, parallel-opposed x-ray beams is a highly advantageous feature; but in others, it may be desirable to achieve a higher dose nearer to the skin. With very high-energy x-ray beams traversing small anatomic thicknesses, the exit dose can exceed the entry dose, and the exact dose distribution in the regions beneath the entry and exit surfaces from parallel-opposed high-energy x-ray beams must be carefully evaluated to consider properly the contribution from both entrance and exit components.

Unequal beam weightings are advantageous if the target volume is not midline. Figure 8.12 shows normalized central-axis dose profiles for other weightings, such as 2 to 1 and 3 to 1. The greater the unequal weighting, the greater will be the shift of the higher dose region toward one surface and away from midline. Although, in some anatomic sites, unequal weighting may be advantageous, special attention must be directed to the anatomic structures in the high-dose volume.

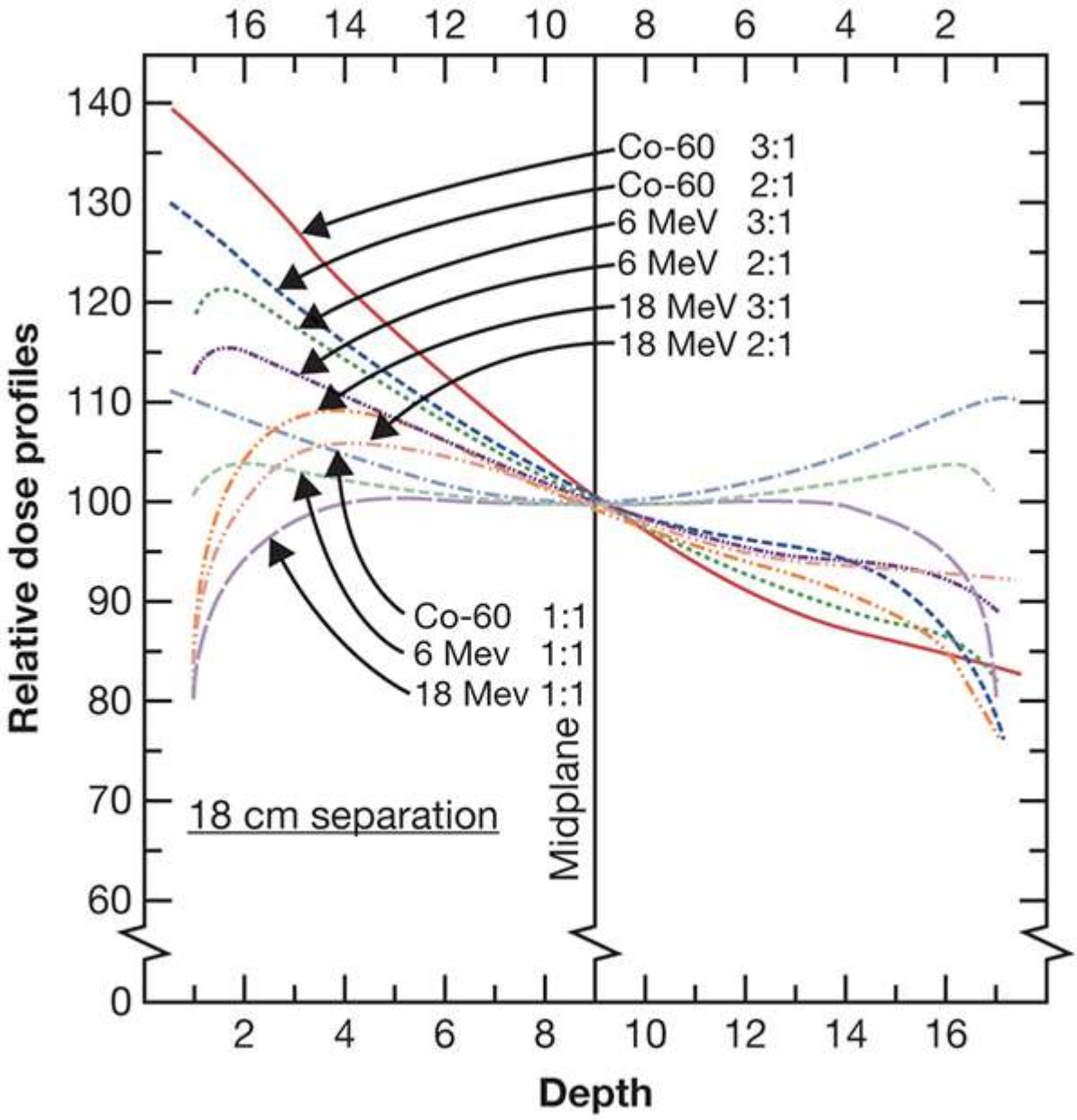
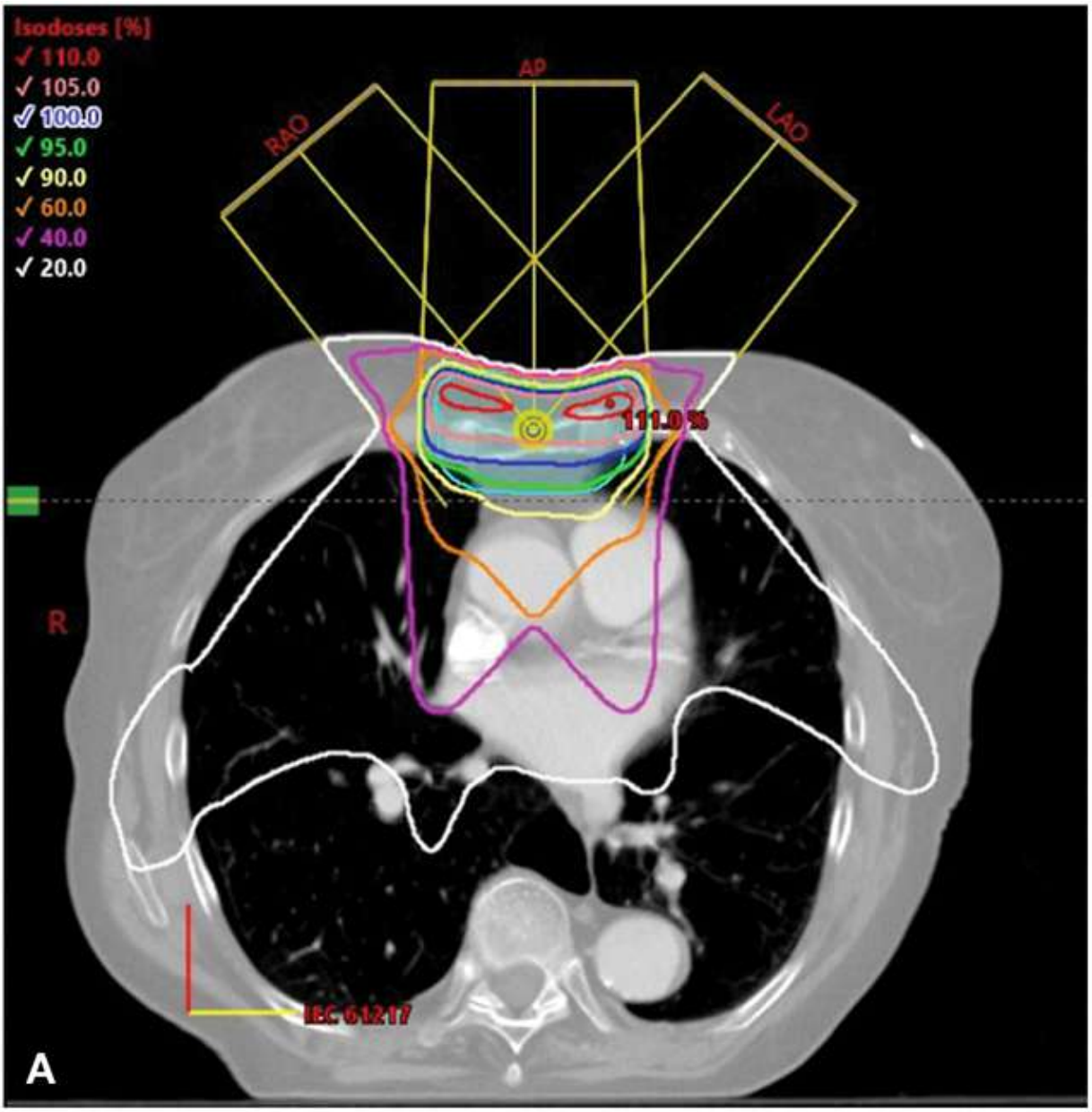


FIGURE 8.12 Dose profiles achieved with unequal weightings of parallel-opposed photon beams; profiles are normalized to unity at midline.

Multiple-Beam Arrangements

Figure 8.13 shows two commonly used coaxial three-field beam arrangements. A direct anterior field with two anterior oblique fields can be used to generate a high-dose region where the three fields overlap, whereas a low-dose region exists beyond this intersection point. For example, if this arrangement is used for treating the mediastinum, the spinal cord might be

included in the anterior beam but spared by the anterior oblique beams. Moving the anterior oblique fields laterally to form a parallel-opposed pair yields a rectangular isodose region with a more uniform dose gradient; however, the magnitude of the dose gradient is determined by the relative weighting of the beams and the thickness of tissue traversed. An anterior field with two symmetrically placed posterior oblique beams yields elongated isodose curves. The degree of elongation is determined by the relative thickness of tissue each beam traverses to the point of intersection and by the relative weights of the beams. Three-field arrangements are often useful for treating tumors lateral to the midline of a patient.


Isodoses [%]
✓ 110.0
✓ 105.0
✓ 100.0
✓ 95.0
✓ 90.0
✓ 60.0
✓ 40.0
✓ 20.0
AP
RAO
LAO
111.0 %
R
IEC 61217
A

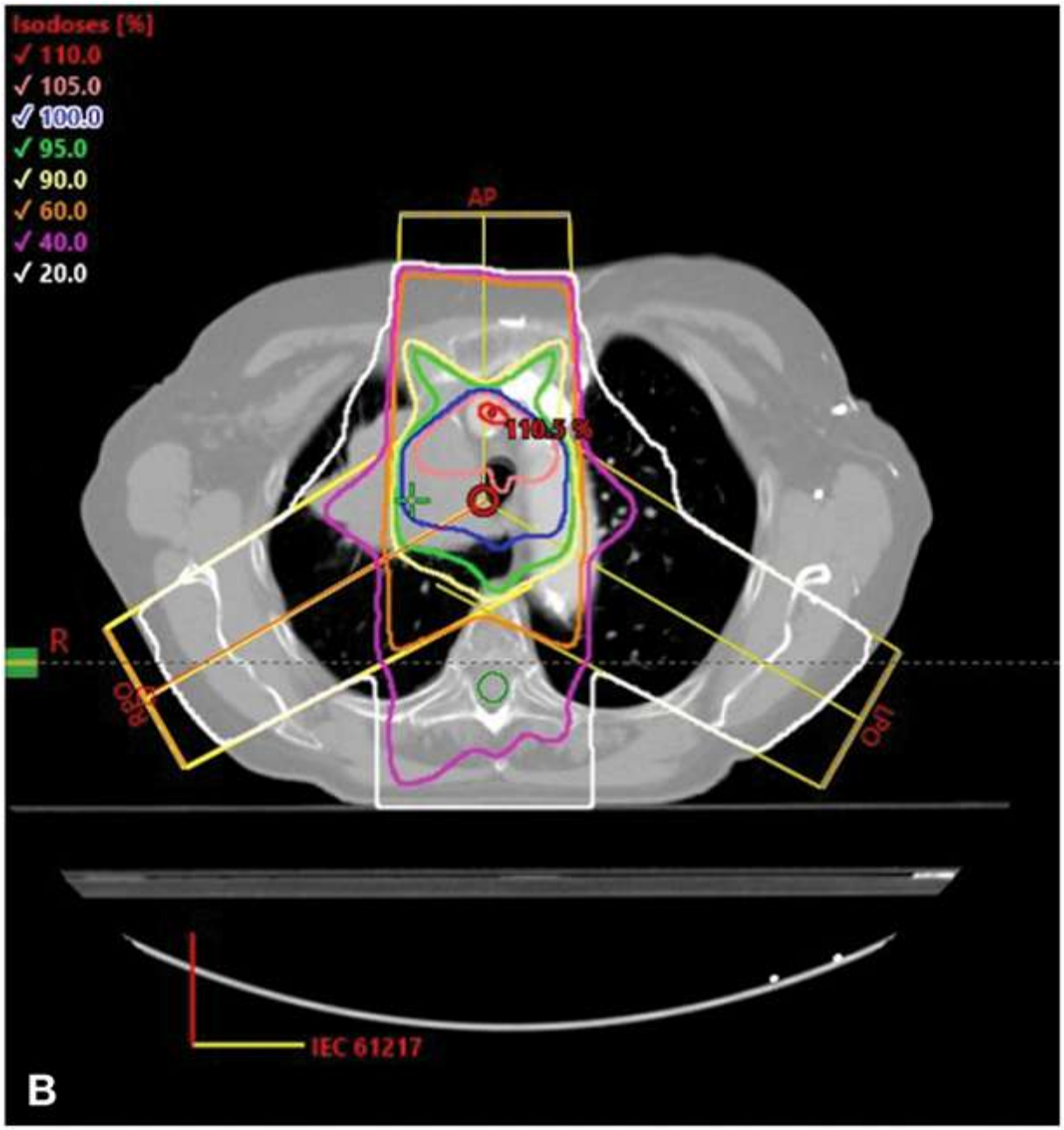
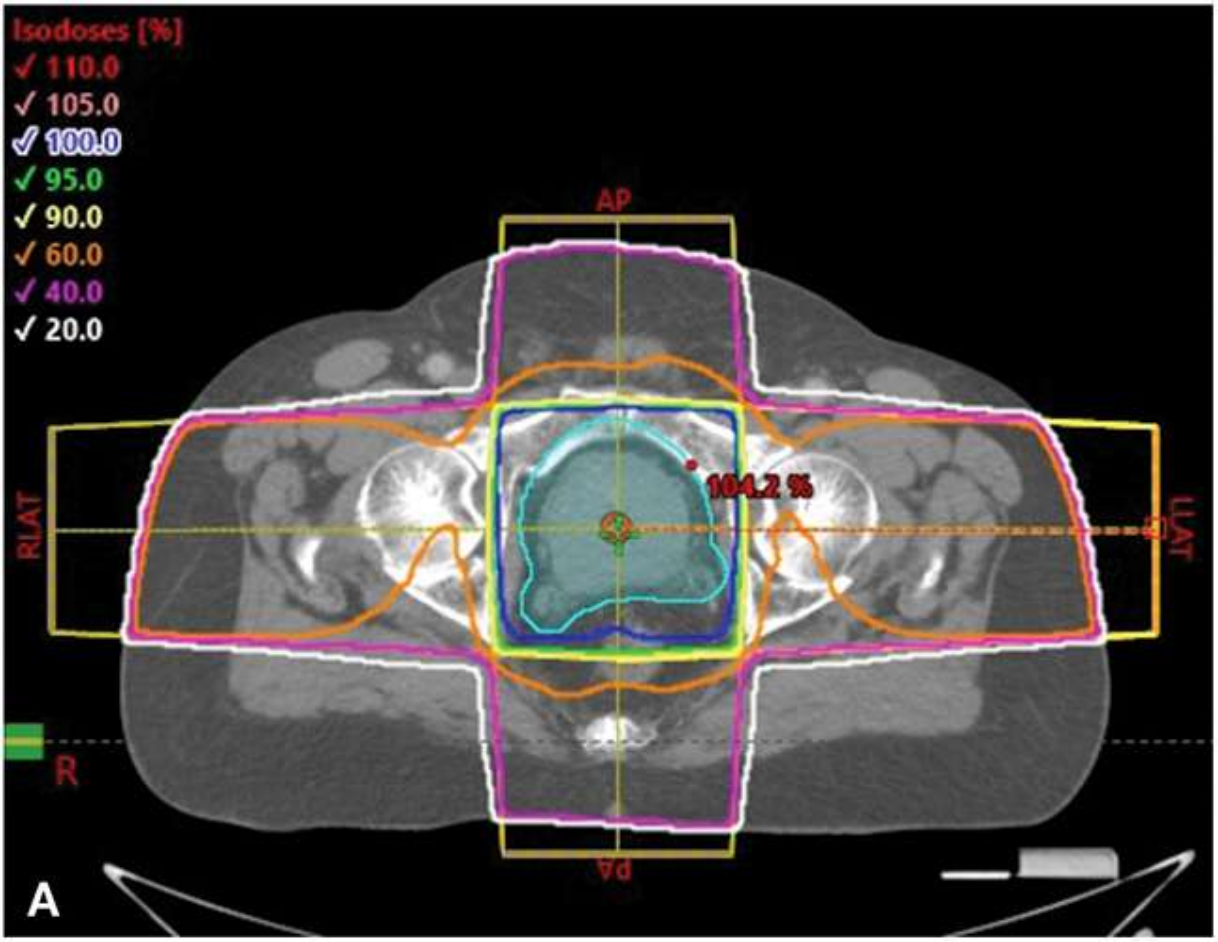


FIGURE 8.13 Three-field coaxial beam arrangements: dose distribution for two different beam arrangements using 6-MV x-ray beams. A. Anterior field with two anterior oblique fields at 40° off the midline. B. Anterior field with a weight of 0.8 with two equally weighted (1) posterior oblique fields separated by 120°.

Three-field nonaxial (noncoplanar) arrangements are readily achieved with linacs by rotating the table and gantry. A common technique for treating pituitary tumors uses two lateral fields and a vertex field with the beam entering through the top of the head. Astrocytomas are often treated

with parallel-opposed lateral fields and a frontal field entering through the forehead. A 90° couch rotation is used with the gantry rotated laterally for the vertex or frontal fields. The lateral fields are also rotated by collimator to ensure the “heels” of the wedges are in the plane of the vertex/frontal field trajectory.

Four-field techniques are typically used in sites such as the abdomen or the pelvis. In most instances, the arrangements consist of pairs of parallel-opposed fields, with a common intersecting point, which yield a “boxlike” isodose distribution. Figure 8.14 compares the dose distributions achieved with a four-field “box technique” for 6- and 18-MV x-ray beams. The central dose distribution is similar for all beam energies, but the greater penetrability of the higher energy beams yields a lower dose to the region outside the box. Variations in the dose gradient are achieved by differential weighting of each pair of beams. Figure 8.15 shows other possible four-beam arrangements. Angulation of the beams yields a diamond-shaped dose distribution. A butterfly-shaped distribution is achieved if each pair of beams has a point of intersection lying on a common line but separated by a few centimeters.


Isodoses [%]
✓ 110.0
✓ 105.0
✓ 100.0
✓ 95.0
✓ 90.0
✓ 60.0
✓ 40.0
✓ 20.0
AP
RLAT
LLAT
PA
104.2 %
R
A

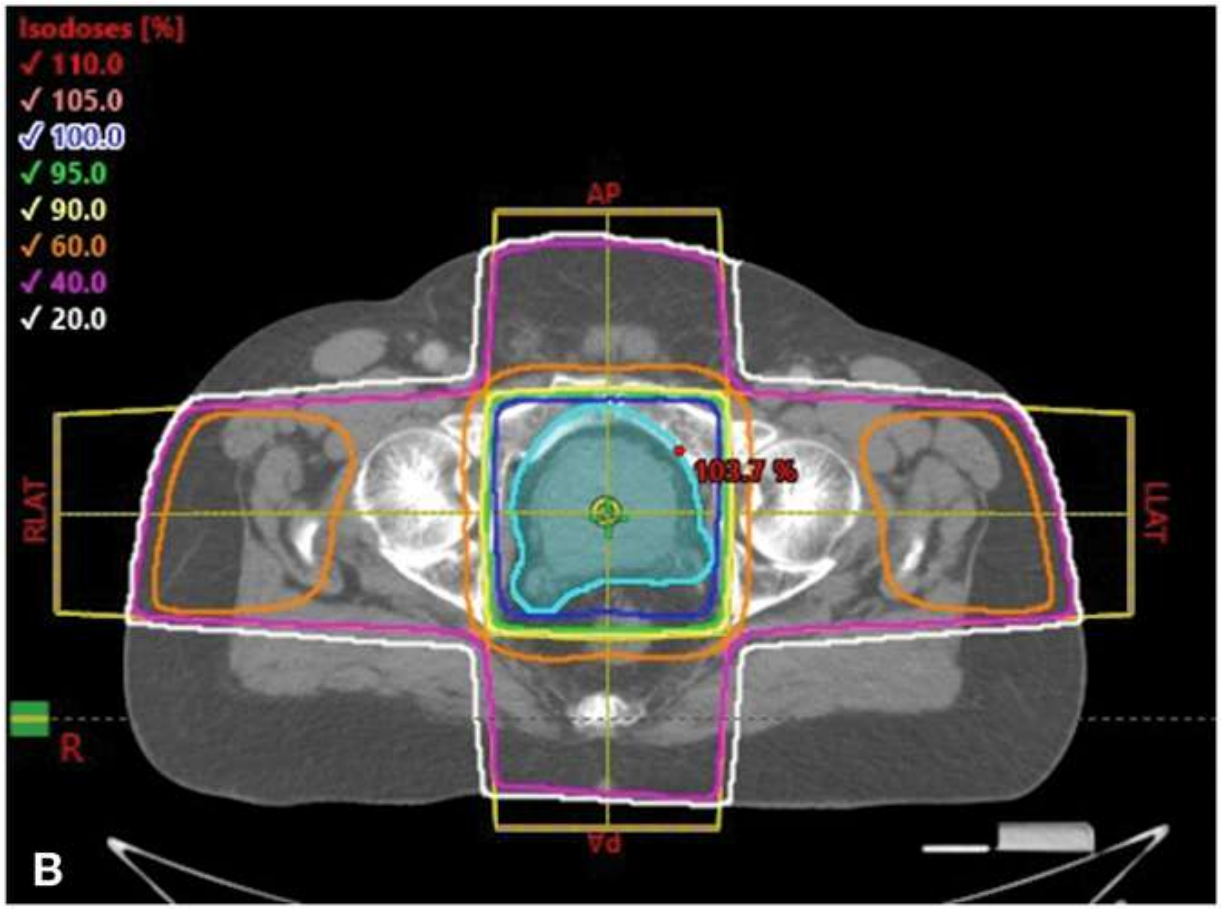
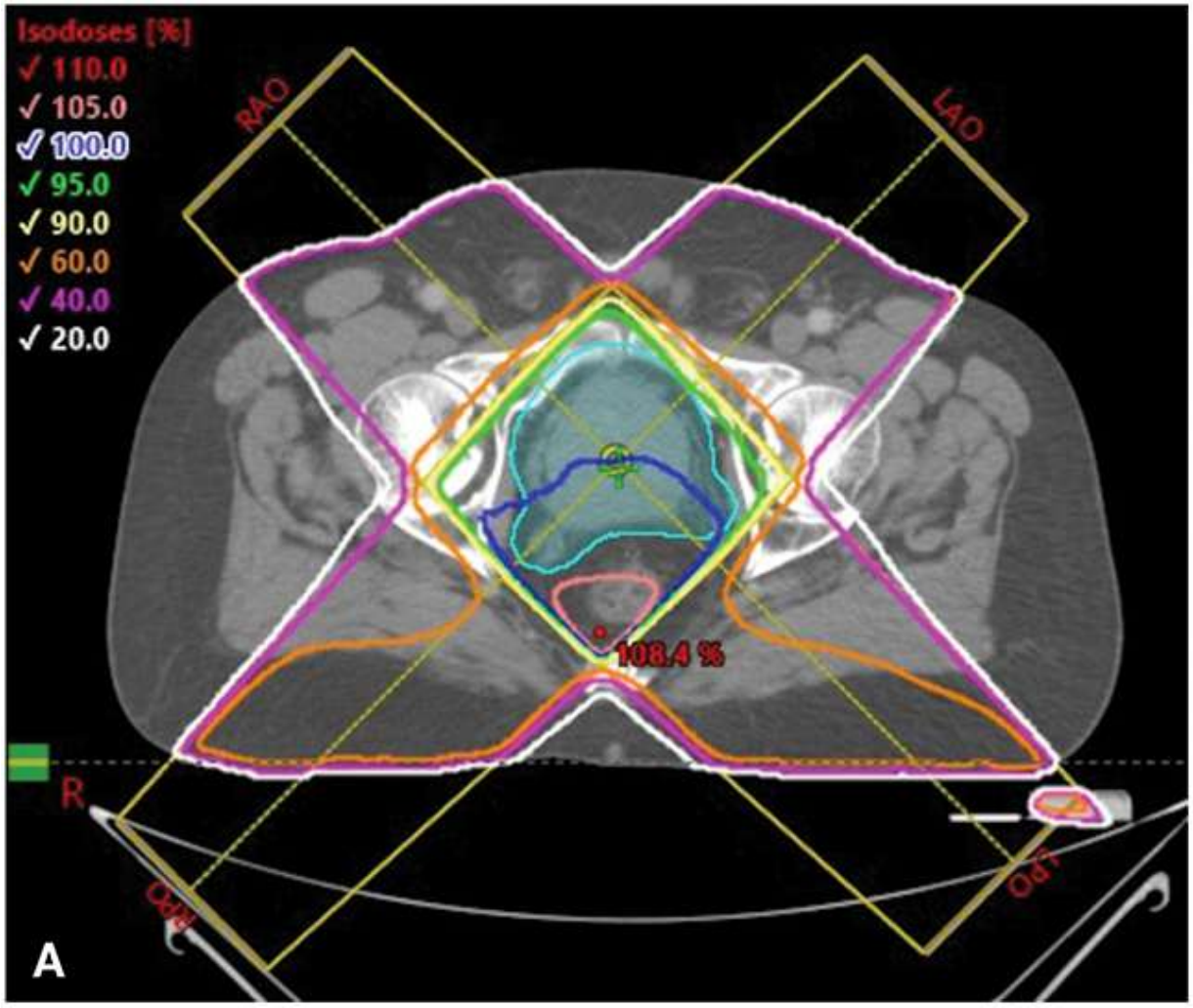


FIGURE 8.14 Four-field "box technique" coaxial beam arrangements (equal beam weightings). A. 6-MV x-ray beams. B. 18-MV x-ray beams. Note the improved dose distribution with the higher energy beam technique (more uniform dose in the target region and lower doses near the femoral head region of the lateral fields) as a result of the increased percentage depth for 18-MV x-rays.


Isodoses [%]
✓ 110.0
✓ 105.0
✓ 100.0
✓ 95.0
✓ 90.0
✓ 60.0
✓ 40.0
✓ 20.0
RAO
LAO
108.4 %
R
A

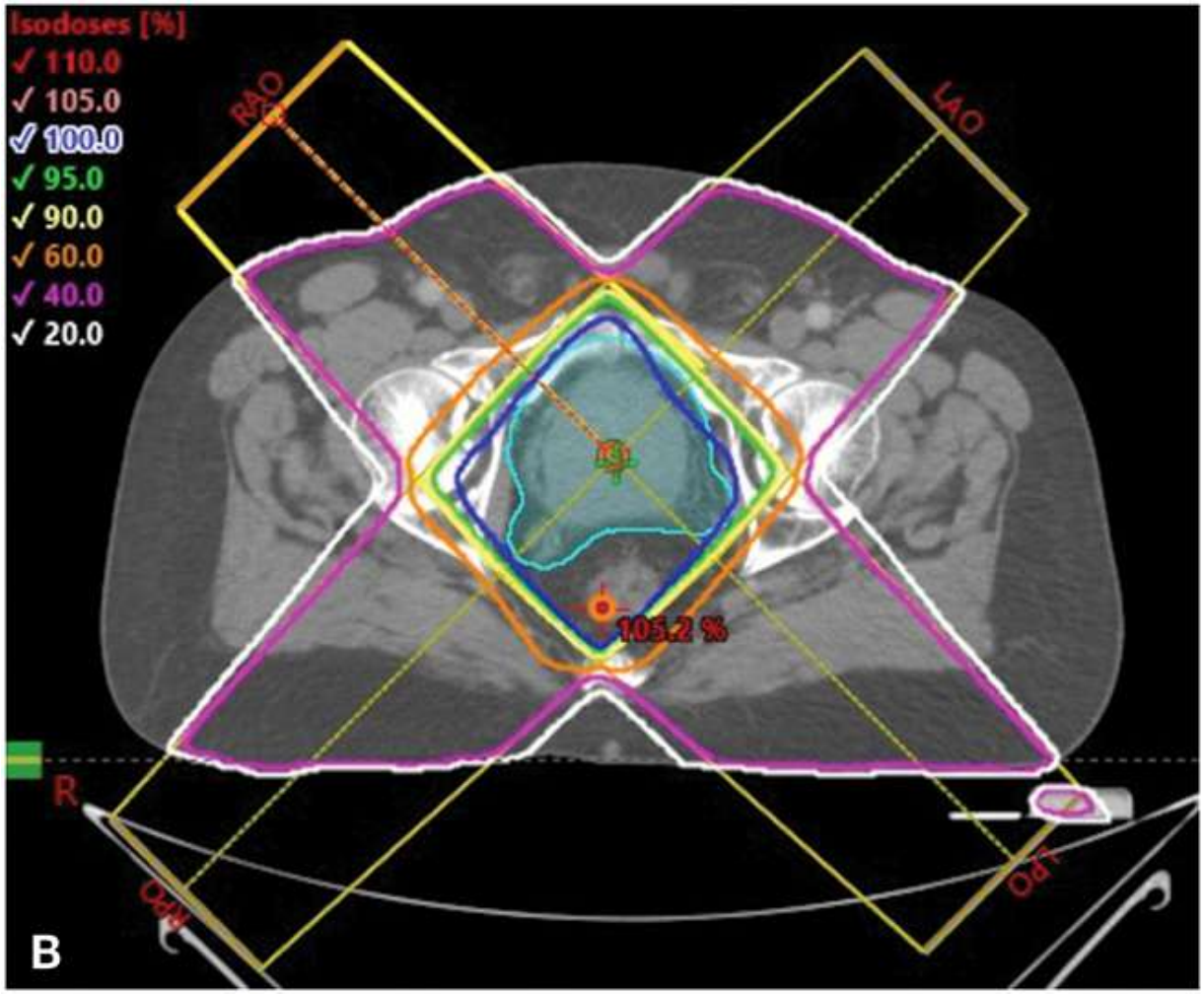


FIGURE 8.15 Four-field "oblique technique" coaxial beam arrangements (6-MV x-rays). A. With equal weighting, resulting in a loss of anterior coverage. B. With custom weighting to improve target coverage.

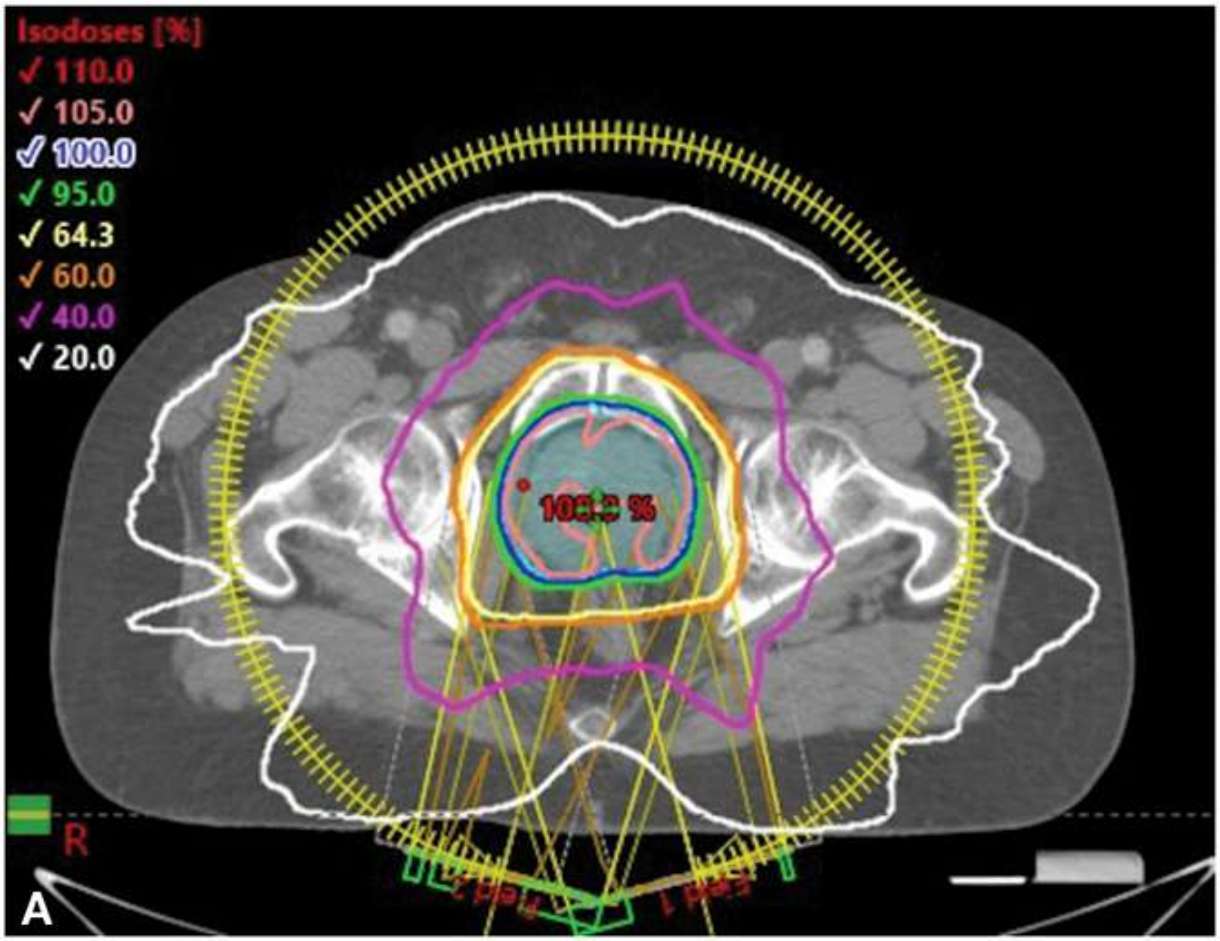
Treatments involving more than four gantry angles, historically required with orthovoltage x-ray units to treat deep, midline lesions, were originally rarely used with high-energy megavoltage therapy units. However, with the broad introduction of *three-dimensional conformal radiation therapy* (3DCRT) and IMRT (discussed in detail in Chapters 10), there has been an increase in multibeam treatments, such as the 3DCRT six-field technique commonly used for the treatment of prostate carcinoma[78] and the nine-field technique commonly used for head and neck cancer IMRT treatments.[79] More recently, these multibeam arrangements are further refined by adding segments of field with the same beam angle either to improve dose

homogeneity or to intentionally generate an inhomogeneous dose distribution (eg, the simultaneous integrated boost technique).[80]

Rotation Therapy

Rotational (or *arc*) *therapy* techniques, in which the treatment is delivered while the gantry (and thus the radiation beam) rotates around the patient, can be thought of as an infinite extension of the multiple-field techniques already described. Originally, this technique was most useful when applied to small, symmetric, deep-seated tumors and was limited to field sizes less than approximately 10 cm in width for the treatment of centrally located lesions (ie, there is approximately an equal amount of tissue in all directions around the lesion). However, intensity-modulated approaches such as VMAT coupled with modern linacs capable of higher dose rates and increased precision in gantry and MLC motion have enabled these techniques to be used throughout the body.

Dose distributions generated by rotational techniques are not very sensitive to the energy of the photon beam. Figure 8.16 illustrates this fact, showing the dose distribution achieved using a 6-MV x-ray beam in the pelvis and in the lung. There is sufficient coverage of the target without high entrance dose in both cases, despite the tissue-equivalent depth in the pelvis being much deeper.


Isodoses [%]
✓ 110.0
✓ 105.0
✓ 100.0
✓ 95.0
✓ 64.3
✓ 60.0
✓ 40.0
✓ 20.0
R
A

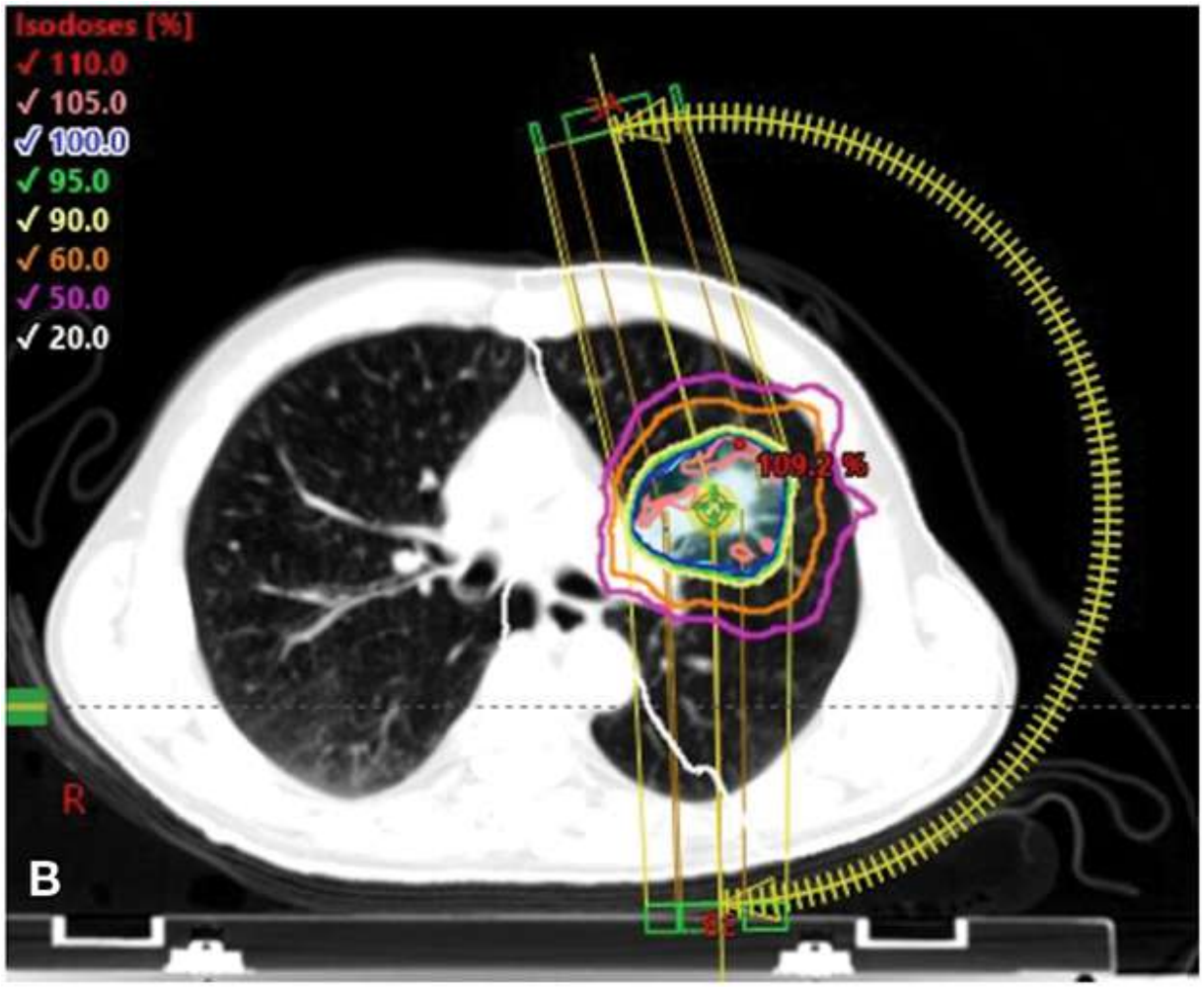


FIGURE 8.16 A 360° rotational therapy technique. A. 6-MV x-ray beams, in pelvis. B. 6-MV x-ray beams, in lung. Note that using the same energy in both cases despite the longer tissue depth in the pelvis results in similar target coverage, demonstrating the decreased sensitivity of planning to energy in rotational techniques versus a limited number of fixed fields.

In arc therapy techniques, one or more sectors of a 360° rotation are skipped to reduce the dose to critical normal structures. When a sector is skipped, the high-dose region is shifted away from the skipped region. Therefore, the isocenter must be moved toward the skipped sector; this technique is referred to as *past pointing*, as illustrated in Figure 8.17. Without past pointing (Figure 8.17A), multiple arcs must be used to gain coverage.

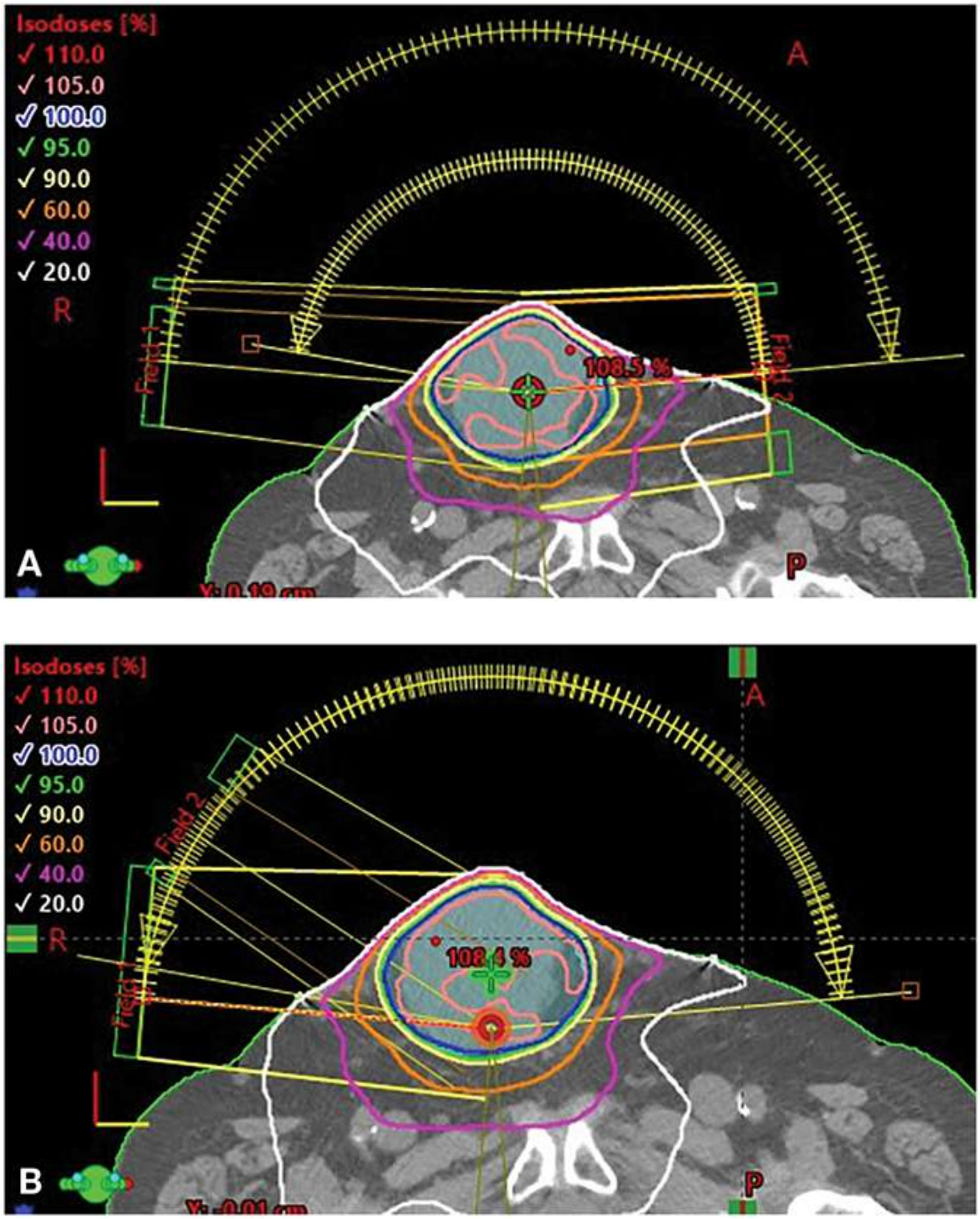


FIGURE 8.17 Arc therapy technique for 6-MV x-rays. A. Two 160° arcs. Two arcs can be custom weighted to obtain sufficient target coverage despite the tendency for higher dose superficial to the isocenter. B. Single 160° arc, but patient positioned so that isocenter is 2 cm lower toward the skipped sector (this technique is called *past pointing*). Note high-dose isodose curves encompass the target volume.

The prostate, bladder, cervix, and pituitary are clinical sites that have been treated, either initially or for boost doses, with rotational or arc therapy techniques. Although the dose distributions achieved by rotation or arc therapy yield high target volume doses, these techniques normally result in a greater volume of normal tissue being irradiated (albeit at low doses) than fixed, multiple-field techniques.

As previously indicated, modern-day rotational therapy is now delivered by a variety of techniques (eg, TomoTherapy, RapidArc, VMAT). Recent developments also include rotational therapy with *flattening filter-free* (FFF) beams.[81] The FFF feature allows dose rates up to 2,400 MUs per minute, thus greatly improving efficiency in dose delivery, which is particularly important for patients receiving treatments where very high daily doses are delivered, such as stereotactic body radiation therapy.[82]

FIELD SHAPING

A major constraint in the treatment of cancer using radiation is the limitation in the dose that can be delivered to the tumor because of the dose tolerance of the tissue (critical organs) surrounding or near the target volume. Shielding normal tissue and critical organs has allowed the radiation oncologist to increase the dose to the tumor volume while maintaining the dose to critical organs below some tolerance level. The frequently used tolerance doses for these organs are not absolute and depend on a number of clinical and treatment factors. Depending on the predominantly serial or parallel organization of the organ at risk, a large dose can sometimes be given to fractional volumes of organs with a parallel structure (liver, kidneys, lungs).[83,84] Shielding is usually accomplished using collimator jaws (with the asymmetric feature) and MLCs, in which the beam aperture (field shape) is customized for individual patients. The use of low melting point alloy blocks has been nearly completely replaced with the MLC technology.

Multileaf Collimator and Associated Dosimetry

Asymmetric Collimator Jaws

Field shaping and abutted field radiation therapy techniques have been made even more versatile with the asymmetric jaw feature found on modern-day linacs. This feature allows each set of jaws to open and close independently of each other (Figure 8.18). The collimator jaw provides greater attenuation than the MLC leaf or alloy block, thus providing an advantage (which is readily apparent on portal films) in reducing the dose to blocked regions.

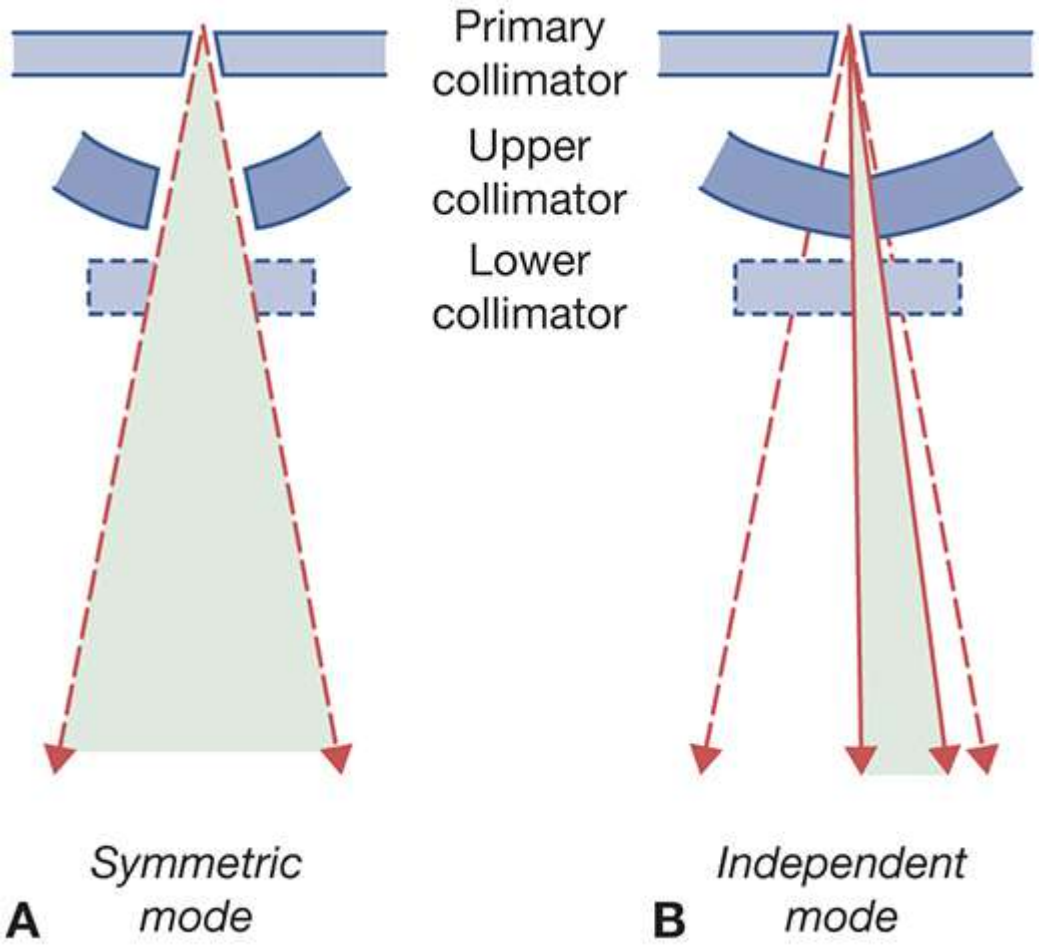


FIGURE 8.18 Independent or asymmetric collimators. A. Conventional symmetric pairs of collimators. B. Asymmetric collimators in which collimator jaws are allowed to move independently of each other.

Depth-dose characteristics for asymmetric fields are similar to those of symmetric fields as long as the degree of asymmetry is not too extreme. Clinical sites where asymmetric jaws are typically used include the breast

(Figure 8.19), head and neck, craniospinal, and prostate. In addition, the use of asymmetric jaws as beam splitters, for field reductions, and with MLCs is helpful for most sites. Several authors have reported on the use of asymmetric jaws to match supraclavicular and tangential fields for breast irradiation.[85,86] Such technology allows a single setup point for all of the treatment fields, including the posterior axillary field. The Y-jaws can beam split the caudal and cephalic regions for the supraclavicular and tangential beams, respectively, and the X-jaws are used to shield the ipsilateral lung and contralateral breast. Hence, a common match plane with one common isocenter can be used for all portals, eliminating the need to move the patient between portals, thus reducing overall patient setup time by almost a factor of two. In addition, the increased attenuation by the jaws reduces the dose to the contralateral breast and lung.[87] A technique for matching lateral head and neck fields and the supraclavicular field using asymmetric jaws was described by Sohn et al.[88]

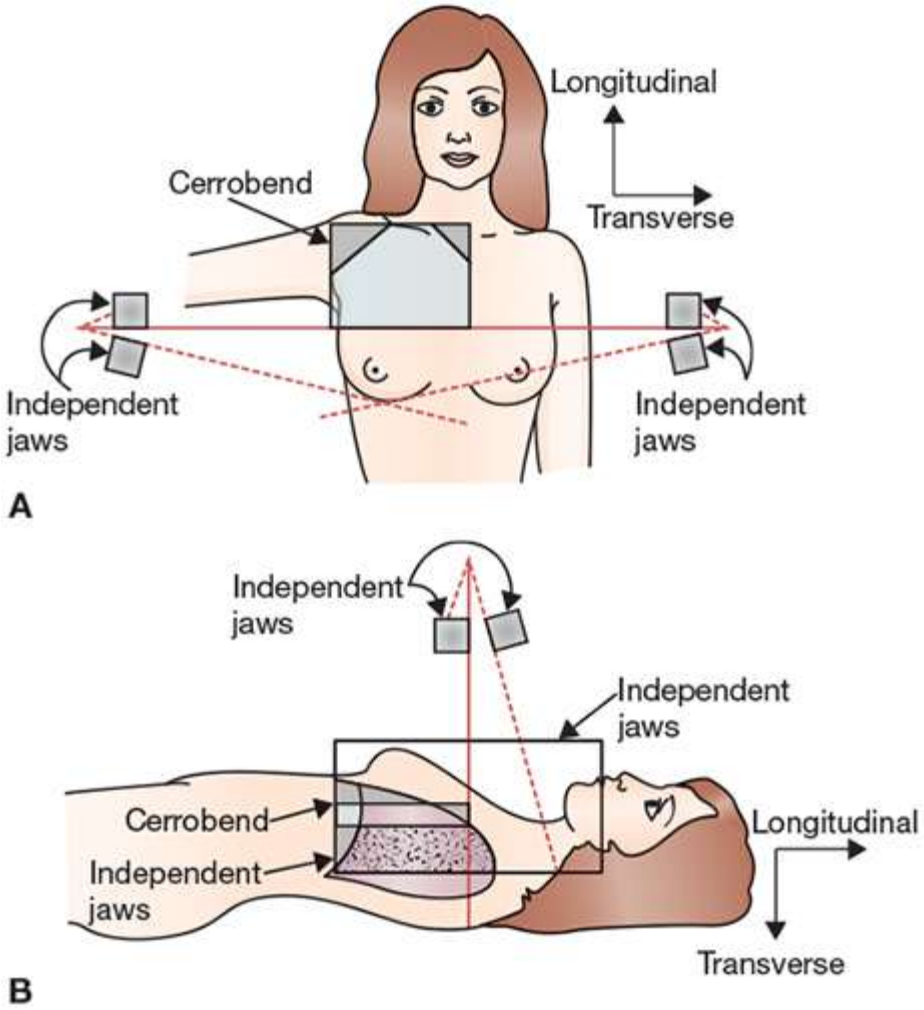


FIGURE 8.19 (A and B) Treatment technique for breast cancer using independent collimators. (Reprinted from Klein EE, Taylor M, Michaletz-Lorenz M, Zoeller D, Umfleet W. A mono isocentric technique for breast and regional nodal therapy using dual asymmetric jaws. *Int J Radiat Oncol Biol Phys*. 1994;28[3]:753-760. Copyright © 1994 Elsevier. With permission.)

Multileaf Collimation

Multileaf collimation, first introduced in Japan in the 1960s,[89] has now gained widespread acceptance and has replaced alloy blocking as the standard of practice for field shaping in modern radiation therapy clinics. The different manufacturers' MLC systems vary with respect to MLC location, leaf design, and field size coverage. The leaves are typically carried on two opposed carriages that transport the leaves in unison. The leaves have individual controls that are computer assigned and positioned.

Initially, most commercial MLC systems were designed to serve as a block replacement but now provide for dynamic IMRT delivery as well.

Elekta first introduced its MLC system in the late 1980s.[90] Their current MLC system replaces the upper photon collimator jaws, and therefore, the maximum field size can open to a full 40 × 40 cm^2. The MLC system is augmented by parallel diaphragms, which increase the leaf's attenuation by an additional two HVLs.

The Varian MLC system is considered a tertiary system placed below the photon collimator jaws. The latest Varian MLC (non-SRS) is a 120-leaf (60 on each side) system, in which the middle 20 cm consists of 0.5-cm-wide leaves, whereas the outer 20-cm leaves still project to 1.0-cm widths. This set of leaves projects to 16.0 cm in length at the isocenter, and the leaf span range (maximum-minimum positions on the same carriage) is limited to 14.5 cm. The leaves move perpendicular to the beam's central axis. The distance from the x-ray target to the bottom of the leaves (on the central axis) is 54.0 cm. The leaves fan away from the central axis so that their sides are divergent from the beam's fan lines. The leaves are interdigitated by a tongue-and-groove design. In May 2017, Varian introduced the Halcyon machine, which does not have movable jaws and only has a double-layer MLC, with the two layers being offset by half of a leaf width and with each leaf being 1 cm wide. This "stacked and staggered" MLC design aims to provide optimized modulation and reduce interleaf leakage. The Halcyon also supports 4 gantry rotations per minute (as opposed to 1 rotation per minute for conventional C-shaped linear accelerators), and the MLC has 5 cm/s speed to support this faster gantry rotation. The MLCs are also designed to have full overtravel and cover the full span of the field.

For the single-layer Varian MLC system, leaf transmission values of 1.5% to 2.0% for a 6-MV beam and 1.5% to 5% for an 18-MV beam have been reported.[91,92] These values are lower than those found for alloy blocks (3.5%) but higher than those for collimator jaw transmission (that being <1.0%). Transmission through abutted (closed) leaf pairs was as high as 28% for 18-MV photons on the central axis. The abutment transmission decreased as a function of off-axis distance to as low as 12%. The data for the double-layer MLC are not available as of this writing, but the MLC is specifically designed to reduce leaf transmission, and it is expected that this will translate into clinical benefits.

Figure 8.20 shows a comparison of MLCs and alloy blocks regarding penumbra. The discrete steps of the MLC systems introduce undulations in the isodose lines. This effect causes an apparent increase in penumbra with wave patterns after the undulations. Single, focused MLC systems have a slightly larger penumbra than do alloy shields and have an even larger difference in comparison with collimator jaws. Boyer et al found the penumbra (80%-20% isodose lines) generated by leaf ends to be wider than those generated by upper collimator jaws by 1.0 to 1.5 mm, and 1.0 to 2.5 mm compared with the lower jaws, depending on energy and field size.[93] Powlis and associates compared multileaf collimation and alloy field shaping and found few differences.[94] LoSasso and Kutcher found similar results and concluded that geometric accuracy is even improved with MLCs.[95] ViewRay recently introduced a double-layer, doubly focused MLC, with the design reviewed by Li et al[96] and the performance characterized by Cai et al.[97] The recently introduced Varian's MLC is also double layered with specially designed leaf tips to improve some of the above-described shortcomings of the conventional MLCs.[98]

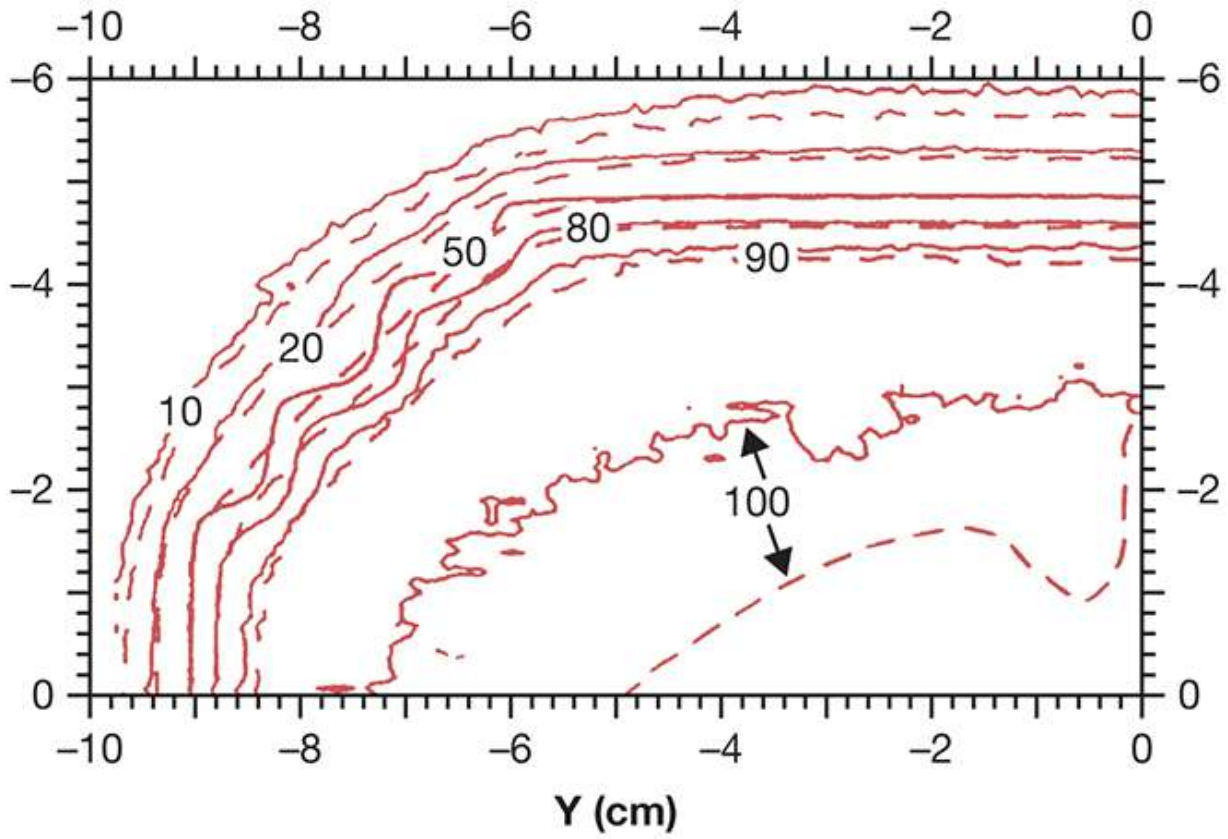


FIGURE 8.20 Comparison of beam's-eye view isodose curves at 10-cm depth for multileaf collimator (solid line) and Cerrobend-shaped (dashed line) beam apertures for 18-MV photons. (Reprinted from Klein EE, Harms WB, Low DA, Willcut V, Purdy JA. Clinical implementation of a commercial multileaf collimator: dosimetry, networking, simulation, and quality assurance. *Int J Radiat Oncol Biol Phys*. 1995;33[5]:1195-1208. Copyright © 1995 Elsevier. With permission.)

The penumbras measured for the leaf sides are comparable with those found for upper jaws because of their divergent nature. The penumbra increase and stair-stepping effect are most prominent at d_{max}. The effects diminish at depth because of the influence of scattered electrons and photons as the scatter-to-primary ratio increases with depth. Adding an opposed beam leads to further smoothing of the undulations, and penumbra differences become less significant. For multibeam arrangements, the differences in dose distribution between MLC and alloy shields are negligible.

The main limitation in optimizing the MLC leaf settings to conform to the shaped field is the discrete leaf steps. Most field shapes require only minor adjustment of the collimator angle to achieve minimal discrepancy

between the desired and resultant field shape. The criteria for optimizing the MLC leaf settings are governed by placing the most leaf ends tangent to the field and also maintaining the same internal area as originally prescribed. MLC shaping systems typically provide an option to place the leaf ends entirely outside the field (exterior), entirely within the field (interior), or crossing the field at midleaf (leaf-center insertion). The last is the most widely used criterion because the desired field area is more closely maintained. However, this choice leads to regions in which some treatment areas are shielded and some normal tissues are irradiated. Zhu et al reported on a variable insertion technique in which leaves are placed only far enough into the field to cause the 50% isodose contour to undulate outside and up to the desired contour.[99] LoSasso et al reported on a method in which each leaf is inserted such that the treatment area covered by the leaf equals the normal tissue area that is not spared.[100] Brahme also demonstrated optimal choices for choosing a collimator angle to optimize leaf direction, depending on whether the field shape is convex or concave.[101] Du et al reported on a method that defines optimal leaf positioning in combination with optimal collimator angulation.[102] Typically, the optimal direction for the leaf motion is along the narrower axis. For a simple ellipse, the optimal leaf direction is parallel to the short axis. Reports on the effects of tissue heterogeneities on penumbra and resultant field definition indicate that the penumbra in lung increases (especially for 18-MV photons), whereas in bone, it decreases for both alloy blocks and MLCs.[91]

As indicated previously, because MLC systems are still evolving, a careful evaluation of the effect of MLCs on MU calculations must be performed before clinical use. Extensive testing over the clinical range of field sizes and shapes should be undertaken before the MLC system is used clinically.

Low Melting Alloy Blocks

Although alloy blocks are rapidly disappearing from clinical use, a short section is included in this chapter for completeness. The Lipowitz metal (Cerrobend) shielding block system was introduced by Powers et al.[103] Lipowitz metal consists of 13.3% tin, 50% bismuth, 26.7% lead, and 10% cadmium. The physical density at 20°C is 9.4 g/cm^3, compared with 11.3

g/cm^3 for lead. The block fabrication procedure is illustrated in Figure 8.21, and more details on using this form of field shaping can be found in the review article by Leavitt and Gibbs.[104]

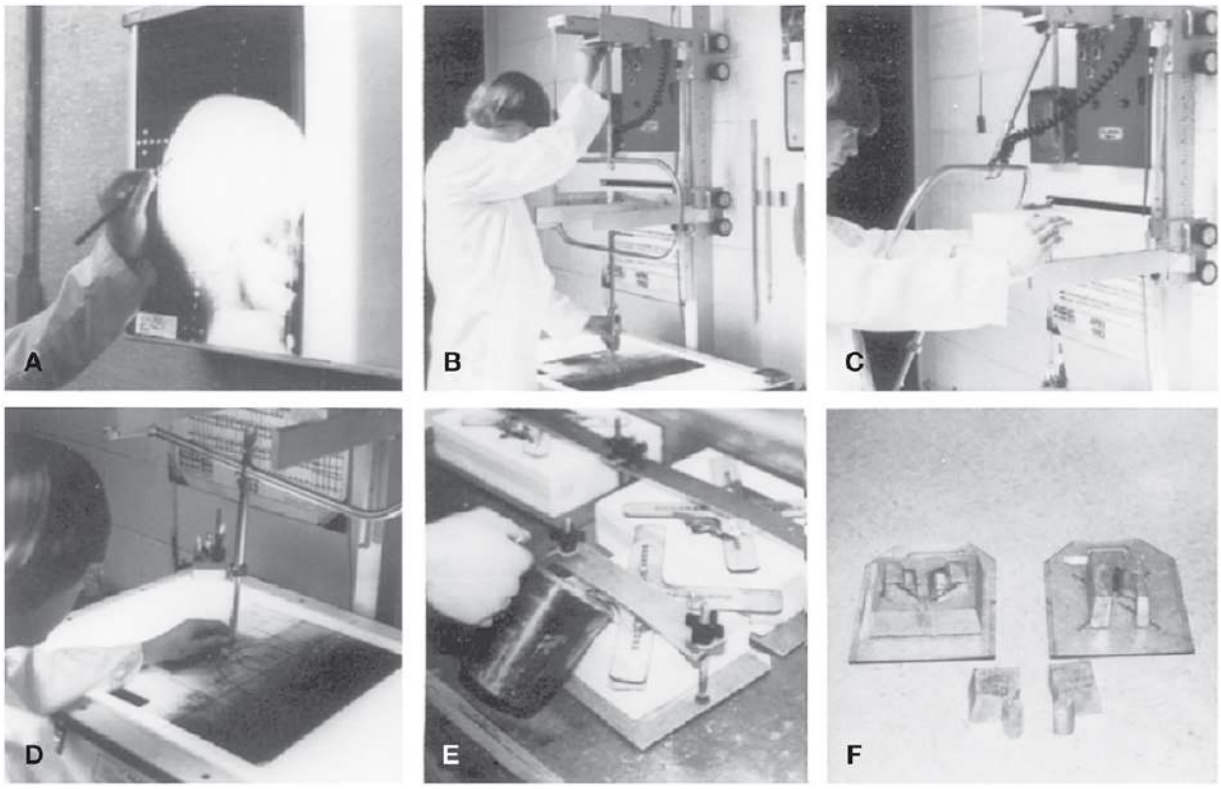


FIGURE 8.21 Composite photographs illustrating the low melting point alloy shielding block design and fabrication process. A. Physician defining the treatment volume on the x-ray simulator radiograph. B. Physics technician adjusting the source-to-skin distance and skin-to-film distance of a hot wire cutter to emulate simulator geometry. C. Proper-thickness foam block aligned to the central axis of the cutter. D. Foam mold cut with hot wire cutter. E. Foam pieces aligned and held in place using a special clamping device. Molten alloy is poured into the mold and allowed to harden. F. Examples of typical shielding blocks cast using this system. (From Purdy JA. Secondary field shaping. In: Wright AE, Boyer AL, eds. *Advances in Radiation Therapy Treatment Planning*. American Institute of Physics; 1983:456-476. Copyright © 1983 by American Association of Physicists in Medicine. Reprinted by permission.)

Specific doses to critical organs may be limited by using either a full-thickness block, usually five HVLs (3.125% transmission) or six HVLs (1.562% transmission), or a partial transmission shield, such as a single HVL (50% transmission) of shielding material. The actual dose delivered under the shielded area is usually greater than these stated transmission

levels because of scatter radiation beneath the blocks from adjacent unshielded portions of the field. The scatter component of the dose increases with depth as more radiation scatters into the shielded volume beneath the block. Thus, the dose to the blocked area is a function of block material, thickness (and width), field size, and energy. Figure 8.22 shows the attenuation of Lipowitz metal of x-rays produced at 2, 4, 10, and 18 MeV and ^{60}Co γ-rays.[105] Alloy blocks made from the standard thickness (7.6 cm) of foam molds reduce the primary beam intensity to 5% of its unattenuated value. Increasing the block thickness usually is not worthwhile because it makes the block heavier, whereas the scatter radiation contributes an equal or greater share of the dose under the blocks.

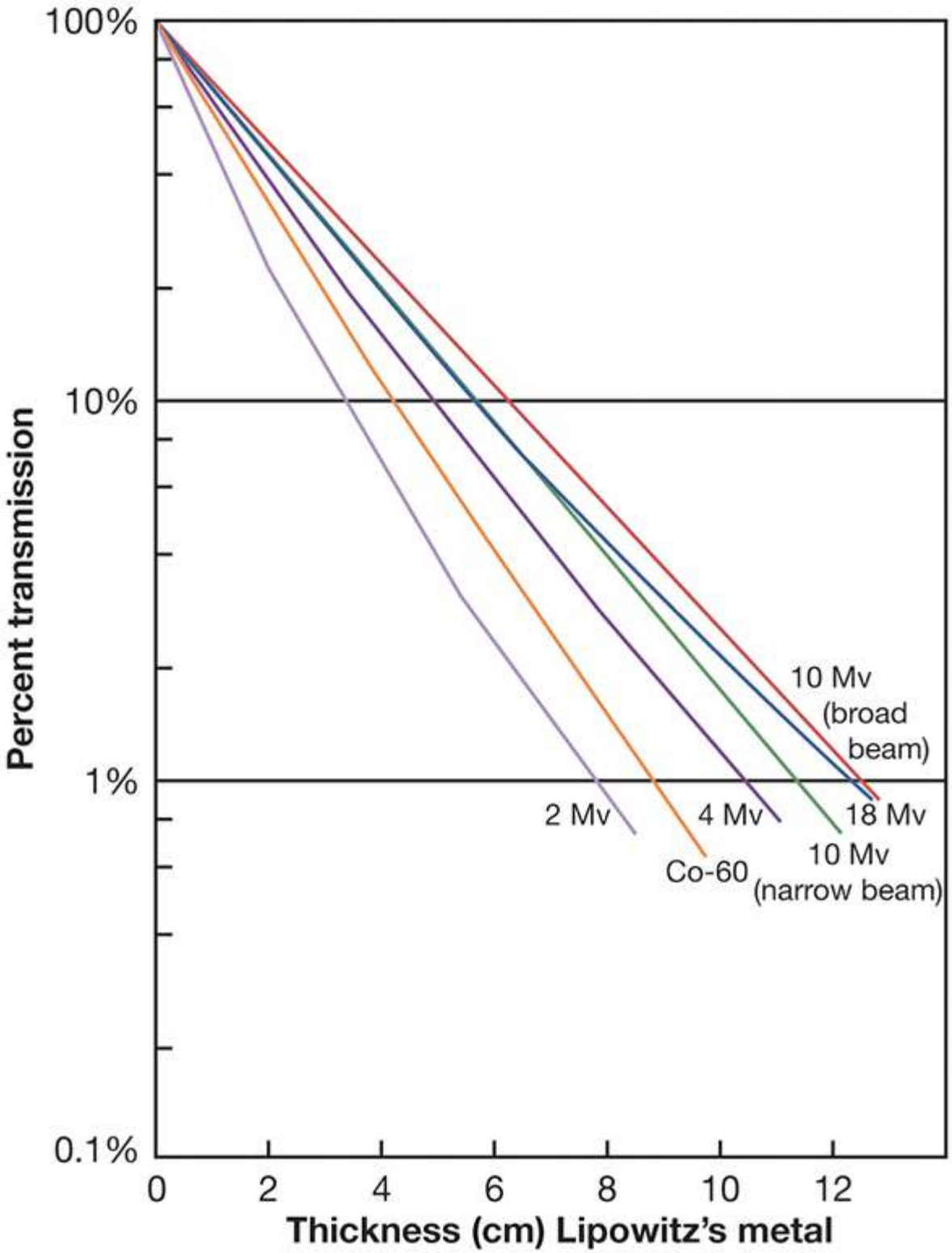


FIGURE 8.22 Attenuation in Lipowitz metal of x-rays produced at 2, 4, 10, and 18 MV and γ-rays from ^{60}Co. (From Huen A, Findley DO, Skov DD. Attenuation in Lipowitz's metal of x-rays produced at 2, 4, 10, and 18 MV and gamma rays from cobalt-60. *Med Phys*.

1979;6[2]:147-148. Copyright © 1979 American Association of Physicists in Medicine. Reprinted by permission of John Wiley & Sons, Inc.)

Because of the advent of multileaf collimation, metal blocks for photon beams are rarely used, as multileaf collimation allows there to be no room entry between treatment fields. In addition, the construction of blocks was time-consuming and expensive. Also, the materials themselves, as they were heated, gave off potentially toxic air, particularly because of the lead and cadmium. The one advantage of blocks is that they provide smooth boundaries by having a continuous shape around the field and incur no field size limitation. However, the weight of the blocks can be excessive, sometimes up to 15 pounds, leading to the potential for injury to therapists and patients should they be mishandled.

COMPENSATING FILTERS

The compensating filter, introduced by Ellis et al[106] counteracts the effects caused by variations in patient surface curvature while still preserving the desirable skin-sparing feature of megavoltage photon beams. This is accomplished by placing the custom-designed compensating filter in the beam, sufficiently "upstream" from the patient's surface, as illustrated in Figure 8.23. Several different compensator systems have been used in the clinic. However, the use of physical compensators to account for patient surface curvature is almost nonexistent in clinics today because of the advent of IMRT. But one particular IMRT delivery method does use a physical compensator, which is designed from the planning system and often constructed from a third-party vendor to deliver a modulated field.[107]

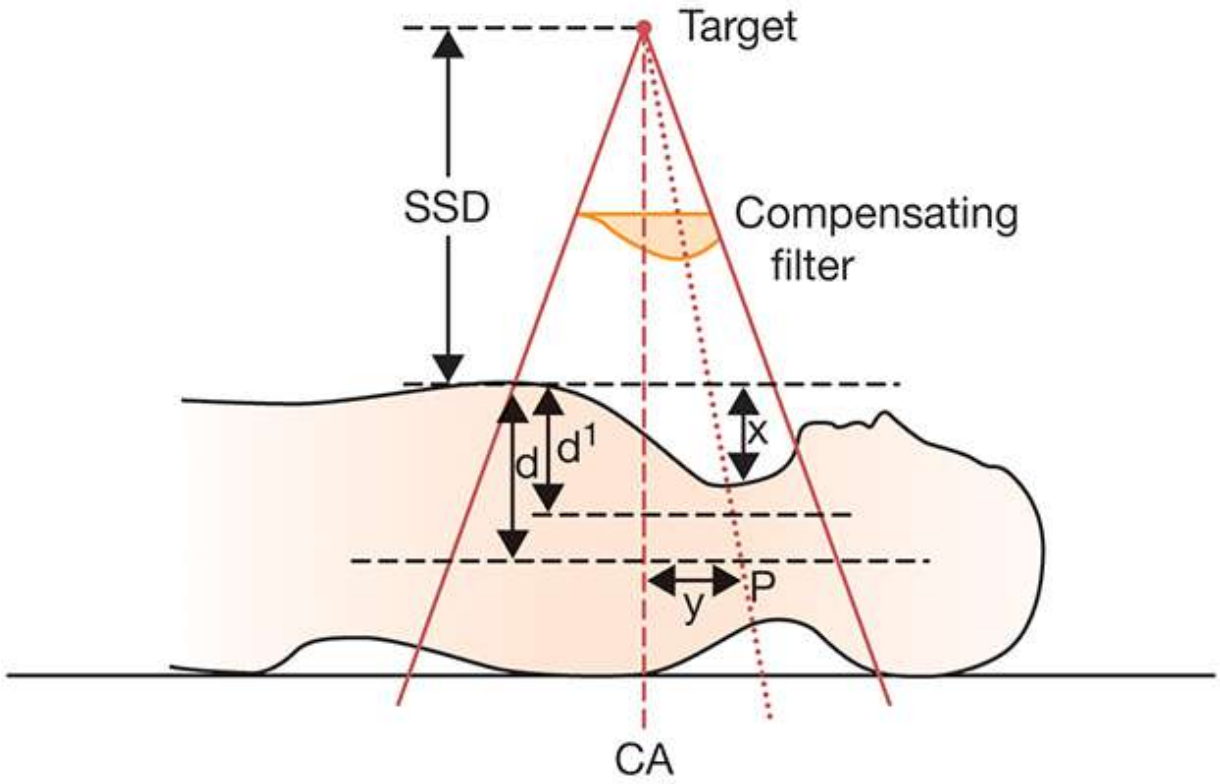


FIGURE 8.23 Schematic illustrating typical geometry used in the design of a compensator filter to account for patient's irregularly shaped surface. CA, central axis; SSD, source-to-skin distance.

One exception where the use of compensating filters or really custom bolus has increased is in electron beam applications.[108] The decimal company (Sanford, FL) offers a product BolusECT, which enables creation of custom 3D bolus to improve the conformality of electron beams at depth. These devices offer a simple and relatively inexpensive method to significantly improve electron beam dosimetry. The main shortcoming is the delay involved in ordering and shipping the devices, but overall, this approach appears to be clinically manageable.

BOLUS

Tissue-equivalent material placed directly on the patient's skin surface to reduce the skin sparing of megavoltage photon beams is referred to as *bolus*. A tissue-equivalent bolus should have electron density, physical density, and atomic number similar to those of tissue or water and be pliable so that it conforms to the skin surface contour. Inexpensive, nearly tissue-

equivalent materials used as a bolus in radiation therapy include slabs of paraffin wax, rice bags filled with soda, gauze coated with petrolatum, and synthetic-based substances, such as Superflab or Super Stuff.[109]

Thin slabs of bolus that follow the surface contour increase the dose to the skin beneath the bolus with a maximum reduction when the bolus thickness is approximately equal to the d_{max} depth for the photon beam. In addition, adding bolus to fill a tissue deficit may smooth an irregular surface. A bolus also can be shaped to alter the dose distribution, but normally, wedges are used to alter the dose distribution for megavoltage photon beams to retain skin sparing.

PATIENT POSITIONING, REGISTRATION, AND IMMOBILIZATION

Ensuring accurate daily positioning of the patient for treatment and minimizing patient movement during treatment is essential to deliver the prescribed dose and achieve the planned dose distribution. The reproducibility achievable when positioning a patient for treatment depends on several factors other than the anatomic site, including the patient's age, general health, and weight. In general, patients who are obese and small children are the most difficult to position.

Numerous patient restraint and repositioning devices have been designed and used in treating specific anatomic sites. For example, a disposable foam plastic head holder provides stability for the head when the patient is in the supine position. If more rigidity is needed, a bite-block system (Figure 8.24) or a thermoplastic face mask system (Figure 8.25) is commonly used to immobilize patients with head and neck tumors. Custom molds constructed from polyurethane formed to patient contours (Figure 8.26) have gained widespread use as aids in immobilization and repositioning of patients being treated for Hodgkin disease, cancer of the thorax, prostate, or involving extremities. These systems are discussed in detail in Chapters 7.

FIGURE 8.24 Example of a bite-block registration and immobilization system used in treatment of head and neck cancer. (Courtesy of Radiation Products Design, Inc.)

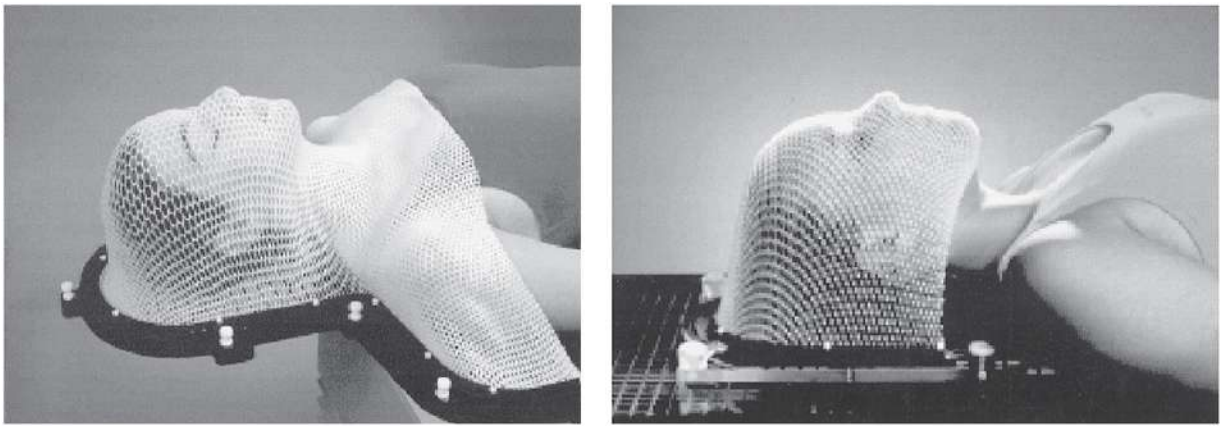


FIGURE 8.25 Example of a registration and immobilization system (thermal plastic mask) used in the treatment of head and neck cancer.

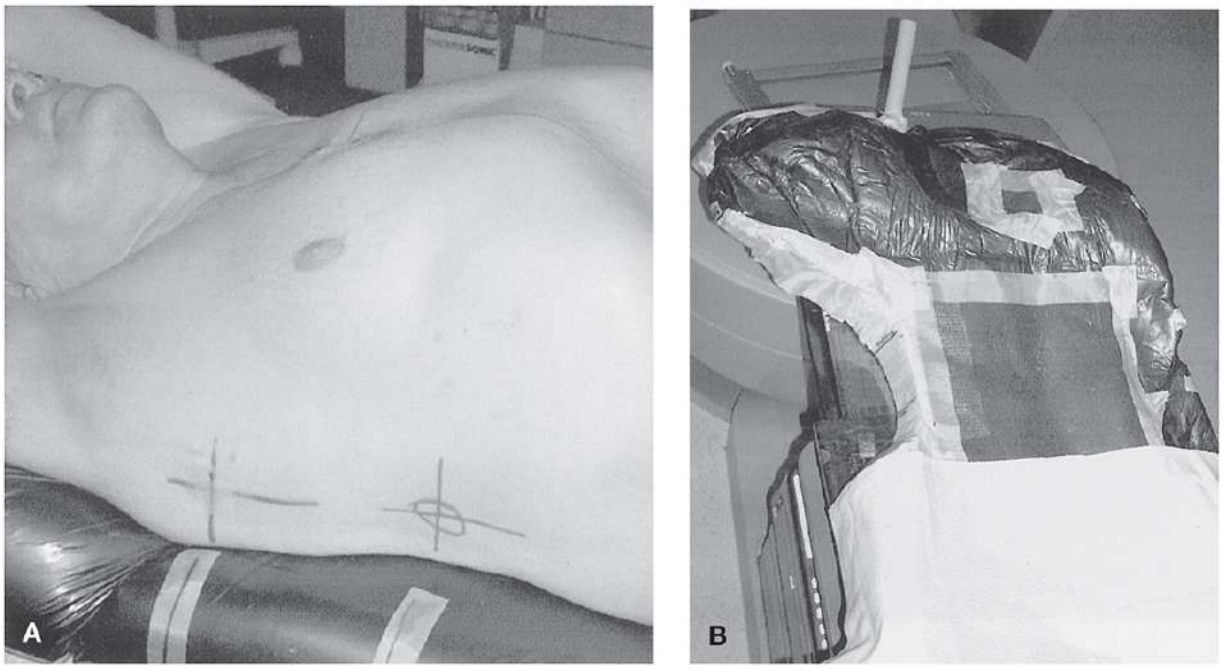


FIGURE 8.26 Examples of registration and immobilization systems (foam mold) used in the treatment of the thorax. A. Mold is registered to table and the patient is registered to the mold by fiducial markings. B. Mold with a cutout area to allow clear access to the treatment area and built-in handgrip.

The radiation fields to be treated are typically delineated in the simulation process using either visible skin markings or skin markings visible only under an ultraviolet light. In some instances, external tattoos are applied. These markings are used in positioning a patient on the treatment machine using the machine's field localization light and distance indicator and the laser alignment lights mounted in the treatment room that project transverse, coronal, and sagittal light lines (or dots) on the patient's skin surface.

It is vital that the rigidity of the immobilization system used maintain consistency over the course of treatment. Therefore, the systems that interface with the immobilization systems used in the simulation process and the treatment couch need to also be rigid and registered. As of now, patients are set up to treatment coordinates once they are fit into the immobilization systems.

One of the concerns with the use of plastic masks is that they occasionally shrink. This shrinkage can cause changes in patient positioning or can introduce discomfort. A problem with discomfort is that patients

often overcorrect their position to avoid pain caused because of poorly fitting immobilization. As a general rule, comfortable patients are easier to reproduce the daily setup and they tend to be less movable during an individual fraction. Note that it is important to carefully follow the manufacturer's instructions for making the masks and to monitor masks for shrinkage over the course of treatments. To overcome some of these hurdles, reduced or passive forms of immobilization are being introduced for clinical use in brain and breast treatments, which have primarily been enabled by 3D surface-guided radiotherapy.[110]

Dosimetric effects caused by immobilization devices as well as couch tops must also be addressed as noted by Olch et al.[111]

The final assessment of accuracy and reproducibility of the daily treatment is typically obtained by radiographic imaging of the area treated because there is the possibility of patient movement within the mask, especially if significant tumor shrinkage or weight loss has taken place. This is generally true for targets that are deep seated (eg, prostate, lung), but in the case of a treatment area located at the surface of a patient (ie, breast cancer), other surrogates including the surface may be acceptable.[110]

SEPARATION OF ADJACENT X-RAY FIELDS

Field Junctions

Different techniques for matching adjacent fields are illustrated in Figure 8.27. A commonly used gap calculation method for adjacent radiation fields is illustrated in Figure 8.28A. The separation between adjacent field edges necessary to produce junction doses similar to central-axis doses follows from the similar triangles formed by the half-field length and SSD in each field. The field edge is defined by the dose at the edge that is 50% of the dose at d_{max}. For two contiguous fields of lengths L_1 and L_2, the separation, S, of these two fields at the skin surface can be calculated using the following expression:

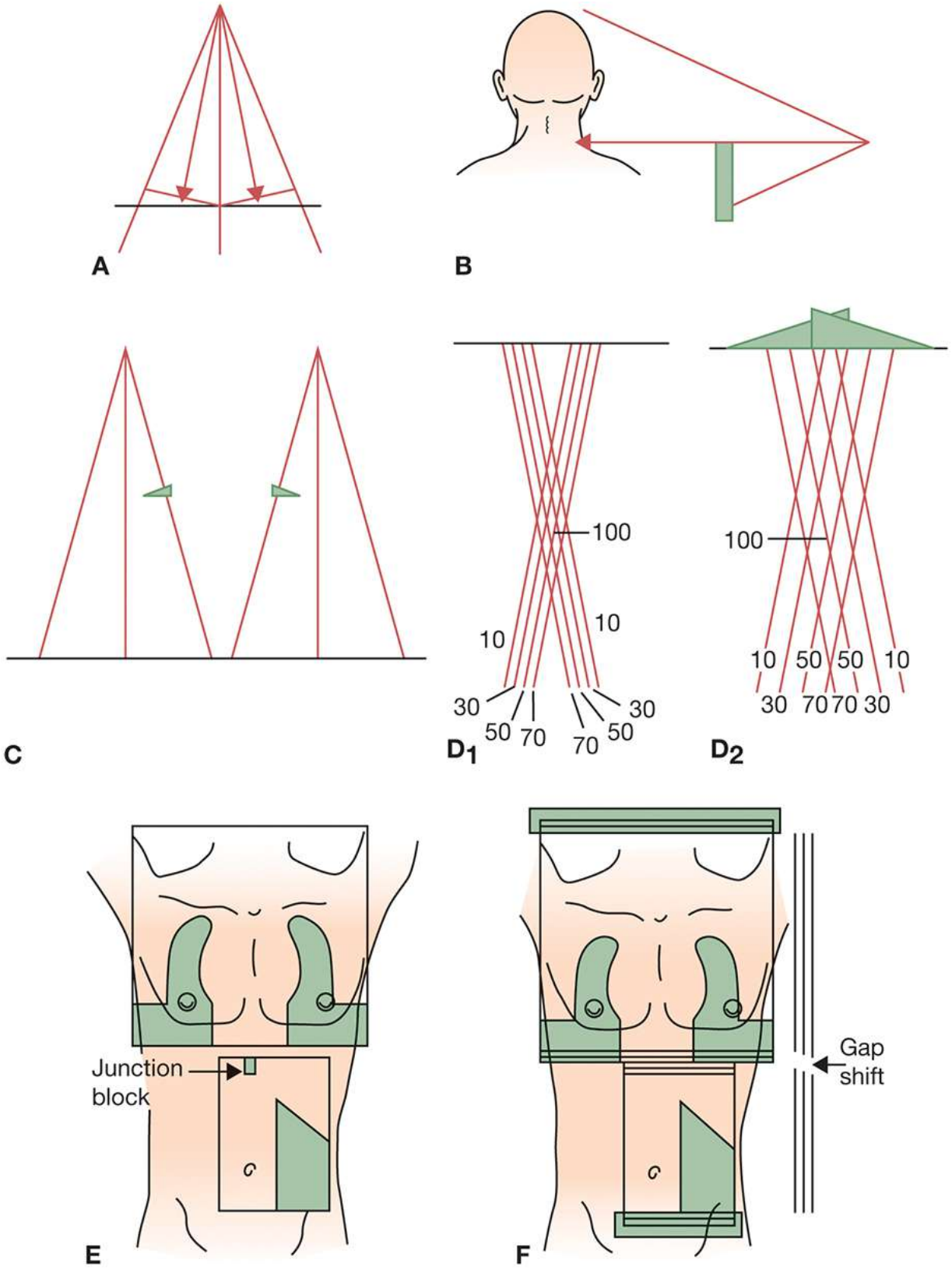


FIGURE 8.27 Different techniques for matching adjacent fields. A. Beam's central rays are angled slightly away from one another so that the diverging beams are parallel. B. Half-

beam block to eliminate divergence. C. Penumbra generators (small wedges) to increase the width of penumbra, as illustrated in D_1 and D_2. E. Junction block over spinal cord. F. Moving gap technique. (Used with permission of McGraw-Hill from Bentel GC, ed. *Radiation Therapy Planning*. 2nd ed. McGraw-Hill; 1996:141, Figure 6.44; permission conveyed through Copyright Clearance Center.)

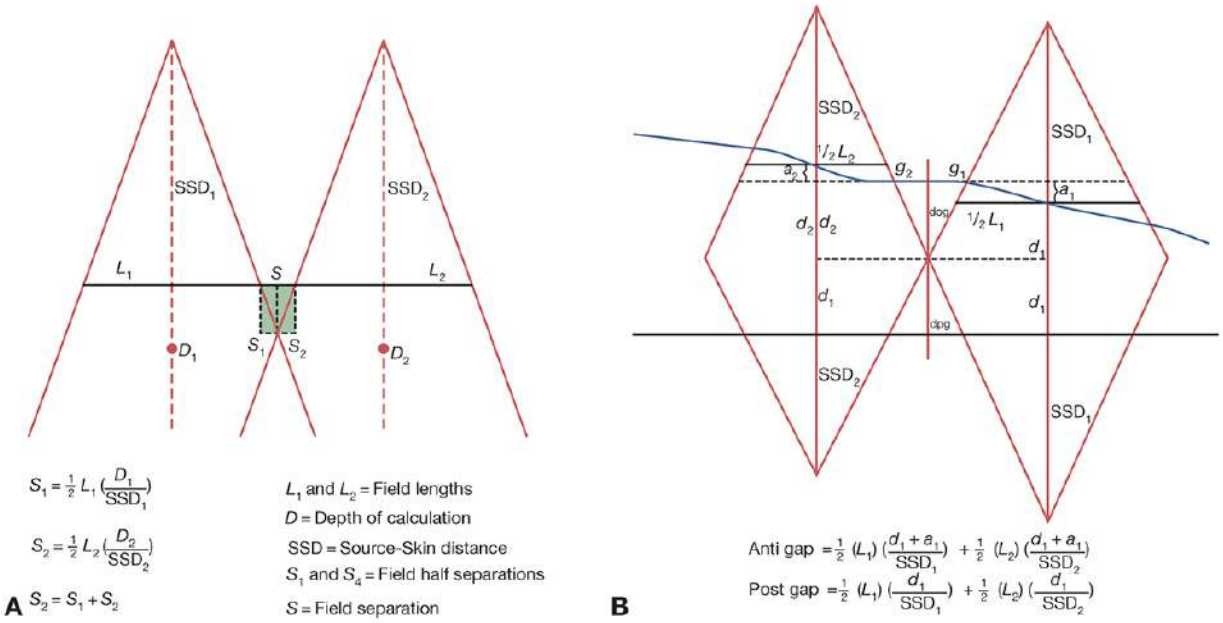


FIGURE 8.28 A. Standard formula for calculating the gap at the skin surface for a given depth using similar triangles. B. Modified formula for calculating the gap for matching four fields on a sloping surface. (Reprinted from Keys R, Grigsby PW. Gapping fields on sloping surfaces. *Int J Radiat Oncol Biol Phys*. 1990;18[5]:1183-1190. Copyright © 1990 Elsevier. With permission.)

$$S = \frac{1}{2} L_1 \left(\frac{d}{\text{SSD}} \right) + \frac{1}{2} L_2 \left(\frac{d}{\text{SSD}} \right)$$

A slight modification of this formula is needed when sloping surfaces are involved, as shown in Figure 8.28B.[112] Typically, the skin gap location is moved a number of times to reduce the hot and cold spots that arise with this technique. Figure 8.29 illustrates the dose distribution for three different field separations.[113]

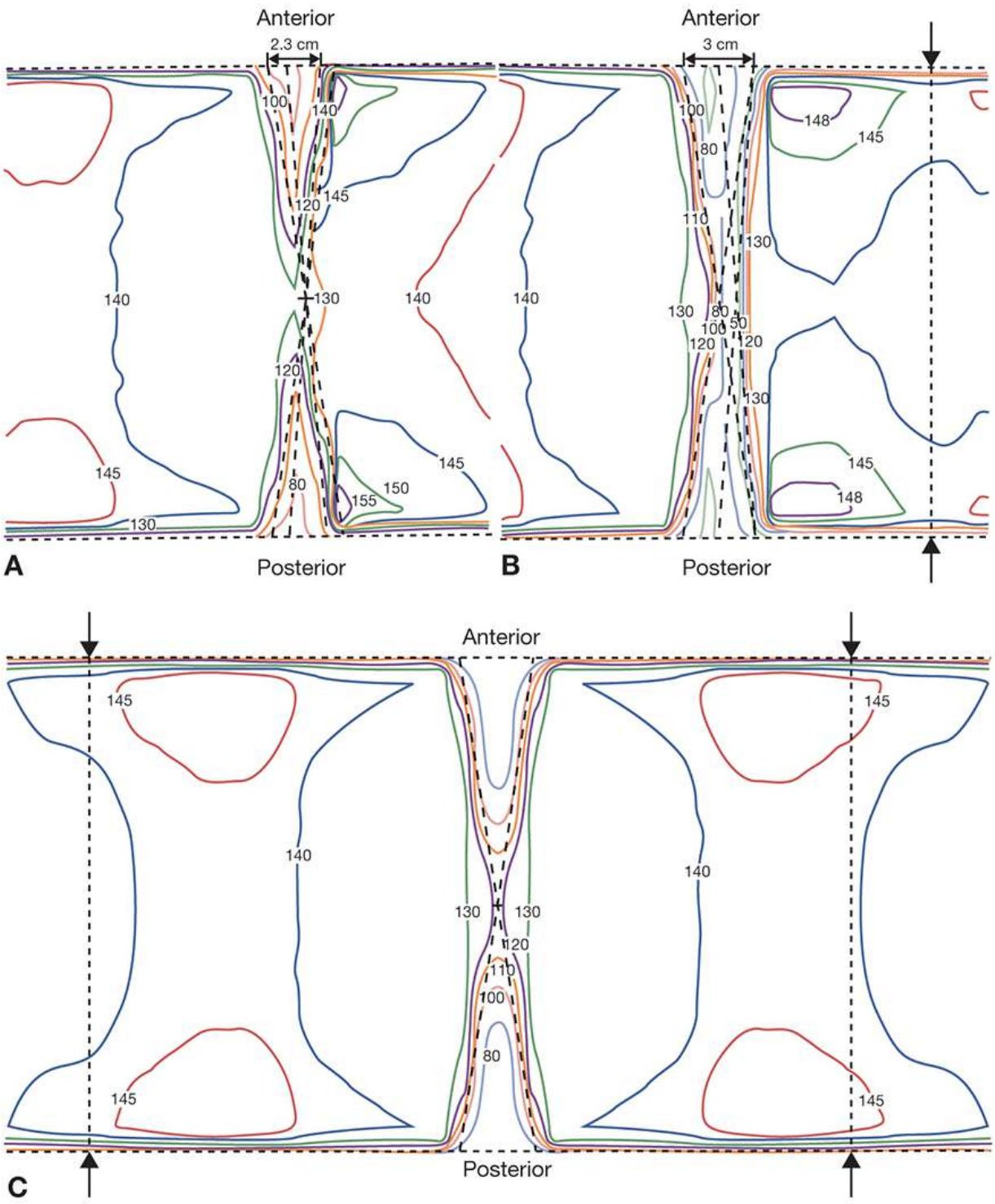


FIGURE 8.29 Dose distribution for geometric separation of fields with all four beams intersecting at midpoint. Adjacent field sizes: 30 × 30 and 15 × 15 cm^2; source-to-skin distance (SSD), 100 cm; anteroposterior thickness, 20 cm; 4-MV x-ray beams. A. Field separation at the surface is 2.3 cm. A three-field overlap exists in this case because the fields have different sizes but the same SSD. B. The adjacent field separation increased to eliminate three-field overlap on the surface. C. Field separation adjusted to 2.7 cm to

eliminate three-field overlap at the cord at 15 cm depth from anterior. (Reprinted with permission from Khan FM. *The Physics of Radiation Therapy*. 2nd ed. Williams & Wilkins; 1994.)

Beam divergence may be eliminated by using a "beam splitter," created using a five- or six-HVL block over half the treatment field. The central axes of the adjacent fields, where there is no divergence, are then matched. As previously discussed, this is a useful method on linacs with the asymmetric jaw feature. Match-line wedges or penumbra generators that generate a broad penumbra for linac beams have been reported but have not found widespread use.[114] Here, the intent is to broaden the narrow penumbra of the linacs so that it is not so difficult to match the 50% isodose levels. The resulting dose distributions are similar to those obtained with a moving gap technique. Finally, there are several reports of edge-matching techniques based on the mathematical relationships between adjacent beams and the allowed angles of the gantry, collimators, and couch.[115]

Orthogonal Field Junctions

Figure 8.30 illustrates the geometry of matching abutting orthogonal photon beams. Such techniques are necessary, particularly in the head and neck region where the spinal cord can be in an area of beam overlap, in the treatment of medulloblastoma with multiple spinal portals and lateral brain portals. A common method of avoiding overlap is to use a half-block, as previously discussed, so that abutting anterior and lateral field edges are perpendicular to the gantry axis. In head and neck cancer, a notch in the posterior corner of the lateral oral cavity portal is commonly used to ensure overlap avoidance of the spinal cord when midline cord blocks cannot be used on anteroposterior portals irradiating the lower neck and matched to the oral cavity portals. Other techniques rotate the couch about a vertical axis to compensate for the divergence of the lateral field.[116] The angle of rotation is given by

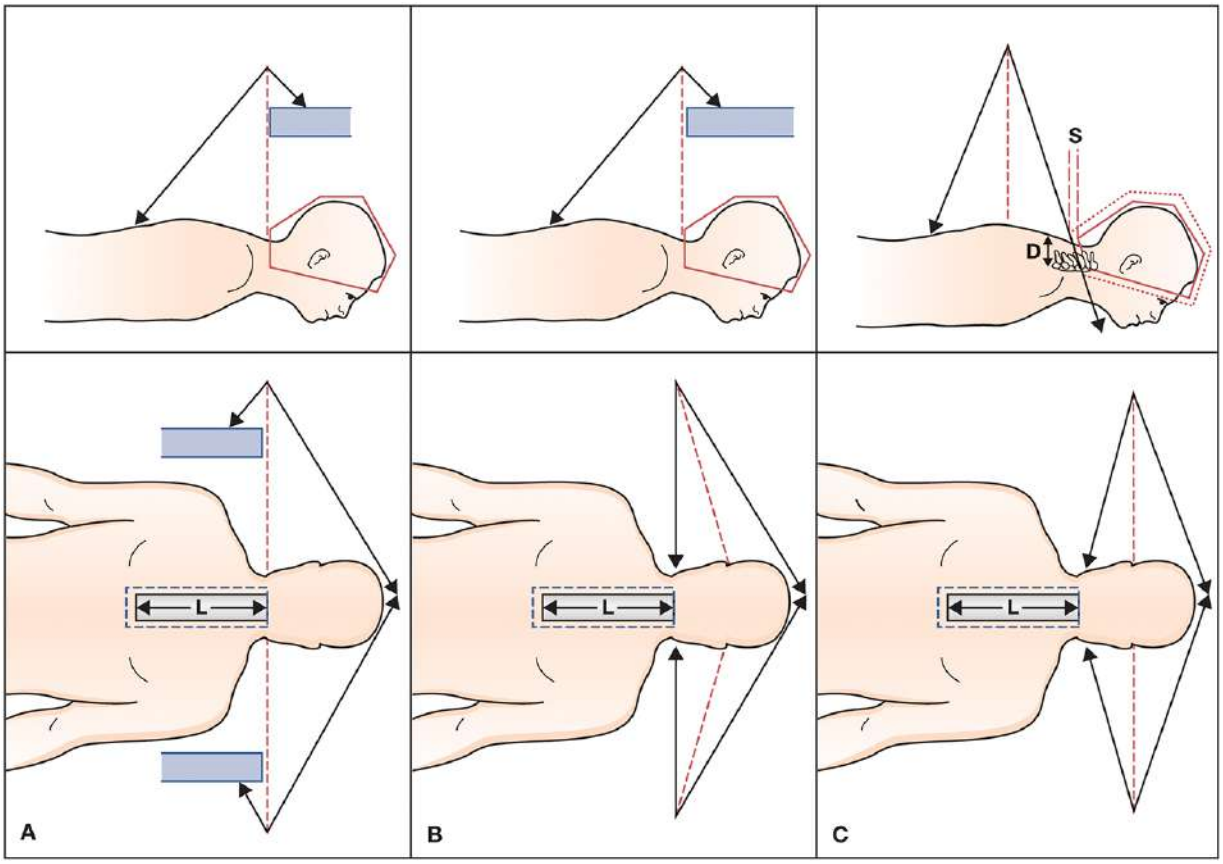


FIGURE 8.30 Some solutions for the problem of overlap for orthogonal fields. A. A beam splitter, a shield that blocks half of the field, is used on the lateral and posterior fields and on the spinal cord portal to match the nondivergent edges of the beams. B. The divergence in the lateral beams may also be removed by angling the lateral beams so that their caudal edges match. Because most therapy units cannot be angled like this, the couch is rotated through small angles in opposite directions to achieve the same effect. C. A gap technique allows the posterior and lateral fields to be matched at depth using a gap *S* on the skin surface. The dashed lines indicate projected field edges at depth *D*, where the orthogonal fields meet. (Reprinted from Williamson TJ. A technique for matching orthogonal megavoltage fields. *Int J Radiat Oncol Biol Phys*. 1979;5[1]:111-116. Copyright © 1979 Elsevier. With permission.)

$$\tan\theta^{-1} = \left(\frac{\frac{1}{2}\,\text{field width}}{\text{SAD}} \right)$$

Another technique is to leave a gap, *S*, on the anterior neck surface between the posterior field of length *L* and the lateral field edges.[117] *S* can be calculated using the following formula where *d* is the depth of the spine beneath the posterior field:

$$S = \frac{1}{2}(L)\left(\frac{d}{\text{SAD}}\right)$$

The potential for the occurrence of radiation myelopathy resulting from a potentially excessive dose from misaligned overlapping fields is always a concern when central nervous system tumors are treated. Craniospinal irradiation is well established as a standard method of treating suprasellar dysgerminoma, pineal tumors, medulloblastomas, and other tumors involving the central nervous system. Uniform treatment of the entire craniospinal target volume is possible using separate parallel-opposed lateral cranial portals rotated so that their inferior borders match with the superior border of the spinal portal, which is treated with either one or two fields, depending on the length of the spine to be treated.[118] Two junctional moves are typically made at one-third and two-thirds of the total dose. The spinal field central axis is shifted away from the brain by 0.5 cm and the field size length reduced by 0.5 cm with corresponding increases in the length of the cranial field, so that a match exists between the inferior border of the brain portal and the superior border of the spine portal. To achieve the match, a collimator rotation for the whole-brain portals must be done for an angle given by the following relationship:

$$\tan\theta^{-1} = \left(\frac{\frac{1}{2}\text{spinal field length}}{\text{SAD}}\right)$$

In addition to eliminating the divergence between the cranial portal and spinal portal, the table is rotated through a floor angle given by the following relationship:

$$\tan\alpha^{-1} = \left(\frac{\frac{1}{2}\,\text{cranial field length}}{\text{SAD}} \right)$$

RADIATION THERAPY PATIENTS WITH CARDIAC PACEMAKERS

As the population ages, the likelihood of encountering patients with either a pacemaker or an implantable cardioverter- defibrillator (ICD) who require radiation therapy for chest and lower neck neoplasms has become commonplace. Pacemakers are electrical devices that may stimulate the atria, ventricles, or both (single-chamber and dual-chamber models, respectively) in order to regulate the heart's natural rhythm.[119] ICDs are generally larger than pacemakers and also actively shock the heart to help control life-threatening, irregular heartbeats, especially those that could cause sudden cardiac arrest; most new ICDs can act as both pacemakers and defibrillators.[119] Modern pacemakers and ICDs incorporate complementary metal oxide semiconductor circuitry into their generator units (encompassing a sealed lithium battery pack and circuitry only). Several groups have shown that these modern devices are much more sensitive to radiation than the older models that utilized bipolar transistor circuitry.[120]

To treat such patients safely and adequately, it is important to understand the potential effects of radiation therapy on these devices' operation and to take steps to minimize any actions that could jeopardize the cardiac health of the patient. The AAPM TG 203 Report provides a list of widely accepted clinical management guidelines.[119] Potential interactions between a functioning pacemaker and the radiation therapy environment fall into two categories: (a) electromagnetic noise interference (EMI) created by the treatment machine in the course of producing high-energy photon and electron beams and (b) damage due to radiation. Most experts now believe

category 1 is no longer a source of concern. However, dose and dose rate are very much a concern.[120] Modern pacemakers are radiosensitive and have a significant probability of failing catastrophically at radiation doses well below normal tissue tolerance and, therefore, should never be irradiated by the direct beam. Also, several authors have shown that recommended maximum doses obtained from the manufacturers have not proven to be reliable and vary greatly among manufacturers. On the other hand, radiation-induced device malfunctions are rare and death associated with that malfunction is even more uncommon. Thus, it is important to consider all aspects of radiation therapy treatment, not just accumulated dose, including the effect of backscatter, dose rate, fractionation, and potential EMI with new technologies, such as IMRT and respiratory gating. Current guidelines recommend that each radiation oncology department employ their own policy for the management of patients with pacemakers and ICDs, potentially based on an updated standard national[119] or international[121] guideline similar to that released by the AAPM TG 203 Report (Table 8.2).

TABLE 8.2 MANAGEMENT GUIDELINES FOR RADIATION THERAPY PATIENTS WITH CARDIAC IMPLANTED ELECTRONIC DEVICES (CIED)

1. Management of patients should be based on device risk levels (low, medium, high) based on pacing dependent and expected dose to the device.
2. CT irradiation of CIED for longer than 3 s should be avoided, whenever possible.
3. CIED compatibility with MRI should be verified prior to MR simulation, and protocols for safe MRI scanning should be developed and implemented.
4. If >10 MV photon, proton, or neutron beams are used, the patient should be managed in the high-risk category.
5. Lower dose rates are preferred.
6. The generator for the device should be kept at least 5 cm from the collimated field edge if possible, including imaging fields, by selection of the appropriate beam angles that increase the distance between the field edge and the CIED.
7. Perform in vivo dosimetry for the first fraction if the device is <10 cm from treatment area. The treatment planning system should be used in lieu of a measurement if the device is within 3 cm (laterally) of the field edge or 5% isodose line for IMRT.
8. Lead should not be used for shielding CIED during treatment.
9. Cumulative dose should be kept at <5 Gy level for CIEDs (ie, low- to medium-risk categories), as much as possible or below the manufacturer's recommended dose threshold if higher.
10. Patients should be monitored with specified frequencies and techniques.

From Miften M, Mihailidis D, Kry SF, et al. Management of radiotherapy patients with implanted cardiac pacemakers and defibrillators: a report of the AAPM TG-203. *Med Phys*. 2019;46(12):e757-e788. Copyright © 2019 American Association of Physicists in Medicine. Reprinted by permission of John Wiley & Sons.

New electronic devices for noncardiac applications including pain pumps and drug delivery systems are becoming more common on the market and in patients presenting for radiation therapy. Similar principles should be used as for ICDs, including contacting the manufacturer for guidance on maximum dose and dose rate, communicating with the physician and the clinical team responsible for overseeing the functioning of the electronic device, and developing a risk-based assessment and plan of action.

FETAL DOSE

Radiation therapy is the standard treatment for several malignancies (eg, Hodgkin lymphoma, breast cancer) in which the population of women is often of childbearing age. The issues are complex, and the patient along with the radiation oncologist must evaluate treatment risk to the fetus in such cases. Radiation effects on the fetus are not fully understood and cannot be comfortably predicted for each individual case. If the decision is to irradiate, the dose levels outside the treatment fields should be quantified, and every effort should be made to lower the dose to the fetus. This may require changes in irradiation technique (ie, modified mantle fields), elimination of double-exposure portal images, and the addition of special patient shields. The AAPM TG 36 Report provides data and techniques to estimate and reduce radiation dose to the fetus for beam energies ranging from ^{60}Co to 18 MV.[122] Before the pregnant patient is treated, the pregnancy stage should be known to estimate the size and location of the fetus throughout the treatment. Dose estimation points should be selected that allow estimation of dose throughout the fetus (eg, fundus, symphysis pubis, and umbilicus).

Two methods can be used to reduce the dose to the fetus, namely, modification of treatment techniques and the use of special shields. Modifications include changing field angle (avoiding placement of the gantry close to the fetus, ie, treatment of a posterior field with the patient lying prone on a false tabletop), reducing field size, choosing a different

radiation energy (avoiding ^{60}Co because of high leakage or energies of over 10 MV because of neutrons), and using tertiary collimation to define the field edge nearest to the fetus. When shields are designed, the shielding device must allow for treatment fields above the diaphragm and on the lower extremities. Safety to the patient and personnel is a primary consideration in shield design. As part of the management of a pregnant patient, the treatment planning tasks listed in Table 8.3 should be performed to ensure that the dose to the fetus is kept to a minimum.[122]

TABLE 8.3 TREATMENT PLANNING TASKS TO ENSURE THAT DOSE TO THE FETUS IS KEPT TO A MINIMUM

1. Complete all planning as though the patient were not pregnant.
2. Consider modifications of the plan that would minimize the fetal dose (eg, changing field size and angle, using a different energy).
3. Estimate dose to fetus without shielding using a phantom or data from the AAPM report.120
4. Design and construct special shielding if necessary; four or five HVLs of lead usually suffice.
5. Measure dose to fetus in a phantom during simulated treatment with shielding in place.
6. Document the treatment plan and discuss the treatment with all personnel involved with the treatment.
7. Check all aspects of safety, including the load-bearing limits of the couch and support and movement of the shields, to ensure that there will be no injury to the patient or to personnel. The setup of each field should be photographed for documentation.
8. Monitor fetal size and location throughout the course of therapy and update estimates of fetal dose if necessary.
9. Document the completion of treatment by estimating the total dose to the fetus because of the radiation therapy.

AAPM, American Association of Physicists in Medicine; HVL, half-value layer.

Modified from Stovall M, Blackwell CR, Cundiff J, et al. Fetal dose from radiotherapy with photon beams: report of AAPM Radiation Therapy Committee Task Group No. 36. *Med Phys*. 1995;22(1):63-82. http://creativecommons.org/licenses/by/3.0/.

Note that the AAPM TG Report was based on treatment machines that predated modern MLCs. One study showed that the use of tertiary MLC systems such as those found on Varian linacs actually reduced fetal dose during irradiation of a pregnant patient.[123] The leaf and carriage system provided some absorption, and if the MLC leaves were oriented in direction along the plane of concern, such as typically when a patient with Hodgkin

disease is treated (ie, leaves oriented along the length of the table), the reduction difference when compared to having no MLCs was on the order of 2.5 to 3. Recently, AAPM TG 158 has provided guidance on out-of-field calculations for modern, MLC-based treatment machines.

GONADAL DOSE

Many of the reports used to estimate peripheral dose and fetal dose apply to dose estimations to both testes and ovaries.[124-126] Simultaneously, there have been studies to determine the genetically significant dose (GSD) as it applies to peripheral radiotherapy dosage to ovaries and testes. Niroomand-Rad and Cumberlin[127] combined measured data and GSD data to determine the GSD for treatment techniques that deliver peripheral dose to ovaries and testes. They summarized that GSDs from conventional therapies are minimal. However, there are circumstances, such as treatment of seminoma, when it is necessary to use a testicular shield to surround the testes to reduce head scatter and leakage, and some internal scatter.[128]

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CHAPTER 9

Electron-Beam Therapy Dosimetry, Treatment Planning, and Techniques

Angélica Pérez-Andújar and Eric E. Klein

Megavoltage photon–based radiation therapy treatment of shallow tumor volumes is complicated by the buildup and radiation transport properties of photon beams. These beams are capable of treating both shallow and deep tumors; however, when treating shallow tumors, the radiation beams transit through the entire patient, exposing distal normal tissues. Megavoltage electron-beams have the property of a finite range and, therefore, do not deliver significant radiation doses to distal depths. Electron-beam therapy is, therefore, suitable for shallow tumors (<5 cm deep), such as head and neck cancers, skin cancers, chest wall irradiation for breast cancer, and boost dose to nodes. Electrons typically provide dose uniformity in these target volumes, with minimal dose to distal organs. In fact, G. H. Fletcher[1] had gone as far as saying, "there is no alternative treatment to electron-beam therapy." Even the strongest proponents of photon or proton therapy acknowledge that electron therapy is necessary to complete any radiotherapy program.

In 1976, Tapley[2] published one of the earlier comprehensive treatises on electron radiation therapy, in which she states, "there is no practical way for every radiation therapy department, in either hospitals or private offices, to be equipped with all modalities of irradiation beams. Ideally, electron beams should be available for those clinical situations where electrons are indispensable or very clearly superior." Electrons are now used at most radiation therapy centers. It still might be advantageous to refer patients to regional centers for special treatment techniques utilizing electrons.

Since the late 1970s, there have been three developments in electron-beam radiation therapy technology that have improved significantly our ability to deliver electron therapy. First, the advent of computed

tomography (CT)-based treatment planning allowed for coverage of the planning target volume (PTV) by the therapeutic dose and the dose to normal tissues and structures to be more accurately assessed. The use of CT provides a physical description of the anatomy, which is required for accurate dose calculations.[3,4] Second, the development of the electron pencil-beam algorithms (PBAs) and their implementation into treatment planning systems in the early 1980s provided a mechanism for accurately calculating the dose.[5,6] More recently, the use of Monte Carlo calculations has moved development to commercial platforms.[7] They have demonstrated high degrees of accuracy, especially with the presence of inhomogeneities. Third, manufacturers have refined the quality of their electron beams (ie, depth dose, off-axis uniformity, and penumbral width) by providing dual-scattering foil systems and electron applicators. Klein et al[8] describe dosimetric improvement with the most recent Varian electron-beam delivery system. Presently, the differences in the electron-beam dose characteristics of various radiation therapy machines from different vendors are minimal. Kashani et al[9] described electron-beam characteristics of a newly configured beam line for the Varian TrueBeam machine.

Electron-beam therapy is advantageous because it delivers a reasonably uniform dose from the surface to a specific depth, after which the dose falls off rapidly, eventually to a near-zero value. The depth of treatment is controlled by selecting the appropriate energy and, when necessary, the bolus thickness. Using electron beams with energies up to 20 MeV allows disease within approximately 6 cm of the surface to be treated effectively, sparing distal normal tissues.

Electron-beam therapy is useful in treating cancer of the skin and lips, upper respiratory and digestive tract, head and neck,[10,11] breast, and a variety of other sites.[2,12,13] Treatment sites of the skin include the eyelids, nose, ear,[14] scalp,[2,15] and more widely spread diseases of the limbs (eg, melanoma and lymphoma)[16] or total skin (eg, mycosis fungoides).[17,18] Treatment sites of the upper respiratory and digestive tract include the floor of mouth, soft palate, retromolar trigone, and salivary glands.[10,19] Treatments of the breast include chest wall irradiation following mastectomy[2,20,21]; nodal irradiation, often internal mammary chain (IMC) and occasionally axillary; and boost to the surgical bed following mastectomy or lumpectomy.[22] Current techniques of using tangential photon adjunct fields abutting

supraclavicular and posterior axillary fields are difficult enough without the addition of treating a separate medial breast internal mammary field with a mixture of photons and electrons. Other sites of electron-beam therapy include the retina,[23] orbit,[24] paraspinal muscles,[3,25] pancreas and other abdominal structures (intraoperative therapy),[26] vulva,[27] and cervix (intracavitary irradiation).[28]

The purpose of this chapter is to discuss the treatment and treatment planning techniques necessary to deliver the most effective electron-beam therapy. This requires a basic knowledge of dose distribution in water, dose in the heterogeneous patient, treatment planning tools and principles, and special techniques using electron beams.

DOSE DISTRIBUTION IN WATER

To appreciate the clinical use of electron beams, their dose distributions in water must be understood. Understanding the properties of depth dose, off-axis ratios (OARs), and two-dimensional (2D) isodose contour plots will clarify the concept of dose distribution in water. As well, an understanding of the dependence of the dose distribution on incident energy, field size, and source-to-surface distance (SSD) is required. It is assumed that the dose distribution for a specified energy, field size, and SSD is machine dependent. Applicator design may have a minor influence on dose distributions.

Depth Dose

This section discusses the percentage of dose (values are normalized to 100% at the depth of dose maximum, R_{100}) versus depth in water. Central-axis depth dose implies that the electron field is symmetric about the central axis, and the focus initially is on square fields. Electron depth dose varies with field size; however, once the field reaches a certain size, side-scatter equilibrium is achieved, and further increasing the size has an insignificant effect on depth dose.[29,30] In the energy range of up to 20 MeV, a 10- by 10-cm^2 field size typically will achieve side-scatter equilibrium on the central axis. The energy dependence of depth dose is illustrated in Figure 9.1, where central-axis depth dose is plotted for a 10- by 10-cm^2 field for

energies in the range of 7 to 18 MeV. The family of curves illustrates how the dosimetric characteristics vary with the incident electron energy:

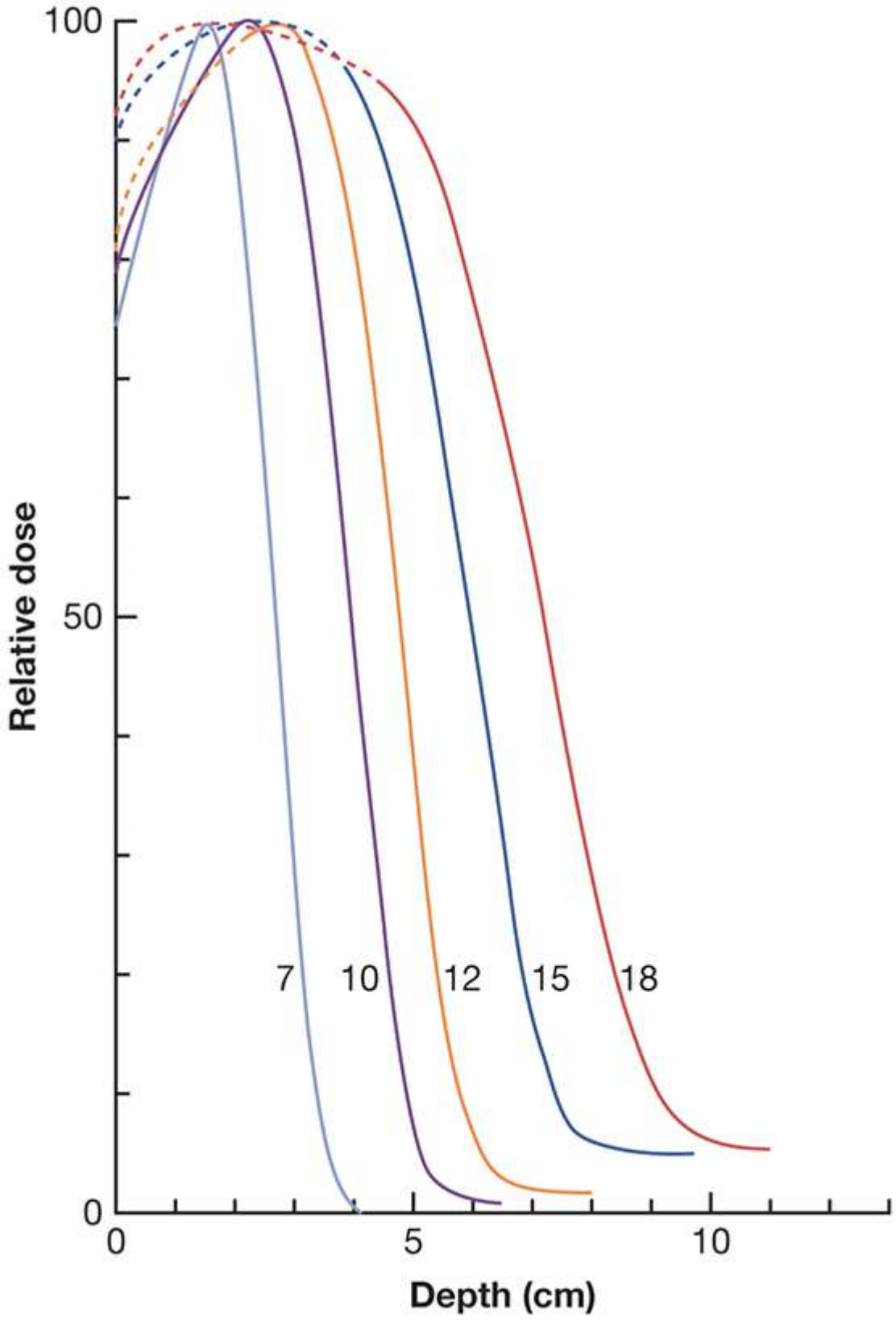

100
50
0
Relative dose
0
5
10
Depth (cm)
7
10
12
15
18

FIGURE 9.1 Energy dependence of depth dose. Plot of relative dose (%) versus depth for a 10- by 10-cm^2 field size for 7- to 18-MeV beams on a Siemens Mevatron 77 radiation therapy unit (source-to-surface distance = 100 cm). (From Meyer JA, Palta JR, Hogstrom KR. Demonstration of relatively new electron dosimetry measurement techniques on the Mevatron 80. *Med Phys*. 1984;11[5]:670-677. Copyright © 1984 American Association of Physicists in Medicine. Reprinted with permission of John Wiley & Sons, Inc.)

1. Surface dose (D_s) increases from approximately 75% to 95% as energy increases. The slow increase in dose from the surface to the depth of maximum dose (R_{100}) occurs as a result of electrons undergoing multiple Coulomb scattering in water.[29]
2. Depth of distal 90% (R_{90}), often the therapeutic prescription depth, increases as energy increases. A physician may also prescribe to the 80% or 100% depth.
3. The practical range (R_p) (maximum penetration) of the electrons increases as energy increases.
4. X-ray dose attributable to bremsstrahlung that lies beyond the electron dose component is characterized by its value (D_x) and is taken from the percentage depth dose (PDD) curve 10 cm beyond the practical range (R_p). D_x increases as energy increases. Machines are designed to provide D_x values to be <5%.
5. The R_{100} depth (d_{max}) can vary irregularly with the depth and model of electron treatment machine; its dependence is insignificant for treatment planning, although it is significant to the medical physicist for constructing percent depth-dose data and in beam calibration.

Table 9.1 gives dosimetric parameters for a modern (Trilogy, Varian) linear accelerator.

TABLE 9.1 VARIAN TRILOGY MEASURED ELECTRON DEPTHS (R_P, R_{50}) AND CALCULATED ENERGIES (E_P, E_0)

Nominal Energy	Measured E_o (MeV)	Measured E_p (MeV)	R_{90}: Depth of 90% (cm)	R_{50}: Depth of 50% (cm)	R_p (cm)	D_x (%)
6	5.55	6.08	1.53	2.38	2.95	0.1

Nominal Energy	Measured E_o (MeV)	Measured E_p (MeV)	R_{90}: Depth of 90% (cm)	R_{50}: Depth of 50% (cm)	R_p (cm)	D_x (%)
9	8.41	8.84	2.69	3.61	4.33	0.3
12	11.77	12.23	3.85	5.05	6.02	0.9
16	15.63	16.02	5.10	6.71	7.900	1.6
20	19.62	20.78	6.14	8.42	10.25	2.1

E_o: Average energy at the surface, where $E_0 = 2.33 \times R_{50}$.

E_p: Most probable electron energy at the surface, where $E_p = C_1 + C_2 R_p = C_3 R_p 2$ and where C1, C2, and C3 are constants, with C1 = 0.22 MeV, C2 = 1.98 MeV cm, and C3 = 0.01025 MeV cm^2.

Depth dose has a significant dependence on field size, which varies with incident electron energy. The primary reason for the field-size dependence is the loss of side-scatter equilibrium, which has been discussed in detail by Hogstrom[29] and Khan et al[30] Figure 9.2, which shows the field-size dependence of PDD at 9 and 20 MeV, clearly illustrates that it is a greater issue at higher energies. Loss of side-scatter equilibrium, which begins first at the deeper depths, results in R_{90} shifting toward the surface as field size decreases. As the field size gets even smaller, the maximum dose decreases; and when it is normalized to 100%, the relative dose at the surface, D_s, increases. In addition, the effects on the distal portion of the depth-dose curve are greater. The most clinically significant effect is the decrease in R_{90} with decreasing field size, which can require a greater energy than initially proposed for treatment using very small fields (<5 cm).

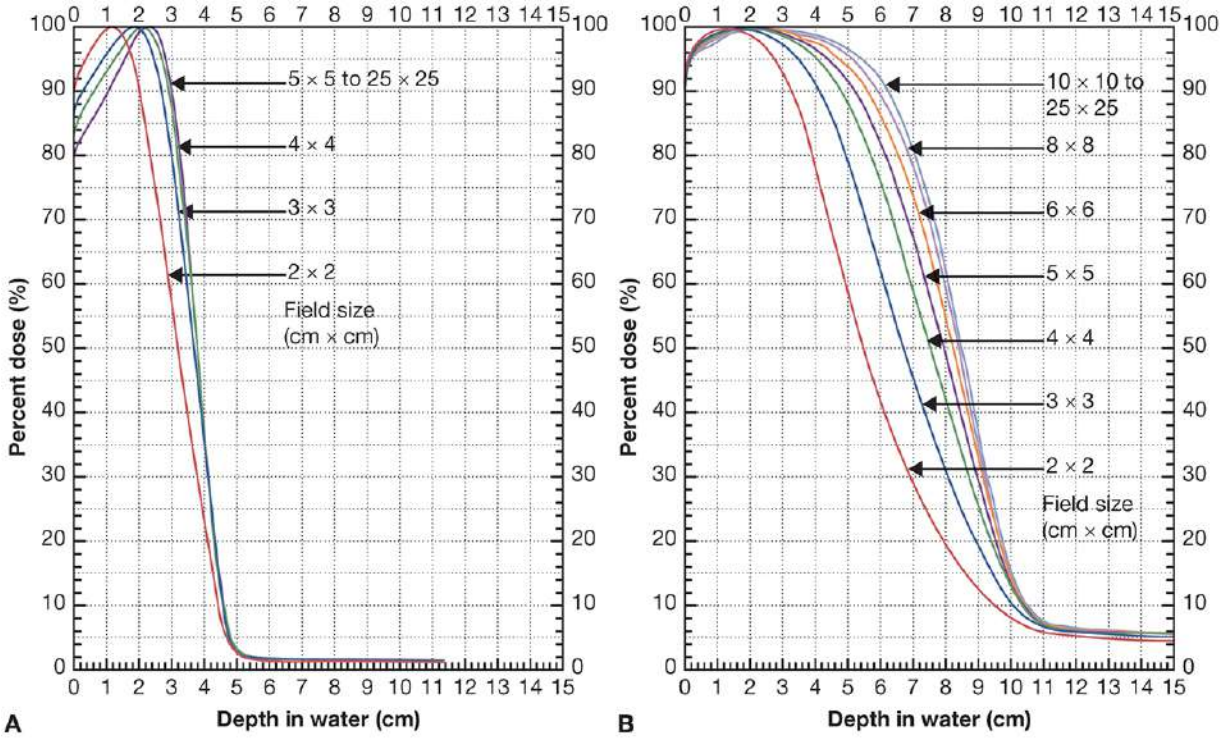


FIGURE 9.2 Field-size dependence of depth dose. Plot of percent dose versus depth for field sizes from 2 by 2 to 25 by 25 cm^2 for 9-MeV (A) and 20-MeV (B) beams on a Varian Clinac 2100C radiation therapy unit (source-to-surface distance = 100 cm). (Courtesy of Varian, Palo Alto, CA.)

Depth-dose variations with SSD are usually minimal. Differences in the depth dose resulting from the inverse square effect are small because electrons do not penetrate that deep (≤6 cm in the therapeutic region) and because the significant growth of penumbra width with SSD restricts the SSD in clinical practice to typically 115 cm or less. The primary effect of an inverse square is that R_{90} penetrates a few millimeters deeper at extended SSD at the higher energies, as illustrated in Figure 9.3. In relatively few cases (eg, when the electron beam has a large component of collimator-scattered electrons), the variation in depth dose with SSD can become more significant. In such cases, the collimator-scattered electrons are scattered out of the beam, resulting in a depth dose with a lower D_s and greater R_{90}.[31]

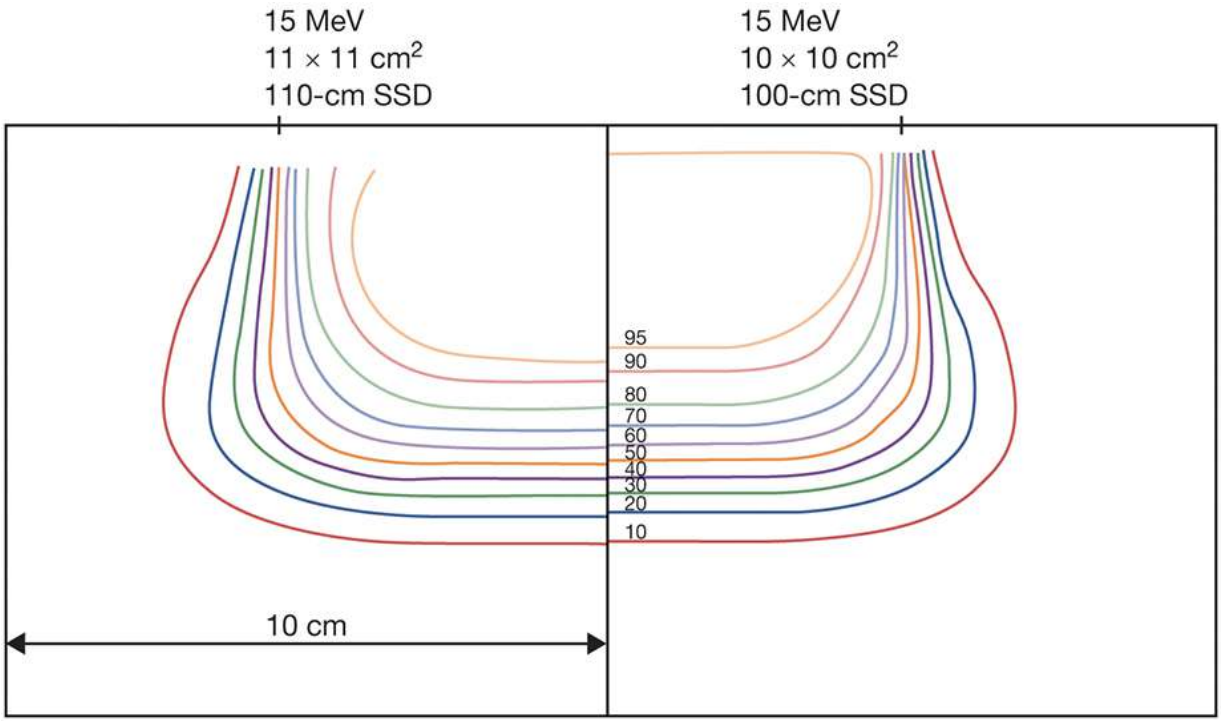


FIGURE 9.3 Source-to-surface distance (SSD) dependence of depth dose. Comparison of isodose plots for 15-MeV beam, 10 by 10 cm^2 at 100-cm SSD with 11- by 11-cm^2 field at 110-cm SSD. (From Hogstrom KR. Clinical electron-beam dosimetry: basic dosimetry data. In: Purdy JA, ed. *Advances in Radiation Oncology Physics: Dosimetry, Treatment Planning, and Brachytherapy*. American Institute of Physics; 1992:390-429. Copyright © 1992 by American Association of Physicists in Medicine. Reprinted by permission.)

For rectangular fields, Hogstrom[32] derived and others have confirmed[31,33] that the percentage of depth dose can be calculated by taking the geometric mean of the percentage of depth doses for a square field of length dimension (L) and one of width dimension (W). That is,

$$D\,(d; L \times W) = \sqrt{\%D\,(d; L \times L) \cdot \%D\,(d; W \times W)} \qquad (1)$$

If the square field percentage of depth-dose curves does not have a common R_{100}, then the result of Equation 1 must be normalized such that its maximum equals 100%. This method is referred to as the square-root method.

In some instances (eg, intraoperative, intraoral, or intravaginal cones), circular fields are used. In such cases, it is necessary to measure dose distributions, independent of those determined for square or rectangular fields.

Usually, a collimating insert is placed inside an electron applicator to form an irregular-shaped field, occasionally blocking the central axis. In this instance, the central-axis depth dose makes little sense, and the term *central-field depth dose* should be used, provided that the field has an axis of symmetry. In cases where the insert is irregular, the depth dose can be approximated using a rectangular-shaped field that approximates the irregular-shaped field.[34] In highly irregularly shaped fields, the dose distribution should be calculated using an appropriate dose algorithm in a three-dimensional (3D) treatment planning system. For very small fields, irregular or otherwise, it is highly recommended that PPD measurements be performed to properly determine prescriptive choices (ie, R_{90}).

Off-Axis Dose

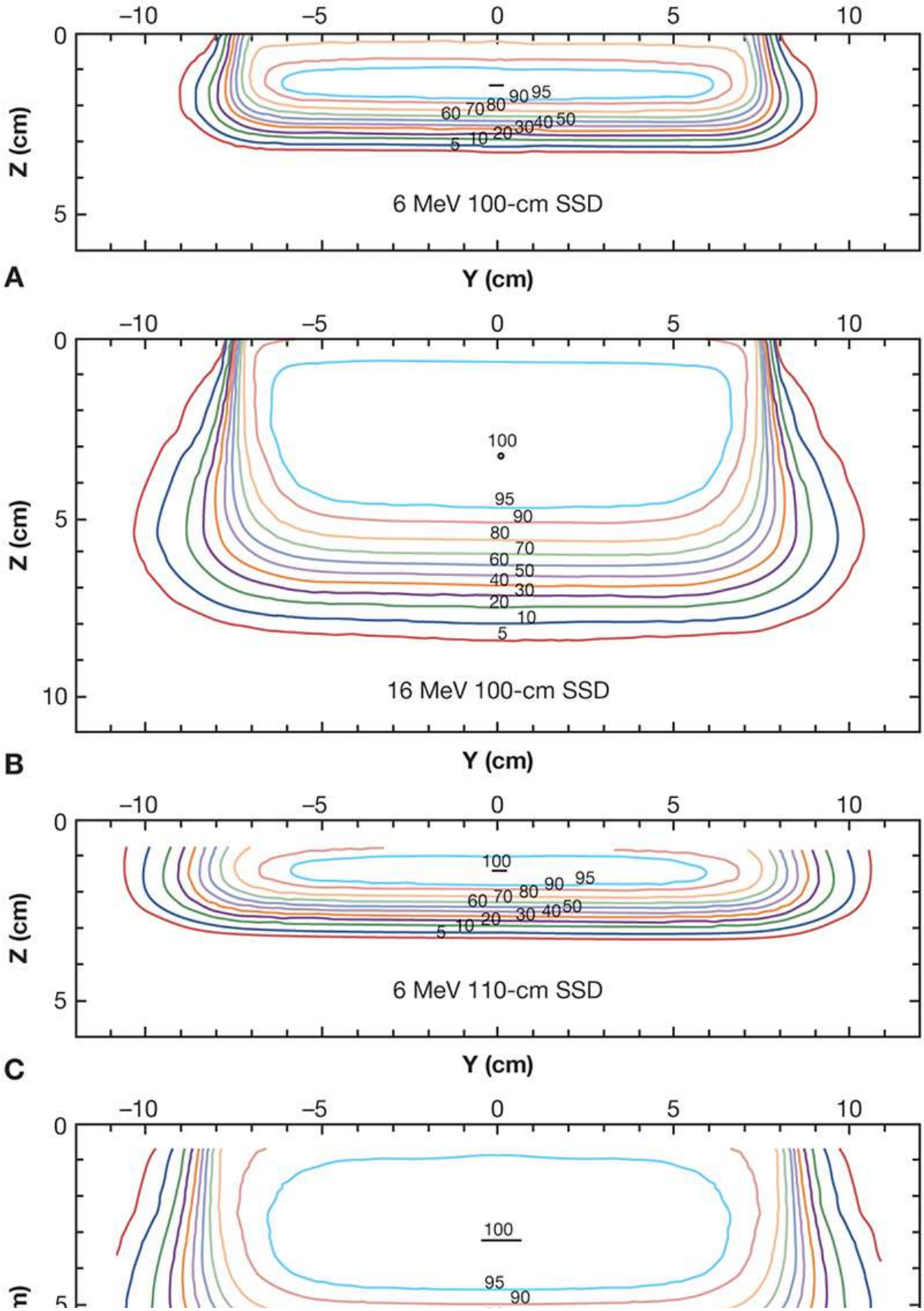
Dose profiles in the dimensions perpendicular to the central axis can be described by OARs. The OAR is defined as the ratio of dose at an off-axis position to that on the central axis at the same depth. The OARs measured in water are used to assess off-axis beam quality, which is characterized by flatness and symmetry in the uniform portion of the beam and by its falloff in the region of the penumbra (eg, 90%-10%, or 80%-20%).

Manufacturers should be able to provide electron beams with a symmetry specification of 2% for opposing points in the beam and a flatness specification of ±3% of the *central-axis value* along the major axes (±4% along diagonals). The American Association of Physicists in Medicine (AAPM) Task Group 25 recommended that flatness and symmetry should be evaluated along the major axes (lines containing the central axis and perpendicular to the collimator edges) and along the diagonal axes.[30] Task Group 25 also recommended that flatness and symmetry be evaluated at depths near the surface and therapeutic depth. Practically, this is performed at R_{100}.

Flatness and symmetry are evaluated inside the penumbra, which is usually ensured by setting the boundaries of evaluation 2 cm inside the

collimating edge (2√2 cm along diagonals). When physicist performs acceptance tests for a treatment machine, and during subsequent annual reviews, they use the AAPM Task Group 142, and the AAPM Medical Physics Practice Guideline 8.b[35] recommendations of 2% symmetry and 5% flatness.[36] This is usually performed for each energy with an average-size applicator but should be tested for each applicator during acceptance. Subsequently, the profiles acquired during acceptance should be reviewed monthly and be consistent to within 1% of the acceptance values.[36,37]

Penumbra of electron beams is predetermined by the design of the beam flattening system, the air gap between the final collimator and the scatter of electrons in water. The penumbra is a function of depth and is the root mean square addition of two penumbral components: one the result of the air gap and one the result of scatter in the water.[6] This dependence is complex but can be appreciated qualitatively by the illustration in Figure 9.4, which compares isodose plots for normal (100 cm) and extended (110 cm) SSD at 6 and 16 MeV, respectively. These data show that penumbra grows in a nonlinear manner with depth, that air gap is more significant at the lower energies, and that scatter in water dominates at the higher energies. Fortunately, the complex dependence of penumbra can be modeled accurately in treatment planning systems using the PBA or more sophisticated dose algorithms.[29,32,34,38]


A
6 MeV 100-cm SSD
Z (cm)
Y (cm)
100
95
90
80
70
60
50
40
30
20
10
5
B
16 MeV 100-cm SSD
Z (cm)
Y (cm)
C
6 MeV 110-cm SSD
Z (cm)
Y (cm)

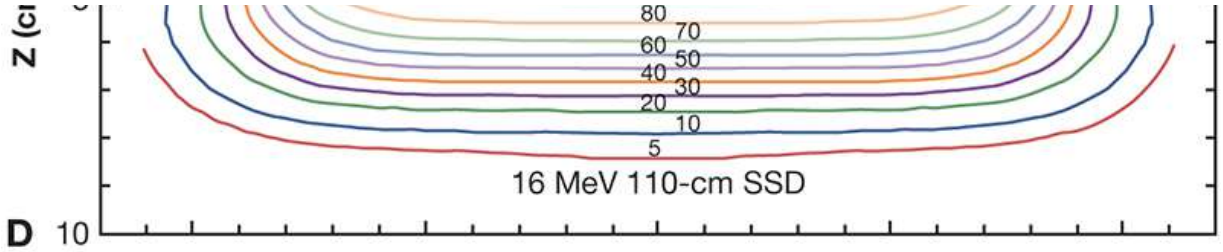
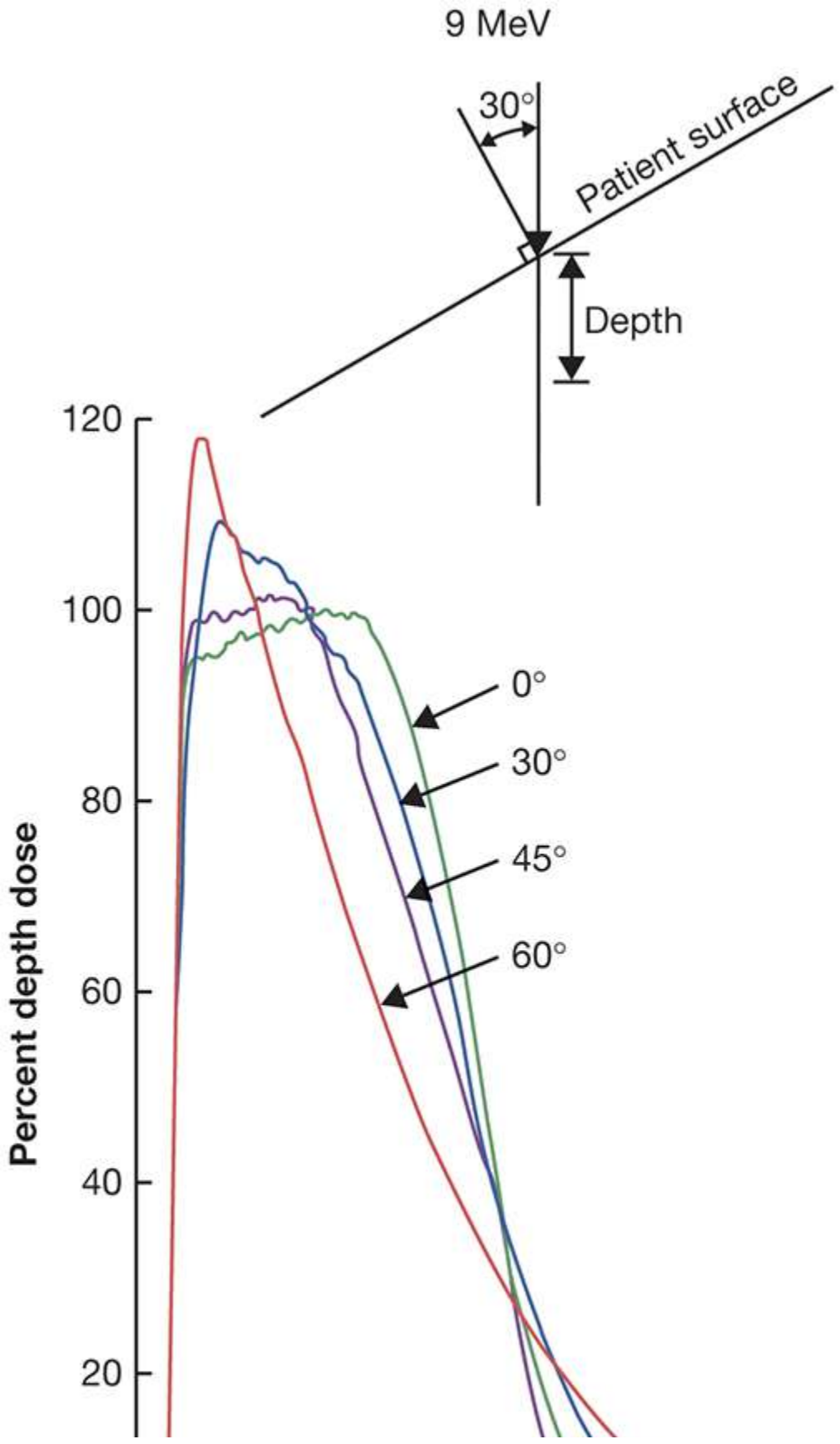


FIGURE 9.4 Variation of dose distribution with energy and source-to-surface distance (SSD). Isodose plots (5%-100%) in water for open 15- by 15-cm^2 applicator and for 6-MeV, 100-cm SSD (A); 16-MeV, 100-cm SSD (B); 6-MeV, 110-cm SSD (C); and 16-MeV, 110-cm SSD (D) (Varian Clinac 2100C). (Courtesy of Varian, Palo Alto, CA.)

Isodose Plots

Combining depth dose with OARs results in the 3D dose distribution, and the properties of the 3D dose distribution can be appreciated by viewing 2D isodose contour plots in a plane containing the central axis and a major axis. Examples of these plots for a 15- by 15-cm^2 field are illustrated in Figure 9.5. As field width decreases or increases, the penumbra shape changes insignificantly because it is most significantly influenced by air gaps and collimation type. Collimating on the skin, for example, reduces penumbra significantly.


9 MeV
30°
Patient surface
Depth
120
100
80
60
40
20
Percent depth dose
0°
30°
45°
60°

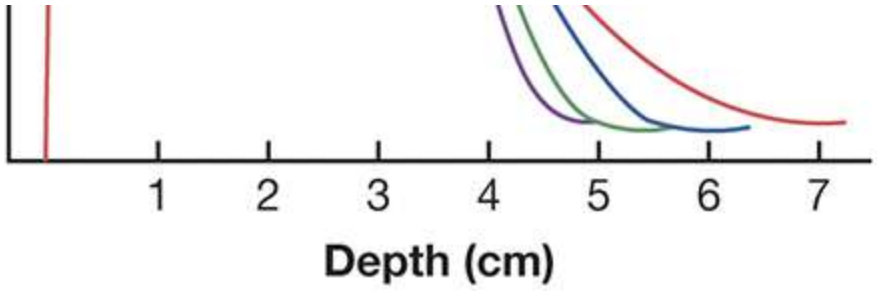


FIGURE 9.5 Effect of angle of incidence on depth dose. Dose versus depth for a 9-MeV beam incident on water angled 0° to 60° from the normal. (From Ekstrand KE, Dixon RL. The problem of obliquely incident beams in electron-beam treatment planning. *Med Phys*. 1982;9[2]:276-278. Copyright © 1982 American Association of Physicists in Medicine. Reprinted with permission of John Wiley & Sons, Inc.)

Data required for isodose contours are acquired for an inclusive spread of field sizes at each energy. 2D isodose contour plots and data are useful for manual treatment planning, input data required by dose algorithms, verification of dose calculated by a treatment planning system, and quality assurance standards.[29,30,39]

DOSE IN THE HETEROGENEOUS PATIENT

For most clinical circumstances, the ideal irradiation condition is for the electron beam to be incidentally normal to a flat surface with underlying homogeneous soft tissues. The dose distribution for this condition, similar to that for a water phantom described previously, contains a reasonably uniform dose inside the penumbra from the surface to R_{90}, and it has the sharpest possible falloff laterally and with depth. As the angle of incidence deviates from normal, as the surface becomes irregular, and as internal heterogeneous tissues (eg, air, lung, and bone) become present, the qualities of the dose distribution degrade.[40] Internal heterogeneities can change the depth of beam penetration as a result of differences in the rate of energy loss, which can result in PTV underdose and critical structure overdose. Both irregular surfaces and internal heterogeneities create changes in side-scatter equilibrium, producing volumes of increased dose (hot spots) and decreased dose (cold spots), potentially leading to an increased dose to critical structures and decreased dose to the PTV.[3,40] These perturbations can be reduced or eliminated by modifying the treatment technique.

Irregular Surfaces

Two geometries that illustrate the effects on the dose distribution caused by an irregular patient surface are the sloped skin surface and the stepped skin surface. Figure 9.5 illustrates changes in the depth-dose curve as a result of nonnormal incidence of an electron beam onto a flat surface. Compared with normal incidence, the nonnormal incident electron beam, central-axis, depth-dose curve shows an increased surface dose, an increased maximum dose, a decreased penetration of the therapeutic dose (R_{90}), and an increased range of penetration.[30,41] These changes can be clinically significant, particularly at angles of incidence >30° from the normal. Such conditions can occur when irradiating curved patient surfaces with large fields (eg, chest wall, limbs, neck, and scalp). In addition, it should be appreciated that the depth of R_{90} is specified along the central axis of the beam; and if the depth is taken perpendicular to the surface, then the depth is further reduced (approximately) by a factor cos (φ), where φ is the deviation of the incident angle from the normal.

Any time a sharp gradient (stepped surface) occurs on the patient's surface, side-scatter equilibrium will be lost, resulting in a cold spot beneath the proximal surface and a hot spot beneath the distal surface.[32,40,42,43] This can occur as a result of a sharp bolus edge, surgical defects, or within normal anatomy. For example, in the use of a uniform-thickness bolus that partially covers a field, a 90° step can result in hot or cold spots as great as 20%, as illustrated in Figure 9.6. In such a case, the bolus should be tapered as much as possible. The results of a 45° tapered bolus in Figure 9.6 show a reduction in the hot spot but more significantly an increased coverage of the 90% isodose contour. The nose is a protrusion that creates a cold spot, often the location of the tumor.[5,33,40] The ear canal (Figure 9.7) and surgical voids, which are characterized by a depression in the patient's surface, can result in hot spots in excess of 50%, depending on void dimension and beam energy.[44,45] Such depressions normally should be filled with some type of bolus material. Normal anatomy contains many irregular surface depressions and protrusions (eg, the ear canal and the nose, respectively) and should be accounted for by accurate treatment planning.

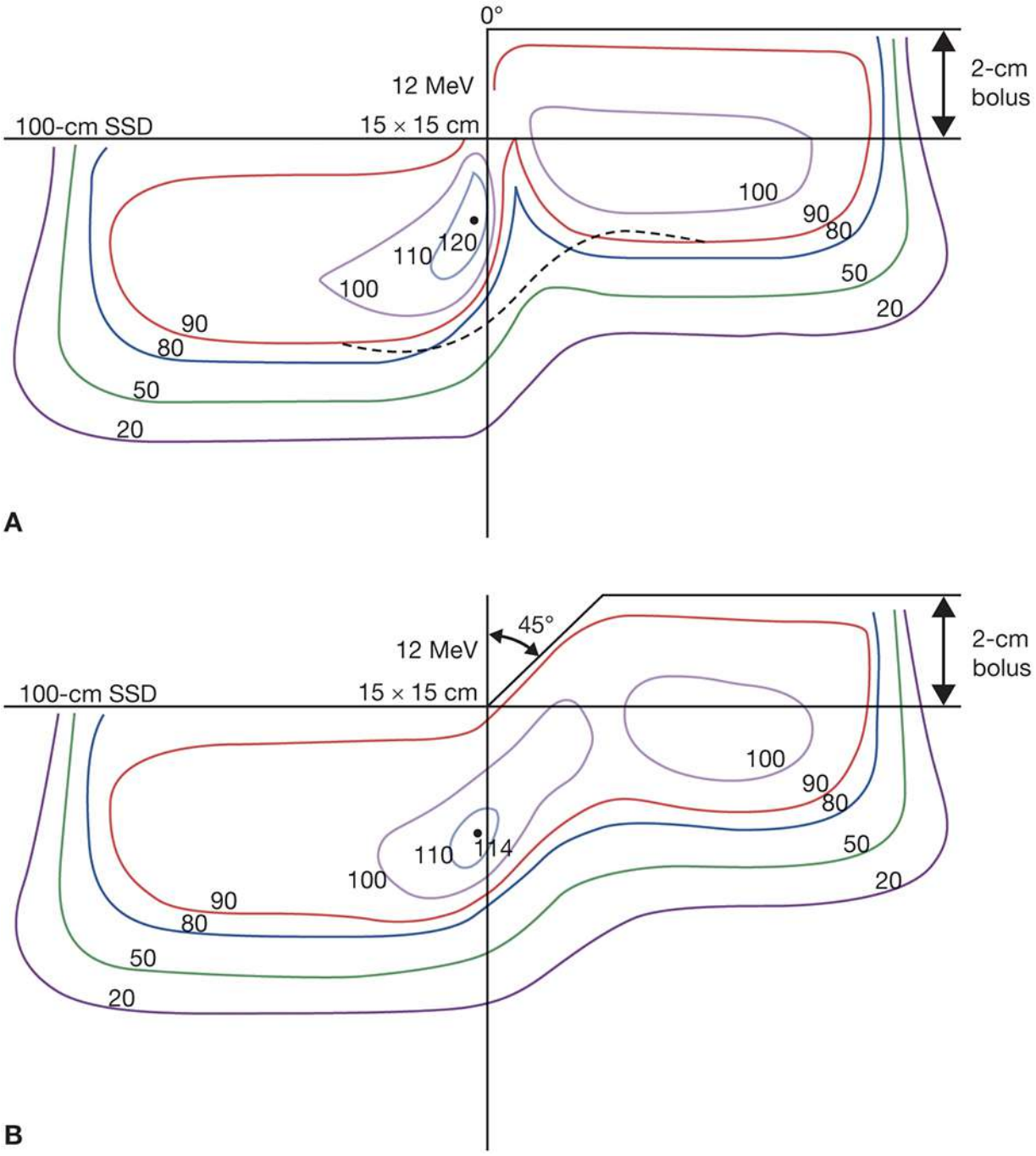


FIGURE 9.6 Effect of irregular patient surface on dose distribution. Plot of isodose contours for a 12-MeV, 15- by 15-cm^2 beam incident on water at 100-cm source-to-surface distance (SSD) having a stepped surface resulting from a 2-cm slab of bolus (A) and a beveled edge (45°) on the stepped surface (B). The dashed line in the top figure shows the location of the 90% isodose contour in the bottom one. (From Hogstrom KR. Treatment planning in electron-beam therapy. In: Vaeth JM, Meyer JL, eds. *The Role of High Energy Electrons in the Treatment of Cancer: 25th Annual San Francisco Cancer Symposium, February 1990*. S. Karger AG; 1991:30-52. Copyright © 1991 S. Karger AG, Basel, Switzerland. Reprinted by permission.)

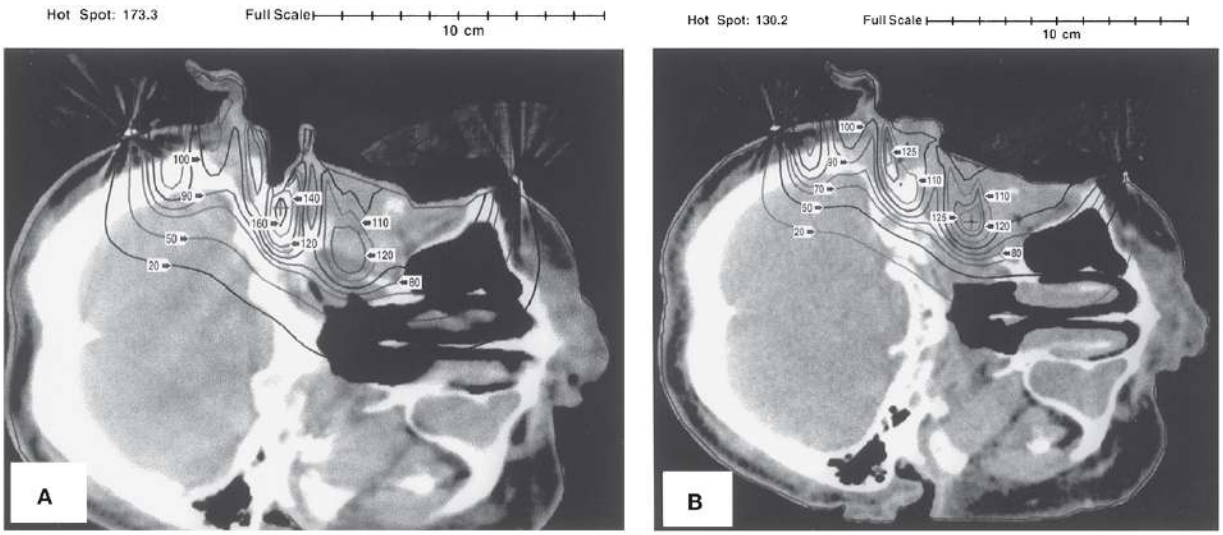


FIGURE 9.7 Impact of irregular surface anatomy on dose distribution. A 15-MeV electron beam irradiates the left side of a patient treated for dermal squamous carcinoma with perineural invasion. A beeswax bolus protects the posterior cranial fossa and the maxillary sinus. Isodose contours, expressed as a percentage of a given dose, show how the ear canal results in an unacceptable hot spot of 160% to the middle ear (A) and how filling the ear canal with bolus (saline solution) eliminates that hot spot (B). The residual hot spot of 125% is a result of the external ear. (Reprinted from Morrison WH, Wong PF, Starkschall G, et al. Water bolus for electron irradiation of the ear canal. *Int J Radiat Oncol Biol Phys*. 1995;33[2]:479-483. Copyright © 1995. With permission of Elsevier.)

Air Cavities

The influence of an internal air cavity is illustrated in Figure 9.8, which compares isodose contours beneath an air cavity to those without the air cavity. Results show that (a) the isodose contours in the shadow of air are shifted distally, (b) the dose beneath the air cavity increases as a result of loss of side-scatter equilibrium, and (c) the influence of the air increases laterally with depth. Internal air cavities of clinical interest primarily occur in the treatment of the head and neck (eg, nasal passages, ethmoid sinuses, maxillary sinuses, larynx, and mastoids).[32,40]

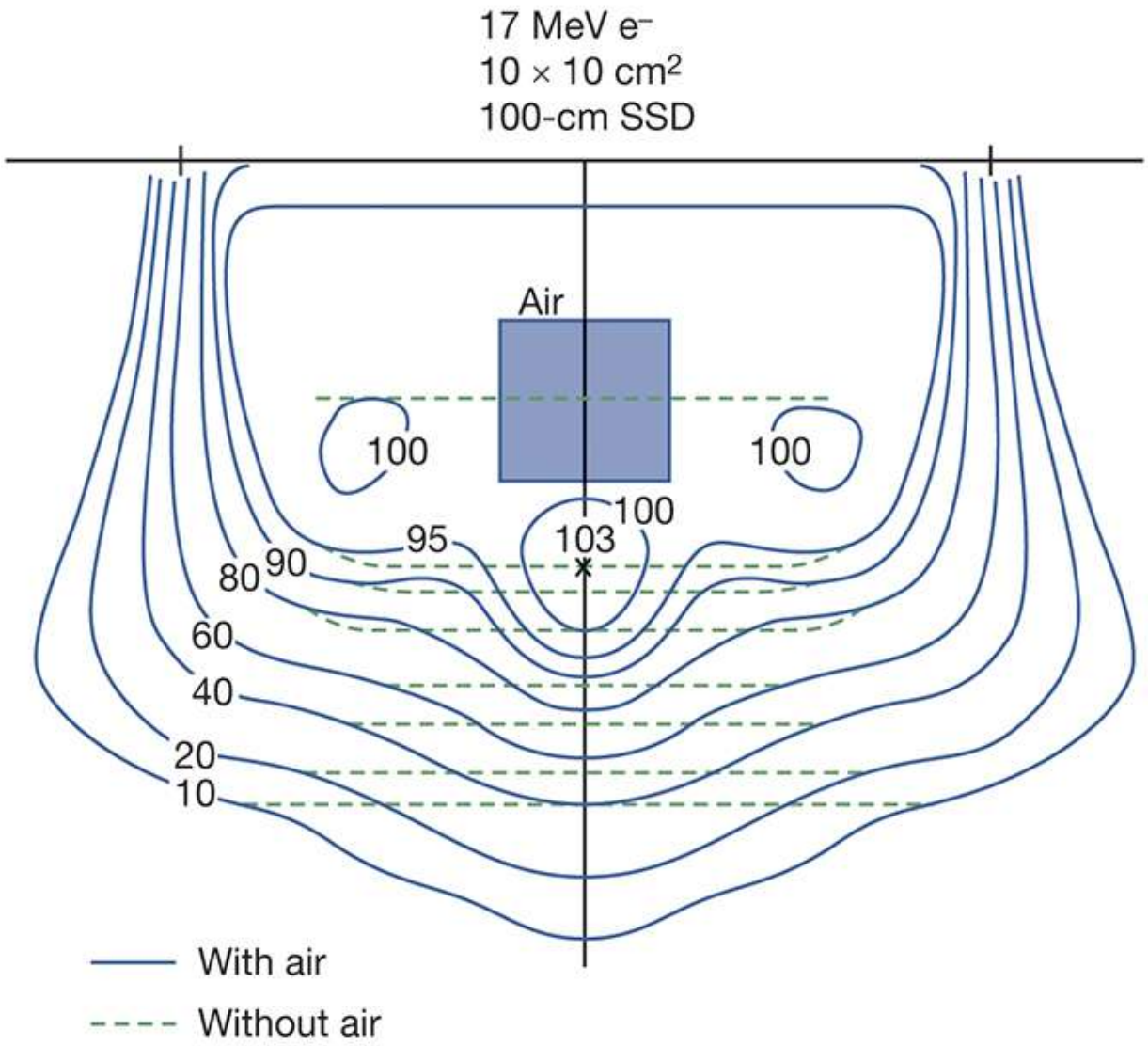


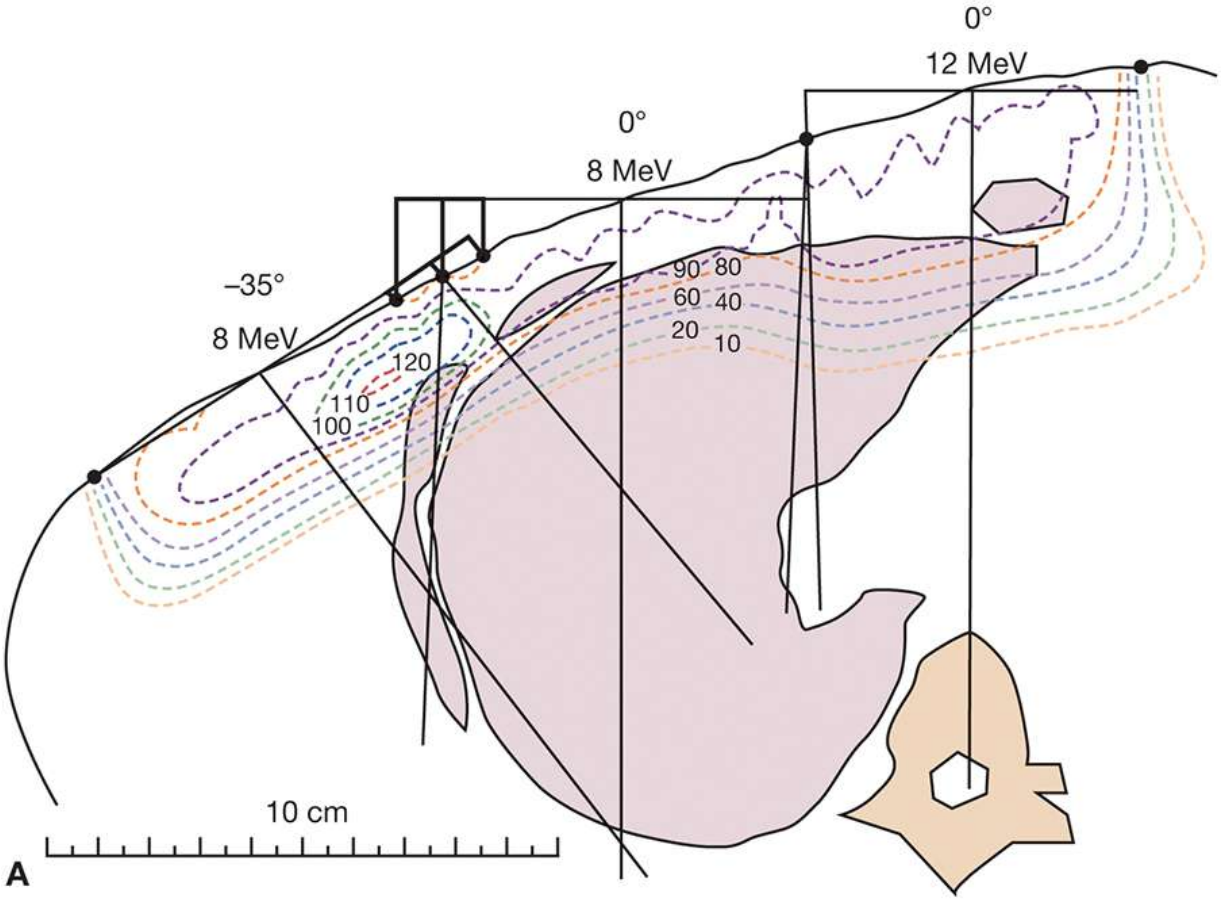
FIGURE 9.8 Effect of internal air cavity on underlying dose distribution. Dose calculated by the pencil-beam algorithm for a 2- by 2-cm^2 cylinder of air located 2 cm below the surface in water is compared to that in its absence. SSD, source-to-surface distance. (From Hogstrom KR. Dosimetry of electron heterogeneities. In: Wright AE, Boyer AL, eds. *Advances in Radiation Therapy Treatment Planning*. American Institute of Physics; 1983:223-243. Copyright © 1983 by American Association of Physicists in Medicine. Reprinted by permission.)

Another significant effect is the reduction in dose in unit density tissue lateral to an air cavity. Electrons scattering from the unit density tissue into the air are not replaced because air is unable to scatter an equal amount back into the unit density tissue. Frequently, nose tumors can spread into

the septum, in which case bolus should be used to eliminate or reduce underdosing.

Lung

In the lung, electrons can penetrate 3 to 4 times farther than in the unit density tissue. This is demonstrated in Figure 9.9, where isodose contours from a typical electron chest wall treatment are compared with those in which the lung is assumed unit density. Assuming a given dose of 50 Gy, the 40% isodose contour corresponds to 20 Gy, approximately the threshold for pneumonitis, if significant lung volume is irradiated. Ignoring the low density of the lung would grossly underestimate the volume of the lung receiving more than 20 Gy.[32]


0°
12 MeV
0°
8 MeV
–35°
8 MeV
90
80
60
40
20
10
120
110
100
10 cm
A

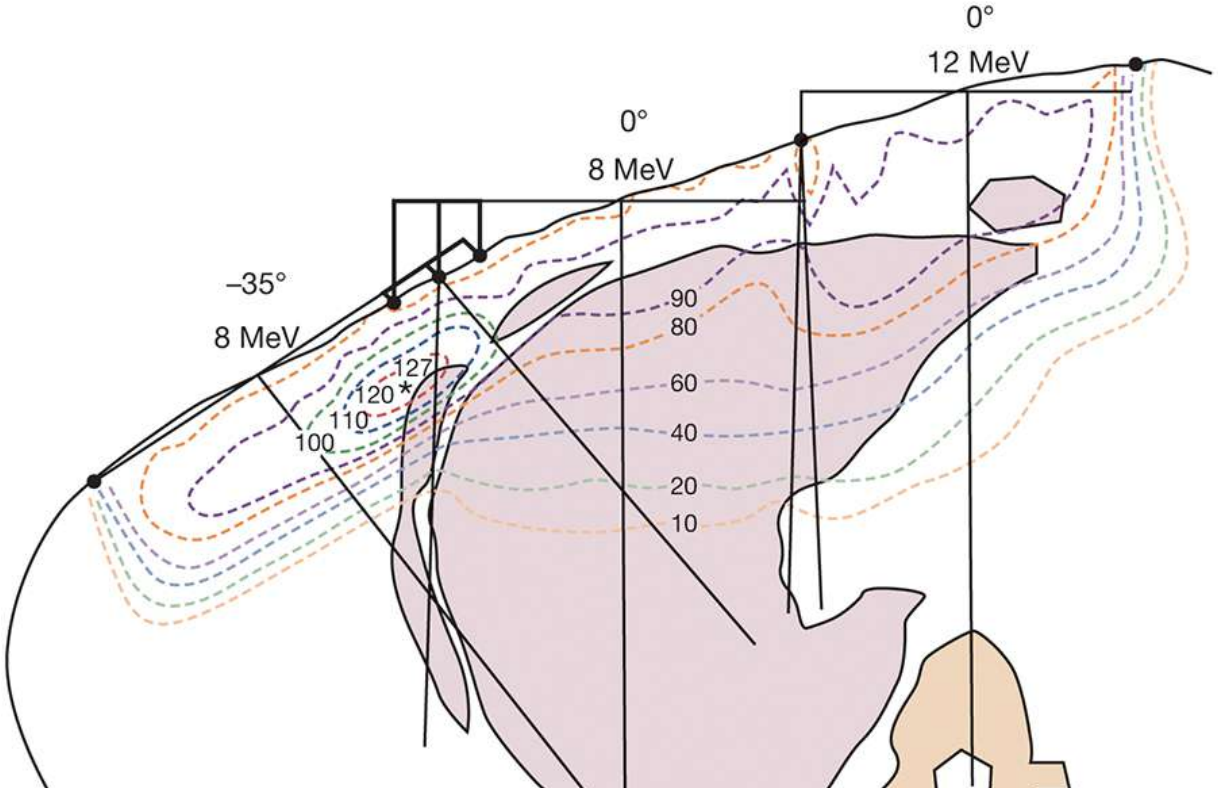

0°
12 MeV
0°
8 MeV
–35°
8 MeV
90
80
60
40
20
10
127
120
110
100

FIGURE 9.9 Effect of lung on dose distribution underlying chest wall. Comparison of dose calculated by the pencil-beam algorithm (PBA) for 8-MeV chest wall irradiation, assuming patient's water (A) and heterogeneous anatomy (B) based on computed tomography data.

This effect increases with energy. For example, increasing the beam energy from 9 to 12 MeV results in an additional 1.5 cm of penetration in water-like tissue (electrons lose energy at a rate of ~2 MeV per centimeter in water), and this corresponds to as much as 6.0 cm in the lung (assuming a lung physical density of 25%). Consider the patient whose chest wall thickness requires an energy of 10 MeV for treatment and that 12 MeV must be selected. This results in as much as 4 cm in depth of needless irradiation in the lung, unless 1 cm of bolus is used to effectively lower the energy incident on the patient to 10 MeV.

Care must be taken when irradiating targets where the lung is immediately distal, such as with entire chest wall postmastectomy irradiation.

Bone

Interactions of electrons with bone are complex and interesting. The influence of bone is illustrated in Figure 9.10, which compares isodose contours beneath the hard bone to those without the bone. The results show that:

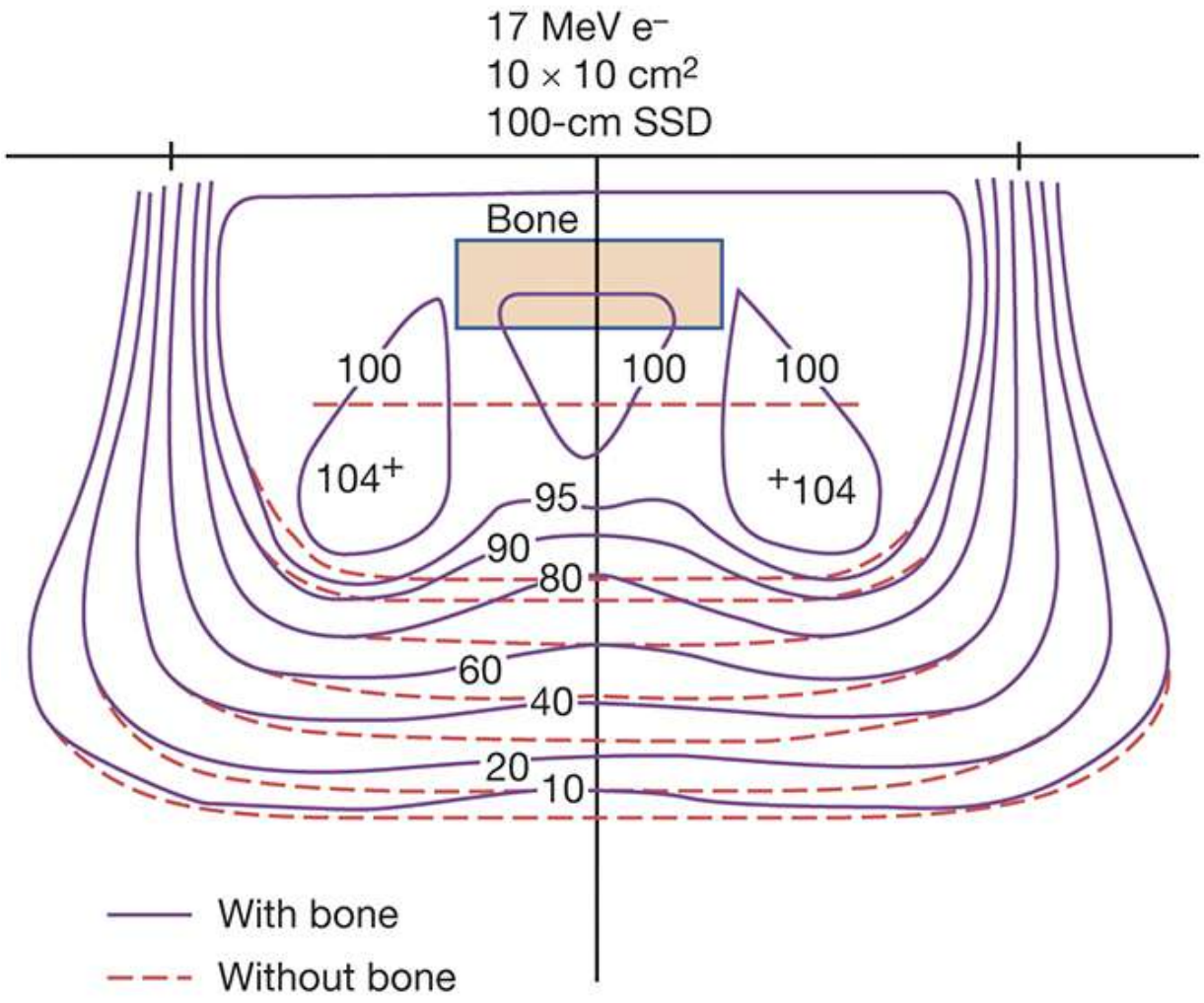


FIGURE 9.10 Effect of hard bone on underlying dose distribution. Dose calculated by the pencil-beam algorithm for a 3- by 1-cm^2 cylinder of hard bone substitute located 1 cm below the surface in water is compared to that in its absence. SSD, source-to-surface distance. (From Hogstrom KR. Dosimetry of electron heterogeneities. In: Wright AE, Boyer AL, eds. *Advances in Radiation Therapy Treatment Planning*. American Institute of Physics; 1983:223-243. Copyright © 1983 by American Association of Physicists in Medicine. Reprinted by permission.)

1. The isodose contours in the shadow of the bone are shifted proximally.
2. Dose outside (inside) the bone-water interface increases (decreases) by approximately 5% as a result of loss of side-scatter equilibrium.
3. The lateral dimension of the region having its dose perturbed by the bone increases with depth.

Living bones are not uniformly dense throughout their cross section, and in most cases, their edges are not parallel to the incident beam. Both differences decrease the influence of bone in generating inhomogeneity in the patient's dose distribution. Dense bones that significantly affect the dose distribution include the mandible, bones of the skull (eg, frontal bone and zygoma in orbit treatment or temporal bone in treatment of parotid), clavicles, and vertebral processes (eg, craniospinal irradiation).

One might ask, "What is the clinical significance of the increase in dose in or around bone because of increased scatter?" The maximum dose increase expected as a result of backscattered electrons is 5%, and the maximum dose increase expected inside the bone and in adjacent exit tissues is approximately 7%.[46] These increases represent maximum dose estimates because actual bones are not as dense through and through as are the bone substitute in which these data were taken. These estimates of the increased dose are not expected to be clinically significant. In fact, untoward effects in or around bone that can be attributed to dosimetry have not been observed in patients treated with electron-beam therapy.

DOSE PRESCRIPTION AND CALCULATION OF MONITOR UNITS

Dose Prescription

It is recommended that dose be prescribed to the given dose or 90% of the given dose. Intermediate or lower prescription (95%, 85%, 80%) can be prescribed if the energy (typically stepped in 3- to 4-MeV increments) choices are too coarse to maintain a single baseline prescription recipe. Given dose is defined as the maximum central-axis dose in a water phantom at the SSD of the patient for the energy, applicator, and field size identical to that used for patient treatment. If the field shape is irregular, then the field size is taken to be a rectangular field representative of the irregular field shape. The most representative rectangular field is not well defined; however, Hogstrom et al[38] have provided one methodology for determining its estimate.

It is recommended that the dose is prescribed to the given dose or a percentage of it and not to a point in the patient. It is quite possible that a dose prescription point in the patient could be in a region of increased or

decreased dose because of tissue heterogeneity or irregular surface, which could result in PTV underdose or overdose, respectively.

Calculation of Monitor Units

Monitor units can be determined by

$$\mathrm{MU} = \frac{D_{\text{prescribed}}/\%D}{O\,(E,C,L \times W,\mathrm{SSD})}, \tag{2}$$

where $D_{\text{prescribed}}$ is the prescribed dose, $\%D$ is the percentage of the given dose to which dose is prescribed (eg, 90%), and $O(E, C, L{\times}W, \mathrm{SSD})$ is the output (dose per monitor unit) for a beam of energy E, applicator C, field size $L{\times}W$, and SSD. To use this methodology, the medical physicist must measure dose output as a function of square field size and SSD for each energy-applicator combination at the time of commissioning the accelerator. Output for rectangular fields can be determined using the square-root method of Mills et al[14,47] and Shiu et al[31]:

$$\mathrm{O}\,(E,\ C,\ L \times W,\ \mathrm{SSD}) = [O\,(E,\ C,\ L \times L,\ \mathrm{SSD}) \cdot O\,(E,\ C,\ W \times W,\ \mathrm{SSD})]^{1/2} \tag{3}$$

Output for rectangular fields can also be determined using an equivalent square method[30,33,48,49]; however, Biggs et al[48] recommend limiting this method to an aspect ratio (L:W) of 2:1. The square-root method is not limited to the aspect ratio, and Shiu et al[31] have shown it to be more accurate. Figure 9.11 illustrates beam output data at 9 MeV for four common applicators used on the Varian Clinac 2100C (Varian Medical Systems, Palo Alto, CA) at 100-cm SSD.

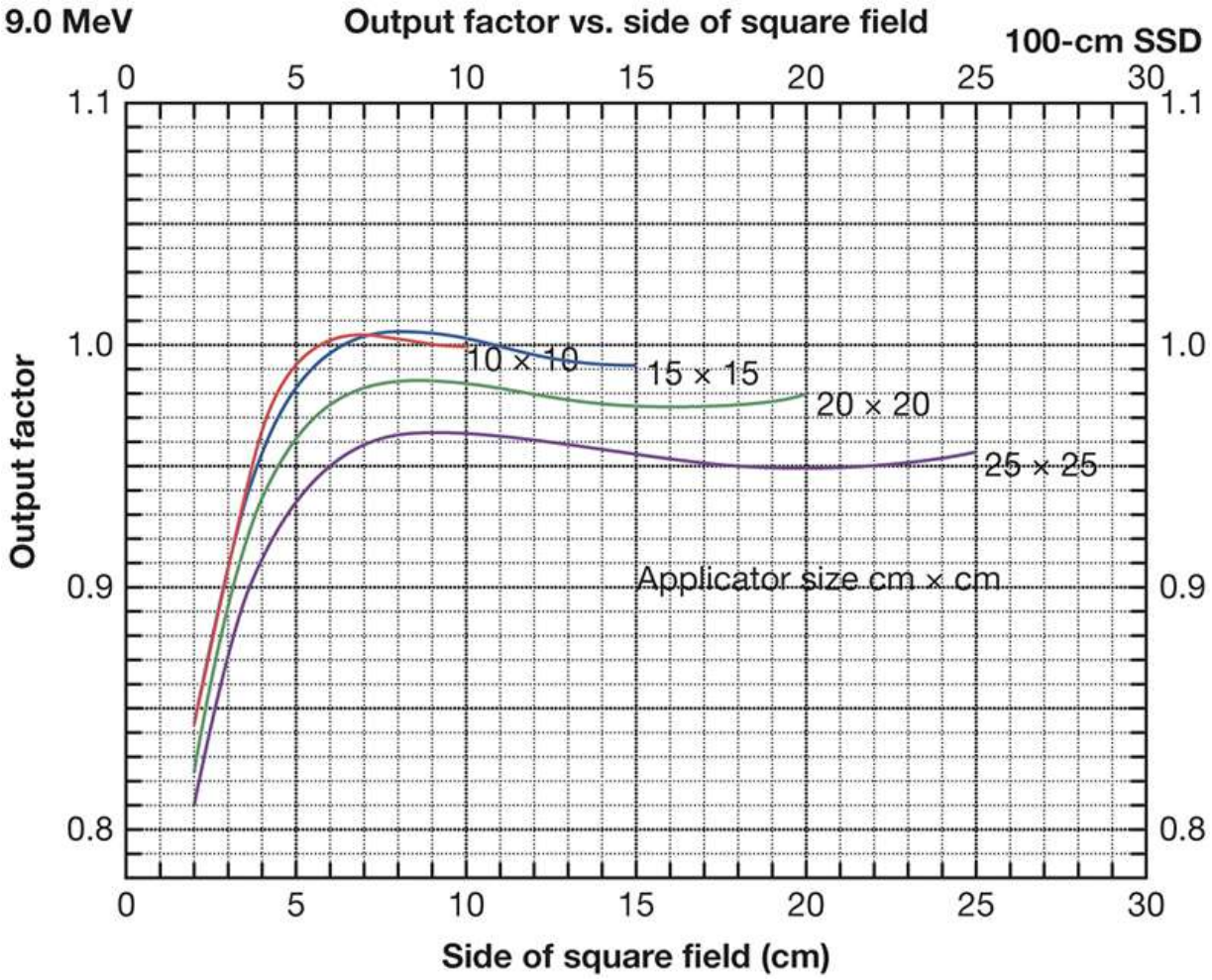


FIGURE 9.11 Field-size dependence of output (dose/monitor unit). Plot of output factor (cGy/MU) versus side of square field from 2 by 2 cm^2 to the open applicator for four applicators and for the 9-MeV beam of a Varian Clinac 2100C. SSD, source-to-surface distance. (Courtesy of Varian, Palo Alto, CA.)

Output at an extended SSD can be determined by either the air-gap method or the effective-source method.[30] The effective-source method is covered in detail by Khan.[49] The air-gap method has a sounder physical basis. Although both methods give similar answers, only the air-gap method is covered here.[33] Output at an extended SSD is given by the product of output at the nominal SSD (SSD_0), the air-gap factor (f_{air}), and an inverse square term as

$$O\,(E, C, L \times W, \mathrm{SSD}) = O\,(E, C, L \times W, \mathrm{SSD})\, f_{\mathrm{air}}\,(E, L \times W, \mathrm{SSD}) \times \frac{\mathrm{SSD}_o + R_{100}}{\mathrm{SSD} + R_{100}} \quad (4)$$

f_{air} is determined by measuring dose output for square fields at the extended SSD and then solving Equation 4. For rectangular fields, the air-gap factor is determined using the square-root method[31]:

$$f_{\mathrm{air}}(E, L \times W, \mathrm{SSD}) = \sqrt{f_{\mathrm{air}}(E, L \times L, \mathrm{SSD}) \cdot f_{\mathrm{air}}(E, W \times W, \mathrm{SSD})} \quad (5)$$

As f_{air} is assumed independent of an applicator, the dose output needs to be measured only for the smallest applicator that contains the square field size. Figure 9.12 plots the square field air-gap factors for the 9-MeV beam of the Varian Clinac 2100C for SSD from 100 to 120 cm. For a more detailed explanation of dose output and sample calculations of monitor units for electron beams, refer to Hogstrom et al[34] Another practical option is to fix incremented SSDs to be used clinically (ie, 100, 105, 110, 115 cm) and establish tabular outputs for each energy-applicator SSD combination.

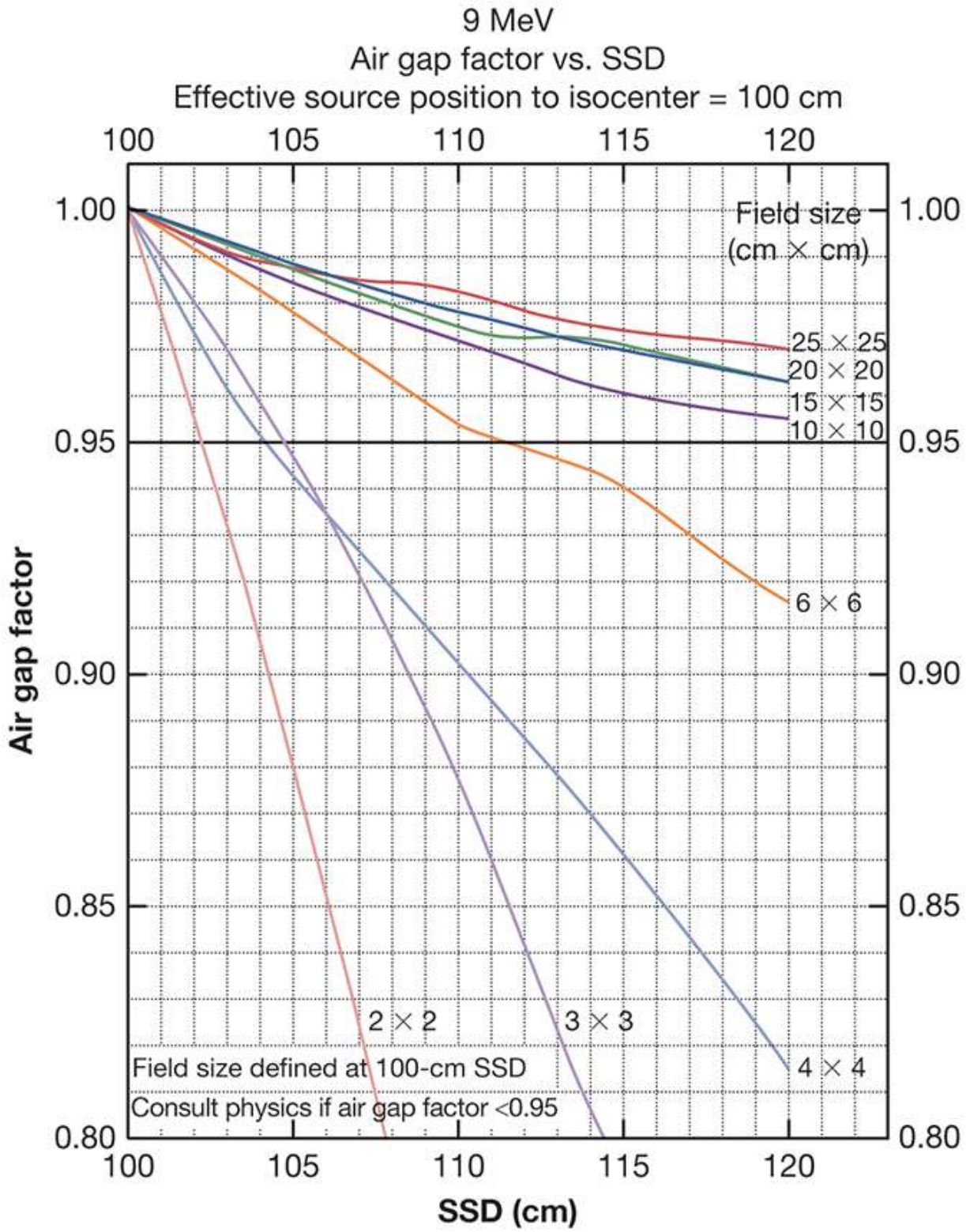


FIGURE 9.12 Dependence of air-gap factors on source-to-surface distance (SSD) and field size. Plot of f_{air} versus SSD for field sizes ranging from 2 by 2 to 25 by 25 cm^2 and for the 9-MeV beam (Varian Clinac 2100C). (Courtesy of Varian, Palo Alto, CA.)

CALCULATION OF DOSE IN PATIENT

Standards for Patient Dose Calculations

Sound treatment planning decisions require accurate dose calculation in the patient. Therefore, the following recommendations are made for electron-beam treatment planning. First, dose should be calculated in the full three dimensions to allow for evaluation of dose homogeneity in the PTV, coverage of the PTV by the 90% isodose contour, and dose to critical structures. Second, the dose algorithm should account for patient heterogeneity. Failure to properly account for patient heterogeneity can result in failure to appreciate dose heterogeneity, PTV underdose, or normal tissue overdose.[5,40,50] Third, the dose algorithm should be accurate; and for those conditions for which this is not the case, physicians and physicists should discuss the proper interpretation of the dose calculations.

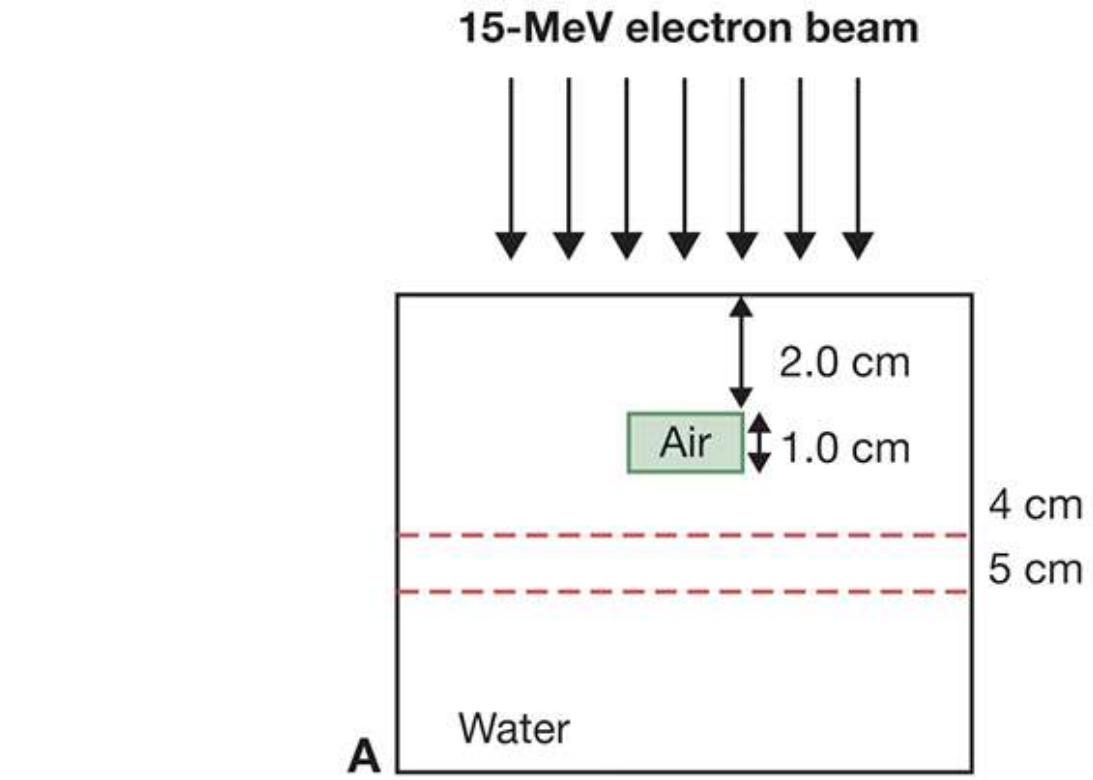
To expand on the final recommendation, a dose algorithm must meet certain criteria to be most effective in the clinic.[51] First, it should be accurate to within 4% in regions of low-dose gradients or within 2 mm in regions of high-dose gradient (eg, penumbra or depth-dose falloff region).[39,52] Second, the dose algorithm should be commissioned easily by a qualified medical physicist. Third, the accuracy of the dose algorithm should be well documented. Since 1981, the PBA has best met this requirement. Presently, several new, more accurate algorithms, both analytical and Monte Carlo based, are being implemented into commercial treatment planning systems and will replace or supplement the PBA in due time.[53] Regardless of the algorithm, it is the medical physicist's responsibility to commission the algorithm, to understand its accuracy, and to train medical dosimetrists and radiation oncologists in its use and limitations.

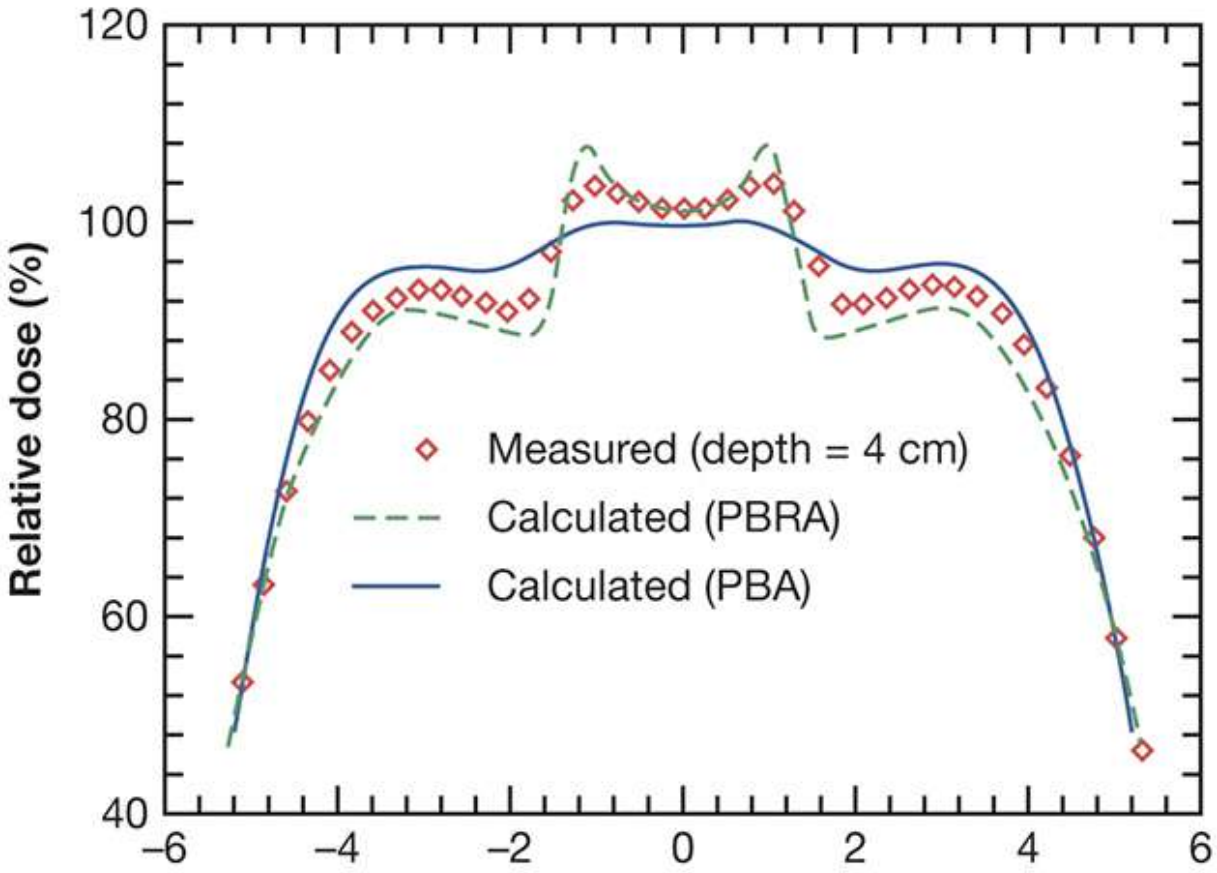
Dose Algorithms

As stated, the standard methodology for dose calculation in the patient has been the PBA. As computing power increased, it was possible to implement the algorithms into 3D format.[54] Detailed instructions for commissioning the dose algorithm and documentation of its accuracy have been published.[5,6,53] The PBA has been shown to be quite accurate in water at the standard and extended SSD, correctly predicting the changes in the

penumbra.[29,32,34] It is also quite accurate in predicting changes in dose resulting from oblique incidence and irregular surfaces.[5,51] Regarding internal heterogeneities, the PBA correctly predicts the penetration in lung and the growth of the penumbra width in lung[51]; however, it tends to underestimate the dose in lung near the mediastinum as a result of its central-axis approximation.[51] In bone, it correctly predicts the shortening of the dose penetration behind the bone, and it slightly underestimates (<5%) the magnitude of the *hot* and *cold* spots under the edge of a thick hard bone, such as the mandible.[5] The PBA does not predict the increased dose (<5%) resulting from backscatter at the proximal tissue-bone interface, nor does it predict the increased dose (>7%) in bone resulting from increased scatter. The PBA underestimates the hot and cold spots under the air-tissue interfaces.[5,51]

New dose algorithms that are accurate to 4% or better are becoming available in commercial treatment planning systems. Many of these algorithms have been reviewed by Hogstrom and Steadham.[51] One of these is the pencil-beam redefinition algorithm (PBRA), whose commissioning is similar to that of the conventional PBA, although its accuracy is significantly improved.[55-57] Figure 9.13 illustrates the improvement of the PBRA.


15-MeV electron beam
2.0 cm
Air
1.0 cm
4 cm
5 cm
Water
A


Relative dose (%)
120
100
80
60
40
–6
–4
–2
0
2
4
6
Measured (depth = 4 cm)
Calculated (PBRA)
Calculated (PBA)

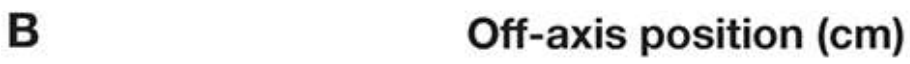


FIGURE 9.13 Evaluation of accuracy of dose algorithms below air cavity. A. Dose is measured distal to an internal air cavity. B. Measured dose profile at a depth of 4 cm is compared to that calculated by the pencil-beam algorithm (PBA) and the pencil-beam redefinition algorithm (PRBA). (From Shiu AS, Hogstrom KR. Pencil-beam redefinition algorithm for electron dose distributions. *Med Phys*. 1991;18[1]:718. Copyright © 1991 American Association of Physicists in Medicine. Reprinted by permission of John Wiley & Sons.)

Many of the newer algorithms are based on Monte Carlo methods, which allow them to be quite accurate.[56,58-62] Cygler et al[53] published a report on the first commercial system using Monte Carlo–based electron calculations, demonstrating excellent results. Ding et al[63] demonstrated outstanding results for a macro–Monte Carlo algorithm, along with a companion report showing superior results for Monte Carlo compared with PBA.[64]

TREATMENT PLANNING PRINCIPLES, TOOLS, AND METHODS

Electron therapy is usually restricted to a PTV that is within 6 cm distal from the patient's surface. Electrons may be used either alone or in conjunction with photon beams. In the case of the former, the objective of the treatment planner is usually to select the appropriate beam direction, energy, and field size to provide as uniform a dose as possible to the PTV while delivering a minimal dose to normal tissue and structures. To optimize dose homogeneity, the beam direction should be as close to normal incidence to the patient surface as practical. Once beam direction is specified, the selection of energy and field-size specification follows. Figure 9.14 compares the isodose contours in water with the beam edges and R_{90}. Electrons are unique in that the uniform region of dose lies inside the 90% isodose contour. Dose outside the 90% isodose contour falls off rapidly. However, the patient's anatomy can differ significantly from water so that the effects resulting from patient heterogeneity make the resulting treatment plan unacceptable, according to the original prescription. In addition, the PTV can be at a variable depth beneath the surface so that a single-beam energy is inadequate. The treatment plan can be improved by utilization of special treatment aids, such as skin or internal collimation, bolus, field abutment, or other special techniques.

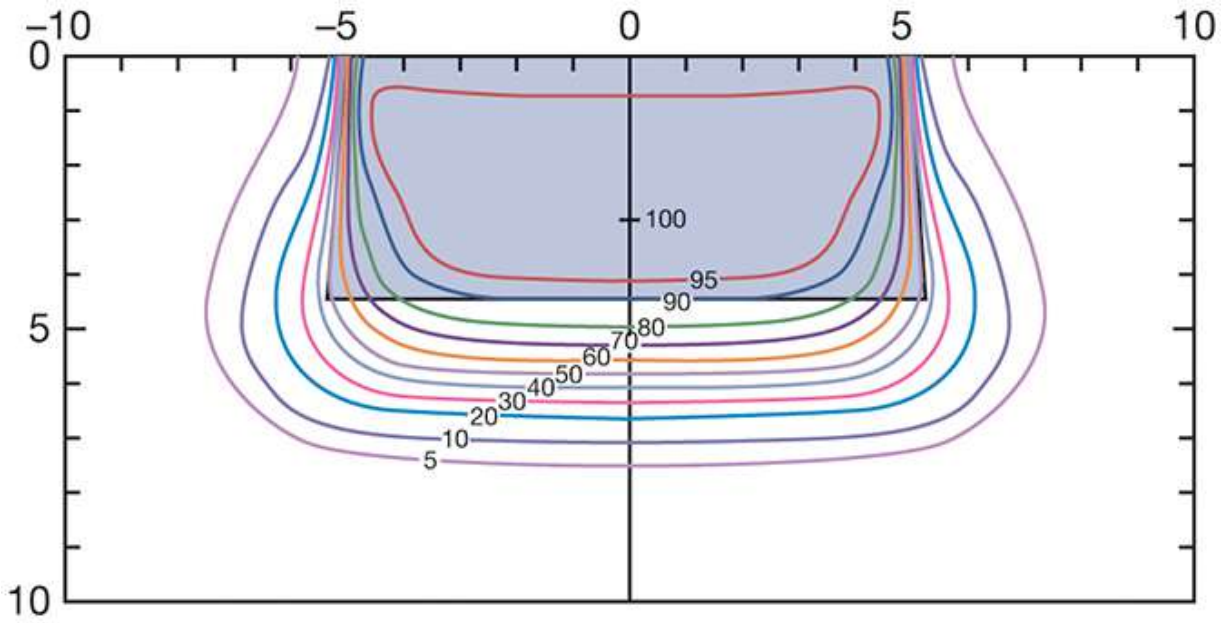


FIGURE 9.14 Plot of isodose curves for a 15-MeV, 10- by 10-cm^2 electron beam in water (source-to-surface distance = 100 cm). Note the shape of the 90% isodose contour with respect to the shaded area, which is framed by the diverging field edges and the R_{90} depth.

Selection of Energy

The energy of the incident electron beam should be selected so that the distal surface of the 90% (of the given dose) dose surface encompasses the PTV and that critical structures lie beyond the maximum penetration of the electrons or at an acceptable dose level. For planning purposes, a general rule is the following:

$$E_{p,0}\ (\text{MeV}) \sim 3.3 \cdot R_{90}\ (\text{cm}), \tag{6}$$

where $E_{p,0}$ is the most probable incident electron energy in MeV. The energy should be selected such that R_{90} just exceeds the maximum depth of the PTV. This approximation is true in water for field sizes large enough to have side-scatter equilibrium on the central axis. For small field sizes that do not have side-scatter equilibrium, R_{90} will be less; thus, a higher energy might be required. As well, heterogeneous tissue (eg, bone or air) can affect the penetration, requiring greater or lesser energy, respectively.

Similarly, for planning purposes, a general rule is the following:

$$E_{p,0}\ (\text{MeV}) = 2 \cdot R_p\ (\text{cm}), \tag{7}$$

where R_p is the practical range in centimeters of the electron beam.[32] The treatment planner can select an energy such that R_p is less than the minimal depth of a critical structure. This approximation has no field-size limitation; however, as before, heterogeneous tissue (eg, bone, lung, or air) can affect the penetration, allowing greater or lesser energy.

As an example of how to use these general rules, consider treating the posterior cervical nodes of the neck with electrons to spare the spinal cord because its dose is already near tolerance. If the maximum depth of the nodes is 3 cm and the minimum depth of the spinal cord is 6 cm, then Equations 6 and 7 indicate that the minimum energy to cover the PTV is 9.9 MeV and the maximum energy that protects the spinal cord is 12 MeV, respectively. Hence, beam energies in the range of 10 to 12 MeV are acceptable. In all cases, the energy of the beam should be confirmed by performing a 3D dose calculation for the planned treatment using a CT representation of the patient. Bolus may be strategically used to tune the beam penetration either globally or in discrete areas and ideally should be placed at the time of the CT.

Design of Electron Collimation

Electron collimation consists of multiple collimating components; however, the electron field shape is usually defined by an applicator's collimating insert and/or skin collimation. Custom electron collimators are constructed from lead or low melting point lead alloy (Lipowitz metal). The lead thickness in millimeters required to stop the primary electrons equals one-half the incident of the most probable energy of the electron beam in MeV.[29,30] To account for small variations in thickness resulting from the lead sheet manufacturing process, a 1-mm surplus can be added. That is,

$$t_{pb}\ (\text{mm}) = 0.5 \cdot E_{p,0}\ (\text{MeV}) + 1 \quad (8)$$

For example, an 18-MeV beam requires 10 mm of lead. Lipowitz metal is comprised mostly of lead along with bismuth that has a density of 20% less lead; therefore, its thickness should be increased by 20%. For example, an 18-MeV beam requires 12 mm of Lipowitz metal. Lipowitz metal collimating inserts are usually fabricated at a constant thickness—namely, that sufficient for the greatest energy on the treatment machine. For a machine whose maximum energy is 20 MeV, the Lipowitz metal thickness should be at least 13 mm.

Skin Collimation

The closer the field-defining collimator to the patient, the sharper the beam's penumbra; hence, skin collimation provides the sharpest possible penumbra. Because of the significant effort often required to fabricate skin collimation, its use is restricted to applications for which it has the greatest benefit, for example, (a) small-field (<4 cm) treatments providing maximal protection to adjacent critical structures, (b) sharpening penumbra (c) reducing penumbra when treating at an extended air gap, (d) reducing penumbra in electron arc therapy, and (e) where patient motion may be an issue. Proper use of skin collimation requires that it be in contact with the skin surface and that it extend sufficiently inwardly and outwardly to intercept the penumbra from upstream collimation.

Skin collimation absorption can be accomplished using lead sheets and normally is taken to be the minimum thickness necessary to shield the maximum. The maximum possible dose beneath the skin collimation occurs at the skin surface with no air gap between the two.[30,33] The transmitted dose, which is the result of bremsstrahlung photons from the incident beam and those generated by electrons stopping in the lead, is slightly greater than that with no lead present. It is recommended that a table of measured dose under the lead, as a function of lead thickness, is available for each beam energy.[29] As the air gap between the lead and the patient increases, the transmitted dose to the patient decreases. These values can be measured at the time of beam commissioning. If not, and for cases where precise

determination of dose beneath a block is critical, in vivo dosimetry (eg, thermoluminescent dosimetry) should be used. Other materials beyond lead have been developed for electron skin collimation. These include leaded vinyl foils and moldable systems like the Heat-Malleable Matrix Thermo shield system, whose production has been stopped, and the most recently developed gamma putty, composed of 91% bismuth. These materials work similarly to lead sheets; nonetheless, it is necessary to commission such materials before using them clinically and determine the minimum thickness necessary to minimize electron transmission.[65-67]

In designing the shape of the aperture of a collimating insert, due consideration is made for the penumbra. Typically, there is approximately a 1-cm margin between the projected edge of the collimator and the outer boundary of target volume when both are projected to the isocenter. This margin varies with energy, depth, and air gap; and it only can be appreciated by utilization of isodose curves (see Figures 9.4 and 9.14). Again, the adequacy of the margin between the aperture and PTV should be confirmed by performing 3D dose calculations using CT images.

The utility of skin collimation for small-field treatments is illustrated in Figure 9.15. A 6-MeV, 3- by 3-cm^2 field with a 10-cm air gap (collimator to surface) is essentially all penumbra, resulting in an unsatisfactory dose distribution. However, by opening the collimator to 6- by 6-cm^2 and then forming the 3- by 3-cm^2 field using skin collimation, the dose distribution becomes clinically satisfactory. This application is used for the treatment of the eyelid, nose, and other small target volumes.

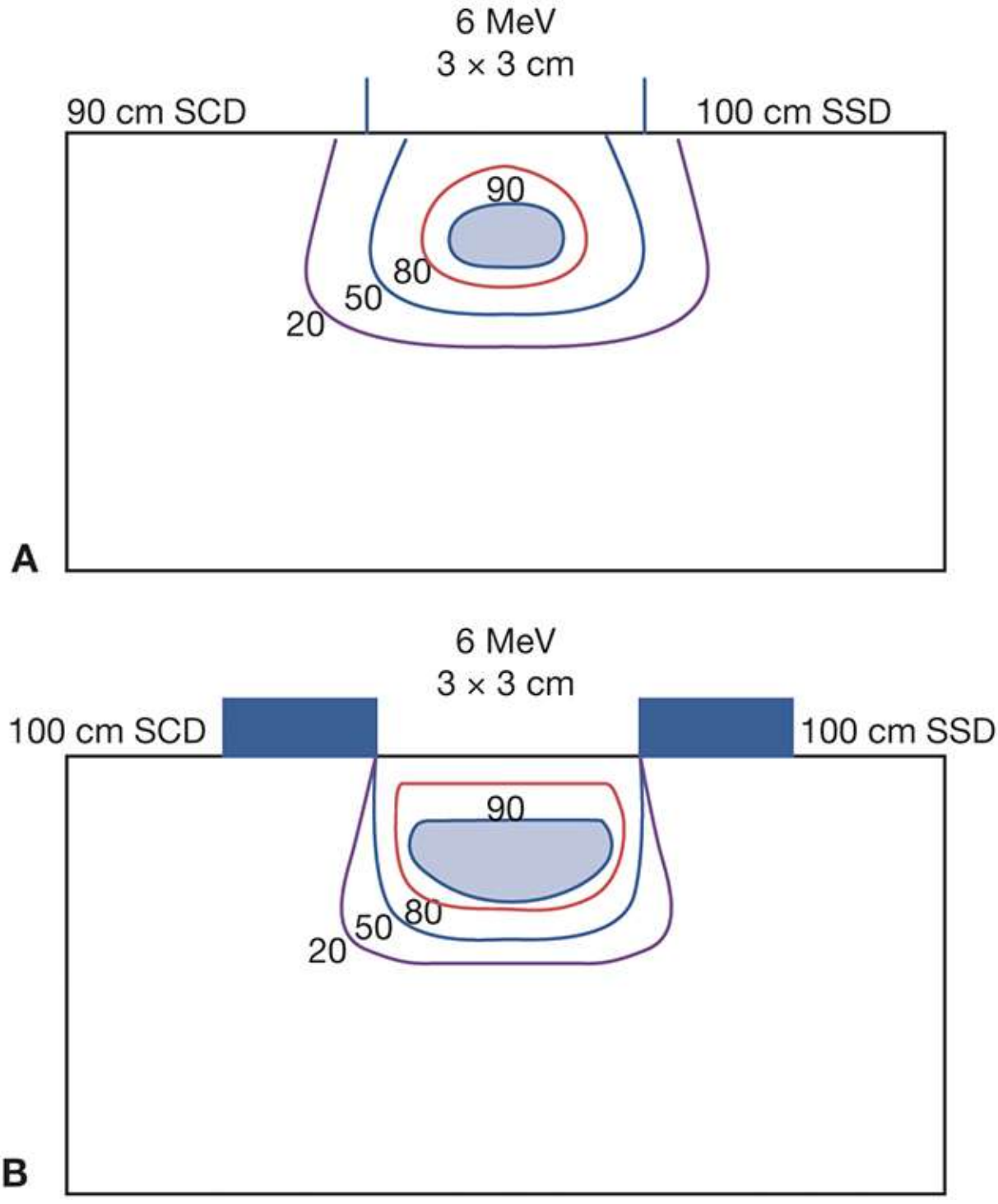


FIGURE 9.15 Impact of skin collimation for small electron fields. Isodose plots are compared for results of a computer simulation of a 6-MeV electron beam in water for a 3- by 3-cm^2 field formed by an applicator insert 10 cm above the patient (A) and a 3- by 3-cm^2 field formed by collimation at the surface with a 6- by 6-cm^2 applicator insert 10 cm above the patient (B). SSD, source-to-surface distance. (From Hogstrom KR. Clinical electron-beam dosimetry: basic dosimetry data. In: Purdy JA, ed. *Advances in Radiation Oncology*

Physics: Dosimetry, Treatment Planning, and Brachytherapy. American Institute of Physics; 1992:390-429. Copyright © 1992 by American Association of Physicists in Medicine. Reprinted by permission.)

In the presence of skin collimation, the depth dose is approximated by that for the field size on the skin surface (ie, that defined by the skin collimator). In contrast, the dose output is approximated by that for the field-size incident on the skin collimation (ie, that defined by the applicator cutout). For the example in Figure 9.15, the depth dose is taken to be that of the 3- by 3-cm^2 field; the dose output is taken to be that of the 6- by 6-cm^2 field. This simple approximation slightly overestimates dose output, if the depths of maximum dose for the two field sizes differ. In such a case, the output of the larger field is multiplied by the depth-dose factor of the larger field at the depth of maximum dose of the smaller field.[34]

Multileaf Collimation

The use of existing photon multileaf collimators (MLCs) to modulate electron beams has been shown to be somewhat feasible, although a report by Klein et al[68] showed that an SSD of 70 cm was necessary to provide clinical acceptable fields using the photon MLC. This is because of the dispersion of the electrons in air. They performed a feasibility study of using existing photon MLC to modulate electron beams, which was shown to be somewhat feasible. An important aspect from that work demonstrated that when using existing photon MLC to produce narrow electron-beam segments, the large penumbra generated could be an advantage in terms of beam matching.

The other possibility is not to use the existing photon MLC but rather to have a tertiary electron MLC system that is closer to the patient, thereby narrowing the penumbra that is produced when the MLC is far from the patient. Lee et al[69] found that replacing air with helium in the treatment head made a significant impact in the predicted dose distributions. Karlsson et al[70] demonstrated that penumbra, effective-source position, field shape, and matching could be optimized by replacing air with helium in the treatment head below the MLC leaves and by shifting the position of the scattering foils, monitor chamber, and MLC position.

Bolus

Bolus is an essential tool for the delivery of optimal electron radiation therapy. Electron bolus is defined as water or near-water equivalent material that normally is placed in direct contact with the patient's skin surface, close to the patient's skin surface, or inside a body cavity. This material is designed to provide extra scattering or energy degradation of the electron beam. Its purpose is usually to shape the dose distribution to conform to the target volume or to provide a more uniform dose inside the target volume.[29,32] More specifically, electron bolus has three primary applications:

- To shape the coverage of the treatment volume in the depth direction to conform as closely as possible to the target volume while avoiding critical structures
- To increase dose to the patient's external surface
- To serve as a missing tissue compensator for surface irregularities and internal air cavities

In the second application, bolus is being used to either eliminate or decrease the adverse effects of patient heterogeneities on the dose distribution, which can result in a geographic miss at depth, dose nonuniformity within the target volume, and excessive dose to distal critical structures.[29,32]

Because dose is typically prescribed to 90% of the given dose, it is often desirable to increase surface dose to 90% or higher when treating with low-energy electrons. To accomplish this, a higher energy beam is selected and a uniformly thick bolus is placed on or near the skin surface. The surface dose of the higher energy electron beam is greater, and the bolus places the skin at a deeper depth, further increasing the surface dose. The energy-bolus thickness combination is selected to place R_{90} at the prescription depth while increasing the surface dose (D_s) to near 90%. To assist in usage of this technique, a table that allows selection of the optimal energy-bolus thickness combination is recommended. Table 9.2 illustrates a sample for the five electron-beam energies of a typical radiation therapy machine.

TABLE 9.2 VALUES OF SURFACE DOSE AND THERAPEUTIC DEPTH FOR VARIOUS ENERGY-BOLUS COMBINATIONS

Superflab Thickness (cm)	0.0	0.3	0.5	1.0	1.5	2.0
Energy: 6 MeV						
D_s (%)	72	79	83	93	100	—
R_{90} (cm)	2.0	1.7	1.5	1.0	0.5	—
Energy: 9 MeV						
D_s (%)	78	83	85	89	95	99
R_{90} (cm)	3.0	2.7	2.5	2.0	1.5	1.0
Energy: 12 MeV						
D_s (%)	83	88	89	91	94	96
R_{90} (cm)	4.0	3.7	3.5	3.0	2.5	2.0
Energy: 16 MeV						
D_s (%)	87	92	93	96	97	98
R_{90} (cm)	5.0	4.7	4.5	4.0	3.5	3.0
Energy: 20 MeV						
D_s (%)	91	96	97	98	99	100
R_{90} (cm)	6.1	5.8	5.6	5.1	4.6	4.1

Two bolus methods are used for this function. One places flexible sheet material (eg, Superflab) directly on the skin surface. Materials are approximately water equivalent and come in thickness increments of 0.3 to 4 cm. It is particularly useful for chest wall irradiation, for both fixed-beam and arced-beam therapies. In some treatments, the bolus is used for only a portion of the field, in which case care must be taken to ensure the edge of the bolus is tapered to reduce the magnitude of the hot or cold spot created by the surface irregularity (such as is seen in Figure 9.6).[29,32]

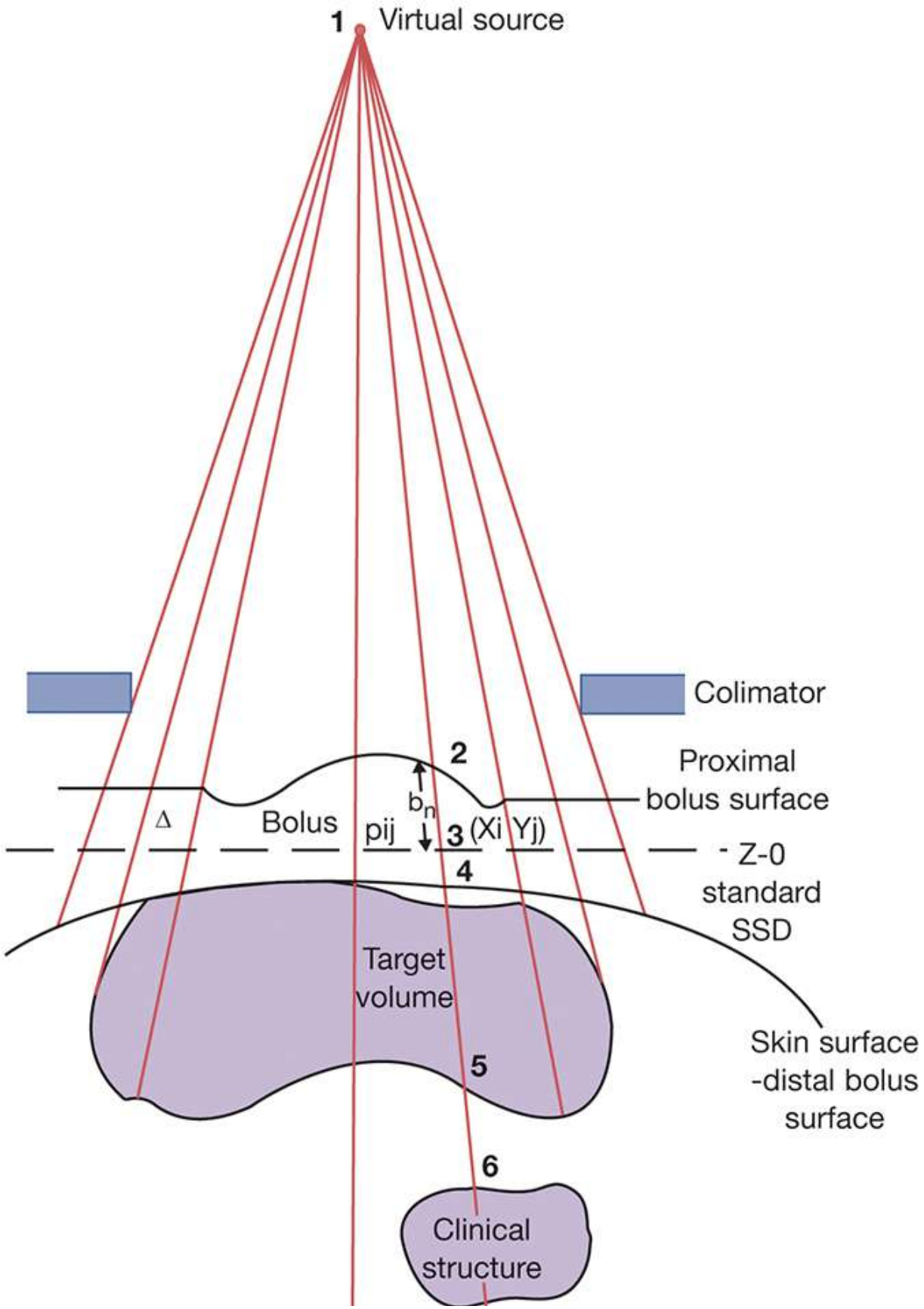
For highly irregular or sensitive skin surfaces, which are often encountered in head and neck or postsurgical irradiations, it is advantageous to have a rigid bolus sheet (often referred to as a scatter plate because it not only degrades the energy of the electron beam but also scatters the beam) close to but not necessarily in direct contact with the patient.[32] For such cases, standard thicknesses of polymethylmethacrylate (0.125-0.25 inches) are placed perpendicular to the beam. To restore a sharp penumbra, skin

collimation is usually recommended with use of the scatter-plate bolus method. Rules for using skin collimation with the bolus have been discussed by Hogstrom.[32] It is important that the bolus be in contact or close to the patient because too large of an air gap can create an exceedingly large penumbra.

Bolus is considered part of the beam; however, it also can be considered part of the patient, effectively shortening the SSD. For uniform bolus thickness (t), it is recommended to adjust the dose output for inverse square.[34] That is,

$$O_{\text{bolus}} = O \cdot \left[\frac{\text{SSD}+t+R_{100}}{\text{SSD}+R_{100}} \right]^2 \tag{9}$$

A more sophisticated use of bolus is to design custom bolus for the purpose of electron conformal therapy. In this application, the bolus is usually designed to conform the 90% isodose line to the PTV while minimizing dose to nearby critical structures and maintaining dose uniformity as much as possible within the 90% dose contour. Proper design of custom bolus requires the use of a 3D treatment planning system[71] that uses bolus design operators[72] and a 3D PBA.[54] The methodology of bolus design to optimize target coverage and critical structure searing is seen in Figure 9.16. Perkins et al[20] showed the use of custom bolus for chest wall irradiation in the cases of highly distorted anatomy and of a chest wall recurrence (Figure 9.17), and Kudchadker et al[73] have demonstrated its use in head and neck treatment. And Low et al[25] have shown its utilization for sparing spinal cord, lung, and kidney in the treatment of the paraspinal muscles.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volume
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Skin surface
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surface
6
Clinical
structure

FIGURE 9.16 Schematic representation of the patient contour, target volume, and compensating bolus designed to optimize the coverage of the target while minimizing the dose to the underlying critical structure. (From Low DA, Starkschall G, Bujnowski SW, Wang LL, Hogstrom KR. Electron bolus design for radiotherapy treatment planning: bolus design algorithms. *Med Phys*. 1992;19[1]:115-124. Copyright © 1992 American Association of Physicists in Medicine. Reprinted by permission of John Wiley & Sons.)

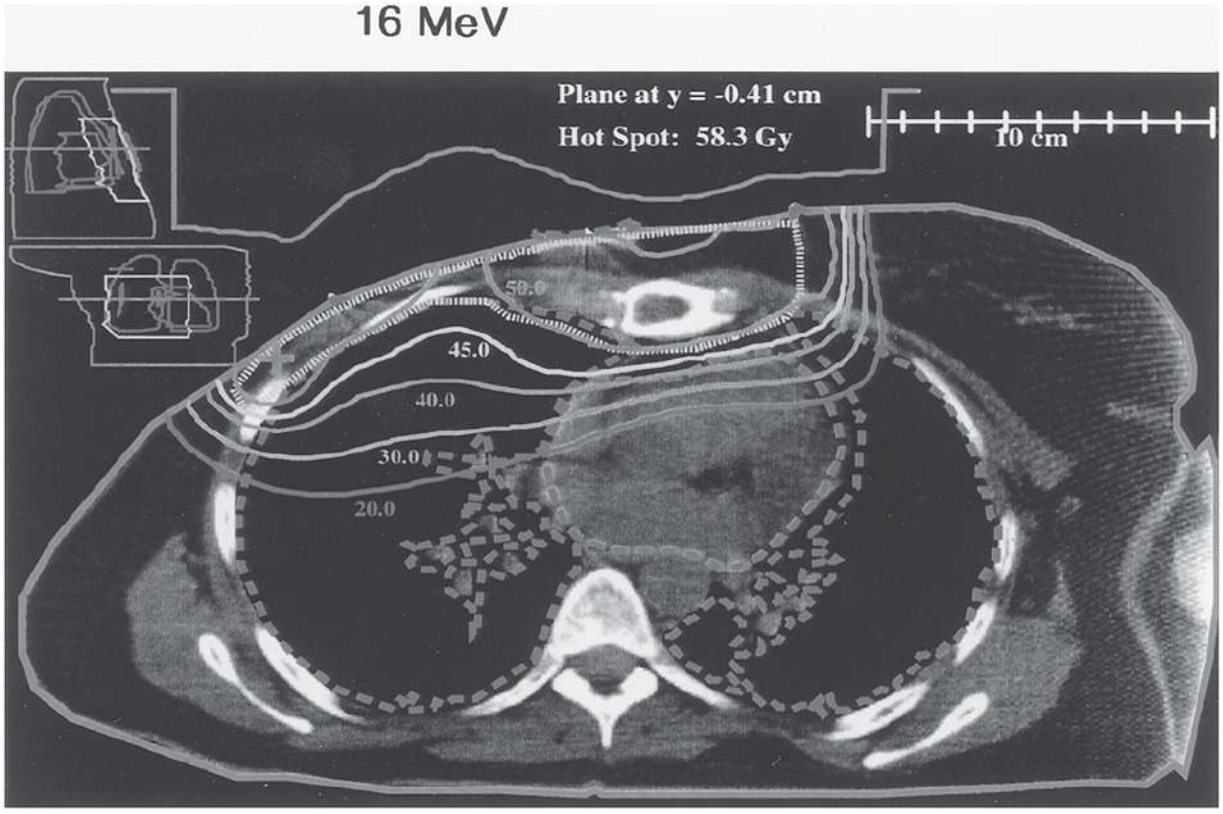


FIGURE 9.17 Conformal electron therapy using variable thickness bolus. Bolus is used to shape the 90% isodose surface (45 Gy) to the distal surface of the chest wall in treating a chest wall occurrence, optimally sparing lung. (Reprinted from Perkins GH, McNeese MD, Antolak JA, Buchholz TA, Strom EA, Hogstrom KR. A custom three-dimensional electron bolus technique for optimization of postmastectomy irradiation. *Int J Radiat Oncol Biol Phys*. 2001;51[4]:1142-1151. Copyright © 2001 Elsevier. With permission.)

It is recommended that the intent of bolus be verified by measurement or calculation. Bolus used to increase skin dose can be verified by performing in vivo dosimetry measurements (eg, using thermoluminescent dosimetry). Complex bolus shapes, as used to remove surface irregularities or for

electron conformal therapy, can be verified by CT scanning the patient with the bolus in place.[20,25] The dose distribution then can be recalculated using the electron dose algorithm in a treatment planning system.

This method of electron conformal therapy may be facilitated by a commercial vendor that can create the custom bolus from treatment plan machinist coordinates.[74]

Along these lines, customization could also be achieved with the use of a 3D printer.[75-77] In this process, a customized bolus is made using the patient's CT with a commercial treatment planning system. Figure 9.18 shows an example of such process. The bolus' structure is sent to a 3D modeling software that will convert the file to the appropriate language (standard tessellation language), which will be used by the 3D printer to manufacture the bolus.[75]

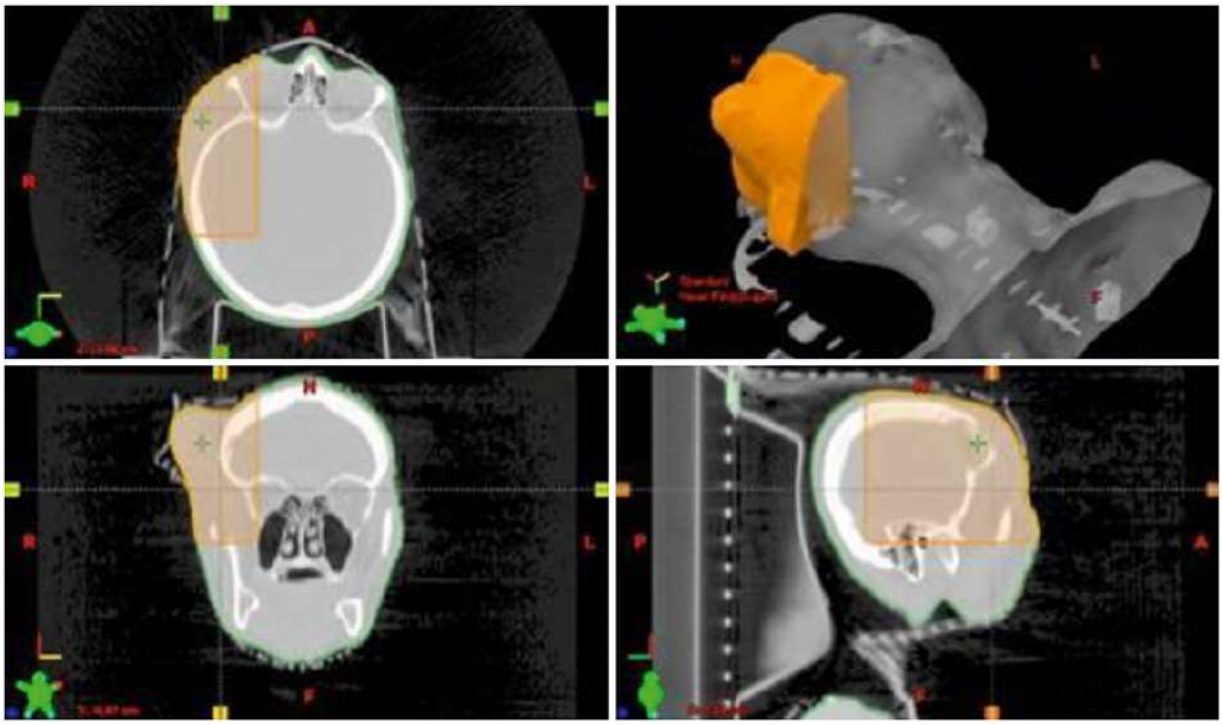


FIGURE 9.18 Example of a bolus structure (shown in orange) defined on the treatment planning system that was subsequently made by a three-dimensional printer. (Reprinted from Burleson S, Baker J, Hsia AT, Xu Z. Use of 3D printers to create a patient-specific 3D bolus for external beam therapy. *J Appl Clin Med Phys*. 2015;16[3]:5247. http://creativecommons.org/licenses/by/3.0/.)

The dimensions of the bolus are dependent on the type of 3D printer available, which will also determine the composition of bolus material. There are printers that could print using only one material, whereas there are others that can print multiple materials at once.[75] Mainly, the materials used are some type of variation of acrylonitrile butadiene styrene and polylactic acid. It is important to clearly characterize the material's electron density in order to calculate the correct dose that will be delivered to the patient. In addition, the 3D printed bolus might have air bubbles, which will affect the dose distribution. It is recommended, as for any type of bolus, to perform the necessary measurement to characterize the 3D printed bolus as well as to develop the necessary quality assurance procedures before using the bolus for any patient.

Two of the main limitations of using 3D printed bolus routinely for radiotherapy are the availability of a 3D printer and the time that it takes to print a complete bolus. Although 3D printers should become more affordable as these are gaining popularity in radiotherapy. The printing time could also vary widely among printers. The time that it takes to print a bolus is highly dependent on the type of printer's filament and, of course, on the dimensions and complexity of the bolus. Printing could take from 4 to 24 hours.[75,76] This time could be doubled if by any chance there is any failure in the printing process. Some companies offer services to print patient 3D boluses. Usually, the patient's CT scan is transferred to the company's software to design the bolus. The bolus is then reimported back into the clinical treatment planning system, and it's integrated into the patient's plan to ensure that the dose distribution is appropriate. The design and dimension of the bolus are then sent to the company, which will manufacture it and send it back before patient treatment takes place. It's important also to account for the additional time that will take to receive the bolus from the company.[74,78,79]

Internal Shielding

Internal shields stop electrons that enter the body before they reach critical structures and deposit any significant dose. Examples of clinical utilization of internal shielding are intraoral blocks protecting salivary glands during head and neck treatments[2]; eye blocks protecting the lens in irradiation of

the eyelid,[80] orbit, or retina; and sheets of lead used to protect internal structures during intraoperative therapy.

There are two important concepts to remember in the use of internal shielding. First, the collimator must be sufficiently thick to stop the energy of the electrons in the beam at depth. Electron-beam energy is reduced by 2 MeV per centimeter in unit density tissue; hence, the energy of a 12-MeV beam at a depth of 2 cm is 8 MeV. The thickness of lead required to stop 8-MeV electrons is 4 mm (8 MeV-0.5 mm/MeV).

One application was ensuring that collimation is sufficiently thick that has been sometimes overlooked is the use of internal eye shields. Shiu et al[80] showed that x-ray eye shields constructed of plastic-coated lead and designed to shield the eyes from kilovoltage x-rays did not stop 6-MeV electrons, resulting in penetration of approximately 50% of the given dose. However, electron eye shields constructed of enamel-coated tungsten can stop electrons with energies as great as 9 MeV (Figure 9.19). By using higher density tungsten (ρ = 19.3 g/cm^3) instead of lead (ρ = 11.5 g/cm^3), the eye shields remain sufficiently thin to fit under the eyelid. If only x-ray eye shields are available, bolus should be placed on top of the eye and eye shield to ensure that the electron energy is reduced sufficiently so that electrons do not penetrate the eye shield.

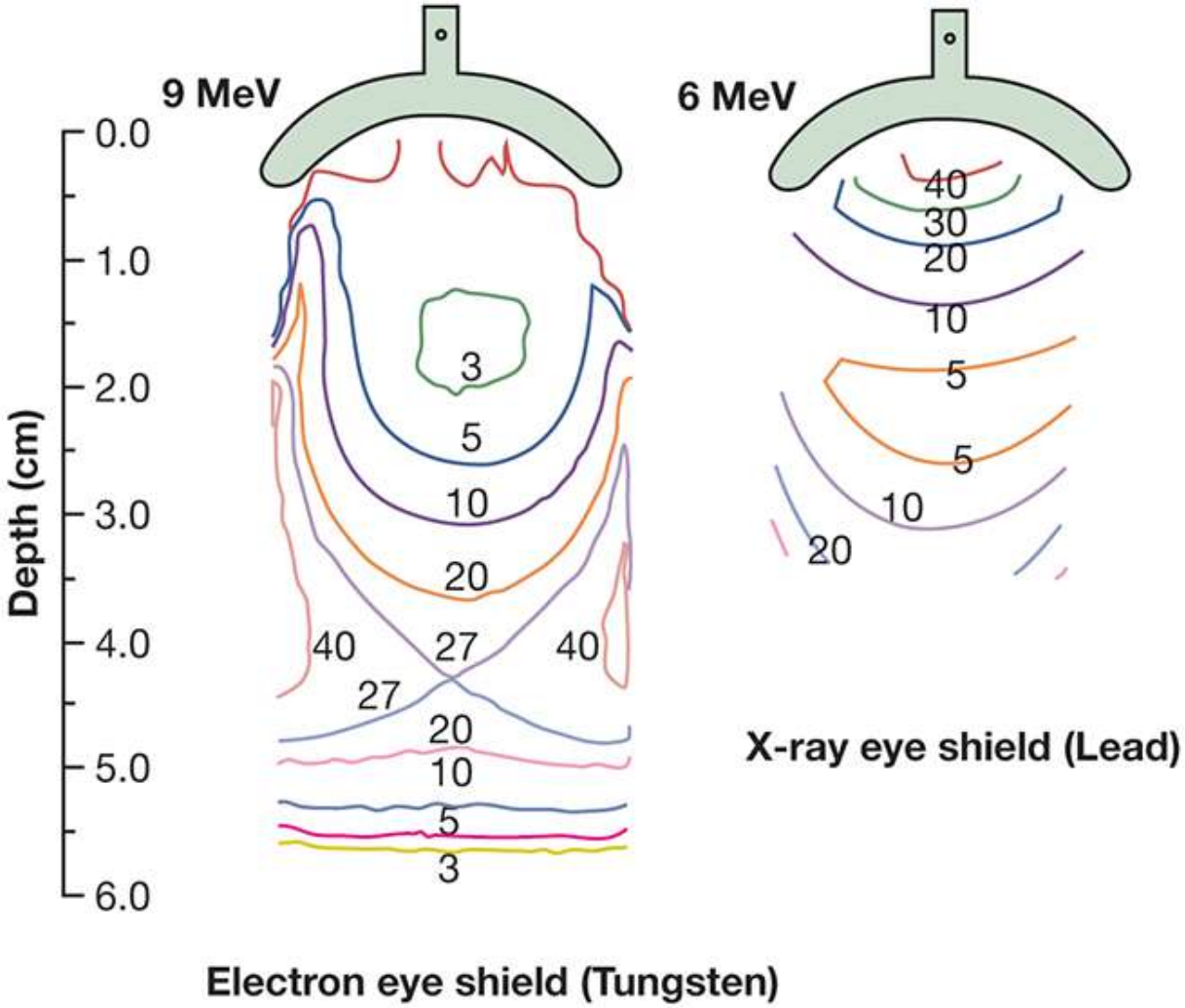


FIGURE 9.19 Electron eye shields. The dose distribution under tungsten electron eye shields demonstrates its ability to stop 9-MeV electrons. The dose distribution under a lead x-ray eye shield shows its inability to stop 6-MeV electrons. (Reprinted from Shiu AS, Tung SS, Gastorf RJ, Hogstrom KR, Morrison WH, Peters LJ. Dosimetric evaluation of lead and tungsten eye shields in electron beam treatment. *Int J Radiat Oncol Biol Phys*. 1996;35[3]:599-604. Copyright © 1995 Elsevier. With permission.)

Second, electrons backscattered from lead at a lead-tissue interface increase dose, the increase ranging from approximately 20% at 20 MeV to 60% at 4 MeV, where the energy is the average energy of electrons incident on the lead.[30,81] Das and Bushe[82] published a comprehensive data set demonstrating the range for backscatter electrons as a function of energy, on the order of a few millimeters, and increases as a function of energy. Inserting two half-value layers of bolus between the lead and the tissue usually reduces the dose to upstream tissue to a clinically acceptable value.

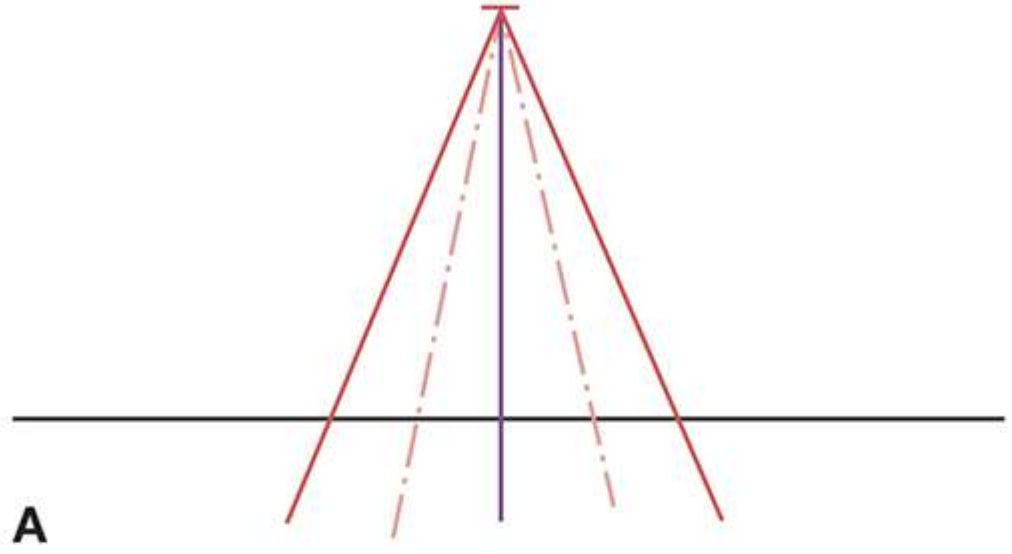
The thickness of one-half-value layer ranges from approximately 1 cm at 10 MeV to 0.5 cm at 3 MeV.[30,83] Intraoral lead stents are routinely coated with acrylic,[28] and a material such as dental wax can be applied easily to lead sheets placed between the mucosa and the gums. Eye shields, however, only have clearance for 1 to 2 mm of coating; hence, backscatter dose to the eyelids is an important consideration in treatment management.[83] When determining lead thickness for an internal shielding at a particular depth, one must first determine the energy of the electron beam at that location. The energy of the electron beam on the surface is $E_{o,p}$, typically close to the nominal stated energy. As electrons lose energy by 2 MeV per centimeter, one can determine the remaining energy of any depth. For example, 12 MeV beams at surface would be approximately 6 MeV after 3 cm.

Recent studies claim that the thickness of lead and bolus, usually calculated for internal shielding considerations, is overestimated.[84] This calculation is usually based on the method explained in Task Group 25.[30] The overestimation is likely to be on the safe side; regardless, these new studies questioned the use of this thicker layer when the shielding is usually used in smaller anatomic spaces. Mc Dermont et al[84] used the work of deVries and Marsh[85] to determine the minimum amount of lead and bolus necessary to keep the dose to a 10% enhancement at the distal end of tissue. They created a looked-up figure (ask how we can get that figure) for the thicknesses of lead and bolus for electron energies going from 4 to 10 MeV.

Field Abutment

The purpose of field abutment is to enlarge the radiation area by using parallel matched beams or to change the beam energy or modality. In either case, beam uniformity requires that three criteria be met. First, the beams must abut along the entire border.[29,30,32,86] If the edges of the two beams coincide exactly (Figure 9.20A), then the two beams will be equivalent to a single beam and optimal uniformity will be achieved. If the central axes of the two beams are parallel (Figure 9.20B), then the diverging beam edges will overlap, creating a cold spot upstream and a hot spot downstream of the region of intersection. This is least significant for narrow fields, as encountered in irradiation of the cervical nodes of the neck or abutting the internal mammary and medial chest wall fields. If the central axes are

converging (Figure 9.20C), then there is an even greater amount of overlap. This is the case for abutting lateral and medial chest wall fields. In such cases, feathering the beam edge ±1 cm can reduce the dose heterogeneity. This is illustrated in Figure 9.21 for a standard postmastectomy chest wall irradiation using electrons.



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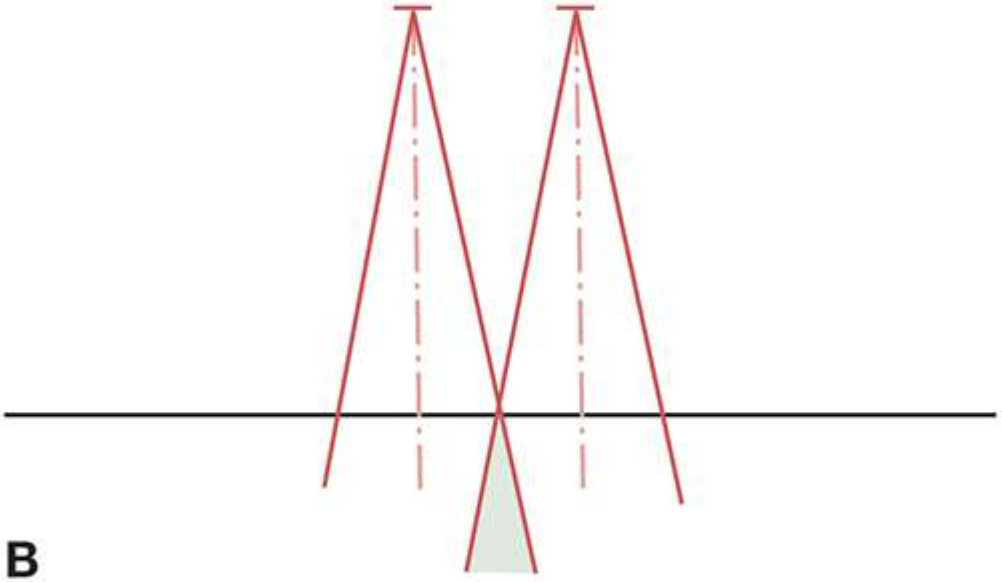

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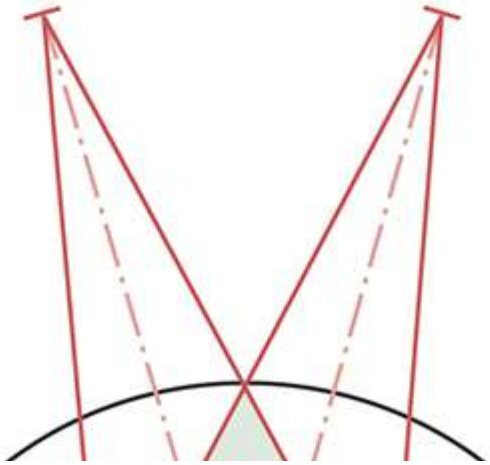


FIGURE 9.20 Comparison of abutment geometries. A. Common edge is created by having diverging central axes. B. Parallel central axes result in overlapping edges. C. Converging central axes result in the greatest overlap. (From Svensson H, Almond P, Brahme A, et al. *ICRU Report 35. Radiation Dosimetry: Electron Beams with Energies Between 1 and 50 MeV*. International Commission on Radiation Units and Measurements; 1984. Copyright © 1984 International Commission on Radiation Units and Measurements. Reprinted by permission of SAGE Publications.)

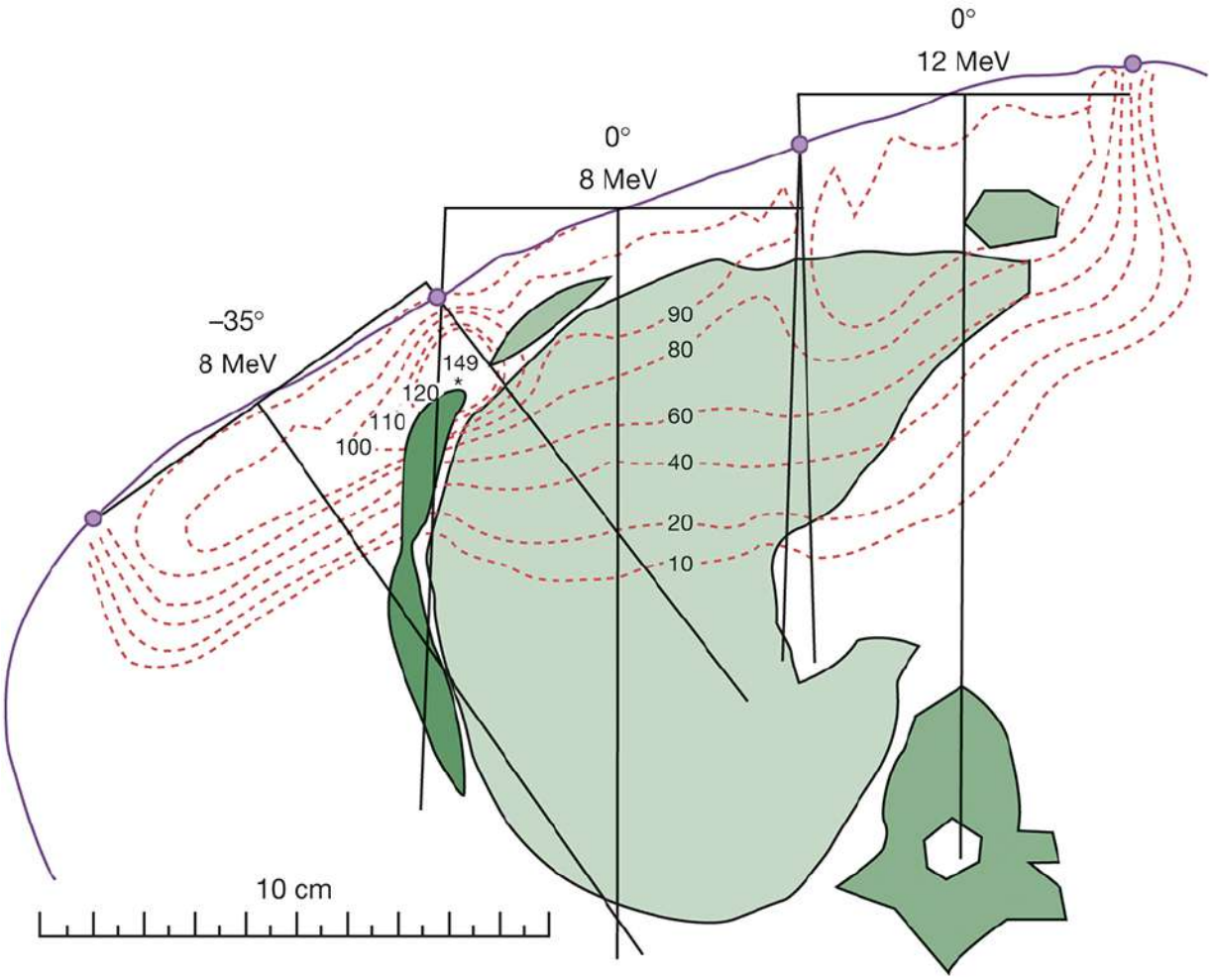


FIGURE 9.21 Clinical example of abutting electron fields in chest wall treatment. Dose homogeneity is acceptable at the border of internal mammary chain and medial chest wall fields because central axes are parallel and field widths are small. Dose homogeneity is unacceptable at the border of medial and lateral chest wall fields because central axes are converging (see Figure 9.10B). Dose homogeneity is improved at the border of medial and lateral chest wall fields by delivering equal doses with the match line being moved 1 cm twice during treatment.

The second criterion is that the beam penumbra must be matched. This is the case for the two spinal fields referred to earlier; however, it is not the case in general, particularly in abutting electron to photon fields. In such cases, either one or both of the field edges must be feathered. Third, it is best that the penumbra be somewhat broad. This reduces the impact of misalignment on the uniformity of dose in the abutted region. Harms and Purdy[50] demonstrated the influence of SSD energy and match bolus on match-line dosimetry. Figure 9.22 displays dose homogeneity for abutted

12-MeV fields depending on gap. In addition, the matching of electron and photo fields is a planning challenge, as two differing penumbra are abutted. Johnson and Khan[87] performed a study of matched electron-photon fields as a function of energy and SSD. Figure 9.23 demonstrates match-line profiles for a typical head and neck field match.

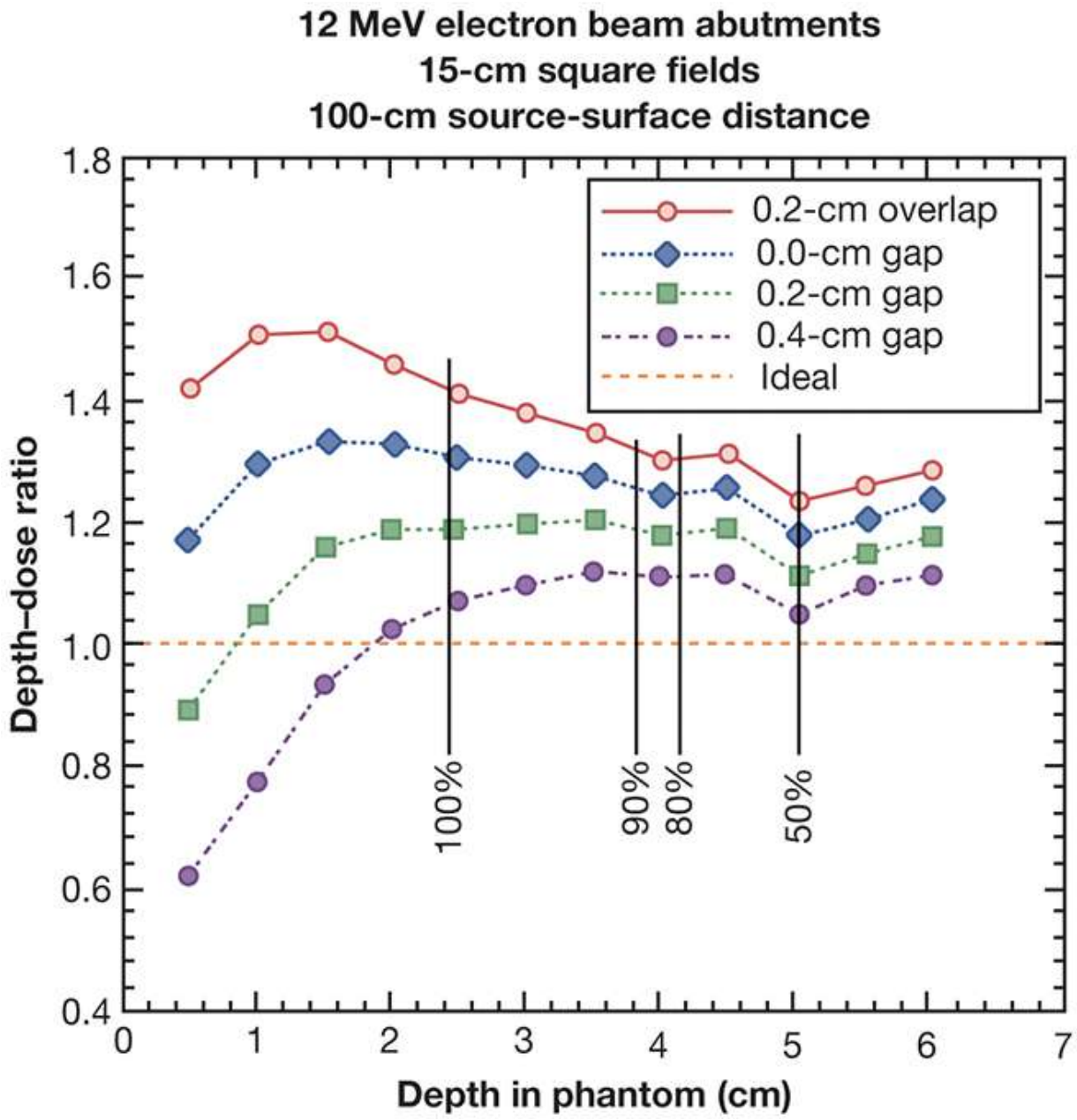
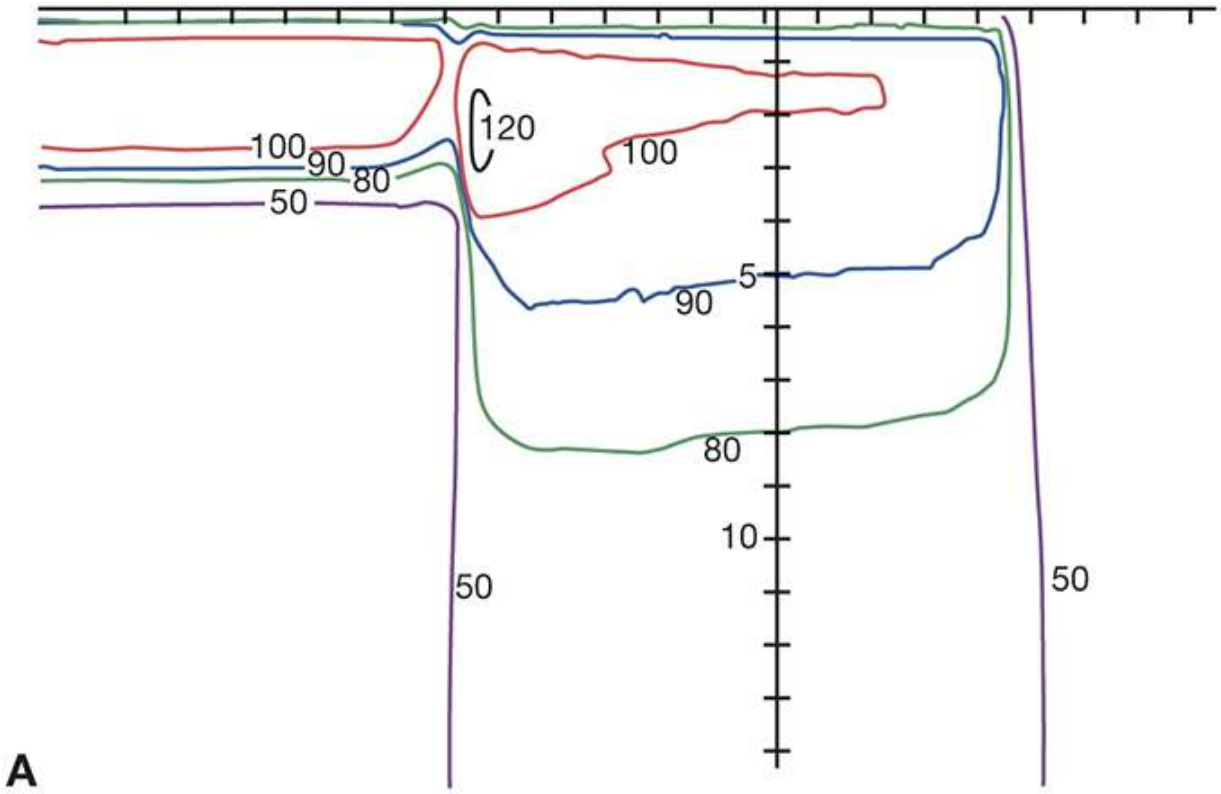


FIGURE 9.22 Graph depicting dose homogeneity for abutted 12-MeV electron fields for a series of gaps. (Reprinted from Harms WB, Purdy JA. Abutment of high energy electron fields. *Int J Radiat Oncol Biol Phys*. 1991;20[4]:853-858. Copyright © 1991. With permission of Elsevier.)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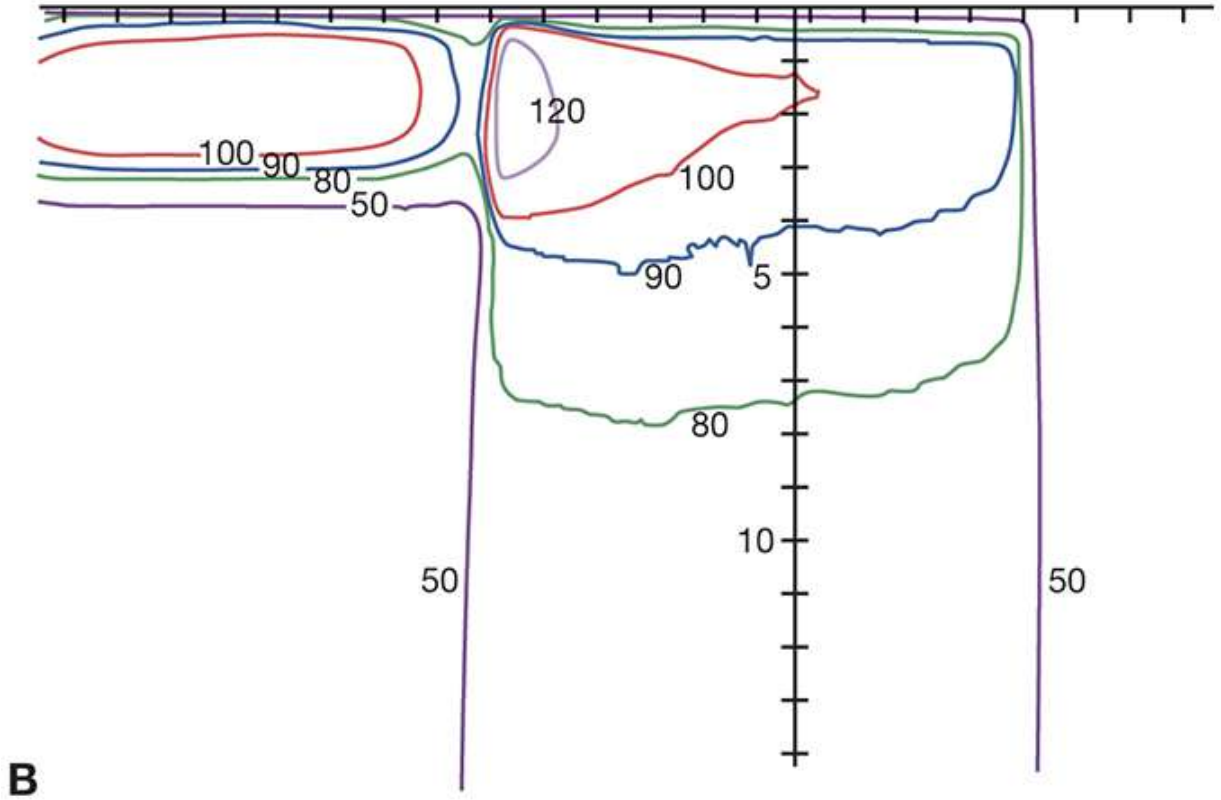
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B

FIGURE 9.23 Isodose curves in a plane perpendicular to the junction line between abutting photon and electron fields. 9-MeV electron beam; field size equals 10 by 10 cm^2; 6-MV photon beam; source-to-surface distance (SSD) equals 100 cm. A. Electron beam at standard SSD of 100 cm. B. Electron beam at extended SSD of 120 cm. (Reprinted from Johnson JM, Khan FM. Dosimetric effects of abutting extended source-to-surface distance electron fields with photon fields in the treatment of head and neck cancers. *Int J Radiat Oncol Biol Phys*. 1994;28[3]:741-747. Copyright © 1994. With permission of Elsevier.)

Mixed-Beam Therapy

Electron beams are frequently mixed with photon beams to create an appropriate treatment. The mixed beams can irradiate a common volume of tissue, or they can be abutted. In the former case, an electron field may be added to a primarily photon-beam treatment, or a photon field may be added to a primarily electron-beam treatment. For example, electron boosts are used to deliver localized dose to the surgical site following photon breast irradiation, to treat the postcervical nodes once spinal cord tolerance is reached, and to reduce spinal cord dose (eg, in lymphoma treatment).[88] In some head and neck treatments, the photon beam is a surrogate to the electron beam, being used to reduce skin dose and to increase dose penetration while still sparing the contralateral salivary gland.[2,10] With the future availability of intensity-modulated photon and modulated electron therapy, the effectiveness of mixed-beam therapy can be expected to increase in breast and head and neck radiation therapy.

Abutted mixed beams are used when separate portions of the anatomy can benefit from two individual beams. The most common application of this process is the utilization of electron fields for irradiation of the IMC, supraclavicular, or axillary lymph nodes as part of breast or chest wall irradiation.[2] Matching of tangential photon fields and IMC electron fields is complex because of surface irregularities and heterogeneities. Careful treatment planning must be performed, especially if prescriptive decisions for electron energy and dosage are predicated on the resultant dose distribution. Figure 9.24 displays a tangential photon IMC electron field initial plan with a plan performed with partially wide tangent, a technique suggested to remove the field abutment dilemma.[89] This technique is also used for irradiating the total scalp or for craniospinal irradiation, which are described later. The use of combined modulated photon and electron fields has been reported. This has the potential to be an ideal therapy for particular

treatment sites. Thus far, this combined therapy has been demonstrated with microtron (helium head) machines. Early publications demonstrated conventional (nonmodulated) use of photons and electrons as collimated by MLC. Zackrisson and Karlsson[90] described a technique for matching of electron and photon beams for conformal therapy of target volumes at moderate depths. Mu et al[91] showed that mixed photon and electron was superior in obtaining planning goals versus intensity-modulated radiotherapy (IMRT) alone. One essential aspect was the reduction of integral dose. The same computer-controlled MLC of microtron model is used for photons and electrons. Das et al[92] developed an algorithm using automated beam orientation and modality selection for optimal beam arrangement selection in IMRT of mixed photon and electron beams. Finally, Ma et al[93] performed a comparative study on tangential photon beams, IMRT, and modulated electron radiotherapy (MERT) for breast cancer treatment. This type of treatment delivery can simplify the use of both techniques, but more electron scatter is also created due to the use of the MLC instead of an electron cut out. This creates a different level of complexity. These types of plans will need a robust QA program to ensure that the plan doses are, in fact, what the patient will be received during treatment. There are publications on the results for quality assurance measurements based on ion chambers and films,[94] the use of log files similar to what is regularly use for photon IMRT plans,[95] and the use of commercial systems with diode arrays.[96]

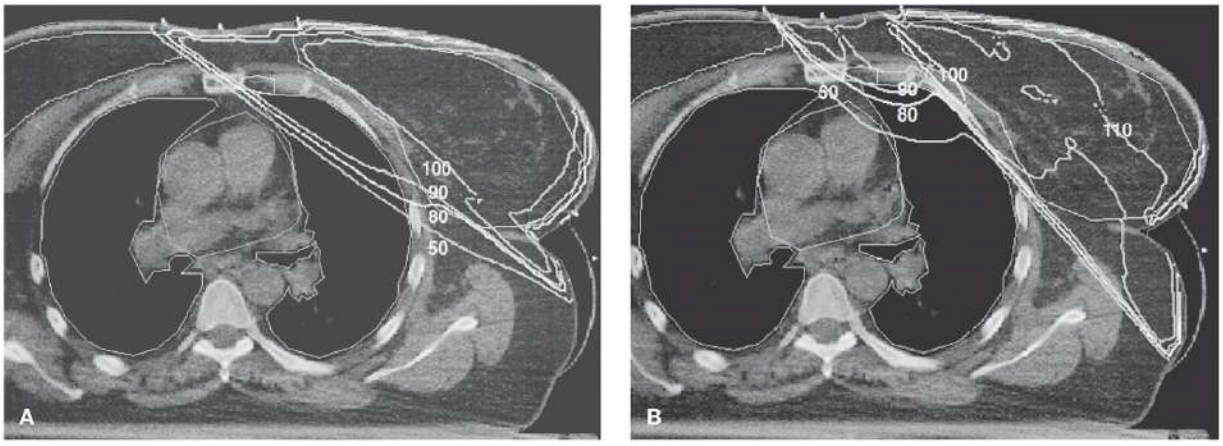

FIGURE 9.24 Dose distribution with partially wide tangentials (PWTs) versus photon/electron (P/E) illustrating difference in position of hot spots. Left lung, heart, internal mammary chain, left breast or chest, and right breast were outlined. The 50%, 80%, 90%, 100%, 110%, and 120% isodose lines are displayed. A. Dose distribution with intact breast and PWT. B. Dose distribution with intact breast and P/E. (Reprinted from Severin D, Connors S, Thompson H, Rathee S, Stavrev P, Hanson J. Breast radiotherapy with inclusion of internal mammary nodes: a comparison of techniques with three-dimensional planning. *Int J Radiat Oncol Biol Phys*. 2003;55[3]:633-644. Copyright © 2003 Elsevier. With permission.)

SPECIALIZED ELECTRON TECHNIQUES

Although electron-beam therapy is used less frequently than is photon-beam therapy, it remains an essential modality. To fully use electron-beam therapy, there must be access to comprehensive electron treatment and treatment planning techniques. This includes specialized electron techniques, which, in the present context, are defined as those that are seldom required and that use a complex treatment geometry, special treatment delivery hardware, or special treatment planning software. It is not recommended that all radiation therapy facilities offer all techniques. However, radiation oncologists should be aware of these techniques and should be able to refer patients to a regional center for those that are impractical in smaller settings. This recommendation is based on the significant time, resources, and costs of implementing, maintaining, and providing some of the more complex special electron procedures. The American College of Medical Physics (absorbed into the AAPM) has reviewed the manpower effort and cost associated with several special procedures, which include electron arc therapy, intraoperative electron therapy, and total skin electron irradiation.[97]

Four types of special techniques are discussed here. First, the treatment of internal tissues is exemplified by intraoperative radiation therapy and intracavitary radiation therapy. Second, the utilization of abutted electron and photon fields is exemplified by craniospinal and total scalp treatment techniques. Third, the treatment of superficial tissues for a cylindrical geometry is exemplified by the total limb and total skin treatment techniques. Fourth, an alternative to fixed-beam therapy of the chest wall is exemplified by arc therapy.

Intracavitary Irradiation

Applicators of appropriate design can be used for intracavitary electron irradiation, which delivers an improved dose distribution over that traditionally delivered using orthovoltage x-rays. Intracavitary irradiation is most frequently used to boost the primary site while sparing nearby normal tissues. Intracavitary irradiation has been a choice for intraoral, transvaginal, and intraoperative treatments. Wang[19] showed the benefit of intraoral cones for boosting the oral lesions of the floor of the mouth, soft palate, tongue, and retromolar trigone while sparing mandible, teeth, gum, and salivary glands. McGinnis et al[28] reported using a transvaginal applicator to boost carcinoma of the cervix with electrons, reducing bulk tumor to subsequently allow intracavitary brachytherapy. Intraoperative radiation therapy can be used in many sites[13]; however, it is used primarily for abdominal sites. Merrick et al[26] reviewed the experience in the United States of using intraoperative radiotherapy for the treatment of pancreatic, biliary, and gastric carcinomas.

The criteria for intracavitary electron irradiation are similar, regardless of site. A treatment applicator is necessary so that healthy tissue can be restrained from intercepting electrons irradiating the tumor. The applicator wall must be sufficiently thick to stop electrons from escaping to outside tissue while being thin enough not to interfere with tumor access. Guidelines for accomplishing this for intraoperative applicators have been discussed by Hogstrom et al[98] Another issue is how to ensure accurate alignment while maintaining patient safety with an applicator. Appropriate cone positioning requires having a method for looking down the cone to view the tumor. Proper alignment of the applicator after inserting it into the

patient requires methods for docking it to the machine. For soft docking, the applicator is not physically attached to the machine[98,99] (Figure 9.25). For hard docking, the applicator is physically attached to the machine, and there are methods for breaking away under stress.[28,100]

INTRAOP

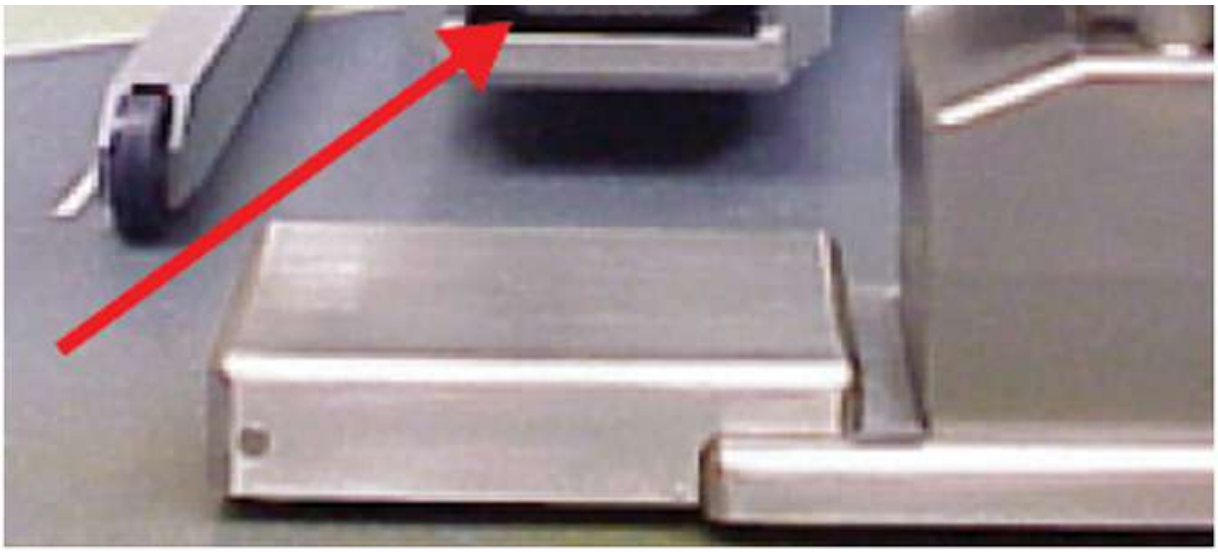

FIGURE 9.25 Intraoperative electron radiation therapy accelerator. View of the Mobetron self-shielded mobile intraoperative radiation therapy unit by IntraOp Medical Corporation. (From Beddar AS, Biggs PJ, Chang S, et al. Intraoperative radiation therapy using mobile electron linear accelerators: report of AAPM Radiation Therapy Committee Task Group No. 72. *Med Phys*. 2006;33[5]:1476-1489.)

Treatment planning for intracavitary cones is typically done manually because it is not possible to CT scan the patient in the treatment position or under operating room conditions. The electron energy and cone size are selected to match measured isodose distributions to the dimensions of the clinical target volume. Examples of dose distributions for intraoperative applicators are shown in Figure 9.26.[101] These examples show two characteristics of such applicators. First, for the larger diameter applicators, scattering off the wall of the applicator can lead to hot spots near the applicator's periphery. Second, ends of the applicator are often beveled to make it easy to establish contact when the anatomic plane is not perpendicular to the direction of approach (ie, the central axis of the beam). Note how the depth of the 90% isodose contour beneath the surface decreases from 3.6 cm at 0° incidence to 3.0 cm at 30° incidence, as a result of the effects described earlier.

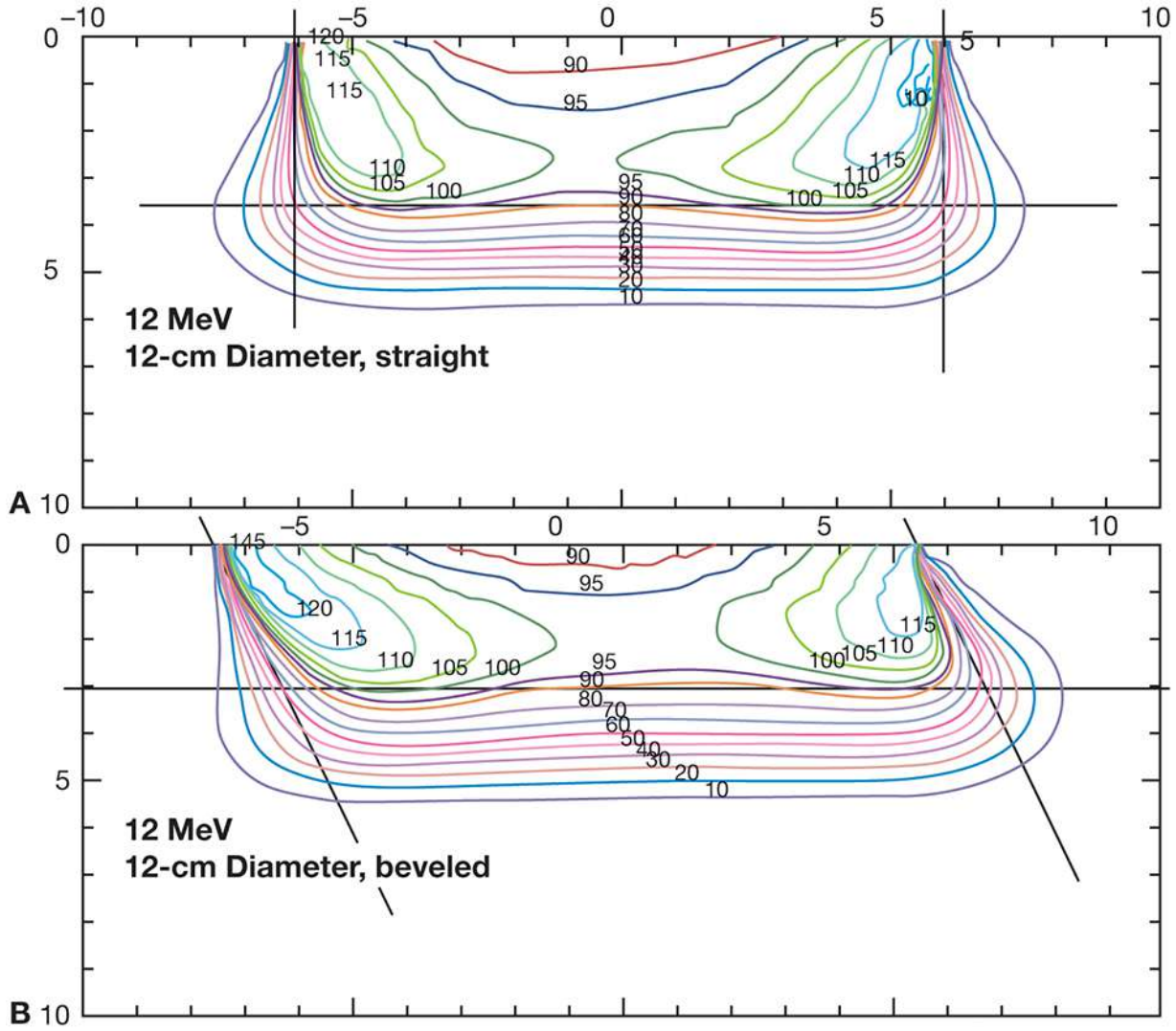

FIGURE 9.26 Isodose plots illustrating typical intraoperative dose distributions at 12 MeV. A. 12-cm diameter cone, normal incidence. B. 30° beveled, 12-cm diameter cone. Note the decreased depth of the 90% dose beneath the surface for the beam 30° from normal incidence relative to that for normal incidence. (Reprinted from Nyerick CE, Ochran TG, Boyer AL, Hogstrom KR. Dosimetry characteristics of metallic cones for intraoperative radiotherapy. *Int J Radiat Oncol Biol Phys*. 1991;21[2]:501-510. Copyright © 1991 Elsevier. With permission.)

Total Scalp Irradiation

Total scalp irradiation is sometimes necessary in the management of malignancies (eg, cutaneous lymphoma, melanoma, and angiosarcoma) that present with widespread involvement of the scalp and forehead.[2,15] Electron-beam therapy is a practical means of achieving the therapeutic goal of delivering a uniform dose to the scalp with minimal dose to underlying

brain. For many years, total scalp irradiation was achieved by patching multiple electron fields.[2,102] Although effective, the treatment was tedious as a result of the large number of fields, their requirement for skin collimation, and the need to move the abutment border to improve dose homogeneity.[102] Akazawa[103] from the University of California-San Francisco reported a simpler technique that abuts lateral electron fields to parallel-opposed photon fields, the latter of which treats the rind of the scalp while avoiding brain tissue. Tung et al[15] modified the abutment scheme to account for beam divergence and demonstrated improved dose uniformity by comparing 3D dose calculations with in vivo dose measurements. Figure 9.27 illustrates the abutment scheme. The outer edge of the electron field overlaps the inner edge of the 6-MV x-ray field by 3 mm to account for the divergence of the contralateral 6-MV x-ray field. Because the electron and x-ray penumbras are not matched, their common border is moved 1 cm toward the beam center halfway through treatment to improve dose homogeneity. Figure 9.28 shows the dose distribution in a transverse CT plane, which illustrates the dose homogeneity achieved in the region of abutment and the sparing of brain tissue. Initially, the common border is set at approximately 0.5 cm inside the inner table of the skull. Moving the common border farther toward the inner table of the skull reduces brain irradiation at the expense of the x-ray beam being replaced by an electron beam that would begin to graze the skull. As discussed earlier, grazing radiation penetrates less deeply, possibly underdosing the scalp in this region. Also noticeable in Figure 9.28 is a 6-mm-thick wax bolus, which increases the surface dose for both the electron and x-ray fields. Although this technique is straightforward to plan and implement, there is a concern of hot spots along the midline superior brain tissue along the plane.

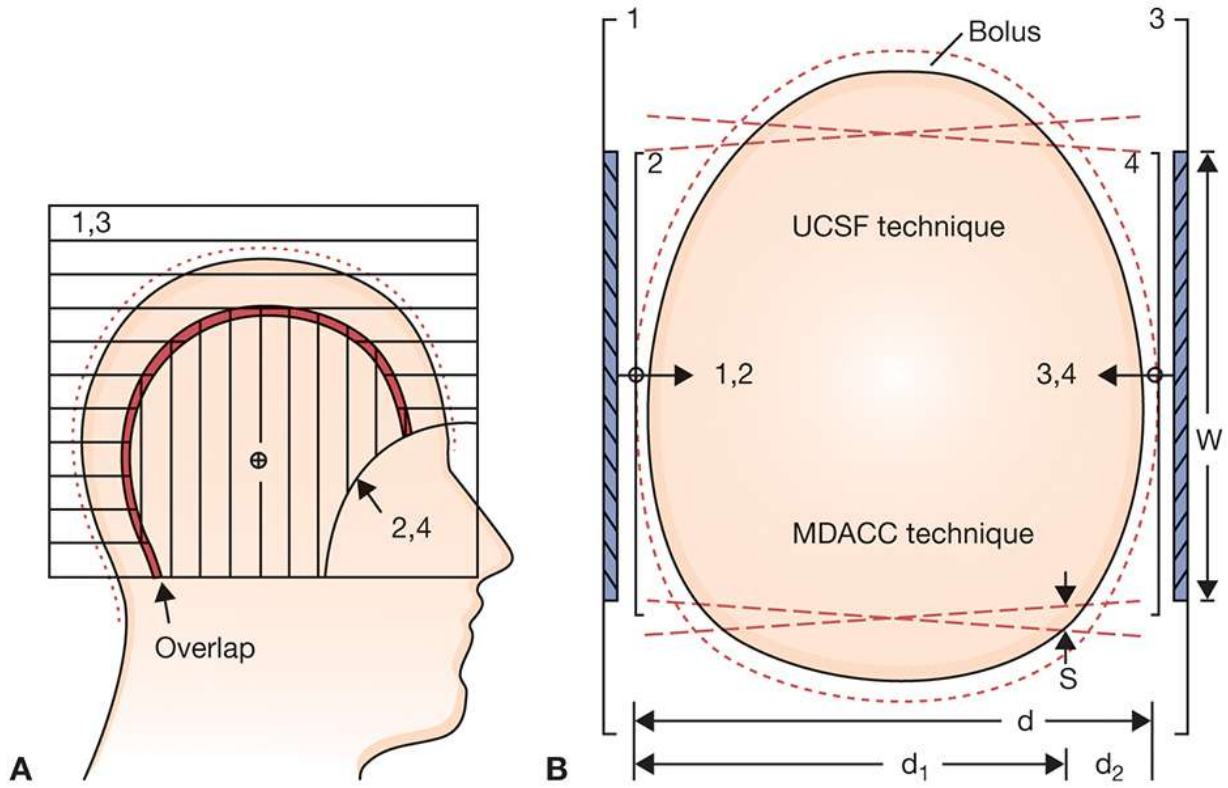

FIGURE 9.27 Abutment scheme for total scalp irradiation (x-ray fields, 1, 3; electron fields, 2, 4). A. The electron field edge, placed just inside the skull, overlaps the edge of the ipsilateral x-ray field by approximately 3 mm to account for divergence of the edge of the contralateral x-ray field. Halfway through treatment, the field edges are moved 1 cm to improve dose homogeneity in the region of abutment. B. The need for the 3-mm overlap (MD Anderson Cancer Center [MDACC] technique) is better appreciated viewing the divergent edges of all fields in a transverse plane. (Reprinted from Tung SS, Shiu AS, Starkschall G, Morrison WH, Hogstrom KR. Dosimetric evaluation of total scalp irradiation using a lateral electron-photon technique. *Int J Radiat Oncol Biol Phys*. 1993;27[1]:153-160. Copyright © 1993 Elsevier. With permission.)

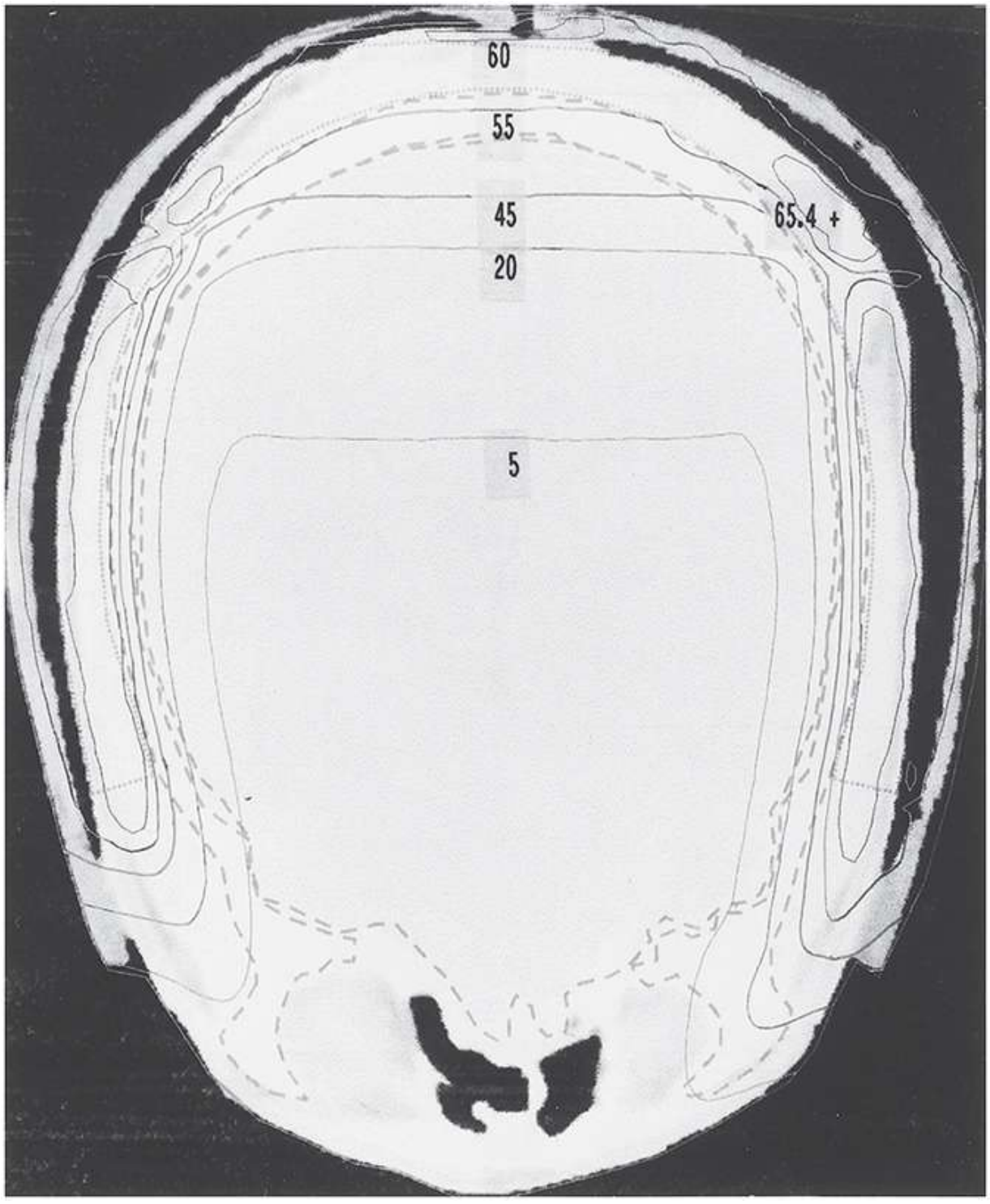

FIGURE 9.28 Dose distribution in a transverse computed tomography plane, illustrating the homogeneity of dose in the abutment region and the degree of brain sparing with this technique. Isodose values in gray. (Reprinted from Tung SS, Shiu AS, Starkschall G, Morrison WH, Hogstrom KR. Dosimetric evaluation of total scalp irradiation using a lateral electron-photon technique. *Int J Radiat Oncol Biol Phys*. 1993;27[1]:153-160. Copyright © 1993 Elsevier. With permission.)

Walker et al[104] described a six-field electron-beam technique for the treatment of mycosis fungoides of the scalp. This technique of overlapping beams was verified with thermoluminescent dosimetry measurements. The dose prescriptions were 20 and 30 Gy for the two patients in this study. Yaparpalvi et al[105] developed a technique for scalp irradiation that used a single posterior-superior field with concentric circles that varied in electron energy. This interesting technique was not confirmed with anthropomorphic phantom dosimetry studies. Peters[106] described the use of an electron reflector to improve dose uniformity to the scalp during total skin electron therapy.

Total Limb Irradiation

It may be advantageous to irradiate the superficial anatomy of a limb for the management of cancer (eg, melanoma, lymphoma, Kaposi sarcoma). If the depth beneath the surface is 2 cm or less, electrons offer a uniform dose while sparing deep tissues and structures. This technique has been described by Wooden et al[16] for the treatment of the lower calf of a patient with Kaposi sarcoma. Illustrated in Figure 9.29, six equally spaced 5-MeV electron beams are used to irradiate a 9-cm diameter cylinder. Each beam is sufficiently wide so that the entire circle falls within the uniform portion of each beam. Tangential radiation to the surface of the cylinder delivers a greater dose as a result of oblique incidence, which is partially offset by the inverse square effect. In addition, the tangential radiation penetrates less deeply. The utilization of six or more beams begins to simulate 360° arc therapy (which is not feasible because of collisions). The resulting dose distribution illustrates three interesting characteristics. First, the average maximum dose along each radius is approximately 2.5 times the given dose of each of the six fields. Second, 90% of the average maximum dose penetrates 8 to 10 mm, reduced from the value of 15 mm for a single-beam incident normally on a flat surface (Figure 9.30). Third, the surface dose has increased to 90% or greater of average maximum dose compared with approximately 70% of the given dose for a single-beam incident normally on a flat surface. This is the result of the self-bolusing effect of tangential electron radiation.

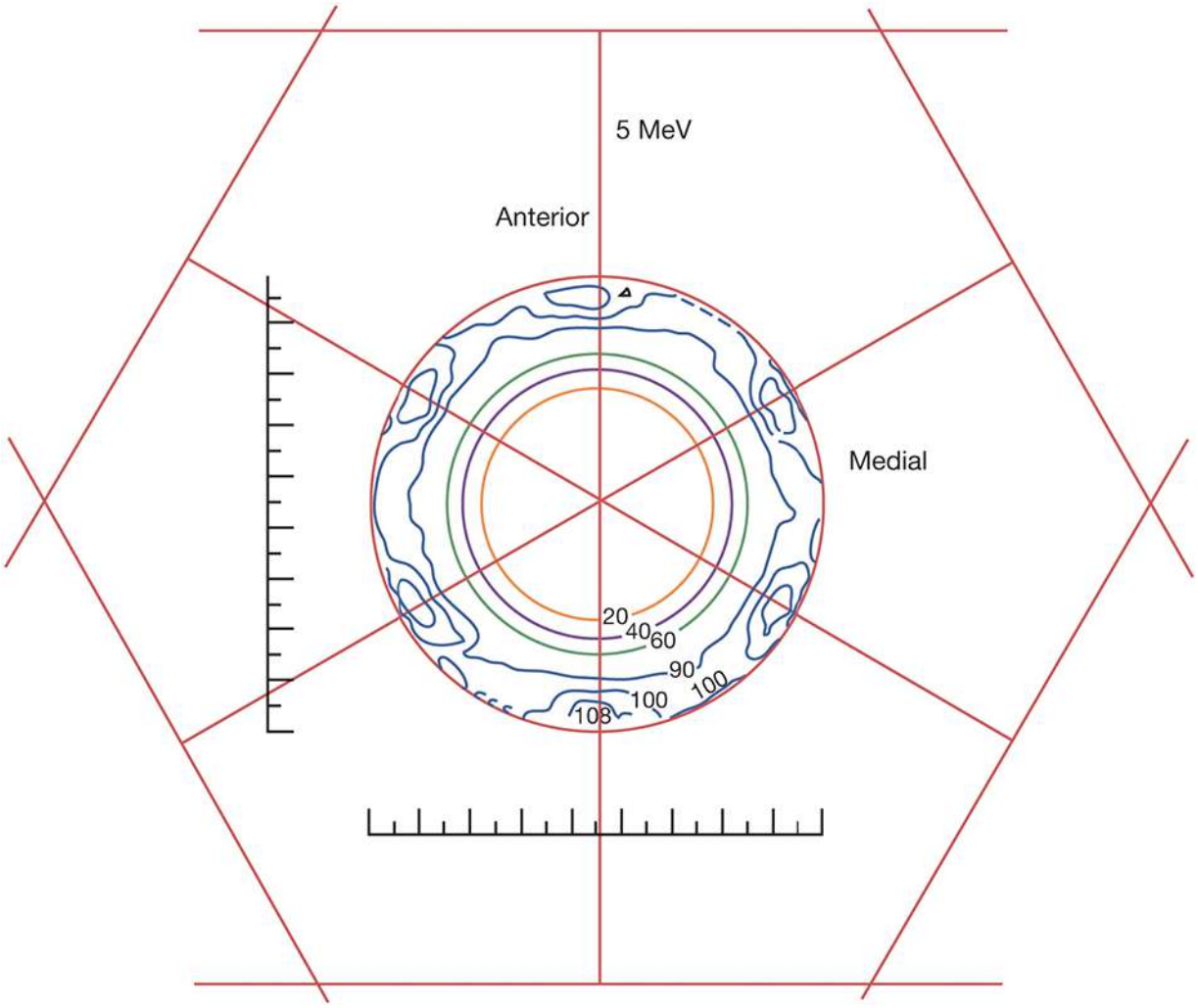

FIGURE 9.29 Dose distribution for total limb irradiation. Six equally spaced 17-cm wide 5-MeV electron beams are used to irradiate a 9-cm diameter cylinder. 100% equals 2.55 times the given dose from a single field. (Reprinted from Wooden KK, Hogstrom KR, Blum P, Gastorf RJ, Cox JD. Whole-limb irradiation of the lower calf using a six-field electron technique. *Med Dosim*. 1996;21[4]:211-218. Copyright © 1996 Elsevier. With permission.)

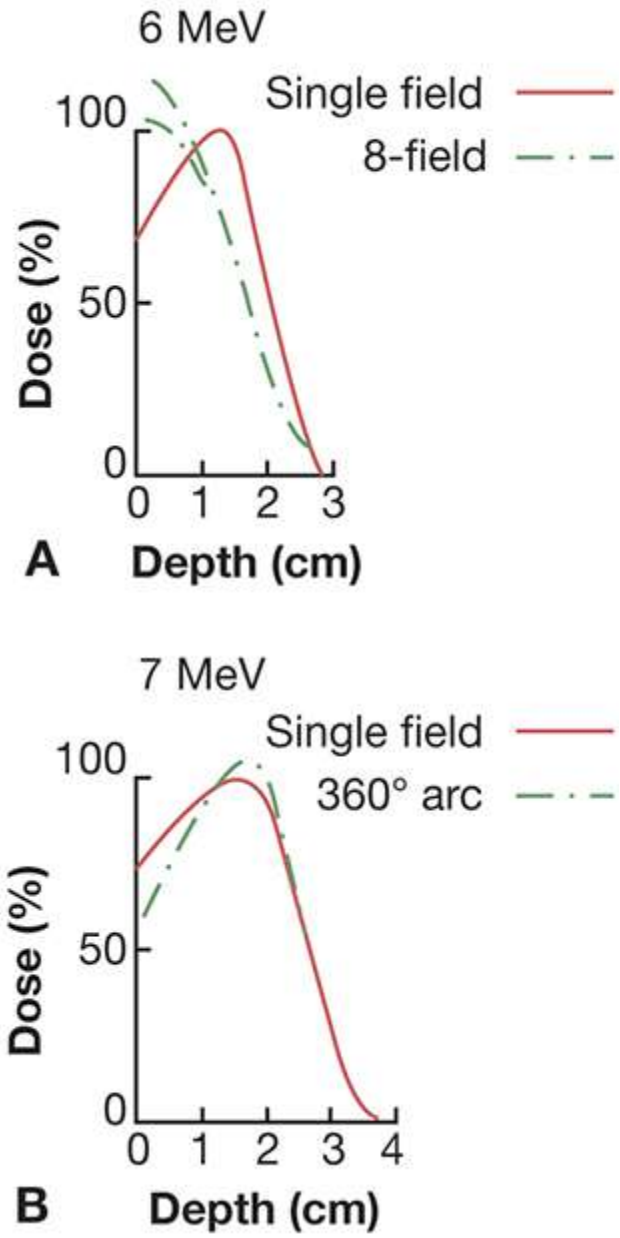

FIGURE 9.30 Treating circular anatomy with multiple beams spaced over 360°. Depth dose along a radial axis depends on the field width. A. Depth dose for a broad, 6-MeV beam, resulting from an eight-field technique around a 20-cm diameter water cylinder, is governed by grazing radiation, typical of total skin and total limb irradiation. B. Depth dose for a narrow, 7-MeV beam, resulting from rotating around a 20-cm diameter water cylinder, is governed by focusing of the radiation toward isocenter, typical of arc electron therapy.

The dosimetric characteristics should be carefully evaluated using one's treatment planning system.

Total Skin Irradiation

Total skin electron irradiation is a modality designed for the management of diseases that require irradiation of the entire skin surface or a significant portion of it. The technique is used most frequently for the treatment of mycosis fungoides, whose management is reviewed by Hoppe,[17] and Kaposi sarcoma.

Multiple techniques for total skin electron therapy have been reviewed in AAPM Report No. 23.[18] The underlying principles of the various techniques are similar, which are exemplified by the modified Stanford technique, illustrated in Figure 9.31. First, the treatment requires a broad beam from right to left, which can be achieved by a combination of treating the patient at an extended SSD (300-400 cm). The beam is made uniform from head to foot by abutting two fields at the 50% OAR (Figure 9.31A). (Note that the 50% OAR lies outside the edge of the light field; thus, when properly abutted, there is a gap between the edges of the respective light fields.) By aiming the beams up and down, the largest bremsstrahlung contribution (central axis) misses the patient. The dose is made uniform around the circumference of the patient by irradiating from six different directions (Figure 9.31B). Similar to total limb irradiation, tangential radiation results in a higher surface dose and a less penetrating dose. Placed upstream of the patient is a plastic screen that serves as both an energy degrader and a scatterer. Dose homogeneity depends on patient's position, and reproducing the positions of the Stanford technique (Figure 9.31C) is important. Despite efforts to create a homogeneous dose, there always will be areas that are underdosed (eg, top of scalp, sole of feet, perineum, and under the breast or under the panniculus of individuals who are obese). These areas and sometimes tumorous lesions require separate treatment and boosting, respectively. In contrast, fingers, feet, and toes typically receive excess dose and are shielded for a portion of the treatment. In vivo measurement of patient dose on an individual basis is important when making decisions on prescriptions for supplemental treatments.

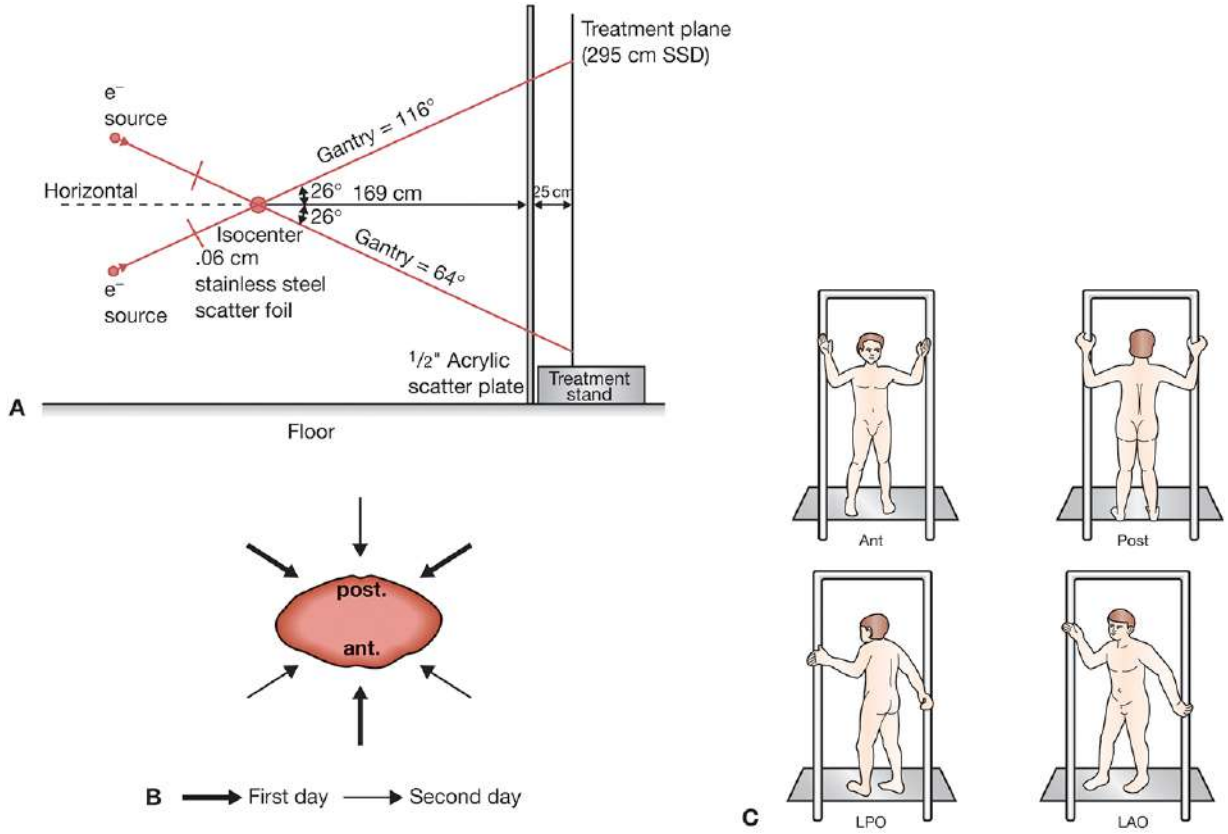

FIGURE 9.31 Schematic of modified Stanford technique for total skin irradiation. Side view of setup shows the relative position of patient plane, scatter plate, isocenter, and gantry angles (A). Six beam directions (B) are achieved by placing the patient in six patient positions (C). SSD, source-to-surface distance. (From Almond PR. Total skin electron irradiation technique and dosimetry. In: Kereiakes JG, Elson HR, Born CG, eds. *Radiation Oncology Physics 1986*. American Institute of Physics;1987:296-332; and Karzmark CJ, Anderson J, Fessenden P, et al. *AAPM Report No. 023—Total Skin Electron Therapy: Technique and Dosimetry*. American Institute of Physics; 1987. Reprinted with permission of American Association of Physicists in Medicine.)

Implementation of this technique is complex. It requires an external patient stand with a plastic diffuser, special dosimetry equipment for quality assurance and calibration, special shields for selected parts of the patient, and access to in vivo dosimetry.[107] It is also necessary for the radiation therapy accelerator to have a high-dose rate mode and interlocks for electron energy, gantry angle, and x-ray jaws. Implementation of this technique has been estimated at 105 hours.[97] An institution must have a warranted patient population requiring this technique.

Electron Arc Therapy

Electron arc therapy is a useful technique for treating postmastectomy chest wall(s).[21] It is used in lieu of parallel-opposed tangential photon irradiation. It is more useful in "barrel-chested" women, where tangential beams can irradiate too much lung. It is also difficult to achieve homogeneous dose in the region where the medial tangential beam used for the chest wall abuts the anterior beam used for the IMC. In such cases, treating both areas with only opposed tangent photon beams irradiates too much lung. In such cases, electron arc therapy is a viable option. This can be particularly important in patients with bilateral disease.

The treatment geometry and dosimetry for arc therapy are unique. There are three levels of collimation in electron arc therapy: the primary x-ray collimators, a shaped secondary Cerrobend insert, and skin collimation (Figure 9.32). The secondary collimator typically projects a 5- to 6-cm beam width at isocenter. There is typically a large air gap between the secondary collimating insert and the patient, resulting in a large penumbra; in addition, the finite width of the field results in a broad edge at the end of the arc. The sharpness of the penumbra is restored utilizing skin collimation. This requires that the edge of the field of the secondary collimator extends well beyond the edge of the field defined by skin collimation. In the plane of rotation, this is achieved by rotating approximately 15° beyond the treatment field edge (Figure 9.33).

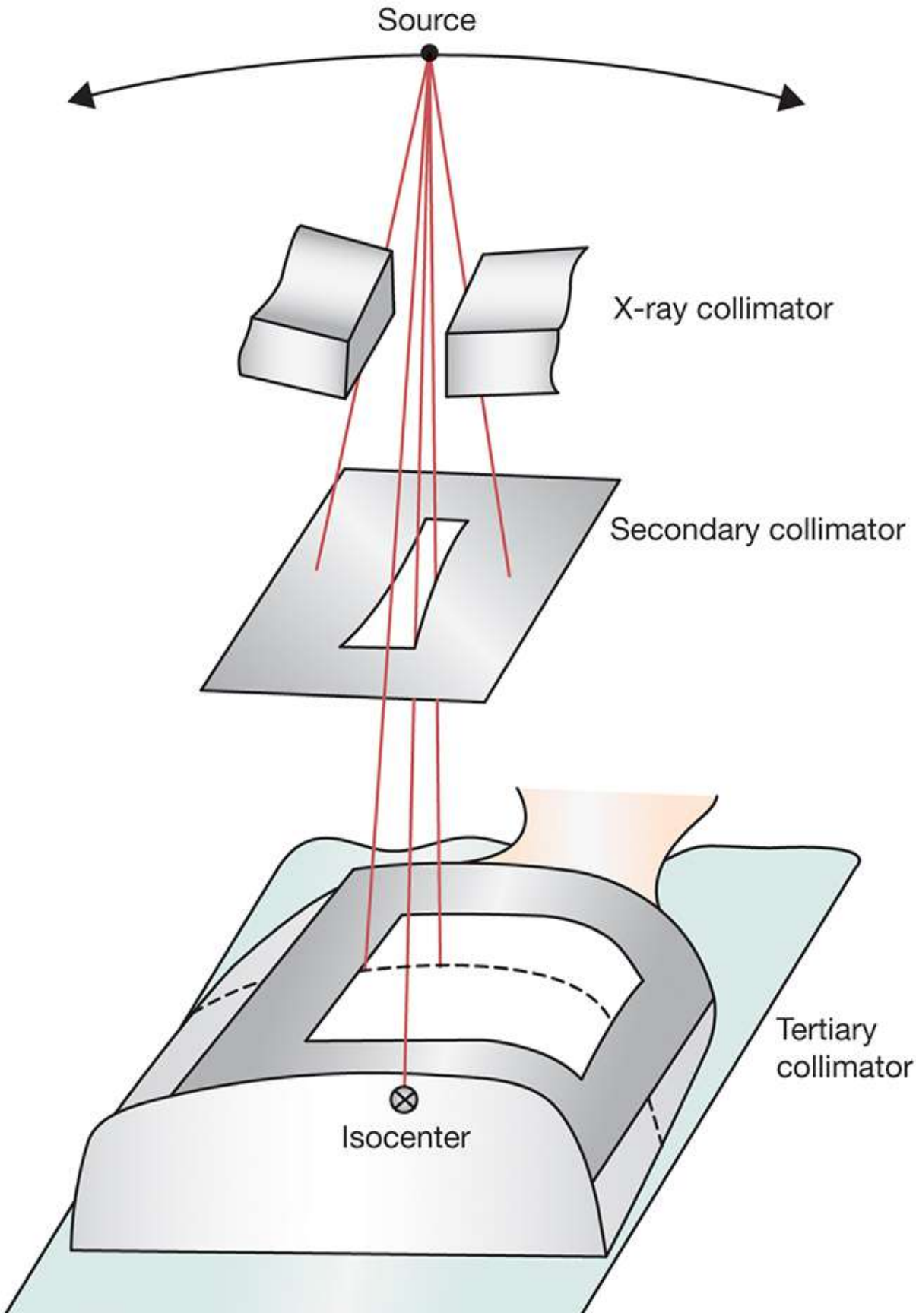
Source
X-ray collimator
Secondary collimator
Tertiary collimator
Isocenter

FIGURE 9.32 Schematic of treatment geometry for electron arc therapy. Skin collimation is required because of the large air gap between secondary collimator and patient, which is needed to allow rotation of the gantry around the patient.

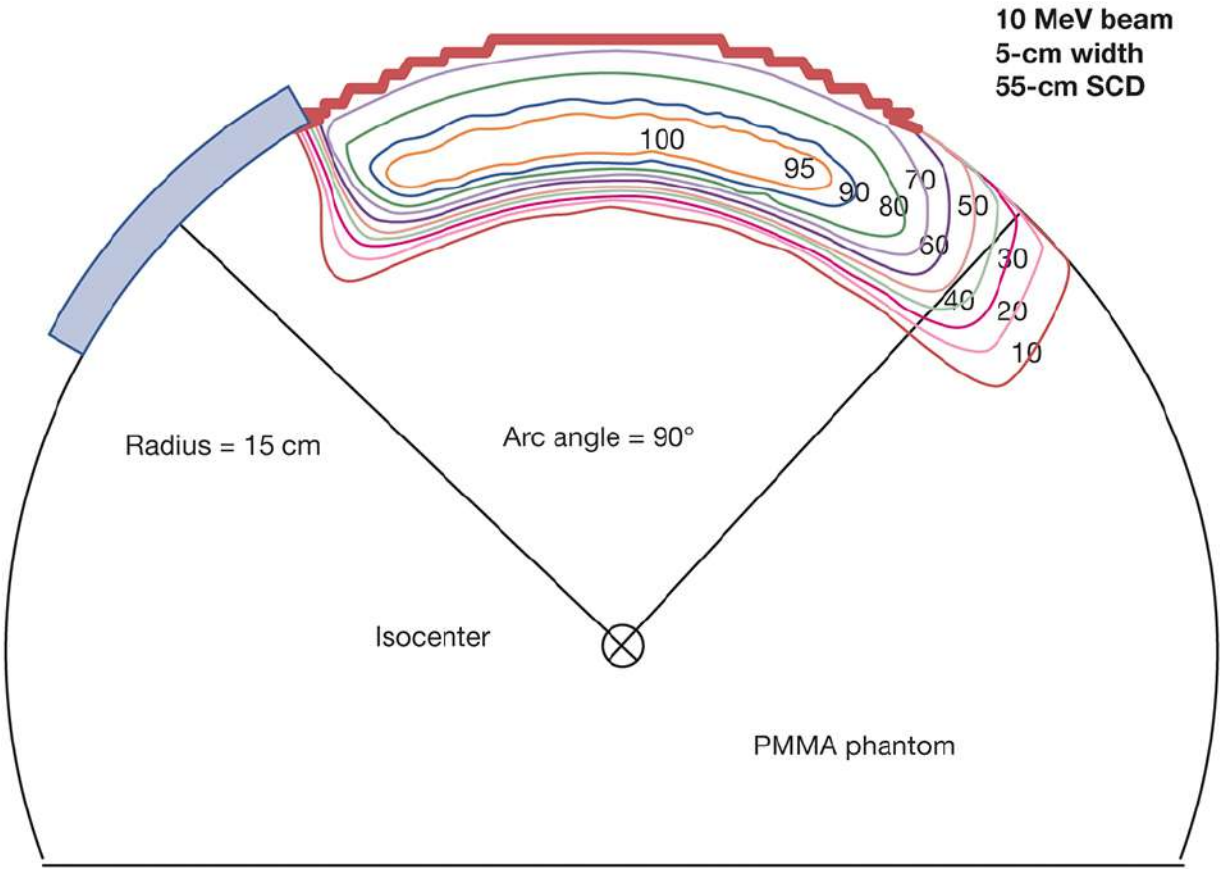

FIGURE 9.33 Comparison of dose distribution with and without skin collimation. The uncollimated edge has a slow dose falloff that is useful for abutting to other arced fields. The skin collimation restores the beam edge but requires rotating the beam 15° beyond the edge of the skin collimator. SSD, source-to-surface distance.

As discussed previously, the depth dose for an arced beam differs from that for a fixed beam (see Figure 9.24B); the surface dose is significantly less, and the dose falloff becomes slightly sharper. Consequently, bolus may be required to deliver adequate dose superficially. Another consequence of beam arcing is that a constant width of the secondary collimator results in dose inhomogeneity in the cephalocaudal direction. The radius of curvature of the patient with respect to the accelerator isocentric axis is typically less

superiorly, as the neck is approached. If the radius of curvature is less, then the skin is farther from the electron source (ie, a greater SSD). Contrary to fixed-beam therapy, the dose to that region increases rather than decreases as a result of focusing of the electron fluence toward isocenter. However, by reducing the collimator width, the dose can be made more uniform.

The treatment planning process for arc therapy requires patient CT scanning, delineation of PTV, selection of isocenter location, specification of electron arc boundaries, energy and slab bolus selection, design of secondary collimator, and calculation of dose and monitor units. Figure 9.34 shows a typical dose distribution that can be achieved using arc therapy for irradiation MERT of the IMC and chest wall. Physics commissioning to initiate this procedure is on the order of 4 to 6 weeks.

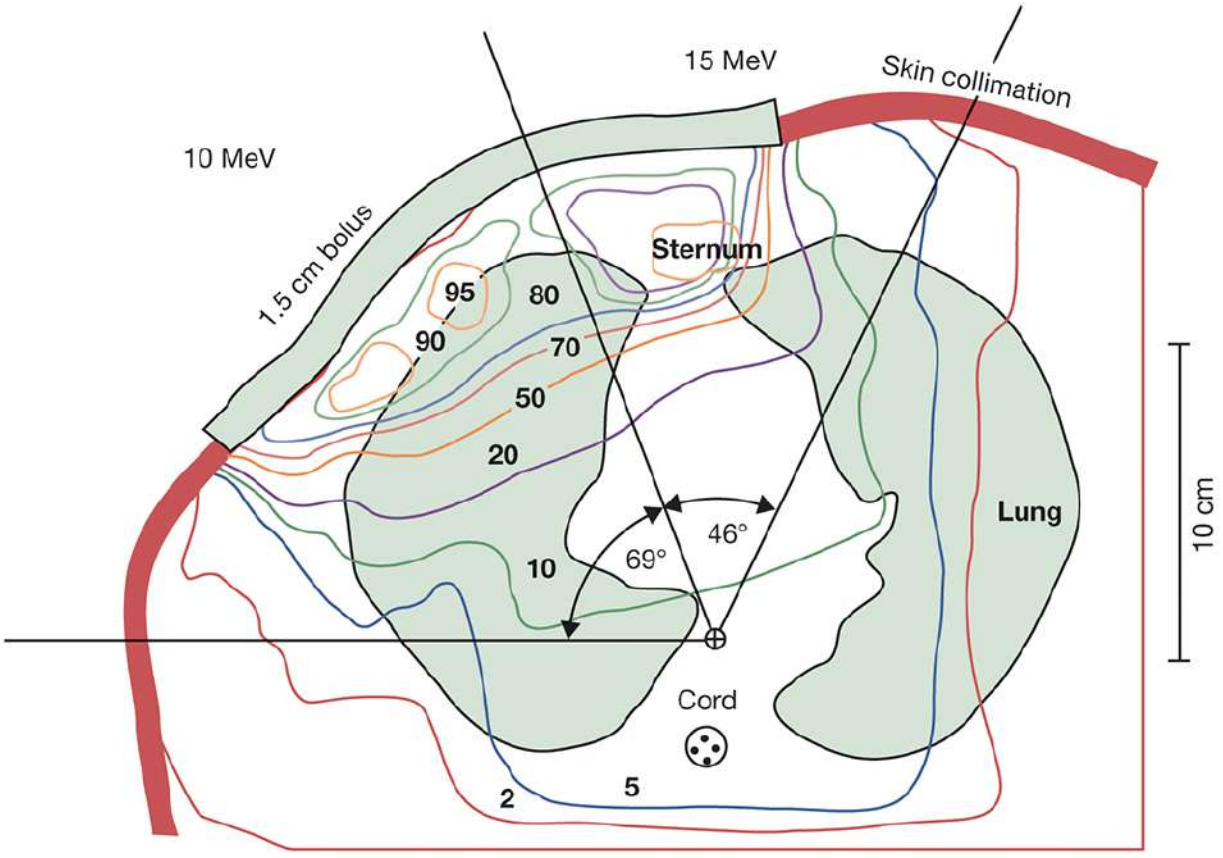

FIGURE 9.34 Typical dose distribution achieved by arc electron therapy. Note the different energies used for the internal mammary chain (IMC) and chest wall fields, the exact abutment of the IMC and chest wall fields, the rotation 15° beyond the skin edges of the skin collimator, and the use of bolus to increase the surface dose. (From Hogstrom KR, Kurup RG, Shiu AS, Starkschall G. A two-dimensional pencil-beam algorithm for calculation of arc electron dose distributions. *Phys Med Biol*. 1989;34[3]:315-341. Copyright © Institute of Physics and Engineering in Medicine. Reproduced by permission of IOP Publishing. All rights reserved.)

Electron radiotherapy has not advanced beyond conventional therapy because of the labor-intensive (cutouts and bolus) tasks to shape and modulate beams, limited conformity in the depth direction, limited lateral conformity, no inverse planning, and no dynamic beam delivery. If these were overcome via an automated method, the conformation of dose distributions to shallow tumors might greatly improve—hence the advent of MERT. There is a definitive niche for MERT to complement a photon IMRT program. MERT will be able to achieve lateral dose conformity by intensity modulation (such as photon IMRT) and dose conformity along the depth direction using energy modulation (unique to electron beams). In

addition, MERT may increase dose uniformity in the target both laterally and along the depth direction, reduce high or moderate concomitant dose to distal organs (eg, lung, heart, and contralateral breast for breast treatments), and improve skin coverage or sparing when combined with photon IMRT.[99,108]

Disease sites such as postmastectomy chest wall, mycosis fungoides or any cutaneous manifestation of lymphoma of the scalp, and so forth are likely best suited for modulated electrons, either with or without photons, or perhaps a combination of both. However, the inherent collimation systems in modern accelerators were optimized for megavoltage photons and are not conducive to electron-beam delivery (in lieu of extended applicators), nor do commercial treatment planning systems model electrons collimated without applicators.

As an example of targeted sites that would be improved with MERT, treatment to the chest wall stands out. Current techniques of using tangential photon adjunct fields abutting supraclavicular and posterior axillary fields are difficult enough without the addition of treating a separate medial breast internal mammary field with a mixture of photons and electrons. Although there has been extensive work to optimize these techniques,[109] there are shortcomings because of match-line problems and delivery of unacceptable doses to volumes of heart, lung, and contralateral breast. Clinical side effects include edema, fibrosis, heart disease, and pneumonitis. Delivery by tangential photon beams to the chest wall is also not ideal because of the heterogeneous dose delivered in the secondary electron buildup region of the breast. Bolus may be used; however, this unfortunately reduces skin sparing. Electron arc therapy was developed in the 1980s to address the limitations of tangential photon-beam treatments,[110] although it was extremely time-consuming to implement. The use of MERT will phase out electron arcs.

Many centers have used photon IMRT to improve dose conformity; however, the fundamental limitations because of megavoltage photon beams, such as excess distal dose and the buildup dose, are still challenges. MERT has been proposed as an alternative, particularly for postmastectomy patients.[8,63] The principal advantage is the rapid distal dose falloff. In principle, electron beams are well suited for these shallow targets, as they will spare distal regions, such as lung and heart.

Optimization is another important aspect for an MERT program. Many people have come up with inverse planning techniques for photons and even more recently for electrons. Al-Yahya et al[111] came up with a method of optimizing electron-beam planning for a few leaf-electron collimator (FLEC). Planning was performed via Monte Carlo calculations and optimization using simulated annealing—a powerful mathematical tool that is the basis for inverse planning. The FLEC system consists of four motor-driven trimmer bars at the end of an applicator that creates rectangular shapes. The report claims potential treatment times of 15 minutes or less. Very comprehensive work by Lee et al[69] described a Monte Carlo optimization scheme for modulated electron-beam radiotherapy based on a stop-and-shoot technique. One of the most challenging things in both calculating and optimizing is the leaf scatter, where distributions could vary up to 20% depending on leaf positions. Lee et al[69] performed MLC planning accomplished by calculating composite distributions for electron beamlets as collimated by tertiary electron MLC. Scatter and leakage contributions were included in the final dose calculation. An inverse planning dose optimization engine designed weights for each beamlet. The particle generation and absorption within the MLC leaves created demanding calculations but were necessary for accurate organ at risk calculations. Therefore, modeling of leaf scatter and transmissions is vital for accurate dose calculations. It is key that a multiple source model be developed. Publications describing the use of photon MLCs to modulate electrons have promoted an effective method to reform conformal electron therapy.[112-114]

SUMMARY

Electron-beam therapy remains an important modality to the practice of radiation therapy. As discussed earlier, its effective use requires knowledge of the unique properties of electron-beam dose distributions, the impact of the patient on the dose distribution, and the basic principles for good practice. It requires access to and the proper use of comprehensive treatment planning and delivery tools. It also requires access to special techniques that offer unique treatment solutions for a limited number but broad range of patient conditions.

Electron therapy can be expected to become more sophisticated in the future as the enthusiasm for MERT grows. Advances in electron dose calculations, methods for electron-beam optimization, and availability of MLCs for electrons will enable the practice of combined intensity-modulated photon and energy-modulated electron therapy. This will advance both electron conformal and mixed-beam therapy.

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CHAPTER 10

Conformal and Intensity-Modulated Radiation Therapy Physics: Treatment Planning and Techniques, and Clinical Applications

James A. Purdy, Geoffrey D. Hugo, and Hania A. Al-Hallaq

Modern anatomic imaging technologies, such as x-ray computed tomography (CT) and magnetic resonance imaging (MRI), provide a fully three-dimensional (3D) model of the anatomy of the patient with cancer, which is often complemented with functional imaging, such as positron emission tomography (PET) or magnetic resonance spectroscopy. Such advanced imaging allows the radiation oncologist to more accurately identify tumor volumes and their relationship with other critical normal organs. Powerful x-ray CT simulation and three-3D treatment planning systems (3DTPS) have now been commercially available since the early 1990s, and 3D conformal radiation therapy (3DCRT) has become the standard of practice for many years.[1-3]

Radiation treatment delivery technology continues to advance through increasing the precision of delivery both spatially and temporally in hopes of continuing to improve clinical outcomes. Recent examples of such technologic advancements include MRI-Linac technology[4] by Elekta (Stockholm, Sweden) and ViewRay (Oakwood Village, OH) as well as developments in proton beam delivery.[5] Specifically, efforts at improved precision rely on improving imaging localization and intrafractional patient monitoring, increasing delivery efficiency, and improving the quality of delivered dose distributions by better aligning the treatment plan with the anatomy of the day through adaptive techniques. Efforts are also being made to reduce the cost of the equipment and simplify use, thus improving global access to modern-day radiotherapy. 3DCRT treatment plans generally use an increased number of radiation beams that are shaped to conform to the target volume. To improve the conformality of the dose

distribution, conventional beam modifiers (eg, wedges, partial transmission blocks, and/or compensating filters) are sometimes used. This *forward planning* approach used for 3DCRT (Figure 10.1) has been supplemented by an *inverse planning* approach used for *intensity-modulated radiation therapy* (IMRT) (Figure 10.2), which can achieve even greater conformity by optimally modulating the individual beamlets that make up the radiation beams.[6,7] IMRT dose distributions can be created to conform much more closely to the target volume, particularly for those volumes having complex/concave shapes, and also shaped to avoid critical normal tissues in the irradiated volume. This increased conformality results in IMRT treatments being much more sensitive to geometric uncertainties than the two-dimensional (2D) or forward-planned 3DCRT approaches and has spurred the development of treatment machines integrated with advanced volumetric imaging capabilities.[2,3,8-10] This has pushed the frontiers in 3DCRT practice from IMRT to what is now referred to as *image-guided radiation therapy* (IGRT).[2,3,11] Of course, the concept of image guidance is not revolutionary and really should be viewed as an evolutionary component in the development of 3DCRT. In the past, many systems and/or processes have been developed to help better localize the patient for treatment (and hence conform the dose), including dedicated x-ray simulators, megavoltage radiographic port films, electronic portal imaging devices (EPIDs), implanted radiopaque markers, ultrasound imaging systems, optical surface tracking systems, etc.[12,13] Even the early isocentric cobalt-60 teletherapy machines in the 1960s came equipped with a kilovolt x-ray tube attached to the beam stop.

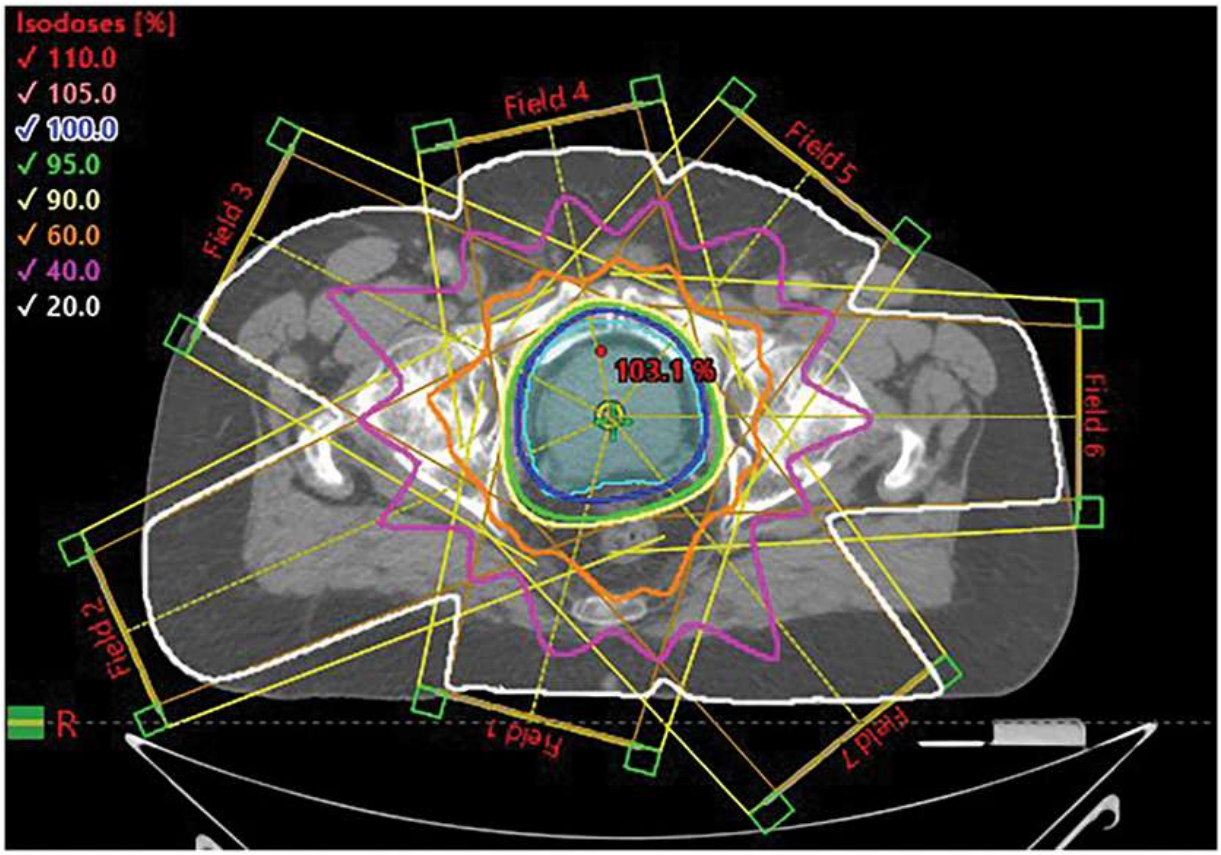


FIGURE 10.1 Three-dimensional conformal radiation therapy is considered a "forward planning" approach that uses an increased number of radiation beams shaped to conform to the target volume. To improve the conformality of the dose distribution, beam modifiers (eg, wedges, partial transmission blocks, and/or compensating filters) are sometimes used. Shown is a prostate seven-field coplanar beam arrangement.

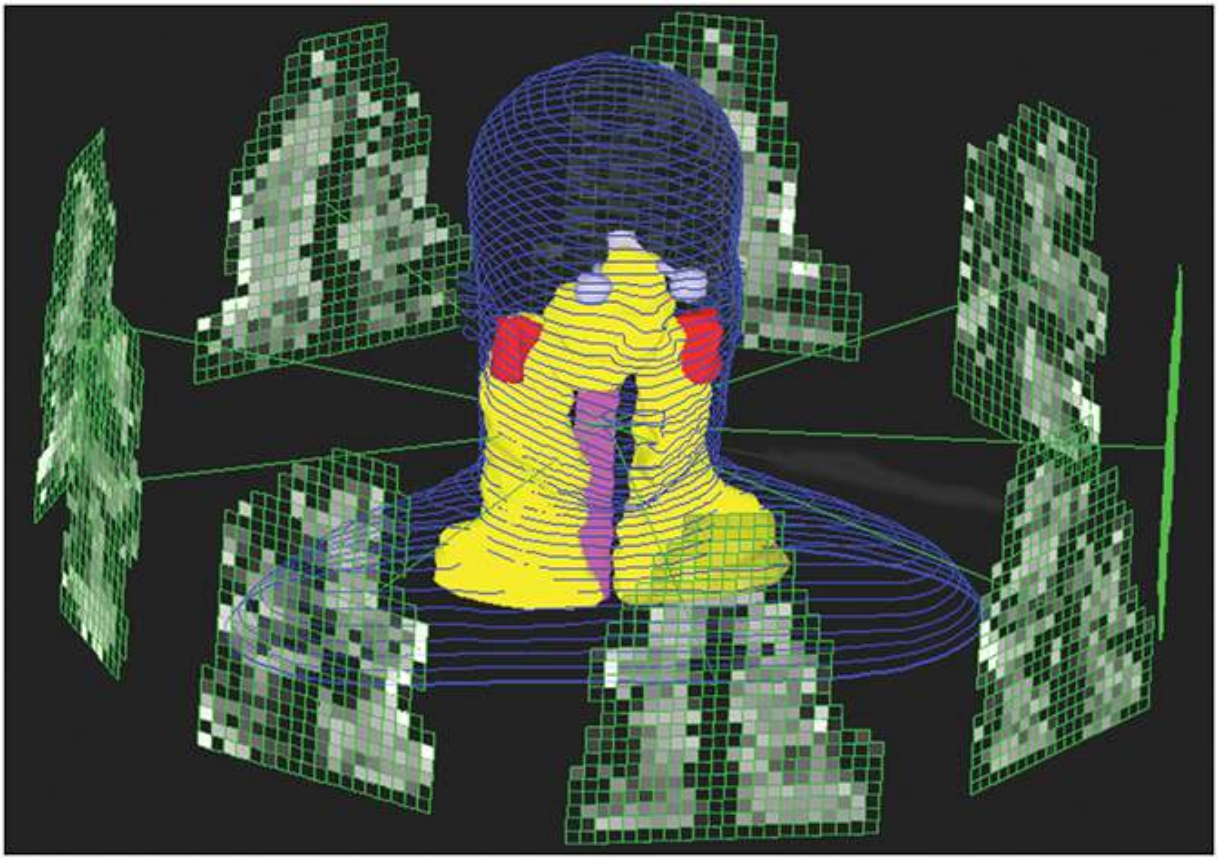


FIGURE 10.2 Intensity-modulated radiation therapy (IMRT) is considered an " inverse planning" conformal radiation therapy approach that can achieve even greater conformity than three-dimensional conformal radiation therapy by optimally modulating the individual beamlets that make up the radiation beams. IMRT dose distributions can be created to conform much more closely to the target volume, particularly for those volumes having complex/concave shapes, and also shaped to avoid critical normal tissues in the irradiated volume.

This chapter will review the critical components that make up the 3DCRT planning and delivery process. The reader should understand that the use of the terms *two-dimensional*, *three-dimensional*, and even *four-dimensional* (4D)[14] as descriptors for the 3DCRT planning and delivery process refers to a process and the various tools used and not merely to beam arrangements. For example, 3D treatment planning certainly does not require the use of "noncoplanar" beams, but does require the ability to plan and visualize volumetric dose distributions for such beam arrangements. Even today, newer tools are being developed that allow 4D, image-based 3DCRT planning, that is, target volume segmentation and dose calculation in the presence of moving organs and target volumes. Hence, the reader will

be able to appreciate the 3DCRT approach much more fully if it is viewed as a constantly evolving planning and treatment delivery workflow process using ever-advancing computer software and technology.

HISTORICAL DEVELOPMENT OF CONFORMAL RADIATION THERAPY AND THREE-DIMENSIONAL TREATMENT PLANNING SYSTEMS

Conformational treatment methods were pioneered in the 1950s and 1960s by several groups, including Takahashi[15] in Japan; Proimos[16] and Trump et al[17] in the United States; and Green et al[18] in Great Britain. Work continued into the 1970s, when several groups actually implemented computer-controlled radiation therapy, including a project of the Joint Center for Radiation Therapy in Boston led by Bjarngard and Kijewski[19] and the Tracking Cobalt Project led by Davy and Brace[20] at the Royal Free Hospital in London.

Sterling et al[21,22] are credited with the first 3D approach to treatment planning (dose calculation and display). They demonstrated a technique by which a computer-generated film loop gave the illusion of a 3D view of the patient's relevant anatomic features and the calculated isodose distribution (2D color washes) throughout a treatment volume. However, this effort did not result in a practical 3DTPS and was viewed as simply a demonstration project. The Rhode Island Hospital/Brown University group made the first real step in implementing a clinically usable 3DTPS based on a new type of display, called beam's eye view (BEV), which simulated the treatment planner's viewing point from the perspective of the radiation source looking out along the axis of the radiation beam, similar to that obtained when viewing a simulation radiograph.[23,24]

The advent of CT spurred further development of 3D planning systems. In 1983, Goitein and coworkers[25,26] reported on their system, which took advantage of CT and increased minicomputer capabilities. The system produced high-quality color BEV displays and could display radiographic images computed from the digital CT data; such computed radiographs are now called digitally reconstructed radiographs (DRRs). By the latter half of the 1980s, several other academic groups had developed 3D planning systems having powerful new features.[27-30]

One of the keys to this development was a series of research contracts funded by the National Cancer Institute (NCI) in the 1980s and 1990s to evaluate the potential of 3D planning and to make recommendations to the NCI for future research in this area.[31] Each of the research contracts funded a collaborative working group (CWG). The participating institutions in each CWG are shown in Table 10.1. Their charge was to evaluate various aspects of this new planning process and develop new software tools needed. The CWGs were composed of physicists, clinicians, and computer scientists. Many important developments and/or refinements in 3D planning came from these NCI research CWGs, particularly planning evaluation software tools such as *dose-volume histograms* (DVHs),[32,33] *electronic view box*,[34] and biologic effect models such as *tumor control probability* (TCP) and *normal tissue complication probability* (NTCP) models.[35] Even IMRT has benefited from the CWG approach, as a consensus statement was developed in 2001 that helped clarify many issues and pointed to important research areas regarding that form of 3DCRT.[36]

TABLE 10.1 NATIONAL CANCER INSTITUTE RESEARCH CONTRACTS IN SUPPORT OF THREE-DIMENSIONAL RADIATION THERAPY TREATMENT PLANNING

Evaluation of Treatment Planning for Heavy Particles (1982-1986)
Lawrence Berkeley Laboratory and University of California
Massachusetts General Hospital, Harvard University
MD Anderson Cancer Center, University of Texas
University of Pennsylvania School of Medicine and Fox Chase Cancer Center
Evaluation of Treatment Planning for External Beam Photons (1984-1987)
Massachusetts General Hospital, Harvard University
Memorial Sloan Kettering Cancer Center
University of Pennsylvania School of Medicine and Fox Chase Cancer Center
Washington University in St. Louis
Evaluation of Treatment Planning for External Beam Electrons (1986-1989)
MD Anderson Cancer Center, University of Texas
University of Michigan
Washington University in St. Louis

Development of Radiation Therapy Treatment Planning Software Tools (1989-1994)

University of North Carolina

University of Washington

Washington University in St. Louis

VOLUME SPECIFICATION FOR CONFORMAL RADIATION THERAPY

The International Commission on Radiation Units and Measurements (ICRU) first addressed the issue of consistent volume and dose specification in radiation therapy with the publication of ICRU Report 29 in 1978.[37] That report defined the *target volume* as *the volume containing those tissues that are to be irradiated to a specified absorbed dose according to a specified time-dose pattern* (Figure 10.3A). It is interesting to note that this report (even though published in the 2D era) attempted to address spatial uncertainties by pointing out that the size and shape of a target volume may change during the course of a treatment and that one should take into account the following parameters when describing the target volume:

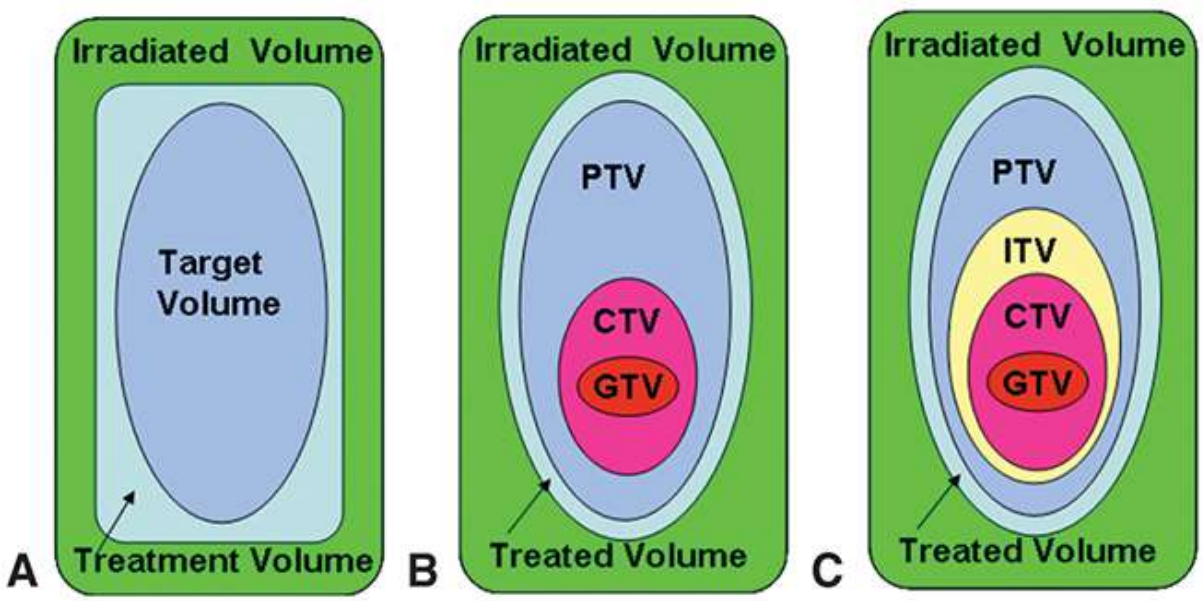


FIGURE 10.3 A. Schematic illustration of the boundaries of the volumes defined by International Commission on Radiation Units and Measures (ICRU) Report 29: target volume, treatment volume, and irradiated volume. B. Boundaries of the volumes defined by ICRU Report 50: gross tumor volume (GTV), clinical target volume (CTV), planning target volume (PTV), treated volume, and irradiated volume. C. Boundaries of the volumes defined by ICRU Report 62: GTV, CTV, internal target volume (ITV), PTV, treated volume, and irradiated volume.

- Expected movements (eg, caused by breathing) of those tissues that contain the target volume relative to anatomic reference points (eg, skin markings, suprasternal notch)
- Expected variation in shape and size of the target volume during the course of treatment (eg, urinary bladder, stomach)
- Inaccuracies or variations in treatment setup during the course of treatment

In addition to the target volume, ICRU Report 29 defined two other volumes: the *treatment volume* and the *irradiated volume*. These volumes were not based on anatomy, but instead were based on the dose distribution. The treatment volume was defined as *the volume enclosed by the isodose surface representing the minimal target dose*, and the irradiated volume was defined as *the volume that receives a dose considered significant in relation to normal tissue tolerance* (eg, 50% isodose surface).

Report 29 defined *organs at risk* (OARs) as *especially radiosensitive organs in or near the target volume whose presence influences treatment planning and/or prescribed dose*. The report also recognized the importance of tissues outside the target area that received a dose higher than 100% of the specified target dose. This was defined as a *hot spot* and was considered clinically meaningful only if the corresponding isodose curve enclosed an area of at least 2 cm^2 in a section.

In 1993, the ICRU updated its recommendations for specifying dose/volume in Report 50, which were well suited for conformal therapy.[38] The target volume definition was separated into three distinct volumes: (1) visible tumor, that is, *gross tumor volume* (GTV); (2) a volume to account for uncertainties in microscopic tumor spread, that is, *clinical target volume* (CTV); and (3) a volume to account for geometric and other uncertainties, that is, *planning target volume* (PTV), as illustrated in Figure 10.3B.

GTV and CTV are anatomic-clinical concepts that should be defined before a choice of treatment modality and technique is made. Labels or subscripts with the GTV nomenclature can be used to distinguish between primary disease and other areas of macroscopic tumor involvement such as involved lymph nodes that are visible on imaging studies (eg, $GTV_{primary}$ and GTV_{nodal}, or GTV-T and GTV-N). Similarly, the GTV together with this surrounding volume of local subclinical involvement that defines the CTV can be denoted as CTV-T. Note that even if the GTV has been removed by radical surgery, the volume can be designated as CTV-T. In specifying the CTV, the physician must consider not only microextensions of the disease near the GTV but also the natural avenues of spread for the particular disease and site, including lymph node, perivascular, and perineural extensions. These may be designated CTV-N (and, if necessary, CTV-N1, CTV-N2, etc).

The *PTV* is defined by specifying the margins that must be added around the CTV to manage the effects of organ, tumor and patient movements, inaccuracies in beam and patient setup, and any other uncertainties. The PTV is a static, geometric concept used for treatment planning and for specification of dose. Its size and shape depend primarily on that of the GTV/CTV and the effects caused by internal motions of organs and the tumor and technical aspects of treatment technique (eg, patient fixation).

The PTV can be considered a 3D envelope in which the tumor and any microscopic extensions reside and move. Once the PTV is defined, appropriate beam sizes to account for penumbra and beam arrangements must be selected to ensure the desired dose coverage of the PTV. Note that multiple PTVs may be defined for a patient's radiation therapy treatment. For example, it is common practice to plan a higher dose to the PTV enclosing the GTV and a lower dose to the PTV containing the CTV. Such planning volumes are typically subscripted using the dose level prescribed; for example, PTVs for 66 and 54 Gy can be represented as PTV_{66} and PTV_{54}, respectively.

ICRU Report 50 essentially retained the definition of the two dose volumes present in ICRU Report 29, changing the treatment volume name to *treated volume* and refining the definition as *the volume enclosed by an isodose surface*, *selected and specified by the radiation oncologist as being appropriate to achieve the purpose of treatment* (eg, tumor eradication, palliation), and the irradiated volume as that *tissue volume that receives a dose that is considered significant in relation to normal tissue tolerance*.

Report 50 refined the definition of OARs as *normal tissues whose radiation sensitivity may significantly influence treatment planning and/or prescribed dose*. The report did state that any possible movement of the OAR during treatment, as well as uncertainties in the setup during the whole treatment course, must be considered, but did not provide a method to do so.

The hot spot definition was modified to be *a volume outside the PTV that received a dose larger than 100% of the specified PTV dose*. This was considered clinically meaningful only if the minimum diameter exceeded 15 mm (note: previously, it had been 2 cm^2). However, if the hot spot occurs in a small organ, such as the optic nerve, a dimension smaller than the recommended 15 mm should be considered.

While Report 50 was well suited to conformal therapy, irradiation techniques continued to evolve (eg, IMRT, IGRT), and advances in imaging procedures (eg, PET, MRI) provided even more information on functionality, the location; shape, and limits of tumor/target volumes; and OARs. In response to these developments, the ICRU in 1999 published Report 62,[39] which expanded on some of the definitions and concepts of

Report 50 and took into account the consequences of the technical and clinical progress referred to previously. However, it should be clearly understood that Report 62 is intended to complement the recommendations contained in Report 50 and not to replace it.

ICRU Report 62 refined the definition of PTV by introducing the concept of an *internal margin* to take into account variations in size, shape, and position of the CTV in reference to the patient's coordinate system using anatomic reference points, as well as the concept of a *setup margin* to take into account all uncertainties in patient beam positioning in reference to the treatment machine coordinate system. Identification of these two types of margins is needed, as they compensate for different types of uncertainties and refer to different coordinate systems. Internal margin uncertainties are due to physiologic variations (eg, filling of the rectum, movements because of respiration) and are difficult or almost impossible to directly control from a practical viewpoint. Setup margin uncertainties are related largely to technical factors that can be dealt with by more accurate setup and immobilization of the patient and improved mechanical stability of the machine. However, exactly how these margins should be combined is still not clear. This point will be discussed further in a later section, but for now, it is necessary to understand that the selection of an overall margin and delineation of the border of the PTV typically involve a compromise that requires the experience and judgment of the radiation oncologist and the treatment planning team.

ICRU Report 62 defines the volume formed by the CTV and the internal margin as the *internal target volume* (ITV) (Figure 10.3C). The ITV represents the movements of the CTV referenced to the patient coordinate system and is specified in relation to internal and external reference points, which preferably should be rigidly related to each other through bony structures. In cases not involving significant internal organ motion, the radiation oncologist can simply ignore having to explicitly define the ITV and use only the GTV, CTV, and PTV concepts. However, in cases involving significant motion, such as often is the case with lung cancer, the ITV concept has proven useful and should be used.[40]

ICRU Report 62 refined the definition of the two dose volumes defined by ICRU Report 50 as follows:

> The treated volume is the tissue volume that (according to the approved treatment plan) is planned to receive at least a dose selected and specified by radiation oncology team as being appropriate to achieve the purpose of the treatment, e.g., tumor eradication or palliation, within the bounds of acceptable complications.

The irradiated volume is the *tissue volume that receives a dose that is considered significant in relation to normal tissue tolerance*.

Report 62 refined the definition of OARs as *normal tissues* (*eg, spinal cord) whose radiation sensitivity may significantly influence treatment planning and/or prescribed dose*. The report also included a discussion regarding a system of classifying OARs as "serial," "parallel," or "serial-parallel." Report 62 also addressed what was perhaps the most criticized limitation of Report 50, which was that it did not provide a method to account for OAR movements and changes in shape and/or size, as well as setup uncertainties. To account for such spatial uncertainties, Report 62 introduced the concept of the *planning organ at risk volume* (PRV), in which a margin is added around the OAR to compensate for that organ's geometric uncertainties. The PRV margin around the OAR is analogous to the PTV margin around the CTV. The introduction of the PRV concept is timely, as its use is even more important for those conformal therapy cases involving IMRT because of the increased sensitivity of this type of treatment to geometric uncertainties. For example, it is common practice to add a 0.5-cm rind around the spinal cord contour. Note that the PTV and the PRV may overlap, and often do so, which implies searching for a compromise in weighing the importance of each in the planning process. A summary of the ICRU volume nomenclature recommendations per report is presented in Table 10.2.

TABLE 10.2 SUMMARY OF THE INTERNATIONAL COMMISSION ON RADIATION UNITS AND MEASUREMENTS (ICRU) NOMENCLATURE FOR VOLUMES (1970S TO PRESENT)

ICRU Report 29: 1970s-1993	ICRU Report 50: 1993-Present	ICRU Report 62: 1999-Present	ICRU Report 83: 2010-Present
Target volume	GTV	GTV	GTV
	CTV	CTV	CTV

ICRU Report 29: 1970s-1993	ICRU Report 50: 1993-Present	ICRU Report 62: 1999-Present	ICRU Report 83: 2010-Present
	PTV	ITV	ITV
		PTV	PTV
Treatment volume	Treated volume	Treated volume	Treated volume
Irradiated volume	Irradiated volume	Irradiated volume	Irradiated volume
Organ at risk	Organ at risk	Organ at risk	Organ at risk
		PRV	PRV
			RVR
Hot spot (area outside target that receives dose >100% of specified target dose; at least 2 cm^2 in a section)	Hot spot (volume outside PTV that receives dose >100% of specified PTV dose; >15 mm diameter)	Hot spot (volume outside PTV that receives dose >100% of specified PTV dose; 15 mm diameter)	High dose to RVR
Dose heterogeneity (no value given)	Dose heterogeneity (+7% to −5% of prescribed dose)	Dose heterogeneity (+7% to −5% of prescribed dose)	Not specified

CTV, clinical target volume; GTV, gross tumor volume; ITV, internal target volume; PRV, planning risk volume; PTV, planning target volume; RVR, remaining volume at risk.

CONFORMAL RADIATION THERAPY PLANNING PROCESS

As previously stated, 3DCRT treatment planning and delivery are best considered as a process along with the tools used. This process is summarized in Table 10.3 and includes the following tasks, which are discussed in the ensuing sections:

TABLE 10.3 CONFORMAL RADIATION THERAPY PROCESS

1. Patient treatment position, immobilization, and planning imaging
   a. Position patient in proposed treatment position.
   b. Fabricate immobilization devices.
   c. Place radiopaque markers, and mark repositioning lines on patient and immobilization devices.

d. Obtain topograms to check patient alignment.
e. Perform volumetric computed tomography (CT) scan of patient in treatment position.
f. Make illustrative photographs to assist in repositioning the patient at the treatment couch.
g. Transfer CT images to three-dimensional treatment planning system (3DTPS).
h. Perform imaging studies (eg, magnetic resonance imaging, positron emission tomography/CT, etc) as requested by the treating physician, and transfer image data to 3DTPS.

2. Delineation of tumor/target volumes and organs at risk
   a. Physician contours target volume(s).
   b. Physician or dosimetrist contours organs at risk.
3. Dose prescription
   a. Physician provides prescription dose for planning target volume (PTV) and dose-volume constraints for organs at risk.
   b. Forward planning (3D conformal radiation therapy)
      i. Set up initial beam configuration and design field shapes; wedges/bolus/no beam modifiers; beam weights.
      ii. Compute 3D dose matrix.
      iii. Compute treatment machine monitor units.
   c. Inverse planning (intensity-modulated radiation therapy [IMRT])
      i. Set up initial beam configuration.
      ii. Enter desired dose-volume constraints for PTV(s) and all regions of interest
      iii. Initiate treatment planning system optimization process, which generates beam fluences, resulting dose distribution, monitor units, and leaf motion files.
4. Plan evaluation and improvement
   a. Evaluate plan (dose-volume histograms, planar isodose display, 3D isodose display) and modify until plan is found to be acceptable by treating physician.
   b. Transfer patient's plan to patient's chart (electronic medical record) and treatment machine verify and record (R&V) system.
5. Plan implementation and treatment verification
   a. Physicist performs second check of treatment plan and transfer of data to R&V system.
   b. For IMRT plans, perform phantom dosimetric verification.
   c. Verify patient position and isocenter placement on treatment machine using orthogonal portal electronic portal imaging devices (EPIDs) vs digitally reconstructed radiograph (DRRs) or using onboard CT vs planning CT.
   d. For 3DCRT, check field shapes by comparing treatment field DRRs with treatment beam EPIDs.
   e. Capture treatment machine settings in R&V system.
   f. Check first-day treatment with in-vivo dosimeter measurements (as needed).

g. Perform periodic imaging verification checks during treatment (eg, orthogonal EPIDs/DRRs or beam EPIDs/DRRs, cone-beam CT/planning CT).

1. Establishing the patient's treatment position, constructing a patient repositioning immobilization device when needed, and obtaining a volumetric image data set of the patient in treatment position
2. Contouring target volumes and OARs using the volumetric planning image data set
3. Specifying a prescription dose for the PTV and dose- volume constraints for any OARs
4. For 3DCRT forward planning, determining beam orientation and designing beam apertures and computing a 3D dose distribution according to the dose prescription; or, for IMRT or volumetric modulated arc therapy (VMAT) inverse planning, setting up initial beam orientations (for IMRT) or arc trajectories (for VMAT) and entering optimization parameters (ie, dose-volume constraints for PTVs and all regions of interest) and initiating the TPS optimization process, which generates beam fluences, resulting dose distribution, monitor units (MUs), and leaf motion files
5. Evaluating the treatment plan and, if needed, modifying the plan (eg, beam orientations, apertures, beam weights, etc) until an acceptable plan is approved by the radiation oncologist
6. Implementing the approved plan on the treatment machine and verifying the patient's treatment using appropriate quality assurance (QA) procedures throughout the treatment

Patient Treatment Position and Immobilization and Planning of Imaging

In the initial part of the 3DCRT process (preplanning), the proposed treatment position of the patient is determined, and the immobilization device to be used during simulation/treatment is selected. It should be clearly understood that repositioning patients and accounting for internal organ movement for fractionated radiation therapy in order to accurately reproduce the planned dose distribution remain difficult technical aspects of the 3DCRT process. Errors may occur if patients are inadequately

immobilized, with resultant treatment fields inaccurately aligned from treatment to treatment (interfraction). In addition, patients and/or their tumor volume may also move during treatment (intrafraction) because of either inadequate immobilization or physiologic activity. Accounting for all of the uncertainties in the 3DCRT planning and delivery process remains a challenge for radiation oncology, and research and development is ongoing.

Determination of the treatment position of the patient and constructing the immobilization device are typically accomplished in a dedicated radiation therapy CT simulator facility. A radiation therapy CT simulator consists of a diagnostic-quality CT scanner, laser patient positioning/marking system, virtual simulation 3D treatment planning software, as well as various digital display systems for viewing the DRRs.[41,42] The CT scanner is used to acquire a volumetric planning CT scan of a patient in treatment position. The use of intravenous or other contrast to help delineate target volumes needs to be considered during simulation in some cases. CT topograms should be generated first and reviewed prior to acquiring the planning scan to ensure that patient alignment is correct, with adjustments to be made if needed. Radiopaque markers can be placed on the patient's skin and the immobilization device to serve as fiducial marks to assist in any coordinate transformation needed as a result of 3D planning and eventual plan implementation. An example of a typical immobilization repositioning system used for patients undergoing radiation therapy for head and neck cancer is shown in Figure 10.4. PET-CT simulators[43] are also used in a number of departments. The trend for replacement of CT simulators with PET-CT simulators was especially active in the 2000s. More recently, there is a trend for use of MR simulators in RT- and MR-only-based simulation, and treatment planning has been an active topic of research and development.[44,45]

FIGURE 10.4 Example of immobilization repositioning system used for patients undergoing radiation therapy for head and neck cancer. It should be clearly understood that being able to accurately reposition the patient and account for internal organ movement in order to accurately deliver the planned dose distribution is one of the most important steps in the conformal therapy process. (Courtesy of CQ Medical.)

Planning CT scan protocols are tumor site dependent and typically range from 2 to 5 mm in slice thickness and 50 to 200 slices. In general, a 3-mm slice thickness provides adequate-quality DRR. In some sites, such as those of head and neck cancer, slice thicknesses of 1 mm are often needed for delineation of very small volumes, such as the optic chiasm and the optic nerves. The same holds true for optimal reconstruction of the position of any implanted markers used, such as in prostate cancer radiation therapy.

The planning CT data set is typically transferred to a 3DTPS via a computer network. The planning CT data set provides an accurate geometric model of the patient, as well as the electron density information needed for the calculation of the 3D dose distribution that takes into account tissue heterogeneities.

Delineation of Tumor/Target Volumes and Organs at Risk

Delineation of tumor/target volume and OAR contours using the volumetric CT data set is typically performed by the radiation oncologist and the medical dosimetrist working as a team. The CT data are displayed at the 3DTPS or a specialized RT image processing workstation (Figure 10.5), and contours are drawn manually by the radiation oncologist/dosimetrist, most often using a computer mouse or stylus on a slice-by-slice basis. Some OARs with distinct boundaries (eg, skin, lung) can be contoured automatically or semi-automatically (eg, through interpolation of intermediate slices between manually contoured slices), with only minor editing required; others (eg, brachial plexus) require the hands-on effort of the radiation oncologist.[46] With modern 3DTPS image segmentation software, contouring generally takes 0.5 to 1 hour, depending on the disease site. However, for some complex sites, such as head and neck cancer, where many OARs and complex tumor/target volumes are the norm, this task can take several hours. Consensus guidelines for delineation of targets and OARs for various anatomic sites are often developed by a panel of experts, through national[47] and international[48] clinical trial organizations. Use of the most recent consensus guidelines aids in standardizing organ delineation and thereby improves overall treatment quality.[49] For reference, the National Research Group (NRG) has developed consensus contouring guidelines for many anatomic sites.[50] To prepare organ contours for use in big data applications including development of treatment planning models, TG-263 recommends an ontology for labeling contours that many clinics have begun to adopt.[51]

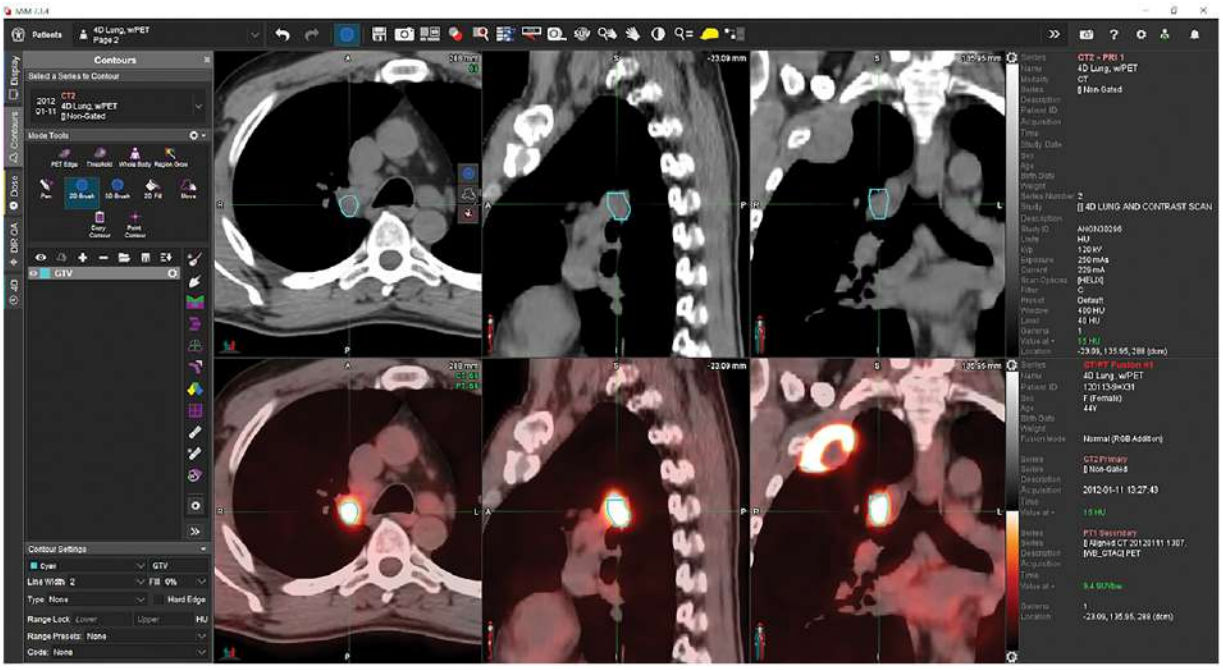
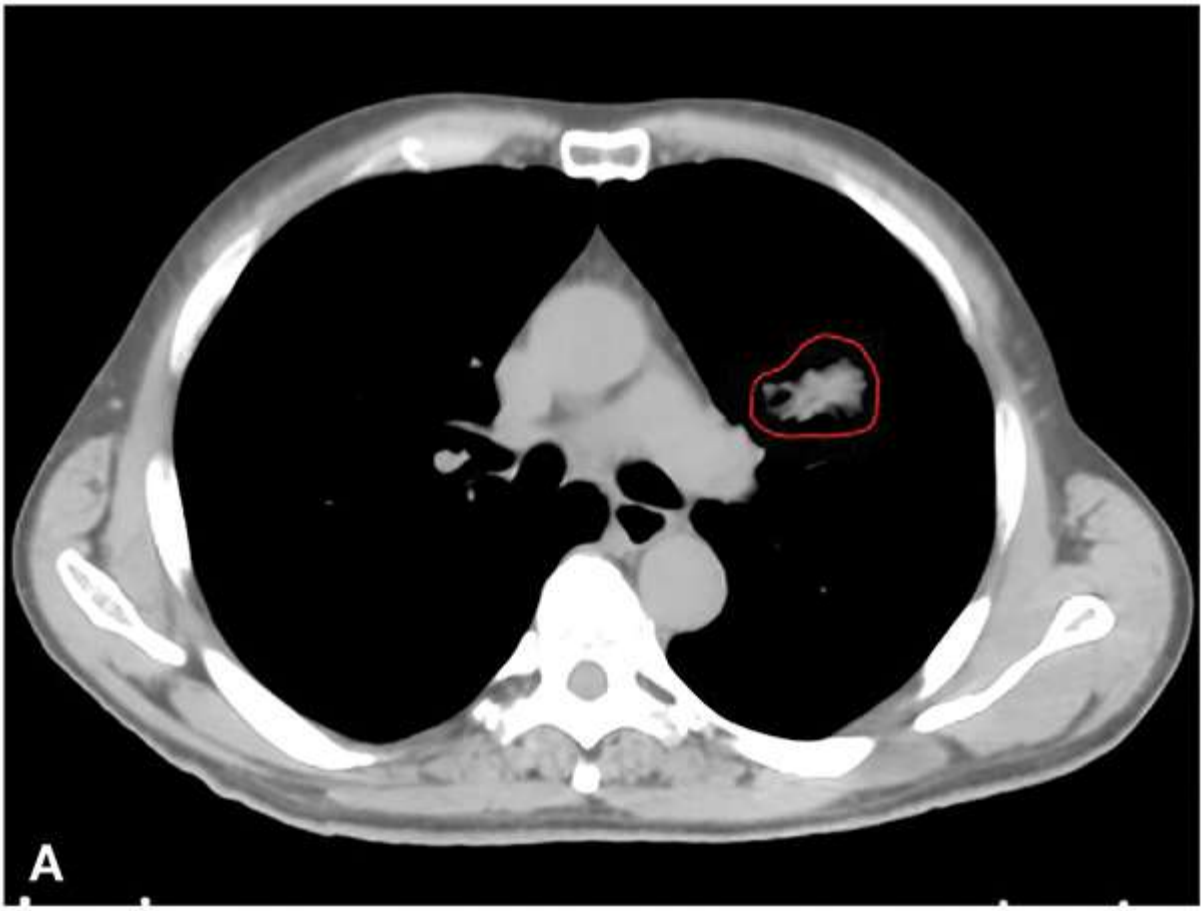
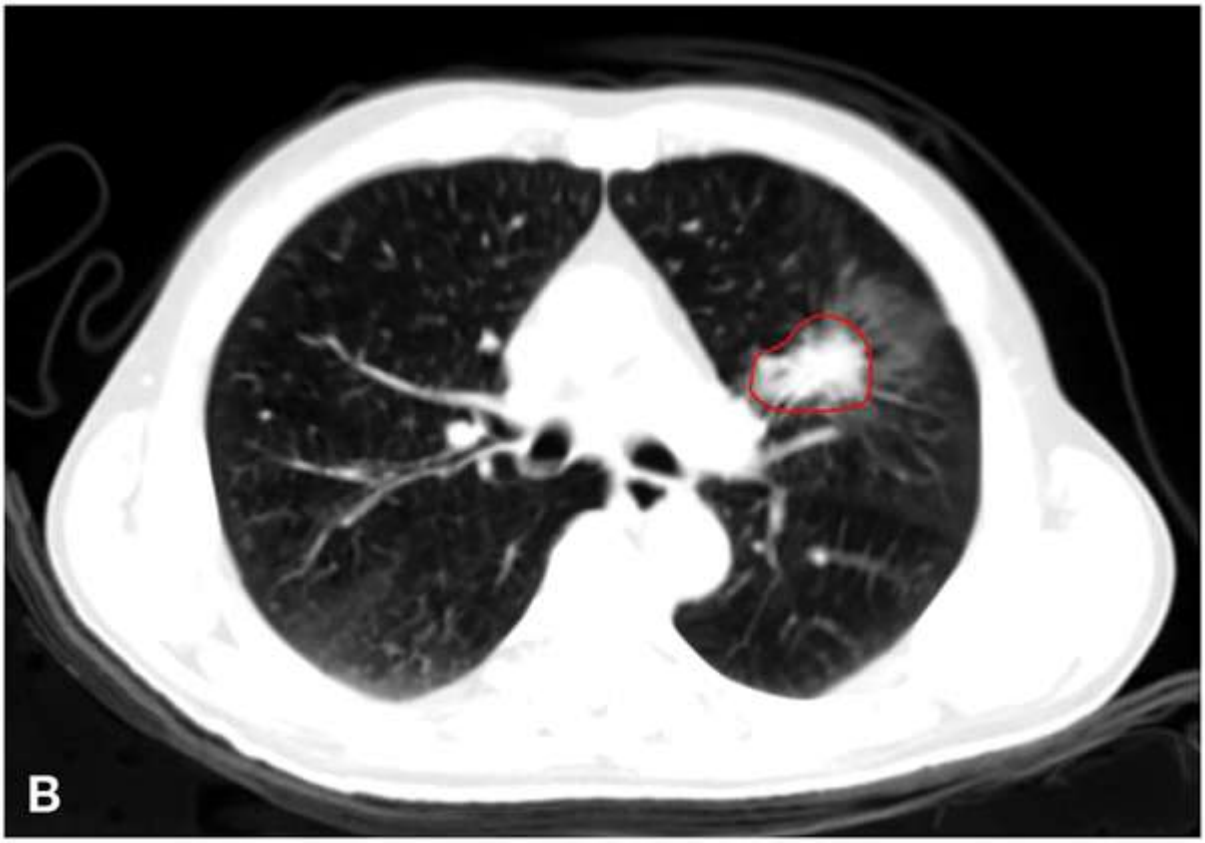


FIGURE 10.5 Advanced image segmentation software provides tools for radiation oncologists and treatment planners to determine critical structures and tumor and target volumes for three-dimensional planning. Computed tomography (CT) data along with ancillary images such as positron emission tomography (PET) are displayed, and contours are drawn by the treatment planner/radiation oncologist around the tumor, target, and normal tissues on a slice-by-slice basis. The bottom row shows PET data with overlying contours after image registration with the CT data.

CT is still the principal source of imaging data used for defining the GTV for most sites, but this imaging modality presents several potential pitfalls. First, when contouring the GTV, it is essential that the appropriate CT window and level settings be used in order to determine the maximum dimension of what is considered potential gross disease (Figure 10.6), often in combination with other imaging modalities such as PET or MRI. Second, for those treatment sites in which there is considerable organ motion, such as for tumors in the thorax, conventional CT acquisitions do not correctly represent either the time-averaged position of the tumor or its shape, and hence 4D CT technology must be used to appropriately capture both the shape and position of the anatomy.[52-54] This can be understood by appreciating the fact that CT simulators rely almost exclusively on the use of fast helical CT technology and thus acquire data essentially in limited width slices and combine them to construct a 3D matrix. This has the effect of capturing the tumor cross-sectional images at particular positions in the

breathing cycle. If the tumor motion is irregular, transverse sections of the tumor could be imaged at different points of the breathing cycle, leading to volume uncertainties. The interpolation process in spiral CT technology adds further to the uncertainty. As a result, the 3D reconstruction of the GTV from temporally variant 2D images often results in a poor representation of the tumor and its motion.


A


B

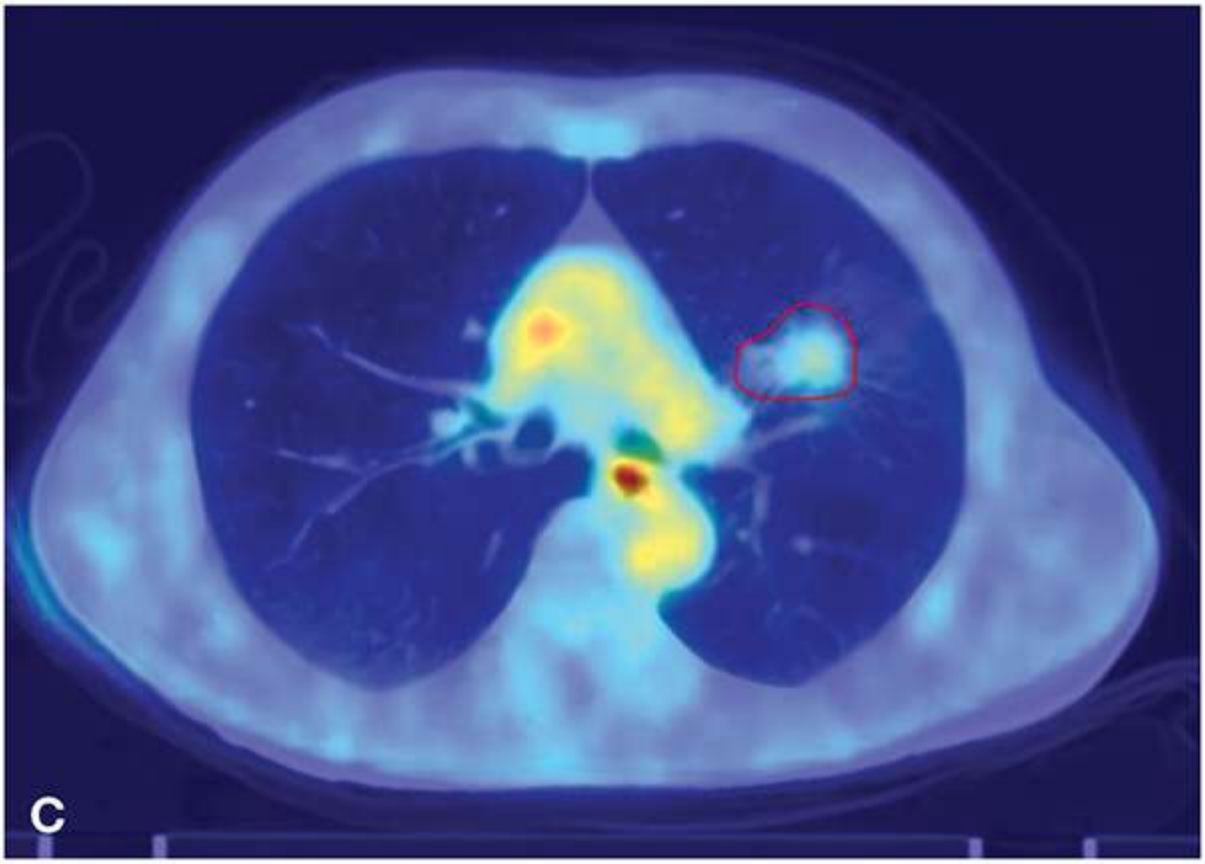


FIGURE 10.6 Computed tomography (CT) slices from a patient with lung cancer demonstrate that the appropriate CT window and level settings must be used to determine the maximum dimensions of the gross tumor volume (GTV). For a lung nodule, a lung window (B) is more appropriate than a soft tissue window (A), although the soft tissue window may be useful to differentiate disease infiltrating the soft tissue, such as the hilum and mediastinum. Note that a much smaller GTV would have been contoured with the settings used in A. C. Positron emission tomography image used to help differentiate tumor from adjacent normal tissue.

4D CT technology has become the standard for CT simulators, making it possible to capture images in each phase of the respiratory cycle.[55,56] In addition, other technologies and methodologies to explicitly help manage the movements induced by the respiratory motion (to the order of <5 mm during treatment preparation and delivery) continue to be developed, including respiratory-gated techniques, respiration- synchronized techniques, breath hold techniques, and forced shallow breathing methods.[57-59] However, a recent survey[59] on clinical practice of respiratory motion management showed that the majority of respondents use a passive (ITV-based) method of management, with a smaller percentage using breath

hold or abdominal compression, and less than 15% using gating or other active management methods.

Critical factors in 4D CT deployment include establishing a high-quality respiratory surrogate, as this signal determines the respiratory phase for sorting of the data during reconstruction. Various systems including belt strain gauges, laser or infrared range finders, or surface imaging can be used as the respiratory surrogate. As the 4D CT acquisition is a slow helical acquisition, typically the tumor and surrounding anatomy is only captured during one or a few breaths. Irregular breathing can thus influence the quality of the 4D CT reconstruction, and the user should understand that the ITV generated from this 4D CT only represents a "snapshot" of the true, underlying respiratory motion expected during treatment.

Delineating the CTV is even more difficult and must be done by the radiation oncologist based on clinical experience (and/or the use of published CTV atlases for certain clinical sites) because current imaging techniques cannot be used to directly detect subclinical tumor involvement. This field has seen a virtual explosion in the use of multimodality imaging over the last decade, and radiation oncologists have developed considerable imaging expertise in order to accurately define GTVs and be able to define nonvisible CTVs. However, the need for a higher level of image-based cross-sectional anatomy training in this field is well recognized.[60] The American Association of Physicists in Medicine (AAPM) Task Group 132 addresses integration of multimodality imaging in the treatment planning and treatment processes.[61]

The PTV margin is specified by the radiation oncologist, often in consultation with the radiation oncology physicist and/or dosimetrist. On most occasions, it is based on published clinical experience that is not calculated based on measurements performed by the department for a particular treatment machine/technique and team. Alternatively, van Herk and colleagues[62,63] reported extensively on the influence of systematic and random errors/variations on the required margins to account for setup error and organ motion and developed margin recipes for calculating individualized (eg, for each department, machine, and team) margins as given by the following equation:

$$\text{PTV margin} = 2.5\sigma + 0.7\sigma$$

where σ is the standard deviation of the systematic setup errors and σ is the standard deviation of the random setup errors.

When defining the PTV, the radiation oncologist should account for the asymmetric nature of positional uncertainties (Figure 10.7). For example, it is recognized that prostate organ motion and daily setup errors may be anisotropic (side-to-side or rotational shifts of the position of the patients are likely to have a different result compared to movement in the anterior-posterior direction). Thus, the PTV margin around a CTV generally should not be uniform.

FIGURE 10.7 Computed tomography images of a patient with prostate cancer showing the contour outlines for the gross tumor volume (GTV), planning target volume (PTV), bladder, and rectum. The physician made the decision that no additional margin around the prostate for the clinical target volume (CTV) was required (ie, CTV = GTV). Note that a nonuniform margin around the GTV/CTV was used to define the PTV in the region of the rectum. Also note the additional PTV contours needed to cap the GTV/CTV.

Typically, when the beam portal is defined, additional margin beyond the PTV is required to obtain dose coverage because of beam penumbra and treatment technique. This emphasizes that treatment portal margins in relation to the PTV must be set according to the dosimetric characteristics of the beams being used. Often for conventional fractionation, a 5-mm margin (portal edge to PTV) is a good starting point, which can be increased if needed, but one must be knowledgeable about the characteristics of the actual beams used to make this starting-point determination. An additional point to understand is that in the case of

coplanar treatment techniques, the margins required across the plane of treatment and the margins orthogonal (say superior-inferior) to this plane will be different. To clarify this point, consider a pelvic four-field axial technique as an example. Portions of the lateral aspects of the PTV that are in the low-dose regions (near the penumbra) of the anterior-posterior and posterior-anterior fields will be in the high-dose regions (well away from the beam penumbra) of the lateral fields. However, the superior and inferior aspects of the PTV will always be in the same low-dose regions of all four fields, so there will be no dose filling from any of the fields. Thus, a larger portal margin in the inferior-superior dimension is needed to ensure that the prescription isodose resulting from all beams contains the PTV, whereas the lateral and anterior-posterior portal margins for each field may be reduced due to the other beams filling in the dose. The same holds true for the portals of the boost fields used in the so-called integrated boost technique, in which the beams used for treating the large volume fill up the dose in the buildup region of the boost volume. Last, the size of the margins will also be affected by the relative beam weighting. Hence, making hard rules about margin sizes is impossible and requires some planning iteration to find the right mix of beam margins.

When a PTV overlaps with a contoured normal structure, it is important to be explicit as to which volume the overlapping voxels are assigned for optimization purposes and for DVH calculations. Planning systems should allow the overlapping voxels to be included in both volumes for plan evaluation and reporting purposes. This ensures that the clinician is aware of the potential for the high-dose region to include part of the normal structure as well as the PTV when reviewing the DVHs. For example, Figure 10.8 illustrates the dosimetric prioritization that is required in clinical trials NRG-BR001 and NRG-BR002 when the PTV overlaps with certain OARs as described by Al-Hallaq et al.[64]

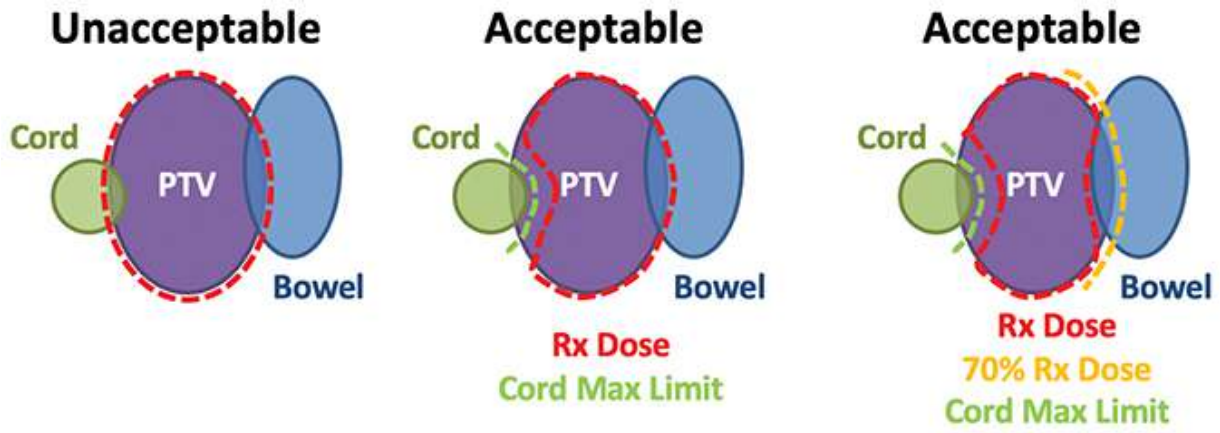


FIGURE 10.8 The treatment protocol for multiple metastases developed for clinical trials National Research Group (NRG)-BR001 and NRG-BR002 prioritizes protection of certain critical organs (eg, spinal cord) that overlap with the planning target volume (PTV) while leaving the decision of whether to cover the PTV or spare the organ at risk to the discretion of the treating physician for other critical organs (eg, bowel). (Reprinted from Al-Hallaq HA, Chmura S, Salama JK, et al. Rationale of technical requirements for NRG-BR001: the first NCI-sponsored trial of SBRT for the treatment of multiple metastases. *Pract Radiat Oncol*. 2016;6[6]:e291-e298. Copyright © 2016 Elsevier. With permission.)

In addition, most 3DTPS cannot accurately account for a PTV contour that extends outside the skin surface, resulting in a DVH that does not reflect clinical reality because of the lack of dose generated in air and in the buildup region just below the skin. In those cases, the best solution is to delineate a planning structure (often termed the *PTV eval*) formed by truncating the PTV 3 to 5 mm below the skin surface. This will also help reduce acute skin reactions by preventing the optimization process from increasing the skin dose to excessive levels in an attempt to compensate for the lack of soft tissue in the PTV outside of the skin surface. In all cases, however, the treating physician should be aware of this approximation when setting or approving actual field margins.

All of the issues discussed in this section point out the fact that the PTV/PRV concept is a useful tool that simplifies accounting for geometric uncertainties. However, its use does give rise to several dilemmas. Particularly important is the loss of actual tumor and normal organ volume information reported for researchers developing TCP and NTCP models. Although it does not appear possible to totally eliminate the PTV concept at this time, it does appear possible to use smaller margins for some sites if more frequent imaging, adaptation of the treatment plan to anatomic

changes, or other technical innovation is used to reduce geometric uncertainties. For example, for prostate cancer, the use of daily imaging and other technologies to relocate the target volume in reference to the machine isocenter does allow for a smaller margin for the PTV.[13,65,66] However, one must still be prudent in the amount of margin reduction for the prostate PTV when using these technologies. The different methods include various trade-offs ranging from treatment machine control, which is not dependent on the patient, to systems that are completely dependent on the patient. Again, regardless of which technique is used to reduce the overall PTV margin, one must be prudent in deciding the amount of margin reduction. Data do exist for support of margin reduction, but one must be systematic in approaching such reductions and ensure that there are no adverse effects on expected patient outcomes.[67]

Dose Prescription

Dose prescription is the responsibility of the radiation oncologist, generally using institutional protocols based on evidence published in the literature combined with institutional experience. Typically, the 3DCRT prescription is specified as a dose at or near the center of the PTV or (particularly for IMRT) as a dose covering a certain percentage of the PTV—for example, $D_{95\%}$, a dose that covers 95% of the PTV. Because the resulting dose distribution can be quite different depending on the dose prescription methodology, it is imperative that publications provide a clear and unambiguous description of the dose specification for the radiation treatment results being reported. The ICRU recently updated their recommendations for dose specification regarding IMRT and these will be discussed in a later section.[68]

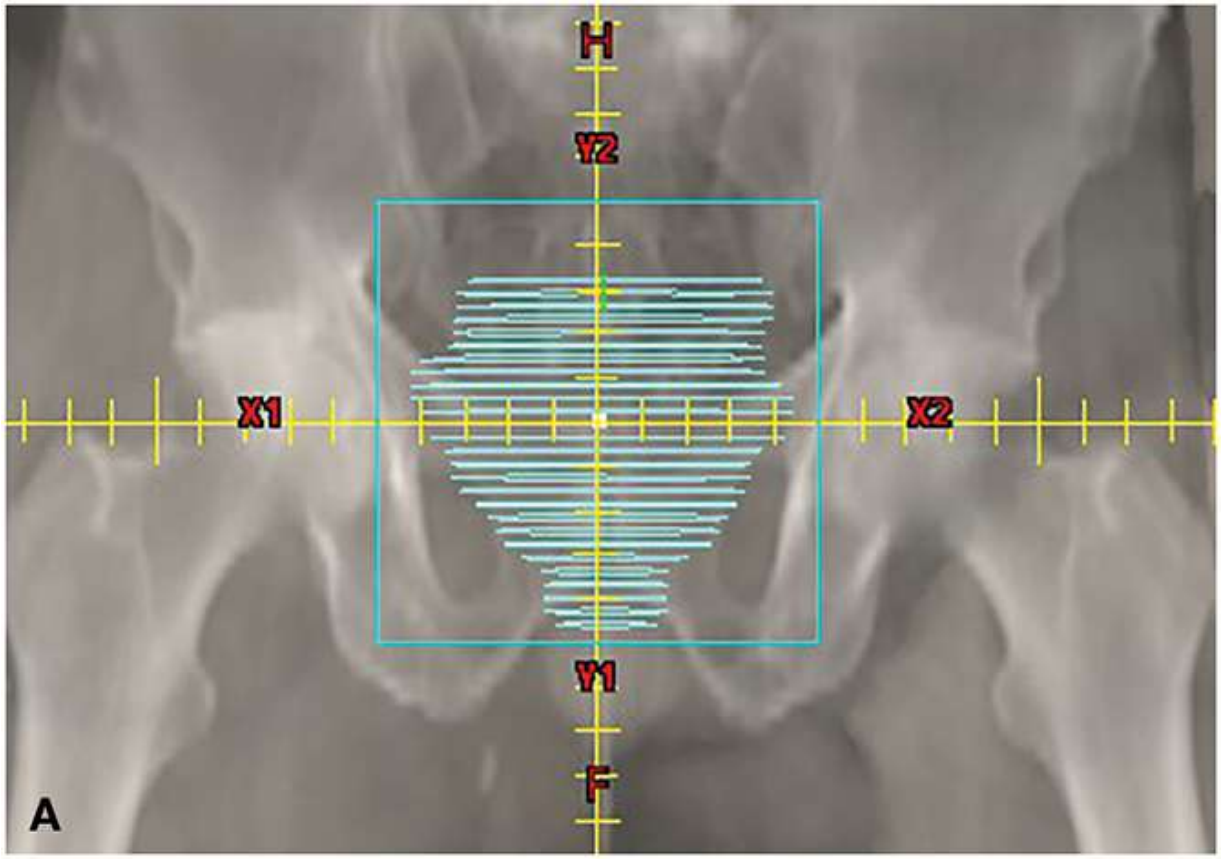
Conformal Planning

For 3DCRT planning, beams can be arranged, and beam apertures shaped with multileaf collimator (MLC) leaves or shielding blocks to help conform the prescribed dose to the PTV and avoid OARs using BEV displays. This "forward planning" approach to 3DCRT has now been supplemented—but

not replaced—by an "inverse planning" approach as used for IMRT, which can achieve even greater conformity and OAR dose avoidance.

Forward Planning: Three-Dimensional Conformal Radiation Therapy

Design of the beam arrangement is the next step in the planning process for 3DCRT. The ability to orient beams in 3D allows one to develop treatment plans that use noncoplanar beams. However, when noncoplanar beam arrangements are used, care must be taken to avoid the selection of gantry and couch angles that result in table/gantry collisions or a conflict with other treatment room restrictions. The *BEV* and the *DRR display*,[26,69] as shown in Figure 10.9, allow the planner to easily view the target volume and OARs so that shielding blocks or MLC apertures can be drawn using a computer mouse or, as available with most current 3DTPS software versions, automatically generated with a chosen margin around the selected volume. DRRs also provide planar reference images that can be used in facilitating the plan implementation and treatment verification phases of 3DCRT.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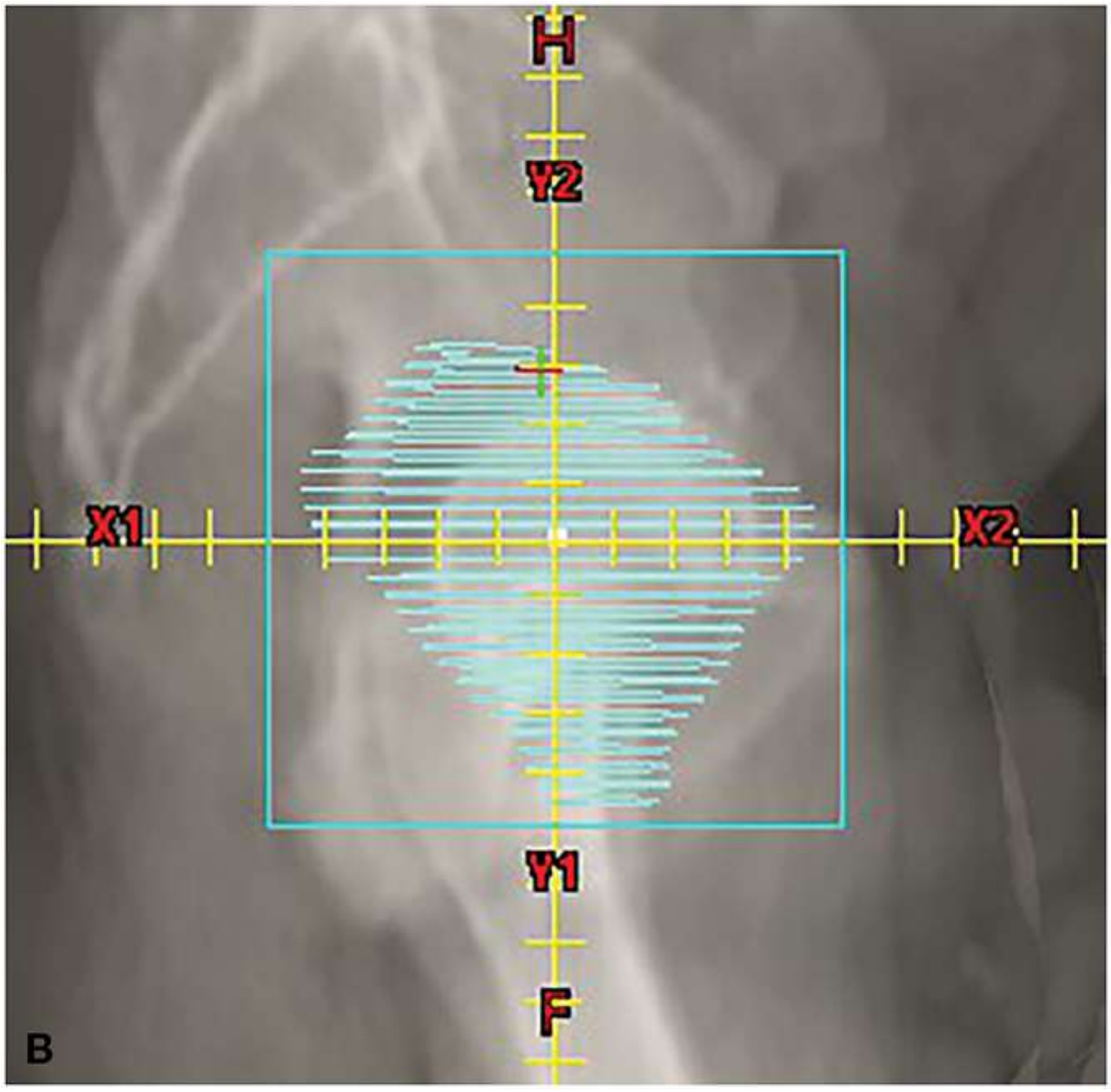
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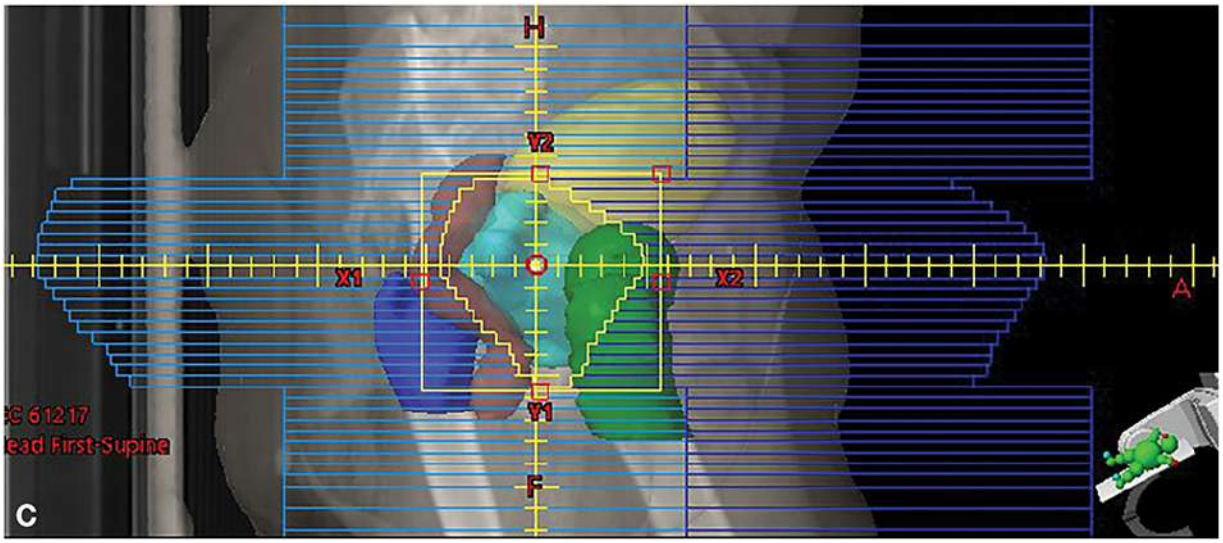

FIGURE 10.9 Anteroposterior (A) and lateral (B) digitally reconstructed radiographs and beam's eye view (BEV; C) display of three-dimensional radiation therapy treatment planning for a patient with prostate cancer. BEV display is useful in identifying best gantry, collimator, and couch angles at which to irradiate the target and avoid irradiating adjacent normal structures by interactively moving patient and treatment beam. Critical structures and target volumes are outlined on the patient's serial computed tomography sections. Contours are seen in perspective, as though the observer's eye is at the radiation source looking out along the axis of the radiation beam. The beam shape is defined by multileaf collimator.

Inverse Planning: Intensity-Modulated Radiation Therapy

The major differences between 3DCRT forward planning and IMRT inverse planning are the use of a computer optimization program that requires a formal description of the requirements using a mathematical *objective function* and constraints that are used by the program to find the solution. For example, after the design of the initial beam geometry, the physician/treatment planner puts into the TPS the desired dose-volume constraints for the PTVs and all OARs. The TPS optimization algorithm then divides each beam into many small *beamlets* (ie, pencil beams that together make up the IMRT beam) and then iteratively alters the beamlet intensities until the 3D dose distribution best conforms to the a priori specified dose-volume objectives. After the optimal beam intensities and resulting dose distribution have been determined, the TPS then calculates the MLC leaf sequence motions that will achieve this dose distribution and the dose recalculated. Typically, there may be some differences in the optimized dose distribution and the final dose distribution that are delivered

with the computer- controlled MLC system, but this difference is usually acceptable.

Noncoplanar Multibeam Delivery

Dong and colleagues[70] recently investigated the benefits of increasing the number of beams in noncoplanar delivery and showed that significant normal tissue sparing and dose conformality gains can be achieved when 14 to 22 beams are used for delivery. In this approach, an optimization algorithm, in addition to conventional fluence optimization, also optimizes noncoplanar beam orientations considering a patient-specific deliverable beam geometry solution space, parameterized with patient and linear accelerator (LINAC) gantry orientations. This delivery technique, dubbed 4π, has been extended to other disease sites and has shown that research can lead to additional improvements in radiotherapy photon dose distributions.[71,72]

Multilesion, Single Isocenter

The increased geometric precision and accuracy of MLCs and linac movements in C-arm systems recently has enabled treatment of highly "off-axis" targets, where an isocenter can be located several centimeters from the intended target. These developments have enabled a host of treatment techniques using a single isocenter to treat multiple targets, starting with brain metastases.[73,74] These methods have been commercialized by Varian (HyperArc) and Brainlab (Elements Multiple Brain Metastases), among other offerings. Treatment plans can be optimized to balance between target conformality while reducing low-dose spillage between targets, particularly through the use of multiple, noncoplanar arcs.

Dose Distribution Calculation

A rectilinear coordinate system affixed to the patient's 3D CT image set is typically used for calculating the dose distribution. This "patient or CT system" coordinate system typically has its x-axis along the horizontal axis of the transverse CT images, the y-axis along the vertical axis, and the z-axis along the couch motion. Contour points are specified as a sequence of points having x-, y-, and z-coordinates in this system. The center of each

voxel in the 3D CT image matrix is computed relative to the same coordinate system and is used to look up the relative electron density values that are related to the CT numbers (see later discussion). The selection of grid spacing for the 3D dose matrix is an important consideration regarding dose computational accuracy, calculation speed, and computer hardware requirements. Drzymala et al[33] pointed out that a 2% dose accuracy or 2-mm isodose positional accuracy can generally be achieved with a grid spacing of 5 mm. However, in regions of high dose gradients, a finer grid is typically needed, which creates larger computer files and increases the 3DTPS memory and mass storage requirements. With modern computing capabilities, these issues are not a practical limitation, and high-resolution dose computations are achievable that can lead to dosimetric benefits.[75]

The reader should also understand that CT numbers are not used directly in photon dose calculations. Instead, the CT numbers are correlated with the electron density of the corresponding tissues at each voxel relative to the electron density of water.[76] This is because Compton scattering is the dominant mode of interaction for the type of photon beam used in radiation therapy (cobalt 60 through 25-MV x-rays), and the absorption and scattering of photons in tissue depend primarily on the electron density of the tissue. Errors in CT numbers can result in inaccurate dose calculations. Generally, however, errors of 10% or less in electron density (CT numbers) will not result in significant errors in the dose distribution.[76] A recent development has been direct electron density imaging[77]; full clinical impact of this technology remains to be investigated.

Details on specific dose calculation algorithms are discussed in a separate chapter, and so only issues pertinent to the 3DCRT planning process are discussed in this section. In the past, dose calculation algorithms were traditionally based on parameterizing dose distributions measured in water phantoms under standard conditions and applying correction factors to the beam representations for the nonuniform surface contour of the patient or the obliquity of the beam, tissue heterogeneities, and beam modifiers such as blocks, wedges, and compensator. However, more advanced models, such as the superposition/convolution method, have been developed for 3DCRT planning[63] and are now the standard of practice for 3DCRT planning. The study by Frank et al[78] provides a clear method for safely

transitioning from a clinical experience based on planning assuming a homogeneous unit density patient to a heterogeneous patient model.

Plan Evaluation and Improvement

The 3DCRT plan evaluation/improvement process involves an iterative, interactive approach. Typically, the initial beam arrangement has been selected based primarily on clinical experience using BEV displays. The generated dose distribution is reviewed by the planner/physician, and the beam arrangement is then modified based on the review of DVHs (Figure 10.10) and multilevel 2D displays showing isodose lines superimposed on CT images (Figure 10.11); sometimes, the display is in the form of a *color wash*, that is, a spectrum of colors superimposed on the anatomic information. Historically, the planned dose distribution approved by the radiation oncologist is most often one in which a uniform dose is delivered to the target volume (eg, +7% and −5% of the prescribed dose), with doses to critical structures held below tolerance levels,[79-82] as well as within the constraints for the absolute maximum dose, median dose, or a volume (eg, V_{20Gy}) that has been specified by the radiation oncologist. With IMRT and stereotactic body radiation therapy (SBRT) approaches, there is an increased acceptance of larger-dose heterogeneities, whereas the approach to other evaluation parameters remains unchanged.

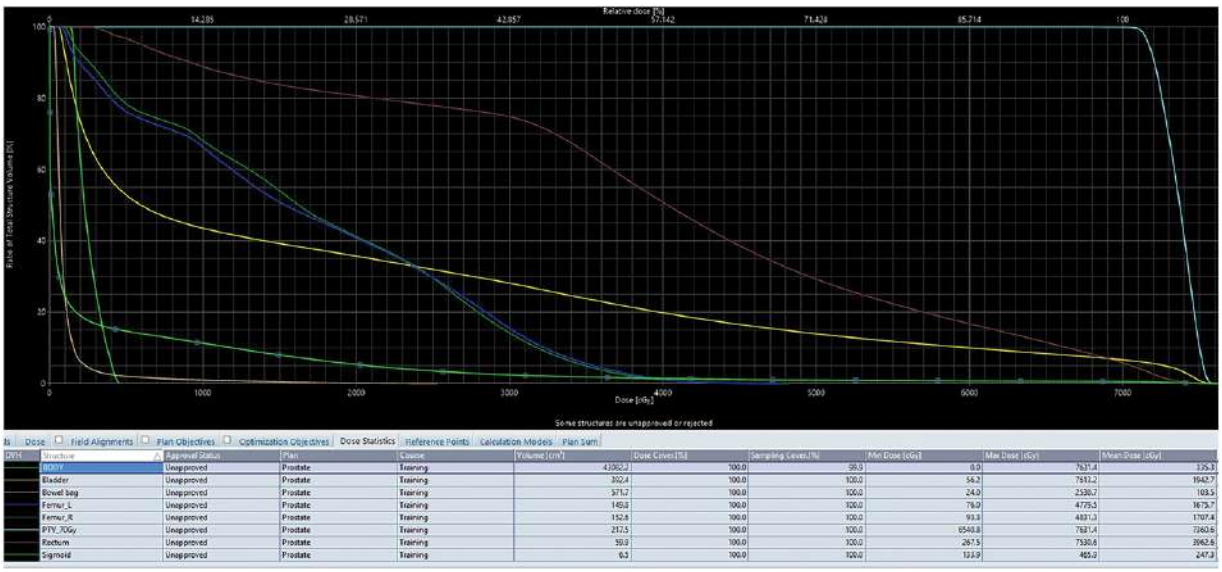

FIGURE 10.10 Example of a treatment planning system display (Varian Eclipse), showing the cumulative dose-volume histograms for the plan of a patient with typical prostate cancer: the prostate planning target volume (cyan) and multiple organs at risk (left and right femurs, rectum, sigmoid colon, bowel bag, and bladder). Also shown are associated dose statistics for the various defined volumes.

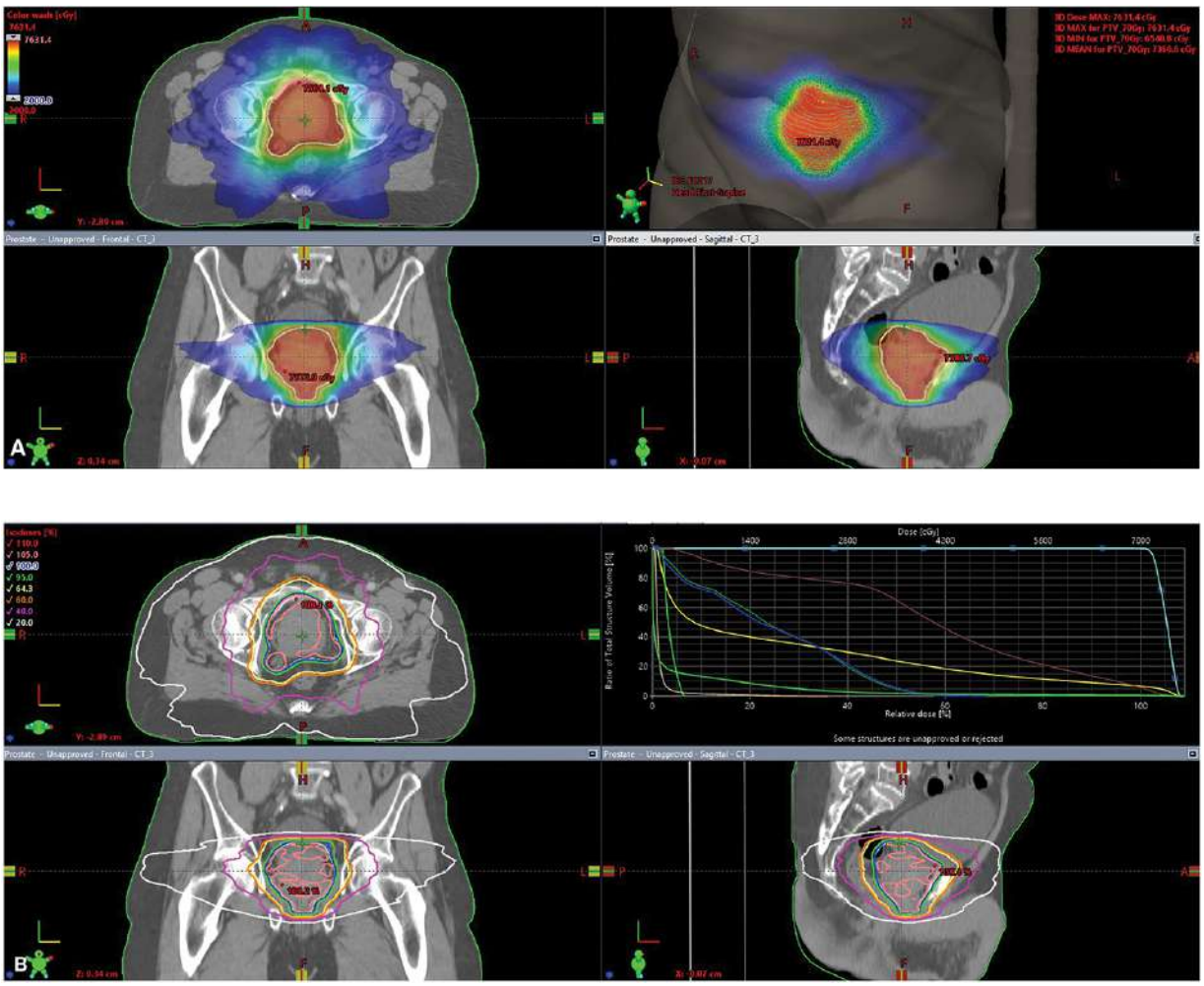

FIGURE 10.11 Dose distribution displays for a patient with prostate cancer showing coronal, sagittal, and two axial computed tomography (CT) sections with superimposed colorwash isodose display (A) and color-coded isodose lines (B). Vertical and horizontal lines displayed on each CT indicate the positions of each section. Evaluating volumetric three-dimensional (3D) dose distributions using only this type of two-dimensional display is difficult and time consuming. Also shown are a 3D dose display (A) and a cumulative dose-volume histogram (B).

In recent years, the plan creation and evaluation process has significantly evolved adding several new options and tools to the process. The calculation of Pareto surfaces in multicriteria optimization (MCO)-based IMRT treatment planning involves creation of several treatment plan options where each plan offers a combination of different dose-volume trade-offs.[83] Pareto optimal plans offer a plan bundle where each plan favors an OAR or a combination of OARs at the expense of some other organ or organs. In other words, radiotherapy treatment planning is all about trade-

offs between doses delivered to target volumes and various OARs. These trade-offs involve physicians making decisions regarding dosimetric sacrifices and sparing, that is, which critical organs to protect from radiation dose at the expense of other organs, or they involve compromises in the balance of dose delivery between targets and OARs. In MCO, a set of plans optimized for unique combinations of dose trade-offs is combined with tools to offer a physician an efficient way to navigate among these trade-offs to select a plan offering the trade-offs favored by that physician. This approach has been shown to have quantifiable dosimetric advantages.[84] Both RaySearch (Garden City, NY) and Varian (Palo Alto, CA) offer MCO approaches. The advantages of this technique include the flexibility offered to physicians in guiding the treatment delivery; however, this cannot mitigate the clinical variability that may result due to differences from a physician's decision to favor one trade-off over another.

In knowledge-based planning (KBP), treatment plans of previously treated patients are used to create models of achievable dose distributions for future plans.[85,86] The historical plans constitute a training data set, and machine learning–like approaches are used to create DVH range predictions unique to a patient's specific organ geometry (Figure 10.12). In the KBP approach, a DVH or 3D dose prediction can be created as soon as there are contours of the patient geometry and the prescription.[87] The proposed solution is driven by prior treatment planning practices and results in a single treatment plan rather than multiple plan options as in the MCO. In this approach, treatment models can be created at one institution or globally and transferred to other, presumably less experienced, institutions[85,86] as well as used to standardize treatment planning quality in multi-institutional trials.[88,89] The ability to standardize plan quality in multi-institutional trials minimizes a significant source of historical variability and shortcoming in these trials, which should translate to an increased confidence in trial outcomes. Another potential benefit is the minimization of variability of transfer of planning protocols from multi-institutional trials to individual clinics if the KBP models used in a trial are made available to individual clinics. The KBP approach is commercially available through Varian's RapidPlan software and has been proposed to alleviate some of the resource challenges that exist in various clinics including in low- and middle-income countries.[90]

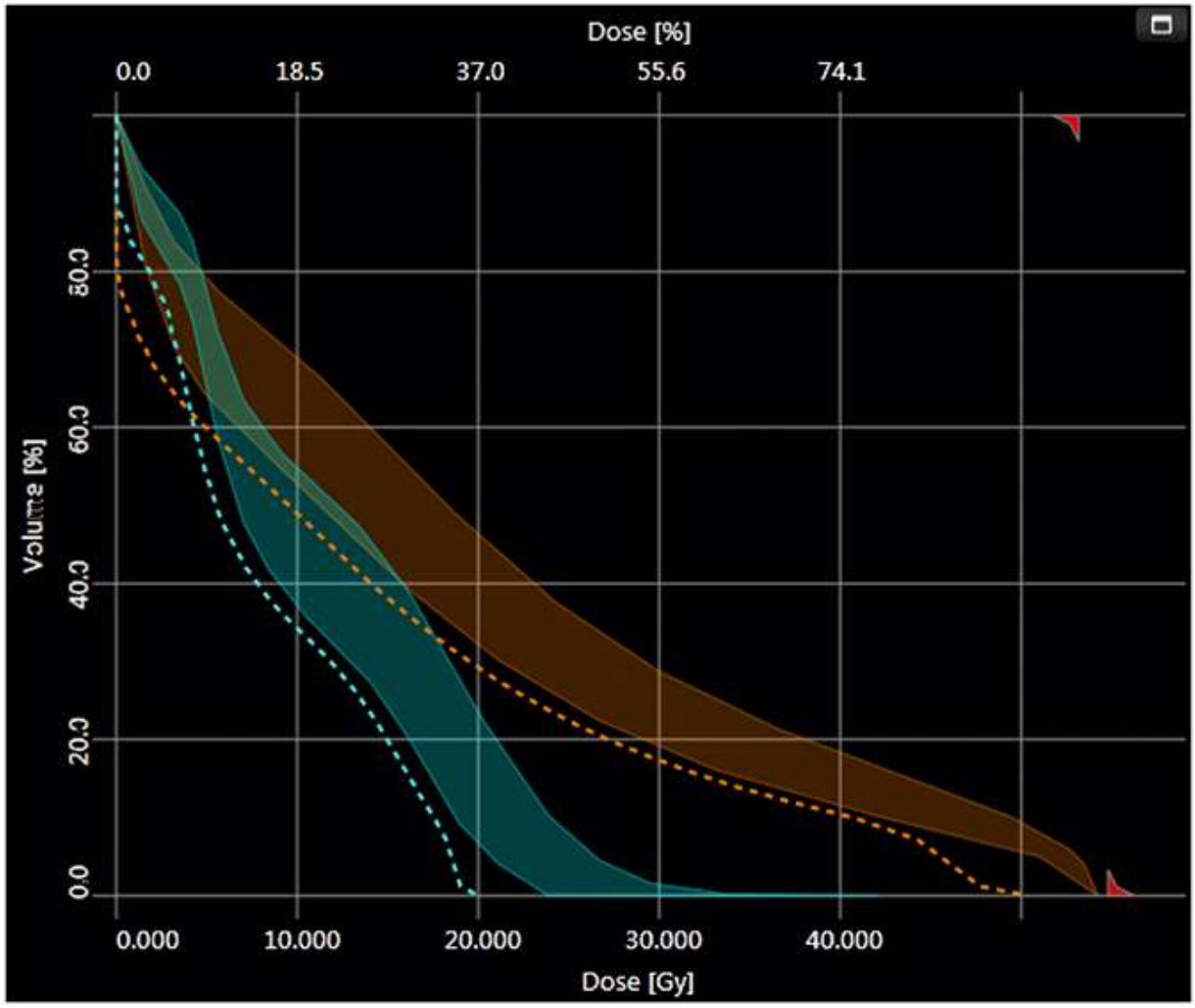

FIGURE 10.12 Colored range is the dose-volume histogram prediction range for two organs at risk, and the dotted lines are treatment planning objectives, which are set at the lower bound of these predictions and are automatically passed to the optimization engine for treatment planning purposes. The use of lower bound setting in the optimization ensures that the system is driven in the direction of optimal dose distributions.

Another powerful display feature in a 3DTPS is the *room view* or *room's eye view* (*REV*) (also referred to as 3D view), in which the planner can simulate any arbitrary viewing location within the treatment room.[29,91] The REV display is used to display *dose clouds* along with rendered PTVs and OARs. Hot or cold spots that occur in the volumes of interest are clearly seen, as shown in Figure 10.13. Another valuable REV display is the so-called skin view, in which the beam aperture projection can be clearly seen on the skin of the (virtual) patient (Figure 10.14).

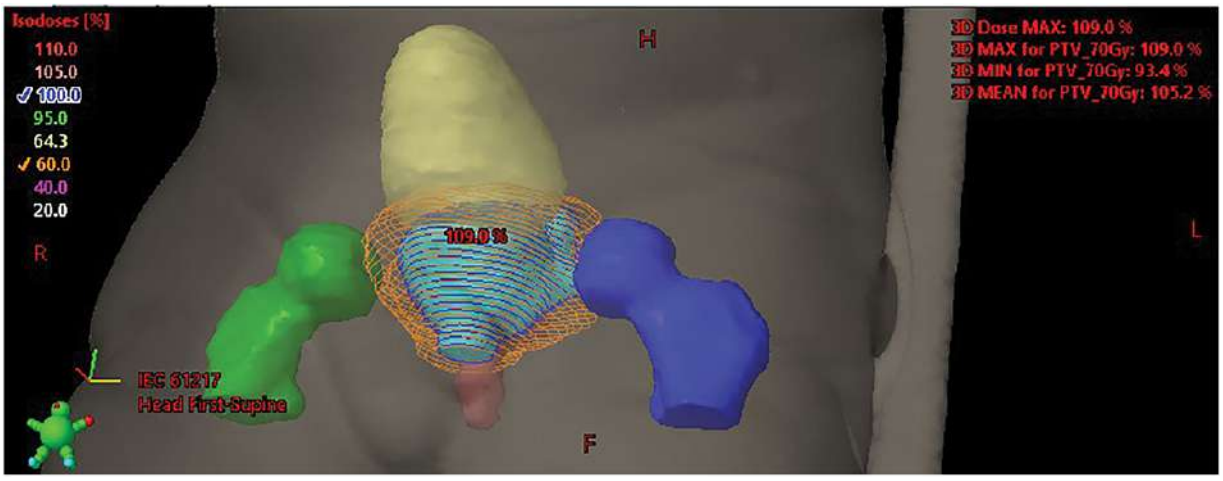

FIGURE 10.13 Room's eye view (REV) three-dimensional (3D) isodose surface display with real-time interactivity is a valuable tool for the evaluation of 3D dose distributions in terms of adequate coverage of target volumes and sparing of critical structures. The REV display enables radiation oncologists to view target volume or normal tissue volume with superimposed isodose surfaces or "dose clouds" from any arbitrary viewing angle. Shown is a four-panel REV display of the 100% and 60% isodose volume, the prostate planning target volume (PTV), bladder, femurs, and rectum of a patient with prostate cancer. The location of the PTV region not covered by the specified dose level is easily discernible using the REV display.

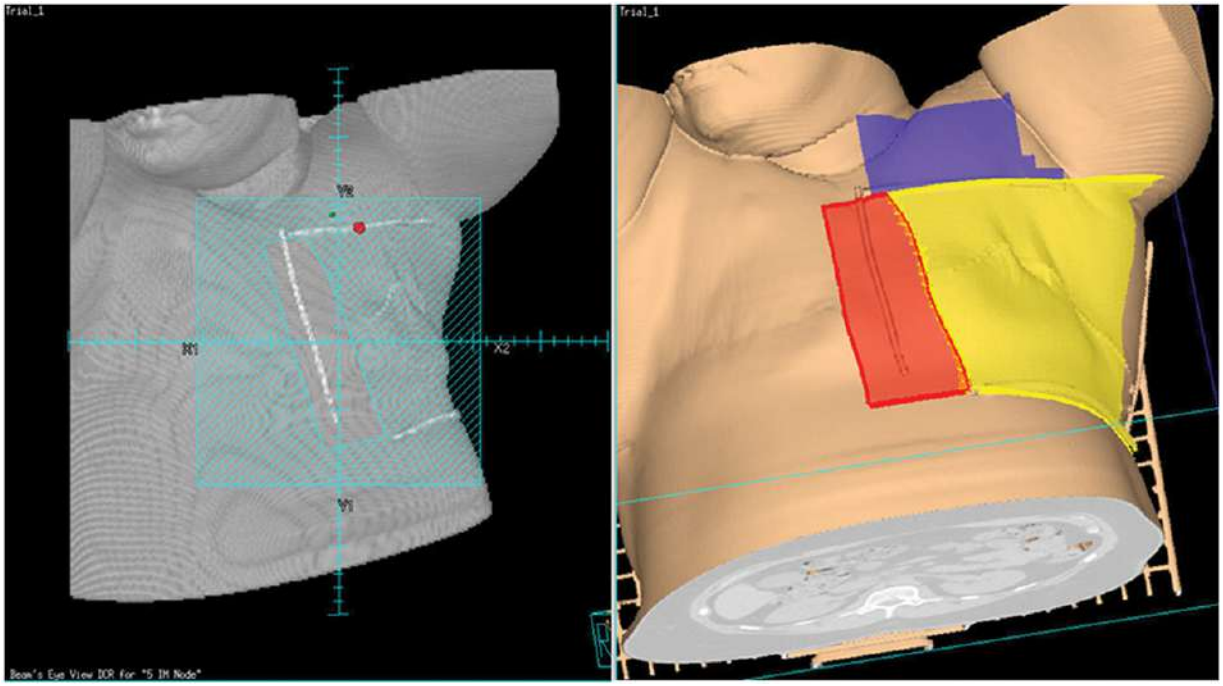

FIGURE 10.14 Room's eye view display showing simulated skin surface for a patient with breast cancer undergoing radiation therapy using tangential, supraclavicular, and internal mammary fields. Beam aperture projection can be clearly seen on the skin of the (virtual) patient.

Plan Implementation and Treatment Verification

Once the treatment plan has been designed, evaluated, and approved, documentation for plan implementation must be generated. Documentation includes beam parameter settings transferred to the treatment machine record and verify (R&V) system. Initially these R&V systems captured beam parameter settings for the treatment unit and, separately, for the MLC parameters communicated over a network to the treatment machine's computer system that controls the MLC system, and transfer of setup or reference images (DRRs, CTs, etc) and the machine's image database. Most modern treatment units now use integrated control systems that manage all of these aspects of treatment imaging and delivery parameters through a centralized control system.

Validation of patient position and treatment setup historically involved acquiring portal images of all individual treatment beams. However, with IMRT, SBRT, TomoTherapy, ViewRay, etc, these processes are not practical and are generally not done, although the portal transmission images may be captured for retrospective review and/or documentation. Instead, orthogonal radiographs, cone-beam CTs (CBCTs), MRIs, or other images of the patient (rather than of treatment beams) are now the preferred method to ensure correct isocenter positioning. When available, the optical distance indicator is also useful in assessing the correctness of the setup of a particular beam. Documentation provides the depth of isocenter below the skin surface on the central ray of the beam, which can then be compared with the isocenter depth measured on the simulator or treatment machine after the beam is set up using the couch and gantry positions specified by the treatment plan.

QA checks used to confirm the validity and accuracy of the 3DCRT plan typically include an independent check of the plan and MU calculation by a physicist; radiation therapists also evaluate the integrity of the plan information that is passed to them for treatment (ie, therapist new start check). Most importantly, careful scrutiny must be given to the input of data into the R&V system to ensure that it is correct. These checks are discussed in more detail in a separate section. Additional information on standards for 3DCRT plan verification can be obtained from the most current AAPM Task Group reports, American College of Radiology, and American Society for Radiation Oncology (ASTRO) practice accreditation guidelines.

Dose Reporting

ICRU Reports 50 and 62 define a series of doses, including the minimum, maximum, mean dose, and *ICRU reference dose* (defined at the *ICRU reference point*), for reporting dose relevant to 3DCRT. The *ICRU reference point* for a particular treatment plan should be chosen based on the following criteria: It should be (1) clinically relevant and defined in an unambiguous way, (2) located where the dose can be accurately determined, and (3) located in a region where there are no steep dose gradients. In general, this point should be in the central part of the PTV. In cases in which the treatment beams intersect at a given point, it is recommended that the intersection point be chosen as the ICRU reference point.

ICRU Report 83[68] updates the previous ICRU recommendation on 3DCRT dose reporting and recommends moving from single-spatial-point reporting (ie, the ICRU reference point dose, minimum and maximum dose) to dose-volume reporting. This is justified based on the availability of more accurate dose calculation algorithms and the advances and ubiquity of modern-day anatomic/functional imaging.

It should also be understood that in the past, *minimum dose* and *maximum dose* referred to point doses in the dose calculation grid assigned to a single voxel. It is now acknowledged that the minimum dose may not be accurately determined because it is often located in a high-gradient region at the edge of the PTV, making it highly sensitive to the resolution of the calculation and the accuracy of delineating the CTV and determining the PTV. Moreover, treatment planning today represents only one single representation of the calculated dose distribution, whereas over the full course of a radiation treatment, the minimum and maximum dose points are likely to shift slightly from one day to another. For all those reasons, ICRU Report 83[68] recommends discontinuing the use of maximum dose and minimum dose and instead recommends for dose reporting the use of the *near-maximum* (corresponding to $D_{2\%}$) and the *near-minimum* ($D_{98\%}$). In addition, the *median dose*, specified by $D_{50\%}$, should be reported, as it is considered to best correspond to the previously defined dose at the ICRU reference point.

The maximum dose as specified by a single calculation point ($D_{\max}$ or $D_{0\%}$) has often been reported for serial-like organs or structures. Previously,

such a reported maximum dose was considered relevant only if the involved organ had a minimum diameter of at least 15 mm, whereas an even smaller dimension was considered appropriate for some organs, such as the eye, optical nerve, or larynx.[38] The ICRU acknowledged that the minimum diameter for the maximum dose region in a structure is not always easy to establish and hence recommended that $D_{2\%}$ be reported. However, the ICRU pointed out that care should be taken in a change from maximum dose to the near-maximum dose, $D_{2\%}$.

As stated previously, with regard to dose homogeneity, ICRU Report 50 recommends that the dose coverage of the PTV be kept within specific limits, namely, +7% and −5% of the prescribed dose.[38] However, this level of dose homogeneity might not be achieved in all cases (particularly for current IMRT techniques), and ICRU Report 50 explicitly states that if this degree of homogeneity cannot be achieved, it is the responsibility of the radiation oncologist to decide whether the dose heterogeneity is acceptable. Similarly, a slight underdose to the PTV might be required (particularly if in close proximity to an OAR) or result for lung tumors surrounded by low-density lung tissue as a result of electronic disequilibrium.

Note that ICRU Reports 50 and 62 do not make strict recommendations regarding dose prescription; instead, the ICRU states that "the radiation oncologist should have the freedom to prescribe the parameters in his/her own way, mainly using what is current practice to produce an expected clinical outcome of the treatment."[38] For dose reporting, however, it is recommended to also state the original prescribed dose if the actual prescription was not done accordingly.

It is now recognized that there is a large variability among institutional results in IMRT planning and reporting.[92,93] Studies strongly support the ICRU Report 83 recommendation to move away from single-spatial-point prescription/reporting to dose-volume prescription/reporting. In addition, ASTRO has gone even further and recommends that specific details of the inverse treatment planning and image-guided treatment processes be recorded in four ways—in an *IMRT treatment planning directive*, a *treatment goal summary*, an *image guidance summary*, and a *motion management summary*.[94] Das et al[95] recently evaluated compliance with ICRU Report 83 prescribing guidelines and found that the overwhelming

majority of patient treatments in the surveyed institutions do not comply with these guidelines. The KBP planning approach and automatic DVH analysis are both aimed at reducing these variabilities. More extensive and standardized methods and supporting software for treatment prescribing currently do not exist. Just as the tools have emerged for more consistent plan creation and evaluation, it is critical that a process be developed, which will improve the standardization and quantification of radiation therapy prescribing. It would be very beneficial if the prescription parameters (treatment planning goals) and the evaluation metrics overlap.

Dose-Volume Histograms

The large amount of dosimetric data that must be analyzed when a 3DCRT plan is evaluated has prompted the development of methods of condensing and presenting the data in more easily understandable formats. One such data reduction tool is the *DVH*.[32,33] Two types of DVHs, *differential* and *cumulative*, are available in 3DCRT planning, with the latter now universally used in plan evaluation for assessing PTV coverage and dose to OARs, as displayed in Figure 10.15. However, it must be clearly understood that the DVH does not provide any spatial information and thus can only complement and not replace spatial dose distribution display tools such as isodose displays.

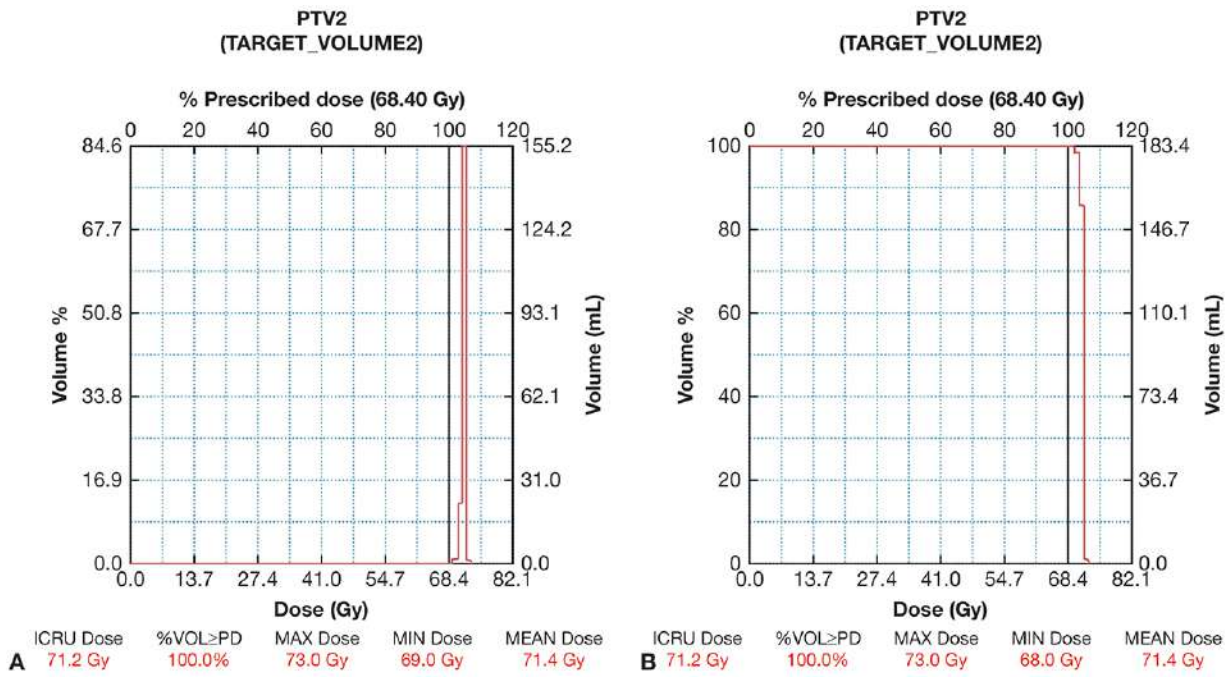

FIGURE 10.15 A. The differential dose-volume histogram (dDVH) for a specified target volume (planning target volume [PTV]2)—the volume is subdivided into individual elements (called voxels) and tagged according to dose received as determined from the three-dimensional dose grid. Voxels are then grouped according to each specified dose bin value without regard to their spatial location. A plot of the number of voxels in each bin (*y*-axis) versus the bin dose range (*x*-axis) is by definition a dDVH. B. The corresponding cumulative DVH is generated by summing for each dose bin all of the voxels of the PTV2 dDVH to the right of each dose bin; the *y*-axis gives the volume, or percentage of volume, that receives a dose equal to or greater than the indicated dose on the *x*-axis. ICRU, International Commission on Radiation Units and Measurements.

The *differential DVH* (dDVH), as shown in Figure 10.15A, is essentially a plot of the frequency distribution of the individual dose distribution elements (called dose voxels) obtained from the dose grid. Typically, the grid size is small enough so that the dose can be assumed to be constant within each voxel. The volume's dose distribution is then divided into *dose bins*, and the voxels are grouped according to their dose bin value without regard to their spatial location. A plot of the number of voxels in each bin (*y*-axis) versus the bin dose range (*x*-axis) is by definition a dDVH. The size of the dose bin used determines the height of each bin of the dDVH. For example, if the bin widths were increased, the heights of the histogram bins would increase because more voxels would fall into any given bin. Thus, it should be clearly understood that the detailed shape of a dDVH depends on

the dose bin size used, even though the underlying dose-volume data are the same.

A *cumulative DVH* (*cDVH*), as shown in Figure 10.15B, is a plot in which each bin represents the volume, or percentage of volume (*y*-axis), that receives a dose equal to or greater than the indicated dose on the *x*-axis. The cDVH is generated by summing all of the voxels of the corresponding dDVH to the right of each dose. The volume value for the first bin (dose origin) is the full volume of the structure because the total volume receives at least zero dose and the volume for the last bin is that which receives the maximum dose. Note that in the literature, the "c" in the cDVH is generally dropped, leaving just DVH.

Explicit values of dose-volume parameters can be extracted from the DVH data and are called dose-volume statistics or simply *dose statistics*. Examples for target volumes include maximum dose, minimum dose, mean dose, and percentage volume receiving greater than or equal to the prescription dose; for OARs, they typically include maximum point dose, mean dose, and percentage volume receiving greater than or equal to an established tolerance dose. As previously stated, ICRU Report 83[68] recommends replacing the *minimum dose* and *maximum dose* point doses with *near-maximum* (corresponding to $D_{2\%}$) and *near-minimum* ($D_{98\%}$).[68]

There is an ever-increasing reliance on DVH-based evaluation of treatment plans. Because the majority of planning objectives in clinical trials and Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) recommendations are based on dose-volume tolerances of individual organs, it is natural to extend the plan evaluation with a primary focus on DVH or derived metric (eg, R_{50}) evaluation. There are now also several commercial and homegrown software packages for automatic extraction and evaluation of these parameters, with easy to assess indicators for which parameters meet the planning goals and which ones fail. Although the automatic evaluation is fundamentally more efficient, its main advantage is reduced likelihood for error and greater efficiency in the evaluation process. Also, the transfer and implementation of multi-institutional plan evaluation parameters are easier and more systematic to implement with automated dose- volume metric evaluation. It should be reemphasized that DVH review is not a substitute for reviewing the actual

isodose distributions, and plans are best evaluated combining all these review parameters.

Biologic Models for Dose-Volume Response

Evaluation of the quality of a treatment plan (ie, is plan A better than plan B?) is difficult and at best a qualitative procedure. For example, it is not clear what degree of dose uniformity within the PTV is optimum, as dose levels can be significantly escalated using 3DCRT techniques, nor is it always clear which plan is best if the two DVHs for a specific OAR cross each other (ie, difficulty in weighing importance of dose vs volume).

Researchers have developed biophysical models that attempt to translate the dose-volume information into estimates of biologic response—TCP and NTCP models.[81,82,96,97] Most authors agree that the TCP and NTCP models developed thus far are not accurate enough such that the absolute values can be used to predict clinical outcome; however, they are used to compare rival plans and as such help to rank plan quality. In any case, such biologic indices should be used clinically only when their utility has been firmly established for well-defined clinical conditions. ICRU Report 83 is clear in stating that if biologically based metrics are to be reported, the assumptions used in the models, their parameters, and the model itself must be unambiguously specified.[68]

Tumor Control Probability

TCP plotted as a function of dose has a classic sigmoid shape, having zero control at some low dose to control at some high dose. Rather than attempt to review in detail the various models, here some relevant issues are discussed. Readers are referred to the article by Moiseenko et al[98] for more details. Simple phenomenologic TCP models can be represented by the logistic function as follows:

$$\mathrm{TCP} = \frac{1}{1 + \left(\frac{D_{50\%}}{D} \right)^{4\gamma_{50\%}}}$$

where $D_{50\%}$ is the dose at which the TCP is 50%, $\gamma_{50\%}$ is the slope of the dose-response curve at 50% tumor control, and D is the dose administered.[99] Note that the use of the logistic function assumes an approximate uniform cell response and a uniform dose distribution.

For a nonuniform dose distribution, the total tumor volume is reduced to smaller volumes having "uniform" doses within each subvolume element v_i. The TCP value for each volume element, TCP(v, D), can be inferred from the TCP for uniform irradiation of the entire tumor volume, TCP(1, D), using the following equation:

$$\text{TCP}(v, D) = \text{TCP}(1, D)^v$$

Thus, the TCP for the tumor receiving an inhomogeneous dose is given by the product of the individual volume element TCPs as follows:

$$\text{TCP} = \prod_{i=1}^{N} \text{TCP}(v_i, D_i)$$

Here, TCP(v_i, D_i) is the TCP for the ith volume element receiving dose D_i, and N is the total number of tumor volume elements. Recall that the validity of this equation is highly dependent on the validity of the assumptions that the individual tumor volume elements are uniformly distributed throughout the tumor volume and are equally radiosensitive.

Normal Tissue Complication Probability

There are mainly two different approaches used in radiation therapy in modeling NTCP: the *empiric model* introduced by Lyman and Wolbarst[100,101] and *functional models* that introduced concepts of *serial* and *parallel* tissue organization and *functional subunits* (*FSUs*).[99,102-104]

The *Lyman NTCP model* can be expressed in terms of an error function of dose (D) and volume (v) as follows:

$$\mathrm{NTCP}\left(D,v\right)=\frac{1}{\sqrt{2\pi}}\int_{-\infty}^{1}\exp\left(-t^{2}/2\right)\mathrm{d}t$$

where

$$t=[\,D-D_{50}\,(v)]\,/\,[\mathrm{m}\cdot D_{50}\,(v)]$$

with v equal to the partial volume (V/V_{ref}) and the tolerance dose-volume dependence given by the following power-law relationship:

$$D_{50}\,(v)=D_{50}\,(1)\cdot v^{-n}$$

$D_{50}(1)$ is the tolerance dose for 50% complications for uniform whole-organ irradiation, and $D_{50}(v)$ is the 50% tolerance dose for uniform partial-organ irradiation to the fractional volume v. The arbitrary variables m and n are found by fitting tolerance doses for uniform whole- and uniform partial-organ irradiation, where m characterizes the gradient (slope) of the dose-response function at D_{50} and n characterizes the effect of volume. When n is near unity, the volume effect is large; conversely, when n is near zero, the volume effect is small. When NTCP is plotted against dose, the NTCP equation demonstrates a sigmoid shape.

Two methods are used to extend this model to nonuniform organ irradiation. The *interpolation method*, proposed by Lyman and Wolbarst,[101] modifies the DVH to one in which the whole organ receives an effective uniform dose, D_{eff}, that is less than or equal to the maximum organ dose. The second method, called the effective volume method, proposed by Kutcher and Burman,[105] modifies the DVH to one in which a fraction of the organ, v_{eff}, receives the maximum organ dose. The Lyman model coupled with the Kutcher-Burman DVH reduction scheme (now called the Lyman-Kutcher-Burman model) is the most widely used NTCP model.[96]

Other NTCP models include two developed by Niemierko and Goitein—the *critical element model*,[106] used for serial-like organs, and the *critical*

volume model,[107] for parallel-like organs. These are similar in form to that of Lyman and Wolbarst[100] but include additional terms to better account for the radiosensitivity of the FSUs.

Equivalent Uniform Dose

Equivalent uniform dose (EUD) is a concept first introduced by Niemierko[108] for use in evaluating and reporting inhomogeneous dose distributions and later redefined by the following equation[109]:

$$\mathrm{EUD} = \left(\sum_i v_i \, D_i^{\alpha} \right)^{1/\alpha}$$

where v_i is the volume of the dose-volume bin with a dose D_i and the exponent α is a complication-specific parameter.

The EUD concept assumes that any two dose distributions are equivalent if they cause the same radiobiologic effect and appears well suited for use in evaluating competing conformal plans. However, McGary et al[110,111] pointed out that there are conditions in which EUD is not adequate as a single parameter to report or analyze inhomogeneous dose distributions—for example, when the minimum dose is significantly lower than the mean dose.[112]

PRECISION MEDICINE MODELS

In contrast to population-based models such as TCP/NTCP, patient-specific models may be developed to guide precision medicine. While imaging scientists have long posited that patterns in medical images are manifestations of the underlying biology, it has become possible to investigate this relationship with recent advances in computing and the increased availability of medical images.[113,114] Mathematical and statistical calculations performed on medical images (ie, radiomics) have been shown to correlate with tumor outcomes[115] and normal tissue toxicities[114,116]

following radiotherapy. Because genetic variations lead to biologic differences, studies have also shown that genetic variations can be detected in medical images (ie, radiogenomics).[115] As these models continue to be refined and investigated, it is important to understand the underlying sources of uncertainty and associated limitations of such models[114,117] in order to enable safe clinical implementation.

ARTIFICIAL INTELLIGENCE IN PLANNING, DELIVERY, AND TREATMENT VERIFICATION

As in many other areas of medicine, machine learning and artificial intelligence (AI) algorithms are beginning to supplant more traditional rule-based algorithms for solving a variety of problems in radiation oncology. Most recently, AI-based auto-contouring has emerged commercially as the state of the art for contouring OARs[118] and is now being investigated for CTV delineation,[119] although GTV delineation remains a challenging problem for AI auto-contouring. As discussed earlier, KBP represents an initial machine learning approach to treatment planning, but fully AI-based approaches are in development.[120] Plan verification through AI rather than measurement remains controversial but is an active area of research.[121]

Because, generally, AI systems are trained models rather than fixed rule-based algorithms, the approach to deployment, commissioning, and QA differs markedly from that used for traditional algorithms.[122,123] Critically, AI systems must be commissioned to ensure that the commercial model is consistent with the expected performance in the clinic, as differences in input data (eg, imaging data) from that used to train the AI model by the vendor can result in unexpected performance degradation of the AI system. Continuous monitoring and tools for ongoing QA of AI systems are in active development currently.[118,124]

MANAGEMENT OF CONFORMAL RADIATION THERAPY DATA

To accurately perform the steps involved in 3DCRT, several forms of patient imaging and other data must be acquired, displayed, manipulated, and stored. Typically, patient image data acquired from several imaging subsystems must be communicated to a TPS to permit these images to be used for treatment planning. Several software components also must be

integrated so that the output of one processing step can be made available for use as input to the next step. Daily IGRT imaging also places large demands on data storage, and the need for more robust image processing tools is evident. These issues in data management in 3DCRT are complex and continue to be somewhat problematic, although some progress is being made through the Integrating the Healthcare Enterprise in Radiation Oncology effort initiated by ASTRO.[125]

This issue is just a part of larger informatics issues facing radiation oncology. There is an explosion in the types and volume of data that must be made available for scientific inquiry. Difficulty in accessing the data in practical ways has become a critical limitation to investigators in the field and to its advancement. Unfortunately, the commercially available radiation oncology information systems are not yet adequate to meet this challenge. The great volume and diversity of the data have rendered their storage, management, and processing extremely problematic, resulting in situations in which important data and information are inefficiently disseminated and sometimes lost. In the busy clinic, failure to manage critical information may compromise patient safety. Here, a major issue is the lack of integration of the radiation oncology electronic medical record (EMR), based on systems such as Elekta-Impac MOSAIQ (Sunnyvale, CA) or Varian ARIA, with the electronic hospital record (EHR), based on systems such as those provided by Epic (Verona, WI). In most cases, one must resort to hybrid charting systems (ad hoc combinations of EMR, EHR, and paper charting), which entails risks and gives rise to a dangerous situation. Immediate and focused efforts in achieving these integrations and improving the radiation oncology informatics infrastructure are urgently needed.

QUALITY ASSURANCE FOR CONFORMAL RADIATION THERAPY

It is most important to realize that a QA program for 3DCRT is an interdisciplinary effort involving radiation oncologists, radiation physicists, dosimetrists, radiation therapists, clinical engineers, and information technology specialists and that the efforts of each group often overlap

substantially. To be effective, it is also essential to have the full support of the department chair and hospital administration.

Although, in general, radiation therapy has a long, successful history of QA, most authors have come to realize that the current approach (which relies heavily on prescriptive QA tests, tolerances, and frequencies as provided by consensus expert groups from national/international professional/scientific organizations) is likely inadequate by itself for more advanced modalities.[126-128]

For example, today's image-guided 3DCRT planning and delivery processes have become much more complex and much less intuitive. These complexities, coupled with the inadequate informatics infrastructure and possibly outdated national QA guidelines, have created enormous QA challenges. Communication among members of the planning team, including physician, resident, simulation therapist, dosimetrist, physicist, and treating therapist, is often rushed, cryptic, and complicated by the lack of integration of the radiation oncology EMR (eg, Elekta-Impac MOSAIQ) with the hospital's EHR (eg, Epic software). In fact, in most cases, one must resort to a hybrid charting system (ad hoc combinations of EMR, EHR, and paper charts), which is a dangerous situation. In addition, multiple imaging modalities are often used to define target volumes, all complicating the processing of the information. 3DCRT plan data, transferred over a network to the R&V system and computer-controlled LINAC systems, carry complex specifications for treatment, including positioning of MLC leaves, sometimes variable dose rates, collimator rotation, gantry angles, and, in some instances, a moving treatment table or gantry or both. In some cases, different vendor software systems are used, and interoperability is not always robust. This continuing increasing complexity of devices and systems is clearly problematic for a totally prescriptive QA approach, and it results in increased time demands on staff and groups where there are already shortages. A series of *New York Times* articles[127] brought needed attention to this issue and spurred national organizations to work to improve the current QA situation.[129,130]

Although it is believed that the prescriptive QA approach is valid and valuable for much of the 3DCRT technology and procedures currently in place, new and different approaches need to be developed in parallel.[131,132] These must be risk/evidence based and process oriented rather than device

and procedure oriented; they likely need to be multidisciplinary in nature, resource and risk optimized, and flexible enough to cope with current and anticipated changes in technology.[133] Such process-oriented QA includes risk-based analysis, process mapping, application of failure modes and effects analysis, and fault tree analysis, including analyses of human actions and responses.[134]

In support of this direction, the AAPM recently published recommendations of Task Group 100 on the application of risk analysis methods to radiation therapy quality management.[135] This report provides a mechanism for individual facilities to create custom QA protocols based on their individual situation and risk profile. This task group also calls on the future AAPM task groups to embrace the same methodology. The significance of Task Group 100 is the shift from more or less purely prescriptive QA guidelines to the provision of a tool kit for individual clinics to establish their own QA methods. Advantages of this approach, as described earlier, include the ability to create custom QA protocols considering the unique needs and circumstances of the particular institution. Shortcomings include the time required to create these QA protocols and potential absence of local expertise that can objectively assess individual facility needs. However, both of these are likely transient limitations as efficiency and proficiency in this process will be developed over time. Another great advantage of this approach is the evaluation of new processes and establishment of QA methods and QA tool development based on that analysis. For example, Noel et al[136] analyzed QA processes and tools needed for implementation of online adaptive radiotherapy, and Acharya et al[137] subsequently relied on that analysis for clinical implementation of an actual online adaptive radiotherapy program. The Task Group 100 Report is poised to make a major impact on QA practices in radiotherapy and our future practices should proceed with that in mind.

That said, radiation oncology departments must take all necessary steps to ensure that processes for the safe planning and delivery of 3DCRT are in place and appropriately resourced. Table 10.4 provides a list of guiding principles to help a department prioritize QA efforts for improving patient safety and quality for 3DCRT. This list is a compilation of pertinent key recommendations made by several national and international groups.[126,129,138-142]

TABLE 10.4 GUIDING PRINCIPLES FOR CONFORMAL RADIATION THERAPY QUALITY ASSURANCE PROGRAM

1. Establish a safety-conscious culture within the department and ensure that the processes for safe delivery of three-dimensional conformal radiation therapy (3DCRT) are in place and appropriately resourced. To that end, perform the following:
   a. Establish a formal covenant and commitment to safety. The radiation therapy team should work under a radiation safety covenant, and each member of the team should pledge a commitment to protect the safety of each and every patient.
   b. Make sure it is clear that each member of the treatment team has the right and the responsibility to declare a "time-out" if they have concerns or questions about the plan or course of treatment for a patient.
   c. Make sure that the quality assurance (QA) program is properly resourced.
2. Seek practice accreditation by the appropriate national body, for example, the American College of Radiology/American Society for Radiation Oncology.
3. Participate in external dosimetric audits such as provided by the Radiological Physics Center (now referred to as IROC-Houston) annual External Reference Dosimetry Audit.
4. Expand the use of checklists in 3DCRT treatment planning and treatment delivery.
5. Implement a formal policy that ensures that 3DCRT policy and procedures (P&Ps), including checklists, are in place and are regularly updated and reviewed on an annual basis (require documentation that this is actually done).
6. Conduct periodic reviews of staffing levels to ensure that the staffing and skills mix are appropriate for the numbers of patients treated and the complexity of treatments delivered.
7. Implement a Clinical Operations Committee, with supervisor representatives from each group, to address any problematic issues in the clinic and to help ensure that good communication exists among all groups involved in the 3DCRT treatment process.
8. Conduct town hall meetings (with QA program being a major focus) with department faculty/staff at least quarterly to help ensure good communication exists among all groups involved in the treatment process.
9. Maintain training records for all staff involved in radiation therapy. They should be detailed and specific to particular procedures, that is, an internal form of 3DCRT credentialing.
10. Maintain funding to support training and continuing education, particularly when new 3DCRT techniques are introduced.
11. Introduction of new 3DCRT techniques always needs to be carefully planned with a thorough risk assessment, review of staffing levels and skills required, and development of pertinent P&Ps. All staff involved in the process should undergo specific training in the new treatment technique or process prior to clinical use.
12. Working environment, particularly in two areas—treatment machine console and treatment planning—needs to be conducive to safety and designed such that it ensures that staff can work without inappropriate interruptions.
13. Prescriptive QA program should be in place but continually evaluated to ensure that each specific test adds value and that those that do not add the required value are

eliminated.

14. Perform systematic risk analysis and improvement using industrial engineering–based tools such as process mapping, failure modes and effects analysis, and fault tree analysis for all advanced treatment modalities.
15. Implement a treatment table registration system (CT simulator and treatment machines) so that all patient/immobilization device positions on the table can be registered.
16. Use treatment planning/delivery systems tolerance tables for specific procedures, and monitor setup variability (ie, any therapist overrides of treatment couch, gantry, collimator position, etc, settings in order to treat patient).
17. Perform on-treatment verification imaging as needed, but be mindful of imaging dose, and look for ways to become more efficient.
18. Perform in vivo dosimetry (eg, diode checks) at the beginning of treatment for all patients undergoing 3DCRT when physically possible.
19. Conduct weekly peer review chart rounds (review prescription, verification images, dose distribution, and other pertinent documentation, eg, signed consent, pathology, etc).
20. Conduct weekly peer review planning conference to review 3DCRT plans. Review of gross tumor volume, clinical target volume, and planning target volume contours, digitally reconstructed radiographs, and dose distributions helps to develop a consistent approach in implementing International Commission on Radiation Units and Measurements 50/62/83 methodology.
21. Implement a treatment planning workflow monitoring software system.
22. Implement a software system for reporting and analyzing errors and near misses, with feedback to the staff at town hall meetings.
23. Strive to have the right balance between accountability and openness in the department's incident reporting culture. Department should strongly endorse a national/international incident reporting system for radiotherapy incidents.

Quality Assurance for the Treatment Planning System

The complexity of 3DTPS continues to increase to better facilitate the accurate delivery of 3DCRT. In a number of instances, the TPS is an integral component of the treatment machine. Hence, this results in having more than one planning system in the department, thus increasing QA complexity.[143] Rigorous acceptance and commissioning of the TPS are essential to ensure it is functioning accurately before it is used clinically; in this respect, it is no different than other medical devices. The AAPM recently published Medical Physics Practice Guideline (MPPG) Report 5.b on commissioning and QA of TPS.[143] There has also been activity in automating QA of TPS, and the automation in this area should offer

improvements in consistency and efficiency as well as reduction in errors.[144] More details on acceptance, commissioning, and periodic QA tests are available elsewhere.[143,145-147]

The accuracy of dose calculations must be examined thoroughly during the 3DTPS commissioning process. Periodic checks of calculations versus measured dose are also essential because of possible data corruptions in the TPS itself and to how well treatment machine parameters such as flatness and symmetry are maintained. It should be appreciated that the 3DTPS can never be fully tested, nor can the manufacturer ensure the user that the system is "bug free." Rather, the system should be tested over a range of parameters that are typical of those used in the clinic. For example, tests should include consistency of input/output data; MU calculations; relative dose distributions; graphical data, including BEV and field aperture display; and plan evaluation tools such as DVHs and DRRs. The test procedures and results should be fully documented, as they will provide the baseline data to which the periodic QA tests can be compared.

It has been a practice to validate IMRT treatments with patient-specific dose measurements. However, for online adaptive radiotherapy, it is not practical to perform a phantom-based measurement, and an alternative approach to validation of dose calculation accuracy is needed.[137] The prevailing method for assurance of online adaptive treatment is to perform a secondary independent dose calculation combined with a rules engine to verify integrity of the treatment plan. As online adaptive radiotherapy becomes more mainstream practice, it is expected that the patient-specific measurement-based QA will diminish in prevalence.

Quality Assurance for Patient Positioning and Immobilization and Imaging Data Acquisition

CT, MRI, PET, and ultrasound imaging are used, depending on the disease site, for acquiring imaging data to determine patient external contours and target and OAR volumes. Hence, there are a number of additional QA demands placed on imaging units that are specific to 3DCRT treatment planning.[42] Guidance specifically on MRI for simulation is available from a recent report of the AAPM Task Group 284.[148] Because the patient needs to be repositioned reproducibly on the treatment machine, special patient

positioning immobilization devices are needed. Such devices should be constructed so that they can be attached in a similar manner to the treatment machine couch and the CT, MR, or PET imaging system couches used in obtaining the planning imaging data. These devices should not only attach and lock to all couches, but they also should do so in a configurable manner to allow indexing of the devices to the treatment couch for daily reproducibility. For MRI simulation, the presence of radiofrequency coils surrounding the patient requires careful design and selection of immobilization equipment, although many MR-compatible systems specifically designed for MRI simulation are now available.

In some instances, the composition of these devices is also important; for example, low atomic number materials are necessary for CT scanners, whereas carbon fiber devices are not compatible with MRI. In addition, patient motion can distort MRI and CT images, which can lead to inaccuracies in organ delineation and plan calculation. Large-bore CT simulators often offer extended or extrapolated field of view option.[149] With this option, the native image field of view can be extended by reconstructing the image in the portion of the CT scanner bore opening where partial data collection occurred. Depending on the scanner model and image reconstruction software age, there can be spatial and quantitative CT distortions in those areas of images, which ultimately can translate to treatment planning errors.

Geometric accuracy of all imaging modalities used for planning must be checked. This can be accomplished by imaging suitably designed phantoms on the various machines and comparing the results with the known values. Special care should be given to MRI units, which may suffer from appreciable spatial distortions. Selection of simulation-specific scanning sequences, if available, may help to reduce spatial distortion. If a PET-CT is used, special attention should be paid to the physical alignment of the table couch and both imaging rings. If images from CT, MR, and/or PET are registered and fused, a QA program must be implemented to ensure that the inherent algorithm used and departmental procedures are able to produce accurate composite images for planning.[61,150,151] Finally, for CT, it is necessary to obtain or confirm the relationship between CT number and electron density.

The transfer of image data routinely occurs directly via a computer network but should be checked on a regular basis. Vigilance is also necessary to eliminate any systematic errors; for example, an error in the specification of a scan diameter can lead to geometric distortions of the image.

Quality Assurance for Volume Delineation

Target volume delineation is viewed by many experts in the field as being the weakest link in the entire 3DCRT workflow chain. A high variation continues to be seen in all studies evaluating consistency of delineation of target volumes and OARs among physicians.[152-157] This can be explained by a lack of generally accepted guidelines for volume delineation and also, most likely, insufficient training of radiation oncology residents in modern cross-sectional imaging. It is clear that errors/inconsistencies in volume delineation can seriously undermine the goals of 3DCRT. One approach toward solving this difficult issue is to adopt guidelines and consensus volumes based on the delineation performed by a number of experts in the field.[156,158] Both the Radiation Therapy Oncology Group and the European Society for Radiotherapy and Oncology and Oncology have placed high priority on this approach and now offer more online guidelines for several sites. Standardization in naming convention of targets and OARs[159] should be a component of the effort to improve organ delineation process. To this end, the AAPM has formed the Task Group 263 on standardizing nomenclature in radiation therapy, and it is expected that the results of this work will lead to significant improvements in standardization in this area.[51]

It is also possible to improperly define an OAR because of faulty or incomplete CT procedures. For example, the base of the brain may be better defined on the CT slice if sagittal reconstructions are also available while contouring. In addition, if contrast is used, density overrides may be needed before treatment planning is performed to avoid the erroneous effects of the high-Z media. Related to this is the situation that occurs when high-Z materials like hip prostheses are found within the patient and density overrides are required to account for artifacts. Because of the likelihood and significance of contouring errors in radiotherapy, there is an ever-increasing emphasis on peer review of contoured volumes. In certain situations (eg,

solo practices, online adaptive radiotherapy), it may not be practical to perform peer review or independent review of contoured organs. It is expected that automatic contour checking will play a role in the future of radiotherapy.[160-162]

Quality Assurance for Designing Beams

MLC leaf settings or block apertures and beam orientation displays must be confirmed prior to clinical use and checked after any software modification. In addition, it is possible to define beam orientations that are physically impossible to set up, and this process requires use of clinical judgment by the dosimetrist generating the treatment plan. Thus, the ability to physically set up a particular beam orientation must be reviewed and verified, particularly for beam orientations involving couch rotation. In such cases, tests might have to be performed to verify clearance between the treatment machine gantry and the patient or the gantry and the treatment couch before finalizing the treatment plan. This is especially true for SBRT treatments and will likely be the case for 4π treatments.

Quality Assurance for Treatment Plan Review

A recent study describing the Radiation Oncology Incident Learning System reported that approximately one-third of all reported errors occurred during treatment planning and plan review.[163] All 3DCRT treatment plans should be reviewed, signed, and dated by the treatment planner. The treating physician should of course also review, approve, and sign the treatment plan. Because most of the clinics are paperless today, various combinations of TPS, R&V systems, and EMR pose unique challenges as to where to approve plans and how to document plan reviews by the treatment planner, medical physicist, and radiation oncologist. Each clinic should develop a process where there is a traceability of these approvals, and it is transparent as to who was involved in the planning and plan review processes. In addition, all plans should be independently checked prior to initiation of radiation therapy by a qualified medical physicist (QMP) who was not involved directly in the production of the plan. Because of the varied implementation of these processes, AAPM Task Group 275[164] and MPPG Report 11.a[165] suggest a risk-based approach in which the exact information

and manner of verification are determined based on potential risk of a safety incident. However, both reports specify key information that should be reported and verified. Most critically, major risk factors such as patient identifiers, treatment site, and prescription should be verified through multiple methods by several independent team members. Additionally, the independent plan check should ensure that setup instructions have been properly recorded—for example, field size, gantry angle, and so on. In addition, beam normalization points (typically at isocenter) can be problematic if they are near nontissue medium or under or near an MLC leaf edge and hence should be moved to a more suitable location. The number of MUs to realize the dose prescription is typically obtained directly from the 3DTPS. These values must be independently checked either by hand calculations or, more typically, independent computer calculations. An action level should be established based upon the accuracy of the computer algorithm and independent dose calculation procedure. Obviously, any MU check system must be tested prior to clinical use and following any change or software upgrade. The AAPM Task Group 114 Report provides valuable information on the verification of MU calculations for non-IMRT treatments.[166]

Note that IMRT plans require additional checks, including review of optimization parameters, plan deliverability checks, and maximum doses in and outside of the target. In addition, in the United States, the patient's plan must undergo phantom measurement checks on the intended treatment machine to verify both point dose and spatial dose distribution agreement.

AAPM plan checks are becoming largely automated through homegrown[167,168] and commercial solutions. These software packages range from basic secondary dose calculation to more sophisticated rules engine and industrial methods–driven software. The AAPM's Task Group 275 on Strategies for Effective Physics Plan and Chart Review in Radiation Therapy is in part charged with developing recommendations for software vendors for the development of patient plan checking software.[164] Although, in the past, most could afford the time needed to perform plan checks manually, the online adaptive radiotherapy process does not afford that time. In the age of adaptive radiotherapy, automated plan checks are becoming the necessity, and that will undoubtedly change the field's overall

approach to plan checks moving systematically away from manual work and toward computer-assisted checks.

Quality Assurance Through the Planning Conference

One of the most important components of a 3DCRT QA program is the establishment of a weekly planning QA conference that is attended by radiation oncologists, medical physicists, radiation therapists, and dosimetrists. This is in addition to the normal new-patient chart rounds conference, at which the patient's pertinent medical history, physical, pathology, and diagnostic imaging findings along with the tumor staging and proposed plan of treatment, including the prescription, are presented by the attending radiation oncologists or residents. In a planning QA conference, the group can review the 3DCRT plans using a high-resolution, large-screen video projector connected to the 3DTPS network. GTV, CTV, and PTV contours, DRRs, and dose distributions can all be reviewed very efficiently. This type of planning conference helps the staff to develop a very consistent approach in implementing ICRU 50/62/83 methodology for specifying volumes and provides a very effective peer review mechanism for a 3DCRT clinical program.

Quality Assurance in Plan Implementation and Treatment Verification

If a clinic is in the initial phases of implementing 3DCRT techniques or if experienced users implement new 3DCRT modalities using nonconventional beam orientations, a verification simulation procedure is recommended to confirm the correctness of the beam orientations. It is important to check that all treatment plan parameters are properly implemented. This can be best accomplished by having the treatment planning team available (or on call) during this procedure so that any detected ambiguities or problems can be addressed immediately. When a beam orientation cannot be simulated, EPIDs can be used to obtain orthogonal images for comparison with similar DRRs to ensure correct isocenter positioning. Today, even more advanced onboard imaging and other data localization systems (ie, ultrasound, video surfacing, static kilovolt imaging, kilovolt CBCT, megavolt helical CT, megavolt CBCT,

and MRI) are available.[13,65] Clearly written policy and procedures (P&Ps) should be in place with regard to (1) localization procedures, (2) therapist instructions and tolerance criteria to move (or not move) a patient, (3) whether post-imaging is required when a move is made, (4) subsequent reviews by physicians, and (5) the process for peer review of verification of images. Special care should be taken to ensure that all beam-modifying devices are correctly positioned. Although errors in MLC settings or block fabrication/mounting should be observed when reviewing the portal images, wedge or compensator misalignment is much more problematic and may only be revealed by careful observation during patient setup.

When available, the optical distance indicator or virtual measurement on volumetric setup imaging such as CBCT is also useful in assessing the correctness of the setup of a particular beam. Documentation provides a depth of isocenter below the skin surface on the central ray of the beam, which can then be compared with the isocenter depth measured on the simulator or treatment machine after the beam is set up using the couch and gantry positions specified by the treatment plan.

An R&V system should be used to ensure that the same parameters (within tolerance limits) are used each day. Such systems are valuable for the verification and recording of at least the following parameters: MUs, energy, mode, collimator settings (including independent jaws and MLC), collimator angle, gantry angle, table position, and wedge number and orientation. However, R&V systems must be used with care because they can give the user a false sense of security. For example, if a setup error is made on the first day and the machine geometry parameters are captured, the system will faithfully verify this erroneous setting from day to day. To reduce the chance of this occurring, the patient should be carefully set up according to the treatment plan (best if there is a direct electronic transfer of plan parameters to the R&V system), and a robust P&P for approval of patient treatment position should be in place; upon approval, the parameters are captured with the R&V system. As vendor implementation of Digital Imaging and Communications in Medicine data exchange has matured significantly, the direct transfer of data from the TPS to the R&V system has undoubtedly reduced such errors; however, a careful check of patient position is still recommended. Guidance regarding testing and

commissioning R&V systems has been developed by the International Atomic Energy Agency.[169]

Thermoluminescent dosimeters, diodes, optically stimulated luminescence dosimeters, and metal-oxide-semiconductor field-effect transistor detectors are often used for in vivo dosimetry as described in Chapters 6. Recently, exit portal dosimetry using EPIDs has been used to provide full-field information, even for IMRT fields.[170] Transmission detectors are also playing an increasing role in patient treatment verification. In transmission dosimetry, a large-area detector is mounted on the exit surface of the gantry head, and it compares radiation (fluence and shape) exiting the LINAC with the expectations from the TPS.[171] There has also been a push to use machine log files for daily analysis of patient treatments.[172-174] It is difficult to determine which one of these methods is most effective as they all have some unique benefits, and a combination of techniques may be needed for in-depth defense. To the extent that some of these processes (eg, log file analysis) are passive and run in the background, they are easy and inexpensive to perform and potentially offer free information for prevention of patient treatment errors.

ROLES AND RESPONSIBILITIES OF A QUALIFIED MEDICAL PHYSICIST

A QMP has an important role to play in ensuring the safety and quality of radiotherapy treatment delivery.[175] While this role is integrated into an overall multidisciplinary team effort, which includes radiation oncologists, therapists, dosimetrists, and nurses, among others, the physicist is uniquely poised to serve as a leader to build consensus and elevate the communication and teamwork among the various members of the department. This is because the QMP has been trained in the scientific method, empowering them to logically implement and refine procedures while identifying accompanying potential pitfalls. In addition, the physicist is one of the few team members in radiation oncology who is not limited to a particular duty (eg, treatment planning) or location (eg, linac) throughout the day, which enhances both their perspective of the entire treatment workflow and the interactions among various team members. Finally, the physicist has been trained as an innovator and is able to identify and adopt

new technologic advances into the clinic. An example focused on supporting clinical trials is presented in AAPM Report 113[176] and enumerates the various responsibilities of the physicist at all stages of this specific workflow, highlighting the breadth and depth of duties of a QMP.

SUMMARY

The use of 3D planning and conformal therapy has had a major impact on the practice of radiation therapy. Advances in computing and medical imaging along with the emergence of AI-based RT tools continue to keep 3DCRT a fertile area for ongoing research and development efforts. Phase I/II and III 3DCRT dose escalation studies in several disease sites have been conducted by the Radiation Therapy Oncology Group, now part of NRG Oncology, under cooperative agreement with the NCI.[177] Current use of 3DCRT in clinical trials focuses more on fractionation alternatives including hypofractionation and SBRT and combination therapies (with chemotherapy, surgery, and/or immunotherapy). In addition, there are many other individual institutional studies that have shown the benefits of 3D planning and conformal therapy, particularly for prostate cancer, head and neck cancer, and lung cancer, as documented in the literature.[178] Patients identified to benefit most from 3D planning and 3DCRT are those with tumors in sites with complex anatomy, irregularly shaped tumor volumes, tumors adjacent to radiation-sensitive normal structures, and undergoing small-volume or high-dose treatments. However, as with any major technical advance in radiation oncology, 3DCRT use must be supported with enhanced QA from all members of the treatment team.

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CHAPTER 11

Physics and Dosimetry of Proton Therapy

Brian Winey

PHYSICS OF PROTONS

As protons travel through media, protons interact with the media through electromagnetic interactions, nuclear interactions, and Coulomb scattering.[1,2] The electromagnetic interactions between the proton and the media can be described according to the stopping power equation, known as the Bethe equation:

$$\frac{S_{\mathrm{el}}}{\rho} = -\frac{1}{\rho}\frac{\mathrm{d}E}{\mathrm{d}x} = \frac{4\pi r_{\mathrm{e}}^2 m_{\mathrm{e}} c^2}{\beta^2}\frac{1}{u}\frac{Z}{A}z^2 L(\beta)$$

where r_e is the electron radius, $m_e c^2$ is the electron rest energy, u is the atomic mass unit, β is the particle velocity, Z is the atomic number of the medium, A is the relative atomic mass of the medium, and z is the charge number of the particle ($p = 1$, $C = 6$).

The term $L(\beta)$ can be expanded as:

$$L(\beta) = L_0(\beta) + zL_1(\beta) + z^2 L_2(\beta)$$

where the individual terms are defined as follows:

$$L_0(\beta) = \frac{1}{2} ln\left(\frac{2m_e c^2 \beta^2 W_m}{1-\beta^2} \right) - \beta^2 - ln(I) - \frac{C}{Z} - \frac{\delta}{2}$$

$$L_1(\beta) = g_1 \beta^{-2g2}$$

$$z^2 L_2(\beta) = -\left(\frac{z\alpha}{\beta} \right)^2 \sum_{n=1}^{\infty} \frac{1}{\left[n\left[n^2 + \left(\frac{z\alpha}{\beta} \right)^2 \right] \right]}$$

where W_m is the largest possible energy loss in a single collision with a free electron, C/Z is the shell correction to account for the bound state of K and L shell electrons, and $\Delta/2$ is the Fermi density effect correction. The second factor, L_1, is known as the Barkas correction factor and is an empirical fit with variable g dependent upon the medium. The final term can be approximated in the limit of the particle traveling faster than the atomic electron as the Bloch approximation:

$$z^2 L_2(\beta) = -\left(\frac{z\alpha}{\beta} \right)^2 \left[1.20 - \left(\frac{z\alpha}{\beta} \right)^2 \left(1.04 - 0.85\left(\frac{z\alpha}{\beta} \right)^2 + 0.343\left(\frac{z\alpha}{\beta} \right)^4 \right) \right]$$

This now gives the Bethe-Bloch equation that describes the proton-stopping power in a medium:

$$\frac{S_{\mathrm{el}}}{\rho} = -\frac{1}{\rho}\frac{\mathrm{d}E}{\mathrm{d}x} = \frac{4\pi r_{\mathrm{e}}^2 m_{\mathrm{e}} c^2}{\beta^2}\frac{1}{u}\frac{Z}{A}z^2$$
$$\left[\frac{1}{2}\ln\left(\frac{2m_{\mathrm{e}}c^2\beta^2 W_m}{1-\beta^2}\right) - \beta^2 - \ln(I) - \frac{C}{Z} - \frac{\delta}{2} + L_1(\beta) + z^2 L_2(\beta)\right]$$

In general, the electromagnetic interactions increase as the proton velocity (energy) decreases (Figure 11.1).

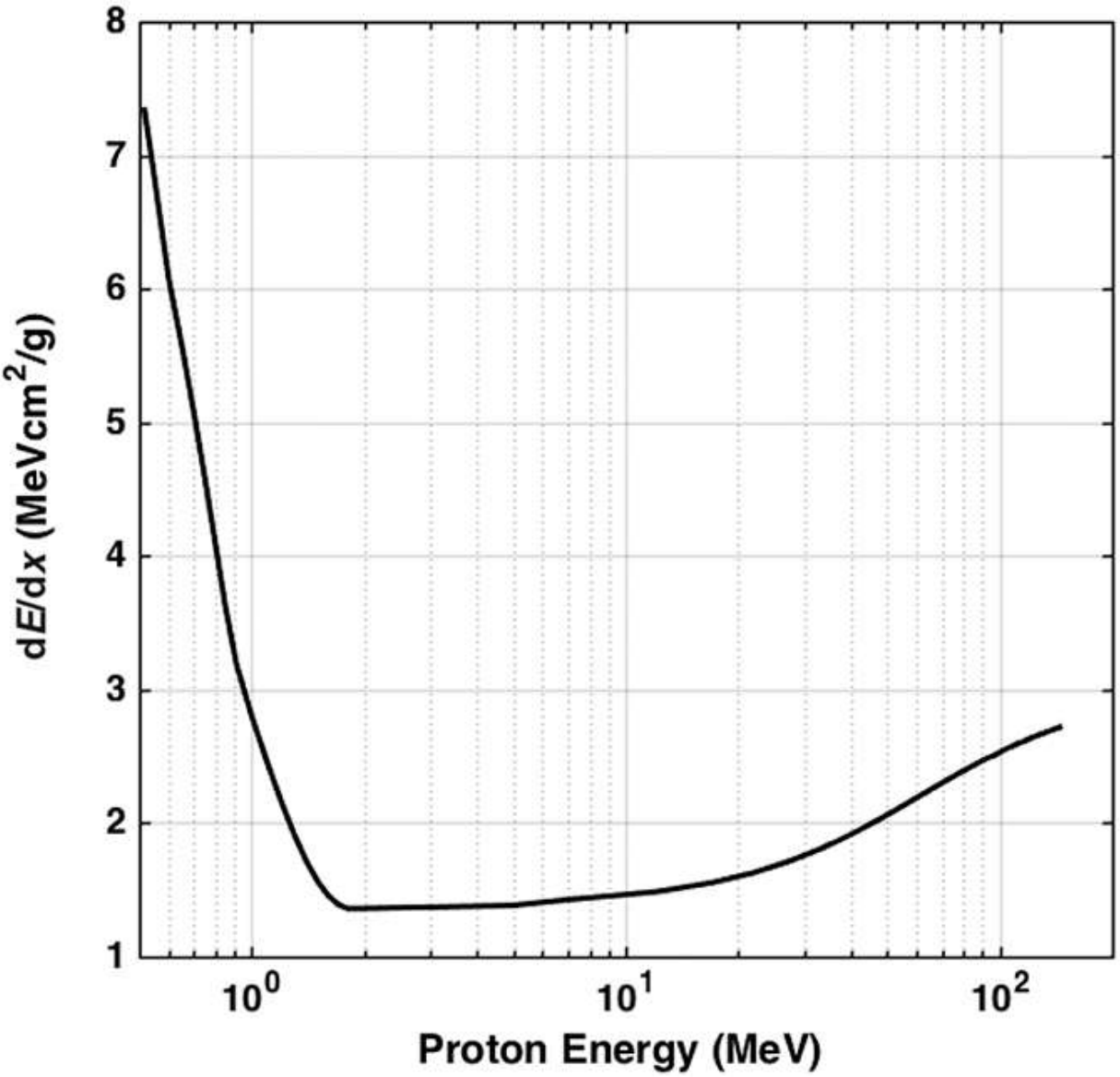

FIGURE 11.1 The energy loss (d*E*/d*x*) as a function of proton kinetic energy for protons traveling through water. Most importantly, the energy loss increases rapidly as the proton slows in the medium. This rapid energy loss gives rise to the Bragg peak.

In addition to the electromagnetic interactions, the nuclear interactions are composed of both elastic and nonelastic interactions with the majority of dose deposited by the nonelastic interactions that result in secondary nuclear particles, primarily protons along with gamma radiation. Some of the gamma radiations produced in the nuclear interactions are "prompt gammas" that can be measured to determine the Bragg peak location in the media (REF). Other nuclear interactions result in positrons, which can be

measured with positron emission tomography imaging as a signal proportional to the proton interactions (REF). The nonelastic nuclear interactions are mostly independent of particle velocity until the particle slows to a resonance velocity, which results in an increase in the nuclear interaction cross section, similar to the electromagnetic interactions. Combined, the nuclear and electromagnetic interactions give rise to the famous Bragg curve of particle therapy (Figure 11.2). The relationship between proton energy and proton range[3] is detailed in Figure 11.3. Typical clinical proton therapy centers provide proton energies from about 70 to 235 or 250 MeV.

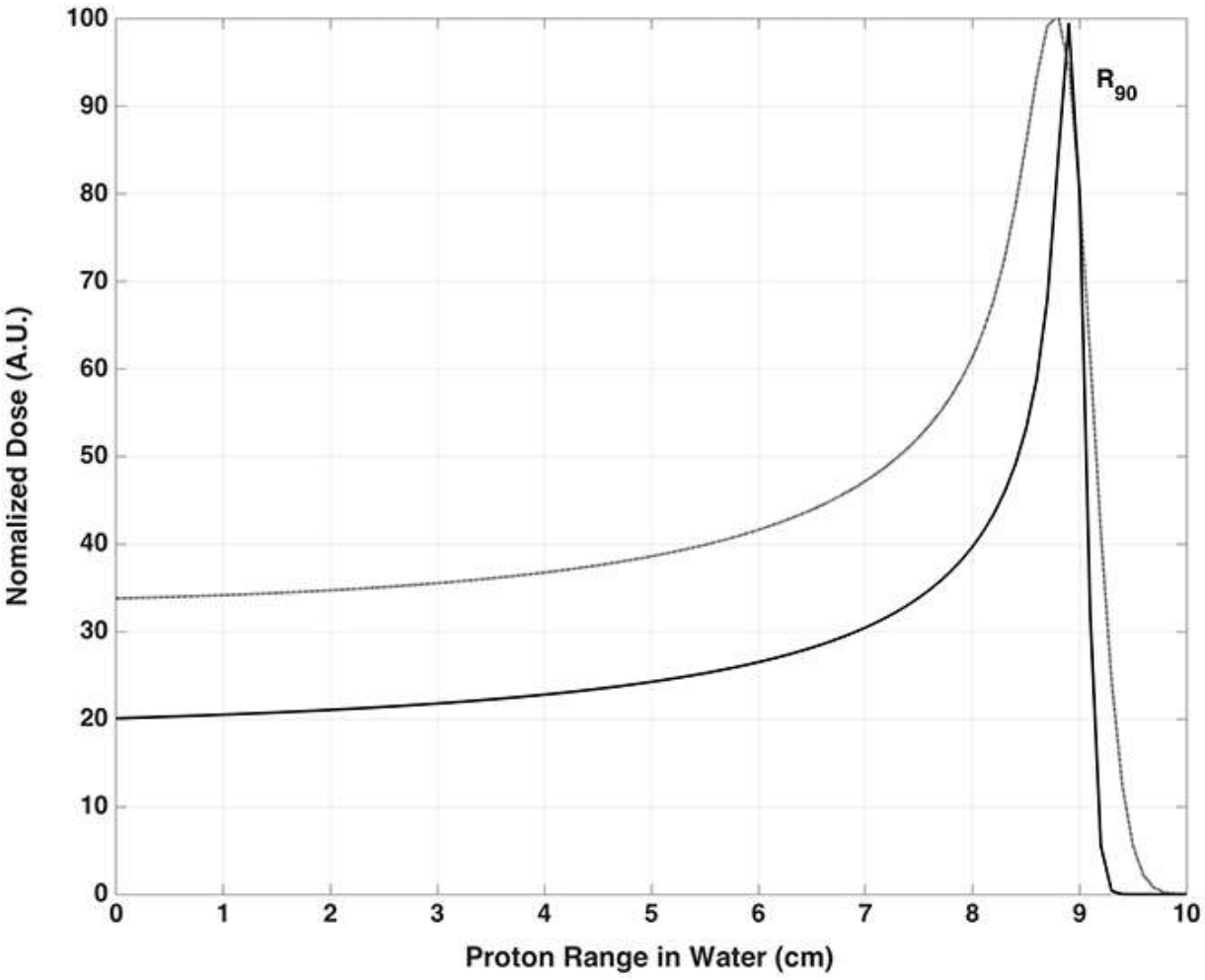

FIGURE 11.2 The proton energy deposited into the medium (water) as a function of proton range. The dotted line represents the effects of proton energy straggling as the protons stochastically interact with the medium. The R_{90} range is labeled.

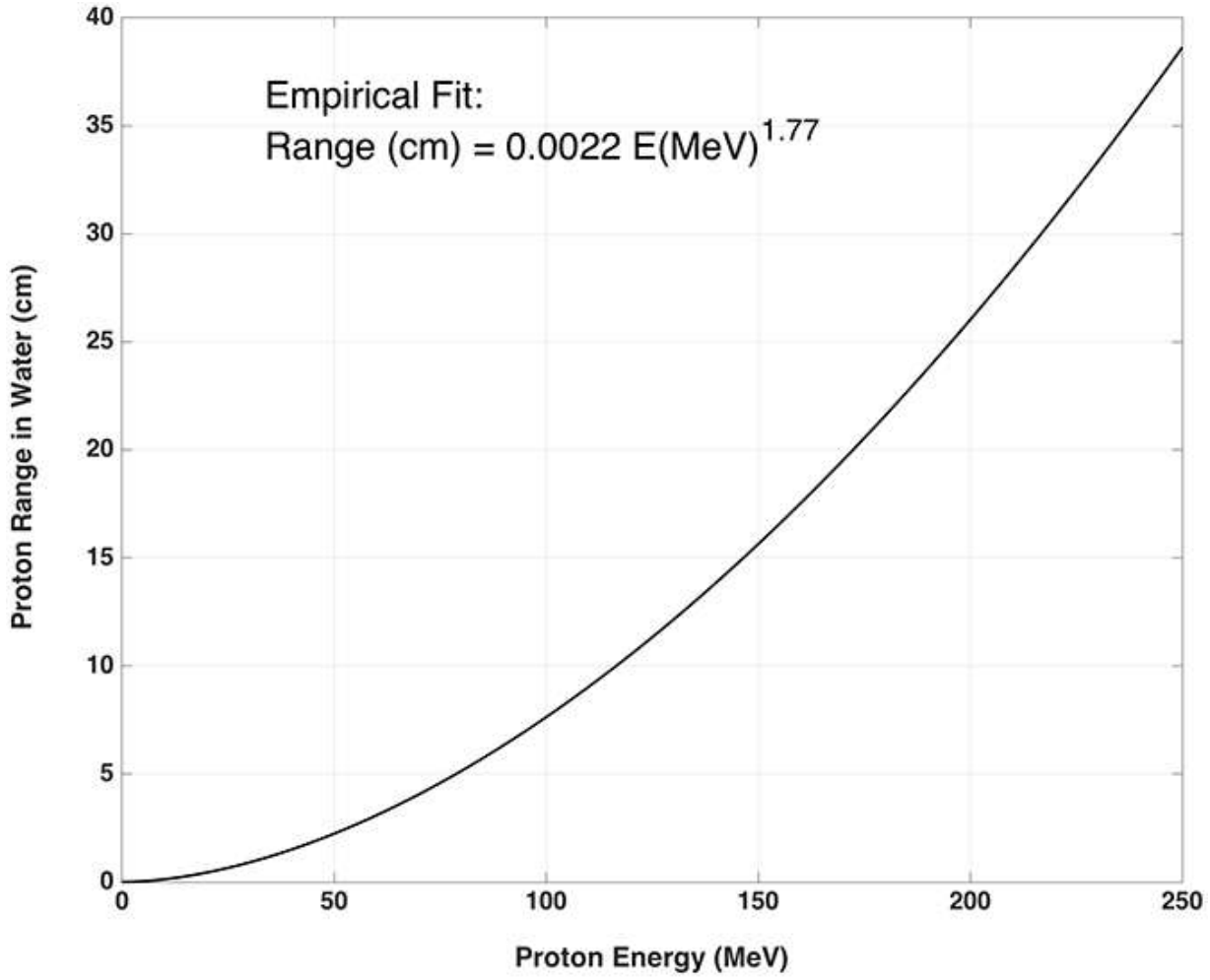

FIGURE 11.3 The relationship of proton energy and range (R_{90}) in water. The graph is a commonly cited fit[3] to empirical data that are not displayed. Typical clinical proton therapy accelerators provide proton energies from about 70 MeV (R_{90} = 4 cm) to 235 MeV (R_{90} = 35 cm).

Since the process of particles traveling through media is stochastic, the particles can lose energy at different rates. The energy straggling of the protons broadens the Bragg peak as the particles travel deeper into the media and the spectrum of energies in the beam increases in width. The clinical result is the broadening of the distal penumbra of the particle beam, particularly evident when treating deep targets (see Figure 11.2).

As the particles travel through the medium, the particles undergo Coulomb scattering events with the nuclei. Due to the elastic nature, little energy is lost in the Coulomb scattering events, but the effect is most pronounced in the shape of the beam as it progresses through the medium.

Multiple Coulomb scattering (MCS) affects the beam output for small fields, dose coverage of targets, dose homogeneity, range straggling, and increased lateral penumbra (Figure 11.4). In fact for small proton beams (diameter <1 cm for ranges >10 cm), the MCS events can result in a loss of the Bragg peak along the central axis and inside the treatment target (Figure 11.4).

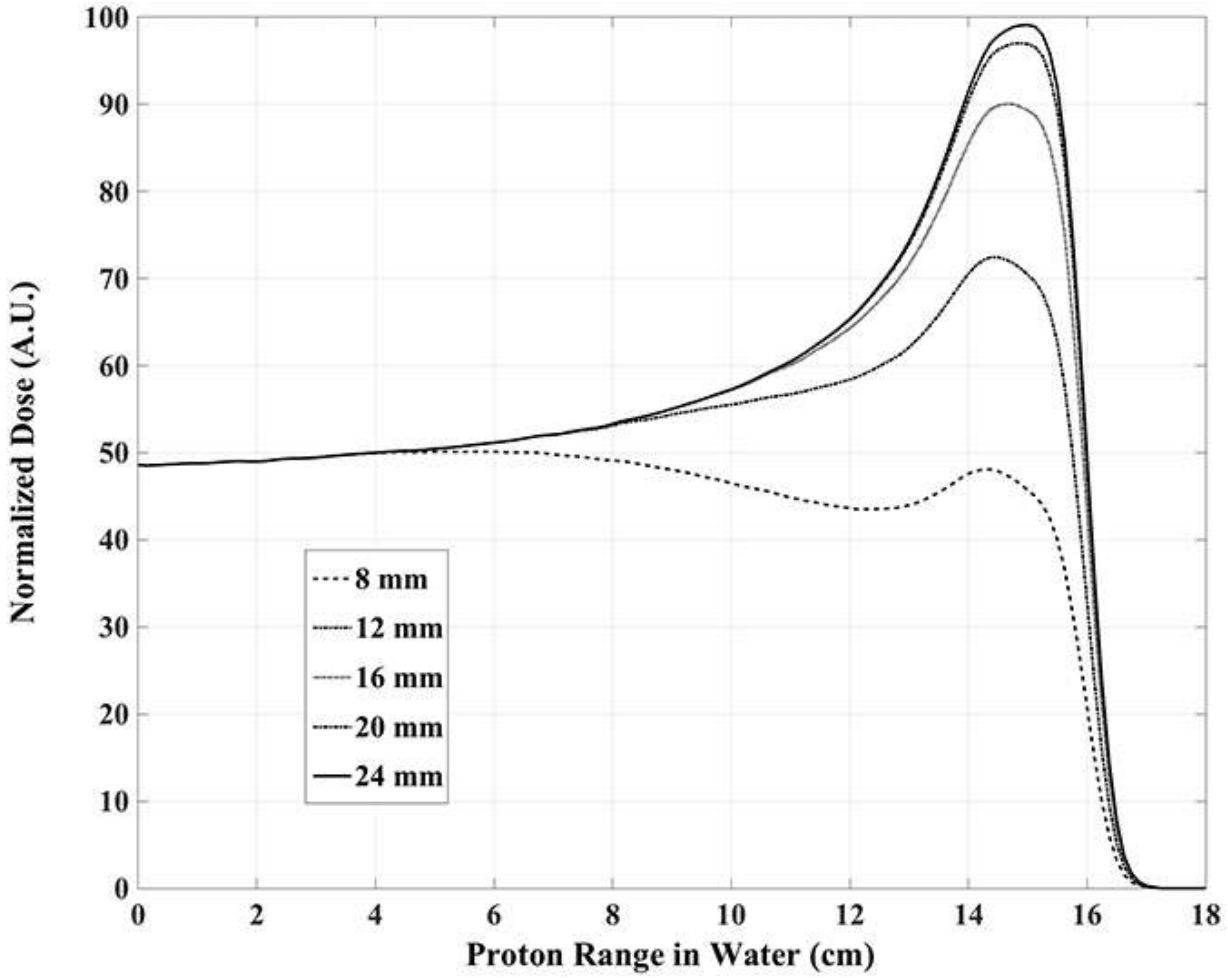

FIGURE 11.4 A central axis depth dose curve for a Bragg peak with a range of 15.5 versus field size. All fields are given for a range of 15.5 cm, and the field size decreases from 24 to 8 mm. Similar effects can be observed with single pencil beams. As the field size increases, the lateral scatter of neighboring pencil beams provides lateral equilibrium along the central axis and restores the Bragg peak.

DOSIMETRY

Absolute dosimetry in proton therapy is typically performed using Faraday cups or calorimetry, with Faraday cups being more common.[2] Aside from absolute dosimetry, most clinical proton therapy centers rely upon ionization chambers to perform beam calibrations. In many ways, proton beam dosimetry is similar to photon therapy. Dosimetry must be traceable to a primary standard radiation source (eg, National Institute of Standards and Technology in the United States) where the radiation dose is typically defined in a free air ionization chamber with a cobalt source. Institutions can rely on Accredited Dosimetry Calibration Laboratories to supply an absolute calibration factor for ionization chambers. Current protocols utilize dose-to-water calculations and correct for the proton beam quality relative to cobalt.

According to Technical Report Series (TRS) published by the IAEA (INTERNATIONAL ATOMIC ENERGY AGENCY) 398 and International Commission on Radiation Units & Measurements (ICRU) Report 78,[1] a calibrated ionization chamber can be used to perform calibration of a proton beam according to the following equation:

$$D_{w,Q_p} = M_{Q_p} N_{D,w,Q_{p0}} k_{Q_p,Q_{p0}}$$

where the measurement, M, is corrected for pressure, temperature, polarization, and recombination. The k_q factor is a function of residual range (R_{res}) of the proton beam, which is correlated with the spectrum of proton energies at the point of measurements.

Of particular note in scanned beam proton therapy, instantaneous dose rates in the volume of the ionization chamber can be significantly higher than the scattered proton beams and recombination can reduce the accuracy of the output measurements. Some proton therapy accelerators can deliver lower beam currents, or an institution can purchase ionization chambers designed for scanned proton beams. A proton beam calibration measurement must be performed in an irradiated volume large enough to reduce the effects of scattering, including Halo dose perturbations, and volume averaging in the volume of the ionization chamber. Typically, an

ionization chamber will be placed in the center of a field size of at least 10 cm × 10 cm and a modulation width of at least 10 cm (R_{res} = 5 cm, assuming the ionization chamber is positioned in the middle of the volume).

While the physical dose of protons is measured and recorded similarly to photon therapy beams, the biologic dosimetry is different. The historical and still common practice is to apply a relative biologic effectiveness (RBE) correction factor of 1.1 to the physical dose in order to correct for the increased clinical effectiveness of the proton physical dose delivered to the patient relative to a photon treatment of the same physical dose.[4] Proton beam radiation therapy is typically quoted in Gy RBE, such that the physical dose is multiplied by the RBE correction factor:

$$D_{Gy,\mathrm{RBE}} = 1.1\, D_{Gy}$$

The RBE factor of 1.1 is not constant for all cell types, clinical end points, or locations along the proton dose curve.[5] There are many studies analyzing the effects of variable RBE or measuring cell and end point–specific RBE values.[4-9] While the clinical use of 1.1 as the standard RBE multiplier continues, there remains uncertainty regarding the most accurate RBE factor for proton beam therapy. In addition to the uncertainty of the RBE value for proton therapy, more recent studies that have begun to explore the potential RBE differences for pencil-beam scanning (PBS) deliveries compared to historical data with scattered proton beams, particularly when the instantaneous dose rate is much higher that the scattered proton beams.[10-15] The biologic dose of proton therapy remains a research topic. Most clinical dose calculations rely upon a static RBE value of 1.1. Since the RBE of protons can depend upon cell type, the position of the cells in the cell cycle, linear energy transfer of the protons, and the local tissue environment, studies continue to evaluate the RBE[9,5,13,16-19] and the local (micro) dosimetry through biological Monte Carlo simulations.[20-22]

UNCERTAINTIES

Physical dose and particle interactions have long been described in the literature, and the fundamental physics is generally well understood. There remains some uncertainty in the cross section interactions between protons

and nuclei (I)[23] in the above equations, but commissioning measurements of clinical systems can greatly reduce the uncertainties of the underlying physics for water measurements and dose calculations.

Uncertainties in proton therapy delivery remain and affect the accuracy of the proton beam delivery to the intended target. Due to the sharpness of the Bragg peak, uncertainties that affect the proton range can result in large underdosing in the target when the Bragg peak stops prematurely or overdosing of the surrounding tissues when the Bragg peak travels farther than intended into the patient.

There are generally two classes of uncertainties that affect the range of the proton Bragg peak in the patient: systematic and random. Uncertainties in both categories can be mitigated with various methods during pretreatment imaging, treatment planning, and treatment room imaging. A summary of both categories of uncertainties can be found in Table 11.1. The important note is the larger dosimetric effect of systematic versus random uncertainties in the proton beam delivery. It is also important to note that many of the uncertainties are present in photon or electron beam therapy but the Bragg peak in proton therapy can create unique dosimetric uncertainties.

TABLE 11.1 A BRIEF AND NONEXHAUSTIVE LIST OF UNCERTAINTIES THAT AFFECT THE DOSIMETRIC DELIVERY OF PROTONS[24]

Systematic	Random
CT stopping power calibration	CT noise
Beam energy/range calibration	Beam energy tuning
Ion chamber calibration	Spot position and weight
Immobilization densities	Patient positioning
Implanted device densities/artifacts	Anatomic motion
Anatomic changes	Anatomic changes
Heterogeneities in silico	Heterogeneities in vivo

The magnitude of the uncertainties is not listed.
CT, computed tomography.

Many of the uncertainties have both systematic and random contributions due to the differences of calibration and delivery or treatment planning system (TPS) calculation versus delivery. For example, anatomy might not be accurately captured in the computed tomography (CT) in the case of a filled sinus cavity that can become a systematic range error for the treatment of a nasopharyngeal lesion if the sinus were to drain prior to the first treatment. Other anatomic changes such as motion can be more random if the motion and interplay with the proton beam delivery varies with each fraction.

To mitigate the dosimetric effects of the listed uncertainties, or increase the robustness of the treatment plan, there are multiple methods that can be employed. One of the simplest and most robust methods is to utilize more than one treatment beam. The use of multiple beams can spread the uncertainty of a single-beam direction and reduce the magnitude of a dose uncertainty to a single location. Depending upon the time scale of the random uncertainties, multiple beams can also reduce the magnitude of the random uncertainty simply by increasing the time of proton beam delivery.

While the Bragg peak reduces both the entrance and exit doses compared to photon beams to greatly reduce the integral dose to organs outside the target, the use of multiple beams can increase the integral dose. It is a clinical decision whether the increase in robustness using multiple beams is worth the increased integral dose. In some treatment sites, the increased integral dose can be deposited in the surrounding tissues that have a low risk of radiation-induced toxicities. In other sites, the risk of toxicities is greater and the clinical decision leads to the use of a single-treatment beam, for example, sacral sarcomas or ocular melanomas.

A second method to increase the robustness of the treatment delivery is to use margins, similar to photon therapy. Specific to proton therapy, the margins at the distal edge of the target are often determined separately from the lateral margins specific to a beam angle geometry. In addition to margins, the distal edge of a treatment beam can be “smeared,” which decreases the distal conformality in the lateral direction of the beam such that tissue motion or patient setup uncertainties have a reduced effect on the target dose, although smearing is much less common in PBS deliveries compared to scattered deliveries.

A third method that can be used in more recent TPSs is a "robust optimization" technique. In addition to the more common dose objectives and constraints for the targets and organs used in common inverse plan optimization, the basic premise of a robust optimizer considers random and systematic uncertainties, including range uncertainties, in the dose optimization cost function that controls the plan optimizer.[25-28] In other words, the optimizer considers not only the dose to the target or organs at risk (OARs) but also the risk of overdosing the OAR or underdosing the target in the presence of range and setup uncertainties. The cost function penalizes plans that have higher risk of dose uncertainty and essentially reduces the presence of high-dose gradients in the optimized plan. More robust plans may have higher OAR doses, but the certainty of the delivery is much higher if the model accurately captures the uncertainties of the treatment workflow. Generally, more robust plans result in less sharp dose gradients in close proximity to avoidance regions, such that the effect of range or dose uncertainties will be reduced.[29-31]

Robustness has been demonstrated to account for systematic and random uncertainties that follow predictable or normal distributions. When an uncertainty is patient specific, varies in a nonnormal distribution, or exceeds predetermined (often site-specific) magnitudes, the robustness model often fails to account for the uncertainty, or the robustness model will require a large volume of normal to be irradiated to increase the probability of target coverage.[32] In these cases, a clinical decision is often made to reduce target coverage, increase dose to the normal tissues, ignore a fringe case of uncertainty, or rescan the patient to generate a new plan.

Robust planning methods can reduce the need for some margins and increase the certainty of the dosimetry calculated in the TPS being delivered to the patient.

In the case of generating a new plan, much work is being pursued to develop adaptive proton therapy following in the pioneering work in the photon clinics. When the dosimetric uncertainties are larger, particularly in the event of large anatomic changes from either weight loss, air pockets, fluid changes, or target migration, the need for triage and new proton planning are essential to increase the fidelity of the proton dose delivery to the targeted tissues. Many recent studies have demonstrated the need and potential avenues for pursuing adaptive proton therapy workflows.[33-38]

Some institutions, such as the Paul Scherrer Institute (PSI) in Switzerland, have begun to deliver adaptive proton therapy treatment plans.

TREATMENT PLANNING AND DELIVERY

While the Bragg peak is commonly known, it is a continual evolution to use the Bragg peak optimally for the treatment of a target volume. There are essential two methods for proton therapy delivery: scattered and scanned. Scattered therapy was the dominant solution for more than 50 years of treatment but has faded as most proton therapy centers now use scanning delivery systems.

Scattered Beams

Briefly, scattered systems use scatterers composed of various plastics and metals to increase the diameter of the proton pencil beam within a specified flatness and symmetry. A proton beam exits the accelerator with a sigma on the scale of millimeters or 1 to 2 cm, depending upon the system and energy selection method. A typical ocular line requires very little scattering, but targets larger than an ocular target require larger beam diameters. Common double-scattering systems use multiple scattering elements to achieve flat proton beams up to a clinically flat 25 cm diameter. Once the beam is scattered to the appropriately specified diameter, apertures are used to laterally shape the proton beam to the shape of the target volume.

In addition to the lateral shape of the proton beam, the size of the beam along the beam axis is variable and specified by the modulation of the Bragg peak. There are multiple methods of modulation, which essentially modulate the energy of the proton beam to change the range of the protons in the patient. The summation of the multiple energy proton beams results in a spread-out Bragg peak, which provides a flat dose distribution inside the target volume (Figure 11.5). The modulation of the proton beam energy can occur at the accelerator, in the energy selection system (ESS), with a modulation wheel, or generally with any technique that adds material in the beam path. One of the more common modulation methods paired with a cyclotron accelerator uses a modulation wheel that is composed of a wheel with increasing steps of material thickness. The wheel rotates through the beam path and essentially sweeps the proton Bragg peak through the

treatment volume multiple (hundreds) times each second. Synchrotron accelerators can generate variable energies, depending upon the number of accelerating revolutions in the ring, and do not require additional materials to change the energy of the protons. More details regarding the differences between accelerators will follow.

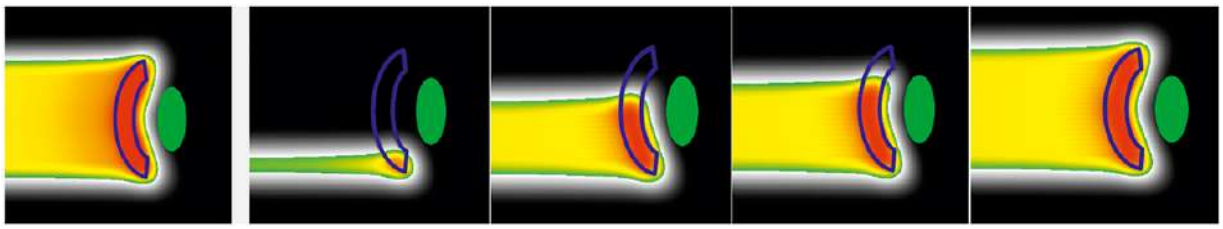

FIGURE 11.5 A comparison of the dose delivered by a scattered beam (left) and a scanned beam at different times in the field delivery beginning with the first pencil beam and scanned across the blue target volume.

Scanned Beams

While scattered beams spread the beam laterally, shaped by an aperture, to deliver a uniform dose to the specific target volume, scanned beams sweep a single proton pencil beam (Figure 11.5) orthogonally to the direction of the beam to deposit dose to a "layer" of tissue, either continuously or spot scanning, changing the energy of the protons to move the "layers" and irradiate a volume. In most scattered beam deliveries, the entire target receives a uniform dose, and the beam continues to deliver a uniform dose to the entire target until the time that the prescription dose is delivered. In a scanning system, a small portion of the target is irradiated with a single Bragg peak pencil beam until the prescribed dose of that pencil beam is delivered and then the pencil beam is scanned to the next location. The pencil beam is scanned over the entire volume, using energy changes when necessary to modulate the depth of the pencil beam, until the prescribed dose pattern is delivered (Figure 11.5).

While a scanned beam delivery does not require apertures to provide lateral conformality to the target volume, apertures can provide additional conformality for shallow targets and larger spot sizes.[39] The target depth when the apertures no longer provide a clinical advantage depends upon the spot size of the delivery system.

In addition to reducing the need for physical hardware, scanning systems can provide multiple dosimetric benefits over scattered beams. The primary benefits include:

- Reduced proximal dose in the entrance region
- Greater proximal conformality due to nonuniform modulation
- Ability to deliver nonuniform doses to the target (intensity modulation)
- Greater conformality and organ sparing for complex-shaped targets
- Gradient match lines for large targets, particularly craniospinal irradiation (CSI) treatments

Scanned beam dosimetry can be less robust to motion and other uncertainties listed above, but the robustness of the scanned beam delivery can be improved using robust optimization, margins, rescanning, rapid scanning, and variable spot sizes.

With greater effort toward the deployment of scanned beam systems, the challenges of robustness are being overcome, and the use of scattered beams is diminishing.

Beam Generation

Proton beam therapy relies on the acceleration of protons to speeds approaching the speed of light with energies around 250 MeV to treat most target locations, higher for proton imaging. There are two predominant accelerators, cyclotrons and synchrotrons,[2] with multiple design variations within each of the two general categories. Some have proposed linear accelerators and other novel acceleration technologies, including dielectric wall and laser driven.

Most of the earliest accelerators for proton therapy were cyclotrons due to the simple elegance of the physics and electronics needed for D-shaped cyclotron design. When proton speeds approach relativistic, the simple D cyclotrons require modifications to address the number of revolutions and increased B fields needed for protons that increase in mass at relativistic speeds. Many of the clinical systems use synchrocyclotrons to reduce the size of the cyclotrons.

Cyclotrons, even synchrocyclotrons, can generate quasi- continuous beams with large beam fluence. Higher and more continuous beam currents can allow for more rapid beam delivery, even at Flash dose rates, and reduce the treatment times. The primary drawback of cyclotrons for beam delivery is the need for a secondary ESS to adjust and reduce the nominal beam energy from the cyclotron to the requested beam energy for the specific “layer” to be delivered in the medium. The ESS can dramatically reduce the proton fluence and increase the pencil-beam dimensions. Much work has been done over the years to reduce the negative impacts of the ESS and maintain a higher dose rate and smaller spot size at the point of treatment.

The second dominant accelerator design is the synchrotron. Synchrotrons are composed of a ring of bending magnets combined with an injection line (typically a linear accelerator), an energy kicker that provides an energy increase to the protons with every revolution, and an extraction line to direct the protons to the therapy beamline. The bending magnets and timing of the energy “kick” are adjusted in both time and, in the case of the bending magnets, magnitude with each revolution such that the ring components are in synchrony with the protons.

The design of the synchrotron results in “bunches” of protons being accelerated together, the bunch revolving a specific number of rotations to achieve the specified energy (speed), the proton bunch being extracted to the beamline, and the process repeating until the total expected number of protons and energies are delivered. One of the primary advantages of a synchrotron is the ability to generate specific energies, depending upon the number of revolutions through the ring and passing through the “kicker,” thus removing the need for an ESS and potentially decreasing the size of the proton beam. Second, higher energies can be achieved with more revolutions in the ring so long as the bending magnets are capable of generating field strengths large enough to maintain the protons along the circular path. With stronger bending magnets, synchrotrons are most frequently used for higher mass particles including carbon ion therapy centers, although work is being done to develop a cyclotron-based carbon ion treatment center.

While synchrotrons can generate proton beams of specific energies without an ESS, the duty cycle of the accelerator can increase the total

beam delivery time due to the "dead" time needed to accelerate another "bunch" of protons. Much research and development have been completed to mitigate the time delays in synchrotron deliveries including larger spill sizes to deliver more protons per bunch, variable energy extraction to reduce the waste of protons at the end of a spill, faster accelerating cycles, and higher scanning speeds. Combined these improvements has allowed synchrotron delivery times to become very similar to cyclotrons, except in the largest treatment volumes.

A final comparison between cyclotrons and synchrotrons might be the practical concern of shielding and building construction. Cyclotrons can be deployed rapidly and can be small when using superconducting magnets in the cyclotron. However, cyclotrons, due to the need for ESS, can require larger amounts of shielding. Synchrotrons have smaller individual components, but the total size is larger than a cyclotron. Synchrotrons require less shielding, and the buildings can be cheaper. Institutions are still discovering which accelerator design is more cost-effective over the long-term use of the devices, including repairs and maintenance, particularly when a synchrotron is more modular and a cyclotron can be simpler. Overall, cyclotrons are used in more clinical installations, and both accelerators can be used to generate clinically stable proton therapy beams for scanned beam deliveries.

Site-Specific Proton Treatment Planning

The earliest proton therapy treatments were delivered to cranial (pituitary) and ocular targets. Currently, ocular proton therapy is the most common proton therapy site by patient numbers worldwide.[40] The primary reasons for the popularity of ocular treatment popularity are the target location, low proton energy, and small treatment fields. When proton therapy began in the physics accelerator laboratories, there were many accelerators capable of reaching 70 MeV and the beam delivery required little scattering to achieve the lateral field sizes needed for the ocular targets. While more details of proton therapy planning will be provided in a later chapter, some of the sites commonly treated with protons as well as some of the treatment planning considerations, given the prior context are highlighted below.

Brain

Cranial targets were the first recorded treatments with proton and ion beams.[41-46] The treatments were straightforward with opposed lateral beams targeting the sella for pituitary therapies. With the advent of three-dimensional (3D) imaging, more diagnoses in the brain are currently treated, including both conventional and stereotactic radiosurgery fractionation techniques.

When considering a treatment plan for a cranial target, protons can reduce the normal brain integral dose and dose to sensitive structures, such as the optic apparatus and the brainstem. The clinical significance of the dose reduction to normal brain is not discussed here. Cranial targets present an excellent proton therapy site due to the ability to use multiple beam entrance angles to increase the dose conformality, reduce the uncertainties from any single beam, and increase the overall robustness of the proton delivery. Typical treatment plans are displayed in Figures 11.6 and 11.7.

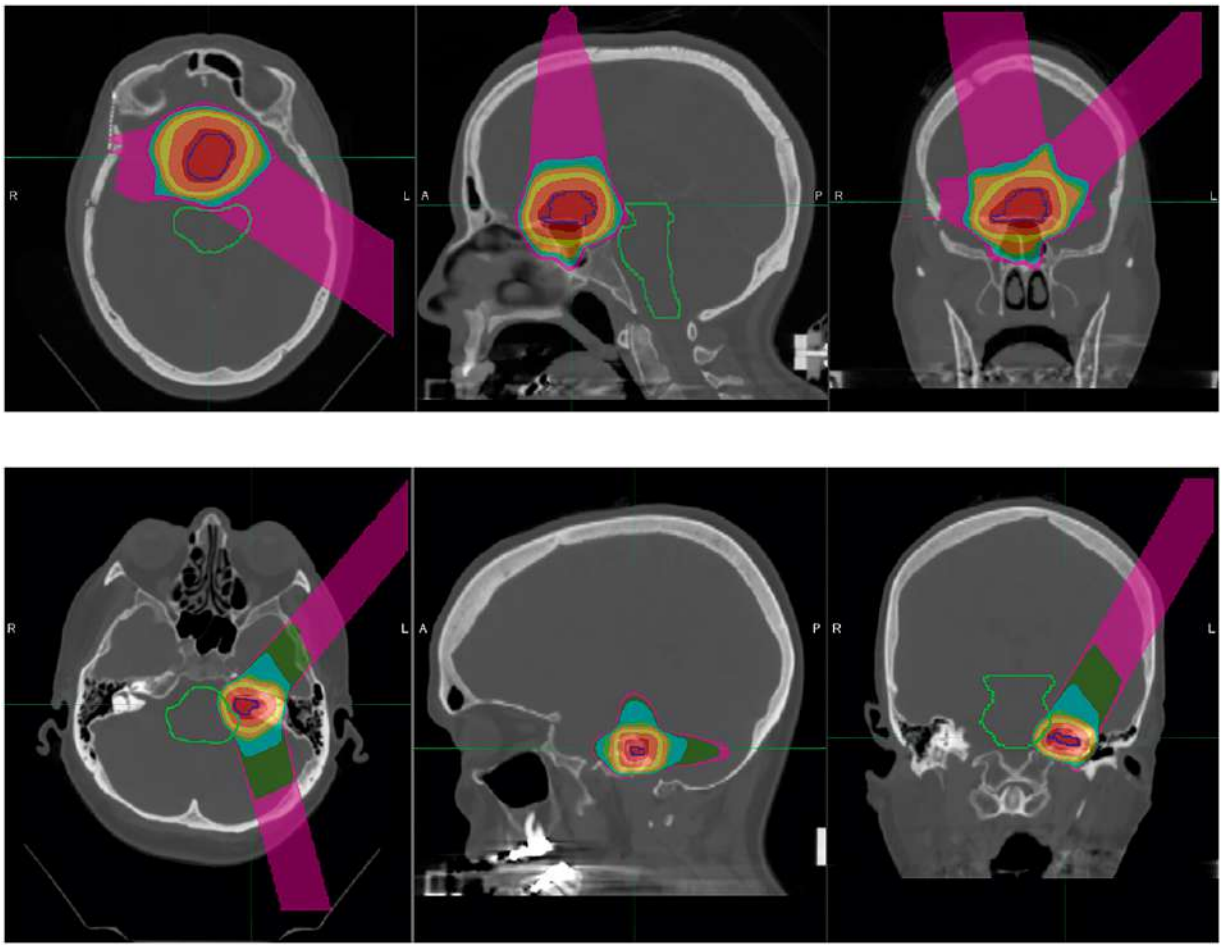

FIGURE 11.6 An example of cranial target treatment plans for a meningioma (top) and an acoustic schwannoma (bottom). The beam angles can be visualized by the low dose.

FIGURE 11.7 A representative treatment plan for a base of skull lesion utilizing beam angles in the axial plane as well as superior oblique beams.

Base of Skull

From a treatment planning perspective, the base of skull targets such as chordomas can be treated with protons to reduce the integral dose to the brain and spare many organs in close proximity to the target volume, particularly the brainstem. Prior to the clinical deployment of scanned beams, the treatment of concave base of skull targets with scattered beams required the use of matched beams inside the target volume. Scanned beam treatment plans can now provide more robust treatments with gradient match lines and increase the dose sparing of organs in close proximity to the targets. Similar to cranial targets, the base of skull lesions can be treated with multiple beam entrance angles, including superior oblique beams to increase the dose conformality, treatment robustness, and normal tissue sparing (Figure 11.7).

Head and Neck

The treatment of head and neck lesions can provide some challenges to treatment planning and delivery, irrespective of the method of proton delivery. Large anatomic variations due to sinus filling, tumor shrinkage, and patient weight loss can greatly affect the accuracy of the proton treatment. The treatment planning advantage for head and neck targets is typically the sparing of normal tissues to reduce acute and chronic toxicities.[47-49]

Typical treatment plans for targets in the nasal region employ two or more treatment fields, but the possible beam angles are often reduced due to the location of the target with respect to the eyes and optic nerves. Beam angles for lesions around the oral cavity and inferior have greater flexibility than nasal targets. In addition, simultaneous boost volumes can also be treated easily with scanned proton beams. Tumor shrinkage or sinus filling/draining can also increase the uncertainty of proton treatment. Adaptive proton therapy will greatly benefit targets in the nasal, oral cavity, and neck locations.

Breast

Proton therapy is now an option for breast radiation therapy.[50-53] The typical treatment employs a single en face proton beam. Breathing motion is mostly oriented along the beam angle such that the motion has little effect

on the treatment delivery. With the use of proton therapy, nodal target volumes can be included in a single scanned beam so long as the total target volume fits in the maximum field size of the treatment delivery system. In addition, simultaneous boost volumes can also be treated easily with scanned proton beams (Figure 11.8).

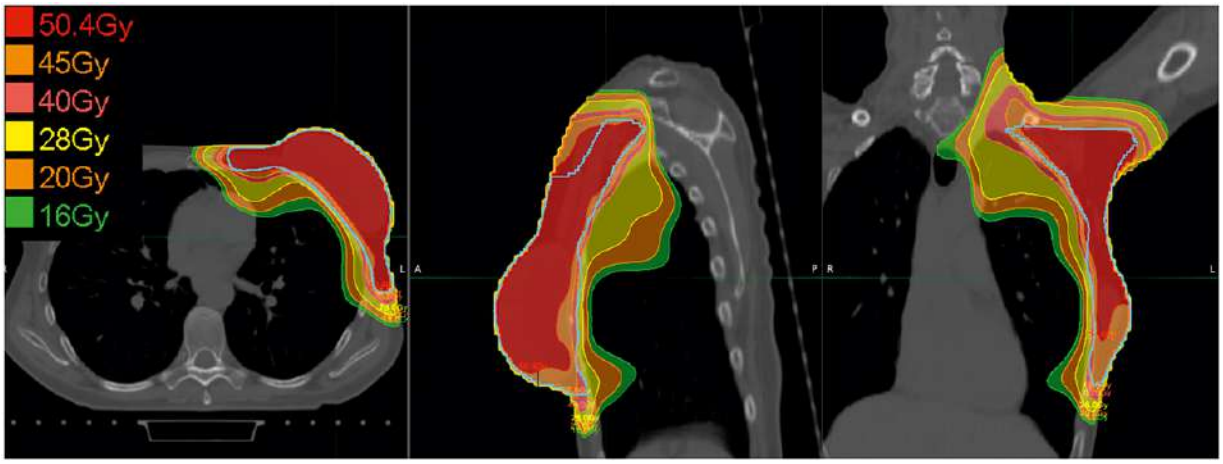

FIGURE 11.8 An example of a scanned beam breast treatment plan with nodal volumes. The treatment uses a single en face proton beam from the anterior oblique direction.

Compared to photon therapy, protons do not have a buildup region since protons are directly ionizing radiation. The increased surface dose can be reduced in the optimization process of a scanned beam plan. In addition, range uncertainties at the distal edge of the treatment volume in the region of the chest wall and lung interface should be accounted in the plan optimization.

Thorax and Abdomen

All thoracic lesions require extensive quality assurance (QA) to determine the optimal method of addressing the tissue heterogeneities in the region of the target volume. Range uncertainties in lung tissue can greatly increase the amount of healthy lung irradiated. In addition, shrinkage of thoracic lesions must be assessed during the course of treatment to reduce the risk of errantly irradiating healthy tissues.

The motion of thoracic and abdominal lesions has long been studied in the context of proton therapy.[2,54-62] Methods to provide robust treatment

plans include density overrides inside the internal target volume, use of 4D CT for optimization, gating, layer rescanning, volumetric rescanning, and tracking.[2,54-62] While there is not yet a consensus regarding the optimal method for treating lesions with large amplitudes of motion (>1-2 cm), it is necessary for any institution to perform a complete analysis of their treatment protocols since the dosimetry is dependent on spot size, scanning speed, dose rate, time for energy (layer) changes, and fractionation scheme.

Generally, as the spot size becomes smaller and the fraction number decreases, the effects of the interplay between the breathing motion and the treatment delivery increase the risk of dosimetric errors. Combinations of the previously mentioned motion management techniques can be deployed to reduce the magnitude of the interplay effects. Briefly, rescanning can effectively increase the number of "fractions" by scanning the same target volume or layer multiple times similar to repeating the same field over multiple fractions.

Sarcomas

Sarcomas can be located in various regions of the body. Some locations, such as the sacral, pelvic, and vertebral locations, can be treated with protons to avoid dose delivery to radiosensitive organs. Typical beam arrangements for sarcomas located along the vertebral column use a single or a couple posterior or posterior oblique beams to provide maximal sparing of organs located anterior to the treated volume.

Children

Pediatric treatments can cover many of the aforementioned treatment sites in the brain and other body sites. More specific and common in the pediatric population is CSI. Proton therapy is commonly used for CSI treatment delivery due to the zero dose exposure in the organs anterior to the vertebral column and whole brain.[63-67] The long-term secondary cancer risk is much lower for protons, especially for soft tissues of the abdomen and thoracic region. Since the in-field doses are similar for both photon and proton pediatric treatments, the secondary risk is assumed to be similar, that is, secondary meningiomas following brain irradiation.

In the past, proton CSI treatments with scattered fields required three levels to reduce the risk of dosimetric hot and cold spots at the match lines. Each level required four to five treatment fields, each with custom apertures and range compensators. The total of 12 to 15 fields and custom hardware can be challenging for treatment planning and delivery workflows. Scanned beams greatly simplified the CSI treatment due to the ability to easily delivery gradient match lines instead of feathering with three levels[26,68-71] (Figure 11.9).

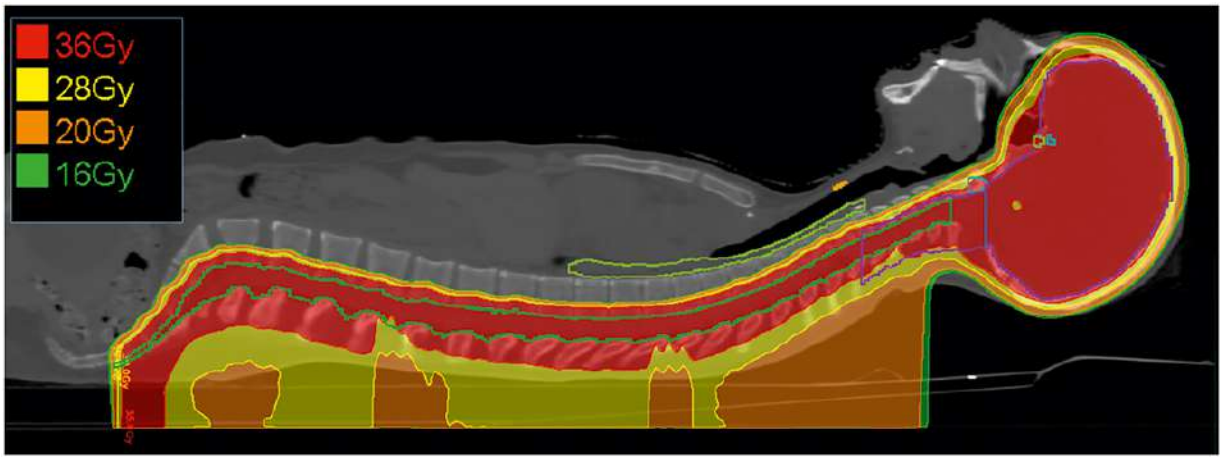

FIGURE 11.9 An example of a scanned beam craniospinal irradiation treatment. The plan uses gradient match lines.

QUALITY ASSURANCE

There are several distinct challenges for QA in a proton therapy clinic.[72] First, there are very few national or international protocols specific for proton therapy QA. The ICRU 78 Report[1] specifies the calibration procedure and recommends other QA measurements. The American Association of Physicists in Medicine (AAPM) has published two proton-specific protocols.[73,74] While the imaging and mechanical systems should operate with similar specifications as photon therapy protocols, the dose delivery systems and dose measurements are very different, including Bragg peak chambers and multilayer ionization chambers to measure Bragg peaks; scintillation screens to measure spot size, shape, and placement; and ionization chambers designed to be less prone to recombination in high-

dose rate PBS deliveries. To supplement the AAPM reports, previously published single-institution studies are often used.[2,75-88]

Second, there are two common TPS dose verification methods. Photon TPS dose verification is typically performed with a secondary dose calculation in an independent software application that is independently commissioned. Monte Carlo dose calculations might be the most similar independent check-in proton therapy, and several institutions have deployed such software for dose checks.[86,89-93] The second method employed by other institutions requires a measurement of every field prior to delivery.[75,81]

Third, the proton therapy user base is much more diverse than the photon radiotherapy clinic. Although there has been a reduction in the number of proton therapy vendors in recent years, there remain multiple proton therapy institutions with different vendors, including multiple beam delivery and verification systems. Each system can have different beam parameters, hardware, and software, in addition to the aforementioned scattered and scanning delivery techniques. Such diversity of systems can make consensus protocols, clinical trials, and credentialing processes difficult to design and requires extensive expertise at each center.

DEVELOPMENTS

Image guidance in proton therapy was the first to deploy 2D image guidance significantly earlier than photon treatment centers but much later to incorporate volumetric imaging solutions. The PSI was one of the first centers to install an in-room CT device. Other centers in Trento (Italy), Dresden (Germany), and the Mayo Clinic (Rochester, MN) have also installed in-room CT devices. The advantage is high-quality imaging and the option for 4D imaging. A diagnostic CT cannot, however, perform imaging at the isocenter and always requires transferring the patient from an imaging position, up to several meters from the isocenter, to the treatment position.

Other institutions have deployed cone beam computed tomography (CBCT) as a volumetric imaging solution. Recent advances in CBCT image quality improvement have allowed for better soft tissue visualization and Hounsfield unit accuracy for dose calculations.[37,35,36,94-100] Some proton vendors have deployed CBCT using the proton gantry as the mechanical

rotation mount, and others have deployed C-arm or couch-mounted 0-ring systems (Figure 11.10).

FIGURE 11.10 Example of a novel cone beam computed tomography design such that the imaging ring is attached to the patient positioner.

Simultaneously with the deployment of in-room volumetric imaging, there are multiple institutions attempting to integrate 3D imaging into adaptive workflows.[38,35,36,94-99] Previously, adaptive proton therapy required separate imaging sessions with external imaging systems such as a CT or magnetic resonance (MR). In-room options can provide more streamlined workflows for adaptations based upon CT information. At this time, there is one in-room MR deployment in Dresden and there have been multiple feasibility studies.[34,101-106]

More than photon therapy, proton therapy greatly benefits from adaptive workflows when the patient has anatomic variations or the target has

motion due to breathing or bowel movements. Even in other target locations, online adaptive proton therapy might reduce the need for some margin expansions. As noted above, adaptive proton therapy can address many of the larger anatomic variations that robust optimization cannot.

While patient setup, anatomic, and dosimetric uncertainties have been addressed by the previous developments, range uncertainties remain in the delivery of proton therapy. There are multiple methods being explored to measure the in vivo range of the proton beam during or after treatment. A simultaneous measurement of the range can be accomplished using implanted devices for lesions located in close proximity to the rectal or vaginal cavity.[107-109] As noted above, protons undergo nuclear interactions to produce prompt gammas and positrons and so methods have been developed to measure these nuclear products of the directly ionizing radiation, both the prompt gammas[110-115] and positrons[116-123] (Figure 11.11). With the in vivo range information, margins might be reduced.

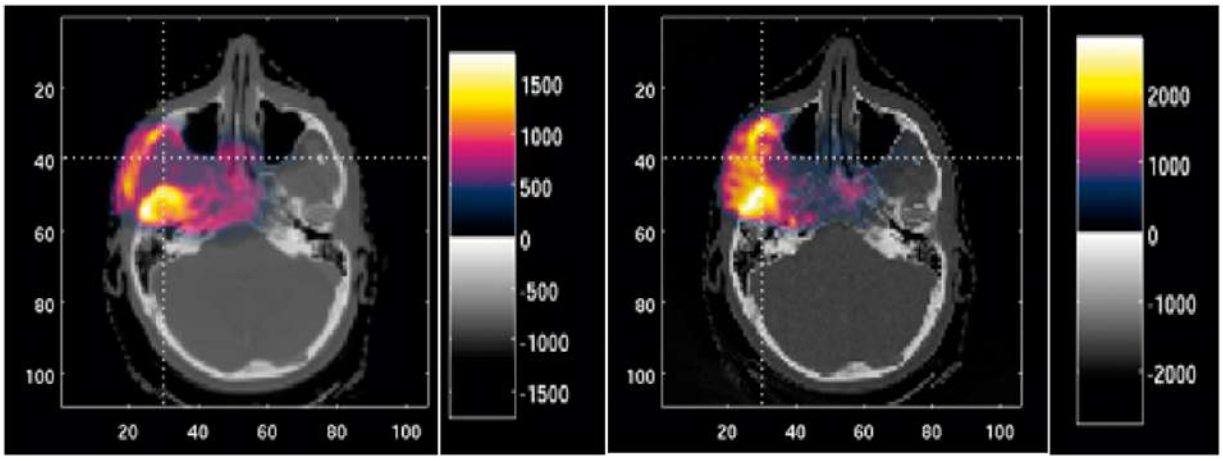

FIGURE 11.11 A sample of a positron emission tomography signal following a proton beam irradiation as simulated in Monte Carlo (left) and measured (right).

CONCLUSION

The physics of proton therapy are generally well understood, and the physical dose distributions greatly reduce the integral dose to healthy tissues as well as organs in close proximity to the targeted volume. There are many topics for further discovery including the integration of 3D

imaging, adaptive workflows, range measurements, and biologic modeling, and more discoveries will increase the therapeutic ratio of proton therapy.

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SECTION II

Techniques, Modalities, and Modifiers in Radiation Oncology

CHAPTER 12

Late Effects, QUANTEC, and HyTEC

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Modern cancer therapy is largely predicated on the safe intensification of radiation, chemotherapy, biologic, and now, immunologic adjuvants. This has resulted in a markedly increased survivorship, which now exceeds 64% overall, and for some malignancies, such as breast and prostate cancer, it is much higher. Malignancies resistant to therapy may demand an aggressive treatment approach that often resides at the limit of, or even exceeds, normal tissue tolerance to some "acceptable" degree. Clearly, the potential to ameliorate or prevent such normal tissue damage, or to manage and rehabilitate affected patients, requires an understanding of tissue tolerance to therapy. Because "late effects" manifest months or years after cessation of treatment, therapeutic decisions intended to obviate such effects can be based only on the probability, not the certainty, that such effects will develop. In making such decisions, the balance between efficacy and potential for toxicity should be considered, as well as the influence of host, disease, and treatment-related risk factors.

Historically, radiation therapy (RT) fields and doses were selected empirically, based largely on physicians' clinical experience and judgment. They understood that these empiric guidelines were imprecise and did not completely reflect the underlying anatomy, physiology, molecular biology, and dose distributions. The introduction of three-dimensional (3D) treatment planning offered the promise of quantitative correlates of doses/volumes with clinical outcomes. This promise was partly delivered. When 3D dosimetric information became widely available, guidelines were needed to help physicians predict the relative safety of proposed treatment plans, although only limited data were available.

In 1991, investigators pooled their clinical experience, judgment, and information regarding partial organ tolerance doses and produced the "Emami paper."[1] As discussed later, this paper clearly stated the uncertainties and limitations in its recommendations, and it is rightly admired for addressing a critical clinical need. Numerous studies have since reported associations between dosimetric parameters and normal tissue outcomes. In 2007, a joint task force of physicists and physicians was formed, with the support of the American Society for Therapeutic Radiology and Oncology and the American Association of Physicists in Medicine (AAPM), to summarize the available data in a format useful to clinicians and to update/ refine the estimates provided by Emami et al.

The resulting QUANTEC reviews[2] (*qu*antitative *a*nalysis of *n*ormal *t*issue *e*ffects in the *c*linic) were published in a special issue of the *International Journal of Radiation Oncology, Biology and Physics* in March 2010. Subsequent similar reviews focused on Hypofraction/High Doses per fraction (HyTEC).[3]

HISTORICAL BACKGROUND

The relationship between dose-volume parameters and outcome has been the focus of numerous investigators for decades. A brief summary of historical landmarks is provided to follow, along with our opinion regarding the key contributions and limitations of these reviews (Figure 12.1; Table 12.1).

TABLE 12.1 HISTORICAL OVERVIEW OF SUMMARIES OF DOSE/VOLUME/OUTCOME INFORMATION

Report	Key Contributions	Key Shortcomings
Rubin et al[4]	Introduced the concept of $TD_{5/5}$ and $TD_{50/5}$	Minimal dose-volume data
Emami et al[1]	Concise summary addressing most clinically meaningful end points in a uniform manner	Dose-volume relationship based on limited data (mostly from 2D treatment planning) and, thus, much expert opinion
QUANTEC[2]	Driven largely by the available 3D dose/volume/outcome data. Systematic review addressing many challenges such as organ delineation and confounding factors such as chemotherapy	Dose/volume/outcome data on meaningful clinical outcomes are *not* available for many organs and issues. For some sites, data from published studies were reviewed, but not amenable to data pooling or modeling of outcomes.
HyTEC[3]	Modern dose/volume/outcome data specific to SBRT and SRS. Some reports were specific to tumor control probability (which was not addressed in the other efforts described here). All reports pooled data for modeling outcomes.	Dose/volume/outcome data on meaningful clinical outcomes are *not* available for many organs and issues.

SBRT, stereotactic body radiotherapy; SRS, stereotactic radiosurgery.

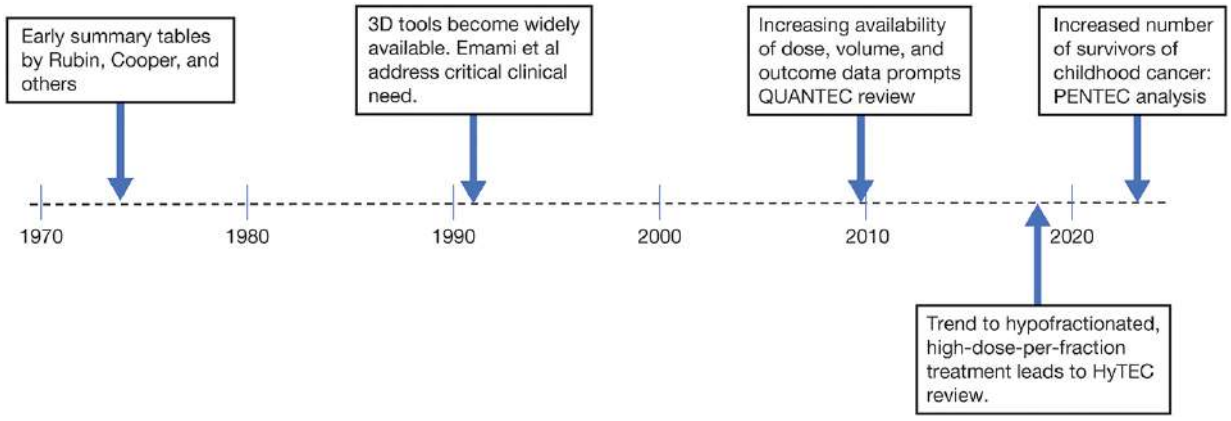


FIGURE 12.1 Key events in the development of dose-volume and normal tissue toxicity relationships in radiation oncology.

INCORPORATION OF 3D DOSE-VOLUME INFORMATION INTO CLINICAL GUIDELINES

The pre-Emami reports[4] were novel in that there were typically no good tools available (to either the authors or clinicians) to accurately quantify the fraction of various organs that were being irradiated. Thus, the dose/volume/outcome information presented consisted largely of estimates based on expert opinion. Similarly, clinicians needed to estimate the partial volumes

of different organs that were being irradiated in their patients in order to apply the provided information.

In the late 1980s and early 1990s, 3D planning systems were providing clinicians with a plethora of information. However, systematic dose/volume/outcome data to guide clinical decisions based on this information were limited. There was an urgent need for clinicians to have some guidance in making clinical dose-volume decisions. The report by Emami et al[1] met this critical need. This report was, and remains, a landmark summary of decades worth of data for a wide variety of organs, supplemented with expert opinion where evidence was lacking.

During the 1990s and 2000s, a large number of studies related dose-volume data to clinical outcomes. The QUANTEC review was an attempt to refine the guidelines based on the available 3D dose/volume/outcome data.

DOSE-VOLUME HISTOGRAMS AND ASSOCIATED FIGURES OF MERIT

Three-dimensional dose-volume data can be difficult for clinicians to readily digest. Visualizing isodose distributions is challenging, and comparing competing distributions is almost impossible. Therefore, dose-volume histograms (DVHs; essentially two-dimensional [2D] representations of the 3D data) were embraced as a rapid way to summarize the dose distribution. Note that DVHs inherently discard information regarding the spatial character of the dose, but it is important to account for and report the variations in fraction size along with the DVH. However, DVHs can also be challenging for clinicians to consider and compare. Therefore, it has become attractive to extract "figures of merit" from the DVH, such as the V_x (the percentage of an organ receiving $\geq x$ Gy). Thus, DVHs and their associated figures of merit are necessary tools to enable clinicians to readily apply 3D information clinically. They are excellent tools but obviously have their shortcomings.

MODEL-BASED ESTIMATES OF OUTCOMES

The Emami et al report systematically used the same DVH-based construct across many organs, for example, the $TD_{5/5}$ and $TD_{50/5}$ for the uniform irradiation of one-third, two-thirds, and the whole volume of an organ. This uniform approach enabled the application of "single unifying models" of dose/volume/outcome across organs. For example, the dose/volume/outcome estimates from Emami et al were used by Burman et al,[5] Kutcher et al,[6] and Lyman et al[7] to generate a set of organ-specific model parameters. Such a uniform approach is attractive to modelers and busy clinicians.

Subsequently, many clinical dose/volume/outcome reports computed parameters for these "unifying models" (eg, Ten Haken et al[8-10]). Other investigators have suggested alternative models that appeared to be better suited to specific organs (vide infra).

The dose/volume/outcome data available for the QUANTEC review were not of a uniform format. Outcomes across organs were correlated with a diverse array of dose-volume metrics (eg, threshold volumes [V_x], threshold doses [D_x], mean doses). Therefore, the QUANTEC review included model-based parameters for just a few organs, and not always in a systematic fashion.

MAJOR DIFFERENCES BETWEEN THE QUANTEC AND EMAMI REVIEWS

Emami et al[1] provided information for 26 organs, judged necessary to support protocols for "three-dimensional treatment planning for high-energy photons (RFP #NCI-CM-36716-21)." Conversely, the QUANTEC review was focused on organs for which the steering committee believed there were meaningful dose/volume/outcome data (Table 12.2).

TABLE 12.2 COMPARISON OF THE CHARACTER/CONTENT OF EMAMI ET AL AND QUANTEC

Characteristics	Emami et al[1]	QUANTEC[2]	HyTEC[3]
Number of organs/tissues reviewed	26	16	7[a]
Data type	Minimal 3D data, Data primarily from 2D era (with 3D exposures inferred)	Mostly 3D data (published in 18-y interval after Emami report)	All 3D data
Format dose-volume limits	Uniform $TD_{5/5}$ and $TD_{50/5}$ for one-third, two-thirds, whole organ	Nonuniform	Nonuniform
End points	Specific, complete	Specific, incomplete	
Expert opinion	Dominant	Much less	None
Impact of chemotherapy	Not explicitly discussed	Addressed individually for each organ	Addressed in each report (but insufficient data for modeling)

[a]Two organs (rectum and bladder) were analyzed specifically for risks after prostate stereotactic body radiotherapy (SBRT).

Emami et al addressed a wide variety of clinical outcomes and thus provided the reader with a set of dose-volume parameters for *essentially* all clinical situations. Conversely, the QUANTEC review was focused on end points where there were dose/volume/outcome data. In this regard, the Emami tables are more complete. For example, consider the QUANTEC summary for the small bowel. A volume restriction is provided for the end point of acute grade greater than or equal to 3 toxicity. No guidance is provided for late small bowel injury, as the authors did not believe that there was meaningful dose/volume/outcome data for late injury. This is a shortcoming of the QUANTEC review, as it is not "complete." When evaluating a proposed 3D treatment plan, one obviously must consider both acute and late injury.

Emami et al presented information in a systematic/uniform manner, facilitating interorgan comparisons and model-based parameter estimates. The QUANTEC review presented dose/volume/outcome data in an organ-specific diverse manner in which they were available in the literature.

DOSE-VOLUME EFFECTS IN HYPOFRACTIONATED HIGH-DOSE-PER-FRACTION TREATMENT

A similar methodology to QUANTEC has been applied to stereotactic body radiotherapy (SBRT) and stereotactic radiosurgery (SRS), in a multidisciplinary effort termed HyTEC, for

High-Dose-per-Fraction, Hypofractionated Treatment Effects in the Clinic,[3,11] addressing hypofractionated treatments versus the predominantly conventionally fractionated regimens in QUANTEC. In addition, whereas QUANTEC focused primarily on normal tissue tolerance, HyTEC addressed tumor control. This collaboration of physicians, physicists, radiobiologists, and biomathematicians was officially organized as the SBRT Working Group (WGSBRT) within the AAPM. The working group received the following charge from AAPM:

> The radiobiology of hypofractionated treatments may differ considerably from that of standard fractionated treatments, in regards to repair, reoxygenation, dose-rate effects, volume effects, fraction size effects, etc. The working group will generate reports, including but not limited to, critically surveying the published data regarding: 1. Tumor response: review of the effect of hypofractionation on local control. 2. Normal tissue response: review of the effect of hypofractionation on normal tissue tolerances. 3. Radiobiology of hypofractionated treatments. 4. Clinical rationales for the diverse prescription schemes in current use (e.g., 20Gy × 3 fractions vs 24Gy × 1 fraction). 5. Standards for reporting outcome, including end points, defining/contouring of target and normal structures, dose definitions.

In this chapter, the HyTEC reviews,[3] published in a special issue of the *International Journal of Radiation Oncology, Biology and Physics* in May 2021, are compared to and synthesized with the QUANTEC studies.

DOSE-VOLUME EFFECTS IN CHILDREN

Pediatric Normal Tissue Effects in the Clinic (PENTEC[12]) is an international multidisciplinary effort to address quantitative dose-volume-outcome relationships for survivors of pediatric cancer. Particular focus was placed on developing tissues that are uniquely sensitive in children; all reviews attempted to account for the impact of biodevelopment[13] on the risks of RT-associated injury.[14] Given the prominent role that chemotherapy plays in the care of children with cancer, the effects of systemic therapies on RT-associated risks were also emphasized.

Because of the often-long latency between RT and the associated late effects in survivors of pediatric cancer, many of the PENTEC reports used decades-old data (eg, from the pre-computed tomography [CT] era). To mitigate this limitation, the physicists involved attempted to estimate the delivered doses (where able) and also semi-objectively scored the quality of the dosimetric data underpinning each of the analyses.[15] This detailed approach was taken by the physicists and modelers in PENTEC—to check the reported doses in the published literature and then modify the doses inputted into their pooled data and associated modeling—is a relatively unique and challenging effort.

Although PENTEC was modeled after QUANTEC, PENTEC was a "more formal" process; *for example*, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses methodology was utilized, and statisticians and epidemiologists played an important role. As with QUANTEC, the PENTEC data were modeled when feasible (which was the case for most of the reports).[16] The full suite of PENTEC papers is expected to be published in early 2024, and several of the early findings from PENTEC are included in this chapter.

MOLECULAR MECHANISMS OF LATE RADIATION DAMAGE

The design of optimal radiation treatment plans and identification of therapeutic strategies to prevent radiation-induced damage would benefit from an understanding of the underlying late effects of ionizing radiation. Both of these issues are further complicated by the variability in sensitivity to radiation observed across disease types and between patients, as well as the current absence of identifiable factors that predict a propensity for radiation-induced toxicity.[17-20]

An early theory for describing the development of acute and late side effects after radiation exposure was based on the target cell hypothesis. This hypothesis is focused on radiation as a direct cause of cell killing in tissues and organs, thus depleting crucial cell populations and resulting in functional deficiency. Radiation is thought to cause irreversible damage to predominantly rapidly proliferating cell populations. These damaged cells in turn lose their ability to replicate and induce a regenerative response. The latent period between radiation exposure and repopulation appears to depend on both tissue turnover time and radiation dose. Both parenchymal cell loss and vascular endothelium damage occur; vascular hyperpermeability and venous exudation follow and have been theorized to contribute to clinically devastating toxicities, such as radiation myelopathy. Although the target cell hypothesis may explain some of the mechanisms by which acute side effects occur, it does not appear to fully explain the development of late side effects. Recent research has shown a complex interaction between multiple cell types, leading to persistent overexpression of reactive oxygen species (ROS), activation of signaling pathways, and production of proinflammatory and profibrotic cytokines.

Although the initial damage done to the DNA, proteins, and membrane lipids of cells by exposure to ionizing radiation is well known, the mechanisms behind the sustained changes in gene expression and signaling pathways that contribute to latent and permanent tissue injury are less clear. This section will focus on the established mechanisms of radiation-induced tissue injury and identify areas in which further efforts are needed to determine the mechanisms driving tissue injury and prognostic markers for the development of radiation injury.

Early Cellular Effects of Radiation

Exposure to ionizing radiation causes direct DNA damage through linear energy transfer as well as indirect damage by radiolytic cleavage of water, yielding hydroxyl radicals capable of abstracting hydrogen from the backbone of DNA to cause double-stranded breaks.[21,22] This damage to genomic DNA causes cell death by apoptosis, mitotic catastrophe, senescence,[23] autophagy, necroptosis, and necrosis.[24,25] Although the ability of hydroxyl radicals to cause DNA damage is significant, the initial increase in hydroxyl radical and other ROS attributable to radiation exposure is negligible compared to the baseline presence of ROS in the cell.[22] Within a few hours of radiation exposure, however, the cell responds by increasing ROS production, creating a cellular environment capable of exacerbating the initial injury by causing oxidative damage to proteins and lipids.[26] This is thought to occur via ROS-mediated activation of mitochondria-dependent and mitochondria-independent metabolic enzymes, including nitric oxide synthases and oxidoreductase enzymes.

Sources of Reactive Oxygen Species

NADPH Oxidases

Nicotinamide adenine dinucleotide phosphate (NADPH) oxidases are a family of broadly distributed oxidoreductase enzymes. Membrane-associated NADPH oxidases are the primary source of ROS in nonphagocytic cells.[27] Under normal conditions, NADPH oxidase–derived superoxide anion is a mediator of maintenance and smooth muscle tone of the vasculature.[28] When these enzymes are induced to begin pathologic overproduction of ROS, however, they can contribute to the development of oxidative stress, resulting in cell damage and disruption of signaling pathways.[29] Nox4, a hydrogen peroxide–producing isoform, is of particular interest, as overproduction of hydrogen peroxide by Nox4 has been shown to be a necessary element of transforming growth factor-β1 (TGF-β1)–mediated cell death.[30]

Mitochondria

Under normal conditions, electrons from the electron transport chain can leak into the mitochondrial matrix and react with oxygen to form a superoxide anion.[31] Following radiation, Leach et al[32] observed that mitochondria in squamous carcinoma cells undergo a permeability transition, causing the release of high levels of ROS into the cytoplasm. They further showed that inhibition of this transition not only attenuates the increase in cytoplasmic free radicals but also prevents radiation-induced activation of mitogen-activated protein kinase, suggesting a causal link between mitochondrial ROS/reactive nitrogen species (RNS) generation and a large group of signal transduction pathways. The role of mitochondrial-generated ROS/RNS in radiation injury is further supported by the radioprotective effect of Mn porphyrin superoxide dismutase (SOD) mimetics, which accumulate preferentially within the mitochondria.[33]

Augmentation of Reactive Oxygen Species From Other Sources

Superoxide anion from any source can react with nitric oxide to form peroxynitrite (ONOO–), which is itself a powerful oxidizing species capable of reacting with other molecules and cellular elements to perpetuate free radical overproduction and cause oxidative damage to the cell.[34]

Free Radicals and the Tissue Response to Radiation

When the increase in ROS production exceeds the antioxidant capacity of the cell, the intracellular environment becomes strongly oxidizing. This change results in altered gene expression as a part of the response to oxidative damage to genomic DNA, modification of redox-sensitive protein activity, and membrane lipid oxidation.[35] All of these insults can affect the structure, function, and signaling capacity of the cell. Of particular importance to the radiation response is the persistent upregulation of transcription factors, including hypoxia-inducible factor-1α (HIF-1α) and nuclear factor κB (NFκB), and cytokines, including TGF-β, TNF-α, bFGF, PDGF, and IL-1, which contributes to the development of radiation-induced tissue injury.[26,36] These molecules all contribute to the vascular changes, inflammation, and cell death observed in response to radiation, but their roles in complex signaling pathways suggest that early changes in the activity of these molecules may also contribute to the disease

process of latent injury. The role of ROS in radiation-induced tissue injury has been confirmed by the finding that SOD overexpression and the use of SOD mimetics can mitigate tissue injury following ionizing radiation exposure.[18,33,37-40] A recent clinical study has shown that targeting ROS-upregulated proinflammatory factors, such as cyclooxygenase-2, interleukin (IL) 1β, tumor necrosis factor (TNF)-α, and TGF-β by synthetic genistein nanoparticles (BIO 300), has a potential to reduce radiation-induced lung toxicity (RILT).[41]

The Role of Inflammation in the Response to Radiation

Although the manifestations of radiation injury can be divided into early and late effects, irradiated tissues show a dynamic population of different inflammatory cell types throughout the "latency" period, suggesting that, on a cellular level, radiation injury is an ongoing disease process.[42] Localization of inflammatory cells is mediated by vascular adhesion markers, and preferentially blocking intercellular adhesion molecule-1 (ICAM-1) does indeed reduce the inflammatory response to radiation in the lungs of C57BL/6 mice.[43,44] The resulting reduction in inflammation was, however, not sufficient to suppress the development of latent pulmonary damage, suggesting that there are other mechanisms at work during this latent period that contribute to disease processes.[43] With the changing inflammatory cell populations come changes in cytokine activity, specifically ILs, TNF-α, TGF-β, monocyte chemoattractant protein-1, and keratinocyte chemoattractant.[42,45,46] Expression of IL-1 messenger RNA (mRNA), together with a two-part upregulation of TGF-β expression, is known to coincide with the development of fibrosis in C57BL/6J mice, suggesting that the inflammatory response does indeed contribute to the development of latent tissue injury.[47] This idea is further supported by the finding that early inhibition of TGF-β reduces radiation-induced pulmonary fibrosis and improves lung function.[48-50] Further studies indicate that administration of exogenous SOD following thoracic radiation reduced the early upregulation of IL-1, TNF-α, and TGF-β and extended postradiation survival.[47] The apparent link between ROS, inflammatory signaling, and latent injury development suggests that early changes in ROS production do affect delayed tissue damage through ongoing perturbations of signaling pathways.

Radiation-Induced Vascular Changes

Exposure to ionizing radiation causes damage to endothelial cells and vascular structural elements, causing increased vascular permeability.[51,52] This vascular dysfunction results in edema as well as decreased perfusion, which can lead to the development of hypoxic regions within the affected tissues.[53] Hypoxia exacerbates the initial injury by increasing the recruitment of inflammatory cells that, in the process of undergoing the respiratory burst, produce ROS and increase tissue hypoxia by consuming the available oxygen.[54] Hypoxia also results in the activation of HIFs. HIF-1α is an ROS-stabilized transcription factor that, under hypoxic conditions, forms a heterodimer with HIF-1β. This heterodimer is translocated to the nucleus, where it binds the hypoxia response element, inducing transcription of genes involved in migration, proliferation, apoptosis, and angiogenesis.[55] This element of the hypoxia response contributes to endothelial cell damage, increasing vascular permeability and, as a result, leakage of fibrin into the extracellular matrix.

Vascular endothelial growth factor (VEGF) is an HIF-mediated growth factor. Under hypoxic conditions, VEGF expression is increased, resulting in aberrant vascular network formation, which leads to irregular perfusion.[56] The resulting cycles of hypoperfusion and reperfusion contribute to oxidative stress, further damaging tissue.[49]

Macrophage accumulation further contributes to the self-perpetuating nature of radiation-induced tissue injury. Accumulation of macrophages is known to occur in areas of low perfusion and inadequate supply of oxygen and is observed in tissues following radiation exposure.[57,58] When activated, these cells produce HIF-1α in order to initiate angiogenesis to correct low perfusion.[58] This response on the part of macrophages increases the level of oxidative stress, continuing the spread of damage through inappropriate continuation of wound healing mechanisms. Inhibition of radiation-induced activation of macrophages has been shown to promote radioprotection of lung tissue.[59,60]

Possible Metabolic Changes

Carbonic anhydrase-9 (CA-9) is commonly used as a hypoxia marker because CA-9 transcription is dependent on HIF-1α. Because carbonic anhydrases act to catalyze the conversion of metabolically produced carbon dioxide to bicarbonate,[61] this increase in CA-9 suggests that cells may also be undergoing a metabolic shift in response to their hypoxic environments. The observed changes in mitochondrial morphology and activity[62] would support altered metabolism in postradiation cells, but further work is necessary to determine the nature of such a change.

Implications

Exposure to ionizing radiation disrupts DNA, causing cell death, but it also causes increased production of ROS in viable cells. The oxidizing environment that results from ROS production exceeding the antioxidant capacity of the cell causes further damage by disrupting cell function and signaling pathways. This disturbance results in changes in vascular integrity, an ongoing inflammatory response, and aberrant angiogenesis. Because the overproduction of ROS is self-perpetuating, these effects are amplified, increasing the area and severity of damage.

Though many of the mechanisms through which ROS production affects the development of late radiation effects remain unclear, it is likely that these early changes initiate disease processes that progress over time to cause the observed late injury. Based on that assumption, the identification of predictive biomarkers of radiation-induced normal tissue injury would individualize radiotherapy and improve treatment outcomes.

SUMMARY BY ORGAN SYSTEM

To provide a consistent summary of the extensive information in the individual organ reviews, the following outline is utilized:

1. Clinical Significance
2. End points
3. Challenges Defining Volumes

4. Dose/Volume/Toxicity Data
5. Factors Affecting Risk
6. Mathematic/Biologic Models
7. Special Situations
8. Recommended Dose-Volume Limits
9. Future Studies
10. Toxicity Scoring Criteria

Note that the brief summaries for each review do not substitute for reading and understanding the original papers and, as necessary, the underlying literature. In addition, the dose-volume limits described in the QUANTEC and HyTEC reviews are intended to supplement, not supplant, clinical judgment.

CENTRAL NERVOUS SYSTEM

Brain

Clinical Significance

The acute and late effects of radiotherapy on the brain are common and represent a significant source of morbidity.[63] In particular, patients with tumor-related neurocognitive dysfunction may exhibit exacerbated deficits after radiotherapy. In addition, the radiation fields used to treat the upper aerodigestive tract (eg, sinuses and pharynx) often include a portion of the brain.

End Points

The acute side effects of RT on the brain include nausea, vomiting, and headache; seizures, visual disturbances, and vertigo are less common.[63] These symptoms are typically transient and generally respond well to medication. The end points for assessing long-term radiation-induced complications are typically radiation necrosis or asymptomatic radiologic changes as seen on serial magnetic resonance imaging (MRI) scans.[63] Other measures have included steroid usage, preservation of performance status, and neurocognitive function.[64-67]

Challenges Defining Volumes

Contouring the entire brain is straightforward, and with appropriate immobilization, there is little intra- or interfraction motion. In contrast, the delineation of subregions (eg, the border between the brainstem and thalamus) and functional segments (eg, the Broca area) of the brain is challenging, and the utility of defining such areas has been difficult to prove.[63] However, recent studies of hippocampal avoidance in patients with brain metastases undergoing whole-brain radiotherapy have shown that minimizing the dose to this structure (contoured with the aid of a high-resolution MRI atlas) can significantly reduce neurocognitive decline.[68,69]

Dose/Volume/Toxicity Data

For fractionated radiotherapy to the brain, the relationship between dose and radiation necrosis for partial brain irradiation is shown in Figure 12.2 for various fractionation schemes.[70-77] Lawrence et al compared different fractionation schemes by calculating the biologically effective dose (BED),[78] with an α/β ratio of 3 Gy.[63] For standard fractionation, a dose-response relationship appears to exist, such that an incidence of side effects of 5% and 10% occurs at a BED of 120 Gy_3 (range, 100-140) and 150 Gy_3 (range, 140-170), respectively (corresponding to 72 Gy [range 60-84] and 90 Gy [range, 84-102] in 2-Gy fractions). For twice-daily fractionation, a steep increase in toxicity is apparent when the BED exceeds 80 Gy. For daily large-fraction sizes (>2.5 Gy), the incidence and severity of toxicity are unpredictable. Lawrence et al[63] caution against overinterpreting this analysis, given the heterogeneity of the data pool (ie, different target volumes, end points, sample sizes, and brain regions).

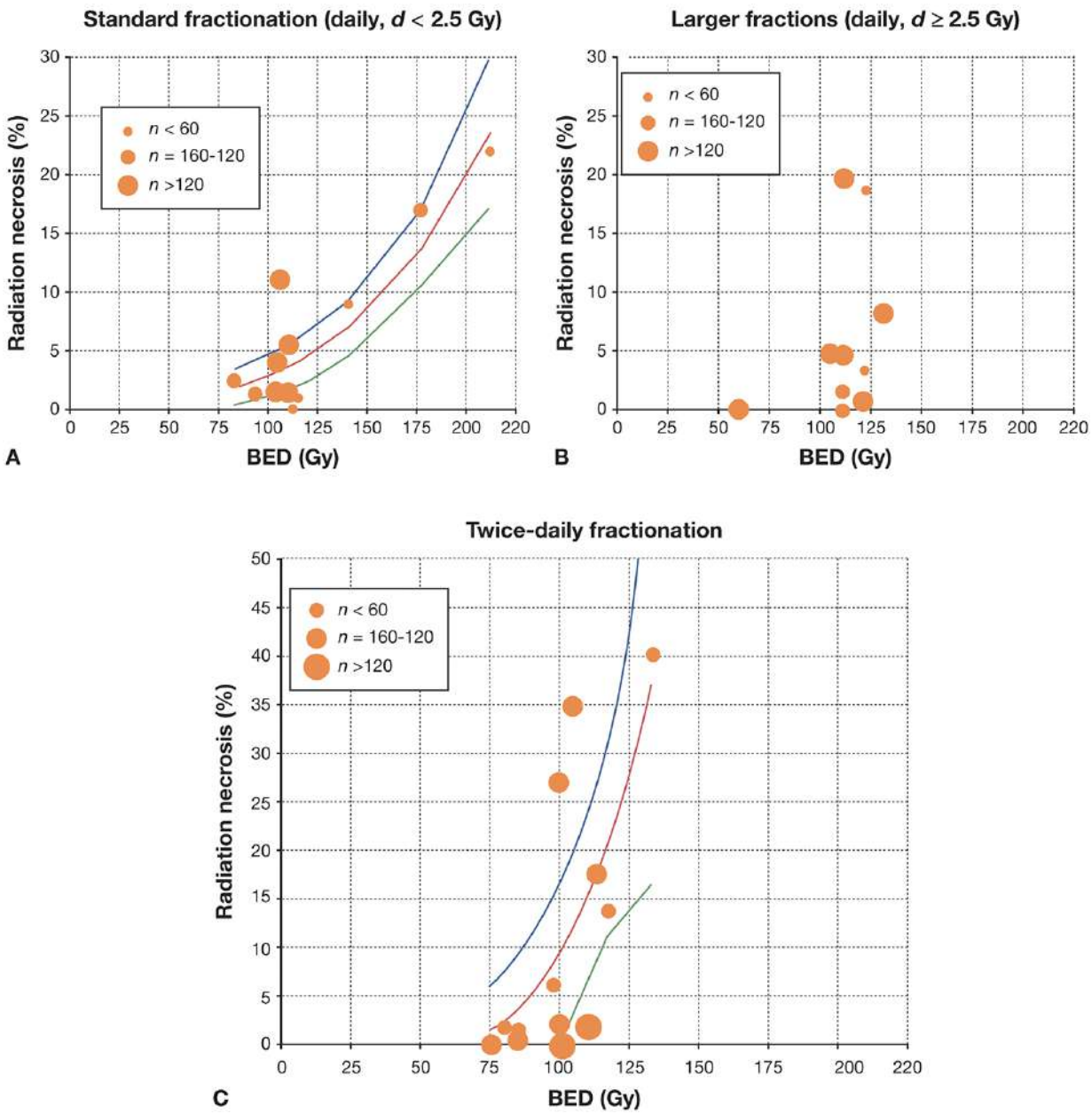


FIGURE 12.2 Incidence of radiation necrosis in brain irradiation from selected studies. Biologically effective dose (BED) calculated from the linear-quadratic model with α/β = 3 Gy; *n* = patient numbers as shown. The solid line represents the least-squares best fit of data to probit model; *dotted lines* represent 95% confidence limits. A. Once-daily fractions <2.5 Gy. B. Once-daily fractions ≥2.5 Gy (data too scattered to allow plotting of "best fit" line). C. Twice-daily radiotherapy. (Reprinted from Lawrence YR, Li XA, el Naqa I, et al. Radiation dose-volume effects in the brain. *Int J Radiat Oncol Biol Phys*. 2010;76[3 suppl]:S20-S27. Copyright © 2010 Elsevier. With permission.)

In children, whole-brain radiotherapy appears associated with neurocognitive decline. With central nervous system prophylaxis for acute lymphoblastic leukemia, the addition of 24-Gy radiation to the whole brain (to a chemotherapy regimen) is associated with a median 13-point intelligence quotient reduction at 5 years after radiotherapy, as well as poorer academic performance and greater psychological distress.[79] Reported toxicities have been lower when 14 to 18 Gy was used.[80-82] In medulloblastoma, the post-RT intelligence quotients were 10 to

15 points higher after a total whole-brain dose of 23.4 versus 36 Gy.[83,84] The PENTEC report[85] provides the following estimates of risks for neurocognitive compromise and necrosis. There is a 5% risk of a subsequent IQ less than 85 when 10%, 20%, 50%, or 100% of the brain is irradiated to 35.7, 29.1, 22.2, or 18.1 Gy, respectively (all at 2 Gy/fraction and without methotrexate). Methotrexate (MTX) increased the risk for an IQ less than 85, similar to a generalized uniform brain dose of 5.9 Gy. The model for predicting expected IQ also includes the effect of dose, age, and MTX. Each of these factors has an independent, but probably cumulative effect on IQ. The necrosis model estimates a 5% risk of necrosis for children after 58.9 Gy or 59.9 Gy (2 Gy/fraction) to any part of the brain if delivered as primary RT or reirradiation, respectively.

In adults, the neurocognitive effects of whole-brain irradiation are now established. The Radiation Therapy Oncology Group (RTOG) 0933 phase II study of hippocampal sparing (which required that 100% dose and maximum dose not exceed 10 and 17 Gy, respectively) analyzed 113 adult patients with brain metastases. With hippocampal sparing, memory preservation at 4 and 6 months was significantly better than that in historical controls (ie, whole-brain radiation therapy [WBRT] without hippocampal sparing). NRG Oncology CC001,[68] a phase III study of hippocampal-sparing WBRT + memantine versus standard WBRT + memantine, randomized 518 adult patients with brain metastases to the two study arms. The risk of cognitive failure was significantly lower after in the hippocampal-sparing arm (adjusted hazard ratio, 0.74; 95% CI, 0.58-0.95; $P = .02$), with this difference attributable to less deterioration in executive function at 4 months (23.3% vs 40.4%; $P = .01$) and learning and memory at 6 months (11.5% vs 24.7% [$P = .049$] and 16.4% vs 33.3% [$P = .02$], respectively). No significant difference in overall survival (OS), intracranial progression free survival (PFS), or toxicity was observed between the two arms. At 6 months, using all data, patients who received hippocampal-sparing WBRT reported less fatigue ($P = .04$), less difficulty with remembering things ($P = .01$), and less difficulty with speaking ($P = .049$) and using imputed data, less interference of neurologic symptoms in daily activities ($P = .008$), and fewer cognitive symptoms ($P = .01$) than those who received standard WBRT (plus memantine in both arms).

Limiting the volume of normal brain irradiated by treating lesions via SRS versus WBRT appears also to reduce neurocognitive deterioration. A trial of patients with one to three intact brain metastases randomized 218 patients to SRS versus SRS + WBRT. Less cognitive deterioration was observed at 3 months after SRS alone (40/63 patients [63.5%]) than when with SRS + WBRT (44/48 patients [91.7%]; difference, −28.2%; 90% CI, −41.9% to −14.4%; $P < .001$). Quality of life was higher at 3 months with SRS alone, including overall quality of life (mean change from baseline, −0.1 vs −12.0 points; mean difference, 11.9; 95% CI, 4.8-19.0 points; $P = .001$). Although time to intracranial failure was significantly shorter for SRS alone (hazard ratio, 3.6; 95% CI, 2.2-5.9; $P < .001$), there was no significant difference in functional independence at 3 months and median overall survival between the treatment groups.[86] Similarly, NCCTG N107C/CEC·3 randomized 194 patients with resected brain metastases to SRS versus WBRT.[87] Cognitive-deterioration-free survival was longer in patients assigned to SRS (median 3.7 months [95% CI 3.45-5.06], 93 events) than in patients receiving WBRT (median 3.0 months [2.86-3.25], 93 events; hazard ratio [HR] 0.47 [95% CI 0.35-0.63]; $P < .0001$), and cognitive deterioration at 6 months was less frequent in patients

who received SRS (28 [52%] of 54 evaluable patients assigned to SRS vs 41 [85%] of 48 evaluable patients assigned to WBRT). As in the treatment of intact brain metastases, there was no significant difference in overall survival between the arms receiving SRS versus WBRT (12.2 months vs 11.6 months, HR 1.07 [95% CI 0.76-1.50]), despite poorer local control with SRS alone.

In SRS of brain lesions, normal tissue toxicity appears to be a function of dose, volume, and location in the brain. The RTOG conducted a dose escalation study (RTOG 9005) of radiosurgery to recurrent brain metastases and primary tumors in patients who previously received whole or partial brain irradiation.[88] The goal of this study was to determine the maximal tolerated dose as a function of the maximum diameter of the lesion. Unacceptable toxicity was defined as acute irreversible severe neurologic symptoms requiring inpatient or outpatient medications, any life-threatening neurologic toxicity, or death. This study found a maximum tolerated prescription dose to the tumor margin of greater than or equal to 24, 18, and 15 Gy for tumors with a maximal diameter of less than or equal to 2.0, 2.1 to 3.0, and 3.1 to 4.0 cm, respectively. The rates of acute and late unacceptable toxicities in patients treated at these doses were 0% and 10%, 0% and 14%, and 0% and 20%, respectively. The dose limits appear to be validated by the results of the RTOG 9508, a randomized study of SRS + WBRT versus WBRT alone in 333 patients with brain metastases.[64] Using the dose constraints developed in RTOG 9005, this study found a 3% and 6% rate of grade 3 and 4 acute and late toxicities, respectively, in the group of 167 patients receiving radiosurgery.

The results of dose-volume studies of the development of "radionecrosis" following single-fraction radiosurgery are shown in Table 12.3.[89-98] Although a common element in many of these studies is the volume receiving a dose of 10 or 12 Gy or more (V_{10} or V_{12}, respectively), there is a broad variation in the crude rate of radionecrosis as a function of volume irradiated. This is likely due to differences in the definition of radionecrosis, the location irradiated, the proximity to and sparing of critical structures, and the length and intensity of clinical follow-up.

TABLE 12.3 SELECTED STUDIES OF RADIONECROSIS IN PATIENTS RECEIVING BRAIN STEREOTACTIC RADIOSURGERY

Reference	Diagnosis	*n*	Mean D_{min}, Gy (Range)	Overall Incidence of RN	Subgroup	Incidence of RN in Subgroup	Primary Predictor of Toxicity	Other Risk Factors
Lax and Karlsson[94]	AVM	823	?	5%			Average dose in 20 cm^3	
Voges et al[99]	Mixed	133	15.0 (7.0-25.0)	12.8%	V_{10} < 10 mL V_{10} > 10 mL	0% 23.7%	V_{10}	Location
Flickinger et al[91]	AVM	307	20.9 (12-30)	10.7%			V_{12}	Location

Reference	Diagnosis	*n*	Mean D_{min}, Gy (Range)	Overall Incidence of RN	Subgroup	Incidence of RN in Subgroup	Primary Predictor of Toxicity	Other Risk Factors
Miyawaki et al[95]	AVM	73	16 (0-22)	14%	Tx volume: <1 mL 1-3.9 mL 4-13.9 mL >14 mL	0% 15% 14% 27%	Tx volume	Dose, prior brain insult
Chin et al[90]	Mixed	243	20 (10-30)	7%			V_{10}	Repeated radiosurgery, glioma
Nakamura et al[96]	Mixed	749	18 (16-19)[a]	?	Rx volume: 0.05-0.66 mL 0.67-3 mL 3.1-8.6 mL 8.7-95.1 mL	0% 3% 7% 9%	Rx volume	
Barker et al[89]	AVM	1,250	10.5 (4-65)	4.1%			Dose and volume combined	Age, location
Friedman et al[92]	AVM	269	?	4.7%			V_{12}	
Varlotto et al[97]	Brain metastases	137	16 (12-25)	11.4%	Tx volume: <2 mL >2 mL	3.7% 16%	Volume	
Korytko et al[93]	Tumor	129	17.3 (11-25)	30%	V_{12}: 0-5 mL 5-10 mL 10-15 mL >15 mL	23% 20% 54% 57%	V_{12}	Location, previous WBRT, male

?, not specified in study; AVM, arteriovenous malformation; RN, radionecrosis; Rx, prescription; Tx, treatment; V_{10}, volume receiving 10 Gy; $_{V12}$, volume receiving 12 Gy; WBRT, whole-brain radiotherapy.

[a]Range refers to 25th to 75th quartile.

Adapted from Lawrence YR, Li XA, el Naqa I, et al. Radiation dose-volume effects in the brain. *Int J Radiat Oncol Biol Phys*. 2010;76(3 suppl):S20-S27. Copyright © 2010 Elsevier. With permission.

For single-fraction SRS to brain metastases, the HyTEC analysis[100] showed that tissue volumes (*including* target volumes) receiving V_{12} of 5 cm^3, 10 cm^3, or greater than 15 cm^3 were associated with risks of symptomatic radionecrosis of approximately 10%, 15%, and 20%, respectively. SRS in the treatment of AVM was associated with modestly lower rates of symptomatic radionecrosis for equivalent V_{12}. In hypofractionated SRS of brain metastases, brain plus target volume V_{20} (three fractions) or V_{24} (five fractions) less than 20 cm^3 was

associated with less than 10% risk of any necrosis or edema and less than 4% risk of radionecrosis requiring resection.

These results suggest that the rate of complications increases rapidly as the V_{12} increases beyond 5 to 10 cm^3. Note, however, that V_{12} will far exceed these limits for lesions 2 cm or greater in mean diameter when the RTOG guidelines are utilized. For example, assume that spherical lesions 1, 2, 3, and 4 cm in diameter are treated under the RTOG guidelines with single-fraction radiosurgery with the plans yielding V_{12}'s of 6, 5, 4, and 3 times the lesion volume, respectively. Then, the calculated V_{12}'s are 3, 21, 57, and 101 cm^3, respectively. So, when two (or more) lesions are each treated with SRS, it might be reasonable to apply these dose/volume data independently to each lesion, whereas if the lesions are close together, it is likely more appropriate to consider the lesions in concert. With the trend toward simultaneously treating an increasingly large number (>4) of brain metastases, it has been suggested that the aggregate volume of the brain receiving 12 Gy should also be considered,[101] though the optimal predictor of adverse radiation effects in this setting is unclear.[100,102]

The location of the lesion is important as the severity of expressed damage is greater in the more eloquent parts of the brain. For example, for a V_{12} of 10 cm^3, Flickinger et al[91] found a less than 5% symptomatic postradiosurgery injury for arteriovenous malformations (AVMs) in the frontal, temporal, and parietal lobes versus greater than 20% for AVMs in the brainstem, thalamus, and basal ganglia.

Factors Affecting Risk

Younger age is associated with a higher risk of neurocognitive decline in children undergoing cranial irradiation.[103,104] Other risk factors include female gender, neurofibromatosis-1 (NF1) mutation, extent of surgical resection, hydrocephalus, concomitant chemotherapy (especially methotrexate), location, and volume of brain irradiated.[105] No evidence has shown that children are at particular risk of radiation necrosis,[106,107] however.

Mathematic/Biologic Models

Although the linear-quadratic model appears useful in comparing dose/fraction for conventionally fractioned radiotherapy schemes, its utility at high doses per fraction (≥8 Gy) is controversial. In general, quantitative dose/volume/clinical toxicity relationships have not been established for neurocognitive function in partial brain irradiation. The apparent increased risk of radionecrosis in twice-daily partial brain irradiation suggests that the time constant for repair of radiation-induced damage may be longer than the typical interfraction interval, but this has not been modeled for this specific system.

Special Situations

Reirradiation of the whole brain is frequently performed in the setting of recurrent, multiple brain metastases. A meta-analysis of whole-brain reirradiation (interval between courses, 3-55 months) found no cases of necrosis when the total radiation dose was less than 100 Gy (normalized to 2 Gy/fraction with an α/β ratio = 2 Gy).[108] In primary central nervous system lymphoma, whole-brain radiotherapy has been associated with an atypically high risk of cognitive decline, especially in those older than 60 years.[109,110] The heightened sensitivity of

this population to irradiation might be explained by the tumor's highly diffuse, angiocentric growth pattern and that most patients receive high-dose methotrexate, a potent neurotoxin. As a result, up-front full-dose RT is now often avoided in older patients with this disease. A lower radiation dose of 23.4 Gy delivered in 1.8-Gy daily fractions appears to be associated with minimal cognitive toxicity, even in older patients.[111]

Recommended Dose-Volume Limit[63]

For partial brain irradiation at a conventional dose per fraction, there is a predicted 5% and 10% risk of symptomatic radiation necrosis at a BED of 120 Gy_3 (range, 100-140) and 150 Gy_3 (range, 140-170), respectively, which corresponds to 72 Gy (range 60-84 Gy) and 90 Gy (range 84-102 Gy) for 2-Gy daily fractions. This is a less conservative estimate than the 5% risk of radionecrosis for one-third of the brain irradiated to 60 Gy in the Emami paper.[1] The authors stress that for most cancers, there is no clinical indication for partial brain dose above 60 Gy and that, in some scenarios, an incidence of 1% to 5% radiation necrosis at 5 years would be unacceptably high. The brain appears especially sensitive to fraction sizes greater than 2 Gy and, surprisingly, twice-daily irradiation.

For radiosurgery, the available data suggest that it is prudent to minimize the volume of normal brain receiving greater than 12 Gy in a single fraction and to consider both target diameter and anatomic location when prescribing dose. However, the QUANTEC authors admit that "the substantial variation between the reported treatment parameters and outcomes from different centers has prevented [more] precise toxicity risk predictions."

The HyTEC authors endorse the limits for single-fraction SRS established in RTOG 9005 but highlight the potential for hypofractionated treatment (eg, 27 Gy in three fractions vs 18 Gy in a single fraction for lesions 2-3 cm in maximum dimension) to improve local control without increasing toxicity.[112]

Future Studies

Key questions that would benefit from systematic study include the following:

1. What is the dose/volume/location/clinical toxicity relationship for brain metastases and other common lesions treated with single-fraction versus multifraction SRS?
2. What is the rate of local and distant failure for the aforementioned sets of patients as a function of the prescribed dose?
3. How does the gross tumor volume (GTV) to planning target volume (PTV) expansion influence the incidence of normal tissue toxicity and failure rates in SRS for brain metastases and in conventionally fractionated conformal radiotherapy for primary brain tumors (particularly GBM)?
4. How do systemic treatments, particularly immunotherapy, affect the incidence of normal tissue toxicity?
5. What is the time interval for repair of radiation-induced damage in the brain? This would be most informative to help guide retreatment.
6. Further clarity is needed in determining if dose/volume metrics should optimally include or excluding the target volume.

Toxicity Scoring Criteria

Studies of brain radiotherapy should report detailed dosimetric and outcome data, including neurocognitive and neurologic dysfunction (eg, per the Common Terminology Criteria for Adverse Events, version 4.0 [CTCAE v. 4.088]), patient-reported quality of life, the prescription dose, dose/fraction, target volume, V_{12}, anatomic location treated, and clinical outcome data (eg, adverse events, patterns of failure).

Optic Apparatus

Clinical Significance

The optic nerves and chiasm frequently receive a substantial dose during therapeutic irradiation of the brain, base of the skull, and head and neck targets, and the optic apparatus is frequently the dose-limiting structure in these cases. Although rare, damage to the optic apparatus can produce devastating and, at present, irreversible visual deficits.[113]

End Points

The primary end point for radiation-induced optic neuropathy (RION) is visual impairment, defined by visual acuity and the size/extent of visual fields.[114] Of course, damage to the lens (development of cataracts), retina (retinitis), lacrimal apparatus, and trigeminal nerve (dry eye syndrome) can also produce impaired vision.[115] Although toxicity may be objectively scored using CTCAE version 4[116] and late effects of normal tissues and subjective, objective, medical management, and analytical (LENT-SOMA) evaluation of injury criteria,[117,118] it is important to obtain a comprehensive ophthalmologic examination of patients with suspected RION.

Challenges Defining Volumes

The optic nerve originates roughly at the posterior center of the globe and is bracketed by the rectus muscles as it tracks posteriorly through the orbit to pass through the optic notch, just medially to the anterior clinoid process. The optic nerves join and decussate to form the optic chiasm, an X-shaped structure that sits just superiorly to the sella turcica with the center immediately anterior to the pituitary stalk.[119] The optic nerves and chiasm are thin (<5 mm diameter), and visualization is best performed using thin-cut (≤3 mm) T1- or T2-weighted MRI. Contouring the optic nerves/chiasm is challenging, and it is important to ensure that these structures are drawn in continuity (ie, there is no gap in the contours). Appropriate contouring of these structures is facilitated by visualizing this region in multiple planes and using fused imaging modalities (eg, utilizing the magnetic resonance images in the axial and coronal planes to track the optic nerves/chiasm and sagittal CT views to see the sella turcica).

Dose/Volume/Toxicity Data

The data for the incidence of RION with conventional fractionation for selected studies[120-127] are summarized in Figure 12.3. The risk of RION appears to rise steeply past 60 Gy. None of the patients in the study by Parsons et al[125] with a maximum point dose (D_{max}) to the optic nerves/chiasm less than 59 Gy developed RION. In the study by Martel et al,[124] the average maximum chiasm and nerve dose was 53.7 Gy (range 28-70 Gy) and 56.8 Gy (range 0-80.5

Gy) for patients without RION. The optic nerves had received a D_{max} of 64 Gy, with 25% of the volume receiving greater than 60 Gy for patients with moderate to severe complications. Jiang et al[122] reported no incidence of ipsilateral RION for a dose less than 56 Gy and a less than 5% incidence at 10 years for a dose less than 60 Gy at approximately 2.5 Gy/fraction.

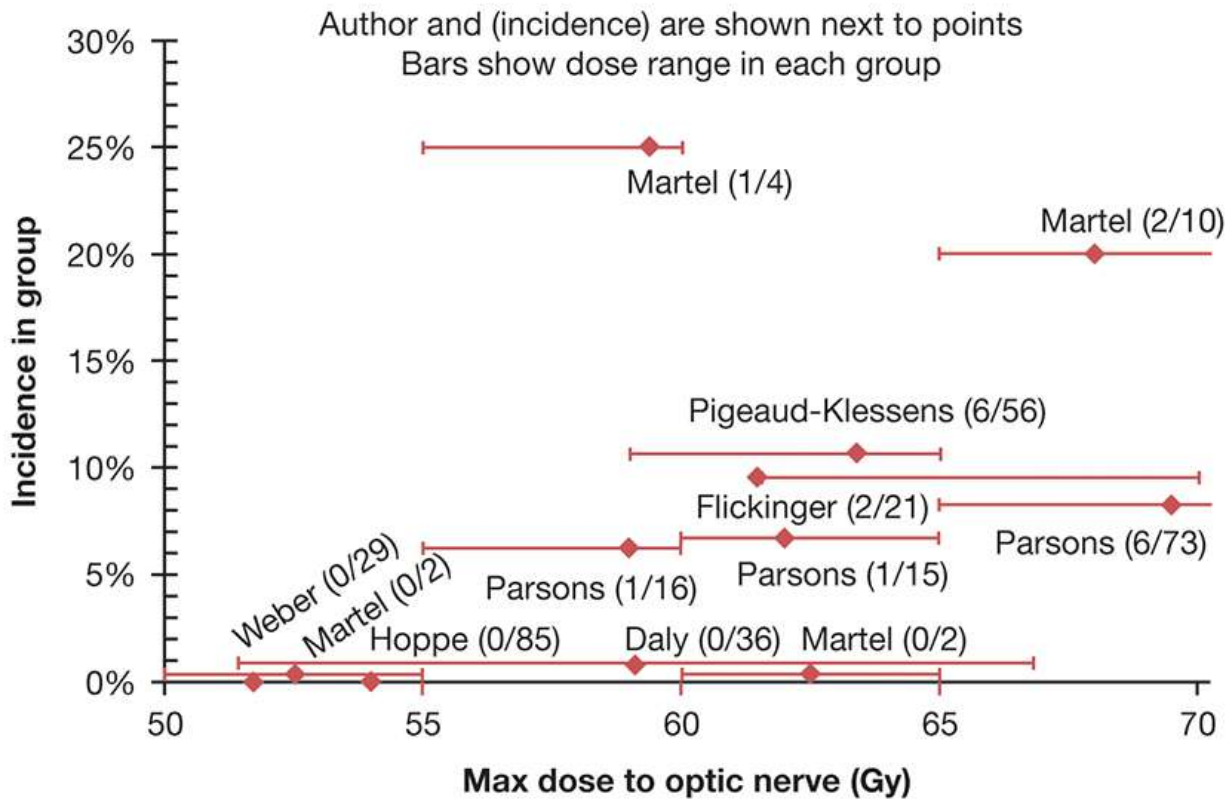


FIGURE 12.3 Incidence of radiation-induced optic neuropathy (RION) in selected studies.[120-127] Points offset from 0% to 1% were shifted to clearly show range bars. The single patients in the studies by Parsons et al[125] and Martel et al[124] with events in the 55 to 60 Gy range were treated to 59 Gy and 59.5 Gy, respectively. (Reprinted from Mayo C, Martel MK, Marks LB, Flickinger J, Nam J, Kirkpatrick J. Radiation dose-volume effects of optic nerves and chiasm. *Int J Radiat Oncol Biol Phys*. 2010;76[3 suppl]:S28-S35. Copyright © 2010 Elsevier. With permission.)

The risk of RION appears to be related to the fraction size. Parsons et al[125] reported 15-year actuarial rates of RION for total doses of 60 to less than 70 Gy of 50% versus 11% at greater than or equal to 1.9 versus less than 1.9 Gy dose/fraction, respectively. No patients treated twice daily with 1.2 Gy/fraction developed RION. At total doses of 70 to 83 Gy, the incidence was 33% versus 11% for greater than or equal to 1.9 versus less than 1.9 Gy/fraction and 12% for 1.2 Gy twice-daily fractions. Bhandare et al[128] noted reductions in RION rates for twice- versus once-daily treatment.

Results from proton treatments appear consistent with those utilizing photons.[127,129-131] Note that the proton doses are reported as cobalt gray equivalent (CGE), reflecting their greater biologic effect, and that photons were often used in combination with protons. Most proton series have reported a very low incidence of RION, and in the few cases of reported RION, a

threshold dose in the range of 55 to 60 CGE has been observed, consistent with the photon experience. As with photons, many patients exceeding this threshold did not develop RION. Wenkel et al, [131] Noel et al,[130] Weber et al,[127], and Nishimura et al[129] used a D_{max} constraint to the optic structures of 54, 55, 56, and 60 CGE, respectively.

Because of the small size of the optic nerves/chiasm and steep dose gradients in radiosurgery, most studies of RION involving SRS use the D_{max} to the optic nerves/chiasm as the critical dose metric.[113] As shown in Table 12.2, single-fraction SRS studies describe a range of threshold D_{max} for RION. In analyzing their early experience with radiosurgery, Tishler et al[132] reported RION at D_{max} as low as 9.7 Gy and recommended 8 Gy as the dose limit for the optic nerves/chiasm in SRS. Stafford et al[133] found RION in 4 of 215 patients receiving a median D_{max} of 10 Gy. The D_{max} in the patients ranged from 0.4 to 16 Gy, and three of the four had received previous external-beam radiotherapy to this area. They estimated a 1.7%, 1.8%, 0%, and 6.9% incidence of RION for D_{max} of less than 8, 8 to 10, 10 to 12, and greater than 12 Gy, respectively.

Pollock et al[134] observed no cases of RION in 62 patients with nonfunctioning pituitary adenomas receiving a median D_{max} of 9.5 ± 1.7 Gy to the optic apparatus during single-fraction SRS, using a 12-Gy D_{max} as the dose constraint for the optic apparatus. From a study of 50 patients with benign base of the skull tumors treated with single-fraction SRS and a median follow-up of 40 months, Leber et al[135] estimated a 0%, 27%, and 78% risk of RION for D_{max} of less than 10, 10 to less than 15, and greater than or equal to 15 Gy, respectively. No data for dose-volume and RION were available for hypofractionated stereotactic radiotherapy (HFSRT) (4-8 Gy/fraction).[113]

In the HyTEC study,[136] 34 studies (1578 patients) were included in the analysis of RION at a high dose/fraction. The authors concluded that the risk of RION was low (<1%) when less than 12 Gy in one fraction, 20 Gy in three fractions, and 25 Gy in five fractions were delivered to optic pathways that were not previously irradiated. Surprisingly, prior resection (76% of patients) was not associated with an increased risk of RION ($P = -0.60$).

Few reports describe the risks of late ocular toxicities after RT for childhood cancers despite their effect on quality of life. The PENTEC group analyzed the available data, and the model for the development of retinopathy suggests a 5% and 50% risk of toxicity at 42 and 62 Gy, respectively.[137] The model for the development of optic neuropathy suggests a 5% and 50% risk of toxicity at 57 and 64 Gy, respectively. More extensive data were available to evaluate the risk of cataract, separated into self-reported versus ophthalmologist-reported versus ophthalmologist-diagnosed cataract. The models suggest a 5% and 50% risk of self-reported cataract at 12 and greater than 40 Gy, respectively, and a 50% risk of ophthalmologist- diagnosed cataract at 9 Gy (>5% long-term risk at 0 Gy in patients treated with chemotherapy only).

Factors Affecting Risk

There appears to be an increased risk of RION with increasing age.[125] Parsons et al[125] reported that none of the 38 patients in the 20- to 50-year-old range developed RION, even though the reported optic nerve doses were greater than 60 Gy for 58% and greater than 70 Gy for 26%.

In contrast, for patients with doses greater than 60 Gy, the incidence was 26% and 56% for the 50- to 70- versus greater than 70-year-old age groups. RION in children is poorly characterized, but the treatment of the developing optic apparatus should be approached cautiously. Reports on the effect of other factors such as adjuvant chemotherapy, diabetes, and hypertension have been inconsistent.

Minimal data are available on the reirradiation of the optic apparatus and the effect of the interval between courses on RION. Flickinger et al[138] found that 1 of 10 patients undergoing reirradiation of the optic apparatus developed RION—the affected received an initial 40 Gy and, after a 7.5-year interval, an additional 46 Gy, both at 2 Gy/fraction. The HyTEC analysis suggested that the risk of RION appeared 10-fold higher in the setting of previous irradiation of the optic pathways.[136]

Mathematic/Biologic Models

The original Lyman-Kutcher-Burman normal tissue complication probability (NTCP) volumetric modeling[5] estimated TD_{50} = 65 Gy, n = 0.25, and m = 0.14. The dose-response data from Jiang et al[122] (1.5-2.2 Gy/fraction) suggest $TD_{50} \approx$ 72 to 75 Gy. Martel et al[124] and Brizel et al[139] estimated TD_{50} at 72 and 70 Gy, respectively. Extrapolation of the Parsons dose-response data[125] suggests that TD_{50} exceeds 70 Gy.

Special Situations

There is a suggestion that RION may occur at lower doses in patients with pituitary tumors, as complications at doses as low as 46 Gy at 1.8 Gy/fraction have been reported.[123,140,141] Mackley et al[123] and van den Bergh et al[141] constrained the optic structure D_{max} to 46 and 45 Gy, respectively. The RION latency also appeared shorter in patients with pituitary tumors. The average latency was 10.5 and 31 months (range 5-168 months) in patients with pituitary targets and nonpituitary targets, respectively.[123,140] The apparent increased sensitivity in these patients could be related to tumor-associated compression and/or postsurgical trauma of these nerves.

Recommended Dose-Volume Limits

The estimate by Emami et al[1] of a 5% risk of blindness within 5 years of treatment for a dose of 50 Gy appears *inaccurate*. The QUANTEC review[113] suggests that the incidence of RION was unusual (<2%) for D_{max} less than 55 Gy, particularly for fraction sizes less than 2 Gy. The risk increases (3%-7%) in the region of 55 to 60 Gy and becomes more substantial (>7%-20%) for doses greater than 60 Gy when a dose per fraction of 1.8 to 2.0 Gy is used. *The patients with RION treated in the 55- to 60-Gy range were typically treated to doses in the very high end of that range (ie, 59 Gy)*. For particles, most investigators found that the incidence of RION was low for a D_{max} less than 54 CGE. One exception to this range was for pituitary tumors, in which investigators used a constraint of D_{max} less than 46 to 48 Gy for 1.8 Gy/fraction.

The aforementioned studies suggest that the incidence of RION in single-fraction radiosurgery is rare for D_{max} less than 10 Gy, increases in the range of 10 to 12 Gy D_{max}, and

begins to rise steeply when D_{max} exceeds 12 Gy. The HyTEC study recommends limiting the maximum point dose to the optic apparatus to less than 10 Gy for single-fraction radiosurgery, 20 Gy for three-fraction radiosurgery, and 25 Gy for five fractions (in patients without prior RT).[136] It is also important to recognize that the low risk of toxicity can only be consistently realized when the radiosurgery practice employs high precision, high accuracy techniques, supported by excellent quality control, appropriate equipment, and well-trained, experienced staff.[142]

Future Studies

In addition to reporting detailed dose-volume data for patients with and without RION receiving radiation to the optic apparatus, investigators must consistently, completely, and accurately contour the optic apparatus, ensuring continuity of the optic nerves and chiasm.

Toxicity Scoring Criteria

Visual deficits should be scored using the CTCAE v. 4.0.[48]

Brainstem

Clinical Significance

As with the optic apparatus, irradiation of the brain, base of the skull, and neck can deliver a significant dose to the brainstem, which is frequently the dose-limiting structure.

End Points

Radiation-induced damage to the brainstem may be manifest as specific cranial neuropathies; focal motor, sensory, or balance deficits; or mild to life-threatening global dysfunction. This is reflected in the CTCAE,[116] which scores brainstem-related toxicity on the basis of symptoms. The study of radiation-induced brainstem injury is challenging because (a) the reported incidence of injury is low, (b) survival time is short for many patients, (c) formal grading of brainstem effects is subjective and is often characterized categorically (ie, “yes-no”) for cranial neuropathy, and (d) for patients with intracranial tumors, it is often difficult to distinguish between side effects and disease progression.[143]

Challenges Defining Volumes

Contouring the brainstem on axial MRI is usually straightforward, although it requires special attention to the superior extent and interfaces at the cerebral and cerebellar peduncles where the borders are indistinct. Coronal and sagittal views, in addition to axial images, are frequently helpful in visualizing the brainstem and its interfaces. The adult brainstem volume is on the order of 35 ± 8 mL.[144]

Dose/Volume/Toxicity Data

Studies of potential radiation-induced brainstem toxicity in the conventionally fractionated partial brain, base-of-skull, or neck irradiation variably report crude radiographic and functional toxicities over typically short follow-up periods.[120,127,129-131,145-154] Reported toxicities

attributable to radiation of the brainstem and dose constraints are presented in Table 12.4. Uy et al[153] reported brainstem necrosis in 1 of 40 adult patients with meningioma treated with intensity-modulated radiation therapy (IMRT). For this patient, the D_{max} was 55.6 Gy, and the absolute volume of the brainstem that exceeded 54 Gy was 4.7 mL. Jian et al[149] noted a grade 1 neurologic deficit in 3 of 48 patients with nasopharyngeal cancer treated with 1.2 Gy twice-daily photons to 74.4 Gy and concomitant chemotherapy.

TABLE 12.4 SELECTED STUDIES OF RADIATION-INDUCED BRAINSTEM TOXICITY WITH CONVENTIONAL FRACTIONATION OR HYPERFRACTIONATION

Reference	Patients/Disease	Modality	Dose Constraint	Radiation-Induced Brainstem Toxicity
Jian et al[149]	48 Adults/nasopharyngeal cavity	Photons	V_{65} < 3 mL, V_{60} < 5 mL	3 grade 1 neurologic toxicities
Hoppe et al[148]	85 Adults/nasal cavity and/or paranasal sinus	Photons	D_{max} < 50 Gy	
Daly et al[120]	36 Adults/nasal cavity and/or paranasal sinus cavity	Photons	$D_{1\%}$ < 54 Gy	
Schoenfeld et al[152]	100 Adults/pharynx or larynx	Photons	V_{55} < 0.1 mL	
Uy et al[153]	40 Adults/intracranial meningioma	Photons	Unknown	1 BS necrosis @ D_{max} 55.6 Gy, V_{54} 4.7 mL
Merchant et al[150]	68 Children/infratentorial ependymoma	Photons	No separate brainstem constraint	1 BS necrosis @ D_{mean} 59 Gy
Freeman et al[147]	136 Children/brainstem glioma	Photons	Prescribed 54-60 Gy at 2 Gy once daily or 75.6 Gy at 1.26 Gy twice daily	None reported
Packer et al[151,154]	98 Children/brainstem glioma	Photons	Prescribed 72 or 78 Gy total @ 1 Gy twice daily	One treatment-related death at 72 Gy total @ 1 Gy twice daily and concurrent β-IFN
Weber et al[127]	29 Adults/chordoma, chondrosarcoma	Protons	Surface ≤ 63 CGE Center ≤ 54 CGE	None reported
Nishimura et al[129]	14 Adults/olfactory neuroblastoma	Protons	Surface < 64 CGE Center < 53 CGE	None reported
Noel et al[130]	45 Adults/BOS tumors	Photons + protons	Surface ≤ 63 CGE Center ≤ 54 CGE	
DeBus et al[145,146]	367 Adults/BOS tumors	Photons + protons	Surface ≤ 64 CGE Center ≤ 53 CGE	19 BS toxicities, including three deaths
Wenkel et al[131]	46 Adults/BOS meningiomas	Photons + protons	Surface ≤ 64 CGE Center ≤ 53 CGE	One BS injury, two neurologic toxicities

β-IFN, recombinant β-interferon; BOS, base of the skull; BS, brainstem; CGE, cobalt gray equivalent.

In the largest study, Debus et al[145,146] reported on 367 patients with base-of-skull tumors with a combination of conformal photon and proton RT. Nineteen late brainstem-related

toxicities were observed, including three deaths. On univariate analysis, significant predictors of toxicity were D_{max} greater than 64 CGE, V_{50} CGE greater than 5.9 mL, V_{55} CGE greater than 2.7 mL, V_{60} CGE greater than 0.9 mL, two or more skull-based surgeries, diabetes, and high blood pressure. On multivariate analysis, only V_{60} greater than 0.9 mL, two or more skull-based surgeries, and diabetes were predictive. In a study of 46 patients with recurrent base-of-skull meningiomas treated to a median brainstem D_{max} of 58.0 CGE, Wenkel et al[131] found that one patient developed brainstem injury at a dose that exceeded an unspecified constraint value by 10%. Two others with neurologic toxicities had brainstem doses that exceeded the constraints as shown in Table 12.4.

In pediatric patients with brainstem glioma (treated with opposed lateral fields that encompassed the majority of the brainstem), no toxicity was reported at doses of 54 to 60 Gy at 2 Gy/fraction, 75.6 Gy at 1.26 Gy twice daily,[147] or 78 Gy at 1 Gy twice daily.[151] The primary limitation of these studies was the short median survival, less than 12 months. Of 32 patients treated to 72 Gy twice daily in combination with recombinant β-interferon, there was at least one treatment-related death.[154]

Most pediatric protocols for central nervous system tumors recommend doses greater than 54 Gy, and separate brainstem dose constraints are often absent. Merchant et al studied 68 patients with infratentorial ependymoma treated with surgery and conformal RT (54-59.4 Gy).[150] In patients with full recovery, a considerable portion of the brainstem received over 60 Gy (V_{60} = 7.8 ± 1.4 mL). There was no difference in brainstem recovery based on absolute or percentage volume of the brainstem that received more than 54 Gy. Differences in these values for patients without full recovery were not statistically significant. One patient died with an autopsy-confirmed residual tumor and focal areas of brainstem necrosis. The mean brainstem dose was 59 Gy, and the patient also exhibited severe perioperative morbidity after two surgeries.

A limited number of studies report brainstem toxicity in single-fraction SRS or HFSRT.[155-159] A broad range of prescription isodose levels and dose metrics are reported, making it difficult to develop a predictive dose-volume model for brainstem toxicity.[143] In the study with the largest number of patients, Foote et al[155] analyzed the outcome in 149 vestibular schwannoma patients treated with SRS between 1988 and 1998; 41 were treated before 1994 when radiosurgery was primarily based on CT imaging, and 108 after 1994, when planning was MRI based. Large single-fraction doses (10-22.5 Gy) were used. Their analysis revealed a "learning curve," with a 5% and 2% actuarial 2-year rate of facial and trigeminal neuropathies, respectively, for patients treated after 1994 compared with 29% for both neuropathies for the earlier patients. This study found a significant difference, with a 2-year actuarial rate of facial and trigeminal neuropathies of 29% and 7% for patients treated before and after 1994, respectively. The authors ascribe this difference to the use of MRI rather than CT-based imaging and lower prescription doses in the latter years. A univariate analysis showed an incidence of cranial nerve neuropathy of 2% for less than 12.5 Gy versus 24% for greater than 12.5 Gy ($P < .0003$). On multivariate analysis, the prescription dose greater than 12.5 Gy, prior surgery, and treatment prior to 1994 were significant variables.

Mathematic/Biologic Models

The Emami review estimates a 5-year, 5% rate of complications, defined in that study as "necrosis/infarct," at 50, 53, and 60 Gy delivered to the whole, two-thirds of, and one-third of the brainstem, respectively.[1] The corresponding Lyman-Kutcher-Berman (LKB) parameters for calculation of the NTCP were $n = 0.16$, $m = 0.14$, and a tolerance dose for 50% probability of these complications (TD_{50}) equal to 65 Gy.[36] These estimates and model parameters appear overly conservative. For example, the LKB model estimates a 12% risk of severe complications for 54 Gy to the whole brainstem or a 3% risk of complications when the proton dose constraints (see Table 12.4) are utilized. The clinical data would suggest that a larger TD_{50}, smaller m, or larger m values might produce more reasonable estimates of toxicity. For example, an LKB model with a larger TD_{50} (72 Gy) or smaller m (0.1) would reduce the predicted risks to less than 5% or less than 1%, respectively. However, there are insufficient existing dose/volume/complication data to generate a more accurate model estimate at this time.

Recommended Dose-Volume Limits

The QUANTEC study concludes that the entire brainstem may be treated to 54 Gy using conventional fractionation with limited risk of severe or permanent neurologic effects.[143,150] Although the precise dose-volume relationship is unclear, partial volumes of the brainstem (1-10 mL) may be irradiated to a maximum dose of 59 Gy for dose fractions less than or equal to 2 Gy. The risk appears to increase markedly at doses greater than 64 Gy. In radiosurgery, it appears that a maximum brainstem dose of 12.5 to 13 Gy is associated with a low (<5%) risk of cranial neuropathy in patients with vestibular schwannomas treated with single-fraction SRS. The risk appears to increase rapidly when the marginal prescription dose is greater than 15 Gy or when the target volume exceeds 4 mL.[143,155,160,161] However, doses of 15 to 20 Gy have been used to treat brainstem metastases with a low reported rate of complications, potentially because of the limited survival time for these patients.[157,162]

Future Studies

Uniform, complete reporting of patient-specific dose/volume/outcome data for patients with and without complications is required.

Toxicity Scoring Criteria

Patients should undergo a complete history and physical examination at regular intervals with particular attention to the neurologic exam. Toxicity should be scored and reported using the CTCAE v. 4.0.[116]

Auditory Apparatus

Clinical Significance

Radiation therapy for brain tumors and head and neck cancers may damage the cochlea and/or acoustic nerve, leading to sensorineural hearing loss (SNHL) and compromised quality of life.[163]

End Points

SNHL following conventionally fractionated radiotherapy is typically measured by a decrease in the bone conduction threshold (BCT) at 0.5 to 4 kHz,[163] the primary range for human speech, using pure-tone audiometry (PTA). Although the technique is well established and standardized, a broad range of specific audiometric parameters are used to characterize SNHL, including the frequency (range) used for testing, the threshold chosen for a clinically significant change in the BCT (10-20 dB), and the control/standard used for comparison. In SRS, SRS, or HFSRT, hearing status is more commonly evaluated using the Gardner-Robertson scale, which is based on both PTA and speech discrimination. HL after SRS/HFSRT may be characterized by changes in Gardner-Robertson hearing grade or retention of serviceable hearing (ie, functional hearing with the aid of a hearing aid) or any measurable hearing. In addition, the length of follow-up will influence reported HL, as deficits may develop more rapidly following single-fraction SRS than HFSRT, and HL increases over time in both situations (Table 12.5).

TABLE 12.5 HEARING PRESERVATION IN STEREOTACTIC RADIOSURGERY AND RADIOTHERAPY

Reference	Technique: Number of Patients	Treatment Dose, Gy	Mean/Median Follow-Up, Months (Range)	Tumor Control, %	Rate of Hearing Preservation, %
Hirsch and Noren[164]	SRS: 126	18-25	56	86	26
Noren et al[165]	SRS: 254 (NF-2: 61)	18-20 10-15	(12-204)	Unilateral: 94 NF-2: 84	22 (moderate vs severe hearing loss: 55% vs 23%)
Foote et al[166]	SRS: 36	16-20	(2.5-36)	100	42 ± 17 at 2 y
Flickinger et al[167]	SRS: 273 (CT vs MRI planned: 118 vs 155)	12-20		CT: 44 MRI: 32	CT: 39 MRI: 68
Kondziolka et al[168]	SRS: 162	12-20 Mean: 16.6	(6-102) (60% >60)	94	47-51
Lunsford et al[169]	SRS: 402	Earlier in the series: 17 later in the series: 12-14	36	93	Earlier in the series: 39 later in the series: 68
Flickinger et al[170]	SRS: 190	11-18 Median: 13	30 (max: 80)	91 at 5 y	74
Andrews et al[171]	SRS: 64 (NF-2: 5) FSRT: 46 (NF-2: 10)	SRS: 12 FSRT: 50 (2 Gy/fx)	SRS: 30 ± 17 SRT: 30 ± 24	SRS: 98 SRT: 97	SRS: 33 SRT: 81
Combs et al[172]	FSRT: 106	57.6 Gy (1.8 Gy/fx)	49 (3-172)	94% @ 3 y 93% @ 5 y	94 @ 5 y
Williams[173]	HFSRT: 125	Tumors <3 cm: 25/5 fxs	22 (12-68)	100	64

Reference	Technique: Number of Patients	Treatment Dose, Gy	Mean/Median Follow-Up, Months (Range)	Tumor Control, %	Rate of Hearing Preservation, %
		Tumors ≥3 cm: 30/10 fxs			
Meijer et al[174]	SRS: 12 HFSRT: 25	SRS: 10-12 HFSRT: 20-25	25 (12-61)	–	91

CT, computed tomography; FSRT, fractionated stereotactic radiotherapy; fx, fraction; HFSRT, hypofractionated stereotactic radiotherapy; MRI, magnetic resonance imaging; NF-2, neurofibromatosis type 2; SRS, stereotactic radiosurgery.

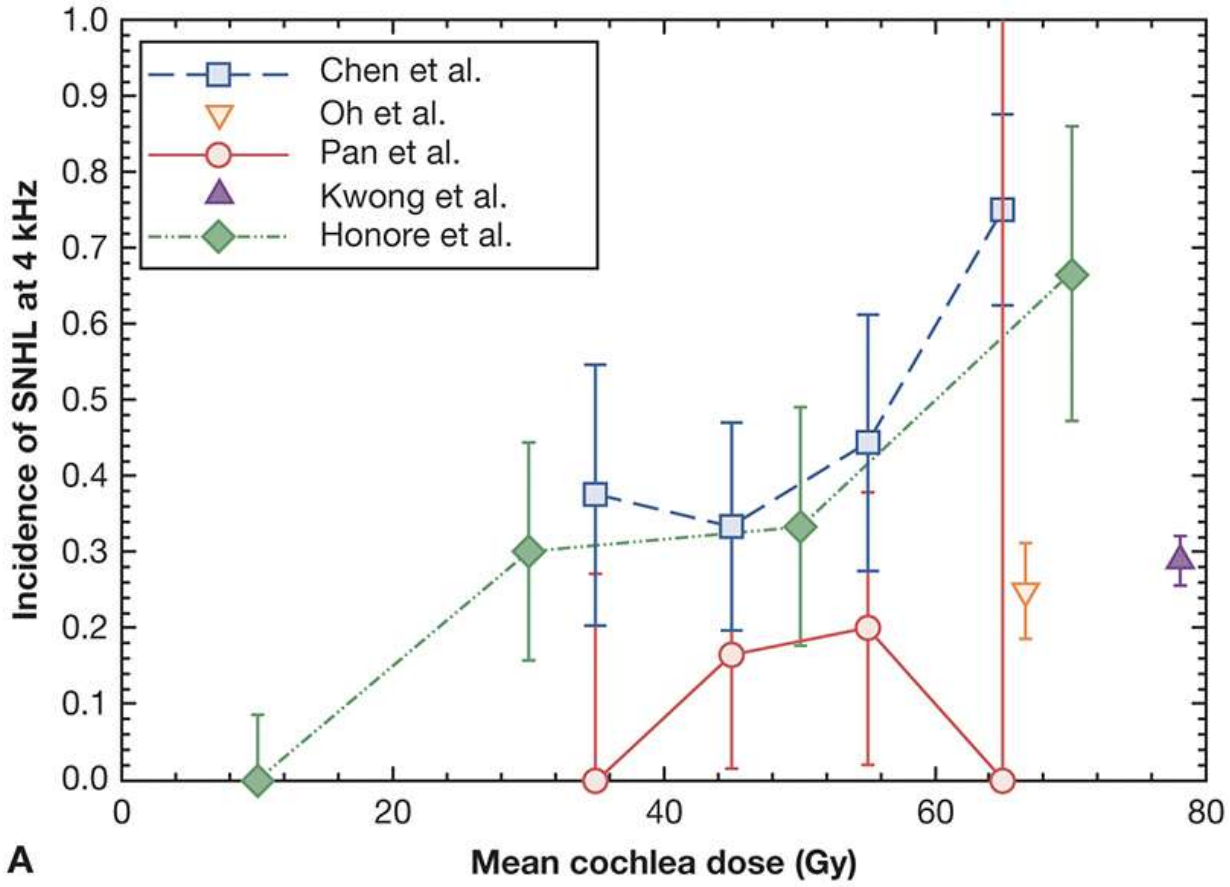
Challenges Defining Volumes

Contouring of the acoustic nerve and brainstem is best accomplished on high-resolution, contrast-enhanced T1-weighted, and fast imaging with steady-state precession MRI. The cochlea and associated bony anatomy are better delineated on fine-cut (≤1 mm slice thickness) CT scans. Both the acoustic nerve and cochlea are small structures, and the dose gradient at the latter structure is often quite steep. Moreover, the acoustic nerve anatomy is distorted by the tumor, significantly increasing its apparent diameter. Thus, the dose to these structures is typically characterized by an average or maximum dose, rather than a dose-volume distribution. In many studies, the primary dose metric was the dose to the acoustic neuroma, rather than the normal tissue structures per se, which is not unreasonable as the dose to the tumor appears to be correlated with the dose received by the acoustic nerve.[56]

Summary of QUANTEC, HyTEC, and PENTEC

The QUANTEC authors[163] summarized nine reports on risks of SNHL after conventionally fractionated radiotherapy for head and neck cancer; four of the studies modeled SNHL based on dosimetric factors (Figure 12.4). The authors recommended a mean dose of less than or equal to 45 Gy to the cochlea (and also considered a more conservative ≤35 Gy) to minimize risks of SNHL, though they conceded that a threshold for SNHL could not be derived from the reviewed data. With a mean dose of less than or equal to 45 Gy, the authors predicted a less than 30% risk of SNHL at the 4-kHz level. The QUANTEC authors also reviewed studies of patients treated for vestibular schwannomas, specifically seven studies of single-fraction SRS (including one with NTCP modeling) and four studies of conventionally fractionated stereotactic radiotherapy, hypofractionated radiotherapy, and/or fractionated SRS. They estimated that a single-fraction SRS prescribed dose of less than or equal to 14 Gy for vestibular schwannoma was associated with a less than 25% loss of serviceable hearing. The HyTEC authors for tumor control probability (TCP) of vestibular schwannomas[175] chose not to pursue pooling and modeling data for hearing preservation due to the multiple confounding factors, including tumor- related susceptibility to HL, multiple organ at risk (OARs) (eg, auditory nerve, cochlea, and brainstem—for which dosimetric exposures are interdependent and directly correlate with prescription dose) and inadequate data to facilitate pooling and NTCP modeling (personal communication, Michael Milano). A non-HyTEC systematic review of 23 studies suggested marginal tumor doses of less than 13 Gy and cochlea maximum doses less than 4 to 5 Gy were the main prognostic factors for hearing preservation.[176] Another systemic review of 21 studies that focused on cochlear exposures

concluded that striving for a mean cochlear dose less than 4 to 6 Gy (without compromising tumor coverage) would be practical but that no clear association was found between cochlear exposures and hearing preservation.[177]


Chen et al.
Oh et al.
Pan et al.
Kwong et al.
Honore et al.
Incidence of SNHL at 4 kHz
Mean cochlea dose (Gy)
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
0
20
40
60
80

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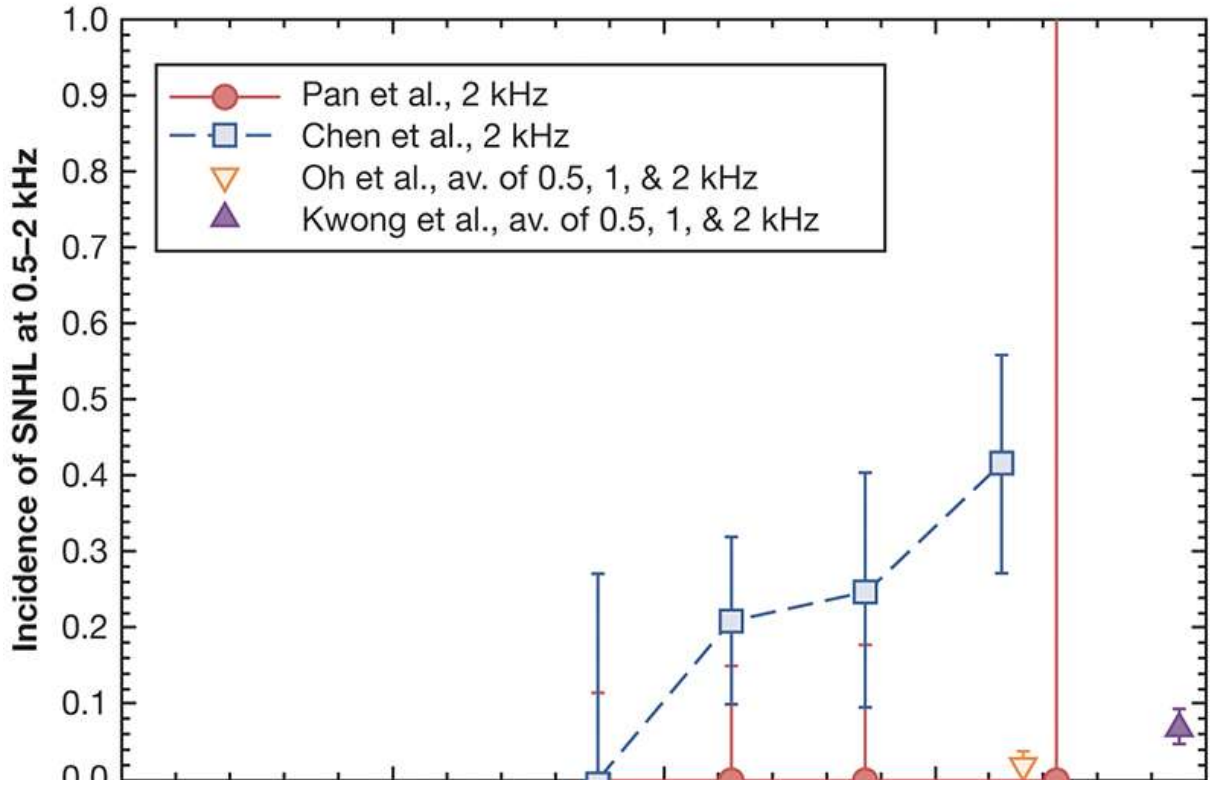
Pan et al., 2 kHz
Chen et al., 2 kHz
Oh et al., av. of 0.5, 1, & 2 kHz
Kwong et al., av. of 0.5, 1, & 2 kHz
Incidence of SNHL at 0.5–2 kHz
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0

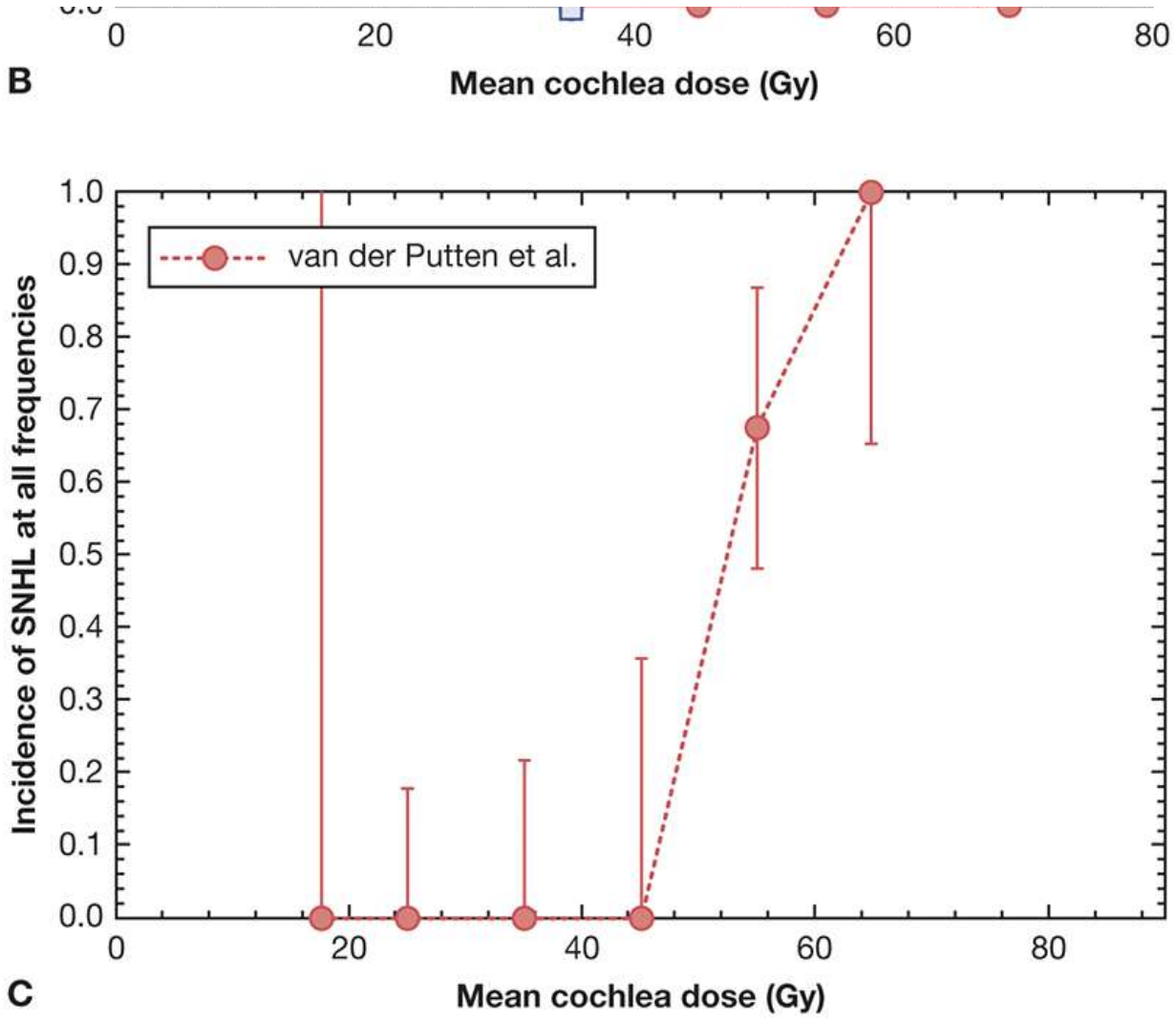

FIGURE 12.4 Mean dose response for sensorineural hearing loss (SNHL) at (A) 4 kHz,[178-182] (B) 0.5 to 2 kHz,[178-182] and (C) all frequencies[182] (0.25-12 kHz). (Reprinted from Bhandare N, Jackson A, Eisbruch A, et al. Radiation therapy and hearing loss. *Int J Radiat Oncol Biol Phys*. 2010;76[3 suppl]:S50-S57. Copyright © 2010 Elsevier. With permission.)

HL in children is particularly important due to its potential to compromise neurocognitive function. The PENTEC analysis demonstrates that the incidence and severity of cochlear HL from RT exposure alone are related to dose and age.[183] Risk of HL was less than 5% in cochlea receiving a mean dose less than 35 Gy but increased to 30% at 50 Gy. HL risk ranged from 25% to 40% in children under the age of 5 years at diagnosis, declining to 10% in older children for any radiation dose. The probability of similar severe HL occurring at doses of 18.3 Gy is higher for children less than 3 versus older than 3 years of age. High-frequency HL was most common, with average onset occurring 3.6 years (range, 0.4-13.2 years) after RT exposure to platinum-based chemotherapies added to the rates of HL at a given cochlear dose level, with 300 mg/m^2 shifting the dose response by 7 Gy.

Factors Affecting Risk

The QUANTEC authors emphasized that cisplatin, administered during or after radiotherapy, may exacerbate SNHL. Other factors that adversely impacted risks include worse preradiotherapy hearing function and older age.

Future Studies

The effects of concurrent chemotherapy in radiotherapy for head and neck cancer, of acoustic nerve length irradiated and fractionation in vestibular schwannomas, and of the absolute dose to the cochlea in all settings would benefit from prospective, multi-institutional studies.

Toxicity Scoring Criteria

An audiometric evaluation should be performed for both ears immediately before radiotherapy and biannually thereafter. The QUANTEC authors recommend that a "clinically significant hearing loss" should be defined as an increase in the threshold of 10 dB in postradiotherapy BCT or a decline of 10% in a speech discrimination evaluation.[163]

Spinal Cord

Clinical Significance

Although the spinal cord proper is from the base of the skull through the top of the lumbar spine, individual nerves continue down the spinal canal to the level of the pelvis. Thus, portions of the spinal cord and canal are often included in radiotherapy fields during the treatment of malignancies involving the neck, thorax, abdomen, and pelvis.[184] In addition, metastatic disease to the bony spine is encountered in approximately 40% of all patients with cancer,[185] and this disease is often treated with radiotherapy. Though rare, radiation-induced spinal cord injury (ie, myelopathy) can be severe, resulting in pain, paresthesias, sensory deficits, paralysis, Brown-Séquard syndrome, and bowel/bladder incontinence.[186]

End Points

Myelopathy is defined as a grade 2 or higher myelitis, per CTCAE v. 4.0.[116] Under this definition, asymptomatic changes in the cord detected radiographically and mild signs/symptoms, such as the Babinski sign or L'hermitte syndrome, would not be classified as myelopathy. Consequently, a diagnosis of myelopathy is based on the appearance of signs/symptoms of sensory or motor deficits, loss of function, or pain, now frequently confirmed by MRI. Radiation myelopathy rarely occurs less than 6 months after completion of radiotherapy and, in most cases, appears within 3 years.[187]

Challenges Defining Volumes

In conventional external-beam RT, the field generally encompasses the entire circumference of the cord, vertebral body, and spinal nerve roots, and precise organ definition is not critical apart from correctly identifying the level of the involved cord. Delineation of the cord in radiosurgery is unsettled, with various studies contouring the critical organ in the axial plane as the spinal cord, the spinal cord expanded 2 to 3 mm, the thecal sac and its contents, or the entire spinal canal.[188] As the volume receiving a high dose often extends superiorly and inferiorly to the target, several studies expand the critical organ volume above and below the

target volume. For example, RTOG protocol 0631, a study of image-guided radiosurgery of spine metastases, defined the cord as the unexpanded cord itself visualized in MRI and extended the volume of the partial spinal cord 5 to 6 mm above and below the target volume.

Summary of QUANTEC and HyTEC

The QUANTEC authors[184,189] analyzed the risk of radiation myelopathy in 335 and 1,946 patients receiving radiotherapy to the full circumference, never previously cervical and thoracic spinal cord/canal,[190-201] respectively (Figure 12.5). Although a small number of these patients received relatively high doses per fraction, none were treated using stereotactic techniques to exclude a portion of the circumference of the cord, and the QUANTEC analysis essentially represents the risk for conventionally fractionated treatment. Note that the dose to the cord is the prescribed dose reported in those studies; typically, dosimetric data were not available to calculate the true cord dose. The rate of myelopathy appears very low below total doses of 50 Gy for conventional radiation delivered at 2 Gy per fraction, as discussed below.

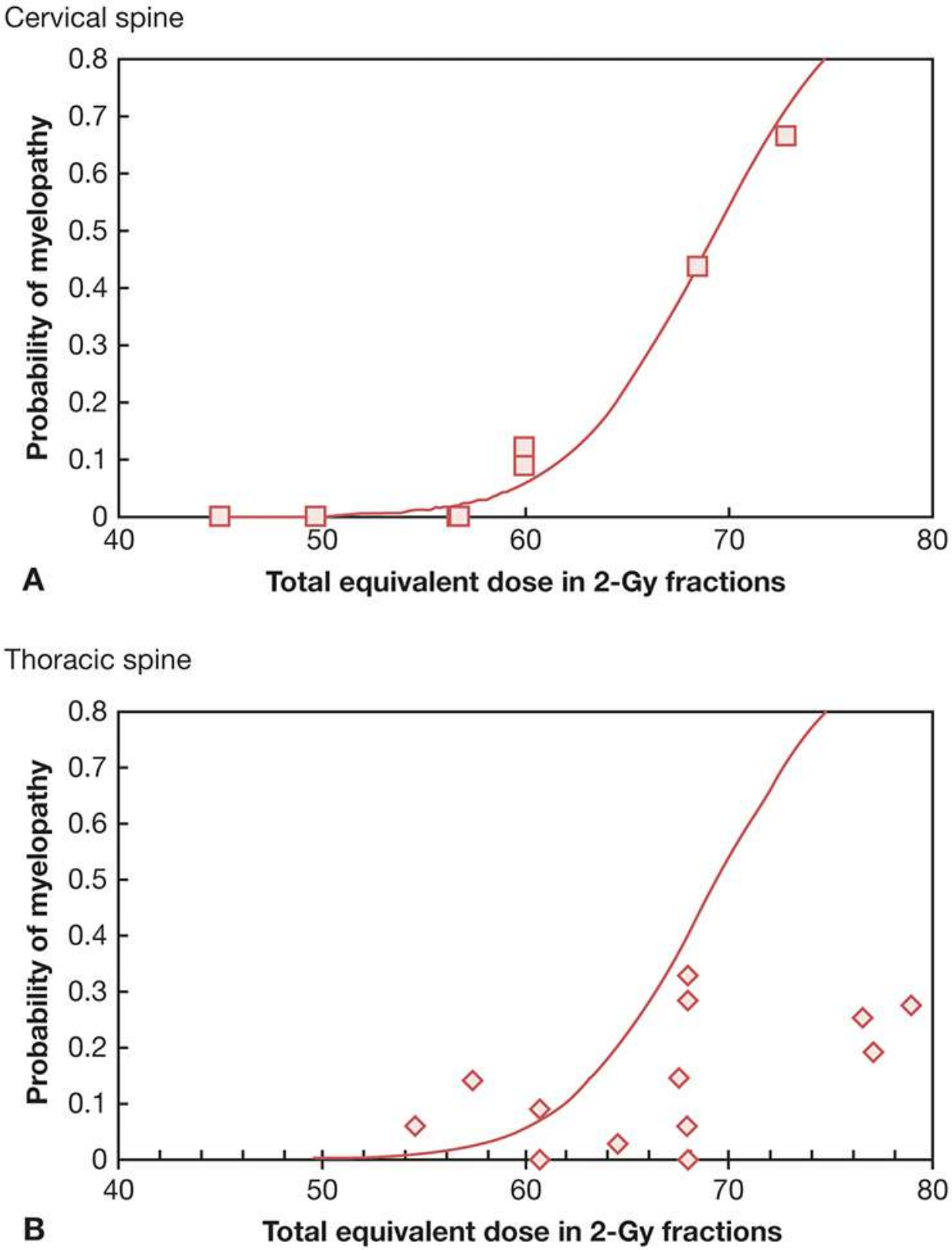

FIGURE 12.5 Incidence of transverse myelopathy from selected studies. A. Cervical cord: data for selected studies[187,202-205] shown by *γ* with probability of myelopathy corrected for estimated survival and solid line fit to these data by the method of Schultheiss. B. Thoracic cord: data for selected studies[190-201] shown by ◊ with probability of myelopathy corrected for estimated survival. A solid line is the best fit for the cervical cord data, as

thoracic cord data were insufficient to permit an adequate fit. (Adapted from Schultheiss TE. The radiation dose-response of the human spinal cord. *Int J Radiat Oncol Biol Phys*. 2008;71[5]:1455-1459. Copyright © 2008 Elsevier. With permission.)

The QUANTEC authors also reviewed the risk of radiation myelopathy to the spine from radiosurgery, summarized in Table 12.6.[206-213] Of the exactly 1,400 cases of spinal radiosurgery presented in the published literature, there are only 12 reported instances of radiation-induced myelopathy, equaling a crude rate of 0.8%. Applying the Schultheiss model[189] to spinal radiosurgery appears to overestimate the risk of myelopathy. For example, using the α/β ratio of 0.87 Gy, the model yields an estimated risk of myelopathy of 0.8%, 13.6%, 50%, and 73% for 12, 13, 13.7, and 14 Gy, respectively, delivered in a single fraction. In contrast, Ryu et al[214] found only one case of myelopathy in 86 patients treated with single-fraction spine radiosurgery at a mean cord D_{max} of 12.2 Gy (±2.5 Gy standard deviation) and no cases in the subset of 39 lesions prescribed 18 Gy and treated to a mean cord D_{max} of 13.8 Gy. Note that the Medin et al[215] study of single-fraction irradiation of the swine spinal cord shows a steep dose-response curve with a median effective D_{max} of 20 Gy. At the high doses per fraction encountered in radiosurgery, the applicability of the linear-quadratic model is controversial, and the biologically equivalent doses presented in Table 12.6 should be used solely for making rough comparisons of the different dose regimens. In particular, the QUANTEC authors stress that data obtained at a low dose per fraction should not be extrapolated to regimens employing doses of 10 Gy or more per fraction.[184,216]

TABLE 12.6 TRANSVERSE MYELOPATHY IN STEREOTACTIC RADIOSURGERY (SRS) OF THE SPINE

Reference	Cases of Myelopathy/Total Patients	Total Dose (Gy)	Dose/Fraction (Gy)	Dose to Cord (Gy)	BED to Cord (Gy_3)	Proportion of Patients Previously Irradiated to Involved Segment of Spine
Gibbs et al[209]	6/1,075	12.5-25 ***25*** ***20*** ***21*** ***24*** ***20*** ***20***	5-25 ***12.5*** ***12.5*** ***10.5*** ***8*** ***10*** ***20***	D_{max}: 3-28 ***D_{max}: 26.2*** ***D_{max}: 29.9*** ***D_{max}: 19.2*** ***D_{max}: 13.9*** ***D_{max}: 10*** ***D_{max}: 8.5***	Range: 24-121 Gy_3 ***D_{max}: 141*** ***D_{max}: 81*** ***D_{max}: 46*** ***D_{max}: 129*** ***D_{max}: 33*** ***D_{max}: 43***	>55%
Ryu et al[214]	1/86	<10-18	<10-18	*Mean ± SD* D_{max}: 12.2 ± 2.5 D_{10}: 8.6 ± 2.1 *Maximum* D_{max}: 19.2 D_{10}: 13	*Mean ± SD* D_{max}: 62 ± 4.6 D_{10}: 33 ± 3.6 *Maximum* D_{max}: 142 D_{10}: 69	0%
		18	18	*Mean ± SD* D_{max}: 13.8 ± 2.2	*Mean ± SD* D_{max}: 77 ± 3.8	

Reference	Cases of Myelopathy/Total Patients	Total Dose (Gy)	Dose/Fraction (Gy)	Dose to Cord (Gy)	BED to Cord (Gy_3)	Proportion of Patients Previously Irradiated to Involved Segment of Spine
				D_{10}: 9.8 ± 1.5	D_{10}: 42 ± 2.3	
		16	***16***	***D_{max}: 14.8*** ***D_1: 13.0*** ***D_{10}: 9.6***	***D_{max}: 88*** ***D_1: 69*** ***D_{10}: 40***	
Gwak et al[210]	2/9	21-44	3-5	*Median* D_{max}: 32.9 D_{25}: 11.0 *Range* D_{max}: 11-37 D_{25}: 1.2-24	*Median* D_{max}: 106 D_{25}: 21 *Range* D_{max}: 19-172 D_{25}: 1-88	33%
		30	***10***	***D_{max}: 35.2*** ***D_{25}: 15.5***	***D_{max}: 172*** ***D_{25}: 42***	
		33	***11***	***D_{max}: 32.9*** ***D_{25}: 24.0***	***D_{max}: 153*** ***D_{25}: 88***	
Benzil et al[206]	3/31	Median: 10 ***100*** ***12*** ***20***	Median: 5 ***50*** ***12*** ***5***	Median: 6.0	Median: 12	Unknown
Sahgal et al[213]	0/38	24	8	*Median* $D_{0.1\ mL}$: 10.5 $D_{1\ mL}$: 7.4	*Median* $D_{0.1\ mL}$: 23 $D_{1\ mL}$: 14	62%
Sahgal et al[212]	0/16	21	7	*Median* D_{max}: 20.9 $D_{1\ mL}$: 13.8 *Range* D_{max}: 4.3-23 $D_{1\ mL}$: 2.8-19	*Median* $D_{1\ mL}$: 22 *Range* $D_{1\ mL}$: 6-54	6%
Chang et al[207]	0/63	30 pts: 30 Gy 33 pts: 27 Gy	30 pts: 6 Gy 33 pts: 9 Gy	30 pts: <10 33 pts: <9	30 pts: <16.7 33 pts: <18	56%
Gerszten et al[208]	0/50	19	19	*Mean* D_{max}: 10 *Range* D_{max}: 6.5-13	*Mean* D_{max}: 21 *Range* D_{max}: 11-32	96%
Nelson et al[211]	0/32	Median: 18	Median: 7	*Mean ± SD*	*Mean ± SD*	58%

Reference	Cases of Myelopathy/Total Patients	Total Dose (Gy)	Dose/Fraction (Gy)	Dose to Cord (Gy)	BED to Cord (Gy_3)	Proportion of Patients Previously Irradiated to Involved Segment of Spine
				D_{max}: 14.4 ± 2.3 D_{10}: 11.5 ± 2.1 *Maximum* D_{max}: 19.2 D_{10}: 15.2	D_{max}: 46.0 ± 13.2 D_{10}: 31.2 ± 8.1 *Maximum* D_{max}: 78.3 D_{10}: 46.5	

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The HyTEC authors[217] reviewed radiation myelopathy in patients undergoing spinal SBRT, drawing data from seven studies[212,218-223] meeting strict inclusion criteria. A total of three cases of radiation myelopathy were observed in the aggregate cohort of 496 patients (0.6%). They also modeled the risk of radiation myelopathy using nine cases observed in the literature with 66 normal controls, yielding a "greater than expected" risk of radiation myelopathy at doses below 12 Gy cord maximum dose for single-fraction treatment. The authors attribute this difference to the inclusion of a case of radiation myelopathy observed at only 10.6 Gy and to the low number of normal control cases. A significant uncertainty in the analysis revolves around the reporting of the maximum dose and contouring of the organ at risk; small differences in the cord/thecal sac volume yield very large difference in the maximum point dose, and the authors make a strong argument for using the D0.03cc as a better estimate of the maximum dose.

Factors Affecting Risk

Animal studies suggest that the immature cord is somewhat more susceptible to radiation-induced complications and the time to manifestation of damage is shorter.[224-227] Though the literature on radiation-induced myelopathy in children is sparse, care should be exercised in irradiating a child's spine because of the increased sensitivity of the developing central nervous system and bone to ionizing radiation.[228] There are a handful of reports of myelopathy at relatively low radiation doses to the spine postchemotherapy.[229] Many chemotherapeutic agents are directly neurotoxic[230] and should be used with caution during irradiation of the central nervous system.[231]

Special Situations

The need to reirradiate previously treated cord is often encountered in the setting of recurrent spine metastases following spinal irradiation or new spine lesions within, for example, a previously treated lung, pancreas, or esophageal field. In evaluating reirradiation of the spinal cord, the dose regimen for each course, the volume and region (re)irradiated, and the time interval between the courses of RT must be considered.[232] Animal studies support a time-dependent model of repair for radiation damage to the spinal cord.[224,233-237] For example, Ang et al[224] treated the thoracic and cervical spines of rhesus monkeys to 44 Gy and then reirradiated these animals with an additional 57 Gy at 1 to 2 years or 66 Gy at 2 to 3 years,

yielding aggregate doses of 101 and 110 Gy, respectively. Of the 45 animals evaluated, four developed myelopathy by the end of the observation period. The reirradiation tolerance model developed from these and similar data[233] estimates a recovery of 34 Gy (76%), 38 Gy (85%), and 45 Gy (101%) at 1, 2, and 3 years, respectively. Under conservative assumptions, an overall recovery of 26 Gy (61%) was calculated.

Table 12.7 summarizes published reports involving reirradiation of the spinal cord in humans using both conventionally fractionated, full-circumference external-beam radiotherapy and SBRT.[232,238-250] For purposes of comparing different regimens, an α/β ratio of 3 Gy was used to calculate the biologically equivalent dose in Gy_3. In all of these studies, the median interval between courses was at least 6 months, and only a small number of cases were treated at intervals less than 6 months. Note that few cases of myelopathy are reported despite large cumulative doses, with essentially no cases of myelopathy observed for cumulative doses less than 60 Gy in 2-Gy equivalent doses. These observations are consistent with the predictions of postradiotherapy repair observed in the animal models. The HyTEC authors[217] identified five papers that met their inclusion criteria for rigorous dose/volume reporting, noting the small numbers of radiation myelopathy events and the heterogeneity of the data. Nonetheless, they developed criteria for minimizing radiation myelopathy based on the cumulative and reirradiation doses to the thecal sac and the time between the initial and reirradiation courses.

TABLE 12.7 TRANSVERSE MYELOPATHY IN REIRRADIATION OF THE SPINE

Reference	Cases of Myelopathy/Total Patients	Median F/U (Months)	BED, Initial Course (Gy_3) Median (Range)	BED, Reirradiation (Gy_3) Median (Range)	Interval Between Courses (Months) Median (Range)	Total BED (Gy_3) Median (Range)	2-Gy Dose Equivalent, α/β = 3 Gy Median (Range)
Wright et al[250]	0/37	8	60 (10-101)	16 (5-50)	19 (2-125)	79 (21-117)	47 (13-70)
Langendijk et al[242]	0/34	–	–	–	–	<100	<60
Nieder et al[232,239,244]	0/15	30	70 (34-83)	50 (38-83)	30 (6-96)	115 (91-166)	69 (54-100)
Schiff et al[247]	4/54 *4*	4[a]	60 *All 60*	37 *73*[b] *(29-115)*	10 (1-51) *9 (5-21)*	97 *133 (109-175)*	58 *80 (65-105)*
Ryu et al[246]	0/1	60	75	72	144	147	88
Kuo et al[241]	0/1	8	75	42	37	117	70
Bauman et al[238]	0/2	>3-9	(40-56)	(18-35)	(8-20)	(58-91)	(35-57)
Sminia et al[248]	0/8	–	56 (29-78)	42 (36-83)	30 (4-152)	106 (65-159)	64 (39-96)

Reference	Cases of Myelopathy/Total Patients	Median F/U (Months)	BED, Initial Course (Gy_3) Median (Range)	BED, Reirradiation (Gy_3) Median (Range)	Interval Between Courses (Months) Median (Range)	Total BED (Gy_3) Median (Range)	2-Gy Dose Equivalent, α/β = 3 Gy Median (Range)
Magrini et al[243]	0/5	168	47 (32-47)	55 (33-67)	24 (12-36)	94 (80-113)	57 (48-68)
Rades et al[245]	0/62	12	29 (29-47)	29 (29-47)	6 (2-40)	69 (59-77)	41 (35-46)
Jackson and Ball[240]	0/6	15	All 73	36 (32-39)	15	106 (103-109)	63 (62-65)
Wong et al[249]	*11/–*[c]	*11*	*72 (28-96)*	*42 (14-86)*	*11 (2-71)*	*115 (100-138)*	*69 (60-83)*

[a]Overall survival.

[b]One patient received two courses of reirradiation; another received three courses.

[c]Total number of patients not reported.

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Recommended Dose-Volume Limits

With conventional fractionation of 2 Gy/day including the full cord cross section, total doses of 50, 60, and approximately 69 Gy are associated with a 0.2%, 6%, and 50% rate of myelopathy. The level of acceptable risk will depend on the clinical scenario; that is, a 5% risk of myelopathy may be acceptable in the treatment of a primary spinal cord tumor but not in the irradiation of a lung lesion. For reirradiation of the full cord cross section at 2 Gy per daily fraction after prior conventionally fractionated treatment, cord tolerance appears to increase at least 25% 6 months after the initial course of RT.

In spine radiosurgery, the HyTEC authors recommend a maximum cord dose of 12.4 to 14.0 Gy in one fraction, 17.0 Gy in two fractions, 20.3 Gy in three fractions, 23.0 Gy in four fractions, and 25.3 Gy in five fractions to limit the risk of radiation myelopathy to 1% to 5%. In comparison, RTOG 0631 specified a cord D_{10} and $D_{0.35\ mL}$ of 10 Gy and D_{max} of 14 Gy for the involved spine. For reirradiation of the cord, HyTEC authors suggest cumulative thecal sac equivalent dose in 2 Gy fractions with an α/β of 2 D_{max} be held below 70 Gy, the SBRT thecal sac $EQD2_2$ D_{max} limited to 25 Gy, thecal sac SBRT $EQD2_2$ D_{max} be limited to less than 50% of the cumulative thecal sac $EQD2_2$, and a minimum time interval to reirradiation of 5 months or more.

Future Studies

A model of dose/volume/outcome for spinal cord toxicity will require that more extensive and detailed data be collected over many years, including data on entire cohorts of patients treated with radiotherapy and radiosurgery, not just those with myelopathy. Extensive dosimetric

parameters should be collected, specifically D_{max}, D_1, D_{10}, D_{50}, $D_{0.1\ mL}$, $D_{0.35\ mL}$, and $D_{1\ mL}$, and the volume of the involved segment of the spinal cord, as well as the prescribed total dose, dose per fraction, involved spinal level(s), portion of the vertebral body irradiated, irradiation technique, patient characteristics/demographics, and, in the case of irradiation, the time interval between courses of spinal RT. In addition, preclinical studies identifying the fundamental mechanisms of radiation-induced toxicity would be valuable.

Toxicity Scoring Criteria

Toxicity should be scored and reported using CTCAE v. 4.0.[116]

NECK

Larynx and Pharynx

Clinical Significance

Radiation therapy is often utilized as the primary treatment of early-stage laryngeal cancers in an effort to preserve speech and swallowing. However, radiation-induced progressive edema and associated fibrosis can lead to long-term problems with phonation and swallowing.[251] Irradiation of the pharynx and larynx, particularly in combination with concurrent chemotherapy, can produce severe dysphagia, compromising nutrition, protection of the airway, and quality of life.

End Points

The critical larynx-specific end points examined were laryngeal edema and vocal function.[252] Dysphagia, resulting from laryngeal and/or pharyngeal dysfunction, may be assessed by instrument-based swallowing studies,[253] by observer-based criteria (eg, CTCAE v. 4.0), or by patient-reported quality of life questionnaires. Pretherapy vocal and swallowing function should be considered when assessing the functional response to RT of the larynx and pharynx.[254]

Challenges Defining Volumes

Phonation and swallowing are complex processes involving multiple anatomic structures in close proximity to one another. The relative importance of various normal tissue structures affecting vocal function and swallowing is controversial. In studying vocal dysfunction, doses to the epiglottis, base of the tongue, lateral pharyngeal walls, preepiglottic space, aryepiglottic folds, false vocal cords, upper esophageal sphincter, and cricoid cartilage have been considered.[252,255,256] Radiation-induced dysphagia has been correlated with the dose to the pharyngeal constrictor muscles and specific points in the supraglottic and glottic larynx.[255,257-260] Precise identification of these structures for treatment planning requires a high-resolution, contrast-enhanced CT scan.

Summary of QUANTEC

The QUANTEC report[252] summarized three studies on radiotherapy dose-volume measures correlated with laryngeal toxicity (edema or vocal function); one study modeled the risks of

laryngeal edema. Based on these studies, the authors estimated less than 20% toxicity risks with whole-organ laryngeal exposures as follows: D_{max} less than 66 Gy (for vocal dysfunction) and mean less than 50 Gy (for aspiration) in patients treated with concurrent chemoradiation for head and neck cancer. Among those treated with radiotherapy alone, a mean dose of less than 44 Gy and $V_{50} < 27\%$ were associated with less than 20% risks of laryngeal edema. The QUANTEC authors also reviewed eight papers on dysphagia as correlated with laryngeal and pharyngeal exposures and developed a model (from two studies) for aspiration risks relative to supraglottic laryngeal mean doses, shown in Figure 12.6. From that model, a supraglottic laryngeal mean dose of 47 Gy was correlated with approximately 20% aspiration risk. From their data review, a pharyngeal constrictor mean dose of less than 50 Gy was estimated to result in less than 20% aspiration risk. The 2023 dysphagia-optimized intensity-modulated radiotherapy versus standard intensity-modulated radiotherapy in patients with head and neck cancer randomized patients undergoing chemoradiotherapy for head and neck cancer to two arms; in one required less than or equal to 50 Gy mean dose to the superior and middle pharyngeal constrictor muscles or inferior pharyngeal constrictor muscles outside the high-dose target volume.[261] The MD Anderson Dysphagia Inventory (MDADI) composite score 12 months after radiotherapy was significantly improved in the arm undergoing pharyngeal constrictor sparing.

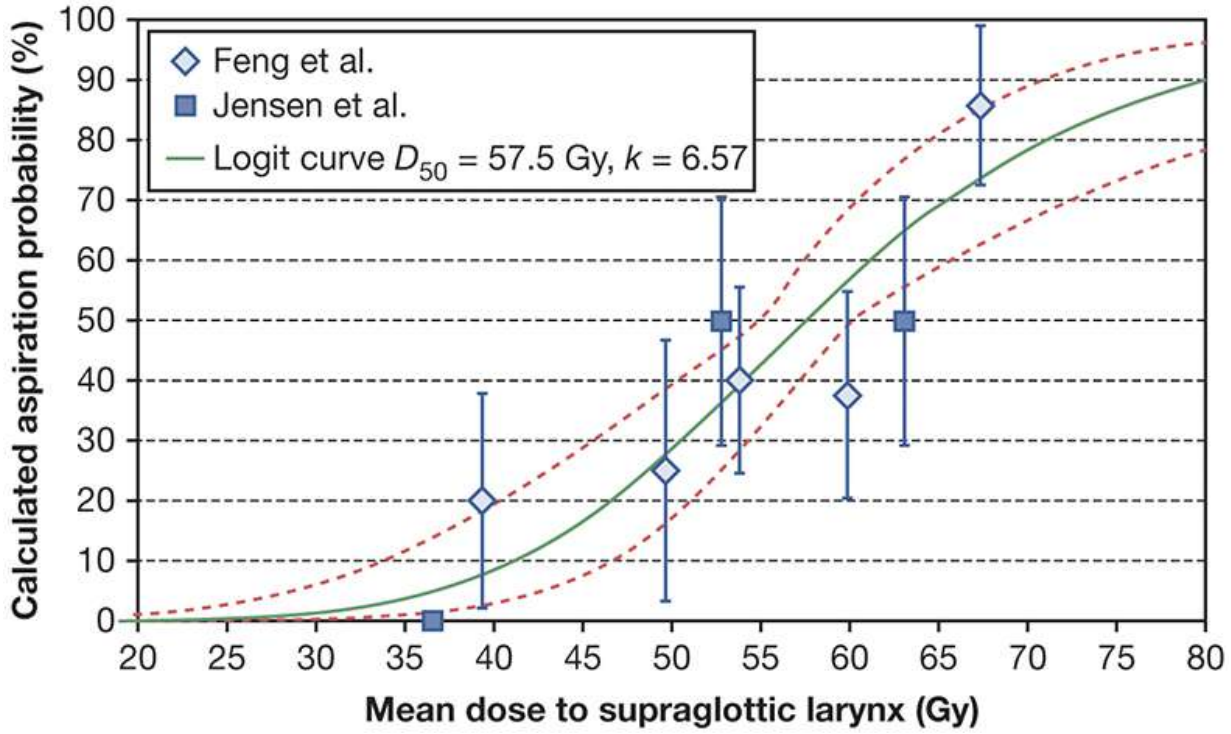

FIGURE 12.6 Probability of aspiration (a proxy for dysphagia) versus larynx dose for selected studies.[258,259] Solid line fit of logit model to combined data; *dotted lines* represent 68% confidence area. (Reprinted from Rancati T, Schwarz M, Allen AM, et al. Radiation dose-volume effects in the larynx and pharynx. *Int J Radiat Oncol Biol Phys*. 2010;76[3 suppl]:S64-S69. Copyright © 2010 Elsevier. With permission.[69])

Factors Affecting Risk

The addition of concurrent chemotherapy to high-dose RT appears to at least double the risk of laryngeal edema and dysfunction.[252] Severe laryngeal dysfunction secondary to the tumor will often persist following radiotherapy, and a laryngectomy may be preferred to chemoradiation in this setting.

Future Studies and Toxicity Scoring Criteria

Prospective studies that include pretherapy assessments of vocal and swallowing function should be conducted to correlate observer-rated scores such as the CTCAE v. 4.0 system,[116] patient-reported quality scores, and objective swallowing.[252] Such studies should focus on patients receiving concurrent chemoradiation, as this population is at the greatest risk of laryngeal/pharyngeal toxicity. Although CTCAE-based scoring is simple and widely utilized, objective measurement by a speech pathologist is often necessary to quantify swallowing dysfunction following radiotherapy.

Salivary Glands

Clinical Significance

In radiotherapy of head and neck tumors, the parotid, submandibular, and minor salivary glands often receive substantial doses of radiation. Reduced salivary production is a common toxicity and adversely affects the patient's quality of life. Inadequate salivary function leads to multiple problems, including poor dental hygiene, a propensity to oral infections, sleep disturbances, pain, and difficulty chewing and swallowing.[262] The majority of stimulated salivary production comes from the parotid glands, whereas resting (unstimulated) salivary production is due primarily to the submandibular, sublingual, and numerous small oral salivary glands.[263]

End Points

Xerostomia (dry mouth secondary to inadequate saliva production) can be assessed based on the patient's symptoms (altered taste or sensation of dryness) and/or quantitative saliva production.

Challenges Defining Volumes

Parotid and submandibular salivary glands can be adequately delineated on contrast-enhanced CT scans. However, parotid glands typically shrink during radiotherapy, potentially resulting in decreased gland sparing. For example, Robar et al[264] found that while the medial position of the parotid gland was stable over the course of RT, the lateral borders shrank approximately 1 mm/week, yielding total displacements of 4 to 6 mm.

Summary of QUANTEC

The QUANTEC authors[262] reviewed several studies on dosimetric predictors of xerostomia as measured by stimulated or unstimulated salivary flow at specific endpoints (ie, 1, 6, and 12 months after treatment; Table 12.8). Some recovery of salivary function occurs over time, with the dose required to obtain an equivalent reduction in salivary flow increasing at longer follow-up times. The QUANTEC report described a wide variation in the observed

dose/volume/toxicity relationships, depending on the patient population, treatment technique, and endpoint selected. As a result, models predicting the risk of xerostomia as a function of dose-volume parameters have yielded a broad range of parameters. Notably, parotid glands seem to respond independently to irradiation of the whole mouth and should be considered separately.

TABLE 12.8 DOSIMETRIC PREDICTORS OF XEROSTOMIA

Reference	Patients (*n*)/Follow-Up	Total Prescribed Target Dose (Gy)[a]	Dose-Volume Parameters	
			Unstimulated	Stimulated
Eisbruch et al[265]	88/1-12 mo	58-72	Mean dose ≤ 22-25 Gy[b] V_{15} < 66% V_{30} < 43% V_{45} < 26%	Mean dose ≤ 25-26 Gy[c] V_{15} < 67% V_{30} < 45% V_{45} < 24%
Maes et al[266]	39/1-4 mo	66-70	–	Mean dose ≤ 20 Gy[d]
Blanco et al[267]	55/6 mo 29/12 mo	50-71	Mean dose < 25.8 Gy	–
Li et al[268]	142/1-24 mo	60-75	Mean dose < 25-30 Gy	Mean dose < 25-30 Gy

[a]Treated at 1.5 to 2.0 Gy per fraction.

[b]24 Gy at 1 and 3 months, 22 Gy at 6 months, and 25 Gy at 12 months; threshold dose defined as mean dose above which saliva production appeared to abruptly approach zero.

[c]26 Gy at 1, 3, and 6 months, 25 Gy at 12 months; threshold dose defined as mean dose above which saliva production appeared to abruptly approach zero.

[d]Corresponds to the probability of 70% that loss of salivary excretion fraction was <50%.

V_x, percentage of gland volume receiving >*x* Gy.

Based on the summary of data, the QUANTEC authors[262] estimated less than 20% risks of long-term parotid function reduced to less than 25% of preradiotherapy level with a mean dose less than 25 Gy when considering bilateral parotid irradiation and a mean dose of less than 20 Gy when considering exposure of one parotid when the other is exposed to higher, potentially injuring, doses, as shown in Figure 12.7. Keeping the mean dose to the submandibular glands at modest levels (<35 Gy) may reduce the severity of xerostomia.[262]

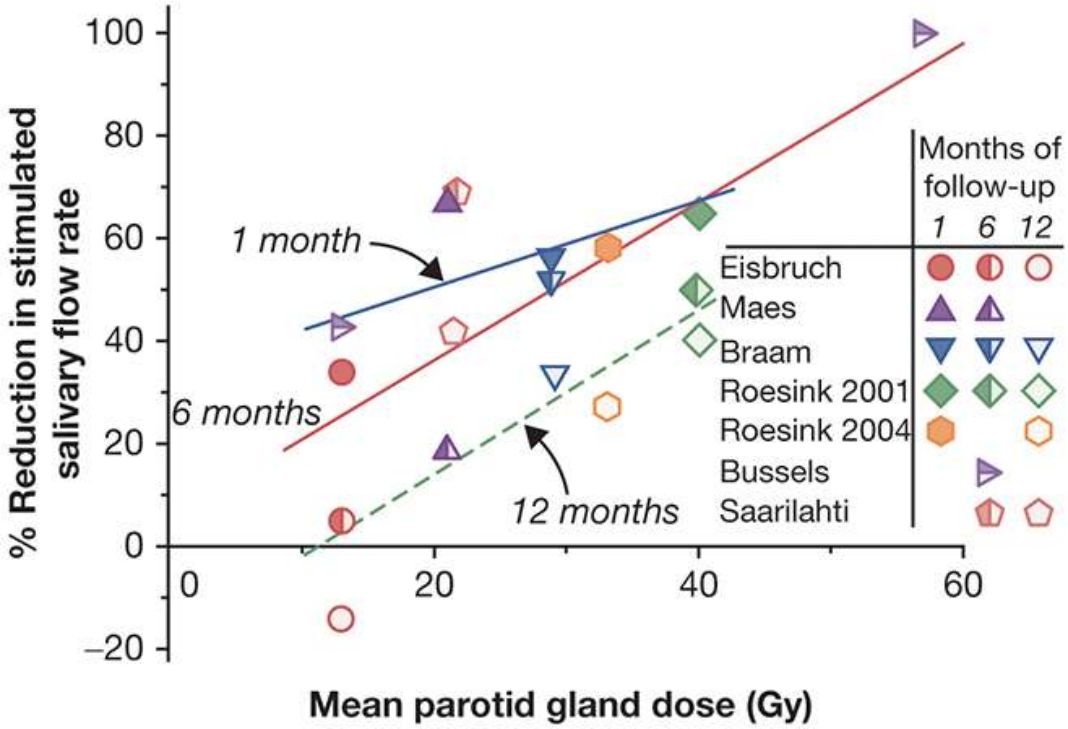

FIGURE 12.7 Mean percentage of reduction in stimulated salivary flow rate versus mean parotid gland dose for selected studies[269-274] using different follow-up durations. Nominal follow-up intervals of 1, 6, and 12 months represent ranges of 1 to 1.5, 6 to 7, and 12 months, respectively. *Lines* represent least-squares fit of data for each nominal follow-up interval. (Reprinted from Deasy JO, Moiseenko V, Marks L, Chao KS, Nam J, Eisbruch A. Radiotherapy dose-volume effects on salivary gland function. *Int J Radiat Oncol Biol Phys*. 2010;76[3 suppl]:S58-S63. Copyright © 2010 Elsevier. With permission.)

Factors Affecting Risk

Patient factors (eg, gender and age) and the use of chemotherapy have typically not correlated with xerostomia risk. However, pretreatment salivary function and medications affecting salivary function can influence the risk of xerostomia.[262]

Future Studies

Key questions on radiation-induced salivary gland dysfunction and xerostomia include the following:

1. Does partially sparing the submandibular glands or salivary minor glands have a positive impact on quality of life (QOL)?
2. Is the (arbitrary) 25% salivary threshold the best quantitative measure with respect to QOL?
3. Should parotid gland shrinkage during RT explicitly be accounted for in functional predictions?
4. How should submandibular sparing be incorporated into predictive salivary function models?
5. How does oral cavity sparing quantitatively affect xerostomia?

6. Does the radioprotector amifostine provide a clinically significant benefit for whole-mouth salivary function?
7. How does the use of lower tumor target doses (as are being increasingly suggested in patients with HPV-associated cancers) impact the dose/volume limits?[275]

Toxicity Scoring Criteria

The QUANTEC authors recommend that an observer-based system (eg, CTCAE v. 4.0) be supplemented by a validated quality of life instrument (eg, the xerostomia questionnaire[269]) and/or quantitative salivary measurements.

CHEST

Lung

Clinical Significance

The lung's primary function is the exchange of oxygen and carbon dioxide. Radiation-associated lung injury is one of the most common side effects seen in clinical oncology, and its risk sometimes limits the dose of radiation that can be used for the treatment of thoracic tumors.

End Points

Radiation damage to the lung can result in symptomatic pneumonitis and fibrosis. Symptomatic radiation pneumonitis is characterized by dyspnea, cough, and occasionally a low-grade fever, typically occurring several weeks to months after radiation. Long-term lung fibrosis can lead to respiratory insufficiency. It is often challenging to distinguish radiation-related pulmonary symptoms from comorbid illnesses (eg, exacerbation of the chronic obstructive pulmonary disease, infection, cardiac events).[276] Objective reductions in the lungs' ability to move and exchange gas can be measured by formal pulmonary function tests (PFTs). The various end points shown in Table 12.9 are segregated by their manifestation (clinical vs subclinical) and whether they reflect regional or global lung function.

TABLE 12.9 END POINTS FOR RADIATION-INDUCED LUNG INJURY

	Geographic Distribution	
Manifestation	**Regional**	**Global**
Clinical	Symptomatic bronchial stenosis	Respiratory symptoms (dyspnea, cough)
Subclinical	Radiologic abnormalities (eg, from computed tomography, perfusion/ventilation scans)	Pulmonary function tests, exercise testing results

The HyTEC study considered both radiation pneumonitis and radiation-induced pulmonary fibrosis in the setting of lung SBRT.[277] Acknowledging that a variety of endpoints were utilized, complicating comparison, the HyTEC study elected to focus on Grade 2+ toxicity, as this was similarly defined by RTOG, LENT-SOMA, and CTCAE criteria.[116,278,279]

Challenges Defining Volumes

Because the lungs move and their volume changes with respiration, there are inherent inaccuracies when defining the lung volume. As the mass of the lung is relatively constant during respiration and its density must decline with increased lung volumes, one could consider using dose-mass histograms rather than DVHs. To our knowledge, this approach has not been widely applied. Because of this variation in volumes with respiration, it is very likely that the dose/volume/outcome data are dependent on the type (if any) of respiratory control. The vast majority of dose/volume/outcome data are derived from free-breathing scans/treatment. These may not apply to patients being treated under, for example, breath hold techniques. Further, there are uncertainties in defining the lung borders in the vicinity of the central airways. Variable inclusion of the conducting airways in the "defined lung" can influence interpatient/institutional comparisons.

Summary of QUANTEC[280] and HyTEC[277]

Several parameters have been shown to be associated with the risk of radiation pneumonitis, including V_5 to V_{70}, mean lung dose (MLD), and model-based parameters.[10,281] These dosimetric parameters are mutually correlated, accounting for the fact that in most studies examining a range of V_x's, many appear statistically significant.[282-297] Figure 12.8 summarizes the studies discussed in the QUANTEC analysis.

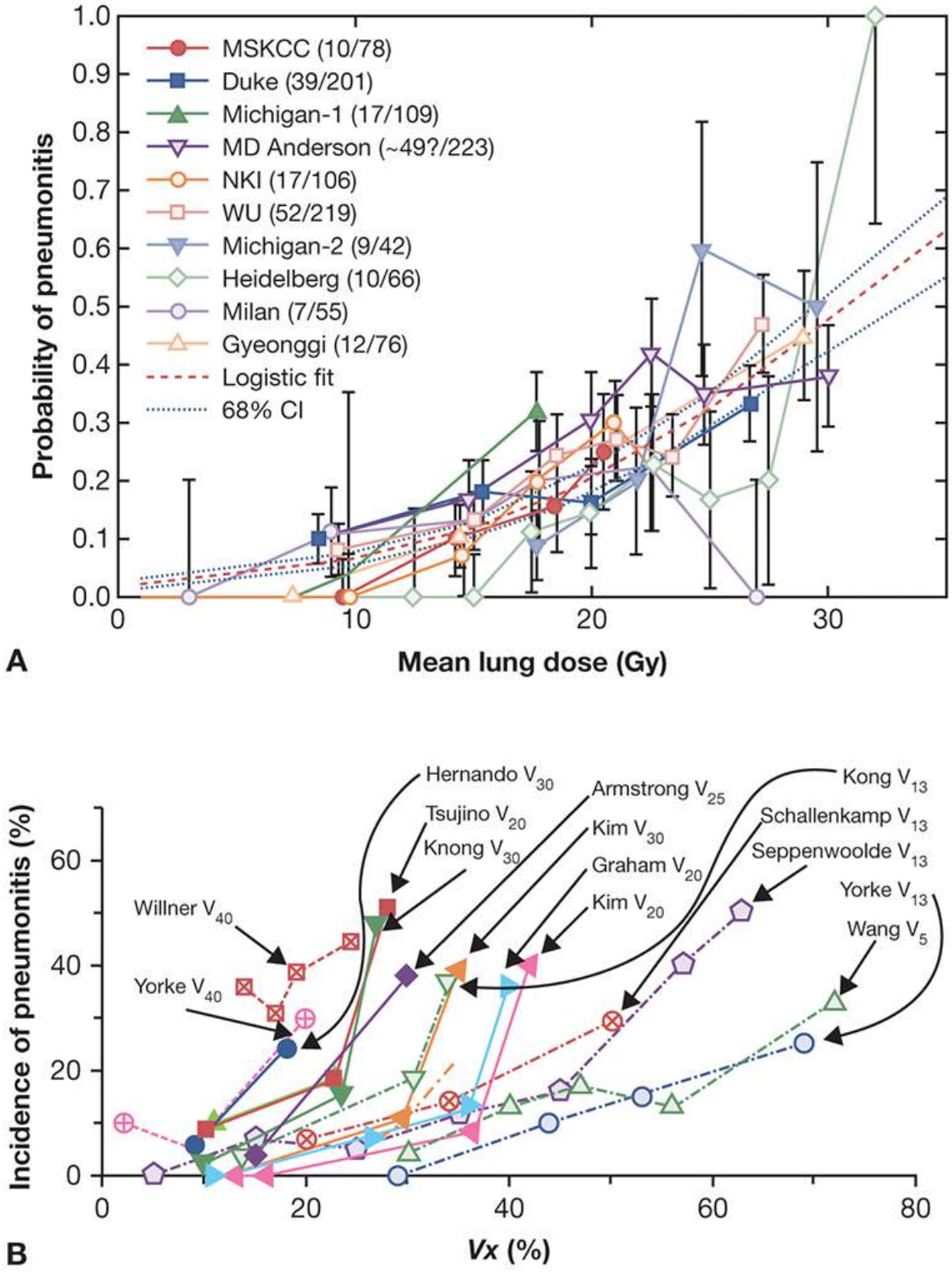

FIGURE 12.8 The rate of radiation pneumonitis after fractionated partial lung radiotherapy as a function of (A) mean lung dose (MLD) and (B) lung volume receiving *x* Gy (V_x). A. MLD: Confidence intervals (bars) represent ±

1 standard deviation. Results from Memorial Sloan-Kettering Cancer Center (MSKCC),[296] Radiation Therapy Oncology Group (RTOG) grade 3 or higher pulmonary toxicity at 6 months; Duke,[285] Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or higher at 6 months; Michigan,[298] Southwest Oncology Group (SWOG) grade 2 or higher at 6 months; MD Anderson Cancer Center,[293] CTCAE grade 3 or higher, 1 year actuarial—includes concurrent chemotherapy patients; Netherlands Cancer Institute (NKI),[299] SWOG grade 2 or higher at 6 months; Washington University (WU),[286] SWOG grade 2 or higher; Michigan,[300] SWOG grade 1 or higher; Heidelberg,[301] RTOG acute grade 1 or higher; Milan,[302] SWOG grade 2 or higher, no time limit, patients without chronic obstructive pulmonary disease, includes induction chemotherapy patients; Gyeonggi,[287] RTOG grade 3 or higher at 6 months, includes concurrent chemotherapy patients. Dashed line is the best fit of these data fit to the logistic expression of the form [*f*/(1 + *f*)], where *f* = exp(b0 + b1 × MLD). Best fit values (95% confidence intervals) are b0 >= −3.87 (−3.33, −4.49) and b1 = 0.126 (0.100, 0.153), corresponding to TD_{50} = 30.75 (28.7, 33.9) Gy and γ_{50} = 0.969 (0.833, 1.122), where γ_{50} represents the increase in response (measured as percentage) per 1% increase in dose around the 50% dose-response level. B. V_x: Data from Yorke et al,[296] Willner et al,[294] Hernando et al,[285] Tsujino et al,[303] Kong et al,[298] Armstrong et al,[304] Kim et al,[287] Graham et al,[281] Seppenwoolde et al,[291] Wang et al,[293] and Schallenkamp et al.[290] Some of the above data were modified or derived from the original publications, as described in Marks et al[280] (Reprinted from Marks LB, Bentzen SM, Deasy JO, et al. Radiation dose-volume effects in the lung. *Int J Radiat Oncol Biol Phys*. 2010;76[3 suppl]:S70-S76. Copyright © 2010 Elsevier. With permission.)

Several total dose escalation studies have used V_{20}, V_{eff}, and/or NTCP to stratify the risk of toxicity as a function of dose.[305-308] In the RTOG 9311 dose escalation study,[305] patients with a V_{20} of less than 25% experienced a 7% to 16% 18-month actuarial rate of grade 3 or higher late lung toxicity with prescribed doses of 70.9 to 90.3 Gy; the absolute risk of grade 2 or higher late lung toxicity was 30% to 45%, with one fatal lung complication at the 90.3-Gy dose level. Patients with a V_{20} of 25% to 36% treated to doses of 70.9 to 77.4 Gy experienced 15% grade 3 or higher late toxicity at 18 months and a 40% to 60% risk of grade 2 or higher late lung toxicity. D_{15} was the most predictive variable for radiation pneumonitis.[283]

SBRT generally involves a few large fractions (eg, three 18-Gy or five 10-Gy fractions) given over 5 to 14 days.[309,310] Typically, the high-dose volumes in SBRT are small, and dose gradients are steep, minimizing the dose to surrounding critical structures. Nonetheless, large volumes of lung receive low to medium doses.[310] Consequently, the dose-volume characteristics of lung SBRT are quite different from those of conventional RT and deserve special consideration.

The HyTEC study of RILT in SBRT[277] considered the findings in 97 papers. In the meta-analysis by Zhao et al,[311] total prescription dose was not significantly correlated with RILT. Although MLD was also not significantly correlated with RILT in that analysis, many of the individual studies identified an increased risk of RILT with elevated MLD.[312-320] The lack of correlation in the meta-analysis was attributed to interstudy variations (eg, in defining lung volumes as well as toxicity)[277]; this is a common phenomenon known as Simpson Paradox (discussed at the end of this chapter). Similarly, many[312,315,318,320-326] but not all[327-329] studies of RILT as a function of V_{20} or other lung volume receiving dose greater than the specified Gy suggested an association between higher V_{dose} and greater risk of RILT. The rate of RILT was low in most studies, making quantification of risk and correlation with dosimetric parameters difficult.

In the PENTEC study, 277 and 507 patients aged 0.04 to 22.7 years were evaluable for acute and late recursive partitioning (RP) analysis, respectively.[330] After partial lung RT, there were 0.4% acute and 2.8% late grade 2, 0.4% acute and 0.8% late grade 3, and no grade 4 to 5 RP. RP risk after partial thoracic RT with MLD less than 14 Gy and total lung V_{20Gy} less than 30% is low. Clinical and self-reported pulmonary outcomes data included 8,628 patients treated from 1970 to 2013, aged 0 to 21.9 years. At a median 2.9- to 21.9-year follow-up, patients were often asymptomatic; abnormal PFTs were common and severity correlated with lung dose. At greater than or equal to 10-year follow-up, multi-institutional studies suggested associations between total or ipsilateral lung doses greater than 10 Gy and pulmonary complications and deaths. After whole-lung irradiation (WLI), pulmonary toxicity may be higher; and no dose-response relationship was identified (though the dose ranges reported were fairly narrow). Bleomycin and other chemotherapeutics at current dose regimens do not contribute substantially to adverse pulmonary outcomes after partial lung irradiation but appear to increase risk with WLI.

Factors Affecting Risk

Recent meta-analyses have shown that patient-related adverse risk factors for radiation pneumonitis among patients with NSCLC[331-333] and patients with breast cancer[334] include older age,[332,333] history of chronic lung disease, or diabetes.[331] The impact of smoking on risk has been inconsistently reported in the literature. Smoking was noted to be an adverse risk factor in one meta-analysis[331] and a *protective* factor in others.[333] This discrepancy may be due to inaccuracies in how smoking history is collected and reported in the medical record and also due to the complex relationship between smoking, chronic lung disease, and pneumonitis.[331] Chemotherapy concurrent with RT, particularly carboplatin/paclitaxel chemotherapy,[332] has been reported to increase the pneumonitis risk.

The effect of dose to regions of the lung was investigated in a Dutch study,[299] dividing the lung into central and peripheral, ipsilateral and contralateral, caudal and cranial, and anterior and posterior subvolumes. The mean regional doses to the posterior, caudal, ipsilateral, central, and peripheral lung subvolumes were significantly correlated with the incidence of steroid-requiring radiation pneumonitis. In a similar study from MSKCC, the risk of radiation pneumonitis was better correlated with the radiation dose to the inferior, as opposed to the superior, aspect of the lung.[297]

Tumor location within the chest may also be a factor affecting the risk of pneumonitis. In the study from Washington University,[286] inferior tumor location was the most significant predictor of radiation pneumonitis. Tumor location was not a strong correlate with radiation pneumonitis in RTOG 9311, perhaps attributable, in part, to differences in treatment (with RTOG 9311 treating smaller volumes to higher doses) and differences in tumor size and location (the RTOG 9311 tumors tended to be smaller and more superiorly located).[283] Using a combined dataset of patients from RTOG 9311 and Washington University, tumor location and MLD were significant predictors of toxicity.

The HyTEC study of RILT post-SBRT highlights the substantially higher rates of radiation pneumonitis reported in patients with interstitial lung disease (ILD).[277,312,320,335,336] For example, in a study of 404 patients treated with lung SBRT, Bahig et al[312] found the rate of G3+ RP was 3.8% for the entire cohort versus 32.1% in the 28-patient subset with ILD. However, a recent

prospective study of patients with ILD treated with SBRT reports much lower rates of toxicity.[322]

Special Situations

IMRT provides unique dose distributions for some patients with advanced-stage non–small cell lung cancer,[337] potentially reducing the risk of normal tissue injury. In a retrospective review of patients treated with lung cancer and concurrent chemotherapy at MD Anderson Cancer Center (MDACC), the rates of grade greater than or equal to 3 pneumonitis following IMRT versus 3D planning were ≈ 8% versus 25% (P = .017), respectively.[338] Similarly, a study from MSKCC found a low rate of clinical lung injury in patients with non–small cell cancer treated with IMRT.[339] Furthermore, a secondary analysis of RTOG 0617 noted lower rates of RP in the patients treated with IMRT versus 3D.[340]

In a study from Dana-Farber,[341] in which patients received thoracic IMRT after pneumonectomy for mesothelioma, 6 of 13 patients developed fatal pneumonitis. The median V_{20}, V_5, and MLD for patients who developed pneumonitis were 17.6%, 98.6%, and 15.2 Gy, respectively, versus 10.9%, 90%, and 12.9 Gy for those who did not develop pneumonitis. Although these differences were not significant, the severity of the toxicities suggests caution in treating patients with large volumes after a pneumonectomy. In a study from Duke,[342] 1 of 13 patients treated with IMRT for mesothelioma died from pneumonitis, and two others developed symptomatic pneumonitis. The median V_{20}, V_5, and MLD for patients developing pneumonitis were 2.3%, 92%, and 7.9 Gy, respectively, versus 0.2%, 66%, and 7.5 Gy for those who did not develop pneumonitis and 6.9%, 92%, and 11.4 Gy for the patient who developed fatal pneumonitis. In a study of patients with mesothelioma treated at MDACC with IMRT,[343] 6 of 63 died from pulmonary-related causes (including two patients with fatal pneumonitis). The V_{20} was significant in univariate and multivariate analyses (P = .017), with V_{20} greater than 7% corresponding to a markedly increased risk of pulmonary death. Lower rates of pulmonary death were seen in patients with absolute lung volumes receiving less than or equal to 10 Gy of greater than 1,200 cm^3, and absolute lung volumes receiving less than or equal to 5 Gy of greater than 300 cm^3.[325]

Radiation pneumonitis is relatively uncommon after SBRT, usually less than 10%[344-346] but as high as 25% in one study.[347] Bronchial injury/stenosis, an unusual complication with conventional dose fractionation,[348] has been associated with SBRT to perihilar/central tumors.[345] The NRG/RTOG dose escalation study (0813) has suggested that a five-fraction SBRT regimen might be associated with a clinically acceptable toxicity rate.[349]

Recommended Dose-Volume Limits

Individual studies note a dose-response relationship for radiation pneumonitis based on a variety of metrics. However, the QUANTEC analysis[280] of the pooled data shows that there is no specific threshold for pneumonitis, with risks increasing gradually as the dose increases. Because many dose-volume parameters of the lung (ie, V_5 through V_{30}, MLD) are correlated with each other, there likely is not an "optimal" parameter. For patients with non–small cell lung cancer, it is prudent to limit the V_{20} to less than 30% to 35%, and the MLD to less than 20 to 23 Gy, in order to reduce the risk of pneumonitis to less than 20%. In patients irradiated

after pneumonectomy for mesothelioma, it is prudent to limit the V_5 to below 60%, V_{20} to less than 4% to 10%, and the MLD to less than 8 Gy.

For SBRT, the HyTEC study notes that there was no apparent threshold "tolerance dose-volume" level. However, they observed that most studies reported safe treatment with a rate of symptomatic RILT of less than 10 to 15% after lung SBRT for an MLD to the combined lungs of less than 8 Gy in three to five fractions and the percentage of total lung volume receiving more than 20 Gy (V_{20}) less than 10% to 15%.

Future Studies

Radiation-induced pneumonitis appears more commonly in patients with lower versus upper lobe tumors and may be better correlated with radiation doses to the lower versus upper lung. The cause of this correlation is presently unknown and requires further investigation, though it may be related to heart irradiation. Additional work is needed to better understand the impact of clinical factors (eg, preradiotherapy functional status, ILD, and tobacco use) and systemic agents (particularly immunotherapy) on the risk of lung injury. The biologic underpinnings to explain the possible protective effect of smoking on risk need to be further refined. Studies aimed at determining and exploiting the ability of biomarkers such as TGF-β (measured before and/or during lung radiotherapy) on radiation pneumonitis would be valuable. Studies are needed to better understand how best to apply hypofractionation for centrally located lesions.

Toxicity Scoring Criteria

The QUANTEC study recommended that the LENT-SOMA system[278] be used for scoring toxicity, as it explicitly captures symptomatic, functional, and radiographic end points. A global score can be generated, but the granular data should be recorded and maintained. The HyTEC paper[277] preferred the RTOG system[279] but considered the RTOG, LENT-SOMA, and CTCAE criteria in its analysis.

Heart

Clinical Significance

The heart is a muscular organ typically located in the left hemithorax, which, via continuous rhythmic contraction, pumps blood throughout the blood vessels. The functional and structural complexity of the heart places it at risk for a spectrum of radiation and chemotherapy injuries that can manifest months to years following therapy.[350]

End Points

All components of the heart and pericardium are susceptible to radiation damage. Radiation-induced cardiac injury includes pericarditis, congestive heart failure, restrictive cardiomyopathy, valvular insufficiency and stenosis, coronary artery disease, ischemia, and infarction.

Challenges Defining Volumes

The substructures of the heart, as well as the intersection/border of the heart, great vessels, liver, diaphragm, and stomach, can be challenging to delineate on CT imaging. The heart moves during the respiratory and cardiac cycles, with different regions moving to different degrees. The uncertainties that accompany these anatomic/physiologic realities must be considered when contouring targets and normal tissue structures and when interpreting DVHs.

Dose/Volume/Toxicity Data

Multiple studies show an increased risk of cardiac morbidity following left-sided versus right-sided thoracic radiation in patients undergoing treatment for breast cancer. It is generally recognized that reducing the dose prescribed to the mediastinum and reducing the volume of the heart in the radiation field reduce the risk of late toxicity. Studies from Duke demonstrated that an increased percentage of the left ventricle irradiated correlates[351-353] with a greater risk of subsequent cardiac perfusion defects.[354-356] Even over the range of low-dose exposure (~8-20 Gy) to small volumes of the cardiac apex, an increased risk of heart disease has been reported.[357]

A study from Stockholm used NTCP modeling to predict the risk of late heart toxicity in women treated for breast cancer.[358] The models predicted a TD_{50} of 52 Gy for the dose to the myocardium. A 5% risk of excess cardiac mortality at 15 years was associated with a myocardial dose of approximately 30 Gy, V_{33} greater than 60%, V_{38} greater than 33%, *or* V_{42} greater than 20%. Calculations using the whole-heart volume (as opposed to myocardium) yielded equivalent results.

The same group from Stockholm used a similar analysis to assess cardiac risk in patients with Hodgkin disease.[359] Patients were stratified based on a V_{38} greater than 35% versus less than 35%. The excess mortality risk at 15 years was 7.9% and 4.7%, respectively. The TD_{50} was calculated to be 70 Gy. Heart doses of 42 and 53 Gy resulted in a 5% and 10% risk of cardiac complications, respectively. The corresponding values in the patients with breast cancer were 37 and 44 Gy, respectively (lower threshold doses and steeper gradient). The differences in complication probabilities and TD_{50} between the breast cancer and Hodgkin disease cohorts (Figure 12.9) suggest that radiation exposure to different portions of the heart results in differences in cardiac risk, though there may be other confounding variables (ie, patient age at treatment, overlapping breast cancer, cardiac disease risk factors, etc).

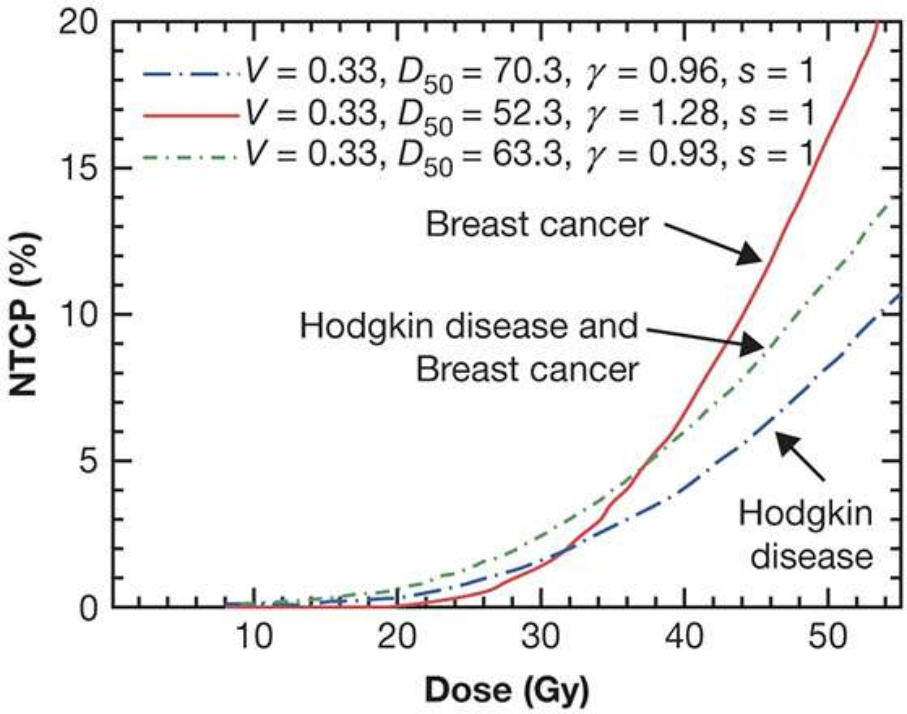

FIGURE 12.9 Dose-response curves for long-term cardiac mortality in patients with Hodgkin disease (HD) and breast cancer treated with thoracic radiotherapy. NTCP = normal tissue complication probability, defined in that study as the excessive risk of ischemic heart disease. *Curves* were obtained by fitting data from breast cancer trials, a cohort of patients with Hodgkin disease, and the combined dataset. *Plotted curves* correspond to uniform irradiation of one-third of the heart volume. (Reprinted from Eriksson F, Gagliardi G, Liedberg A, et al. Long-term cardiac mortality following radiation therapy for Hodgkin's disease: analysis with the relative seriality model. *Radiother Oncol*. 2000;55[2]:153-162. Copyright © 2000 Elsevier Science Ireland Ltd. With permission.)

A study from MDACC described the risk of pericardial effusions in patients treated for esophageal cancer.[360] A mean dose greater than 26 Gy and relative volumes of the pericardium treated at doses greater than 3 to 50 Gy (V_3-V_{50}) showed the greatest risk, with the association strongest at V_{30}. For V_{30} less than 46% versus greater than 46%, the rate of pericardial effusion was 73% versus 13% (P = .001) 18 months postradiation. For a mean pericardium dose less than 26 versus greater than 26 Gy, the rate of pericardial effusion was 73% versus 13% (P = .001). A study from the University of Michigan[361] also demonstrated that a mean dose greater than 27 Gy and a maximum dose of 47 Gy correlated with the risk of pericardial effusion. However, only patients treated with 3.5-Gy fractions developed pericardial effusions.

The incidence of valvular disease has been related to mediastinal radiation doses greater than 30 Gy and younger age at irradiation.[362] Subclinical valvular disease has been detected at 2 to 20+ years postradiation, but it appears to take much longer for clinical symptoms to become apparent (median interval 22 years from radiation to symptoms). For patients treated for Hodgkin lymphoma more than 10 years prior with radiation, aortic disease, usually consisting of mixed stenosis and regurgitation, is more common than mitral and right-sided valvular disease.[362,363]

Studies have demonstrated a clear dose response for RT-associated heart injury. For example, in an analysis of 112 patients irradiated to 70 to 90 Gy for lung cancer, the 2-year

competing risk–adjusted cardiac event rates for patients with heart mean doses of less than 10 Gy, 10 to 20 Gy, or greater than 20 Gy were 4%, 7%, and 21%, respectively.[364] Similarly, distinct types of cardiac disease have been associated with doses to specific subvolumes of the heart.[365]

Factors Affecting Risk and Special Situations

Anthracycline chemotherapy can exacerbate radiation-related cardiac toxicity. In patients with Hodgkin disease, radiation exposure, in conjunction with anthracyclines, may impair ejection fraction and increase the risk of myocardial infarction, congestive heart failure, and valvular disorders. A Dutch study[366] of 1,474 Hodgkin lymphoma survivors showed that risks of myocardial infarction and congestive heart failure were significantly increased, with standard incidence ratios of 3.6 and 4.9, respectively, for these survivors versus the general population. Mediastinal radiation alone increases the risks of myocardial infarction, angina pectoris, congestive heart failure, and valvular disorders (2- to 7-fold). The addition of anthracyclines further elevated the risks of congestive heart failure and valvular disorders, with hazard ratios of 2.81 and 2.10, respectively. The 25-year cumulative incidence of congestive heart failure following combined radiation and anthracycline chemotherapy was 7.9%.

Other risk factors for cardiac disease, particularly coronary artery disease, also must be considered. For example, a University of Rochester study[367] assessed the risk of coronary artery disease in survivors of Hodgkin lymphoma and also the prevalence of cardiac risk factors. The relative risk of cardiac death was 3.1 for males versus 1.8 for females. Other risk factors were more common than in the general population; among patients with Hodgkin lymphoma experiencing morbid cardiac events, 72% smoked, 72% were male, 78% had hypercholesterolemia, 61% were obese, 28% had a positive family history, 33% had hypertension, and 6% had diabetes.

Evolving data from patients irradiated for breast or lung cancer suggest that RT-associated cardiac injury may occur earlier than previously believed (ie, within a few years of RT).[340,364,368,369] For example, in patients with non–small cell lung cancer prescribed to receive greater than 70 Gy, the mean heart dose and preexisting cardiac disease have been implicated as predictors for cardiac injury[340]; the 2-year competing risk–adjusted cardiac event rates for patients with heart mean doses less than 10 Gy, 10 to 20 Gy, or greater than or equal to 20 Gy were 4%, 7%, and 21%, respectively.

For children, PENTEC found that for each 10-Gy increase in corrected mean cardiac radiation dose in 1.8-to 2.0-Gy fractions, the estimated hazard ratio was 2.01 (95% confidence interval [CI], 1.79-2.25) for coronary artery disease, 1.87 (95% CI, 1.70-2.06) for heart failure (HF), 1.87 (95% CI, 1.78-1.96) for valvular disease, and 1.88 (95% CI, 1.75-2.03) for any cardiac disease.[370] From the same model, for each 100-mg/m^2 increase in cumulative anthracycline dose, the hazard ratio for the development of HF was 1.93 (95% CI, 1.58-2.36), equivalent to an increase in mean heart dose of approximately 10.5 Gy. Other nontreatment factors were inconsistently reported in the analyzed articles.

Mathematic/Biologic Models

There are no well-accepted models for cardiac toxicities. Nevertheless, several authors have computed model parameters for various cardiac end points, as summarized in the QUANTEC

review.[350]

Recommended Dose-Volume Limits

A heart V_{30} to V_{40} of approximately 30% to 35% is associated with an approximately 5% excess risk of cardiac death at approximately 15 years. A heart V_{30} of greater than 45% and a mean cardiac dose of greater than 26 Gy are associated with a higher risk of pericarditis. In patients with breast and lung cancer, it is recommended that the irradiated heart volume be minimized as much as possible without compromising target coverage. In patients with lymphoma, the whole heart should be limited to 30 Gy if treated with radiation alone and to 15 Gy for patients also receiving anthracycline chemotherapy. Although there is no direct evidence that eliminating traditional cardiac risk factors alters the natural history of radiation-associated cardiac disease, it seems prudent to minimize such factors.[350,371,372]

Future Studies

Issues that would benefit from further systematic study are the effects of radiation on *specific subvolumes* of the heart, the impact of modern radiotherapy techniques on cardiac toxicity, the relationship between heart irradiation and baseline cardiovascular risk factors on the development of cardiac disease, the effect of hypofractionation encountered in thoracic SBRT, and the global physiologic effects of thoracic radiotherapy (eg, interactions between simultaneous heart and lung irradiation).[350]

Toxicity Scoring Criteria

The QUANTEC authors recommend that the LENT-SOMA system[118,373] be considered to describe cardiac toxicity, as it explicitly includes clinical, radiologic, and functional assessments of cardiac dysfunction.

Esophagus

Clinical Significance

Acute esophagitis is very common and often severe in patients receiving radiation for intrathoracic malignancies (eg, primary lung cancer and esophageal cancer). Patients with severe esophagitis may require a feeding tube and/or treatment interruptions.

End Points

Because most patients with thoracic cancers have a poor prognosis, acute toxicity may be considered more clinically relevant than late injury. Late esophageal complications include dysphagia, stricture, dysmotility, odynophagia, and rarely necrosis or fistula.

Challenges Defining Volumes

The esophagus can be challenging to visualize on axial imaging, and the use of dilute oral contrast can assist in its identification. Also, the esophagus often has folds such that its external contour as seen on an axial image may not accurately represent its true circumference. Indeed, in CT imaging, the circumference of the esophagus appears highly

variable on different axial levels, when in fact the esophagus has a relatively uniform circumference. One study has suggested that the dosimetric parameters that apply this prior anatomic knowledge are better predictors of acute and late esophageal injury than are traditional dosimetric parameters.[374]

Dose/Volume/Toxicity Data

A variety of dose-volume parameters have been associated with the incidence of esophagitis.[360,375-412] Although a continuous dose-response curve for acute esophagitis is observed based on a range of dosimetric parameters, as shown in Figure 12.10, there is no consensus as to the optimal dosimetric predictors of esophageal injury.

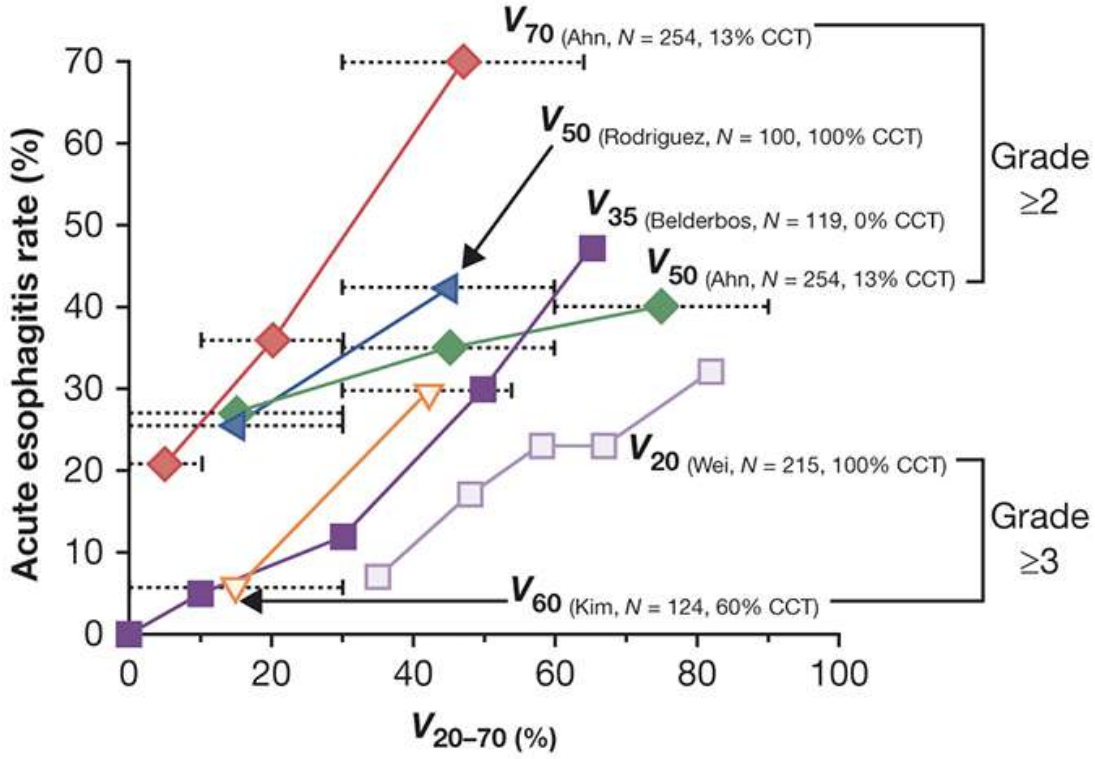

FIGURE 12.10 Incidence of acute esophagitis according to V_x (volume receiving more than x Gy) for selected studies. X-axis values estimated from the range of doses reported. Datasets annotated as follows: V_{dose} (investigator, number of patients, percentage with concurrent chemotherapy [CCT]). (Reprinted from Werner-Wasik M, Yorke E, Deasy J, Nam J, Marks LB. Radiation dose-volume effects in the esophagus. *Int J Radiat Oncol Biol Phys*. 2010;76[3 suppl]:S86-S93. Copyright © 2010 Elsevier. With permission.)

In a series from Washington University, grade 3 to 5 esophageal toxicity (acute and late) was associated with a maximal dose (D_{max}) of greater than 58 Gy, a mean dose of greater than 34 Gy, and the administration of concurrent chemotherapy.[407] The V_{55} was not significant. A study from China reported that a maximal dose greater than 60 Gy, as well as the use of concurrent chemotherapy, was a significant factor for esophageal toxicity (acute and late).[402] In a study from Duke, V_{50}, the surface dose receiving greater than or equal to 50 Gy (S_{50}), the length of esophagus receiving greater than 50 to 60 Gy, and a circumferential D_{max} greater

than 80 Gy were significant predictors of late esophageal toxicity.[396] A V_{50} greater than 32% or an S_{50} greater than 32% resulted in crude rates of approximately 30% late esophageal toxicity versus 7% below these thresholds. With greater than 3.2 cm of the esophagus receiving greater than 50 Gy, late toxicity occurred in approximately 30%, versus 4% in those with less than 3.2 cm receiving greater than 50 Gy ($P = .008$).

In another study from Duke, grade 1 or higher late toxicity was correlated with several dose parameters: the entire circumference receiving greater than or equal to 50 and greater than or equal to 55 Gy; 75% of the circumference receiving greater than or equal to 70 Gy; and the maximal percentage of circumference receiving greater than or equal to 60 to 80 Gy.[375] The rate of grade 1 or higher late toxicity was approximately 5% in patients with a V_{50} to V_{70} of 0% to 30% versus approximately 25% in those with a V_{70} of 31% to 64% and approximately 10% in those with a V_{50} greater than 60% (nonsignificant). Acute esophageal toxicity was the greatest predictor of late toxicity. In two studies, most of the patients who developed late grade 3 or higher toxicity had developed acute grade 3 or higher toxicity, though roughly 25% to 40% of patients who developed grade 3 or higher late toxicity had only grade 0 to 2 acute esophageal toxicity.[402,407]

A 2013 meta-analysis (published after QUANTEC) of 1,082 patients with NSCLC treated with chemoradiation analyzed esophageal V_5 to V_{70} parameters (in 5-Gy increments); all significant predictors of grade greater than or equal to 2 esophagitis and on multivariate analyses, V_{60} proved to be the most significant predictor of grade greater than or equal to 2 to 3 esophagitis.[413] Recursive partitioning identified three risk groups: low (29% and 4% risk of grade ≥2 and ≥3 esophagitis with $V_{60} < 0.07\%$), intermediate (41% and 10% risk of grade ≥2 and ≥3 esophagitis with V_{60} 0.07% to 17%), and high (59% and 22% risk of grade ≥2 and ≥3 esophagitis with $V_{60} \geq 17\%$).

Factors Affecting Risk

Greater rates of acute esophagitis have been observed with more aggressive radiotherapy regimens (eg, hyperfractionation, concurrent boost), the addition of concurrent chemotherapy, increasing age, and several other clinical factors (eg, preexisting dysphagia, increasing nodal stage). The incidence of grade 3 or higher acute esophagitis is approximately 1% for patients treated with once-daily radiotherapy alone versus as high as 49% with concurrent gemcitabine. Several studies have assessed the putative radioprotector amifostine. Three single-institution phase III studies suggested a benefit of amifostine in reducing the rate of grade 2 or higher esophagitis, but this result was not confirmed in a large cooperative group phase III randomized trial (RTOG trial 9801).[376,391,394,398]

Mathematic/Biologic Models

Using data on grade 2 or higher acute esophagitis, two studies obtained relatively consistent estimates of Lyman- Kutcher-Burman model parameters, including TD_{50} of 47 to 51 Gy.[8,378] Note that these parameters differ significantly from those derived from the Emami data,[5] which examined a more clinically severe end point (stricture and perforation).

Special Situations

Esophageal toxicity data for hypofractionated treatments in SBRT to central thoracic lesions are quite limited,[399] and long-term data in this and other altered fractionation settings (eg, accelerated fraction and concomitant boosts) have not been comprehensively reported.[410]

Recommended Dose-Volume Limits

Given the available data, there are no strict dose-volume limits for the esophagus. Several parameters are associated with the risk of adverse events, and clinicians can apply these data as seem reasonable for the clinical situation. Unfortunately, the anatomic reality for many patients with locally advanced non–small cell lung cancer is that the PTV (and certainly the GTV) is often immediately adjacent to the esophagus, and thus, it is not possible to limit the doses as desired without compromising the target coverage. The ongoing phase III intergroup trial, RTOG 0617, has recommended (but has not mandated) that the mean dose to the esophagus be kept to less than 34 Gy.

Future Studies

IMRT may provide increased flexibility in sparing the esophagus during lung irradiation,[414] and outcome as a function of dose-volume should be systematically studied for this treatment technique. As in other organ systems, detailed outcome and dosimetric data should be reported, based on clearly defined methods of contouring the target and organs at risk.

Toxicity Scoring Criteria

Esophageal toxicities should be scored using the CTCAE v. 4.0.[116]

ABDOMEN/PELVIS

Liver

Clinical Significance

The liver is a vital organ, involved in the metabolism of ingested nutrients, detoxification, protein synthesis, bile production, glycogen storage, and red blood cell decomposition. The liver may be incidentally irradiated during RT of abdominal or thoracic tumors and will be irradiated in patients undergoing partial hepatic radiation for liver metastases or hepatocellular carcinoma. There is no effective treatment to reverse the process of radiation-induced liver disease (RILD); therefore, prophylaxis and prevention are best. Anticoagulants, paracentesis, and diuretics can be used to mitigate symptoms, whereas liver transplantation is required for frank radiation hepatopathy.

End Points

RILD generally presents as vague to intense right upper abdominal pain followed by abdominal swelling because of hepatomegaly and ascites, resulting in weight gain. Anicteric ascites often develops 2 to 4 months after irradiation; chemoradiation-induced liver disease may occur more rapidly (eg, 1-4 weeks post RT in a bone marrow transplantation setting).

Other sequelae of RILD include elevation of liver enzymes, jaundice, asterixis (tremor), encephalopathy, or coma.

The basic pathophysiologic sequelae of classic RILD is central vein thrombosis at the lobular level, which results in retrograde congestion leading to hemorrhage and secondary alterations in surrounding hepatocytes. This often occurs between 2 weeks and 3 months after therapy. Severe acute hepatic changes often progress to fibrosis or cirrhosis and liver failure.

Nonclassic RILD implies dramatic elevations of liver transaminases (>5 times the upper limit) or a decline in liver function in the absence of classic RILD. The underlying pathology of nonclassic RILD is unclear.[401]

Challenges Defining Volumes

The liver parenchyma is composed of innumerable, redundant, parallel functional subunits, which allows the liver to potentially tolerate focal injury without clinical sequelae if adequate normal liver parenchyma can be spared. The liver is readily identified on CT and MRI. For radiation planning, it must be recognized that the liver moves with the respiratory cycle.[401]

Summary of QUANTEC, HyTEC, and PENTEC

The QUANTEC report on RILD (described as "anicteric hepatomegaly and ascites") summarized data from six studies that described risks of RILD from conventionally fractionated partial liver irradiation (Table 12.10; Figure 12.11), though these data were not amenable to pooling and NTCP modeling.[401] From their data summary, the authors predicted risks of RILD of less than 5% and less than 50% with mean doses less than 30 to 32 Gy and less than 42 Gy, respectively, in patients without preexisting liver disease or hepatocellular carcinoma (for whom risks are higher). Among those with preexisting Child-Pugh A liver disease or hepatocellular carcinoma, mean doses of less than 28 and less than 36 Gy, respectively, were associated with less than 5% and less than 50% risks. For patients undergoing palliative whole-liver radiotherapy, approximately 10% of risks of RILD occur with 33 Gy in 1.5-Gy fractions.

TABLE 12.10 RADIATION-INDUCED LIVER DISEASE IN PARTIAL LIVER IRRADIATION

Reference	*n*/% C-P A	Diagnosis	Dose Fractionation	Crude Rate of RILD	Mean Normal Liver Dose in Patients With vs Without RILD
Michigan[383,386]	203/100%	PLC + LMC	1.5 Gy bid	9%	37 vs 31.3 Gy
Taipei[381]	89/76%	HCC	1.8-3 Gy qd	19%	23 vs 19 Gy
Shanghai[395,412]	109/85%	PLC	4-6 Gy qd	16%	24.9 vs 19.9 Gy
Guangdong[411]	94/46%	HCC	4-8 Gy qd	17%	Not stated
S. Korea (Seong et al)[406]	158/74%	HCC	1.8 Gy qd	7%	Not stated
S. Korea (Kim et al)[390]	105/81%	HCC	2.0 Gy qd	12%	25.4 vs 19.1 Gy

% C-P A, percentage of patients with baseline Child-Pugh A score (in all studies, patients were either A or B); bid, twice-daily treatment; HCC, hepatocellular carcinoma; LMC, metastatic disease to the liver; PLC, primary liver

cancer; qd, once-daily treatment; RILD, radiation-induced liver disease.
After Pan CC, Kavanagh BD, Dawson LA, et al. Radiation-associated liver injury. *Int J Radiat Oncol Biol Phys*. 2010;76(3 suppl):S94-S100. Copyright © 2010 Elsevier. With permission.

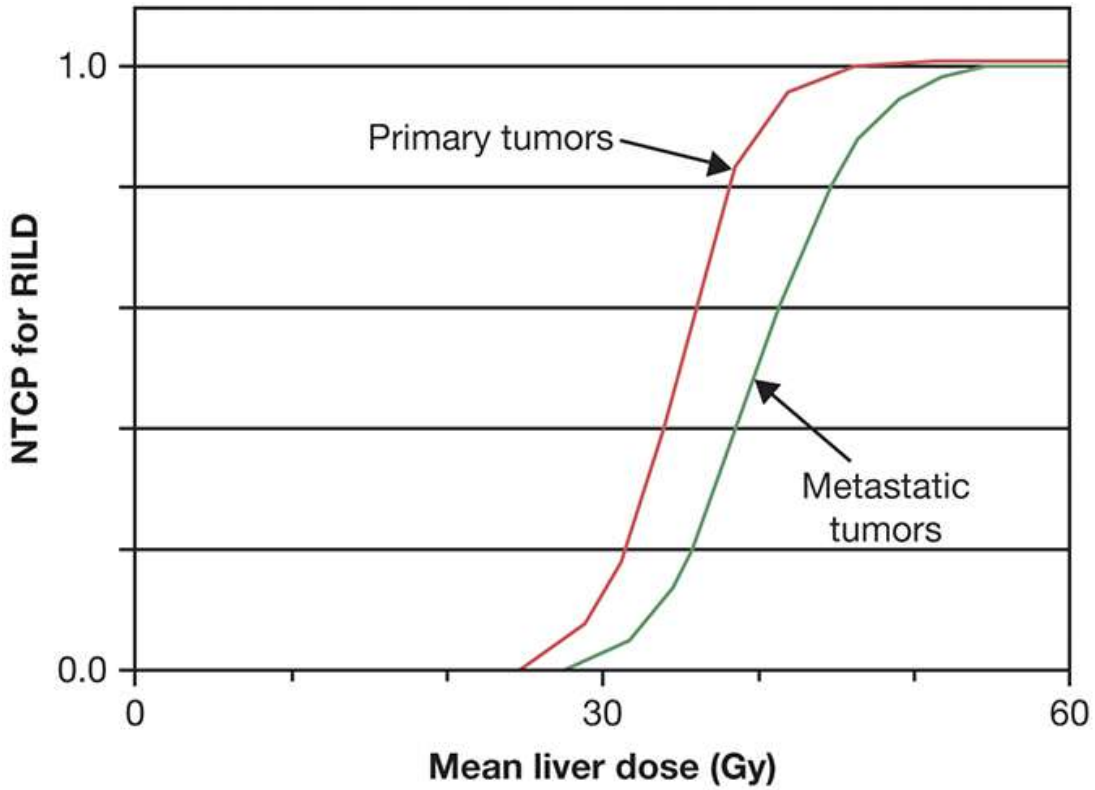

FIGURE 12.11 Mean liver dose, corrected with linear-quadratic modeling for 2-Gy fractions versus Lyman normal tissue complication probability (NTCP) of classic radiation-induced liver disease (RILD) for primary and metastatic liver cancer. (Reprinted from Pan CC, Kavanagh BD, Dawson LA, et al. Radiation-associated liver injury. *Int J Radiat Oncol Biol Phys*. 2010;76[3 suppl]:S94-S100. Copyright © 2010 Elsevier. With permission.)

The HyTEC report[415] summarized data from 12 studies to generate separate NTCP models for grade 3 liver enzyme toxicity as a function of physical mean dose (n = 5 studies), and grade greater than or equal to 2 (n = 7 studies) or grade greater than or equal to 3 (n = 8 studies) general gastrointestinal (GI) toxicity as a function of prescription dose in three to six fractions. From the NTCP models, approximately 5% of risks of grade 3 liver enzyme toxicity were associated with mean liver doses of approximately 12 Gy. For grade greater than or equal to 2 GI toxicity, 20% risks were associated with prescribed doses of approximately 27 Gy, and for grade greater than or equal to 3 GI toxicity, 10% risks were associated with prescribed doses of approximately 50 Gy. Based on published reports, the authors predicted less than 13% risks of liver dysfunction and grade 3 to 5 general GI toxicity with greater than or equal to 700 mL of liver (minus GTVs) receiving less than or equal to 15 to 17 Gy; these data were not amenable to modeling though.

The PENTEC group developed a model to calculate the risk of developing sinusoidal obstructive syndrome (SOS) after whole-liver RT.[416] RT dose (P = .006) and receipt of nonalkylating chemotherapy (P = .01) were significant. Age less than 20 years at the time of

RT was borderline significant (P = .058). The model predicted a 2% risk of SOS with zero RT dose, 6.1% following 10 Gy, and 14.5% following 20 Gy to the whole liver (modeled as the linear-quadratic equivalent dose in 2-Gy fractions [a/b = 3 Gy]). Patients with Wilms tumor treated with right flank RT had a higher observed rate of SOS than patients receiving left flank RT, but data were insufficient to generate an NTCP model for partial liver irradiation. Data were sparse regarding rates of late liver injury after RT, which suggests low rates of severe toxicity after treatment for common pediatric malignancies.

Factors Affecting Risk

A wide variety of systemic agents have been reported to elevate liver enzymes: nitrosoureas (BCNU), methotrexate, and some combinations of chemotherapy agents such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and proMace-MOPP (prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide, and MOPP [mechlorethamine, vincristine (Oncovin), procarbazine, and prednisone]). In bone marrow transplantation, preparatory regimens can be toxic. Underlying liver disease and hepatobiliary carcinoma (as opposed to liver-metastatic disease) were described in the QUANTEC and HyTEC reports as added risk factors.

Recommended Dose-Volume Limits

For patients with liver metastases undergoing partial volume liver radiation, the risk of radiation-induced liver toxicity appears to be more dependent on the volume of liver irradiated. Partial volumes of the liver can tolerate relatively high doses. Liver tolerances, however, are lower for patients with primary liver cancer (who are more apt to have underlying liver disease). For whole-liver radiation, doses less than or equal to 28 to 30 Gy in 2-Gy fractions (28 Gy for liver metastases and 30 Gy for primary liver cancer) and less than or equal to 21 Gy in 3-Gy fractions are recommended. For partial liver radiation, treated with standard fractionation, the mean dose to normal liver (liver minus GTV) is suggested to be less than 30 Gy for liver metastases and less than 28 Gy for primary liver cancer.

Future Studies

Studies that better correlate dose-volume parameters with long-term clinical/objective outcomes are needed. The impact of treatment-related (including fractional dose and systemic therapies) and host-related variables should be better defined.

Toxicity Scoring Criteria

The CTCAE v. 3.0 grades hepatobiliary toxicity according to clinical criteria of jaundice, asterixis, and encephalopathy or coma for grades 2, 3, and 4, respectively. The much more commonly occurring alteration in liver enzymes, in the absence of symptomatic manifestations, is classified under the CTCAE metabolic/laboratory category of elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The use of CTCAE criteria for elevations of AST and ALT and other metabolic effects is advisable to promote consistency of reporting.

Small Bowel/Stomach

Clinical Significance

The stomach and small bowel aid in the digestion and absorption of food and nutrients. Symptoms from radiation-related late toxicities include dyspepsia, gastric ulceration, diarrhea, bowel obstruction, and ulceration, fistula, or perforation.[387]

End Points

Nausea and vomiting can occur immediately or within hours after RT to the stomach or small bowel. The radiosensitivity of the gastric mucosa is reflected in the early depression of hydrochloric acid and pepsin secretion after modest radiation doses of 15 to 20 Gy. Although some recovery of cellular structure occurs, suppression can continue for 6 months to many years after irradiation. Usually, at total doses at or above 50 Gy, cellular and functional recovery is never complete. Ulcers are the most common complication of gastric irradiation and present clinically with dyspepsia, significant pain, and sometimes hemorrhage. An ulcer in this anatomic setting can lead to hemorrhage and perforation, which, although rare, can be fatal. Ulcerations have been described as typically antral, perhaps because of the placement of RT fields, and develop as early as 2 to 12 months after treatment. Pyloric obstruction may be a late development because of fibrosis after ulcer healing.

The early onset of malabsorption of fat and hypermotility after modest doses of radiation illustrates the radiosensitivity of the small intestine. Usually, recovery at dose levels below 40 to 45 Gy occurs, although some persistence of small bowel dysfunction and mesenteric cramping may be noted. Surgical intervention and adhesions can precipitate a more serious course of events. Higher doses result in diarrhea, malabsorption of fat, and leakage of albumin into the bowel. If an obliterative arteritis develops, the risk of infarction and perforation remains despite recovery. The underlying lesion is one of ulceration and segmental enteritis that can lead to stenosis of the bowel lumen, with varying degrees of obstruction during the chronic period.

Challenges Defining Volumes

The stomach and small bowel are well visualized, particularly with the use of intravenous contrast and/or oral contrast. The stomach and small bowel position can be variable, and it is therefore recommended that patients avoid large meals or carbonated beverages prior to simulation and treatment.

Summary of QUANTEC and HyTEC

The QUANTEC authors summarized data from studies of acute and late radiation-related risks of small bowel and stomach toxicity,[387] as shown in Figure 12.12. Because the stomach and small bowel are mobile and distensible, determining accurate dose-volume (or dose-surface) constraints is challenging. For acute small bowel toxicity, all or most of the patients (from 6 summarized studies) had received concurrent chemotherapy for rectal or cervical cancers. The QUANTEC report also summarized studies that modeled data for acute (most of the studies) or late (1 study) small bowel complications. Based on their summary of the data, the authors predicted less than 7% risk of stomach ulceration with whole stomach doses

(D100) less than 45 Gy. With small bowel delineated as individual loops of bowel, they estimated less than 10% risks of grade greater than or equal to 3 acute toxicity with a V_{15} less than 120 mL, while when the entire potential space (often referred to as "bowel bag") was contoured, they estimated less than 10% risks of grade greater than or equal to 3 acute toxicity with a V_{45} less than 165 mL. The HyTEC authors did not specifically evaluate dosimetric factors associated with risks to the small bowel or stomach after SBRT, though they discussed the importance of sparing these OARs with SBRT for pancreatic tumors.[417] Among patients undergoing three- to five-fraction SBRT for liver metastases, bowel toxicity has been reported to occur with maximal doses to the bowel of greater than 30 Gy.[401]

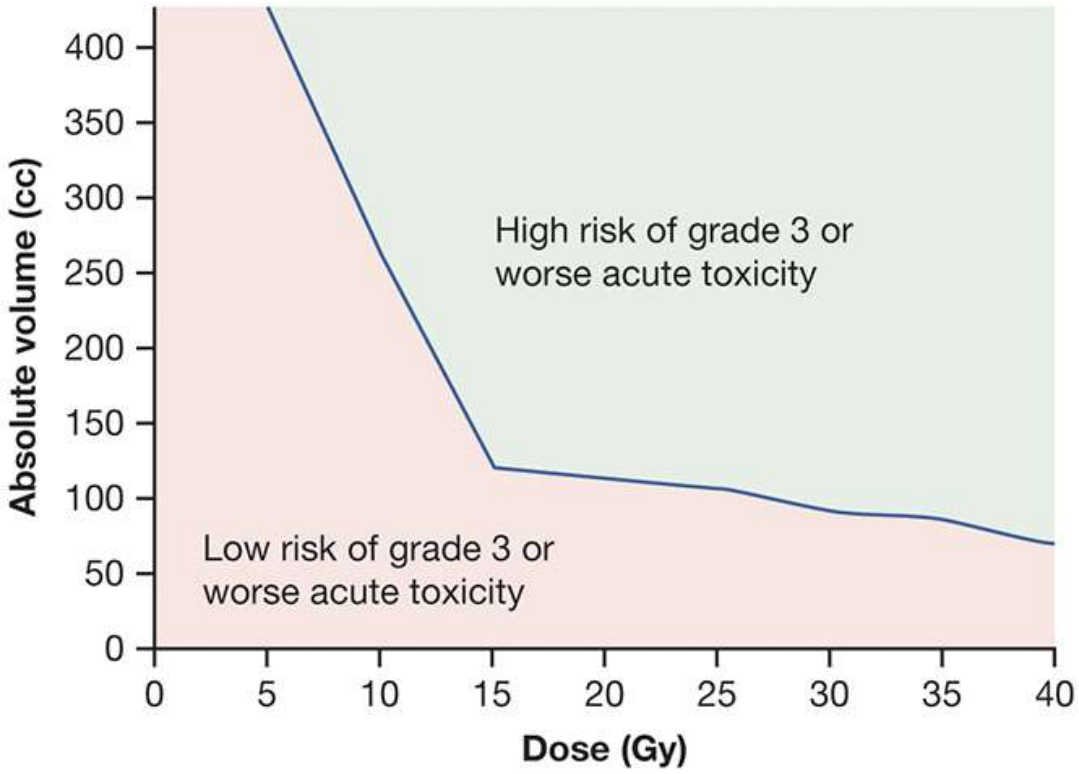

FIGURE 12.12 Graphic representation of the Baglan-Robertson[287,288] threshold model for acute small bowel toxicity. "Low risk" implies <10% and "high risk" >40% grade 3 toxicity. Absolute volume is based on contouring individual bowel loops, not the entire peritoneal space. (Reprinted from Kavanagh BD, Pan CC, Dawson LA, et al. Radiation dose-volume effects in the stomach and small bowel. *Int J Radiat Oncol Biol Phys*. 2010;76[3 suppl]:S101-S107. Copyright © 2010 Elsevier. With permission.)

Factors Affecting Risk

Factors affecting the risk of late toxicity include total dose (with doses in excess of 40 to 50 Gy increasing the risk of late complications), fractional dose, prior abdominal surgery (which increases the risk of bowel obstruction), and concurrent chemotherapy use. In the European Organization for Research and Treatment of Cancer (EORTC) Hodgkin lymphoma study, the rate of complications was 3% without prior abdominal surgery versus 12% with prior abdominal surgery.[382]

Future Studies

More detailed dose-volume effects for late bowel toxicity are needed, particularly for altered fractionation (ie, SBRT). As many GI cancers are treated with chemotherapy, data on the impact of chemotherapy on acute and late stomach and bowel toxicity are needed.

Toxicity Scoring Criteria

The CTCAE v. 4.0 is used to grade gastric and small bowel toxicity.[116]

Kidneys

Clinical Significance

The kidney functions to remove wastes; regulate electrolytes; produce erythropoietin, which stimulates red blood cell production; and modulate blood pressure through the renin-angiotensin pathway as well as through fluid/electrolyte balance. Radiation nephropathy is an uncommonly reported toxicity, not because kidneys are radioresistant but because clinicians carefully respect renal tolerance doses.

End Points

Five distinct clinical syndromes may overlap in symptoms, signs, and time sequence: acute radiation nephropathy, chronic radiation nephropathy, benign hypertension, malignant hypertension, and hyperreninemic hypertension secondary to a scarred encapsulated kidney (Goldblatt kidney). The signs (ie, decreased glomerular filtration rate) and symptoms of radiation nephropathy are not distinguishable from other causes of renal damage, and these should be excluded. Acute (within 6 months) radiation-induced kidney injury is generally subclinical. Urinary findings consist of microscopic hematuria, proteinuria, and urinary casts. Blood alterations in β_2-microglobulin correlate linearly with both inulin and creatinine clearance and with later elevations of blood urea nitrogen (BUN). There is a 6- to 12-month latency period before the clinical expression of acute radiation nephropathy. In this subacute phase, the signs and symptoms include dyspnea, headaches, ankle edema, lassitude, anemia, hypertension, albuminuria, papilledema, elevated blood urea, and urinary abnormalities (granular and hyaline casts, red blood cells). Death may occur from chronic uremia or left ventricular failure, pulmonary edema, pleural effusion, and hepatic congestion. Chronic radiation nephropathy and hypertension do not develop until after 12 to 18 months. When chronic nephropathy is severe, death may result.

Challenges Defining Volumes

The kidneys are readily defined on contrast and noncontrast CT imaging. Ideally, the "functional" kidney parenchyma as opposed to the collecting system should be contoured.

Summary of QUANTEC and PENTEC

QUANTEC summarized NTCP data of renal toxicity after total body irradiation (TBI; 12 studies), non-TBI, bilateral whole kidney radiation (six studies, of which all but two were from the 1950s to 1970s) as well as partial kidney radiation (14 studies).[418] Although

endpoints of proteinuria and hypertension were discussed, these endpoints were not addressed as separate outcomes. The QUANTEC authors estimated the risk of nephrotoxicity based on published data, including some NTCP models, though they conceded "substantial uncertainty" in these estimates. For partial kidney radiation, they estimated that bilateral kidney V_{12} less than 55%, V_{20} to V_{23} less than 30% to 32%, and V_{28} less than 20% were associated with less than 5% risks of clinically relevant renal dysfunction. For whole kidney radiation, mean doses of less than 15 to 18 Gy and less than 28 Gy were estimated to be associated with less than 5% and less than 50% risks of clinically relevant renal dysfunction, respectively (Figure 12.13). HyTEC did not include a report on renal toxicity.

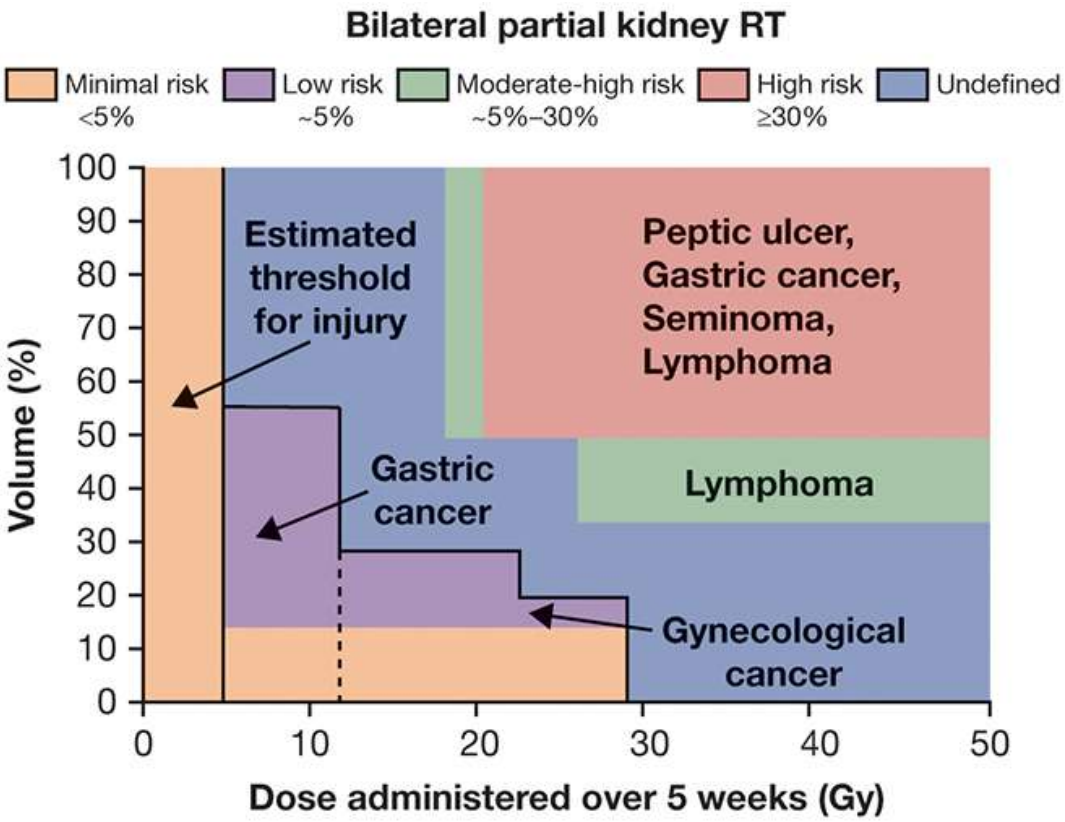

FIGURE 12.13 Schematic diagram of bilateral kidney dose-volume histogram from selected studies, represented as regions associated with minimal (<5%), low (~5%), moderate to high (~5%-30%), high (>30%), or undefined estimated risk of toxicity. Clinical situation that yielded risk estimates for each region is also indicated. Actual risks are patient and plan specific and are associated with substantial uncertainty. (Adapted from Dawson LA, Kavanagh BD, Paulino AC, et al. Radiation-associated kidney injury. *Int J Radiat Oncol Biol Phys*. 2010;76[3 suppl]:S108-S115. Copyright © 2010 Elsevier. With permission.)

In the PENTEC review, the risk of dysfunction was modeled by RT dose and grade of toxicity.[419] Normal tissue complication rates greater than or equal to 5%, expressed as equivalent doses of 2 Gy/fraction for whole kidney exposures, occurred at 8.5, 10.2, and 14.5 Gy for National Kidney Foundation grades greater than or equal to 1, 2, and 3, respectively. Conventional Wilms whole abdominal irradiation (WAI) of 10.5 Gy in six fractions had risks of greater than or equal to grade 2 toxicity 4% and greater than or equal to grade 3 toxicity

1%. For fractionated 12 Gy TBI, those risks were 8% and less than 3%, respectively. Data did not support whole kidney modeling with chemotherapy. Partial kidney modeling from 439 survivors who received RT (median age, 7.3 years) demonstrated that 5 or 10 Gy to 100% kidney gave a less than 5% risk of grades 3 to 5 toxicity with 1,500 mg/m^2 carboplatin or no chemo. With 480 mg/m^2 cisplatin, a 3% risk of greater than or equal to grade 3 toxicity occurred without RT and a 5% risk when 26% of kidney received greater than or equal to 10 Gy. With 63 g/m^2 of ifosfamide, a 5% risk of greater than or equal to grade 3 toxicity occurred with no RT, and a 10% toxicity risk occurred when 42% of kidney received greater than or equal to 10 Gy.

Factors Affecting Risk

A variety of agents have been implicated as toxic or as radiosensitizers (ie, retinoic acid, cisplatin, BCNU, actinomycin D), administered either singly or in combination with chemotherapy. Of note, angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers have been shown to delay the progression of radiation injury in the experimental setting.[420] TBI dose rates (≤6 cGy/min vs ≥10 cGy/min) have been shown to significantly impact the risk of renal toxicity.[421] Patient-related factors may include underlying renal insufficiency, diabetes, hypertension, liver disease, heart disease, and smoking.[418]

Future Studies

Studies are needed to better define partial kidney tolerance to radiation, investigating the impact of underlying kidney function, dose-volume exposure (accounting for regional variation), fractionated dose delivery, and radiation protectors.

Toxicity Scoring Criteria

The CTCAE v. 4.0 can be used to grade renal toxicity.[116] Severity of injury can also be graded according to the glomerular filtration rate, serial urine protein, serum BUN, creatinine clearance, blood pressure, and symptoms of renal failure.

Rectum

Clinical Significance

The rectum is the terminal portion of the large intestines that functions as a temporary storage for feces, as well as providing the urge to defecate. A portion of the rectum is irradiated in patients undergoing radiation for prostate cancer, gynecologic cancers, and other pelvic tumors (such as sarcomas).

End Points

Acute rectal toxicity includes diarrhea or loose stools, tenesmus, proctitis, and rectal urgency and/or frequency. The most common late radiation-related rectal complication is bleeding. Rectal ulceration and fistula are much less common. Other late injuries include stricture and decreased rectal compliance, which can result in frequent small stool and/or tenesmus. The anus is also at risk of late complications including stricture and laxity, leading to fecal incontinence.

Challenges Defining Volumes

The rectum extends from the rectosigmoid junction to the anus, with the inferior extent variably defined as the level of the anal verge of the ischial tuberosities or 2 cm below the ischial tuberosities or above the anus (the most inferior 3 cm of the intestines). The rectum should be segmented from above the anal verge to the turn into the sigmoid colon, though the superior and inferior borders of the rectum are not always easy to define on CT imaging, and the definition of the cranial and caudal extents is variable.[422] The rectum is mobile and distensible, and therefore, its position and volume can vary between and during radiation fractions.

The percentage of rectum or rectal wall receiving a given dose can be somewhat subjective (ie, based on how much of the rectum is segmented); using the absolute volume of rectum[423] or rectal wall is less subjective, though defining the rectal wall is not standardized. William Beaumont Hospital demonstrated that the rectal volume as well as rectal wall V_{50} to V_{70} values predict late toxicity, with the rectal wall being more predictive of grade 2 to 3 late effects; acute toxicity is also predictive of late toxicity.[424] MDACC has also shown the rectal wall to be better predictive of late rectal bleeding.[425]

Summary of QUANTEC and HyTEC

Abundant dosimetric data have shown a correlation of risk with rectal volume and surface/rectal wall doses among patients undergoing radiation for prostate cancer. Figure 12.14 summarizes many of the relevant studies.

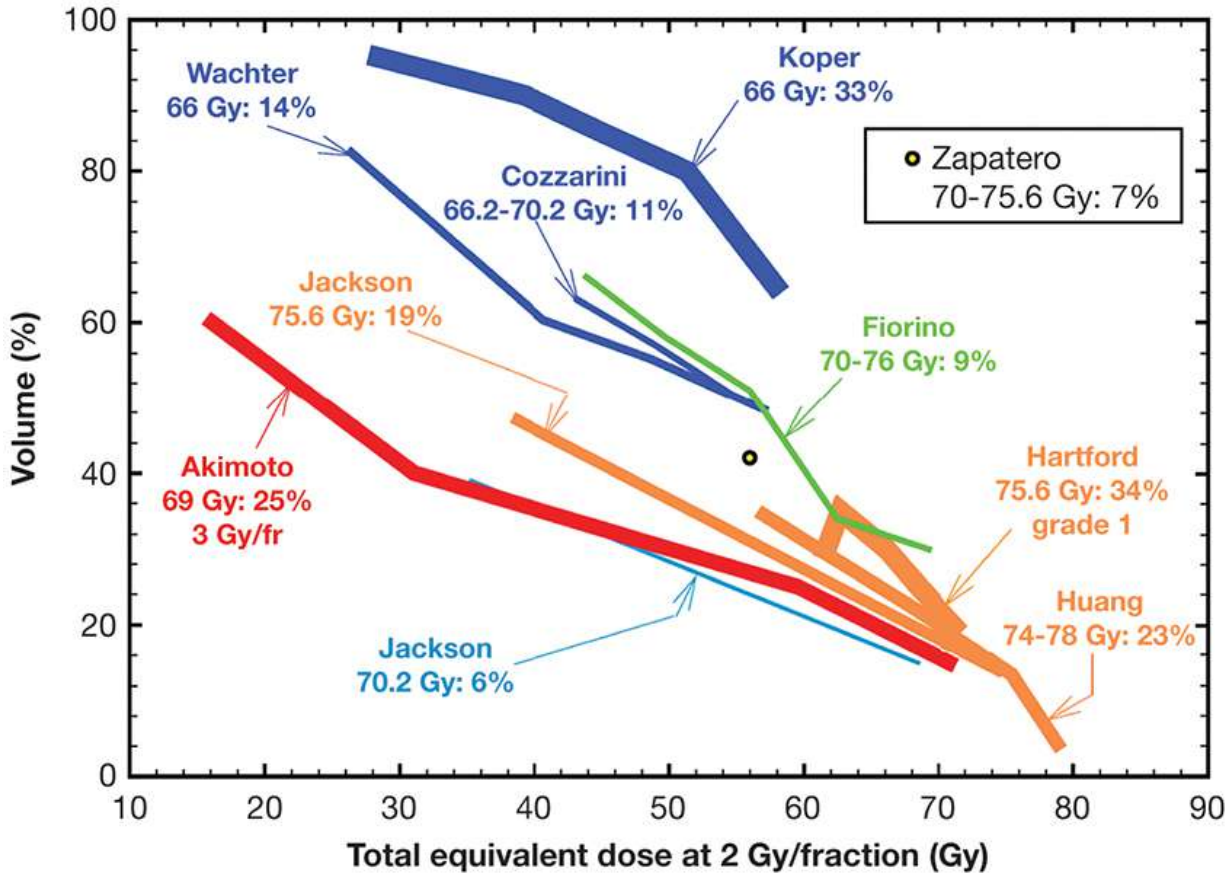

FIGURE 12.14 Dose-volume histogram thresholds for grade 2 or higher rectal toxicity from selected studies.[427-435] *Thicker lines* indicate higher rates of overall toxicity (percentages are indicated on the figure along with the physical prescription dose). Threshold doses are expressed as the total equivalent dose delivered in 2-Gy fractions, adjusted using the linear-quadratic model with α/β = 3 Gy. The associated equivalent prescription doses are coded by color spectrum from lowest (blue) to highest (red). Volumes shown in the graph are based on the full length of the anatomic rectum. Note that these curves converge in the high-dose range, implying that doses in this range are more consistently associated with rectal toxicity. (Reprinted from Michalski JM, Gay H, Jackson A, Tucker SL, Deasy JO. Radiation dose-volume effects in radiation-induced rectal injury. *Int J Radiat Oncol Biol Phys*. 2010;76[3 suppl]:S123-S129. Copyright © 2010 Elsevier. With permission.)

The QUANTEC report[422] summarized data from five studies that performed NTCP modeling for rectal toxicity among patients with prostate cancer treated with 3DCRT to doses less than 80 Gy, and also discussed a meta-analysis that included four of these studies. Various endpoints, and OAR contours (rectum plus contents vs anorectal wall) were used in these studies, with the QUANTEC authors ultimately recommending contouring of the rectum plus contents. The authors estimated that V_{50} less than 50%, V_{60} less than 35%, V_{65} less than 25%, V_{70} less than 20%, and V_{75} less than 15% would be associated with less than 15% risks of grade greater than or equal to 2 late rectal toxicity and less than 10% risks of grade greater than or equal to 3 late rectal toxicity when prescribing up to 79.2 Gy in 1.8- to 2-Gy fractions. They suggested greater priority on the V_{70} to V_{75} exposures, for which relatively small incremental increases had a greater impact on toxicity risks versus lower-dose exposures.

The HyTEC authors[426] summarized data from six studies on dosimetric predictors of rectal toxicity among patients undergoing SBRT for prostate cancer, as well as NTCP modeling from one study. A rectum (contoured as a solid organ) maximum dose of less than 35 to 38 was associated with less than 3% risks of grade greater than or equal to 3 late rectal toxicity with four- to five-fraction SBRT. Women undergoing radiation for gynecologic malignancies are also susceptible to rectal toxicity. With modern radiation delivery, particularly with IMRT planning, the rate of severe GI toxicity is low.

Factors Affecting Risk

The QUANTEC report summarized studies describing increased risk of late rectal toxicity associated with diabetes, hemorrhoids, inflammatory bowel disease, older age, androgen deprivation therapy, rectum size, and prior abdominal surgery. Those who develop severe acute rectal toxicity are also at increased risk of late rectal toxicity. Among 1,010 patients with prostate cancer enrolled in the RTOG 9406 trial, cardiovascular disease was significantly (P = .015) associated with a higher rate of late rectal toxicity, whereas diabetes, hypertension, rectal volume, rectal length, neoadjuvant hormone therapy, and prescribed dose per fraction (1.8 vs 2 Gy) were not significant factors.

Future Studies

Future studies should be directed at achieving accurate dose-volume distributions for the rectum, which is a mobile, distensible structure, and correlating these dosimetric characteristics with toxicity. More robust data are needed for hypofractionated radiation delivery to the rectum, as with SBRT or high dose rate (HDR) brachytherapy, as well as with low-dose brachytherapy and combined modality approaches.

Toxicity Scoring Criteria

The CTCAE v. 4.0[116] or RTOG scoring criteria can be used to grade rectal toxicity.

Urinary Bladder

Clinical Significance

The bladder is a highly distensible organ that collects urine. Symptoms from late radiation-related toxicities include increased urinary frequency, hematuria, and dysuria. Necrosis, contracted bladder, and hemorrhage are less common, severe effects. Perhaps late bladder toxicity is underreported due to its long latency as well as toxicity being attributed to more common causes.

End Points

Bladder injury can be broadly classified as focal damage (eg, bleeding) or more global injury (eg, reduced bladder capacity with secondary urinary frequency). Acute side effects from incidental bladder irradiation are common and include urinary frequency, urgency, and dysuria (symptoms that may also reflect acute urethral toxicity). Late effects attributable to global injury include dysuria, frequency, urgency, contracture, spasm, reduced flow, and

incontinence. In contrast, late effects arising from focal injury include hematuria, fistula, obstruction, ulceration, and necrosis.

Challenges Defining Volumes

The bladder is a mobile and distensible structure, depending on the volume of urine within the bladder. Postvoid residuals may vary due to variable emptying and constant filling. In contouring the bladder, either the volume of the bladder and contents or the bladder wall alone can be segmented (with the latter more representative of a surface).

Dose/Volume/Toxicity Data

Because the bladder is mobile and distensible, determining accurate dose-volume (or dose-surface) constraints is challenging. Detailed dose-volume (or dose-surface) constraints have not been published, in part because of the complexities of assigning dose-volume or dose-surface metrics to a mobile, distensible structure. Whole-bladder tolerances have been mostly studied in patients with urinary bladder cancer, whereas partial bladder tolerances have been mostly studied in patients with genitourinary (mostly prostate) and gynecologic cancers.[436]

For whole-bladder irradiation, doses in excess of 60 Gy, particularly with fraction sizes greater than 2 Gy and/or accelerated radiation regimens, result in a significant risk of grade 3 or higher late toxicity. Risks are lower when the whole bladder receives 45 to 55 Gy followed by a boost to greater than 60 Gy to a portion of the bladder, though toxicity risk has not been correlated to dose-volume metrics. With prostate cancer treated to high doses (≥72 Gy), the inferior portion of the bladder (eg, trigone area) also receives greater than or equal to 70 Gy. This tends to be well tolerated with respect to bladder toxicity. Arguably, the urinary toxicity that does develop after radiation is due in part to the prostatic urethra receiving suprathreshold doses.

Mean bladder dose and area under the DVH were significant predictors of grade greater than or equal to 2 genitourinary toxicity in a study of 503 patients with prostate cancer.[437] In a study of 296 patients with prostate cancer (in whom the bladder was contoured as a whole organ, after drainage and infusion of 120 mL of saline), no bladder dose-volume relationships were associated with the risk of grade greater than or equal to 2 genitourinary toxicity.[438]

Factors Affecting Risk

Prior pelvic surgery can result in an increased risk of bladder toxicity as a direct result of bladder or urethral trauma and/or denervation of the bladder, which can cause urinary hesitancy or retention, resulting in overflow incontinence.[436] Patients receiving anticoagulants may be at greater risk of hematuria. Cytoxan, independently or with radiation, can cause chronic hemorrhagic cystitis, incontinence, contractions, and vesicoureteral reflux. Radiation-sensitizing chemotherapy may increase the risk of acute and late bladder toxicity, though data supporting this are lacking.

Mathematic/Biologic Models

Quantitative mathematical modeling of bladder toxicity is lacking.

Special Situations

SBRT for prostate cancer is an emerging investigative approach. In one study, after SBRT (7.25 Gy × 5), grade 1 to 2 genitourinary toxicity occurred in 28%, and grade 3 toxicity was reported in 3% of patients (two patients required cystoscopies and dilation procedures for dysuria).[439] Urinary incontinence, complete obstruction, or persistent hematuria was not observed. In another study, after SBRT (9.5 Gy × 4), acute grade 1 to 2 and 3 acute genitourinary toxicity occurred in 71% and 0% of patients, respectively, and grade 1 to 2 and 3 late acute genitourinary toxicity occurred in 11% and 5%, respectively; grade 3 toxicity included temporary urinary catheterization and intermittent self-catheterization.[440]

Recommended Dose-Volume Limits

For whole-bladder radiation, the reported risks of grade 3 or higher toxicity in doses of 50 to 60 Gy range from less than or equal to 5% to 40%. This variation is likely attributable to the challenges of correlating toxicity with the dose delivered to a mobile structure, which is even more problematic when correlating partial volume exposures to toxicity. With the caveat of these issues, bladder constraints of approximately 15%, 25%, 35%, and 50% receiving greater than or equal to 80, 75, 70, and 65 Gy, respectively, as recommended in the RTOG 0415 study of prostate cancer, are suggested. The protocol advises an empty bladder at the time of simulation and treatment; the bladder is segmented from the base to the dome.

Future Studies

Studies that incorporate the changing size and shape of the bladder may provide a better understanding of the dose-volume tolerance of the bladder. Incorporating day-to-day variation with adaptive planning DVHs and/or the use of deformable modeling would be informative. More detailed studies are needed to assess regional variation in radiation susceptibility (ie, trigone vs dome).

Toxicity Scoring Criteria

The CTCAE v. 4.0 or RTOG scoring criteria can be used to grade genitourinary toxicity.

Penile Bulb

Clinical Significance

Radiation dose to the penile bulb can affect erectile function, as a direct result either of damage to this structure or of damage to surrounding structures, whose radiation-induced damage is correlated with the dose exposure of the penile bulb. The most common scenario in which the penile bulb is irradiated is in the treatment of prostate cancer. IMRT is often used to minimize the dose to the penile bulb.[441,442]

End Points

Erectile dysfunction reported by the patient can be the result of treatment or other confounding factors including age, medications (particularly hormonal therapy), or comorbid conditions (eg, diabetes, peripheral vascular disease, hypertension). Objective diagnostic tests can be performed to help establish the etiology of erectile dysfunction; these include nocturnal

penile tumescence, somatosensory-evoked potentials, bulbocavernosus reflex latency, penile electromyography, color duplex Doppler ultrasound, dynamic infusion cavernosometry, and pharmacologic testing.

Challenges Defining Volumes

The anatomy of the pelvic floor is challenging to visualize on CT or MRI, and hence, the definition of the penile bulb is somewhat subjective. The QUANTEC authors recommend defining the penile bulb as the most proximal portion of the penis sitting immediately caudal to the prostate.[442,443]

Summary of QUANTEC and HyTEC

The QUANTEC authors[443] summarized data from 10 studies on erectile dysfunction after external-beam radiotherapy. Six studies described the incidence of severe erectile dysfunction as a function of penile bulb D_{60} or D_{70}. Although the data were "conflicting" and "sparse," the authors surmised that they were "consistent with either a causal or surrogate relationship." They estimated a less than 35% risk of severe erectile dysfunction, with a mean dose of 95% less than 50 Gy, a D_{90} less than 50 Gy and D_{60} to 70 less than 70 Gy. A randomized controlled study of 117 men showed that although it was safe and feasible to spare the penile bulb and corporal bodies, doing so was not associated with improved potency preservation outcomes at 2 years.[444] The authors conceded that this was an unplanned analysis and that the statistical power for potency assessment was limited. Furthermore, even in the control arm, these structures were relatively spared (compared to historical non-IMRT treatments). The HyTEC authors summarized three reports on penile bulb exposure and concluded that "it is currently unclear how dosimetric factors contribute to sexual function outcomes after SBRT."[426]

Factors Affecting Risk

The etiology of erectile dysfunction following radiation is likely multifactorial. In addition to radiation effects, pretreatment erectile function, diabetes, smoking history, and a history of hypertension have been implicated as important factors affecting risk, though the data to date have been somewhat conflicting.[445]

Special Situations

Hormonal therapy, which is commonly used in patients with early-stage intermediate- to high-risk prostate cancer or advanced-stage prostate cancer, in and of itself can result in erectile dysfunction. However, the interaction (if any) of hormonal therapy and dose-volume delivery to the penile bulb is not well established.[443]

Future Studies

Studies should be directed at better anatomic definition of the putative anatomic sites impacted by erectile dysfunction and rigorous prospective correlation of dose-volume parameters with erectile dysfunction.

Toxicity Scoring Criteria

Pre- and posttreatment assessment of erectile dysfunction should be performed using the International Index of Erectile Function Scale.[443]

COMPOSITE SUMMARY OF DOSE/VOLUME/OUTCOME DATA

Table 12.11 summarizes the dose/volume/outcome findings in the QUANTEC reviews. Note that clinicians must understand the clinical situations from which the QUANTEC recommendations were derived, and there is no substitute for reading the original QUANTEC papers. At the same time, clinical judgment as applied to a specific patient is essential. In addition to the QUANTEC papers, the Emami paper continues to play an important role in estimating normal tissue toxicity during radiotherapy. Finally, as more comprehensive dose/volume/outcome data are developed—particularly in combination with emerging and evolving chemotherapy regimens—the radiation oncologist will need to continually and critically keep abreast of the clinical literature on normal tissue toxicity. There is an ongoing effort to perform a similar dose-volume outcome summary for organs that are of particular interest for pediatric patients (PENTEC) that is underway and expected to be complete in 2024.

TABLE 12.11 QUANTEC SUMMARY: CLINICAL DOSE/VOLUME/OUTCOME DATA

Organ	Volume Segmented	Irradiation Type (Partial Organ Unless Otherwise Stated)	End Point	Dose (Gy), or Dose-Volume Parameters		Rate (%)	Notes on Dose-Volume Parameters
Brain	Whole organ	3DCRT	Symptomatic necrosis	D_{max}	≤60 Gy	<3	
	Whole organ	3DCRT	Symptomatic necrosis	D_{max}	72 Gy	5	
	Whole organ	3DCRT	Symptomatic necrosis	D_{max}	90 Gy	10	
Brain, metastases	Whole organ, including the target	SRS (1 fraction)	Symptomatic necrosis	V_{12Gy}	≤5 mL	10	Prior whole-brain RT appears to not markedly increase risks in most reports (with the exception of the brainstem). However, repeat SRS/HF-SRS in the same area has been associated with markedly increased risks.
		SRS (1 fraction)	Symptomatic necrosis	V_{12Gy}	≤10 mL	≤15	
		SRS (1 fraction)	Symptomatic necrosis	V_{12Gy}	≤15 mL	≤20	

Organ	Volume Segmented	Irradiation Type (Partial Organ Unless Otherwise Stated)	End Point	Dose (Gy), or Dose-Volume Parameters		Rate (%)	Notes on Dose-Volume Parameters
		SRS (3 fractions)	Edema or necrosis	V_{20Gy}	≤20 mL	≤10	
		SRS (3 fractions)	Edema or necrosis	V_{20Gy}	≤30 mL	≤20	
		SRS (5 fractions)	Edema or necrosis	V_{24Gy}	≤20 mL	≤10	
		SRS (5 fractions)	Edema or necrosis	V_{24Gy}	≤20 mL	≤20	
Brain, AVM	Whole organ, including target	SRS (1 fraction)	Symptomatic necrosis	V_{12Gy}	≤10 mL	≤10	
Brainstem	Whole organ	3DCRT	Permanent cranial neuropathy or necrosis	D_{max}	<54 Gy	<5	
	Whole organ	3DCRT	Permanent cranial neuropathy or necrosis	$D_{1\text{-}10\ mL}$	≤59 Gy	<5	
	Whole organ	3DCRT	Permanent cranial neuropathy or necrosis	D_{max}	<64 Gy	<5	Point dose << 1 mL
	Whole organ	SRS (1 fraction)	Permanent cranial neuropathy or necrosis	D_{max}	<12.5	<5	For patients with acoustic neuromas/vestibular schwannomas
Optic pathways	Optic nerves and chiasm	3DCRT	Optic neuropathy	D_{max}	<55	<3	Given the small size, 3DCRT often covers the whole circumference of the organ.
		3DCRT	Optic neuropathy	D_{max}	55-60	3–7	
		3DCRT	Optic neuropathy	D_{max}	>60	>7–20	
		SRS (1 fraction)	Optic neuropathy	D_{max}	<10-12	<1	

Organ	Volume Segmented	Irradiation Type (Partial Organ Unless Otherwise Stated)	End Point	Dose (Gy), or Dose-Volume Parameters		Rate (%)	Notes on Dose-Volume Parameters
		SRS (3 fractions)	Optic neuropathy	D_{max}	<20	<1	
		SRS (5 fractions)	Optic neuropathy	D_{max}	<25	<1	
Carotid artery (reirradiation)	Each carotid artery	SRS (5 fractions)	Grade 3-5 bleeding	D_{max}	<20-30	<2-12	Dose-volume metric shown is for the reirradiation SBRT dose in patients with prior RT.
Spinal cord	Partial organ	3DCRT	Myelopathy	D_{max}	50	0.2	Including full cord cross section; no previous irradiation to the involved level of the spine
	Partial organ	3DCRT	Myelopathy	D_{max}	60	6	
	Partial organ	3DCRT	Myelopathy	D_{max}	69	50	
	Spinal cord, thecal sac, or canal	SBRT (1 fraction)	Myelopathy	D_{max}	<12.4-14	1-5	Partial cord cross section irradiated; no previous irradiation to the involved level of the spine.
		SBRT (2 fractions)	Myelopathy	D_{max}	<17-19.3	1-5	
		SBRT (3 fractions)	Myelopathy	D_{max}	<20.3-23.1	1-5	
		SBRT (4 fractions)	Myelopathy	D_{max}	<23-26.2	1-5	
		SRS (5 fractions)	Myelopathy	D_{max}	<25.3-28.8	1-5	
Cochlea	Whole organ	3DCRT	Sensory neural hearing loss	Mean dose	≤45	<30	Mean dose to the cochlea, hearing at 4 kHz
	Whole organ	SRS (1 fraction)	Sensory neural hearing loss	Prescription dose	≤14	<25	Serviceable hearing

Organ	Volume Segmented	Irradiation Type (Partial Organ Unless Otherwise Stated)	End Point	Dose (Gy), or Dose-Volume Parameters		Rate (%)	Notes on Dose-Volume Parameters
Parotid	Bilateral whole parotid glands	3DCRT	Long-term parotid salivary function reduced to <25% of pre-RT level	Mean dose	<25	<20	For combined parotid glands
	Unilateral whole parotid gland	3DCRT	Long-term parotid salivary function reduced to <25% of pre-RT level	Mean dose	<20	<20%	For single parotid gland At least one parotid gland spared to <20 Gy
	Bilateral whole parotid glands	3DCRT	Long-term parotid salivary function reduced to <25% of pre-RT level	Mean dose	<39	<50%	For combined parotid glands
Pharynx	Pharyngeal constrictors	Whole organ	Symptomatic dysphagia and aspiration	Mean dose	<50	<20	Based on Section B4 of the paper
Larynx	Whole organ	3DCRT	Vocal dysfunction	D_{max}	<66	<20	With chemotherapy
	Whole organ	3DCRT	Aspiration	Mean dose	<50	<30	With chemotherapy
	Whole organ	3DCRT	Edema	Mean dose	<44	<20	Without chemotherapy, based on a single study in patients without larynx cancer
	Whole organ	3DCRT	Edema	V_{50}	<27%	<20	
Lung	Whole organ	3DCRT	Symptomatic pneumonitis	V_{20}	≤30%	<20	For combined lung. Gradual dose response
	Whole organ	3DCRT	Symptomatic pneumonitis	Mean dose	7	5	Excludes purposeful whole-lung irradiation

Organ	Volume Segmented	Irradiation Type (Partial Organ Unless Otherwise Stated)	End Point	Dose (Gy), or Dose-Volume Parameters		Rate (%)	Notes on Dose-Volume Parameters
	Whole organ	3DCRT	Symptomatic pneumonitis	Mean dose	13	10	
	Whole organ	3DCRT	Symptomatic pneumonitis	Mean dose	20	20	
	Whole organ	3DCRT	Symptomatic pneumonitis	Mean dose	24	30	
	Whole organ	3DCRT	Symptomatic pneumonitis	Mean dose	27	40	
	Combined lungs minus target	SBRT (3-5 fractions)	Grade ≥2 toxicity	Mean dose V_{20Gy}	<8 Gy <10-15	10-15	Preexisting interstitial lung disease appears to increase toxicity risk.
Esophagus	Whole organ	3DCRT	Grade ≥3 acute esophagitis	Mean dose	<34	5-20	Based on RTOG and several studies
	Whole organ	3DCRT	Grade ≥2 acute esophagitis	V_{35}	<50%	<30	A variety of alternate threshold doses have been implicated. Appears to be a dose-volume response
	Whole organ	3DCRT	Grade ≥2 acute esophagitis	V_{50}	<40%	<30	
	Whole organ	3DCRT	Grade ≥2 acute esophagitis	V_{70}	<20%	<30	
Heart	Pericardium	3DCRT	Pericarditis	Mean dose	<26	<15	Based on a single study
	Pericardium	3DCRT	Pericarditis	V_{30}	<46%	<15	
	Whole organ	3DCRT	Long-term cardiac mortality	V_{25}	<10%	<1	Overly safe risk estimates based on model predictions
Liver	Whole liver—GTV	3DCRT or whole organ	Classic RILD	Mean dose	<30-32	<5	Excluding patients with preexisting liver disease or hepatocellular carcinoma, as tolerance doses are lower in these patients
	Whole liver—GTV	3DCRT	Classic RILD	Mean dose	<42	<50	

Organ	Volume Segmented	Irradiation Type (Partial Organ Unless Otherwise Stated)	End Point	Dose (Gy), or Dose-Volume Parameters		Rate (%)	Notes on Dose-Volume Parameters
	Whole liver—GTV	3DCRT or whole organ	Classic RILD	Mean dose	<28	<5	In patients with Child-Pugh A preexisting liver disease or hepatocellular carcinoma, excluding hepatitis B reactivation as an endpoint
	Whole liver—GTV	3DCRT	Classic RILD	Mean dose	<36	<50	
Liver, primary lesions	Whole liver—GTV	SBRT (3 fractions)	Grade ≥3 liver enzyme change	Mean dose	≤13	<20	
		SBRT (6 fractions)	Grade ≥3 liver enzyme change	Mean dose	≤18	<20	
Liver, metastases	Whole liver—GTV	SBRT (3 fractions)	Grade ≥3 liver enzyme change	Mean dose	≤15	<20	
		SBRT (6 fractions)	Grade ≥3 liver enzyme change	Mean dose	≤20	<20	
		SBRT (3-6 fractions)	Liver dysfunction and grades 3-5 general GI toxicity	≥700 mL	≤15-17	<13	
Kidney	Bilateral whole kidney	Bilateral whole-organ or 3DCRT	Clinically relevant renal dysfunction	Mean dose	<15-18	<5	
	Bilateral whole kidney	Bilateral whole organ	Clinically relevant renal dysfunction	Mean dose	<28	<50	
	Bilateral whole kidney	3DCRT	Clinically relevant renal dysfunction	V_{12} V_{20} V_{23} V_{28}	<55% <32% <30% <20%	<5	For combined kidney
Stomach	Whole organ	Whole organ	Ulceration	D_{max}	<45	<7	
Small bowel	Individual small	3DCRT	Grade ≥3 acute toxicity	V_{15}	<120 mL	<10	Volume based on segmentation of the individual loops of

Organ	Volume Segmented	Irradiation Type (Partial Organ Unless Otherwise Stated)	End Point	Dose (Gy), or Dose-Volume Parameters		Rate (%)	Notes on Dose-Volume Parameters
	bowel loops						the bowel, not the entire potential space within the peritoneal cavity
	Entire potential space within the peritoneal cavity	3DCRT	Grade ≥3 acute toxicity	V_{45}	<195 mL	<10	Volume based on the entire potential space within the peritoneal cavity
Rectum	Whole organ	3DCRT	Grade ≥2 late rectal toxicity Grade ≥3 late rectal toxicity	V_{50}	<50%	<15 <10	Prostate cancer treatment
	Whole organ	3DCRT	Grade ≥2 late rectal toxicity Grade ≥ late rectal toxicity	V_{60}	<35%	<15 <10	
	Whole organ	3DCRT	Grade ≥2 late rectal toxicity Grade ≥3 late rectal toxicity	V_{65}	<25%	<15 <10	
	Whole organ	3DCRT	Grade ≥2 late rectal toxicity Grade ≥3 late rectal toxicity	V_{70}	<20%	<15 <10	
	Whole organ	3DCRT	Grade ≥2 late rectal toxicity Grade ≥3 late rectal toxicity	V_{75}	<15%	<15 <10	
	Whole rectum (as a solid organ)	SBRT (4-5 fractions)	Late grade ≥3 bowel toxicity	D_{max}	35-38	<3	In the context of prostate SBRT
Bladder	Whole organ	3DCRT	Grade ≥3 late RTOG	D_{max}	<65	<6	Bladder cancer treatment

Organ	Volume Segmented	Irradiation Type (Partial Organ Unless Otherwise Stated)	End Point	Dose (Gy), or Dose-Volume Parameters		Rate (%)	Notes on Dose-Volume Parameters
							Variations in bladder size/shape/location during RT hamper the ability to generate accurate data.
	Whole organ	3DCRT	Grade ≥3 late RTOG	V_{65} V_{70} V_{75} V_{80}	≤50% ≤35% ≤25% ≤15%		Prostate cancer treatment Based on the current RTOG 0415 recommendation
	Whole bladder (as a solid organ)	SBRT (4-5 fractions)	Late grade ≥2 urinary toxicity	$V_{PrescribedDose}$	<5-10 mL		In the context of prostate SBRT
Urethra	Whole organ	SBRT (4-5 fractions)	Late grade ≥2 urinary toxicity	D_{max}	<38-42 Gy	<20	In the context of prostate SBRT
Penile bulb	Whole organ	3DCRT	Severe erectile dysfunction	Mean dose to 95% of gland	<50	<35	
	Whole organ	3DCRT	Severe erectile dysfunction	D_{90}	<50	<35	
	Whole organ	3DCRT	Severe erectile dysfunction	D_{60-70}	<70	<55	

Adapted from Marks LB, Yorke ED, Jackson A, et al. Use of normal tissue complication probability models in the clinic. *Int J Radiat Oncol Biol Phys*. 2010;76(3 suppl):S10-S19. Copyright © 2010 Elsevier. With permission; and Grimm J, Marks LB, Jackson A, Kavanagh BD, Xue J, Yorke E. High Dose per Fraction, Hypofractionated Treatment Effects in the Clinic (HyTEC): an overview. *Int J Radiat Oncol Biol Phys*. 2021;110(1):1-10.

CLINICAL APPLICATION, LIMITATIONS, AND IMPLICATIONS OF QUANTEC AND HYTEC

Implications for Understanding the Underlying Mechanisms of Radiation-Induced Normal Tissue Injury

The consistent structure of the Emami dose-volume limits and the application of that information to predictive models may be taken to imply a uniform mechanism of radiation-induced injury. The diversity of the structure of the information obtained in the QUANTEC review suggests a more diverse mechanism of radiation-induced injury. An interorgan comparison of dose-response functions from the QUANTEC review is interesting (Figure

12.15) and may have implications for our understanding of radiation-induced normal tissue injury.

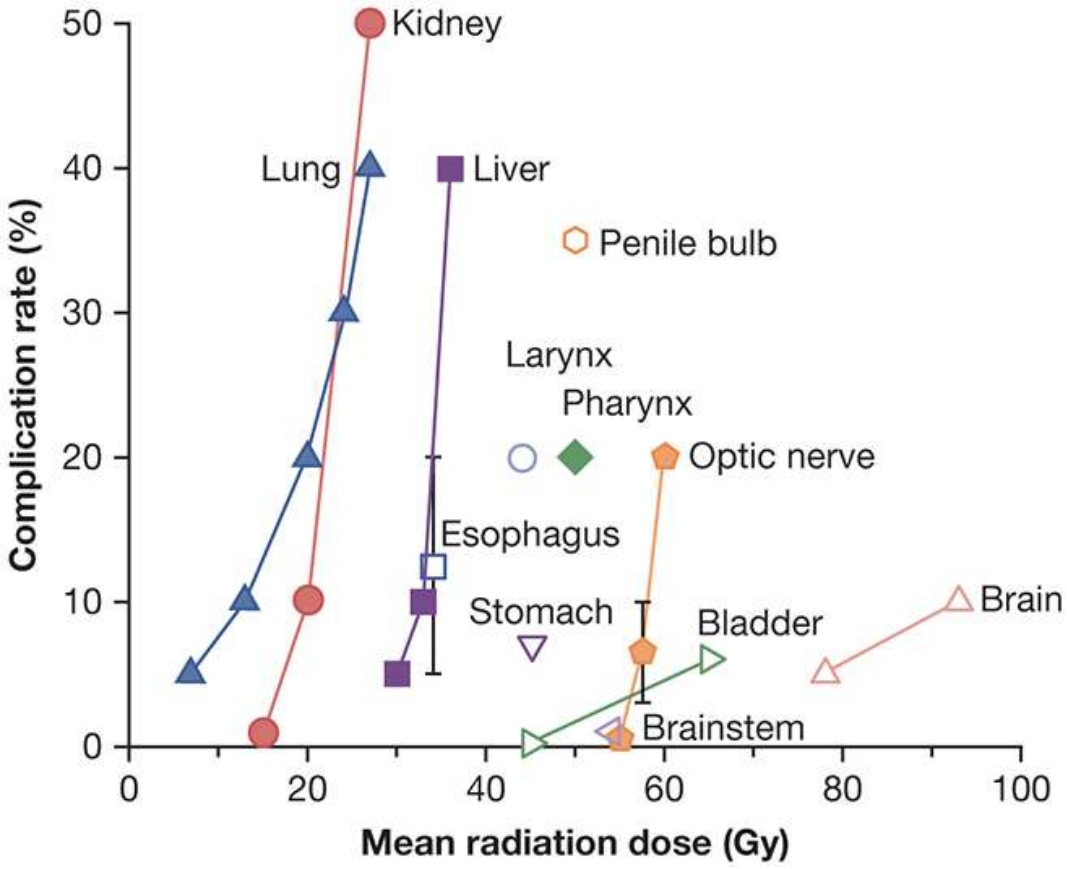

FIGURE 12.15 Composite diagram of normal tissue complication rates versus mean radiation dose.

1. There are marked variations in the dose-response curves for different organs, suggesting that there are different mechanisms for radiation-induced injury in different organs and/or that the end points selected for the different organs reflect a varied type of injury.
2. Organs that are classically considered structured in series (eg, spinal cord, optic nerve, and small bowel, analogous to electrical circuits in series) have steep dose-response curves at doses beyond an apparent critical threshold. This is expected based on our understanding of the structure/anatomy of the series of organs: damage to a functional subunit can render the entire structure dysfunctional.
3. Several neural structures exhibit a similar threshold dose for injury: ≈55 to 60 Gy (corresponding to a BED of ≈100 for an α/β ratio of 3 Gy) for the brain, brainstem, optic nerve, and spinal cord. This suggests that there may be a common mechanism of injury in these structures. Because all of these organs are dependent on the vasculature, it is tempting to implicate vascular injury as the common target for these organs.
4. Organs that are classically considered structured in parallel (eg, lung, liver, parotid, and kidney, analogous to electrical circuits) experience injury at far lower doses and have

more gradual dose-response curves compared to series organs. The presence of injury at lower doses suggests that a different mechanism of injury is occurring in these organs as compared to series organs. It appears that these organs each have critical components that are more sensitive to radiation than are the critical components within the neuronal tissues. It is thus tempting to conclude that subunits such as hepatocytes, nephrons, and alveoli are relatively radiation sensitive.

5. During heterogeneous organ irradiation, the predictive value of mean organ dose in some parallel-structured organs is interesting but counterintuitive. Consider the lung. Relatively uniform fractionated whole-lung doses as high as 15 to 23 Gy have a very low risk of symptomatic pneumonitis. Thus, the lung's "functional subunit" must generally be able to tolerate these doses. However, heterogeneous lung irradiation to an MLD of ≈15 to 23 Gy is associated with a 10% to 25% risk of symptomatic pneumonitis. Thus, during heterogeneous lung irradiation, it is likely that the mean dose is merely a surrogate for the percentage of lung exposed to various other doses of radiation. The same phenomenon may be true in other parallel organs as well.[446]

There are many hazards related to the pooling of data from several studies that may undermine the interpretation of the pooled data. A particularly interesting hazard of pooling data (often termed *Simpson Paradox) is* (for example) the masking of dose/response relationships. Consider several studies that each individually demonstrates a dose response; the pooling of data can mask this dose response (Figure 12.16A). The underlying reason for the "offset" between the data can be multifactorial but can include things such as differences in the tools used to assess toxicity, scales used to score toxicity, or perhaps interstudy differences in the vulnerability for toxicity. Similarly, the pooled data can suggest a dose response when indeed none really exists (Figure 12.16B).

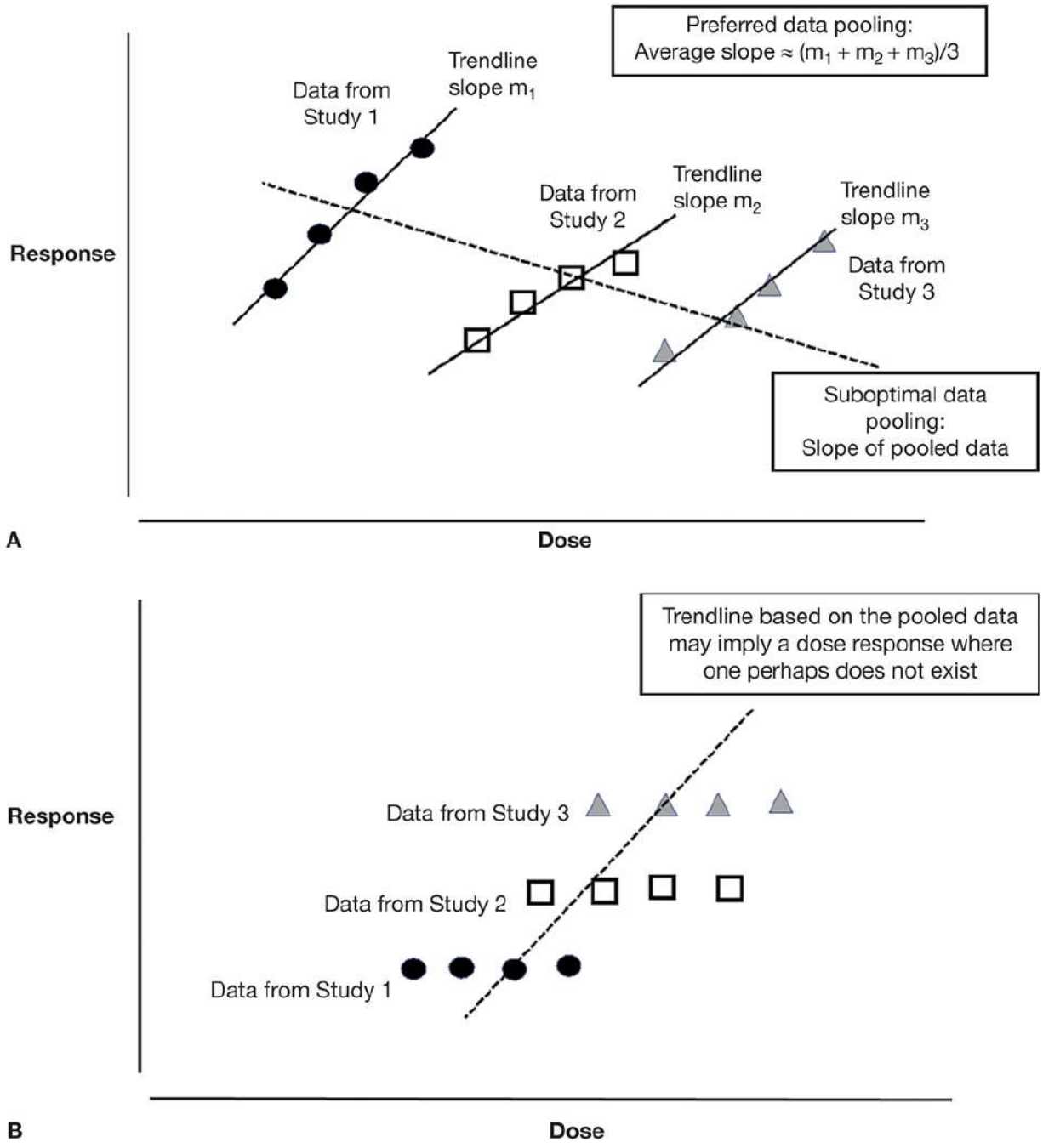

FIGURE 12.16 A cartoon of fictitious data illustrating a possible shortcoming of data pooling, often termed Simpson Paradox. In panel A, three separate studies, each individually with a clear dose response, are pooled. If the individual data points from each study are considered when pooling the data, the dose response might *not* be appreciated. A more appropriate approach might be to consider the slopes from the individual studies. In B, a similar situation is illustrated, in which a dose response might be inferred from the pooled data though no true dose response exists.

The tools of artificial intelligence (AI) will likely play an important role in assessing the risk of treatment, predicting toxicity, and ultimately optimizing the risk/reward ratio in clinical radiation oncology.[447] AI offers the potential for more readily extracting large quantities of

data, including full treatment planning data, patient demographics and outcomes, molecular pathology, longitudinal imaging, and details on adjunctive treatments, such as chemotherapy, immunotherapy, and surgery, and then analyzing these data. Of course, while AI facilitates data mining and analysis, it is essential that complete and accurate data be made accessible, as described earlier.

CONCLUSION

The QUANTEC and HyTEC efforts represent incremental improvements in our field's decades-long effort to better quantify the relationship between dose-volume parameters and clinical outcomes. As the scope of the QUANTEC and HyTEC reviews was largely limited to organ systems with meaningful dose/volume/outcome data, they are often not completely adequate tools to guide clinical care. Consistent and clear reporting of dose/volume/outcome data[448] will enable further refinements to clinical guidelines and will hopefully improve patient care.

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CHAPTER 13

Quality Assurance and Error Avoidance in Radiation Therapy

Wesley J. Talcott, Kelly Paradis, Eric Ford, and Suzanne Evans

A man undergoing routine treatment for oropharyngeal cancer dies after four fractions due to failed transfer of multileaf collimator trajectories in an intensity-modulated plan.[1] Over 700 patients are overdosed due to a problem in dosimetry software, leading to 24 severe injuries and 5 deaths.[2] A pediatric patient experiences a potentially lethal overdose to their brain after an incorrect manual calculation of monitor units.[3]

Many in the field of radiation oncology (RO) have already heard of these tragic cases and may cite their occurrence as the need for continuous safety improvements in our field. Others may cite their relative rarity amidst the tens of thousands of treatments safely delivered each day as evidence of the success of our ongoing safety initiatives. Both perspectives are valid; while consequential clinical error or other deviation from effective treatment is not the norm in the day-to-day practice of RO, even the most confident practitioners of radiation medicine know that similar episodes could happen again today, including at their own practices. Though the aforementioned tragic incidents are indeed uncommon in RO, the underlying contributing factors and latent errors are not. There is not a department in the world that does not have a history of errors. In addition, even in the most experienced and diligent of departments, deviations in treatment quality occur. Centers of safety excellence cannot rest on their laurels, because as treatment paradigms and technology evolve, new pathways for error can appear. These factors conspire to threaten patient outcomes (as well as the sound sleep of radiation oncologists and medical physicists) everywhere.

Thus, it is in everyone's best interests (and for the benefit of a well-rested workforce) to continue to examine and improve the safety and quality of the medicine we practice. In a field rife with healthy disagreement, this

represents an area of universal consensus. We have already dedicated considerable energy and resources to improving in response to the past experience, but there is still substantial room for improvement. This chapter reviews the current quality and safety initiatives, while also providing actionable direction to those looking to improve quality and safety in their own programs.

ETIOLOGY OF ERROR

An important foundational aspect of quality and safety is to understand the terminology used in the literature and in practice. "Harm," "error," "mistakes," "slips," and "complications" and other terms are words that may seem interchangeable but actually represent different concepts in safety.

Harm is perhaps the most straightforward of these concepts. The World Health Organization defines health care– related harm as "impairment of structure or function of the body and/or any deleterious effect … arising from or associated with plans or actions taken during the provision of healthcare."[4] Avoidance of harm is fundamental to good medicine, a principle immortalized in modern translations of the Hippocratic Oath: "First, do no harm." Ultimately, the most important outcome of a safety program is the minimization of harm to patients, and when the term "getting to zero" is used, it refers to zero harm, not the unattainable state of zero errors. However, an absence of harm does not equal safety. An optimal safety program will record and assess all errors, whether they result in patient harm.

An "error" is an action preceding and contributing to potential harm. The inverse is not always the case, in that not all harm results from an error. Treatment can result in unintended, negative consequences due to the unpredictable and complex nature of medicine. A patient can have a previously undiagnosed connective tissue disorder resulting in unanticipated toxicity from radiation, but the initiation of radiation therapy in this setting was not an error. Similarly, necessary risks are required in medicine. A course of reirradiation with a known high morbidity rate may be the only option for a patient facing death or disability without

intervention. It may not truly be an error if a patient experiences morbidity or even death as a result of undergoing this high-risk procedure.

How then should error in the health care setting be defined? Intuitively, error arises from deviations from accepted practice standards in situations where adherence to practice standards is an option. It also involves a risk (but not guarantee) of harm that a patient might not experience under standard of care treatment. Thus, errors could reasonably be defined as "deviations from the process of care, which may or may not cause harm to the patient."[5]

An "event" refers to any deviation from normal operations or planned treatment parameters, even if minimal to no patient impact or harm occurred. This definition is broader than that of an error and would include not only errors but also treatment variations, such as machine downtime, nonadherence to treatment recommendations by a patient, or unanticipated anatomic change. An "incident" refers to an unplanned change from normal system behavior that could have or did result in harm, treatment variation, or dosimetric impact outside accepted criteria.[6] An incident can be caused not only by an error but also by nonhuman factors that cannot realistically be controlled, such as flooding or power outage. Implicit in the classification of an incident is expected harm as an outcome, though this is not always the case with an event or error.

A key goal in quality and safety activities is to understand what causes error. For this purpose, it is helpful to understand that errors can be classified as "active" or "latent." Active errors occur at the point of contact between caregiver and patient. For example, a surgeon performing a craniotomy incision at the wrong site would be committing an active error. In fact, active errors are described as occurring at the "sharp end" of care, referencing the point at which scalpel meets skin. Latent errors, also called latent conditions, instead occur at the "blunt end" of care—the layers of care that precede or exist in parallel to the point at which harm befalls a patient. Omission of a mandated pretreatment pause for independent patient and plan verification is one such latent condition, as is failure to book a translator at a simulation appointment for a non–English-speaking patient. Latent conditions, as defined by the American Association of Physicists in Medicine (AAPM), are "underlying inadequacies in the design organization, training, or maintenance that have the potential to lead to

operator errors."[6] Latent conditions may also arise from elements well outside the care team, such as departmental, institutional, or governmental policy makers, device or pharmaceutical manufacturers, and outside practitioners and support staff. For instance, an ambiguous error message from the treatment planning system (TPS) was a latent error implicated in the fatal error causing the death of a patient in one highly publicized case.[1] The radiation oncology incident learning system (RO-ILS) has identified a number of vendor targets for product improvements to reduce latent errors.[7] A patient safety incident typically involves many more latent errors than active errors. Potential error origination far removed from patient contact illustrates the need for engagement in and practice of safety culture principles throughout the health care machine.

Somewhat different than latent conditions is the concept of "contributory factors," as notably presented in the Systems Analysis of Clinical Incidents: The London Protocol (Table 13.1).[8] These can be thought of as the conditions in which errors occur. This framework is tremendously helpful in incident investigation. Especially in the setting of an excellent team who nonetheless has a significant error occur, one should approach incident investigation with full knowledge that there is a rich background of factors that drive error. Understanding this not only improves the quality of the investigation but also alleviates the causation from being falsely attributed to a single act. These events never happen in a vacuum, and multiple contributory factors are at work to make an error happen. One study in RO suggested a median of seven causal factors per event.[9]

TABLE 13.1 FRAMEWORK OF CONTRIBUTORY FACTORS INFLUENCING CLINICAL PRACTICE

Factor Types	Contributory Influencing Factor
Patient factors	Condition (complexity and seriousness) Language and communication Personality and social factors
Task and technology factors	Task design and clarity of structure Availability and use of protocols Availability and accuracy of test results Decision-making aids
Individual (staff) factors	Knowledge and skills Competence

Factor Types	Contributory Influencing Factor
	Physical and mental health
Team factors	Verbal communication Written communication Supervision and seeking help Team structure (congruence, consistency, leadership, etc)
Work environmental factors	Staffing levels and skills mix Workload and shift patterns Design, availability, and maintenance of equipment Administrative and managerial support Environment Physical
Organizational and management factors	Financial resources and constraints Organizational structure Policy, standards, and goals Safety culture and priorities
Institutional context factors	Economic and regulatory context National health service executive Links with external organizations

From Taylor-Adams S, Vincent C. Systems analysis of clinical incidents: the London protocol. *Clin Risk*. 2004;10(6):211-220. Copyright © 2004 SAGE Publications. Reprinted by permission of SAGE Publications.

"Mistakes" and "slips" are other terms that are encountered and are closely related to active and latent error classifications. A mistake is the formulation of an inadequate plan of action, due to faulty knowledge, judgment, or thinking. Even if carried out exactly as intended, the plan will lead to medical error. A slip is a failure to execute an adequate plan in its intended manner, typically due to attentional lapses, forgetfulness, or fatigue. To take an example, a "slip" could cause a wrong site craniotomy if the surgeon correctly identified the site of the tumor preoperatively, but intraoperatively misidentified the intended site. However, if the motion artifact on preoperative imaging was incorrectly interpreted by the surgeon as an intracranial lesion, the error could be better classified as a mistake.

Not every adverse patient outcome is due to errors or poor quality care inflicting harm on patients. Problems that arise during an illness or treatment course (complications) can occur even when treatment is delivered in lockstep with best practices.[10] These complications should be

distinguished from harm resulting from error because they can occur without deviation from standards of care and are part of the inherent risk of cancer therapy. However, an unusual complication or an unusually high rate of complications may be indicative of systemic errors embedded in the workflow, such as a commissioning error.[11]

Finally, the harm caused by errors varies from clinically insignificant to devastating. Even two identical errors can differ dramatically in impact. An inappropriate setup may lead to a clinically inconsequential dosimetric deviation in a palliative case with large margins, or a lethal injury in a radiosurgery case. It is important, when analyzing events, to consider not only their actual impact but also their potential impact. The RO-ILS has select incidents reviewed by the Radiation Oncology Health Advisory Committee, a multidisciplinary group that (among other things) assigns a severity score to each incident (Table 13.2). This severity score notably includes both actual and potential harm. AAPM Task Group (TG)-100: Application of risk analysis methods to radiation therapy quality management[12] is a tremendous resource that also emphasizes that severity should be considered in potential as well as actual terms (Table 13.3). Although these scoring systems do not incorporate multiple scores for a single entry, the purpose of identifying workflows/processes that are the highest priority for corrective actions is kept in mind when scoring. A near miss that narrowly avoided a major overdose or wrong site administration would appropriately warrant a root cause analysis (RCA), whereas a harmless event involving a <5% dose deviation may not, despite the difference in error propagation. This is an important dimension and is discussed later in the chapter.

TABLE 13.2 ROHAC SEVERITY SCORE

Severity Index	Severity Description	Criteria
1	No potential or real harm	Event does not pose downstream risk in workflow. Event is not related to patient safety or quality of treatment.
2	Mild potential or real harm	Event may enhance the risk of other downstream errors.

Severity Index	Severity Description	Criteria
		Event may cause emotional distress or inconvenience to patient with no clinical impact.
3	Moderate potential or real harm	Event enhances the risk of other critical downstream errors. Temporary pain or discomfort for patient Deviations from best practices, but with no obvious clinical impact
4	Severe potential or real harm	Limited barriers to prevention of problem Event with potential clinical impact that is noncritical
5	Critical potential or real harm	Extremely limited barriers to prevention of problem Event with potentially critical clinical impact

Adapted from Nyflot MJ, Zeng J, Kusano AS, et al. Metrics of success: measuring impact of a departmental near-miss incident learning system. *Pract Radiat Oncol*. 2015;5(5):e409-e416. Copyright © 2015 American Society for Radiation Oncology. With permission.

TABLE 13.3 TERMINOLOGY RELATING TO SEVERITY AS USED IN THE TG-100 FMEA

Severity Term	*S* Values	Description
Wrong dose distribution	5-8	A failure in the delivery accuracy of the dose distribution that would be expected to increase adverse clinical outcomes (eg, reduced tumor control or increased likelihood of moderate-grade late toxicity) to a level that is statistically detectable in a large patient population. For definitive radiotherapy, a variation in the dose to the target or organs at risk of 5%-10% from the practice standard is suggested.
Very wrong dose distribution	9-10	A failure in the delivery accuracy of the dose distribution to an individual patient that is highly likely to cause a serious adverse clinical outcome (eg, tumor recurrence or grade III/V late toxicity) in that individual patient. For definitive radiotherapy, a threshold of about 10%-20% from the practice standard is suggested, depending on biologic sensitivities for the tissues under consideration.
Wrong absolute dose	5-8	A specific type of wrong dose delivery error in which the relative dose distribution is correctly delivered but the entire dose distribution is incorrectly scaled, due to variation in dose to the prescription point or isodose line, for example, caused by faulty machine calibration or MU calculation error. For definitive radiotherapy, a variation in the dose of 5%-10% is suggested.

Severity Term	*S* Values	Description
Very wrong absolute dose	9-10	A specific type of very wrong dose delivery error in which the relative dose distribution is correctly delivered but the entire dose distribution is incorrectly scaled, due to variation in dose to the prescription point or isodose line, for example, caused by faulty machine calibration or MU calculation error. For definitive high-dose therapy, a threshold of about 10%-20% is suggested.
Wrong location for dose	5-8	A failure in delivering the dose to the correct location that would be expected to increase adverse clinical outcomes (eg, reduced tumor control or increased likelihood of moderate-grade late toxicities) to a level that is statistically detectable in a large patient population. The size of the difference in positioning that constitutes such a failure depends on the anatomy of the target and OARs and the defined margins, but generally, differences of 3-5 mm between the locations of the reference and treated volumes are realistic for standard fractionation treatment.
Very wrong location for dose	9-10	A failure in delivering the dose to the correct location in an individual patient that is highly likely to cause a serious adverse clinical outcome (eg, tumor recurrence or grade III/V late toxicity) in that individual patient. The size of the difference in positioning that constitutes such a failure depends on the anatomy of the target and OARs, but generally, differences of more than 5 mm between the locations of the reference and treated volumes or inclusion of excessive normal tissue in the treated volume would be classified as “very wrong location.”
Wrong volume	5-8	A failure in delivering the dose to the correct target volume that would be expected to increase adverse clinical outcomes (eg, reduced tumor control or increased likelihood of moderate-grade late toxicities) to a level that is statistically detectable in a large patient population. Volume differences that constitute such a failure depend on the anatomy of the target and OARs and correspond to a marginal miss of the target volume or partial irradiation of an OAR to a sufficiently high dose that statistically detectable increases in complications are likely.
Very wrong volume	9-10	A failure in delivering the dose to the correct target volume in an individual patient that is highly likely to cause a serious adverse clinical outcome (eg, tumor recurrence or grade III/V late toxicity) in that individual patient Volume differences that constitute such a failure depend on the anatomy of the target

Severity Term	*S* Values	Description
		and OARs, and correspond to a geographical miss of the target volume or irradiation of an OAR to a dose sufficient to cause a complication or treatment failure in the patients.
Suboptimal plan	4	A treatment plan with characteristics unlikely to achieve the stated goals
Non–radiation-related physical injury	5-10	Injury resulting from causes other than radiation, for example, from physical trauma
Inconvenience patient	2-3	Failures that inconvenience the patient, for example, requiring an otherwise unexpected trip to the radiotherapy facility
Inconvenience staff or increased cost	1-2	Failures that inconvenience the staff, creating extra work, and cost of treatment or increasing stress

OAR, organ at risk.

From Huq MS, Fraass BA, Dunscombe PB, et al. The report of Task Group 100 of the AAPM: application of risk analysis methods to radiation therapy quality management. *Med Phys*. 2016;43(7):4209. Copyright © 2016 American Association of Physicists in Medicine. Reprinted by permission of John Wiley & Sons, Inc.

The above definitions and concepts are synthesized into a model of errors and accidents in Figure 13.1. One can see that there are many factors driving error, from latent failures to active failures of various forms. There are also defenses or "barriers" that prevent an error (once it has happened) from reaching the patient and potentially causing harm. An example of such a safety barrier would be the time-out to verify the site of surgery prior to a craniotomy. Although there are safety barriers in place, there may be deficiencies in these barriers that allow an error to reach the patient and become an incident. This is the so-called Swiss cheese model of Jim Reasons, in which each barrier is visualized as a slice of cheese with the holes in the cheese representing defects in the barriers.

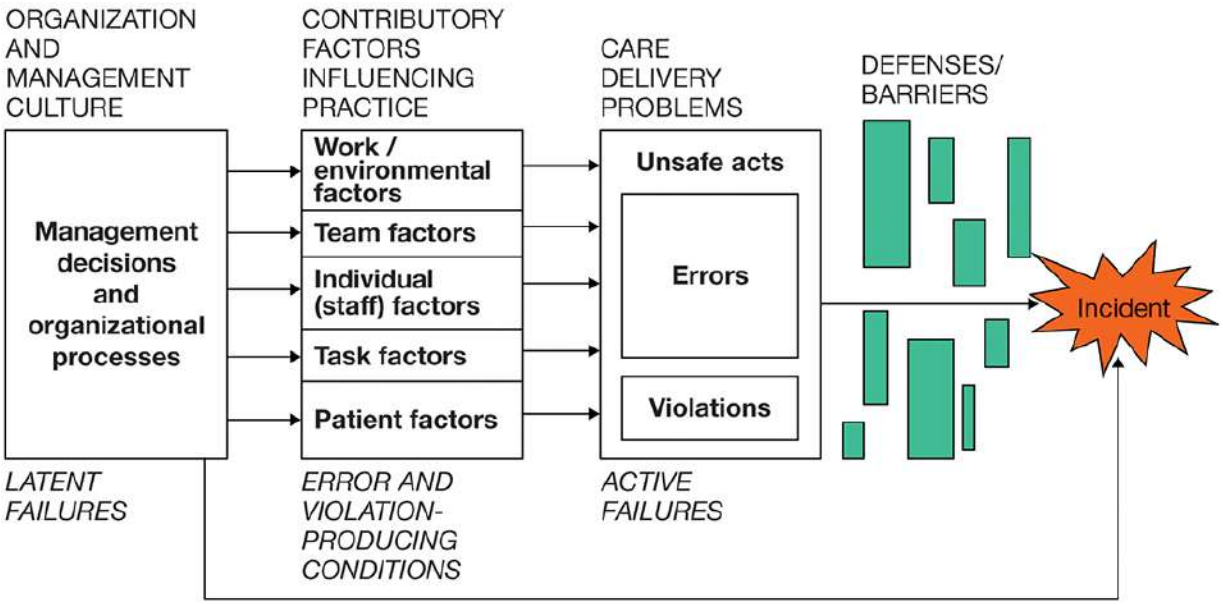

FIGURE 13.1 Adapted organization accident causation model. (From Taylor-Adams S, Vincent C. Systems analysis of clinical incidents: the London protocol. *Clin Risk*. 2004;10[6]:211-220. Copyright © 2004 SAGE Publications. Reprinted by permission of SAGE Publications.)

There are some data that indicate how permeable these safety barriers are in the RO context. Prospective studies of simulated error to gauge the effectiveness of chart rounds peer review[13] and the physics chart check[14] suggest detection rates well below 75%, with another study suggesting a chart round effectiveness of <20%.[15] Ultimately, we can conclude that errors are likely significantly more common than rates of reporting would suggest and are clinically consequential to the field on a day-to-day basis.

THE QUALITY GAP

Harm through error is not the only modifiable driver of suboptimal care in our field. Radiation therapy is an impressive product with great promise. Our understanding of disease biology continues to be refined, new technologies and therapeutics are incorporated into clinics, and practice patterns from even 10 years ago may diverge dramatically from modern guidelines. However, like any product, gaps exist between the expected and actual benefits to the consumer (or patient). This differential, known as the "quality gap," illustrates other important opportunities for improvement.

Error, as previously defined, does contribute to this gap in part. However, much of the gap arises from decisions that deviate from optimal clinical practice while still falling within acceptable practice standards. For example, using a nonstandardized dosing regimen may not meet the definition of error, but still undermine the quality of care; while a therapeutic breast radiation dose can be delivered with a 33-fraction course of breast radiation for a small, uncomplicated, resected primary in an older patient, a shorter course with a similar control benefit but with less treatment burden and fewer acute side effects would be a preferred solution. These choices that negatively impact the quality of radiation treatment delivered, despite being executed exactly as intended, represent a "leak" of therapeutic benefit. A review of treatment in even the most rigid, controlled settings suggests that this leak (and the resultant widening of the quality gap from radiation treatment) is substantial.

An excellent example of the quality gap comes from the quality assurance (QA) review of treatment plans as part of clinical trials. These studies are the most direct way one could measure the quality gap in a real-life scenario. These studies reveal that deviations in care are common and impactful. In a post hoc analysis of TROG 02.02, a phase III trial enrolling patients with head and neck cancer to chemoradiation with or without tirapazamine, 25% of radiation treatment plans were found to be noncompliant with the study protocol.[16] About half of these noncompliant plans were found to have a deficiency that predicted a potential impact on tumor control, despite receiving a complete course of radiation. These patients had a markedly inferior outcome compared with those whose treatment was protocol compliant, with a significantly lower overall survival (OS) at 2 years of 50% versus 70%. A similar analysis of RTOG 9704, which randomized patients with resected pancreatic cancer to two different chemoradiation regimens, found that 48% of plans assessed were not per protocol.[17] Remarkably, per protocol radiation treatment was found to be a stronger predictor for median survival than randomized treatment arm. Indeed, a meta-analysis of QA reports from cooperative group trials found that radiation plan deviations were associated with a statistically significant decrease in both OS and treatment failure.[18]

We can also see how treatment promise and outcome can diverge from suboptimal plan generation and approval. While there may be numerous

valid approaches to treatment planning a specific case, some will inevitably be better than others, in the sense of either improving prescription coverage, sparing organs at risk (OAR), or shortening time on the table. This was highlighted through planning competitions run by radiation societies[19,20] or vendors.[21] All submissions to these contests were required to meet set criteria and were subsequently scored on nonrequired quality metrics, such as the degree of OAR sparing. Submission scores covered a large range, from barely adequate to outstanding.[19,20] Ideally, all radiation treatment plans would be selected from the highest scoring plans of these treatment contests. However, many of these lower scoring plans were put forward as the best effort of the submitter. This missed opportunity for treatment plan optimization further contributes to the RO quality gap.

The concepts of safety and quality are linked because both attempt to achieve the same end: bringing the care we do deliver closer to the level of superior care we could deliver. While safety primarily focuses on reducing harm, narrowing the quality gap may lead to the additional benefit of reducing waste, delays, and both under- and overtreatment.[22] Thus, it is an important and effective framework to use when launching a quality improvement initiative.

CHALLENGES IN ERROR MONITORING

Errors in RO are reported at a rate of ~0.2 to 0.7 per patient.[23-25] However, it is reasonable to assume that many errors do not get reported. In fact, studies indicate that 80% to 90% of errors committed are not reported.[26]

The reason for this reporting gap is likely to be multifactorial. Reporting of errors may be avoided due to additional documentation burden.[27,28] Staff members who may observe an error may not report it under the incorrect assumption that someone else may do so ("bystander effect").[28-30] The reasons given may vary by professional group. An analysis of attitudes about reporting among the multidisciplinary team found that physicians were significantly more concerned about getting colleagues in trouble, liability, effect on departmental reputation, and embarrassment than their colleagues.[31] Some staff may prioritize fixing the immediate problem rather than reporting the issue.[32] Another significant factor is whether reporters receive feedback about the errors they submit. Lack of feedback may

disincentivize reporting due to the resulting perception that submissions are being ignored.[33] In a large Agency for Healthcare Research and Quality (AHRQ) survey, the most significant predictor for the frequency of reporting any type of event was feedback about errors.[34]

In addition to these issues with reporting known errors, there is also an entirely separate issue that not all errors will be discovered. It can be difficult to detect errors when there is uncertainty associated with the outcomes of therapy and there are multiple teams (medical oncology, pathology, surgery, and radiology) who all contribute to the outcome of a patient's treatment. Poor decisions can be made, but it is not possible to know with certainty that an error in judgment definitively was responsible for a poor outcome, especially with poor prognosis cancers. Some errors may not result in a noticeable clinical impact. A patient treated with suboptimally homogenized breast radiation may never experience symptoms from resultant fibrosis. Others may contribute to clinical outcomes but be overlooked due to the accepted treatment-related uncertainty. Grade 3 dermatitis is a known toxicity in head and neck cancer and is thus likely accepted as an unavoidable complication if an incorrect dose calculation led to a 10% increase in skin dose. Other errors may only result in clinically apparent findings years after treatment, obfuscating the connection between suboptimal radiation treatment and late toxicity in the setting of other treatments or progression that occurs in the interval. Some late toxicity may never manifest at all due to the competing risk of cancer-related mortality. Even if the resources existed to comb through every treated patient's chart, error detection rates are unlikely to be favorable. Many would be impossible to detect retrospectively due to unclear or lacking documentation. If treatment is delivered via clinical setup (ie, without imaging documentation) to the wrong location on a patient's body, for example, without photographic documentation, it can be almost impossible to "reconstruct" this error in retrospect.

Despite these challenges, maximizing error identification and reporting is an objective for centers of safety excellence. Strong patient safety culture has been associated with higher rates of error reporting. This relationship is likely bidirectional, as data from event reporting refine and improve organizational culture, and as trust in the existence of a "just culture" normalizes blame-free error reporting.[23,35-37] This leads to the paradox that

more events reports may actually indicate a safer work environment. Hartvigson et al[38] found that as the number of events increased, the severity of these events decreased.

We can draw upon reported data to better estimate error prevalence. The EORTC "dummy-runs" QA program—where each institution must segment and plan on a "dummy" computed tomography (CT) prior to credentialing—showed major deviation rates of 35% to 95% with first submission across disease sites.[39] This is confirmed by real-world data from RO-ILS demonstrating that "problematic plan approved for treatment" is a common error pathway.[40] Clinical trial QA review provides further insight, also discussed in section "The Quality Gap." Protocol deviations (often segmentation not per protocol or dose not per protocol, analogous to segmentation or dose not as per agreed standards of practice)[41] detected as part of QA for multi-institutional prospective trials were common and are found among all disease sites.[16-18,42] While there are multiple paths to a patient plan with a "major" deviation from mandated protocol, presumably, many are due to error.

CONTRIBUTORS TO ERROR

Now that we have defined errors and established their frequent occurrence, what contributes to error occurrence in the first place, and how do we mitigate these contributing factors?

Wellsprings of Error: Human Beings

Errors tend to originate from human beings ("human error"). However, this categorization is the least useful in error categorization, because it is immutable. The reality is that so long as human beings are involved in health care, then errors will be committed, though this does not mean we must resign ourselves to errors frequently reaching the patient and compromising health care provision. It seems logical that given the human origin of most errors, focusing energy on "exhortation" (encouraging vigilance) is the best way to improve safety. Unfortunately, this conclusion is misguided, as other than the rare case of a health care worker who is exhibiting poor judgment to the point of recklessness, exhortation is one of the least effective safety measures at our disposal[43] (Table 13.4), even

though it is commonly used.[56] As previously mentioned, instilling a "culture of blame" with fault attributed primarily to individuals after an error may disincentivize reporting, leading to more errors in the future as vulnerabilities of that system remain unilluminated. Instead, error occurrence, in the sense of a patient's treatments deviating from standard of care, is better attributed to failures of the overall system in which the error occurs and is propagated.

TABLE 13.4 HIERARCHY OF INTERVENTIONS

Intervention Type	Example
Forcing functions	A radiotherapy treatment plan cannot be delivered to a patient unless the plan has been approved by a physician and a medical physicist. Linear accelerator interlocks turn the treatment beam off if an error in delivery is detected.
Automation, computerization, and technology	Quality assurance tasks are automatically completed and uploaded into the patient record.[44] AI is used for the automation of SBRT treatments.[45]
Standardization and protocols	ASTRO publishes "Clinical Practice Guidelines"[46] and "Consensus Documents,"[47] and including many safety-focused white papers. A practice achieves APEx accreditation.[48]
Staffing organization	Published staffing guidelines[49] are followed at a minimum.
Policies, rules, and expectations	A centralized resource[50] is used to support the management of departmental policies and procedures.
Checklists and double-checks	An automated checklist[51,52] is used to verify treatment plan quality.
Risk assessment and learning from errors	RO-ILS publishes aggregate data reports[53] that show trends in events, as well as case studies that explore more deeply into a single event.
Education and information	An email is sent out to treatment team members to remind them how to perform a certain procedure. Team members participate in continuing education and competency review, with retraining as needed. New staff receive onboarding.
Personal initiative—vigilance	Workers remain in a state of "chronic unease," that is, they maintain "a healthy skepticism about one's own decisions

Intervention Type	Example
	and the risks that are inherent in work environments."[54,55]
Exhortation	Reminders to be more vigilant

AI, artificial intelligence; APEx, Accreditation Program for Excellence; ASTRO, American Society for Radiation Oncology; RO-ILS, radiation oncology incident learning system; SBRT, stereotactic body radiation therapy.

The Importance of a Culture of Safety

Institutional culture is a critical driver of error occurrence, just as it is a driver of error detection. Any high-performing radiation safety program has a robust safety culture as its centerpiece. Safety culture has been defined as the "culture that allows the boss to hear bad news."[57] The American Society for Radiation Oncology Accreditation Program for Excellence (ASTRO APEx) thoroughly defines the standard for safety culture in RO (Table 13.5),[58] and other standards are available.[59]

TABLE 13.5 ASTRO APEX ACCREDITATION PROGRAM STANDARDS FOR A "CULTURE OF SAFETY"

The Radiation Oncology Practice (ROP) has a policy on patient safety that:

- Articulates the practice's approach to patient safety.
- Specifies that patient safety events, including patient safety incidents and near misses, are to be reported and tracked within the practice.
- Identifies methods for staff to report patient safety events and unsafe conditions, including a method for staff to report anonymously.
- Encourages timely reporting of patient safety events and unsafe conditions by all staff.
- Specifies periodic reporting back to staff on activities and findings of the culture of safety program.
- Specifies that procedures are not started until all questions and/or concerns are resolved.
- Provides assurances that there will be no reprisals based on reporting of patient safety events and unsafe conditions.
- Identifies a role for patients in the culture of safety programs.

Designates an accountable individual from the practice leadership who is:

- Responsible for implementing the requirements of Standard 7, which states that the ROP fosters a culture of safety in which all team members participate in assuring safety, the practice capitalizes on opportunities to improve safety, and no reprisals are taken for staff that report safety concerns.

- Responsible for collection of information and investigation of patient safety events and unsafe conditions.
- The lead on convening Interdisciplinary Safety Rounds.
- Evaluated in part for providing leadership to the practice's culture of safety program.

Conducts Interdisciplinary Safety Rounds at least quarterly to:

- Promote a team-based approach to safety.
- Review all patient safety event and unsafe condition data from patients, staff, and equipment.
- Proactively assess the ROP's structure and processes that promote safety.
- Develop, implement, and assess progress of action plans to improve safety.

If a patient safety incident occurs, the ROP:

- Undertakes an immediate review, with the goal of understanding underlying factors and taking action to prevent future occurrence.
- Complies with institutional, state, local, and national requirements for reportable patient safety incidents.

Reports to and participates in:

- A patient safety organization (PSO)

APEx, Accreditation Program for Excellence; ASTRO, American Society for Radiation Oncology.

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However, organizational culture is not purely defined by stated policies. Rather, it is built by establishing a universal trust that these policies are valued and respected, even when they may come in conflict with competing practice priorities. For example, a high-performing safety culture necessitates time to be invested in performing the necessary checks designed to ensure safe care.[60] This conflicts with pressures in health care to increase patient volumes and revenue generation. Another example is the pressure in health care to avoid interfering with patients under the direct care of others (to avoid "stepping on toes"), in particular within a tertiary referral field like RO. This tendency may serve as an intrinsic barrier to airing concerns about the care plan of a colleague's patient, along with the desire to avoid ego dystonia for oneself and one's colleagues. Nonetheless,

a strong departmental and institutional culture will make such discussions better tolerated, as the desire to improve is the clear motivation for such discussions.

A poor culture will undermine sound policies by reducing adherence and implementation. Validated measures of organizational safety culture are inversely correlated with patient outcomes[61] and adverse events.[62] On a more granular level, a culture internally perceived as unsupporting of safety practices is associated with poorer performance in elements of RO QA. Using participation in peer review as an example, a published survey demonstrated that physicians in a pro-peer review environment were nearly 70 times more likely to be involved in peer review compared with physicians in hostile, anti–peer-review environments and that less than 2% of those who work in a hostile environment were involved in ongoing peer review.[35] Absence of a "just culture" or failure of leadership to inspire confidence that such a culture will be upheld in practice is a major contributor to disengagement from safety practice. Steps to build and maintain a strong culture of safety are described in the sections that follow.

Burnout

Professional burnout, a "syndrome characterized by exhaustion, cynicism, and reduced effectiveness," can drive error occurrence and impair detection and correction.[63] Burnout is markedly higher in medicine than in other fields nationally and has been directly associated with worse quality and safety outcomes. Radiation oncologists have high estimated rates of burnout at all career stages.[64] An individual displaying the symptoms of burnout is likely less attentive, more prone to circumventing safety procedures due to fatigue or apathy, and less effective at applying their knowledge to identify errors they encounter. The contributors to burnout are similar to those that threaten safety culture, including increasing productivity expectations, documentation burden not directly related to patient care, value misalignment between staff and leadership, and support staff turnover.

Hierarchy and Fear of Reprisal

Aversion to antagonizing more senior colleagues perpetuates the propagation of errors through to the patient. Medicine is hierarchical by

nature, and physicians, physicists, and other members of the radiation workforce typically spend many years as trainees in graduate school and internship/residency before becoming fully certified practitioners. A culture of deference to seniors is firmly instilled from these years of training, and even after board certification, there may be a pause to identify another practitioner's treatment as unsafe.[65] Stopping the treatment workflow of a colleague (or superior) to question an aspect of care being delivered is intimidating and can indeed lead to blowback if unchecked narcissistic personalities are involved.[66,67]

The threat of adverse consequences from error reporting, or operating in a punitive culture, clearly disincentivizes error reporting. Beyond concerns about coming off as noncollegial, the reputational consequences of publicizing an error can be embarrassing. Medical professionals may also be opening themselves up for civil or even criminal prosecution. In a particularly notable example of a punitive culture in action, a nurse who accidentally substituted vecuronium for Versed to a patient resulting in death was prosecuted and convicted of homicide after immediately disclosing their error to their employer.[68] This occurred even though they were operating in a weak system that allowed them to override it and obtain the potentially lethal drug. It is easy to see how such prosecutions disincentivize honesty and error disclosure. A "reporting culture" is ultimately beneficial to patients: Not only do greater numbers of reported events make emerging risks more apparent, but rapid reporting of serious events can ultimately save lives.[69]

Cognitive Biases

Beyond these environmental barriers, a major contributor to error is the very hardwiring of our brains. We are capable of deep and careful thought, but frequently find ourselves in time-constrained scenarios where we rely on mental shortcuts, or "heuristics." These heuristics will help us come to a solution more quickly, but unfortunately do not ensure we come to the optimal solution, or even a good solution. According to Gonzalez,[70] "heuristics are the 'shortcuts' that humans use to reduce task complexity in judgment and choice, and biases are the resulting gaps between normative behavior and the heuristically determined behavior."

Medicine is full of examples of cognitive bias affecting care. Particularly recognizable examples include confirmation bias, which is our tendency to interpret new information in a way that fits our preexisting narrative; search-satisfying bias, whereby an error detected in a plan may lead to a decrease in vigilance for a second concurrent error; expectation bias, where we see what we expect to see even when it is not present; anchoring, whereby one demonstrates a proclivity to their initial impression; sunk cost fallacy, where we are reluctant to abandon work put into achieving a task one way, even when a second, more efficient option presents itself; and even cutoff bias, whereby continuous variables are dichotomized into two groups of "larger" and "smaller," leading to irrational decision-making around the point of dichotomization.[71,72] All these examples have been shown to impact patients in the RO clinic (Table 13.6).

TABLE 13.6 DEFINITIONS AND EXAMPLES OF COMMON COGNITIVE BIASES PRESENT IN MEDICINE

Bias Name	Definition	Example
Confirmation bias	Tendency to interpret new information in a way that fits one's preexisting narrative	After documenting in the chart that a tumor histology has a low risk of nodal metastases, assuming suspicious regional nodes identified on staging imaging are reactive and forgoing further workup
Search-satisfying (bounded rationality) bias	Once an error has been detected during review, discontinuing the search for additional, concurrent errors.	After noting that a superior field border on a breast plan should be raised, adjusting that border and forgoing further review without noting simultaneous use of inappropriate dose/fractionation schema
Expectation bias	Seeing what we expect to see even when it is not present	After reviewing charts prior to consult and seeing a 65-year-old patient with early-stage breast cancer following lumpectomy, concluding adjuvant radiation is necessary even after the patient arrives and reports numerous other comorbidities making them a poor candidate.
Anchoring	A proclivity to their initial impression	Being unwilling to deviate from initial tumor board recommendation even

Bias Name	Definition	Example
		when a more favorable treatment regimen is suggested
Sunk cost fallacy	Reluctance to abandon work put into achieving a task one way, even when a more favorable path opens	Rationalizing keeping a treatment plan unchanged due to effort spent contouring and planning after significant modifications recommended at peer review rounds
Cutoff bias (left digit bias)	Dichotomizing continuous variables into two groups of "larger" and "smaller," leading to irrational decision-making around the point of dichotomization	Recommending adjuvant radiation therapy to all 69-year-olds with early-stage breast cancer evaluated in clinic, and observation to all 70-year-olds because they are "older"

There are internal and external contributors to the likelihood that cognitive biases manifest in a harmful way. These biases arise from mental shortcuts we subconsciously implement, so the more time restricted we are, the more likely we are to fall into using these tools.

Technology and Increasing Complexity

Technological advancement may make error occurrence more frequent and error detection more challenging.[73] As the pathway of treatment becomes more opaque to human users, it can be less clear when a poor-quality treatment is being delivered. With two-dimensional fields, the relationship between an incorrectly positioned light field and altered dose distribution would likely be more apparent to a planning and therapy team than if the same site were treated with a multiisocenter volumetric modulated arc therapy (VMAT) plan. Complexity of treatment may offer more pathways for failure, or more reliance on additional safety checks and QA features, further straining workflow and creating opportunities for skipped steps. The more staff are expected to know, the less experience they may have with any one of a diverse array of techniques; indeed, after introduction of a more modern treatment technique, one study showed that the error rate during performance of an older, simpler technique increased.[74] The authors speculate this may be due to decreasing familiarity with older (but still important) techniques as new ones are internalized. Adaptive treatment,

artificial intelligence (AI)-based delineation, decision support tools, and ablative treatment across multiple sites simultaneously may represent particular challenges for our field, given rapid adoption but limited safety reporting.[75] In particular, adaptive planning may require the involvement of multiple physicians, physicists, dosimetrists, and radiation therapists to cover replanning, and the need to communicate the clinical scenario, target location, necessary margins, directive priorities, and respiratory gating—all creating opportunities for error introduction within the cognitively more challenging cross-coverage situation.[76] Recommendations for personnel, communication, QA, and workflow requirements have been published, and further guidance is anticipated.[77]

Mistake-Prone Design

Finally, the systems we use in radiation therapy may not be designed with error prevention as a priority. No one benefits from medical error. Yet safety functions can be dissatisfiers to the end user and so not embraced by the vendor. Restricting permissions, mandatory warnings, and other forcing functions can slow the process of care. Economic or advanced technological benefits are more frequently factored into purchase decisions, and vendors may be more interested in promoting those benefits. In addition, while competition is welcome between vendors in RO to promote innovation, it can also prevent standardization between sites using different vendors. In a notable example, two of the most popular documentation systems used in RO display total prescription dose and dose per fraction in reverse order,[78] and as of this writing, vendors still have failed to adopt the ASTRO standard prescription or switch to cGy as the standard unit of dose. This choice of display works against reducing episodes of dose/fractionation reversal, a potentially impactful error known to occur with high frequency.[40,53] Nonstandardized character limits for structure name and variation in default coloration schemes for preloaded contours and isodose lines are further examples.[79] “Mistake proofing” is the concept of making errors more difficult to achieve, or more detectable once manifest. In *The Design of Everyday Things* by Donald Norman, the operation of a modern stove is used as an example.[80] By mapping the position of switches to that of the stovetop burners and using a light to signal the stove is on, the system

aligns user expectation and output, making unintended outcomes (activating the wrong burner and starting a kitchen fire) less likely. Similar principles have been applied to the design of therapy workstations.[81] Partnering with vendors to "mistake proof" increasingly complex hardware and software is an opportunity, and a responsibility, that should not be overlooked.

PREVENTION AND RESPONSE TO RISK AND ERROR

Building and Maintaining a Strong Safety Culture

As introduced above, a critical aspect of error prevention is the development of a strong safety culture among all members of the RO team. ASTRO's "Safety is No Accident" defines a safety-minded culture as an environment where "all staff are encouraged to suggest and effect change to improve safety, quality, and efficiency." RO departments are fast-paced environments where new technology and treatment strategies are continuously being implemented, and workflows are being updated to accommodate these changes. The exchange of information between team members, both intra- and interdepartmentally, is constant and occurs via multiple channels, such as email, text, phone calls, department or hospital-based electronic information systems, or even quick chats in the hallway. Each year new team members join, creating the opportunity for innovation and learning but at the same time increasing the risk of error due to incomplete onboarding, and others may leave, potentially leaving experience gaps in their wake. Because of these features, the focus on a culture of safety must also be continuous, such that all team members are empowered to speak up when there is a concern for patient safety or an opportunity for process improvement.

Quantitative survey instruments exist for evaluating and identifying any weak points in team safety culture that should be addressed. For example, the AHRQ developed the freely available Hospital Survey of Patient Safety Culture (SOPS).[82] These types of surveys can be used on an ongoing basis to track progress and highlight potential gaps. A 2010 study by Mardon et al[36] showed that there was an inverse relationship between hospital patient safety culture as quantified by AHRQ's Hospital SOPS and adverse events. Interestingly, safety culture as quantified by SOPS was significantly

associated with patient satisfaction, though the correlation was weak (r = 0.4).[83]

At Michigan Medicine, safety culture in the department of RO is evaluated on an annual basis using an all team member survey that asks about perceptions of safety culture and attempts to determine any barriers to achieving a stronger safety culture. Survey participants are also given the opportunity to provide qualitative feedback. Survey results are reported back to the department along with each of the (anonymized) qualitative comments and information about how each has been or will be addressed. To the extent that survey participant confidentiality can be maintained, (optional) demographic information such as gender, age, level of experience, and departmental role are collected. This allows the stratification of safety culture perceptions across groups by the four largest teams in the department (Figure 13.2).

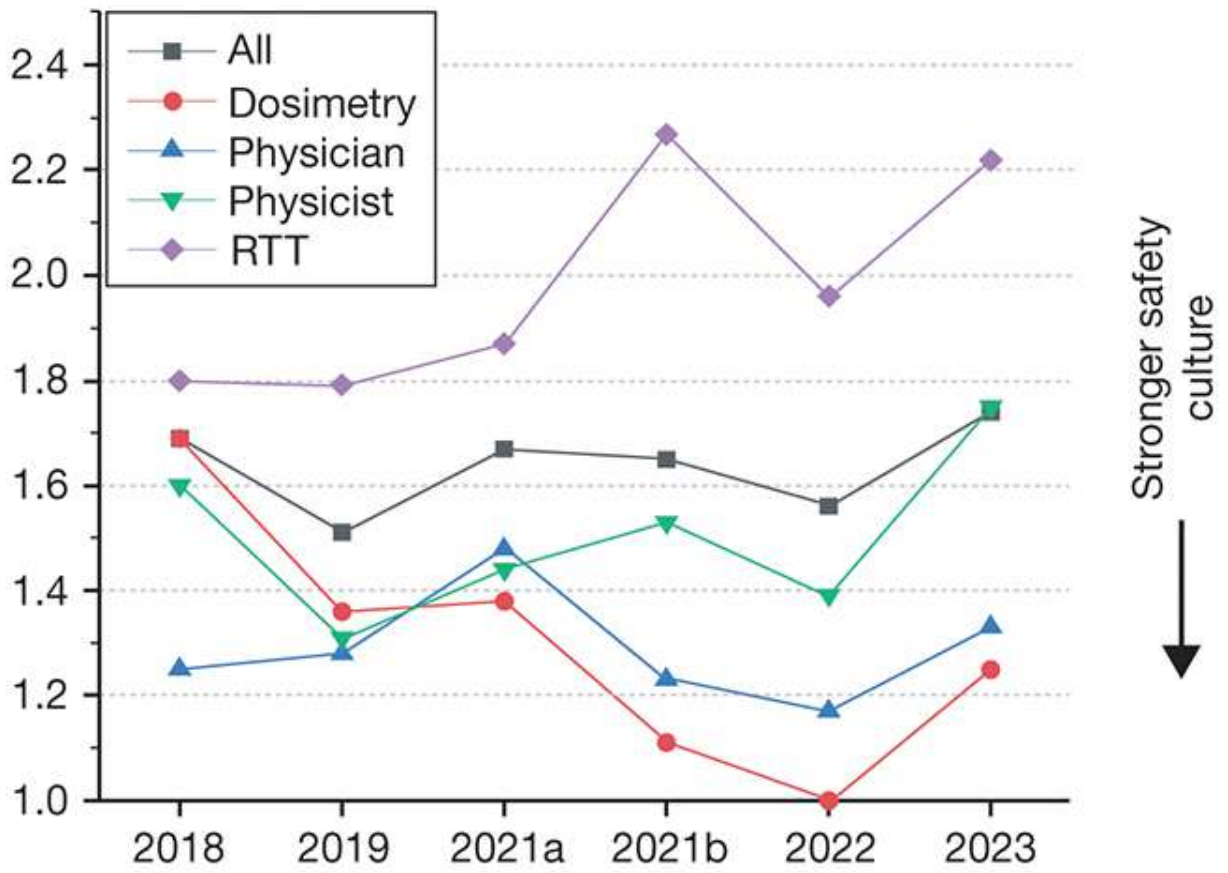

FIGURE 13.2 Results of the safety culture assessment survey in the department of radiation oncology at Michigan Medicine over 6 years. Responses graphed are to the question: Overall, I would rank the safety culture in our department as excellent (1), good (2), average (3), poor (4), or terrible (5). The 2020 survey was delayed by the COVID pandemic, resulting in two surveys separated by 8 months in 2021.

Work Environment and Leadership

Leadership in an RO department set the tone for the safety culture. In fact, one of the sections of the AHRQ Hospital SOPS focuses specifically on leadership, using the questions "[Leadership] seriously considers staff suggestions for improving patient safety," "[Leadership] wants us to work faster during busy times, even if it means taking shortcuts," and "[Leadership] takes action to address patient safety concerns that are brought to their attention."

The term "leadership" is deliberately left broad, because of the broad range of personnel involved in radiotherapy treatment. It includes not only the Medical Director or Chair but also administrative directors, division directors, team leaders, and those in supervisory or mentorship roles,

whether formal or informal. Leaders must support the open, nonjudgmental, and nonpunitive discussion of errors and safety events. The viewpoints and experiences of front-line staff are critical in both the prevention of and response to errors. These personnel should be approached with humble inquiry: "the gentle art of drawing someone out, of asking questions to which you do not know the answer, of building relationships based on curiosity and interest in the other person," rather than handing down decisions "from above."[84] The focus should be on creating a "just culture," which is different from a blame-free culture.[85] Each team member is held accountable for their actions, while at the same time acknowledging that most errors originate at the systems level. An example of a framework for determining consequences in response to incidents is given in Figure 13.3; this emphasizes punitive measures only for reckless or negligent behavior.

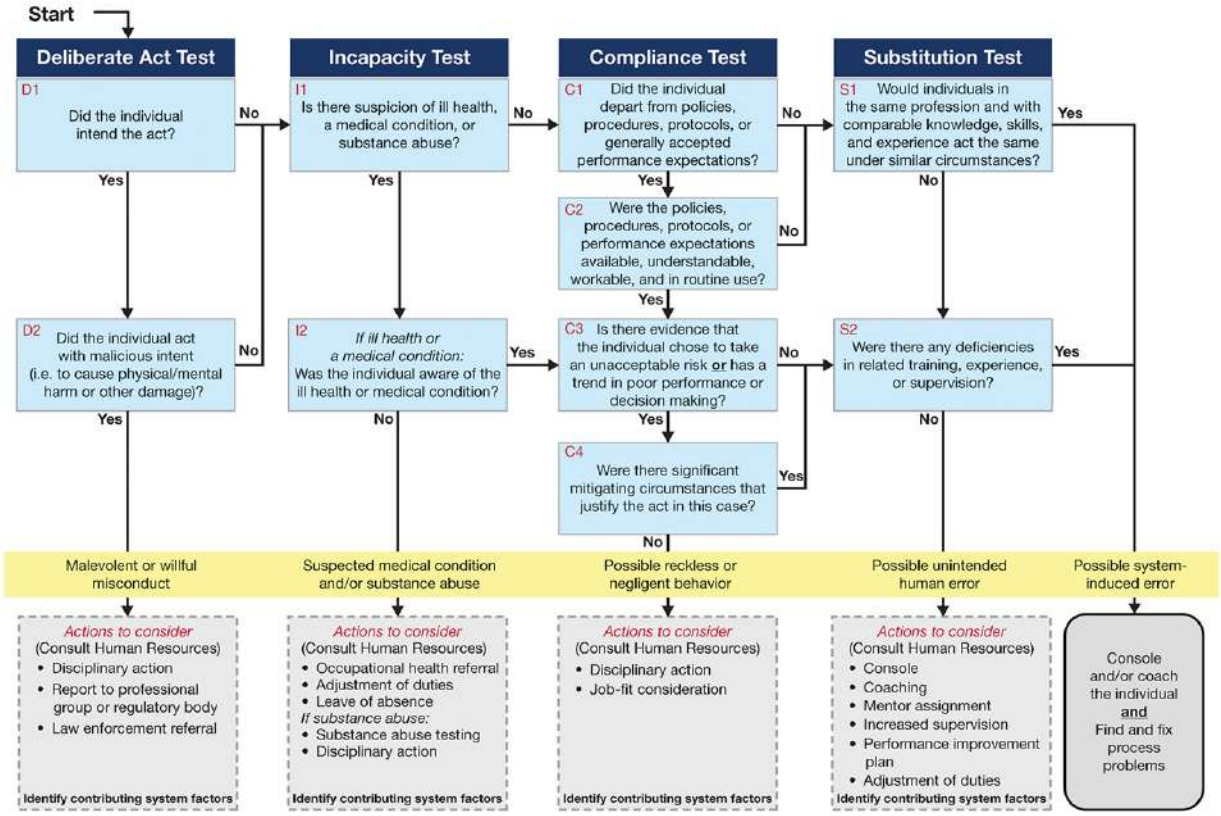

FIGURE 13.3 Performance management guide. (Adapted from James Reason's "Decision Tree for Determining the Culpability of Unsafe Acts" and the Incident Decision Tree of the National Patient Safety Agency. Reprinted with permission from Press Ganey Associates, LLC.)

The way that communication is conducted between team members forms the foundation of safety culture in an RO department. Fundamentally, everyone has a need to feel respected, that their contributions are valued and their work appreciated, and that their opinions are taken seriously. When an error happens, there may be many complex underlying and unspoken emotions. How each team member responds in the face of these events will impact not only the current situation but also the response to any future events that occur. Consider an example where a patient is being treated to a site that is nearby to a previously irradiated site. The treatment planning is complicated and requires considerable back-and-forth email communication between the physician and the dosimetrist. During these exchanges, an email message from the physician to create a composite plan with the prior treatment is not seen by the dosimetrist. During the physics chart check, the physicist creates a composite plan and finds that there is a high-dose overlap between the treatment sites.

Communication about this event now becomes paramount. The physicist could blame the dosimetrist, asking how they could forget when it is documented on the planning directive that a plan sum was needed. The dosimetrist could blame the physician, asking why they would approve a plan without documentation that it did not overlap with a prior treatment. The physician could blame the physicist, asking why the software and established workflows would allow them to approve a plan without sufficient documentation of the overlap. An email could be sent out reminding people that reirradiation status should be reviewed repeatedly during planning. A new checklist item could be added to remind everyone to check the status of prior radiation before moving on to the next workflow step. These are deeply unsatisfactory solutions that leave everyone feeling like they failed and that similar events could easily recur in the future and perhaps even would not be reported due to fear of blame or retribution.

Alternatively, the team could approach the event as a problem to be solved together without blame or focus on the individual, from a systems-level view. The team would examine the root causes, which likely also contribute to other similar events in the same department and identify solutions that not only make future events less likely but also leave the team feeling supported, valued, and respected.

Hierarchy of Interventions

When either prospectively trying to prevent or retrospectively responding to a safety event or process concern, there is often an inverse relationship between the difficulty of an intervention and its effectiveness. Interestingly, people favor additive solutions, where steps are added on to a process, despite the fact that there may be more elegant solutions that eliminate steps and improve the reliability of the process.[86] In addition, because of the limited time available in a busy department, the focus tends to be on the faster interventions first, such as reminders (exhortation) and reeducation, as described in the example above.

A hierarchy of interventions was developed by the Institute for Safe Medical Practices[87] to address the prevention of medication errors (see Table 13.6). This framework was later adapted more broadly with a focus on communication by Woods et al.[43]

Accreditation

Accreditation is an important component of establishing a robust safety program, not the least of which because it involves the review of a program from the outside, which may uncover issues that those working within the program may not be able to identify. The goal of accreditation is to "ensure patients receive consistently high-quality, team-based care."[88] Recent practice guidelines have emphasized this importance.[89]

The accrediting bodies for RO are ASTRO's APEx, American College of Radiology (ACR) Radiation Oncology Practice Accreditation (ROPA), and ACRO. APEx, established by ASTRO in 2014, has five pillars: the process of care, the RO team, safety, quality management, and patient-centered care.[58,88] The process begins with an internal self-assessment, followed by an external assessment ("facility visit"). The self-assessment allows an institution to clearly understand the expectations of the accreditation program, as well as to find and address any potential areas for improvement, increasing the chances that the external assessment will be successful. The ACR's ROPA program has been in place since 1987. It begins with an online application including equipment, staffing, and QA/QC (quality control) documentation, and like APEx, includes a detailed

assessment by board-certified surveyors. More details about both these programs can be found on their associated websites.

SPECIFIC QUALITY ASSURANCE TOOLS TO REDUCE ERROR

The sections above focus on factors or interventions at a system level, for example, culture of safety and practice accreditation. However, there are also many highly specific QA tools available in RO that work to reduce errors or minimize their impact. Here we consider a few of these.

QUALITY ASSURANCE OF PHYSICAL DOSIMETRY

There are numerous QA tools that lie in the professional realm of medical physics with the overall goal of delivering the prescribed dose to the intended target for each patient. While a full description of these is beyond the scope of this chapter, a comprehensive compendium can be found in Dieterich et al[90] as well as TG reports[91] and Medical Physics Practice Guideline (MPPG)[92] from the AAPM. Some of these QA tests are performed on each specific patient plan, such as the recommendation to perform a secondary dose calculation (see AAPM TG 219).[93] Other tests are more systemic in nature and affect all patient treatments, such as the recommendation to verify the radiation output of a linear accelerator each month to an accuracy of at least 2% (see MPPG 8).[94] This is an example of a QA test that is performed on a regular basis. Other QA tests are less frequent, such as the verification tests that are performed when installing and commissioning a new treatment planning system (see MPPG 5).[95]

PEER REVIEW

Peer review is a crucial concept in RO, health care, and scientific pursuit in general that refers to the review of one's work by an equally competent reviewer ("peer"). There are numerous forms of peer review present in radiation planning and treatment delivery, serving as QC checkpoints in the generation of a radiation treatment plan. Each instance of peer review in the RO process targets a specific dimension of treatment and planning (eg, the decision to treat, plan contours, dosimetric verification). Peer review may

also involve duplicative, overlapping checks of elements that are also included in other QA steps either upstream or downstream.

Two major forms of peer review in the RO workflow are physicist chart checks and chart rounds.

Physicist Plan and Chart Review

Physicist plan and chart review represent a universal element of the clinical workflow mandated by societies for accreditation (AAPM, ASTRO). They represent some of the highest performing safety checks in the RO workflow in terms of the breadth of errors detected.[96] These chart checks encompass pretreatment, on-treatment, and post-treatment review of the radiation plan quality, safety, technical feasibility, and treatment delivery. The AAPM TG 275 report and the MPPG 11.A both provide the contemporary guidance on the performance of this QA step.[97,98]

Chart Rounds

Chart rounds occur in some form in essentially every North American RO department and are the point at which many radiation oncologists most actively engage in departmental quality and safety.[99] Chart rounds have several components and are ideally conducted in a multidisciplinary manner. Physician peer review, "the evaluation of components of a radiation treatment plan by a second radiation oncologist … to ensure it is appropriate from both patient safety and treatment effectiveness perspectives," occurs here, but is by no means the only review.[100] To meet accreditation standards, the structure of chart rounds typically entails presentation of individual cases and review (at a minimum) of clinical background and targets.[35,101] Physicists, dosimetrists, therapists, and nurses all have a valuable role in this process. Therapists may comment about the reproducibility of a chosen immobilization device; physics might comment about the high Hounsfield units in a breast expander introducing unanticipated ambiguity about the accuracy of dose calculation; dosimetry might inquire about whether an avoidance sector was used in a VMAT plan to avoid a previously treated field; nursing might have valuable insight about a patient's understanding about their treatment or ability to adhere to the proposed course. Chart round is a time to globally assess the

appropriateness of treatment, and the contributions of all team members are to be valued and heard. An important concept to chart rounds is that as opposed to most QA processes, a major focus of chart rounds assesses if something was *done optimally* rather than simply *done*. It also serves as a uniquely comprehensive review at the treatment planning step, by offering the opportunity to review target volume delineation, OAR delineation, dose and fractionation schema, normal structure and coverage directives, and the decision to pursue radiation therapy in each clinical scenario. Many errors or suboptimal decisions that widen the quality gap involving these elements are either detected at this stage or are at high risk to go undetected. Despite its resource-intensive nature (potentially occupying the focus of a department's entire multidisciplinary cohort for hours each week), it provides a singular opportunity to close the quality gap, resulting in a demonstrable positive effect on quality of care.

This can be seen in practice: Almost everyone in the field of RO has a story of a "good catch" during chart rounds. For example, dose unnecessarily deposited into an overlooked portion of bowel to a degree that could have caused significant toxicity, or a situation where prior irradiation was not considered. By the nature of making these changes, peer review is clearly contributing to improved patient outcomes. We can also see the potential of QA when it was retrospectively performed on large cooperative group trials. As previously mentioned, protocol deviations were correlated with adverse outcomes across several large cooperative group trials.[18] Prospective review would have identified these deviations while there was still the opportunity to correct them, presumably "closing" the significant gap in survival outcomes between plans with and without deviations.

Finally, chart rounds may standardize practice across a health network where the multidisciplinary team may practice in silos, and as an educational opportunity not only for trainee but also for all team members.

Given the importance of chart rounds, one would expect it to be performed optimally. Unfortunately, there is no clear understanding of what "optimal" review looks like.[102] There is incredible heterogeneity in performance nationally, with variation in frequency (from daily to monthly or on demand), range of staff present, modifications made (active changes to contours to dictated addenda to the patient record to word-of-honor

follow-up), virtual versus in person (in some cases with the actual patient present), to the selection of cases for review (ranging from all cases, to only those submitted, to a random selection). Indeed, even within institutions, practice between disease groups can vary widely. Establishing guidance on optimal physician peer review performance remains a priority for the field, although it is complicated by the variety of practices that require it. Such guidance must be applicable to not only the 20 physicist and 26 physician academic practice but also the single physicist, single physician practice.

Limitations of Peer Review

Among this heterogeneity, we know that there is likely room for significant improvement in typical practice. Reports show detection rates of ~70% during the physics chart check and ~50% during chart rounds.[13,14] The challenges underlying this suboptimal performance look very similar to those threatening safety in general. Increasing complexity of treatment modalities, contour number, plan coverage goals, and constraints may increase the necessary intensity of review.[103] Time itself is in short supply, with competing priorities drawing physicians' and physicists' focus and physical presence away from review.[104] Cultural barriers (such as fear of critiquing plans originating from up the hierarchy)[65] and numerous cognitive biases (such as sunk cost and search-satisfying biases) also come into play.[71]

There is evidence to suggest some best practices for establishing optimal peer review. As mentioned, guidance for physics chart checks can be found in recent publications from medical physics professional groups.[97,98]

With regard to chart rounds, it may be most efficient to prioritize certain plan elements for assessment during review sessions. Multiple observational studies of peer review performance have shown that the most common elements altered during review include target volume delineation, dose and fractionation selection, OAR volume delineation, and normal tissue sparing.[101,105-107] Thus, these elements of the plan should be prioritized for physician peer review.

Prospective review, before plan start or treatment planning, is associated with higher rates of scrutiny and suggested modifications.[108,109] Incorporation of the suggested modifications was more likely if peer review

was conducted prior to treatment start.[110] This has been hypothesized to be due to a reduction of sunk cost fallacy, described earlier in this chapter. Given the amount of work that has already gone into planning, scheduling, or, in many cases, delivering treatment to a patient, the less likely one is to "start from square one" and begin the replanning process, and the less likely one is to put colleagues through that process by putting forward a modification suggestion. In addition, prospective review allows this process to be opaque to the patient, which can be important in maintaining trust of the treatment team. The aversion to more burdensome alterations was illustrated in a study of compliance with peer review recommendations, whereby "major" suggested plan alterations were less likely to be acted on than "minor" alterations.[111] The authors speculated this was due to the excess work needed to pivot to adopt a major recommendation versus a minor one and the increased incidence of rationalizing noncompliance to avoid this major inconvenience. Prospective contouring rounds during which the target and OAR contours are reviewed prior to plan initiation further decrease the inertia opposing implementation of feedback and may lead to additional input.[112] As the objective of peer review is to provide and implement meaningful treatment improvements and prevent any suboptimal treatment from reaching the patient, moving review further up in the workflow is likely beneficial.

Time and focus can be limited by performing efficient, structured peer review with a similarly structured accompanying clinical presentation. Excessive details about tangentially related prior therapies and medical episodes that did not influence the radiation decision only make effective review more challenging. Protected time for peer review during the day may lead to increased attendance and participation.[99]

Standardization of review elements may be helpful. One proposal has been for a sequence of plan element evaluation abbreviated CB-CHOP,[113] which stands for contours, beams, coverage, heterogeneity, OARs, and prescription. Following this abbreviation ensures review of the highest priority targets; standardization of the sequence of review decreases the likelihood of inadvertently neglecting an element. Standardization should extend to presentation of clinical history (age, stage, prior treatments, prescription, and target), structure and plan naming, and the appearance of any images projected (such as standardizing the color of the target and OAR

contours) to facilitate efficient presentation and pattern recognition. It should be noted that other forms of peer review exist in the RO workflow and may overlap with some elements of physicist plan checks and chart rounds. Many institutions hold tumor boards, in which treatment strategies for a patient are discussed in the multidisciplinary setting. Informal peer review may also take place during the planning phase, if dosimetrists, physicists, or physicians wish to confirm whether a plan has been adequately optimized. These varied other forms of peer review are important but beyond the scope of this chapter.

HAZARD AND RISK ANALYSIS

Risk analysis methods may be roughly broken up into two categories, those that are prospective (sometimes referred to as proactive), where analysis takes place before an event occurs, often as part of the initial design of a new procedure or program, and those that are retrospective, where analysis takes place after an event occurs, with the goal of reducing the likelihood of future similar events. These approaches are complementary and should not be considered exclusive of each other. For example, Yang et al[114] studied how failure modes identified via failure mode and effects analysis (FMEA—a prospective method of risk analysis) intersected with events that actually occurred in a radiotherapy clinic as reported in an ILS (a retrospective method of risk analysis). They found that for stereotactic body radiation therapy (SBRT) treatment planning, both methods missed potential failure modes and that using the two strategies simultaneously could yield an improved evaluation of the safety of a given process.

PROSPECTIVE RISK ANALYSIS

The most well-known method of prospective risk analysis in the field of RO is likely to be FMEA, which was described in detail as it applies to the field specifically by AAPM TG-100.[12] Other methods included in this report are process mapping (often a subcomponent of FMEA) and fault tree analysis.

FMEA begins with composing a multidisciplinary team of RO professionals. FMEA cannot be performed by a single individual—representatives from all parts of a given workflow should be included. One of the first steps is to create a process map, which is a visual representation

of the process being analyzed by the FMEA. Through the creation of the process map, it quickly becomes clear why a multidisciplinary team is needed, because one individual rarely understands the complete details of an entire workflow. TG-100 contains an example process map for intensity-modulated radiation therapy (IMRT), and numerous other publications have included process maps for other workflows in the field. However, because each radiotherapy program has unique aspects, it is encouraged that an individual institution creates its own process maps, even if a published example is used to start.

The next step is to use the process map to identify potential failure modes and their associated effect(s). The set of failure modes is then "scored," typically on a scale of 1 to 10, in three categories: severity, occurrence, and detectability. A risk priority number is generated by multiplying the three scores together. The purpose of the scoring is 2-fold: first, to identify any high-risk failure modes, which should be addressed urgently, and second, to order the remaining failure modes according to risk in order to prioritize additional safety interventions. TG-100 included example scales in each of the three categories; however, some publications have used alternative scales tailored to the specific process being addressed.[115] A key point is that all team members who score failure modes should have the same understanding of both the individual failure modes and effects, as well as how to apply the scales, such that the final ranking is accurate.

FMEA is a time-intensive process that has been used in the field of RO with varying degrees of success. Efforts have been made to streamline the process[116] to make it more accessible to the RO community.[117]

RETROSPECTIVE RISK ANALYSIS

Before appropriate changes can be made in response to a safety event, two things must occur: one, knowing that the event happened and two, understanding why it happened. Here, we discuss ILS, as a method of reporting events, and RCA, as a method of understanding the underlying causes of an event.

Incident Learning Systems

ILS allows patient safety events to be reported by individuals after an event has occurred. Perceived unsafe conditions may also be reported. These reports allow the retrospective analysis of events by a multidisciplinary team of individuals who can then provide and enact recommendations based on the report.

Efforts have been made in some countries to create a system of pooled incidents for large-scale learning. Examples include the Radiation Oncology Safety Information System sponsored by European Society for Radiotherapy and Oncology, Safety in Radiation Oncology (SAFRON) sponsored by the International Atomic Energy Agency, the RO-ILS sponsored by multiple professional societies and commercial organizations in the United States, and the Radiotherapy Incident Reporting and Analysis System in use by the U.S. Veterans Health Affairs enterprise. There are many other national ILS programs in operation.

Previously, Ford et al,[6,118] as part of AAPM's Work Group on Prevention of Errors in Radiation Oncology, described consensus recommendations for how ILS programs could be structured for use in RO. In 2018, Ford and Evans[119] provided an overview of ILS in RO, including how they can be used on a department level for patient safety improvements. Importantly, ILS programs can only be successful when there is a robust culture of safety in place, where individuals can feel safe to honestly report and openly discuss events. In 2020, the World Health Organization provided further guidance on how these systems can be used and their associated limitations, noting that their use in health care had still not matched "the scale and speed that compares with some other high-risk industries."[120]

Although there are limitations to retrospective risk analysis using ILSs, prior publications have described their use in RO and subsequent improvements in patient safety. For example, Kusano et al[37] and Mazur et al[121] both demonstrated an improvement in patient safety culture in the presence of a departmental ILS program. It must be emphasized that the objective of reporting is not to simply collect as many reports as possible but instead to learn from them, identifying issues that require further investigation or intervention.[122,123]

To begin an ILS program, departments must make a number of decisions as to how the system will be implemented, used, and maintained. The first such decision is whether the department will use an existing national system

or use a custom in-house or hospital-based system (or a combination of these). The use of a pooled system such as those listed earlier enables learning across multiple institutions. To support impactful event analysis, a standard terminology library and taxonomy should be used, such as the one developed by the AAPM.[6] The system should be designed for ease of use to mitigate one of the most common reasons for not reporting, which is a lack of time available to report.[124] Individuals should be trained in how to use the system and how to complete an event narrative that provides enough detail for investigation without directing blame at any individuals.

Root Cause Analysis and the London Protocol

RCA is a method of retrospectively determining the underlying cause(s) of an error. When a safety event occurs in the process of radiotherapy, it can be tempting to draw immediate conclusions as to the cause of the event. These causes are often defined in terms of a "lack of" something, such as lack of communication or lack of time to complete a task, the solution to which is then to add more of the thing that is lacking. However, this rush to implement solutions without fully understanding the causal factors of the event can lead to bloated and ineffectual workflows and QA programs.

The goal of an RCA is to fully understand the details of a safety event and why it happened, such that effective solutions can be put into place to reduce the likelihood of similar events happening again. Focusing first on understanding the event as opposed to proposing solutions is a key aspect. With the understanding that human beings are fallible and make mistakes, the RCA should look to workflow and process-based solutions instead of blaming individuals.

Understanding the underlying cause of an event involves asking a series of "why" questions, reaching as deep into the process as possible.[125] Similar to FMEA, the RCA team should be multidisciplinary and include team members from all relevant parts of the workflow so that the "why" questions can be answered correctly. An effort to be made to avoid giving an answer that involves the "lack of" something, as described above, because this presupposes that the solution is to add more of whatever is lacking. The VHA National Center for Patient Safety offers an overview of RCA with associated examples on their website.[126]

Similar to an RCA, the London Protocol, as mentioned earlier in this chapter, attempts to determine contributing factors to an event. In addition, this method takes the approach that often it is a chain of events that leads to the final outcome rather than one or a few "root causes." It also takes the goal of the investigation one step forward from RCA, from determining why a given event occurred to finding ways to achieve a safer health care system.[8]

As an example of determining root causes, consider a medical event where the wrong vertebral body was treated during a course of spine SBRT. The patient was treated with nonstandard immobilization because they were also being treated to other bony sites during the same course. Larger than normal shifts after imaging were noted during treatment, but this was attributed to the nonstandard immobilization and, therefore, the misalignment was not caught prior to treatment. A potential immediate reaction to this event description is that nonstandard immobilization should not be allowed for spine SBRT and that the patient in question should have used two independent immobilization methods at the treatment unit. However, upon closer investigation of the event, it was discovered that a narrow field of view cone-beam CT was acquired as part of image guided radiation therapy (IGRT), such that there were no indisputable anatomic landmarks present and that the use of auto-registration software created an anchoring bias that was difficult to overcome. The complexity of the patient's treatment (multiple sites, patient in pain and needing to get off the table quickly, specialty SBRT workflow, multiple personnel present at the treatment unit and varied personnel by day, pressure to complete treatment within a given treatment times lot) were all contributing factors that together produced the negative outcome, and a change to any one of these may have altered the outcome. Often, one of the first urges in error analysis is to add additional checks or disallow certain workflows. However, care must be taken to ensure that these changes produce the desired impact, which always must be to create a safer health care system. Additional checks and QA procedures are not added without cost. They take away time that team members have to perform other work that may be equally as vital. The patient in this example was treated in a single immobilization because they were in a great deal of pain and the goal was to complete treatment as quickly as possible. Before enforcing restrictions on the types of allowed

immobilization, all relevant team members should be consulted to ensure the consequences of these decisions are fully understood.

ARTIFICIAL INTELLIGENCE AS A QUALITY AND SAFETY TOOL

Integrating AI algorithms into the quality and safety workflow is a rapidly evolving area of investigation.[127] One of the most appealing use cases for AI is as an additional "set of eyes" to confirm optimal plan creation and delivery. In some clinical contexts, auto-segmentation of both targets and OARs by AI tools can result in contours on par with those created by human experts.[128,129] By extension, AI tools could be utilized to assess and correct contours from another source. Though such tools require additional layers of complexity (such as determining whether a contour deviation is clinically meaningful and warrants attention or integrating clinical information beyond the information supplied to AI), models have demonstrated an ability to flag deliberate contouring errors[130] or suboptimal auto-contours[131,132] in experimental validation data sets. Some models are undergoing prospective validation in the trial setting; for example, in ongoing cooperative group trials, AI scoring algorithms are being compared to human expert scoring of submitted patient contours as part of trial QA.[133,134] Physics plan and chart review can also be supplemented with the addition of AI tools. Error detection algorithms have been developed that have the capability to assist pretreatment plan checks by flagging plan parameters (ie, stage, dose, and treatment technique) that have low probability of coexisting based on historical practice patterns.[135,136] Patient-specific and machine QA have been performed by validated AI tools in such contexts as IMRT QA[137] and predicting machine failure[138] and may serve to augment current human-performed workflows. It must also be understood that AI offers new potential pathways for failure; prospective risk analysis should be performed with the introduction of AI tools into clinical practice, along with ongoing monitoring of output accuracy over time.[139] Finally, supplanting human performance of QA and safety checks entirely with AI or other automated processes would be a grave error, given the known existence of automation bias[140] and the need for decision-making currently beyond the capability of AI.

ETHICS OF ERROR DISCLOSURE

Despite our best efforts, any health care provider reading this chapter is statistically likely to have an error reach a patient at some point during their career.[141,142] When this occurs, it can have long-lasting effects on patients, the provider-patient relationship, and the providers themselves. The steps taken after an error occurs can mitigate or exacerbate these potential consequences. Thus, aside from analyzing the event to prevent future occurrences, the immediate effects of the error must be managed responsibly.

After an error that impacts a patient is recognized, it should be promptly disclosed to the patient. Does this mean all errors? Debate exists about this, but some suggest that a reasonable threshold for disclosure is that which requires additional care (more frequent lab draws, a replan, etc).[143] This can be an extremely challenging conversation, and providers should prepare by learning about the error in as much detail as time allows prior to the meeting and rehearse what they intend to communicate. Some institutions have disclosure coaches who are specially trained to prepare a physician for this conversation (typically, but not always, the physician involved in treatment will disclose the error). The ultimate objective is disclosure in a manner that serves the patient's needs. This includes delivering the bad news in a straightforward manner, assuming a humble conversational posture, nonjudgmental listening, providing ample opportunity for the patient to express their feelings, and, ultimately, provide a path forward for remedy of the situation in a manner that fits with the patient's goals and desires.[144] Risk management involvement can provide guidance and assist providers through this process and provide resources to patients and their families to help address the consequences of the error. It is important to note that conjecture has no place in this disclosure. Prompt disclosure means that much is yet to be known about the event, and the patient should be advised that some of their questions cannot be answered, and a date for a follow-up conversation should be given.

It must be acknowledged that a stance of "deny and defend" was prevalent through much of the 20th century. This was rationalized by the assumption that informing patients of an error would only harm them further by jeopardizing the doctor- patient relationship or contributing to

psychological distress. Both ethical and practical arguments can be made for prompt error disclosure. First, it is the only way to uphold patient autonomy, a key tenant of patient-centered care. Knowing a mistake was made may understandably lead a patient to reassess their future options—whether that means seeking care elsewhere, seeking a different type of care, or seeking additional care (such as additional lab or imaging testing) on top of the current regimen. Autonomy is absent from care if relevant information is being kept from a patient. Second, error disclosure has been shown to reduce medical legal costs and improve patient satisfaction following an error. If a patient is suspicious that information is being withheld, they are more likely to hire a lawyer and begin a costly and contentious discovery process. While early settlements are often provided on ethical grounds, they also reflect the understanding at an administrative level that open acknowledgment and apology are of interest to all parties involved.[144-146] (Sue Paper on error disclosure, citation on decreased costs with early disclosure/settlement, citation on provider perception correlating with litigiousness.)

THE IMPAIRED COLLEAGUE

In a "just culture," it is not only acceptable but expected that departmental members hold each other to account.[85] If one staff member notices a potential mistake during their practice, they are expected to report that mistake, even if they were not directly involved. This action is performed with the understanding that the purpose of reporting is not to distribute blame, but to make systematic changes that improve outcomes. This holds true in the situation of an impaired colleague.

Colleagues may be impaired for several reasons. Sleep deprivation, distraction, and, in more severe cases, mental health crises or substance abuse issues may compromise a staff member's ability to perform their role safely. In the event of a report of this nature, a confidential investigation should be undertaken to determine whether suspected impairment did indeed occur, if there has been a pattern of such behavior occurring, corrective steps and appropriate monitoring for the impaired individual going forward, and institutional safeguards to prevent future episodes from compromising care (should they arise).[147] Although tremendously

challenging, it is critical to be able to get help for impaired colleagues, ideally without affecting their future ability to practice once recovered.

SECOND VICTIM PHENOMENON

Errors, even if detected before the patient comes to any resulting harm, can have a lasting effect on those involved. Intrusive feelings of guilt, doubt, fear, and regret are common, and this emotional distress can impair a provider's ability to provide care and diminish interest in further practice.[5,142] Health care workers experiencing trauma from a committed error have been referred to as "second victims."[148,149] The consequences of error can thus ripple outward, depriving a community of a practitioner who is most likely skilled, compassionate, and no more risk prone than anyone else in their role.

The second victim phenomenon is perpetuated by long-standing toxic components of the health care system. Health care settings are high stress with long work hours, high patient volume, and regular interaction with complex patient cases, all of which can instill doubt and vulnerability. A blame-oriented culture, where errors are met with inquisitional, punitive measures rather than a focus on improvement, exacerbates the distress experienced by second victims. Lack of support for providers managing these feelings of failure or inadequacy further compound the distress experienced.

Preventing disengagement, burnout, and dropout because of the second victim phenomenon is an important element of a robust safety culture. Making provider workload reasonable and shifting away from a culture of blame are obvious steps with other safety benefits. Active steps in the event of a case of second victimhood may be beneficial as well.[149] Surveys of health care providers suggest that early, proactive intervention leads to subjective improvement in undesired "symptoms" of second victimhood after the episode.[149-151] These interventions may include peer counseling with a focus on the emotions and experience of the provider. To ensure this occurs rapidly, at some centers, this "emotional first aid" has been triggered by activation of an on-call pager (much like medical "codes" for other urgent care issues).[150,151] Longer term counseling with psychologists may be helpful, given the risk of symptoms similar to post-traumatic stress

disorder.[152,153] Finally, support from colleagues during clinical duties immediately following a safety event can be reassuring. Interestingly, this has long been a practice in other industries with a strong safety track record.[154] Time-off clinical duties following an incident can provide space to process and come to terms with the acute feelings naturally accompanying a safety event. It can be difficult to effectively engage in care with clarity and presence of mind until the acute feelings associated with an error are processed, and a majority of surveyed providers expressed strong support for emergent cross-coverage in the event of a significant error.[149]

Not all errors induce the "second victim phenomenon," but when they do, the consequences can be severe. History of error has been associated with suicidality and substance abuse, and while data suggest most individuals do recover from the effects of an error, a significant proportion reports never recovering.[149,155,156] Any departmental quality and safety committee should thus ensure that involved staff receive careful and empathetic attention.

FUTURE DIRECTIONS

The U.S. aviation industry has long been touted as exemplifying the gold standard safety framework. The industry has a historic track record of avoidance of catastrophic failure despite operation of advanced technology in circumstances that can be unpredictable and pressured, and parlance from the aviation industry has penetrated other industries looking to replicate its success. However, it is humbling and frightening that even this highly tuned system has in recent times come under stress, resulting in an uncomfortable spike in close calls.[157] Similarly, though we have arguably produced few high-profile RO safety incidents over the past decade, this is not a sign that we can coast on current practices. We must continue to adapt to the challenges to patient safety that come our way and be humble in acknowledging our limitations as health care workers. It will be important to prospectively test and continuously improve features increasing the quality, reliability, and efficiency of the treatment we deliver, and for everyone in our field to keep abreast of developments in this research space.

This should start with instructing our trainees in the importance of quality improvement and being open about our own experiences. We must share teachable moments and overcome the embarrassment of sharing our own

failings with colleagues. As previously referenced, there is unlikely to be an experienced health care provider who has not committed a significant error in the span of a career.[141,142] Those who do not have such cases to report are possibly just the ones who are unwilling to examine their work closely. Contributions to ILS are a way to identify patterns of error early and make the appropriate adjustments at the department or national level. Providing staff the time, instruction, and encouragement to regularly report in these systems allows for them to be used to their full potential.

Finally, while every department should aspire to a culture of safety and consistent, high-quality treatment, this does not mean we should shy away from all risk. Medicine, even the relatively calm waters of RO, is full of uncertainty, incomplete information, and time pressure. A weekend clinical setup for a pediatric cord compression is a physically, emotionally, and intellectually taxing process even with the guardrails discussed above. Every effort can be made to optimize the quality of treatment delivered. However, some degree of risk will always be present, and a cautious embrace of risk is part of our duty to our patients. With a strong safety culture in place, we can at least walk into these challenging situations with confidence and peace of mind.

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CHAPTER 14

Methodology of Clinical Trials

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In this chapter, we discuss the design, conduct, and analysis of oncology clinical trials, along the way pointing out areas of particular interest to radiation oncology and reviewing some recent ideas in clinical trials and related research studies. This chapter provides only a brief and essentially nontechnical sketch of the main concepts and current research areas, and we refer the reader to comprehensive texts on clinical trial conduct in oncology for further details. A recent monograph[1] and focused texts, including the *Handbook of Statistics in Clinical Oncology*,[2] *Clinical Trials in Oncology*,[3] and *Oncology Clinical Trials: Successful Design, Conduct and Analysis*,[4] provide the fundamentals, as well as up-to-date discussion of new challenges and active research in statistical methods for oncology clinical trials. We have elected to emphasize interventional therapeutic trials.

Clinical trials enable physicians to advance medical care in a safe, scientific, and ethical manner. Formally defined, clinical trials are a set of procedures in medical research conducted to allow safety and efficacy data to be collected for health interventions. A more detailed definition for our purposes would describe a clinical trial as a prospective study that includes an active intervention, carried out in a well-defined patient cohort and producing interpretable information about the action of the intervention; notably, this definition characterizes an interventional trial, contrasted with an observational trial that is largely outside the scope of this chapter.[5] Although in some ways similar to a well-designed laboratory experiment, the involvement of living human subjects demands adherence to strict ethical principles, while also adding to the complexity of interpretation of the results. The last 70 years have witnessed an unprecedented appreciation of the importance of clinical trials and a consequent surge in the number of clinical trials performed.

Over the course of less than a century, the evidence upon which medicine is practiced has evolved from being entirely empirical into a highly regulated scientific process based on vigorously designed prospective clinical trials tightly overseen by numerous scientific and governmental agencies. Cardinal chapters in the history of clinical trial design and implementation include:

- 1747: James Lind's work on the effect of citrus fruits in the prevention of scurvy among sailors in the Royal Navy.
- 1863: Austin Flint's use of a placebo group for comparison with an experimental treatment in the treatment of rheumatic fever.
- 1947: Nuremberg Codex, a result of the appreciation that much of the medical experimentation performed by physicians in Nazi Germany was both ethically wrong and scientifically uninterpretable.
- 1948: The first double-blind trial, performed by the British Medical Research Council to assess the value of streptomycin in the treatment of tuberculosis.
- 1964: Declaration of Helsinki, ethical guidelines for the performance of clinical trials developed by the World Medical Association, and frequently updated since.
- 2000: Creation of ClinicalTrials.gov website, a registry of clinical trials under the auspices of the National Institutes of Health (NIH).

The performance of high-quality cancer clinical trials involves the cooperation of multiple bodies, so-called stakeholders, including patients with cancer and their families, physicians (who accrue the patients), their operating environment (academic institution or practice), the research team (who run the trial on a day-to-day basis), sponsors (who oversee and fund the trial), independent monitors (to ensure the correct performance of the research team), government regulatory agencies, contract research organizations (who may carry out specific aspect of the trial such as auditing), and medical insurance companies. Modern clinical trials may often require the involvement of translational scientists, clinical psychologists, and experts in quality of life, cost-effectiveness, and myriad other disciplines. The complexity of clinical trials adds to the regulatory work involved; for instance, a multi-institutional federally sponsored

clinical trial protocol will require the approval of at least three different research ethics oversight committees (institutional review boards [IRBs]); within the group coordinating the trial, at each institution that opens the trial to accrue patients, and at the sponsor.

While many phase I and phase II trials are carried out by investigators within a single institution, many larger phase II and most phase III trials are multi-institutional. Thus, clinical trial investigator networks have emerged as important components in the performance of large phase II and III clinical trials. Integrated national cooperative group structures have led to the United States National Cancer Institute's National Clinical Trials Network (NCTN), which includes amalgamated cooperative group structures (including groups now known as Alliance for Clinical Trials in Oncology [Alliance], ECOG-ACRIN Cancer Research Group [ECOG-ACRIN], Children's Oncology Group [COG], NRG Oncology, and SWOG [formerly the Southwest Oncology Group]); the US-based NCTN further includes partnership with the Canadian Cancer Trials Group, and parallels similar groups elsewhere including the European Organisation for Research and Treatment of Cancer.[6] One key cooperative group in the context of radiation oncology is the Radiation Therapy Oncology Group (RTOG), founded by Simon Kramer in 1968, which in 2014 was incorporated into the current NRG Oncology cooperative group (which merged RTOG, the National Surgical Adjuvant Breast and Bowel Project, and the Gynecologic Oncology Group). During its history through 2014, the RTOG activated over 500 protocols and accrued over 110,000 patients to cooperative group studies. This included earlier studies that sought to answer questions regarding radiation dose and fractionation. As cancer therapy became multimodal, the group addressed questions relating to combining systemic therapy (primarily chemotherapy) with radiation therapy. Many recent cooperative group trials through NRG Oncology and other groups seek to combine targeted agents or other novel therapeutics with contemporary radiation therapy techniques.

Clinical trials are exceedingly expensive to perform, with costs continuing to rise due to both increased regulatory oversight and greater trial complexity. For instance, it has been estimated that implementation of the European Union's Clinical Trials Directive (laws and regulations relating to the implementation of good clinical practice (GCP) in the

conduct of clinical trials) led to a doubling of the cost of running noncommercial cancer trials in the UK.[7] Large phase III trials can cost in excess of $250 million, and as a result, clinical trials are frequently financed by the pharmaceutical industry. An unfortunate consequence is that clinical trials are rarely performed on established "generic drugs" where there is little commercial interest in establishing new indications. Conversely, the performance of rigorous clinical trials contributes significantly to the costs involved in the development of new pharmaceutical agents, which are subsequently reflected in the commercial pricing of the product.

This collective dynamic has led to a marked shift in the funding of cancer clinical trials over the last 40 years. Whereas previously the vast majority of late-phase (phase II/III) cancer trials were supported by cooperative groups and their forebears, in the 2010s and early 2020s, over 85% of phase III cancer clinical trials were supported by the biopharmaceutical industry.[8] "Generic drugs" may, conceptually, include many local therapies, including radiotherapy as well as surgery; a recent analysis of ClinicalTrials.gov highlights that only 3% of identified phase III cancer clinical trials from 2002 to 2020 assessed a local therapy.[9] With radiotherapy-based trials underrepresented and underfunded in the current clinical trials landscape, the future of radiotherapy clinical trials remains uncertain, requiring innovative approaches likely with increased collaboration with the biopharmaceutical industry.

RESPONSIBILITIES OF THE PRINCIPAL INVESTIGATOR

Although much progress has been made over the past several decades since the Tuskegee Study and other unethical research debacles came to widespread public attention, there persists an inconsistency in the conduct of rigorous research, both preclinical and clinical, to the extent that it is becoming well known that a significant portion of research results are not readily reproducible.[10] The radiation oncology research community is not immune to this quandary and must be committed to improving the research climate on multiple levels.

High-quality research involving human subjects demands accountability on multiple levels, starting foremost with the *responsibilities* of the principal investigator (PI). While we recommend that prospective PIs

proactively enroll in courses that have been developed by one's IRB, we will briefly summarize some of the essential elements.

All clinical trials must include testable objectives that are based on a sound scientific hypothesis. This necessarily means that a trial must utilize appropriate endpoints that can actually measure whether the objectives have been met. The eligibility, trial design, and statistical power (including estimate of the effect size, accrual, specimen availability, imaging interpretation, and more) must be defined upfront. Molecular assays and imaging should be performed by qualified personnel, ideally in a blinded fashion such that those personnel do not have any knowledge of the outcome for patients enrolled in the study. The study data must be maintained in a secure database at a recognized institution; this is particularly crucial, as increased attention is given to threats of cyberterrorism and the importance of cybersecurity, especially in the field of radiation oncology.[11]

The PI is responsible for making sure that research is conducted in a manner that is consistent with the guidelines of the International Council for Harmonization (ICH) by using accepted best practices, also known as good clinical practice (GCP). To participate in the conduct of clinical trials, the PI will need to review and sign the investigator statement (form Food and Drug Administration [FDA] 1572), which essentially is a voluntary commitment to follow the IRB-approved protocol and related requirements, including all applicable federal, state, and institutional regulations. The PI is responsible for controlling all investigational devices and/or agents for a protocol. For the radiation oncologist, this requires a cadre that may include a diverse collection of members of the research team, including but not limited to nurses, research associates, protocol coordinators, regulatory and budget coordinators, medical physicists, dosimetrists, lead radiation therapists, and multidisciplinary coinvestigators. Finally, the PI must be committed to protecting the rights, safety, and overall welfare of patients who are evaluated and eventually enrolled in the trial.

There are core *qualifications* of the PI. Primarily, the PI should possess the necessary qualifications with respect to educational training and experience to make sure that research, including a clinical trial, can be conducted properly and ethically. The PI should be cognizant of the essentials of GCP and be committed to complying. While intuitive to most

readers, it is necessary to reiterate that the PI should be familiar with the use of investigational treatment approaches, including devices and/or agents. The PI should have a dedicated and substantial time commitment to the successful execution of the trial. This commitment includes reading and approving the protocol as well as being involved in a rational plan to identify and enroll patients, proactively addressing barriers to the conduct of increasingly common ancillary or translational research components of trials, such as procurement of blood, tissue, and/or novel imaging tests. The PI should have an assessment plan to make sure that endpoints are designed and calibrated to measure the objectives of the trial, especially the primary objective. The PI needs to have a team and the necessary resources to conduct the trial; if not, then it is not ethical to open a trial regardless of the scientific enthusiasm or merit; generally, absent sufficient resources and infrastructure, an IRB will prevent a protocol from opening, emphasizing the importance of all of these key components preactivation. The PI must understand that certain tasks are delegated to qualified members of the research team; among these, one important task that may be overlooked is the analysis of trial results—a function for the dedicated biostatistician. Trial analysis and review must be conducted per institutional policy and procedure, often including the role of the Data Safety Monitoring Board (DSMB); anecdotally, many PIs have run afoul of the DSMB by engaging in their own analysis and interpretation of trial results without appropriate involvement of the DSMB. Regulatory considerations are similarly important, as there should be an expectation that routine auditing and expectation by sponsoring organizations, as well as government and institutional regulatory bodies, is normal. Finally, it is critical that the PI is committed to evaluating the results and dissemination to the scientific community via a peer-reviewed manuscript submission, as above, with the involvement and assent of the dedicated biostatistical team as well as DSMB. Presenting meeting abstracts alone undermines the credibility and impact of cancer research.[12]

All patients must submit truly *informed consent* that includes both verbal and written components. The consent *process* is not transactional, but part of a relationship between the patient and the PI. The phases of the consent process include the following:

1. Prestudy review and approval by the IRB
2. During the recruitment of subjects with a number of caveats, the patient must understand, primarily that any conflict of interest (COI) on the part of the PI is proactively disclosed and that subjects can withdraw from the study at any time without prejudice.
3. Prior to beginning the trial, a signed copy of the consent must be given to the patient (or qualified surrogate such as a parent in the case of a pediatric radiation oncology trial) and also remain on file in the official medical record as well as the protocol office.
4. During the trial, any revised consent form must have IRB approval, and new information that can impact the outcome for patients must be proactively shared.

Earlier, we mentioned the concept of GCP. The essential values of GCP are listed below[13]:

- Comply with ethical principles.
- Minimize risk to human subjects.
- Maintain dignity, welfare, and human rights.
- Accurate investigational study product information
- Rigorous peer-reviewed protocol
- IRB review and approval of protocol
- Bioethics review (either separate or in concert with IRB approval)
- PI must be qualified.
- The research team must be qualified to carry out delegated responsibilities.
- Enrolled patients must sign uncoerced and voluntary informed consent (written and verbal).
- Data generated must be accurate and verifiable.
- Study records must be kept confidential in a secure environment and readily made available to auditing and/or regulatory authorizes.
- Investigational produce functionality and manufacturing standards should be verifiable.

- Quality assurance (QA) and quality control must be in place.

Table 14.1 lists questions for the primary investigator to consider.

TABLE 14.1 ESSENTIAL QUESTIONS FOR THE PRIMARY INVESTIGATOR TO CONSIDER

1. It is absolutely critical that the PI be clear on why it is of value to perform the trial and what the rationale is. The scientific insights, including the robustness of the preclinical and other published data, must be understood. Is there a gap in efficacy?
2. If the trial is positive, will a meaningful vertical impact and penetration in the field result? Some trials may prove a proof of concept and others may have a clinical impact.
3. Where does the trial concept lay within the innovation spectrum? If low-risk question, will the field really care about the results, and is the research question worth the investment in resources (ie, time, money, and patients)? If a high-risk question, will the feasibility and dissemination be limited to a few very specialized centers?
4. Does the study have a primary clinical endpoint and what are the pros/cons of candidate endpoints? It is important to have an idea as to how quickly one can determine an early endpoint (ie, response rate), reliability (ie, overall survival), clinical significance, and impact of subsequent factors on the endpoint (ie, PFS vs overall survival). Since no endpoint will be perfect to show an increase in the therapeutic ratio, the PI should have a rationale justification for choosing it.
5. The study must be feasible with respect to scientific, pragmatic, financial, and ethical boundaries.
6. Are you able to assemble the nonphysician investigative team, beginning with an experienced biostatistician? Other component personnel include imaging and basic science investigators, research nurses, study coordinator, pharmacist, regulatory affairs, and IRB.
7. The PI must have dedicated (protected) time to remain engaged in the study.
8. Barriers always exist. It is important that the PI learn, early on, which barriers are permanent vs temporary, which require a doable work-a-round vs a fatal flaw. A mentor who is committed to helping navigate the oncopolitical landscape is valued.
9. It should be clear who and what are competing in this research space. Is a more capable investigator at another institution more capable of executing your original idea? Are your colleagues as enthusiastic about your concept as you are? Is there a competing institutional and/or multi-institution trial that will limit patients? If so, is this a temporary concern?
10. The PI needs to discern if they are ready to start working on the protocol immediately or perhaps at a time in the future. Time management is paramount.
11. Will the study maintain relevancy over the course of the study and for the time it takes for the endpoint results to mature? (see #2 and #4 above)

IRB, institutional review boards; PFS, progression-free survival; PI, principal investigator.
Adapted with permission from Lillian Siu, MD and Patricia LoRusso, DO.

Informed consent remains a key area of focus for clinical trial design and optimization. The Common Rule provides federal guidance on protection of human research subjects.[14] Data suggest that 10% to 20% of modern cancer clinical trials did not appropriately complete or obtain informed consent from patients.[15,16] Furthermore, it is noteworthy that informed consent is not a static concept, but rather continues to evolve now into the 21st century and beyond.[17] Novel trial designs, continued efforts to ensure patients are receiving acceptable therapies irrespective of treatment arm,[18] and the integration of genomic data as well as artificial intelligence all warrant continued attention to the central role of informed consent in patient participation in clinical trials.

OVERVIEW OF ETHICAL CONSIDERATIONS

Parallel to these considerations regarding informed consent, medical ethics are based on the principles of autonomy (the patient's right to refuse or choose their treatment), beneficence (a practitioner should act in the best interest of the patient), nonmaleficence (first, do no harm), justice (fairness and equality), dignity, and honesty. Without due diligence, physicians may infringe upon these principles when encouraging patient participation in clinical trials. Are the physicians confident that the proposed treatment is beneficial and not harmful? Are the potential subjects fully aware of the implications of participation? Do all segments of the population have an equivalent chance to participate and receive potentially better treatment? Despite the universal acceptance of these principles, there have been numerous examples of grossly unethical research being performed in the Western world within living memory. Documents seeking to address these issues include the Nuremberg Code, the Declaration of Helsinki, and the Belmont Report. Emanuel has listed seven requirements that provide a systematic and coherent framework for determining whether clinical research is ethical.[19]

Ethical principles themselves and the creation of guidelines are insufficient to ensure the ethical conduct of medical research. Physicians within Nazi Germany performed atrocities despite the existence of German guidelines published in 1931,[20] reflecting the need for legislation. The International Conference on Harmonisation of Technical Requirements for

Registration of Pharmaceuticals for Human Use (ICH) brought together the regulatory authorities of Europe, Japan, and the United States and experts from the pharmaceutical industry to regulate scientific and technical aspects of pharmaceutical product registration. The ICH guidelines are legally binding in many countries (although not the United States) and are updated every few years, reflecting the increasing sophistication of the field. An example of a recent addition is the introduction of data and safety monitoring committees (DSMCs), an independent group of experts who monitor patient safety and treatment efficacy data while a clinical trial is ongoing (this may include a DSMB as highlighted earlier). Another recent advance is the requirement for the registration of clinical trials, such as through ClinicalTrials.gov. Such registration both improves transparency concerning what clinical trials have been/are being performed and empowers patients to find relevant clinical trials. Notably, while registration has aimed to improve trial transparency, many concerns remain regarding poor compliance with reporting requirements.[21]

OVERVIEW OF TRADITIONAL CLINICAL TRIAL DEVELOPMENT

Traditionally, a new anticancer agent is tested in a three-step process, starting with a small dose-finding trial (phase I), followed by a pilot efficacy trial (phase II), and culminating with a large comparative randomized (phase III) trial. While this development paradigm was created and established in the era of cytotoxic chemotherapies, it continues to be used today in the era of targeted therapies, immunotherapies, and cellular therapies, with some adaptations and innovations that we discuss later. Here, we review the traditional paradigm without technical details, which can be found in many excellent sources for clinical trials design and conduct.[3,5]

Phase I

Phase I trials are the first step in evaluating a treatment in humans. As each treatment carries unique risks, the primary objective of a phase I trial is to assess the safety and tolerability of the treatment at preselected dose levels, with secondary objectives of collecting preliminary efficacy data.[22,23] The dose-limiting toxicity (DLT), commonly defined as any grade 3 to 4

nonhematologic or grade 4 hematologic toxicity at least possibly related to the treatment, is a widely adopted primary endpoint. However, the DLT definition may vary depending on disease types or stages. Given the exploratory nature of phase I trials, researchers typically study three to six dose levels with a limited sample size, usually ranging from 10 to 30 participants. Upon completion, a key goal is to identify the recommended phase II dose (RP2D) for further investigation in subsequent trials. Consequently, phase I oncology trials are often referred to as dose-finding or dose escalation studies.

In the era of cytotoxic chemotherapies, the RP2D is frequently selected as the maximum tolerated dose (MTD), defined as the dose level with a DLT rate closest to or below a prespecified target, typically 25% or 30%. This approach is based on the monotonicity assumption that treatment toxicity and efficacy increase with dose. To ensure patient safety and adherence to ethical standards, phase I trials employ staggered enrollment, starting at a relatively low dose and gradually escalating. Dosing decisions are adaptively made based on the outcomes of previously enrolled patients. Popular designs for MTD determination include the 3+3 rule, the Bayesian optimal interval (BOIN) design, and other Bayesian model-informed designs.[24,25]

The landscape of phase I oncology trials is evolving due to advancements in targeted therapies, immunotherapies, and cellular therapies. These novel agents are generally safer, and efficacy often plateaus at a middle dose rather than continuously increasing with the dose. Consequently, a lower dose may offer similar efficacy with lower toxicity compared to the MTD, optimizing the risk-benefit profile. Traditional phase I trial designs, primarily developed for scenarios where higher doses are assumed to be better, may identify an unnecessarily high RP2D. To address this challenge, innovative phase I/II designs have been developed that concurrently utilize early toxicity and efficacy endpoints to guide dose escalation/de- escalation and final dose selection for targeted agents.[25,26] The Bayesian EffTox design and the BOIN12 design are two widely used examples in both academia and industry. Recently, the US FDA launched the “Project Optimus”[27] initiative to reform dose finding and optimization for anticancer treatments. As a result, an increasing number of novel designs that leverage the totality

of data and employ adaptive strategies are being developed to facilitate dose optimization in oncology.

Phase II

The primary purpose of the phase II trial is to determine the response rate of the treatment, seeking early evidence of clinical activity. An important secondary purpose is to gather more robust adverse event (AE) information at the established dose (eg, RP2D). The primary efficacy endpoint of the phase II trial has traditionally been tumor response, but the duration of response, progression-free survival (PFS), and site-specific activity such as locoregional control are all relevant and well-used among phase II studies. Measures of patient survival (such as overall survival [OS]) are usually secondary endpoints in phase II trials, due to the limited sample size and follow-up duration of these trials. In general, phase II trials are not designed to provide definitive evidence that the test treatment is superior to current options. Modern phase II trials may incorporate several interim analyses over the course of the trial to make "go/no-go" decisions. For example, under Simon's two-stage design framework, a treatment will be terminated early if there is insufficient efficacy observed during the first stage of the trial.

Many phase II trials have traditionally been single-arm studies comparing against a benchmark historical response rate. Reliance on this nonconcurrent external control rate can be highly problematic.[28-30] Furthermore, patient selection factors can influence the results, for example, overall response rates in single-institution phase II trials can be significantly higher than in multicenter studies or subsequent phase III–controlled trials.[31] Randomized phase II trials have historically had a role in multi-arm trials aimed at selecting the best treatment(s) to take forward for further testing,[32] and have more recently become favored as a means of providing more reliable pilot efficacy data.[33] However, the preferred approach is changing as described later.

Phase III

Phase III trials are randomized comparisons between a new treatment regimen that has already shown promise in phase I/II trials and the current

best standard of care (ie, the control). Randomization offers a critical advantage over nonrandomized studies. Specifically, randomization balances the distribution of prognostic factors between treatment arms and assures that treatment is assigned independent of these factors, thereby minimizing or eliminating these effects when comparing outcomes by treatment. When randomization is combined with treatment blinding of patients, researchers, or both, then even subjective outcomes can be assessed with minimal bias. Also, in multicenter studies, randomization can balance any systematic bias of the treating physicians or institutions.

Phase III trials can address one of several types of primary questions. For example, a study can be designed to determine if standard treatment is better than best supportive care. More often, phase III studies are designed to compare a new treatment with the current standard treatment. Phase III studies can also compare two or three different regimens with each other, as well as with standard treatment. Finally, a trial may be designed to demonstrate that a given treatment option is not worse than another by more than a tolerable margin. This last group of trials, known as noninferiority trials, plays an important role in the development of less invasive or less burdensome treatment regimens.

The primary endpoint of phase III trials is the subject of substantial discussion as well. Historically, phase III trials generally utilized a primary endpoint of OS (time to death from any cause), or in certain cases an endpoint such as disease-free survival (DFS). However, only a minority of modern phase III cancer trials utilize OS as the primary endpoint, instead generally favoring a so-called surrogate endpoint such as PFS.[9] Much ink has been spilled regarding the role of such surrogate endpoints, which in the case of PFS are based on radiographic size changes of lesions; surrogate endpoints may or may not be valid based on a number of criteria,[34,35] and similarly may or may not be clinically meaningful to patients if they do not reasonably reflect changes to either quantity or quality of life.[36,37] Given the general acceptance of surrogate endpoints by regulatory agencies such as the Food and Drug Administration in the United States, and the European Medicines Agency in Europe, much attention continues to be given to the selection of appropriate and patient-centered endpoints for phase III trials. This includes ongoing considerations regarding the selection of patient-reported quality of life outcomes as primary endpoints,[38] high-resolution,

targeted, and valid surrogate endpoint for precision oncology trials,[39] and beyond.

Phase III trials aim to definitively demonstrate benefit and potentially change the current standard of care. Therefore, the number of participants and follow-up period required for a phase III trial are generally significantly greater than in phase II trials. Notably, surrogate endpoints aim to mitigate these factors in phase III trials by measuring "earlier" events (such as lesion growth as an "event" for PFS, compared with death for OS), conceivably allowing trials to reach primary endpoint results sooner and with fewer patients enrolled (concomitantly decreasing trial costs). Important secondary endpoints can include locoregional control and other site-specific failure or disease control endpoints, AE profiles, and quality of life measures.

Phase IV

Phase IV trial is also known as postmarketing surveillance trial. Phase IV trials involve the safety surveillance of a drug after it receives regulatory approval for standard use. The safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer time period than was possible during the phase I-III clinical trials.

Phase 0 or Window Studies

The goal of phase 0 trials is to evaluate the pharmacodynamics (PD) and/or pharmacokinetics (PK) of an antitumor modality prior to traditional phase I studies[40].

PD is considered to represent "what the modality does to the body," while PK measures "what the body does to the modality," be it radiation and/or a systemic agent.[41] PD parameters may include nadir hematologic counts, nonhematologic toxicity, molecular correlates, and/or imaging endpoints. PK parameters such as C_{max}, AUC (area under the curve drug exposure), half-life, and clearance, all help to quantitate absorption, distribution, metabolism, and/or excretion of an agent. This can impact the bioavailability of an agent that is intended to sensitize radiation. Phase 0 studies can help to refine a target or biomarker assay for drug impact in

human samples by incorporating methods developed and validated in representative preclinical models.

Therapeutic clinical trials in radiation oncology typically involve the introduction of new technologies (eg, the use of stereotactic body radiation for a new indication) or more frequently the novel combination of radiation therapy with a systemic agent. There are unique challenges—biologic and clinical—that characterize clinical trials in radiation oncology compared to those not involving radiation.

Response rate is frequently used in early-phase medical oncology trials to indicate activity for a systemic therapy; however, since radiation therapy itself is highly effective at shrinking tumors, this endpoint is not useful in radiation trials. A more appropriate "activity" endpoint for radiation trials may be PFS, but this itself is often difficult to objectively assess. Modern imaging endpoints (such as FDG uptake or other radiomic features) show promise as early read-outs of activity, but still require vigorous validation for individual disease sites. Furthermore, efficacy and toxicity endpoints in radiation trials are dependent on multiple biologic factors including size of the target, the proximity of the tumor to sensitive normal tissues, accuracy of target volume definition, degree of patient immobilization, dose of radiation, and fractionation scheme. Consequently, quality assurance measures are an essential feature of radiation trials, especially in the multi-institutional setting.[42,43,209] Inadequate QA and lack of consistency in radiation delivery have led to the conclusions obtained from large expensive clinical trials being questioned.[44-50] As an example, we turn to the RTOG 9704 trial that evaluated postoperative adjuvant chemoradiation treatment of pancreatic cancer; subtle protocol violations in target definition influenced both toxicity and survival.[51] The impact of high-quality radiotherapy QA on patient outcomes in clinical trials has been demonstrated numerous times,[52-54] and the importance of such QA has only grown with increased sophistication and diversity of radiation oncology tools and techniques, including intensity-modulated radiotherapy, stereotactic body radiotherapy, stereotactic radiosurgery, particle therapy, brachytherapy, and more.[43]

In medical oncology trials, AEs typically occur during or within days of completing treatment. In contrast, toxicity following radiation therapy may follow a biphasic course, early (within 3 months of starting treatment) and

late (months to years later). Late toxicity is typically irreversible and hence important in determining the tolerability of an experimental treatment. Although utilizing long-term toxicity as the primary endpoint in clinical trials is not practical, it is nonetheless imperative to collect and report robust information on long-term outcomes from radiation therapy trials. In fact, even in phase I radiation therapy trials, the follow-up period can be substantially longer than for those evaluating chemotherapy. An approach to dose escalation in phase I trials that considers late toxicities when deciding whether to advance to the next dosing level is discussed later.[55]

A further difference relates to the population studied. In medical oncology early-phase trials, participants have often received several lines of treatment and lack further therapeutic options. In contrast, patients on phase I radiation trials typically receive full-dose radiation treatment, and subjects may be treatment naive. Furthermore, phase I trials in medical oncology are frequently "first in human" experience for the agent; toxicity is unpredictable, and pharmacokinetic studies are essential. Conversely, most multimodality phase I trials in radiation oncology involve systemic agents that have already been through extensive clinical testing; systemic toxicity is known, and pharmacokinetic studies are of generally more limited utility. The purpose of the trial is to define the extent of local toxicity within the radiation field or the extent of radioprotection afforded by a combination radioprotective agent; consequently, radiation oncology phase I trials are more likely to be organ specific/field confined. One study demonstrated that in reality, radiation phase I trials rarely utilize "first-in human" agents, are associated with qualitatively predictable toxicity, and are comparatively safe.[56] Other data suggest that phase I assessments of combination approaches of radiotherapy with novel anticancer agents occur earlier and earlier in the "life cycle" of novel systemic therapies.[57]

STATISTICAL ISSUES IN CLINICAL TRIAL DESIGN

Patient Population Definition and Stratification

A key issue in a clinical trial is a well-defined patient population to which the potential therapy applies. This is typically defined in terms of traditional disease characteristics reflecting putative prognosis, such as stage or its components. Increasingly, tumor pathology or marker features, as well as

genomic data, may be included. In any case, these must be unambiguously defined. Because factors defining eligibility are often critically related to prognosis, any randomized comparative study may use a stratified randomization approach to ensure equal representation of prognostic risk among treatment arms. Stratification factors need to be limited to a reasonable number since the total number of strata equals the product of the number of categories for each. For example, in a completed RTOG prostate cancer trial (RTOG 9408), stratification factors consisted of two levels of Prostate-Specific Antigen (PSA) (<4 vs 4-20), three cell differentiation categories (well, moderate, poor), and nodal status (N0 vs NX).[58] The possible combinations of these variables create $2 \times 3 \times 2 = 12$ strata within which treatments are to be balanced in allocation.

Randomization

Randomization is used differently in different phases of development but serves a similar purpose, which is to render treatment groups similar (to each other) with respect to factors other than treatment allocation that can influence outcomes. In phase I trials, there typically are no comparative groups, although there are situations where parallel cohorts of patients are being evaluated, and thus randomization into cohorts assures that these groups can be compared later for response biomarkers or other factors of interest. In phase II trials, randomization has been used in two similar but distinct ways. First, so-called selection designs have been used to help decide which of several potential candidate treatments to take forward to further definitive testing ("pick the winner," so to speak).[32] In these trials, interest is not in statistically significant differences between treatments, but rather the ability to nominally rank candidate therapies or approaches in terms of best potential efficacy. It can be shown that this approach has a high probability of identifying the most likely superior arm, but at the cost of false-positive findings, particularly if misused.[59] A second role of randomization in phase II trials is to provide evidence, albeit at a less stringent criteria, that a test treatment is indeed promising, conceivably against the current standard of care.[33] In phase III trials, randomization is critical for definitive unbiased evaluation of an experimental therapy against a standard-of-care control.

Regarding implementation, randomization assignments can be simple, or more commonly, implemented using blocking or dynamic approaches with respect to balancing treatment arms by key factors, such as stratification variables mentioned earlier. A number of proven methods are available.[5] Innovative adaptive randomization strategies have been developed to achieve important goals beyond balancing patient populations between arms. In adaptive randomization, the probability of assigning patients to each arm is adaptively modified based on predefined rules and observed trial data.[60,61] For instance, outcome-adaptive randomization can allocate more patients to the better-performing arm or the arm that provides the highest inference precision. The strategy of adaptively allocating more patients to the better-performing arm has several appealing features, such as increasing patient enthusiasm for enrollment and addressing ethical concerns. Similarly, covariate-adaptive randomization periodically assesses imbalances in patient characteristics between treatment and control arms and assigns new patients to minimize these imbalances.

It is important to note that investigators must protect against practices that can erode or nullify the benefits of randomization. Any breach of the random assignment process has an irreparable effect on the validity of the trial. Second, a large number (or differential number per treatment arm) of patient withdrawals can make the validity of the comparison suspect. Similarly, differential follow-up and consequently ascertainment of patient status between treatment arms can bias the treatment effect estimate; differential censoring by the treatment arm can also create a substantial source of bias.[62,63] Third, bias in the assessment of outcomes can have a major impact on the estimated treatment effect, and thus objective outcome measures and blinding of treatment assignment become important. Treatment assignment blinding is often not feasible for radiotherapy and other local therapy trials (in contrast to systemic therapy trials which may more readily be amenable to blinding of both patients and investigators —“double-blinding”). Irrespective of blinding, and particularly for trials where patients and/or investigators are unblinded, unambiguous and objectively defined endpoints are crucial. In cases where determination of the endpoint involves possible observer subjectivity, such as when reading a diagnostic scan to determine disease progression, keeping assessors unaware of treatment assignment may be necessary. This is relevant for the

commonly utilized method of assessing PFS in late-phase cancer clinical trials, which is the use of blinded independent central review for assessment of progression on radiographic scans.[64]

Phase 1 Studies

The phase team includes the patients, caregivers, biostatisticians, oncologist investigators, clinical trial nurses, research associates and data coordinators, pharmacologist and/or pharmacists, imaging and pathology specialists, along with sponsoring agencies (government, industry, academic, or combinations thereof).

There are multiple types of phase I trials. They may be testing an investigational agent plus another investigational agent, an investigational agent plus an approved modality (ie, radiation therapy [RT]) or agent(s), an approved modality (ie, RT) or agent plus another approved agent(s), an approved or investigational agent with a PK focus (ie, adding a poly (ADP-ribose) polymerase [PARP] inhibitor), or an approved or investigational agent with a PD focus (eg, evaluation using functional imaging).

If RT is tested with a systemic agent, there should be a preclinical rationale to pursue an early-phase human trial. Ideally, there should be convincing preclinical data that indicates the combination is either efficacious (radiation sensitization) and/or shows no overlapping toxicities (toxicity independence). There should be evidence of *in vitro* radiosensitization in human tumor cell lines, in-*vivo* radiosensitization in human tumor models, lack of sensitization of normal tissues, preclinical use of clinically relevant doses, and schedules of agents & RT. Similarly, conceptual frameworks apply for combination approaches that assess radioprotection rather than radiosensitization.

Generally, in the phase I setting, the primary objective is to determine the MTD based on scientifically defined DLTs. The MTD found in phase I stage is often used as the RP2D. DLT is often defined as a toxicity (or toxicities) that is considered serious, typically based on standard criteria of toxicity such as the most recent Common Terminology Criteria for Adverse Events (CTCAE). DLTs must be defined in advance prior to beginning the trial, are protocol specific, and usually based, in the case of a systemic agent, on toxicity seen in the first cycle. The MTD is a dose level that yields

a reasonable rate of DLTs in targeting patient populations. It is a dose that is believed to be efficacious and adequately safe. A dose higher than the MTD is considered unacceptable. The secondary objectives of phase I studies are to define the toxicity profile of new therapy(s) or schedule of an existing modality, such as radiotherapy, under evaluation. The PK and PD effects in tumor and/or normal tissues can be determined along with a preliminary assessment of antitumor activity.

Phase I

Broadly, the main objective of the phase I trial is to determine the maximum tolerable dose of an agent to be subsequently used in testing for efficacy. Although initially developed in the setting of drug testing, this concept has been adapted to test radiation alone and combined drug/radiation regimens. The basic conceptual approach is that of sequential dose increases, or escalation, in small patient cohorts until the treatment-related AE rate reaches a predetermined level or unexpected toxicity is seen. This stepwise testing in phase I trials determines what is known as the MTD, which is putatively the most effective level at which to evaluate efficacy.

The key parameters to be defined at the outset of a phase I trial include patient eligibility criteria, starting dose and the schedule of dose escalation (which should frame the expected MTD), events comprising the AE/toxicity response and the expected MTD, and finally the escalation design plan.[65] The dominant design for the phase I setting has been the so-called 3+3 approach, where cohorts of three patients are exposed to a given dose, and based on the outcomes in that cohort, de-escalation, escalation, or additional enrollment takes place. There are a large number of other designs, one of which may be particularly suited for radiation therapy trials, as we discuss shortly. It should be appreciated that the MTD is a relative concept that can change over time. For example, hematologic toxicity may be less dose-limiting today than it was before the development of bone marrow stimulators.

Design Challenges

When setting up an early-phase RT trial, it is critical to keep in mind the next step in development. There are several considerations that are paramount, including What should the study doses (including the starting dose) be? How many patients should each cohort include? What is the standard therapy for the tumor site being treated? How quickly can doses be escalated? What is the role of conventional chemotherapy? How should surgery (if appropriate) be integrated? How should chemotherapy be integrated? Can the validation of biomarkers be assessed? and To what extent will a subsequent phase II/III trial utilize a selected or unselected patient population?

A phase I trial can include RT as the single modality undergoing testing. Often, a second modality, such as concomitant systemic therapy, is included. In the latter case, data that will be helpful for the design of the study should include single-agent pharmacokinetic data from a pragmatic and relevant scheduling regimen such as consideration of continuous dosing during RT versus once-a-week dosing. Single-agent pharmacodynamic data including the agent's effect (if known) on a molecular target that is relevant to the interaction between RT and radiation are necessary, alongside safety data.

Dose escalation guidelines have been developed and refined to effectively identify the RP2D. Basic principles of dose escalation include starting with a safe starting dose, minimizing the number of patients treated at subtoxic (potentially subtherapeutic) doses, escalating the dose rapidly in the absence of toxicity, and adjusting the dose slowly in the presence of toxicity.

The Fibonacci sequence typically includes three patients per cohort until the DLT is reached, then an additional three patients are accrued at the dose level. Some of the accelerated titration designs attempt to minimize patients within the early dose levels. Typically, a single patient is enrolled at each cohort until greater than or equal to grade 2 toxicity and then the number of patients accrued at the dose level is increased to three (or perhaps a total of six if that turns out to be the MTD). Standard dose escalation rules are acceptable, especially if multiple agents are being utilized (including conventional chemotherapy). The maximum administered dose (MAD) and MTD may have variable definitions by trial and country of origin but can be conceptually framed as per Figure 14.1. Importantly, the RP2D is often one

dose level below which the DLT occurred in a prespecified proportion of patients (eg, ≥33%).

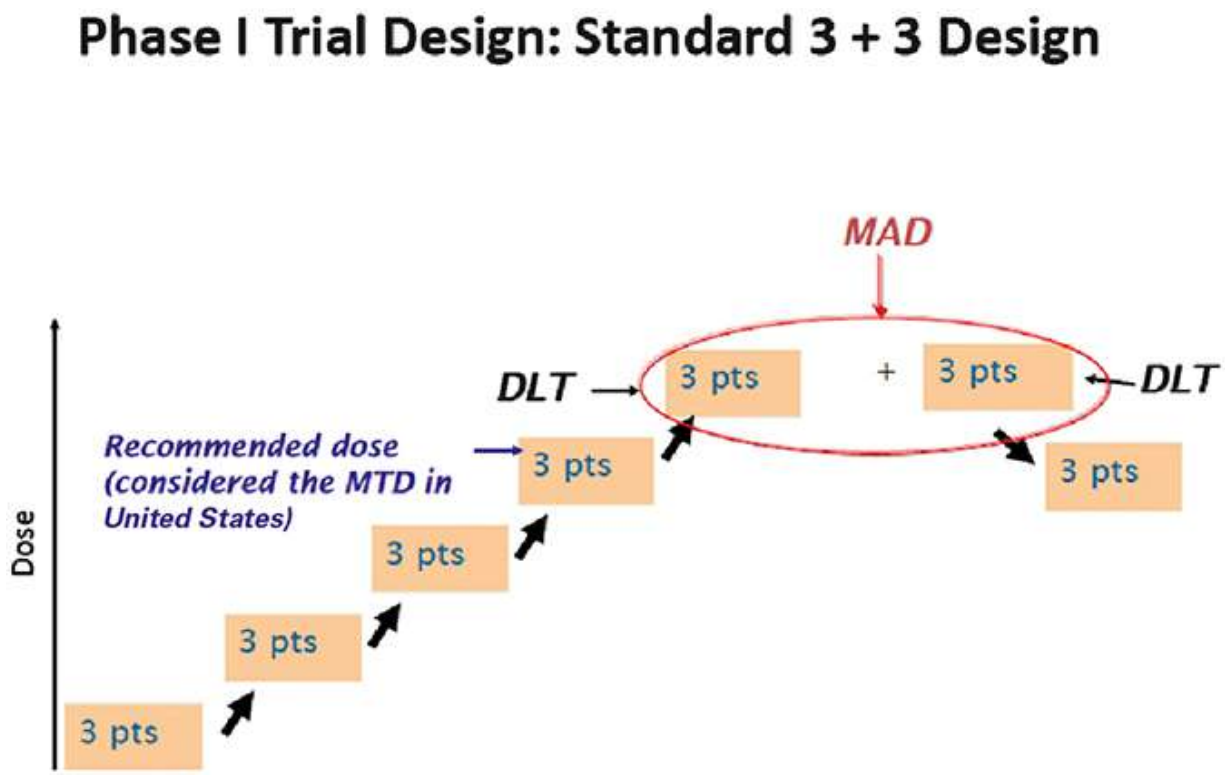

FIGURE 14.1 Example of standard 3+3 phase I design. DLT, dose-limiting toxicity; MAD, maximum administered dose; MTD, maximally tolerated dose.

It is recommended to consider using a toxicity assessment in association with clinical or biologic endpoints. With targeted agents, it may be necessary to define the optimal biologic dose (OBD) as opposed to MTD. OBD is the dose associated with a prespecified desired effect on a biomarker or tumor response while being safe enough (eg, not exceeding the MTD). For example, the OBD may be the modality dose at which greater than or equal to XX% of patients have inhibition of a key target in tumor/surrogate tissues. It may also be the modality dose at which greater than or equal to XX% of patients achieve a prespecified immunologic parameter. Caution is advised since such a biologic endpoint is often considered a surrogate for therapeutic effect, and the validity as well as interpretability of such a surrogate may not be completely understood during the early drug development period.

Patient selection is important in early-phase study design. For example, the tumor site(s) to be studied needs to be defined since this will impact the assessment of toxicity. Not all normal tissues are equal. The selection of tumor site may also be impacted by the agent being used in combination with RT. Also, are the patients being enrolled in a phase I study going to receive curative, palliative, or consolidative radiotherapy? This will affect the total radiation dose and fractionation utilized. This will affect the patient population and perhaps the ability to tolerate combined modality therapy. In general, phase I data are generated from studies that are cancer specific and/or site specific.

Starting dose and schedules of the modality under investigation will need to be defined. If the goal is radiosensitization, then delivery of the agent during as many fractions of radiation is desirable. Timing may be critical. A typical approach, especially in the curative setting, is to start with a standard radiation dose; however, escalation (or even de-escalation) of the radiation dose may be desirable in certain clinical situations.

A limited dose escalation design is also utilized. DLT may include, though are not limited to, the following: grade 4 hematologic toxicity, grade 3 nonhematologic toxicity with exceptions for grade 3 gastrointestinal (nausea and emesis) in the setting of upper abdominal RT, unscheduled breaks during the RT course, inability to administer systemic agent, and/or surgical morbidity for trials where the dose escalation component occurs in the preoperative setting.

As stated earlier, not all normal tissues are equal. A parallel track dose escalation design may allow one to test the combination of one (or more) agent(s) plus different doses of RT for different anatomic disease sites. After the RP2D of the dual-targeted agents is identified and thereafter fixed, the RT dose is escalated.

Lead-in administration of a novel agent, prior to piggybacking onto a standard combined modality backbone, may allow for independent assessment of toxicity as well as evaluation of a biomarker with respect to proof of principle preliminary exploration of possible mechanisms of target inhibition.

In addition, this approach may be particularly helpful in selecting patients for phase II studies. Furthermore, an expanded cohort at the final dose may allow for a more precise evaluation of the biomarker.

Endpoints

In clinical trials, endpoints must be unambiguously defined, be assessable and reproducible, and reflect the action of the intervention. Typically, there is a single primary endpoint in a clinical trial, but there may be numerous secondary endpoints.

Traditionally, in phase II cancer trials, treatment activity has been defined in terms of reduction in tumor burden. The most recent criteria for measuring activity are known as the Response Evaluation Criteria in Solid Tumors (RECIST).[66] The criteria require the identification of target and nontarget lesions at baseline and their largest single dimensions. Categories of response are then defined, for example, complete response (CR, disappearance of all target and nontarget lesions and no new lesions), partial response (PR, 30% or greater decrease in the sum of the longest diameter of all target lesions, no progression of nontarget lesions, and no new lesions), and progressive disease (PD, 20% or greater increase in target lesions, progression of nontarget lesions, or the occurrence of new lesions). A patient not satisfying either response or progression criteria is classified as having a stable disease (SD). Those achieving either a CR or PR are typically defined as objective responders, and the proportion of patients responding is then the primary endpoint of interest. Although widely used, there has long been concern that response defined this way is an inadequate substitute for more clinically relevant and objective endpoints such as survival time. In one study, less than 25% of agents that produced tumor response were eventually found to extend survival in comparative trials,[67] while others suggested that tumor response is a reasonable surrogate for survival extension.[68] Additional problems with the use of response rates in phase II trials include subjectivity and lack of reproducible assessments.[69]

As mentioned earlier, tumor response is not as frequently used when radiation therapy (and local therapies more broadly) is the test question, and in any case, other discrete binary endpoints can readily be used. For example, the proportion free of a given event (ie, proportion alive, proportion recurrence free, etc) at a fixed time landmark such as 2 years is a common and straightforward endpoint. Notably, however, fixed single-timepoint endpoints (eg, 1-year OS or 5-year recurrence-free survival) often

do a disservice in comparative trials in that they ignore information from the "full" survival curves.

A more informative endpoint that is used in many phase II and most phase III trials is the elapsed time from trial entry until the occurrence of some event. The most straightforward of these is OS time or time to death from any cause. This simple endpoint does not depend on adjudication of cause of death and its attendant complexities and naturally corrects for both favorable and unfavorable consequences of treatment. Although it can be verified or even ascertained from public records due to its simplicity, active follow-up per protocol remains of paramount importance. Cause-specific survival endpoints may also be considered, although as mentioned, assigning cause of death is not simple, and one must account for "other cause" deaths and whether these have any relationship to treatment. Also, whenever cause-specific deaths or other site-specific failure endpoints are used, methods for appropriately dealing with competing risks are required.[70,71] Time-to-event outcomes are often subject to censoring due to patient dropout or trial termination. Special care must be taken when analyzing these outcomes in the presence of censoring. Summary statistics such as median survival and restricted mean survival time are widely used to quantify the treatment effect on time-to-event endpoints.

Other commonly used time-to-event endpoints include DFS (time to recurrence or death from any cause) or PFS (time to disease progression, possibly determined via imaging or other assessments at regular intervals), although definitions of these are not standardized (see, for example, Hudis et al[72]) and the specific failure events comprising a given endpoint should be carefully specified. The main advantage of using DFS or PFS is the more rapid rate of events, leading to a smaller required sample size. In many cancer types, benefit with respect to these endpoints does not necessarily imply subsequent lengthened survival, although they may still represent clinical benefit for patients. For other disease settings (eg, adjuvant therapy in colon cancer), DFS may be a reliable and well-accepted primary endpoint that is correlated with survival.[73] This raises the topic of so-called surrogate endpoints, which are endpoints upon which treatment benefits can be reliably measured. Various biomarkers and clinical endpoints have been studied and have been proposed as surrogate endpoints in clinical trials. Prentice specified criteria that a surrogate endpoint must fulfill if it is used

to substitute for a clinical endpoint: the therapeutic intervention must exert benefit on both the surrogate and the clinical endpoint; the surrogate and clinical endpoint must be associated; and the effect of intervention on surrogate endpoint must mediate the clinical effect.[34] An example of a widely studied surrogate marker is a PSA, applied either as a static measure or as dynamic measures (PSA velocity; PSA doubling time; time to PSA nadir, particularly useful after radiation therapy of the intact prostate), to assess time to biochemical failure in patients with nonmetastatic adenocarcinoma of the prostate.[74,75] This continues to be a developing area, and there remain many caveats and cautions regarding surrogate endpoints in clinical trials.[76] We encourage the reader to explore this issue further, particularly regarding the commonly encountered situation in oncology of utilization of surrogate endpoints such as PFS as part of regulatory approvals, potentially in the absence of validity of PFS as a surrogate in diverse disease settings.[37,77-79]

Statistical Power and Sample Size

The overarching design consideration in clinical trials is to obtain sufficient information about an intervention so that a reliable decision can be made regarding its further development or use. In the frequentist statistical hypothesis testing paradigm, one sets up a null hypothesis of no treatment effect and an alternative hypothesis (which one hopes to validate) indicating a treatment effect. The type II or b error equals the probability that a statistical test fails to produce a decision in favor of a treatment effect when in fact the treatment is superior in the population. The complement of this probability (1 − b) is referred to as *statistical power* and equals the probability of correctly deciding in favor of a treatment benefit. Statistical power depends on the other principal parameters considered when planning the trial, specifically the probability of incorrectly finding in favor of a difference when none exists (type I or α error, usually set to 0.05 or 0.01 by convention), the *a priori* specification of a treatment effect that is considered both realistic and clinically material, and of course the sample size. It is imperative that trials be designed to achieve adequate statistical power, typically 0.80 to 0.90 is desirable, so as not to obtain equivocal findings concerning the potential worth of new treatments under

consideration. Studies with low statistical power can cause delay or even abandonment of the development of promising treatments, and waste valuable resources, not least of which is the participation and goodwill of patients.[80] In contrast, a "negative" trial that does not find the test treatment to be superior, if adequately powered, is informative, in that resources can be directed to other more promising alternatives.

Thus, the sample size to satisfy the type I error and the power desired for the specified effect of interest is a key calculation in phase II and III clinical trials (phase I trials generally do not rely on hypothesis-driven sample size calculations, and the sample size derives from the specific design used). The specific sample size calculation depends on the endpoint and technical details will not be provided here, but the two most common types of endpoints can be summarized as follows.

For a discrete binary endpoint in a phase II trial, for example, responded/did not respond, sample size calculations are straightforwardly performed using formulas for comparison of proportions. In a single-arm study, one aims to compare the observed response rate for the new agent to some historical response proportion, p_0, the response rate achievable with standard therapy in the target population. The main objective is to determine whether there is sufficient evidence to conclude that the response rate for the new regimen is greater than p_0. We designate p_A a response rate which, if true, would be clinically material. We test the null hypothesis H_o : $p = p_o$, against the alternative hypothesis H_A : $p = p_A$, The values of p_0 and p_A (and more importantly the difference between p_0 and p_A), along with the sample size, will determine the power of the study. Note that detecting a small improvement (say, ≤10%) requires a large sample size to achieve the desired level of statistical power. For example, given a one-sided type I error rate of 10%, to detect an improvement from a historical value of 20% to 30% with 85% power, over 120 subjects are required. Also, the value for both p_o, and p_A must be realistic; it is of little value to design and carry out a study to detect an effect size $p_A - p_0$ that is unlikely to be realized, simply because it is compatible with the number of patients that can be recruited.

For two-arm randomized phase II trials with discrete endpoints, the above is simply redefined in terms of two-sample comparisons of

proportions, and the sample size is consequently much larger. Finally, if the endpoint is a fixed time landmark such as proportion event-free or alive at 1 year, then the estimates of the proportions may be derived from survival analysis methods to appropriately account for losses to follow-up.

In many randomized phase II and nearly all phase III trials, the time from randomization until the occurrence of the event is of principal interest, rather than the event status at some fixed time landmark. In larger phase II and phase III trials, recruitment may take place over a lengthy interval and each patient will have a different follow-up duration, and the use of follow-up time per patient is more efficient than waiting until all patients have reached some fixed time. The treatment effect measure is then specified in terms of failure *hazards*, which can be thought of as failure rates per unit of time. Hypotheses are thus usually formulated in terms of the hazard ratio (HR) as $H_0 : \lambda_A / \lambda_B = HR = 1.0$, where λ_A and λ_B are the hazards for treatments A and B, versus alternative $H_A : HR < 1.0$, for some value of the HR that represents a clinically important difference in outcomes. A key assumption for many HR-based analyses is that the HR is relatively constant over time (over the length of the survival curve); this assumption can be routinely violated and is discussed later in this chapter. Notably, a common error in the interpretation of the HR is that an HR of 0.75 corresponds to a 25% reduction in the relative risk of the endpoint of interest (eg, a 25% reduction in risk of death for an HR of 0.75 for an endpoint of OS). However, although this is commonly how HR values are reported and interpreted, this does not address the statistical distinction between reduction in hazard versus reduction in risk, which is outside the scope of this chapter but is elaborated on elsewhere in the literature.[81]

From the specification of difference of interest or effect size, then the sample size in terms of the number of *events* required to detect this difference with desired statistical power and significance level is determined. Depending on the anticipated accrual rate and the prognosis (eg, rapidity of failure events) in the control treatment group, the number of *patients* required can then be approximated. The number of events required depends strongly on the HR, becoming dramatically larger as the HR approaches 1.0. The number of patients required, and the total duration of the trial depend on the rate of patient accrual and the failure rate in the

control group, both of which contribute to the determination of how rapidly the requisite events will be observed. The accrual rate is typically estimated from previous experience and may also involve querying investigators to project the accrual rate per unit of time. Similarly, the failure rate for patients under standard therapy is derived from available data. The final computations are often straightforward but generally require computer programs,[82] but under certain assumptions, can be approximated.[83] Sample size methods have been extended to take into account other factors that will influence power, such as patients withdrawing from treatment (drop-out), switching from the assigned treatment to the other group (crossover), or deviating from protocol treatment (noncompliance).[84-86]

Traditionally, the sample size of a phase I trial has been determined based on practical or budgetary considerations. For the 3+3 design, the maximum sample size is theoretically the number of study dose levels multiplied by six. However, due to the early-stopping rules used in the 3+3 design and many other phase I designs, the actual sample size required for a trial may vary. For innovative Bayesian dose-finding designs, a practical approach to specify the sample size is to use the maximum sample size of the 3+3 design. However, computer simulation studies are strongly recommended to calculate the operating characteristics of the design, such as the percentage of correct dose selection and the number of patients overdosed, under a variety of dose-response scenarios to justify the sample size selected.

Interim Analysis and Stopping Rules

Primarily for ethical considerations but also to make the best use of resources, interim analysis plans are used in all phases of clinical trials. These plans provide for early decision-making in a trial regarding continuation, disclosure of findings, or modification of the trial, while preserving integrity of the study with respect to power and type I error control described earlier. These methods are needed because, with repeated hypothesis tests, the probability of at least one test resulting in an erroneous rejection of the null hypothesis increases.

Phase I trials rely on observed cumulative AE rates at a given time to inform dose escalation/de-escalation decisions and determine when to

terminate enrollment at a specific dose level, which are integral components of the trial design. We refer to a review of the designs for more details.[2]

Phase II trials more formally incorporate go/no-go stopping rules, usually restricted to futility/safety stopping, or discontinuation when results do not appear promising. For trials with discrete endpoints such as tumor response, this is accomplished through multistage study designs, whereby a cohort of patients is enrolled and assessed for response, and if a specific minimum response proportion is observed, the trial continues to accrual, otherwise, it discontinues enrollment. Likewise, early stopping for toxicity can occur when an excessive number of patients have experienced the DLT during the trial. The most commonly used designs are those proposed by Simon,[87] although there are other similar approaches. In trials with time-to-event primary endpoints, futility rules similar to those for phase III trials (discussed next) can be used to discontinue after a period of follow-up if results appear unpromising. Early stopping of single-arm phase II trials for extraordinary efficacy is unusual though not prohibited. Early stopping for efficacy can limit patients' access to promising treatments and may result in insufficient data (for other endpoints) at the time of analysis.

Phase III trials commonly use repeated testing strategies derived from an area of statistics known as group sequential methods. Briefly, the primary hypothesis is evaluated at predefined increments (typically 3-5 looks) of the total information (usually in the form of failure events) needed for definitive analysis. The individual tests are designed to (a) protect against spurious early stopping due to the unstable nature of "early" results and (b) correct for the effect of repeated testing on type I error, which can also lead to spurious declaration of treatment effects that may not be reliable. Conceptually, this can be considered through the lens of "alpha spending," where interim analysis boundaries are controlled to prevent inflation of the type I error rate.[88] Commonly used approaches include the Haybittle- Peto approach, for which each test through the penultimate look requires a constant highly significant result, such as $P < .0001$ in order to stop,[89,90] and the O'Brien-Fleming approach and its subsequent approaches,[91] in which the required significance level decreases over the looks, becoming less extreme as more information accumulates. There are many variations and extensions of the latter approach, with different properties and advantages in special circumstances. In addition to efficacy monitoring rules, phase III

trials increasingly incorporate formal futility-stopping rules, although methods such as conditional power calculations have been available and used for some time.[92,93] Futility-stopping rules similarly involve setting a boundary such that when the test statistic falls beyond it, then one considers stopping because the new treatment will not ultimately prevail. Stopping for futility is a complex decision requiring careful consideration,[94] and methods continue to be studied and developed.[95,96]

Definitive Analysis and Secondary Analyses

When the trial reaches maturity either as planned or earlier as a result of the monitoring plan, then definitive analysis takes place. Prior to this, it is not conventional or recommended to disclose any results from the trial.[97]

A critical aspect of clinical trial analysis is the definition of the analyzed cohort. The concept of analysis by *intention-to-treat* (ITT) is often cited for randomized trials, but the definition of this term can sometimes be unclear, so it is best to explicitly describe which patients are included.[98] In the strictest sense, the ITT cohort includes all patients randomized, regardless of eligibility, adherence to assigned treatment, or any other postrandomization deviations from the protocol. However, it is often the case that patients found ineligible for the trial after randomization due to having been incorrectly staged or for other reasons are excluded from the primary analysis, and this practice (used with caution) is sometimes advocated, as it allows for evaluation of the therapy in the population for whom it was intended.[3] A rarely acceptable practice involves exclusion of patients who did not or could not comply with assigned therapy regimens or received nonprotocol therapy, or other postrandomization conditions. Such exclusions can easily lead to biased comparisons, and in general *post hoc* analyses of treatment benefit by dose received carries interpretational difficulties.[99] That said, a more nuanced view of ITT and alternatives is increasingly coming into the fore, with sensitivity analyses for those treated per-protocol or “as-treated” analyses potentially playing an increasing role in trials assessing medical devices, for instance. Depending on the trial design, consideration may be given to non-ITT approaches in consultation with expert statisticians as well as other key stakeholders (including those with regulatory interface or expertise).[100]

The primary analysis methods follow naturally from a well-written protocol (see below) and thus should be straightforward. Given that major journals now generally mandate that study protocols be provided at the time of publication and that regulatory agencies and public sponsors do likewise, it behooves the trialist to outline the analysis plan in the protocol and then carry it out at study conclusion.[101] This does not suggest that additional analyses cannot be carried out, but having a framework for the planned analysis adds credibility to the findings. Deviation from study protocol in the primary endpoint analysis in particular carries substantial implications regarding the veracity and believability of reported data.[102]

Secondary prognostic factor analysis using statistical models or other techniques often follows a primary analysis of phase III trials. Of particular interest is whether there are particularly responsive or nonresponsive subsets of patients, in an attempt to render the findings more relevant to practice. The modeling process, which entails deciding which factors to include, determining the correct way to represent a given factor (ie, in categories, on a continuous scale, etc), consideration of interrelationships (eg, interactions) among factors, and many other issues, can be complex, and it should be recognized that these analyses will be largely viewed as exploratory. While possibly worth exploring, true differential effects of treatment by other factors usually require a large sample size, unless the effects are very large.[103] Analysis of differential treatment effects within subgroups is further subject to low credibility absent appropriate interaction testing, among other elements.[104,105] A comprehensive review of current modeling methods applied to oncology data is provided by Schmoor et al.[103]

PRACTICAL ISSUES IN THE DESIGN, CONDUCT, AND REPORTING OF CLINICAL TRIALS

Protocol Document and Study Conduct

The goal of a clinical trial is to answer a well-formulated question that will change clinical practice. To achieve that, the investigators must know the current state of knowledge on the studied disease; clearly describe the eligibility criteria of the studied population; understand the number of patients who will be eligible in their institution/cooperative group; choose simple and achievable endpoints; establish statistical assumptions based on

a thorough review of preexisting data; and collaborate with a biostatistician to decide on study design, sample size, and power.

The clinical trial protocol document must contain the title, investigators and sponsor's name, phase (I, II, or III), protocol synopsis, background knowledge, study design and schema, objectives, methodology, subject selection criteria, registration procedures, treatment plan, dosing modifications, AEs reporting, data and safety monitoring plan, study calendar, outcome measures, data reporting, statistical considerations, and the informed consent.[106]

Choosing the right study endpoints is crucial, as it needs to reflect the primary goal of the trial. Any number of endpoints may be of suitable scientific and clinical value, but if there is interest in regulatory approval, then obviously the endpoint must reflect the requirements of those parties involved. Overall survival largely remains the "gold standard" for a registration trial designed to gain marketing approval. However, survival length may be affected by effective salvage therapies or by the patient's "crossing over" to the other study arm. Endpoints such as DFS and PFS have been used for either expedited drug approval or regular approval, depending on the disease site.[107] If endpoints subject to assessment bias are to be used (eg, PFS or tumor response), then appropriate bias reduction measures are needed. One approach to circumvent this problem is an independent review panel (eg, radiologists reviewing baseline and follow-up images to quantify tumor responses and note the moment of tumor progression), consisting of experts not associated with the trial and unaware of the arm to which the patient was enrolled; this is discussed further earlier in this chapter. One must also consider the validity of modern endpoints even under unbiased review. For example, the phenomena of pseudoprogression and pseudoresponse have made imaging-based end points, including overall radiographic response and PFS, problematic.[108]

Successful completion of a clinical trial requires constant attention to its practical aspects. Sufficient personnel are necessary in order to ensure the smooth running of the study and the safety of the participating subjects. Clinical research nurses, clinical research associates, data managers, and investigational pharmacists are crucial components of the research team.[109] Of particular importance is the careful and immediate recording and attribution of all AEs. Severe AEs have to be reported promptly to

appropriate regulatory agencies (IRB in the institution where the study is open; FDA and others) and to the study sponsor. Since most protocols have amendments added during their lifetime and new toxicities are reported from other studies, the research protocol commonly evolves over several successive versions. It is highly recommended that in reporting results from clinical trials, trialists not only provide the study protocol as a supplemental material but also a history of protocol changes over the course of a trial's lifetime; this practice is increasingly encouraged to augment transparency and reduce risk of incomplete or incorrect analyses or results reporting.[102] As a result of protocol changes over the course of a trial, new versions of consent forms may be created as well, and IRB approval may again be required. It is imperative that patients enrolled in the study sign the most current version of the consent form. All the prescribed follow-up tests (imaging, blood work, etc) must be scheduled ahead of time and coincide with the study calendar, requiring coordination and organization by research personnel. Departures from any of the procedures are often scored as protocol deviations during periodic audits and will adversely impact the study's validity. Additionally, designated independent medical monitors are assigned to high-risk trials (such as most single-institution investigator-initiated trials) to continuously review any reported events, which are later evaluated periodically by the institutional data safety monitoring committee.

Data and Safety Monitoring Committees

The decision to alter clinical trial in progress, including discontinuation of accrual and/or treatment, depending on its current state), and early release findings is typically vested in an independent DSMC. In addition to evaluating according to the monitoring rules described earlier, the DSMC considers the information available from the trial as well as external information that bears on treatment for the disease under study. Specifically, it should be noted that the early stopping rules described previously are meant to serve as guidelines, and there may at any decision point be additional considerations that must be taken into account.[110] The policies and procedures for cooperative group trials provide a good overview of DSMC structure and function.[111]

Trial Reporting

Once the study is completed and the data are fully analyzed, results should be reported promptly. Publication of the results of the trial in a scientific journal represents the culmination of the investigators' efforts and allows wide distribution of the findings. However, lack of precise requirements for reporting may lead to inaccurate or biased results presentation. The CONSORT (Consolidated Standards of Reporting Trials) statement is used worldwide to improve the quality of reporting of randomized controlled trials (RCTs).[112] It provides a 25-item checklist of all required elements and a flow diagram to ensure that all patients enrolled are accounted for. Most journals require authors to follow the CONSORT guidelines, since "diligent adherence by authors to the checklist items facilitates clarity, completeness, and transparency of reporting."[112] The ICMJE (International Committee of Medical Journal Editors) similarly publishes guidelines on uniform requirements for manuscripts submitted to biomedical journals.[113] There have also been calls for improvements in reporting of phase I and II trials.[114,115] In addition to quality with respect to content, a full disclosure of the financial COI by the investigators to the readers is necessary as well. It is particularly important for investigators to publish negative studies, decreasing the overall incidence of publication bias and trial "dark matter" (unpublished trial results).[12] Study of the publication rate of cancer cooperative group trials regardless of findings shows there is room for improvement with respect to a responsible approach to clinical trial conduct.[116]

In the United States, reporting requirements are currently trending toward an expansion to more "open access" sources, based on mandates arising from legislation. ClinicalTrials.gov is the largest clinical trials database in the world and is led by the National Library of Medicine in the NIH in the United States. Initially, including information only on NIH-sponsored studies, NLM now also contains studies sponsored by pharmaceutical companies and demands "basic results" information not later than 1 year after the study's primary completion date (ClinicalTrials.gov). The requirements for results reporting were prompted by the removal of several drugs from the market due to earlier unrealized toxicity, knowledge about which was obscured by lack of publication or other public documentation.

However, analysis of clinical trials suggests that compliance with federally mandated reporting requirements in ClinicalTrials.gov remains poor, and further efforts at multiple stakeholder levels aim to improve this compliance and transparency.[21]

RECENT APPROACHES TO CLINICAL TRIAL DESIGN

Alternative Phase I Trial Designs for Radiation Oncology Trials

As mentioned earlier, phase I trials in radiation therapy present a unique challenge in that toxicities may occur long after treatment and need to be incorporated into dose evaluation. The traditional stepwise designs do not accommodate this, and thus an extension of the Continual Reassessment Method (CRM)[117] that incorporates the time-to-event (ie, time to toxicity) information for each patient was developed.[118] Designated the TiTE-CRM approach, a dose-response model is first posited that identifies the starting dose and range to be considered, along with a time frame for events occurring anywhere up to T time units from the administration of therapy. Rather than waiting for each cohort of patients to be followed for this length of time, however, one can enter new patients at, say, half-month intervals. As in the original CRM, the first patient is assigned to a dose level based on prior information or, as in the modified CRM, to the lowest candidate dose. At the time the next patient(s) is (are) to be enrolled, the observed toxicities and follow-up up times of patients already entered are used to form an updated estimate of the β parameter that defines the dose-response curve, and the dose level for the next patient(s) selected according to the usual CRM or modified CRM criteria. In simulation studies, the TiTE-CRM produced results comparable to its CRM counterpart, while significantly reducing the average duration of the trial. However, the TiTE-CRM method was associated with slightly more toxicities, particularly in situations where events tend to occur near the end of the observation period, since escalation to the next dose may have already occurred before toxicities were observed.[118] Another problematic issue is rapid accrual, where premature escalation of dose may be indicated. A recent review and suggested modifications may make this approach even more suitable for radiation oncology trials.[119]

The TiTE-CRM design is a model-based design that uses a parametric dose-response model to make dose escalation/de-escalation decisions. Despite its statistical appeal and generally good performance, its application in real clinical trials is limited. Many practitioners consider it statistically and computationally complex due to the requirement of specifying the model and prior, as well as the need for repeated model fitting and estimation. This leads practitioners to perceive dosing decisions as coming from a "black box." On the other hand, model-assisted designs combine the simplicity of the 3+3 design with the good performance of model-based designs. To address late-onset toxicities or rapid accrual, the Time-to-Event Bayesian Optimal Interval (TiTE-BOIN) design,[120] built on the BOIN design (the first FDA-designated fit-for-purpose design for oncology dose finding), has emerged as an easy-to-implement alternative to TiTE-CRM. One of the prominent features of the TiTE-BOIN design is that its rules for dose escalation/de-escalation can be pretabulated before the trial begins, making the trial decision-making process more transparent. For example, the TiTE-BOIN design has been applied to the first-in-human VOYAGER study (NCT03192578) to determine the maximum safe radiation dose of the TheraSphere Prostate Cancer device in patients with clinically localized prostate cancer.

Due to the flexibility and good performance, Bayesian adaptive design for early-phase trials can be further modified to accommodate unique features of radiation oncology.[121] In one recent example, trialists aimed to assess whether an investigational radioprotection agent (vs placebo) would reduce late-onset toxicity for patients with pancreatic cancer; concurrently, investigators were including an RT dose-finding component to the study.[122] Collectively, statisticians developed a Bayesian adaptive approach using two co-primary endpoints of 90-day toxicity rates and 90-day tumor control. This late-onset efficacy/toxicity (LO-ET) design allowed trialists to adaptively randomize enrolled patients to receipt of the investigational radioprotector (vs placebo) as well as RT dose level and identify an "optimal" combination based on both receipt of investigational radioprotector plus RT dose. Promising results of this trial highlight successful implementation and utilization of advanced and adaptive early-phase trial design approaches within radiation oncology.[123]

Alternative Phase II Trial Designs

As indicated earlier, the value of traditional single-arm phase II trials has been called into question in terms of providing a reliable basis for further pursuit of promising treatments. The currently favored design is a randomized phase II trial with a standard-of-care comparison group[29],[33],[124] This approach and the goal of accelerating development has led to consideration enhancements to the phase II design, including adaptive randomization, where one favors enrollment to the arm(s) that seem to be prevailing while reducing probability of enrollment on other arms, and even dropping some treatment arms. This is an idea with a long history,[125] but recent innovations in computing and Bayesian methods, as well as a newfound interest in accelerated development, have brought it to wider use in some settings.[126] In some instances, it may offer advantages but must be weighed against simpler approaches with similar or even greater efficiency.[127]

Changes in therapeutic approaches also suggest design changes. Because primarily cytostatic agents are not expected to necessarily result in tumor response in the traditional sense, there is a need to consider alternative phase II designs based on endpoints other than response rates. For trials enrolling patients who have failed prior therapy, Mick et al[128] propose a method that uses each patient as their own control, comparing the time to progression (possibly censored) under the new agent with the time to progression under prior therapy. Rosner et al[129] propose a randomized discontinuation design to evaluate cytostatic drugs in which all patients are initially treated with the experimental agent. After a specified interval, responders remain on drug and those who progress discontinue, while those patients with SD are randomized to either continued active treatment or placebo. This randomized comparison allows one to assess whether the drug is truly slowing the rate of growth of the tumor, as opposed to the investigators having simply selected patients with slow-growing tumors. Since the patients with SD form a more homogeneous subgroup, this design also requires a smaller sample size than would a trial that randomized all patients at entry. It is important to note that the purpose of this design is to determine whether the drug is active in an explanatory sense. Whether the percentage of patients exhibiting SD is high or low has a bearing on the

efficiency of the approach, since in the latter case the total sample size required may be quite large and any demonstration of activity in the randomized component would only be relevant to a small subset of the population. Korn et al point out other caveats with this design; for example, patients may find it unattractive to potentially discontinue a treatment that they perceive to be helping their disease.[130]

Using Biomarkers as Inclusion Criteria

It is increasingly understood that the response of tumors to targeted agents is highly dependent on their molecular subtype. Consequently, trials increasingly screen for molecular characteristics of tumors to use as eligibility criteria, or at a minimum, stratification factors. Consider, as examples, brain tumor trials requiring specific O[6]-methylguanine-DNA methyltransferase (MGMT) status or head-and-neck cancer trials requiring tumor human papillomavirus (HPV) status at entry for eligibility. When studies enroll sufficient numbers of patients, then treatment by marker synergisms, referred to statistically as interaction effects, can be investigated. Robust evaluation of true differential benefit according to markers requires that treatments be randomized, and so randomized phase II and phase III trials are ideal settings for developing tailored treatments.

In many instances, potentially responsive subsets of patients may be small and may also be identified after trials have initiated enrollment. For instance, anaplastic lymphoma kinase (ALK) inhibitors are highly effective, but only in the 3% to 5% of lung cancers that have *ALK* gene rearrangements. It may simply not be feasible to perform separate phase III trials for each molecular subtype. One possible alternative is "adaptive randomized" trial designs in which the data gathered as the trial progresses are used to change some aspect of the trial as it progresses. Some recent examples are the Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial in lung cancer[131] and the I-SPY trials in breast cancer.[132] However, there are limitations and challenges to these trial designs. For example, in order to be able to acquire information rapidly enough to undertake weighted randomization favoring more promising arms or eliminate nonresponsive arms, surrogate endpoints such as "disease control rate at 8 weeks" must be used. It is not clear if such

short-term endpoints are relevant to radiation oncology where durable local control is often achieved, and more nuanced considerations may exist still in an emerging field of trials where local therapy is utilized as the primary randomization intervention for patients with metastatic disease. This may include patients with oligometastatic or oligoprogressive disease, and we would direct readers to recent reviews on this subject, including nuances in trial design and execution for the use of radiotherapy in the setting of metastatic cancer.[133,134]

A number of papers in the clinical literature have further provided excellent reviews of the opportunities and challenges involved in incorporating modern molecular medicine into clinical trial design.[135,136]

Innovative Designs

The process of developing drugs, particularly in the field of oncology, is associated with high costs and lengthy timelines. Conventional clinical trials in oncology often employ a "one-treatment-one-cancer-at-a-time" strategy, which can be inefficient and may compromise scientific integrity, resulting in a low rate of success. To address the unmet need for identifying promising therapies for specific patient populations with cancer, researchers have developed sophisticated and innovative trial designs. These include umbrella trials, which investigate multiple treatments for a single cancer type; basket trials, which evaluate a single treatment across multiple cancer types; adaptive enrichment trials, which adaptively modify enrollment criteria based on accrued data; and platform trials, which study multiple treatments and diseases within a master trial infrastructure. Most of these designs are guided by a "master protocol," enabling the concurrent evaluation of several drugs, potentially from different pharmaceutical companies, or various cancer types and subtypes.

An umbrella trial is a type of clinical trial design that evaluates multiple therapeutic agents in patients with the same cancer type but different subtypes, which are determined by genetic mutations or biomarkers. The primary objective of an umbrella trial is to identify the most effective treatment for each specific cancer subtype. A well-known example of an umbrella trial is the BATTLE trial, led by the MD Anderson Cancer Center. This trial investigated four targeted therapies based on biomarkers in

patients with advanced non–small cell lung cancer (NSCLC). The cancer subtypes in the BATTLE trial were defined according to the presence of EGFR mutation/amplification, KRAS and BRAF mutations, VEGF and VEGFR expressions, and CyclinD1/RXR. One notable finding from this trial was that sorafenib demonstrated a higher disease control rate in patients whose tumors expressed KRAS and BRAF mutations.

Basket trials are a type of clinical trial that evaluates the efficacy of a single therapeutic intervention across multiple cancer types sharing a common genetic mutation or biomarker targeted by the treatment. This approach expedites the drug development process by concurrently assessing treatment effectiveness in various cancer types and rapidly advancing those showing promising results to later stages of development. Numerous Bayesian adaptive information borrowing techniques have been developed to facilitate the design and analysis of basket trials. These methods enable information sharing among different cancer types, thereby enhancing trial efficiency and reducing the required sample size. In the field of radiation oncology, the lead-in phase of the EXTEND[137] trial (NCT03599765) serves as an example of a basket trial. This phase investigated the efficacy of local consolidative therapy across diverse histologies, including colorectal, sarcoma, lung, and head and neck cancers, among others. Prostate, breast, pancreatic, and kidney cancers exhibited the highest enrollment rates and were selected for independent accrual in the randomization phase of the trial.[138,139]

Platform trials, also known as “multi-arm, multi-stage” (MAMS) trials, provide an efficient means of evaluating multiple treatments or treatment combinations by comparing their effects to a shared control arm. This design eliminates the white space between traditional one-treatment-versus-control trials, reduces the number of patients allocated to the control arm, and allows for the addition of new treatment arms and adaptive randomization between arms during the trial. The I-SPY2 trial[140,141] is a well-known example of a platform trial, designed as a phase II, multicenter, adaptively randomized study investigating various experimental agents in combination with standard neoadjuvant chemotherapy for patients with high-risk neoadjuvant breast cancer. The primary objective of the I-SPY2 trial is to expedite the identification of promising agents and biomarker profiles that are likely to succeed in subsequent phase III trials. A key

feature of the I-SPY2 trial is its ability to graduate successful regimens, drop unsuccessful ones, and add newly available regimens during the trial, without the need to initiate a new protocol. This approach saves considerable time and accelerates the entire drug development process. To date, the I-SPY2 trial has successfully identified two treatment combinations that demonstrate higher rates of pathologic CR compared to standard therapy alone, warranting further evaluation in phase III trials.

MOVING BEYOND CLINICAL TRIALS

Comparative Effectiveness Research

The randomized phase III clinical trial is considered the most robust method of comparing the efficacy of a new treatment with the standard of care. Grading systems for evaluating clinical evidence universally place "Randomized controlled trials" above observational trials.[142] More recently, this hierarchical approach to scientific evidence has been attacked,[42] and criticisms include the high fiscal cost of clinical trials, the length of time that it takes to obtain a conclusion (by which time the results are frequently no longer relevant since the standard of care has changed), and the large number of trials with negative results.

A specific criticism relates to clinical protocols that typically allow enrollment of only the fittest patients who lack comorbidities and have good performance status, criteria that subsequently limit the generalizability of the results. Studies have indeed shown that, for example, older patients are excluded unnecessarily out of concern for potential AEs[143-146] There have indeed long been calls for simpler and more inclusive eligibility criteria.[147,148]

In some sense, the desire to reduce exclusivity and broaden trial enrollment to more closely match the population is antithetical to "personalized medicine" and more focused trials as mentioned earlier. However, there are some ways in which the two concepts can possibly work in concert. Larger trials that can robustly support subset analysis according to biologic, clinical, and health history/behavior factors can at once be more inclusive and address questions about particularly responsive subgroups.

Another response to the criticism of phase III trials has been a reappreciation of the importance of population-based retrospective studies

as a means to appreciate and assess a treatment's effectiveness in the "real world."[149] Even more useful are well-designed prospective cohort studies, such as the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) study in prostate cancer, which will provide information on both factors driving treatment choice and the effects of specific intervention strategies[150,151] Another key strategy is conducting trials in parallel with concurrent registries of patients treated according to physician and patient choice and/or common convention, such as the **T**rial **A**ssigning **I**ndividua**L**ized **O**ptions for Treatment (**Rx**) (TAILORx) trial.[152] In this trial, over 10,000 women with breast cancer were screened using a molecular profiling tool, and for those with profiles in the range where the utility of the tool is uncertain, randomization between "hormonal therapy alone" and "hormonal therapy plus chemotherapy" was performed. Although efficacy was similar for the two arms, this trial highlights the effective integration of a molecular profiling tool in trial design.[153]

Meta-Analysis

A formal quantitative means of combining evidence from multiple clinical trials is by meta-analysis, a widely used analytic tool in many areas of social and medical science. Meta-analysis refers to a process whereby data from independent studies are combined to form a quantitative summary estimate of a given effect. Meta-analyses are considered by some to represent so-called level I evidence source along with (often large/phase III) randomized clinical trials. A meta-analysis combines the results of several studies, all of which ask a similar research question, but may be individually too small to have enough statistical power to definitively answer the question. Performing a systematic analysis of data from all identified randomized trials can define a modest but real advantage associated with a new therapeutic approach.

TIME-TO-EVENT CONTINUAL REASSESSMENT METHOD

The TiTE-CRM was initially described by Cheung and Chappell[118] where the time to toxicity was incorporated for each patient. This allows both acute and late toxicity to be accounted for, all while patient enrollment continues. Studies have shown that the TiTE-CRM design is usually more

efficient, treating more patients closer to the MTD and shorter trial durations. Here we will briefly discuss TiTE-CRM in further detail, but note to the reader as highlighted earlier that the ongoing evolution of optimized early-phase trial design continues, with Bayesian methodology (ie, TiTE-BOIN) and other paradigms gaining increased utilization and prominence.

Statistically, the TiTE-CRM design assumes that the hazard of developing toxicity is constant over time. In radiotherapy, that is often not the case. For example, pneumonitis is a subacute toxicity after thoracic radiotherapy that occurs 1 to 6 months after the end of radiotherapy, but not before or after. Therefore, assuming a constant risk for pneumonitis over time is inaccurate.

In radiotherapy, where late toxicity is a major concern, the TiTE-CRM has multiple advantages. Normolle and Lawrence performed a Monte Carlo simulation and found that, compared with a traditional 3+3 design, it can produce more accurate estimates of the MTD and not expose patients to significant excess risk.[55]

One concern in chemoradiotherapy trials is that with fast patient accrual and late toxicities, the TiTE-CRM could lead to overdose. Polley has proposed a modification to the TiTE-CRM[119] using accrual suspension. Bekele et al proposed yet another variation on the TiTE-CRM using time to toxicity. In this model, if the anticipated risk to patients while conducting a trial becomes too high, but then normalizes, the trial is restarted. The authors propose that this affords greater safety than the classic TiTE-CRM, although the trial may take longer (Figure 14.2).[154]

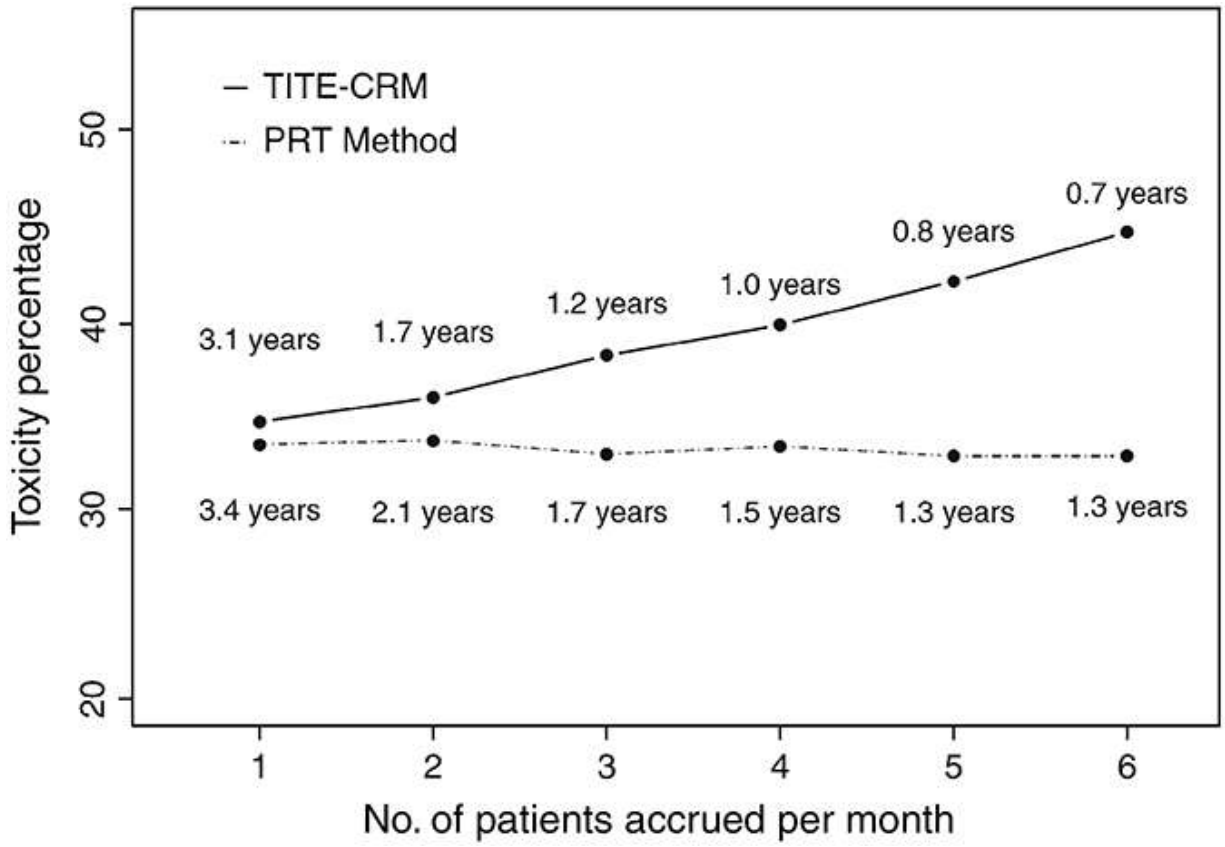

FIGURE 14.2 Comparison of toxicities seen using both methods with different accrual rates. (From Bekele BN, Ji Y, Shen Y, Thall PF. Monitoring late-onset toxicities in phase I trials using predicted risks. *Biostatistics*. 2008;9[3]:442-457. Reproduced by permission of Oxford University Press.)

A radiotherapy-specific model-based method has also been developed. Mehta et al reported on an alternative Bayesian methodology, which determines the probability of pneumonitis as a function of mean normalized lung dose and the dose per fraction is escalated accordingly.[155]

Despite the advantages of CRM design, Rogatko et al have shown that only 1.6% of 1235 phase I cancer trials published between 1991 and 2006 used Bayesian designs.[156] Le Tourneau et al found that only 3.3% of 181 evaluable phase I trials performed from 2007 to 2008 used CRM design (five modified CRM, one TiTE-CRM).[157]

Multiple combined modality therapy studies have used the TiTE-CRM design. For example, in pancreatic cancer, TiTE-CRM has been used in a phase I/II to dose escalate the radiotherapy dose with fixed-dose gemcitabine.[158] It has been used to dose escalate both oxaliplatin and

gemcitabine with fixed-dose radiotherapy.[159] And, lastly, it has been used to escalate cisplatin with fixed-dose gemcitabine and radiotherapy.[160]

Lawrence et al published on the early-stage development of radiosensitizers.[161] They advocated for the use of the TiTE-CRM design in its ability to enroll new patients while simultaneously monitoring for the development of late toxicity and incorporating that data into the model. They specifically note that intrapatient dose escalation is likely not appropriate in trials that use radiotherapy because of the cumulative nature of radiation toxicity. Likewise, TiTE-CRM has been used to dose escalate radiotherapy when combined with radioprotectants, for example, in liver radiation and concurrent amifostine.[162]

Accordingly, there is an urgent need for predictive biomarkers of normal tissue toxicity, particularly for late effects. Finding such biomarkers may hold promise; for instance, the use of troponin and/or N-terminal pro-B-type natriuretic peptide (NT-proBNP) blood levels along with strain analysis of 2D speckle tracking echocardiography may correspond to cardiac toxicity risk.[163-166]

Pitfalls

Chronic and cumulative toxicities usually cannot be assessed and may be missed if long-term follow-up is not incorporated into these study designs effectively. Furthermore, uncommon toxicities may be missed since few patients are enrolled in early-phase trials. Finally, the variations in target delineation by different investigators have the potential to inadvertently impact the toxicity profile. The use of anatomic atlases may help mitigate this critical variable.

History of Phase I RT-Drug Trials

Over the past several decades, most early-phase clinical trials (n = 162 phase I only, n = 66 phase I-II) have utilized a rule-based design for dose escalation, usually a 3+3.[167] RT has only been tested for dose escalation approximately one-eighth of the time when combined with a drug. In these trials, RT was the only modality being tested for dose escalation two-thirds of the time. Only a single anatomic site has been usually studied (98%), with head and neck (20%), lung (18%), brain (11%), and pancreas (10%)

being the most common. Over 90% of published studies did report grade 3 to 4 AEs, with two-fifths (42%) comprising hematologic AEs and 50% nonhematologic (with the plurality being mucositis). The mean number of events described as DLT per number of grade 3 to 4 AE was reported to be four, and the description of the DLT period (mean of 69 days) was only described in nearly two-thirds (62%) of the studies. This published benchmark while helpful cannot account for the much larger number of trials that were never written up in full manuscript form. Career development courses, including those through ASCO (American Society of Clinical Oncology)/AACR (American Association for Cancer Research) Methods in Clinical Cancer Research Vail Workshop, the ECCO (European CanCer Organisation) Methods in Clinical Cancer Research Zeist (formerly Flims) Workshop, and other smaller courses, suggest that the future of an ever-growing cadre of radiation oncology trialists is brighter.

Phase II Trials

The decision to proceed with phase II study is generally dependent on the safety (and often early efficacy) results from the corresponding phase I trial. A major goal of a combined modality study, for instance, is *efficacy* or clinical activity, as defined as increasing the therapeutic window (or therapeutic ratio).[168,169] These trials can screen out suboptimal treatments and identify promising strategies worthy of further validation in a more definitive or confirmatory trial setting. Phase II trials can also provide a more extended safety profile than may have been possible in the phase I trial.

Design

When designing phase II trials involving RT, there are a number of challenges, some of which are unique to the modality and others that are compounded by combined modality therapeutic designs. These include the fact that (1) many phase II studies are of relatively unselected patient populations, (2) they may be introduced in the curative setting (ie, plus/minus RT boost for ductal carcinoma in situ) such that the interval for observation may be extended (ie, years or longer), and (3) the low prioritization from the drug development industry. Because of this latter

reality, there is a prolonged delay (median 6 years [interquartile range 5-8 years]) between the opening of the phase I trial without RT and the opening of phase I with RT.[57] In addition, the median lag time-P between the *published* phase I trial without RT and the *opening* phase I with RT was 3 years (interquartile range 1-6 years).

An important consideration is cost efficiency in the design of the trial, as the PI should seek to minimize the number of patients exposed to an ineffective treatment by enrolling as few patients as "necessary" to show benefit or futility.

One of the most important design decisions is to determine if a single-arm study will suffice or whether a multi-arm trial is preferable. The latter may be required if the historical data for comparison are lacking or considered generally weak, and historical control arms are fraught with anachronistic (among other) challenges. Single-arm studies may include a two-stage design with early stopping rules for futility or lack of response. The most common single-arm trial designs are the Simon 2-stage,[87] the Balanced Design,[170] Gehan 2-stage,[171] and the Fleming 2-stage.[172] These are considered frequentist approaches (as opposed to Bayesian designs). A multi-arm phase II trial may include a (1) phase II selection design (prioritization) or (2) phase II design with a reference control arm (control). The former involves parallel single-arm studies that do not directly compare the arms to each other. They compare each to the "null rate." The Simon "pick the winner" design is an example.[32] This approach is useful when there are more than one candidate for new drugs, new schedules, new doses, or even combinations of different drugs, schedules, and doses to be evaluated. It is not powered to directly compare the treatment efficacies and hence the number of patients needed to complete the study is smaller. On the other hand, a randomized phase II design with a reference control arm directly compares the new treatment with the control treatment. The randomization is effective in removing potential biases that are often unavoidable in single-arm trials where treatment effect of the new treatment (represented by efficacy endpoints, eg, local control, response rate, colostomy-free survival, nodal failure, etc) is indirectly compared with the historical controls. The comparison is indirect in that the point estimate from historical controls is often treated as the null hypothesis in the single-arm trials. Therefore, the uncertainty associated with the estimate is

neglected in the testing. As a consequence, single-arm trials often require a one-third or a smaller sample size compared to randomized two-arm trials with the same hypothesis to be tested. As a trade-off, the findings in the single-arm trial are often much unreliable compared with randomized trials.[173] A practical approach to addressing the issue of large sample sizes in clinical trials is to relax the stringency of the type I error rate. For instance, researchers may consider designing trials with a 15% or 20% type I error rate, rather than adhering to the conventional 5% threshold. However, it is crucial to carefully consider the potential implications of increased type I error rates on the reliability and interpretability of trial results. Much interest in the statistical community also centers on the use of external, synthetic, or other combination control arm approaches.[174]

Phase II studies may often include patients for whom RT is a standard and definitive therapy. In these instances, the savvy radiation oncology investigator has an opportunity to carefully define goals, strategic diagnostic, and/or therapeutic interventions, to achieve a well-defined and clinically meaningful endpoint for the patient's benefit. Adaptive designs are becoming more common in cancer medicine, including radiation oncology-based trials. For instance, the definition of response rate is important to consider. Some data suggest that a well-defined *a priori* change in metabolic response rate via functional imaging assessment with FDG-PET (positron emission tomography) may harbor useful imaging biomarkers of tumor response or resistance much earlier than classic pure anatomic imaging using conventional CT scanning.[175-177] Along similar lines, recent phase II data suggest that integration of functional imaging for hypoxia may allow for safe and effective treatment de-escalation for patients with HPV-related oropharyngeal carcinoma.[178] Adaptive trials will need to incorporate serial data inputs, including though not limited to imaging, -omic (genomic and proteomic), and anatomic changes during treatment to enhance response and get ahead of the tendency of tumors to develop radioresistant phenotypes (Figure 14.3).

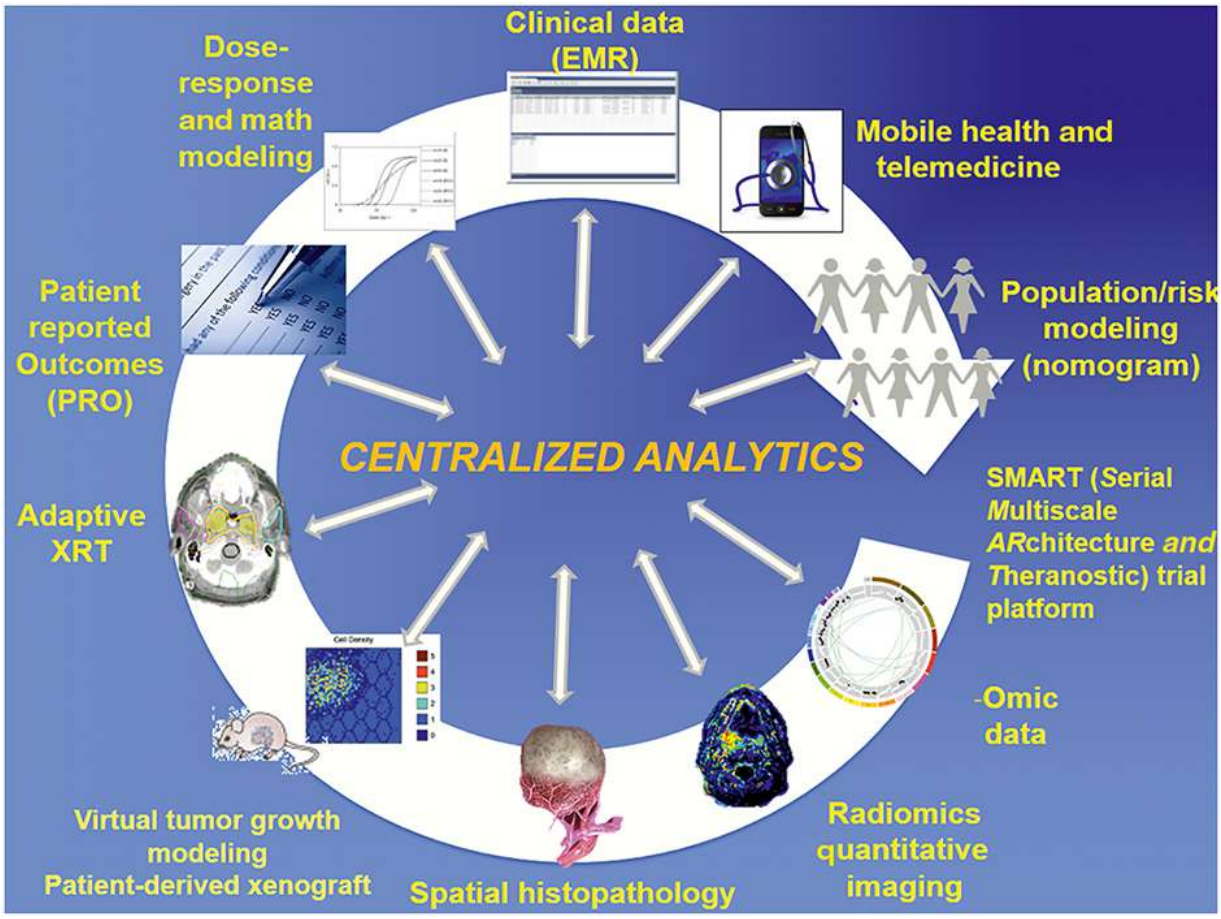

FIGURE 14.3 Centralized analytics allows for phenotyping using all patient and tumor-specific data.

To exploit the promise of precision medicine, alternative phase II designs have emerged in the form of umbrella and basket trials.[179] The umbrella trial is set up to test one type of cancer (ie, lung) which may harbor multiple mutations, some of which may be actionable with various therapeutic interventions. The basket trial can include patients with multiple anatomic types of cancer though each tumor must harbor a common genetic mutation for which the same candidate therapy is tested. Relevant for radiation oncologists, basket approaches may similarly be designed to allow disease-site-specific baskets for shared clinical scenarios, such as oligometastatic disease.[138]

Endpoints

Response rates alone may be challenging for selecting efficacious regimens, due to several factors, including delayed time to response with RT, residual unevaluable masses versus scarring or fibrosis, PD outside of the RT field, and underlying high local response rates to RT.

Response rate is commonly measured by the RECIST and sometimes the PRECIST (Positron Emission Tomography Response Criteria in Solid Tumors) criteria. A CR plus a PR are added together to determine the overall objective response rate. If patients whose best response is an SD or no change, that may also be important since many of the targeted agents (which may be cytostatic in activity) inactivate a driver tumor target though not objective shrinkage of the tumor may be noted by conventional imaging.

Efficacy endpoints commonly used include (1) CR rate, (2) pathologic CR rate based on examination of tissue, (3) undetectable blood biomarkers such as circulating tumor DNA and/or circulating tumor cells, (4) local or locoregional control rates, (5) time to progression, (6) survival, and/or (7) a decrease in toxicity. In the instance of the latter endpoint of decreased toxicity, RTOG-0529 is a good example of a clinical trial that was primarily designed to show that the way that RT was delivered (ie, Intensity-Modulated Radiation Therapy [IMRT]) may yield a preferable therapeutic window compared to historical experience for invasive anal cancer.[180,181] The endpoint selected will depend on the tumor and the current standard therapy.

Robust documentation of both acute and late toxicities is essential. Collection of late toxicity data is particularly important for subsequent phase III trial design. This should involve provider assessment via the usual tools such as the CTCAE, as well as validated patient-related outcome (PRO) tools. There is emerging data that the concordance of AE documentation between patients and providers in cancer cooperative group setting could even impact OS.[182]

To account for late-onset toxicities that may be induced by radiation treatment, it is important to specify a meaningful patient evaluation window that will be used in decision-making. However, adaptive designs with go/no-go decision-making generally require a short-term evaluation window so that treated patients' outcomes are available by the time the next trial decisions are made. Although there are some available adaptive design

methodologies to account for late-onset events, such as the time-to-event Bayesian optimal phase II (TOP) design,[183] their implementation in real clinical trials requires ever- increasing close collaboration among the investigational team, including clinical faculty and biostatisticians.

Summary

Phase II trials are designed to generate a signal of antitumor activity and to inform the phase III decision. The ideal phase II trial, in one framework, uses a PK/PD-optimal drug against a validated target and shows convincing antitumor activity. Results of phase II trials must be interpreted cautiously, in the context of the availability of other therapies. That said, phase II estimation of clinical activity as well as safety is crucial in the subsequent "go/no-go" decision for a phase III trial. A randomized phase II trial is still generally considered exploratory and does not obviate the need for a larger confirmatory phase III trial. Adaptive designs can be very efficient for selection but require more trial-level maintenance.

Phase III Trials

These trials usually involve two or more arms, including one that is considered a standard of care. The goal may be to show superiority of a new therapeutic approach, such as the addition of postoperative (adjuvant) chemoradiotherapy for resected gastric cancer,[184] or perhaps to demonstrate noninferiority, the latter which can lead to a more cost-effective treatment approach, such as hypofractionated radiotherapy for breast cancer.[185] The essential components to consider for phase III trials are study design, randomization approach, blinding strategy, and monitoring of endpoints. The CONSORT checklist (www.consort-statement.org) summarizes information that must be considered when analyzing phase III trial reports.[186]

Design

Randomization in phase III trials allows for comparison of treatment arms; notably, this does not mean that arms are intrinsically balanced in all variables. Often trialists will report baseline (pretreatment/prerandomization) characteristics in a "Table 1" for their trial

report and report inferential testing results (*P* values) for those characteristics. However, this practice is discouraged, as randomization does not guarantee balance, but rather decreases systematic differences in baseline variables.[187,188] also known as the *Table 1 Fallacy*. For prognostic variables, these should generally be included in a stratification/blocking schema as part of the study design.

Within phase III studies, a *parallel* design involves randomization to a standard (or control) intervention versus an experimental (new) intervention. The experimental intervention may include more than one arm. *Factorial* designs, such as those utilized in 2 × 2 design in the ACT II anal cancer trial, allow for more multiple intervention variables to be compared to a single gold standard or control.[189] Crossover designs allow for patients randomized to arm A to undergo crossover therapy to Arm B after the efficacy endpoint of arm A has been measured. This may occur when the efficacy endpoint is PFS.[190] Crossover is an important consideration, as it may impact or bias subsequent OS estimates (or estimates of postprogression survival); crossover is further crucial in considering patient centeredness of trials and enthusiasm for patient accrual.[37,191] Patients may be more willing to enroll in the study if control-arm-randomized patients are still eligible to receive the experimental therapy at the time of progression.

Randomization

Randomization generally provides each patient an equal chance of being assigned to an intervention arm or a control arm, unless it has been predetermined that an unequal randomization allocation (ie, 2:1) is warranted (for instance, to enhance accrual). Ideally, the patient and the PI should not influence or be aware of which arm the former will be randomized to prior to the decision being made to provide informed consent to participate in the study. This requires equipoise on the part of the investigator, an area of active controversy among the radiation oncology community when deciding how to study new and expensive technology, such as particle therapy. The following section on statistical issues will provide a more in-depth discussion of randomization and blinding considerations in clinical trials.

Superiority, Noninferiority, and Equivalence Designs

A superiority design is common and seeks to show that a new approach (ie, higher dose of radiotherapy) is superior to that standard of care.

A noninferiority design is often used to show that a less aggressive (or potentially toxic) approach (ie, lower dose of radiotherapy or less intense systemic therapy) is not worse to a clinically meaningful degree compared to the standard intervention. The difference or delta (Δ) in the *a priori*–defined endpoint should only be slightly worse (or inferior) to the standard. Confidence intervals estimate the difference in outcome between the control and experimental arms as an approach to confirm the hypothesis. Sample sizes of noninferiority trials are often bigger than superiority trials.[192] Several studies have been *a priori*–designed and reported on for localized prostate cancer,[193] resectable rectal cancer,[194] and brain metastases.[195] Some trials combine noninferiority and superiority testing into one study. This is because the noninferiority and superiority can both be evaluated at a 0.05 significance level without a need to adjust for multiple testing due to the closed testing principle.[192] Two things need to be paid attention to when conducting such combination testings: (1) the study needs to be powered for noninferiority and (2) the noninferiority needs to be tested before testing for the superiority. Noninferiority trials in general, though, should be justified in the use of this approach; this may include cost reduction or increased convenience for patients (ie, an oral agent compared with an injectable agent) and may also include improved toxicity.[196] We submit that improved toxicity generally should be assessed via established toxicity metrics, and therefore a "purely" noninferiority study may not be appropriate as compared with a combined superiority/noninferiority approach (in which oncologic efficacy is the "noninferiority" component of the trial, while toxicity is the "superiority" component). Much ink has similarly been spilled regarding the noninferiority "margin" used in such trials, which may be excessively wide, and therefore allow declaration of noninferiority when the observed difference in oncologic outcomes is not acceptable clinically.[197]

An equivalence design seeks to show that the control and the experimental arm(s) are equal with respect to the primary outcome. Equivalence can be defined as the treatment effect residing between

negative delta ($-\Delta$) and delta (Δ) (two-sided problem). This design *is not* the same as a noninferiority design. RTOG 87-04 was a phase III trial that sought to show that by excluding mitomycin C (an antitumor antibiotic with a well-known profile of significant hematologic and renal toxicity) from a backbone of fluorinated pyrimidine chemotherapy (5-fluorouracil) and external-beam radiotherapy for anal canal cancer, the therapeutic outcomes would remain equal while the therapeutic ratio would be increased by lessening the toxicity.[198] This study showed that the doublet, including mitomycin C, was in fact *superior*. It is problematic to routinely rely on null hypothesis testing of equality if the statistical significance of the *a priori* differences is not met.

Quality Assurance/Contouring

In the era of highly conformal radiation treatment, safe and effective treatment planning depends increasingly on precisely identifying tumor and normal tissues through contour delineation, with evidence from clinical trials emerging that correlates poor contouring with inferior outcomes. In head-and-neck cancer, both TROG 02.02 and RTOG 0129 found a 20% decrease in OS for patients with radiation protocol violations.[52,199] Similar trends have been identified in pancreatic cancer and Hodgkin lymphoma.[51,200] While multiple aspects of the radiation planning process can lead to protocol violations.[201,202] between 13% and 83% of protocol violations have been attributed to contouring.[51,52,200,203] In response, an increasing emphasis is being placed on trial QA programs that actively perform contour evaluation and train providers.

First, the development of a visual atlas for anorectal cancer was shown to reduce contour variation[204] and improve predicted toxicity[205] among providers that intended to enroll patients in a SWOG-sponsored study (SWOG S0713). This atlas was initially developed for RTOG 0529 in response to the observation from the first five cases submitted that coverage of the mesorectum and elective nodes.[180] Visual atlases have been duplicated in contouring studies performed outside of the clinical trial setting for disease sites that have a well-defined high-risk clinical target volume such as prostate fossa[206] and nasopharyngeal cancer.[206] However, RTOG 1106 reported that the development of a visual atlas for lung cancer,

which relies primarily on the identification of gross tumor, did not reduce variation in contours submitted through its trial QA credentialing process.[207]

Given the limitations of a visual atlas, disease sites such as lung cancer have moved toward prospective centralized contour review prior to patient treatment. However, the administrative burden and potential for treatment delays warrant consideration by the QA committee when determining the feasibility of their contouring QA program. Multiple trials show that radiation protocol deviations are more frequent among low-accruing treatment centers,[52,199-201,208] so perhaps a risk-stratified approach should be considered. It is important to keep in mind that the more stringent the trial QA, the less generalizable the results may be to routine practice. Instead, the development of robust resources and training processes that could be implemented and easy to use in routine practice would be ideal.[43,209]

STATISTICAL ISSUES IN TRADITIONAL CLINICAL TRIAL DESIGN

Patient Population and Subject Eligibility

Defining the eligible patient population is an essential step in the design of clinical trial. The inclusion and exclusion criteria of the subject should be carefully defined and specified for any clinical trial before study initiation. Several aspects need to be considered when defining the subject eligibility of enrollment to specific trials: (1) generalizability, (2) feasibility, (3) competing risks, (4) projected AEs, and (5) homogeneity. The patient inclusion and exclusion criteria of a trial should be the result of balancing all the above aspects.

Generalizability and Feasibility

To begin with, investigators should first think about the target patient population to which the new treatment will be adopted. Ideally, a phase III clinical trial should relax the exclusion criteria as much as possible to mirror the target patient population. Less restrictive eligibility criteria will make the findings in the trial more generalizable to the target population. In addition, relatively relaxed inclusion criteria are likely to lead to brisker accrual and make the study treatment more available to a broader patient population who may benefit from it.

Adverse Events, Competing Risks, and Homogeneity

Although inclusive eligibility criteria will boost the generalizability and feasibility, it can be risky and harmful to include subjects who should be excluded. For instance, if participants with HIV/AIDS are suspected to have an exceptionally high risk of experiencing treatment-related toxicity in a given cancer trial, they may be excluded; however, in the era of highly active antiretroviral therapy, justification for exclusion based on HIV status alone (rather than CD4 count or presence of AIDS-defining conditions) has become more challenging.[210,211] Indeed, we recommend trialists to consider each eligibility criterion carefully and to the greatest extent possible utilize liberal eligibility criteria to optimize generalizability as well as trial access equity.[212-214] However, in cases where select subgroups of patients are exposed to a particularly high risk of toxicity, including them may put the whole trial at the risk of closure for excessive toxicity. Even if the trial continues as planned, these subjects are likely to add complexity to the efficacy and toxicity analysis of the trial.

Another thing to keep in mind is the notion of competing risks. For example, if a trial is to evaluate the response rate after six cycles of a given therapy, then including subjects with a high risk of dying before completing the six cycles is undesired. In this example, the competing risk is the death of cancer or other disease before treatment completion or before the primary endpoint becomes available/is measured.

The last thing to be aware of is the homogeneity of subjects as defined in the eligibility criteria. Exclusive eligibility criteria often help select more homogeneous subjects, which could add signal to the "signal-to-noise" ratio in detecting a true treatment effect if the certain type of subjects as defined in the eligibility criteria has a good response to the treatment. However, as discussed previously, findings of a trial with exclusive eligibility criteria lack generalizability, and exclusive eligibility criteria may also jeopardize the speed of accrual. Furthermore, exclusionary eligibility criteria impact trial access equity and could contribute toward clinical trial disparities, as noted above. Therefore, it is often understandable to have more exclusive eligibility criteria in earlier-phase trials, but these criteria should be relaxed to be more inclusive in the phase III setting. A relatively heterogeneous patient population in a phase III trial may also allow the detection of

efficacy differences in subgroups of subjects, which is a bonus of having inclusive eligibility criteria in a clinical trial with a relatively large sample size; naturally, ensuring that subgroup-based analyses are done appropriately is critical as well and preplanned to the greatest extent possible.[105]

Randomization

Randomization is an effective way to assign patients to treatment groups without systematic imbalances in important factors and patient characteristics. A well-designed and implemented randomized trial is often viewed as the gold standard for evaluating an experimental treatment when compared with either placebo or standard treatment.

In this section, we introduce a few randomization schemes that are most well known or widely used for implementing random treatment assignments.

Simple Randomization

Considering a randomized controlled study where subjects are to be 1:1 assigned to either an experimental treatment or a control group, the simple randomization paradigm is no different from flipping a fair coin and assigning subjects to the experimental group if "Heads" and to the control group if "Tails." While in theory, the assignment can be reasonably balanced in treatment assignment and in patient characteristics between groups on average, very few trials choose to use simple randomization in practice. This is because reasonable balance can only be achieved using simple randomization if the sample size is large. However, large clinical trials often are multisite and have interim analyses. A multisite trial typically requires stratified randomization by site, and interim analyses require balance in assignment to be achieved with a relatively smaller sample size.

Permuted Block Randomization

One easy way to address the unbalanced group size at interim analysis or at other time points during the trial is to use permuted block randomization (PBR), which imposes a balance restriction by blocks. The size of the block

can be prefixed or be selected at random. If we again consider a 1:1 RCT, implementing PBR with a block size of 4 will ensure balance in group size for every four subjects. That means for every four subjects, two must be assigned to the experimental group (E) and two must be assigned to the control group (C). We can easily permute the potential sequences for the assignment of two treatments for a block size of 4: EECC, CCEE, CECE, ECEC, CEEC, and ECCE. The same can be done essentially for any block size. Common choices of block sizes are 2, 4, 6, and 8. We may randomly pick one of the generated sequences for any block if using PBR with a fixed block size. For using PBR with random block size, one additional random pick needs to be made before starting any block: randomly pick the block size for the coming block from all available choices, say, 2, 4, or 6. Once the size of the coming block is determined, we can use the same procedure as PBR to implement the randomization.

We discourage using a block size of 2 for PBR with fixed block size because that adds an excess restriction on randomization. We also discourage using a block size of 8 or more for any PBR as the imbalance can still be substantial with larger block sizes. A well-known and criticized drawback of PBR with fixed block size is that it may hinder blinding. With a relatively small block size, there is a good chance for physicians or researchers to determine or suspect which patients are assigned to which treatment when they should be blinded to such assignment. Therefore, we suggest using PBR with random block size over PBR with fixed block size whenever appropriate and necessary.

Stratified Randomization and Covariate-Adaptive Randomization

Achieving balance in the number of subjects assigned to each arm throughout the trial is often not sufficient for most randomized clinical trials in oncology. It is also important to ensure balancing on known covariates that may affect outcomes. If the covariates to be balanced are all categorical variables and the number of covariates is less than three, stratified randomization is often appropriate for achieving balance in covariates. The idea of stratified randomization is straightforward: we first create different strata based on the covariates to be stratified, then conduct population

reference bureau (PRB) or simple randomization within each stratum. The number of strata is jointly determined by the number of stratifying covariates and the levels of each covariate. For k stratifying covariates with levels of each covariate denoted by l_1, l_2, . . . , l_k, the number of strata is $l_1 \times l_2 \times \ldots \times l_k$. For example, if a randomized trial has two stratifying covariates: site (three participating sites) and type of cancer (breast and prostate cancer), then the number of strata is 6. The number of strata increases quickly with more stratifying covariates. Once the number of subjects in each stratum becomes too small, there is an increased chance of imbalanced assignment within each stratum, which influences the balance of the whole trial. Similarly, with too few patients in each stratum, interpretation of such small cohorts for a stratum becomes challenging in assessing possible differential treatment effects by subgroups. Therefore, when the number of stratifying factors exceeds 3, or if one or more continuous covariates are to be balanced, we suggest using covariate-adaptive randomization, also called minimization. The covariate-adaptive randomization assigns treatment to a new subject to minimize the covariate imbalances within treatment groups. There are multiple ways of doing so, such as Zelen rule, the Pocock- Simon procedure, and Wei marginal urn design.[215]

Response-Adaptive Randomization

Most adaptive clinical trials that use Bayesian designs adopt response-adaptive randomization, which has a changing probability of assigning a new patient to treatments based on the observed data from previously treated patients in the trial. The response-adaptive randomization allows more subjects to be assigned to the more promising treatment arm and thus is viewed as a design with ethical benefits. The response-adaptive randomization is preferred for many trials, but not all, because it typically requires added complexity in designing, implementing, managing, and analyzing the trial, and may have slightly reduced power in detecting treatment differences for a fixed sample size.

Statistical Power and Sample Size

All clinical trials require the computation and justification of sample size because the number of subjects evaluated in the trial is a key factor that determines the quality of scientific findings in the study. A clinical trial with too small a sample size fails to yield meaningful scientific results, while a trial with too large a sample size will waste resources in finding a result, and may expose more subjects than necessary to inferior treatment. Notably, a trial with incomplete accrual may have insufficient power to meaningfully address the study question, a situation that happens not infrequently even in the phase III setting and should be strenuously avoided through optimization of expected and obtained accrual as well as associated funding for the study.[8]

We need to know the design of a clinical trial and the variable type of the primary endpoint before doing sample size computation. In general, if hypothesis testing is going to be conducted, we should specify the desired power, the null and the alternative hypothesis, the statistical test procedure to be conducted, and the type I error rate. The type I error is the probability of rejecting the null hypothesis when the null hypothesis is true. In other words, it is the chance of claiming a new drug is effective while it is not. As type I error can be a very serious error for all clinical trials, it is typically controlled at a low rate (a) of 0.05 or less. Another error we take into consideration when computing sample size is the type II error, the probability of not rejecting the null hypothesis when the alternative hypothesis is true. It can be viewed as the chance of incorrectly determining a therapy is not effective when it is. Generally, it is acceptable for a trial to have a 20% or less type II error rate (b). The power is simply 1 − b. Therefore, clinical trials are typically designed to have 80% or greater power.

For certain early-phase pilot studies, the major goal may not be to determine whether a treatment is effective or not, but to gain preliminary information on the level of effectiveness for planning future studies. For such a trial, it makes sense to plan the sample size based on the precision of a confidence interval. The precision of an estimate is directly based on the width of a confidence limit. The smaller the width, the narrower is the confidence interval, and the better precision is the estimate. For example, if we want to gain preliminary information on the 6-month objective response rate for a new radiation therapy in a single-arm phase II pilot trial, and we

believe a 95% confidence limit ± 0.15 is narrow enough no matter what the estimated response rate locates, we can then propose a sample size of 47 evaluable subjects to ensure the computed width of the confidence interval is within 0.3.

Figure 14.4 shows the relationship between width of confidence limit, sample size, and the estimated proportion computed using the Clopper-Pearson exact method (produced by Power Analysis and Sample size Software, 2017, NCSS, LLC. Kaysville, Utah). We can tell the width of the confidence limit monotonically gets smaller as the sample size increases, and the width of confidence is also influenced by the point estimate of the response rate. The width is always the widest at a point estimate of 0.5 and gets narrower as the point estimate moves away from 0.5 in either direction.

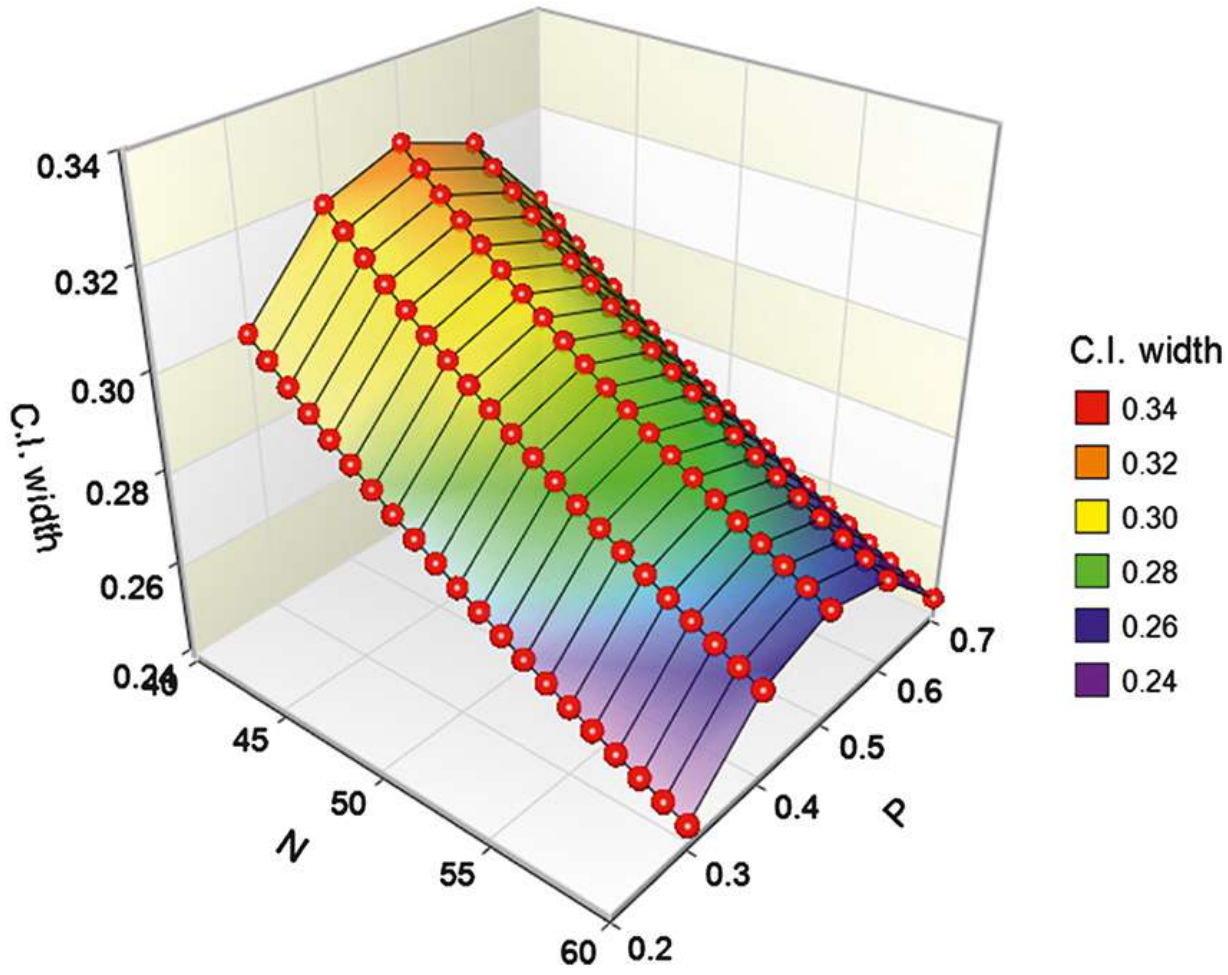

FIGURE 14.4 Relationship between width of confidence limit, sample size, and the estimated proportion.

We should keep in mind that the proposed sample size of enrollment in a clinical trial typically is larger than the computed sample size, owing to some fraction of patients that drop out of the trial or else are unevaluable for analysis. The proposed sample size should be inflated accordingly to ensure that the final evaluable sample size has adequate power.

Although most trials require a predetermined fixed sample size at the design stage, some allow flexible total sample size depending on the findings during the trial. For example, the well-known 3+3 design, continual reassessment design, and Simon's two-stage design all allow flexible total sample size. Any clinical trial with interim analyses and associated stopping rules allow flexible total sample size. However, the procedures of determining the sample size based on findings in the trial and the potential range of the trial need to be specified clearly in the protocol at the design stage.

Interim Analysis and Stopping Rules

Most phase III clinical trials and some phase II trials are designed to have interim analyses that allow the trial to be stopped early based on the findings in the interim analysis. A major purpose of a stopping rule is to protect patients from unsafe and/or ineffective drug. Many trials with interim analysis only allow early stopping due to evidence of futility or excessive toxicity. For example, Simon's two-stage design only stops the trial for futility (rather than efficacy). In this design, n_1 subjects are enrolled to Stage 1. If only r_1 or fewer subjects had successes, the trial would be stopped early. Otherwise, it will continue to enroll other n_2 subjects. The final analysis is based on all $n_1 + n_2$ subjects. In general, the decision on whether to stop early for futility is predetermined based on the conditional power, the conditional probability of having statistically significant result if the trial continues to the end, given the accumulated data in the interim analysis.[216] If such a probability is very low, lower than a prespecified threshold, then the trial may be terminated early due to futility.

Many other trials with interim analyses also incorporate efficacy in some or all interim assessments. For such trials, it is critical to make sure the overall type I error rate is not inflated by the interim looks, as discussed

previously in the context of "alpha spending."[88] For example, the well-known Pocock group sequential design[217] and the O'Brien-Fleming group sequential design proposed stopping boundaries for interim analyses with appropriate alpha spending functions.[91] The Pocock design makes interim analyses equally spaced and requires the same level of evidence (ie, using the same *z*, the boundary of rejection for the test statistic) for early and late interim analyses. These requirements may be overly restrictive. Therefore, O'Brien and Fleming proposed a group sequential design that makes it less likely a trial will stop in early interim analyses by having the boundaries of early stopping decrease with the sequential number of analyses being conducted.

Many other sequential or group sequential designs have been proposed and implemented. The key requirements for such trials are as follows:

- The endpoint for interim analysis is relatively quick to evaluate. It is not desirable to use an endpoint that requires a long time follow-up (eg, 10-year OS), because the trial will be halted for each interim analysis.
- The number of interim analyses, when to take the looks, and under which condition the trial will be stopped early should all be clearly specified in the protocol before the initiation of the trial.
- An appropriate spending function is used to control for the overall type I error rate.

In general, unplanned interim analyses are not authorized for clinical trials. An exception is when the unplanned interim analysis is proposed by the DSMB in the interest of protecting patients. In such situations, stopping boundaries can be constructed and modified for the additional or unplanned interim analysis.[218]

Many sequential and group sequential clinical trials are designed using Bayesian methods. Unlike the frequentist methods that completely rely on the data in the current trial to make inferences and decisions, Bayesian methods incorporate outside information (eg, published similar studies, pilot data, expert's opinion) into the procedure. A Bayesian method typically starts with specifying a prior distribution for the parameters of interest and updates the distributions using data from the trial. The updated distribution is called the posterior distribution, and the updates can be

applied as many times as necessary, in theory. The stopping rule of a Bayesian group sequential design is based on the posterior probability of efficacy or futility, which is computed by combining the prior and the current data of the trial. We encourage the reader to explore Bayesian statistical inference, including in literature within radiation oncology.[219]

SURVIVAL ANALYSIS AND CATEGORICAL DATA ANALYSIS

Many oncology clinical trials include OS or time to PFS as primary or secondary endpoints. Such endpoints are called time-to-event endpoints, and statistical analysis for time-to-event endpoints is called survival analysis. Patients are followed sufficiently long so that a subset of subjects will experience the event of interest during the trial. The event of interest is death for OS and is progression or death for time to PFS.

Without loss of generalizability, we use OS as the event of interest from now on. The method is the same for all other time-to-event endpoints, and as noted earlier, there are specific considerations and caveats for the use of surrogate endpoints, including surrogate time-to-event endpoints such as PFS.[36,37]

The survival endpoint is a combination of two measures: (1) a binary variable indicating whether the subject died by the end of the study or at the last follow-up of the subject and (2) a continuous variable measuring time from a common starting point (eg, the initiation of treatment or at the time of randomization) to death if the subject has died. For those subjects who are still alive by their last follow-up time, the component b of the survival time is not known and is thus treated as missing. Notice that the information is only partially missing for these subjects because we do know they were still alive by the time of their last follow-up. A special term is used in survival analysis for such partial "missingness": *censored*.

For most survival data, the first step is to use the Kaplan-Meier estimate to describe the distribution of survival time.[220] The Kaplan-Meier method utilizes the information of all subjects, including those who had observed death and those who were censored, to describe the cumulative survival over time, which is the product of the survival ratio of the number of subjects still alive to those who are at risk.

We can illustrate the computation and the plot of the Kaplan-Meier curve using a simple example. Suppose that we have 20 patients randomized to two arms. The observed survival time for subjects in each arm is as follows (the unit is months, and + indicates a censored observation):

A: 8+, 11+, 16+, 18+, 23, 24, 26, 28, 30, 31

B: 9, 13, 13, 14, 14, 16, 19+, 22+, 23+, 29+

Figure 14.5 shows the plot of the Kaplan-Meier curve. Using Arm A as an example, we can show step by step how the Kaplan-Meier curve was determined. Before plotting, the data should be sorted from low to high, regardless of whether the subject is censored or not. The Kaplan-Meier plot is a step function with steps formulated at one or more observed deaths. Starting at baseline, all 10 patients are alive, so the initial ratio of subjects still alive to those who are at risk is 1 (= 10/10). This is also the cumulative survival at baseline. At 8 months, one subject had been censored, so the ratio of subjects still alive to those at risk remains the same 1 (= 9/9). As the baseline cumulative survival is 1, the cumulative survival at 8 months is still 1 (= 1 × 1). Afterward, three more subjects were censored, which did not change the ratio while the number of subjects at risk dropped to 6. The fifth subject died at 23 months. This makes the ratio drop to 0.83 (= 5/6). The cumulative survival at 23 months is still 0.83 because the cumulative survival at 18 months (the previous time point) is 1, thus 0.83 × 1 = 0.83. The ratio was further dropped to 0.8 (= 4/5) in the 24^{th} month, making the cumulative survival 0.664 (= 0.8 × 0.83). The seventh subject died at month 26, with the computed ratio being 0.75 (= 3/4) and the cumulative survival being 0.498 (= 0.75 × 0.664). The ratio for the last subject at 31 months was 0 (= 0/1), making the cumulative survival become 0 as well. For a Kaplan-Meier plot, the cumulative survival is always 0 if the last subject is an observed death, as shown in the plot for Arm A. Otherwise, if the last subject is censored, the Kaplan-Meier plot is flat with a positive cumulative survival, as seen in the plot for Arm B.

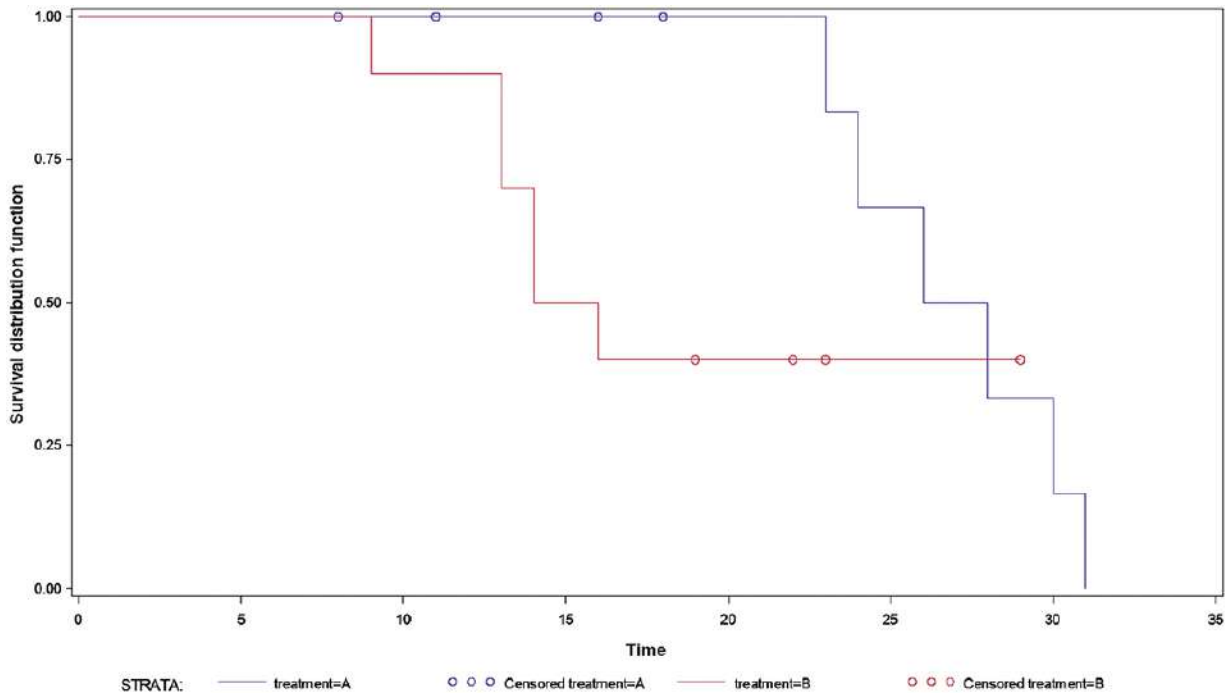

FIGURE 14.5 Plot of the Kaplan-Meier curve for example given in text.

The Kaplan-Meier plot can be used to compute the median survival time, a common statistic of interest showing the estimated time that half of the patients will have died. Again, using the Arm A plot as an example, the median survival is month 26, when the cumulative survival first fell under 0.5. The median survival time is often reported with a confidence interval because this is an estimate. We omit the computation of the confidence interval here due to limited space. The median survival time and its associated confidence interval typically can be computed by almost all software for survival analysis. However, sometimes the median survival is not estimable. This is because the Kaplan-Meier curve never fell below 0.5 for the study or for the arm under evaluation. It should be noted that as a single-timepoint estimate (the estimated point in time when 50% of patients had an event), the median survival time may be unstable, with a wide confidence interval; conceptually, a single-timepoint estimate such as the median, or for instance, 2-year survival time, are "local" measures, and do not include full information from the entire Kaplan-Meier survival curves.[221]

As the observed survival data rely a lot on the length of follow-up, it is important for any clinical trials with survival analysis to report the follow-

up time.

The Kaplan-Meier plot is often accompanied by a log-rank test, a nonparametric test for comparing the survival distribution in two treatment groups. A "significant" log-rank test suggests the survival distribution in the Kaplan-Meier plot differs for the two treatment arms.

The log-rank test only compares the survival distribution of the two arms without considering and controlling the effect of other influential factors, potential confounders, and effect modifiers. To control for those covariates, the Cox proportional hazards regression model is typically used to estimate the HR of the two treatments.[222] In survival analysis, the hazard rate is the instantaneous risk of death at a given time and can be thought of loosely as the probability of death at time t, given that the patient is alive just before time t^2. Please see above for a discussion of the HR and its correct (and incorrect) lay interpretations. The Cox model is appropriately termed the Cox proportional hazards regression model because it assumes the HR for two specified arms is constant over time. In the era of immunotherapy, this assumption of proportional hazards may be increasingly violated; this may be related to subsets of patients (such as those with high expression of specific immune checkpoint markers) that differentially benefit from immunotherapy. In this example, all-comer patients may benefit earlier from cytotoxic chemotherapy, making the chemotherapy arm look "better" earlier in the time course of the survival curve, but then the curves may "cross" such that the patients who are immunotherapy treated, now enriched for those excellent responders such as those with high immunotherapy-related markers, outperform chemotherapy-treated patients.[223] Proportional hazard violations occur frequently in late-phase cancer clinical trials, and many methods to address these violations have been described.[224] Use of the restricted mean survival time, for instance, allows investigators to compare "areas under the curve" for survival curves, leading to robust measures of treatment effect in the absence of proportional hazards.[225]

Another type of endpoint often seen in oncology clinical trials is the categorical endpoint, such as tumor response or objective response rate. The first thing to describe for categorical endpoints is the response rate and the associated confidence interval in each arm if this is a randomized trial. Pearson Chi-square test is the most often used test to evaluate the difference in response rate for two treatments without controlling for other factors.

When the sample size is small, *P* values from Fisher's exact test are often reported instead. Logistic regression model is the most common choice for comparing treatment effects using statistical modeling. It provides an estimation of the odds ratio of treatment after controlling for important covariates other than the treatment.

In addition to traditional statistical modeling, machine learning methods may be increasingly utilized to analyze survival endpoint and categorical endpoints, in addition to other areas of possible integration of machine learning methodology in cancer clinical trials.[226,227]

PRACTICAL ISSUES IN THE DESIGN, EXECUTION, AND REPORTING OF CLINICAL TRIALS

The Institutional Review Board

Several different groups share responsibility for the monitoring and oversight of ethical and safety issues in clinical trials. According to US federal regulations, the role of the institutional review board is primarily to ensure that "risks to subjects are minimized" and "risks to subjects are reasonable in relation to anticipated benefits."[143] This involves a review of the study protocol, informed consent document, background information, and proposed research plan.

Data and Safety Monitoring Committees

Once trials are initiated, ongoing monitoring of accumulating data regarding safety, effectiveness, and trial conduct is required. In the late 1960s, federal agencies (such as the NIH and the Department of Veterans Affairs in the United States) began to mandate an *external* review by a DSMC, since investigators may not be fully objective in their interim data analysis. Some data suggest that industry-sponsored trials have been slower to incorporate this practice.[127] However, not all trials warrant the cost of a DSMC, including trials of short duration or those that have endpoints such as relief of symptoms (rather than survival or severe toxicity). For this reason, the IRB review serves to inquire about the safety monitoring plan and can request the establishment of a DSMC, if warranted due to perceived potential risk to patients.

Conflict of Interest

Industry sponsorship of clinical trials in oncology has increased over the past several decades, as discussed previously. Compared to the pharmaceutical industry, radiation oncology is limited to a relatively small number of equipment vendors. Nonetheless, one study found that among clinical trials led by radiation oncologists and reporting conflicts of interest, over half of COI was related to industry sponsorship.[228] A literature review of COI in radiation therapy trials for breast cancer from 2004 to 2014 found that 13% of studies reported funding from for-profit organizations, while an additional 49% of trials were supported by not-for-profit organizations.[229] They found that funded trials and those with a positive conclusion were more likely to be published in journals with a higher impact factor, but the presence of COI did not influence study conclusions. In a randomized survey of internal medicine physicians, the perceived impact of trial results from industry-sponsored studies was lower than that from NIH-sponsored studies.[230] Nonetheless, any financial support should be reported, given the potential for COI to arise.

Registry on ClinicalTrials.gov

As noted previously, ClinicalTrials.gov serves to inform researchers, physicians, and patients of ongoing and completed clinical trials both in the United States and worldwide. The website was created as part of the Food and Drug Administration Modernization Act of 1997, which mandated that both federally and privately funded trials conducted under investigational new drug applications be registered in a publicly accessible platform. Requirements for registration were expanded in 2007, and as noted previously, requirements for reporting via ClinicalTrials.gov continue to have challenges as regards compliance.[21] The trial sponsor or PI is responsible for registering trials at ClinicalTrials.gov at study initiation, as well as providing timely updates and submitting summary results in accordance with this federal legislation.

CONsolidated Standards of Reporting Trials

By the early 1990s, medical journal editors and clinical trialists identified a need for a scale to assess the quality of RCTs. Groups of these experts meeting separately in Canada and the United States created the SORT and Asilomar reports, respectively, which merged in 1996 into a single, coherent evidence-based recommendation known as the CONSORT Statement. Most notably, this guideline statement includes both a checklist and flow diagram to enable readers to understand a trial's design, conduct, and analysis, and to encourage adherence and transparency by authors.[231]

NOVEL APPROACHES TO CLINICAL TRIAL DESIGN

Seamless Phase I-II Trial

As have been discussed thus far, typically, phase I trials evaluate toxicity, and phase II trials evaluate efficacy. However, seamless phase I/II trials—or trials that achieve the goals of both phase I and II in one umbrella protocol —have been developed to address both questions.[45] In these two-stage designs, information from the initial phase I study is incorporated into the phase II study. Different variations of this have been developed. Figure 14.6 shows the concept behind a seamless phase I/II trial using two drugs, A and B, given either concurrently or sequentially in one of the 10 dose combinations indicated by the yellow dots.[232] This adaptive randomization considers the toxicity and efficacy of these combinations.

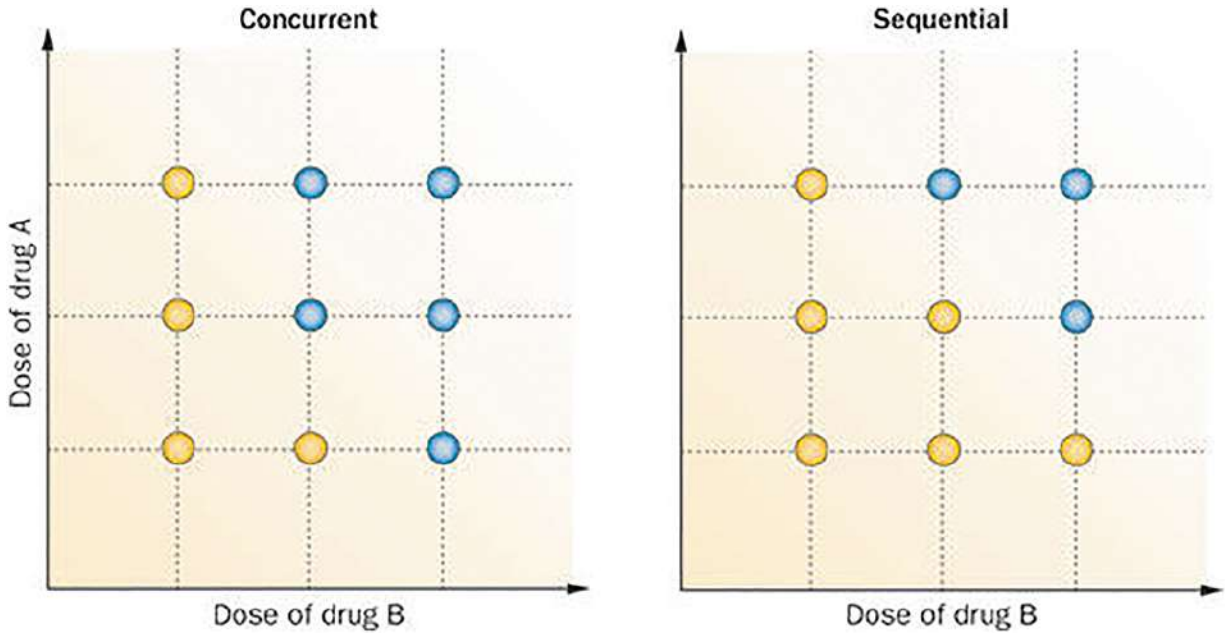

FIGURE 14.6 Different schedules of two drugs given concurrently or sequentially. (Reprinted by permission from *Nature*: Berry DA. Adaptive clinical trials in oncology. *Nat Rev Clin Oncol*. 2011;9[4]:199-207. Copyright © 2011 Springer Nature..)

Another Bayesian adaptive phase I/II clinical trial has been designed for evaluating efficacy and toxicity with delayed outcomes,[233] which, as previously discussed, is crucial in radiotherapy trials. This approach evaluates both efficacy and toxicity as binary outcomes, both as time-to-event models. The authors' simulations showed that this method significantly reduces the study duration.

Pan et al propose a phase I/II seamless dose escalation/expansion with adaptive randomization scheme (SEARS).[234] There are three critical components to this model: first, it applies the modified toxicity probability interval (mTPI) method as a way of monitoring toxicity. Then, in the phase II portion, it adaptively randomizes, based on efficacy, patients to any doses showing promising efficacy and safety. Posterior probabilities are calculated using both the phase I and II information[234] (Figure 14.7). Further integrated novel phase I/II approaches with Bayesian methodology have been piloted within radiation oncology as noted previously with the use of the LO-ET design for assessment of a radioprotector with ablative-dose RT for locally advanced pancreatic cancer.[122,123]

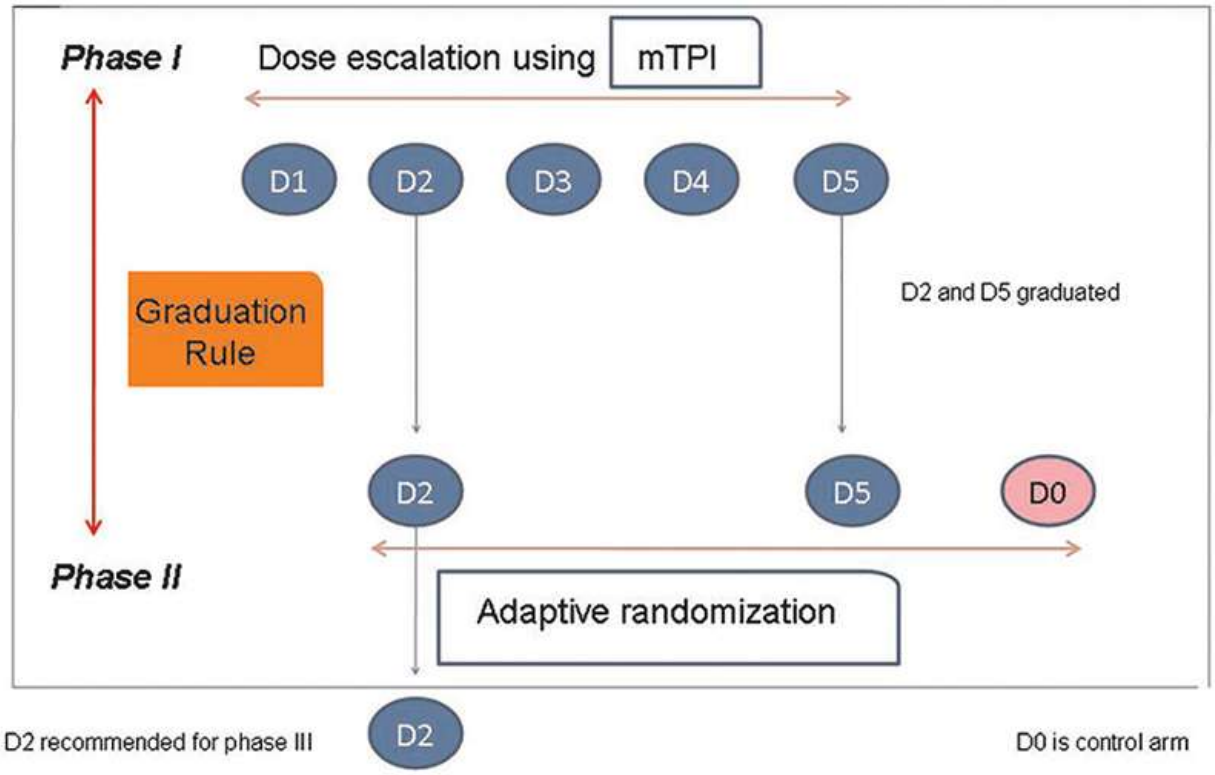

FIGURE 14.7 Phase I/II seamless dose escalation/expansion with adaptive randomization scheme (SEARS). mTPI, modified toxicity probability interval. (From Pan H, Xie F, Liu P, Xia J, Ji Y. A phase I/II seamless dose escalation/expansion with adaptive randomization scheme (SEARS). *Clin Trials*. 2014;11[1]:49-59. Copyright © 2014 SAGE Publications. Reprinted by permission of SAGE Publications.)

REDEFINING THE APPROACH TO CLINICAL TRIALS

The randomized phase III clinical trial is considered the most robust method of comparing the efficacy of a new treatment with the standard of care. Grading systems for evaluating clinical evidence universally place RCTs above observational trials. However, multiple features of modern medicine challenge the feasibility or rigidity of this traditional approach. First, as medicine progresses through incremental improvements in treatment as well as earlier detection, the potential effect size of the next intervention decreases while the time to event increases. The result of increasing trial size and duration of follow-up increases the cost. The age of the patient population diagnosed with cancer continues to increase, as mortality from competing comorbidities such as cardiac disease decreases. Because this population of older patients with comorbidities is often excluded from clinical trials, the applicability of trial results to this population is

difficult.[146,214] Meanwhile, technologic advances in imaging and treatment as well as the incorporation of molecular profiling can cause the question being addressed to become obsolete by the time trial results have matured. Specifically in radiation therapy, rapidly evolving technology has often led to increasing complexity of treatment, such as with improvements in treatment conformality and target volume assessment/image guidance through IMRT, stereotactic body radiation therapy (SBRT), biologically guided radiotherapy, magnetic resonance imaging–guided radiotherapy, and beyond. Increasing complexity often warrants stricter QA mechanisms to ensure that the intervention is applied appropriately to adequately test its utility, thereby reducing the ability to generalize the results to routine clinical practice.

Pragmatic Clinical Trials

The concept of pragmatic clinical trials arose out of the concern that clinical trials were being optimized to determine efficacy, while potentially overestimating benefit and underestimating harm when applied to the general population.[235] Pragmatic trials thus focus on the applicability of a new intervention to general practice, while explanatory trials aim to address questions of biologic mechanisms. In 2009, a tool called the PRagmatic-Explanatory Continuum Indicator Summary (PRECIS) was published to provide clinical trialists with a guide to understanding how different components of design would impact the applicability, or pragmatism, of the trial.[236] An updated version (PRECIS-2) was published in 2013 in which nine domains were scored on a Likert-type scale (1 = most explanatory, 5 = most pragmatic).[237] The primary goal of PRECIS-2 is to match the trial design to the intended application of trial results.

Meanwhile, CONSORT published an "extension for pragmatic trials" that specifies that trial publications include all the information on the context of their conducted trial so that future readers can judge the applicability of the results to their own clinical context, where they may be considering implementing the intervention tested in that randomized trial.[238] So, while PRECIS-2 encourages appropriate trial design, CONSORT ensures trial results and information are reported adequately for health

system decision-makers to determine the applicability of trial results to their clinical setting.

A study design often employed in pragmatic trials is cluster randomization. This allows the intervention to be implemented at the group level rather than the individual level, which affords more opportunity for the training of interdisciplinary teams of professionals and assurance that implementation is appropriate for the clinical context. Furthermore, as a result, all patients within a center are treated uniformly, which improves efficiency and reduces the risk of errors. The comparator arm, meanwhile, is generally usual or standard care. By facilitating training, cluster designs also help to address differences in provider experience, which have been shown in radiation oncology to influence outcomes and must be considered to avoid confounding. While pragmatic trials often include providers with a representative mix of experience levels to increase generalizability, trial quality must always be closely monitored. A pragmatic trial conducted poorly is of limited to no use for decision support.

Pragmatic trials rely more heavily on electronic health records (EHR) and patient registries to collect patient information, as this reduces the cost of trial coordinators. Of note, many registries were established prior to the implementation of EHRs, so they often collect data in parallel, with work ongoing to synchronize the system. Some health systems have developed robust national quality registries that are disease based or intervention based, which has facilitated large clinical trials. For example, the Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial was a multicenter, prospective, open-label, randomized, controlled clinical trial that used the infrastructure of a population-based registry in 29 Swedish centers and 1 Icelandic center, to facilitate enrollment and long-term data collection on 11,709 patients treated for heart attacks from 2008 to 2009.[239]

Comparative Effectiveness Research

The 1999 Institute of Medicine's report "To Err is Human" called attention to serious concerns about patient safety in the United States. The Agency for Healthcare Research and Quality (AHRQ) was established to address these concerns by focusing on the safety and quality improvement in health

care delivery. The AHRQ defines comparative effectiveness research as that which is "designed to inform health-care decisions by providing evidence on the effectiveness, benefits, and harms of different treatment options."[135] Then in 2010, an independent nonprofit, nongovernmental organization called the Patient-Centered Outcomes Research Institute (PCORI) was authorized by Congress to further address the need for information to guide better-informed health decisions by patients, providers, and policy makers. PCORI is the single largest public funder of clinical effectiveness research (CER) in the United States, supporting primarily large pragmatic studies and large-scale observational studies.[136]

Over the past few decades, government agencies, professional societies, and private corporations have established patient registries that collect standardized data from patients diagnosed and treated in a variety of settings, to provide data regarding patterns of care and patient outcomes.

The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute was established in 1974 to provide cancer statistics in order to reduce the burden of cancer.[132] SEER is a population-based registry representing 17 regions and 28% of the US population. It is therefore a useful epidemiologic tool for calculating incidence (new cases per population), prevalence (existing cases per population), and mortality (deaths per population) for different cancers, and it documents tumor-specific information. SEER, a clinical database, is often linked to the Medicare claims data, to provide more detailed indirect information regarding the treatment of cancer (including the number of fractions of radiation) as well as diagnosis codes and interventions that could relate to toxicity (such as cystoscopy, colonoscopy, coronary angioplasty). The use of Medicare linkage restricts the data to over 65 years, however. This parallels the separate entity known as the Medicare Chronic Conditions Warehouse (CCW), which is an administrative database that can be used independently to investigate broader patterns of care than SEER-linked data, though it lacks detailed cancer information that is available in SEER, such as stage.

The National Cancer Database (NCDB) is jointly sponsored by the American College of Surgeons and the American Cancer Society. It includes patients from 1,500 Commission on Cancer (COC)-accredited programs, representing 70% of cancer diagnoses.[131] The initial goal of

NCDB was to monitor patterns of care at the local hospital level and provide feedback regarding quality measures. NCDB requires COC accreditation and therefore does not represent all patients in a population. It is therefore technically not a population-based database and thus not appropriate for incidence/prevalence but can be used to assess outcomes after diagnosis. NCDB includes details of margin status, radiation dose, and technique, which are not captured in the SEER database. While NCDB enables important patterns of care studies, it lacks robust outcomes data, including cancer-specific survival, and recently has been used extensively to assess the efficacy of radiation treatment with OS as the primary endpoint, which has significant limitations. Because of the observational nature of this registry, confounders exist in treatment selection (including patient performance status) which can bias the perceived efficacy of the treatment. In a retrospective database, one can never fully control for this selection bias and therefore should interpret OS results with extreme caution. Indeed, data suggest that there is minimal agreement beyond what is expected by chance between registry-driven observational studies and matched RCTs, reinforcing the persistent and continued centrality of late-phase randomized trials in defining the standard of care.[240]

A major limitation of SEER, NCDB, and CCW, however, is the lack of patient-reported outcomes. The CaPSURE represents a prostate-specific registry that was initiated in 1995 to enable prospective cohort studies in men with prostate cancer that focused on incorporating patient-reported outcomes.[241] Approximately 40 urology practices, primarily community-based, enroll patients in a database that tracks over 1,000 clinical and patient- reported variables. Though this is not a population-based sample, it provides much richer clinical detail than SEER. Given the long natural history of prostate cancer, CaPSURE is regarded as a cost-effective alternative to randomized trials that reflects “real-world” practice and has resulted in numerous publications.

Newer registries are being developed to address the limitations of current databases, and therefore include a robust interface for data collection that facilitates prospective clinical trials (such as the Swedish TASTE trial), and incorporation of radiation-specific information (including that captured in Digital Imaging and Communications in Medicine [DICOM] files). Cancer Learning Intelligence Network for Quality (CancerLinQ) is a national

initiative sponsored by the ASCO that involves a cloud-based platform that communicates nightly with the EHR at each individual practice to collect, de-identify, and update patient information, which serves as both a database to evaluate quality metrics and a real-time decision support tool that recommends guideline-concordant therapies.[242] By 2016, CancerLinQ had registered over 1 million patients treated at 70 clinics by 1,500 oncologists, and shortly thereafter, the American Society for Radiation Oncology (ASTRO) announced a partnership to incorporate critical radiation-specific data into the database.[130] Developing a DICOM-based registry for radiation oncology requires first standardizing naming conventions to enable harmonization of the digital information. This process is in progress in the United States, with American Association of Physicists in Medicine (AAPM) Task Group 263 defining the naming convention and the Radiation Oncology Institute developing the National Radiation Oncology Registry and piloting it in prostate cancer at 30 centers. Meanwhile, Sweden has successfully implemented the naming convention and is collecting RT data in DICOM files through their Medical Information Quality Archive at most of their radiation centers.[243]

Meta-Analysis

A formal quantitative means of combining evidence from multiple clinical trials is meta-analysis, a widely used analytic tool in many areas of social and medical science. Meta-analysis refers to a process whereby data from independent studies are combined to form a quantitative summary estimate of a given effect.

Meta-analyses are considered by some to be a source of level I evidence along with large randomized clinical trials. A meta-analysis combines the results of several studies, all of which ask a similar research question but may be individually too small to have enough statistical power to definitively answer the question. Performing a systematic analysis of data from all identified randomized trials can define a modest yet real advantage associated with a therapeutic approach, such as OS associated with adjuvant radiation in breast cancer[244] and concurrent chemotherapy with radiation in head-and-neck cancer.[245] To address the likelihood of publication bias (ie, a greater representation of trials with positive results appearing in the

literature), a meta-analysis should include unpublished studies as well, though assessing quality is critical, given the lack of peer review.

Meta-analyses can be performed with or without access to the raw data, though the methods employed are critical to ensuring quality results. Cochrane is an independent, nonprofit, nongovernmental organization consisting of a group of more than 37,000 volunteers in more than 130 countries that aims to improve access to high-quality reviews that guide decision-making.[128] Researchers interested in undertaking meta-analyses are encouraged to contact the Cochrane Methods groups, which provide access to methodologists who can assist with responsible conduct of meta-analyses (http://methods.cochrane.org/methods-groups).

Clinical trials in radiation therapy often restrict access to raw patient data, including detailed treatment planning information in DICOM files, much of which is not reported or even investigated in the primary publication. For example, multiple trials have reported the presence of major protocol deviations predicting inferior OS.[208] Even determining the reason for the deviation can be difficult to find, since the process has been retrospectively defined until only recently. Access to the original images, treatment plans, and setup images could elucidate important information regarding details in QA that could better explain the differences in patient outcomes. An ideal system would promote the public availability of trial data to facilitate further research with a currently available resource, such as FigShare (https://figshare.com/).

NEXT-GENERATION RADIATION ONCOLOGY TRIALS

Next-generation trials will need to include iterative, adaptive designs that are not *a priori* committed to studying uniform fraction intervals (ie, q daily, Monday to Friday *or* qod, Mon, Wed, Fri), but are based on the constant incorporation of serial imaging and liquid biopsies which can serve as surrogates of early response and/or resistance for most or a small component of the tumor. Growth of -omic information, and even patient-derived xenograft generation, all portend increasingly complex and innovative clinical trials in radiation oncology. With a growing role for the integration of immunotherapy with radiotherapy, an emerging landscape of combined modality therapy trials with immunotherapies, cellular therapies,

and beyond will challenge existing paradigms and classical designs in clinical trials for radiotherapy (Figure 14.8).

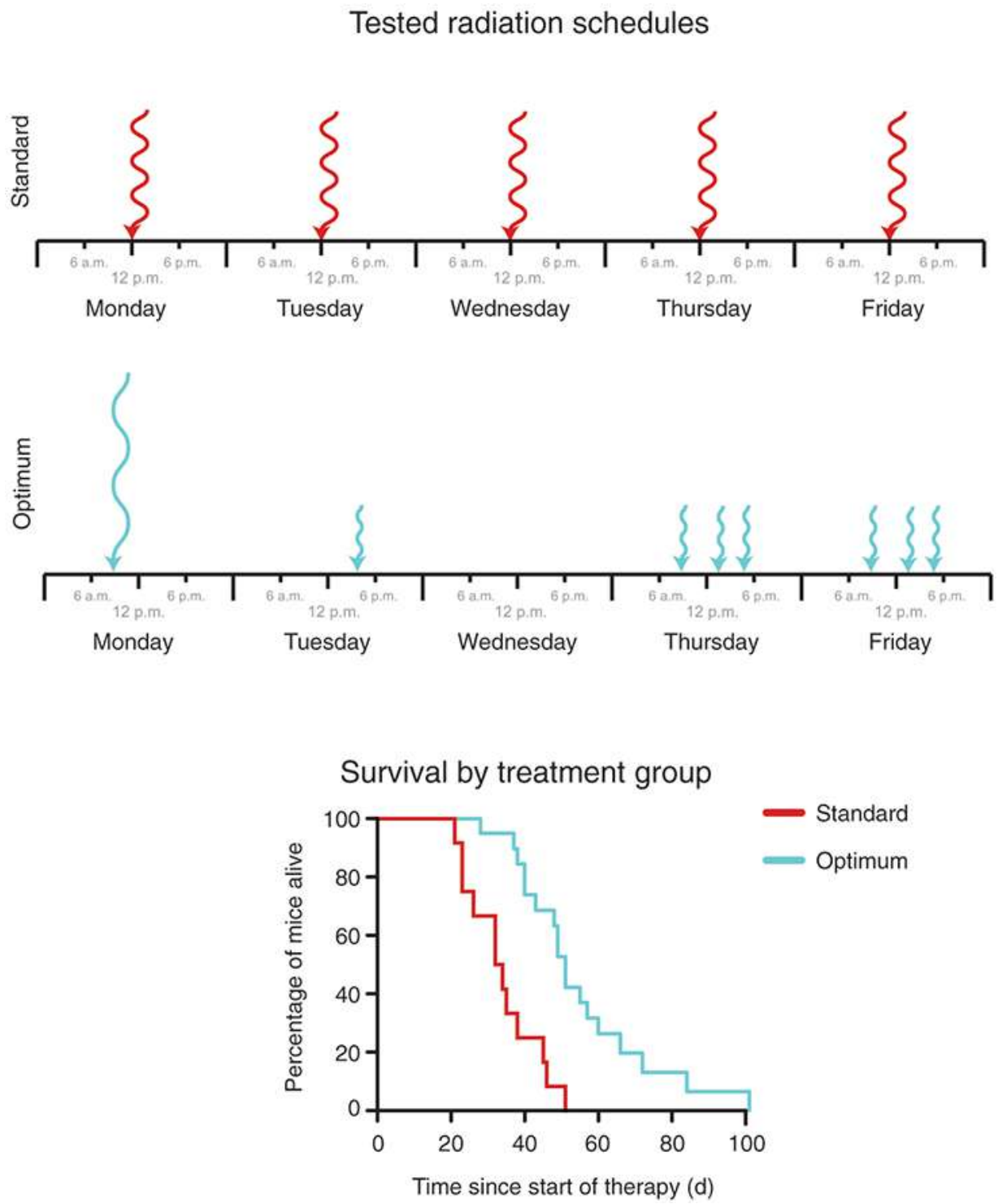

FIGURE 14.8 Testing of two radiation schedules in a mouse model. (Adapted from Leder K, Pitter K, LaPlant Q, et al. Mathematical modeling of PDGF-driven glioblastoma reveals optimized radiation dosing schedules. *Cell*. 2014;156[3]:603-616. Copyright © 2014 Elsevier. With permission.)

Emerging fields of radiomics[246] and mathematical modeling,[247] an outgrowth of evolutionary biology, will provide personalized radiotherapy prescriptions that may change multiple times during a course of treatment.[248-252]

Although the patient and providers may not know the length and schedule of the prescription at the time of the initial consultation, positive results will demand that trials incorporate disruptive algorithms to test promising and disruptive treatment paradigms. Figure 14.9 provides just one of many potential snapshots of the next-generation clinical trial approaches for radiation-based cancer research.

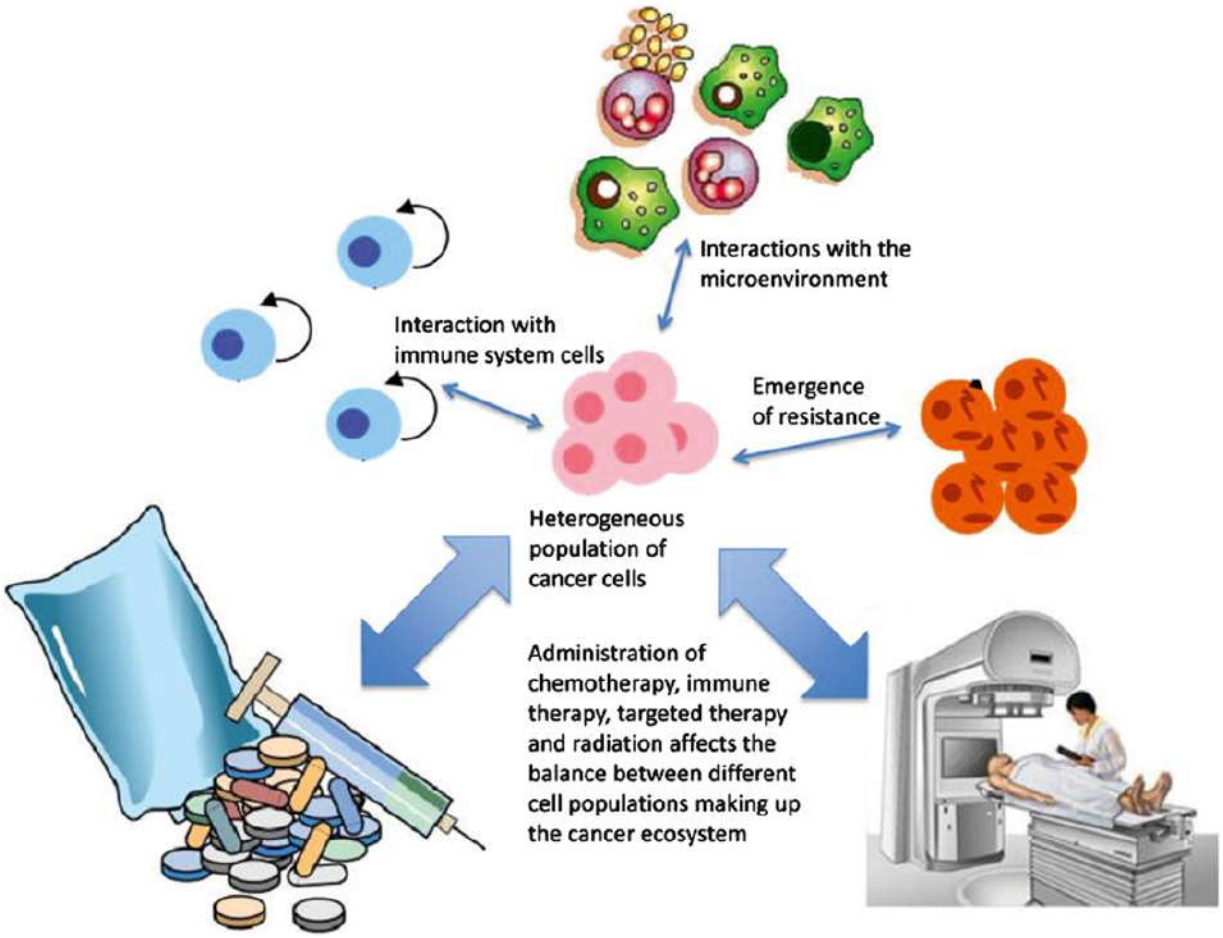

FIGURE 14.9 The varied considerations of the interplay of a heterogeneous population of cancer cells. (Adapted from Michor F, Beal K. Improving cancer treatment via mathematical modeling: surmounting the challenges is worth the effort. *Cell*. 2015;163[5]:1059-1063. Copyright © 2015 Elsevier. With permission.).

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CHAPTER 15

Stem Cell Transplantation and Radiation Therapy Techniques

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Historically, total body irradiation (TBI) was used without stem cell support for palliation of radiation-sensitive diseases such as chronic lymphocytic leukemia (CLL) and follicular lymphoma. Currently, TBI is primarily performed in the context of hematopoietic stem cell transplantation (SCT) for its cytotoxic and immunosuppressive effects. The patient's hematopoietic system is reconstituted after high-dose chemotherapy, with or without TBI, from either the patient's own stem cells (autologous) or stem cells from a donor (allogeneic). In the case of donor stem cells from an identical twin, the term "syngeneic transplantation" is appropriate. Total marrow irradiation (TMI) and total marrow and lymphoid irradiation (TMLI) utilize more targeted delivery of radiation therapy (RT) with increased sparing of surrounding normal tissues. This chapter will also briefly address hemibody irradiation (HBI), which is occasionally utilized for palliation of diffuse metastatic disease, and total lymphoid irradiation (TLI), which is utilized in a variety of clinical settings. Stem cell support is not required in these settings.

RATIONALE FOR STEM CELL TRANSPLANTATION

Hematopoietic SCT, while utilized in a variety of settings, is primarily pursued for patients with high-risk or relapsed/refractory hematologic malignancies to decrease the risk of disease recurrence. Multipotent stem cells have the capacity to differentiate into all blood cell lineages and can be obtained from several sources including bone marrow, peripheral blood, and umbilical cord blood. Stem cells can be harvested directly from the marrow or through apheresis of the peripheral blood following administration of granulocyte colony-stimulating factor. The conditioning regimen for hematopoietic SCT has several important functions and depends on the type of transplant—autologous (auto-SCT) or allogeneic (allo-SCT). For the former, the sole purpose of the conditioning regimen is cytotoxicity. For allo-SCT, the conditioning regimen also facilitates immunosuppression (helping to prevent host rejection of donor stem cells) and creates space in the bone marrow for the graft. Conditioning

regimens can consist of chemotherapy alone or a combination of chemotherapy and TBI.

Autologous Transplantation

Autologous transplantation relies upon higher doses of chemotherapy to overcome the resistance of malignant cells with subsequent reinfusion of stem cells to reconstitute the hematopoietic system. The most common indications for auto-SCT are multiple myeloma, relapsed diffuse large B-cell lymphoma, and relapsed Hodgkin lymphoma. Peripheral blood stem cells are the graft product of choice for auto-SCT and are associated with improvements in rates of engraftment, quality of life, and reduced cost when compared with cells derived from bone marrow.[1] Patients undergoing auto-SCT must be reasonably fit to tolerate high-dose chemotherapy and/or TBI. With modern supportive care and increasing experience with this procedure, the risk of mortality from auto-SCT is quite low (~1%).

The timing of auto-SCT depends on the underlying disease. For most patients with relapsed aggressive lymphomas, auto-SCT is preceded by a salvage chemotherapy regimen. If the patient has chemotherapy-sensitive disease, ideally demonstrated by achievement of a negative positron emission tomography-computed tomography (CT) scan,[2] then the patient proceeds with high-dose chemotherapy and auto-SCT. Choice of high-dose chemotherapy regimen is based on the underlying disease. For example, in the setting of relapsed Hodgkin lymphoma, BEAM (carmustine, etoposide, cytarabine, melphalan) is often utilized. High-dose melphalan is the most common conditioning regimen for multiple myeloma.

When consolidation RT is indicated, it is typically administered after recovery from the auto-SCT procedure. However, there is increasing experience with giving it before, especially in patients not achieving a complete response with salvage chemotherapy. Some concern exists for administering RT to the chest prior to auto-SCT as a higher risk of pneumonitis has been observed.[3]

Allogeneic Transplantation

As opposed to auto-SCT, which relies completely on cytotoxicity from high-dose chemotherapy and/or TBI to eradicate persistent tumor clones, allo-SCT relies on an immunologic graft-versus-tumor effect to eradicate malignant cells. The most common indication for allo-SCT is high-risk and relapsed acute leukemia, particularly acute myelogenous leukemia (AML) and acute lymphocytic leukemia (ALL). Allo-SCT may be preceded by full-dose (myeloablative) conditioning designed to have maximal antitumor effect and also to condition the patient for the infusion of the donor cells as an immunologic therapy. Increasingly, allo-SCT is preceded by a non-myeloablative or reduced-intensity conditioning program. In this latter situation, the

major antitumor effect is postulated to derive from the infused donor stem cells, and the intensity of the conditioning regimen is reduced to allow the procedure in patient populations previously ineligible due to age or other medical conditions. Non-myeloablative allogeneic transplants are associated with lower treatment-related morbidity compared with myeloablative allogeneic transplants. Most transplant centers utilize peripheral blood progenitor cells, as opposed to bone marrow, for allo-SCT.

Thus, allo-SCT is largely an immunologic therapy. Allogeneic hematopoietic cells are ideally matched with the recipient for all the major histocompatibility antigens to avoid rejection and minimize graft-versus-host disease (GVHD). For patients with matched donors, differences in minor human leukocyte antigens (HLAs) facilitate the graft-versus-tumor effect that enhances transplantation efficacy. Transplantation with half-matched family members (haploidentical transplantation) or mismatched unrelated cord blood stem cell grafts now provides comparable outcomes to a matched donor transplant. Early studies demonstrated improved leukemia control with allogeneic bone marrow cells as compared to syngeneic (identical twin) donor cells.[4] Further evidence for graft-versus-tumor effect derives from the efficacy of donor lymphocyte infusions after relapse of leukemia following allo-SCT.[5]

Despite HLA matching, allo-SCT is limited by GVHD. GVHD results from the release of inflammatory cytokines as a result of activation of mature donor T cells that recognize recipient HLA allo-antigens, presented as peptide molecules by antigen-presenting cells. Acute GVHD includes clinical damage to the skin, gastrointestinal tract, and liver, but other organs can also be involved. GVHD may evolve, or develop de novo, later after transplantation with distinct clinical features resembling sporadic autoimmune diseases (termed chronic GVHD). Common presentations include sicca syndrome, sclerotic or lichenoid skin disease, and immune hepatitis. Fasciitis/myositis and bronchiolitis obliterans syndrome are less common presentations, which may cause significant morbidity.

Posttransplant high-dose cyclophosphamide is the current standard to prevent acute and chronic GVHD.[6] Increased immunosuppression may ameliorate symptoms from GVHD but may also abrogate the graft-versus-tumor effect and place patients at higher risk for posttransplant infections. Acute GVHD can also be effectively prevented by T-cell depletion of the donor cells prior to stem cell infusion, but this may also lead to an increased risk for infections as well as the concern that the desirable graft-versus-tumor effects will be diminished or lost. Nevertheless, there has been clinical success with T-cell-depleted allo-SCT in reducing GVHD. Such techniques require more intensive immunosuppression to prevent graft rejection and therefore often employ TBI in the conditioning regimens.

Myeloablative Allogeneic Stem Cell Transplantation

TBI has been a central part of allo-SCT for leukemias since the late 1950s. Historically, a single dose of 10 Gy utilizing a low dose rate (~10 cGy/min) was used. The premise that TBI had to be given as a single fraction was challenged in the late 1970s. It was concluded that with the same total dose, an improved therapeutic ratio would be expected from a reduction in the dose rate of single-fraction TBI or by TBI fractionation. A variety of fractionated TBI schedules are currently employed in clinical practice with no one regimen clearly superior to another. Currently, most myeloablative TBI programs use a 2 or 3 times a day fractionation scheme over 3 to 5 days to deliver a total dose of 12 to 15 Gy.

Non-myeloablative or Reduced-Intensity Allogeneic Stem Cell Transplantation

In the past decade, growing recognition of the immunotherapeutic potential of allografts has led to a reconsideration of the need for high-dose myeloablative conditioning regimens traditionally administered prior to transplantation. Numerous clinical trials have established that a spectrum of non-myeloablative conditioning regimens of varying intensity may allow engraftment of donor cells with reduction in transplant-related toxicity, permitting transplantation of patients traditionally excluded from allo-SCT because of age or medical comorbidities.[7] The primary purpose of a non- myeloablative preparatory regimen is to suppress the patient's immune system sufficiently to allow the engraftment of donor cells with minimal host toxicity. The graft-versus-tumor effect is relied upon to eradicate tumor cells.

Common to these regimens is sufficient immunosuppression to overcome host resistance to engraftment using either the purine analog fludarabine, TBI, or both, in combination with other agents. Other factors, such as patient age, HLA disparity with the donor, tumor burden, and prior therapy, may also affect the degree of engraftment. For example, a series from the Seattle transplant group demonstrated that a single 2-Gy fraction of TBI, in combination with postgrafting cyclosporine and mycophenolate mofetil, is sufficient to achieve a high rate of donor engraftment in patients with a prior history of auto-SCT, but additional immunosuppression in the form of fludarabine is necessary to ensure engraftment in less heavily pretreated patients or patients receiving unrelated donor grafts.[8]

Reduced-intensity transplants now account for a significant number of all allo-SCTs. While reduced-intensity transplants allow older and less robust patients to undergo allogeneic SCT, in many circumstances, myeloablative conditioning is superior. In a randomized trial, patients aged 18 to 65 with a comorbidity index of 4 or less with acute myeloid leukemia and myelodysplastic syndromes were randomized to myeloablative versus reduced-intensity conditioning.[9] The trial was discontinued early after 272 patients were enrolled due to excess relapses in the reduced-intensity arm. Relapse-free survival (RFS) at 18 months was 47% versus 68%, favoring the

myeloablative arm ($P < .01$). As expected, treatment-related mortality favored the reduced-intensity conditioning arm (4.4% vs 15.8%, $P = .02$).

PURPOSES OF CONDITIONING

The purpose of high-dose chemotherapy, with or without TBI, prior to auto-SCT is simply to give a higher intensity of treatment to overcome intrinsic tumor resistance, thereby decreasing the risk of a relapse. The purpose of conditioning in the setting of allo-SCT is more complex and serves three key functions: to provide sufficient immunosuppression in the recipient to prevent rejection of the graft, to create space in the bone marrow for donor stem cells, and to provide further cytoreduction to achieve a minimal residual disease state prior to transplant. Myeloablative regimens address all three, whereas reduced-intensity regimens provide immunosuppression and create space for the donor stem cells but with variable, and lesser degrees of, further cytoreduction.

The choice of conditioning regimen prior to transplantation depends upon a variety of factors that include the type of transplant (allogeneic vs autologous), conditioning intensity (myeloablative vs non-myeloablative), disease type (eg, AML vs ALL), expected patient tolerance (eg, age, medical comorbidities), and disease status.

Total Body Irradiation–Based Conditioning Regimens

There is wide variability between centers in regard to the techniques utilized for TBI including total dose, fractionation scheme, dose rate, lung shielding, and technique/patient positioning. Some aspects have been formally evaluated with randomized studies, whereas many others have not.

In regard to total dose, two randomized trials have compared 12 versus 15.75 Gy in patients with AML and chronic myelogenous leukemia (CML). In the AML study, patients randomized to the higher-dose arm were noted to have improved RFS ($P = .06$) but at the cost of increased non-relapse mortality (NRM) ($P = .04$) and moderate-to-severe GVHD ($P = .02$).[10] There was no difference in overall survival (OS). In the CML series, a disease that is rarely transplanted anymore given the efficacy of tyrosine kinase inhibitors, the investigators also noted improvement in RFS ($P = .008$), with a nonsignificant trend toward increased NRM ($P = .13$) and moderate-to-severe GVHD ($P = .15$) in patients receiving the 15.75 Gy regimen.[11] As OS was not improved in either study, more moderate total doses seem preferable.

Several studies have evaluated single fraction compared with multifraction regimens. Deeg et al[12] evaluated 75 patients with acute non-lymphoblastic leukemia in first remission. The first 22 patients enrolled on the study received 9.2 Gy in a single fraction at 4 to 6 cGy/min utilizing opposed cobalt sources. The remaining patients were randomized to either 10 Gy in a single fraction or 12 Gy in six fractions.

Survival was improved in the patients receiving either 9.2 Gy in a single fraction or 12 Gy in six fractions compared to 10 Gy in a single fraction (P = .04). There was an increase in early toxicity, particularly hepatic veno-occlusive disease/sinusoidal obstructive syndrome (VOD/SOS), in patients receiving 10 Gy in a single fraction. Pneumonitis appeared more common in single fraction (both 10 and 9.2 Gy) compared to the fractionated regimen. Girinsky et al[13] randomized 160 patients to either 10-Gy single-fraction (12.5 cGy/min instantaneous dose rate, 4.5 cGy/min average dose rate) or hyperfractionated TBI to 14.85 Gy in 11 fractions (25 cGy/min instantaneous dose rate). They noted no difference in OS or cause-specific survival. There was an increase in incidence of VOD/SOS in patients who received single-fraction TBI (P = .044). In a study from the Hôspital Tenon in Paris, 157 patients were randomized to single-fraction TBI with variable dose rate (6 vs 15 cGy/min) or fractionated TBI with variable dose rate (3 vs 6 cGy/min).[14] No significant differences were noted between the single-fraction and fractionated TBI schedules, or by dose rate. The preponderance of data favors a fractionated regimen using a low-dose-rate approach.

The choice of chemotherapy agents used in conjunction with TBI depends on the underlying disease. For AML, and in many other settings, high-dose cyclophosphamide is utilized given its effectiveness in both immunosuppression and cytotoxicity. A typical dose is 120 mg/kg over 2 days. In other settings, agents such as etoposide, melphalan, and/or fludarabine are combined with TBI. Reduced-intensity or non-myeloablative transplant regimens using low-dose TBI are often combined with fludarabine.

Chemotherapy and TBI are given sequentially rather than concurrently to avoid any potential increase in normal tissue toxicity. Whether chemotherapy should be given before or after TBI is unclear. One study of 1,769 patients undergoing myeloablative allo-SCT for acute leukemia did not show any differences in outcomes with cyclophosphamide given before or after TBI.[15] Typically, TBI over 3 to 5 days is best delivered during the regular work week, when the full technical support staff is available. TBI may be better tolerated if given first when the patient is less fatigued and not experiencing the side effects of chemotherapy. The risk of nosocomial infections may be marginally lower when the patient travels to the RT department before becoming neutropenic later in the conditioning course. Alternatively, TBI at the end of the preparative regimen allows the SCT to proceed immediately thereafter. Unlike chemotherapy, there is no washout period needed for TBI, theoretically decreasing the time the patient spends neutropenic prior to engraftment.

Chemotherapy-Alone Conditioning Regimens

Although the evolution of TBI has led to significant reduction in toxicities, initial concern about the risk of fatal radiation pneumonitis led to the development of non-

TBI regimens. In addition, conditioning with chemotherapy alone can be used in practice settings where TBI is unavailable. Combinations have been developed based on biologic activity of a particular drug, drug tolerability, and non-overlapping drug toxicities. The most commonly used ablative regimens to condition patients with AML are the combination of busulfan and cyclophosphamide (BuCy) or busulfan and fludarabine. Single-agent high-dose melphalan is also used frequently prior to auto-SCT for treatment of multiple myeloma. For patients with aplastic anemia, the combination of cyclophosphamide and antithymocyte globulin is often used for immunosuppression while avoiding excessive myelotoxicity. There is interfacility variation in dosing and drug delivery schedules, making it somewhat difficult to make direct comparisons between these regimens.

Most of the initial trials using BuCy used high-dose oral busulfan, which has highly variable pharmacokinetics, poor gastrointestinal tolerability, high rates of VOD/SOS, and increased frequency of seizures. An intravenous formulation of busulfan has been developed, which is much better tolerated, has more predictable pharmacokinetics, and has been associated with less toxicity.

Total Body Irradiation–Based Versus Chemotherapy-Alone Conditioning Regimens

Randomized studies comparing chemotherapy-alone conditioning regimens to TBI-based regimens are few, often enrolled multiple leukemia subtypes, included a variety of patients (eg, first complete remission, relapse, etc), and used antiquated TBI and chemotherapy platforms. These limitations make it difficult to reach firm conclusions.

Considering AML (Table 15.1), a French randomized trial compared BuCy to TBI-Cy before allo-SCT for adult AML in first remission.[16] TBI-Cy was superior for disease-free survival (DFS) ($P < .01$), leukemia relapse ($P < .04$), and NRM ($P < .06$). Long-term follow-up also demonstrated worse OS and leukemia-free survival (LFS) in the patients receiving BuCy compared to TBI-Cy, felt to be the result of higher transplant-related mortality and relapse rates.[17]

TABLE 15.1 TRIALS EVALUATING CONDITIONING REGIMENS FOR AML

Study	*N*	Conditioning Regimen	Leukemia-Free Survival	Comments
Randomized Trials				
Blaise et al[17]	101	TBI-Cy BuCy	55% 35% ($P = .02$)	PO busulfan
SWOG 8612[58]	122	TBI-etoposide BuCy	NS ($P = .69$)[a]	PO busulfan

Study	*N*	Conditioning Regimen	Leukemia-Free Survival	Comments
Randomized Trials				
Ringdén et al[30]	69	TBI-Cy BuCy	56% 59% (*P* = .7)	PO busulfan Increased incidence of VOD/SOS, hemorrhagic cystitis, chronic GVHD, and obstructive bronchiolitis with BuCy. Cataracts more frequent with TBI-Cy[a]
Meta-analysis				
Socié et al[31]	172	TBI-Cy BuCy	57% 47% (*P* = .051)	PO busulfan
Shi-Xia et al[33]	1,289	TBI-Cy BuCy	OR 1.49 (1.01, 2.20) in favor of TBI	PO busulfan Higher rates of cataracts, interstitial pneumonitis, and developmental problems for patients receiving TBI-Cy. Higher rates of VOD/SOS and hemorrhagic cystitis in patients receiving BuCy
Registry Studies				
Nagler et al[18]	1,659	TBI-Cy BuCy	64% 61% (*P* = .27)	Intravenous busulfan Lower incidence of acute GVHD (grades 2-4) and chronic GVHD in IV BuCy group
Copelan et al[21]	1,230	TBI-Cy BuCy	RR 0.70 (0.55, 0.88) (*P* = .003) in favor of IV busulfan	Examined both IV and PO busulfan formulations No statistically significant difference between oral busulfan and TBI-based regimens
Litzow et al[153]	581	TBI-Cy BuCy	58% 54% (*P* = .438)	PO busulfan Higher rates of VOD/SOS with busulfan-based regimen
Ringdén et al[154]	824	TBI-Cy BuCy	66% 64% (NS)	PO busulfan Higher rates of VOD/SOS and hemorrhagic cystitis with busulfan-based regimen
Institutional Series				
Stephens et al[20]	206	Cy-TBI BuCy	43% 30% (*P* = .12)	PO busulfan LFS improved with Cy-TBI on multivariate analysis Higher rates of pulmonary toxicity in TBI-based regimen

ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; Bu, busulfan; CML, chronic myelogenous leukemia; Cy, cyclophosphamide; GVHD, graft-versus-host disease; IV, intravenous; LFS, leukemia-free survival; NS, not significant; OR, odds ratio; PO, by mouth; RR, respiratory rate; SWOG, Southwest Oncology Group; TBI, total body irradiation; VOD/SOS, veno-occlusive disease/sinusoidal obstructive syndrome.

[a]Included data from patients with ALL/CML.

Several retrospective series, most using registry data, have evaluated TBI-based versus chemotherapy-alone conditioning regimens in AML. Most retrospective analyses demonstrate equivalent outcomes when comparing oral busulfan-containing regimens compared to TBI-Cy.[18,19] A single-institution retrospective series from Duke showed superior LFS and OS in patients with AML treated with TBI-Cy compared to BuCy, at the expense of increased pulmonary toxicity.[20] Intravenous busulfan has the added advantage of better tolerability and pharmacokinetics. The data are inconsistent whether intravenous BuCy is more effective than TBI-Cy regimens.[21,22]

In regard to ALL (Table 15.2), Bunin et al[23] published a randomized series of pediatric and adolescent young adult (AYA) patients with ALL treated with either etoposide- cyclophosphamide-TBI or etoposide-BuCy. The authors found an improvement in event-free survival (EFS; $P = .03$) for patients in the TBI arm. The For Omitting Radiation Under Majority age (FORUM) trial was a multicenter, noninferiority study comparing TBI-etoposide to fludarabine/thiotepa and either treosulfan or busulfan in pediatric and AYA patients with high-risk ALL in complete remission. Two-year OS was significantly higher following the TBI-based regimen ($P < .01$), with decreased incidence of relapse ($P < .01$) and NRM ($P = .027$). Based on the interim analysis, the futility stopping rule was applied and random assignment was discontinued.[24] Finally, a multi-institutional Chinese trial randomized patients with standard-risk ALL undergoing allo-SCT in first complete remission to TBI-Cy or BuCy and found no difference in OS, incidence of relapse, DFS, or NRM at 2 years with no difference in regimen-related toxicity, GVHD, or late effects.[25]

TABLE 15.2 TRIALS EVALUATING CONDITIONING REGIMENS FOR ALL

Study	*N*	Conditioning Regimen	Event-Free Survival[a]	Comments
Randomized Trials				
Bunin et al[23]	43	TBI-Etop-Cy Bu-Etop-Cy	58% 29% (3 y; $P = .03$)	PO busulfan
FORUM[24]	417	TBI-Etop Chemo only[b]	86% 58% (2 y; $P < .0001$)	
Zhang et al[25]	545	TBI-Cy BuCy	18% 20% (2 y; $P = .616$)[c]	
Meta-analysis				
Shi-Xia et al[33]	1,289	TBI-Cy BuCy	OR 1.49 in favor of TBI	PO busulfan

ALL, acute lymphocytic leukemia; Bu, busulfan; Cy, cyclophosphamide; Etop, etoposide; FORUM, For Omitting Radiation Under Majority age; PO, by mouth; TBI, total body irradiation.

[a]Unless otherwise indicated.

[b]Fludarabine/thiotepa and busulfan or treosulfan.

[c]Relapse rate.

A randomized trial from the French Society of Bone Marrow Graft, which also evaluated the impact of single- fraction versus fractionated TBI, showed no difference in overall 5-year OS or DFS for patients with CML treated with BuCy versus TBI-Cy.[26] Similarly, the study by Clift et al[27] showed no significant difference for 3-year OS, relapse, EFS, or speed of engraftment for BuCy versus TBI-Cy for CML.

Multiple trials have evaluated conditioning regimens in patients with different underlying diagnoses. A randomized study from the Southwest Oncology Group 8612 compared fractionated TBI plus etoposide versus high-dose BuCy in patients who had failed prior conventional therapy for ALL (36%), CML (35%), and AML (29%). Patients were stratified as "good risk" (second complete remission for acute leukemia or accelerated phase CML) or "poor risk" (more advanced stages of leukemia). There was no difference noted in OS or DFS between the two treatment groups.[28]

Ringdén et al[29] of the Nordic Bone Marrow Transplantation Group compared BuCy to TBI-Cy in patients with AML (41%), CML (36%), and ALL (23%). Patients treated with BuCy had higher rates of VOD/SOS ($P = .009$), hemorrhagic cystitis ($P = .003$), NRM in those with advanced disease ($P = .002$), seizures ($P = .03$), high-grade chronic GVHD ($P = .04$), and death associated with GVHD ($P = .003$). There were similar rates of acute GVHD between the two groups. RFS was similar upon analysis of all patients, but in the subgroup of adult patients ($P = .05$) and advanced disease ($P = .005$), the TBI-containing regimen appeared superior. Long-term follow-up of this study demonstrated a 7-year relapse rate of 29% in both groups. In patients with advanced disease, there was a significant increase in NRM in patients who received BuCy ($P = .004$). There was no difference in LFS in patients with early disease, but there was an improvement in LFS in patients with advanced disease receiving TBI ($P < .01$).[30]

Socié et al[31] published long-term follow-up of four randomized controlled trials. For patients with AML, there was a strong trend toward improved OS ($P = .068$) and DFS ($P = .051$) with TBI-Cy. A meta-analysis by Hartman et al[32] evaluated five prospective randomized controlled trials with 652 patients treated from 1966 to 1996 and showed trends not reaching statistical significance in favor of TBI for both OS and DFS. Another meta-analysis by Shi-Xia et al[33] evaluated 18 trials with a total of 3,172 patients. For patients with ALL or AML, TBI-Cy was associated with lower rates of leukemia relapse, lower NRM, and higher rates of DFS. However, for patients with CML, the TBI-Cy regimen was associated with higher rates of leukemia relapse, lower NRM, and similar DFS. The risk for cataracts ($P = .01$), pneumonitis, and growth/developmental problems ($P = .008$) was higher with a TBI-containing regimen. Alternatively, the risk of VOD/SOS ($P < .00001$), hemorrhagic cystitis, and transplant-related mortality appeared higher for patients treated with BuCy.

To summarize, limited randomized data, with obvious limitations, have not demonstrated any difference in outcomes with TBI and non-TBI-based regimens for

CML. For AML, the available randomized studies and meta-analyses favor TBI-Cy, although this is controversial given negative findings from nonrandomized registry studies (Table 15.1). For ALL, TBI appears to be an important component of the conditioning regimen (Table 15.2).

The side-effect profile of different conditioning regimens is also an important consideration. Although there can be significant overlap in treatment-related toxicities between chemotherapy and TBI-based conditioning regimens, such as fatigue and nausea, some toxicities are more common with one modality versus another. Although both chemotherapy and TBI can cause lung toxicity, TBI-based regimens appear to be associated with a higher risk of pneumonitis and other lung complications.[16,20] Prior thoracic RT may increase the risk of fatal pneumonitis. One study demonstrated a 32% risk of fatal pneumonitis after TBI in patients with prior chest radiation doses above 20 Gy.[34] Avoiding TBI may be prudent in such patients. One contemporary series of allo-SCT documented a 33% risk of severe pulmonary toxicity after TBI-based conditioning, with the number of prior chemotherapy regimens being the only independent risk factor for lung toxicity.[35] Cataracts and endocrine deficiencies are also more common with TBI.

In contrast, hepatic VOD/SOS and hemorrhagic cystitis are more common with BuCy.[32] The Nordic Bone Marrow Transplantation series showed a VOD/SOS incidence of 12% in patients treated with busulfan compared to 1% for the TBI-treated patients (P = .009). Hemorrhagic cystitis risk was 24% for busulfan-based therapy versus 8% for TBI (P = .002).[29]

A relative advantage in using TBI for SCT is that the dose delivery throughout the body is highly controllable. In contrast to chemotherapy, dose distribution is independent of such factors as blood supply, and there are no concerns about agent activation, metabolism, excretion, or dose modifications based on liver or kidney function. TBI may also reach chemotherapy sanctuary sites, which is of particular concern in patients at risk for testicular or central nervous system (CNS) involvement.

GRAFT FAILURE

Failure to engraft is a potential life-threatening complication of allo-SCT. Approximately 6% of patients fail to engraft with myeloablative conditioning, with a similar number of patients experiencing secondary graft failure thereafter.[36,37] Not surprisingly, graft failure is associated with worse outcomes. For those patients who fail to engraft after a myeloablative conditioning regimen, salvage allo-SCT with a TBI-based regimen is possible. Several small, single-institution studies have described using a non-myeloablative regimen in this setting,[38,39] Reduced-intensity regimens can be used to escalate host immunosuppression and increase the probability of successful engraftment without exposing patients to the risks of a second myeloablative regimen.

TOTAL BODY IRRADIATION

Radiobiology

Radiobiologic Effects on the Normal Hematopoietic System

In addition to the hematopoietic elements, the bone marrow also contains mesenchymal stromal cells that play a critical role in the formation of blood cellular components. Hematopoietic stem cells reside in specialized niches within the bone marrow and are regulated by bone marrow stromal cells.[40] Successful hematopoietic stem cell engraftment in the setting of an allo-SCT requires (a) eradication of the recipient's own stem cells, (b) immunosuppression to prevent rejection of donor stem cells, and (c) relative sparing of the recipient's bone marrow stromal cells. Ionizing RT appears to have a differential effect on hematopoietic stem cells and marrow stromal cells.

The use of the classic radiobiologic parameter D_0 gives a rough indication of the radiosensitivity of various cell populations. With the caveat that many factors can affect observed D_0 values (eg, dose rate and fractionation), the reported D_0 values of hematopoietic cells usually range from 0.5 to 1.6 Gy, with little or no shoulder associated with dose-survival curves.[41,42] This intrinsic radiosensitivity is due, in part, to a limited capacity to repair sublethal damage. Hematopoietic cells are consequently affected less by changes in dose rate or fractionation.

If bone marrow stromal cells and their progenitors (colony- forming unit fibroblasts) are damaged, delayed engraftment or even graft failure may follow. Progenitors of human bone marrow stromal cells have been found to have a D_0 of 1.46 Gy.[42] D_0 values in mice and dogs have been shown to be higher, with a broad shoulder on dose-survival curves. Thus, radiation fractionation and utilization of low dose rates are expected to spare bone marrow stromal cells and their progenitors.

Immunosuppression in the setting of allogeneic SCT is necessary to avoid rejection of donor stem cells. TBI is a very efficient immunosuppressant. In animal work by Storb and colleagues, equivalent doses of fractionated TBI were significantly less effective than single-dose TBI to condition dog leukocyte antigen–identical littermate dogs before bone marrow transplantation.[43] The investigators concluded that significant repair of DNA damage by lymphoid cells occurs during interfraction intervals. In a murine model, Salomon et al[44] looked at three TBI schemas from schedules that had been developed for human TBI therapy (8.5 Gy single-fraction TBI, 2 Gy × 6 fractions of TBI, and 1.2 Gy × 12 fractions of hyperfractionated TBI). In terms of the immunosuppressive effects, the results favored single-fraction TBI. A marked initial shoulder on the dose-survival curve has been reported for T-lymphocyte precursors[45] and for a human lymphoblastoid cell line.[46] The immunosuppressive effects of TBI show marked fractionation sensitivity, leading one to conclude

fractionated TBI might be associated with more graft rejections than the same dose delivered in a single fraction.

Radiobiologic Effects on Leukemia

In the setting of allo-SCT, TBI achieves significant leukemia cell killing in conjunction with chemotherapy and the subsequent graft-versus-tumor effect, leading to eradication of malignant clones in a significant portion of cases. Most D_0 values for both animal and human leukemia cell lines range from 0.8 to 1.5 Gy,[47,48] although extreme values range from 0.3 to more than 5 Gy. Leukemia cells do retain some degree of sublethal repair capacity, which is likely more operational in more differentiated leukemias. Further, heterogeneity in inherent radiosensitivity inevitably exists between leukemic cell lines. Most studies suggest that fractionated TBI is likely less effective than single-dose TBI (utilizing the same dose) for leukemia cell killing.[42]

Techniques and Dosimetry

Basic Requirements

Historically, radiation oncologists have aimed to deliver a relatively homogeneous dose of radiation throughout the body to (a) eradicate host stem cells that are localized to bone marrow niches, (b) eliminate residual circulating leukemia cells, and (c) deplete host immune cells, where both microscopic leukemia cells and host immune cells are likely widely distributed throughout the body. Hence, *total body irradiation*. Newer techniques including TMI and TMLI have challenged this paradigm. With any approach, where there is concern for a higher burden of disease, boost radiation fields may be utilized. Augmented doses of radiation may be delivered to the brain in the setting of CNS involvement or to the testes in males with ALL, for example.

To ensure the planned dose distribution is accurately delivered, all TBI techniques must undergo a rigorous and comprehensive dosimetric characterization. Because of large variations in body geometry and tissue density between patients, it is recommended that dose homogeneity remain within a specified window of plus or minus 10% of the prescribed dose, although plus or minus 5% is typically attainable. For TBI and HBI, there is evidence that a 5% change in lung dose could result in 20% change in the incidence of radiation pneumonitis, a complication that is sometimes fatal.[49,50] Therefore, the basic dosimetry of TBI (and HBI) techniques should be performed as precise as readily achievable. Accurate dosimetry coupled with an effective quality assurance program, including adjustments to dose delivery after in vivo measurements on the first day of treatment, will ensure not only safe delivery of TBI treatments but also accurate dosimetry data for meaningful dose-response analysis. Once a patient begins a course of TBI, within a comprehensive conditioning

program, the timing of successive fractions becomes critical to the outcome of the procedure. It is imperative to have a backup TBI system either within the same institution or in a nearby RT department when establishing a TBI program. When the primary system is down, a fully commissioned backup TBI system can be utilized to complete the remaining treatments.

Standard Total Body Irradiation Techniques

Many TBI techniques have been described and improvements in both the irradiation technique and physical dosimetry continue.[51] Nuances and specifics of particular techniques are outside the scope of this chapter. To be brief, many centers have facilities designed specifically for large-field irradiation. Although a few dedicated systems still exist, current TBI procedures are largely performed with techniques established on linear accelerators that are also used for conventional RT. Common to these TBI techniques is the use of radiation fields that are larger than the maximum field size (~40 by 40 cm) available at standard source-to-surface distance (SSD), requiring patients with TBI to be treated at extended SSDs of 200 to 600 cm. For treatment rooms large enough to accommodate an SSD of 5 m or more, a single square field at maximum collimator opening is usually sufficient to completely encompass patients of typical height placed along the diagonal of the field (Figure 15.1A-E). At shorter SSDs, multiple abutting fields may be necessary, and irradiation of the whole body can be achieved by translating the radiation field or the patient, or by sweeping the radiation field over a stationary patient (Figure 15.1F-H). For these irradiation techniques, patients are typically treated with two parallel-opposed fields. When a single radiation source is used, this can be accomplished by rotating the patient 180° along the patient's longitudinal axis between the two fields. In a dedicated system with two radiation sources mounted opposite to each other, the treatment can be accomplished by irradiating the two fields simultaneously without changing the patient's position. Various patient positions, ranging from sitting, standing upright, to lying horizontally in a supine or lateral decubitus position, have been used (Figure 15.1A-H).

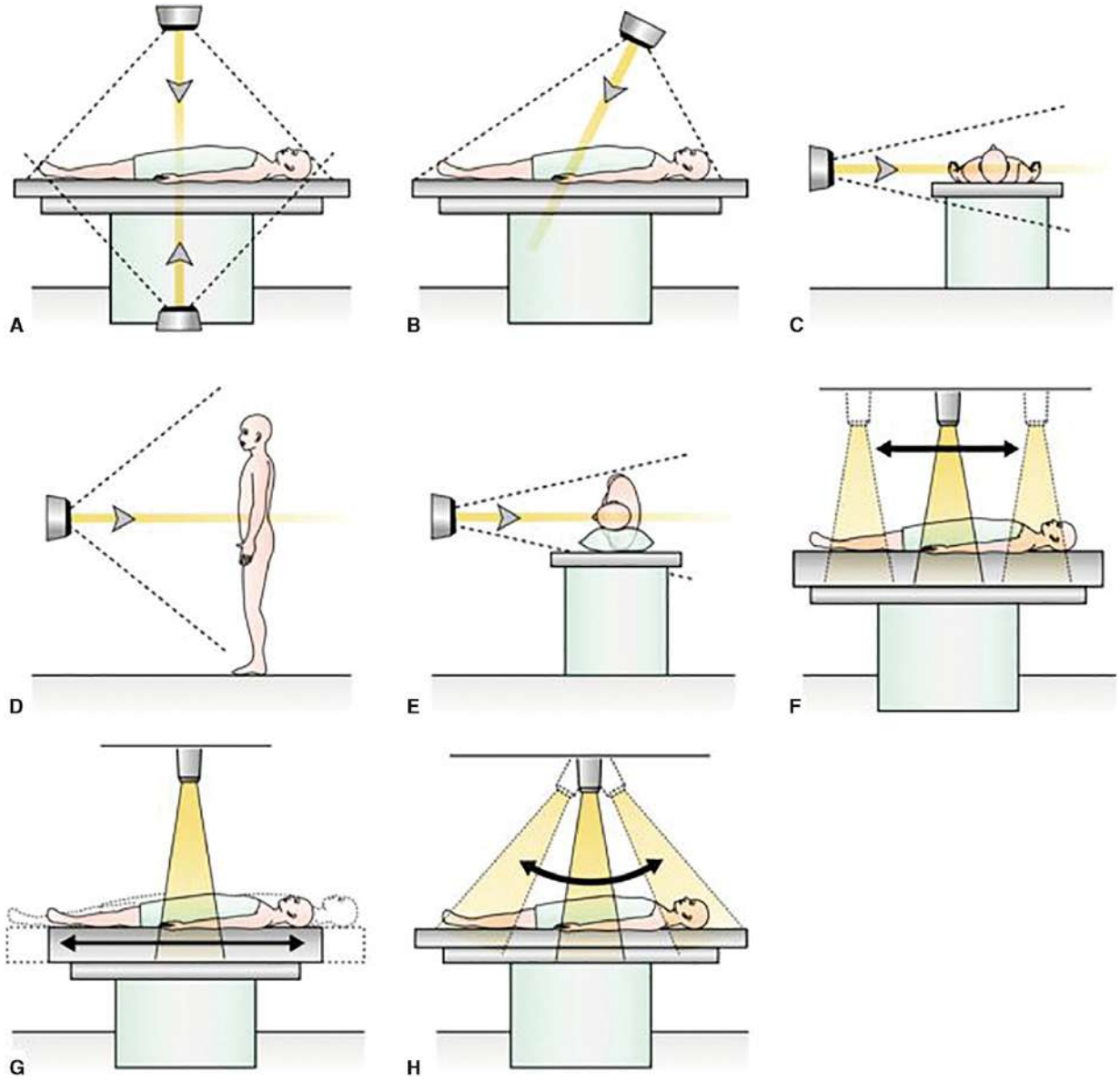


FIGURE 15.1 Some of the traditional large-field total body irradiation (TBI) techniques in which patient and beams are stationary. A. Two vertical beams. B. One vertical beam. C. One horizontal beam, patient in supine position. D. One horizontal beam, patient standing or sitting. E. One horizontal beam, patient in lateral decubitus position. F-H. Some of the small-field TBI techniques in which patient or beam moves. F. Source scans horizontally. G. Patient moves horizontally. H. Sweeping beam.

Techniques using a single large field encompassing the entire patient at extended SSD is by far the simplest and the most prevalent TBI technique used today. Such approaches eliminate the dosimetry complications occurring in the junctions of multiple abutting fields. They also alleviate the concern that cells circulating through the body may potentially receive a reduced dose when abutting fields are delivered sequentially.

Dosimetric Characterization of Total Body Irradiation Techniques

Once an irradiation technique is chosen, a careful characterization of the dosimetric properties of the technique should be performed by a qualified medical physicist. The dosimetric data needed to model the treatment planning system for accurate planning of TBI for individual patients should be carefully measured and validated. The technical issues and method of radiation dosimetry for TBI have been reviewed in several reports. In particular, a report from the American Association of Physicists in Medicine (AAPM) task group 29 (TG-29) on the physical aspects of TBI and HBI provides a comprehensive discussion on dosimetry issues and techniques specific to large-field TBI.[51] It is a good resource for medical physicists charged to commission a large-field TBI technique.

Since publication of the TG-29 report, the reference dosimetry protocol for external beams at standard treatment SSD, known as the TG-21 protocol, has been updated by a new calibration protocol (TG-51). For photon beams at standard SSD, the TG-51 protocol produces similar results as the TG-21 protocol. However, the TG-51 protocol cannot be applied directly for large fields at extended SSD as encountered in TBI. The calibration of a TBI beam can be established with direct traceability to TG-51 by using an approach similar to that proposed by Curran et al.[52] In this approach, the photon source of the TBI beam is first calibrated under the TG-51 reference condition at standard SSD. The dose per unit beam-on time at a reference point of the TBI beam under TBI treatment conditions is then related to the dose per unit beam-on time of the same photon source at the TG-51 reference point by a correction factor that accounts for the TBI setup geometry and scattering conditions. This correction factor, as well as the relative dose factors that characterize the spatial distribution of the TBI beam, such as the percent depth dose or tissue maximum ratio along the central axis, can be measured directly under the TBI treatment conditions using a phantom with size similar to that of a typical patient. In-phantom off-axis beam profiles at various depths, especially along the diagonal near the corners of the field, should also be measured at TBI treatment distances to evaluate the dose variation across the radiation beam. Independent verification of the TBI calibration should be performed after the initial commissioning. The modeling of the treatment planning system should also be verified on an anthropomorphic phantom.[53,54] A thermoluminescent dosimeter (TLD) or optically stimulated luminescence dosimeters (OSLDs) calibrated on an independent linear accelerator can be used to verify TBI calibration and doses at other points of interest. Other types of dosimeters such as ion chambers and film may be used to assess dose distributions.[55]

Skin Surface Dose

Although skin sparing is often a desirable feature of megavoltage irradiation in conventional RT, for TBI it may be desirable to have the skin surface receive close to

the full prescription dose, such as the setting of leukemia cutis. When needed, the skin dose can be increased by using either bolus placed on the skin or a beam spoiler positioned between the source and the patient. As photons of the TBI beam pass through the beam spoiler, scattered electrons are produced, which deposit most of their energy at shallow depths near the skin surface. The aim is to increase the skin dose to more than 90% of the prescription dose. In addition to the attenuation of the photon beam, use of a beam spoiler alters the depth-dose characteristics of the TBI beam in the buildup region. The magnitude of this modifying effect depends on the photon energy of the beam, the composition and thickness of the scatter screen, and the distance between the screen and the patient. It should be carefully evaluated as part of the commissioning task for the TBI technique. The dosimetric effect of the beam spoiler can be treated separately or included in the TBI beam calibration. When the beam spoiler is included in the calibration, choice of the calibration depth becomes an important consideration. Calibration measurements performed at a depth of 5 cm or greater decrease the influence of beam spoiler–generated electrons significantly.

Dose Rate

As discussed in the preceding sections, the rate of TBI dose delivery can have an impact on the clinical outcome after TBI.[56] Many clinical protocols require low-dose-rate treatment (0.05 to 0.20 Gy/min). Modern linear accelerators offer a wide range of dose rates (eg, from 1 to 6 Gy/min in increments of 1 Gy/min), to the depth of maximum buildup at standard SSD. At extended SSD, the nominal dose rate will be smaller because of inverse-square falloff of photon fluence with SSD. The dose rate at the TBI treatment distance is dependent on the combination of SSD and the nominal dose rate programmed at the linear accelerator console. The correct dose rate should be selected based on the prescription and patient geometry so that the absorbed dose rate in the patient does not exceed the limit. If a given combination of SSD and nominal dose rate does not produce a desired dose rate, a custom-made attenuator can be placed in the beam path to help achieve a desired dose rate.

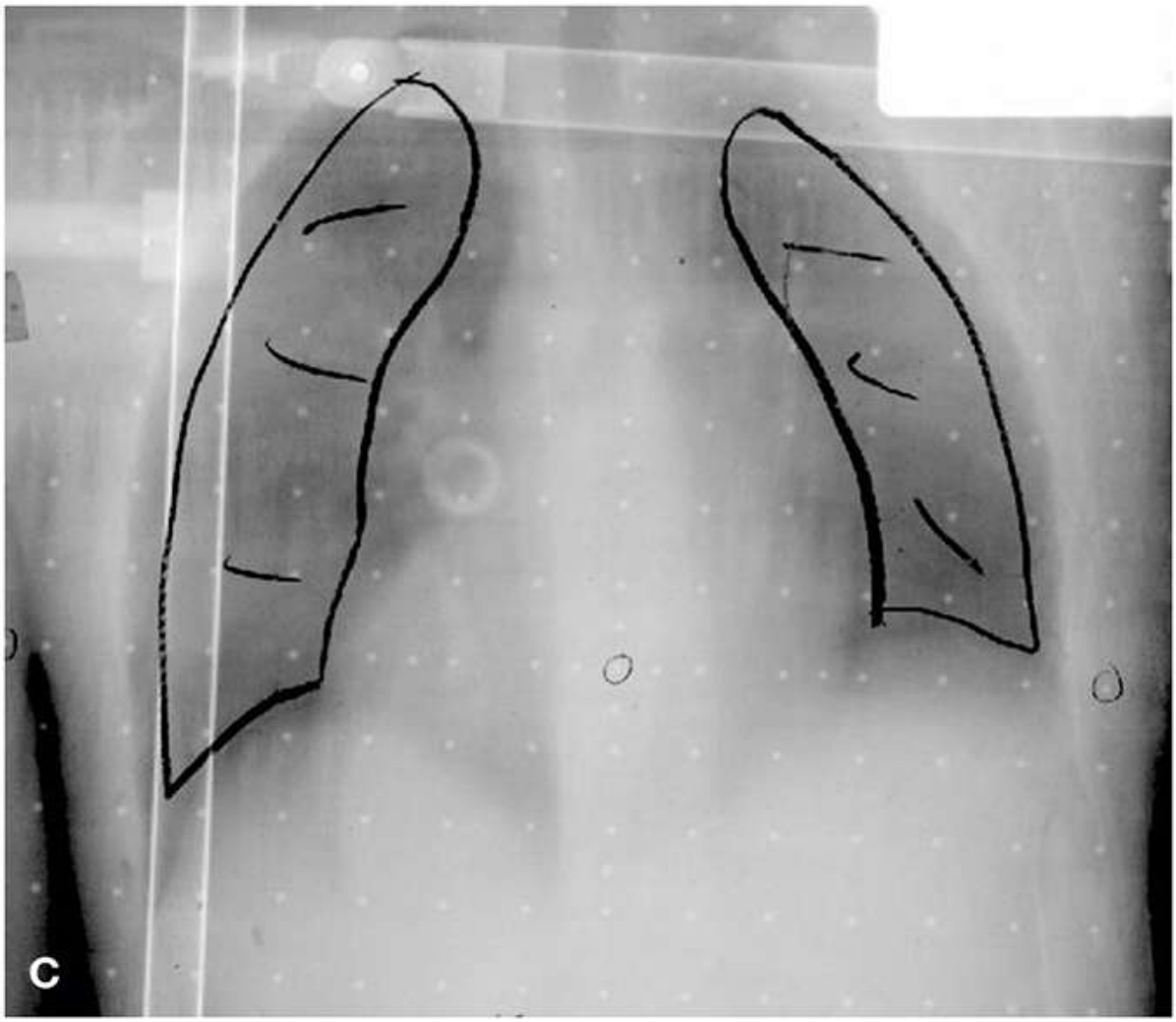
Patient Positioning

As treatment times may last up to 30 or 40 minutes for each fraction of a TBI protocol (even longer for single-fraction protocols), patients must be placed in a comfortable and reproducible position. When a pair of parallel-opposed fields is used, irradiation along the anteroposterior/posteroanterior (AP/PA) direction is advantageous as the body thickness in the AP/PA direction is usually smaller than in the lateral direction, which results in better dose uniformity along the beam path for a given photon energy. As depicted in Figure 15.1A and B, this may be accomplished with the patient lying in the supine/prone position under a vertical beam arrangement or with the patient lying

on the side in a lateral decubitus position when a horizontally directed beam is used (Figures 15.1E and 15.2A, B). Irradiation with the patient lying supine using a horizontally directed beam (Figures 15.1C and 15.2E) is also a reasonable technique, especially for patients with small lateral separations, such as pediatric patients, or when a higher- energy photon beam is employed. Because of clinical problems associated with patient fatigue and orthostatic hypotension, special patient stands are used in some institutions to facilitate upright patient positioning (Figure 15.1D). For most children and all adults, an extended SSD will still be required for full body coverage.

A

B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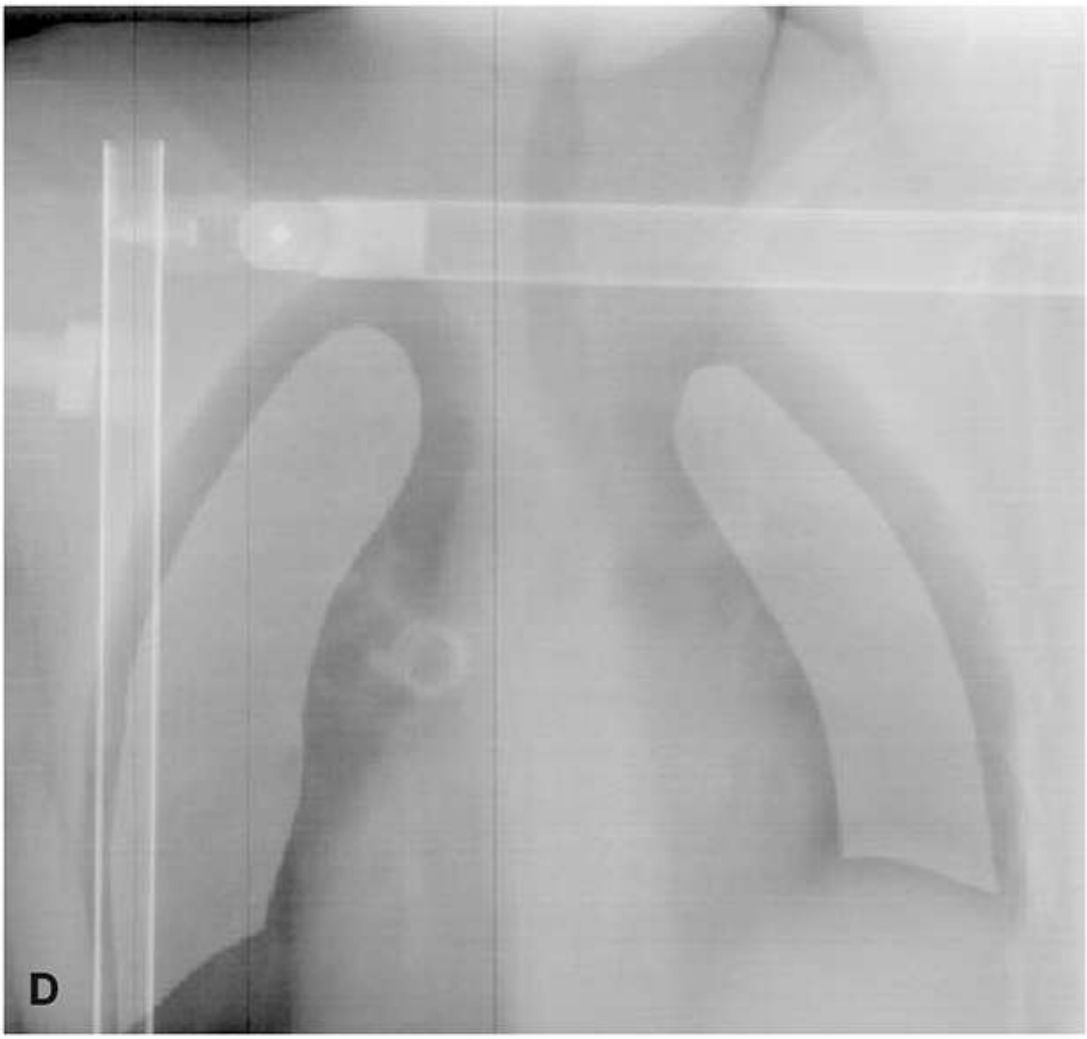
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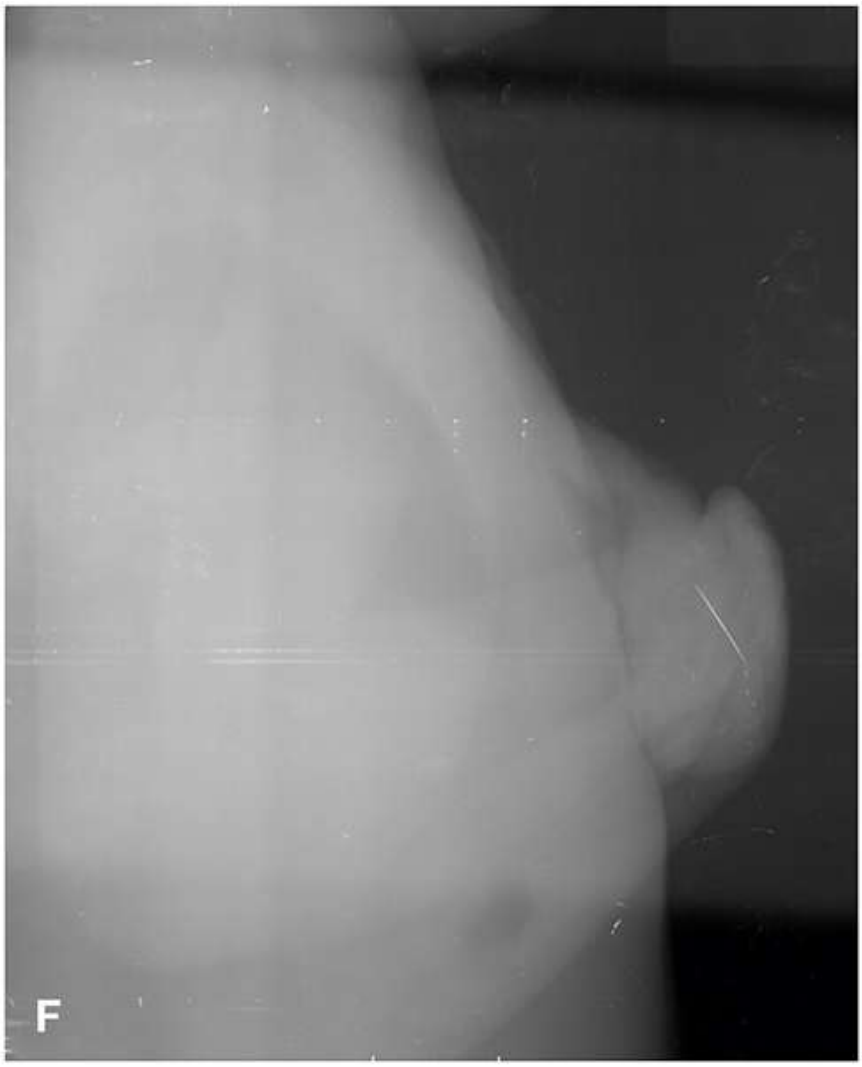

FIGURE 15.2 A. Patient in decubitus position for total body irradiation (TBI), anterior beam. B. Thin lung blocks placed close to thorax using a Velcro-plexiglass system to reposition blocks with each fraction. C. A megavoltage simulation film taken in decubitus position. D. Treatment portal imaging taken in decubitus position. E. Patient in supine position for TBI using lateral fields. F. A megavoltage port film confirming position of brass compensators to attenuate the dose to the lungs when lateral fields are used.

Treatment Planning

Radiation beam-on times for a prescribed TBI dose are often calculated with a specialized in-house program or by manual computation. This is because most commercial treatment planning systems are designed and commissioned using standard datasets for conventional RT at SSD near 100 cm, which do not automatically apply to a TBI configuration at extended SSD of up to 400 cm. Some newer versions of commercial treatment planning systems can be adapted for isodose planning of TBI at extended SSDs by using depth dose, beam profiles, and other parameters measured directly under TBI conditions.

In addition to TBI beam characteristics, an accurate description of patient geometry is needed for patient-specific treatment planning. The external body contour of a patient with TBI in the treatment position can be reconstructed from the measurements of body thickness at representative anatomic points judiciously distributed over the patient's body. A CT scan of the entire body provides the best description of patient geometry and is required for intensity-modulated radiation therapy (IMRT)-based TBI/TMI techniques. For extended SSD TBI techniques using two parallel-opposed beams, dose variation over the patient's body arises primarily from (a) photon attenuation along the beam path, (b) the changing body contour across the patient, (c) variations in tissue density, and (d) dose profile dependence on off-axis distance.

The dose variation caused by photon attenuation along the beam path is dependent upon both the beam energy and the body thickness. It decreases with decreasing body thickness and increasing photon energy. Because the body is typically thinner in the AP direction, treating patients using an AP/PA technique with higher photon energy will improve the dose uniformity along the beam path. Using lateral-opposed beams will usually result in greater dose variation compared to AP/PA treatments, especially for adult patients. The dose variation caused by changing body contour may be reduced by using missing-tissue compensators or tissue-equivalent bolus material placed directly on the patient. The ability to compute isodose distribution across the body is highly desirable for compensator design. Missing-tissue compensator for TBI is typically constructed to even out the variation of body thickness along the head to toe direction. Such a one-dimensional compensator can be constructed manually using multiple thin brass (or other material) plates. As the compensator is usually mounted at the head of the linear accelerator (blocking tray), small variations in the placement of compensating plates will be magnified at extended SSD distance. Care must be exercised in constructing these compensators and placement during treatment. For example, when compensating plates are used for the head and neck region, mounting the compensator too far inferiorly could result in a lower dose to the shoulders. In addition, careful alignment of the patient to the planned position becomes important to achieve the desired missing-tissue compensation.

Dose variation caused by tissue heterogeneity in the thoracic region requires special attention because the lungs are a critical dose-limiting structure with TBI. Without compensation for air density, particularly for AP/PA treatments, dose inhomogeneity can exceed the prescribed dose by 10% to 24%, depending on the energy of beams used.[51] In order to reduce lung toxicity, correction for lung air density should be taken into account. Further, many institutions attenuate the dose to the lungs further using lung shielding. This can take many forms including customized lung blocks (typically in the setting of AP/PA fields; Figure 15.2B, C) or attenuation using brass compensators (typically in the setting of lateral fields; Figure 15.2F). The use of lung

blocks increases the complexity of the TBI procedure, and accurate repositioning of lung blocks can be a challenge for fractionated treatments. At some institutions, individualized thin lung blocks (with ~85% photon transmission) are mounted close to the patient on an acrylic resin tray using a hook and loop fastener system that allows easy repositioning of lung blocks for each fraction. At Duke, partial transmission blocks made of cerrobend alloy are mounted on a plastic tray placed 10 cm from the patient skin (Figure 15.3). Verification of correct lung block positioning is carried out by using customized online electronic portal imaging. For the lateral technique, the arms can be used, in addition to shielding using brass compensators, to decrease dose to the lungs (Figure 15.2E). For pediatric patients, the arm may not be large enough laterally to cover the entire lung.

FIGURE 15.3 Partial transmission blocks for lungs and kidneys made of cerrobend alloy mounted on a plastic tray placed 10 cm from the patient skin.

Dose Description and Reporting

Because there is no standard treatment technique for TBI, significant differences in dose distributions can exist with different treatment methods. Two institutions can prescribe the same dose at some selected prescription point, but dose to other points could vary considerably if different treatment techniques are used. Without supplemental information on the dose distribution, it would be difficult to assess the clinical effectiveness of different TBI programs based on the reported prescription dose alone. To facilitate treatment comparison among institutions, various methods for prescribing the dose for TBI treatments have been reported.[57,58] One method uses a single-point prescription dose supplemented with the specified limits of highest and lowest dose levels acceptable for any point within the body. In addition, dose limits are also set for certain tissues, such as the lungs. An example of such a TBI prescription is given in AAPM TG-29, which uses the midpoint at the level of the umbilicus as the prescription point. A prescription would read as follows: “The dose

to the midpoint at the level of the umbilicus is 14 Gy to be delivered in 8 fractions with 2 fractions on each day separated by at least 6 hours. All points in the body should receive doses within the limits of −5% and +10% of prescription dose. The dose to lung should be no more than 85% of the prescription dose." When reporting results from a TBI-based conditioning regimen, ideally, the actual values of the corresponding dose descriptors would be provided. When CT-based TBI treatment planning is available, dose statistics or a dose-volume histogram of the target volume and critical organs should be reported.

Quality Assurance

To improve dosimetric accuracy and consistency, periodic assessment of TBI calibration and beam characteristics should be performed as part of an ongoing quality assurance program. Each patient's treatment plan, including the design of customized tissue compensators when used, should be checked by an independent physicist. In addition, in vivo dosimetry verification of the treatment plan should be performed during the first fraction for all patients with TBI. Changes in patient body shape (eg, due to weight loss between the time of simulation and treatment delivery) and positioning can alter the dose distribution. Adjustment of radiation beam-on time and tissue compensators may be needed for subsequent treatments based on the in vivo verification (assuming the accuracy and confidence of in vivo measurement have already been established). TLD (or OSLD) and diode detectors are typical choices for in vivo monitoring of doses delivered to patients. These dosimeters should be calibrated to be suitable in the TBI beam under the treatment condition prior to commencing patient treatment. A diode dosimetry system with multiple diode detectors is especially convenient for these types of measurements because they allow simultaneous measurement of doses at multiple anatomic sites in nearly real time.

Lung (and Other Organ) Dose Attenuation

Many transplant centers use lung blocks or lung shielding during TBI in order to correct for the dosimetric effects of lung density or to specifically reduce the dose to lung tissue, thereby reducing the risk for pneumonitis. This is particularly important in patients who have baseline lung dysfunction.[59] Lung shielding will reduce the risk of pneumonitis, all other factors being equal.[60] Overcompensation, however, risks an increase in leukemia recurrence. A study from the Institut Gustave Roussy delivering 10 Gy as a single fraction of TBI over 4 hours showed a higher incidence of relapse in patients whose lung dose was reduced to 6 Gy with lung blocks compared with 8 Gy.[61]

There are many techniques to attenuate the dose to the lungs. Where lateral TBI fields are utilized, the dose to the lungs can be attenuated using brass compensators (Figure 15.2F). The required thickness and the size of the brass compensators can be estimated based on the patient chest x-ray and verified with portal imaging. The

downside of this approach is that the RT dose is reduced not only to the lungs but also to the mediastinum and chest wall. Where AP/PA fields are utilized, lung blocks can be utilized to reduce lung dose (Figure 15.2A-D). Some, but not all, centers employ electron boosts to the chest wall under the blocks. There are considerable dosimetric challenges with this technique: overlap issues of photon and electron fields; surface contour variability, especially from breast tissue in women; and delivering unwanted radiation dose to some limited volume of the lungs.

When TBI is used for non-neoplastic diseases (eg, aplastic anemia), where the main objective is immunosuppression, one may also consider shielding radiosensitive structures such as the gonads or eyes (ie, the lens).

Boosting of Selected Organs With Total Body Irradiation

A relative advantage of TBI is the treatment of chemotherapy sanctuary sites. This is particularly important when treating diseases with a propensity to involve the CNS or testes. Theoretically, regions of the body where there is a higher burden of disease at the time of transplant may be boosted with additional radiation to supplement TBI. In selected patients with acute lymphoblastic leukemia, CNS-preventative therapy may include cranial irradiation. When such patients are determined at diagnosis to be best managed with an allo-SCT, it is reasonable to defer prophylactic cranial irradiation until the time of TBI. Augmented doses of radiation may be delivered to the CNS, bringing the cumulative cranial dose to approximately 18 Gy (a current standard in children and many adults with ALL). Higher total doses to the brain and perhaps the spine can be considered in patients being managed with overt CNS leukemia. Boost doses to the brain using lateral fields may be given in 1.5 to 2.0 Gy fractions. Caution is necessary for additional CNS boost treatments when patients have received prior cranial irradiation because of toxicity concerns. Similarly, the testes in males with ALL may be boosted to a cumulative dose of approximately 16 to 18 Gy. The scrotum may be treated with en face electrons of appropriate energy or a single superior/anterior/oblique photon field. Dose prescriptions for testicular boosting are generally 4 Gy in a single fraction or 4 Gy in two fractions. Not all institutions pursue a testicular boost in ALL.

Total Marrow Irradiation and Total Marrow/Lymphoid Irradiation

TMI is the delivery of a targeted form of TBI using large-field IMRT. TMI allows targeting of dose and dose escalation to sites of disease while significantly reducing dose to multiple organs at risk (OARs). Since the first patient treated with TMI,[62,63] there has been rapid adoption driven by encouraging results from multiple centers and an expansion of technology platforms capable of delivering this therapy.[64-69] Figure 15.4 provides examples of TMI and TMLI dose distributions. Details regarding

planning, setup, and delivery have varied at each center and have been recently reviewed.[64,68,70]

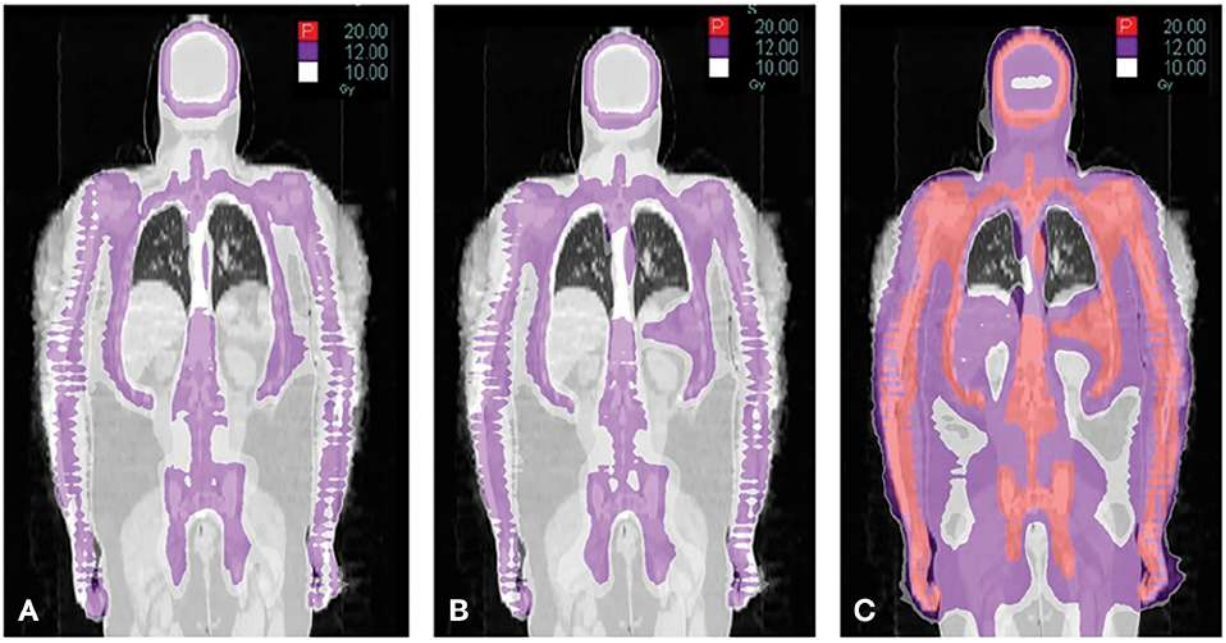

FIGURE 15.4 A. Total marrow irradiation (TMI) where the target is bone. B. Total marrow/lymphoid irradiation (TMLI) adds the major lymph node chains and spleen as target regions. C. In some studies, TMLI also includes the liver and brain to 12 Gy while other target regions (bone, lymph nodes, and spleen) are escalated to 20 Gy.

The concept of TMI, when introduced in 2002,[71] represented a significant departure from standard TBI, leading to a number of questions before the first patient was treated. Were the new helical tomographic and volumetric modulated arc therapy (VMAT)/IMRT technologies able to accurately deliver such a complex dose distribution? Was dose escalation feasible with acceptable toxicities? Would the higher average dose rates with TMI (70-200 cGy/min) compared to conventional TBI (less than 20-30 cGy/min) result in increased toxicities? Would dose reduction to organs and circulating leukemia cells increase relapse rates? Due to these concerns, the logical first step was to evaluate TMI in more advanced patients with refractory or relapse disease where survival rates are less than 20%,[72] who have no standard hematopoietic cell transplantation (HCT) options, and who typically are not transplanted. This offered the opportunity to expand the use of RT to a new HCT population and address an unmet need.[73]

Table 15.3 summarizes the results of select TMI and TMLI clinical studies to date. Early trials were in patients with multiple myeloma and investigated combining TMI with standard melphalan-based conditioning prior to autologous transplant.[74-78] Most studies have since focused on patients with acute leukemia undergoing allogeneic

HCT. Fraction sizes of 1.5-2.0 Gy delivered twice a day is used most frequently, with a few centers using 3, 4, or 5 Gy fractions. The target regions have been bone and bone marrow (TMI) or bone/marrow and lymph nodes and spleen (TMLI) for added immunosuppression needed with allogeneic HCT.

TABLE 15.3 SELECT TMI AND TMLI CLINICAL STUDIES

Study Info	*N*	Disease	Targets	TMI Dose (Gy) (Fraction)	Chemotherapy GVHD Regimen	NRM Survival GVHD
Wong et al[155] (2013) Phase I NCT00540995	20	AML relapsed or refractory age <60 19/20 persistent marrow blasts median age 41 (23-52)	Bone, nodes, testes, spleen, 12 Gy liver, brain	12, 13.5 (1.5 bid)	Bu 4800 μM/min VP-16 30 mg/kg Tacrolimus/sirolimus	Median f/u 7.3 mo NRM 40% (8 of 20) 5/20 CR 20.8-49.4 mo DLT mucositis and VOD 4/20 grade 3-4 aGVHD 6/14 extensive cGVHD
Stein et al[79] (2017) Phase I NCT02446964	51	AML, ALL relapsed or refractory age <60 42/51 ≥10% marrow blasts 21/51 ≥10% circulating blasts Median age 34 (16-57)	Bone, nodes, testes, spleen, 12 Gy liver, brain	12-20 (1.5-2.0 bid)	Cy 100 mg/kg VP-16 60 mg/kg Tacrolimus/sirolimus	Median f/u 24.6 mo RP2D 20 Gy; mo DLT NRM 3.9% 100 d, 8.1% 1 y 1-y PFS 40% (33 patients relapsed) 1-y OS 55.5%; 2-y OS 41.5% Grade 3-4 aGVHD 14% Extensive cGVHD 47%
Stein et al[80,81] Phase II NCT02094794	57	AML or ALL IF, relapsed or >CR2 Age < 60 Median age 40 (16-59)	Bone, spleen, nodes, 12 Gy liver, brain	20 (2.0 bid)	Cy 100 mg/kg VP-16 60 mg/kg Tacrolimus/sirolimus	Median f/u 21.8 mo NRM 4% 100 d, 9% 1 y 2-y PFS 33% 2-y OS 48% 2-y relapse rate 58% Relapse 70% (40)

Study Info	*N*	Disease	Targets	TMI Dose (Gy) (Fraction)	Chemotherapy GVHD Regimen	NRM Survival GVHD
Rosenthal et al[86] (2011) Jensen et al[87] (2018) Pilot NCT00544466	61	AML, ALL, NHL, CMML, MDS, MM >50 y old or comorbidities CR1, >CR2, relapsed or refractory Median age 55 (9-70)	bone, nodes, spleen, ALL testes, brain	12 (1.5 bid)	Flu 25 mg/m^2/d × 4 Mel 140 mg/m^2 Tacrolimus/sirolimus	Median f/u 7.4 y 2- and 5-y NRM 30% and 33% 2- and 5-y EFS 49% and 41% 2- and 5-y OS 50% and 42% Grade 3-4 aGVHD 17% Extensive cGVHD 67%
Al Malki et al[96,156,157] (2022) Phase I NCT02446964	31	AML, ALL, MDS CR1 high risk, CR2, CR3, refractory Haploidentical Median age 37 (21-58)	Bone, nodes, testes 12-20 Gy 12 Gy liver, spleen 12 Gy brain ALL	12-20 (1.5-2.0 bid)	Flu 25 mg/m^2/d × 5 Cy 14.5 mg/kg/d × 2 PTCy 50 mg/kg/d × 2 with Tacrolimus, MMF	Median f/u 23.9 mo alive patients RP2D 20 Gy NRM 3% 100 d, 13% 2 y 2-y OS 64% 2-y PFS 57% 2-y relapse rate 30% Grade 3-4 aGVHD at 100 d 6% Moderate-to-severe cGVHD 23% day 365+
Pierini et al[97] (2021) Phase II NCT03977103	50 31 TMLI 19 TBI	AML CR1, ≥CR2, MRD+, advanced Haploidentical Median age 53 (20-65)	Bone 13.5 Gy, nodes 11.5 Gy 19 TBI 13.5 Gy	13.5 (1.5 bid) TMLI if >50 y old TBI if ≤50 y old	TT 5-10 mg/kg Flu 150-200 mg/m^2 Cy 30 mg/kg Treg/Tcon/CD34$^+$	Median f/u 29 mo NRM 10/50 (21%) Relapse 2/50 (4%) OS 77%; GRFS 48% Mod/severe cGVHD/RFS 75% 12/50 grade 3-4 aGVHD; 1/50 cGVHD

Study Info	*N*	Disease	Targets	TMI Dose (Gy) (Fraction)	Chemotherapy GVHD Regimen	NRM Survival GVHD
Haraldsson et al[99,100] (2021) Prospective observational	37	ALL, MPAL, AML < MPN, MM, NHL, CML CR1, >CR1 Median age 29 (5-57)	Bone, spleen CNS and testes for ALL	12 Gy (2.0 Gy bid)	Cy or VP-16 CsA, MTX, ATG	Median f/u 13 mo 1-y GRFS 67.5% Four patients grade >2 aGVHD Three patients moderate-to-severe cGVHD GRFS and time to engraftment (not GVHD) better than historical TBI Dmean lung, liver, heart, kidney, bowel 61%-77% of the Rx dose
Somlo et al[74] (2011) Ladbury et al[75] (2022) Phase I/II NCT00112827	54	MM Durie-Salmon stage I-III Stable or responding disease and ≤18 mo from diagnosis Median age 54 (31-66)	Bone	10-18 Gy 2.0 Gy/d or bid	Tandem autologous HCT Mel 100 mg/m^2/d × 2 (first ASCT) Followed by 60 d later TMI (second ASCT) Maintenance thalidomide and decadron	Median f/u alive patients 12.3 y MTD 18 Gy (DLT pneumonitis, enterocolitis, and hypotension engraftment syndrome) RP2D 16 Gy 30 patients treated with TMI at 16 Gy CR 48.1%, VGPR 22.2% after maintenance 10-y PFS 20.4%, OS 38.8%

Study Info	N	Disease	Targets	TMI Dose (Gy) (Fraction)	Chemotherapy GVHD Regimen	NRM Survival GVHD
Giebel et al[76] (2021) Phase II NCT01665014	50	MM Durie-Salmon stage I-III At least partial response after initial therapy Median age 58 (41-64)	Bone	12 Gy 12 Gy boost to PET positive sites (five patients) 4.0 Gy/d)	Tandem autologous HCT TMI (first ASCT) Followed 100-120 d later with Mel 100 mg/m^2/d × 2 (second ASCT) Thalidomide maintenance if no CR (10 patients)	Median f/u 75 mo VGPR 82% CR 42% 5-y PFS 55%, OS 74%

Listed at www.clinicaltrials.gov

aGVHD, acute graft-versus-host disease; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; ASCT, autologous stem cell transplantation; ATG, antithymocyte globulin; bid, twice a day; Bu, busulfan; cGVHD, chronic graft-versus-host disease; CML, chronic myelogenous leukemia; CMML, chronic myelomonocytic leukemia; CNS, central nervous system; CR, complete remission; CR1, first complete remission; CR2, second complete remission; CR3, third complete remission; CsA, cyclosporine; Cy, cyclophosphamide; DLT, dose-limiting toxicity; Dmean, mean dose; EFS, event-free survival; f/u, follow-up; Flu, fludarabine; GRFS, GVHD-free/relapse-free survival; HCT, hematopoietic cell transplantation; IF, induction failure; MDS, myelodysplastic syndrome; Mel, melphalan; MM, multiple myeloma; MMF, mycophenolate mofetil; MPAL, mixed phenotype acute leukemia; MPN, myeloproliferative neoplasm; MTD, maximum tolerable dose; MTX, methotrexate; NHL, non-Hodgkin lymphoma; NRM, non-relapse mortality; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PTCy, posttransplant cyclophosphamide; RFS, relapse-free survival; RP2D, recommended phase 2 dose; Rx, prescription; TBI, total body irradiation; Tcon, conventional T cells; TMI, total marrow irradiation; TMLI, total marrow and lymphoid irradiation; Treg, regulatory T cells; TT, thiotepa; VGPR, very good partial response; VOD, veno-occlusive disease; VP-16, etoposide.

In younger patients (60 years of age or younger) with advanced relapsed/refractory acute leukemia, phase I and II studies[79-81] demonstrate that TMLI dose escalation up to 20 Gy with cyclophosphamide and etoposide is feasible, resulting in 2-year NRM rate of 9%, OS of 48%, and RFS of 33%, which are superior to historical results.[72] Dose escalation to 15-18 Gy using 3 Gy fractions or to 8-10 Gy using 4-5 Gy fractions has also shown promise.[82-85]

Older patients (>60 years of age), those with comorbidities or those who have relapsed after prior HCT, cannot tolerate myeloablative TBI regimens and are often conditioned with reduced-intensity chemotherapy (RIC) regimens. This can be associated with increased relapse rates especially in patients with active disease prior to HCT.[9] TMLI has been successfully added to established RIC regimens to reduce relapse rates with acceptable toxicities and with promising results. With a median follow-up of 7.4 years, TMLI 12 Gy added to the RIC regimen of fludarabine and melphalan was associated with a 5-year OS and EFS of 42% and 41%, respectively, which is superior to historical results where 3-year OS rates are less than 20%.[72,86-88] TMLI has also been utilized with radiolabeled antibody conditioning, which recently

reported a 6-month EFS of 26%.[89] Dose-escalated TMI has also been combined with fludarabine and busulfan, reaching a recommended phase II dose of 6 to 9 Gy in older patients.[90,91] Combining 9 to 12 Gy TMI with RIC regimens in patients who have recurred after prior allogeneic HCT also demonstrates promise.[92,93]

Transplants are now possible with haploidentical donors using posttransplant cyclophosphamide and other strategies to reduce GVHD.[94,95] Initial regimens used low-dose 2 Gy TBI.[94] To further reduce relapse rates, myeloablative doses of TMLI up to 20 Gy have successfully been incorporated into haploidentical HCT regimens.[96,97] Phase II studies are ongoing.

Recent studies have evaluated TMI and TMLI as a replacement for standard TBI in patients with acute leukemia in complete remission.[83,98-101] TMLI 20 Gy and posttransplant cyclophosphamide were associated with reduced moderate-to-severe GVHD (11%), no grade 3 to 4 toxicities, no treatment-related deaths, and 2-year OS of 86.7%, RFS of 83.3%, and GVHD-free/relapse-free survival (GRFS) of 59.3%.[98] This was superior to the 2-year GRFS of 39% and RFS of 62% with TBI and Cy or vincristine and prednisone (VP)-16 at the same institution.[102] Similar conclusions were reached with a study of TMLI 12 Gy with cyclophosphamide or etoposide, which reported a superior 1-year GRFS of 67.5% and time to engraftment compared to historical results with TBI at the same center.[100] TMI 12 Gy + cyclophosphamide has also been evaluated in older patients with acute leukemia in remission.[101]

IMRT is also being used to deliver standard TBI dose distributions with reduction in dose to the lungs and, at some centers, to the kidneys (Table 15.4). IMRT offers the advantage of eliminating the inaccuracy of positioning transmission blocks, better organ sparing, and reduced toxicities.[60,103-105] A recent analysis of patients receiving conventional TBI demonstrated a significant increase in OS if mean lung dose was 8 Gy or less.[106] As with conventional TBI, a limitation of IMRT TBI is the inability to dose escalate and treat older patients.

TABLE 15.4 SELECT IMRT TBI STUDIES

Study Year Type	*N*	Disease Type	TMI Dose (Gy) (Fraction) Chemotherapy GVHD Prophylaxis	PTV and OAR Dose Constraints	Device Dose Rate PTV and Organ Doses Delivered	Clinical Outcomes
Gruen et al[158] 2013 Prospective pilot study	10	AML, ALL CR high risk, R/R Mean age 12.9 (4-22)	12 Gy (2 Gy bid)	PTV 95% receives Rx dose Lung—mean dose ≤10 Gy; minimum dose 8 Gy	Tomotherapy PTV—mean D95 11.7 Gy PTV—mean coverage 97.5% Mean lung dose	1-5 mo f/u No grade 3-4 toxicity 8/10 CR

Study Year Type	*N*	Disease Type	TMI Dose (Gy) (Fraction) Chemotherapy GVHD Prophylaxis	PTV and OAR Dose Constraints	Device Dose Rate PTV and Organ Doses Delivered	Clinical Outcomes
					9.27/9.25 Gy left/right	
Corvo et al[159] 2011 Prospective pilot study	15	AML, ALL CR1, CR2, CR3 Median age 35 (18-55)	12 Gy AP/PA TBI with lung blocks (2 Gy bid) followed by TMI bone 2 Gy Cy CsA, MTX	Lung—mean dose ≤10 Gy with TBI	Tomotherapy For TMI PTV—mean D95 93.3% For TMI median OAR dose reduced 30%-65% of TMI Rx dose Median lung dose (TBI + TMI) 11.0 Gy Median kidney dose (TBI + TMI) 12.7 Gy	Median 310 d f/u NRM 3/15 10/15 alive NED Grade III aGVHD 3/15 Severe cGVHD 2/15
Jiang et al[160] 2018 Prospective pilot study	14	ALL CR1, CR2, PR, R/R Haploidentical Median age 22.5 (12-50)	10 Gy TBI 12 Gy SIB to bone, CNS and extramedullary sites 3.33-4 Gy/d Cy CsA, MTX, MMF	PTV 80% receive 10 Gy Lung—mean dose ≤8 Gy; minimum dose 6 Gy	Tomotherapy PTV—median D95 8.2 Gy (7.5-9.0) PTV—median Dmean 11.4 Gy (10.1-12.2) Median lung dose 7.43/7.42 Gy left/right Median kidney dose 11.0/11.1 Gy left/right	Median f/u 14.6 mo (4-28) Grade 3 mucositis 4/14 NRM 4/14 patients 10/14 alive NED 1-y OS and DFS 70.7% 90-d grade 2-4 aGVHD 38.5% 1-y cGVHD 25.3%
Kobyzeva et al[161] 2021 Retrospective study	220	ALL, AML, NHL, CR1, CR2, CR3, >CR3, active disease Pediatric Median age 10 (3-21) Haploidentical (88%)	12 Gy (2 Gy bid or 3 Gy/d) SIB to bone marrow to 15 Gy in 29 patients Flu, TT, VP-16 TCR$\alpha\beta$/CD19-depleted grafts	PTV mean dose 12 Gy PTV D98% >11.4 Gy Lung V8 <40% Lung D99% >6 Gy Kidney Dmean <8 Gy	179 Tomotherapy and 41 VMAT Elekta PTV Dmean 12.05, 12.16 Gy Lung left Dmean 7.88 Gy, 7.62 Gy Lung right Dmean 7.84 Gy, 7.57 Gy	Median f/u 2.8 y 1/191 (0.4%) pneumonitis 3/29 (10%) VOD in patients with SIB OS 63%, EFS 58% TRM <100 d 5%; >100 d 5.7%;

Study Year Type	N	Disease Type	TMI Dose (Gy) (Fraction) Chemotherapy GVHD Prophylaxis	PTV and OAR Dose Constraints	Device Dose Rate PTV and Organ Doses Delivered	Clinical Outcomes
				Lens as low as possible	Kidney left Dmean 7.44 Gy, 7.31 Gy Kidney right 7.49 Gy, 7.40 Gy	cumulative incidence TRM 10.7%
Konishi et al[162] 2022 Prospective study	39	ALL, CML, AML, mixed phenotypic acute leukemia, NHL, HL CR (33 patients); active disease (6 patients) Median age 44 (19-54)	12 Gy (2 Gy bid) Cy CsA or tacro and MTX or MMF	Mean lung dose <8 Gy Lung D2% <12 Gy Mean kidney dose <10 Gy Kidney D2% <12 Gy Mean lens dose <6 Gy Lens D2% 10 Gy	Tomotherapy Mean lung dose 7.5 Gy Mean kidney dose 9.11 Gy	Median f/u 935 d 2-y OS 69%, 2-y DFS 64% 2-y NRM 18% Chronic renal disease in six patients No pneumonitis No grade 3-4 aGVHD 1 patient severe cGVHD

Listed at www.clinicaltrials.gov.

aGVHD, acute graft-versus-host disease; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; AP/PA, anteroposterior/posteroanterior; bid, twice per day; cGVHD, chronic graft-versus-host disease; CNS, central nervous system; CR, complete remission; CR1, first complete remission; CR2, second complete remission; CR3, third complete remission; CsA, cyclosporine; Cy, cyclophosphamide; DFS, disease-free survival; Dmean, mean dose; EFS, event-free survival; Flu, fludarabine; f/u, follow-up; HL, Hodgkin lymphoma; IMRT, intensity-modulated radiation therapy; MMF, mycophenolate mofetil; MTX, methotrexate; NED, no evidence of disease; NHL, non-Hodgkin lymphoma; NRM, non-relapse mortality; OAR, organ at risk; OS, overall survival; PR, partial response; PTV, planning tumor volume; Rx, prescription; tacro, tacrolimus; R/R, relapsed/refractory; SIB, simultaneous integrated boost; TBI, total body irradiation; TMI, total marrow irradiation; TRM, treatment-related mortality; TT, thiotepa; VMAT, volumetric modulated arc therapy; VOD, venous occlusive disease; VP-16, etoposide.

To date, hundreds of patients have received TMI and TMLI at multiple centers. Initial concerns regarding TMI have not been realized. Toxicities have been lower than reported for standard TBI. Shinde et al[107] reported a cumulative incidence of pneumonitis, nephropathy, cataract formation, and hypothyroidism of 0.7%, 0%, 7%, and 6%, respectively, in patients receiving TMI or TMLI up to 19 Gy. Mean lung dose of 8 Gy or less was associated with a significant reduction in lung infection and pneumonitis. Kim et al[108] reported no increase in extramedullary relapse rates when compared to TBI, suggesting that organ sparing does not increase relapse rates. There

has been no increase in non-engraftment with myeloablative doses of TMI. This collective experience suggests that the higher dose rates with TMI do not increase toxicities. This can be explained by preclinical[109,110] and clinical studies,[111] which demonstrate that dose rate effects are primarily seen below 30 cGy/min and become nonsignificant above approximately 50 cGy/min.

In summary, TMI expands the use of RT to a new population of patients undergoing HCT. Dose-escalated TMI regimens in younger patients and myeloablative TMI added to RIC regimens in older patients demonstrate superior results compared to current standard of care and should be further evaluated in multicenter studies. For patients with acute leukemia in remission, TMI or some form of multiorgan-sparing TBI may eventually replace conventional TBI given the promising results seen with TMI in this population.

Acute and Late Toxicities

Side effects from TBI in the setting of SCT have complex interactions with cytotoxic drugs and posttransplant immunosuppressive agents. In addition, GVHD has its own unique toxicities, which have complex interactions with the conditioning regimen. Infectious complications are also prevalent after transplant and subject to variable prophylactic treatment regimens. Isolating which toxicities are strictly related to TBI is not always straightforward.

Low-Dose Total Body Irradiation (Non-myeloablative Regimens)

With TBI-based non-myeloablative regimens, 2 Gy in a single fraction being commonly employed, the chief side effect immediately after treatment is nausea and vomiting, which can be ameliorated using prophylactic antiemetics. The primary long-term risk is cataract development, which can be corrected surgically. The risk of injury to other normal organs with a single 2 Gy fraction is probably very low.

Non-myeloablative regimens seem to be associated with less acute and long-term toxicity relative to myeloablative regimens.[112] This is particularly notable for noninfectious pulmonary toxicity. A number of studies have demonstrated reduced rates of noninfectious pulmonary toxicity following non-myeloablative regimens. Fukuda et al[113] first demonstrated a significantly lower risk of idiopathic pneumonia syndrome following non-myeloablative conditioning compared to myeloablative regimens for both malignant and nonmalignant indications at a single institution. A large study involving 21,574 patients from the Center for International Blood and Marrow Transplant Research showed that non-myeloablative TBI-based conditioning was associated with decreased risk of noninfectious pulmonary toxicity on multivariable analysis.[114]

Full-Dose Total Body Irradiation (Myeloablative Regimens)

Acute Toxicity

Nausea, vomiting, and diarrhea are the most common early side effects when a single fraction of 8 to 10 Gy TBI is given. Xerostomia, headaches, fevers, and hypertension were historically reported in roughly half of patients receiving single- fraction TBI.[115] The use of fractionated TBI reduces the incidence as well as the severity of these and other side effects. Moreover, fever and hypertension are rarely seen with fractionated TBI. Patients can also develop a transient xerostomia, reduction in tear formation, and mucositis within 10 days. Reversible alopecia develops at approximately 2 weeks in all patients. Parotitis, which usually occurs after the first day of irradiation and subsides within 24 to 48 hours, is unique to TBI and is very common with single-fraction RT but occurs in less than 10% of cases with fractionated regimens.[116]

Nausea may be controlled with the use of serotonin receptor-3 antagonists, as shown in several small randomized trials.[117,118] Mucositis, resulting from both radiation and chemotherapy, may be ameliorated by good dental hygiene[119] along with a variety of topical agents. Recombinant human keratinocyte growth factor was found to reduce mucositis after TBI and intensive chemotherapy, resulting in reduced narcotic and parenteral nutrition usage in one auto-SCT study.[120] Despite such supportive care, parenteral nutrition and narcotics are often necessary.

Late Toxicity

Lung. Interstitial pneumonitis is the major dose-limiting toxicity for TBI. Reduction in the risk of pneumonitis by fractionation is supported by the previously described randomized clinical trial comparing single-fraction TBI (9.2 or 10 Gy) with fractionated TBI (12 Gy in six fractions over 3 days) for patients with AML in first remission. This study demonstrated a significant improvement in EFS with fractionation, primarily due to a reduction in early mortality. Interstitial pneumonitis was decreased from 26% to 15% with fractionation.[12] Another radiobiologic approach to reduce the incidence of interstitial pneumonitis is to lower the radiation dose rate. Within the context of fractionated TBI schemes, instantaneous dose rates of 5 to 20 cGy/min have been generally employed and are often determined by the available output of linear accelerators at extended treatment distances. It is unclear whether or not higher instantaneous dose rates are detrimental despite theoretical concerns in this regard. Several nonrandomized studies have demonstrated an association between higher dose rates and the development of pulmonary toxicity, including interstitial pneumonitis.[121,122] Other studies have not shown dose rate to be an important predictor of pneumonitis from fractionated TBI, but rather total dose to the lung is the more critical determinant.[60]

Pneumonitis in the transplant setting has a multifactorial etiology, reflecting not only the effects of radiation but undoubtedly the effects of prior chemotherapy exposure,[35] underlying performance status, GVHD, baseline lung function,

development of opportunistic infections, patient age, and other risk factors. Many chemotherapy drugs are known to injure the lung. GVHD may cause lung injury directly and the drugs used to control GVHD may also cause pulmonary toxicity. T-cell-depleted transplants tend to have lower risk for pneumonitis.[123]

Lens. The lens of the eye is one of the most radiation-sensitive structures in the body. The risk of developing cataracts is markedly reduced with fractionation. For example, Ozsahin et al[124] calculated a difference in the 5-year estimated cataract incidence between single-fraction TBI (39%) and fractionated TBI (13%) while also showing a beneficial effect of lower dose rate. Studies also show that older age is associated with faster time to onset of cataract formation independent of TBI regimen dose.[112] Steroid therapy is also an independent risk factor for cataract formation after SCT, even in the absence of TBI. Lens shielding during TBI is not recommended because of the risk of retro-ocular relapse of leukemia but is a consideration in aplastic anemia and other non-neoplastic diseases managed with SCT.

Growth and Gonadal and Endocrine Effects. Almost all children who undergo bone marrow transplantation with TBI experience decreased growth velocity, which is less with fractionated than single-dose TBI.[125] Growth hormone deficiency may be detected in 34% of adults who received TBI in their childhood. Other endocrine effects in this setting include Leydig cell dysfunction in 23% and primary hypothyroidism in 34%.[126] High-dose TBI produces primary gonadal failure in almost all patients, but recovery may occur in females.[127] In children, puberty is usually delayed but can be induced by appropriate hormone replacement. Thyroid dysfunction is reported in as many as 43% of patients after TBI.[125] Subclinical hypothyroidism is the most common picture, with elevated thyroid-stimulating hormone but normal thyroxine levels. The incidence of thyroid dysfunction is lower when hyperfractionated TBI is used.[128]

Liver. Hepatic VOD has been renamed SOS given the recognition that this clinical problem, principally seen in myeloablative transplants, is an endothelial injury to hepatic sinusoids and hepatocyte injury and hepatic thrombosis are secondary late-stage effects. This syndrome, accounting for significant morbidity and mortality in high-dose transplant regimens, is characterized by hepatic enlargement, ascites, jaundice, encephalopathy, and weight gain. SOS, which needs to be distinguished from cholestatic drug injury and acute GVHD, is best diagnosed by transvenous hepatic biopsy where an elevated hepatic venous pressure gradient is documented along with characteristic histology showing hepatic sinusoidal and central vein fibrosis and accompanying hepatocyte necrosis. The etiology of VOD/SOS is thought to be related to acrolein, a cyclophosphamide metabolite also implicated in causing hemorrhagic cystitis, which acts as an endothelial toxin. Other toxic agents give rise

to this disease, but in the transplant setting, TBI, busulfan, cytosine arabinoside, and preexisting or concomitant liver disease are risk factors, possibly due to depletion of intracellular glutathione levels or matrix metalloproteinase activity. TBI-based regimens are associated with lower rates of VOD/SOS compared with regimens employing only chemotherapy.

The incidence of VOD/SOS has been minimized by fractionating TBI and keeping total doses below 13.2 Gy. The Seattle group has reported considerably more VOD/SOS after 10-Gy single-fraction TBI than after 12-Gy fractionated TBI in a randomized trial.[12] A lower dose rate may also reduce the risk. Prevention strategies for VOD/SOS include the administration of low-molecular-weight heparins and ursodiol as part of the pretransplant supportive care regimen. In one well-designed clinical trial, ursodiol prevented cholestatic liver injury and GVHD, but had no effect on VOD/SOS.[129] Standard of care treatment is defibrotide, a single-stranded polydeoxyribonucleotide drug with antithrombotic and anti-ischemic properties.

Kidney. Renal toxicity has been underreported as a major late complication of SCT. A report by Tarbell et al[130] in 1988 showed a 35% rate of renal dysfunction in patients with ALL receiving transplants. More contemporary reports place this risk at ~17%, influenced by the use of TBI, cyclosporine for immunosuppression, and presence of significant GVHD.[131] Because transplant patients also receive various nephrotoxic drugs (etoposide, teniposide, amphotericin B, aminoglycoside antibiotics) before, during, and after intensive cytoreductive therapy, the contribution of TBI to renal dysfunction can be difficult to determine. GVHD also has complex interactions with TBI in affecting the risk of transplant-related nephritis. Studies suggest that TBI and chronic GVHD are risk factors for posttransplant chronic kidney disease.[131,132] Miralbell et al[133] showed a high risk of renal dysfunction after TBI, independent of the presence or absence of GVHD. Some transplant programs have reduced the dose to the kidneys using partial transmission blocks and have suggested that such a strategy decreases the risk of posttransplant nephropathy.[134]

Secondary Cancers. The risk of developing a secondary malignancy 15 years after intensive chemotherapy and radiation followed by SCT is estimated to be 6% to 20%.[135-137] The risk of developing a secondary malignancy is approximately 4 times higher than the general population. A large series from combined registries of the International Bone and Marrow Transplant Research Centers and the Fred Hutchinson Cancer Research Center observed 189 solid cancers among 28,874 transplant patients, more than 6,000 of whom had survived more than 5 years.[138] Two-thirds of this cohort received RT as part of their conditioning and this was a major determinant for secondary cancer development along with chronic immunosuppression. Chronic GVHD and male age increased the risk for squamous cell cancers. Common posttransplant nonsquamous cell cancers included melanoma, cervical or uterine

cancer, thyroid cancer, breast cancer, and gliomas. Patients less than 30 years of age at the time of treatment had an approximately 9-fold increased risk for nonsquamous cell cancers over those who did not receive RT. Myelodysplastic syndrome and AML are the most common secondary tumors in patients treated for lymphoid malignancies. Patients who are older, who experienced acute GVHD, who were treated with antithymocyte globulin or anti-CD3 antibodies, or who receive TBI are at greatest risk. Some lymphoproliferative disorders that occur after allo-SCT are associated with Epstein-Barr virus and may be successfully managed with anti–B-cell antibodies such as rituximab, adoptive immunotherapy, or donor lymphocyte transfusions.

HEMIBODY IRRADIATION

Though utilized less frequently at present, HBI has been used for many years to palliate widely metastatic solid tumors, typically diffuse symptomatic bone metastases, often very late in the course of the disease. As the field of medical oncology has developed a larger array of systemic therapies for disseminated cancers, this form of RT has been less frequently employed.

Applications

Patients with osseous metastases tend to have multiple sites of disease, often with multiple painful areas that can be challenging to treat efficiently with conventional RT. The pain relief produced by single-fraction HBI for skeletal metastases is prompt, with nearly 50% of all responding patients doing so within 48 hours and 80% within 1 week after treatment.[139,140] More than 70% of treated patients experience pain relief as documented in a number of studies including various Radiation Therapy Oncology Group (RTOG) trials from the 1980s.[139,141] The most effective HBI dose found by the RTOG was 6 Gy for upper HBI and 8 Gy for middle and lower HBI. Doses beyond these levels do not appear to increase pain relief, duration of pain relief, or rapidity of response.

When treatment of the other half of the body is also indicated, it is advisable to wait 6 to 8 weeks to allow sufficient recovery of blood cells and irradiated marrow. Planned sequential upper and lower HBI 6 to 8 weeks apart has been used to treat multiple myeloma, malignant lymphoma, and other widely disseminated tumors. HBI should be utilized for symptomatic disease only. For example, a randomized trial in multiple myeloma did not support routine use of HBI as part of an overall treatment plan. In this trial, patients were initially treated with chemotherapy. Eligible patients were then randomized to 1 year of vincristine, melphalan, cyclophosphamide, and prednisone (VMCP) versus sequential HBI with VP. RFS and OS were better with VMCP than with HBI ($P = .04$ and $P = .018$, respectively).[142]

Technique

The physical considerations for HBI are similar to those for TBI. The field size required for HBI is much smaller than that for TBI, and HBI can often be delivered on a conventional linear accelerator, albeit using extended distances. The desired field can be customized based on the distribution of disease that requires palliation though classic fields have been described.[143] Treatment is traditionally delivered using AP/PA parallel-opposed fields. The patient is positioned with a vertical beam allowing coverage of the hemibody and the treatment table is lowered to the appropriate level or to the floor. Shielding of previously irradiated areas or other body regions to reduce toxicity, such as the salivary glands and the lungs, may be employed. The dose is prescribed to the midplane of the patient at the central axis of the beam.

Complications

In general, HBI is well tolerated. The most common side effects associated with single-dose HBI are nausea and vomiting, mainly when the abdomen is included within the fields. These occur shortly after radiation administration and last a few hours. Premedication with steroids and antiemetics is highly recommended. As these patients are frequently anorexic or cachectic from their underlying illness, dehydration and need for intravenous fluids are common with HBI and hospitalization for supportive care may be desirable. A series from the University of Maryland examined single-fraction HBI with escalating doses of 4 to 10 Gy, split-course HBI with two 4-Gy fractions separated by 2 weeks, and daily fractionated HBI with 15 Gy given in five fractions.[144] Fractionated HBI was found to be more acutely tolerable, similar to the experience with TBI. A subsequent randomized study demonstrated that a total dose of 6 Gy given over 2 days (3 Gy/fraction) was similarly efficacious.[145] Diarrhea occurs commonly when a significant volume of the intestines is irradiated and may last for several days. The severity of this side effect can be reduced utilizing lower doses. The risk of pneumonitis is very low if the single-fraction dose to the whole lungs is limited to 7 Gy (uncorrected for air density). If 8 Gy is delivered to the upper body, partial transmission lung block to limit the lung dose at 6 to 7 Gy is recommended. Hematologic recovery usually occurs in 4 to 6 weeks.

TOTAL LYMPHOID IRRADIATION

TLI was originally designed to treat Hodgkin lymphoma. TLI consists of a mantle field (encompassing all major supra- diaphragmatic lymph node regions) matched to an inverted-Y field (encompassing the spleen and major infra-diaphragmatic lymph node regions with the inferior extent including the inguinal lymph nodes) (Figure 15.5). A small gap is placed in-between these two fields. Using three-dimensional techniques, an extended SSD (eg, 120 cm) is necessary for the inverted-Y field given

its greater longitudinal dimensions but an SAD (source-to-axis) approach is almost always suitable for the mantle field. TLI can also be treated using more advanced techniques such as IMRT/VMAT or helical tomotherapy.[146]

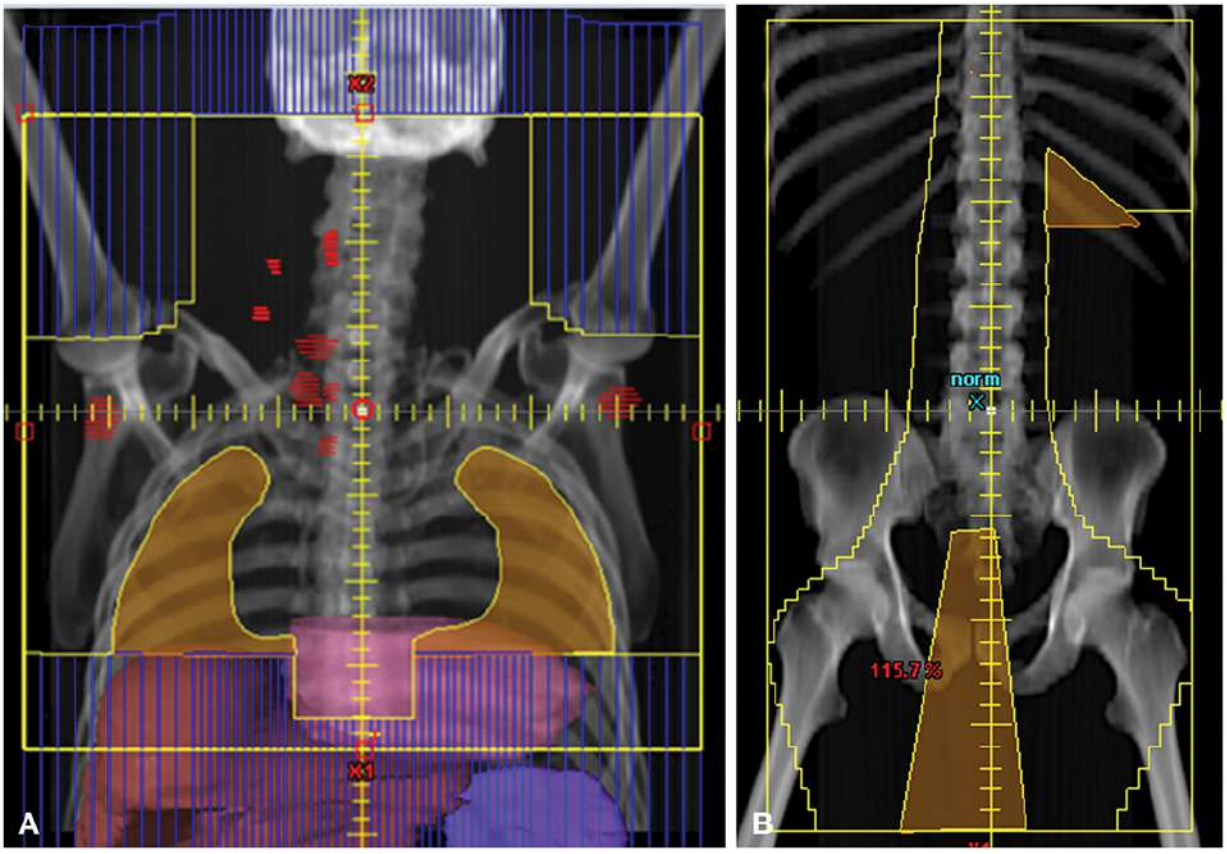

FIGURE 15.5 Total lymphoid irradiation fields including a mantle field (A), which encompasses all of the major lymph node bearing areas above the diaphragm, matched to an inverted-Y field (B), which encompasses the spleen and the major lymph node bearing areas below the diaphragm.

While uncommonly utilized at present, TLI has been investigated in numerous clinical scenarios with extensive published literature. First, while TLI is no longer employed for newly diagnosed Hodgkin lymphoma, it has been combined with high-dose chemotherapy prior to autologous SCT in relapsed and refractory disease.[147] Second, as discussed earlier, some centers are investigating replacing TBI with TMLI. In this circumstance, not only is the entire marrow space included in the clinical target volume but also the lymph node chains and spleen that would be encompassed in classic TLI fields. Some studies have used TLI alone with chemotherapy prior to non-myeloablative allogeneic SCT.[148] Third, TLI is occasionally used in the solid organ transplant setting as an immunosuppressive agent that can replace immunosuppressive medications.[149] Patients suffering from progressive bronchiolitis obliterans syndrome after lung transplant have been treated with TLI with some success.[150] Fourth, TLI has

been explored in the past as an immunosuppressive agent in intractable rheumatoid arthritis.[151] Fifth, TLI has been used for drug-resistant chronic GVHD.[152] Finally, in select patients, TLI can be utilized as an effective cytoreductive agent prior to allogeneic SCT in patients with lymphoma (eg, CLL/small lymphocytic lymphoma).

At our center, we have primarily utilized TLI in the setting of relapsed/refractory Hodgkin lymphoma when the disease involves diffuse lymph node regions on both sides of the diaphragm and for the occasional young patient with CLL, with RT being used to achieve a minimal residual disease state prior to allogeneic transplant. While total doses will vary depending upon the clinical scenario, we generally treat with small daily doses (eg, 1.5 Gy) with prophylactic antiemetics to decrease the risk of treatment-induced nausea.

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CHAPTER 16

Stereotactic Irradiation of Tumors of the Central Nervous System

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Stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT) are techniques to administer precisely directed, high-dose irradiation that tightly conforms to a well-defined target to create a desired response while minimizing radiation dose to surrounding normal tissue. Compared to conventional radiotherapy with standard 5- to 20-mm treatment margins allowing for patient movement and setup error, stereotactic techniques reduce complication risks for any radiation dose delivered by minimizing or eliminating normal tissue treatment margins. Table 16.1 lists the key requirements for successful stereotactic irradiation. Significant advances in diagnostic imaging, treatment planning, and radiation delivery systems have led to the development of a variety of different SRS/radiotherapy techniques and broader applications. This chapter will review the role of SRS and SRT for benign and malignant neoplasms as well as functional indications within the central nervous system (CNS).

TABLE 16.1 KEY REQUIREMENTS FOR OPTIMAL STEREOTACTIC IRRADIATION

Requirement	Rationale
Small target/treatment volume	Reducing the volume of normal and target tissue irradiated to high doses improves tolerance.
Sharply defined target	Sharply defined targets can be treated with little or no extra margin of surrounding normal tissue and/or without unintentional underdosage of the target (marginal miss).
Accurate radiation delivery	No margin of normal tissue needed for setup error and/or reduced chance of underdosing target
High conformality	Reduces the treatment volume to match the target volume

Requirement	Rationale
Sensitive structures excluded from target	Dose-limiting structures (optic chiasm, spinal cord, etc) should be able to be defined and excluded from the target volume to limit the risk of radiation injury.

TERMINOLOGY

Stereotactic refers to using a precise three-dimensional mapping technique to guide a procedure. The terminology used in stereotactic irradiation can be confusing. The term *radiosurgery* or *stereotactic radiosurgery* (SRS) is best used for stereotactically guided conformal irradiation of a defined target volume in a single session but may also be used for two to five sessions, although *fractionated stereotactic radiosurgery* (fSRS) is a clearer description of that use. Radiosurgery or SRS can be delivered with Gamma Knife, modified linear accelerator (LINAC) radiosurgery systems (including CyberKnife and image-guided radiotherapy systems), TomoTherapy, or proton beam systems. The terms *stereotactic radiation therapy* (SRT), *stereotactic body radiotherapy* (SBRT), and *stereotactic ablative radiotherapy* can be used to refer to stereotactically guided delivery of highly conformal radiation to a defined target volume in six or more fractions, typically using noninvasive positioning techniques; however, they are often used with treatment courses with two to five fractions as well. Adding specific references to intensity-modulated radiation therapy (IMRT) to the nomenclature can further complicate or confuse the terminology. Any radiation treatment plan that uses individual treatment beams that irradiate only part of the target at a time is IMRT. Strictly speaking, multiple-isocenter radiosurgery (of a single target volume) meets the criteria for IMRT or stereotactic IMRT (SIMRT), although the term SIMRT is usually only used when multileaf collimators are employed. The terminology is useful to distinguish when the same LINAC is equipped to treat with either fixed circular collimators for radiosurgery (SRS or SRT mode) or to deliver IMRT using multileaf collimators (SIMRT mode).

RADIOBIOLOGIC CONSIDERATIONS

Before the introduction of radiosurgery, essentially all clinical irradiation was administered with radiation dose fractions between 1.2 and 3 Gy for intracranial targets. Extracranial targets were usually treated with 1.2- to 4-Gy fractions, and 6- to 8-Gy fractions were used occasionally to treat bone metastases or malignant melanoma. Before the adoption of radiosurgery into the clinic in the late 1980s, most radiation oncologists and radiation biologists believed that fractionating radiation treatment decreased the relative risk of injury to normal tissue compared to tumor in essentially all circumstances. Radiobiologic analysis of a limited number of malignant tumors in cell culture and clinical experience with conventionally fractionated radiotherapy of fast-growing malignant tumors established this radiobiologic dogma. Increasing the fractionation of radiotherapy for slow-growing benign tumors may not necessarily improve the balance between tumor control and radiation complication, however. Slow-growing benign tumors are challenging to study in either cell culture or animal models, so the effect of fractionation has not been well described. SRS allowed clinicians to administer high doses of radiation to intracranial targets with relative safety, thereby leading to a new appreciation of the underlying radiobiology. Laboratory studies suggest that the radiation response for the high-dose single fraction used in radiosurgery is likely related to the supporting endothelial cells.[1,2] Pathology studies of benign and malignant tumors treated by radiosurgery also support a vascular response dominated by the response of endothelial cells.[1-3] In addition to vascular effects, radiosurgery has been associated with immune modulatory effects creating antitumor immunity.[2,4-8]

RADIOSURGICAL TECHNIQUES

Gamma Knife Radiosurgery

After Leksell's initial experiences with stereotactic treatment using orthovoltage radiotherapy in 1951 and proton beam irradiation in 1957, Leksell and Larson created the first prototype of the Gamma Knife in 1967. The Gamma Knife uses a relatively hemispherical array of multiple fixed Cobalt-60 (Co-60) beams (201 in most models) that are sharply collimated to create small, relatively spherical treatment volumes of varied diameter with sharp dose falloff. The earlier model was originally referred to as the U

(for university) style and contained cobalt sources arranged in a hemispherical array, including sources at the pole of the hemisphere. These units present challenging loading and reloading issues with the cobalt-60 sources, particularly with radiation protection. To eliminate this problem, the B-unit (named after Bergen, Norway, the first site) was redesigned to arrange sources in an annular section of a hemisphere, similar to the northern hemisphere with the Arctic Circle excluded. In 1999, the Model C version of the Gamma Knife was introduced with the option to use robotic positioning to set treatment coordinates. This expedited the execution of multiple-isocenter treatment plans. Manual positioning was still needed for some targets away from the center of the head. The Model 4-C, introduced in 2005, was equipped with enhancements designed to improve workflow, increase accuracy, and provide integrated imaging capabilities. The Perfexion model introduced in 2006 uses a larger patient aperture and internally mounted secondary collimators that can be blocked or treated with different diameters of 4, 8, or 16 mm for any of eight different sectors around the circumference of the unit. Because of the larger patient aperture, the Perfexion unit is able to treat all intracranial and even C1-2 level spine targets quickly and efficiently with robotic positioning.

The latest version, the Icon unit, is equipped with a cone-beam computed tomography (CT) scan for use with a frameless thermoplastic mask system with infrared patient position monitoring to facilitate fSRS. Clinical experience with the Icon unit has found that despite the relatively tight thermoplastic immobilization mask used, patient motion exceeding 1.0- or 1.5-mm total deviation (requiring repeat cone-beam CT for realignment) tends to occur more frequently with treatments over 30 minutes and in patients who fall asleep during treatment. Patients requiring longer treatments or sedation are more easily treated with stereotactic frame-based techniques with this unit. In addition to reducing patient motion, another advantage of using a magnetic resonance (MR)-compatible stereotactic frame is to eliminate error (though usually small) from MR to CT image coregistration.

Rotating Gamma System

A radiosurgery device called the rotating gamma system (RGS) was developed in China. The RGS (OUR International Inc, Shenzhen, China) employs 30 cobalt-60 radiation sources in a revolving hemispherical shell. The secondary collimator is a coaxial hemispheric shell with six groups of five different collimators to produce spherical treatment volumes of varying sizes. The experience with this system is somewhat limited.

Proton Radiosurgery

The chief advantage of charged proton radiosurgery is that the beams stop at a depth related to the beam's energy. Electron beams also use charged particles but lack the sharp beam edge of the proton beam. The lack of an exit dose and the sharp beam profile of protons allow target irradiation with lower integral doses than are delivered with photon (LINAC x-ray or cobalt-60 gamma) irradiation. An unmodified proton beam deposits increased energy in the last 2 mm of the path length. This area of increased ionization, where cell killing is even higher because of an increased radiobiologic effect, is termed the Bragg peak or Bragg-Gray peak. To allow homogeneous irradiation of targets greater than a millimeter or two, the Bragg peak is spread out throughout the target or modulated with differing beam energies. The first treatment of a malignant tumor by irradiation with a proton beam Bragg peak was carried out in 1957, followed by functional neurosurgery done for advanced Parkinson disease in 1958. Presently, proton beam irradiation is available at a limited number of centers because of the high cost of equipment and maintenance.

Linear Accelerator Radiosurgery

The pioneering work of many researchers in the 1980s led to the gradual modifications of LINACs designed for conventional radiotherapy to be used for radiosurgery. LINAC technologies were modified by incorporating improved guiding (stereotactic) devices and methods to measure and improve the accuracy of various components. Most early LINAC-based radiosurgery techniques used multiple radiation arcs with circular secondary collimators to create spherical dose distributions for stereotactically defined 3-D targets. Improved hardware and advanced dose planning software have been developed to enhance conformity. These include beam shaping with

micromultileaf collimators and intensity modulation with inverse treatment planning algorithms. Many LINAC-based systems are commercially available. Most are modifications of standard LINACs equipped with more precise treatment couches and highly stable treatment isocenters, usually with cone-beam CT scans for targeting and often with patient monitoring systems.

The CyberKnife combines a miniaturized LINAC mounted on an industrial robot with a system for orthogonal x-ray target tracking and beam realignment. This system utilizes a 6-MeV LINAC with different-sized circular collimators attached to a six-axis robotic manipulator. Stereotactic frames are not normally used for targeting. CyberKnife plans employ multiple fixed beam positions and multiple isocenters. Before the radiation is delivered from any beam position, the target position is tracked using an integrated x-ray image processing system (IPS) consisting of two orthogonal diagnostic x-ray cameras and an optical tracking system. During treatment, the IPS acquires x-ray images of the patient's body multiple times throughout the treatment, while stealth tracking software compares the actual images with the target images to correct the alignment of the beam. The tracking interval is set by the user with many CyberKnife centers, usually using 1-minute intervals.

There are some other LINAC radiosurgery systems that have the capability for intratreatment patient movement monitoring and correction and others that do not. The combination of diagnostic 3-D imaging with highly conformal treatment delivery in a single unit to maintain accuracy is the basis of various treatment techniques and processes collectively known as image-guided radiation therapy (IGRT). Most IGRT techniques add CT imaging capability to a LINAC radiotherapy unit equipped for stereotactic and IMRT use. Because any patient movement between image acquisition and treatment delivery can introduce error, these IGRT systems utilize noninvasive immobilization devices and patient position tracking systems. Several manufacturers currently offer IGRT using LINAC technology capable of delivering SRS and radiotherapy.

TomoTherapy

TomoTherapy, literally “slice” therapy, is a form of radiotherapy that modifies the design of a diagnostic CT scan into a treatment delivery machine, thereby combining the precision of CT imaging with radiation treatment. This is done by adding a LINAC megavoltage treatment beam to the rotating x-ray source and moving table design of a diagnostic CT unit, which normally uses only a kilovoltage diagnostic x-ray beam. Unlike traditional radiation therapy systems with a slow-moving external gantry designed for positioning individual beams onto the tumor from a few different directions, TomoTherapy rapidly rotates the beam around the patient, thus allowing the beam to enter the patient from many different angles in succession. Beam intensity modulation (IMRT) is possible through a multileaf collimator system. The inclusion of CT imaging technology within the TomoTherapy unit allows precise target localization before and during treatment.

NORMAL TISSUE TOLERANCE IN CENTRAL NERVOUS SYSTEM RADIOSURGERY

Radiosensitivity

Estimating the risks of a proposed treatment plan with various radiation doses is essential to treatment planning and dose prescription for SRS and SRT. The ability of normal tissue to tolerate radiation without injury depends on the radiation dose administered, the volume of tissue irradiated, the sensitivity of the tissue affected, history of any prior radiation treatment to the region, and any individual variation in radiation sensitivity between different people. With the exception of patients with known increased radiation sensitivity, such as those with ataxia-telangiectasia and collagen vascular diseases, there is usually no information routinely available to modify treatment plans for individual differences in radiosensitivity. Prior fractionated radiotherapy appears to have limited effects on the risks of developing postradiosurgery parenchymal edema and neurologic sequelae after radiosurgery but has been observed to effect optic nerve tolerance.

Radiosurgery Dose Escalation Studies

The Radiation Therapy Oncology Group (RTOG) Radiosurgery Dose-Escalation Study (90-05) established tolerance doses for radiosurgery of recurrent brain metastases and high-grade gliomas not involving the brainstem.[9] They administered radiosurgery to 156 patients with brain metastases or primary brain tumors that recurred or progressed after conventional radiotherapy following a dose escalation protocol. Starting with initial doses of 18, 15, and 12 Gy for diameters less than 20, 21 to 30, and 31 to 40 mm, respectively, they escalated prescription doses in 3-Gy intervals until irreversible toxicity was seen in over 20% of patients within 3 months. The exception was with tumors less than 20 mm in diameter, for which dose-limiting toxicity was not reached, and investigators were reluctant to escalate above 24 to 27 Gy. The recommended tolerance doses from that protocol were 24, 18, and 15 Gy for diameters less than 20, 21 to 30, and 31 to 40 mm, respectively. The data with longer follow-up beyond 3 months to assess late toxicity were fitted to individual logistic dose-response curves in Figure 16.1. These tolerance doses have been widely used as guidelines for single-fraction radiosurgery of malignant tumors, often with interpolation for tumors close to 20 and 30 mm in diameter (eg, 20 Gy for 18- to 22-mm diameter and 16.5 Gy for 28- to 32-mm diameter treatment volumes).

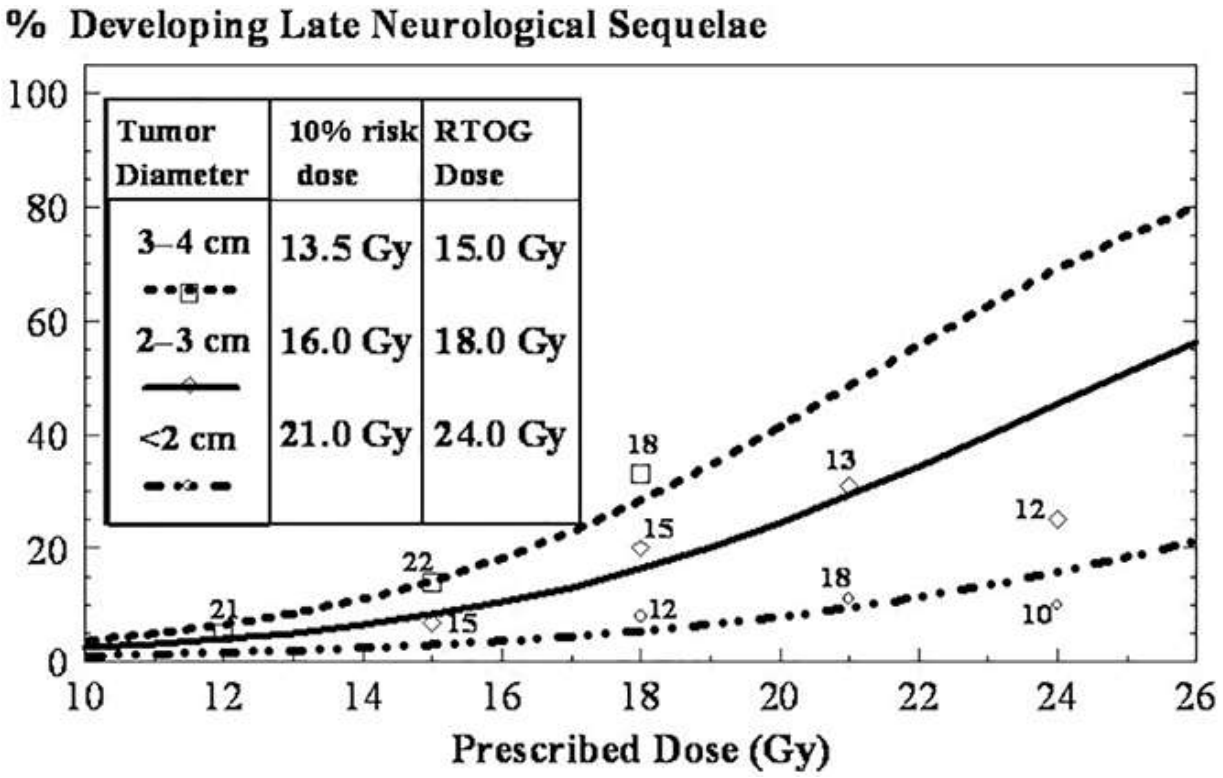

FIGURE 16.1 Phase 1 RTOG dose escalation data for radiosurgery of recurrent brain metastases and glioblastoma fit to logistic dose-response curves. The numbers at each data point indicate the number of patients in each dose/diameter group. (Derived from Dewan MZ, Galloway AE, Kawashima N, et al. Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. *Clin Cancer Res*. 2009;15[17]:5379-5388.)

Murai et al[10] performed a limited dose escalation study of CyberKnife radiosurgery of 48 brain metastases 2.5 to 4 cm in average diameter with 18 to 30 Gy in three fractions and 13 metastases greater than 4 cm diameter with 21 to 35 Gy in five fractions. Grade 1 radiation necrosis developed in 1 of 20 patients at the penultimate level of the three-fraction regimen, and grade 1/2 radiation necrosis developed in 3 of 25 patients at the highest dose level (27 to 30 Gy in three fractions, 31-35 Gy in 5 fractions).

Schwer et al[11] performed a three-fraction fSRS dose escalation study from 18 to 36 Gy in 15 patients with recurrent gliomas treated in combination with gefitinib. With a median treatment volume of 41 cm^3 (8-151 cm^3), three patients were treated at the 18, 24, and 30 Gy levels and 16 at 36 Gy. They did not identify any radiation-related toxicity.

Kim et al[12] performed a three-fraction dose escalation study of 24, 27, and 30 Gy with fractionated Gamma Knife radiosurgery for large (>3 cm) brain metastases in 60 patients. Of 48 evaluable patients, the rate of radiation necrosis was 0% in 24 Gy, 13% in 27 Gy, and 37% in 30 Gy groups, while local progression-free survival (PFS) was 65%, 80%, and 75% in each respective group. Given the high rates of radiation necrosis in the 30 Gy group, 27 Gy was considered the most effective regimen.

Clarke et al[13] reported a dose escalation study of three fractions of radiosurgery delivered with 10 mg/kg bevacizumab q2 weeks to doses of 27, 30, and 33 Gy in groups of three, five, and seven patients, respectively, with recurrent glioblastoma and anaplastic astrocytoma after prior conventional chemoradiotherapy. They identified no cases of clearly symptomatic radionecrosis, but one patient in the 33-Gy level exhibited cognitive deterioration and grade 3 fatigue, which they counted as treatment-related toxicity.

The High Dose per Fraction, Hypofractionated Treatment Effects in the Clinic (HyTEC) analysis of tumor control probability for intact brain metastases identified 56 sufficient manuscripts with over 13,000 brain metastases for analysis. Local control for tumors was stratified by RTOG 90-05 size thresholds, and for tumors less than or equal to 20 mm, single-fraction doses of 18 and 24 Gy corresponded with greater than 85% and 95% 1-year local control rates, respectively. Notably, while 18 Gy resulted in excellent local control for most tumors less than or equal to 20 mm, patients with melanoma brain metastases required a mean dose of 23.4 Gy to achieve a 90% tumor control probability. For tumors 21 to 30 mm, an 18 Gy single-fraction dose was associated with 75% local control, and for tumors 31 to 40 mm, a 15-Gy single-fraction dose yielded approximately 69% local control. For fractionated radiosurgery, three- to five-fraction remove SRS using doses in the range of 27 to 35 Gy corresponded to 80% 1-year local control for tumors of 21 to 40 mm in diameter.[14]

Radiation Necrosis

Radiation necrosis, or treatment-induced necrosis, is a delayed and often progressive form of radiation-induced inflammation or injury to normal brain tissue.[15] The pathophysiology remains unclear. It is likely mediated

due to glial and vascular endothelial cell injury and can cause a cascade of inflammatory markers, which may lead to neurologic symptoms.[16] Almost half of patients with radiation necrosis will go on to develop neurologic symptoms,[17-19] requiring medical management typically first with corticosteroids. Other noninvasive management strategies include hyperbaric oxygen therapy, pentoxifylline, vitamin E, and bevacizumab. In some cases, surgical intervention is required. For a more detailed discussion of the management of radiation necrosis, please see Chapters 107.

For single-fraction radiosurgery, the risk of radiation necrosis has been correlated dosimetrically with the volume of the brain receiving 12 Gy or more or V12Gy(cm^3). The HyTEC analysis for brain tolerance summarized 51 reports in 9,828 patients and 13,913 targets receiving radiosurgery, often for brain metastases or arteriovenous malformations (AVMs).[20] For dosimetric reporting, the brain tissue volume included both the brain and target lesions. For single-fraction SRS for brain metastases, brain tissue volume receiving V12Gy of 5, 10, or greater than 15 cm^3 was associated with risks of symptomatic radiation necrosis of approximately 10%, 15%, and 20%, respectively. For fractionated SRS for brain metastases, brain tissue volume V20Gy (three fractions) or V24Gy (five fractions) less than 20 cm^3 was associated with less than 10% risk of any radiation necrosis or edema, and less than 4% risk of radiation necrosis requiring resection. Single-fraction radiosurgery for AVM was associated with modestly lower rates of symptomatic radionecrosis for equivalent V12Gy of 10 cm^3 less than 10%; however, this did not take into account AVM location.

Prior analysis of postradiosurgery injury reactions in patients with AVM revealed no difference in the likelihood of postradiosurgery injury imaging changes (increased signal developing in the surrounding brain on long relaxation time or T2 images) in different regions of the brain.[8,21] However, dramatic differences were seen in the rates of developing persistent neurologic sequelae after AVM radiosurgery among the brainstem, thalamus, and other regions of the brain, as shown in Table 16.2. Additionally, RTOG 90-05 and other large radiosurgery trials evaluating treatment of brain metastases have excluded patients with lesions located or abutting the brainstem due to concerns of toxicity.[9,22,23] As such, management of brainstem metastases has varied with differing single-fraction and fractionated radiosurgery approaches with favorable reported

results. A multi-institutional pooled analysis of 547 patients with 596 brainstem metastases treated with Gamma Knife radiosurgery showed that 7.4% of lesions developed grade 3 or higher toxicity.[24] Similarly, a meta-analysis including 1,446 patients with 1,590 brainstem lesions, treated mostly with single-fraction radiosurgery, found a grade 3 or higher toxicity rate of 2.4%.[25]

TABLE 16.2 PREDICTED RISKS OF DEVELOPING ANY SYMPTOMATIC (AND PERMANENT) NEUROLOGIC SEQUELAE AFTER ARTERIOVENOUS MALFORMATIONS RADIOSURGERY ACCORDING TO 12-GY VOLUME AND LOCATION FROM 755 PATIENTS WITH 2-YEAR MINIMUM FOLLOW-UP

12-Gy Volume (cm^3)	Brainstem (%)	Thalamus (%)	Other (%)
0.1	11 (8)	5 (3)	1 (0.3)
10	28 (15)	15 (7)	4 (1)
20	55 (30)	37 (15)	10 (2)
30	79 (50)	64 (28)	27 (5)
40	92 (69)	84 (48)	53 (12)

Derived from Kano H, Flickinger JC, Tonetti D, et al. Estimating the risks of adverse radiation effects after Gamma Knife radiosurgery for arteriovenous malformations. *Stroke*. 2017;48(1):84-90.

Radiation-Induced Malignancy

Radiation-induced malignancy is an established risk of exposure to ionizing radiation. In the setting of therapeutic radiotherapy, the risk of radiation-induced malignancy is dependent on many factors, including age, gender, radiation dose, technique, type, and site and volume of radiation exposure. Because radiosurgery is often used to treat patients with functional conditions and benign tumors with potentially long life expectancy, the patient's decision-making may be impacted by the potential risk of future malignant transformation of benign tumors or developing a new benign/malignant neoplasm. Prior reports of radiation-induced malignancy following radiosurgery are rare and typically published in case reports or small case series.[26] Estimation of risk is also challenging, given the rare occurrence and desired length of follow-up, as secondary malignancy can arise up to 30 years or more after treatment.[27]

The Mayo Clinic published their 25-year experience of 1,142 patients who underwent single-fraction radiosurgery for AVM and benign tumors, evaluating the risk of radiation-induced tumor or malignant transformations. This did not include patients who had received prior or concurrent radiotherapy, had a genetic predisposition syndrome, or had less than 5 years of follow-up imaging. With a median follow-up of 9 years, no radiation-induced tumors were identified in 11,262 patient-years of follow-up after radiosurgery. Of the 909 patients with benign tumors, malignant transformation was seen in 8 (0.9%) patients, of which 7 had meningioma and one had vestibular schwannoma.[28] Similarly, Wolf et al[29] reported a population-based, multi-institutional cohort study of 4,905 patients who underwent radiosurgery for benign tumors with at least 5 years of imaging follow-up and no prior radiation. With a median follow-up of 8.1 years, 2 (0.02%) of 3,251 patients developed suspected malignant transformation and 1 (0.02%) patient developed likely radiation-induced malignancy. Notably, these experiences included only single-fraction radiosurgery delivered with Gamma Knife Platform, did not account for possible extracranial malignancy from low-dose radiation exposure, and reported a median follow-up of 9 years.

Optic Nerve Tolerance for Radiosurgery

The first analysis of optic nerve tolerance to radiosurgery, a combined Harvard/University of Pittsburgh study of patients with cavernous sinus meningiomas, craniopharyngioma, and pituitary adenomas, recommended 8 Gy as a safe maximum dose limit for the optic nerves/chiasm, although most centers now use 10 Gy.[30] The lowest optic chiasm dose at which optic neuropathy developed in that study was reported as being 9.7 Gy. Optic nerve/chiasm doses were estimated from isodose distributions overlaid on CT images, unlike the present day when the entire optic system is usually outlined on detailed MR images and maximum doses are assessed from dose-volume histograms. It is highly likely that the true maximum doses to the optic system were higher and lay in portions of the nerve that were poorly visualized.

Stafford et al[31] reported a later analysis of four cases of optic neuropathy occurring out of 215 Mayo Clinic radiosurgery patients with a median dose

of 10 Gy to the optic chiasm. One case developed after an optic nerve/chiasm dose of 12.8 Gy with radiosurgery alone, at which the risk level appeared to be approximately 3%. The other cases developed in patients with prior fractionated radiotherapy (7 Gy after 58.8 Gy, 9 Gy after 45 Gy, and two procedures delivering 9, and later 12 Gy to the optic system after 50.4 Gy). In two more recent studies,[32,33] over 300 patients with no prior radiation treatment and with a median maximum dose to the optic apparatus of 9.2 to 10 Gy, there was one case of optic neuropathy. This occurred at a maximum dose of 12.8 Gy.

Leber et al[34] analyzed optic nerve injury risks in 50 patients with 24- to 60-month follow-up who underwent Gamma Knife radiosurgery for benign skull base tumors. The risks of optic neuropathy were 0% with 10 Gy. They found no cavernous sinus nerve injury with doses of 5 to 30 Gy.

Hiniker et al[35] found less than 1% risk of optic neuropathy with 12 Gy in one fraction, 19.5 Gy in three fractions, and 25 Gy among 262 patients with perioptic tumors treated with SRS. Similarly, the HyTEC analysis pooled 34 studies with 1,578 patients treated with single and fractionated SRS to evaluate the tolerances of the optic pathways.[36] With a calculated normal tissue complication probability of 1%, the recommendation was for maximum doses to optic structures as 10, 20, and 25 Gy in one, three, and five fractions, respectively.

Tolerance of Other Cranial Nerves

From clinical experience with fractionated conventional radiosurgery and radiosurgery, it appears that special sensory nerves (optic and auditory) are the most radiosensitive, followed by somatic sensory nerves (trigeminal), and, finally, the motor nerves (cranial nerves II, IV, VI, VII, and IX to XII). After acoustic schwannoma radiosurgery to doses of 12 to 13 Gy, fractionated SRS to 18 Gy in three fractions, or SRT to 45 to 50 Gy in 25 to 28 fractions, decreased hearing developed in 30% to 50% of patients, facial numbness in 2% to 3%, and facial weakness in 0.5% or less. Single-fraction radiosurgery with present techniques for meningiomas involving the cavernous sinus is associated with a risk of trigeminal neuropathy of approximately 3% of patients with radiation injuries to cranial nerves III,

IV, or VI more uncommon.[37-41] The risk of injury correlates with the length of nerve irradiated.[42]

CLINICAL USES OF RADIOSURGERY FOR CENTRAL NERVOUS SYSTEM CONDITIONS AND NEOPLASMS

Table 16.3 lists the most common indications for radiosurgery with representative references. Except for functional radiosurgery, there are varied levels of experience with SRT for each of these indications.

TABLE 16.3 COMMON INDICATIONS FOR RADIOSURGERY OR HYPOFRACTIONATED STEREOTACTIC RADIOTHERAPY

Indication	Experience	Value
Functional		
a. Trigeminal neuralgia	a. Extensive	1. Less numbness than rhizotomy
b. Unilateral tremor	b. Moderate	2. In poor candidates for deep brain stimulation
Vascular		
a. AVM	a. Extensive	a. High
b. Cavernous	b. Moderate	b. Controversial
Benign tumors: schwannoma, pituitary adenoma, meningioma, etc	Extensive	High tumor control, acceptable morbidity for selected small tumors
Rare benign tumors: glomus tumor, hemangioblastoma, neurocytoma	Moderate	High tumor control, acceptable morbidity for selected small tumors
Brain metastases	Extensive	Control rates ≥ surgery for small metastases
Primary malignant brain tumors	Extensive for GBM. Limited for other uses	Initial SRS appears ineffective for GBM. Helpful for recurrent tumors

AVM, arteriovenous malformation; GBM, glioblastoma multiforme.

Functional Radiosurgery

The most widely used functional application for radiosurgery is in the management of typical trigeminal neuralgia refractory to medical therapy.[42-47] Atypical or constant pain does not respond. Other alternatives for managing typical trigeminal neuralgia are medication, open surgery with microvascular decompression, and rhizotomy procedures using glycerol injection, balloon compression, or radiofrequency injury to the nerve. Typically, 4-mm collimators are used for radiosurgery to a maximum dose of 80 to 90 Gy. Response rates reach approximately 85%, typically 1 week to 4 months after the procedure, but can develop as late as 6 months afterward. Approximately 50% of typical trigeminal neuralgia patients remain pain free and off medication 5 years following radiosurgery. A typical radiosurgery plan for trigeminal neuralgia is shown in Figure 16.2. Kotecha et al[45] analyzed the dose response for trigeminal neuralgia in 352, 85, and 433 patients undergoing SRS with maximum doses of less than or equal to 82, 83 to 86, and greater than or equal to 90 Gy. They found 4-year pain responses of 79%, 82%, and 92% and 4-year rates of Barrow Neurological Institute (BNI) class 3 to 4 numbness developing in 25%, 49%, and 40% of patients at maximum doses of 90 Gy, respectively. The numbness in nine patients (1%) was classified as anesthesia dolorosa, all with maximum doses less than or equal to 86 Gy.

FIGURE 16.2 Typical radiosurgery plan for right trigeminal neuralgia. The right trigeminal nerve is outlined in white. The 30% and 50% isodose volumes from treating a single isocenter with 4-mm diameter collimators with a gamma unit are shown. A maximum dose of 80 Gy will deliver 40 Gy to the 50% isodose value and 16 Gy to the 20% volume.

Studies have suggested that radiosurgery within 4 years of onset of trigeminal neuralgia leads to better long-term pain control and that selective dose reduction to 70 to 75 Gy may reduce risks of radiation-induced trigeminal neuropathy in patients with larger treatment volumes resulting from having thicker trigeminal nerves.[46-48] In patients who have symptoms recur, repeat radiosurgery is feasible.[49-51] In a large series of 125 patients

with long-term follow-up, Helis et al[51] reported an 84% response rate of BNI IIIb or better pain relief with repeat Gamma Knife radiosurgery and 46% of patients reached BNI I response. Two patients developed anesthesia dolorosa, and one patient experienced bothersome numbness. Predictors of favorable outcomes for repeat treatment were facial numbness and a positive pain response after the first radiosurgery.

To alleviate medically refractory unilateral tremor in patients with essential tremor and/or Parkinson disease, a small destructive lesion in the ventralis intermedius nucleus of the thalamus can be created either invasively with a needle equipped with a radiofrequency generator or noninvasively with radiosurgery using 4-mm diameter collimators and a maximum dose of 130 Gy.[52-55] Nondestructive management through insertion of a deep brain stimulator is preferred in most patients, but not all patients are acceptable candidates and radiosurgery appears more cost effective.[55] Witjas et al[56] reported a prospective single-arm study of 50 patients with severe refractory tremors (36 essential, 14 parkinsonian). Upper limb tremor score improved by more than 50%, with all tremor components improved. There was one adverse event of transient hemiparesis due to posttreatment edema. Although targeting the globus pallidus for bradykinesia, rigidity, and dyskinesia from Parkinson has been successful with deep brain stimulation, limited early radiosurgical pallidotomy has not established success.[57,58]

There is limited experience with bilateral radiosurgical capsulotomy (targeting the anterior limb of the internal capsule) for managing severe, refractory obsessive-compulsive disorder, including a small randomized controlled study that was retracted after it was found that only two of eight patients responded to radiosurgery (vs three of eight as originally thought) compared to none of 8 without radiosurgery.[59]

The use of radiosurgery for medically refractory seizure disorders has shown promise. Radiosurgery versus Open Surgery for mesial temporal lobe Epilepsy (ROSE) trial randomized 58 patients between radiosurgery and anterior temporal lobectomy;[60] 24 Gy was prescribed to the 50% isodose line, targeting the mesial temporal lobe. Sixteen of 31 (52%) and 21 of 27 (78%) patients achieved seizure remission with radiosurgery and surgery, respectively, with quicker remission achieved with surgery. There were five serious adverse events in the radiosurgery cohort—one patient

with headache, one with cerebral edema, one with new neurologic deficit, and two with seizure exacerbation—and two serious events in the surgery cohort—two patients with wound dehiscence and infection. The trial was closed early due to slow accrual but did show that radiosurgery may be a potential option for nonsurgical candidates. Similarly, radiosurgery for hypothalamic hamartomas may help control refractory gelastic seizures.[61]

Vascular Malformations

Untreated intracranial AVMs have a bleeding risk of approximately 2% to 3% per year or higher if prior bleeds have occurred.[62-64] This results in an average of 1% of untreated patients with AVM dying per year from hemorrhage. Management options include observation, surgical resection, embolization, and radiosurgery. The ARUBA (A Randomized Trial of Unruptured Brain Arteriovenous Malformations) trial for AVMs with no prior bleeds compared observation to treatment intervention with institutional choices of embolization, resection, and/or radiosurgery.[65] Because the initial morbidity from intervention by surgery, embolization, and/or radiosurgery was compared to the relatively low annual bleeding risk of unruptured AVM with observation, the ARUBA trial identified observation as the best management option for their relatively short 33-month mean follow-up period. The final follow-up, published in 2020 (mean follow-up of 50.4 months), continued to favor observation over intervention.[66] Although this trial could be used to justify observation for older patients with low-risk AVMs, the relatively short follow-up ARUBA trial was inadequate to see the long-term benefits from definitive management of AVM with surgery or radiosurgery in younger patients.

After 3 to 5 years, radiosurgery can dramatically reduce the risk of hemorrhage. Radiosurgery obliterates the AVM nidus in approximately 75% of patients within 3 years of the procedure.[67-69] Individual obliteration rates vary from 50% to 88% depending on the marginal dose administered, as shown in the dose-response curve illustrated in Figure 16.3. Although AVM obliteration rates appear to be optimized with marginal doses of approximately 23 Gy, lower doses are selected for most patients to minimize complications. The risk of neurologic sequelae from radiosurgery averages approximately 3% but varies with treatment volume, dose, and

location (Table 16.2). The risk of hemorrhage while waiting for complete obliteration to develop seems unaltered.[62] All of these risks and benefits of radiosurgery need to be considered together to optimize the management of individual patients with AVM.

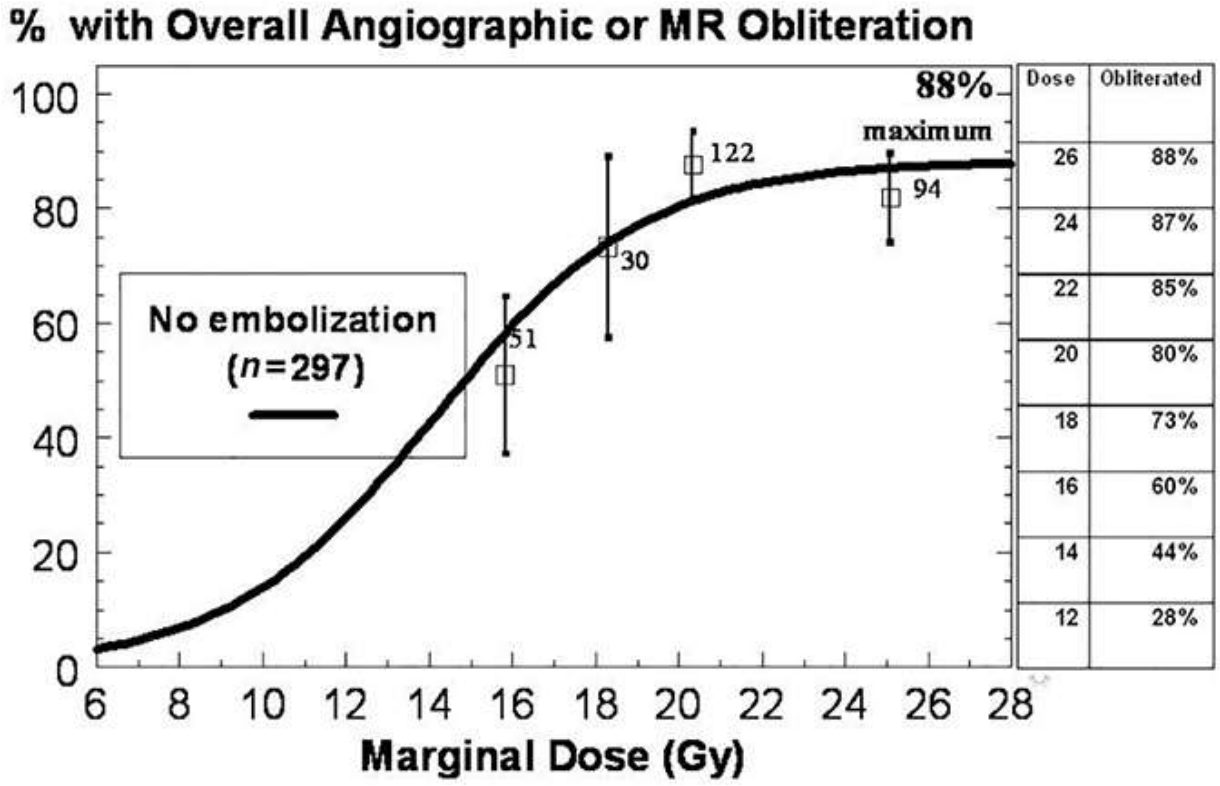

FIGURE 16.3 Dose response for obliteration of AVM after radiosurgery from 297 patients treated at the University of Pittsburgh without embolization. AVM, arteriovenous malformation; MR, magnetic resonance (From Flickinger JC, Kondziolka D, Lunsford LD. Radiobiological analysis of tissue responses following radiosurgery. *Technol Cancer Res Treat*. 2003;2[2]:87-92. Copyright © 2003 SAGE Publications. Reprinted by permission of SAGE Publications.)

When an AVM nidus fails to completely obliterate by 3 years after radiosurgery, irradiation can be repeated with acceptable morbidity.[70-72] Although some residual radiation injury effect would be expected within the previously irradiated unobliterated AVM nidus vasculature, retreatment appears to require similar, if not higher doses to achieve similar rates of complete obliteration as initial radiosurgery.[70-72]

Management of large AVMs is presently difficult because radiosurgery may be associated with high complication risks and low obliteration rates.

Improvements in embolization with liquid glue or onyx polymer can sometimes help reduce the target volume but add to the total risks of the overall management.[73] Another promising approach is staged radiosurgery, where large AVMs are treated in two or three sections separated by 4- to 6-month intervals to reduce acute toxicity.[74-76] A third approach has been fractionated radiosurgery using doses of 30 to 35 Gy delivered daily or every other day in five fractions.[77]

Cavernous malformations do not show detectable flow on angiography but nevertheless are vascular lesions with annual hemorrhage risks of 0.5% per year with no prior bleed, 4.5% with one prior hemorrhage, and approximately 32% per year after a history of two or more hemorrhages.[78-82] Lower pressures in these lesions lead to smaller bleeds than are typically seen with AVM. Repeated bleeds from brainstem cavernous malformations can cause considerable neurologic morbidity. Symptomatic, surgically accessible lesions should be resected. Radiosurgery of brainstem cavernous malformations with a history of two or more prior hemorrhages appears to reduce the risk of subsequent bleeds to approximately 1% per year with acceptable morbidity.[83-89]

Benign Tumors

Most small benign intracranial tumors are well managed with radiosurgery, fractionated radiosurgery, or SRT. Radiosurgery control rates are high with radiosurgery with single-fraction prescription doses on the order of 12 to 14 Gy or their equivalent with hypofractionation.[37-41,90-128] Kondziolka et al[37] evaluated long-term tumor control in 285 consecutive patients who underwent radiosurgery for benign intracranial tumors between 1987 and 1992, with a median follow-up period of 10 years. This included 157 patients with vestibular schwannomas, 10 with other cranial nerve schwannomas, 85 with meningiomas, 28 with pituitary adenomas, and 5 with craniopharyngiomas. In all, 44% had prior surgical resection and 5% had prior fractionated radiotherapy. They found that 95% of the 285 patients had imaging-defined local tumor control. The crude tumor control was 95% (271/285 patients) with a 15-year actuarial tumor control rate of 93.7%. In 5% of the patients, delayed tumor growth was identified. Resection was performed after radiosurgery in 13 patients (5%) for tumor growth.

Vestibular Schwannomas

Vestibular schwannomas, also known as acoustic neuromas, are benign tumors arising from Schwann cells. They are associated with the loss of genetic information on chromosome 22.93. Vestibular schwannomas either occur on one side as spontaneous mutations or bilaterally as the hallmark of type 2 neurofibromatosis (NF-2). Vestibular schwannomas usually arise within the internal auditory canal and later extend intracranially into the cerebellar-pontine angle. Because these tumors lack the ability to invade bone, the portion of tumor outside the canal in the cerebellar-pontine angle eventually grows into a globular extension that is larger than the intracanalicular portion (Figure 16.4). The differential diagnosis of a cerebellar-pontine angle tumor includes vestibular schwannoma (90%), meningioma (close to 10%), cholesteatomas, facial or trigeminal schwannoma, and rare primary or metastatic malignant tumors. Cerebellar-pontine angle meningiomas, which can be managed similarly to vestibular schwannomas, also may involve the internal auditory canal but usually are distinguished by a broad, flat, dural attachment.

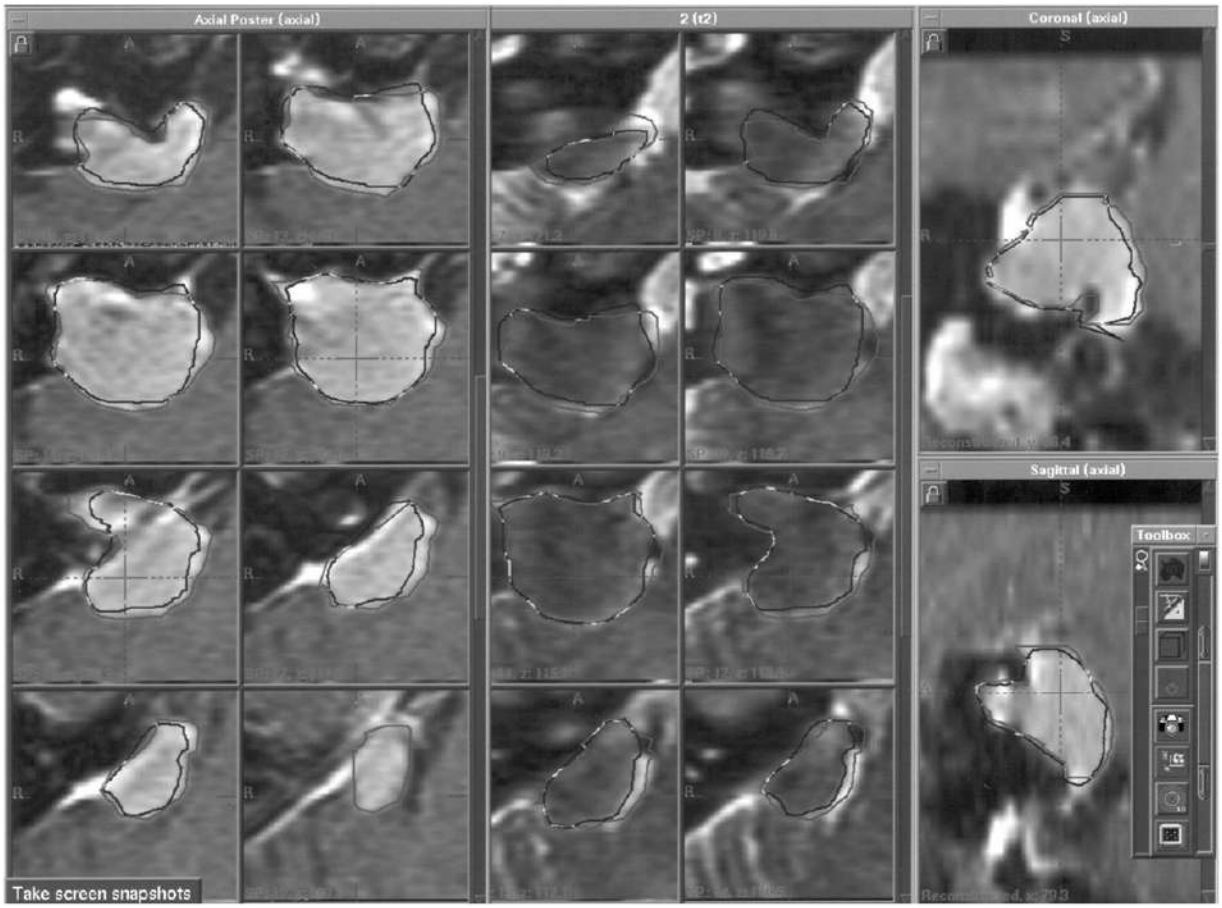

FIGURE 16.4 Comparisons of acoustic schwannoma contours drawn from T1 contrast MR images (eight axial images on the left side with coronal and sagittal images on the right side) with contours drawn from T2 MR images (the darker eight axial images in the center). T1 contours can sometimes slightly overestimate extension into the internal auditory canal and unnecessarily include adjacent blood vessels.

Observation and surgical resection were essentially the only management strategies offered to patients with acoustic schwannoma until favorable experiences with Gamma Knife radiosurgery were reported in the 1980s. For small to medium vestibular schwannomas, tumor control rates with radiosurgery or fractionated radiotherapy are comparable to surgical resection.[90-111,121-125] Observation may be appropriate in selected patients with NF-2 and some older patients with small, minimally symptomatic vestibular schwannomas, but early intervention appears to be the best strategy for long-term hearing preservation for most patients.[121,122]

Early radiosurgery series, including patients treated during the 1980s with higher doses (14-18 Gy) and less conformal treatment plans, had

higher rates of postradiosurgery cranial neuropathies (15%-20% trigeminal and/or facial and 67% with a drop in their Gardner-Robertson hearing level).[125] This prompted some groups to pursue SRT for vestibular schwannomas, whereas others pursued radiosurgery with refined techniques and lower doses. Both approaches led to improved results.[90-108,119-125] The University of Pittsburgh reported on 313 previously untreated patients with unilateral acoustic schwannoma who underwent Gamma Knife radiosurgery doses of 12 to 13 Gy between February 1991 and February 2001.[91] Median follow-up was 24 months and maximum follow-up 115 months, and 36 patients had greater than 60 months of follow-up. The actuarial clinical tumor control rate, free of surgical intervention, was 98.6% at 7 years. The 7-year actuarial rates for unchanged facial strength, unchanged facial sensation, unchanged hearing level, and useful hearing preservation were 100%, 95.6%, 70.3%, and 78.6%, respectively. Eight patients developed new trigeminal neuropathy, six of whom developed numbness (7-year actuarial rate = 2.5%), whereas the other two developed new typical trigeminal neuralgia (7-year actuarial rate = 1.9%). The risk of developing postradiosurgery trigeminal neuropathy was associated with increasing tumor volume. Similar results with low-dose radiosurgery of vestibular schwannomas were reported by Iwai et al,[94] Muacevic et al,[95] Paek et al,[97] and Rowe et al.[99]

Various hypofractionated schemes (18 Gy/3, 20 Gy/4 to 5, 25 Gy/5 fractions) have been used to treat vestibular schwannoma with minor differences in results.[102,129-132] For HyTEC, Soltys et al[133] evaluated 35 publications encompassing 5,162 patients undergoing one to five fractions of radiosurgery to estimate the tumor control probability for vestibular schwannoma. With typical doses of 12 Gy in one fraction, 18 Gy in three fractions, and 25 Gy in five fractions, the tumor control probability at 3 and 5 years exceeded 91% for all treatment regimens.

After accounting for length and quality of follow-up, results from hypofractionated[102,129-132] and conventionally fractionated[103,106] treatments seem similar to radiosurgery with 12 to 13 Gy, but an advantage for fractionation cannot be excluded entirely.[96] The University of California, Los Angeles reported unusually good hearing preservation (93%) for their experience with 50 patients with unilateral acoustic schwannoma irradiated to 54 Gy in 30 fractions to a 90% isodose treatment volume, including a 1-

to 3-mm margin around gross tumor.[109] All tumors were controlled with a median follow-up of 36 months (range 6-74 months). They defined useful hearing preservation as the ability to talk on the telephone with the affected ear. After radiosurgery, new facial numbness developed in one patient (2%) and facial weakness developed in one patient (2%).

Andrews et al[103] analyzed the Jefferson vestibular schwannoma experience, comparing 69 radiosurgery patients to 50 SRT patients who received 50 Gy in 25 fractions. Their first 25 patients with vestibular schwannoma were treated using a LINAC, whereas later radiosurgery patients were treated with Gamma Knife radiosurgery. The authors reported similar facial and trigeminal neuropathy rates for the radiosurgery and fractionated radiotherapy groups, but the rate of hearing loss was significantly higher in their radiosurgery group. There were only a small number of patients with serviceable (useful) hearing in each group prior to irradiation (12 in the radiosurgery and 21 in the SRT groups), and follow-up was limited. Meijer et al[102] also reported a single-institution comparison of radiosurgery (LINAC to 10 or 12.5 Gy) and SRT (20 Gy in four or five fractions) for vestibular schwannoma. They selected 49 edentulous patients (mean age 63 years) for radiosurgery and 80 patients (mean age 43 years) with intact dentition for SRT. They found a higher rate of trigeminal neuropathy following radiosurgery (8%) than SRT (2%) at 5 years, but similar hearing loss with radiosurgery (25%) and SRT (39%), similar, but higher than usual rates of new facial neuropathy (7% radiosurgery vs 3% SRT), and similar 5-year actuarial tumor control rates (100% with radiosurgery vs 94% with SRT). Combs et al[106] compared the results of vestibular schwannoma management with single-fraction radiosurgery (median dose of 13 Gy) in 169 patients to SRT at 1.8 Gy per fraction to a median dose of 57.6 Gy in 291 patients with a median follow-up of 67 months. Local control rates were similar at 95% and 94% at 5 and 10 years. Useful hearing preservation rates were also similar at 84% and 86% in the SRS and SRT groups, as was trigeminal and facial neuropathy at approximately 1% for both. Akpinar et al[111] reported the results of hearing preservation after single-fraction radiosurgery with a median dose of 12.5 Gy (11-13 Gy) to a median volume of 0.72 cm^3 (0.11-12.8 cm^3) in 88 patients with vestibular schwannomas with no subjective hearing loss at the time of diagnosis. With 75 months of median follow-up, for the 57 patients

who underwent SRS less than or equal to 2 years from diagnosis, the serviceable hearing (class 1-2) and normal hearing preservation rates (class 1) at 5 years after SRS were 88% and 77%, whereas those for the 31 patients who underwent late SRS (>2 years after diagnosis) were 55% and 33%, respectively.

More recently, the Vestibular Schwannoma, Radiosurgery or Expectation (V-Rex) trial,[134] which randomized 100 patients with newly diagnosed unilateral vestibular schwannomas less than 2 cm to upfront radiosurgery (12 Gy to 40%-60% isodose line) versus yearly surveillance imaging with treatment only upon growth, found at 4 years decreased size of the vestibular schwannoma in the upfront radiosurgery group as compared to the wait-and-see cohort. There was a similar hearing acuity decline in both groups. There was no reported radiation toxicity. Twenty-one (42%) patients in the wait-and-see required intervention upon tumor growth. A 10-year follow-up report is planned and will be more informative of the long-term clinical outcomes of this strategy for small to medium tumors.

For large tumors, typically greater than or equal to 2.5 cm and/or Koos grade IV designation,[135] surgery often appears to be the best initial strategy due to concerns of symptomatic brainstem compression with obstructive hydrocephalus. Single-fraction radiosurgery, however, is feasible in these patients who cannot or wish not to undergo surgical resection.[136-141] Pikis et al[140] reported from a large, multi- institutional analysis of 627 patients with Koos grade IV vestibular schwannoma treated with a median dose of 12 Gy. The median tumor volume was 8.7 cm^3. At a median radiologic follow-up of 38 (interquartile range [IQR] 54) months, tumor control was achieved in 94.1% of patients. Actuarial 5- and 10-year PFS rates were 92.3% and 87.6%, respectively. Facial nerve function deterioration occurred in 19 (3.0%) patients at the last follow-up and was associated with margin doses greater than or equal to 13 Gy (P = .03) and early tumor expansion (P = .04). Fifty-seven patients developed T2-weighted hyperintensities in the brainstem, and 37 developed cyst formation, requiring medical/surgical management in 34 and 18 patients, respectively. Notably, after SRS, 33 (6%) patients developed hydrocephalus requiring shunting.

Nonacoustic Schwannomas

Schwannomas may occasionally involve other cranial nerves. Tumor control rates are similar, but postradiosurgery neuropathies seem less common as somatic sensory and motor nerves, particularly, seem less sensitive to radiation injury than special sensory nerves like VIII.[112-115,142-146] Langlois et al[146] reported on a small, multicenter cohort study of 25 patients who underwent a single-fraction dose of 12.5 Gy for an oculomotor cranial nerve schwannoma (CN III, IV, or VI). Tumor control was 92%. Diplopia improved in 11 of 21 patients and worsened in 3 patients, 2 of which were due to tumor progression. Kano et al[142] reported on 92 jugular foramen schwannomas managed at multiple institutions with a median single-fraction dose of 12.5 Gy (10-18 Gy) to volumes of 0.8 to 22.6 cm^3 (median 4.1 cm^3). Tumor control rates at 5 and 10 years were 87% and 82%. Preexisting cranial neuropathies improved in 32% and 37% of patients. Because spinal schwannomas involving motor nerves are difficult to completely resect without causing motor deficits, they are often managed with radiosurgery. Shin et al[147] reported one of the larger series of neurogenic spinal nerve root tumors (47 schwannomas, seven neurofibromas, and four malignant peripheral nerve sheath tumors managed with radiosurgery). Local control for the schwannomas was 86%.

Meningiomas

Radiosurgery and SRS are both excellent management options for most small benign meningiomas with infield tumor control rates well above 90%, as seen with most other benign tumors.[37,116] Marginal recurrence rates as high as 25% may develop because of the tight margins used for radiosurgery or SRT treatment volumes limited to small recurrences or residual tumors after resection of large parasagittal meningiomas.[37,116,126-128] Marginal recurrences are far less of a problem with unresected (and usually unbiopsied) meningiomas. A University of Pittsburgh study[116] analyzed 219 imaging-diagnosed (unbiopsied) meningiomas managed with single-fraction Gamma Knife radiosurgery to a prescription dose of 8.9 to 20 Gy (14 Gy median) and treatment volumes of 0.47 to 56.5 mL (median 5.0 mL) with 2 to 164 months of follow-up (median 29 months). Tumors progressed in seven patients, two of which proved to be different tumors (metastatic nasopharyngeal adenoid cystic carcinoma and chondrosarcoma). Another

patient with local control of the lesion developed a subsequent brain metastasis, changing the diagnosis of the first lesion to the same. The actuarial tumor control rate was 93.2% at 5 and 10 years. The actuarial rate of identifying a diagnosis other than meningioma was at 5 and 10 years. No pretreatment variables, including dose, correlated with tumor control in univariate or multivariate analysis. The actuarial rate for developing any postradiosurgical injury reaction was 8.8% at 5 and 10 years but was lower (5.3%) after 1991 with stereotactic MRI and lower doses.

Atypical and malignant (anaplastic) meningiomas have higher rates of local and marginal recurrence after therapeutic intervention. Complete surgical resection is advocated whenever feasible and followed by a full course of conventional radiotherapy. Radiosurgery has been recommended to improve local control of unresectable tumor.[128,148-150] Malik et al[128] reported 5-year actuarial control rates of 87% for typical meningiomas, 49% for atypical, and 0% for malignant meningioma in the Sheffield Gamma Knife experience. Harris et al[149] reported the Pittsburgh Gamma Knife experience in 12 malignant and 18 atypical meningiomas. Their 5-year local tumor control was 72% for malignant and 83% for atypical meningiomas; however, 10-year actuarial survival rates were only 59% and 0%, respectively. Katz et al[150] could not substantiate that either accelerated fractionated radiotherapy or a radiosurgery boost improved tumor control or survival in their analysis of 27 atypical and nine patients with malignant meningioma managed at the University of Florida. Shepard et al[151] reported on 233 patients with atypical meningioma and 38 patients with anaplastic meningioma treated at 12 institutions with SRS. 98.5% had prior resections and 25.8% had prior radiotherapy. Five-year PFS and overall survival were 33.6% and 70%, respectively.

One controversy in the radiosurgical management of meningiomas is whether an additional dural margin or dural tail needs to be routinely included in the treatment volume. Dibiase et al[152] analyzed a series of 162 benign meningioma patients treated to a median single fraction of 14 Gy and found improved tumor control with the treatment of the dural tail (96% vs 78%). Most centers do not follow this policy, and other authors[153] have argued against this policy for World Health Organization (WHO) grade I meningiomas. Current consensus guidelines do not include dural tail in gross tumor volume definition for grade 1 meningiomas.[154,155] Outlining the

tumor target volume with T2 imaging sometimes discloses gross tumor extension into what otherwise appears to be normal dura adjacent to the tumor. Any WHO grade 2 or 3 meningioma should be treated with at least a 5- to 15-mm margin of additional normal dura whenever possible.[154,155]

Pituitary Adenoma

Management of pituitary adenomas requires a multidisciplinary approach to properly select which patients are suitable for different approaches with medical therapy, surgery, fractionated radiotherapy and radiosurgery, or combinations of these approaches. Most patients with visual compromise, particularly with hemianopsia or greater, will do better with initial surgical decompression. Prolactinomas are usually initially managed with medical therapy.[117] Most other small pituitary adenomas, where the target volume can be separated from the optic nerves, are reasonable candidates for radiosurgery.[37,117-119] Sheehan et al[119] reviewed 35 peer-reviewed reports of radiosurgery for pituitary adenoma, which included 1,621 patients. Most studies reported a greater than 90% control of tumor size (range 68%-100%). The weighted average tumor control rate for all published series (encompassing 1,283 patients) was 96%. In eight published series with mean or median patient follow-up periods of 4 or more years, tumor growth control rates varied from 83% to 100%.

Higher radiosurgery doses are required for functional pituitary adenomas. Twenty-two series results published radiosurgery results for 314 patients with Cushing disease. The mean radiosurgical prescription (margin) doses for these series varied from 15 to 32 Gy. In those series with at least 10 patients and a median follow-up of 2 years, endocrinologic remission rates range from 17% to 83%. Many of the patients in older series were treated in the pre-CT and MRI era of radiosurgery, sometimes as often as 4 times before their Cushing disease went into remission. Mehta et al[120] reported a multi- institutional experience with radiosurgery to a mean single-fraction dose of 23.7 Gy in 278 patients with Cushing disease with a mean follow-up of 5.6 years (0.5-20.5 years). Cumulative initial control of hypercortisolism was 80% at 10 years, with a mean time to cortisol normalization of 14.5 months. Recurrences after initial cortisol normalization developed in 18% of patients, which made the overall rate of

durable hormonal control to 64% at 10 years and 68% among patients who received SRS as a primary treatment. Acute radiation effects (AREs) included hypopituitarism (25%) and cranial neuropathy (3%). Development of visual deficits correlated with tumors involving the suprasellar cistern (P = .01), whereas both visual (P < .0001) and nonvisual cranial neuropathies (P = .02) were related to prior pituitary irradiation.

Lower radiosurgical doses are effective for nonfunctioning pituitary adenomas. The North American Gamma Knife Consortium series[121] of 512 patients with nonfunctioning pituitary adenoma reported 5- and 10-year tumor control rates of 91% and 85% with a mean dose of 16 Gy (range 5-35 Gy) to a mean volume of 3.33 Gy (range 0.08-33 cm^3). Higher tumor control rates were found in tumors <5 cm^3 and those without suprasellar extension. Tumor control rates in patients receiving <12 Gy, 12-20 Gy, and >20 Gy were 73.5%, 95.5%, and 92%. New or progressive cranial neuropathies developed in 9% of patients (including 6.6% optic). Decreasing age, increasing volume, history of prior radiation therapy, and history of prior pituitary axis deficiency correlated with new or worsening cranial neuropathy.

Glomus Tumors

Glomus tumors, or paragangliomas, are rare tumors of neural crest origin cells (chromaffin) of the extra-adrenal autonomic paraganglia. These tumors may arise from sympathetic or parasympathetic paraganglia and may have catecholamine-secreting functions. Parasympathetic-derived tumors are typically benign and nonsecreting and are often found in the skull base and neck near cranial nerves.[156] These tumors are subclassified further by location as carotid paraganglioma, glomus jugulare, glomus tympanicum, and vagal paraganglioma. Given the location, patients with head and neck paragangliomas often present with symptoms of pulsatile tinnitus, hearing loss, a nontender neck mass, or have ipsilateral cranial neuropathies.

Historically, resection has been considered the preferred approach, and radiation treatment was reserved for unresectable or recurrent glomus tumors. Radiosurgery has often been used for the treatment of glomus jugulare tumors because of the risk of surgical morbidity, particularly cranial neuropathies.[157,158] Multiple-dose fractionation regimens have been

used, including a single-fraction dose of 12 to 15 Gy or fractionated radiosurgery at 25 Gy in five fractions. Reported local control rates with radiosurgery typically approach 95% to 100% and are well tolerated.[157-168] Patel et al[165] reported a 5-year PFS rate of 98% in 85 patients undergoing Gamma Knife radiosurgery at Mayo Clinic, with only 2 patients (3%) developing a new lower cranial neuropathy. After 10 years of initial radiosurgery, three tumors did radiographically progress without the need for intervention, suggesting the need for long-term tumor surveillance.

Hemangioblastomas

Hemangioblastomas are rare, benign vascular tumors of the CNS that occur sporadically or are associated with von Hippel-Lindau syndrome (VHL). According to the WHO classification system, these tumors are grade 1 mesenchymal, nonmeningothelial tumors.[169] Management of hemangioblastomas includes observation, surgical resection, and radiation therapy, including radiosurgery or conventionally fractionated radiotherapy. Although surgical resection is the primary treatment, radiosurgery offers a noninvasive approach for lesions in eloquent locations in the brain or in patients with VHL, who may require multiple procedures over time.

Kano et al[170] reported the largest series of patients with intracranial hemangioblastomas treated with radiosurgery. In 186 patients with 517 lesions, local control was 89% and 79% at 5 and 10 years, respectively. Thirteen (7%) of patients experienced AREs, with one patient dying due to refractory peritumoral edema. Similar local control outcomes have been seen in other studies.[170-173] Improved tumor control has been observed for VHL-associated hemangioblastoma compared to sporadic tumors in other radiosurgery[170,171] and conventionally fractionated radiotherapy reports.[174]

Pan et al[175] conducted a systemic review and meta-analysis of 596 patients and 1,535 lesions receiving radiosurgery for intracranial and spinal hemangioblastomas. The calculated PFS at 5 years was 88.4%. The 10-year PFS reported by a small number of studies varied widely—50% to 96%. This included a small prospective observational study by Asthagiri et al,[176] which projected the control rate at 15 years to be 51%, drawing concerns that radiosurgery may lose effectiveness with time. However, this study was small and included only patients with VHL-associated tumors.

Central Neurocytomas

Central neurocytomas are rare, neuronal-glial brain tumors typically located in the supratentorial ventricular system. The WHO classifies central neurocytomas as grade II.[169] A more aggressive subset termed atypical neurocytoma is designated by a proliferation index greater than or equal to 2% (MIB-1 labeling index) and was established after a meta- analysis determined an increased risk of local failure and death in patients with MIB-1 indexes greater than 3.[177] Primary treatment of central neurocytomas is gross total resection[178,179]; however, because of their location, maximal safe resection is often achieved. Radiotherapy should be considered definitively for inoperable patients or adjuvantly for atypical histology, residual, or recurrent disease.[178,180-184]

Both conventionally fractionated radiotherapy and radiosurgery have been used in the treatment of these rare tumors. From an international retrospective cohort study, Hung et al[185] reported outcomes for 60 patients following radiosurgery for recurrence (12%), adjuvant therapy (72%), or definitive treatment (17%). Mean margin dose was 13 Gy. The 5- and 10-year PFS were 89% and 80%, respectively. Adverse events were observed in four (7%) patients. Yamanaka et al[186] reported similar 5- and 10-year PFS of 94% and 86% in 36 patients undergoing Gamma Knife radiosurgery, with a mean marginal dose of 15 Gy. Genc et al[187] reported on 18 patients, and local control of 93% followed single-fraction radiosurgery. Karlsson et al[188] reported a 5- and 10-year PFS of 91% and 81%, respectively, in 42 patients with a median prescribed dose of 13 Gy. Notably, in this study, 45% of patients experienced enlargement of the ventricular system, and six patients required interventions. Careful monitoring for treatment effects after treatment is necessary.

Malignant Central Nervous System Tumors

The overall management of brain metastases and malignant glioma is discussed elsewhere in this book. In 1989, the RTOG Brain Tumor Committee initiated an SRS clinical trials program. The first study, RTOG 90-05, evaluated patients with prior radiation for either brain metastases or malignant glioma and was designed as a phase 1 dose escalation study for single-fraction SRS. This patient cohort was chosen due to (1) high

expected numbers of potential patients due to poor local control with conventionally fractionated radiotherapy, (2) few subsequent therapeutic options for these patients, and (3) anticipation that the data would be used on future RTOG radiosurgery trials.[9] Over time, the management of brain metastases with radiosurgery has become much more complex due to the multitude and potential combinations of currently available treatment options, including surgery, SRS, whole-brain radiation therapy (WBRT) with and without hippocampal avoidance (HA-WBRT), chemotherapy, targeted drug therapies, and immunotherapies.[189] On the other hand, the management of malignant gliomas with radiosurgery has been more challenging and is typically reserved in special situations of low-volume disease recurrence.

Brain Metastases

Brain metastases are the most common and best-studied indications for SRS. Early clinical investigations found impressive tumor control with radiosurgery for brain metastases that progressed after prior WBRT. RTOG 90-05 dose escalation trial in recurrent brain tumors to some degree standardized dose prescription for brain metastasis radiosurgery.[9] Because of the success of radiosurgery in controlling brain metastases after WBRT and the high rate of eventual local tumor progression in brain metastases after conventional WBRT, radiosurgery has been increasingly used in the initial management of brain metastases.[190] The RTOG's subsequent phase III randomized trial, RTOG 95-08, established that radiosurgery immediately following standard WBRT (37.5 Gy in 15 fractions) improves local control and quality of life for patients with one to three brain metastases while also improving overall survival for patients with solitary metastasis, all compared to patients initially managed with only WBRT.[191]

Although RTOG 95-08 established radiosurgery's role after WBRT in managing one to three brain metastases, questions remained about managing brain metastases with radiosurgery alone and preserving full-dose WBRT as an option for later managing cases with subsequent progression. Aoyama et al[192] published the outcome of a prospective randomized controlled trial to evaluate whether initial WBRT provides better outcomes when added to SRS compared to using SRS alone. This study randomized

132 patients with one to four brain metastases less than 3 cm in diameter to radiosurgery with or without initial WBRT. They found the median survival time and the 1-year actuarial survival rates were not significantly different with or without WBRT. Later, Brown et al[193] demonstrated that SRS alone had less cognitive deterioration at 3 months compared with a combination of WBRT and SRS in patients with one to three brain metastases. The N107C/CEC.3 study compared SRS alone versus whole-brain radiotherapy in patients undergoing postoperative radiotherapy for resected metastatic disease and found more cognitive decline, no difference in overall survival, and worse quality of life with WBRT.[23,194] At the same time, Mahajan et al[195] reported a single institutional study of 128 patients comparing observation or radiosurgery after radiographic gross total resection of brain metastasis. With a median follow-up of 11.1 months, freedom from local recurrence was 43% in the observation arm and 72% with SRS. There were no adverse events or treatment- related deaths. Because four large prospective trials[192,193,196,197] have shown WBRT adds no survival benefit over SRS alone in patients with low-volume intracranial disease and a good performance status, SRS is the preferred radiotherapeutic option over WBRT for intact and resected brain metastases.[189]

The optimal number and volume of brain metastases treated effectively with radiosurgery remain unclear. Although large, prospective trials have included up to four brain metastases,[192,193,195-197] favorable cancer control and neurologic outcomes for SRS have been seen retrospectively in the upfront and repeat SRS setting in well-selective patients with five or more brain lesions.[198-202] To minimize the risk of radiation necrosis, fractionated SRS regimens have been utilized, showing favorable local control, while, at the same time, hippocampal avoidance whole-brain radiotherapy with memantine has become another option when feasible.[203] Currently, the Canadian Cancer Trials Group is accruing CE.7, a phase III trial randomizing patients with 5 to 15 newly diagnosed brain metastases to either SRS or hippocampal-avoidant whole-brain radiotherapy plus memantine with primary endpoints of overall survival and neurocognitive function (NCT03550391).

Guidelines endorsed by multiple specialty associations (ASTRO, SNO ASCO) have emphasized the importance of prognosis in order to appropriately individualize care.[189] Gaspar et al[204] published the RTOG

Recursive Partitioning Analysis for brain metastases in 1997, which comprised three classes: I (age < 65, Karnofsky Performance Score [KPS] > 70, controlled primary tumor, no extracranial metastases), II (all patients not in class I or III), and III (KPS < 70) which correlated with median survival of 7.7, 4.5, and 2.3 months, respectively. Over the past 25 years, Sperduto and colleagues[205-216] have expanded the graded prognostic assessment (GPA) dramatically by pooling RTOG trials and large multi-institutional databases. In their efforts, disease-specific GPAs now exist for multiple histologies, showing that the factors that predict survival vary by diagnosis. The GPA incorporates clinical factors and relevant molecular biomarkers such as PDL-1, *EGFR*, and *ALK* gene status for non–small cell lung cancer[215,216] and *BRAF* status in melanoma.[207,209,210] An online GPA calculator is available for clinical use at https://brainmetgpa.com. The GPA is a practical tool for estimating survival, individualizing treatment, guiding supportive care, and stratifying clinical trials. The GPA has been used for stratification in the initial design and secondary analyses of multiple prospective trials.[214,217-222] These data can also be used to improve surveillance and expand eligibility for clinical trials.[213] These studies have shown that although survival has improved overall, this patient population remains heterogeneous, and survival varies widely by prognosis (GPA score). Thus, the nihilistic approach of the past to these patients is no longer appropriate.

One of the more challenging patient scenarios in brain metastasis radiosurgery involves the management of larger brain metastases. For brain metastasis radiosurgery, both local tumor recurrence rates and complication rates increase with increasing tumor target volume, particularly for tumors greater than 3 cm in diameter. Strategies to improve the radiosurgical management of brain metastases include switching from single-fraction to fractionated SRS and combining radiosurgery with surgical resection. Two different types of fractionation strategies have been used. One strategy is to fractionate the radiation treatment for a single treatment plan over a short time period, usually within 1 to 2 weeks, to limit tumor repopulation. Cho et al,[223] for example, compared the outcome of treating 81 small brain metastases with a median volume of 1.0 cm^3 (range 0.12-4.4 cm^3), with single-fraction radiosurgery to a median dose of 22 Gy to that with 38 larger brain metastases with a median volume of 17.6 cm^3 (range 12.8-23.7 cm^3) treated with three to five fractions to a median dose of 35 Gy. Tumor

control rates at 1 year for single versus three to five fractions were similar at 89.7% versus 87%, as were radiation necrosis rates at 12.3% versus 15.8%, respectively. Likewise, Minniti et al[19] compared single-fraction radiosurgery and fractionated SRS (typically 27 Gy in three fractions) in 289 patients with brain metastases greater than 2 cm and found improved local control rates (77% vs 91%) and less radiation necrosis (18% vs 9%), favoring fractionated SRS. The second strategy for radiosurgery of large brain metastases is a two-staged adaptive radiosurgery with time in between to allow for tumor shrinkage. Angelov et al,[224] for example, treated 63 brain metastases with a median volume of 10.5 cm^3 in 54 patients with a median initial dose of 15 Gy (12-18 Gy) and to a median second dose of 15 Gy (range 12-15 Gy) to a median volume of 7.0 cm^3 (1.0-29.7 cm^3) and a median of 34 days later. Tumor control was 88% at 6 months, and only 11% developed adverse radiation effects.

The other approach for managing large brain metastases is combining surgical resection with radiosurgery to the tumor bed, which has historically been postoperative.[23,195,225,226] Similar to large, intact brain metastases, postoperative surgical beds may benefit from fractionated SRS. A large, multi-institutional cohort of 558 patients treated with fractionated SRS (median dose 30 Gy in five fractions) following resected brain metastases found 84% and 75% local control rates at 1 and 2 years, respectively. Radiation necrosis and leptomeningeal disease developed in 8.6% and 13.1% of patients, respectively.[227] Currently, Alliance A071801 is a phase III trial exploring postoperative single-fraction or fractionated SRS for resected brain metastasis (NCT04114981).

Because of the observation of higher rates of leptomeningeal disease (28% in Mahajan et al[195]) and radiation necrosis following tumor resection with postoperative radiosurgery, preoperative radiosurgery strategies have been and are currently being explored.[228-230] Patel et al[231] compared the results of surgical resection of brain metastases with radiosurgery delivered either preoperatively to a median dose of 14.5 Gy with no margin in 66 patients or postoperatively with a 2-mm margin in 114 patients. Although no significant differences were found in overall survival, local recurrence, or distant brain recurrence, patients undergoing postoperative radiosurgery developed significantly more leptomeningeal disease (16.6% vs 3.2%) and symptomatic radiation injury (16.4% vs 4.9%) at 2 years. In an expanded,

multi-institutional analysis totaling 404 patients with 416 indexed, resected brain metastases compared preoperative treatment with single-fraction (median dose 15 Gy) and fractionated SRS (median dose 24 Gy in three fractions). Most patients received single-fraction SRS (78.5%). Median volume was 9.9 mL. Local recurrence at 2 years with single-fraction SRS was 16.3% compared with 2.9% with fractionated SRS (P = .004). There was no difference in the incidence of any grade ARE, with the 2-year any grade ARE rate of 6.7% for single-fraction and 10.7% for fractionated SRS. There was no difference in leptomeningeal disease, with a rate of 6.1% for single-fraction and 3.8% for fractionated SRS (P = .94).[232] The role of preoperative SRS is currently being investigated on NRG-BN012, which is a phase III, randomized controlled trial presently evaluating preoperative versus postoperative SRS for patients with resected brain metastasis (NCT05438212).

High-Grade Gliomas

During the late 1980s and 1990s, many centers that had been using brachytherapy for recurrent high-grade gliomas and as boosts after conventional radiotherapy transitioned to radiosurgery. Although retrospective series appeared to show that initial brachytherapy or radiosurgery boosts after conventional radiotherapy improved the survival of patients with glioblastoma, prospective randomized trials of both modalities used prior to conventional radiotherapy of glioblastoma patients were negative.[233-235]

The use of radiosurgery in the management of newly diagnosed high-grade gliomas continues to be investigational. Pollom et al[236] and Azoulay et al[237] reported a dose escalation trial of five-fraction radiosurgery to doses of 25, 30, 35, and 40 Gy delivered with a 5-mm margin along with concurrent and adjuvant temozolomide in 30 patients with newly diagnosed supratentorial glioblastoma. Six patients were entered at each of the four lower-dose levels and 12 at the highest level of 40 Gy. With a median follow-up of 13.8 months, the median PFS and overall survival were 8.2 and 14.8 months, respectively. For quality-of-life (QOL) assessment, 8 of 30 showed evidence of ARE, which was symptomatic in 6 patients. The 12-month ARE rate was 38%, with four of five survivors with more than 2

years of health-related QOL follow-up developing ARE. Survival and tumor control seemed similar to that expected with standard chemoradiotherapy.[238]

For recurrent high-grade gliomas, there is no standard treatment approach, and multiple treatment options, including resection, systemic therapies, and reirradiation, are possible. Treatment decisions are often based on multiple factors, including patient performance status, disease volume, focal versus diffuse recurrence, prior interventions, and time since prior radiation treatment. Radiosurgery appears to be a reasonable option for small, well-circumscribed, high-grade gliomas that recur after prior conventional large-field radiotherapy and chemotherapy. At this time, there is no clear consensus on patient selection, treatment technique, radiosurgery dose, or volume for patients with recurrent high-grade gliomas.[239] Multiple studies have confirmed the safety of bevacizumab with radiosurgery, and the combination of the two may reduce the risk of symptomatic edema and radiation necrosis.[240-243] Clarke et al[13] reported dose-escalated radiosurgery delivered with bevacizumab to 27, 30, and 33 Gy for recurrent glioblastoma and anaplastic astrocytoma in three, five, and seven patients with no cases of clearly symptomatic radiation necrosis but with one patient in the 33-Gy level exhibiting cognitive deterioration and grade 3 fatigue. Three patients underwent subsequent resections for presumed local progression, and viable tumor and substantial radiation necrosis were found in each; of which one had necrosis in more than 90% of the specimen.

SUMMARY

SRS and radiotherapy techniques have become the standard of care for managing a large number of benign and malignant tumors and other conditions in the brain and CNS. The safety and effectiveness of these techniques continue to improve along with technical improvements in radiation targeting and delivery, as well as improvements in our understanding of radiobiologic responses.

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CHAPTER 17

Stereotactic Irradiation of Tumors Outside the Central Nervous System and Oligometastases

Ambrosia J. Simmons, Brian D. Kavanagh, and Robert D. Timmerman

Departing from the established traditions of conventionally fractionated external-beam radiotherapy (RT), in the late 1980s and early 1990s, investigators in the United States, Sweden, and Japan began to explore the use of extremely brief hypofractionated radiation treatment regimens for the spine, lung, liver, and selected other malignant extracranial tumors.[1-3] In essence, these clinical researchers were modifying techniques proven clinically valuable in the context of cranial stereotactic radiosurgery to exploit the efficiency and biologic potency of high-dose per fraction irradiation.[4] This idea was soon appreciated for its clinical promise by other researchers in numerous countries worldwide.

As early as the late 1980s, investigators began exploring ultrahypofractionated treatment regimens for extracranial malignancies in the spine, liver, and lung, expanding on the success of intracranial stereotactic radiosurgical techniques.[1-4] Pioneers in the field initially used customized ancillary equipment constructed in their institutions to immobilize patients and adapt ordinary linear accelerators for precise internal tumor targeting. Now, however, the administration of high-dose, tightly focused external-beam radiation therapy is greatly facilitated by a wide assortment of commercially available systems that immobilize patients, address the problem of respiratory motion during treatment, and ensure accurate treatment with image guidance. The newest generation of linear accelerators from several manufacturers is either exclusively dedicated to cranial or extracranial stereotactic RT or equipped with a built-in package of features that provide an effective means of administering this type of treatment.

Stereotactic body radiation therapy, better known as stereotactic ablative radiotherapy (SAbR), is now a widely accepted form of radiation therapy for both primary and metastatic disease. These terms are used to describe radiation treatments that occur in typically five or fewer fractions and deliver significantly higher doses per fraction than conventionally fractionated RT. Delivery of such high ablative doses of radiation necessitates rapid dose fall off and precise tumor targeting, both externally with immobilization techniques and internally with image guidance and motion management. These techniques are greatly facilitated by the widely available array of commercial products.

BIOLOGIC AND ONCOLOGIC RATIONALE FOR STEREOTACTIC ABLATIVE RADIOTHERAPY

The appeal of SAbR is based on the nonlinear relation between radiation dose and cytotoxic effect, whereby one or a few large individual doses of radiation therapy may have substantially more cell-killing effect than the same dose of radiation given in smaller individual doses. Traditionally, the expected relation between radiation dose and tumor cell kill has been commonly estimated by the well-known linear-quadratic (LQ) model of radiation dose response, often relied on to compare the biologic potency of different conventionally fractionated radiation therapy schedules. However, in the range of dose per fraction used in SAbR, there has been an emerging appreciation that the LQ model overestimates the potency of fraction sizes on the order of 8 to 10 Gy or higher.

Various alternative mathematical models have been proposed to account for the observed inaccuracy of the LQ model for doses in this range. For example, Guerrero and Li[5] have proposed a modification of Curtis[6] lethal-potentially lethal model that accounts for ongoing repair processes that occur during an individual's radiation treatment, thus predicting lower cytotoxicity from high doses administered over time intervals resembling typical clinical treatment times. Experimental data modeling cranial radiosurgery offers support for this concept.[7] Alternatively, Park et al[8] have offered the universal survival curve formalism, which combines the LQ model for doses in the range used in conventional fractionation with a multitarget model for doses in the range used for SAbR. This piecewise

function effectively achieves the same key mathematical outcome as other deviations from the LQ model applied to SAbR, specifically a more linear relationship between dose and log cell kill in the high-dose region (exponential, nonrepairable cell killing).

None of the aforementioned in vitro models of high-dose per fraction tumor cell–killing effects explicitly incorporate a mechanism of tumor cell kill that might be of equal or greater importance than tumor DNA damage-based injury, such as the antiangiogenic effect of endothelial cell apoptosis occurring above an apparent threshold dose on the order of 8 to 10 Gy. First observed preclinically and reported by Garcia-Barros et al,[9] clinical evidence indirectly supporting the importance of this mechanism includes measures of an increase in serum markers of apoptosis post-SAbR.[10] Challenging the importance of this mechanism, however, is the work of Kirsch and colleagues,[11,12] who used a genetically engineered mouse model to evaluate the influence of endothelial cell apoptosis in a mouse sarcoma model, observing minimal impact on tumor radiosensitivity from the degree of endothelial apoptosis achieved.

The impact of high-dose per fraction RT upon immune responses has been of great interest in recent years. Radiation therapy has been shown to have an immunomodulatory effect through antigen presentation, stimulation of tumor antigen release, and maturation of T cells. One early preclinical study demonstrated that a single dose of 20 Gy, unlike a fractionated regimen of lower dose per fraction, can trigger a strong T-cell response that enhances the cytotoxic effect in a preclinical melanoma model.[13] Likewise Filatenkov et al[14] showed that a single ablative dose of radiation was sufficient to induce antigen presentation and increased T-cell tumor infiltration in a model of colon cancer, whereas a protracted conventional regimen did not yield similar results. Sharabi et al[15] demonstrated that SAbR not only induced an increase in immune cell tumor infiltration but also stimulated direct presentation of tumor antigens in preclinical models of melanoma and breast cancer. This group further demonstrated that the combination of SAbR with checkpoint blockade immunotherapy significantly enhanced the immune-stimulated effects of radiation.

OLIGOMETASTATIC DISEASE

Beyond its uses as primary therapy for selected early-stage cancers, SAbR can also be used as a noninvasive and efficient means of eradicating discrete tumors in the setting of oligometastatic disease. As articulated by Hellman and Weichselbaum,[16] the spectrum theory or theory of oligometastases proposes that there is a subgroup of patients with metastatic disease that is intermediate between completely absent and widely metastatic. For such patients, the entire systemic disease burden is confined to a finite number of individual sites of gross disease identified by the relevant imaging studies. This condition would reflect an intermediate point in the natural history of that individual's cancer; therefore, these patients might be cured if their limited numbers of metastatic sites are eradicated. There have been numerous reports of patients enjoying clinically significant rates of 3- to 5-year survival following various forms of aggressive local treatment (eg, surgical resection, radiofrequency ablation [RFA], cryotherapy) for limited metastases in the liver or lung from an assortment of solid tumor types.[17] SAbR is a valid, noninvasive substitute for other local modalities if it can provide similar efficacy and the same or less toxicity.

Many prospective studies have now evaluated the role of SAbR in oligometastatic disease, demonstrating the benefit of this aggressive local treatment on both progression-free survival (PFS) and overall survival (OS).[18] The Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastases[19] multicenter randomized phase II trial assessed the impact of a comprehensive oligometastatic SAbR treatment program on OS and quality of life in patients with up to five metastatic cancer lesions compared to patients who receive standard of care treatment alone. Patients were then stratified by the number of metastases (one to three vs four to five) and randomized between Arm 1: current standard of care treatment and Arm 2: standard of care treatment + SAbR to all sites of known disease with OS as a primary end point. Any primary was allowed, however; the trial was predominantly colorectal (CRC), lung, breast, or prostate cancers. They demonstrated significant improvement in OS for patients who received SAbR compared to those who underwent standard palliative treatment, with a median OS was 41 months in the SAbR group versus 28 months in the standard treatment group. Patients treated with SAbR also had a longer PFS. While most patients had minimal toxicity, this

group did experience significantly higher toxicity compared to the standard arm, with 4.5% succumbing to treatment-related death.

Another trial by Iyengar et al[20] showed that patients with limited metastatic non–small cell lung cancer (NSCLC) who received consolidative RT to both the primary and oligometastatic sites followed by maintenance chemotherapy had significantly improved PFS compared to patients treated with chemotherapy alone. No patients treated with SAbR had infield progression, and the toxicity was similar in the SAbR and chemotherapy-only arms. This was similar to the results of another trial by Gomez et al[21,22] investigating the role of local consolidative therapy in limited metastatic NSCLC; however, this study included other forms of consolidation, including surgery.

Analogous studies in metastatic prostate cancer have also shown promising results. In the phase II Optimal Radiation Treatment in Oligometastatic Disease trial,[23] patients with recurrent hormone-sensitive prostate cancer, limited to one to three metastatic lesions, were randomly assigned to either the observation or SAbR groups, with PFS at 6 months as the primary end point. Disease progression at 6 months was 19% in the SAbR group compared to 61% in the observation group. The results showed that patients who received SAbR had significantly improved outcomes compared to those in the observation group with no grade 3 toxicities. Likewise, the Systemic Therapy for Oligometastatic Prostate Cancer trial[24,25] reported a significant increase in 5-year androgen deprivation therapy (ADT) free survival (8% vs 34%, log-rank $P = .06$) in patients with aggressive metastases-directed therapy, either surgery or radiation, compared to surveillance alone.

Especially intriguing is the possibility that stereotactic irradiation can initiate immunologic responses that can trigger an abscopal response to novel agents. This approach has now gained much attention and has been reviewed extensively.[26,27] One such primary study reports patients with metastatic melanoma receiving ipilimumab and SAbR to one lesion, resulting in a response in 26% of nonirradiated tumors.[28] The optimal timing of immunotherapeutic agents and dose prescription for RT remains a topic of active investigation at numerous centers.

SAbR has revolutionized the management of oligometastatic disease by providing a highly precise and effective treatment option. As our

understanding of the biology of oligometastasis continues to evolve, the role of SAbR in achieving local control (LC) and potentially altering the natural history of metastatic disease becomes increasingly evident.

STEREOTACTIC BODY RADIATION THERAPY GUIDELINES, PHYSICS OVERVIEW, AND SAFETY CONSIDERATIONS

American Society for Radiation Oncology (ASTRO) and the American College of Radiology (ACR) have published guidelines that characterize the personnel qualifications and responsibilities, documentation, quality control, and clinical operations recommended for the safe and proper administration of SAbR and follow-up care for patients treated.[29] The ASTRO-ACR guidelines advise that the following components should be in place within an institution's SAbR program:

1. Qualified personnel
    a. Board-certified radiation oncologist
    b. Qualified medical physicist
    c. Licensed radiation therapist
    d. Other support staff as indicated (dosimetrists, oncology nurses, and so forth)
2. Ongoing machine quality assurance program
3. Documentation in accordance with the *ACR Practice Guideline for Communication: Radiation Oncology*
4. Quality control of treatment accessories
5. Quality control of planning and treatment images
6. Quality control of treatment planning system
7. Simulation and treatment systems that account for systematic and random errors associated with setup and target motion in a manner that is based on actual measurement of organ motion and setup uncertainty.

The American Association of Physicist in Medicine Task Group 101 (TG101) moved forward from the ASTRO-ACR guidelines to generate a report that considers additional important nuances in the planning and treatment delivery of SAbR.[30] Included within the TG101 report are

discussions of potential imaging artifacts and their impact on treatment planning, the challenges of small-field dosimetry, and the importance of using an acceptable dose calculation algorithm, among other issues.

Proper patient repositioning, target localization, and management of breathing-related motion are essential for SAbR. Various patient immobilization devices, including several body frames with external fiducial markers, are available. The so-called frameless systems incorporate ultrasound, kilovolt-range imaging, or near real-time computed tomography (CT) scanning to verify the location of internal targets relative to the beams used. Because SAbR treatment sessions are lengthier than conventional external-beam treatments, patient comfort is an important issue.

Breathing-related motion control devices and systems fall into three general categories: dampening, gating, and tracking or "chasing." Respiratory dampening techniques include systems of abdominal compression intended to diminish one of the most significant contributors to breathing-related motion, namely, diaphragmatic excursion, by obliging the inspiratory-expiratory lung motion pattern to involve more intercostal expansion provided by accessory muscles of respiration and shallower breathing overall compared to diaphragmatic breathing. Also included in this category are the systems employing breath-holding maneuvers to stabilize the tumor in a reproducible stage of the respiratory cycle (eg, deep inspiration). Gating systems for SAbR, as for any RT application, follow the respiratory cycle using a surrogate indicator for respiratory motion, for example, abdominal wall motion, and employ an electronic beam activation trigger allowing irradiation to occur only during a specified range of expected tumor locations. Tracking or "chasing" systems move the radiation beam or patient to mirror the movement of the tumor.

Regardless of the system employed, the treatment planning procedure must include the same consideration for respiratory motion management to be used during treatment. Despite available motion control equipment, some positional uncertainty will remain. The planning target volume (PTV) margins used to account for this residual motion of the gross tumor volume (GTV) will typically range from 3 to 5 mm.

The word *stereotactic* implies that some external reference markers indexed to internal structures facilitate internal target relocalization. The definition has expanded to include systems of image-guided radiation

therapy (IGRT) that relate the position of internal targets to a three-dimensional coordinate geometry registered to the treatment machine without the use of external markers on the patient. SAbR always involves some form of IGRT to guide treatment delivery.

Most reports describing SAbR published to date have employed high-energy photons (x-rays) as the therapeutic radiation source, although any type of radiation, including charged particles, can also be used. There is no absolute standard for the combination of beam or arc angles ideal for any given clinical situation, and each case can present unique challenges. In general, to achieve a tightly focused high-dose distribution within the PTV and rapid dose falloff outside the PTV, a combination of multiple (often 10 or more) ideally noncoplanar beams or multiple arcs are required. Intensity modulation across the individual beams or arc segments can be incorporated within SAbR.

As part of ASTRO's Target Safely campaign, the Multidisciplinary Quality Assurance Subcommittee of the Clinical Affairs and Quality Committee of ASTRO commissioned a white paper on the topic of cranial radiosurgery and SAbR titled "Quality and Safety Considerations in Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy."[31] Of particular importance within the white paper are sections emphasizing the importance of creating a proactive culture of safety with procedural checkpoints and error analysis mechanisms.

CLINICAL EXPERIENCE WITH STEREOTACTIC BODY RADIATION THERAPY IN SELECTED SITES

Liver

The three major reasons for considering SAbR for hepatocellular cancer (HCC) are that underlying severe liver disease often renders patients medically inoperable, other nonsurgical therapies have generally achieved modest success at best, and HCC is more sensitive to large dose per fraction therapy. The natural history of untreated HCC has been reported to involve a median survival in the range of 3 to 8 months,[32-34] and so a safe and effective therapy is needed in this setting.

The earliest observations following SAbR for HCC were reported by a group at Karolinska Hospital,[2] followed by more recent formal prospective

studies. The Princess Margaret Hospital group utilized a six-fraction regimen in a prospective phase I study in patients with HCC (n = 31) or intrahepatic cholangiocarcinoma (n = 10).[35] Prescription doses were selected according to a normal tissue complication probability (NTCP) model based on conventionally fractionated RT for the liver. The median dose to the tumor was 36 Gy (range, 24-54 Gy). The NTCP model overestimated the chance of radiation-induced liver disease, and it is possible that the dose could have been escalated to a higher level in most cases. Nevertheless, in this group of heavily pretreated patients (over 60% had had at least one prior therapy for HCC), a remarkable median survival of 12 months was observed.

Previously, SAbR for HCC has been reserved for patients who had failed previous therapies, and most preliminary studies have been performed in this patient population. However, newer studies have emerged that evaluate SAbR in treatment-naïve patients. Durand-Labrunie et al[36] published a prospective phase II study of 43 treatment-naïve patients with a dose of 45 Gy delivered in 3 fractions, achieving a 2-year LC rate of 98% and an OS rate of 69%. Notably, 31% of the patients experienced toxicities classified as grade III or higher, most of which were abnormal liver function blood tests. In another prospective phase II study by Kimura et al,[37] 36 treatment-naïve patients received 40 Gy delivered in five fractions with a 3-year OS rate of 78% and an LC rate of 90%; however, they noted far fewer toxicities classified as grade III or higher in only 11% of the patients. Unfortunately, this trial was terminated early due to slow accrual.

Consideration of SAbR as a first-line therapy has prompted studies comparing it to other treatment modalities such as RFA and even surgery. Many meta-analyses have evaluated the results of SAbR compared to RFA. One analysis by Wang et al[38] evaluated 7 studies with 7,928 patients and demonstrated that SAbR was superior to RFA in LC (HR = 0.54, 95% CI = 0.35-0.84, P = .006). This improvement was driven by tumors larger than 2 cm (HR = 0.41, 95% CI = 0.23-0.74, P = .003) and was insignificant in tumors smaller than 2 cm (HR = 0.56, 95% CI = 0.25-1.28, P = .17). Another analysis by Facciorusso et al[39] evaluated 9 studies with 6,545 patients and found the recurrence-free survival at 2 and 3 years to be superior in patients treated with SAbR compared to RFA (OR = 2.06, 95% CI = 1.48-2.88 and OR = 1.86, 95% CI = 1.07-3.26, respectively). There

was no difference between the two treatments in 1-year recurrence-free survival (OR 2.11, 0.67-6.63). Neither analysis found any difference in OS or toxicity between the treatments. However, it should be noted that a smaller meta-analysis by Pan et al[40] found OS in patients treated with SAbR to be inferior to that of patients treated with RFA (1-year OS, OR = 1.52, 95% CI = 1.21-1.90, *P* = .0003; and 2-year OS, OR = 1.66, 95% CI = 1.38-2.01, *P* < .00001, respectively). This was attributed to higher tumor burden or liver profiles in the SAbR cohorts, and LC remained superior in these patients.

Comparisons to surgery have also been performed using propensity-matching analyses. Su et al[41] paired 82 patients who received SAbR with 35 patients who underwent liver resection. Before propensity score matching, the 1-, 3-, and 5-year OS was 96.3%, 81.8%, and 70.0% in the SAbR group and 93.9%, 83.1%, and 64.4% in the resection group, respectively (*P* = NS [NS, not statistically significant]). After propensity score matching, 33 paired patients were selected from the SAbR and resection groups revealing 1-, 3-, and 5-year OS was 100%, 91.8%, and 74.3% in the SAbR group and 96.7%, 89.3%, and 69.2% in the resection group, respectively (*P* = NS). There was a similarity in hepatotoxicity between the two groups. A subsequent propensity score-matched analysis by Sun et al[42] in treatment-naïve patients with hepatitis B or C cirrhosis similarly reported comparable OS and PFS outcomes for SAbR and resection with 5-year OS rates of 71.0% and 70.7%, respectively (*P* = .67) and 5-year PFS of 49.0% and 47.3%, respectively (*P* = .35). In contrast to these studies, however, another propensity score-matched analysis from Japan[43] found that OS and PFS favored surgery compared to SAbR, with rates of 75.2% versus 47.8% (*P* = .0149) and 33.8% versus 16.4% (*P* = .0512), respectively. In their study, patients with fewer and smaller tumors tended to benefit the most from surgery.

Beyond definitive treatment, SAbR is also employed as a method of downstaging or bridging to transplant. Maintaining LC while awaiting transplant is critical to ensure patients remain transplant eligible. One small study by O'Connor et al[44] reported that all 11 patients treated with 33 to 54 Gy in 3 fractions made it to transplant. Complete pathologic response was noted in 27% of patients overall but was as high as 60% in patients who

received 54 Gy. Albeit small, this study impressively reported 5-year OS and disease-free survival (DFS) of 100%.

With the advent of magnetic resonance (MR)–based treatment delivery, preliminary studies[45] have demonstrated the feasibility of this treatment modality for both primary and metastatic liver tumors. These areas remain active in research, and further work is needed to evaluate treatment outcomes.

Target delineation and image guidance can be difficult in the liver because liver metastases are poorly visualized on CT scans or in-room volumetric imaging used for IGRT. In many centers, radiopaque fiducial markers are placed in or near the metastases to facilitate IGRT. In all centers, the PTV is an expansion of the GTV considering the setup and intrafraction motion to be expected with the particular setup and delivery system employed. Typically, the margin used to expand a GTV into a PTV is on the order of 5 mm axially and 5 to 10 mm craniocaudally. Consideration of motion management is key, particularly in lesions near the dome, with some centers employing abdominal compression or breath-hold techniques.

A University of Colorado consortium first applied the critical volume approach to normal liver dose constraints in their initial phase I study[46] and subsequent phase II study. Assuming the liver is a functioning parallel structure, it was estimated that at least 700 cm^3 is essential for organ function in an average patient and should therefore receive less than 15 Gy in three fractions, a dose felt to be below a threshold for injury. This was derived from a combination of prior reports of outcomes after partial hepatectomy documenting approximate minimum volumes required and estimates of the effects of that dose of radiation extrapolated from prior reports of conventionally fractionated treatment.

Additionally, posttreatment imaging follow-up in the liver has some unique challenges and considerations. Evaluation of treatment response, failure, and expected normal tissue changes has been extensively reviewed in these articles.[47-49] Critical attention to follow-up imaging is imperative. Increasing use of MR in both diagnostic imaging and now MR-based treatment delivery will continue to evolve the treatment and follow-up of liver lesions treated with SAbR.

Case Study: Liver Stereotactic Body Radiation Therapy

A 25-year-old man with complex cyanotic congenital heart disease has developed cardiac cirrhosis. He developed multiple liver lesions which remained stable under close surveillance for 4 years with one progressive lesion in segment 2. Biopsy showed moderately differentiated hepatocellular carcinoma in the background of congestion and cirrhosis. He is not a surgical candidate and the lesion was not amenable to ablation or vascular approaches. He was offered SAbR as a bridge to heart/liver transplant.

The 12.9 cm^3 GTV was expanded by 3 mm radially and 5 mm in the superior-inferior direction to generate the 26.7 cm^3 PTV (Figure 17.1). The dose distribution shown was administered in three fractions within 1 week using two dynamic conformal arcs and a controlled breath-holding device. The nominal prescription dose was 48 Gy. The maximum point dose was 59 Gy, and the equivalent uniform dose was 53 Gy. The volume of normal liver receiving less than 15 Gy was 110 cm^3. The maximum dose to the heart was 1.3 Gy. The lesion remained controlled for nearly 3 years until he was able to undergo heart and liver transplant for definitive management.

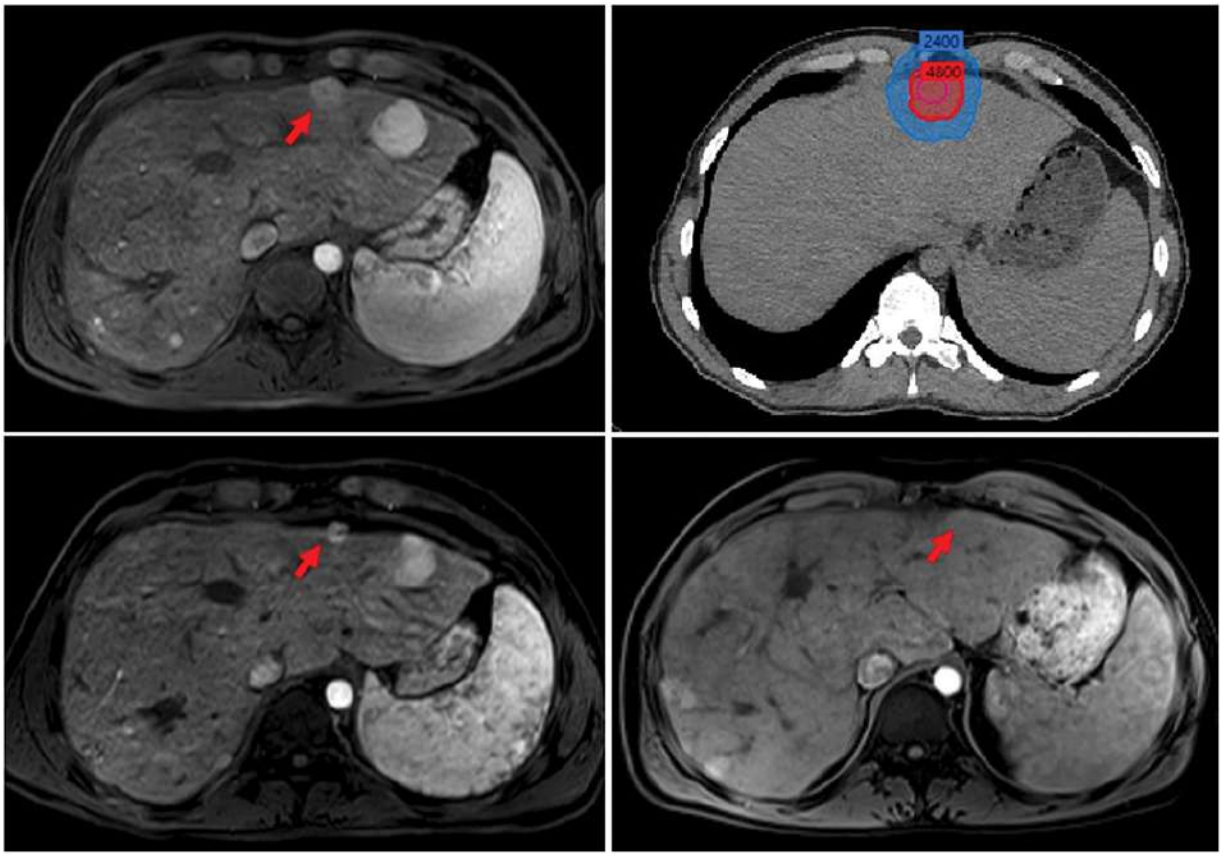

FIGURE 17.1 Example of liver stereotactic ablative radiotherapy (SAbR). Top: Pre-SAbR T1 post-contrast magnetic resonance (MR) image showing progressive segment II lesion (red arrow) and treatment plan with dose levels outlined (4,800 cGy red, 2,400 cGy blue). Bottom: MR image 3 months (left) and 3 years after SAbR with responding lesion (red arrow).

Lung

Medically inoperable early-stage lung cancer has historically provided a substantial management challenge. Conventionally fractionated RT has generally yielded unsatisfactory outcomes with high rates of local failure and 3-year survival rates of approximately 30%. For this reason, medically inoperable early-stage lung cancer was the first clinical indication for which SAbR was studied in prospective clinical trials. Following the early exploratory studies of lung SAbR for stage I NSCLC at the Karolinska Hospital in Stockholm[50] and National Medical Defense Hospital in Saitama,[3] numerous formal prospective studies of SAbR for medically inoperable NSCLC have now been reported. The consistent observation is that 3-year survival is achieved on the order of 50% to 60%. A randomized

clinical trial comparing SAbR (66 Gy in three fractions) to conventionally fractionated RT (70 Gy in 35 fractions) in this setting revealed equivalent OS despite slightly worse prognostic features in the SAbR arm. Patients who received SAbR also had lower rates of pulmonary toxicity and better self-reported quality of life.[51]

One important observation from the Indiana University studies was that although the treatment was generally well tolerated, tumor location near large airways near the pulmonary hilum (called the zone of the proximal bronchial tree) was associated with a markedly higher risk of toxicity. For this reason, in the Radiation Therapy Oncology Group's (RTOG) study RTOG-0236 of SAbR for medically inoperable NSCLC, patients with tumors located in the zone of the proximal bronchial tree were excluded.[52] The RTOG launched a separate dose-escalation study (ROTG-0813) in which tumors near the proximal bronchial tree were treated to doses of 50 to 60 Gy in five fractions.[53] Protocol specified dose-limiting toxicity (DLT) rates were low, though some late toxicity outside those definitions occurred. The ASTRO has issued a guideline on SAbR for early-stage lung cancer that addresses key questions of patient selection and dose regimen for peripheral and central tumors.[54]

Recent multicenter prospective studies have confirmed the superiority of SAbR to conventional RT for inoperable NSCLC in terms of toxicity outcomes and quality of life with equivalent disease control. The Scandinavian multicenter randomized phase II trial, Stereotactic Body Radiation Therapy for Patients With Peripheral Lung Cancer,[51] included 102 patients with inoperable peripheral T1-T2 tumors (6 cm or smaller) and compared SAbR (66 Gy in 3 fractions) with conventional RT (70 Gy in 35 fractions). With a median follow-up period of 37 months, the results showed NS differences in OS or LC between the two treatment groups. Likewise, the Convenient Hypofractionated Image-guided Stereotactic Ablative Radiotherapy for Lung Cancer[55] multicenter phase III trial based in Australia and New Zealand randomized 101 patients with inoperable peripheral T1-T2, N0, M0 tumors to SAbR or conventional RT. In the SAbR arm, patients received either 54 Gy in 3 fractions or 48 Gy in 4 fractions (if the tumor was <2 cm from the chest wall), while those in the conventional RT arm were treated with either 66 Gy in 33 fractions or 50 Gy in 20 fractions. The study reported a statistically significant

improvement in LC (HR 0.32) and OS (HR 0.53) in favor of SAbR with a median follow-up of over 2 years.

The use of SAbR in medically operable patients has also been the subject of retrospective studies and ongoing prospective trials. Zheng et al[56] conducted a meta-analysis of 63 (40 studies on SAbR involving 4,850 patients and 23 studies on surgery involving 7,071 patients) to compare treatment outcomes specifically for patients with T1-T2, N0, M0 disease. After adjusting for factors such as the proportion of patients suitable for surgery and patient age, the analysis revealed that SAbR and surgery exhibited similar results regarding LC, OS, and DFS. More recently, a prospectively collected cohort analysis compared long-term outcomes of patients treated with SAbR and surgery in patients with newly diagnosed cT1a-bN0M0 NSCLC. The study, which combined 2 separate prospectively collected cohorts (International Early Lung Cancer Action Program and Initiative for Early Lung Cancer Research on Treatment) for a total of 1,115 patients, found that 10-year-ling-cancer-specific survival was similar between surgery and SAbR (90% and 88%, respectively; $P = .48$).[57] RTOG-0618,[58] a single-arm phase II, evaluated SAbR outcomes prospectively in 26 operable patients with biopsy-proven peripheral T1-T2 (tumor size 5 cm or smaller), N0, M0 NSCLC. Patients received 54 Gy in 3 fractions. The study reported 4-year local-regional control of 88% and 4-year OS of 56%. Prospective analyses directly comparing SAbR with surgery have proven difficult with the SAbR for Lung Tumors: A Randomized Study, Stereotactic Ablative Radiotherapy for Early Stage Lung Cancer, and American College of Surgeons Oncology Group/Radiation Therapy Oncology Group), three randomized phase III trials, closing early due to poor accrual. A pooled analysis of these studies reported better OS and lower toxicities in the SAbR arm; however, this study has been criticized for reporting higher rates of surgery toxicity than historical data.[59] Multiple new prospective randomized trials, including the Joint Lung Cancer Trialist's Coalition STABLEMATES trial and the Veterans Affairs Lung Cancer Surgery or Stereotactic Radiotherapy trial, are ongoing.

Importantly, while LC of early-stage lung tumors has been demonstrated with SAbR, these patients not infrequently (~43%) develop regional or distant metastases.[60] To address this, a recent phase II randomized study evaluated the combination of SAbR and immunotherapy. They report

significantly improved event-free survival at 4 years in patients with early-stage lung cancer who were treated with nivolumab and SAbR over those treated with SAbR alone (77% vs 53%, respectively; $P = .006$).[61] Randomized phase III studies are needed to test the robustness of this observation.

As discussed earlier, SAbR to pulmonary metastases in oligometastatic disease is a widely accepted treatment with good LC and minimal toxicity. A recent review by a Japanese group[62] highlights treatment considerations based on the primary disease site and tumor location. These findings imply that certain pathologies, such as CRC metastasis, may warrant higher doses to increase better LC.

Case Study: Lung Stereotactic Body Radiation Therapy

A 90-year-old with a 40+ pack-year smoker with history of multiple strokes without sequela and coronary artery bypass graft developed shortness of breath or cough and was found to have a cT1cN0M0 squamous cell carcinoma of the right upper lobe. He was not a surgical candidate due to his multiple comorbidities and was offered SAbR. The patient did not comfortably tolerate a breath-holding technique; therefore, an abdominal compression technique was used during the simulation and treatment. An internal target volume (ITV) was generated by contouring the GTV over the breathing cycle. The 7.7 cm^3 ITV was expanded by 5 mm symmetrically to generate the 23.9 cm^3 PTV (Figure 17.2). The dose distribution shown was administered in 3 fractions within 1 week using 10 noncoplanar beams. The nominal prescription dose was 60 Gy. The maximum point dose was 88 Gy, and the equivalent uniform dose was 72 Gy. The portion of normal lungs receiving less than 15 Gy was 6.5%. Eighteen months following treatment, the patient was noted to have a new primary malignancy in his right lower lobe on follow-up imaging. He was again offered SAbR to the new lesion. The new 2.9 cm^3 ITV was expanded by 5 mm symmetrically to generate the 12.4 cm^3 PTV (Figure 17.2). The dose distribution shown was administered in 5 fractions over 2 weeks using 10 noncoplanar beams. The nominal prescription dose was 60 Gy. The maximum point dose was 90 Gy, and the equivalent uniform dose was 73 Gy. The portion of normal lung receiving

less than 15 Gy was 5.7%. Both lesions have remained controlled to date, greater than 4 and 2 years, respectively.

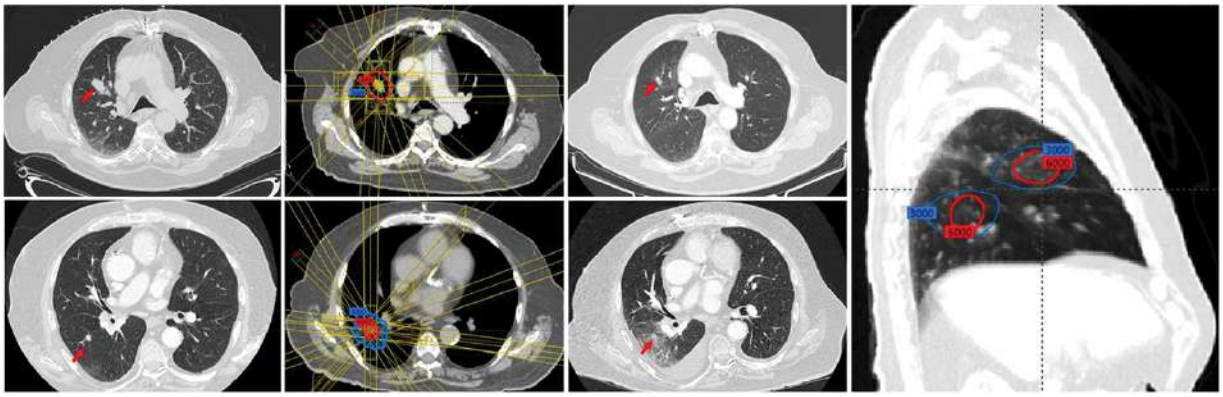

FIGURE 17.2 Example of lung stereotactic ablative radiotherapy (SAbR). Top: Pre-SAbR computed tomography (CT) image showing initial right upper lobe lesion (red arrow), treatment plan with fields and dose levels outlined (6,000 cGy red, 3,000 cGy blue), and CT image 6 months after SAbR. Bottom: Pre-SAbR CT image showing secondary right lower lobe lesion (red arrow), treatment plan with fields and dose levels outlined (6,000 cGy red, 3,000 cGy blue), and CT image 6 months after SAbR. Right: Sagittal CT showing dose distribution of two plans.

Spine Cancer

Early investigations of spine SAbR involved delivering a single-fraction boost of 6 to 10 Gy following conventionally fractionated therapy either as one course of treatment or for retreatment of recurrent disease. This had overall good outcomes with excellent pain relief and no complications.[1,63,64]

MD Anderson Cancer Center performed a prospective phase I dose-escalation study in treating spinal metastases.[65,66] The equipment used included a "CT on rails" that allowed for imaging immediately to guide patient repositioning. Approximately half of the 63 patients received 30 Gy in 5 fractions, and the other half received 27 Gy in 3 fractions. A conservative constraint of 9 to 10 Gy maximum dose to the spinal cord was applied. No neuropathy or myelopathy was observed during a median follow-up period of nearly 2 years. The actuarial 1-year tumor progression-free rate was 84%. The investigators noted two characteristic patterns of failure: (a) recurrence in the bone adjacent to the site of previous treatment and (b) recurrence in the epidural space adjacent to the spinal cord.

Several observations of reasonable tumor control and minimal toxicity have been reported from other centers. Commonly used fractionation schemes now include 16 to 24 Gy in one fraction, 24 Gy in two fractions, 24 to 40 Gy in three fractions, and 25 to 40 Gy in five fractions.[67] A review of 5,655 patients showed 1-year rates of local tumor failure of only 10% to 20% following spine SAbR.[68]

Fortunately, spinal cord toxicity has only rarely been observed after SAbR. Case-control comparisons offer some suggestions of parameters that might elevate the risk, but the paucity of events evaluable makes it challenging to draw firm conclusions.[69,70] Constraints used to guide spine SAbR have included maximum point dose to the cord in the range of 10 to 14 Gy and limiting the volume of adjacent spinal cord receiving more than 10 Gy in a single fraction to 0.35 mL or less.

The International Spine Radiosurgery Consortium (ISRC) group has published guidelines for target definition and response assessment after spine SAbR.[71] The SPIne response assessment in Neuro-Oncology Group has likewise issued guidance on response assessment.[72] While the ISRC recommends treating the entire vertebra segment based on disease location, it is unclear whether normal bone adjacent to the GTV needs to be treated to such ablative doses. Higher doses, such as 20 Gy in a single fraction, improve rates of LC; however, they are associated with a higher vertebral fracture (VF) risk, which is the most commonly reported toxicity, with rates of up to 40% in some series for spine SAbR.[73] Memorial Sloan-Kettering Cancer Center reported that lytic disease involving more than 40% of the vertebral body and location at or below T10 increased this risk.[74] MD Anderson Cancer Center found that VF was more common among patients over 55 years, those with a preexisting fracture, and those experiencing pain at the time of treatment.[75]

The group at the University of Texas Southwestern has established a treatment protocol designed to minimize the risk of single-fraction toxicities by applying a lower dose of 14 Gy to the ISRC-defined clinical target volume and a higher ablative dose of 20 Gy to the GTV followed by prophylactic vertebroplasty.[76] They report excellent pain control in 95% of patients at 3 months and LC of 92% with 9-month follow-up. The higher rate of pain control observed was durable, as the freedom from VF rate persisted beyond 90% past 1-year with ongoing follow-up.

Prostate Cancer

The first publication on SAbR for prostate cancer was the work of Madsen et al,[77] who recently updated their observations. In a prospective trial, 40 patients with low-risk cancer (Gleason score ≤6 and prostate-specific antigen ≤10 ng/mL) were treated to a dose of 33.5 Gy in 5 daily fractions. Most of these patients were treated with SAbR after being found ineligible for brachytherapy due to pubic arch interference. The median age was 69 years (50-82), and the median follow-up period was 5 years. The overall 5-year Phoenix definition (nadir plus 2 ng/mL) biochemical relapse-free survival (bRFS) rate was 93%. No patients died of prostate cancer. Late grade 3 genitourinary (GU) toxicity was rare, occurring in only one patient, and no late grade 3 or higher gastrointestinal (GI) was observed.[78]

Over the past several years, prostate SAbR treatments have rapidly increased. The Stereotactic Body Radiotherapy for High-Risk Localized Carcinoma of the Prostate Consortium[79] recently evaluated the results of seven institutional phase II trials and prospective registries. The group pooled individual data for 344 patients to assess the rates of bRFS and distant metastasis-free survival (DMFS). Patients were treated with five fractions of 7 to 8 Gy. ADT was used in 72% of patients. With a median follow-up of 49.5 months, they reported 4-year biochemical recurrence-free survival of 81.7% and DMFS of 89.1%. In addition, they found no acute grade 3 or higher GU and GI toxicities with a crude incidence of late grade 3 or higher GU and GI toxicity of 2.3% and 0.9%, respectively. Doses of 8 Gy or more were associated with higher GU and GI toxicities rates.

The Hypofractionated Radiotherapy for Prostate Cancer trial,[80] a randomized, noninferiority, phase III study comparing ultrahypofractionated RT 42.7 Gy in 7 fractions over 2.5 weeks with conventionally fractionated RT 78 Gy in 39 fractions for prostate cancer, revealed promising results at 5-year follow-up. The trial enrolled 1,200 patients from 2005 to 2015 with intermediate and high-risk prostate cancer. The results showed that ultrahypofractionated RT was not inferior to conventional fractionation, with a failure-free survival of 84.0% in both groups (P = .99). Patients treated with the SAbR regimen did have worse acute grade 2 or higher urinary and bowel toxicity upon completion of treatment; however, there was no longer an increase in bowel toxicity

observed at follow-up. Urinary toxicity remained increased in the SAbR group at 1-year follow-up (6% vs 2% of patients with grade 2 or higher, P = .018) but was similar to the conventional group at all subsequent time points. There were no differences in erectile function between the two groups.

In contrast, the Prostate Adaptive Conformal Radiotherapy: Evaluation of Stereotactic Body Radiotherapy trial,[81] which compared SAbR (36.25 Gy in 5 fractions over 1 to 2 weeks) with conventionally or moderately hypofractionated radiation (78 Gy in 39 fractions or 62 Gy in 20 fractions, daily) in patients with low- to intermediate-risk prostate cancer, found no significant increase in either GI or GU acute toxicity in patients receiving SAbR compared to those receiving other fractionations. SAbR provided a 5-year biochemical failure-free rate of 95.7% (93.2%-97.3%), compared to 94.6% (91.9%-96.4%) for those treated with conventional or moderately hypofractionated radiation, demonstrating that SAbR was noninferior to the other regimens (90% CI; P for noninferiority = .007).[82] The early safety signals also held up with a longer follow-up, with no significant difference seen in GU or GI grade 2 or higher toxicity at the 2- or 5-year time points.[81,82]

Boike et al[83] from the University of Texas Southwestern have completed a dose escalation for prostate SAbR, aiming for a more aggressive regimen potentially suitable for patients with intermediate- or high-risk disease. At the highest dose level of 50 Gy in five fractions, 6.6% of patients treated (6 of 91) developed high-grade rectal toxicity, five of whom required colostomy.[84] Grade 3+ delayed rectal toxicity was strongly correlated with the volume of the rectal wall receiving 50 Gy to more than 3 cm^3 (P < .0001) and treatment of over 35% circumference of the rectal wall to 39 Gy (P = .003). Grade 2+ acute rectal toxicity was significantly correlated with treatment of more than 50% of the circumference of the rectal wall to 24 Gy (P = .010).

The use of rectal spacers in patients receiving SAbR for prostate cancer has been associated with lower observed late GI toxicity rates. A recent meta-analysis[85] of 7 studies and 1,011 patients showed that the radiation dose (V70) to the rectum was 66% less in patients with a spacer than those without. This corresponded to comparable acute grade 2 or higher toxicities between the two groups (4.5% in the spacer group vs 4.1% in the control

group) and improved late grade 2 or higher toxicities (1.5% vs 5.7%, respectively; $P = .05$). Procedural complications ranged from 0% to 10% across studies but were mild and transient.

Outside of initial management, there is growing interest in SAbR for salvage treatment after intraprostatic relapse. European Society for Radiotherapy and Oncology-Advisory Committee on Radiation Oncology Practice released consensus recommendations for consideration of this treatment. They set no maximum age for treatment but recommended patients have an ECOG (Eastern Cooperative Oncology Group) score of 0 or 1 and recommended a thorough metastatic workup with choline-positron emission tomography. They do not recommend concomitant ADT with reirradiation. A full list of their recommendations was recently published.[86]

Pancreatic Cancer

The role of conventionally fractionated RT in combination with chemotherapy for locally advanced pancreatic cancer remains unresolved. An effect on OS is not seen consistently, though there is likely at least a moderate benefit in achieving treatment-free intervals in this challenging clinical scenario.[87,88] SAbR offers the ability to treat with greater biologic potency than conventional fractionation, which is associated with better LC rates, while also minimizing disruptions to chemotherapy due to the shorter duration of treatment.[89]

SAbR regimens for pancreas cancer have included treatments given in one to five fractions. The proximity to many radiosensitive organs at risk (OAR) demonstrated unacceptably high toxicities in early studies. This led to the incorporation of smaller treatment volumes and tighter margins, often very different than conventional fractionated RT approaches. However, as discussed later, treatment margins of high-risk areas may reduce local failure risk. Careful consideration must be given to balancing toxicity and local recurrence risk.

Koong et al[90] published one of the initial investigations on SAbR in pancreatic ductal adenocarcinoma. Their phase I dose-escalation trial involving 15 patients delivered a single fraction of 15 to 25 Gy with no instances of DLT observed. Metallic fiducial marker tracking and breath hold were used to minimize target motion. This treatment technique

remains widely used in clinical practice. Since then, many retrospective studies have demonstrated reasonable LC with low toxicity.

Newer studies have continued to evaluate the role of SAbR prospectively. The Alliance A021501[91] was a multicenter randomized phase II trial comparing patients with borderline resectable and unresectable pancreatic cancer receiving mFOLFIRINOX chemotherapy with or without SAbR. Patients were randomized to chemotherapy with conventional hypofractionated RT of 33 to 40 Gy in five fractions or 25 Gy in five fractions or to chemotherapy alone. Disappointingly, overall and event-free survival were adversely impacted by the addition of SAbR to chemotherapy. Both the AGITG MASTERPLAN[92] and the Stanford phase III PanCRS studies are currently evaluating the role of SAbR 40 Gy in five fractions in patients receiving FOLFIRINOX. These results may further elucidate the preoperative role of SAbR in this patient population.

Kharofa et al[93] reported their experiences on patterns of marginal local failure following SAbR in resectable and borderline resectable pancreatic cancer. In this phase II study, patients were treated with three cycles of gemcitabine/ nab-paclitaxel or FOLFIRINOX and restaged. Patients without evidence of progression after their systemic therapy were eligible for enrollment and were treated with SAbR 33 Gy in five fractions, followed by surgery 6 weeks later. The trial was amended to include radiation to at-risk vasculature at a dose of 25 Gy. Six patients had disease progression by the time of surgery, one of which was local. Following surgery, 60% of resected patients had local failure. Although limited by size, they reported a PFS and OS benefit in patients who received RT to the vasculature compared to those who received treatment to the primary alone. Likewise, a large series of 510 patients from China reported local recurrences in 42.5%, with over 50% of those occurring at the celiac trunk or superior mesenteric artery.[94] Although treatment volumes have yet to be fully defined, coverage of high-risk vasculature should be considered.

The addition of dismutase mimetics with SAbR is currently under investigation to improve outcomes in this setting. An initial phase I/II study using a selective dismutase mimetic has proven to be safe with promising overall and PFS.[95] This led to the ongoing multi-institutional study GRECO-2,[96] which is evaluating the effects of adding a selective dismutase mimetic to SAbR at a dose of 50 Gy in five fractions, following

gemcitabine doublet or FOLFIRINOX-based chemotherapy in patients with borderline resectable or unresectable nonmetastatic pancreatic cancer.

Additionally, the use of Magnetic Resonance Linear Accelerators to better delineate disease and OARs in pancreatic SAbR is another area of active investigation. A multi- institutional review of stereotactic MR-guided adaptive radiation therapy (SMART) evaluated 148 patients with borderline resectable, locally advanced, or medically inoperable pancreatic cancer who received 40 to 50 Gy in 5 fractions.[97] They found 1- and 2-year LC rates of 94.6% and 83%, respectively, with no grade 4 or 5 toxicities. The recent prospective, single-arm, phase II SMART trial, evaluating the outcomes of 136 patients with locally advanced or borderline resectable pancreatic cancer treated to 50 Gy in 5 fractions, reported a 1-year LC, distant PFS, and OS of 82.9%, 50.6%, and 65%, respectively.[98] Patients who were able to undergo resection had improved outcomes across each domain compared to those that did not. The authors also report an 8.8% rate of grade 3 or higher acute GI toxicities.

Renal Cancer

Renal cell carcinoma has long been regarded as radioresistant. SAbR in inoperable patients has been increasingly adopted and serves as an excellent alternative to more invasive techniques, such as RFA or cryoablation, especially for larger tumors or those in close proximity to vessels and ureters.

The International Radiosurgery Oncology Consortium for the Kidney (IROCK) released a consensus statement[99] outlining treatment recommendations for kidney SAbR. This was followed by a pooled analysis of 223 patients treated with SAbR.[100] Over half of the patients (118 of 223) received single-fraction SAbR with a median dose of 25 Gy (range 14-26 Gy). The multifraction cohort received a median of 40 Gy (range 24-70 Gy) in 2 to 10 fractions. LC at 4 years was 97.8% and did not differ between the single-fraction and multifraction groups. They did report that patients who received single-fraction treatment had better OS, PFS, and cancer-specific survival at 4 years due to improved distant tumor control. While patients who received single-fraction treatment were younger, had better ECOG scores, and had smaller tumors, these factors were not found to be

independently related to survival. Single treatment was associated with a higher rate of nausea compared to multifractionated treatments. Renal function was minimally affected in either group. Several groups have reported similar outstanding rates of LC.[101]

More recently, IROCK has published their meta-analysis of individual patient data providing 5-year outcomes in 190 patients treated with SAbR for primary renal cell carcinoma.[102] Most patients were treated in a single fraction (43%) with a median dose of 25 Gy. The estimated glomerular filtration rate decreased by a median of 14.2 mL/min/1.73 m^2 5 years after treatment. At 5 years, the cumulative incidence of local failure was only 5.5% for the group, with an estimated cancer-specific survival of 63.6%. Patients treated in a single fraction had improved PFS than those treated with multifraction treatment regardless of tumor size. LC was also improved in single-fraction regimens. However, this study has similar biases of younger, higher performing patients receiving single-fraction treatment, and fractionation regimens remain to be tested prospectively.

SAbR for metastatic renal cell carcinoma has also increased over the past several years, spurred on by the promising use of SAbR in other oligometastatic settings and the increased use of immunotherapy. Several phase II studies, such as RADVAX RCC and NIVES,[103] have shown safety and preliminary efficacy in patients treated with immune checkpoint inhibitors in combination with SAbR to one or two lesions. Longer-term follow-up and randomized phase III studies are still needed in this ever-growing setting.

CONCLUSIONS

SAbR has emerged as a versatile strategy with a wide range of applications for many different types and stages of cancer. As with any form of radiation therapy, careful attention to patient selection and technical quality assurance is essential for the effective and safe implementation of SAbR. Future advances will refine our understanding of the biologic mechanisms and optimal integration and sequencing of SAbR with other anticancer therapies. While the durable efficacy of SAbR is apparent in many clinical models described in this chapter, the lack of severe, late toxicity predicted

by many antagonists is also apparent even with widespread implementation and decades of follow-up.

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CHAPTER 18

High-Dose, Ultra-High Dose Rate (FLASH), and Spatially Fractionated Radiotherapy

Robert J. Griffin, Yolanda Prezado, and Nina A. Mayr

The discipline of radiation oncology and radiation therapy (RT) research has had a major infusion of interest in nontraditional uses of ionizing radiation, specifically in the FLASH, high-dose, and spatial fractionation domains in recent years, a notable trend since the last edition of this textbook. No longer exclusively seen as a "kill all the tumor cells," "fee for service" modality, radiation as one of the multiple available tools in multidisciplinary care plans against cancer has brought the concepts of FLASH and various forms of spatial fractionation (GRID, lattice, minibeam, and microbeam) to the forefront in the continual search for normal tissue–sparing and tumor-controlling treatment plans. Principally, this is due to the long-standing concept of dividing the dose into "on and off" or hot and cold regions, which spares/allows normal tissue damage recovery and repair, yet adds a boost dose to the tumor. More recent work also suggests that increased antitumor effects of these new delivery techniques are due to bystander effects, engagement of the inflammatory/immune system, and inducing a tumor environment that is susceptible to concomitant or subsequent rounds of chemoradiation. Similarly, but more recent, is the flurry of preclinical and early clinical results demonstrating a sparing of normal tissue relative to tumor tissue using dose rates in the 50 to 500 Gy/s window, a situation that has been coined "FLASH" radiotherapy. In both cases, spatially fractionated radiation therapy (SFRT) and FLASH, the dose per fraction has been higher than conventional wisdom, a feature that calls into question the ideas and mechanisms by which stereotactic body radiation therapy (SBRT) has now been defined by vascular damage, indirect cell death, and shorter overall courses of treatment. Hand in hand with these intriguing concepts and growing proof of responses that benefit the therapeutic ratio, the increasing capabilities of present-day radiation delivery technology are a major contributor to the explosion of these approaches. Figure 18.1 is an example of the dose deposition characteristics from all the modalities to be discussed in this chapter. It is our hope that we can illustrate the preclinical, translational, and clinical results and the challenges that remain in preclinical and clinical implementation. With more participation by wider portions of the radiation oncology field, it is expected that these value-added new beam parameters in a variety of formats will produce continued evidence of patient benefit. Among the most important concepts to remember when considering these unconventional radiation treatments is that due to the reduced normal tissue effects, prior or subsequent standard-of-care regimens are commonly administered, which further increases the chance of improved patient outcomes.

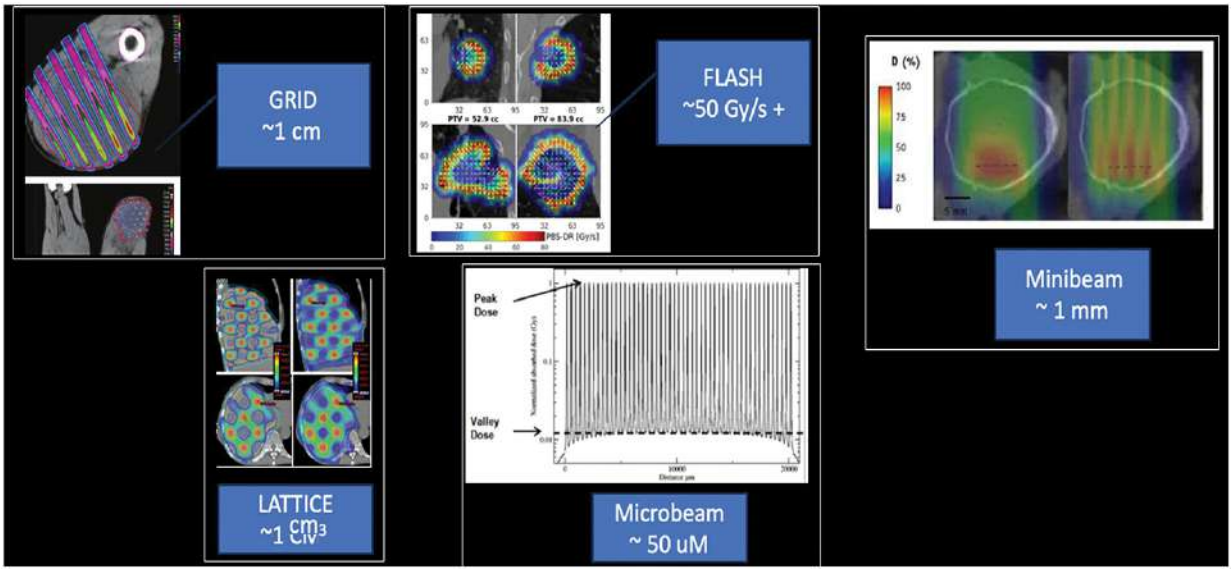

FIGURE 18.1 Examples of treatment planning and dosimetry (peak beam width and output) used in GRID, lattice, FLASH, and microbeam or minibeam preclinical or clinical studies.

HISTORY AND BACKGROUND

Spatially Fractionated Radiation Therapy

SFRT has been clinically defined as the treatment of tumors with highly heterogeneous dose distributions since its first installment in the early 1900s when Alban Köhler introduced the concept. In that era, SFRT was used to overcome the limitations of poor depth dose and high skin toxicity from kilo—and orthovoltage radiotherapy, which were the only available teletherapy technologies at the time.[1,2] Although SFRT fell out of favor with the introduction of megavoltage technologies with their improved depth dose properties, achieving local control in bulky voluminous tumors and therapy-resistant/refractory tumors continued to pose significant and persistent challenges. This dilemma gave rise to the reintroduction, development, and further advancement of SFRT as a megavoltage application in the late 1980s[3] and its subsequent expansion in clinical practice. The current SFRT addresses this challenge by combining megavoltage-generated dose heterogeneity with large dose fractions in the hypofractionation/ablative domain to both escalate tumor dose and reduce normal tissue dose.

In a variety of single-institution pilot studies over the past three decades, promising outcomes of unexpectedly robust tumor responses along with low toxicity rates have been observed with SFRT in challenging bulky, treatment-refractory recurrent/metastatic tumors.[4-6] More recent studies showed similar favorable responses to SFRT in several malignancies treated with curative intent.[5,7] Most of these studies have implemented two variations on spatial fractionation in terms of the geometry of dose deposition. The one with the longest history and most overall clinical experience is commonly referred to as "GRID" therapy, paying homage to the early 1900s when Köhler placed an actual metal screen over the skin to allow a well-defined geometric pattern of radiation exposure and blocking.[1] The other, more recently developed approach has been coined "Lattice" therapy since the dose deposition is targeted to deliver three-dimensional variably spaced high-dose spheres (vertices) within a tumor volume. Lattice treatment has been gaining steady interest and clinical implementation in a number of centers, and a growing number of clinical reports suggesting value for the treatment are available.[7-9]

Over the many years since it was first utilized, GRID has typically been applied using a fixed screen placed on the patient with open and closed apertures, or a "honeycomb" collimator has been placed in the beam of the linear accelerator or the multileaf collimation system in modern linear accelerators (MLC) is used to "shape" the GRID pattern. In all cases, the primary goal was, and continues to be, avoiding normal tissue damage, and most studies report just that very low, often negligible increase in any toxicity profile. A more advanced approach, termed Lattice therapy, can exploit the 3D dosimetry capabilities in current planning stations to deposit a lattice of nodes of high doses in a target tumor volume. More often than in the case of GRID, Lattice therapy has been studied when given in multiple fractions for pain relief or palliation, akin to a course of palliative SBRT.[8] An important aspect of both GRID and Lattice is that they are often followed by conventional chemoradiation regimens. Few

instances are available from the clinical literature of a single use of SFRT without additional radiotherapy. However, a more significant portion of the preclinical data available has been obtained from studies that only treated with SFRT. Regardless, it has been postulated multiple times that the effects of SFRT on the primary tumor may include mechanisms of sensitization or other sorts of priming to improve subsequent therapy effects.[6,10] This is a disconnect in the translational potential of these unconventional therapy approaches. To date, few if any multi-institutional or prospective randomized clinical trials using SFRT with or without other therapy have been conducted. However, in parallel with the growing database of preclinical information and increased focus on standardizing clinical SFRT delivery in single-center studies, there is more clinical trial rationale emerging that should provide answers for the broader field of radiation oncology to adopt. For example, new consensus statements have been recently published, derived from a survey of many radiation oncologists in the fields of radiosurgery and stereotactic radiation treatments for lung and ovarian tumors,[8,11] with other disease sites currently being surveyed in a similar fashion. Other groups are investigating and developing best practice recommendations for the physical aspects of treatment goals in heterogeneous dosing to produce results from a variety of centers that can be compared with confidence in how the treatments were applied.[9,12-15]

It is also worth recognizing here that versions of heterogeneous dosing are also being investigated related to the same theme but with slightly different features. Exciting work from multiple centers has emerged regarding the effects of low-dose radiation exposure and immune stimulation. Partial irradiation or purposeful low-dose/high-dose exposures to specific metastatic lesions in the same patient may have similar beneficial mechanisms of action to those hypothesized to be involved with GRID and Lattice.[16-18] Even more analogous to GRID and Lattice, microbeam/minibeam radiation therapy (MRT) has continued to develop a new rationale for implementation, thanks to a growing stream of compelling preclinical data.[19,20] Microbeam is mostly in preclinical stages, but many of the same principles apply as in GRID or Lattice-scale treatment fields, and there are several international groups working on the launch of initial clinical studies.[19,20] Minibeam therapy, especially with protons or photons using beams around 1 mm wide, has made a major increase in the pace of investigation in the past decade or so.[21-23] No matter the specific modality, the common features that apply to all SFRT methods employed to date are potential primary tumor debulking with lower damage to normal tissue and engagement of pro-antitumor immunity mechanisms, warranting the further development and study of the various approaches available to the radiation oncology clinic at present. However, even if the mechanisms of action might be generally the same, none are well understood at a detailed level at this time. Certainly, in addition to added direct cell killing by virtue of the high peak doses, bystander, abscopal effects, vascular damage, and angiogenic and immune responses are likely involved, and the current literature and understanding or gaps in knowledge will be discussed further on in this chapter.

Ultra-High Dose Rate (FLASH) Radiation Therapy

The availability of more advanced radiation technology in the mid-20th century led to some very early observations of what was coined the “FLASH effect” in recent years.[24-26] These possible normal tissue–sparing effects of ultra-high dose rates (UHDRs; many tens or hundreds of Gy/s) have now been the subject of an array of preclinical and emerging clinical testing of the paradigm (for an extensive review of the field, please refer to refs[1,27,28]). High, single-dose therapy at more conventional dose rates has been increasingly studied with the massive technologic advances available in our treatment machines and the growing database of safe, effective, and time-saving SBRT and stereotactic radiosurgery (SRS) regimens,[29,30] yet significant threat to normal tissue remains. Therefore, the seminal renewal of the use of UHDRs published by Favaudon and Vozenin et al nearly 10 years ago demonstrating the potential for high dose sparing of normal tissues only when delivered at extremely high dose rates has been a reawakening for the translational radiation oncology field. As things have progressed and very rapidly been transferred to clinical use, there has been a general realization that the beam parameters for true FLASH benefit are complex and the site of the tumor may dictate a very select set of disease conditions in which electrons or protons/photons could be successfully adopted for FLASH treatment and patient benefit.[31,32]

Indeed, negative results have also been recently reported from preclinical experiments and veterinary trials of FLASH radiation.[32] This indicates that parameters other than UHDR may contribute to the FLASH effect. These may include beam structure (ie, pulse width or repetition rate), radiation dose, irradiated volume, and oxygen concentration in radiation-exposed healthy tissue.[33] Concerning the latter, there have been several reports pointing to the disappearance of the FLASH effect in well-oxygenated tissues.[34] Moreover, in a recent study, it was observed that UHDR in oxygenated tissues induced even more severe damage than conventional irradiations.[35]

Further research is needed to investigate the impact of the dose, fractionation scheme and volume/dose conformality, oxygen content, and linear energy transfer on the FLASH effect.

To move toward FLASH-RT clinical trials of large radioresistant or recurrent tumors, further and comprehensive studies exploring FLASH-RT are still lacking. First, the current evidence on tumor control by FLASH therapy is much more limited than normal tissue sparing, and most of the studies use a single-dose scheme. Studies assessing the maximum dose and the time delay between fractions for which the FLASH effect still stands are requested. All those evaluations are necessary to critically evaluate its toxicity and efficacy under a more clinically relevant scenario. No evaluation of the FLASH effect in reirradiations has been carried out. The radiobiologic mechanisms governing the differential dose sparing in FLASH irradiations and the probability of occurrence are still unclear. To analyze these uncertainties, FLASH treatments require additional standardized reporting of the application and of the physical and technical parameters that may influence the efficacy of the FLASH effect, as argued in the previous review.

PRECLINICAL UNDERSTANDING OF MECHANISMS OF ACTION

Figures 18.2 and 18.3 illustrate a basic outlay of the major mechanistic factors that have been identified empirically or hypothesized and studied in the search for developing a complete mechanistic understanding of SFRT (Figure 18.2) and UHDRs (FLASH) (Figure 18.3). These topics have been investigated in varying levels of detail over the last century or more, with most of the results coming in the last 30+ years.

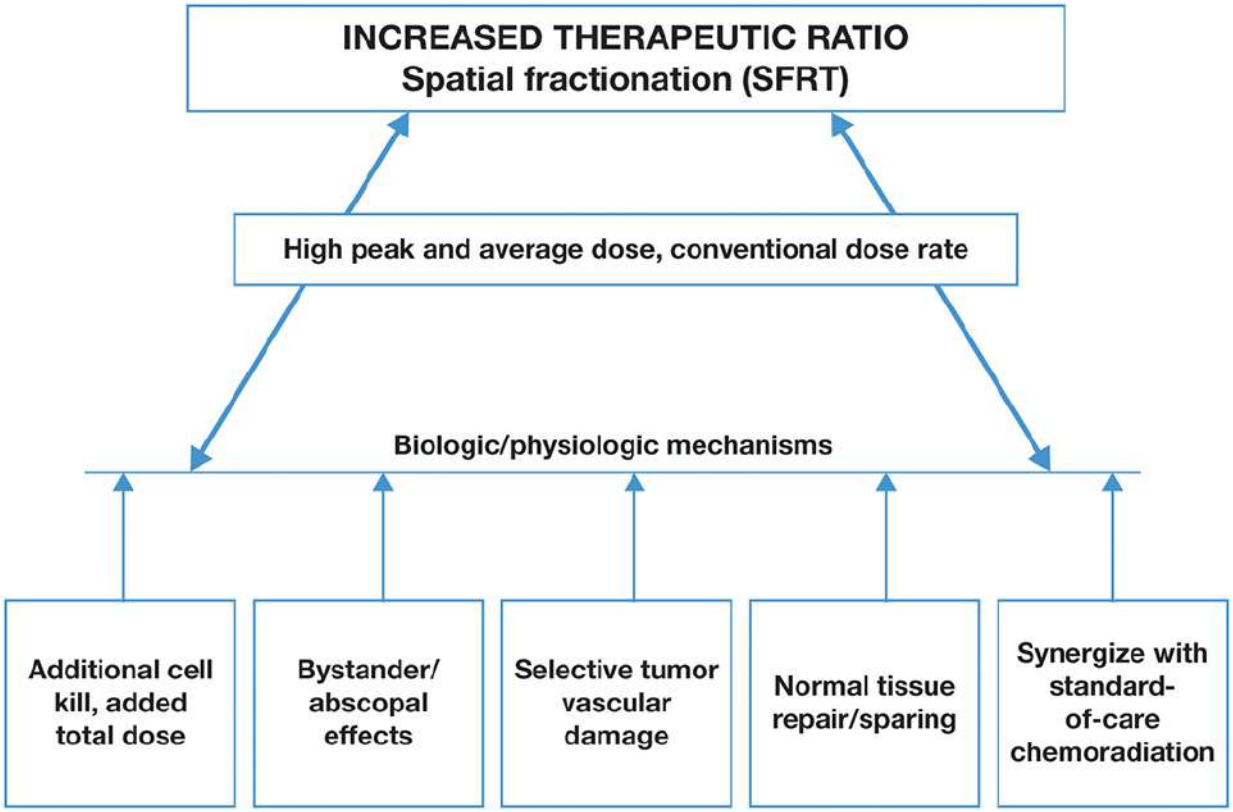

FIGURE 18.2 Current hypothesized mechanisms and effects of SFRT contributing to improved therapeutic ratio. Relatively more is known about the SFRT effects, but there are still large questions to be answered to standardize applications. SFRT, spatially fractionated radiation therapy.

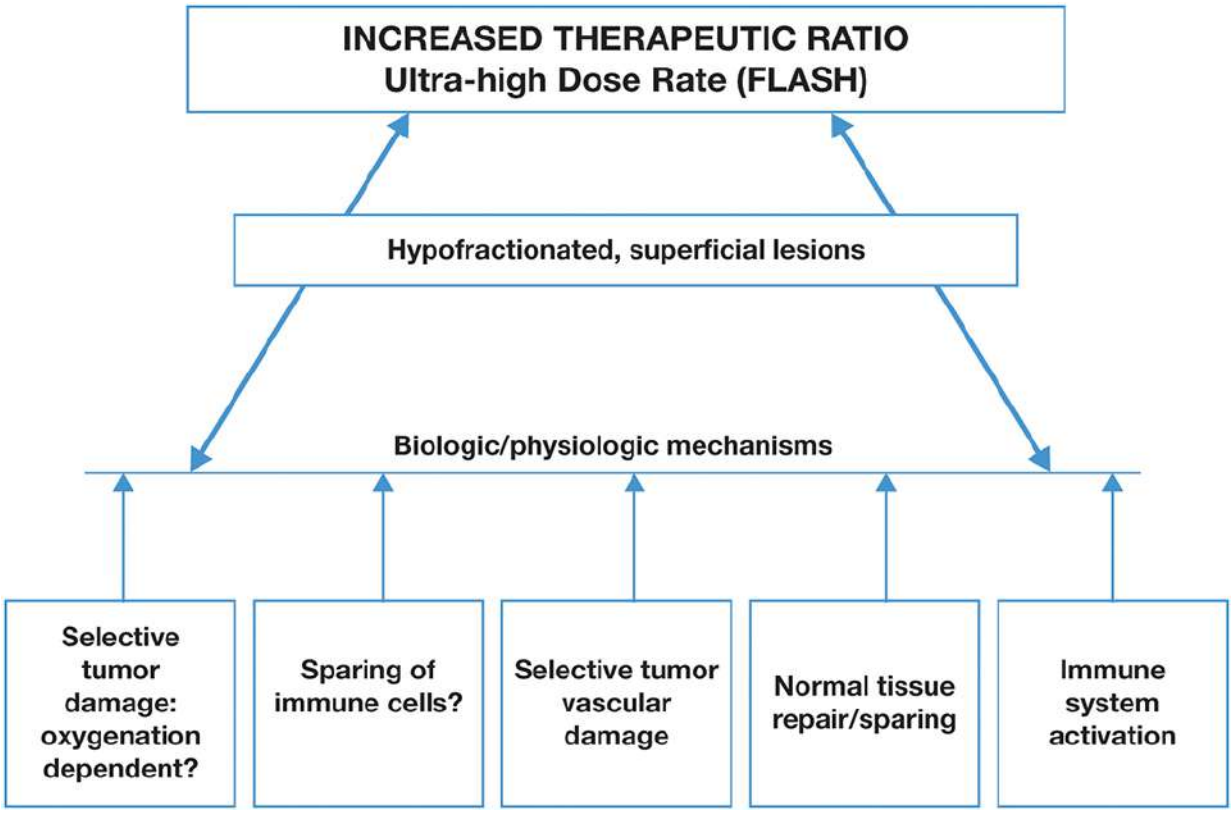

FIGURE 18.3 Current hypothesized mechanisms and effects of FLASH dose rate exposures contributing to improved therapeutic ratio. The combination of SFRT and FLASH occurs in some SFRT formats but has not been fully studied to date.[19] SFRT, spatially fractionated radiation therapy.

Spatially Fractionated Modalities Preclinical Research

The possible biologic mechanisms by which any form of SFRT contributes to overall tumor control alone or in the context of standard-of-care chemoradiation regimens are still not entirely clear. Important aspects of immune activation, vascular damage/modulation, tumor microenvironment, and bystander effects that contribute to the overall response to SFRT alone and with subsequent standard-of-care regimens are being gradually uncovered, and improved clinical trial designs may be the results in upcoming years. In between microbeam and GRID, there is the rapidly growing field of minibeam therapy, which is finding great potential and might be in the "sweet spot" considering all aspects of the physics and biology of SFRT. There are many studies in the recent literature that demonstrated better tumor control and normal tissue tolerance in rodent and canine studies at very high peak doses, especially for brain tumors; (bystander) induced differentiation may also play a role and could be used for benign conditions. In general, the orthovoltage minibeam may have value due to the very high peak-to-valley dose ratios (PVDRs) that can be obtained in comparison to high-energy/high-dose SFRT type of therapy. However, megavoltage photon as well as proton and heavier ion beams are also being actively investigated with promising preclinical results and demonstrated steps toward clinical implementation, taking advantage of improved energy deposition patterns possible, especially with proton or other particle beams.[22,36-42]

Preclinical studies employing small animal conformal irradiation systems have suggested that biologic mechanisms of action of SFRT are related to bystander killing as well as vascular damage and remodeling, leading to debulking and improved tumor oxygenation.[43-45] These aspects of biologic response by the tumor have been studied in both aerobic and hypoxic conditions, and it was found that hypoxia modifies the bystander killing in some cases.[46,47] In general, the bystander effect is short range between adjacent cells within the same tissue while the abscopal effect has been coined to describe a long-range, whole-organism phenomenon by which changes induced in the primary tumor are communicated to remote tissues, likely via cytokine release or extracellular vesicles. Traditionally, the bystander effect is often considered harmful and abscopal as beneficial, but these concepts are being rethought in the context of spatial fractionation effects. For example, the bystander effect could

play a protective role in normal tissue and at the same time induce cell death in tumors. In particular, induced differentiation and tissue recompartmentalization could be an underlying mechanism of the bystander effect in either normal or malignant tissue.

In addition, the role of vascular damage/repair and angiogenesis inhibition strategies has been demonstrated to affect the outcome of GRID or microbeam in several preclinical studies.[48,49] For all beam sizes between micron and millimeter width, the capillary blood vessels seem to repair themselves promptly in normal tissues, that is, within hours to days after SFRT exposure. In the tumor, there is less repair and evidence of permanent dysfunction in some cases induced by high peak dose SFRT. Most likely, these effects are modulated by the normal and tumor tissue microenvironment; however, mechanisms could be different depending on specific irradiation parameters.

A major factor in the recent rise of interest in unconventional radiation exposure scenarios such as SFRT has been the explosion of interest in immunotherapy, including the quest to solve the mystery of why some patients turn on immunity and others do not. Radiotherapy can certainly modify features of the immune response, and SFRT, in particular, seems to have the potential to "turn on" aspects of immune control of the primary tumor as well as metastasis. Therefore, this section will summarize what is known at present and the suggested paths for clinical engagement of using SFRT as a part of the immunotherapy armamentarium.

In many cases, advanced tumors are radio- and chemo-resistant due to poor blood flow, hypoxia, and low pH in the tumor. These factors may also influence the degree of immune surveillance generated by SFRT or the response to other standards-of-care regimens.[50] Clearly, large tumor volume and hypoxia have been found to correlate with decreased local control and survival in patients receiving chemoradiotherapy and/or subsequent immunotherapy in the form of checkpoint inhibiting antibodies. Thus, treatment modalities such as SFRT that can increase the tumor total dose and possibly activate beneficial bystander and abscopal immune effects while minimizing effects on normal tissues are an attractive proposition. A growing number of studies published in the preclinical literature of late suggest that there are primary tumor and abscopal/systemically expressed effects when spatial fractionation is applied to a locally advanced tumor and that they may be greater than those observed with conventional whole tumor fractionated or SBRT radiotherapy practices.[51-53] Other groups have reported similar and fascinating trends in tumor immunity and control with partial tumor or gradient radiation exposures.[54,55]

As an excellent example from the available literature, a recent study presents a group of preclinical studies using SFRT for single tumor volumes with detailed dosimetry and a biologic outcome study. In these studies, the investigators were able to compare several distinct partial, spatial, and whole tumor radiation exposures. These comparisons are critical to improve our understanding of which parameters may have the highest clinical impact and should be retained in treatment planning, when normal tissue dosimetry, tumor position/shape, and other factors become significantly influential in reaching planning goals.[53] A Kv source was used to create either 1-mm GRID peak dose openings or a 1 × 20 mm bar pattern (analogous to the microbeam radiotherapy field) or hemi-tumor and whole tumor radiation exposure. In terms of immunity, a big portion of the authors' attention was devoted to keeping the valley doses below a level that has been shown to be significantly toxic to T cells (3 Gy). Therefore, they constricted their treatment plans to allow only 1.5 Gy maximum in the valleys. Another important task included the assessment of motion on the accuracy of the dose deposition, which resulted in little to negligible effect of tumor motion during their exposures. This finding confirmed that the treatment outcomes were truly elicited from exposure to SFRT for various patterns and bode well for the results that could be expected when a carefully planned clinical version can be studied.

Although the results in tumor response were similar to those from other studies, they were different from those obtained in a tumor/mouse model in a recent hemi-irradiation protocol.[54] An important realization from this work and similar studies should be noted in that many, if not all, clinical PVDRs (ie, the degree of spatial modulation) are substantially less than preclinical studies that have observed potentially new types of radiobiologic responses. Therefore, there is a growing interest in research and clinical circles that PVDR quantification should be reported in as much detail as possible in every study that employs SFRT in any format to better understand and interpret the mechanisms of action.

Why is the peak and valley dose ratio so important? Maybe foremost is the attention to retaining or increasing an effective antitumor immune response using SFRT. One finer detail about having spatial dose modulation and dose gradients is that the immune system is activated by differing mechanisms across doses from low to high.[56] For example, the ablative damage in the peaks could produce new antigens; in the midrange, we may have ablation of the immune cells present during radiation, and in the lower valley dose, regions there may be immunomodulatory induction within the tumor microenvironment. It must also be remembered that the "Rs" of RT still apply, and there will be a significant repopulation in the valley dose regions, adjacent to peak dose areas where little cell

regrowth may occur. Intertwined with all these factors is the absolute percentage of target volume that receives either peak or valley dose, which is a variable that is rarely taken into account judging by the available literature.

The value of keeping the valley dose at or below a dose that would induce widespread lymphocyte killing (which is theorized to be in the 1- to 2-Gy range) is under debate. In theory, avoiding doses that kill resident lymphocytes would be beneficial to the antitumor immune response, yet there are plentiful examples of preclinical work using minibeams or microbeams where the valley dose is significantly higher than 1 to 2 Gy, yet induction of positive immune response has been observed. One possible explanation is that SFRT induces cellular damage in the peak dose areas and allows interaction with new antigens by dendritic cells in the valley areas that may not have as much vascular damage, leading to the generation of activated T cells against the tumor. Lymphocyte presence in the tumor either before or after SFRT treatment continues to be an important consideration that needs to be accounted for in the interpretation of tumor response to these regimens.

Temporal fractionation in SFRT is another relevant question, which has not been very well investigated, especially in the context of how to best induce immune priming and avoid immune suppression by subsequent fractions. A related approach termed personalized ultrafractionated stereotactic adaptive radiotherapy (PULSAR) in recent years to purposely give rest periods between radiation fractions to allow for immune adaptation is a clear example of what also may end up being a major consideration in optimizing the design of studies implementing SFRT.[29,57] However, it should be noted that very good survival and outcome results have been obtained in preclinical studies with as little as a 48-hour interval (80% long-term survival free of tumors). More attention to this paradigm-changing topic is clearly needed.[58,59]

To be clear, regardless of the SFRT approach, the interval between a single- or multiple-fraction GRID or lattice dose and the beginning of any conventional fractionation treatment remains to be optimized. Prior to the explosion of excitement around the immunotherapy field, it was generally thought that beginning chemoradiation within 3 days of the last SFRT fraction was optimal. Weighing the interval time for increased immune actions versus the risk of tumor repopulation or reassortment and progression continues to be discussed.[8,9,13,27,60] Overall, the evidence suggests that SFRT used at proven safe levels in combination with standard-of-care regimens is an acceptable and valid tool to increase beneficial patient outcomes.

Ultra-High Dose Rate (FLASH) Preclinical Research

The initial excitement of a tumor-selective effect of radiotherapy with decreased normal tissue response was largely theorized to be driven by the imbalance of oxygen levels between normal and tumor tissues. There are three major postulates being debated and studied, and no clear understanding has emerged at the time this chapter is being written. These are the facts that FLASH-induced transient oxygen depletion is possible; relatedly, there are cell type–specific differences in the ability to detoxify and recover from damage caused by reactive oxygen species, and finally, the idea that FLASH differs from conventional radiation in self-annihilation of radicals by bimolecular recombination.[61] Thereby, one or more of these differential effects FLASH will cause relatively less cellular damage in normal tissues than in solid tumor tissue. However, in a series of recent papers, this theory or variations on the oxygen theory have been introduced, which leave us without a clear answer at present.[61-63] Another aspect of FLASH mechanistic understanding is the potential differential vascular effects of FLASH between normal and tumor tissues. It seems that a general effect of vascular damage, lack of repair in tumor tissue, and vascular protection/sparing in normal tissue may help explain in vivo results on a tissue-by-tissue/model-by-model basis.[64] Some SFRT techniques such as MRT also lead to a similar differential effect between normal and tumoral vascular effects. However, even if MRT is delivered at UHDR, the presence of true FLASH effects in the tissue response is not certain since even the low-dose areas (valleys) usually receive doses higher than the maximum ones that demonstrated sparing in other FLASH studies in the same model (mouse brain).[30,65-67]

Finally, the immune system response FLASH has been suggested in a variety of studies to be greater than normal dose rate regimens due to sparing of circulating immune cells and immune organ function, while equal immune activation independent of dose rate has also been observed in other work.[68-70] After the initial excitement of the clinical potential, the field of FLASH has more quickly been introduced to clinical study with somewhat less preclinical work to establish mechanisms of action. Without that information, and the cautionary results coming from a comparative oncology setting where total dose was a major factor and may have clouded the occurrence of FLASH effects,[32] tissue/disease site selection and customization of treatment goals will be extremely important.

The current evidence on tumor control by FLASH therapy is, nevertheless, more limited than the normal tissue sparing, and most of the studies use a single-dose scheme. In contrast, conventional RT usually employs temporal

fractionation of the dose to profit from both a reoxygenation of the tumor and a redistribution of cells to more sensitive phases of the cell cycle (late G2 and M phases). Local tissue toxicity is also reduced due to the resulting increased time available for the repair of sublethal damage and cell repopulation. Thus, temporal fractionation effects might add up to the level of the inherent benefit of FLASH therapy for normal tissue preservation, and thus the value of either approach over the other is still not certain. Thus far, only one study evaluated the effect of temporal fractionation using FLASH dose rates, focusing on tumor control.[71] In this study, the tumor response following three hypofractionation schemes was assessed. As a result of the experimental design, the effects on normal tissue (FLASH effect) were only possible in the short term. To move toward FLASH-RT clinical trials of large radioresistant tumors (the ones that would most benefit from the normal tissue preservation potential of using UHDRs), we need comprehensive studies exploring temporally fractionated FLASH-RT, which have not been performed to date. Studies assessing the maximum dose and the time delay between fractions for which the FLASH effect still stands would be highly instructive. As with every new approach, these types of studies are necessary to critically evaluate the modality-associated toxicity and efficacy under a more clinically relevant scenario in radiation oncology terms.

CURRENT CLINICAL ACTIVITY

Spatially Fractionated Radiation Therapy

Best possible control of the primary or metastatic tumor sites remains a major goal of radiotherapy for both reduction of recurrence risk and improvement of survival in curative-intent radiotherapy; and symptom control and often lengthening of disease-free survival (DSF) in the palliative setting. Despite major advancements in radiotherapy technologies and delivery, the challenge of achieving adequate tumor control persists, owing to the inability to deliver a sufficiently high dose while effectively protecting normal tissues, particularly in therapy refractory and bulky/voluminous tumors. This challenge is further intensified in the current era of improved systemic therapy with ensuing prolonged survival, which calls for more effective local treatment of recurrent or metastatic tumor masses.

Current clinically practiced SFRT falls into two major categories: GRID therapy and the more recently developed Lattice therapy. Both deliver profoundly heterogeneous doses but with different geometric configurations of the heterogeneity dose pattern. Early clinical experience suggests that both have the potential to enhance tumor control in palliatively treated bulky metastatic and recurrent tumors and in selected advanced voluminous primary tumors. The reader is referred to recent reviews as an overview, and a summary of selected clinical approaches and data is given below.[28,3,72-77]

GRID Therapy

The original megavoltage SFRT modality was GRID therapy, delivered with a Cerrobend GRID block, which was subsequently developed into commercially available GRID collimators. The inaugural study showed 91% palliation (21/22) in 22 patients treated with 10 to 15 Gy in one-fraction GRID block–based SFRT for bulky tumors 6 to 25 cm in diameter.[3] Two subsequent palliative series corroborate these results in larger cohorts of 61 (72 tumor sites, predominately gastrointestinal [GI] lesions and sarcomas) and 71 patients (87 tumor sites, predominately lung, head, and neck tumors and sarcomas).[74] Overall response rates were 91% and 76%, toxicities were rare and minimal, with the exception of one carotid blowout after rapid tumor regression. These two studies established an important dose/response relationship. An SFRT dose higher than 15 Gy was associated with a higher response (100%) than a lower dose (79%). These early studies also established that durable response and local control require that conventional external radiation (cERT) with a dose of at least 40 Gy is added to the SFRT.[74] Therefore, most current SFRT regimens, with the exception of very short-term palliation, include both an SFRT and a cERT component. Further experience with GRID using commercial GRID collimators has confirmed high response and local tumor control rates and low toxicity.[4,6,10,73,76]

GRID options were broadened with the development of multileaf collimator (MLC)-based GRID therapy that emulates the principal dosimetric properties of the GRID collimator–generated treatment, and in addition, allows further individualization of the treatment volumes and normal tissue exclusion. Comparison between GRID collimator–based and MLC-based GRID therapy showed equivalent responses in an earlier study.[73]

Planning workflows have undergone further refinement, and both MLC-based and fixed collimator-based GRID are in use in about equal amounts according to recent clinical survey results.[78] For example, rapid-planning approaches are feasible with MLC-based GRID therapy.[79] These approaches allow for same-day treatment with a

spatial fractionation pattern, greatly improving the ability of many clinics to give SFRT dosing. Other recent reports highlight suggested workflows to integrate fixed collimator-based SFRT into treatment planning and a growing database of sarcoma and other disease sites.[5,15,80,81] The ease of implementation for MLC and fixed GRID block usage and same-day planning and treatment are a major advantage to the average clinical center. The recommended and most commonly used dose schedule for palliative SFRT is a single fraction of 15 Gy or 18 Gy, while larger fractions (20 Gy) or fractionated treatment are uncommon.[78]

Meanwhile, the favorable results of the palliative GRID experience have spawned exploration of SFRT to bulky primary tumor sites. The early series by Mohiuddin contained a small cohort of eight patients with far-advanced bulky but nonmetastatic head and neck (H&N) or skin cancer. Clinical complete response (cCR) was 63% (five of eight patients) and pathologic complete response (pCR) was 100% among four patients who underwent subsequent surgery.[74] The encouraging results in H&N cancer have been replicated by several smaller series of definitively treated patients.[4,10,76] GRID therapy has since also been explored in primary sarcoma.[6] Snider et al[6] showed in a retrospective series of bulky sarcomas (median 14.2 cm; all but 2 over 10 cm in diameter) a pCR of 32% (6/17 patients) among high-grade soft-tissue sarcomas, and of 50% (4/8) among extremity soft-tissue sarcoma, exceeding the pCR rate in major clinical sarcoma trials (19.4% and 27.5%).[82,83] Patients were treated with preoperative 15 Gy in one-fraction GRID therapy, followed by 45 to 50.4 Gy cERT and resection. Overall local control was 85%, and overall survival was 86%. Table 18.1 summarizes a selected range of representative series of SFRT to primary tumor sites, including GRID and Lattice-based applications.

TABLE 18.1 CLINICAL SERIES OF SFRT (GRID AND LATTICE) TO PRIMARY TUMOR SITES

Author, Publication Year	Patient Number, Stage	Follow-up (mo) Median, Range	SFRT Dose Per Fraction,[a] SFRT Type	cERT Dose[a]	SFRT Target	Response	Local Control, DSS, OS	Toxicities	Conc
Head and neck cancer									
Neuner (2012)[73]	14 Bulky H&N ca (of total 79)[b] Median 7.6 cm	2 (0-51.6) for the entire group of 79[c]	10-20 Gy (median 15 Gy) GRID	70.2 Gy for H&N ca[d,e]	Lymph nodes predominantly	Pain: 75%, 74%[f] Mass effect: 67%, 73%[f] Bleeding: 50%, 80%	LC n/r OS 29% (23/79)[g]	2 early gr 4 (skin) 3 late gr 3-4 (skin: chronic skin ulceration; two of three had skin involvement)	High low
Huhn (2006)[76]	27[h] Bulky H&N SCC, advanced neck disease	*Def RT:* 10 (3-44) *Preop RT:* 38 (5-116)	15 Gy GRID	*Def RT:* 70 Gy[e] (68-79 Gy) *Preop RT:* 59.4 Gy)[e] (54-72 Gy)	Lymph nodes	pCR 85% (*preop RT* group)	*Def RT:* LC (in neck) 93% DSS 50% *Preop RT:* LC 92% DSS 85%	Early gr 2-3 (skin, number n/r) Three wound healing complications (preop RT group) No late gr 3	Very adv inv High in t Mana
Penagaricano (2010)[10]	14 Bulky H&N SCC, >6 cm	19.5 (2-38)	20 Gy[i] GRID	66 Gy[i] (primary PTV), 60 Gy (IR PTV) 54 Gy (LR PTV)	Primary (6 pts) Lymph nodes (8 pts)	pCR 80% (8/10 pts with resection or biopsy)	LC 79% (11/14) DSS 79% OS 71%	Early: gr 3 (skin) 7/14 gr 3 (mucosal): 4/14 Late: gr 3 (fibrosis): 1/14; trismus 2/14 1 gr 5 carotid blowout after neck dissection	High rec tre Early 1 gr 5
Edwards (2015)[90]	53 T4 or N3 H&N SCC, >6 cm	34 (mean) (1-239)	15 Gy GRID	60 Gy (48-79 Gy)	Lymph nodes predominantly	n/r	LC 81% Metastasis 9% OS 23%	Two late toxicities requiring a feeding tube	Acce Lowe dis
Choi (2019)[74]	21[k] Bulky H&N SCC, >5	*Def:* 7 (4-16) *Pall:*	15-20 Gy GRID	*Def*[e]*:* 70-72 Gy *Pall:*	n/r	*Def:* CR 4/9 PR 1/9	LC n/r *Def:* 7/9 alive (at 7	5 gr 3-4 skin No gr >3 mucosal Late toxicities: n/r	Favo Acce

Author, Publication Year	Patient Number, Stage	Follow-up (mo) Median, Range	SFRT Dose Per Fraction,[a] SFRT Type	cERT Dose[a]	SFRT Target	Response	Local Control, DSS, OS	Toxicities	Conc
	(median 9.5) cm (9 def)	2 (0.5-9)		25-78 Gy		*Pall:* Symptom response 8/9	mo)		
Sarcoma									
Mohiuddin (2009)[91]	33 Bulky, unresectable recurrent, 6-32 (median 13) cm	n/r[l]	12-20 Gy (median 15 Gy) GRID	22-70 Gy, (no cERT in 4 pts)	Primary	CR 26% PR 50% If cERT >50 Gy, CR 45% (vs 10%)	LC n/r OS 9/33 alive >1 yr	2 gr 3 (skin) Note late toxicities	High uni sof Resp >5
Mohuiddin (2014)[92]	14 Bulky >8 cm, median 11.5 (8-26) cm	14 (3-34)	18 Gy[m] GRID	50 Gy	Primary (preop)	pCR 84.6 Limb salvage: 13/14	LC 100%	1 gr 3 (skin), two delayed wound healing, one midtherapy amputation	High lim ind che
Snider (2020)[76]	26 Bulky all but 2 pts >10 cm, median 14.2 cm	25 (range n/r)	15 Gy GRID	45-50 Gy	Primary (preop)	35.3%, 50% high-grade extremity sarcoma	LC 85% PFS 65% OS 86%	34.6% major wound healing complications	pCR cor RT Toxic
Lung cancer									
Amendola (2019)[86]	10 Bulky, unresectable, recurrent NSCLC (5 def)	6 (1-71)	18 Gy LRT	45-58 Gy	Primary, lymph nodes	Metabolic CR (FDG PET) 3/10, PR 2/10	DSS 3/10 alive/NED OS 5/10 alive	No gr >2 early or late toxicity	LRT i in a tre lun
Larrea (2021)[j,58]	11 Bulky >45 cm^3, unresectable, or unfit for chemotherapy	n/r	15 Gy LRT	55 Gy[n,o]	Primary, lymph nodes	CR 2/11 PR 6/11	LC n/r	One patient died of immunotherapy toxicity	High poo NS
Cervical cancer									
Amendola (2020)[89]	10 Bulky, stage IIIB, IVA, >7 cm and/or brachytherapy nonfeasible	16 (1-77)	24 Gy/3 fractions[p] LRT	40-45[j]	Primary	Metabolic CR: 78%, PR 22% pCR in 5[q] pts with surgery: 50%	LC 100% DSS 53% OS 47%	No gr >2 early or late toxicity	High an rat Low cor che inc fra

Selected studies are presented. In some studies, treatment of patients with primary tumors that are also metastatic is also included in the series.

ca, cancer; cERT, conventional eternal radiation therapy; CR, complete response; Def, definitive; DSS, disease-specific survival; FDG, fluorodeoxyglucose; gr, grade; H&N, head and neck; IR, intermediate risk; LC, local control; LR, low risk; LRT, Lattice radiation therapy; NED, no evidence of disease; n/r, not reported; NSCLC, non–small cell lung cancer; OS, overall survival; Pall, palliative; pCR, pathologic complete response; PET, positron emission tomography; PR, partial response; PTV, planning target volume; RT, radiation therapy; SCC, squamous cell carcinoma; SFRT, spatially fractionated radiation therapy.

[a]Range of doses is given in parentheses when available.

[b]Fourteen of the total 79 patients in this mixed palliative and curative cohort had H&N cancer that was definitively treated; 4 patients with H&N cancer were treated preoperatively.

[c]The follow-up time of the group of patients with definitively treated H&N cancer was not separately reported.

[d]The cERT dose was not reduced because of the dose received from SFRT.

[e]Concurrent chemotherapy was given with the cERT.

[f]Responses reported for collimator (block)-based (first percentage) and multi-leaf collimator based GRID therapy (second percentage), respectively, as this study retrospectively compared the outcomes between the two techniques.

[g]The overall reported survival was calculated (based on the reported data) for the entire mixed palliative and curative cohort, as the study was not intended to report survival.

[h]Fourteen patients were treated with definitive radiation, and 13 with preoperative radiation.

[i]Concurrent chemotherapy was given with the SFRT fraction and the cERT.

[j]Study reported as abstract.

[k]Nine of the 21 patients were treated with definitive intent, and the remainder palliatively.

[l]The follow-up time was not reported; the survival time ranges from 2 to 44 (median 99) months.

[m]Concurrent chemotherapy with ifosfamide/mesna.

[n]Hypofractionated at 2.75 Gy/fraction.

[o]Nine of the 11 patients received concurrent chemotherapy.

[p]Concurrent weekly cisplatin with SFRT fractions and cERT.

[q]Four patients with surgery following radiation therapy reported in Amendola (2020), with 1 additional patient per information from the author.

Lattice Therapy

Approximately half of SFRT is currently delivered with Lattice therapy,[78] indicating the development of the SFRT toward leveraging advanced technologies, such as intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), and image-guided radiation therapy (IGRT). In contrast to collimator-based GRID therapy, which has a largely fixed heterogeneity pattern, Lattice therapy enables the highly variable placement of high-dose spheres within the tumor, and this is used to further reduce areas of closely approximated sensitive normal tissues, such as the bowel. Lattice therapy has been used clinically for palliative lesions and for primary advanced cervical cancer,[8] other gynecologic tumors,[84,85] and lung cancers.[86] A series of 10 patients with far-advanced cervical cancer with excessive tumor bulk of more than 7 cm or severe anatomic distortion was reported in 2020. A Lattice radiation therapy (LRT) dose of 24 Gy in three fractions LRT was delivered with VMAT and IGRT, and immediately followed by 45.0 to 50.4 Gy cERT to the pelvis and regional nodal involvement. The dose at the periphery of the internal target volume (ITV) was reduced to 9 Gy in three fractions, and Radiation Therapy Oncology Group (RTOG) criteria for normal tissue doses[87,88] were applied. Patients received concurrent weekly cisplatin during LRT and cERT. No brachytherapy was given.

This early data suggests a high complete response rate, with frequently rapid tumor regression during therapy, requiring adaptive replanning. Local (pelvic) tumor control was 100% at a median follow-up of 16 (range 1-77) months, 2-year disease-specific survival was 53.3%, and toxicity was minimal. Five of the 10 patients underwent posttherapy hysterectomy, and 3 of the 5 had a complete pathologic response. Nine of the total group of 10 patients were followed with fludeoxyglucose-18 (FDG) positron emission tomography/computed tomography (PET/CT), and 8 of the 9 maintained complete metabolic response at the last follow-up. This experience in cervical cancer mirrors prior results of rapid tumor regression and high local control in GRID therapy for H&N cancers[4,10,73,76]; however, these pilot results must be confirmed with future studies and clinical trials with larger patient numbers.

The first series of LRT in lung cancer was published by the Innovative Cancer Institute and builds on the experience with GRID therapy in lung cancer from previous multidisease studies.[74,73] The series consists of 10 patients with locally advanced or recurrent non–small cell lung cancer (NSCLC), with tumor sizes ranging from 5 to 14 (mean, 8) cm.[1] Patients received a single fraction of LRT, delivered with IGRT and respiratory motion management. The dose to the peripheral gross tumor volume (GTV) was limited to 3 Gy. LRT was followed by 45.0 to 59.4 Gy cERT and additional tumor boost as indicated for residual tumor. All but one patient with a large cavitary lesion had imaging-based response therapy with a 15% to 83% (mean, 52) tumor volume reduction at therapy completion. Five of the 10 patients were alive at the last follow-up (18-86 months after therapy), 3 maintained complete metabolic response by FDG PET/CT, and 2 had partial response in the lung along with extrathoracic disease. There was no toxicity higher than clinical grade 1. However, as for the overall GRID and LRT experience in the definitive treatment of primary malignancies, the promising early outcome results require rigorous further study through well-designed clinical trials with the outcome as well as translational components. Recent consensus efforts have been undertaken to facilitate clinical trial design.[8,11,13,60,9]

The low clinical toxicity to multiple critical normal structures observed in LRT for gynecologic cancer, lung cancer,[84-86,89] and in the GRID experience[4,6,10,74,76,73] suggests an early clinical outcome correlate as a strong feature of SFRT.[60] As nearly all of the available preclinical and clinical literature report, compared to tumor tissue, normal tissue can withstand higher peak doses of GRID or Lattice therapy due to the spatial features and well-proven ability of normal tissues to repair and recover to spatially fractionated doses. The avoidance of additional toxicity

provides further promise for SFRT as a feasible clinical modality. Once again, the clinical results from a selected set from different tumor sites for both GRID and Lattice SFRT studies to date are summarized in Table 18.1.

FLASH

After a few case reports and first in-clinic applications of dose rates in the FLASH range, there have been a number of trials planned and now begun in the United States and Switzerland. As mentioned, a comparative oncology trial was performed in companion cats with oral squamous cell carcinomas.[32] This study reported some severe normal tissue reactions at FLASH dose rates when large volumes and total doses were involved, which has been a stark reminder of the focus on using FLASH with moderate total doses and prioritized superficial targets. There are at least two other known veterinary oncology trials ongoing, one in Sweden with electrons and the other in U Penn with protons.[94] The Swedish study revealed that single- fraction high-dose FLASH-RT was generally effective in this mixed group of malignant oral tumors, but the risk of osteoradionecrosis is a serious clinical concern. It is possible that the risk of osteonecrosis can be mitigated through fractionation and improved dose conformity, which needs to be addressed before moving forward with clinical trials in patients with cancer.

In line with these realizations, two clinical studies of FLASH based on the use of electrons are actively being developed and/or recruited.[95,96] Another nonrandomized study in the United States has treated 10 patients with bone metastases using proton FLASH therapy and demonstrated clinical feasibility,[97,98] but no conclusions on reduction of side effects have been made, somewhat expected since to date the total doses were purposely kept below the tolerance levels as a precaution. A table or other summary of FLASH clinical outcomes has not been included since at the date of this writing there are not enough completed studies to indicate any trends or average characteristics in patient outcomes. However, the field is extremely active and the number of data sets from more expanded clinical series is sure to increase in the near future.

FUTURE OUTLOOK AND PERSPECTIVES

Considering the growing interest in exploiting both the implicated biologic (changes in perfusion, oxygenation, and immune activation) and dosimetric advantages (protection of normal tissues and preserving tolerance dosing), the use of heterogeneous, partial, or spatial dosing at conventional or UHDRs can now be considered to revolutionize modern radiation oncology. Furthermore, it has been demonstrated that the elusive goal of inducing remote effects by increasing the ability of the immune system to feed off antigens induced by high-dose radiation and adding low-dose radiation to stimulate vascular and inflammatory cascades to assist the host in controlling metastatic progression may be within reach. If indeed these new beam modalities prove to be widely useful, the field of radiation oncology becomes even more significant in the armamentarium of cancer care. Larger, well-controlled, multi-institution studies need to be performed to establish the realistic gains for different tumor types by either the spatial fractionation of primary tumor masses or the selective high- and low-dose treatment regimen to allow the desired immune interplay for each patient. At present, there is a growing database of clinical outcomes from SFRT to base new clinical studies on, potentially including immunotherapy. Refer to Table 18.1 for SFRT primary tumor studies from the literature and a more expansive tally in Tubin et al.[28]

Low-dose/high-dose synergies have similarities across the spectrum of spatial fractionation approaches when applied to a single advanced primary tumor, but also obvious distinctions. However, as we uncover more about the ability of radiation to induce abscopal effects between tumors and distant unirradiated metastases, a connection between low- and high-dose RT response within a single tumor versus multiple distant lesions is likely, that is, systemic antitumor effects driven by variations in radiation exposure levels. To update the major concepts at the time of printing this edition, we present a revised and updated version of the conclusions from the original 2018 National Institutes of Health (NIH) meeting on GRID/Lattice, FLASH, and microbeam in Table 18.2. Even with an intervening pandemic, strides have been made in the past 5 years, and more advances in the next 5 years are sure to accumulate.

TABLE 18.2 PROS AND CONS AND CURRENT STATE OF KNOWLEDGE (PRECLINICAL OR CLINICAL LITERATURE) FOR SPATIAL FRACTIONATION AND ULTRA-HIGH DOSE RATES

	GRID/Lattice	FLASH (UHDR)	Microbeam	Minibeam
PROS				
Reduction in treatment	Not determined	Not determined	Not determined	Not determined

	GRID/Lattice	FLASH (UHDR)	Microbeam	Minibeam
dose/time				
Normal tissue sparing	Yes	Yes, specific cases	Yes	Yes
Increased tumor response	Yes	ND	Yes	Yes
Mechanism of action	Yes, partially known	Hypotheses being tested	Yes, partially known	Yes, partially known
Enhanced antitumor immune activity	Yes	Equivalent	Yes	Yes
CONS				
Limited applications	Wide applicability, multiple modalities	Yes, still under study	Yes, facility dependent	No, orthovoltage, MV, and proton
Difficult to obtain technology	No	Yes/still developing	Yes	No (proton facilities more available)
Cost	Low	High	High	Low for photon
Site access	Nearly all sites (VMAT/tomotherapy)	Limited, safety of deep-seated still under study	Limited with traditional synchrotron	Moderate, depending on modality

Modified from Griffin RJ, Prise KM, McMahon SJ, Zhang X, Penagaricano J, Butterworth KT. History and current perspectives on the biological effects of high-dose spatial fractionation and high dose-rate approaches: GRID, microbeam and FLASH radiotherapy. *Br J Radiol*. 2020;93(1113):20200217.

Creating a standard for the treatment planning parameters required for spatial and ultra-high dose treatment will provide each patient the best chance of having a successful outcome, ultimately determining the value of these unconventional approaches to radiation medicine. This compilation of standards depends on efforts from a dedicated set of workgroups, physicians, and scientists, many of whom are actively working to fulfill these needs and inform and recruit the greater clinical community to participate. As with any new clinical modality, a careful approach to get the best outcomes possible and solidify the value of implementing cutting-edge rationale for novel effects will be required to expand clinical usage and establish new standards of care.

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CHAPTER 19

Intraoperative Radiotherapy

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Intraoperative radiotherapy (IORT) is the delivery of a single, high dose of radiation during surgery to achieve higher effective target doses while displacing dose-limiting organs at risk (OARs). In the earliest preclinical studies and clinical trials, IORT was delivered as a solitary modality. Over time, IORT became part of multidisciplinary management as a boost dose in conjunction with conventionally fractionated external beam radiotherapy (EBRT) ± surgery ± chemotherapy. The EBRT-IORT combination theoretically can (1) improve locoregional control by reducing the risk of marginal relapse, (2) capitalize on the radiobiologic benefits of fractionated radiation, and (3) minimize normal tissue damage. Multiple methods of delivering IORT have been developed: intraoperative electron radiotherapy (IOERT), high-dose-rate intraoperative radiotherapy (HDR-IORT), and electronic brachytherapy/low-kilovoltage (kV) IORT. Despite advancements in techniques and technology, the bulk of IORT literature remains limited to small, retrospective, and often single-institution studies. Only five phase III randomized, controlled IORT trials have been published: four in Europe and one in the United States for patients with breast cancer and retroperitoneal sarcoma, respectively. National guidelines have no level I evidence, and there is no uniform expert consensus across US-based institutions on the appropriate use of IORT.

The following chapter begins with an abbreviated history of IORT followed by a discussion of the rationale behind IORT—using the linear-quadratic survival model and the four Rs of radiobiology. The physical and technical considerations, advantages, and disadvantages of each IORT technique— IOERT, HDR-IORT, electronic brachytherapy/low-kV IORT—will then be reviewed. Subsequently, the current evidence for using IORT and ongoing trials per disease site will be discussed. Two sections will be dedicated to discussing normal tissue tolerance and toxicity followed by a

practical step-by-step approach to an IOERT case. The chapter will conclude with a presentation of future directions for IORT as well as a list of suggested readings.

HISTORY OF INTRAOPERATIVE RADIOTHERAPY

A comprehensive history of IORT is beyond the scope of this chapter, but this section draws attention to some of the key developments in the evolution of the field. One of the earliest reported IORT-like procedures was performed on a 33-year-old woman with cervical cancer on March 11, 1905, in Barcelona, Spain.[1] After undergoing a total abdominal hysterectomy, pelvic lymph node dissection, and partial cystectomy, radiation was delivered through the open abdominal wall incision, which was protected by sterile lead sheets. She then received five additional fractions of postoperative EBRT and reportedly was alive and cancer free 10 years later.[1] From the 1930s through the 1950s, institutions in both the United States and Europe sought to treat a variety of malignancies by intraoperatively employing low-energy (50-250 kV) radiation, which was minimally effective due to poor tissue penetration. With the introduction of a linear accelerator (LINAC) producing megavoltage radiation in the early 1960s, Abe and Takahashi[2] at Kyoto University first combined tumor excision with a single high dose (25-40 Gy) of IOERT. In 1965, the first betatron was installed in an operating room, and these patients were treated with cobalt-60. Over the next 15 to 20 years, 717 patients with cancers of the stomach, pancreas, biliary tract, colon, prostate, bladder, lung, mediastinum, brain, and soft tissues were treated with IOERT at 27 Japanese hospitals.[2] Meanwhile, Howard University, Massachusetts General Hospital (MGH), the National Cancer Institute (NCI), and Mayo Clinic in Rochester, Minnesota, were the earliest US institutions to implement IORT programs, build IORT-dedicated operating rooms, and combine IORT with fractionated EBRT.[3-6]

Early IOERT had its limitations: LINACs and dedicated facilities were expensive, transporting anesthetized patients was not feasible, and applicators could not access deep and complex anatomic surfaces. During the late 1980s to early 1990s, these problems were overcome with the introduction of portable HDR-IORT and the flexible Harrison- Anderson-

Mick (HAM) applicator, allowing for greater target accessibility and treatments to be completed without patients being hospitalized overnight. Even as over 100 US institutions developed IORT programs, usage varied, and accrual of patients to phase III randomized trials remained difficult, which led to the dissolution of the Radiation Therapy Oncology Group (RTOG) IORT committee. Enthusiasm, collaboration, and widespread adoption of IORT have been promising across Europe, as evidenced by the formation of the International Society of IORT (ISIORT) in 1998 in Pamplona, Spain. Since the late 1990s, mobile HDR-IORT and IOERT units revitalized US interest and became cost-effective options for patients. The remainder of this chapter will provide an update on the IORT landscape from the early 2000s to the present day.

RADIOBIOLOGIC RATIONALE FOR INTRAOPERATIVE RADIOTHERAPY

The radiobiologic foundation for IORT is based on the linear-quadratic model (LQM) and the four Rs of radiobiology (*repair*, *repopulate*, *redistribute*, *reoxygenate*). The bulk of preclinical radiobiology research investigated the effect of single-fraction irradiation on tumor and normal tissue tolerance.[7] The LQM was developed to define a relationship between cell survival and radiation dose. The LQM suggests that cell killing is affected by two components—the linear (proportional to dose) and the quadratic (proportional to dose squared). These components contribute equally to cell killing at a dose equal to α/β. High α/β values (>7 Gy) correspond with acute-reacting tissues and most solid tumors, and low α/β values (<5 Gy) correspond with late-reacting normal tissues. Although the LQM has been widely adopted, ample evidence points to the overestimation of the effectiveness of cell killing at high doses.[8] One of the multiple proposed alternative models is the generalized LQM (gLQM), which predicts the high-dose response of cell lines based on the notion that high-dose radiation causes less sublethal damage and more lethal damage than low-dose radiation.[9] Each model has inherent weaknesses; for example, the gLQM does not account for cell cycle redistribution, reoxygenation, or the host immune response against tumor cells.[9] All models do, however, aim to

address the variable radiation sensitivities of normal tissues and tumors by producing dose-fractionation regimens that optimize the therapeutic ratio.

Modifications to the LQM have been made to better incorporate the four Rs of radiobiology. A single dose of radiation causes DNA double-strand breaks (DSBs) in tumor cells. Tumor cells either die or *repair* and *repopulate*. DNA DSBs are repaired via template-driven faithful homologous recombination or error-prone nonhomologous end joining, which are associated with radioresistance and radiosensitivity, respectively. Tumor cells can also become more radiosensitive by *redistributing* into late G1, G2, and M cell cycle phases and *reoxygenating* hypoxic areas.[10] The predominant benefit from IORT is derived from exposing the tumor to a single high dose of radiation and physically displacing normal tissues out of the IORT field. The four Rs justify the value of fractionated radiotherapy and why IORT is often combined with EBRT. Figure 19.1A demonstrates how IORT places normal tissues at a disadvantage and how a smaller dose per treatment is less toxic. For IORT to be successful, dose-limiting structures must be excluded from the radiation field. Maximizing tumor control and minimizing toxicity requires a knowledge of normal tissue tolerance and α/β ratios to estimate the biologically equivalent doses between single-fraction IORT and conventionally fractionated EBRT regimens (Figure 19.1B).

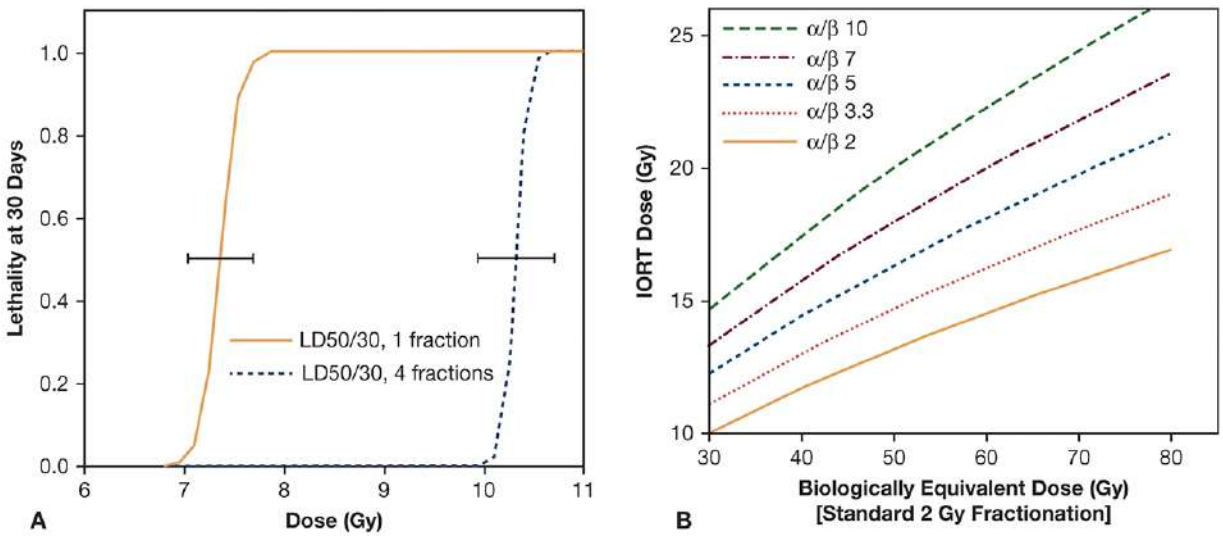

FIGURE 19.1 Lethal dose-fractionation benefit and biologically equivalent dose. A. Normal tissues benefit greatly from fractionation. $LD_{50/30}$ = dose of radiation expected to cause death to 50% of an exposed population within 30 days. Error bars represent a 95% confidence interval of $LD_{50/30}$. B. The estimated biologic effect of a given IORT dose is compared with that of radiation given in standard 2-Gy daily fractionation. α/β values = tumor (10), acute-reacting normal tissue (7), brain (3.3), and late-reacting normal tissue (2). IORT, intraoperative radiotherapy. (Reprinted by permission from Springer: Okunieff P, Sundararaman S, Metcalfe S, Chen Y. Biology of large dose per fraction irradiation. In: Gunderson L, Willett C, Calvo F, Harrison L, eds. *Intraoperative Irradiation: Techniques and Results*. 2nd ed. Humana Press; 2011:27-47. Copyright © 2011 Springer Science+Business Media.)

PHYSICAL AND TECHNICAL CONSIDERATIONS

Intraoperative Electron Radiation

IOERT was popularized in the 1970s and 1980s using conventional stationary LINACs; since 1999, mobile units have become more commonplace. The three commercially available mobile linear accelerators (LINACs)—Mobetron (United States), LIAC (Italy), and Novac 7 (Italy)—have transformed the delivery of IORT and made it more accessible by eliminating the need to transport the patient to a radiation suite. These LINACs produce electrons ranging from 4 to 12 MeV and benefit from low-stray, focused, straight beams.[11] Their design avoids high Z materials and minimizes bremsstrahlung. Electrons continuously lose energy as they traverse tissue, thus making them most effective at treating superficial tumors. Nevertheless, a bolus (0.5 or 1 cm thick) may be necessary, especially at lower electron energies, to improve surface dose. For IOERT

LINACs with electron energies up to 12 MeV, neutron production is minimal.[12,13] Mobile LINACs are lightweight and have no bending magnets, so low-penetrating photon leakage and electron scatter are relatively negligible.[14] With self-shielding and beam stoppers, there is little to no role for additional operating room (OR) shielding.[14]

Decision making surrounding IOERT dose (typically 7.5-20 Gy) and electron energy depends on the total EBRT dose and the amount of tumor remaining after surgical resection. Prescribed doses are often set to the 90% isodose line. IOERT disadvantages include, but are not limited to, fluid accumulation (such as in the posterior pelvis), which reduces beam penetration, and areas at risk may be too large to be covered within a reasonable treatment field.[15] Gantry and table movements enhance target localization, but some treatment fields remain anatomically inaccessible due to machine limitations. Cylindrical applicators come in various sizes and shapes with different bevel angles (Figure 19.2A). The applicator diameter must be slightly larger than the target diameter. Noncylindrical applicators also have been developed to address larger and more rectangular targets often encountered in the treatment of extremity and retroperitoneal sarcomas. Once the sterile applicator is positioned over the target and secured to the operating table, the LINAC is moved into position and docked. The Mobetron uses a laser guidance feedback system to achieve soft docking—the optical and mechanical alignment of the central axis of the LINAC and the applicator without forming a physical connection (Figure 19.2B). If there is unexpected movement of the patient, applicator, or machine, the decoupled soft-docking process reduces the risk of patient injury. Hard-docking systems, utilized by the Novac 7 and LIAC, directly connect a receptor on the radiation head to a thick-walled clear, plastic applicator.

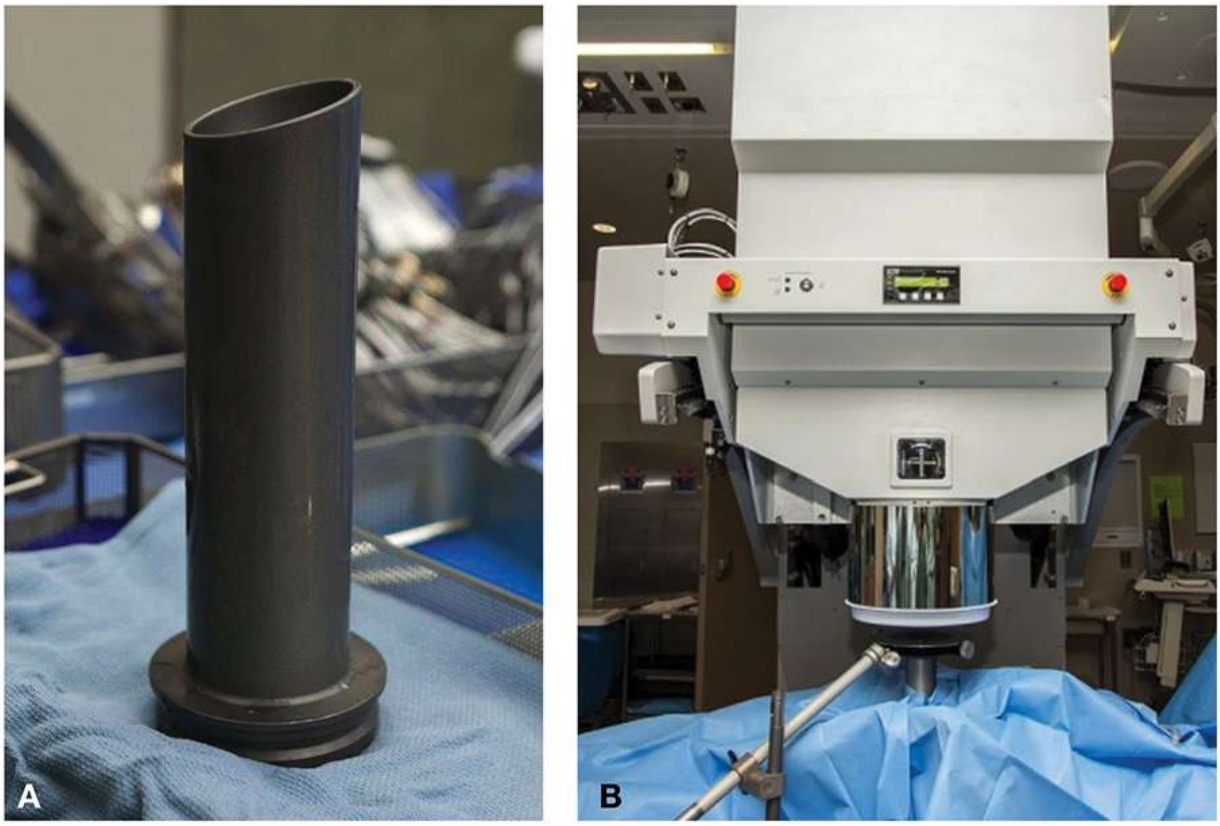

FIGURE 19.2 A. An 8-cm diameter circular applicator with a 15-degree bevel. B. Soft docking.

Quality assurance (QA) for a mobile IOERT LINAC is similar to that for a stationary LINAC, with a few distinguishing steps. Given the limited window of opportunity to deliver IORT, a careful, systematic, and efficient approach to QA is of the utmost importance. Mobile machines do not have adjustable collimators or bending magnets. Calibration at all electron beam energies determines scatter foil selection and is performed on the day of surgery. Output and docking must be scrutinized. Employing small water phantoms and limiting beam-on time in an unshielded OR improve QA efficiency. The American Association for Physicists in Medicine (AAPM) Radiation Therapy Committee Task Group published a report discussing the differences between stationary and mobile IOERT LINACs as well as recommendations for implementing an IORT program, given the unique issues of radiation protection, machine commissioning, and efficient QA.[16] Reducing uncertainties with treatment calibration and dosimetry (distribution, effect, inhomogeneity) and refining manufacturer

documentation and atlases will help standardize IORT procedures and establish its therapeutic benefit.[11]

High-Dose-Rate Intraoperative Radiotherapy

In the 1960s, IORT using HDR brachytherapy gained traction, thanks to the development of the remote afterloader and the HAM applicator. HDR-IORT takes advantage of physically displacing or shielding OARs to deliver a single high dose of radiation to a superficial target. Remote afterloaders direct the source, typically iridium-192, through a small catheter into the patient applicator, which must rigidly secure the catheter yet flexibly conform to the target. The HAM applicator is available in different sizes and can be cut lengthwise in the OR to customize the number of channels needed to cover the target. One of its strengths is physical flexibility, which allows for better conformality along curved surfaces like the pelvis and the ability to treat targets geometrically inaccessible to electrons, such as the anterior pelvis. The downside of HDR-IORT is longer treatment time, which increases surgical risk and OR cost. Also, ORs must be shielded similar to brachytherapy suites. Compared to IOERT dose distributions, those created by HAM applicators are more heterogeneous, which increases the risk of hot spots in nerves and in-field normal tissues like the duodenum in unresectable pancreas cancer. These advantages and disadvantages of HDR-IORT with the HAM applicator versus IOERT must be taken into consideration to select the most appropriate IORT technique. In mid-2022, the AAPM issued an HDR brachytherapy practice guideline presenting the infrastructure necessary to create an afterloader-based HDR brachytherapy program.[17] Two governing bodies, the US-based Nuclear Regulatory Commission (NRC) and the International Atomic Energy Agency (IAEA), have standardized regulations for the safe use of radioactive material (RAM) and nuclear technologies to minimize staff and patient exposure. The report outlines regulatory requirements (RAM licensing, personnel monitoring, shielding, source security, proper transportation, record-keeping), clinical practice recommendations (professional society and manufacturing guidelines), facility specifications (dedicated/shared suites, OR settings, mobile HDR units, kV/computed tomography [CT]/magnetic resonance imaging [MR] imaging), and staffing considerations (training,

certification, credentialing).[17] Afterloaders have intrinsic safety features: authorized use with a key and password, emergency switches, storage in a locked cabinet, and rechargeable batteries.[18] Additionally, source extension has numerous fail-safes. Automatic source retraction occurs when resistance is met, treatment is complete, or the treatment door is opened.[18]

QA for HDR-IORT involves a series of tests to verify the functionality of the remote afterloader, source, applicator, guide tubes, and treatment planning system (TPS). The AAPM-recommended frequency of these various tests has been tabulated.[17] Within 24 hours of an HDR-IORT procedure, a systematic checklist of tasks must be completed. The afterloader/source QA checks (1) source strength, positioning, and retractability; (2) door interlocks; (3) audiovisual monitoring and emergency response; (4) catheter connections; (5) calibration equipment; and (6) communication between console and TPS.[17] The length and integrity of the applicator and guide tube connections must be visually inspected before each treatment. Finally, before adopting a new modification or software update to the HDR-IORT process, a comprehensive dry run is warranted. A more in-depth review of the physics, biology, and clinical applications of low-dose and HDR brachytherapy will be covered in subsequent chapters.

Low-Kilovoltage-Intraoperative Radiotherapy and Electronic Brachytherapy

Two IORT devices—the Zeiss Intrabeam and the Xoft Axxent—have been developed using low-energy x-rays (30-50 keV) in an unshielded OR. The minimal radiation protection requirements make these technologies appealing to treatment modalities. The inherent steep dose gradient of low-energy x-rays minimizes normal tissue toxicity. Tungsten shields and wet gauze are used to protect normal tissue. The Zeiss Intrabeam system was introduced in the late 1990s and accelerates electrons down a miniature tube to hit a hemispheric gold target, producing an isotropic x-ray distribution. The unit is small, lightweight, and maneuverable. Meanwhile, the Xoft Axxent electronic brachytherapy has been in clinical use since 2008 and employs a microminiature tube and a Wolfram target. Its water-cooling system and heavier filtration enable higher dose rates and quicker dose

falloff. The Axxent can perform ^{192}Ir HDR brachytherapy. Source lifetime is over 10 years and about 2.5 hours for Intrabeam and Xoft Axxent systems, respectively.[19] More frequent source replacement necessitates new calibration and QA.

The Intrabeam uses a source centered within a solid, 1.5- to 5-cm-diameter spherical applicator, which produces a homogenous surface dose. The Axxent system utilizes three applicator types: 3- to 6-cm-diameter spherical or 5- to 7-cm-diameter ellipsoidal inflatable balloons, 2- to 3.5-cm-diameter vaginal cylinders, and skin applicators.[11] Spherical and balloon applicators must closely adhere to the surgical cavity. Dose is prescribed to the spherical applicator surface, and steep dose gradients allow for lower exposure to surrounding normal tissues. The multiple channels in balloon applicators enhance dose distribution and enable the treatment of asymmetrical targets. By using low-energy radiation, these portable IORT units can be safely operated in unshielded operating rooms. Poor tissue penetration, which limits the depth of treatment and restricts clinical application, is a major disadvantage to low-energy radiation. Both systems have safety features involving on/off status indicators, emergency switches, and real-time output dose monitoring. Intrabeam/Axxent commissioning, calibration, and QA processes have been summarized.[11,19] Nag et al[15] compared IOERT, HDR brachytherapy, and low-kV x-rays in regard to treatment field size and timing, the rationale for IORT multimodality, as well as the potential advantages and disadvantages.

EVIDENCE BY DISEASE SITE

Breast Cancer

Three IORT studies investigated the contemporary trend of de-escalating treatment time and treated breast volume—known as accelerated partial-breast irradiation (APBI)—in patients with early-stage breast cancer. Key findings from these trials are summarized in Table 19.1. Two randomized phase III equivalence trials (ELIOT and NSABP B-39/RTOG 0413) demonstrated that postlumpectomy APBI and whole-breast irradiation (WBI) were not equivalent.[20,21] In the ELIOT trial, patients who received IOERT experienced higher rates of ipsilateral breast tumor recurrence (IBTR) and no difference in overall survival (OS).[20] The ELIOT trial had

the longest follow-up among all randomized APBI studies and showed IOERT may be used for select patients at low risk of IBTR.[20] NSABP B-39/RTOG 0413 had a large heterogeneous patient population, included multiple APBI techniques not only IORT, and favored postlumpectomy WBI over APBI; however, the 10-year IBTR absolute difference between WBI and APBI was less than 1%—suggesting APBI may be an acceptable alternative.[21] One additional randomized phase III trial concluded that APBI was noninferior to WBI.[22,23] Risk-adapted single-dose 50-kV photon–targeted IORT delivered via a spherical applicator to the tumor bed at the time of breast-conserving surgery was found to be a suitable alternative to EBRT with similar 5-year local control and survival outcomes and reduced nonbreast cancer mortality.[22,23] Taken together, these three trials had mixed results, suggesting partial-breast IORT may be used in carefully selected patients. The results of two completed phase III trials conducted in Italy (NCT01276938) and England (NCT00983684) are eagerly awaited.

TABLE 19.1 SUMMARY OF THE PHASE III RANDOMIZED IORT TRIALS FOR EARLY-STAGE BREAST CANCER

Trial	*N*	Dose Regimen A: IORT B: WBI	IBTR % at 10 y A: IORT B: WBI	OS % at 10 y A: IORT B: WBI	Grade 3 Toxicity Rate (%) A: IORT B: WBI
ELIOT	1,305	A: 21 Gy/1 Fx B: 50 Gy/25 Fx (+10 Gy boost)	A: 8.1 (SS) B: 1.1	A: 90.7 B: 92.7	A: 0 B: 3
NSABP B-39 (RTOG 0413)	4,216	A: 34 Gy brachy or 38.5 Gy/10 Fx BID B: 50 Gy/25 Fx (±10 Gy boost)	A: 4.6 B: 3.9	A: 90.6 B: 91.3	A: 10 B: 7
TARGIT-A	2,298	A: 20 Gy/1 Fx B: 40-56 Gy (±10-16 Gy boost)	A: 3.2[a] B: 1.2	A: 96.3[b] B: 95.2	A: 0.2[c] (SS) B: 0.75

BID, twice daily; Fx, fraction; IBTR, ipsilateral breast tumor recurrence; IORT, intraoperative radiation therapy; *N*, number of patients; OS, overall survival; RTOG, Radiation Therapy Oncology Group; SS, statistically significant difference between A and B; WBI, whole-breast irradiation.

[a]IBTR rates at a median follow-up of 8.6 years.

[b]OS rates at 5 years.
[c]Reported as grade 3 or 4 toxicity.

A prospective registry trial accrued 1,367 patients with breast cancer treated to a dose of 20 Gy using 50-kV IORT at Hoag Memorial Hospital Presbyterian in California from 2010 to 2020 and observed similar local, regional, and distant recurrence rates to those reported in the TARGIT-A and ELIOT trials.[24] Although IORT achieved slightly higher recurrence rates compared to whole breast radiation therapy (WBRT), Silverstein et al[24] reported 10,000 to 100,000 patient-hours saved with IORT and encouraged physicians to gauge patient interest in receiving IORT and accepting a significantly increased risk of local recurrence with no apparent impact on survival in exchange for a single precise dose that saves time, money, medical environment exposures, and surrounding normal tissue. Another prospective trial investigated using a 10-Gy IOERT tumor bed boost (in 52 patients postlumpectomy with R0 resections) followed by 48-Gy/24-fraction WBI for early-stage breast cancer.[25] Wong et al[25] reported favorable 6-year local control and cosmetic outcomes but additionally advised caution in performing secondary surgical procedures on the lumpectomy bed after IOERT boost, given more pronounced breast fibrosis and wound healing difficulty. Nevertheless, in the United States, no randomized phase III trials evaluating IORT for patients with breast cancer have been conducted. Given that IOERT has achieved mild acute and late toxicities as well as minimally impaired cosmetic outcomes, the ESTRO/ACROP IORT Task Force supports the use of IOERT-boost and full-dose IOERT in patients at a higher risk (tumor size >2 cm, axillary nodal involvement, grade 3, triple-negative hormone receptor status) and low risk of in-breast recurrence, respectively.[26]

Brain Cancer

IORT has been used to treat primary and secondary brain tumors. The gold standard treatment for newly diagnosed glioblastoma (GBM) is surgical resection followed by concomitant EBRT and temozolomide chemotherapy and then maintenance temozolomide.[27] Unfortunately, GBM tends to progress over 6 to 7 months, and most recurrences occur within the

resection cavity.[27] Delayed adjuvant treatments allow tumor cells to repopulate, and IORT may be able to address these spatial and temporal issues. In phase I/II, dose-escalation Intraoperative Radiotherapy in Newly Diagnosed Glioblastoma (INTRAGO) trial, Giordano et al[28] demonstrated the delivery of Intrabeam low-energy IORT via a spherical applicator to the surgical cavity of 15 patients was safe with manageable toxicity and promising local control. The international phase III INTRAGO II trial is actively accruing, and results are eagerly awaited (NCT02685605).

GliaSite brachytherapy has been used to treat recurrent GBM and brain metastases. The GliaSite balloon catheter provides a precise, conformal, relatively homogenous, easily reproducible dose distribution. The goal is to deliver radiation near the resection margins—the area at the highest risk of recurrence. Twenty-four patients with unifocal recurrent GBM tumors (≤30 cc, not extending across the midline) underwent surgical resection followed by GliaSite radiotherapy at Johns Hopkins Hospital and experienced mild short- and long-term side effects, but survival was similar to patients who had re-resection, chemotherapy, or external beam reirradiation.[29] Performance status (KPS < 70 or ≥70) at the time of GliaSite was significantly associated with improved survival.[29] Two groups from Henry Ford Hospital and the Cleveland Clinic conducted nonrandomized prospective studies using GliaSite brachytherapy and Intrabeam mobile IORT, respectively, for solitary brain metastases and concluded these technologies were safe, effective, and well tolerated but only achieved comparable local control and survival to other treatment modalities.[30,31] With only modest results and the need for a second operation to remove the device, GliaSite manufacturing has largely been discontinued. A group in Barcelona, Spain, is actively recruiting for their phase II trial evaluating Intrabeam IORT after surgical resection of brain metastases (NCT05084092). IORT for solitary brain metastases is investigational at best, and stereotactic radiosurgery (SRS) remains the mainstay treatment for these patients.

Sarcoma

Adult

The role of IORT has been investigated in the management of primary and recurrent soft-tissue sarcomas predominantly located in the retroperitoneum or extremities. Retroperitoneal sarcomas are invasive, expansile, and challenging to manage with resection alone. These patients tend to experience high local recurrence rates, which is the most common cause of death. In the only phase III randomized controlled trial using IORT for retroperitoneal sarcoma, Sindelar et al[32] found patients receiving IORT experienced significantly lower locoregional recurrence and radiation-enteritis rates yet higher radiation-related peripheral neuropathy rates. In a German single-center, single-armed, prospective phase II clinical trial where 27 patients with retroperitoneal sarcoma received IORT, the study's primary endpoint of 5-year local control of 70% was not met likely due to enrollment of patients with recurrent disease, high-grade lesions, and leiomyosarcoma histology. These situations often derive less benefit from IORT.[33] Also of note, the STRASS trial comparing the efficacy of preoperative radiotherapy to surgery alone on abdominal recurrence-free survival in patients with primary retroperitoneal sarcoma did not include IORT.[34]

Postoperative EBRT boosts may not be effective, given the potential for tumor repopulation and hypoxia in the tumor bed as well as the presence of adjacent bowel, but IORT mitigates these factors.[35] Two Mayo Clinic retrospective series report encouragingly high long-term local control (LC), limb preservation, and survival rates in patients who received IORT for upper-extremity soft-tissue sarcoma.[35,36] Roeder et al[37] summarize the major IORT series published between 1988 and 2017 and the ESTRO/ACROP IORT Task Force recommendations informing the management of extremity and retroperitoneal soft-tissue sarcoma. The ESTRO/ACROP guideline discusses patient selection and care, IORT's role in multimodal therapy, and treatment dose, volume, and delivery.[37] Although favorable disease control and toxicity have been demonstrated, further phase III randomized clinical trials are needed to elucidate if IORT provides a true survival benefit for this disease entity.

Pediatric

Pediatric sarcomas are rare and heterogeneous, and data in support of using IORT for these patients primarily come from small, single-institution experiences. Nine children with incompletely resected sarcomas received IOERT (8-15 Gy) in combination with EBRT at the University of Heidelberg and achieved 3-year OS and actuarial disease-free survival (DFS) of 77% and 67%, respectively.[38] Given low toxicity and late morbidity rates, the group concluded that IOERT is safe and allows for a higher probability of local control than EBRT alone.[38] In a 20-year experience, the Mayo Clinic reported favorable long-term local control and survival outcomes for 13 pediatric patients with sarcomas who received IOERT (7.5-25 Gy) along with EBRT.[39] Memorial Sloan-Kettering Cancer Center (MSKCC) published a 20-year experience of 75 pediatric patients with sarcoma who received HDR intraoperative brachytherapy as part of their multimodal treatment.[40] The MSKCC study highlighted the strengths of intraoperative brachytherapy: versatility, flexible applicators, ease of access to anatomic locations, ^{192}Ir rapid dose falloff, and sparing of sensitive structures.[40] IORT may be suitable for select cases, but the routine use of image-guided, intensity-modulated, and proton radiotherapy has changed the treatment paradigm for pediatric malignancies.

Gastrointestinal Cancers

Gastric Cancer

Extended lymph node dissection and regional failure after surgical resection for gastric cancer contribute to poor prognosis in this patient population. Developing adjuvant tumoricidal approaches, like IORT, to treat recurrent/residual disease may improve regional control. Two studies from Jiao Tong University in Shanghai, China, have investigated adding IOERT to surgery and trimodality, respectively.[41-43] Between 1992 and 1998, 106 patients ages 25 to 80 with gastric adenocarcinoma were treated with total/subtotal gastrectomy combined with D2 or D3 lymphadenectomy plus IOERT, and survival rates were compared to 441 patients who underwent surgery alone.[41] Statistically significant improvements in 5-year survival rates by 15% to 20% were noted for stage II and III patients treated with IOERT, respectively.[41] Of the 48 stage III patients, those who had D2 resections achieved a 5-year survival benefit (60% vs 35.7%) and those

who had D3 resections achieved a 4-year survival benefit (85.5% vs 62.2%) when IOERT was performed compared to those undergoing surgery alone.[41] A prospective, nonrandomized series found adding IOERT to trimodality therapy was well tolerated and significantly improved 3-year locoregional control in patients with locally advanced (stage T3, T4, or N+) gastric adenocarcinoma.[42] Multivariate analysis showed statistically significant prognostic factors for locoregional control (adjuvant IORT, extent of residual disease [R0 vs R1], pN disease [pN0, N1, N2, N3]) and OS (pT category [pT1-T2, T3, T4] and pN disease [pN0, N1, N2, N3]).[42] A nonsignificant marginal increase in DFS was observed in this cohort treated with D2 gastrectomy and IOERT followed by adjuvant chemoradiotherapy.[43] To date, the largest phase II trial of patients with gastric cancer who underwent curative surgery plus IORT was conducted in Freiburg, Germany, and concluded that lower locoregional recurrence rates did not translate into a 5-year OS benefit.[44] Calvo et al[45] reported high local control and 5-year OS of 54.6% in their contemporary retrospective series of 32 patients with stage II or III primary gastric adenocarcinoma treated with a curative-intent D2 resection and IORT. The limited clinical data in this space can be attributed somewhat to gastric cancer being a rare disease entity and specialized IORT facilities being geographically scattered. Although the locoregional benefit of IORT in gastric cancer has been established, long-term survival outcomes across treatment modalities deserve to be examined in prospective, randomized controlled trials.

Pancreatic Cancer

Most patients with pancreatic cancer will present with metastatic disease or develop metastatic disease after local therapy. Only a selected group of patients may benefit from IORT. From 1978 to 2001, 150 patients at MGH with locally advanced pancreatic cancer (LAPC) received IOERT combined with definitive EBRT and 5-fluorouracil-based chemotherapy.[46] Although only modest 3- and 5-year survival rates (7% and 4%, respectively) were reported, long-term survival was achieved in eight patients, five of which were alive at or beyond 5 years, and improved OS was significantly related to smaller IOERT applicator diameter (tumor size surrogate).[46] Since 2006, MGH has used induction gemcitabine to screen for patients with LAPC

most likely to benefit from chemoradiation and IORT instead of post-IORT maintenance chemotherapy.[47] MGH studied 194 patients with LAPC treated with IORT and those who received chemotherapy, had small tumors, and had low pretreatment Charlson age-comorbidity indices achieved a median OS of 21.2 months and 3-year OS of 20%.[47] Between 2002 and 2010, 28 patients with borderline resectable or locally unresectable pancreas cancer underwent preoperative chemoradiation followed by restaging, surgical resection, and IOERT at Mayo Clinic Arizona.[48] Extent of surgical resection had a statistically significant impact on OS: 3-year OS was 36% after R0/R1 resection, whereas no patients with R2 resections were alive at 3 years.[48] Another contemporary MGH retrospective review of 158 patients with borderline resectable or LAPC reported the combination of IORT with surgical resection improved survival for those with positive/close margins or unresectable, nonmetastatic disease.[49] The disease control and survival outcomes findings were consistent across the studies described earlier.

Given the high propensity for patients with LAPC to develop abdominal relapses and distant metastases, more effective systemic therapies must be developed to see improved survival outcomes in this patient population. The MGH Phase II Pancreatic AdenoCarcinoma with Electron intraoperative Radiation therapy (PACER) trial is actively recruiting and is examining the efficacy of IORT in treating pancreatic cancer after 3 to 6 months of chemotherapy and EBRT (NCT03716531). The ESTRO/ACROP IORT Task Force formally published recommendations for IOERT in unresected and borderline- unresected pancreatic cancer, as it has been shown to be a risk-adaptive technique that improves local control and long-term survival in well-selected patients.[50,51] In the United States, however, no formal guidelines exist for treating pancreatic cancer with IORT, and it is only performed in specialized centers.

Colorectal Cancer

Optimal management of locally advanced rectal cancer (LARC) requires aggressive chemoradiotherapy and radical surgical resection. Complete resections are difficult to obtain due to the frequent involvement of pelvic bones. Only two randomized controlled trials have examined standard-of-care treatment plus IORT for rectal cancer. The Japanese study found

equivalent oncologic outcomes between the control (bilateral lateral lymph node dissection [LLND] + limited pelvic autonomic nerve preservation [PANP]) and IORT (bilateral LLND + complete PANP + IORT) groups and was limited by sample size (n = 44).[52] The French study enrolled 142 patients with LARC, randomized them to 4 weeks of preoperative radiotherapy + surgical resection ± IORT, and failed to demonstrate an LC and DFS benefit between groups.[53] The latter study may not have included the ideal candidates for IORT, as nearly 90% of patients had stage T3 disease.[53] Two prospective cohort pooled analyses have shown the benefit of IORT in local control and survival in patients with LARC and positive margins.[54,55] Alberda et al[56] retrospectively analyzed patients with microscopically involved circumferential resection margins and reported 5-year local recurrence-free survival favoring those who were treated with IORT versus without IORT (84% vs 41%, P = .01). The ESTRO/ACROP have formally published recommendations for using IORT in patients with primary locally advanced and locally recurrent rectal cancer, as IOERT has consistently achieved long-term local control and higher survival rates.[57,58]

Gynecologic Cancers

The evidence for a potential benefit of IORT in gynecologic cancers is predominantly from small, single-institution, retrospective series involving heterogeneous cancer types. A group at Stanford Cancer Center retrospectively reviewed 36 patients with gynecologic cancers treated with IORT between 1986 and 2005, and multivariate analysis demonstrated numerous significant prognostic factors.[59] Disease-free interval as a continuous variable was prognostic for locoregional control; smaller tumor size was associated with improved distant metastasis-free survival, and longer disease-specific survival correlated with cervix primary, prior surgery, and lower locoregional relapse rates.[59] Long-term survival was even demonstrated in two patients who received IORT for positive margins after pelvic exenteration.[59] Between 1994 and 2011, 32 patients with advanced or recurrent gynecologic malignancies were treated with IOERT at MGH, and 5-year OS was significantly improved in patients who had microscopic disease (40.9%) versus gross residual disease (9.1%).[60] Three Mayo Clinic studies have been informative in this space. A small but

significant number of women with recurrent endometrial cancer, locally advanced cervical cancer, or recurrent cervical cancer received combined modality therapy plus IOERT and experienced long-term survival even if extensive pelvic surgeries had to be performed.[61,62] Three-year progression-free survival and OS benefits were observed in patients with locally recurrent gynecologic cancer who experienced complete tumor resections with curative-intent radical extirpation, irrespective of whether or not patients received IORT.[63] Backes and Martin[64] published a literature review in 2015 summarizing the role of IORT in treating cervical, endometrial, and ovarian cancers. Altogether, promising results have been published; however, high-level evidence is lacking, and routine use of IORT to treat gynecologic malignancies remains controversial.

Other Sites

Clinical data supporting IORT remains limited for many disease sites. In 2017, Pilar et al[65] published a review article summarizing the IORT literature to date for both more commonly (breast, soft-tissue sarcoma, gastrointestinal) and less commonly (head and neck, gynecologic, genitourinary, pediatric) studied disease sites.

NORMAL TISSUE TOLERANCE AND TOXICITY

One of the primary goals of IORT is to deliver the maximal effective dose to the tumor while limiting toxicities. Preclinical research using canine models in the early 1980s helped establish normal tissue tolerance guidelines. Most of these studies focused on abdominopelvic tissue tolerance and were conducted at the NCI and Colorado State University (CSU). A comprehensive list of the NCI experimental studies and radiation parameters is provided.[66] Table 19.2 summarizes maximum IOERT dose tolerance values and toxicity thresholds for normal canine tissues observed in the foundational NCI studies.

TABLE 19.2 TOLERANCE DOSES TO IORT IN CANINE MODELS

System	Organ	Maximum Tolerated IORT Dose (Gy)	Maximum Follow-Up (mo)	Comments
Cardiothoracic	Aorta	30	60	Threshold for fibrosis, patency to 60 Gy
	Vena cava	30	60	Threshold for fibrosis, patency to 60 Gy
	Arterial anastomosis	30	36	Threshold for stenotic occlusion
	Arterial graft	30	24	Threshold for occlusion
	Heart	30	60	Threshold for fibrosis, no clinical effects to 40 Gy
	Tracheobronchus	30	60	Threshold for fibrosis, no clinical effects to 40 Gy
	Bronchial suture line	40	60	Intact to 40 Gy, bronchovascular fistulae at 20 Gy
	Lung	20	60	Threshold for fibrotic pneumonitis, no clinical effects to 40 Gy
Gastrointestinal	Esophagus	20	60	Ulceration and stricture with full-thickness exposure, no sequelae to 40-Gy partial thickness
	Duodenum	18	6	Threshold for ulceration, obstruction, or perforation
	Small intestine diverted loop	45	60	Defunctionalized bowel loop, no clinical effects, fibrosis at ≥20 Gy
Hepatobiliary-pancreatic	Bile duct	20	60	Threshold for fibrosis and stenosis
	Bile duct anastomosis	<20	12	Dehiscence at all doses ≥20 Gy

System	Organ	Maximum Tolerated IORT Dose (Gy)	Maximum Follow-Up (mo)	Comments
Urinary	Kidney	15	60	Threshold for tubular loss
	Ureter	30	60	Threshold for fibrosis and stenosis
	Bladder	30	60	Threshold for ureterovesical junction stenosis, normal contractility to 40 Gy
Nervous	Peripheral nerve	15	60	Threshold for motor neuropathy

IORT, intraoperative radiotherapy.

The canine experience with incremental dose escalation provides valuable insights into specific tolerances of common OARs.[66] Maximum single IOERT dose tolerated by any tissue is influenced by prior EBRT. The aorta and vena cava can tolerate large, single doses of radiation, but extrapolating to smaller vessels requires caution. Ureteral volume within the irradiated field must be considered to minimize the risk of ureteral stenosis and obstruction. IOERT doses above 20 Gy may cause ureteral and renal damage whereas doses below 20 Gy are unlikely to lead to chronic toxicity. IORT is often indicated when tumor compression or invasion causes painful peripheral neuropathy. In general, IORT doses of 10 to 12.5 Gy have been associated with low neuropathy risk compared to doses of 15 Gy or higher.[67] Vujaskovic et al[66] described in detail the above takeaways and other considerations for the spinal cord, bone, soft tissue, and gastrointestinal and thoracic organs. IORT-associated malignancies are exceedingly rare. Given that higher bone absorption is seen with orthovoltage compared to electron radiation, care must be exercised to minimize the risk of IORT-related bone necrosis and secondary malignancy.

PRACTICAL APPROACH TO AN INTRAOPERATIVE ELECTRONS RADIOTHERAPY CASE

Although clinical scenarios will vary by disease site, available technology, and physician expertise, the following steps provide a generalizable stepwise approach to an IOERT case using a Mobetron.

1. A pretreatment evaluation includes history and physical examination, routine labs, CT/MRI imaging, and often a staging positron emission tomography (PET)/CT scan. It is prudent to obtain a confirmatory biopsy prior to surgery when planning a potential IORT case.
2. Selecting appropriate candidates for IORT requires shared decision making. Localized disease with a high likelihood of incomplete resection and increased risk of local failure within the tumor bed are important selection criteria. Surgeons and radiation oncologists may hold a multidisciplinary tumor board discussion to determine the appropriate sequence of surgery/IOERT and EBRT. Preoperative EBRT is favored as it may downstage the tumor, facilitate curative-intent surgery, keep vasculature intact for improved oxygenation, limit OAR exposure, and limit IOERT dose.
3. Surgical and radiation oncologists review treatment goals, risks, benefits, alternatives, and logistics with the patient and obtain informed consent.
4. The patient is brought to the operating room. Surgical resection is performed. Frozen section pathologic analysis, if available, can guide the real-time decision to use IOERT or not. If there are close margins or microscopic/gross residual disease, the surgeon and radiation oncologist discuss further excision versus proceeding with IOERT. Multidisciplinary teamwork and communication between the surgeon, radiation oncologist, medical physicist, anesthesiologist, and operating room staff are crucial.
5. Normal uninvolved tissue is mobilized and excluded from the anticipated radiation field. Alternatively, lead shielding can be used for adjacent structures that are uninvolved by the tumor but cannot be mobilized, such as the ureter or nerve.
6. The radiation oncologist measures the treatment field and chooses a site-specific applicator based on size, shape, anatomic configuration, and whether a beveled applicator is necessary or not.

7. Choice of electron energy factors in real-time intraoperative measurements, presurgical imaging, and ensures the target is within the 90% isodose line with appropriate surface dose. Medical physics support is valuable for this decision-making process.
8. IOERT prescription dose depends on the extent of residual tumor, prior radiation received, and the normal tissue type and volume included in the radiation field. Generally, 10 to 12.5 Gy is used for microscopic close margins, 15 Gy for microscopic positive margin, and 17.5 to 20 Gy for gross residual disease. Bolus is considered to ensure adequate surface dose.
9. Once the applicator is docked and aligned with the gantry, everyone exits the operating room. Prior to treatment delivery, a timeout is taken and the medical physicist and radiation oncologist double-check the electron energy, applicator placement, and monitor unit calculations.
10. The treatment is delivered rapidly (typically over 1-2 minutes), and then the team enters the operating room to carefully remove the applicator. The surgery resumes, and afterward, documentation is completed, including the operative notes and anesthesiology report. Professional clinical photographs may be obtained at any point throughout the procedure.

FUTURE DIRECTIONS

Intraoperative Radiotherapy and Global Health

In resource-limited developing countries, single-fraction IORT is an attractive option. To our knowledge, two groups in South Africa have used IORT to replace EBRT in the treatment of breast cancer. Baatjes and Apffelstaedt[68] stress the value of IORT to extend breast conservation to underserved patients who cannot adhere to lengthy EBRT regimens. Ramdas et al[69] reported the viability of IORT and favorable short-term oncologic outcomes of the 107 patients with breast cancer treated at the first IORT facility on the African continent. The cost- effectiveness of IORT should be part of the shared decision-making process between physicians and patients. Two groups used Markov decision-analysis models over 10-year time spans to investigate the cost-effectiveness of IORT for patients

with early-stage breast cancer after breast-conserving surgery. When comparing single-dose IORT versus 6-week WBI in the TARGIT-A patients, IORT was the preferred, more convenient, cost-effective option, and demonstrated a quality-adjusted life-year benefit.[70] The model determined the local recurrence risk (LRR) for IORT would need to be over 23% at 10 years for a 6-week WBI to be a cost-effective strategy.[70] Meanwhile, Deshmukh et al[71] studied cost-effectiveness from societal and health care sector perspectives considering when radiation- associated disutility either persisted beyond or ceased at 5 years after treatment. Their comparison of conventional fractionation (CF)-WBI (5-7 weeks) versus hypofractionated (HF) WBI (3-4 weeks) versus IORT (1 day) revealed that HF-WBI was the most cost-effective option across all modeling scenarios.[71] With an increasing emphasis on climate change and sustainability, IORT has been estimated to save 20 million miles of travel when used to treat over 45,000 patients with early-stage breast cancer at 260 centers in 35 countries.[72] Patient values, therapy costs, local control rates, treatment time commitment, quality of life, and IORT accessibility will remain at the heart of this decision for women.

Intraoperative Radiotherapy and Novel Therapies

IORT may contribute to the abscopal effect—a radiation-induced, T-cell-mediated distant tumor inhibition—and has the potential to act synergistically with immunotherapy.[73,74] A small exploratory study of patients with early-stage breast cancer who received 20 Gy of IORT at the time of breast-conserving surgery used flow cytometry to assess peripheral blood samples (collected preoperatively and postradiation at 48 hours, 3 weeks, and 10 weeks) and found increased peripheral natural killer cells, which may harbor antitumor capacity.[75] SRS in conjunction with immune checkpoint inhibitors for patients with resected brain metastases may provide an OS benefit, and replacing SRS with IORT may have a similar effect while irradiating a smaller volume of normal brain and avoiding the healing time needed after brain metastasectomy.[76] Another exciting opportunity, currently under preclinical investigation, is the work exploring the effect of delivering radiosensitizing nanoparticles at the time of IORT.[74] Conceivably, as more is understood regarding proton beam and carbon-ion

radiation therapy, IORT may be delivered using these technologies.[74] Furthermore, one actively recruiting trial out of Columbia University will shed light on the molecular signatures of the luminal A and triple-negative breast tumor microenvironments before and after IORT is delivered (NCT03165487). The ongoing clinical trials mentioned throughout this chapter will enhance our understanding of the dynamic role of IORT. Inspired by ISIORT pooled analyses across Europe, international collaboration and data sharing will facilitate the much-needed prospective, randomized phase III IORT trials.

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CHAPTER 20

Particle Therapy: Protons, Heavy Ions, and Neutrons

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This chapter discusses the rationale, current and emerging technologies, applications, outcomes, and challenges associated with particle therapy. While the terms *hadron* and *light ion therapy* are sometimes used in the literature to describe treatment with protons or various charged nuclei, their use has been inconsistent and overlaps with other terms, leading to some confusion. The nomenclature we use in this chapter and recommend for clarity in the future is as follows: "particle therapy" refers to treatment with any charged particle or neutrons; "charged particle therapy" refers to treatment with protons or any other charged particle; and "heavy ion therapy" refers to treatment with ions heavier than protons ($^{1}H^{+1}$)), including helium ($^{4}He^{+2}$), carbon ($^{12}C^{+6}$), and ($^{16}O^{+8}$).

RATIONALE

Therapeutic Ratio

With any medical intervention, there is an optimal balance between the potential to benefit and the potential to harm a patient, known as the therapeutic ratio. In radiation oncology, it is the balance between radiation effects on the tumor and normal, nontargeted tissues. This ratio informs every physician and patient decision. Different priorities drive different decisions in certain clinical situations. For example, in a sinonasal tumor, one physician might recommend a treatment that results in a lower probability of disease control but minimizes the risk of optic nerve damage, whereas another physician might recommend a treatment that results in a higher probability of disease control but carries a greater risk of optic nerve damage. In another example, the potential risks of low-dose radiation exposure to a large volume of brain tissue may be of greater concern to the parents of a young child than to an older patient with a short life expectancy. When radiation therapy is indicated in any clinical situation, the first question is whether there is a potential to improve the therapeutic ratio by using a specific radiation modality, delivery mechanism, or technique.

The Impact of Dose Distribution on the Therapeutic Ratio

Many factors influence radiation effects and the therapeutic ratio: total dose, dose intensity (the overall time), the number and size of daily radiation fractions, as well as the interfraction interval, dose rate, relative biologic effectiveness (RBE), and modifying factors, such as chemotherapy, patient age, and comorbidities. No factor is as important as the dose distribution—the dose to the target compared with the dose to nontargeted normal tissues—because radiation therapy is a nonspecific intervention that affects both normal and cancerous cells. A basic principle in radiation oncology is that the higher and/or more intense the radiation dose, the greater the probability of tumor control. Similarly, the higher and/or more intense the radiation dose to a normal tissue, the greater the probability of injury. A second less well-understood principle is that the volume of tumor or normal tissue exposed to various radiation dose levels impacts the effect. For example, a higher dose of radiation to an organ may be tolerated if the absolute or relative volume of exposure to the organ at risk (OAR) is limited. In addition, critical components of either an OAR or a tumor may require a higher or lower dose for a clinical response. For example, the hypoxic section or the positron emission tomography (PET)-avid portion of a tumor may require a higher dose than the rest of the tumor for disease control. These principles of dose- and volume-response relationships have been observed in both malignancies and normal tissues. However, these principles may not always be discernible if effective doses are not delivered to critical volumes (of tumor or normal tissue), if adequate tools for measuring response (toxicity or functional compromise) are not available, or if observation time is insufficient for the effect to manifest.

The primary barrier to maximizing local tumor control through dose escalation or intensification is the risk of damaging normal tissues, either by delivering too high a dose to a critical tissue or by exposing too great a volume of the critical normal tissue to a potentially harmful dose of radiation. *The most direct means of improving the therapeutic ratio is reducing radiation dose and exposure to nontargeted tissues, which both reduces toxicity and*

facilitates dose escalation for increased tumor control. Herein lies the primary rationale for charged particle therapy (proton [$^{1}H^{+1}$] and heavy ions [eg, $^{4}He^{+2}$, $^{12}C^{+6}$, $^{16}O^{+8}$]).

The Problem With Photons (X-Rays) and the Promise and Challenge of Charged Particles

The pattern of dose deposition with photon-based external beam radiotherapy (Figure 20.1) is problematic because the dose to tissues along the beam entrance path is always higher than the dose to the target and additional dose is deposited in nontargeted tissues along the exit path of the beam. *Thus, most of the radiation dose with photon-based therapy is deposited outside the target.*

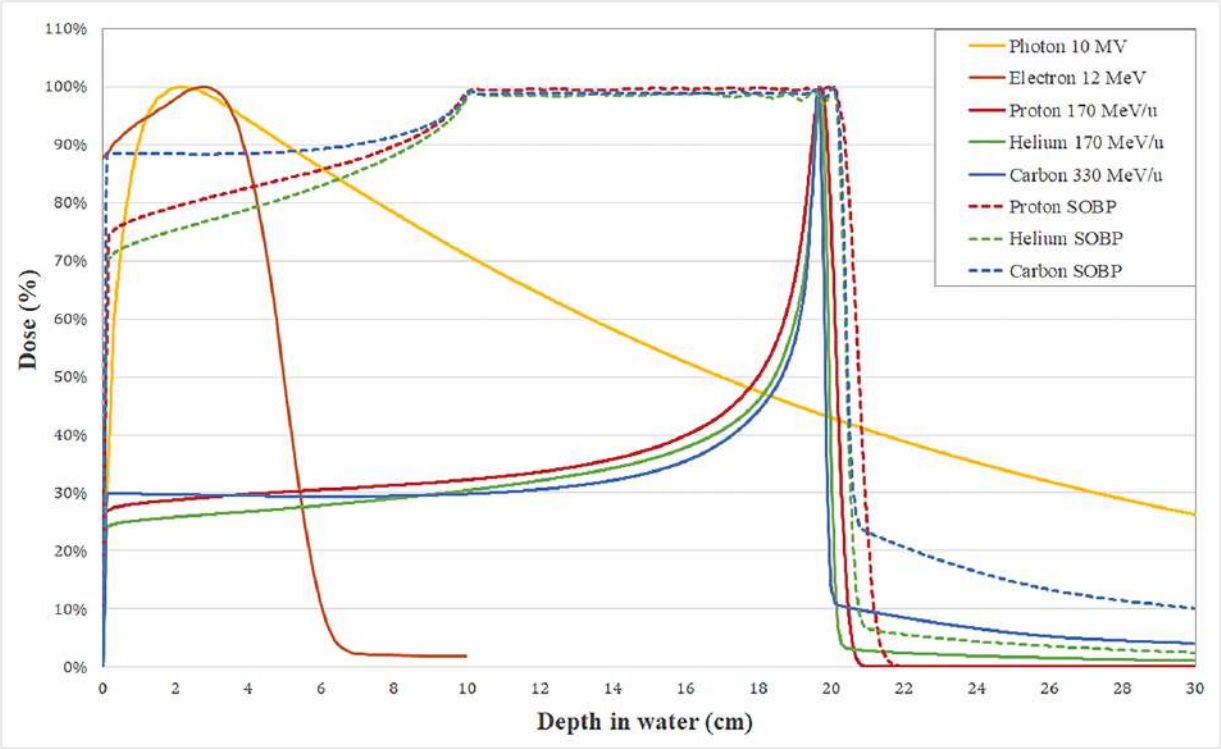


FIGURE 20.1 As shown here, the shapes of the relative depth-dose curves for 10 MV photons (yellow), 12 MeV electrons (orange), and pristine proton (red), helium (green), and carbon (blue) Bragg peaks. Compared to photons and electrons, the ratio of entrance dose to target dose is reduced when using proton, helium, or carbon ions. In addition, compared to electrons, the potential depth of penetration is significantly deeper and the dose falloff at the end of range is much sharper. With protons, there is no exit dose, while for helium and carbon, a small tail of dose exists due to nuclear fragmentation. This phenomenon is also responsible for the slightly higher entrance dose of carbon beams when compared to protons (not accounting for radiobiologic differences). Spread-out Bragg peaks (SOBPs) for protons (red dashed), helium (green dashed), and carbon (blue dashed) are shown in this graph. These curves are created by stacking multiple pristine Bragg peaks with varying acceleration energies. The width of the SOBP can be made to correspond to the thickness of the target.

Many elegant strategies have been developed for offsetting this basic problem (eg, three-dimensional conformal radiation therapy [3DCRT], intensity-modulated radiation therapy [IMRT], volumetric modulated arc therapy [VMAT], stereotactic radiosurgery [SRS], and stereotactic radiation therapy [SRT]), but with these technologies, radiation to nontargeted tissues is primarily redistributed rather than reduced. Because the total dose to a given tissue is one of the key determinants of toxicity, certain toxicities are reduced when using these sophisticated techniques. It is likely, however, that other toxicities will increase owing to methods that redistribute the integral dose over a greater volume of normal tissue. Some effects from low-dose exposure may require more time for clinical manifestation (second malignancies), and some may require more subtle tools for detection (neurocognitive testing), leading to an early underestimation of toxicity with these sophisticated photon delivery methods.

The dose deposition pattern with charged particles differs significantly from that of photons. Protons and heavy ions carry a positive charge, which means each particle type can be accelerated and directed by magnets. Charged

particles have mass, meaning they will not travel an infinite distance but only to the range or depth in tissue determined by the acceleration energy. In a patient, particles can be made to stop at a depth corresponding to the tumor depth. As charged particles traverse matter, they lose energy primarily through interactions with atomic electrons. Because of the significantly larger mass of protons (≈1,800×), carbon (≈21,600×), and other heavy ions relative to electrons, charged particles lose only a small portion of their energy in each interaction (in contrast to x-rays) and experience only small directional changes. The energy deposition pattern of a particular type of radiation is determined by the particle's track structure, including its core, which reflects interactions of the primary particle, and its halo, which includes secondary interactions.[1]

As charged particles traverse matter, the rate of energy loss in electronic interactions is described by the linear stopping power, S(E), defined as dE/dx, where dE is the mean energy lost by a particle in electronic collisions over a distance of dx in media. A more commonly used function is the mass-stopping power, s = S(E)/ρ, which denotes the energy loss dE when particles travel through a distance of dx in a media of mass density ρ. Mass-stopping power can be described by the Beth-Bloch formula. In this formulation, mass-stopping power is inversely proportional to the square of the particle's velocity. Thus, as velocity (energy) decreases, the mass-stopping power rapidly increases, creating the characteristic pattern of dose deposition known as the Bragg peak, a sharp peak in energy deposition immediately before the particle stops in the media. With heavy ions such as carbon, nuclear fragmentation at the end of range results in a small tail of dose deposition beyond the Bragg peak (see Figure 20.1).

Linear energy transfer (LET) is closely related to stopping power and defines the density of energy deposition along a particle track. As charged particles lose velocity, the distance between consecutive energy deposition events decreases. As a result, the density of the ionization pattern, that is, LET, increases, particularly within the Bragg peak. When protons are used in particle therapy, LET ranges from 2 to 10 keV μm^{-1}; for heavy ions such as helium, LET ranges from 4 to 40 keV μm^{-1}; and for heavier ions such as carbon, LET can exceed well over 100 keV μm^{-1}. LET is important in relation to the propensity of the radiation for causing double-stranded DNA breaks (DSBs), which are the principal mechanism for inducing cell death. Low LET radiation, such as photon therapy, often requires the conjunction of several tracks to produce DSBs, while a single track of high LET radiation is independently capable of producing multiple DSBs. Thus, for a given dose, high LET radiation is more effective at inducing cell death than low LET radiation. While the LET with particle therapy increases with reduced velocity in the Bragg peak at the end of the particle's range, the highest LET for a given particle beam is just downstream or beyond the Bragg peak.

Much work has been done toward modeling the correlation between LET, a physical quantity, and RBE, a biologic parameter defined as the ratio of the doses of two different radiation modalities necessary to cause the same biologic effect.[2] In vitro studies suggest the correlation is complex and sensitive to the α/β value and potentially the genetic profile of individual cell lines. Several phenomenologic models have been developed based on these studies; however, many models produce different results when considering the α/β values of different tissues.[3,4] Of importance, the current clinical practice in charged particle therapy is to prescribe an RBE-weighted absorbed dose, Gy (RBE), equal to the measured physical dose in Gy multiplied by either a constant or model-based RBE factor.[5] In proton therapy (PT) treatment planning currently, an RBE multiplicative factor of 1.1 is uniformly applied to the physical dose without explicitly accounting for the increase in RBE values near the end of a proton-beam range.[5] However, RBE ratios within the Bragg peak can range from 1.3 to 2.2 depending on which model is utilized.[3]

RBE effects are more significant for ions such as carbon. The lack of convergent and validated RBE models, particularly for heavy ions, is a major source of uncertainty. Two carbon ion therapy models are in current use: the Microdosimetric Kinetic Model developed at the National Institute of Radiological Sciences and largely in use in facilities in Japan,[6-8] and the Local Effect Model (LEM) developed at Gesellschaft fur Schwerionenforschung mbH, validated and largely in use by German carbon facilities.[9,10] Ishikawa et al reported a large and successful experience in prostate treatment using an RBE value of 3.[11] Kang et al, in reviewing the outcomes achieved with various dose fractionation schema with carbon in low-risk prostate cancer, determined an effective RBE of 2.19 to 2.12 for Gy (RBE) delivered in fractions of 3.3 to 4.3 Gy (RBE), with a decreasing RBE associated with increasing fraction size.[12] A recent prospective controlled trial comparing protons and carbon in prostate cancer using the LEM reported similar acute effects between protons and carbon[13] but significantly lower disease control rates with carbon compared to protons[14]; the inferior disease control rates with carbon were attributed by the investigators to an overestimation of the RBE of carbon by the LEM. Although much work has been done, more research on

carbon effects at various doses, doses per fraction, and tissue types is needed to inform treatment planning for clinical applications with carbon ion therapy.[15]

While such challenges exist, the broad relationship between LET and RBE can be used to inform the treatment planning approach. LET evaluation, whereby the LET distribution is displayed during treatment planning, is now widely available in PT and can be used to help select beam arrangements and design blocking structures that preferentially place higher LET values within the target and outside organs at risk (OAR). Going further, LET-guided optimization is now available in at least one treatment planning system and is primed for widespread adoption. The technique affords a low barrier to entry in that treatment plans that mimic the physical dose of current plans can be created to provide optimized LET distributions. It is possible that these techniques will unlock unrealized benefits of PT for several treatment sites and/or explain unanticipated normal tissue effects. As an example, in treating the prostate with protons, the classic beam arrangement involves opposed lateral beams that end up placing many of the proton Bragg peaks distal to the clinical target in the expanded planning target volume (PTV); this is done to account for uncertainties related to radiologic beam path and target motion. However, with LET-guided optimization, the beam arrangement can abut the prostate's interior, leading to a boost in LET within the clinical target that may be significant for an organ such as the prostate with a low α/β value. Such solutions offer hope for improved outcomes in the future but have not yet been tested clinically.

In addition to energy loss through electronic collisions and their impact on dose and LET, high-energy charged particles also experience nuclear interactions in media. Such interactions remove particles from the initial fluence and produce secondary protons, neutrons, and heavier particles, such as deuterons, tritons, and α particles; these particles contribute only a small percentage of the dose along the beam path.[1] Although negligible, most of the dose from the neutrons produced in these nuclear interactions is deposited downstream from the stopping point of the particle beam, beyond the Bragg peak. The neutrons produced by protons within the patient, as well as those produced in the beam delivery mechanical components, have been under intense investigation for their potential secondary cancer-inducing effects. Hall raised concerns that such scattered neutrons may increase the incidence of secondary tumors in patients treated with historical PT systems,[16] similar to concerns with the transition from conventional 3DCRT to IMRT.[17] Much research has been done to estimate secondary cancer risks from contemporary PT systems using scattering beam or scanning beam techniques.[18] Consistent reductions in secondary cancer induction have been predicted with protons compared to photons in studies of medulloblastoma, prostate cancer, and liver cancer.[19-21] A clinical outcome study comparing actual secondary cancers between a cohort of patients treated with protons at the Harvard Cyclotron and a cohort of photon-treated patients matched by age and tumor type from the Surveillance, Epidemiology, and End Results database showed nearly twice as many secondary cancers in the photon cohort.[22] A more recent analysis of the National Cancer Database (NCDB) showed a statistically significant increase in secondary malignancies (5×) after photon radiation with either 3DCRT or IMRT compared with protons apparent as early as 2 years after treatment for men with prostate cancer.[23] A retrospective study comparing secondary cancer incidence in men treated for prostate cancer with carbon therapy, photon therapy, and surgery has similarly demonstrated a significantly lower risk of secondary cancer with carbon compared with photon radiation and no demonstrable increase in secondary malignancies with carbon compared with surgery.[24] Given these results and the fact that modern PT techniques contribute fewer neutron contaminants than early PT sources, it is evident that neutron production is of much less concern for late effects than excess integral doses as delivered in photon therapy.

The primary rationale for an improved therapeutic ratio with charged particles, compared with photons, is thus the significant reduction in integral dose (dose to nontargeted tissues) that stems from a lower entrance path dose and the absence (protons) or near absence (heavy ions) of any exit path dose. These dosimetric differences should translate into a lower risk of complications for a given target dose, a greater probability of tumor control, and potentially lower secondary cancer risks for patients. A lower risk of complications could also be leveraged to permit dose escalation or intensification (yielding higher disease control in certain settings) or to facilitate hypofractionation (reducing patient inconvenience and treatment costs in other settings).

It is also important to note that aside from differences in integral dose, differences between photon and charged particle interactions with tissue may impact clinical effects through differences in cell-killing efficiency, DNA damage patterns, response signaling and repair pathways, and variation in sensitivity due to genetic variations. Recently, much work in this domain has been well summarized in a series of recent reviews.[25-35] However, much more work will be necessary to understand whether differences between photon and charged particle interactions with tissue can be leveraged to improve clinical outcomes.

TECHNOLOGY

Beam Production and Transport in Proton Therapy

Protons are produced from either hydrogen gas obtained from the electrolysis of deionized water or commercially available sources of high-purity hydrogen gas. Applying a high-voltage electric current to hydrogen gas strips the electrons from the hydrogen atoms, leaving positively charged protons. The protons are then accelerated to energies applicable to clinical PT with either a cyclotron or a synchrotron (Figure 20.2). In a classic cyclotron, protons are magnetically confined by a static magnetic field that exists orthogonal to the direction of travel. Due to this magnetic field, protons originally move in circular orbits, gaining energy as they cross the gap between two D-shaped electrodes aptly described as "dees." An oscillating electrical field is induced between the dees by radio frequency (RF) energy and timed such that particles are bunched and accelerated together in a resonant process. Each time protons cross the gap, they gain more energy and their orbit increases. Once reaching the exit energy of the cyclotron, they are extracted and enter the beamline.

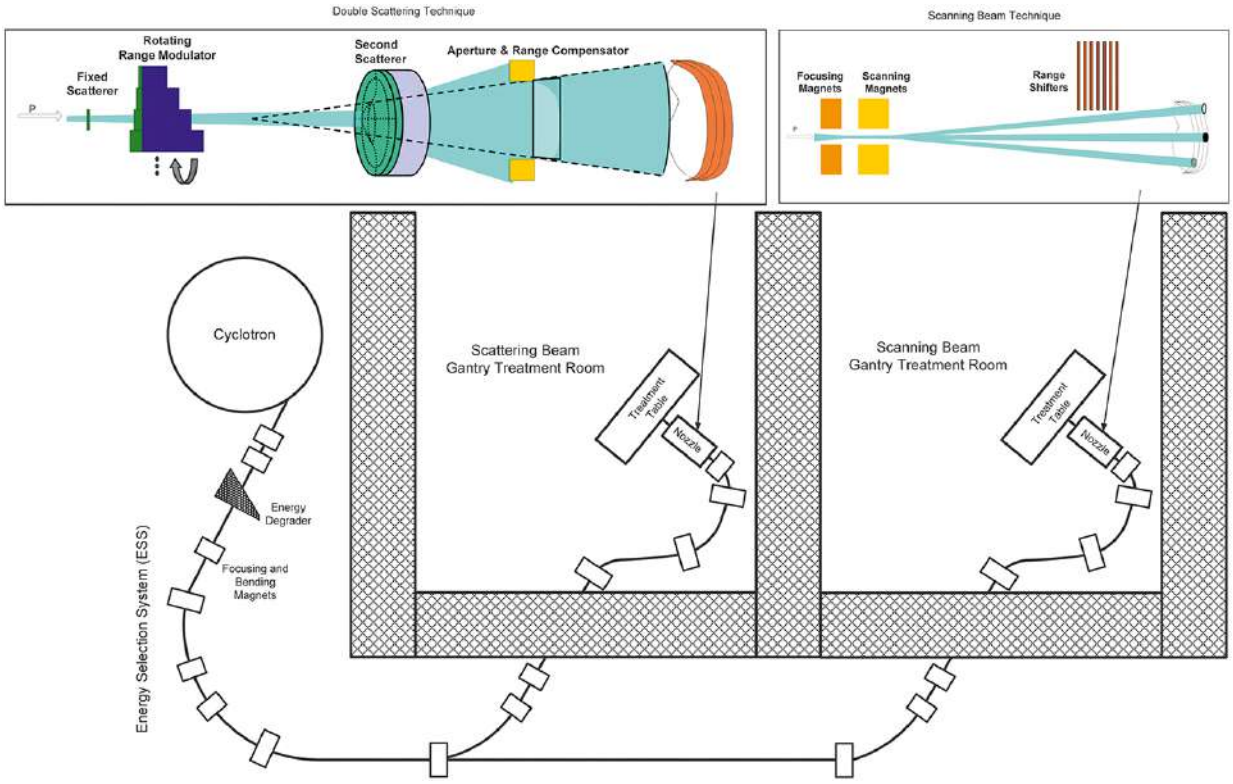


FIGURE 20.2 A proton therapy system with a cyclotron, energy selection system, beamline, gantry, and nozzle. Scattering is illustrated in the nozzle on the left and scanning in the nozzle on the right.

Energies as high as 230 MeV are required to penetrate deep into the body. At these energies, protons travel at approximately 60% of the speed of light, and relativistic effects cannot be ignored. Medical cyclotrons, therefore, must be designed to accommodate for the relativistic increase in the mass of the protons as they gain energy. In an isochronous cyclotron, this is handled by increasing the magnetic field strength along the radius of the proton orbits. As protons gain mass, it takes more magnetic focus to keep them in a tight orbit and in phase with the constant RF field. In a synchrocyclotron, the magnetic field remains constant with respect to the radius, but the RF is adjusted to maintain resonance. Because the RF is variable with respect to time, the system operates as a pulsed beam versus the isochronous cyclotron, which effectively operates as a continuous beam. Isochronous cyclotrons are typically larger and require a higher power consumption than synchrocyclotrons but are also generally better understood, involve a less complex RF system, and can produce higher peak beam intensities. Both systems have been configured with superconducting magnets to increase the magnetic field strength and confine the protons to tighter orbits. In such cases, the cyclotron's diameter, weight, and space requirements can be greatly reduced. For

example, the diameter of IBA's C230 isochronous cyclotron is approximately 4.5 m, and the system weighs nearly 240 tons. However, IBA's superconducting S2C2 synchrocyclotron has a diameter of 2.2 m and weighs only 46 tons. The drawback of a superconducting system is that it requires more complex ancillary systems and can experience several hours of downtime if cooling is lost and superconductivity is interrupted.

Cyclotrons produce nearly monoenergetic and unidirectional protons. Once the protons are accelerated to the preconfigured extraction energy of the cyclotron, they enter the energy selection system (ESS), which consists of a degrader, collimator, bending magnets, and momentum or "energy slits." The degrader has movable segments that introduce a variable amount of material, typically graphite, into the beam path. The beam energy is degraded (reduced) through interactions within the material to provide the appropriate range for a given treatment field. This process introduces an unfavorable dispersion in the energy spectrum. To mitigate this effect, achromatic bending is introduced using electromagnets whereby protons with higher energy follow a larger bending radius than protons with lower energy. The spread-out beam then passes through energy slits, which eliminate protons with bending radii that are different from that of the desired energy. The minimum energy achieved by the ESS is typically 70 to 100 MeV. Further energy reduction requires using an acrylic block or "range shifter" located on the beam exit immediately prior to the patient.

In contrast to the systems described above, synchrotrons produce proton beams of varying energies, which can be selected, eliminating the need for energy degraders and selection devices. A proton pulse exiting a preaccelerator, with energy typically up to 7 MeV, is injected into the ring-shaped accelerator. Each complete circuit of the proton pulse through the accelerator ring structure incrementally increases the proton pulse energy. When the desired beam energy is reached, the proton pulse is extracted from the accelerator. The time segment between pulses depends on the final energy required of the proton beam, ranging from subseconds to several seconds for the highest beam energy. Beam currents from synchrotrons are typically much lower than with cyclotrons, thus limiting the maximum dose rates that can be used for patient treatment, especially for larger field sizes. The maximum dose rate from a commercially available synchrotron-based PT system for a 25-cm × 25-cm field has been specified at 0.8 Gy/min.[36] The elimination of the energy degrader and selection system removes a major source of neutron production and, thus, the subsequent activation of beamline components in the accelerator vault. A synchrotron vault is, therefore, accessible for maintenance immediately after the beam is stopped, whereas approximately 30 minutes is necessary to allow the neutron-activated parts of a cyclotron and ESS to "cool down" before maintenance can be performed, sometimes longer if access to internal parts of the cyclotron is required. The shielding requirements for cyclotrons are also higher than for synchrotrons because of the higher neutron radiation produced by the ESS. However, the overall footprint of a cyclotron vault, including the additional shielding required, is actually similar to or smaller than that of a synchrotron vault because of the smaller physical dimensions of cyclotrons.

The proton beam is transported to the treatment room(s) by the beam transport system on exiting the ESS for a cyclotron-based system or exiting the accelerator for a synchrotron-based system. The ability to maintain beam focusing, centering, spot size, and divergence throughout the beam transport system is critical to delivering high-quality PT. Paganetti et al performed Monte Carlo calculations of the dosimetric effect of proton-beam energy spread, spot size, and angular energy spread on the shape of the Bragg peak.[37] They found that small deviations in these parameters from their nominal values result in a widening of the Bragg peak and increased entrance doses. Beam transport systems in clinical proton facilities, therefore, include bending (dipole) and focusing (quadrupole) magnets and beam profile monitors so that the proton-beam quality may be monitored and adjusted ("tuned") as it is transported through the beam transport system. At the end of the transport system, the beam enters the room either at a fixed angle (eg, horizontal beam), a combination of fixed angles sometimes termed an "inclined beamline" (eg, horizontal beam and one angled 30° off the vertical), or at various angles through the use of a movable gantry. Gantry-based systems are extremely large (up to 10 m in height) due to the wide radius needed to bend high-energy beams (up to 250 MeV) using magnetic fields.

The beam transport system can be configured to accommodate single- or multi-room facilities. With a multi-room system, queuing is necessary as the beam can only be available in one room at a time. Large multi-room facilities were the dominant format for PT until the mid-2010s when single-room designs were introduced. Since then, single-room systems have grown in popularity due to their lower cost of entry. These systems are often designed with compact gantries (approximately 200° of rotation) that utilize a robotic couch to rotate the patient along a vertical axis. In this way, the system can achieve all of the beam angles of a standard gantry but within a smaller footprint and with a more open design. Taking this concept further, upright delivery is a reemerging technology/technique that combines a fixed treatment beam with a rotating chair-based platform. Here, the patient

is rotated around a superior-inferior axis to deliver PT from multiple directions without needing a large gantry. Several challenges exist in translating the imaging and treatment paradigm from a supine to an upright position, but if successful, the concept will further reduce the size and cost of the equipment needed for PT.

Beam Delivery in Proton Therapy

The proton beam exiting the transport system (Figure 20.2) is a pencil-shaped beam with minimal energy and directional spread. The beam has a small cross-sectional (spot) size and a narrow Bragg peak at the end of its range in water. Two basic techniques have been developed to convert this narrow pencil beam into a dose distribution suitable for treating a 3D target, broadly categorized into the "scattering" or "passive scattering" techniques and the "scanning, active scanning, or pencil beam scanning (PBS) technique." These techniques are implemented in the machine treatment head or "nozzle," which is the section of the system that extends into the treatment room.

The scattering technique produces a dose distribution with a dispersed, typically flat lateral profile and a depth-dose curve that includes an entrance "plateau region" with a lower dose, and a high-dose region known as the "spread-out Bragg peak" (SOBP). The SOBP is produced by summing several individual Bragg peaks, each with progressively reduced maximum energy and range, to produce a sufficient width (along the beam path) to cover the thickness of the target. The weights of the individual Bragg peaks are optimized to achieve dose uniformity within the SOBP. A proton beam that produces constant energy may be used for such treatments, with range-reducing materials inserted into the beam path to create the individual Bragg peaks that form the SOBP. Range modulation wheels consisting of variable thicknesses of "acrylic glass" (polymerized methyl methacrylate) or graphite steps are traditionally used for this purpose.[37] The proton beam travels through the variable thickness steps, with each step creating a Bragg peak of a precalibrated range. When the desired width of the SOBP is reached, the beam is turned off. Alternatively, a "ridge filter" may be used to create an SOBP[38] with the advantage of eliminating sensitivity to organ motion in the formation of the SOBP but with the added complexity that each ridge filter is designed to achieve a single SOBP width.

The scattering technique produces a large, dispersed lateral dose profile through physical scattering filters placed in the proton-beam path. One scattering filter may be used, which creates a wide beam with a Gaussian dose profile known as a single scattering beam. A single scattering beam, with limited field sizes, is used primarily in dedicated treatment rooms for PT of ocular tumors, such as choroidal melanoma, and proton SRS treatments of brain lesions. Alternatively, and more often, a second scattering filter (double scattering [DS]) can be added to the beam that flattens the lateral dose profile. Apertures fabricated out of brass or other metals are used to confine the treatment field to the target. A tissue-equivalent range compensator, or bolus, is designed to adjust the beam range within the field to conform to the distal profile of the target. With the scattering technique, it is not possible to achieve conformity of the dose distribution to the proximal contour of the target. The passive scattering technique is an analog to 3DCRT historically used in photon therapy.

In the scanning technique, as the pencil beam exits the transport system, it is magnetically steered laterally to deliver the dose across the treatment field. The technique is colloquially known as "spot scanning" or "pencil beam scanning" (PBS), in that the dose is delivered as a series of individual spots within a given layer. The depth of the layer is determined by the beam energy, which is sequentially decreased to deposit the dose at multiple layers, moving from distal layers first to proximal layers through the target until the prescribed dose has been delivered to the target volume. A given layer may have hundreds of spots, and the intensity of each spot can be modulated to achieve intensity-modulated proton therapy (IMPT). The size of the spot, represented by the σ of the Gaussian function describing the pencil beam profile, is a critical parameter of the pencil beam. Smaller beam σ values allow intricate sculpting of the intensity-modulated dose distribution but require increased control system complexity and delivery time; larger beam σ values result in faster dose delivery but produce a greater lateral penumbra and a reduced dose gradient at interface regions of the target and critical organs.

Similar to the interplay effect reported for IMRT,[39] scanning techniques are sensitive to respiratory motion because time is required to move the pencil beam across a given layer and between layers. During this time, target or organ motion can occur, resulting in underdosage and/or overdosage of parts of the target. A potential strategy for mitigating this interplay effect is to deliver multiple smaller, incremental doses to each spot either by "repainting" each layer multiple times before changing the beam energy to scan the next layer (layer repainting) or by consecutively scanning each layer of a given target volume once, followed by rescanning of the entire target volume several additional times during each treatment fraction (volumetric repainting). Studies have shown that limiting each volumetric repainting to approximately 4% of the prescription dose can significantly reduce the

interplay effect in certain cases.[40] Standard motion mitigation measures, such as breath-holding, gated therapy, and abdominal compression, may also be necessary to minimize the dosimetric effects of organ motion. Other motion mitigation strategies include using a larger spot size, selecting beam angles along the trajectory of motion, balancing the dose evenly among multiple beams, and/or using 4D accumulated or dynamic accumulated dose calculation.[41]

The advantages of active scanning over passive scattering are the reduction in dose proximal to the target, the ability to create complex dose distributions through intensity modulation, the decreased need for apertures and compensators, and the reduction in secondary neutron contamination, which affords less radiation shielding in the design of the facility. The advantages of passive scattering over active scanning include a faster beam delivery, which negates the interplay effect and improves operational efficiency. Of the two, active scanning is the newer technique, and over the past several years, proton vendors have switched to active scanning both in their new systems and as upgrades to legacy, passive scatter systems.

Treatment Planning in Proton Therapy

Treatment planning for PT requires a volumetric computed tomography (CT) scan data set that includes the target volume and surrounding tissue through which beams will pass. The CT Hounsfield unit (HU) numbers are converted to proton-stopping power values to calculate the proton range required for the treatment field.[42] Unlike the relatively reliable conversion of CT numbers to relative electron density for photon dose calculations, errors and uncertainties in converting CT numbers to proton-stopping power in proton dose calculations translate into proton range calculation uncertainties and errors. In clinical practice, these uncertainties are handled during the treatment planning process by bracketing the target with a distal and proximal margin in the range calculation of each treatment field. Other considerations in determining the values for distal and proximal margins include target motion, daily setup errors, beam delivery uncertainties, and uncertainties in patient anatomy and physiology changes throughout treatment that could affect the water-equivalent depth of the target. It is worth noting that the concept of a PTV, as defined in the various International Commission on Radiation Units and Measurements reports,[43,44] does not strictly apply to PT. Generally, a PTV expansion, with either uniform or nonuniform margins, is used for photon planning, accommodating maximum target motion and setup error in each of the patient axes (longitudinal, lateral, and anterior/posterior). In contrast to photon planning, the PTV for PT is specific for each treatment field. In the lateral direction of the beam's eye view of a proton field, margins are identical to traditional definitions, but the distal and proximal margins along the beam axis are calculated to account for proton-specific uncertainties. The lower entrance dose and absence of exit dose of a proton beam afford additional flexibility in selecting beam angles for which lateral target motion and setup error are minimal.

With its additional ability to modulate dose intensity within and outside the target region, the active scanning technique requires additional considerations in treatment plan optimization. Single-field optimization (SFO) allows the treatment planning system to optimize the plan on a field-by-field basis so that each field will deliver a nearly uniform dose that covers the target to the extent that OAR constraints permit. SFO improves plan robustness by reducing the plan's sensitivity to deviations in the delivery of any single treatment field. Multifield optimization (MFO), on the other hand, allows each treatment field to deliver a heavily modulated dose distribution to a subvolume of the target and relies on the accurate delivery and combination of all fields to achieve plan goals. The MFO optimization technique can thus achieve the highest plan quality but potentially increases sensitivity to the effects of delivery uncertainties. IMPT plans may use either SFO, MFO, or a combination. IMPT plans are further optimized with consideration for various sources and magnitudes of delivery uncertainties, such as range uncertainties, setup errors, and breathing motion that are included within the optimizer through various perturbed plan scenarios. The number of scenarios to include within the robust optimization process can be as high as several thousand, significantly increasing the computational burden on the treatment planning system. However, the recent utilization of graphical processing units for robust optimization has mitigated these concerns, and IMPT plans can now be robustly optimized within a few minutes or hours instead of several hours or days. Robustly optimized plans are evaluated by calculating the nominal treatment plan on a number of perturbed CT data sets, which simulate various range uncertainties and patient shifts, for example, +3.5% HU and +3 mm anterior shift. The resulting dose-volume histogram (DVH) bands can be assessed with regard to their spread, and individual scenarios can be compared against institutional standards.

Even with strategies to account for proton range uncertainties, comparisons of treatment plans involving proton and photon techniques generally demonstrate a striking advantage with protons for reducing the volume of

nontargeted normal tissue receiving a low to medium dose. In some cases, the volume of nontargeted tissue receiving a moderate to high dose is also reduced. With passively scattered proton delivery modes, the target dose homogeneity and conformity index can sometimes, but not always, be inferior to IMRT/VMAT. With scanned proton delivery modes, IMPT plans can, in addition to reducing low and moderate integral doses, also improve dose homogeneity and conformity indexes when compared with IMRT/VMAT.

State-of-the-art PT dose calculations use pencil beam algorithms that model proton interactions and scattering in various media of the beam path, including the nozzle, range compensators, and patient. Monte Carlo calculations have been used to study the accuracy of such dose calculation algorithms, with results indicating errors near-tissue interfaces, particularly near interfaces of media differing in density and composition, such as the air cavity and bone in head and neck treatments.[45,46] Several fast Monte Carlo calculation algorithms are now included in modern treatment planning systems and greatly improve PT dose calculation accuracy.

Technical Summary of Heavy Ion Therapy

Carbon Ion Therapy

In many ways, the treatment planning and delivery of heavy ion therapy is very similar to PT. Charged nuclei, specifically carbon ions, are accelerated using large synchrotrons to energies between 400 and 480 MeV. Most facilities incorporate fixed-beam lines (either horizontal, vertical, or both), though at least three offer rotating gantries. The first such gantry was installed in 2009 at the Heidelberg Ion Therapy Center (HIT) in Germany; it had a diameter of 13 m and an overall weight of 600 tons! Due to the impressively large but prohibitively costly size of the system, subsequent designs have incorporated superconducting magnets in the gantry to increase the magnetic field strength and decrease the bending radius. The system installed at Yamagata University in Japan, for example, uses this technique to reduce the diameter of the gantry to 11 m and the overall weight to 200 tons (for reference, proton gantries currently have diameters of 7.5-11 m and weights of 100-200 tons).[47,48] Older carbon ion systems rely on passive scattering for beam delivery, while newer and upgraded systems offer active scanning. For the latter, both SFO and MFO planning techniques are utilized, and the interplay effect is managed for moving targets through a variety of techniques, including gating and volumetric repainting.[49]

Compared to protons, carbon ion beams have a sharper lateral penumbra and a more distinct Bragg peak. This is due to the additional mass of carbon ions, which leads to less coulomb scattering and less range straggling. Alternatively, a "fragmentation tail" exists in carbon ion beams, representing a small percentage (2%-5%) of a dose beyond the Bragg peak. This is due to nuclear reactions that produce light ions that travel beyond the range of the primary beam.[50] Regardless of these conditions, in clinical scenarios where treatment plans are created using multiple beams and robust optimization is used to purposefully blur sharp dose gradients, the physical dose distributions between the two modalities are not very different. The main rationale for using carbon ions over protons is thus their superior biologic effectiveness, which, while theoretically sound, remains a controversial topic due to the uncertainty in translating LET to RBE and the lack of clinical evidence supporting better outcomes.[51] Several recent studies, in fact, have demonstrated no significant difference between PT and carbon ion therapy for skull base chordomas[52,53] and head and neck cancers.[14] Indeed, one recent report of a randomized trial of carbon versus protons in prostate cancer demonstrated significantly lower disease control rates with carbon, attributed by the authors to an overestimation of the carbon RBE.[54] One area where differences are expected is in the treatment of hypoxic tumors. There is strong evidence that ions with LET greater than 200 to 300 keV μm^{-1} can reduce the oxygen enhancement ratio (OER), defined as the ratio of the dose needed for the same cell survival in anaerobic and aerobic conditions.[55,56] While clinical outcomes are sparse, encouraging results have been seen in pancreatic adenocarcinoma[57,58] and uterine cervical cancer,[59,60] two malignancies with a high level of hypoxia. As carbon ion therapy matures and more centers come online, there will be further opportunities to explore these unique advantages and establish best practices for clinical use.

Various Other Ion-Based Therapies

In addition to carbon ions, other species have been investigated, including helium, oxygen, and neon. Given their size, the latter two choices require further acceleration to 500 MeV or greater to achieve the same maximum treatment depths (approximately 30 cm) available in proton or carbon ion beams. As previously discussed, this increase in energy necessitates a larger bending radius for both the synchrotron and treatment gantry (if configured in this manner), increasing the system footprint and driving up costs. As such, any future development may focus on intermediate and superficial targets that can be reached with lower energy. While the theoretical RBE is higher

for oxygen and neon ions, fragmentation also plays a larger role, creating unwanted dose beyond the Bragg peak. Similar to carbon ions, the high LET in and around the Bragg peak is predicted to reduce the OER and help overcome resistance in hypoxic tumors.

In the modern era, treatment with oxygen, neon, or heavier ions has yet to occur. However, the first modern delivery of helium ion therapy took place in 2021 using an actively scanned beam at HIT.[61] Helium ions represent, in many ways, a balance between the benefits and limitations of proton and carbon ions for radiotherapy. Compared to protons, helium ions have sharper distal and lateral penumbra and are associated with higher LET and potentially higher RBE (1.3-3 Gy). The variability in their biologic effect, while nontrivial, is expected to be less than what is seen with heavier ions,[62] and the fragmentation tail due to nuclear interactions is significantly reduced. Because helium ions have an equivalent range to protons in water for the same energy per nucleon,[63] the maximum energy produced by the accelerating structure only needs to be on the order of 230 MeV. This enables several possible designs, with various novel, compact systems having been proposed.[64] That said, no vendors offering technology for helium ion therapy currently exist, and upgrades to existing PT equipment are not feasible. Presently, HIT is the only carbon ion facility to have enabled helium delivery, though other centers are readily equipped for a similar transition. Ultimately, the early experience from HIT will be very important in driving the adoption of this technique and an emerging interest in "multi-ion" radiotherapy whereby lower LET beams (protons and ^{4}He) are used near normoxic, healthy tissues, and higher LET beams (^{12}C) are used within hypoxic regions.[65] These new methods are also expected to foster new technological developments and clinical implementations.

Technical Summary of Neutron Therapy

Fast Neutron Therapy

The rationale for neutrons is similar to that of other particles used for radiotherapy but with some differences. Fast and ultrafast neutrons with energies of 1 to 70 MeV are recognized to have relatively high LET (20-100 keV μm^{-1}) with correspondingly low OER and high RBE. The latter is conventionally valued around 3 but is also quite sensitive to fractionation and the elemental composition of the tissue medium. Notably, neutrons are more likely to undergo scatter reactions with low Z materials (eg, hydrogen) than with higher Z materials (eg, carbon, oxygen, nitrogen, or calcium). When compared to low LET photon therapy using conventional fractionation (≈2 Gy/d), studies have reported RBE values of 3 to 3.5 Gy for normal tissue late effects, 4 to 4.5 for damage to the central nervous system, and up to 8 for malignant disease in the salivary glands.[66]

Unlike charged particles, fast neutrons do not exhibit a Bragg peak and are instead continuously attenuated, primarily through elastic scattering with hydrogen nuclei (≈85% of the dose comes from recoil protons). As such, the physical depth dose in tissue is more similar to photon therapy than PT or carbon ion therapy. A variety of systems have been used for fast neutron therapy (FNT), including cyclotrons, linear accelerators, D-T neutron generators, and both research and commercial nuclear (fission) reactors. Generally, cyclotron-based systems produce neutrons with energies between 20 and 70 MeV (considered ultrafast), while D-T neutron generators produce neutrons with energies between 10 and 20 MeV (fast). Fission neutrons have much lower energies (<4 MeV) and correspondingly different radiation transport in human tissues. The term "fission neutron therapy" has been used to demarcate a difference between FNT using higher energy neutrons.[67,68] Only the higher energy, fast, and ultrafast beams can effectively treat deep-seated targets. In terms of delivery, fixed-beam lines with rotating chairs, as well as gantry-based systems, have been used to enable treatment from multiple angles.

Over the years, approximately 41 centers have offered FNT, with over 35,000 patients treated worldwide.[69] Usage peaked in the early 1990s but waned in the following years for a variety of reasons, including the emergence of better photon therapy techniques, the focus on PT and carbon therapy, the absence of explicit guidelines for FNT, and the lack of broad superiority in early comparative trials of FNT versus 3D conformal photon therapy.[70] Another important but somewhat contentious factor in the decline of FNT was the apparent increase in severe toxicities for several treatment sites, particularly those with late-responding normal tissues. This can be attributed to (1) the inherent physics of neutron beams, which lack a Bragg peak and impart high LET radiation throughout the beam path, and (2) the early technology, which began with low-energy beams that produced hotter plans, lacked sophisticated planning tools, and provided no way to modulate the intensity of the beam nor provide dose conformality. In order to reduce normal tissue toxicity, later studies frequently incorporated a photon component (2/5 neutrons, 3/5 photons) as a form of "mixed beam therapy."[71] This resulted in dose distributions with better depth-dose profiles and moderation of the late effects in normal tissues.

As of 2023, only one institution still offers FNT using ultrafast neutrons. The University of Washington Medical Cyclotron Facility (UWMCF) was commissioned in 1984 as the first hospital-based facility in North America to offer 3D conformal FNT with an isocenter gantry, wedge fields, and a multileaf collimator–based collimation system. The facility has continued to design new technology and techniques and recently implemented intensity-modulated neutron therapy (IMNT) through the adaptation of a commercial treatment planning system and upgrades to its control and quality assurance processes.[72-74] The first patient was treated with IMNT in October 2022, and early clinical studies show an improved therapeutic ratio compared to 3D conformal FNT with no evident concerns about acute radiation toxicity.[75] Consequently, IMNT has largely supplanted 3D conformal treatments as the preferred method of FNT for the treatment of head and neck cancers at UWMCF.

FNT has historically shown promise for malignancies of the salivary gland(s), such as adenocystic carcinoma.[76] The site is favorably suited for the modality due to its superficial location, slow growth rate, and distinctly high RBE for neutrons. As with other high LET radiation, FNT is assumed to be most beneficial for radioresistant cancers, including recurrent Merkel cell carcinoma,[77,78] sarcomas, and head and neck cancers.[79] Hybrid treatment approaches that combine and respectively leverage the strengths of high LET neutrons and lower LET protons,[80] or neutrons and photons,[81] have also been shown to be beneficial for some patients. FNT may also be useful as a way to stimulate out-of-field responses with potential synergies with immunotherapy.[77] The new technological capabilities at UWMCF may offer further benefits for properly selected patients, although longer follow-ups and new prospective trials are needed to expand knowledge in this area.

Boron Neutron Capture Therapy

An alternative approach to neutron therapy is through the capture of thermal neutrons (≈0.025 eV) by boron-10, which is introduced into the body as a radiosensitizing agent. Boron-10 has a very high cross section for thermal neutron capture, with the dominant reaction resulting in the fission of boron-11 into an energetic α particle and lithium-7 isotope ($^{10}B + {}^{1}n_{(th)} \rightarrow {}^{4}He$ [1.47 MeV] $+{}^{7}Li$ [0.84 MeV] + γ [0.48 MeV]). The range of each particle in tissue is on the order of a few microns, and thus, the energy deposition (≈180 keV μm^{-1}) and associated cell kill are highly localized to the immediate area surrounding the boron-10 agent. The rationale for boron neutron capture therapy (BNCT) is thus the uptake of boron-10 in cancerous tissues, which are subsequently targeted by an external neutron beam and destroyed by high LET interactions with the fission products resulting from the boron neutron capture reaction.

BNCT has a long but sporadic history, with estimates of less than 1,000 patients treated as of 2012, primarily in Japan and Finland.[70] Before this date, nuclear reactors were the predominant source of thermal or epithermal (≈10 keV) neutrons for BNCT. The more energetic epithermal spectrum provides better neutron penetration for treating deeper tumors (up to 10 cm). Epithermal neutrons are moderated to the thermal range within the first few centimeters in tissue. A limitation is that this expands the type of nuclear interactions, potentially making the dosimetry and radiobiology more complex.[82] Over the past decade, there has been a dramatic shift from nuclear reactors to accelerator-based systems for BNCT, leading to its reemergence as a modality of interest. This was prompted by the Fukushima nuclear disaster in Japan in 2011 and the desire for a more accessible and compact delivery system. A limited number of systems are currently in operation in Japan and Finland, with others planned worldwide.[83-85] The platforms are designed to accelerate protons to bombard either a lithium-7 or beryllium-9 target to generate (*p*,*n*) reactions. In both cases, the resulting neutron beam must be moderated, filtered, reflected, and collimated using a beam-shaping assembly (BSA). The goal of the BSA is to reduce contamination from γ rays and fast neutrons while maximizing the thermal/epithermal neutron yield. For delivery, patients are treated using a robotic chair or couch and either horizontal or vertical fixed beams, depending on the system design.

Although several boron-containing compounds have been investigated, boronophenylalanine (BPA) and sodium borocaptate (BSH), the so-called “second-generation” agents, are the only two that have been examined in clinical trials. BSH has a very high boron content and accumulates in tumors such as gliomas by diffusing across an impaired blood-brain barrier.[86] BPA is a phenylalanine analog that attaches to cell membranes and has also been used to treat gliomas as well as glioblastoma multiform, melanoma, and recurrent head and neck cancers.[87] Unfortunately, neither agent has a particularly strong specificity for malignant tissue, though of the two, BPA has shown a greater affinity for tumor cells in clinical trials. Uptake, quantified as the tumor-to-normal tissue ratio (*T*/*N*) or tumor-to-blood ratio (*T*/*B*), is assessed from blood samples acquired after the intravenous administration of the boron agent. Values are calculated based on tissue-to-blood concentration ratios taken from biodistribution studies. Criteria for effective treatment include a boron-10 concentration ≥ 20 to 35 μg/g (≥10^9 boron-10 atoms per

cell) and a *T*/*N* or *T*/*B* ratio greater than 2.5 to 3. To improve accuracy, BPA can be tagged with radioactive fluorine to assess boron uptake through PET.[88] Since these types of images can be acquired beforehand, PET scans can be used to screen patients for BNCT treatment.

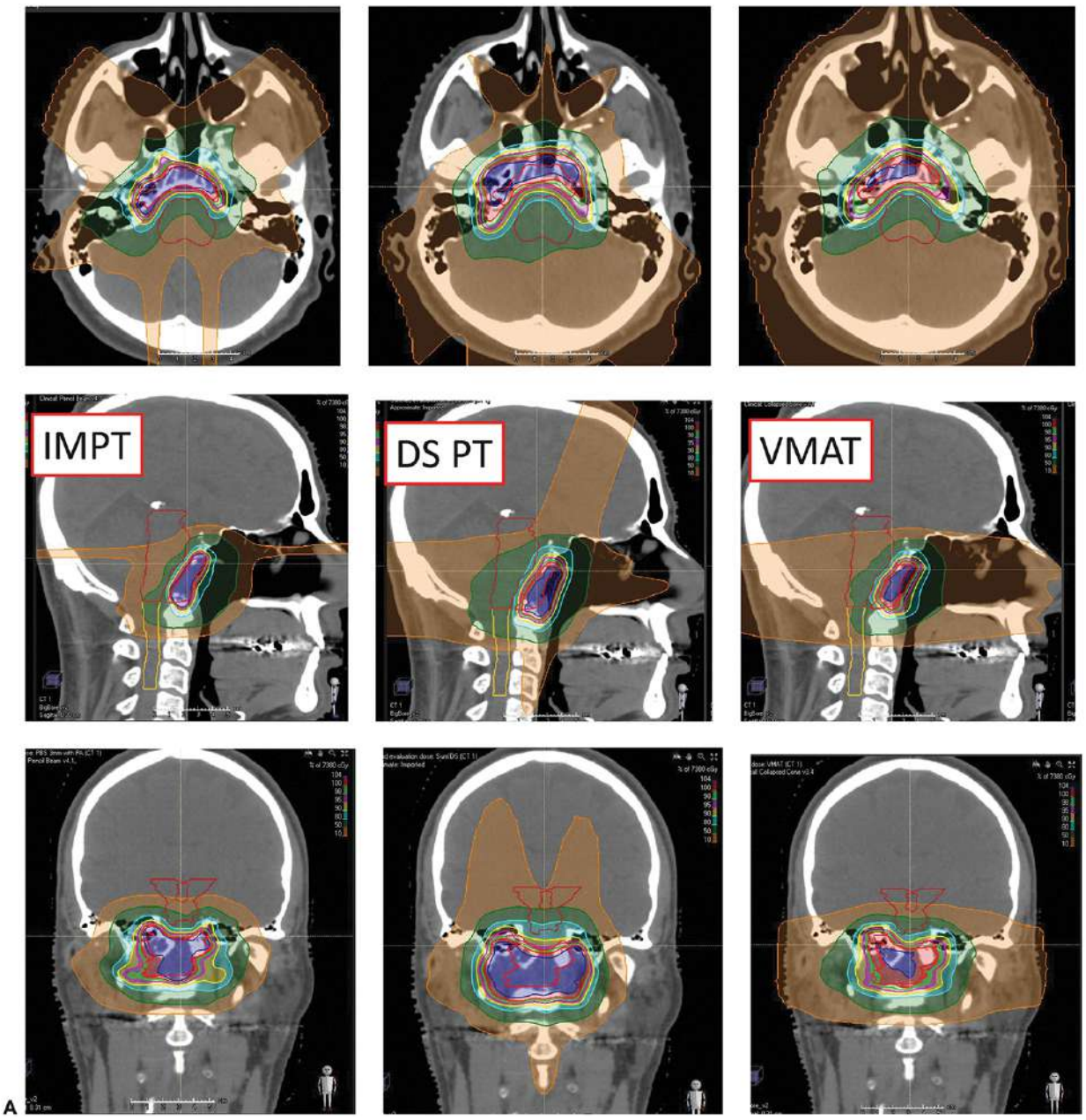
As noted, BNCT has primarily been used to treat radioresistant brain tumors, melanomas, and recurrent disease in the head and neck. Work is ongoing to expand the number of treatment indications by developing third-generation delivery agents. Such compounds are intended to improve the *T*/*N* ratio by specifically targeting uptake in tumor cell nuclei and DNA. Various biomolecules, including peptides, proteins, and liposomes, are currently under investigation, some of which have been further enhanced through the attachment of boron nanoparticles.[89,90] Whether these efforts should take precedence over optimizing the current clinical paradigm using BPA and BSH is an ongoing debate.[86,90] Notably, several hurdles exist in translating preclinical BNCT research into phase I trials, including the cost of clinical biodistribution studies and that historically, there has been little enthusiasm from the pharmaceutical industry in sponsoring such studies, be it lack of convincing experimental evidence or otherwise.[90] However, as with FNT and He ion therapy, enough therapeutic potential exists to warrant further research.

APPLICATIONS AND OUTCOMES

Many publications have reported significant differences in dose distribution between proton- and photon-based treatment plans in a wide range of malignancies and benign lesions throughout the body. The integral dose with proton plans is typically ≤50% of the integral dose with any photon-based plan. Frequently, the dose to critical structures such as heart, lung, brain, brain substructures, optic structures, mucosa, bowel, bladder, kidney, and liver can be reduced with protons compared with photon-based plans, particularly if IMPT is available.

Despite the relatively few facilities with technology capable of proton delivery to most cancers, the efficacy and safety of PT have already been demonstrated in a variety of malignancies and clinical situations.

The following examples demonstrate deep-seated tumors where protons may offer advantages over conventional radiation. Figures 20.3 through 20.13 illustrate comparative treatment plans for 12 common clinical settings where the improved dose distribution possible with PT may improve clinical outcomes. The examples are not comprehensive but representative and accompanied by highlights from the current clinical literature. Currently, some proton facilities provide only double-scattering proton therapy (DS PT), an increasing number provide only PBS, and a few provide both. Most of the following examples, therefore, are IMPT versus IMRT comparisons. The term “intensity-modulated proton therapy” (IMPT) in the examples below refers to PBS using single-field and/or multifield optimization. Treatment planning techniques, particularly with IMPT and VMAT, are rapidly evolving, and current dose prescription and treatment planning methods are not standardized across the field. Thus, it may be possible to improve upon some of the treatment plans depicted below with other techniques, delivery modes, and better treatment planning systems.


IMPT
DS PT
VMAT
A

Targets	Goal Value	IMPT	DS PT	VMAT
PTV1	V50.4 Gy ≥95%	99.40%	99.97%	99.76%
PTV1	D95% ≥50.4 Gy	54.52	59.77	54.62
PTV2	V73.8 Gy ≥95%	65.4%	74.6%	46.0%
PTV2	D95% ≥73.8 Gy	66.33	66.39	62.11
GTV	V73.8 Gy ≥99%	96%	92%	79%
GTV	D99% ≥70.1 Gy	71.31	69.09	60.52

OARs	Goal Value	IMPT	DS PT	VMAT
Brainstem	D0.1 cc ≤55 Gy	59.32	64.22	62.74
Brainstem	Max dose ≤60 Gy	67.85	68.12	68.16
Brainstem core	D0.1 cc ≤50 Gy	47.98	60.01	52.63
Brainstem surface	D0.1 cc ≤55 Gy	59.30	64.23	62.72
Cochlea, left	Mean dose ≤36 Gy	18.40	30.85	41.38
Cochlea, right	Mean dose ≤36 Gy	57.30	65.92	67.10
HippoHead, left	Mean dose ≤5 GY	0.94	4.59	2.36
HippoHead, right	Mean dose ≤5 GY	8.12	28.83	9.73
HippoTail, left	Mean dose ≤20 Gy	10.88	26.44	9.37
HippoTail, right	Mean dose ≤20 Gy	0.48	7.01	2.19
Hypothalamus	Mean dose ≤5 Gy	0.78	13.39	2.81
Optic chiasm	D0.1 cc ≤55 Gy	6.54	35.38	11.46
Optic nerve, left	D0.1 cc ≤55 Gy	11.11	23.72	14.32
Optic nerve, right	D0.1 cc ≤55 Gy	8.11	33.59	15.78
Pituitary	Mean dose ≤30 Gy	54.79	61.81	57.72
Spinal cord	D0.1 cc ≤50 Gy	49.66	51.02	48.37
Temporal lobe, left	V20 Gy ≤10%	9%	12%	12%
Temporal lobe, right	V20 Gy ≤10%	10%	17%	15%
Brain	Mean dose (Gy)	3.09	8.93	5.78
Conformity index	GTV2	0.62	0.35	0.62
Homogeneity index	GTV2	0.53	0.68	0.71

B

FIGURE 20.3 A. Axial, sagittal, and coronal displays of the dose distributions achieved with intensity-modulated proton therapy (IMPT), with a 3-mm spot size, double-scatter proton therapy (DS PT), and photon-based volumetric modulated arc therapy (VMAT) for a **skull base chondrosarcoma of the clivus**. The thick red line indicates the target volume containing gross residual tumor, the thin yellow line indicates the spinal cord, and the thin red line indicates the brainstem. The color wash indicates the radiation dose levels achieved with each treatment plan; the inner bright blue wash and line indicate the isodose volume receiving 104% of the prescribed radiation dose. The colored shaded areas indicate the following volumes: red, isodose volume receiving the prescribed dose of 73.8 Gy (RBE); bright green, volume receiving 98% of the prescribed dose; magenta, volume receiving 95% of the prescribed dose; yellow, volume receiving 90% of the prescribed dose; aqua, volume receiving 80% of the prescribed dose; dark green, volume receiving 50% of the prescribed dose; and orange, volume receiving 10% of the prescribed dose. B. Dose distribution goals for skull base tumors. Different institutions use different dose distribution goals for evaluating skull base tumor plans. In this case, the target coverage goals were to deliver a dose of 50.4 Gy (RBE) to at least 95% of the planning target volume (PTV1), a dose of 73.8 Gy (RBE) to at least 95% of the PTV2, and a dose of 73.8 Gy (RBE) to at least 99% of the gross target volume (GTV). As is apparent in the goal sheet above, target coverage goals for the PTV1 were met with all three plans, but target coverage goals for PTV2 could not be achieved with any of the plans. The goals for the GTV likewise were not achieved with any of the plans but were better met with the proton plans than the volumetric modulated arc therapy (VMAT) plan and best met with the pencil beam scanning proton therapy plan, with the GTV receiving 96%, 92%, and 79% of the prescribed dose with intensity-modulated proton therapy (IMPT), double-scatter proton therapy (DS PT), and VMAT plans, respectively. With respect to OAR, several parameters must be considered simultaneously, including “hot spots” reflected by the absolute dose to at least 0.1 cm^3 (D0.1 cm^3) and max dose, mean organ doses, and various relative or absolute volumes of an organ receiving certain doses. The DS PT plan involved the use of matched “patch” fields that treat partial target volumes to achieve better coverage of the target but can result in hot spots or higher mean organ doses in some cases. In this case, all three plans produced “hot spots” in the brainstem that exceeded the very conservative planning goal of D0.1 cm^3 ≤55 Gy. Using a volumetric definition of the outer 3-mm rim of the brainstem as the “brainstem surface” and the remaining volume inside the brainstem surface as the “brainstem core,” it was felt that all plans would carry only a very small risk of brainstem injury, because the “hot spots” were small. None of the plans could avoid a significant risk of injury to the right cochlea, but both proton plans provided a good chance of preserving the left cochlea, with mean doses to the left cochlea of 18 Gy (RBE), 31 Gy (RBE), and 41 Gy with IMPT, DS PT, and VMAT, respectively. Considering both target coverage and OAR protection, the best plan for this patient was the IMPT plan. Although mean and maximum doses of some structures were better with VMAT than DS PT, the

improved target coverage with DS PT would generally warrant selection of the DS PT plan over VMAT, if IMPT were not available. RBE, relative biologic effectiveness.

Skull Base Sarcomas

Skull base sarcomas are typically not amenable to complete resection and require very high radiation doses for disease control. Their adjacency to the brainstem, optic chiasm, and optic nerves often precludes the delivery of optimal tumor doses for fear of fatal or severe functional radiation injuries. PT, in these cases, can achieve dose distributions that often provide better target coverage and permit the delivery of potentially curative doses of radiation to the tumor with minimal risk of brainstem necrosis or blindness; in some cases, PT may offer the patient the only realistic chance of cure. Outcomes from several institutions suggest that up to 81% of chordomas and 94% of chondrosarcomas of the skull base can be controlled with PT with a low risk of serious toxicity such as brain necrosis.[53,91-98] In one of the larger experiences with 112 patients with skull base chordoma, Holtzman et al from the University of Florida reported 5-year overall survival, disease-specific survival, local control, and freedom from distant metastasis rates of 78%, 83%, 74%, and 99%, respectively.[98] A systematic review of PT outcomes among seven studies reporting on 478 patients found 2- and 3-year local control rates of 93% and 87% and survival rates of 99% and 89%, respectively, with only rare grade 3 or higher toxicities.[99] A meta-analysis found PT to be more effective for chordoma than conventional radiation for survival at 3, 5, and 10 years,[100] and a retrospective study of the NCDB also demonstrated improved 5-year survival rates with PT compared with conventional radiation.[101] A review restricted to pure PT not admixed with a photon component has also reported excellent outcomes in the skull base chordoma and chondrosarcoma.[99] A more recent review of particle therapy for skull base tumors provides an algorithm for approaching both unresectable and resectable skull base tumors with definitive or adjuvant particle therapy and suggests a potential role for carbon therapy in unresectable skull base tumors. Hug et al and Nikoghosyan have described ongoing prospective randomized controlled trials of protons and carbon in skull base chondrosarcoma.[102,103]

Figure 20.3A shows axial, sagittal, and coronal color wash displays of the dose distributions for IMPT, DS PT, and photon-based VMAT treatment plans for a skull base chondrosarcoma. Figure 20.3B shows an analysis of DVH data for the three plans. The VMAT plan delivers low-dose irradiation to a much larger volume of nontargeted tissue than either proton plan, specifically to the nose and posterior fossa, and provides inferior target coverage compared with the proton plans. To deliver ≥70 Gy (RBE) to the gross residual tumor volume, the doses achieved (D99%) were 71 Gy (RBE) with IMPT, 69 Gy (RBE) with DS PT, and 60 Gy with VMAT. Sparing of all OARs was best with IMPT. Conformality was similar between IMPT and VMAT, whereas homogeneity was similar between DS PT and VMAT.

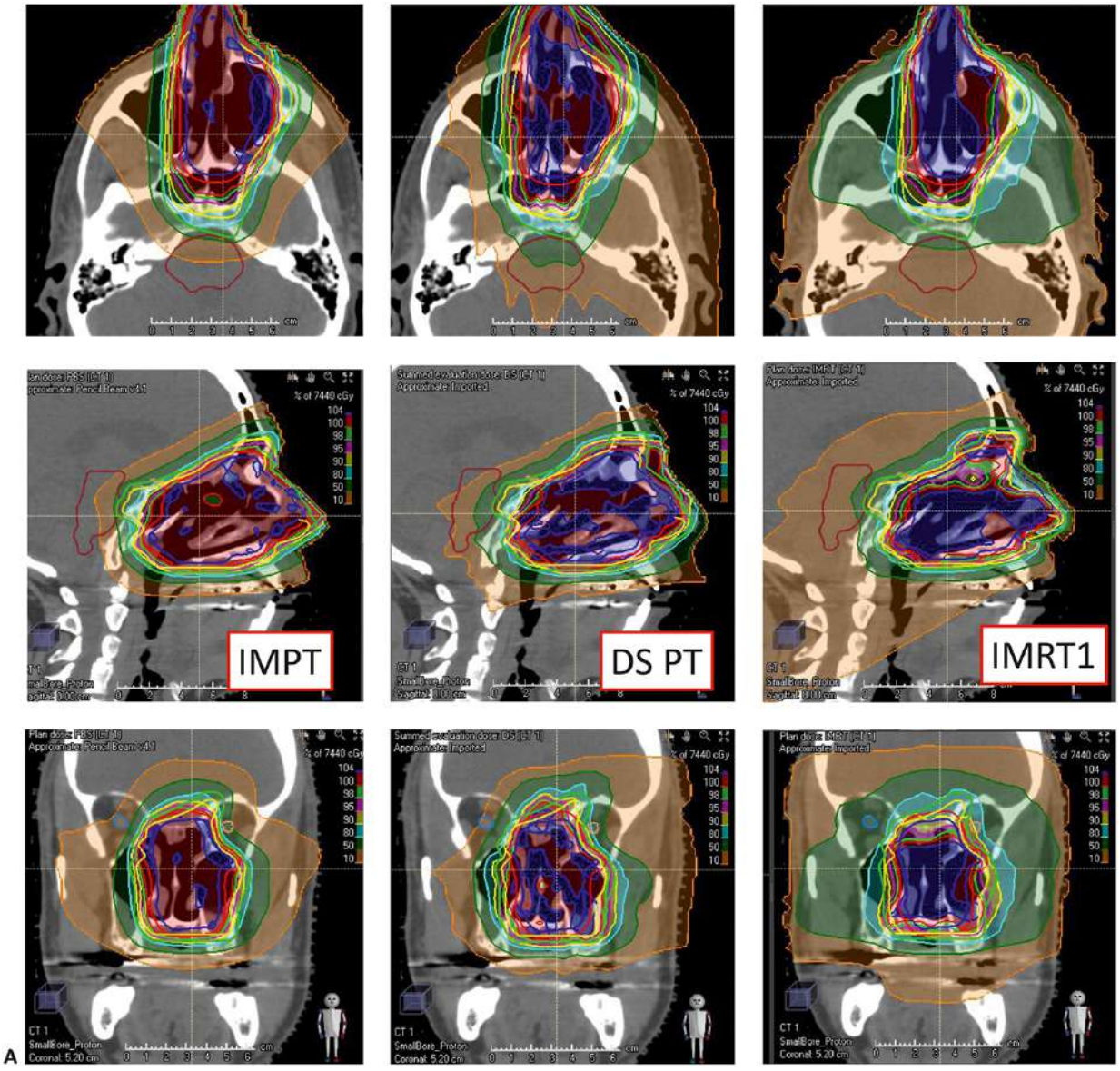
Additional factors in comparing plans include the complexity of delivery, the robustness of the treatment plan, and the number of fields and time required for delivery. DS PT generally requires more fields and treatment delivery time; “through and patch” fields, which cover only parts of the target volume, are often necessary, with some fields treating “through” the target, whereas others are “patched” in to fill gaps in dose coverage. Care must be taken to avoid placing potential hot spots in critical structures.

Advantages of IMPT over DS PT are the avoidance of patch fields, less need for apertures and compensators, increased dose homogeneity within the target, and reduced utilization of room time; however, depending on spot size, the penumbra of the scanned beams for IMPT may preclude its use in some cases. In this case, with minimal concern for organ motion, IMPT provided the best treatment plan. In other skull base sarcomas, the benefits from PT may differ in degree.

Multiple investigators have documented excellent outcomes with particle therapy for sarcomas involving other sites such as the sacrum,[104,105] spine and facial bones,[106-112] chest wall,[113] and retroperitoneum.[114]

Paranasal Sinus Tumors

Paranasal sinus tumors frequently extend into the orbit or anterior cranial fossa adjacent to critical optic structures, such as the chiasm, optic nerves, retinae, lacrimal glands, cornea, and lens. With photon-based therapy, delivering adequate doses to the entire tumor target without injury to at least one of the critical optic structures is often difficult.[115] The physician often must choose between prioritizing tumor control and preserving vision. Figure 20.4 shows a comparison of IMRT and proton plans with both DS PT and IMPT delivery in a patient with a paranasal sinus tumor. All three plans were specified to deliver the prescribed dose of 50.4 Gy to the volume at standard risk for clinical and subclinical disease and 74.4 Gy to the high-risk volume containing gross disease.


IMPT
DS PT
IMRT1
A

Targets	Goal Value	IMPT	DS PT	IMRT1	IMRT2
PTV SR (N/A PT)	D95% ≥50.4 Gy	53.35	53.22	44.45	67.08
PTV HR (N/A PT)	D95% ≥74.4 Gy	69.91	71.46	53.34	76.68
CTV SR	D99% ≥50.4 Gy	58.11	58.07	55.58	66.10
CTV HR	D99% ≥74.4 Gy	74.70	74.22	62.41	74.22

OARs	Goal Value	IMPT	DS PT	IMRT1	IMRT2
Brainstem	D0.1 cc <55 Gy	46.83	59.12	48.55	57.74
Brainstem	D0.01 cc <60 Gy	51.64	61.58	51.04	60.69
Brainstem core	D0.1cc ≤50 Gy	35.14	56.18	43.64	51.69
Brainstem surface	D0.1 cc ≤55 Gy	46.86	59.03	48.45	57.62
Cochlea, left	Mean dose < 36 Gy	3.49	12.66	26.37	31.36
Cochlea, right	Mean dose < 36 Gy	1.28	4.38	20.82	24.75
HippoHead, left	Mean dose ≤5 Gy	20.81	32.94	41.61	49.48
HippoHead, right	Mean dose ≤5 Gy	6.32	8.45	23.38	27.80
HippoTail, left	Mean dose ≤20 Gy	1.16	8.37	18.08	21.50
HippoTail, right	Mean dose ≤20 Gy	0.20	0.14	8.50	10.11
Hypothalamus	Mean dose ≤5 Gy	13.76	15.60	22.13	22.13
Optic chiasm	D0.1 cc ≤55 Gy	43.76	49.49	43.23	51.42
Optic nerve, left	D0.1 cc ≤55 Gy	66.96	64.06	68.49	81.46
Optic nerve, right	D0.1 cc ≤55 Gy	57.22	54.07	56.37	67.03
Pituitary	Mean dose ≤30 Gy	58.09	64.47	55.06	65.48
Temporal lobe, left	V20 Gy ≤10%	11%	17%	46%	54%
Temporal lobe, right	V20 Gy ≤10%	5%	5%	26%	31%
Brain	Mean dose (Gy)	3.25	5.13	10.60	12.61

B

FIGURE 20.4 A. Axial, sagittal, and coronal displays of the dose distributions achieved with intensity-modulated proton therapy (IMPT), double-scatter proton therapy (DS PT), and intensity-modulated radiation therapy (IMRT) for a **paranasal sinus tumor**. The thick red line indicates the gross target volume (GTV), and the thin red line indicates the brainstem. The color wash indicates the radiation dose levels achieved with each treatment plan; the inner bright blue wash and line indicate the isodose volume receiving 104% of the prescribed radiation dose. The remaining colored regions indicate the following: red, isodose volume receiving the prescribed dose of 74.4 Gy (RBE); bright green, volume receiving 98% of the prescribed dose; magenta, volume receiving 95% of the prescribed dose; yellow, volume receiving 90% of the prescribed dose; aqua, volume receiving 80% of the prescribed dose; dark green, volume receiving 50% of the prescribed dose, and orange, volume receiving 10% of the prescribed dose. The goals of the plans were to deliver at least 50.4 Gy (RBE) to the standard-risk planning target volume (PTV SR), at least 74.4 Gy (RBE) to the high-risk planning target volume (PTV HR), and a dose of 74.4 Gy (RBE) to 99% of the high-risk clinical target volume (CTV HR) while respecting dose constraint goals for organs at risk (OARs). The treatment plan delivered a total daily dose of 2.4 Gy (RBE) divided into 2 fractions of 1.2 Gy (RBE) delivered at least 6 hours apart. Two IMRT plans were created for comparison with the two proton plans, one prioritizing OAR protection (IMRT1) and one prioritizing target coverage (IMRT2), which is not shown. B. A dose-volume histogram (DVH) analysis of IMPT, DS PT, and IMRT for the **paranasal sinus tumor** depicted in (A). The goals of the plans were to deliver at least 50.4 Gy (RBE) to the PTV SR, at least 74.4 Gy (RBE) to the PTV HR, and a dose of 74.4 Gy (RBE) to 99% of the CTV HR while respecting dose constraint goals for the OARs. Treatment was planned to deliver a total daily dose of 2.4 Gy (RBE) in 2 fractions of 1.2 Gy/d (RBE) as smaller doses per fraction have been associated with improved radiation tolerance in the optic structures, which, in this case, are partially contained within the PTV HR. Two IMRT plans were created for comparison with the two proton plans, one which prioritized OAR protection (IMRT1) and one which prioritized target coverage (IMRT2). Both proton plans and the IMRT2 plan were significantly better able than the IMRT1 plan to deliver the prescribed dose of 50.4 Gy (RBE) to the PTV SR with doses of 53, 53, 44, and 67 Gy (RBE) to 95% of the PTV SR with IMPT, DS PT, IMRT1, and IMRT2, respectively. Although the IMRT2 plan best achieved the goal of delivering at least 74.4 Gy (RBE) to at least 95% of the PTV HR, it did so with a "hot spot" of 98.85 Gy (RBE) to 2% of the PTV HR (not shown). Although not achieving the PTV HR goal, the proton plans both provided acceptable coverage of the PTV HR, in contrast to the IMRT1 plan, with doses of 70, 71, 53, and 77 Gy (RBE) to 95% of the PTV HR with IMPT, DS PT, IMRT1, and IMRT2, respectively. With respect to OAR protection, all four plans would likely preserve optic chiasm function but result in left optic nerve injury and unilateral blindness. Therefore, preservation of the right optic nerve was a high priority. The IMRT2 plan would almost certainly result in right optic nerve injury and thus bilateral blindness; the DS PT plan provided the lowest dose to the right optic nerve and thus the best hope of preserving unilateral vision. The better sparing of the right optic nerve with DS PT compared with IMPT is related to the penumbra at a depth of even a 3-mm pencil beam scanning spot size and the sharper penumbra achievable with apertures with the DS PT. The best preservation of unilateral vision with DS PT would carry a small risk of brainstem injury. Most of the other OARs show significant dose reduction with both proton plans compared to both IMRT plans, generally with the best sparing achievable with IMPT. In this case, the IMRT2 plan would be rejected due to the risk of bilateral blindness and an unacceptable hot spot of 98.9 Gy (RBE). The IMRT1 plan would be rejected due to inferior target coverage. The choice between IMPT and DS PT would be difficult

but probably favors DS PT for the best chance of unilateral vision preservation with only a very small risk of brainstem injury. RBE, relative biologic effectiveness.

As indicated in Figure 20.4A and B, target coverage with the IMRT1 plan (which was optimized for OAR protection) is inferior to both proton plans; the doses to 95% of the PTV1, 95% of PTV2, and 99% of the gross tumor volume (GTV) were only 44, 53, and 62 Gy with the IMRT1 plan, respectively, compared to 53, 71, and 74 Gy (RBE) with the DS PT plan and 53, 70, and 75 Gy (RBE) with the IMPT plan. The IMRT2 plan, which was optimized for target coverage, produced excellent target coverage but was considered unacceptable because of OAR exposures and hot spots in the PTV. As apparent in Figure 20.4A, compared with both proton plans, the IMRT plan exposes a much larger volume of nontargeted tissue to low-dose radiation, which includes the right temporal lobe, posterior fossa, oral cavity, and supratentorial brain. For example, the volumes of left and right temporal lobes receiving 20 Gy are 54% and 31% with the IMRT2 plan, respectively, 46% and 26% with the IMRT1 plan, 17% and 5% with the DS PT plan, and 11% and 5% with the IMPT plan.

All four plans struggle with the difficulty of target coverage and sparing of the critical structures. With each of these plans, there is only a small risk of brainstem and optic chiasm injury. However, none could sufficiently spare the left optic nerve to avoid a high risk of vision loss in the left eye. Despite adding apertures to the IMPT plan to increase the sharpness of the dose gradient between the optic nerve and target volume, the DS PT plan still offered the best chance of preserving the right optic nerve. Although the proton plans both offer obvious advantages over the photon-based plan, neither avoids the necessity of prioritizing either tumor control or avoidance of injury to a critical organ.

Dagan et al from the University of Florida have reported on 143 adult patients with a variety of sinonasal tumors treated with PT, most with accelerated hyperfractionated regimens and chemotherapy.[116] Local control, disease-free survival, and overall survival rates at 5 years were 80%, 62%, and 59%, respectively, with grade 3 or higher unilateral vision loss rate of 6%. Russo et al from the Massachusetts General Hospital reported very similar results on 54 patients with nasal cavity and paranasal sinus tumors treated with PT with a median follow-up of 82 months[117]; 2- and 5-year local control rates were 80%, and 2- and 5-year survival rates were 67% and 47%, respectively. Similar results have been reported with recurrent tumors, other histologies, and other clinical situations in this anatomic area.[118-127] Similar to sinonasal tumors, it is likely that PT will improve outcomes in skin cancers with clinical perineural invasion where treatment fields include neural pathways to the base of skull[128] and radioresistant tumors in this location.[129] A comparative study by McDonald et al has demonstrated a reduction in acute toxicity with PT compared to IMRT.[130] Because of the difficulties in treatment planning for this challenging anatomic site, a collaborative network was formed between European proton centers to harmonize treatment planning and conduct trials.[131]

Oropharyngeal Cancers

Oropharyngeal carcinoma is the most common head and neck cancer. There is a rising incidence of p16-positive oropharyngeal carcinomas related to human papillomavirus exposure. In contrast to tobacco-related carcinomas, this p16-positive population is generally younger and healthier, has a better chance for disease control, and is thus more likely to experience the late effects of radiation than their tobacco-related p16- negative counterpart.

Figure 20.5 depicts IMRT, DS PT, and IMPT plans in a patient with oropharyngeal carcinoma. As apparent in the figure, there is significant sparing of the oral cavity, posterior neck, and contralateral parotid with both proton plans compared with the IMRT plan, likely impacting the risks of acute mucositis, alopecia, and xerostomia and the need for a feeding tube. The mean OAR doses (Gy [RBE]) for the IMRT, DS PT, and IMPT plans were 39, 22, and 10 for the esophagus, respectively; 26, 26, and 5 for the right cochlea; 53, 27, and 18 for the left submandibular gland; 46, 18, and 11 for the larynx; 58, 45, and 38 for the pharyngeal constrictors; 39, 19, and 16 for the oral cavity; 40, 20, and 17 for the mandible; 22, 11, and 10 for the left parotid; and 51, 48, and 40 for the right parotid. Although DS PT has some advantages over IMRT, the benefits with IMPT are more striking and consistent and suggest the possibility of significant improvements in xerostomia and swallowing compared with IMRT.

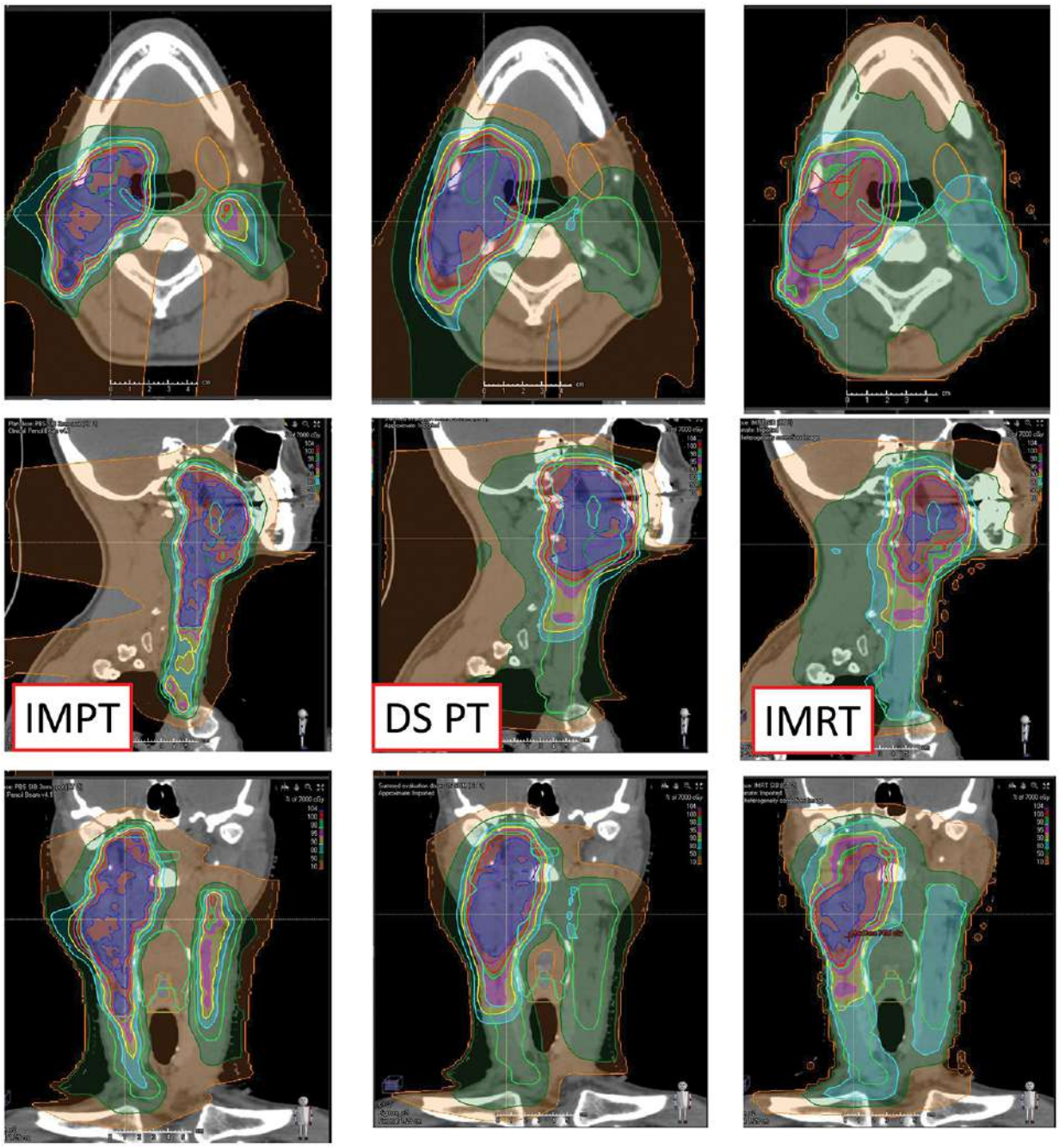


FIGURE 20.5 Intensity-modulated proton therapy (IMPT), double-scatter proton therapy (DS PT), and intensity-modulated radiation therapy (IMRT) plans for a patient with a node-positive right-sided **oropharyngeal cancer**. The high-risk clinical target volume (CTV HR) is indicated by the thick red line. The goals of the treatment plans were to deliver at least 50 Gy (RBE) to the standard-risk planning target volume (PTV SR), 63 Gy (RBE) to the intermediate-risk planning target volume (PTV IR), and 70 Gy (RBE) to the high-risk planning target volume (PTV HR). All plans provided adequate and similar doses to the PTV SR, PTV IR, and PTV HR, with the IMPT plan slightly below goals. However, with the exception of the right (ipsilateral) submandibular gland, the doses to all organs at risk (OARs) were significantly reduced with IMPT compared with the DS PT and IMRT plans. The DS PT plan provided reduced doses to the esophagus, left submandibular gland, mandible, pharyngeal muscle constrictors, and larynx compared to the IMRT plan. In this case, both proton plans appear to be superior to the IMRT plan, but the IMPT plan was also superior to the DS PT plan for OAR protection. RBE, relative biologic effectiveness.

An early report from Slater et al from Loma Linda University suggested better tolerance of oropharyngeal radiation therapy with the use of protons for a portion of the treatment.[132] In an updated 12-year experience with PT in head and neck cancer in 573 patients, Gunn reported 5-year overall and disease-free survival rates in

advanced oropharyngeal carcinoma of approximately 90% and 80%, respectively.[133] Blanchard et al[134] reported a case-matched analysis of patients treated for oropharyngeal cancer at the MD Anderson Cancer Center with either IMRT or IMPT and showed equal disease control and survival rates but reduced rates of feeding tube dependency and severe weight loss among the patients treated with IMPT.[134] Similarly, Youssef et al from Memorial Sloan Kettering Cancer Center reported a retrospective cohort study of 292 patients with human papillomavirus p16-positive oropharyngeal cancer,[135] 20% of whom were treated with IMPT and 80% with IMRT. At a median follow-up of 26 months, there was no difference between 3-year overall survival rates or locoregional recurrence. However, there was a significantly higher rate of acute toxic effects with IMRT compared with IMPT, including oral pain (93% vs 72%), xerostomia (29% vs 21%), dysgeusia (57% vs 28%), dysphagia (12% vs 7%), mucositis (70% vs 53%), nausea (8% vs 0%), and weight loss (59% vs 37%). Four of the 215 IMRT patients required endoscopic gastrostomy tubes for longer than 6 months compared to none of the IMPT patients. Bahig et al reported patient-reported quality of life outcomes after IMPT,[136] suggesting rapid recovery after acute side effects, with most patient concerns resolved by 4 weeks after treatment. A review of current outcomes for PT in oropharyngeal squamous cell carcinoma identified technical factors that can affect the improvement in therapeutic ratio with protons compared with conventional radiation.[137]

A key driver for PT in head and neck cancer is the reduction of both acute and late toxicity. Langendijk et al used photon-based normal tissue complication probability (NTCP) models to identify patients with head and neck cancer likely to benefit from PT and have thus secured broad access in the Netherlands to PT for patients meeting dosimetric criteria.[138] In an excellent discussion of modeling late effects, Stieb et al cite the current photon-based NTCP algorithms and the problems with applying these to patients treated with PT.[139] As the population affected by oropharyngeal carcinoma is shifting to a younger and otherwise healthier cohort, late effects are an increasing concern, and de-escalation of treatment is a major initiative, potentially increasing the attraction of PT. A consensus paper on guidelines for the use of particle therapy in head and neck cancer has been published by the Proton Therapy Co-Operative Group (PTCOG) Head and Neck Subcommittee.[140] Similar to the oropharynx, PT may improve outcomes in nasopharyngeal carcinoma,[141,142] unknown primaries,[143] unilateral head and neck cancers,[144] and major salivary gland tumors.[145] Because of anatomic locations near critical structures, it is also likely that protons will be useful in other tumors in the head and neck region, including angiosarcoma,[146] skin cancers,[147] thyroid cancer,[148,149] radioresistant tumors such as adenoid cystic carcinomas and melanoma,[150] and in reirradiation after initial photon-based therapy.[151]

Craniopharyngioma

Craniopharyngioma is usually diagnosed in children and adolescents. Its suprasellar location places the temporal lobes, hippocampi, hypothalamus, optic chiasm, and optic nerves at risk for radiation injury. Figure 20.6 shows VMAT and IMPT plans in an adolescent patient. Both plans achieve target coverage goals of 54 Gy. Mean nontarget brain doses are 5.8 cobalt gray equivalent (CGE) Gy with the IMPT plan and 8.5 Gy with the VMAT plan. Right and left mean cochlea doses were 6.8 and 7.2 CGE, respectively, with the IMPT plan versus 17.2 and 16.7 Gy with the VMAT plan. Right and left hippocampi doses were 10.3 and 7.4 CGE, respectively, with the IMPT plan versus 20.5 and 18.2 Gy with the VMAT plan. The volumes of right and left temporal lobes receiving 20 CGE/Gy were 17.8% and 15.6%, respectively, with the IMPT plan versus 46.1% and 42.7% with the VMAT plan. Integral dose was 12.3 J with the IMPT plan versus 21 J with the VMAT plan.

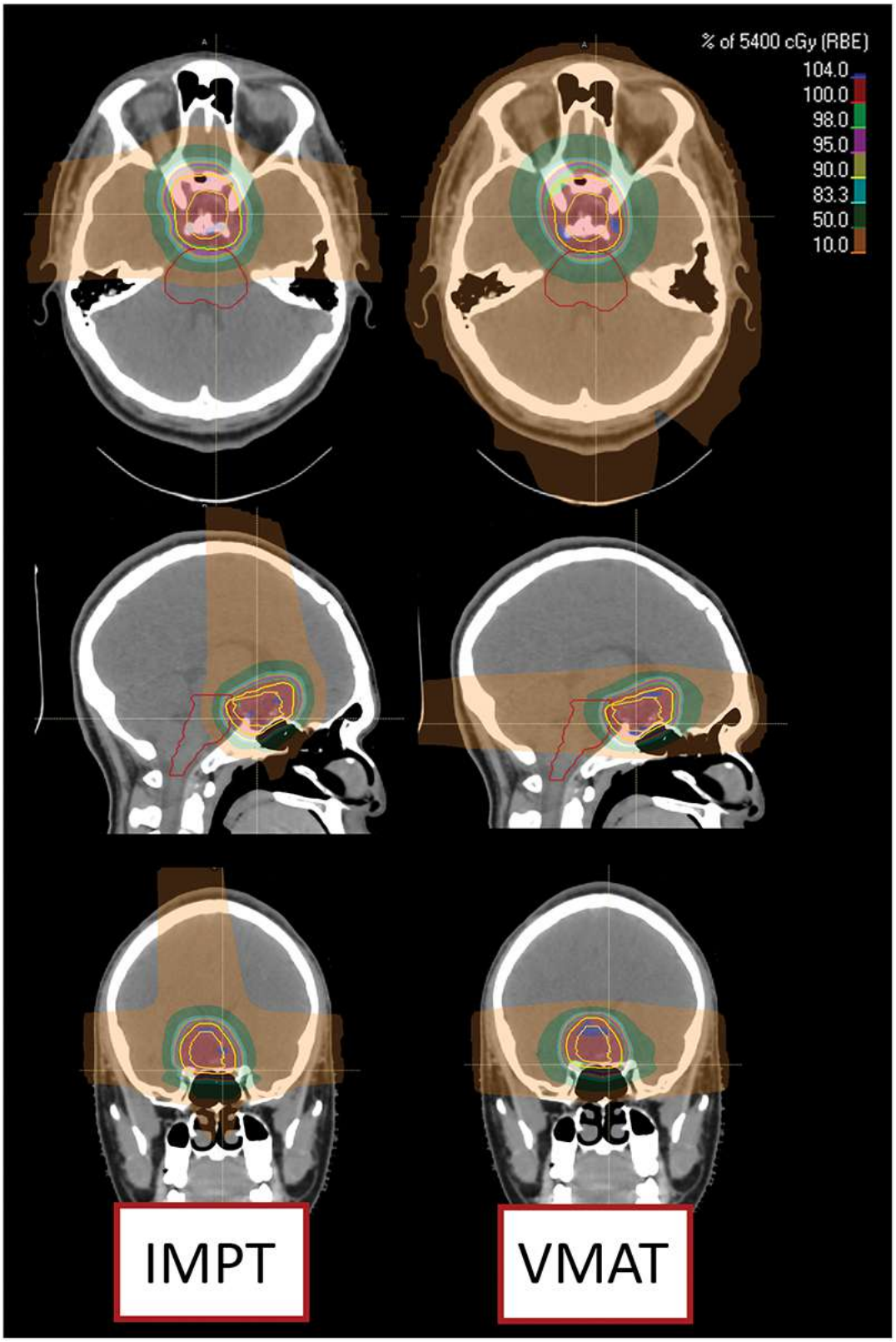


FIGURE 20.6 Axial, sagittal, and coronal displays of the dose distributions achieved with intensity-modulated proton therapy (IMPT) (left) and volumetric modulated arc therapy (VMAT) (right) plans for a small **craniopharyngioma**. The prescription dose was 54 Gy (RBE) to the planning target volume. Both treatment techniques provided excellent conformal coverage of the target. As apparent, the volume of tissue exposed to low- and intermediate-dose irradiation is reduced with the IMPT plan. Where integral dose means dose delivered to

nontargeted tissue, a dose-volume histogram comparison of doses to organs at risk showed integral doses of 12.3 and 21.0 J for the IMPT and VMAT plans, respectively. The volumes of right and left temporal lobes receiving 20 Gy (RBE) were 17.8% and 15.6% with the IMPT plan, respectively, compared with 46.1% and 42.7% with the VMAT plan. The mean absolute doses to the right and left hippocampi were 10.3 and 7.4 Gy (RBE) with the IMPT plan compared with 20.5 and 18.2 Gy with the VMAT plan. The absolute dose received by 50% of the brainstem was 4.6 Gy (RBE) with the IMPT plan compared with 23 Gy with the VMAT plan. Mean absolute doses to the right and left cochlea were 6.8 and 7.2 Gy (RBE) with the IMPT plan compared with 16.7 and 17.2 Gy with the VMAT plan. RBE, relative biologic effectiveness.

A number of investigators have reported early outcomes in medulloblastoma, ependymoma, craniopharyngioma, and other tumors. Indelicato et al reported on a variety of pediatric brain tumors referred for treatment from overseas[152]; within this cohort, the 3-year disease control rate for craniopharyngioma was 100%. PT outcomes in 91 adult patients with craniopharyngioma reported by Beddok et al were similarly excellent.[153] Of note, three of the five patients developing local recurrence were among the five (of 31 patients with on-treatment reimaging) who required replanning, suggesting a need for a routine policy of reimaging (particularly in patients with a cystic component) and adaptive therapy.

Extensive work from Merchant et al at the St Jude Children's Research Hospital in a variety of pediatric brain tumors has correlated the risk of radiation-related neurocognitive decline to radiation dose level and distribution.[154] Early outcomes provided evidence that PT may cause less neurocognitive decline than conventional radiation, consistent with dosimetric predictions.[155] Gross et al reported a retrospective study of a variety of midline brain tumors in children,[156] showing better long-term neurocognitive outcomes in children treated with PT compared to IMRT. A prospective comparative study of neurocognitive outcomes between children treated with IMRT and PT for craniopharyngioma from St Jude Research Hospital and the University of Florida showed a decline over time in IQ after IMRT, but not after PT.[157] Indelicato et al carefully detailed the incidence and dosimetric parameters associated with pediatric brainstem toxicity after PT[158]; while the incidence of toxicity in the high-dose volume is low, it is unclear whether the same dosimetric guidelines that are useful in photon-based radiation are optimal for PT and whether all factors affecting toxicity are well understood. It is likely that many other brain and central nervous system tumors in both children and adults will benefit from the dosimetric advantages of PT for similar reasons.[159-164] It is clear from a phase II randomized study that the smaller volume of brain exposed to low-dose radiation with PT compared with photon-based radiation produces less radiation-induced lymphopenia,[165] which offers improved opportunities for combined modality therapy and positively affects disease control in tumors, such as glioblastoma. The European Particle Therapy Network consensus has conducted a literature search in the neuro-oncologic literature to identify papers that include dose constraints for OARs and generated a consensus report to guide future treatment decisions using a dosimetry model approach and for future comparative studies.[166]

Craniospinal Axis Irradiation

Craniospinal axis irradiation is required in most medulloblastomas and occasionally in other brain tumors, such as advanced or metastatic germ cell tumors, primitive neuroectodermal tumors, and ependymomas. Most patients with these tumors are young and at risk for the late effects of radiation. As shown in Figure 20.7 from an adolescent girl, the exit dose from photon therapy exposes the thyroid, heart, lung, gut, and gonads to functional and neoplastic risks that can be minimized with PT. As expected, doses to all target structures within the craniospinal irradiation (CSI) field are similar between the IMPT and VMAT plans. However, in this case, the total-body integral dose is 175 J with the IMPT plan compared with 331 J with the VMAT plan. The mean doses to the right and left lacrimal glands are 13.5 and 8.6 CGE with the IMPT plan, respectively, compared with 19.4 Gy bilaterally with the VMAT plan. Mean right and left lens doses are 1.6 and 1.8 CGE with the proton pan, respectively, compared to 12.9 and 18.5 Gy with the VMAT plan. The mean absolute lung dose with the IMPT plan is 3.4 CGE versus 8.3 Gy with the VMAT plan. The mean thyroid dose with the IMPT plan is 0 versus 19.3 Gy with the VMAT plan. The mean heart dose is 0.1 CGE with the IMPT plan versus 9.2 Gy with the VMAT plan. Mean right and left kidney doses were 1.6 and 2.6 CGE with the IMPT plan, respectively, versus 7.4 and 8.9 Gy with the VMAT plan.

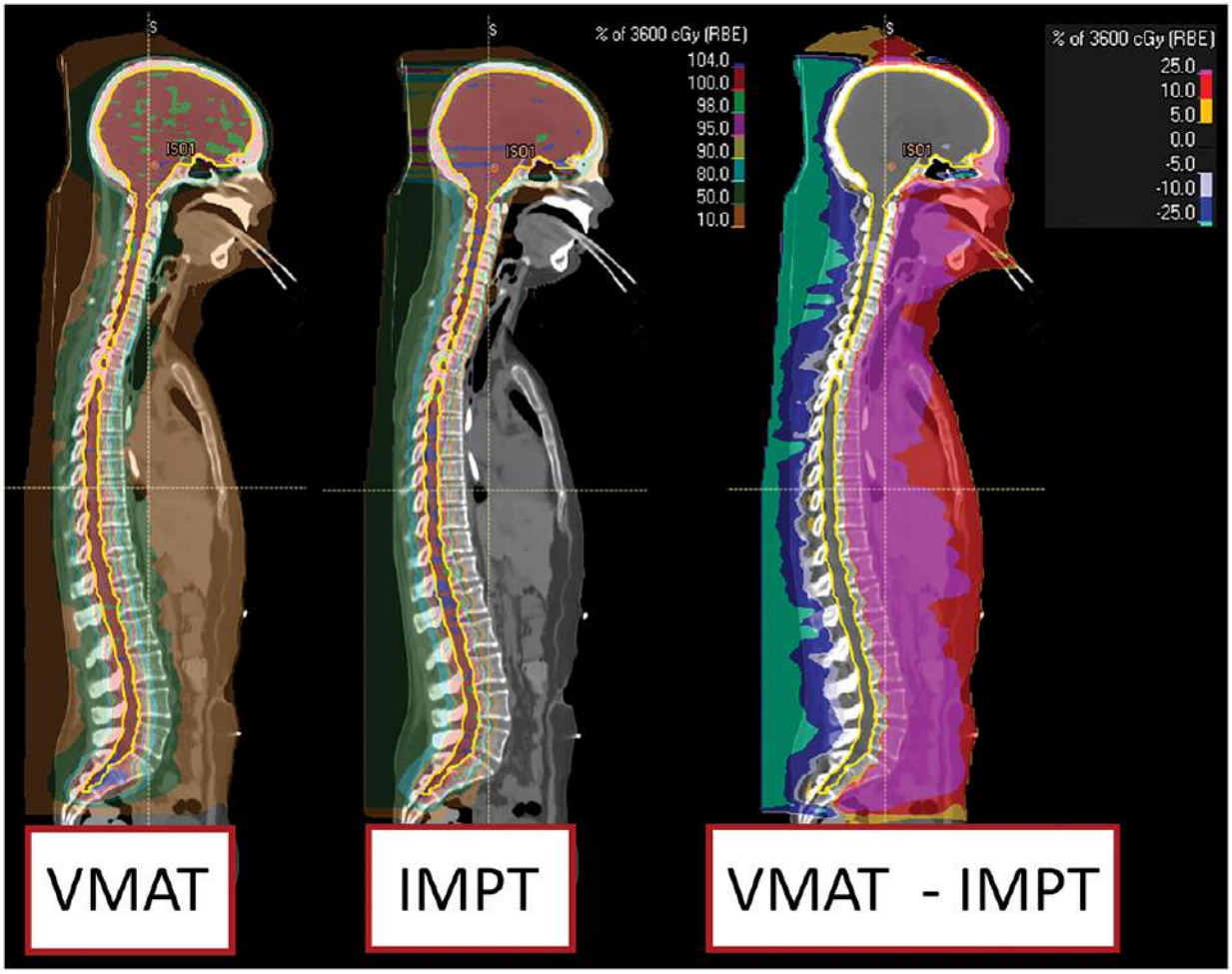


FIGURE 20.7 **Craniospinal irradiation** is necessary in a variety of brain tumors, most of which occur in young patients at risk for late effects. This figure of a 13-year-old female shows sagittal planes from volumetric modulated arc therapy (VMAT) plans (left) and intensity-modulated proton therapy (IMPT) plans (center) and integral dose in which the dose deposited by the IMPT plan is subtracted from the dose deposited by the VMAT plan (right). As apparent in the figure, the risks for functional and neoplastic effects in the thyroid, heart, lungs, breasts, gut, and gonads from photon therapy can be significantly minimized with proton therapy because of the lack of an exit dose. The integral doses are 175.4 J with the IMPT plan compared with 331.3 J with the VMAT plan. A comparison of plan metrics showed mean absolute doses with the IMPT and VMAT plans of 0.1 Gy (RBE) and 9.2 Gy to the heart, 1.6 Gy (RBE) and 7.4 Gy to the right kidney, 2.6 Gy (RBE) and 8.9 Gy to the left kidney, 8.6 Gy (RBE) and 19.4 Gy to the left lacrimal gland, 1.8 Gy (RBE) and 18.5 Gy left lens, and 3.3 Gy (RBE) and 8 Gy to the left lung. RBE, relative biologic effectiveness.

In a multi-institutional cohort study of 88 children treated with chemotherapy and either photon or proton radiation for standard-risk medulloblastoma, Eaton et al found no significant difference in disease control, survival, or patterns of failure rates between proton and photon radiation, suggesting equivalent efficacy.[167] Barney et al, reporting on 50 patients treated with proton CSI at the MD Anderson Cancer Center between 2007 and 2011, documented extremely low median radiation doses to the thyroid of 0.003 Gy (RBE); the lung, 1.1 Gy (RBE); heart, 0.002 Gy (RBE); kidney, 0.04 Gy (RBE); bowel, 0.02 Gy (RBE); testicles, 0.003 Gy (RBE); and ovaries, 0.003 Gy (RBE).[168] Treatment-related morbidity in this series included grade 3 leukopenia in 9%, thrombocytopenia in 2%, and median weight loss of 1.1 kg (1.6% loss from baseline). Progression-free survival rates at 2 and 5 years were 82% and 68%, respectively, with 80% of treatment failures involving a local recurrence. Vázquez et al reported on the outcomes of 71 children and young adolescents treated with proton CSI for medulloblastoma and ependymoma,[169] including overall survival, with a median follow-up of 24 months, the estimated local control, distant control, overall survival and freedom from late grade ≥3 rates were 86.3%, 80.5%, 84.7%, and 92.6%, respectively. These data suggest that CSI with PT is effective but potentially much less acutely toxic and much less likely to result in late effects. While CSI is most commonly used in medulloblastoma and other aggressive pediatric brain tumors, it may also be used for the control of leptomeningeal metastases in solid

tumors in adults. In the palliative setting, photon CSI is not often used because of the acute morbidity associated with lung and gastrointestinal exposure. Involved field photon irradiation is considered standard of care and achieves temporary palliation but does not stop disease progression along the craniospinal axis. Yang et al reported on a randomized phase II trial of proton CSI versus photon-involved field radiotherapy for patients with solid tumor leptomeningeal metastases, which showed improved central nervous system progression-free survival rates in the proton arm without increased treatment-related adverse events.[170]

Lymphomas

Lymphomas frequently involve the mediastinum and often require a low-to-moderate dose of radiation therapy in conjunction with chemotherapy for maximum probability of disease control. Unfortunately, even low-to-moderate radiation doses place the patient at risk for late cardiac injury and second cancers, particularly breast cancers. Figure 20.8 shows a comparison of an IMPT and IMRT plan in a young woman with Hodgkin lymphoma who had disease in the left axilla and mediastinum. The proton plan shows a significant reduction in the volume of the heart, lung, right breast, spinal cord, and other soft tissues exposed to low-dose irradiation. The mean heart dose is 10.4 CGE with the IMPT plan compared with 14.6 Gy with the IMRT plan. The mean lung dose is 8.4 CGE with the IMPT plan versus 12.9 Gy with the IMRT plan. The mean dose to the right breast is 1.7 CGE with the IMPT plan versus 6.6 Gy with the IMRT plan. The mean dose to the stomach is 6.6 CGE with the IMPT plan versus 25.4 Gy with the IMRT plan. The mean dose to the right kidney is 0 with the IMPT plan versus 6.1 Gy with the IMRT plan. The mean dose to the left kidney is 6.5 CGE with the IMPT plan versus 20.6 Gy with the IMRT plan. The mean dose to the oral cavity is 4 CGE versus 12.5 Gy with the IMRT plan. The integral dose is 105 J with the IMPT plan versus 235.4 J with the IMRT plan.

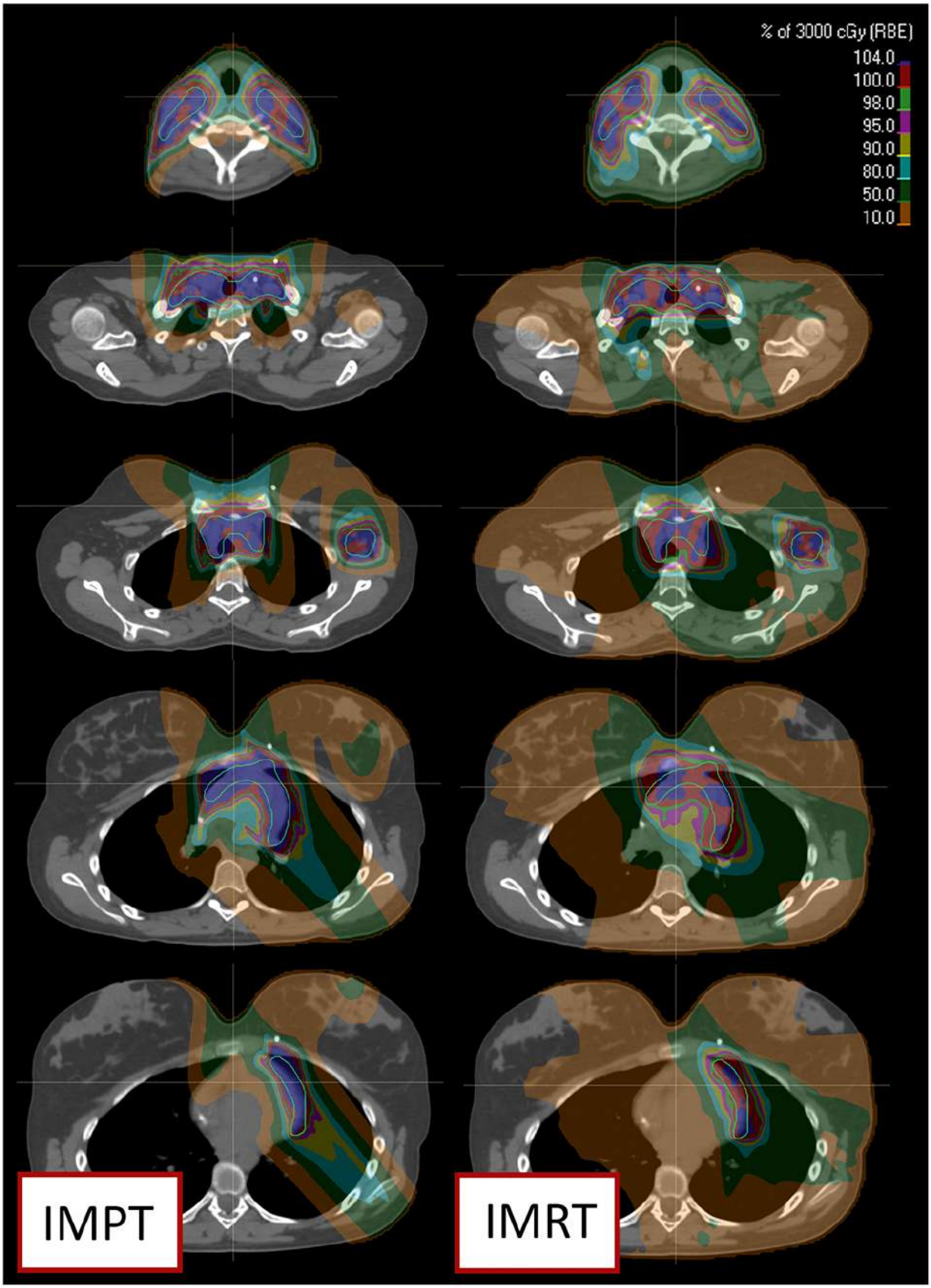

% of 3000 cGy (RBE)
104.0
100.0
98.0
95.0
90.0
80.0
50.0
10.0
IMPT
IMRT

FIGURE 20.8 Axial planes are shown for intensity-modulated proton therapy (IMPT) (left) and intensity-modulated radiation therapy (IMRT) (right) for a female patient with neck and mediastinal involvement with **Hodgkin lymphoma**. As apparent, the proton therapy plans expose a smaller volume of nontargeted tissue (particularly the heart, lung, spinal cord, stomach, left kidney, and right breast) to radiation than the IMRT plan. Integral dose with the IMPT plan was 105.1 J compared with 235.4 J with the IMRT plan. Mean heart dose is 10.4 Gy (RBE) with protons and 14.6 Gy with IMRT. The volume of lung receiving at least 5 Gy (V5 Gy) and 20 Gy (V20 Gy) are 42.4% and 18.8% with IMPT, respectively, compared with 69.1% and 24.8% with IMRT. Maximum dose to the spinal cord was 16.3 Gy (RBE) with IMPT compared with 21.5 Gy with the IMRT plan. Mean stomach dose was 6 Gy (RBE) with the IMPT plan compared with 25.4 Gy with the IMRT plan. Mean absolute dose to the left kidney was 6.5 Gy (RBE) with the proton plan compared with 20.6 Gy with the IMRT plan. Mean right breast dose is 1.7 Gy (RBE) with the IMPT plan compared to 6.6 Gy with the IMRT plan. RBE, relative biologic effectiveness.

The strong interest in PT for Hodgkin lymphoma relates to the high cure rate and longevity of its survivors, who unfortunately frequently succumb to secondary malignancy and heart disease. In a variety of settings in a single- and multi-institutional registry study, several studies reported minimal acute toxicity and excellent early disease control outcomes with PT in lymphoma.[171-176] Pinnix et al (MD Anderson Cancer Center) reported that small doses to large volumes of lung had the greatest influence on the risk of radiation pneumonitis in patients receiving IMRT for lymphoma[177]; thus, it is likely that the reductions in volumes of lung receiving low doses with PT, compared with IMRT, will result in lower rates of pulmonary injury. Several international cooperative groups have endorsed the usefulness of PT in lymphoma, including the International Lymphoma Radiation Oncology Group (ILROG)[178] and the PTCOG Lymphoma Subcommittee.[179] On behalf of the PTCOG Lymphoma Subcommittee and for ILROG, Patel et al reported a systematic review of the studies comparing PT with or without deep inspiration breath-hold (DIBH) techniques with IMRT with DIBH.[180] This review showed an advantage in lung and heart exposure with PT over IMRT, regardless of whether DIBH was used with PT. They also found that some studies showed a benefit for DIBH with PT over PT alone. Finally, in a study of secondary malignancies after radiation using the NCDB, Xiang et al reported an approximately 3-fold reduction in secondary malignancies after lymphoma radiation with protons compared to photons apparent at a median of 5 years after treatment.[23] Given the very long life expectancy of patients with most Hodgkin and many other lymphoma, this significant reduction in secondary malignancies is a compelling rationale for PT by itself.

Lung Cancers

Lung cancers are typically diagnosed at an advanced stage and often occur in patients with underlying lung damage. Consequently, concern for protecting unaffected lung tissue often mandates compromise in the tumor dose. Chun et al reporting secondary analyses from radiation therapy oncology group (RTOG) 0617 (a randomized trial of 60 Gy vs 74 Gy with concurrent chemotherapy using carboplatin and paclitaxel with or without cetuximab) showed that lung V20 was associated with increased ≥3 pneumonitis risk ($P = .026$) and that the cardiac V40 was associated with overall survival ($P < .05$).[181] In a retrospective study, Wang et al found significant associations between mean heart dose and symptomatic cardiac events in an analysis that accounted for World Health Organization/International Society of Hypertension scores and history of coronary artery disease.[182] The 2-year competing risk-adjusted event rates for patients with heart mean doses of <10, 10 to 20, and ≥20 Gy were 4%, 7%, and 21%, respectively. These studies set the stage for improved outcomes with protons in patients with more advanced lung cancer through cardiac and lung sparing.

The first application of PT was reported from Loma Linda University. It utilized a hypofractionated regimen and produced excellent results, which have been successfully replicated at many centers worldwide.[183] However, clinical results subsequently have been mixed. The first randomized trial directly comparing IMRT and PT (NCT00915005) had mixed results.[184] Passively scattered proton plans and IMRT plans were completed on patients prior to study enrollment; patients were eligible for study only if all dosimetry objectives could be met with the same tumor dose by both the proton and IMRT plans. Two dose levels were offered, with the higher dose level used only if both the IMRT and PSPT (passive scattering proton therapy) plans met all dosimetric objectives. It is likely that most patients who would have benefited from PT were thus not included in the study since the IMRT plans could meet the prescribed objectives. Not surprisingly, dosimetry comparison between the treatment arms showed improvements in cardiac dose with the proton plans, but not in esophageal or lung doses. At 12 months, there was no difference between the treatment arms for either pneumonitis or local disease control rates. In a secondary analysis,[184] the pneumonitis rate in the latter part of the study was significantly lower than in the initial part of the study for both the IMRT and proton arms but more significantly so for the proton arm, suggesting a steep learning curve in treatment planning and delivery in the proton arm. The combined event rate of local failure and pneumonitis for patients treated during the initial half of the study was 21.1% for IMRT versus 31% for PT,

and for the latter half of the study, 18.2% for IMRT versus 13.1% for PT. In another secondary analysis, there was no difference in local recurrence and particularly marginal failure between the arms, suggesting that the rapid dose falloff associated with proton plans outside the target volume was not a problem.[185] In a third secondary analysis, the volume of the lung receiving high doses was the best predictor of pneumonitis.[186] The authors speculated that IMPT might produce a better outcome than passive scatted PT by achieving the high-dose conformality of an IMRT but with a much lower integral dose to the rest of the lung. The ongoing trial RTOG 1308 (NCT01525446) randomizes patients with advanced non–small cell lung cancer to IMRT or PT and allows for IMPT or passively scattered PT. A consensus statement from the Thoracic Subcommittee of the PTCOG discusses the potential advantages in many scenarios in non–small cell lung cancer as well as the complexities of PT planning and delivery to the lung.[187]

Figure 20.9 shows IMPT and VMAT plans in a patient with stage III lung cancer. In this case, the volume of nontargeted lung tissue, breast, and heart exposed to radiation can be reduced with PT compared with IMRT. However, in some cases, there may be more or less of a benefit depending on the tumor's size and location and the treatment planner's expertise.

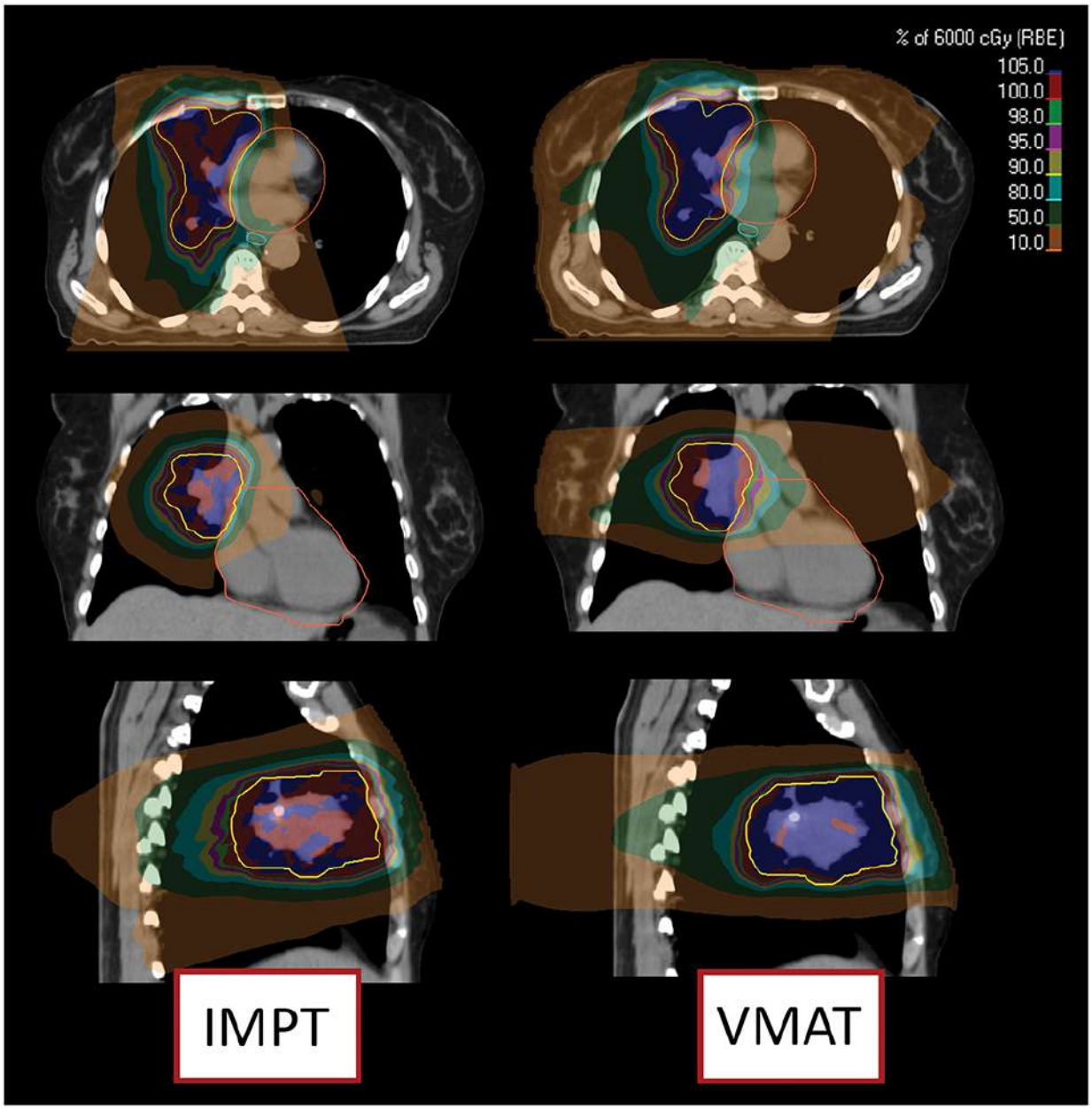


FIGURE 20.9 Axial, coronal, and sagittal planes are shown for intensity-modulated proton therapy (IMPT) (left) and volumetric modulated arc therapy (VMAT) (right) for a female patient with **lung cancer**. Integral doses for the IMPT and VMAT plans were 79.2 and 107.2 J, respectively. As apparent, the IMPT plan minimized the volumes of breast, lung, and heart exposed to radiation. The mean absolute doses with IMPT and VMAT to the lung were 13.8 Gy (RBE) and 15.1 Gy and to the heart were 6.9 Gy (RBE) and 12.9 Gy, respectively.

For other malignancies present in the lung, such as mesothelioma,[188] several studies have suggested that there may be fewer high-grade toxicities and shorter hospital stays with patients with esophageal cancer receiving PT compared with photon-based therapy.

Eye Malignancies

Passively scattered PT has been used for melanomas or other malignancies of the retina and optic structures for many years in Europe and the United States before the development of modern gantry-based proton facilities and more gantry-based scanning and/or PBS.[189-197] Given the lethality of ocular melanoma and the ability to preserve the globe and some vision with radiation strategies, most patients with ocular melanoma are treated with radiation

by either brachytherapy plaques with ruthenium, cobalt, or iridium or external beam radiation with PT or stereotactic body radiation therapy. In an excellent review of long-term visual outcomes, Jarczak et al described the various radiation strategies, including brachytherapy and PT, and the subsequent high incidence of visual deterioration, as well as potential strategies for mitigating visual deterioration.[198] Typically, the ophthalmologist identifies the target, and clips are placed behind the retina to guide tumor localization. Late visual effects have been associated with tumor size and dose to the macula or optic nerve. In recent years, efforts to improve the planning system and utilize magnetic resonance imaging in tumor identification will likely improve future PT applications in this rare tumor.

Pancreatic Cancers

Pancreatic cancers have extremely low survival rates with either conventional radiation alone or combined with surgery and chemotherapy. The disease is frequently localized for a window of time before spreading, providing a potential opportunity to improve the overall outcome by intensifying local therapy. Figure 20.10 shows IMPT and VMAT plans for a patient with cancer in the pancreatic head. As apparent, there is much less low-to-intermediate dose to the bowel, liver, kidney, and stomach with the IMPT plan. Integral doses with the IMPT and VMAT plans are 35.1 and 61.4 J, respectively. Mean doses with IMPT and VMAT are 5.7 Gy (RBE) and 15.1 Gy to the stomach and 14.3 Gy (RBE) and 9.4 Gy to the overall bowel space, respectively. The left kidney is also relatively spared with the proton plan, with a volume receiving 20 Gy of 0.2% with IMPT and 16.9% with the VMAT plan.

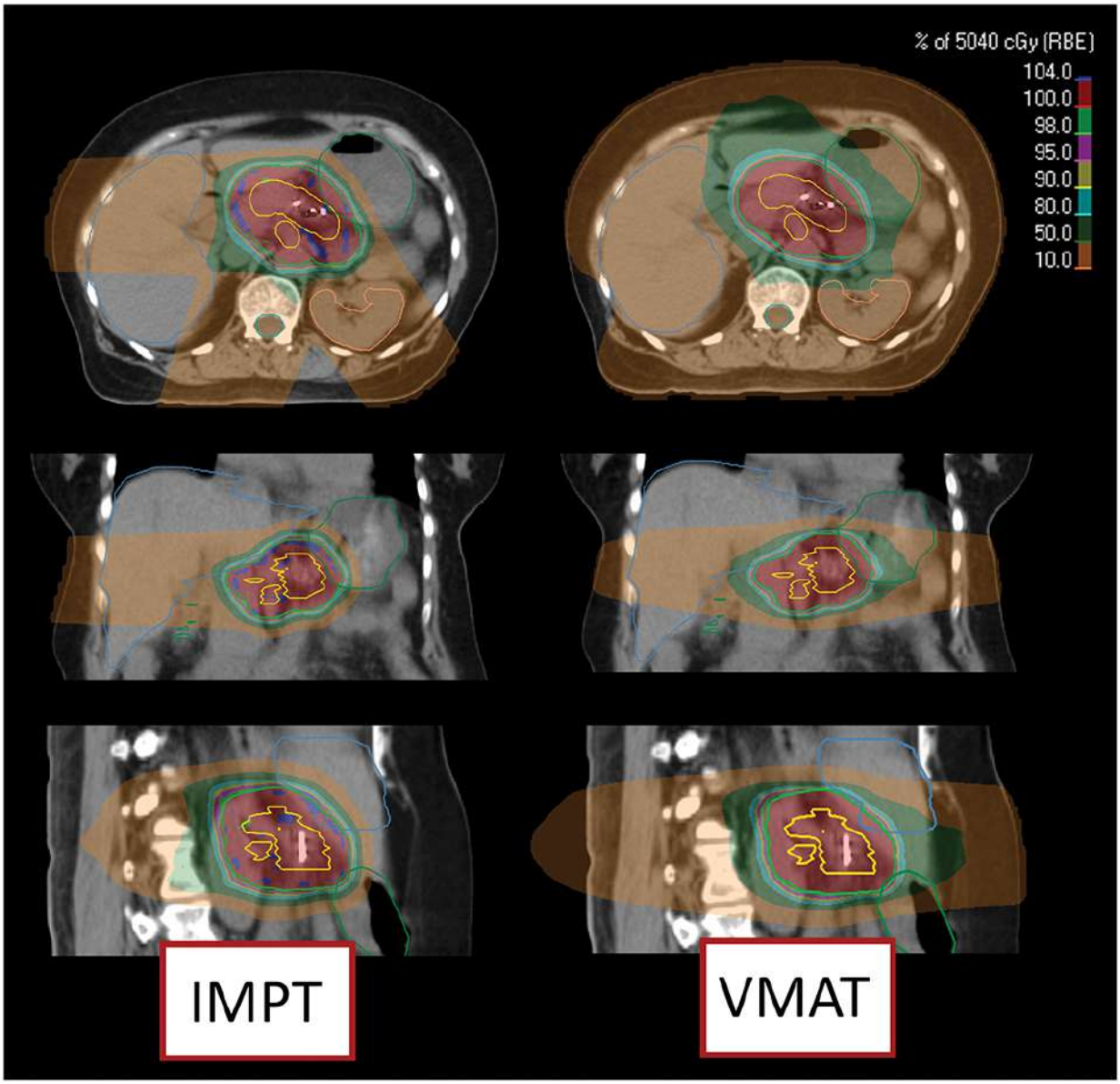


FIGURE 20.10 Axial, coronal, and sagittal planes of intensity-modulated proton therapy (IMPT) (left) and volumetric modulated arc therapy (VMAT) (right) plans for a **pancreatic head carcinoma**. As apparent, there is much less low-to-intermediate dose to the stomach, bowel, and kidney with the IMPT plan. Integral doses with the IMPT and VMAT plans are 35.1 and 61.4 J, respectively. Mean doses with IMPT and VMAT are 6.4 Gy (RBE) and 15.1 Gy to the stomach and 4.3 Gy (RBE) and 9.4 Gy to the overall bowel space, respectively. The left kidney is also relatively spared with the proton plan with the volume of lung receiving at least 20 Gy (V20 Gy) of 0.2% with IMPT and 16.9% with the VMAT plan. The lower doses to stomach and bowel may make combined modality therapy more easily tolerated and allow for dose escalation or intensification to the pancreas. RBE, relative biologic effectiveness.

Several clinical studies have documented the efficacy and safety of PT in treating pancreatic cancer, either as neoadjuvant, adjuvant, or definitive treatment.[199-205] Hong et al reported a phase I/II trial from Massachusetts General Hospital of neoadjuvant short-course PT with capecitabine followed by surgery and adjuvant gemcitabine for pancreatic carcinoma.[202] PT was delivered to the pancreas and draining lymphatics to 25 Gy (RBE) in 5 fractions. Surgery was performed in 37 of the 50 patients, with the findings of positive nodes in 81%, positive margins in 16%, and no pathologic complete responses. The median progression-free and overall survival times in the 37 patients who had surgery were 14.5 and 27 months, with 16% experiencing locoregional recurrence. The rate of grade 3 or higher toxicity was 4.1%. The same institution performed a separate phase I trial of photon-based stereotactic body radiation therapy using the same treatment volumes and dose fractionation regimen, but this

study was terminated early because of intraoperative toxicity.[206] The investigators concluded that preoperative PT was feasible, well tolerated, and did not delay surgical resection. Nichols et al reported on the University of Florida experience with 22 patients treated with concomitant capecitabine and passively scattered PT for resected (n = 5), marginally resectable (n = 5), and inoperable (n = 12) pancreatic and ampullary carcinomas.[203] Doses ranged from 50.4 to 59.4 Gy (RBE). No grade 3 or higher toxicity was observed. Median weight loss was 1.3 kg or 1.75% of the body weight, and 99% of the prescribed chemotherapy doses were given. Two of the 12 patients with inoperable disease achieved excellent radiographic responses, including one pathologically documented complete response. Despite the much higher radiation dose delivered in the University of Florida experience, the University of Florida experience confirmed the low rate of gastrointestinal toxicity with PT observed by Hong et al,[202] suggesting the potential for improvement in efficacy through dose escalation to accomplish complete pathologic responses. Neither proton experience delayed surgery or resulted in increased surgical complications, suggesting an additional potential value of PT in facilitating both surgical resection and chemotherapy intensification. Three excellent reviews of outcomes with particle therapy for pancreatic carcinoma have reported on the challenges of motion management, range uncertainties, and online volumetric imaging with early proton studies but offer promising results with respect to efficacy and toxicity.[207-209] With the availability of cone-beam CT on proton gantries, target location can be monitored easily, making IMPT feasible in most cases and further improving the dose distribution attainable with protons compared to photon-based treatment planning. More clinical data using modern PT planning and delivery and volumetric imaging are needed to determine the potential for PT to improve the therapeutic ratio in pancreatic cancer.

Esophageal Cancers

Many of the issues affecting the therapeutic ratio of radiation therapy in esophageal carcinoma in the esophagus are similar to issues in the lung, pancreas, breast, and oropharynx disease. Figure 20.11 shows comparative VMAT and proton plans. A meta-analysis of 45 studies by Zhou et al also confirmed a significant reduction in doses to OARs, toxicity, and improved prognosis for PT compared with IMRT in esophageal carcinoma.[210] A prospective randomized IIB trial of protons versus IMRT in locally advanced esophageal cancer demonstrated a significantly lower total toxicity burden with protons at a median follow-up of 44 months, meeting the criteria for early closure.[211] This study will be followed by another comparative trial conducted by the NRG-GI006.

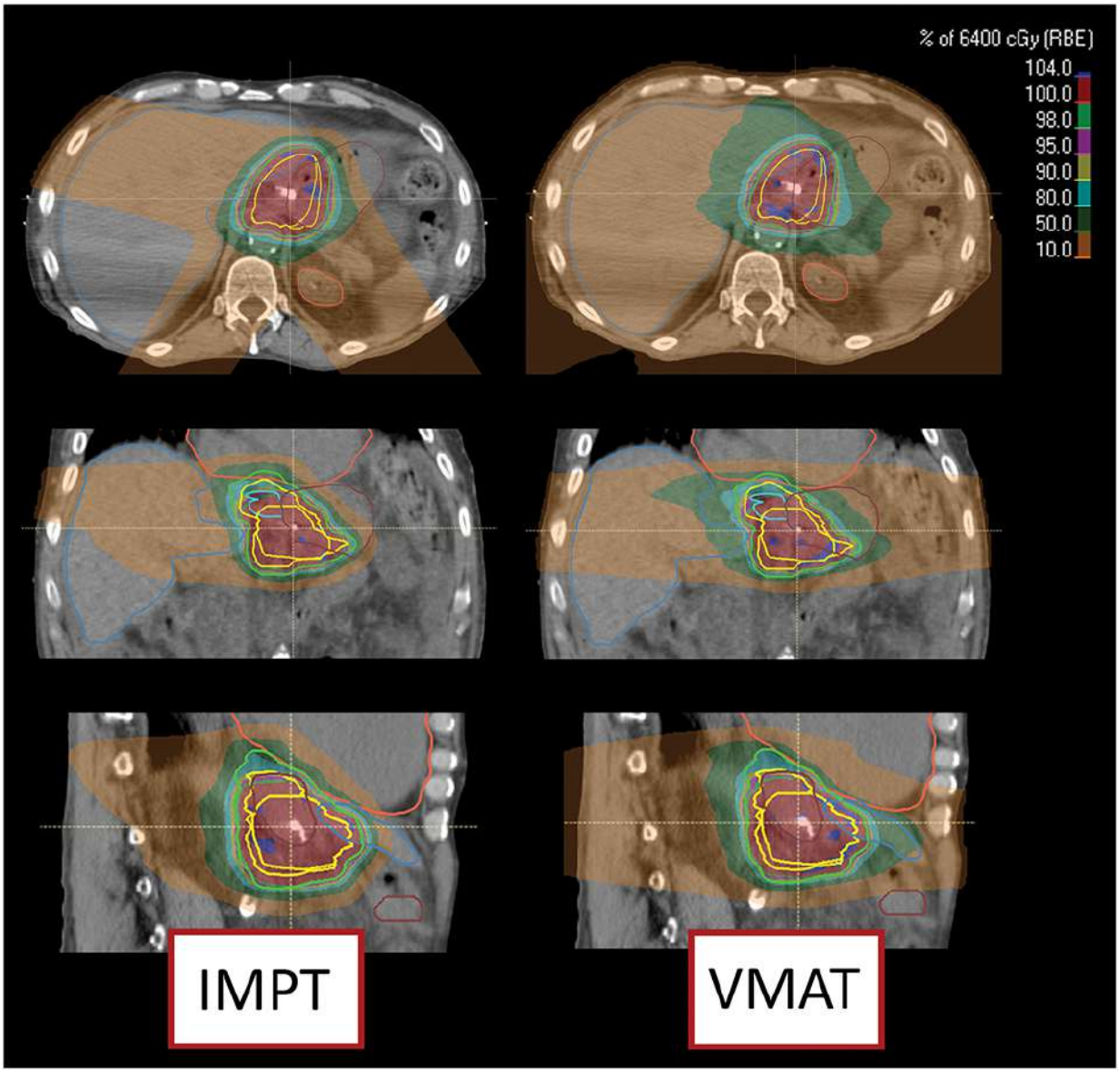


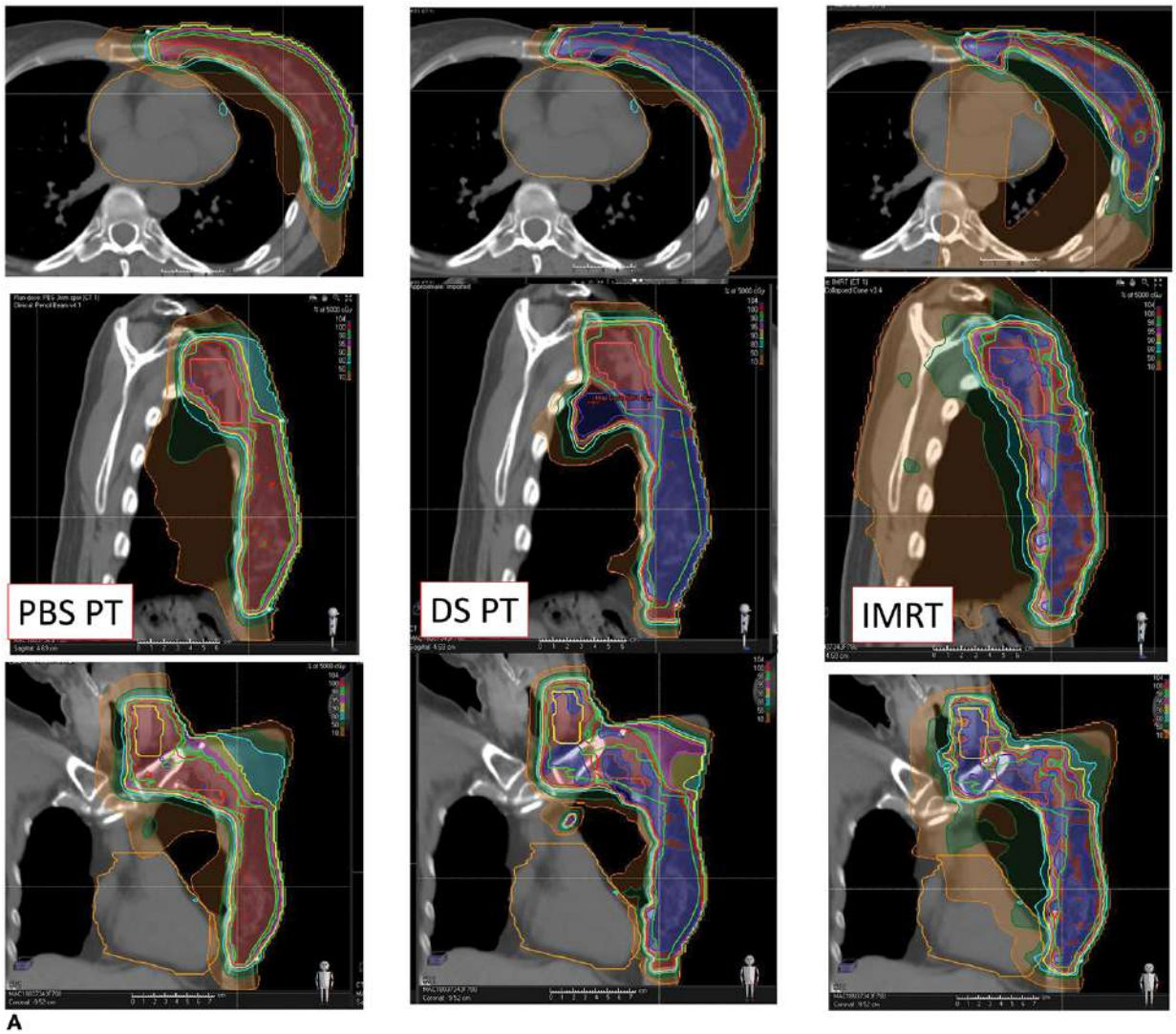
FIGURE 20.11 Axial, coronal, and sagittal planes of intensity-modulated proton therapy (IMPT) (left) and volumetric modulated arch therapy (VMAT) (right) plans for a patient with distal **esophageal carcinoma**. As apparent, there is much less low-to-intermediate dose to the heart, stomach, bowel, and liver with the IMPT plan compared to the VMAT plan. Integral dose was 57 J with the IMPT plan compared to 121.3 J with the VMAT plan. Mean absolute doses with the IMPT and VMAT to the heart were 2.6 Gy (RBE) with 5.7 Gy, to the liver were 8.3 Gy (RBE) and 16.7 Gy, to the kidneys were 6.7 Gy (RBE) and 9.3 Gy, and to the stomach were 25.07 Gy (RBE) and 35.45 Gy, respectively. The volume of nontargeted bowel receiving at least 20 Gy (V20 Gy) with the IMPT and VMAT plans were 7.2% and 49.5%, respectively. RBE, relative biologic effectiveness.

Breast Cancer

In patients with breast cancer, there is level I evidence for treating all regional nodes, including internal mammary nodes and axillary nodes, in patients at risk for residual disease after surgery because of positive axillary nodes, tumor size, and, in some cases, tumor location and grade.[212-220] There is also growing interest in minimizing dose to the heart and lung as increases in late cardiac and pulmonary morbidity and mortality continue to be documented.[212,213,215,221-224] The excess in cardiac disease has primarily been associated with patients with left-sided breast cancer, presumably because a greater volume of the heart is exposed to radiation with left-sided breast cancers compared with right-sided breast cancers.[213,221,222] More recently, evidence suggests that the risk of heart disease may be related to DVH parameters,[223] which has led to the goal of achieving as low as reasonably achievable doses to the heart and lung with dose constraint goals built into the guidelines for modern breast cancer

trials.[225,226] While it is widely accepted that patients with node-positive left-sided breast cancer generally benefit from heart and lung sparing with PT compared to photon-based alternatives, some patients with right-sided breast cancer have challenging anatomy, making target coverage and/or cardiac and lung sparing difficult.

Figure 20.12A shows comparative treatment plans for a patient with breast cancer receiving left-sided breast and regional node irradiation using IMRT, DS PT, and IMPT plans. Coverage of the axillary and supraclavicular nodes is similar among the plans, but coverage of the internal mammary nodes is inferior with IMRT (44 Gy) compared with both the DS PT and IMPT plans (50 Gy [RBE]). Striking differences are apparent among the IMPT, DS PT, and IMRT plans in heart V10 Gy at 3%, 2%, and 23%, respectively; mean heart doses, 1, <1, and 7; mean left anterior descending artery doses, 2, 2, and 14; and left lung V5 Gy, 38%, 27%, and 85%.



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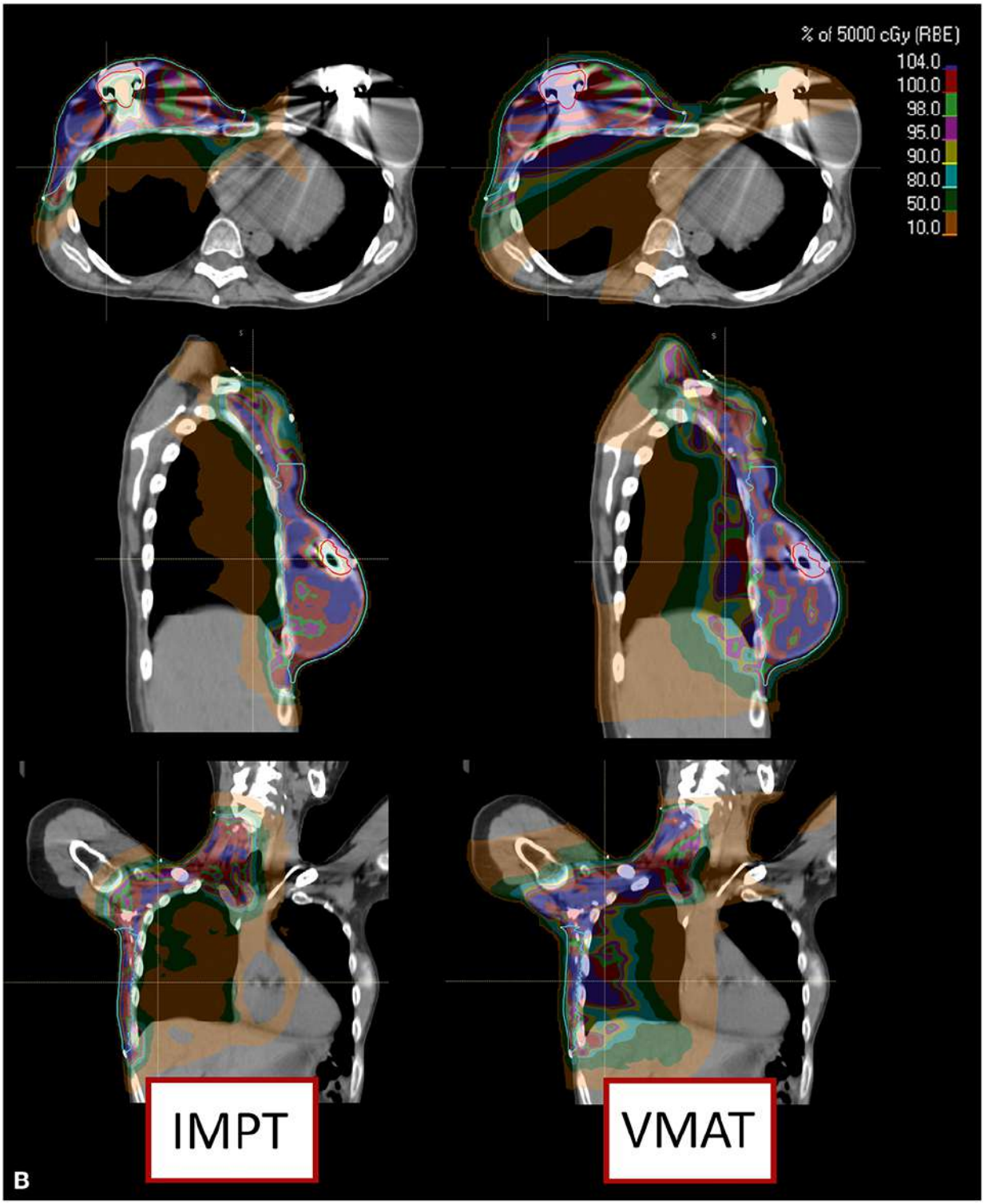


FIGURE 20.12 A. Intensity-modulated proton therapy (IMPT), double-scatter proton therapy (DS PT), and intensity-modulated radiation therapy (IMRT) plans for a woman with a **left-sided node-positive breast cancer**. Targets included the internal mammary nodes; levels I, II, and III axillary nodes; and supraclavicular nodal areas as well as the breast. The prescribed dose is 50 Gy to the breast planning target volume (PTV) and nodal PTV. Coverage of the internal mammary nodes is best with the IMPT plan compared to the DS PT and IMRT plans, with 95% of the internal mammary chain volume receiving 50 Gy (RBE) with both proton plans but only 44 Gy with the IMRT plan. The volume of heart receiving at least 10 Gy (V10 Gy) was 3%, 2%, and 23% with the IMPT, DS PT, and IMRT plans, respectively. Mean left anterior descending artery doses were 2 Gy (RBE), 2 Gy (RBE), and 14 Gy with the IMPT, DS PT, and IMRT plans, respectively. The volume of left lung receiving at least 5 Gy (V5 Gy) was 38%, 27%, and 85% with the IMPT, DS PT, and IMRT plans, respectively. Although

metrics appear similar or even better with DS PT compared with IMPT, skin reactions historically have been worse and daily setup is more difficult and time-consuming, so IMPT is the preferred proton delivery mode for breast cancer. B. It is generally accepted that protons produce more cardiac sparing and better internal mammary node coverage in patients with left-sided node-positive breast cancers, after either mastectomy or breast-conserving therapy. However, there is also a role for protons in some **right-sided breast cancers**. The figure below shows a woman who is postmastectomy for node-positive right-sided breast cancer and has had a reconstruction with temporary tissue expanders. With expanders or implants, the breast mound and attendant chest wall flap at risk for subclinical disease protrude anteriorly, making it difficult to cover with photon beams without exiting into the contralateral breast. The medial location of the internal mammary nodes may also be impossible to cover with photons without excessive exposure of the heart. In the case shown here, it was impossible to cover the right chest wall and regional nodal target without excess exposure of the ipsilateral lung, contralateral left breast, and heart. The volume of right lung receiving at least 20 Gy (V20 Gy) was 28.4% with IMPT and 46.2% with the IMRT plan. The mean absolute heart doses with IMPT and IMRT were 3 Gy (RBE) and 4.8 Gy, respectively. Integral doses with the IMPT plan and IMRT plans were 79.2 and 161 J, respectively. RBE, relative biologic effectiveness.

Figure 20.12B shows comparative plans for a 48-year-old female with node-positive right-sided lobular carcinoma s/p mastectomy with expander placement. The initial simulation revealed that an expander with a double port was used; the double port created substantial dose shadowing with proton planning and also created uncertainties with photon planning. The expander was replaced, but her anatomy made coverage of the internal mammary nodes and cardiac sparing impossible with a photon-based plan. The DVH comparison showed reduced doses to the lung and heart with IMPT compared to IMRT.

MacDonald et al from the Massachusetts General Hospital reported the acute toxicity and feasibility of PT in a prospective trial of 12 postmastectomy patients[227]; at a median follow-up of 6 months, there were no cases of pneumonitis, and maximum skin toxicity was grade 2. Bradley et al from the University of Florida reported a pilot study of PT for right- and left-sided cancers (stages IIA to IIIB) after either breast-conserving therapy or mastectomy.[228] The study included a treatment plan comparison of PT DS and conventional radiation plans, with the best treatment plan recommended to the patient. The proton plans were consistently better for coverage of the internal mammary nodes ($P = .0005$), minimization of cardiac V5 ($P < .0001$), and minimization of ipsilateral lung V5 and V20 ($P < .0001$). The only grade 3 toxicity was radiation dermatitis, observed in 22% of patients. An ongoing prospective randomized trial comparing IMRT and PT in patients who need internal mammary node irradiation should help define which groups of patients benefit most from PT in the future. Jimenez et al reported on a trial in patients with breast cancer requiring regional node irradiation, also showing excellent early disease control with minimal toxicity.[229]

There may be other indications in breast cancer where protons can be very useful when limiting the dose to OARs is important, such as bilateral breast cancer,[230] reirradiation for breast or chest wall recurrence or angiosarcoma,[231-233] radiation in patients with genetic mutations placing them at risk for radiation injury, men with challenging anatomy,[234] and women with reconstruction after mastectomy[235] and partial breast irradiation.[236] Much work is ongoing to determine the best treatment planning and delivery techniques to optimize PT results,[236] especially concerning rib fractures and skin reactions.[237-240] Mutter et al, on behalf of the PTCOG, published an excellent consensus analysis on the state of PT in breast cancer.[238] Holt et al published a systematic review and meta-analysis of clinical outcomes with PT in early breast cancer, concluding that while early results are promising, more clinical follow-up and randomized trials will be necessary.[241] An ongoing randomized trial comparing the outcomes of proton and IMRT patients who required internal mammary node irradiation will shed light on the ultimate clinical benefit of PT in breast cancer.[242]

Prostate Cancer

The ProtecT trial has underscored the importance of early definitive treatment for prostate cancer in men with a ≥10-year life expectancy to maximize freedom from distant metastases and documented increased toxicity with surgery compared to radiation therapy without an attendant increase in disease control rates.[243-245] Prostate cancer results with radiation therapy are generally excellent, and dose escalation trials indicate that increasing the dose to the prostate is associated with improved disease control rates.[246-249] However, dose escalation photon-based trials from the RTOG also show that increasing dose, dose per fraction, and the volume of the rectum exposed to a high radiation dose are associated with an increased risk of rectal toxicity.[250] Analysis of outcome data with PT indicates a similar correlation between the increasing volume of the rectal wall receiving high doses and the risk of gastrointestinal toxicity.[251] Hypofractionation of the treatment regimen is of great interest in prostate cancer, and while studies have demonstrated similar outcomes,[252,253] they also have sometimes reported more toxicity with hypofractionation,[254] so that attention given to the radiation exposure of OARs is critically important.[255] Most physician-reported gastrointestinal toxicity has been temporary rectal bleeding or ulceration.[251] However, rectal

urgency, frequency, and incontinence have been identified as problems that may occur later, persist, and significantly impact long-term patient-reported quality of life.[256-258] This symptom complex has been found to be related to reduced rectal elasticity and sphincter tone,[257,259] and these symptoms have been associated with the volumes of anus and rectum receiving 5 to 40 Gy.[247,255,260] Comparative IMRT and proton dosimetry studies have shown that with historical techniques for prostate stabilization, the volumes of the rectum and rectal wall receiving high radiation doses associated with rectal bleeding and ulceration are similar.[261,262] However, the volume of the rectum and rectal wall receiving low-to-moderate doses is significantly less with PT compared to IMRT. It is likely that strategies that create distance between the anterior rectal wall and posterior prostate have reduced the risk of rectal bleeding and/or ulceration in eligible patients receiving either photon- or proton-based radiation.[263,264] Thus, the main late gastrointestinal issue is rectal urgency and frequency. At this point, bladder and urethral toxicities with photon- and proton-based external beam radiation have not clearly been associated with dose-volume parameters; however, this may change with dose escalation or hypofractionation of treatment.

The most controversial indication for PT at this time is prostate cancer. The first experience came from Loma Linda University.[265] It is estimated that more than 30,000 men with prostate cancer have been treated with PT or a combination of PT and photon therapy with excellent results with both standard and moderately hypofractionated regimens. A consensus paper from the genitourinary subcommittee of the PTCOG has described the state of PT for prostate cancer.[266] Table 20.1 shows results from selected IMRT and PT experiences with long-term follow-up.[267-275] The longest follow-up for patients with prostate cancer treated with radiation therapy is in an IMRT experience from Memorial Sloan Kettering[275]; in this study of high dose (>80 Gy), the investigators report relapse-free survival rates of 76%, 65%, and 55% at 15 years for men with low-, intermediate-, and high-risk prostate cancers with rates of grade ≥3 genitourinary and gastrointestinal toxicity of 1% and 2%, respectively, and a secondary malignancy rates of 12.3%. Of note, the 5- and 10-year results from multiple PT experiences across two continents are strikingly consistent in disease control and toxicity rates. These disease control and toxicity rates with protons compare favorably with contemporaneous external beam photon experiences, but second malignancy rates have not been reported. A comparison of prospectively collected patient-reported quality of life data from cohorts of men treated with IMRT and PT has shown similar overall functional summary scores but significant differences in selected questions regarding bowel frequency and urgency that potentially reflect radiation injuries associated with the volume of the rectum receiving low-to-moderate doses, perhaps providing the first evidence of anticipated differences in functional outcomes related to PT and photon therapy reported directly by patients.[276] Importantly, a retrospective query of the NCDB by Xiang et al demonstrated a 3-fold increase in secondary malignancy in patients treated with photon-based therapy compared with PT[23]; within this study, the difference in secondary malignancy apparent at a median of 5 years in men with prostate cancer was 5-fold, making secondary malignancy risk a highly relevant concern. Two prospectively controlled clinical trials comparing outcomes between IMRT and protons for localized prostate cancer have completed enrollment. The first is a randomized comparison of IMRT and protons in 400 men with an end point of 2-year bowel summary score.[277] The second is a comparison of outcomes between prospective cohorts of 2,524 men treated with either IMRT or PT with the simultaneous end points of bowel frequency and urgency, rectal toxicity, and freedom from biochemical progression.[278] Early results from both trials should be available within the next few years, but assessment of important late outcomes such as disease control, long-term bowel function, and risk of secondary malignancy will require additional observational time.

TABLE 20.1 RECENT EXPERIENCES WITH IMRT AND PROTON THERAPY IN PROSTATE CANCER

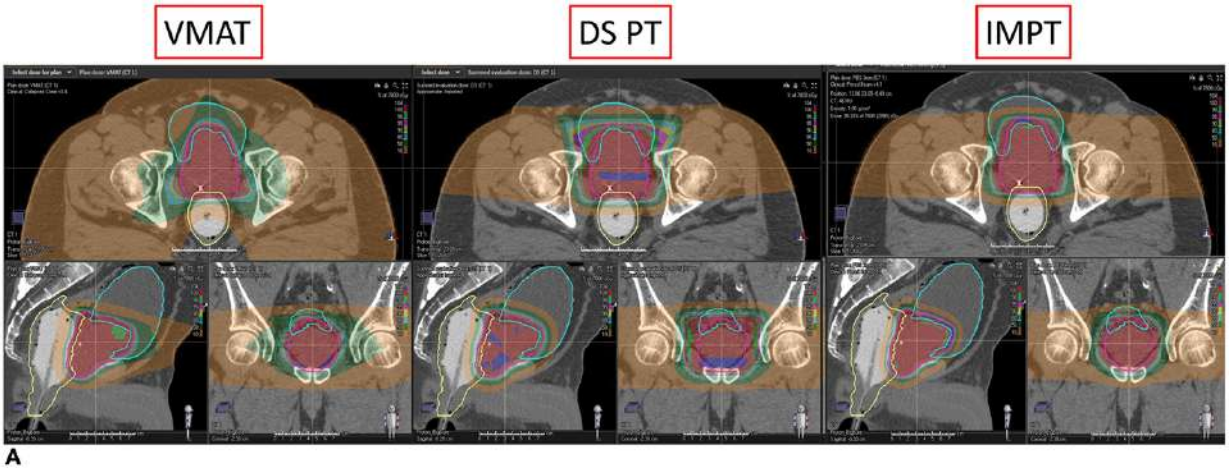
Study	Spratt, 2013[272]	Weg, 2019[275]	Vora, 2013[274]	Schild, 2017[269]	Bryant, 2016[268]	Takagi, 2021[273]	Sosa, 2023[271]	Abu-Gheida, 2019[267]	Lee, 2016[252]	Catton, 2017[253]	Henderson, 2022[279]	Slat 2019
Location	MSKCC	MSKCC	Mayo	Mayo	Florida FL	Hyogo	MDACC	Cleveland Clinic	RTOG	Multi-institutional	Univ Florida	LLUI
Therapy	IMRT	IMRT	IMRT	IMRT/SIB	PSPT	PSPT	PSPT	IMRT	IMRT	IMRT	PSPT	PT
Dose Gy/Gy (RBE)	86	81-86	75.6	82	78	74	78	70	70	60	70-72.5	60
Dose/fraction (Gy)	1.8	1.8	1.8	1.95	2	2	1.8-2.0	2.5	2.5	3.0	2.5	3
Patients (*n*)	1,002	301	302	71	1,327	2,021	2,772	854	550	608	582	146

Study	Spratt, 2013[272]	Weg, 2019[275]	Vora, 2013[274]	Schild, 2017[269]	Bryant, 2016[268]	Takagi, 2021[273]	Sosa, 2023[271]	Abu-Gheida, 2019[267]	Lee, 2016[252]	Catton, 2017[253]	Henderson, 2022[279]	Slat 2019
Median F/U (years)	5.5		7.5	10	5.5	7	7	11	6	6	8	3.5
% FFBP												
VLR	98 (7 y)	76 (15 y)[a]	77 (9 y)	84 (10 y)	99 (5 y)	100 (10 y)	–	–	–			
LR						88 (10 y)	97 (10 y)	88 (10 y)	94 (5 y)	–	98.8 (7 y)	99 (3
FIR	85 (7 y)	65 (15 y)[a]	69 (9 y)	84 (10 y)	94 (5 y)	86 (10 y)	94 (10 y)	78 (10 y)	–	85 (5 y)	95.2 (7 y)	–
UIR						79(10 y)	90 (10 y)	71 (10 y)	–		88.8 (7 y)	–
HR	68 (7 y)	55 (15)[a]	53 (9 y)	90 (10 y)	74 (5 y)	68 (10 y)	85 (10 y)	42 (10 y)	–	–	–	–
VHR						63 (10)	69 (10 y)	–	–	–		–
Grade ≥3 toxicity												
GU	2.2%	2%	XX	XX	2.9%	XX	XX	2%	3.3%	2.1%	2.1%	0.7%
GI	0.7%	1%	XX	XX	0.6%	XX	XX	1%	0.6%	XX	1.4%	0

FFBP, freedom from biochemical progression; FIR, favorable intermediate risk; F/U, follow-up; GI, gastrointestinal; GU, genitourinary; HR, high risk; IMRT, intensity-modulated radiation therapy; LLUMC, Loma Linda University Medical Center; LR, low risk; MDACC, MD Anderson Cancer Center; MSKCC, Memorial Sloan Kettering Cancer Center; PSPT, passive scattering proton therapy; RBE, relative biologic effectiveness; RTOG, Radiation Therapy Oncology Group; SIB, simultaneously integrated boost; UIR, unfavorable intermediate risk; VHR, very high risk; VLR, very low risk.

[a]Relapse-free survival rather than FFBP.

Figure 20.13A shows VMAT, DS PT, and IMPT plans for a patient with low-risk prostate cancer who has a large median lobe. As apparent, the rectal volumes receiving 25 and 45 Gy are generally lower with both proton plans than with the VMAT plan and lowest with the IMPT plan. Treatment planning is rapidly evolving for both VMAT and IMPT, and the relative value of high-dose conformality versus minimization of the integral dose in prostate cancer will require further investigation.



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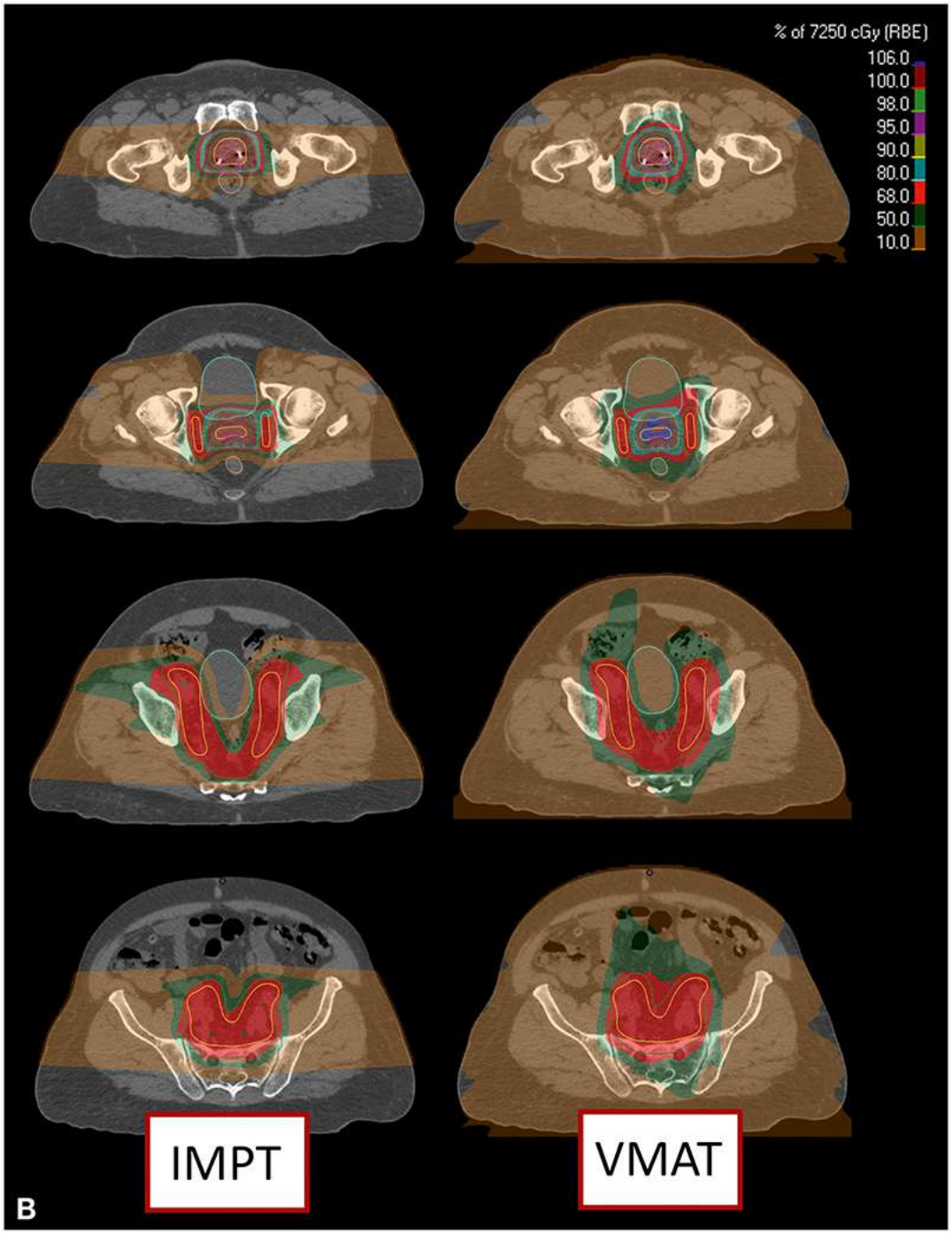

FIGURE 20.13 A. Axial, sagittal, and coronal planes of treatment plans with volumetric modulated arc therapy (VMAT), double-scatter proton therapy (DS PT), and intensity-modulated proton therapy (IMPT) for a patient with **prostate cancer** with a very large median lobe, which protruded into the bladder, making it difficult to meet dose constraints to the bladder wall. The target volume is shown in the heavy magenta line, the bladder is outlined in aqua, and the rectum is in yellow. A rectal balloon was used to stabilize the prostate and reduce the dose to the posterior portion of the rectum. As apparent, the VMAT plan delivered a low dose to a larger volume of nontargeted pelvic tissue, including the rectum. The target coverage goals were to deliver 100% of the prescribed dose to 95% of the planning target volume (PTV) and to deliver 95% of the prescribed dose to 100% of the PTV. As apparent, all plans met both target coverage goals with a high degree of dose homogeneity. The protection goals for the bladder wall, volume receiving at least 30 Gy less than 35 mL (V30 Gy <35 mL) and 80 Gy less than 8 mL (V80 Gy <8 mL), could not be met with the VMAT plan; the DS PT plan met the goal for the volume of bladder receiving 80 Gy, but not the volume receiving 30 Gy. The IMPT plan met all bladder protection goals. All plans met the relative rectal wall dose goals, but not the rectum absolute dose goals, though the IMPT plan came the closest to fulfilling this objective. A gel spacer may have helped in this case to meet the rectum dose constraint. B. Comparative plans for prostate, proximal seminal vesicle, and **pelvic node treatment in prostate cancer** using IMPT and photon-based VMAT treatment planning with a rectal spacer. Both plans achieved excellent

target coverage. The rectal spacer allowed both plans to minimize exposure of the anterior rectal wall to high doses (>59 Gy). The major difference is the substantial low- to moderate-dose bath covering the rectum and pelvic soft tissues in VMAT plans compared with the IMPT plan. With the IMPT and VMAT plans, the relative volumes of rectum exposed to 40 Gy (RBE) were 11.1% and 33.5%, to 30 Gy (RBE) were 18.3% and 59%, and to 20 Gy (RBE) were 28.7% and 68.5%, respectively. The volume of bowel space receiving 45 Gy (RBE) was 331.8 mL with the IMPT plan and 502.4 mL with the VMAT plan. Bladder exposure was similar between the two plans, but integral doses were 237.3 J for the IMPT plan and 442 J for the VMAT plan. RBE, relative biologic effectiveness.

Figure 20.13B shows VMAT and IMPT plans for a patient requiring prostate, proximal seminal vesicle, and elective pelvic node irradiation. The DVH comparison demonstrates substantial improvement in low-dose exposure to the rectum and bowel space with the VMAT plan. For example, the relative volume of rectum exposed to 25 Gy was 63.4% with the VMAT plan and 23.1% with the IMPT plan; the absolute volume of bowel space receiving 45 Gy was 502.4 cm^3 with the VMAT plan and 331.8 cm^3 with the IMPT plan. The overall integral dose with the VMAT and IMPT plans were 442 and 237.3 J, respectively.

COMPARATIVE EFFECTIVENESS OF PROTON AND PHOTON THERAPY

In medical interventions, level I evidence of comparative effectiveness is desirable but frequently difficult to generate: Fewer than 5% of adults currently participate in clinical trials in the United States. Among the reasons cited for low clinical trial participation are restrictive eligibility criteria, insurance coverage, distrust of physicians or the medical system, patient preference for either the “tried and true” or the “new” approach, physician equipoise, and institutional disincentives. In radiation therapy, randomized trials were not conducted to compare orthovoltage and cobalt, cobalt and x-rays, or 3DCRT with either SRT or IMRT before the general adoption of each of these technologies; each technology was adopted based on improved radiation dose distribution and the expectation of consequent improved clinical outcomes. However, many entities have called for comparative effectiveness evidence before adopting PT.

With respect to the design of comparative effectiveness studies in PT, the basic difference between protons and photons is the difference in beam entrance dose and exit dose that leads to significant differences in integral dose to nontargeted tissues. The essence of a randomized clinical trial of PT and photon-based therapy thus would be to test whether changes in integral dose result in clinical outcomes that can be measured, that is, toxicity or functional loss from injury to nontargeted tissue. Altruism, therefore, would be the primary motivation for patient participation if the informed consent process allowed for autonomy. It is unclear how willing patients would be to participate in such trials. Although there has been a significant increase in proton facilities in the United States and worldwide over recent years (Figure 20.14), only 44 operational proton facilities and no carbon ion facilities exist in the United States,[280] and particle therapy accounts for only 1% to 2% of radiation treatments delivered in the United States. Of note, the growth in the number of proton facilities in the United States mirrors the global growth. Unsurprisingly, no particle therapy facilities are located in nations deemed low- and middle-income countries by Research4Life due to being under-resourced.[281] Given the relatively few sites currently providing PT, some practical issues affecting comparative effectiveness research in protons also exist. For example, some patients would not be able to travel to receive PT, and others who might travel to receive PT might withdraw from a randomized study if assigned to receive conventional radiation therapy, which could be delivered more conveniently in their hometown. Insurance coverage with PT has continued to be unpredictable in patients without traditional Medicare coverage[282-284] and is often not verified in a time frame that would permit study participation. Finally, the number of patients and resources required for randomized controlled trials raise concerns regarding the best use of currently available PT treatment and research slots. Some investigators believe that more questions could be answered in the same time frame as a randomized controlled trial with a series of well-designed sequential studies to optimize PT through dose escalation and hypofractionation or comparative effectiveness cohort studies. As much is rapidly developing in treatment planning and delivery of PT, there are substantial risks to premature comparative trials, particularly in a multi-institutional design, because of the learning curve necessary to produce and deliver optimal PT.[285]

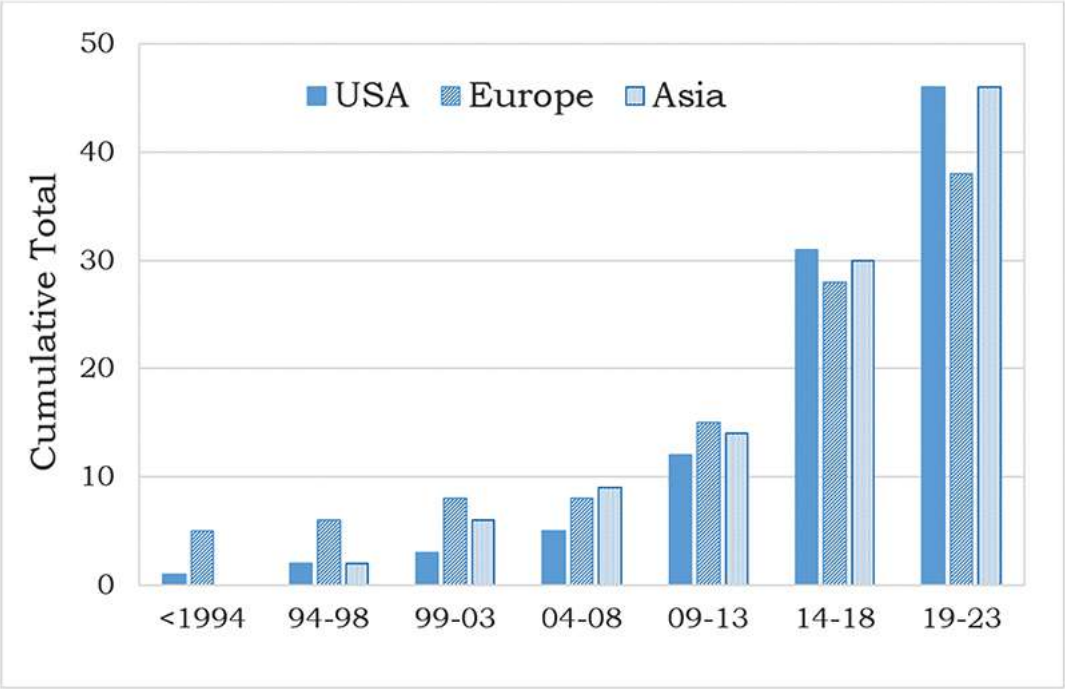

FIGURE 20.14 This graph depicts the cumulative number of particle therapy facilities over time in the United States, Europe, and Asia. All facilities before 1990 had "fixed" beams; Loma Linda University in California, which opened in 1990, was the first facility to have a rotational gantry. Of note, at the end of 2023, there were 130 operational particle therapy facilities across the world, including 14 carbon and 116 proton facilities. Whereas there was a similar slope for the growth in number of particle facilities in the United States, Europe, and Asia, there were no carbon facilities in the United States at the end of 2023. (In this graph, the Middle East is included in Asia and Russia and the Scandinavian countries are included in Europe.)

Despite these challenges, there are a few completed or ongoing randomized trials comparing photon- and proton-based therapy in lung cancer,[285-287] prostate cancer,[277] oropharyngeal carcinoma,[288] glioblastoma,[289] and breast cancer,[290] as well as trials comparing proton- and carbon-based therapy in skull base sarcomas,[102] glioblastoma,[291] and prostate cancer.[13,14]

In pediatric cancer survivors, increased risks of second malignancies and cardiovascular disease have been associated with radiation doses as low as 4 to 15 Gy.[292] In addition, elegant dose modeling studies at St Jude Children's Research Hospital have suggested no threshold dose for radiation injury in the childhood brain.[157] Thousands of children and many years of follow-up would be required to assess the results of a hypothetical controlled trial of PT and conventional radiation to determine whether the reduction in low-dose exposure to the brain and total body with PT would indeed result in a lower incidence of second malignancies or late cardiac injury. In the process, many children would intentionally be exposed to low-dose radiation in nontargeted tissues in the brain, likely resulting in permanent decreased neurocognitive function. Therefore, comparative trials will likely not be done in pediatric patients. Similar arguments may follow for Hodgkin lymphoma, another uncommon malignancy that affects relatively young patients with a high cure rate, long life expectancy, and substantial risks for second malignancy and late cardiac injury.

Comparative Cost-Effectiveness

Many factors must be accounted for in comparing the costliness and cost-effectiveness of different radiation technologies. These include facility and equipment costs, operating and maintenance costs, patient throughput, clinical outcomes, and the global and individual impact of those clinical outcomes.

Current PT equipment and facilities are up to 10-fold more expensive to construct than conventional radiation therapy facilities capable of treating a similar patient volume. In addition, operating costs are higher by 1- to 3-fold but vary significantly between countries[293] and even regions within the United States. Carbon facilities are 4-fold the cost of proton facilities with 2- to 3-fold the operational costs. Substantial differences exist between patient throughput in conventional radiation and proton facilities; however, that may offset differences in initial and

operating costs. Typically, conventional radiation equipment is used for a single daily work shift and is replaced every 7 to 10 years. Most PT facilities, however, operate two shifts a day, and equipment is expected to last 20 years or more. The Harvard Cyclotron was in use for over 40 years and closed primarily because of the availability of a new gantry-based clinical facility. The Loma Linda University synchrotron and most of its gantries have continuously operated for over 33 years. PT equipment appears to be substantially more durable than linear accelerators. Thus, the actual patient throughput (*for a given patient mix*) in a proton facility may be substantially higher than typical for a conventional radiation therapy facility, perhaps double the patients per day (because of double shifts) for 2 to 6 times as many years of operation, leading to a 4- to 12-fold increased throughput with proton facilities compared to photon facilities. PT throughput may be further enhanced if hypofractionation is more feasible with PT than with x-rays. Although the initial cost of the facilities and equipment is a known factor, ultimate throughput and clinical outcomes evolve over time so that the true cost-effectiveness of PT relative to conventional radiation will not be known until there are long-term facility performance and clinical outcome data. Different societies may interpret these data differently based on cultural values and prioritization of long-term cost-effectiveness for society or rapid return on investment for investors.

The impact of a particular clinical outcome may affect stakeholders differently. For example, if no intervention (cost) is associated with a radiation injury affecting a patient's quality of life, that particular clinical outcome may be valued differently by a patient and their insurer. Currently, there is no objective way to resolve such valuation differences. Meaningful cost-effectiveness analyses must account for a number of variables that are ill-defined and difficult to reduce to financial units. Regardless of the outcomes of cost and cost- effectiveness analyses, a shift to PT as a predominant radiation modality will likely require a paradigm shift in philosophy about both profit and daily operations.

CHALLENGES

The multiple challenges facing PT are complex and interrelated.

The first involves **technical developments** necessary to realize the full clinical outcome potential of PT, including the following:

- Improved treatment planning systems that better account for proton-stopping power and biologic effects of variations in LET and RBE along the beam path
- Online volumetric imaging and real-time range verification to ensure accuracy
- Real-time treatment plan adaptation to changes in tumor and/or normal tissue
- Increased delivery speed to minimize motion mitigation and improve operational workflow

The second challenge is generating reasonable evidence for the improved clinical outcomes anticipated with improved dose distributions. The development of reasonable evidence requires a critical mass of treatment facilities, a sufficient number of patients, sufficient technology maturation to reflect the modality's potential for outcome improvements, sufficient physician expertise to employ optimal techniques, and clinical trials that are scientifically credible, appealing to patients, nondisruptive to general clinical operations, and supported by funding agencies. The larger the anticipated clinical difference between treatment arms, the less likely a physician would have equipoise and a patient would consent to randomization, making accrual to a randomized study difficult. With smaller anticipated differences, accrual might be feasible, but larger numbers of patients would be required to assess the difference. A full assessment of clinical outcomes typically involves long follow-ups to document differences in late effects as well as early outcomes. Thus, comparative studies of PT and photon therapy will likely require large numbers of patients, possibly nonrandomized study designs, and long-term follow-up, making the funding of such studies challenging.

The third challenge is the development of **less expensive equipment** to lower the cost of participation in PT by patients, providers, hospitals, and payers. Despite the paucity of comparative effectiveness data for PT, the compelling dosimetric rationale drives increased capacity, although not as rapidly as commonly perceived. Although PT facilities have been described as increasing in number exponentially, studies by Miller et al and Waddle et al have shown minimal diffusion.[294,295] The primary barrier to more rapid diffusion has been the cost of facilities. Vendors' current solutions to lowering the cost of PT have converged on developing one-room facilities. Instead of installing a single large cyclotron or synchrotron that provides a proton beam for three to five treatment rooms, a smaller cyclotron could service only a single room, permitting access to the technology for 30% to 40%

of the cost of a full facility but with a commensurate reduction in capacity. True cost reduction will likely require significant technology development, which may only be driven by a significant increase in market demands.

Finally, the fourth challenge to progress in PT is attaining a **critical mass of facilities**. In 2005, just three proton facilities treated nonocular tumors in the United States. In 2015, just a decade later, there were 5 times as many facilities in operation in the United States, treating approximately 5,000 patients annually.[296] In 2017, there were only 26 centers in operation in the United States, and by 2024, this jumped to 47 proton facilities.[280] However, despite the 10-fold increase in proton facilities in the United States over the past 17 years, this pales compared to the over 4,000 conventional radiation facilities in operation. A critical mass of facilities, physicians, and physicists is necessary to collaborate with industry on technological developments, conduct sound clinical research, and drive significant market-driven cost reduction developments.

EMERGING TECHNOLOGIES IN PARTICLE THERAPY

Several new and emerging technologies are expected within the next several years. At the very top of this list is ultrahigh dose rate radiotherapy, known colloquially as FLASH. Preclinical studies have shown that radiation delivered in this manner, at dose rates higher than 40 to 100 Gy/s, can significantly improve the therapeutic ratio compared to radiation delivered at conventional dose rates of several Gray per minute.[297] The mechanism of the FLASH response is not entirely understood but is thought to be related to the instantaneous depletion of oxygen along the beam path, which leads to transient radioresistance in normal tissues. While early studies used modified electron beams and preclinical x-ray irradiators, commercial PT systems have garnered significant interest as the likely best option for near-term clinical implementation. “Shoot-through” FLASH, which utilizes the entrance region of the proton depth-dose curve, has already been used in the first known patient trial of FLASH radiotherapy. The FAST-01 study at the University of Cincinnati Cancer Center recently reported favorable outcomes in eight patients treated for bone metastases in the extremities, and a follow-up study, FAST-02, is currently enrolling up to 10 patients with bone metastases in the thorax.[298]

The shoot-through technique avoids beam losses in the degrader and beam transport system by utilizing the maximum energy produced by the cyclotron. In this way, it efficiently achieves FLASH dose rates without the need for significant modification of the PT system. The downside, of course, is the loss of the Bragg peak and its ability to limit dose beyond the target. Conformal FLASH is another technique currently under investigation that uses patient-specific ridge filters and range shifters to modulate the beam’s energy while also distally conforming it to the target. Ideally, conformal FLASH will further enhance the therapeutic ratio by combining the benefits of both conventional PT and the FLASH effect. While quite promising, considerable work is needed prior to the realization of this technique involving various aspects of dosimetry, beam monitoring and system design, quality assurance, and radiobiology.

Aside from FLASH, the other technological leap expected in the near future is proton arc therapy (PAT), a PBS technique that allows for the automated delivery of multiple proton beams either as a discrete set of gantry angles or in a dynamic, sweeping motion. Compared to IMPT, PAT is expected to improve dose conformity, delivery efficiency, and robustness and provide a more favorable LET distribution.[299-301] PAT is currently under development by multiple vendors and clinical programs working to establish the technology, treatment planning algorithms, quality assurance tools and methods, and the clinical implications of the technique.[302-304] A unique challenge to dynamic PAT is distributing the energy layers that must be delivered within specified windows and optimized to limit upward jumps that increase energy but take several seconds to complete. One proposed method is to assign spots to a single energy layer within a discretized segment of the larger arc. The weighting of the spots is then optimized along with energy layer sequencing that sorts energy layers from high to low along the arc’s path.[305] Tradeoffs exist between the number of spots, energy layers, arcs, and upward energy jumps, as well as parameters such as optimization time, plan quality, and delivery efficiency. While these tradeoffs and other similar questions posed by PAT are still being investigated, proponents of the method are rapidly establishing the framework for clinical implementation. Early adoption of PAT is forthcoming, with the potential for widespread clinical use once the benefits and limitations have clearly been defined.

CONCLUSIONS

Particle therapy offers the promise of reduced toxicity to patients compared with photon therapy—by reducing the radiation dose to nontargeted tissues—and possibly enhanced disease control through differential tumor effects and normal tissue biologic responses. Reduced toxicity may be leveraged to increase disease control through dose

escalation or intensification (hypofractionation). Hypofractionation may result in lower health care costs as well as increased disease control and reduced toxicity. Additional clinical research and technical development are needed to optimize treatment planning and delivery of particle therapy, to document and maximize its potential clinical benefits, and to understand its full impact on health care economics.

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CHAPTER 21

Physics and Radiobiology of Brachytherapy

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Brachytherapy (BT) (*brachy* means short in Greek) consists of placing sealed radioactive sources very close to or within the target tissue. Because the absorbed dose falls off rapidly with increasing distance from the sources, high doses may be delivered safely to a localized target region over a short time. This chapter reviews the properties and applications of commonly used sealed radionuclides and sources, methods of source strength specification and dose calculation, principles of implant design and dose specification for interstitial and intracavitary BT, and the basic radiobiologic principles governing clinical response to BT.

BASIC TERMINOLOGY

BT source implantation techniques may be classified in terms of the geometric approach to irradiating the target volume (interstitial, intracavitary, transluminal, or surface applications); the means of controlling source delivery (temporary or permanent implants); the source loading technology (preloaded, manually afterloaded, or remotely afterloaded); and the dose rate (low, medium, or high).

Interstitial BT consists of surgically implanting small radioactive sources directly into the target tissues either temporarily or permanently. A *permanent* interstitial implant remains in place indefinitely and is not removed; the initial source strength is chosen so that the prescribed dose is fully delivered only when the implanted radioactivity has decayed to a negligible level. Low-energy photon-emitting sources are typically used.

Intracavitary BT consists of positioning applicators (bearing the radioactive sources) into a body cavity in proximity to or within the target tissue. Intracavitary BT is used most widely for the treatment of localized gynecologic malignancies and postoperative treatment in early-stage conservatively managed breast cancer. Intracavitary implants are mostly *temporary implants;* they are left in the patient for a specified time to deliver the prescribed dose. Some intracavitary implants place radioactive sources, such as GammaTiles, permanently into the surgical cavity. With a few exceptions for temporary implants, the patient must be confined to a controlled, if not shielded, area in the hospital to manage the radiation safety hazard posed by the large ambient exposure rates around implants using high-energy photon-emitting radionuclides.

Transluminal BT consists of inserting a single-line source into a body lumen to treat its surface and adjacent tissues. This is done most commonly for endobronchial, esophageal, biliary, and coronary artery treatments.

Surface BT (sometimes called plesiotherapy or mold therapy) uses an applicator permitting an array of radioactive sources or dwell positions, usually designed to deliver a

uniform dose distribution, that is placed on the skin or mucosal surface immediately adjacent to the target tissue.

Until the early 1960s, radioactive sources (needles or seeds for interstitial therapy or preloaded applicators for intracavitary therapy) were implanted directly into the patient. Radiation exposure to the radiation oncologist and operating room staff was reduced significantly with the advent of *afterloading* technology.[1,2] *Manual afterloading* consists of implanting nonradioactive tubes or intracavitary applicators into the patient. Following the transport of the patient to a dedicated room in the hospital, sources are manipulated into the applicators by means of forceps and other handheld tools. Exposure to staff responsible for source loading and the care of BT patients can be greatly reduced or eliminated by the use of a *remote afterloading system*, which consists of a motor-driven source transport system for robotically positioning radioactive material within the patient (see Chapters 23 and 24).

According to the International Commission on Radiation Units and Measurements (ICRU) Report 38,[3] *low-dose rate (LDR)* implants deliver doses at the rate of 40 to 200 cGy/hour (0.4-2 Gy/hour), requiring treatment times of 24 to 144 hours, during which the patient is confined to an inpatient treatment room. At the other extreme, *high-dose rate (HDR)* BT uses dose rates in excess of 0.2 Gy/min (12 Gy/hour). In fact, modern HDR iridium-192 (^{192}Ir) remote afterloaders deliver instantaneous dose rates as high as 0.12 Gy/s (440 Gy/hour) at a distance of 1 cm, resulting in treatment times of a few minutes. Such treatments must be delivered in shielded vaults using remote afterloading systems but allow fractionated BT to be delivered on an outpatient basis. Medium-dose rate delivery, defined as the 2 to 12 Gy/hour range, is rarely used today. Although not recognized by ICRU Report 38, the ultra-low dose rate (ULDR) range (0.01-0.3 Gy/hour) is also of great importance today as it is the dose rate domain used in permanent implants with ^{125}I, ^{103}Pd, and ^{131}Cs seeds.

PROPERTIES OF BRACHYTHERAPY SOURCES AND RADIONUCLIDES

The clinical utility of any radionuclide depends on practical properties, such as emission energies and radiation type, radioactive decay half-life, radiation output per unit of radioactivity, and the specific activity (radioactivity per unit mass; Ci/g). In addition, the methods of producing the radionuclide and its physical and chemical forms strongly influence cost-effectiveness, safety, and toxicity. Detailed properties of BT radionuclides are listed in Table 21.1.

TABLE 21.1 PHYSICAL PROPERTIES AND USES OF BRACHYTHERAPY RADIONUCLIDES

Element	Radionuclide	Average Energy (MeV)	Half-Life	HVL Lead (mm)	Exposure Rate Constant[a] ΓΔ	Source Form	Clinical Application
Obsolete sealed sources of historical significance							
Radium	^{226}Ra	0.83 (average)	1,620 y	16	8.25[b]	Tubes and needles	LDR intracavitary and interstitial

Element	Radionuclide	Average Energy (MeV)	Half-Life	HVL Lead (mm)	Exposure Rate Constant[a] ΓΔ	Source Form	Clinical Application
Radon	^{222}Rn	0.83 (average)	3.83 d	16	8.25[b]	Gas encapsulated in gold tubing	Permanent interstitial temporary molds
Currently used sealed sources							
Cesium	^{137}Cs	0.662	30.1 y	3.28		Tubes and needles	LDR intracavitary and interstitial
Cesium	^{131}Cs	0.030	9.69 d	0.030	0.64	Seeds	LDR permanent implants
Iridium	^{192}Ir	0.397 (average)	73.8 d	6	4.69	Seeds in nylon ribbon; metal wires	LDR temporary interstitial Intravascular brachytherapy; cardiac
						Encapsulated source on cable	HDR interstitial and intracavitary
							Intravascular brachytherapy: peripheral
Cobalt	^{60}Co	1.25	1,925.3 d	11	13.07	Encapsulated source on cable	HDR interstitial intracavitary
Iodine	^{125}I	0.028	59.4 d	0.025	1.45	Seeds	Permanent interstitial
Palladium	^{103}Pd	0.020	17.0 d	0.013	1.48	Seeds	Permanent interstitial
Gold	^{198}Au	0.412	2.7 d	6	2.35	Seeds	Permanent interstitial
Strontium/yttrium	^{90}Sr–^{90}Y	2.24 β_{max}	28.9 y	—	—	Plaque	Treatment of superficial ocular lesions
						Seeds	Intravascular brachytherapy
Electronic x-ray source	—	0.034	—	<0.03	—		Intracavitary breast brachytherapy
Developmental sealed sources							
Americium	^{241}Am	0.060	432.6 y	0.12	0.12	Tubes	LDR intracavitary
Ytterbium	^{169}Yb	0.093	32.0 d	0.48	1.80	Seeds	HDR interstitial

Element	Radionuclide	Average Energy (MeV)	Half-Life	HVL Lead (mm)	Exposure Rate Constant[a] ΓΔ	Source Form	Clinical Application
Californium	^{252}Cf	2.4 (average) neutron	2.65 y	—	—	Tubes	High LET LDR intracavitary
Samarium	^{145}Sm	0.043	340 d	0.060	0.885	Seeds	LDR temporary interstitial

HDR, high-dose rate; HVL, half-value layer; LDR, low-dose rate; LET, linear energy transfer.

[a]No filtration in units of $R \cdot cm^2 \cdot mCi^{-1} \cdot h^{-1}$.

[b]0.5-mm platinum filtration; units of $R \cdot cm^2 \cdot mg^{-1} \cdot h^{-1}$.

Photon Spectrum and Dosimetric Characteristics of Brachytherapy Sources

The dose delivered by a BT procedure depends on the individual source strengths, source arrangement, and implant duration as well as the dosimetric characteristics of the implanted sources. These dosimetric characteristics are described by specifying the distribution of dose rates per unit strength about the source, often in terms of an "away-and-along" table[4] in Cartesian coordinates or in terms of the Task Group (TG) 43 protocol[5] described later in this chapter. The single-source dose distribution is of central importance to BT treatment planning because commercial computer planning systems estimate dose distribution from the spatial coordinates of the implanted sources using the principle of superposition. The source-superposition algorithm estimates the contributions of each source to each point of interest. These contributions are summed to estimate the total dose rate at each point. Often, total dose rates are calculated over a two-dimensional (2D) grid of points and are represented as isodose rate curves.

For conventional BT, for which the therapeutically relevant distance range is 2 to 20-mm, only photons (γ-rays or characteristic x-rays) with energies in excess of 15 keV contribute to the therapeutic effect. In general, four factors influence the single-source dose distribution for photon-emitting sources: (1) distance (inverse-square law); (2) radiation absorption and scattering in the source core and encapsulation; (3) photon attenuation; and (4) scattering in the surrounding medium (Figure 21.1). Encapsulation prevents radioactive material from leaking out of the source and absorbs nonpenetrating radiation (β-rays, α-particles, and low-energy photons) that would otherwise give rise to high surface doses while negligibly contributing dose to the target.

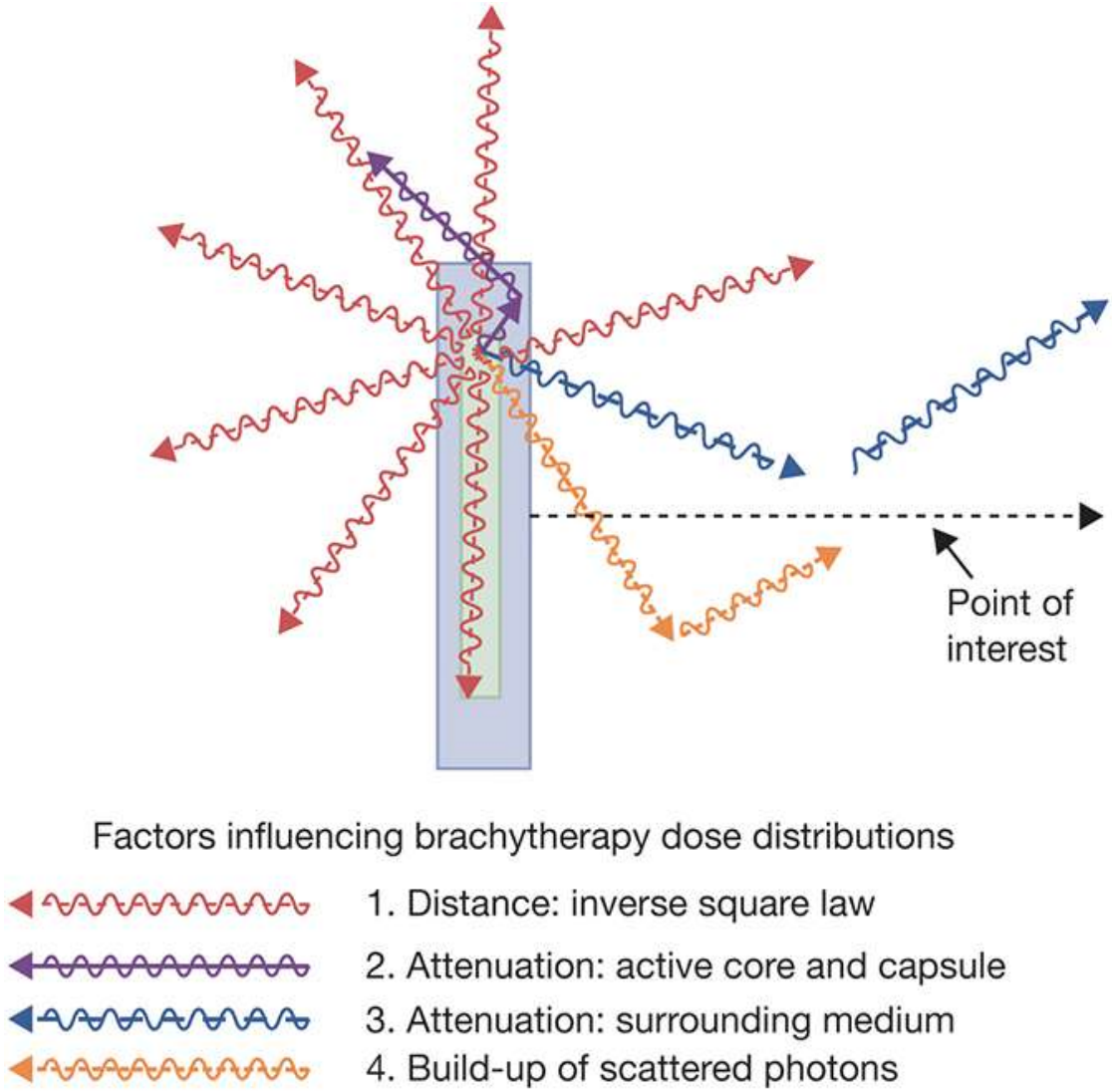


FIGURE 21.1 Typical cylindrical brachytherapy source, consisting of an active core (inner cylinder within which radioactivity is uniformly distributed) and the surrounding encapsulation (usually stainless steel or titanium for modern sources). The four principal factors influencing the relative dose distribution are (1) distance, (2) attenuation and scattering of photons by the source structure and two competing effects of the surrounding medium: attenuation of primary photons (3) and accumulation of scattered photons (4) originating throughout the medium.

Each voxel of radioactive core material shown in Figure 21.1 can be assumed to be an isotropic point source (Figure 21.2). Because of the straight line emission of photons with equal likelihood in all directions, photon intensity or fluence, $\Phi(r)$, at any point is proportional to the inverse square of its distance, r:

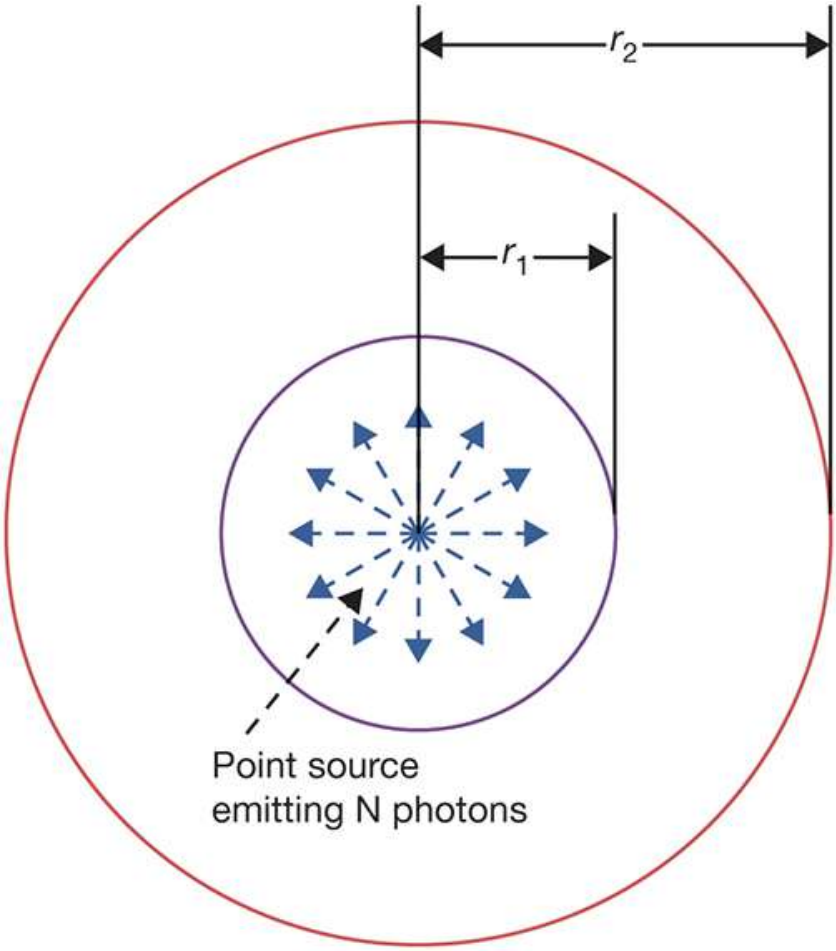


FIGURE 21.2 An *isotropic point source* of activity, *A*. To illustrate the derivation of inverse-square law, the source is surrounded by vacuum and placed at the center of two concentric spherical surfaces of radii r_1 and r_2. By definition, an *isotropic point source* has no extension and radiates photons with equal likelihood in all directions in straight line paths.

$$\Phi(r) = \frac{\text{No. incident photons}}{\text{Unit area irradiated}} = \frac{\text{No. photons emitted}}{4\pi r^2} \propto \text{Dose}(r) \propto \text{Exposure}(r) \tag{21.1}$$

assuming that attenuation and scattering can be neglected.

As a result of this purely geometric effect, the absorbed doses $D(r_1)$ and $D(r_2)$ at the two distances r_1 and r_2 (Figure 21.2) are related by:

$$\frac{D(r_1)}{D(r_2)} = \frac{\Phi(r_1)}{\Phi(r_2)} = \left(\frac{r_2}{r_1}\right)^2 \qquad (21.2)$$

This fundamental law applies exactly to each point of the radioactive core of the source shown in Figure 21.1, assuming that there is no attenuation and scattering of photons by the surrounding medium. However, Eq. 21.2 will not accurately describe the "collective" dose falloff arising from the combined action of the point sources distributed throughout the core, unless both r_1 and r_2 are large relative to the active source dimensions. Of the four factors influencing the dose distribution (see Figure 21.1), inverse-square law is by far the most important. For a pure isotropic point source, dose will decrease by more than a factor of 100 between 0.5 and 5 cm. The influence of the remaining factors over the same distance range rarely exceeds a factor of 2 or 3. Consequently, the dosimetric characteristics of implants (eg, the heterogeneous dose distribution within the target tissue and rapid fall off dose outside the implanted volume) can be accounted for by applying inverse-square law to each point-like element of radioactivity within the implant. Control of intersource spacing and positioning relative to the target and dose-limiting tissues is the most challenging issue in delivering BT.

Although the inverse-square law dominates BT dose distributions, the surrounding medium and the source structure significantly affect the dose distribution (see Figure 21.1). The source core and surrounding capsule reduce dose at the point of interest through absorption and scattering of primary photons. Primary photons contributing dose to points located near the longitudinal source axis (cylindrical axis of the source or axis of rotation) must traverse longer pathlengths of capsule and core material and, therefore, experience more attenuation than photons contributing dose to equidistant points on the transverse source axis (plane perpendicular to the longitudinal source axis that bisects its active core). For any fixed distance from the source center, doses near the longitudinal axis are usually smaller than on the transverse axis. This phenomenon is known as *oblique filtration* and is the main cause of dose *anisotropy* (variation of dose as a function of polar angle at each fixed distance relative to the source center) characteristic of BT sources. Because BT sources are cylindrically symmetric, the dose distribution will be equatorially isotropic (constancy of dose as a function of azimuthal angle for each fixed polar angle and distance).

The tissue equivalent medium surrounding the source affects the dose distribution in two competing ways (factors 3 and 4 described above and in Figure 21.1). At each point of interest, the intervening medium reduces the dose distribution by attenuating primary photons (deflecting them from their straight line trajectories). At the same time, photons are being emitted in all directions from the source and interacting with the medium by means of Compton scattering and photoelectric absorption. Thus, each volume element of tissue is effectively radiating scattered photons in all directions, many of which contribute to dose at the point of interest. This mechanism, known as scattered photon build-up, enhances the dose. The overall influence of the surrounding medium is the combined effect of these two

competing processes: photon attenuation and scattered photon build-up. In contrast to external beam radiotherapy (EBRT), in which the scattering volume is limited to a narrow cone, scattered photons dominate BT dose distributions at distances greater than 2 and 5 cm for low- and high-energy photon emitters, respectively. Photon scattering is the main source of complexity in BT dose measurement and algorithm development.

Figure 21.3 demonstrates that the relative dose versus distance from the source is nearly independent of its photon energy so long as the average photon energy is greater than 200 keV. In this energy range, dose deviates from inverse-square law by less than 5% over the 1- to 5 cm distance range. All of the "radium equivalent" radionuclides, including ^{60}Co, ^{137}Cs, ^{192}Ir, and ^{198}Au, fall into this energy range. This behavior greatly simplifies BT dosimetry and is the result of equilibrium between primary photon attenuation and build-up of scattered photons. Only for low-energy sources (eg, ^{103}Pd, ^{125}I, and ^{131}Cs) does the depth-dose curve significantly deviate from inverse-square law. Because photon absorption rather than Compton scattering dominates energy deposition below 40 keV, scatter build-up is unable to compensate for loss of dose resulting from attenuation.

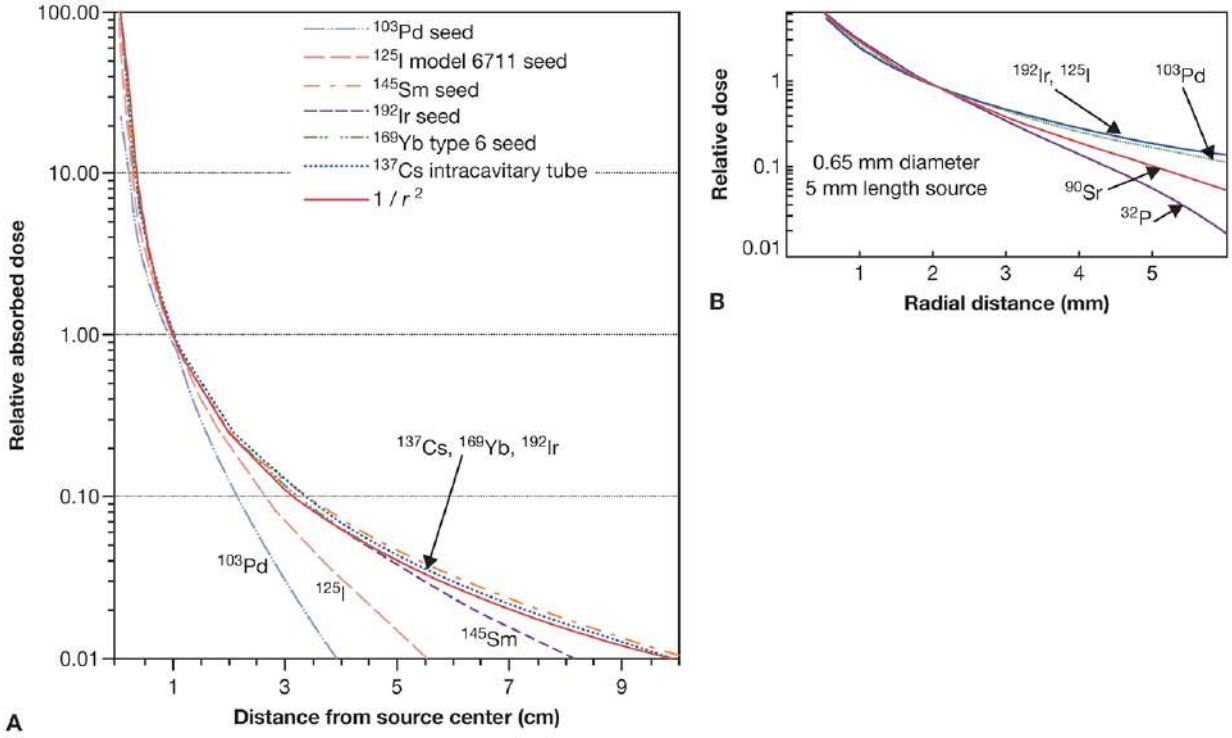


FIGURE 21.3 A. Variation of dose as a function of distance for point sources of ^{60}Co, ^{226}Ra, ^{137}Cs, ^{198}Au, ^{192}Ir, and ^{125}I. The results are normalized to 100% at 1 cm distance. The function ($1/r^2$) is plotted for comparison. B. Relative dose (normalized to 1.0 at 1 mm) versus distance for various cylindrical sources (0.65 mm diameter and 5 mm long) over the 1 to 5 mm distance range. (Reprinted from Amols HI, Zaider M, Weinberger J, Ennis R, Schiff PB, Reinstein LE. Dosimetric considerations for catheter-based beta and gamma emitters in the therapy of neointimal hyperplasia in human coronary arteries. *Int J Radiat Oncol Biol Phys*. 1996;36[4]:913-921. Copyright © 1996 Elsevier. With permission.)

For high-energy radionuclides, Figure 21.4A and B show that both absolute dose rates (cGy/hour to fat or water tissue per mgRaEq or unit air-kerma strength [S_K]) and relative dose distributions are nearly independent of energy and composition of the surrounding medium above 100 keV. Compton scattering, which dominates photon absorption and scattering above 100 keV, depends mainly on the electron density (electrons/g) of the medium, which is nearly constant for all biologic materials. Below this energy range, absolute and relative dose distributions vary significantly with energy and composition (atomic number) of the surrounding medium. Implanting a ^{125}I seed in fat medium (effective atomic number of Z_{eff} = 6) will deliver about half the absorbed dose at 1 cm, compared to the expected dose in water (Z_{eff} = 7.5). This is because energy absorption per unit mass from photoelectric interactions is proportional to the cube of the atomic number (Z_{eff}^3) of the medium. Despite the significant impact of tissue composition heterogeneities on low-energy seed BT dose delivery, only recently have treatment planning and dose measurement practices began to address tissue and applicator inhomogeneities.[6]

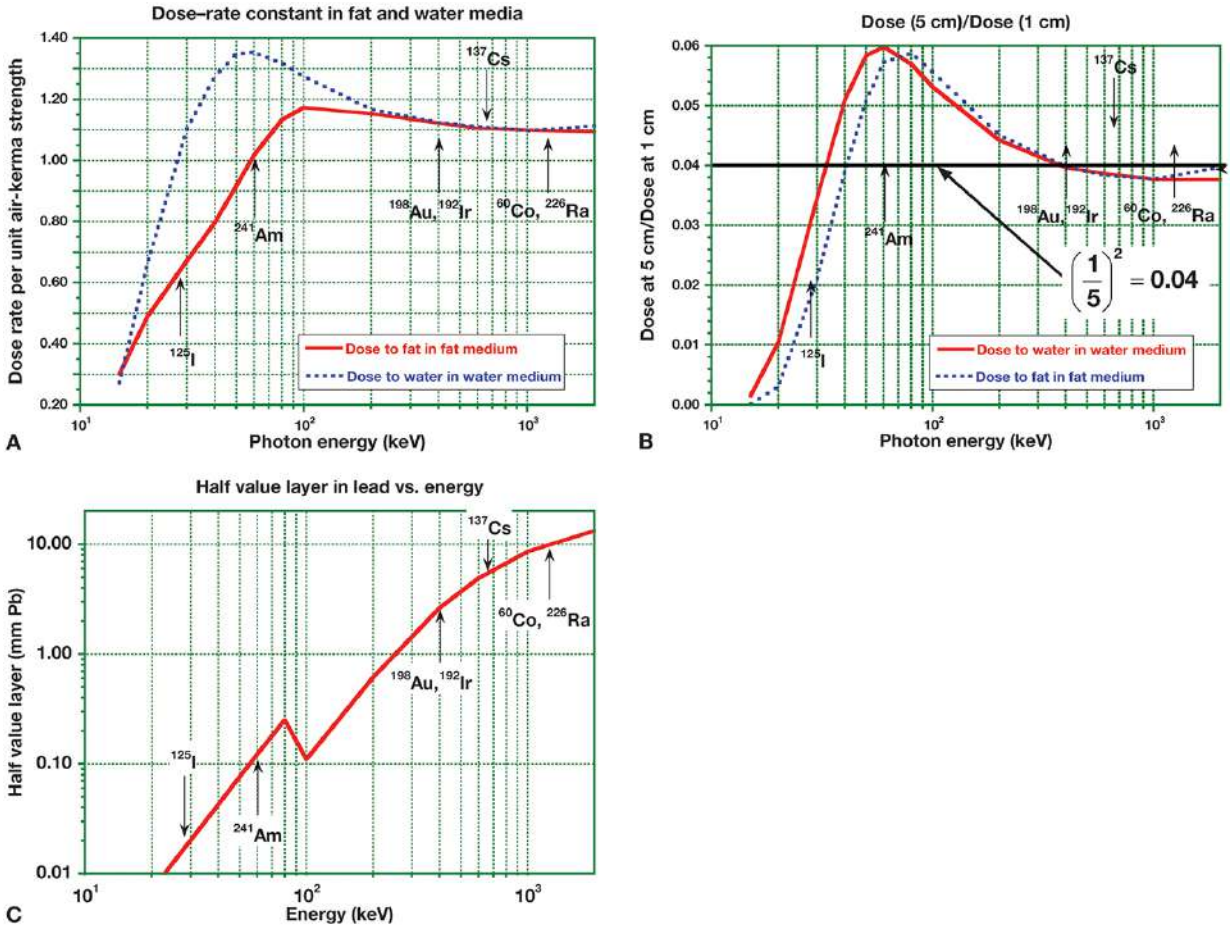


FIGURE 21.4 Variation of dosimetric properties of monoenergetic point sources as a function of photon energy. The location (in terms of average energy) of commonly used radionuclides is indicated by the labeled vertical arrows. A. Absolute dose rate per unit source strength in fat and water media at 1 cm distance. Source strength is specified in terms of output in air. B. Dose at 5 cm as a fraction of dose at 1 cm in fat and water media. The effect of inverse-square law, $(1/5)^2 = 0.04$, is shown for comparison as a broken line. C. Half-value layer in lead and the thickness (mm) in lead required to reduce primary dose by a factor of 2.

Figure 21.4B demonstrates that the inverse-square law actually underestimates relative dose at 5 cm by as much as a factor of 2 in the 60 to 100 keV energy range. In this narrow energy range, the photoelectric effect is negligible, whereas Compton scattering transfers most of the colliding primary photon energy to the scattered photon rather than to the Compton electron. As a result of this imbalance between energy absorption and photon scattering, build-up of scattered photons overcompensates for loss of dose as a result of primary photon attenuation out to distances of about 5 cm. Above the 100 keV threshold, the photon-energy spectrum is much less important to optimizing BT dose rate distributions than in EBRT.

Figure 21.4C demonstrates that although the high-energy photon spectrum is a relatively unimportant determinant of radium equivalent tissue dosimetry, it significantly influences the cost, weight, and thickness of shielding required to protect critical anatomic structures in the patient and personnel involved in patient care. The half-value layer (HVL) in lead

varies from 0.5 mm for a 100-keV source to 12 mm for ^{60}Co BT sources. Thus, for high-energy BT, a radionuclide with a mean energy of about 100 to 200 keV is optimal. The major benefit of low-energy sources is their ability to provide complete protection by thin lead foils (0.1-0.2 mm), greatly reducing exposure to physicians during the implant procedure and allowing permanent implant patients to be immediately released without posing a radiation safety hazard to the general public. There is interest in using radionuclides in the intermediate-energy range (60-120 keV).[7-9] Tissue dose distributions are still approximately radium equivalent in this energy range, and thin layers of lead provide significant sparing of dose-limiting normal tissues near the implanted volume.

Intracavitary Sources for Low-Dose Rate Gynecologic Brachytherapy

Since the 1930s, sources for classic LDR intracavitary BT have taken the form of "tubes" having a physical length of 2 to 2.5 cm and an external diameter of about 0.3 cm. For treatment systems influenced by the Manchester[10] and MD Anderson[11] treatment techniques, active lengths (ALs) of 1.3 to 1.5 cm are typical. Radionuclides for intracavitary applications should have a half-life long enough to support a +10-year working life without large variations in prescription dose rate so that the high cost of these reusable sources to be amortized over a large number of patient treatments. The average photon energy should be at least 60 keV, as the dose fall off for lower energy sources (eg, ^{125}I) is too rapid to adequately treat the target volume periphery (>2 cm from the applicator center) without overtreating mucosal tissues in contact with the applicator.

Radium-226 Sources

Radium-226 (^{226}Ra), a naturally occurring radionuclide, was the first radionuclide isolated, intensively investigated, and used in clinical BT. The unit of activity, the curie (Ci), originally was defined as the rate of disintegration within 1 g of ^{226}Ra. ^{226}Ra has a complex decay scheme, consisting of a cascade of transformations from one daughter product to another, ending with a stable isotope of lead, $^{206}_{82}\mathrm{Pb}$. ^{226}Ra decays to gaseous ^{222}Rn with a half-life of 1,600 years. Per disintegration, approximately 75 γ-rays are emitted by radium and its decay products, ranging in energy from about 0.05 to 2.4 MeV, giving an average energy of about 0.8 MeV. The maximum β-ray energy is about 3.3 MeV. The exposure-weighted average energy of ^{226}Ra is 1.25 MeV when its photon spectrum is filtered by 0.5 mm of platinum. Nearly all ^{226}Ra BT sources were filtered by at least 0.5 mm Pt, which reduces the surface dose contributed by β-particles to a negligible level.

Clinical ^{226}Ra sources consisted of discrete cells of radium salt (radium sulfate plus filler) placed in needles or tubes with platinum wall thicknesses of 0.5 and 1.0 mm, respectively. Intracavitary radium tubes were usually 22 mm long, containing 5 to 30 mg of radium (S_K = 30 to 200 μGy·m^2/hour), with ALs of 15 mm. For interstitial BT, the full-, half-, and quarter-intensity needles popularized by the Manchester LDR implant system typically contained 0.66, 0.33, or 0.165 mg of radium per centimeter of AL, respectively.

The clinical use of ^{226}Ra has disappeared and is now only of historic interest. The potential of damaged sources to leak radioactive salts or emit radon gas (^{222}Rn) is the major reason for its decline, and the exposure hazard to interstitial BT practitioners.[12] Also, the long half and disposal costs of spent ^{226}Ra sources present a significant financial liability. However, because of its many years of therapeutic use, several widely used quantities for source strength specification and prescription of intracavitary treatment are derived from the early experience with ^{226}Ra.

Cesium-137 Sources

Cesium-137 (^{137}Cs), a fission byproduct, was a popular radium substitute because of its 30-year half-life, dominating gynecologic intracavitary BT from 1970 to 2000. Its single γ-ray (0.66 MeV) is less penetrating (HVL_{Pb} = 0.65 cm) than the γ-rays from radium (HVL_{Pb} = 1.4 cm) or ^{60}Co (HVL_{Pb} = 1.1 cm). Because ^{137}Cs decays to solid ^{137}Ba, ^{137}Cs sources replaced ^{226}Ra in LDR gynecologic applications.

^{137}Cs BT sources were introduced in the early 1960s.[13,14] The most recent sources, for example, the Amersham model CDCS-J tube and 3M model 6500 intracavitary tube, consisted of radioactive cesium distributed within an insoluble glass or ceramic matrix,[4] which produced far less radiochemical hazard from ruptured sources than radon gas or cesium salts. ^{137}Cs sources were encapsulated in stainless steel sheaths with wall thicknesses of 0.5 to 1.0 mm, ALs of 13.5 to 15 mm, diameters of 2.6 to 3.1 mm, and total lengths of about 20 mm. In contrast, lightly filtered ^{137}Cs tubes produce nearly elliptical isodose curves. Consequently, vaginal applicator systems containing modern ^{137}Cs sources with their axes positioned perpendicular to the coronal patient plane (eg, the Fletcher colpostat) caused higher bladder and rectal doses than when loaded with ^{226}Ra tubes.[15] However, high-energy LDR BT has been largely abandoned in favor of high-energy HDR BT using high-intensity ^{192}Ir sources, with 85% of respondents in a survey reporting use of HDR or pulsed-dose rate (PDR) BT.[16] ^{137}Cs intracavitary tubes and other source configurations ceased to be commercially available in the United States after 2014, largely due to the National Nuclear Security Agency effort to remove ^{137}CsCl sources due to potential use as a radiologic dirty bomb.

Experimental Intracavitary Brachytherapy Radionuclides

Californium-252 (^{252}Cf) is a unique radionuclide with a 2.65-year half-life that decays by either α-particle emission (97%) or spontaneous fission (3%). Depending on the distance from the source, one-half to two-thirds of the total absorbed dose in tissue are the result of the neutron component. Assuming a relative biologic effectiveness (RBE) of 6 for the neutron component for LDR applications, approximately 90% of the biologically effective dose (BED) derives from the neutron component. The radiobiologic rationale for using ^{252}Cf, especially in treating bulky gynecologic malignancies, is that the high linear energy transfer (LET) neutron component more effectively depopulates the hypoxic core of a radioresistant tumor, thereby improving local control, while the rapid dose falloff maintains an acceptable level of late complications.[17] ^{252}Cf tube sources[18] required carefully designed

radiation protection and source handling procedures to reduce radiation exposure hazards to an acceptable level, due to the high neutron quality factor of 10 to 20 that is assumed by radiation protection standards.[19] Oak Ridge National Laboratory ceased fabrication of ^{252}Cf sources for medical use in 1997 and are currently not available elsewhere in the world. However, ^{252}Cf BT continues to be of clinical interest. Two groups using HDR ^{252}Cf BT remote afterloading systems have reported long-term clinical experiences[20,21] based on cohorts of locally advanced cervical cancer patients.

Ytterbium-169 (^{169}Yb)[8] and americium-241 (^{241}Am)[7] are examples of intermediate-energy photon emitters with average energies of 93 and 60 keV with half-lives of 32 days and 432 years, respectively. These radionuclides have been investigated as possible substitutes for ^{192}Ir.[22] Despite ^{169}Yb having an extremely high specific activity, none of these experimental prototype LDR sources[23] and HDR sources[9] have been commercially realized. Other promising intermediate-energy photon emitters include ^{57}Co,[24] ^{153}Gd,[25] and ^{101}Rh.[26]

Sources for Low-Dose Rate Temporary Interstitial Brachytherapy

The main additional requirement for radionuclides used in temporary interstitial BT is having a specific activity sufficient to support fabrication of miniaturized sources (less than 0.2 cm external diameter) so as to minimize trauma to the implanted tissues. Current interstitial implantation techniques favor disposable sources containing short-lived radionuclides that support afterloading and customization of AL.

Nonafterloading ("Preloaded") Sources: Radium and Cesium Needles

Radium-226 needles were the mainstay of interstitial BT until about 1970. These sources had external diameters of ~0.2 cm, ALs ranging from 0.3 to 4.5 cm, and Pt-Ir alloy encapsulation ranging from 0.5 to 0.65 mm in thickness. Because needle implantation can result in large exposures to the radiation oncologist's fingers, as well as whole-body exposure to operating room and implant imaging staff, interstitial implantation of ^{226}Ra or ^{137}Cs needles is no longer practiced.

Afterloading Interstitial Sources: ^{192}Ir Ribbons and Wires

Temporary interstitial BT experienced a renaissance in the 1960s because of the introduction of ^{192}Ir.[12] High specific activities can be achieved, and miniaturized interstitial sources can be fabricated relatively cheaply. The use of ^{192}Ir in BT was pioneered by Ulrich Henschke et al,[27] who developed a family of widely used afterloading techniques, and to Pierquin and Dutreix,[28] who developed the ^{192}Ir-based Paris interstitial system in the early 1960s.

^{192}Ir has a 73.8-day half-life and a complex decay scheme, not only dominated (95%) by β-decay to ^{192}Pt but also including electron capture (5%) to ^{192}O. Its photon spectrum includes characteristic x-rays and γ-rays ranging from 63 keV to 1.4 MeV and has an exposure-weighted average energy of 0.4 MeV. Compared with higher energy ^{137}Cs, the thicknesses of lead and concrete shielding can be reduced by 33% and 20%, respectively.[29]

More important advantages of ^{192}Ir sources are compatibility with afterloading techniques, technical flexibility, and patient comfort.

In the United States, LDR ^{192}Ir BT is still available (but rarely used) in the form of seeds, 0.05 cm in diameter and 0.3 cm long. The seeds are encapsulated in a 0.08-cm diameter nylon ribbon spaced at 0.5- to 1 cm center-to-center intervals and are available in strengths of 1 to 150 μGy·m^2/hour (0.1-20 mgRaEq). In Europe, ^{192}Ir was used in the form of a wire (0.03- or 0.06 cm outer diameter) consisting of an Ir-Pt core encased in a 0.01-cm Pt sheath. In addition to eliminating radiation exposure hazards in the operating room, ^{192}Ir ribbons and wires can be trimmed to the appropriate length for each catheter. Manual and remotely afterloading LDR interstitial BT utilization has declined in the developed world over the past two decades. A survey[30] indicated that in high-income European countries, only 11% of BT procedures performed in 2007 used LDR techniques compared to HDR (52%), PDR (10%), and permanent seed implants (21%).

Low-Energy Sources for Temporary Interstitial Brachytherapy

High-intensity ^{125}I sources[31] have been proposed for temporary interstitial implantation at classic dose rates. High-intensity ^{125}I seeds[32,33] now are used routinely as temporary interstitial sources for episcleral plaque treatment of ocular lesions.[34] By placing a 0.05-cm-thick Au shield over the episcleral plaque, tissues posterior to the eye are shielded, and radiation directed toward the tumor is partially collimated.[35] A disadvantage of high-intensity ^{125}I seed therapy is their higher cost relative to ^{192}Ir seeds. ^{103}Pd and ^{131}Cs sources have also been used as temporary interstitial sources in ocular plaque BT.[36]

Sources for Permanent Interstitial Brachytherapy

There are two basic approaches to permanent implantation. Classic LDR permanent BT originally used ^{222}Rn seeds and then ^{198}Au seeds, both of which have half-lives of a few days. To manage the radiation hazard resulting from their high-energy γ-rays, the patient must be confined to the hospital until the source strength decays to a safe level (2-3 half-lives or about 10 days). The contemporary approach to permanent implantation, ULDR BT, uses longer lived but low-energy photon emitters (eg, ^{103}Pd, ^{125}I, and ^{131}Cs). The patient tissue or a thin Pb foil is sufficient to limit ambient exposure rates to negligible levels, eliminating the need to hospitalize patients solely for radiation protection. During the implant procedure, low-energy photon sources markedly reduce radiation exposure to operating room personnel and to the radiation oncologist's hands.

Mathematics of Radioactive Decay

The phenomenon of exponential decay results in a reciprocal relationship between dose rate achieved and radionuclide half-life. The total activity, $A(t)$, present in the implant after an interval of time t has elapsed after source insertion, is given by Eq. 21.3, and exponential decay is demonstrated in Figure 21.5.

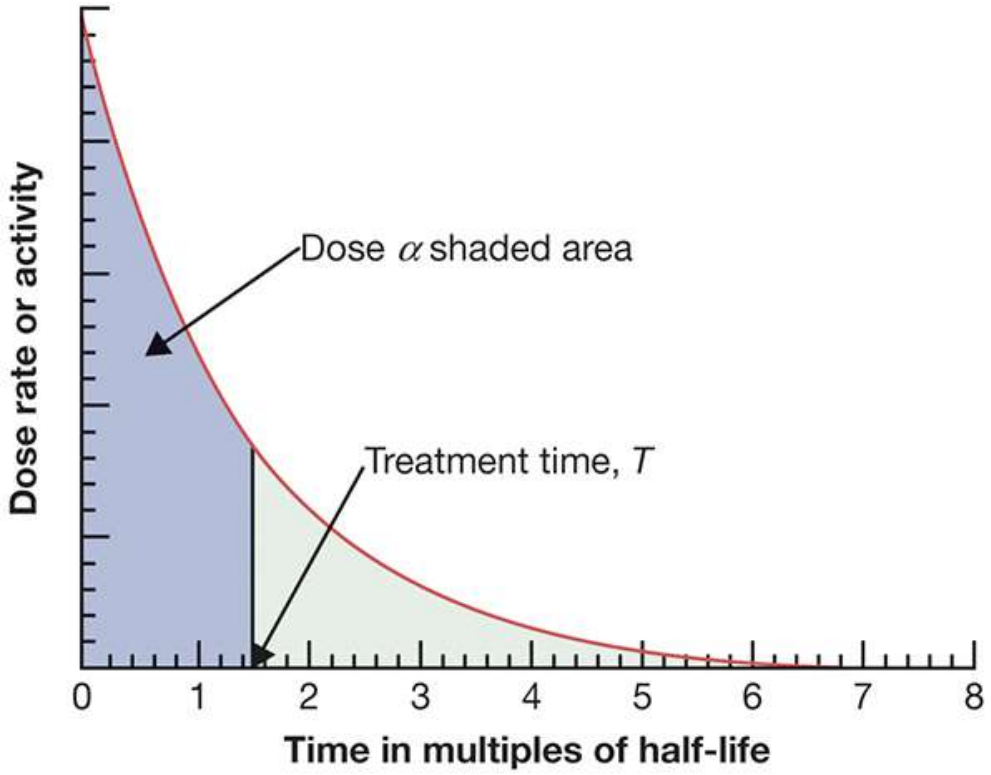


FIGURE 21.5 Illustration of exponential decay of source strength and dose rate. The area of the shaded region is the total dose administered to the patient over treatment time, *T*.

$$A(t) = A(0) \cdot e^{-\ln 2 \cdot t / T_{1/2}} \tag{21.3}$$

where $A(0)$ is the activity at the time of insertion, ln2 is the natural logarithm of 2 (equal to 0.693), and $T_{1/2}$ is the radionuclide half-life. The quantity $\ln 2/T_{1/2}$, represented by the symbol λ, is called the decay constant. Equation 21.3 is applicable to any measure of source strength (S_K, equivalent mass of radium, etc). Because dose rate, $\dot{D}(t)$, at time t is proportional to activity, that is, $\dot{D}(t) \propto A(t)$, we can write:

$$\dot{D}(t) = \dot{D}(0) \cdot e^{-t \cdot \ln 2 / T_{1/2}} \tag{21.4}$$

where $\dot{D}(0)$ is the dose rate at the time of source insertion. The total dose, $D(T)$, accumulated over time interval T after source insertion, is the shaded area under the curve of Figure 21.5 and can be obtained by integrating Eq. 21.4:

$$D(T) = \dot{D}(0) \cdot \int_0^T e^{-t \cdot \ln 2/T_{1/2}} \cdot dt$$
$$= \dot{D}(0) \cdot T_{1/2} \cdot 1.443 \cdot [1 - e^{-T \cdot 0.693/T_{1/2}}] \quad (21.5)$$

The product $T_a = 1.443 T_{1/2}$ is called the average life of the radionuclide and is the time required for all radioactive atoms to decay assuming the rate of decay remains fixed at its initial value, $A(0)$. Equation 21.5 should be used to calculate the total dose delivered by any implant when the treatment time, T, is more than 5% of the half-life. For shorter treatment times (less than 4 days for ^{192}Ir or less than 3 days for ^{125}I), the approximate expression

$$D(T) = \dot{D}(0) \cdot T \quad (21.6)$$

is accurate within 2% since decay during the implant is negligible.

For permanent implants, the total dose administered to the patient, D_{tot}, resulting from complete decay of the implant can be obtained from Eq. 21.5:

$$D_{tot} = \lim_{T \to \infty} D(T) = 1.443 \cdot T_{1/2} \cdot \dot{D}(0) = T_a \cdot \dot{D}(0) \quad (21.7)$$

This equation demonstrates that initial dose rate and radionuclide half-life are in reciprocal relationship with one another: The longer the half-life, the lower the initial dose rate will be. Typical initial dose rates and total doses are given in Table 21.2 for commonly used permanent implant sources. These sources fall into two categories: short-lived high-energy sources with initial dose rates within the classic LDR range and longer lived low-energy sources with initial dose rates below the classic range, that is, ULDR.

TABLE 21.2 TOTAL DOSE AND INITIAL DOSE RATES FOR PERMANENTLY IMPLANTED RADIONUCLIDES

Radionuclide	Mean Photon Energy	$T_{1/2}$ (days)	Typical Prescribed Dose (Gy)	Initial Dose Rate (cGy/hour)
^{222}Rn	1.2 MeV	3.83	100	75
^{198}Au	412 keV	2.7	100	107
^{131}Cs	31 keV	9.7	115	34.2[1]
^{125}I	28 keV	59.4	145	7.0

Radionuclide	Mean Photon Energy	$T_{1/2}$ (days)	Typical Prescribed Dose (Gy)	Initial Dose Rate (cGy/hour)
^{103}Pd	21 keV	17.0	125	21.2

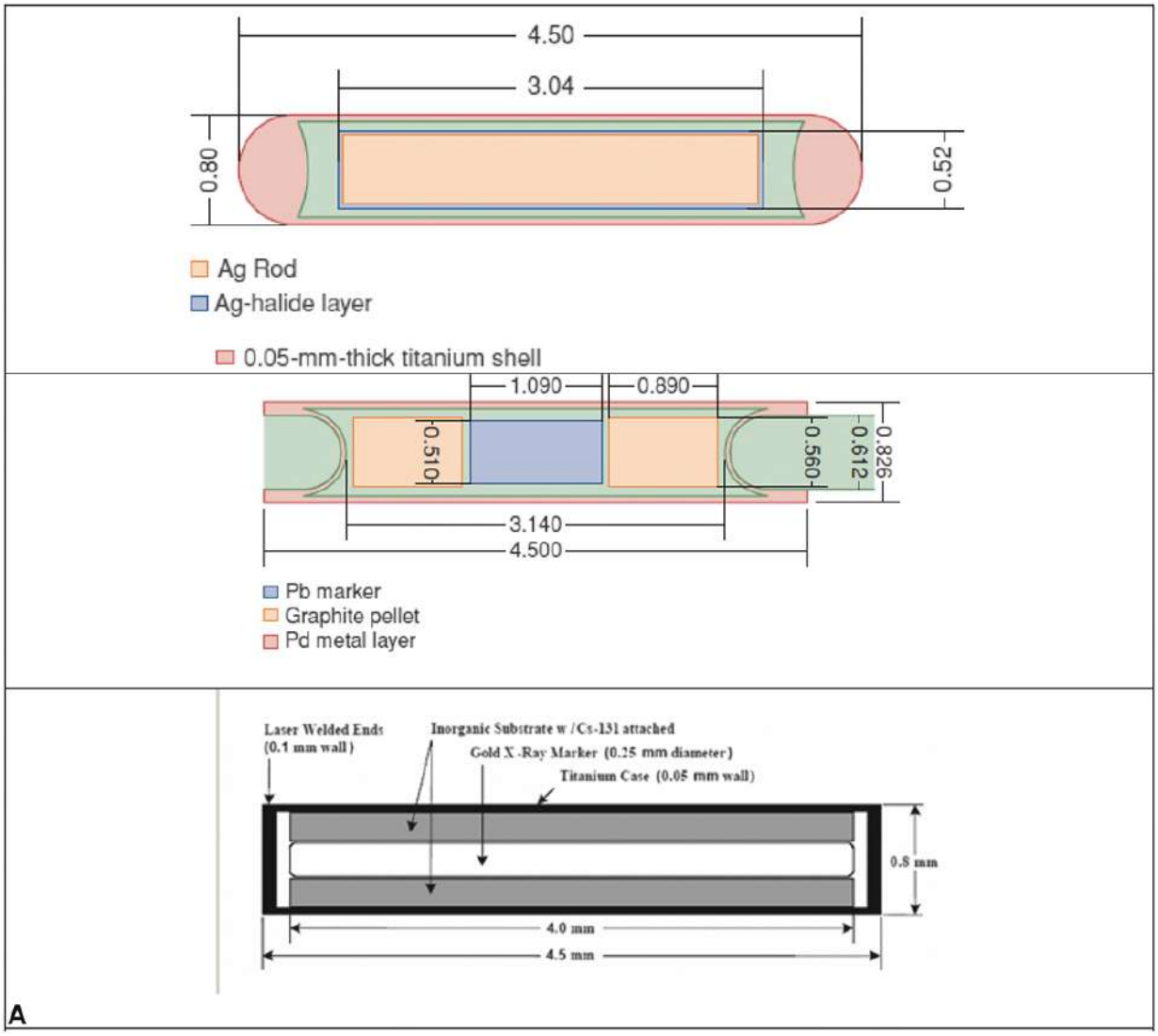
Ultra-Low-Dose Rate and Low-Energy Permanent Implant Sources

An important development was the introduction of interstitial seeds using electron capture decay radionuclides, which have moderately long half-lives (10-60 days) and emit cascades of low-energy (20-40 keV) characteristic x- and γ-rays. The first practical K capture source, the Ti-encapsulated ^{125}I seed (half-life: 59.4 days, mean energy: 28 keV), was developed by Donald Lawrence[37] in the early 1960s and its clinical applications developed in the late 1960s by Basil Hilaris and his colleagues[38-40] at Memorial Sloan-Kettering Hospital. ^{125}I is produced by neutron activation in a specially equipped reactor designed to minimize activation of the contaminant radioisotope, ^{126}I. It decays by electron capture, producing a single 35-keV γ-ray. The captured K-shell electron produces a cascade of 27- to 32 keV characteristic x-rays. In addition, 93% of the γ-rays are internally converted, producing a second characteristic x-ray cascade. Thus, ^{125}I is an "x-ray emitter" because 95% of the useful primary photons are characteristic x-rays of atomic rather than nuclear origin.

Other important radionuclides are ^{103}Pd (17.0-day half-life and 20 keV mean energy), commercially realized in 1987, and ^{131}Cs (9.65-day half-life and 30 keV mean energy), which was initially proposed by Lawrence and Henschke[41] but became available as a commercial product in 2006.[42,43] The low-energy photons emitted by these radionuclides dramatically reduce external exposure hazards: An 8-cm thickness of tissue reduces exposure 10-fold. Thin (0.02 cm) Pb foils also produce almost complete shielding. Thus, there is usually no need to confine patients to the hospital solely for radiation safety reasons. The rapid growth trajectory of transperineal ultrasound (TRUS)-guided permanent seed BT[44,45] in the 1990s for definitive treatment of low- and intermediate-risk prostate cancer,[46,47] resulted in the introduction of approximately 25 different models of ^{125}I and ^{103}Pd to the market from 1997 to 2005. (See the American Association of Physicists in Medicine [AAPM] revised TG-43 reports[5,48,49] for a review of many of the available sources.) While BT remains a widely elected treatment modality for localized prostate cancer, its utilization has fallen from 24% in 2002 to 12% in 2010[50] and is even lower today. As a result, there has been consolidation in the low-energy seed market. The Brachytherapy Source Registry, managed jointly by the AAPM and the Imaging and Radiation Oncology Core (IROC) Houston QA Center (IROC-Houston, formerly the Radiological Physics Center),[51,52] lists all commercially available and clinically used orphan sources that meet the AAPM dosimetric prerequisites for use in clinical trials and everyday practice.[53] According to the Brachytherapy Source Registry, there are six ^{125}I, four ^{103}Pd, and one ^{131}Cs seed models that are commercially available.

Most low-energy interstitial seeds are encapsulated in thin (0.005-cm-thick) titanium tubing (exception: polymer-encapsulated CivaSheet and CivaString ^{103}Pd sources[54]) with external dimensions of 0.08 cm × 0.45 cm (Figure 21.6). Most of the available ^{125}I seed products are variations on the model 6711 seed[55] design, which was the only ^{125}I source

available from 1983 to 1998. It contained a 0.3-cm long Ag rod on which radioactive iodine was absorbed and was available in strengths of 0.5 to 13 $\mu Gy \cdot m^2$/hour (Figure 21.6A, top). The radio-opaque Ag rod enabled seeds to be visualized on orthogonal or stereo-shift radiographs as well as computed tomography (CT) imaging.


4.50
3.04
0.80
0.52
Ag Rod
Ag-halide layer
0.05-mm-thick titanium shell
1.090
0.890
0.510
0.560
0.612
0.826
3.140
4.500
Pb marker
Graphite pellet
Pd metal layer
Laser Welded Ends
(0.1 mm wall)
Inorganic Substrate w /Cs-131 attached
Gold X-Ray Marker (0.25 mm diameter)
Titanium Case (0.05 mm wall)
0.8 mm
4.0 mm
4.5 mm

A

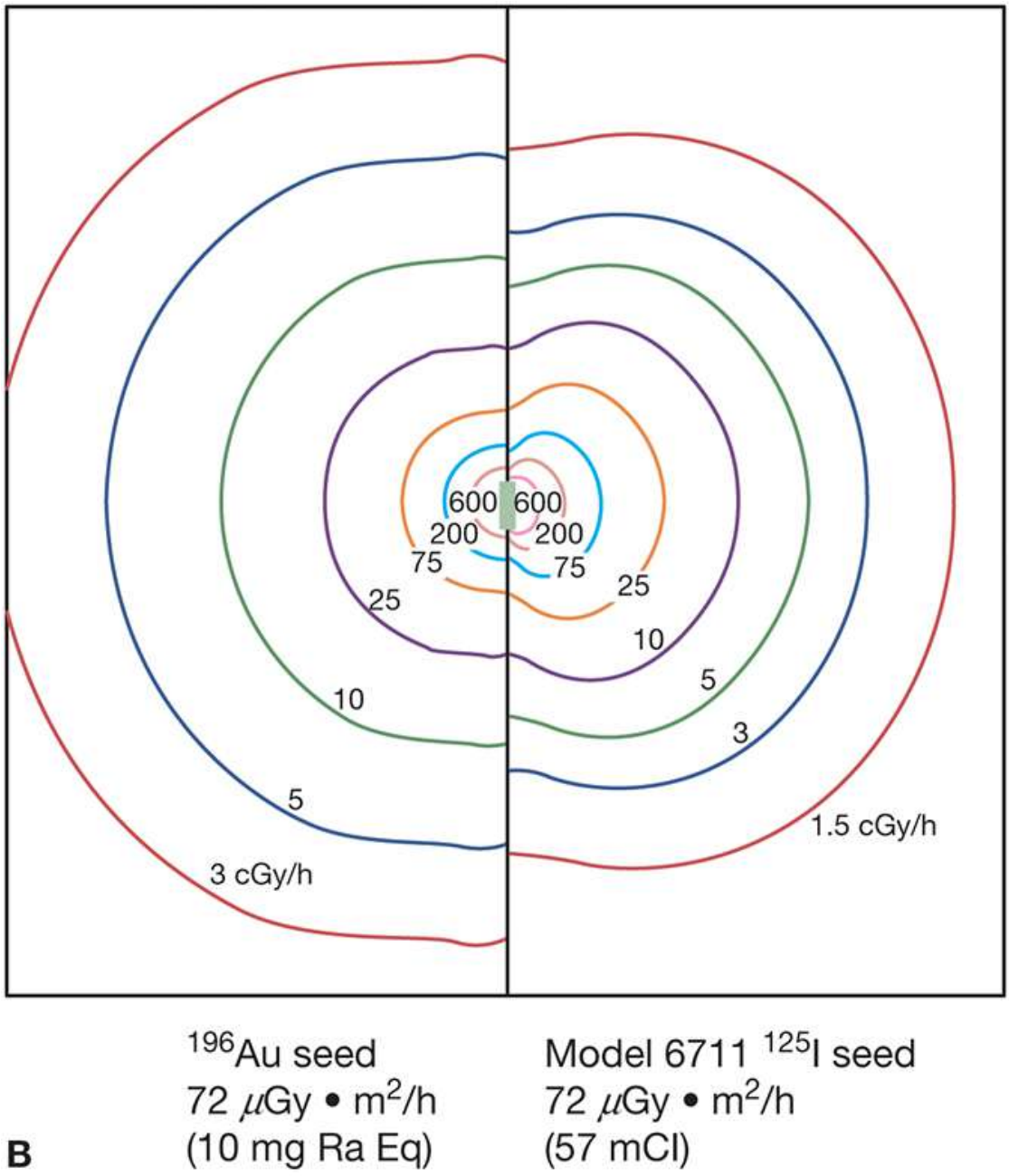


FIGURE 21.6 A. Design characteristics of three commercially available low-energy interstitial seed types. Top: A generic ^{125}I seed with silver rod radiographic marker derived from Model 6711 source (previously marketed by GE Healthcare, Amersham, and 3M) and now offered by several seed manufacturers. (A. Top: From Williamson JF, Rivard MJ. Quantitative dosimetry methods for brachytherapy. In: Thomadsen BR, Rivard MJ, Butler WM, eds. *Brachytherapy Physics*. 2nd ed. Medical Physics Publishing; 2005:233-294. Reprinted by permission of Medical Physics Publishing.) Middle: Theragenics Model 200 103Pd seed. (From Monroe JI, Williamson JF. Monte carlo-aided dosimetry of the theragenics TheraSeed® Model 200 ^{103}Pd interstitial brachytherapy seed. *Med Phys*. 2002;29[4]:609-621. Copyright © 2002 American Association of Physicists in Medicine. Reprinted by permission of John Wiley & Sons, Inc.) Bottom: The IsoRay Medical Inc. Model CS-1 (Rev 2) ^{131}Cs seed. (From IROC-Houston. Joint AAPM/IROC Houston Registry of brachytherapy sources meeting the AAPM dosimetric prerequisites. Vol. 2017. 2017. Reprinted by permission of American Association

of Physicists in Medicine.) B. Isodose curves for a ^{198}Au seed (left half) and Model 6711 ^{125}I seed (right half) both with air-kerma strengths of 72 μGy·m^2/hour (equivalent to 35 mCi of ^{198}Au and 57 mCi of ^{125}I).

^{103}Pd decays by K-electron capture and emits characteristic x-rays of 21 keV. While needing a slightly thicker container to shield γ-rays exceeding 200 keV, it has all the radiation protection advantages of ^{125}I along with a significantly shorter half-life of 17 days. With this source, a monotherapy implant can deliver 112 Gy (90% of the prescribed dose) in approximately 8 weeks at an initial peripheral dose rate of 21 cGy/hour. The model 200 seed (Figure 21.6A middle) was the only commercially available ^{103}Pd seed from 1988 to 1999. The radioactive ^{103}Pd is distributed within a thin Pd metal coating of the two graphite pellets, which are encapsulated in Ti tubing of the same dimensions as ^{125}I seeds. The biologic rationale for using shorter lived ^{103}Pd and ^{131}Cs interstitial sources is discussed later in the "The Radiobiology of Brachytherapy" section.

Low-energy seed implantation poses a number of challenges. Their dose distributions are not radium equivalent (Figure 21.6B), falling off more rapidly with distance. Dose estimation is inherently more complex, depending significantly on photon energy and composition of the surrounding medium (see Figure 21.4),[56,57] and is more sensitive to the internal seed geometry.[58,59] ^{125}I and ^{103}Pd dosimetry has been uncertain and variable over most of the clinical life of these products because of shifts in calibration standards, large uncertainties in dose measurement, and questionable applicability of classic dose calculation model.[12] For example, between 1975 and 1999, the ^{125}I dose rate constant was revised downward, in several steps, by nearly 50%.[12] Only with development and validation of more sophisticated experimental and computation dosimetry techniques can we claim to know low-energy seed dose rate distributions with an uncertainty of 3% to 7%.[60] Because of the very LDRs used, permanent low-energy seed implantation is effectively a different therapeutic modality than classic LDR BT. In addition, 20 to 30 keV photons have a significantly higher LET, which results in an RBE for ^{125}I of 1.3 to 2.1 in in vitro systems compared with unity for high-energy photon spectra.[61-63] Thus, classic LDR clinical experience cannot be used to guide therapeutic decision- making for ^{125}I permanent implantation. Despite these limitations, low-energy source permanent implantation has been demonstrated to be a highly effective and convenient treatment for prostate cancer,[64,65] which produces tumor control rates and toxicity profiles comparable or superior to competing modalities.

Sources for High-Dose Rate Brachytherapy

Radionuclide Sources

In contrast to inpatient-based LDR BT, HDR BT uses high-intensity sources to deliver discrete fractions ranging from 3 to 10 Gy in an outpatient setting. As described in more detail in Chapters 23 and 24, a remote afterloading device must be used. Typically, a cable-mounted HDR source is sequentially inserted to each catheter (see Figure 21.7A), mechanically driven to its distal end, and retracted, stopping at each programmed dwell position for the programmed dwell time (typically 1-60 seconds). A radionuclide with high

specific activity is needed so that overall treatment dose rates of at least 12 Gy/hour can be achieved without sacrificing the level of miniaturization needed to support intracavitary and interstitial BT. A source no larger than 1 mm outer diameter by 4 mm long with an air-kerma rate of at least 1 cGy/s at 1 cm is required. Figure 21.7A and C illustrate typical PDR and HDR sources, respectively.

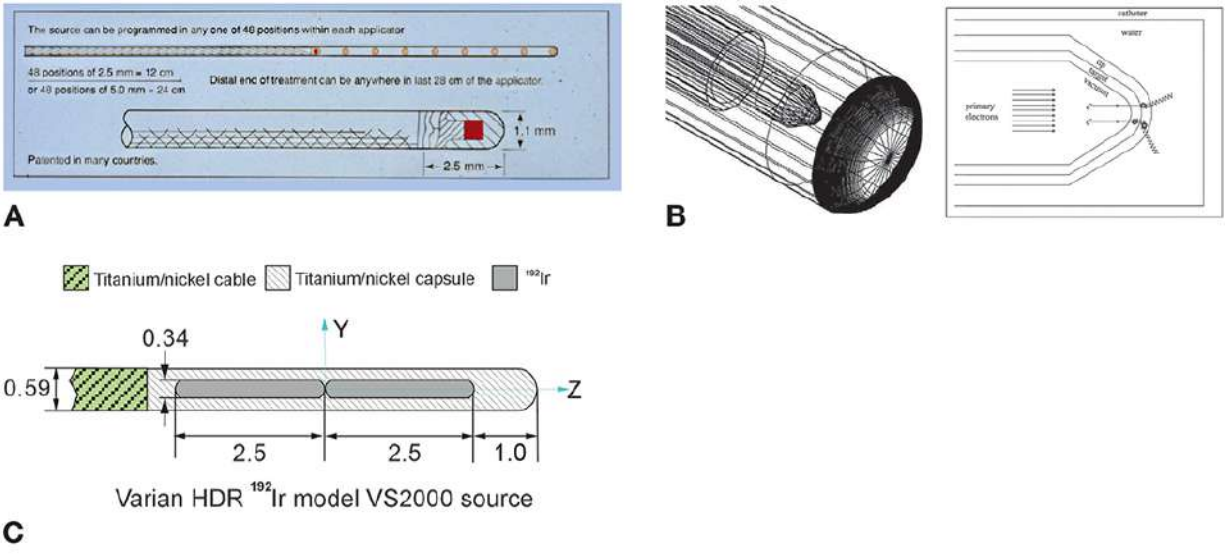


FIGURE 21.7 A. Top: a single-stepping source being withdrawn along the catheter axis from right to left illustrating the concepts of discrete dwell positions. Bottom: Geometry of the original pulsed-dose rate ^{192}Ir source introduced by Nucletron in 1993. B. Geometric model (left) of the Xoft electronic brachytherapy source consisting of an inner catheter terminated by a 0.07-μm-thick tungsten transmission target. Also illustrated is the oversized (5.3 mm OD) outer catheter needed to water cool the approximately 2.25-mm diameter by 15-mm-long x-ray tube (see right figure), which can support an air-kerma rate of 170,000 μGy·m^2/hour when operated at 50 kVp and 300 μA. (From Liu D, Poon E, Bazalova M, et al. Spectroscopic characterization of a novel electronic brachytherapy system. *Phys Med Biol*. 2008;53[1]:61-75. © Institute of Physics and Engineering in Medicine. Reproduced by permission of IOP Publishing. All rights reserved.) C. A modern high-dose rate (HDR) source, consisting of a 0.34-mm diameter by 5-mm long Pt-Ir core sealed in a nickel-titanium (Ni-Ti) alloy capsule, which is welded to a flexible Ni-Ti alloy cable.[72] (From Perez-Calatayud J, Ballester F, Das RK, et al. Dose calculation for photon-emitting brachytherapy sources with average energy higher than 50 keV: report of the AAPM and ESTRO. *Med Phys*. 2012;39[5]:2904-2929. Copyright © 2012 by American Association of Physicists in Medicine. Reprinted by permission.)

The upper limit on specific activity of any substance, achieved when 100% of its atoms are radioactive, is a fundamental property that depends on its number of atoms per gram:

$$\text{Atoms/g} = \left[\frac{\text{Avogadro's no.}(6.023 \times 10^{23}\ \text{atoms/mole})}{\text{Atomic weight}}\right] \quad (21.8)$$

For radionuclides produced by neutron activation, competition with radioactive decay precludes activating 100% of the target atoms. The theoretically achievable maximum Ci/g (Table 21.3) depends on the neutron capture cross section of the target and the neutron flux in the reactor.[66] The extent to which this limit can be reached in practice depends on isotopic purity of the target, limits on reactor activation time, and the time required for shorter lived contaminant radionuclides to decay to a negligible level. Finally, the air-kerma rate achieved by a small source (eg, a 1 mm × 4 mm cylinder as shown in Table 21.3) depends on the chemical form (ie, relative mass of nonradioactive atoms) of the source, its density, dose rate constant of the source model, and photon self-absorption.

TABLE 21.3 SPECIFIC ACTIVITIES AND MAXIMUM EXPOSURE RATES ACHIEVABLE FOR DIFFERENT RADIONUCLIDES

Radionuclide	Maximum Ci/g Possible	Fraction Practicably Achievable (%)	Exposure Rate[a] (R/s) at 1 cm From 1 mm × 4 mm Seed (R·cm^2/s)
^{226}Ra	0.98	100	0.04
^{137}Cs	87	23	0.22
^{60}Co	1,020[b]	49	50
^{192}Ir	7,760[b]	35	248
^{169}Yb	33,700[b]	14	51

[a]Neglecting self-absorption.

[b]Reactor produced by neutron activation: a flux $\phi = 10^{14}$ $n \cdot cm^{-2} \cdot s^{-1}$ and 100% target purity are assumed.

Table 21.3 shows that ^{226}Ra cannot support HDR BT and that ^{137}Cs is, at best, a marginal choice. ^{60}Co (1,925-day half-life with 1.17 and 1.33 MeV γ-rays) has been widely used as an intracavitary HDR source in the form of small spherical pellets. Based solely on specific activity considerations, ^{192}Ir is the optimal choice for HDR BT and is the most widely used radionuclide for this application. Sources with external diameters as small as 0.6 mm (see Figure 21.7C) are now available for use in single-stepping source remote afterloading devices. In contrast to ^{60}Co, the lower energy ^{192}Ir photons are shielded effectively by the scatter and leakage barriers present in linear accelerator vaults. Because of their short half-lives, HDR ^{192}Ir sources are usually replaced at quarterly intervals. Because of the relative ease with which its low-energy photons can be shielded, ^{169}Yb sources have also been proposed for HDR intraoperative and intravascular BT.[9]

Electronic Brachytherapy Sources

Currently, there are two established BT delivery systems on the market that use miniaturized low kilovoltage x-ray tubes to eliminate radionuclide sources of radiation. The Zeiss IntraBeam system uses magnetic focusing and steering to transport externally accelerated 50 keV electrons down a long 3.2-mm diameter drift tube, which collides with a thin gold transmission target at the end of the implanted catheter.[67,68] In contrast, the Xoft Axxent electronic brachytherapy (eBT) system[69] is based upon miniaturizing the entire x-

ray tube (see Figure 21.7), which is placed in a somewhat larger diameter (5.4 mm) intracavitary catheter to allow system cooling. While the INTRABEAM system has been used for several tumor sites, including skin cancer,[70] the main application for both systems has been intraoperative accelerated partial breast irradiation (APBI). While the use of eBT for APBI is supported by a randomized, phase III prospective noninferiority trial,[71] its equivalence to ^{192}Ir-based APBI remains controversial.[72] However, due to its lower penetration and more rapid falloff compared to ^{192}Ir, for a fixed level of APBI planning target volume (PTV) coverage, eBT gives rise to larger $V_{150\%}$ and $V_{200\%}$ values.[73] A provocative debate[74] highlights many of the operational and physical differences between the two classes of HDR delivery systems.

BRACHYTHERAPY SOURCE STRENGTH SPECIFICATION AND DOSIMETRY

Two eras of BT dosimetry can be distinguished. The *classic era* (1940-1980) encompassed the maturation of the classic BT systems, the transition from ^{226}Ra to artificial radionuclide sources, and the rise of modern BT. It began with the successful application of Bragg-Gray cavity theory[75] to the calibration of ^{226}Ra and other high-energy sources in terms of exposure,[76] which allowed BT treatment intensity to be quantified using the same system of units and quantities as the external orthovoltage beam therapy of the day. Classic or semiempirical dose computation models are based on the dose distribution of an idealized point source. Dose rates around needle and tube sources were calculated by integrating the basic point-source model over their extended radioactivity distributions. Because of the technical difficulties in measuring the absorbed dose in the presence of steep dose gradients, BT treatment planning relied largely on calculated rather than measured dose distributions.

The modern or *quantitative* era of BT dosimetry began in the 1980s and continues to the present. Quantitative dosimetry relies on the measurement of source model–specific dose distributions by means of small thermoluminescent dosimeters (TLDs), radiochromic film (RCF), or silicon diode dosimeters.[77] Alternatively, radiation transport calculations in the form of 3D Monte Carlo simulations are accepted as an accurate and reliable source of clinically useful dosimetry data.[77] These technical developments were motivated by concerns that semiempirical dose calculation algorithms were not valid in the low-energy regime of ^{125}I and ^{103}Pd sources. To clinically utilize dose measurements and Monte Carlo calculations with an empirical dose calculation formalism, the AAPM TG-43 protocol[5] was developed. Both the classic and quantitative dosimetry methods are based on the principle that BT source strength should be specified in terms of air-kerma strength.

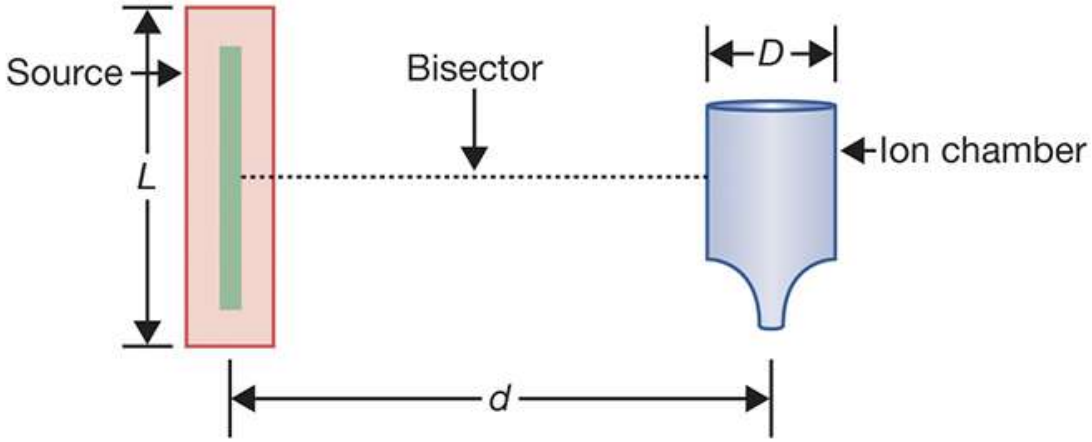
Source Strength Specification Quantities and Units

BT calibration is an unnecessarily confusing topic due to the multitude of quantities that have been used to specify source strength throughout its history. Many of the historically obsolete but still widely used quantities (eg, apparent activity and mgRaEq) were defined in terms of ^{226}Ra properties, the only BT radionuclide intensively studied until about 1940. Such quantities obscure the experimental origin of calibration measurements by describing output measurements in activity units. Finally, the BT literature has added to the lack of

conceptual clarity by obscuring the important distinction between quantities and units. A *quantity* is a property of nature that is directly or indirectly measurable (eg, kerma, equivalent mass of radium, length, time), whereas a *unit* is a selected sample of a quantity to which the magnitude unity (1.0) is assigned (eg, gray, mgRaEq, meter, second). A quantity such as absorbed dose can have many units (eg, cGy, Gy, J/kg).

Regardless of the units and quantity chosen to describe a calibration, all photon-emitting sealed BT sources are calibrated in terms of output (kerma rate, dose rate, or exposure rate) in air at a distance from the source on its transverse bisecting plane. Much like superficial x-ray beam calibration, a calibrated ion chamber (Figure 21.8) is used to measure the BT source output in a free-air geometry in which the source and chamber are suspended in air in a large room.

Output specification

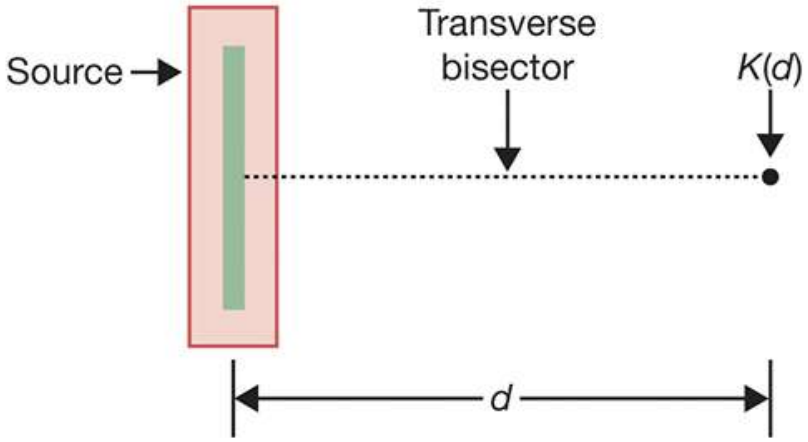


Conditions

1. Large distance *d*: $L << d$, $D << d$
2. Free in space
   - Measured in air
   - Corrected for air attenuation
   - Corrected for scattering from air, walls, etc.

A

Air-kerma strength: S_k



$S_k = K(d) \bullet d^2$

where $K(d)$ is air-kerma rate in free space on transverse bisector of source at large distance $d >> L$

B

Units: 1 μGy • m^2 • h^{-1} = 1 cGy • cm^2 • h^{-1} = 1 U

FIGURE 21.8 A. Illustration of a free-air geometry for measuring brachytherapy source strength in terms of a radiation output quantity such as air-kerma. In practice, the source and cavity chamber are suspended in air in a large room and separated by 20 to 100 cm (which must be large in relation to the detector and source dimensions). The measured air-kerma must be corrected for photon scattering from walls, floor, and ceiling and for photon scattering and attenuation by the intervening air. B. Definition of air-kerma strength. For an actual source, the air-kerma rate must be measured at a distance, d, which is large in relation to the source dimensions.

Air-Kerma Strength

In North America, photon-emitting source strength is specified in terms of air-kerma strength, denoted by S_K, a practice that was introduced by the AAPM in 1987.[78] The AAPM[5] currently defines S_K as the air-kerma rate, $\dot{K}_{\Delta,air}(d)$ at distance d, in vacuo and due to photons of energy greater than Δ, multiplied by the square of this distance, d^2.

$$S_K = \dot{K}_{\delta,air}(d) \cdot d^2 \qquad (21.9)$$

d is the distance from the source center to the point of air-kerma rate specification (usually but not necessarily the point of measurement), which must be on the transverse plane of the source (the plane normal to the long axis of the source that bisects its radioactivity distribution). S_K is independent of specification distance so long as d is large relative to the maximum linear dimension of the radioactivity distribution. $\dot{K}_{\Delta,air}(d)$ is usually inferred from transverse plane air-kerma rate measurements performed in a free-air geometry (see Figure 21.8) at distances large in relation to the maximum linear dimensions of the detector and source, typically of the order of 1 m. The "in vacuo" qualifier (equivalent in meaning to "in free space") means that $\dot{K}_{\Delta,air}(d)$ must be specified as if the source and small mass of air, producing ionization at distance d, were immersed in a vacuum of infinite extent. Air-kerma rate measurements must be corrected for photon attenuation and radiation scattering by the surrounding air as well as for scattering from nearby objects. The energy cutoff, Δ, is intended to exclude low-energy or contaminant photons (eg, characteristic x-rays originating in the outer layers of steel or titanium source cladding[79]) that increase $\dot{K}_{\Delta,air}(d)$ without contributing significantly to dose at distances greater than 0.1 cm in tissue. The value of Δ is typically 5 keV for low-energy photon-emitting BT sources. The unit of air-kerma strength is $\mu Gy \cdot m^2$/hour and is often denoted in the literature by the symbol "U," where 1 U = 1 $\mu Gy \cdot m^2$/hour.

Air-kerma strength is numerically (but not dimensionally) equal to the quantity reference air-kerma rate, $\dot{K}_{ref}$, a very similar quantity defined by the ICRU[3] and used outside North America. $\dot{K}_{ref}$ is defined as the air-kerma rate in free space at a reference distance, l (taken to be 1 m), on the transverse axis; it has units of μGy/hour at 1 m. Thus, $\dot{K}_{ref} = S_K/l^2$. The procedures for standardizing and measuring $\dot{K}_{ref}$ and S_K are identical.

The U.S. National Institute of Standards and Technology (NIST) maintains primary S_K standards for commercially available ^{137}Cs sources,[80] LDR ^{192}Ir seeds,[81] and all ^{103}Pd, ^{131}Cs, and ^{125}I seeds.[82] A *primary standard* is an instrument against which all other S_K measurement devices, called secondary or tertiary standards, must be intercompared. Primary standards are designed to permit inference of air-kerma values from the measured charge and instrument design using first principles. For ^{137}Cs and ^{192}Ir sources, the S_K standard is based on transverse-axis air-kerma measurements using spherical ion chambers with carbon walls[80,81]—the same instruments used to maintain the ^{60}Co teletherapy air-kerma standard. For low-energy interstitial seeds, a special free-air chamber,[82] called the wide-angle free-air chamber (WAFAC), is used. BT sources calibrated directly by the NIST standard or one of the AAPM-Accredited Dosimetry and Calibration Laboratories (ADCLs) are said to have *directly NIST-traceable calibrations*. Sources that are calibrated against sources or ion chambers, which themselves have directly traceable NIST calibrations, are said to have *indirectly NIST-traceable* calibrations. The Xoft eBT source has its own air-kerma standard based on the Lamperti free-air chamber for low-energy x-ray beams.[83] Because accurate estimation of the air attenuation correction for 50-kVp x-rays is conceptually and technically challenging, NIST chose to specify eBT source strength in terms of $\dot{K}_{air}$(50 cm), the air-kerma rate in air (rather than free space) at 50 cm source-to-detector distance, rather than S_K. For a more detailed description of air-kerma–based standards, measurement techniques, and traceability requirements, the reader is referred to a review by Sander.[84] The AAPM recommends[85] that individual clinics using BT sources maintain instrumentation able to make indirectly traceable calibration measurements for verification of vendor-supplied calibrations.

Kerma (kinetic energy released in the matter of interest), K_x, is the ratio $\Delta E_{tr}/\Delta m$, where ΔE_{tr} is the total kinetic energy transferred to charged particles by photon interactions with atoms in small mass, Δm, of medium x.[86] For photons, ΔE_{tr} includes the initial kinetic energies of any secondary charged particles (eg, Compton electrons, photoelectrons, and positrons) liberated by Compton, photoelectric, and pair production interactions. Kerma is defined only for indirectly ionizing radiation (eg, photons and neutrons) and quantifies the transfer of energy from these radiation fields to matter. It takes the same units (cGy and Gy) as the related quantity absorbed dose. Although kerma can be specified in any medium x, usually air medium (x = air) is assumed for radiation metrology. K_{air} replaces the obsolete quantity exposure and is closely related to absorbed dose, D, the ratio, $\Delta E_{ab}/\Delta m$, where ΔE_{ab} is the energy imparted to Δm by the radiation field. Because the secondary electrons released by photon collisions may travel a significant distance before depositing their energy and may convert some of their kinetic energy to bremsstrahlung radiation, D_{air} and K_{air} are not necessarily equal. When kerma remains relatively constant over the range of the secondary electrons, a special condition, secondary charged particle equilibrium (CPE), exists.[66,87] When the CPE is obtained, the rates of energy absorption and energy transfer are approximately equal so that kerma closely approximates absorbed dose:

$$D_{\text{air}} = X \cdot \left(\frac{W}{e}\right) = K_{\text{air}} \cdot (1 - g) \qquad (21.10)$$

where X represents the quantity exposure. The quantity (W/e) is the average energy imparted to air per ion pair created and is a constant, independent of photon energy: (W/e) = 33.97 eV/ion pair = 33.97 J/C = 0.876 cGy/R.[88] The factor g is the fraction of kinetic energy transferred to the medium converted back to radiant energy (photons) by the bremsstrahlung process; g is less than 0.001 at BT energies and is usually ignored, further simplifying Eq. 21.10. Most BT dose calculation algorithms and dosimetric analyses assume that CPE occurs and that dose, D_{med}, can be well approximated by kerma, K_{med}, everywhere. Although generally valid, CPE can be expected to break down in the presence of steep dose gradients near sources,[89] near metal-tissue interfaces,[90] and within the active elements of thin, bounded detectors.[91] The combination of CPE failure and β-ray transmission gives rise to $(D_{\text{med}}/K_{\text{med}})$ ratios that deviate from unity by 10% to 50% at 0.4 to 1.5 mm from the surface of lightly encapsulated HDR ^{192}Ir sources.[92]

Activity

The quantity activity, A, is defined as the rate of nuclear disintegration or transformation within a radioactive source. The contemporary unit of activity is the Becquerel (1 Bq = 1 disintegration/s). We will freely use the more traditional but obsolete unit, the curie (1 Ci = 3.7×10^{10} disintegrations/s = 3.7×10^{10} Bq). A more convenient multiple of the curie, the millicurie, is defined as 1 mCi = 10^{-3} Ci = 3.7×10^{7} disintegrations/s. Each disintegration represents the spontaneous transformation of an atom from one nuclear state to another. For most BT radionuclides, such transformations of nuclear state give rise to photons in the form of unconverted γ-rays, annihilation photons, characteristic x-rays, and bremsstrahlung photons. Activity is measured by counting the number of photons, β-particles, or other particles emitted by an unencapsulated point source of the radionuclide by means of scintillation or coincidence counters, from which its activity is inferred.[93] For sealed BT sources, A refers to activity contained inside the sealed source.

Contained activity, as defined in this strict sense, is no longer used in BT dosimetry. However, activity continues to serve as the basis for treatment specification and dosimetry of unsealed radiopharmaceuticals used for diagnosis and therapy and may play a future role in dosimetry of sealed β-emitting sources for intravascular BT and other clinical applications. NIST maintains contained activity standards for a wide variety of radionuclides in aqueous solution.[94]

The activity, A, of a radioactive nuclide–emitting photons and the air-kerma rate in free space, $\dot{K}_{\Delta}(r)$ (in Gy/s) at distance r (in meters) due to photons of energy greater than Δ, are related by a fundamental quantity, the air-kerma rate constant, $(\Gamma_{\Delta})_{K}$, defined as follows[86]:

$$\left(\Gamma_{\delta}\right)_{\mathrm{K}} = \frac{\dot{K}_{\delta}\left(r\right)\cdot r^{2}}{A}\ \text{air-kerma rate} \qquad (21.11)$$

$$\text{constant}\left(\mathrm{m}^{2}\cdot\mathrm{Gy}\cdot\mathrm{Bq}^{-1}\cdot\mathrm{s}^{-1}\right)$$

A closely related fundamental quantity, not used nowadays but of historical importance, is the exposure rate constant, $(\Gamma_{\Delta})_{\mathrm{X}}$,

$$\left(\Gamma_{\delta}\right)_{\mathrm{X}} = \frac{\dot{X}_{\square}\left(r\right)\cdot r^{2}}{A}\ \text{exposure rate} \qquad (21.12)$$

$$\text{constant}\ (\mathrm{cm}^{2}\cdot\mathrm{R}\cdot\mathrm{mCi}^{-1}\cdot\mathrm{h}^{-1})$$

$(\Gamma_{\Delta})_{\mathrm{X}}$, which equals to the exposure rate in *R*/hour at 1 cm from a 1-mCi point source, describes the rate at which air is ionized as a result of the emission of photons resulting from radioactive decay. The energy cutoff Δ eliminates low-energy bremsstrahlung and characteristic x-rays from consideration that are always absorbed within any practical source. The precise value of Δ depends on the application; it is usually assumed to be about 10 keV. Because $(\Gamma_{\Delta})_{\mathrm{X}}$ is defined in terms of an isotropic point source with exposure rates corrected for air attenuation and scattering, inverse-square law applies exactly. Thus, $(\Gamma_{\Delta})_{\mathrm{X}}$ is independent of the distance *r* used in Eq. 21.12.

$(\Gamma_{\Delta})_{\mathrm{X}}$ depends only on the number and energy of the photons emitted per disintegration. Suppose there are *N* different photons emitted per disintegration with energies E_1, E_2, …, E_{N} in units of MeV, and each nuclear decay emits P_{i} photons of energy E_{i}, where $i = 1, \ldots, N$, then $(\Gamma_{\Delta})_{\mathrm{x}}$ can be calculated by:

$$\left(\Gamma_{\square}\right)_{\mathrm{X}} = 193.7\cdot\sum_{i=1}^{N} P_{i}\cdot E_{i}\cdot\left(\mu_{\mathrm{en}}/\rho\right)_{i}^{\mathrm{air}} \qquad (21.13)$$

where $\left(\mu_{\mathrm{en}}/\rho\right)_{i}^{\mathrm{air}}$ is the mass-energy absorption coefficient (in units of cm^2/g) for air at energy *Ei*. A detailed derivation of this fundamental relationship is given elsewhere.[95,96] $(\Gamma_{\Delta})_{\mathrm{X}}$ and $(\Gamma_{\Delta})_{\mathrm{K}}$ are fundamental properties of the radionuclide's

unencapsulated photon spectrum that apply only to an ideal point source and neglect many significant properties of real sources, such as self-absorption, filtration, and extension.

Integrated Reference Air-Kerma

The ICRU[97] recommends total reference air-kerma (TRAK), which is defined in terms of air-kerma strength, as a prescription or reporting quantity. TRAK, symbolized by K_{ref} is given by:

$$K_{\text{ref}} = \sum_{i=1}^{N} \left(S_{\text{K},i} / l^2 \right) \cdot t_i \qquad (21.14)$$

where $S_{K,i}$ and t_i are the air-kerma strength and treatment time in hours, respectively, of the ith source, and l is the reference distance (taken to be 1 m or 1 cm). Thus, 1 unit of TRAK = 1 cGy at 1 cm = 1 μGy at 1 m. TRAK is related to obsolete quantities of milligram radium hour (mg-h) and milligram radium equivalent hour (mgRaEq-h):

$$K_{\text{ref}} = \begin{cases} \text{mg-h} \cdot 6.754 & \text{for filtration } t = 1 \text{ mm Pt} \\ \text{mgRaEq-h} \cdot 7.227 & \text{for filtration } t = 0.5 \text{ mm Pt} \end{cases} \qquad (21.15)$$

Intracavitary treatment systems[11] historically based on ^{226}Ra tubes (1-mm Pt encapsulation) typically use mg-h, whereas systems based on ^{137}Cs or other radium substitutes prescribe therapy in units of mgRaEq-h. Because of the difference in platinum filtration assumed by these 2 mg–based quantities, numerically identical prescriptions can deliver quantities of TRAK that differ by 7%. The use of TRAK as an integrated output reporting quantity eliminates this 7% ambiguity that has confused comparison of different implant systems since the appearance of radium-substitute sources for BT.

Classic Dose Calculation Formalism: Isotropic Point Source

Consider an unencapsulated point source as illustrated in Figure 21.9. Because this source has no extension, there is no attenuation of the emitted radiation by the source itself. Isotropy (see Figure 21.2) implies that photons are emitted with equal likelihood in all directions and travel in straight lines. In reality, actual BT sources are encapsulated, have finite dimensions, and are usually cylindrically rather than spherically symmetric. The dose rate, $\dot{D}(r)$ (cGy/hour), at distance r (cm) in the water equivalent medium surrounding the source is given by:

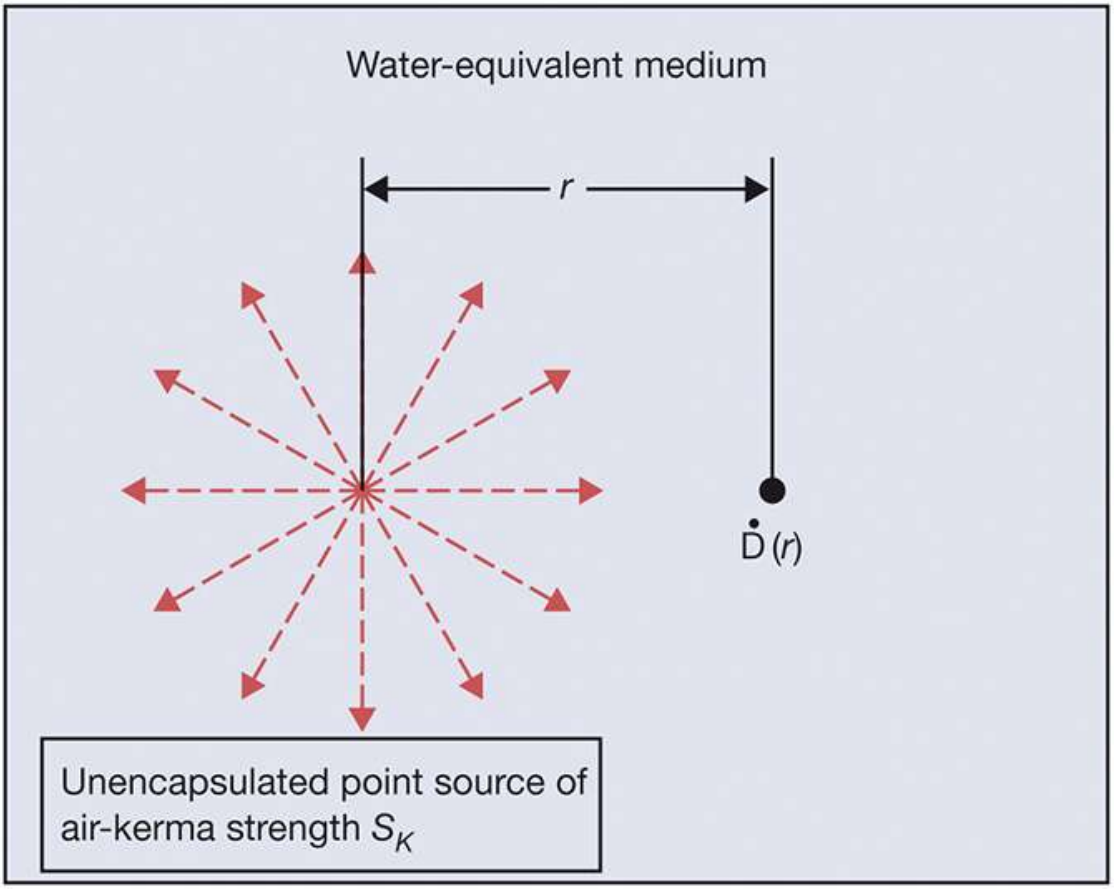


FIGURE 21.9 Unencapsulated point source of strength S_K immersed in an unbounded water equivalent medium.

$$\dot{D}_{med}(r) = S_K \cdot \frac{\overline{(\mu_{en}/\rho)}^{med}_{air}}{r^2} \cdot T(r) \qquad (21.16)$$

The inverse-square law term corrects for the difference in dose specification distance, r, and the 1-cm reference point is assumed by the units of air-kerma strength. The quantity $\overline{(\mu_{en}/\rho)}^{med}_{air}$ is the ratio of mass-energy absorption coefficients in medium to that in air averaged over the photon spectrum in free space. This correction, equal to $\dot{K}_{med}/\dot{K}_{air}$ in free space, is a consequence of the fundamental relationship between particle fluence and dose.[95,96] It corrects for the efficiency with which the medium extracts energy from the emitted photons compared with air. For all radionuclides emitting photons with energies greater than 200 keV, including all radium substitutes, $\overline{(\mu_{en}/\rho)}^{med}_{air}$ has the value 1.11 in water medium.

The last term of Eq. 21.16—the kerma-to-dose conversion factor, $T(r)$—describes the net influence of primary photon attenuation and build-up of scattered photons in the surrounding medium. Sometimes, this factor is termed the *effective attenuation factor* or the *scatter build-up factor*.

$$T(r) = \frac{\text{Dose in medium}}{\text{Medium} - \text{kerma in free space}} \qquad (21.17)$$

$$= \left.\frac{\text{Exposure in medium}}{\text{Exposure in air}}\right\} \begin{array}{l}\text{at distance } r \\ \text{from a point source}\end{array}$$

Figure 21.10 shows $T(r)$ for several high-energy radionuclides as well as for a few low-energy radionuclides. For high-energy radionuclides, $T(r)$ deviates less than 5% from unity (1.00) out to distances, r, of 5 cm. Numerous tabulations of $T(r)$ are available in the literature; those of Meisberger and colleagues,[98] Berger,[99] and Van Kleffens and Star[100] are among the best known. Most of these data are derived from theoretic photon transport calculations. The classic semiempirical model assumes that $T(r)$ is a function only of the radionuclide photon spectrum and that a single data set (eg, for ^{192}Ir) can be used for all ^{192}Ir source models, regardless of their construction.

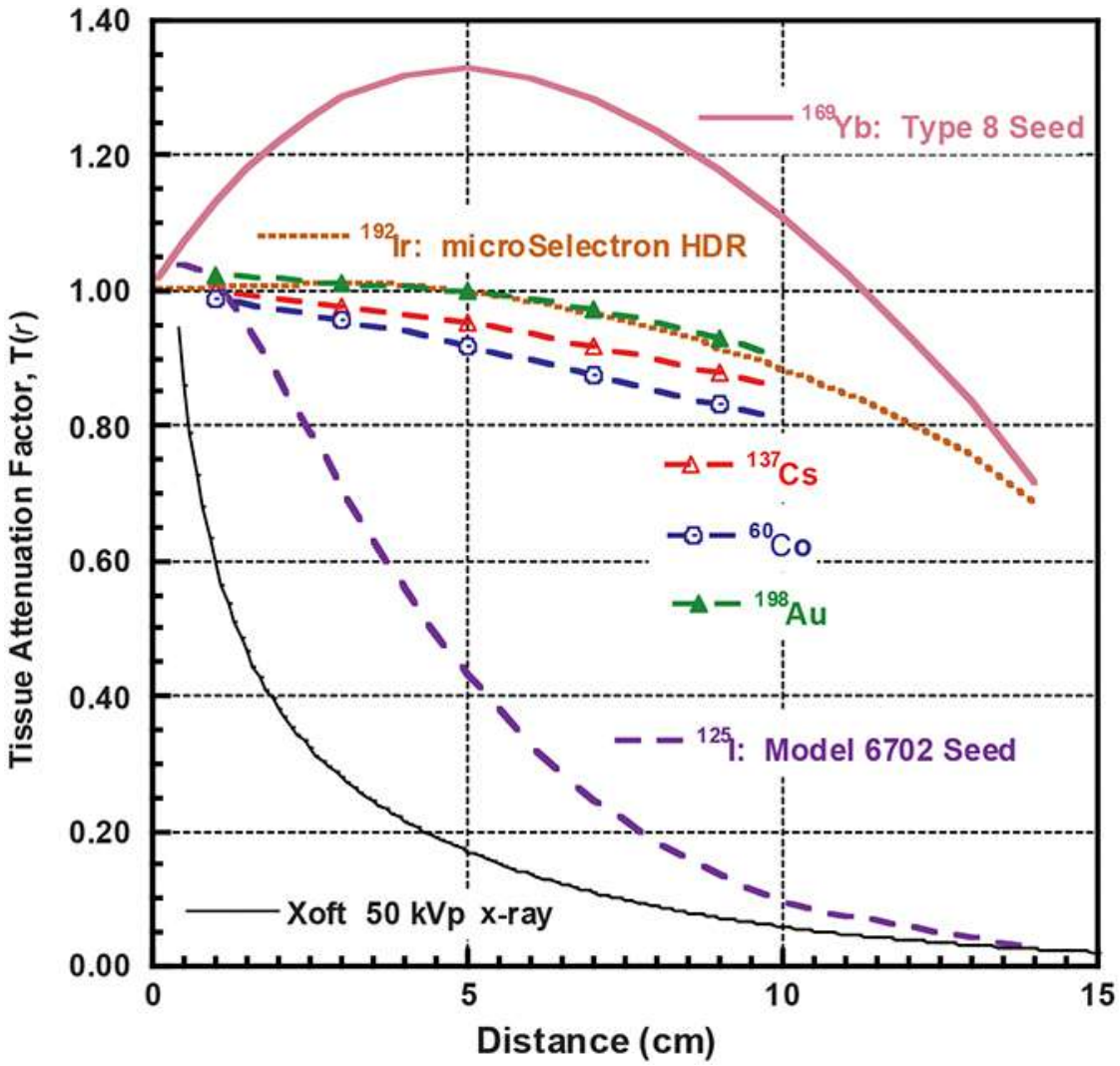


FIGURE 21.10 Photon attenuation and scatter factors, $T(r)$, for a number of brachytherapy radionuclides. The data for ^{137}Cs, ^{198}Au, and ^{60}Co are from the classic paper by Meisberger et al.[98] The high-dose rate (HDR) ^{192}Ir, Model 6702 ^{125}I, and Xoft 50=kVp x-ray $T(r)$ are from Daskalov et al,[394] Dolan et al,[136] and Hiatt et al.[395]

Modeling of Source Anisotropy: The Anisotropy Factor

Despite its simplicity, the classic isotropic point-source model (Eq. 21.16) accurately predicts the transverse-axis dose rate distributions of most actual radium-substitute sources. Simply by using an output quantity to calibrate the source, rather than contained activity, A, the influence of its internal structure (filtration and self-absorption) has been implicitly accounted for. Any uncertainties in $\{E_i, P_i\}_{i=1}^{N}$ (which are large for many radionuclides) and filtration corrections would directly degrade dose calculation accuracy. In addition, fundamental activity measurements are technically difficult for the high-intensity sources used in BT. For these reasons, contained activity does not play a role in photon BT dosimetry. In contrast, Eq. 21.16 infers dose rate from a quantity measured outside the source, which is not influenced significantly by knowledge of the unfiltered

photon spectrum. The required quantities, $\overline{(\mu_{\square\square}/\rho)}^{\text{med}}_{\text{air}}$ and $T(r)$, are ratios and are, therefore, insensitive to errors in the assumed spectrum.

Practically, all BT sources are cylindrical, giving rise to anisotropic dose distributions. In addition, some sources, especially those used in intracavitary BT, have ALs that are comparable to typical calculation distances. Thus, the dose rate, $\dot{D}(r, \theta)$, around a BT source depends on both distance r, and polar angle, θ (Figure 21.11). $\dot{D}(r, \theta)$ may deviate significantly from the transverse-axis dose rate, $\dot{D}(r, \pi/2)$, predicted by Eq. 21.16, especially near the long axis of the seed.

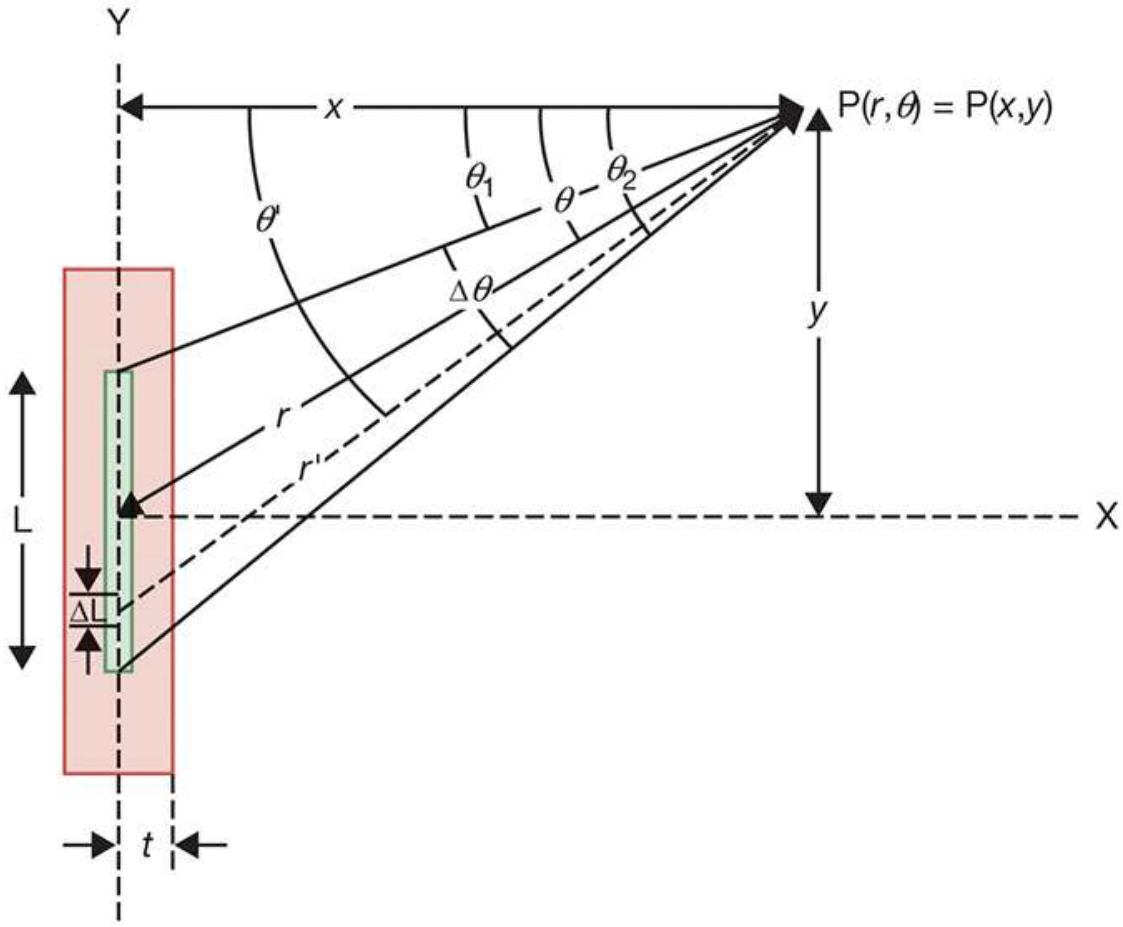


FIGURE 21.11 A typical encapsulated line source, illustrating calculation of dose rate at point P at (x, y) relative to the source center by the Sievert integral method. The active length and radial encapsulation thickness are denoted by L and t, respectively. The distances x and y are referred to as "distance away" and "distance along," respectively, in the literature.

In the case of implants consisting of many randomly oriented seeds with ALs less than the minimum distance of interest, Eq. 21.16 will accurately represent the multiple-seed dose distribution if an average correction for single-seed dose anisotropy is applied.[101] This

correction factor, which the TG-43 protocol refers to as the 1D anisotropy function, $\phi_{an}(r)$, is defined by averaging the dose at each fixed distance r with respect to solid angle, Ω:

$$\phi_{an}(r) = \frac{\text{Average dose at } r}{\text{Transverse-axis dose at } r} = \frac{\int_{4\pi} \dot{D}(r,\theta) \cdot d\Omega}{4\pi \dot{D}(r,\pi/2)} \cdot \qquad (21.18)$$

$$= \frac{\int_0^{\pi} \dot{D}(r,\theta) \cdot \sin\theta \cdot d\theta}{2 \cdot \dot{D}(r,\pi/2)}$$

Often, a distance-independent average value of $\phi_{an}(r)$, called the anisotropy constant, $\bar{\phi}_{an}$, is used. Incorporating this average correction into Eq. 21.16, leads to:

$$\dot{D}_{med}(r) = \frac{S_K \cdot \overline{(\mu_{en}/\rho)}_{air}^{med}}{r^2} \cdot T(r) \cdot \bar{\phi}_{an} \qquad (21.19)$$

For early radium-substitute sources, $\bar{\phi}_{an}$ was often evaluated by measuring relative photon fluence in air at relatively large distances (30-100 cm) using a NaI or GeLi scintillation detector.[55,102]

Equation 21.19 implies that source strength should be increased by a constant fraction ranging from 2% (^{192}Ir seeds) to 10% (^{103}Pd seeds) to correct for polar anisotropy effects. Lindsay et al[103] compared prostate implant 3D dose distributions derived from the isotropic point-source model, $\dot{D}(r)$, to those derived from the full 2D single-source dose calculation model, $\dot{D}(r, \theta)$. Based on voxel-by-voxel comparisons, they found that the isotropic point-source model introduced errors exceeding 10% of the D_{90} in 8% and 33% of the target volume for the model 6711 ^{125}I and model 200 ^{103}Pd sources, respectively. Corbett and colleagues[104] found that despite large local dose distribution differences, including 2D anisotropy effects did not alter the dose-volume histogram (DVH): Neither the V_{100} nor the margin between D_{100} and prostate boundary was altered significantly. For volume implants consisting of parallel arrays of ^{192}Ir seeds, a similar finding has been reported.[101]

Dose Calculation for Extended Sources: The Sievert Integral Model

Dose distributions around larger sources, such as intracavitary tubes and interstitial needles, are calculated by partitioning the extended source into a set of point sources to which corrections for distance, oblique filtration, attenuation, and scattering are applied separately. By summing these point-source contributions, the dose at point P can be estimated. This class of algorithms, first described by Rolf Sievert in 1921,[105] is known as the Sievert integral algorithm, or more generally, the 1D pathlength model.[95,106]

Assume that the source illustrated in Figure 21.11 has an air-kerma strength, S_K, and contained activity, A. The classic Sievert integral approximates the cylindrical active core by a line of radioactivity positioned along its axis. The axial length of the core is called the active length, L. Oblique filtration is modeled by assuming that the capsule reduces dose by exponential attenuation using an effective filtration coefficient, μ'. The dose rate $\Delta\dot{D}(x, y)$ at point (x, y) from the incremental source ΔL located at angle θ is

$$\Delta\dot{D}(x,y) = S_K \cdot \frac{\Delta L}{L} \cdot e^{\mu' \cdot t} \cdot \frac{\overline{(\mu_{en}/\rho)}^{med}_{air}}{(x/\cos\theta)^2} \cdot T(x/\cos\theta) \cdot e^{-\mu' \cdot t/\cos\theta} \quad (21.20)$$

By summing over all these incremental sources (ie, integrating with respect to θ') and transforming to polar coordinates, we obtain the Sievert integral:

$$\dot{D}(r,\theta) = \frac{S_K \cdot \overline{(\mu_{en}/\rho)}^{med}_{air} \cdot e^{\mu' \cdot t}}{L \cdot r \cdot \cos\theta} \cdot \int_{\theta_1}^{\theta_2} e^{-\mu' t \cdot \sec\theta} \cdot T(x \cdot \sec\theta) \cdot d\theta \quad (21.21)$$

The extra $e^{\mu' t}$ term outside the integral is needed to avoid global "double correction" for filtration.

Variants of Eq. 21.21 applicable to the regions near the source capsule ends are available. Numerous improvements to the basic model have been introduced over the years,[107,108] including modeling of photon absorption by the source core, extension to noncylindrical sources, generalization to radioactivity distributed over a volume,[4] extension to low-energy sources,[106] and treatment of applicator shielding and attenuation.[109,110]

The Sievert integral model was widely used to model 2D dose distributions around ^{137}Cs tubes and needles for clinical treatment planning prior to acceptance of the TG-43 table lookup method. Both experimental[111,112] and Monte Carlo studies[4,113] have demonstrated that it accurately predicts dose rate distributions in this energy range. When the filtration coefficient μ' is approximated[114] by the linear energy absorption coefficient, μ_{en} (0.023/mm for steel-clad ^{137}Cs sources), maximum errors are no larger than 8% and are much smaller (less than 3%) near the transverse axis. Published dose rate distributions derived from the Sievert model, tabulated in terms of distances away and along, are available for several

types of ^{137}Cs sources[4,115] and ^{226}Ra sources.[116] Williamson[106] showed that the classic Sievert integral gives rise to large errors (20%-37% maximum error, 7%-16% average error) when applied to lower energy sources of ^{192}Ir, ^{169}Yb, and ^{125}I. Although accuracy can be improved by modifying the basic model,[106] classic semiempirical models should be used cautiously at photon energies below ^{137}Cs (0.66 MeV). Tabulated dose rate distributions derived from direct measurement or Monte Carlo simulation are preferable for these sources.

If the encapsulation thickness is set to zero (t = 0) in Eq. 21.21, the Sievert integral reduces to a simple closed-form analytic expression:

$$\dot{D}(x,y) = S_K \cdot \overline{\left(\mu_{en} / \rho\right)}_{air}^{med} \cdot \frac{\Delta\theta}{L \cdot x} \qquad (21.22)$$

where $\Delta\theta$ is the angle, in radians, subtended by the active length, L, with respect to the point of interest (Figure 21.11). When the interest point lies on the transverse axis (y = 0), then $\Delta\theta = 2 \cdot \tan^{-1}(L/2x)$, where $\tan^{-1}$ denotes the inverse tangent or arctan function. Angles must be specified in units of radians rather than degrees (180° = π radians). This approximation is extremely useful as a manual calculation aid and is highly accurate near the transverse axis of lightly encapsulated ^{137}Cs sources.

Figure 21.12 shows that as the distance $r = \sqrt{(x^2 + y^2)}$ becomes large in relation to active length, L, Eq. 21.22 reduces to the point-source formula. For distances less than L (1.5 cm for intracavitary tubes), the use of Eq. 21.16 will yield errors of at least 10%. For distances greater than 1.5L (2.5 cm for gynecologic tubes), the point-source approximation is accurate within 5%.

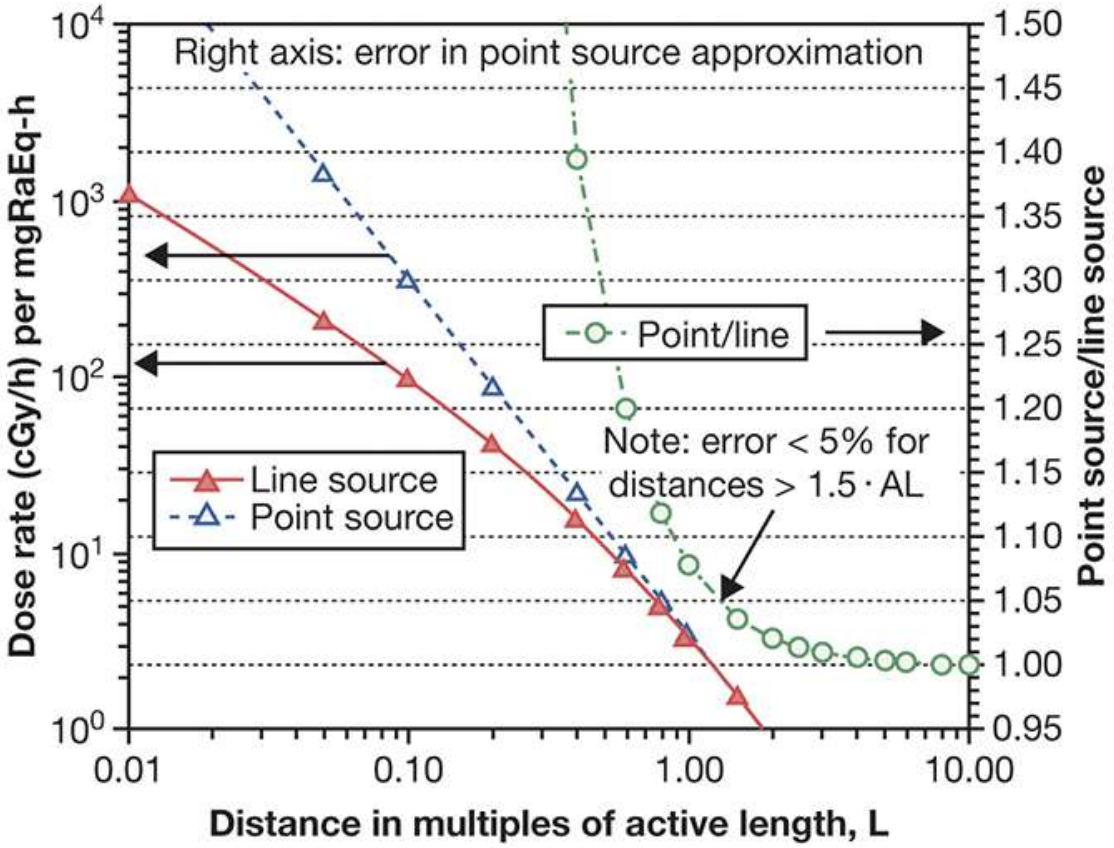


FIGURE 21.12 Error in the isotropic point source model relative to the line source model Eq. 21.22 as a function of transverse-axis distance expressed in multiples of active length (AL).

Source-Specific Dosimetric Characterization

The classic dose calculation models assume that the parameters $T(r)$ and $\overline{(\mu_{en}/\rho)}^{wat}_{air}$ depend only on the radionuclide used. This assumption began to break down with the introduction of ^{125}I interstitial seeds in the early 1970s, as this 30-keV x-ray emitter clearly fell outside the scope of validated analytic models.[12] While ^{125}I dose distributions derived from semiempirical models were published[117] and widely used, it was recognized[55] that internal seed structure could modulate the emitted photon spectrum and significantly alter the absorbed dose distribution. The growing use of ^{125}I and the introduction of a primary exposure standard in 1985[118] motivated investigations in the quantitative determination of source-geometry and source-construction-material–specific dosimetry parameters for each type of source. Currently, both experimental methods and sophisticated computational dosimetry approaches are routinely used to derive such source-specific parameters. Another characteristic of quantitative dose estimates is traceability to closely related primary standards, currently the air-kerma strength standards maintained by NIST. Finally, the total uncertainty[119] of the estimated dose, including both type A (random) and type B (systematic), typically less than 10%, must be well understood and validated.

Experimental Dosimetry Approaches

Direct use of measured dose rates in BT for treatment planning purposes is a relatively recent phenomenon, beginning in the mid-1980s. Historically, dose measurement was thought to be so difficult and intrinsically inaccurate that even simplistic theoretic models were more reliable. BT dose measurement does indeed place severe demands on detectors because the dose distributions are characterized by large dose gradients, a large range of dose rates, and relatively low photon energies. The most severe measurement artifact is the exquisite sensitivity of detector response to positioning errors; measurement of dose near a point source with 2% accuracy requires that the source-to-detector distance be specified with accuracy of 20, 50, 100, and 200 μm, respectively, at distances of 2, 5, 10, and 20 mm. Thus, a good detector system must have small size, high sensitivity, a stable and reproducible response, and reasonably flat energy response. Finally, a useful system should be sufficiently convenient that adequate spatial sampling of high-gradient dose distributions is feasible.

Commonly used single-element dose detectors include TLDs, small ion chambers, diode detectors, solid-state detectors, inorganic scintillators, and plastic scintillators. RCF[120-122] and plastic scintillator sheets[123] have been investigated as planar dose measurement systems. 3D dose measurement technologies under investigation include liquid scintillation cocktails[124] and polymer gel dosimetry[125,126] using either magnetic resonance imaging (MRI) or optical transmission tomography to quantify the detector signal. For various reasons, most of these approaches have not met with widespread acceptance by quantitative dosimetry investigators. In the case of the 2D/3D dosimetry media, the techniques have not been sufficiently developed that they can compete with the 5% total uncertainty supported by TLD-100. One consideration in selecting a detector for BT dosimetry is minimizing energy response artifacts, which arise from compositional differences between water and the detector and can result in variation of detector reading/unit dose in medium as the photon spectrum changes with position.

Silicon diodes have proven to be precise and accurate dosimeters for measuring relative dose distributions around low-energy sources, for example, ^{103}Pd and ^{125}I, as their sensitivity is nearly independent of the measurement point location.[127,128] However, for higher energy BT sources, variations in sensitivity with position in the phantom as large as 15% for ^{137}Cs and 75% for ^{192}Ir have been reported.[129] While plastic scintillation detectors have a well-established role in quantitative β-emitting eye plaque and applicator dosimetry,[130] the current focus of scintillation detector research is tertiary dose measurement applications, such as quality assurance (QA) and in vivo dosimetry, rather than reference quality dose measurement.[131]

LiF TLD, while hardly an ideal technology, has emerged as the best compromise between convenience and quantitative accuracy and is currently the de facto standard of practice[49]: All of the consensus data sets referenced by the AAPM TG-43 reports[5,48,49] rely on TLD-100. Quantitative TLD BT was developed and first validated by a 3-year (1987-1989) NCI-funded multi-institutional research effort, the Interstitial Collaborative Working Group (ICWG).[132] Using TLD-100 chips and powder capsules, embedded in machined solid-water phantoms to ensure positional accuracy, the ICWG developed the procedures used to this

day, including TLD dose calibration and energy response corrections, for making quantitative estimates of absolute dose rates in water. For the ^{125}I and ^{192}Ir sources then available, independent transverse-axis dose rate measurements showed excellent agreement among the three collaborating institutions, validating the TLD measurement methodology.[132] More complete 2D dose distributions about ^{125}I, ^{192}Ir, and ^{103}Pd BT sources[127,133,134] soon followed. While good agreement among the different measurements was observed, for ^{125}I seeds, there were substantial differences (10%-14%) between the measured dose rates and classically computed dose rates when normalized to the available air-kerma strength standard,[118] $S_{K,N85}$. However, good agreement between the classic and experimental approaches was observed for ^{192}Ir.

Estimation of the absorbed dose sensitivity, $S_{AD,med}(Q)$, has emerged over the past decade as the dominant source of uncertainty for TLD. For a given BT energy spectrum, Q, $S_{AD,med}(Q)$ is the TLD reading, $M(Q)$, per unit dose in medium, $D_{med}(_Q)$ at the TLD center in its absence:

$$S_{\mathrm{AD,med}}(Q)=\frac{M(Q)}{D_{\mathrm{med}}(Q)}=\left(\frac{M(Q)}{\overline{D_{\mathrm{TLD}}}(Q)}\right)\left(\frac{\overline{D_{\mathrm{TLD}}}(Q)}{D_{\mathrm{med}}(Q)}\right)=\frac{1}{k_{\mathrm{bq}}(Q)f(Q)} \quad (21.23)$$

where $\overline{D_{\mathrm{TLD}}}$ is the dose absorbed by the TLD medium averaged over its volume. As Eq. 21.23 shows, it can be factored into two components: the absorbed dose energy dependence, $f(Q)$, which is due to differences between energy deposition in the TLD material and the medium it displaces, and the intrinsic energy dependence, $k_{bq}(Q)$, which depends on the TLD signal formation process. $f(Q)$ can be calculated by Monte Carlo or cavity theory, but $k_{bq}(Q)$ can only be measured. Until recently, most TLD studies for ^{125}I and ^{103}Pd seeds adopted a generic absorbed dose-response factor of $S^{\mathrm{rel}}_{\mathrm{AD,med}}=1.41$ (relative to 4- or 6-MV x-rays used to calibrate TLDs) based upon old ICWG measurements,[135] which ignored the factorization above and many other subtleties by modern standards. Most Monte Carlo studies[136,137] neglected or otherwise assumed relative $k_{bq}(Q)$ = 1.0. Despite these uncertainties, the average agreement between TLD and Monte Carlo dose rates at 1 cm was 2% for 25 ^{125}I studies and 14% for ^{103}Pd studies.[77] However, subsequent measurements (see Table III in Reed et al[138] for a nice summary) over the past decade show that k_{bq}^{rel} values for ^{125}I to ^{103}Pd relative to megavoltage x-ray beams range from 0.93 to 0.87. Even for ^{192}Ir, $k^{\mathrm{rel}}_{\mathrm{bq}}\approx 0.95$ has been reported.[139] Rodriguez and Rogers[140] performed a rigorous Monte Carlo "reconstruction" of 24 published TLD-100 studies and found that universal k_{bq}^{rel} values of 0.931 and 0.922 for ^{125}I and ^{103}Pd, respectively, minimized the discrepancy between Monte Carlo and measured dose rates. Given the

possible dependence k_{bq}^{rel} on TLD structure and annealing/readout procedures, the most recent TG-43 guidance[49] states that additional research is needed before AAPM can take a position on whether or how to implement nonunity k_{bq}^{rel} into past and ongoing experimental consensus dosimetry studies. Thus, at minimum, a 5% (k = 1 corresponding to a 67% confidence interval) uncertainty must be included in uncertainty budgets for published experimental consensus data sets. This implies that with careful correction for TLD linearity, individual chip sensitivity, $f^{rel}(Q)$, and phantom corrections, absolute dose rate (cGy/hour in tissue per unit S_K) in water can be measured with a total uncertainty (k = 1) of 6%.[136,141] Should policies be put in place that reduce k_{bq}^{rel} uncertainty to 2%, TLD has the potential to achieve 3% uncertainties.[49]

Interest in RCF for BT dosimetry is growing, owing to its very high spatial resolution.[121] The need for improved (≈1 mm) spatial resolution is becoming more urgent as the field moves away from the determination of reference quality single-source distributions toward measurements in more complex geometries, including shielded applicators,[142] shielded eye plaques,[36] and, potentially, intensity-modulated BT. The value of RCF for quantitative dosimetry for HDR BT using higher energy photon sources[120] and β-emitting plaque therapy has long been appreciated.[143] The currently available EBT3 dosimetry media are much improved over their historical counterparts in terms of sensitivity, spatial uniformity, rapidity of film darkening, and flatness of energy response, making accurate HDR measurements more feasible (see §5.E[121] for a recent literature review). Low-energy seed RCF dosimetry is much more challenging. While doping the EBT3 active layer with alumina has been shown to diminish both intrinsic ($f_{bq}^{rel}(Q)$) and absorbed dose ($f^{rel}(Q)$) low-energy response artifacts, 20% to 30% variations in the 15 to 60 keV range continue to persist.[144,145] For example, 5% dose estimation accuracy about Xoft electronic source with EBT3 RCF was achieved, when energy-dependent dose-response curves were used to convert film readings into doses, which, in turn, required Monte Carlo simulations of the photon spectrum as a function of depth.[146]

Measured dose rate distributions using TLD are available for many common BT sources, including nearly all commercially available ^{125}I and ^{103}Pd sources (see the updated TG-43 report[5] and its supplements[49,147] for more comprehensive discussions). Measured dose rates are available for many ^{192}Ir LDR, HDR, and PDR sources as well as for many investigational sources.[148] For high-energy sources, the measurements are in close agreement with the classic semiempirical models: isotropic point-source and Sievert integral models.[4,95,106] For ^{125}I sources normalized to the $S_{K,N85}$ standard,[118] measured dose rates were found to be 10% to 20% lower than those predicted by Eq. 21.16.[149] A better agreement[77] was observed between classic models and measurements with calibrations traceable to the 1999 WAFAC standard ($S_{K,N99}$).[82] However, classic models such as the Sievert integral are not recommended for the low-energy source regime as they poorly predict low-energy source anisotropy and do not take into account modulation of the dose distribution by internal source geometry.[106]

Computational Dosimetry Methods: Monte Carlo Photon Transport Simulation

Concurrent with the above dosimetry developments, Monte Carlo photon transport techniques were being developed as tools for quantitative evaluation of single-source dose distributions. Based on an accurate and detailed geometric model of the internal source structure, photon histories can be generated and then evaluated to assess the absorbed dose. Monte Carlo techniques are now accepted as a reliable and probably the most accurate source of BT dosimetry data.[5,77] As illustrated in Figure 21.13, this theoretical method uses a digital computer to randomly select a small number (10^5-10^8) of photon trajectories or "histories." The geometric model must specify the location of all media boundaries and photon sources. By using probability distributions derived from total and differential cross sections, a photon is randomly constructed by following each photon from birth through successive scattering events and, eventually, to absorption or escape from the system. At each decision point, random sampling is used to decide the fate of the photon. The process of randomly constructing photon trajectories is equivalent to selecting photon histories from the set of all those possible by random sampling. To statistically estimate the dose rate at a specified point, the dose contributed by each simulated collision is estimated and then averaged over all collisions. Monte Carlo simulation techniques are reviewed in more detail elsewhere.[77] Because particle histories can be accurately and efficiently constructed even in the presence of complex 3D geometries, approximation free but statistically inexact solutions, derived from first principles, are possible for a wide range of geometrically complex but clinically relevant BT problems.

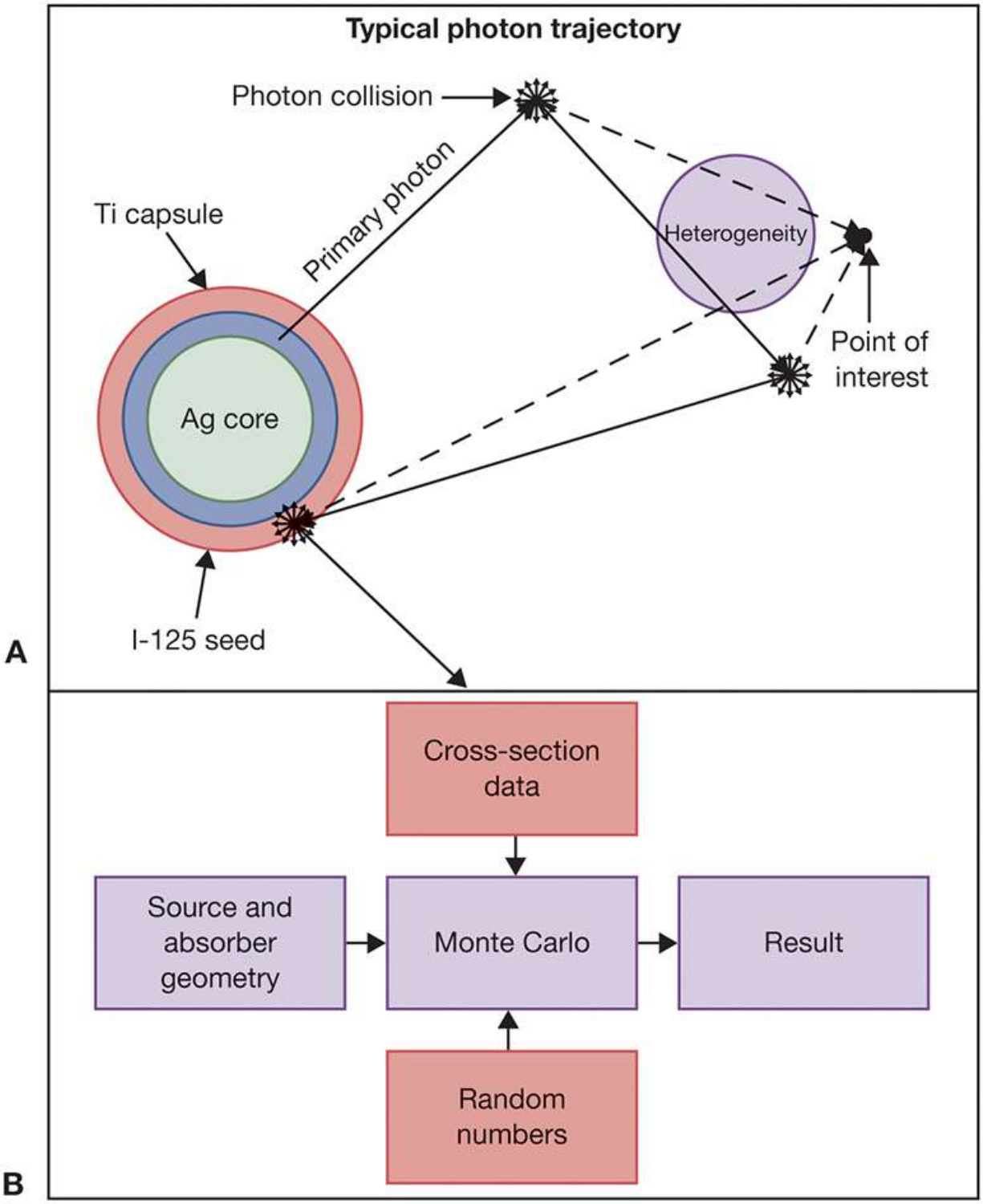


FIGURE 21.13 A. Two-dimensional representation of a typical photon history. The heavy solid lines illustrate the origin of the primary photon (randomly selected from the assumed distribution of radioactivity), and each successive collision, which is randomly selected from the competing collision mechanisms (photo effect, Compton scattering, and coherent scattering) is based on their relative probabilities. The dashed lines illustrate the problem of estimation (ie, calculating the probable contribution of each simulated collision to the point of interest). B. Functional diagram of a Monte Carlo code illustrating the required input data. Cross section data include total attenuation coefficients, total cross sections for each collision process, and differential cross

sections, which are used to randomly sample the distance between successive collisions, the interaction mechanism at each collision, and the angle and energy of the scattered photon leaving each collision, respectively. Sequences of random numbers are obtained from a "random number generator," a computer program designed to generate a pseudorandom sequence of numbers uniformly distributed between 0 and 1.

The dosimetric accuracy of Monte Carlo simulation has been confirmed across the entire energy spectrum from ^{103}Pd to ^{226}Ra. The agreement between Monte Carlo and TLD and precision diode measurements ranges from 2% to 6%, both in homogeneous medium and in the presence of tissue and applicator heterogeneities.[8,57,129,150,151] In contrast to experimental methods, Monte Carlo accuracy is not limited by dosimeter artifacts, such as energy response and volume averaging. Because the geometric relationship can be specified exactly, it is also free from detector positioning uncertainties. Recent analyses[60,48,136] have shown that the uncertainty (including all known systematic and random error sources) of Monte Carlo absolute dose rate estimates on the transverse axis of ^{125}I seeds is 2.5% to 5% over the 1 to 5 cm distance range. Unlike dose measurements, Monte Carlo dose calculations cannot account for unsuspected deviations from the design specifications of the problem (eg, a contaminant radionuclide in the source or an error in measuring its source strength).[152] The Rodriguez analysis,[140] described above, found average differences between measurement and calculation of 3.8% and 2.8% for ^{125}I and ^{103}Pd seeds, respectively, based upon treating TLD intrinsic energy response corrections as best fit parameters.

Historically, the most important role of Monte Carlo simulation was calculation of reference quality transverse-axis dose rate distributions and anisotropy functions for low- and medium-energy BT sources. In addition to Williamson's code PTRAN,[77] the most common public domain codes validated for this purpose are EGSnrc user codes,[153,154] Monte Carlo N-Particle (MCNP),[155,156] and GEANT4 user codes.[157,158] For all low-energy interstitial seed models used in routine clinical care, the AAPM recommends[53] that both experimental and Monte Carlo–based dosimetry studies that meet the AAPM's standards of rigor and completeness and are published in peer-reviewed journals being available. In addition, the vendor must supply secondarily traceable S_K calibrations. Finally, at annual intervals, S_K standards of the vendor, the ADCLs, and NIST must be intercompared. For stainless steel–encapsulated single-stepping ^{192}Ir sources, a published experimental dosimetry study is not necessary.[52] Commercially available sources that satisfy the AAPM-recommended prerequisites are posted on the Joint IROC-Houston/AAPM Source Registry.[51]

Monte Carlo simulation is useful in many other applications, such as characterizing the effects of applicator-shielding materials[8] and tissue heterogeneities[57] on BT dose distributions, validating heuristic dose calculation algorithms,[159] and optimizing new source and applicator designs.[160] Over the past 20 years, validating more approximate model-based dose calculation algorithms (MBDCAs) has emerged as one of the most important Monte Carlo applications. This is because Monte Carlo provides an unbiased but statistically imprecise partial solution of the Boltzmann Transport Equation (BTE), the fundamental integro-differential equation that completely describes the transport, absorption, and scattering of ionizing radiation in any system of media and sources in a 7D phase space.[115] As described in "Advanced Model-Based Dose Calculation Algorithms" section, the

MBDCAs commercially available to date are approximate deterministic BTE solutions that must be tuned and validated against the Monte Carlo benchmark for acceptable accuracy in each clinical problem domain.[161,162] This has helped spur the development of fast Monte Carlo codes capable of efficiently estimating 3D dose distributions in a high-resolution (1-2 mm) grid for complex analytically defined and voxel-based geometries. Two of the many 3D CT-based Monte Carlo codes developed in the past decade include PTRAN_CMC[163] and egs_brachy.[154] Both support high spatial resolution dose calculation times for clinical implants that are short enough for forward treatment planning.

American Association of Physicists in Medicine Task Group 43 Table-Based Dose Calculation Formalism

An important milestone in modern BT is the publication of the original AAPM TG-43 report in 1995[164] and a substantially revised and expanded version in 2004,[49] including two more recent supplements.[48,49] The TG-43 approach consists of using measured and Monte Carlo–generated dose rate distributions directly for clinical dose calculation aided by a standard table lookup formalism. For low-energy seeds, the revised TG-43 report and its supplements include the following:

1. A recommended table-based dose calculation formalism for representing 2D and 1D dose distributions around interstitial sources specifically designed to use a sparse matrix of Monte Carlo or measured dose rates as its input
2. A critically reviewed set of 2D dose distribution data for a total of 27 ^{125}I, ^{103}Pd, and ^{131}Cs seed models that satisfy the AAPM dosimetric prerequisites.[53] For each of these source types, a consensus dose distribution in TG-43 formalism format is recommended based upon "merging" published TG-43-compliant Monte Carlo and experimental dosimetry data sets.
3. A history of air-kerma strength primary standards,[82,118] which summarizes previous AAPM guidance,[165,166] including the impact of calibration shifts on the delivered-to-prescribed dose ratio[167]
4. Methodological recommendations for obtaining TG-43 dosimetry parameters from TLD measurements or Monte Carlo simulations, including uncertainty analyses
5. Guidance on clinical implementation of TG-43 report recommendations

The TG-43 report recommends that all treatment planning software systems utilize the TG-43 formalism as the basis of dose calculation or at least for data entry, allowing users to easily input the new data into their systems. With the introduction of the new WAFAC-based air-kerma strength standard by NIST and over 20 low-energy interstitial BT sources into the marketplace at various times, the radiotherapy community has embraced the TG-43 dose calculation formalism as well as many AAPM recommendations associated with its implementation. Most important among these are the AAPM dosimetric prerequisites for routine non–institutional review board (IRB)-approved BT procedures.[53] Only low-energy sources with NIST-traceable S_K calibrations supported by annual intercomparisons among NIST, the ADCLs, and the vendor[168] and two independent Monte Carlo and experimental

dosimetry studies published in the peer-reviewed literature will be posted on the Joint IROC-Houston/AAPM Registry website[51] or included in future TG-43 supplements. In 2012, a similar dosimetry validation process was introduced for higher energy sources.[148]

Because embracing new calibration standards and dosimetry parameters alters prescribed-to-delivered dose ratios, radiation oncologists must understand the implications for selection of prescribed dose, interpreting published outcome studies, and consistently reproducing their clinical experience through time. AAPM reports provide detailed discussions and recommendations on managing these changes. For example, in ^{125}I monotherapy for prostate cancer, the pre–TG-43 prescribed dose of 160 Gy is equivalent to 145 Gy using the TG-43 dosimetry parameters.[167] This document also addresses the management of up to 10% variations in prescribed-to-administered dose ratios due to the complex dosimetric history of ^{103}Pd monotherapy.

General Formalism for the Two-Dimensional Case

For a cylindrically symmetric source of strength S_K (Figure 21.14), dose rate, $\dot{D}(r, \theta)$, at the point (r, θ) is calculated in the TG-43 formalism as follows:

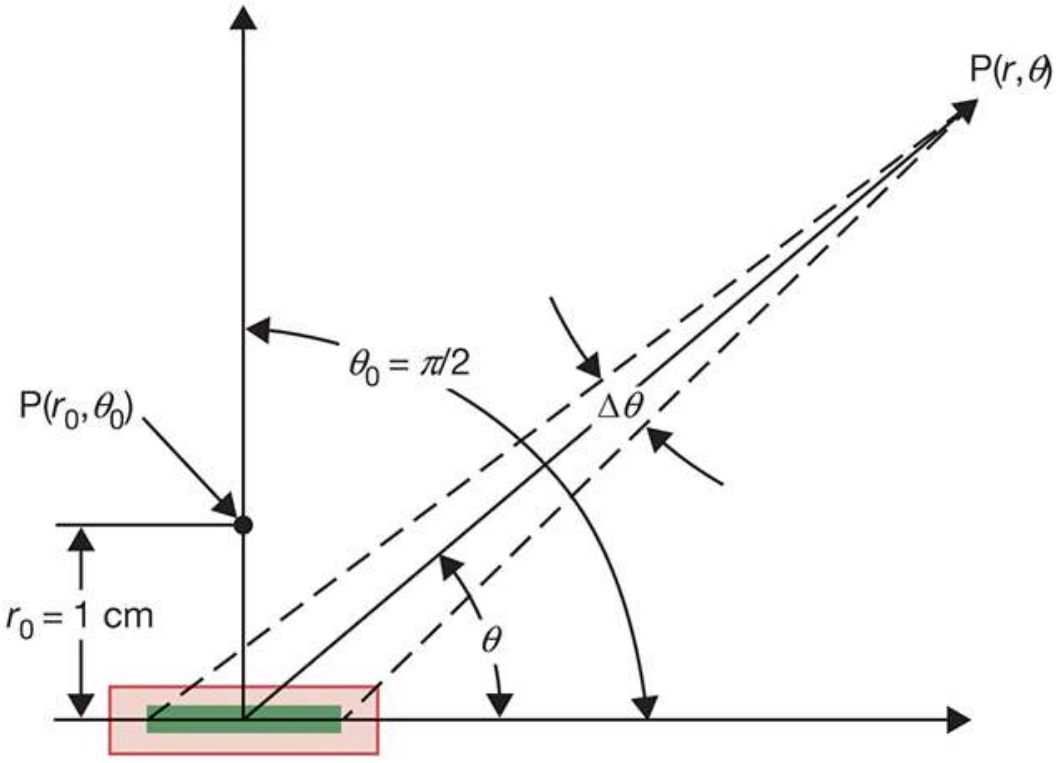


FIGURE 21.14 Illustration of Task Group 43 formalism for calculation of absorbed dose rate, $\dot{D}(r, \theta)$, at (r, θ), in a polar coordinate system centered about the source active core.

$$\dot{D}(r,\theta) = S_K \cdot \Lambda \cdot \frac{G_L(r,\theta)}{G_L(r_0,\theta_0)} \cdot g_L(r) \cdot F(r,\theta) \qquad (21.24)$$

where r denotes the distance (in cm) from the center of the active source to the point of interest, θ denotes the polar angle specifying the point of interest relative to the source longitudinal axis, r_0 denotes the reference distance (specified to be 1 cm), and θ_0 is the reference angle (90° or $\pi/2$ radians) that defines the source transverse plane. For ^{125}I and ^{103}Pd sources, AAPM Guidance[167] uses the symbols $S_{K,N99}$ and $S_{K,N85}$ to designate the 1999 WAFAC-based NIST standard[82] and the prior Loftus[118] free-air standard introduced in 1985. The other symbols in Eq. 21.24 denote the following quantities:

$G_L(r, \theta)$ is the line-source geometry function in units of cm^{-2}.

Λ is the dose rate constant of the source type in units of cGy/h·U^{-1}.

$F(r, \theta)$ is the dimensionless 2D anisotropy function that takes the value unity for θ_0 at all r.

$g(r)$ is the dimensionless radial dose function that takes the value unity at $r = r_0$.

The dose rate constant in liquid-water medium is defined by:

$$\Lambda = \frac{\dot{D}(r_0,\ \theta_0)}{S_K} = \frac{\dot{D}(1\,\text{cm},\ 90°)}{S_K} \qquad (21.25)$$

where $\dot{D}$ (r_0, θ_0) is the measured dose rate at the reference point. Λ includes the effects of source geometry, spatial distribution of radioactivity, encapsulation, self-filtration in the source, and attenuation and scattering of photons in the surrounding medium. It also depends on the standardization measurements to which the S_K calibration of the source is traceable.

For high-energy point sources, $\Lambda \approx \overline{(\mu_{en}/\rho)}^{med}_{air} \cdot T(r) \cdot G_L(1\,\text{cm}, \pi/2)$. Table 21.4 shows that during the $S_{K,N85}$ era (1984-1999), the classic point-source model overestimated absolute doses by as much as 15% for ^{125}I sources relative to TLD measurements and Monte Carlo calculations. In 1999, the WAFAC ($S_{K,N99}$) standard replaced $S_{K,N85}$, which required an upward adjustment of these Λ values, bringing the classic and quantitative values closer together. The old and new dose calculations are in close agreement for ^{192}Ir and other radium substitutes.

TABLE 21.4 DOSE RATE CONSTANTS FOR SELECTED INTERSTITIAL SEEDS Λ (CGY·CM^2/U)

Source	1983 Pre–TG-43 $\Lambda_{83D,N85S}$ $S_{K,N85}$	1995 TG-43[164] $\Lambda_{95D,N85S}$ $S_{K,N85}$	2000 AAPM Guidance[166] $\Lambda_{95D,N99S}$ $S_{K,N99}$	2004 TG-43[167] $\Lambda_{04D,N99S}$ $S_{K,N99}$	Modern Values $\Lambda_{>06D,N99S}$ $S_{K,N99}$
Model 6711 I-125	1.035	0.88	0.981	0.964	0.954 (130.002: TG-43 2017[49]) 0.940 (I25.S17+: TG-43 2017[49]) 0.952 (AgX100: TG-43 2017[49]) 0.956 (6711: Dolan 2006[136])
Model 6702 I-125	1.035	0.93	1.037	1.036	—
Model 200 Pd-103	—	0.74 $S_{K,T88}$	0.665	0.686	—
LDR/HDR sources Ir-192	1.12	1.12	1.12	1.12	1.109 (Elekta mHDR-v2) 1.100 (Varian VS2000) 1.117 (Gamma Med HDR+) 1.124 (Gamma Med PDR+) 1.110 (Best LDR seed) (AAPM HEBD Report 2012[148])

The purpose of the geometry function, $G_X(r, \theta)$—where the subscript X denotes point (P) or line source (L)—is to improve the accuracy with which dose rates can be estimated by interpolation from data tabulated at discrete points. Physically, $G_X(r, \theta)$ neglects scattering and attenuation and provides an effective inverse-square law correction based upon an *approximate model* of the spatial radioactivity distribution within the source. Because the geometry function is used only to interpolate between tabulated dose rate values at defined points, highly simplistic approximations yield sufficient accuracy for treatment planning.[5] To improve the accuracy of linear interpolation near the source, the AAPM protocol requires the use of (r, θ) for 2D calculations and prefers $G_L(r, \theta)$ to $G_P(r, \theta)$ for 1D calculations. For small cylindrical seeds, $G_X(r, \theta)$ is approximated by a line source.

$$G_{\mathrm{P}}(r,\theta) = r^{-2} \quad \text{point-source approximation}$$

$$G_{\mathrm{L}}(r,\theta) = \begin{cases} \dfrac{\Delta\beta}{Lr\sin\theta} & \text{if } \theta \neq 0^\circ \\ \left(r^2 - L^2/4\right)^{-1} & \text{if } \theta = 0^\circ \end{cases} \quad \text{line-source approximation} \tag{21.26}$$

where $\Delta\beta = \theta_2 - \theta_1$ is the angle subtended by the active source with respect to the point (r, θ). For sources where the radioactivity is distributed over or within a right cylindrical volume or annulus, L can be taken as the length of this cylinder. For sources containing uniformly spaced multiple radioactive components, L should be taken as the effective length, L_{eff}, given by, $L_{\mathrm{eff}} = \mathrm{DS} \times N$, where N represents the number of discrete pellets contained in the source with a nominal pellet center-to-center spacing, DS.

The 2D anisotropy function $F(r, \theta)$ gives the angular variation of dose about the source at each distance as a result of self-filtration, oblique filtration of primary photons through the encapsulating material, and photon attenuation and scattering in the surrounding medium.

$$F(r,\theta) = \frac{\dot{D}(r,\theta)}{\dot{D}(r,\theta_0)} \frac{G_{\mathrm{L}}(r,\theta_0)}{G_{\mathrm{L}}(r,\theta)} \tag{21.27}$$

where the dose rates, $\dot{D}(r, \theta)$, are obtained by measurement or Monte Carlo simulation. The line-source geometry function is used to suppress the influence of inverse-square law on the angular dose distribution at short distances. Thus, $F(r, \theta)$ need be tabulated only at a few distances, r, to facilitate accurate interpolation at all distances. Examples of anisotropy functions for various interstitial sources are illustrated in Figure 21.15 and in Table 21.6.

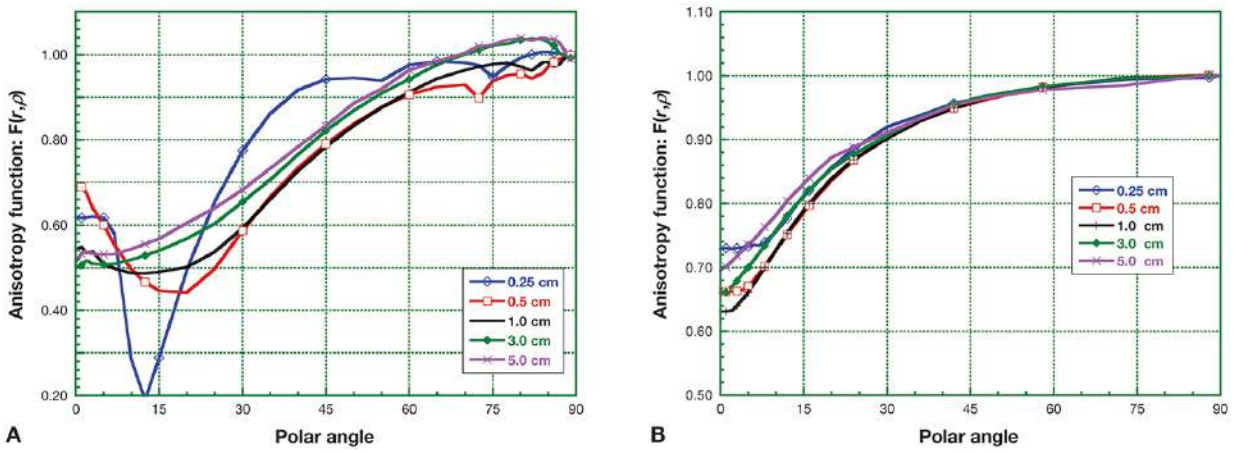


FIGURE 21.15 Examples of two-dimensional anisotropy functions evaluated for two different interstitial sources by the author's group. A. Theragenics Model 200 "light seed" ^{103}Pd source.[58] B. Nucletron/Elekta MicroSelectron Model V2 high-dose rate ^{192}Ir source.[394]

The radial dose function, $g_X(r)$, accounts for the falloff of dose along the transverse axis as a result of attenuation and scattering in the medium, capsule filtration, and self-absorption.

$$g_X(r) = \frac{\dot{D}(r,\theta_0)}{\dot{D}(r_0,\theta_0)} \frac{G_X(r_0\theta_0)}{G_X(r,\theta_0)} \tag{21.28}$$

$g_X(r)$ is normalized to unity at 1 cm distance and is illustrated by Table 21.5. For 2D dose calculations, TG-43 recommends that X = L.

TABLE 21.5 LINE-SOURCE RADIAL DOSE FUNCTIONS FOR VARIOUS LOW-ENERGY PHOTON-EMITTING SEED SOURCES.

r (cm)	BEBIG S17plus	Elekta 130.002	Theragenics AgX100	CivaTech CS10	IsoAid 1APd-103A	IsoRay CS-1 Rev2
	^{125}I	^{125}I	^{125}I	^{103}Pd	^{103}Pd	^{131}Cs
0.10	1.059	1.042	1.066	1.010	0.788	0.960
0.15	1.080	**1.062**	1.086	1.164	1.080	0.971
0.25	1.092	**1.085**	1.098	1.263	1.254	0.989
0.50	1.073	1.078	1.076	1.232	1.238	1.006
0.75	1.040	**1.044**	1.042	1.124	1.122	1.009
1.00	1.000	1.000	1.000	1.000	1.000	1.000
1.50	0.909	0.907	0.908	0.770	0.758	0.962
2.00	0.814	0.808	0.813	0.580	0.569	0.908

r (cm)	BEBIG S17plus	Elekta 130.002	Theragenics AgX100	CivaTech CS10	IsoAid 1APd-103A	IsoRay CS-1 Rev2
3.00	0.635	0.627	0.633	0.320	0.313	0.777
4.00	0.482	0.477	0.482	0.1726	0.1686	0.642
5.00	0.363	0.357	0.361	0.0924	0.0911	0.518
6.00	0.270	0.265	0.269	0.0496	0.0487	0.411
7.00	0.1995	0.1963	0.1990	0.0268	0.0265	0.323
8.00	0.1467	0.1442	0.1470	0.01471	0.01472	0.251
9.00	0.1087	0.1058	0.1080	0.00816	0.00841	0.1931
10.00	0.0792	0.0776	0.0790	0.00473	0.00504	0.1481

Bold entries indicate interpolated values.

Adapted from Rivard MJ, Ballester F, Butler WM, et al. Supplement 2 for the 2004 update of the AAPM Task Group No. 43 report: joint recommendations by the AAPM and GEC-ESTRO. *Med Phys*. 2017;44(9):e297-e338. Copyright © 2017 American Association of Physicists in Medicine. Reprinted by permission of John Wiley & Sons.

One-Dimensional Isotropic Source Approximation

Most commercial treatment planning systems used for permanent implant dose computation support only 1D isotropic point-source calculations. Thus, the TG-43 formalism includes a 1D equation analogous to the classic isotropic point-source model (Eq. 21.19).

$$\dot{D}(r) = S_K \cdot \Lambda \cdot \frac{G_L(r,\theta_0)}{G_L(r_0,\theta_0)} \cdot g_L(r) \cdot \phi_{an}(r) \qquad (21.29)$$

where $\phi_{an}(r)$ is the 1D anisotropy function defined by Eq. 21.18 and illustrated in Table 21.6. Both the 1D and 2D TG-43 cases assume that each source implanted in the patient is positioned at the center of a large water sphere. The single-source superposition dose calculation algorithm found in all treatment planning systems thus ignores intersource attenuation effects (attention of one source by other sources), deviation of local tissue composition from that of water, and applicator attenuation effects. Avoiding these 2% to 50% dose calculation artifacts is the role of MBDCAs described in the next section.[6]

TABLE 21.6 EXAMPLE OF A TABULATED 2D ANISOTROPY FUNCTION, $F(R, \Theta)$ TABLE, ALONG WITH ITS ASSOCIATED 1D ANISOTROPY FUNCTION, $\Phi_{AN}(R)$, VALUES FOR THE THERAGENICS MODEL 200 ^{58}PD SOURCE.

	r (cm)								
Polar Angle θ (degrees)	0.25	0.5	0.75	1	2	3	4	5	7.5
0	*0.619*	*0.694*	*0.601*	0.541	0.526	0.504	0.497	0.513	*0.547*
1	*0.617*	*0.689*	*0.597*	0.549	0.492	0.505	0.513	0.533	*0.580*

	r (cm)								
Polar Angle *θ* (degrees)	**0.25**	**0.5**	**0.75**	**1**	**2**	**3**	**4**	**5**	**7.5**
2	*0.618*	*0.674*	*0.574*	0.534	0.514	0.517	0.524	0.538	*0.568*
3	*0.620*	*0.642*	*0.577*	0.538	0.506	0.509	0.519	0.532	*0.570*
5	*0.617*	*0.600*	*0.540*	0.510	0.499	0.508	0.514	0.531	*0.571*
7	*0.579*	*0.553*	*0.519*	0.498	0.498	0.509	0.521	0.532	*0.568*
10	*0.284*	*0.496*	*0.495*	0.487	0.504	0.519	0.530	0.544	*0.590*
12	*0.191*	*0.466*	*0.486*	0.487	0.512	0.529	0.544	0.555	*0.614*
15	*0.289*	*0.446*	*0.482*	0.490	0.523	0.540	0.556	0.567	*0.614*
20	*0.496*	*0.442*	*0.486*	0.501	0.547	0.568	0.585	0.605	*0.642*
25	*0.655*	*0.497*	*0.524*	0.537	0.582	0.603	0.621	0.640	*0.684*
30	*0.775*	*0.586*	*0.585*	0.593	0.633	0.654	0.667	0.683	*0.719*
40	*0.917*	*0.734*	*0.726*	0.727	0.750	0.766	0.778	0.784	*0.820*
50	*0.945*	*0.837*	*0.831*	0.834	0.853	0.869	0.881	0.886	*0.912*
60	*0.976*	*0.906*	*0.907*	0.912	0.931	0.942	0.960	0.964	*0.974*
70	*0.981*	*0.929*	*0.954*	0.964	0.989	1.001	1.008	1.004	*1.011*
75	0.947	*0.938*	*0.961*	0.978	1.006	1.021	1.029	1.024	*1.033*
80	*0.992*	*0.955*	*0.959*	0.972	1.017	1.035	1.046	1.037	*1.043*
85	*1.007*	*0.973*	0.960	0.982	0.998	1.030	1.041	1.036	*1.043*
$\phi_{an}(r)$	*1.130*	*0.880*	*0.859*	0.855	0.870	0.884	0.895	0.897	*0.918*

Italicized entries indicate extrapolated values.

From Monroe JI, Williamson JF. Monte carlo-aided dosimetry of the theragenics TheraSeed® Model 200 103Pd interstitial brachytherapy seed. *Med Phys*. 2002;29(4):609-621. Copyright © 2002 American Association of Physicists in Medicine. Reprinted by permission of John Wiley & Sons.

Advanced Model-Based Dose Calculation Algorithms

The TG-43 source-superposition algorithm[5] assumes that patients consist of uniform liquid water, ignoring tissue composition inhomogeneities, seed-to-seed attenuation, and applicator-shielding effects. For ^{192}Ir BT, tissue composition heterogeneities introduce relatively small dose perturbations. However, both Monte Carlo and deterministic model-based dose calculations demonstrate skin contours (missing scatter volume), can reduce skin and rib doses by 4% to 8% for breast BT[169] while shielded vaginal applicators can reduce bladder and rectal doses by 8% to 25%.[170,171] In contrast, doses delivered by low-energy permanent seed BT and eBT are very sensitive to deviations of target tissues and organs at risk (OARs) from water equivalence, since photoelectric effect dominates energy deposition in this energy range. Using standard ICRP[172] bulk tissue compositions for prostate tissue, Carrier et al[173] found that TG-43 formalism underestimated D_{90} from ^{125}I seed implants by 9% relative to Monte Carlo studies, with 18/28 prostate cancer patients showing a 10% effect or more. Calcifications as small as 1% to 2% of the prostate mass

perturb DVH metrics by as much as 35%.[174] Even larger and highly variable (4%-50%) deviations of Monte Carlo D_{90} estimates from corresponding TG-43 estimates[163,175] was found for low-energy seed breast implants, because the breast tissue consists of a mixture of adipose and glandular tissues, which varies significantly from patient to patient. To address the potentially large impact of tissue and applicator heterogeneities on BT dose evaluation, sophisticated MBDCAs have been developed.[6]

Available Model-Based Dose Calculation Algorithms

Three major MBDCAs have been implemented in BT.[6,162] Monte Carlo simulation, as discussed earlier in source-specific dosimetry parameter determination, is the most widely investigated methodology. Because Monte Carlo simulation statistical uncertainty is proportional to the square root of computing time; the computing times (several hours or even days in the early development) associated with general-purpose codes used for dosimetry have limited Monte Carlo–based treatment planning[176] to the research setting. However, with advances in hardware and sophisticated variance reduction techniques,[177] this logistic barrier has been effectively overcome. As early as 2005 single-processor calculation times of the order of a minute for clinical prostate seed implants were reported.[174] Even faster specialized BT codes have been introduced, including a fast correlated sampling code[163] and an efficient EGSnrc-based planning code.[154]

Other groups have investigated deterministic transport solutions, mainly discrete ordinates codes[178] (also called "grid-based Boltzmann solvers" by some investigators) or heuristic 3D algorithms based on superposition/convolution of scatter dose point kernels.[159,179] Interestingly, planning software vendors have gravitated toward deterministic rather than Monte Carlo solutions. Varian Medical Systems has integrated a discrete ordinates dose calculation engine (ACUROS)[180,181] into its BrachyVision HDR planning system, the first commercially available BT dose calculation engine based on a rigorous radiation transport solution. Elekta BT (formerly Nucletron) has incorporated an Advanced Collapsed Cone (ACE) algorithm[159,182] into its planning system, which was adapted from the external beam collapsed cone scatter superposition/convolution algorithm.[183]

These advanced MBDCAs offer the possibility of departing from the TG-43 water-only geometries by modeling radiation transport in nonwater media (tissues, applicators, air-tissue interfaces), resulting in a much more physically accurate reconstruction of the dose distribution actually delivered to the patient. It also opens the possibility for innovative treatment modalities using novel applicators.[6,162]

Model-Based Dose Calculation Algorithm Commissioning and Clinical Implementation

To guide early clinical adopters of the emerging MBDCAs, the AAPM has published a major guidance document in 2012, the TG-186 report,[6] providing guidelines for clinical implementation and commissioning of MBDCAs in BT. The companion AAPM WGDCAB Report 372, published in 2023, further provided detailed workflow and data set of well-characterized test cases for commissioning commercially available MBDCAs (Varian

ACUROS and Elekta ACE) for ^{192}Ir-based afterloading BT.[162] The data set for the well-characterized test cases as well as step-by-step guides are available with open access in the Joint IROC-Houston/AAPM Brachytherapy Source Registry website.[162] The workflow outlined in these reports can be used to validate both the basic and advanced dose calculation features of commercial MBDCAs.

In addition to accurate commissioning, other issues associated with the use of MBDCAs, such as the choice of dose specification medium and voxel-by-voxel cross section assignment, could also affect their clinical implementation. MBDCA-calculated doses are sensitive to the dose specification medium. Energy-dependent differences exist between the dose calculated to water in a homogeneous water geometry (TG-43), dose calculated to the local medium in the heterogeneous medium, and dose calculated to a small volume of water in the heterogeneous medium (a theoretical construct).[6] The dose calculated to the local medium in the heterogeneous medium is a conceptually well-defined quantity and is recommended by the AAPM TG-186 for reporting when using MBDCAs. MBDCA-calculated doses are also sensitive to voxel-by-voxel interaction cross sections. Accurate geometrical descriptions of the patient and implanted applicators, including assignment of cross sections to all media, must be provided on a voxel-by-voxel or component-by-component basis in order to account for all sources of scatter and heterogeneities.[6] However, assigning voxel-by-voxel cross sections is challenging because the electron density information extracted from the conventional single-energy CT images cannot be used to distinguish between different materials that have the same density. AAPM TG-186 recommends the use of a number of standardized materials to maintain uniformity across institutions when using MBDCAs. Detailed discussions on these and other related issues can be found in the AAPM TG-186 report.[6]

INTERSTITIAL BRACHYTHERAPY

Interstitial BT typically uses multiple radioactive sources (or source dwell locations) to create extended dose distributions that are needed to cover clinical target volumes (CTVs) of various sizes and shapes. The classic implant systems (Manchester, Quimby, and Paris) that arose early in the 20th century were developed to guide the radiation oncologist in arranging and positioning radium needles within the surgically identified target volume. In contrast, most implant procedures today, such as the transperineal permanent implants of the prostate, use image guidance to position the sources. In place of classic system lookup tables and nomograms, 3D computerized planning is used to calculate and prescribe dose, as well as to optimize the implant geometry. Nonetheless, even the most sophisticated commercially available dwell-weight optimization software used with single-stepping source remote afterloaders (see Chapters 23 and 24) still requires the operator to specify the source and needle locations. In this regard, the concepts of the classic implant systems and their later variants can still offer some guidance in interstitial BT. This section reviews the relationship between implanted sources (strength, number, spatial arrangement, and implant duration) and the resultant spatial dose distributions and discusses the challenges in dose specification in interstitial BT.

Classic Implant Systems for Temporary Implants

The Manchester and Quimby systems were developed before the advent of computer-aided dosimetry in interstitial BT, whereas the Paris system is based on multiplanar isodose distributions. They all consist of the following components:

Source distribution rules: These rules specify how to distribute the radioactive sources and applicators in and around a given target volume.

Dose specification and implant-optimization criteria: At the heart of each system is a dose specification criterion (ie, a definition of prescribed dose). In the Manchester system, for example, the prescribed dose is the modal dose in the volume bounded by the peripheral sources. The distribution rules and dose specification criterion together often reflect a compromise between mutually exclusive goals such as dose homogeneity, normal tissue sparing, number of catheters implanted, dosimetric margins around the target, and the presence of high-dose regions outside the target.

Dose calculation aids: These devices are used to estimate the source strengths required to achieve the prescribed dose rate as defined by the system for source arrangements satisfying its distribution rules. The Manchester and Quimby systems use tables that give the dose delivered per mgRaEq-h (or TRAK in modern units) as a function of treatment volume or area. The Paris system makes extensive use of computerized treatment planning to relate the absorbed dose to source strength and treatment time.

The Manchester System

The Manchester system was developed by Ralston Paterson (radiation oncologist) and Herbert Parker (physicist) in the 1930s[184-187] and is often called the Paterson-Parker (P-P) system. Its distribution rules, anticipating the "peripheral loading technique," were designed to maximize dose homogeneity inside the implanted volume for volume implants and in the treatment plane (plane parallel to the needles at the treatment distance) for surface or planar implants (Figure 21.16). Its volume and area lookup tables remain useful as QA tools for optimized HDR volume implants.

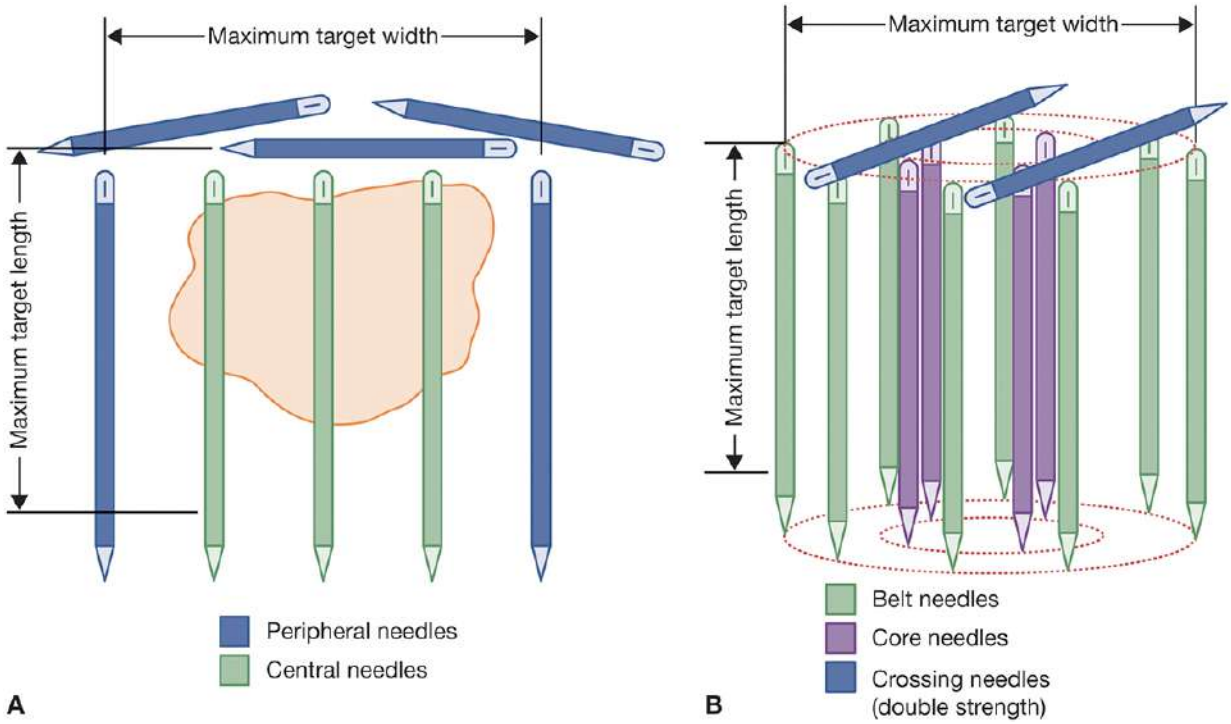


FIGURE 21.16 A. Relationship between target volume or area and peripheral needles (solid color active regions) and central needles (hatched active regions). Notice that peripheral needles always are placed on the boundary of the target region. B. For a cylindrical volume implant, the peripheral needles distributed on the cylindrical surface of the target are called *belt* needles, whereas those at right angles are called *end* or *crossing* needles. Because the inferior end of the implant is uncrossed, the target volume effectively treated is 7.5% shorter than the active length of the belt needles.

The P-P system rules preferentially concentrate radioactivity in the rind or periphery of the implant, compensating for the dose falloff characteristic of a uniform-density implant, thereby improving dose uniformity. After deriving the optimal fraction of radioactivity to be implanted in the rind and core (4:2 ratio) using a radioactive fluid model, Parker coalesced the continuous radioactivity distribution into several concentric cylindrical surfaces and then further discretized these surfaces into individual needles. A more detailed discussion of the mathematical derivation of the Manchester system is given by Anderson and Presser.[188] Table 21.7 lists the rules of the Manchester system, and Table 21.8 lists the stated dose per mgRaEq-h and per unit TRAK as a function of treated area or volume.

TABLE 21.7 MANCHESTER SYSTEM RULES

Feature	Paterson and Parker (Manchester System) Rules
Dose and dose rate	6,000-8,000 R in 6-8 days (1,000 R/day; 40 R/hour)
Dose specification criterion	Effective minimum dose is 10% above the absolute minimum dose in treatment plane or volume.
Dose gradient	Dose in treatment volume or plane varies by no more than ±10% from stated dose, except for localized hot spots.
	For double-plane implants with a separation greater than 1 cm, dose is specified on interior plane 0.5 cm from implanted plane resulting in 10%-30% midplane

Feature	Paterson and Parker (Manchester System) Rules					
	cold spot. Single-plane mgRaEq-h is multiplied by a separation factor to obtain total double-plane mgRaEq-h.					
Linear activity	Variable: 0.66 and 0.33 mgRaEq/cm					
Source strength distribution: planar	Area < 25 cm^2	2/3 periphery; 1/3 center				
	25 < area < 100 cm^2	1/2 periphery; 1/2 center				
	Area >100 cm^2	1/3 periphery; 2/3 center				
Source strength distribution: volume	Cylinder	Belt:core:end:end = 4:2:1:1				
	Sphere	Belt:core = 6:2				
	Cube	1/8 of the activity in each face				
		2/8 of the activity in the core				
Source implant pattern and spacing between sources	Constant uniform spacing: 1 cm separation between sources recommended. Smaller spacings must be used to satisfy distribution rules for small implants.					
Crossing needles	Perpendicular to and at the active ends of the parallel needles; if placed beyond the active ends of the needles, should be double strength. Crossing needles used when possible.					
	Planar implant: Target area effectively treated is reduced in length by 10% per uncrossed end.					
	Volume implant: Target volume effectively treated is reduced by 7.5% per uncrossed end.					
	1 uncrossed end:belt:core = 4:2:1					
	2 uncrossed end:belt:core = 4:2					
Elongation corrections	Long:short dimension	1.5:1	2:1	2.5:1	3:1	4:1
	Correction factors (applied to mgRaEq-h, not area or volume)					
	Planar	1.025	1.05	1.07	1.09	1.12
	Volume	1.03	1.06	1.10	1.15	1.23
Relation between implanted volume/area and treated (target) volume/area	Peripheral and crossing needles placed on the target volume boundaries. Active length determines target length.					

TABLE 21.8 MANCHESTER IMPLANT TABLES

Volume Implants			Planar Implants		
Volume (cm^3)	mgRaEq-h/1,000 "P-P" R[a]	Min Dose/TRAK[b] cGy/(μGy·m^2)	Area (cm^2)	mgRaEq-h/1,000 "P-P" R[a]	Min Dose/TRAK[b] cGy/(μGy·m^2)
1	34	3.49	0	30	3.97
2	54	2.20	2	97	1.23

Volume Implants			Planar Implants		
Volume (cm^3)	mgRaEq-h/1,000 "P-P" R[a]	Min Dose/TRAK[b] cGy/(μGy·m^2)	Area (cm^2)	mgRaEq-h/1,000 "P-P" R[a]	Min Dose/TRAK[b] cGy/(μGy·m^2)
3	70	1.68	4	141	0.844
4	85	1.38	6	177	0.672
5	99	1.194	8	206	0.578
10	158	0.752	10	235	0.506
15	207	0.574	12	261	0.456
20	251	0.474	14	288	0.413
25	291	0.408	16	315	0.378
30	329	0.361	18	342	0.348
40	398	0.298	20	368	0.323
50	462	0.257	24	417	0.285
60	522	0.228	28	466	0.255
70	579	0.206	32	513	0.232
80	633	0.188	36	558	0.213
90	684	0.174	40	603	0.197
100	734	0.162	44	644	0.185
110	782	0.152	48	685	0.174
120	829	0.143	52	725	0.164
140	919	0.129	56	762	0.156
160	1,005	0.118	60	800	0.149
180	1,087	0.110	64	837	0.142
200	1,166	0.102	68	873	0.136
220	1,242	0.0958	72	908	0.131
240	1,316	0.0904	76	945	0.126
260	1,389	0.0857	80	981	0.121
280	1,459	0.0815	84	1,016	0.117
300	1,528	0.0779	88	1,052	0.113
320	1,595	0.0746	92	1,087	0.109
340	1,661	0.0716	96	1,122	0.106
360	1,725	0.0690	100	1,155	0.103
380	1,788	0.0665	120	1,307	0.0910
400	1,851	0.0643	140	1,463	0.0813
—	—	—	160	1,608	0.0740
—	—	—	180	1,746	0.0682
—	—	—	200	1,880	0.0633

Volume Implants			Planar Implants		
Volume (cm^3)	mgRaEq-h/1,000 "P-P" R[a]	Min Dose/TRAK[b] cGy/(μGy·m^2)	Area (cm^2)	mgRaEq-h/1,000 "P-P" R[a]	Min Dose/TRAK[b] cGy/(μGy·m^2)
—	—	—	220	2,008	0.0593
—	—	—	240	2,132	0.0558
—	—	—	260	2,256	0.0527
—	—	—	280	2,372	0.0502
—	—	—	300	2,495	0.0477

[a]Original Manchester values from Paterson R, Parker HM. A dosage system for interstitial radium therapy. *Br J Radiol*. 1938;11:313-339.

[b]Modified from original values for Ir-192 assuming 860 cGy minimum peripheral dose per 1,000 "P-P" R and 7.227 μGy·m^2/mgRaEq-h.

The P-P rules are designed to yield the target area or volume dose distribution that deviates by no more than ±10% of the stated dose, excluding cold spots in the corners and local hot spots at distances less than 5 mm from the source centers. For planar implants, the target or treatment surface (Figure 21.16) is that area bounded by the peripheral needles, which is parallel to and 5 mm from the needle plane. For volume implants, the target volume is that region bounded by the peripheral sources. Fixed 1-cm needle spacing is recommended, with full-intensity sources placed on the periphery of the implants and partial strength needles used as central needles. For volume implants, these two groups of sources are called "belt" and "core" sources, respectively. The distribution rules assume that both planar and volume implants will be crossed at both ends by needles placed orthogonal to the predominant direction of insertion and at the level of the belt needle active tips. The stated or prescribed dose, the modal dose in the target region, is approximately 10% higher than the minimum peripheral dose (minimum dose to the implanted volume or area) and 10% below the effective maximum dose.

In effect, single-plane interstitial implants with crossed ends treat a 1-cm-thick target volume with an area equal to that bounded by the peripheral sources. Target volumes thicker than 1 cm must be treated by using two parallel planes of needles placed on the target volume boundaries (double-plane implant), with source strength arranged in each plane according to the single-plane rules. The mgRaEq-h is calculated from the 0.5-cm single-plane table, multiplied by the appropriate two-plane separation factor, and divided between the two planes. The dose actually is delivered to the inner plane 0.5 cm from each needle plane, resulting in midplane cold spots ranging from 10% to 30% for separations of 1.5 to 2.5 cm. Target volumes thicker than 2.5 cm must be treated by the volume implant system.

Volume implants can treat cylindrical, spherical, or cubic target volumes in which needles or seeds are arranged on concentric cylinders, concentric spheres, or parallel planes, using a 1-cm needle-to-needle spacing when possible. The target region is the volume encompassed by the peripheral sources. Regardless of implant size, 75% of the source

strength should be placed in the rind and 25% in the core, with more specific rules for cylinder implants.

To apply the P-P system, the relationship between target volume, implanted volume (region enclosed by peripheral sources), and treated volume (region receiving 90% of the stated dose) must be appreciated for crossed and uncrossed end cases. The treated volume may be larger than the target volume but always should contain the latter. The relationships between the AL required and target length (TL) for planar and volume implants with uncrossed end(s) are given below:

$$\begin{aligned}
&\text{Two crossed ends} && \text{AL} = \text{TL planar and volume} \\
&\text{One crossed end} && \text{AL} = \begin{cases} \text{TL} / 0.90 & \text{planar} \\ \text{TL} / 0.925 & \text{volume} \end{cases} \\
&\text{No crossed ends} && \text{AL} = \begin{cases} \text{TL} / 0.81 & \text{planar} \\ \text{TL} / 0.85 & \text{volume} \end{cases}
\end{aligned} \tag{21.30}$$

The area and volume used for looking up dose per mgRaEq-h from Table 21.8 should be calculated using the TL. For example, for a single-plane implant with two uncrossed ends, width W, and needles of active length AL, the area, A, used for table lookup is given by $A = W \times \text{AL} \times 0.81$.

To apply P-P tables to modern implants using ^{192}Ir wires or ribbons, several corrections must be applied. The 1938 P-P tables assumed a Γ value of 8.4, ignored attenuation and scattering, neglected oblique filtration, and specified treatment in terms of exposure rather than the absorbed dose. For ^{226}Ra needles, an average correction of 0.90[116] is needed to convert exposure in the original P-P tables to the absorbed dose. Applying these corrections for ^{137}Cs needles and ^{192}Ir seeds and adding an additional factor of 10% to convert from stated (modal target dose) to minimum target volume dose, we obtain the following equivalencies:

$$1\text{'}P\text{–}P\text{'}R = \left\{ \begin{array}{llll} 0.97 \cdot \dfrac{8.25}{8.4} & 0.98 & 0.98 & 0.90 \\ 0.97 \cdot \dfrac{8.25}{8.4} & 1.00 & 0.98 & 0.90 \\ 0.97 \cdot \dfrac{8.25}{8.4} & 1.00 & 1.00 & 0.90 \\ (cGy/R) \cdot \left(\dfrac{\Gamma_{new}}{\Gamma_{old}} \right) & \text{(filtration)} & \text{(attenuation / buildup)} & \left(\dfrac{\min}{\text{stated}} \text{ dose} \right) \end{array} \right\} = \left\{ \begin{array}{l} 0.82 \text{ cGy radium needles} \\ 0.84 \text{ cGy cesium needles} \\ 0.86 \text{ cGy iridium ribbons} \\ \left(\dfrac{\text{Modern cGy}}{\text{'P–P'R}} \right) \end{array} \right. \tag{21.31}$$

Using the 0.90 cGy/P-P R conversion factor, Stovall and Shalek[116] found excellent agreement between computer calculations and the P-P tables for a variety of planar and cylindrical implants following the Manchester distribution rules. For single-plane implants, 90% of the stated dose in cGy covers 94% to 99% of the target area. For cubic arrays of seeds using fixed 1-cm spacing, agreement between the tables and computer calculations is excellent for treatment volumes of more than 100 cm^3[189,190] but results in errors ranging from 10% to 40% for smaller arrays. These discrepancies probably result from deviations from the 4:2 activity ratio and use of a dose specification criterion incompatible with the Manchester system.

The classic implant systems are based on interstitial needles or ^{192}Ir wires consisting of continuous distributions of radioactivity (ie, line sources) with well-defined ALs. To apply the classic systems to modern interstitial sources consisting of discrete equispaced seeds or single-stepping source dwell positions, the dosimetric equivalence between linear arrays of discrete seed sources and line sources must be appreciated (Figure 21.17). An array consisting of N seeds with center-to-center separations, *S*, has a dose distribution that closely approximates that of a continuous line source of active length, AL, and strength $(S_K)_{line}$[101,191]:

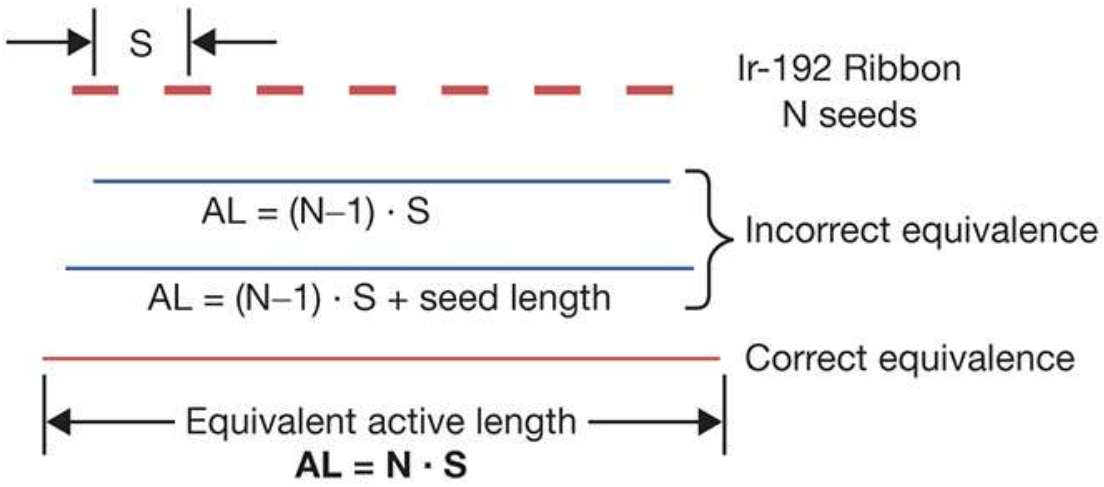


FIGURE 21.17 Relationship between a linear array of equally spaced discrete seeds and its dosimetrically equivalent line source. Both sources are assumed to have the same total strength. Common errors in defining this equivalence are illustrated. AL, active length.

$$\left.\begin{aligned} \mathrm{AL} &= N \cdot S \\ (S_K)_{line} &= N \cdot (S_K)_{seed} \end{aligned}\right\} \qquad (21.32)$$

This equivalence tends to break down at distances less than *S*/2: The cylindrical isodose curves break up into ellipsoidal shapes centered about each seed. In addition, the ribbon

isodose curves undulate significantly at distances comparable with or less than the gap, *S*, between adjacent seeds, although on average the equivalence remains accurate.

Because the P-P system uses 1-cm interneedle spacing, the fraction of sources in the core (vs periphery) increases as volume increases. Thus, using uniform strength ^{192}Ir ribbons and fixed spacing results in underloading the core for very small implants and overloading the core for very large implants, relative to the P-P distribution rules. In the latter case, the gap between minimum peripheral dose and central maximum dose widens. An alternative to the differential loading method is to vary the ribbon spacing with implant size, using smaller (less than 1 cm) spacing for very small implants and larger spacing (up to a limit of 1.5 cm) for larger implants so that the relative number of central ribbons complies approximately with the P-P rules, allowing uniform seed strengths to be used.

To use the Manchester tables for verification of computerized dose calculations requires a method for objectively identifying the computer-generated isodose surface that corresponds to the minimum peripheral dose rate predicted by the Manchester system. For volume implants, mean central dose (MCD), a quantity proposed by the ICRU Report 58 on dose specification in interstitial BT, is useful[192] (Figure 21.18). In the authors' experience, the maximum dose (110% of the stated dose) of the Manchester system is closely approximated by MCD. Minimum peripheral dose and stated dose are given by 80% and 89%, respectively, of MCD. For planar implants, the minimum dose/MCD ratio varies from 55% to 70%, depending on catheter spacing, and is of limited value.

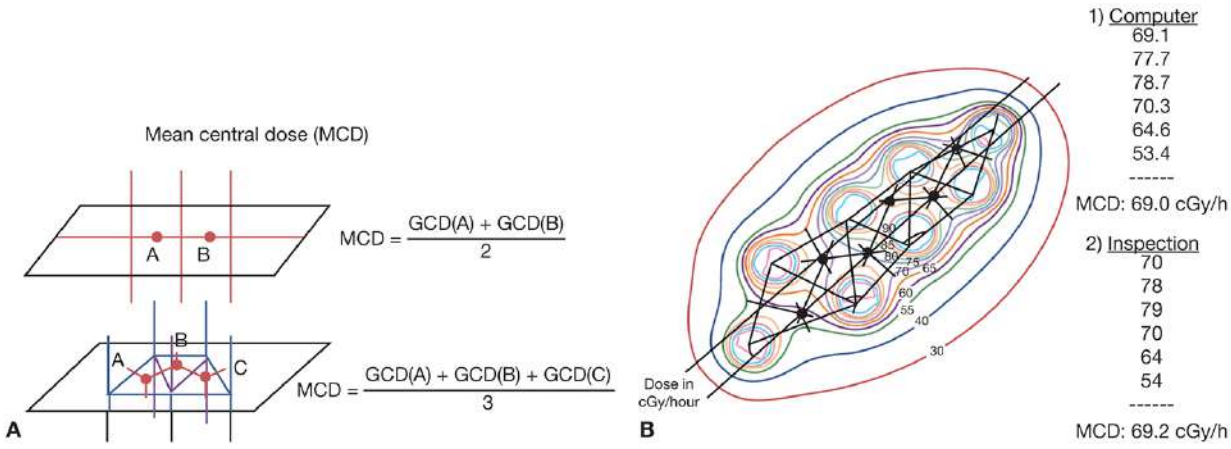


FIGURE 21.18 A. Calculation of mean central dose (MCD) as the arithmetic mean of the doses at mid-distance between each pair of adjacent sources for single-plane implants and the mean of the local minimum doses between each group of three adjacent sources in a multiple-plane implant. All local minimum doses are specified in the "central transverse" plane, which is normal to and bisects the source axes. B. Illustration of a practical specification of MCD for a computer plan.

The Quimby System

The Quimby system was developed by Edith Quimby and colleagues[193-195] at New York Memorial Hospital from 1920 to 1940. Unlike the Manchester system, equal linear intensity (mgRaEq/cm) needles are distributed uniformly (fixed spacing) in each implant. Like the

Manchester system, the associated Quimby tables give the mgRaEq-h needed to deliver a stated exposure of 1,000 R as a function of target volume or area.

The so-called planar implant tables were intended for surface molds; none of the early Memorial publications suggest that it was used for single-plane interstitial implants. In part because Quimby stated dose is the maximum dose in the treatment plane, Quimby planar implants deliver 30% to 40% less radiation (TRAK) per unit stated dose than an equivalent Manchester implant delivers. Rules for distributing radium needles (relationship to target area boundaries, crossed ends, spacing, etc) are not clearly described.

Volume implant needle arrangements are similar to their Manchester counterparts; both systems recommend crossed ends and placing peripheral needles on or beyond the target volume boundaries. However, Quimby allows the needle spacing to vary with implant size and specifies dose as the absolute minimum to the target volume. The physical and mathematical origins of the widely cited Quimby volume implant table are obscure; the tables published in the 1951 edition of *Physical Foundations of Radiology*[194] use 25% to 90% more mgRaEq-h per unit dose than P-P volume implants of similar size. Although vague on the subject, Quimby appears to specify a minimum dose at a point located 3 to 5 mm from the peripheral needles (and therefore outside the target volume) near their active tips.[195] This corresponds to a treatment volume (volume encompassed by prescription isodose surface) that is 6 to 10 mm larger than the implanted volume (used for table lookup) in each linear dimension. The Quimby planar and volume dose specification criteria are clearly inconsistent, and a detailed derivation of the associated tables is lacking. For these reasons, we do not recommend Quimby tables for clinical use.

The Paris System

The Paris system was developed in the early 1960s by Pierquin, Chassagne, Dutreix, and Marinello[196,197] and was motivated by the ^{192}Ir afterloading techniques developed by Henschke. Outside the United States, the Paris system is still widely used to guide definitive BT of localized lesions in the head and neck, breast, and many other sites. An up-to-date summary of the system has been published by Gillin and Mourtada.[198]

The starting point of the Paris system is the definition of the target volume, which is described in terms of thickness *T*, length *L*, and width *W*. The system provides rules for constructing implants, which, if followed, guarantee that the target volume is completely covered by the prescription isodose surface (Table 21.9). The prescription dose level, called the "reference dose," is a fixed percentage (85%) of the basal dose (see Figure 21.19), which closely resembles the more general concept of MCD in Figure 21.18. ^{192}Ir wire sources are arranged in parallel rectilinear arrays with their centers located in the central plane, which is perpendicular to the sources. Adjacent sources must be equidistant from one another, resulting in single-plane implants with equal spacing and double-plane implants with groups of adjacent sources arranged in equilateral triangles or squares in the central plane. The linear density (μGy·m2/h·cm) must be uniform and the same for all sources. Interneedle spacing scales with the thickness, *T*, of the target volume. The number of sources is determined largely by the relative shape of the target volume cross-sectional area,

$W \times T$. In contrast, the Manchester system uses fixed spacing and increases the number of sources as the cross-sectional area of the target volume increases.

TABLE 21.9 PARIS SYSTEM CHARACTERISTICS

Feature	Paris System Rules
Dose and dose rate	6,000-7,000 cGy in 3-11 days (25-90 cGy/hour)
Dose specification criterion	Reference dose (prescribed dose) is 85% of the basal dose and encompasses the target volume when distribution rules are followed. Basal dose is the average of the minimum doses between pairs or groups of adjacent sources in the central transverse plane.
Dose gradient	Fixed 15% gradient between reference dose and basal dose. The "hyperdose sleeve" (region receiving at least twice the reference dose) diameter should be less than 8-10 mm.
Linear activity	Constant (4-14 μGy·m2/h·cm) linear density ^{192}Ir wires used.
Source arrangement geometry for target volume of thickness, width, and length of $T \times W \times L$	Only single- and double-plane implants allowed. Spacing, S, and lateral margin (called "safety margin" for double-plane case), M, are fixed fractions of T and constant within a given implant. Active length, AL, is a fixed fraction of L, which varies with S.
	Single plane: T = 12 mm
	$S = 2 \times T$ (2 sources)
	$S = 1.67 \times T$ (3 sources)
	$M = 0.37 \times T$
	AL = (1.3 − 1.49) × T
	Double plane: (square pattern) (triangle pattern)
	$S = 0.62 \times T$ $S = 0.77 \times T$
	$M = 0.27 \times T$ $M = 0.15 \times T$
	AL = (1.37 − 1.62) × L AL = (1.33 − 1.49) × L
Source spacing, S, limits	Short sources (1-4 cm):
	Long sources (≤10 cm): 15 mm ≤ S ≤ 22 mm
Crossing needles	Generally not used; AL ~1.45 × L to compensate for uncrossed ends
	For oral cavity implants, hairpins are common, which approximate crossed ends.
Relation between target volume and implanted volume	W = distance between outermost sources + 2 × M L = (1.3 − 1.62) × L
	$T = \begin{cases} S/1.67 & \text{Single plane} \\ S + 2 \times M & \text{Double plane : squares} \\ S \times \cos 30^\circ + 2 \times M & \text{Double plane : triangles} \end{cases}$

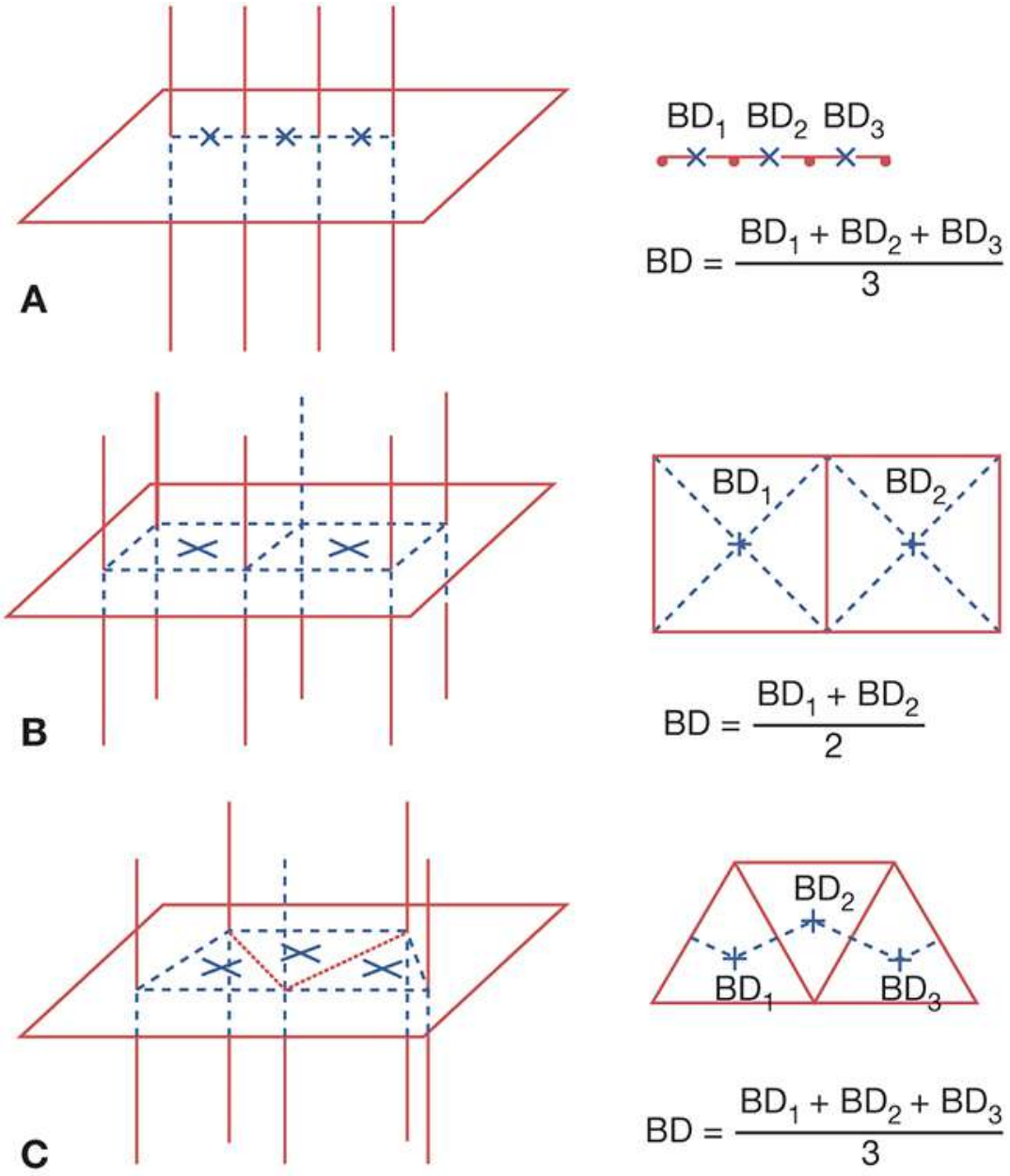


FIGURE 21.19 The three central plane configurations allowed by the Paris system: (A) single-plane implant, (B) double-plane implant using the pattern of squares, and (C) double-plane implant using the pattern of equilateral triangles. The calculation of basal dose (BD) rate at a point equidistant from each group of adjacent sources is illustrated for each configuration. (From Gillin MT, Albano KS, Erickson B. Classical systems II for planar and volume temporary interstitial implants: the Paris and other systems. In: Williamson JF, Thomadsen BR, Nath R, eds. *Brachytherapy Physics*. Medical Physics Publishing; 1995:232-343. Reprinted by permission of Medical Physics Publishing.)

Table 21.9 shows that the location of the peripheral sources relative to the treated volume (region encompassed by the reference isodose rate surface, as shown in Figure 21.20) differs from the Manchester system, which implants to the boundary of the treated tissue. In the transverse plane, the peripheral sources lie 2 to 4 mm (the lateral margin distance, *M*) inside the treatment surface, whereas longitudinally, the AL extends 15% to 20% beyond

the distal and proximal margins of the target volume. In practice, the margin, *M*, is treated as a safety margin, and the peripheral needles are implanted along the margins of the CTV. The maximum thickness, *T*, of a target volume treatable in the Paris system is about 2.5 cm. An example of a double-plane implant arranged in squares is shown in Figure 21.21.

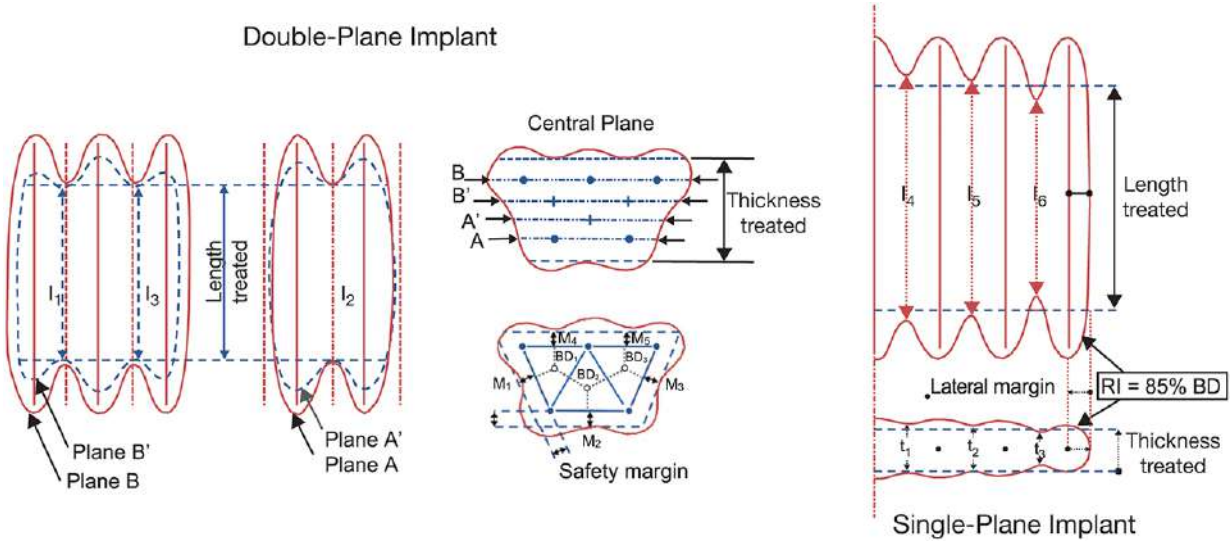


FIGURE 21.20 Relationship of the reference isodose (RI), source locations, and target volume dimensions for an illustrative a single-plane and a double-plane implant following the Paris system. The concept of safety margin (lateral margin), M, and location of basal dose (BD) points are illustrated. (Adapted from Thomadsen B, Miller R. Brachytherapy physics. In: Brahme A, ed. *Comprehensive Biomedical Physics*. Elsevier; 2014:315-381. *Radiation Therapy Physics and Treatment Optimization*; vol 9. Copyright © 2014 Elsevier. With permission.)

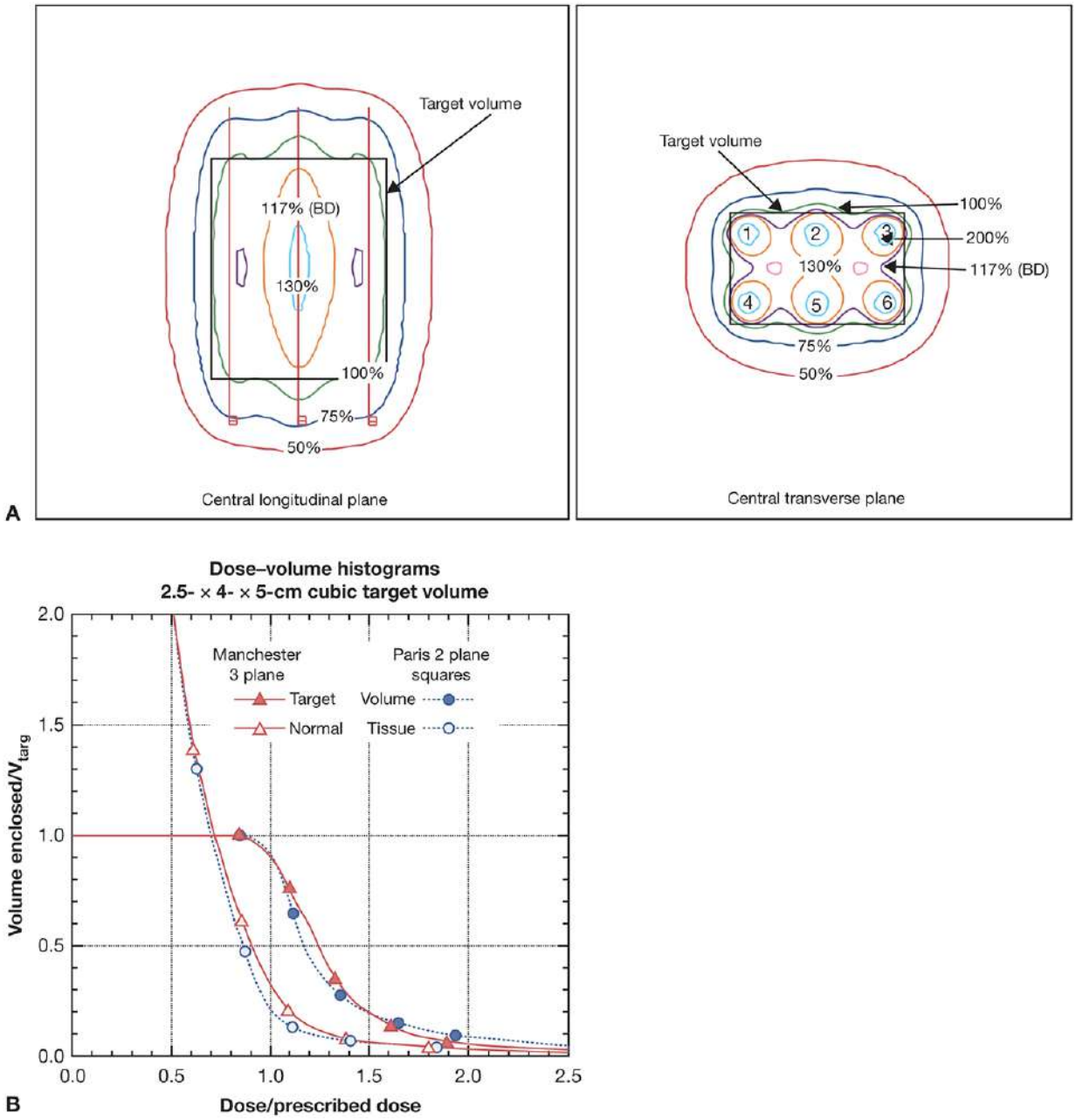


FIGURE 21.21 A. Isodose curves of a Paris system double-plane implant arranged "in squares" to treat a 2.5-cm × 4-cm × 5-cm target volume (heavy lines). The separation and active lengths of the ^{192}Ir wires are 1.6 and 7.3 cm, respectively. A linear strength of 6 μGy·m2/h·cm gives reference (100%) and basal (117%) dose (BD) rates of 60 and 70.6 cGy/hour, respectively. B. Comparison of dose-volume histograms calculated separately for the 2.5-cm × 4-cm × 5-cm target volume and the tissue outside the target for the Paris implant shown and a Manchester implant consisting of three planes, 15 ^{192}Ir ribbons with six seeds each, and 1.25-cm spacing between planes and ribbons. Each graph shows volume of tissue (in multiples of volume of the target) receiving at least the specified dose (in multiples of the prescribed dose). For the Paris and Manchester implants, respectively, the prescribed dose is calculated reference dose and minimum target dose predicted by the Paterson-Parker volume table. In both systems, the prescription isodose surface covers about 90% of the target. Surprisingly, both normal tissue sparing and dose homogeneity in the target are slightly better for the Paris implant.

To apply the Paris system, the target thickness *T* must be known, which defines the spacing and determines whether single- plane or double-plane geometry is required. The number of sources and selection of a square or triangular arrangement are defined by the relative cross-sectional shape of the target volume in the central plane perpendicular to the sources. Finally, the AL is calculated. The source tip and end coordinates are reconstructed from orthogonal radiographs, and the dose distribution and basal dose are calculated by computer for the actual implant geometry realized in the patient, not the idealized implant of clinical intention. This approach differs from the classic Manchester method, which bases dose prescription on the P-P table and, in general, ignores deviations of the actual implant geometry from the ideal. The Paris system addresses only single- and double-plane implants; large-volume implants for treating pelvic masses and brain tumors were not part of the original system. Extensions of Paris system principles to large-volume implants are discussed by Leung[199] and Gillin and coworkers.[200]

Modern Approaches for Temporary Implantation

A major development of the past three decades is a pronounced shift from LDR manual afterloading to HDR BT. Single-stepping HDR source remote afterloading (see Chapters 23 for a detailed treatment) allows the treatment time (dwell time) to be individually specified at each treatment (dwell) position in the catheter. This permits the use of dwell-weight optimization as a tool for improving dose uniformity and target coverage within implants. In contrast to the classic systems, which assume that ribbons and needles are of uniform linear density, dwell-weight optimization supports far more elaborate nonuniform source strength distributions than those envisioned by the Manchester system rules.

The published experience, confined largely to Paris-like double-plane breast implants, demonstrates that geometric optimization[201] preferentially increases the dwell times at dwell positions near the catheter ends. The most striking finding is that optimization allows the AL/TL ratio to be reduced from 1.33 to 1.5 and 1.1 to 1.25.[202-204] In the transverse plane, target coverage remains unchanged, whereas dose homogeneity is improved modestly, depending on the figure of merit (FOM) used to quantify this effect. When dose point optimization (specifying dose constraints at dose calculation points throughout the treatment volume) is used, acceptable dose homogeneity results with even smaller AL/TL ratios, even when all peripheral dwell positions are placed inside the target volume (AL/TL = 1.0)[205,206] for idealized volume implants and clinical volume implants.[203] These early efforts did not address the practical problem of how to distribute dose-constraint points in clinical volume implants with irregular catheter spacings and how to select dwell positions to be activated in each catheter. While dwell-weight optimization techniques have the potential to reduce AL/TL ratios to near unity with good conformal index (CI) and homogeneity index (HI), the selection of catheter direction and location relative to the target volume is still manual, with guidance drawn from the distribution rules of the classic systems or one's own clinical experience.

Three-Dimensional Imaging and Dosimetry

The use of 3D imaging to preplan implants or intraoperatively guide catheter or seed insertion is growing rapidly. The most widely practiced form of image-guided BT is use of intraoperative TRUS to guide transperineal insertion of needles used to implant the prostate gland with low-energy seeds.[44,45] However, image-guided implant methodologies have been developed for HDR interstitial implantation for prostate cancer[207] and HDR multicatheter interstitial[208] implants for accelerated APBI following lumpectomy. All of these approaches require delineation of the target volume and critical structure surfaces from 3D imaging studies. Then catheter or needle trajectories and, ultimately, seed or dwell position locations can be selected to improve target volume coverage while minimizing unnecessary dose to critical structures. The issues involved in utilizing image-guided and image-based BT in HDR interstitial BT, including treatment planning, selection of imaging modality, and impact on clinical workflow are covered in detail elsewhere.[209]

As practiced by most radiation oncologists, image-guided, intraoperatively planned implants continue to rely on the planner's judgment for selecting source locations. These decisions are guided by a "loading approach," or set of guidelines that specify margins, seed locations relative to the target boundary, spacings, and approximate periphery-to-core loading ratios.[210,211] Dose calculations and DVH quality indices are often used to guide manual source position adjustments to improve target volume coverage, improve dose homogeneity, and select source strengths (or dwell times) and the prescription isodose.

Anatomy-Based Optimization

An important advance upon standard dose point optimization is anatomy-based optimization in which constraints and treatment goals are defined in terms of doses to the CTV or normal tissues contoured from 3D imaging studies rather than surfaces defined relative to dwell positions. The simulated annealing HDR dwell-time optimization technique developed by Lessard and Pouliot[212] illustrates the general features of the various optimization approaches[213-216] that have been brought to bear on this problem (see Ezzell's[217] review for a highly readable introduction to BT optimization techniques). An objective function, consisting of penalty factors summed over the dose calculation points in the CTV, urethra, rectum, and other organs, is minimized. The penalty factors are used to penalize candidate dose distributions that deviate from the specified constraints and planning goals (see Ezzell's[217] review cited earlier). The inverse planning technique of Lessard and Pouliot[212] reduces CTV dose heterogeneity (V_{150} of 29% vs 50%) and urethral doses in clinical prostate implants compared to geometric optimization[218] and solves the problem of selecting active dwell positions and locations for dose-constraint points faced by the older dose point optimization algorithms. While anatomy-based inverse planning does not optimize catheter trajectories, its proponents argue[219] that it reduces the dependence of implant quality on the number and accurate positioning of the catheters relative to the CTV boundary. If true, inverse planning could reduce the dependence of implant quality on operator skill and reduce the need to follow system-based needle insertion rules.

Computerized dose calculation, dwell-weight optimization, and image-guided BT have made anatomy-based dose specification and meaningful implant optimization a reality in some clinical settings. However, as currently available, these innovations still require users

to conceptually plan implants in terms of specified source and needle distribution patterns, implant-target volume margins, and loading ratios. Specific rules borrowed from the classic systems (eg, AL/TL ratios) may require significant modification when adapted to these modern technologies.

Permanent Implantation

In contrast to temporary implantation, in which treatment time is varied to control the total dose delivered, the dose delivered by a permanent implant is determined by the initial geometric arrangement of sources and S_K per source: once the sources are implanted, neither the total dose delivered nor the relative distribution can be modified easily. Up through the mid-1980s, manual planning and dose calculation tools were used widely to estimate the number and density of sources needed to deliver the prescribed dose or to intraoperatively correct for deviations between the planned and actual source locations. While 3D treatment planning and dose calculation have replaced manual preplanning tools (see section "Modern Approaches"), manual aids can still be used for verifying the correctness of patient treatment plans.

Manual Approaches

For high-energy sources (eg, ^{198}Au), the Manchester, Laughlin et al,[189] or Shalek et al[190] tables and associated distribution rules have been used as manual planning aids. These manual planning aids for high-energy sources cannot be applied to low-energy seed (^{125}I, ^{103}Pd, and ^{131}Cs) implants because of the importance of tissue attenuation in this energy range. The influence of photon energy on the relationship between dose rate, $\dot{D}$, and implanted volume, V, is illustrated by Figure 21.22. Parker[184] recognized that this relationship can be described accurately by a power law formula, of the form

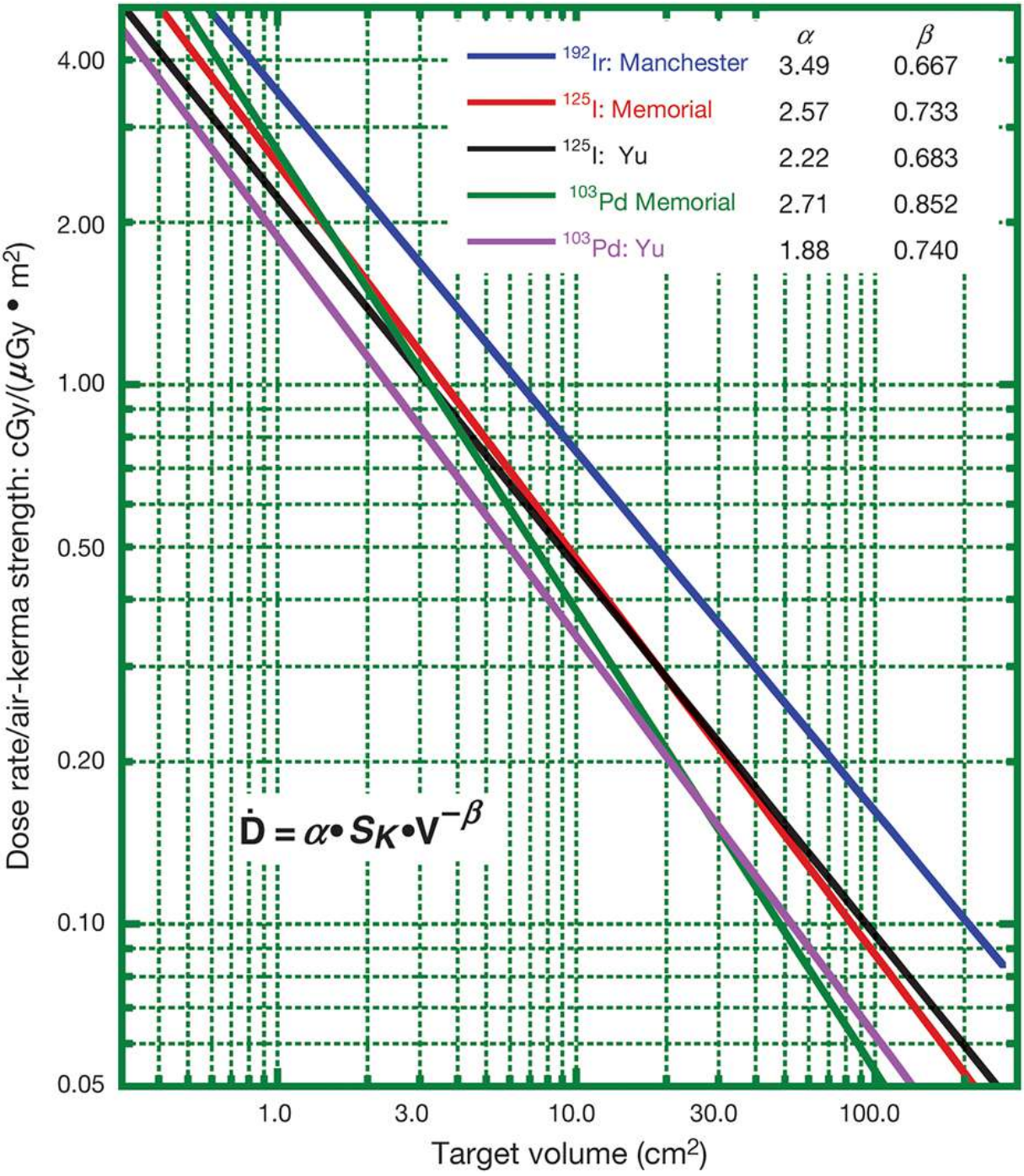


FIGURE 21.22 Comparison of reference dose rate per unit air-kerma strength versus volume of the target volume for Manchester volume implants and ^{103}Pd and ^{125}I permanent prostate implants. The inset gives the exponents and proportionality constants needed to describe these relationships in terms of a simple power law equation. The data in the figure are from Yu,[221] Memorial,[220] and Manchester.[184]

$$\dot{D} = \alpha \cdot S_{\mathrm{K}} \cdot V^{-\beta} \tag{21.33}$$

In fact, the original Manchester table (Table 21.8), converted to modern units and quantities, can be derived from equation 21.33 by setting $\alpha = 3.49$ and $\beta = 2/3$. While ^{103}Pd and ^{125}I volume implants also can be described by the power law formula, they have somewhat larger exponents, β, since dose rate falls off faster with increasing volume than for high- energy sources.[220,221] The proportionality constant, α, is substantially lower, indicating that low-energy seed implants require higher source strengths to achieve a stated dose rate. The author-to-author variations in α values for the same radionuclide are due, in part, to differences in dose specification and implant construction. Anderson's analysis,[220] based on the pre-TRUS era Memorial nomogram, assumes that dose is specified in terms of matched peripheral dose (MPD) and that all seeds are implanted 2 to 5 mm inside the target (prostate) boundary, whereas the Yu nomogram assumes[221] that peripheral seeds are implanted on or outside the boundary and that minimum target dose is specified. Before using a nomogram or lookup table for QA checks or preplanning, readers should carefully assess its consistency with dose calculation and planning methods used in their clinical practices.

The best known manual planning tool for permanent ^{125}I implantation is the Memorial dimension averaging method[220,222] and its associated nomogram. It was designed to guide direct implantation of seeds into the prostate following surgical exposure via the retropubic approach. The method name is derived from the fact that the mean of the three measured orthogonal dimensions of the prostate is the main input to the nomogram. By means of several juxtaposed logarithmic scales, the nomogram predicts the total apparent activity, the number of seeds, and the needle spacing. The seeds were implanted inside the prostate, such that peripheral needle-to-target boundary distance is less than 50% of the interneedle spacing.

The calculation method is designed to deliver an MPD of 160 Gy over the life of the implant when d_a is more than 3 cm.[220] MPD is defined as the dose level whose corresponding 3D isodose surface encompasses a volume, V_E, equal to that of an ellipsoid having the same orthogonal dimensions as the originally measured target volume ($V_E = \pi d_x d_y d_z/6$). For a given implant, MPD is derived from the corresponding cumulative DVH, $V(D)$, according to $V_E = V(\text{MPD})$. Note that the prescribed doses of 160 Gy delivered in the 1985-1999 era correspond to doses of 144 Gy when corrected for implementation of the WAFAC primary standard and TG-43 dosimetry parameters.[167] The MPD overestimates minimum target dose (mPD) because the prostate gland is rarely ellipsoidal and has small protrusions that may extend outside the MPD isodose surface. Likewise, small deviations of the peripheral seeds from their planned locations can alter dramatically the shape of the MPD isodose surface. One study[223] found that, on average, MPD was twice the D_{99} level (the dose ensuring 99% target coverage on postoperative CT imaging) and that only 69% to 89% of the target volume received a dose equal to or greater than MPD.

Modern Approaches

The most important advance in permanent implantation in the past four decades is the rise of image-based and image-guided techniques in prostate BT. The retropubic approach has

been abandoned in favor of the transperineal approach using intraoperative TRUS imaging,[44,224] which typically consists[209] of (a) preplanning using a TRUS examination, or "volume" study, obtained 2 to 3 weeks before the scheduled implant; (b) inserting the needles using interactive real-time TRUS imaging; and (c) followed by CT-based postprocedural planning 0 to 30 days after the procedure. During preplanning, the PTV is often defined as the contoured prostate gland plus a discretionary margin. Most radiation oncologists practice some form of peripheral loading to improve uniformity and reduce dose to the urethra. For example, the modified uniform loading as defined by Butler et al[210] distributes about 75% of the source activity in the periphery and emphasizes insertion of peripheral needles on or near the PTV boundary. Typically, needle locations and seed strengths are manipulated to achieve a prescribed minimum target dose (mPD or $D_{100\%}$) of 145 Gy for ^{125}I monotherapy. For ^{103}Pd monotherapy, the American Brachytherapy Society (ABS)[147] recommends retaining the prescribed dose of 125 Gy (compared to 115 Gy used before 2000) following implementation of the NIST $S_{K,N99}$ standard and recently revised TG-43 parameters based on the AAPM's most recent reconstruction[167] of historical ^{103}Pd prescribed-to-administered dose ratios. For ^{131}Cs monotherapy, a prescribed dose of 115 Gy prescription has been used.[225] More detailed discussion can be found in Chapters 22 and AAPM TG-137 report.[226]

Dose specification, for recording and reporting doses actually administered by a permanent prostate implant, is based on postimplant dose evaluation.[226,227] Following the implant procedure, a CT examination is obtained; the prostate gland, rectum, and bladder are contoured; and the seed locations are identified from the transverse images. The choice of dose specification parameter for this purpose has been the subject of intense investigation. Based on analysis of both idealized and actual implants, Yu and colleagues[221] found that the postimplant D_{100} was very sensitive to small random displacements of the seeds from their intended positions, which resulted in underdoses of 15% or more to small volumes in the target periphery. However, they found that the mPD of the idealized implant (no seed displacement) covered at least 90% of the target (ie, $D_{90} \geq$ mPD and $V_{100} \geq 90\%$), even in the face of 6-mm seed displacements. In a study of 60 consecutive implant patients, Merrick and associates[228] found mean V_{100} and D_{90} values of 94% of the CT prostate volume and 108% of the prescribed dose (mPD of the preplanned implant), respectively. Of these patients, 82% had a D_{90} exceeding the preplanned mPD and no patient had a D_{90} smaller than 90% of mPD. In contrast, D_{100} was only 68% of the prescribed mPD, on average. Two groups[229,230] have found a correlation between prostate-specific antigen (PSA) relapse-free survival at 4 years and D_{90}. In particular, Potters and colleagues[229] found a D_{90} dose-response cutoff of 90% of the prescribed dose but could find no statistically significant cutoffs for D_{100} and V_{100}.

An important contemporary development is "intraoperative planning"[209,231] in which TRUS-based planning (and postimplant dose evaluation as well, in some implementations) is performed during the procedure itself rather than on a volume study acquired weeks before. Intraoperative planning eliminates uncertainties due to differences in planning and

treatment anatomy due to probe positioning errors or impact of hormone ablation or external beam therapy. An extension of intraoperative planning is dose-guided implantation[209,232] or "dynamic dose planning,"[233] in which intraoperative planning is repeated 1 or more times during the implantation procedure, thereby allowing optimized insertion of needles yet to be implanted to overcome errors in previously inserted sources.

Dose Specification in Interstitial Brachytherapy

The ability to objectively compare different interstitial implant plans as to target volume coverage, normal tissue sparing, and dose homogeneity depends on dose specification. The term "dose specification" means objective identification of a spatial volume or location for evaluating absorbed dose for the purposes of prescription, for describing the quantity of radiation actually delivered to the patient, or for reporting. The "specified dose" sometimes is called "reference dose." The dose that an implant actually delivers to the patient, based on postimplant treatment planning, may differ significantly from the dose prescribed for a variety of reasons. For example, anatomic or technical constraints may preclude accurate positioning of sources at their intended locations, resulting in a partial geometric miss or underdose of the specified volume.

Because of the high-dose gradients near the peripheral sources or the target volume boundary, reproducible specification of dose and evaluation of implant quality is difficult. Small differences in dose specification criteria can lead to large differences in treatment time or in the geometric relationship between implanted and treated volume. Many of the differences between the Manchester, Paris, and Quimby systems can be attributed to fundamental differences in dose specification. Several divergent and rather abstract approaches to dose specification have been developed and promoted by various national and international advisory groups; no single approach to dose specification has been widely accepted within the BT community.

Minimum Dose to an Anatomically Defined Target Volume

The minimum dose to the anatomically defined target volume harboring malignant cells is conceptually attractive because it is based on the intuitively satisfying premise that local tumor control will be determined by the minimum dose received by tumor cells. The ABS[234] recommends that minimum dose should be identified as accurately as possible by the best means available and should be used for dose prescription, evaluation, and reporting.

In practice, minimum target dose specification is difficult to implement clinically for many implants. In the prostate BT literature,[227] minimum target dose is usually called "minimum peripheral dose," or mPD, when used for implant preplanning prescription and D_{100} (see discussion on dose-volume histograms) when used for postimplant dose evaluation. When imaging data showing the target volume in relation to the sources is not available, the ABS recommends approximate target localization by means of intraoperatively placed surgical clips, orthogonal planar imaging, or measurements relative to peripheral sources.

A clear disadvantage of minimum dose specification is that the target volume surface lies within the zone of largest dose gradient. This can result in large patient-to-patient fluctuations in the central-to-specified dose ratio because of small variations in the peripheral source locations relative to the apparent target boundary or uncertainties in delineating the target volume. As discussed earlier in the "Permanent Implantation" section, reviews of CT-based prostate implant dose evaluations showed that absolute minimum delivered doses (D_{100}) relative to the prescribed dose exhibited large patient-to-patient variabilities and average about 30% to 60%.[228,235] The minimum dose covering at least 99% (or 95%) of the target volume was found to be much less sensitive to small changes in the peripheral seed locations or uncertainties in the target volume surface location.

Minimum Implant Dose Relative to Sources

Historically, treatment planning utilized planar radiographs for 3D reconstruction of radioactive source positions, yielding accurate dose estimates relative to the sources, but not to an anatomic target volume.[95,209] Thus, it was natural to prescribe treatment to a point or surface that has a fixed relationship to the peripheral sources. The minimum implant dose (MID) is the minimum dose received by the "target" volume defined relative to the implanted volume, the smallest regular geometric shape circumscribing the peripheral sources. Often, this specification volume is taken to be that volume that is 2 to 5 mm larger in each linear dimension relative to the implanted volume, as in the Paris and Quimby systems. Prior to the acceptance of image-guided BT, MID was perhaps the most widely used specification approach and is the basis of the classic systems and the U.S. practice of selecting prescription isodose surfaces from 2D isodose curve plots.

However, MID yields information about tumor coverage only to the extent that the radiation oncologist has implanted peripheral sources at known distances from the anatomic target volume boundaries. In addition, MID lies in the zone of maximum dose gradient and can be difficult to evaluate objectively for an implant of irregular shape, again leading to large patient-to-patient variations and variations in the central-to-prescribed dose ratio. The Paris and Manchester systems eliminate the possibility of subjective isodose selection by rigidly specifying dose rate by means of basal dose rate and implant tables, respectively.

Mean Central Dose

The ICRU report on dose specification in interstitial BT[192] emphasizes reporting MCD (see Figure 21.18), although it recommends reporting the prescribed dose, the peripheral dose (minimum target dose), and a description of dose uniformity as well. MCD specifies dose in the low-gradient regions located between adjacent source locations in the central plane of the implant. Thus, MCD is relatively free of the variability inherent in minimum peripheral or target dose specification. It is a generalization of the Paris system basal dose.

As a reporting parameter, MCD can be reproducibly estimated from 2D central transverse plane isodoses and should be very useful for comparing implants performed using different clinical systems. However, for systems other than the Paris and Manchester systems (which rigidly specify how sources are to be arranged relative to the target volume), MCD does not

have a known relationship to minimum peripheral or target dose. Thus, its value as a prescription parameter is limited.

Dose-Volume Histogram Representations

DVHs are 1D plots that describe the distribution of tissue volumes, V, irradiated by the implant with respect to dose, D. DVHs can be presented in either differential, $\Delta V(D)/\Delta D$, or cumulative, $V(D)$, forms. Differential DVH computation involves calculating dose over a fine 3D grid over a defined volume, dividing the dose axis into small bins of width ΔD, and then counting the number of voxels falling into each dose interval. The cumulative DVH gives the volume of tissue, $V(D)$, receiving a dose of at least D.

DVHs can be evaluated for specific anatomic regions (eg, target and normal tissue as illustrated by Figure 21.21) or can be evaluated for tissue irradiated by the implant without regard to anatomic boundaries. For bounded volumes, $V(D)$ is flat below the minimum dose received by the volume. When evaluated over unbounded space, $V(D)$ steeply increases with decreasing dose and asymptotically approaches the central point-source DVH, $V_{\text{point}}(\dot{D}) = (4\pi/3)\cdot[S_K\cdot\Lambda/\dot{D}]^{3/2}$. The use of DVHs has enriched discussions of dose specification by focusing attention on describing the 3D dose distribution rather than on single parameters. However, in the absence of target volume and normal tissue geometry, DVHs in themselves do not solve the dose specification problem.

Because 3D anatomic models were often lacking until recently, several FOMs derived from DVHs have been proposed that do not require an anatomically defined target volume. Such FOMs may be useful for ranking the quality of competing implant geometries in terms of uniformity and normal tissue sparing or for optimally selecting a specification dose rate for a given implant geometry. An important contribution is the "natural" DVH introduced by Anderson.[236,237] The natural DVH is a plot of $\Delta V(u)/\Delta u$, where $u = D^{-3/2}$. The natural DVH plots as a horizontal line for a central point source. It suppresses r^{-2} effects, which dominate the conventional $V(D)$ plot, making its detailed implant geometry-specific structure more evident. Low and Williamson[206] introduced an alternative modified DVH, $R_p(D) = V_{\text{impl}}(D)/V_{\text{point}}(D)$. Both of these modified DVHs show a sharply defined peak centered about MCD, the width and height of which quantify the volume of tissue receiving an approximately uniform dose. Other useful quality measures include the uniformity index[238] and the dose nonuniformity ratio (DNR).[239] The DNR, usually plotted as a function of reference dose, D_r, is defined as the ratio of volume receiving a specified multiple of D_r (usually 1.25 or 1.5) to that receiving at least D_r.

Target volume–dependent DVH quality indices were introduced into BT by Saw and Suntharalingam.[240] For single- and double-plane implants designed to cover specified cubic target volumes, respectively, they defined three indices as a function of reference dose rate D_r. The coverage index, CI(D_r), is that fraction of the target tissue receiving a dose rate $\geq D_r$. The homogeneity index, HI(D_r), is the fraction of target volume receiving dose rates between D_r and 1.5 D_r. The external volume index, EI(D_r), is the volume of tissue outside the target volume, expressed in multiples of the target volume, receiving dose rates $\geq D_r$.

When these indices are plotted (Figure 21.23), the tradeoffs among these clinical end points are evident. If a prescription dose rate is selected to maximize dose homogeneity (ie, maximize HI), then 85% to 95% coverage of the target must be accepted. To minimize irradiation of tissue outside the target, both target coverage and dose homogeneity must be compromised. Low and Williamson[206] suggested ranking competing implant geometries by specifying the HI achieved for the maximum reference dose level that yields a CI of unity.

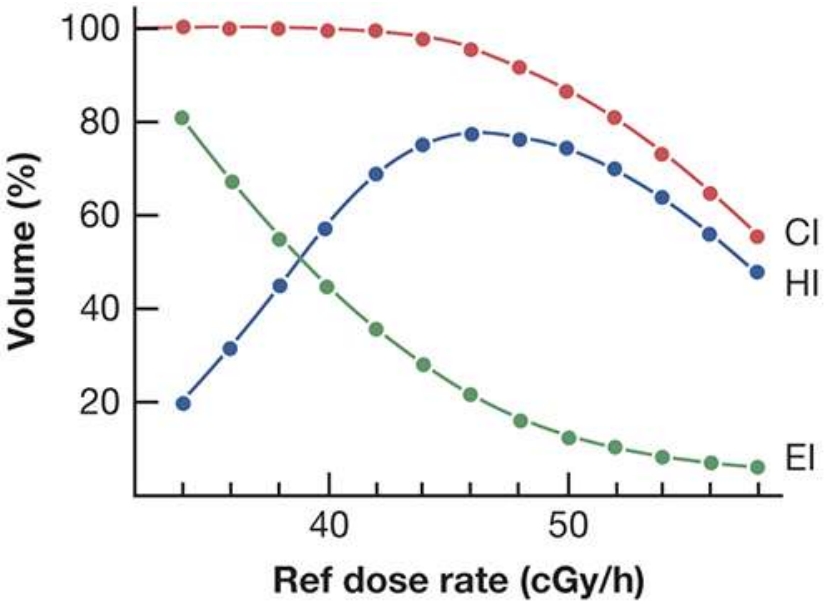


FIGURE 21.23 Plot of coverage index (CI), external index (EI), and homogeneity index (HI) as a function of reference dose rate for double-plane implant consisting of five ^{192}Ir ribbons with seven 1-mCi seeds in each plane and a 6-cm × 6-cm × 2.5-cm target volume. Ribbon and plane spacings of 1.5 cm were used. (From Saw CB, Suntharalingam N. Reference dose rates for single and double plane 192Ir implants. *Med Phys*. 1988;15[3]:391-396. Copyright © 1988 American Association of Physicists in Medicine. Reprinted by permission of John Wiley & Sons.)

For TRUS-guided prostate implantation, DVH metrics such as D_{100}, D_{99}, and D_{90}, denoting the minimum doses administered to the highest dose volumes covering 100%, 99%, and 90% of the contoured CTV or PTV, respectively, have become widely accepted as reporting parameters.[226,241] Volumetric indices, such as the V_{150}, V_{100}, and V_{90}, which denote the fraction of the CTV or PTV receiving at least 150%, 100%, and 90%, respectively, of the prescribed dose, are recommended to assess dose homogeneity and adequacy with which the prescription has been fulfilled.

INTRACAVITARY BRACHYTHERAPY

In contrast to the comparatively uniform dose distributions of interstitial BT, the unidirectional source arrangements used in intracavitary BT give rise to dose distributions that fall off rapidly with distance from the applicator surface. This produces large dose gradients across the target volume, making target volume–based dose specification difficult,

yielding a highly empirical treatment modality. Numerous parameters have been used to prescribe, constrain, or report intracavitary therapy applications. These include: mg-h, mgRaEq-h, reference point doses (points *A* and *B*), bladder and rectal reference point doses, vaginal surface dose, treatment time, the ICRU Report 38[3] 60-Gy reference volume, and, more recently, TRAK, rectovaginal reference point dose, and $D_{2\text{cm}^3}$ and $D_{0.1\text{cm}^3}$ for the bladder and rectum.[97] This section emphasizes the physical relationships among these parameters and their dependence on applicator characteristics. Systems for treating carcinoma of the cervix, the most intensively studied form of intracavitary therapy, are reviewed. Our focus is further restricted to applicator geometries and treatment systems derived from the Manchester system. This limited focus is justified by the fact that Manchester- or Fletcher-style applicators continue to be the dominant choice across the world for both HDR and LDR treatments.

The Manchester Family of Intracavitary Therapy Systems

The Manchester system, developed in 1938 by Tod and Meredith,[10] has heavily influenced intracavitary treatment practice patterns throughout the world, especially in North America. The widely used Fletcher-Suit applicator system, the Fletcher loadings, and point *A* and *B* reference points are all derived from the Manchester system. This system was the first to use applicators and loadings designed to satisfy specific dosimetric constraints.[10,242] It was also the first system to use a radiation field quantity, exposure at point *A*, rather than mg-h, to specify treatment.

The Classic Manchester System

The original Manchester applicator system consisted of a rubber intrauterine tandem and two vaginal "ovoids," whose ellipsoidal shape was designed to conform to the isodose curves arising from ^{226}Ra tubes placed along their long axes. The small, medium, and large ovoid minimum diameters were 2, 2.5, and 3 cm, respectively, and are the same as those used for the Fletcher colpostats.[243] The preloaded ovoids contained no shielding and relied on extensive anterior and posterior packing to spare bladder and rectal tissue.

The reference point *A* (Figure 21.24) was originally defined as the point "2 cm lateral to the center of the uterine canal and 2 cm from the mucous membrane of the lateral fornix in the plane of the uterus."[10] Point *A* was designed to represent average dose to the uterine vessels and ureters, an area termed "the paracervical triangle," which was believed to be the limiting factor in the treatment of cervical cancer. In current practice, point *A* dose is used to approximate the average or minimum dose to the tumor. Point *B*, defined to be 5 cm from the patient's midline at the same level as point *A*, was intended to quantify the dose delivered to the obturator lymph nodes.

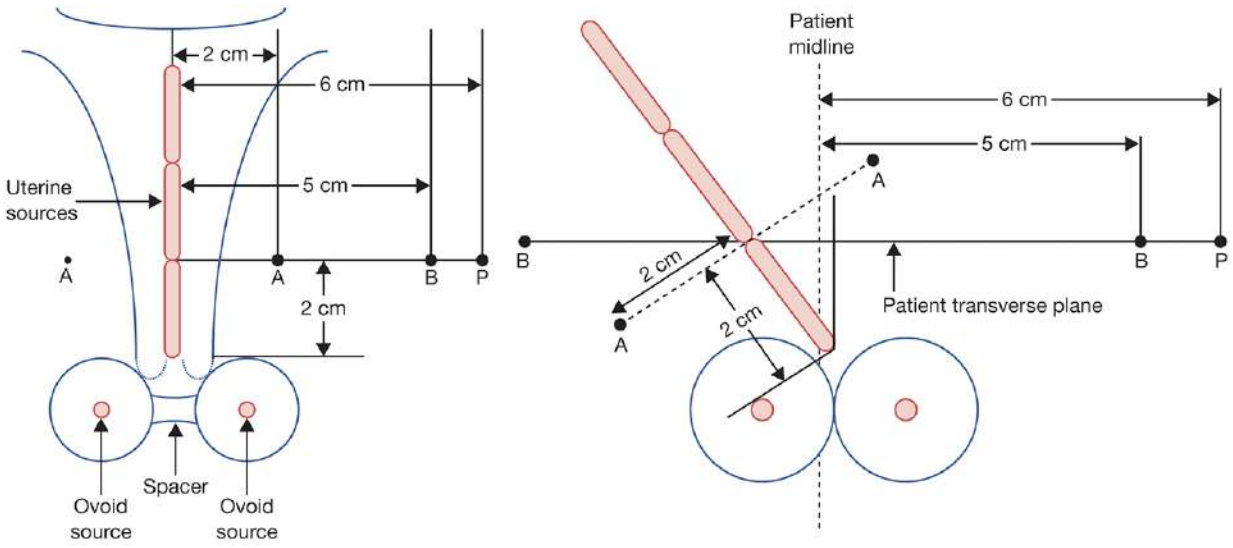


FIGURE 21.24 Definition of points *A* and *B* in an ideal application (left) and a distorted application (right), which is displaced to the left of the patient's midline, and a uterus, which is tilted toward the right. Note that point *A* is carried with the uterus, whereas points *B* and *P* are defined to be 5 and 6 cm, respectively, to the right and left of patient midline. Point *P* is used by the Mallinckrodt Institute of Radiology System to specify minimum dose to the pelvic lymph nodes. (Left: Adapted from Tod M, Meredith WJ. Treatment of cancer of the cervix uteri, a revised Manchester method. *Br J Radiol*. 1953;26(305):252-257. Reproduced by permission of The British Institute of Radiology; Right: Reprinted from Bacorro W, Dumas I, Levy A, et al. Contribution of image-guided adaptive brachytherapy to pelvic nodes treatment in locally advanced cervical cancer. *Brachytherapy*. 2017;16(2):366-372. Copyright © 2016 American Brachytherapy Society. With permission.)

The Manchester ovoid dimensions and applicator loadings were designed to ensure a constant point A dose rate (about 0.52 Gy/hour) for all allowed combinations. The design also ensured that the vaginal contribution to point *A* was limited to 40% of the total dose. Classic loading patterns included 17.5, 20, and 22.5 mg of radium for the small, medium, and large ovoids (to compensate for increased source-to-point *A* distance with increasing diameter), as well as 10 and 15 mg or 10, 10, and 15 mg sources for the medium (4 cm) and long (6 cm) tandems. These loadings satisfied the dosimetric constraints within 2%. The point *B* dose, determined largely by inverse-square law, is approximately 9 Gy for every 4,000 mg-h administered.

Without external beam treatment to the whole pelvis, a total point A dose of 72.8 Gy in 140 hours split between two applications was prescribed.[242] Regardless of applicator loading, delivery of a fixed point *A* dose amounts to using time, as the factor that terminates the treatment, compared to the Paris and Stockholm systems that prescribed a fixed number of mg-h (equivalent Manchester treatment regimens could deliver from 8,400 to 11,200 mg-h, a 33% variation).

As the size of an intracavitary application (ie, colpostat diameter and tandem length) increases, the penetration of the dose distribution increases. As colpostat diameter increases from 2 to 3 cm, the vaginal surface dose decreases by 35% relative to the dose 2 cm from the applicator surface; this is simply a consequence of increasing the source-to-surface distance. Similarly, increasing the tandem length increases the point *B* contribution relative to the uterine cavity surface dose; the radioactivity near the ends of the long tandem

contributes little to the surface dose (because of inverse-square law), whereas each tandem segment makes roughly equal contributions to points remote from the applicator. These physical principles underlie the practice of using the largest colpostats and longest tandem that the patient's anatomy can accommodate.[11,242]

Modern Fletcher-Suit Applicator Systems

The Fletcher applicator system (Figure 21.25A) adhered to the basic Manchester design while incorporating many improvements, including internal shielding. These shields are located on the medial aspects of the anterior and posterior colpostat faces (Figure 21.25B) and consist of 180° and 150° disk-shaped tungsten sectors 3- to 5-mm thick to shield the rectum and bladder, respectively.[243] The cylindrical colpostat body has a diameter of 2 cm that can be increased to 2.5 and 3 cm by the use of small and large slip-on plastic caps, thereby retaining the Manchester ovoid dimensions. Afterloading capability was added to the Fletcher applicator by Suit and coworkers.[2] The Fletcher loadings—15, 20, and 25 mg for small, medium, and large colpostats, respectively—are similar to those of the Manchester system, whereas tandem loadings are identical to their Manchester counterparts. Because of the similarity of Fletcher loadings to the Manchester loadings, point *A* dose rates are nearly independent of applicator dimensions.

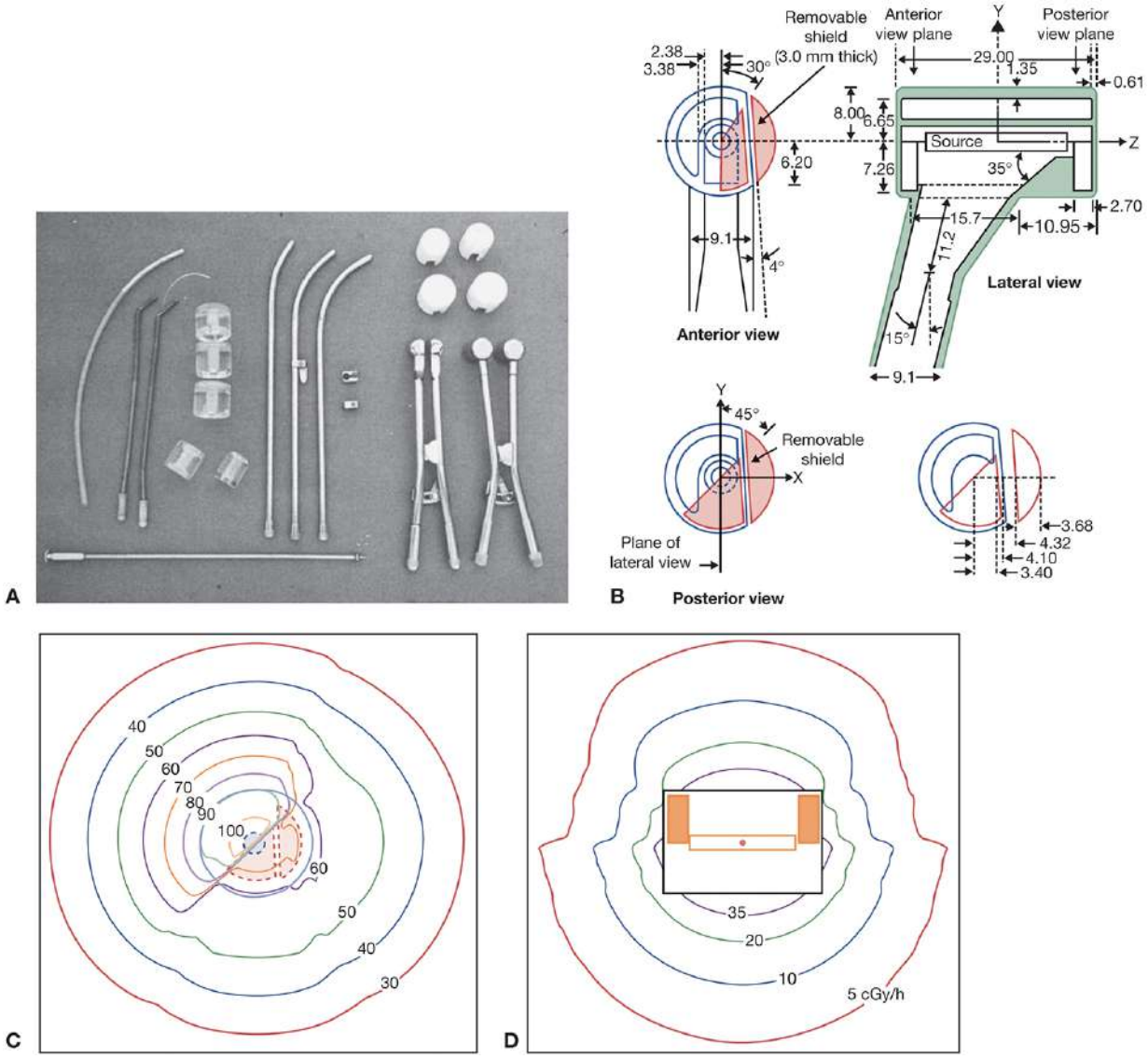


FIGURE 21.25 A. Fletcher-Suit applicator system. From left to right are tandem inserts loaded with dummy sources, colpostat source holders, vaginal cylinder sleeves, three curvatures of intrauterine tandems, cervical collars, Delclos mini-colpostats, and round handled Fletcher-Suit colpostats with small and medium caps. The tube-like instrument in the left foreground is a cervical localization seed implanter. (A. Reprinted with permission from Fletcher GH, Hamberger AD. Squamous cell carcinoma of the uterine cervix: treatment techniques according to size of the cervical lesion and extension. In: Fletcher GH, ed. *Textbook of Radiotherapy*. 3rd ed. Lea & Febiger; 1980;732-772.). B. Three orthogonal views of the 3M Fletcher-Suit Delclos colpostat consisting of a stainless steel body. The removable parts of the tungsten alloy shield, which allow conversion of the applicator to a shielded Delclos mini-colpostat, are inset into a nylon cap (not shown) with an outer diameter of 2 cm. Shown are isodose curves (C) in the coronal plane 10 mm from the posterior face of the applicator and (D) in the transverse plane of the colpostat for a 72 μGy·m^2/hour ^{137}Cs tube. (B-D. Reprinted from Williamson JF. Dose calculations about shielded gynecological colpostats. *Int J Radiat Oncol Biol Phys*. 1990;19[1]:167-178. Copyright © 1990 Elsevier. With permission.)

The shielded Fletcher colpostat was designed to reduce dose to the bladder trigone and the anterior rectal wall without decreasing irradiation to the uterosacral and broad ligaments, thereby reducing the need for the extensive vaginal packing characteristic of

Manchester insertions.[243] For a single colpostat (Figure 21.25B-D), the maximum dose reduction varies from 40% to 50%.[15,244,245] When the effects of the intrauterine tandem and the contralateral colpostat are included, applicator shielding reduces midline rectal and bladder doses by 21% to 34% relative to conventional treatment planning calculations, which ignore shielding and include only the effects of source encapsulation.[171] CT-based dose evaluation studies reveal that colpostat shielding modestly reduces rectal doses, reducing the rectal $D_{2\%}$ by 2% to 11%[246] and D_{2cc} by 10%.[247] Modern versions of the shielded Fletcher colpostat for LDR BT include the LDR 3M Fletcher-Suit Delclos (FSD)[15] and reproductions of the round handled Fletcher-Suit[244] colpostats. For HDR BT, the Fletcher-Williamson[248] applicator duplicates the original Fletcher shielding configuration. Weeks and Montana[249] have designed a CT-compatible version with afterloadable shields and an aluminum body having the same dimensions as the FSD applicator. Vendors of HDR remote afterloading systems and equipment also offer MRI- and CT-compatible variations of the Fletcher applicator.

Dose Specification in Intracavitary Brachytherapy

Point A Dose and Total Reference Air-Kerma

Two quantities are used widely to prescribe intracavitary BT: a product of source strength and treatment time (TRAK or, traditionally, mg-h) and point *A*. The first approach is mainly used in practices influenced by the MD Anderson Cancer Center system,[11,250,251] whereas some form of the Manchester point A dose specification is used by most other practitioners. Efforts to unify these two prescription practices by identifying a linear relationship between the two quantities are misguided[252] from the perspective of the Manchester system. A fixed point *A* dose will result in a range of TRAK due to source strength loading differences between the smallest and largest applicators, whereas a fixed TRAK delivery will result in large variations in treatment time and point *A* dose.

The proportionality of point *A* dose and treatment time applies only to the classic (Manchester) definition of point *A*. Many radiation oncologists use a revised definition of point *A* (Figure 21.26) that references its location to the cervical os (tandem collar, proximal aspect of the most caudal tandem source, or a gold seed implanted in the cervix) rather than to the lateral fornix. This practice obscures the relationship between point *A* and milligram-hour prescription philosophies. Potish and Gerbi's[252] study of 90 Fletcher applications demonstrates that the revised point *A* dose rates vary widely from patient to patient and are, on average, significantly higher than the classic Manchester value. Because point *A* is fixed to the tandem and the vertical tandem-to-colpostat displacement varies with each patient, the vaginal contribution to point *A* is highly variable. In contrast, classically defined point *A* dose rates are tightly grouped, independent of the loading, and in close agreement with the Tod-Meredith value. The vaginal contribution to classic point *A* is fixed by definition, whereas the intrauterine contribution is insensitive to colpostat-to-tandem displacement because of the parallel tandem isodose curves. Thus, the revised point *A* definition does not have the physical significance of the classic quantity. The use of revised point *A* dose to prescribe therapy for "free-floating" tandem and colpostat insertions may introduce large

patient-to-patient fluctuations in treatment times because of small, clinically insignificant variations in implant geometry. Significantly, the recent ICRU Report 89[97] on prescribing and reporting BT for cervical cancer has endorsed the classic point A definition.

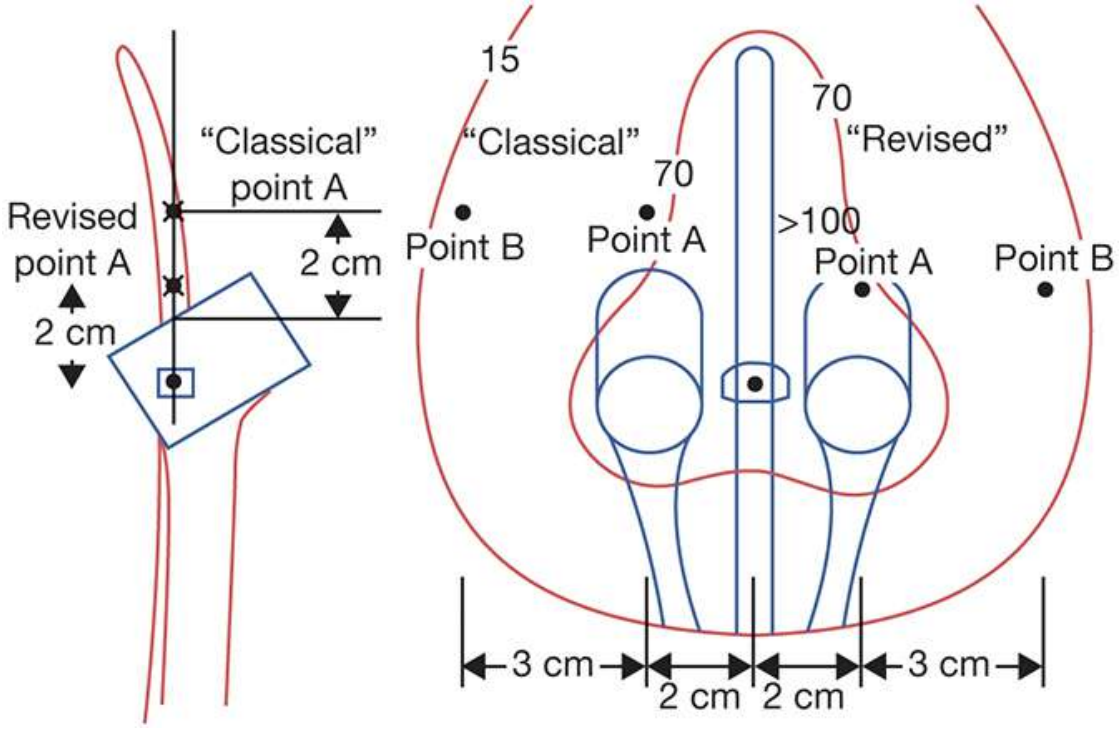


FIGURE 21.26 Radiographic definition of classic point *A* (2 cm above the cephalic-most aspect of the colpostat in the tilted coronal plane) and the revised point *A* (2 cm above the cervical collar top or center). Because the distance from caudal most intrauterine source tip to colpostat center (tandem-to-colpostat displacement) varies from patient to patient, the vaginal contribution to revised point *A* is highly variable. The revised definition was suggested by Tod and Meredith in their 1953 article.[242] (Used with permission of Radiological Society of North America from Potish RA, Gerbi BJ. Role of point A in the era of computerized dosimetry. *Radiology*. 1986;158[3]:827-831; permission conveyed through Copyright Clearance Center.)

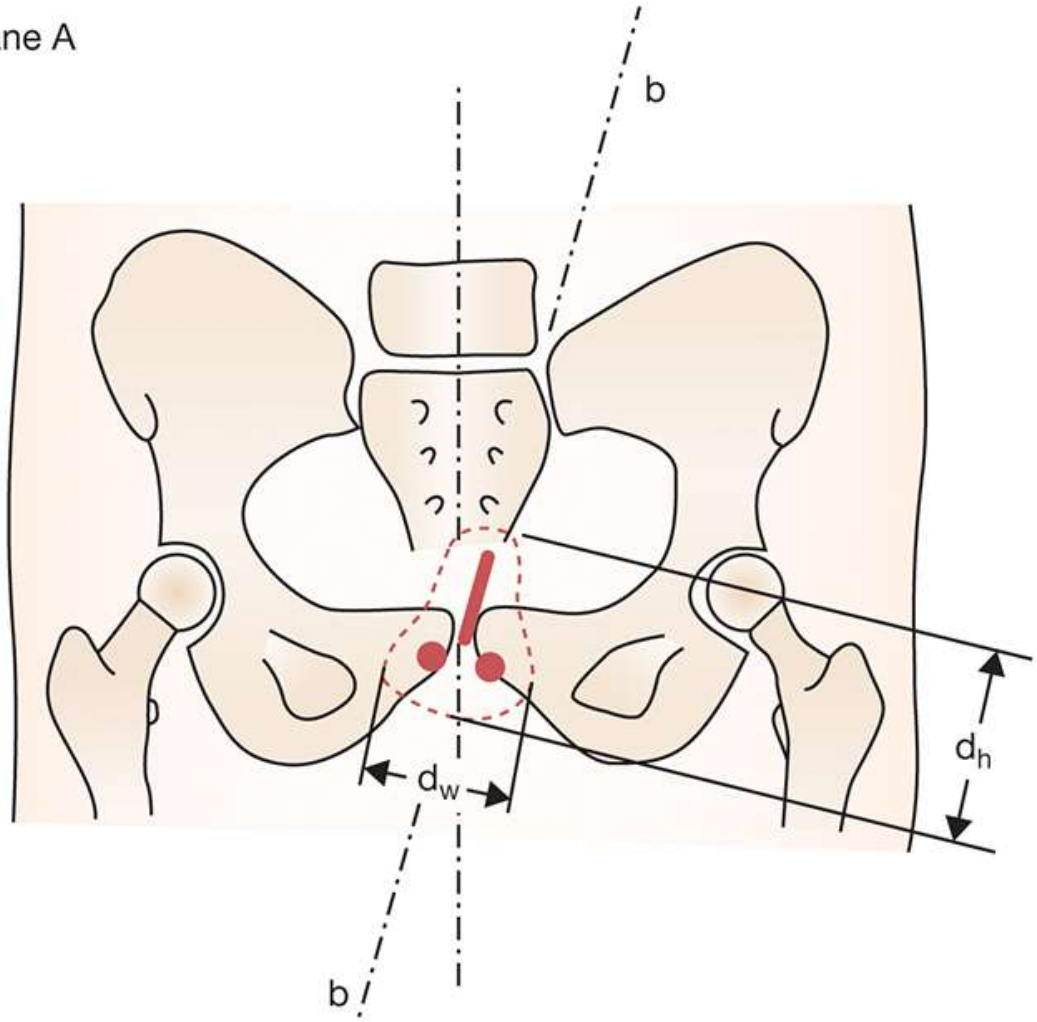
The previous discussion is applicable only to the Fletcher applicator system with relative loadings approximating those of the Manchester system. As the intrauterine to vaginal loading ratio (1:1 for the Manchester system) increases, the maximum width of the pear-shaped reference isodoses falls and the rectal dose increases.[253] Understanding how loading influences isodose shape and normal tissue doses is especially important in HDR BT, as well weight optimization can lead to deviations from the classical loading rules. Using judiciously placed dose points to control the relative dimensions of the point *A* isodose surface, Mai et al[254] were able to increase tapering near the cephalad aspect of the tandem, to reduce the vaginal surface dose, and to modestly reduce the rectal dose with only slight loss of the maximum width of the pear-shaped isodose. These considerations suggest that dose point–driven optimization of the dwell-weight distribution should be accompanied by a geometric analysis of the point *A* isodose surface so that changes to target coverage can be assessed at least approximately.

Other applicators in current use include the HDR tandem and ring applicator[255] and the LDR Henschke applicator.[1] The latter consists of hemispheric colpostats rigidly attached to the tandem with the vaginal source axes parallel to the intrauterine sources rather than transverse as in the Fletcher system. Henschke colpostats with internal shielding[256] are available. The vaginal ring applicator consists of a circular guide tube (usually 34 mm outer diameter) with its plane fixed rigidly normal to the tandem. It is placed up against the cervix and vaginal fornices with a donut-shaped cap attached, which increases the distance between the vaginal mucosa and the circular array of dwell positions (of which only the lateral dwell positions are activated) to 7 mm (compared to 10-15 mm for the Fletcher colpostat). Thus, the fraction of source strength loaded into the ring must be reduced to avoid overdosing the vaginal mucosa.[254,257] Although rectal and vaginal vault doses relative to the point *A* dose similar to that of the Fletcher system can be achieved through careful optimization, the lateral coverage, (ie, maximum coronal width of the point A isodose) is reduced.[254] Care must be taken in positioning the applicator system to avoid underdosing the gross tumor volume (GTV). Applicator geometry and loading practices should be changed only after extensive comparative evaluation of the old and new dose distributions to avoid dose distribution changes that would invalidate the evaluated clinical experience on which the radiation oncologist's knowledge of dose-response rests. Finally, for applicator systems that deviate from the classic Manchester geometry or relative loading rules, one cannot assume that point *A* dose is proportional to treatment time over all allowed variations of applicator sizes and loadings.

Volumetric Specification of Intracavitary Treatment: International Commission on Radiation Units and Measurements Report 38 Recommendations

While the recommendations in ICRU Report 38 have been superseded by ICRU Report 89, an overview of the Report 38 recommendations is included for completeness. The ICRU[3] introduced the concept of reference volume enclosed by the reference isodose surface for reporting and comparing intracavitary treatments performed in different centers, regardless of the applicator system, insertion technique, and method of treatment prescription used. For gynecologic BT, ICRU Report 38 recommended that the reference volume be taken as the 60-Gy isodose surface, including dose from external beam irradiation and intracavitary BT. The ICRU proposed that this pear-shaped reference volume (Figure 21.27) be described in terms of its three orthogonal maximal dimensions: height (d_h), width (d_w), and thickness (d_t), measured in the oblique coronal and sagittal planes containing the intrauterine sources. In addition to the 60-Gy volume, ICRU 38 also recommended reporting the dose to the bladder and rectal reference points, which are illustrated in Figure 21.28.

Plane A



Plane B

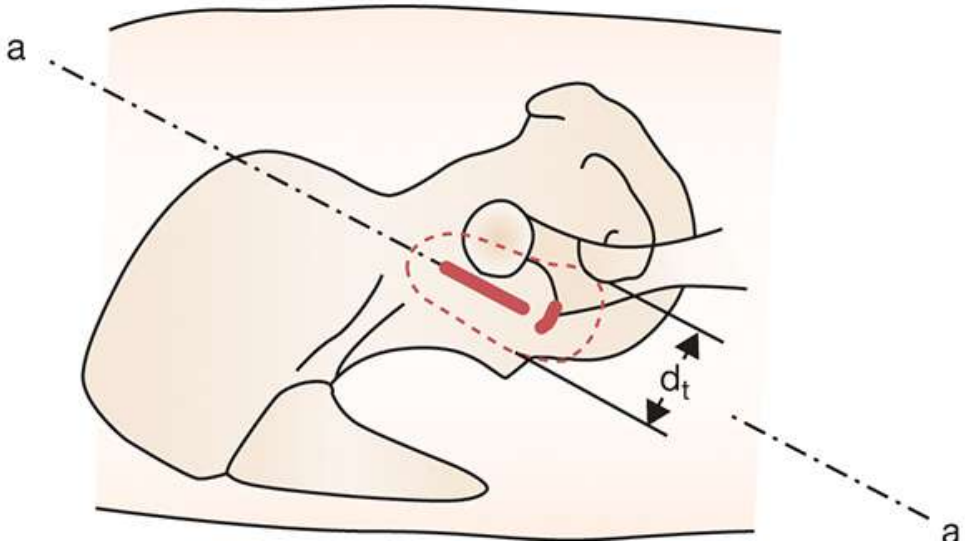


FIGURE 21.27 Geometry for measuring the three orthogonal dimensions of the pear-shaped International Commission on Radiation Units and Measurements reference isodose surface (broken line) in a typical treatment of cervix carcinoma using one rod-shaped uterine applicator and two vaginal applicators. Plane A is the "oblique" frontal plane that contains the intrauterine device. The oblique frontal plane is obtained by rotation of the frontal plane around a transverse axis. Plane B is the "oblique" sagittal plane that contains the intrauterine device. The oblique sagittal plane is obtained by rotation of the sagittal plane around the anteroposterior axis. The height (d_h) and the width (d_w) of the reference volume are measured in plane A as the maximal sizes parallel and perpendicular to the uterine applicator, respectively. The thickness (d_t) of the reference volume is measured in plane B as the maximal size perpendicular to the uterine applicator. (From International Commission of Radiation Units and Measurements. *ICRU Report 38, Dose and Volume Specification for Reporting Intracavitary Therapy in Gynecology*. International Commission of Radiation Units and Measurements; 1985. Copyright © 1985 International Commission on Radiation Units and Measurements. Reprinted by permission of SAGE Publications.)

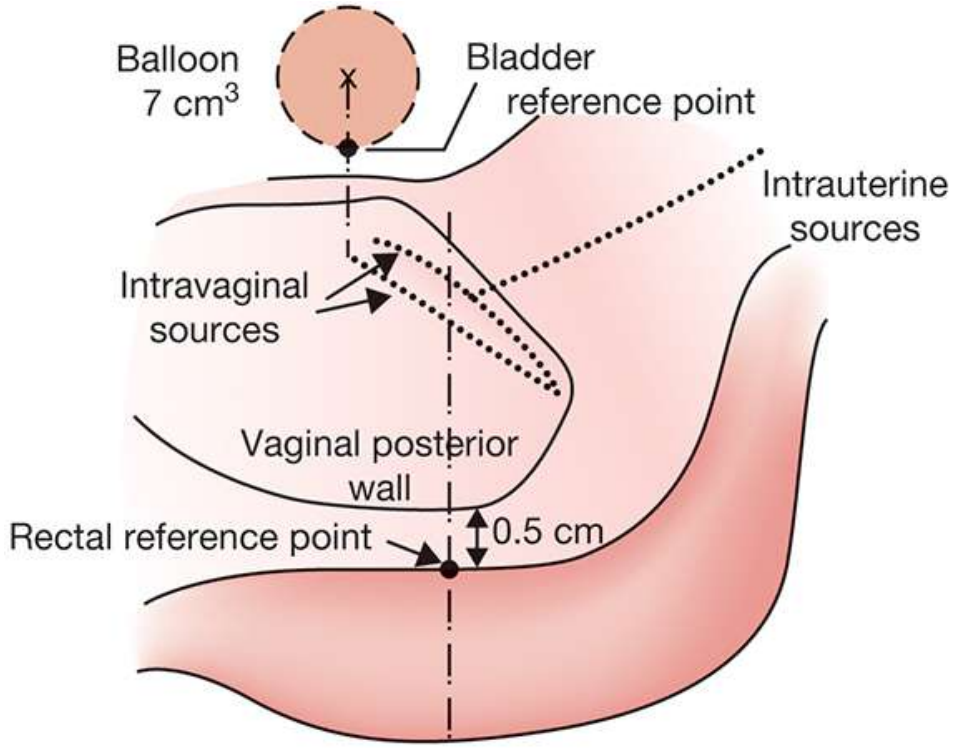


FIGURE 21.28 Reference points for bladder and rectal brachytherapy doses proposed by International Commission on Radiation Units and Measurements Report 38.[3] (From International Commission of Radiation Units and Measurements. ICRU Report 38, Dose and Volume Specification for Reporting Intracavitary Therapy in Gynecology. International Commission of Radiation Units and Measurements; 1985. Copyright © 1985 International Commission on Radiation Units and Measurements. Reprinted by permission of SAGE Publications.)

In contrast to point *A* dose, the ICRU proposal is only a means of describing or reporting treatment. No guidance is given as to how to prescribe treatment, use these measurements to evaluate implant quality, or correlate reference volume dimensions with clinical outcome. The 60-Gy dose-level choice appears to have been motivated by the preoperative radiotherapy regimen popular at that time within the French school of radiotherapy.[258] The current ICRU Report 89[97] discards the concept of a reference isodose surface for a single

fixed total (external plus intracavitary) dose level, for example, the volume enclosed by the prescription isodose surfaces (typically 85 and 60 Gy) for the high- and intermediate-risk CTVs (CTVHR and CTVIR) (typically 85 and 60 Gy) to the high- and intermediate-risk CTVs (CTV_{HR} and CTV_{IR}). The ICRU 38 and 89 reference volume concepts appropriately emphasize that the volume of tissue irradiated, as well as dose, is an important predictor of clinical response to intracavitary irradiation. Wilkinson and Ramachandran[259] and Eisbruch et al[260] used DVHs to study the correlation between volume enclosed by intracavitary isodose surfaces and other prescription parameters. The latter analyzed the volumetric characteristics of 204 intracavitary insertions in 128 patients with carcinoma of the cervix and demonstrated that intracavitary implants delivering the same TRAK have nearly identical DVHs over the dose range of clinical interest despite significant differences in geometry and loadings. They also showed that the volume, $V(D, T)$, enclosed by isodose surfaces can be estimated accurately from a modified power law model requiring knowledge of only the intracavitary dose in cGy (D) and TRAK (T). The consequences of the findings above can be summarized as follows:

1. Volumetrically, an intracavitary implant behaves like a central point source: $V(D, M) \propto (M/D)^{3/2}$.
2. Describing an implant in terms of volume contained within its isodose curves carries no more information content than a statement of TRAK (historically mgRaEq-h).
3. The volume of tissue irradiated to a specified dose is closely related to total exposure given by the implant in terms of TRAK.

Consequence 2 suggests that the correlation between clinical outcome, in terms of tumor control and complications and isodose surface volume, should be no better or worse than the correlation between clinical outcome and TRAK for a fixed external pelvis dose. Consequence 3 suggests a new and fundamental physical interpretation of TRAK (a derivative of mgRaEq-h). Prescribing intracavitary BT by TRAK is equivalent to treating until each specified isodose surface achieves a fixed volume, independent of the underlying implant geometry. The use of TRAK to constrain intracavitary treatment, therefore, limits the volume of tissue irradiated to high doses. This observation may help explain the clinical utility of TRAK (and historically mgRaEq-h) as a dose specification parameter. Finally, the individual reference isodose dimensions, which are more strongly influenced by implant geometry than their product, clearly convey additional information about the spatial extension of the reference isodose surface in their respective planes and cannot be reduced to a statement of total exposure from the implant and may have additional prognostic significance.

Practical Systems for Intracavitary Prescription and Reporting

For Manchester-like loadings and applicators, if treatment were to be prescribed as a fixed TRAK without regard to the diameter and length of the applicators, the treatment times and total point A doses would differ by the ratio of total source strengths in the applications. Small applications would have unacceptably high point A and vaginal vault surface doses

and excessively long treatment times. Additionally, large applications treated to a fixed TRAK prescription would underdose these reference points. In contrast, the ICRU reference volume for fixed levels of whole-pelvic irradiation and TRAK would be independent of the loading because the TRAK is constant. Conversely, when the point *A* dose is held constant, the TRAK needed to deliver these doses will vary significantly, introducing corresponding variations in the volume of the ICRU reference isodose.

Physically, TRAK controls the volume of tissue treated to high doses, and parameters such as time, colpostat surface dose, and point *A* are used to control doses at points near the applicator to ensure that normal tissue tolerance is not exceeded and that the tumor is not undertreated. For each applicator combination and choice of external beam dose, a compromise between volume of tissue treated and dose delivered near the applicator must be reached. For example, the Fletcher system[11,261] specifies both a maximum treatment time and maximum milligram-hour constraint for each combination of external beam and intracavitary therapy (Table 21.10). Whichever constraint is reached first terminates the application. Small applications tend to be terminated by the maximum time constraint, which limits the milligram-hour and prevents tissues near the applicator from exceeding tolerance doses, whereas larger applications are terminated by the milligram-hour constraint, ensuring adequate dose to the tumor. Although the historical Fletcher system does not use the point *A* dose for either prescription or reporting, the total point *A* dose is constant within 12% for allowed tandem and colpostat loadings within each treatment scheme (A-E) of Table 21.10. The reader should note that the Fletcher system is a complex, highly individualized treatment system that resists formulation in terms of a few rules. Table 21.10 is a highly condensed and simplified summary derived from the literature, not from observation of current MD Anderson Cancer Center practice patterns.

TABLE 21.10 SIMPLIFIED FLETCHER SYSTEM PRESCRIPTIONS

		External Beam		Intracavitary Maximum		Range: Smallest to Largest Insertion		
Treatment Scheme	Indications	Whole Pelvis	Split Field	mg-h[a]	Time (hours)	Point *A*	Point *B*[b]	mg-h[a]
A	<1 cm tumor	0 Gy	0 Gy	6,000	72	59-63 Gy	17-22	6,600-10,000
				4,000	48			
B	IB/IIB 1-3 cm tumor	0	<40	5,400	72	56-59	57-60	6,600-9,000
				3,600	48			
C		20	<20	3,600	48	67-69	54-56	5,500-7,500
				3,900	52			
D	Endocervical tumor; Ib/IIb moderate bulk (3-6 cm) disease;	40	<10[b]	3,250	48	81-90	63-64	5,280-6,500
	IIB/IIIB bulky (>6 cm) tumor with good			3,250	48			

		External Beam		Intracavitary Maximum		Range: Smallest to Largest Insertion		
Treatment Scheme	Indications	Whole Pelvis	Split Field	mg-h[a]	Time (hours)	Point *A*	Point *B*[b]	mg-h[a]
	regression							
E	Bulky disease with poor regression	50	0	2,500 2,500 or 5,000	48 48 or 72	81-94	62	5,000

[a]Radium tubes with 1-mm platinum filtration.

[b]With maximum split-field dose.

Derived from Potish RA, Gerbi BJ. Cervical cancer: intracavitary dose specification and prescription. *Radiology*. 1987;165(2):555-560.

Manchester-like applicator loadings used for LDR applications yield an approximately constant point *A* dose rate of 65 cGy/hour. For HDR applications, the dwell weights are selected to duplicate the relative Manchester loadings and the TRAK per insertion is reduced to reflect the increased radiobiologic effectiveness of the HDR fractionation schedule relative to the LDR regimen. Classically defined point *A* doses are calculated for reporting purposes, although this quantity plays no role in prescribing therapy. Dose to the pelvic lymph nodes is calculated at point *P*, located 2 cm superior to the lateral fornix and 6 cm lateral to the patient's midline. The 2013 ICRU Report 89[97] continues to recommend the ICRU Report No. 38[3] bladder and rectal reference points for conventional 2D orthogonal film dosimetry.

Summary Principles: Intracavitary Brachytherapy Dose Specification

The most widely used intracavitary BT systems in North America are based on Manchester-type loadings and applicators, in which the point *A* dose rate is approximately constant and independent of loading, leading to a linear relationship between point A dose and time, not TRAK. Practical TRAK systems use various dose specification parameters to constrain and guide treatment and are far more Manchester like than the "strict" milligram-hour philosophy would suggest. These parameters have the following roles: (a) TRAK limits the volume of tissue treated to a high dose; (b) point *A* dose ensures that tumor periphery receives adequate dose; (c) vaginal surface dose ensures that dose to mucosal surfaces in contact with the applicator system remains within tolerance; and (d) treatment time ensures indirect control of point *A* dose.

Although the traditional treatment specification quantities have clear physical meanings and interrelationships, these concepts can be applied to patient treatment only within a clinical system supported by a base of evaluated clinical experience. In current practice, implant placement is guided by direct visualization and palpation, and treatment prescription is guided by the radiation oncologist's knowledge of treatment outcome averaged over groups of uniformly treated patients with similar tumor size and location and medical condition. This implies that the implant system must be applied as a whole: Mixing

dose specification methods, insertion techniques, and normal tissue dose-response relationships from different clinical systems are dangerous practices that can lead to suboptimal or indeterminate clinical outcomes. Second, because classic dose specification quantities incompletely describe the dose distribution, a radiation oncologist must be trained in all details of an intracavitary system to duplicate the results of its developers. Finally, for the clinical physicist, consistency of current dosimetric practice with past clinical experience may be more important than absolute dose computation accuracy or compliance with a practice standard external to the treatment system.

Image-Guided Intracavitary Brachytherapy

Classic intracavitary BT, with its empirically based rules, prescription practices, and feedback derived from patient follow-up to shape and position intracavitary dose distributions, demonstrates that even massive cervical cancers are potentially curable with concomitant chemoradiation therapy. In an effort to improve clinical outcomes in locally advanced cervical cancer and to reduce the significant incidence of local failure and late normal tissue toxicity, anatomy-based dose specification using 3D x-ray CT or MRI studies acquired with the applicator system in place has been intensively investigated. Early studies[262-264] consistently demonstrated that conventional orthogonal film-based reference points (2D planning) overestimate minimum doses to the cervix and underestimate maximum doses to critical structures by factors of 1.5 to 2.3 with large patient-to-patient variations. Because MRI has been shown to be far superior to CT for distinguishing tumor from normal cervical stroma[265] and for delineating surrounding critical structures, advisory groups[49,266] recommend using T2-weighted MRI studies acquired prior to initiating treatment and after each intracavitary insertion for BT planning and dose reconstruction. This has culminated in the publication of a revised ICRU Report 89[97] that provides detailed guidance for planning, prescribing, and reporting intracavitary BT in the MRI-guided era. An important innovation is a widely accepted target volume nomenclature (high-risk, intermediate-risk, and low-risk CTVs, denoted by CTV_{HR}, CTV_{IR}, and CTV_{LR}, respectively) and specific DVH parameters[267] for assessing the correlation between clinical outcome and the delivered dose distribution. The CTV_{HR} includes the entire cervix along with all palpable or presumed residual gross tumor volume (GTV_{res}) at the time of each intracavitary insertion. ICRU Report 89 recommends a dynamic adaptive treatment philosophy: The goal of each insertion is to deliver the prescribed D_{90} dose (roughly comparable to point *A* dose) to the "residual" CTV_{HR} for a total (external beam and BT) $D_{2Gy,90}$ dose (in 2-Gy fraction equivalents) of 85 to 90 Gy. The CTV_{IR} consists of the initial CTV_{HR} (based on the pretreatment GTV_{init} plus a margin for microscopic disease (typically 5 mm anterior-posteriorly and 10 mm elsewhere)). It typically receives a total D_{90} dose (D_{2Gy}) of 65 to 70 Gy for locally advanced disease. In addition to recommending tracking the classic dose specification quantities (TRAK and point *A*, bladder, and rectal reference doses), ICRU Report 89[97] recommends tracking D_{90} and D_{98} for CTV_{HR} and CTV_{IR} coverage and

$D_{2\text{cm}^3}$ and $D_{0.1\text{cm}^3}$ for assessing bladder and rectal doses. The report also provides a simplified linear-quadratic (LQ) model for converting LDR, HDR, and external beam doses into equivalent 2-Gy fractionated doses.

In addition to the ICRU, the Groupe Européen de Curithérapie European Society for Radiation Oncology (GEC-ESTRO) also offers consensus guidelines, drafted along with other national BT societies such as the ABS, the Indian Brachytherapy Society, and the Canadian Brachytherapy Group, pertaining to CT-based contouring for image-guided adaptive BT, target definition, and quality indicators for cervical cancers.[268-270]

Early reports of image-based conformal therapy in locally advanced cervical cancer are promising. For example, the use of intensity-modulated radiation therapy (IMRT) to replace traditional whole- and split-pelvis fields[271,272] suggests that grade III/IV late toxicity is significantly reduced relative to historical controls without increasing local recurrence. The most extensively reported experience with MRI-based intracavitary BT planning (156 patients at Medical University of Vienna) achieved excellent 3-year local control rates of 86% to 100% (International Federation of Gynecology and Obstetrics [FIGO] Ib-IIIb) with 3-year grade II/IV late toxicities of 4% or less[273] and demonstrated a robust dose-response relationship between CTV_{HR}, D_{90} and D_{100} for large tumors[274] and a good correlation between bladder and rectal DVH parameters, for example, $D_{2\text{cm}^3}$, and major late complications.[275]

The group at Aarhus University Hospital, in Aarhus, Denmark, reported on the use of MRI-guided adaptive radiotherapy for the treatment of cervical cancer in 2013.[276] For a cohort of 140 patients, they used MRI-guided adaptive radiotherapy, which included IMRT or volumetric modulated arc therapy (VMAT) treatment to 40 to 60 Gy (with 60 Gy used for simultaneous integrated boost to nodes), concurrent chemotherapy for 79% of patients, BT using a PDR source, and a tandem and ring applicator with a needle cap and plastic needles in cases needing hybrid intracavitary/interstitial treatment. They compared these results with previous results of a CT-based 3D conformal EBRT technique with BT boost planned using x-ray imaging. They found 3-year local control rates of 91%, compared to 63% in the previous study and a reduction in moderate and severe late morbidity of approximately 50%,[276] highlighting the improvements that can be obtained with image-guided adaptive BT.

The EMBRACE collaboration reported the results of their multicenter prospective study regarding MRI guidance in cervical cancer in 2021.[277] The aim of the EMBRACE-I trial was to evaluate the rates of morbidity and local control using MRI-based adaptive BT. The study included 24 centers from across Europe, Asia, and North America and included patients with biopsy-proven cancer of the uterine cervix, with FIGO stage IB to IVA disease and FIGO stage IVB disease restricted to node metastasis below the L1-L2 interspace. Treatment included chemoradiotherapy (cisplatin plus 3D conformal, IMRT, or VMAT EBRT), followed by MRI-based image-guided adaptive BT. They found that, at a median follow-up of 51 months, morbidity for genitourinary, gastrointestinal, vaginal, and fistulae events were all below 8.5%, and overall 5-year control was 92%,[277] illustrating the

effectiveness and long-term control offered by MRI-guided adaptive BT combined with chemoradiotherapy.

Challenges to image-guided intracavitary therapy include substantial soft tissue displacement and deformation due to applicator insertion and removal, tumor regression, and bladder and rectal filling variations (all ignored by clinical experiences cited above), making it difficult to meaningfully evaluate cumulative dose distributions. An important area of research is application of deformable image registration to account explicitly for the temporal sequence of deforming 3D anatomies needed to accurately characterize a multiple insertion course of intracavitary and external beam therapy.[278] Using dose summation over weekly MRI sets that had been contoured and nonrigidly registered, Lim et al[279] demonstrated that 5-mm PTV expansion of CTV_{IR} for the IMRT component of treatment was adequate for most patients, although large variations between planned and cumulative normal tissue doses was observed for some patients. As IMRT is used to create more conformal external beam dose distributions and to address peripheral CTV_{HR} underdoses by the intracavitary treatment components, the need to accurately account for local tissue deformation will become more acute.[280]

THE RADIOBIOLOGY OF BRACHYTHERAPY

The highly conformal dose distribution characteristic of BT sources significantly reduces the exposed volume, and often, the maximum dose in adjacent normal tissues, compared to EBRT.[12,281] Such dose sparing helps reduce both early- and late-responding normal tissue sequelae, making the short treatment times commonly used in temporary implant BT tolerable. This is in contrast to conventional EBRT where the risk of early-responding tissue sequelae requires treatment times to be prolonged for up to about 8 weeks, potentially reducing tumor control through tumor cell repopulation. Modern image-guided EBRT, such as stereotactic radiosurgery and stereotactic body radiotherapy, also takes advantage of the geometric dose sparing of adjacent normal tissues (via reduced PTV margin) to enable shortened overall treatment time (via hypofractionation). The short overall treatment times used in temporary implants confer both clinical and socioeconomic benefits for those tumor sites (eg, cervix, head and neck, and lung) where long overall treatment time is associated with reduced local control.

In addition to the dose-sparing advantages, the development of high-strength remote-afterloading stepping sources and low-energy permanently implantable sources has also resulted in clinical utilization of dose rates and dose-time- fractionation patterns that can differ radically from conventional LDR BT and EBRT. The interaction of such diverse temporal dose delivery patterns with the underlying cellular processes of the irradiated tumor and normal tissues could lead to different treatment responses for the same prescribed total dose.[282] A clear understanding of the radiobiologic implications of the spatial-temporal dose delivery patterns used in BT and combined EBRT and BT has become an essential clinical need.

Biophysical Modeling of Brachytherapy

The interactions of tissue biologic factors with BT dose delivery are complex and can be influenced by not only the total dose but also the dose rate, dose fractionation pattern, and photon energy emitted by the BT sources. Mathematical modeling of the radiobiologic interactions between relevant factors of the radiation field and the irradiated tissue has offered useful tools for elucidating the basic radiobiologic features of different BT techniques, comparing relative effects of different spatial-temporal dose delivery patterns, and designing iso-effective dose delivery schemes.

Most biophysical models use radiation-induced cell kill (or cell survival) as a surrogate for radiotherapeutic responses. Although not the sole determinant of biologic response, there is now a wealth of evidence that cell killing, that is, loss of reproductive integrity, is the dominant determinant of radiotherapeutic response, both for early- and late-responding endpoints.[283] Of the available cell survival models, the LQ model, which is based on mechanistic notions about how cells are killed by radiation and unequivocally distinguishes between early and late responses, is used most often in radiation oncology. After several decades of investigation and use, the basic ideas and parameters in the LQ model have been well supported by clinical experience and outcome data. The application of the LQ formalism to radiation therapy has been reviewed by Thames and Hendry,[283] Dale,[284] Fowler,[285] and many others.

The Linear-Quadratic Model

Central to the LQ approach is a biologic model of radiation action, which was spelled out in detail more than 70 years ago by Lea and Catcheside,[286,287] based on a mechanistic analysis of radiation-induced chromosomal aberration induction. In the most basic LQ approach, cellular survival, S, from dose D given in a single acute exposure or fraction, is written as

$$S(D) = \exp(-\alpha D - \beta D^2) \tag{21.34}$$

The mechanistic interpretation of Eq. 21.34 is that cell killing results from the interaction of two elementary damaged species, most often DNA double-strand breaks (DSBs), to produce species that cause cell lethality, such as dicentric chromosomal aberrations. The first term in Eq. 21.34, which is linear in dose, describes production of two DSBs by the same ionizing radiation quantum (usually a charged particle), while the second term, quadratic in dose, describes production of multiple DSBs by two independent quanta. Equation 21.34 for acute irradiation captures the intrinsic radiosensitivity of the irradiated cells but lacks explicit accounting of the cellular repair, repopulation, redistribution, and reoxygenation—the four "Rs" of radiobiology—that often dominate the radiobiologic responses.[288] Equation 21.34 can be extended to include these four "Rs," as described below, which is necessary for modeling the effects of different temporal dose delivery patterns used in BT.

Cellular Damage Repair

If the radiation is delivered over a protracted period rather than delivered acutely, two DSBs may be formed at different times. Therefore, it is possible that the first may be repaired before it has a chance to interact with the second. This will not affect the first term in Eq. 21.34, because the two DSBs are formed simultaneously from a single-particle track, but DSB repair during a prolonged exposure will result in a reduction of the second, quadratic term in Eq. 21.34, by a factor denoted by "G"[286,287]:

$$S(D) = \exp(-\alpha D - G \cdot \beta D^2) \qquad (21.35)$$

where, for acute exposures, $G \rightarrow 1$, and for very long exposures, $G \rightarrow 0$. In this context, "acute" and "long" are defined relative to the half-time (T_r) for DSB repair of sublethal damage. In general, G will depend on the detailed temporal distribution of dose delivery as well as on T_r. For many BT temporal dose delivery patterns, G can be expressed analytically in closed forms.[282] For example, LDR implants with dose delivered at a constant dose rate over an extended period T, $G = 2[\exp(-mT) + mT - 1]/(mT)^2$, where m ($=0.693/T_r$) is the sublethal damage repair rate. Formulae for G for many other schemes, such as fractionated, PDR, and permanent BT dose delivery, have been derived,[287,289] as has a general formalism for any possible protraction scheme.[290]

The LQ formalism, described by Eqs. 21.34 and 21.35, can be derived from a variety of underlying mechanistic models via first-order time-dependent perturbation theory when the dose or dose rate is not too high, a constraint that includes most clinically and experimentally relevant doses and dose rates.[291] For example, the theory of dual radiation action[292] is only one of several different approaches to describing radiobiology damage mechanistically. The approach devised by Lea and his coworkers[286,287] deals instead with the kinetics of damage development. Typical kinetic models track the temporal evolution of lesions as a cell gradually repairs or misrepairs the initial damage.[293-295] Many different molecular mechanisms have been studied kinetically, such as pairwise misrepair of DNA DSBs, direct one-hit induction of lethal lesions, and saturable repair pathways in which the repair enzyme system can be overloaded.

Cell Repopulation

For temporary implants or HDR, the effect of tumor cell repopulation is generally small over the treatment course, but this is not necessarily the case with longer permanent implants. Equation 21.35 can be simply modified to take into account repopulation, hence the effects of overall time. Following the original formulation by Travis and Tucker,[296] repopulation is taken into account by increasing the surviving fraction by a factor $\exp(gT)$, where T is the overall treatment time. One can also take into account delay in the onset of accelerated repopulation, by replacing T with $(T - T_D)$, where T_D is the delay after the

beginning of the treatment before tumor cell proliferation begins.[285] Then the surviving fraction is given by

$$S = \exp\left[-\alpha D - G \cdot \beta D^2 + \gamma\left(T - T_D\right)\right] \qquad (21.36)$$

The parameter g determines the rate of repopulation and is given by $\gamma = 0.693/T_P$, where T_P is the effective doubling time of cells in the tumor. When cell loss is negligible, T_P is the same as T_{POT}, which is the measurable[297] in vitro doubling time of the tumor cells.

Redistribution and Reoxygenation

The LQ model can be further extended to include redistribution of cell cycle progression and reoxygenation during irradiation by treating these two "Rs" as aspects of a single phenomenon, termed *resensitization*,[298] which occurs when a radiation exposure preferentially kills the more radiosensitive cells in a diverse population, leaving a cell population with decreased average radiosensitivity. Subsequent biologically driven changes tend to gradually restore the original population average radiosensitivity. The resultant linear-quadratic resensitization (LQR) model uses two additional adjustable parameters—an overall resensitization rate τ_S (analogous to sublethal damage repair rate) and overall resensitization amplitude $\frac{1}{2}\sigma^2$. The LQR model replaces the LQ Eq. 21.35 with:

$$S(D) = \exp(-\alpha D - G\beta D^2 + \tfrac{1}{2}\sigma^2 \hat{G}^2 D^2) \qquad (21.37)$$

The new term, $\frac{1}{2}\sigma^2\hat{G}D^2$, is the product of $\frac{1}{2}\sigma^2$ (representing the average of the dominant resensitization effects over the heterogeneous tumor), while the factor $\hat{G}$ models the influence of fractionation on resensitization. $\hat{G}$ is assumed to have exactly the same form as the sublethal damage repair function, G, except that μ is replaced by τ_S. In contrast to repair, resensitization tends to increase radiosensitivity as the overall time increases. For example, tumor cells in a resistant part of the cell cycle at the beginning of the treatment, and thus were spared preferentially, may move to a more sensitive part of the cell cycle as the treatment progresses. While mechanistically driven, LQR is sufficiently simple that it can be used for isoeffect calculations in radiation therapy and supporting reasonable fits to relevant experimental data.[298]

General Utility of the Linear Quadratic Model

The LQ model (Eqs. 21.34-21.37) can be used to elucidate the general radiobiologic properties of major BT delivery techniques by using G and $\hat{G}$ factors appropriate for their respective temporal dose delivery patterns.[282] We discuss some of the key radiobiologic

features of BT delineated by the LQ model in Section 6.3 (see section "Radiobiologic Features of Brachytherapy").

The LQ model can also be used as a convenient tool to compare the relative effectiveness of different BT dose delivery techniques or to design "equivalent" dose protraction protocols (ie, design a regimen with the same tumor response, or the same late complications, as a "tried-and-tested" regimen). To design a new dose protraction protocol (labeled "2"), which will have the same effect as a current protocol (labeled "1"), based on Eq. 21.35, we need to ensure the quantity ($aD + GbD^2$) is equal for the two protocols, that is,

$$D_1\left[1 + G_1 D_1 / (\alpha / \beta)\right] = D_2\left[1 + G_2 D_2 / (\alpha / \beta)\right] \qquad (21.38)$$

The quantity on either side of Eq. 21.38 is often called the biologically effective dose (BED),[285] that is,

$$\mathrm{BED} = D[1 + \mathrm{GD}/(\alpha/\beta)] \qquad (21.39)$$

Comparing the relative effectiveness of different BT protocols amounts to comparing their BED values, and generating a new "equivalent" regime amounts to matching BEDs for the old and new regimes.

When the new dose protraction protocol (the right-hand side of Eq. 21.38) is chosen as conventional EBRT delivered in 2-Gy per fraction, Eq. 21.38 can be used to determine the equivalent total dose, EQD2, which, when delivered in 2 Gy per fraction, will result in the same BED (ie, cell kill) of the current BT protocol, that is,

$$\mathrm{EQD2} = \mathrm{BED}/[1 + 2/(\alpha/\beta)] \qquad (21.40)$$

EQD2 is a more intuitive LQ-based biophysical index to use clinically as it is easily relatable to the clinical experiences of conventional EBRT given in 2-Gy fractions.

If tumor repopulation, reoxygenation, or redistribution are relevant, then, in order to design a new equivalent regimen, rather than comparing/match the quantity ($\alpha\, D + G \cdot \beta\, D^2$), we need to compare/match the quantity ($\alpha\, D + G \cdot \beta\, D^2 - \gamma\, [T - T_D]$) or

$\left(\alpha D + G \cdot \beta D^2 - \frac{1}{2}\sigma^2 \hat{G} D^2 - \gamma\left[T - T_D\right]\right)$. Equations 21.39 and 21.40 can be modified accordingly to take into account these cellular processes.

In addition, LQ model can be used as input to high-level models, such as tumor-control probabilities (TCPs) or normal tissue complication probabilities (NTCPs). To do so, we need additional models relating cellular survival (S) with TCP or NTCP. The simplest approach, originating with Munro and Gilbert,[299] equates TCP with the probability that after radiation treatment there are no remaining tumor stem cells capable of initiating tumor regrowth. Let us suppose that a dose, D, delivered in a given protraction pattern, produces a stem cell survival probability, S. Then, the probability that any given stem cell will be unable to initiate tumor regrowth is $(1 - S)$. Let K be the initial number of potential stem cells in the tumor. The TCP for the irradiated tumor is thus simply $(1 - S)^K$, which, for small values of S, can be approximated as

$$\mathrm{TCP} = \exp\left(-S \cdot K\right) \tag{21.41}$$

If cell survival, S, is described by Eq. 21.35, then

$$\begin{aligned}\mathrm{TCP}(D) &= \exp\left[-K \cdot \exp\left(-\alpha D - G \cdot \beta D^2\right)\right] \\ &= \exp\left[-\exp\left(\ln K - \alpha D - G \cdot \beta D^2\right)\right]\end{aligned} \tag{21.42}$$

Equation 21.42 may also be used to calculate NTCPs, except that now the parameter K does not refer to the number of tumor cells that need to be sterilized, but rather to the number of groups of cells in the normal tissue ("tissue-rescuing units"),[300] whose destruction would result in the late complication.

A problem with Eq. 21.42, or similar approaches to estimate clinical outcomes de novo, is that absolute values of TCP or NTCP are exquisitely sensitive to the parameter values, particularly the K parameter. In contrast, using the LQ model to compare competing protraction regimens or design equivalent dose protraction protocols (Eq. 21.38 and its extensions described above) makes no assumptions about the relationship between surviving fraction and clinical outcome and, therefore, is much less sensitive to the LQ parameter values.[301] The latter is a more robust application of the LQ model.

To improve the clinical utility of TCP or NTCP models, extensive efforts have been made to fit these models to clinical data, yielding tumor-/tissue-specific model parameters, for example, for head and neck tumors,[302,303] breast tumors,[304,305] prostate cancer,[306,307] brain

tumors,[308] rectal cancer,[309] and liver cancer.[310] In addition, empirical NTCP models such as Lyman-Kutcher-Burman (LKB) models were often used to model normal tissue complications.

Radiobiologic Features of Brachytherapy

Rationale for Low-Dose Rate Brachytherapy

It has long been known that lowering the dose rate generally reduces biologic damage[311] because of increased opportunity to repair the sublethal damages.[286,287] It also has been clear since the pioneering work of Coutard[312] that fractionating or protracting a radiotherapeutic exposure improves the "therapeutic ratio" (ratio of tumor control to complications). However, the exact link between these observations was not clearly made until the 1980s by Withers and colleagues.[313,314]

To understand their insight, consider the observed isoeffect curves shown in Figure 21.29 representing "equivalent" schemes for either early- or late-responding endpoints as a function of dose per fraction, a surrogate for dose rate. The generally steeper slopes of the solid line indicate that the late-responding tissues are more sensitive than early-responding tissues to changes in the protraction of a given radiation dose. For higher dose rates, the dose reduction needed to match late effects is larger than the dose reduction needed to match early effects, such as tumor control for typical tumors. For any selected dose, increasing the dose rate will increase late effects much more than it will increase tumor control. Conversely, decreasing the dose rate will decrease late effects much more than it will decrease tumor control. Thus, the therapeutic ratio increases as the dose rate decreases.

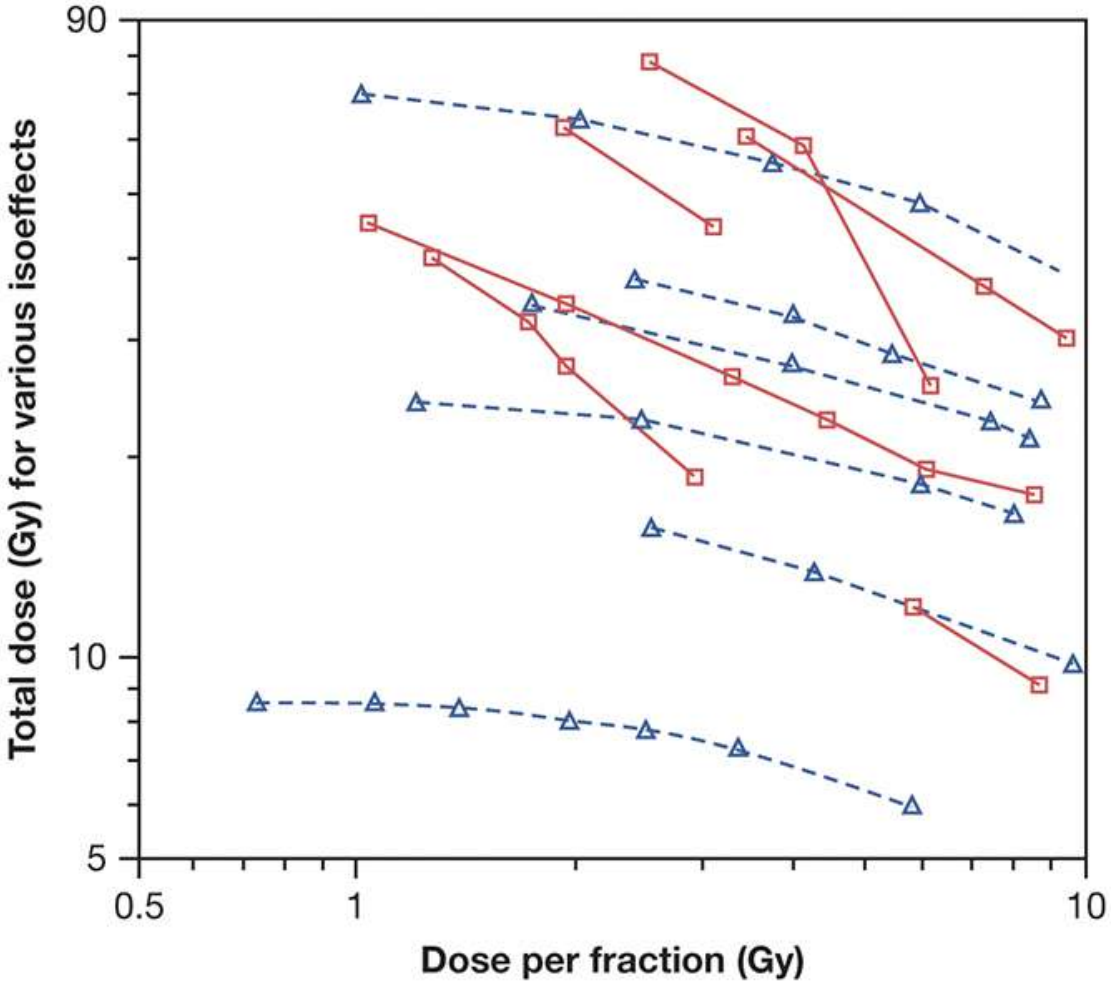


FIGURE 21.29 Isoeffect curves showing the total dose to produce a given end point, plotted against dose per fraction, a surrogate, in this context, for dose rate. The triangles, joined by dashed lines, refer to a variety of early-responding end points (of which tumor control is an example), whereas the squares, joined by solid lines, refer to a variety of late-responding sequelae. Note the generally steeper slopes of the solid lines, suggesting that late-responding tissues are more sensitive than early-responding tissues to changes in the protraction of a given radiation dose. (Adapted from Withers HR, Taylor JM, Maciejewski B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. *Acta Oncol*. 1988;27[2]:131-146.[396])

These observations can be interpreted in terms of the α/β ratio[313] in the LQ Eq. 21.38. In terms of survival curves (Figure 21.30), the α/β ratio essentially describes the degree of "curviness" of the acute survival curve. A small value of α/β means that the β (dose squared) term dominates cell killing at radiotherapeutic doses, resulting in a curvy survival curve (Figure 21.30). A large value of α/β means that the linear in-dose α term dominates, resulting in a straighter semi-log survival curve. Now, as a first approximation, the dose-response relation for a fractionated (or LDR) regimen can be thought of as simply the result of multiple repeats of the initial part of the survival curve. It is clear that repeating the early part of a curvy survival curve many times will result in far more sparing than repeating the early part of a straighter survival curve.

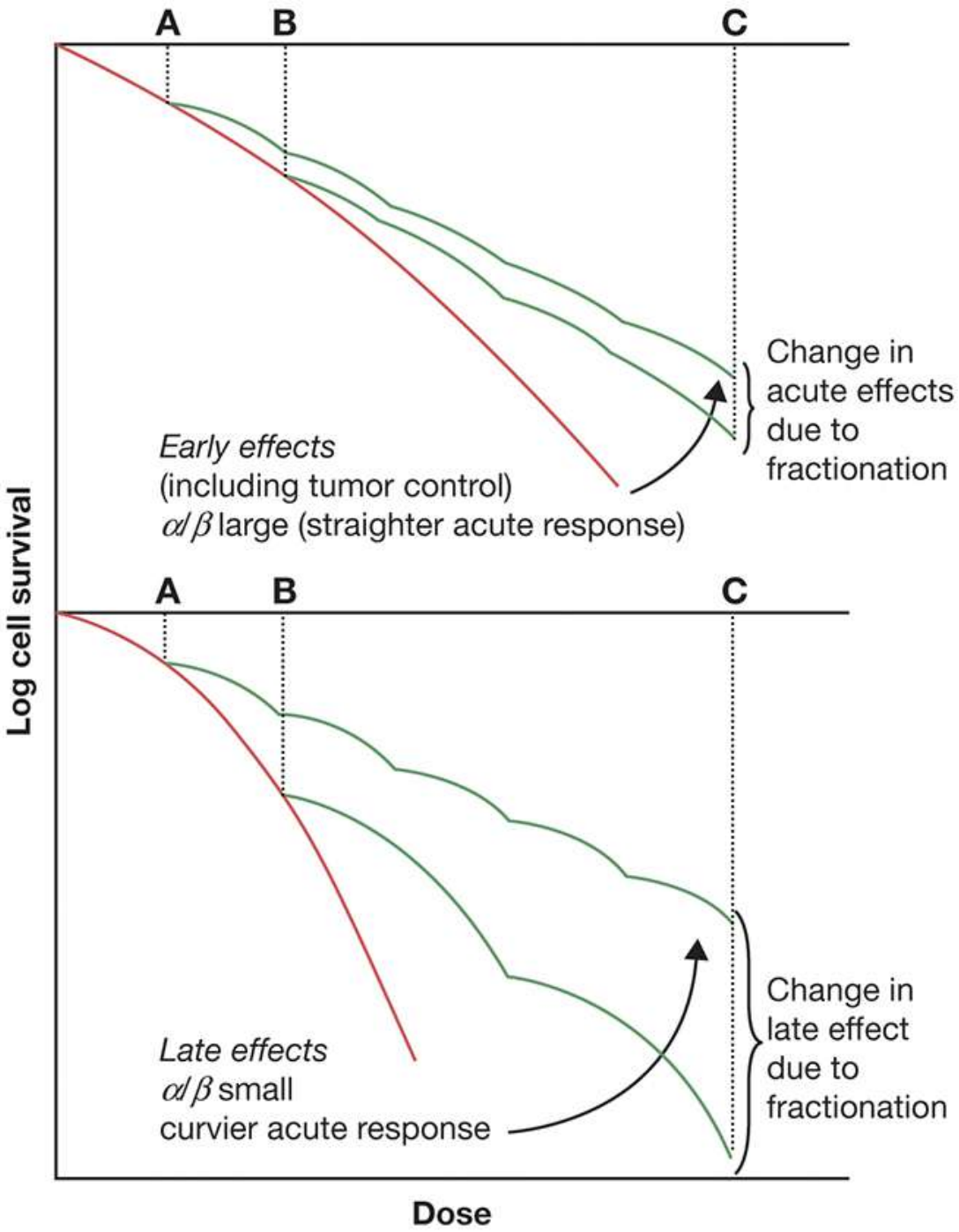


FIGURE 21.30 Illustration of the differing effects of protraction on early- and late-responding tissues, as elucidated by Thames and colleagues.[313] (Reprinted from Thames HD Jr, Withers HR, Peters LJ, Fletcher GH. Changes in early and late radiation responses with altered dose fractionation: implications for dose-survival relationships. *Int J Radiat Oncol Biol Phys*. 1982;8(2):219-226. Copyright © 1982 Elsevier. With permission.)

Thus, late effects, which are very sensitive to changes in fractionation, are characterized by small values of α/β (a typical value is 3 Gy), and early effects (tumor control or early-responding normal tissue sequelae) are characterized by large values of α/β, a typical value

for most tumors being about 10 Gy. As clinical data from which α/β ratios can be derived have accumulated, the dichotomy between α/β ratios for early and late effects has held up remarkably well. Consequently, when using the LQ model, it is essential to be clear about whether the calculation is designed to refer to early- or late-responding tissue and to then use the appropriate a/b value. From Eq. 21.38, it is clear that the use of different values of α/β will result in different predictions for the isoeffect dose.

High Dose Rate Intracavitary Brachytherapy for Cervical Cancer

There has been a trend moving toward increased use of fractionated HDR BT in many tumor sites, driven initially by the economic and logistical benefits of outpatient-based fractionated HDR BT. While in some situations, such as palliative or intraoperative BT, the therapeutic ratio between tumor control and late sequelae is not a primary consideration, in general for curative intent treatments, increasing the dose rate is likely to *decrease* the therapeutic advantage between tumor control and late sequelae as discussed in the previous section, unless significantly more fractions are used in the HDR regimens. However, there are two curative applications (intracavitary BT for cancer of the uterine cervix and interstitial BT for prostate cancer) where, for differing reasons, HDR BT is as effective, or potentially even more effective, compared to LDR BT.

The radiobiologic principles involved in converting LDR to HDR intracavitary BT are illustrated schematically in Figure 21.31, which shows typical dose-response relationships for early- and late-responding tissues. Suppose that we want to replace an LDR treatment delivering dose D by an HDR treatment that gives identical tumor control. As illustrated in the left panel of Figure 21.31, we need to reduce the dose by a dose reduction factor DRF. As discussed in the previous section, the dose-response relations for late effects are significantly "curvier" (smaller α/β ratio) than for early-responding tissues such as tumors that typically have larger α/β ratios. It can be seen, from the right panel of Figure 21.31, that this adjusted dose, DRF × D, will result in increased late effects compared to LDR. However, the LDR dose to OAR giving rise to the late effects is not the treatment dose D, but often at some lower dose value, $f \times D$, where $0 < f \leq 1$. This is the case for cervical BT because the bladder and rectum are generally some significant distance from the cervical implant. For example, if $f = ½$, that is, the OAR dose is half the treatment dose ($D/2$), we see, from the right-hand panel in Figure 21.31, that if HDR preserves the LDR level of dose sparing, that is, delivers dose DRF × D/2 to the OAR, where DRF matches tumor control, the late effects for HDR could be comparable to LDR because we are further up the survival curve for HDR late effects. Indeed, if the rectal dose were an even smaller fraction of the treatment dose (say $D/3$, in Figure 21.31), HDR would have even *less* late effects than the equivalent LDR regimen. In fact, if the cervical BT results in a dose to the bladder/rectum that is less than about ¾ of the treatment dose, the HDR late effects should not be worse than the LDR late effects when the HDR dose is reduced to give equal tumor control compared with LDR.[290,315]

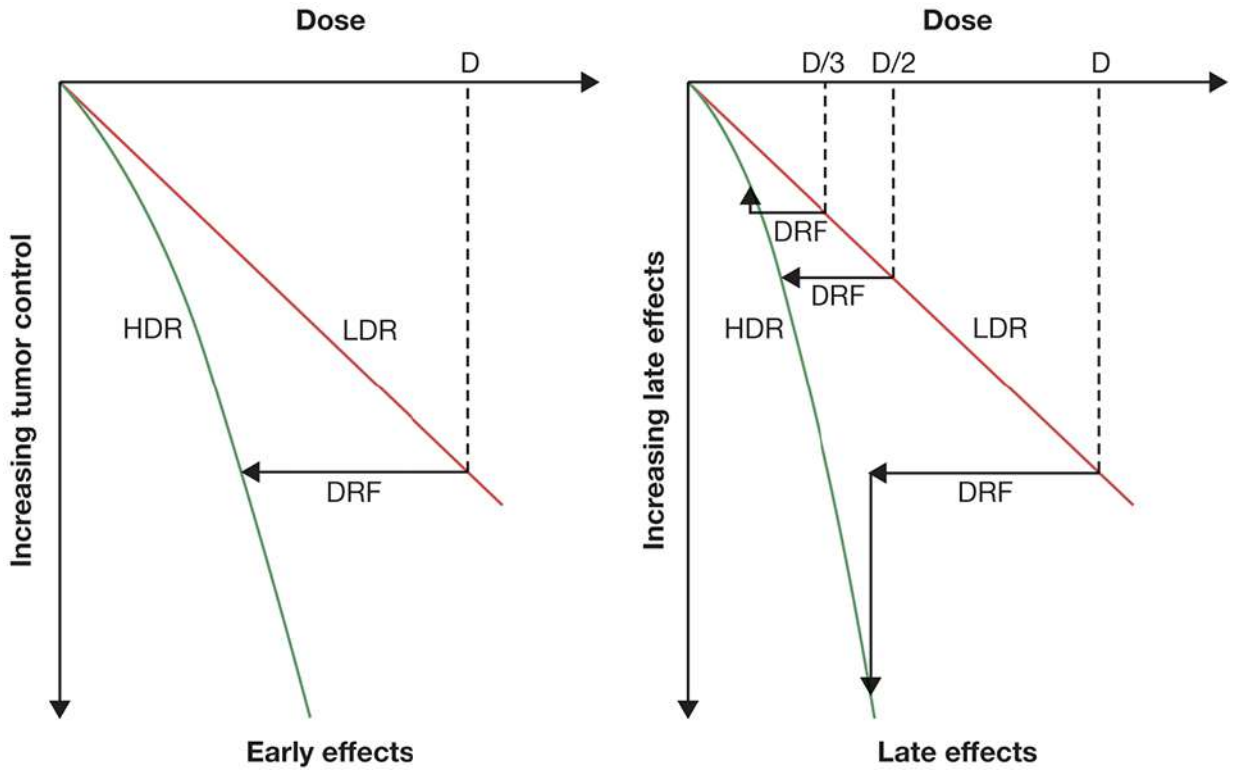


FIGURE 21.31 Illustration of the interplay between early and late effects for low-dose rate (LDR) and high-dose rate (HDR) brachytherapy for cervical cancer. DRF is the dose reduction factor that produces the same early effects (tumor control) for HDR as LDR. If *D* is the LDR giving rise to late effects, then reducing *D* by DRF for HDR will result in more late effects than at LDR. As the HDR dose to late-responding tissue is reduced by treatment planning, then reducing that dose by the factor DRF no longer produces worse late effects than at LDR.

There is another related factor to consider, that is, the short treatment time characteristic of HDR allows packing and retraction of the sensitive organs, which typically results in a 20% further decrease in the rectal/bladder dose compared to that achievable with LDR.[316] This gives an extra physically based advantage to HDR, in addition to the biologic factors discussed here.

The above radiobiologic consideration suggests that when the dose to the dose-limiting critical normal tissues (bladder/rectum) is less than about three-fourths of the prescribed dose, HDR (with at least about five fractions to ensure adequate tumor reoxygenation) results in comparable (or less) late effects than LDR—for the same level of tumor control for cervical cancer BT. These considerations are supported by a number of clinical studies.[317-323] These reports generally show that HDR and LDR for cervical BT produce similar local control and late complications.

As *BT* is often combined with pelvic *EBRT*, different time dose patterns of *EBRT* and intracavitary *BT* should be taken into account to calculate the combined effects to tumor and *OAR*s. The *EQD*2 from *EBRT* and *BT* may be summed up, assuming that the volumes and points of interest of *BT* receive the full *EBRT* dose. This estimate serves as a worst-case assumption for *OAR*s and is reasonable for the target volume of *BT*, which is often a boost

volume of the *PTV* of *EBRT*. A more appropriate calculation should consider highly heterogeneous dose of *BT* as discussed in the "Relative Biologic Effectiveness of Different Brachytherapy Sources" section.

High-Dose Rate Interstitial Brachytherapy for Prostate Cancer

As discussed earlier in the "Rationale for Low-Dose Rate Brachytherapy" section, one of the main reasons for protracting any radiotherapeutic exposure is that late sequelae are characterized by relatively low α/β ratios (3 Gy is typical) while tumors typically have higher α/β ratios (10 Gy is typical); lowering the dose rate generally spares late-responding tissues more than the tumor. The higher tumor α/β ratios are thought to be due to the larger proportion of cycling cells in tumors compared with normal tissues. However, because prostate tumors contain unusually small fractions of cycling cells,[297] it has been hypothesized that they may have α/β ratios and responses to protraction more typical of late-responding normal tissues.[306,324] If so, much of the rationale for LDR, or highly fractionated regimens would disappear.

A first estimate of α/β for prostate cancer was made in 1999,[306] by comparing results from EBRT with those from permanent seed ^{125}I BT. Consistent with the theoretical hypotheses (discussed above), the estimated value of α/β was 1.5 Gy [95% confidence interval: 0.8-2.2 Gy], indeed comparable to α/β values for late-responding normal tissues, and much smaller than those for most tumors. The problem with this α/β estimate, and almost all subsequent ones[307,325-329] is that they involved comparing or equating EBRT results with permanent implantation results. There are many pertinent differences between EBRT and BT (different dose distributions, different RBEs, different overall times, different institutions, different PSA distributions, hypoxia), any or all of which could bias the α/β estimate. Much debate has been centered on the significance of these biases and how to take them into account. For example, it has been reported that the consideration of hypoxia can significantly impact the α/β estimate.[330] Despite these problems, most of the analyses above support the hypothesis that the α/β value for prostate cancer is indeed quite low, probably in the 1 to 4 Gy range, which is similar to the values for most late-responding tissues.

One analysis[331] avoids many, though not all, of the potential biases involved in comparing EBRT and HDR BT: EBRT + two HDR boost fractions were compared with EBRT + three HDR boost fractions, all done with the same technique at the same institution. The resulting estimated α/β ratio for prostate cancer was 1.2 Gy [95% confidence interval: 0.03-4.1 Gy], again comparable with α/β values for late-responding normal tissues. A meta-analysis of four reports summarizing 21 studies yielded an estimated α/β ratio of 1.3 Gy.[332] A recent analysis of pooled multi-institutional data sets[333] led to $\alpha/\beta = 1.4$. A critical review of α/β ratio estimation methodologies and clinical analyses has been published by Oliveira et al.[334]

If the α/β value for prostate cancer is indeed similar to that for the surrounding late-responding normal tissue, HDR or hypofractionated external beam therapy regimens could be employed to match conventional fractionated regimens with respect to tumor control and late sequelae while reducing early urinary sequelae[335] and improving cost-effectiveness and patient convenience.

The arguments presented here really relate to the α/β value for prostate cancer in relation to the α/β value for the relevant late-responding normal tissue. Brenner reported an α/β value for radiation therapy oncology group (RTOG) grade ≥2 late rectal toxicity of 5.4 ±1.5 Gy based on an analysis of clinical data.[336] Another recent analysis of RTOG 94-06 data suggested that the α/β value for grade ≥2 late rectal toxicity was 4.8 Gy.[337] These α/β values, which are larger than that of most late-responding tissues, are higher than recent estimates of prostate tumor α/β ratio. This suggests that HDR prostate BT, as well as being logistically convenient, might actually improve the therapeutic outcome of prostate cancer BT.

HDR (or hypofractionation) in a curative setting, even when the dose is appropriately lowered, is a prima facie unsettling idea. However, there is now a significant body of clinical evidence suggesting that these approaches do not lead to increased early or late sequelae after prostate radiotherapy, either for EBRT or for BT, providing further evidence to support the underlying radiobiologic rationale. For EBRT, in those hypofractionation studies that have reported on potential late sequelae, there is to date little indication of any unexpected late sequelae after median follow-up periods of 21,[338] 31,[339] 48,[340] 59,[341] 66,[342] and 97 months.[343] HDR has been used in prostate BT as both a monotherapy[344,345] and, more commonly, a boost to EBRT.[346-349] In both cases, the results are promising with no evidence for excessive normal tissue complications.

However, mature long-term data on the effectiveness of tumor control are still needed for extremely hypofractionated *HDR* monotherapy for prostate cancer. In a single- fraction (19-Gy) *HDR* ^{192}Ir monotherapy trial, which included 441 patients with localized prostate cancer, the 3-year biochemical recurrence-free survival rate was 100% for low-risk patients, but dropped to 86% and 75%, respectively, for intermediate- and high-risk patients.[350] Importantly, the relapses after 19-Gy *HDR* BT monotherapy were mainly intraprostatic, predominantly associated with the site of initial disease.[351] While many factors could have contributed to the reported results, the loss of resensitization in single- fraction treatments and the increased sublethal damage repair during the prolonged dose delivery of large single-fraction dose[352] could also contributed to reduce the biologic effectiveness of the delivered dose.

Permanent Interstitial Brachytherapy for Prostate Cancer

Permanent interstitial BT delivers dose over the entire life of the implanted sources, making it necessary to consider cellular processes such as sublethal damage repair as well as tumor cell repopulation when examining its biologic effects. However, due to radioactive decay, the rate of dose deposition decreases exponentially over time. At certain point, the rate of cell kill produced by the implant will become equal to the rate of cell creation from repopulation, a time termed tactically as the effective treatment time, T_{eff}, by Dale.[353] Beyond T_{eff}, the dose delivered will not produce a net tumor cell reduction and the dose is considered “wasted.” The effective time is given by

$$T_{\text{eff}} = -\frac{1}{\lambda}\ln\left[\frac{0.693}{\alpha \dot{D}_0 T_{\text{p}}}\right] = -\frac{1}{\lambda}\ln\left[\frac{\gamma}{\alpha \dot{D}_0}\right] \qquad (21.43)$$

where λ is the radioactive decay constant of the particular nuclide used, and T_{p} is the potential doubling time of the tumor. At time T_{eff}, the dose that has been delivered is not the total dose, D, but rather a smaller effective dose, given by

$$D_{\text{eff}} = D\left(1 - \text{e}^{-\lambda T_{\text{eff}}}\right) \qquad (21.44)$$

As an example, using reasonable parameters for prostate tumors, the effective dose for a 145-Gy ^{125}I permanent seed implant is actually 139 Gy, which is the value that would be used in LQ-based calculations. The introduction of T_{eff} is necessary to avoid a conceptual difficulty encountered by the LQ-based model in handling permanent implants with proliferating tumors. The conceptual difficulty can be overcome using a more general TCP model introduced by Zaider and Minerbo.[354]

Many of the radiobiologic features of permanent prostate implant can still be elucidated using the LQ-based radiobiologic model (see AAPM TG-267 report for more details[282]). For example, the LQ model can be used to optimize the choice of radionuclide for a permanent implant.[355-357] The most common sources in current use are ^{125}I, ^{103}Pd, and ^{131}Cs (with half-lives of 59, 17, and 9.7 days, respectively). The optimal radionuclide for a given tumor depends on, among other factors, its growth rate, α/β value, radiosensitivity (α), and DSB repair rate. Generally speaking, short-lived radionuclides are more advantageous for treating fast-growing tumors, while longer lived radionuclides are more optimal for slow-growing tumors. However, short-lived radionuclides can effectively treat both fast- and slow-growing tumors[355,356] and, in addition, are less sensitive to the tumor properties and LQ parameter values assumed than is the case for long-lived radionuclides.

The discussions above assume that the geometric relationship between the implanted sources and the tissue remains unchanged. This assumption breaks down when the tumor shrinks over time[358,359] or when the implant volume expands and contracts in response to the surgical trauma of source implantation, such as the procedure-induced prostate edema.[235] The biologic effects of such intrairradiation tumor volume changes can be quantified using the LQ-based radiobiologic models.[358-360]

For tumor shrinkage during the implant, the reference surface to which dose is prescribed diminishes in size as the tumor shrinks, the physical dose rate and total dose delivered will increase as cells near the dose specification surface are moving closer to the implanted sources. Dale and colleagues reported[358,359] that, for permanent implants in tumors with long doubling times, tumor shrinkage may significantly enhance the clinical potential of longer

lived permanent implant radionuclides such as ^{125}I, but would have much less effect for short-lived radionuclides such as ^{103}Pd or ^{131}Cs, or for rapidly growing tumors. In fact, this is one argument against the use of long-lived nuclides for permanent implant BT, in that the outcome may depend on shrinkage parameters that are not easily predicted.

For procedure-induced prostate edema, on the other hand, the treatment volume and the location of the implanted sources expand initially followed by gradual edema resolution, making its biologic effect dependent on the interplay between the kinetics of edema resolution, the source radioactive decay, and the tumor cell sublethal damage repair and repopulation.[360] Chen and colleagues reported that, in general, the presence of prostate edema increases the cell survival and decreases the probability of local control.[360] The magnitude of edema-induced increase in cell survival and hence reduction in TCP increases with increasing edema severity, decreasing decay half-life, and decreasing photon energy. The magnitude of TCP reduction as a function of edema magnitude and resolution half-life was more rapid for implants using short-lived radionuclides, such as ^{103}Pd or ^{131}Cs. At the current level of dose prescription for prostate cancer, implants using ^{125}I sources are less affected by edema than those using ^{131}Cs or ^{103}Pd sources. Between ^{131}Cs and ^{103}Pd implants, the effect of edema on ^{103}Pd implant is slightly greater, even though the decay half-life of ^{103}Pd is longer than that of ^{131}Cs, because the advantage of the longer decay half-life of ^{103}Pd is negated by the lower effective energy of its emitted photons, making it more susceptible to source position variations.[360] The theoretical advantage of sources with shorter decay half-lives (eg, ^{131}Cs) discussed earlier could, therefore, be offset by their greater susceptibility to edema-induced dose reductions in LDR prostate BT.

Biologic Effects of Nonuniform Dose Distributions

Many implementations of the LQ and other radiobiologic models assume that an implant dose delivery can be approximated by a single uniformly administered prescribed dose, an assumption that ignores the highly nonuniform dose distributions produced by BT. The biologic effect of nonuniform dose could be estimated using the physical models derived from the LQ model based on cell survival.

A simple scalar metric for quantifying impact of such nonuniform dose is the equivalent uniform dose (EUD) concept proposed by Niemierko[361] or the corresponding equivalent uniform biologically effective dose (EUBED).[226,362-364] EUD is defined as the uniform dose which, if delivered with the same dose protraction regimen as the nonuniform dose distribution of interest, yields the same cell survival, hence the radiobiologic effect. The related concept, EUBED,[226,362,364] addresses both spatially nonuniform dose distributions and spatially variable temporal dose distributions, by replacing physical dose with BED. Suppose the dose distribution over an organ or tumor is described by a DVH, $\{D_i, v_i\}_{i=1}^{N}$, where v_i is the fractional volume of dose bin D_i. Then, EUBED is given by

$$\mathrm{EUBED} = -\frac{1}{\alpha}\ln\left(\sum_i v_i \mathrm{e}^{-\alpha\cdot \mathrm{BED}_i}\right) \tag{21.45}$$

where n_i is the fraction of the tumor target receiving the ith physical or biologically effective dose, D_i and BED_i.

Alternatively, dose inhomogeneity may be taken into account using other measures of cell survival, S, also weighted with the DVH[365-367]:

$$S = \sum_i v_i S(\mathrm{BED}_i)\cdot \tag{21.46}$$

This equation can also be used to estimate the overall TCP or to estimate equivalences between different treatments.[365-367]

To extend the concept of EUD to normal tissues, Niemierko (1999)[368] proposed a phenomenologic formula referred to as the generalized EUD or gEUD:

$$\mathrm{gEUD} = \left(\sum_i v_i D_i^a\right)^{1/a} \tag{21.47}$$

where v_i is the fractional organ volume receiving a dose D_i and a is a tissue-specific parameter that describes the volume effect. For $a \to -\infty$, gEUD approaches the minimum dose; thus, negative values of a are used for tumors. For $a \to +\infty$, gEUD approaches the maximum dose (serial organs). For $a = 1$, gEUD is equal to the arithmetic mean dose. For $a = 0$, gEUD is equal to the geometric mean dose. The original EUD concept has a more mechanistic interpretation than the empirical gEUD (described below). However, the gEUD is often used in plan comparison and optimization metric for EBRT and may be used for comparing different protraction schemes in BT because the same functional form can be applied to both targets and OARs with a single parameter capturing (it is hoped) the dosimetric "essence" of the biologic response. By replacing the physical dose DVH $\{D_i, v_i\}_{i=1}^N$ with biologically equivalent counterpart, $\{\mathrm{BED}_i, v_i\}_{i=1}^N$, the related metric, generalized EUBED (gEUBED),[281] is obtained.

The NTCP and TCP formalisms can also be generalized to accommodate nonuniform dose distributions. To compare different inhomogeneous dose distributions, TCP and NTCP can be computed by substituting equation Eq. 21.46 into the Poisson TCP model (Eq. 21.41), yielding

$$\mathrm{TCP}\left(\{D_i, v_i\}\right) = \exp\left(-K \cdot \sum_i v_i S(\mathrm{BED}_i)\right)$$
$$= \prod_i \left[\exp\left(-K \cdot S(\mathrm{BED}_i)\right)\right]^{vi} = \exp\left(-K \cdot \mathrm{e}^{-\alpha \cdot \mathrm{EUBED}}\right) \quad (21.48)$$

The second equation shows that inhomogeneous dose TCP, $\mathrm{TCP}\left(\{D_i, v_i\}\right)$, is the product of exponentially scaled (by volume fraction, v_i) TCPs, each describing uniform tumor irradiation by dose bin Di. The third equation shows that substituting the EUBED value derived from the DVH $\{D_i, v_i\}_{i=1}^{N}$ into the uniform dose TCP also reproduces $\mathrm{TCP}\left(\{D_i, v_i\}\right)$. Several authors[363,366,367] have extended this approach to spatial dose inhomogeneity to also include the possibility of inhomogeneous distributions of target cells within the tumor and radiosensitivities over the population of tumors.

Similar approaches for accounting for dose heterogeneity can also be applied to NTCP models[369] based on the survival of functional subunits (FSU). Many organs are best modeled by FSUs organized with a parallel architecture such that a complication results only when a sufficiently large number of FSUs are inactivated,[370] although serial architectures such as the spine can also be modeled.[366]

The literature suggests that dose nonuniformity can have a large impact on biophysical surrogates of clinical outcome. For example, for permanent seed prostate implants, Ling et al[364] demonstrated that doses between 100% and 130% of the D_{99} prescribed dose enhanced EUBED by 20% to 70% while Fatyga et al[281] found that dose inhomogeneity enhanced EUBED by 22% for HDR prostate implants. In a population of 423 patients with prostate cancer with minimum follow-up of 3 years and individual 3D dose distributions, Haworth et al[371] were able to identify a TCP cutpoint ($TCP > 0.62$) that was significantly correlated with freedom from biochemical failure at 5 and 8 years. In contrast, conventional D_{90} doses were not significantly correlated with outcomes in this population. Lindsay et al[372] found that α/β values derived by equating external beam and ^{125}I monotherapy TCPs ranged from

1.9 to 5.9 Gy when postimplant dose heterogeneity was accounted for compared to $\alpha/\beta \approx 1.5$ for assumed uniform BT dose distributions. However, they cautioned that in their spatially uniform clonogen density model, α/β estimates for individual patients were highly sensitive to peripheral cold spots.

While the above studies leave no doubt that BT dose heterogeneity can profoundly impact the results of biophysical model predictions, a major source of uncertainty is the sensitivity of TCP, NTCP, and EUBED calculations to the ubiquitous focal hot and cold spots characteristic of BT. Most applications of TCP and EUBED to 3D BT dose distributions assume a spatially uniform clonogen density and employ a cutoff (typically 110 Gy[373] or D_{99}[364]), which excludes low-dose voxels from the calculation, thereby avoiding unrealistically low estimates for clinical implant geometries. In a study of 613 postprocedural ^{125}I prostate implant dose distributions, Miksys et al[374] found that the mean EUBED ranged from 78 to 122 Gy for BED cutoffs ranging from 30 to 130 Gy (EUBED = 108 Gy for BED > 110 Gy). The corresponding range of mean TCP was 0.20 to 1.0 (TCP = 0.92 for BED > 110 Gy). In a study of 10 HDR prostate boost dose distributions, Fatyga et al[281] found that gEUBED for bladder and rectal tissue was highly sensitive to focal hot spots, requiring the use of a high BED cutoff taken to be the prescribed BED_{98}. Including higher dose focal hot spots for rectal complications was found to reverse the relative ranking of HDR and IMRT plans. This result is significant, since the gEUD formalism is equivalent to the DVH reduction scheme employed by the widely used LKB NTCP model.[375,376] In summary, straightforward application of EUBED and TCP to 3D dose calculations without arbitrary dose cutoffs requires patient-specific GTV and realistic spatially variant clonogen density models. Avoiding arbitrary high-dose cutoffs for normal tissue response modeling requires a yet-to-be-advanced model for predicting local injury saturation.

Relative Biologic Effectiveness of Different Brachytherapy Sources

As discussed earlier in this chapter, the mean photon energies of currently used BT radionuclides range from 21 keV (^{103}Pd) to 1,250 keV (^{60}Co). It is well established that biologic effectiveness varies with photon energy, as a result of different patterns of energy deposition produced by the different photon spectra.[63,377] It is possible, however, to estimate the RBE of these different isotopes directly from the energy deposition patterns—the subject matter of microdosimetry.[378] In this approach, the response per unit dose at LDRs (or low doses), R_i, to a particular radiation, i, can be written as[379]

$$R_i = \int w(y) \cdot \mathrm{d}_i(y) \cdot \mathrm{d}y \qquad (21.49)$$

where y is the stochastic quantity, lineal energy,[378] defined as the energy imparted to a cellular target arising from all ionizing radiation events caused by a single-photon track and

its secondary particles, divided by the target's mean chord length. The quantity $d_i(y)$ is the dose-weighted probability that a photon will deposit lineal energy y in the target volume of interest. The quantity $d_i(y)$ is often referred to as the microdosimetric single-event spectrum. It can be measured using a low-pressure proportional counter or calculated.[378] The quantity $w(y)$ describes the response of an individual cellular target to a lineal energy deposition, y. For sparsely ionizing radiations, for example, photons and electrons, it is reasonable to assume that $w(y)$ is proportional to y.[378] Thus, at LDRs

$$\mathrm{RBE}_i \propto \int y \cdot \mathrm{d}_i(y) \cdot \mathrm{d}y \qquad (21.50)$$

where $d_i(y)$ is the dose-averaged lineal energy.

Based on this approach, RBE values have been estimated from measured or calculated microdosimetric spectra.[63,380] For example, Wuu et al[63] report LDR RBE values relative to ^{60}Co of 1.3, 2.1, 2.1, and 2.3, respectively, for ^{192}Ir, ^{241}Am, ^{125}I, and ^{103}Pd. These values are comparable to those obtained experimentally. The approach outlined above is applicable only to LDR BT, but it can be generalized to HDR regimens.[379] Incorporating the LDR RBE into the LQ equations[381] requires a simple modification of the α term in Eq. 21.38 to $\alpha \cdot$RBE.

Use of Biophysical Models in Brachytherapy

The presentation above demonstrates that biophysical models, such as the basic LQ model, are very helpful in elucidating the radiobiologic properties of different BT regimes, with predictions consistent with the clinical experiences. More sophisticated TCP and NTCP models, while not sufficiently robust for use in clinical planning, are able to semiquantitatively account for the LDR and HDR BT clinical outcomes in several sites in terms of underlying descriptive radiobiologic mechanisms. Because of the simplistic nature of the models and the lack of tools for reliably determining patient-specific model parameters, these models are best used for comparing the relative effectiveness of different BT techniques, developing equivalent fractionation regimes, or optimizing therapeutic ratios in many clinical settings. Further guidance with regard to the use of biologic models in BT can be found in the recently published AAPM TG-267 report.[282]

CONCLUSIONS

This chapter has focused on several basic topics including the interplay between physical properties, source strength specification, single-source dosimetry, classic interstitial and intracavitary BT systems, dose specification, image guidance, computerized dosimetry and optimization, and biologic effects and clinical utility of BT sources. Many topics usually covered in an introductory survey have been omitted. For a review of radiographic imaging and localization of BT sources, the reader is referred to more specialized reviews.[382,383] For

discussions on QA of manual and remote afterloading BT and treatment planning, the reader is referred to Chapters 23 of this text as well as a number of excellent reviews,[384-388] including appropriate chapters from *Brachytherapy Physics*, 2nd edition,[389] and *Clinical Brachytherapy Physics*.[390] For useful reviews of the radiobiology of BT, the reader is referred to excellent reviews by Dale and Jones,[381] King,[391] Carlson et al,[392] and Chen et al.[282] For a discussion of BT licensing and regulatory issues, the review by Glasgow[393] is suggested.

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CHAPTER 22

Clinical Applications of Brachytherapy: Low Dose Rate and Pulsed Dose Rate

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HISTORY

Brachytherapy was the first form of conformal radiation therapy, using placement of radioactive sources within or very close to a tumor allowing high cancer to normal tissue dose ratios. After the isolation of radium, Henri Becquerel and Pierre Curie reported radium burns similar to those experienced by the early x-ray users. Radium was first used to treat skin lesions and superficial tumors, using boxes and tubes as applicators. From there, radium in metal needles or radon gas in glass seeds were placed in direct contact with tumors, using surface applicators, namely intracavitary and interstitial implants.[1] Source positioning within the tumor allowed high doses within the cancer, with small volumes of normal tissue irradiated and a sufficient dose at the margin between cancer and normal tissue to eradicate microscopic tumor foci. Early results were promising and they revolutionized cancer treatment.

In the 1950s, the use of brachytherapy was widespread; however, at that time, brachytherapy had several disadvantages. Classical radium needles were rigid and have a wide outer diameter ($\geq$1.5 mm^2). Brachytherapists had to have a high level of surgical skill to site the needles accurately, to achieve good dosimetry, and quickly, to minimize their own and others' exposure to radiation. Therefore, the emergence of teletherapy with the advantages of decreased staff exposure to radiation and radiation accessibility to more areas of the body with no dependency on surgical techniques led to a decrease in the use of brachytherapy.

However, brachytherapy has experienced a revival due to the emergence of newer artificial high-activity isotopes, afterloading systems, and

improved radiologic imaging with more sophisticated dose-planning techniques. Modern radiotherapy techniques have focused on escalating the dose to the target but decreasing the dose to normal tissues. Brachytherapy can meet both objectives in a highly conformal manner over a wide variety of disease sites.

Early texts describe the important principles of brachytherapy as uniformity in cross-section, uniformity in depth, and uniformity in opportunity (time).[2] These principles remain the cornerstone of modern brachytherapy practice, though modern techniques allow better assessment of them. Computerized tomography (CT) ultrasound and magnetic resonance imaging (MRI) scanning have enabled enhanced imaging in brachytherapy, allowing more accurate target definition, superior determination of applicator position, and improved evaluation of the position of normal tissues. In combination with computerized dosimetry, they have allowed better determination of the dosimetric coverage of a brachytherapy implant and an estimation of the subsequent risk of normal tissue toxicity.

DOSE RATE DEFINITIONS

Three categories of brachytherapy were defined in Report 38 of the International Commission on Radiation Units and Measurements[3]:

- low dose rate (LDR)—a range of 0.4 to 2 Gy/h. In clinical practice, the usual range is 0.4 to 1 Gy/h,
- medium dose rate (MDR)—a range of 2 to 12 Gy/h, and
- high dose rate (HDR)—over 12 Gy/h.

Pulsed dose rate (PDR) brachytherapy, first used in San Francisco in 1992, was developed in an effort to simulate the radiobiologic advantages and dosimetric properties of LDR, but with the advantages of computer optimization of dose, a stepping source, and remote afterloading usually achieved by HDR. The pathway of a single high-activity source through the implanted catheter can be accurately calculated by a computer with the dwell time adjusted as a function of its pathway within the implanted volume. PDR is a misnomer; in fact, the dose rate is often high, but the pulse intervals are short, so that the radiobiologic effect is similar to LDR.

PDR uses a single stepping ^{192}Iridium source of 15 to 37 GBq (0.5-1Ci), in the realm of one-tenth of HDR activity. Generally, the same total dose and total time as that of LDR are prescribed, but the radiation is administered in a large number of small fractions, usually a pulse every 1 to 4 hours. This produces treatment dose rates averaging 3 Gy/h. A typical pulse length is 10 minutes, which may increase to 30 minutes as the ^{192}Iridium source decays. It also has the advantage of a single afterloaded source compared to an inventory of LDR sources of different strengths, and all brachytherapy is feasible with one machine: intracavitary, interstitial, intraoperative, and intraluminal. This may become increasingly important as manufacture of traditional LDR sources ceases and disposal costs of existing LDR sources rise. Published series in a variety of tumor sites indicates that the clinical efficacy and the toxicity of PDR are similar to that of LDR/HDR.[4]

Permanent seed implants deliver a high total dose at a very low dose rate (vLDR), usually at <0.4 Gy/h. LDR sources can be placed directly into the body; however, with higher activity sources and large implants, this can result in exposure of the brachytherapist and operating room staff to a high radiation. To overcome this problem, afterloading techniques were developed. Initial techniques required applicator placement in the operating room and manual afterloading of sources in a shielded room at a later time. This has mainly been supplanted by remote afterloading techniques, where the patient has the applicators placed in the operating room and is later connected to a remote afterloading machine in a shielded room. The sources will only enter the patient when all personnel are at a safe distance from the patient; this can be used for LDR and is essential for PDR. During the course of an implant, careful monitoring of the sources must be maintained to detect applicator or source displacement. During a PDR implant, this may be done under direct vision or using radiologic confirmation. With both an LDR and a PDR implant, the patient should be safe to be left unsupervised for short periods of time to minimize staff exposure to radiation. This is where a PDR implant may have more advantage because those time periods will be briefer.

Table 22.1 demonstrates the advantages and disadvantages of LDR and PDR brachytherapy.

TABLE 22.1 THE ADVANTAGES AND DISADVANTAGES OF LDR AND PDR BRACHYTHERAPY

Advantages		Disadvantages	
LDR	**PDR**	**LDR**	**PDR**
>100 y of data	Source easily available	Often inpatient treatment with prolonged bed rest	One machine per patient used for 3-5 d
Standardized doses	Standard source strength	Radiation exposure to staff	More intense maintenance
Standardized treatment plans	Minimal staff exposure	Limited by available source strength	Requires more physician/physicist time in certain locations
Less source changes needed (depending on the isotope used)	Dose optimization of normal tissues	Many LDR sources no longer being manufactured	More expensive than LDR[5]
Less shielding needed during treatment	Radiation-free periods aid nursing care		Caution with conversion of dose from LDR to PDR, especially as intervals increase
	No source inventory required		May require prolonged bed rest depending on implant location
	With short pulse intervals, uses doses with known safety and efficacy		

CLINICAL USES OF BRACHYTHERAPY ISOTOPES

Brachytherapy uses radioactive isotopes to deliver therapeutic doses of radiation. The ideal radioisotope for brachytherapy should have a relatively short half-life to deliver the radiation in the shortest time possible and a high specific activity so that the source is small and, therefore, more versatile to implant. The emissions produced should have an adequate

penetration to deliver the dose to the desired depth, with rapid falloff to prevent damage to the surrounding normal tissue. Particular source characteristics such as half-life or specific activity can be tailored to the tumor and the surrounding organs at risk (OAR).

Temporary Implants

Traditional LDR sources such as iridium-192 and cesium-137 are no longer available in Europe and are becoming scarce in the rest of the world. Most radiation oncology departments wishing to continue using LDR-style dose and characteristics have switched to isotopes more suitable for remote afterloading, often using PDR techniques. Cobalt-60 (^{60}Co) is still used in afterloaders in the developing countries, with the advantage of decreased pressure on quality assurance and cost,[6,7] though more often using an HDR afterloader.[8,9]

Strontium-90 (^{90}Sr) is a pure β emitter and, therefore, is suitable for very superficial applications. It is commonly used for coronary brachytherapy and ophthalmic problems such as pterygium. It has a half-life of 28.1 years, so many departments are still using applicators purchased in the 1980s. Ruthenium-106 (^{106}Ru) is also a β emitter used in ophthalmic brachytherapy and has a much shorter half-life (1 year), making disposal concerns less and treatment delivery faster.

Permanent Implants

The artificial isotopes iodine-125 (^{125}I), palladium-103 (^{103}Pd), and cesium-131 (^{131}Cs) are all used in modern permanent vLDR implants. The isotope to be used can be chosen according to its individual characteristics, which may be desirable in different implants—for example, slower dose delivery may decrease normal tissue toxicity or a tumor with a higher α/β ratio may theoretically have more cells to kill using an isotope with a shorter half-life. All three isotopes are almost completely shielded with 0.2 cm of lead foil, making radiation protection easier.

CLINICAL SUITABILITY FOR BRACHYTHERAPY

Cancers with clinically and radiologically well-defined margins with a low risk of regional and metastatic spread are the most suitable for brachytherapy as a single modality. However, brachytherapy is becoming increasingly important when integrated with external beam radiation therapy (EBRT) to give a highly localized boost. EBRT is used to sterilize a larger area of possible microscopic or nodal spread, with brachytherapy used for areas of gross macroscopic or microscopic residual disease. This ensures that high doses are achieved within tumors, while normal tissues are not exposed to doses beyond recognized organ tolerance levels. It also has the potential for highly conformal localized dose escalation to areas at high risk of tumor recurrence.

In EBRT, the dosimetric goal is to achieve a homogeneous dose distribution, with doses ranging from 95% to 107% of the prescribed dose.[10] In contrast, brachytherapy has an extremely heterogeneous dose distribution, with isolated areas receiving more than 200% of the dose. The steep gradients are a consequence of the proximity of the clinical target volume (CTV) to the sources and decreasing dose with distance secondary to the inverse square law. As the dose falls off with distance, the normal tissues experience not only a reduced dose but also a reduced dose rate, which results in enhanced cell sparing. The sharp dose falloff with brachytherapy contrasts with the more gradual dose falloff seen with photon-based EBRT.

Brachytherapy can be used anywhere in the body that can be accessed for direct source placement. For many years, surface applicators and intracavitary gynecologic brachytherapy were the predominant modes of brachytherapy. However, with the advent of modern surgical techniques and interventional radiology, many more areas of the body are now accessible to the brachytherapist. Brachytherapy applicators can be placed within tubular organs in the body, either under direct vision (eg, cervix or vagina) or with the use of radiologic or endoscopic guidance (eg, bile ducts or esophagus). Interstitial implants can be placed with or without image guidance—for example, prostate implants using rectal ultrasound guidance and a template or a freehand extremity sarcoma implant. Interstitial implants can take the form of free seeds, or seeds within linked strands or catheters that will be afterloaded with the radioactive source. Of course, surface applicator

techniques are still used with the added benefits of modern imaging and dosimetry techniques to ensure target coverage.

TARGET DEFINITION

Many of the same definitions for delineation of treatment volumes in EBRT are used for brachytherapy.[10,11] There may be delineation of high-risk and low-risk areas if discrete areas of dose escalation are required within the CTV. The high-risk area has the highest risk of local recurrence, usually due to the presence of gross residual disease. An intermediate area may be defined as areas where there was macroscopic tumor during diagnosis that has regressed by the time of brachytherapy implant. The low-risk area includes potential microscopic spread—that is, the traditionally defined CTV. In EBRT, the planning target volume (PTV) traditionally consists of the CTV and a margin that will allow for physiologic movement and set-up uncertainty. Generally, in brachytherapy, these variations are minimized and, therefore, the PTV is usually the same as the CTV.

In a brachytherapy implant, there will be *high dose regions* around each source. Generally, the volume of the region receiving over 150% of dose is reported (V150).[3] *Low dose regions* are those within the CTV receiving <90% of the prescribed dose. Due to the heterogeneity of dose in brachytherapy, the average dose within the prescribed volume is usually far higher than the prescribed dose at the reference isodose point on the periphery of the implant. This is tolerated due to the volume-effect relationship: very small normal tissue volumes (eg, 1-2 cm^3) can tolerate very high radiation doses that larger volumes would not tolerate. The dose to OAR should be reported either as a total dose or as a ratio of volume. Parameters such as the minimum dose received by the most irradiated 2 cm^3 of tissue (D2 cm^3) or the volume receiving over 90% of the dose (V90) or dose received by 90% of the CTV (D90) are assessed.

RADIOBIOLOGIC CONSIDERATIONS

Radiobiologic principles are important in the daily clinical use of all forms of brachytherapy. Brachytherapy was initially developed empirically, with doses being determined by clinical effect. These correspond to many of the LDR and PDR dose schedules in current use. In the modern era,

radiobiologic modeling is used to predict the biologic effect of varying dose prescriptions. The importance of radiobiology and its use within brachytherapy was emphasized by the move from LDR treatment to PDR and fractionated HDR treatment. Of course, it must be remembered that applicator and source placement remains the single most important factor in brachytherapy such that, in an implant with poor geometry, changing radiobiologic parameters, such as fractionation or dose rate, will not improve the outcome.

Factors contributing to the response of tissues to radiotherapy have been labeled the "4 Rs of radiotherapy"[12]: repair, reassortment, repopulation, and reoxygenation. The way in which these radiobiologic characteristics relate clinically to the use of LDR and PDR either alone or in comparison to HDR is discussed in the following section.

Repair

Sublethally damaged cells are capable of repair if they are allowed sufficient time and if the cell contains all the necessary DNA repair proteins and enzymes. If sublethally damaged cells are exposed to further irradiation before repair occurs, the damage may become lethal. Late-reacting normal tissues seem more capable of repair than do tumor cells; therefore, at a given therapeutic dose, tumor is preferentially killed over normal tissue.

LDR or PDR treatment over several days allows time for sublethal damage repair in normal tissues. In contrast, the short treatment time of HDR treatment prohibits this repair during the actual irradiation. In PDR, generally the same total dose and total time as LDR are prescribed.

Dose rate is a key factor in determining the biologic effects of brachytherapy. In general, the effects of radiotherapy increase as the dose rate increases, predominantly due to a decrease in repair. It has been suggested that the total dose of LDR prescribed should be corrected for overall time of the implant,[13] though some investigators have found no difference in local control with the same total dose administered using a dose rate ranging from 0.05 to 0.167 Gy/min.[14] A randomized study in cervix carcinoma showed no difference in overall survival or local control for an LDR of 0.4 versus 0.8 Gy/h.[15,16] However, there was a significant increase in late complications in the higher dose rate group. A similar trend

has also been seen in LDR brachytherapy for breast cancer and head and neck carcinoma.[17,18] Therefore, it is recommended that the LDR (and PDR equivalence) should be in the range of 0.3 to 1 Gy/h due to the effects on late complications rather than local control. If the dose rate exceeds 1 Gy/h, a reduction in the total dose can be calculated using the biological effective dose (BED) equation.

Reassortment

In normal cells, proliferation occurs in a sequence of events termed the cell cycle.[19] There is a theoretical advantage of an improved effect on reassortment using LDR treatment since, during the overall treatment time, cells will pass out of the relatively radio-resistant cell cycle phases of late S and early G_2 into the more radiosensitive phases of late G_2 and M. This has been shown in vitro,[20] but in vivo, the effect of reassortment has not been shown to give a true advantage, possibly due to a disruption of the mechanisms of the cell cycle in cancer cells.[19]

Repopulation

In squamous cell carcinoma, studies have shown improved tumor control and increased survival when a radiotherapy course is given in the shortest overall time.[21-24] This may be because shorter treatment times allow less time for tumor cell repopulation or for accelerated repopulation to occur. The continuous administration of LDR and PDR probably prevents repopulation during treatment.

Reoxygenation

The response of cells to radiation is strongly dependent on oxygen. Radiation results in free radical formation within a tumor, and oxygen reacts with these free radicals to make DNA damage irreparable. The effect of hypoxia on tumor control has been well documented with decreased survival in certain patients with a low initial hemoglobin level.[25-27] When using LDR and PDR, transient hypoxia may correct during the treatment time,[28] which is not possible during the short duration of HDR

brachytherapy. If the brachytherapy is fractionated, tumor shrinkage and reoxygenation of areas of chronic hypoxia may occur between insertions.

MEASUREMENT OF BRACHYTHERAPY DOSE

Dosimetry systems aim to give the brachytherapist a set of guidelines to follow, which result in a prescribed dose being delivered to a patient in a predictable fashion. Initial brachytherapy dosimetry systems were developed for LDR implants using an empirical approach toward source placement and dose calculation. More modern techniques use computer programs to generate isodose distributions, which can then be analyzed in two dimensions, three dimensions, and volumetrically. To achieve the best ratio of cancer to normal tissue dose, the selection of an appropriate prescription point is essential. Applicator positioning is of primary importance, as differential loading cannot compensate for a poorly sited implant. Improved radiologic imaging has allowed a more accurate definition of the CTV and associated normal tissues, giving dose specification according to patient anatomy rather than to applicator position. This is more likely to correlate with patient outcome than previous dosimetry systems. This may result in not only better tumor control but also decreased risk of late complications.

LDR dosimetry is based on dosimetry systems originating in the 1930s with modifications over time, namely the Manchester, Quimby, and Paris rules (see Chapters 6). Where LDR uses fixed source positions and strengths to calculate the dose at the prescription point, afterloading machines and computerized dosimetry systems allow optimization of source dwell times to customize dose delivery to the patient's individual anatomy and tumor volume. PDR takes advantage of this dose optimization in a way that LDR cannot. Optimization results in nonuniform source loadings that give greater dose uniformity and CTV coverage that is often similar to those in an idealized Manchester dosimetry system implant.[29] The steep dose gradient around each wire/catheter needs to be accounted for, and widely spaced sources/applicators may form large high dose regions and increase the risk of necrosis. The maximum source separations and treatment thickness in the Paris system are useful rules to remember to decrease this risk. Traditionally, brachytherapy dose delivery was thought

not to be affected by alterations in the treatment position. While this may be true for dose delivery to the target volume, the position of OAR in relation to the brachytherapy implant may be altered, thereby increasing the dose delivered. For temporary implants, treatment should take place in the planning position to allow accurate determination of OAR dose.

CLINICAL SITES

There are areas where LDR techniques continue to predominate and areas where HDR techniques predominate. In some disease sites, the use of HDR and LDR was generally equal (eg, cervix cancer), but now HDR predominates, with a small but significant proportion of centers worldwide using PDR treatment. An overview of clinical uses for LDR and PDR is presented in the following section, with an emphasis on the brachytherapy dose rate rather than on the treatment technique. Individual indications will be described in the site-specific chapters.

Cervix

The use of LDR for cervix cancer treatment was first described with intracavitary implants in 1903 and with interstitial implants in 1913.[30] Brachytherapy has withstood technological innovations to remain an essential part of curative cervix cancer treatment[31,32] for all but the very earliest stages of the disease. The use of LDR has many years of safety and efficacy data, and physicians can be confident in their choice of brachytherapy dose. The four trials that compared LDR and HDR brachytherapy were all completed before the era of concurrent chemoradiation. They all concluded, however, that there are no differences between HDR and LDR in local control and survival, with HDR exhibiting a more favorable side effect profile, especially in regard to rectal complications[33] (Figure 22.1). A randomized controlled trial has shown that there is no significant difference between late rectal, bladder, and vaginal toxicity and survival when comparing PDR with HDR brachytherapy.[34] The American Brachytherapy Society guidelines for the use of LDR and PDR in cervix cancer[35] incorporate the volume-based dosimetry and updated quality control recommendations.

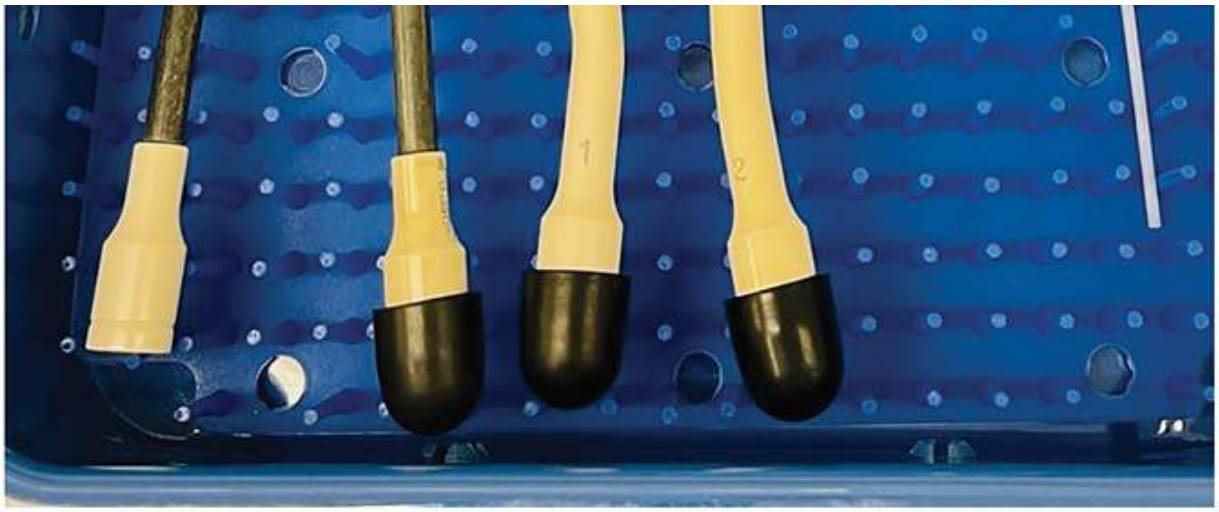


FIGURE 22.1 Tandem and ovoid kit. (Courtesy of Dr. Alexandra Stewart, St Luke's Cancer Center, Brachytherapy Department, Royal Surrey Hospital, Guildford, UK.)

With the use of CT- and MRI-based target volume and organ at risk definition, dose reporting in cervix cancer brachytherapy has changed from point based to volume based.[36-38] This means that tumor coverage is improved, and the doses to normal tissues can be decreased (Figure 22.2). This method relies on the use of dose optimization and thus has moved cervix brachytherapy away from LDR; therefore, PDR is the treatment of choice in those wishing to use a similar treatment modality.[39,40] The longer time taken to deliver one overall fraction of PDR than HDR is important when optimizing dose away from normal tissues, and it is important to recognize that the dose delivered to normal tissues over the whole treatment time may differ from that predicted, up to 33% more.[41] Rectal volume has been shown to increase during the course of delivery of PDR and, therefore, serial imaging and adaptive planning may be necessary as the cumulative rectal dose correlated with late rectal toxicity better than the planned dose.[42] A comprehensive description of this volume-based dosing is given in Chapters 23.

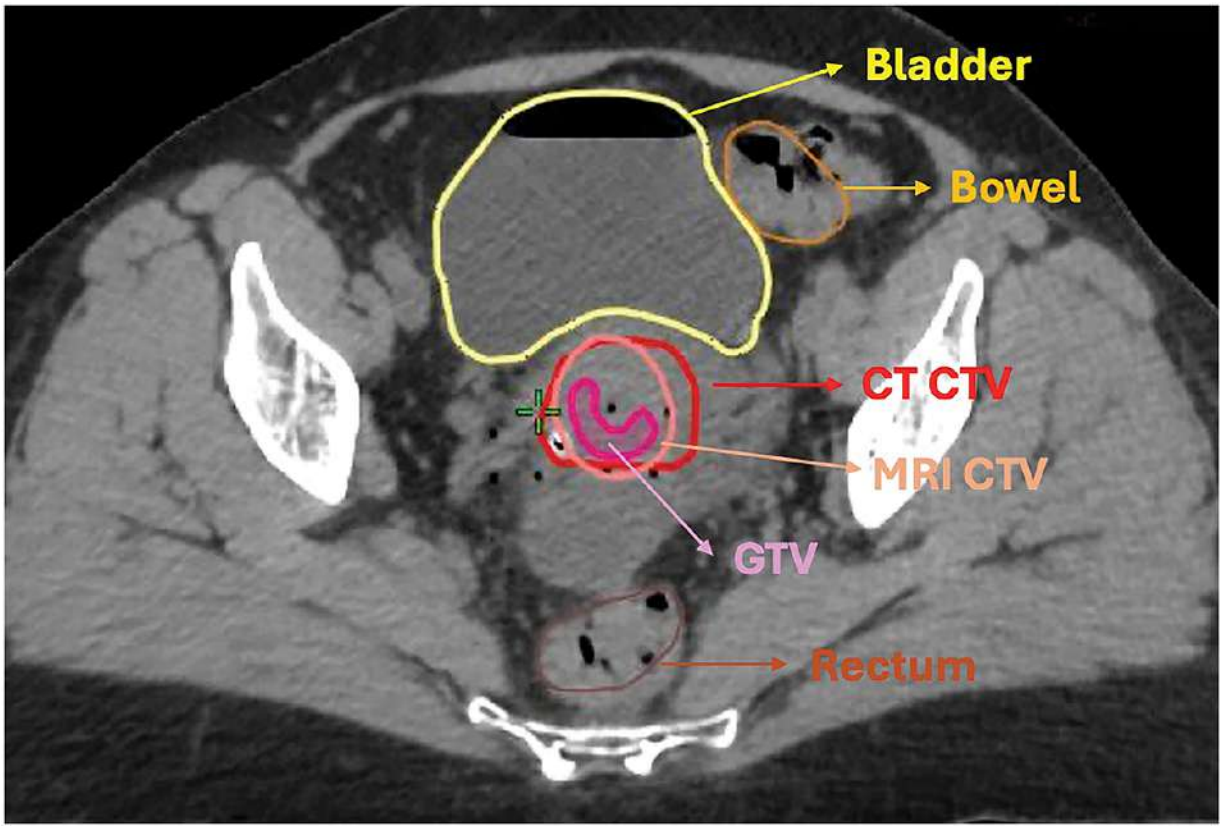


FIGURE 22.2 Axial CT scan views of cervical brachytherapy planning, volumes shown: GTV (pink), CT-CTV (red), and MRI CTV (orange). Two organs at risk are shown, bladder, bowel, and rectum. (Courtesy of Dr. Alexandra Stewart, St Luke's Cancer Center, Brachytherapy Department, Royal Surrey Hospital, Guildford, UK.)

PHRC Tridicol is a prospective French phase II study aiming to increase the dose delivered to the target volume during PDR brachytherapy for locally advanced cervical cancers.[43] Eight centers recruited 48 patients who were treated with concurrent chemo-radiotherapy followed by PDR brachytherapy. The 5-year local control rates were examined and were compared against the STIC PDR group and the retroEMBRACE cohort. The CTV dose delivered was below the target (85 Gy), which was thought to be due to low use of parametrial interstitial needles. The 5-year local control rate was improved compared to that of the STIC PDR group (78%) but lower than that of the retroEMBRACE cohort (89%). The complication rate was higher than that of the STIC PDR group but close to that of the retroEMBRACE cohort.

In cervical brachytherapy, the applicator is generally placed under operative conditions. The patient may require a general anesthetic, but

spinal anesthesia (Figure 22.3) has been shown to provide excellent analgesia, which can be maintained throughout the length of the implant by using a spinal catheter.[44] Spinal anesthesia does not affect tumor oxygenation during an HDR implant[45] and, thus, is not expected to during the whole duration of an LDR or PDR implant. When patients have the applicator in situ, they will remain lying flat, with prophylaxis against venous thromboembolism. Typically, agents are given to slow bowel motility. A urinary catheter is maintained throughout treatment. Prophylactic antibiotics are not routinely required but can be considered during interstitial implants. Pain and discomfort may be managed by epidural or intravenous patient-controlled analgesia. Use of a short-acting inhaled anesthetic agent for analgesia during episodes of acute pain such as toileting or applicator removal may improve the patient experience.[46]

FIGURE 22.3 Administration of a spinal anesthetic prior to a pelvic brachytherapy procedure.

Endometrium

Brachytherapy for the management of endometrial carcinoma was first described in 1935 by Heyman,[47] prior to the routine use of hysterectomy for

uterine cancer. Currently, the primary treatment for endometrial cancer is surgery with or without adjuvant radiotherapy and chemotherapy, based on the histology of the tumor and stage of presentation. As endometrial carcinoma is linked to obesity and hypertension, some patients have medical comorbidities that preclude surgery; for those patients, radiation therapy may be the definitive treatment of choice. In this group, treatment is delivered via intracavitary uterine brachytherapy, with or without EBRT.[48-50] With the decrease in LDR radioactive source availability, PDR has become the alternative modality to HDR. De Felice et al[51] give recommendations to manage the transition in modality.

For definitive treatment, packing the uterus with capsules allows excellent coverage of the entire endometrial cavity that can be adapted to every patient's individual anatomy,[52,53] but standardized applicators may provide more straightforward and reproducible dosimetry. Double channel applicators such as the Rotte applicator[54] can be used with CT planning, and computerized optimization with HDR delivers a dose very similar to the serosa[55]; this could be replicated with PDR (Figures 22.4 and 22.5). Various whole uterus prescription points have been described[56,57]; however, CT planning allows contouring of the outer contour of the uterus for volume-based dose prescriptions. A typical dose is 70 to 80 Gy (prescribed to the outer contour of the uterus alone), or 35 to 50 Gy in combination with 30 to 45 Gy EBRT.[58] GEC-ESTRO has published guidelines on converting LDR schedules to PDR schedules for all gynecologic cancers.[59]

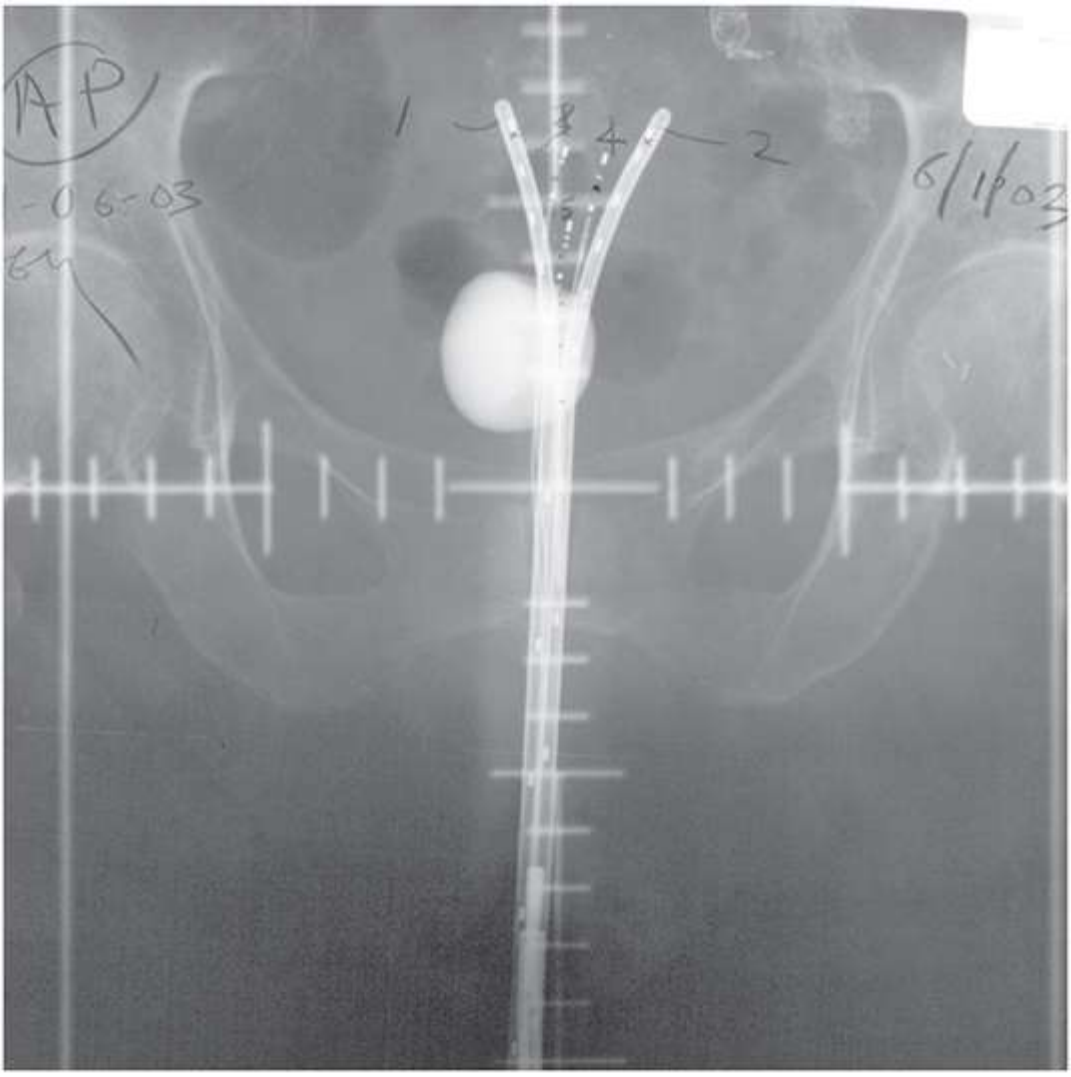


FIGURE 22.4 Double tandem Martinez applicator in place with three Heyman capsules placed within the uterus.

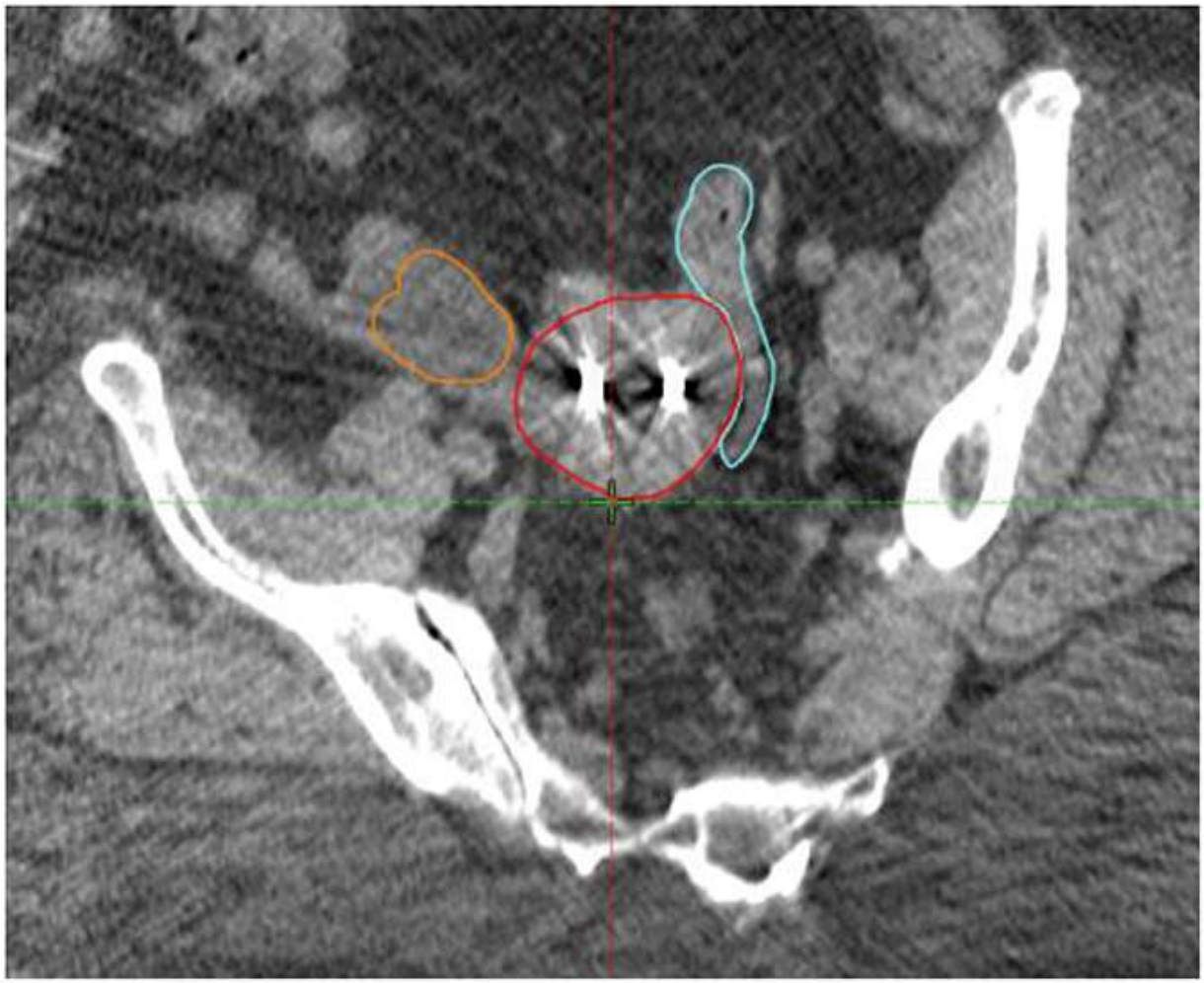


FIGURE 22.5 Axial CT slice demonstrating the Martinez applicator in situ. The high-risk CTV is outlined in red, sigmoid in blue, and bowel in orange.

Vaginal vault brachytherapy can be used in the adjuvant treatment of endometrial cancer and vaginal vault recurrence of endometrial carcinoma and also in other gynecologic malignancies such postoperative early-stage cervix cancer or early-stage vaginal cancer[60-63] (Figure 22.6). PDR vaginal vault brachytherapy is not frequently used as a boost to EBRT because the longer time of the application imposes the requirement for a urinary catheter. In addition, the side effects of thrombotic risk[64] and bowel dysfunction are not warranted for the low doses required in the adjuvant boost setting. The radiation dose received by the pelvic organs varies according to physiologic variations, for example, the bladder dose may vary according to the extent of bladder filling, which may also affect the amount

of small bowel in the field,[65,66] making the catheterization required for PDR less desirable.

FIGURE 22.6 Vaginal applicator. (Courtesy of Dr. Alexandra Stewart, St Luke's Cancer Center, Brachytherapy Department, Royal Surrey Hospital, Guildford, UK.)

Prostate

Prostate brachytherapy has become part of the treatment paradigm in prostate cancer for all stages of localized disease (see Table 22.2). It can be used as monotherapy or in combination with EBRT and/or hormone therapy for higher risk disease. A surveillance, epidemiology, and end results database (SEER) database analysis of men <60 years old has shown that prostate cancer-specific mortality was reduced in those treated with brachytherapy (±EBRT) compared to those treated with EBRT alone.[67] The most common prostate brachytherapy application has historically been LDR permanent seeds for monotherapy although more recently the use of single dose HDR as a boost is rising; however, LDR,[68] HDR,[69] and PDR[70,71] techniques can all be utilized.

TABLE 22.2 SELECTION CRITERIA FOR PROSTATE BRACHYTHERAPY[72,73]

Patient Factors
Life expectancy >5 y
IPSS <15
Prostate volume <60 mL No defect if previous TURP
Minimal pubic arch interference
Tumor Factors
Monotherapy: T1-T2b, Gleason ≤7, PSA ≤15[a]
Boost therapy: ≥T2c, Gleason ≥7, PSA ≥10

IPSS, International Prostate Symptom Score; PSA, XXX; TURP, transurethral resection of prostate.

[a]Gleason 7 and PSA >10 may be considered for either monotherapy or boost therapy.

Ash D, Flynn A, Battermann J, et al. ESTRO/EAU/EORTC recommendations on permanent seed implantation for localized prostate cancer. *Radiother Oncol*. 2000;57(3):315-321; Expert Panel on Radiation Oncology-Prostate, Frank SJ, Arterbery VE, et al. American College of Radiology Appropriateness Criteria permanent source brachytherapy for prostate cancer. *Brachytherapy* 2011;10(5):357-362.

Tumor criteria depend on whether monotherapy or boost therapy is planned. Typically, monotherapy is reserved for patients with the so-called favorable risk disease (eg, low- intermediate risk disease: T1-2b disease, Gleason <7, prostate specific antigen (PSA) <15 ng/mL). However, there is emerging evidence that some intermediate-risk disease may also be treated effectively with monotherapy[74]; therefore, boost therapy may be reserved for patients with unfavorable intermediate- risk and high-risk disease.[75,76]

In intermediate- to high-risk prostate cancer, brachytherapy in combination with EBRT has been evaluated in retrospective series with both LDR permanent seeds and HDR brachytherapy.[77-80] The ASCENDE-RT trial compared LDR brachytherapy (LDR-PB) with dose-escalated external beam boost (DE-EBRT), in patients with intermediate- and high-risk prostate cancers.[81] The DE-EBRT arm received an additional 32 Gy in 16 fractions, and the LDR-PB arm received an ^{125}I implant prescribed to a minimum peripheral dose of 115 Gy. Two hundred patients were randomized to the DE-EBRT arm and 198 to the LDR boost. The endpoint was biochemical progression-free survival. The distant relapse rate was 11% in the LDR-PB group and 14% in the DE-EBRT group. The 15-year metastasis-free survival (MFS) was 84% for LDR-PB and 79% for DE-EBRT. Six percent of patients in the LDR-PB arm and 9% in the DE-EBRT group died from prostate cancer. LDR brachytherapy demonstrated an advantage in biochemical progression-free survival, though this did come with a risk of toxicity.[82] At 5 years, the cumulative incidence of grade 3 genitourinary toxicity was 18% for LDR-PB versus 5% for DE-EBRT, and for grade 3 GI toxicity, it was 8% versus 3%. Conversely, LDR-PB allowed 45% of men to maintain similar erectile function compared to 37% after DE-EBRT. There was no significant difference detected in OS and MFS, though the authors note that the study was insufficiently powered to show a

survival difference. This is where the HDR brachytherapy could offer a dosimetric advantage over LDR. In a randomized phase III trial, Hoskin et al compared 106 patients receiving EBRT alone to 110 receiving EBRT combined with HDR brachytherapy boost (HDR-BTb).[83] At a median follow-up of 131 months, a median time to relapse of 137 months was seen in the HDR-BTb group compared to 82 months for the EBRT alone group ($p = 0.01$). There was 27% risk of recurrence with EBRT alone ($P = 0.001$), with a 21% improvement of the relapse free survival (RFS) at 12 years with the combination of EBRT+HDR-BTb. In this study, there was no difference in GU or GI toxicity with the addition of HDR-BTb. Consequently, the use of HDR as a boost modality is rising, and the use of LDR is falling. The same techniques used in HDR boost brachytherapy can be applied to PDR brachytherapy. PDR boost brachytherapy is not as extensively studied as HDR or permanent implants, but preliminary studies[84,71] show acceptable toxicity and tumor control with limited follow-up. In the study by Pieters et al, patients were treated with ≤1.2 Gy/pulse at short time intervals (≤2.2 hours). The doses in their study are relatively low with an EQD_2 between 68.8 and 74.4 Gy. They noted that tumor control at 5 years was comparable to many HDR studies and that there are large areas of prostate receiving >20% of the prescription dose because of the heterogeneous nature of brachytherapy. They recorded low rectal and urinary toxicity, and the International Prostate Symptom Score (IPSS) returned to baseline by 12 weeks post brachytherapy. Further dose escalation with PDR was felt to be worth pursuing because of the low rectal and urinary toxicity.

Cosset et al treated 675 patients with LDR monotherapy for low- and intermediate-risk prostate cancer.[85] Sixty-one percent retained sexual function within a 11-year follow-up period. The overall survival was 92% but for the intermediate-risk group, the RFS rate was only 71%. The side effect profile, specifically the likelihood of erectile dysfunction, was comparable to that of a series of 141 HDR monotherapy patients in the study by Behmueller et al. In this study, the RFS was 84% for intermediate-risk patients, though these comprised only 23% of the series.[86]

Prostate brachytherapy is also being investigated as salvage therapy after external beam radiation.[87,88] The International Delphi consensus study offers practical advice on salvage brachytherapy.[89] In a group of 30 international

experts, the majority agreed that HDR brachytherapy as a focal treatment or whole gland technique is appropriate. RTOG-0526, a phase 2 trial, investigated the option of salvage LDR brachytherapy for local recurrence after EBRT in 100 patients across 20 centers.[90] The median follow-up was 6.7 years with a median prior EBRT dose of 74 Gy. Androgen blockade treatment was combined with salvage brachytherapy (BT) in 16% of patients. The 10-year OS was 70% with 19 patients dying, five of those from prostate cancer. The 10-year failure rates were local 5%, distant 19%, and biochemical 46%. The 5-year freedom from biochemical failure was 68%, which was comparable to those reported for other salvage modalities. Although it is rare to have a repeat local failure (5%), the risk of biochemical failure was 46% by 10 years.

The role of EBRT and hormone therapy in combination with LDR brachytherapy is unclear and under investigation. Adjuvant androgen deprivation therapy (ADT) is used for prostatic cytoreduction in patients who do not have ideal prostatic geometry.[76,91] Cytoreduction may be achieved with use of lutenizing hormone-releasing hormone agonists and antiandrogens or antiandrogen in combination with 5α reductase-inhibitors.[91] ADT is also considered in patients thought to be at higher risk of prostate cancer recurrence; however, the benefit of ADT in this setting is not well defined.[92-95] The RTOG 0815 study investigated the benefit of dose-escalated RT alone (750 patients) versus RT combined with total androgen suppression (TAS, 742 patients) in patients with intermediate-risk prostate cancer. Early results reported at a median follow-up of 6.2 years show overall survival rates of 90% and 91%, respectively. More patients developed PSA failure and distant metastases in the RT alone group with statistically significant *P* values. In addition, more deaths relevant to prostate cancer were documented in the RT alone group compared to the combination treatment arm [HR 0.10 (0.01 − 0.80); $P = 0.007$]. This has shown that while TAS does not change the overall survival in men with intermediate-risk cancer, it may offer a significant decrease in the rates of biochemical failure and distant metastases.

A transrectal ultrasound-guided transperineal technique is the most popular technique for implanting the prostate. Axial images of the prostate from the base to the apex are taken and then used for brachytherapy planning (Figure 22.7). Other modalities incorporating MRI[96] and MRI

spectroscopy imaging have also been proposed.[97] The techniques for implanting ^{125}I and ^{103}Pd have been well described.[98-100] The patient criteria for selection include ability to undergo a general, spinal or less commonly local anesthetic,[101] prostate volume of <60 mL,[68] favorable anatomy (minimal or no pubic arch interference, median lobe), and minimal obstructive uropathy. However, Stock and Stone demonstrated that patients with larger prostate glands, ranging from 100 to 205 cm^3 (mean 126 cm^3), can also be treated successfully.[102] Thirty-four patients were assessed with a mean follow-up time of 6.7 years to document toxicities and biochemical freedom from failure rates (bFFF). The 10-year bFFF was 84.5%, with no differences in bFFF between PV100 and smaller glands (82.4% vs 84.5%, P = 0.71). Although urinary retention rates were higher, urinary toxicity scores were similar to those of patients with a prostate volume <100 cm^3.

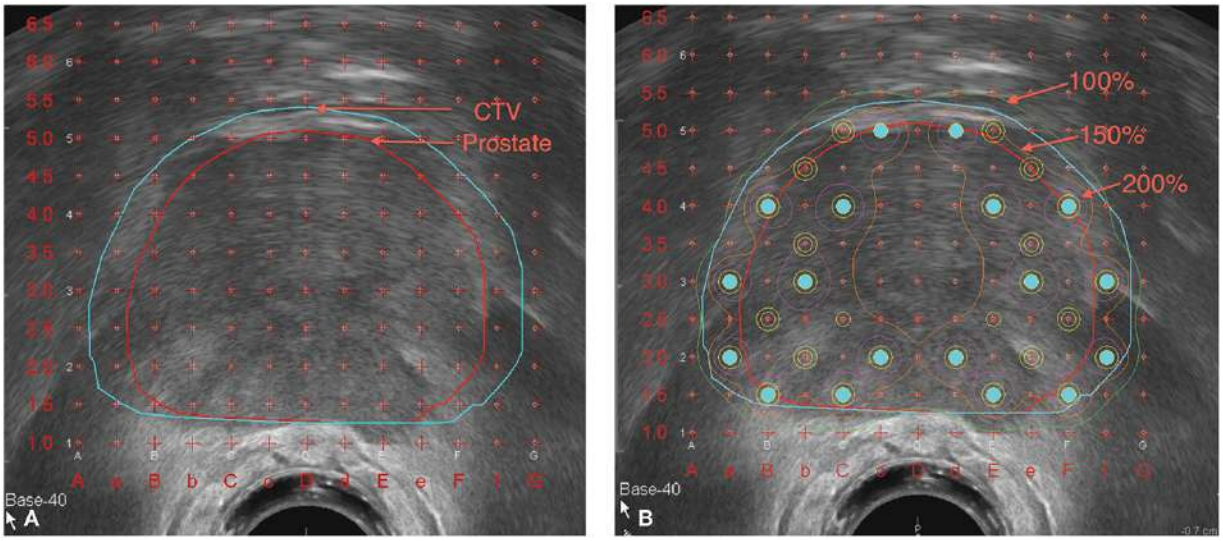


FIGURE 22.7 Prostate volume study with prostate and CTV defined (A), preplan with peripheral loading technique (B).

Current permanent LDR techniques involve implanting ^{125}I or ^{103}Pd seeds. ^{131}Cs is also approved for prostate brachytherapy and is used at some institutions. These isotopes have differing energies and half-life and, therefore, initial dose rates. Table 22.3 shows the various prescription doses for permanent LDR when used as monotherapy or as a boost in combination with 40 to 50 Gy of external beam radiotherapy. It had been postulated that ^{103}Pd compared with ^{125}I was more effective at treating

dedifferentiated tumors as the dose rate is higher; however, studies evaluating clinical outcomes for patients with prostate cancer have shown no difference.[103-105] Studies evaluating the toxicity to OAR (including the rectum and bladder) and sexual function have shown no difference in acute or long-term toxicity or difference in sexual function.[106-108] There is a difference in the time for the IPSS score to return to the preimplant baseline, with ^{103}Pd returning to baseline faster.[109] ^{131}Cs has not been studied as extensively. Commercially, ^{125}I and ^{103}Pd seeds are available as either loose or stranded seeds. Dosimetrically, the two are similar. The incidence of seed migration is decreased with stranded seeds as compared with that of loose seeds with the greatest difference being in migration to the lung and perineum.[110]

TABLE 22.3 PRESCRIPTION DOSE FOR PERMANENT LDR BRACHYTHERAPY WHEN USED AS MONOTHERAPY OR AS A BOOST COMBINED WITH 40 TO 50 GY EXTERNAL BEAM RADIATION THERAPY

	Monotherapy (Gy)	Boost (Gy)
^{125}I	145	110
^{103}Pd	125	100
^{131}Cs	115	85

The prescription dose for permanent LDR brachytherapy is dependent on the isotope and the indication for the implant, either monotherapy or as a boost. Table 22.3 describes the recommended doses for ^{125}I, ^{103}Pd, and ^{131}Cs when used as monotherapy or when combined with 40 to 50 Gy external beam radiation.[111-113] The prescription dose covers the entire prostate (CTV) and typically includes a margin. The dose for ^{131}Cs is still under investigation.

In the preoperative technique, the dose to the target volume as well as the OAR are evaluated. The source placement with ^{131}Cs is different to ^{125}I and ^{103}Pd, with needles placed further from the urethra and rectum.[112] Good pre-implantation dosimetry and toxicity levels correlate with a V100 >95% of CTV, D90 >100%, V150 ≤50% of CTV, rectum D2 cm^3 <reference prescription dose, D_{max} <150% of reference prescription dose, prostatic

urethra D10<150%, and D30 <130%.[114] Dose limits to structures such as the penile bulb and neurovascular bundles are under investigation.

Postimplant dose reporting in a structured quality assurance program is highly recommended and should include dose parameters to both the target and the OAR.[113,72] Timing of the post implant imaging varies at different centers but ideally should relate to the time at which edema is at a minimum. Evaluation at either day 0 or 30 is most common. Seed localization is crucial as is the contouring of the prostate and normal structures. CT/MRI fusion allows for identification of both the seeds and accurate definition of the prostate, particularly at the apex and base, which tend to be difficult to delineate on CT (Figure 22.8). Primary parameters to report and evaluate include the intended dose, D90, D100, V100, V150 to the prostate gland and rectal volume and dose and urethral doses. For patients with unacceptably cold implants, consideration for reimplantation should be given. There are no dosimetric parameters at present for penile bulb and neurovascular bundles.

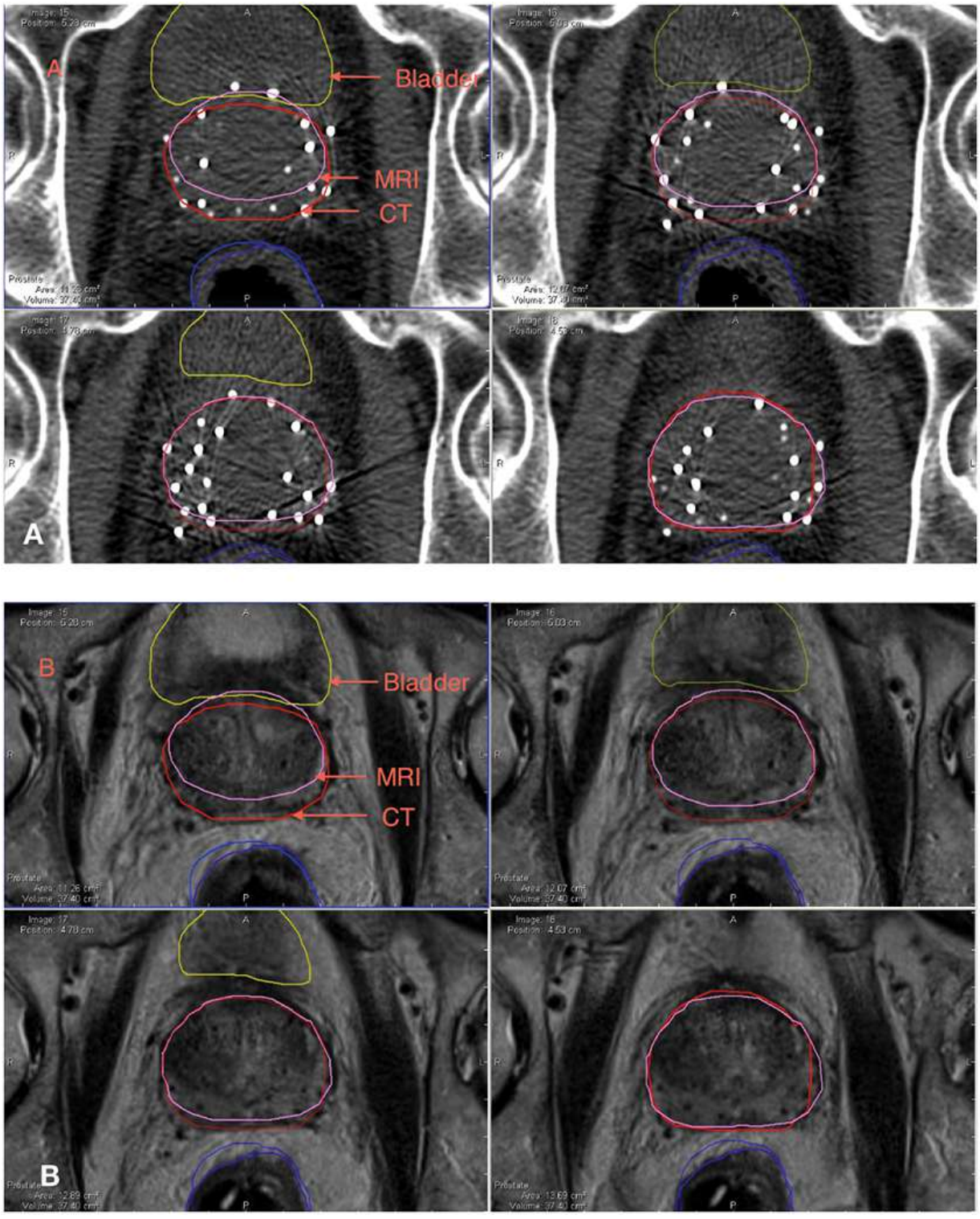


FIGURE 22.8 Prostate brachytherapy post plan with computed tomography and magnetic resonance (CT-MRI) fusion. The prostate volumes were drawn independently on the CT (A) and MRI (B) to show the difference in contours at the base of the prostate. The MRI images are better able to delineate the prostate, whereas the CT scan is better able to give information on the brachytherapy seed location.

Each hollow bore needle has a beveled edge and central stylet. Ultrasound images in both the axial and sagittal views (if available) guide the placement of the needle. Once the first needle is in the correct position (in three-dimensional coordinates), the retraction plane is set for positioning of the remaining needles. To drop the seeds within the prostate, the central stylet is held securely in place, and the outer needle is slowly pulled back along the stylet. On-demand fluoroscopy can be taken to check seed position relative to bony and organ anatomy. Additional seeds may be placed at the end of the procedure as required. Bladder irrigation and cystoscopy can be performed to evacuate migrated seeds in the bladder. Patients are conveniently discharged home the same day of the procedure; the majority of patients do not require a urinary catheter on discharge.

Penis

Penile cancer is rare in Western countries, representing only 1% of male malignancies. Squamous cell carcinoma is the predominant histology. Brachytherapy is used as an organ-sparing technique in T1, T2, and select T3 lesions (<4 cm) that do not involve the shaft of the penis.[115-117] When brachytherapy is compared with surgical treatment for the treatment of penile cancer, brachytherapy appears to be associated with better erectile function scores, and high quality-of-life scores with good satisfaction ratings in cosmetic appearance.[118] Both surface mold techniques (lesions <5 mm)[119,120] and interstitial techniques[121-125] (Figure 22.9) have been described. The 5-year local control with interstitial brachytherapy is 70% to 86% with penile preservation of 72% to 88%. Typical doses range from 50 to 65 Gy delivered in 4 to 7 days. Typically, at least two planes of catheters are required because it is difficult to assess the depth of disease. Crook et al[126] describe their implantation technique in detail for 75 cases implanted between 1989 and 2009 with both ^{192}Ir wire/seeds and PDR techniques. The implants are based on the Paris system using rigid templates with spacing between 12 and 18 mm. Computerized dosimetry mimics the Paris system and allows for visualization of dose to the target and OAR. They prescribed 60 Gy at a dose rate of 0.5 to 0.6 Gy/h with manually afterloaded ^{192}Ir or 0.5 to 0.6 Gy in hourly fractions when using PDR. Treatment takes approximately 5 days.[117] Penile preservation was 88% at 5 years and 67% at

10 years with actuarial survival of 59% at 10 years and cause-specific survival of 83.6%.[122] They reported a soft tissue necrosis rate of 12% and urethral stenosis rate of 9%. The soft tissue necrosis rate quoted in the literature ranges from 12% to 26% and increases with dose greater than 60 Gy, T3 disease, large volume implants (>30 mL), and more than two needle planes.[122-125,127] If conservative measures fail to manage soft tissue necrosis, hyperbaric oxygen therapy has shown success prior to resorting to surgical interventions such as debridement or amputation.[128] Urethral stenosis is reported in 10% to 45%[122-125,129] of cases and relates to the proximity of the needles to the urethra and the number of treatment planes. Achkar et al described PDR interstitial brachytherapy as an organ preservation approach.[130] Sixty-five patients with a median follow-up of 37 months received a median brachytherapy dose of 60 Gy and a median treated volume of 36 cm^3. The median reference dose rate and number of pulses were 0.42 Gy/pulse/h (0.4-0.5 Gy/pulse/h) and 150 pulses (87-175 pulses). Twelve patients (18.4%) relapsed locally (inguinal lymph nodes metastases), with a median time to local failure of 11 months. Six patients (9%) underwent partial surgery and four patients (6%) underwent total penectomy. The 3-year overall survival rate and 3-year disease-free survival (DFS) were 88.2% and 74.4%, respectively. Twelve patients (20%) experienced grade 2 painful ulceration resolving spontaneously, and 13 patients (21.5%) developed grade 2 meatal stenosis needing at least one meatal dilatation. The risk of meatal stenosis was strongly correlated with distal urethra D0.1 cm^3 (p = 0.0016) and D0.2 cm^3 (p = 0.0019) dose parameters in multivariate analysis. The optimal cutoff for these constraints were recommended as 82 and 78 Gy, respectively.

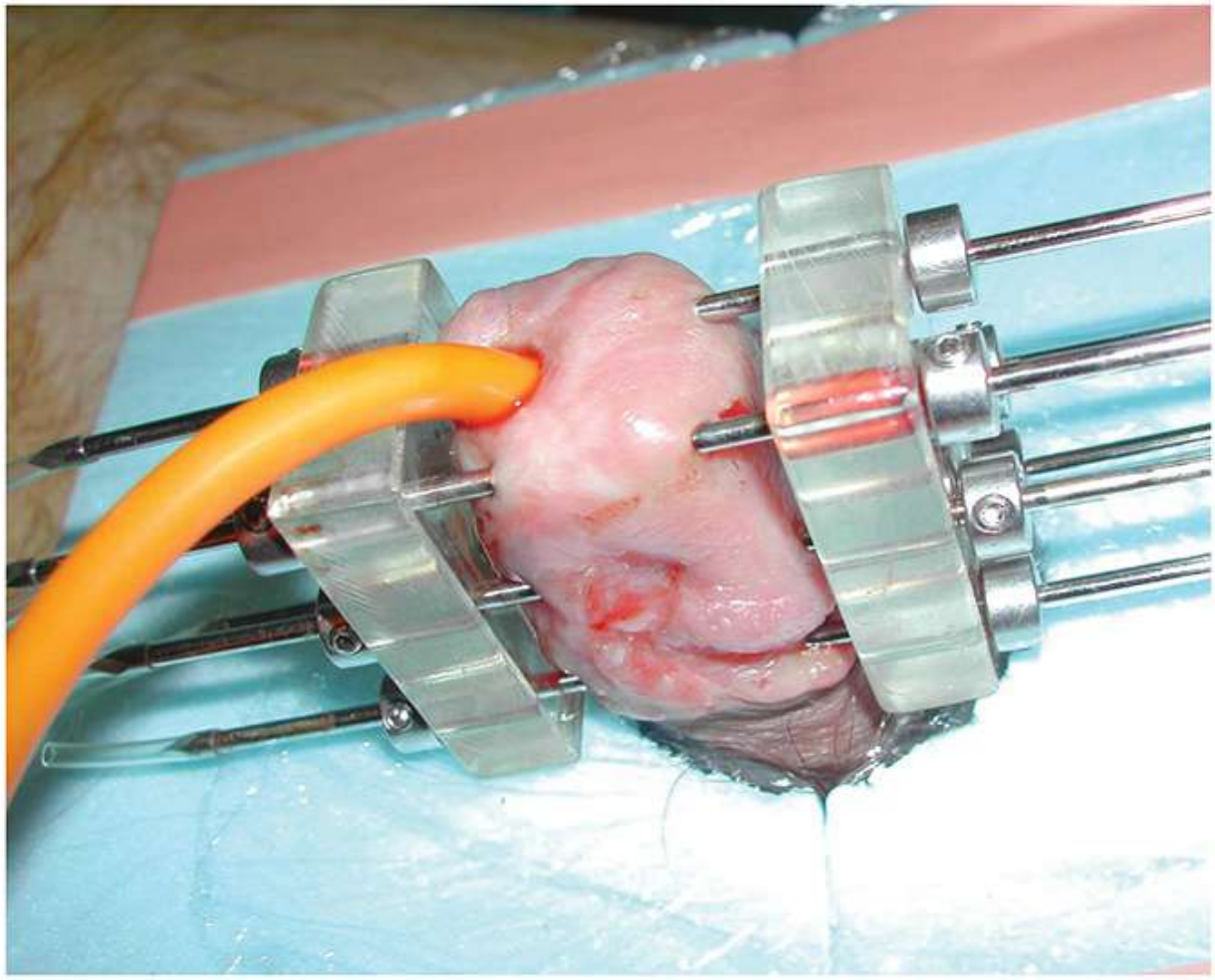


FIGURE 22.9 Low dose rate interstitial multiplane penile implant.

It is recommended that all men undergo circumcision prior to brachytherapy as this exposes the tumor, potentially removes disease allowing for a smaller implant, and decreases the risk of ulceration and necrosis to the foreskin.[124,126] Dose to the urethra and testes should be recorded. In men wishing to retain fertility, lead shielding can be placed around the testes.

Urethra

Brachytherapy may be used in the treatment of both male and female urethral cancers. Paraurethral cancers (PUC) are rare and aggressive, and account for less than 1% of genitourinary cancers. Intraluminal, intracavitary, and interstitial techniques have been described. Intraluminal

brachytherapy is limited to superficial lesions and involves a single catheter into the urethra.[131] Interstitial implants for the penile urethra are like penile implants. In treatment of the female urethra, an interstitial implant may be used in combination with a molded vaginal applicator[131] or alone (Figure 22.10). The dose with LDR as a monotherapy is 60 to 70 Gy in 3 to 5 days (0.5-1 Gy/h PDR) and 20 to 25 Gy, if used as a boost.

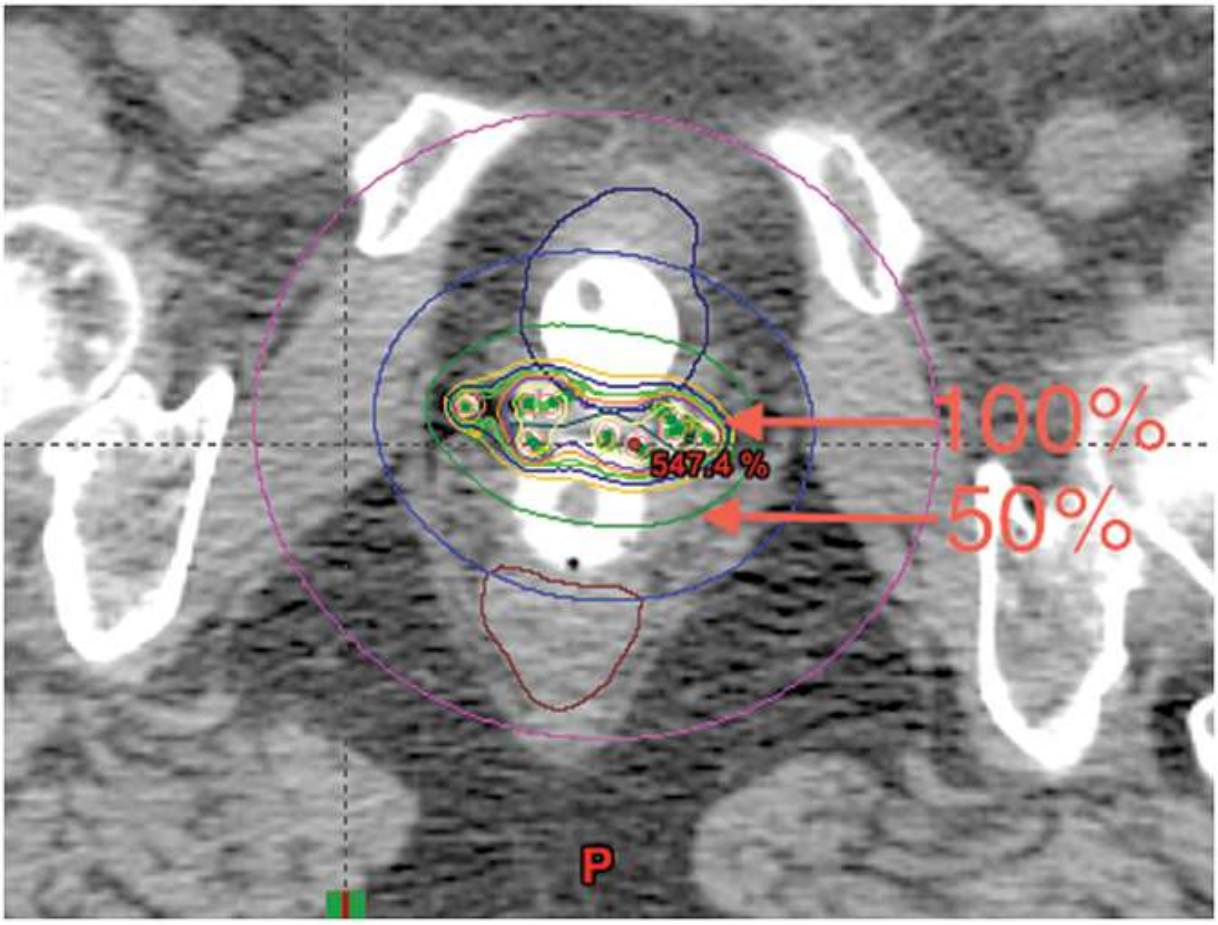


FIGURE 22.10 Low dose rate interstitial multiplanar urethral implant.

PUC may arise from the urethra directly, or from vaginal endometrial or cervical cancers. Andraud et al[132] conducted a retrospective review of 44 patients treated between 1990 and 2018. Of the total patients, 22 had primary PUC and 22 had a recurrence. Fifty percent arose from gynecologic sites (including cervix, uterus, and vulva) and 50% from the urethra. Prior to 2014, treatments were delivered using LDR brachytherapy. Thereafter, treatments were delivered using PDR. The median prescribed dose was 60

Gy for the 24 patients treated with BT alone and 20 Gy for the 20 patients treated with brachytherapy in conjunction with EBRT. Transperineal free-hand interstitial needles were implanted for patients with a tumor thickness of >7 mm. The median follow-up was 21.5 months during which six patients (17.5%) experienced local relapse. The 2 year overall survival probability was 63%. Milosevic et al[133] published their experience of 34 patients treated with radiation. Twenty of these patients received brachytherapy (five brachytherapy alone, 15 EBRT+brachytherapy). The tumors treated with brachytherapy tended to be ≤4 cm, involve the distal urethra, and did not invade adjacent organs. Most of the patients underwent volume implants. Patients who had brachytherapy as part of their treatment had better local control with 7-year local relapse-free rates of 77% versus 32% with EBRT alone. There was no difference in cause-specific survival, and the 7-year actuarial overall survival was 41%. The risk of vesico-vaginal fistula was reported as 15%.

Bladder

Bladder cancer can be treated with radical cystectomy or with chemoradiotherapy for an organ-preserving approach.[134,135] Several studies have shown good results with the addition of brachytherapy to EBRT.[136,137] Aluwini et al[136] reported on 192 patients with muscle invasive bladder cancer who were treated with EBRT followed by surgical exploration (with or without partial cystectomy) and interstitial brachytherapy (LDR or PDR). Salvage cystectomy-free survival at 5 and 10 years was 93% and 85%, respectively. The 5- and 10-year overall survival rates were 65% and 46%, whereas cancer-specific survival at 5 and 10 years was 75% and 67%. The distant metastases-free survival rate was 76% and 69% at 5 and 10 years. Multivariate analysis revealed no independent predictors of local recurrence-free survival. RTOG grade ≥3 late bladder and rectum toxicity were recorded in 11 patients (5.7%) and 2 patients (1%), respectively.

GEC-ESTRO guidelines have recently been published and recommend that EBRT and brachytherapy are reserved for patients with a solitary tumor of <5 cm, T2 to T3, no additional carcinoma in situ, and not located at the bladder neck or prostatic urethra.[138] Radiotherapy doses and schedules vary but a typical schedule is 40 Gy in 20 fractions EBRT followed by 25 to 30

Gy brachytherapy (HDR or PDR). The implant can be sited by open surgery (retropubic approach) or endoscopically (simultaneous laparoscopy and cystoscopy). The catheters are passed through the abdominal wall into the detrusor muscle and out to the opposite side of the abdominal wall.

Head and Neck

Brachytherapy can be used to treat head and neck cancers either as definitive treatment or as a boost following EBRT. Use of brachytherapy may avoid disfiguring or mutilating surgery and allow organ conservation. Brachytherapy can also be used as a method of reirradiation for localized recurrence.[139] There are many years of safety and efficacy data for LDR brachytherapy, and PDR appears to replicate these results.[140-144] Intensity modulated radiotherapy (IMRT) is becoming increasingly standard for head and neck cancer; however, there are indications that delivery of CT-planned optimized brachytherapy continues to deliver superior results over IMRT.[145,146] Plan quality aspects that are important for local control and risk of toxicity are similar to those of other interstitial implants.[147]

GEC-ESTRO have issued consensus recommendations for the use of head and neck brachytherapy[148,149] with a particular focus on dose, treatment selection, and quality assurance in the 2017 update. Data supports the use of both hourly pulses and two-hourly pulses, with a dose of 0.4 Gy per pulse (24 pulses per day) or 0.8 Gy per pulse (12 pulses per day). The overall dose is decreased slightly when using 12 pulses per day, for example, a monotherapy dose for a T1N0 cancer would be 70 Gy using 24 pulses per day and 60 Gy using 12 pulses per day. The ABS have recently updated guidelines for head and neck brachytherapy focusing on treatment selection in the era of advanced EBRT techniques.[150]

Patient selection is key for head and neck brachytherapy. Patients who are unfit for radical surgery may still be poor candidates for brachytherapy. PDR may allow the use of brachytherapy for patients with more complex nursing needs in whom LDR would have been contraindicated. It is important that the patient is fully assessed prior to brachytherapy. Dental assessment is essential, tooth extractions may be required, and for implants encompassing the oral cavity, customized leaded mandibular shields decrease the risk of osteo-radionecrosis. Feeding needs should be assessed

and where necessary, naso-gastric or percutaneous gastrostomy feeding tubes should be placed before the implant. For base of tongue implants, the patient should be prepared to have a tracheostomy, which can be reversed as soon as the postimplant edema subsides. The patient should be assessed regularly during the duration of the implant for displacement of the sources or applicators. Analgesia should be administered and mouthwashes are often helpful.

The majority of head and neck implants are placed in an operative procedure by freehand technique in a multiplane implant (Figures 22.11 and 22.12). These can be sited using a variety of techniques with use of afterloading catheters being preferred in the modern era for radiation safety reasons.[151] Standard applicators such as the Rotterdam applicator, which can be sited under local anesthetic without image guidance, are also available (Figures 22.13 and 22.14). Similar to other sites described later, interstitial ^{125}I seed implants can be used in cases of unresectable disease with favorable rates of control and toxicity.[152-155]

FIGURE 22.11 Catheters placed to deliver a brachytherapy boost to the pharynx.

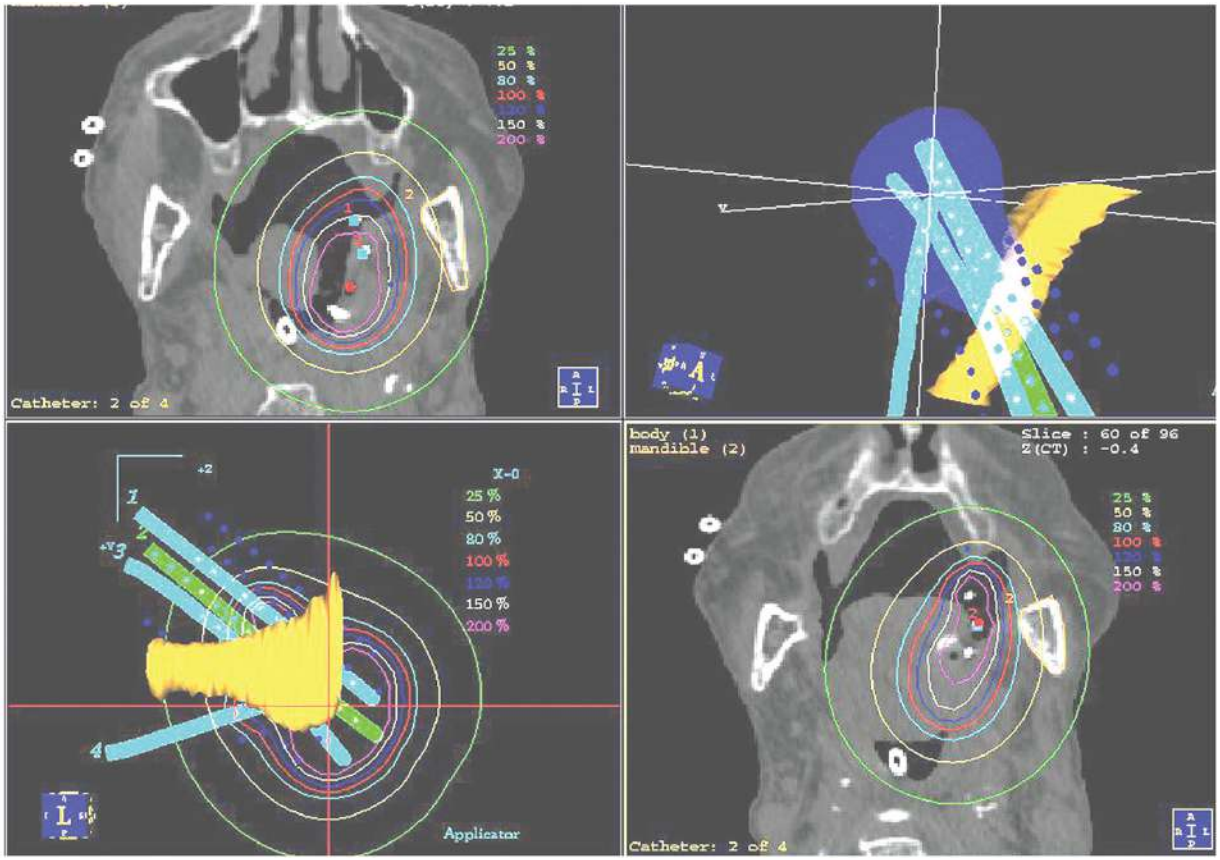


FIGURE 22.12 Three-dimensional computer-optimized dosimetry of the pharynx implant.

FIGURE 22.13 Patient with a Rotterdam applicator in situ within the nasopharynx.

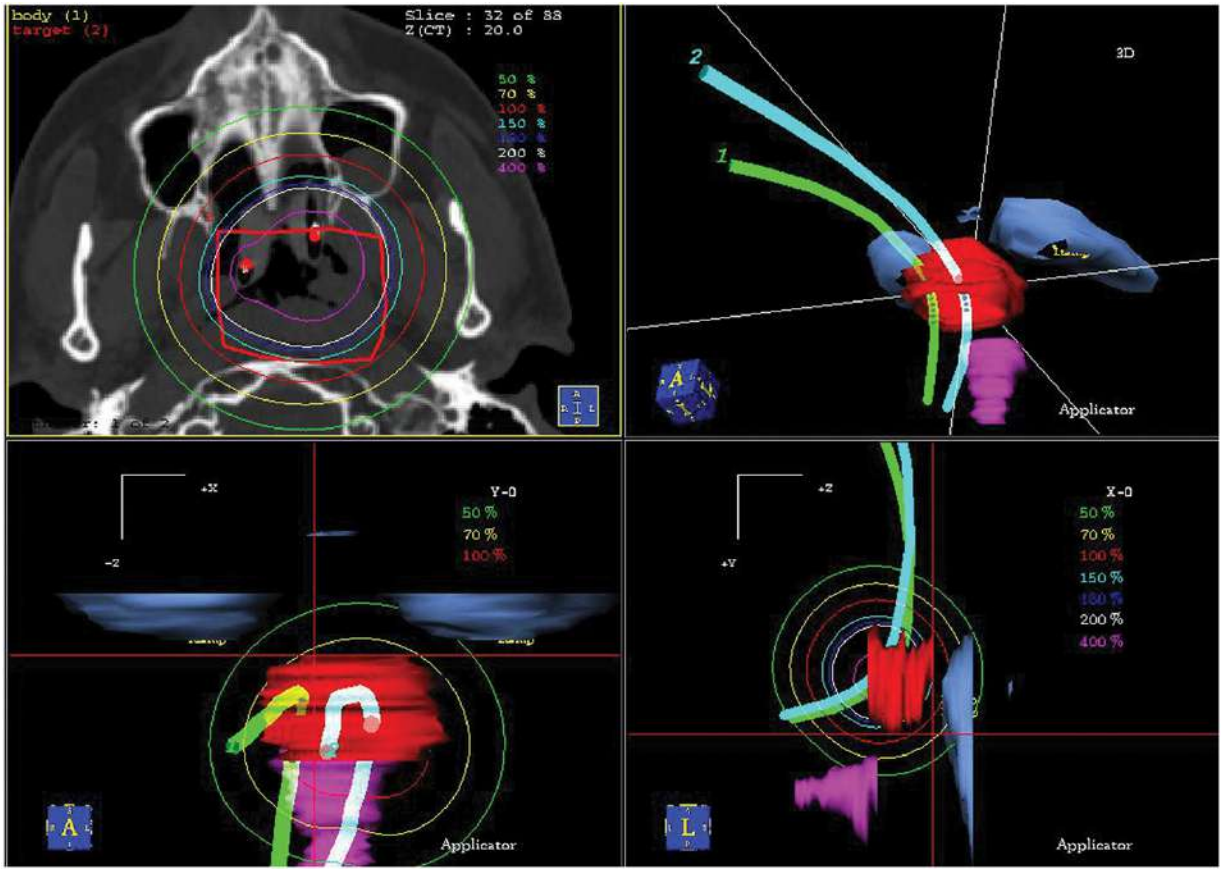


FIGURE 22.14 Three-dimensional dosimetry of the Rotterdam applicator, delivering computer-optimized brachytherapy.

Brachytherapy is indicated in most lip cancers, either as sole modality in tumors 0.5 to 5 cm or as a boost following EBRT in tumors >5 cm. For very superficial tumors, a surface applicator may be appropriate (Figure 22.15), thus preventing scars from puncture wounds. However, most tumors require the placement of two or three interstitial catheters across the tumor (Figure 22.16), which are placed freehand under local anesthetic. Typical doses are 45 to 75 Gy at the 85% reference isodose (higher doses for larger tumors, although at the risk of decreased cosmesis). Five-year local control rates with LDR are 90% to 95%[151,156] and 94% with PDR.[157,158]

FIGURE 22.15 Surface applicator technique used to deliver a boost dose to a lower lip sarcoma following external beam radiation therapy. The wax mouth bite was used to displace the tongue and could be placed for every pulse of the pulsed dose rate.

FIGURE 22.16 Multicatheter single-plane cheek implant. The metal gum shield can be placed for every pulse of the pulsed dose rate.

For oral tongue tumors, brachytherapy offers control rates similar to those of surgery with the benefit of organ and function preservation. Brachytherapy alone can be used for smaller lesions or as a boost for larger lesions. Interstitial implants are preferred, placed under general anesthetic using a metal trocar and threading the afterloading catheters through these. Looped catheters were popular when using ^{192}Ir ribbons, but with optimized PDR, it is difficult for the source to pass into the curved tube; therefore, individual button-ended catheters are preferred for source excursion (Figure 22.17). To prevent a cold spot on the tongue, an extra spacer can maintain the catheter above the tongue or dose optimization can be used, taking care not to cause a localized hot spot. Mandibular shielding is preferred. A dose of 65 Gy is typical as sole treatment and 20 to 25 Gy as a boost.[159] Local

control compares well to surgery with small superficial tumors showing local control rates >90%.[18] When combined with EBRT, a PDR boost for base of tongue tumors gives results at least equivalent to LDR with 5-year local control of 89%.[160]

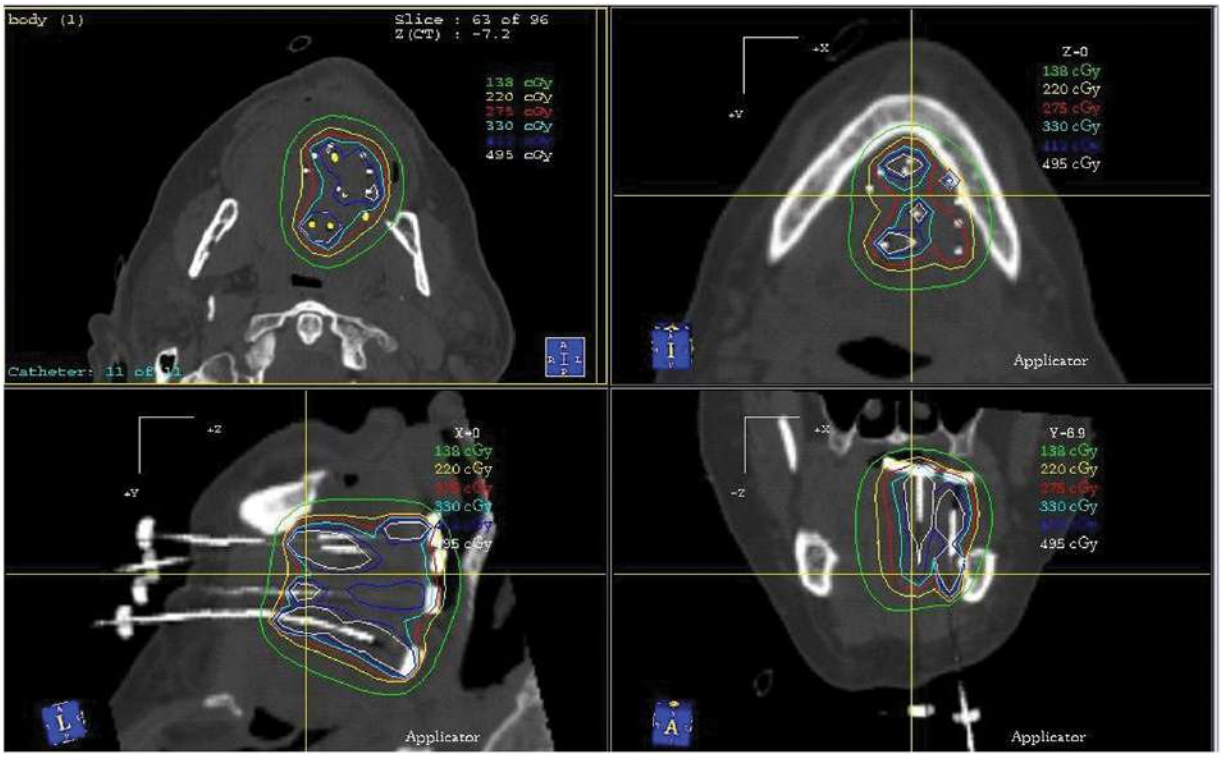


FIGURE 22.17 Three-dimensional computer-optimized dosimetry of a tongue implant using button-ended catheters.

Tumors on the floor of mouth are also best treated with interstitial implants with techniques similar to those of tongue implants. Distance to the mandible is critical to prevent osteo-radionecrosis. It may be preferable to perform surgery with reconstruction rather than risk late sequelae. Elective nodal dissection may be preferable to EBRT in advanced cases.[161] A dose of 65 Gy for sole treatment and 20 to 30 Gy boost is recommended, keeping overall treatment time as short as possible. Control rates range from 50% to 92% depending on tumor size, but bone necrosis is more common than other sites up to 30%.[151,161]

Mattei et al[162] recruited 79 patients with oral cavity squamous cell carcinomas, of whom 38 received LDR brachytherapy and 41 had PDR. All

patients underwent surgical resection of the primary tumor. The mean preoperative tumor size was 20 mm with brachytherapy indicated for patients at high risk of recurrence, who were not suitable for further resection. The median time interval between surgery and brachytherapy was 55 days. The median number of catheters used was four and the median total dose 55 Gy, with a median delivery time of 80 hours and a median dose rate of 0.7 Gy/h. The median follow-up period was 65.1 months. Totally, 15 patients (19%) experienced a local recurrence in the LDR group and 5 (12%) in the PDR group. The 1-, 3-, and 5-year local control rates for the study were 93%, 78%, and 76%, respectively. The 1-, 3-, and 5-year DFS rates were 86%, 63%, and 62%, respectively. Treatment modality had no significant impact on the DFS. In contrast, the presence of LVI (p = 0.055) and an excision margin less than 3 mm (p = 0.058) were approaching statistical significance, with positive excisional margins indicating a clear relevance (p = 0.007).

In a feasibility and safety study of 28 patients undergoing intratumor α radiation-based tumor ablation for oral squamous cell carcinoma termed Diffusing Alpha-emitters Radiation Therapy[163,164] 10 patients had oral squamous cell carcinoma (SCC) and 18 were diagnosed with cutaneous SCC, with a total of 31 lesions. They had a tumor size of ≤5 cm in the largest diameter. Treatment was delivered based on a CT-simulation pretreatment plan. Radium-224 (Ra-224) seeds were used, with each carrying a dose of 2 μCi and placed up to 5 mm apart. CT was used to confirm the position of the radioactive seeds. Two weeks after implantation, the seeds were removed, and 6 weeks after treatment, a CT scan was performed to assess the effect of treatment. Within 6 weeks after insertion of Ra-224 seeds, complete response was observed in 22 lesions (78.6%), and partial response in six lesions (21.4%). Five of the 22 complete response lesions relapsed at a median of 4.9 months. The 1-year local progression-free survival probability was 60%, and overall survival rate was 93% among complete responders.

Oropharyngeal cancers traditionally present at an advanced stage due to their location in an area that is not visible with few pain fibers. Surgery can be very debilitating; therefore, EBRT and localized boost techniques are favored. A boost of 20 to 30 Gy is delivered using an interstitial implant. The implant is performed under general anesthetic with nasal intubation,

and a covering tracheostomy is usually required. Hemorrhage may occur in implant removal, so it is important to remove the catheters under controlled conditions with wide bore venous access, suction, and surgical support.

Most nasopharyngeal tumors are inoperable due to their position at the base of the skull. However, the nasopharynx is easily accessible to brachytherapy catheters. These can be placed under topical anesthetic (eg, the Rotterdam applicator) or under direct vision using a Le Fort osteotomy. The main role of brachytherapy is as a localized boost or as a sole reirradiation technique, with typical doses of 12 to 20 Gy and 60 Gy, respectively. Local control is excellent even in reirradiation where control rates of at least 50% are reported.[151]

Brachytherapy is particularly suitable for reirradiation of head and neck cancer, administered with curative intent. A series of 104 patients with recurrent head and neck cancer were treated with brachytherapy alone (81) or with a brachytherapy boost (23), often with concomitant chemotherapy (56%) or hyperthermia (32%). At a median follow-up of 60 months, the 5-year local control was 82%, with acceptable rates of late toxicity, requiring surgery for toxicity in only 3% of cases.[165]

Thorax

Intraoperative permanent radioactive ^{125}I seed implantation can be used in the treatment of malignant thoracic tumors when resection margins are close or macroscopically or microscopically involved with tumor[166-181] or for palliation of inoperable disease.[182] The surgeon selects patients preoperatively when there is a concern of incomplete tumor resection or close or positive margins and refers to the brachytherapist. The patient consents in advance for a permanent implant to be placed intraoperatively, if required. Details of previous radiotherapy and chemotherapy treatment are carefully reviewed prior to surgery. The brachytherapy team is on call for the surgical procedure. Frozen section analysis of margins may be needed to assess whether an implant is needed. Seeds are placed directly into a tumor as a volume implant or woven in a grid pattern in a planar implant. Volume implants require the use of an applicator or preloaded needles to deliver the seeds directly to the tumor. A planar implant can be ordered readymade in advance (Figure 22.18) or custom made

intraoperatively[183] (Figure 22.19). I^{125} seeds set into Vicryl suture with 1-cm spacing between seeds can be woven into a mesh or sutured directly to the area at risk. The Vicryl suture and accompanying mesh degrade naturally after approximately 60 days; at this point, much of the dose has been delivered, and the seeds are often held in position by local fibrotic reactions. The mesh can be used in open surgery, thoracoscopically or utilizing a robotic system.[184] Seeds can be placed at equally spaced intervals into a layer of foam,[173,185] but this implant may be more difficult to suture in place, as the seeds are not easily visible and are therefore at risk of being displaced or damaged by the suture needle. Alternative seed-placement devices may aid seed placement such as the customized suture gun (Figure 22.20). Radiation exposure during the procedure to the implanting radiation oncologist and surgeon is very low[186] and well within occupational radiation exposure guidelines. When the implant has been sited, the operating room is surveyed for the presence of radiation. The patient is surveyed at the outer body surface over the implant, at 0.5 m and 1 m. In the immediate postoperative period, no change in patient care is required, subject to standard post-vLDR implant precautions of preventing exposure to children or pregnant women.[187]

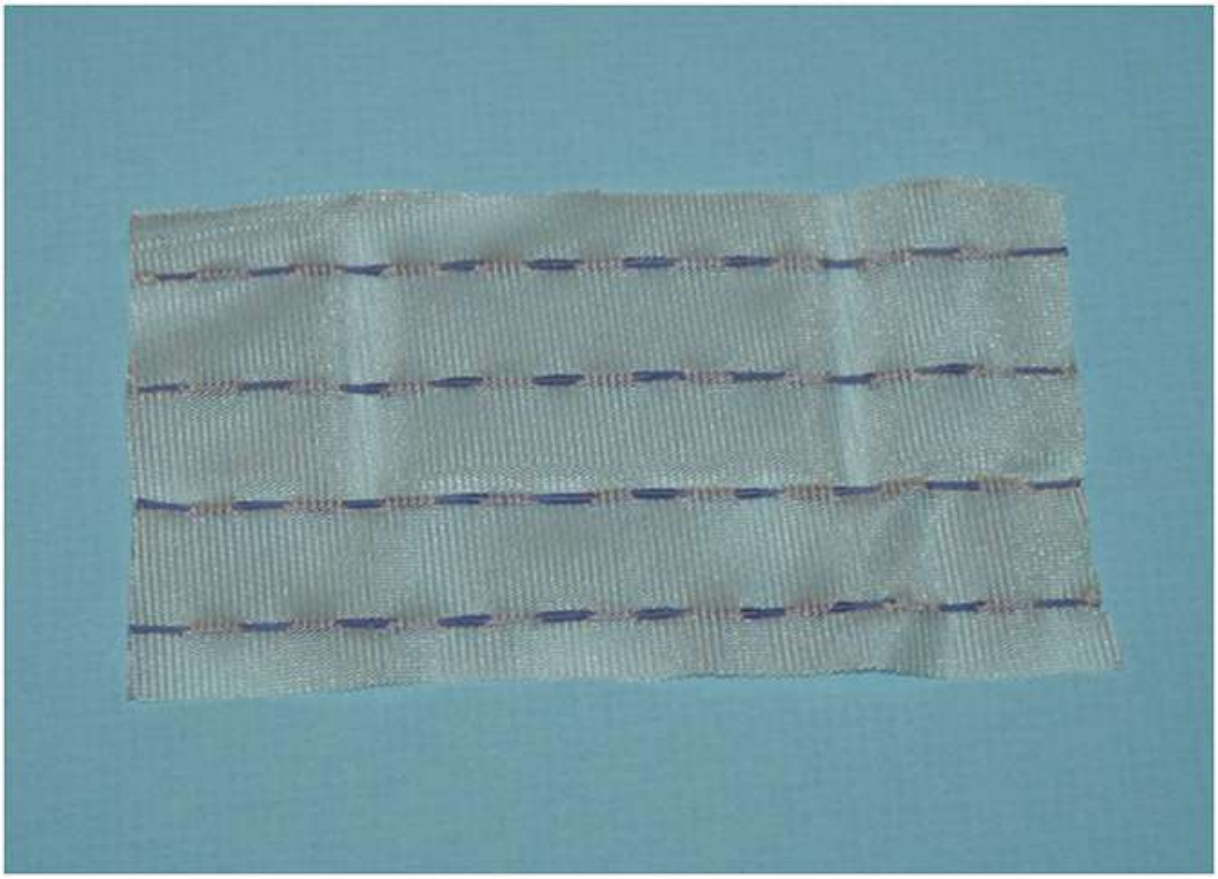


FIGURE 22.18 Premade seed mesh.

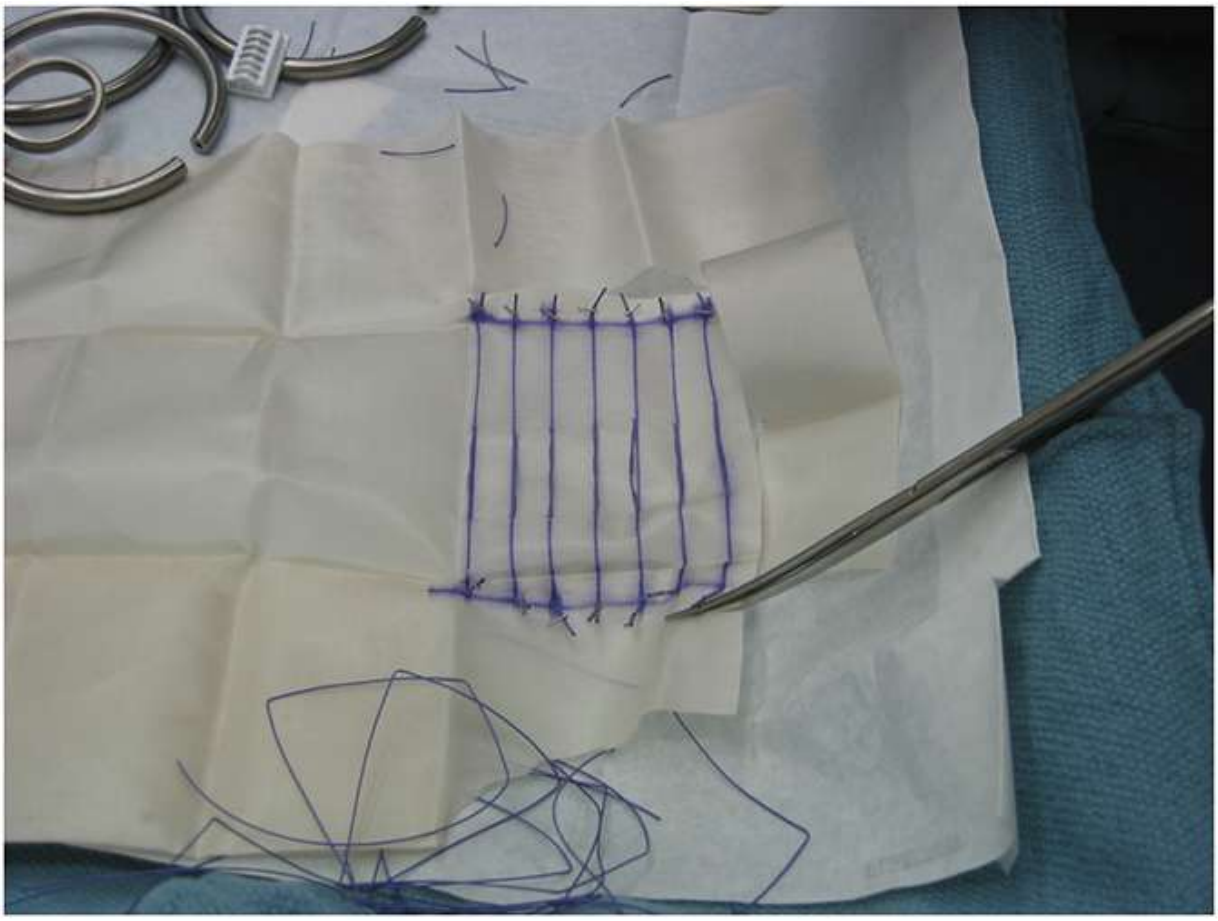
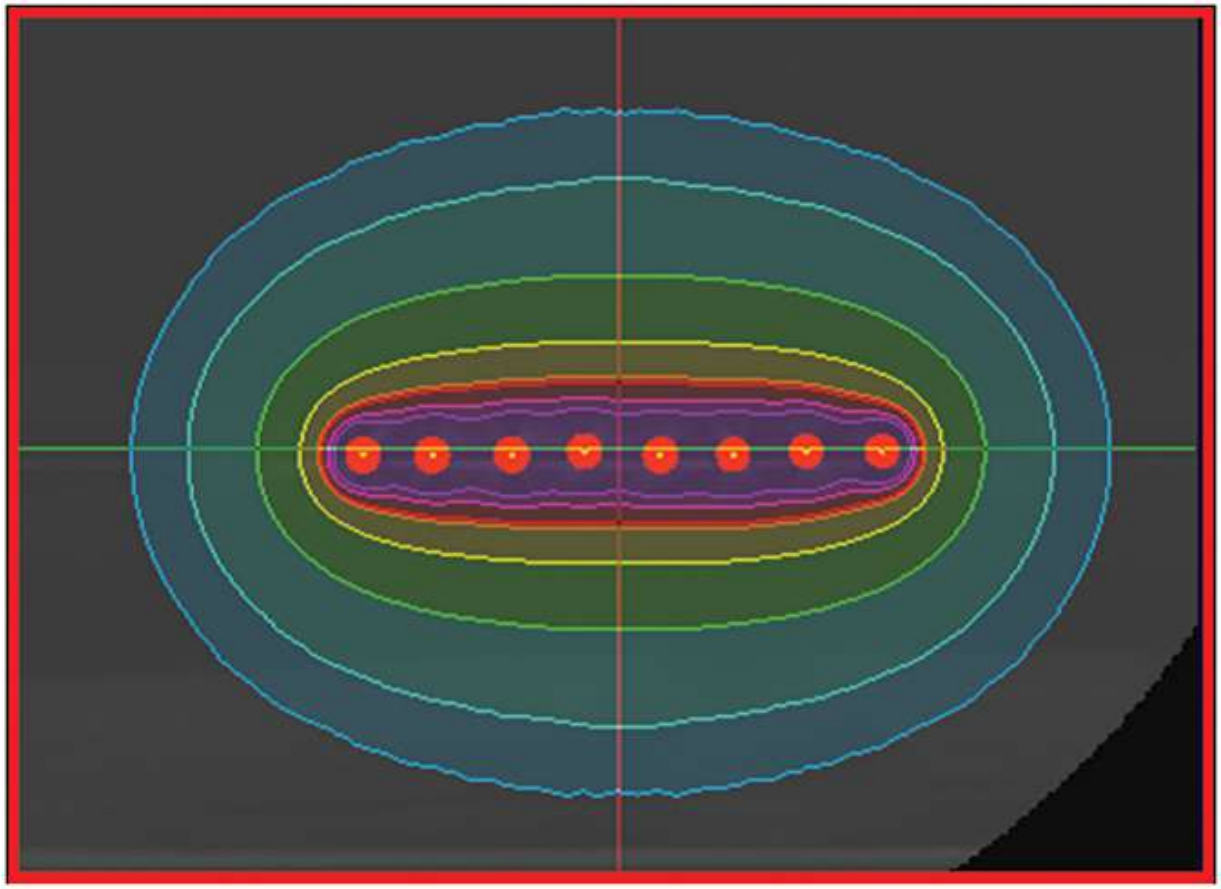


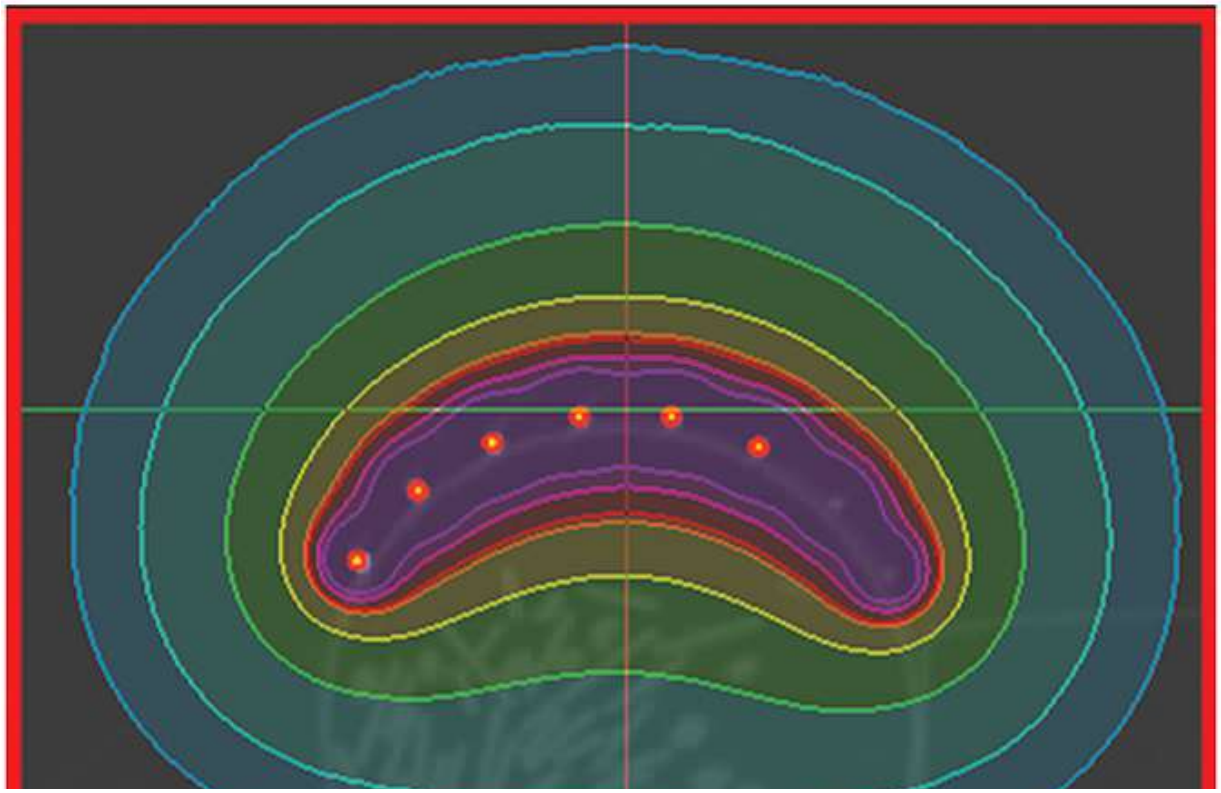
FIGURE 22.19 Custom-made 6-by-10-cm mesh implant using iodine-125 seeds in Vicryl carrier. The steel rings used to shield the isotope in transit can be seen at the *top left* of the picture.

FIGURE 22.20 Seed staple gun.

For sublobar resection, the dose recommended is 100 Gy, at 5 mm from the mesh or 7 mm from the central axis of the implant. For incomplete resection of tumor/positive margins, the dose chosen will depend on many factors such as adjacent structures or previous radiation; the type of surgery performed must also be considered in case there is an increased risk of late

normal tissue toxicity.[188] The curvature of the implant should also be assessed because over a curved surface, dose penetration is asymmetric compared to a linear implant.[189] Isodoses on the concave side of a curvature are further from the implant surface potentially decreasing the dose delivered. The asymmetry increases with decreasing radii of curvature (Figure 22.21). Interestingly, in vitro studies have shown that selected human lung cancer cell lines show a sensitivity to ^{125}I seed brachytherapy greater than HDR irradiation, an effect that was further potentiated with the use of radiosensitizers.[190]





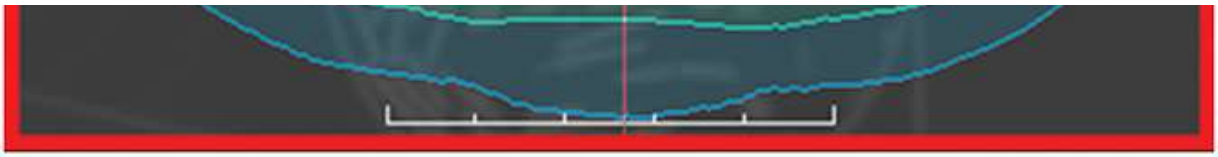


FIGURE 22.21 Effect of curvature on the dosimetry of a single planar mesh seed implant.

Lobectomy is the standard of care for patients with operable Stage I NSCLC; however, intraoperative ^{125}I seed placement has been used in conjunction with sublobar resection in patients with lung cancer who are medically unfit for lobar resection.[171,174,175,177-181] Retrospective studies showed that patients undergoing sublobar resection had similar rates of disease-free and overall survival but that patterns of relapse differed with higher rates of local recurrence in the sublobar resection group.[191] Thus, intraoperative permanent seed implant brachytherapy was evaluated in a multi- institution randomized phase III prospective trial by the American College of Surgeons Oncology Group (ACOSOG) Z4032.[192,193] This demonstrated that there was no difference in 5-year local recurrence with the addition of brachytherapy (17% with brachytherapy vs 14% without, $P = 0.59$). There was no difference in disease-free or overall survival. There was a trend toward favoring brachytherapy in patients with positive staple line cytology. Better than expected rates of negative margins were achieved, so the trial may have been underpowered to detect a small difference. Therefore, the ABS consensus recommendations do not recommend this outside the confines of a clinical trial.[194]

For intrathoracic tumors with incomplete resection or microscopic close margins, retrospective and prospective series have shown disease-free and overall survival rates, with the addition of an intraoperative permanent seed implant are improved over those that would be expected with incomplete resection alone[166-169,172] (Figure 22.22). Radioactive seed implantation (RSI)-BT can be used in early lung cancer in patients who cannot have surgery or tolerate EBRT or are unresectable (stages III/IV), with a PD between 100 and 120 Gy and local control rates between 80% and 100%.[195] The 1-year survival rates were documented as 90% to 95% and 2-year survival rates as 70% to 80%. Li et al treated 12 patients with RSI-BT in the inoperable setting and found that the local control rate achieved by RSI-BT was 97%, 67%, and 42% at 6, 12, and 24 months, respectively.[196] However, primary

image–guided RSI-BT is not routinely recommended for lung cancer patients unless there are no other treatment options, and more comparative data is required. For recurrent lung cancer after surgical resection, image-guided RSI-BT can be considered as palliation and may be applied in the majority of cases involving recurrent tumors in the chest, including lesions in the lung parenchyma and tumors that metastasize to the mediastinum, chest wall, vertebral body, and lymph nodes. Platinum-based chemotherapy with concurrent BT was investigated by Rezaei et al.[197] The use of conventional platinum-based drugs did not change the lung absorbed dose, while unconventional platinum-based drugs led to >2% dose changes when the platinum concentration exceeded 0.2 mg/g of lung tissue. This approach needs to be further investigated to clarify the usefulness of concurrent chemo-BT in lung cancer patients.

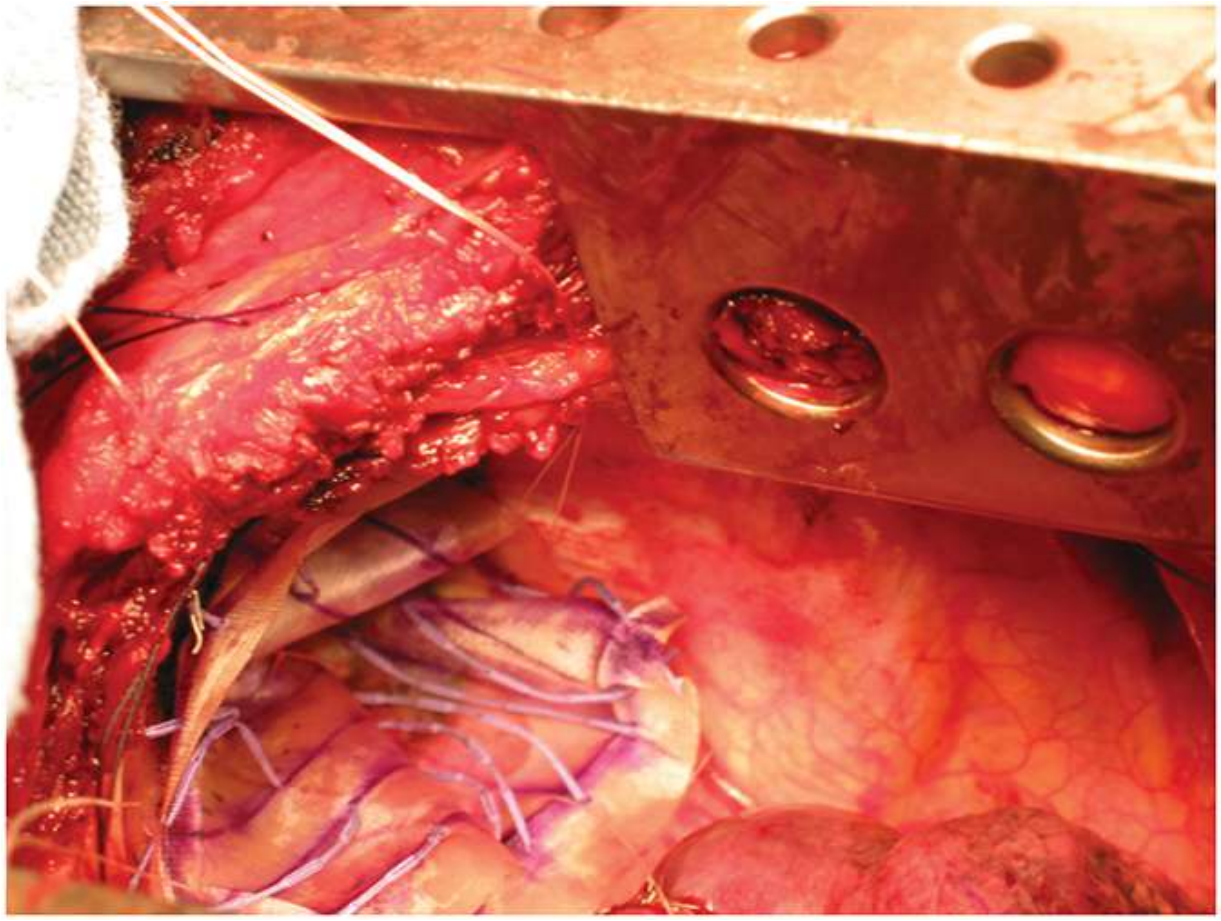
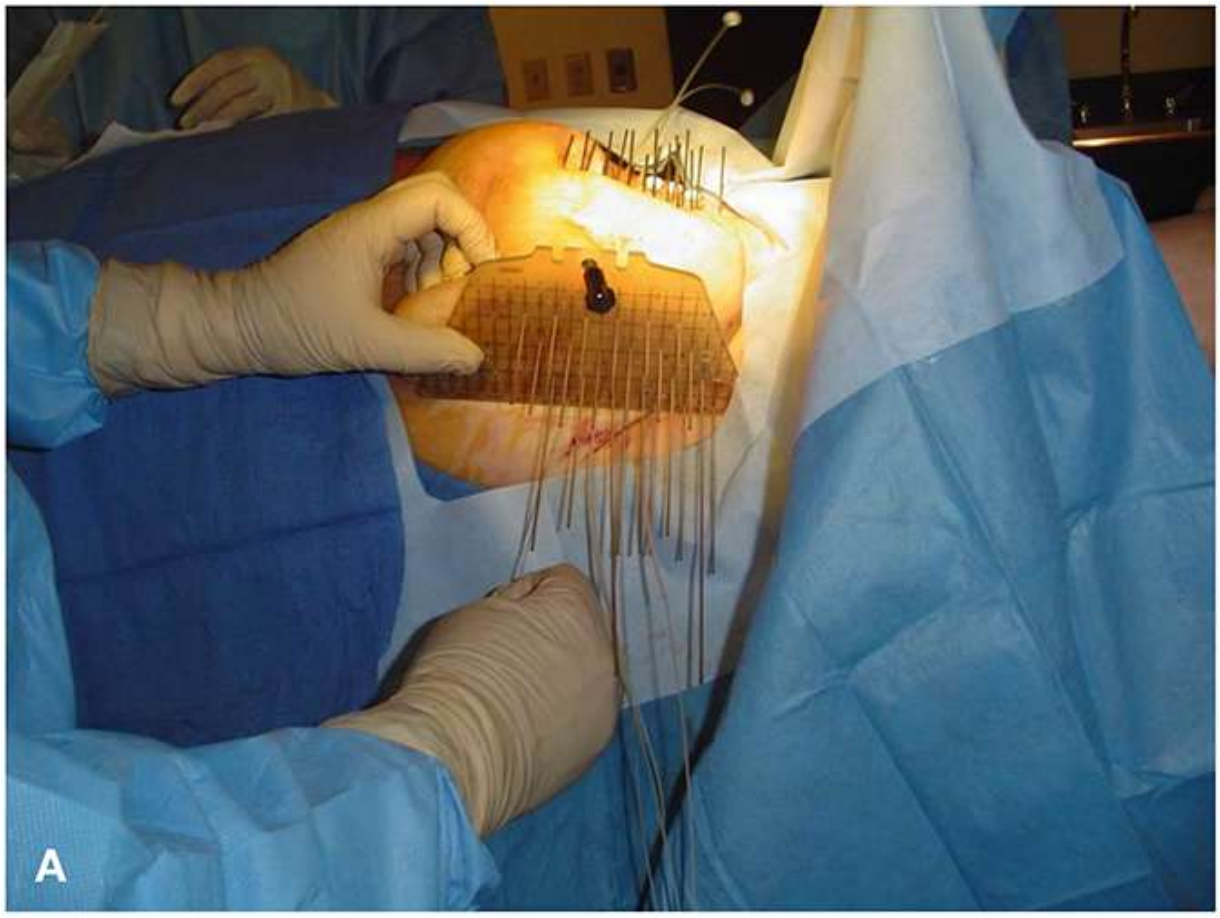


FIGURE 22.22 Intraoperative photograph of a custom-made mesh interstitial vLDR brachytherapy implant placed at the apex of the thoracic cavity following resection of a Pancoast tumor with close resection margins. The surgically collapsed lung can be seen at the base of the image.

Breast

Breast-conserving surgery is a proven alternative to mastectomy in patients with early-stage breast cancer, offering equivalent disease-free and overall survival.[198-200] Adjuvant radiotherapy is required since it results in a significant reduction in the risk of death due to breast cancer; unfortunately, this is offset by an increase in deaths due to other causes.[200] In the nonirradiated breast, recurrences tend to occur in the tumor bed with an elsewhere recurrence rate of up to 3.5%.[198,199,201,202] Accelerated partial breast irradiation (APBI) has similar ipsilateral breast recurrence and survival rates to whole breast IMRT but lower acute and late toxicities and better cosmetic outcome.[203] APBI can be delivered with brachytherapy, localized radiotherapy, or intraoperatively with electrons[204] or photons.[205]

Postoperative APBI using brachytherapy was initially developed using interstitial implants. A number of needles or tubes are placed across the tumor bed usually under a general anesthetic, either using a template or freehand (Figures 22.23 and 22.24). The treatment volume is generally the tumor cavity and a 1- to 2-cm margin. The dose is custom-shaped to this treatment volume. The dose can be delivered using LDR or PDR brachytherapy, typically over 4 to 5 days. The large number of catheters in an interstitial implant allows more control over skin and chest wall doses than single catheter techniques, especially with PDR dose optimization. The dose within the tumor is more homogenous with lots of smaller hot-spots, compared to one large hot-spot with single catheter techniques.[206] Single catheter technique for left-sided tumors has also been shown to have a higher mean heart dose than deep inspiration breath hold whole breast radiotherapy,[207] whereas this is less likely to happen with multicatheter brachytherapy.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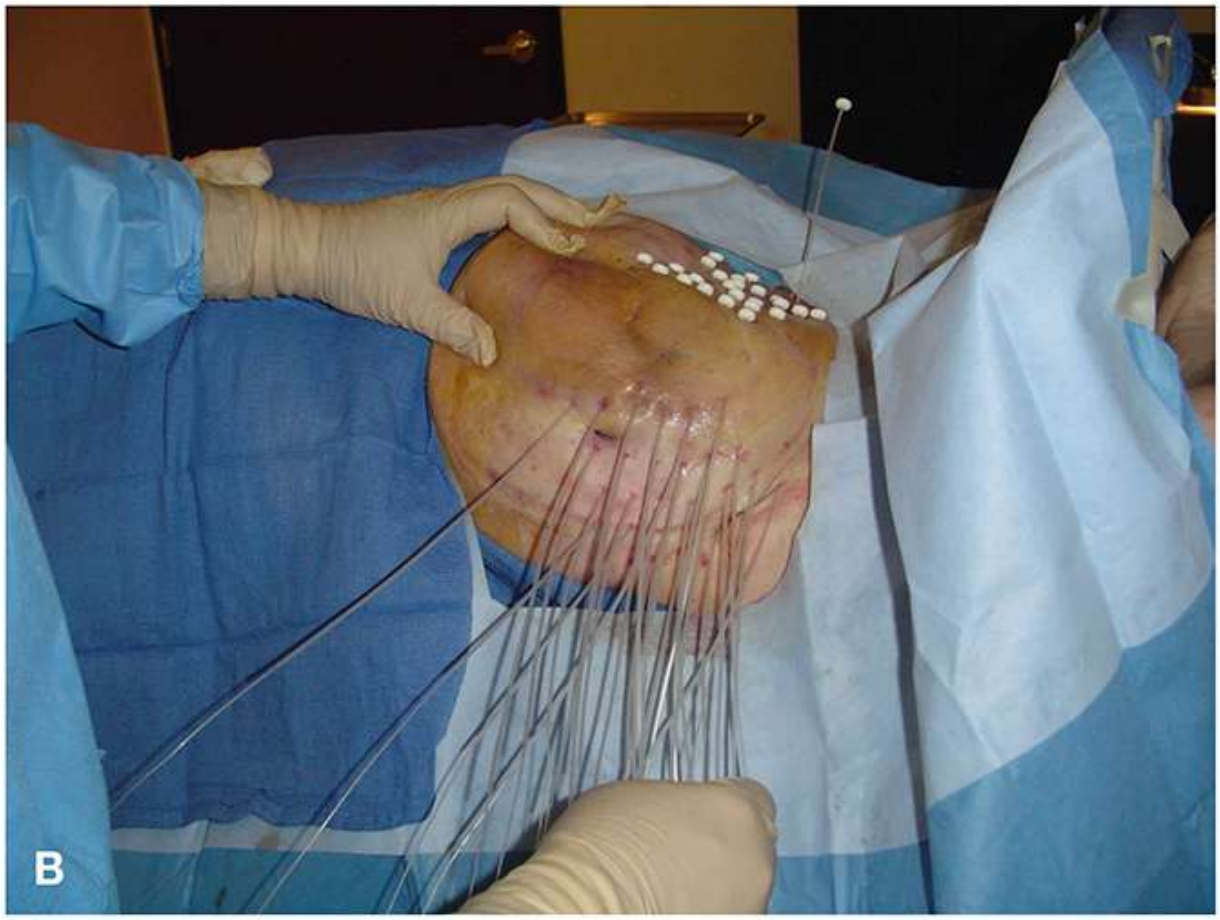
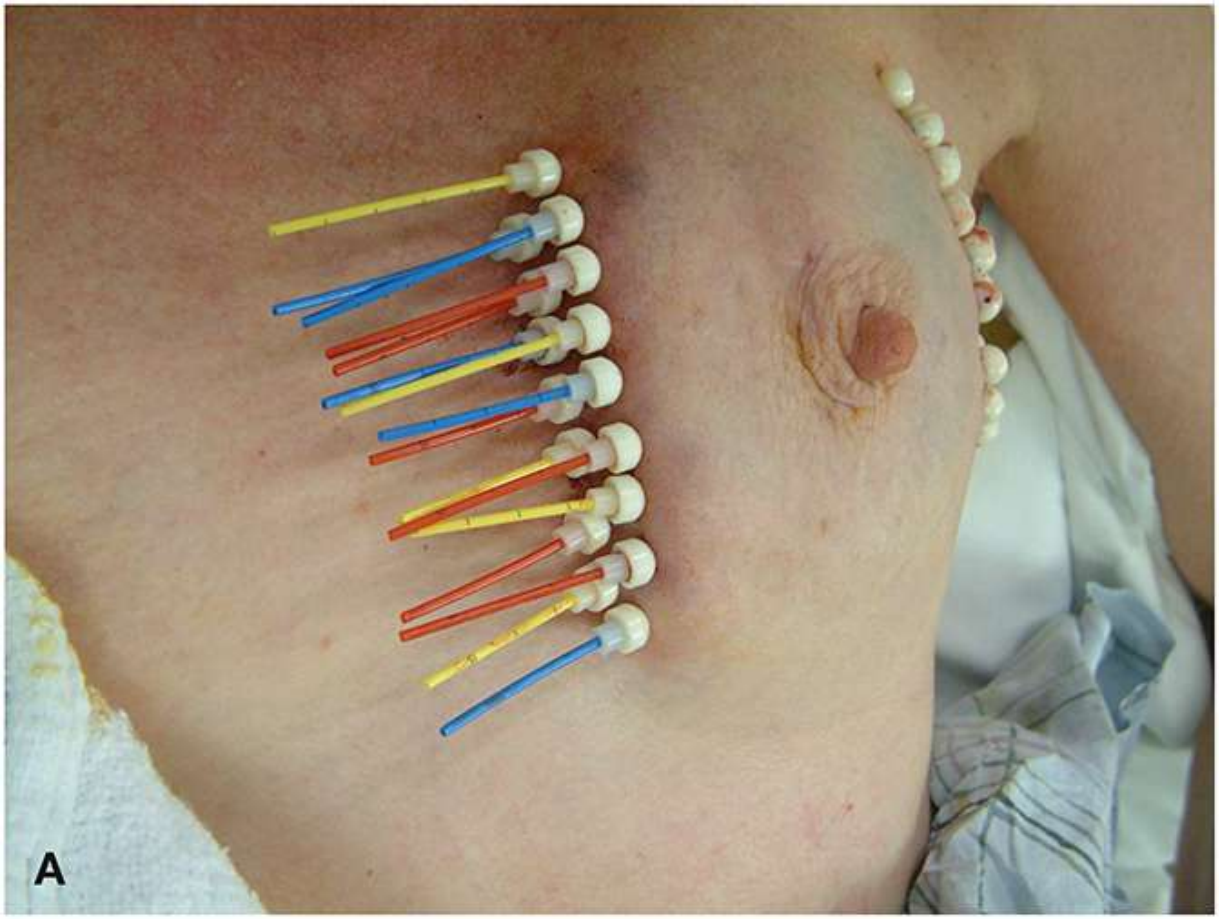


FIGURE 22.23 Template interstitial breast implant. A. Intraoperative photograph of insertion of needles for a multiplane template interstitial breast implant. B. Photograph to demonstrate catheter position after template removal. (Courtesy of Dr Bob Kuske.)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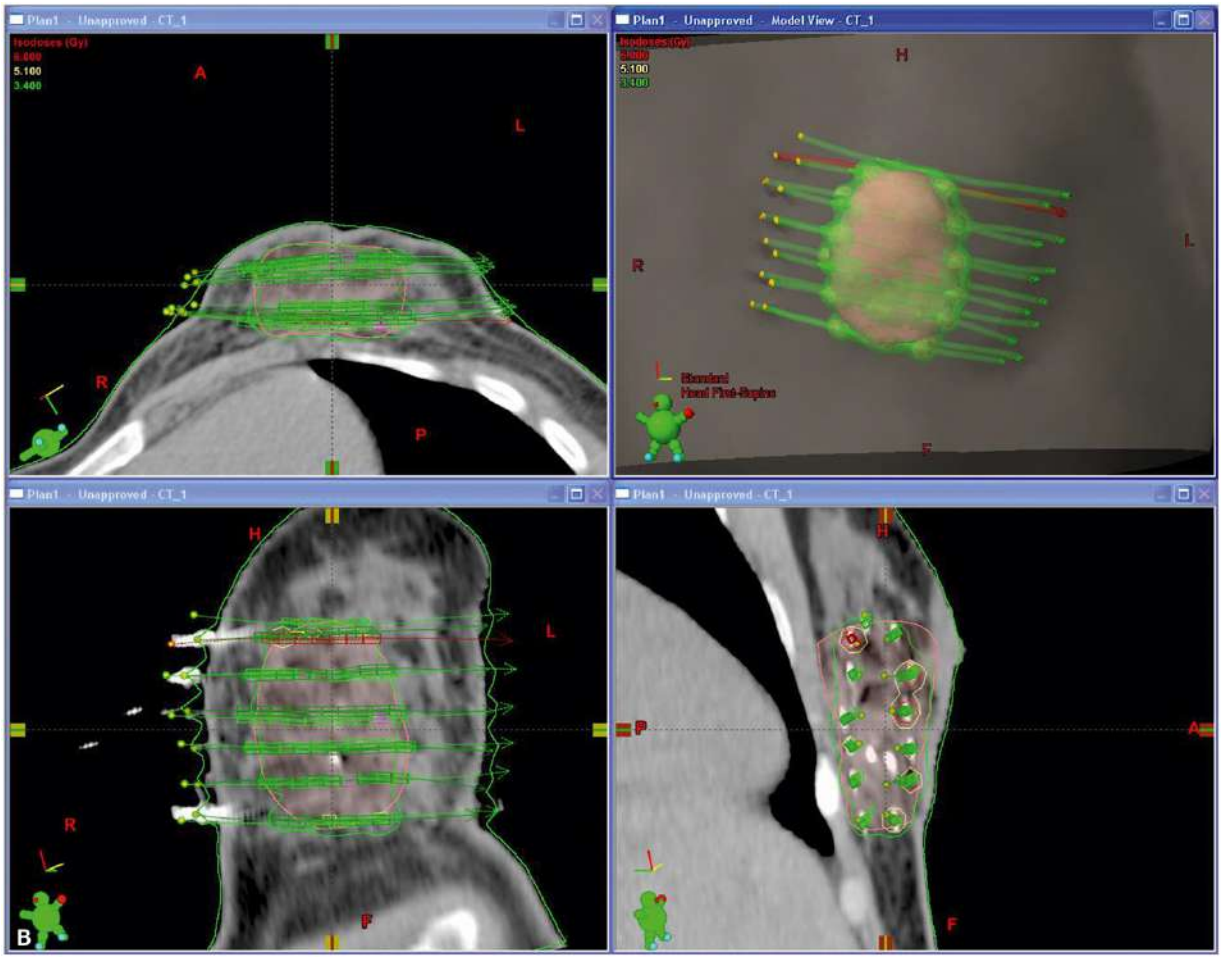

FIGURE 22.24 Freehand breast implant. A. Catheter position of a 2-plane breast implant. B. CT images demonstrating the dosimetry of the implant. The 100% isodose is marked in *green* (3.4 Gy). (Courtesy Dr David Wazer and Dr Dorin Todor.)

Interstitial implants have been in use for over 10 years. Phase 3 trials have shown that PDR or HDR APBI is noninferior to whole breast radiotherapy with respect to 5-year local control, disease-free, and overall survival in low-risk invasive or ductal carcinoma in situ.[208] Early toxicity was dramatically reduced in the brachytherapy APBI arm (86% vs 21%) for grades 1 to 2 early skin toxicity.[209] The 5-year toxicity and cosmetic outcomes were similar between the groups, although grade 2 to 3 late skin toxicity was significantly reduced in the brachytherapy arm.[210] APBI with LDR, PDR, or HDR brachytherapy after lumpectomy is also an option for patients with ipsilateral local recurrence with an overall survival rate equivalent to salvage mastectomy.[211]

Permanent interstitial seed implant has been described for APBI[212] (Figure 22.25). ^{103}Pd seeds were implanted using ultrasound guidance and a dose of 90 Gy prescribed to the tumor cavity and a 1.5-cm margin. In a group of 134 patients from 3 clinical trials, the observed local recurrence rate was 1.2% at 63 months, which is similar to the estimate for whole breast irradiation. Toxicity rates were acceptable. A radiobiologic dosimetric modeling study predicts that for APBI using brachytherapy, toxicity will be lower for a seed implant than for a multicatheter interstitial technique.[213]

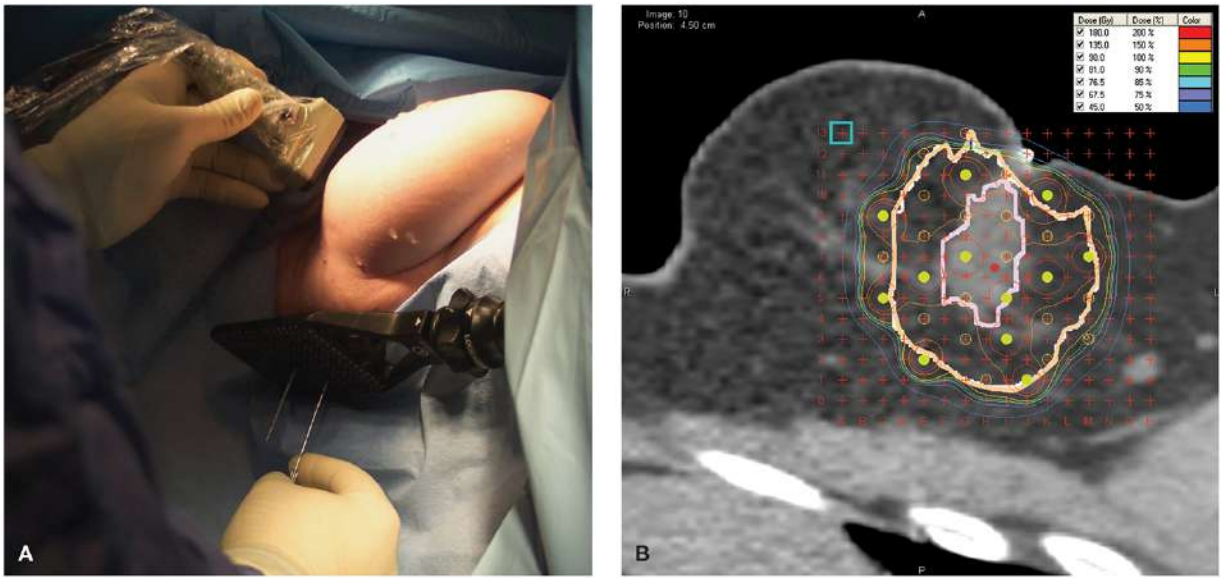

FIGURE 22.25 A. Intraoperative photograph demonstrating a template partial breast implant using iodine-125 seeds under ultrasound guidance. B. Sagittal computed tomography image to demonstrate the postoperative dosimetry of the implant. (Courtesy Dr Jean-Phillipe Pignol.)

Sarcoma

Soft tissue sarcomas (STSs) remain a challenge, given their rarity, multiple sites of origin, numerous histologies, and proximity to OARs. In the modern era, sarcoma surgery has become more refined moving away from disfiguring, disabling surgery and toward a multidisciplinary approach combining surgery and EBRT and, in certain tumors, chemotherapy.[214,215] Radiation therapy is an essential part of the treatment for most types of STSs. EBRT in the form of IMRT or volumetric modulated arc therapy

remains the main radiation technique for the treatment of STS. This can be given postoperatively or as a neo-adjuvant therapy with small fields required and lower doses. However, brachytherapy remains an important and versatile treatment option for STS of all organ sites. Temporary LDR implants were commonly used in the past; in general, these have been replaced by HDR and PDR. LDR interstitial implants have been described, and more recently, the use of a palladium-103 implant has shown promising results.[216] The American Brachytherapy Society recently updated their consensus recommendations for the use of brachytherapy in patients with STS.[217] Table 22.4 presents a summary of the general principles for STS brachytherapy. PDR BT can be used as monotherapy or a boost after EBRT. When delivered as monotherapy, the recommended dose is 45 to 50 Gy over 4 to 6 days, at 0.35 to 0.6 Gy/h. As a boost, the recommended LDR/PDR dose is 15 to 25 Gy, over 2 to 4 days, at 0.35 to 0.6 Gy/h. A brachytherapy boost can be considered in larger tumors, close surgical margins, and in high-risk cases such as local recurrence without previous radiotherapy, positive margins, challenging locations, and an inability to meet OAR constraints with EBRT alone. Brachytherapy catheters are usually placed at the time of initial resection using either a single-entry sealed-end catheter (Figure 22.26) or double-entry button-ended catheters and after-loaded 5 days postoperatively, enabling the whole STS treatment to be completed within 10 to 14 days. Placement under direct vision allows accurate coverage of the resection cavity. There may be less hypoxia immediately postoperatively, enabling the radiotherapy to be more effective. The catheter is secured with plastic buttons, which do not produce artifacts in CT or MRI scanning. The CTV is the tumor bed and a margin of 2 cm craniocaudally and 1 to 2 cm laterally.[218]

TABLE 22.4 GENERAL RECOMMENDATIONS FOR SOFT TISSUE SARCOMA BRACHYTHERAPY (INCORPORATING AMERICAN BRACHYTHERAPY SOCIETY GUIDELINES)[217,219]

- Discuss patient preoperatively in a multidisciplinary setting
- Determine CTV by radiographic, surgical, and pathologic findings
- Place catheters to encompass CTV, demarcate CTV with surgical clips, if possible
- Identify and demarcate normal structures that are at risk for complications
- Cover tenuous wounds with well-vascularized flaps

- Place microvascular anastomoses away from radiation target area
- Use drains over catheters to act as a spacer to increase the distance of the wound from the implant
- Use spacers (eg, Gelfoam) to increase the distance between catheters and critical normal structures
- Ensure catheters enter skin at least 1 cm from surgical incision
- Space catheters at 1- to 1.5-cm intervals in parallel arrays
- Secure catheters carefully, immobilizing extremity, if necessary
- Use CT to determine the CTV and organs at risk
- Do not load catheters until after the fifth day postoperatively

Adapted from ASTRO Guidelines.

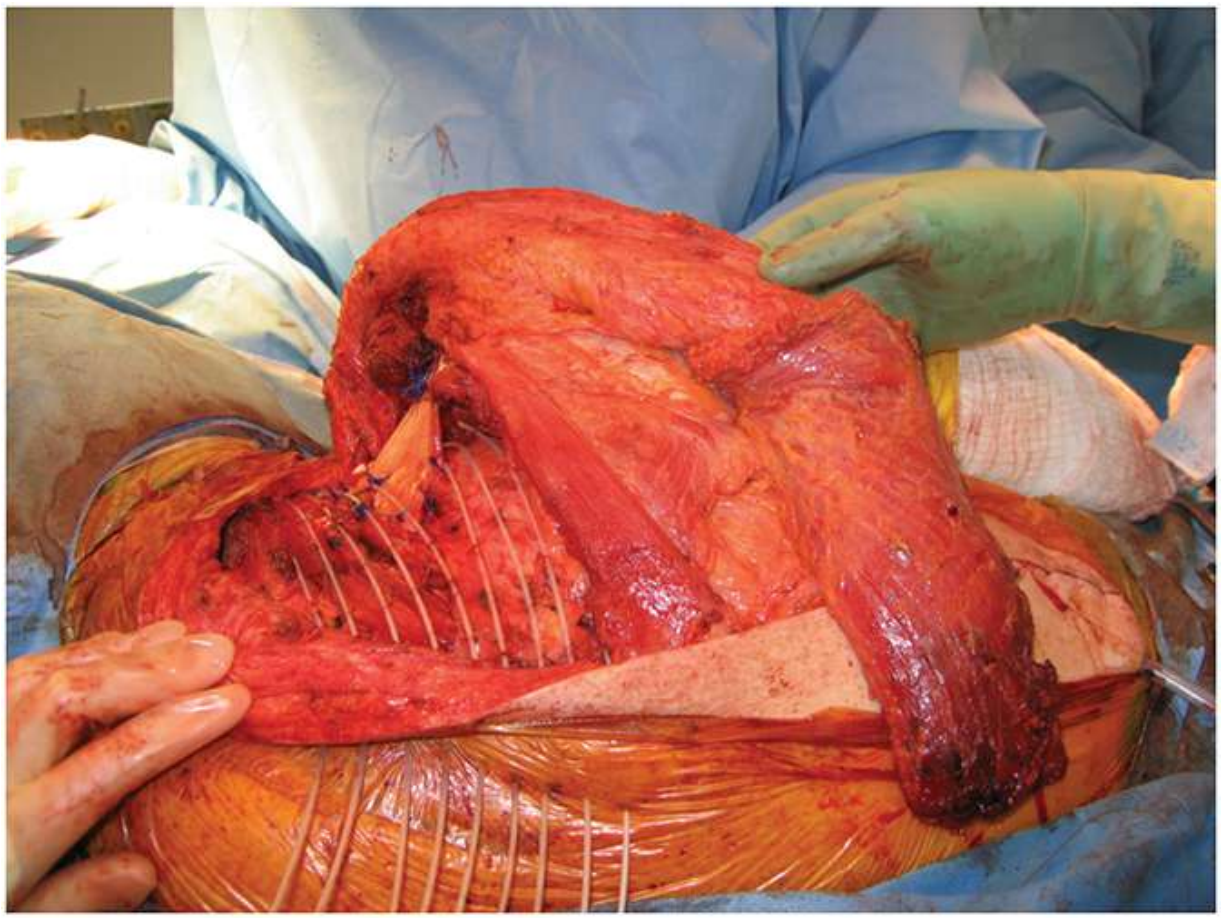

FIGURE 22.26 Intraoperative photograph of a multicatheter interstitial pulsed dose rate brachytherapy implant following excision of a sarcoma of the upper back.

Phase 2 trials showed the utility of LDR brachytherapy for postoperative STS treatment[169,220] and therefore, a randomized phase 3 trial was

conducted.[221] One hundred and seventeen patients were randomized to brachytherapy or no brachytherapy following R0 or R1 resection; patients were stratified by various factors including size and grade. The 5-year actuarial local control for all patients was 82% versus 69% (p = 0.04), but on subgroup analysis, no effect was seen in the patients with low grade tumors. With longer follow-up of the high-grade tumors only, local control was 89% versus 66% (p = 0.0025), but no effect was seen on distant metastases or overall survival. Functional parameters were well maintained post brachytherapy. PDR brachytherapy has been used in adults and children, either as a boost (for large tumors where compartmental surgery proved difficult) or as radical treatment.[222-224] Studies report excellent local control with good cosmetic results and acceptable toxicity, comparable to results achieved with LDR. However, a retrospective study of adjuvant LDR brachytherapy to pre- or postoperative IMRT in primary extremity sarcoma showed 5-year local control with IMRT to be better than brachytherapy (92% vs 81% P =.04). This is despite the fact that the IMRT group had significantly higher rates of adverse features (eg, tumors sized over 10 cm and with close or positive surgical margins).

Superficial Sites

Brachytherapy surface applicators can be used to treat a variety of superficial targets using LDR or PDR. For curved or irregular surfaces or thicker lesions, a customized mold can be constructed, often using an acrylic or thermoplastic cast (Figure 22.27) or a customized three-dimensional printed mold. The brachytherapy catheters can be laid directly onto the mold or used with a spacer to ensure uniform catheter distribution. When used with computerized optimization, this surface applicator technique has been shown to give dose distributions that are more homogeneous than conventional electron techniques.[225] A survey of members of ABS showed that many respondents preferred brachytherapy over EBRT due to shorter overall treatment times, conformality of treatment for irregularly shaped targets, and shallow dose deposition.[226] PDR carries the benefit of dose optimization, which allows the treatment depth to vary along different points of an individual catheter for lesions of varying thicknesses. Suitable superficial targets can also be treated with interstitial

implants, which can give greater penetration of dose beneath the skin surface.

FIGURE 22.27 Surface applicator mold used to administer brachytherapy to the dorsum of the foot following incomplete excision of an STS.

Surface applicator techniques have been used to treat primary tumors in both the radical and the palliative settings. A meta-analysis has shown that radiotherapy following surgery yields a lower keloid recurrence rate compared to radiotherapy alone and that brachytherapy had the lowest recurrence rate when comparing radiotherapy modalities (15% for brachytherapy compared to 23% for photons and 23% for electrons).[227] There does not appear to be a difference in recurrence rate between LDR and HDR.[228]

Surface applicator brachytherapy techniques have been used to treat locally recurrent breast cancer following previous chest wall irradiation. Using LDR ^{192}Ir implanted into flexible silicone sheets delivered in 2 to 3 fractions at monthly intervals to administer a total dose of 65 Gy 2 to 4 mm below the skin surface, Delanian et al[229] showed a complete regression of tumor in 9/11 patients. The two patients who did not respond died from pulmonary lymphangitis 4 and 5 months after brachytherapy. One patient developed a necrotic ulcer in the skin, which healed after 8 weeks of symptomatic treatment. One patient died from respiratory failure, which may have been related to cumulative pulmonary toxicity and must be considered as a treatment complication. Some patients also received interstitial implants in the chest wall, which would have increased the dose at depth to the previously irradiated tissue and to the underlying lung.

Harms et al used PDR brachytherapy and flexible rubber surface applicator molds in 58 patients with local recurrence of breast cancer who had received previous breast or chest wall EBRT. A median dose of 40 Gy to the skin surface in two fractions was administered at a median time interval of 31 days.[230] The local recurrence-free survival at 1 year was 96% for patients with microscopic disease at the time of brachytherapy and 89% for patients with macroscopic disease, 75% and 71%, respectively, at 3 years. Seven percentage of patients developed chronic ulcer, of whom two had undergone surgical treatment prior to reirradiation, and 50% of patients developed grade 3 telangiectasia in the treatment field. The skin toxicity was higher in this study, but this may have been a result of improved reporting of skin complications since the incidence of telangiectasia and fibrosis was not reported in the LDR study. A prospective cohort study recruited patients with unresectable malignant skin or soft tissue tumors.[231] Ten patients underwent DaRT to deliver a physical dose of 10 Gy to the

tumor (equivalent dose of 200 Cobalt Gy Equivalent). At 12 weeks following treatment, there was a 100% complete response rate. Nine of the 10 complete responses (90%) were confirmed by CT imaging. This suggests the feasibility of DaRT in unresectable skin and soft tissue cancers.

Eye

Ophthalmic brachytherapy applicators can be applied directly to the eye to deliver a highly localized dose with rapid falloff (Figure 22.28). These deliver dose to the conjunctiva of the eye, most commonly for malignant tumors of the conjunctiva such as squamous carcinoma, melanoma, and lymphoma or to prevent recurrence of pterygium following surgical excision. ^{125}I seeds are inserted into plaques formed of a silicone rubber inner seed holder with a gold exterior shield and are then sutured to the sclera. ^{90}Sr and ^{106}Ru are manufactured as curved applicators, and ^{90}Sr as a fixed-diameter applicator (typically 12 mm) (Figure 22.29), and ^{106}Ru in a range of diameters. The eye is anesthetized with installation of local anesthetic eye drops. The applicator is soaked in an antiseptic solution, followed by double-rinsing in sterile saline. Sterile lubricant is then applied to the active surface of the applicator to lessen trauma to the cornea and sclera. The applicator is then gently applied over the area of bare sclera, adjacent limbus, and affected cornea and held in place by the operator for short applications or sutured to the sclera for longer applications. Undue pressure must be avoided, as this increases trauma and reduces the distance from the applicator to the lens, which is the dose limiting normal tissue. If necessary, two treated fields can be overlapped if the area to be treated exceeds that of the active surface of the applicator—though this, inevitably, carries a risk of increased acute and chronic sequelae. After treatment, the patient wears an eye patch for 2 hours until the local anesthetic wears off. Some degree of conjunctivitis is common and, if mild, can be treated with antibiotic eye drops. If moderate to severe, a steroid-containing eye drop should be used. Long-term sequelae are unusual but more likely with a higher fraction size and a higher total dose. Scleral ulceration is the most common early complication in doses up to 52 Gy, with occasional development of symblepharon-fusion of the eyelid to the globe. Surgical trauma also plays a part in these sequelae. The most common late side

effect of ocular brachytherapy is the formation of cataracts.[232] The frequency ranges from 4.2% to 53.8% for ruthenium plaques and from 2% to 82% for iodine plaques. The incidence of radiation retinopathy and maculopathy is 10% to 63% and 13% to 52%, respectively, with a mean time of 25.6 months from treatment to maculopathy development. After treatment, tumor necrosis can cause retinal ischemia, leading to secondary neovascular glaucoma. The risk of this after iodine brachytherapy ranges from 4% to 45%, and the risk increases with time. Papillopathy secondary to optic nerve damage from ionizing radiation is rare with a documented range of 0% to 16%, and a median time to its occurrence is 22 months. Scleral necrosis is extremely rare (1%-2%). The main risk factors identified were location of the anterior tumor margin, tumor thickness >6 mm, and radiation dose >400 Gy to the external sclera.

FIGURE 22.28 Patient receiving a strontium ophthalmic application. (Courtesy Dr Steve Whitaker.)

FIGURE 22.29 Strontium ophthalmic applicator.

The Collaborative Ocular Melanoma Study (COMS) group conducted two randomized trials in North America, examining the use of ^{125}I for choroidal melanoma. The study examining the use of ^{125}I brachytherapy versus enucleation for tumors of 3- to 8-mm depth demonstrated no difference in survival and similar rates of toxicity[233,234] for the two techniques, thus supporting the use of ^{125}I. A SEER database analysis has shown similar survival outcomes for plaque brachytherapy compared to EBRT for choroidal melanoma.[235]

The use of palladium-103 and cesium-131 seeds has also been investigated with promising dosimetric results.[236,237] In fact, ^{103}Pd has efficacy similar to that of ^{125}I, but patients have an improved visual acuity following treatment with ^{103}Pd.[238] Modern dosimetry planning is being employed to investigate whether side effects may be lessened with optimal planning techniques.[237,239,240] Planning can be challenging, and rhuthenium-

106 plaques are MRI incompatible and create significant metal artifacts on conventional CT scans. Dual energy CT scans (DECT) may be used therefore to suppress these artifacts. A study by Detorakis et al[241] examined the possibility of creating fusion images from the preoperative MRI and postoperative (plaque in place) DECT scans, as a tool in confirming the anatomic placement of the plaque. They treated six patients with intraocular lesions, five with choroidal melanoma, and one with a retinal vasoproliferative lesion. The findings indicated that the elevation from the posterior plaque edge was slightly higher for anterior lesions, but overall the fusion images can be used to accurately confirm the plaque placement in relation to intraocular tumors in ophthalmic brachytherapy.

Strictly speaking, ^{90}Sr delivers HDR brachytherapy (a β emitter with a typical dose rate of 100 Gy/h compared to ^{125}I, a γ emitter with a dose rate of 0.5-1 Gy/h). Thus, ^{90}Sr delivers a single-fraction treatment dose over 2 to 3 hours, whereas ^{125}I delivers a treatment dose over 30 to 300 hours. The percentage depth dose in tissue falls from 100% at the surface to 4% at 4 mm, 1% at 6.5 mm, and 0.9% at 8 mm (corresponding to the anterior surface of the lens, equator, and posterior surface of the lens, respectively). Van Ginderdeuren et al[242] demonstrated a 90% 15-year-tumor control for sclera melanoma using an ^{90}Sr applicator with a proportion of the recurrences at the edges possibly due to the small applicator size, using doses of 450 to 800 Gy at the sclera. There was a 45% preservation of good vision, which was generally dependent on tumor position rather than on dose delivered. Ruthenium-106 eye plaques can also be used and may become the β emitter of choice, as ^{90}Sr eye plaques gradually decay beyond useful dose delivery. They deliver results similar to those of ^{90}Sr and have even been used with thermotherapy to deliver improved outcomes.[243,244]

Pterygium is a benign proliferation of the conjunctiva over the cornea, occurring most commonly in areas with high sun exposure. Surgery can be performed for irritative symptoms and effects on vision or cosmesis, but it carries a high recurrence rate. Locally applied ^{90}Sr has been used to decrease the rate of recurrence to as low as 0.5%,[245] using doses varying from 20 to 60 Gy in one to six fractions. The incidence of sclera complications is lower with fractionated treatment (4.5% vs 1%). However, alternative treatments such as topical chemotherapy and conjunctival autografting are replacing ophthalmic plaque brachytherapy.[246,247]

Brachytherapy should not be combined with topical chemotherapy due to the risk of scleral melting.

^{90}Sr has been used in the treatment of neovascular age- related macular degeneration (AMD), visual impairment caused by neovascularization beneath the retinal pigment of the retina. However, a phase 3 trial comparing patients with active AMD who were already on a vascular endothelial growth factor (VEGF) inhibitor to either vitrectomy followed by 24 Gy brachytherapy (and continuing prn anti-VEGF treatment) or to anti-VEGF treatment on an as-required basis alone showed that visual acuity and disease activity were actually better in the as-required anti-VEGF arm.[248]

Anus

Squamous cell carcinoma of the anus is a rare cancer usually treated with chemo-radiotherapy with good rates of sphincter preservation. The most common site of relapse is locally and, thus, methods of local dose escalation have been explored. EBRT, preferably with chemotherapy, is necessary to treat the tumor and wider nodal area and then the tumor boost can be delivered using brachytherapy.[249] Interstitial brachytherapy implants typically consist of a single plane catheter implant using a plastic perineal template curved around the anus. Catheter placement may be optimized by the use of advanced imaging techniques such as three-dimensional endoluminal ultrasound.[250,251] Papillon[252] described an LDR boost using ^{192}Ir to deliver 20 to 30 Gy in 221 patients two months after completing EBRT. Local control rates were comparable to surgical techniques, and 90% of the patients with no evidence of relapse remained colostomy-free. It has been suggested that when using a split course technique, if treatment time is extended over 80 days, a brachytherapy boost may provide better local control than EBRT.[253] PDR techniques have been described with rates of disease control and toxicity similar to those of LDR.[254-256]

Rectum

A retrospective analysis described 13 patients with colorectal cancer with pelvic or retroperitoneal recurrences, who underwent 18 minimally invasive CT-guided LDR brachytherapy implants—17 for pelvic recurrences and one

for a retrocaval nodal recurrence—with a median follow-up time of 17 months.[257] All patients were previously treated for either locally advanced (eight patients) or limited metastatic disease (five patients), four were treated for isolated pelvic recurrences, and 13 for oligo-progressive or oligorecurrent metastatic disease. Patients underwent dose calculation based on preimplantation CT imaging and contouring of gross tumor volume (GTV), followed by CT-guided percutaneous interstitial needle placement of either iodine-125 or palladium-103 permanent seed implants prescribed to the GTV. The median dose prescribed to the target volume was 80 Gy, with a median target volume of 5.0 cm^3 (range 0.6-25.5 cm^3). The 1-year estimated rates of overall survival and in-field control were 94.4% and 82.4%, respectively. All in-field failures occurred in targets above the median target volume of 5 mL. None of the patients experienced grade 2 or higher toxicities.

Esophagus

Esophageal brachytherapy is very useful in T1-T2 inoperable tumors, as palliation for dysphagia, as a boost prior to chemoradiotherapy, to achieve further downsizing post chemoradiotherapy, to control local relapse after primary chemoradiotherapy, and to avoid reobliteration of a stent. In general, HDR brachytherapy is the preferred modality. A phase 3 randomized trial of conventional stents versus stents loaded with ^{125}I seeds showed that median overall survival was increased in the irradiation stent arm compared to that in the conventional stent arm, but side effects were similar.[258]

Biliary Tract

Intraluminal biliary brachytherapy can be given with both curative and palliative intent. If the intention is curative, this is given after chemoradiotherapy to escalate the tumor dose.[259] The main indication in the palliative setting is to alleviate biliary obstruction. As with esophageal cancer, catheter-based HDR is the most used brachytherapy modality. When PDR is used in combination with EBRT, it is prescribed as a single dose of 20 or 40 Gy in two fractions. Stent insertion with insertion of I^{125} seeds for

malignant obstructive jaundice has been shown to increase the mean stent patency time (191 vs 88 days) and the median survival (241 vs 142 days).[260]

Central Nervous System

Although initial treatment for glioblastoma has improved over the past decade, most glioblastomas recur, with the majority of these were found within 2 cm of the original tumor cavity. Since most patients will have received 60 Gy to the tumor at the time of initial diagnosis, retreatment techniques may be limited; ^{125}I seeds can be used to deliver a conformal dose of reirradiation. At the time of recurrence, the surgeon will perform the maximal resection possible and implant ^{125}I seeds in the excision cavity at 0.5 to 1 cm intervals. This gives a highly localized boost, assuming the volume of disease residual is small since the dose falloff is rapid. The procedure appears to be well tolerated, and survival compares favorably to similar patients who did not receive brachytherapy.[238,261,262] The use of ^{125}I seeds at the time of initial radiotherapy has been investigated, but no difference was seen in randomized trials.[263,264] Thus, if a boost is required, this technique has generally been supplanted by stereotactic radiosurgery, which does not require a second invasive surgical procedure. Gliasite balloon brachytherapy (GBST) is a past technique no longer in use where a balloon is sited in the resection cavity and liquid ^{125}I is injected through a subcutaneous port for either primary or recurrent glioblastoma.[265] Results appear favorable.

^{125}I seed placement has also been described in patients with paraspinal tumors with a low rate of toxicity and good local control rates.[170,176] The procedure was well tolerated, and no myelitis was seen despite cumulative cord doses of up to 167 Gy.

Customized yttrium-90 dural plaques have been used intraoperatively in patients with spinal or paraspinal sarcomas to deliver a high localized dose to the dura while minimizing the dose delivered to the underlying spinal cord (Figure 22.30). Local control rates are promising, and there were no acute or late complications from brachytherapy.[266]

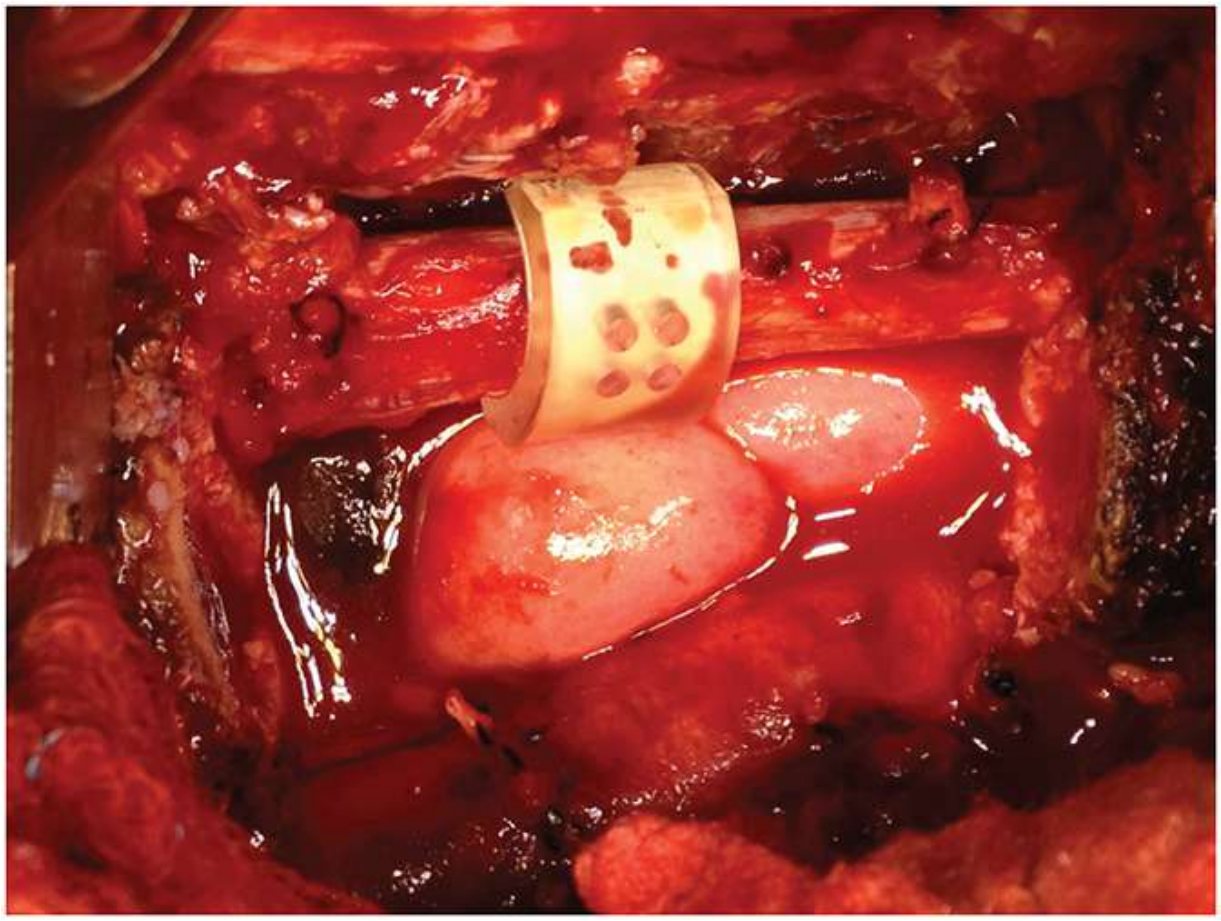

FIGURE 22.30 A dural plaque utilizes phosphorus-32 chemically bonded to a flexible polymeric film. The film is 0.5-mm thick and is backed by 4.5 mm of polycarbonate. Typical dose rates at time of treatment are in the 1.5- to 2.5-Gy/min range.

Cs-131 has gained a lot of interest in the brachytherapy treatment of newly diagnosed brain metastases as well as recurrent metastases of >3 cm.[267] It has a short half-life (9.6 days) and a higher dose rate (0.342 Gy/h) than I-125 (half-life 59.4 days and dose rate of 0.069 Gy/h). Cs-131 allows patients with brain metastases to start adjuvant systemic therapy as early as 1 month after resection. New studies are investigating Cs-131 in glioblastomas and anaplastic meningiomas. In addition, further studies will aim to evaluate the outcomes and effectiveness of Cs-131 brachytherapy with a special consideration for the implementation of the newer GammaTile technology. This newer technique has high activity Cs-131 seeds arranged geometrically in small Gelfoam tiles with unequal distance

to either surface for a more customizable coverage of brain tumor operative beds.

CONCLUSION

The dosimetry of LDR brachytherapy treatment planning has evolved from estimation of dose delivered to accurate image-guided computer-optimized determinations of dose. Exact knowledge of the position of OAR and that of the conformation of target volumes combined with dose optimization achievable with PDR computerized afterloading source delivery allows the brachytherapist to tailor dose delivery to highly specific ideals and deliver with great fidelity. This has allowed improved prediction of late toxicity and the possibility for dose escalation in areas with a high tumor burden.

Brachytherapy is particularly suited to subvolume dose escalation due to the ability to deliver a highly localized dose with rapid dose falloff in the surrounding tissue. This can allow increased dose to subvolumes within a CTV without a corresponding increase in dose to surrounding normal tissues. It is important with the advent of these new techniques that the accepted methods of practice are constantly reexamined to ensure that the patient receives the optimum treatment with the lowest risk of complications in the future.

Dosimetry remains critically important within modern brachytherapy practice. Knowledge of the established dosimetry systems is critical to prevent late complications resulting from suboptimal catheter placement, with reliance on computerized optimization to overcome this. Modern imaging techniques can provide three-dimensional information about a target volume and surrounding normal structures. It is important to generate methods of incorporating this new knowledge with existing practice.

LDR and PDR brachytherapy often require indwelling applicators or catheters that necessitate hospitalization for the duration of the brachytherapy course. Surgical procedures are often required to place the brachytherapy seeds and applicators. Special skill and training are required to perform brachytherapy, much of which is not generally a part of oncology training rotations. Fellowships in brachytherapy are valuable but rare.

LDR brachytherapy may result in radiation exposure to medical staff, although remote afterloaders and PDR techniques minimize this exposure. HDR techniques are more prevalent than PDR due in part to the ability to treat more patients each day with a single machine. However, PDR still appeals to many centers, especially those with a high throughput of interstitial brachytherapy cases. Such a highly localized treatment can result in little or no dose to adjacent areas at risk of tumor spread, risking marginal misses and tumor recurrence if case selection is not carefully considered.

Brachytherapy also requires a high initial capital outlay. The choice of brachytherapy as a radiotherapeutic modality must be made carefully with consideration of many factors; patient centered, tumor centered, and resource centered. As the "ultimate conformal therapy," the place of LDR and PDR brachytherapy (in addition to HDR) is firmly ensconced in the radiotherapy armamentarium and should not be overlooked.

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CHAPTER 23

The Physics and Dosimetry of High-Dose Rate Brachytherapy

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NATURE OF HIGH-DOSE RATE BRACHYTHERAPY

Conventional brachytherapy was developed soon after the discovery of radium. The limited amount of radium that could be packaged into the needles and tubes dictated the use of many sources to treat the target volume. Even with many sources, treatment durations ranged from 1 day to 1 week. When new radionuclides became available, their source strengths were matched to extant radium sources to draw upon clinical experience gained through the decades of ^{226}Ra treatments. This treatment format describes low-dose rate (LDR) brachytherapy as discussed in greater detail within Chapters 21.

A new approach to brachytherapy developed around 1962. Using intense, smaller sources (usually ^{60}Co in the early machines and often three in number) on the ends of cables, a treatment unit would move the source through the intended treatment volume in a relatively short time (<1 hour). This rapid treatment delivery was designated as high-dose rate (HDR) brachytherapy. The original treatment units most often oscillated the source along a catheter's treatment length, a method in common use until the modern generation of units developed in the early 1980s. Treatments took so little time that the therapy proceeded on an outpatient basis; however, the treatment was divided into several fractions and was delivered over days or weeks. Modern HDR brachytherapy units move a single source through the treatment volume in a stepwise manner, moving at intervals determined by the machine design and the operator, to positions where the source pauses (dwell positions) for durations (dwell times) determined through the treatment planning process.

Advantages and Disadvantages

Advantages

In comparison to LDR brachytherapy, HDR brachytherapy has the following advantages:

1. *Dose uniformity*. LDR sources positioned along the length of a needle or catheter have dose cold spots between the sources due to the abutting encapsulations, and seeds are often spaced with 1.0-cm spacings. For HDR brachytherapy, a single source is moved along the same length with 0.5-cm dwell spaced commonly used, and possibilities for dwell spacings that are smaller than the physical length of the radionuclide distribution. Also with less dose anisotropy than LDR seeds, HDR brachytherapy is less subject to dose cold spots.
2. *Optimization*. The stepping-source design permits high spatial and temporal control of the source through the target volume. In most treatments, determination of the dwell times comes from inverse planning, that is, specifying the doses desired at various locations and using an algorithm to calculate the dwell times that best fit the dose optimization constraints. The dwell times and positions can be finely tailored to the geometry and needs of a particular patient because of the wide range of dwell times available. This process constitutes *optimization*. Optimization is not commonly used with LDR brachytherapy (permanent or temporary) as the source strengths are usually all the same and are inserted (and removed) at the same time.
3. *Immobilization and stability*. The comparatively short duration of HDR treatments allows better stability of many intracavitary treatment applicators during the treatment and thus higher precision to deliver dose to the target. In addition to diminishing time for applicator motion, the applicator and the patient can both be immobilized with respect to the treatment table over the treatment duration. Such fixation is not possible with LDR brachytherapy because the patient would not tolerate the immobility for long periods. Interstitial cases may or may not exhibit better stability. Needles often tend to slide outward over time for prostate or gynecologic implants, even with a template sutured to the patient that affixes the needles. In such a patient, the needles require

positional adjustment before each fraction yet move very little during treatment delivery. Performing the same treatment using temporary LDR brachytherapy would be subject to needle movement during the slower delivery and require larger margins around the clinical target volume (CTV). On the other hand, LDR head and neck implants with buttons anchoring the catheters at both ends may have little movement from the time of insertion through removal. Such cases would not find improved stability with HDR brachytherapy.

4. *Dose reduction to normal tissue*. Again, the short duration of HDR intracavitary treatments often allows displacement of normal tissue structure to a greater extent than with LDR treatments. This holds true for gynecologic and oral intracavitary cases, but not for intraluminal applications, such as endo-esophageal or endobronchial treatments. Most interstitial cases cannot make use of this feature because the needles or catheters fix all the tissues in place. Exceptions are mostly in the head, where the tongue sometimes can be moved away from the treatment site.
5. *Outpatient treatment*. Most HDR patients receive treatment as an outpatient. Exceptions include patients with indwelling needles such as prostate or gynecologic implants delivered in multiple fractions. Implants using plastic catheters that enter the patient on one end and exit the patient on the other (ie, not with sharp needle tips poking into flesh) almost always leave the hospital between treatment fractions. All intracavitary treatments are performed on an outpatient basis unless there are medical conditions that keep the patient in the hospital between fractions. Outpatient treatments present many advantages over the inpatient treatments characteristic of LDR brachytherapy:
    - *Patient comfort*. Patients confined to a room during LDR treatments often feel closed in. Compounding the claustrophobic effects, radiation safety considerations for high-energy sources limit the time nursing staff can spend with the patient, leading the patient to feel like a pariah.
    - *Patient health*. Many LDR brachytherapy applications require the patients to stay in bed, disturbing urination and bowel movements

and increasing the probability of thrombosis or bedsores. Although pneumatic socks greatly reduce the likelihood of thrombosis, aching muscles from immobility still create discomfort. In many cases, patients who could not tolerate protracted LDR treatments will be able to receive treatment using HDR techniques.

- *Economics*. The cost of staying in the hospital greatly exceeds that of outpatient treatment. Counterbalancing the cost of hospitalization, the costs of the HDR remote afterloading equipment far exceed those for LDR applications. However, the costs for HDR equipment quickly become amortized with a modest patient load, whereas the hospitalization costs remain constant, or continually increasing, for each LDR brachytherapy patient.

6. *Less discomfort due to small size*. Because the encapsulated HDR source is approximately 1 mm in diameter, the gynecologic intrauterine tandem need only be <3 mm in diameter compared with 7 mm for a standard LDR tandem. Another way of looking at this comparison is to recognize that the diameter of the HDR tandem equals the smallest size dilator used to stretch the cervical os to accept the LDR tandem. Much of the pain and discomfort from a cervical cancer treatment arises from the dilation. Eliminating that step eliminates much of the pain. Some facilities use only light sedation for the HDR tandem insertion rather than a general anesthetic as is common with LDR procedures.
7. *Elimination of delays*. When applications fail to follow a plan or when plans have to change because of a finding in the operating room during the procedure, HDR treatments can still proceed following localization with little, if any, delay. Permanent LDR treatments likely would require ordering new sources to match the new situation and a delay in treatment to await delivery. The HDR model eliminates extra charges accruing from multiple-source orders.
8. *Intraoperative procedures*. HDR brachytherapy allows treatment intraoperatively, with suitable shielding in the operating room. With the short duration for dose delivery, a surgeon can add placement of the applicator and treatment to the surgery with little additional time.

9. *Radiation safety*. HDR brachytherapy eliminates radiation exposure to personnel.

Disadvantages

Unfortunately, HDR brachytherapy has the following disadvantages in comparison to LDR brachytherapy:

1. *Radiobiology*. Compared with LDR brachytherapy, HDR treatments have worse therapeutic ratios, that is the amount of damage to tumor cells compared with damage to normal tissue cells for the same dose. Damage to both cell types per unit dose increases with dose rate, but the increase is greater for normal cells. Just as with external beam radiotherapy, which also is HDR delivery, fractionated treatments mitigate this effect. Although LDR therapy usually entails a single session or two, most curative HDR regimens use three or more fractions. The next section discusses the radiobiology in greater detail.
2. *Error hazard*. The increased complexity of HDR procedures and the compressed time frame of delivery increase the probability of treatment errors compared with LDR therapy.
3. *Potential for very high radiation doses to patients and unit operators following failure of the source to retract*. A new HDR source can deliver almost 10 Gy/min at 1 cm in the patient. If the source stops moving or separates from the drive cable, serious injury can occur in a short time.
4. *Resources*. HDR treatments demand more resources than LDR treatments:
    - *Personnel*. Because many HDR treatments proceed quickly from applicator placement to treatment delivery, all of the persons involved with the treatment must be available at the same time or in relatively quick succession. That means that the facility must have sufficient staffing to release these persons from other duties on demand for HDR brachytherapy cases.
    - *Economics*. HDR afterloading equipment comes with a large initial investment of about $1M (at the time of writing), not including the significant costs of shielding the treatment room.

High-Dose Rare Brachytherapy Fractionation

Due to the differing radiobiological characteristics between HDR and LDR treatments, careful consideration is required when planning the time course of the therapy regimen. When starting an HDR brachytherapy program, key questions often arise regarding the number of fractions and the appropriate dose per fraction. The larger the number of fractions, the better the therapeutic effect, measured as the ratio of the damage to tumor cells to the damage to normal tissue cells. This ratio improves with each additional fraction, but the amount by which the ratio increases will decrease with each added fraction. As an example, going from four to five fractions can improve the therapeutic ratio by 4.0%. Adding a sixth fraction improves the therapeutic ratio but only by another 3.5%. Each additional fraction carries with it costs in departmental resources (particularly the time of those persons involved) and inconvenience (and possibly discomfort) to the patient. Thus, selecting the number of fractions becomes a compromise. Most curative regimens use five or six fractions if applicator insertion procedures are involved, and 8 to 12 fractions if the applicator can be left in place and the patient simply treated. Small-volume applications, such as vaginal cuff or most endobronchial treatments, may require only three or four fractions. After establishing the number of fractions, determining the dose per fraction comes next. One method that uses the LDR experience sets the BED equal for the two modalities and then solves for the dose per fraction. However, the LDR situation is more complicated because repair takes place during the continual irradiation, reducing its effectiveness.

High-Dose Rate Devices

Remote Afterloaders

A remote afterloader (RAL) is a computer-driven system that transports the radioactive source from a shielded safe into the needle or applicator placed within the patient. On termination or interruption of the treatment, the source is driven back to its safe. A stepping-source RAL is a particular design of a treatment unit that consists of a source delivery cable that moves the source through applicators placed in the treated volume. The treatment unit can treat implants consisting of many needles or catheters in the patient. Multiple catheters are often required to cover the target with

uniform radiation doses. Each catheter or part of an applicator is connected to the RAL through a channel. The computer instructs the motor to drive the cable so the source moves from the safe through a given channel to the programmed dwell position for a specific dwell time. In any applicator, there may be many dwell positions. After treating all the positions in a given catheter (channel), the source is retracted to its safe and then driven to the next channel. There can be several dwell positions per centimeter in each channel, and the dwell time can vary from 0 to almost 1,000 seconds in 0.1-second increments, thereby giving a high level of flexibility of dose delivery. All currently available HDR RALs use the stepping-source design. Five models of HDR RALs are common. Three are marketed in the United States: Flexitron (Elekta Company, GA) and GammaMed and VariSource (both from Varian Medical Systems, Palo Alto, CA). The microSelectron (Elekta Company, GA) is no longer sold but is one of the most common units in clinical use. In Europe, the BEBIG MultiSource (Eckert & Ziegler BEBIG, Seneffe, Belgium) is also available. Figure 23.1 shows two of these units. Even though they may vary in details, all available HDR RALs consist of the same general components: shielded housing, radioactive source, source-drive mechanism (cable, reel stepper motor), channel indexer, transfer tube (all shown in Figure 23.2), and treatment control station and treatment control panel (not shown).

Flexitron
A

B

FIGURE 23.1 A. Elekta Flexitron. (Courtesy of Elekta.) B. The Varian VariSource. (Courtesy of Varian, Palo Alto, CA.)

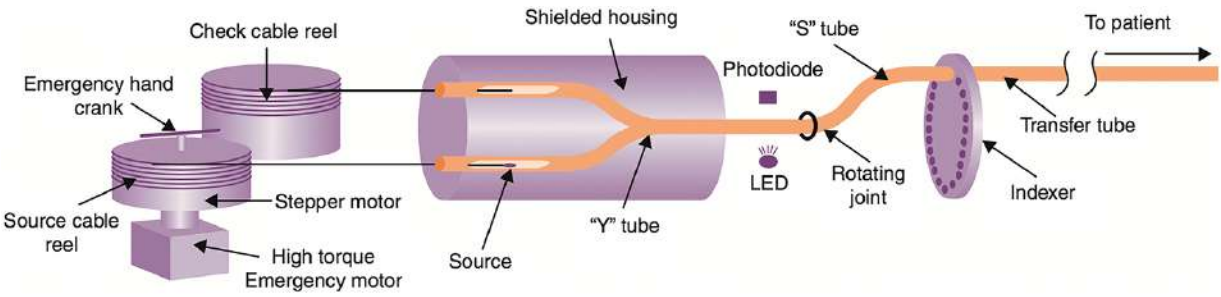


FIGURE 23.2 Components of a high-dose rate brachytherapy remote afterloader. (Image by Adam Uselmann after a draft by Liyong Lin.)

Sources

Whereas delivering HDR brachytherapy requires an intense source, passing the source through needles placed through a tumor requires one of a small size. The radioactive source in an HDR RAL is usually 3 to 10 mm in length and <1 mm in diameter, fixed at the end of a flexible steel delivery cable. The microSelectron source is placed in a stainless steel capsule and welded to the cable, whereas the Varian source is placed in a hole drilled into a nitinol cable and closed by welding. Figure 23.3 shows diagrams of the sources. While ^{192}Ir is most commonly used for HDR RALs, ^{60}Co is increasing in popularity outside the United States. ^{192}Ir emits many photon energies, mostly between 110 and 704 keV, with an effective energy of about 380 keV. A new HDR ^{192}Ir source has an activity near 0.4 TBq (12 Ci, 48 mGy m^2 h^{-1}). Because ^{192}Ir has a 74-day half-life, the source should be replaced at least 4 times annually to keep treatments in the HDR radiobiologic regimen (see later discussion). The potential advantage of using ^{60}Co is the 5.27-year half-life (26 times longer), extending the time between source changes to approximately 5 years. ^{60}Co γ-ray emissions are 1,173 and 1,332 keV[1] and require considerably more shielding than for devices using ^{192}Ir. A medical physicist calibrates HDR sources after each installation using a reentrant, well-type ionization chamber (as discussed later). The resulting source calibration is verified against the manufacturer' source- calibration certificate.

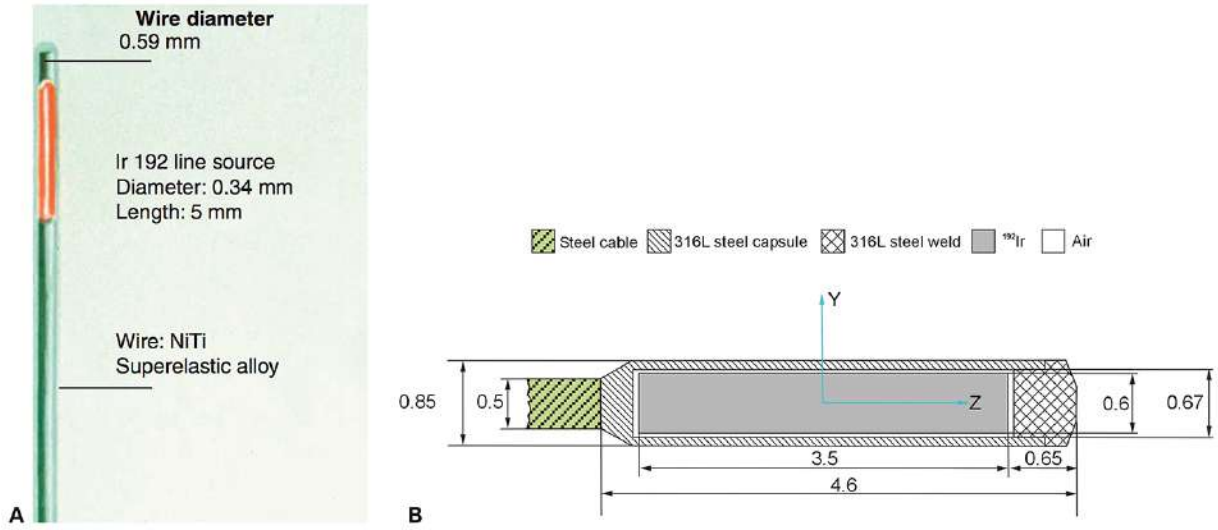


FIGURE 23.3 Diagrams of two HDR 192Ir brachytherapy sources: for A (left) VariSource and B (right) Flexisource. All numerical dimensions are millimeters. (A. Courtesy of Varian, Palo Alto, CA. B. Courtesy of Elekta)

Applicators

Each vendor markets an array of applicators for different treatment sites with vendor-specific designs that can only be used with their system. Before an applicator is used clinically, tests should be performed to verify the functionality. An applicator should also be imaged with dummy sources to verify agreement with the vendor specifications. The length of each applicator, location of the dwell positions with respect to the applicator, and physical integrity should all be a part of a routine quality assurance (QA) program to ensure the safe and precise delivery of a radiation treatment plan. Figure 23.4 shows a comparison between LDR ^{137}Cs and HDR ^{192}Ir tandem and ovoid applicators. The newer applicators are magnetic resonance imaging (MRI) safe and can accommodate the thinner HDR ^{192}Ir source.

A

B

FIGURE 23.4 A comparison of tandem and ovoid applicators for low-dose rate (LDR) ^{137}Cs from the 1990s (A) and high-dose rate (HDR) ^{192}Ir from the 2020s (B). The differing tandems permit anatomic fitting for different uterine tilting, even for retroverted uteri. Both types allow selection of ovoid diameters. The modern HDR applicators are plastic and

compatible with both computed tomography and magnetic resonance imaging. Metal HDR applicators may be smaller in diameter with a higher risk of uterine perforation.

OPERATION

Personnel Roles

The American Association of Physicists in Medicine (AAPM) Task Group (TG)-59 Report discusses the roles of treatment team members for HDR brachytherapy.[2] For the most part, the personnel roles follow standard procedures for any brachytherapy, with the physician inserting the treatment appliance and prescribing the treatment, the nurse monitoring the patient's condition and welfare, therapists or radiographers performing the imaging for localization, a dosimetrist or physicist performing optimization and dose calculation, a physicist checking the plan for correctness and assuring the correct calibration of the source, and the physician and physicist evaluating the plan. Who performs some of the functional roles discussed in what follows varies by institution but needs clarification, so all persons involved understand the distribution of responsibilities.

Daily Quality Assurance

There are several required tests of the treatment unit at the beginning of the treatment day. The duty to perform these tests often falls to a trained radiation therapist or dosimetrist. The medical physicist reviews the results of the tests before treatments commence.

Treatment Planning Calculation

The TG-59 Report discusses options for entering patient data into the dose calculation computer and generating the treatment parameters (dwell positions and dwell times).[2] One model presented had a dosimetrist running the program and a physicist monitoring the input to correct any errors as they occur. Studies have shown that such supervision provides little protection against errors.[3] The other model presented has the physicist generate the treatment plan.

Quality Assurance on the Treatment Plan

Regardless of who generates the treatment plan, a medical physicist should review the plan for appropriateness and correctness. The reviewing medical physicist should not be the same person who generated the plan, so in facilities with only one medical physicist, a dosimetrist should perform HDR brachytherapy treatment planning.

Delivery of the Treatment

Several factors enter considerations of who should staff the control panel during the treatment. In a handful of states, regulations dictate that only therapists may deliver treatments and control treatment units. The regulations in the other states and from the U.S. Nuclear Regulatory Commission (NRC) are silent on this issue. At the time of writing, regulations uniformly require the attendance of a radiation oncologist and a medical physicist at the treatment (or within unamplified voice communication of the unit operator). As a result, many facilities have the medical physicist remain in the area of the control console during treatments. One important reason for this is that the radiation oncologist and medical physicist must be ready and willing to enter the room and take appropriate actions in case of any treatment delivery error. This would include reacting to the source getting stuck outside its shielded housing in the RAL (eg, potentially in an applicator within the patient).

Normal Procedures

When the afterloader receives a command from the treatment control panel to initiate a treatment, the source cable advances from the shielded safe through a Y-shaped tube (to accommodate either the dummy source or radioactive source), then an S-shaped tube guiding either source from the safe to the first channel in the RAL indexer, and then along a path constrained by transfer tubes to the first treated dwell position in the applicator (see Figure 23.2). The source dwells at that position for a predetermined duration. After completing that dwell, it goes to subsequent dwell positions. Some RAL units step as the source drives out (Flexitron, microSelectron, and GammaMed), stopping first at the dwell position most proximal to the afterloader, whereas in the other units (ie, VariSource), the source travels first to the most distal dwell (toward the applicator distal tip)

and then steps as the source returns toward the safe. Stepping on the outward drive obviates any concern about the effect of slack in the drive mechanism affecting the accuracy of the source position. The units that step on the way back toward the unit include correction for cable slack for the source location. Regardless of the stepping direction, upon completing treatment of the first channel, the source is retracted into the safe and redirected to travel to the second channel. The process is repeated for all the subsequent used channels. The programmed movement of the source is verified by means of an optical encoder or other device that compares the angular rotation of a stepper motor or cable length ejected or retracted with the number of pulses sent to the drive motor. These systems are capable of detecting a catheter obstruction or constriction as increased friction in the cable movement. Under certain fault conditions, such as the stepper motor failing to retract the source, a high-torque direct current emergency motor will retract the source.

Confirmation of the source exit from and return to the safe is carried out by an opto pair, consisting of a light-sensitive detector and an infrared light source to detect the cable when its tip obstructs the light path. All the currently marketed afterloaders are also equipped with check cables. The check cable is an exact duplicate of the radioactive source along with its cable, except that it is not radioactive. Before ejection of the radioactive source, the check cable is first ejected to check the integrity of the delivery path. After an uneventful evaluation by the check cable, the radioactive source is then ejected for treatment.

Emergency Procedures

Because HDR RALs are complicated devices containing very high activity radioactive sources, if the unit malfunctions, serious accidents can happen very quickly. This demands many safety features and operational interlocks to prevent erroneous dose to the patient or clinical staff. Each of the following safety features are equally important; however, some, like the emergency switch, have their own potential failure points, requiring additional fail safes.

Door Interlock

Interlock switches prevent initiation of a treatment with the treatment room door open. In the fast-paced clinical environment, ensuring that the door is shut before having radiation flood the room is important. In addition, if the door accidentally is opened during the treatment, this interlock ensures an immediate retraction of the radiation source to its safe in the RAL. The treatment can be resumed at the same point where it was interrupted by closing the door and pressing the start or the resume button at the control panel. This safety feature protects the medical personnel from radiation exposure in the event someone enters the treatment room without the knowledge of the operator.

Emergency Switches

Numerous emergency-off switches are located at places convenient for the operator(s) and are easily accessible in case a situation arises. One is located on the control panel of the HDR unit for quick retraction by the clinicians local to the HDR unit. If this switch does not retract the source and the physicist must enter the room, Vendors install two or more switches in the lower radiation areas of the treatment room. In addition, another one is located on the top of the RAL treatment unit. In the event a treatment is initiated with someone other than the patient in the treatment room, that person can stop the treatment and retract the source by pressing any of the emergency-off switches.

Emergency Crank

In the event of the failure of a source to retract normally and if none of the emergency switches work, all HDR RAL units have emergency cranks to retract the source cable. The operator must enter the room to use the crank.

Emergency Service Instruments

If the radioactive source fails to retract after termination or interruption, pushing the emergency switch, or cranking the stepper motor manually, the immediate priority is to remove the source from the patient. Because the source could be trapped in the applicator that is in contact (or within) the patient, it can cause severe injury in a very short time. However, radiation dose falloff is governed by the inverse square law; therefore, working at a

greater distance, it is unlikely that the operator will receive a dose exceeding the annual regulatory limit, let alone one that would cause health problems. Once the trapped source is located and moved >1 m from the patient and staff, actions can be taken to remove the patient from the room.

The safest approach to an unretractable source is to remove the applicator from the patient quickly and place the applicator containing the source in a lead-shielded storage container (ie, a lead pig). If it is clear that the source cable (ie, source) is caught in the transfer tube and not in the applicator, the applicator may be disconnected from the transfer tube and the patient removed from the treatment room. In some cases, this will be faster than extracting the applicator. The reason to avoid disconnecting the applicator from the transfer tube is that a source may stay in the applicator if the source encapsulation is compromised or separates from the cable. In that case, removing the applicator attached to the transfer tube contains the radioactivity, whereas disconnecting the two allows a potentially broken source to fall from the applicator into body cavities or crevices or roll onto the floor.

A situation might arise when the source needs to be detached manually from the treatment unit. Such a rare situation might occur if the unit with an unretractable source fell on a person and could not be moved by hand (perhaps by something else falling on the unit). The source could be close to the person, but not inside. In this situation, the source cable should be cut from the unit and the source placed in the shielded container that is always present in the room. In cutting the source cable, it must be clear that the cut is *not* through the source capsule. For units with the capsule welded on the cable, the cut must be through the braided cable as opposed to the smooth steel capsule. For sources imbedded within the cable, several centimeters of cable must be seen to ensure that the cut does not compromise the source. Thus, emergency tools that must be present in the treatment room and always readily accessible include a wire cutter, a pair of forceps, and a shielded storage container. The source should *never* be cut from the cable while the source is still in an applicator within the patient!

FACILITY DESIGN

Typically, an HDR ^{192}Ir source will have a maximum air kerma strength of approximately 48 mGy/m^2/h. According to the rules and regulations of the NRC, the annual limit for radiation exposure to the public is 1 mSv and the annual occupational limit is 5 mSv. The occupational exposure limit is 50 mSv/y, but following the principle of maintaining exposures as low as is reasonably achievable, the NRC usually holds licensees to limit exposure to one-tenth of the actual limit. In addition to the annual limit, NRC regulations require that in an unrestricted area, the dose equivalent rate should not be more than 0.02 mSv in any hour. Thus, the RAL unit needs to be housed in a room that has walls and a door of the proper thicknesses and materials to shield the surrounding areas from the high levels of radiation exiting the room. Since the radiation dose rate diminishes following the inverse square, larger rooms will need less shielding. In general, an adequately sized HDR ^{192}Ir room will require concrete walls of about 50 cm, 5 cm of lead, or an equivalent thickness dependent on a combination of materials. The tenth-value layer thicknesses for ^{192}Ir are 15 cm for concrete and 1.6 cm for lead. For details on the procedures for calculating barrier thicknesses for a particular facility, see a health physics text such as that by Cember and Johnson[4] or McGinley[5] or Report 151 from the National Council on Radiation Protection and Measurements.[6]

Imaging plays an important part in most brachytherapy, so consideration of required imaging modalities should enter into the room design. Having fluoroscopy and radiography in the treatment room can facilitate checking for applicator movement if moving the patient is required for computed tomography (CT) or MRI. It would be best to have the necessary imaging modalities in the procedure room. Having space and access for anesthesia in the room facilitates HDR brachytherapy for interstitial procedures, such as prostate and gynecologic procedures.

In a radiotherapy clinic, the HDR room may share a wall with a LINAC or other radiation treatment room. The complication arises when consideration of the nearby areas, since the annual radiation limits are known and strictly enforced, these situations require additional shielding. This circumstance complicates the shielding calculations, but properly dealing with this nuance is crucial to ensure proper radiation safety.

All HDR brachytherapy rooms must have video and audio communication for monitoring the patient. Radiation detectors are also

required for monitoring radiation levels in the room and indicating when the source is out of its safe.

QUALITY ASSURANCE OF A REMOTE AFTERLOADING UNIT

Several of the disadvantages of HDR brachytherapy concern the probability of failure, either human or mechanical. Both aspects require effective quality management. Reports from the AAPM discuss this topic.[2,7-13] Williamson et al summarized much of the important material.[14] For a comprehensive discussion, the reader is directed to Thomadsen.[15] Although many of these references are not recent, the QA tasks appropriate for these RAL units have not changed very much.[16] Many of these QA tasks are required by the local regulatory agency.

As for any piece of radiotherapy equipment, QA begins with acceptance testing and commissioning. Periodic QA includes tests performed with each new source (approximately quarterly for most centers) and at the beginning of each treatment day. Of all of these, the daily QA checks form the basic set of essential tests.

Daily Quality Assurance Checks

Although the following list of safety checks seems long, their evaluation need not consume a great deal of time (typically less than 15 minutes). Most of these items can be tested in numerous manners, but only one method is described here and individual units may differ in the exact methods. The procedure in the list often assumes the successful completion of all preceding items. Failure of any item requires evaluation by the physicist for the appropriateness to continue with patient treatments. Daily QA checks demonstrate that the system is operating safely, correctly, and as expected.

Safety Checks

The following items should be considered for safety checks:

Room monitoring. See that the television and intercom systems function.

Handheld radiation survey meter. The survey meter is to be carried into the treatment room any time after a source run. To test its functionality, place

the survey meter in a geometric reproducible manner such as in contact with the RAL unit or elsewhere for comparison to an expected reading.

Catheter attachment lock. Attach a transfer tube to one of the channels of the unit, but do not lock the transfer tube in place (often accomplished by the locking ring). Program the unit to send the source to a dwell position that would be in an applicator where one attached and initiate a source run. A program time for a single dwell of about 20 seconds would allow execution of the tests to follow. The unit should detect that the transfer tube has not been locked in place and prevent the source run. Were a treatment to take place in this condition, the source cable could push the transfer tube out of the unit and never enter the applicator.

Applicator attachment. Keeping the same program, lock the transfer tube in place but still do not attach an applicator to the transfer tube. Again, attempt to initiate a source run. The check cable run should detect the absence of an applicator and prevent sending out the source. Failure of the unit to detect this situation could lead to the source indicating that it treated a catheter when, in reality, the catheter was never attached. This test also checks that the unit will not send out a source if the pathway is blocked, because, for most transfer tubes, the applicators push aside a blockage of the tube when they lock in place.

Door interlock. Lock an applicator into the transfer tube. For future tests, it is convenient to use a needle or catheter in a well-type ionization chamber. Keeping the same program as in the previous tests and with the door to the room open, try to initiate a run. The unit should refuse to initiate the treatment and indicate that the door is open.

Source-out indicators. Close the door, and initiate the source run. Observe that the indication lamps operate on the control console. Most treatment rooms have three beam-on indicator lamps: one connected to a treatment unit microswitch that triggers when the source leaves its shielded housing, one that lights when the signal on the room radiation detector exceeds its threshold, and one from the Geiger counter in the RAL unit.

Door interrupt. With the source out, open the vault door and observe the RAL unit to retract the source. The retraction should take no longer than 6 seconds to return the source to its shielded location.

Emergency stop. Close the door and reinitiate the exposure. Once the source reaches the dwell position, press the emergency-off button. The unit must immediately retract the source and likely require a reset.

Treatment interrupt. Reinitiate the exposure, and once the source goes back to the dwell position, press the treatment interrupt button. Again, the unit must immediately retract the source.

Timer termination. Reinitiate the exposure and let it continue until the elapsed duration equals the time set on the timer. At that time, the unit stops the exposure and retracts the source.

Dosimetry Checks

The thrust of the dosimetry checks focuses on the delivery of the correct dose to the proper location.

Source Positioning Accuracy

Proper treatment requires that the source occupy the position along the catheter corresponding to that used in the treatment plan. The uncertainty of the determination of the dwell positions on the treatment plan is discussed elsewhere in this chapter. Here, the issue becomes duplicating the dwell locations on the treatment plan during execution. A usual criterion for coincidence with the planned treatment dwells is 2 mm, although the HDR units are able to place the source in a given location within 1 mm. Precision <0.5 mm begins to be less reproducible. To direct the source to correct locations corresponding to each dwell position, the source controller requires the distance along the catheter corresponding to the first dwell position. The distance may refer to the length from some part of the unit (such as the front face, the point of catheter insertion, or a microswitch that tells the unit when the source enters the catheter), or it may be from some fictitious point (similar in concept to the virtual source distance for electron beams). Verifying that the unit can place the center of the source at a specified distance becomes an important part of the daily QA practice.

The most expeditious method uses the ruler provided with the unit. Such a ruler provides a channel for the source to follow alongside a scale marked in the distance. Using any ruler requires a high-definition video monitoring system that can clearly distinguish the source capsule and resolve the ruler

markers. Lighting this ruler becomes an important variable. For one vendor's unit, a televised check of the source positions on an integrated ruler forms a routine part of any treatment. For another vendor, the ruler is an external part of the QA equipment and requires a separate video monitoring system, such as that used to monitor the patient. To perform the check, attach the ruler and program the source to the desired distance. Watch on the video monitor as the source moves into position. The source tip should be farther than the programmed distance. From the distance of the tip, subtract the known distance from the tip to the source center as shown in Figure 23.5. This check is performed with the source cable; for some units, the check cable does not go to the same distance as the source cable and would give an incorrect result.

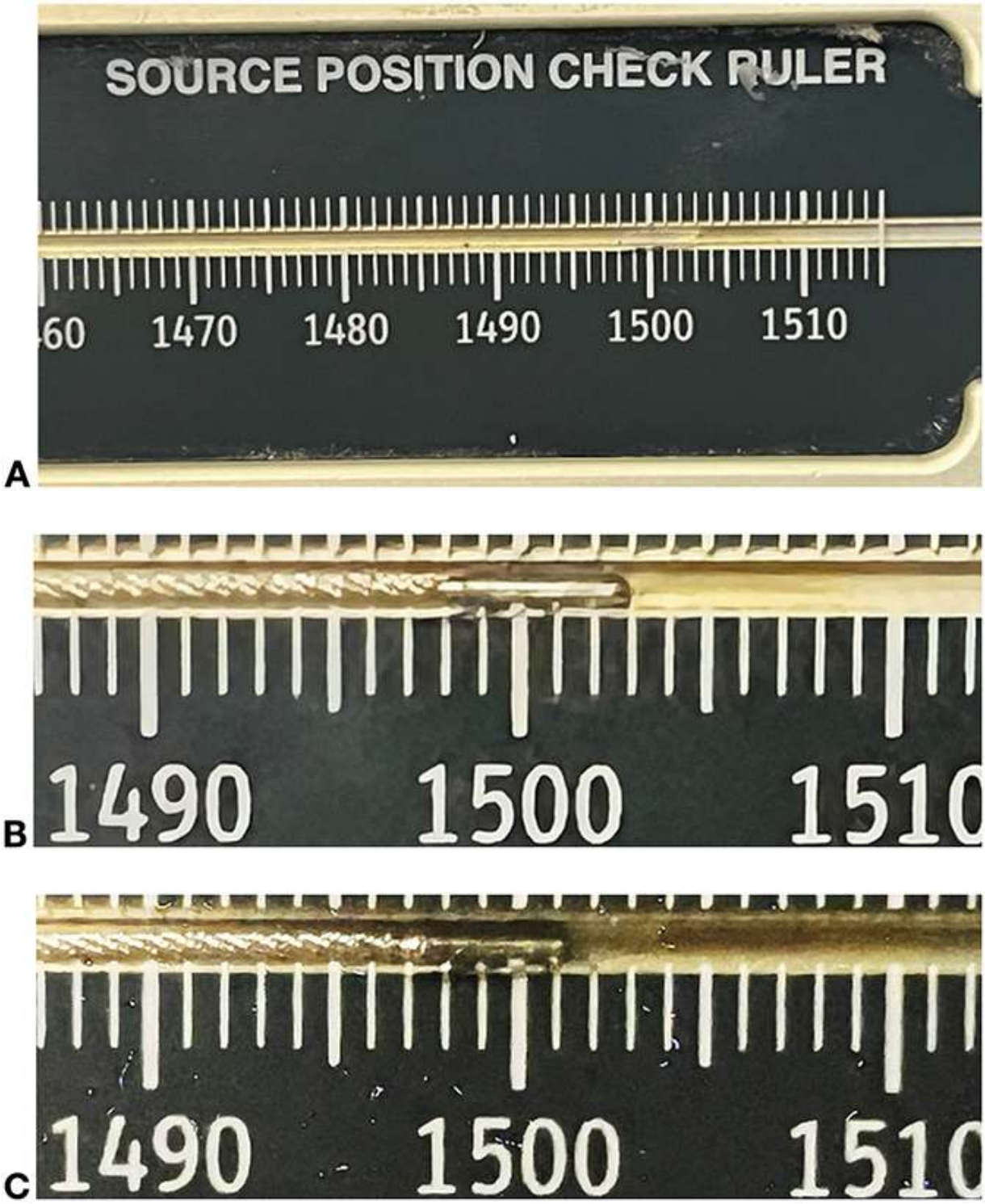


FIGURE 23.5 As part of a high-dose rate (HDR) brachytherapy quality management program, quality assurance (QA) positioning checks of the check source and HDR ^{192}Ir source can use the manufacturer source position check ruler. A. The source position check ruler showing darkening (accumulation of microscopic debris) ahead of the most distal position occupied by capsules of either the check source or HDR ^{192}Ir source. Friction has

cleaned elsewhere. B. Extension <1 mm of the check source beyond the HDR ^{192}Ir source as a safety measure to validate patency as required for some surface brachytherapy applicators is shown with the source tip at 1502.95 mm. Image resolution is 0.05 mm under these circumstances. Viewing perspective and divergence should be considered. C. The HDR ^{192}Ir source center is positioned at 1499.3 mm (0.7 mm proximal to the reference position) with a purposeful curvature of the source transfer tube imposed to validate that the source center remains within the 1 mm tolerance permitted by U.S. regulations. For QA purposes, localization uncertainties are minimized when identifying the distal edge of the source encapsulation instead of estimating the invisible center of the radionuclide distribution or considering variability when visualizing the cable:capsule weld. The picture also shows white electron artifacts in the camera speckle the image, resulting from proximity to the radioactive source.

A simple and more precise method of verifying source positioning follows the technique determined by DeWerd et a.[17] This method uses a well-type ionization with a special insert that includes lead attenuators and plastic transmission discs. The lead attenuators reduce the signal from the source to approximately one-third of its unshielded value, whereas the plastic discs have little effect. As the source passes through the needle centered in this insert, the measured signal peaks when the source is centered on the plastic discs, and the greatest gradient occurs when half the source is shielded and half is on the plastic. At these points, the signal depends critically on the precise position of the source, with the signal changing approximately 3.5%/mm. The signal at the plateau changes a little over 2 mm. Dividing the current signal at the high-gradient point by that at the plateau removes any variations in the reading due to source decay, timer miscalibration, or atmospheric density. Thus, the ratio of signals gives a sensitive indication of whether the unit accurately places the source to the correct location. Making measurements at two high-gradient points and the peak assesses not only the correct placement of the source at one point but also the correct interval between. The use of this method requires measurement of the signal profile as a function of distance along the axis of the well chamber after initial verification of the source position using one of the other methods. Once put in place, this approach takes <1 minute. If the insert is left in the well chamber, the needle can be used for the safety checks, and this test can follow the safety checks without requiring reentry into the room. Source position can also be checked using radiochromic film, marking the intended position of the source in a catheter using the

radiographic markers and then making an autoradiograph with the source. However, using film takes more time and carries a larger uncertainty than either of the two aforementioned methods.

Dose Consistency

Correct dose delivery hinges on the proper operation of the timer controlling the exposure. The proper operation does not depend on the timer accurately keeping true clock time. The only important features of the timer are that it operates linearly and that its operation remains consistent over time. The daily QA generally needs only check 2 times to evaluate timer consistency and linearity, compared with the tests performed during the source exchange. The uncertainty in the measurement should be on the order of a few tenths of a second in order to check the shorter times.

One technique for checking the timer observes the reading produced in a radiation detector as a function of the timer settings. To evaluate the timer, the measurement system must respond linearly to radiation dose and the setup provide a stable and reproducible geometry. A well chamber, such as that used for calibration, performs this function well. Such measurements in a well chamber include the effects of source decay and the source transit time. Source decay should not deviate from that expected based on half-life, but should still be checked because there have been sources with radio contaminants that produced anomalous decay. Because the reading varies directly with the set exposure time, these readings can form a timer check. The chamber reading needs a baseline, for example, a reading taken during source calibration. The expected reading can be tabulated as a function of days by correcting the initial reading by the decay factor, $e^{-0.693t/73.83}$ days, where t is the time in days since the initial reading for ^{192}Ir. The reading should remain within 1% of the projected reading, values that also could be in the decay table. Deviations from the projected values indicate changes in the timer operation (linearity or consistency), changes in the unit's transit time, or anomalous source decay. Further tests would be required to sort out the actual problem.

Source Strength Value

The value for the source strength at any time should be the same within 0.5% in the treatment delivery computer, treatment planning computer, independent dose calculation software, and decay table. The dates and times must also be correct to correctly account for source decay, and all systems should use the same value for the radionuclide half-life. The date format, American or European or ISO 8601, must be the same as that expected by the computer.

Initial Checks

Each source change requires a number of procedures in addition to the daily checks.

Safety Checks

The initial safety checks include the following:

Treatment unit backup batteries. In case of loss of power to the treatment unit, the RAL unit has backup batteries to retract the source and save the record of the treatment up to the time of retraction. Checking the batteries entails initiating a source run, pulling the circuit breaker for power to the unit, and verifying that the source retracts; the history is then saved, and the unit resumes the program where it left off when restarted after restoring the power.

In-room radiation monitor backup batteries. The in-room radiation monitor also has backup batteries allowing it to continue functioning in case of a power loss. Continued operation at such times becomes extremely important in case the source fails to retract. Verifying operation of these batteries simply requires unplugging the unit from the wall socket and performing the standard check.

Dosimetry Checks

The following are the initial dosimetry checks:

Calibration. The accepted method for calibration of an HDR source uses a well-type ionization chamber that has been calibrated in terms of HDR source strength per unit current. The calibration factor for the same

chamber will differ for LDR ^{192}Ir and HDR ^{192}Ir sources because of differences in source construction. The uncertainty (k = 1) in source strength calibrations using such chambers is about 2%. Brachytherapy source strength is in terms of air kerma strength, S_K, with units of μ Gy m^2 h^{-1}, often called U for convenience.[18] HDR source strengths range from 20,000 to 50,000 U. It is not recommended to use apparent activity anytime for brachytherapy sources; contained activity is used only for regulatory purposes, such as licensing and transportation.

Timer linearity. The verification for timer linearity uses several readings, R_i, for various increasing times, t_i, taken in the well chamber. The free-running reading rate, $R.$, can be defined as $R. = (R_{i+1} - R_i)/(t_{i+1} - t_i)$ and contains no effect from the source transit,[19] which cancels during the subtractions. Taking approximately five readings covering the range of dwell times common in treatments gives four values for the free-running reading rate using adjacent times. These values should differ by <0.5%.

The transit time from the unit to the dwell position is typically <1 second, but is hard to measure and is not important directly. What is important is that the transit time remains constant. An effective transit time can be defined as the time it would take to deliver the extra reading in the chamber because of the irradiation during the time the source moves into and then leaves the measurement dwell position, *if* the extra reading were delivered at the free-running reading rate.

Computer data entry. The new source strength must be entered into the treatment planning computer and the treatment unit computer. Special attention needs to be paid to selecting the units for the source strength, particularly if the system automatically defaults to given units.

Checks Preceding Treatment

Other than the check of the treatment plan just before treatment, connecting the patient also requires care and verification. For most gynecologic applicators, the three parts of a tandem and ovoid set, or the two parts for a tandem and ring, have mechanically keyed connectors that only allow for the correct transfer tubes to attach, and the transfer tubes also can only connect to the correct holes in the indexer. However, for implants with

needles or catheters, no interlocking prevents mismatches between channels and catheter or needle tracks. For large implants on older units, the treatments often require first connecting the number of catheters equal to the number of channels and delivering the part of treatment that uses those channels. Those channels are then disconnected, and the next set of catheters is then connected to the indexers starting again with channel number 1. One of the most likely errors would be connecting a channel during the second set to a catheter from the first or vice versa. Newer treatment units often have enough channels to accommodate implants needing many channels.

Also for interstitial implants, between fractions the catheters often move from the position they occupied during the imaging used for treatment planning. Immediately before treatment, the catheters must be returned to their original position, for example, by snugging the buttons on one side to the skin.

During the treatment, the operator needs to watch for movement by the patient that could affect the treatment and ensure that the source moves through its program.

Checks after Treatment

At the end of a treatment, the operator verifies complete source retraction by taking the following steps:

- Noting treatment completion as indicated by the control console
- Observing the room radiation monitor status
- Measuring the radiation levels at the patient with the radiation survey meter
- Measuring the radiation levels at the treatment unit with the radiation survey meter

DOSIMETRY AND TREATMENT PLANNING

Time Course of Procedures

As with LDR brachytherapy, treatment planning for HDR cases may follow different patterns based on the treatment approach. For example, cervical

cancer treatment using a tandem and ovoid usually has the physician place the treatment appliance followed by imaging and dose calculations. Less likely than with LDR approach, there can still be planning first based on an idealized application, such as a surface application using a standardized applicator and dose calculation method. Some HDR treatment planning may be interactive, such as with prostate implants where dosimetry following needle placement can direct subsequent needle placement in an adaptive manner. Despite this range of options, in most HDR cases, the treatment plan generation follows applicator placement and this model is assumed in the following discussion.

Differences between Low- and High-Dose Rate Brachytherapy Treatment Planning

HDR and LDR brachytherapy treatment planning differ in three ways. The first difference results from the treatment time course. For several sites, particularly gynecologic and prostate brachytherapy applications, the patient waits in the treatment position during the treatment plan generation. Most interstitial and intraluminal treatments differ little from the LDR approach, with treatment plan generation performed while the patient awaits. For those cases with the patient waiting in the treatment position, time becomes an important factor. If the plan generation takes too long, the patient will begin moving and the imaging data will not represent the treatment geometry to varying degrees. Additional problems with excessively long planning sessions include patient discomfort (other than leading to movement) and cost of support staff, such as anesthesiologists.

A second difference entails the quantities involved with the dose calculation. Temporary LDR brachytherapy applications often use source strength input by the user and calculate resulting dose rates based on the source configuration. The problem in many cases becomes selecting the dose rate isodose surface for which to base the treatment duration. The implant may require many sources, possibly of various strengths, but only a single implant duration for all sources. HDR brachytherapy has one source strength but with many different dwell times. In both cases, the dose calculation algorithm uses the product of the source strength and time at a given location as the basis for the resultant dose distribution.

The third difference concerns the role of input or output quantities. As noted earlier, LDR brachytherapy dose calculations most often input the source strengths and calculate the resultant dose rate distribution. Sometimes, the treatment duration is also specified to generate a dose distribution, but these are mostly permanent nowadays. HDR brachytherapy planning usually reverses the process, starting with the dose pattern desired and working backward to the dwell time distribution necessary to achieve that dose, a process termed *inverse planning*. A common part of inverse treatment planning is dose *optimization*, a process to achieve a treatment plan that satisfies some dosimetric criteria.

Optimization

For brachytherapy treatment planning, the term *optimization* implies the process to find the *best achievable* radiation treatment plan through quantitative iteration, given weighting of competing desires of delivering the therapeutic dose to the target region and ensuring minimal dose to surrounding healthy tissues. Many approaches actually only address finding a set of dwell times that deliver a specified dose to specified locations. Other approaches also try to control the dose distribution more finely and possibly limit the dose to specified organs at risk (OARs). The umbrella of optimization covers many disparate processes.

Optimization Approaches

Optimization in brachytherapy has taken many forms. The approaches fall into general categories, although considerable controversy surrounds the classifications. Ezzell[20] presents an excellent review of optimization. The discussion here can only brush the surface of the topic. The following sections outline popular optimization categories.

Stochastic approaches to optimization start with an initial generated time for each of the selected dwell positions. The starting dwell time distribution may be arbitrary, but knowledge-based information from similar cases can aid this optimization method and can reduce the time to generate a solution. Through the initial set of dwell times, the program calculates a value for an *objective function* (OF), which assigns a numerical value to the solution set that allows ranking the set according to quality. The OF may be as simple as

the difference between the value of dose calculated at a set of points and the dose desired. OFs often become more complicated, as in the following equation:

$$\mathrm{OF} = w_t\,(0.95D_{\mathrm{pre}} - D_{t,m})_{D_{t,m}<0.95D_{\mathrm{pre}}} + \sum_i w_{\mathrm{OAR},i}\,(\bar{D}_{\mathrm{OAR},i,\mathrm{calc}} - D_{\mathrm{OAR},i,\mathrm{limit}})^2_{\bar{D}_{\mathrm{OAR},i,\mathrm{calc}}>D_{\mathrm{OAR},i,\mathrm{limit}}} \quad (1)$$

In Equation 1, D_{pre} represents the prescription dose and $D_{t,m}$ stands for the minimum dose in the planning target volume. In this example, the person running the optimization wants to evaluate whether the dwell time set results in part of the target receiving <95% of the prescribed dose and, if so, to keep track of how much less. The second term considers the average doses ($\bar{D}$) to each of the OARs and determines for each the amount over some limiting dose assigned to that organ. The OF in this case is a penalty paid for the dwell time distribution. The first term would be omitted as long as the minimum target dose equaled or exceeded 95% of the prescription dose, and the term for any of the OARs would be zero as long as the dose remained below the limiting value. The exponential power of 2 allows some excess dose but imposes serious penalties for larger values. The weighting factors, *w*, allow a differentiation between the importance given to achieving the desired dose distribution and limiting the dose to a given OAR. In addition to the OF, the dwell time set might also be subject to *hard constraints* that would reject the set outright if the target dose fell to <90% of the prescribed dose or an OAR exceeded a different maximum limit. Because the OF value increases as the dose distribution gets worse, the program tries to minimize this function. Keep in mind that this equation only illustrates the concepts and is not intended to serve as a model of a good OF.

In *simulated annealing*,[21-24] random changes, often sizable, are made from an arbitrary initial solution for the dwell times of some or all of the dwell positions. After the changes and recalculation of the OF, the program holds on to the better of the two dwell time sets. New random changes are made

from the better set, and again the sets are compared using the OF. The randomness of the changes allows for greater variance throughout the iterative process, as a wider distribution of potential solutions is analyzed. As this process continues, the ideal area of the distribution is identified and investigation tightens to this local region, the allowed changes become smaller, and only direct improvements without random input over the previous iterations are accepted. As the process moves toward the solution, the OF improves and the optimal plan is the one with no further improvement in OF. If one properly creates the optimization parameters, the best OF should coincide with the best treatment plan.

The process as described can fall into a local minimum for the OF, where any small change will make the OF worse, a very different solution would be better. The small changes could not get to better solution. The methodology for finding the best set of dwell times differs among the stochastic approaches as each has its own method to avoid iteratively driving to a local minimum instead of the global minimum, which would result in a suboptimal plan approaches.

To avoid such traps, simulated annealing allows for the program periodically allowing for large jumps in the dwell times to investigate completely different regions of dwell times. If the new region does not seem promising because the OFs are worse, the program goes back to the better region.

Often, the value of the OF changes little with fairly large changes in individual dwell times in the neighborhood of the optimal solution. Going from a close dwell time set to the true optimum can require a considerable amount of computer time and often more than getting close in the first place. Most programs contain a criterion for stopping the process once the OF finds an adequate solution instead of continuing to the true optimum.

Other stochastic approaches, such as the *genetic algorithm*,[25] use different search mechanisms, but the overall procedures tend to be similar.

A nonstochastic approach, *geometric optimization*, solves for dwell times that would give the same doses to the vicinities around each of the dwell positions, based on several simplifying assumptions.[26] This approach recognizes that the dose near any dwell position results not only from the nearby dwell but also from the sum of the contributions from all the other sources. This method first calculates how much dose would be deposited to

a dwell position from all the other dwell positions and then weights the dwell time at that dwell position under consideration by the inverse of this dose. Thus, each dwell position needs only make up for the difference between the dose it already receives from the other positions and the dose desired. The first step sets the relative dwell weight, τ_i (the relative dwell time, normalized as described later), for dwell position *I*, based on the dose contributions of the other dwell positions. Using the point-source dose calculation formalism of AAPM TG-43,[27,28]

$$\tau_i = \left[\sum_{j \neq i} \frac{g\,(r_{i \leftarrow j})\ \varphi\,(r_{i \leftarrow j})}{r^2_{i \leftarrow j}} \right]^{-1}, \qquad (2)$$

where $r_{i \leftarrow j}$ is the distance between dwell positions *i* and *j*, $g(r_{i \leftarrow j})$ is the radial dose function, and $\varphi\,(r_{i \leftarrow j})$ is the one- dimensional (1D) anisotropy function. Commercial versions of this algorithm usually ignore the ^{192}Ir radial dose function, which remains within 2% of unity for $r < 5$ cm, and the 1D anisotropy function, which falls within 3.5% of 0.98 over that same radial range. Errors from these omissions and the point-source approximation (inherent in the inverse square relationship) remain smaller than errors that manifest later.

Determining the absolute dwell times then requires specifying the dose desired to a point or the average of several points. For the average dose to several points (indicated by *q*), the equation for the average dose to the points is

$$\bar{D}_{\text{initial pass}} = \frac{S_K \cdot \Lambda}{n} \sum_{q=n}^{1} \sum_{j=m}^{1} \frac{\tau_j \cdot g\,(r_{q \leftarrow j}) \cdot \varphi\,(r_{q \leftarrow j})}{r^2_{q \leftarrow i}}, \qquad (3)$$

where S_K is the air kerma strength in cGy cm^2 h^{-1}, Λ is the dose rate constant in cGy cm^2/unit source strength, n is the number of dose points in the average, m is the number of dwell positions, and t_j from Equation 2 serves as the initial estimate of the dwell time at position j.

Adjusting $\bar{D}_{\text{initial pass}}$ to become $D_{\text{prescribed}}$ requires scaling the dwell times. Letting each of the t_j be the time to deliver $D_{\text{prescribed}}$ and c be the scaling factor such that $t_j = c\tau_j$, then we have

$$C = \frac{\bar{D}_{\text{initial pass}}}{D_{\text{prescribed}}}. \tag{4}$$

This process calculated the doses to a dwell position assuming that all the dwell times were the same. That is not the case in Equation 3, which means that the calculated dwell times are not quite correct. The uniformity could be improved by iterating the process, at the sacrifice of its very high speed. The process also assumes that the implant, and particularly the dwell positions, matches the target volume.

Adjacent dwell positions along the same catheter track can produce the greatest effect on the dwell weights, resulting in isodose surfaces that tend to follow the catheters rather than conform to the shape of the implanted volume. This is especially the case if the separation between dwell positions along a catheter is much less than the separation between catheters. To reduce this effect, a version of the algorithm neglects all other dwell positions along the same catheter track when calculating the dwell weights in a given catheter. This variation is called *volume optimization* because it tends to spread the doses throughout the implanted volume. The original version, which includes the contributions of all other dwell positions for the calculation of any dwell weight, is called *distance optimization* because the isodose surfaces tend to follow a catheter at a constant distance.

The analytic approach, also known as *point optimization* or *point-dose optimization*, attempts to solve algebraically for the set of dwell times that produce the desired dose distribution, as represented by a set of points,

called *optimization points*, each with its own specified desired dose. In the most basic form, the specified doses and the dwell times establish a set of simultaneous equations of the form,[29,30]

$$D_i = \sum_{j=1}^{m} C_{i,j} \cdot t_j, \tag{5}$$

where D_i is the dose specified to point i, m is the number of dwell positions, t_j is the dwell time at position j, and the $C_{i,j}$ are factors that give the dose contribution at i because of the source at position j, with the sum over all sources. The source strength at each dwell position forms a variable (unknown), and each dose specification point yields an equation. Equal numbers of dwell times and dose points form a *determined* system with an exact solution. In more complex cases, there may be more optimization points than source positions, resulting in an *overdetermined* system (less variables than equations). This would be the situation in which optimization points were spread around a region of interest (ROI) contour and scattered through the volume. Faced with this situation, one can vary the dwell times to minimize the square of the differences between the desired and calculated doses at the optimization points. At the other extreme, a case may have more source positions than optimization points (more variables than equations), resulting in an *underdetermined* system. This situation most often happens with large implants and a minimum of optimization points or complicated gynecologic applicators with only a few dose control points. With this situation, the dwell times have no well-defined values; many solutions would possibly exist with the same value for the square of the difference between the doses desired and those calculated. Distinguishing between the solutions requires some other criteria. One is often a minimization of the total dwell time, under the assumption that such would also minimize the integral dose to the patient.

Determined and overdetermined systems can (and often do) generate solutions with negative dwell times. Simply truncating the negative dwell

times often results in an unsatisfactory dose distribution. Avoiding this nonphysical situation also requires an additional criterion. One possible criterion minimizes the differences between adjacent dwell times. For m dwell positions, this term becomes

$$\delta_i = \sum_{j=1}^{n-1} (t_j - t_{j+1})^2. \tag{6}$$

Including this term in the optimization limits time fluctuations between adjacent dwells. To deliver a dose to the target volume requires a net positive total dwell time, and so limiting the amount of difference between the dwell times eventually results in all positive times. An additional condition for underdetermined systems selects solutions that minimize the total radiation to the patient as a whole, which depends directly on the total dwell time. The final optimization becomes minimizing the chi-square value in

$$X^2 = \Sigma_{i=1}^{m} w_i \left(D_i - C_{ij} \sum_{j=1}^{n} t_j \right)^2 + v \sum_{j=1}^{n-1} (t_j - t_{j+1})^2 + u \sum_{j=1}^{n} t_j, \tag{7}$$

where, in addition to those quantities defined earlier, n is the number of dose points specified, w_i is the weighting given to the dose specification at point i (how much the operator wants the correct dose there), v represents the importance in minimizing the fluctuations between adjacent sources, and u represents the importance of minimizing the integral dose to the patient.

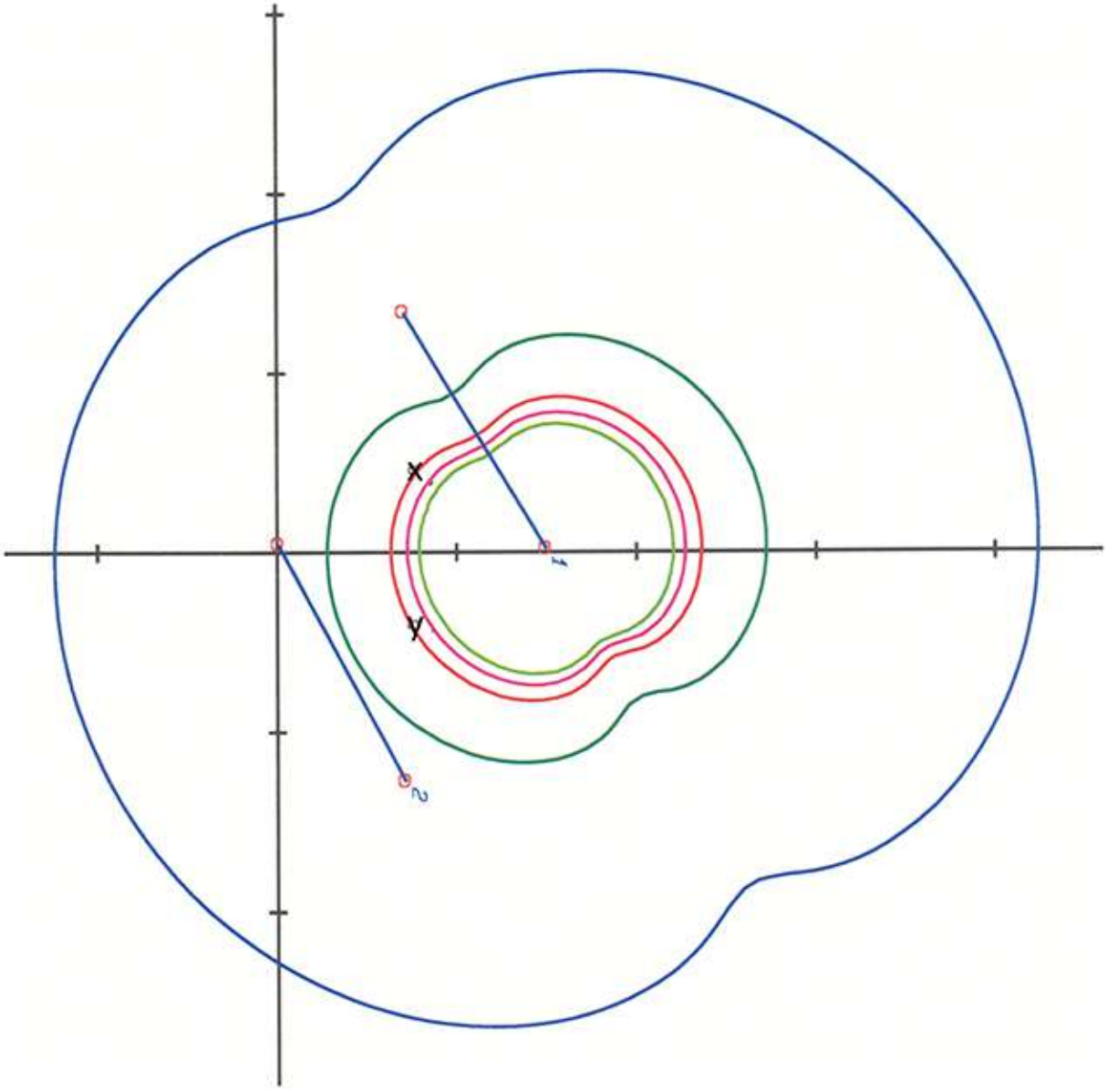
With a large number of optimization points or source positions, or both, the running of the program solving the equations becomes long, and approximations cut the calculation time greatly without significantly compromising the accuracy of the final dose distribution. By setting the dwell time

$$t_i = \sum_{k=1}^{p} a_k \cdot F_k\,(j-1), \tag{8}$$

where F is a fitting function, such as a polynomial or Fourier series of order p, and a_k is the coefficient for the kth element, and substituting that into the X^2 in Equation 7, the optimization now needs to solve only for the fitting coefficients, presumably a much smaller set of values. An alternative approach to solving the equation follows Newton's method.[31,32]

Obviously, the selection of the optimization points becomes very important. The number of points must adequately describe the shape of the dose distribution desired. The dose distributions may satisfy the specifications established for the optimization points but leave portions of the target without dose specification points untreated. However, the points should avoid regions of large dose gradients because specification there can produce unexpected and inappropriate results.

In general, lower values for v in Equation 7 allow better conformality of the dose distribution, and the optimum value often is that just sufficient to prevent negative dwell times. However, simply solving for the dose to specified points can produce an unwanted dose distribution, even when the approach seems to follow normal guidelines. Thomadsen et al[33] give an example similar to that in Figure 23.6. Here, the dose points mirror the basal dose points equidistant from the surrounding catheters. With a low value for v in the optimization equation, the simple solution places all of the dwell time in the center bottom needle—not at all what was really desired. The situation could be avoided by limiting the dwell time variations or using more dose points, particularly on the outside of the implant. Alternatively, performing a geometric optimization to obtain an approximate source distribution, followed by optimization on the points, also alleviates the problem.


x
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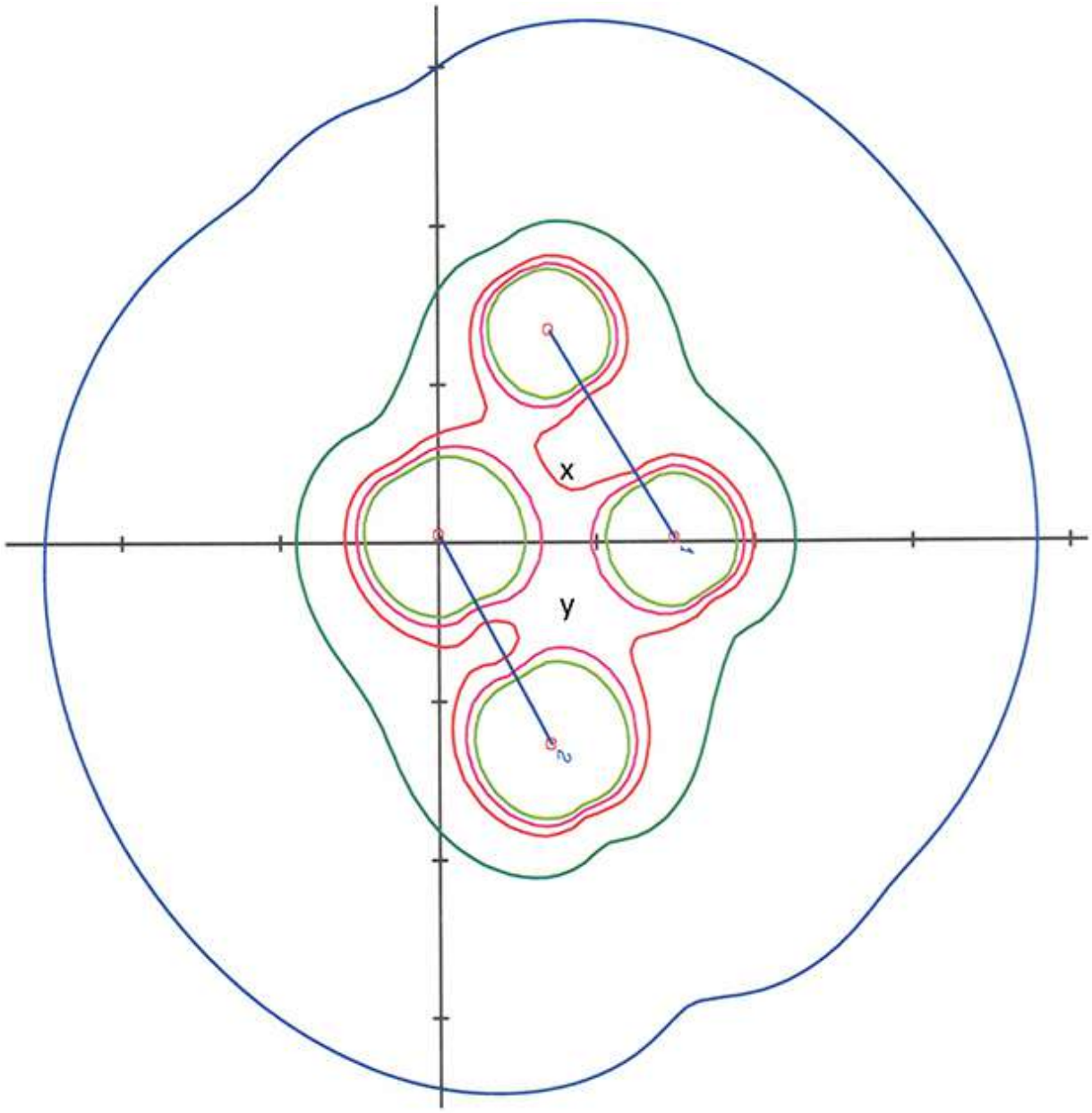

FIGURE 23.6 An example of potential optimization problem. Left: The criterion was that the two optimization points (X and Y) receive the same dose, which was satisfied by a single active dwell position. Right: Adding constraints on the dwell time variation solved the problem.

The output of any optimization approach may leave the operator wanting to make modifications. One method commercially available works on the computer screen display of the dose distribution and allows the operator to "grab" a dose line on the display with the cursor and move the line to a desired location. These fine adjustments make changes that would be

difficult to describe in the optimization routine's specifications. Most treatment planning systems (TPSs) allow adjustment of the dwell times over a range of spatial scales such as globally scaling the entire dose distribution, modifying weighting of individual needles, and as small as changing a single dwell time (affecting very local changes). However, even local changes will influence the dose distribution on image planes other than the one on which the change was made because the radiation extends beyond the immediate locale.

With 1-cm needle spacing and 0.5-cm dwells, it is more direct to adjust weighting along a needle instead of in a bisecting plane adjusting dwell times on multiple needles. Changes in the dose distribution to produce the desired modifications can also produce unintended changes. Of particular concern would be expanding the prescription isodose surface and inadvertently also expanding the higher dose surfaces, possibly into a significant volume. During any manipulation of the isodose surfaces, the display should also show the higher isodoses. Assuming that most of the manipulation occurs with the 100% surface, the 150% surface should also be on display.

Figure 23.7 shows some of the simpler optimization techniques. Usually, a single technique or a combination of two techniques can quickly produce the desired dose distribution. Geometric stability (patient anatomy and brachytherapy applicator or needles) should be considered to prevent high modulation of dwell times when reproducibility is suspect. A fixed approach to the entire treatment planning process should be established for each type of implant to provide a consistent and high standard of care.

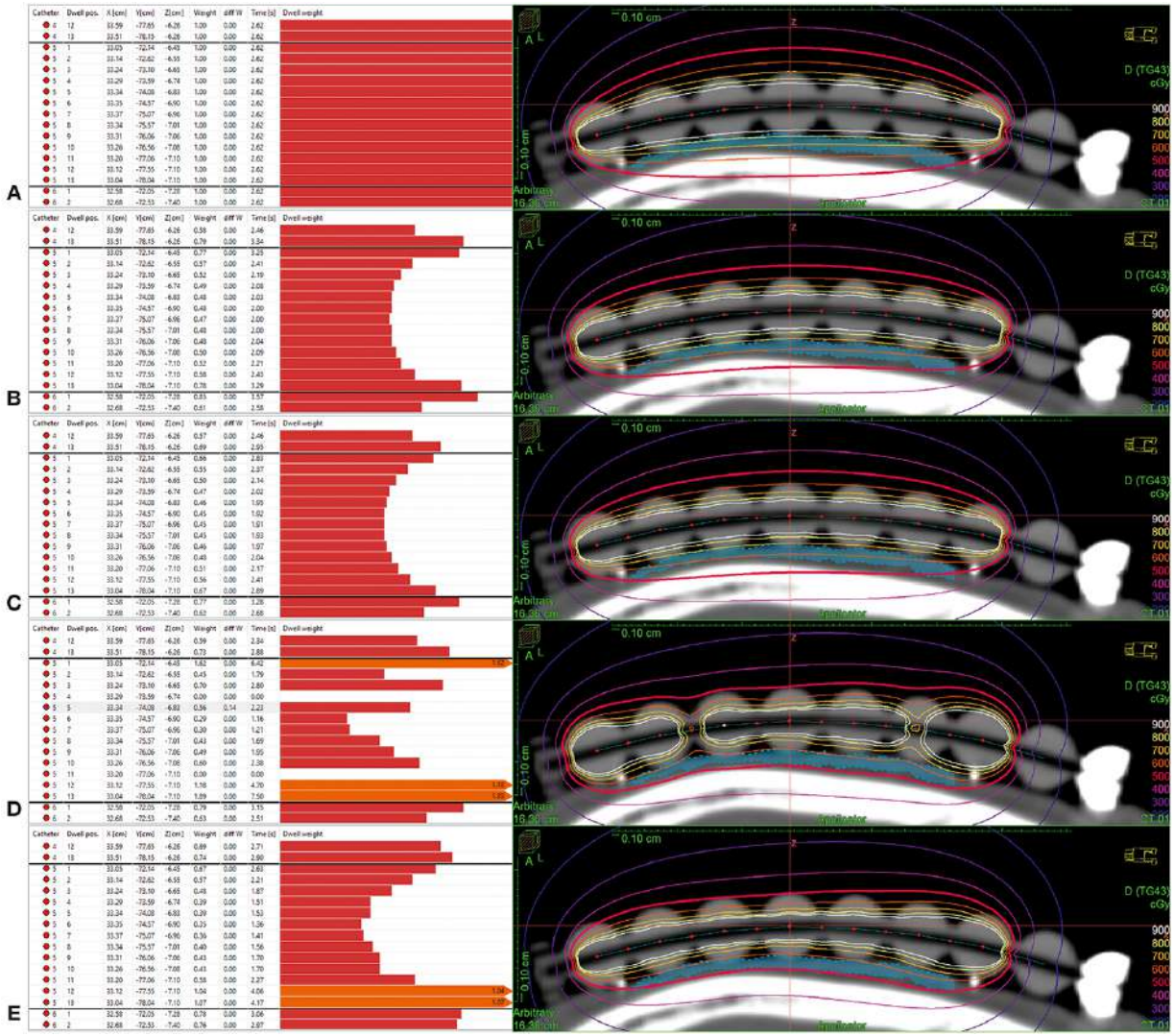

FIGURE 23.7 The aforementioned optimization approaches are shown graphically for a high-dose rate brachytherapy treatment plan of the scalp with a surface flap having dwell spacings of 0.5 cm and the catheter spacings and flap thickness being 1.0 cm. A. Equal dwell weightings are used throughout the implant. B. Geometric volume optimization. C. Geometric distance optimization. D. Geometric volume optimization refined with extreme graphical optimization. E. Geometric volume optimization refined with moderate graphical optimization. Dwell times for each optimization approach are shown on the left, while dose distributions are shown on the right for a plane through the central catheter of the flap. All plans were normalized to 98% clinical target volume coverage, yet the dose hotspots were 170%, 150%, 146%, 132%, and 138% of the prescription dose, respectively. A typical planning goal is <150% for dose hotspots and no intrusion of the prescription dose into healthy tissues such as the underlying bone. For implants with flexible geometry due to the applicator shape or the patient anatomy, extreme modulation of source dwell times is discouraged since the optimized approach may not be realized in clinical implementation.

Multicriteria optimization (MCO) delivers multiple Pareto optimized plans, one for each of the investigated criteria. Each of these plans possess one Pareto optimized condition, which means that the condition is fully optimized within the realm of the other conditions. The full set of Pareto optimized plans are presented to the planner as a Pareto front. The main advantage of this optimization method is that it allows the planner to quickly view the dosimetric effects resulting from each constraint.[34] Consequently, the planner can identify which constraints can be realistically met toward determining the ideal plan. At the time of writing, MCO is available only in a research setting.

Evaluation of Dose Distributions

Dose optimization calculates and sculpts relative dose distributions and requires only spatial dose information. After establishing the dose distribution shape, the entire distribution must be raised or lowered to give the correct absolute dose according to the prescriptive goals. This process requires evaluation of the dose distribution for prescriptive compliance. Other than visually examining the isodose distribution resulting from the optimization routine, there are tools that provide quantitative assessments of various aspects. Thomadsen provides a fuller discussion.[15]

Competing treatment plans may have quite different features. Some quantities that can help condense some characteristics into values include the following dose metrics. Some of these quantities originally applied to the dose distribution in the absence of any regions of interest but have been adapted to the modern situation in which volumetric imaging provides a context for assessment and evaluation. Unless indicated, the volumes are fractions of the whole ROI.

Coverage is usually specified in terms of the faction of the CTV raised to a required dose. As an example, if it were felt that all the CTV should receive at least 95% of the prescribed dose, this would be specified as $_{CTV}V_{95\%} = 100\%$. It might also be desirable that in a given fraction, 90% of the CTV receive at least 5 Gy, or $_{CTV}D_{90\%} = 5$ Gy.

High-dose volume (HDV)[35-37] is the volume of an ROI raised to a dose significantly higher than the target dose, often higher by a factor of 1.5. HDV = $_{ROI}V_{150\%}$.

Dose nonuniformity ratio (DNR)[37-39] is the ratio of the CTV HDV to that taken to at least the target dose. DNR = ${}_{CTV}V_{150\%}/{}_{CTV}V_{100\%}$.

Relative dose homogeneity index (DHI)[37,38] is the fraction of the target volume receiving a dose between the target dose and the high-dose level. DHI = ${}_{CTV}V_{150\%} - {}_{CTV}V_{100\%}$. Rarely are DNR and DHI used together.

Conformation number or *conformal index* (CN or COIN)[40,41] is a measure of how well the dose distribution fits the target. CN = $({}_{CTV}V_{100\%}/{}_{total}V_{100\%}) \times ({}_{CTV}V_{100\%}/{}_{CTV}V)$, where all the volumes are absolute such as in cm^3.

Each of these dose metrics tells a small part of the dose distribution's entire story. Each can help evaluate a dose distribution, and taken altogether gives a better picture. However, none of these—even together—captures the complexity and nuances of the total dose distribution. Inspection of the results of the optimization remains a necessity.

The *maximum significant dose* (MSD) refers to the highest level isodose surface that encompasses more than one needle track. The dose very close to a needle track becomes very high, but the body seems to tolerate these small local volumes. The MSD provides a convenient criterion for when the HDVs become "significant" and likely to produce biologic consequences. For most implants, the MSD should remain <150% of the prescription dose, assuming that the prescription dose encompasses the target volume. For vary large volumes (>30 cm^3), the limiting value should decrease to about 125% of the prescription dose.[42]

Evaluation of the treatment plan quality also entails assessing OAR doses.[43] This evaluation may use quantities such as ${}_{rectum}D_{2\ cc}$ as a review criterion. Limitations on the doses to normal tissue structures are discussed in detail in Chapters 12 and in most of the chapters on clinical applications.

Quality Control of Treatment Plan

The use of HDR brachytherapy in the definitive management of gynecologic cancer,[44] early-stage breast cancer,[45,46] and prostate cancer[47] has made the RAL unit a common treatment modality in most radiotherapy clinics. HDR TPSs integrate multimodality images (CT, MRI, and ultrasound [US]) and dose optimization software such as inverse planning or interactive graphical optimizers, which enable the planner to maximize

the dose uniformity while minimizing the implant volume needed to cover the target volume while reducing OAR doses. Such capability creates a challenge for the verification of optimized dose calculations with practical hand calculation techniques. With the time constraint following HDR treatment planning and the onset of treatment delivery, an efficient, precise, and easy method for checking complex computer calculation is necessary for quality control of the treatment plan. Every institution should have an established quality control program that takes only a few minutes yet provides a high probability of detecting significant errors, because the NRC considers a 20% difference between the administered dose and prescribed dose a reportable medical event.[48]

Simplistic models to verify TPS calculations quickly have drawbacks because applicators or interstitial implants used in HDR treatments are complex in design, and simple point-dose or linear source calculations tend to fall apart in most circumstances.[14,49,50] Because all TPS scan generate dose-volume histograms, it is logical that volume-based QA is preferred. Das et al[51,52] addressed this possibility and provided an easy and quick calculation check for most HDR interstitial and intracavitary implants.

DISEASE SITES COMMONLY TREATED WITH HIGH-DOSE RATE BRACHYTHERAPY

Several disease sites are especially amenable for treatment using HDR brachytherapy. This is due to a combination of favorable implant geometry and dose avoidance with respect to adjacent critical structures. Other chapters in this book discuss the therapeutic issues in greater detail.

Cervical Cancer Brachytherapy

Intracavitary brachytherapy has been a major part of the treatment for cervical cancer for almost 100 years, with most experience using HDR brachytherapy since the mid-1980s. Of the advantages of HDR over LDR brachytherapy given earlier, several apply directly to these treatments, particularly the small source size and the resultant smaller diameter of the intrauterine tandem, the greater stability of the treatment appliance and higher accuracy and relevance of the calculated dose distribution, and the ability to hold OARs more distant from the applicator and source path.

Imaging plays a major role in these modern treatments with the future likely seeing an increase in that role.[53] US can provide guidance during the placement of the intrauterine tandem, particularly to avoid fundus perforation or when the tumor obliterates the external cervical os. Fluoroscopy provides guidance during applicator placement, assisting in the assessment of applicator geometry (eg, evaluating the centering of the tandem with the ovoids in both the anteroposterior and lateral projections), correct applicator assembly and securement, and positions of the rectum and bladder.

The role of HDR gynecologic brachytherapy imaging is evolving. The European Society for Therapeutic Radiology and Oncology (Groupe Européen de Curiethérapie [GEC-ESTRO]),[54-58] the American Brachytherapy Society consensus guidelines for locally advanced cervical carcinoma,[59-61] and the International Commission on Radiation Units and Measurements (ICRU)[62] recommended moving toward image-based target prescriptions. At the time of writing, the AAPM TG-236 Report is under review and will issue recommendation on volume image–based treatment planning, dosimetry, and quality management for HDR intracavitary brachytherapy. Identifying the target (ie, tumor tissue in the uterus) requires MRI, the only form of imaging that also reliably differentiates the uterus from other pelvic tissues. GEC-ESTRO defines a high-risk clinical target volume (CTV_{HR}) as any tumor detectable by physical examination or imaging plus the entire cervix. Typically, 95% of the prescription dose should cover 95% of the CTV_{HR} volume. The formalism also defines an intermediate-risk clinical target volume (CTV_{IR}) based on disease extent at the time of diagnosis. Generally, the CTV_{IR} should receive about two-thirds of the dose to the CTV_{HR}. (The definition of the CTV_{IR} is actually more nuanced, and practitioners should study the references thoroughly before implementation.) The recommended integrated dose to the CTV_{HR} in 2-Gy per fraction radiobiologic equivalence (EQD_2) is 80 to 90 Gy, depending on tumor size and external beam radiation therapy dose contributions. To maintain a connection to historic experience while prescribing the dose to a target volume, ICRU 89 recommends also reporting dose to the conventional point A as defined per the ABS.[59]

Although only MRI identifies the target and the uterus, CT images the rectum and the bladder well. Although using CT localization does not permit as detailed target information as MRI, it does allow moderate target definition and facilitate determining the doses to the OAR when using conventional treatment prescriptions.[62] Dose calculations based on either CT or MRI often indicate that the maximum bladder dose is 2 to 4 cm superior to the conventional point indicated following ICRU 38 and may be 2 to 4 times the dose to the conventional point.[63] The ICRU-indicated rectal point differs less than the bladder point, with the true maximum falling between 1 and 3 cm superiorly and the true maximum dose being 1 to 3 times the conventional point. The GEC-ESTRO and the ICRU 89 formalism specify the dose of interest to OAR in terms of volumes rather than points. The locations of the highest dose to the rectum, bladder, and sigmoid are found, and these points locate the volumes of interest. For each OAR, the minimum doses in the most highly irradiated 2 and 0.1-cm^3 volumes are generally recorded.

The accuracy and precision of determining the dose matter much more in HDR intracavitary brachytherapy for the cervix than for LDR treatments for two reasons. The first is concerned for the precision of dose delivery. King et al[64] demonstrated that the typical LDR tandem and ovoids move an average of 2 cm over the course of treatment. HDR tandems and ovoids move a maximum of 0.3 cm when not moving the patient.[50] Thus, the added precision of volumetric, image-based dose calculations would be lost in the general positional uncertainty of LDR intracavitary brachytherapy. In the second place, HDR applications not only can use the dosimetric accuracy, but they may also require it. Because of the radiobiologic disadvantage of HDR brachytherapy, knowing the dose distribution with a high certainty is necessary to avoid complications.

Avoiding complications leads to several differences between HDR and LDR brachytherapy of cervical cancer. To prevent rectal complications, the dose to the rectum should remain <70% of the dose to the Manchester point A or the CTV_{HR}.[44,61] Treating with a rectal retractor in place usually accomplishes this goal. As noted under the advantages of HDR brachytherapy, patients would not tolerate such a practice over long durations with LDR applications. Adding distance to the bladder generally

uses copious packing anterior to the ovoids, taking care not to let the packing slip between the ovoid surface and the superior or lateral fornices. An unpublished 1988 review of LDR cervical cases at the University of Wisconsin found the beginning of late complications in the superior bowel (fistulae) at about 13 years after treatment and that the prevalence increased continually over time. That problem with LDR treatments generated concern that the situation might be worse with HDR treatments because of the unfavorable radiobiology. With HDR, unlike LDR, the dose to the superior bowel can be reduced by not loading the tandem as high into the uterus and making the dose distribution more square than the LDR applications.[44]

Prostate Brachytherapy

A radiobiologic parameter termed α/β characterizes the radiation sensitivity of specific cells like tumorous or healthy tissues and is discussed in detail in Chapters 21. Unlike most cancers, the radiobiologic α/β value for prostate cancer is low, possibly as low as 1.2 Gy and lower than that of most normal tissues.[65,66] The slow delivery of radiation with LDR treatments allows normal tissues to recover better than tumors, whereas HDR treatments cause a greater increase in the damage to the normal tissues than to tumors. When the relative size of the α/β inverts, as in prostate cancer, the advantages also invert. High doses per fraction cause a greater increase in damage to the tumor cells having an α/β value of 2 in comparison to normal tissue cells with an α/β value of 3. This situation makes HDR brachytherapy look attractive.[67,68]

Currently, the process for HDR prostate brachytherapy follows the LDR model fairly closely. US images provide guidance for the insertion of the catheters, although CT and MRI guidance has become more common.[69-71] Generally, catheter placement follows a pattern such as four around the urethra and then at 1.0- to 1.5-cm intervals around the gland periphery. The rectangular template grid complicates catheter placement at regular intervals, but the final dose distribution is relatively insensitive to the exact location of the catheters. Commercial software exists to guide the user for catheter placement, but those experienced in prostate implants probably perform as well without computer assistance.

After catheter placement, the optimization routine calculates dwell times to achieve the dosimetric criteria specified for the patient. The resultant dose distribution may still require small adjustment through graphical optimization. Following treatment plan approval, the operator connects the needles to the treatment unit using the transfer tubes. Because the needles have no inherent numbering, great care must be taken during this process to ensure the correct correlation between the needles in the patient and those in the treatment plan.

The location of the first dwell position in the needles would have been determined previously. Radiographing the needles with the x-ray markers in place forms one of the simplest methods. If the treatment unit does not seek the end of the needle to establish the first dwell position, all needles must be tested for uniformity of length.

Treating multiple fractions with the same insertion requires verification of the needle depth. Between fractions, the needles tend to slide outward and may need repositioning under US or fluoroscopic guidance. Marks on the needles where they enter the patient also can serve as indicators for possible repositioning.

Breast Brachytherapy

Accelerated partial-breast irradiation (APBI) for patients with breast cancer with HDR brachytherapy as monotherapy following lumpectomy has produced excellent local control rates and cosmesis.[51,72] Interstitial and intracavitary (catheter balloon) implants are used for this treatment modality. Usually within 8 weeks of lumpectomy and axillary nodal evaluation, the patient undergoes an interstitial implant with one of three methods: a prone stereotactic template method with digital mammographic guidance, a supine US-guided technique; or a supine template–guided CT technique. All three methods are performed under local anesthesia. Because of the perceived technical challenge of multicatheter interstitial implants, alternative intracavitary methods for APBI have been developed. One approach uses multiple catheters around the central catheter within a balloon that is placed within the lumpectomy cavity closed, often under US guidance, and inflated with saline or diluted contrast medium. Two such systems are the Contura (SenoRx, Bard Biopsy System, Tempe, AZ) and

multicatheter MammoSite (Hologic, Bedford, MA). An alternative is the SAVI device (Cienna Medical, Aliso Viejo, CA) that uses six to 10 struts in a configuration that looks similar to an egg whisk to hold the tylectomy cavity open instead of a balloon. The struts also serve as the paths for the source travel. Another device consisting of a double balloon (Best Industries, Springfield, VA) contains a single central treatment catheter and four peripheral treatment catheters that can be customized for radiation dosage coverage. The inner balloon can be filled with 7 to 30 cm^3 of saline to increase separation of the peripheral catheters, and an outer balloon can be filled with 35 to 110 cm^3 of saline to displace the breast tissue from the peripheral catheters. The multiple catheters for each of these devices allow some shaping of the dose distribution, but not comparable to that obtainable with multicatheter interstitial implants. Imaging of the balloon for its integrity, as well as rotation of the multiple catheter devices, should be performed before initiating each treatment.

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CHAPTER 24

Clinical Aspects and Applications of High-Dose-Rate Brachytherapy

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High-dose-rate (HDR) brachytherapy (BT) is a standard-of-care treatment option for many disease sites in radiation oncology. This modality is capable of delivering an extremely high dose of radiation to the tumor while sparing critical surrounding organs-at-risk (OAR) due to rapid dose falloff. Radiation is delivered by a HDR radioactive source (≥12 Gy/hour),[1] which passes within hollow catheters placed in close proximity to the tumor. The position of the radioactive source is precisely controlled via cable by a remote afterloader.

HDR brachytherapy has numerous clinical advantages. Most importantly, HDR brachytherapy has been shown to be highly effective, with high rates of local control and relatively low rates of significant late toxicity in prospective trials across multiple disease sites.[2–5] Its high therapeutic ratio has allowed HDR brachytherapy to become the universally accepted clinical standard-of-care for malignancies, including the adjuvant treatment of high-intermediate-risk, early-stage endometrial cancer[2] and the definitive treatment of locally advanced cervical cancer.[4] HDR brachytherapy is convenient because single or multiple treatments can be delivered with relatively short treatment delivery times, often in an outpatient setting. HDR brachytherapy can be used to create highly conformal treatment plans that can account for variations in both anatomy and applicator placement. This is possible due to the ability to fine-tune dwell positions at submillimeter step sizes along multiple catheters. HDR brachytherapy can incorporate contemporary three-dimensional (3D) imaging modalities (eg, computed tomography [CT], magnetic resonance imaging [MRI], and high-resolution ultrasound) into the treatment planning process. In addition, since radiation is delivered within a shielded room via a remote afterloader, there is no personnel exposure to radiation.

However, the safe and effective practice of brachytherapy requires processes and workflows that are quite unique to radiation oncology departments accustomed to delivering external beam radiation therapy (EBRT). An interdisciplinary team of radiation oncologists, medical physicists, radiation therapists, registered nurses, and surgical technicians must function efficiently in real time for the patient to receive the treatment in a safe and timely manner. Furthermore, for treatments requiring sedation, this team must collaborate with members outside the radiation oncology department, such as anesthesiologists, surgical oncologists, recovery nurses, and the admitting inpatient team. With the widespread adoption of 3D treatment planning as well as adaptive image-guided radiation therapy (IGRT),[6,7] patients undergoing brachytherapy may require CT and/or MRI scans in the perioperative period. Due to the extremely high doses delivered, a rigorous quality assurance program is needed to ensure that the treatment is delivered in a safe and effective manner. Additional time may be needed for assessing brachytherapy candidacy, obtaining patient education/consent, acquiring preoperative clearance, and ensuring patient comfort during and after the brachytherapy treatment process.

Over the past decade, multiinstitutional prospective and even randomized controlled trials have greatly enhanced the understanding of the benefits and risks of HDR brachytherapy. The purpose of this chapter is to review the clinical role of HDR brachytherapy across multiple disease sites. At the end of the chapter, practical aspects of an HDR quality management program are provided.

CERVICAL CANCER

Clinical Indications

Brachytherapy is a critical component in the standard-of-care management of locally advanced cervical cancer. Large national database studies have suggested that the addition of brachytherapy boost has been associated with improved survival for patients who received definitive pelvic EBRT and concurrent chemotherapy.[8,9] Furthermore, the multiinstitutional prospective study EMBRACE-I recently reported high local control rates across all tumor stages and low severe single-organ toxicity rates at 5 years.[4] Many patients with locally advanced cervical cancer would lose the chance for cure without the incorporation of HDR brachytherapy boost.

The success of HDR brachytherapy for cervical cancer has resulted in part from three critical advances over the past two decades. The first advance is the transition from two-dimensional (2D) to 3D treatment planning. With 2D

treatment planning, the dose was prescribed to point A, which is located 2 cm superior to the ovoid and 2 cm lateral to the tandem, on x-ray imaging. The same dose was prescribed regardless of differences in tumor size or OAR proximity. With 3D treatment planning on CT and/or MRI, dose can be prescribed to a specific treatment volume but can be minimized to surrounding OARs, based on patient-specific anatomy. Studies have reported that 3D BT exhibits improved local control[10] and reduced toxicity compared to 2D BT.[11]

The second advance is standardized target volume and dose reporting recommendations from Groupe Européen de Curiethérapie and the European Society for Radiation Oncology (GEC-ESTRO).[6,7] These recommendations defined the high-risk clinical target volume (HR-CTV), which includes the cervix and any gross residual disease on MRI after chemoradiation therapy. These volumes account for potential dose response (ie, tumor regression) from previous chemoradiation therapy at the time of brachytherapy. Target volume delineation from an MRI with applicator in place is recommended due to the optimal soft tissue contrast.[12] However, since MRI at the time of brachytherapy may not be available in many centers around the world, consensus recommendations from the Indian Brachytherapy Society (IBS)-GEC-ESTRO-American Brachytherapy Society (ABS) have been recently published for CT-based planning.[13]

The third advance is the utilization of hybrid intracavitary/interstitial applicators. These hybrid applicators allow for the insertion of interstitial needles in parallel to the intrauterine tandem.[14] Such implants have been associated with improved dosimetric coverage for and local control of larger tumors, but without added toxicity.[15] With all three components, marked dose escalation to the target volume can be achieved without exceeding OAR constraints.

For nonsurgical treatment of cervical cancer, the overall treatment workflow involves upfront chemoradiation therapy followed by HDR brachytherapy boost. The chemoradiation portion typically spans 5 weeks. A typical dosing regimen is 45 Gy in 25 fractions of EBRT to the pelvis. The para-aortic (PA) lymph nodes can be included if the patient has gross PA nodal disease or is at high risk of having PA nodal spread (eg, gross common iliac lymph nodes). The patient can also undergo a simultaneous integrated boost of ~55 Gy to suspicious gross pelvic lymph nodes and up to 60 Gy for the PA nodes. During EBRT, the patient also receives chemotherapy, in the form of cisplatin 40 mg/m^2, once weekly for 5 to 6 weeks. Following this, the patient undergoes HDR brachytherapy boost. An example of a dosing regimen involves delivery of 7 Gy over 4 fractions in two implants, with two fractions per implant (Table 24.1). The overall goal for treatment is to achieve an HR-CTV D90 (minimum dose to 90% of the target volume) dose of at least 85 Gy in equivalent dose in 2 Gy fractions (EQD2α/β=10.). The overall treatment time should span less than 50 days, in order to maximize the chance for achieving high local control.[16] It has been estimated that an additional 5 Gy dose to the HR-CTV would be needed to compensate for an increase in overall treatment time by 1 week.

TABLE 24.1 SAMPLE SCHEDULE OF NUMBER OF MULTIMODALITY TREATMENTS FOR CERVICAL CANCER BY WEEK

Week	External Beam	Chemotherapy	Brachytherapy
1	5	1	
2	5	1	
3	5	1	
4	5	1	
5	5	1	
6			2
7			2

Regarding eligibility criteria, patients should undergo a comprehensive history and physical exam, with a bimanual exam to fully understand the clinical extent of spread (eg, parametrial invasion and vaginal extension). Disease extent can be captured in a comprehensive manner with standardized schematic diagrams.[6] Patients must have biopsy-proven disease and should undergo comprehensive staging with a positron emission tomography (PET) and an MRI scan. Patients with 2018 International Federation of Gynecology and Obstetrics (FIGO) IB-IVA disease who choose to undergo primary chemoradiation therapy with curative intent would be eligible. Patients with prior pelvic or abdominal radiotherapy or prior hysterectomy may not be eligible for this treatment regimen.

Outcomes

The clinical outcomes of HDR brachytherapy are best encapsulated in relatively recent multiinstitutional experiences of MRI-guided adaptive brachytherapy. The multiinstitutional, retrospective, retroEMBRACE study included 731 patients treated with definitive radiation therapy followed by brachytherapy across 12 centers.[17] In total, 77.4% received concurrent chemotherapy and 23.0% of patients had combined intracavitary/interstitial implants. The mean HR-CTV D90 was 87 ± 15 Gy $EQD2_{10}$. Respective D2cc values for the bladder, rectum, sigmoid, and bowel in EQD_3 were 81 ± 22 Gy, 64 ± 9 Gy, 66 ± 10 Gy, and 64 ± 9 Gy. Five-year local control was 89%, with lower control rates for more advanced stages (98% for IB, 91% for IIB, and 75% for IIIB). Actuarial grade 3 to 5 morbidity rates were 5%, 7%, and 5% for the bladder, gastrointestinal tract, and vagina, respectively.

In the multiinstitutional prospective EMBRACE-1 study, 1,416 patients with 2009 FIGO stage IB-IVA disease or IVB with PA nodal disease below the L1-L2 interspace were registered across 24 international centers.[4] Patients were treated with chemoradiation therapy, involving five to six cycles of weekly cisplatin 40 mg/m^2 and 45-Gy to 50-Gy of EBRT. PA nodal fields and pelvic sidewall boosts were allowed. Patients then underwent MRI-based image-guided adaptive brachytherapy, with target volume delineation and dose reporting performed per GEC-ESTRO recommendations.[6,7] MRI-based treatment planning with applicator in place was mandatory for the first treatment. Brachytherapy dose prescription was given per institutional guidelines.

The median D90 to the HR-CTV was 90 Gy (interquartile range [IQR] 85-94 Gy) $EQD2_{10}$, with 43.0% patients with combined intracavitary/interstitial implants. Respective median D2cc values for the bladder, rectum, sigmoid, and bowel were 76 Gy (interquartile range [IQR]: 69-83), 62 Gy (57-68), 64 Gy (59-69), and 58 Gy (49-67). At a median follow-up of 51 months, the 5-year local control was 92% (95% CI 90-93), with rates similar across all stages (P =.13). The 5-year nodal control was 87% (95% CI 85-89), with values of 93% (90-95) for N0 versus 81% (77-84) for N1 patients. Two-thirds of nodal failures for node-positive patients occurred in the para-aortic region.[18] The 5-year disease-free survival and overall survival rates were 68% (65-70) and 74% (72-77), respectively. Rates for both indices varied by stage (P <.0001). The cumulative incidences for grade 3 to 5 morbidity per Common Terminology Criteria for Adverse Events version 3.0 were 6.8% (5.8-8.6) for genitourinary events, 8.5% (6.9-10.6) for gastrointestinal events, 5.7% (4.3-7.6) for vaginal events, and 3.5% for fistula. Rates of fistula and ureteric strictures were greater for patients with stage IIIA to IIIB cancer compared with those with IB1 to IIB cancer, likely reflecting increased tumor involvement at diagnosis.

A recent follow-up study reported 5-year Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer grade 3+ events of 26.6% (23.8%-29.6%), with organ-related events reported as 18.4%.[19] Though these results in aggregate are high, organ-specific morbidities (eg, severe GI, fistula, and vaginal) compared favorably with those of prior prospective series based on 2D planning, with no clear trend for GU morbidity.

Technique

A preimplant anesthesia evaluation before brachytherapy is important because most patients will still be experiencing the side effects from the proceeding chemoradiation therapy. Special medical considerations may be necessary for patients on anticoagulation or with low blood counts (eg, absolute neutrophil count <500 mm^3) due to recent chemotherapy, given the goal of completing treatment within 50 days. Furthermore, the physician needs to select an applicator based on the patient's tumor response after chemoradiation therapy. This information can be obtained from a repeat gynecologic exam and prebrachytherapy MRI.

The operative procedure involves the insertion of an intracavitary applicator under anesthesia (eg, general, spinal, or conscious sedation).[20] The applicator most often includes a tandem placed within the uterus, as well as an ovoid or ring pushed against the uterine cervix. Interstitial needles can also be inserted into the tumor, either through the ring/ovoid (eg, hybrid applicator[14,21]) or a perineal template, to ensure adequate dosimetric coverage for larger tumors. Regarding the actual procedure, the patient is induced under anesthesia and placed in dorsal lithotomy position. The patient is prepped and draped. The Foley catheter is inserted under sterile conditions, and the balloon is inflated. A uterine sound can then be inserted, potentially under ultrasound guidance (eg, transabdominal or transrectal), and the cervix is dilated. After this, the applicator is inserted (eg, tandem, ring/ovoid, or interstitial needles) and fixed with packing, balloons, or sutures. The patient is then removed from the dorsal lithotomy position. After the acquisition of CT and/or MRI scans, treatment planning can commence.

Treatment Planning

In the contemporary era, HDR brachytherapy is performed with 3D-treatment planning under MRI or CT guidance with the applicator in place. OAR contours for the bladder, rectum, sigmoid, and bowel loops are delineated. The following target volumes are delineated, per GEC-ESTRO and ICRU 89 guidelines:[6,22]

Residual Gross Tumor Volume (GTV) (GTV_{res}): This consists of gross residual disease, as noted on MRI.

High-risk clinical target volume (HR-CTV): This consists of the entire cervix, the gross residual tumor on MRI, as well as presumed residual microscopic tissue within the initial based on imaging (eg, MRI gray zones) and clinical examination. The HR-CTV can be remarkably smaller than the initial tumor volume, especially if there is a pronounced tumor response.

Intermediate-risk CTV (IR-CTV): This includes the HR-CTV as well as the GTV at the time of diagnosis, plus a safety margin (eg, GEC-ESTRO recommends 10 mm lateral and craniocaudal; 5 mm anterior/posterior). The margins should not extend into any OAR, except for the bladder or rectal wall for FIGO stage IVA disease. The margins, however, can extend into the vagina.

For centers without an MRI available at the time of brachytherapy, target delineation should be performed using CT with applicator in place according to recent guidelines from IBS-GEC-ESTRO-ABS.[13] These guidelines introduce four brachytherapy target remission categories based on imaging response after EBRT and provide recommendations for HR-CTV delineation based on the type of imaging available at the time of diagnosis (CT, MRI) and brachytherapy (CT with or without prebrachytherapy MRI). The guidelines also introduce the concept of "near minimum distance," which measures the lateral extension from the cervical os for each (right and left) parametrium.

Treatment planning is then performed. Dose is prescribed to the HR-CTV. Target volume planning aims include an HR-CTV D90 between 90 and 95 Gy, a GTV_{res} D98 > 95 Gy, and an IR-CTV D90 > 60 Gy, each in $EQD2_{10}$. OAR planning aims include bladder D2cc < 80 Gy, rectum D2cc < 65 Gy, sigmoid D2cc < 70 Gy, and bowel D2cc < 70 Gy, each in $EQD2_3$. In addition, the rectovaginal point dose, defined as 5 mm posterior to the vaginal mucosa in the axial plane, should have a dose <65 Gy $EQD2_3$. Planning aims from the ongoing EMBRACE-II[23] trial are shown in Table 24.2. An example treatment plan is provided in Figure 24.1.

TABLE 24.2 PLANNING AIMS FOR TARGET ORGANS AND OAR RISK FOR HDR BRACHYTHERAPY FOR CERVICAL CANCER FROM EMBRACE-II

Target	Planning Aims	Limits for Prescribed Dose
D90 HR-CTV $EQD2_{10}$	90-95 Gy	>85 Gy
D98 HR-CTV $EQD2_{10}$	>75 Gy	
D98 GTV_{res} $EQD2_{10}$	>95 Gy	>90 Gy
D98 IR-CTV $EQD2_{10}$	>60 Gy	
Point A $EQD2_{10}$	>65 Gy	
Bladder D2cc $EQD2_3$	<80 Gy	<90 Gy
Rectum D2cc $EQD2_3$	<65 Gy	<75 Gy
Rectovaginal point $EQD2_3$	<65 Gy	<75 Gy
Sigmoid D2cc $EQD2_3$	<70 Gy	<75 Gy
Bowel D2cc $EQD2_3$	<70 Gy	<75 Gy

Adapted from Pötter R, Tanderup K, Kirisits C, et al. The EMBRACE II study: the outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies. *Clin Transl Radiat Oncol*. 2018;9:48-60. With permission.

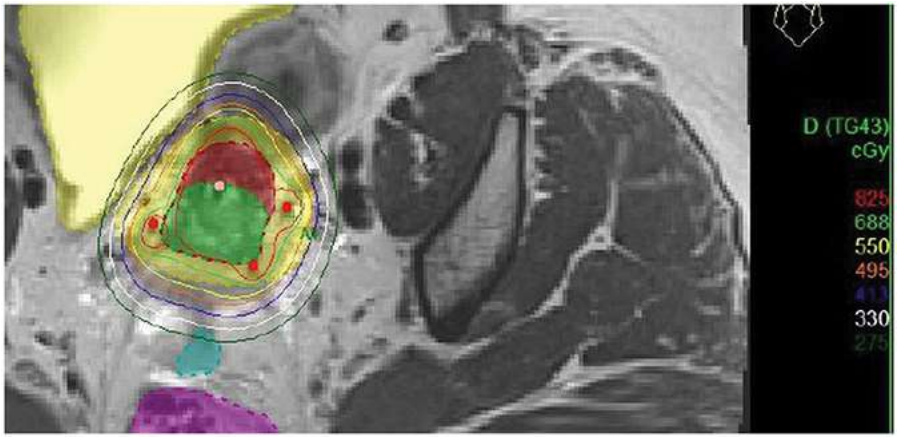

FIGURE 24.1 Axial view of MR-guided HDR brachytherapy (27.5 Gy/5 fractions) for FIGO IIIC2 (T2bN2) cervical squamous cell carcinoma, treated with chemoradiation therapy (45 Gy/25 fractions). The patient had an intracavitary hybrid applicator placed with six interstitial needles. Contours: GTV_{res}, green HR-CTV—red; IR-CTV—yellow; sigmoid—cyan; bladder—yellow; rectum—purple. Target volume dosimetry metrics in $EQD2_{10}$ were HR-CTV D90 97.4 Gy, GTV_{res} D98 95.0 Gy, IR-CTV D98 69.4 Gy. OAR dosimetry metrics in EQD_3 were rectum D2cc 52.9 Gy, bladder D2cc 81.6 Gy, sigmoid D2cc 75.3, and bowel D2cc 49.4 Gy.

Follow-Up

Following brachytherapy, patients should have a repeat pelvic exam with pap smear, with consideration of PET/CT[24] in 3 months. If concerning findings are noted, further evaluation, including MRI and colposcopy, is recommended. Otherwise, the patient should undergo follow-up with routine pelvic exams and pap smears every 3 to 6 months for the first 5 years, and yearly thereafter. Utilization of a vaginal dilator is recommended. Patients with persistent symptoms should be followed closely. Many symptoms (eg, gastrointestinal bleeding or cystitis) will resolve or improve, whereas others (vaginal stenosis) may persist.[19]

ENDOMETRIAL CANCER

HDR brachytherapy is a critical treatment modality for endometrial cancer. Many radiation oncology centers offer HDR brachytherapy for the sole purpose of treating patients with localized endometrial cancer, using vaginal cuff brachytherapy (VBT) after hysterectomy. More specialized centers offer HDR brachytherapy for the definitive treatment of vaginal cuff recurrences after hysterectomy, as well as medically inoperable disease.

Adjuvant Vaginal Cuff Brachytherapy

Clinical Indications

The PORTEC-2 trial established VBT as the standard-of-care adjuvant treatment for localized disease with adverse risk factors. This trial randomized 427 patients with high–intermediate-risk disease (predominantly 2009 FIGO stage IA grade 3 or stage IB grade 1 or 2 endometrioid carcinoma) to pelvic EBRT (46 Gy in 23 fractions) versus VBT (predominantly 7 Gy over three fractions to 5 mm depth). At 5 years, VBT demonstrated noninferior vaginal recurrence compared with EBRT (1.8% vs 1.6%; HR 0.78 [0.17, 3.49]; P =.74), along with significantly less acute grade 1 to 2 gastrointestinal toxicity (12.6% vs 53.8%).[25] Vaginal cuff recurrences at 10 years remained low (3.4% vs 2.4%; P =.55), although pelvic recurrences were more frequent in the VBT group (6.3% vs 0.9%; P = 0.004).[2]

The indications of VBT in patients who have undergone hysterectomy based on 2009 FIGO staging are listed in Table 24.3. These recommendations do not account for the recently released 2023 FIGO staging requiring molecular classification.[26] VBT in the adjuvant setting is recommended for 2009 FIGO stage IA grade 3 endometrioid carcinoma and stage IB grade 1 or 2 endometrioid carcinoma without substantial lymphovascular space invasion (LVSI). Patients with substantial LVSI should undergo EBRT, particularly if a pathologic lymph node assessment was not performed.[27] For FIGO stage IA grade 1 or 2 endometrioid endometrial carcinoma, VBT should only be considered if there are risk factors for recurrence (age ≥ 60 years, focal LVSI, or substantial LVSI).[28]

TABLE 24.3 CLINICAL INDICATIONS OF ADJUVANT VAGINAL CUFF BRACHYTHERAPY AFTER HYSTERECTOMY IN PATIENTS WITH ENDOMETRIAL CARCINOMA BASED ON 2009 FIGO STAGING

Stage IA grade 1 or 2 endometrioid carcinoma with risk factors for recurrence (age > 60, LVSI)
Stage IA grade 3 endometrioid carcinoma, without substantial LVSI
Stage IB grade 1 or 2 endometrioid carcinoma, without substantial LVSI
Stage IB grade 3 endometrioid carcinoma, without LVSI and negative SLNBx
Stage II grade 1 or 2 endometrioid endometrial carcinoma, with microscopic stromal invasion and negative SLNBx
Myoinvasive stage IA serous carcinoma, clear cell carcinoma, or carcinosarcoma, with intended chemotherapy

LVSI, lymphovascular space invasion; SLNBx, sentinel lymph node biopsy.

For IB grade 3 disease, EBRT remains the standard modality, as these patients were not eligible for PORTEC-2. The Gynecologic Oncology Group (GOG)-249 showed equivalent oncologic outcomes between pelvic EBRT ± VBT versus VBT plus three cycles of carboplatin/paclitaxel, for patients with FIGO high-intermediate-risk stage I endometrioid, FIGO stage II endometrioid, and FIGO stage I to II serous/clear cell carcinomas.[29] However, VBT alone could be considered for select patients with IB, grade 3 endometrioid disease, without LVSI and negative pelvic lymph nodes.[28]

For stage II disease, EBRT ± VBT is considered the standard-of-care.[30] However, a multiinstitutional analysis suggested that VBT monotherapy alone could be sufficient for patients with stage II, grade 1 or 2 disease and microscopic cervical stromal invasion who underwent pelvic lymphadenectomy, given the low 5-year vaginal (2.6%) and pelvic (4.2%) failure rates.[31]

Regarding high-risk histologies, vaginal brachytherapy with chemotherapy could be considered for patients with myoinvasive FIGO stage IA serous carcinoma,[32] clear cell carcinoma,[33] or carcinosarcomas.[34,35] Vaginal brachytherapy without chemotherapy could be considered in patients with small polyp-confined serous or clear cell carcinoma.[36]

Technique

It is imperative to perform a speculum examination to ensure adequate healing of the vaginal cuff in order to avoid inadvertent perforation. VBT should be performed between 4 and 8 after hysterectomy. During the speculum exam, fiducial markers could be inserted into the vaginal apex if fluoroscopy is used for conformation of vaginal cylinder placement.

Following this, a vaginal cylinder can be inserted into the vagina. Vaginal cylinders are most often single-channel and span 2 to 4 cm in diameter. The largest cylinder that can fit snugly against the vaginal cuff should be utilized to minimize dose inhomogeneity. Oral pain medications and/or topical anesthesia may be needed to reduce discomfort during the insertion process. The position of the cylinder is then fixed with an external immobilization device. The patient can then undergo imaging. If fiducial markers were inserted, fluoroscopic imaging should show the cylinder near the fiducial markers, provided that the markers did not migrate. If a CT simulation is utilized, the cylinder should fit closely against the vaginal cuff without air gaps.

Treatment Planning

The most commonly used dose fractionation regimen for VBT is 7 Gy × 3 fractions to 5 mm depth, as prescribed from the PORTEC-2 trial.[25] For most patients, the upper 3 to 5 cm of the vaginal length can be treated. However, the whole vaginal length can be treated if pathology demonstrates high-risk histology, grade 3 disease, or LVSI. 2D-treatment planning can be utilized for patients undergoing fluoroscopy. For patients undergoing CT, both 2D or 3D treatment planning can be used. Further details can be found in guidelines from the ABS.[37]

Follow-up

Patients should be counseled regarding the use of vaginal dilators and resumption of sexual activity to prevent vaginal stenosis. Pelvic examination should be conducted every 3 to 6 months for up to 5 years, then annually. Common toxicities of VBT include fatigue, urinary symptoms, vaginal stenosis, and sexual dysfunction.

Vaginal Cuff Recurrences

Clinical Indications

HDR brachytherapy can be utilized in combination with EBRT for the definitive treatment of vaginal recurrences after hysterectomy. Eligible patients should have biopsy-proven recurrence and disease localized to the vagina without or with pelvic lymph nodes on staging imaging (ie, PET and MRI). Patients with a prior history of radiation therapy may be eligible if a definitive dose can be given to the target volume while accounting for previous dose to OARs.[38,39] Recent studies of image-guided brachytherapy have reported 2- to 3-year local control rates surpassing 90%.[40–42]

EBRT consists of treating pelvic lymph nodes and the vaginal cuff (40-45 Gy), while chemotherapy could be considered if patients have large (>4 cm) cuff recurrences or pelvic nodal disease. A repeat MRI, preferably with vaginal jelly, should be performed toward the end of EBRT. Nonbulky recurrences with a residual thickness <0.5 cm can be considered for intracavitary brachytherapy boost, preferably with a multichannel cylinder.[43] All other cases should be treated with interstitial brachytherapy under anesthesia, per guidelines from the ABS.[38]

Technique

Patients who are candidates for a multichannel cylinder can typically be treated on an outpatient basis. After applicator insertion, a CT simulation scan is required. MR simulation could also be considered to better define the location of the tumor with respect to the multichannel cylinder. Treatment planning then commences.

Patients who require an interstitial applicator typically undergo anesthesia. First, a careful exam under anesthesia is performed to better define the radial and proximal-distal extent of disease within the vaginal cuff. A urinary catheter is also inserted. A template-based applicator, most commonly a Syed applicator, is then inserted. A central obturator is inserted through the template and into the vaginal cuff. Following this, needles are inserted into the holes at predefined spaces around the central obturator. Care should be taken to ensure that the inserted needles can allow for adequate coverage of the disease. Finally, the template is sutured to the perineum. Once the applicator is placed, the patient can undergo planning scans with CT without or with MRI.

Treatment Planning

Recent ABS guidelines recommend prescription doses of EBRT with brachytherapy between 75 and 79 Gy.[38] These doses can be achieved with an EBRT dose of 45 Gy in 25 fractions and a brachytherapy dose of 25 Gy in five fractions. Target volume delineation guidelines are now available from the GEC-ESTRO, ABS, and the Canadian Brachytherapy Group (CBG) for image-guided adaptive brachytherapy in the setting of vaginal recurrences.[44] On the treatment planning scan, the GTV is the residual disease noted on treatment planning imaging. The HR-CTV is the GTV plus areas on imaging and examination that are concerning for harboring microscopic disease. The IR-CTV, which represents all potentially significant microscopic disease, is defined as the GTV at diagnosis plus the HR-CTV plus an expansion of 0.5 cm. The normal remaining vagina outside the target volume should be contoured as an OAR. OAR dose constraints can be adopted from cervical cancer (D2cc < 65 Gy for rectum, D2cc < 70 Gy for sigmoid, and D2cc < 80 Gy for bladder). An example treatment plan is provided in Figure 24.2.

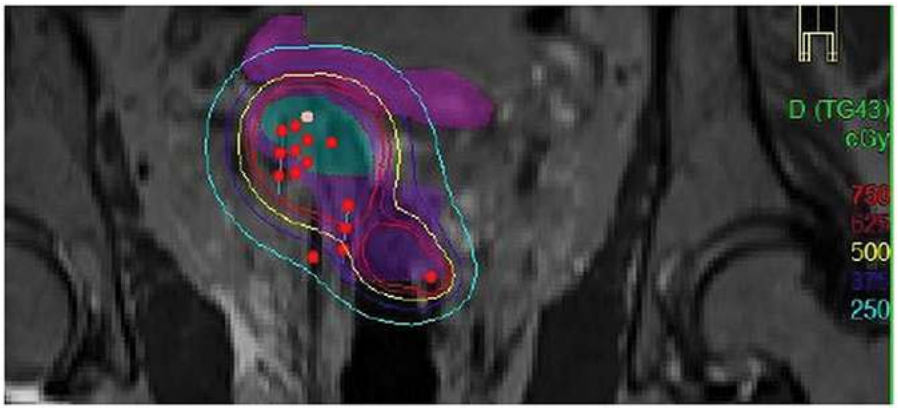

FIGURE 24.2 Coronal view of MR-guided HDR brachytherapy (25 Gy/5 fx) for recurrent endometrial cancer, treated with chemoradiation therapy (45 Gy/25 fractions). The patient had a template-based interstitial applicator placed with a central obturator and 14 interstitial needles. Contours: HR-CTV—cyan; IR-CTV—dark purple; sigmoid—light purple. Target volume dosimetry metrics in $EQD2_{10}$ were HR-CTV D90 96.4 Gy and IR-CTV D98 65.0 Gy. OAR dosimetry metrics in EQD_3 were rectum D2cc 55.1 Gy, bladder D2cc 82.8 Gy, sigmoid D2cc 71.0, and bowel D2cc 44.5 Gy.

Follow-up

Similar to VBT, patients who undergo treatment for vaginal cuff recurrences should undergo a pelvic examination every 3 to 6 months for 5 years, and then annually. This patient population is at a higher risk of developing bowel and bladder toxicities and, as such, requires close follow-up.

Inoperable Endometrial Carcinoma

Clinical Indications

About 5% to 10% of patients with endometrial carcinoma cannot undergo staging hysterectomy due to medical comorbidities.[45] Such patients could be candidates for HDR brachytherapy. Numerous retrospective series have demonstrated favorable outcomes with HDR brachytherapy alone or in combination with EBRT.[46-48] Such patients should undergo a biopsy to determine tumor grade. Staging with PET for detecting distant disease plus MRI for characterizing the depth of myometrial invasion is recommended.

Per ABS guidelines, patients with FIGO stage I, grade 1 or 2, disease with minimal myometrial invasion on MRI are candidates for HDR brachytherapy alone. Patients with FIGO stage I disease, who have deep myometrial invasion (>50%) on MRI or grade 3 pathology, or stage II disease, should undergo a combination of EBRT and BT.[49]

Technique

During the procedure, the patient is placed in dorsal lithotomy position and examined under anesthesia. A Foley catheter is inserted, and the cervix can be serially dilated, potentially under ultrasound guidance. A variety of applicators are available, including single tandem with ovoids, modified Heyman capsules,[50] double tandem applicators,[51] and triple tandem applicators.[52] Once the applicator is inserted, the vagina is packed, and the applicator is fixed in place.

Treatment Planning

The GTV encompasses the T2 weighted abnormality. The CTV encompasses the entire uterus, cervix, and upper 1 to 2 cm of the vagina. OARs include the sigmoid, rectum, bladder, bowel, and uninvolved lower third of the vagina. Both CT and MRI-based treatment planning can be done. Prescription dose targets include a CTV D90 of 48 (6 Gy × 6) to 62.5 (5 Gy × 10) Gy for the monotherapy setting and a CTV D90 of 65 to 75 Gy in total $EQD2_{10}$ for the combination setting.

Follow-up

Pelvic examination should be done every 3 to 6 months for 2 to 3 years, every 6 to 12 months for up to 5 years, and then annually.

PROSTATE CANCER

Clinical Indications

HDR prostate brachytherapy is a suitable option for the definitive treatment of prostate cancer. For low-risk and favorable intermediate-risk (FIR) disease, HDR brachytherapy can be delivered over two fractions as monotherapy. For unfavorable intermediate-risk (UIR) or high-risk disease, HDR brachytherapy can be delivered over one or two fractions in combination with EBRT.[53] There has also been increasing literature on the utilization of HDR brachytherapy as a salvage therapy for radiorecurrent prostate cancer in which there is persistent or recurrent prostate cancer after prior radiotherapy (RT).[54]

HDR brachytherapy involves the insertion of hollow catheters into the prostate gland under transrectal ultrasound (TRUS) guidance, most often with general or spinal anesthesia. A scan of the prostate with needles-in-place is then obtained using CT, TRUS, or MRI. The prostate and OARs (ie, urethra and rectum) are contoured. A treatment plan ensuring adequate prescription dose to the entire prostate while also satisfying OAR constraints is created. After quality assurance, the radiation is then delivered by a remote afterloader, in a shielded room. After treatment, the applicator is removed. The patient will not retain any radioactivity after the procedure.

HDR brachytherapy has certain dosimetric advantages compared with alternative radiotherapeutic techniques. Compared with low-dose-rate (LDR) brachytherapy, HDR brachytherapy provides more consistent dosimetry and treatment plans, due to the ability to optimize individual dwell positions along the implanted catheters.[55] Compared with EBRT/stereotactic body radiation therapy (SBRT) techniques, HDR brachytherapy may provide higher intraprostatic doses while still meeting rigid rectal dose constraints due to the rapid dose falloff with the lower energy Ir-192 source (average energy 380 keV). A phase 2 study involving TRUS/MR fusion at the time of HDR brachytherapy demonstrated that marked dose escalation to the dominant intra-prostatic lesion (DIL) (D90 142.7%; range 131.4%-151.7%) could be achieved while still achieving OAR constraints.[56] This degree of dose escalation likely surpasses the dose escalation that could be achieved with focal EBRT or SBRT boosts.[57-59]

Table 24.4 lists key eligibility criteria for prostate HDR brachytherapy. In general, patients should have sufficient life expectancy (≥10 years for intermediate risk and >5 years for high risk). Patients should have adequate urinary function, often reflected as an International Prostate Symptom Score (IPSS) ≤ 15. Special consideration should be made for patients with large prostate glands (≥60), due to concern for pubic arch inteference,[60] as well as large trans-urethral resection of prostate (TURP) defects.[61] For the latter, careful attention to dosimetry, particularly at interfaces between the remnant prostate and adjacent OAR (eg, urethra and bladder neck), may be necessary. Absolute contraindications for HDR prostate brachytherapy include inability to tolerate general or spinal anesthesia in the dorsal lithotomy position, absence of a rectum, active inflammatory bowel disease, or unacceptable operative risks.

TABLE 24.4 KEY ELIGIBILITY CRITERIA FOR PROSTATE HDR BRACHYTHERAPY

Key Eligibility Criteria
Sufficient life expectancy (>5 y)
IPSS ≤ 15
Prostate gland size ≤ 60 cm^3
No prior TURP
Amenable to undergo general anesthesia

Before brachytherapy, a comprehensive preanesthesia work-up is necessary to minimize the risk of unexpected medical events during the procedure. Screening colonoscopy could be considered for patients who have not had a colonoscopy within 3 years before the prostate cancer diagnosis in order to detect asymptomatic colorectal cancer and minimize the risk of unnecessary biopsies, which could lead to severe rectal complications in the years immediately after brachytherapy.[62]

Specific indications of HDR brachytherapy in favorable, unfavorable, and radiorecurrent disease settings will be reviewed in the following sections.

Outcomes

Favorable Disease

HDR brachytherapy is a standard-of-care treatment option for low-risk and FIR disease. HDR brachytherapy can be performed as monotherapy without the addition of androgen deprivation therapy (ADT). Historically, HDR brachytherapy involved the delivery of multiple fractions over a few days. Previously published regimens included the delivery of 6 to 6.5 Gy × 7 to 9 fractions over one implant,[63] 9.5 Gy × 4 fractions over two implants,[64] 7 Gy × 6 fractions over three implants,[65] and 10.5 to 11.5 Gy × 3 fractions.[66,67] However, over the past decade, the contemporary practice of HDR brachytherapy has drifted toward fewer fractions, with many practicing 13.5 Gy × 2 fractions over two implants.[68] Table 24.5 shows the outcomes from select HDR monotherapy series.

TABLE 24.5 SELECT MULTIFRACTION HDR MONOTHERAPY SERIES WITH CANCER CONTROL AND TOXICITY OUTCOMES

Author	Single or Multi	Type of Study	Year of Study	Treatment	ADT	Patients (*n*)	Risk Stratification	Median Follow-up	Biochemical Progression-Free Survival	GU Toxicity	
Morton et al[68,69] (Sunnybrook)	Single	Randomized	2013-2015	19 Gy × 1	None	87	Low: 19% Favorable int: 51% Unfavorable int: 30%	5.0 y	5-y bPFS: 73.5%	5-y CI late G2: 60.0% G3: 2.4%	5 (
				13.5 Gy × 2	None	83			95%	G2: 46.6% G3: 0%	(
Yoshioka et al[63] (Japan multicenter)	Multi (5)	Retrospective	1995-2013	13.5 Gy × 2: 13% 6.5 Gy × 7: 32% 7 Gy × 7: 28% 6 Gy × 9: 25% Other: 2%	ADT: None: 39% <1 y: 21% 1-3 y: 10% >3 y:	524	Low:14% Int:40% High:46%	5.9 y	5-y bPFS: 92%	5-y CI late G2-G3: 19% G3: 1%	5 (
Jawad et al.[64] (William Beaumont)	Single	Retrospective	1999-2013	9.5 Gy × 4	Yes: 19% No: 81%	319	Low: 73% Int: 27%	5.5 y	5-y bPFS 97%	Late G2/G3 frequency: 19%/1%	L
				12 Gy × 2	Yes: 5% No: 95%	79	Low: 61% Int: 39%	3.5 y	87%	23%/0%	3
				13.5 Gy × 2	Yes: 3% No: 97%	96	Low: 58% Int: 42%	2.9 y	90%	20%/3%	1
Hauswald et al[65] (CET/UCLA)	Single	Retrospective	1996-2009	43.5 Gy/6 fx	ADT: Yes: 9% No: 91%	448	Low: 64% Int: 36%	6.5 y	6/10-y bPFS: 98.6%/97.8%	Late G3-4: 4.9%	L
Hoskin et al[66] (Mt Vernon)	Single	Prospective	2005-2013	19-20 Gy × 1	74% (6.9 mo)	49	Int: 57% High: 43%	4.1 y	4-y bPFS: 94%	4-y G2+/G3: 15%/2%	4
				13 Gy × 2	76% (6.4 mo)	138	Int: 50% High: 50%	5.3 y	93%	11%/2%	2
				10.5 Gy × 3	87% (6.3 mo)	106	Int: 46% High: 54%	9 y	91%	33%/11%	6
Strouthos et al[67] (University of Frankfurt)	Single	Retrospective	2008-2012	11.5 Gy × 3	ADT: Yes: 12.8% No: 87.2%	450	Low: 44% Int: 30% High: 26%	4.7 y	5-y bPFS: 95.0%	Late G2/G3: 14.2%/0.8%	L (

ADT, androgen deprivation therapy; bPFS, biochemical progression-free survival; CI, cumulative incidence; GI, gastrointestinal; GU, genitourinary.

There are no randomized trials comparing HDR brachytherapy monotherapy with alternative modalities. However, a single-institution randomized trial from the Sunnybrook Odette Cancer Centre randomized 170 patients with low (19%), favorable intermediate (51%), or UIR (30%) disease to either two-fraction (13.5 Gy × 2) or single-fraction (19 Gy × 1) HDR monotherapy without ADT. The 5-year biochemical disease-free survival was 95% versus 73.5% (P =.001) for the two-fraction versus single-fraction arms. Respective cumulative incidences of

local failure were 2.8% and 29.4.[68] A follow-up study reported respective 5-year cumulative incidences of grade 2+ GU toxicity (47% vs 62%), grade 3 GU toxicity (0% vs 2%), and grade 2 GI toxicity (9% vs 12%). There was no difference in mean urinary or bowel health related quality of life (HRQOL) at 2 to 5 years from baseline in the two-fraction arm, although differences were noted for sexual QOL.[69] This trial demonstrated high-intermediate-term oncologic control for the two-fraction arm. This trial also showed that single-fraction HDR brachytherapy yielded poor biochemical control results that were consistent with other single-arm prospective series, some of which utilized dose escalation beyond 19 Gy.[70–73]

Unfavorable Disease

HDR brachytherapy is also a standard-of-care treatment option for UIR and HR disease. For this scenario, HDR brachytherapy is typically performed in combination with pelvic or prostate-only EBRT as well as ADT. Contemporary fractionation schemes for HDR brachytherapy include 9.5 to 10 Gy × 2 fractions over one implant[3] as well as 15 Gy × 1[74] fraction. Acceptable EBRT doses are 45 to 50.4 Gy over 25 to 28 fractions or 37.5 Gy over 15 fractions. Standard ADT durations include 6 months for UIR disease and 18 months for high-risk disease.[75] Table 24.6 shows the outcomes from select HDR boost series.

TABLE 24.6 SELECT COMBINATION EBRT AND HDR BRACHYTHERAPY BOOST SERIES WITH CANCER CONTROL AND TOXICITY OUTCOMES

Author	Single or Multi	Type of Study	Year of Study	Treatment	ADT	Patients (*n*)	Risk Stratification	Median Follow-up	Biochemical Progression-Free Survival	GU Toxicity
Hoskin et al[76] (Mt Vernon)	Single	Randomized	1997-2005	EBRT (55 Gy/20 fx)	Yes: 76%	108	Low: 7% Int: 40% High: 53%	7.1 y	7 y: 48%	Dische severe (7 y): 30%
				EBRT (35.75 Gy/13 fx) + BT (8.5 Gy × 2)	Yes: 76%	110	Low: 2% Int: 44% High: 54%		7 y: 66% (*P* =.04)	31% (*P* =.5)
Hsu et al[3] (RTOG 0321)	Multi (14)	Prospective	2004-2006	EBRT (45 Gy/25 fx) + HDR (9.5 Gy × 2)	Yes: 43%	125	Int: 76% High: 16% Very high: 8%	NA	5/10 y: 14%/23% Local failure: 2%/2%	5/10-y rate (G3-5: 4%
Helou et al[74,77] (Sunnybrook)	Single	Prospective	2005-2007	HDR (15 Gy × 1) + EBRT (37.5 Gy/15 fx)	0%	123	GS6: 7% GS7: 93%	6.1 y	5 y bPFS: 97.4%	Late G2/G3: 59%/4%
		Prospective	2004-2005	HDR (10 Gy × 2) + EBRT (45 GY/25 fx)	0%	61	GS6: 20% GS7: 80%	8.3 y	92.7%	—
Martell et al[78] (Sunnybrook)	Single	Retrospective	2009-2016	HDR (15 Gy × 1) + EBRT (37.5 Gy/15 fx)	Yes: 16% No: 80%	518	FIR: 28% UIR: 72%	5.2 y	5 y FFBF: FIR: 94% UIR: 89%	—
Tharmalingam et al[79] (Mt Vernon)	Single	Retrospective	2009-2013	HDR (15 Gy × 1) + EBRT (37.5 Gy/15 fx	<6 mo: 9% 6-12 mo: 20% 12-18 mo: 11 mo	812	Int: 21% High: 79%	4.7 y	5 y bPFS Whole pelvis: 89% Prostate only: 81%	Any G3 tox all time po

Author	Single or Multi	Type of Study	Year of Study	Treatment	ADT	Patients (*n*)	Risk Stratification	Median Follow-up	Biochemical Progression-Free Survival	GU Toxicity
				or 46 Gy/23 fx)	≥18 mo: 59%					
Joseph (TROG RADAR)[75]	Multi	Randomized (6 vs 18 mo ADT)	2003-2007	66 Gy EBRT	6 mo: 50% 18 mo: 50% (randomized)	125	FIR/UIR/Hi: 2%/42%/56%	10.5 y	10 y LP/DP: 12.3%/26.1%	—
				70 Gy EBRT		427	4%/40%/57%		7.5%/26.7%	—
				74 Gy EBRT		262	3%/28%/69%		7.3%/24.9%	—
				46Gy/23 fx EBRT + HDRB (6.5 Gy × 3)		237	0%/14%/86%		2.2%/19.7%	—

ADT, androgen deprivation therapy; bPFS, biochemical progression-free survival; CI, cumulative incidence; DP, distant progression; FFBF, freedom from biochemical failure; FIR, favorable intermediate risk; GI, gastrointestinal; GU, genitourinary; LP, local progression; UIR, unfavorable intermediate risk.

One randomized trial from Mount Vernon Hospital in the United Kingdom compared combination EBRT + HDR brachytherapy boost against EBRT alone. In this trial, 218 patients, mostly with intermediate- or high-risk disease, were randomized to EBRT (55 Gy in 20 fractions) versus combination EBRT (35.75 Gy in 13 fractions), followed by HDR brachytherapy boost (8.5 Gy × 2 fractions). The 12-year relapse-free survival estimates were 55% and 27%, respectively. There were no differences in severe genitourinary, gastrointestinal, or urethral strictures between arms. Of note, doses for the EBRT alone and EBRT + HDR brachytherapy boost arms were lower than contemporary doses.[76]

Radiation Therapy Oncology Group (RTOG) 0321 was a multi-institutional prospective single-arm trial of 129 patients who underwent EBRT (45 Gy in 25 fractions) followed by HDR brachytherapy boost (19 Gy in two fractions). All patients had intermediate- or high-risk disease, and 43% received ADT. At a median follow-up of 10 years, biochemical, local, and distant failure rates at 10 years were 23%, 2%, and 8%, respectively. The 10-year rate of late grade 3 GI and GU adverse events was 4% and 5%. This trial demonstrated the feasibility of combination therapy in a cooperative group setting.[3]

There has also been a trend toward single-fraction HDR brachytherapy boost regimens. A single-arm prospective trial from the Sunnybrook Odette Cancer Centre enrolled 123 men with predominantly intermediate-risk disease who received HDR brachytherapy (15 Gy in one fraction), followed by hypofractionated EBRT (37.5 Gy in 15 fraction). The 5-year bPFS of 97.4% was comparable with the 92.7% rate observed in a historical series of 61 men who received a 2-fraction HDR boost (10 Gy × 2 fraction) followed by EBRT (45 Gy in 25 fractions).[74] In a follow-up analysis of the single-fraction regimen, rates of late GU grade 2 and grade 3 toxicities were 59% and 4%, respectively. Corresponding rates of late GI toxicities were 19% and 0%. Larger prostate volume was associated with late GU 2+ urinary toxicity.[77]

Pelvic radiation therapy could be considered for patients with high-risk disease undergoing combination HDR brachytherapy boost. In a study of 812 patients who received 15 Gy × 1 HDR brachytherapy boost from Mt Vernon Hospital, 5-year bPFS was 89% for patients who received whole pelvic RT versus 81% for prostate-only RT, with the benefit of whole pelvic RT observed only in the high-risk subgroup (84% vs 77%; P =.001). The prevalence of grade 3+ toxicity was no greater than 1.5% across all time points.[79]

The optimal duration of ADT for patients undergoing combination HDR brachytherapy remains unknown. However, there may still be a benefit of prolonged ADT for such patients. The TROG 03.04 RADAR trial randomized patients with locally advanced prostate cancer to 6 versus 18 months of ADT. Patients were stratified by RT regimen, which included 66 Gy, 70 Gy, or 74 Gy EBRT, or 46 Gy EBRT plus HDR boost (19.5 Gy in three fractions). The trial demonstrated that 18 months of ADT reduced distant progression independently of radiation dose for all patients (sub-distribution hazard ratio [sHR] 0.70; 95% CI 0.50-0.87; P =.002), including the HDR brachytherapy subgroup (sHR 0.61; 0.38-0.97; P =.036). Reported cumulative incidences of 10-year local progression/distant progression were 2.2%/19.7% for HDR boost, compared with 7.3%/24.9% for 74 Gy,

7.5%/26.7% for 70 Gy, and 12.3%/26.1% for 66 Gy EBRT.[75] Of note, patients who received HDR brachytherapy boost were more likely to have stage T3 or T4 (64.1% vs 24.8%-31.7%) and grade group 4 to 5 (51.1% vs 27.2%-34.3%) tumors, compared with the EBRT dose groups.

Radiorecurrent Disease

The role of salvage HDR brachytherapy for the treatment of radiorecurrent prostate cancer continues to evolve. Most evidence involves single-institutional prospective series with short-term or intermediate-term oncologic follow-up. Furthermore, these institutional series varied with respect to fractionation regimens (6 Gy × 6,[80] 8 Gy × 4,[81] 10 Gy × 3,[82] 10.5 Gy × 2,[83] 19 Gy × 1[84]), treatment volumes (whole-gland vs focal[83,84]), and initial staging, with more recent series[84] incorporating prostate-specific membrane antigen (PSMA) PET imaging. A recent meta-analysis reported that HDR brachytherapy was associated with less severe genitourinary toxicity (9.6% vs 20.0%; P <.001) and gastrointestinal toxicity (0 vs 1.8%; P <.01), but similar oncologic efficacy (59.7% vs 53.9%) at 5 years, compared with salvage radical prostatectomy.[85]

More stringent eligibility criteria should be applied in the salvage setting. Patients should have a prostate size ≤45 cc, an IPSS score ≤15, a >30-month interval since prior RT, as well as resolution of grade 2+ GI or GU toxicity per RTOG 0526, a multiinstitutional phase 2 study of salvage LDR brachytherapy.[86] Ideal candidates should have isolated disease localized only within the prostate on PSMA-PET staging because this modality is more sensitive than conventional and even 18F-fluciclovine PET for the detection of metastases.[87,88] Post-RT biopsies documenting pathologic evidence of radiorecurrent disease are warranted, given the small potential for significant GI/GU toxicity with salvage HDR brachytherapy.

Technique

For HDR brachytherapy, the needle insertion procedure is performed under general or spinal anesthesia with the patient in dorsal lithotomy position. Needles are inserted into the prostate gland under TRUS guidance. For whole-gland treatments, approximately 16 needles can be placed (12 peripherally, four centrally) to allow for comprehensive dosimetric coverage of the entire prostate gland.[53] Additional needles can be placed into the dominant intraprostatic GTV if focal boost is performed. TRUS/MR fusion may help in identifying the GTV on TRUS imaging.[89]

Treatment Planning

CT-based treatment planning is widely available in most radiation oncology departments. A key advantage of CT-based planning is that multiple fractions can be delivered, typically 6 hours apart, after the CT simulation scan. In fact, two-fraction HDR monotherapy delivered in 1 day after a single implant has been reported as safe and efficacious.[90] Key disadvantages of this monotherapy are as follows: First, catheters may migrate caudally after the patient is moved out of the dorsal lithotomy position. Cystoscopy while the patient is in the supine position or catheter manipulations at the time of CT simulation could help ensure that catheters reach the prostate base. Second, the prostate may be difficult to contour due to a lack of contrast between the prostate and surrounding tissues. Fiducial markers placed within the prostate could aid in identifying the prostate base and apex. MRI, if available, could assist in prostate delineation due to superior soft-tissue contrast. Third, catheter migration, typically caudal, may occur between CT simulation and treatment delivery.[91,92] Pretreatment imaging verification utilizing x-rays, cone-beam CTs,[93] or CT[94] is recommended. Catheter or treatment plan adjustments could then be made.

Ultrasound-based treatment planning is typically performed at institutions with access to an operating room appropriately shielded for HDR brachytherapy. A key advantage of ultrasound-based brachytherapy is that treatment planning and delivery can be performed in the dorsal lithotomy position. Moving the patient out of the lithotomy position, which is required for CT- or MR-based planning, could lead to the caudal displacement of catheters.[95] Furthermore, time to treatment delivery can be minimized without patient movement. However, only one treatment can be delivered with ultrasound-based treatment planning, such that patients who require two fractions need to undergo a repeat ultrasound-guided implant or repeat treatment planning in the supine position with CT or MRI. Furthermore, prostate contouring and needle digitization can be challenging in the presence of needle artifacts.

Treatment planning should be performed to maximize coverage of the prostate while minimizing OAR doses. Sample OAR constraints are listed in Table 24.7. An example of a TRUS-based treatment plan is provided in Figure 24.3.

TABLE 24.7 TARGET VOLUME AND OAR CONSTRAINTS FOR HDR BRACHYTHERAPY

	HDR Monotherapy From Sunnybrook Randomized Trial[68]	GEC-ESTRO for HDR Boost[96]	GEC-ESTRO for HDR Boost (15 Gy)[96]
Prostate	V100 > 95%, V150 < 35%; V200 < 12%	V100 > 95%; D90 > 100%; V150 ≤ 40%	V100 > 95%; D90 > 100%; V150 ≤ 40%
Urethra	Urethra D_{max} < 120%; D10 < 115%	D10% ≤ 120 Gy EQD2 D30% < 105 Gy EQD2	D10 ≤ 17 Gy D30 ≤ 15 Gy
Rectum	Dmax 90%; V80 < 0.2 cc	D2cc ≤ 75 Gy EQD2	D2cc ≤ 10 Gy

EQD2 dose constraints represent the sum of a combination of EBRT and HDR doses.
EQ2D, equivalent dose in 2-Gy fractions.

FIGURE 24.3 Axial view of ultrasound-based HDR brachytherapy (15 Gy/1 fx) for high-volume unfavorable intermediate-risk prostate cancer (Gleason 4+3, 9/12 cores), treated with ADT and pelvic EBRT (45 Gy/25 fractions). The patient had a template-based interstitial applicator placed with 23 interstitial needles for a 40.4 cc gland. Contours: Prostate—red; DIL—blue; urethra—yellow; rectum—brown. Target volume metrics included prostate V100 95.7%, prostate V150 29.9%, prostate V200 6.2%, urethra D0.1 cc 113.75%, bladder D2cc 63.2%, and rectum D0.1 cc 84.2%. The D90 to the DIL was 145.9%.

Follow-up

Patients treated with HDR brachytherapy in any setting should undergo regularly scheduled follow-up to monitor treatment response with serial prostate specific antigen (PSA) values and manage potential acute and late toxicities. Follow-up exams should be performed every 6 months for the first 5 years, and yearly thereafter. Prompt urology referral should be considered if the patient has urologic symptoms, despite alpha-adrenergic antagonists, and negative urinalysis/urine culture. Gastroenterologists who perform a colonoscopy after brachytherapy should be informed that the patient had prior brachytherapy, in order to decrease the risk of unnecessary biopsies that could lead to severe rectal complications.

BREAST CANCER

Clinical Indications

Many patients with early-stage breast cancer are candidates for breast conservation therapy, which consists of lumpectomy followed by RT rather than mastectomy. The most common method of RT involves whole breast irradiation (WBI) using EBRT. Typical WBI regimens include conventionally fractionated regimens (5-6 weeks), moderately hypofractionated regimens (3-4 weeks),[97] and more recently ultrahypofractionated regimens (1 week).[98]

However, over the past two decades, there has been increasing interest in accelerated partial breast irradiation (APBI) for patients with very favorable risk disease. APBI consists of delivering a similar biologically equivalent radiation dose as WBI, but to a much smaller volume consisting of the lumpectomy cavity plus 1 to 2 cm margin over 1 week.[99]

Patients with favorable risk disease are ideal candidates for APBI. The ABS recommends consideration of APBI in patients who are at least 45 years old, with invasive histology or ductal carcinoma in situ (DCIS).[99] Additional criteria include tumor size ≤3 cm, negative nodes, any estrogen receptor (ER) status, negative human epidermal growth factor receptor (Her)-2 status, and no extensive LVSI. Patients should have no tumor on ink for invasive disease and ≥2 mm margins for DCIS. Eligibility recommendations from the ABS, American Society of Radiation Oncology, and GEC-ESTRO are provided in Table 24.8.

TABLE 24.8 OPTIMAL ELIGIBILITY CANDIDACY FOR APBI MONOTHERAPY PUBLISHED BY VARIOUS MEDICAL SOCIETIES

	ABS[99]	ASTRO (Suitable)[100]	GEC-ESTRO (Low-Risk)[101]
Age	≥45	≥50	≥50
Histology	All invasive carcinoma histologies	Invasive ductal or other favorable subtypes (mucinous, tubular, colloid)	Invasive ductal, mucinous, tubular, medullary, colloid
DCIS	Allowed	Low-risk DCIS defined as: screen-detected, low to intermediate nuclear grade, ≤2.5 cm in size, resected with negative margins ≥3 mm	Not allowed
Tumor size	≤3 cm	≤2 cm (T1)	≤3 cm
Grade	Any	Any	Any
Multicentricity	NS	Unicentric only	Unicentric
Multifocality	NS	Clinically unifocal with total size ≤2 cm	Unifocal
ER	Any	Positive	Any
Her2 receptor	Negative	NS	NS
LVSI	Not allowed (extensive)	No	Not allowed
Extensive intraductal component	NS	No	Not allowed
Associated LCIS	NS	Allowed	Allowed
Margins	No tumor on ink for invasive and≥2 mm margin for DCIS.	Negative by at least 2 mm	Negative by at least 2 mm
Node	Negative	Negative	Negative

ABS, American Brachytherapy Society; APBI, accelerated partial breast irradiation; ASTRO, American Society of Radiation Oncology; DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; GEC-ESTRO, Groupe Européen de Curiethérapie European Society for Radiation Oncology; NS, not specified.

APBI has been associated with low rates of risk of in-breast tumor recurrence (IBTR) (<5% at 10 years)[5,102-105] that are comparable to WBI in randomized trials. Furthermore, APBI has been associated with improved late toxicity[5] and cosmesis[105-107] compared with WBI. APBI arms have included multiple forms of RT, including EBRT (3D conformal radiation therapy [3DCRT][103,108] and intensity-modulated radiation therapy [IMRT][102,104,105]), intraoperative radiotherapy (IORT)[107,109] and HDR brachytherapy (BT).[5,103,106] HDR-BT is an attractive modality for APBI, due to the ability to obtain a highly conformal dose distribution around the lumpectomy cavity with less scatter dose to surrounding structures.

The two main forms of HDR-BT include intracavitary and interstitial brachytherapy. Intracavitary brachytherapy involves the insertion of a device into the lumpectomy cavity through a single point of entry. These applicators include balloon (eg, single-lumen or multilumen) and hybrid (eg, strut-based) systems. Although single-lumen balloon systems only allow for relatively spherical dose distributions, multilumen balloon and hybrid intracavitary systems allow for increased dose modulation for sparing surrounding OARs, such as the skin and ribs.[110,111] Interstitial brachytherapy, on the other hand, involves the insertion of multiple catheters across the

lumpectomy cavity. Although interstitial brachytherapy can provide conformal dosimetric coverage across nonspherical geometries, these implants are technically challenging.[112,113] Both forms of HDR brachytherapy are discussed below.

Outcomes

Three randomized trials comparing WBI and APBI have included HDR brachytherapy on the APBI arms (Table 24.9). Two trials have involved interstitial brachytherapy. The GEC-ESTRO group randomized 1,328 patients between 2004 and 2009 to WBI (50 Gy/25 fractions + 10 Gy boost) versus APBI (30.1 Gy/7 fractions or 32 Gy/8 fractions HDR over 5 days, or 50 Gy pulse dose rate). APBI was deemed noninferior to WBI with respect to 5-year local recurrence (1.44% vs 0.92%; P =.42).[114] The 10-year in-breast tumor recurrence rates (IBTR) were 3.51% for APBI versus 1.58% for WBI (P =.074). APBI was associated with lower late grade 3+ side effects (1% vs 4%; P =.021).[5]

TABLE 24.9 RANDOMIZED PHASE III TRIALS IN APBI MONOTHERAPY

Trial	Patients (*n*)	Year Enrolled	APBI Regimen	WBI Regimen	Median Follow-Up (years)	In-Breast Tumor Recurrence	Toxicity or Cosmesis
NSABP B-39/RTOG 0413 (Vicini et al[103])	4216	2005-2013	EBRT: 38.5 Gy in 10 fx twice a day IC: 34 Gy in 10 fx twice a day IS: 34 Gy in 10 fx twice a day	50 Gy WB EBRT ± boost	10.2	10-y: APBI: 4·6% WBI: 3.9%	Grade 3 toxicity: APBI: 10% WBI: 7%
GEC-ESTRO (Strnad et al[5])	1328	2004-2009	IS HDR: 32 Gy in 8 fx or 30.1 Gy in 7 fx IS PDR: 50 Gy	50 Gy + boost WB EBRT	10.36	10-y: APBI: 3.51% WBI: 1.58%	Late grade 3 toxicity: APBI: 1% WBI: 4%
NIO (Polgár et al[106])	258	1998-2004	IS: 36.4 Gy in 7 fx EBRT: 50 Gy	50 Gy WB EBRT	17	20-y: APBI: 9.6% WBI: 7.9%	Excellent or good cosmesis: APBI: 79.2% WBI: 59.5%

APBI, accelerated partial breast irradiation; EBRT, external beam radiation therapy; IC, intracavitary; IS, interstitial; WB, whole breast; WBI, whole breast irradiation.

The National Institute of Oncology from Hungary randomized 258 patients between 1998 and 2004 to APBI (interstitial: 88; electrons: 40) versus WBI (50 Gy). The prescription dose was 36.4 Gy in seven fractions, twice daily. The 20-year IBTR was 9.6% for APBI versus 7.9% for WBI (P =.59). More patients with APBI had excellent or good cosmetic results (79.2% vs 59.5%; P =.0007).[106]

NSABP-B39/RTOG 0413 randomized 4,216 patients to WBI (50 Gy/5 weeks) versus APBI. APBI consisted of 3D-CRT (21%; 38.5 Gy in 10 fx twice a day), intracavitary (21%; 34 Gy in 10 fx twice a day), and interstitial (6%; 34 Gy in 10 fx twice a day). The 10-year IBTR was 3.9% for WBI versus 4.6% for APBI. Although the HR for IBTR of 1.22 (90% CI: 0.94-1.58) favored WBI, the difference in 10-year IBTR between both modalities was less than 1%. Rates of grade 3 toxicity were 10% for APBI and 7% for WBI. The trial was not designed to evaluate clinical outcomes among different APBI techniques.

Two large registry trials have been conducted for intracavitary HDR-BT applicators. In the American Society of Breast Surgeons MammoSite Breast Brachytherapy Registry Trial, 1,449 patients (87% invasive; 13% DCIS) were treated with the single-lumen balloon intracavitary device at a dose of 34 Gy in 10 fractions twice daily. The 5-year actuarial rate of IBTR was 3.8%. The percentage of patients with excellent/good cosmetic results at 5 years was 91.3%.[115] In the strut-based registry trial, 250 patients were treated with a strut-based hybrid intracavitary device at a dose of 34 Gy in 10 fractions, twice daily. The 4-year IBTR was 3.6%. 85.9% of patients had excellent/good cosmesis at 5 years.[116]

Technique

Intracavitary

Intracavitary applicators are inserted into the lumpectomy cavity, either during the time of the lumpectomy surgery or during a separate procedure under ultrasound guidance. Once the applicator is placed, a treatment-planning CT scan is obtained with the applicator expanded. The radiation oncologist must ensure that the applicator conforms well to the cavity, ideally with adequate distance (~5 mm for single- lumen balloon; less for multilumen balloon) between the balloon and skin.

Interstitial

The ABS and GEC-ESTRO guidelines provide detailed guidelines for using this technique.[112,113] The implant can be performed either intraoperatively or postoperatively (nearly 4-12 weeks after lumpectomy) with the use of template-guided or free-hand needles under appropriate anesthesia. A preplan based on ultrasound or CT could aid in defining the optimal needle configuration and orientation prior to the implant. Once the applicator is placed, a treatment-planning CT scan is performed.

Treatment Planning

Treatment planning is most often performed with a CT scan with an applicator in place. The CTV often consists of the lumpectomy cavity plus a 1- to 2-cm margin. OARs may include the skin, ribs, contralateral breast, lung, and heart. Tables 24.10 and 24.11 show the recommended target volumes and OAR constraints for intracavitary and interstitial applicators, based on the NSABP B39/RTOG 0413 protocol.[103] Prescription doses could include 34 Gy in 10 fractions, twice daily, as used in NSABP B39/RTOG 0413, or either 32 Gy in eight fractions or 30.1 Gy in seven fractions, as used in the GEC-ESTRO trial.[5]

TABLE 24.10 PLANNING VOLUMES AND CONSTRAINTS FOR INTRACAVITARY BRACHYTHERAPY, BASED ON NSABP B-39/RTOG 0413 (PRESCRIPTION DOSE 34 GY IN 10 FRACTIONS, TWICE DAILY)

Target volumes	• CTV: resection cavity and device surface with a 10-mm expansion • PTV: equal to CTV • PTV_EVAL: equal to CTV but cropped 5 mm from the skin and by the posterior extent of the breast
Parameters and constraints	• Dose prescribed at a depth of 1 cm from the device surface • ≥90% of dose covering ≥90% of PTV_EVAL • V150 ≤50 cc and V200 ≤10 cc • Uninvolved breast: <60% of WB receiving ≥50% of prescribed dose • Maximum skin dose ≤145% of prescription dose • Minimum skin thickness of 5 mm

TABLE 24.11 PLANNING VOLUMES AND CONSTRAINTS FOR INTERSTITIAL BRACHYTHERAPY, BASED ON NSABP B-39/RTOG 0413 (PRESCRIPTION DOSE 34 GY IN 10 FRACTIONS, TWICE DAILY)

Target volumes	• CTV: resection cavity with a 15-mm expansion • PTV: equal to CTV • PTV_EVAL: equal to CTV but cropped 5 mm from the skin and by the posterior extent of the breast
Parameters and constraints	• ≥90% of dose covering ≥90% of PTV_EVAL • V150 ≤70 cc and V200 ≤20 cc • Dose homogeneity index (DHI) = (1 − V150/V100) ≥ 0.75 • Uninvolved breast: <60% of WB receiving ≥50% of prescribed dose

Follow-up

It is recommended that patients who undergo brachytherapy for APBI be seen in follow-up from every 3 months for the first 2 years, every 6 months for the next 3 years, and yearly thereafter.[5] More frequent early follow-ups are warranted, in order to monitor for hematoma or infectious complications.

RECTAL CANCER

Clinical Indications

HDR brachytherapy can be considered for the definitive treatment of locally advanced rectal cancers. The standard of care for locally advanced rectal cancer over the past two decades has involved long-course preoperative

chemoradiation therapy followed by surgery with total mesorectal excision.[117] HDR brachytherapy boost can provide profound dose escalation far beyond than what is possible with conventional IMRT techniques.[118] This profound dose escalation may lead to improved pathologic complete response (pCR) rates. In a recent systemic review, preoperative chemoradiotherapy regimens involving HDR brachytherapy boost were associated with a greater pathologic complete response (pCR) rate (weighted mean, 22.2%)[119] than that observed with chemoradiation alone (weighted mean 11.8%).[120] An association between pCR and survival has been observed in a large pooled analysis of individual patient data.[121]

Over the past decade, there has been increasing interest in the nonoperative management of locally advanced rectal cancer. After initial treatment involving chemoradiation therapy[122] or total neoadjuvant regimens involving high-dose preoperative systemic therapy,[123] patients with complete clinical responses undergo watchful waiting rather than total mesorectal excision. Profound dose escalation with brachytherapy may improve the chance of complete clinical response and organ preservation, as suggested by the recently reported organ preservation in early cT2–cT3 rectal adenocarcinoma (OPERA) trial. In this trial, 148 patients were randomized to contact brachytherapy boost (90 Gy in three weekly fractions) versus EBRT boost (9 Gy in five fractions) after chemoradiation therapy (45 Gy/25 fractions). Contact brachytherapy boost improved greater complete response rates (81% vs 58%; P =.0006). Furthermore, this treatment improved 3-year organ preservation rates (81% vs 59%; P =.0026). Respective rates for tumors <3 cm were 97% and 63%.[124] However, contact brachytherapy was associated with increased late-grade 1 to 2 rectal bleeding (63% vs 12%).

Endoluminal HDR brachytherapy involves delivering radiation to the tumor through a single-channel or multichannel endoluminal applicator placed in the rectum. Compared with contact brachytherapy, this form of treatment may be able to treat larger (≥3 cm at the time of brachytherapy) as well as deeper tumors (prescription depth of ~1 cm). HDR brachytherapy boost after EBRT has been investigated by multiple groups.[125–127] In a registry study of 94 medically inoperable patients who received pelvic EBRT (40 Gy in 15 fractions) followed by weekly adaptive HDR brachytherapy (30 Gy in three weekly fractions to 1 cm depth), the complete clinical response rate was 86.2%.[127] The 2-year local control among all patients was 71.5%, with only 12.8% reporting late grade 3 bleeding.

Technique

Brachytherapy can be considered about 3 weeks after EBRT in order to allow for resolution of proctitis. After completion of EBRT, a gastroenterologist can examine the tumor with a flexible rectosigmoidoscope in order to confirm adequate response and place radio-opaque clips at the proximal and distal extents of the residual tumor. Then, a single-channel or multichannel applicator is inserted into the rectum. Applicators with shielding and/or a double-balloon system could help shield the uninvolved rectum from high-dose radiation. A CT simulation of the applicator in place is obtained. Care must be taken to ensure that there is no material between the tumor and the applicator. Furthermore, the thickness of the tumor should be at most 1 cm.[127]

Treatment Planning

The CTV is defined as residual macroscopic tumor. Surrounding OARs should be contoured. Dose can be prescribed up to 1-cm depth to limit mucosal dose to 200%. The dose to the uninvolved rectum should be minimized. Weekly adaptive treatment planning could be considered to account for tumor regression in-between fractions and to minimize dose to OAR.[127]

Follow-up

In the non-operative setting, endoscopic evaluation should be performed at 6 to 8 weeks after brachytherapy to document response. Following this, clinical examinations with endoscopies should be considered every 3 months for the first 2 years, every 6 months between years 2 and 5, and yearly thereafter. Imaging with pelvic MRI or staging CT scans could be considered on a semi-annual or annual basis.

SKIN CANCER

Clinical Indications

HDR brachytherapy is a suitable treatment modality for the nonoperative management of skin cancers, such as squamous cell carcinoma and basal cell carcinoma.[128] This is a particularly useful form of treatment for patients who decline surgery, are nonoperative candidates, or may have poor cosmetic or functional outcomes after surgery. Numerous single-institutional studies have reported on the oncologic and cosmetic outcomes of HDR brachytherapy.[129-131] Recently, a meta-analysis compared HDR brachytherapy against EBRT, Mohs micrographic surgery, and conventional excision for T1-T2N0 skin cancers (≤4 cm). Brachytherapy and Mohs surgery had improved cosmesis compared to EBRT and conventional excision. Furthermore, 1-year local recurrence rates were low across all modalities.[132]

HDR brachytherapy is ideally suited for patients with localized, well-defined, clinical T1-T2N0M0 cancers with limited predisposition for spread (no perineural or lymphovascular invasion). HDR brachytherapy may not be ideal for treating cancers that are large (>4 cm), poorly defined, locally invasive (eg, perineural invasion and deep extension beyond cutaneous fat), or associated with chronic immunosuppression. Other contraindications include poorly controlled connective tissue disorders or conditions associated with increased radiosensitivity (eg, Li-Fraumeni syndrome, nevoid basal cell carcinoma, and ataxia telangiectasia). Of note, HDR brachytherapy has also been effective in other types of skin conditions, including Merkel cell carcinoma,[133] keloid scars,[134] cutaneous T-cell lymphoma,[135,136] and angiosarcoma.[137]

A careful physical exam is required for all skin cancers treated with HDR brachytherapy. The tumor should be carefully measured and photographed, in order to select the ideal applicator and assess treatment response. Cross-sectional imaging should only be considered for tumors at higher risk of regional or nodal spread.

Technique

HDR brachytherapy can be delivered using rigid applicators, flaps/custom molds, or interstitial techniques.

Rigid Applicators

Rigid conical and nonconical applicators are ideal for contact-based treatment of small, superficial skin lesions. These applicators are small, fixed-geometry, shielded devices with a dwell position for the HDR source at its vertex. Applicators vary with respect to size (most often 20 mm or 30 mm), as well as the presence or absence of a flattening filter. The dosimetry of these applicators has been well characterized.[138,139] A proper-sized applicator should be selected and secured, while ensuring full contact with the skin.

Custom Surface Flaps/Molds

Custom surface flaps or molds are ideal for superficial cutaneous lesions on curved or irregular surfaces (eg, extremities, waist, and face). Flaps consist of customizable silicone-based sheets or beads with embedded catheters.[131] Molds, on the other hand, are made of synthetic materials (wax, rubber, 3D printed) that can be attached to catheters.[129,130] Both are placed on the target volume and immobilized utilizing tape, bandages, or towels. Detailed descriptive and image documentation of the clinical setup is of utmost importance to ensure reproducibility during subsequent treatments.

Interstitial Brachytherapy

Interstitial brachytherapy is ideal for deeper lesions (>0.5 cm) not amenable to other techniques, such as those around the lip[140] or eyelid.[141] While the patient is under anesthesia, trocars with attached catheters are inserted through the skin, approximately 1 cm apart, to cover the extent of the lesion. Catheters ideally are inserted 5 mm from the skin surface in order to limit skin toxicity.

Treatment Planning

For all applicators, a CTV and PTV can be delineated by inking around the tumor. A 1-cm CTV margin can often be used but may be adjusted to 0.5 cm for more indolent tumors (eg, low-risk basal cell carcinoma) or 2 cm for more aggressive tumors (larger tumors, moderate/poor differentiation). PTV margins range from 0 to 5 mm in diameter and up to 1 mm in depth.[128]

For rigid applicators, treatment optimization is not possible due to the single dwell position. For surface molds, flaps, and interstitial brachytherapy, CT simulation is necessary for dosimetric optimization. Prior to CT simulation, a radio-opaque wire should be placed on the PTV. During treatment planning, the 100% isodose line

should encompass the PTV and the surface dose should be limited to <140% of the prescription dose. With the exception of interstitial brachytherapy, the maximal prescription depth is about 3 to 4 mm. Figure 24.4 demonstrates an example of an RT plan using a custom surface flap.

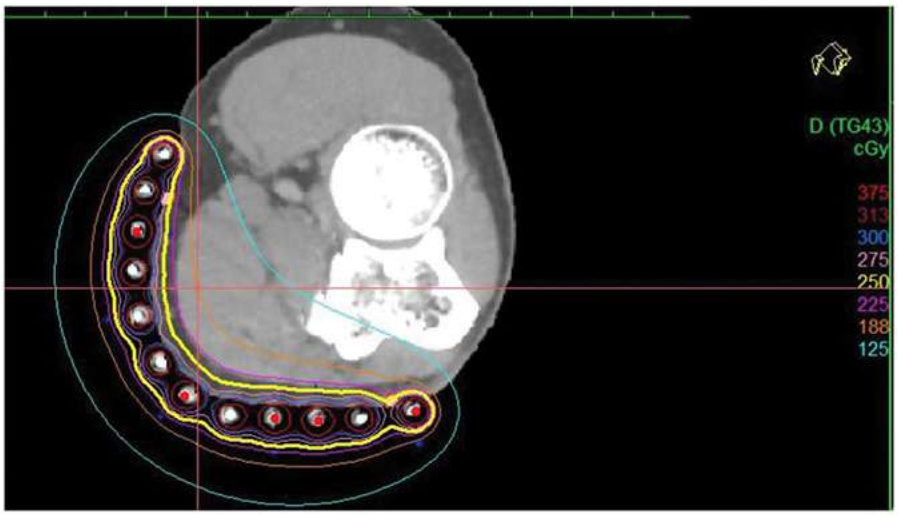

FIGURE 24.4 CT-based treatment plan of surface applicator brachytherapy (20 Gy/8 fractions) for patient with primary cutaneous marginal B-cell lymphoma of the elbow.

Both conventional and hypofractionated regimens can be utilized. Hypofractionated regimens have been associated with good cosmesis at a similar biologically equivalent dose in a recent meta-analysis,[142] and are recommended due to patient convenience. Recommended regimens in ABS guidelines include 42 Gy in six fractions, delivered every other day; 42 Gy in seven fractions, delivered every other day; or 40 Gy in eight fractions, delivered every other day or twice weekly. More sensitive areas or larger tumors could be treated using more conventional fractionation schemes, such as 55 Gy in 20 fractions or 60 to 70 Gy in 30 to 35 fractions.[128]

Follow-up

Follow-up regular examinations can be performed every 3 to 12 months for the first 3 years and then annually thereafter. More frequent follow-ups should be performed for tumors at higher risk of recurrence.

OTHER CANCERS

The roles of HDR brachytherapy for the definitive treatment of endobronchial, esophageal, biliary, soft tissue sarcoma, and head and neck cancers have evolved, given recent advances in intensity-modulated radiation therapy/SBRT, surgical techniques, systemic therapy (eg, immunotherapy), as well as combination regimens. However, HDR brachytherapy remains a treatment option for specific scenarios.

For endobronchial tumors, HDR brachytherapy is predominantly used for the palliation of symptoms, particularly in patients who are not good candidates for additional EBRT due to poor lung function or receipt of prior radiation doses. Endobronchial brachytherapy has been associated with improvements in both symptoms and tumor regression on bronchoscopy.[143-145] This form of brachytherapy involves the insertion of a brachytherapy catheter through a bronchoscope. The catheter should be inserted until it passes by the endobronchial tumor and is lodged within smaller bronchi. The other end of the catheter is then taped to the nose and marked in order to monitor for displacement. CT-based planning is recommended to maximize dose to the target volume while minimizing dose to OARs. Dose fractionation regimens recommended for palliation per ABS guidelines include 10 Gy in one fraction, 15 Gy in one fraction, 14.2 to 20 Gy in two fractions, 22.5 Gy in three fractions, 24 Gy in four fractions, and 30 Gy in five fractions.[146] A randomized controlled trial revealed improved tumor response with 14.4 Gy in two fractions compared with 15.2 Gy in four fractions.[145] A Cochrane analysis concluded that there was insufficient evidence to recommend the addition of a brachytherapy boost to EBRT alone for symptom palliation.[147]

For esophageal carcinoma, HDR brachytherapy is used for palliation of tumors causing symptoms (eg, dysphagia), particularly in patients who are not good candidates for EBRT (eg, poor lung function or prior EBRT dose). This form of treatment has been associated with good symptom palliation in the majority of patients. Esophageal brachytherapy involves the insertion of a catheter or esophageal applicator either intraorally or intranasally under endoscopy. The applicator should pass the tumor. The proximal end of the catheter is then taped to the nose or the mouth and marked, in order to monitor for displacement. CT-based planning is recommended to maximize the dose to the target volume while minimizing the dose to OARs. Dose fractionation regimens include 16 Gy in two fractions and 18 Gy in three fractions based on equivalent rates of symptom palliation in a randomized trial.[148] Another randomized trial did not show the benefit of the addition of EBRT to HDR brachytherapy alone for symptom palliation.[149] Of note, HDR brachytherapy boost has not been incorporated in the definitive management of esophageal cancer, given the high risk of esophageal fistula (12%) observed after chemoradiation therapy (50 Gy RT; cisplatin 75/5-FU 1,000 mg/m^2 every 3 weeks × 4) and HDR brachytherapy boost (15 Gy in three fractions or 10 Gy in second fractions) in RTOG 9207.[150]

For biliary cancers, HDR brachytherapy is predominantly used for addressing biliary tract obstruction from unresectable hepatobiliary tumors. Although biliary tract obstruction is most often managed through decompression using stents and/or drains, multiple decompression procedures may be needed due to occlusion or stent migration. A recent systemic review reported that the delivery of intraluminal HDR brachytherapy was associated with a longer duration of stent patency (10 months) compared to its absence (4-6 months).[151] Briefly, a biliary drainage catheter is placed either through transhepatic cholangiogram or through endoscopic retrograde techniques. The HDR brachytherapy catheter is inserted through this drainage catheter. After CT simulation is performed with the catheter affixed, HDR brachytherapy is performed. Potential dose- fractionation schemes for HDR monotherapy include 25 Gy in five fractions and 30 Gy in six fractions.

For head and neck cancers, HDR brachytherapy can be considered in the definitive or palliative settings. The type of brachytherapy that is performed depends on the subsite. For example, oropharyngeal cancers are typically treated with interstitial brachytherapy. A recent randomized trial reported that HDR brachytherapy boost (21 Gy in seven fractions) after radiation therapy (50 Gy in 25 fractions) was associated with reduced xerostomia on salivary scintigraphy (14% vs 44%) compared with EBRT boost (20 Gy in 10 fractions) in patients with T1-T2N0M0 oropharyngeal cancers. There was no difference in 3-year local control between arms.[152] Interstitial brachytherapy could also be used to treat deeper tumors of the oral cavity. On the other hand, intracavitary applicators or molds could be used for more superficial tumors of the oral cavity, sinuses, or nasopharynx.

For soft tissue sarcoma, preoperative EBRT is now the preferred standard-of-care, given that a randomized trial of preoperative versus postoperative EBRT reported reduced late-onset fibrosis in the preoperative arm.[153,154] Furthermore, a single-institutional study reported improved local control rates observed with IMRT compared with low-dose rate brachytherapy.[155] However, sarcoma brachytherapy in the postoperative setting can be considered for the definitive treatment of sarcomas in patients who are not good candidates for preoperative EBRT due to prior EBRT or OAR considerations. Briefly, the patient undergoes an oncologic resection of the sarcoma tumor. Clips can be placed in the resection bed to mark the appropriate resection margins. Catheters are then inserted through the skin and laid across the resection bed in a parallel, equally spaced manner. After allowing a few days for wound healing (4-7 days), the patient undergoes CT simulation. Target volumes and OARs are delineated, followed by treatment planning. Potential prescription doses include 30 to 54 Gy, given over 4 to 7 days with twice-daily fractions for HDR monotherapy, or 12 to 20 Gy, given over 2 to 3 days with twice-daily fractions for HDR combination therapy followed by EBRT (45-50 Gy) boost.[156]

QUALITY MANAGEMENT PROGRAM

Design of the modern HDR brachytherapy program includes development of step-by-step treatment procedures, specification and qualification of personnel, technical solutions for treatment planning and treatment delivery equipment, implementation of the patient and personnel safety standards, and development of the comprehensive quality assurance program.

To implement the most effective HDR brachytherapy program while minimizing treatment delivery errors and other safety hazards, each institution should develop a comprehensive HDR brachytherapy quality management program (BQMP). The main components of this BQMP are (a) quality assurance (QA) as a set of written policies and procedures that are designed to maintain the standard of quality over a time period, (b) quality control that describes the measurement aspects of the QA program, and (c) continuous quality improvement in order to

improve outcome on a continuing basis. More specifically, QA in HDR brachytherapy involves performing the following documentation: quality management plan, acceptance QA procedures, annual QA procedures, monthly QA procedures, daily QA procedures, treatment plan QA, pretreatment QA, emergency procedure, and chart QA (end of treatment checks). The procedures for implementing all aspects of QA are described in the American Association of Physicists in Medicine (AAPM) Task group reports 40 and 59.[157,158]

Roles and responsibilities in the comprehensive BQMP are defined for radiation oncologists, medical physicists, medical dosimetrists, and radiation therapists. Such programs become exceedingly important in HDR brachytherapy because the planning and the treatments tend to happen very quickly, thus increasing the likelihood of accidents and mistakes. QA is performed at various intervals: some for each patient, some once each treatment day, and others with each source change. Moreover, for HDR machines, the Nuclear Regulatory Commission or the State mandates that users meet certain standards, including education and training on operating the machine, emergency procedures, radiation monitoring, pretreatment safety checks, safe and accurate delivery of the treatment, and monthly/initial calibration of the source. The latest practice guidelines in HDR brachytherapy are given in the AAPM Practice Guideline 13.[159]

Practical Aspects of High-Dose-Rate Quality Management Program

Treatment Planning Preparation

An authorized user (physician) must date and sign a written directive for a specific patient before administration of the radioisotope. The directive must include the radioisotope, treatment site, total dose, dose per fraction, and the overall treatment period. Any modification to the treatment requires a modification before the following treatment. The authorized user and licensed therapist (operator) shall verify the patient's identity by two means: (a) verbal response by the patient and (b) photo identification in the radiation oncology (electronic) chart. For patients who cannot meet one of these requirements, an alternative second means such as hospital wristband identification or hospital card can be used. A radiation oncologist must obtain a signed, dated informed consent from the patient prior to the administration of any treatment.

A radiation oncologist will place the applicator and verify the dummy source locations with appropriate CT/MRI scans or radiographs before commencing any treatments unless the implants use fixed geometries and that all physical parameters of the applicator are known for dosimetry purposes. The radiographs or 3D images will be reviewed by both the authorized physicist and the authorized user. Prior to the administration of the treatment, an independent check of the computer-generated dose calculations will be performed by a physicist and radiation oncologist. The checks shall include computer input data, computer output data, and data transferred from the treatment planning computer to the treatment unit. The data will include the prescription, treatment length/distance, the number of dwell positions, dwell times, total treatment time, channel numbers, and source activity. The person checking the computer data will initial the data printout from the control console. The treatment plan must have a signature approval from an authorized medical physicist, as indicated in the institutional HDR daily pretreatment procedures. The pretreatment record will be filed in the patient's chart and saved in the electronic record. Prior to the administration of the treatment, the authorized user shall check, sign, and date a copy of both the treatment data printout and isodose plan.

Treatment Delivery

When the source is not in use, it is normally stored in the locked radioisotope room. The operator and/or the physicist will perform the appropriate QA tests listed as follows. The operator must follow the written and/or verbal instructions provided. No treatment procedure will be conducted if a decoupled or jammed source cannot be removed expeditiously from the patient and placed in a shielded container. If the daily check of interlocks for the remote afterloading device indicates that the interlock is not operating properly, the physicist must be informed, and no treatment will be carried out until the problems are resolved.

Only the patient will be in the treatment room during activation of the device. Both the authorized user and the authorized medical physicist must be physically present in the console area during all patient treatments. The door to the treatment room will be interlocked, and a sign restricting access to the treatment area will be posted to minimize the risk of inadvertent exposure to personnel not directly involved in a possible emergency source recovery. The patient will be surveyed immediately after the treatment and before removal from the treatment room to ensure that the source has been withdrawn from the patient. Immediately implement the appropriate emergency procedures if the survey indicates that the source is not fully retracted to a shielded position. The

authorized user and the medical physicist will immediately be notified of any problem requiring implementation of emergency procedures. Upon administration of the treatment, the authorized user will sign and date the patient's chart to verify that the correct prescription was administered. The radiation oncologist will also note the loading sequence of the applicator/applicators and the treatment length in the patient's chart for each procedure. A survey of the device will be performed immediately after each use of the device, including the connectors and applicators apparatus, the full catheter guide tube length, and the device's external surface. The device and the console will be locked, and the source will be moved back to the storage room by the physicist or operator.

Emergency Procedures

Based on the existing statistics, the likelihood of major emergencies in HDR brachytherapy is low. This is greatly due to the regulatory requirements—for example, well-developed emergency procedures, training of the personnel, and proper maintenance of the equipment via implementation of the comprehensive BQMP. A routine emergency check should be performed in the department. An emergency kit containing surgical clamps, long forceps, emergency containers, and additional medical supplies should be readily available. In the event the radioactive source fails to retract after termination or interruption after the emergency off switch is pushed or after the stepper motor is cranked manually, the immediate priority is to remove the source from the patient. The emergency procedures should be regularly reviewed and approved by an authorized user. Copies of these emergency procedures should be provided to all device operators, authorized users, medical physicists, and other personnel as necessary. A copy should be posted at the treatment console.

Quality Assurance

Users will be trained to perform each QA test using written and oral instructions.

Daily Quality Assurance Checks or at the Beginning of Each Use

The permanent radiation monitor will be checked for proper operation with a dedicated check source prior to use. The viewing and intercom systems will be verified for proper operation. Treatment Control System or console function tests, including verification of the proper operation of indicator lamps and other status/operational displays, will be performed. A printer test will be performed if the procedure requires it; this test is optional in the paperless procedures. Source status indicators will be tested utilizing a dedicated check source. The mechanical integrity of the applicator(s) (including the placement of internal shields), source guide tubes, and connectors shall be determined by a visual and/or radiographic inspection before use. Treatment room door interlocks will be tested for proper operation.

Monthly Quality Assurance Checks

Monthly QA checks include (a) accuracy of the source activity using a calibrated well chamber, (b) timer accuracy and linearity, and (c) accuracy of sources positioning to within ±1 mm of the programmed position utilizing a radiograph. Records of this test will include the date of the test, the programmed position, the actual position, and the initials of the individual who performed the test. The authorized user will be notified if the test fails to meet the ±1-mm specification. Other checks include (d) measurement of the source transfer tubes to confirm that the total length is within ±1 mm of the specified length, and (e) backup battery test to verify the emergency source retraction upon power failure during each Preventive Maintenance Inspection.

Other Periodic Checks

Calibration of the remote afterloading device will be performed following installation of a new source prior to any patient treatment. This test can be performed more frequently, such as monthly, to be in accordance with the institutional procedures developed by the authorized physicist. A comparison with the manufacturers' stated activity, correcting for decay should be performed. The expected and actual measured values shall be within ±5.0%, according to the Nuclear Regulatory Commission. If the deviation exceeds ±5.0%, the results shall be reviewed by a board-certified physicist prior to any further patient treatments. Each institution can develop a policy with a tighter constraint on HDR source activity. Calibration will be performed by an authorized physicist using a well chamber and an electrometer calibrated by a laboratory accredited by the National Institute of Standards and Technology or AAPM within the previous 2 years and after any servicing that may have affected the dosimetry system. The system is specifically calibrated for several isotopes, including iridium. The calibration will

be countersigned by a second authorized physicist. To confirm source homogeneity, an autoradiograph of the source shall be performed after source installation and prior to resumption of patient treatments. Acceptance testing and computer dose calculation checks for each new treatment planning computer system will be performed by a qualified physicist.

Periodic Reviews

HDR brachytherapy patient charts will be reviewed by other radiation oncologists at least once per month. Annually, a sample of HDR administrations will be reviewed by the Radiation Safety Committee to monitor the effectiveness of the qualified medical physicist (QMP). The sample size will be at least 10% of HDR patients. The results of the review will be reported to the Radiation Safety Committee bi-monthly. In the event of a misadministration, the lot size will be increased by 10% for a year. If any of the QMP monitors are found to be deficient by the Radiation Safety Committee, the monitor deficiencies will be analyzed, and procedures to improve their performance will be initiated.

Inventory Control

The institutional Radiation Safety Office (RSO) tracks the incoming and outgoing of the iridium sources for the HDR program. Except for the purpose of a source exchange, only a limited number of sources should be kept in the department per the institution licenses. The possession of this iridium source will be checked by the RSO office at intervals of not more than 3 months. This physical inventory check will be conducted by the RSO (or a health physics representative) and the authorized physicist. The inventory records shall contain the model number of each source and the serial number, the activity of the iridium source, the location of the iridium source when not in use, the date of the inventory, and the signature of the individual performing the inventory.

Record Keeping

Patient records, including the written prescription, record of the administered dose, and treatment plan, will be stored in the department record room for a minimum of 3 years. Survey records of the device and the patient will be maintained for 3 years and will include the survey date, patient identification, and the initials of the individual performing the survey. Records of all survey meter calibrations will be maintained, and the calibration due dates will be checked daily. Those survey meters that are not calibrated within 1 year will be removed from the clinic and will be sent for calibration. All radioactive sources that are received for the afterloader will be entered in the brachytherapy source inventory and will be summarized quarterly. All inventory records will be kept for a period of 3 years. All QA records (calibration, periodic checks) will be kept in the department for a period of 3 years.

SUMMARY

Over the past two decades, multiple prospective and retrospective analyses have highlighted the clinical value of brachytherapy across multiple disease sites. High local control rates along with low toxicity rates have been reported for cervical cancer,[4,17] prostate cancer,[3,75] endometrial cancer,[2,40,41] and breast cancer[5,106] treated with contemporary HDR brachytherapy techniques. These excellent outcomes were obtained by well-trained brachytherapy practitioners who were devoted to maximizing clinical outcomes for their patients. Unfortunately, the utilization of brachytherapy has been declining due to its time-intensive nature with respect to current reimbursement levels,[160] along with advances in external beam technologies. As a result, graduating radiation oncology residents have reported a lack of confidence in practicing brachytherapy due to insufficient training volume.[161] Continuing education initiatives through workshops[162,163] and externships[164] are essential in ensuring that interested early-career radiation oncologists can gain the training, confidence, and mentorship to practice high-quality brachytherapy. Only through these efforts can the clinical value of HDR brachytherapy be sustained well into the future.

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CHAPTER 25

Beyond the Beam: Radiopharmaceutical Therapy

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HISTORY AND OVERVIEW

Radiopharmaceutical therapy (RPT) is the delivery of radionuclides that can localize to and treat patients with cancer. While this approach dates to the 1940s, modern advances and positive prospective clinical trials have recently put this modality on the map and raised the interest of keen radiation oncologists.

In this chapter, we present a brief origin story of RPT, frame it in the context of other early radiation therapy approaches, and review radiation emissions and their biologic implications, including biomedical applications. In addition, we discuss tumor-targeting approaches using biomolecules and how these influence the pharmacokinetics and biodistribution of a given radiopharmaceutical agent. Pivotal trials of currently approved agents and their indications as well as late-stage clinical trials that readers may wish to follow are highlighted. As this field is experiencing a renaissance, we recommend readers to periodically reassess the RPT agent landscape to remain up to date. Importantly, because there are differences in medical training and which specialties administer and manage patients receiving RPTs, when relevant, our focus here is on implementation in the United States.

Birth of Radiation Medicine

Not long after Wilhelm Röntgen first described x-rays out of the University of Wurzburg in Germany in 1895, Henri Becquerel, Marie Curie, and Pierre Curie discovered similar emissions from uranium, radium, and polonium in 1896 and 1898. These groundbreaking discoveries earned Röntgen the inaugural Nobel Prize in Physics in 1901. Becquerel and the Curies earned the honor in 1903.

The properties of these radionuclides were almost immediately applied toward the treatment of cancers. In fact, as early as 1903, the idea of introducing radioactive elements in close proximity to tumors that are deep in the body—that is, brachytherapy—was suggested by an esteemed reader of *Nature*, Dr Alexander Graham Bell.[1] Others used x-rays to successfully treat cancers, including a young

girl with lymphoma treated in 1905 described in the 1923 textbook *La Radiothérapie Profonde*.[2] In the 1930s and 1940s, work by John Lawrence, brother to Ernest of cyclotron fame, used radioactive phosphorous to treat leukemias, first preclinically and then in patients, after learning that leukemic cells took up the radioisotope.[3] Contemporaneously, Saul Hertz and Sam Seidlin used radioiodine to treat hyperthyroidism and thyroid cancers, leveraging the recent discovery of iodine within the thyroid gland by Eugen Baumann.[4-6] RPT was born.

Because both therapeutic and diagnostic radiation evolved in parallel, it is, perhaps, unsurprising that the portmanteaux *theranostics* and *radiotheranostics* emerged consequently—some will often retain the "g" to yield *theragnostics*. Initially, the terms tended to specifically refer to the concept that a tumor-targeted ligand could be transformed from a molecular imaging agent to a therapeutic one by switching from a radionuclide with emissions conducive for imaging (eg, positron and γ emitters) to radioisotopes with therapeutic radiation emissions (eg, β, α, Auger). More recently, the terms could expanded to include the use of molecular imaging agents to be predict responses to other molecularly targeted therapies (eg, biologics, antibody-drug conjugates, chimeric antigen receptor T cells) in addition to RPT. Table 25.1 is an overview of RPT-related terms.

TABLE 25.1 DEFINITION OF TERMS

Term	Definition
Active targeting	Using a biomolecule specific to a tumor or tumor microenvironment target to guide delivery of a radionuclide
Biologic half-life	Biologic half-life ($t_{½b}$) of a radiopharmaceutical is the time taken for the concentration of the agent to be reduced by 50% of its maximum concentration in tissue, organ, or whole body, not considering radioactive decay.
Biomolecule	These are any of the numerous substances that are produced by cells and living organisms. The four major types of biomolecules are carbohydrates, lipids, nucleic acids, and proteins.
Chelate/chelator	A class of coordination or complex compounds consisting of a central metal atom attached to a large molecule, called a ligand, in a cyclic or ring structure
Effective half-life	The effective half-life ($t_{½e}$) is the half-life of a radiopharmaceutical in each tissue, organ, or whole body and is determined by a relationship including both the physical half-life and the biologic half-life. The effective half-life is important in calculation of the optimal dose of radiopharmaceutical to be administered and in monitoring the amount of radiation exposure. It can be calculated from the formula:

Term	Definition
	$t_{½e} = \frac{(t_{½b} \times t_{½p})}{(t_{½b} + t_{½p})}$
Ligand	Any molecule that binds to another molecule (eg, [^{177}Lu] Lu-DOTATATE is a ligand that binds to somatostatin receptors)
Molecular radiotherapy	See radiopharmaceutical therapy.
Passive targeting	Leveraging the natural accumulation of a radionuclide to a given organ system to achieve localization to tumors (eg, $^{223}RaCl_2$ localizing to areas of bone metastases, or ^{131}I localizing to thyroid cancers)
Peptide receptor radionuclide therapy (PRRT)	It is a form of targeted radiopharmaceutical therapy currently approved to treat neuroendocrine tumors ([^{177}Lu] Lu-DOTATATE). A radioactive chemical is linked to a peptide that targets cancer cells. When this radioactive peptide is injected into the body, it binds to a specific receptor found in neuroendocrine cancer cells.
Personalized dosimetry	This is a measurement of patient-specific biophysical parameters to individualize treatment to optimize the antitumor effect while minimizing toxicity.
Pharmacodynamics	Pharmacodynamics is the quantitative study of the relationship between drug exposure (concentrations or dose) and pharmacologic or toxicologic responses. It entails a drug's molecular, biochemical, and physiologic effects or actions.
Pharmacokinetics	Pharmacokinetics is the study of dynamic movements of foreign chemicals during their passage through the body. It illustrates the sequence of its absorption, bioavailability, distribution, metabolism, and excretion over time.
Physical half-life	The physical half-life of a radionuclide ($t_{½p}$) is the time in which the amount of radioactivity decreases to one half of its original value.
Radioconjugate	A biochemical or immunologic conjugate that includes a radionuclide
Radioimmunotherapy	Radioimmunotherapy entails combining a small amount of radioactive material (radionuclide) with a molecule engineered in a laboratory (monoclonal antibody). Monoclonal antibodies can recognize and bind to specific features of cells, such as antigens and cell receptors. (Note: Some investigators use this term to refer to radiotherapy combined with immunotherapy such as immune checkpoint inhibition.)
Radioligand therapy (RLT)	See radiopharmaceutical therapy.
Radionuclide	A radionuclide, or radioisotope, is an unstable element that releases radiation in the form of positron, electron or β particle, α particle,

Term	Definition
	Auger, or γ ray emissions.
Radiopharmaceuticals	Radiopharmaceuticals are unique medicinal formulations containing radioisotopes, which are used in major clinical areas for diagnosis and/or therapy.
Radiopharmaceutical Therapy (RPT)	Radiopharmaceutical therapy is defined as the targeted delivery of radionuclides to tumor cells or to the tumor microenvironment.
Radiotheranostics	See theranostics.
Theranostics	It is a portmanteau of therapeutics and diagnostics. Generally, it involves the use of a target-specific imaging agent to select patients for a corresponding radiopharmaceutical therapy agent specific to the same target (eg, ^{68}Ga-DOTATATE and [^{177}Lu] Lu-DOTATATE).
Tracer	A compound that is labeled by a radioactive or nonradioactive isotope to assist in the study of its transport or metabolism. Tracer dosing involves the administration of a very low mass of agent that can be detected (eg, ^{18}FDG PET imaging).

^{18}FDG, ^{18}F-conjugated fluorodeoxyglucose; PET, photon-emission tomography.
Adapted from Salerno KE, Roy S, Ribaudo C, et al. A primer on radiopharmaceutical therapy. *Int J Radiat Oncol Biol Phys*. 2023;115(1):48-59. With permission.

Types of Radiation and Radiobiologic Implications

The positron-emitting ^{18}F-conjugated fluorodeoxyglucose (^{18}FDG) and positron emission tomography (PET) imaging have been routinely used to diagnose, assess treatment response, and surveille patients with cancer for decades. Other routinely used imaging approaches include scintigraphy and single-photon emission computed tomography (SPECT), which use γ emissions from radionuclides for planar or three-dimensional imaging, respectively. It is critical to emphasize the tracer principle here, which underscores the orders of magnitude differences between the activities administered for imaging purposes (<0.37 GBq, <10 mCi) and those administered with therapeutic intent (>3.7 GBq, >100 mCi). These differences have obvious implications when it comes to radiation safety and the tension between administering activities that are "as low as reasonably achievable" and yet high enough to exert a clinically meaningful therapeutic effect.

As detailed elsewhere in this text, ionizing radiation kills cells through direct or indirect induction of DNA damage, including single- and DNA double-strand breaks (SSB, DSB). Because DNA DSBs are more challenging to repair, accumulation of such damage can become irreparable and result in cell death.[7]

The specific properties of different types of ionizing radiation emissions result in varying degrees of cellular and DNA damage (Figure 25.1). As with external beam radiotherapy (EBRT), RPT also exhibits dose rate and linear energy transfer (LET) considerations when it comes to the type and extent of damage caused. Canonically, lower LET emissions, such as β particles, are less energetic, less densely ionizing, and have a longer pathlength (0.1-10 mm), or range traveled. In contrast, high LET emissions have high energy, are more ionizing, and travel shorter distances. For example, α particles and Auger electrons have pathlength ranges of <100 and <1 μm, respectively. These properties inform how radionuclides are harnessed for therapeutic ends. It is generally accepted, for instance, that internalization of an Auger-emitting radiopharmaceutical agent is required to exert its cytotoxic effect because it needs to be near the nucleus to cause sufficient DNA damage.[8] That said, preclinical data suggest that plasma membrane irradiation can be cytotoxic, suggesting that damage to subcellular structures beyond the nucleus contributes to cell death.[9] We go into further detail in the next section.

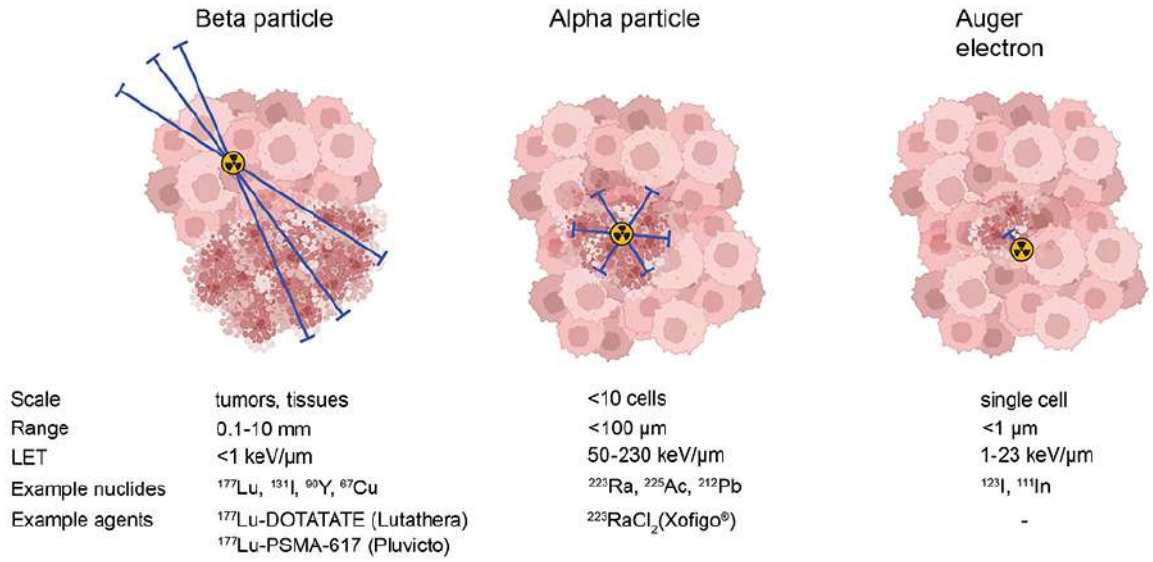

FIGURE 25.1 Types and properties of radiation emissions used for radiopharmaceutical therapy. LET, linear energy transfer. (Adapted from Salerno KE, Roy S, Ribaudo C, et al. A primer on radiopharmaceutical therapy. *Int J Radiat Oncol Biol Phys*. 2023;115[1]:48-59. With permission.)

Radiobiology

Dose Rate and Absorbed Dose Distribution Considerations

EBRT and RPT share the same primary anticancer mechanism: They cause deleterious ionization events in DNA either through direct interactions or through

the hydrolysis of water and production of reactive oxygen species, which cause "indirect" DNA damage. There are, however, important differences in the type, generation rate, and kinetics of repair of DNA lesions that result from exposure to the two modalities.[10] This is partly explained by their profoundly different dose rates. The absorbed dose rate for EBRT, typically about 1 Gy/min, is one to two orders of magnitude faster than that of RPT, which is about 0.01 Gy/min. While the dose rate of EBRT is constant during delivery, that of RPT diminishes exponentially over time. Furthermore, in the case of RPT, DNA repair responses are invoked even as further damage accumulates due to ongoing radioactive decay.

The spatial distribution of DNA lesions can influence the fate of the irradiated cell. α particles have high LET and cause clustered damage, defined as two or more modifications per helix turn, which is often repair resistant. In contrast, β particles maybe include protons as low LET, and most high-energy photon sources used for EBRT have low LET, causing more sparsely distributed lesions.[11]

The pattern of energy deposition in tissues is another important difference between EBRT and RPT, and this also contributes to their divergent radiobiologic effects. RPT is associated with heterogeneously distributed absorbed dose because, as for any systemically administered drug, local physiologic factors such as vascularity or interstitial pressure determine where drug accumulates within a tumor or tissue. Furthermore, the molecular target to which the RPT binds may be unevenly expressed throughout a tumor, being abundant in some cells, yet sparse in others, again leading to variation in the distribution of RPT agent, subsequent absorbed dose, DNA damage, and treatment outcome.[12,13] Another reason for uneven dose distribution is the isotropic nature of radionuclide decay, causing dose to fall rapidly with distance from the source, according to the inverse square law. In contrast, EBRT is unaffected by these variables and delivers a relatively uniform dose throughout a target volume.

The differences in the spatiotemporal pattern of DNA damage that RPT and EBRT cause trigger divergent effects on many cellular processes, including the intratumoral and systemic immune responses, cell cycle, signaling pathways, and mode of cell death.

Immune Effects

It is well established that EBRT can induce an antitumor immune response, and there is now strong evidence that RPT is also able to promote such a response. However, differences in dose rate, LET, and duration of exposure may affect the immune response in diverse ways. Importantly, the systemic nature of RPT may be advantageous as it has been shown that simultaneous treatment of all tumor

lesions enhances induction of an immune response[14] and that even low-dose RPT, when combined with an immune checkpoint inhibitor, can result in the eradication of tumors wherever they are located.[15] There are several explanations for this, including the expression of different tumor-associated antigens (TAAs) in individual lesions. Activated T cells will be directed against the specific TAAs released from an irradiated tumor, whereas, if they differ, TAAs from other sites will not be targeted. It is possible that the immunosuppressive effects of the tumor microenvironment may only be alleviated by radiation locally, and thus while activated antitumor T cells may enter the circulation, their effect may be limited in nonirradiated tumors. RPT results in lower total absorbed dose compared to EBRT, which likely influences the nature of the immune response, as there is accumulating evidence that high doses tend to be immunosuppressive whereas low-dose effects are immune modulatory.[16] RPT has been shown to be capable of inducing proimmunogenic changes such as immunogenic cell death[17] and the cyclic guanosine monophosphate-adenosine monophosphate synthase pathway (cGAMP), which canonically recognizes double-strand DNA as part of antiviral host immune response.[18] Currently, it is not clear how RPT impacts immunosuppressive factors such as macrophage polarization and myeloid-derived suppressor cell recruitment. A deeper understanding of the immunomodulatory effects of RPT will inform the selection of RPT-immunotherapy combinations going forward.

Low Dose-Rate Effects: Hypersensitivity, Cell Cycle, and Cell Death

Experimental investigation of the specific radiobiologic consequences of the low dose-rate (LDR) exposure associated with RPT is challenging, with current knowledge mainly extrapolated from studies in which continuous LDR EBRT was applied to biologic models.[19] An inverse dose-rate effect has been reported whereby, at dose rates in the RPT range (below 0.1 Gy/min), cells exhibit hypersensitivity to radiation, and this is hypothesized to be due to the existence of a dose threshold below which DNA repair processes remain uninduced.[20] This phenomenon appears to be cell line specific, with some investigators observing changes in cell cycle progression in response to LDR exposure with increases in survival, and accumulation of cells in G2 phase with delayed DNA synthesis.[20] Unrepaired DNA damage following exposure to radiation results in cell death of various types.[21] Recent work has highlighted differences in the mode of cell death caused by RPT compared to high dose-rate radiation. In particular, protracted LDR exposure may not cause immediate cell death, but instead triggers long-term growth arrest, or senescence.[22]

There is much to be learned regarding the radiobiology of RPT on tumors and the tumor microenvironment. As our understanding improves, investigators are keen on identifying RPT combinations with other treatments that can improve therapeutic outcomes for patients.

Passive Versus Active Targeting

As previously introduced, some radionuclides have an intrinsic tropism for certain tissues, which can be exploited to treat specific cancers. Because the thyroid gland requires iodine to synthesize thyroid hormones, it will also take up the β particle–emitting iodine-131. Accordingly, radioiodine has been used to treat papillary and follicular thyroid cancers, which exhibit iodine uptake as does their tissue of origin. Similarly, strontium-89, samarium-153, and radium-223 naturally localize to areas of bone turnover and are approved to treat cancers that have metastasized to bone. On the imaging side, technetium-99m methylene diphosphate (^{99m}Tc-MDP) and sodium fluoride-18 (Na^{18}F) also localize to bone metastases and are used for bone scintigraphy (a.k.a. bone scans) and PET of these lesions, respectively (Figure 25.2; Table 25.3).

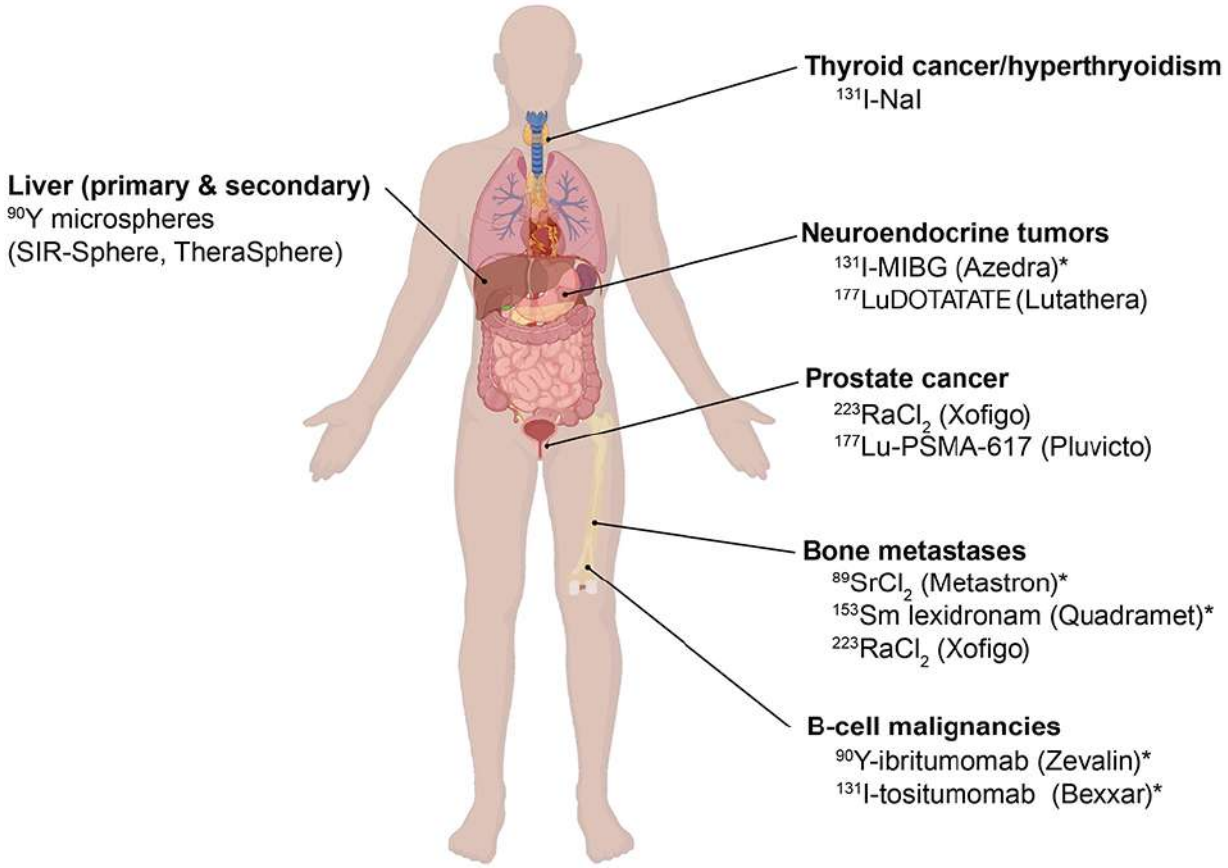

FIGURE 25.2 Food and Drug Administration–approved radiopharmaceutical therapy agents. *Agent no longer commercially available. (Created in part with Biorender.com. Adapted from Salerno KE, Roy S, Ribaudo C, et al. A primer on radiopharmaceutical therapy. *Int J Radiat Oncol Biol Phys*. 2023;115[1]:48-59. With permission.)

Leveraging the natural biodistribution of radionuclides, while successful, limits the spectrum of biomedical applications and the types of tumors clinicians could treat. Active targeting uses biomolecules (eg, peptides, antibodies) that can bind to tumor- or tumor microenvironment–specific targets to deliver radionuclides either by covalently attaching the desired radionuclide directly or by using a chelator, which can tightly bind to a radiometal (Figure 25.3).

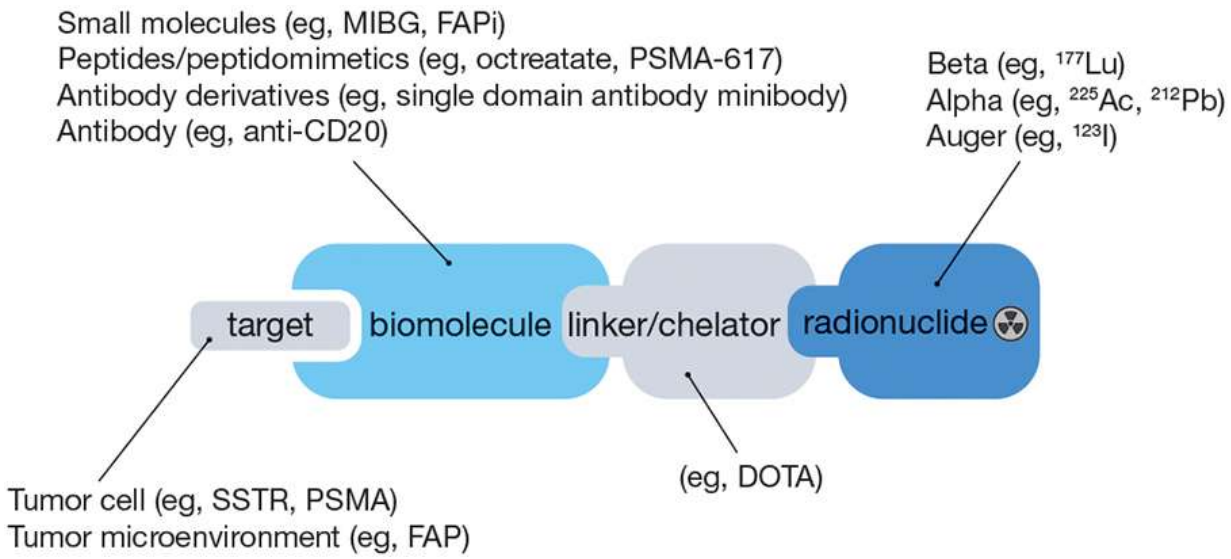

FIGURE 25.3 Generalized structure of a tumor or tumor microenvironment–selective radiopharmaceutical therapeutic agent. FAPi, fibroblast-activating protein inhibitor; PSMA, prostate-specific membrane antigen; SSTR, somatostatin receptor. (Adapted from Salerno KE, Roy S, Ribaudo C, et al. A primer on radiopharmaceutical therapy. *Int J Radiat Oncol Biol Phys*. 2023;115[1]:48-59. With permission.)

The choice of radionuclide depends on both the intended application, namely, imaging or therapy, and the *type* of imaging—that is, PET, SPECT, or the therapy desired, including with β or α particles, or Auger electrons.

Biomolecular Scaffolds and Pharmacokinetic Implications

The choice of molecular scaffold for use in RPT has been historically limited by ones already available to tumor- or tumor microenvironment–selective targets. Advances in phage and yeast display technology, however, have made de novo discovery or peptides or antibody fragments much easier and more economical. Paired with powerful in silico modeling of ligand-target binding, including artificial intelligence–based developments, these tools could allow for not only discovery but also optimization of these molecules with respect to binding affinity and pharmacokinetic performance.

Pharmacokinetics, or how the body interacts with a given drug, is a critical feature of any systemically administered agent, and radiopharmaceuticals are no exception. The molecular weight of the drug in question is directly proportional to the biologic half-life, that is, the lower the molecular weight, the faster the drug is typically cleared from the blood (Figure 25.4). The elimination route of the drug also depends on the molecular weight, where smaller molecules (<50 kDa) are

typically cleared by the kidney and larger molecules (>50 kDa) are cleared by the reticuloendothelial system (liver and spleen), or through the gastrointestinal tract.

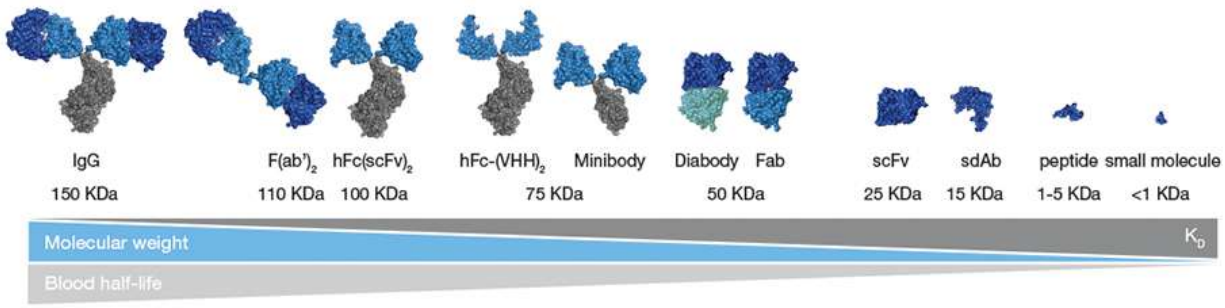

FIGURE 25.4 Incomplete list of biomolecules being explored as scaffolds for radiopharmaceutical imaging and therapy ranging from full-length antibody (immunoglobulin G or IgG), through antibody fragments, to peptides and small molecules.

Several scaffolds have been explored in the preceding decades and are too numerous to include here. Antibody-based scaffolds include full-length antibodies (150 kDa); engineered antibodies including minibodies (80 kDa) or diabodies (60 kDa); antibody fragments including F(ab) (50 kDa), $F(ab')_2$ (110 kDa), and single-chain variable fragments (25 kDa); and, more recently, single-domain antibodies (15 kDa). Typically, bivalent antibodies, that is, antibodies that contain two target-binding sites, allow for much better target-binding affinity due to avidity effects. Because of their high affinity and relative ease of production, antibody-based agents have been part of research and development since the advent of recombinant monoclonal antibody production.[23]

Additional molecules, including designed ankyrin repeat proteins, can similarly be selected for specificity to the desired antigens and have been tested in humans, and there are plans to explore this scaffold for radiopharmaceuticals in clinical trials.[24] Aptamers, single-stranded DNA or RNA molecules that can be selected for specificity against targets of interest, are also being explored, however, to date, have been limited to preclinical studies. Affibodies (6 kDa) are proprietary proteins that have been designed to have high specificity to HER2 as a radiotheranostic as well,[25] and a PET imaging agent has been shown to predict for early metabolic response in patients with breast cancer.[26] More recently, peptides and peptidomimetics, which comprise the most recent cohort of Food and Drug Administration (FDA)-approved RPT agents (Table 25.1; Figure 25.1), have sparked significant enthusiasm in RPTs and their applications in cancer.

Which biomolecular scaffolds are used for imaging, therapy, or both depends nearly entirely on their in vivo performance, that is, their ability to successfully

engage its putative target in preclinical and clinical settings, its broader biodistribution, or where the agents may differentially accumulate in the body, as well as the mode of clearance and the kinetics of that clearance. Charge, molecular weight, and shape influence the biodistribution and clearance of the agent in vivo. Low-molecular-weight proteins (<50 kDa) are generally excreted and sometimes resorbed in the proximal tubule of the kidney. Positively charged proteins tend to get preferentially resorbed. This property is exploited by using positively charged amino acids (eg, arginine and lysine) prior to, during, and following administration of the somatostatin receptor (SSTR)-targeted [^{177}Lu] Lu-DOTATATE used to mitigate nephrotoxicity when treating well-differentiated gastroenteropancreatic neuroendocrine tumors (GEP-NETs). For other agents, including the prostate-specific membrane antigen (PSMA)-targeting peptidomimetics (eg, [^{177}Lu]Lu-PSMA-617), the fact that endogenous PSMA expression is present in the kidney, as well as the lacrimal and salivary glands, can help clinicians predict and mitigate normal tissue toxicities.

These pharmacokinetic considerations are especially critical when choosing with which radionuclide to pair with a particular biomolecule. For RPT, the effective half-life of the radiopharmaceutical as determined by the biologic half-life of the carrier and the physical half-life of the radioisotope needs to be considered and is denoted as follows:

$$t_{½e} = \frac{(t_{½b} \times t_{½p})}{(t_{½b} + t_{½p})} \quad (1)$$

Here, $t_{½e}$, $t_{½b}$, and $t_{½p}$ represent effective, biologic, and physical half-live, respectively. Canonically, the biologic half-life of the biomolecule and the physical half-life of the radionuclide should be similar. Otherwise, if, for example, a peptide with a fast blood clearance and, therefore, a short biologic half-life, is coupled to a long-lived radionuclide, a significant proportion of the resulting radioconjugate will be excreted entirely intact in the urine, without much decay within the tumor. The converse is true of a short-lived radionuclide being coupled to a long-lived biomolecule, where most of the decay would likely occur in the blood before much of the biomolecule accumulates within the tumor. That said, there is evidence, however, that pairings of long-lived radionuclides (days) with short biologic half-life ligands (minutes to hours) can still result in favorable therapeutic effect clinically as is presented later.

CLINICALLY APPROVED RADIOPHARMACEUTICAL THERAPY AGENTS

We have covered some approved and experimental radiopharmaceutical agents in earlier sections of this chapter while describing the components and features of these drugs. For completeness, we include RPT agents that are FDA approved, including those that are not commercially available at the time of this writing (Table 25.1 and Figure 25.1).

Although the oral formulation of radioiodine (sodium iodide I-131, $Na^{131}I$) was approved by the FDA in 1971 to treat hyperthyroidism and thyroid carcinomas, it had been in use for these indications since the 1940s. For patients with intact thyroid carcinoma, therapeutic doses range from 3.70-5.55 GBq (100-150 mCi). For postoperative residual disease, the dose is typically 1.85 GBq (50 mCi).[27] Treatment planning can involve the use of diagnostic oral capsule formulation of radioiodine ($Na^{131}I$ or $Na^{123}I$), using trace activities ranging from 0.185 to 3.7 MBq (5-100 μCi) or 3.7 to 14.8 MBq (100-400 μCi), respectively, to confirm uptake of the radioiodine prior to administering the therapeutic doses.

Modern agents that leverage radionuclide tropism has focused on bone turnover, as happens in regions with metastatic disease. Samarium-153 (^{153}Sm) lexidronam (Quadramet)[28] and strontium-89 (^{89}Sr, Metastron)[29] were evaluated and subsequently approved to treat painful bone metastases, though, at the time of this writing, neither were being provided by their respective manufacturers. More recently, the phase 3 ALSYMPCA trial compared radium-223 dichloride ($^{223}RaCl_2$, Xofigo) versus placebo in patients with metastatic castration-resistant prostate cancer (mCRPC) with bone metastases and no known visceral metastases. The trial showed overall survival (OS) benefit (14.0 vs 11.2 months, hazard ratio [HR] 0.70, 95% confidence interval [CI] 0.55-0.88, $P = .002$) and longer time-to-first symptomatic skeletal event (eg, symptomatic fracture, EBRT for skeletal symptoms).[30] Importantly, when $^{223}RaCl_2$ was combined with abiraterone acetate and steroids in patients with mCRPC, it showed neither improved OS benefit nor improved time-to-first symptomatic skeletal event and was associated with increased fracture risk compared to placebo in the ERA 223 phase 3 clinical trial.[31] Theoretically, any of these bone-seeking radioisotopes should be able to deliver therapeutic radiation to metastases to the bone of other, non–prostate cancer histologies and may demonstrate benefit in patients with bone-only or bone-dominant disease. This question was tackled by a pooled analysis of two phase 2 randomized controlled trials (RCTs) of patients with metastatic breast cancer assessing the effectiveness of ^{223}Ra versus placebo in delaying symptomatic skeletal event-free survival and radiologic progression-free survival (rPFS) and

showed no differences in these primary end points.[32] While the original studies terminated early and the results do not support the use of ^{223}Ra in these patients, authors mentioned that the presence of visceral metastases, which $^{223}RaCl_2$ cannot treat, may have affected the outcomes. Without a reliable way to chelate ^{223}Ra and link it to tumor-targeted biomolecules to address soft tissue disease, therapy with ^{223}Ra will be limited. Preclinical efforts to this end have been reported, though have yet to yield a tumor-targeted ^{223}Ra-based conjugate to date.[33]

The first active targeted agents that were FDA approved leveraged the excitement surrounding recombinant antibody engineering and focused on the B-cell–specific marker CD20. The CD20-specific full-length antibody-based agents, ^{90}Y-ibritumomab tiuxetan (Zevalin), which used a chelating group that binds the β particle–emitting ^{90}Y, and ^{131}I-tositumomab (Bexxar), which used covalent radioiodination with the β particle–emitting ^{131}I, received FDA approvals in 2002 and 2003, respectively. Both agents had indications for patients with relapsed or refractory, low-grade, or follicular B-cell non-Hodgkin lymphoma, which express CD20. Notably, ^{131}I-tositumomab did include a "dosimetric dose" of 0.185 GBq (5 mCi), with 35 mg of antibody followed by γ camera counts and imaging at three separate time points postinjection (1 hour; day 2, 3, or 4; day 6 or 7). Data from these time points could then be used to calculate the therapeutic dose for each patient. Still, this attempt at personalized dosimetry was a logistical challenge in the context of other logistical challenges in a disease that had alternative approved therapies that more easily fit within existing clinical oncology workflows (eg, rituximab). At the time of this writing, neither agent is commercially available as their use has been largely supplanted by other systemic therapies.[34,35]

Following the commercial failure of these antibody-based agents, interest in RPT development waned. Although a few of the modern targeted agents appeared to demonstrate therapeutic benefit when given to patients based on bioplausibility, because these agents were not studied in RCTs, interest was limited to specialty centers in Europe. Notably, these modern RPT agents typically also have a diagnostic agent with which they are paired and often precede the development of the therapeutic partner.

The first phase 3 RCT that demonstrated improved clinical outcomes in patients with tumors harboring a tumor- selective target was the NETTER-1 trial. This was a phase 3 trial of patients with SSTR-positive GEP-NETs randomized to receive standard of care somatostatin (a.k.a. octreotide)-based therapy versus somatostatin combined with [^{177}Lu] Lu-DOTATATE delivered in 7.4 GBq (200 mCi) doses every 8 weeks for a total of four doses. Intravenous amino acid infusion is required prior to, during, and following [^{177}Lu] Lu-DOTATATE infusion. The

primary end point for NETTER-1 was PFS, and secondary end points were objective response rates (ORRs), overall survival (OS), safety, and side-effect profiles. The interim report published in 2017 showed superior 20-month PFS in the RPT arm (65.2%, 95% CI 50.0-76.8) over the control arm (10.8%, 95% CI 3.5-23.0). ORRs and OS were also significantly improved in the [^{177}Lu] Lu-DOTATATE arm.[36] These results led to FDA approval in 2018. Importantly, while the OS benefit seen in the interim analysis did not hold up in the final report (median OS of 48.0 months in the [^{177}Lu] Lu-DOTATATE group versus 36.3 months in the control group, HR 0.84, 95% CI 0.60-1.17, P = .30), both PFS and the quality of life of patients in the RPT group were superior to the control arm.[37,38] Authors posit that the loss of the OS signal may be due to 36% of patients in the control arm receiving postprotocol SSTR-targeted RPT at progression in the form of [^{177}Lu] Lu-DOTATATE, ^{177}Lu-DOTANOC, ^{90}Y-DOTANOC, ^{90}Y-DOTATOC (edotreotide), or ^{90}Y-DOTATATE. These similar agents, if tested prospectively for efficacy, may join [^{177}Lu] Lu-DOTATATE (Lu-177 oxodotreotide, Lutathera) for similar indications.

Pheochromocytomas and paragangliomas, types of NETs associated with hypertension due to increased catecholamine production, have also been the focus of targeted RPT. Iodine-131 iobenguane (^{131}I-MIBG, Azedra) is a small molecule similar in structure to the neurotransmitter norepinephrine and binds to the norepinephrine receptor overexpressed in pheochromocytomas and paragangliomas. This agent was FDA approved in 2018 following a multicenter phase 2 single-arm study, showing that patients who received at least 18.5 GBq (500 mCi) demonstrated durable reduction in antihypertensive medications compared to baseline and 92% of patients exhibited partial response or stable disease.[39,40] Like ^{131}I-tositumomab, ^{131}I-MIBG also used a dosimetry dose to tailor the administered activity for each patient. At the time of this writing, however, this agent is not commercially available and the manufacturer has discontinued its production.

The gene encoding PSMA, also known as folate hydrolase 1 and glutamate carboxypeptidase II, was first cloned in 1993. In the intervening years, first antibodies and later small molecules specific to the target were developed with both diagnostic and therapeutic intent.[41] Diagnostically, because prostate adenocarcinomas do not typically take up the standard PET tracer ^{18}FDG, FDG was not routinely used to help with staging, treatment response monitoring, and surveillance of patients with prostate cancer. Instead, computed tomography (CT) and bone scintigraphy, or bone scans, with ^{99m}Tc-MDP were the main imaging modalities for staging. With the recent testing and subsequent approvals of PSMA-selective PET imaging agents, including ^{68}Ga-PSMA-11 (Ga-68 gozetotide,

Locametz and Illuccix), ^{18}F-DCFPyL (piflufolastat F-18), and ^{18}F-rhPSMA-7.3 (flotufolastat F-18, Posluma), allowed for more precise patient selection for the PSMA-targeted β particle–emitting RPT [^{177}Lu]Lu-PSMA-617 (Lu-177 vipivotide tetraxetan, Pluvicto). These imaging agents are already being used to change treatment recommendations for patients, although improved outcomes for patients as a consequence of this change remain to be determined.[42]

The first prospective RCT of PSMA-targeted RPT was first reported in the TheraP phase 2 trial that enrolled patients with mCRPC who progressed after first-line taxane (docetaxel) and randomized patients to treatment with [^{177}Lu]Lu-PSMA-617 or cabazitaxel.[43] The trial required patients to be imaged with both FDG and PSMA PET (^{68}Ga-PSMA-11), having stringent imaging criteria requiring both PSMA-positive disease and no sites of metastatic disease with discordant FDG-positive and PSMA-negative findings. The primary end point was prostate-specific antigen (PSA) response defined by reduction of at least 50% from baseline. In the intention-to-treat analysis, authors showed 66% versus 37% PSA response in the experimental arm compared to cabazitaxel. In addition, there were fewer grade 3 or 4 adverse events in the experimental arm. OS was no different between patients treated with [^{177}Lu]Lu-PSMA-617 versus those treated with cabazitaxel.[44] These findings showed that RPT could be an effective alternative to chemotherapy with more favorable toxicity profiles in patients.

On the heels of TheraP, the phase 3 VISION study enrolled patients with mCRPC, who had progressed after first-line taxane and/or were not eligible to receive second-line taxane therapy, and randomized them to [^{177}Lu]Lu-PSMA-617 (7.4 GBq, 200 mCi every 6 weeks for four to six cycles) or to protocol- defined standard of care. Notably, the protocol-defined standard of care permitted hormonal treatments, bisphosphonates, radiation, denosumab, and glucocorticoids, but not cytotoxic chemotherapy, ^{223}Ra, immunotherapy, or other investigational drugs. This definition of standard of care raised criticism regarding the use of a substandard control arm. In response, authors have highlighted the idea that clinicians would be much more willing to offer [^{177}Lu]Lu-PSMA-617 to patients who might be too fragile for chemotherapy. Eligible patients underwent ^{68}Ga-PSMA-11 imaging and had one or more PSMA-positive lesions. Primary end points were imaging-based PFS and OS. With a median follow-up of 20.9 months, [^{177}Lu]Lu-PSMA-617 demonstrated prolonged imaging-based PFS (median 8.7 vs 3.4; HR 0.40, 99.2% CI 0.29-0.57, $P < .001$) and OS (median 15.3 vs 11.3 months; HR 0.62, 95% CI 0.52-0.74, $P < .001$).[45] Importantly, health-related quality of life and pain outcomes were superior in patients who received [^{177}Lu]Lu-PSMA-617.[46] Following the results of VISION, the FDA approved [^{177}Lu]Lu-PSMA-617 (lutetium Lu-177 vipivotide tetraxetan, Pluvicto) in 2022.

There are several trials looking to test [^{177}Lu] Lu-DOTATATE and [^{177}Lu]Lu-PSMA-617/[^{177}Lu]Lu-PSMA-I&T earlier in the course of disease, as well as in combination with surgery, external radiotherapy, immune checkpoint blockade, or DNA damage repair inhibitors. These are discussed in detail in Future Directions.

Before closing this section, we wanted to touch on transarterial radioembolization (TARE, a.k.a. radiation segmentectomy, and selective internal radiotherapy), which uses β particle–emitting yttrium-90 (^{90}Y) glass (TheraSphere) or resin (SIR-spheres) microspheres for transarterial therapy of primary and/or secondary liver cancers, respectively. These agents are distinct from the others discussed so far in that they exploit the fact that primary and secondary liver tumors are primarily perfused arterially, whereas non–tumor-bearing liver is perfused mostly by the portal circulation. Assuming that the lung shunt fraction is low, by use of ^{99m}Tc-labeled macroaggregated albumin as a surrogate for the biodistribution of the microspheres, the radioactive microspheres will preferentially accumulate in tumors.[47] While randomized controlled studies assessing the ability of this approach to improve OS were negative,[48-50] TARE can achieve excellent local control and can be used in multifocal hepatocellular carcinoma (HCC).[51]

In contrast to RPT, microspheres can remain localized within tumors, allowing for more reliable tumor-absorbed dose estimates, and recent prospective data suggest that dose escalation in this setting results in improved patient ORRs.[52] Recently, the American Association for the Study of Liver Diseases guidelines recommended TARE along with stereotactic body radiotherapy to treat patients with unresectable liver HCC tumors >3 cm.[53]

Managing Adverse Events of Radiopharmaceutical Therapy Agents

Toxicities for the approved agents are well described and correspond with the biodistribution of the associated agents. For example, [^{177}Lu]Lu-PSMA-617 has known renal, bone marrow, and salivary gland toxicity. Accordingly, threshold laboratory values for serum creatinine/estimated glomerular filtration rate, hemoglobin, white blood cell count, and platelets included in the relevant studies have been reported.[54] The European Association of Nuclear Medicine (EANM) and Society of Nuclear Medicine and Molecular Imaging (SNMMI) published their guidelines for the use of [^{177}Lu]Lu-PSMA radioligand therapy and expanded on the management of adverse events of this agent.[55] Hematologic toxicity (eg, anemia, leukopenia, thrombocytopenia), nephrotoxicity, xerostomia, nausea/vomiting, and fatigue are among the common acute adverse events expected in patients receiving [^{177}Lu]Lu-PSMA radioligand therapy.

Generally, for grade ≥2 toxicities, postponing the subsequent cycle or reduction of administered activity (eg, by 20%) to allow recovery is recommended. As with other cytotoxic systemic agents, growth factors (eg, granulocyte colony-stimulating factor) can be used to support treatment-induced neutropenia, and red blood cells or platelet transfusions can be used to address clinically meaningful anemia or thrombocytopenia.

To address xerostomia, which is anticipated for the approved [^{177}Lu]Lu-PSMA-617 as well as other investigational peptidomimetic PSMA-targeted agents (eg, [^{225}Ac]Ac-PSMA-617, [^{177}Lu]Lu-PSMA-I&T, [^{225}Ac]Ac-PSMA-I&T), recommendations range from proper hydration, use of humidifiers at home, to use of gum and lozenges, salivary substitutes, and pharmacotherapy with pilocarpine or cevimeline. Experimental approaches aiming at the prevention of xerostomia involve the use of cooling of glands prior to therapy, or administering a nonradioactive PSMA-targeting molecule to block uptake in salivary glands either systemically or directly into the ducts in preclinical studies.[56-58] Others have shown decreased uptake of [^{225}Ac]Ac-PSMA-617 by pretreating with intraglandular injection of botulinum toxin; however, this approach raises concerns regarding the effects of the toxin itself on the health of the gland.[59]

In addition to xerostomia, because there is a renal tubular expression of PSMA and [^{177}Lu]Lu-PSMA–targeted ligands are excreted renally, nephrotoxicity is of concern. Investigators have reported mean absorbed doses of 20 and 31 Gy for four to six cycles of [^{177}Lu]Lu-PSMA-617 or [^{177}Lu]Lu-PSMA-I&T and that, unsurprisingly, the number of cycles administered correlates with toxicity.[60-62] To date, 23 Gy, which is extrapolated from the external beam, has been used as an albeit imperfect limit for late renal toxicities following treatment with RPT. We have already touched on the need to administer amino acids as part of [^{177}Lu] Lu-DOTATATE therapy, which helps to mitigate renal failure to <2%.[63]

Other late toxicities can include myelodysplasia, leukemias, or chronic cytopenias; although, described for patients receiving [^{177}Lu] Lu-DOTATATE, these toxicities are reported to be in the range of 2% to 7% and skew higher if patients also receive alkylating agents.[63,64] Perhaps because patients receiving [^{177}Lu]Lu-PSMA targeted ligands tend to have a shorter survival time, these therapy-related myeloid neoplasms have not yet had the time to declare themselves in patients with prostate cancer who received this treatment. That said, given the growing interest in moving peptidomimetic PSMA-targeted RPT (eg., PSMA-617 and PSMA-I&T) to earlier lines of therapy, these late toxicities become a much more salient competing risk.

NUTS AND BOLTS OF A RADIOPHARMACEUTICAL THERAPY PROGRAM

Implementation

Following [^{177}Lu]Lu-PSMA-617 approval by the FDA, challenges in securing sufficient radioisotope and additional supply chain issues caused significant delays in having this agent, and [^{177}Lu] Lu-DOTATATE, available for eligible patients. These growing pains resulting in treatment interruptions for many patients, though, should resolve over time as more production facilities come online.

Among the first challenges in implementation is ensuring that standard operating procedures (SOPs) for the receipt of, handling, ensuring quality, and administration of the relevant RPTs are established. These SOPs will require close collaboration with the drug manufacturers, who can share wisdom gained from implementing programs globally. In addition, dose calibrators, shielded areas for dose handling, and dedicated spaces for patient administration are needed to perform quality assurance testing of RPT agents. While not all agents will require significant space and shielding, investments required to establish and maintain this infrastructure and trained personnel represent a rate-limiting step in the broader implementation of RPT. In the United States, other challenges with respect to billing and reimbursement are being addressed, but are still in flux.[65,66]

Multisociety white papers including the American College of Radiology, the American College of Nuclear Medicine, the American Radium Society, the American Society for Radiation Oncology, and SNMMI Practice Parameter are a good place to start when first learning about the agents and how to administer them in clinic.[67] International collaborations such as the white paper published by the EANM, SNMMI, and the International Atomic Energy Agency (IAEA) offer additional guidance in launching a theranostics center.[68] Because regulations differ depending on local regulations, close collaboration with radiation safety officers to ensure compliance is critical.

Early considerations when launching a theranostics clinical service are identifying which agents will be used and ensuring the facilities are able to adequately accommodate these agents with respect to shielded rooms, dedicated bathrooms, and ability to quickly address any acute medical issues. Long-lived contaminants that may be present based on the manufacturing methods used to make radionuclides need to be considered as well. For example, ^{177}Lu, when made via direct neutron irradiation of ^{176}Lu targets, ^{177m}Lu ($t_{1/2}$ = 161 d) is also generated and items need to be stored and allowed to decay to acceptable levels for disposal per local regulatory requirements.

Zoberi et al published a comprehensive report on getting a[^{177}Lu]Lu-PSMA-617 therapy program up and running, echoing many of the important considerations laid out by the EANM/SNMMI/IAEA guide.[69] The same group also published on their experience launching a [^{177}Lu] Lu-DOTATATE program.[70] While both agents use the same radionuclide, the workflow for administration differs. Specifically, unlike [^{177}Lu]Lu-PSMA radioligand therapy, [^{177}Lu] Lu-DOTATATE therapy requires infusion of amino acids prior to, during, and after RPT delivery lasting ~4 hours, which needs to be considered as part of clinical workflows. Both publications offer excellent step-by-step guidance for departments and institutions interested in incorporating RPT as part of comprehensive cancer care.

Workforce

Training and Certification

To ensure that approved RPT agents are available for the patients who need them, it is critical to have a workforce who understands how to use the approved RPT agents, their indications and contraindications, how to administer them safely and appropriately, and how to manage adverse events. A formalized curriculum would be helpful for standardization and competency. Nuclear medicine physicians and radiation oncologists are all eligible for Clinical Authorized User (AU) status and will lead the way shaping how this modality is used along with multidisciplinary teams. Nuclear medicine technologists, medical physicists, and nurses trained to work with radiopharmaceuticals will also be needed to round out the clinical care team.

Historically, the extent of training in RPT within radiation oncology residencies varies widely from program to program. The ASTRO RPT Workgroup proposed a framework to ensure that radiation oncology trainees have both the prerequisite didactics and hands-on exposure as part of a standard residency curriculum.[71]

Demonstrating sufficient knowledge and skills in radiation protection practices and procedures is necessary for qualifying individuals who want to be approved as an AU physician. The United States Nuclear Regulatory Commission (NRC) has established training and experience requirements they deem essential for the use of therapeutic radiopharmaceuticals in 10 CFR 35.390.[72] These requirements include completion of 700 hours of training and experience, including a minimum of 200 hours of classroom and laboratory training in basic radionuclide handling techniques applicable to the medical use of therapeutic radiopharmaceuticals (Table 25.2). The requirements in this section are understandably skewed toward physicians specializing in nuclear medicine.

TABLE 25.2 SUMMARY OF FDA-APPROVED RADIOPHARMACEUTICAL AGENTS

Agent	Disease	Type of Emission	Known Adverse Events	Contraindications
^{131}I (radioiodine)	Well-differentiated thyroid cancer Toxic adenoma Toxic multinodular goiter Nontoxic multinodular goiter	β	Early Xerostomia Nausea and vomiting Transient myelosuppression Radiation thyroiditis Nasolacrimal duct obstruction Transient thyrotoxicosis Late Second malignancy Pulmonary fibrosis Hypothyroidism Permanent myelosuppression	Lactation and pregnancy Moderate to severe Graves ophthalmopathy Severe thyrotoxicosis Thyroid cancer with no iodine uptake
^{153}Sm lexidronam (Quadramet)	Painful multifocal osteoblastic skeletal metastases from prostate, breast, and lung cancer, and osteosarcoma	β	Myelosuppression Nausea and vomiting Constipation Asthenia Fever Anorexia Spinal cord compression Pain flare UTI	Absolute Severe myelosuppression Severe renal dysfunction Relative Solitary or limited bone metastasis Osteolytic lesion Lesions with poor uptake on bone scan
$^{89}SrCl_2$ (Metastron)	Painful multifocal osteoblastic skeletal metastases from prostate, breast, and lung cancer mCRPC	β	Pain flare Myelosuppression Hot flush	Absolute None Relative Bone marrow infiltration Bone marrow dysfunction Pregnancy
$^{223}RaCl_2$ (Xofigo)	mCRPC with symptomatic ≥2 bone metastases and no visceral metastasis	α	Bone pain Anemia Spinal cord compression Myelosuppression Constipation Nausea and vomiting	Visceral metastasis Imminent or established spinal cord compression Malignant lymphadenopathy Concurrent use of abiraterone and

Agent	Disease	Type of Emission	Known Adverse Events	Contraindications
			Asthenia	$^{223}RaCl_2$
[^{177}Lu]Lu-PSMA-617 (Pluvicto)	mCRPC (pretreated with docetaxel)	β	Myelosuppression Fatigue Xerostomia Nausea and vomiting	Absolute None Relative Urinary tract obstruction
[^{90}Y]Y-ibritumomab (Zevalin)	CD20$^+$ antigen-expressing relapsed or refractory, low-grade, follicular, or transformed NHL, including patients with rituximab-refractory NHL	β	Myelosuppression Diarrhea Nausea and vomiting Asthenia Arthralgia URTI Colitis Sepsis UTI	Absolute Pregnancy Lactation Hypersensitivity to murine antibodies Myelosuppression >25% marrow involvement or treated with radiation therapy Prior autologous SCT Elevated HAMA titers with biodistribution
[^{131}I]I-tositumomab (Bexxar)[a]	CD20$^+$ antigen-expressing relapsed or refractory, low-grade, follicular, or transformed NHL, including patients with rituximab-refractory NHL	β	Myelosuppression Diarrhea Nausea and vomiting Asthenia Arthralgia URTI Colitis Sepsis UTI	Absolute Pregnancy Lactation Hypersensitivity to murine antibodies Myelosuppression >25% marrow involvement or treated with radiation therapy Prior autologous SCT Elevated HAMA titers with biodistribution Iodine allergy Creatinine >1.5 Relative Urinary incontinence
[^{131}I]I-MIBG (Azedra)[a]	Neuroblastoma[b] Unresectable, locally advanced, or metastatic	β	Myelosuppression Fatigue Increased INR Nausea and vomiting	Absolute None Relative Pregnancy Lactation

Agent	Disease	Type of Emission	Known Adverse Events	Contraindications
	pheochromocytoma and paraganglioma		Hypertension Dizziness Hypothyroidism Second malignancy Infertility	Renal failure
[^{177}Lu]Lu-DOTATATE	Advanced SSTR^{+} gastroenteropancreatic neuroendocrine tumors	β	Myelosuppression Nausea and vomiting Diarrhea Asthenia Anorexia Musculoskeletal pain Flushing Alopecia Myelodysplastic syndrome	None
^{90}Y-labeled glass microspheres (TheraSphere)	Solitary 1-8 cm of HCC and Child-Pugh class A cirrhosis Colorectal liver metastasis (progressed on first-line chemotherapy)	β	Myelosuppression Nausea and vomiting Fatigue Fever Gallbladder obstruction Hyperbilirubinemia Cerebrovascular accident	^{99m}Tc-MAA hepatic arterial perfusion scintigraphy showing any deposition to the gastrointestinal tract that may not be corrected by angiographic techniques Shunting of blood to the lungs that could result in delivery of greater than 16.5 mCi of Y-90 to the lungs Contraindications to hepatic artery catheterization Pulmonary insufficiency (Pa_{O_2} <60 and Sa_{O_2} <80) Severe liver dysfunction, hepatic encephalopathy, clinically evident ascites

Agent	Disease	Type of Emission	Known Adverse Events	Contraindications
				Tumor replacing >70% of liver Portal vein thrombosis with type 4 involvement Pregnancy
^{90}Y-labeled resin microspheres (SIR-spheres)	Unresectable secondary liver cancer from colorectal primary with adjuvant intrahepatic artery chemotherapy of floxuridine	β	Myelosuppression Diarrhea Fatigue Peripheral neuropathy Nausea and vomiting Radiation hepatitis Gastric/duodenal ulcer Hypoalbuminemia	Prior external beam radiation therapy to the liver Clinically evident ascites or are in clinical liver failure Markedly abnormal synthetic and excretory liver function tests >20% lung shunting of the hepatic artery blood flow determined by ^{99m}Tc-MAA scan Preassessment angiogram demonstrating abnormal vascular anatomy that would result in significant reflux of hepatic arterial blood to the stomach, pancreas, or bowel Disseminated extrahepatic malignant disease Prior treatment with capecitabine within the 2 previous months, or planned to be treated with capecitabine at any time following treatment with SIR-spheres

Agent	Disease	Type of Emission	Known Adverse Events	Contraindications
				Portal vein thrombosis

^{99m}Tc-MAA, technetium-99m macroaggregated human albumin; DLBCL, diffuse large B-cell lymphoma; EBRT, external beam radiation therapy; FDA, Food and Drug Administration; HAMA, human anti-mouse antibody; HCC, hepatocellular carcinoma; INR, international normalized ratio; mCRPC, metastatic castrate-resistant prostate cancer; NHL, non-Hodgkin lymphoma; PSA, prostate-specific antigen; SCT, stem cell transplant; URTI, upper respiratory tract infection; UTI, urinary tract infection.

[a]No longer commercially available.

[b]Not FDA approved for this indication.

Adapted from Salerno KE, Roy S, Ribaudo C, et al. A primer on radiopharmaceutical therapy. *Int J Radiat Oncol Biol Phys*. 2023;115(1):48-59. With permission.

The NRC has similar requirements for physicians specializing in radiation oncology. Requirements for the authorization of radiation oncology uses can be found in 10 CFR 35.490 for manual brachytherapy sources and 10 CFR 35.690 for remote afterloaders, teletherapy units, and γ stereotactic radiosurgery units.[73,74]

Most of the required didactic subject matter overlaps between nuclear medicine and radiation oncology, including radiation physics and instrumentation, radiation protection, and radiation biology. However, while nuclear medicine training includes information regarding the chemistry of byproduct material for medical use as a topic, radiation oncology typically does not.

The authorization requirements for the two specialties also diverge in the required areas of supervised work experience. Where the nuclear medicine resident must log experience in ordering, receiving, and unpacking radioactive materials, quality control for instruments used to assay doses, determining patient dosages, and spill response, a radiation oncology resident must instead log experience in reviewing calibration measurements and periodic spot-checks, treatment planning for sealed sources, implanting and removal of brachytherapy sources, and emergency procedures during abnormal operation of devices. Most, if not all the required training and experience, is accrued during a residency program. However, a resident in a radiation oncology program may only be able to accrue the training and experience specific to therapeutic radiopharmaceuticals during dedicated nuclear medicine rotations. That said, accruing enough work experience hours to meet the requirements in 10 CFR 35.390 may be onerous.

Until December 2023, the American Board of Radiology (ABR) offered an "AU-Eligible" designation on board certifications of candidates submitting training and experience documentation to the ABR.[75] Due to this change, it will

now be necessary for a physician seeking authorization for more typical radiation oncology uses (manual brachytherapy sources, teletherapy units, remote afterloader units, γ stereotactic radiosurgery units) to submit training and experience documentation to the NRC or the Institutional Radiation Safety Committee overseeing the radioactive materials license on which the physician intends to practice. In addition to this documentation, a written attestation from a preceptor or residency program director that the candidate has completed all requirements and is independently able to fulfill radiation safety-related duties will be required.

To add authorization for the use of therapeutic radiopharmaceuticals, additional training and experience documentation will be necessary. If a physician is already approved on a radioactive materials license under 10 CFR 35.490 and/or 10 CFR 35.690, the NRC regulations provide an option for expanding that authorization to therapeutic radiopharmaceutical uses. These requirements can be found in 10 CFR 35.394 (oral administration of $Na^{131}I$) and 10 CFR 35.396 (parenteral administrations).[76,77] By pursuing this pathway, the 200 hours of classroom and laboratory training required by 10 CFR 35.390 is reduced to 80 hours. Supervised work experience in specific areas is needed under these regulations, but there is no longer a required number of hours. A written attestation from a preceptor approved for RPTs is still required.

Ideally, residency program directors could work with the radiation safety officers and have senior residents to apply for authorization for radiation oncology uses on their home institution license as soon as they meet all requirements in 10 CFR 35.490 and/or 10 CFR 35.690. If this is not possible, the resident should ensure they have acquired any necessary written attestations and training and work experience documentation for their records so they are prepared to apply for authorization as soon as they are able. These records should include those associated with RPTs, such as participation in at least three cases of oral administrations of $Na^{131}I$ and three cases of parenteral administrations; additional training in materials ordering, receipt, and surveying; training in spill response; and a written attestation from a preceptor approved for RPT uses. Once the radiation oncology authorization is acquired, the pathway for approval to administer RPTs is available by meeting the requirements in 10 CFR 35.396. Time is of the essence when applying for authorizations. The NRC requires that the training and experience applied toward the authorization process be completed within 7 years preceding the date of application (10 CFR 35.59).[76] For a summary of these requirements, see Table 25.3. Readers are encouraged to speak with the radiation safety officers at their institutions who will be able to offer up-to-date guidance.

TABLE 25.3 SUMMARY OF US NUCLEAR REGULATORY COMMISSION REQUIREMENTS FOR RADIONUCLIDES

Classroom and Laboratory (200 h)	Work Experience (500 h)	Additional Requirements
Radiation physics and instrumentation	Ordering, receiving, and unpacking radioactive materials safely and performing the related radiation surveys	Involvement in a minimum of three cases in each of the following categories: • Oral administration of ≤1.22 GBq (33 mCi) of sodium iodide I-131 requiring a written directive • Oral administration of >1.22 GBq (33 mCi) of sodium iodide I-131 • Parenteral administration of any radioactive drug that contains a radionuclide that is primarily used for its electron emission, β characteristics, α radiation characteristics, or photon energy of less than 150 keV requiring a written directive
Radiation protection	Performing quality control procedures on instruments used to determine the activity of dosages, and performing checks for proper operation of survey meters	
Mathematics pertaining to the use and measurement of radioactivity	Calculating, measuring, and safely preparing patient or human research subject dosages	
Chemistry of byproduct material for medical use	Using administrative controls to prevent a medical event involving the use of unsealed byproduct material	
Radiation biology	Using procedures to contain spilled byproduct material safely and using proper decontamination procedures	Written attestation from a preceptor-authorized user or residency program director to the satisfactory completion of these requirements

Beyond the Basics

To launch an independent and sustainable RPT clinical program, our radiation oncology programs must recognize that we need to provide a more comprehensive educational experience for our trainees. While the ASTRO RPT Committee framework represents a step in the right direction, it is insufficient for radiation oncologists who wish to start their own independent program from scratch. Alternative training paradigms that include cross-pollination between nuclear medicine and radiation oncology residency programs could simultaneously offer more rigorous oncology training to nuclear medicine residents and more hands-on training in delivery of RPT and interpretation of PET and SPECT images for radiation oncology residents.

More formalized options for residents of both specialties could include an in-depth nuclear medicine rotation or even extend to dual board certification in

nuclear medicine and radiation oncology, a pathway that already exists in the ABR Diagnostic Radiology certification and has been explored by radiation oncology residency programs.

For interested radiation oncology faculty, well-established RPT programs are considering intensive courses along with certification programs for those who wish to obtain the needed training and credentials (eg, NRC requirements). Similarly, physicists and therapists with dual training in external radiation and RPT may be needed. Dosimetry calculations between external beam and RPT differ significantly, though, brachytherapy specialists may be able to extend upon their foundational knowledge.

At the program level, metrics to ensure best practices and quality assurance should be considered. The SNMMI launched Centers of Excellence designation, and ASTRO's Accreditation Program for Excellence could include RPT accreditation as well. Whether any, one, or both accreditations should be mandatory remains to be determined.

FUTURE DIRECTIONS

It is always a risky proposition to make predictions regarding a dynamic field. That said, there are some natural lines of inquiry to be pursued when it comes to RPT, which is touched on below. Where relevant, we touch on some open clinical trials; however, the list is not intended to be comprehensive.

Optimization of Existing Agents

Personalized Dosimetry

With the notable exception of ^{131}I-MIBG and ^{131}I-tositumomab, administration of RPTs does not currently consider patient tumor burden. Instead, RPT agents are administered as flat or weight-based activity per session akin to many systemic chemotherapy regimens, with dose adjustments based on observed toxicities. Accounting for tumor burden could significantly improve antitumor effect and mitigate toxicity. A patient with low burden of disease may quickly saturate targets with a standard flat dose of an RPT agent, resulting in high excess radioligand circulating in nontarget tissues, only contributing to toxicity and radiation safety concerns. Conversely, a patient with high burden of disease may require a higher administered activity to effectively saturate targets on tumors and might have been undertreated with use of the standard activity approach. In addition, such patients could benefit from receiving more than the number of treatments studied in the corresponding clinical trials. Tumor burden may also change over time. For instance, a patient with good response may have very little tumor burden and

hence uptake by the last treatment and may not require the same injected activity by the final treatment fraction as they did earlier in their course. Such dose-based optimizations may yield improved patient outcomes but need to be evaluated prospectively.

While radiation oncologists take it as a given that dose matters when it comes to both tumor control and organ-level toxicity, because there are limited prospective data demonstrating benefit of personalized dosimetry for RPT, it remains a point of debate. Bodei et al made the case for individualized dosimetry to tailor radiation-absorbed dose to maximize the efficacy of tumor treatment and minimize toxicity to organs at risk.[78] Strosberg et al, in contrast, recommended waiting for clinical trials to demonstrate a clinical benefit before fully endorsing the endeavor and associated time and costs.[79] Of course, one has to perform high-quality dosimetry studies with RPT agents as part of systematic investigations to definitively determine dose-response effects.[80]

A persistent logistical challenge for personalized dosimetry is that, ideally, SPECT images over several days are needed to accurately estimate the absorbed doses in patients. This approach adds more visits for patients and presents a challenge as to who should pay for these scans. Furthermore, typical SPECT scanners would subject patients to at least an hour of scanning for each time point, though, modern scanners can significantly decrease these times.[81] Appreciating these barriers, some investigators have successfully devised single time point–based dosimetry.[82,83]

A recent dosimetric analysis of the VISION trial estimated that the observed and predicted absorbed dose to the kidneys were comparable (15 ± 5 and 19 ± 7 Gy, respectively), both of which were below the historically established limit of 23 Gy based on external beam, suggesting that, at least with respect to renal toxicity, it is theoretically possible to administer more cumulative activity per patient.[62] Importantly, because PSMA is endogenously expressed in the lacrimal and salivary glands, PSMA-targeted RPT will specifically localize to these tissues. The observed absorbed dose to the lacrimal and salivary glands were significant, with a mean of 77 Gy (53-115 Gy) and 30 Gy (11-58 Gy), resulting in any grade dry eye and mouth of 3% and 39%, respectively.[45] These findings support the importance of organ-level dosimetry and assessing tissue-specific radiosensitivity differences with RPT agents.

The LUMEN phase 2 single-arm study used multimodality imaging in patients with GEP-NETs to predict outcomes with [^{177}Lu] Lu-DOTATATE therapy. Investigators used ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT imaging and SPECT/CT imaging at three time points for each of the four 7.4-GBq cycles. The

results showed that both the absorbed dose of ≥35 Gy in all targets and ≥10% tumor volume decrease following cycle 1 correlated with longer PFS.[84]

Methods for Radiopharmaceutical Therapy Dosimetry

While clinical use of RPT largely relies on weight- or toxicity-based activity, administration efforts for personalized dosimetry have been an area of significant interest. Personalized dosimetry methods for RPT have long been developed by researchers, yet they have not been routinely implemented in the clinical setting due to many barriers, including challenges in performing post-treatment imaging, having dedicated expertise and software tools for RPT dosimetry, and reimbursement-related issues. ASTRO, AAPM, and SNMMI have recognized the importance of patient-specific dosimetry for RPT and have been actively working on resolving these barriers. The SNMMI committee on medical internal radiation dose (MIRD) has released the MIRDfit and MIRDcalc software products for providing dosimetry calculation tools for the community and hosted a dosimetry challenge in 2021, with the goal of advancing personalized RPT dosimetry.[85,86] ASTRO has also been actively working on increasing the utilization of personalized RPT dosimetry, including by developing a working group to develop reimbursable RPT dosimetry codes and hosting a think tank to connect differing groups within the RPT space.[66] In addition, in 2023, AAPM hosted its summer school on Radiopharmaceutical Therapy and Dosimetry to improve training for personalized RPT dosimetry within the clinical medical physics community.

Various mathematical methods for personalized dosimetry have been developed, yet many, even current solutions, rely on the MIRD schema, which was developed in the 1960s.[87] The MIRD equation estimates the mean absorbed dose to a volume (or organ) depending on the time integral of activity; the mean energy of radiation type, which is dependent on the type of radionuclide; absorbed dose fraction; and mass of target volume. While the MIRD schema has been validated for RPT dosimetry applications, it does take several assumptions into account including static and homogeneous size, shape, position, composition, and density of each region (tumor/normal tissue organ) as well as assumptions regarding the residence time of various source regions within a region of interest.[88] To overcome these limitations, more recent RPT software packages have incorporated Monte Carlo, MIRD voxel S-values, or point kernel convolution methods and multi-time point post-treatment SPECT/CT imaging to generate a more accurate representation of changes in source activity position and tumor/organ position, composition, and density.[89,90] The general workflow of RPT dosimetry includes recording the time of administration, then performing post-treatment imaging with SPECT/CT,

preferably at multiple time points, contouring regions of interest such as normal tissues and areas of tumor, and then performing organ- or voxel-based, radionuclide-specific dosimetric calculations of the absorbed dose to these tissues (Figure 25.5). Several commercially available software packages are available for RPT dosimetry, and others are currently in development.[91] Understandably, the ease with which methods to calculate the absorbed doses to tumors and organs at risk can be incorporated into existing clinical workflows as well as whether the work will be reimbursed will influence adoption.

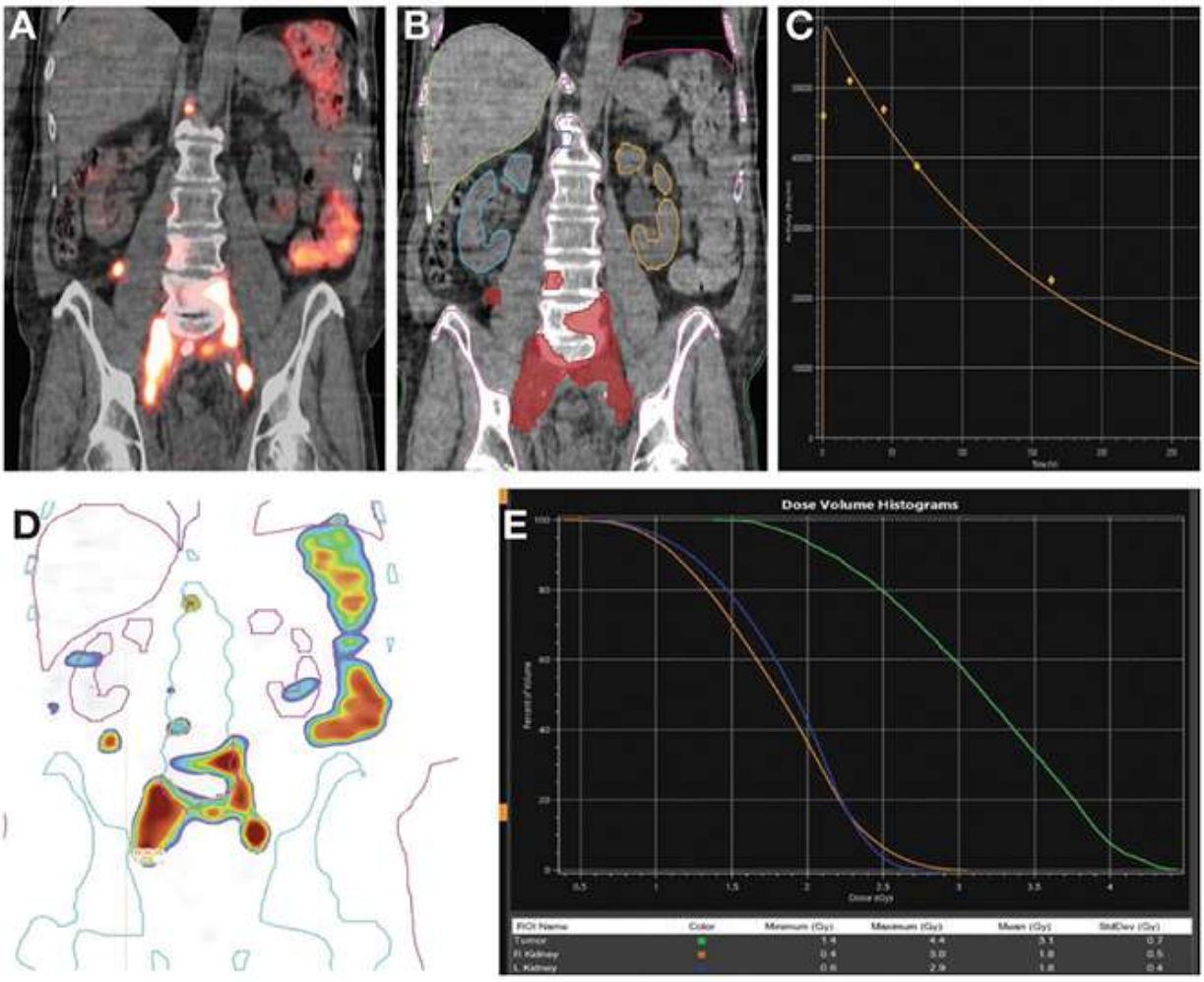

FIGURE 25.5 Workflow for radiopharmaceutical therapy (RPT) dosimetry. Post-treatment single-photon computed tomography/computed tomography imaging is obtained (preferably at multiple time points) (A), and normal and target tissue (red) contours are segmented (B). After imaging and segmentation, time activity curves of RPT agent in tumors and organs at risk are obtained (C), dose is calculated (MIRD Voxel S-Values, Monte Carlo, point kernel convolution); (D), and dose-volume histogram curve can be obtained for a three-dimensional dose plan (E).

While we can calculate the absorbed dose to tumor and normal tissues with currently available solutions, another significant barrier to implementation of RPT dosimetry is the lack of radiobiologic correlates.[92] Currently, most RPT dose constraints rely on values from conventionally fractionated EBRT; however, these are unlikely to be accurate for β particle–emitting radioisotopes with long half-lives (days) or high LET α particle–emitting radioisotopes. In addition, accounting for redistribution of daughter radionuclides (eg, Ac-225, Ra-223) adds more uncertainty in dose predictions. That said, biologically effective dose calculations to harmonize external beam and radiopharmaceutical absorbed dose response with respect to nephrotoxicity[93] and tumors[94] could allow more facile interpretation of how EBRT and RPT doses interface.

In summary, the current evidence supporting rigorous absorbed dose estimates for tumors and organs at risk, or personalized dosimetry, is sparse, though growing. Much work to streamline and standardize the process is needed, which can help inform the prospective clinical studies to provide the definitive answers on its utility. For a discussion on the debates surrounding the matter and a more in-depth dive on how to calculate the absorbed dose for RPT, we encourage readers to review Blaickner and Carter and Kesner, respectively.[80,95]

New Indications

Expansion of RPT use in additional clinical indications is under active investigation. Several ongoing studies are moving toward the use of RPT agents earlier in the course of disease. For example, LuTectomy (NCT04430192), a phase 1/2 trial assessing the effect of either one or two cycles (5 GBq each) of neoadjuvant [^{177}Lu]Lu-PSMA-617 prior to surgery for high-risk prostate cancer. Authors reported on the primary outcome of the absorbed dose and calculated a median tumor-absorbed dose of 35.5Gy,[96] and 19 of 20 patients having ≥10 Gy, which has been previously reported as associated with ≥50% reduction in PSA for trials in patients with more advanced disease.[97]

The PSMAddition (NCT04343885) phase 3 RCT is enrolling patients with metastatic hormone-sensitive prostate cancer and will compare standard of care (androgen deprivation therapy and androgen receptor pathway inhibitor [ARPi]) to standard of care plus [^{177}Lu]Lu-PSMA-617.[98]

PSMAfore, a phase 3 RCT trial of taxane-naïve patients with mCRPC randomized to [^{177}Lu]Lu-PSMA-617 (7.4 GBq every 6 weeks for six cycles) or switch of ARPi, reported results in abstract form after 15.9 months of follow-up. The results demonstrate promising radiographic PFS benefit of 12.0 months (95% CI 9.30-14.4) versus 5.59 months (95% CI 4.17-5.95) that was statistically

significant (HR 0.43, 95% CI 0.33-0.54, $P > .0001$).[99] Critics of the study argue that a taxane, and not ARPi switch, should be the appropriate control arm. Similarly, the SPLASH trial compares another PSMA-targeted agent ^{177}Lu-PNT2002 (ie, PSMA-I&T, 6.8 GBq every 8 weeks for four cycles) versus ARPi switch in patients with mCRPC. Like in PSMAfore, the primary end point in SPLASH was rPFS in favor of RPT 9.5 versus 6 months (HR 0.71, $P = .0088$). For both studies, the OS was not a primary end point, but did not differ when compared with control arms at the time of reports of either trial. Adverse events were comparable between the experimental and control arms for both. The ECLIPSE phase 3 trial (NCT05204927) is evaluating patients with mCRPC and randomizing them to either [^{177}Lu]Lu-PSMA-I&T (7.4 GBq for six cycles) or abiraterone or enzalutamide. Of note, this control arm has been called into question, given that patients have already developed mCRPC and could be eligible for taxane therapy.

Of particular interest to radiation oncologists, the PSMA-DC phase 3 RCT will randomize patients with oligometastatic prostate cancer to stereotactic radiotherapy followed by either [^{177}Lu]Lu-PSMA-617 (7.4 GBq every 6 weeks for four cycles) or placebo (NCT05939414). The primary end point is metastasis-free survival. RPT, in this setting, is thought to be able to target and treat micrometastatic disease below the limits of detection of clinical scanners.

[^{177}Lu] Lu-DOTATATE (7.4 GBq for four cycles) combined with long-acting octreotide is also being compared to long-acting octreotide alone as first-line therapy in a phase 3 clinical trial for patients with grade 2 and 3 well-differentiated GEP-NETs (NETTER-2, NCT03972488). Of note, NETTER-1 enrolled patients with grade 1 or 2 well-differentiated GEP-NETs. The primary end point is PFS, and this end point has been called into question for systemic agents.[100] Late toxicities, including nephrotoxicity[101] associated become of particular importance in this setting given a longer anticipated survival time of patients with earlier stage disease. Interim analysis was reported in January 2024, which demonstrated superior median PFS in the experimental arm (22.8 months, 95% CI 19.4—not estimable) versus the control arm (8.5 months, 95% CI 7.6-13.8) with a stratified HR of 0.276 (95% CI: 0.182-0.418, $P < .0001$).

LUTIA phase 2 study randomized patients to treatment of either the right or left hepatic lobes with intra-arterial [^{177}Lu] Lu-DOTATATE in patients with GEP-NET liver metastases in addition to systemically administered [^{177}Lu] Lu-DOTATATE. Investigators found no differences in tumor uptake of the RPT agent as measured by planar scintigraphy and/or SPECT between the experimental and control arms, concluding their data do not support the intra-arterial administration of this RPT agent.

As these agents are tested and approved for patients earlier in their disease course and who are more likely to survive for many years, late toxicities become much more relevant and need to be considered when choosing treatment options.

α Versus β

At the interface between existing RPT agents and novel ones, are agents that share the same targeting ligand, but are instead "armed" with α particle–emitting radionuclides such as [^{225}Ac]Ac or ^{212}Pb, in lieu of β-emitting ^{177}Lu. Given that the higher LET of α compared to β emissions, it is thought that tumors refractory to the β-emitting agents may still respond to the α-emitting agents.[102] PSMA and SSTR-targeting ligands are being actively investigated and have demonstrated promising activity thus far.[103-105]

In the multicenter retrospective WARMTH Act study, Sathekge et al evaluated [^{225}Ac]Ac-PSMA radioligand therapy— authors did not specify which ligand, PSMA-617 or PSMA-I&T, was used—in patients with mCRPC (n = 488). The study confirmed good antitumor effect in patients with prior treatments including with docetaxel (66%), [^{177}Lu]Lu-PSMA RLT (32%), or radium-223 (4%). Unsurprisingly, xerostomia was reported in 68% of patients after the first cycle, and all patients who had more than seven cycles eventually developed this side effect.[106]

The ACTION prospective phase 3 RCT is randomizing patients who progressed following ^{177}Lu-based SSTR-targeted RPT to [^{225}Ac]Ac-DOTATATE (RYZ101) versus best standard of care including everolimus, sunitinib, octreotide, or lanreotide (NCT05477576).[107] TATCIST is a single-arm phase 2 trial evaluating the efficacy of [^{225}Ac]Ac-PSMA-I&T in patients with mCRPC, allowing inclusion of patients with prior treatments with ^{177}Lu-based PSMA-targeted RPT (NCT05219500).

We note that, against conventional wisdom, the physical half-life of [^{225}Ac]Ac (~10 days) is much longer than the biologic half-life of the peptidomimetic PSMA-targeting or SSTR- targeted peptide ligands (minutes to hours). Still, these agents have demonstrated some activity in prior clinical studies including of patients who had disease refractory to ^{177}Lu-based RPT.[105,108] More canonical pairings using the theranostic pairs ^{203}Pb and ^{212}Pb for imaging and therapy, respectively, coupled to novel SSTR-targeting ligands for patients with NETs are also being investigated[104] (NCT05636618, NCT05153772).

Same Agents, Different Diseases

Approved agents could be tested for use in patients with other malignancies. As referenced earlier, ^{223}Ra was evaluated in patients with metastatic breast cancer; however, that trial did not demonstrate benefit.[32] Other RPT agents may be more promising. For example, while PSMA is overexpressed on prostate cancer cells, it is also expressed in the neovasculature of renal cell carcinoma[109] and HCC,[110,111] opening the potential utility of PSMA-targeting RPT for these indications. Similarly, SSTRs are also present in pituitary tumors[112] and meningiomas,[113] and therapeutic DOTATATE or DOTATOC (edotreotide) RPT agents may have utility in these diseases. ^{131}I-MIBG, which is used off-label for neuroblastoma, is being compared with a kinase inhibitor (lorlatinib) in pediatric patients with ganglioneuroblastoma and neuroblastomas undergoing intensive standard of care therapy as part of a phase 3 RCT (NCT03126916).

It should go without saying that before these agents can be routinely repurposed for other uses, prospective clinical studies should be performed. One could envision the pursuit of disease-agnostic indications based on the presence of the clinically relevant target as evinced by the diagnostic imaging agent serving as a noninvasive biomarker predictive of response to the therapeutic agent—radiotheranostics in action. Similar histology agnostic approvals exist for patients with tumors harboring mismatch repair deficiency, microsatellite instability high, and neurotrophin tropomyosin receptor kinase rearrangements, for example.[114]

Combination Therapy

Because monotherapy with RPT is not curative, rational combinations with EBRT (Ra-223 with SABR, RaVENS NCT04037358[115]; SABR with [^{177}Lu]Lu-PSMA for oligometastatic prostate cancer, NCT05079698), or systemic therapies ([^{177}Lu] Lu-DOTATATE with cabozantinib, NCT05249114) such as immunotherapy ([^{177}Lu]Lu-PSMA with ipilimumab/nivolumab NCT05150236; [^{177}Lu]Lu-PSMA with pembrolizumab NCT03805594[116]) or inhibitors of DNA damage repair pathways ([^{177}Lu]Lu-PSMA with olaparib, NCT03874884; [^{177}Lu] Lu-DOTATATE with olaparib, NCT04086485; [^{177}Lu] Lu-DOTATATE with DNA-PK inhibitor, NCT04750954) are active areas of exploration in clinical trials. Additional studies with rational combinations will surely emerge over time as we learn more about the interplay between the biology of these cancers and these therapeutic agents.

New Agents, Same Targets

A good place to preview what targets and agents are coming down the line as RPTs is to consider the novel molecular imaging agents that are being developed. For example, the peptidomimetic imaging agents, including the ^{18}F-rh-PSMA7.3

agent, which was FDA approved in 2023,[117] and its therapeutic counterpart ^{177}Lu-rhPSMA-10.1 is being evaluated in clinical trials (NCT05413850).[118] Chemistry-oriented readers will note that this ligand can chelate either a β-emitting ^{177}Lu or nonradioactive natural lutetium and that the fluorine can be either the positron-emitting ^{18}F or stable nonradioactive ^{19}F. Therefore, both the imaging, ^{nat}Lu/^{18}F-rhPSMA, and therapeutic, ^{177}Lu/ ^{19}F-rhPSMA, are elementally identical and would have the same biodistribution.[119] This contrasts with currently approved theranostic pairs and could facilitate prospective personalized dosimetry. Interestingly, while we have more or less treated all peptidomimetic PSMA-targeting ligands (ie, PSMA-617, PSMA-I&T, rhPSMA-10.1), each has distinct pharmacokinetics and biodistribution, which influence the subsequent absorbed dose to tumors and organs at risk. For example, a case report of a patient with mCRPC, whose disease progressed on [^{177}Lu]Lu-PSMA-I&T by PSA and PSMA PET, demonstrated a response to ^{177}Lu-rhPSMA-10.1.[120] While this does not make evidence, it is clear that there is more to be explored on how these differences in chemical composition affect therapeutic outcomes.[120]

Radioconjugates of the PSMA-specific human antibody J591 are being tested in prospective clinical trials. ^{177}Lu-J591 (TLX591, rosopatamab) is being tested in a phase 3 RCT as second-line therapy for patients with mCRPC who have progressed on modern hormone therapy and randomizes them to standard of care or standard of care plus the RPT agent (2.8 GBq for two cycles separated by 14 days) (NCT04876651). The results of the phase 1 dose-escalation study of [^{225}Ac]Ac-J591 in patients with mCRPC (NCT03276572), including some who received prior [^{177}Lu]Lu-PSMA-617 RPT, recently reported that the maximal tolerated dose was not reached, and the recommended phase 2 dose was the highest dose level of 93.3 KBq/kg[121] and fractionated dosing is being evaluated in another phase 1/2 study (NCT04506567). It is important to emphasize that these full-length antibodies exhibit dramatically different biodistributions when compared with the peptidomimetic RPT agents. Namely, antibodies have longer circulations times (days to weeks vs minutes to hours), are not renally cleared, and are not seen to bind to the PSMA expressed in the lacrimal and salivary glands. Notably, while grade 1 xerostomia is <2% in patients in trials of ^{177}Lu-J591, Tagawa reports 34% grade 1 and 3% grade 2 xerostomia in patients treated with [^{225}Ac]Ac-J591, suggesting a potency difference due to the LET differences between β and α particles.[121]

Leveraging the avidity effects of having two groups specific to a given target can be used to extend the potential utility and efficacy of existing targeting ligands. For example, the novel theranostic pairs, [^{64}Cu]Cu-SAR-bisPSMA and [^{67}Cu]Cu-SAR-bisPSMA, each of which contains two PSMA-binding ligands

along with a chelator cage aims to improve tumor binding and anticipated improvements in imaging and therapy, respectively, are being tested in clinical studies (NCT04868604). Somewhat related are investigators using heterodimers, or ligands that are specific to two targets. It is well known that tumors exhibit heterogeneity in expression of these therapeutic targets and investigators could couple two (or more) ligands specific to different tumor- or tumor microenvironment–selective targets as part of one molecule to increase tumor-binding ability.[122,123]

Novel variations of existing agents that have extended blood half-lives have been developed to alter the pharmacokinetics and biodistribution of agents targeting SSTR and PSMA. The rationale is that because the intrinsic blood half-life of peptide and peptidomimetic agents is short, a significant proportion of the activity administered will be excreted and not contribute to therapy. By coupling these molecules to albumin-binding domains, for example, the blood half-lives can be extended by days and potentially allow for more absorbed dose to tumors[124-126] (NCT03478358). On the other hand, however, this also allows for blood pool irradiation, which can cause hematopoietic toxicities seen in other longer lived agents, such as full-length antibody-based radioconjugates. Whether these agents supplant or become part of the therapeutic repertoire remains to be seen.

Emerging Targets and Applications

Long-standing research in radiopharmaceutical imaging and RPT has yielded many promising targets beyond PSMA and SSTR. To some extent, antibody-drug conjugates, other antibody-based cancer therapies (eg, bispecific antibodies, T-cell engagers), and cellular therapies share the same targets of interest for theranostics as well. Efforts to systematize novel target and biomolecule discovery for theranostics development are challenging but are worth the investment, especially in the context of decreasing costs for the pursuit.

There are many targets and targeting biomolecules being investigated at varying stages of development—too many to list here, there are two general categories of agents: ones that are selective to a target that is generally present on a few tumor types and others that are more broadly applicable by targeting either a molecule expressed on several tumor types or the tumor microenvironment.

Small molecules including those targeting fibroblast- activating protein (FAP) with FAP inhibitors, which can selectively bind to cancer-associated fibroblasts[127] as a pan-cancer agent, are also being investigated in clinical trials for both imaging and therapy. Other targets, including C-X-C motif chemokine receptor 4, which is expressed in several solid tumors and hematologic malignancies and being

targeted by the diagnostic agent ^{68}Ga-pentixafor[128] and therapeutic agents ^{177}Lu-pentixather[129] and ^{212}Pb-pentixather (NCT05557708), are actively being evaluated in early-phase clinical trials. Integrins, nectin-4, melanocortin 1 receptor (NCT05655312), B7-H3, carbonic anhydrase IX, fibroblast growth factor (NCT05363605), and gastrin-releasing peptide receptor are among the expanding number of targets actively being explored.[130-135]

Beyond the traditional applications for RPT, some groups have explored nontraditional uses. For example, the anti-CD45 antibody (^{131}I-apamistamab, Iomab-B, NCT02665065) has been creatively applied as part of the bone marrow conditioning regimen for hematopoietic stem cell transplant. Others have employed a topical β particle–emitting rhenium-188 for nonmelanoma skin cancers (NCT05135052).[136]

New Technologies

New technologies could complement RPTs in the clinic. For example, total body PET, which has much higher sensitivity when compared with conventional PET, could be used to better define the pharmacokinetics of a PET agent. This information could be used to prospectively calculate the administered activity needed to deliver a desired absorbed radiation dose from the RPT partner (eg, personalized dosimetry). Similarly, the latest generation of SPECT scanner is now able to achieve comparable imaging quality as PET in much shorter time frames, allowing for easier post-treatment absorbed dose estimates that may guide the subsequent cycle of administered activities.[81]

In addition, the novel combined PET/linear accelerator technology could theoretically use the 511-keV photons from the positron-electron annihilation event to guide therapeutic photon delivery.[137] Because many RPTs are first evaluated as imaging agents, this technology could expand the utility of such positron-emitting agents from diagnostic agents to beacons for EBRT delivery. Importantly, the workflow, including having user-friendly treatment planning software and speed with which treatments are completed, needs to be optimized for adoption beyond specialty centers. Automation of some of these processes could extend expertise more broadly.

FURTHER READING

Entire books could be and have been written to cover this rapidly evolving topic. This book chapter aimed to present the fundamentals and offer a framework upon which interested radiation oncologists can build. For additional depth, we encourage interested readers to consider *Radiopharmaceutical Therapy*, edited by

Bodei, Lewis, and Zeglis, as well as *Beyond Becquerel and Biology to Precision Radiomolecular Oncology* edited by Prasad.[138,139] Another useful resource is a contemporaneous issue in Seminars in Radiation Oncology on RPT that covers many of the topics presented in this text in additional detail.[140] Readers should be cautioned that, while the fundamentals will not change, any allusions to novel agents and future perspectives are but a snapshot in time and likely out of date as soon as published. Accordingly, to remain up to date, we encourage those interested to regularly visit www.clinicaltrials.gov to identify any new trials of both radiopharmaceutical imaging and RPT agents.

CONCLUSIONS

The renaissance of RPTs hinges on novel agents that have demonstrated improvements in survival and quality of life in patients eligible for treatment with this modality. Despite this success, there is significant room for optimization even in already FDA approved agents.

As investments in both academic and industry settings yield dividends in the form of new agents and new indications, we will require clinicians who understand the fundamentals of RPTs and how they are best used in the context of the broader cancer therapy spectrum. In the United States, radiation oncologists and nuclear medicine physicians both have the expertise needed to appropriately offer RPTs to patients. In fact, both specialties will need to be ready to ensure sufficient workforce to be able to meet the anticipated demand for RPTs, especially in patients with mCRPC, as clinically authorized users. Many radiation oncologists are early movers, and already serving patients in this way.[141,142] Multidisciplinary Theranostics Centers with participation from all clinical stakeholders could serve as a model for collaboration across disciplines.

Radiation oncology departments should continue to invest in basic and translational science in general and in RPTs specifically, to expand our understanding on how to best use this modality in the context of existing treatments. It is only through such investments that novel, previously unforeseen opportunities arise. Departments could help promote research from de novo design, synthesis, and testing, through mechanistic studies of unique radiobiology in preclinical studies, to clinical trials of next-generation molecular imaging for image-guided radiotherapy and RPT combinations with external beam and systemic therapies.

There are many exciting avenues yet to be explored and others yet to be defined. As we move forward, we should take the words of esteemed computer

scientist and Turing award winner, Alan Kay to heart: “The best way to predict the future is to create it.”

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CHAPTER 26

Radiation Therapy and the Immune System

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The immune system's primary function is to maintain tissue integrity by protecting against foreign pathogens and by removing damaged or malignant cells. As with most physiologic systems, the immune system functions on a principle of homeostasis. Inappropriate activation, magnitude, or duration of the immune response can lead to inflammatory and autoimmune conditions. Conversely, a feeble immune response can lead to infections and malignancy. The immune system must precisely recognize and eradicate harmful entities while maintaining self-tolerance. This requires a delicate balance between immune stimulatory and immune-suppressive mechanisms to protect normal tissues from both harmful foreign agents and the immune system itself. Due to the precision and power of the immune system, understanding the mechanisms governing inflammation and immune suppression, and learning how to manipulate the cells and molecules of the immune system for therapeutic benefit, remains a promising frontier of medicine in general and oncology in particular.

Radiation therapy (RT) has been a mainstay of cancer treatment for over a century. The primary mechanisms of cancer cell killing or growth arrest through irreparable DNA damage are well studied, but there is a growing understanding that RT also heavily relies on the immune system for anticancer effects.[1] The possible role of RT in stimulating the immune system and antitumor immunity has been long known and studied. There are case reports dating back to the 1950s detailing out-of-field treatment responses at distant metastatic sites after localized RT. This is known as the abscopal effect and is an immune-mediated phenomenon.[2-5] Studies demonstrate that the immune-modulating effects of RT are not a potential alternative mechanism of action only relevant in certain circumstances but are central and requisite for the antitumor effects of RT. Studies in immune

cell (T cells and dendritic cells [DCs]) depleted mice have repeatedly demonstrated that depletion of immune function significantly and almost completely diminishes the antitumor efficacy of RT.[6,7] Likewise, clinical data suggest that immune-compromised patients respond poorly to RT and have inferior outcomes.[8-10] Thus, not only can RT modulate immune function, but immune function is also essential for RT efficacy.

The advances in molecular techniques over the past few decades and subsequent studies have helped further elucidate the interplay between RT and the immune system and shed light on the underlying mechanisms. Due to the growing power of manipulating the immune system, understanding the immune-modulatory effects of RT and how best to use these effects for therapeutic benefit, either alone or in conjunction with other immune-modulating agents, has become one of the most dynamic fields of study in radiation oncology. Since clinical trials in this field are rapidly evolving, the goal of this text is not to provide a comprehensive overview of ongoing and completed clinical trials. The specific disease site chapters will review some of these data. Rather, the goal of this chapter is to provide a foundation for approaching this field of study, to highlight some of the critical understandings in the field, and to outline some of the key gaps in knowledge that limit progress.

IMMUNE FUNCTION

The function of the immune system is highly complex with numerous cell types (and subtypes) and molecules involved. The pace of discovery in the field is daunting with regular discovery of new cell subclasses or novel molecular pathways. A thorough introduction to immunology is beyond the scope of this textbook, and we refer the reader to other available texts on the topic. However, any discussion of RT and the immune system requires a basic foundation of immune function and tumor immunology for context. Thus, at the risk of oversimplification, we briefly highlight a few key concepts in this section and the next on tumor immunology, as a refresher for the nonimmunologist reader, that provides context for the rest of the chapter and can serve as a springboard into deeper study of immunology-specific texts.

In a nutshell, the immune system functions to sense damage or pathogens, signal the danger (and amplify that signal), take effect to neutralize the danger, and then resolve the immune response. The sensing and effector systems of the immune system are broadly categorized into innate and adaptive immunity. The effector systems of the immune system are also broadly categorized into humoral and cellular immunity. These systems are described in more detail below. It is important to keep in mind that the lines between these categories are quite blurred as cell types and molecules can actively participate in both and the systems are intimately dependent on one another. It is also important to keep in mind that the immune system is plastic and that a molecule or cell type may play different roles depending on tissue and context.

The immune system can be conceived as an offshoot of a wound repair system that serves to eliminate organisms that have penetrated the organism due to a barrier breach. If we were to design an immune system from the first principles, we would have to address how to provide fully functional immune readiness at all potential sites of entry. The ancestral immune system still found in horseshoe crabs employs amebocytes, which function to identify invading pathogens via innate receptors for molecular patterns (known as pathogen-associated molecular patterns or PAMPs) consistently and specifically expressed by bacteria (or other infectious agents), such as lipopolysaccharide (LPS). Amebocyte activation triggers a clotting cascade to repair the damage and releases innate antibacterial peptides to control the infection.[11] In this example, the entire immune response is localized to the infection site with integrated sensing and response pathways.

Though more complex, our immune system is built upon these evolutionarily conserved sensing and response pathways. We inherit this immune sensing system, which is broadly unchanging through our lifetime; thus, it is described as innate immunity. In addition, over the past 500 million years, we have evolved an additional immune system that changes in response to our unique history of infections[12] and is, therefore, described as adaptive immunity. The principle adaptive immune cells are known as B and T cells based on tissue of origin (bone marrow and thymus, respectively). These are the dominant focus of immunology research due to the ability of B cells to produce antibodies (Abs) that can bind almost any molecular shape, or the ability of T cells to directly recognize the infected

or mutated cells. An adaptive immune response against a specific virus can result in viral antigen–specific B cells and T cells that remain throughout life.[13] A similar response to tumor antigens is a goal for cancer immunity.

The development and selection of B and T cells is fundamental to immunology but is beyond the scope of this chapter. However, it is critical to understand a series of facts. The first fact is that these cells are highly diverse in target recognition. The B-cell receptor is theoretically unique on each new B cell, can be refined through immune responses, and may result in up to 10^{18} potential structures.[14] T cells have a similarly diverse potential structure in their T-cell receptor (TCR), with children producing more than 10^9 unique T cells each day.[15] The diversity of TCR declines with age, in part as a result of decreased output of new T cells, but of the approximately 10^{12} to 10^{13} T cells in a human, there may be as high as 10^8 to 10^9 unique TCR in a young adult.[16] The targets of B-cell receptor and TCR are called antigens and represent a molecular shape directly recognized by either the Ab surface of the B-cell receptor or the TCR when a fragment is bound to the surface of a major histocompatibility complex (MHC) molecule. The second fact is that these B or T cells have the potential to recognize our own cells, but any "autoreactive" cells are (almost entirely) eliminated during the development process by negative selection. This results in a B- and T-cell repertoire that theoretically recognizes nothing in the individual. On infection, new molecular shapes, which are different that self, are introduced by the infectious agent and some B and T cells are able to recognize them, as they were not part of the negative selection. This is the essence of self versus nonself recognition that forms the basis for adaptive immunity. Importantly, mutation of our genes can create novel molecular shapes that have the potential to be recognized by our own immune cells as nonself, permitting anticancer immunity. The final critical fact in adaptive immunity is expansion and memory. Again, the details of this process are beyond the scope of the review, but newly emerged B and T cells are known as naïve cells and have a finite lifespan. Following antigen recognition, these cells rapidly expand, and while most of these cells differentiate into an effector population specialized to control the acute phase of the infection, a portion of the cells differentiate into memory cells that can last for the lifetime of the individual.[13] These clonally expanded memory cells

represent the adaptive immunity that develops in response to each person's unique infectious history.

B cells, once activated and expanded, can secrete Ab for the duration of the animal's lifespan,[13] and the Ab can permeate the body. T cells, in contrast, must come into physical proximity to a cell-presenting antigen (nonself molecular shape) on their cell surface MHC molecule to control infections. For this reason, T cells are very dynamic in their movement, and they enter and exit secondary lymphoid organs and pass into and out of tissues as they scan for their targets.[17,18] Innate sensors serve not only to activate innate immunity but also as a recruitment tool to mobilize T-cell responses to a location of infection. For any new infection, the innate response will occur first and provide the first line of defense. It also triggers adaptive immunity and guides adaptive immune cells back to the infection site to provide a second layer of response. These phases are highly integrated and not yet fully understood. However, the field has identified critical trigger points for productive immunity that can be manipulated to artificially guide immune responses against infectious agents and, recently, cancer.

The core pathways of innate immunity are structured to detect viral and bacterial infection. The best studied innate sensors are the Toll-like receptors (TLRs),[19] a family of molecules that activate inflammatory mechanisms following recognition of their specific ligands (which are generally molecular patterns ubiquitously and specifically expressed by infectious agents, but not by self during normal circumstances known as PAMPs). These ligands include LPS from bacterial cell walls that signals through TLR4 and unmethylated CpG dinucleotides from nonmammalian cells that signal through TLR9 (reviewed in Yin et al[20] and Iwasaki and Medzhitov[21]). In general, TLRs are on the cell surface membrane or located on intracellular cell membranes (endoplasmic reticulum, etc) and share a common cytoplasmic signaling domain, thought to oligomerize and recruit adaptor proteins, which include critical signaling molecules such as MyD88, TRIF, and TRAM.[22] In addition, there are cytoplasmic sensors of infection, such as RIG-I and cGAS, that signal through MAVS and STING, respectively, which like MyD88, TRIF, and TRAM link nucleic acid sensing to innate signaling pathways. MAVS links the cytoplasmic sensors of viral RNA (RIG-I, MDA5, and LGP2) to downstream signaling.[23-25]

STING links signals from the cytoplasmic DNA sensor, cGAS, to downstream signaling[26] following viral or bacterial infection.[27,28] STING can also be directly activated by cyclic dinucleotides produced by bacteria.[29] In each case, following sensing and activation of the adaptor protein, downstream signaling results in inflammation focused around interferon (IFN) gene transcription (reviewed in Honda et al[30]). Finally, there is a complex system of pattern recognition receptors centered around the inflammasome. Inflammasome activation is often part of a two-step activation process where innate sensing through TLRs initially causes upregulation of nod-like receptors (NLRs) as well as transcription of interleukin (IL)-1b and IL-18 in their pro-form. The second step causes inflammasome sensors to recruit apoptosis-associated speck-like protein containing a CARD that serves as an adapter protein for the oligomerization of the inflammasome complex.[31] A series of homotypic interactions and autocatalytic activations result in activation of caspase 1.[31] Caspase 1 is then able to process IL-1b and IL-18 to their mature forms, resulting in potent inflammation. The inflammasome is particularly sensitive to molecular patterns that are absent from our cells but present following infection, which includes not only specific bacterial toxins,[32] but also more general features of abnormal behavior such as lysosomal disruption, protein aggregates, or crystals (reviewed in Broz and Dixit[33]).

Many of the mechanisms that the innate immune system employs to identify infection can also recognize abnormal responses in our own cells in the absence of infection. These innate sensing mechanisms can not only discriminate PAMPs but can also respond to damage-associated molecular patterns (DAMPs), which result from abnormal processes in our own cells. For example, while LPS is uniquely a PAMP, the same TLR4 signaling pathway can be activated by high mobility group box 1 (HMGB1), which can be released from dying cells.[34,35] Dying cells can similarly provide DAMPs via heat shock proteins,[36-38] such as calreticulin,[39] and lysis can activate innate sensors via uric acid.[40,41] Innate signaling is critical to immunity; for this reason, when we discuss anticancer immunity and the impact of radiation, we show how DAMPs play a critical role in immune mechanisms following radiation.[42,43]

Large, complex organisms, such as ourselves, may simultaneously have multiple ongoing immune responses at different sites. However, we would

not necessarily want to mobilize the entire immune system to respond to one location since most immune cells would not be specific for this particular pathogen. Instead, our immune system employs selective sensors, which provide an initial indication of the type of immune response required, to mobilize suitable cells. For example, intracellular sensors for nucleic acids that might detect a viral infection, such as TLR3, RIG-I–like receptors, and cGAS/STING, can generate a different pattern of cytokine responses as compared with extracellular sensors for bacterial components, such as TLR2 and TLR4.[21,44] The various sensors are not uniformly shared across cell types, so specific immune cells can specialize in detecting specific infections[21] or types of damage.[43] In this way, the immune response is prewarned of the nature of the infection, and the appropriate adaptive response is activated and recruited.

The DC is the essential link between innate sensing of infection and adaptive T-cell responses. DCs are able to move antigen from peripheral sites to lymph nodes,[45] which is one of the few locations where naïve T cells can meet antigen. DCs are the highest expressors of TLR3,[46] which is focused on sensing the kind of intracellular infectious agents that demand T cells for effective immune control.[47,48] In addition, DCs are uniquely able to cross present antigens phagocytosed from other cells or extracellular locations on their MHC class I[49] (as opposed to the canonical pathway where these antigens would be presented on MHC class II). These features ensure that DCs have all of the required tools to sense infection, carry antigen to T cells, and present that antigen to initiate T-cell immune responses. As we have recently reviewed, these features of DCs are also critical for immune responses to RT.[50] Also critical is the array of co-stimulatory molecules expressed by DCs to support T-cell activation. While the TCR on T cells recognizes the specific MHC-peptide combinations being presented by the DC, this signal alone is insufficient for T-cell activation. Effective signal transduction in the T cell is supported by co-stimulation (signal 2) through CD80 and CD86 on DCs engaging CD28 on T cells. Naïve cells are particularly dependent on co-stimulation for initial activation, as compared to reactivation of memory cells.[51] Adhesion molecules regulate a strong interaction with the DC for a strong and prolonged TCR signal that can result in T-cell activation and proliferation,[52] and an array of additional co-stimulatory as well as co-inhibitory receptors

that are regulated on T cells and DCs in response to initial activation regulate the scale of the T-cell response to its target antigen.[53-58] It is here that most of the current immunotherapy (IT) targets are found, regulating the interactions between T cells and antigen-presenting cells (APCs) or similarly regulating the interactions between T cells and their targets. These include autocrine or paracrine cytokines such as IL-2 that support TCR signals for effective T-cell proliferation.[59]

While T-cell effector functions are discussed more in relation to cancer IT, one additional feature of the transition to adaptive immunity is critical to understanding the immunobiology of cancer. The initial innate sensing of infection results in secretion of a range of cytokines that accompany DCs to the lymph node and remain present in the infectious site. The specific cytokines present during T-cell activation (signal 3) can guide their differentiation, such that a T cell specific for a single antigen could become a cell that secretes IFN-γ on activation, or instead one that secretes IL-4 on activation.[60] In infectious diseases, T cells that produce these cytokines represent important patterns of response to intracellular infections, such as viruses versus parasites. There are a range of other differentiation patterns that T cells can undergo, and the resulting cell types are particularly notable for CD4 T cells. Each differentiation choice can be guided by cytokines,[60,61] and one critical pattern is the differentiation of CD4 T cells into suppressive regulatory T cells (Tregs). T-regulatory cells are defined by differentiation in the presence of transforming growth factor β (TGF-β)[62] and can suppress adaptive immune responses by other T cells with special relevance in cancer and radiation. Thus, the innate response to infection guides T-cell differentiation via cytokines, which has direct implications for cancer. This multilayered integration of innate and adaptive immunity is critical to our ability to generate a diversity of immune responses, and as we discuss, the dysregulation of these responses plays an important role in the success and failure of antitumor immunity.

IMMUNO-ONCOLOGY

The tumor is a dynamic, continuously evolving environment encompassing the cancer cells and normal cells and consists of a diverse array of resident and infiltrating cells. These include immune cells, fibroblasts, stroma, and

vasculature, with all their accompanying secreted factors and signaling pathways. Some portion of this environment is entirely populated by normal cells—the tumor stroma—and cells in the tumor stroma may not directly interact with cancer cells. In the immediate vicinity of the cancer cells is the tumor microenvironment (TME), which may have a distinct set of cells and molecules due to the dominant impact of the cancer. The TME has a decisive role in tumor growth and progression.[63] Immune cells within the TME can include innate cells such as APCs and other myeloid-derived cells, as well as lymphocytes and others. The interactions between the host immune system and malignancy, which occur within the TME but can have systemic ramifications, are the basis of immuno-oncology.

Immune Recognition of Tumors

As with most immune responses, the antitumor immune response begins with innate immunity. Conditions within the TME, such as hypoxia and nutrient exhaustion, can give rise to unique metabolic features that can lead to cellular stress and extensive death of cancer cells and other cells in the midst of a growing tumor.[64-67] These processes cause intracellular release, extracellular release, or cell surface expression of a range of stress ligands, cytokines, chemokines, and DAMPs that are associated with the TME and less prevalent in normal tissues. As outlined above, these can not only initiate an immune response but also impact the infiltration and activation of immune cells in the TME. The generated innate immune response can have direct antitumor effects and also trigger an adaptive immune response against tumors.

Regarding recognition by the adaptive immune system, cancer cells straddle the line between “self” and “nonself.” Cancer cells are derived from host cells and are, therefore, considered “self.” Yet, by definition, cancer cells have developed DNA mutations that can give rise to mutated proteins, which are not found in normal cells. These altered proteins can be recognized as foreign by adaptive immune cells since they were not present during the negative selection process that eliminates autoreactive immune cells. In addition, alternative splicing, translation, and post-translational modifications in cancer cells also produce novel antigens not found in normal healthy cells. Tumor cells express these novel antigens, termed

neoantigens, which arise from tumor-specific alterations and mutations and permit the immune system to distinguish cancer cells from normal "self" cells.[68,69] The immune system can form an antitumor response against these neoantigens, also known as tumor-specific antigens (TSAs). The immune system can also recognize aberrantly expressed self-proteins, known as tumor-associated antigens (TAAs), which are self-proteins but inappropriately expressed in terms of time, tissue, or quantity (eg, carcinoembryonic antigen or CEA, expressed during embryogenesis, but not in normal adult tissues).[70] The immune response generated against epitopes from these tumor antigens can potentially eliminate cancers and precancerous cells. In fact, it is possible that mutated cells with malignant potential arise often but are eliminated by the immune system, in a process termed *immune surveillance*.[71] Only those mutated cells that evolve a mechanism to escape immune surveillance or that arise in a niche where immune surveillance is suppressed can progress to clinically relevant malignancies.

As outlined above, the main principle of T-cell–mediated adaptive immunity is the recognition of peptide antigens presented on cell surface MHC molecules by TCRs. To generate T-cell immunity against tumors, the epitopes from tumor antigens must first be presented to T cells in a manner that can prime them (ie, in the context of MHC on APCs, which can provide co-stimulatory signals). This generally occurs as there is some extent of necrosis in the TME and APCs infiltrate the TME and phagocytose the debris from dying cancer cells. The APCs can then migrate to the draining lymph nodes. Phagocytosed antigens from the debris are digested, and the peptides are presented on the cell surface in the context of MHC. The APCs involved are most often mononuclear phagocytes, such as macrophages and DCs. DCs play a critical role in this biology since they are the most effective APC for T-cell priming. In addition, some DC subsets have the capacity for cross-presentation, which allows them to present exogenous extracellular peptides on MHC class I rather than only on MHC class II, which is the canonical pathway for phagocytosed antigens. Thus, both CD4+ and CD8+ T cells can be primed against tumor antigens in the draining lymph nodes. These cells then clonally expand and migrate into tissues carrying out effector functions, including direct killing of tumor cells. Tumor killing is triggered by activated CD8+ cytotoxic TCR

recognition of tumor antigen presented on MHC class I on the surface of cancer cells.

Mechanisms of Escaping Immune Surveillance

As outlined the section "Immune Recognition of Tumors," an active antitumor immune response culminates in the infiltration of the TME with effector cells, primarily cytotoxic T-lymphocytes (CTLs), which target the tumor. In a hypothesis termed *immune surveillance*, this process may eradicate many malignancies early in their development before they are clinically detectable, akin to how our immune system eradicates innumerable infectious pathogens that we are exposed to on a daily basis before they have the opportunity to cause illness. This hypothesis is supported by the increased rates of malignancy in immune-compromised patients.[72-74] Once a malignancy has become clinically detectable, it is rarely eradicated by the immune system alone, primarily because it must have evolved mechanisms to escape immune surveillance to get to this stage. The immune system has tightly regulated suppressive mechanisms to limit overactivation and resolve inflammation since uncontrolled immune activity can be highly pathogenic. Malignant tumors often hijack and exploit these natural homeostatic pathways to attain immune evasion through mutations, cellular changes, and alterations in the TME and local tissue architecture.[75,76] These mechanisms can prevent the initiation or TME access of the antitumor immune response yielding immunologically "cold" tumors characterized by a lack of TME T cells. Other mechanisms can disrupt the immune response within the TME yielding tumors that are "hot" or "T-cell inflamed." Understanding these broad categories is important because it may dictate the best application of RT and IT to bolster antitumor immunity. A complete discussion of mechanisms of immune surveillance escape is beyond the scope of this chapter; however, a basic understanding is required as many current IT approaches seek to address these mechanisms. A cursory outline of some mechanisms is presented below.

Decreased Tumor Immunogenicity

Immune surveillance eradicates tumor clones expressing strongly immunogenic neoantigens. Thus, the tumor evolves under selective pressure

from the immune system, and clones, which express fewer or less immunogenic antigens, survive. In addition, cancer cells often have deficiencies in antigen processing and presentation machinery, such as downregulation of class I MHC molecules, enabling them to evade recognition by T cells.[77]

Exclusion of Immune Cells

Immune cells, particularly T cells, can be excluded from the TME via immune based or mechanical means yielding cold tumors. Tumor cells and stroma can downregulate CXCR3 ligands, which CTLs require for migration into the TME.[78] Factors such as vascular endothelial growth factor (VEGF) can alter tumor endothelial cells to limit the expression of adhesion molecules necessary for T-cell extravasation and migration. Finally, suppressive immune cells and fibroblasts in the TME can produce a desmoplastic reaction and dense extracellular matrix (ECM) acting as a physical barrier to T-cell infiltration.

Upregulation of Immune-Suppressive Cells and Molecules

The TME recruits/induces immune-suppressive cells that can limit the efficacy of an antitumor immune response. Many suppressive immune cell types can be found within the TME, but myeloid-derived suppressor cells (MDSCs), M2-polarized macrophages, and Tregs are the best described. MDSCs can generate immunosuppressive factors, including arginase, inducible nitric oxide synthase (iNOS), and TGF-β. M2-polarized macrophages produce IL-10 and other suppressive cytokines and factors. Tregs can not only produce immune-suppressive cytokines (IL-10, IL-35, TGF-β) but can also be directly cytotoxic to other immune cells including CTLs. Within the TME, many cells also express immune-suppressive cell surface molecules including co-inhibitory ligands for TCRs (or checkpoints). For example, MDSCs and cancer cells can express programmed death-ligand 1 (PD-L1), which binds programmed cell death protein 1 (PD-1) on T cells, and Tregs can express cytotoxic T-lymphocyte associated protein 4 (CTLA-4), which binds CD28 on T cells. T cells also express other checkpoint molecules including Tim-3, TIGIT, and LAG-3 whose ligands can be expressed by tumor cells or immune cells in the TME.

Overall, signaling via these co-inhibitory receptors leads to decreased functionality and exhaustion of T cells.

Poor Priming of T-Cell Responses

The various immune-suppressive cytokines and cells listed above can limit the maturation of DCs and decrease the expression of co-stimulatory molecules by APCs from the TME, thereby limiting their ability to prime T-cell responses.

Metabolic Immune Suppression

Rapid growth of tumors, dense ECM, and altered metabolism of cancer cells can lead to a TME that is hypoxic and acidic. Furthermore, the TME is also starved of essential nutrients, which T cells require for activation and functionality. There is direct competition with cancer cells for nutrients. Furthermore, immune-suppressive enzymes such as arginase, mentioned above, and indolamine-2,3-dioxygenase (IDO), described by Munn and Mellor,[79] can be expressed by immune cells and cancer cells in the TME. These enzymes can catabolize essential nutrients (arginine and tryptophan) required for immune cell activity and produce catabolites, which are immune suppressive. Overall, the TME can be very hostile to T cells and other immune cells, limiting their ability to carry out effector functions.

Modern Immunotherapy Approaches

Immuno-oncology aims to direct, expand, and engineer immune responses against tumors capable of eradicating local and systemic disease. As outlined above, understanding the normal function of the immune system and the mechanisms that limit effective immune responses during malignancy are critical to designing therapies that can initiate a new or reinvigorate an existing antitumor immune response. For this discussion of IT, we focus on the most salient ITs that have reached clinical approval rather than the wide array of ITs in preclinical development or failed in the clinic. Later, in discussion of RT, we discuss more preclinical work and clinical pipelines to consider the near future of cancer IT in the context of radiation.

Cellular Therapies

As discussed above, most antigens presented by cancer cells are the normal self-antigens that are not generally recognized by T cells. Yet cancer cells have DNA mutations, some of which generate mutated proteins that are not found in normal cells and were not part of the selection process that generated the T-cell repertoire. These are referred to as neoantigens and are an important target for patient-specific immunity.[68,69] Most mutations are random and, therefore, unique to each patient, requiring that T cells targeting such mutations to be generated for each individual.[80] However, there are specific mutations in key genes that drive malignant transformation that may be shared between individuals. An example would be activating mutations in Kras that are widely shared. These "driver" mutations are particularly attractive in that they are central to the malignant program of these cells and cannot be readily silenced to acquire resistance to therapy. Tumor-specific T-cell therapies have been developed to target these mutations but require that patients share both the correct mutation and the correct MHC allele to present the mutated peptide.[81,82]

A range of other potential antigens can also be recognized by T cells.[70,83-85] These include self-antigens that have not been effectively eliminated from the T-cell repertoire and generated by alternative modes of translation and post-translational modifications in cancer cells, for example, CEA or MAGE.[86] The immune response generated against epitopes from these tumor antigens can potentially eliminate cancers and precancerous cells in a similar manner to neoantigens, but with some risk of on-target effects in other tissues that may also express that protein. In general, there are likely to be similar mechanisms by which T cells are directed against neoantigens and TAAs and similar mechanisms of resistance.

An alternative to approaches that require preknowledge of tumor antigens is the isolation and ex vivo expansion of tumor-infiltrating T cells (tumor-infiltrating lymphocytes [TILs]) for adoptive transfer back into the patient as pioneered by Rosenberg at the National Cancer Institute. Logically, the tumor represents the richest source of tumor-specific T cells, and multiple decades of research have refined the procedure for expanding T cells from tumors, enriching for tumor specificity, and reinfusion into patients.[80] One of the most important developments has been the procedure to support these

cells in vivo after infusion back into the patient. Following ex vivo stimulation, the T-cell product is dominated by effector T cells, which have good effector capacity but limited long-term survival capacity. Using a combination of pretransfusion lymphopenia and support with IL-2, T cells can alter into memory phenotypes during homeostatic expansion,[87,88] resulting in both long-term persistence and increased effector function. Like vaccines (as discussed in the next section), the development of improved genomic profiling has allowed investigators to guide the expansion of patient's T cells using patient-specific, tumor-specific neoantigens.[89,90] These include shared neoantigens such as mutated Kras.[82] Importantly, investigators have started to clone the TCRs that recognize these mutated neoantigens,[80] and there is the potential to build a library of TCRs to cover each MHC haplotype to expand such responses to all patients. These developments have permitted TCR gene therapy, with adoptive transfer of T cells genetically engineered to express TCR specific for shared antigens in patients with an appropriate combination of antigen and MHC.[81,91] This is an active area of development in a well- established but not widely applied IT. One important point in adoptive T-cell therapy is that while this changes the proportion of tumor-specific T cells in the patient, these cells are subject to the same resistance mechanisms that were faced by the original T cells. The hope is that ex vivo expansion and infusion of an overwhelming number of T cells can overcome resistance sufficiently to control tumors, but immune evasion still remains a problem. For example, where the neoantigen is nonessential, cancer clones that delete or repress the mutated gene have a selective advantage. Where the gene is essential, as with Kras, cancer cell clones with MHC loss have emerged following adoptive therapy.[82] In addition, the suppressive features of the tumor and TME may still suppress adoptively transferred T cells. For example, expression of PD-L1 can limit the efficacy of adoptively transferred T cells, and there is the opportunity to combine adoptive transfer with deletion of PD-1 in the T cells.[92] We discuss approaches targeting the TME more below.

An alternative to adoptive transfer of TILs and TCR therapy is T cells engineered to express chimeric antigen receptors (CARs). In this approach, Abs provide the recognition component and the recognition domain is linked to an engineered receptor incorporating features of the TCR and co-receptor signaling domains.[93] The limitation of CAR-T approaches is that

there needs to be a unique structure on the surface of the target cell since the TCR has been replaced with an Ab. Surface- expressed proteins are a small proportion of our protein repertoire, and while there are cancer-selective modifications, selectivity has been a difficulty in CAR-T approaches, resulting in toxicity.[94] Where CAR-T has been effective in hematopoietic malignancies, it has been possible to eliminate an entire lineage based on surface receptor expression, such as CD19+ B cells for B-cell lymphoma.[95-97] Nevertheless, CAR-T is now a mainstay of cancer IT, and solutions to expand their use to solid tumors are in active investigation. While CAR engineering can incorporate a potentially unlimited array of regulatory features in CAR-T, as above, the features of the TME that limit T-cell efficacy can also limit CAR-T effectiveness.[92]

Vaccines

The presence of TAAs raises the prospect of using vaccines to generate or bolster tumor-directed immune responses against antigens expressed in common across patients. A number of different vaccine approaches such as DCs, bacteria, yeast, virus, DNA plasmids, and messenger RNA have been tested. Oncolytic viruses are vectors that both carry the vaccination targets and have direct cytolytic effects against the cancer cells. While there has been some success of vaccine approaches for cancer therapy, the clinical impact has been modest. Clinical trials using vaccines against TAAs, such as CEA, MUC-1, PSA, and HPV, have been completed, showing moderate levels of efficacy and promise. For example, PANVAC, a poxvirus-based vaccine encoding the tumor antigens CEA and MUC-1, along with three T-cell co-stimulatory molecules (TRICOM), demonstrated high progression-free survival (PFS) in clinical trials compared to control groups.[98] The first Food and Drug Administration (FDA)-approved cancer vaccine is sipuleucel-T, which is an autologous DC vaccine loaded ex vivo with a recombinant fusion protein consisting of the tumor antigen prostatic acid phosphatase linked to granulocyte-macrophage colony-stimulating factor (GM-CSF), for patients with metastatic castration-resistant prostate cancer.[99,100] However, significant time and cost constraints associated with this approach as well as the modest clinical benefit have limited widespread adoption of this vaccine approach. General shortcomings of targeting TAAs

are that since these are self-antigens that are inappropriately expressed, it is possible that they are poorly immunogenic and/or they present the possibility of injury to other normal tissues that might express the antigen.

Since many patients have T cells that can recognize TSAs (neoantigens), another vaccine approach is to generate or expand these T cells in vivo. This is the basis of personalized vaccine approaches, and a variety of personalized vaccine approaches have been attempted. Personalized vaccine strategies, like general cancer vaccine strategies, have had limited success,[101] partly because neoantigens are broadly unique to each patient, requiring patient-specific vaccines, and shared nonmutated antigens (TAAs) are not entirely cancer specific. The rapid development of genomic sequencing has increased the feasibility of patient-specific neoantigen vaccines, and this is an area of active investigation.[102] As with cellular therapies described above, vaccines against shared commonly mutated TSAs such as Kras may overcome some of these roadblocks of personalized vaccines and are in clinical development.[103] As discussed later, there is also the possibility of using the patient's own tumor in situ as the source of antigens for vaccination, allowing the generation of antitumor immunity without the need to sequence or know the individual antigens.

Many novel vaccine approaches are being developed, and it is likely that vaccines will be a more important part of our cancer IT arsenal in the future.

Antibody Therapies

Abs can not only be engineered as targeting mechanisms for CAR-T cells but also be directly used as therapies. For example, while anti–B-cell Abs are the target recognition component of CAR-T, they were long preceded by infusion of free anti–B-cell Abs.[104,105] In selecting Abs as therapeutics, it is essential to consider the mechanism of action as this will determine the design.[106] For example, with B cell targeting Ab for B-cell lymphomas, as discussed above, the aim is to cause death of B cells via immune mechanisms. While the binding domains of Ab provide target recognition, the Fc domain provides function. Cells coated with Ab can be killed via an array of mechanisms, including complement activation, opsonized phagocytosis, and Fc-mediated cellular cytotoxicity. This latter method

results in effector cells such as NK cells binding the Fc portion and killing cells recognized by the binding domain. This is an endogenous version of what CAR-T tries to achieve and can be extremely potent. However, some Ab therapeutics are not intended to cause cytotoxicity. For example, anti-epidermal growth factor receptor (EGFR) Abs are intended to block the increased EGFR signaling in EGFR overexpressing cancer cells.[107] However, the Fc-mediated activation of immune responses was found to play a critical role in patient responses.[108] Fc engineering is, therefore, critical in the design of therapeutic Abs.[106]

Abs can also serve as therapeutic or diagnostic radionuclide delivery systems.[109] These design criteria can take advantage of the stability of Abs as a platform, with the pharmacodynamics of Abs having half-lives measured in weeks, permitting stable systemic engagement. However, isotopes used in diagnosis and therapy have much shorter half-lives for a range of reasons, including safety. This impacts design decisions for the combination.[110] The use of radionuclide Abs in radiation and IT is discussed elsewhere in this text.

Immune-Modulating Antibodies (Checkpoint Inhibitors)

T cells (and other immune cells) can express a variety of co-receptors, which help modulate their activity. Some of these co-receptors can be inhibitory and are known as checkpoints (or co-inhibitory), and some of these can be activating and are known as co-stimulatory. Sometimes, a T cell may receive multiple suppressive and stimulatory signals at once, and it is the synthesis of these various signals that determines the activity of the T cells. In the past two decades, Abs targeting immune checkpoints dominated the landscape of cancer IT and revolutionized the clinical care of patients with cancer. For the first time, curing patients with metastatic cancers such as melanoma and non–small cell lung cancer (NSCLC) is possible, albeit only achieved in a small fraction of patients.

One of the main challenges in cancer IT is the tumor's inherent ability to evade immune responses. Unlike infectious immunity, tumor immunity must remain active over a prolonged period, which often leads to exhaustion of tumor- specific CD4+ and CD8+ T cells. Exhaustion is driven by negative inhibitory interactions, in which either inhibitory receptors, like

CTLA-4 binding to co-stimulatory ligands B7-1/B7-2, or specific inhibitory ligands, such as PD-L1/PD-L2 binding to PD-1, B7-H3 to Lag3, or galectin to TIM3, mediate the suppression.[111] To address this, monoclonal antibodies (mAbs) can be used to target and block these interactions. These are also known as immune checkpoint inhibitors (ICIs), since they overcome a regulatory checkpoint to permit full function of T cells. Abs targeting CTLA-4 and the PD-1/PD-L1 interaction have been clinically approved,[112] with various versions blocking PD-1/PD-L1 making a dramatic impact across diverse malignancies.[113-116] Blocking CTLA-4 and PD-1 with specific mAbs limits CTL exhaustion and enhances T-cell proliferation and function in the early phases of the response.[117] The clinically approved Abs block either the PD-1-PD-L1 interaction or the CTLA-4-CD80/86 interaction, which play important regulatory roles in limiting T-cell function. PD-1 is upregulated on T cells following activation and is likely most important during the effector phase of T-cell function. When PD-1 is engaged by its ligand, PD-L1, this limits TCR-CD28 co-receptor activation.[118] PD-L1 is upregulated on cells following exposure to IFNs, as well as other stimuli, and provides negative feedback to T cells. Expression of PD-L1 by cancer cells and suppressive immune cells in the TME limits T-cell control of tumors. Chronic engagement of PD-1 on T cells by PD-L1, as often occurs in the TME, can induce exhaustion characterized by decreased proliferative and effector function of T cells. CTLA-4 is rapidly upregulated on T cells during activation and displaces CD28 (signal 2) in binding the CD80/86 co-stimulatory molecules.[119,120] Again, the consequence is that TCR-CD28 co-receptor activation is limited. This dampens and modulates T-cell activation during the initial priming phase. Therapeutic Abs block these interactions and allow T cells to overcome this regulatory suppression. Notably, the Fc portion of these Abs again plays an important function. In the preclinical models used to develop these therapies,[121] the Fc portion plays a critical role, and Fc receptor binding is essential.[122] In preclinical models, the anti–CTLA-4 Ab results in the depletion of T-regulatory cells, which are high expressors of CTLA-4.[123] Thus, in using Abs as a therapeutic, actions beyond target binding are often critical. To date, many Abs blocking immune checkpoints have been FDA approved for the treatment of cancer. Ipilimumab and tremelimumab are anti–CTLA-4 Abs. PD-1 inhibiting Abs include pembrolizumab, nivolumab, cemiplimab, and dostarlimab. PD-L1

blocking Abs include atezolizumab, durvalumab, and avelumab. PD-1/PD-L1 and CTLA-4 are not the only immune checkpoint molecules, and strategies targeting other immune checkpoints associated with T-cell exhaustion, including Lag3, Tim3, and TIGIT, are actively moving forward.[124] Recently, the FDA approved a Lag3 inhibiting Ab (relatlimab) to be used in combination with nivolumab for advanced melanoma.[125,126] While ICIs may provide significant initial benefit, resistance to them may eventually develop. For example, resistance to CTLA-4 inhibition can arise from the upregulation of PD-L1 on melanoma cells, leading to T-cell exhaustion.[127] Persistent type I and II IFN signaling can also contribute to resistance, resulting in PD-L1–dependent and PD-L1–independent adaptive resistance to immune checkpoint blockade.[128] Strategies to overcome this adaptive resistance include incorporating multiple checkpoint inhibitors or inhibiting chronic IFN signaling, among many others. For instance, combining anti–CTLA-4 and anti–PD-L1 therapies has shown promise in melanoma and NSCLC.[129]

Many of the co-receptors that are upregulated on T cells, such as OX40, 4-1BB, and GITR, serve to provide further co-stimulation to T cells rather than inhibition.[124] Abs targeting these pathways aim to be agonistic, which activate the receptor rather than blocking it, as is the aim of Abs targeting the checkpoint molecules. This area of research has seen a number of failures in clinical translation, despite often dramatic preclinical efficacy, suggesting that there is much left to learn in the application of immunoregulatory Abs for cancer therapy. Critically, radiation has proven to be a dramatically effective partner for immunoregulatory Abs in preclinical models, as further discussed.

Innate Immunotherapy

Another major subclass of immuno-oncology relates to more general manipulation of the antitumor immune response using innate immune mechanisms. For the purposes of this discussion, we can also consider cytokines in this context (although addressed under the next subheading), since while they may be produced by or act on adaptive immune cells, they are normally regulated as part of more general inflammatory responses and accompanied by many other cytokines, rather than induced alone.

If the immune system most commonly functions as a series of stimuli resulting from infection and causing elimination of the infectious agent, the logical solution to generate immunity in a tumor is to introduce an infectious agent. While this may not direct immunity to the cancer cells, it can provide the authentic innate signals to generate and support immunity in the vicinity of the tumor, which can extend to tumor antigens as the immune cells infiltrating to clear infection will also take up debris from dying tumor. If TAAs are not successfully generating immunity, inflammatory signals from infectious agents may turn this around. The archetype for this is Coley toxins, an intratumoral administration of infectious agents with the intent to clear cancer either through direct infection and destruction of the cancer cells or via immune mechanisms, though the latter were not appreciated at the time.[130] This has been the mechanistic basis of Bacillus Calmette-Guérin instillation in bladder cancer,[131] as well as similar intralesional injections in other cancer types.[132] More recently, engineered selectively replication-competent viruses have been approved for the treatment of melanoma.[133] As with Coley toxin, a combination of mechanisms can influence the response. The agents are designed to directly infect cancer cells and can cause the death of the infected cells. In addition, innate sensing mechanisms can recognize the infectious virus and locally activate inflammatory cytokine secretion that can induce cancer cell death, such as tumor necrosis factor α (TNF-α), or additionally remodel the TME. Finally, these various components can result in an in situ vaccine effect yielding adaptive immune responses against the tumor. Despite the theoretical potential of this approach, it is clear that injection of an infectious agent is not universally effective. The inflammatory signals may not be sufficient to induce in situ vaccination against tumors, and bacterial or viral clearance does not necessarily result in epitope spreading and generation of an immune response against the unrelated tumor antigens. Also, clearance of the infectious agent may result in inflammatory resolution and allow the tumor to restore a suppressive TME. For this reason, it may be important to combine innate initiators of response with additional therapies such as anti–PD-1 to support ongoing antitumor immunity[134] or additional inflammatory agents such as RT.

As an alternative to infectious agents, synthetic triggers of innate immunity have been widely tested in cancer. In particular, a range studies

have shown that ligands for nucleic acid sensors have particular therapeutic efficacy in preclinical models (reviewed in Medler et al[42]). Innate triggers have been shown to synergize well with radiation in preclinical models[43] as discussed later. However, these have not translated into approved clinical therapies thus far. This has been particular disappointing for agents targeting STING, which are dramatically effective in preclinical models,[135,136] synergize well with radiation,[137] but have not shown similar efficacy in patients.[138,139] However, this is an area of active research, and novel targets and agents are in development.

Cytokine Immunotherapy

Cytokine therapies are among the earliest employed ITs in the modern era. In the 1990s, the FDA approved two cytokine ITs: IL-2 for melanoma and renal cell cancers and IFN-α (type I IFN) for melanoma. Many of the innate pathways discussed above result in the production of cytokines in the form of either type I IFN or TNF-α. Both have been applied as cancer therapies. Type I IFN is induced downstream of many of the innate immune activators mentioned above. Type I IFN has been studied as a therapy for melanoma and can improve recurrence-free survival[140,141] but does not impact overall survival (OS).[142] However, the toxicities of type I IFN have limited its broader use. For example, in patients receiving type I IFN along with adjuvant chemoradiation (chemo-RT), efficacy was observed in early-stage studies[143]; however, multicenter studies also reported improved outcomes but resulted in grade III or IV toxicity in 90% of patients.[144] A range of delivery approaches have been proposed and tested to overcome systemic toxicities. It is important to note that RT locally induces type I IFN for immune activation[145] and does not induce the toxicities seen with systemic IFN therapy. TNF-α has shown a similar clinical trajectory to type I IFN. TNF-α has long been identified as the active factor, resulting in necrosis of tumors following infection.[146,147] However, TNF-α is the main factor contributing to systemic shock, and extensive systemic toxicities limit clinical use. Again, local delivery has been attempted through a range of strategies, and TNF-α has been effectively combined with RT clinically and preclinically.[148,149] At present, TNF-α is not an independent cancer therapy

but may play a role in radiation efficacy and toxicity, so it is an ongoing topic of investigation.

High-dose IL-2 is a cytokine therapy approved for the treatment of metastatic melanoma and renal cell carcinoma.[150] Despite developments in immunoregulatory Abs, IL-2 remains a viable and effective therapy for these patients.[151,152] As discussed above, IL-2 is a backbone of adoptive transfer therapy,[153] and novel molecules targeting IL-2 receptor signaling are in late-phase clinical trials.[154] This development is important since toxicity management is critical in delivery of high-dose IL-2, so agents with a similar efficacy but decreased toxicity have high value. This is relevant to RT since high-dose IL-2 has shown evidence of increased responses in combination with radiation in early-phase studies.[155,156] There is potential for IL-2 support of T-cell responses generated following RT,[157] given an increasing understanding of the impact of IL-2 timing on T-cell responses.[158] Numerous other inflammatory cytokine therapies are being developed as cancer therapy, including GM-CSF, IL-7, IL-12, IL-15, IL-18, and IL-21. Additional work is ongoing on therapies to neutralize suppressive cytokines, such as IL-10 and TGF-β.

Current Directions in Immuno-Oncology

The recent status of the field was that we had more candidate therapies than the capacity to test them. However, the high failure rate of ITs on clinical translation has narrowed the field significantly. Likely, many potentially efficacious candidates have been discarded as a result of poorly designed clinical trials or an as-of-yet incomplete understanding of mechanisms of action. A critical ongoing endeavor is identification of biomarkers of response to focus therapies on those likely to respond and reveal mechanisms governing failures. However, to date, few biomarkers are so strongly predictive of poor response that treatments are *not* given to patients. The current status of the field is dominated by combination treatments. In these, the common denominator is generally anti–PD-1/PD-L1, given the widespread efficacy across malignancies and clinical scenarios, albeit in a subgroup of patients. It is in this setting that radiation finds its strongest role. Radiation alone is very rarely able to impact immunity to tumors outside the treatment field,[159] but preclinical studies and

clinical anecdotes have shown that in combination with IT, radiation is an effective partner for local and distant tumor control.[160,161] Clinical translation of preclinical therapies that include radiation has also not been simple.[127] but as we will discuss, there is enormous potential.

RADIATION IMMUNE MODULATION

The principle of RT traditionally involves delivery of ionizing radiation to a focal tumor while minimizing dose and damage to the surrounding healthy tissues with the goal of producing local effects on the target volume. Advances in our understanding of the immune-modulating effects of ionizing radiation have increased focus on RT's ability to stimulate the immune system, locally and systemically, to induce antitumor effects manifesting as regression in distant, unirradiated sites, known as the abscopal effect.[162] The phenomenon underlying the abscopal effect has been mechanistically referred to as in situ vaccination, where the irradiated local tumor acts as a vaccine activating the immune system to produce systemic antitumor effects targeted against nonself, TSAs. However, the immunomodulatory effects of RT are generated by multiple radiation-induced effects on the tumor, TME, and immune system[1] and likely extend beyond in situ vaccination and antigen-specific responses. RT induces a complex interplay of immune responses involving cytokines, DNA sensing pathways, and the activation of pattern recognition receptors. Understanding these interactions is crucial for harnessing the immune-modulatory properties of RT and developing effective combination strategies with IT.

In Situ Vaccination

An idealized and simplified overview of RT-induced in situ vaccination is presented in Figure 26.1 and summarized below. The subsequent sections present more detail on each of these processes. RT is primarily a local modality, and the effects of radiation on the immune system begin directly at the site of the tumor irradiation (and draining lymph nodes). RT can affect the TME, which consists of various immune cells, an intricate network of fibroblasts, blood vessels, lymphatics, and the cancer cells themselves. These components of the TME are enclosed within a dense

stroma formed by collagen and elastin fibers, collectively known as the ECM. The TME has been acknowledged as a vital factor influencing the signaling pathways and tumor characteristics that promote or suppress antitumor immunity and disease progression.[63] RT can alter the stroma and TME structure to increase the diapedesis of immune cells. Infiltrating APCs, such as DCs, can take up antigens from dying tumor cells and present them to T cells to activate the adaptive immune response against the tumor.[163] Thus, the first local action of RT is to alter the stroma and TME to allow an influx of immune cells.

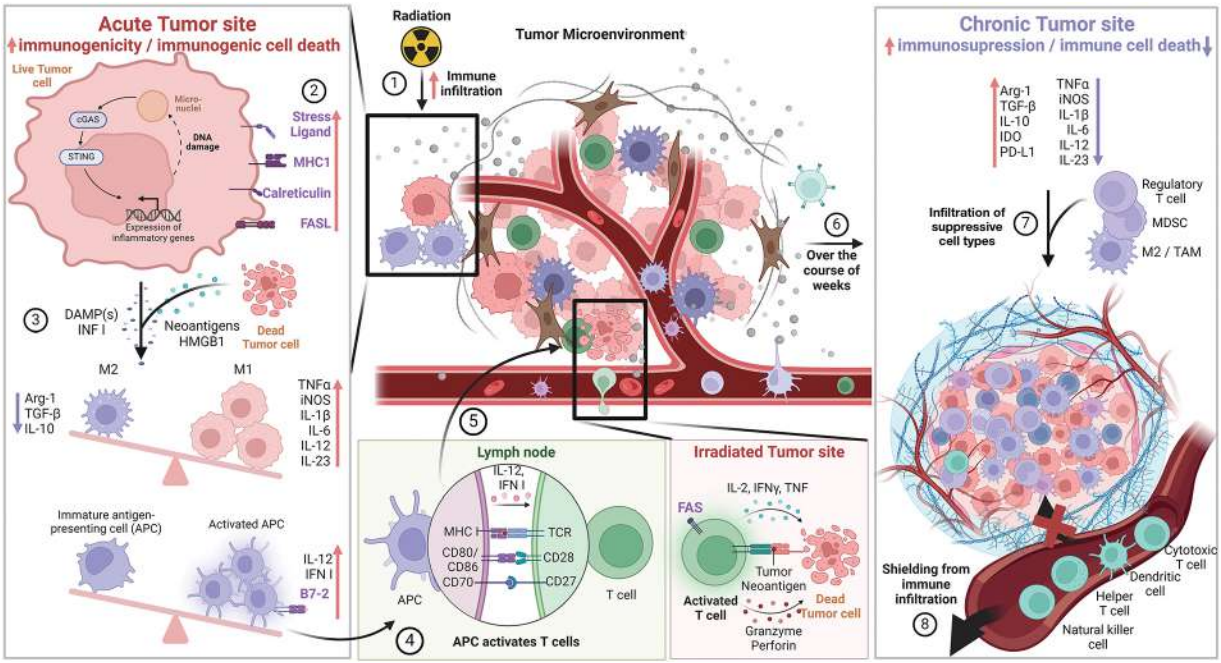

FIGURE 26.1 Simplified overview of radiotherapy-induced in situ vaccination. 1. Radiation alters the stroma and vasculature to increase the diapedesis of immune cells, thereby changing the TME's endogenous composition and dynamic features. 2. Radiation also induces DNA damage that ignites nucleic acid spillage into the cytoplasm, thereby triggering the endogenous viral detection systems to initiate a sequence of events, including increased presentation of intracellular contents and self-tagging for destruction, all leading to immunogenic cell death. 3. Immunogenic cell death releases the intracellular contents as DAMPs and neoantigens to repolarize the M2 to M1 macrophages and activate APCs that phagocytose neoantigens. 4. These newly loaded APCs then migrate to draining lymph nodes and cross-present to activate T cells. 5. The activated T cells then return to the primary tumor site or any other site (abscopal effect) and trigger tumor cell death, which may also be immunogenic and potentially self-propagating. 6. However, tolerance takes hold if the signal becomes chronic, increasing immunosuppression and decreasing immunogenic cell death. 7. Over time, immune suppressive cells infiltrate or develop within the TME, promoted by various signal changes. 8. The ECM/stroma around the tumor regenerates, reducing the number of functional immune cells infiltrating into the TME and functionally evading immunosurveillance. NK cell and B-cell mechanisms are intentionally excluded from this scheme for simplicity. APC, antigen-presenting cell, DAMPs, damage-associated molecular patterns; ECM, extracellular matrix; IDO, indolamine-2,3-dioxygenase; IL-10, interleukin-10; INF, interferon; iNOS, inducible nitric oxide synthase; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; NK, natural killer; PD-L1, programmed death-ligand 1; TCR, T-cell receptor; TGF, transforming growth factor; TME, tumor microenvironment; TNF, tumor necrosis factor. (Created with BioRender.com.)

Irradiated cancer cells undergo immunogenic cell death (ICD), resulting in more efficient uptake and presentation of TSAs from dying cancer cells by APCs. Thus, RT can increase the influx of APCs and also increase their

functionality. The dying cancer cells release DAMPs, resulting in the upregulation of IFNs, which feed into this process and activate the inflammatory cascade.[164] RT augments type I IFN and TLR signaling.[145] These effects can increase the functionality of APCs to more efficiently present tumor neoantigens and can upregulate antigen presentation machinery on cancer cells. Due to DNA and RNA alterations and protein misfolding, cancer cells may also generate new nonself antigens, referred to as neoantigens, which the immune system can identify as foreign.[165] The increased antigen presentation can generate new and bolster preexisting antitumor T-cell responses. The chemokine and cytokine changes in the TME can help support T-cell functionality, and increased expression of MHC and stress ligands on tumor cells can sensitize them to T-cell killing. Thus, RT augments existing T-cell responses as well as stimulates new T-cell responses. RT increases the infiltration of T cells into the TME and also sensitizes tumor cells to killing by CTLs and other immune cells through increased expression of MHC I and upregulation of stress ligands including Fas.[162,164,166] Only when T cells are generated with sufficient function and numbers to enter, the systemic circulation and eradicate distant tumors in a clinically meaningful way can this be considered a true in situ vaccination, resulting in an abscopal response.

Stroma and Vascular Changes

RT induces a number of changes that facilitate trafficking of immune cells into the TME. Changes in chemokines and cytokines attract immune cell infiltrates into the TME and are discussed below. RT can also effect changes in the tumor stroma and vasculature, which result from RT effects directly on fibroblasts and endothelial cells or can result from the effects of RT-driven signaling molecules on these cells. Hammerling and colleagues[167] at the German Cancer Research Center described RT effects on tumor vasculature in two elegant reports 11 years apart. They demonstrate that RT induces remodeling and normalization of the structure of tumor vasculature, which facilitates immune cell infiltration into the TME. Furthermore, they indicate that RT-induced changes in macrophage polarization can induce activation of endothelial cells by iNOS. This results in normalization of vasculature and secretion of T-cell recruiting Th1 chemokines increasing

TILs.[168] This process is critical to the success of adoptive T-cell IT in their models. Numerous preclinical and clinical studies demonstrate that radiation also upregulates adhesion molecules on both immune cells and the vasculature and stroma, which increases homing and extravasation of immune cells into the TME. Initial preclinical studies demonstrated increased levels of vascular cell adhesion molecule 1 (VCAM-1) on endothelial cells after RT.[169] Clinical data from patients with irradiated head and neck cancer report RT-induced increases in β-2 integrin on leukocytes and intercellular adhesion molecule 1 (ICAM-1) on endothelial cells.[170] Taken together, these effects indicate that RT can induce the trafficking of immune cells into the TME, which is now a well-accepted immune-modulatory effect of RT. Clinical data from UC Davis in a cohort of patients with sarcoma treated with neoadjuvant RT clearly demonstrate a significant increase in TILs post-RT.[171] In the clinic, it is difficult to distinguish between an influx of immune cells into the TME and the proliferation of immune cells within the TME.

Immunogenic Cell Death and Radiation-Induced Danger-Associated Molecular Patterns

Several studies demonstrate that tumor cells undergoing radiation-induced cell death release a milieu of DAMPs (also known as alarmins), which interact with pattern recognition receptors on immune cells and other cells in the TME to help activate the immune system. This is referred to as ICD and is different than the traditional apoptotic cell death pathway, which is considered to be immunologically silent. Landmark studies by Zitvogel, Kroemer, and colleagues[172,173] reported that irradiated tumor cells (as well as cells killed by certain chemotherapeutic agents such as anthracyclines) die in a manner that increases phagocytosis, processing, and display of their antigens by DCs. Preapoptotic cancer cells undergoing radiation-induced cell death translocate calreticulin from the endoplasmic reticulum to the cell surface. Cell surface calreticulin on the tumor cells can interact with receptors, including CD91, expressed on the surfaces of DCs and other APCs, which act as an “eat me” signal upregulating phagocytosis of the dying tumor cells. Furthermore, these dying tumor cells release the nuclear protein HMGB1, which interacts with TLR4 on DCs to increase the

processing and cross-presentation of antigens from phagocytized dying tumor cells.[34] Likewise, the release of adenosine triphosphate from these dying cancer cells can also help recruit DCs to the TME.[174] Studies by Formenti, DeMaria, and colleagues[175] built on this concept of RT-induced ICD by identifying another mechanism whereby dying irradiated cancer cells induce recruitment and activation of TME DCs. RT induces the release of double-strand DNA into the cytosol, which acts as a DAMP that is sensed by cGAS. cGAS, via its downstream effector STING, induces transcription factors such as IRF3 and NF-κB for the production of type I IFNs, which recruit and activate DCs and have various other immunologic effects. Other danger signals, such as heat shock proteins, also play a role in these processes. Together, these processes can increase the maturation and activation of DCs and increase their ability to take up and cross present tumor antigens to the adaptive immune system. Furthermore, these activated DCs will upregulate co-stimulatory molecules such as CD80/86 and inflammatory cytokines such as IL-1β, IL-6, and TNF-α, thereby also providing signals two and three required for T-cell priming (Figure 26.1, panels 3-5). Thus, the induction of ICD is key for in situ vaccination.

Radiation Effects on Surviving Tumor Cells

RT may not consistently achieve the death of every tumor cell. The inherent sensitivity variations of tumor cells to radiation and limitations in dose delivery due to surrounding normal tissue structures often allow some tumor clonogens to survive. Numerous studies have demonstrated that RT-induced cell stress in surviving cancer cells triggers a range of phenotypic changes, collectively increasing their vulnerability to being targeted and killed by the immune system.[176] After RT, the surviving fraction of tumor cells upregulates cell surface stress ligands and death receptors, intercellular adhesion molecules, proapoptotic TNF family member receptors, and various co-stimulatory molecules. Conversely, there is downregulation of antiapoptotic and prosurvival genes, as well as an overall increase in the presentation of tumor antigens.[177] Thus, while ICD helps induce an in situ vaccination bolstering the antitumor immune response, the surviving fraction of irradiated tumor cells is not left unscathed and becomes sensitized to targeting and killing by the generated immune response. In

clinical practice, it is likely that RT relies not only on direct cancer cell cytotoxicity but also on the immune system to clear surviving clones.

Stress ligands are upregulated on tumor cells in response to RT-induced DNA damage. Natural killer cell group 2D (NKG2D) ligands are upregulated on the cancer cell surface in response to DNA damage[178] and RT.[179] The NKG2D receptor is expressed on several potent effector cells including NK cells, NKT cells, γΔT cells, and CTLs, and recognition of the ligand on the surface of irradiated tumor cells can lead to cell killing in an antigen-nonspecific manner. Coleman, Hodge, and colleagues[180] demonstrate that irradiated cancer cells upregulate the Fas/CD95 death receptor, which renders them more susceptible to antigen-specific killing by CTLs expressing Fas ligand. They also demonstrate upregulation of TRAIL death receptor sensitizing cells to antigen-specific killing by TRAIL expressing effector cells.[181] Studies from UC Davis demonstrate RT-induced upregulation of Fas and MICA/B (NKG2D ligands) on stressed radiation-resistant cancer cells, which renders them susceptible to killing by NK cells in an antigen-nonspecific manner.[179]

In addition to stress ligands that can target irradiated cancer cells for immune-mediated cytotoxicity, there is also increased expression of adhesion molecules like ICAM-1/CD54 and lymphocyte function-associated antigen 3 (LFA-3/CD58), which enable immune cells to form a stable immunologic synapse for interaction with the stress ligands and MHC molecules on these cancer cells. RT also upregulates cell surface expression of co-stimulatory ligands on tumor cells, including B7-1, B7-2, OX40L, and 41BBL, which are critical for overcoming tumor-specific anergy and sustaining effective CTL responses.[182-184] Some of these co-stimulatory molecules have also been associated with reduced levels of Tregs, which may further help counteract immunosuppression.[184] Critically, RT also upregulates the machinery involved in antigen processing and presentation on cancer cells. RT increases the pool of antigens presented on cell surface MHC by cancer cells by increasing translation, degradation, and processing of peptides, resulting in increased and novel intracellular peptides available for presentation by MHC I.[185] Furthermore, RT increases the cell surface expression of MHC I, facilitating recognition and killing of cancer cells by CTLs.[185] Gough, Crittenden, and colleagues[186] demonstrated that RT-induced upregulation of MHC I on surviving cancer cells via

NLRC5 is a critical mechanism whereby RT contributes to a successful antitumor immune response.

Radiation-Induced Cytokines and Chemokines

Much of the work examining RT-induced cytokines has focused on examining their contribution to RT-induced toxicity. However, cytokine and chemokine induction are essential for an RT-generated immune response. One of the critical immunogenic properties of RT-induced ICD is induction of type I IFNs (ie, IFN-α, IFN-β) by cancer cells, which can help recruit and activate DCs. Numerous cytokines and chemokines are upregulated by cancer cells, immune cells, and/or stromal cells in response to RT. Many of the immune-modulatory effects of RT described in the preceding sections are signaled or effected, at least in part, through cytokine and chemokine signaling. For example, type II IFNs (ie, IFN-γ) are also critical mediators of the RT-induced immune response generating several changes within the TME. RT-induced IFN-γ in the TME upregulates VCAM-1 on endothelial cells and MHC I on tumor cells, augmenting the TME to one that is conducive to infiltration and tumor cell recognition by T cells.[187] DCs activated by the processes outlined in the above sections secrete numerous cytokines, including IL-6, IL-1b, TNF-α, and IFN-γ, which are critical for the induction and activation of antitumor T cells. RT-induced chemokines such as CCL2 and CCL5 recruit T cells and macrophages to the irradiated TME, and CCL20 recruits DCs. Likewise, the production of CXCL16 (a chemokine that binds to the chemokine receptor CXCR6 on activated T cells) by irradiated breast cancer cells was shown to be critical to RT-induced T-cell infiltration of the TME and the efficacy of combining RT with ICI IT.[188] The upregulation of RT-induced TLR signaling in macrophages has been associated with increased macrophage secretion of the immune-activating cytokines IL-12 and IL-18.[189]

Radiation Therapy Modulation of Effector Cells

RT modulates immune effector cell function primarily in an indirect manner via induced changes in the TME, including changes in tumor cells, cytokines/chemokines, APCs, and tumor vasculature, which are described in the preceding sections (Figure 26.1). Much of the focus of RT studies has

been on adaptive T-cell responses and CTLs as effectors, but there is also an important role for B cells and innate effector cells in the RT-induced antitumor immune response.

RT induces a wide array of changes in the TME, which support existing and generate new T-cell responses. RT augments existing T-cell responses via numerous mechanisms described in the preceding sections. RT sensitizes tumor cells to T-cell cytotoxicity by increasing expression of MHC I, Fas, Trail, and other ligands. Upregulation of inflammatory cytokines including IL-1b, TNF-α, and IL-6 supports the function, expansion, and differentiation of antigen-experienced T cells. The concept of increasing TILs to transform the TME from "cold" to "T-cell inflamed" is a common rationale for combining RT with IT. As outlined above, RT induces changes in vasculature, adhesion molecules, chemokines, and cytokines that increase the homing and infiltration of T cells into the TME. In addition to inducing infiltration of T cells, RT also induces the proliferation of T cells (Ki-67+ T cells) within the TME and draining lymph nodes. Studies of clinical specimens from resected oral squamous cell carcinomas and renal cell carcinomas demonstrated an increase in proliferating CD8+ T cells post-RT.[190,191] RT can also generate new T-cell responses by increasing antigen expression by cancer cells, increasing the uptake and presentation of those antigens by DCs, and increasing the activation of DCs (which increases expression of co-stimulatory molecules and cytokines), all of which can serve to prime a T-cell response by providing signals 1, 2, and 3. Studies using TCR sequencing to interrogate how RT alters T-cell clonality demonstrated RT increases the diversity as well as expansion of new and preexisting T-cell clones, supporting the idea that RT immune modulation supports existing and generates new T-cell responses.[127,192,193] All of these processes serve to increase the number of T cells in the TME post-RT.

RT has also been shown to induce changes in B cells. In the TME of mouse NSCLC models, RT is reported to increase tertiary lymphoid structures, which have germinal centers with proliferating B cells.[194] However, other studies have suggested that RT can transiently deplete tertiary lymphoid structures.[195] The presence of tertiary lymphoid structures in tumors has been linked with positive clinical outcomes in general and in response to IT. Many studies have also focused on increased T-cell

infiltrates in the TME after RT, but it appears that infiltrating B lymphocytes are also increased. The aforementioned examination of soft tissue sarcomas also demonstrates increased B-cell infiltrate in the TME after standard neoadjuvant RT.[171] Likewise, Sharabi and colleagues[196] demonstrate that RT increased B-cell infiltrates and B-cell activation marker expression in the TME of their preclinical models.

As outlined in the above section, RT can induce upregulation of many stress ligands on cancer cells, which serve to target them for killing in an antigen-nonspecific manner by innate effector cells. As demonstrated by Minn and colleagues,[197] these innate effector pathways may be particularly important when tumors have developed strategies, such as downregulating MHC, to reduce their antigenicity. Historically, interest in the innate immune system was focused on its role in activating and managing the adaptive immune reactions, but there is a growing interest in the effect of RT on innate immune cells such as the NK cells and their direct role in tumor cell killing in solid tumors. While NK cells have been known for their involvement in hematologic malignancies, mounting evidence suggests that they also play a role in solid tumors. Several preclinical studies have shown that RT upregulates NK cell ligands and induces NK cell migration into tumors.[171,198-201] Moreover, radiation-induced DNA damage pathways can activate NK cells to eliminate tumor cells through upregulation of specific molecules that promote the efficient killing of tumor cells by NK cells.[178] RT upregulates NK cell ligands and induces NK cell migration into tumors. NK cell activity is mediated through receptors such as NKG2D (activating) and killer cell immunoglobulin-like receptors (activating and inhibitory).[202] Radiation-induced DNA damage pathways, mediated by the ataxia telangiectasia–mutated protein and p53, can activate NK cells. These pathways lead to the upregulation of NK cell ligands (MIC-A, MIC-B, and ULBP) on irradiated tumor cells that interact with the activating NK cell receptor NKG2D, promoting the efficient killing of tumor cells by NK cells.[178,179] Restoring p53 expression in tumors lacking it can trigger complete tumor regression. This occurs through p53-mediated cellular senescence, followed by increased production of inflammatory cytokines and the initiation of tumor-directed innate immune responses, rather than through RT-induced apoptosis.[111,179] Preclinical studies indicate that RT increases NK cell killing of several murine solid tumor cell lines as

well as human cancer cell lines and primary cultured human cancer cells that are co-cultured with NK cells.[171,198-201]

RADIATION IMMUNE SUPPRESSION

Inflammation is a double-edged sword. As with other physiologic processes, the inflammatory cascade is under tight regulatory and counterregulatory mechanisms function to maintain homeostasis. RT can have positive immune- modulating effects, but it can also induce immune suppression. RT induces immune suppression via regulatory pathways, which are activated to limit the degree and duration of inflammation, as well as through direct cytotoxic effects on immune cells. While data clearly support the radiation-induced immune events outlined in Figure 26.1, the full story is more complex, as the TME consists of a milieu of supportive and suppressive immune cells. RT can be directly cytotoxic to immune cells and can also increase the release of immunosuppressive cytokines, such as VEGF, TGF-β, and IL-10. These cytokines can promote suppressive immune cell function in the TME and reduce the overall lymphocyte count in systemic circulation.[171,203] RT can also upregulate other immune-suppressive factors such as PD-L1 and the enzyme IDO.[204,205] These effects are time dependent. While the exact kinetics are model dependent and not wholly deciphered, it generally appears that RT introduces a window of pro-inflammatory opportunity before counterregulatory immune-suppressive networks set in.

Radiation Therapy–Induced Immune Cell Cytotoxicity

Conventional RT induces some degree of immune suppression due to the loss of radiosensitive immune cells within the irradiated field.[111,206] The impact of RT on lymphocyte populations has been long recognized.[207] Studies in numerous cancers including high-grade glioma, squamous head and neck cancer, pancreatic adenocarcinoma, and NSCLC treated with RT or chemo-RT demonstrate treatment-induced lymphopenia and correlate severe lymphopenia with poor clinical outcomes.[208-213] Focusing solely on blood counts might underestimate the effects of cytotoxic therapies on the immune system. Schuler et al[214] studied lymphocyte subtypes in patients with head and neck cancer undergoing chemo-RT and found that chemo-RT

led to a decrease in overall circulating CD4 helper cells, but increased CD4+ CD39+ Tregs, which dampen the immune response. Moreover, they found that this increase in Tregs persisted years after treatment conclusion. Radiation-induced lymphopenia is further exacerbated by the fact that it is often accompanied by tumor-driven granulocytosis that drives an elevation in the neutrophil-to-lymphocyte ratio—a factor that has been validated in numerous studies as an independent predictor for OS in various cancer clinical trials.[215]

Yet, it is unclear precisely which lymphocyte populations are affected. While circulating and naïve lymphocytes are very radiation sensitive, Weichselbaum et al[216] have demonstrated that tissue-resident and TME T cells are more radioresistant. Sharabi et al[196] also demonstrated that activated and class-switched B cells are more radiation resistant than their naïve counterparts. Likewise, it has been shown that tissue-resident macrophages and DCs are more radiation resistant than the circulating monocytes from which they derive.[217] The impact of RT on peripheral blood counts is often attributed to bone marrow irradiation, where normal stem cells are particularly sensitive to DNA damage, but the data above suggest that dose to the circulating blood pool may be most critical. Yovino and Grossman[208] suggest that lymphopenia arises from apoptosis of lymphocytes passing through the radiation field. They estimate that during a fractionated course of partial brain irradiation, about 99% of lymphocytes received at least 0.5 Gy, with an average circulating lymphocyte dose of 2 Gy—doses sufficient to induce apoptosis in circulating lymphocytes. Their simulations also predict that a single fraction of RT would deliver 0.5 Gy to only 5% of circulating lymphocytes. It, therefore, appears that highly critical variables in RT-induced cytotoxicity of immune cells are the field size and number of fractions that determine the volume of irradiated blood pool since this is where the most radiosensitive immune cells are present. For a more detailed review of this topic, we refer the reader to two thorough and expertly written reviews by Gough and Crittenden[161] and Paganetti.[218]

Rebound Immune Suppression

The immune system is a homeostatic system with built-in regulatory pathways to limit the magnitude and duration of the inflammatory response.

Inflammation is meant to be short-lived and resolved once the infection or offending agent has been cleared. Chronic inflammation, as can occur with certain infections and cancers, can ultimately be immunosuppressive as multiple regulatory pathways are activated to control the inflammatory response that has not resolved. Likewise, RT can induce chronic inflammatory changes, which lead to upregulation of immune-suppressive pathways, a process we coin "rebound immune suppression."[205] Thus, while acute inflammation can be beneficial and RT can initially stimulate the immune system during the acute inflammatory phase, this can give way to chronic inflammation and rebound immune suppression as the immune system attempts to reestablish homeostasis. RT-induced hypoxia-inducible factor-1α (HIF-1α) and chronic IFN-γ may be the master signals governing this immune suppression. Several immune-suppressive cell types including Tregs, M2-polarized tumor-associated macrophages (TAMs), and MDSCs have also been reported to be involved in this process. Further long-term changes to the stroma and vasculature also affect the TME and the ability of the immune system to eradicate tumor.[205,219-221]

Over time, RT-induced inflammation gives rise to pathways used for the resolution of immune responses in which bone marrow–derived myeloid cells and vasculogenesis play a key role. RT upregulates HIF-1α and, in turn, CXCL12, CCL2, CSF1, and VEGF, which recruit bone marrow–derived MDSCs and TAMs to the TME and increase their immunosuppressive functions.[222-225] Of note, the HIF-1–dependent chemokine CXCL12 and its receptor CXCR4 have been strongly implicated in recruiting immune-suppressive myeloid cells to the TME.[223] Inhibiting CXCR4 has shown to inhibit tumor regrowth and lung metastasis while enhancing the effectiveness of anti–PD-L1 IT in mouse cancer models.[226] HIF-1α and IFN-γ signaling also induce the expression of PD-L1 on MDSCs, TAMs, and tumor cells, which increases their suppression of the antitumor immune response.[227] TAMs and MDSCs also upregulate anti-inflammatory cytokines such as TGF-β and IL-10 and enzymes such of arginase-1.[228] While these effects can occur days to weeks after RT, acutely RT reduces circulating myeloid cell numbers, suggesting that RT may create a therapeutic window for IT at the time of minimal myeloid-induced immunosuppression.[229] Likewise, preventing this myeloid induction may prolong the beneficial immune modulatory effects of RT. Preclinical studies

from Shiao et al[228,230] demonstrate that depleting myeloid-derived cells enhances RT efficacy.

RT-induced IFN signaling, while critical for many of the antitumor and immune-modulatory effects of RT, can also upregulate resistance pathways. Minn and colleagues[197] report that chronic IFN signaling can drive tumor cell resistance to immune attack. IFN signaling is also known to upregulate IDO, an enzyme implicated as a master regulator of immune suppression and known to potently induce Tregs. Studies demonstrate that RT can induce IDO expression in the TME and limit the efficacy of RT + IT, while blocking IDO decreases Tregs and improves the efficacy of therapy.[205] Welsh and colleagues further demonstrated that RT-induced IDO is linked to increased MDSCs in the TME.[231]

OPTIMIZING RADIATION THERAPY VARIABLES FOR IMMUNE MODULATION

The immune-modulatory effects of RT, as described above, are diverse, and the effects are highly dependent on factors of RT delivery, such as dose, fractionation, quality, timing, and the volume and type of tissue being irradiated. In this setting, RT should not be considered a single treatment modality but rather as many different drugs with varying immune-modulatory effects depending on how it is employed. The best RT approach will thus depend on the desired immune-modulatory effects. This will likely also depend heavily on the type of cancer and the existing TME, as well as the type of IT that RT is being partnered with if a combinatorial strategy is undertaken. This is an area of study where large gaps in knowledge remain and highly systematic preclinical and clinical studies testing these variables are required.

Radiation Therapy Dose and Fractionation

The variable with the largest consequences for RT immune modulation is likely dose and fractionation. A recent review has expertly discussed many of the issues, which we summarize below.[232] External beam RT (EBRT) can be administered in different ways, such as standard fractionation (1.8-2.0 Gy daily for several weeks) or with larger doses in fewer fractions

(hypofractionation).[177] For the purpose of this discussion, we consider four approaches (the distinction between which is arbitrary and hazy):

1. Low-dose RT is considered a small fraction number + small dose per fraction (<2 Gy), which would not be considered sufficient for tumor control.
2. Standard fractionated RT is considered 1.8 to 2 Gy per fraction to a sufficient dose to obtain tumor control (generally several weeks).
3. Hypofractionated RT is generally considered subablative doses delivered in a limited number of fractions.
4. Ablative RT is considered high dose (>10 Gy) delivered in one to five fractions.

Low-Dose Radiation Therapy

Low doses of RT may be insufficient to kill all tumor cells but, as discussed above in the section on RT effects on the surviving fraction of tumor cells, may be sufficient to stress cells and alter the TME. Studies have shown that RT induces the upregulation of MHC class I expression in a dose-dependent manner starting at doses as low as 1 Gy or less, leading to increased presentation of tumor antigens on the tumor cell surface. Nonlethal radiation has also been shown to activate the mammalian target of rapamycin, facilitating increased protein synthesis and availability of peptides for MHC class I loading.[177] These effects lead to elevated antigen presentation on the surface of the tumor. In addition, very low doses of radiation (0.5 Gy × 4) have been found to reprogram macrophages and stimulate effective T-cell immunity against tumors, offering a novel approach to modulating the TME.[168,233] In these preclinical studies, this low dose is sufficient to induce vascular remodeling of tumors. Two randomized clinical studies organized by the National Cancer Institute's Experimental Therapeutics Clinical Trials Network (ETCTN) and led by Schoenfeld, Monjazeb, and Hodi[129,234] tested a low-dose RT approach in combination with dual ICI for colorectal cancer and NSCLC but failed to show a clinical benefit over dual ICI alone. Preclinical studies and clinical reports from Welsh and colleagues suggest that RT + IT strategies using low-dose RT may be most useful when combined with high-dose RT to at least one lesion

to induce in situ vaccination at the high-dose lesion but take advantage of RT immune modulation at other sites of disease treated with low dose.[235,236] This concept is discussed further below when considering spatially fractionated RT.

Standard Fractionated Radiation Therapy

Traditionally, radiation oncology has equated increased dose with improved tumor control based on clonogenic cell survival assays.[237] The survival curves imply an intimate connection between radiation dose and cell kill. In the clinic, fractionation enables higher radiation doses to achieve local control but allows for sparing effects on normal tissues. A certain minimum dose is likely required for disease control, but escalating doses further has not yielded additional improvements in outcomes across various cancer types, including esophageal, low-grade glioma, glioblastoma, and NSCLC.[238,239] These principles were developed based on in vitro systems and fail to consider RT effects on the immune system and TME, including the cytotoxic effects on local and circulating immune cells discussed in preceding sections. Standard fractionated RT also generally utilizes larger field sizes, which treat not only the gross tumor but also areas at high risk for subclinical disease, often including draining lymph node basins. Thus, due to increased field size and fraction number, standard fractionation RT irradiates more normal tissue and blood pool, causing more local and systemic immune suppression. Crittenden, Gough, and colleagues[240] tackled this issue by examining the impact of neoadjuvant standard fractionated and hypofractionated chemo-RT on immune cells among patients with locally advanced and borderline resectable pancreatic adenocarcinoma. They report that standard fractionated chemo-RT caused a substantial and prolonged reduction in lymphocytes, not attributed to deficiencies in homeostatic cytokines or cytokine responses. Conversely, hypofractionated RT avoided the lymphocyte loss associated with conventional fractionation. It is difficult to separate the effects of standard fractionation from those of larger field size, and this topic is discussed more below.

Hypofractionated Radiation Therapy and Ablative Radiation Therapy

Ablative and hypofractionated RT employ larger doses per fraction. The line between hypofractionated and ablative RT is quite blurred, but most radiation oncologists would classify 8 Gy × 3 or 6 Gy × 5 as hypofractionated, whereas regimens such as 20 Gy × 1 or 10 Gy × 5 would be considered ablative. Larger fractional doses may induce higher levels of ICD, generating a more intense radiation-induced antitumor immune response.[7,206] In addition, tumor cells that survive may be more immunogenic, rendering them more susceptible to attack. Furthermore, these approaches, particularly ablative RT, often treat more limited field sizes and thus avoid the detrimental effects of multiple fractions and large field sizes discussed above. Larger doses have demonstrated promise in combination with tumor vaccines[181] and immune checkpoint blockade.[241]

Ablative RT is usually delivered in one to five fractions and yields very high rates of local tumor control. The use of ablative RT has demonstrated high control rates for tumors that are resistant to fractionated RT, and there is a suggestion that tumor control is dependent on both direct cell kill and endothelial cell injury.[242,243] These effects are most prominent above a single dose of 12 Gy and increase with increasing doses above this threshold.[70] Hypofractionated RT often has lower rates of tumor control likely due to a delivery of a lower BED. Seminal work by Demaria, Formenti, and colleagues studied the role of dose fractionation, particularly single-fraction versus hypofractionated RT, for RT combined with anti–CTLA-4 immune checkpoint blockade, in mediating abscopal effects in murine models of breast and colon cancer.[241] They found that hypofractionated RT (eg, 8 Gy × 3 or 6 Gy × 5 fractions on consecutive days) induced an abscopal effect when combined with anti–CTLA-4 therapy, but single high doses of RT (eg, 20 Gy × 1) failed to do so. Their follow-up studies indicated that ablative RT doses (>12-18 Gy), compared to hypofractionated doses, were less effective and immunogenic, inducing less cGAS/STING pathway activation due to the breakdown of intratumoral cytosolic DNA by an exonuclease called Trex1, which is induced by higher RT doses.[175] As previously discussed, sensing of RT-induced cytosolic DNA by cGAS/STING resulting in IFN signaling is among the most important RT immune-modulatory effects. The expression of Trex after RT may be an important biomarker to guide the selection of RT dose and fractionation for IT. Despite these findings, it is important to note that the impact of fractionation schedules on

RT immune modulation should be considered an unresolved issue and that the use of ablative doses for immune modulation cannot be discounted. Clinical success combining RT and IT has been reported for both ablative and hypofractionated RT approaches. Two recent studies evaluating ablative RT + ICI in early-stage NSCLC by Monjazeb, Daly, and colleagues[244] and Heymach and colleagues[245] suggest a benefit of this approach. Another, similar recent study in early-stage NSCLC by Formenti and colleagues[246] used instead hypofractionated RT + ICI and also noted a benefit to this approach. None of these trials was phase III, and none of them compared ablative versus hypofractionated RT.

In summary, different RT fractionations can be seen as various immunomodulatory drugs, with functions ranging from immunogenic ablation and immune modulation of tumor cells to modulation of the TME's stromal cells.

Field Size and Irradiated Target

An issue that goes hand in hand with dose and fractionation is field size, as described above. Standard fractionation approaches often employ larger field sizes and may also target draining lymph node regions, whereas hypofractionated and ablative RT fields are often more tightly defined. As outlined in sections above, larger field sizes and increased fraction numbers will irradiate more blood pool and induce more cytotoxicity of circulating immune cells. Thus, strategies with large field sizes and many fractions may not be the optimal approach for maximizing the immune-modulatory effects of RT. In prostate cancer, an unexpected and unexplained interaction between RT field size (whole-pelvic radiation vs targeting the prostate only) and androgen deprivation was observed in RTOG 9413.[247] This interaction was confirmed in a large meta-analysis that also hypothesized that the field size interaction could be immune related.[248] The effects of field size may also explain the disparate outcomes between PACIFIC-1[249] and PACIFIC-2, which is discussed in the section "Sequencing."

An important concept is not just the volume of tissue being irradiated but also the nature of the tissue. As noted above in the introductory section on immune function, priming and activation of T cells occur primarily in the draining lymph nodes. Thus, elective nodal irradiation (ENI), which is

commonly employed in many standard fractionation approaches, may have unintended detrimental effects on RT immune modulation. This is an active field of study. Preclinical studies by Drake and colleagues[250] found that irradiation of draining lymph nodes limits adaptive immune responses by altering RT-induced chemokines and CD8+ T-cell trafficking and is detrimental to combining RT with IT. This was confirmed in preclinical studies by Karam and colleagues[251] in head and neck cancer models, which found that ENI limited the RT-induced immune response and the success of combining RT + IT. ENI decreased the systemic immune response including antigen-specific T cells and epitope spreading leading to increased local and systemic tumor growth. However, eliminating ENI increased regional nodal recurrence, serving as a clear caution that more study is needed to determine if and when ENI should be omitted.

Another point of consideration is that the irradiated site may also play a role in dictating the induction of immune-modulatory effects. For example, the liver is thought to be inherently immune suppressive and liver metastases have been reported to be less sensitive to IT than metastases at other sites.[252] A study at UC Davis by McGee et al[253] demonstrates differential immune effects of stereotactic body RT (SBRT) depending on the irradiated site. Irradiation of parenchymal sites significantly increased circulating levels of activated memory T cells, which was not observed with irradiation of nonparenchymal sites (bone, brain, etc).

Overall, these data suggest that in theory, standard fractionated RT may have the least favorable immune-modulatory effects and be the least well suited to combine with IT. However, before discounting standard fractionated RT as a viable partner for IT, it is important to note that in clinical practice perhaps, the most impactful application of RT + IT has been in the setting of standard fractionated chemo-RT for locally advanced NSCLC (PACIFIC-1).[249]

Sequencing

Similar to dose and fractionation, there is no established consensus as to the optimal sequencing of RT in combination with IT. Most likely, the optimal sequencing will be multifactorial depending on the IT strategy employed, the type of RT, and patient and TME factors. For example, preclinical

reports suggest that optimal sequencing of RT with IT may differ for Abs that block checkpoint molecules versus those that activate co-stimulatory molecules. In a report from Young et al[254] combining 20 Gy with either an inhibitor of CTLA-4 or an agonist of OX40 (CD134), the optimal timing depended on the mechanism of action of the IT agent. Anti–CTLA-4 was the most effective delivered prior to RT due to depletion of Tregs and anti-OX40 agonist Ab was the most effective sequentially 1 day following RT during the period of increased antigen presentation. Dovedi et al report that anti–PD-L1 Abs are the most effective delivered concurrently with RT. Clinical studies employ IT before, after, and concurrent with RT treatment without a strong rationale for the sequencing. Data and evidence examining how the sequencing of therapies influences the synergy of RT and IT agents represent a clear area of unmet need.

Recently, it has been reported that the PACIFIC-2 trial failed to meet its end points. Like PACIFIC-1, PACIFIC-2 tested standard fractionated chemo-RT + ICI for locally advanced NSCLC. While PACIFIC-1 enrolled patients and started ICI after completion of chemo-RT, PACIFIC-2 sought to test concurrent use of chemo-RT + ICI. The reason for the disparate outcomes between PACIFIC-1,[249] which was a strongly positive landmark trial, and PACIFIC-2 is not yet clear. It could be due to patient selection since PACIFIC-1 enrolled patients who did not progress on chemo-RT and who tolerated chemo-RT. Thus, patients destined to progress on or with poor tolerance of chemo-RT were enrolled in PACIFIC-2 and not on PACIFIC-1. However, beyond patient selection, there may be a genuine biologic difference between the approaches of these two trials. It is possible that chemo-RT given prior to ICI primes the immune system for response to ICI. It is also possible that chemo-RT given concurrently with ICI inhibits the efficacy of ICI. Since this is standard fractionated RT with large field sizes, it is possible that the very T cells being reinvigorated by ICI were being depleted by chemo-RT. These possibilities help illustrate the complexity and nuisance of the field.

Spatially Fractionated Radiation Therapy

A central principle of traditional RT is “Don’t miss the target.” Using a traditional cell-kill mentality, missed tumor is the untreated tumor and is

bound to recur. However, when thinking about radiation immune modulation, it is unknown if treating the entire tumor volume is necessary or beneficial for inducing immune modulation, since untreated tumor may be eradicated by the immune system. This consideration is particularly relevant as sometimes treating the entire tumor with the prescribed radiation dose is not possible due to the tumor's heterogeneous nature or potential harm to surrounding healthy tissue. To address this, spatially fractionated GRID RT (SFGRT) was developed.[255] This technique involves delivering the prescribed radiation dose to only a portion of the tumor volume, aiming to reduce local tumor burden and trigger a systemic immune response.[177] Originally, this approach utilized two-dimensional (2D) grid fields with orthovoltage beams to achieve spatially alternating dose distribution. Successful clinical responses were observed, particularly in the treatment of large bulky tumors. Preclinical studies using SFGRT have also shown abscopal effects, indicating that the treated tumors may have prompted immune cells to produce inhibitory factors, hindering tumor growth.[177] More recent preclinical studies have advanced SFGRT by modifying it into 3D GRID, allowing for a comparison between the effects of high-dose RT targeting the entire tumor volume versus only partial tumor volumes. This is because the irradiation of partial tumor volumes can induce the secretion of immune-related cytokines and activate the ceramide pathway, which affects both the nonirradiated intratumoral environment and distant metastases.[256] In a recent study, patients with bulky tumors were treated with partial tumor irradiation using SBRT to target hypoxic areas. Bystander response rate was 96%, while abscopal response rate in distant nontargeted tumors was 52%.[257] These studies demonstrated that irradiating partial tumor volumes with focused high-dose beams using lattice RT (3D SFGRT) might lead to immune stimulation. One consideration of this approach is that tumor areas in the dose peaks can receive high doses capable of inducing ICD whereas the areas in the dose valleys may still receive immune- modulating doses of RT.

FLASH Radiation Therapy

FLASH radiation therapy (FLASH-RT) involves the delivery of RT at very high dose rates compared to conventional RT. Generally, dose rates >40

Gy/s have been considered for FLASH-RT, but there is no single universally accepted cutoff. FLASH-RT has shown remarkable normal tissue-sparing properties, which enhances the differential effects of RT on tumor in relation normal tissues, and thus has shown great potential for significant increase in the therapeutic ratio. FLASH-RT is not a new concept. Initial published studies were completed as far back as the 1960s and 1970s[258,259]; however, given the technological advances over the past few decades and the significant potential for a paradigm shift from pursuing FLASH-RT, it is again attracting significant interest.[260] The underlying mechanism for FLASH-RT is still being studied. Proposed causes of the differential response between FLASH-RT and conventional RT include oxygen depletion and immune sparing. The oxygen depletion hypothesis is based on the idea that oxygen depletion in normal tissues protects them from damage due to reactive oxygen species while tumors are comparatively more hypoxic and thus less affected.[261] In contrast, the immune hypothesis posits that conventional RT results in greater irradiation of radiation-sensitive, circulating lymphocytes (larger total blood volume irradiated) in contrast to FLASH-RT, which provides greater immune sparing.[261] This strong immune-sparing effect was noted in a computation study that models the effects of FLASH-RT and found that the killing of circulating immune cells was reduced from 90% to 100% in conventional RT to 5% to 10% with FLASH-RT. It was also found that this sparing effect increased and reaches a plateau at doses/fraction of 30 to 50 Gy/fraction and almost completely vanished at lower doses of 2 Gy/fraction.[262] One study of proton FLASH-RT in mice found significantly smaller tumors in mice treated with proton FLASH-RT compared to conventional proton therapy as well as increased recruitment of CD8+ T lymphocytes while simultaneously reducing the percentage of immune-suppressive Treg among lymphocytes in the TME in tumors treated with FLASH-RT.[263] The early studies of FLASH-RT and its potential for immune sparing are promising. Further studies are needed to improve understanding of the underlying mechanisms and to also specifically exploit its immune-sparing effects, in combination with ITs and potentially with other immune-sparing techniques, such as spatially fractionated RT.[264]

Radiation Therapy Quality

EBRT most commonly employs photons, which are massless particles or waves. Photon radiation is characterized by its high penetration capability, which increases with energy, but dose deposition starts promptly upon entering the tissue.[265] Particle therapy involves depositing lower energy upon entry into tissue and generating Bragg peak radiation, which allows for more specific dose deposition into the target volume.[266] In addition to differences in the physics of dose deposition, particle therapy may have different biologic effects, which could also manifest as different or more pronounced immune-modulatory effects. For example, carbon ion RT (CIRT) has high linear energy transfer and a focused dose with reduced beam scattering, resulting in more precise dose distribution. Compared to traditional photon therapy, CIRT shows less sensitivity to cell cycles, making it a promising candidate for future combination treatment strategies.[267,268] Preclinical studies have demonstrated the potential of CIRT in inducing systemic antitumoral immunity in mouse models.[269-271] Preclinical studies by Drake and colleagues[272] and Zhou, Wang, and colleagues[273] suggest improved synergy of CIRT versus photon RT in combination with ICI. They also demonstrate in murine melanoma models that compared to photon RT, carbon ion induces a greater influx of lymphocytes into the TME, greater functionality of those lymphocytes, and also reduces MDSCs to a greater extent.[274]

RADIOTHERAPY PLUS IMMUNOTHERAPY

The antitumor immune response induced by RT is rarely strong enough to induce clinically meaningful regression of systemic disease (abscopal effect). While altering methods of RT delivery to improve its immunogenic effects may help to some degree, combinations strategies with IT are likely needed to amplify RT's immunogenic properties. Strategies combining RT and IT make mechanistic sense in that each therapy can benefit the other. RT's cytotoxic and immune-modulatory properties can enhance IT by debulking tumors, boosting the tumor's antigenic properties, inducing T-cell activation and influx, and making surviving tumor cells more vulnerable to immune-mediated elimination. IT can reciprocally assist RT by activating

the immune system to eradicate lingering disease both within and beyond the radiation field.

Significant progress has been made in our understanding of the interactions between RT and the immune system, and preclinical studies have demonstrated that RT can stimulate antitumor immunity and synergize with IT.[39,275] With multiple completed randomized trials, there is limited clinical evidence of the expected synergy between RT and IT,[129,276-280] but most of the focus has been on combining RT with ICI. Additional preclinical and clinical studies are required to further elucidate optimal strategies for combining RT and IT.

Devising an optimized methodology for combining RT with IT can be explored in the context of the cancer immunity cycle.[281] This cycle involves several steps: (1) RT-induced release of cancer antigens, (2) antigen presentation by DCs and other APCs, (3) T-cell priming and activation in draining lymph nodes, (4) trafficking of activated T cells from draining lymph nodes to the bloodstream, (5) infiltration of T cells into tumors, and (6) recognition and killing of cancer cells. RT can be combined with various tumor vaccines and immune adjuvants such as TLR agonists, STING ligands, and agonist anti-CD40 for the first two steps. For step 3, agonistic Abs that enhance T-cell activation (eg, anti-OX40, anti-CD27, and anti-CD137), cytokines (eg, IL-2 and IL-12), and immune checkpoint blockade (eg, anti–CTLA-4) can be used during the immune priming phase. To improve T-cell infiltration into tumors (steps 4 and 5), low-dose regimens of RT and anti-VEGF therapy can be employed. Finally, to enhance cancer cell recognition and killing by tumor-infiltrating CTLs (step 6), epigenetic modulation can be utilized to increase RT-induced antigen presentation and class I MHC expression in tumor cells. Immune checkpoint blockade with agents targeting anti–PD-1, anti–PD-L1, anti-Tim3, and anti-LAG3 can then counter tumor-evading strategies and reinvigorate exhausted T cells, sustaining a robust antitumoral immune response.

Cellular Therapies

As outlined in the section “Radiation Immune Modulation,” RT can both induce influx of effector cells into the TME and sensitize cancer cells to killing by effector cells. For these reasons, combining RT with adoptive

transfer of effector cells in the form of ex vivo expanded TILs, TCR transgenic T cells, CAR-T cells, or CAR-NK cells is a rational approach with a strong preclinical foundation. Preclinical studies demonstrate that adoptive transfer of T cells[167,168] or NK cells[179] is more effective when combined with RT due to increased immune-attracting chemokines, vascular normalization increasing tumor infiltration of immune cells, and increased sensitization of the tumor cells to killing by effector immune cells. Likewise, a translational study from a pancreatic clinical trial incorporating chemo-RT demonstrated that RT increased CXCL8 and NK cells systemically and, in the TME, the magnitude of which was associated with improved clinical outcomes.[282] Several preclinical studies also demonstrate synergy of combining CAR-T cells with RT. A preclinical study using EGFR targeting CAR-T cells in triple negative breast cancer demonstrated that RT increased lymphocyte infiltration into tumors and enhanced the efficacy of CAR-T therapy.[283] Clinical studies in hematologic malignancies have reported that bridging strategies using RT prior to CAR-T therapy appear to be safe and effective. Analysis of a Chinese clinical trial using CAR-T for patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) reveals that pretransplant conditioning with RT (vs chemotherapy) increased response rates.[284] Likewise, a multicenter retrospective analysis of DLBCL treated with CAR-T demonstrates that patients who received bridging or salvage RT had no increased toxicity but had improved clinical outcomes.[285] While there is an abundance of preclinical data and circumstantial evidence to support this combination, conclusive clinical evidence is still needed and many studies are underway.[286]

Antibody Therapies

As outlined in the section on immuno-oncology, numerous Ab therapy approaches exist. For the purpose of this discussion, we focus on Ab therapies that seek to inhibit T-cell signaling through suppressive T-cell co-receptors (ie, ICIs or ICI) and those that seek to agonize stimulatory T-cell co-receptors.

Immune Checkpoint Inhibitors

ICI therapy has spear headed the cancer IT revolution. Likewise, the greatest abundance of preclinical and clinical studies in combining RT + IT has focused on ICI. Numerous preclinical studies demonstrate a strong synergy between RT and ICI. We will not attempt to review the body of preclinical data here. These preclinical studies in conjunction with clinical case reports that demonstrated the abscopal effect of RT + ICI (eg, Postow et al[287] and Hiniker et al[288]) sparked unprecedented interest in the field and a frenzy of clinical trials followed. However, replicating the results of preclinical studies and case reports with RT + ICI has been challenging, indicating that the design of clinical trials may play a crucial role in testing these combinations. In retrospect, it is reasonable to conclude that the pace of development was too fast, based on too little science, incorporated too little collaboration with seemingly every academic cancer center having their own iteration of an RT + ICI trial, and ultimately was harmful to the development of the field. The abundance of studies is such that they cannot be encompassed here, but salient studies are highlighted to outline the progress made and lessons learned.

The most experience and greatest body of clinical data for combining RT + IT exists in the setting of NSCLC. Retrospective data and some clinical trials have shown that the combination of RT and checkpoint inhibitors offers significant benefits in several disease sites. The phase 1 KEYNOTE-001 trial assessed the safety, side-effect profile, and antitumor activity of pembrolizumab. A secondary analysis compared patients who had received prior RT with those who had not. The OS with pembrolizumab was significantly longer in patients who had received any form of prior RT compared to those without previous RT. The same trend was observed for patients who had received extracranial RT compared to those without previous extracranial RT. However, patients who had previously received thoracic RT also experienced higher rates of pulmonary toxicity. Overall, the study suggests that prior treatment with RT in patients with advanced NSCLC resulted in longer PFS and OS with pembrolizumab treatment, while maintaining an acceptable safety profile.[289]

The groundbreaking PACIFIC trial established the role of IT as standard of care in the definitive treatment of locally advanced NSCLC. In this phase 3 study, durvalumab, an anti–PD-L1 Ab, was compared with placebo as consolidation therapy after chemo-RT in patients with stage III NSCLC

who had not experienced disease progression after two or more cycles of platinum-based chemo-RT. The results were impressive, with durvalumab attaining significant improvement in median PFS (17.2 vs 5.6 months) and OS (2 year OS of 66.3% vs 55.6%) when compared to placebo. In addition, durvalumab showed higher response rates and longer duration of response without significant increase in toxicity.[249,290] These exciting results led to the subsequent stage III PACIFIC-2 trial evaluating the addition of concurrent durvalumab with chemo-RT. Unfortunately, the results show that concurrent durvalumab does not significantly improve PFS. While there were several differences between the trials, the discrepancy in results may indicate that the timing of IT in relation to RT is a critical factor in unleashing the full synergistic effect of both treatments. As outlined previously, combining IT concurrently with large field fractionated RT may be counterproductive due to the volume of irradiated blood pool.

RT + ICI is also being studied for early-stage NSCLC. Studies evaluating ablative RT with ICI patients with in medically inoperable NSCLC who are rarely offered systemic therapy demonstrated the safety and suggest a benefit with this approach.[244,245] Similarly, the use of hypofractionated RT with ICI has also been evaluated, also showing a benefit with this approach.[246] These early trials have led to several prospective randomized stage III trials evaluating the role of IT in combination with RT in early-stage NSCLC. This includes the phase III PACIFIC-4 trial[291] of adjuvant durvalumab with SBRT; the phase III SWOG 1914 trial[292] of induction, concurrent, and adjuvant atezolizumab with SBRT; and the phase III KEYNOTE-867 trial of concurrent and adjuvant pembrolizumab with SBRT,[293] all for early-stage NSCLC. These trials are not only studying different ICI regimens/durations but also employing different timing of the IT in relation to RT, which may provide additional insights.

Clinical successes are not limited to NSCLC. The randomized, double-blind, placebo-controlled phase 3 CheckMate 577 trial testing nivolumab as adjuvant therapy in patients with locally advanced esophageal or gastroesophageal junction cancers with pathologic residual disease after neoadjuvant chemo-RT and surgery was practice changing. The results showed that the addition of adjuvant nivolumab significantly improved disease-free survival (DFS) from 11 to 22.4 months.[294] Another recent trial with positive results is the phase 3 KEYNOTE-A18/GOG-3047 trial

evaluating the addition of concurrent and adjuvant pembrolizumab to concurrent chemo-RT followed by brachytherapy in patients with high-risk locally advanced cervical cancer. After a median follow-up of 17.9 months, there was a statistically significant improvement in 2-year PFS to 67.8% with the addition of pembrolizumab compared to 57.3% with placebo.[295] While there have been significant successes and the practice-changing studies are quite encouraging, there have also been multiple completed randomized trials with limited clinical evidence of the expected synergy between RT and IT.[129,276-280] For example, the GI002 trial, which evaluated the addition of pembrolizumab to neoadjuvant chemo-RT in locally advanced rectal cancer, did not show an improvement in DFS.[296] Similarly, the JAVELIN Head and Neck phase 3 trial, which evaluated the addition of avelumab to definitive concurrent chemo-RT followed by maintenance of avelumab in locally advanced head and neck squamous cell carcinomas, failed to show a benefit in PFS.[297] Importantly, these studies, whether showing a clinical benefit, have generally demonstrated the safety of combining ICI with RT in various types of cancers (including cervix, head and neck, lung, and brain[298] cancers and more). When used alongside RT, single-agent PD-1/PD-L1 or CTLA-4 inhibitors seem to have minimal added toxicity and more recent studies also show little added toxicity of adding RT to dual-checkpoint blockade.[129,234]

What has been particularly disappointing is not the number of negative trials, but the lack of data demonstrating synergy between RT and ICI. While there have been positive randomized trials, these trials generally demonstrate the benefit of adding ICI to standard-of-care RT or chemo-RT, which could be the result of independent additive effects of each therapy as opposed to a true synergism relying on RT immune modulation. Studies trying to demonstrate a true synergy by demonstrating that RT can induce a systemic response to ICI in patients with primary or acquired resistance to ICI or in histologies otherwise unresponsive to ICI have been negative. For example, both of these scenarios were tested by Schoenfeld and colleagues[129,234] through the ETCTN by combining RT with dual-checkpoint inhibition in patients with metastatic NSCLC resistant to ICI and in metastatic microsatellite stable colorectal cancer, both of which failed to show a benefit to RT + dual ICI.

Co-stimulatory Molecules

It is possible that RT alone does not provide enough T-cell activation and in situ vaccine effect to produce meaningful antitumor immunity. Combining RT with immune stimulants may help address this issue. The activation of antigen-specific T-cell responses necessitates the presentation of antigens and the presence of co-stimulatory molecules (B7-1/2, OX40L, CD40, or 41BBL) on DCs to interact with their respective ligands/receptors on T cells.[111] Preclinical trials have indicated that exposing human prostate cancer cells to ionizing radiation enhances the expression of co-stimulatory ligands (OX40L and 41BBL) while decreasing PD-L1 levels, resulting in improved CTL function.[182] This led to the idea that localized expression of co-stimulatory molecules and cytokines within the TME could enhance the activation of effector T cells. Preclinical studies have shown that introducing co-stimulatory ligands into the tumor can bolster antitumor immune responses.[299] The OX40 (TNF-receptor family member) on activated T cells stimulates T-cell proliferation, effector differentiation, and expansion of effector memory T-cell populations while suppressing Treg function. In a murine sarcoma model, combining RT with agonistic Abs for OX40 demonstrates promising results with increased tumor control and OS.[300] Several preclinical studies also suggest a benefit of combining RT with CD40 agonists. CD40 is expressed on DCs, B cells, and macrophages and upregulates the activity of these cell types when engaged by its ligand CD40L, which is primarily expressed on activated T cells. RT was combined with an agonist anti-CD40 Ab to treat B-cell lymphoma, leading to improved long-term survival.[301] Another study by Vonderheide and colleagues[302] demonstrated that adding CD40 agonist Ab to RT + ICI in a pancreatic cancer model was able to eradicate irradiated and unirradiated tumors. A recent clinical trial tested combinations of ICI, 41BB agonist, OX40 agonist, and RT in advanced gynecologic malignancies and observed a response rate of 3%.[303] Patients were accrued in a nonrandomized manner, there were only 35 evaluable patients across 6 arms, and very few patients were treated on the arms incorporating RT, limiting interpretation of the results.

Innate Agonists

One of the critical steps in generating an immune response is the activation of innate immunity by DAMPs and PAMPs, which is key to the eventual production of adaptive immunity. Many of the immune-modulatory effects of RT and the induction of ICD are thought to be mediated by the generation of DAMPs. However, since RT rarely induces abscopal effects alone, it stands to reason that combining RT with agonists of the innate receptors that recognize DAMPs and PAMPs may increase its vaccine effect. While this area has received relatively little attention compared to ICI, perhaps the best clinical data for synergy of RT and IT employ innate agonists as outlined in our prior review.[43]

The TLRs are among the best studied of all pattern recognition receptors. Exciting preclinical data exist for combining RT with various TLRs, including TLR4 and TLR7.[43] We focus our discussion on TLR3 and TLR9 since these have been tested clinically in combination with RT. TLR3 senses double-stranded RNA and can be activated by the synthetic ligand poly(I:C). No randomized studies employing RT and TLR3 agonists have been reported, but two phase II studies demonstrated improved survival compared to historical controls in patients with glioblastoma.[43] Brody and colleagues[304] further reported abscopal responses and complete remission in patients with indolent non-Hodgkin lymphoma treated with RT, TLR3 agonist, and Fms-like tyrosine kinase receptor 3 ligand (FLT3L). TLR9, like TLR3, has a broad expression profile, in B cells, DCs, and macrophages. TLR9 is a receptor for unmethylated CpG oligonucleotide DNA sequences that are present in pathogens, but not for mammalian DNA. It also recognizes endogenous DAMPs, such as chromatin DNA complexes and ribonucleoproteins. Synthetic CpG oligonucleotides are used therapeutically and can be administered systemically but, in the setting of cancer therapy, are most often administered intralesional. Clinical studies combining RT + TLR9 agonists demonstrate that this combination is safe and effective. A series of clinical trials by Levy and colleagues in low-grade lymphomas demonstrate a genuine synergy of this approach by inducing abscopal responses outside the irradiated and injected lesion in about 20% of patients with heavily pretreated systemic[305] or cutaneous[306] indolent lymphoma. Many of the responses were durable and lasted for months or years. This is particularly exciting, given that CpG is not known to have single-agent activity and RT rarely induces abscopal effects alone; thus, the systemic

response rates in these trials likely demonstrate a true synergy between these agents. Building on these findings, Monjazeb and colleagues[205] tested combining this approach with IDO inhibition to prevent rebound immune suppression triggered by the strong inflammation induced by RT + CpG. They report promising systemic efficacy and abscopal response of this approach in solid tumors when tested in mice and in a canine clinical trial in pet dogs with spontaneous cancers. This has since been translated into a human clinical trial with preliminary reports suggesting activity in solid tumors and lymphomas (NCT03322384 presented at ASTRO 2020). However, two similar trials using this approach with a different CpG agent and incorporating ICI instead of IDO inhibition reported limited activity of this approach.[307,308]

Other innate agonist pathways such as RIG-I–like receptors, FLT3, and STING have also shown great promise in preclinical studies.[43] STING agonists are being tested in clinical trials, but there are no reports publishing the outcomes of STING + RT in clinical trials. Likewise, there are no clinical reports of RIG-I agonists + RT. However, it is important to note that the TLR3 agonist poly(I:C) likely also exerts some effects through agonism of RIG-I. FLT3 is a receptor, which, like CD40, is expressed on a variety of APCs (B cells, macrophages, DCs) and, when triggered, can lead to the expansion and maturation of APCs. FLT3L is a cytokine that activates FLT3, and various agents targeting this pathway are being tested in clinical trials. Preclinical studies from Guha and colleagues[309,310] in murine models of metastatic lung cancer and hepatocellular carcinoma demonstrate a systemic effect of RT + FLT3L mediated by DC expansion. Combining RT of the primary tumor with the administration of FLT3L not only controlled the primary tumor but also suppressed the spread of metastasis and resulted in a cure.[309] Numerous clinical trials are testing various combinations, including FLT3L and RT or radiopharmaceuticals. Also, the published study mentioned above when discussing TLR3 agonists shows promising outcomes when combining FLT3L, RT, and poly(I:C).[304]

Cytokines

Among the first ITs was administration of IL-2 or IFN. IL-2 is a strongly immune-stimulating cytokine that is critical to T-cell activity. The high-

affinity receptor for it is expressed on activated T cells (but also on suppressive Tregs), and it may synergize with RT but support an RT-induced T-cell response. Combining local tumor irradiation with systemic IL-2 therapy or intratumoral injection of an immunocytokine has shown positive results in reducing tumor burden and enhancing Ab-dependent cell-mediated cytotoxicity and tumor-specific memory T-cell responses in preclinical mouse models of cancer.[311-313] Two clinical studies from the Earl Chiles Research Institute in metastatic melanoma and renal cell cancer have demonstrated the promise of this approach and suggest that combining IL-2 with ablative RT can increase systemic response rates beyond IL-2 alone.[155,156] Given the toxicity of high-dose systemic IL-2, there are also trials underway testing RT in combination with intralesional IL-2 and with engineered formulations of IL-2, which are less toxic. The CapRI regimen incorporating chemo-RT with type I IFN garnered significant attention for pancreatic cancer based on work out of Virginia Mason, which showed 42% 5-year survival for patients after pancreaticoduodenectomy.[314] The toxicity of this approach as well as the negative results of a larger trial from Germany has dampened enthusiasm for this approach, but ongoing trials are still exploring type I IFN + RT. Preclinical studies have also suggested a potential benefit for combining RT with various other immune-stimulatory cytokines, including IL-12 and IL-15.

Vaccines

There is a strong mechanistic rationale for combining RT with vaccine approaches. A vaccine aims to generate T cells directed against cancer antigens. RT can enhance the effectiveness of cancer vaccines via cytotoxic and immunomodulatory effects on the TME. RT can increase cancer cell antigen presentation and stress ligand expression, yielding them easier to detect and kill by vaccine-generated T cells. RT also alters the TME vasculature and cytokines, increasing the trafficking and homing of T cells to the TME. RT debulking effects improve oxygen and nutrient delivery in the TME, providing a less hostile environment for T-cell function. Clinical trials have demonstrated increased tumor immunity when combining DC vaccines with RT. For instance, one phase I study involving 14 patients with advanced-stage/metastatic hepatoma showed improved tumor-specific

immune responses in 7 out of 10 assessable patients when RT was combined with the injection of autologous immature DCs.[315] Another recent trial with 40 patients having recurrent, metastatic, or locally advanced tumors of the head and neck, pancreas, lung, esophagus, or uterus, treated with an autologous DC-based vaccine in combination with conformal RT also showed promising clinical responses.[316] However, to date, despite many clinical trials, there are no practice-changing or widely clinically used RT + vaccine approaches. As the development of personalized neoantigen vaccines continues, the potential of this combination may become realized.

CONCLUSION

After decades of research, the promise of cancer IT is now changing the lives of patients. Yet, we are just at the nascent stages of understanding how cancers evade immune attack and how to best harness the immune response to fight cancer. It is likely only through the perspective of the coming decades that we will understand the full scale of the revolution we are witnessing. Likewise, we are just beginning to understand the potential effects of RT in modulating the immune system. The complexity of radiation responses and the complexity of the immune system itself indicate that the optimal strategies to capitalize on the immune modulatory effects of RT and to combine RT with IT are likely to be complex as well. While we have made remarkable advances, we must also take the time to learn from our many failures and mistakes. As a field, we must have the humility to acknowledge that the path forward requires improved understanding and renewed commitment and that investment in scientific endeavor is needed. Unquestionably, our path forward will continue to be fraught with many failures and mistakes, but the potential reward for our patients is why we make the journey.

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CHAPTER 27

Hyperthermia

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Hyperthermia (HT), the therapeutic application of heat, has potential and in several scenarios established benefit in treatment of malignancies. While ablative temperatures can result in direct tumor kill, application of moderate temperature elevation in the range of 39 to 45 °C can enhance the effectiveness of radiation, chemotherapy (CT), and potentially immunotherapy. Since the introduction of HT into the clinic in the 1980s, similar to radiation therapy, significant advancements have been made. These advancements include better appreciation of how to exploit the underlying biology, treatment device development to meet clinical needs, establishment of quality assurance guidelines, and successful completion of randomized trials.

THE BIOLOGY OF HYPERTHERMIA

Definition of Hyperthermia

When cells or tumor tissues are subjected to elevated temperatures, several effects occur that have important biologic consequences for cancer therapy: (1) HT is cytotoxic and sensitizes tumor cells to radiotherapy (RT) and CT. (2) Thermally induced reoxygenation improves tumor responses to RT and CT.[1] (3) HT inhibits RT and CT-induced DNA damage repair.[2] (4) HT increases tumor microvessel permeability and pore size, increasing macromolecular and nanoparticle drug delivery, respectively.[3] (5) HT augments host immune responses against tumor cells in ways complementary to immune effects of RT and CT.[4]

Effects of Hyperthermia Alone on Cell Survival

HT kills cells in a log-linear fashion depending on the time at a defined temperature (Figure 27.1A). At *T* of less than 43 °C, a resistant tail may appear; the tail is caused by induction of thermotolerance that increases resistance to further HT damage.[5] Thermotolerance is not observed during HT above 43 °C but is observed for varying lengths of time (hours to several days) after HT[5] depending upon the temperature and length of heating. HT kills hypoxic cells as efficiently as aerobic cells. However, cells that are nutrient deprived, as might occur in chronically hypoxic tumor regions, are more heat sensitive than aerobic cells.

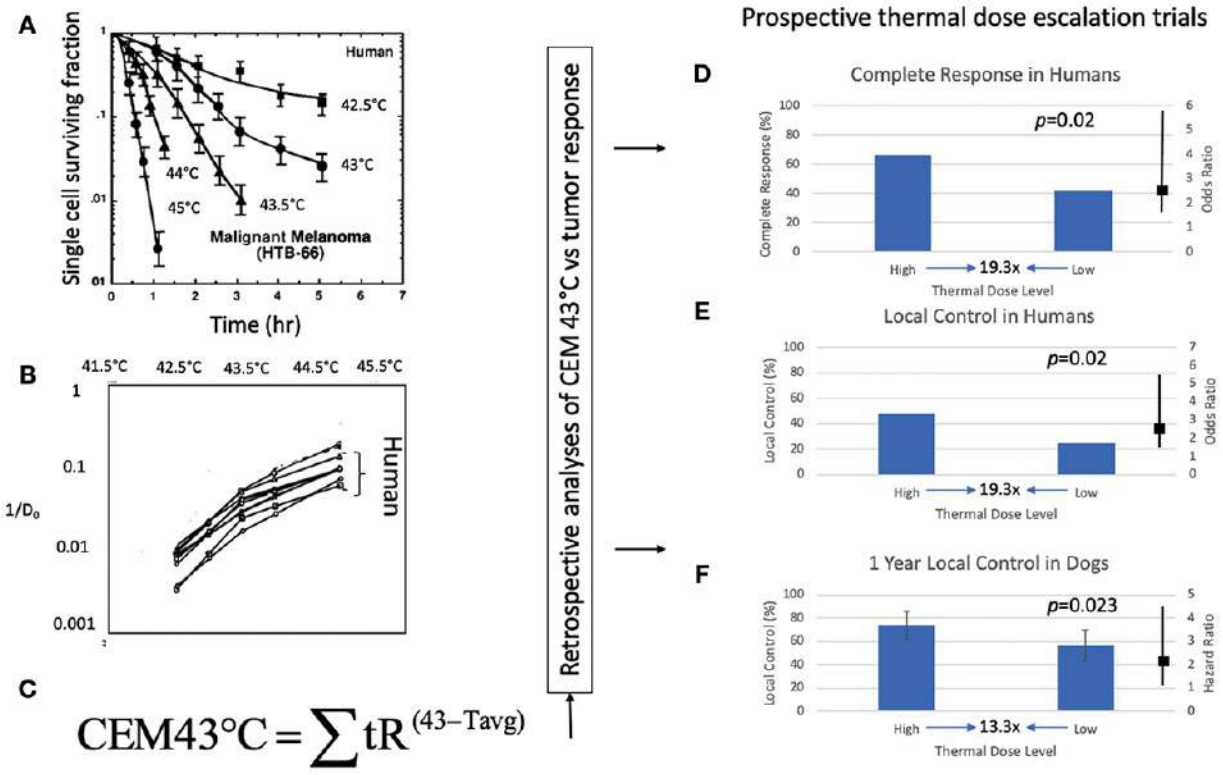

FIGURE 27.1 Summary of key principles of thermal dosimetry. A. The fundamental basis for thermal dosimetry is based upon characteristics of in vitro cell survival curves. The rate of cell killing is temperature dependent. The change in slope during heating for *T* 43 °C or less is caused by induction of thermotolerance. Thermotolerance is an adaptive response to thermal stress and leads to transient resistance to hyperthermia (HT). B. Arrhenius analysis of cell-killing rate versus temperature. A cluster of human cell lines is highlighted by the bracket to the right of the plot. A break point (change in slope) is observed between *T* of less than 43 °C versus more than 43 °C. Above the break point, the rate of cell killing doubles for each 1 °C temperature elevation, whereas below the break point, the rate of cell killing drops by a factor of 4 to 8 for each 1 °C temperature drop. C. The characteristics of the Arrhenius relationship enable straightforward conversion of any time-temperature history to cumulative equivalent number of minutes at 43 °C (CEM43°C) using the equation depicted here. *t*, time of heating; *R*, coefficient related to change in slope of the Arrhenius plot. Typically for *T* more than 43 °C, *R* = 0.5, for *T* less than 43 °C, *R* = 0.25; T_{avg} is the average temperature during the time interval *t*. For a complex time-temperature history, the heating profile is broken into intervals of time (*t*) length, where temperature remains relatively constant. CEM43°C is calculated using the average *T* (T_{avg}) for each interval, and the resultant data are summed to give a final CEM43°C for the entire heating regimen. Because multiple locations are measured in each tumor, descriptors of the temperature distribution are used. Examples include T_{50} = median and T_{90} = 10th percentile of the distribution. Retrospective analysis of thermal data from several clinical trials showed relationships between thermal dose and outcome. To further test the value of thermal dose to influence HT + RT (radiotherapy) outcome, two prospective randomized clinical trials were conducted. In the human and canine trials, the delivered thermal dose (CEM43°C T_{90}) varied by factors of 19 and 13 between low and high thermal dose groups, respectively. D

and E. Key results from the human trial with superficial tumors treated with HT + RT. The higher thermal dose group (N = 56; 19.3× higher than low thermal dose group N = 52) was associated with significantly higher response rate and longer duration of local control. Odds ratios are shown on the right side of each panel. The relative difference in CEM43°C T_{90} for the low and high thermal dose groups is indicated on the X-axis. F. Key results from a study of companion dogs with soft tissue sarcomas treated with HT + RT. The higher thermal dose group (N = 58) had a 13.3× higher thermal dose than the low thermal dose group (N = 64; P < .0001). The high thermal dose group exhibited significant prolongation of local tumor control compared with the low dose group. The hazard ratio is shown on the right side of the panel. The relative difference in CEM43°C T_{90} for the low and high thermal dose groups is indicated on the X-axis. These trials were provocative, but much more work is required to verify the validity of this approach for thermoradiotherapy. Further, thermal dosimetry has not been tested in trials involving chemotherapy.

Thermal Isoeffect Dose: The Arrhenius Relationship

The temperature dependence of cell-killing rate by HT has been studied using Arrhenius analysis.[5] The log of the slope ($1/D_o$) of cell survival curves versus temperature (Figure 27.1B) shows a biphasic curve. The temperature at which the slope changes is referred to as a "break point." The break point is near 43 °C for rodent cells but closer to 43.5 to 44 °C for human cells. Above the break point, an increase in temperature of 1 °C doubles cell-killing rate. Below the break point, the cell-killing rate drops by a factor of 4 to 8 for every temperature drop of 1 °C. Sapareto and Dewey[6] proposed normalizing thermal data by converting any time-temperature data to a cumulative equivalent number of minutes at 43 °C (CEM43°C) (Figure 27.1C). HT creates nonuniform temperatures within tumors, so multiple measurements are made. Descriptors of the temperature distribution are used to describe aspects of the spatial variation, such as the median (T_{50}), or the 10th percentile (T_{90}). CEM43°C T_{90} and T_{50} represent the lower end and average of the temperature distribution, respectively. Both CEM43°C T_{90} and T_{50} have been frequently associated with treatment outcomes in retrospective analysis of thermoradiotherapy trials.[7,8] Two prospective clinical trials showed therapeutic benefit of deliberately creating a 10- to 15-fold difference in CEM43°C T_{90} between low and high HT dose groups[1] (Figure 27.1D, E). Thermal analyses of some trials have not shown a thermal dose effect, which is likely due to inadequate thermometry.[9]

Standardization of treatment, thermometry, and reporting are needed for future studies.[7,10-14]

Mechanisms of Hyperthermic Cytotoxicity

Cellular and Tissue Responses to Hyperthermia: Targets for Hyperthermic Cytotoxicity

Proteins are the predominant molecular targets for hyperthermic cell killing.[15] When cells are exposed to HT, proteins are denatured at rates paralleling those for cell killing. Further, synthesis of nearly all proteins is stopped with the exception of heat shock proteins, the synthesis of which is upregulated.[16] One of the primary functions of heat shock proteins is to refold other proteins that have been denatured or damaged.[17]

The cytoskeleton of cells is particularly heat sensitive.[18] Cytoskeletal collapse disrupts cytoskeletal-dependent signal transduction pathways.[19] Enzymes in the respiratory chain are more heat sensitive than enzymes in the glycolytic pathway.[1] Most DNA repair proteins responsible for repairing RT and CT damage are relatively heat sensitive.[2]

Thermotolerance and Clinical Trial Design

Thermotolerance is a transient adaptation to thermal stress that renders surviving heated cells more resistant to additional heat stress. Whether or not a cell dies as a result of thermal insult is dependent on the net balance between how much protein is damaged and how much is protected and repaired via upregulated heat shock proteins. Thermotolerance develops either during or after heat stress and can persist for several days. The time of peak thermal resistance and the time of thermotolerance decay are related to the severity of the heat shock.[5] Concerns over the persistence of thermotolerance after HT impacted the design of many HT + RT clinical trials. In most trials, a minimum of 48 hours between HT fractions has been used to avoid reheating when cells are thermotolerant. The potential for thermotolerance after HT gave pause to the concept of delivering HT daily in conjunction with daily RT.

It has been argued that one should take advantage of HT-radiosensitization by giving HT multiple times per week. The degree of HT-

mediated cytotoxicity is low because temperatures are largely below that needed for direct cell killing. Further, HT-radiosensitization is relatively unaffected by thermotolerance.[20] A canine clinical trial was conducted using patients with soft tissue sarcomas. HT was given either once or 4 times a week in combination with fractionated RT.[21] By design, total CEM43°C T_{90} was equivalent between the two arms, meaning that the CEM43°C per fraction was higher in the arm that had a lower number of HT treatments. Treatment outcome was better for one fraction per week arm. These results suggest that thermotolerance induction in the more fractionated HT schedule inhibited direct HT cell killing, which blunted the HT + RT response. In other words, direct HT cytotoxicity is an important component governing HT + RT treatment outcome.

Immunologic Implications of the Heat Shock Response

Like RT, HT augments immunologic responses toward tumors.[4] Examples of effects that are known to occur after HT include: (1) increased immunogenicity, (2) increased T cell, natural killer cell, and dendritic cell maturation and activity, and (3) enhanced IL6-mediated trafficking of immune effector cells into tumors and lymphatic organs. These effects have been shown to be complementary to immune stimulation by RT.[22]

Hyperthermia and Physiology

As temperatures are elevated, tissue perfusion increases, but at higher temperatures, vascular stasis, hemorrhage, and hypoxia develop.[23] The change in normal tissue perfusion in response to HT is greater than one sees in tumors. Muscle and skin perfusion increase by about 10-fold, whereas tumor perfusion may increase by 1.5- to 2-fold. The difference in vascular response between tumor and normal tissue may be clinically advantageous since it can contribute to preferential tumor heating.

Effects of Hyperthermia on Tumor Metabolism and Oxygenation

Aerobic metabolic enzymes (respiration) are more heat sensitive than enzymes driving anaerobic metabolism.[1] About 43 to 44 °C HT for 30 to 60 minutes reduce adenosine triphosphate concentrations, which reflects

reduced mitochondrial activity. Decreases in mitochondrial activity reduce oxygen consumption rates in murine and human tumor lines.[1] A reduction in respiration rate decreases oxygen consumption rate, which contributes to improved tumor oxygenation. Oleson[24] suggested that clinical benefits of HT may result from improvements in oxygenation. It must be kept in mind, however, that higher HT exposure causes vascular damage (eg, median $T >$ 44 °C, 60 minutes) and decreases tumor oxygenation.[23]

The combination of reduced oxygen consumption rate and improved perfusion after HT improves tumor oxygenation in a majority of canine (sarcoma) and human tumors (sarcoma and locally advanced breast cancer).[1] HT-induced reoxygenation is complimentary to RT-induced reoxygenation. Further study is needed to fully understand whether there is a consistent link between HT-mediated reoxygenation and HT + RT treatment outcome.

Physiologic Approaches to Enhance Thermal Cytotoxicity: pH Modification

Chronically acidic cells are not more sensitive to HT than normal cells, but acute reduction in intracellular pH (pH_i) of such cells can greatly enhance their HT sensitivity.[25] The enhancement in killing is substantial if the pH_i drop is greater than 0.2 pH units. Hyperglycemia pushes tumors toward glycolysis and increases lactic acid production. In humans, the drop in extracellular pH after induction of hyperglycemia is about 0.17 pH units, which is not sufficient to reduce pH_i and create thermal sensitization.[26] One could further drop pH_i by using pharmacologic agents that block hydrogen ion extrusion from cells, which is normally accomplished via membrane-bound pumps. Although promising, this approach has not been tested in clinical trials.

Blood Flow Manipulation

Pharmacologic tumor perfusion reduction leads to increased tumor temperatures. Preclinically, vasoactive agents (hydralazine, nitroprusside, and angiotensin II) reduce tumor blood flow and enhance antitumor effects of HT. Clinically, however, drug-induced changes in blood pressure limit

doses of vasoactive drugs. Accordingly, tumor temperatures were not changed in either human or canine patients treated with HT and vasoactive drugs.[27,28]

Radiation and Hyperthermia

Rationale for Combining Hyperthermia + Radiotherapy

When RT is combined with HT, complementary effects occur. Cells in cell cycle S phase are relatively radioresistant, but these cells are most sensitive to HT. Hypoxic cells are 3 times more resistant to RT, compared with aerobic cells. In contrast, there is no difference in HT sensitivity between aerobic and acutely hypoxic cells, but chronically hypoxic, nutrient-deprived cells are more HT sensitive than aerobic cells.

The interaction between RT and HT is described by the "thermal enhancement ratio" (TER), defined as the ratio of doses of RT to achieve an isoeffect for RT + HT versus RT alone. TERs for local tumor control have been estimated for several human tumors.[29] In most tumor types examined, TERs were greater than 1.5 to 2 indicating that HT enhanced local tumor control compared with RT alone. TERs for normal tissue damage have been less than those for tumors in the same patient populations, suggesting potential for therapeutic gain for RT + HT. Prospective randomized trials in dogs with spontaneous tumors have shown improved local tumor control with RT + HT versus RT alone[30] with no observable increase in the frequency of clinically relevant late normal tissue complications. In summary, most available data from preclinical and clinical studies indicate that therapeutic gain is achievable for HT + RT.

Hyperthermia and Chemotherapy

Rationale for Using Hyperthermia With Chemotherapy

Many chemotherapeutic agents exhibit synergistic cell kill with HT including cisplatin, melphalan, cyclophosphamide, nitrogen mustards, anthracyclines, nitrosoureas, bleomycin, mitomycin C (MMC), and hypoxic cell sensitizers.[31] The mechanisms include (a) increased cellular drug uptake, (b) increased oxygen free radical production, (c) increased DNA damage and inhibition of DNA damage repair.[2] For drugs listed earlier, the

optimal sequence is to simultaneously administer HT + drug or to give the drug immediately before the onset of heating. The degree of interaction between drugs and HT is temperature and cell line dependent.[31] HT can reverse, at least partially, drug resistance for cisplatin, melphalan, and nitrosoureas.

For some drugs, in vitro results show no HT-induced synergism with CT, whereas there is a strong in vivo effect. Paclitaxel and MMC, for example, show little in vitro activity with HT + RT or CT, but clinical results for these combinations have been encouraging.[32] Stimulation of antitumor immunity toward stem cells is likely important for in vivo effects.[22]

Most antimetabolites do not interact with HT when given simultaneously.[31] 5-Fluorouracil (5FU) given simultaneously with HT yields only additive effects.[31] However, 39 to 41 °C HT enhances conversion of 5FU to active metabolites, thereby increasing drug cytotoxicity. Continuous infusion with 5FU leads to a cell cycle block in S phase, a relatively sensitive part of the cell cycle to HT. HT + etoposide yields unpredictable results; the current consensus is that synergistic interactions with etoposide are unlikely.[31] There is no evidence for synergistic interactions between vinca alkaloids and HT.

HT inhibits repair of both sublethal and potentially lethal damage by inactivating double-strand break DNA repair pathways.[2] Importantly, HT induces BRCA2 (BRCA2, DNA repair associated) degradation, providing rationale for combining HT with poly[ADP-ribose] polymerase-1 (PARP-1) inhibition. Enhancement of cytotoxicity to cisplatin and doxorubicin has been reported with the combination of HT and PARP-1 inhibitors.[33]

HT increases nanoscale drug delivery. These effects occur by selectively increasing microvessel pore size, thereby permitting enhanced transvascular delivery of nanoparticles, such as liposomes.[3] Further, enhancement of small drug delivery and efficacy can occur via the use of thermosensitive liposomes, which rapidly release drugs intravascularly, driving the drug into the interstitial space down an enhanced concentration gradient.[3]

Summary

In this brief review, we have shown multiple means by which HT augments RT and CT efficacy. For the most part, we have not emphasized the

temperature dependence of the different effects described in the text. Temperature dependence of primary effects is summarized in Figure 27.2.

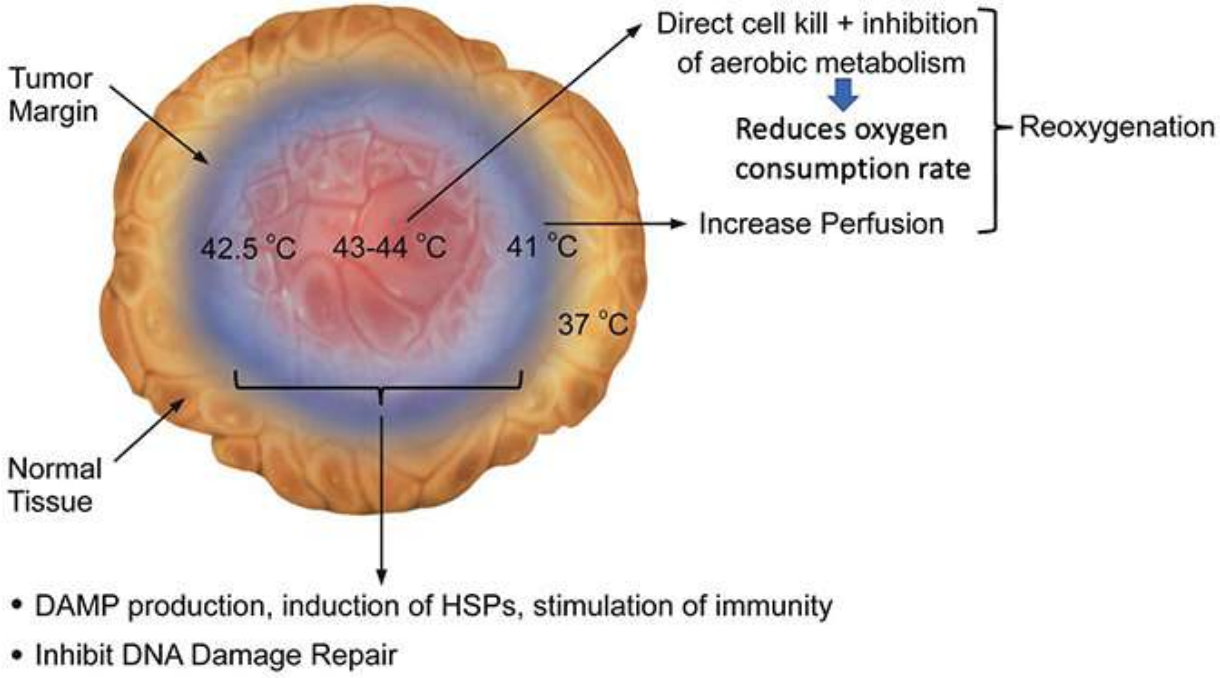

FIGURE 27.2 Key biologic effects of hyperthermia (HT) that contribute to enhanced HT + RT (radiotherapy) and HT + CT (chemotherapy) tumor response. Typical temperature distributions in heated tumors show a peaked profile, with higher temperatures in the center and lower temperatures toward the edge. Heating at temperatures of 41.5 °C and greater stimulates immunity and inhibits repair of DNA damage. Higher temperatures of 43 to 44 °C decrease oxygen consumption rates by killing some cells and by inhibiting respiration in remaining surviving cells. Hypoxic, nutrient-deprived cells are sensitized to HT killing. Reduction in oxygen consumption rate, combined with increases in tumor perfusion associated with milder temperatures, leads to reoxygenation. Reoxygenation has been associated with better treatment outcomes in several clinical trials. The important concept here is that the effects depicted occur simultaneously in different parts of a tumor either during or after heating. DAMP, damage associated molecular patterns; HSP, heat shock proteins. (Adapted from Dewhirst MW, Oleson JR, Kirkpatrick J, Secomb TW. Accurate three-dimensional thermal dosimetry and assessment of physiologic response are essential for optimizing thermoradiotherapy. *Cancers (Basel)*. 2022;14[7]:1701. https://creativecommons.org/licenses/by/4.0/.)

For typical peaked temperature distributions, the beneficial effects described occur simultaneously in different parts of a tumor.[34] In the future, HT prescriptions may focus on key characteristics of the tumor temperature distribution, which can simultaneously induce a plethora of beneficial HT

effects, including reoxygenation, inhibition of DNA damage repair, and stimulation of antitumor immunity. It is likely that therapeutically beneficial temperature distributions are already achieved in many tumors, which likely contribute to the success of the reported positive randomized trials.[35] Alternatively, uniform temperature distributions, which are not currently clinically achievable, are likely counterproductive. Uniform temperature distributions may not efficiently decrease oxygen consumption rate while reliably improving perfusion. Ultimately, thoughtful application of HT based on sound biologic principles holds great promise for enhancing clinical outcomes.

HYPERTHERMIA PHYSICS AND APPLICATION

Since the 1980s many different devices have been developed for inducing HT at 40 to 43 °C for 1 hour, aiming at tumor-selective sensitization for RT and CT. This section and Figure 27.3 outline the heating techniques used for different tumor sites.[34,36-38]

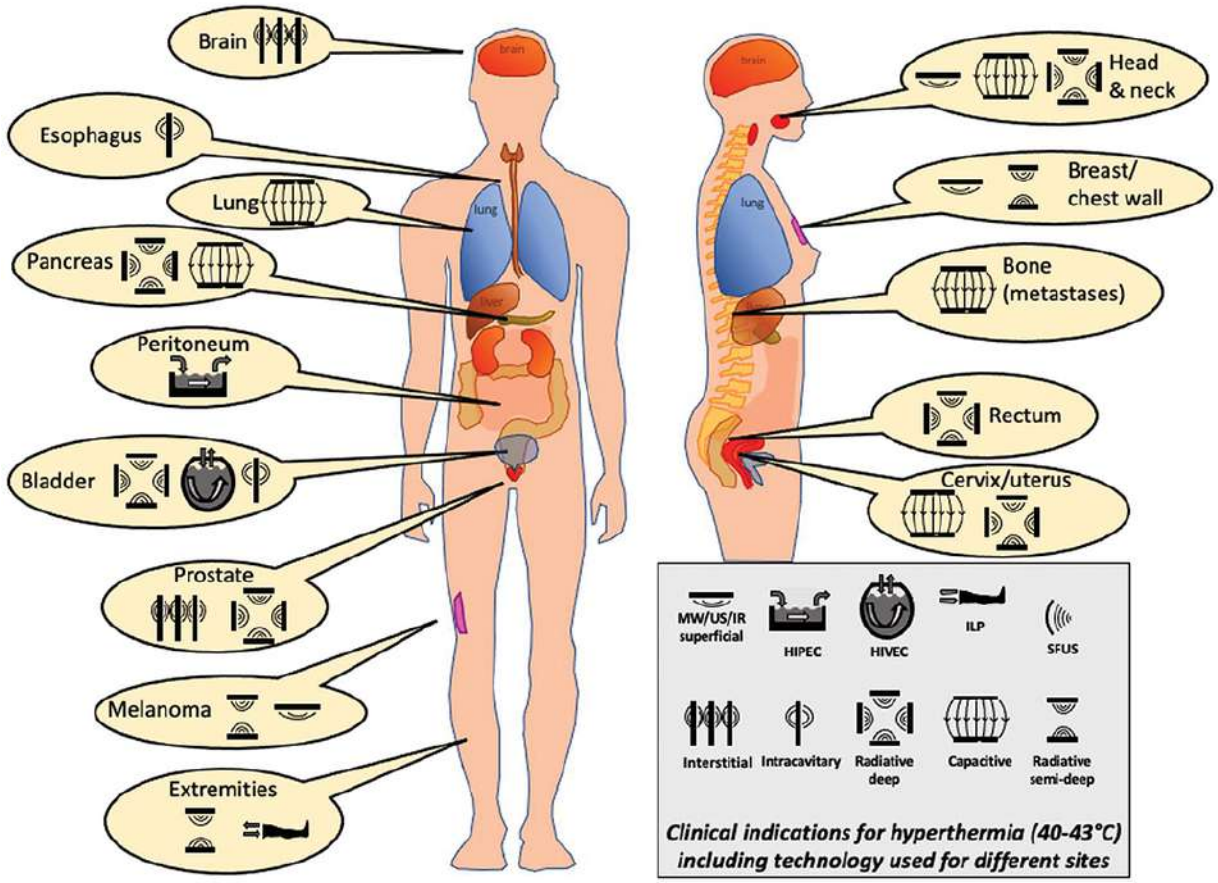

FIGURE 27.3 Overview of clinically used moderate hyperthermia techniques used for various indications and tumor locations. All techniques shown are or have been clinically applied for moderate hyperthermia at 40 to 43 °C in combination with radiotherapy and/or chemotherapy. The different categories of devices are indicated with symbols and discussed in the physics section.[34] HIPEC, hyperthermic intraperitoneal chemotherapy; HIVEC, hyperthermic intravesical chemotherapy; ILP, isolated limb perfusion; MW/US/IR, microwave/ultrasound/infrared; SFUS, scanned focused ultrasound. (Reprinted from Kok HP, Cressman ENK, Ceelen W, et al. Heating technology for malignant tumors: a review. *Int J Hyperthermia*. 2020;37(1):711-741. http://creativecommons.org/licenses/by/4.0/.)

Local and Locoregional Hyperthermia Approaches

Techniques that focus on localized tumor heating employ external applicators for superficial lesions, while invasive interstitial or intracavitary approaches are used for treating deeper sites. Superficial heating targets tumors located up to 4 cm below the skin, using applicators outside the patient. Proven clinical applications include (recurrent) breast, melanoma, and head and neck cancer.[12,13,34,36-38] Interstitial and intracavitary strategies are used for brain, prostate, head and neck, cervix, bladder, breast, and

cervix tumors.[14,34,36,39] Interstitial heating mainly aims to achieve higher temperatures for thermal tumor ablation; temperatures of 40 to 43 °C are less commonly used due to the intrinsically heterogeneous temperature distributions in interstitial HT.[34] Intracavitary heating uses applicators in natural body cavities like bladder, rectum, vagina, cervix, esophagus, urethra. Locoregional approaches use external applicators to heat deep-seated tumors and surrounding tissue. Inclusion of normal tissue is acceptable as temperatures of less than 45 °C induce tumor-selective radiosensitization. Tumors treated include cervix, rectum, bladder, prostate, pancreas, and soft tissue sarcoma.[34]

In all approaches, heating is induced using nonionizing electromagnetic (EM) or ultrasound (US) energy deposition, perfusion with heated fluids, or conductive heating. Energy deposition is quantified by the specific absorption rate (SAR) in W/kg. The resulting temperature increase depends on the energy deposition and on heat removal by thermal conduction, perfusion by small vessels, and convection by large vessels. Perfusion is important in heat transfer and can strongly increase in response to elevated temperatures.[40] EM devices apply radiofrequency (RF) and microwave (MW) radiation, capacitively coupled RF currents, or infrared (IR) radiation. RF and MW exposure causes dielectric tissue heating, which can lead to heterogeneous temperature distributions due to significant differences in electrical conductivity and permittivity between tissue types.[41] This may lead to excessive, treatment-limiting temperatures (hot spots) at tissue interfaces.[34]

Radiative Electromagnetic Heating

Radiative RF/MW devices are used for the majority of tumor sites and are responsible for gaining clinical evidence. The operating frequency determines tissue penetration depth (PD), with a descending PD for ascending frequency, moving from RF, MW, and IR to laser heating. Radiative RF/MW heating requires the use of a temperature-controlled conformal water bolus between skin and antennas to guide energy into the skin without reflections, for skin cooling when treating deep-seated tumors, and to provide skin heating for surface tumor locations. Radiative superficial systems aim at a PD of less than 4 cm and operate at MW

frequencies, mostly at industrial, scientific, and medical (ISM) frequencies (434, 915 MHz). Clinically proven radiative devices are available and include 915 MHz rectangular waveguides and circular spiral antennas (BSD-500, Pyrexar Medical) and 434 MHz microstrip applicators consisting of two coplanar active electrodes and a shield electrode mounted on a fluoroplastic substrate (ALBA ON 4000, ALBA Hyperthermia; Yahta-4, SRPC "Istok").[34] An example of a clinically proven intracavitary MW heating device is a 915 MHz antenna used in a Foley bladder catheter combined with MMC instillation for non-muscle invasive bladder cancer (Synergo, Medical Enterprises).[34,42] Radiative locoregional systems for deep-seated tumors operate at 60 to 150 MHz, non-ISM RF frequencies which need shielded rooms in a metal Faraday cage. These systems use phased arrays of multiple antennas with a dominant E-field in the cranial-caudal direction, creating a 10- to 15-cm focal region through constructive interference.[34] Steering the focal region to the tumor location and suppressing treatment-limiting hot spots in normal tissue are achieved by phase and amplitude steering,[43] with antenna settings based on HT treatment planning.[44] Commercially available phased-array systems use one or more circular, elliptical (BSD-2000, Pyrexar Medical) or adaptable shape (ALBA 4D, ALBA Hyperthermia) rings of independent antennas around the patient. Phase steering of individual antennas allows 2D spatial power steering within a single ring of antennas, while three rings permit 3D power steering.[34] Temperature monitoring is invasive or noninvasive and described in the next section. A new site-specific device is the Hypercollar phased array of 434 MHz antennas for treatment of deep-seated head and neck tumors.[34]

IR radiation at frequencies greater than 300 GHz is another approach. IR is strongly absorbed in tissue with a PD of less than 1 cm. The Hydrosun TWH1500 system (Hydrosun medizintechnik GmbH) is used for HT of superficial tumor lesions with water-filtered IR-A radiation (215-430 THz) lamps to increase PD to 1.5 to 2 cm and avoid skin overheating and dehydration.[34] No water bolus is used, and IR thermography gives real-time noninvasive temperature feedback.

Capacitive Electromagnetic Heating

Capacitive heating uses current fields between electrodes placed on the body on either side of the target region operating at 8 to 30 MHz.[34] The RF currents enter the body through water bolus bags for skin cooling and to prevent hot spots in superficial fat. Energy deposition is spatially steered by using different-sized electrodes, concentrating heat deposition under the smallest electrode. The technique is clinically used for superficial and semi-deep tumors; heating of deep-seated tumors can be challenging: The main EM field component is perpendicular to the skin and may result in excessive heating in skin fat layers, thus limiting power at depth.[34] Capacitive heating is primarily used in patients with thin fat layers, where skin hot spots can be prevented by strong surface cooling using a saline water bolus, for example, using the Thermotron RF-8 (Yamamoto Vinita). Successfully treated tumors include cervix, head and neck, and bone metastases.[34]

Ultrasound Heating

US techniques employ acoustic energy at 0.5 to 10 MHz to induce tumor heating with a PD up to 8 cm.[34,38,45] Clinical US devices have been developed for sequential and concomitant use in combination with RT for treatment of groin/trunk, axilla, breast, chest wall, head and neck tumors. The Sonotherm 1000 device (Labthermics Technologies Inc) provides multisector applicators in a non-focused planar array with a variable PD depending on the selected frequency. Another approach is high intensity focused ultrasound, which focuses pressure waves in small focal zones of a few millimeters in diameter, up to approximately 1 cm long. Scanned focused ultrasound (SFUS) is widely used for thermal ablation by scanning a focused US beam through the tumor region guided by noninvasive US or magnetic resonance (MR) thermometry to achieve conformal tumor treatment. Techniques are also under development to use SFUS for inducing moderate HT elevations under guidance of noninvasive MR thermometry.[46] Studies also aim at targeted drug delivery by combining heat with temperature-sensitive liposomes.[46-48] Advantage of SFUS-based HT is superior SAR focusing and noninvasive MR thermometry guidance. The disadvantages are that (1) limited target volumes can be heated uniformly during HT treatment and (2) the need for selecting acoustic entrance

windows to avoid overheating at bone or air cavities. These limitations reduce the number of suitable tumor sites.

Conductive Heating

Heating can also be induced by thermal conduction, for instance by implanting hot sources into the tumor. Perfusional heating is currently the most clinically relevant conductive technique; it uses circulating heated fluids containing chemotherapeutic agents to augment local drug delivery in areas such as the peritoneal or thoracic cavities. Hyperthermic intraperitoneal chemotherapy (HIPEC) is widely used to circulate chemotherapeutic solutions heated to approximately 42 °C in the peritoneal cavity to eradicate microscopic lesions, prophylactically or after surgical removal of larger peritoneal metastases of various origins, with good results.[49] CT vapors are applied in pressurized intraperitoneal aerosolized chemotherapy. Hyperthermic intrathoracic chemotherapy is used for intrathoracic lesions. Hyperthermic intravesical chemotherapy is a treatment of non-muscle invasive bladder cancer by circulating a hyperthermic MMC solution in the bladder, serving as a potential alternative to RF/MW-based bladder heating.[42] Hyperthermic isolated limb perfusion refers to infusion of heated perfusate into the vascular system of isolated limbs and used in some centers. Conductive heating has limited thermal PD and is thus only used in case of limited tumor depth, as one sees for HIPEC after resection of macroscopic disease.

Magnetic nanoparticles (MNPs) are a highly targeted conductive heating strategy for challenging tumor sites. MNPs are composed of magnetic materials, typically around 100 nm in size, and are injected into the tumor suspended in a biocompatible fluid.[50] MNPs are then magnetized by exposure to an external magnetic field of approximately 0.1 to 0.2 MHz, generating heat via magnetic hysteresis. An advantage is the option to coat MNPs with biomaterials and extend MNPs to a theranostics platform. A disadvantage is the challenge of obtaining uniform MNPs throughout the treatment volume, as temperature distributions depend on the injected MNP distribution. Clinical use for glioblastoma and prostate cancer is approved for NanoTherm AS1 (MagForce Nanotechnologies AG) for use in Europe and the United States.[34] Other technologies are in development.[51]

Monitoring Temperature and Thermal Dose

Achieving clinically effective tumor temperatures of greater than 40 °C is crucial for an optimal therapeutic gain in view of the temperature dose-effect relationship,[8,52] at the same time normal tissue temperatures of greater than 44 °C must be avoided to prevent vascular damage and other side effects.[5,23,53] Good temperature control is needed during treatment, requiring good SAR control and reliable pretreatment prediction of SAR and resulting temperature. This is challenging due to uncertainty in the patient-dependent tissue and perfusion values during treatment. Measured temperature data are thus crucial but often sparse. An alternative is to combine measured temperature data with treatment planning data to reconstruct the real 3D temperature distribution. Thermometry and treatment planning are thus both important tools for achieving good treatment control.

International HT quality assurance guidelines prescribe the use of validated devices, temperature monitoring guided by sufficient thermometry, trained staff, and documentation of relevant treatment parameters.[10-14,39,45,54-57] As described in the biology section, measured temperature distributions are reported using temperature descriptors T_{90}, T_{50}, T_{10}. Guidelines also recommend the use of the thermal dose parameter CEM43°C T_{50} and T_{90} to convert the time-temperature exposure during treatment to an equivalent exposure time at 43 °C.[6,9,15]

Thermometry is performed with single- or multisensor probes in or near the target volume. Probe locations are the skin and minimally invasive sites in natural body cavities such as the bladder, rectum, vagina, and urethra. If needed, invasive thermometry can be performed using thermometers inserted into catheters that are placed in the target region. For pelvic tumors, probes are placed in all available cavities to monitor both tumor and region heating. High-resolution skin thermometry is needed to avoid toxicity when heating superficial lesions.[58] Probe types include thermistors, thermocouples, and fiber-optic sensors, depending on compatibility with the HT method. High-resistance lead thermistor probes are relatively insensitive to EM fields; thermal mapping can be used to extend the monitoring trajectory of these single-sensor probes. Thermocouple probes have the advantage of multisensor probes giving continuous read-out along

their active length, but their metal wires need to be aligned perpendicular to the direction of the EM field to prevent interference with the EM field. Fiber-optic probes are nearly insensitive to EM interference but may be disturbed by US or laser-based HT. Regular calibration of thermometry is obligatory to ensure safe treatment delivery. Invasive thermometry is challenging for some tumor locations and as a result, noninvasive thermometry has been under development for the past two decades. Magnetic resonance imaging thermometry based on the proton resonance frequency shift method is routinely used for guiding thermal ablation procedures, and MR thermometry is also in use in locoregional HT.[58] The Sigma-30 and Sigma-Eye system can be integrated in 1.5 T MR scanners for noninvasive MR thermometry,[37] but reliability and accuracy are challenged by motion artifacts.[59] Current use is limited to select tumor locations and is always accompanied by (minimally) invasive thermometry probes.[10] Work is ongoing to improve reliability of MR thermometry.[59]

Hyperthermia Treatment Planning

The large number of independent antennas in phased-array systems makes hyperthermia treatment planning (HTP) indispensable for optimization of the antenna phase and amplitude settings.[44] HT simulation software has been developed[60] and integrated into HTP systems to compute and optimize SAR and temperature distributions in patients.[44,61] The clinical application of HTP has been validated for EM-based HT by comparing the quality of HTP-guided and experience-based steering.[62-64] HTP is now being integrated into the clinical workflow for EM-based HT.[44,61] Quantitative accuracy of HTP is limited by uncertainties in patient models, tissue properties, and dynamic changes in perfusion,[44] but HTP is qualitatively sufficiently accurate[63] and proven useful in clinical applications, such as evaluation of heating potential, applicator selection, effect of different treatment strategies, and real-time treatment control.[44]

Adaptive HTP is used to adapt antenna phase/amplitude settings in real time during treatment, enhancing tumor heating and suppressing treatment-limiting hot spots in normal tissue. The clinical benefit of adaptive HTP has been shown.[63] A next step is biologic planning to quantify and optimize the radiosensitizing effect of HT in terms of equivalent radiation dose, that is,

the radiation dose yielding the same biologic effect as the combination of RT and HT. The effect of adding HT to RT can be expressed in RT dose escalations expressed in Gy.[65] Biologic modeling can be useful in answering clinically relevant questions, such as the optimal scheduling between RT and HT and how to orient the heating field to maximize cell killing. Thermoradiotherapy planning is feasible and a next step for further optimizing combined HT and RT treatments in individual patients.[65]

Summary of Hyperthermia Physics

This review has shown that devices are available for routine HT delivery at 40 to 43 °C for a wide range of tumor sites, and with clinical benefit proven in randomized trials. High-quality treatment delivery must be safeguarded by adherence to quality assurance and temperature monitoring protocols. Treatment planning is an increasingly important tool for real-time treatment guidance. Novel site-specific devices, heat-induced targeted drug delivery, and noninvasive temperature monitoring are under development for even more effective HT treatments.

CLINICAL STUDIES

Numerous trials including randomized phase II and III studies have demonstrated clinical benefit across a wide range of malignancies and clinical settings to the use of HT in combination with radiation or CT (Figure 27.4).[35] Taken as a whole, research to date has defined specific indications for the use of HT and several other promising therapeutic approaches for which further investigation is warranted.

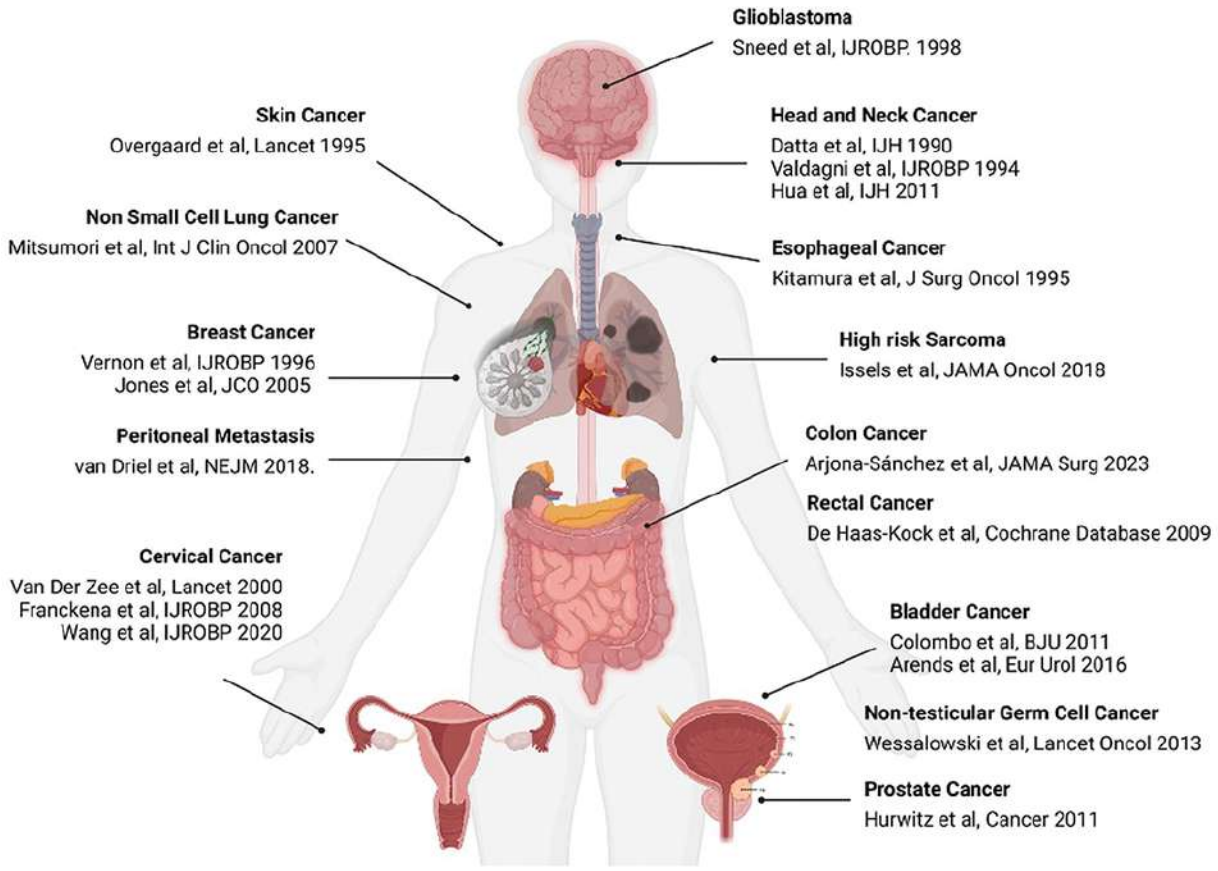

FIGURE 27.4 Overview of key hyperthermia clinical trials for various indications and tumor locations. (Created with BioRender.com. Figure adapted from BioRender. Diseased human body. 2023.)

Radiation and Hyperthermia: Key Randomized Trials

Early Cooperative Group Studies

The rapidly evolving understanding of the biologic rationale for combining HT and radiation in the 1980s led to the initiation of several phase III clinical trials, including two Radiation Therapy Oncology Group (RTOG) studies to assess the role of HT in superficial and deep regional disease. Unfortunately, HT technology, meaningful therapeutic goals, and quality guidelines necessary for successful treatment lagged in development. RTOG-8104 compared RT with or without HT for a variety of superficial malignancies. There was no difference in complete response between groups; however, benefit was noted for tumors smaller than 3 cm, suggesting that if tumors could be effectively heated, meaningful clinical responses could be achieved.[66] RTOG-8419 was intended to assess

interstitial radiation alone or with HT for persistent or recurrent tumors after previous RT or surgery. No differences were noted; however, only 1 of 173 evaluable patients met protocol-defined minimum accepted criteria for adequate HT, and there were quality concerns with brachytherapy as well. Therefore, the authors concluded that the study lacked the ability to assess the question of benefit in this clinical setting.[67] Despite challenges identified in the RTOG trials, several early randomized studies revealed benefits with the addition of HT to RT. Subsequent development of quality assurance guidelines, clinically meaningful thermal dose parameters, and improvements in treatment technology have helped to move the field forward.

Superficial Hyperthermia

HT has been shown to be beneficial for several superficial disease presentations including for breast, head and neck, melanoma, and skin cancers. MW devices that treat up to a depth of 3 cm are most commonly used. US with soft tissue penetration up to 6 to 8 cm and occasionally other modalities are also employed in the treatment of superficial malignancies.

Breast Cancer

HT can improve complete response and local control for women with breast cancer, particularly in the setting of recurrent chest wall disease. Vernon et al[68] reported combined results of five randomized breast cancer trials including locally advanced primary or recurrent disease with or without prior RT. The primary end point in each trial was local tumor response. Due to slow accrual, a combined analysis was developed including a prospective statistical plan to allow for the assessment of the initial objectives. Three hundred and six eligible patients were enrolled. Treated lesions included chest wall (71%) and intact breast tissue (26%). Forty-eight percent of cases had multiple lesions. There were more patients who had received prior CT and lesion size was greater in the HT plus radiation treatment arm. A highly significant difference in complete response was noted for combined RT and HT, 59%, versus radiation alone, 41%. Further analysis determined that this difference was driven by benefits in patients undergoing reirradiation for whom RT doses were limited. There was nearly a doubling in complete

response with HT and RT of 59% versus 31% with radiation alone. Patients achieving a complete response with HT had a reduced risk of recurrence with a hazard ratio (HR) of 0.67 compared to patients who received RT alone. Treatment with HT was well tolerated. Apart from the acute occurrence of skin blistering 11% with versus 2% without HT, no other differences in acute or late toxicity were noted.

Treating a range of superficial malignancies, Jones et al[69] confirmed a dose-response relationship for HT in a randomized trial in which patients with superficial tumors at a depth of 3 cm or less received either "low" versus "high" dose HT combined with RT. Sixty-five percent of patients had breast cancer, 13% head and neck cancer, 11% melanoma, and the remainder had various other malignancies. Prior studies had shown a thermal dose of CEM43°C T_{90} (the number of cumulative equivalent minutes at 43 °C exceeded by 90% of monitored points within the tumor) equated with improved treatment outcome. HT was prescribed to achieve either CEM43°C T_{90} of less than 1 or greater. Eighty-nine percent were determined at the time of first HT treatment to have heatable tumors. These 109 patients were randomized to no additional HT or twice weekly HT over their course of RT up to 10 treatments. Patients were stratified by whether they had received prior RT and by disease site. Median CEM43°C T_{90} in the low- and high-dose HT groups was 0.74 and 14.3, respectively. Thirty-six percent of patients had received prior RT. Median RT dose was 4,100 cGy in previously treated patients versus 6,000 cGy for those not previously irradiated. Complete response rate in the high-dose arm was 66% versus 42% in the low-dose arm. The odds ratio for complete response was 2.7. This improvement in complete response translated into improved local control, with rates of 48% versus 25% at the time of death or the last follow-up. Previously irradiated patients had the greatest incremental gain in complete response, with rates of 68% versus 23% in the high- versus low-dose arms as compared to 65% versus 51% for patients without prior RT. The study demonstrated that thermal dose can be prospectively prescribed and delivered, correlating with treatment outcome.

Skin Cancer

HT has also demonstrated efficacy in treatment of skin cancers including melanoma. A European Society of Hyperthermic Oncology phase III trial, performed in the 1990s, randomized 134 metastatic or recurrent melanoma lesions to receive 3 fractions of 800 or 900 cGy over 8 days with or without HT. Local control was significantly increased from 28% to 46% with the addition of HT. Overall 5-year survival in this study predating immunotherapy was 19% with note made of 38% overall survival for subjects for whom all known disease was controlled demonstrating the importance of local control.[70,71]

Head and Neck Cancer

Two early studies from the 1980s, prior to the use of CT, demonstrated the potential for improved outcomes with the addition of HT to radiation therapy. Datta et al[72] randomized 65 subjects to RT with or without HT twice weekly. Total RT doses were 6,000 to 6,500 cGy. For 50 patients with stage III or IV disease, complete response was 20% for radiation alone versus 58% with addition of HT. Valdagni and Amichetti[73] performed a randomized study to assess the impact of HT on local control and acute toxicity for patients with cervical adenopathy. A planned interim analysis after 41 patients were accrued revealed a highly significant improvement in the complete response of 85% with HT translating into 5-year local control of 69% versus 24%. Five-year overall survival was notably 53% versus 0%. Hua et al[74] randomized 180 nasopharynx patients to 7,000 cGy with cisplatin/5FU with or without HT with statistically significant improved overall survival with HT of 73% versus 63%.

Deep Regional Hyperthermia

The refinement of systems for deeply penetrating HT, primarily with use of RF, has led to successful clinical trials for a wide range of deep-seated malignancies. Additional techniques including HIPEC, interstitial or intraluminal HT also have been employed. Phase II and III studies have demonstrated benefits for cancers of the cervix, rectum, bladder, esophagus, lung, and sarcoma among others.

Cervical Cancer

A Dutch multicenter phase III trial assessed the benefit of HT in addition to RT for the treatment of locally advanced pelvic tumors. Three hundred and sixty-three patients with bulky stage IIB, III, or IVA cervical, T3 or T4 bladder or unresectable or recurrent rectal cancers were stratified based on primary disease site. Local control at 2 years with RT and HT versus radiation alone was 56% versus 39%. A highly significant improvement for patients with cervical cancer in 3-year overall survival of 51% versus 27% was noted.[75] This benefit was sustained at 12 years with overall survival of 37% versus 20%.[76] A HT dose effect was noted.[52] A Cochrane review of six randomized controlled trials assessing RT with or without HT for locally advanced cervical cancer found HT resulted in a significantly higher complete response rate (HR 0.56); significantly reduced local recurrence rate (HR 0.48); and significantly better overall survival (HR 0.67). No increase in short- or long-term toxicity was observed. Several limitations were noted including the limited number of patients available for analysis, methodologic flaws in some studies, and a significant overrepresentation of patients with International Federation of Gynecology and Obstetrics (FIGO) stage IIIB (74%), which prohibited drawing definite conclusions. Nevertheless, reviewers noted that available data do suggest addition of HT improves local tumor control and overall survival in patients with locally advanced cervix carcinoma, without affecting treatment-related grade 3 to 4 acute or late toxicity.[77] Concurrent with the publication of the Dutch Deep Hyperthermia trial results, five studies were reported that demonstrated similar benefits with the addition of cisplatin to RT. Subsequent studies have sought to evaluate the benefit of HT in addition to RT and CT including a phase III trial reported by Wang et al.[78] Three hundred and seventy-three patients with FIGO stage 1B-IV disease were randomized to radiochemotherapy versus radical hysterectomy alone. Significantly improved 5-year overall survival was noted with the addition of HT 82% versus 72% with no differences in toxicity.

Rectal Cancer

A Cochrane review identified six randomized controlled trials including 520 patients. Significantly higher complete rates were observed (HR 2.8). Overall survival was significantly improved with addition of HT at 2 years

(HR 2.1); however, this benefit was not sustained with longer follow-up. No significant differences were noted in acute toxicity. While promising, the authors concluded that additional high-quality phase III randomized studies are needed to definitively define the role of HT in rectal cancer.[79]

Glioblastoma

A randomized trial at University of California, San Francisco showed a remarkable improvement in overall survival for patients with glioblastoma multiforme with the addition of interstitial HT to brachytherapy boost in 79 patients following standard external beam radiation and CT. Time to progression and overall survival were significantly increased with the addition of HT. Two-year overall survival was 31% with versus 15% without HT. A multivariate analysis adjusting for age and Karnofsky performance status showed that improved survival was significantly associated with randomization to HT with a HR of 0.51.[80]

Esophageal Cancer

A Japanese randomized study including 66 patients with resectable squamous cell carcinoma of the thoracic esophagus compared standard neoadjuvant chemoradiotherapy with or without HT. Complete response was significantly improved with HT, 25% versus 5% as was 3-year survival, 50% versus 24%.[81]

Chemotherapy and Hyperthermia: Key Randomized Trials

HT has also been shown in randomized trials to improve outcomes with CT using a range of delivery strategies. The European Organisation for Research and Treatment of Cancer conducted a phase III randomized study to assess the use of HT in the treatment of localized high-risk sarcoma. All patients received standard surgery, RT, and neoadjuvant CT with or without RF deep regional HT. A total of 341 patients were enrolled. The primary end point was local progression-free survival and secondary end points included overall and disease-free survival. With a median follow-up of over 11 years, adding regional HT improved local progression-free survival (HR 0.65). Survival was also improved with the addition of HT (HR 0.73) with a 10-year survival of 53% versus 43%.[82] Colombo et al[83] reported notable

improvement in progression-free survival with combined intravesical HT and MMC as opposed to mitomycin alone for treatment of superficial bladder cancer following transurethral resection of bladder tumor. Eighty-three patients were randomized. The primary end point of recurrence-free survival at 10 years was 53% with HT versus 15% with CT alone. These results were consistent with findings of a subsequent study comparing intravesical BCG with intravesical MMC and HT.[84] HIPEC has shown efficacy in treatment of peritoneal metastases in phase III trials. A Dutch multicenter trial with 245 enrolled patients revealed the benefits of cisplatin-based HIPEC compared to systemic CT alone after interval cytoreductive surgery (CRS) in the treatment of stage III epithelial ovarian cancer, with no added toxicity. Two hundred and forty-five patients were enrolled. Disease recurrence or death was reduced in the HIPEC arm, 81% versus 89% (HR 0.66). Median overall survival was 46 versus 34 months.[85] A Spanish multicenter randomized trial of HIPEC for locally advanced colon cancer revealed the primary end point of 3-year locoregional control was improved with CRS followed by MMC-based HIPEC: 98% versus 88% (HR 0.22).[86]

Other Notable Studies

HT has shown promise across widely ranging malignancies and clinical scenarios apart from randomized trials. A German series reported the benefits of using deep regional HT in conjunction with standard CT for the salvage treatment of children with refractory or recurrent non-testicular germ cell tumors. Among 35 evaluable patients, 86% had an objective response with 5-year event-free and overall survival of 62% and 72%, respectively. These results were notable for nearly approximating outcomes with first-line CT alone.[87]

Several trials have shown promise for HT in the treatment of prostate cancer including Dana Farber 94-13, a phase II trial of trans-rectal US HT in combination with standard RT and androgen deprivation in treatment of unfavorable intermediate- to high-risk locally advanced disease. Thirty-seven subjects were matched both in regard to known prognostic factors and treatment approach to historical controls from RTOG-9202. The primary end point was absolute 2-year disease-free survival which was 84%

versus 64% in the control group. With a median follow-up of 70 months, overall survival was 94% and 61% remained failure-free.[88] HT has also demonstrated the potential for better outcomes for lung cancer. An International Atomic Energy Agency sponsored, multi- institutional prospective randomized trial including 80 patients assessed if the combination of HT and radiation improves the response rate of locally advanced non–small cell lung cancer compared with radiation alone. No significant differences between the two arms in local response rate or overall survival rate were noted. However, local progression-free survival was significantly better with the addition of HT. Toxicity as typical of most HT trials was generally mild and limited.[89]

FUTURE DIRECTIONS

HT has been shown to have clinical benefits for many patients with cancer. Realization of the full potential of this cancer treatment modality, however, remains to be achieved. Barriers to widespread adoption need to be fully addressed. The ability to reliably prescribe and deliver HT remains challenging at times. The added complexity of treatment which requires real-time attention to physiology in addition to physics necessitates added clinical effort for treatment delivery. New user and patient-friendly technology, such as noninvasive thermometry, will further increase utilization. While the rationale of thermal biology is robust, incorporation of biology and heat for the betterment of patients with cancer has yet to be fully exploited in the clinic.

Targeted use of HT with other established cancer therapies holds tremendous potential. In regard to CT, both enhanced delivery with temperature-sensitive liposomes and mechanistic synergy as per combination of HT with agents such as cisplatin and PARP inhibitors have yet to be fully exploited.[90] Systems for simultaneous treatment with RT with the potential to greatly enhance TER are in development.[51,91] Noting the impact of HT on the sphingomyelin/ceramide pathway, clinical studies combining HT with stereotactic body radiation therapy may impact a great number of patients.[92] HT also has great potential to improve results with immunotherapy through a wide range of mechanisms. Tumor-specific immune responses generated by heat might also be generated by partial

tumor heating abrogating the demands of whole tumor heating.[1] Should HT prove beneficial when added to immunotherapy, as opposed to the limitations of repeated use of ionizing radiation, HT can be administered repeatedly in combination with immunotherapeutic agents.[93] While HT has been shown in several scenarios to have clinical benefit, the full potential of this cancer treatment modality has yet to be fully realized for patients.

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CHAPTER 28

Reirradiation

Carsten Nieder and Anthony E. Dragun

A second course of radiotherapy (RT) to a previously treated, overlapping anatomic region poses considerable challenges if a high cumulative total dose is attempted. In palliative clinical scenarios, for example, painful bone metastases, such treatment is well established.[1,2] Occasional patients might even benefit from a third course. Reirradiation has been prescribed for local/regional relapse or second primary tumors, the latter often after very long time intervals, as well as benign diseases. The history of head and neck and other reirradiation dates back many decades.[3] First in 2022, a collaborative effort by the European Society for Radiotherapy and Oncology (ESTRO) and European Organisation for Research and Treatment of Cancer (EORTC) led to a consensus report on definition, reporting, and clinical decision-making.[4] In this report, reirradiation is defined as a new course of RT, either to a previously irradiated volume (irrespective of concerns of toxicity) or where the cumulative dose raises concerns of toxicity. Type 1 is a new course of RT that has geometrical overlap with the irradiated volume of previous courses, and type 2 is a new course with concerns of toxicity from the cumulative doses but in which there is no overlap with the irradiated volume of previous courses, for example, in the lungs. Repeat organ irradiation is a new course of RT to a previously irradiated organ but without overlap of the irradiated volumes and without concerns for toxicity from cumulative doses. Despite a long-standing legacy, few prospective randomized clinical studies have provided high-level evidence clarifying the optimal approach toward previously irradiated tumors.[5] Phase II studies often included a single arm only.[6-9] Therefore, the clinical practice of reirradiation, prescribed as either monotherapy or combined with other modalities, is highly variable. Recent guidelines endorse repeat RT in selected patients,[10-12] and international recommendations inform clinical strategies.[13-16] Workflow solutions have also been suggested.[17]

TISSUE TOLERANCE AND RECOVERY

General Aspects

Animal studies and clinical data on reirradiation of head and neck tumors, breast cancer, lung cancer, and others showed that acute skin and mucosal reactions after reirradiation were well within the range observed after the first course of RT.[18-20] If the previous treatment has caused persistent severe mucosal damage, reirradiation might be poorly tolerated. Clinical data related to many cancer types revealed that late complications were more frequent than anticipated after reirradiation to high cumulative doses. The majority of data is derived from head and neck cancer retreatment. Lee et al[21] reported that the major determinant of postretreatment complications was the severity of damage during the initial course. Severe toxicity occurred also after intensity-modulated radiotherapy (IMRT), but no prospective randomized head-to-head comparison of salvage IMRT versus three-dimensional (3D) conformal RT is available.[22] In the IMRT study reported by Duprez et al,[23] 84 patients were reirradiated to a median cumulative total dose of 130 Gy (median time interval 49.5 months, median reirradiation dose 69 Gy). Late toxicity was scored in 52 patients, with at least 6 months of follow-up. Eight patients developed grade 3 or 4 late dysphagia, and three developed osteoradionecrosis. Overall, 30 different grade 3 or 4 late complications were recorded. Updated results from the University of Texas MD Anderson Cancer Center (n = 206, IMRT) revealed actuarial rates of grade ≥3 toxicity of 48% at 5 years, most often dysphagia and odynophagia.[24] Increased toxicity was associated with retreatment volume >50 mL. Stereotactic body (SBRT) reirradiation for recurrent head and neck cancer resulted in higher late toxicity rates if the larynx or hypopharynx were treated.[25] It is unrealistic to expect zero risk of any severe late toxicity after IMRT or other highly conformal techniques, since certain parts of the mucosal and/or connective tissues will always be part of the planning target volume and receive high cumulative doses. With proton therapy, grade ≥3 toxicities were seen in 15% acutely and 25% in the late setting, including treatment-related deaths.[26] Overall, the available literature indicates that mesenchymal tissues recover from radiation injury less than rapidly reacting tissues like the epidermis and mucosa, at least in the head and neck region.

Large Arteries

Recent reports of high-dose reirradiation have also identified the large arteries as critical organs at risk (OARs). Evans et al[27] analyzed the end point of grade 5 aortic toxicity in 35 patients with lung cancer. The median prescribed dose was 54 Gy in 1.8-Gy fractions and 60 Gy in 2-Gy fractions. The median interval between the two courses was 32 months. The median raw composite dose to 1 mL of the aorta was 110 Gy. Toxicity developed in 25% of patients who received ≥120 Gy, but not in

patients irradiated to lower cumulative doses. A dose constraint of 120 Gy has also been suggested for the carotid arteries.[28] The issue of carotid blowout syndrome (CBOS) has been studied by Yamazaki et al.[29] They pooled data from seven Japanese Cyber Knife institutions and analyzed 381 patients. Of these, 32 (8.4%) developed CBOS after a median of 5 months from reirradiation. Twenty-two (69%) patients died. Later, a predictive model (CBOS index) was developed, which includes carotid invasion of >180°, presence of ulceration, and lymph node area irradiation (0-3 points).[30]

Lung/Thorax

In animal experiments, the lungs recover at least partially from occult injury, as reviewed by Nieder et al.[18] Experimental data on trachea, bronchi, or esophagus are lacking. Most clinical series did not describe particular problems with these critical structures, except for stereotactic treatment of central lesions and recurrent disease with infiltration or likely infiltration, where it is often difficult to determine the cause of fistula or hemoptysis (tumor progression vs treatment toxicity).[31] Table 28.1 shows different treatment regimens.

TABLE 28.1 PUBLISHED CONCEPTS FOR REIRRADIATION OF HEAD AND NECK (HN), LUNG, AND BRAIN TUMORS (WITH OR WITHOUT CONCOMITANT SYSTEMIC THERAPY)

Regimen	HN Tumors	Lung Tumors	Brain Tumors
External beam, conventional fractionation 1.8-2 Gy	x	x	x
External beam, hyperfractionation, twice daily	x		x
External beam, hypofractionation 2.2-2.5 Gy	x	x	x
External beam, hypofractionation 3-4 Gy		x	x
External beam, hypofractionation 5-7 Gy	x	x	x
External beam, hypofractionation 3 Gy twice daily	x		
External beam, RTOG quad shot, 3.7 Gy twice daily	x		
External beam, two fractions of 8 Gy		x	
External beam, severely hypofractionated SABR		x	
External beam, single-dose radiosurgery			x
External beam, pulsed-reduced dose rate			x
High-dose rate brachytherapy	x	x	x
Pulsed-dose rate brachytherapy	x		x

RTOG, Radiation Therapy Oncology Group; SABR, stereotactic ablative body radiotherapy.

Spinal Cord

The spinal cord has been studied in several experimental settings. Clinically applicable data were generated in adult rhesus monkeys by Ang et al.[32] The cervical spinal cord of these primates was irradiated with 2.2 Gy per fraction after an identical initial course of 44 Gy. Reirradiation dose was 57.2 Gy, given after 1-year (n = 16) or 2-year (n = 20) intervals, or 66 Gy, given after 2-year (n = 4) or 3-year (n = 14) intervals. Of the 45 monkeys that completed the required observation period of up to 2.5 years, four developed myelopathy. Fitting the data with a model, assuming that all (single course and reirradiation) dose-response curves were parallel, yielded recovery estimates of 33.6 Gy (76%), 37.6 Gy (85%), and 44.6 Gy (101%) of the initial dose, after 1, 2, and 3 years, respectively, at the 5% incidence level. Another way to look at these results is to estimate the total cumulative dose that can be tolerated, expressed in EQD_2 that is equivalent dose in 2-Gy fractions calculated using the linear-quadratic approach. For a time interval of 1, 2, and 3 years between the treatment courses, cumulative doses of 150%, 156%, and 167% of the first-line setting's tolerance dose appear possible. If true in humans, an initial exposure equivalent to 46 Gy in 2-Gy fractions (arbitrarily selected to represent 100% of the tolerance dose at the 5% myelopathy risk level because many institutions limit the spinal cord dose to lower levels than true tolerance) might be followed by an additional 23 to 24 Gy in 2-Gy fractions (50% of the tolerance dose) 1 or 2 years later. Clinical data from different institutions supporting this interpretation have been published.[33] Nieder et al[34] have published a risk prediction model, based on time interval, cumulative dose, and the presence or absence of any treatment course, resulting in quite high spinal cord exposure. Besides cumulative dose, interval <6 months and total dose equivalent to >50 Gy in 2-Gy fractions in one of the two courses increase the risk of myelopathy. The introduction of SBRT has resulted in new challenges. Rather than irradiating complete spinal cord cross sections with homogeneous doses, small areas are exposed and steep dose gradients achieved. Medin et al[35] developed a swine model where a 10-cm length of the spinal cord (C3-T1) was uniformly irradiated to 30 Gy in 10 fractions and reirradiated 1 year later with a single radiosurgery dose centered within the previously irradiated segment. Follow-up after reirradiation was 1 year. Summarized briefly, pigs receiving radiosurgery 1 year following 30 Gy in 10 fractions were not at significantly higher risk of developing motor deficits than pigs that received radiosurgery alone. Sahgal et al[36] provided a recommendation of presumably safe stereotactic reirradiation doses after initial conventional RT (interval at least 5 months). A thecal sac point maximum P(max) EQD_2 of 20 to 25 Gy appeared to be safe, provided the total P(max) EQD_2 does not

exceed approximately 70 Gy, and the SBRT thecal sac *P*(max) EQD_2 comprises no more than approximately 50% of the total normalized biologically equivalent dose. The feasibility of salvaging spinal metastases initially irradiated with SBRT, who subsequently progressed with imaging-confirmed local tumor progression, with a second SBRT course to the same level has also been confirmed.[37]

Brain

In contrast to the spinal cord, no animal experiments on reirradiation of the brain are available. Clinical data mainly relate to temporal lobe injury after treatment of recurrent nasopharynx cancer[38] or reirradiation of glioma, meningioma, and brain metastases. Shepherd et al[39] retreated glioma with fractionated SBRT (five fractions per week, 5 Gy per fraction) after a median initial dose of 55 Gy (Table 28.2). All patients treated with more than 40 Gy developed late toxicity, whereas only 25% of those who received 30 to 40 Gy developed such adverse events. Several institutions have used reirradiation doses of 30 to 40 Gy with fraction sizes below 4 Gy with acceptable rates of toxicity, and prospective trials such as NRG Oncology/RTOG1205 are in line with these findings. An interstudy comparison between retrospective series is difficult because the literature is confounded by a lack of standardized recording of RT and outcome variables. In addition, some patients were treated at first and others at second or third progression. Recent prospective data from a multicenter study in 92 patients with recurrent high-grade gliomas suggest that reirradiation has no negative impact on health-related quality of life, comparable to other options such as surgery and chemotherapy.[48] Currently, there is no standard recommendation on what imaging modality has to be incorporated and what specific margins should be applied. The minimal consensus may be summarized as to confine gross tumor volume definition to gadolinium-enhancing regions. The GLIAA (NOA 10) study (NCT01252459), an ongoing multicenter, prospective randomized, phase II clinical trial, evaluates the impact of [18F]-fluoro-ethyl-l-tyrosine-positron emission tomography versus T1Gd magnetic resonance imaging (MRI) target volume delineation on the outcome of patients with recurrent glioblastoma treated with high-precision radiation therapy (39 Gy, 3 Gy per fraction). As evident from the review of treated volumes with different modalities, such as single-dose and fractionated stereotactic irradiation, some institutions preferred hypofractionation for recurrences that others treated with a single dose. This finding reflects the lack of universally agreed dose constraints for reirradiation. In the randomized phase II NRG Oncology/RTOG1205 study of systemically administered bevacizumab with or without reirradiation, 35 Gy in 10 fractions was prescribed.[47] The maximum tumor diameter was 6 cm, and the

minimum time interval from previous RT was 6 months. The brainstem, optic nerves, and chiasm were expanded by 3 mm to create planning organ at risk volume (PRV). The maximum per protocol dose of 0.03-mL PRV was 24 Gy (brainstem) and 20 Gy (optic nerves and chiasm), respectively. Acceptable variations included 30 and 25 Gy, respectively. According to a Swiss study, reirradiation appeared both safe and effective in patients with recurrent primary or secondary brain tumors with doses to the brain up to 120 Gy_2 EQD_2, doses below 100 Gy_2 EQD_2 for brainstem, and doses below 75 Gy_2 EQD_2 to chiasm and optic nerves.[49] Figure 28.1 shows a clinical example of a patient treated with conventionally fractionated reirradiation.

TABLE 28.2 A COMPARISON OF SELECTED STUDIES FROM THE GLIOMA LITERATURE: RESULTS PUBLISHED BEFORE 2000 VERSUS AFTER 2010

Sneed et al (1997)[40]	66 GBM 45 WHO III	Brachytherapy I-125 64.4 Gy	11.7 mo 12.3 mo
Kickingereder et al (2014)[41]	98 GBM	Brachytherapy I-125 60 Gy	10.4 mo
Schwartz et al (2015)[42]	40 GBM 28 WHO III	Brachytherapy I-125 50 Gy	9.3 mo 28.1 mo
Stereotactic Radiosurgery			
Martínez-Carrillo et al (2014)[43]	46 GBM 41 WHO III	Stereotactic radiosurgery Median 18 Gy (14-20 Gy)	7.5 mo 17.0 mo
Pinzi et al (2015)[44]	128 high grade	Stereotactic radiosurgery or hypofractionated	11.5 mo
Navarria et al (2022)[45]	90 high grade incl. 65 GBM	Stereotactic radiosurgery or hypofractionated	14.0 mo (GBM), all: 17 m
Hypofractionated Stereotactic Radiotherapy			
Shepherd et al (1997)[39]	33 GBM	Hypofractionated conformal radiotherapy Escalation 20-50 Gy	11.0 mo
Fogh et al (2010)[46]	105 GBM 42 WHO III	Stereotactic hypofractionated radiotherapy Median 35 Gy in 10 fractions	11.0 mo 10.0 mo
Tsien et al (2023)[47]	86 GBM	Bevacizumab and 35 Gy in 10 fractions	10.1 mo

GBM, glioblastoma; WHO, World Health Organization.

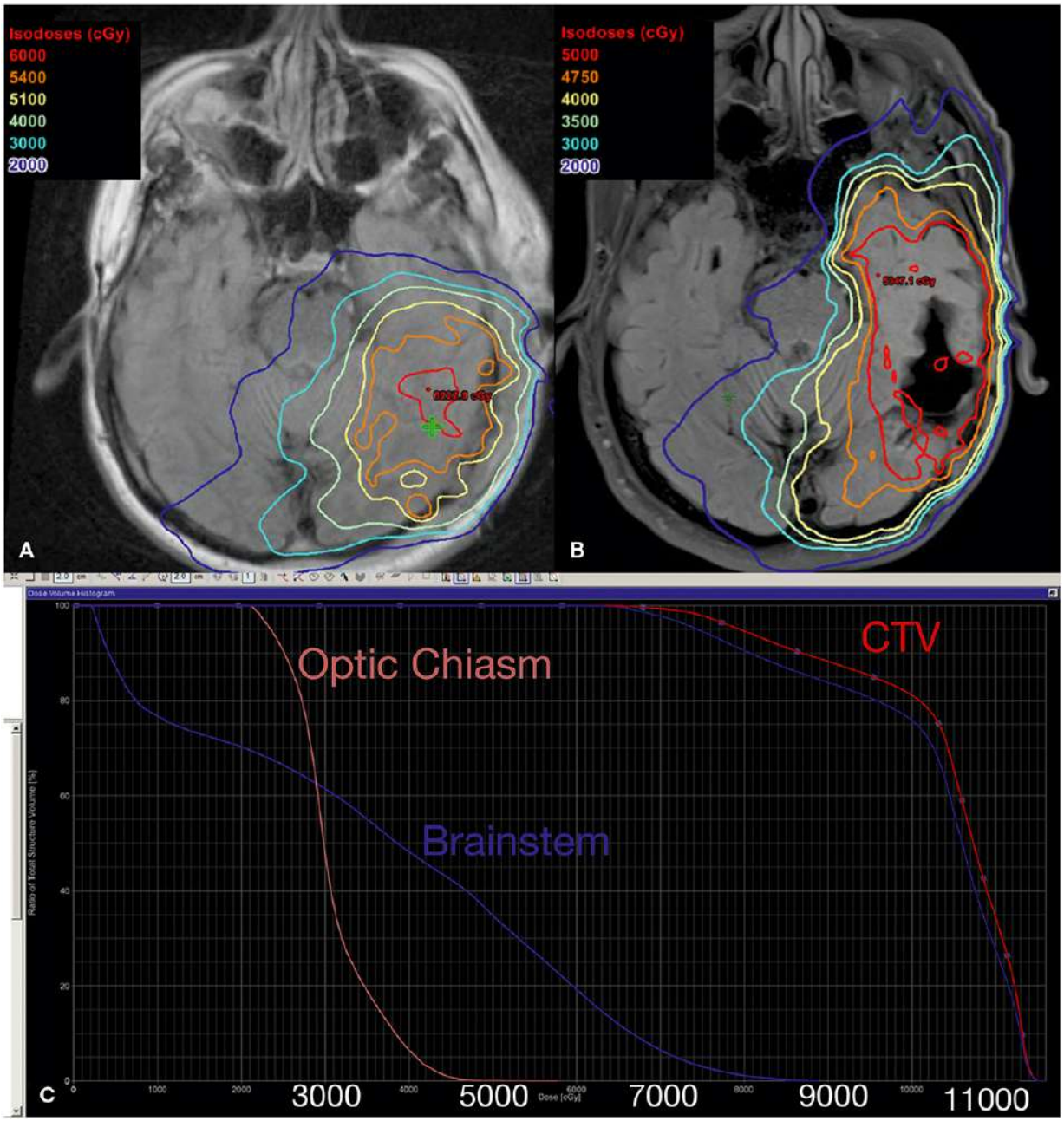

FIGURE 28.1 A. Representative axial slices from a T2-weighted fluid attenuation inversion recovery magnetic resonance image of a 66-year-old man with a left temporoparietal glioblastoma originally treated after surgical resection to 60 Gy in 30 fractions with concurrent temozolomide. B. He subsequently had an in-field recurrence 4 years after the completion of his original treatment and was treated to 50 Gy in 25 fractions. C. A dose-volume histogram. Cumulative brainstem dose to 0.3 cm^3 was limited to 80 Gy. Treatment was successfully delivered without serious toxicity. (Courtesy of Mark Amsbaugh, MD, University of Louisville School of Medicine.)

Radiosurgery was systematically studied by the Radiation Therapy Oncology Group (RTOG).[50] Adults with cerebral or cerebellar solitary nonbrainstem tumors

≤40 mm in maximum diameter were eligible. Initial radiosurgical doses were 18 Gy for tumors ≤20 mm, 15 Gy for that 21 to 30 mm, and 12 Gy for that 31 to 40 mm in maximum diameter. Dose was prescribed to the 50% to 90% isodose line. Doses were escalated in 3-Gy increments, providing the incidence of irreversible grade 3 or any grade 4 or 5 RTOG central nervous system toxicity was <20% within 3 months of radiosurgery. Between 1990 and 1994, 156 analyzable patients were entered, 36% of whom had recurrent primary brain tumors (median prior dose 60 Gy) and 64% recurrent brain metastases (median prior dose 30 Gy). The median interval was 11 months, minimum 3 months. The maximum tolerated doses were 24, 18, and 15 Gy for tumors ≤20, 21 to 30, and 31 to 40 mm in maximum diameter, respectively. However, for tumors ≤20 mm, investigators' reluctance to escalate to 27 Gy, rather than excessive toxicity, determined the maximum tolerated dose. The actuarial incidence of radionecrosis was 5%, 8%, 9%, and 11% at 6, 12, 18, and 24 months following radiosurgery, respectively. Unacceptable toxicity was more likely in patients with larger tumors. Sneed et al[51] reported that radiosurgery followed by a second radiosurgery for recurrent brain metastases resulted in a 20% 1-year cumulative incidence of symptomatic adverse radiation effect (median reirradiation dose 18 Gy, n = 72, crude risk 14%). Compared to patients who had not received prior radiosurgery to the same lesion, the hazard ratio (HR) for any adverse radiation effect was 5.05 (95% confidence interval [CI] 1.9-13.2). Another study of 46 retreated lesions reported symptomatic radiation necrosis in 24% (actuarial 1-year rate 29%), while local control at 1 year was 79%.[52]

Heart

Wondergem et al[53] assessed the reirradiation tolerance of the heart at intervals of up to 9 months in a rat model by measuring cardiac function ex vivo 6 months after reirradiation. The cardiac tolerance dose was arbitrarily defined as the dose causing at least 50% function loss in one half of the treated animals (ED_{50}). Up to a 6-month interval, the reirradiation ED_{50} was close to the single course ED_{50} but dropped significantly when the interval was longer than 6 months. The reirradiation tolerance also decreased with an increasing priming dose. A slow progression of damage induced by the priming dose is a plausible explanation for the decrease in tolerance with increasing time from the initial course. Systematic clinical data are not available.

Kidney and Bladder

Experimental data caution also against whole-bladder reirradiation.[54] With respect to late bladder damage in mice (end point defined as >50% reduction in bladder volume, increased urination frequency at ≥27 weeks after reirradiation), no long-term recovery was observed in up to a 9-month interval. Unfortunately, neither experimental data for partial organ reirradiation nor larger clinical studies on bladder reexposure are available, despite considerable evidence for prostate cancer reirradiation feasibility.[14] Studies on mouse, rat, and pig kidney suggested that radiation-induced toxicity progresses rather than recovers with time.[55,56]

SELECTED HEAD AND NECK CANCER STUDIES

The randomized Chinese phase II trial by Tian et al[19] that included 117 patients evaluated de-escalation of the biologically equivalent dose for late-responding normal tissues, while maintaining the same EQD_2 for nasopharynx cancer cells. This was accomplished by selecting a slightly hypofractionated experimental regimen (60 Gy in 27 fractions, IMRT), which was compared to a conventional regimen with 2-Gy fractions (total dose 68 Gy, IMRT) and longer overall treatment time. It was assumed that normal tissue sparing would result in less life-threatening toxicity and thus better overall survival, that is, a better therapeutic ratio. In principle, the results confirmed this hypothesis, with a 5-year overall survival rate of 44% versus 30%, but the difference was not statistically significant ($P = .06$). A subsequent randomized trial compared 60 Gy in 27 fractions to a regimen with further de-escalated EQD_2, employing hyperfractionation (65 Gy in 54 fractions twice daily [bid]) with identical overall treatment time.[57] The rate of severe late complications was significantly lower in the hyperfractionation arm, while overall survival improved. Serious toxicity was not uncommon, and therefore, continued research efforts are necessary.

The Groupe d'Oncologie Radiothérapie Tête et Cou/Groupe d'Étude des Tumeurs de la Tête et du Cou reported on a prospective study in which 130 patients who underwent salvage surgery were randomly assigned to receive full-dose reirradiation (60 Gy) combined with concomitant chemotherapy (5-fluorouracil and hydroxyurea) versus no adjuvant treatment.[58] All patients underwent a macroscopic complete resection, and in the majority, the surgical margins were sufficient. A significant improvement with regard to the primary end point of locoregional tumor control (HR 2.7; 95% CI 1.7-4.5; $P < .001$) and disease-free survival (HR 1.7; 95% CI 1.1-2.5; $P = .01$) was observed in those patients who were assigned to receive postoperative chemo-reirradiation compared to those who underwent surgery alone. However, this benefit in disease-free survival did not translate into a significant improvement in overall survival, which

may be due to the higher incidence of distant metastases in the chemo-reirradiation arm. The gain in locoregional tumor control and disease-free survival was achieved at the cost of significantly higher rates of grade 3 and 4 late side effects (39% vs 10% at 2 years). It should be noted that participants allocated to the wait-and-see arm could receive salvage chemo-reirradiation at the time of locoregional recurrence after salvage surgery, which was the case in 25% of patients. This type of crossover reduces the likelihood of improved overall survival. Postoperative chemo-reirradiation should be considered in selected cases, in particular given the very low locoregional control rate after salvage surgery alone, which was only 20% at 2 years. However, in light of the high rate of late toxicity, the optimal postoperative regimen in the reirradiation setting has yet to be defined. Based on the results of this study, a wait-and-see policy could also be considered, in particular when patients suffer from severe late toxicities from the first course of treatment. Ho et al[59] in a retrospective comparison of primary closure to flap reconstruction (n = 59 and 37, respectively) reported that nonflap patients experienced a significantly greater incidence of severe late toxicities (47.5% vs 21.6%, P = .02), while acute toxicities and 5-year survival were comparable.

As shown in Figure 28.2, median survival is limited,[6,23,24,60-64] but a proportion of patients experience long-term survival after reirradiation, a finding that has already been described in historical studies. Patients with new primary tumors fared better than those with local relapse. Target volumes should be kept tight, and elective nodal irradiation should be avoided in order to minimize severe toxicity.[13,67]

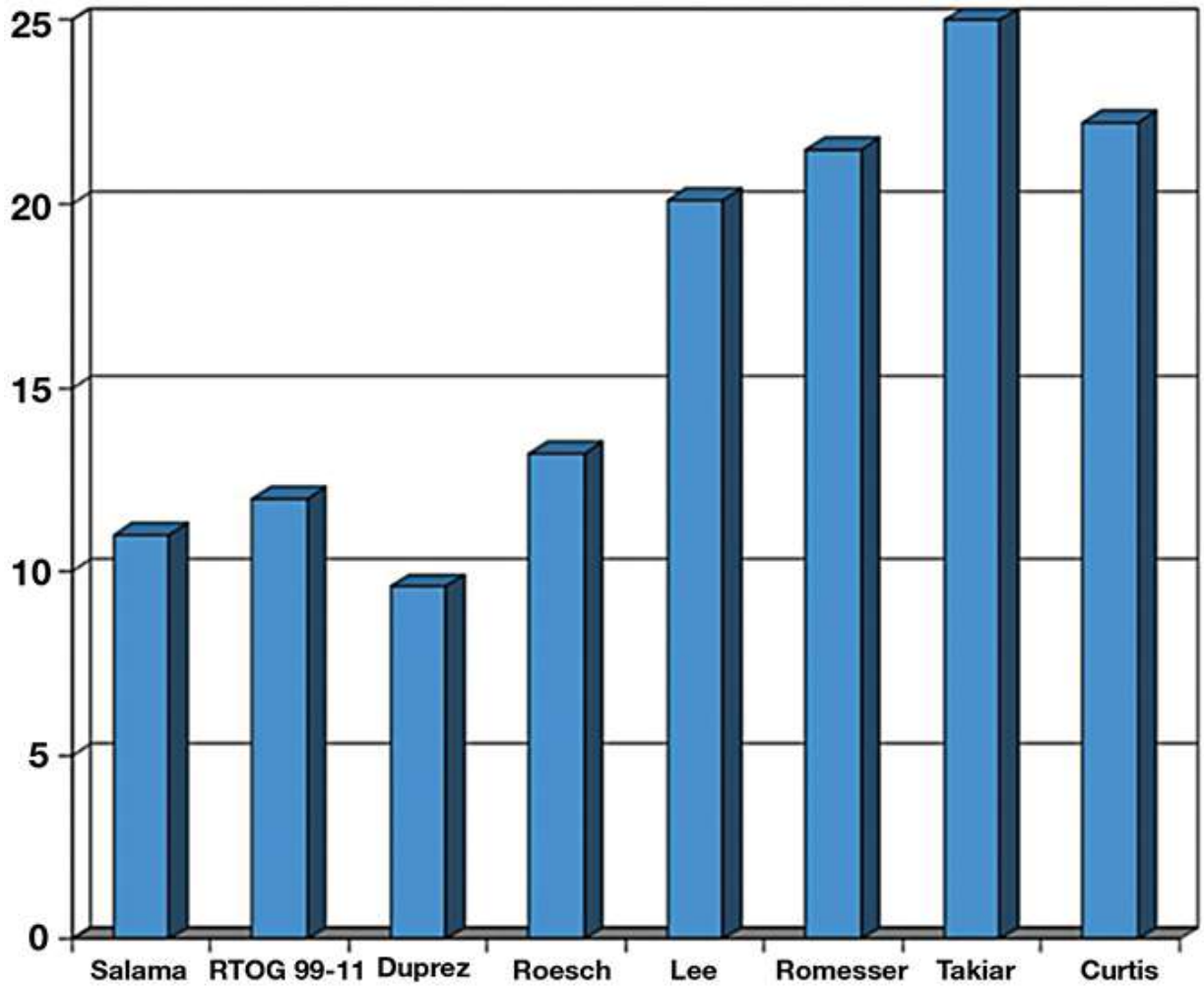

FIGURE 28.2 Median overall survival in months after reirradiation of head and neck cancers (selected studies[6,23,24,60-64]). The studies by Takiar et al,[24] Lee et al,[62] Romesser et al,[63] and Curtis et al[64] included mixed populations, that is, patients treated after salvage surgery or without resection. Limited recurrence treated with stereotactic body at an experienced center was associated with a median survival of 44 months.[65] In a pooled analysis of 500 patients, the risk of progression or death was approximately 4 times the risk of radiation-related severe late toxicity.[66]

BREAST CANCER

In-Breast Tumor Recurrence After Prior Breast-Conserving Surgery and Whole-Breast Radiation Therapy

It is generally accepted that in-breast tumor recurrence (IBTR) is expected to occur in approximately 5% to 10% of patients within 10 years after initial breast-conserving surgery (BCS) plus whole-breast radiation therapy (WBRT), equating to a cumulative risk of 0.5% to 1% per annum. The most often recommended treatment for IBTR is salvage mastectomy, which imparts excellent local regional control and 5-year survival rates.[68] Given the fact that there are subgroups of

patients who refuse mastectomy after IBTR, a number of series have described the approach of repeat BCS alone, without additional reirradiation. In these studies, local regional recurrence is unacceptably high, with rates approaching 40%,[69] as opposed to 10% following mastectomy.[68] Even so, radiation oncologists have generally shown a reluctance to offer reirradiation in the treatment of locally recurrent breast cancer.[70] However, with an increase in technological sophistication of radiation therapy techniques over the past two decades, a number of studies have investigated the feasibility and efficacy of adding reirradiation to BCS for IBTR.

Table 28.3 shows a summary of the modern series (published since 2010) of repeat BCS and reirradiation in the setting of IBTR. The overwhelming majority of the data exists for partial breast irradiation (PBI) using interstitial, multicatheter brachytherapy with low-dose rate, pulsed-dose rate, or high-dose rate source techniques.[71-81] Pooled data from European experience using all three of the aforementioned methods represent the largest study of this approach published to date.[73] In a total of 217 patients, this collaborative multi-institutional analysis from high-volume centers in Europe found that interstitial brachytherapy was very well tolerated with local control rates much more comparable to salvage mastectomy (93%) as well as good to excellent cosmetic outcome in the overwhelming majority of patients (85%). Simplified interstitial techniques using single- catheter balloon brachytherapy have been described with similar outcomes.[74]

TABLE 28.3 COMPARATIVE OUTCOMES AMONG PUBLISHED SERIES OF BREAST REIRRADIATION FOLLOWING REPEAT BREAST-CONSERVING SURGERY FOR IBTR

Study (year)	Type of Reirradiation	*N*	Reirradiation Total Dose (Gy)	Median Follow-Up (mo)	Toxicity (% ≥G3)	Local Control (%)	Overall Survival (%)	Cosmesis (% Good or Excellent)
Guix et al (2010)[71]	HDR	36	30	89	0	89	97	90
Kauer-Dorner et al (2012)[72]	PDR	39	50	57	17	93	87	37
GEC-ESTRO (2013)[73]	HDR PDR LDR	102 88 27	32 50 46	47	11	93	76	85
Trombetta et al (2014)[74]	HDR	18	34	40	5	89	94	83
Blandino et al	eIORT	30	18	47	21	92	91	51

Study (year)	Type of Reirradiation	*N*	Reirradiation Total Dose (Gy)	Median Follow-Up (mo)	Toxicity (% ≥G3)	Local Control (%)	Overall Survival (%)	Cosmesis (% Good or Excellent)
(2017)[75]								
Thangarajah et al (2018)[76]	xIORT	41	20	58	0	90	87	NR
Janssen et al (2018)[77]	EBRT	83	45 (qd)	35	0	85	76	NR
Forster et al (2019)[78]	HDR PDR	11 8	32-34 50	65	0	100	100	NR
Montagne et al (2019)[79]	HDR LDR	117 26	28-34 30-55	71	0	98	91	85
Smanykó et al (2019)[80]	HDR	39	22	59	8	81	94	70
Arthur et al (2020)[81]	EBRT	58	45 (bid)	66	7	95	95	NR

Published since 2010 with >3-year median follow-up.
bid, twice daily; EBRT, external beam radiotherapy; eIORT, electron-based intraoperative radiotherapy; HDR, high-dose rate; IBTR, in-breast tumor recurrence; LDR, low-dose rate; PDR, pulsed-dose rate; qd, once daily; xIORT, 50-kV x-ray–based intraoperative radiotherapy.

An emerging modality to address the challenge of reirradiation after the second BCS for IBTR is intraoperative radiation therapy (IORT) at the time of salvage lumpectomy, using either electron[75] or "soft" x-rays.[76] IORT is delivered using a single dose of approximately 18 or 20 Gy with intraoperative electrons or 50 kV x-rays. In these two small studies of approximately 20 patients each, IORT was associated with local control of >90% at 4 years, with higher grade 3 toxicity reported for electron (21%) than for x-rays (0%). Cosmetic outcome was also somewhat disappointing compared to other techniques, with only 51% of patients treated with electron-based IORT reporting satisfactory results.

In terms of breast reirradiation using external beam radiation therapy (EBRT), the data are more scant, but growing. A modern study of its kind from Europe included 83 patients treated with once-daily conventionally fractionated RT (45 Gy in 1.8 Gy/fx) directed at the tumor bed after repeat BCS.[77] At a median follow-up of 3 years, the therapy was generally well tolerated with local control rates at 85% and no grade 3 or higher toxicity. In the United States, a multi-institutional phase II

trial (NRG Oncology/RTOG1014) evaluated the safety and efficacy of repeat PBI using bid accelerated hyperfractionated 3D conformal RT (45 Gy in 1.5 Gy/fx) over 3 treatment weeks.[81] In this study, 58 patients with small invasive or preinvasive lesions completely excised with negative surgical margins completed reirradiation and were assessed at over 5-year median follow-up. This regimen was well tolerated with excellent rates of local control (95%) and very few grade 3 toxicities.[75] Data from these trials serve to increase the use and availability of breast reirradiation among centers that do not offer interstitial brachytherapy or IORT.

As more data accumulate, there are two modern published consensus guidelines from Germany (DEGRO) and Italy to inform clinicians in routine practice of how to approach these challenging and heterogeneous populations.[12,82] Although the panels both recognize that mastectomy is generally regarded as a standard of care for patients with IBRT, but that a subset of patients may be appropriately offered reirradiation after a second BCS. Since the largest experience to date exists for a multicatheter brachytherapy, other techniques such as EBRT or IORT should preferentially be performed on a clinical trial.

Management of Local Regional Recurrence After Prior Mastectomy and Postmastectomy Radiation Therapy

The Early Breast Cancer Trialists' Collaborative Group estimated that the addition of RT significantly reduced the 10-year risk of isolated local recurrence from approximately 25% to 7%.[83] The addition of modern systemic therapy has fortunately made this type of event even more rare. That does not diminish the clinical challenge that is experienced by physicians in cases of isolated chest wall or regional nodal recurrences in patients who have had prior postmastectomy radiation therapy. Published series that address this issue tend to be single institution and small experiences with heterogeneous mix of patients, including those who have undergone prior mastectomy or breast conservation, as well as some who have unresectable gross disease present at the time of therapy.[84-92] These situations favor external beam approaches, rather than brachytherapy or IORT, including (more recently) proton beam radiotherapy (PBRT).

A selection of the most modern published series in the reirradiation for chest wall and regional recurrences is presented in Table 28.4. Historically, the majority of investigators use concurrent hyperthermia (HT) combined with EBRT that is typically conventionally fractionated or hypofractionated.[85-89] Although HT is not available at a majority of RT centers, it does have a proven benefit in the treatment of advanced superficial local recurrences such as these. Two of the largest studies,

both published by Linthorst et al, used large fraction external beam doses along with HT to produce reasonable local control rates (40%-78%) and relatively low rates of grade 3 toxicity (<15%). A recent small series combining PBRT with HT (62%) for a cohort of 19 patients mainly treated to the chest wall only with reirradiation to a total median dose of 50 CGyE showed outstanding local control at 19 months (100%) at the cost of >30% grade 3 toxicity.[89]

TABLE 28.4 COMPARATIVE OUTCOMES AMONG PUBLISHED SERIES OF CHEST WALL AND/OR REGIONAL NODAL REIRRADIATION FOLLOWING LOCOREGIONAL RECURRENCE AFTER INITIAL MASTECTOMY AND PMRT

Study (year)	Type of Reirradiation	*N*	Reirradiation Dose (median, Gy or CGyE)	Concurrent Treatment	Median Follow-Up (mo)	Toxicity (% ≥G3)	Local Control (%)
Harkenrider et al (2011)[84]	EBRT	12	47	CT (63%)	30	8	92
Müller et al (2011)[85]	EBRT	42	60	HT (69%)	41	0	62
Linthorst et al (2013)[86]	EBRT	198	8 × 4	HT (100%)	42	12	78
Merino et al (2015)[87]	EBRT	56	50	CT (12%)	17	12.5	63
Linthorst et al (2015)[88]	EBRT	248	8 × 4	HT (100%)	32	1	40
Gabani et al (2019)[89]	PBRT	19	50	HT (62%)	19	31	100
Thorpe et al (2019)[90]	PBRT	50	55	CT (10%)	13	16	94
Choi et al (2021)[91]	PBRT	46	50	NA	21	8	100
LaRiviere et al (2021)[92]	PBRT	27	51	CT (11%)	17	20	96

Some trials included breast-conservation patients as well.

CT, cytotoxic chemotherapy; EBRT, external beam radiotherapy; HT, hyperthermia; PBRT, proton beam radiotherapy; PMRT, postmastectomy radiotherapy.

Series that omit HT generally include fewer, more favorable patients treated for high-risk, microscopic disease post limited resection treated with conventionally fractionated photons[84,87] or PBRT[90-92] with or without concurrent chemotherapy. Local disease control rates are favorable (63%-100%), with lower rates of toxicity compared to combined HT. There is a great deal of enthusiasm for the emerging experience of PBRT to maximize normal tissue avoidance as well as dose escalate.[90-92] Although these relatively large series of PBRT show excellent rates of local control (>93%) with a low toxicity profile (<20% grade 3), the rates of distant disease failure remain very high, even in the setting of concurrent or sequential chemotherapy. The aforementioned DEGRO expert panel currently recommends the use of reirradiation both in cases of unresectable recurrences and after surgical resection in high-risk patients.[12] This group recommends reirradiation with doses between 45 and 50 Gy in conventional fractionation, not exceeding cumulative doses of 100 to 110 Gy, and notes that HT can further improve tumor control in this population.

Isolated Regional Nodal Recurrences After Prior Radiotherapy

Isolated supraclavicular and/or axillary recurrences are very uncommon in breast cancer, especially after appropriate adjuvant radiation therapy in the up-front setting. These clinical scenarios, however, pose the most significant clinical challenges for physicians and patients alike, due to the difficulty in early diagnosis and high-risk surgical management. In these situations, the risk of injury to clinical OARs such as the brachial plexus from repeat RT must be weighed against the certain involvement of these structures due to direct invasion of progressive disease.

In the largest series of its kind, a multi-institutional study from the Netherlands, 42 patients with isolated supraclavicular recurrence treated with a combination of systemic and local regional RT were examined.[93] The 5-year overall survival and disease-free survival rates were significantly worse than are seen with chest wall recurrences (38% and 22%, respectively). What is more striking is that outcomes were even worse for patients who did not receive RT as a component of their salvage treatment. Given the grim prognosis, there are small emerging series that address isolated nodal recurrences with a combination of either concurrent or sequential chemotherapy and reirradiation[89-95] using photon and PBRT techniques to median doses of 50 Gy. Even in these most conformal techniques, point doses to the brachial plexus are well above historically cited tolerance with cumulative doses in excess of 100 Gy. Since overall survival in these patients is less than half

that of patients with chest wall recurrences,[93] clinicians must weigh the risks of a tumor-induced plexopathy versus iatrogenic injury in each particular case.

Patients with isolated axillary recurrences tend to fare somewhat better due to the fact that they lend themselves more often to surgical excision and reirradiation without compromising the brachial plexus. In a series of axillary recurrences from the MD Anderson Cancer Center, the authors found that durable control was able to be achieved in 31 (70%) of 44 patients.[96] Success was most often seen in patients who were able to undergo up-front surgery and multimodality therapy. Twenty percent of these patients had prior axillary RT, and the addition of reirradiation to the axilla significantly improved local disease control (81% vs 56%). As of now, the DEGRO expert panel acknowledges that in cases of isolated nodal recurrences, approximately half to two-thirds of patients will eventually develop distant metastatic disease. Durable local regional control is more often achieved in patients with axillary nodal involvement only, and reirradiation improves local control and should be applied wherever feasible.[12] Newer technologies such as PBRT, MR-guided adaptive RT, and novel concurrent radiosensitizing systemic agents are likely to lead the next generation of reirradiation techniques for locoregionally recurrent breast cancer.

DISCUSSION

Reirradiation should only be considered if the radiation tolerance of critical tissues or organs has not been exceeded during the first treatment, that is, after an in-depth review of the initial plan and dose distribution, and assessment of organ status and side effects after the first treatment.[4] Moreover, reasonable performance status; the absence of other, less toxic treatment alternatives; and careful dose summation are prerequisites. It is important to weigh the expected benefits against morbidity and compromised quality of life. Several studies, especially on lung and head and neck cancers, demonstrated that reirradiation can either cause or prevent a fatal outcome. In many scenarios, including, but not limited to, pelvic tumors, the ability of reirradiation to palliate pain and other symptoms has repeatedly been confirmed[7,97,98] (Figure 28.3). For many tissues, organs, and indications, an increasing body of clinical data is now emerging. These include settings with much higher single-course equivalent doses than previously prescribed, for example, SBRT for early-stage lung cancer.[99] Nevertheless, limited knowledge exists for a number of end points, such as neurocognitive function and damage to endocrine organs or second reirradiation tolerance.[100] Acutely responding tissues, in general, recover radiation changes practically completely within a few months and, therefore, can tolerate a repeat treatment course.

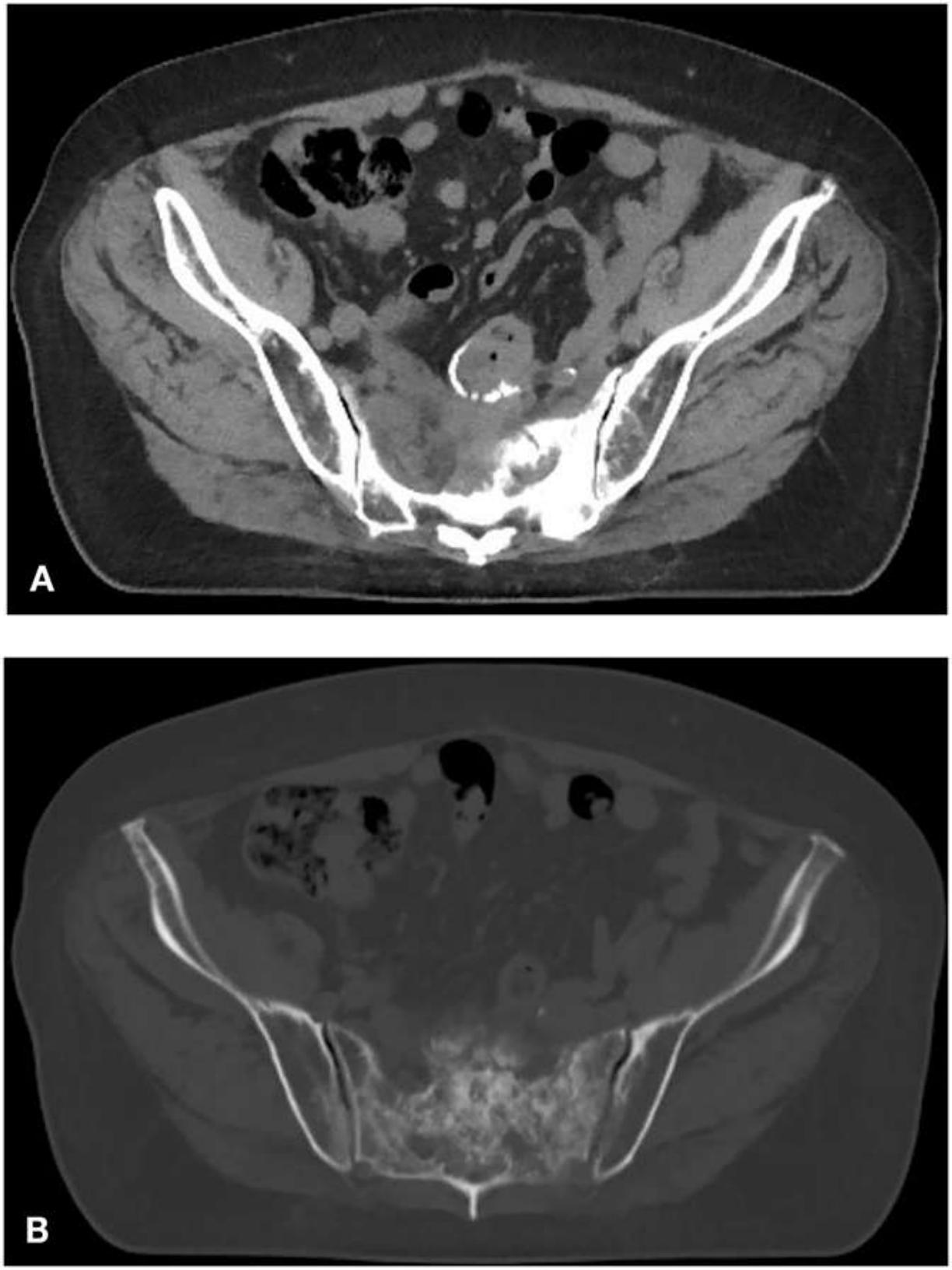

FIGURE 28.3 Representative axial slices from planning computed tomography images (soft tissue [A] and bone [B] window) of a 64-year-old female patient initially treated surgically for cancer in the

sigmoid colon in 2013. She relapsed in the sacral bone in 2014 and received long-course chemoradiation (50 Gy in 25 fractions with concomitant capecitabine) without surgery. Due to local progression chemotherapy with an oxaliplatin/5-fluorouracil regimen was initiated in 2016. Due to increasing pain, reirradiation was offered in June 2016. A hyperfractionated regimen was chosen (1.25 Gy bid, total dose 40 Gy) concomitant to capecitabine. Symptom improvement was achieved without high-grade treatment-related toxicity.

Clinical evidence dating back many decades[101] suggests that fibrosis, impaired blood perfusion, and, in general, late normal tissue injury in humans continue to progress for many years. These findings have triggered a trend toward highly sophisticated, conformal image-guided reirradiation approaches aiming at better normal tissue sparing. Brachytherapy (including intraoperative administration), stereotactic techniques, proton, and carbon ion beams are under clinical investigation.[9,102-110] However, severe dysphagia and fatal bleeding might still occur after proton beam reirradiation for head and neck cancer. It is hoped that models that predict the risk of serious complications might contribute to optimized patient selection. Proton beam reirradiation of non–small cell lung cancer was associated with six grade 5 toxicities in a multi-institutional study of 57 patients.[105] Increased overlap with the central airways, mean esophagus and heart dose, and simultaneous chemotherapy were risk factors for grade ≥3 toxicity.

While small target volumes can be treated with fraction sizes above 2 Gy, radiobiologic principles and clinical data suggest that large-volume reirradiation might be less toxic if hyperfractionation is employed.[7,57,111,112] Despite strong rationales, this logistically difficult approach has only been studied in a single randomized head-to-head comparison to once-daily reirradiation (nasopharynx cancer). Many institutions consider reirradiation for primary and secondary brain tumors; bone and lymph node metastases; head and neck, lung (Figure 28.4), breast, prostate, gynecologic, and rectal cancer; lymphoma; and soft tissue sarcoma. Fewer reports were published regarding hepatic, pancreatic, and esophageal tumors.[112-116] The EORTC/ESTRO ReCare multicenter study will gather real-world data on patients treated with high-dose reirradiation for local recurrence and new primary or secondary cancer in line with recently published reporting recommendations and definitions.[4]

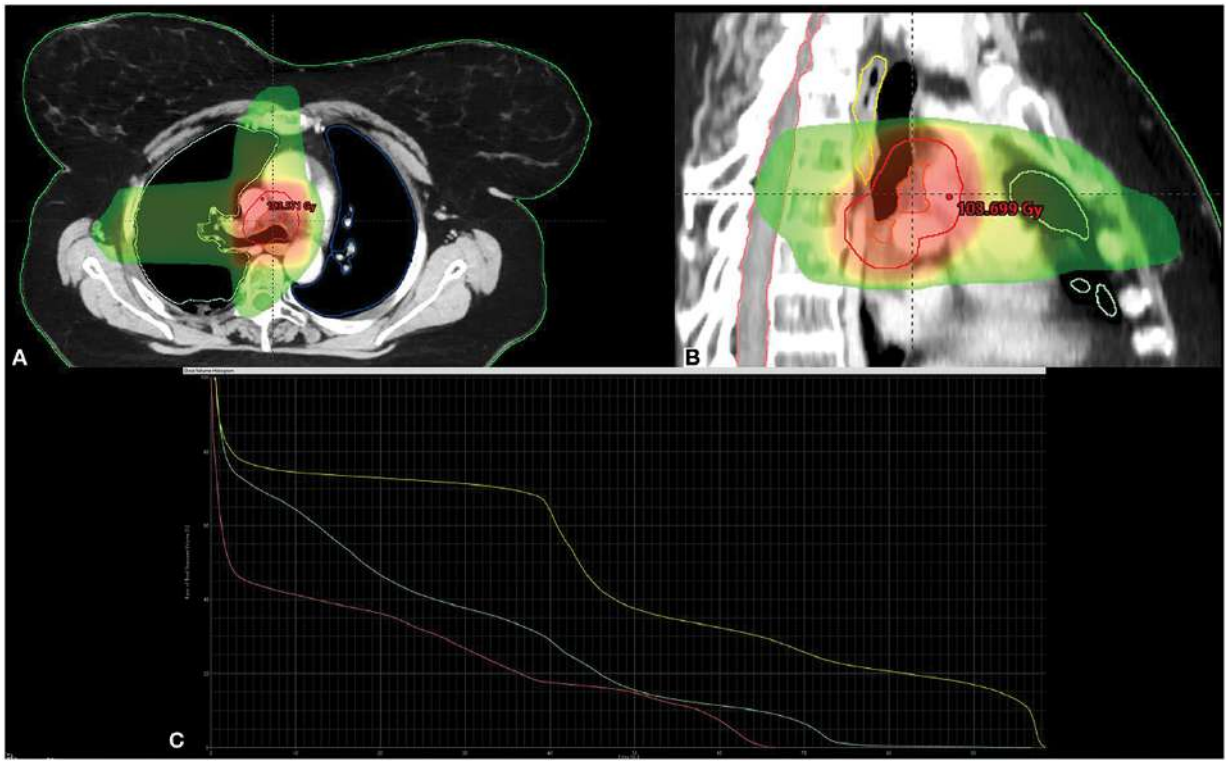

FIGURE 28.4 Representative axial slices from planning computed tomography images (A) and sagittal (B) from computed tomography images of a 59-year-old female patient initially treated in November 2015 for right-sided small cell lung cancer (chemoradiation with cisplatin/etoposide and bid radiation to 45 Gy in two daily fractions of 1.5 Gy). In February 2017, mediastinal in-field relapse was confirmed. The patient again received chemoradiation, however to an escalated dose of 57 Gy, two daily fractions of 1.5 Gy. In February 2022, surgery was performed for a left-sided second primary lung cancer (squamous cell, stage I). Severe late toxicity from reirradiation was not observed. C. The cumulative dose-volume histogram shows a D_{max} of 98.6 Gy in the esophagus (yellow curve) and 66.6 Gy in the spinal canal (brown curve). Mean lung dose was 25 Gy (green curve).

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CHAPTER 29

Chemical Modifiers of Radiation Response

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Chemical agents have been administered in conjunction with radiation therapy (RT) for both the enhancement of antitumor therapeutic efficacy and the amelioration of treatment-induced toxicity. Two concepts are fundamental to understanding the rationale for chemical modification of radiation response and to interpreting the studies that have addressed this issue. The first is the therapeutic ratio (TR), which is defined as the TCP/NTCP where TCP is the tumor control probability and NTCP is the normal tissue complication probability. Both parameters have sigmoid dose-response curves (Figure 29.1). The horizontal separation between these two curves for any given treatment will often determine its overall utility. As the separation between these curves increases, the likelihood becomes greater that the treatment will be effective without causing an unacceptable level of morbidity. Conversely, when the two curves are closer together, the treatment may be less effective while causing an unacceptable level of morbidity.

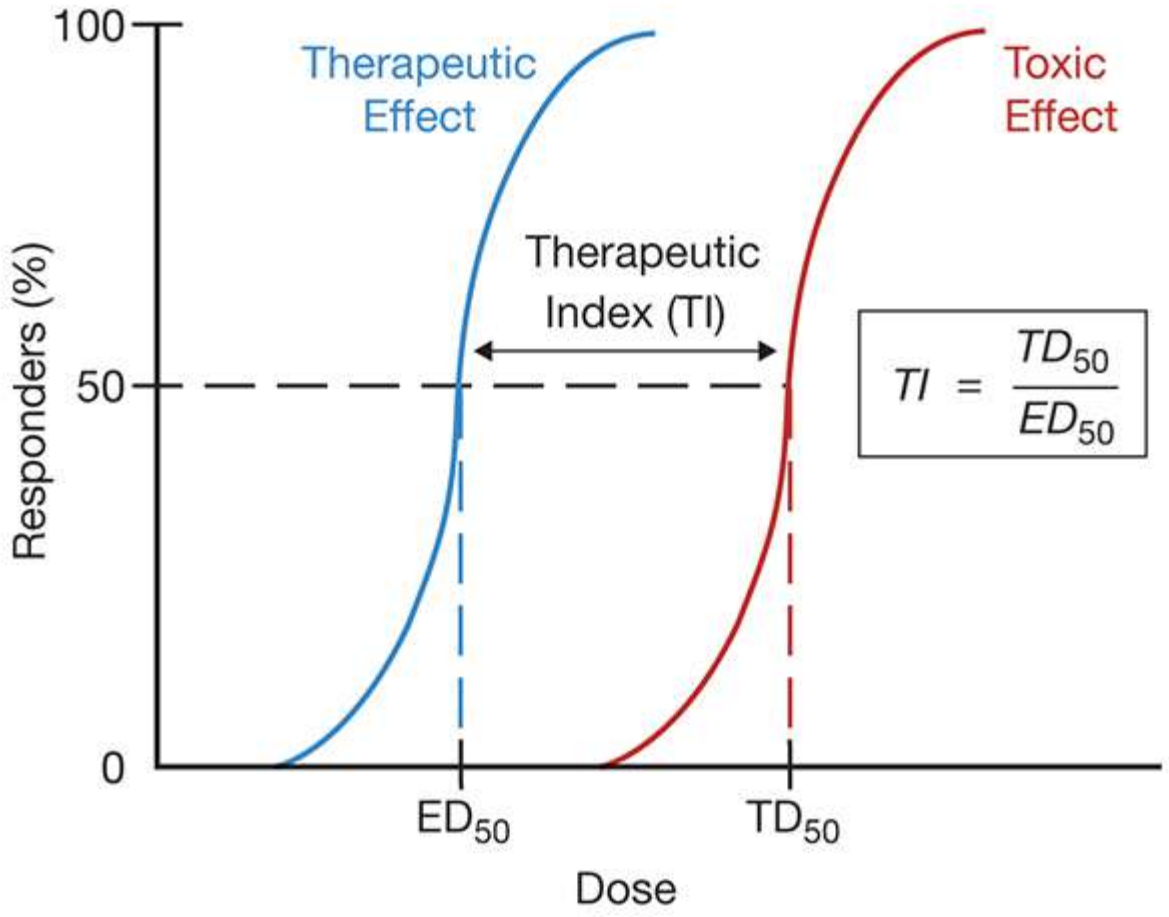

FIGURE 29.1 A graphic representation of the therapeutic index (TI). The tumor control probability (TCP) is to the left of the normal tissue complication probability (NTCP), and both are displayed as sigmoid dose-response curves. Larger separations are indicative of higher TIs. Ideally, normal tissue protection strategies would move the NTCP curve to the right without compromising TCP (moving the TCP curve to the right). Ideal therapeutic intensification strategies would move the TCP curve to the left without worsening NTCP (moving the NTCP curve to the left).

The second concept is the efficacy/toxicity profile of the putative chemical modifier, which can directly affect the TR. A radiosensitizing agent that exacerbates toxicity to the same extent that it improves efficacy (shifting both NTCP and TCP curves to the left) may leave the TR unchanged or worsened and, therefore, not be clinically practical. Conversely, a radioprotective agent that also reduces RT efficacy against the tumor (shifting both NTCP and TCP curves to the right) may not affect or even reduce the TR. The intrinsic toxicity of a radioprotector must also be

considered when reduction of NTCP is the primary goal of a given chemical modification strategy. A compound that causes significant side effects may render it unsuitable, even if it can reduce the treatment-induced toxicity in question. This chapter explores chemical radiosensitization and radioprotective strategies. The primary focus is on treatments that have been clinically tested in head and neck cancer to amplify these concepts.

CHEMICAL RADIOSENSITIZATION

The Oxygen Effect

Tumor cell killing is produced by direct ionizations within critical cellular targets, as well as by the indirect effect of energy deposited in other cellular molecules like water. Ionizing radiation generates free radicals, which can lead to cellular death by inducing single- and double-strand DNA breaks. This damage can be fixed or repaired by the chemical processes of oxidation and reduction, respectively.[1] The addition of molecular oxygen to target free radicals produces altered chemical structures that are potentially lethal. When a tumor is hypoxic, reduced availability of molecular oxygen leads to fewer reactive oxygen species induced by radiation, thus decreasing radiosensitivity in vitro and in vivo.[2,3] Well-oxygenated tumors (partial pressure of oxygen or pO_2 >10 mm Hg) are at least 2.5 times more sensitive to a given dose of ionizing radiation than their hypoxic counterparts.

Clinical data clearly demonstrate the existence of tumor hypoxia in head and neck cancer,[4,5] and there are extremely strong correlations between hypoxia and both infield treatment failure and overall survival.[6,7] This effect is independent of the disease stage at diagnosis.[7] Tumor hypoxia has also been correlated with local and distant recurrence in cervical carcinoma treated with surgery[8,9] or RT[10] and with distant failure in soft tissue sarcomas treated with surgery and adjuvant RT.[11]

Augmentation of Tumor Oxygenation

Therapeutic attempts to overcome the deleterious effect of tumor hypoxia have followed three general lines of investigation: increased delivery of oxygen to tumor, preferential sensitization of hypoxic cells with oxygen-mimetic agents, or cytotoxic agents that selectively target hypoxic tumor

cells. Hemoglobin concentration is the major determinant of the oxygen delivery capability of blood to tissue. Hemoglobin oxygen saturation exceeds 90% when the arterial pO_2 is >70 mm Hg. Still, oxygen is relatively insoluble in plasma under normobaric conditions. Under hyperbaric conditions, considerable quantities of oxygen can be dissolved into plasma and thus be potentially available for delivery to hypoxic tissues.

Clinical trials of hyperbaric oxygen (HBO) and RT were conducted from the 1950s to the 1970s. Trials conducted in patients with cancers of the central nervous system,[12] lung,[13] bladder,[14] and skin[15] showed no benefit from the addition of HBO to RT. However, randomized controlled trials in carcinoma of the cervix[16] and head and neck[17,18] did show improvements in locoregional control and overall survival. The cumbersome logistics associated with HBO delivery in conjunction with RT necessitated the utilization of nonconventional hypofractionated treatment regimens, which has prevented HBO from being incorporated into routine clinical use.

Carbogen (95% oxygen [O_2]/5% carbon dioxide [CO_2]) breathing, with or without concurrent nicotinamide administration, has also been utilized in attempts to improve tumor oxygenation and enhance RT response. CO_2 addition in the gas-breathing mixture induces a mild acidosis that shifts the oxyhemoglobin association curve to the right, facilitating more unloading of oxygen into hypoxic tissues. The rationale for adding nicotinamide, a vitamin B derivative, is based on preclinical studies showing enhancement of tumor blood flow.[19,20] Polarographic electrode assessments in cervical and head and neck cancer have demonstrated that carbogen breathing and nicotinamide administration improve tumor oxygenation in some patients.[21-23]

A randomized trial of hyperfractionated RT with or without carbogen was conducted at the University of Florida from 1996 to 2002.[24] The study included patients with cT2-T4 squamous cell carcinoma (SCC) of the oropharynx, larynx, and hypopharynx. It was designed to detect a 20% improvement in a 2-year local control in the carbogen arm relative to the RT-alone arm, with a 15% improvement in a 4-year cause-specific survival. Virtually all enrolled patients in both arms completed their prescribed courses of treatment. The addition of carbogen to RT did not appear to improve any of the planned end points of this trial. However, while the

design of this trial called for enrollment of 675 patients, only 101 were accrued over a 5-year period. The trial was, therefore, significantly underpowered to detect the hypothesized treatment effects. The inability to accrue patients also called into question the overall viability of strategies utilizing carbogen.

The use of accelerated RT with carbogen inhalation and nicotinamide (ARCON) was tested in a phase II trial of 215 patients with head and neck cancer.[25] Ninety-seven percent had stage III or IV disease, and the primary tumor site was larynx in 46%, hypopharynx in 23%, and oropharynx in 23%. Full compliance with carbogen breathing during RT occurred in 88% of patients. Nicotinamide was administered 1 to 1.5 hours prior to RT at 60 to 80 mg/kg. Nicotinamide-induced nausea and vomiting necessitated discontinuation of the drug in 10% of patients receiving the lower dose and 31% of patients receiving the higher dose. Five-year locoregional control rates were 48% for hypopharynx, 77% for larynx, and 72% for oropharynx primaries.[26] A subsequent phase III trial randomized 345 patients with cT2-T4 laryngeal SCC to ARCON versus accelerated RT.[27] Local tumor control did not differ between treatment arms, but 5-year regional control was significantly higher with ARCON compared to accelerated RT alone (93% vs 86%; $P = .04$). A subgroup analysis indicated that this beneficial effect of ARCON is limited to patients with tumors having a high hypoxic fraction.

Allosteric modifiers of hemoglobin structure have been identified that can shift the oxyhemoglobin dissociation curve to the right and increase O_2 delivery to hypoxic tissues.[28] One such compound, RSR13 (efaproxiral), has been shown to improve tumor oxygenation[29] and enhance the effectiveness of RT in preclinical models.[30] A phase III open-label trial of whole-brain RT and oxygen breathing with or without daily infusion of efaproxiral was conducted in 538 patients with brain metastases.[31] Fifty-four percent of patients had metastatic non–small cell lung cancer, and 20% had metastatic breast cancer. Overall, no improvement in survival was detected. A planned subset analysis suggested significant improvement in median survival in patients with breast cancer with sufficient efaproxiral levels in their erythrocytes.[32] However, the phase III ENRICH trial, which examined efaproxiral and supplemental oxygen with whole-brain RT (30 Gy in 10

fractions) in 368 patients with breast cancer with brain metastases, showed no significant difference in overall survival.[33]

Sensitization of Hypoxic Cells

Electron-affinity compounds can oxidize radiation-induced free radical damage in the cell to produce increased kill.[34] The use of these agents would be particularly attractive in the hypoxic tumor microenvironment, where low oxygen concentrations impair RT efficacy. The 2-nitroimidazoles are one such class of compounds that are metabolized into their active form under hypoxic conditions. Misonidazole, the prototype 2-nitroimidazole, was tested in two randomized trials. The Danish Head and Neck Cancer Study 2 (DAHANCA-2) performed a double-blind randomized trial evaluating the effect of misonidazole given in two drug schedules with split-course irradiation in the treatment of carcinoma of the larynx and pharynx.[35] Patients (n = 626) were stratified according to tumor site (larynx vs pharynx), nodal status, and institution. The total misonidazole dose was 11 g/m^2. Overall, the misonidazole group did not have significantly better local tumor control than the placebo group. Serious peripheral neuropathy, the dose-limiting toxicity of all nitroimidazole compounds, occurred in 26% of misonidazole-treated patients. The European Organisation for Research and Treatment of Cancer conducted a randomized study of conventional fractionation RT versus modified fractionation RT (three fractions per day) with or without misonidazole in 523 patients with advanced head and neck cancer. No differences were seen in treatment outcome.[36]

Etanidazole (SR2508) is a misonidazole analog with lower lipid solubility and less neurotoxicity in phase II studies in head and neck cancer.[37] A Radiation Therapy Oncology Group (RTOG) phase III study randomized 521 patients with stage III or IV head and neck cancer to receive conventionally fractionated (CF) irradiation with or without etanidazole 2 mg/m^2 delivered 3 times per week.[38] Of those on the etanidazole arm, 77% received at least 14 doses of the drug. No grade 3 or 4 central nervous system or peripheral neuropathy was observed. The 2-year actuarial local tumor control was 40% in each arm, and survival was 41% and 43% in the irradiation alone and irradiation plus etanidazole arms, respectively. A similar study of 374 patients performed in Europe showed

increased neurotoxicity and no improvement in outcomes in patients who received etanidazole.[39]

Nimorazole is a 5-nitroimidazole of the same structural class as metronidazole.[40] Its dose-limiting toxicity is nausea and vomiting; however, the drug can be administered with each radiation treatment. DAHANCA conducted a phase III trial of nimorazole (1.2 g/m^2 vs placebo) for SCC of the supraglottic larynx and pharynx.[41] There was a statistically significant improvement in locoregional tumor control (49% vs 33% at 5 years; P = .002), but not in survival, which is consistent with the DAHANCA misonidazole trial. The use of nimorazole administered 60 to 120 minutes prior to each radiation fraction has become the standard of care (SOC) for head and neck SCC in Denmark, but it has not been adopted in other countries. An international multicenter phase II randomized trial of nimorazole with accelerated RT for stage I to IV head and neck SCC (excluding nasopharynx and stage I to II larynx) failed to meet accrual goals, enrolling only 104 of a planned 600 patients.[42] Although premature closure resulted in this trial being underpowered, there was a trend toward reduced 18-month locoregional failure with nimorazole (33% vs 51% in control group, P = .1). The difference in overall death (19%; 95% CI, −3% to 42%; P = .1) also favored nimorazole but did not meet statistical significance. NIMRAD (NCT01950689) was a randomized, placebo-controlled phase III trial in the United Kingdom assessing nimorazole (1.2 g/m^2 daily prior to RT vs placebo) with a 6-week course of intensity-modulated radiation therapy (IMRT: 65 Gy in 30 fractions) for patients with locally advanced head and neck cancer not suitable for concurrent cetuximab or platinum chemotherapy.[43] In 338 patients with median follow-up of 3.1 years, there were no significant improvements in locoregional control or overall survival in the nimorazole group compared to placebo. Similarly, a subgroup of 139 patients with hypoxic tumors did not benefit significantly from the addition of nimorazole in terms of locoregional control (adjusted hazard ratio [HR] 0.72; 95% confidence interval [CI] 0.36-1.44; P = .35) or overall survival (adjusted HR 0.96; 0.53-1.72; P = .88). In addition, patients receiving nimorazole reported higher rates of acute nausea compared to the placebo group.[44]

Pharmacologic Targeting of Hypoxic Cells

Mitomycin C (MMC) is an alkylating agent metabolized in regions of low oxygen concentration and preferentially cytotoxic to hypoxic cells. MMC plays an integral role in conjunction with RT and 5-fluorouracil (5-FU) in the definitive nonsurgical management of anal SCC.[45] Yale University investigators examined the concurrent use of MMC in 195 patients with head and neck cancer treated on two randomized trials.[46] Their treatment program consisted of 68 Gy with or without MMC on days 1 and 43 of RT. Locoregional recurrence-free survival was improved with the addition of MMC from 54% to 76% ($P = .003$). Overall survival improved from 42% to 48%, but this was not statistically significant. The majority of patients in these trials received postoperative or preoperative irradiation. Only 74 (38%) received definitive primary RT, and the benefit from the addition of MMC in this subset is unclear.

A three-armed randomized trial conducted at the University of Vienna compared CF RT (2 Gy daily to 70 Gy) against continuous hyperfractionated accelerated RT with or without MMC (V-CHART + MMC and V-CHART, respectively).[47] RT was given as an initial 2.5 Gy fraction followed by 1.65 Gy twice a day to a total dose of 55.3 Gy in 17 days. MMC was given as a 20 mg/m^2 bolus on day 5 of RT. Of the 239 patients enrolled, 85% had T3 or T4 primaries and 79% had nodal involvement. Three-year actuarial locoregional control was 48% for V-CHART + MMC versus 32% for V-CHART and 31% for CF ($P = .05$ and .03, respectively). Overall survival was also significantly higher in the V-CHART + MMC arm at 41%, compared to 31% for V-CHART and 24% for CF ($P = .03$). The incidence of confluent mucositis was 90% in both experimental arms as compared with 33% in the CF arm. The median time to complete resolution of mucositis was 6 to 7 weeks in all three arms. Grade 3 or 4 hematologic toxicity, primarily thrombocytopenia, occurred in 18% of the V-CHART + MMC patients.

Porfiromycin, a derivative of MMC, provides greater differential cytotoxicity between hypoxic and oxygenated cells in vitro.[48] The Yale investigators also conducted a phase III study that compared patients treated with CF RT + MMC versus RT + porfiromycin.[49] Hematologic and nonhematologic toxicities were equivalent in the two treatment arms. With

a median follow-up >6 years, MMC was superior to porfiromycin with respect to 5-year local relapse-free survival (91.6% vs 72.7%; P = .01), locoregional relapse-free survival (82% vs 65.3%; P = .05), and disease-free survival (72.8% vs 52.9%; P = .03). There were no significant differences between the two arms with respect to overall survival (49% vs 54%) or distant metastasis- free survival (80% vs 76%). Their data supported the continued use of MMC as an adjunct to RT in advanced head and neck cancer; however, this regimen is no longer used on a routine basis.

Tirapazamine (also known as SR-4233; WIN 59075; 3-amino-1,2,4-benzotriazine 1,4-dioxide) is a bioreductive agent preferentially cytotoxic to hypoxic cells in vitro. Twenty-five to 200 times more drug is required to produce the same level of cell killing in aerobic compared to anaerobic conditions.[50,51] Under hypoxic conditions, a free radical one- electron reduction product rapidly forms and is believed to be the toxic species, causing oxidative damage to pyrimidines and inducing DNA strand breaks.[52] Analysis of DNA and chromosomal breaks following hypoxic exposure to tirapazamine suggests that DNA double-strand breaks are the primary lesions involved in cell death.

This bioreductive agent differs from oxygen-mimetic sensitizers, such as the nitroimidazoles, in that it is itself cytotoxic to hypoxic tissues. Therefore, unlike the oxygen-mimetic sensitizers, tirapazamine-mediated therapeutic enhancement occurs whether the drug is given before or after irradiation.[53,54] In fractionated RT of murine tumors, tirapazamine is as effective as, if not superior to, etanidazole.[55] The efficacy of this radiation modifier depends on the number of “effective doses” that can be administered during a course of RT and the presence of hypoxic tumor cells.[56] Tirapazamine can also enhance the cytotoxicity of cisplatin.[57]

Rischin et al. investigated the use of concurrent tirapazamine, cisplatin, and RT in advanced head and neck cancer in a series of trials. A phase I trial established the dosing schedule for tirapazamine given with RT and cisplatin.[58] A randomized phase II study compared RT with cisplatin/tirapazamine versus RT with cisplatin/5-FU and suggested a benefit in the tirapazamine treatment arm (3-year locoregional failure-free survival 84% vs 66%; P = .07).[59] Tumor hypoxia imaging was performed with 18-fluorodeoxyglucose-misonidazole positron emission tomography scanning in 45 patients in these studies.[60] Hypoxia was identified in primary

or nodal sites in 71% of these patients. Eight (62%) of 13 patients with hypoxic tumors who received cisplatin/5-FU experienced subsequent locoregional failure compared to only one (5%) of 19 patients with hypoxic tumors who received tirapazamine (HR = 15; P = .001). Only one of 10 patients with nonhypoxic tumors who received cisplatin/5-FU had a locoregional failure. These findings strongly suggested that the benefit of tirapazamine resulted from improved treatment efficacy against tumor hypoxia.

Two phase III trials were initiated to validate the use of tirapazamine in head and neck cancer. The HeadSTART study enrolled 861 patients and compared standard fractionation RT (70 Gy) with concurrent cisplatin/tirapazamine versus concurrent cisplatin alone.[61] The primary end point was overall survival, with 2-year rates of 65.7% in the cisplatin-alone arm and 66.2% in the cisplatin/tirapazamine cohort. No differences were seen in failure-free survival, time to locoregional failure, or quality of life. Of note, patients in this study were not selected based on the presence of tumor hypoxia. Moreover, 12% had major RT planning deficiencies, with those patients having significantly worse locoregional control and overall survival compared to those in protocol compliance.[62] A second trial with a planned enrollment of 550 patients was closed prior to completion of accrual because of an excess number of early deaths in the cisplatin/tirapazamine arm.[63]

Hyperthermia

Hyperthermia (HT) involves elevation of tissue temperature, typically 40 °C to 45 °C, for a therapeutic effect.[64] Although HT monotherapy can result in some cells being killed, it has been more widely used for its radiosensitizing effect in tumors. Physiologic changes induced by HT include increased perfusion, causing tissue reoxygenation and altered metabolism associated with reduced oxygen consumption. This improved oxygenation confers increased tumor radiation sensitivity and is correlated with pathologic complete response in patients with soft tissue sarcoma undergoing preoperative irradiation and HT.[65] In addition, cells are particularly sensitive to HT under conditions associated with radioresistance, including hypoxia, low pH, and the presence in S phase of

the cell cycle. Heat may also interfere with repair of radiation-induced DNA damage.[66,67] The thermal enhancement ratio (TER) quantifies the synergistic effect of HT and RT. TER is defined as the ratio of RT dose without HT to the isoeffective RT dose with HT:TER = RT dose without HT/RT dose for equivalent effect with HT. TER is >1 for most tumor types when HT is administered within 2 hours of RT.[68]

Several randomized clinical trials have assessed RT with HT compared to RT alone. Results have been mixed, but a meta-analysis suggests overall improved tumor response with combined RT and HT for multiple tumor types.[68,69] Combined RT and HT have been most widely studied for head and neck cancer and cervical cancer, largely because of the association between tumor hypoxia and poor clinical outcomes in these diseases as discussed above. The Dutch Deep Hyperthermia group performed the largest randomized controlled trial comparing RT alone to RT with HT in 358 patients with locally advanced bladder, cervical, or rectal cancer. HT was administered once weekly within 1 to 4 hours of RT for five total treatments. Complete response rates were significantly higher with RT and HT compared to RT alone (55% vs 39%; $P < .001$), and local control duration was longer with combined therapy. On multivariate analysis adjusting for age, tumor site, and tumor size/stage, RT combined with HT was also associated with reduced death (relative HR, 0.74; 95% CI, 0.57-0.97; $P = .03$). Acute and late radiation toxicity did not differ by treatment group.[70] Although results with combined HT and RT have been promising, enthusiasm for HT has waned due in large part to technical challenges in uniformly heating tumors, particularly at deep-seated locations.[71]

Chemotherapy

Chemotherapeutic agents are often utilized in conjunction with RT for their radiosensitizing effect.[72,73] Concurrent chemoradiation with platinum agents, particularly cisplatin, improves survival in numerous malignancies, including head and neck cancer,[74,75] cervical cancer,[76,77] and lung cancer.[78] Multiple potential mechanisms for platinum-induced radiosensitization have been proposed, including blocking DNA repair and inducing cell cycle arrest.[72,79] Several clinical trials are investigating the addition of new agents to cisplatin-based chemoradiation. For example, the ribonucleotide

reductase inhibitor triapine showed promise in a phase II clinical trial for cervical cancer,[80] and a randomized phase III trial is ongoing (NCT02466971). Taxanes are also widely employed with RT for the treatment of head and neck cancer, lung cancer, and esophageal cancer. These drugs facilitate radiation-induced cell killing by synchronizing cell cycle and causing cell cycle arrest in the radiosensitive G2/M phase.[81-83] Fluoropyrimidines such as 5-FU are commonly administered concurrently with RT for gastrointestinal malignancies because of their radiosensitizing effect. Slowed repair of radiation-induced double-strand DNA breaks and alteration of cell cycle progression by fluoropyrimidines likely result in radiosensitization.[84] Although mechanistic understanding of the interactions between RT and chemotherapy remains poorly understood, combined chemoradiation has dramatically improved outcomes for multiple malignancies.[74]

Biologic Modifiers of Radiation Response

Overexpression of the epidermal growth factor receptor 1 (EGFR-1) is associated with adverse outcomes in head and neck SCC.[85] Cetuximab (C225) is a chimeric monoclonal antibody to EGFR. Preclinical studies have demonstrated that cetuximab sensitizes cells to the cytotoxic effects of ionizing irradiation.[86-88] An open-label phase III trial compared outcomes for RT alone versus RT with weekly cetuximab after a loading dose.[89] Most patients received accelerated fractionation with concomitant boost, although hyperfractionation and standard fractionation schemes were also permitted. Oral cavity primary tumors were ineligible for enrollment. Two-year locoregional control was 56% with RT and cetuximab versus 48% with RT alone ($P = .02$). The incidence of distant metastatic recurrence was the same in both treatment arms. The initial survival advantage seen with the addition of cetuximab to RT has persisted, with updated 5-year overall survival rates of 45.6% versus 36.4% ($P = .018$).[90]

This trial provided an important proof of principle that adding a biologically targeted agent to a physically targeted modality can improve therapeutic outcome and that enhanced locoregional control can lead to enhanced survival. However, one-third of enrolled patients had stage III disease and thus had less advanced disease with more favorable prognoses

than a significant proportion of patients who typically undergo chemoradiotherapy (CRT). A more favorable prognosis and improved treatment response has also been seen in patients with oropharyngeal SCC associated with the human papillomavirus (HPV).[91] Whether RT with cetuximab is as effective or less toxic than RT with cisplatin in this select population was recently evaluated in the phase III RTOG 1016 study and De-ESCALaTE trial. With a median follow-up of 4.5 years for RTOG 1016 (NCT01302834), 5-year overall survival was 77.9% for cetuximab and 84.5% for cisplatin. This did not meet prespecified noninferiority criteria. In addition, 5-year progression-free survival was significantly lower in the cetuximab group compared to cisplatin in the cisplatin group (67.3% vs 78.4%; P = .0002). Acute and late toxicities were similar in both groups. The authors concluded that concurrent cisplatin with RT is the SOC for patients with HPV-positive oropharyngeal carcinoma without contraindications to cisplatin.[92] Similarly, concurrent cetuximab was inferior to cisplatin with RT for HPV-related oropharyngeal SCC in the De-ESCALaTE trial (NCT01874171). The 2-year overall survival and recurrence rates were significantly worse in the cetuximab group (P = .0001 and P = .0007, respectively), and toxicity rates were similar for both groups.[93] A phase II Italian trial comparing cetuximab to weekly cisplatin (40 mg/m^2) for stages III to IVB head and neck SCC was closed early because of slow accrual (n = 70 of planned 130 patients). Unlike the other trials, serious adverse events were more common among patients receiving cetuximab compared to cisplatin (19% vs 3%, P = .044). Two-year overall survival rates were similar in both arms (68% for cetuximab and 78% for cisplatin).[94]

A separate phase III study, RTOG 0522, randomized patients with locally advanced head and neck cancer to receive RT and concurrent cisplatin with or without cetuximab.[95] Treatment intensification with the addition of cetuximab to CRT did not improve 2-year progression-free or overall survival. Patients with p16-positive oropharyngeal cancer had better progression-free and overall survival than those with p16-negative oropharyngeal cancer. No significant interaction was present between p16 status and treatment, although there was a trend toward worse overall survival for p16- positive patients receiving cetuximab (HR 1.42, P = .13). Toxicity was more pronounced in patients who received cisplatin and

cetuximab. Still, EGFR inhibition remains a very active area of investigation in head and neck cancer. Agents currently in clinical trials include fully humanized monoclonal antibodies and orally administered small molecule inhibitors of the tyrosine kinase domains of the EGFR family of receptors.

A relatively new drug class with radiosensitizing potential is second mitochondria-derived activator of caspase (SMAC) mimetics, which trigger apoptosis and reduce prosurvival signaling by inhibiting the activity of proteins in the inhibitor of apoptosis family. Circumventing apoptosis is a key mechanism for causing radioresistance, particularly in glioblastoma multiforme (GBM).[96] In a preclinical study utilizing two heterotopic xenograft GBM models (U-251 and U-87) and an orthotopic intracranial xenograft model (U-251), the SMAC mimetic birinapant combined with RT significant delayed tumor growth compared to RT alone (P = .01).[97] Currently, there is an active phase I clinical trial combining birinapant with intensity- modulated reirradiation therapy in patients with locally recurrent head and neck SCC (NCT02567422). Study completion is anticipated in July 2024.

Targeting DNA damage response pathways is another approach to radiosensitizing tumors that is under active investigation. RT combined with inhibitors of DNA damage sensors, such as ataxia-telangiectasia mutated (ATM) or ATM- and rad3-related (ATR), forces cells to replicate with unrepaired DNA damage, eventually culminating in cell death. Preclinically, increased radiosensitivity with ATR inhibitors has been reported in hepatocellular carcinoma,[98] colorectal cancer,[99,100] head and neck SCC,[101] and pancreatic cancer.[102] Most ongoing clinical trials evaluating RT combinations with ATR inhibitors are focused on evaluating safety and determining the maximum tolerated dose. In a phase I dose-escalation trial, the ATR inhibitor berzosertib (M6620) was combined with chemoradiation for esophageal cancer (NCT03641547). Initial results reported no dose-limiting toxicities when combined with RT (35 Gy/15 fractions in 3 weeks).[103] A phase I trial evaluating berzosertib with weekly cisplatin and RT for locally advanced head and neck SCC was initiated in 2016, with anticipated completion in late 2023 (NCT02567422). Another ongoing phase I trial is evaluating the ATR inhibitor elimusertib (BAY 1895344) with stereotactic body radiation therapy (SBRT) and pembrolizumab in

patients with recurrent or metachronous primary head and neck SCC within a previously irradiated field (NCT04576091).

Nanoparticles

Nanoparticles are emerging as a promising method for enhancing radiosensitivity. Because radiation-mediated damage is dependent on the atomic number (Z) of the target, higher Z materials generally correlate with increased radiobiologic effects at megavoltage energies. Nanoparticle technology facilitates the accumulation of high-Z atoms within a solid tumor, increasing direct and indirect DNA damage. NBTXR3, a hafnium oxide (HfO_2, Z = 72) nanoparticle, was tested in this capacity in a phase II/III randomized trial of patients undergoing preoperative RT for locally advanced soft tissue sarcoma (NCT02379845). One hundred and eighty patients were randomized to receive RT + NBTXR3 or RT alone. In both groups, 50 Gy of external beam RT was delivered over 25 fractions. In the RT + NBTXR3 group, NBTXR3 (53.3 g/L) was delivered intratumorally pre-RT. In the RT + NBTXR3 group, 16% of patients demonstrated a pathologic complete response compared to 8% in the RT group (P = .044). While there were no treatment-related deaths, grade 3 to 4 adverse events were noted, with the most common being postoperative wound complications (9% in both groups).[104] NBTXR3 was also studied in a phase I clinical trial for hepatocellular carcinoma (NCT02721056). No grade 4 to 5 adverse events were observed, and efficacy appears promising with five complete responses, five partial responses, one patient with stable disease, and two nonevaluable patients.[105] There are additional active clinical trials investigating NBTXR3 with RT in pancreatic cancer (NCT04484909), inoperable recurrent non–small cell lung cancer (NCT04505267), recurrent and metastatic head and neck SCC (NCT04862455), esophageal cancer (NCT04615013), and locally advanced SCC of the oral cavity or oropharynx (NCT01946867). Combinations with RT, NBTXR3, and immunotherapies are also gaining interest.

CHEMICAL RADIOPROTECTION

The protection of normal tissues from the deleterious effects of radiation is a critical component in the development of a comprehensive treatment plan. Strategies for accomplishing this aim include the physical manipulation of the beam, modification of the fractionation schedule, and pharmacologic manipulation of the radiation response. Physical radiation protection rests on the principle of exclusion of normal tissue from the high-dose region and may be accomplished by contouring the shape of the radiation beam, the use of multiple treatment fields, the use of different beam energies, modulation of the dose delivery from each beam with IMRT, and utilizing particle therapy (eg, proton or carbon ion therapy). Modified fractionation typically uses multiple fractions of RT per day as opposed to the conventional once-daily paradigm to exploit the differing radiation repair capabilities of normal tissues as opposed to tumors. Physical modification of the treatment beam and altered fractionation are discussed elsewhere.

Protection

Pharmacologic radioprotection itself can be classified into three categories: protection, mitigation, and treatment. The direct cytotoxicity of ionizing irradiation results from the generation of free radicals that cause DNA strand breaks and lead to mitotic cell death. Amifostine (WR2721; Ethyol, Medimmune, Inc, Gaithersburg, MD) is the prototype pharmacologic radioprotector that functions via free radical scavenging. Amifostine is a thiol-containing prodrug that preferentially accumulates in the kidneys and salivary glands where it is metabolized to its active moiety, WR1065.[106]

An open-label phase III randomized trial was conducted from 1995 to 1997 to assess the ability of this drug to reduce the incidence of grade 2 or higher acute and late xerostomia and grade 3 or higher acute mucositis.[107] Patients enrolled in this trial received curative intent or adjuvant postoperative irradiation without concurrent chemotherapy. All treatment was delivered with conventional once-daily fractionation of 1.8 to 2.0 Gy. Definitive RT consisted of 66 to 70 Gy total dose, and postoperative irradiation was delivered at 50 to 60 Gy total dose depending on the patient's assessed risk for recurrence. IMRT was not utilized, and inclusion of >75% of both parotid glands was required for inclusion in the study. Patients randomized to receive amifostine received a daily dose of 200

mg/m^2 intravenously for 15 to 30 minutes every day prior to each fraction of RT.

Three hundred and three patients were enrolled in this trial, and the minimum follow-up was 2 years. Amifostine did not reduce the incidence of grade 3 mucositis but did significantly reduce the incidence of acute and long-term grade >2 xerostomia (34% in the amifostine group vs 56% for patients in the control arm; $P = .002$). Unstimulated saliva production >0.1 g was also more common in patients who had received amifostine (72% vs 49%; $P = .003$). Two years post-RT, amifostine use was still associated with a significantly lower incidence of xerostomia, although the magnitude of benefit was lower (19% vs 36%; $P = .05$). The lower incidences in both groups of patients also suggest some late recovery of salivary function. Reinforcing this idea of late recovery of salivary function is the fact that the percentage of patients in the control group who could exceed the >0.1 g of unstimulated saliva threshold had increased to 57%.[108]

Severe toxicity (CTCAE grade >3) attributable to amifostine occurred in <10% of patients in this trial and consisted of nausea and vomiting and transient hypotension. Nearly two-thirds of the patients had less severe grades of these side effects. Drug-related toxicity caused approximately 20% of patients to discontinue amifostine prior to completing RT. Subcutaneous administration of the drug causes less nausea, vomiting, and hypotension than intravenous dosing but is associated with increased risk of cutaneous toxicity, leading to 15% to 20% of patients discontinuing amifostine prior to RT completion.[109] The incidence of severe cutaneous toxicity, including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis, is 6 to 9 in 100,000.[110]

A criticism of this trial is that it was underpowered to detect a very small compromise in survival caused by amifostine (tumor protection).[111] This argument is correct but overlooks the reality that absolute refutation of a small compromise of antitumor efficacy attributable to amifostine would have required an equivalence trial. Demonstration that amifostine reduced survival from a hypothetical 45% to 40% ($P = .05$; 80% power) would have necessitated >1,200 patients per study arm.[112] Such large studies have rarely been performed in head and neck cancer, because patient resources are too scarce. The largest randomized head and neck trial ever conducted, RTOG 9003, required 8 years to enroll 1,113 patients into four treatment arms.[113] A

meta-analysis of amifostine that used individual patient data from 12 trials and 1,119 patients examined the impact of this drug on survival in patients treated with RT or CRT. The majority of patients (65%) had head and neck cancer, with 33% lung cancers and 2% pelvic carcinomas. The HR of death was 0.98 (95% CI, 0.84-1.14; $P = .78$).[114]

The potential of amifostine as a protector against radiation- induced esophagitis during the treatment of non–small cell lung cancer was studied in a randomized trial conducted by the RTOG.[115,116] No reduction in the incidence of grade 3 esophagitis was observed, although less swallowing dysfunction occurred in the patients who received amifostine. Part of the explanation for this absence may be attributable to the study design, which utilized a hyperfractionated radiation schedule 5 days per week (69.6 Gy total dose) and concurrent carboplatin/paclitaxel. Amifostine 500 mg intravenous was delivered 4 days per week prior to the afternoon fraction only. Moreover, 28% of the patients did not complete the full course of the drug either because of toxicity or refusal. Consequently, approximately 50% of the RT was delivered in the absence of the radioprotective drug among patients randomized to receive amifostine. Preclinical studies of amifostine delivered daily in conjunction with fractionated lung and esophageal irradiation have demonstrated morphologic and immunohistochemical evidence of radioprotection.[117-119]

Amifostine is approved by the U.S. Food and Drug Administration (FDA) for xerostomia in the setting of RT alone. The majority of both curative-intent and adjuvant RT for head and neck cancers, with large target volumes that put the parotid glands at risk, are now delivered in conjunction with concurrent chemotherapy. Small phase II and III trials suggest that amifostine has a cytoprotective benefit in the chemoradiation setting, but level 1 evidence is lacking.[120,121] Moreover, the widespread adoption of IMRT with its ability to spare one or both parotid glands and reduce the incidence of xerostomia compared to conventional, non-IMRT techniques has further reduced the role for this drug.[122] The utility of amifostine in conjunction with IMRT has been investigated in small settings with inconclusive results.[123]

Superoxide dismutase (SOD) mimetics represent a new class of radioprotectors that are currently under active investigation. These drugs convert the radiation-induced toxic reactive oxygen species superoxide

anion (O^{-}_{2}) to hydrogen peroxide and molecular oxygen to mitigate radiation-induced toxicity. Similarly, these drugs interact with other potentially damaging reactive oxygen and reactive nitrogen species. A phase Ib/IIa clinical trial of the SOD mimetic avasopasem (GC4419) in patients with oral cavity or oropharyngeal cancer showed delayed development of oral mucositis, as well as reduced severity, incidence, and duration.[124] In a subsequent double-blind phase IIb trial, patients receiving an intravenous infusion of avasopasem prior to each fraction of RT for locally advanced oral cavity or oropharyngeal cancer exhibited significantly reduced severe oral mucositis incidence and severity compared to patients receiving placebo.[125] At 2 years post-treatment, there was no significant difference in overall survival, progression-free survival, locoregional control, or distant metastasis-free survival.[125] In the randomized phase III ROMAN trial, patients with locally advanced head and neck cancer receiving avasopasem prior to RT had a 10% absolute decrease in grades 3 to 4 mucositis compared to placebo (64% vs 54%, $P = .045$) and reduced median days of severe mucositis (18 vs 8 days, $P = .002$).[126] However, the FDA rejected the New Drug Application for avasopasem in 2023, citing insufficient evidence of its efficacy in reducing radiation-induced severe oral mucositis in patients undergoing RT for head and neck cancer. The recently completed single-arm phase 2 open-label study of avasopasem prior to RT in patients undergoing chemoradiation for nonmetastatic lung cancer showed low rates of grade 3 esophagitis in an unscheduled interim analysis, but no follow-up studies in lung cancer are ongoing.[127] Preliminary results from a randomized, double-blinded, placebo-controlled trial in locally advanced pancreatic cancer showed improved locoregional tumor control, progression-free survival, and overall survival for patients receiving avasopasem compared to placebo prior to RT with a 5- fraction SBRT regimen.[128]

Another SOD mimetic, Mn(III)meso-tetrakis (*N*-*n*-butoxyethylpyridinium-2-yl)porphyrin (MnBuOE), has been shown to mitigate oral mucositis, xerostomia, and salivary gland fibrosis in preclinical models.[129,130] Mice treated subcutaneously with MnBuOE twice daily or 3 times per week for 1 week prior to single-fraction RT to the oral cavity and ventral neck, followed by continued MnBuOE dosing after RT,

exhibited significantly decreased incidence and severity of oral mucositis. This was demonstrated by fluorescence molecular tomography assessing cathepsin activity as a marker of mucositis.[90] Stimulated saliva production was also significantly greater in mice treated with MnBuOE compared to saline control at 2 to 4 and 11 weeks post-RT. At 6 and 12 weeks post-RT, significantly decreased salivary gland fibrosis was observed in MnBuOE-treated mice.[129,130] Importantly, MnBuOE does not appear to protect tumor cells from RT. In FaDu flank models of head and neck cancer, MnBuOE with RT resulted in further slowing of tumor growth[129] or no change in radiation-induced tumor growth delay.[130] Analogs of MnBuOE have also been shown to reduce radiation-induced erectile dysfunction[131] and pulmonary injury in mice.[132-134] A recent phase I/II single-arm clinical trial investigated the effect of MnBuOE (also known as BMX-001) on mucositis and xerostomia in 29 patients with locally advanced head and neck cancer (NCT02990468). Early results indicate that BMX-001 is well tolerated, with only three serious adverse events (hypotension, fever with pancytopenia, and hyponatremia). In addition, severe oral mucositis had resolved by 5 weeks postchemoradiation in 83.3% of patients. Grade >2 xerostomia incidence was 18% at 1 month postchemoradiation and decreased to 8% and 9% at 6 and 12 months postchemoradiation, respectively.[135] Based on these promising results, a placebo-controlled randomized phase II trial in patients undergoing definitive chemoradiation for head and neck cancer is in development. An ongoing phase I/II trial is also assessing MnBuOE in patients with high-grade glioma receiving concurrent RT and temozolomide to determine the maximum tolerated dose and assess median overall survival compared to historical controls (NCT02655601).

Mitigation

Administration of compounds that mitigate damage caused by previous radiation exposure constitutes a different approach to the management of radiation-induced toxicity. This strategy contrasts to the classic free radical scavenging radioprotective mechanism of drugs, such as amifostine. The leading drug under development in this category is palifermin. Palifermin is a recombinant human keratinocyte growth factor that belongs to the

fibroblast growth factor family of cytokines. It stimulates cellular proliferation and differentiation in a variety of epithelial tissues, including mucosa throughout the alimentary tract, salivary glands, and type II pneumocytes. Palifermin also regulates intrinsic glutathione-mediated cytoprotective mechanisms. Administration of palifermin in preclinical rodent models leads to a significant thickening of oral tongue mucosa.[136] Preclinical studies of fractionated RT have revealed that the administration of palifermin leads to increase in the dose of RT necessary to induce ulcerative mucositis and to reduction in the duration of this ulceration when it does occur.[137,138] Parotid gland production of saliva is also preserved when palifermin is administered in the setting of RT in preclinical systems. Preclinical evaluation of palifermin in a rodent model has also demonstrated that administration of a single dose of this drug after completion of a course of fractionated thoracic irradiation significantly reduces the severity and duration of pneumonitis and the severity of pulmonary fibrosis.[139]

The ability of palifermin to reduce mucositis in a clinical setting has been tested in a pivotal phase III double-blind placebo- controlled trial of patients with non-Hodgkin lymphoma undergoing bone marrow transplantation.[140] The bone marrow ablative regimen consisted of 12 Gy of total body irradiation (TBI) given at 1.5 Gy twice a day. Thereafter, etoposide (VP-16) and cyclophosphamide were administered. Palifermin was delivered prior to the initiation of TBI and again after the completion of chemotherapy, which also corresponded to 5 days after the completion of TBI. The dose schedule of palifermin was 60 μg/kg/d 3 times for both administrations. This trial enrolled 212 patients who were equally divided between the placebo and palifermin arms. The World Health Organization (WHO) scoring system was used. The incidence of grade 3 or 4 mucositis approached 90% in the placebo arm as opposed to approximately 60% in the palifermin arm. For those patients who developed this level of toxicity, the duration was significantly reduced from 10.4 days in the placebo arm to 3.7 days in the palifermin arm ($P < .001$). Grade 3 mucositis developed in 62% of the placebo arm patients and only 20% of the palifermin arm patients ($P < .001$). The mean duration of grade 4 mucositis was reduced from 6.2 to 3.3 days with the use of this drug ($P < .001$).

A phase II study examined the safety and efficacy of palifermin in patients with locally advanced head and neck cancer.[141] Patients were randomized 2 to 1 between palifermin and placebo. Palifermin was delivered at a dose of 60 μg/kg. Institutions had the discretion to deliver RT via conventional once-daily 2-Gy fractions or with an accelerated hyperfractionated regimen of 1.25 Gy twice daily. One hundred patients were enrolled, of whom 34 received accelerated hyperfractionation and the remainder received standard fractionation. The first dose was delivered prior to the initiation of CRT and then every Friday afternoon after the last fraction of radiation. Two additional doses of palifermin were given 1 and 2 weeks after the completion of RT for a total of 10 doses of the drug. Palifermin did not reduce the incidence or duration of mucosal or salivary gland toxicity. The subset of patients receiving hyperfractionated radiation, however, showed significant improvements in the duration and severity of mucositis (Figure 29.2). They also had improved swallowing function and less salivary gland toxicity relative to patients who received placebo.

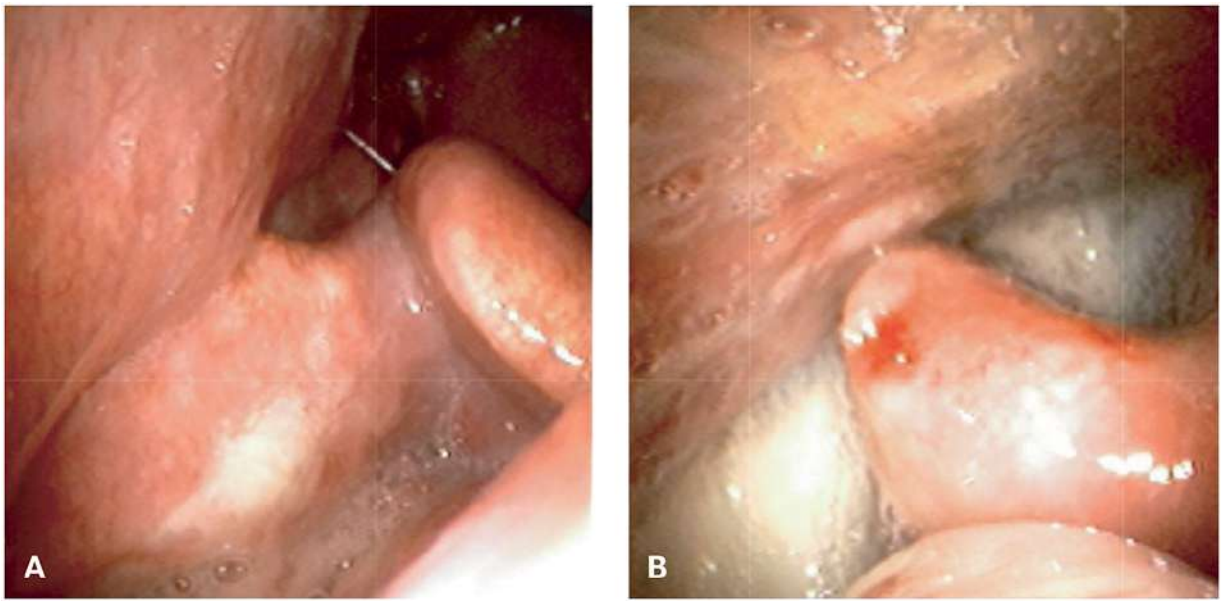

FIGURE 29.2 Confluent mucositis induced by concurrent chemoradiation in the base of tongue and supraglottic larynx regions. A. Normal mucosa prior to the initiation of treatment. B. The pseudomembranous exudate, hemorrhage, and edema that are characteristic of this confluent mucositis.

A subsequent randomized phase III study examined a higher dose of palifermin at 180 μg/kg to reduce oral mucositis in 188 patients with locally advanced head and neck cancer treated with CRT.[142] Palifermin was administered prior to starting CRT and once weekly for 7 weeks. The incidence of severe oral mucositis, the primary endpoint, was significantly lower in the palifermin arm compared to placebo (54% vs 69%; $P = .041$). Both overall survival and progression-free survival were similar as well. However, no statistically significant differences emerged in secondary efficacy end points, such as narcotic doses and duration of treatment breaks. A similar randomized phase III study examined palifermin at 120 μg/kg in 186 patients with head and neck cancer treated with postoperative CRT.[143] Palifermin again reduced the time to development and duration of WHO grade 3 or 4 oral mucositis without differences in patient-reported pain scores, treatment breaks, or efficacy. The precise role of palifermin in the management of head and neck cancer remains to be established.

SUMMARY

The chemical modification of radiation response for both enhancing treatment efficacy and reducing therapy-induced toxicity remains an area of active investigation. Promising candidates identified in preclinical and early-phase trials have been less successful in randomized phase III settings. Attempts to improve treatment efficacy by augmenting tumor oxygen delivery have a mixed record of success. The use of drugs that are preferentially cytotoxic to hypoxic cells holds promise, although improved tools to identify those patients most likely to benefit from targeted therapy are needed. Proof of principle for chemical radioprotection has been established in salivary glands but not elsewhere and is associated with significant toxicity. Growth factor utilization appears to protect against treatment-induced mucositis, but not to an extent to change clinical practice. As RT regimens evolve and new technological advances continue to improve treatment delivery, investigators will continue to seek agents that optimize the TR.

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CHAPTER 30

Oncologic Imaging and Oncologic Anatomy

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This chapter addresses two topics central to the management of patients with cancer: oncologic anatomy and oncologic imaging. Although these topics are relevant for all specialties involved in the treatment of cancer, they are particularly germane for radiation oncologists. A sound understanding of anatomy, especially pertaining to malignant processes, facilitates interpretation of imaging studies. Likewise, understanding the advantages and limitations of individual imaging modalities assists in defining rational clinical target volumes (CTVs) that maximize the therapeutic ratio.

There has been great progress in the past decade with the development of consensus guidelines for target and critical organ delineation in most disease sites (Table 30.1). While some of the volume definitions may be conceived primarily based on expert opinion, they facilitate the rational demarcation of nodal stations at risk, reporting of patterns of spread and failure, and communication with surgical colleagues. These guidelines and atlases should be seen as living works, refined and revised on a regular basis. These should complement, and not replace, the judgment of the treating physician, since anatomic variations, prior surgery, and unusual patterns of disease spread can invalidate the applicability of an atlas to an individual patient.

TABLE 30.1 ATLASES AND GUIDELINES AVAILABLE FOR TARGET AND NORMAL TISSUE DELINEATION

Atlas	Associated Group	Availability
CNS/Brain		
Hippocampal Sparing	NRG	https://www.nrgoncology.org/ciro-brain

Atlas	Associated Group	Availability
Head and Neck		
Cranial Nerves Atlas	NRG	https://www.nrgoncology.org/ciro-head-and-neck
Nodal Regions in the N0 Neck—2013 Update	NRG	https://www.nrgoncology.org/ciro-head-and-neck
Brachial Plexus Contouring Atlas	NRG	https://www.nrgoncology.org/ciro-head-and-neck
Breast		
Breast Cancer Atlas	NRG	https://www.nrgoncology.org/ciro-breast
Lung		
RTOG 1106 OAR (Lung)	NRG	https://www.nrgoncology.org/ciro-lung
RTOG 1106 Target Atlas (Lung)	NRG	https://www.nrgoncology.org/ciro-lung
Mesothelioma Contouring Atlas	NRG	https://www.nrgoncology.org/ciro-lung
GI		
Upper Abdominal Normal Organ Contouring Consensus Guidelines	NRG	https://www.nrgoncology.org/ciro-gastrointestinal
Liver Atlas	NRG	https://www.nrgoncology.org/ciro-gastrointestinal
Pancreas Atlas	NRG	https://www.nrgoncology.org/ciro-gastrointestinal
Esophageal and Gastroesophageal Junction Cancer	Ad hoc group	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4481325/
Anorectal	NRG	https://www.nrgoncology.org/ciro-gastrointestinal
GYN		
Female RTOG Normal Pelvis Atlas	NRG	https://www.nrgoncology.org/ciro-gynecologic
GYN (postop Cervix and Uterine)	NRG	https://www.nrgoncology.org/ciro-gynecologic

Atlas	Associated Group	Availability
Intact Cervix	NRG	https://www.nrgoncology.org/ciro-gynecologic
Vulva	NRG	https://www.nrgoncology.org/ciro-gynecologic
MRI contours for Image Guided Brachytherapy	GEC-ESTRO	https://www.thegreenjournal.com/article/S0167-8140(04)00579-1/abstract
GU		
Male RTOG Normal Pelvis Atlas	NRG	https://www.nrgoncology.org/ciro-genitourinary
Postop Positive Apex Margins	NRG	https://www.nrgoncology.org/ciro-genitourinary
Postop Positive Seminal Vesicle	NRG	https://www.nrgoncology.org/ciro-genitourinary
Pelvic Lymph Node Volumes for Prostate Cancer Atlas	RMH and NRG	https://www.redjournal.org/article/S0360-3016(15)00331-4/abstract
Bladder	NRG	https://www.nrgoncology.org/ciro-genitourinary
Sarcoma		
RTOG Extremity Soft Tissue Sarcoma Atlas	NRG	https://www.nrgoncology.org/ciro-other

CNS, central nervous system; GI, gastrointestinal; GU, genitourinary; GYN, gynecology; MRI, magnetic resonance imaging; RTOG, Radiation Therapy Oncology Group.

IMAGING MODALITIES

Radiography

In conventional radiography, a two-dimensional grayscale image is produced from the differential attenuation of x-rays passing through soft tissues and osseous structures of varying density. Tissues that are very dense, such as bone, will attenuate more x-rays than tissues that are less dense, such as lung. The loss of source x-rays identified by the x-ray detector is directly proportional to tissue density, resulting in a processed image where highly dense objects appear bright (radiopaque) and less dense objects are dark (radiolucent). Radiographs are, therefore, best suited to

detect pathology when a lesion differs greatly in density from adjacent structures, such as a soft tissue mass surrounded by aerated lung or a lytic lesion surrounded by dense bone. Radiographs have excellent spatial resolution, however, and are suboptimal when there are only subtle differences in tissue density, and even large lesions may not be distinguished if they are of similar density to surrounding structures. Further, determining spatial relationships to adjacent structures is limited due to the two-dimensional geometry. Radiographs may help identify an abnormality, but additional imaging modalities are often required for further characterization.

Cross-Sectional Imaging

Computed Tomography

Computed tomography (CT) generates cross-sectional images from the transmission of radiation through tissue. A patient is positioned on the scanner table that moves through a gantry housing an x-ray generator opposite multiple rows of detectors, hence the term *multidetector CT* (MDCT). As the gantry rotates, the detectors measure x-ray transmission through the rotation, or slice. The patient is moved through the scanner as the gantry rotates, resulting in a helical or spiral course at very thin-slice thickness, typically 0.625 mm. The spatial and temporal data from multiple projections are then processed by a Fourier transform mechanism generating two-dimensional axial images. The thin-slice volume data set is isotropic, meaning that images can be reconstructed in orthogonal and oblique planes without a loss in image quality.

CT images are displayed within a matrix composed of voxels, each representing a volume of tissue density. These densities are quantified by a linear attenuation value called a Hounsfield unit (HU). Densities are standardized into HU, which are obtained by a linear transformation of the measured attenuation coefficient. By convention, air is the least dense material with an HU value of −1,000, while water has an HU value of 0. Soft tissues have a range of attenuation with typical HU values as follows: fat (−120 HU), blood (30 HU), muscle (40 HU), and bone (>300 HU). HU analysis is more accurate than visual assessment of tissue composition and is particularly useful in characterizing enhancement of tissues following intravascular contrast administration.

Both intravenous (IV) and oral contrast agents may be utilized to improve spatial resolution. Oral contrast agents are routinely used for abdominal and pelvic imaging to distinguish bowel from adjacent organs, lymph nodes, and tumors. The use of an intravascular contrast agent during CT depends on the study indication, target organ, and patient status. IV contrast agents contain variable concentrations of iodinated compounds that attenuate x-rays, improving the distinction of vascular structures. Administration of IV contrast media is required for thorough assessment of vessels (eg, aorta, pulmonary arteries) and solid organs (eg, liver, kidneys) and characterization of lesion vascularity. Contrast-enhanced CT is often necessary to detect solid organ metastases (eg, liver, adrenal gland, brain). Contrast is usually not necessary for routine pulmonary imaging due to the inherent contrast of solid lesions in a background of aerated lung, although it does improve the characterization of hilar lymph nodes.

Given that the administration of contrast media can alter tissue attenuation, the HU value of a lesion or tissue may differ depending on whether the study was performed with or without contrast and based on the timing of image acquisition (eg, arterial vs portal venous phase). HUs are used during radiation treatment planning dose calculations; therefore, both IV and bowel contrast can affect these calculations. If indicated, the HU within a structure enhanced by contrast (eg, the bladder when planning for prostate cancer treatment) can be set to an alternate value prior to dose calculations. A similar phenomenon often occurs when materials with a high atomic number are within the scanned volume. These materials (eg, dental fillings, hip prostheses) can cause artifacts that can make it challenging to accurately segment the image and affect dose calculations. The latter can also be corrected by setting the HU within the affected area to the desired value. Metal artifact reduction algorithms have also been developed to improve image quality and recover anatomic information otherwise obscured.

IV contrast agents are excreted through the kidneys and are not typically administered to patients with impaired renal function (glomerular filtration rate [GFR] <60, creatine [Cr] <2.0, though institutional policies vary) unless on dialysis or emergently necessary. IV contrast media should also not be given to patients with a known contrast allergy resulting in anaphylaxis or laryngeal edema. Minor reactions, such as pruritus, are not absolute

contraindications, and IV contrast may be administered following a proper steroid pretreatment protocol. Alternative imaging modalities should be considered if a contrast-enhanced study is required in the setting of a severe contrast allergy. An allergy to shellfish is not considered a contraindication to iodinated contrast administration.

CT utilizes ionizing radiation, and although dose modulation and optimal scanning parameters can significantly reduce patient radiation exposure, the cumulative effects of CT radiation may be of clinical concern. Photon-counting CT, which can quantify single-photon incident on detectors, may further reduce patient exposure and image noise, improve image resolution, and allow for novel spectral applications.[1] However, alternative imaging modalities should always be considered and performed in lieu of CT when appropriate.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) generates cross-sectional images without ionizing radiation. MRI utilizes strong magnets to generate images, typically 1.5 or 3.0 T for clinical applications. A 3.0-T magnet is 60,000 times greater than the earth's magnetic field. The magnetic field uniformly aligns the nuclei of hydrogen protons within tissue. Applying a radiofrequency (RF) pulse sequence and gradient to the magnetic field disrupts this alignment and equilibrium. When the RF pulse is removed, the protons realign, or relax, within the field and emit a measurable resonance radio signal. The detected radio signals, referred to as *echoes* or *spin echoes* (SEs), are then used to generate an image. The most important tissue properties for image generation are the proton density, the spin-lattice relaxation time (T1), and the spin-spin relaxation time (T2). Different tissues have different proton density and relaxation times, absorbing and releasing radiowave energy at different rates, which, in part, accounts for the high tissue contrast obtained by MRI.

Different RF pulse sequences can accentuate different tissue characteristics by varying parameters such as the repetition time (TR)—the time between RF pulses in the sequence, which determines how much time protons have to realign within the magnetic field—and the echo time (TE)—the time between the RF pulse and the peak returning signal. TR and TE dramatically affect image contrast and determine which tissue properties are

selected. T1-weighted images, in which fluid is dark and fat is bright, are generally good at depicting anatomy; T1-weighted images are generated by selecting short TR (typically ≤800 ms) and short TE values (≤30 ms). T2-weighted images, in which fluid is bright and fat is dark, are fluid sensitive and can depict areas of pathology; T2-weighted images are generated by selecting long TR (≥2,000 ms) and long TE values (≥60 ms) (Table 30.2). Scan sequences are composed of variations in RF pulses and TR and TE settings. Although these vary by MRI scanner manufacturer using proprietary names, the underlying principles are similar. Common sequence techniques include:

TABLE 30.2 MAGNETIC RESONANCE IMAGING SIGNAL INTENSITIES (SPIN-ECHO IMAGING)

	T1WI	T2WI	FLAIR
Cerebrospinal fluid	Dark	Bright	Dark
Fat[a]	Bright	Dark	Bright
Solid mass (tumor)	Dark	Bright	Bright
Edema	Dark	Bright	Bright
Cyst	Dark	Bright	Dark

bright, hyperintense; dark, hypointense; FLAIR, fluid-attenuation inversion recovery; T1WI, T1-weighted image; T2WI, T2-weighted image.

[a]Fat is bright on T2 fast spin-echo or gradient echo sequences.

Spin Echo (SE) sequences produce standard T1- and T2-weighted images.

Multiple spin-echo (MSE) sequences allow for faster image acquisition and are also referred to as turbo SE, fast SE, or rapid-acquisition relaxation-enhanced imaging. The signal intensity and image quality are less than those of conventional SE sequences. Furthermore, fat is bright on MSE T2-weighted images, which can limit sensitivity for detecting pathology. Fat suppression techniques can be used to offset this limitation. Fast low-angle acquisition with relaxation enhancement and half Fourier acquisition single-shot turbo SE sequences are MSE variations.

Inversion recovery (IR) pulse sequences emphasize differences in T1 properties of tissues. A time of inversion (TI) is added to the sequence that can be set to target specific tissue properties. Short TI recovery

sequences suppress tissues with short T1 relaxation times, such as fat, and enhance tissues with high T2 properties, such as fluid, resulting in added tissue contrast. The opposite effect may be achieved with fluid-attenuation inversion recovery (FLAIR) sequences. In addition to IR, tissue suppression may be achieved with fat or fluid saturation and opposed-imaging techniques.

Gradient-recalled echo (GRE) pulse sequences are used for rapid image acquisition, which minimizes motion artifact associated with breathing, the cardiac cycle, vessel pulsation, and bowel peristalsis. GRE sequences have low tissue contrast, with the exception of flowing blood, which is bright in signal, and are, therefore, ideal for cardiac and vascular applications. Fast low-angle shot and true fast imaging with steady-state precession are examples of this technique.

Although the inherent tissue contrast with MRI is excellent, the administration of contrast media can further improve the detection of pathology and subtle differences in tissue properties. Gadolinium chelates are the most used MRI contrast agents, which, like the iodinated CT equivalents, are confined to the vasculature and do not cross an intact blood-brain barrier. Hepatobiliary contrast agents and intravascular superparamagnetic iron oxides are also sometimes used for specific imaging.

Gadolinium is a heavy metal ion with paramagnetic effects that shorten T1 and T2 relaxation times. Although there are flow-related techniques for vascular imaging that do not require contrast media (eg, time-of-flight imaging), the use of a contrast agent is essential for characterizing tissue perfusion. The use of gadolinium-based contrast agents is associated with nephrogenic systemic fibrosis (NSF), a debilitating and potentially fatal condition of fibrin deposition within the skin and other organs in patients with impaired renal function.[2] Although the precise mechanism is not understood, patients with severe renal dysfunction (GFR <30) are at increased risk of developing NSF, with additional contributing factors including an underlying inflammatory state, higher doses of gadolinium, or repeated dosing over short intervals. Careful patient evaluation, including a risk/benefit analysis, should be performed before administering gadolinium-based contrast agents in patients with impaired renal function.

MRI techniques allow for tissue diffusion and perfusion imaging, quantification of blood flow by velocity phase encoding, and magnetic resonance proton spectroscopy, which provides biochemical quantification of tissues. Dynamic contrast-enhanced (DCE)-MRI uses sequential images after contrast administration to calculate the volume transfer constant k^{trans}, providing information on the microvascular leakiness and rate of exchange. In a variety of malignancies, including brain, head and neck, esophageal, and breast cancers, k^{trans} correlates with tumor stage and response to treatment.[3-5] DCE-MRI–derived k^{trans} may also help distinguish recurrent glioma from radiation necrosis.[6] However, k^{trans} values cannot be generally applied to all malignancies and may be specific to different tumor types and their distinct microenvironment.

Diffusion-weighted imaging (DW or DWI) measures Brownian motion within the cellular microenvironment and calculates an apparent diffusion coefficient (ADC) map. A region of low intensity in an ADC map represents restricted diffusion, a state that may correlated with increased cellularity, as seen with malignancy or fibrosis. This may improve the specificity of breast MRIs for differentiating malignancy from benign processes, and even predicting the grade of the lesion.[7] DWI has also improved the detection rate of hepatic lesions and differentiation between benign and malignant processes.[8] Conversely, high pretreatment ADC in cervical cancers may be associated with poorer eventual disease-free survival, again reflecting how functional imaging may be revealing a complex interaction in the tumor microenvironment.[9]

As with other imaging techniques, MRI has modality-specific artifacts that can limit image quality. Motion artifact can be problematic with MRI due to long scan times and breath holding required with some sequences. Chemical shift artifact results in a loss of signal at the interface of tissues with highly variable contrast properties. MRI is also sensitive to magnetic field distortions that can produce artifacts. Susceptibility artifact is one of the most common problems with MRI and is frequently attributable to objects that alter the magnetic field such as metallic hardware or devices, resulting in signal voids or distortion of MRI. The magnetization of such objects also presents a safety hazard as items can overheat or become displaced, resulting in injury. Patients must be carefully screened to ensure that any medical devices or surgical hardware is MRI compliant.

Ultrasonography

Ultrasonography (US) is an imaging modality that uses high-frequency sound waves with pulse-echo techniques rather than radiation to produce an image and characterize tissues. The US transducer converts electrical energy into a high-frequency pulse that is transmitted through tissues. The pulse interacts at tissue interfaces, generating a reflected echo signal that is detected by the transducer. The returning sound waves are transformed into grayscale images in real time. Image quality is, in large part, determined by the pulse frequency. High-frequency transducers (5-12 MHz) produce high-resolution images but have limited ability to penetrate tissue. Therefore, they are best suited to imaging superficial structures, such as the breast or thyroid. Low-frequency transducers (1-3.5 MHz) generate lower quality images but have better tissue penetration and are most often used for imaging abdominal and pelvic organs. The degree to which tissues are visualized by US is called *echogenicity*. Fat is highly echogenic (bright), whereas fluid-containing structures, such as simple cysts, are anechoic (dark).

The quality of US images is highly dependent upon the technical skill of the operator and affects the reproducibility and interpretation of US examinations. US is also prone to artifacts. Bone almost completely absorbs sound waves, resulting in acoustic shadowing that completely obscures tissues located beyond the bone. Air is also problematic as it almost completely reflects sound waves, leaving little pulse energy to penetrate tissues deep to the air. Artifacts secondary to air markedly limit the evaluation of lesions near the lung or bowel. In contrast, fluid readily transmits sound and makes an excellent “acoustic window” for imaging. Thus, a water-soluble gel between the transducer and the patient’s skin eliminates air at the skin surface and improves the transmission of the US beam. Patients are encouraged to drink plenty of fluids prior to a pelvic US examination—so that the bladder is fully distended.

Color Doppler US is an important adjunct to conventional grayscale sonography. The Doppler effect is a change in the frequency of returning sound waves reflected by a moving object, such as flowing blood. If blood flows away from the transducer, the echo frequency decreases; whereas if blood flows toward the transducer, the echo frequency increases. The change in frequency is directly proportional to the flow velocity and

produces a color overlay in areas of flow on the standard grayscale US image. Color Doppler US is useful in characterizing blood flow within lesions and assisting in image-guided procedures.

Endoscopic ultrasound (EUS) was introduced in the early 1980s and has become an important tool in oncologic staging. It allows for high-resolution images of internal structures not typically accessible by high-frequency transducers by passing the probe through bowel or airways. It is most widely applied in the setting of gastrointestinal (GI) malignancies, especially esophageal and rectal carcinomas. A 5- to 12-MHz transducer can readily identify five of the layers of the GI tract (Table 30.3 and Figure 30.1). Higher frequency transducers can identify additional layers, such as the muscularis mucosa and lamina propria of the esophagus, which has important staging implications. EUS is also utilized for characterization and image-guided sampling of regional lymph nodes in GI or bronchopulmonary disease. The ability of EUS to predict the tumor (T) stage is generally superior to its ability to predict the node (N) stage, although some imaging patterns of nodal involvement are recognized. Normal lymph nodes are usually ovoid, <10 mm in short axis, and have a homogeneous but variable echogenic appearance that may be isoechoic, hyperechoic, or hypoechoic to surrounding tissues. An echogenic (bright) center is common and represents the normal fatty hilum. Suspicious lymph nodes are typically round, >10 mm in short axis, have distinct margins, and are often hypoechoic. If all four features are present, the likelihood of malignancy is 80% to 100%.[10] There is, however, considerable overlap between benign and malignant features of lymph nodes on EUS in addition to wide interobserver variability. Tissue sampling is, therefore, recommended for accurate staging. When describing clinical T and N staging by EUS, the prefix *u* should be utilized (eg, uT3N1).

TABLE 30.3 ENDOSCOPIC ULTRASOUND WALL LAYERS OF THE ESOPHAGUS

Layer	EUS Characteristic	Histologic Layer	AJCC T Stage
1	Hyperechoic	Superficial mucosa	T1 *m*
2	Hypoechoic	Deep mucosa	T1 *m*
3	Hyperechoic	Submucosa	T1 *sm*
4	Hypoechoic	Muscularis propria	T2

Layer	EUS Characteristic	Histologic Layer	AJCC T Stage
5	Hyperechoic	Subserosa, serosa, adventitia	T3

AJCC, American Joint Committee on Cancer; EUS, endoscopic ultrasound; *m*, mucosa; *sm*, submucosa.

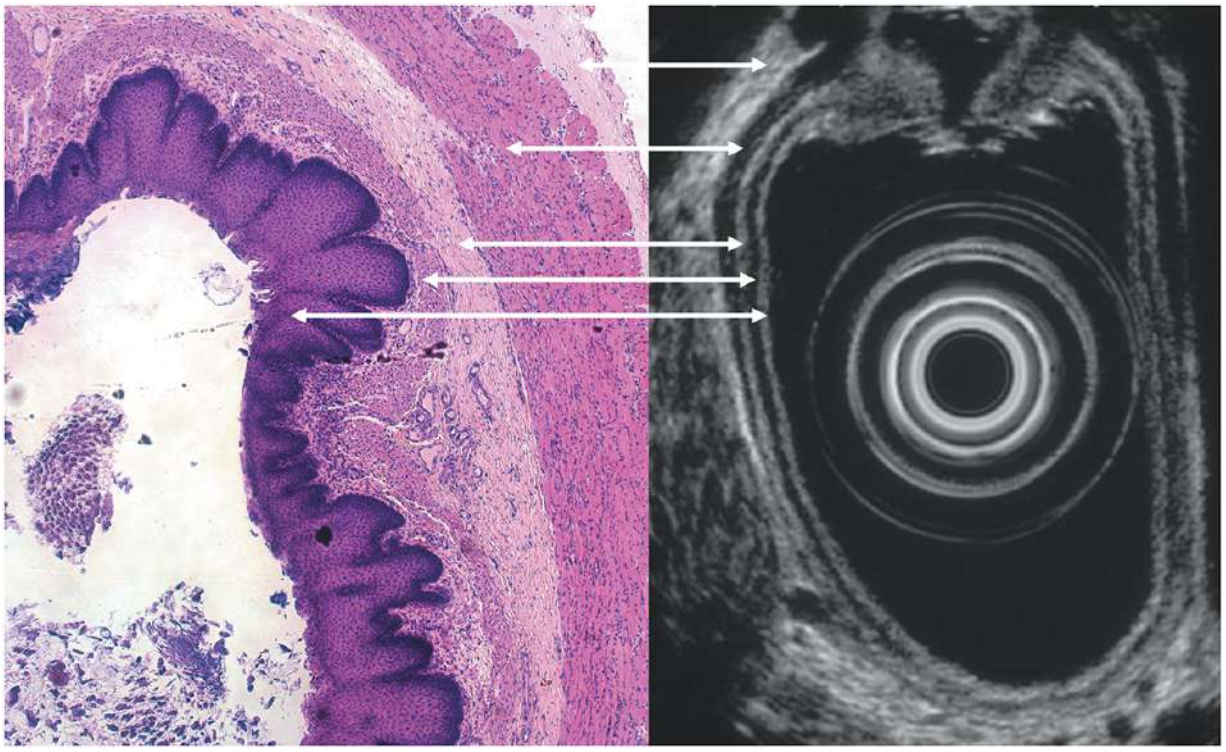


FIGURE 30.1 Axial endoscopic ultrasound image (right) and histologic specimen (left) from a normal esophagus. The endoscopic ultrasound layers and histologic layers of the esophagus are correlated (see Table 30.3). (Endoscopic ultrasound image courtesy of Dr Frank Gress. Histologic image courtesy of Dr Daniel Goodenough.)

Nuclear Imaging

Although radiographic and cross-sectional studies provide important anatomic information regarding pathologic processes, nuclear radiology provides physiologic information based on the distribution of an injected or ingested radiopharmaceutical. Radiopharmaceuticals consist of a radioactive substrate (radionuclide, radioisotope, or radiotracer) that is coupled with a physiologically active compound or analog. For example, technetium-99m (^{99m}Tc) may be coupled to pertechnetate, a water-soluble ion salt that distributes similar to iodine, such that it is specific for imaging of the thyroid, bladder, stomach, and colon, among other organs. The timing of

imaging depends on the kinetics of absorption, metabolism, and half-life of the radionuclide. Gamma rays emitted by nuclear decay of the radionuclide are detected using a γ-camera corresponding to radiotracer activity that is described in terms of uptake.

There are numerous available nuclear imaging studies that take advantage of differing radiopharmaceuticals for oncologic imaging. Many of these play a primary role in the management of oncology patients with specific malignancies. However, the primary nuclear imaging studies relevant to general oncologic imaging are positron-emission tomography (PET) and bone scintigraphy. These studies have broad applications for many malignant processes in the diagnosis, staging, and surveillance of disease.

Positron-Emission Tomography

Although several radionuclides for PET are available, the most common is 18-fluorodeoxyglucose (FDG). FDG is a glucose analog that concentrates in areas of high metabolic activity. Tumor cells are often highly metabolic, with rapid cell division and an increased number of glucose transporters. However, FDG uptake is not specific for malignancy and accumulates in any cell with increased metabolic activity, including myocardium, gastric mucosa, brain tissue, thyroid, and salivary glands, which limits PET evaluation of these organs. Furthermore, FDG tracer is excreted within the urinary system; therefore, activity within the kidneys, collecting system, and bladder can obscure the malignancy of these structures. Notwithstanding these limitations, PET-CT has become the preferred imaging modality for clinical staging in many malignancies, facilitating the characterization of benign versus malignant pathology, detecting sites of unsuspected disease, identifying optimal sites for tissue sampling, assessing treatment response, and monitoring for recurrence.

PET is now routinely obtained in conjunction with CT. PET-CT combines the physiologic assessment of PET with the anatomic assessment of CT, resulting in improved diagnostic accuracy.[11] PET and CT may be obtained independently on the same day but are more commonly performed on a combined PET-CT scanner, which more precisely aligns the two imaging data sets for fusion such that the patient does not have to move between examinations. Patients must fast for 4 to 6 hours prior to scanning in order to limit metabolic activity within the GI tract. Blood glucose levels should

be well controlled (<150 mg/dL) to limit glucose receptor competition with FDG, as high glucose levels can result in a false-negative scan. Speech and motion should be restricted to minimize muscle uptake, which could obscure pathology. Approximately 1 hour following FDG administration, a CT scan is performed immediately followed by PET imaging, which can take up to 60 minutes. CT and PET data sets are then reconstructed in separate axial, coronal, and sagittal series as well as fused PET-CT images.

FDG uptake is quantified by the standard uptake value (SUV). Most malignant tumors have a maximum SUV >2.5, while physiologic uptake is typically <2.5. SUVs are not absolute and can be affected by the timing of imaging, improper attenuation correction, partial volume effects, patient weight, FDG dose, and other factors affecting FDG uptake. It is, therefore, difficult to accurately compare SUVs between scans. However, if care is taken to ensure that variables between studies are similar, such as performing the examination on the same scanner with similar patient preparation, FDG dosing, and image timing, comparing SUVs between studies may be reliable. Clinical studies to date have documented that under such uniform conditions, changes in SUV have prognostic value, indicating that most tumors responding to therapy show a 20% to 40% decrease in SUV early in the course of treatment.[12-14]

The registration of CT and PET has led to novel ways of quantifying the burden of disease. Total lesion glycolysis, for example, is calculated by multiplying the mean SUV in a segmented lesion by its volume. This metric essentially weights the volume of disease by its metabolic activity in an attempt to reflect the true burden and has been associated with worse prognosis in non–small cell lung cancer (NSCLC).[15] Metabolic tumor volume (MTV), on the other hand, is a measure of tumor volume only counting voxels above a certain SUV threshold, either relative (such as a percentage of SUVmax) or an absolute SUV value. Higher pretreatment MTV is associated with poorer eventual outcome in head and neck cancers.[16]

Other radionuclides with potential application to oncologists include ^{18}F-fluoromisondazole, ^{18}F-fluoroazaomycin arabinoside, and copper-64 diacetyl-bis-N4-methylthiosemicarbazone, all of which have different mechanisms of co-locating to intratumoral hypoxic regions.[17] As hypoxia is a driver of both prosurvival factors such as hypoxia-inducible factor 1α, and

resistance to radiotherapy (RT), these agents are of considerable research interest, though not yet of routine clinical utility. Recent advances in radiopharmaceuticals include gallium-68 (^{68}Ga) or lutetium-177 (^{177}Lu) bound to the somatostatin analog DOTATATE for imaging and therapy of neuroendocrine tumors, respectively. Newer specific agents for prostate cancer include ^{18}F-fluciclovine and ^{68}Ga prostate-specific membrane antigen (^{68}Ga-PSMA).[18]

PET-MRI is an emerging hybrid technique combining the functional information of PET with anatomic and soft tissue definition of MRI. Benefits of this multimodality imaging over PET-CT include offering lower ionizing radiation and superior soft tissue contrast and image resolution. Coupled with the previously described DCE-MRI and DWI, simultaneous assessment of tumor properties such as perfusion and cellularity in addition to metabolism may be obtained. PET-MRI is of particular interest for repeated longitudinal studies and for pediatric imaging.[19]

Bone Scintigraphy

Normal bone undergoes continuous remodeling, maintaining a balance between osteoblastic and osteoclastic activity. Most bone metastases originate as intramedullary lesions, having gained access to the bone through the vasculature. As the lesions enlarge, reactive osteoblastic and osteoclastic activity results in characteristic radiographic changes indicative of bone metastases (sclerotic, lytic, or mixed lesions). Rapidly growing metastases tend to produce lytic lesions, while more slowly growing metastases typically produce sclerotic (or blastic) lesions. Metastases from multiple myeloma, thyroid cancer, and renal cell carcinoma are predominantly lytic, while blastic lesions are associated with breast and prostate cancers.

Bone scintigraphy or bone scan imaging utilizes radiopharmaceuticals composed of bisphosphonates; the most common of which is the radionuclide technetium-99m methylene diphosphonate (^{99m}Tc-MDP). ^{99m}Tc-MDP localizes to areas of new bone mineralization, which occurs in a wide array of bone pathology and is, therefore, highly sensitive to osseous disease, but not specific. Bone scans are relatively inexpensive, convenient, and visualize the entire skeleton, including sites that are difficult to assess on plain films (eg, ribs, sternum, scapula, sacrum). Reported sensitivities

range from 62% to 100% with similar specificity rates (78%-100%).[20] Recently, advances in bone imaging incorporate the positron emitter ^{18}F-NaF with PET/CT. Research into this agent shows increased specificity and sensitivity compared to ^{99m}Tc-MDP and marked improved resolution of osseous metastatic disease.[21]

Two primary patterns of radiotracer activity can be associated with malignancy: increased or decreased activity. Increased uptake occurs in areas of increased blood flow and osteoblastic activity; this is a common finding in metabolically active tumors and small sclerotic metastatic foci. Decreased radiotracer activity occurs as a "cold" area on bone scan and is associated with lytic bone disease and aggressive tumors that outgrow their blood supply. Rapidly progressing and purely lytic diseases are the main causes of false-negative findings on bone scintigraphy, while false-positive findings can be related to trauma, healing, benign bone tumors, or arthritic changes. The false-positive rate of planar bone scintigraphy can be reduced by the use of single-photon emission CT (SPECT), which can be obtained in conjunction with conventional CT or MRI for more precise localization of disease.[22,23]

New developments in cancer response criteria (RECIST 1.1) have stressed the importance of reporting the response of bone metastases such that bone metastases with soft tissue components >10 mm are now considered measurable disease.[24] A number of facts need to be considered when interpreting the degree of uptake in follow-up bone imaging studies: First, tumor treatment response may cause a "flare phenomenon," resulting in increased bone scan uptake secondary to new osteoblastic activity concomitant with new bone formation. This may be falsely attributed to progressive disease. Similarly, lytic lesions that were previously "cold" on bone scan can transform into "hot" spots (areas of uptake) after treatment. Second, rapidly progressive disease with overwhelming bone destruction without new bone formation can be misinterpreted as stable or responding disease on bone scan.

Radiomics

Radiomics is a burgeoning field, combining large databases of radiographic data extracted from clinical imaging (usually of CT, MRI, or PET origin) with high-throughput computing capabilities to detect emergent patterns of

data associated with clinically relevant outcomes.[25] It borrows its name and much of its terminology from genomics and proteomics, employing similar computational techniques to detect signatures within the data that may correlate to underlying tumor biology. An example of this is texture analysis, which derives several features of the intensity of not only a single voxel but also its relationship to all neighboring voxels, which may potentially derive quantifiable measures of tumor heterogeneity, necrosis, and hypoxia.[26] However, it is worth noting that radiomics is susceptible to multiple comparisons and testing. Given the increasing interest in radiomics, it is incumbent for research in this area to understand its limitations, and that findings are confirmed in independent data sets prior to clinical application.

BRAIN AND SPINE

Oncologic Anatomy

The Brain

The central nervous system (CNS) consists of the brain and spinal cord, which are covered with three meningeal layers—the dura mater, arachnoid mater, and pia mater. Meningiomas are the most common tumors arising from the meninges. They arise from arachnoid cells but are usually affixed to the underside of the dura mater. They are well-circumscribed tumors that do not typically invade the underlying brain parenchyma. The arachnoid mater and pia mater are considered the leptomeninges, with the intervening space (subarachnoid space) filled with cerebrospinal fluid (CSF). Cancer can breach the CSF space through several routes, including hematogenous spread or by direct extension. Once cancer breaches the subarachnoid space, the entire craniospinal axis is at risk, and tumor deposits can lead to increased intracranial pressure, cranial nerve (CN) deficits, radiculopathies, and seizures. Leptomeningeal involvement occurs most frequently with pediatric brain tumors (eg, medulloblastoma), acute lymphoblastic leukemia, and some solid cancers (eg, breast cancer, melanoma, and lung cancer in particular).[27]

The major units of the brain include the cerebral hemispheres, diencephalon, cerebellum, and brainstem. The cerebral hemispheres consist of the frontal, parietal, temporal, and occipital lobes; basal ganglia; and lateral ventricles. The diencephalon includes the thalamus, hypothalamus,

and third ventricle. The brainstem consists of the midbrain, the pons, and the medulla oblongata. The fourth ventricle lies between the pons and the cerebellum. Although more than half of pediatric brain tumors arise in the posterior fossa (cerebellum and brainstem), most primary brain tumors in adults arise in the cerebral hemispheres or diencephalon.

The hippocampus is a portion of the limbic system located in the deep medial temporal lobes. It plays an important part in the development and maintenance of memory. It is also seldom a site of metastasis and, therefore, may be spared under select circumstances to improve the therapeutic ratio of whole-brain radiotherapy (WBRT). After WBRT, dose-dependent hippocampal atrophy and neurocognitive decline have been demonstrated.[28] Multiple trials have since found decreased cognitive decline in subjects treated with hippocampal-sparing WBRT.[29,30]

Cranial Nerves

The CNs consist of 12 paired nerves whose nuclei (except CN I) are in the brainstem and upper spinal cord. They are termed *cranial nerves* because they exit the cranium through foramina in the base of skull and are encased by sheaths formed from the meninges (Table 30.4). Although spinal motor neurons are innervated by the corticospinal tracts, many of the lower motor neurons in the brainstem are innervated by the corticobulbar tracts. These upper motor neurons innervate the cranial motor nuclei bilaterally (with some exceptions), in contrast to the nerves within the corticospinal tracts, which largely cross in the medulla, leading to contralateral innervation.

TABLE 30.4 MAJOR FORAMINA AND OTHER APERTURES IN THE CRANIAL FOSSAE AND THEIR PRIMARY CONTENTS

Foramina/Opening	Contents
Anterior cranial fossa	
Foramina in cribriform plate	Axons of olfactory cells (CN I)
Middle cranial fossa	
Optic canal	Optic nerve (CN II)
	Ophthalmic artery
Superior orbital fissure	Oculomotor nerve (CN III)

Foramina/Opening	Contents
	Trochlear nerve (CN IV)
	Abducens nerve (CN VI)
	Ophthalmic nerve (CN V_1)
Foramen rotundum	Maxillary nerve (CN V_2)
Foramen ovale	Mandibular nerve (CN V_3)
Foramen spinosum	Meningeal branch of CN V_3
	Middle meningeal artery/vein
Foramen lacerum	Internal carotid artery[a]
Petrous portion of the temporal bone	
Internal acoustic meatus	Facial nerve (CN VII)[b]
	Vestibulocochlear nerve (CN VIII)
	Labyrinthine artery
Posterior cranial fossa	
Jugular foramen	Glossopharyngeal nerve (CN IX)
	Vagus nerve (CN X)
	Spinal accessory nerve (CN XI)
	Internal jugular vein (superior bulb)
Foramen magnum	Spinal roots of spinal accessory nerve (CN XI)
	Medulla
	Vertebral artery
	Anterior/posterior spinal artery
Hypoglossal canal	Hypoglossal nerve (CN XII)

CN, cranial nerve.

[a]After entering the skull through the carotid canal.

[b]The facial nerve exits the skull through the stylomastoid foramen.

Multiple tumors, both benign and malignant, commonly involve the CNs, leading to focal neurologic deficits. Some of the more common include meningiomas involving the optic nerves (CN II), vestibular schwannomas

(CN VIII) (Figure 30.2), parotid gland tumors (CN VII), nasopharyngeal carcinoma (NPC) (multiple), and brainstem gliomas (multiple).

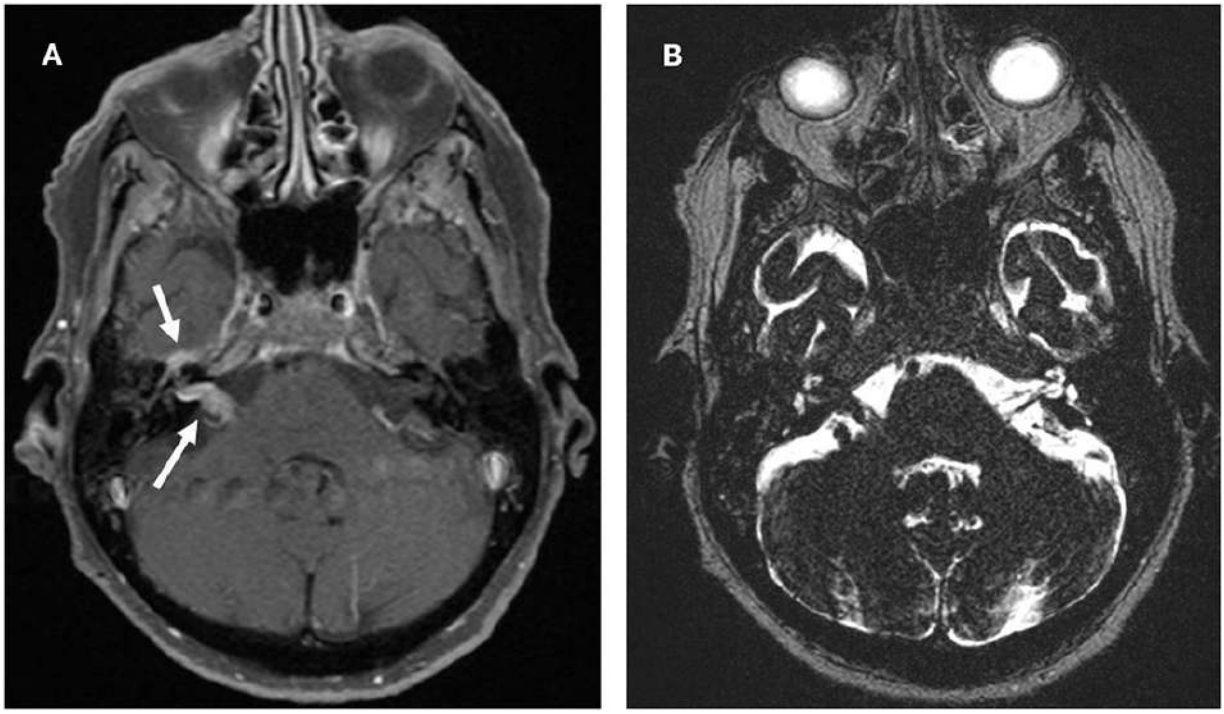


FIGURE 30.2 Magnetic resonance imaging (MRI) sequences demonstrating an enhancing lesion concerning for vestibular schwannoma in the right seventh/eighth cranial nerve complex as it originates from the right cerebellopontine angle bulging into the prepontine cistern. There is perineural spread with involvement of the geniculate ganglion and tympanic segment of the facial nerve. A. Representative axial slice on T1 weighted postcontrast. B. Representative axial slice on steady-state free precession (a type of gradient echo MRI pulse sequence).

The classic presenting symptoms of diffuse pontine gliomas illustrate the intricate anatomy of the pons. A unilateral lesion in the ventral pons with involvement of the pyramidal tracts (upper motor neurons) can cause contralateral motor weakness in the arms or legs. In addition, CNs within the pons might also be affected unilaterally, without complete resulting paralysis, because of bilateral innervation of the CNs by fibers in the corticobulbar tracts. Ataxia, denoting impairment of coordination without weakness, can be caused by involvement of fibers projecting from the pons to the cerebellum within the middle cerebellar peduncle. Through this pathway, the cerebellum receives a copy of the information for muscle

movement that the corticospinal tracts relay to lower motor neurons, facilitating the complicated act of coordination.

The CNs should also be carefully examined when evaluating a patient with NPC. One-fifth of patients with NPC present with symptoms of CN involvement. The most involved CNs are the abducens nerve (CN VI) and the trigeminal nerve (CN V). CN VI originates in the ventral aspect of the brainstem, ascends on the clivus, and crosses the internal carotid artery near the superior aspect of foramen lacerum before entering the cavernous sinus. It then exits the skull through the superior orbital fissure. The motor and sensory nerve roots of CN V exit the pons and pass underneath the free edge of the tentorium cerebelli into Meckel cave, forming the trigeminal (Gasserian) ganglion. From the ganglion, V_1 and V_2 enter the cavernous sinus and subsequently exit the skull through the superior orbital fissure and foramen rotundum, respectively. V_3 exits the skull through the foramen ovale.

The nasopharynx is near the foramina lacerum, rotundum, and ovale, hence the frequent tumor involvement of CN V and CN VI. Invasion superiorly to the foramen lacerum and involvement of the trigeminal ganglion could lead to dysfunction in all three branches of CN V. In fact, most patients with NPC and CN V involvement have isolated deficits of V_2 or V_3. This occurs due to extension into the foramen rotundum and ovale, respectively. After gaining access to the middle cranial fossa, NPC may extend superiorly into the cavernous sinus. The nerves of the cavernous sinus include CN III, CN IV, CN V_1, CN V_2, CN VI, and the sympathetic plexus around the internal carotid artery. Within the sinus, CN III is located most superiorly, while CN V_2 is located most inferiorly. CNs located more superiorly in the cavernous sinus are less frequently involved than those located closer to the base of skull. Lower CN involvement can occur without intracranial extension. The fossa of Rosenmüller (the posterolateral pharyngeal recess) is the most common site of origin of NPC. The lateral border of the fossa of Rosenmüller is the pharyngeal space. Direct tumor extension laterally into the parapharyngeal space or lymphatic metastases to high parapharyngeal lymph nodes can affect the CNs exiting the jugular foramen (CN IX, CN X, and CN XI) and hypoglossal canal (CN XII). This may result in loss of the gag reflex (CN IX), hoarseness or dysphagia (CN

X), atrophy or paralysis of trapezius and sternocleidomastoid (SCM) (CN XI), as well as tongue deviation (CN XII).

Spine

The vertebral column typically consists of 33 bones (7 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 4 coccygeal). Although all individuals have seven cervical vertebral bodies, variations in the number of the other vertebral levels are occasionally observed. The spinal cord is housed within the spinal canal and encased by the meninges. Spinal cord levels do not correspond with levels of the vertebral column. In adults, the spinal cord typically ends at the L1-2 interspace (termed the *conus medullaris*). In an infant, the spinal cord typically terminates at L2 or L3. However, the spinal nerves continue to descend within the spinal canal (termed the *cauda equina*). The subarachnoid space, containing CSF, typically extends to the second sacral vertebral body. At this level, the meninges fuse together and extend caudally as the filum terminale, which anchors the spinal cord to the coccyx. These anatomic distinctions have implications when evaluating a patient with spinal cord compression, designing craniospinal fields, and when setting up palliative spine fields.

Oncologic Imaging

Intracranial Metastases

Approximately 50% of adult intracranial neoplasms are metastatic, with lung, breast, and melanoma being the most common primaries, in order of decreasing frequency.[31] Most metastases gain access to the brain through the vasculature and typically arise at the junction of the gray and white matter, presumably because the caliber of blood vessels decreases at this point, acting as a trap for tumor emboli.[32] Approximately 80% of brain metastases are found in the cerebral hemispheres, with less frequent involvement of the cerebellum (15%) and brainstem (5%), reflecting their smaller volume and blood flow.[33]

The preferred imaging modality for the diagnosis of intracranial metastasis is contrast-enhanced MRI.[33] Brain metastases are typically well circumscribed and avidly contrast enhancing. They are also typically associated with a disproportionate amount of surrounding edema, best

visualized on T2-weighted sequences. The detection of multiple lesions helps to distinguish metastases from primary brain tumors, which are more commonly solitary.

Primary Brain Tumors

Primary brain tumors account for approximately 50% of adult intracranial masses, of which half are malignant. The most common malignant primary brain tumor in adults is glioblastoma (GBM). As with brain metastases, MRI is more accurate than CT in delineating the local gross extent of disease, given its superior soft tissue resolution.

GBM most commonly develops along white matter tracts and does not typically involve the dura or skull. GBM and primary CNS lymphoma have the potential to spread into the contralateral cerebral hemisphere via tracts of the corpus callosum. Other potential routes of spread, including subependymal extension with CSF contamination or hematogenous dissemination, are possible but unusual. GBMs are typically expansile masses that are isointense to hypointense to surrounding tissue on T1-weighted images, with central necrosis and peripheral ring enhancement postcontrast administration. T2-weighted imaging shows a heterogeneous mass with surrounding T2-signal abnormality corresponding to vasogenic edema, in which malignant cells are known to frequently reside. Central areas of low signal reflect a combination of blood products, necrosis, and vascular flow voids.[34]

Low-grade gliomas generally appear as non–contrast enhancing, T2/FLAIR-hyperintense lesions without associated vasogenic edema, while primary CNS lymphomas appear T2 hypointense and enhance with contrast. Meningiomas are the most common benign brain tumor in adults, and many small meningiomas are found incidentally. On CT imaging, most meningiomas are hyperdense or isodense compared to cortex. About 20% to 25% have associated calcification or adjacent bone hyperostosis. On MRI, most meningiomas are isointense to gray matter and fairly homogeneously contrast enhancing (Figure 30.3). A CSF cleft can often be seen between the tumor and the brain parenchyma. Many meningiomas will have a linear area of enhancement on MRI, extending from the tumor along the dura. This so-called dural tail is generally not felt to represent direct extension of tumor

but rather vascular congestion within the dura, leading to the characteristic enhancement.[35]

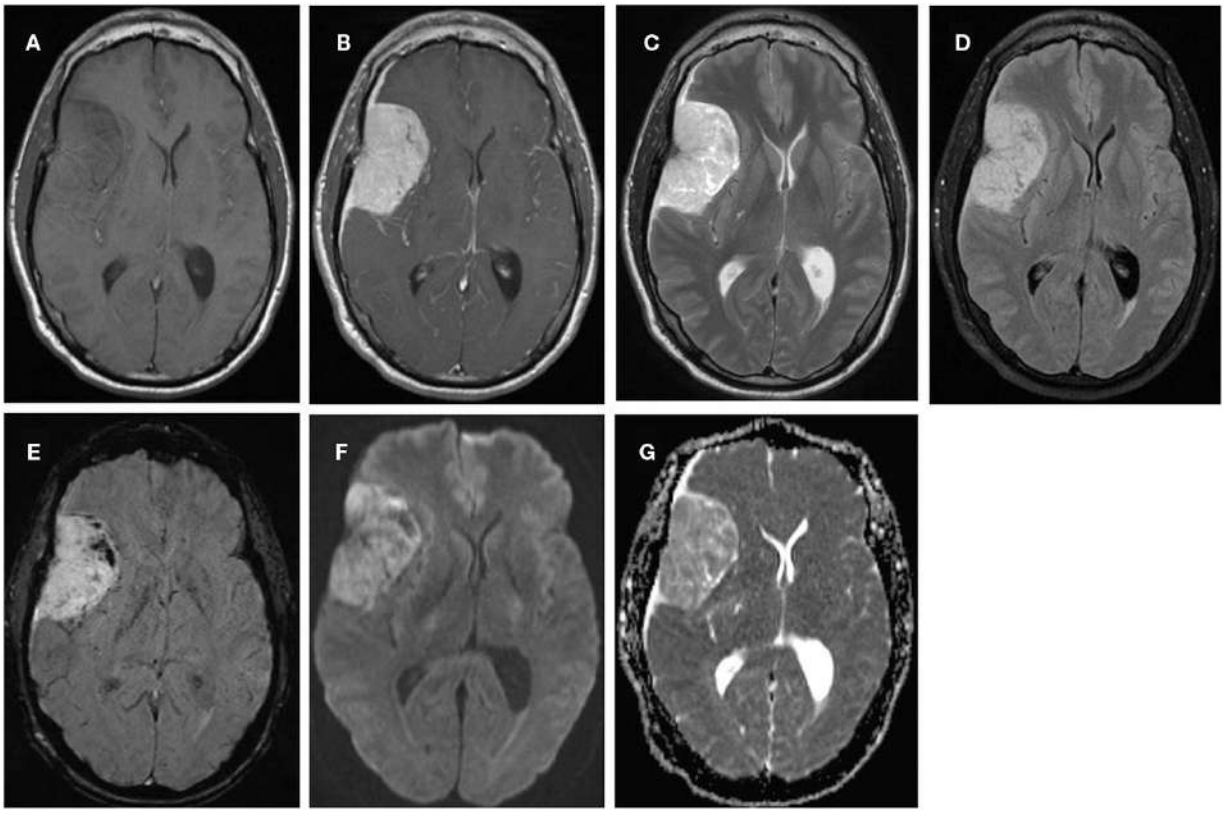


FIGURE 30.3 Magnetic resonance imaging sequences demonstrating meningioma. A. T1 weighted noncontrast. B. T1 weighted postcontrast. C. T2 weighted. D. T2 fluid-attenuation inversion recovery. E. Susceptibility-weighted imaging. F. Diffusion-weighted imaging. G. Apparent diffusion coefficient.

Pituitary adenomas are common benign neuroendocrine brain tumors. They are broadly classified into pituitary microadenomas (<10 mm in size) and pituitary macroadenomas (>10 mm in size). Pituitary macroadenomas are the most common suprasellar mass in adults. MRI is the preferred imaging modality to delineate both pituitary microadenoma and pituitary macroadenoma. On imaging, macroadenomas usually present as a solid tumor that is isointense to gray matter both on T1- and T2-weighted MRI (Figure 30.4). Imaging characteristics can vary depending on tumor components (eg, hemorrhage, cystic transformation).

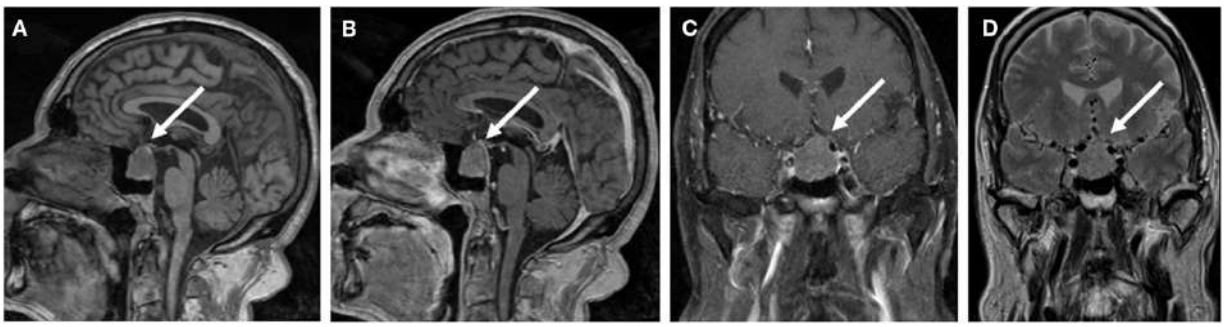


FIGURE 30.4 Magnetic resonance imaging sequences demonstrating pituitary macroadenoma (indicated by arrow). A. Representative sagittal slice on T1 weighted noncontrast. B. Representative sagittal slice on T1 weighted postcontrast. C. Representative coronal slice on T1 weighted postcontrast. D. Representative coronal slice on T2 weighted.

Advanced imaging techniques are also beneficial in characterizing intracranial malignancy. Magnetic resonance spectroscopy (MRS) provides metabolic and biochemical information about tumors in relation to normal brain tissue by quantifying five metabolite peaks: choline (Cho)-containing compounds, Cr, *N*-acetylaspartate (NAA), lactate, and lipid. The Cho peak reflects cell membrane turnover, while Cr is a surrogate for energy synthesis, and NAA is a marker exclusive to neuronal cells. Lactate is detected in necrotic tumors and infarcted tissue, a byproduct of anaerobic metabolism. Lipid peaks result from cellular and myelin breakdown products. The hallmark spectroscopic pattern of brain tumors is an increase in Cho-containing compounds and a decrease in NAA relative to normal brain tissue. MRS can also aid in the evaluation of tumor type and grade. High-grade gliomas tend to exhibit higher Cho:Cr and Cho:NAA ratios and also typically have higher lipid and lactate peaks as a result of necrosis. MRS can additionally distinguish metastatic disease from high-grade gliomas, particularly when combined with perfusion MRI.[36] Differentiating radiation necrosis from recurrent or progressive tumor remains a significant challenge in imaging, though delayed contrast extravasation (DCE) MRI has shown early promise in differentiating between active tumor (fast extravasation) and benign processes (slow extravasation).[37]

Conventional PET-CT has limited utility in the assessment of brain neoplasms due to the high metabolic rate of normal brain tissue. However, delayed-phase PET performed approximately 3.5 hours following FDG injection, allowing for washout of FDG from normal brain cells, while

abnormal tissue retains FDG. Delayed-phase PET has been shown to be beneficial in detecting both primary and metastatic brain lesions as well as differentiating between residual or recurrent tumor and radiation necrosis following treatment.[38] The development of new radioisotopes for neurologic applications, such as ^{11}C-methionine for targeting gliomas, has demonstrated clinical utility and advantages over FDG and might have similar utility in metastases. Many of these new tracers target different cellular processes, such as apoptosis, angiogenesis, and hypoxia; the latter being of particular prognostic importance as hypoxic tissue is less sensitive to chemotherapies.[39] The utility of delayed-phase PET may be further enhanced through fusion with MRI.[40]

Spinal Metastases

Osseous metastases are common in many malignancies, and the vertebral bodies are frequently involved due to the extensive vascular distribution to the spine. MRI is more sensitive than both radiographs and CT at detecting early vertebral body metastases, as it can detect changes within the marrow space before cortical destruction occurs. Given, however, that PET has similar sensitivity as MRI for osseous metastatic disease, is performed as part of routine staging, and can image the entire body, MRI is reserved for more specific characterization, such as determining the extent of tumor invasion into adjacent tissues. One notable exception is the use of urgent MRI for the identification of cord compression in the setting of acute neurologic compromise. In this situation, it is often the T2-weighted sequences that are most useful: the high signal CSF provides contrast to identify disease encroaching into the spinal canal. Spinal cord edema can also be identified. Screening the entire spine is often indicated when evaluating for cord compression due to the possibility of additional disease above or below the index lesion.

HEAD AND NECK

Oncologic Anatomy

Lymphatic Drainage of the Head and Neck

The lymphatics in the head and neck region largely proceed in an orderly manner from sites in the upper aerodigestive tract into the common jugular

chains, which eventually empty into systemic circulation near the junction of the internal jugular and subclavian veins.

The lymphatic basins of the neck are divided into multiple distinct levels. Level I is defined as both the submental basins (level IA) and the submandibular basins (level IB) and receive drainage from the oral cavity, although this basin may also be at risk from other sites in the setting of advanced nodal disease (N2b or greater). Level II contains the upper jugular nodes, extending from the C1 vertebral body to the hyoid bone, including the contents of the carotid sheath and the space deep to the SCM muscle. Level II is subdivided into anterior (level IIA) and posterior (level IIB) regions, as defined by the posterior border of the jugular vein. Level II contains the jugulodigastric node at the level of the jugular vein as it crosses the posterior belly of the digastric muscle and is a common lymphatic pathway for the majority of the upper aerodigestive tract. Level III follows the carotid sheath and space posterior to the SCM from the hyoid bone to the cricoid and receives efferent lymph drainage from level II. Level IV continues to follow the same jugular chain to the level of the clavicle. Level V contains the posterior triangle of the neck, boarded by the trapezius posteriorly, the SCM anteriorly, and the clavicle inferiorly. Level VI are the prelaryngeal lymph nodes (Delphian nodes), which extend from the inferior edge of the thyroid cartilage to the sternal notch, bounded laterally by the sternal heads of the SCM. Level VI is at risk in laryngeal cancers with subglottic or transglottic extension and for hypopharyngeal cancers with esophageal extension.[41]

There are two regions not included in this level classification. Just superior to level II, following the carotid sheath to the skull base are the junctional or retrostyloid nodes, which may be at risk when there is ipsilateral nodal disease. Medial to these nodes and to level II lie the retropharyngeal nodes (nodes of Rouvière), which lie in the regions anterior to the prevertebral fascia, which, in turn, surrounds the longus capitis and longus colli muscles. The retropharyngeal nodes extend superiorly to the skull base and inferiorly to the hyoid bone and are at risk of cancers of the nasopharynx, posterior pharyngeal wall, and the pyriform sinus.

The Oral Cavity

Oral cavity cancer sites include the lip, floor of the mouth, oral tongue (anterior two-thirds of the tongue), lower alveolar ridge, upper alveolar ridge, retromolar trigone, hard palate, and buccal mucosa. Carcinomas originating from the oral tongue have the potential to spread locally through the intrinsic and extrinsic muscles of the tongue, inferiorly to the floor of mouth, and posteriorly to the anterior tonsillar pillar. For the floor of mouth, the genioglossus, geniohyoid, and root muscles of the tongue are at risk for local disease spread, as well as levels IA and IB of the neck, laterally to the alveolar ridge and mandible. Tumors of the buccal mucosa may extend superiorly to the infratemporal fossa, inferiorly to the submandibular region, anteriorly to the lip commissure, and posteriorly to the retromolar trigone.

Nasopharynx

The nasopharynx is bounded superiorly and posteriorly by the sphenoid sinus, clivus, and the prevertebral fascia of C1 and C2. The parapharyngeal space lies laterally to the nasopharynx, which, in turn, is bounded laterally by the medial pterygoid muscle. The parapharyngeal space offers few anatomic barriers for the direct invasion of tumors superiorly and laterally to the base of skull, resulting in CN deficits as noted above. The eustachian tube empties into the nasopharynx at the torus tubarius; just posterior to the torus is the pharyngeal recess (or fossa of Rosenmüller), a fold of mucosa that is a frequent site for primary malignancies of this region.

Oropharynx

The oropharynx is bounded anteriorly by the base of tongue, laterally by the tonsils, superiorly by the soft palate, and posteriorly by the posterior pharynx. Tumors arising from the base of tongue are often difficult to assess for extent of disease. PET/CT or MRI may aid in delineation of the gross tumor volume for this site.

The pharyngeal constrictor muscles (PCMs) lie along the posterior aspect of the nasopharynx and oropharynx, bounded by the parapharyngeal space. The PCM may be further divided into (1) the superior PCM starting at the occipital condyle to the hyoid; (2) the middle PCM, starting 0.5 cm superior to the hyoid and ending at the inferior edge of the hyoid; and (3) the inferior PCM, which continues from the inferior aspect of the hyoid to the

esophagus. The middle PCM was initially investigated as an organ at risk, with dose-volume metrics associated with late swallowing problems.[42] Dose to other swallowing structures, including the genioglossus, mylohyoid/geniohyoid complex, and anterior digastric muscle has also been implicated in addition to the superior PCM and the middle PCM.[43]

Hypopharynx

The hypopharynx is divided into three anatomic subsites: the pyriform sinus, the posterior pharyngeal wall, and the postcricoid space. Cancers arising from the pyriform sinus account for approximately 65% to 85% of hypopharyngeal cancers. The posterior pharyngeal wall is formed by the constrictor muscles covered with a mucosal lining and is the origin of approximately 10% to 20% of cancers. Cancers arising from the postcricoid space account for the remaining 5% to 15% of hypopharyngeal tumors.

Larynx

The larynx is subdivided into three anatomic regions: the supraglottis (containing the epiglottis, the arytenoid and aryepiglottic folds, and the ventricular bands or false cords), the glottis (a 1-cm plane extending inferiorly from the lateral margin of the ventricle, including the true vocal cords and commissures), and the subglottis (from the inferior border of the glottis to the inferior aspect of the cricoid). The true cords have essentially no lymphatic drainage, allowing for focal treatment of a limited primary tumor without elective nodal treatment. In contrast, the supraglottic larynx has a rich and bilateral lymphatic system, requiring either dissection or elective nodal RT for even early tumors. The subglottis is a rare site of primary tumors and may invade locally into soft tissue as well as metastasize to laryngeal and tracheal lymphatics.

Oncologic Imaging

For cancer of the head and neck, staging relies on careful physical examination, fiberoptic and direct laryngoscopy, directed biopsies, and integration of imaging modalities. Contrast- enhanced CT is the standard imaging modality for carcinomas of the head and neck region (Figure 30.5). MRI may be a superior imaging modality for evaluating the extent of

primary tumors of the oral cavity, oropharynx, and nasopharynx. DW MRI may provide information about the cellularity of a tumor mass or involved lymph node; an increase in the ADC (corresponding to a decrease in cellularity) during chemoradiation has been correlated with improved 2-year local control in one series.[44]

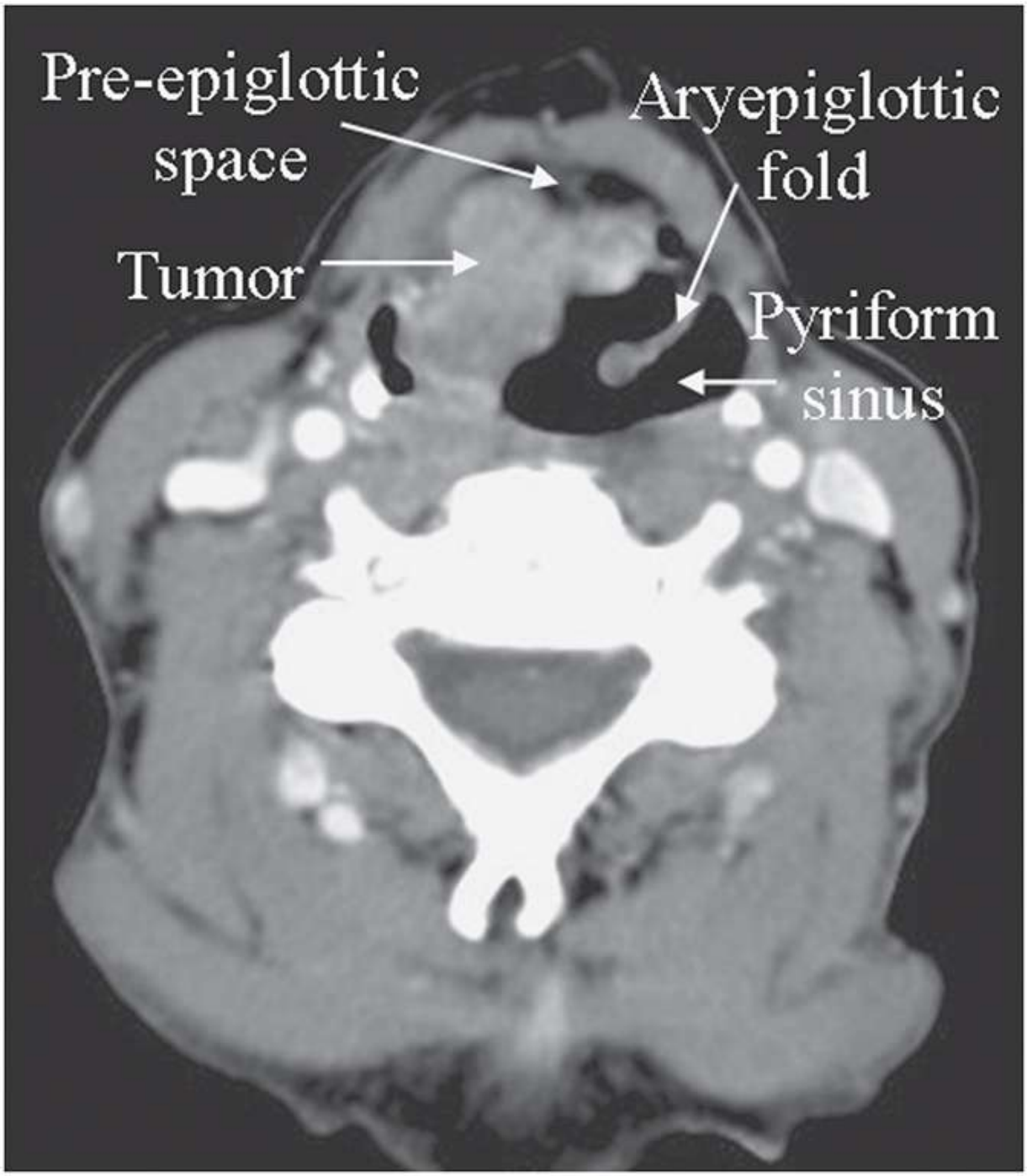


FIGURE 30.5 Axial computed tomography image demonstrating a squamous cell carcinoma involving the right aryepiglottic fold with anterior extension into the pre-epiglottic space.

FDG-PET imaging for head and neck cancer is a useful as an adjunct to CT, particularly in clarifying the significance of intermediate lesions (Figure 30.6). In one series, the addition of FDG-PET imaging improved the

accuracy of tumor delineation from 40% to 70% with MRI or CT alone to 97% to 100%, altering the management of 23% of the patient under study.[45] Another series found FDG-PET to have a sensitivity of 88% in determining the primary tumor and a sensitivity of 82% and specificity of 100% for lymph node metastases.[46] However, in initial staging, no noninvasive imaging modality has a high enough negative predictive value to forgo appropriate dissection or elective nodal irradiation when the characteristics of the primary tumor suggest a significant risk of spread. This contrasts with the value of FDG-PET after chemoradiation for the detection of residual nodal disease. The sensitivity for the detection of persistent disease was 96% with a specificity of 72% in a post-treatment series, with a negative predictive value in some series as high as 99%, allowing for the abandonment of routine post-treatment neck dissections in patients with a complete clinical and PET response.[47,48]

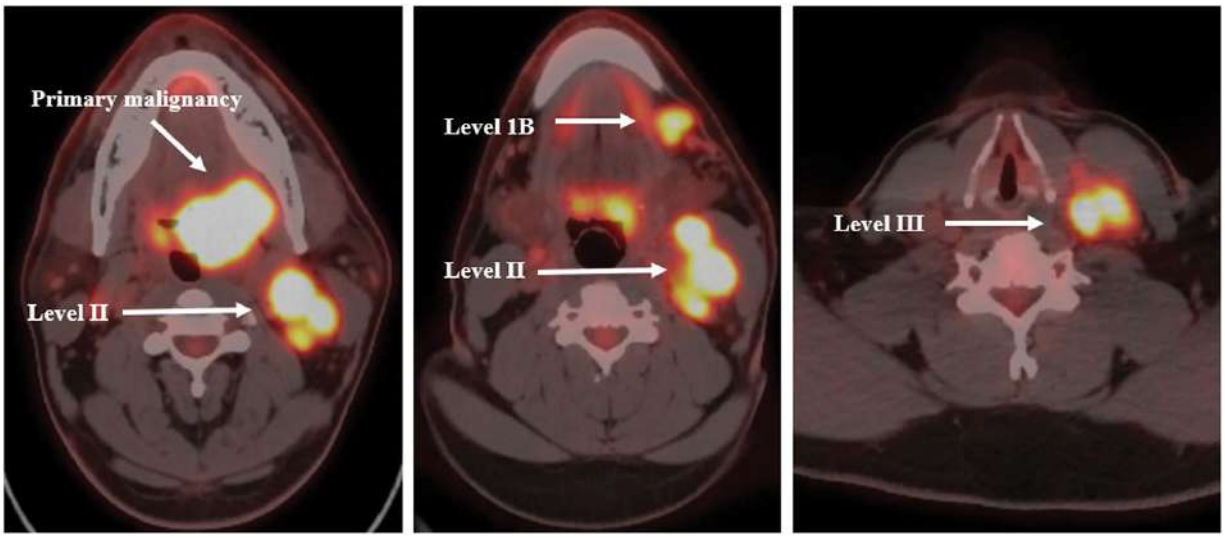


FIGURE 30.6 Positron-emission tomography computed tomography images demonstrating a large hypermetabolic mass centered in the left palatine tonsil and crossing midline. There are multiple level IB-IV cervical lymph nodes. Pathology showed squamous cell carcinoma.

THE BRACHIAL PLEXUS

Oncologic Anatomy

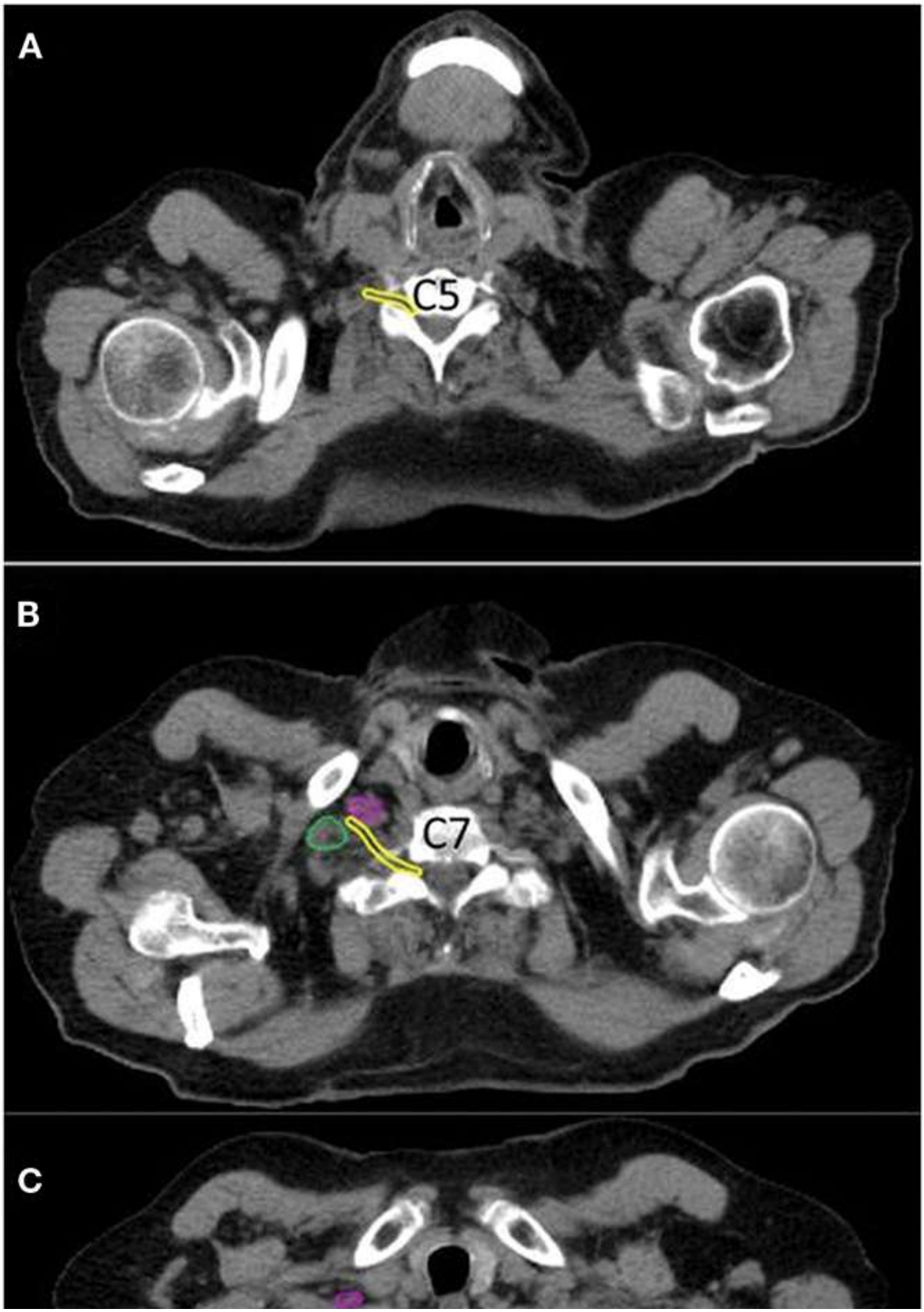
The brachial plexus originates from the primary rami of the C5 through T1 vertebral levels and joins to form three nerve trunks (superior, middle, and inferior) in the neck. These trunks divide as they course beneath the clavicle

forming three cords (lateral, medial, and posterior) in close approximation to the axillary artery, posterior to the pectoralis minor. The cords then form the three primary terminal nerves for the arm (the median, ulnar, and radial nerves) as well as the musculocutaneous and axillary nerves.

The brachial plexus is a critical organ at risk due to the significant morbidity associated with injury, either from direct tumor invasion or from treatment-related toxicity. As the plexus traverses the neck, crosses over the apex of the lung, and continues into the axilla, it is of relevance when treating tumors of the head and neck, upper thorax, and breast.

Oncologic Imaging

Identifying the brachial plexus is difficult on CT imaging and is most directly visualized using MRI. However, one may accurately contour the position of the brachial plexus on CT imaging using bony, muscular, and vascular landmarks.[49] The method put forward by Hall et al begins by contouring at the origination of the vertebral foramina of C5 through T1 (Figure 30.7). The brachial plexus trunks pass between the anterior and middle scalene muscles. The middle scalene will end at the superior aspect of the first rib just as the divisions of the plexus will be joining with the subclavian vasculature as a neurovascular bundle. The posterior aspect of the subclavian vasculature can be followed laterally as a surrogate for the remainder of the cords into the arm.


A
C5
B
C7
C

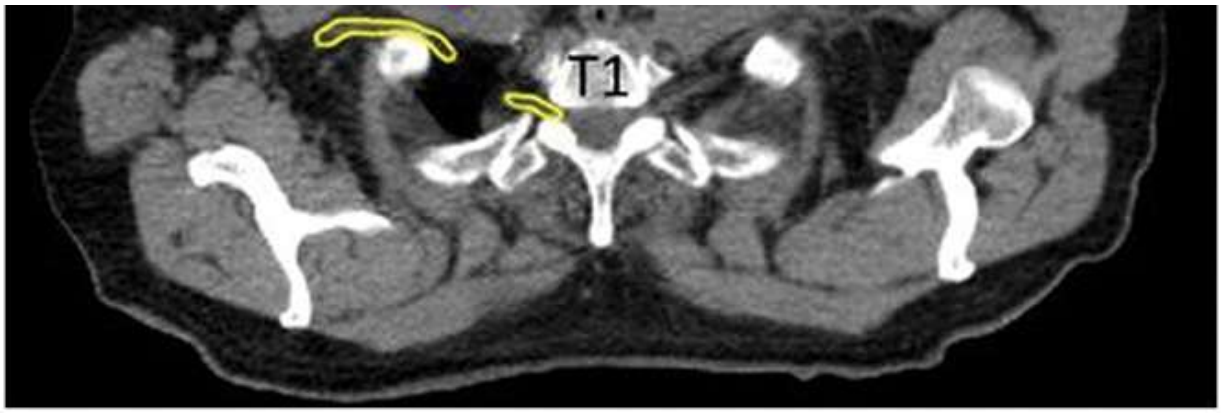


FIGURE 30.7 The brachial plexus (yellow contour) is delineated on axial computed tomography images. A. C5 ventral ramus. B. Brachial plexus coursing between anterior (pink) and middle (green) scalene muscles at C7. C. T1 ventral ramus and brachial plexus coursing behind subclavian neurovascular bundle.

THE THORAX

Oncologic Anatomy

The thoracic cavity contains several important structures, including the lungs, esophagus, thymus, pleura, and heart. Common malignancies arising in the thorax include lung cancer, esophageal cancer, thymic malignancies, malignant pleural mesothelioma, and Hodgkin (HL) and non-Hodgkin lymphomas (NHL). Primary tumors of the heart are extremely rare.

There are many clinically relevant anatomic issues when evaluating patients with cancers of the thorax, particularly lung cancer. These include lobe-specific patterns of lymphatic spread, the complex anatomy surrounding the lung apex, the extent of the pleural space, esophageal landmarks, thymic architecture, and cardiac anatomy.

Patterns of Lymphatic Spread

Lung cancers frequently metastasize to regional lymph nodes. The mediastinal nodes are a complex system, and it is challenging to predict where lymph node metastases will develop. However, these basic patterns provide a framework for customizing local treatment approaches (ie, surgery and RT).[49-51]

Bronchogenic tumors frequently spread directly into mediastinal lymph nodes, bypassing intrapulmonary and hilar lymph nodes. This phenomenon appears to occur more frequently for upper lobe tumors. For right-sided

tumors, these pathways most frequently lead to ipsilateral paratracheal and subcarinal lymph node stations. For left upper lobe tumors, direct spread to para-aortic and aortopulmonary window stations predominates. While right lung segments drain predominantly into the ipsilateral mediastinum, left lung tumors commonly spread to both sides of the mediastinum, especially left lower lobe tumors. Direct passageways to the supraclavicular fossa exist but are rare. Clinically, supraclavicular lymph node involvement is almost always associated with involvement of upper paratracheal lymph node stations. Subcarinal lymph nodes are frequently involved by both upper and lower lobe tumors.

The Superior Sulcus

The superior sulcus of the lung is surrounded by multiple critical structures. The subclavian artery and vein pass anterior to the lung apex, the brachial plexus and its branches cross over the apex of the lung toward the arm, and the stellate ganglia lies posteriorly alongside the exiting nerve roots of the lower cervical and upper thoracic spine. Other structures that can be involved by superior sulcus tumors include the ribs, vertebral bodies, trachea, and esophagus. Patients with superior sulcus tumors present with a variety of presentations (arm edema, hand weakness, sensory deficits, and/or Horner syndrome) related to the local extent of their disease.

The Pleura

The lungs are enclosed within a pleural sac. The visceral pleura is adherent to all of the surfaces of the lung, including the individual lobes where the pleura extends into the fissures. The parietal pleura is adherent to the thoracic wall, mediastinum, and diaphragm. The pleural recesses are potential spaces where portions of opposed parietal pleura are in contact during quiet respiration (Figure 30.8). The inferior extension of the costodiaphragmatic recess can be easily underestimated, as can the medial extent of the costomediastinal recess. The inferior aspect of the costodiaphragmatic recess often extends to the level of the mid-kidney. The posteromedial extent of the pleura often wraps anteriorly over the descending aorta. These considerations are important when managing pleural mesothelioma or drop metastases from thymic malignancies.

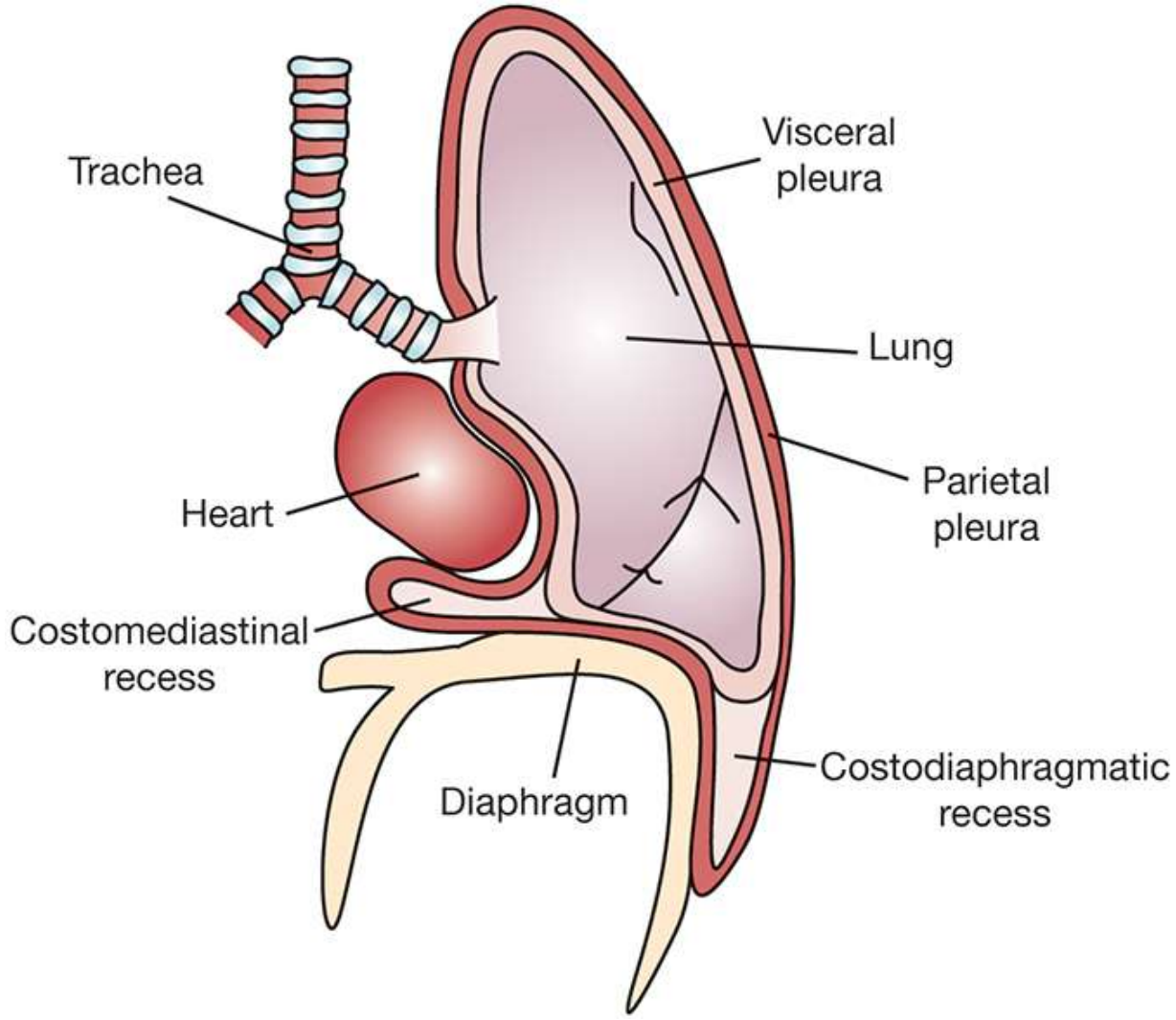


FIGURE 30.8 The extent of the pleura is illustrated. Note the inferior extension of the costodiaphragmatic recess and the medial extension of the costomediastinal recesses. (Courtesy of the University of Bristol, Department of Anatomy.)

Esophageal Anatomy

The esophagus extends from the cricopharyngeus muscle at the level of the cricoid cartilage to the gastroesophageal junction in the abdomen. The cervical esophagus extends from the cricopharyngeus muscle (approximately 15 cm from the incisors) to the level of the thoracic inlet (approximately 18 cm from the incisors). The thoracic esophagus extends from the thoracic inlet to the diaphragm and is sometimes divided into upper, middle, and lower sections. The carina is located at approximately 25 cm from the incisors, and the gastroesophageal junction is located at

approximately 40 cm. These general numbers are helpful when planning radiation fields based on staging studies that include endoscopy, EUS, and PET-CT.

Thymus Architecture

The thymus is an encapsulated, bilobed gland situated in the superior anterior mediastinum and is involved in adaptive immunity. Although prominent in size during infancy and early childhood, it begins to involute during adolescence. Thymic neoplasms are a common cause of anterior mediastinal masses. The thymus gland is composed of both lymphocytes and epithelial cells. Thymomas and thymic carcinomas arise from epithelial elements within the thymus. Primary mediastinal (thymic) large B-cell lymphoma arises from B cells within the thymus, and T-cell lymphoblastic lymphomas arise from T cells within the thymus.

Thymic malignancies are the second most common primary mediastinal neoplasm in adults following lymphoma and are classified on a histologic spectrum from thymoma to thymic carcinoma. Once a thymic malignancy extends through the capsule, it can invade other regional structures including the lungs and great vessels, sometimes rendering it inoperable. The thymus gland lies within the pleural envelope. For thymomas, the most common pattern of spread is within the pleural and pericardial spaces. Lymphatic and hematogenous metastases are rare.

Cardiac Anatomy

The heart is composed of several subunits, including the valves, coronary arteries, pericardium, and individual chambers. There is an increasing awareness that radiation dose to the individual subunits is correlated with toxicity though many uncertainties exist. One component of the heart that has garnered recent attention is the left anterior descending artery (LAD). The LAD is the largest coronary artery. The left coronary artery branches to create the LAD and the circumflex. The LAD runs along the interventricular septum, supplying blood to the anterior and left sides of the heart (Figure 30.9). Studies have shown that dose to the LAD (V15 Gy >10%) is associated with a higher risk of major cardiac events and all-cause mortality.[52,53]

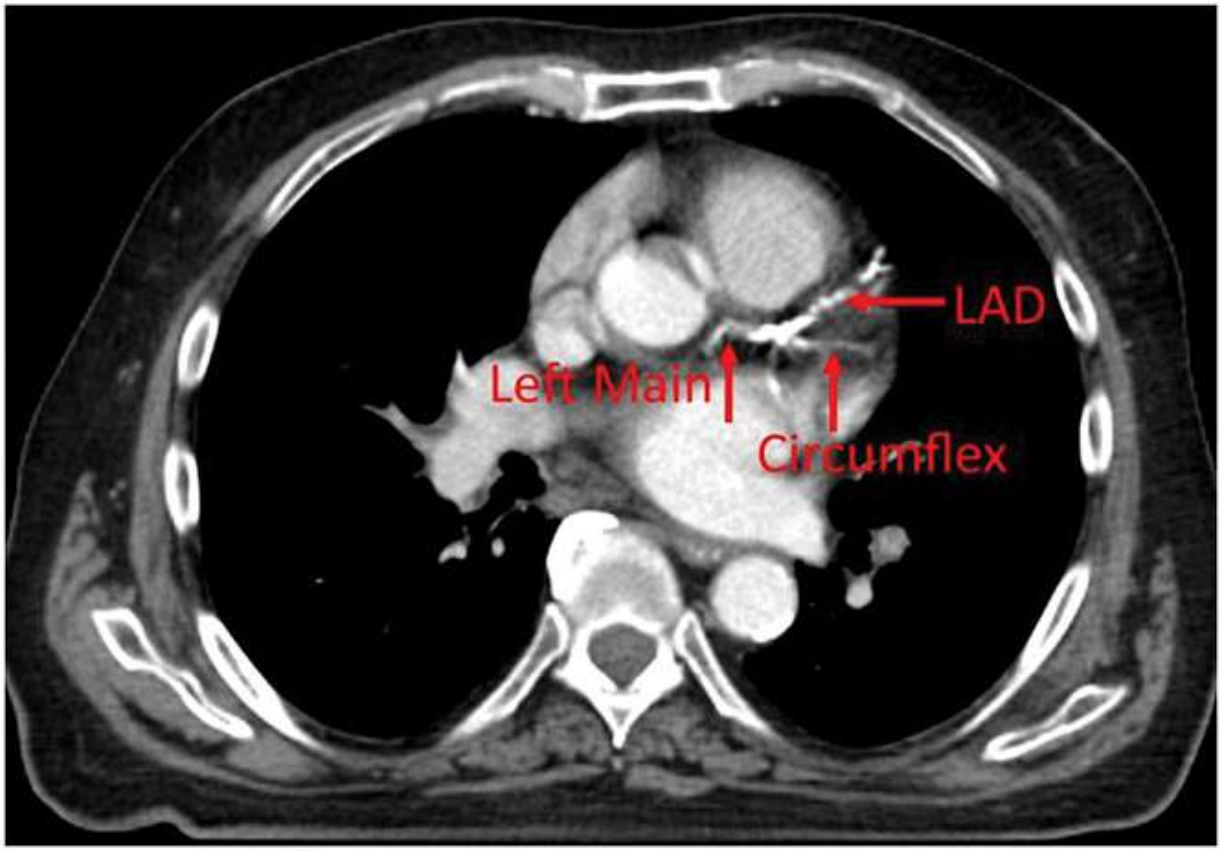


FIGURE 30.9 On a representative axial computed tomography image, the left anterior descending artery (LAD) is shown in the interventricular septal region. The left main coronary artery and circumflex are also delineated.

Oncologic Imaging

Non–Small Cell Lung Cancer

Treatment decisions are often predicated on the status of the mediastinum in patients with NSCLC. Patients with operable disease, without mediastinal lymph node involvement, generally proceed directly to resection. Patients with operable disease but involved ipsilateral mediastinal lymph nodes (N2) typically receive induction therapy or definitive chemoradiotherapy. Patients with contralateral mediastinal or supraclavicular disease (N3) are not considered appropriate surgical candidates.

PET-CT is superior to CT in staging the mediastinum and is the standard noninvasive staging tool for NSCLC. The sensitivity of PET-CT in detecting mediastinal lymph node involvement is generally about 80% to 85% with a specificity of 80% to 90%.[54] However, PET-CT is not sensitive enough to

replace pathologic staging. Thus, mediastinoscopy or endobronchial ultrasound is often utilized to pathologically stage the mediastinum.[55]

Localization of the esophagus is important during treatment planning of lung cancer. The esophagus is often well visualized on CT. However, its course can be tortuous and its exact location is often uncertain, especially in the subcarinal region. Having the patient swallow dilute contrast during the planning CT can be helpful. IV contrast helps delineate several important cardiac substructures such as the coronary arteries and aortic valve, but more advanced cardiac imaging is necessary to visualize others. Motion of the heart and lungs degrades resolution of the heart on standard planning CT scans.

Esophageal Carcinoma

The most used staging tools for esophageal carcinoma are barium swallow, EUS, CT, and PET-CT. EUS, as previously discussed, is the most accurate modality to assess depth of invasion (T stage) but is slightly less accurate in assessing nodal involvement (N stage) (Figure 30.10). The ability to perform fine-needle aspiration biopsies of suspicious nodes has significantly increased the accuracy of EUS staging of regional nodes.[56] The reported accuracy of EUS for esophageal staging is approximately 90%, especially for experienced gastroenterologists.[57] PET-CT is primarily used to evaluate for metastatic disease and is superior to CT.[58] PET-CT may also be helpful in identifying patients who have achieved a complete response to neoadjuvant chemoradiotherapy, potentially sparing them from the morbidity of surgery. This is most relevant for patients with squamous cell carcinomas.

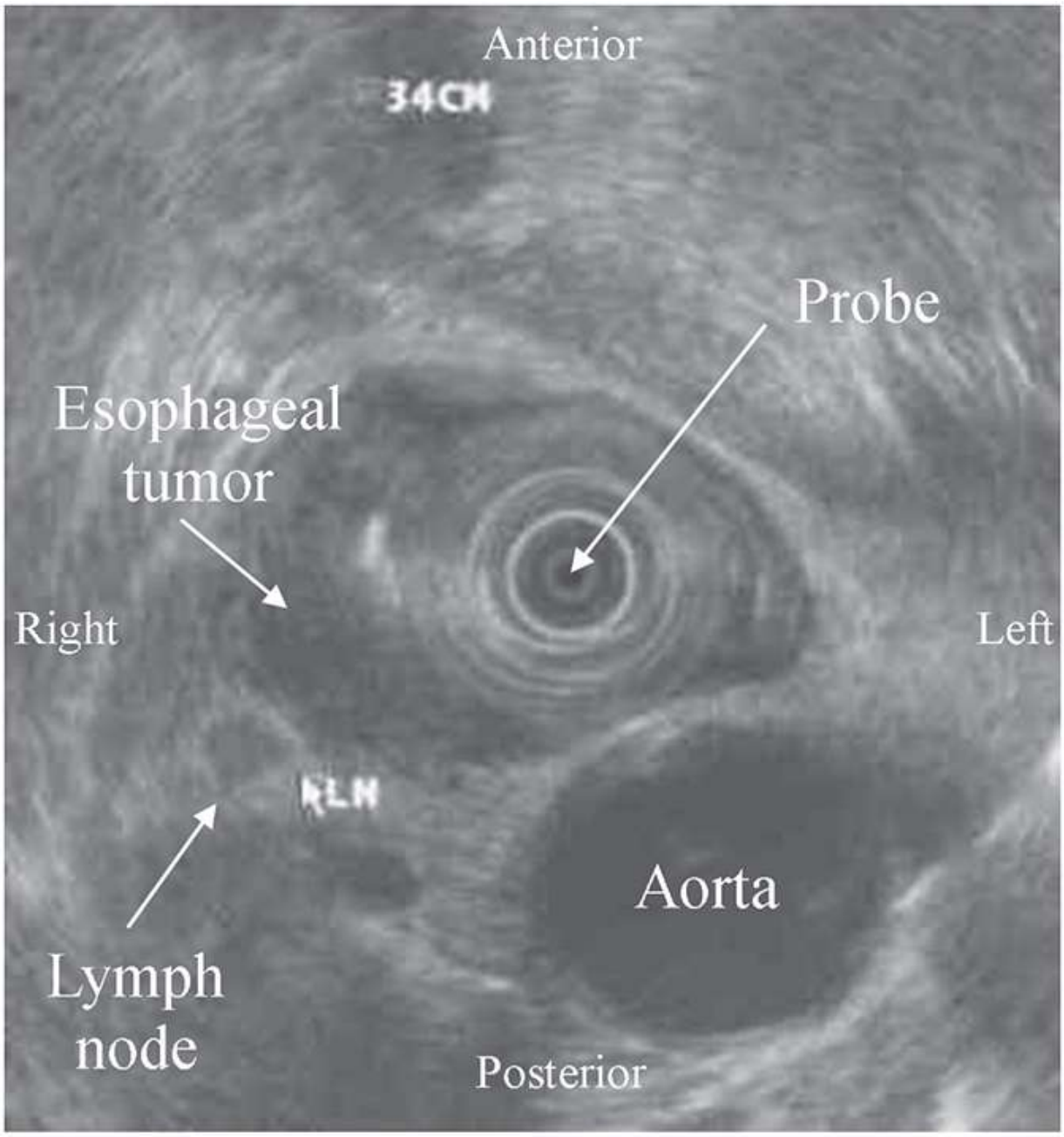


FIGURE 30.10 Endoscopic ultrasound image demonstrating a T3 esophageal tumor with an abnormal peritumoral lymph node. (Courtesy of Dr Frank Gress.)

Mesothelioma

The characteristic CT appearance of pleural mesothelioma is focal or diffuse nodular pleural thickening, which demonstrates enhancement postcontrast administration. MRI is not routinely used in the diagnosis of mesothelioma but can be helpful in special circumstances (eg, evaluating cardiac invasion).

PET-CT is often performed for staging to detect distant and nodal metastases. However, it can also be helpful in establishing the initial diagnosis when CT findings are subtle, as even small foci of disease are typically highly FDG avid.

Superior Sulcus

Superior sulcus tumors are NSCLCs that arise in the apex of the lungs and invade surrounding structures, such as the chest wall, vertebral bodies, and/or brachial plexus. CT is best to define the primary tumor and detect rib or vertebral body invasion. Contrast-enhanced MRI using T1-weighted sequences is best for determining resectability by assessing the brachial plexus and surrounding vascular structures.[59] The primary role of PET-CT is to identify distant and nodal metastases.

Thymic Malignancy

Thymic neoplasms develop in the anterior mediastinum (Figure 30.11) and are often discovered incidentally when imaging is obtained of the chest. They are rarely symptomatic unless they become quite large or if a paraneoplastic process develops. Contrast-enhanced CT is best for characterizing thymomas and assessing for local invasion into the lung, great vessels, and/or pericardium. A preserved fat plane between tumor and adjacent structures is a negative predictor of invasion. However, mere contiguity of tumor with a structure or loss of normal anatomic planes is not sufficient to rule out surgical resection. CT features that have been correlated with stage III or greater disease include primary tumor size 7 cm or larger, lobulated margins, and infiltrative changes of the mediastinal fat surrounding the mass.[60] PET-CT is useful to detect distant disease, including pleural or pericardial drop metastases.

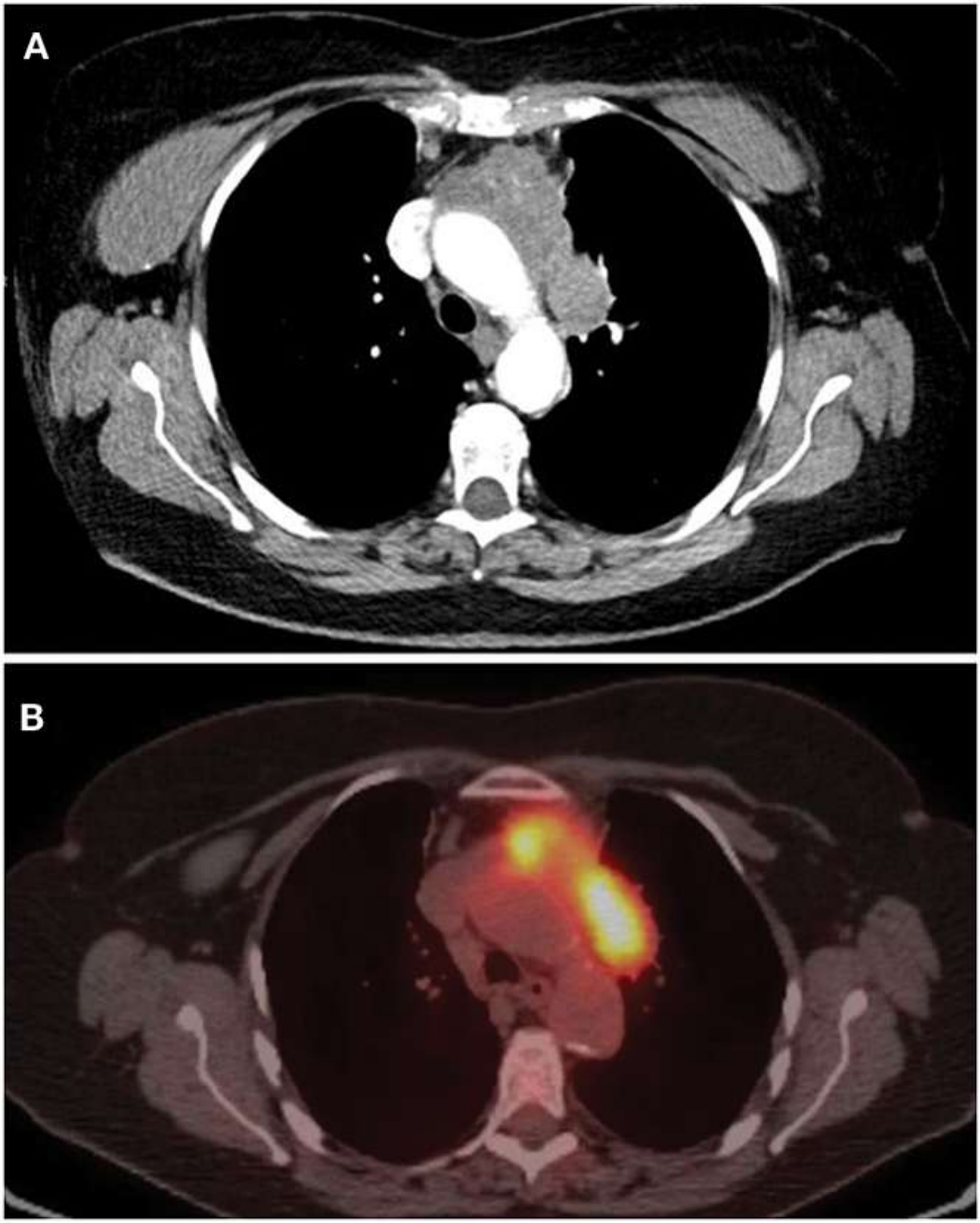


FIGURE 30.11 A. Lobulated anterior mediastinal mass originating in the anterior mediastinum. B. The mass is hypermetabolic on positron-emission tomography computed tomography. Pathology showed a thymic carcinoma.

THE BREAST

Oncologic Anatomy

Breast tissue consists of lactiferous ducts that each drain 15 to 20 mammary gland lobules. The majority of noninvasive (in situ) and invasive ductal carcinomas originate within these ducts. Both males and females have breast tissue, although, with the onset of puberty, it is only well developed in females. Male breast tissue generally contains few ducts, which nonetheless can rarely develop into malignancy, particularly in the context of *BRCA2* mutations.[61] The breast originates from a roughly circular base or bed, with longitudinal extent from the lateral border of the sternum to the midaxillary line, and craniocaudal (CC) extent generally from the second through the sixth ribs. The upper outer quadrant extends along the pectoralis major toward the axilla, forming the axillary tail of Spence. Primary breast cancers are most prevalent in the upper outer quadrant (~40%), likely due to the additional breast tissue associated with the tail. The retromammary space consists of loose connective tissue, allowing for movement of the breast on the chest wall. Two-thirds of the breast rests on the deep pectoral fascia, which overlies the pectoralis major; the remainder rests on the fascia of the serratus anterior. The breast is then anchored to the skin by suspensory ligaments (or Cooper ligaments) and interspersed with fat lobules. These ligamentous attachments to the skin become more prominent with breast edema or congestion due to tumor involvement of the dermal lymphatics, resulting in the characteristic appearance of *peau d'orange*.

The lymphatic drainage of the breast is primarily to the axilla, although the upper outer quadrant in particular may drain to the intermediary intrapectoral nodes (Rotter nodes) lying between the pectoralis major and pectoralis minor muscles. The inner quadrants in particular may drain to the internal mammary nodes (IMNs). The axilla is divided into three sections, designated relative to the pectoralis minor muscle. The nodes inferolateral to the muscle are termed level I, while those beneath the muscle are termed level II, and those medial to the muscle are level III. Level I and II nodes are generally removed in a standard axillary dissection, while level III as well as infraclavicular and supraclavicular nodes are generally considered unresectable.

In surgical series in which the IMNs were routinely dissected, the incidence of isolated IMN involvement was limited to 4% to 16%.[62-64] The risk of pathologic involvement increased when the axilla was also involved and was dependent on the axillary disease burden and of the involved breast quadrant (Table 30.5). When IMNs are involved, the majority (>85%) tend to be located in the first three intercostal interspaces. Elective irradiation of the IMN nodes remains controversial, though recent randomized data have shown a modest benefit in terms of recurrence rates and cancer-specific survival when IMN and medial supraclavicular fields are treated, particularly in patients with medially or centrally located tumors.[65-67]

TABLE 30.5 RISK OF INTERNAL MAMMARY LYMPH NODE INVOLVEMENT BASED ON STATUS OF AXILLA AND LOCATION WITHIN THE BREAST

Scenario	Livingston and Arlen[62] (%)	Urban and Marjani[63] (%)	Huang et al[64] (%)
Negative axilla	8	16	4
Outer quadrant primary	5	13	3
Medial/central primary	14	20	7
Positive axilla	32	52	28
Outer quadrant primary	23	42	24
Medial/central primary	59	65	36
1-3 + axillary nodes	ns	ns	19
≥4 + axillary nodes	ns	ns	43

ns, not stated.

Oncologic Imaging

Mammography remains the preferred imaging modality for the diagnosis and follow-up of both invasive and noninvasive diseases. Multiple randomized trials have shown that screening mammography reduces the risk of breast cancer mortality by 20% to 35% in women aged 40 to 70 years. Screening mammography includes two standard views of each breast: CC

and mediolateral oblique (MLO). The CC view is oriented in the long axis of the patient, and the MLO view is oriented in the medial-superior/lateral-inferior direction. The MLO view increases visualization of the upper outer quadrant and tail of the breast, while the CC view ensures adequate visualization of the inferior and medial aspects of the breast. Most women (approximately 95%) with abnormalities on a screening mammogram do not have breast cancer, rendering the positive predictive value (PPV) low. Overall, the sensitivity of screening mammography is approximately 75%, with 25% of women diagnosed with breast cancer have a normal mammogram 12 to 24 months prior to diagnosis. Sensitivity and specificity vary significantly based on breast density. For fatty versus dense fibroglandular breasts, reported sensitivities are 87% versus 63%, while specificities are 92% versus 68%.

The Breast Imaging Reporting and Data System was developed to standardize reporting and quality assurance of screening mammography within the United States (Table 30.6).[68] Mammographic features concerning for malignancy include focal masses, irregular borders, and microcalcifications. Spiculation can be due to invasion into or reactive changes within the surrounding breast parenchyma. Spiculated masses, however, can also be secondary to fat necrosis, postoperative scarring, or other nonmalignant processes. Calcifications associated with ductal carcinoma in situ or invasive carcinoma are typically pleomorphic (heterogeneous) in appearance and clustered in a localized area (Figure 30.12). Linear, branching calcifications are suggestive of intraductal carcinoma. Round, well-circumscribed lesions, with or without coarse calcifications, are often benign.

TABLE 30.6 BREAST IMAGING REPORTING AND DATA SYSTEM (BI-RADS) CATEGORIES USED FOR MAMMOGRAPHY EXAMINATIONS AND RISK OF MALIGNANCY

Assessment Category	Assessment	Risk of Malignancy (%)
0	Need additional imaging evaluation	na
1	Negative	<0.1
2	Benign finding	<0.1

Assessment Category	Assessment	Risk of Malignancy (%)
3	Probably benign finding—short-interval follow-up suggested	<2
4	Suspicious abnormality—biopsy should be considered	2-95
5	Highly suggestive of malignancy	>95
6	Known biopsy-proven malignancy	100

na, not available.

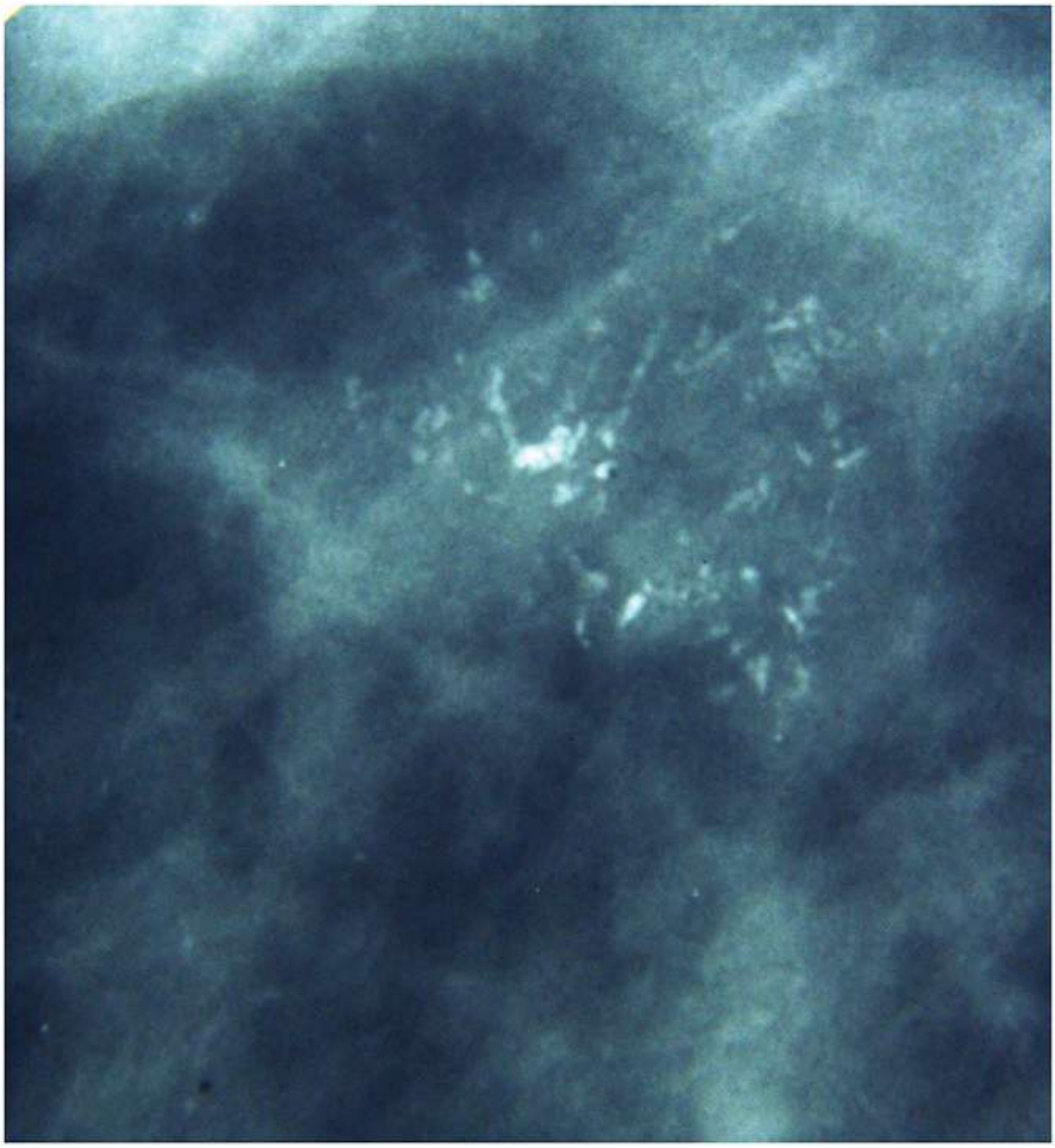


FIGURE 30.12 Clustered, pleomorphic calcifications visualized on mammography. The patient was found to have ductal carcinoma in situ.

Patients with abnormal clinical examinations, specific breast symptoms, and/or abnormalities on screening mammogram are generally evaluated with a diagnostic mammogram. In addition to CC and MLO views, supplemental compression and magnified views may be obtained to detect and characterize microcalcifications (Figure 30.13). Breast US is also often

performed to further characterize suspicious lesions, guide core biopsy, and assess regional lymph nodes. It is most helpful in differentiating fluid-filled cysts from solid tumors.

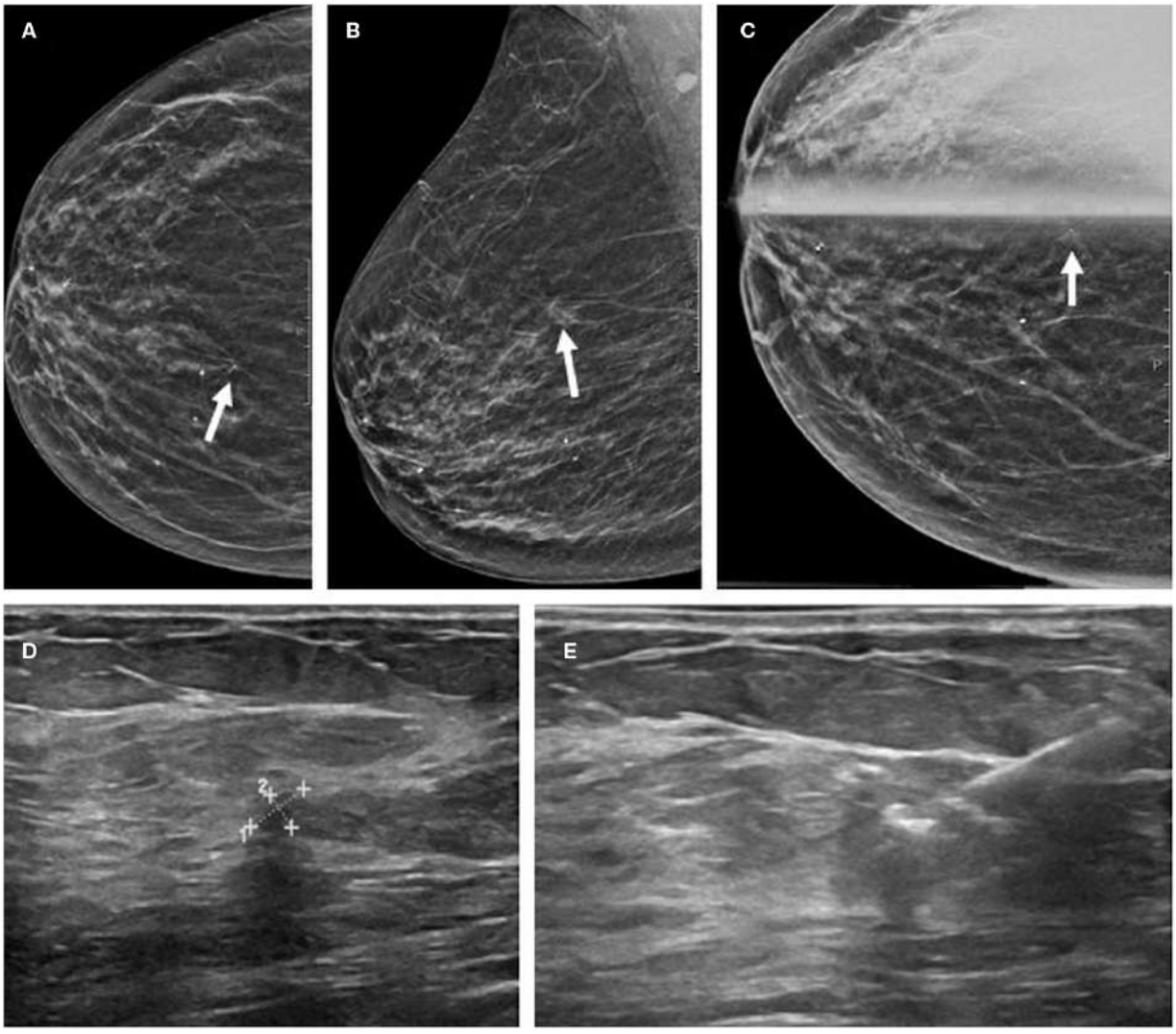


FIGURE 30.13 Invasive ductal carcinoma (indicated by arrow) on mammogram and ultrasound. A. Craniocaudal view (CC view). B. Mediolateral oblique view. C. Spot compression CC view. D. Area of concern demarcated on breast ultrasound. E. Ultrasound-guided breast biopsy.

MRI is not routinely recommended for upfront screening, except in patients at very high risk for primary breast malignancy, including those with *BRCA* mutations, a strong family history of breast cancer, or those who received chest RT at a young age (typically <30 years old).[69] The utility of

routine preoperative MRI in patients with biopsy-proven malignancy has also been studied. One trial found that preoperative MRI resulted in additional contralateral breast biopsies in 12% of patients, with resultant malignant pathology in only 3% of patients. Preoperative MRI was also not shown to reduce the requirement for reoperation in a randomized UK trial.[70] In addition, the routine use of preoperative MRI is associated with an increase in the percentage of women undergoing mastectomy, as opposed to breast conservation, with unclear oncologic benefit.[71] While preoperative MRI may be useful in select circumstances, given its limited specificity, routine usage is not recommended.

Digital breast tomosynthesis (DBT) is a method of generating three-dimensional (3D) breast imaging from several planar x-ray images taken at differing angles. As with conventional two-dimensional mammography, the images are not taken in axial sections, and only a limited rotational angle is utilized. Generally, DBT appears to result in higher cancer detection rates with fewer false positives, as it allows for distinguishing overlapping lesions that may confound planar imaging.[72] As such, it is beginning to supplement screening for high-risk individuals, particularly in follow-up after radiation treatment.[73]

THE ABDOMEN

Oncologic Anatomy

Gastric Cancer: Patterns of Lymphatic Spread

The stomach is divided into four subsites: the gastroesophageal junction (cardia), fundus, body, and pylorus (antrum). The incidence of epithelial malignancies of the distal stomach has declined in Western countries over the past century, while the incidence of malignancies involving the gastroesophageal junction has increased.[74] Lymph node involvement is common in gastric cancer, likely due to the extensive submucosal and subserosal lymphatic networks. This rich lymphatic network places all lymph node regions within the abdomen at risk of harboring regional metastases, irrespective of the location of the gastric tumor. Some general patterns have been observed, however, which can guide radiation treatment planning. The perigastric region located along the greater and lesser curvatures of the stomach is typically the initial draining lymph node basin;

this region is typically addressed by a D1 lymph node dissection and is covered in radiation treatment plans. The other primary lymph node basins lie along the three arterial branches of the celiac axis (common hepatic, left gastric, splenic) and are typically explored in a D2 dissection. These nodal basins should also be covered in most radiation treatment plans, though coverage of the splenic artery/hilum can potentially be limited when treating more distal tumors. Secondary and tertiary drainage sites include lymph nodes in the hepatoduodenal, peripancreatic, para-aortic, mesenteric, and middle colic basins. Detailed guidelines have been published outlining proposed radiation fields for gastric cancer based on the extent of surgery and site of involvement within the stomach.[75]

Pancreas

The pancreas is an elongated digestive gland located posterior to the stomach. It is classically divided into four parts: the head, neck, body, and tail. Most pancreatic carcinomas arise within the pancreatic head, which is nestled within the curve of the duodenum. The pancreas has a rich lymphatic network and is in close proximity to multiple other abdominal organs and structures, making surgical resection challenging, which can subsequently negatively impact long-term survival. Surgery offers a chance of cure for pancreatic carcinomas, but most tumors are not resectable at diagnosis.

Biliary Tree

Hepatocytes within the liver secrete bile into bile canaliculi, the initial branches of the intrahepatic duct system. These canaliculi drain bile into larger channels that eventually form the left and right hepatic ducts, draining bile from the respective lobes of the liver. These ducts exit the liver via the porta hepatis and join to form the common hepatic duct. The cystic duct joins the common hepatic duct to form the common bile duct and empties into the duodenum (Figure 30.14).

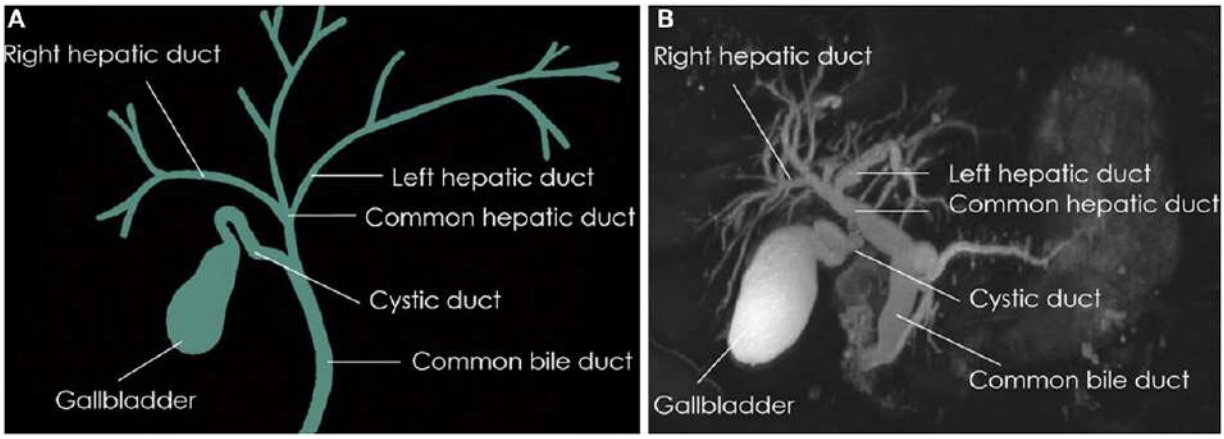


FIGURE 30.14 Anatomy of the biliary tract in an illustrated schematic (A) and on magnetic resonance cholangiopancreatography imaging (B).

Biliary tract cancers include cholangiocarcinomas of the gallbladder and bile ducts. These include intrahepatic, perihilar, and extrahepatic biliary malignancies. Klatskin tumors are perihilar tumors that involve the bifurcation of the common hepatic duct. Distally located biliary tumors tend to have improved resectability and prognosis.

Oncologic Imaging

Pancreatic Cancer

The pancreas can be imaged with US, CT, and MRI. The clinical stage of pancreatic cancers can be determined with accurate pretreatment CT imaging. MDCT with IV contrast and thin-section reconstructions optimize pancreatic tissue characterization and allow for detection of small tumors as well as vascular and ductal invasion. CT with thin-section reconstructions and IV contrast enhancement is important for assessing whether a tumor is resectable, borderline resectable, locally advanced, or metastatic. On CT, pancreatic adenocarcinoma usually appears hypodense mass relative to the normal pancreatic tissue. Encasement of the superior mesenteric artery (SMA) or celiac trunk defines an unresectable T4 tumor. Conversely, the presence of a fat plane around the celiac trunk and SMA, along with a patent superior mesenteric (SMV) or portal vein, indicated potentially resectable disease. Borderline cases include those with tumor abutment of the SMA, severe unilateral SMV or portal vein impingement, or adjacent organ invasion (Figure 30.15). CT does not, however, sensitively detect small

volume peritoneal or surface liver metastases; these can be identified with laparoscopy as indicated. MRI may also be performed when CT findings are equivocal or there is a contraindication to administering iodinated contrast; however, there is no diagnostic advantage of MRI over contrast-enhanced CT (sensitivity of 84% vs 86%).[76] The role of FDG-PET for pancreatic cancer diagnosis and staging remains uncertain and is not routinely performed.

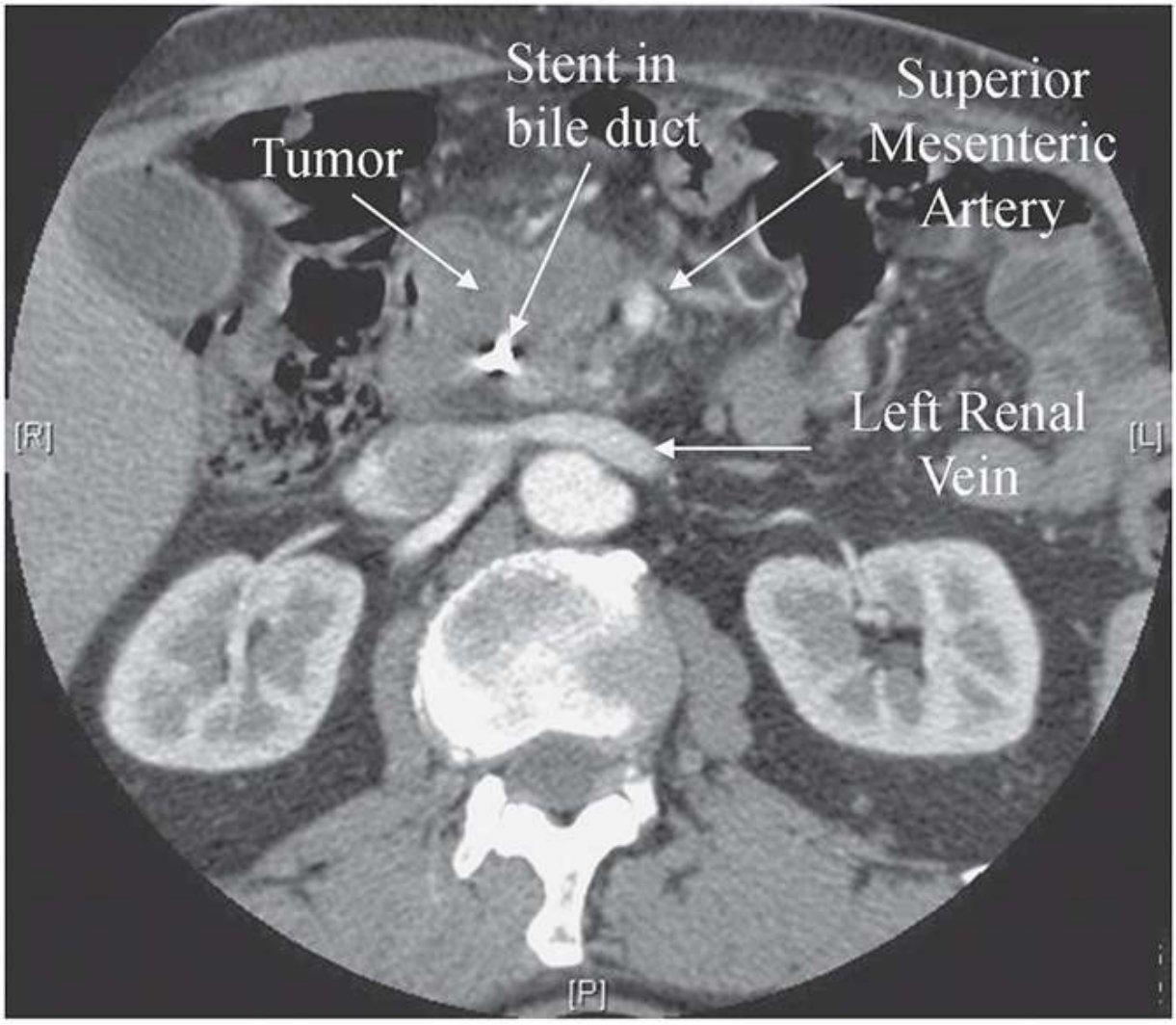


FIGURE 30.15 Axial computed tomography image demonstrating an adenocarcinoma of the pancreatic head, with tumor abutting the superior mesenteric artery.

Hepatic Imaging

Multiphase CT and MRI with IV contrast allow for morphologic characterization of the liver and biliary system. The administration of IV contrast is essential as many hepatic tumors are of similar attenuation as normal liver parenchyma and are not identifiable until central necrosis is present. Imaging is performed in the arterial, portal venous, and delayed phases of enhancement. This allows for detection of both early- and late-enhancing lesions, as well as characterization of enhancement patterns that can differentiate between benign and malignant disease. For example, hepatic hemangiomas, which are the most common benign vascular liver lesions, classically exhibit low attenuation on noncontrast CT images, have peripheral enhancement on the arterial phase and demonstrate central filling on the portal venous phase. Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy and is characteristically hypervascular with pronounced enhancement throughout the solid tumor components on arterial phase images and diminished enhancement on portal venous phase images. Contrast-enhanced imaging can also identify invasion of tumor into the portal and hepatic veins, which is frequently associated with portal vein thrombosis. Liver Imaging Reporting and Data System (LI-RADS) is a standardized method of categorizing liver lesions in patients at risk for developing HCC and applies to imaging with ultrasound (LI-RADS US) and CT/MRI (LI-RADS CT/MRI). CT and MRI have similar sensitivity and specificity for evaluation of focal, larger lesions.[77,78]

The liver is also one of the most common sites for metastatic disease. Contrast-enhanced CT is fairly sensitive (74%) and specific (77%) for detecting hepatic metastases. CT of the liver to assess for metastatic disease is typically performed with biphasic technique. Although most metastases are identified on the portal venous phase, some hypervascular tumors (eg, melanoma, renal cell carcinoma) may only be identified on arterial phase imaging. MRI has superior diagnostic sensitivity of up to 95% and outperforms CT imaging in this regard, particularly in the detection of small liver metastases.

Biliary Imaging

US is typically the initial imaging study for patients with suspected biliary or pancreatic disease. The primary goals of evaluation include assessing for abnormal biliary and pancreatic ductal dilatation (>3 mm), identifying

calculi, characterizing the gallbladder wall, and excluding a pancreatic head mass. US does not, however, image the entire pancreatic and biliary ductal system. In the presence of an US abnormality, further imaging is required.

Endoscopic retrograde cholangiopancreatography (ERCP) is a minimally invasive procedure that involves passing an endoscope into the duodenum and cannulating the main bile duct at the ampulla of Vater. Contrast is then infused to image both the biliary and pancreatic ductal system. Though it is minimally invasive, ERCP can induce pancreatitis in 1.3% to 8.6% of patients.[79] Any evidence of biliary obstruction in the absence of calculi typically prompts further evaluation with cross- sectional imaging to exclude malignancy. ERCP can itself, however, directly visualize ampullary carcinomas and permit tissue diagnosis using needle aspiration, brush cytology, or forceps biopsy. ERCP may also provide palliation via stent placement in the setting of known obstructive biliary malignancy.

Magnetic resonance cholangiopancreatography (MRCP) is a noninvasive method of imaging the intrahepatic and extrahepatic biliary and pancreatic ductal system. MRCP does not require IV contrast: Imaging relies on heavily T2-weighted sequences and high-resolution techniques, resulting in the pancreatic and biliary ducts appearing hyperintense in contrast to surrounding soft tissues. MRCP can be a useful adjunctive tool in terms of defining the anatomic extent of potential malignant biliary obstruction.

THE PELVIC LYMPH NODES

Oncologic Anatomy

The lymphatic drainage of pelvic organs follows the iliac vessels throughout their branching within the pelvis. Most superiorly within the pelvis, the common iliac chains receive the majority of lymph drainage from intrapelvic organs, which then empty to the para-aortic chains superiorly. The gonadal veins and arteries are notable exceptions to this orderly flow of lymph from the pelvis and are discussed separately below. Also of note, the rectum, sigmoid, and distal colon have a separate path for lymphatic metastasis via the inferior mesenteric chain to the preaortic basin.

The common iliac pathway receives lymphatic drainage from three primary routes: the external iliac chain, the internal iliac chain, and the presacral chain. The external iliac pathway begins at the point where the

femoral vessels cross the inguinal ligament to become the external iliac chains, which courses more proximally to the common bifurcation. The internal iliac chain (also termed the *hypogastric chain*) is a more complex plexus, flowing back from the distal elaborations of the same artery. Just as these branches of the internal iliac vessels provide blood supply for the pelvic organs, the corresponding lymph node chains provide the majority of lymph drainage. The obturator nodes are part of the internal iliac system and may be found at the point in which the obturator vessels perforate the obturator internus muscle. Radiographically, these nodes lay medial to the femoral head, just superior to the bony obturator foramen. The presacral chain is located just anterior to the sacrum and receives lymphatic drainage from the rectum, the cervix, and posterior vagina and the prostate.[80,81]

The testicles have lymphatic drainage that differs with laterality, mirroring the differences in venous drainage. On the right, the testicle drains into the para-aortic nodes along the lower portion of the inferior vena cava at about the level of L3-L4 following the left testicular vein. On the left, the testicle drains to the renal hilar nodes following the left testicular vein.

Oncologic Imaging

CT is the preferred means of identifying vessels within the pelvis and is an acceptable method of delineating the pelvic lymph node basins for elective RT. A 7-mm margin may be applied to the internal and external iliac vessels to arrive at a nodal CTV, with uninvolved bone, muscle (such as the psoas), and bowel excluded from the volume. The 7-mm margin was determined as the minimum margin on CT visible vessels needed to cover 95% of all nodes identified using ultrasmall iron oxide particles as an MRI contrast agent.[82,83] Special care, however, should be taken to include visualized lymph nodes, even if they lie outside this margin.

Symmetric expansion margins on vessels are not adequate in the para-aortic or inguinal regions. In the para-aortic region, the most common location for nodal involvement includes the region to the left of the aorta, a basin that extends to the medial margin of the psoas muscle.[84] This region is often inadequately covered by a symmetric expansion. Similarly, in the inguinal region, nodes lie medial to the femoral neurovascular bundle, often

at a distance ≥2 cm. In this region, the space bounded by the regional musculature is the preferred CTV.[85]

One centimeter of soft tissue anterior to the sacrum, bridging between the common and internal nodal CTVs, should be added when presacral coverage is required. The Radiation Therapy Oncology Group (now part of the NRG) developed several atlases to aid the clinician in the contouring of pelvic CTVs. With 3D CT imaging, bony landmarks are no longer the ideal determinant of block or multileaf collimator shapes when treating the pelvis.[86]

THE RECTUM

Oncologic Anatomy

The rectum is the final, straight portion of the large intestine, beginning at the transition of the sigmoid colon with the fusion of the taenia coli into the circumferential longitudinal muscle. It terminates with the rectal ampulla, leading to the anal canal and dentate (or pectinate) line. Posteriorly, the rectum is extraperitoneal, whereas anteriorly, the peritoneal reflection occurs at approximately 7 to 9 cm from the anal verge at the posterior aspect of the bladder in males (superior to the prostate), and 5 to 8 cm from the verge in females, forming the rectouterine pouch, or pouch of Douglas. Below this point, the distal third of the rectum is extraperitoneal.

The mesorectum is the supportive mesentery of the rectum, located in the extraperitoneal space between the rectum anteriorly and the sacrum posteriorly. It is at risk for both direct and lymphatic spread of rectal cancers. High-quality total mesorectal excision with sharp dissection has been associated with excellent local control when compared to blunt dissections for rectal cancers. However, this has not obviated the need for perioperative RT, as demonstrated by an increase in local recurrences with omission.[87,88]

Oncologic Imaging

Colonoscopy is the most accurate diagnostic test for colorectal cancer. Biopsies can be performed with endoscopically visible lesions. A complete colonoscopy can also assess synchronous second primary colorectal cancers. For suspected rectal cancer, pelvic MRI is the recommended imaging

modality for initial tumor and nodal staging as well as post-therapy restaging. MRI not only allows for high accuracy clinical staging (~90% concordance with pathologic T staging) but can also further stratify patients for appropriate therapies based on the presence of various high-risk features, such as extramural venous invasion and close circumferential resection margins (Figure 30.16).[89,90] Recommendations for standardized MRI evaluation and reporting have been published.[91] Transrectal endoscopic ultrasound (TEUS) is an alternative imaging modality for tumor and nodal staging, particularly for early-stage tumors. The accuracy of TEUS may be limited by the inability to adequately image bulky or proximal tumors.[92] TEUS can, however, still be utilized when there is a contraindication to pelvic MRI and may provide complementary information in some cases. Contrast-enhanced CT is the preferred imaging modality to detect distant metastatic disease, particularly synchronous liver metastases, which can occur in up to 20% of patients.[93]

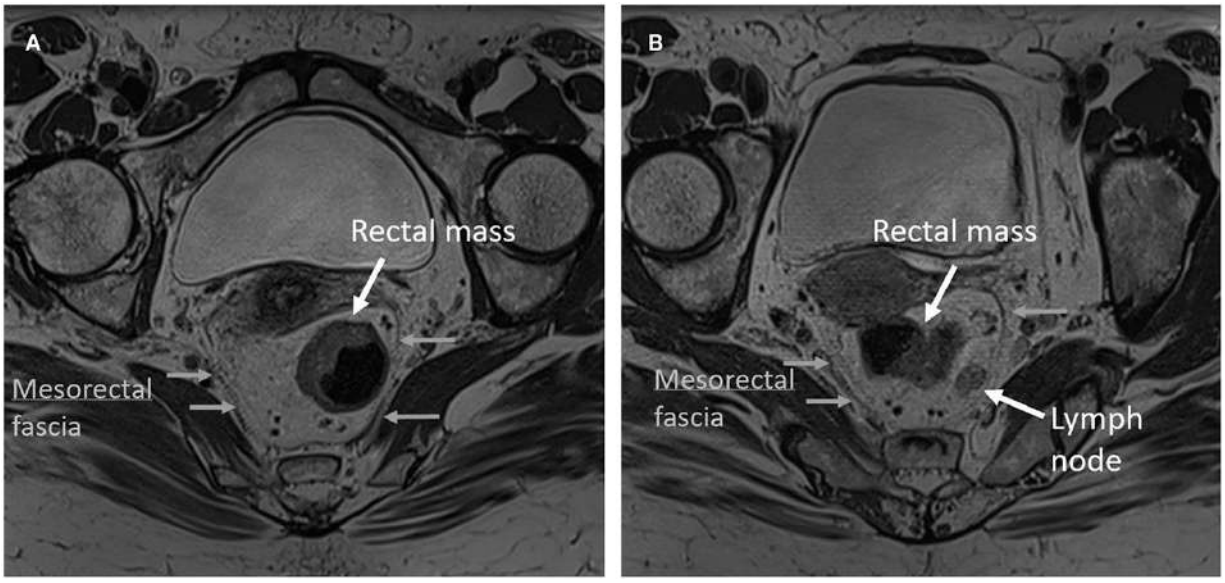


FIGURE 30.16 Rectal carcinoma on magnetic resonance imaging (MRI). A. Representative axial slice on a T2-weighted MRI. B. Representative axial slice on a T2-weighted MRI.

THE BLADDER AND URETHRA

Oncologic Anatomy

The bladder is an expansile muscular organ, which may be contained completely within the pelvis when empty and may extend far into the

abdominal cavity when distended. The trigone is the posterior and inferior portion of the bladder, defined by the two ureteral orifices and the internal urethral meatus. The trigone remains fixed at the base, while the superior portion of the bladder expands to accommodate urine. Due to this distensibility, the bladder is surrounded by loose connective tissue and fat. Anteriorly, this connective tissue is termed the *space of Retzius*, or the *retropubic space*.

The urethra traverses a short distance to the introitus in females, measuring approximately 4 to 5 cm in length. In males, it is approximately 20 cm in length and traverses the prostate and penis to reach the meatus.

The base and posterior wall of the bladder preferentially drain to the obturator and internal iliac lymphatic basins via anterior pathways. In contrast, the external iliac chain receives primary drainage from the lateral and superior bladder wall. Cancer arising from the bladder neck may also metastasize to the presacral nodal basins. Bladder cancer is the most common malignancy involving the urinary system, though direct spread from other pelvic malignancies should be considered (prostate or cervix).

Oncologic Imaging

Cystoscopy with biopsy is considered the gold standard for the initial diagnosis of bladder cancer. CT or MRI can be used to assess the extent of local invasion of primary muscle-invasive bladder tumors, though sensitivity and specificity for detection of lymph node metastases are low.[94] CT urography (CT of the abdomen and pelvis with IV contrast and excretory imaging) is useful for the diagnosis of superficial bladder tumors and for imaging of the upper urinary tract, but cannot differentiate the depth of bladder wall invasion (Figure 30.17). MR urography may be appropriate in patients with poor renal function or iodinated contrast allergy. FDG-PET has limited utility in tumor staging due to obscuration with urinary excretion of FDG. Chest radiographs are often used for the initial evaluation of metastatic disease, but CT chest may be preferred in some scenarios, such as muscle-invasive bladder cancer.

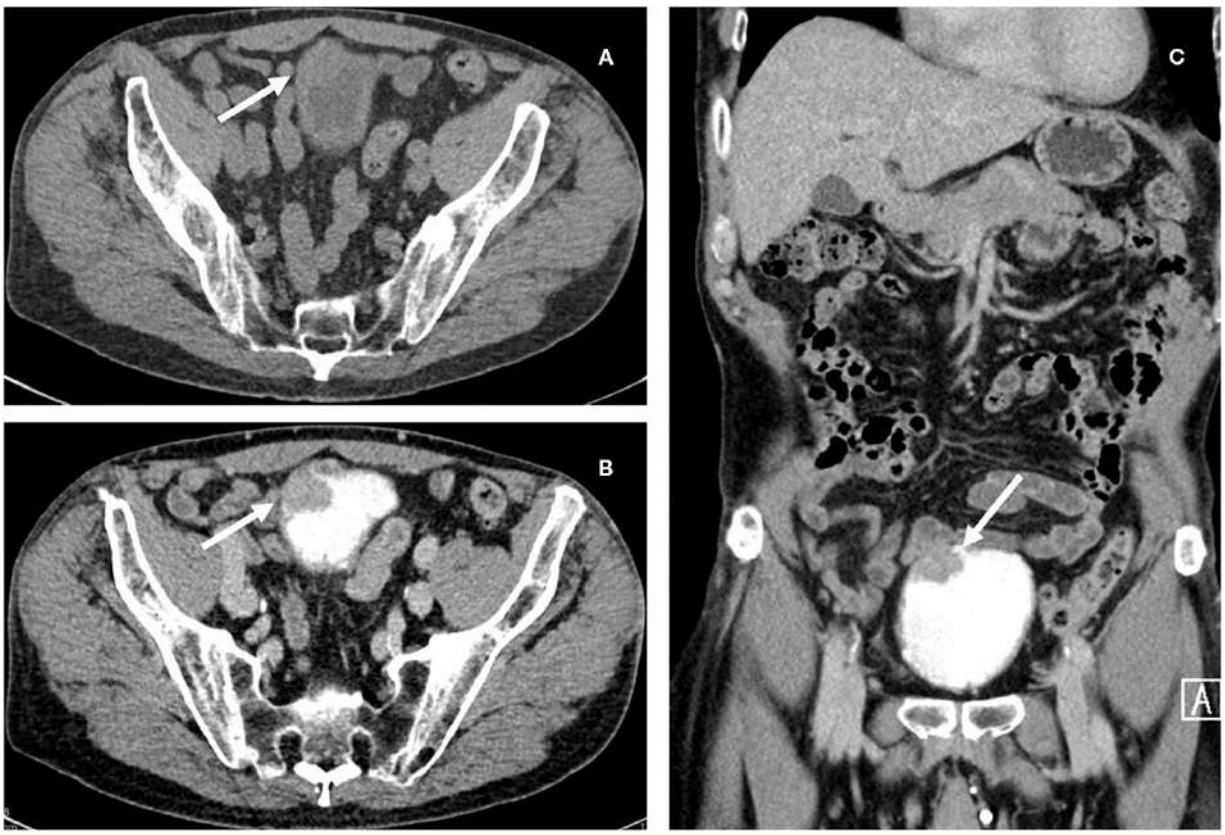


FIGURE 30.17 High-grade urothelial carcinoma (indicated by arrow) on computed tomography (CT) and CT urogram. A. Representative axial slice on pelvic CT scan. B. Representative axial slice on CT urogram. C. Representative coronal slice on CT urogram.

CERVIX, UTERUS, AND OVARIES

Oncologic Anatomy

The uterus lies between the bladder anteriorly and the rectum posteriorly, covered by a layer of peritoneum. Laterally lie the fallopian tubes and ovaries, which are anchored medially by the ovarian ligament (or utero-ovarian ligament) and laterally by the suspensory ligament of the ovary (or infundibulopelvic [IP] ligament). The ovarian arteries originate from the abdominal aorta, just inferior to the renal vessels, following a course anterior to the psoas on the left and crossing anterior to the inferior vena cava to the psoas on the right, both sides crossing anterior to the ureter and then crossing medially with the IP ligament to the ovaries. The fold of the peritoneum over the uterus continues laterally over these structures, forming the broad ligament. Similar to the testes, the right ovarian vein drains to the inferior vena cava, while the left ovary drains to the left renal vein.

The uterine corpus or body is the cephalad two-thirds of the organ and is lined internally by the endometrium, which varies in thickness by the menstrual cycle and by menopausal status. The middle muscular layer, the myometrium, is primarily smooth muscle. The final outer layer is the serosa or perimetrium and is continuous with the peritoneum. The caudal one-third of the organ is the uterine cervix, which consists of firm connective tissue, approximately one-half of which extends into the vagina. The intravaginal portion is lined by nonkeratinized squamous epithelium (the ectocervix), whereas the cervical canal is lined by columnar epithelium (the endocervix).

Lateral to the uterine cervix and corpus is the parametrium, consisting of the paracervical tissue, including the cardinal ligament, uterine artery and vein, and the ureter as it courses anteriorly to the bladder. This caudal portion of the parametrium is of importance for evaluation of lateral spread of cervical cancer and can best appreciated on physical examination by a rectovaginal examination, where the examining rectal finger can palpate these structures. Cephalad to this, the parametrium continues as the broad ligament, terminating at the suspensory ligament of the ovary. Posteriorly the cervix is anchored to the sacrum via the uterosacral ligament, which classically attaches at the third sacral foramen, although MRI studies would suggest a fair amount of individual variation.[95]

Oncologic Imaging

MRI of the pelvis is the most useful modality outside the physical examination to determine the extent of disease within the uterus and cervix with an accuracy of approximately 85% (Figure 30.18).[96,97] For endometrial carcinoma, T2- and postcontrast T1-weighted sequences are beneficial in staging, such as identifying the primary tumor, extent of invasion, and involvement of regional pelvic lymph nodes. In the setting of cervical cancer, T2-weighted sequences are often the most useful in determining the extent of disease and are preferred for MRI-guided brachytherapy.[98] Either CT or MRI may be used for image-guided brachytherapy to potentially improve central disease control and reduce toxicity. However, CT systematically provides larger estimates of target size compared to MRI, particularly in the lateral extent.[99,100] US (either via a transabdominal or through transrectal approach) can be useful during intracavitary

brachytherapy to ensure the proper placement of a uterine tandem and prevent uterine perforation.

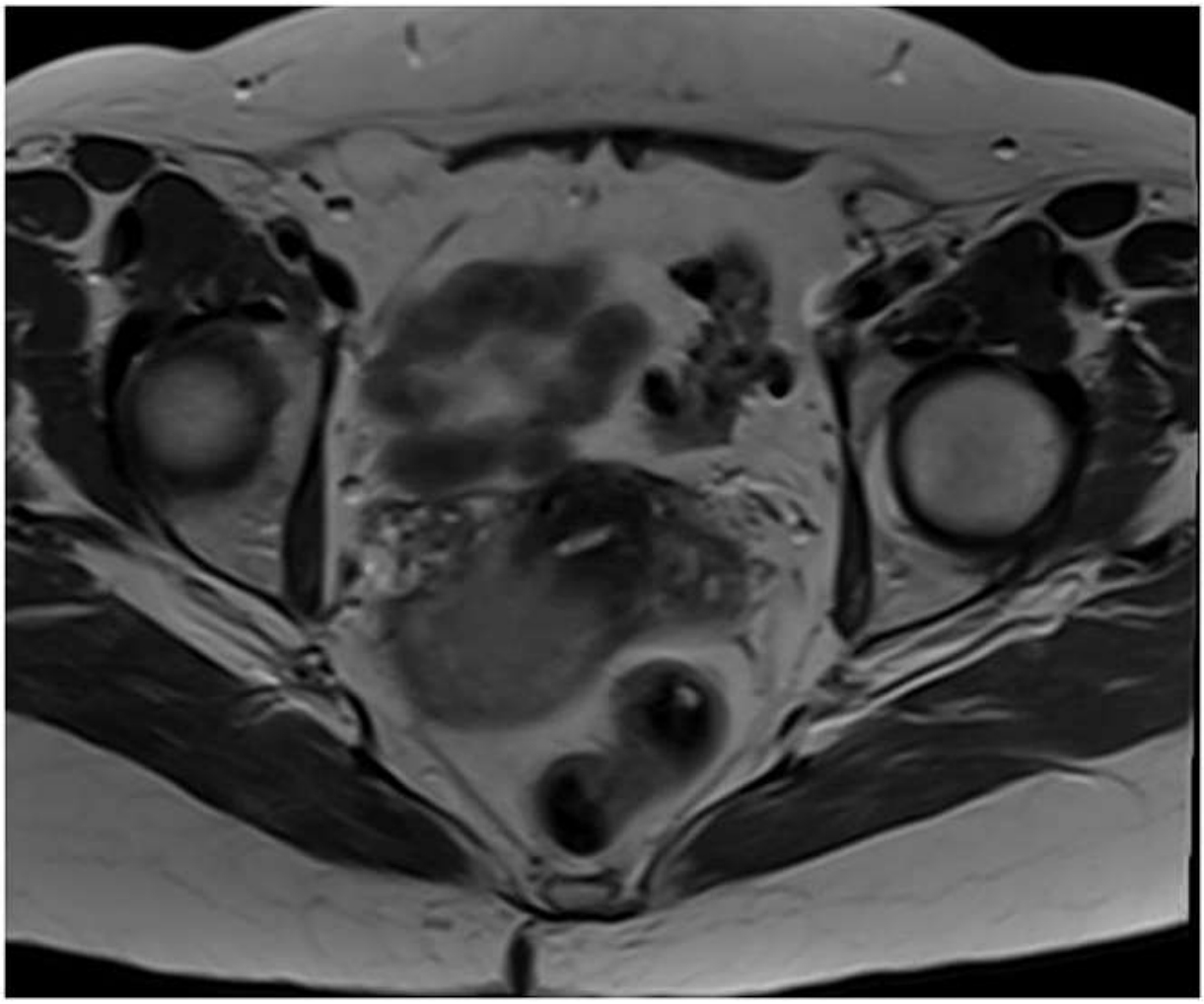


FIGURE 30.18 T2-weighted magnetic resonance imaging of a patient with cervical cancer showing right-sided sidewall extension (FIGO IIIB). The normal stromal cervix is dark on T2-weighted imaging, while tumor extension appears gray.

PET-CT has been proven to be sensitive and specific in the evaluation of lymph nodes within the pelvic and para-aortic chains with squamous cell carcinoma of the cervix (sensitivity approximately 85% and specificity 95% for para-aortic nodes), although it is less well studied in endometrial and other primary gynecologic sites[101] (Figure 30.19). Investigators from Washington University have extensively studied FDG-PET in cervical cancer, showing that the initial maximum SUV of the primary tumor is

predictive of response to treatment.[102] In addition, they found that a complete metabolic response to treatment was predictive of progression-free survival (PFS); at 3 years, with complete response, PFS was 78% versus 33% in partial responders and 0% with PET progression, findings that have been independently confirmed.[103,104]

FIGURE 30.19 Positron-emission tomography imaging of a patient with cervical cancer showing an 18-fluorodeoxyglucose–avid left internal iliac lymph node.

PROSTATE

Oncologic Anatomy

The prostate lies centrally within the male pelvis, with its widest portion, the base, closely approximating the bladder neck superiorly and narrowing to the apex inferiorly with support from the urogenital diaphragm (UGD).

The prostate consists of the peripheral zone, the central zone, the transitional zone, and the anterior fibromuscular stroma. The peripheral zone constitutes the majority of the gland and is the location of the majority of prostate cancers (60%-70%). The central zone accounts for an additional

25% of glandular tissue and lies near the origin of the seminal vesicles; it is the location of approximately 10% of prostate cancers. The transitional zone surrounds the urethra cephalad to the insertion of the ejaculatory duct, may hypertrophy with age, and is the origin of the remaining 10% to 20% of prostate cancers. The neurovascular bundles are posterolateral to the prostate capsule bilaterally and are a potential site of extraprostatic extension. The seminal vesicles are located superiorly and posteriorly to the prostate and extend laterally and can also be involved by tumor (ie, seminal vesicle invasion or SVI).

The Batson venous plexus is a series of valveless veins located anterior to the vertebral bodies that receives drainage from the deep pelvic veins and prostate gland. It has been postulated that the lack of valves facilitates a pathway for metastatic spread, providing anatomic rationale for the propensity of prostate cancer to involve the lumbosacral vertebral bodies.[105]

The T staging of prostate cancer is based primarily on digital rectal examination. It is important to palpate the lateral sulci of the gland, as evidence of effacement is highly suggestive of extraprostatic extension of disease. However, it may not always be possible to detect prostate cancer or determine extraprostatic extension from the digital rectal examination.

Oncologic Imaging

Transrectal US is invaluable for guiding biopsies for the diagnosis of prostatic disease; however, it has limited specificity and sensitivity (approximately 40%-50%) for the determination of seminal vesicle involvement and extraprostatic extension.

While it can detect gross extraprostatic extension, as well as nodal and distant metastatic disease, CT imaging has limitations, as the prostate gland has similar attenuation characteristics as the anterior and lateral venous plexus, the UGD inferiorly, and the bladder wall superiorly. MRI is an increasingly used imaging modality for the evaluation of the prostate and aids treatment planning. T1-weighted images are used to help determine the presence of hemorrhage and delineate the outline of the prostate gland. T2-weighted imaging can be used to distinguish the zonal anatomy of the prostate, and the prostatic apex can be clearly distinguished from the UGD and other neighboring structures (Figure 30.20). The joint maximum

sensitivity and specificity of detecting extraprostatic extension on MRI is approximately 70%, although this may be improved with endorectal coils.[106,107]

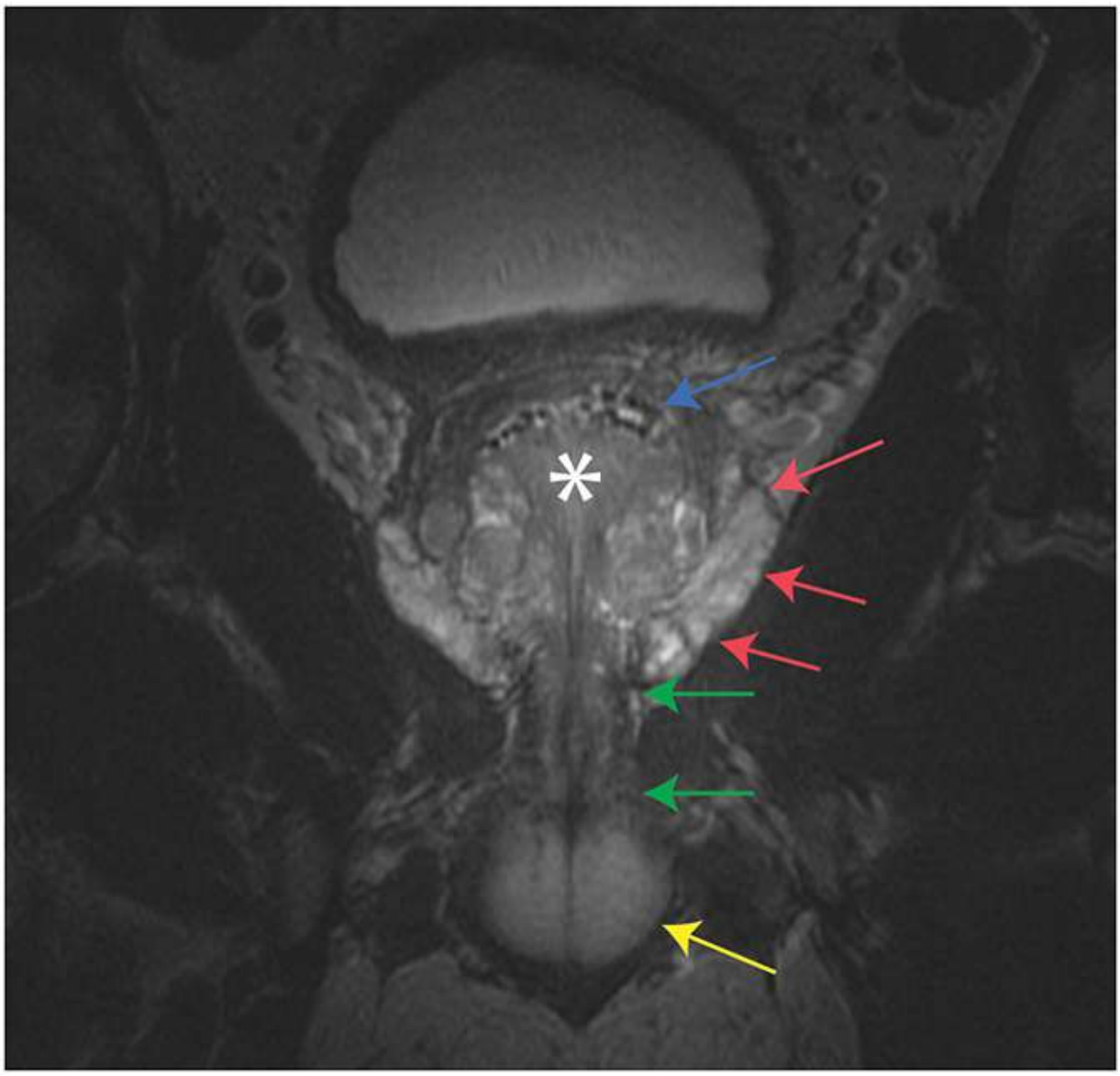


FIGURE 30.20 A coronal T2-weighted magnetic resonance imaging demonstrating the anatomy of the prostate. The regional anatomy is labeled as follows: the asterisk (*) is the central gland—a combination of the central zone and transitional zone; red arrows indicate the peripheral zone; blue arrow indicates the seminal vesicles and their insertion in the base; green arrow indicates the urogenital diaphragm; and yellow arrows indicate the penile bulb.

Multiparametric MRI (mpMRI) consists of different sequences, including T1-weighted imaging, T2-weighted imaging, DWI, and DCE. Combining

the unique characteristics of each of these sequences (discussed in section "Magnetic Resonance Imaging") has led to an increased specificity (>90%) of lesion localization within prostate and in the detection of extraprostatic extension.[108,109] Since prostate cancer has increased cell density, there may be focally restricted free water diffusion on DWI, hypointense on ADC maps (Figure 30.21). The Prostate Imaging Reporting and Data System (PI-RADS) has been developed to serve as a standardized system for reporting findings of mpMRI in the evaluation of suspected prostate cancers.[110] PI-RADS categorizes prostate lesions based on the likelihood of cancer according to a five-point scale (Table 30.7).

TABLE 30.7 PROSTATE IMAGING REPORTING AND DATA SYSTEM (PI-RADS) FOR MULTIPARAMETRIC PROSTATE MRI IN THE EVALUATION OF SUSPECTED PROSTATE CANCER

Assessment Category	Definition
1	Clinically significant cancer is highly unlikely to be present.
2	Clinically significant cancer is unlikely to be present.
3	The presence of clinically significant cancer is equivocal.
4	Clinically significant cancer is likely to be present.
5	Clinically significant cancer is highly likely to be present.

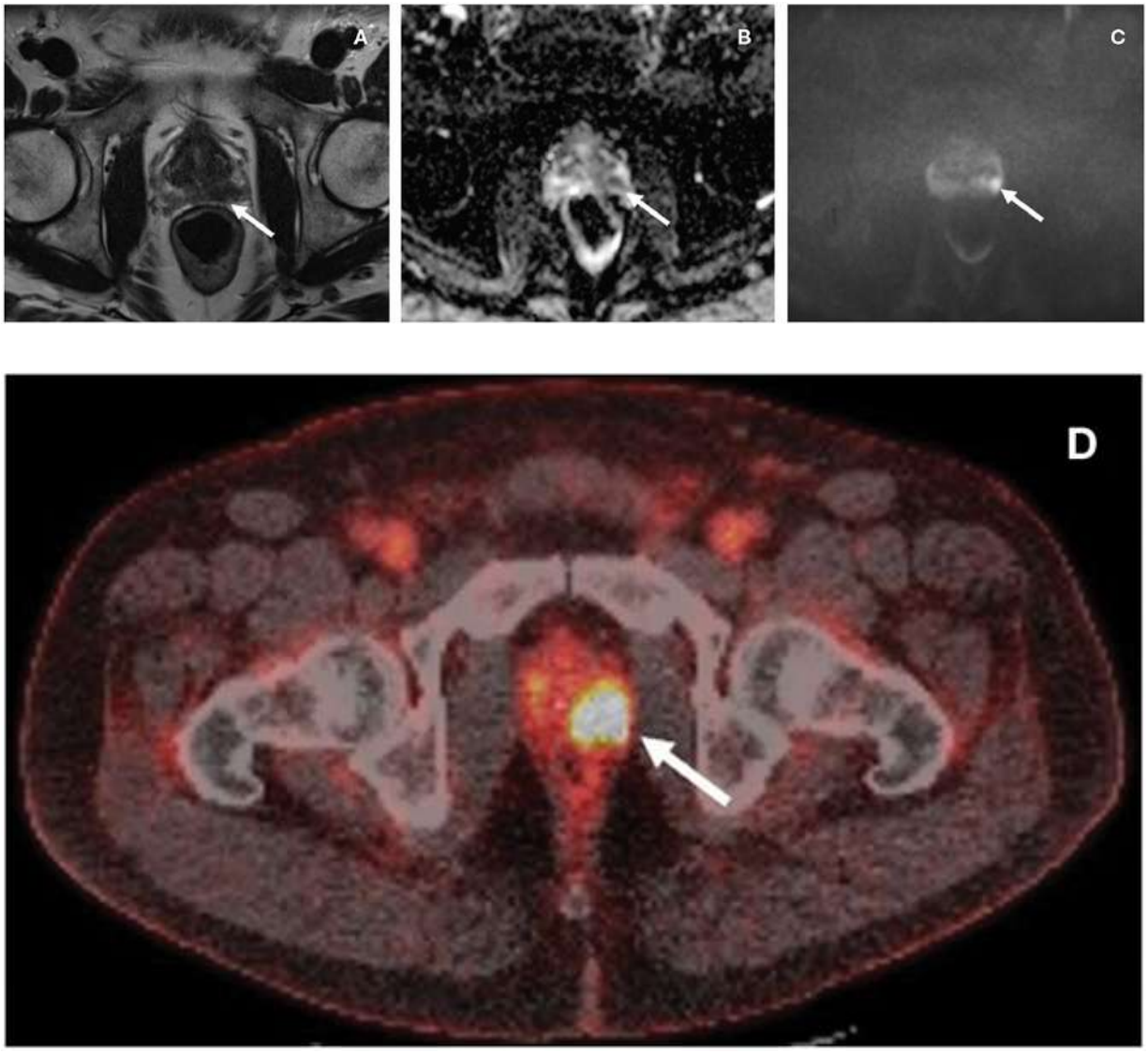


FIGURE 30.21 Prostate carcinoma (indicated by arrow) on T2-weighted magnetic resonance imaging (MRI) (A), apparent diffusion coefficient MRI, (B) diffusion-weighted imaging MRI (C), and prostate-specific membrane antigen positron-emission tomography (D).

In addition to transrectal ultrasound-guided biopsy, mpMRI has become useful for directing targeted prostate biopsies. Prostate MRI can also be useful for the identification of appropriate RT coverage of the prostate apex, areas of extraprostatic extension, and SVI.[111] Compared with CT, MRI better depicts the prostate apex, thus allowing dose reduction to the genitourinary diaphragm, which contains the external urethral sphincter. Prostate MRI can be used to identify areas of dominant intraprostatic lesions and thus direct delivery of a heterogeneous RT dose to the prostate gland.[112] It is important

to keep in mind that prostate imaging and pathologic analyses can be somewhat discordant. The lesions seen with improved imaging techniques can appear focal. However, prostate cancer is mainly a multifocal disease with prostatectomy specimens usually demonstrating the microscopic presence of cancer in multiple regions of the gland. Thus, delivery of heterogeneous RT dose to the prostate gland based on imaging findings is still an area of study in prospective trials.

For evaluation of osseous disease, ^{99m}Tc-MDP bone scintigraphy is the most used modality to detect osteoblastic activity from prostate cancer metastases. However, in recent years, there have been many new sensitive radiotracers. There are Food and Drug Administration-approved prostate-specific PET tracers: Cho ^{11}C, fluciclovine ^{18}F, sodium fluoride ^{18}F, piflufolastat ^{18}F, and ^{68}Ga-PSMA-11. All of these tracers have been approved for the evaluation of patients with biochemical recurrent prostate cancer. Studies have shown that PSMA tracers (^{68}Ga-PSMA-11 and piflufolastat ^{18}F) may have higher sensitivity for disease detection than other modalities, particularly in patients with lower PSA values (PPV 92%).[113,114]

PSMA-PET is now additionally considered an alternative to standard bone and soft tissue imaging for initial staging of patients at high risk for metastatic disease, with sensitivity and specificity of 31% to 42%, and 95% to 99%, respectively.[115] PSMA-PET has been shown to frequently alter radiation treatment planning in patients with high risk or biochemically recurrent prostate cancer, though whether these changes impact survival outcomes is yet unknown.[116,117]

THE LYMPHATIC SYSTEM

Oncologic Anatomy

The lymphatic system is a component of the circulatory system, and wherever arteries and veins pass, lymphatic vessels are also present (with the notable exceptions of the placenta and CNS). In the CNS, lymph is carried within perivascular lymph sheaths as opposed to distinct lymphatic vessels. The lymphatic system includes lymphatic vessels, lymph nodes, lymphatic organs such as the spleen, and the lymphocytes themselves. It is loosely organized but generally follows somewhat predictable paths. Small lymphatic vessels form within the tissues of the body, drain into one or more

lymph nodes, and eventually drain into larger lymph trunks. These unite to form either the thoracic duct or right lymphatic duct, which empties into the venous system at the subclavian vein-internal jugular vein junction. The lymphatics are primarily involved in returning plasma from the interstitial space to the venous system, although they are also involved in the absorption and transport of fat and in defense mechanisms. Site-specific lymphatic spread has been reviewed in prior sections.

Oncologic Imaging

Lymphoma

Lymphomas can arise virtually anywhere in the body, including both nodal and extranodal sites. Consequently, comprehensive imaging with PET-CT plays an integral role in the staging and management of both HL and many NHLs (Figure 30.22). Current guidelines recommend that PET-CT be employed for initial staging of all lymphomas that are FDG avid.[118] CT alone is appropriate for the minority that are not, such as chronic lymphocytic leukemia/small lymphocytic lymphoma. Postchemotherapy response assessment with PET-CT is also standard and should utilize the Deauville criteria (Table 30.8).[119] These criteria are under revision to better define Deauville 4 and 5 responses, which, under various circumstances, can represent either a partial response, stable disease, or progressive disease. A negative (Deauville 1-3) PET-CT scan after chemotherapy does not necessarily mean that all disease has been eradicated, simply that an excellent response was achieved. This point has been confirmed in randomized trials of HL, where patients were randomized to observation or consolidation RT after achieving a complete response by PET-CT after chemotherapy. Even in the setting of a negative post-chemo PET, consolidation RT still decreased the risk of recurrence.[120]

TABLE 30.8 PET-CT RESPONSE ASSESSMENT FOR LYMPHOMAS

Deauville Criteria (Five-Point Scale)	Degree of FDG Avidity	Clinical Interpretation[a]
1	No uptake (below background)	Complete response
2	Above background but equal to or below mediastinal blood pool	Complete response

Deauville Criteria (Five-Point Scale)	Degree of FDG Avidity	Clinical Interpretation[a]
3	Above mediastinal blood pool but below or equal to liver	Complete response
4	Slightly to moderately higher than liver	Partial response, stable disease, or progressive disease
5	Markedly increased uptake than liver or new lesion(s)	Partial response, stable disease, or progressive disease

CT, computed tomography; FDG, 18-fluorodeoxyglucose; PET, positron-emission tomography.

[a]Some clinical trials have defined a “negative” PET-CT as Deauville 1-2 and positive PET-CT as Deauville 3-5.

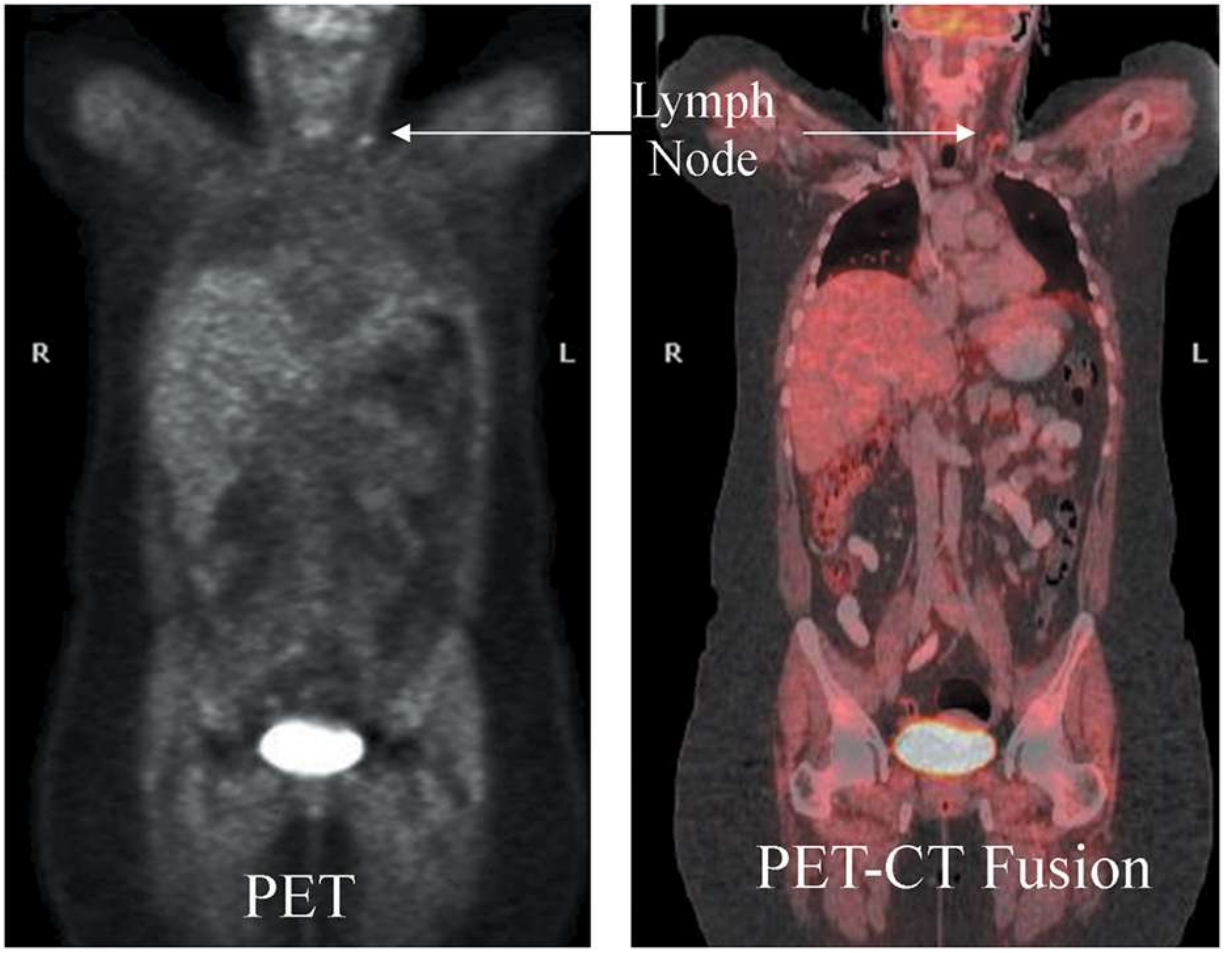


FIGURE 30.22 Postchemotherapy coronal positron-emission tomography (PET) scan images of a patient with stage IVa Hodgkin disease demonstrating a hypermetabolic left supraclavicular lymph node. The lymph node was <1 cm on computed tomography (CT) and would not be considered suspicious. Biopsy confirmed persistent disease. Left: PET image. Right: PET-CT fusion image. (Courtesy of Dr Edward Coleman.)

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CHAPTER 31

Basic Concepts of Chemotherapy and Irradiation Interaction

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For decades, radiation therapy (RT) has been a major treatment modality for locally or regionally confined cancers. The rate of treatment failure is still high, particularly for large tumors or advanced disease. Technological improvements in RT have continuously been made that allow delivery of higher radiation doses to the tumor while simultaneously allowing for better dose sparing to normal tissues. In addition, the implementation of strategies that modulate the biologic response of tumors or normal tissues to radiation has been employed, including altered fractionation scheduling including extreme hypofractionation (eg, stereotactic body RT, stereotactic radiosurgery), combined modality treatments using chemical or biologic agents, and, more recently, targeting molecular processes and signaling pathways that have become dysregulated in cancer cells.

The combination of chemotherapeutic drugs with radiation has perhaps had one of the strongest impacts on current cancer RT practice. This is particularly true for concurrent chemoradiation therapy, which has now been shown in multiple practice-changing clinical trials to be superior to RT alone in controlling locoregional disease and improving patient survival. Combining chemotherapeutic drugs with RT has a strong biologic rationale. Such agents reduce the number of cells in tumors undergoing RT by their independent cytotoxic action and by rendering tumor cells more susceptible to killing by ionizing radiation. An additional benefit of combined treatment is that chemotherapeutic drugs, by virtue of their systemic activity, may also act on potential microscopic distant metastatic disease. Most drugs have been chosen for combination with RT based on their known clinical activity in particular disease sites. Alternatively, agents that are effective in overcoming resistance mechanisms associated with RT could be chosen.

There have been clinical successes with concurrent chemoradiation therapy using traditional drugs, such as cisplatin and 5-fluorouracil (5-FU), and these studies have led to extensive research on exploring newer chemotherapeutic agents for their interactions with radiation. A number of potent chemotherapeutic agents, subsequently, have entered clinical trials or practice. There are also molecular targeting strategies aimed at improving the efficacy of RT. In this era, there is a significant explosion of activity revolving around the exciting and emerging data suggesting the potential benefit to combining immunotherapy agents with RT. This chapter reviews the biologic rationale and principles fundamental to the use of chemotherapy in conjunction with radiation treatments and discusses mechanistic interactions between drugs and radiation, the knowledge of which is essential in developing the optimal treatment strategies and designing appropriate clinical trials.[1-11]

THERAPEUTIC INDEX

Both radiation and chemotherapeutic drugs are cytotoxic to tumor and normal tissue cells. This lack of specificity is a major limitation in their use when applied either as individual treatments or in combination. Radiation inflicts damage to tumor and normal tissues in the radiation treatment field, whereas drugs, because of their systemic action, can affect any tissue in the body. Damage is often accentuated when the two agents are combined and when they affect the same tissue. In general, both the antitumor effectiveness and the severity of normal tissue damage produced by either radiation or drugs are increased as their dose is increased. This dose-effect relationship is sigmoidal and enables estimation of the therapeutic index (ratio), which is defined as the ratio between the doses (radiation, drug) that produce the same level (probability) of antitumor efficacy and normal tissue damage. To be therapeutically beneficial, the therapeutic ratio must be positive (>1); that is, individual agents or their combination must be more effective against tumors than normal tissues. To define therapeutic benefit in clinical settings, many factors must be taken into account, such as whether the treatment is curative or palliative, which tissues are dose limiting (critical tissues), and what degree of tissue damage is acceptable. The balance between a given level of antitumor efficacy and acceptable

normal tissue complications gives a measure of the therapeutic ratio of a treatment.

EXPLOITABLE STRATEGIES IN CHEMORADIATION THERAPY

The goals of combining chemotherapeutic drugs with RT are to increase patient survival by improving locoregional tumor control, decrease or eliminate distant metastases, or both while preserving organ and tissue integrity and function. Combined modality treatment can further improve positive therapeutic outcome of individual treatments through a number of specific strategies, which Steel and Peckham classified into four groups: "spatial cooperation," independent toxicity, enhancement of tumor response, and protection of normal tissues.[12]

Spatial cooperation was the initial rationale for combining chemotherapy with RT, in which the action of radiation and chemotherapeutic drugs is directed toward different anatomic sites. Localized tumors would be the domain of RT because large doses of radiation can be given. On the other hand, chemotherapeutic drugs are likely to be more effective in eliminating disseminated micrometastases than in eradicating larger primary tumors. Thus, the cooperation between radiation and chemotherapy is achieved through the independent action of two agents. Spatial cooperation is the basis for adjuvant chemoradiation therapy, in which radiation is given first to control the primary tumor and chemotherapy is given later to cope with micrometastases. The concept of spatial cooperation is also applied in the treatment of hematologic malignancies that have spread to "sanctuary" sites, such as the brain. These sites are poorly accessible to chemotherapeutic agents, and thus, they are more appropriately treated with RT.

Independent toxicity is another important strategy for increasing the therapeutic ratio of chemoradiation therapy. Normal tissue toxicity is the main dose-limiting factor for both chemotherapy and RT. Therefore, combinations of radiation and drugs would be better tolerated if drugs were selected such that toxicities to specific cell types and tissues do not overlap with, or minimally add to, radiation-induced toxicities. This strategy requires a thorough knowledge of drug toxicity, underlying mechanisms, and drug pharmacokinetics. Another strategy in chemoradiation therapy is

to exploit the ability of chemotherapeutic agents to *enhance tumor radioresponse*. The enhancement denotes the existence of some type of interaction between drugs and radiation at the molecular, cellular, or pathophysiologic (microenvironmental, metabolic) level, resulting in an antitumor effect greater than would be expected on the basis of additive actions. Many mechanisms may be involved in drug-radiation interactions leading to tumor radio enhancement, and some of them are elaborated on further in the text. The enhancement must be selective or preferential to tumors compared with critical normal tissues to achieve therapeutic gain. The ability of chemotherapeutic agents to enhance tumor radioresponse by counteracting determinants associated with tumor radioresistance is a major rationale for concurrent RT.

An additional strategy is to *protect normal tissues* so that higher doses of radiation can be delivered to the tumor. This can be achieved through technical improvements in radiation delivery or administration of chemical or biologic agents that selectively or preferentially protect normal tissues against the damage by radiation or drugs.

ASSESSMENT OF DRUG-RADIATION INTERACTION

Any drug considered for use in combination with RT needs to undergo preclinical evaluation for its interaction with radiation both in in vitro cell culture systems and in vivo, with the aim of assessing antitumor activity and normal tissue toxicity. The interaction between two agents is more easily defined and quantified in vitro because complete cell survival curves are readily obtained. The in vitro cell survival assay measures the ability of cells to produce colonies of a defined minimum size. The cell survival curve after irradiation characteristically has a “shoulder” of varying width that denotes the capacity of cells to repair radiation damage. The curves that describe survival after chemotherapeutic agents show much more variation both in absolute sensitivity to drugs and their shape than those after radiation, all depending on the drug tested. Some curves possess shoulders, some lack them, and some show resistant “tails” at higher drug doses. The tails denote the existence of cell subpopulations resistant to chemotherapeutic agents.

To assess the effect of the drug on cell radiosensitivity, the combined drug-radiation curve is commonly plotted after the cytotoxicity produced by the drug alone is excluded ("normalized"). The radiation cell survival curve is not changed if the drug does not influence cell radiosensitivity, regardless of whether the drug is cytotoxic on its own. In this case, the cytotoxicity of the drug contributes only to the overall cell killing by the combined treatment (*additive effect*) of both agents. Chemotherapeutic agents may interact with radiation by altering cell radiosensitivity such that the combination results in a *supra-additive* or *subadditive effect*, depending on whether the cell killing is greater or smaller than the sum of cell killings produced by individual agents. Drugs may eliminate the shoulder on the radiation survival curve, implying that drugs can inhibit cell repair from radiation damage, or they may change the slope of the exponential portion of the survival curve. A steeper slope indicates increased sensitization to radiation, whereas a shallower slope indicates protection.

Because of non–linear dose-related characteristics in cell killing by both chemotherapeutic agents and radiation, the effects of the combined treatment are best assessed using the "isobologram," an isoeffect plot for the dose response to the combination of two agents (Figure 31.1).[12] Dose-response curves are determined for each agent to generate the isobologram, an envelope of additivity, which denotes the expected additive response over a range of doses of the agents used. If the interaction between drugs and radiation is supra-additive or synergistic (ie, the effect is caused by lower doses of the two agents than the envelope of additivity would predict), the effect is shown on the left side of the envelope. In contrast, the effect of the subadditive or antagonistic interaction is shown to the right of the envelope: The effect required higher doses of the two agents than predicted. The width of the envelope of additivity depends on the degree of the nonlinearity in the dose response to individual agents. The envelope is wider as the degree of nonlinearity increases. In the case of a linear dose-response relationship for each agent, which is rare, the isobologram is also linear, represented by a single straight line.

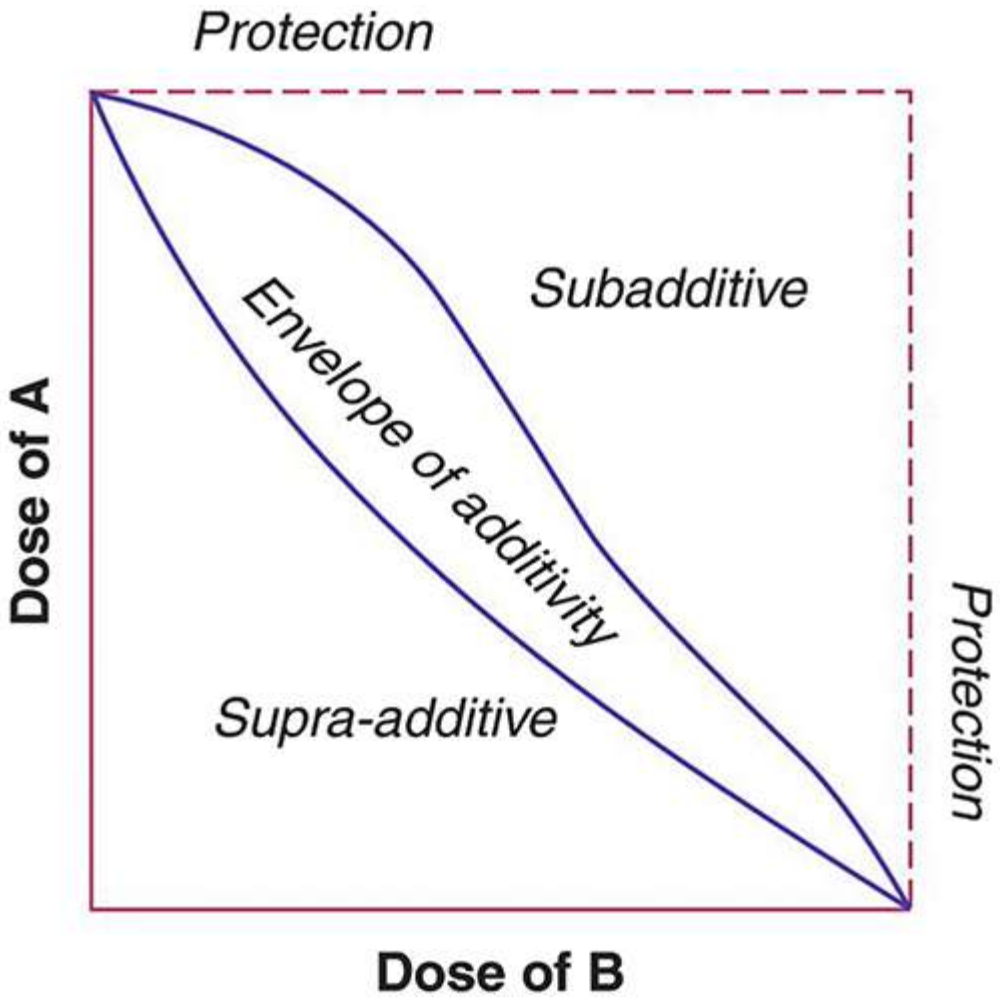

FIGURE 31.1 An isobologram for two agents when their dose-response curves are nonlinear. The isobologram shows the envelope of additivity and regions of supra-additivity and subadditivity. (Reprinted from Steel GG, Peckham MJ. Exploitable mechanisms in combined radiotherapy-chemotherapy: the concept of additivity. *Int J Radiat Oncol Biol Phys*. 1979;5[1]:85-91. Copyright © 1979 Elsevier. With permission.)

In vitro testing is often followed by in vivo exploration of drug-radiation interactions, which allows assessment of the combined treatment on both tumors and normal tissues. This is essential for the determination of therapeutic gain, as discussed earlier in this chapter. Syngeneic animal tumors or human tumor xenografts in nude mice are most often used for this purpose. The efficacy of the treatment is determined by the extent of tumor growth delay or the rate of tumor cure. In normal tissues, the effect of chemotherapeutic drugs on radiation response of acutely and late-responding tissues can be assessed using a variety of available assays. Some

of these assays are clonogenic, such as the jejunal crypt assay, where the endpoint depends directly on the reproductive integrity of individual cells. More frequently, however, dose-response relationships for normal tissues are based on functional endpoints (such as breathing rate in lung damage and paralysis in spinal cord damage). These end points tend to reflect the minimum number of functional cells remaining in tissues or organs and not the proportion of cells retaining reproductive integrity.

MECHANISTIC CONSIDERATIONS IN DRUG-RADIATION INTERACTIONS

Increasing Initial Radiation Damage

Radiation induces many different lesions in the DNA molecule, which is the critical target for radiation damage. The lesions consist of single-strand breaks (SSBs), double-strand breaks (DSBs), base damage, DNA-DNA and DNA-protein cross-links, and so forth. DSBs and chromosome aberrations that occur in association with or as a consequence of DSBs are usually considered to be the principal damage that results in cell death.[13] Any agent that makes DNA more susceptible to radiation damage may enhance cell killing. Certain drugs, such as halogenated pyrimidines, incorporate into DNA and make it more susceptible to radiation damage.[14]

Inhibition of Cellular Repair

Both sublethal and potentially lethal damage inflicted by radiation can be repaired.[15-17] Although sublethal damage repair (SLDR) denotes the increase in cell survival when the radiation dose is split into two fractions of radiation separated by a time interval, potentially lethal damage repair (PLDR) designates the increase in cell survival as the result of postirradiation environmental conditions. SLDR is rapid, with a half-time of approximately 1 hour, and is complete within 4 to 6 hours after irradiation. This time between two radiation fractions allows radiation-induced DSBs in DNA to rejoin and repair. SLDR is expressed as the restitution of the shoulder on the cell survival curve for the second dose. PLDR occurs when environmental conditions prevent cells from dividing for several hours, such as keeping in vitro growing cells in plateau phase after irradiation.

Preventing cells from division allows the completion of repair of DNA lesions that would have been lethal had DNA undergone replication within several hours after irradiation. PLDR is considered to be a major determinant responsible for radioresistance in some tumor types, such as melanomas. The repair can be achieved through restoration of damaged molecules by reducing species that donate electrons to oxidized substrates or through involvement of enzymes mediating homologous and nonhomologous recombination repair of DNA DSBs, base excision repair of base damage, and nucleotide excision repair of DNA-protein cross-links.

Many chemotherapeutic agents used in chemoradiation therapy interact with cellular repair mechanisms and inhibit repair and hence may enhance cell or tissue response to radiation. The aforementioned halogenated pyrimidines enhance cell radiosensitivity, not only through increasing initial radiation damage but also by inhibiting cellular repair.[14,18] Nucleoside analogs, such as gemcitabine, are a class of chemotherapeutic agents potent in inhibiting the repair of radiation-induced DNA and chromosome damage.[19,20] They have been shown strongly to enhance tumor radioresponse in preclinical studies and have been, and are continuing to be, extensively investigated for such activity in patients with cancer.[21,22]

Cell Cycle Redistribution

Both chemotherapeutic agents and radiation are more effective against proliferating than nonproliferating cells. Their cytotoxic action further depends on the position of cells in the cell cycle. Cell cycle dependency in response to radiation was first described almost 40 years ago.[23] Terasima and Tolmach reported that the sensitivity of the cell response to radiation varied widely depending on which phase of the cell cycle the cells were in at the time of irradiation and that cells in the G_2 and M cell cycle phases were approximately 3 times more sensitive than cells in the S phase.[23] The exact reason for this variability is still unknown.

The influence of the cell cycle on cell response to cytotoxic agents can be therapeutically exploited in chemoradiation therapy using cell cycle redistribution strategies. For example, some chemotherapeutic drugs, such as taxanes, can block transition of cells through mitosis, with the result that cells accumulate in the radiosensitive G_2 and M phases of the cell cycle.

Radiation delivered at the time of significant accumulation of cells in both the G_2 and M phases results in enhanced radioresponse of cells in vitro and of tumors in vivo.[24-27] However, this cell cycle mechanism of taxane-induced enhancement of tumor radioresponse is dominant only in tumors that are resistant to paclitaxel or docetaxel as a single treatment. Although tumor growth in taxane-resistant tumors is not substantially affected by the drug, tumors do exhibit significant transient accumulation of cells in mitosis 6 to 12 hours after the treatment.[27] Taxanes also enhance the radioresponse of tumors that respond by significant tumor growth delay to taxanes given as a single treatment modality, but a major mechanism for radio enhancement in such tumors is reoxygenation of radioresistant hypoxic cells, as discussed later.[26]

Elimination of the radioresistant S-phase cells by the chemotherapeutic agents may be another cell cycle redistribution strategy in chemoradiation therapy. Nucleoside analogs, such as fludarabine or gemcitabine, are good examples of the agents that become incorporated into S-phase cells and eliminate them by inducing apoptosis.[19,21] In addition to purging S-phase cells, the analogs induce the surviving cells to undergo parasynchronous movement to accumulate in the G_2 and M phases of the cell cycle between 1 and 2 days after drug administration, a time when the highest enhancement of tumor radioresponse was observed.[21] Tumors with a high cell growth fraction are likely to respond better to the cell cycle redistribution strategy in chemoradiation therapy than tumors with a low cell growth fraction.

Counteracting Hypoxia-Associated Tumor Radioresistance

Solid malignant tumors are usually characterized by defective vascularization, both in the number of blood vessels and vessel function. Because of this, blood supply to tumor cells is inadequate, cells lack oxygen and nutrients, and multiple tumor microregions become hypoxic, acidic, and, eventually, necrotic. Hypoxia occurs at distances from blood vessels larger than 100 to 150 μm. The hypoxic cell content in tumors varies widely and can be more than 50%. The presence of hypoxia makes tumors more aggressive (hypoxia is conducive to the emergence of more virulent tumor cell variants) and stimulates metastatic spread and more resistant to radiation as well as most chemotherapeutic agents.[28,29] Hypoxic cells are 2.5

to 3 times more resistant to radiation than well-oxygenated cells. The fact that hypoxia may be a cure-limiting factor in RT, at least in some clinical situations, is suggested by the findings that reduced hemoglobin levels and low tumor pO_2, are associated with higher treatment failure rates.[30-32] Also, there are reports showing that local tumor control by RT can be improved by the use of hypoxic cell radiosensitizers or hyperbaric oxygen.[33-35] With respect to the effects of chemotherapy, hypoxic regions are less accessible to chemotherapeutic drugs; in addition, hypoxic tumor cells are either nonproliferating or proliferate poorly and as such do not respond well to drugs.

Combining chemotherapeutic agents with RT can reduce or eliminate hypoxia or its negative influence on tumor radioresponse. Most chemotherapeutic drugs preferentially kill proliferating cells, primarily found in well-oxygenated regions of the tumor. Because these regions are located close to blood vessels, they are easily accessible to chemotherapeutic agents. Destruction of tumor cells in these areas leads to an increased oxygen supply to hypoxic regions and hence reoxygenates hypoxic tumor cells. Massive loss of cells after chemotherapy lowers the interstitial pressure, which then allows the reopening of previously closed capillaries and the reestablishment of blood supply. It also causes tumor shrinkage so that previously hypoxic areas are closer to capillaries and thus accessible to oxygen. Finally, by eliminating oxygenated cells, more oxygen becomes available to cells that survived chemotherapy. It was recently shown that tumor reoxygenation is a major mechanism underlying the enhancement of tumor radioresponse induced by taxanes in tumors sensitive to these drugs.[26]

Another approach to counteract the negative impact of hypoxia is selective killing of hypoxic cells through bioreductive drugs, such as tirapazamine, which undergo reductive activation in a hypoxic milieu, rendering them cytotoxic.[28] A related possibility is to exploit the acidic state (low pH) of tumors, which develops as a result of hypoxia-driven anaerobic metabolism that produces lactic acid, through the use of drugs that selectively accumulate in acidic environments or become activated by a low pH.[36,37]

The use of agents that selectively radiosensitize hypoxic cells to reduce their negative impact has been considered and tested in clinical trials. These drugs increase radiation damage by mimicking the effect of oxygen. Many clinical trials have tested these drugs, particularly misonidazole, in combination with RT, but few of them have shown an improved treatment outcome. The exception is nimorazole, which also does not elicit the neurotoxicity commonly associated with hypoxic cell sensitizers that prevented the delivery of clinically effective doses of these agents.[38]

Inhibition of Tumor Cell Repopulation

The constant balance between cell production and cell loss maintains the integrity of normal tissues. When this balance is perturbed by cytotoxic action of chemotherapeutic drugs or radiation, the integrity of tissues is reestablished by an increased rate of cell production. The cell loss after each fraction of radiation during RT induces compensatory cell regeneration (repopulation), the extent of which determines tissue tolerance to RT. In contrast to normal tissues, malignant tumors are characterized by an imbalance between cell production and cell loss in favor of cell production. As with normal tissues, tumors also respond to radiation- or drug-induced cell loss with a compensatory regenerative response. Preclinical studies provided ample evidence demonstrating that the rate of cell proliferation in tumors treated by radiation or chemotherapeutic drugs is higher than that in untreated tumors.[39-41] This increased rate of treatment-induced cell proliferation is commonly termed *accelerated repopulation*. Accelerated repopulation of tumor clonogens has been shown to occur during clinical RT as well. Withers et al showed that the total dose of radiation needed to control 50% of head and neck carcinomas progressively increased with time whenever RT treatment was prolonged beyond 1 month.[42] This increase in radiation dose required to achieve tumor control was greater than what would be anticipated based on the pretreatment tumor volume doubling time of approximately 60 days for head and neck tumors. The increase was attributed to accelerated repopulation, and it was estimated to average approximately 0.6 Gy/d but may be as high as 1 Gy/d.[42,43]

Although accelerated cell proliferation is beneficial for normal tissues because it spares them from radiation damage, it has an adverse impact on

tumor control by RT or chemotherapy. Chemotherapeutic drugs, because of their cytotoxic or cytostatic activity, can reduce the rate of proliferation when given concurrently with RT and hence increase the effectiveness of the treatment. Caution must be taken to select drugs that preferentially affect rapidly proliferating cells and preferentially localize in malignant tumors. However, the main limitation of concurrent chemoradiation therapy is the enhanced toxicity of rapidly dividing normal tissues because most available chemotherapeutic agents show poor tumor selectivity. Moreover, accelerated repopulation induced by chemotherapeutic drugs may have a negative influence on the outcome of tumor response to radiation when drugs are used in induction or neoadjuvant chemotherapy protocols. In this strategy, chemotherapy precedes RT. Treatment outcomes after induction chemotherapy followed by RT have not been overly encouraging in terms of both local tumor control and patient survival, even if a large proportion of tumors initially responded with total or partial clinical regression by the time of RT implementation. Some experimental evidence suggests that the drug-induced accelerated cell repopulation can actually make the tumor more difficult to control with radiation.[39,40]

TIMING OF DRUG ADMINISTRATION IN RELATION TO RADIATION THERAPY

Most clinical chemoradiation therapy regimens evolved empirically: increasingly, information from preclinical studies is being considered in planning the optimal timing of drug administration in relation to RT. Depending on the principal aim of the therapy, drugs are administered before (*induction* or *neoadjuvant chemotherapy*), during (*concurrent* or *concomitant chemotherapy*), or after (*adjuvant chemotherapy*) the course of RT. The advantages and disadvantages of each approach are summarized in Table 31.1.

TABLE 31.1 ADVANTAGES AND DISADVANTAGES OF DIFFERENT CHEMORADIATION SEQUENCING STRATEGIES

Strategy	Advantages	Disadvantages
Sequential chemoradiation	• Least toxic	• Increased treatment time • Lack of local synergy

Strategy	Advantages	Disadvantages
	• Maximizes systemic therapy • Smaller radiation fields if induction shrinks tumor	
Concurrent chemoradiation	• Shorter treatment time • Radiation enhancement	• Compromised systemic therapy • Increased toxicity • No cytoreduction of tumor
Concurrent chemoradiation and adjuvant chemotherapy	• Maximizes systemic therapy • Radiation enhancement • Both local and distant therapy delivered up front	• Increased toxicity • Increased treatment time • Difficult to complete chemotherapy after chemoradiation
Induction chemotherapy and concurrent chemoradiation	• Maximizes systemic therapy • Radiation enhancement	• Increased toxicity • Increased treatment time • Difficult to complete chemoradiation after induction therapy

In regard to the primary tumor, induction chemotherapy may reduce the number of clonogenic cells and cause the reoxygenation of the surviving hypoxic cells, both of which render tumors more controllable by radiation. In addition, chemotherapy-induced tumor shrinkage may allow the use of smaller radiation fields, in which case less normal tissue is exposed and damaged by radiation. This treatment approach is often used in the therapy of solid tumors in children and of lymphomas. Induction chemotherapy precedes RT for a few weeks to a few months, which improves tolerability of the combined treatment.

Induction chemotherapy has resulted in therapeutic improvement in several clinical trials compared with RT, but in general, the therapeutic benefits are below expectations. A number of factors could account for this, including accelerated proliferation of tumor cell clonogens and selection or induction of drug-resistant cells that are cross-resistant to radiation. The preclinical findings provide solid evidence for the existence of accelerated

repopulation in tumors treated with chemotherapeutic agents. On the other hand, although development of drug resistance is a significant problem in chemotherapy, the evidence that cells that acquire drug resistance are also resistant to radiation is not convincing.

When chemotherapy is given during a course of RT, it is referred to as *concurrent chemotherapy*. This form of treatment is intended to cope with both disseminated lesions and the primary tumor, but it takes advantage of drug-radiation interactions to maximize tumor radioresponse. The drug scheduling in relation to individual radiation fractions is highly important, and the selection of optimal timing of drug administration must be based on mechanisms of tumor radio enhancement by a given drug, the drug's normal tissue toxicity, and the conditions under which the highest enhancement is achieved. The data from preclinical studies can greatly contribute to the selection of the most optimal schedules. For example, it has been demonstrated that murine tumors sensitive to taxanes show enhanced radioresponse, but the best effect is achieved if drug treatment precedes radiation by 1 to 3 days.[26] A major mechanism for tumor radio enhancement was reoxygenation of hypoxic cells. Based on this preclinical information, one would anticipate that in clinical protocols such tumors would best respond to a bolus of a taxane given once or twice weekly during RT. In contrast, tumors resistant to taxanes on their own would call for daily administration of a taxane because they show accumulation of radiosensitive G_2- and M-phase cells 6 to 12 hours after drug administration. If the objective is to counteract rapid repopulation of tumor cell clonogens induced by radiation, then administration of cell cycle–specific chemotherapeutic agents during the second half of RT, when accelerated repopulation is more expressed, might be more effective. At present, the enhancement in normal tissue complications remains the major limitation of concurrently combining chemotherapy with RT. Nevertheless, as is made evident later in the text, concurrent chemoradiation therapy has provided better clinical results in terms of both local tumor control and patient survival than have other modes of chemoradiation therapy combinations.[44,45]

Adjuvant chemotherapy designates a treatment modality in which chemotherapeutic drugs are given some time after completion of RT. The

primary objective is to eradicate disseminated disease; however, the control of the primary tumor may also be improved by the ability of drugs to deal with tumor cells that survived radiation.

INTERACTION OF SPECIFIC CHEMOTHERAPIES AND RADIATION IN THE TREATMENT OF CANCER

This section provides an overview of the evidence that exists for combining particular chemotherapies with radiation. In many cases, the level of support that exists for combined therapy mirrors the age of the drug. However, as would be expected, newer drugs have generally been subject to more rigorous preclinical assessment of their efficacy before their introduction into the clinical setting (Table 31.2).

TABLE 31.2 MECHANISMS OF CHEMOTHERAPY-INDUCED RADIATION SENSITIZATION

Class of Compound	Mechanism of Radiosensitization	References
Platinum-based compounds	Inhibition of DNA synthesis Inhibition of transcription elongation by DNA interstrand cross-links Inhibition of repair of radiation-induced DNA damage	46-49
Taxanes	Cellular arrest in the G_2M phase of the cell cycle	26,27,50,51
	Induction of apoptosis	
	Reoxygenation of tumor cells	
Topoisomerase I inhibitors	Inhibition of repair of radiation-induced DNA strand breaks	52-54
	Redistribution into G_2 phase of the cell cycle	
	Conversion of radiation-induced SSBs into DSBs	
Hypoxic cell cytotoxins	Complementary cytotoxicity with radiation on euoxic and hypoxic tumor cells	55,56
Antimetabolites	Nucleotide pool perturbation	19,20,57,58
	Lowering apoptotic threshold	
	Cell cycle redistribution	
	Tumor cell reoxygenation	

Class of Compound	Mechanism of Radiosensitization	References
Temozolomide	DNA repair inhibition (radiosensitization effect may be subject to MGMT status)	59,60

DSBs, double-strand DNA breaks; MGMT, O^6-methylguanine-DNA methyltransferase; SSBs, single-strand DNA breaks.

Platinum-Based Drugs

This group of compounds, distinguished from most others by its metallic element base, has come to be recognized as one of the most potent chemotherapies available to date. Cisplatin (*cis*-diamminedichloroplatinum II), which is the prototype drug, has been acknowledged to be a potent radiosensitizer for many years and has a significant role in clinical practice to date. Preclinical work done using murine models by Rosenberg et al in the late 1960s showed that cisplatin is an effective antitumor chemotherapy. Subsequent efforts have shown that its primary mechanism of inhibition of tumor growth appears to involve the inhibition of DNA synthesis by formation of DNA cross-links.[61-63] Another secondary mechanism includes the inhibition of transcription elongation by DNA interstrand cross-links.[64]

Cisplatin-free radical–mediated sensitization may involve the ability to scavenge free electrons formed by the interaction between radiation and DNA. The reduction of the platinum moiety may serve to stabilize DNA damage that would otherwise be repairable.[65] Greater than additive effects of cisplatin and radiation are seen in tumor models most reliably when the drug is administered with fractionated radiation, explained by its inhibition of SLDR.[65] Bladder cancer, head and neck cancer, lung cancer, esophageal cancer, and cervix cancer are some of the disease sites where cisplatinum is approved for use in combination with RT.

Carboplatin, a second-generation platinum compound with a different toxicity profile, has also been studied as a radiosensitizer.[48,49] Mechanism of action also involves interfering with function of DNA by producing interstrand DNA cross-links. Carboplatin tends to have less nephrotoxic or neurotoxic effects compared to cisplatin, but hematologic toxicity is slightly increased. Its potential efficacy as a radiosensitizer has allowed for its incorporation into regimens used in several randomized trials including, but not limited to, landmark trials that allowed for its indication for use in

esophageal cancer, head and neck cancer, and lung cancer. Oxaliplatin, although sharing a similar mode of action as other platinum compounds, has been shown to have activity in cisplatin- resistant systems in vitro.[4] One potential explanation for this is that oxaliplatin is not affected by loss of mismatch repair, which leads to cisplatin resistance in vitro, and there are those that postulate that adducts formed by oxaliplatin are less well recognized by DNA repair systems.[66,67] Whether oxaliplatin is truly active against cisplatin-resistant cancer clinically is an area of active investigation.[68] Despite encouraging findings in phase I to II rectal cancer studies, phase III studies integrating neoadjuvant oxaliplatin with 5-FU or capecitabine with RT, with the exception of the CAO/ARO/AIO-04 study, have yielded negative findings (STAR-01, ACCORD 12, NSABP R04, PETACC-6).[69] In esophageal cancer, oxaliplatin-based chemoradiation therapy, although did not demonstrate improvement in efficacy over cisplatinum/5-FU–based regimen, was suggested to be a more convenient regimen and was not found to be more toxic.[70] Oxaliplatin-based regimens with RT are being further studied in additional randomized phase II studies in comparison to carboplatin-based regimen (NEOSCOPE and PROTECT-1402).[69,71]

Antimicrotubules: Taxanes

The radiosensitizing properties of plant-derived chemotherapeutic agents, the taxanes, have been studied extensively in both preclinical models and clinical trials. Paclitaxel (Taxol) and docetaxel (Taxotere) act as mitotic spindle inhibitors through their promotion of microtubule assembly and inhibition of disaggregation.[72] Both taxanes bind to the *N*-terminal 31-amino-acid sequence of the β-tubulin subunit of cellular tubulin polymers, stabilizing the polymers by shifting the dynamic equilibrium that exists between tubulin dimers and microtubules in favor of the polymerized state.[73,74] Although there is preclinical evidence that docetaxel has both a higher affinity for the tubulin-binding site and greater in vitro cytotoxicity than paclitaxel, this has not necessarily translated into greater clinical efficacy because the toxicity profiles of the two drugs also differ.[75,76]

The administration of a taxane leads to cellular arrest in the G_2/M phase of the cell cycle, which is the precise point associated with increased

sensitivity to the lethal effects of ionizing radiation.[77] Early laboratory studies with a human lung cancer cell line and human astrocytoma cells bore out the prospect of significant radiosensitization, with relative enhancement ratios in the 1.48 to 1.8 range when paclitaxel was administered before irradiation.[24,25]

The exact conditions used in various studies appear to determine the strength of the interaction between radiation and paclitaxel because subadditive effects have been seen in addition to the more widely reported additive and supra-additive effects.[27] In general, enhancement of radiation effects is seen when proliferating cells have been incubated with moderate concentrations of paclitaxel for 24 hours before irradiation. Conditions leading to a less than optimal response include paclitaxel-mediated G_1 arrest, wherein a more resistant cell subpopulation counteracts the effects of a G_2/M block; paclitaxel-induced cell cycle effects such as the G_2/M block in cells destined to die before irradiation; and incubation conditions insufficient to exert cellular effects. The fact that nonproliferating cells are also sensitized to the effects of radiation by the use of paclitaxel suggests that mechanisms other than the cell cycle arrest in the G_2/M phase underlie paclitaxel's sensitizing abilities.

Paclitaxel also acts to induce programmed cell death; work from the MD Anderson Cancer Center has examined the relationship between mitotic arrest, apoptosis, and the antineoplastic activity of paclitaxel in 16 murine tumors.[27] Single-dose paclitaxel (40 mg/kg) induced mitotic arrest to varying degrees in all tumors; however, apoptosis was induced in only 50% of tumors. This study also revealed that pretreatment levels of apoptosis correlated with both paclitaxel-induced apoptosis and tumor growth delay. Therefore, both the pretreatment apoptotic rate and the paclitaxel-induced apoptotic rate could potentially act as predictors of the response to paclitaxel.

Milas et al summarized observations that showed that (1) there was massive loss of tumor cells though the apoptotic pathway was restricted to the perivascular region and (2) radio enhancement occurring during this period of cell loss became even more impressive when apoptotic cells were removed from the tumor.[27] Experiments in which tumor xenografts were treated with paclitaxel and exposed to radiation under hypoxic or air-

ambient conditions were pursued.[26] It was found that the creation of hypoxic conditions greatly reduced the efficacy of paclitaxel in its enhancement of radioresponse. It appears that a combination of cell cycle effects, drug-induced reoxygenation, and drug-induced apoptosis underlies paclitaxel's radiosensitizing abilities.

Docetaxel has also been found to be a respectable radiosensitizer in both in vitro and in vivo models.[50,51] Radiation response in the presence of docetaxel was examined in three different cell lines that have widely different responses to radiation alone.[78] Their findings suggest that the p53 status of tumor cells may have a profound effect on the radiosensitizing effects of a taxane. Other novel taxanes and analogs that continue to attract the interest of investigators for their potential to enhance radiation effects include Abraxane, paclitaxel poliglumex, larotaxel, cabazitaxel, and orally available taxanes.[79-81]

Antimetabolites

5-Fluorouracil

The radiosensitizing properties of 5-FU has been known for years.[82] Several mechanisms have been proposed for the cytotoxicity of this drug:

- Its incorporation into ribonucleic acid (RNA), which leads to a disruption of RNA function
- Inhibition of thymidylate synthase function and subsequently of DNA synthesis
- Direct incorporation of the drug into DNA

It is believed that a combination of these effects underlies its radiosensitizing properties.[83] Optimization of its schedule of delivery is crucial to obtaining an effect with this combination, and it is accepted that cytotoxic doses of 5-FU are needed to obtain a radiosensitizing effect. In general, it is thought that a continuous infusion of the drug is needed to obtain the desired drug levels after irradiation.[84] Long-standing clinical experience with this drug bears out much of the laboratory studies of its effectiveness as a radiation sensitizer. Gastrointestinal tract cancers, bladder cancer, and head and neck cancers are some of the disease sites where 5-

FU–based combined modality therapy with radiation is used as standard of care.

Capecitabine

Capecitabine is an oral prodrug of 5-FU. It is converted to its cytotoxic form in three enzymatic steps, the last of which is mediated by thymidine phosphorylase. One of the potential advantages of this mechanism for increasing tumor cytotoxicity is that thymidine phosphorylase is overexpressed in tumor tissues. Interestingly, radiation has been shown to stimulate expression of thymidine phosphorylase, which provides a further rationale for considering combined therapy with radiation treatments.[85] Capecitabine was shown to be safe to replace 5-FU in chemoradiotherapy regimen for rectal cancer.[86] It is being used in the combined modality setting as standard therapy, and in clinical trials, for many tumor types (including, but not limited to, rectal cancer, gastric cancer, esophageal cancer) requiring fluorouracil-based chemoradiation.

Gemcitabine

Gemcitabine is another nucleoside analog that acts as a very potent radiosensitizer. The biologic action of gemcitabine is due almost completely to its effects on DNA metabolism. Early studies of this drug in leukemic cell lines found that notable decreases in cellular deoxynucleotide triphosphates occurred with the use of the drug.[87]

Direct incorporation of the drug into DNA and drug-induced apoptosis are also thought to underlie its cytotoxicity.[87] The metabolism of gemcitabine in the cell is complex, and it is able to potentiate its cytotoxicity as a sole therapy.[87] Depending on the conditions, relative enhancement ratios in the range of 1.1 to 2.5 have been reported.

Gemcitabine is S phase specific and as such should be selectively toxic to proliferating cells, decreasing the amount of proliferation that can occur during fractionated RT.[88] In addition, cell cycle redistribution induced by these agents may improve cell kill by allowing more cells to be treated in the more sensitive parts of the cell cycle.[89] As DNA synthesis inhibitors, these drugs may act to inhibit the repair of radiation-induced DNA

damage.[19] Finally, as DNA chain terminators, they may serve to trigger the apoptotic response.[20]

Milas et al found the largest enhancement of growth delay when gemcitabine was delivered 24 to 60 hours before irradiation in a murine sarcoma tumor model.[21] The use of gemcitabine with radiation also decreased the risk for the development of lung metastases in those mice that attained durable local control (73% in the radiation-alone group vs 40% in the combined modality group), which was confirmed in a second study with a larger number of mice.[58] This preclinical work is supportive of the principles of combined modality therapy in that better local control translated into decreased systemic spread of tumor cells. The same authors also report a dose-dependent increase in the apoptotic rate after the administration of gemcitabine, which they believe correlates with the elimination of the more radioresistant S-phase population of cells and a redistribution of the remaining cells into more radiosensitive parts of the cell cycle.[21] They also report that reoxygenation of the resistant hypoxic fraction of tumor cells is a mechanism for the radiosensitizing action of gemcitabine.[58]

In summary, the preclinical evidence suggests that gemcitabine acts through several mechanisms (nucleotide pool perturbation, lowering of the apoptotic threshold, cell cycle redistribution, and tumor cell reoxygenation) to enhance the effect of ionizing radiation on tumors. Clinical experience has shown that this drug is indeed a potent sensitizer with the potential for significant toxicity as well as improvement in tumor control when combined with radiation.[90-96]

Pemetrexed

Pemetrexed is a novel multitargeted agent, exerting its effect via simultaneous inhibition of multiple folate-requiring enzymes, including thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl-transferase.[97] Pemetrexed has shown synergistic activity with radiation treatments, likely because of interference with DNA synthesis.[98] There are indications that radiosensitization by pemetrexed is not cell cycle phase specific in vitro.[99] Others have suggested that a combination of RT and pemetrexed results in supra-additive effects, which

may be in part because of apoptosis induction.[100] Phase III study in non–small cell lung cancer (NSCLC) has demonstrated nonsuperiority for pemetrexed-cisplatin with radiation, compared to cisplatin-etoposide and radiation, and although trial closed early because of futility, it is considered to be a potential alternative regimen.[101]

Topoisomerase I Inhibitors

Camptothecin is a plant alkaloid obtained from the *Camptotheca acuminata* tree. Its initial clinical evaluation in the 1960s and 1970s was abandoned because of severe and unpredictable hemorrhagic cystitis.[102,103] Camptothecin and its derivatives (eg, irinotecan, topotecan, 9-aminocamptothecin, SN-38) target DNA topoisomerase I.[104-106] This enzyme relaxes both positively and negatively supercoiled DNA and allows for diverse essential cellular processes, including replication and transcription, to proceed. In the presence of camptothecin, a camptothecin-topoisomerase I-DNA complex becomes stabilized with the 5′-phosphoryl terminus of the enzyme-catalyzed DNA SSB bound covalently to a tyrosine residue of topoisomerase I. These stabilized cleavable complexes interact with the advancing replication fork during the S phase or during unscheduled DNA replication after genomic stress and cause the conversion of SSBs into irreversible DNA DSBs, resulting in cell death.[106]

Several investigators have reported that camptothecin enhances the cytotoxic effect of radiation in vitro and in vivo.[52-54] Chen et al showed that cells exposed to 20(S)-10,11 methylenedioxy-camptothecin before or during radiation had sensitization ratios of 1.6, whereas those treated with the drug after radiation had substantially less enhancement of radiation-induced DNA damage.[53] There are several hypotheses regarding the mechanism of interaction between radiation and irinotecan: (1) inhibition of topoisomerase I by irinotecan leads to inhibition of repair of radiation-induced DNA strand breaks; (2) irinotecan causes a redistribution of the cells into the more radiosensitive G_2 phase of the cell cycle; and (3) topoisomerase I-DNA adducts are trapped by irinotecan at the sites of radiation-induced SSBs, leading to their conversion into DSBs.[107] Although there is currently insufficient evidence to identify the underlying mechanism with certainty, the primary mechanism involved with

radiosensitization may depend on which camptothecin derivative is being used.

Data from in vivo experiments demonstrate that combination 9-aminocamptothecin and irradiation is more effective when fractionated, compared with single doses.[108] There is also evidence for circadian-dependent cytotoxicity and radiation sensitization when camptothecin derivatives like 9-aminocamptothecin are used as radiation sensitizers.[108] The integration of this group of drugs into clinical treatments with RT has been explored in NSCLC and brain tumors.[109-112]

Alkylating Agents: Temozolomide

Temozolomide is a second-generation alkylating agent, which is orally administered, is readily bioavailable, and demonstrates broad-spectrum activity in a variety of difficult-to-treat malignancies, including glioma and melanoma.[113] It is unique in its ability to cross the blood-brain barrier (about 30%-40% of plasma concentration found in cerebrospinal fluid). In vitro studies demonstrate increased inhibition of cell growth in combination with RT.[114] Radiosensitization appears to occur via inhibition of DNA repair, leading to an increase in mitotic catastrophe.[59] It has proven efficacy as a first-line therapy for patients with glioblastoma multiforme (GBM) in conjunction with RT based on a randomized phase III clinical study demonstrating survival benefit.[115] Temozolomide spontaneously converts to the reactive methylating agent 5-(3-methyl-1-triazeno)imidazole-4-carboxamide and transfers methyl groups to DNA, the most important one being at the O6 position of guanine, an important site for DNA alkylation.[116] The MGMT gene encodes a DNA repair protein that removes the alkyl group from the O6 position of guanine, and high MGMT activity levels abrogate the effectiveness of alkylating agents. In vitro, temozolomide enhances the radiation response most effectively in MGMT-negative glioblastomas, and likely because of decreased double-strand DNA repair capacity and increased DNA DSB damage, which occurs when the combination of temozolomide and RT was administered.[60] Analysis of a randomized study by the European Organization for Research and Treatment of Cancer (EORTC) and National Cancer Institute of Canada demonstrated that loss of MGMT expression by promoter methylation is

correlated with a better outcome after treatment with radiation and temozolomide.[117] Temozolomide and radiation combination is considered the backbone standard therapy for newly diagnosed GBM, upon which combination of additional new investigational agents are being studied.

Other Agents

Mitomycin-C

Mitomycin-C is a quinone, whose mechanisms of action include inhibition of DNA and RNA synthesis.[118] When combined with radiation, the rationale for the use of mitomycin-C is based on its ability to target hypoxic cells that are known to be relatively radiation resistant.[119] There is preclinical evidence to suggest that mitomycin-C administered before irradiation leads to a supra-additive interaction.[55,120] The postulated mechanisms of action for supra-additivity include prevention of repopulation and hypoxic cell sensitization, although the definitive action is not fully elucidated. Given that normal tissues are not hypoxic, the selective targeting of this cell population with mitomycin-C has the potential to improve cures without compromising normal tissue complication rates. The use of mitomycin-C is limited by its hematologic toxicities. Mitomycin-C combined with RT remains the standard-of-care therapy for anal carcinoma based on multiple clinical studies.[121]

Hypoxic Sensitizers

Tirapazamine

Investigators have pursued a similar strategy as outlined previously with the development of tirapazamine, a hypoxic cell cytotoxin.[28,56] Brown has discovered that tirapazamine, which is a benzotriazine di-*N*-oxide, is toxic to hypoxic cells at concentrations much lower than what is needed to radiosensitize cells.[56] It has the greatest differential toxicity known between hypoxic and well-oxygenated cells. Essentially, this drug functions through its intracellular reduction to form a highly reactive radical capable of causing both SSBs and DSBs.[122] In the presence of oxygen, a free electron is absorbed, and the compound is back-oxidized to the parent compound with the concomitant release of a superoxide radical, which is much less cytotoxic than the tirapazamine radical. Clinical trials are ongoing or have

been completed in multiple tumor sites, including cervix, head and neck, GBM, and lung malignancies (small cell lung cancer).[123-135] Although most studies have demonstrated a reasonable toxicity profile, several studies have suggested caution in the appropriate selection of a dose and delivery regimen when combining tirapazamine to a standard chemoradiation regimen.[127,130,136]

Fairly promising earlier phase trials led to phase III studies in head and neck and cervical cancer. A phase III study by the Trans-Tasman Group (TROG 02.02) suggested no significant improvement in survival outcome in patients with locally advanced head and neck cancer, unselected for hypoxia, with the addition of tirapazamine to a standard platinum-based chemoradiation regimen.[133] A subset analysis of the phase II study from the Trans-Tasman Group suggested that tumors with a hypoxic component as assessed by ^{18}F-fluoromisonidazole positron emission tomography imaging had a higher likelihood of locoregional failure, whereas an improvement in local control was identified for those treated with the addition of tirapazamine, suggesting that it specifically targets hypoxic tumor cells.[129] Similarly, GOG phase III trial studying the role of addition of tirapazamine to platinum-based RT in cervical cancer was closed early and demonstrated no improvement in survival outcomes with the addition of tirapazamine.[136] Study was closed early because of the lack of available study drug and limits future development of this drug.[136-138]

Nimorazole

Nimorazole is another hypoxic cell radiosensitizer belonging to a class of chemical known as 5-nitroimidazoles, with less neuropathic toxicity than misonidazole; it has demonstrated improved tumor control outcome and tolerability with RT, in supraglottic laryngeal and pharyngeal tumors in the DAHANCA 5 study.[38] A randomized multicenter study, IAEA- HypoX study with nimorazole and concomitant accelerated RT in head and neck squamous cell carcinoma, was attempted but closed prematurely in 2014 because of poor recruitment (100 of the intended 600 patients were accrued).[137] Although closed early, it suggested an improvement in locoregional tumor control with the addition of nimorazole. Additional ongoing trials include NIMRAD, a phase III study of addition of

nimorazole to RT in patients with locally advanced head and neck cancer not suitable for chemotherapy or cetuximab.[138] EORTC has opened a phase III multicenter study of radiation with or without nimorazole using a 15-gene signature for hypoxia in the treatment of head and neck squamous cell carcinoma. DAHANCA 30, a randomized noninferiority study of hypoxia-profile guided selection of patients who are predicted to be nonresponders to chemoradiotherapy with or without nimorazole, is recruiting patients.

EMERGING STRATEGIES FOR IMPROVEMENT OF CHEMORADIATION THERAPY

In spite of increasing therapeutic achievements of chemoradiation therapy, the use of this form of therapy is still very much restricted by its narrow therapeutic index. The available agents are either insufficiently effective on their own or in combination with radiation against tumors, or normal tissue toxicity prevents the use of effective doses of drugs or radiation. Significant research efforts, both preclinical and clinical, have been undertaken to improve chemoradiation therapy. They include developing more selective and more effective chemotherapeutic agents, incorporating additional agents into chemoradiation therapy that protect normal tissues from injury by drugs or radiation, and improving the technique of RT delivery to minimize treatment of adjacent normal tissue while maximizing tumor dose delivery.

Increasing Antitumor Efficacy of Chemotherapeutic Drugs

A number of newer chemotherapeutic agents are being developed with the goal of enhancing antitumor effects by improving on the selective targeting of tumor cells via strategies such as chemical modification of known compounds including agents currently in use with RT because of their radiosensitizing properties.

Approaches for improvement of drug safety, convenience, or efficacy could include chemical modifications or modifications of the formulation of a known drug. One example is that of Abraxane (nab-paclitaxel, ABI-007). Abraxane is a 130-nM particle form of paclitaxel that is bound to albumin and is solvent free. This avoids the need for Cremophor-based vehicles and lowers the risk of hypersensitivity reactions.[79] Such vehicles have the

potential for altered pharmacokinetics by drug entrapment, leading to decreased drug clearance, decreased volume of distribution, and, ultimately, nonlinear pharmacokinetics. Interestingly, Abraxane has been demonstrated to have higher antitumor activity compared to Taxol in preclinical studies. This is in part mediated via utilization of albumin receptor–mediated endothelial transport, which leads to higher intracellular accumulation compared to standard paclitaxel.[139] Clinically, Abraxane has demonstrated efficacy in metastatic breast cancer in a phase III study.[140] Phase I/II studies in advanced NSCLC, melanoma, bladder cancer, high-risk prostate cancer, and gynecologic malignancy have been reported.[140-151] Preclinical studies have demonstrated Abraxane to have radiosensitizing properties.[152] Therefore, there is significant interest in determining the potential efficacy of Abraxane in disease sites where combined therapy with taxanes and radiation has demonstrated therapeutic advantage. Phase I and phase I/II study of nab-paclitaxel with radiation in lung cancer and head and neck cancer have been completed and reported demonstrating tolerability.[153,154]

Another approach to make current chemotherapeutic drugs more effective against tumors and at the same time less toxic to normal tissues is compound modification via conjugation with water-soluble polymeric drugs, such as polyglutamic acid. These conjugates accumulate in tumors and release the active drug into the tumor in high concentrations and for a longer time. The enhancement in uptake by and prolongation of drug release in tumors are thought to be due to the enhanced permeability and retention effect of macromolecular compounds in solid tumors.[155,156] The abnormal vasculature in tumors is porous to macromolecules, but high concentrations of drug can build up in tumors owing to inadequate lymphatic drainage, whereas polymer-drug conjugates are confined to the bloodstream in normal tissue.[155] This leads to improved spatial localization of the cytotoxic drug within tumor. A promising polyglutamic acid-paclitaxel conjugate (paclitaxel poliglumex) was developed. It is less toxic, more effective against tumors, and more enhancing of tumor radioresponse in preclinical studies than unconjugated paclitaxel.[156,157] Furthermore, there are in vivo laboratory data suggesting that radiation adds to the accumulation of drug within tumors by modification of tumor vasculature.[158] Therefore, multiple mechanisms for spatial localization and cooperation, including inherent drug properties, radiation modification of

vasculature, and radiation-based targeting of sites within the body, could make this an attractive strategy for combining this agent with radiation treatments. Clinical trials in esophageal cancer (phase II), gastric cancer (phase I), and glioblastoma without MGMT methylation (phase II) have been reported in combination with radiation treatments.[159-161]

Normal Tissue Protection

Because normal tissue toxicity represents a major limitation of concurrent chemoradiation therapy, every effort must be taken to prevent or minimize complications. This could be achieved through the incorporation into the treatment of radioprotective or chemoprotective agents or through improvements of radiation delivery. A number of chemical and biologic compounds are available that exhibited either selective or preferential protection of normal tissues in preclinical in vivo testing.[162-166] In addition, there are many candidate compounds, particularly extracts from plants used in traditional medicine settings, that are undergoing in vitro evaluation.[167-169] The most commonly tested radioprotectors are thiol compounds, such as WR-2721 (amifostine), a prodrug that must be converted in vivo to its active metabolite WR-1065. Amifostine is currently the only Food and Drug Administration–approved radioprotector. The principal mechanisms of protection by these agents include scavenging of free radicals generated by ionizing radiation and some chemotherapy agents, such as alkylating agents, and donating hydrogen atoms to facilitate direct chemical repair of DNA damage. However, amifostine modulates transcriptional regulation of genes involved in apoptosis, cell cycle regulation, and DNA repair as well.[170] The protector is taken up preferentially by normal tissues, where the entry into cells is accomplished by active transport. In contrast, the drug diffuses passively into tumors, where its availability is also reduced by deficient tumor vasculature. Amifostine has been shown to reduce normal tissue toxicity in a number of clinical settings, including protection of salivary glands in head and neck RT, prevention of acute and late normal tissue toxicities from chemoradiation in cancers of the head and neck, and the esophagus in chemoradiation therapy of lung cancer, without adversely affecting tumor response to treatment.[171-175] The drug significantly protects against cisplatin-induced nephrotoxicity, ototoxicity, and neuropathy.

Technology-Based Strategies to Improve Radiation Therapy

Several technological strategies to improve the efficacy and decrease the toxicity of RT have been developed. These advances include improvements in RT delivery, such as three- dimensional (3D) treatment planning, conformational radiation therapy (CRT), intensity-modulated radiation therapy (IMRT), and image-guided radiation therapy (IGRT). Use of heavy particles, such as protons or carbons, which have a more favorable beam profile, is another approach likely to minimize the toxicity, and combining such treatments with chemotherapy may lead to enhancement of the effectiveness of not only RT but also chemoradiation treatments. The principle primarily exploited with this would be that of maximizing spatial localization, with technological advances and/or heavy particles being used to maximize RT's spatial localization. Further advances in imaging, with the advent of molecular-based imaging applications in oncology, will lead to further refinement of IGRT techniques. Because there are significant discussions of 3DCRT, IMRT, IGRT, and heavy particles detailed in other chapters, we refer readers to those chapters for more in-depth discussion.

Altering Fractionation Schemes to Improve Therapeutic Ratio for Chemoradiation Treatments

Accelerated fractionation regimens are designed to counteract tumor repopulation, and accelerated fractionation with concomitant boost technique has shown superiority in terms of local control to the standard fractionation regimen in a large randomized study for patients with head and neck cancer.[176] Head and neck cancer remains one of the best paradigms for effectiveness of accelerated fractionation methods in clinical use. However, when combined with chemotherapy, a benefit to accelerated fractionation over standard fractionation was not demonstrated.[177]

Hyperfractionation is another strategy aimed at increasing the tumoricidal dose by delivering smaller doses/fractions, which allows a higher total dose to be administered as smaller doses/fractions lead to improved tolerance of late-responding normal tissues.[77] The efficacy of hyperfractionation over standard fractionation has been demonstrated in several disease sites, including lung and head and neck cancer.[176,178,179] In head and neck cancer, hyperfractionated RT with chemotherapy has yielded

superior outcomes compared to hyperfractionated RT alone; however, there has been no trial to demonstrate superiority of hyperfractionated RT and chemotherapy compared to conventional RT and chemotherapy.[180] Perhaps, given the limited success of concurrent therapy, methods of combining systemic agents sequentially either before or after radiation treatments with altered fractionation can be considered.

CLINICAL EXPERIENCE WITH CHEMORADIATION IN CANCER THERAPY

The level of clinical experience with the combination of radiation and chemotherapy has increased dramatically during the years. In many tumor types, the sequencing and method of administration of the combination have been very important in attaining improved outcomes seen in randomized trials. Improved local control and better overall survival rates have resulted from combination therapy in several diseases, including rectal cancer, limited-stage small cell lung cancer, locally advanced NSCLC, esophageal cancer, gastric cancer, cervical cancer, glioblastoma, and rhabdomyosarcomas. Equally important are the successes seen in the realm of organ preservation in sarcomas of the extremity, bladder cancers, carcinomas of the anal canal, head and neck cancers, and breast cancer.

As the role for combined modality therapy and studies leading to such for each of the tumor types are well represented in individual chapters addressing the disease site, readers will be referred to individual disease site chapters in the text for details. Briefly summarized in Table 31.3, however, are some representative disease sites in adult malignancies, where combined modality therapy with chemotherapy and/or targeted biologic agents and RT is accepted as the standard of care. The table also summarizes the commonly used systemic agent for these different disease sites. The list, while not comprehensive, is certainly extensive and impressive, and the clinical impact that combined modality therapy has had in each of these disease sites cannot be understated.

TABLE 31.3 CHEMORADIATION THERAPY AS STANDARD OF CARE BY SELECTED DISEASE SITES

Disease Site	Commonly Used Chemotherapeutic Agents	Sequencing and Intent of Therapy	Benefit of Combined Modality Approach
Locally advanced head and neck cancer	Cisplatin, 5-FU, hydroxyurea, carboplatin, cetuximab	• Definitive concurrent • Postoperative concurrent	Definitive: organ preservation/survival benefit Postoperative: DFS/LRC benefit; OS benefit in subset of patients
Glioblastoma multiforme	Temozolomide	• Postoperative concurrent • Definitive concurrent in unresectable cases	OS
Locally advanced/unresectable non–small cell lung cancer	Cisplatin, carboplatin, paclitaxel, etoposide, vinblastine	• Definitive concurrent • Sequential	OS
Limited-stage small cell lung cancer	Cisplatin/etoposide	Definitive concurrent	OS
Esophageal cancer	Cisplatin/5-FU	• Preoperative concurrent • Definitive concurrent	Local control, OS
Gastric cancer	5-FU, leucovorin	Postoperative concurrent	OS
Pancreatic cancer	5-FU, gemcitabine	• Postoperative concurrent • Definitive concurrent in unresectable patients	LRC, possibly survival
Locally advanced rectal cancer	5-FU, Xeloda	Preoperative concurrent	Improved sphincter preservation, improved DFS
Anal cancer	5-FU, mitomycin-C	Definitive concurrent	Improved colostomy free survival

Disease Site	Commonly Used Chemotherapeutic Agents	Sequencing and Intent of Therapy	Benefit of Combined Modality Approach
Cervical cancer	Cisplatin, 5-FU, hydroxyurea	Definitive concurrent	OS benefit
Bladder cancer	Cisplatin, 5-FU, mitomycin-C	Definitive concurrent	Bladder preservation

DFS, disease-free survival; LRC, locoregional control; OS, overall survival; 5-FU, 5-fluorouracil.

As outcomes in each of the solid tumors improve with concurrent therapy, we need to become cognizant of the potential for significant long-term toxicity from combination chemoradiation and do our best to minimize the risks that these side effects pose to patient survival and quality of life. Several well-documented chemoradiation-imposed late effects are summarized in Table 31.4.

TABLE 31.4 REPRESENTATIVE LONG-TERM TOXICITY OF COMBINED CHEMORADIATION THERAPY

Agent	Toxicity	Mechanism	References
Bleomycin	Pneumonitis/pulmonary fibrosis	Undefined but related to total drug dose and effects on pulmonary macrophages, type I and II alveolar cells; effects/lethality exacerbated by the administration of radiation	181-183
Actinomycin-D	Hepatopathy	Altered liver function postradiation leads to decreased metabolism of agents, including actinomycin, which in turn worsens the hepatopathy.	184,185
Doxorubicin	Cardiomyopathy	There is an additive interaction between doxorubicin and radiation with recall of radiation effects occurring. Primary radiation effect is on the endothelial cell, whereas doxorubicin affects the connective tissue stroma of the myocardium.	186-189

Agent	Toxicity	Mechanism	References
Methotrexate	Leukoencephalopathy	Methotrexate may cause this syndrome on its own. Radiation effects on the blood-brain barrier and the choroid plexus can alter methotrexate clearance, leading to higher levels in the brain. Effects are increased when both modalities are used.	190-192
Cisplatin	Sensorineural hearing loss	Although cisplatinum alone can cause this, reports suggests radiation therapy concurrently with cisplatin may contribute to sensorineural hearing loss.	193-196

CONCLUSION

The combination of chemotherapy and RT has become a common strategic practice in the therapy of locally advanced cancers, with emphasis on the concurrent delivery of both modalities. Improvements in treatment outcome in terms of both local control and patient survival have been achieved with traditional chemotherapeutic agents such as cisplatin and 5-FU. However, there is considerable room for improvement of the combined treatment strategies. Selection of the most effective drug or the optimal treatment approach remains a significant challenge.

Newer chemotherapies are becoming available at an increasing rate. These agents have high potential for increasing the therapeutic effectiveness when used in conjunction with RT, and therefore, their evaluation—both in the laboratory and in the clinic, in combination with RT—is essential for improvement of cancer treatment.

Biomarkers, molecular therapeutics, immunotherapy advances, advanced imaging technology, and advances in understanding of effective chemotherapy/immunotherapy and radiation treatment integration have led to an era where personalized medicine for cancer therapy is becoming a reality. There are certainly challenges that we can anticipate along the way toward an era of personalized medicine.

Finally, despite significant improvements rendered to cancer therapy in the past decades, it is sobering to realize that cancer, particularly when

advanced, remains a deadly disease for many. As we continue to engage in novel ideas to further strengthen our arsenal, it will be essential to design well-thought-out and effective combined modality therapy clinical trials to further improve the odds in the battle against cancer.

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CHAPTER 32

Artificial Intelligence and Data Science as Applied to Radiation Oncology

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As artificial intelligence (AI) technologies are increasingly integrated into both research and clinical facets of oncology, radiation oncologists will need to understand the nuances of AI and its applications. This chapter delves into the foundational principles of AI, its integration within radiation oncology workflows, medical image acquisition, reconstruction and analysis, natural language processing (NLP), advanced modeling of oncology data, and the challenges (ethical or otherwise) and prospects AI presents in radiation oncology. While this chapter provides a comprehensive overview for clinical radiation oncologists and resident physicians, it does not delve into the depth suited for data scientists, engineers/developers, or AI technologists. Advanced readers are encouraged to consult the data science and AI-focused literature for a more nuanced examination of AI methodologies and technologies.

ARTIFICIAL INTELLIGENCE, MACHINE LEARNING TECHNIQUES, AND APPLICATIONS TO RADIATION ONCOLOGY WORKFLOW

Artificial Intelligence Methods and Applications to Radiation Oncology in Perspective

Radiation oncology is undergoing transformative changes. The integration of AI systems, advanced pattern recognition and predictive modeling software, and automation tools into clinical workflows is ushering in a new era of streamlined patient care, adaptive and personalized radiotherapy (RT), and unparalleled innovation and advancement (Table 32.1).

TABLE 32.1 NONEXHAUSTIVE LIST OF COMMONLY USED MACHINE LEARNING AND ARTIFICIAL INTELLIGENCE METHODS AND EXAMPLES OF CLINICAL APPLICATION IN ONCOLOGY

Method	Description	Clinical Application Example
Conventional Machine Learning		
Linear regression	Predicts a continuous variable by fitting a line through data points	Predicting tumor growth rates over time[110]
Logistic regression	Used for classification, predicting the likelihood of an input belonging to a class based on a threshold	Predicting likelihood of cancer recurrence after radiation[111]
Decision trees	Tree-like structures for classification and regression, recursively dividing data based on input features	Selecting the most relevant prognostic factors for accurately predicting breast cancer relapse to assist clinicians in choosing appropriate adjuvant treatments[112]
Support vector machines	Used for classification and regression by determining a hyperplane to separate or predict data	Classifying tissue samples as malignant or benign based on histopathologic features[113]
Random forests	An ensemble of decision trees, mainly for classification and regression	Identifying key biomarkers associated with cancer prognosis[114]
K-means	Unsupervised learning to identify data clusters or patterns	Clustering patients based on gene expression profiles[115]
Deep Learning		
Convolutional neural networks (CNNs)	Analyze visual data like images by applying filters to identify patterns and features	• Auto-segmentation of OARs and tumor targets[68] • Extracting features from images to predict outcomes[49] • Image classification, such as determining tumor histology from digital pathology slide or CT[37]
Recurrent neural networks (RNNs)	Analyze sequential data by capturing and conveying information stepwise, although	Outcome prediction from a time series such as serial follow-up CT scans[48]

Method	Description	Clinical Application Example
	susceptible to the “vanishing gradient” issue in long sequences	
Transformers	Process sequential data using a self-attention mechanism to evaluate element importance, overcoming RNN’s long-range dependency limitations	Extracting various types of clinical concepts from medical text to facilitate downstream natural language processing tasks in the medical domain[116]
Generative adversarial networks (GANs)	Generate synthetic data samples resembling a training data set, using a cyclic process between a generator and a discriminator	Generating realistic synthetic EHRs to overcome limited access to real EHR data and accelerate research in medical informatics[117]
Deep reinforcement learning	Learning through trial and error to make decisions with unstructured data	Image enhancement such as CT reconstruction[56]
Foundation models	Adaptable AI models proficient in handling tasks related to text, audio, and images, capable of learning from labeled and unlabeled data to serve as a base for specialized applications	Integrating textual patient history with medical imaging data for comprehensive diagnostic decision-making[109]
Multimodal models	AI models designed to process and integrate multiple types of data inputs, such as text, images, and audio, for more comprehensive analysis and decision-making	Personalizing prostate cancer therapy by predicting long-term, clinically relevant outcomes using a combination of clinical data and digital histopathology from prostate biopsies[47]
Generative AI	AI algorithms designed to generate new data that mimic the properties of the training data, useful for simulation and augmentation tasks	Creation of personalized patient clinic letters with limited clinical input using LLMs providing high-quality, understandable, and human-like outputs adapted to clinical communication scenarios[118]
Large language models	AI models specifically trained on large amounts of text data to understand and generate human-like text	Utilization LLM to communicate clinical advice or reports to patients[118]

AI, artificial intelligence; CT, computed tomography; EHR, electronic health records; LLM, language learning model

While the term "AI" is used somewhat liberally in the modern literature, the definition and boundaries of AI have been dynamic, shifting as technological advancements were achieved and by preference in the popular media. Current systems mostly fall within a "narrow AI" definition, where models focus on a specific, singular, or limited task, such as image recognition or outcomes prediction but lack self-awareness, consciousness, or the ability to think independently. These models are often trained on vast amounts of data in a supervised, unsupervised, semisupervised, or self-supervised manner, allowing them to accomplish specific tasks on data sets within the same domain (eg, health care or finance) and data modality (eg, natural images or language). "General AI," by contrast, refers to systems that can handle a range of cognitive tasks with little supervision and have the capacity for creativity, novel insight, adapting to new situations to exhibit competence on multiple tasks. These systems would theoretically pass the Turing test for independent human-level intelligent behavior.[1] Current systems do not pass the litmus test for "general AI," and some developers question if this form of artificial general intelligence (AGI) can indeed be realized (Table 32.2).

TABLE 32.2 GLOSSARY OF ARTIFICIAL INTELLIGENCE/MACHINE LEARNING-RELATED TERMS

Term	Definition
API	Application Programming Interfaces that allow different software applications to communicate with each other, commonly used to integrate ML models into software systems
Artificial general intelligence	Hypothetical AI with the ability to understand, learn, and apply knowledge in multiple domains, resembling human cognitive functions
Autoencoder	Unsupervised AI algorithms that learn to encode the important features of data and then decode it, often used for dimensionality reduction or anomaly detection
Back-propagation	Optimization technique to minimize an objective function in a web of nonlinear mappings by calculating the gradient of the loss function in a neural network

Term	Definition
Black box	A model or system where the internal mechanisms or logic is not directly observable or understandable. Often used to describe complex ML models like deep learning (DL) networks
Contrastive learning	An unsupervised learning approach that trains models to differentiate between similar data points, thereby learning useful feature representations from the data
Data augmentation	Techniques used to increase the size and diversity of training data sets through transformations such as rotation, scaling, and flipping, aimed at improving model generalization
Data curation	The process of collecting, organizing, and validating data for use in ML models
Developed from scratch	Refers to developing an AI algorithm without using pre-existing code or frameworks
Digital twins	Virtual replicas of physical systems or processes that are used for simulation, analysis, and control
Dimensionality reduction	Techniques to reduce the number of variables in a data set while preserving its essential features, often used for visualization or to improve model performance
Deep learning	DL is a subfield of ML where algorithms model and process hierarchical complex patterns in data using multiple layers of nonlinear transformations, popularized as “neurons.”
Explainability	The capacity for the logic or reasoning behind an AI model’s decisions to be easily understood by its users
Interpretability	The quality of an AI model that allows users to understand the underlying factors leading to its predictions
Few-shot learning	An ML paradigm that aims to train models to perform well with only a small number of labeled examples for each class, often used in situations where data are scarce
Fine-tuning	The process of adapting a pretrained model to a specific task or data set
Fully connected	In neural networks, a fully connected layer is one where each neuron is connected to every neuron in the previous and next layer.
Generalizability	The ability of an AI model to make accurate predictions when applied to diverse conditions or data sets
Hallucinations	The term is borrowed from psychiatric vernacular to denote model errors related to overconfident incorrect responses or fixed false beliefs by LLMs.

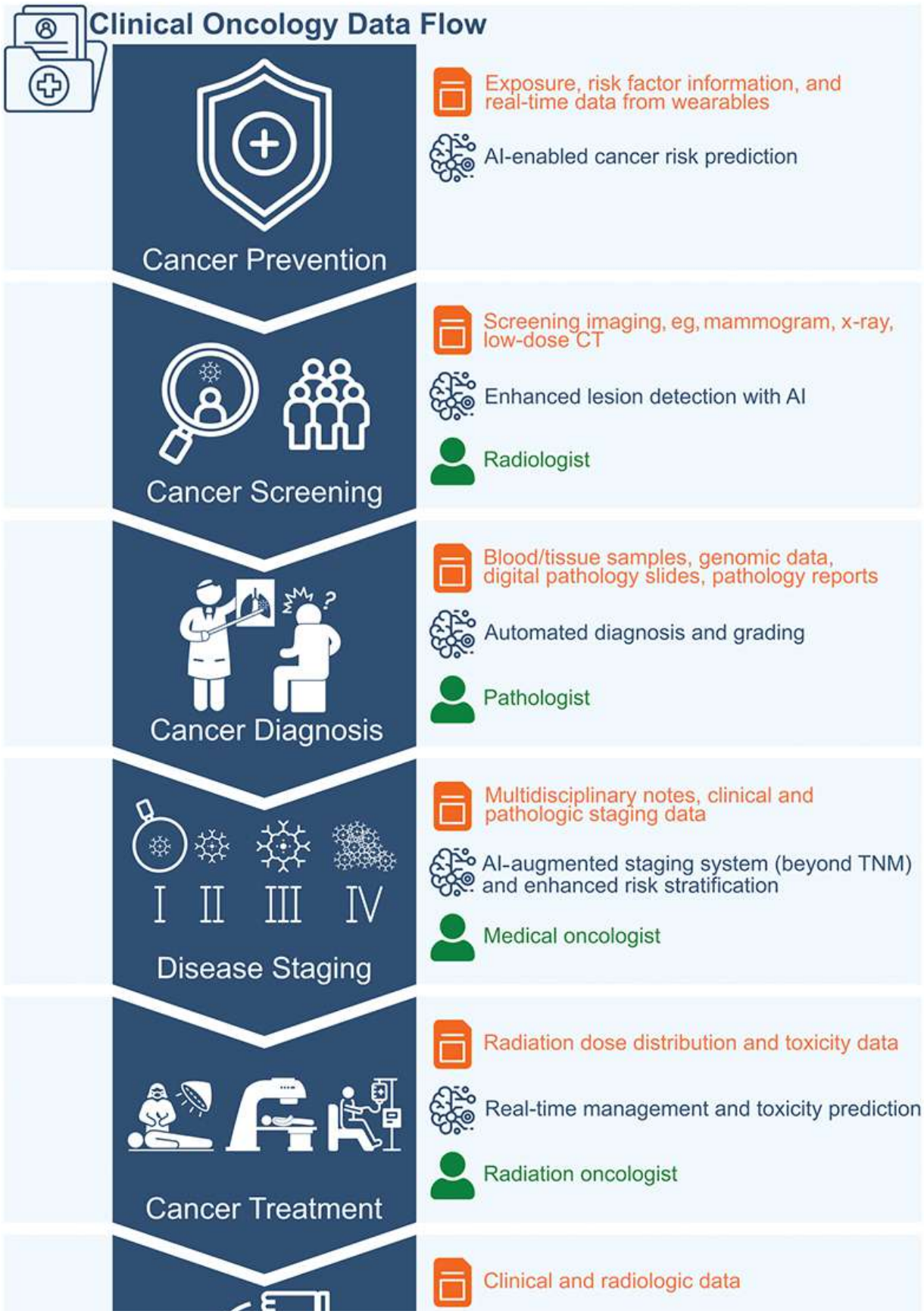
Term	Definition
Multi-GPU multinode data parallelism	A distributed computing setup that leverages multiple GPUs across multiple nodes to parallelize data processing and model training, enhancing computational power and efficiency
Parameters	In ML, parameters are internal variables that the model learns through training. They define the transformations that the model applies to its input data to make predictions or decisions.
Pretraining	Initial training phase where a model learns from a general data set before being fine-tuned for a specific task
Principal components analysis	A statistical procedure that uses orthogonal transformation to convert correlated variables into a set of linearly uncorrelated variables called principal components; often used for dimensionality reduction
Prompts	Short questions or cues used to guide the behavior of language models, often employed to narrow down the focus or topic that the model will generate text about
PyTorch	An open-source ML framework developed on the Python interface and utilized for computer vision tasks
Radiomics	The extraction of a large number of advanced quantitative features from medical images, often used for predicting patient outcomes or treatment responses
Radiogenomics	The study of the relationship between radiologic imaging data and genomic data to predict disease characteristics or patient outcomes
Reproducibility	The ability of a clinical AI model to achieve the same results when applied to new data of the same type
Saliency maps	Visual tools used to highlight regions in an input (like an image) that are most important for a model's prediction, aiding in interpretability
Softmax	A function that takes an unnormalized vector and normalizes it into a probability distribution, typically used in the output layer of a classification neural network to represent probabilities
Supervised learning	A specific type of ML where a model is trained on labeled data. The model makes predictions or decisions based on input data and is corrected when its predictions are incorrect.
Survival models	Analyze time-to-event data with known covariates, predicting survival probabilities or hazard ratios

Term	Definition
T-distributed stochastic neighbor embedding	An ML algorithm used for dimensionality reduction and data visualization; it is often used for embedding high-dimensional data into a space of two or three dimensions.
Transparency	The degree to which the inner workings or decision-making processes of an AI model are open and understandable
Turing test	A test, proposed by Alan Turing in his seminal 1950 paper to evaluate a machine's ability to exhibit human-like intelligence
Unsupervised learning	A specific type of ML that involves modeling with data sets that contain input data without labeled responses. The system tries to learn the patterns and structure from the data without any supervision.
Visual representation learning	A subset of ML focused on training models to understand and generate visual features from raw data, commonly used in image recognition and computer vision tasks

AI, artificial intelligence; CT, computed tomography; EHR, electronic health record; LLMs, language learning models; ML, machine learning; OARs, organs at risk.

Nevertheless, existing methods in narrow AI are seeing widespread adoption in many facets of society and within oncology, accelerating the pace of discovery and automation in clinical workflows (Figure 32.1). Early iterations of these systems, such as, early computer-aided diagnosis systems,[2] were rule based, with programs that followed specific steps handcrafted by experts (often hard-coded) or by engineers with guidance from those with the respective domain expertise (eg, internists or radiologists). While these systems were functional, they had limitations and struggled when encountering situations or data that did not fit their prespecified rules. More advanced techniques for pattern recognition based on neural networks and their foundational architecture were popularized in the late 1980s and early 1990s, with the advent of early models such as the Le-Net.[3] These models consisted of multilayer nonlinear transformations trained with back-propagation, and they vastly outperformed existing techniques at the time. However, early adoption was limited by a paucity of computational power in contemporary processors. This changed in the 2010s with the computing performance offered by graphical processing units (GPUs). Initially designed to enhance three-dimensional (3D) graphics rendering in video games, GPUs evolved to become more flexible and

programmable, paving the way for leaps in machine learning (ML) and opening new possibilities for advanced numerical methods and scientific computing. This facilitated a resurgence in the popularity of convolutional neural networks (CNNs), with these models gaining significant attention and becoming a mainstay in deep learning (DL), especially for image-processing tasks.


Clinical Oncology Data Flow
Cancer Prevention
Exposure, risk factor information, and real-time data from wearables
AI-enabled cancer risk prediction
Cancer Screening
Screening imaging, eg, mammogram, x-ray, low-dose CT
Enhanced lesion detection with AI
Radiologist
Cancer Diagnosis
Blood/tissue samples, genomic data, digital pathology slides, pathology reports
Automated diagnosis and grading
Pathologist
I II III IV
Disease Staging
Multidisciplinary notes, clinical and pathologic staging data
AI-augmented staging system (beyond TNM) and enhanced risk stratification
Medical oncologist
Cancer Treatment
Radiation dose distribution and toxicity data
Real-time management and toxicity prediction
Radiation oncologist
Clinical and radiologic data

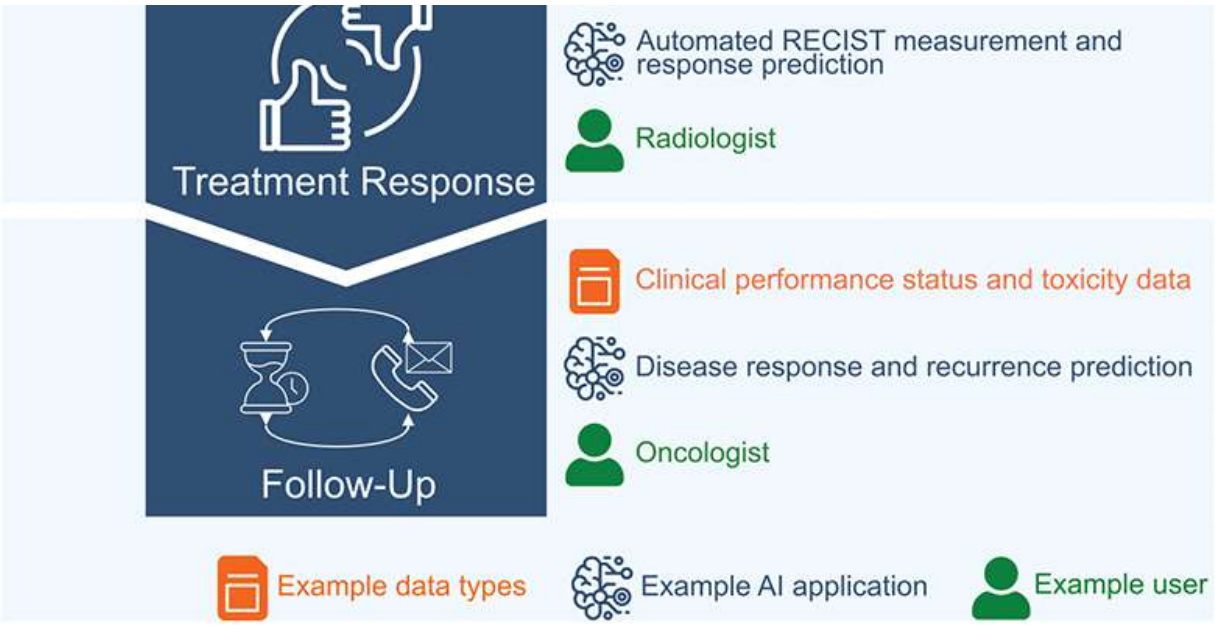


FIGURE 32.1 Clinical oncology data flow. This figure illustrates a prototypical pathway for care of a patient with cancer with an escalating flow of data. It captures a series of critical touchpoints, starting from preventive care, cancer screening, initial cancer diagnosis, disease assessment and staging, primary oncologic treatment, response assessment, and follow-up care. At each step, example data types that are collected, either routinely or as part of advanced care, are listed, along with potential AI applications and example users. The figure illustrates the interface between AI technology and the clinical environment in the delivery of personalized management of oncology patients through their cancer care journey. AI, artificial intelligence; CT, computed tomography; RECIST, Response Evaluation Criteria in Solid Tumors.

The rise of more sophisticated architectures and the availability of large digital data sets (made possible in large part by the internet), coupled with the increased computational power of GPUs over the ensuing decade, accelerated advances in this field. In the domain of NLP, this included the groundbreaking introduction of transformer architectures[4] with the self-attention mechanism. Subsequent iterations, including Generative Pre-trained Transformer (GPT) and GPT-like models, gained widespread adoption and perhaps shifted public perceptions and attitudes toward AI, given seemingly coherent outputs that mimic human language and could mask potential limitations, for example, in oncology domain-specific predictions.[5] The current generation of AI, therefore, presents both exciting opportunities and potential pitfalls with new modes of failure that will require the radiation oncologist to be well versed on their inner workings to

take full advantage of these technologies in the streamlined delivery of cancer care and RT, while effectively minimizing the risk for harm to patients (Table 32.1).

Machine Learning Paradigms in Oncology Data Analysis

ML is a subset of the broader AI domain that offers various methodologies to decipher patterns and make predictions based on data. This field has evolved from simplistic models, such as logistic regression assuming independent input variables, to more advanced algorithms, such as random forest, which can weigh and characterize input variable interrelationships, enabling them to fit more complex data. Current methodologies vary based on the nature and structure of the data, as well as the objective of the analysis. Within different learning paradigms, multiple specific model types can be employed, each relying on different approaches for training and discerning patterns from the data.

In "supervised learning," models are trained on labeled data to predict future instances based on learned features from the data. This approach excels in tasks such as image classification and clinical outcomes prediction. Common examples include regression models to project survival rates from labeled data sets or support vector machines (SVMs) for identifying optimal hyperplanes that separate data classes, for example, in tumor histopathologic subtyping. By contrast, unsupervised learning identifies inherent patterns within unlabeled data, grouping similar instances without explicit guidance. A typical application is in identifying distinct, previously unknown, tumor subtypes using genomic data. Frequently used methods for unsupervised learning include dimensionality reduction algorithms such as autoencoders—a generalized form of principal component analysis (PCA)—and t-distributed stochastic neighbor embedding used widely for visualization of high-dimensional data in the two or three dimensions that are readily understandable to the human observer. "Semisupervised learning" blends supervised and unsupervised approaches, leveraging labeled and unlabeled data for enhanced accuracy. Initially, it utilizes labels to hone a classifier, which subsequently aids in labeling more data, potentially reducing the demand for human annotations.

"Self-supervised learning" operates on unstructured data by automatically generating labels. It might train a model to predict missing sections of an image or masked words in a sentence, honing its capability to learn generalizable features about that data type that can be employed to improve performance on downstream tasks, such as segmentation or classification. Variations or augmentations are often introduced to unlabeled data, teaching the models to identify inherent features from the data. In recent years, unsupervised algorithms, for example, for visual representation learning, have shown better performance and improved robustness to perturbation than supervised approaches.[6] This has been largely driven by the paradigm of contrastive learning, where representations are learned by contrasting negative and positive examples. Contrastive learning has shown great promise in extracting high-level features from volumetric tumor information.[7] Finally, "reinforcement learning" employs an iterative feedback system where a model learns optimal actions through rewards and penalties, analogous to a cat refining its jump based on previous experience. These algorithms shape strategies that yield the most advantageous outcomes, finding applications in domains ranging from gaming to potentially streamlining radiation treatment planning.

Overall, each ML paradigm serves specific needs, guiding the choice of method for various tasks. Of note, a recent shift in the ML community toward creating large general-purpose models that can be fine-tuned for specific tasks rather than training separate models for each task has led to the concept of "foundation models." These models are pretrained on vast amounts of data in a self-supervised, task-agnostic manner to capture a broad understanding of language, images, and other data types and can be adapted to specific tasks with relatively small amounts of task-specific data. Foundation models open exciting new avenues for biomarker discovery in cancer imaging[8] and other applications. However, questions on whether ML models generalize even with such broad training remain.

Advances in oncology research, increased data generation in clinical practice, and computational innovations have shifted the way patient data are represented from a low-dimensional to a high-dimensional framework. Historically, due to data and computational constraints, patient data, such as diagnostic imaging and pathology, were simplified into digestible measures,

such as the American Joint Committee on Cancer TNM cancer staging system for decision management in clinical oncology. However, the introduction of electronic medical records (EMR), The Cancer Imaging Archive, The Cancer Genome Atlas, and others have enabled the development of more complex risk stratification models. These models, combined with the expanding data streams through EMR mining, allow for detailed profiling of patients as they progress through the cancer care pathway (Figure 32.1). With expanding data availability in oncology, ML algorithms can be employed for the advanced modeling of oncology data to identify patterns that could help guide treatment decision-making for specific patient groups or individual patients. This convergence of comprehensive data and precision in care underscores the potential of AI and ML techniques in revolutionizing oncology, although their full promise remains to be realized.

Artificial Intelligence and Machine Learning Applications to Radiation Oncology

As an inherently technology-driven specialty, with frequent use of radiologic imaging, repetitive protocol-driven tasks such as target delineation and treatment planning, and the generation of vast amounts of digital, quantitative, and multimodal data, radiation oncology is a field ripe for AI applications (Figure 32.2). However, current AI tools in radiation oncology are predominantly designed for singular tasks like segmentation. This presents integration challenges in clinical workflows. Holistic approaches, embedding these AI solutions within existing systems, can enhance workflow efficacy and user acceptance.

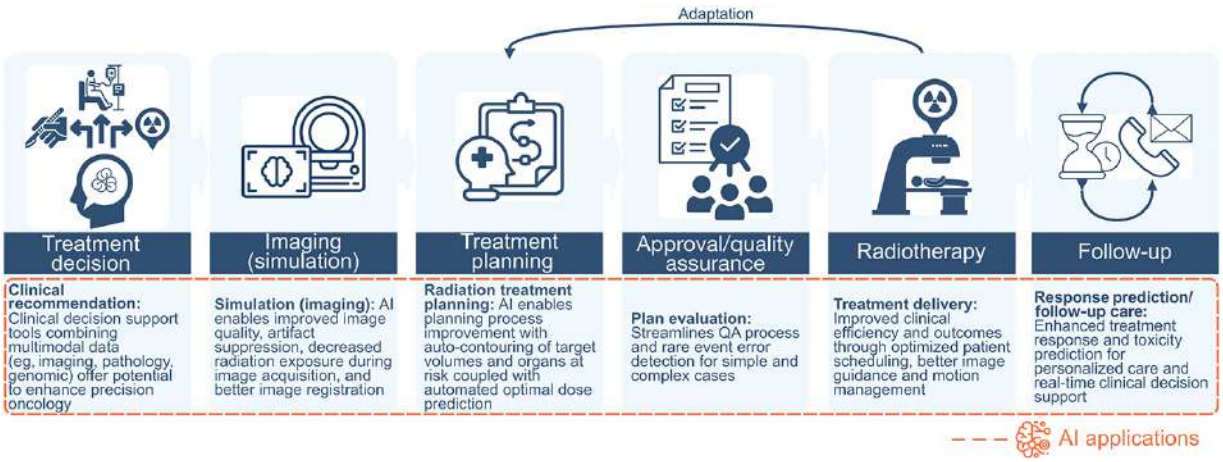


FIGURE 32.2 Integration of AI in radiation therapy workflow. This figure shows the stages of the radiation therapy workflows and highlights corresponding areas where AI can be integrated to enhance each step. The process starts with a treatment decision where a clinical recommendation regarding radiation therapy is made, leading to simulation where patient anatomy and imaging data are acquired for treatment planning. Following the generation of a tailored treatment plan, meticulous plan review and QA protocols are followed prior to the delivery of radiation. Follow-up care includes response assessment and toxicity management. AI applications can potentially augment operational efficiency for radiation oncology care team, improve the precision and quality of radiation treatments, and enhance predictive and prognostic modeling to inform and refine decision-making. AI, artificial intelligence; QA, quality assurance.

AI in radiation oncology already offers potential efficiency improvements, notably in auto-segmentation and auto-planning (Figure 32.3). However, its role in direct clinical decision-making is still limited. To bridge this gap, radiation oncologist training in AI is essential to promote collaboration between clinicians and data scientists, build trust in these technologies as they evolve, and optimize several steps within the radiation oncology workflow.

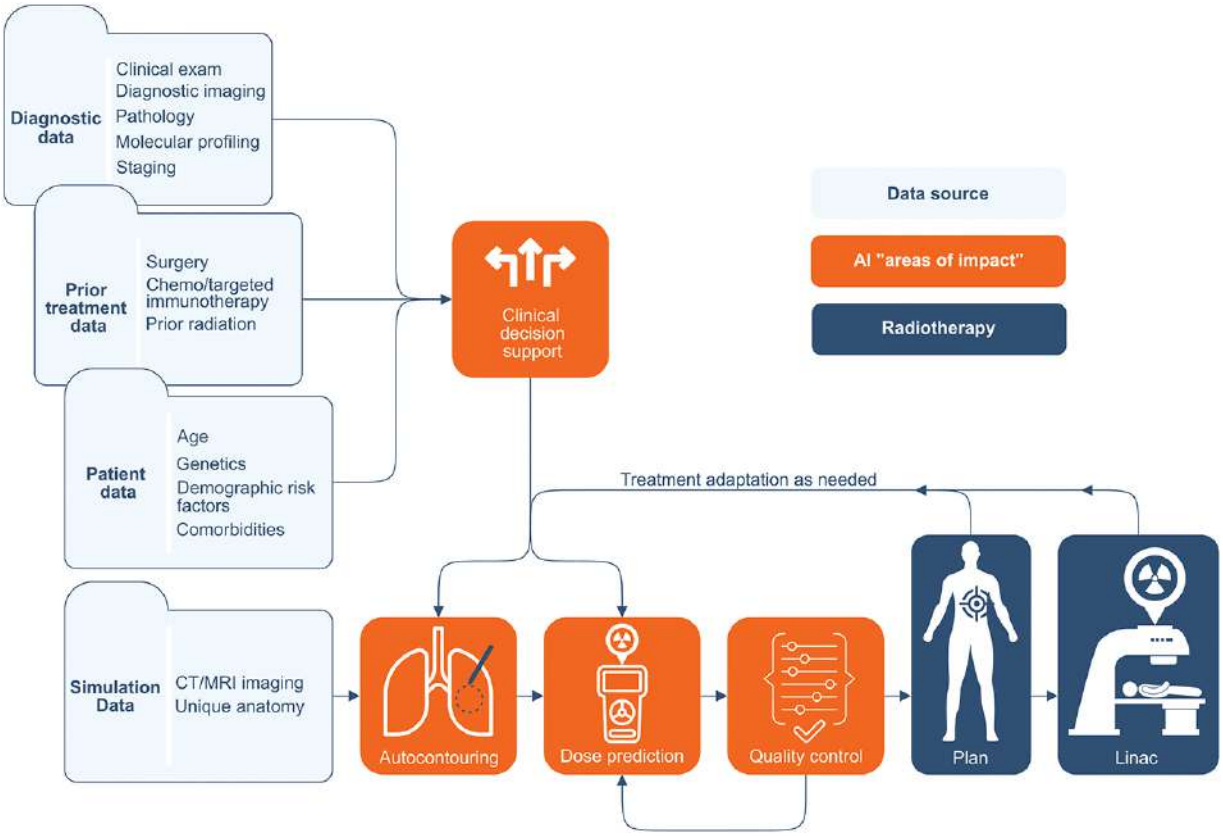


FIGURE 32.3 Utilizing artificial intelligence (AI) in radiation therapy planning and delivery. This figure shows the multiple data sources utilized in radiation therapy decision-making, planning, and treatment delivery, highlighting areas where AI can be meaningfully integrated. The key data sources include diagnostic data, prior treatment information, patient-specific data, and simulation data. Simulation data are typically collected in the later stages of the process. AI assists in tasks like treatment decision, auto-contouring and dose prediction, and quality control. A radiation treatment plan is then formulated and delivered. The plan can be adapted as needed over the course of a patient's treatment. AI can assist in real-time treatment adaptation to enhance efficiency and precision. CT, computed tomography; MRI, magnetic resonance imaging.

The RT workflow can be parsed into several key steps: initial treatment decision, treatment planning, quality assurance (QA), the delivery of RT with on-treatment monitoring, and post-treatment follow-up care (Figure 32.3). The following subsections provide an in-depth exploration of each step, highlighting the key tasks, stakeholders, and innovative ways in which AI can enhance these processes.

CLINICAL INFORMATICS, NATURAL LANGUAGE PROCESSING, AND LARGE LANGUAGE MODEL APPLICATIONS

NLP is a subdomain of AI that seeks to transform human language into formats that computers can analyze, offering a method to extract valuable information from text (Figure 32.4). Current iterations of this technology can improve our comprehension of multiple data sources, including information stored in the EMR. In radiation oncology, NLP algorithms offer a promising avenue for enhancing several aspects of care and research, for example, by refining patient data management and presentation, automating radiation oncology data integration into cancer registries, and uncovering new insights into cancer treatment and outcomes.[9] However, several hurdles exist to realizing NLP's full potential in radiation oncology. This includes inconsistent naming conventions in radiation oncology (eg, in contoured treatment planning structure sets, requiring efforts to standardize naming conventions and generate radiation oncology ontologies that map, integrate, and query radiation oncology data from various sources[10,11]), specialized radiation oncology terminology or jargon that pretrained models may not be able to handle, the scarcity of publicly available labeled radiation oncology– specific data sets for model training, and integration challenges across data systems, particularly given the prevalence of radiation oncology data silos across health systems.

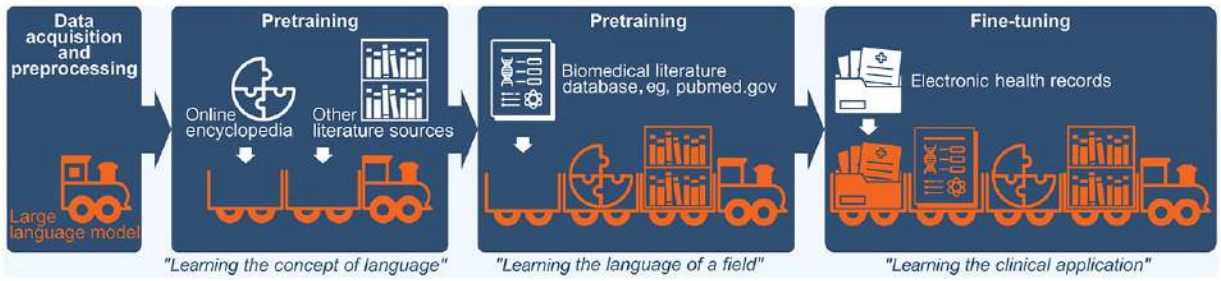


FIGURE 32.4 Language learning model (LLM) training for clinical applications. This figure illustrates the stages of training an LLM, each represented as a train stop on the model's journey through training. The first stop is Pretraining on general literature sources such as online encyclopedias to help the model learn the concept of language. The models then go through a second Pretraining phase focused on biomedical literature databases, such as PubMed, to enable it to learn clinical domain-specific language. Finally, the model goes through Fine-tuning, where it is fed clinical text from electronic health records to adapt to a specific clinical application. Each phase enhances the model's abilities, from understanding language fundamentals to becoming adept at specialized clinical tasks.

NLP pipeline evaluation and implementation in radiation oncology remains limited, although some applications are beginning to emerge. An open-source NLP platform, Apache Clinical Text Analysis Knowledge Extraction System, demonstrated an ability to extract toxicity data from unstructured notes from RT on-treatment visits, outperforming human interrater variability for positive symptoms.[12] The pipeline, however, underperformed against humans in negative instances. Some small studies have investigated using NLP to standardize planning structure naming from inconsistent physician-assigned labels of prostate and lung organs at risk (OARs) with TG-263 standardized terms.[13,14] The model attained high F1 scores on both internal validation and external test sets for each organ.

More recently, emerging work shows the potential of fine-tuning neural language models with transformer architectures to support RT (Figure 32.4). An end-to-end pipeline of fine-tuned pretrained language models demonstrated strong performance in extracting comprehensive details of patients' radiation treatments from clinical notes.[15] Similarly, fine-tuned language models showed excellent performance in extracting radiation esophagitis toxicity severity in patients with lung cancer.[16] However, performance dropped when applied to patients with esophageal cancer, highlighting the common challenge of domain transfer with language models. These early studies demonstrate the potential of neural language models to support real-world databases and electronic health record (EHR) mining.

Increases in computational power and pretraining data set size have led to the development of current state-of-the-art large language models (eg, those based on DL transformer architectures and trained on extremely extensive data from the internet). Language learning models (LLMs) are generally over 6 to 13B parameters in size, and the most state-of-the-art LLM, such as OpenAI's GPT-3.5, is 137B parameters in size. There is growing interest in LLMs, including expanding use by the general public. While earlier generations of language models required fine-tuning on task-specific data to carry out NLP tasks, LLMs exhibit emergent abilities to process and understand language without additional fine-tuning. This is especially exciting for the medical domain, where labeled data sets of clinic notes are scarce, and data and model sharing are limited by patient privacy concerns. In fact, LLMs appear to learn a representation of biomedical and clinical

knowledge during their pretraining and have been shown to pass the USMLE.[17] The fact that LLMs can provide coherent responses with no updates to their parameters has created a new emphasis on prompt engineering, which is designing optimal methods to elicit the correct response from LLMs. For example, providing examples of correct input/output along with the query (few-shot) can improve performance in some cases. More consistently, instructing the LLM to lay out its reasoning via Chain-of-Thought prompting, that is, "think step by step," boosts LLM performance.[18] Automated prompt refinement is an actively evolving field. It is important to note that prompt engineering, which is the process of developing and refining how to prompt the LLM to provide a response, is not trivial and can be time-, compute-, and data-intensive.

Given the rapid adoption of LLMs, work evaluating the models' utility in oncology is of high priority for both oncology practitioners and patients. Limitations, particularly in oncology domain-specific knowledge, can pose a risk for radiation oncology patients seeking information about their disease and treatment options.[5] Moreover, the propensity for "hallucinations" in model outputs can potentially undermine oncologist recommendations and also limit the models' clinical utility if clinicians cannot ascertain the accuracy of the outputs and recommendations. However, there have been attempts to tailor LLMs with oncology-specific knowledge to construct models that can be more reliably used in clinical practice. One such attempt, RadOnc-GPT, aimed to demonstrate potential in three primary areas: formulating RT treatment plans, deciding the best radiation treatment approaches, and assigning diagnostic descriptions and *International Classification of Diseases* codes based on patient information.[19] Other exploratory clinical language model examples include GatorTron,[20] which was developed from scratch using clinical text and showed a more than 9% improvement at tasks such as medical question answering; ClinicalBERT;[21] and OncoBERT,[22] which is tailored for oncology applications. OncoBERT was designed to predict cancer outcomes by analyzing unstructured clinical notes about three distinct cancer types: brain, prostate, and breast. Compared to general language models, the fine-tuned model outputs were clearer, more specific, and more likely to be clinically pertinent. These examples highlight the

transformative potential of domain-specialized language models in clinical oncology.

Health disparities persist, and research into the etiologies of these disparities in cancer care is often limited by the challenge of analyzing unstructured clinical data that are often asymmetrically recorded, particularly with regard to sociodemographic factors. NLP can transform human language into analyzable formats, unlocking insights from such data. Analysis of unstructured clinical notes using NLP may help uncover Social Determinants of Health (SDoH) that contributes to disparities in cancer care and outcomes.[23,24] The development of NLP tools also promises enhanced access to clinical trials for marginalized populations and improved communication in health care settings.[25]

NLP systems are poised to become increasingly integrated into the EMR, offering several potential benefits to clinical practice. If fully realized, these technologies could streamline the radiation oncology workflow by automatically generating oncologic histories, standardizing radiation oncology naming conventions, enhancing QA in treatment planning, and facilitating research via EHR mining for real-world evidence. In addition, as NLP evolves, it may play a direct role in patient care through interactive generative LLMs (eg, OpenAI's ChatGPT) that provide guidance, assist with minor toxicity management, and even match patients to suitable clinical trials.

However, rigorous and nuanced interrogation of NLP systems will be crucial before the clinical integration of the models. The models must be appropriately evaluated for their specific patient populations and end-use to avoid inaccuracies and resultant medical errors. For instance, misinformation in public sources, particularly in critical domains like breast oncology,[26] can adversely influence the outputs of language models. It is, therefore, vital that language models capture accurate information in the training phase to be reliable sources of oncology recommendations and mitigate the propagation of any biases from the training data that could disproportionately impact marginalized groups and potentially cause harm. Moreover, radiation oncology is continually evolving, and the knowledge or guidelines from any given period may diverge from future accepted practices. Accounting for these potential shifts in clinical knowledge may pose an intractable challenge in model training, fine-tuning, and evaluation

processes. Outputs from locked language models trained on older data, even within a year, may not reflect accepted practices in contemporary clinical scenarios. As such, there will be a need for an iterative and continuous process to train and fine-tune state-of-the-art language models on fresh data to produce outputs mirroring the latest insights and recommendations. In this context, continuously learning AI systems may seem ideal; however, these systems would also present their own set of challenges, particularly with regard to regulatory oversight, for example, Food and Drug Administration (FDA) approval (if interfacing with patients or leading to clinically meaningful interventions). More work is needed to understand the extent of biomedical knowledge represented in LLMs and how to elicit correct clinical responses.

Going forward, research studies on NLP will need to provide clarity on metrics or evaluation criteria used to quantify errors, elaborating on the benchmarks or standards determining clinical reliability to aid the broad clinical and data science community in contextualizing conclusions about the models' clinical utility. Studies must have a robust methodology that accounts for factors such as potential temporal disparities in information. To the extent possible while protecting patient privacy, it would be ideal for clinically applied NLP models to be available open source so that the clinical AI/computer science community can access model parameters and have the capacity to thoroughly evaluate and fine-tune models.

RADIOMICS AND IMAGING-BASED RISK PREDICTIONS

Traditionally, radiation oncology clinical workflows and oncology research have relied on human visual interpretation for clinical imaging studies, which is often subjective. However, advances in medical image analysis have introduced concepts such as radiomics, which uses mathematical formulas applied to image pixel (or voxel) intensity values to quantitatively analyze images, extract features, and uncover patterns not discernible to the human observer.[27] Radiomic features can then be coupled with statistical and ML models to predict a number of outputs, including disease outcome, survival, toxicity, or, in the case of radiogenomics, underlying tumor genomics. These modern techniques provide objective and precise

quantitative imaging descriptors, holding potential as noninvasive biomarkers and clinical decision-making tools across various cancer types.

Radiomic investigations in radiation oncology ideally follow a systematic approach to ensure the validity and utility of the developed models. First, researchers identify the clinical question and hypothesis, asking if the problem is suitable for radiomics and if radiomics is essential for the specific clinical problem. Key steps during this phase include defining the study end points, setting the benchmark for current standards, and understanding how the model's implementation will impact clinical decisions. This is followed by meticulous data collection and curation, including choosing the best imaging modality, labeling and annotating the data, and performing quality checks. Image preprocessing can include suppressing unwanted artifacts, enhancing essential features, and ensuring consistent imaging data across all samples. Knowledge of scanner models, pixel resolution, postacquisition algorithms, and other parameters is required for image preprocessing. Feature selection then allows researchers to decide which radiomic features to use (from a range of shape, first order, and texture features), considering their consistency and stability across various test scenarios. Dimensionality reduction methods such as PCA and least absolute shrinkage and selection operator are often employed for this step. When features are selected, the best ML technique is chosen, taking into account data set size, outcome variable type, feature number, and available computational resources. The model is then trained, validated, and benchmarked to evaluate its performance against the standard of care. Postvalidation assessment is vital, emphasizing feature importance, model generalizability across different patient groups, stability testing, and analysis of model failures. This rigorous roadmap ensures that radiomic models are accurate, reliable, and clinically valuable. These methods have been implemented to decode imaging phenotypes noninvasively using images.[27] A generalized summary of DL/ML model development is shown in Figure 32.5.

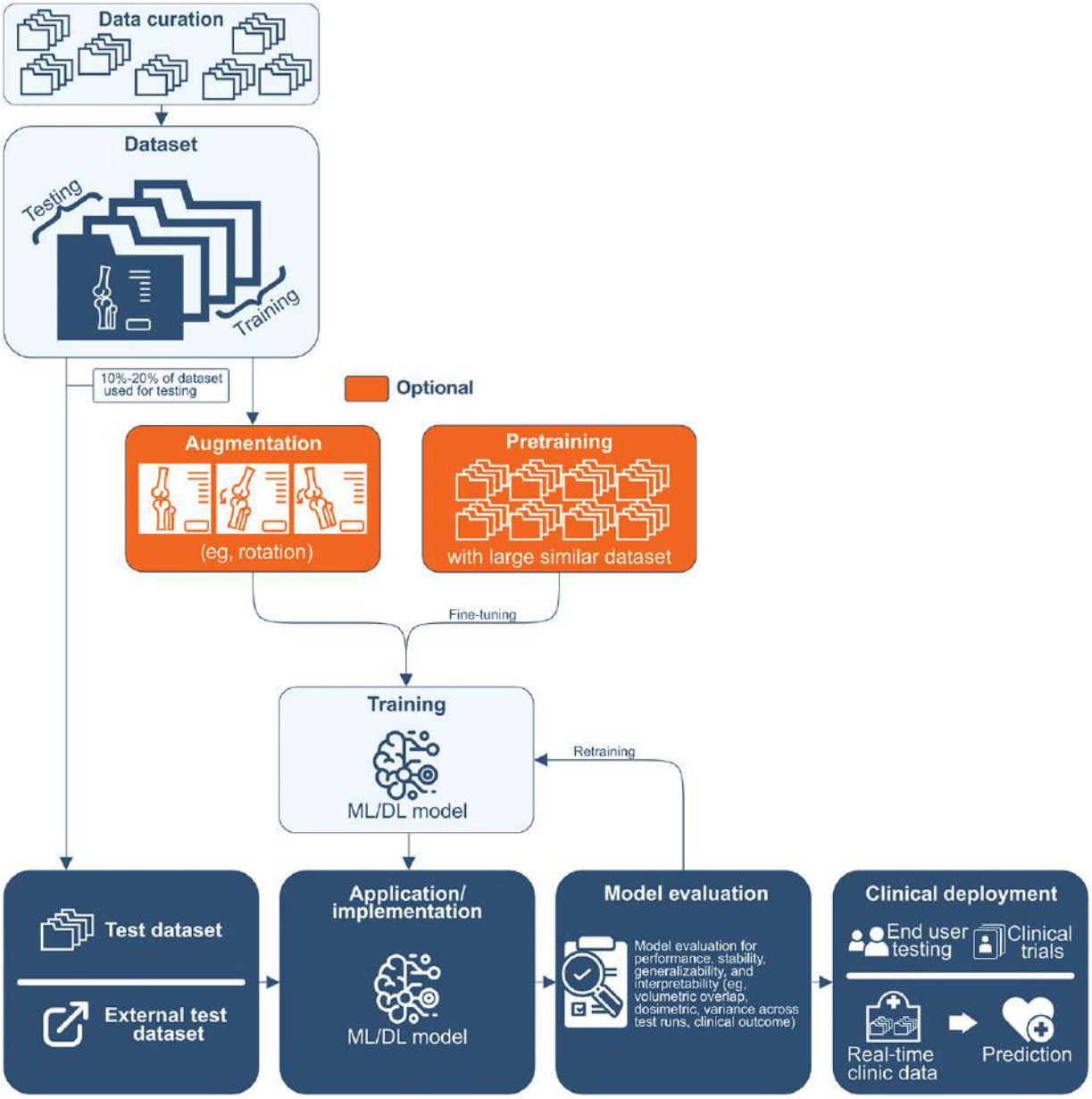


FIGURE 32.5 Comprehensive DL/ML model development and development for clinical applications: This figure presents a detailed schematic for the DL/ML model development pipeline, highlighting key phases from initial data handling to final clinical application. The process begins with a "train-test split," in which the data set is divided into training and validation subsets, ensuring the model can be tested against previously unseen data. An optional "data augmentation" step follows, where the training set may be artificially expanded to improve model robustness. The "pretraining phase" is illustrated as an initial step to initialize the model weights, which can be particularly beneficial for DL models. The core of the pipeline is the "model training" phase where the algorithm learns to identify patterns within the data. Following training, the model is evaluated using a "held-out" test data set as well as any external test samples to assess generalizability. This evaluation may initiate a feedback look of "retraining" and "fine-tuning" to refine the model based on performance metrics Once the model achieves satisfactory performance, it can then the

deployed for clinical use, for example, in trials. End user testing ensures usability and effectiveness in a clinical environment. DL, deep learning; ML, machine learning.

Dosiomics is a recent advancement within the radiomics field, focusing on the radiomic analysis of 3D dose distribution data from radiation treatment plans. Unlike traditional models, which rely on dose-volume histograms (DVHs) and normal tissue complication probability, dosiomics offers a more reliable and granular voxel-level method to predict radiation treatment-related toxicity and prognosis. This is achieved by integrating spatial and statistical data from the 3D dose distribution, capturing spatial relationships between doses at the voxel level.[28] Methods utilizing dosiomic features were first used to predict gastrointestinal (GI) and genitourinary (GU) toxicity following RT for prostate cancer with improved predictive capacity compared to conventional methods (eg, DVH and clinical parameters), particularly with regard to GI toxicity.[29] Subsequent studies demonstrated the utility of dosiomic analyses in predicting radiation pneumonitis in patients with non–small cell lung cancer (NSCLC) receiving stereotactic ablative radiotherapy (SART) and xerostomia in patients with head and neck cancer treated with radiation.[30,31] This predictive value was noted to be driven by texture-based radiomics features. Dosiomics has also been implemented to predict weight loss in patients with NSCLC treated with RT[32] and as a prognostic indicator in radiation oncology patients. Dosiomic features from CT enhance the capability to stratify risk for biochemical recurrence in prostate cancer treated with intensity-modulated radiation therapy (IMRT), outperforming traditional models.[33] Models combining dosiomic features with positron-emission tomography (PET) and CT characteristics outperformed conventional radiomics at predicting local recurrence in patients with head and neck cancer receiving radiation.[34] Dosiomic signatures emerged as a reliable predictor for local control in rare tumors such as skull-base chordomas treated with heavy ion therapy.[35] Moreover, a combination of dosiomic features and treatment plan parameters using ML methods was shown to improve prediction for the γ passing rate in a large sample of patients undergoing complex treatment using volumetric modulated arc therapy.[36]

While image analyses have historically relied on manual annotation and explicit extraction of hand-crafted features based on predefined

mathematical representations from imaging data, recent studies have shifted toward learned features obtained automatically from raw imaging data using DL models, such as CNNs.[37] For example, autoencoders—unsupervised CNN variants—can compress image content into a concise yet representative feature vector using a series of single-layer neural networks trained to detect image structures pertinent to classification problems. The extracted abstract features can be used for classification either within the neural network (fully connected, softmax) or processed using conventional ML classifiers like decision trees, SVM, or regression models. These techniques can overcome challenges associated with the often-demanding workflows, the need for manual or semiautomatic lesion annotations, insufficient feature standards, and multicenter validation. For example, conventional radiomic approaches (eg, using the PyRadiomics platform) would require volumetric segmentations for feature extraction, while DL-based methods may only need a single click seedpoint to localize to the structure of interest[37] or operate on unsegmentated data entirely. By obviating the need for manual segmentation in imaging analyses, DL approaches may be more practical, generalizable, and clinically useful than their traditional radiomic counterparts. DL/ML-based techniques are increasingly utilized for radiomic analyses and automated image segmentation tasks relevant to radiation oncology. Several studies have demonstrated the utility of DL-based approaches to automatically localize and contour primary and metastatic intracranial tumors for RT planning using advanced multisequence magnetic resonance imaging (MRI).[38,39] Moreover, DL-based dosiomics has also shown promise and can outperform the conventional approach.[40]

Beyond abstract feature analysis, AI methods also have the capacity to accelerate the analysis of images in various lines of investigation related to radiation oncology and help uncover new insights into disease prognosis based on clinical imaging data to inform treatment decision-making. Automated sarcopenia assessment using AI pipelines, for example, for patients with head and neck squamous cell carcinoma receiving primary RT, can inform treatment decisions and triage of patients receiving RT.[41] AI-derived body composition from CT data can also predict outcomes and toxicity in patients treated with immunotherapy, which is increasingly offered to patients receiving radiation treatment.[42] Computer vision methods

have also been used for automated patient data cleaning by standardizing RT organ labeling for patients with prostate or head and neck cancer.[43]

CURRENT CHALLENGES IN COMPUTER VISION MODEL DEVELOPMENT

Most DL models implemented for computer vision and clinical tasks are often trained in a supervised manner. While supervised learning has proven valuable in numerous applications, it comes with inherent limitations. One of the primary challenges is the extensive manual annotations required, which can be both time-consuming and costly. Linear algebra principles would dictate that as model complexity increases, more data are necessary to train it effectively and prevent overfitting. Annotation quality can vary significantly, with instances where the designated "ground truth" might even be inaccurate. Furthermore, training on specific data types can introduce bias, making the models more apt to a particular annotator's style, acquisition method, or domain, resulting in overfitting with diminished generalization capabilities. Certain data types, like thick slice images, are often challenging for manual annotation. Anatomic changes, such as the growth of a lesion, may be difficult to annotate accurately, even when using high-quality data sources. Moreover, supervised models often lack robustness, becoming overly sensitive to minor changes or perturbations in the input data, compromising their accuracy and dependability. Imbalanced data sets, where one class far outnumbers another, can be problematic for supervised models. Such imbalances can lead to predictions that are biased toward the majority class. Furthermore, conducting longitudinal assessments using these models poses its own set of challenges. An approach that offers a possible solution to these challenges is self-supervised learning. In self-supervised learning, a model is trained without explicit labels. Instead, it predicts parts of its input based on other parts of the same input. This method leverages unlabeled data, which are often more readily available than labeled data. Foundation models for medical image analysis and visual representation learning pretrain on large-scale medical imaging data sets in a task-agnostic manner to capture generic visual patterns. They are then fine-tuned on a specific task, allowing for more

robust and accurate predictions even with limited task-specific labeled data (Figure 32.5).

With the growth in clinical AI applications to medical imaging, there is a need for standardization in model development and evaluation. There is also a need for community collaboration to ensure solutions meet real-world demands, have flexibility and portability, and are scalable. Medical Open Network for AI (MONAI) is one such open-source framework tailored for DL applications in biomedical imaging. It aims to establish a collaborative platform for academic/clinical researchers and industry and is built on PyTorch (an open-source ML framework developed on the Python interface and utilized for computer vision tasks). The framework offers flexible preprocessing for multidimensional medical imaging data, compositional and portable application programming interfaces, domain-specific implementations for networks, and evaluation metrics. In addition, MONAI supports a customizable design suitable for various user expertise levels and provides multi-GPU multinode data parallelism capabilities. The MONAI Model Zoo is a repository where researchers and data scientists can access and contribute cutting-edge models. The use of the MONAI Bundle format simplifies the integration of these models into MONAI-based workflows. Another platform that seeks to enable data scientists and clinical AI researchers to develop and share generalizable and portable AI model implementations is Modelhub.ai. This is a National Cancer Institute/National Cancer Institute-supported repository of DL models sourced from contributions by the scientific community and highlights current trends in DL, focusing on reproducible AI.

PATIENT JOURNEY

Workup and Treatment Decision-Making

Intake and comprehensive patient evaluation are the initial steps in the RT workflow. Traditionally, the radiation oncologist evaluates the patient's symptoms and clinical history, performs a physical examination, and evaluates a wide range of clinical data and diagnostic tests, including pathology, radiology, genomic data, and potential risks associated with RT. After aggregating and synthesizing this broad range of data, a treatment plan is proposed by the clinician. However, the rapid accumulation of

medical data coupled with the growth in patient volume presents a mounting challenge for radiation oncologists. AI can be a powerful tool for automatically interpreting clinically relevant data to provide real-time clinical decision support at initial consultation. AI-driven methods for medical image analysis and NLP tools for processing large amounts of data from the EMR have shown promise in this domain. For instance, utilizing AI to identify the presence of extranodal extension on pretreatment imaging can guide decisions regarding adjuvant treatment escalation in patients with head and neck cancers.[44] Similarly, quantitative methods have been used to predict response in patients undergoing chemoradiotherapy for NSCLC with the potential to reshape therapeutic strategies.[45] Moreover, AI tools for noninvasive pathology prediction may help guide clinical decision-making in cases where tissue sampling may be clinically contraindicated.[37]

AI applications to digital pathology have emerged as well,[46] and AI algorithms have been developed to quantify relevant histopathologic features and automate risk prediction. A multimodal DL-based prognostic biomarker, ArteraAI Prostate Test, predicts long-term outcomes for localized prostate cancer using digital pathology and patient clinical data.[47] The model was developed and validated using a large sample of phase III randomized data (including the RTOG 9202, 9408, 9413, 9910, 0126, 0521 trials) and outperforms current national consensus guidelines risk groups at risk-stratifying localized patients with prostate cancer using multiple end points, such as distant metastasis, biochemical failure, prostate cancer–specific mortality, and overall survival (OS). It is currently implemented as a clinical decision aid, specifically guiding decisions regarding the use of androgen deprivation therapy in patients with localized prostate cancer.

In addition, AI models could enhance cancer prognostication and help predict radiation treatment response[48] and outcomes.[49] In addition to risk stratification based on tumor features, AI can also assist clinicians with quantitative assessment of baseline patient health to better inform treatment selection.[50] For example, DL-based, automated body composition measures can identify patients with sarcopenia who may be at higher risk for toxicity[41] or automated cardiac health assessments via DL-based quantification of coronary artery calcium can identify individuals who may be at higher risk for cardiac toxicity.[51] Furthermore, innovative analyses, including analysis of natural images of the face acquired before radiation

treatment in patients with advanced cancer, could provide invaluable insights into oncology patient baseline health and prognosis, to inform clinical decision-making with regard to palliative treatments.[52]

Shared decision-making in cancer care relies on the patient and physician reviewing the best available evidence with the patient supported to make informed preferences. AI can enable shared decision-making in radiation oncology practice by assisting in synthesizing vast amounts of medical literature, clinical studies, and patient data to provide up-to-date and relevant evidence to all stakeholders, offering personalized recommendations pertinent to the patient's unique risk profile and biology, and bias mitigation through the generation of objective and data-driven insights. Although their seamless integration into standard clinical practice has not yet been fully realized, AI models promise to advance different facets of clinical decision-making in radiation oncology.

Radiation Treatment Prescription

Before finalizing the treatment strategy, the radiation oncologist determines the radiation dose targeting the tumor and sets constraints for adjacent OARs, grounding their decisions in national standards and clinical trial outcomes. However, significant variations in tumor biology influence radiation sensitivity, even within the same cancer type or patient. The spatial location of the tumor in relation to OARs can also pose challenges, often rendering the desired treatment dose unattainable. Compounding the problem, these limitations are often realized late in the planning process. Al can be leveraged to address this challenge by both predicting a tumor's sensitivity to radiation and determining an achievable optimal dose based on tumor characteristics and OARs.[53,54] Both applications facilitate a shift toward personalized RT.

Radiotherapy Simulation

AI has the potential to transform the simulation process, which in the modern era, often includes complex immobilization and multimodality (eg, CT, MRI) image acquisition followed by image reconstruction, processing, and registration. The simulation process can be complex depending on patient- and body site–specific factors and anatomy, requiring significant

collaboration between radiation oncologists, radiation therapists, and medical physics. For example, collision between the patient or immobilization devices and treatment machines could occur if special consideration is not paid to patient-specific parameters such as any unique anatomy and how this might interact with the intended treatment beam angles. There is the potential for AI to anticipate these issues during the treatment simulation phase based on preexisting anatomic knowledge sourced from diagnostic imaging or other ancillary data.[54,55] This could expedite and optimize the planning process.

Optimal image quality for tumor targeting is also paramount, and AI algorithms based on deep reinforcement learning have been used in CT image reconstruction (as a parameter tuning policy network) and achieved image quality similar to or better than images reconstructed using manually tuned parameters.[56] Further examples of AI applications for image enhancement include the reduction of noise and metal artifacts.[57]

Postsimulation Image Processing

After acquisition of scans during simulation, postprocessing will include registration of simulation scans and diagnostic imaging if needed. Historically, CT scans are most commonly utilized, given the need for electron density information for dose calculations. Scans are typically acquired in the treatment position for CT simulation. Other modalities, such as MRI and PET scans, are also obtained for enhanced tumor delineation, and these ancillary imaging modalities are still most currently obtained in diagnostic imaging studies (eg, diagnostic MRIs for central nervous system [CNS] cases or PET scans for lung cancer delineation), which may have been obtained with the patient in different orientations. This introduces uncertainty when attempting to co-register these studies for target delineation.

AI can generate synthetic CT images from MRI from several sites, including the pelvis or the CNS, with modest deviation from ground truth CT electron density.[58,59] This suggests the potential utility of AI-derived synthetic CT in treatment plan generation. Another creative application has been to generate synthetic CT from non–attenuation-corrected PET with results that qualitatively and quantitatively resemble CT.[60] These methods

could effectively reduce uncertainty introduced by acquiring and registering multiple different scans, streamline clinical operations by reducing the number of imaging appointments for patients, and minimize patient radiation exposure from CT scans.

Another potential AI application is to improve image registration. Automatic image registration is crucial in radiation oncology; however, conventional methods can be slow and lack precision. Standard commercial algorithms for image registration have predominantly been designed to perform well only for modality-specific registration tasks. One considerable limitation of these algorithms is their sensitivity to image artifacts, which can compromise their accuracy and often necessitate manual corrections to achieve clinically acceptable registration. This demands additional labor and potentially introduces human error, making the registration process less efficient.

A salient feature of AI-based registration tools is their adaptability across different imaging modalities—a departure from the traditional modality-specific algorithms. Improved generalizability also allows for more reliable implementation across data types within different systems, which may make them more desirable for standardizing the registration process in the setting of multi-institutional trials. Moreover, AI tools have been shown to mitigate the impact of both motion and image artifacts on registration. For instance, AI tools have been shown to reduce distortion and registration inaccuracies that may be introduced in x-ray images of the spine that contain metal artifacts.[61] These methods have been implemented for image registration across various modalities, including MRI, x-ray, CT-MRI, and MRI-PET. While many of these algorithms were not developed initially with RT in mind, they address issues that are similarly encountered in this domain. Consequently, there is potential for these algorithms to enhance the workflow within RT.

Recent years have seen the integration of what was previously thought to be fundamentally incompatible technologies in combining MRI scanners with linear accelerators to achieve MR-guided Linac systems. Fundamental challenges were presented by the magnetic field's interference with radiation beams and the linear accelerator's potential to induce magnetic artifacts. Moreover, diagnostic quality MRI requires extended times for high-resolution low noise image and sequence acquisition, which would

take from the practicality of this modality in efficient treatment planning and delivery. As some of the measures implemented to circumvent these challenges, low-field strength magnets, typically ranging from 0.35 to 1.5 T have been utilized, with undersampling to improve on the image acquisition time. This results in a compromise in image quality relative to traditional high-field strength MRI systems. AI can be leveraged for the reconstruction of high-resolution MRI from undersampled data[62] and generate images, resembling results from data acquired with a higher strength magnetic field, which would be advantageous for enhancing tumor visualization throughout treatment.

Automation of Contouring

Manual contouring of target volumes and OARs has been a mainstay of the RT workflow in the modern era. This typically requires meticulous manual assessment of both diagnostic and planning imaging data and other clinical data (including pathology and surgical reports) by the radiation oncologist, which can be time-consuming and labor-intensive. Accurate delineation is crucial for optimizing therapeutic outcomes and minimizing toxicity, but there is significant interobserver variation in contouring both target and OARs volumes among clinicians, even when comparing experienced radiation oncologists. Such variations can result in disparities in treatment plan quality, potentially influencing oncologic outcomes, and efforts to standardize contours and provide training through consensus guidelines and contouring atlases can be effective. Previous iterations of semiautomated contouring tools utilized prior data from reference images, like segmentation atlases, were unreliable (often-demanding significant manual corrections) and remained out of reach for most radiation oncologists, given prohibitive costs.[63] In recent years, AI-driven auto-contouring tools have been developed that generate results that parallel human expert contours with efficiency gains in a range of settings.[64]

With the increased adoption of auto-contouring tools, clinicians only need to evaluate and approve automatically generated contours (particularly when it comes to OARs), but clinical integration should still be cautiously approached by both developers and radiation oncologists, as potential risks for harm with inaccurate contours can be significant. First, the performance

of a given auto-segmentation algorithm will be driven by the underlying training data, and thus, it is important for clinicians to understand these details, including whether the algorithm is based on real-world, clinical data with its underlying inherent variation or from contours specifically generated from atlases for a given use case. Since contouring standards may differ from clinician to clinician, institution to institution, and indication by indication, the end user should have an understanding of the intended use of a given algorithm before utilizing its output, but currently, there has not been widespread adoption of algorithmic transparency (eg, through presentation of AI "labels" that provide algorithmic training, failure modes, and intended use, similar to FDA medication labels).[65]

In addition, end users will need to understand and benchmark AI performance, and standard methods for evaluating the quality of auto-contouring tools include geometric overlap measures, such as the Dice similarity coefficient.[66] This method compares autogenerated segmentations to contours manually generated by experts. However, a notable drawback is that such metrics often do not align with crucial considerations, for example, when the agreement is with an inaccurate clinician-generated ground truth, which may not be clinically acceptable, or the impact of patient variation, the potential influence of ancillary data such as the clinical exam, pathology reports, endoscopic examination, or other imaging modalities (eg, PET or MRI). As such, DICE values do not necessarily signify a superior contour, and a variety of other overlap metrics might be valuable to assess depending on the clinical context,[66] but more importantly, functional auto-segmentation validation through verification of prediction of dosimetric values and clinically relevant end points against gold standard contours is critical.[67,68] It is also essential to recognize the significance of clinical data that are not captured by imaging (eg, physical examination findings), which may greatly inform radiation oncology contouring and planning decisions. Prospective studies directly evaluating the efficiency, precision, and consistency of these AI tools compared to the established gold standard methods in RT will be valuable.

As commercial AI solutions for auto-segmentation are increasingly integrated into clinical and treatment planning systems, there' is a heightened need for QA mechanisms to detect inaccuracies. Manual QA for auto-segmentations is notably resource-intensive and time-consuming. This

creates an opportunity for AI-based QA tools, potentially minimizing the time and resources required with current methods.[69] Future iterations of target delineation algorithms could leverage multimodal data embedding to integrate other clinical information, such as pathology, radiology reports, and surgical procedural notes, to accurately delineate the clinical target volumes (CTVs) or areas at risk for microscopic disease in the postoperative setting.

AI solutions being rolled out to the clinic for contouring tasks have shown great promise at contouring various OARs, but many radiation oncology–specific applications are restricted to contouring commonly constrained organs and conforming to existing contouring atlases. It is possible to implement even more advanced and granular OAR delineation systems with current solutions for total body segmentation (eg, looking at lobar-level segmentations in the lung or other substructures).[70] Total Segmentator is one such platform based on the nn-U-NET architecture. It can automatically segment more than 100 anatomic structures (including 27 organs, 59 bones, 10 muscles, and 8 vessels) on full-body CT images.[70] Wasserthal et al trained the model on 1,204 CT scans with 117 anatomic structures segmented from a range of use cases, including RT planning CTs. It is available as open source and provides an alternative to commercially available products.

Previously, time constraints made it such that only so many OARs could be contoured. This often meant the radiation oncologist had to exercise clinical judgment in deciding which OARs to focus on. However, that did not necessarily mean that some structures that were not contoured were not clinically relevant, with the potential to impact clinical outcomes. With AI, radiation oncologists may be able to contour many substructures that were not previously part of routine practice, optimizing the dose to these structures using modulated RT or protons to improve patient outcomes. Examples include cardiac substructures such as the left anterior descending artery, which may be clinically important.

Beyond OAR contouring, AI algorithms are beginning to show promise in auto-contouring of gross tumor volume[68] and malignant nodal segmentation and CTV.[71] Target volume segmentation poses a tougher challenge to AI than OARs in that a higher level of expertise and knowledge is required, contours often rely on data outside available

imaging (eg, biopsy findings), and there is inherent institutional and practitioner-level variability. Despite these challenges, with steady improvements in methodology and data, AI-enabled target contouring may help improve contour standardization, efficiency, and quality.[68]

Automation of Treatment Planning

Historically, medical dosimetrists meticulously design the plan and dose distribution, making modifications through a trial-and-error approach to align with the objectives of the radiation oncologist's treatment intent. The quality of such radiation plans hinges on various human-influenced factors, such as selecting radiation beam angles and setting optimization parameters. As such, there can be significant variation in treatment plan quality, within and between institutions. Conventional methods aimed at standardizing and improving the efficiency of treatment planning lean on automating repetitive tasks based on predefined, hard-coded rules, refining plan parameters based on set objectives using statistical techniques.[72] Automating treatment planning follows a two-step process. First, predicting the optimal dose distribution and then finding the best machine parameters necessary to realize that ideal dose distribution. Early approaches of applying ML techniques to treatment planning aimed to identify hand-crafted features for predicting dose metrics that were fed into the optimization engine, allowing a semiautomated planning approach. More recently, DL approaches are used to predict the entire clinical dose distribution in 3D. To allow evaluating the trade-off space for a given patient, Pareto optimal dose prediction algorithms have been proposed. These prior knowledge-based approaches are generally designed for specific anatomic sites and have a restricted capacity for adjusting to the nuances and range of complexity in modern plans or adapting to individualized patient-specific considerations. Several studies have shown the proficiency of DL models in predicting the optimal dose distributions tailored to individual patients, factoring in their unique anatomy. Moreover, these algorithms have shown promise in cutting the time required for dose calculations.[73] Once the optimal dose distribution is found, beam orientation and machine parameters need to be selected and optimized. Traditionally, beam orientation follows standardized clinical protocol, which may, on a

patient-to-patient basis, lead to suboptimal configurations. Converting a dose distribution to a deliverable treatment plan is an inverse optimization problem that has to fine-tune the radiation machine-specific parameters. Since the underlying problem is highly complex, one optimization cycle can take several minutes. To speed this up, AI-based methods are used to predict fluence maps and machine parameters, given an optimal dose distribution. DL-based approaches try to solve these problems with various techniques, reducing the required optimization times from minutes of calculation to a subseconds timescale. All discussed methods are still in an early stage and have not been clinically implemented.

For proton therapy, accurate dose calculation is essential. While pencil beam calculations are quick, they lack precision, especially in inhomogeneous regions, whereas Monte Carlo methods are accurate but slow. A DL model, based on the U-Net architecture, was developed to enhance pencil beam accuracy to Monte Carlo level, using patient CT images and pencil beam doses. This model improved dose accuracy and can be integrated into clinical proton therapy planning, adaptable to various tumor types and data sets via transfer learning.[74] Other AI models have been used for 3D dose prediction for IMRT,[75] beam orientation optimization,[76] intelligent inverse planning in high dose-rate cervical brachytherapy,[77] dose prediction in prostate cancer and lung cancer RT, improving DVH parameter predictions to within 1.6%,[78,79] and patient anatomy–specific dose distributions.[54]

For AI-driven treatment planning algorithms to produce high-quality plans, complex decision-making processes must be embedded in the underlying models. This approach mirrors the strategies employed in AI algorithms proficient at playing games like Atari or the board game Go.[77] The underlying reinforcement learning technique has the potential for solving sequential-type clinical problems. Thus, treatment planning with time-intensive and repetitive tasks, often based on a trial-and-error method, could potentially benefit from large-scale application of these methods. The gamification concepts for auto-treatment plan generation have been explored in retrospective studies generating radiation dose adaptation schemas in NSCLC and controlling treatment planning parameters for external RT as well as brachytherapy, outperforming human planners.[77]

Peer Review

Early, prospective (before treatment starts) peer review of contours and plans has been identified as a critical component of high-quality RT, but manual detection of errors remains a challenge.[80] AI-supported peer review might include deployment of auto-segmentation and auto-planning algorithms to deploy automatically in the background and detect outliers in the clinical workflow by comparing clinical contours/plans with AI-generated "digital twins,"[81] or conversely development of AI/ML algorithms that directly detect outliers based on historical data or learned features. Conversely, as AI automation technologies proliferate in radiation oncology clinics, novel QA frameworks to ensure human expertise is integrated to detect AI-based errors will be critical.

Preradiation Treatment Verification and Quality Assurance

Once the treatment plan receives approval from the radiation oncologist, the medical physicist conducts plan evaluation and QA verification. This ensures that every technical element for treatment delivery is operational and accurately configured to safely deliver the specified dose to the patient, which includes patient- and machine-specific QA. Patient-specific QA focuses on detecting issues that could impact the patient's treatment. This includes a thorough assessment of the accuracy and suitability of the plan and treatment parameters and verifying the consistency between the planned dose and prescription. Solutions for automation are tools that check treatment plans based on a heuristic approach, which uses hand-crafted rules to check a patients' chart. More recently, AI tools have demonstrated the capability to accelerate this process and identify rare errors.[82] In addition, it is a regulatory requirement to verify that a given treatment plan can be delivered and that the resulting dose distribution matches the planned dose distribution. This requires physical measurements of the delivered dose using a dosimeter-containing phantom. To reduce the amount of measurements and focus on plans that are more likely to fail a measurement, AI algorithms have been developed to predict QA passing rates by analyzing the treatment plan itself, obviating the need for physical dose measurements.[83] The integration of these AI tools has the potential to enhance the efficiency of the QA process, thereby enabling medical

physicists to invest more time in other important tasks, but currently, those methods are still in a developmental phase and only tested by few institutions.

Machine QA assessment involves a broad range of verifications and evaluations of treatment machine function, precision, and accuracy. The wealth of data generated during these assessments has provided avenues to develop AI systems capable of predicting trends, such as in cone-beam computed tomography (CBCT) image quality degradation, identifying errors like treatment beam asymmetry and positional errors in the multileaf collimators.[84,85] Since patient- and machine-specific QA have always been well documented and data have been collected over years, there will be ample opportunity to harness AI's power to analyze these data as they are increasingly collected to improve RT delivery.

Treatment Setup and Delivery

Scheduling

Radiation oncology patients typically present for multiple appointments over the course of their radiation treatment. Prolonged waiting times can impact the clinic's operational efficiency, contribute to patient anxiety, and negatively affect patient satisfaction. AI can help identify key factors influencing patient waiting times within a department's daily operations, such as the time of day, number of fractions, historical average treatment duration, and number of treatment fields. Using AI to predict waiting times can optimize clinic workflows and efficiency.[86] Appointment scheduling can be refined and optimized using AI to organize the patient sequence based on anatomic treatment site and the specific immobilization and treatment techniques employed. This approach can reduce room turnover times between patients and increase capacity to efficiently accommodate more patients.

AI systems can also be readily combined with sensors to track patients in real time over the course of their visit, allowing the radiation oncology care team to keep track of how the patient is progressing through their visit. These AI-enabled real-time locating systems allow the care team to localize the patient and keep track of treatment and appointment durations, therefore

minimizing wait times and the risk for errors and ultimately optimizing the scheduling of treatments and patient experience.

Image Guidance and Motion Management

Precisely setting up a patient in the same position as at the time of simulation is critical for the safe and effective delivery of RT. Current methods for on-treatment patient positioning include utilizing CBCT mounted on the treatment machine. However, CBCT image quality is usually lower than the higher resolution planning CT images. AI has been implemented to enhance CBCT image quality, enabling more precise patient positioning for treatment.[87] AI algorithms are also adept at automatically detecting imaging artifacts, such as scatter artifacts,[88] and can be implemented to improve CBCT image quality to support target verification and online adaptive RT.[89] Other imaging modalities, including ultrasound, onboard MRI, and optical surface imaging, are increasingly utilized in image-guided RT. These present a unique opportunity for AI-driven methods to enhance or synthesize complex data in real time during treatment appointments.

Patient or organ motion may necessitate motion management techniques to mitigate, capture, and monitor motion stemming from physiologic processes, such as breathing or digestion. However, there is significant variation in the degree of motion (magnitude or frequency) between individuals, and even for any given individual, the movement of organs relative to each other may vary between fractions. This variability poses challenges when attempting to construct predictive models for tumor motion. AI can help address these variations by creating patient-specific dynamic motion management models that can adapt to shifts in motion patterns to enhance tracking of the target volume during treatment. Research in this domain has focused on predicting respiratory motion, utilizing data obtained from external surrogate positional markers as predictive model inputs.[90] These algorithms can automatically adapt to complex respiratory patterns in real time, ensuring precise tumor motion tracking and predicting the tumor's position up to 0.8 seconds in advance.[90]

Adaptive Radiotherapy

Significant changes in patient anatomy reflecting tumor growth or shrinkage, or due to internal organ motion (eg, from physiologic movement of gas or liquid in the GI or GU tracts), can occur in the days to weeks between simulation/planning and actual treatment delivery. These changes can result in significant alterations in the dose received by the treatment target and normal tissues, and potentially necessitating adaptive replanning, but the clinical criteria for adapting a new plan are currently not standardized and often require the radiation oncologist to make subjective judgments regarding the clinical significance of the anatomic changes. AI can help predict which patients require treatment replanning and the optimal timing for adaptation. AI models have been used to identify the need for replanning in lung cancer to reduce the risk for radiation pneumonitis.[91,92] Similar methods have been used to predict geometric changes in patients with head and neck cancers throughout treatment and identified the fourth week as the ideal time for the adaptation of treatment.[93]

Post-Treatment Evaluation and Continuation of Care

The Response Evaluation Criteria in Solid Tumors (RECIST) is the most commonly used system for evaluating solid tumor response to treatment-based on tumor size changes. However, with the introduction and increased adoption of immunotherapy and targeted agents in clinical practice, the RECIST method for response assessment has become inadequate (eg, due to phenomena such as pseudoprogression),[94] and even revised criteria do not accurately capture nuances, especially in immunotherapy patients. AI algorithms show promise in automating such assessments and can provide more comprehensive insights into tumor response over the course of RT. This includes capturing changes in tumor phenotype using advanced visual representations and learning of imaging characteristics, potentially enabling superior assessments of treatment response and more accurate outcome prediction than tumor size alone. For example, AI has been evaluated for early assessment of lung cancer response to different therapies, predicting cancer-specific outcomes, such as disease progression, locoregional or distant recurrence, and OS.[48,53] In particular, Xu et al demonstrated that tumor tracking using AI for serial image analysis looking at follow-up CT scans at 1, 3, and 6 months after RT for lung cancer predicted oncologic

outcomes and tumor pathologic response in those receiving trimodality therapy. This model worked without the need for manual contours and was robust to radiation-related changes. Furthermore, AI-generated volumetric RECIST measurement was shown to be better at risk-stratifying patients with lung cancer than manually generated annotations.[95] Similarly, AI has been used to estimate RECIST in patients receiving immunotherapy (which is increasingly given with RT either sequentially or concurrently as is currently evaluated on clinical trials for future treatment paradigms).[96] Radiation-related tissue damage undermines the precision of manual RECIST measurements and complicates disease recurrence identification. AI algorithms can identify early and easy-to-overlook alterations in the lung that may be associated with local recurrence (often mistaken for radiation-induced fibrosis).[97] This information can facilitate early intervention to improve patient outcomes.

Toxicity Prediction and Management

The management of acute and late radiation-related toxicities is complicated by their difficult-to-predict nature and variable severity. Although preemptive/proactive management of these adverse effects would be ideal, the unpredictability of both stochastic and deterministic effects makes this a complex issue to navigate. Predictive models for radiation-induced toxicities can nonetheless be developed based on risk factors, such as germline genomic variations (eg, radiation sensitivity related to ataxia telangiectasia mutated [*ATM*] gene mutations), comorbidities, other treatments (eg, radiation recall pneumonitis in patients receiving immunotherapy), radiation dose distribution, and imaging characteristics. These models can be implemented to guide treatment planning. Existing methodologies have predominantly focused on subsets of these modalities of information and, in some instances, relied on the extrapolation of radiobiologic models from observational and preclinical studies.[98]

AI can enhance the processing of these multimodal data to develop robust predictive models that seamlessly incorporate factors such as clinical characteristics, radiation dose, and imaging data acquired before treatment to aid in clinical decision support for the prevention of radiation-related toxicities and preemptive management. Examples include AI-driven

probability models designed to predict the severity of acute dysphagia, xerostomia, and oral mucositis in patients with malignancies of the head and neck.[31,99,100] Prediction models for radiation-induced pneumonitis, esophagitis, rectal toxicities, and even seizure risk have been successfully developed using AI.[101] A study focusing on late-stage cervical cancer RT used an AI model to analyze rectum dose distribution and predict toxicity. The results showed the feasibility of the prediction model, with saliency maps highlighting regions indicating potential locations for rectal toxicity.[102]

In addition, there have been promising real-time monitoring approaches, such as prospective testing of an ML algorithm trained on clinical data to predict acute toxicities that could result in emergency department visits or hospital admissions for patients receiving RT or chemoradiotherapy with high sensitivity and specificity.[103] These applications underscore the potential of AI to integrate multiple clinical data streams to develop real-time, actionable clinical decision support for advanced prediction of adverse events during radiation treatment.

REGULATORY/ETHICS

The FDA and international regulatory bodies (eg, The International Medical Device Regulators Forum) categorize AI and ML technologies as "Software as a medical device" (SaMD).[104] SaMD refers to software designed for a medical function, such as treating, diagnosing, or preventing disease, without being integrated into or forming a component of a hardware-based medical device.[105] Most AI technologies applied to radiation oncology are subject to these regulatory guidelines. For example, software for treatment planning decision support has been distinctly labeled as SaMD.[104] Despite a surge in AI-related medical publications, the implementation of AI tools in radiation oncology (and medicine more broadly) has been relatively limited aside from auto-segmentation algorithms. However, there has been a significant uptick in approvals from a few dozen FDA-approved AI algorithms in 2019 to a total of 500 by the end of 2022, of which over 75% were medical imaging applications. Nevertheless, the adoption of AI remains measured, as many AI models do not progress beyond the proof-of-concept stage due to various limitations, such as deficiencies in clinical

utility, reproducibility or transparency, generalizability, explainability, or trust.

The regulatory sphere has focused on reevaluation schedules for new devices and the requirements for locked versus continuously learning AI systems. More clear standards are needed to govern the clinical evaluation of these tools. Clinical AI implementation has potentially significant implications for patient outcomes, which can only be evaluated in comprehensive prospective studies or retrospective data collected in representative cohorts. While randomized clinical trials are the benchmark for evaluating anticancer therapies, they may not always be feasible or necessary for every AI device. However, prospective evaluation should still be considered for any system that has the potential to impact patient outcomes, cost of care, and efficiency of the cancer care delivery workflow. In the context of AI, protocols that assess various technologies within a single category across multiple cancer types could help make prospective evaluation more practical and efficient.[106] For low-risk tools that operate under continuous monitoring by health care professionals, phase I/II studies may suffice. Conversely, high-risk devices, especially those used without routine expert human or clinician supervision, demand rigorous phase III studies.

Postmarketing monitoring is needed to gauge the value of AI-based RT tools. Such scrutiny is essential, given that these tools' functionality could be influenced by their interaction with other software and hardware systems and broader user adoption (ie, human-AI interactions). High-quality, risk-assessed clinical validation is the cornerstone to determining the value of and instilling confidence in AI technologies. Given their potentially profound impact on cancer care, this trust becomes especially important for these "black box" systems. It is imperative to establish safety measures due to the potential risks associated with AI applications. While image registration and auto-segmentation AI platforms allow human expert review, possible errors from AI tools in radiation treatment QA require robust safeguards. Proposed solutions include AI models that predict errors in QA algorithms. Current practice holds clinicians accountable for errors, and regulatory entities are formulating guidelines addressing AI's legal implications.

It is also worth noting that AI systems are increasingly used in clinical trials, many of which do not require informed consent due to their classification as minimal risk, potentially leaving patients unaware of their participation.[107] Given the unique challenges in AI system risk assessment, including the unknown impact of human-AI interactions and data limitations, patients need to be informed when AI influences their clinical decisions. To uphold ethical standards, AI clinical trials should disclose to patients when their data are used, ensuring patients retain the right to determine their health care decisions.[107]

AI model development often requires extensive, multi- institutional data sets that may contain sensitive personal information. Providing data security and preventing leakage is critical, but achieving complete anonymization can be challenging, particularly with genetic, textual, or radiologic data that might inadvertently identify individuals. Federated learning has been introduced as a potential solution, allowing for decentralized data usage where only model weights, not actual data, are shared between institutions. However, even with this approach, there is a risk that models might inadvertently reveal personal health information through back-engineering of parameter weights, posing privacy concerns.

ARTIFICIAL INTELLIGENCE IN RADIATION ONCOLOGY RESEARCH

Research is a cornerstone of radiation oncology. It drives the understanding of patient-specific risk factors, refines our ability to predict outcomes following RT, and provides evidence-based guidance on escalating or de-escalating treatment. Therein, clinical trials offer controlled environments to test the efficacy and safety of interventions, typically following strict protocols and patient selection criteria. While the highest level of evidence within oncology continues to be randomized phase III studies, robust analyses of real-world data may offer valuable insights in instances where the barriers to conducting a clinical trial are intractable (eg, problems with accrual in studies of rare malignancies such as sarcoma or comparing SART to surgery in early-stage lung cancer) or when navigating new “data-free zones” in clinical practice as new evidence emerges (eg, management of some locally advanced NSCLC cases in the immunotherapy era). Real-

world data capture the diverse experiences of patients in routine clinical settings, reflecting a broader range of outcomes and variables not typically seen in the controlled clinical trial setting, while enabling detection of very rare events that may never occur in a smaller trial cohort. Advanced modeling of these data using robust statistical learning methods and AI algorithms can help shift the balance toward more use and trust of insights from real-world data analyses.

Several key distinctions arise in comparing AI methods to conventional statistical methods for research applications. Traditional statistics often require the specification of a hypothesis a priori and use parametric and nonparametric comparisons between groups with methods such as linear regression and survival models with linear projectors. They offer stability by adhering to predetermined statistical plans. Their strength lies in handling data with fewer predictors, statistical inference, and hypothesis testing. Reproducibility in conventional statistics is ideally external, with clear interpretability due to explicit features and parameters. Their less flexible and more explicit nature allows for more straightforward equity checks when data are available. On the other hand, AI approaches tend to be agnostic to a priori hypothesis and can be more general. They utilize techniques like random forests, XGBoost, and neural networks and are more prone to instability based on domain and user choices. Their primary applications include image analysis and large data set processing, focusing on pattern discovery and prediction. Reproducibility in AI is often internal (due to robustness limitations in the supervised training methods that are widely implemented to date, and additional barriers include the rise of proprietary algorithms and a lack of transparency). AI methods can also be a “black box,” leading to challenges in interpretability. They might magnify biases in data sets, potentially exacerbating inequities. Overall, AI’s strength is in pattern discovery, dimensionality reduction, and automatic feature selection, compared to the statistical inference and quantification of uncertainty in conventional methods.

In radiation oncology research, statistical models based on expert radiation oncologist judgment, manual data curation, and selection of features and measurements that predict outcomes with RT are a mainstay. They have offered a reliable method to test hypotheses and assess the impact of radiation treatments, resulting in reproducible study conclusions.

However, it is difficult to scale these analyses to large data sets combining multiple data streams. Statistical learning and AI models can automatically search and extract abstract features that predict outcomes or perform other tasks at scale. They can handle vast multimodal data sets and derive useful —potentially orthogonal—information from the high-dimensional data sets. A trade-off is that these systems can be opaque, and reproducibility challenges may persist despite model optimization.[108]

FUTURE DIRECTIONS

AI is a rapidly evolving field. Innovations continue to emerge with the promise to revolutionize cancer care, particularly in the technology-driven discipline of radiation oncology. Several advances and challenges will warrant close attention in the near future.

Multimodal Models

Effectively consolidating various patient data streams, including imaging and genetic markers, will help generate new insights and a more comprehensive view of patient health. This is particularly invaluable in oncology, where individual patient treatment pathways will demand increasingly nuanced personalized approaches.

Foundation and Generalist Medical Artificial Intelligence Models

Foundation models serve as broad-based systems trained on massive data sets, often in a task-agnostic manner, to develop strong baseline performance within an application domain. These adaptable frameworks can be subsequently tailored for specific tasks with few data points needed for fine-tuning to achieve optimal performance at the particular task. Generalist models extend these foundations across diverse medical tasks, for example, analyzing the EMR and providing treatment recommendations.[109] Both promise flexibility, adaptability, and potentially better generalizability.

Generative Artificial Intelligence

Generative AI is characterized by its capacity to produce new content—be it text or image generation or medical report formulation—in response to specific prompts. This is achieved by systematically training AI models on existing data sets, enabling them to identify and replicate patterns in order to subsequently generate new and pertinent content. Popular generative models included large language models such as ChatGPT. Within oncology, there is potential for generative AI to create medical images, which can be invaluable for data augmentation during the training phase of AI model development. The models may also help generate medical reports, clinical annotations, and comprehensive patient summaries, although clinical integration should be approached with caution pending further research.[5,9]

CHALLENGES

Data Availability and Quality

High-quality data sets for training and validation are critical in this domain. The unmet need for standardized definitions and consistency across various data types in radiation oncology impedes seamless data sharing and AI model development.

Proprietary Software Limitations

Treatment planning software often remains proprietary, limiting knowledge and integration capabilities. However, vendors are beginning to offer interfaces for research endeavors.

Clinical Relevance

Early AI analyses have tended to focus on readily measurable patient outcomes such as OS, or on performance metrics compared to a gold standard. There will need to be a shift toward other outcomes that are directly relevant to RT, including radiation-induced toxicity, which can be more challenging to measure and study but provide more direct evidence on the benefit of the specific AI system. Demonstrating benefit on patient-centered outcomes will be essential for uptake by patients, providers, and payers.

Clinical Implementation

Many AI tools remain experimental and lack external validation. Achieving trust is crucial, given the "black box" nature of most algorithms. The legal landscape regarding clinical liability and responsibilities may change with increased AI utilization and buy-in from all stakeholders.

Transparency and Ethics

Despite improvements in AI interpretability, the lack of transparency makes it difficult for developers, end users, and regulators alike to comprehend the mode outputs and predictions. This also makes it challenging to uncover any potential systematic biases that are trained into the models from imbalanced data sets, which may impact underrepresented groups in those training sets, resulting in the propagation of cancer disparities. Ethical concerns, from racial biases to potential misuse for financial gains, are also an important consideration.

CONCLUSION

In the era of AI, radiation oncologists need to be well versed with these tools and the AI landscape. While AI promises to be a powerful ally in patient care, it also requires rigorous oversight, understanding, ethical deployment, and constant collaboration among various stakeholders to truly benefit patients and radiation oncology practitioners.

Integrating AI into radiation oncology will inevitably transform the roles and responsibilities of the workforce. The radiation oncologist will see their role move away from manual tasks such as contouring and pivoting toward ensuring the quality of AI-generated parameters and spending more time on direct patient interactions. This shift will place a premium on human-centric activities, such as patient counseling, education, clinical management, and providing emotional support. AI will also lead to more standardization in tumor contouring and treatment planning, minimizing disparities, particularly in health care settings with limited resources. Moreover, clinical radiation oncology training will likely shift away from the rote learning of clinical trial data and extended apprenticeship to master manual contouring and treatment planning. Instead, training programs of the future will be

tailored to equip radiation oncology residents with skills that will help them to navigate, assimilate, and derive insights from expansive data sets, fortifying their clinical decision-making capabilities in an AI-enabled clinical landscape.

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SECTION III

Policy, Economics, Education, Ethics, and Technology Assessment

CHAPTER 33

Technology Assessment, Outcome Analysis Research, Comparative Effectiveness, and Evidence-Based Radiation Oncology

James B. Yu and Ronald C. Chen

Radiation oncology (RO) is a technologically intensive discipline. Innovations in computing, radiation technology, genetics, cancer biology, diagnostic imaging, and artificial intelligence (AI) all have the potential to impact the field. Because RO teams treat multiple cancer types and medical conditions, the practical application of these new technologies and innovations across multiple clinical situations can occur almost immediately. As a result, given the rapid and continuous pace of technological innovation, it is important for all radiation oncologists and their teams to understand how new technologies disseminate, are evaluated, and are compared to older technologies. As well, it is critical for radiation oncologists and researchers to apply radiation in an evidence-based manner.

This chapter provides a review of technology assessment, assessment of health outcomes from radiotherapy, comparative effectiveness research (CER), and how evidence is generated for radiotherapy.

ASSESSMENT OF TECHNOLOGY

In 2015, the Institute of Medicine National Cancer Policy Forum Board on Health Care Services convened a workshop to discuss the appropriate use of advanced technologies for radiation therapy and surgery.[1] The goal of the workshop was to discuss how to ensure appropriate use and evaluation of technologies such as proton beam radiation, as well as how these new technologies disseminate. The workshop highlighted the importance of evidence generation as new technologies are adopted and identified several potential areas of research and improvement. The workshop centered

around the themes of regulatory oversight, training and monitoring of performance, generation of evidence assessing medical technology, optimal payment strategies, and recommendations for utilization and clinical guidance. A key recommendation included the encouragement of "coverage with evidence development," which means that evidence is generated during the adoption of the technology by linking practice and provider reimbursement for the new technology in question with participation in prospective clinical data and evidence generation.

Though much of the 2015 workshop focused on proton beam radiation, many other new radiation technologies have been introduced or continued to disseminate over the past decade. The list of new or disseminating technology includes intensity-modulated proton beam therapy (distinct from "three-dimensional conformal" proton beam therapy), magnetic resonance imaging–guided linear accelerators, new radiopharmaceutical therapy, positron emission tomography (PET)-guided linear accelerators, the so-called adaptive radiotherapy, as well as incremental innovations in imaging technology, patient body surface tracking, patient positioning and immobilization, innovations in brachytherapy delivery (both high- and low-dose rate), intraoperative radiotherapy, and new systems to improve the frameless delivery of intracranial stereotactic radiosurgery. This list is growing constantly.

Traditionally, as discussed in the section on evidence generation, innovations in medical care are best evaluated in well-designed prospective randomized trials. However, these studies can be prohibitively expensive, and cancers with long natural histories often require a prolonged response assessment (such as prostate cancer). By the time randomized trials have completed and are ready for analysis, newer technologies have been invented and are already in the market. Furthermore, it is often impossible to test a technology in all areas of potential application (all cancers where the technology will be used) simultaneously. Therefore, how to ensure that technology is applied based on evidence but without depriving patients of new innovations is at times an intractable problem.

Governmental Assessment

One potential path for evaluating new technology is through the U.S. Food and Drug Administration (FDA). The FDA is responsible for regulating medical devices used in the United States, including radiation devices that do not use nuclear decay, such as linear accelerators. New radiation technologies are typically evaluated using the 510(k) pathway.[2] This pathway assumes that the new radiation therapy technology is still fundamentally similar to other applications of radiotherapy in its use of therapeutic doses of radiation. The 510(k) pathway, therefore, evaluates safety and similarity, rather than treatment efficacy. A device is considered substantially equivalent as the preceding device if it has the same intended use and the same technological characteristics. If the new device has different technological characteristics, it must not raise different questions of safety and effectiveness. Another pathway is to receive "de novo" approval for a device that is not substantially equivalent to prior devices. A recent example of this type of approval is the RefleXion Medical PET-guided platform.[3]

Once a technology is FDA approved, how rapidly the technology disseminates often depends greatly on the reimbursement that a physician or health system receives for its use. At the governmental level, reimbursement for RO services is set by the Center for Medicare & Medicaid Services (CMS) based on recommendations of a committee of medical professionals and others nominated by professional societies known as the Relative Value Scale Update Committee (RUC).[4] The American Society for Radiology Oncology (ASTRO) participates in the RUC committee, though there is no radiation oncologist on the committee. New Current Procedural Terminology (CPT) codes for new radiation treatment are set by the CPT Editorial Panel of the American Medical Association.

Medicare coverage decisions regarding medical services are made at the national and regional levels. The national determination of treatment coverage is done in consultation with the Medicare Evidence Development & Coverage Advisory Committee.[5] In the absence of a national determination, regional coverage decisions (known as a *local coverage determination*, or LCD) are made by the Medicare administrative contractor (MAC) administering the claims within a region. There are 12 MAC jurisdictions nationwide.[6] These LCDs also often rely on RO society

practice guidelines as well as review and consultation with experts, with a period of public comment and an open meeting. Requests for an LCD or revision of an existing LCD can be made as further evidence accumulates.[7]

Other government institutions perform their own assessment of new technologies. For example, the U.S. Veterans Administration (VA) launched a system of health technology assessment in 2022 called the Value-Driven Framework.[8] The framework evaluates a technology based on measures of value, access, effectiveness, and equity. As well, the VA evidence-based synthesis program has performed past evaluations of radiation technology, including proton therapy.[9] Overseas, the National Health Service of England's Health Technology Assessment (HTA) Programme performs a similar function on a broad array of radiotherapy technologies. Evaluation by the HTA typically involves a systematic review and cost- effectiveness evaluation via a cost-utility decision-analytic model.

Insurance Company Assessment

Outside government approval of new technology, health insurance companies provide their own assessment of new technology. Differences in insurance coverage for stereotactic body radiotherapy (SBRT) and proton beam radiation can be illustrative of how insurance companies evaluate technology.[10,11] Insurance companies and benefits managers can vary widely in what they consider to be "medically necessary."[12] Given the complexity of radiation treatment and application, as well as the perceived high cost of radiation, radiation oncologists face the highest burden in terms of prior authorization administration compared to other specialties.[13] Prior authorization requirements were estimated to be over $40 million nationwide, using data from 2017 to 2018.

How an insurance company decides on coverage may depend on a combination of clinical evidence and cost- effectiveness. However, insurance denials occurred for 17% of in-network claims in nationwide data released by CMS for 2021[14] and varied by insurer from less than 10% to nearly half, suggesting that other factors beyond clinical evidence were being brought to bear.

Outcomes Assessment

Before discussing how evidence is generated (in later sections of this chapter) via CER, it is useful to discuss how and what types of outcomes and end points are assessed.

Standard outcomes for clinical trials include overall survival (how long a patient lives) and cause-specific survival (how long a patient lives before dying of a specific cause, usually the cancer that was treated by radiotherapy). Other types of "survival" can include how long a patient lives before the disease progresses after treatment, how long before metastasis, or how long before experiencing toxicity from treatment. How an investigator chooses the type of survival to investigate is a deliberate choice that can impact the success of an investigation. For example, comparing the overall survival between two technologies may not be as informative as measuring disease-specific survival if patients are more likely to die from comorbid illnesses.

Survival is usually compared using estimation methods such as the Kaplan-Meier method that aggregates group data into data that provide a proportion of patients surviving over time.[15] These results can be graphically represented as "survival curves." In this method, patients who are lost to follow up are censored as noninformative at the time of last contact. Survival curves can be compared using statistical tests, such as log-rank testing. Alternately, if assumptions regarding proportional hazards and noninformative censoring are met, there are statistical techniques to compare the "hazard" of nonsurvival between groups using techniques such as Cox proportional hazards regression.[16] If there are risks that compete with the outcome in question (such as the competing risk of noncancer death in older patients undergoing treatment for prostate cancer), a competing risks regression can be performed, showing the risk of an outcome taking into account a competing risk that may preclude the outcome in question.[17]

Regardless of the statistical technique used, finding an improvement in overall or cancer-specific survival is the highest hurdle for most new radiation technologies. Often, improvements in survival due to radiotherapy (compared to no radiotherapy) have to be tested or validated in randomized studies that are not radiation platform or vendor specific, especially if the studies are funded by the National Cancer Institute (NCI's) National Clinical Trials Network cooperative groups. These studies often require

large patient cohorts. As a result, most initial claims of improvement on behalf of new technology innovators (compared to older radiation technology or techniques) are for improved safety or quality of life.

Measures of Cancer Response Outcomes

Given the rapid pace of desired technology change and adoption, and the long-term follow-up required to detect improvements in overall survival and cancer-specific survival, there is considerable interest in finding surrogate clinical end points that can be assessed sooner. Radiographic development of metastatic disease is often used as a measurement of treatment success or failure, given the importance of metastatic disease for cancer mortality. Radiographic assessment has also been used to define patients who require further treatment with radiation (eg, patients with early-stage Hodgkin lymphoma with persistent PET after two cycles of chemotherapy).[18] Further, assessment of treatment response with imaging is also performed. Commonly used in response assessment is the Response Evaluation Criteria in Solid Tumors criteria.[19] Radiomics, the science of using all available radiographic signals and features including those not readily identifiable to the human eye, has been used for head and neck and lung cancers to assess outcomes and remains an active area of investigation.[20]

Other potential surrogates include the use of tumor markers such as CA19-9, CEA, and prostrate-specific antigen (PSA).[21,22] Many other tumor markers exist.[23] Circulating tumor cells, circulating tumor DNA, and other sophisticated markers of tumor burden are also being considered.[24,25] These promising tests may provide early signals on treatment response and tumor progression.

With all these potential measures of cancer response, rigorous comparison to actual outcomes is needed. For example, for potentially indolent cancers such as prostate cancer, an intermediate clinical end point would allow for clinical trials to report findings earlier, but it is important to consider whether these earlier end points are clinically meaningful. Though PSA end points have been validated in patients with prostate cancer treated with radiotherapy,[26] one meta-analysis was only able to validate metastasis-free survival as being a consistent surrogate for overall survival.[27]

Nonetheless, PSA remains an important end point, given its association with salvage treatment and clinical decision-making.[28]

Measuring Quality of Life and Treatment-Related Toxicity

Toxicity assessment commonly takes two forms: physician- or provider-assessed toxicity, and patient-reported symptoms or quality of life.

Physician- or provider-assessed toxicity commonly uses a standardized scale, such as the Common Terminology Criteria for Adverse Events (CTCAE), at discrete time points. For example, clinical trial protocols may recommend the assessment of skin toxicity from breast radiotherapy at specific time points after radiation. Some studies use insurance claims data (eg, Medicare data), looking for billing codes that represent diagnoses of certain toxicities (eg, hematuria) or procedures that are consistent with treatment-related complications. For example, the incidence of laser coagulation procedures for rectal bleeding after radiation therapy for prostate cancer can be used as a surrogate for treatment-related toxicity.

Alternately, patient-reported outcomes can be collected before, during, and after radiation treatment. Patient-reported outcomes can range from specific questions about episodic toxicity such as the PRO-CTCAE (patient-reported outcomes version of the CTCAE),[29] to survey instruments that assess a diverse range of patient experiences from global physical and mental health, to organ-specific symptoms, to financial toxicity.[30]

Survey instrument creation requires methodological rigor to ensure appropriateness, reliability, validity, discrimination, and interpretability, while minimizing question burden.[31,32] Appropriateness means how well the domain of interest is related to the conceptual framework that will be used to build a survey instrument. This connection between domain of interest and framework should be assessed through qualitative patient interviews and focus groups. Reliability of a survey instrument refers to the internal consistency (the degree to which questions within the survey are inter-related and nonconflicting) and test-retest reliability (the ability of an instrument to produce consistent scores from the same population). Validity is the extent to which the survey instrument actually measures the concept it purports to measure. The discriminatory ability of the survey instrument measures the ability to detect differences between individuals and health

states. The interpretability of an instrument is its ability to be translated into relevant clinical outcomes or states. Typically, one estimates a minimal clinically important difference to interpret the minimal difference in a survey domain that leads to differences in clinical experience. Finally, question burden is minimized by reducing redundant questions with answers that are shown to be highly correlated in a survey sample, via an iterative process.

Cost-Effectiveness as a Cancer Outcome

The cost of new radiation technology is often (but not always) more expensive than the technology that it is replacing or improving upon. Since the choice of a radiation treatment does not take place in a vacuum, but within a health care environment that is limited in resources and access, weighing the cost of a new technology against its improvement in outcomes is critical.

Economic analysis of new technology is broadly considered "cost-effectiveness research." Practically, this work involves the assessment of a "choice" between two or more treatments and then the probabilistic simulation of potential outcomes from that choice. Therefore, there are several elements to a formal cost-effectiveness study. First, the investigator must decide on the time horizon for the study—how much time will the analysis consider? Often, the time horizon is long enough that a patient's life span can be considered. However, in cases where only acute outcomes are important, the time horizon can be shorter. Second, the investigator must consider what health states a patient may pass through from treatment to the final end point of the study. Each health state should be assigned a "health utility," which is a value between 0 and 1 that places a numerical value on the quality of life in that health state. Health utilities are obtained via a formal process— either through surveys that have been developed with scores that are anchored to health utility values or through asking a representative group of patients to consider existing in the health state and their willingness to "gamble" to exit the state for perfect health. This technique is called the *standard gamble* technique.[33] When the health utility is integrated over the timescale of years, this produces a measure called a *quality-adjusted life year* (QALY). QALYs are commonly used in economic

analysis. Alternatives to the QALY include disability- adjusted life year and life years gained (without "discounting" years lived with disability,[34] which can be problematic). Third, the investigator must estimate the probability the patients will pass between different disease states. These probabilities are ideally obtained from contemporary clinical trial data. Fourth, the investigator must define the cost of treatment choices as well as the cost of existing within each disease state. These costs must be defined from a prespecified point of view, or "payer perspective," such as Medicare.

How much a payer is able or willing to pay for a treatment relative to a benefit is known as a "willingness to pay." Payers with more resources are postulated to have a higher willingness to pay compared to those with lower resources. The willingness of a country or society to pay for treatment that provides incremental gain is known as a "societal willingness to pay."[35] Societal willingness to pay is often reported in cost per QALY and has been hypothesized to range from $50,000 per QALY to $200,000 per QALY and more in the United States.[36,37]

Once this model has been created, the investigators can calculate the cost of each choice via a "decision tree." However, it is often useful to consider how changes in parameters may influence the cost-effectiveness of a treatment choice. For example, it is useful to take into account a range of potential probabilities for transitions between health states, as well as the range of potential values for health utility and cost of care. If one knows (or hypothesizes) about the relative distribution of potential values, one can model the impact of parameter changes as well as the likelihood that a treatment is cost-effective by simulating a cohort of patients. One method of simulation is known as a "Markov analysis" and is a powerful tool for probabilistic analysis of treatment decisions and chance-based outcomes.[38]

The economics of cancer care and new radiation technology is complex and requires a holistic view of structural societal factors, economic inputs, and policy factors as they relate to the cancer control continuum (including treatment) (Figure 33.1). Economic analysis of cancer treatment (including radiotherapy) requires improved data, training, and prospective economic study of cancer treatment. Unfortunately, the NCI Cancer Therapy Evaluation Program and Division of Cancer Prevention do not provide funding for economic research, and proposals to integrate economic data collection are rarely approved. As well, unfortunately, the NCI Biomarker,

Imaging and Quality of Life Studies Funding Program cannot be used to fund comparative effectiveness or cost-focused studies associated with cooperative group clinical trials.[39] Therefore, with these structural barriers, economic data collection currently must utilize passively collected data, such as insurance claims or institutional billing.

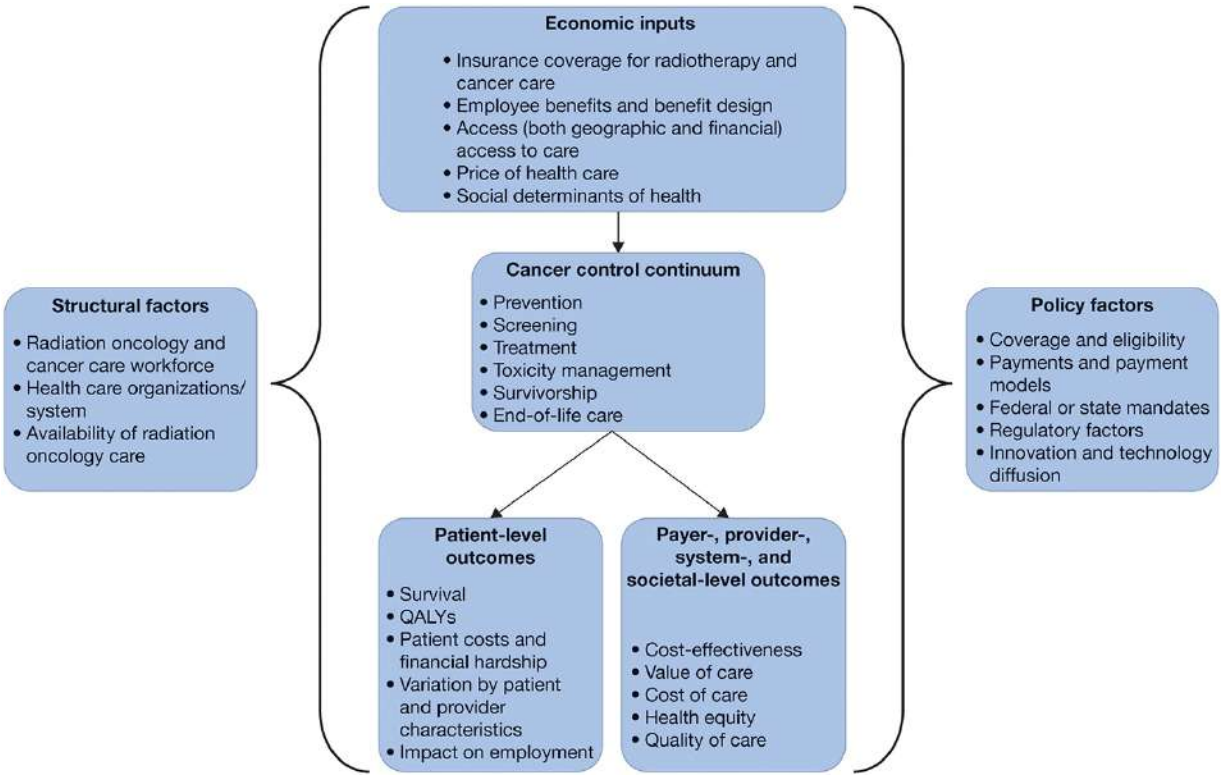

FIGURE 33.1 Interconnectedness between structural factors, economics of cancer care, patient outcomes, and policy. QALY, quality-adjusted life year. (Adapted from Halpern MT, Shih YT, Yabroff KR, et al. A framework for cancer health economics research. *Cancer*. 2021;127[7]:994-996. Copyright © 2020 American Cancer Society. Reprinted by permission of John Wiley & Sons.)

GENERATION OF EVIDENCE

Except in rare cases of obvious benefit, the adoption of a new radiation technology generally requires evidence supporting its improved efficacy, reduction in toxicity, and/or improvement in cost-effectiveness compared to older technology or the absence of treatment. Not all clinical evidence is considered to be equal. Traditionally, the evidence pyramid creates a hierarchy of evidence from lowest to highest quality (Figure 33.2). At the bottom of the hierarchy are case series and expert opinion. Above those

levels are case-control studies, cohort and observational data studies, and randomized controlled studies. Traditionally, evidence that has been synthesized such as systematic reviews and meta-analyses is considered the top of the hierarchy. This hierarchy is also reflected in the levels of evidence used to measure therapeutic studies, with "level 1" evidence defined as randomized clinical trial evidence and levels 4 and 5 as case series or expert opinion.[40]

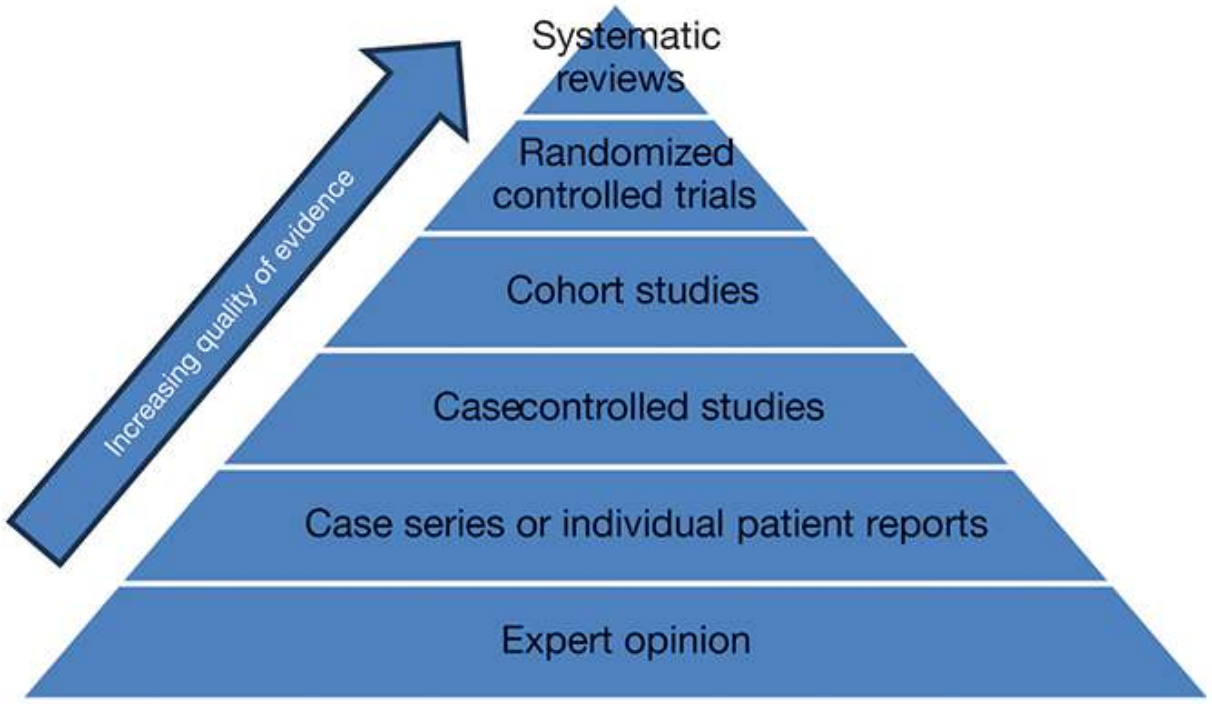

FIGURE 33.2 Pyramid of strength of evidence.

Generally, randomized controlled trials are considered the best source of clinical evidence. Randomized controlled trials often have the benefit of being able to isolate a treatment effect from confounding variables through randomization of intervention. However, randomized controlled trials are not foolproof, as pitfalls may remain. For example, if a randomized new treatment is associated with a higher level of overall clinical care compared to no treatment, the clinical benefit observed with the randomized new treatment may actually be due to enhanced clinical care rather than the supposedly tested intervention. As well, clinical trials have been criticized for being limited in its external validity to patient groups who were not

robustly included in trials with limited representativeness.[41] Finally, clinical trials are expensive, often with long periods between trial conception, activation, accrual, analysis, and completion.[42] Thus, answering every clinical question using a randomized clinical trial is simply not practical.

In light of these issues, alternative forms of evidence generation are needed to compare the *effectiveness* of radiation technologies, in addition to the *efficacy* of the treatment. The efficacy of a treatment is what is tested in a randomized controlled trial—the benefit of a treatment in ideal conditions, with the treatment impact isolated from all other factors. The effectiveness of a treatment is how the treatment impacts outcomes in real-world practice, in normal and not idealized situations. Alternative forms of evidence may also address the "efficacy-effectiveness" gap.[43]

COMPARATIVE EFFECTIVENESS RESEARCH

Though in an ideal world, all treatment decisions would have a supporting prospective randomized clinical trial, this is unrealistic given the rapid pace of change in cancer treatment and radiation technology. CER addresses this need for clinical evidence regarding the effectiveness of a new radiation technology. The Institute of Medicine defines CER as "the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels."[44] Technically, this also includes clinical trials, but generally has been understood to involve nonprospective trial investigation with studies that use observational registry data, insurance claims, and other large data sets to compare medical practice that would otherwise be difficult to compare.

Examples of CER in RO include comparisons of radiation to surgery, adjuvant radiation to no adjuvant treatment,[45] as well as comparisons of different radiation techniques (extreme hypofractionation to standard fractionation, proton to photon, brachytherapy to external beam radiotherapy, etc). Great care should be taken when attempting to compare radiation to surgery, given the huge inherent bias in patient selection that

favors surgery.[46] It has been shown that bias favoring surgery for prostate cancer cannot be adequately adjusted using standard statistical techniques.

Limitations of CER comparing radiation technologies center around the limitations of retrospective data as well as the potential bias inherent in patients who are selected for new versus older technologies. It is possible that patients treated in more recent years benefit from improved staging, supportive care, and medical care in general. These benefits (and others) cannot be adjusted for with statistical methods if their values are unknown and unmeasured. This unmeasured confounding is a key limitation of retrospective data. Furthermore, as technology matures, its impact may change and indications for use may change in ways not accounted for in retrospective data sets.[45]

To address limitations in the analysis of observational and registry data sets with standard regression models such as logistic regression and Cox proportional hazards analysis, additional analytic methods have been applied. These methods include techniques involving propensity scores, such as inverse propensity weighting and propensity score matching.[47] Instrumental variable analysis attempts to get around the question of unmeasured confounding variables. An instrumental variable is a measured variable that cannot influence the outcome, except through the treatment in question, and at the same time is not related to any other variable, except the treatment variable.

For an instrumental variable to be used to avoid treatment selection bias, the instrumental variable must be related to the outcome of interest without being related to selection bias. For example, if hospital's overall SBRT utilization rate is related to the use of SBRT for lung cancer (vs surgery) and you believe that SBRT utilization can theoretically only affect survival through choice of clinical treatment, it would make a reasonable instrument.[48] However, one could hypothesize that the overall use of SBRT is also related to other factors (eg, overall hospital technology, presence of multidisciplinary tumor boards, academic practice) that could influence patient outcomes. Therefore, though instrumental variable analysis is a compelling technique to avoid unmeasured confounding variables, it is difficult to find the perfect instrumental variable in actual practice.

ASSESSING THE ROLE OF ARTIFICIAL INTELLIGENCE IN RADIATION ONCOLOGY

The term *machine learning* (ML) broadly means computerized algorithms that work without explicit coding but instead by analyzing data that are fed into the algorithm. AI is often considered a broader area of study investigating the ability of a computer to perform tasks that traditionally require human intelligence. In this chapter, we use the two concepts interchangeably. The data fed into the algorithm are generally known as "training data," which can be curated with known outcomes (in the so-called supervised learning) or left to the algorithm to organize into recognizable features (the so-called unsupervised learning). The algorithms themselves can vary from readily understandable multivariable logistic regression models to inscrutable deep learning neural networks that have been compared to a "black box." Furthermore, not only has AI been used to interpret and classify data, but algorithms trained on images and languages are being increasingly used to generate output in response to prompts and questions from the user. This "generative AI" is an area in which AI is going beyond analysis of data to potentially directly impacting patient care.

How to evaluate analytic and generative AI algorithms is a question that is important for regulators tasked with determining the safety of medical technology such as the FDA. To address the question of AI in drug development, the FDA released a discussion paper that characterized the risks of AI-developed drugs, including biased data, and inaccuracies in the completeness of the data.[49] Ultimately, the differences between standard FDA postmarket monitoring for non-AI and AI-informed drugs will likely be similar.

In the United States, AI-based medical devices are largely cleared through the FDA's 510(k) pathway for "substantially equivalent" devices.[50] As with drugs, postmarket surveillance does not substantially differ for AI-utilizing medical devices. Relevant to RO, a recall of a software that utilized AI/ML for treatment planning and analysis of radiation was affected by an error that would have resulted in local underestimation of expected dose (FDA recall number Z-2341-2020). It is not clear whether AI/ML-based machines are more or less likely to be involved in recalls by the FDA.

To address the evaluation of AI/ML-based software, the FDA released an action plan, following a discussion and request for feedback.[51-53] This action plan focused in part on how algorithms are updated as more data are evaluated by an algorithm. As a result, the FDA recommended a "predetermined change control plan" in premarket submissions that required anticipating modifications to an algorithm and how to implement those changes in a controlled manner. As well, the FDA is expecting transparent and real-world monitoring of the AI/ML-based software once approved. This is the goal of the FDA's Digital Health Center of Excellence.[54]

Finally, best practices in AI/ML technology development are needed. Known as *Good Machine Learning Practice*, this includes areas such as data management, training data, unsupervised feature extraction, algorithm interpretability, and documentation.[55] Arguably, whether a technology is developed in adherence to Good Machine Learning Practice could be used to assess its quality. Further, the Minimum Information about Clinical Artificial Intelligence Modeling (MI-CLAIM) checklist has been developed to describe the minimum amount of documentation required for proper interpretability, transparency, and utility of health care AI models.[56] The six parts of the MI-CLAIM process are proper reporting of study design, proper partitioning of data for training and testing of the model, final model selection, performance evaluation, model examination, and evaluation of model-building pipeline reproducibility.

Ultimately, an AI/ML technology will need to be evaluated in the same manner as any medical technology. The same can be said for AI/ML-developed drugs. Is the tool based on a transparent algorithm that uses plausible features and good training data (analogous to the question, "is the mechanism of action explainable")? Is the tool biased? Is the technology reliable and robust? Once approved, the performance of the AI/ML technology will need to be evaluated in a similar manner to any technology. Unique to AI/ML technology is the potential for continuous change as more contemporary data are being fed into the algorithm. Monitoring the algorithm as it changes in response to additional data is an area of intense focus by the FDA.

TOWARD EVIDENCE-BASED RADIATION ONCOLOGY

Evidence-based medicine (EBM) is the conscious use of current best evidence in decision-making in clinical care and health services delivery. Arguably, EBM should provide an underpinning for our understanding of the clinical literature and thus our daily RO clinical practice. EBM involves the clinician using the best evidence available, in consultation with the patient, to decide on a clinical course that suits the patient best.

Synthesizing outcomes data and CER, the American College of Radiology (ACR) began documenting RO national benchmarks with the Patterns of Care Studies (PCS), performed under a grant first awarded by the National Institutes of Health in 1973.[51,52] This move toward EBM followed a discrete move across medicine, led by Canadian researchers.[53]

In many ways, the PCS represented the first nationwide assessment of practice within a medical discipline. These studies described essential requirements of the proper clinical, physics, and administrative aspects of contemporary RO practice. By focusing on this process in the context of specific pretreatment and treatment factors, improvement in the treatment process contributed not simply to better quality of care but ultimately to improved survival of patients with cancer.[51]

In the early 1990s, data from the PCS developed into decision trees. These may be recognized as early versions of clinical pathways. Similarly, practice guidelines involved the use of expert panel review with application of a consensus tool such as the Delphi technique[54] to document appropriate techniques for clinical cancer cases. Clinical pathways and practice guidelines became the mechanisms by which EBM was integrated into active clinical usage in the late 1990s and early 2000s.

In contemporary practice, many radiation oncologists now rely on treatment guidelines published and updated by expert committees from ASTRO, ACR, and other societies or practice groups. Some departments have created their own internal clinical practice guidelines.[57] These national and institutional clinical guidelines have the potential benefit of providing treatment recommendations where evidence is lacking, though caution is required where bias and conflicts of interest exist.[58,59]

CONCLUSION

Given the rapid and continuous pace of technological innovation, it is important for all radiation oncologists and their teams to understand how new technologies understand how new technologies disseminate, are evaluated, and are compared to older technologies. Comparative effectiveness researchers, clinical trial groups, as well as government and health care payers are continuously attempting to measure the efficacy of new technologies against their cost to patients and payers. Because of the rapid pace of change and inherent difficulties in comparing new technologies to old, analytic techniques that attempt to reduce bias and overcome limitations of retrospective data have been developed and are being used. Patient-reported outcomes, physician-measured outcomes, and other outcomes such as financial burden and toxicity are being assessed to obtain the full impact and benefit of the new innovations in radiotherapy. The breadth of research can be considered in clinical guidelines advising physicians in the optimal use of radiation technology, both old and new.

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CHAPTER 34

Global Radiation Oncology

Timothy P. Hanna, Melinda Mushonga, Fabio Ynoe de Moraes, and C. Norman Coleman*

Global radiation oncology links the discipline of radiation oncology to global health, where the latter may be defined as "… an area for study, research, and practice that places a priority on improving health and achieving equity in health for all people worldwide."[1] This chapter provides an overview of the unique challenges to providing radiation oncology in low- and middle-income countries (LMICs). It also provides reasons for hope that the global challenge of cancer can be met and provides some innovative models of how cancer care should be considered integral to health care and not an "expensive add-on." Low-income countries have a 2025 per-capita gross national income of US$1,145 or less, and for middle-income countries, the range is US$1,146 to $14,005.[2,3] Nations falling into these income groups are sometimes described as developing countries.

GLOBAL BURDEN OF DISEASE

In 2019, an estimated 17% of all deaths worldwide were due to cancer.[4,5] In comparison to the worldwide burden of cancer, cardiovascular disease and other chronic conditions are responsible for, respectively, 32% and 25% of deaths globally. In total, 74% of mortality worldwide is the result of noncommunicable diseases (NCDs). Seventy-six percent of these deaths occur in LMICs.[4,5] In low-income countries, where deaths from communicable diseases and other related causes are common, deaths due to NCDs are 42% of all deaths.[4,5]

In 2020, 59% of cancers worldwide occurred in LMICs, as did 71% of all cancer deaths.[6-8] In 2020, 55% of all cancer incidence was in Asia and Africa alone, and deaths were 65%.[9] The continual increase in the burden of cancer in LMIC relates to an increasing life expectancy in LMIC, coupled

with a rising incidence of risk factors for chronic diseases.[10,11] For example, an estimated 65% of people 60 years of age or above lived in less developed countries in 2010, and this is expected to rise to 79% by 2050.[4] The growing burden of cancer and other NCDs in LMIC represents a significant epidemiologic transition and a dual challenge for disease control efforts in countries already faced with a high burden of communicable disease.

EPIDEMIOLOGY OF CANCER WORLDWIDE

Worldwide, there were 18.1 million new cases of cancer and 9.9 million cancer deaths in 2020.[6,12] Breast cancer is the most common cancer worldwide (2.3 million new cases in 2020), followed by lung cancer (2.2 million) and colorectal cancer (1.9 million).[6,7] Lung cancer is the most common cause of cancer death, with 1.8 million deaths in 2020, followed by colorectal cancer (0.9 million), liver cancer (0.8 million), and gastric cancer (0.8 million).[6,7] Figure 34.1 illustrates trends in cancer incidence and mortality by country income, comparing high-income (HICs) and upper-middle-income countries. Age-standardized incidence rates of cancer in HICs are more than double the rates in low-income countries, though age-standardized mortality rates are far more similar. These findings reflect a variation in the prevalence and distribution of major risk factors and limitations in early detection and treatment resources in low-income countries.[13]

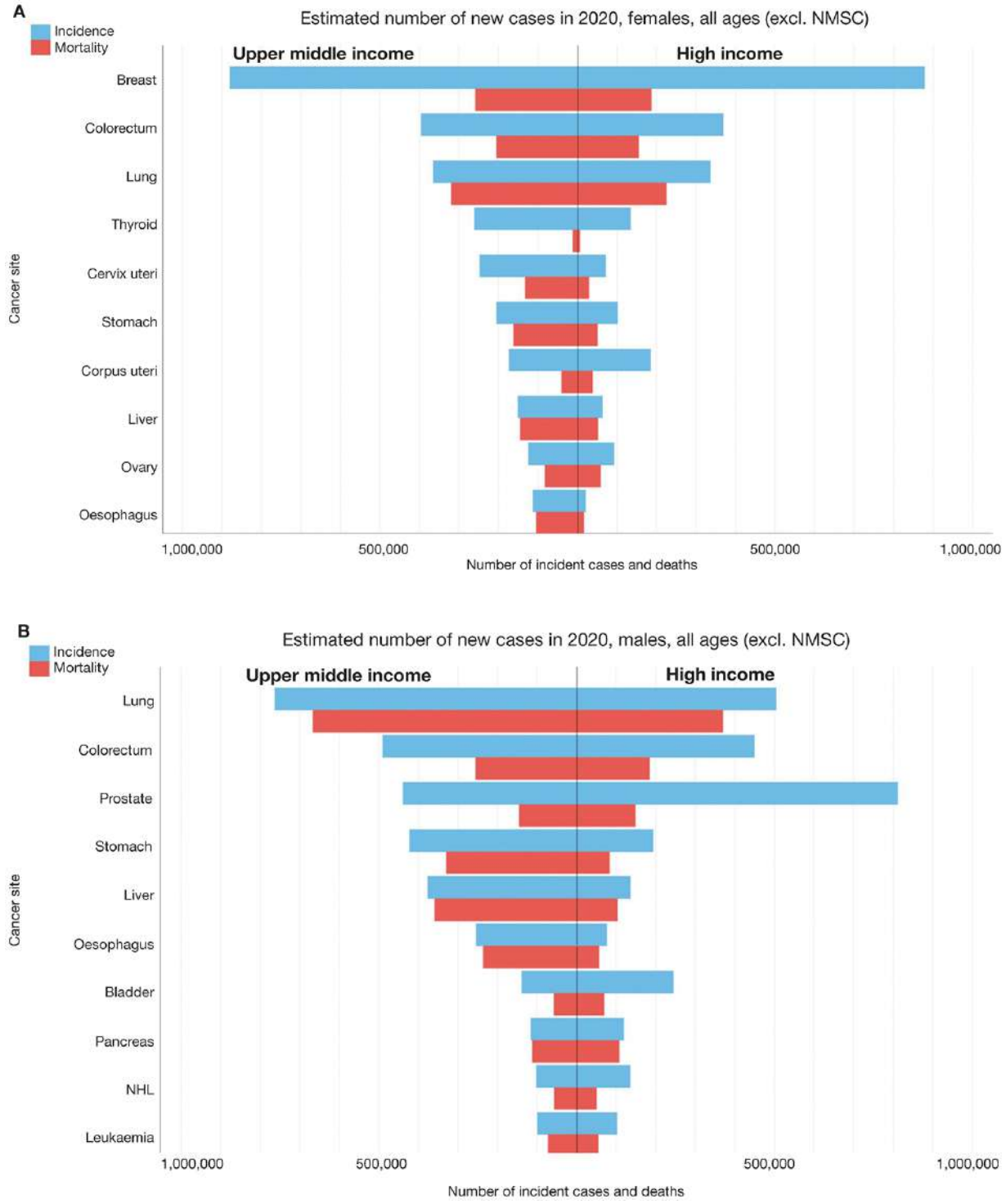
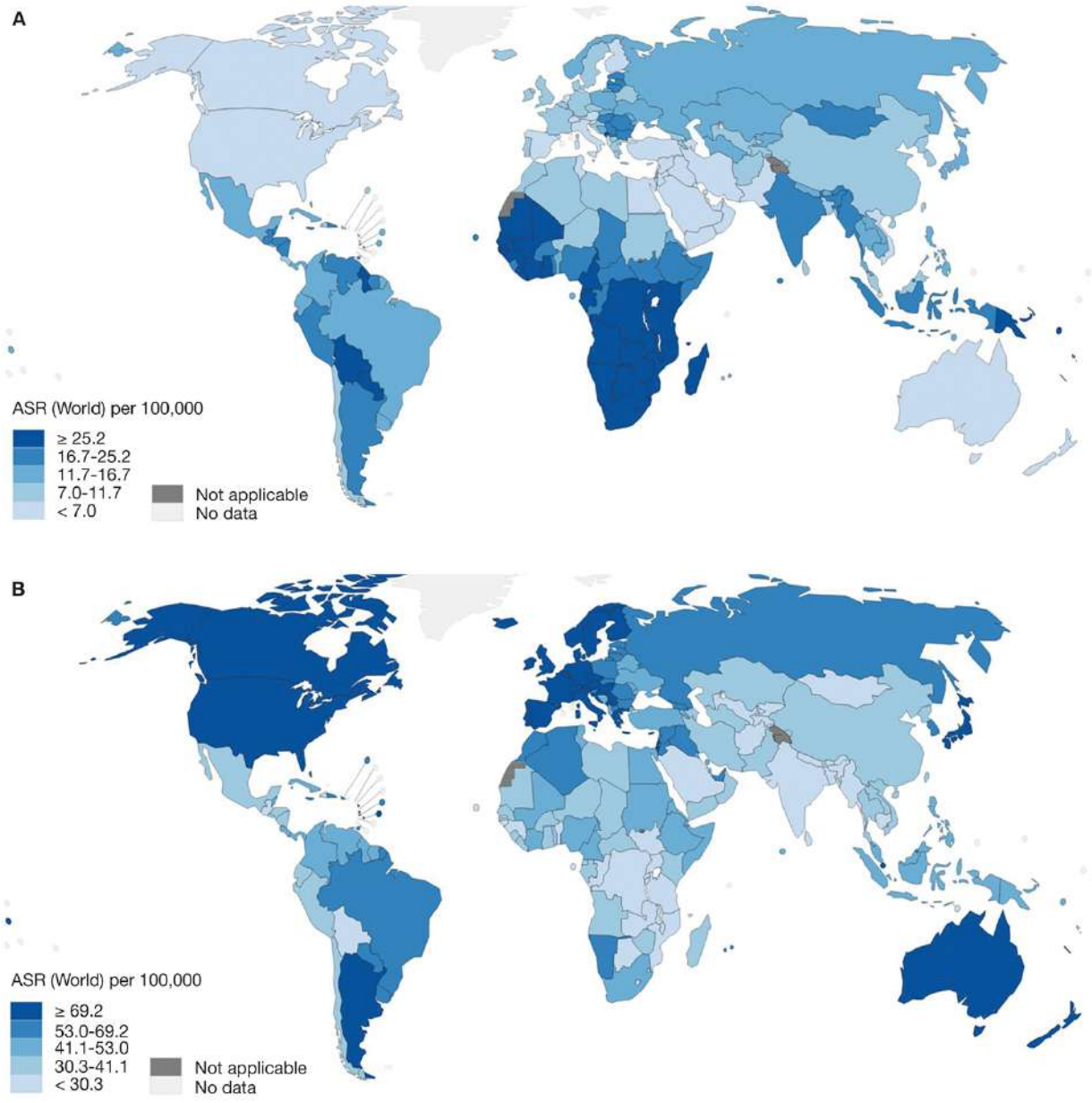


FIGURE 34.1 Estimated number of new cancer cases (incidence) and deaths (mortality) in upper-middle-income countries compared to high-income countries. Data are shown for 10 common cancer sites according to sex, ranked by cancer incidence in upper-middle-income countries. NMSC, non-melanoma skin cancer. (Reprinted with permission from Ferlay J, Ervik M, Lam F, et al. Global cancer observatory: cancer today. International Agency for Research on Cancer; 2020. Accessed September 18, 2023. https://gco.iarc.fr/today.)

Although cervix cancer is the 11th most diagnosed cancer among women in developed countries, it is second only to breast cancer in many developing nations and first in many Sub-Saharan African countries.[7] It is also an extremely common cancer in Latin America and parts of Asia, such as India (Figure 34.2). This suggests the lack of sufficient prevention of cervical cancer in many LMICs or a reflection of yet-to-be-realized human papillomavirus (HPV) vaccination efforts. Gastric cancer and hepatocellular carcinoma are also common in many LMICs, with 43% of all cases of gastric cancer in the world occurring in China alone (Figure 34.2).[7] Esophageal cancer has the highest incidence rates worldwide in some regions of Asia and Africa.[7] Oral cancer has a high incidence in South Asia, particularly among men.[14]


A
ASR (World) per 100,000
≥ 25.2
16.7-25.2
11.7-16.7
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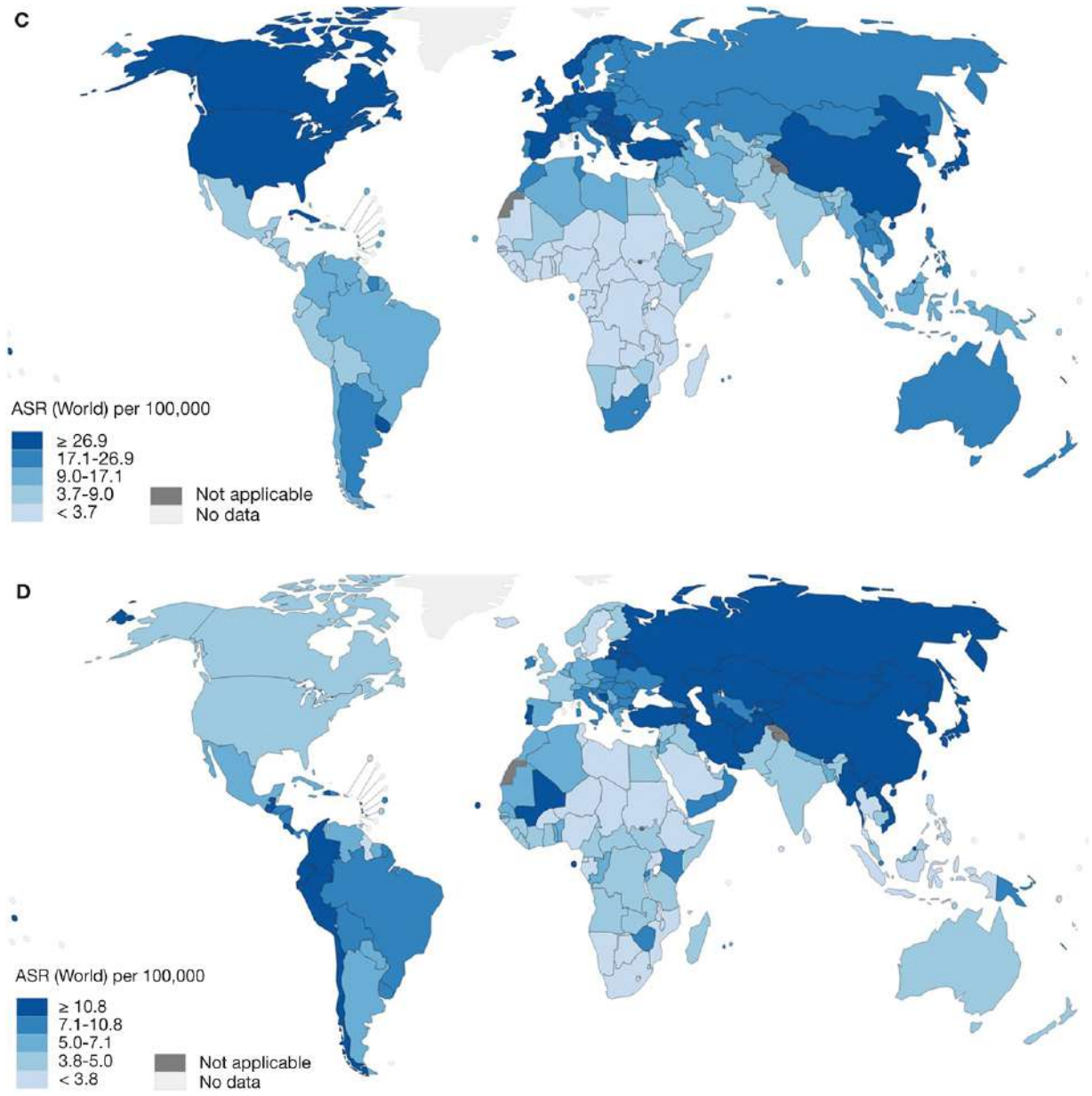

FIGURE 34.2 Global variation in estimated age-standardized cancer incidence per 100,000 population in 2020 for specific cancers based on International Agency for Research on Cancer statistics. Incidence is grouped with higher incidence indicated by darker color. Rates for both sexes are shown for lung and stomach cancer. A. Cervix cancer rates are highest in Latin America, Sub-Saharan Africa, and parts of Asia, including India. B. Breast cancer rates are high among high-income countries. Among low- and middle-income countries, rates are high in parts of Latin America and lower in parts of Africa and Asia. ASR, age-standardized rate. C. Lung cancer rates are high in both developed and developing parts of the world, including China, Southeast Asian countries, and parts of South America. D. Rates of stomach cancer are highest in East Asia. High rates are found in Latin America, other parts of Asia, and Eastern Europe. ASR, age-standardized rate. (Reprinted with permission from Ferlay J, Ervik M, Lam F, et al. Global cancer observatory:

cancer today. International Agency for Research on Cancer; 2020. Accessed September 18, 2023. https://gco.iarc.fr/today.)

Among nine common modifiable risk factors for cancer, tobacco smoking is associated with the largest proportion of attributable risk.[15] There are over one billion people globally who smoke, and 80% live in LMICs.[16] With large populations and high tobacco use in China and India, tobacco is an extremely important risk factor for cancer in Asia.[17] In general, many LMICs have demonstrated increased tobacco use between 1970 and 2004.[18] History has shown a 30- to 40-year delay between the peak in smoking rates in a population and the peak in tobacco-related mortality.[19] Thus, an increasing rate of tobacco-related malignancies is expected in LMIC during the next half century.[20]

Over 26% of cancers in developing countries are attributed to infectious causes.[21] Hepatitis B is a major risk factor for hepatocellular carcinoma in LMIC. Other factors are hepatitis C[22] and aflatoxin produced from *Aspergillus* in certain poorly preserved foods.[23] HPV and *Helicobacter pylori* are important etiologic agents, and there are numerous other infectious agents relevant to cancer in the developing world. These include Epstein-Barr virus, human immunodeficiency virus (HIV), schistosomiasis, human T-cell leukemia virus type, and human herpesvirus 8.[21,24] The prevalence of infectious causes is notable, given the preventability of many of these causes through public health measures (eg, hepatitis B, HPV vaccine). The prevalence of infectious causes helps raise the issue of how to merge the investment of NCDs and infectious diseases, where the latter has generally been the dominant focus of global investment in the developing world. This issue is considered in the “innovation” section.

There are a few other risk factors relevant to current patterns of global cancer incidence. Diet and obesity are recognized risk factors for some cancers.[25,26] This is notable, given increasing trends in the adoption of unhealthy diet and sedentary lifestyle in LMIC.[27] The impact of genetic polymorphisms on patterns of global cancer incidence has not been fully elucidated in LMICs, but there is some suggestion of their relevance.[28,29] Similarly, the role of occupational and environmental exposures to cancer in LMIC requires continued exploration.[30]

In many LMICs, cancer often presents in advanced stages, due to factors such as the lack of comprehensive screening and poor access to diagnostic services.[31] In addition, where there is a lack of access to treatment, case fatality rates are expected to be much higher. For example, Beaulieu et al found the case fatality rates for breast and cervical cancer in low-income countries to be more than double compared to rates in HICs.[32] About half of all cancers in LMICs require radiotherapy.[33,34] Cervical cancer is common in LMIC, and advanced cancer presentations requiring chemoradiation and brachytherapy are common. Therefore, radiation therapy has an extremely important role in LMIC. Accordingly, the World Health Organization (WHO) considers external beam radiation machines, remote afterloading brachytherapy systems, and their supporting technologies as priority medical devices for cancer management.[35] The following sections describe radiation oncology in LMIC in terms of access, quality, and economics.

GLOBAL STATUS OF ACCESS TO RADIATION THERAPY

Access to radiation therapy is a multifactorial issue. Availability of machines and personnel for treatment is a key part of access to care. Other considerations include spatial accessibility, temporal accessibility, acceptability, affordability, accommodation, awareness, and adoption of optimal radiation departmental practices.[36,37] The most pertinent elements of access to radiation therapy in LMIC are discussed here.

Availability of equipment and personnel for radiation therapy are common limiting factors in LMIC. Less than 5% of global medical spending on cancer is in LMIC.[38] This is despite LMIC containing over 80% of the world's population[10] and over 70% of the world's deaths from cancer.[6] Oncology medical training programs are steadily growing; however, more needs to be done to address the lack of key personnel for radiation oncology and refine the curriculums in line with treatment advances in radiation oncology.[39-43] LMICs only have about one-third of the world's 13,136 megavoltage radiation therapy units despite an estimated need for more than double the current number.[44,45] In Africa, as of March 2020, 430 external beam radiotherapy units were available in 28 of 52 countries; however, more than half of these units were in either South Africa or Egypt.[46]

The greatest limitations in machine supply are strongly associated with low national economic status (Figure 34.3).[33] Given the expected rise in cancer incidence in LMIC, these large mismatches between need and availability will widen if current machine supply remains inadequate. In addition to machine availability, other physical resources need to be considered. These include clinical space, bunkers, other equipment (brachytherapy, simulation, immobilization, treatment planning, beam modification, dosimetry, quality assurance), a reliable power supply for linear accelerators, and the availability of parts and technical support for machine maintenance and repair.[47]

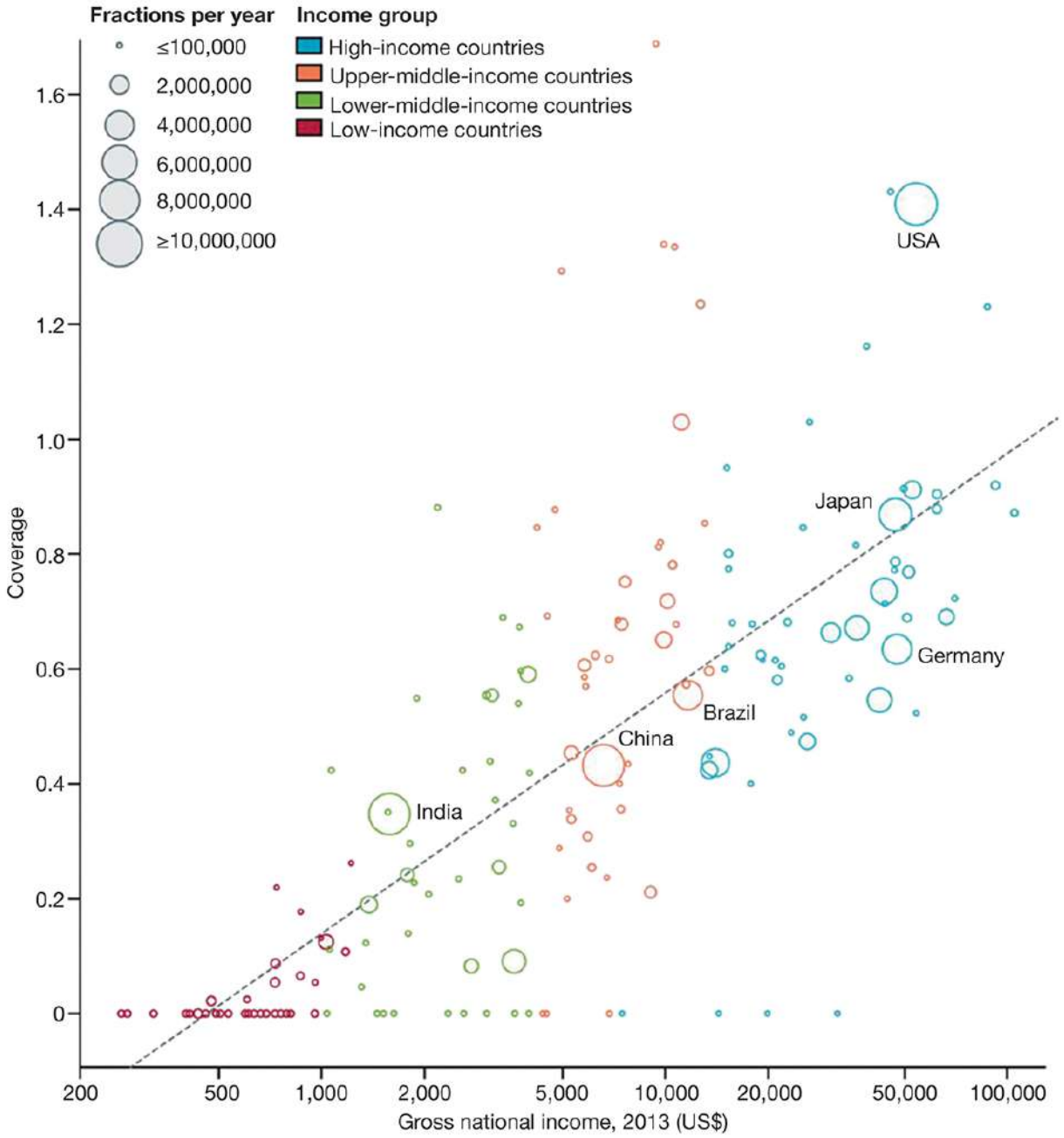

FIGURE 34.3 Radiotherapy coverage according to country gross national income per capita. Each circle represents a single country. The diameter corresponds to the actual annual number of fractions delivered by each country. Color corresponds to country income group. Coverage is reported assuming an 8-hour operating day. (Reprinted from Atun R, Jaffray DA, Barton MB, et al. Expanding global access to radiotherapy. *Lancet Oncol*. 2015;16[10]:1153-1186. Copyright © 2015 Elsevier. With permission.)

The state of radiation therapy resources varies between LMICs and regions.[40,43,48,49] Some selected examples are provided for illustration. In

1999, Levin et al[49] documented the availability and distribution of radiation therapy equipment in Africa. Only 22 of 56 countries in Africa were confidently known to have megavoltage radiation therapy facilities. In total, more than 400 million Africans had effectively no access to radiation therapy. Although machine supply has since increased, there are still dramatic shortfalls in machine supply in Sub-Saharan Africa.[44,45]

In the Asia and Pacific Region, Tatsuzaki and Levin[40] found an 82-fold variation in the number of megavoltage machines per million population in 1999. China's and India's machine supply has increased in recent years, though capacity is still well below what is needed to treat all patients.[8,44,50] Workforce resources vary considerably between countries, and most countries have less than two radiation oncologists per 1,000 incident cancers annually.[8,41,44] Many more physicists and radiation therapists are required to expand global treatment capacity.[33,41,51]

Cancer care is multidisciplinary, and these disciplines triage patients who eventually require radiotherapy. Surgical oncology, medical oncology, oncology nursing, pathology, radiology, rehabilitation, supportive care, and palliative care all have a role to play in effective cancer management.[52] Limitations in pathology and radiology compromise diagnosis and the ability to distinguish curative-intent treatment from palliative cases. Surgical oncology plays a central role in curative treatment of early-stage cancer. The Lancet Oncology Commission on Global Cancer Surgery reported that despite over 80% of cancer cases needing surgery globally, less than 25% of patients with cancer get safe, affordable, or timely surgery.[53] Access to palliative care, including pain control for moderate-to-severe pain, is a major issue. The WHO estimates that 5 billion people live in countries with limited or no access to narcotic analgesics and other controlled substances, with an estimated 5.5 million patients with terminal cancer dying each year without adequate treatment.[54] Therefore, if the disciplines that triage patients who may eventually need radiotherapy are not supported, the number of patients able to access appropriate radiotherapy as part of cancer care will remain low.

Spatial accessibility refers to the geographic accessibility of medical treatments. Available information suggests spatial accessibility is of concern in LMIC as less than 25% of the Sub-Saharan African population is estimated to be within 2 hours of radiation therapy.[44,55,56] With radiation

therapy centers often in large cities, rural populations may face substantial financial challenges when traveling into cities for the duration of radiation treatment. For example, in Ghana, only 47% of the population lived within 100 km of the nearest radiotherapy facility.[57] Notable is that there are "LMIC"-like situations within HICs such that there are both solutions in common among the range of resource rich and limited. This is particularly relevant to geographically isolated regions, often indigenous populations.[58-60] One of our early career leaders in the International Cancer Expert Corps (ICEC) has dubbed this "local-global"[61] an important consideration when seeking investment in global health, discussed in the "Innovation" section.

Temporal accessibility refers to accessing radiotherapy without undue delay. Delays in cancer treatment, including radiotherapy, are in many cases associated with patient anxiety, and with adverse clinical outcomes, including reductions in local control, and potentially worse survival.[62-64] Professional societies and health systems have established benchmarks that set reasonable standards for timely treatment.[65-67] Though data are limited, particularly for low-income countries, available information suggests that despite these wait time targets, waiting for cancer diagnosis and treatment can be lengthy across all country income levels and should be addressed.[68,69]

Acceptability of available care options can impact an individual's willingness to take advantage of services and adhere to recommended therapies. For example, a small study from Cameroon found beliefs, fears, cultural factors, and awareness were among the explanations for the delay in seeking medical attention for cancer.[70] Values surrounding the effects of pelvic radiation treatment on fertility, loss of hair with some chemotherapy, and anatomic changes associated with surgery such as mastectomy are some potential factors in need of further description and quantification in LMIC. Culturally appropriate cancer control plans sensitive to a region's social and political concerns are needed, including initiatives to overcome stigma and improve awareness.[71]

Affordability of radiation therapy and other forms of cancer therapy is a major concern in LMIC.[72] Households in LMICs often have limited or no health insurance coverage.[38,73] Cancer-related publicly funded treatment may be limited or nonexistent.[74] The cost of travel to the nearest cancer center can itself be another major financial obstacle, and the costs of staying for the length of radiation treatment in another location can mean lost

income and more cost to the patient and family.[72] A family may lose additional income due to the caregiver absence from work.[72,75]

Awareness of the basic cancer principles and the value of cancer screening and early detection potentially limit timely access to cancer services for the public in LMIC. A large Union for International Cancer Control (UICC) survey of multiple LMICs found a substantial lack of awareness of common preventable causes of cancer and found that a quarter or more of respondents in Asia and Africa did not think cancer could be cured.[76] Limited awareness of principles of cancer diagnosis among health care workers and poor coordination of care can further compromise access to cancer treatment.[68,77,78] Moreover, a lack of awareness of indications for radiotherapy among the public and referring physicians can further limit access to radiotherapy. For example, there may be a lack of awareness of the role of radiotherapy in hemostasis for cervical cancer or palliation of painful bone metastasis.

Adoption of optimal departmental practices is an important part of improving access to radiotherapy. Increased waiting times to start radiotherapy have been reported in many Sub-Saharan African countries because of the reduced availability of radiotherapy machines.[79,80] Adoption of hypofractionation regimens for breast, prostate, and other cancers can potentially result in reduced machine time for individual patients; hence, many more patients can be treated compared to protracted treatments. There is established evidence in breast cancer treatment for hypofractionation but poor adoption in LMICs, suggesting the need for targeted interventions that aid knowledge translation to clinical practice in LMICs.[81] Moreover, capacity can be further improved with sufficient departmental staffing, longer operating hours, and less machine downtime due to appropriate maintenance and servicing.

Access to and adoption of new techniques requires training. New radiotherapy machines have been commissioned in some countries in Sub-Saharan Africa, and these can be used to deliver stereotactic treatments in keeping with advances in radiation oncology management protocols with the right support. There is no data on the status of advanced radiotherapy techniques to organize support for institutions with potential capability based on the already existing infrastructure. As highlighted, cervical cancer is one of the most common cancers in LMICs, and most patients present

with advanced disease. Interstitial brachytherapy has an established role in the management of locally advanced cervical cancer. There are 101 brachytherapy units in 20 African countries according to the International Atomic Energy Agency (IAEA) data, but limited information on access to interstitial brachytherapy in these countries.[82] There is, therefore, an opportunity for the global oncology community to focus on clinical skills transfer programs onsite to complement the established and traditional observorships, which, in most cases, are not hands-on.

QUALITY OF RADIATION ONCOLOGY IN LOW- AND MIDDLE-INCOME COUNTRIES

Key dimensions of quality are described by the Institute of Medicine as safety, effectiveness, patient centeredness, timeliness, efficiency, and equity.[83] Quality can be assessed through consideration of a health system's structure, process, and outcomes.[84] Elements of structure are physical resources, human resources, and organizational structure. Limitations in physical and human resources in LMIC have already been described. The access issues that relate to late presentation and failure to receive indicated treatment arguably have the greatest impact on outcomes and quality of radiation therapy in LMIC. Quality may be further degraded by the inequitable access of the few available resources between country and city, rich and poor.

The organizational structure of health care in LMIC has historically revolved around communicable disease, nutritional deficiencies, and child and maternal health. The additional burden of NCD in LMIC, commonly cancer, cardiovascular disease, chronic lung disease, and mental illness, imposes a major strain on current resources and health care models. Other issues may include political or social instability, conflict, corruption, and fragmented service provision. Challenges to the structure of cancer control in limited-resource settings may also include insufficient priority of cancer control among some governments and donor agencies with many competing priorities. Cancer infrastructure may be considered expensive. However, health investment is not a zero-sum game. There is a global need for sustainable local health care infrastructure relevant to all conditions, and focusing on cancer can help catalyze its development. Moreover, though

prevention must be part of this, it is emphasized that targets set by WHO for reducing mortality from NCDs by 2025 will not be met by prevention alone.[85] Effective cancer control requires prevention, timely and accurate diagnosis, and access to treatment. The immediate need for cancer care once a diagnosis is made and that cancer is a problem in upper income countries altogether makes it a good focal point for investment in LMIC.

The process of health care refers to what occurs while care is provided. For radiation oncology, this includes technical elements of quality assurance, treatment prescription, treatment planning, and treatment delivery. It includes the integration of multidisciplinary services needed alongside radiation oncology for effective cancer management. A major process issue in some countries is system-related delay in diagnosis.[86,87] This contributes to high rates of advanced disease at presentation. System-related diagnostic delay can relate to weak or nonexistent referral systems or limited resources for diagnosis. It is compounded by patient-related delay in seeking medical attention due to previously described access issues.[88] The additional impact on delay due to waiting times for radiation following radiation oncology consultation may be substantial.[89] Treatment delays for radiation, systemic therapy, and surgery have been associated with worse overall survival in many high-quality studies.[62]

The technical process of radiotherapy is a vital element of quality. For this reason, the IAEA and WHO have maintained a postal dose audit program using thermoluminescent devices (TLDs). A report focusing on measurements from LMIC found acceptable results, with most machines calibrated within the ±5% dose acceptance limit. Sixteen percent of machines registered measurements outside this range in the first round of testing, with 91% measuring dose within 5% of the standard after the second round.[90] Notably, a dosimetric audit in Latin America and the Caribbean suggested an association between on-duty medical physics support and acceptable TLD results.[91] This emphasizes the importance of adequate staffing to a radiation department's quality assurance process as well as the development of robust treatment equipment capable of functioning in challenging environments. An example of efforts underway to develop such equipment is the ICEC STELLA project (Smart Technology to Extend Lives with Linear Accelerators).[92]

There are opportunities for gains in the process of clinical care in LMIC, as there are in HIC. Improving the volume and quality of training programs are clear needs for high-quality national radiation treatment programs. For example, in a survey of 26 African countries, 17 countries identified insufficient staffing/human resources and/or limited training opportunities as one of the main challenges facing their radiotherapy centers.[93] Taking advantage of hypofractionation to increase throughput where there is supportive evidence has not always occurred.[94,95] Implementation of multidisciplinary decision-making among oncologists in LMIC is important, but not always present.[96,97] Treatment refusal or nonadherence by patients can be a major issue in some cases and is an important area for quality improvement where it exists.[55,75,98] Audits of the clinical decision-making and the treatment planning process provide a useful means of ensuring patient safety, improving processes, and creating opportunities for continuing education.[99,100] This is particularly important with the introduction of technology at new locations. For example, initial experience with this approach in a new radiation therapy center in an Asian developing country found suboptimal management in 52% of cases.[99]

Adverse event rates in LMIC treated with radiation are largely unknown. A report examining the risk profile of radiation therapy for the WHO could not identify any detailed reports of adverse events from Africa or Asia.[101] It is important to highlight the need for adverse event recording and reporting for the purpose of patient safety and quality improvement for all countries utilizing radiation therapy.

Importantly, the quality of radiation oncology in LMIC relates to outcomes. Of all cancer outcomes, there is the most information on survival. Generally, overall survival for patients with cancer is lower, and sometimes dramatically so, for populations in LMIC. In a large multinational series from the International Agency for Research on Cancer (IARC), 5-year age-standardized relative survival for cervix cancer was 79% in Seoul, South Korea, but 46% in Mumbai, India; 22% in The Gambia; and only 13% in Kampala, Uganda.[102] Similarly, for breast cancer, survival rates ranged from 90% in Hong Kong SAR to 13% in The Gambia. When absolute survival was stratified by the extent of disease, in many cases, treatment outcomes were still inferior in regions with less developed health services compared to regions with more developed services (eg, local

and regional extent breast cancer and larynx cancer). This may reflect access and quality issues in diagnosis, treatment, and follow-up and/or limitations of the available data.

Finally, corruption is a complex and multifaceted challenge in the global health care sector that significantly undermines the efficiency, equity, and quality of health services.[103] Corruption significantly impacts the quality of health care globally, manifesting through increased wait times, inequitable care, poorer patient treatment, compromised supply chains, unjustified fees, and misallocation of funds. These practices erode trust in both governments and health care systems, leading to poorer care quality and health outcomes.

The spectrum of corrupt practices ranges from smaller scale acts, such as health care professionals demanding bribes for services, to larger scale corruption at the ministerial or administrative level, where funds are misappropriated for personal gain.[104] Annually, the health care sector sees an estimated $455 billion lost to fraud and corruption out of a global expenditure of $7.35 trillion,[105] reflecting a grave issue where around 45% of the global population perceives the health sector as corrupt or very corrupt.[106]

Chronic underfunding by governments, insufficient regulatory oversight, and a lack of transparency in health governance foster an environment ripe for corruption, which, in turn, diminishes the quality of health care delivery. In contrast, environments where good governance prevails demonstrate the importance of transparency and accountability in ensuring that public health expenditures translate into positive health outcomes.[103]

The adverse effects of corruption and bureaucratic states are vividly illustrated through various global instances,[107] through countries including, but not limited to, India, Costa Rica, Cameroon and other parts of Africa, Albania, and through initiatives like Brazil's PER-SUS.[108-110] These examples highlight the direct financial extortion from patients, collusion for personal gain, delays in capacity building and the promotion of unnecessary treatments for profit, showcasing the complex nature of corruption within health care.

To counteract corruption, effective strategies include investing in health care infrastructure and worker salaries, enhancing accountability, public reporting, and strengthening regulatory institutions. Achieving improved governance, accountability, and transparency, while challenging, is crucial

for reducing corruption in health care and enhancing outcomes. Integrity is fundamental to achieving quality health care, emphasizing the need for robust governance structures to protect against corruption, promote ethical practices, and ensure equitable care for all. A concerted, collaborative effort is required to dismantle the systemic corruption that plagues global health care,[110] underscoring the need for a unified approach to foster a more equitable and efficient health care environment worldwide.

ECONOMICS OF RADIATION THERAPY IN LOW- AND MIDDLE-INCOME COUNTRIES

In 2013, the Global Task Force on Radiotherapy for Cancer Control (GTFRCC) was commissioned by the UICC to determine the investment needed to achieve equitable access to radiotherapy in LMIC by 2035.[33] This was a broad collaborative effort, involving radiation oncologists, physicists, industry, economists, and global health experts. GTFRCC published their findings as a Lancet Oncology Commission, as part of the Lancet Cancer Campaign. Dramatic shortfalls in radiotherapy coverage were evident (Figure 34.3). The cost of scaling up radiotherapy services from 2015 to 2035 was estimated to be US$26.6 billion in low-income countries, $62.6 billion in lower-middle-income countries, and $94.8 billion in upper-middle-income countries. By comparison, 1 year of immunotherapy (budgeted at $295,000 per patient) for the current burden of metastatic cancer in the United States would cost an estimated $174 billion.[111]

What could be gained by investment in radiotherapy for LMIC? The GTFRCC estimated that scaling up radiotherapy from observed levels in 2015 to 2035 could save 26.9 million life-years in LMIC over the lifetime of patients receiving treatment. Moreover, the estimated net economic benefit derived from investment in radiotherapy from 2015 to 2035 was found to be substantial. These estimates utilized a full-income method, which is rooted in the societal or individual willingness to pay to avoid a shortened life expectancy. Investment in radiotherapy could produce a net benefit of $265.2 million in low-income countries, $38·5 billion in lower-middle-income countries, and $239·3 billion in upper-middle-income countries. That the analysis of the benefit of radiation therapy for cancer care and the benefit of the overall economy is compelling, yet the progress

in the 8 years, since the report is so limited, is both a source of frustration and evidence of the need for innovative paradigms for cancer care. Not only has the investment in NCDs historically been limited compared to infectious diseases, but the COVID-19 pandemic has further raised the global concern for and investment in the pandemics. In the "Innovation" section, the concept of "flex-competence" is considered (Figure 34.4).[112]

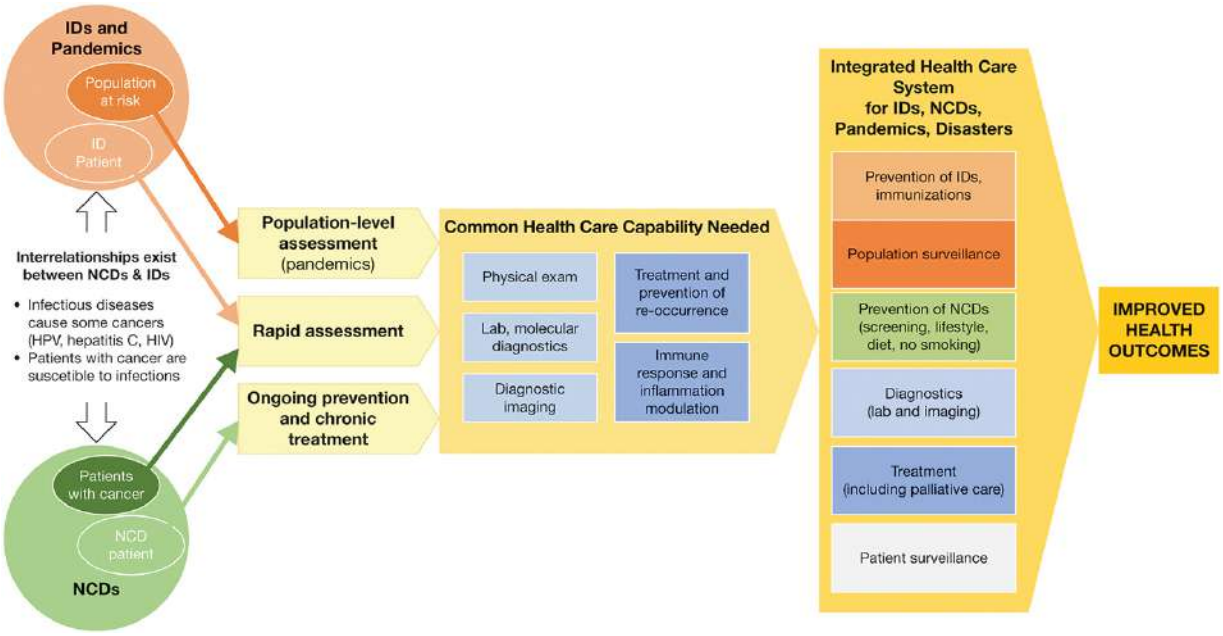

FIGURE 34.4 Flex-competence health care system approach. Approaches to control infectious diseases (IDs) and noncommunicable diseases (NCDs) are similar and often share common etiology. They also often share the same urgency, requiring prompt intervention. There is a common health care capability and capacity needed to control these conditions. HIV, human immunodeficiency virus; Hep C, hepatitis C; HPV, human papillomavirus. (Reproduced from Coleman CN, Mansoura MK, Marinissen MJ, et al. Achieving flexible competence: bridging the investment dichotomy between infectious diseases and cancer. *BMJ Glob Health*. 2020;5[12]:e003252, with permission from BMJ Publishing Group.)

Undoubtedly, applications of various radiation therapy techniques and modern equipment will yield opportunities to maximize the cost-benefit ratio of radiation treatment in LMIC. The GTFRCC found that economic benefits from efficiency gains in radiotherapy delivery could be substantial. These efficiency gains included automation of treatment planning and quality assurance.[33] Hypofractionation yields opportunities to treat more patients with the same supply of equipment.[113] Hypofractionation for

cervical cancer and lung cancer are examples of identified areas for research.[114-116] Investigation of brachytherapy or intraoperative radiation therapy may provide a means of delivering adjuvant treatments rapidly. High-dose rate (HDR) brachytherapy markedly increases patient throughput (eg, for cervical cancer) compared to low-dose rate (LDR) brachytherapy per machine.[117] An IAEA study of accelerated radiation therapy for head and neck cancer in LMIC suggests an opportunity for increasing the effectiveness of treatment without increasing departmental resources, though with increased, but tolerable, acute toxicity.[118] It should be emphasized that prevention and early detection are critical to reducing the number of people diagnosed with cancer and the number of advanced cancers requiring more complex, multimodality treatments.

TRANSLATING KNOWLEDGE INTO ACTION

Recognized priorities for action fall into six categories: advocacy, investment, planning, capacity building, quality, and innovation.[38,119-123] The varying resources, priorities, and disease burden seen in countries at different stages of development mean that there is no single solution that will apply in all cases.[78] In low-income countries with extreme resource limitations, a strategy focusing on cost-effective prevention, raising awareness of cancer within the population, monitoring of process and outcomes, good palliative care, and focused early detection and treatment goals would be a reasonable starting point.[80]

Advocacy

An international coalition to support cancer control and cancer care in LMIC is emerging. The UICC plays an important role as an umbrella organization for advocacy, notably commissioning the GTFRCC, whose efforts have been described earlier. The GTFRCC called for action on five items: population-based cancer control plans, expansion of access to radiotherapy, human resources for radiotherapy, sustainable financing to expand access to radiotherapy, and aligning radiotherapy access with universal health coverage.[33] We elaborate on some of these items in a review of the six priority categories for action covered in this section.

Other groups involved in advocacy range from international agencies (eg, IAEA, WHO, IARC), to national organizations (eg, U.S. National Cancer Institute), to professional groups (eg, American Society for Radiation Oncology, European Society for Radiotherapy and Oncology, American Society of Clinical Oncology, African Organization for Research and Training in Cancer, International Organization for Medical Physics), to nongovernmental organizations (NGOs) (eg, International Network for Cancer Treatment and Research [INCTR], Axios International, AfrOx, American Cancer Society), to academic institutions and hospitals (eg, the Global Task Force on Expanded Access to Cancer Care and Control in Developing Countries [GTF.CCC] convened by Harvard, St Jude Children's Research Hospital). Through the advocacy of the UICC and many other partners (eg, NCD Alliance), the 2011 Political Declaration[124] of the United Nations High-Level Meeting on the Prevention and Control of Non-communicable Diseases was an important acknowledgment by governments of the global problem of cancer and other NCDs. It was also a substantial step toward specific and concerted action by the international community.

Investment

Substantial investment is required, though the potential return on investment is considerable. The GTFRCC called for $46 billion of investment by 2025 to establish radiotherapy infrastructure and training in LMIC.[33] Particularly in middle-income countries, incorporation of cancer care into public health insurance for those living in poverty is an important goal to meet.[38,125] The GTFRCC set a target for 80% of LMICs to include radiotherapy services as part of their universal health coverage by 2020. Given the shortage of national funding for cancer care in poorer countries, international private and public donor support and advocacy for tiered pricing will be notably important in improving access to cancer therapy.

Planning

Development of radiation therapy capacity cannot occur in isolation. Radiation therapy resources must be integrated into a broader context of multidisciplinary cancer control and into a functional health system capable of tackling the double burden of communicable and NCDs afflicting

LMIC.[126] For this reason, the GTFRCC called for population-based cancer control plans, with a target of 80% of countries with cancer plans that include radiotherapy by 2020. A national cancer control plan and collection of cancer registry and health data are central to organizing resources in an equitable and appropriate manner.[127] Notably, the GTF.CCC has published an important resource for planning, advocacy, and priority setting entitled *Closing the Cancer Divide: A Blueprint to Expand Access in Low and Middle Income Countries*.[128] The Global Coalition for Radiotherapy has also developed recommendations on essentials for radiotherapy in cancer control plans for both LMIC and HIC.[129]

Prevention (eg, tobacco control, hepatitis B and HPV vaccination) and early detection are crucial in reducing the burden of advanced cancers in LMIC. When early detection and prevention are combined with timely access to effective cancer therapy, there is great potential for reducing deaths from cancer in LMIC as well as minimizing national costs of cancer therapy.[38]

The IAEA plays a prominent role in quality assurance, safety standards, and dose calibration of radiation therapy equipment internationally. It has also been involved in numerous technical cooperation projects and radiation therapy clinical trials in LMIC. In 2004, the IAEA launched the Program of Action for Cancer Treatment (PACT) to widen the scope of its work in radiation therapy planning and capacity building. Its wide-ranging plan started with the development of sustainable demonstration radiation treatment sites in six countries throughout the developing world (Albania, Nicaragua, Sri Lanka, Tanzania, Vietnam, and Yemen). Recently, IAEA launched Rays of Hope, an initiative to support countries to establish or scale up safe, secure, and effective radiation capabilities in an effort to bridge the major shortfall in equipment and highly skilled personnel common to developing countries.

At a global level, breast cancer guidelines stratified by availability of resources have been developed through groups such as the Breast Health Global Initiative.[130] This is a useful paradigm for developing resource-appropriate and stepwise, scalable goals and guidelines for cancer care that is being adopted for other cancers.[131] A related approach has been used by the IAEA to describe additional resource requirements, benefits, and risks

for specific approaches in lung cancer treatment, including curative and palliative radiation.[132]

Developing innovative means of organizing and funding cancer services is needed. The IAEA's PACT program offers opportunities to identify successful models of service delivery and planning. A model of radiotherapy service provision utilizing geographically dispersed telemedicine-linked sites with varying levels of capacity has also been proposed by an Indian group to maximize available resources.[133] Another concept that is being explored is utilizing community health workers and primary care to expand cancer-related service provision. Proposed activities are cancer prevention, early detection, some treatment (eg, systemic therapy), palliation, and follow-up.[38]

Capacity Building

The importance of improving human resources for radiation oncology and oncology in general cannot be overstated, given the global workforce shortage of trained health care professionals. Some initial efforts have been made in developing curricula and educational approaches specific to the discipline of radiation medicine.[134-136] The IAEA has been notably involved in these efforts. The issue of loss of trained staff from developing to developed countries is especially important to consider in developing educational programs. Urban regions in LMIC may have high-level expertise that can be utilized in developing national training programs. A complementary approach is online training. This is the approach of the Virtual University for Cancer Control and Regional Training Network initiative in Africa. A growing number of cancer centers, regional groups, and specific nations have been involved in twinning projects building capacity for cancer therapy in limited-resource countries. These initiatives have been particularly strong in pediatric oncology, with demonstrated success.[137,138] They provide an appealing means for broad participation in improving cancer control in LMIC.

Surge in Career Interest and Opportunities

Over the past decade, particularly following the United Nations declaration that emphasized the importance of addressing NCDs in 2011,[124] there has

been a surge in interest in radiation and clinical oncology in making global health an integral part of a career. With support from visionary senior leadership, much of the initiative has been undertaken by trainees and early career leaders in defining a career path[139,140] and for establishing resources for idea sharing and opportunities for clinical rotations.[141] The ICEC has established an Early Career Leaders Working Group and Fund[142] to provide support for small grants for global health projects. The hurdle that must be overcome is the issue of how one supports a career in global health because it is not a revenue-generating activity. This can be surmounted with both the appreciation of the need for service as an essential component of a career in health care and the tangible and intangible benefits to institutions and individuals that come from establishing a means of sustainable service to society. New creative paradigms have the potential to bring in interest and investment in global health from a wide range of economic sectors,[143] including science, education, economics, and industry. The data from the GTFRCC[33] indicate that treating cancer provides economic as well as health benefits and is, indeed, a wise investment.

What is obvious is that visionary leaders interested in (1) innovation in career path development, (2) enhancing the capability of existing technology and creating new robust technology and connectivity, and (3) expanding the scope of what is a bona fide medical career are needed to address the gap in global cancer care in both capacity and capability. This will represent a paradigm shift to address an issue of health care inequality that is morally unacceptable, requiring immediate attention with effective action and a sustainable commitment to a problem that will take decades to solve. On the very positive side, the absolute need for radiation therapy for effective global cancer care is an extraordinary opportunity for global contribution and leadership and expanding the reach of radiation oncology.[144-146]

Indigenous Populations in High-Income Countries

Expanding the number of stakeholders in global health will benefit those in need and may enhance the interest and investment from resource-rich countries or HICs, including a recognition that they have similar problems within their own country. Optimism for investment in global health by

radiation oncology over the past few years is the result of remarkable interest by trainees and early career leaders and understanding that this is not simply a problem in the developing world. The level of interest is demonstrated by two reviews, in *Clinical Oncology*[147] and *Seminars in Radiation Oncology*.[148]

Indigenous populations in HICs, particularly people living in geographically isolated or remote regions, have economic, social, and societal issues that are often quite similar to the underserved in LMIC.[59] Similar to LMIC, poor access to screening, presentation with more advanced stages of disease, and poor access to treatment are common. While there is substantial overlap in terms of access and the need for care between indigenous and indigent populations and in the social determinants of health, a distinction is being made between indigent populations in urban centers who are near medical facilities but with limited access often due to other reasons, compared to geographically isolated indigenous people who may be many miles away and for whom physical access to facilities is limited by distance, expense, and the need to be at home to care for families. Success is possible when investment is made, as demonstrated in the Walking Forward Program[149] and the Native Navigators and the Cancer Continuum.[150] Indeed in the National Cancer Institute's Cancer Disparities Research Partnership Program, the program with the Lakota Sioux demonstrated that clinical and translational research can be accomplished.[151,152] The UICC has included an indigenous populations session in its last two World Congress meetings, with participation from Australia, New Zealand, Canada, and the United States.

What is critical to remember is that the health care disparities within geographically remote indigenous populations are experienced by nonindigenous people who are neighbors of the tribes so that they, too, benefit from investment in cancer care. Addressing this common need serves to build a link among the local communities. For those seeking investment from HICs for global health, there is an advantage in including indigenous populations among the needs for LMIC. This approach serves to make the investment more immediate to those in HICs and helps address the frequently raised question as to why invest abroad when problems exist at home.

Quality

Embedded within the themes of investment, planning, and capacity building is the implicit theme of structure-related quality improvement. Process-related initiatives in quality are another very important part of ensuring optimal outcomes. These are often referred to indirectly (eg, safety, effectiveness, patient centeredness, timeliness, efficiency, equity).[83] Quality improvement relating to process and organizational structure is important as it holds the potential for improving some outcomes more rapidly than other drivers of health, such as economic growth.[153] Many aspects of quality improvement have already been discussed in this chapter. One important element of quality for radiation oncology in LMIC is safety, given the potential for unsafe treatment to negate any benefit of available treatment.[154] Safety includes the clinical process, the various elements of technical quality assurance, maintenance, worker safety, public safety, and source security.[155,156] Safety requires investment in appropriate dosimetry equipment, sufficiently trained human resources, and time for quality assurance activities.[156] Internal and external audits, peer review, regulation, accreditation, certification, checklists, adverse event reporting, common protocols, quality improvement, and independent checking are examples of interventions ensuring safety and quality assurance in radiation oncology.[101,157,158]

Innovation

There are many fundamental questions that remain unanswered for cancer in LMIC. It cannot be assumed that evidence-based treatment protocols from specific HIC settings will produce the same results when applied in other countries. Considerations include potential differences in disease burden, malnutrition, rates of chronic infections such as HIV/tuberculosis/hepatitis B, and genetic polymorphisms affecting disease biology and treatment response.[159-163] There are many unknowns in cancer epidemiology and basic science, and, as mentioned, more health services research is emphatically needed into areas such as access, quality, and economics.[127]

International research partnerships are essential in the interconnected and interdependent world we live in.[164] Many LMICs have advanced resources

to sustain research activities; for instance, clinical trials for cervical cancer radiotherapy in India (eg, HDR vs LDR brachytherapy, radiation vs chemoradiation).[165,166] India is also home of the Advanced Center for Treatment, Research and Education in Cancer, part of the Tata Memorial Center. Regional research collaborations are developing, for example, the Forum for Nuclear Cooperation in Asia. In addition, several research/teaching twinning partnerships between developed and LMIC have been formed.[137,138,167] Supporting research on cancer by investigators in the LMIC is important as it can build local research capacity and provide a means of adapting scientific knowledge to local circumstances to meet national health priorities.[164] The U.S. National Cancer Institute has also been involved with numerous international collaborations. Protocol-driven clinical research can also strengthen local treatment capacity. The INCTR has been involved in designing clinical trials relevant to LMIC, as has the IAEA.

Clinical trials are often geared to expensive innovations that require complex and expensive supporting infrastructure to deliver (eg, companion diagnostics or gene panel testing). The IAEA has provided leadership in undertaking clinical trials in radiation oncology relevant to low-resource settings. For example, the HYPNO pragmatic trial investigated hypofractioned (20 fractions in 4 weeks) versus normofractionated accelerated radiation (33 fractions in 5.5 weeks) with or without cisplatin for locally advanced head and neck squamous cell carcinoma, a major problem in LMIC. This trial involved 792 patients from 12 centers in 10 LMIC in 4 continents. They found that the resource-sparing hypofractionated approach was noninferior with respect to late adverse events and locoregional tumor control.[168] Other international agencies and cooperative groups have an opportunity to advance access to radiotherapy by developing innovations sensitive to the context of low and middle income where the majority of the world's cancer is diagnosed and resources are most constrained.

What should be implicit in capacity building is capability of the workforce and of the technology to provide state-of-the-art care. It is debated about what is the best technology for the developing world between the relative simplicity of cobalt-60 and the more sophisticated ability of linear accelerators, which are dependent on effective physical infrastructure.

Logically, a range of technologies is needed,[169] including brachytherapy. However, to fill the enormous gap in global cancer care, it is imperative to look forward toward longer term solutions because while incremental steps and small projects are useful, innovative systems solutions are necessary to reach the necessary capacity and capability. The medical device industry has a responsibility to develop technologies that are accessible to countries with limited physical infrastructure and human capacity. The preponderance of equipment that is costly and complex to maintain effectively excludes low-income countries from scaling up radiotherapy services.

An example of novel partnerships emerged from the White House's Interagency Working Group on Alternatives to High-Activity Radioactive Sources[170] that brought together experts interested in reducing the availability of potentially dangerous radiation sources (including medical radionuclides of cobalt-60 and cesium-137), radiation oncologists and medical physicists, and also groups interested in nuclear nonproliferation. Pomper et al developed a new concept, "Treatment, not terror," which highlights the importance in providing safe alternatives to radionuclides, which, for cobalt-60, require expertise for delivering linear accelerator treatment.[171] The relatively lower initial cost of cobalt-60 is offset by a very high cost of disposal of the source at the end of its useful life, a number that is often not included in the purchase price. Certainly, treatment with both cobalt and linear accelerators is important for cancer care; however, as the huge shortage of capacity is addressed, it is worthwhile to look toward the future with improvements possible in technology, telecommunications, economic models, and efficient use of expert personnel. Recognizing the need for improved infrastructure to support linear accelerators, a workshop was conducted by the ICEC in Geneva at CERN[172] to address this complex topic. This included people with expertise in accelerator design, technology modularization, telemedicine, industrial design, and education/training. Task Groups will address unique solutions for training, education, the use of current technology, and the potential for innovative technology. Feain et al have highlighted new approaches to radiation technology for LMIC, including software, information management, and technological solutions.[173]

Closing the gap in cancer care also includes increasing the opportunities for a career in global health and recruiting, training, and retaining people

willing to serve within the challenging environments. Detailed discussions for issues raised in the sections in this chapter on capacity and capability building are in the radiation oncology reviews mentioned earlier, in *Clinical Oncology*[147] and *Seminars in Radiation Oncology*.[148]

ARTIFICIAL INTELLIGENCE IN GLOBAL ONCOLOGY

Artificial intelligence (AI) has emerged as a potentially transformative force in the field of oncology, aiming to reshape how we detect, diagnose, treat, and manage cancer. By harnessing the capabilities of AI, health care professionals worldwide may be able to make more precise and timely decisions, to improve patient outcomes.[174] AI encompasses the development of computer systems capable of performing tasks traditionally reliant on human intelligence, such as learning, reasoning, and problem-solving.[174]

Machine learning (ML) is a subset of AI that focuses on the development of algorithms and statistical models that enable computers to learn from and make predictions or decisions based on data, without being explicitly programmed. In essence, it is a way to teach machines how to improve their performance on a specific task through experience and data.

In the context of global oncology, AI algorithms can be meticulously crafted to analyze extensive medical data sets, including patient records, diagnostic imaging, genomic profiles, and clinical trial data. These algorithms can uncover patterns, predict outcomes, and assist health care professionals in making well-informed decisions in a timely manner.[175,176]

Applications of Artificial Intelligence in Low- and Middle-Income Countries

Early Detection

AI holds enormous promise in the early detection of cancer. ML algorithms adeptly scrutinize medical images, such as mammograms or computed tomography scans, to identify suspicious lesions or tumors that might otherwise go unnoticed.[177] Early cancer detection in LMICs has a far-reaching impact, potentially improving survival rates, reducing treatment costs, and enhancing the overall quality of life for patients.

Clinical Decision Support Systems

AI-powered clinical decision support systems aid health care professionals in formulating treatment recommendations by methodically analyzing patient data, medical literature, and treatment guidelines. The clinical decision support system could be a valuable tool for enhancing health care delivery and addressing the unique challenges faced by these regions in providing high-quality medical care with limited resources.

Resource Allocation

AI has the capacity to optimize resource allocation within oncology by evaluating data pertaining to patient demographics, disease prevalence, and treatment outcomes. This information could empower health care providers to allocate scarce resources efficiently and equitably, ensuring that patients receive timely and appropriate care, even in resource-constrained settings.

Automating Treatment Planning

A large amount of a radiation oncologist's and dosimetrist's time is spent in preparing radiation treatment plans for patient care. Limited human resources in LMIC could be scaled up to serve a much larger patient population if treatment planning could be automated, thus improving timely access to care. Efforts to harness AI to do this exist, and notably, the Artificial Intelligence Based Radiotherapy Treatment Planning for Cervical, Head and Neck and Prostate Cancer study (ARCHERY) is evaluating the use of AI for contouring and determination of beam geometry across sites in LMIC.[178]

Other Applications

Other aspects of radiation oncology not considered earlier include automation of quality assurance, image guidance, adaptive treatment, prediction and management of side effects, response assessment, and follow-up.[175]

AI in global oncology holds tremendous promise. As technology advances, AI algorithms will become increasingly refined and accessible, resulting in greater accuracy in early detection, enhanced treatment planning, and pioneering new treatments approaches. The integration of AI

with other emerging technologies, such as telemedicine and remote planning, could further enhance the delivery of cancer care on a global scale.[179]

Challenges of Artificial Intelligence in Low- and Middle-Income Countries

Despite encouraging developments, it is crucial to acknowledge the need for robust, long-term evaluations before definitively asserting that these approaches will mitigate late-stage diagnoses or offer other hoped-for benefits. Without rigorous scrutiny, there is a risk of deploying expensive technology that offers little value or, worse, proves detrimental or is more costly without added benefit. It could fail to meet expectations, not enhance the efficacy of care, become financially unsustainable, or impractical to scale, ultimately squandering valuable resources that could be more effectively utilized to enhance patient outcomes.

It is imperative that AI projects prioritize building local capacity for technology usage and testing and establish comprehensive plans for outcome evaluation through clinical trials. To date, comprehensive approaches and prospective or randomized controlled trials involving patients in low- and middle-income countries remain the exception. Without rigorous testing, we cannot assume that AI-based interventions will render complex care pathways more affordable and efficient, ultimately improving individual lives.[179]

While AI presents immense potential in global oncology, it also presents several challenges that demand attention. Ethical considerations, patient privacy, data security, and regulatory frameworks are crucial to ensuring the responsible and equitable use of AI in cancer care.

Ethical Considerations

The ethical implications of AI in oncology are multifaceted. Health care professionals and policymakers must grapple with questions about the fairness of AI-driven health care access, the potential for bias in AI algorithms, and the ethical use of patient data. Ensuring that AI benefits all patients, regardless of socioeconomic factors, age, gender, race, ethnicity, indigeneity, nationality, or disability, is a paramount ethical concern. AI

algorithms can inherit biases present in historical health care data, potentially leading to disparities in diagnosis and treatment among equity-deserving groups. Identifying and mitigating bias in AI systems is an ongoing challenge. Efforts to diversify training data sets and develop fairness-aware algorithms are essential to promote equitable health care outcomes. Development and testing of AI solutions within low-resource settings need particular attention.[179] Similarly, AI algorithms can be complex and difficult to interpret, making it challenging to explain their decisions to patients, decision makers, and health care providers. Ensuring transparency and explainability in AI-driven diagnoses and treatment recommendations is vital for fostering trust and acceptance.

Patient Privacy

The use of AI in health care involves the collection and analysis of vast amounts of patient data, including sensitive medical records and genomic information. Protecting patient privacy is essential. Stringent data anonymization and de-identification techniques, along with robust encryption methods, are necessary to safeguard patient confidentiality.

Data Security

Health care data are a prime target for cyberattacks. AI systems must adhere to stringent data security protocols to protect against breaches and unauthorized access. Regular security audits, encryption, and secure data storage practices are imperative to maintain data integrity.

Regulatory Frameworks

The deployment of AI in health care is subject to varying regulatory landscapes across different countries. Harmonizing regulatory frameworks to ensure AI systems comply with safety, efficacy, and ethical standards is a significant challenge. In addition, global standards on data structure and essential variables for cancer information systems require attention, to allow for national and international benchmarking of quality of care, access to care, and value of care. Developing clear and globally recognized guidelines is crucial for fostering trust in AI-driven oncology.

The intersection of AI and global oncology holds promise and presents challenges that we must address. AI has started to show its potential to transform cancer care by enhancing early detection, optimizing resource allocation, and providing valuable clinical decision support. However, we must remain vigilant in addressing the ethical, privacy, security, and regulatory considerations that come with this transformative technology.

The future of global radiation oncology is intertwined with AI, and by addressing these challenges head-on, we can make it a future of improved patient outcomes and enhanced health care worldwide. As we move forward, collaboration among stakeholders is crucial. Governments, health care institutions, technology developers, ethicists, and patients must work together to create a responsible and equitable AI-driven ecosystem for global cancer care. By doing so, we can ensure that AI benefits all patients, regardless of their geographic location, personal characteristics, or economic status. While challenges lie ahead, the potential rewards are immense. With continued research, innovation, and a commitment to ethical AI implementation, we can revolutionize cancer care and take significant strides toward a world free from the current high burden of cancer.

THE COVID-19 GLOBAL PANDEMIC AND GLOBAL ONCOLOGY

The global COVID-19 pandemic led to lockdowns and restrictions to movement, inevitably impacting overall cancer care globally. It exposed health disparities across the globe, including among indigenous peoples, immigrant populations, and by income, race, gender, and among other equity-deserving groups in LMIC. The impact on vulnerable populations within HICs as well as LMICs confirmed the relevance of global health, and global oncology, regardless of country income group.

In LMIC, families were financially insecure as many wage earners could not work, particularly those who were entrepreneurs in these settings. Health care was no longer a priority as households focused on putting food on the table rather than expensive out-of-pocket costs related to cancer care. Therefore, there were disruptions to care for those who had initiated treatment and delays in seeking care.[180] Due to underreporting, limited health data infrastructure, and limited research in LMICs, we may never

know the full mortality impact on patients with cancer in LMIC during this period.

There were ongoing cancer research projects and those at the implementation stage spearheaded by the global oncology community when the pandemic started. These included research activities, in-person educational sessions for clinical skills transfer, scientific meetings, and radiotherapy machine installations/commissioning, among others. These activities were unexpectedly put to a halt, therefore resulting in further delays in realizing the positive impact of ongoing efforts that had been in motion to support oncology capacity building in LMICs.

On the other hand, the pandemic inspired innovative solutions in clinical care delivery relevant to the broader oncology field, irrespective of country income group. For example, educational seminars were conducted virtually, including major oncology conferences. Clinicians who could not travel due to costs had an opportunity to attend and share ideas. This has accelerated knowledge sharing across regions with potential to improve care. Follow-up clinics and simple consultations, which may not require an in-person visit, have been conducted virtually, potentially reducing the cost of transport to cancer centers. During the pandemic, shorter fractionation regimens in radiation oncology were implemented with the support of several oncology groups as guided by current evidence.[181,182] It remains to be seen whether changes in practice toward hypofractionation will be durable following the pandemic.

Redefining the Problem

The size and scope of the global burden of cancer, with the very limited progress since obvious arguments for the need and benefit for radiotherapy by the GTFRCC,[33] suggests that totally new approaches building on experience are required. The basics of how to provide radiation therapy and how to wisely adapt it have been described above. Two issues that we and colleagues perceive as impediments to progress are first, the dichotomy of investment in infectious diseases and NCDs and the often siloed efforts by institutions, professional groups, NGOs, and philanthropy, and, second, to some extent, the competitive situation of grants. Recognizing the need for idea sharing on a global scale, the ICEC has proposed a model designated

as “flex-competence” wherein the overlap in resources for basic health care, infectious diseases, cancer care, and pandemic response is considered an essential component with the flexibility and competence built into the health care system from the outset so that the day-to-day capacity for routine health care includes the capability to rapidly rebalance efforts in the face of pandemics or other potential natural or human-induced disasters (Figure 34.4).[112] Building on global partnerships for mentorship, ongoing training, and supply lines, such a system can rapidly adapt while maintaining the routine care needs. The COVID-19 pandemic was a good lesson of the need to sustain care for the ongoing health care needs while mustering the pandemic/disaster response. Basic cancer care requires maternal-child care, prevention, diagnostics, imaging, and expertise in infectious diseases. The more “expensive” aspects such as radiation therapy, which build on the imaging and diagnostics for routine care, can be cost-effective early additions rather than later-in-development add-ons, especially with the potential for “smart technology.”[92]

The global impact of patient-centered cancer care includes what was described by GTFRCC and more.[33,183] Broadening career opportunities for radiation oncology for early career leaders has been discussed earlier, but what is required for new programs in resource-limited environments is the expertise of mid-career and senior members of both academia and clinical practice who often have the hands-on experience in cancer treatment that was necessary before the advanced high-technology era over the past few decades. Finally, a resource all-too-often underutilized, which may be available largely on a voluntary basis, is that of the retirees whose experience, wisdom, patience, and time should be incorporated as proposed.[184] From experience over the past decade, this is certainly a win-win situation.

Bringing resources together, often through their power of convening, are global agencies such as the IAEA via their Human Health Division. The recently launched initiative “Rays of Hope” is aimed to help build capacity[185] with an Anchor Centre and network model[186] for which the broad range of radiation oncology professional societies and select NGOs have agreed to work together. It is not possible to list the many academic institutions, NGOs, and efforts from the individual professional societies in this chapter. A key message is that a good deal of the problem and the

necessary solutions is well known. It remains for those working in global oncology, often on their own time and resources, to look for ways to work together to solve a problem far greater than any one group could accomplish. A metric that often draws attention to the scope of the problem is that with the immediate global need now of more than 5,000 linacs, if one well-staffed unit was commissioned per week it would take a century to address the current need. The proposed "century-challenge" is this: How quickly could we work together to accomplish that century?

CONCLUSION

Cancer in the developing world is an urgent problem, reaching critical proportions. Almost 60% of all cancer cases occur in the developing world. Vast numbers of people in LMIC have either limited access or no access to radiation therapy. At a time when new gains in oncology outcomes in the developed world are often incremental, oncologists have the chance to help make some of the largest survival gains in history in the developing world. In addition, the potential for health care gains through cancer prevention and early detection, and the relief of suffering through palliative care is enormous. Global access to quality cancer care is a moral imperative. The challenge will now be to deliver this in a thoughtful and contextually appropriate way.

ACKNOWLEDGMENTS

This chapter is dedicated to Dr C. Norman Coleman (1945-2024). May we all take up the challenge of increasing justice and equity in global radiation oncology, as Norm did with skill, good humor, and gusto. As Norm would say, the world needs *you*.

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* Deceased.

CHAPTER 35

Radiation Oncology Undergraduate, Graduate, and Continuing Medical Education

Eulanca Y. Liu and Ann C. Raldow

Radiation oncology is a unique specialty that requires a broad knowledge base, as it is one of the few specialties that delivers care to patients from all age groups and all genders and interfaces with a multitude of medical specialties. The radiation oncologist must have the requisite clinical skills necessary to evaluate a new patient at the time of consultation, appropriately stage a tumor,[1] assess treatment planning scans for the extent of tumor to delineate target volumes and organs at risk accurately,[2] and evaluate patients during and after treatment for radiation toxicities and signs of tumor recurrence.[3] A subset of these physicians must also have the surgical skills for brachytherapy implant placement, such as suturing, operating a bedside ultrasound, and performing endoscopies.[4] To do this, radiation oncologists must not only have a solid foundational knowledge of oncology, anatomy, tumor biology, physics, and radiation delivery but also be well versed in a variety of additional areas including communication, collaboration, patient advocacy, and health system management.[5,6] Other professions that work as part of the radiation oncology care team, including medical physics,[7,8] dosimetry,[9] radiation therapy,[10] nursing,[11,12] social work,[13] physical therapy,[14] as well as those who function as part of the brachytherapy surgical team, such as circulating nurses and surgical technicians,[15,16] also have specific skill sets that are acquired during training and continue to develop while working in the radiation oncology department. Although the focus of this chapter is education for radiation oncologists, to provide optimal patient-centered care, the educational process for all of these professions ideally is coordinated in a complementary manner, with each member of the interprofessional and interdisciplinary radiation oncology team optimally trained to deliver high-quality, effective, and compassionate patient care (Figure 35.1).

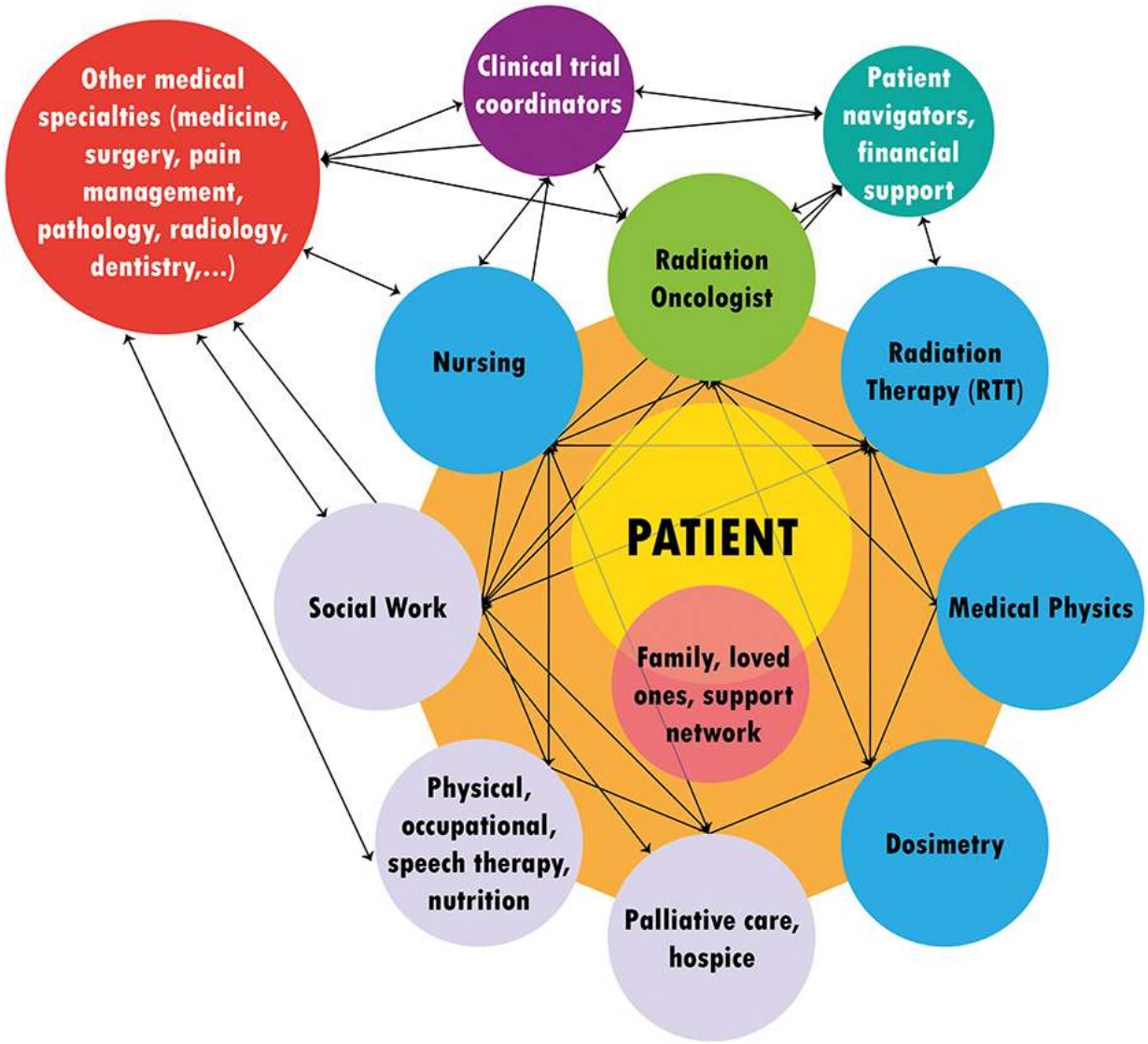


FIGURE 35.1 Interprofessional care of the radiation oncology patient.

Descriptions of radiation oncology educational training programs can be found in the literature dating from the 1950s,[17] and currently, radiation oncology training programs exist worldwide.[18-26] Despite the abundance of established training programs, there is little literature discussing the core aspects of medical education and its application to radiation oncology. The goals of this chapter, therefore, are to describe fundamental educational theory and processes necessary to develop an effective radiation oncology educational curriculum, to review current educational practices in radiation oncology, and to identify potential areas for radiation oncology educational scholarship. Physician training at the undergraduate (medical school), graduate (residency and fellowship), and continuing medical education (CME) (attending physician) levels will be used primarily to frame this discussion, but the concepts, theory, and methods described can be applied to education of other health professions involved in radiation oncology clinical care.

BACKGROUND

The day-to-day practice of medical education in radiation oncology needs to be considered within the broader context of learning theories. It is essential to look beyond the oncology literature, and even outside the medical literature, to understand best practices for medical education and curriculum development.

Learning Theory

Much of the literature surrounding learning has differentiated between "andragogy," or adult learning defined as "the method and practice of teaching adult learners," viewed as unique from "pedagogy," which is defined as "the method and practice of teaching" but which literally means "leading children." There is considerable debate surrounding this differentiation. Rather than present a detailed discussion of the history and controversies in learning theory, concepts of learning theories will be discussed in relation to the range of adult learners in radiation oncology from medical students to practicing radiation oncologists. The basic concepts of most learning theories are based on behavioral change and transformative experiences. The goal of any educational intervention is to effect a behavioral change in the learner through some form of experience. Examples within radiation oncology include improving physician-patient interactions (behavior) through an objective simulated clinical exam (experience),[27] improving brachytherapy technique (behavior) through simulation-based education (experience),[28] and improving contour accuracy (behavior) through a simulated contouring workshop (experience).[2,29]

Learning models can be helpful for understanding the process by which educational interventions can result in changes in behaviors. Kolb's experiential learning model (Figure 35.2) describes a four-step cycle of learning that involves a concrete experience, reflective observation, abstract conceptualization, and active experimentation.[30] Similarly, Merriam et al[31] described three keys to transformational learning—experience, critical reflection, and development. Collins[32] frames adult learning in the context of studying theory and applying it to practice. Others have proposed that the two fundamental components of adult learning are critical thinking and self-directed learning.[33,34] Taken together, educational opportunities that allow for concrete experiences, application, and the opportunity for reflection are best aligned with these principles.

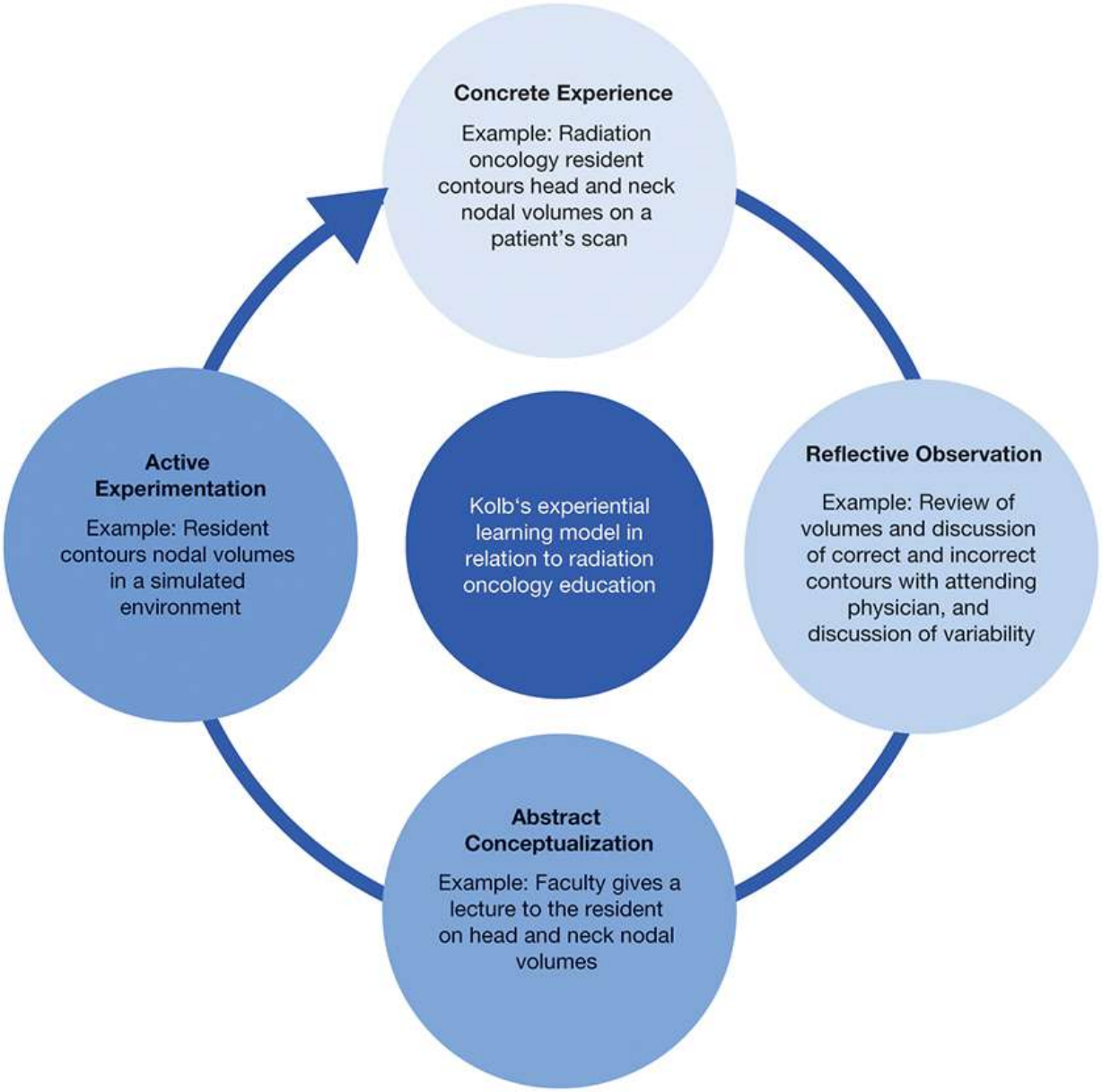


FIGURE 35.2 Kolb's experiential learning model in relation to radiation oncology educational activities. (Adapted from Wijnen-Meijer M, Brandhuber T, Schneider A, Berberat PO. Implementing Kolb's experiential learning cycle by linking real experience, case-based discussion and simulation. *J Med Educ Curric Dev*. 2022;9:23821205221091511. Copyright © 2022 SAGE Publications. Reprinted by permission of SAGE Publications.)

Learning theory can be enhanced by an understanding of the six assumptions regarding characteristics of the adult learner as defined by Knowles et al[35] (Figure 35.3). These six assumptions can be applied to learning in radiation oncology. For example, in the case of a radiation oncology residency training program, the residents must understand why, what, and how they are going to learn their chosen profession. They need to have some autonomy and control over their learning within the structure of the residency training program. Therefore, when the radiation oncology educator is developing an adult learning experience, consideration should be given to Knowles' six assumptions, what behavior the curriculum or educational intervention intends to change, and how the learning experiences will stimulate critical thinking, self-directed learning, and transformation.

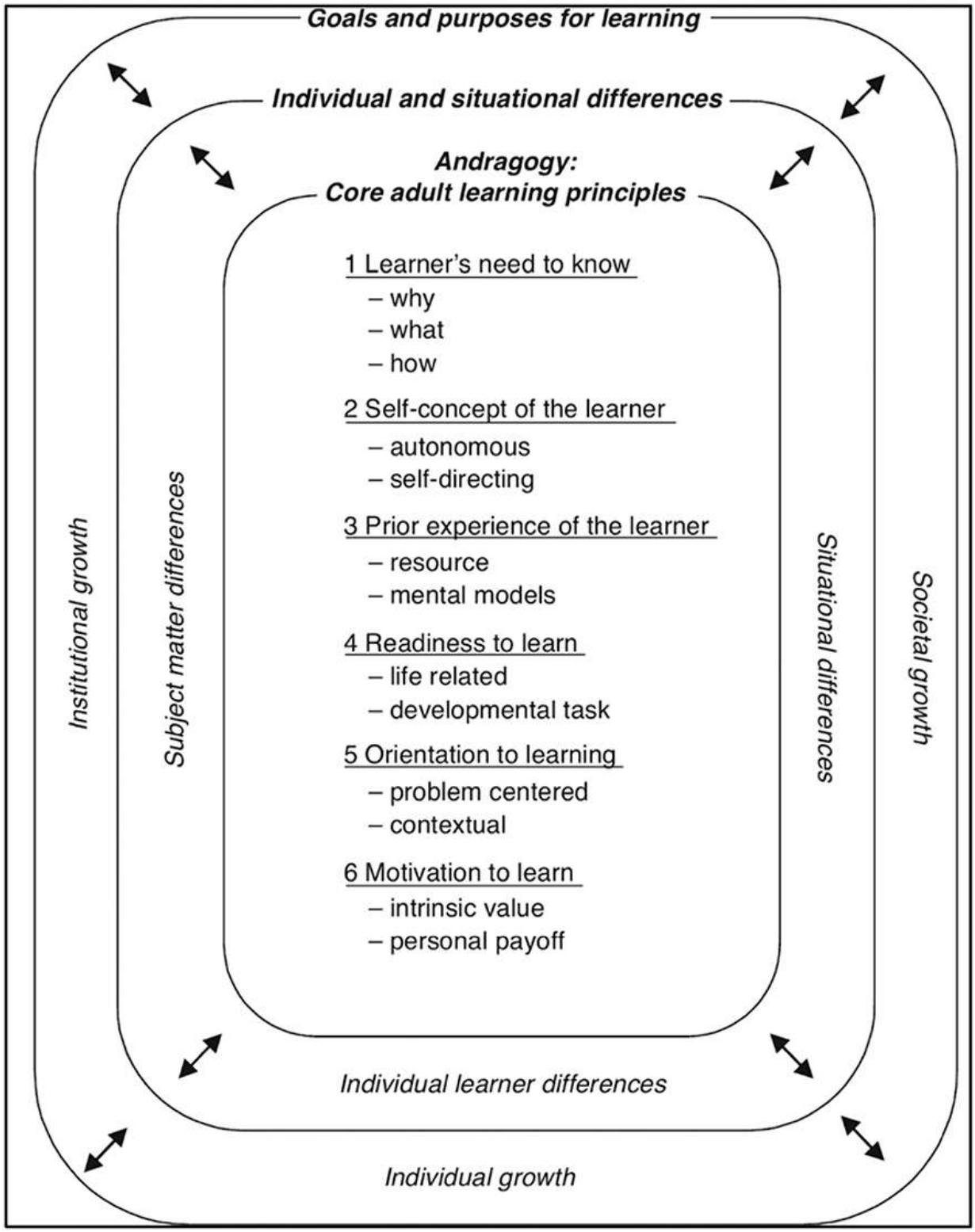


FIGURE 35.3 Knowles and Swanson's six assumptions of adult learning. (Used with permission of Taylor & Francis Informa UK Ltd—Books from Knowles MS, Holton EF III, Swanson RA. *The Adult Learner: The Definitive Classic in Adult Education and Human Resource Development*. 5th ed. Gulf Publishing; 1998; permission conveyed through Copyright Clearance Center.)

Lastly, to optimize learning, it is important for medical educators to consider the learning environment when designing an educational program. The Hebbian version of the Yerkes-Dodson law suggests that learners have an optimal level of arousal, or stress, that will promote optimal learning (Figure 35.4).[36,37] At very low levels of stress and arousal, the learner is not stimulated enough to learn. An example is an early morning resident lecture with no postlecture knowledge assessment. The stakes for the resident learner are low, and the resident may not engage with the presentation to learn. As arousal increases, an optimal point is encountered on the learning curve where stress optimally enhances learning without negatively impacting it. As stress continues to increase, learning begins to decline because of stress impeding higher level cognitive process, such as attention, working memory, and problem-solving. Thus, the radiation oncology educator must consider stressors on the trainees (both positive and negative) and determine if the amount of stress within a given learning environment will facilitate optimal learning. Examples of pertinent stressors include medical student anxiety about securing a residency position, resident anxiety about certification boards, presenting in front of a group versus a single listener, or a multiple-choice test with a minimum score required to obtain credit as a component of a self-Assessment CME (SA-CME) module. Educators should work to minimize undue (negative) stressors while emphasizing the rationale for planned positive stressors, such as postlecture knowledge assessments.

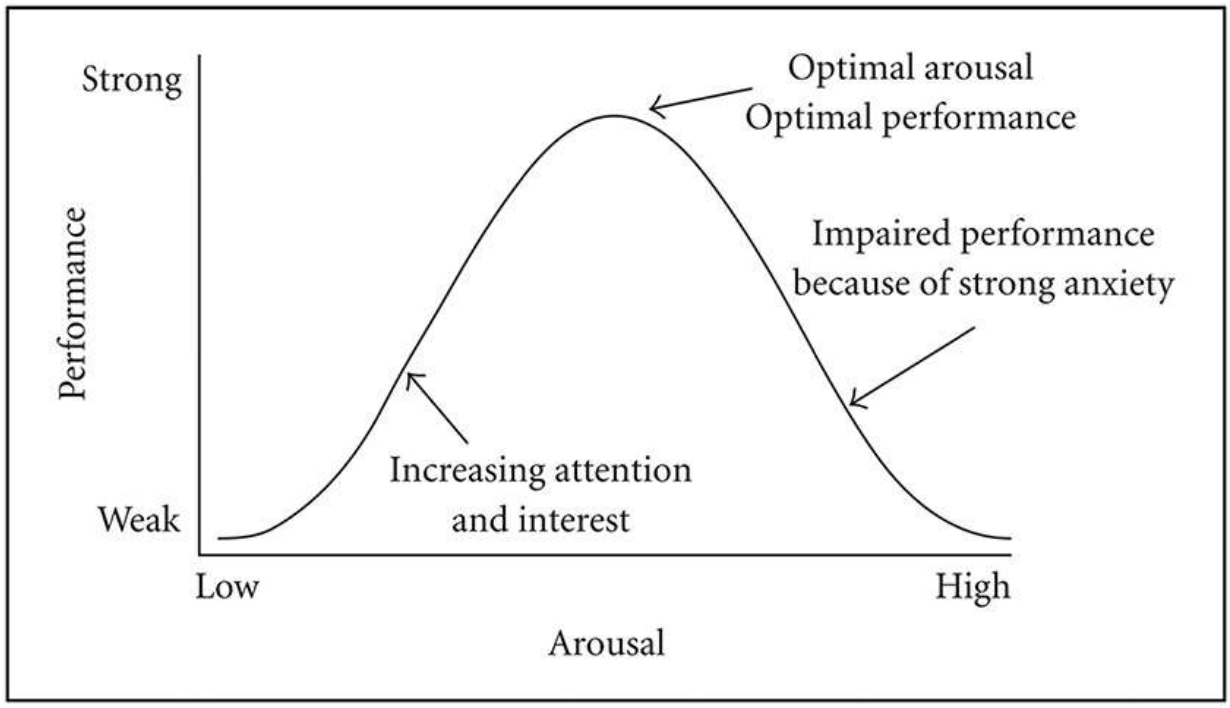


FIGURE 35.4 Hebbian version of the Yerkes-Dodson law correlating arousal with performance.

Recently, investigators have piloted the "flipped classroom curriculum" to promote greater engagement and critical thinking.[38,39] These didactics typically include prerecorded video lectures, key journal articles, and slides containing key points reviewed by residents independently prior to the live didactic session. The live session then consists of case review or live quizzes that review the concepts presented in the presession study materials. Ongoing work is underway to determine the flipped curriculum's efficacy in promoting knowledge comprehension and retention for medical residents.

SCHOLARSHIP OF RADIATION ONCOLOGY EDUCATION

Methods for successful curriculum development and implementation draw from both social sciences and business theory. The research methodology for scholarship of radiation oncology education incorporates qualitative research, an approach that may not be familiar to radiation oncology educators, whose training is focused in the biologic and physical sciences. This section reviews the concepts of scholarship as relevant to radiation oncology education and provides an introduction to qualitative methods and conceptual frameworks useful to radiation oncology educational scholarship.

Scholarship in Medical Education

When undertaking any medical education intervention, careful attention should be given at the outset for opportunities for scholarship.[40] Boyer[41] defines four types of scholarship: the scholarship of discovery, the scholarship of application, the scholarship of integration, and the scholarship of teaching. The scholarship of discovery refers to scholarly activities for the purpose of finding new knowledge and best encompasses our traditional view of research.[41,42] The scholarship of integration refers to scholarship that draws on other research and draws across disciplines or extends research to new areas and beyond boundaries helping to illuminate relationships.[41,42] The scholarship of application takes knowledge and applies it in new and practical ways.[41,43] Finally, the scholarship of teaching refers to teaching practices approached with a scholarly lens. This expanded definition of scholarship allows for many activities in medical education to be viewed as grounds for scholarship outside research projects.

Scholarship is defined as a tangible product of knowledge or its presentation that is peer reviewed and disseminated publicly.[44] Hutchings and Shulman[45] defined the following three criteria as essential for scholarship:

1. The work must be made public.
2. The work must be available for peer review and critique according to accepted standards.
3. The work must be able to be reproduced and built on by other scholars.

Criteria for excellence in scholarship can be applied to educational scholarship and help to assess the quality of scholarship. Glassick[46] defined six criteria by which to assess scholarship: clear goals, adequate preparation, appropriate methods, significant results, effective presentation, and reflective critique.

Application of these criteria assists the radiation oncology educator to evaluate the potential to turn a medical education project into a work of scholarship. For example, a novel resident training curriculum implemented at a single institution and not disseminated in peer-reviewed literature does not qualify as scholarship based on the abovementioned definition. However, if the residency program director publishes learner assessment and program evaluation data in a peer-reviewed journal or disseminates the curriculum materials using *MedEdPORTAL*, an open-access journal of teaching and learning resources in the health professions published by the Association of American Medical Colleges, the implementation and evaluation of the curriculum qualify as scholarship.

The difference between scholarly teaching and the scholarship of teaching must also be defined. Fincher and Work[47] defined three levels of teaching (Figure 35.5). The first level is basic teaching. In radiation oncology, basic teaching examples include giving a lecture, facilitating a case conference, demonstrating proper history-taking or brachytherapy techniques to trainees, or educating patients regarding the radiation treatment process and potential toxicities. The second level is scholarly teaching. This implies that the instructor is using evidence-based practices when teaching trainees. Examples in radiation oncology could include using best practices when delivering a PowerPoint presentation,[48] providing patient educational materials at or below the sixth-grade reading level,[49] or

using the 1-minute preceptor model to teach a clinical pearl to a resident after an initial consultation.[50] The third level is scholarship of teaching, which includes developing and disseminating new knowledge through discovery, integration, or application.

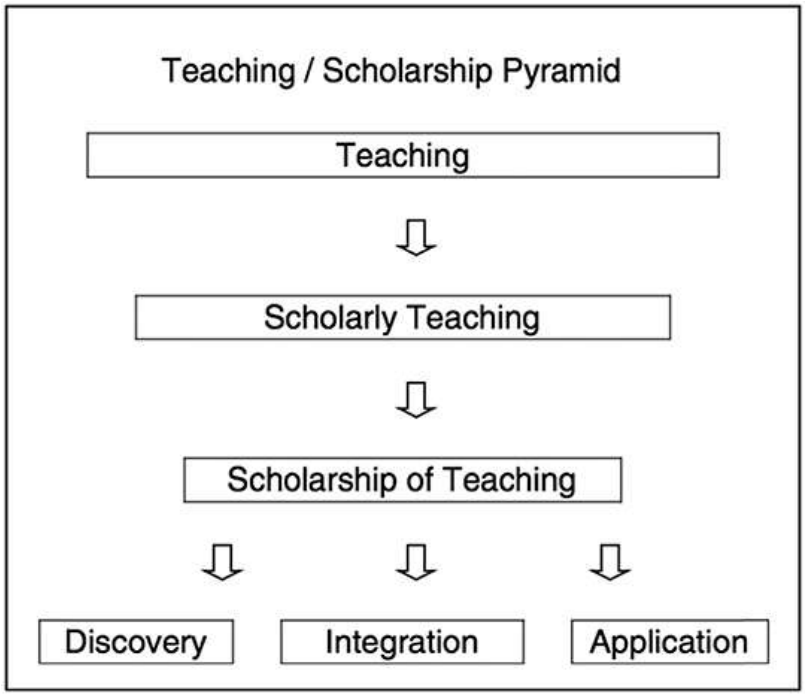


FIGURE 35.5 Fincher and Work's pyramid of teaching and scholarship. (From Fincher RM E, Work JA. Perspectives on the scholarship of teaching. *Med Educ.* 2006;40[4]:293-295. Copyright © 2006 Blackwell Publishing Ltd. Reprinted by permission of John Wiley & Sons, Inc.)

Drawing from Boyer,[41,46] discovery refers to obtaining new knowledge in a discipline. Scholarship examples in this context include the evaluation of new innovations or interventions. Examples in radiation oncology include demonstrating that students who participate in a radiation oncology clerkship with a didactic curriculum report increased confidence to function as a resident,[51] utilizing a novel internet-based contouring tool that can improve target delineation accuracy,[52] and demonstrating that inclusion of a radiation oncology lecture in the medical school curriculum is feasible and increases objective knowledge of the specialty.[53]

Scholarship of integration refers to making connections across scholarship and synthesizing data across studies.[46] Examples include a literature review of radiation oncology teaching in the undergraduate setting[54] or a Best Evidence in Medical Education systematic review on faculty development initiatives aimed to improve teaching effectiveness.[55]

The scholarship of application bridges theory with practice, often drawing together fields and disciplines.[41,56] In the context of radiation oncology, this could include assessing the value of simulation in brachytherapy training,[28,29] bringing simulation that is well utilized in other specialties to radiation oncology, and evaluating the impact on learner performance.

Without scholarship in radiation oncology education, educational programs will advance slowly. Individual training programs will be unaware of the best practices implemented at other training programs and may develop redundant educational material, which introduces inefficiency in a process that is already limited in resources. Just as clinical oncology and basic science research is disseminated as manuscripts in peer-reviewed journals, novel radiation oncology educational initiatives must be

rigorously developed and evaluated in preparation for dissemination to the international radiation oncology community.[40] However, because of limitations of journal publication alone in effecting change,[57] programs such as the Radiation Oncology Education Collaborative Study Group[58] have been established to improve dissemination and implementation of educational research and programs. These processes allow other institutions to adopt or adapt novel educational initiatives and subsequently build on them for further dissemination.

Qualitative Versus Quantitative Research

For health profession educators, scholarly research comes from both quantitative and qualitative sources, and many studies benefit from the use of both simultaneously.[59] Some studies refer to the term "mixed methods," which is a reference to the use of both quantitative and qualitative methods. While many radiation oncologists are familiar with quantitative research, they may be less aware of qualitative research methods. Qualitative methods are distinct from quantitative methods in their research paradigm, research design, method of data collection, types of data collected, and methods of data analysis.

With respect to research design, most quantitative research is hypothesis driven with the researcher developing research methods and collecting data to support or refute the hypothesis. In the case of qualitative methods, researchers start at the observational level and then move to explanation by building a theory. Several strategies for qualitative inquiry are commonly used, and a complete description is beyond the scope of this chapter. Some of the more commonly referenced terms in qualitative methods include ethnography, narrative inquiry, and grounded theory approach. Ethnographic research encompasses a variety of research techniques aimed at characterizing the authentic everyday experiences of subjects through observation and interviews.[60,61] An example of ethnographic research is a study utilizing detailed interviews with teaching faculty and observations of their teaching patterns on the ward to identify the characteristics of effective clinical teachers.[62] Narrative research is the study of participants through the analysis of documents, such as journals, letters, conversations, and transcripts of interviews.[61] Usually, the participant describes one or more pivotal life events, and the researcher interprets the construction of this narrative. Finally, *grounded theory* is a term used in qualitative methods to describe the process in which a "theory" is generated from data of the experiences of the participants.[61] Unlike quantitative research that starts with a theory, the grounded approach uses data to generate theory by looking for emerging themes through a process of constant comparative analysis.[60] Data are collected through interviews, document analysis, and focus groups. In a grounded theory approach, as data are collected, a theory is generated, then more data are collected, and the theory is revised as needed, continuing the process until it appears that the theory is relatively robust. An example of grounded theory methodology in radiation oncology is the use of focus groups and in-depth interviews to develop a four-step learning process for implementation of high-precision radiation technology[63]:

1. Anxiety as new skills are acquired
2. Learning to interpret new imaging and findings while continuing to experience uncertainty
3. Questioning assumptions and critical reflection resulting in new understanding
4. Constructing new knowledge through research, development, and dialogue

The processes and methods used in qualitative studies include distinguishable methods that help to build observations to support explanations.[64] Methods of data collection include focus groups, one-on-one interviews, surveys with open-ended questions, observations of behaviors, and document analysis (eg, themes in portfolios). Unlike quantitative data that are numeric, the data collected in a qualitative study are usually text or words. The analysis of qualitative data is an iterative process to conceptualize

and reduce data, analyze it to develop themes, elaborate on categories, and find relationships.[60] Common to qualitative methods, steps are taken to ensure reliability of the themes developed through stages of analysis. This may include having multiple raters of themes, peer review from others not involved in the study, checking the themes with study participants, and triangulation with established literature. Ultimately, the goal of qualitative research is to develop hypotheses, build theory through descriptions of observations, and describe and explain complex phenomena by analyzing data for themes and relationships. Table 35.1 summarizes key differences between quantitative and qualitative methods.

TABLE 35.1 SUMMARY OF DIFFERENCES BETWEEN QUALITATIVE AND QUANTITATIVE RESEARCH

	Quantitative Research	Qualitative Research
Research paradigm	• Deductive research • Collect data to test hypothesis	• Inductive research • Observations to explain and then develop theory
Research method examples	• Closed-ended surveys (ie, demographics of current radiation training programs) • Observations of time taken to complete a task (ie, contouring)	• Open-ended surveys (ie, resident descriptions of current challenges in training programs) • Observational study (ie, observations of differences of learner's contouring abilities at different stages of training) • Document analysis (ie, analysis of learner's portfolio reflections on dealing with patients with difficult cancer)
Data	• Numeric data	• Words as data

Qualitative research is important to medical education. There are certain educational research questions that are best approached using qualitative research methods,[65] such as:

- "How does charting influence the quality and quantity of communication between different health care professionals?
- How do health care professionals learn to teach on the job?
- What constitutes "professional competence," and how is that different from "professional identity"?
- What influences patients' adherence with their doctor's suggestions?"

Qualitative methods can be used specifically for radiation oncology scholarship in multiple settings (Table 35.2). For example, qualitative methods can be used to develop and evaluate a program to teach radiation oncology residents communication skills with older patients with cancer. One-on-one interviews, focus groups, and surveys with open-ended questions could be used to conduct a targeted needs assessment of learners (see "Curriculum Development") prior to developing a new educational program. The results would inform the development of the syllabus. Later, reflections on the new training program, collected through repeated one-on-one interviews, surveys, and analysis of reflective writing exercises, could be used to systematically evaluate the program once implemented. Years later, the clinical behaviors of oncologists in practice could be observed to reflect on the retention of skills in learners and the impact of the program on their communication skills. Utilizing both qualitative and quantitative methods for program development facilitates development and improvement of a training program in a scholarly manner.

TABLE 35.2 EXAMPLES OF USE OF QUALITATIVE METHODS IN RADIATION ONCOLOGY EDUCATION

Educational Issue	Qualitative Approach
Analyzing "memorable" in-training experiences of medical students on radiation oncology rotations[321]	Thematic analysis of written narratives to describe the training experiences of learners in a clinical education program
Needs assessment for development of a radiation oncology curriculum for medical students[189]	Analysis of written responses to open-ended surveys to analyze for gaps and strengths in current training Thematic analysis of one-on-one interviews with stakeholders
Establishing needs and priorities in a global radiation oncology training programs[322]	Facilitated group discussion with analysis of themes to develop consensus on possible goals and objectives for a training program
Evaluation of a contouring boot camp[21]	Thematic analysis of open-ended survey questions to provide evaluation data
Evaluation of a didactic curriculum for a radiation oncology medical student clerkship[198]	Thematic analysis of open-ended survey questions to provide evaluation data

Conceptual Frameworks

When approaching radiation oncology medical education endeavors through a scholarly lens, it is critical to define one or more conceptual frameworks used to guide the educational process. While medical education scholars often employ conceptual frameworks in curriculum development and program evaluation, it is helpful to be able to identify them. A systematic review found that a lack of a conceptual framework is one of the most common reasons education scholarship is rejected for publication.[66]

Conceptual frameworks are "ways of thinking about a problem or a study, or ways of representing how complex things work the way they do. Different frameworks will emphasize different variables and outcomes, and their interrelatedness."[67] Conceptual frameworks are not mutually exclusive, and there is the potential to apply multiple conceptual frameworks to a single curriculum development endeavor. For example, a radiation oncology educator developing a simulation-based education curriculum to train residents how to perform interstitial breast brachytherapy may use the six-step approach to curriculum development[68] to guide the overarching curriculum development process; the theory of deliberate practice from Ericsson.[69] when developing the specific educational method to develop adequate breast brachytherapy psychomotor skills; and Kirkpatrick's four-step framework[70] when developing a plan for program evaluation. Bordage defines 11 key points pertaining to conceptual frameworks (Table 35.3) that clarify the critical nature of conceptual frameworks to educational scholarship, both to guide curriculum development and to move the field of radiation oncology education forward in a logical and coherent manner.[67]

TABLE 35.3 KEY POINTS REGARDING CONCEPTUAL FRAMEWORKS

- Conceptual frameworks help understand (illuminate) problems.
- Different conceptual frameworks emphasize (magnify) different aspects of the problem or elements of the solutions.
- More than one conceptual framework may be relevant to a given situation.
- Any given conceptual framework, or combination of frameworks, can lead to a variety of alternative solutions.
- Conceptual frameworks can come from theories, models, or evidence-based best practices.
- Scholars need to apply the principles outlined in the conceptual framework(s) selected.
- Conceptual frameworks help identify important variables and their potential relationships; this also means that some variables are disregarded.
- Conceptual frameworks are dynamic entities and benefit from being challenged and altered as needed.
- Conceptual frameworks allow scholars to build upon one another's work and allow individuals to develop programs of research.
- Programmatic, conceptually based research helps accumulate deeper understanding over time and thus moves the field forward.

- Relevant conceptual frameworks can be found outside one's specialty or field.

From Bordage G. Conceptual frameworks to illuminate and magnify. *Med Educ*. 2009;43(4):312-319. Copyright © 2009 Blackwell Publishing Ltd. Reprinted by permission of John Wiley & Sons.

There are numerous conceptual frameworks in the medical education and general education literature that can be applied to radiation oncology educational scholarship. If an applicable conceptual framework is not available for a particular curriculum development program, existing conceptual frameworks can be modified and adapted to fit, or a new conceptual framework can be developed and reported in the peer-reviewed literature. To help guide the development of new literature in radiation oncology education, Table 35.4 provides examples of conceptual frameworks that may be applied when approaching common radiation oncology education issues. In summary, the radiation oncology educator should be able to identify the conceptual framework that applies to their educational intervention.

TABLE 35.4 EXAMPLES OF CONCEPTUAL FRAMEWORKS APPLICABLE TO DOMAINS OF RADIATION ONCOLOGY EDUCATION

Curriculum development
Six-step approach to curriculum development[68] 1. Problem identification 2. Needs assessment of the learners 3. Goals and objectives 4. Educational strategies 5. Implementation 6. Evaluation and feedback
Goals and objectives
Bloom's revised taxonomy of learning objectives[119,120] • Knowledge → Remember • Comprehension → Understand • Application → Apply • Analysis → Analyze • Synthesis → Evaluate • Evaluation → Create
Educational methods/learning theory
Miller's pyramid of clinical competence[126,127] • Knows • Knows how • Shows • Does Kolb's experiential model[30] • Concrete experience • Reflective observation • Analysis and integration • Application to new situations Ericsson's theory of deliberate (mixed) practice with feedback[69] • Motivate through improvement in real-life performance • Take into account the learner's preexisting knowledge (difficulty of the task tailored to the individual) • Allow repetition of the skills multiple times • Accompanied by feedback that is constructive and timely Merrill's first principles to facilitate learning[323]

Curriculum development

- Problem—Learners are engaged in solving real-world problems.
- Activation—Existing knowledge is activated as a foundation for new knowledge.
- Demonstration—New knowledge is demonstrated to the learner.
- Application—New knowledge is applied by the learner.
- Integration—New knowledge is integrated into the learner's world.

Skills acquisition/simulation-based education

Mastery learning[324]

- Baseline testing
- Clear objectives
- Engagement in educational activities
- Clear minimum passing standards
- Formative testing
- Advancement dependent on achievement
- Individualized time frame

Features of effective simulation education[325]

- Feedback to the learner
- Repetition
- Simulation integrated into the overall curriculum
- Learners practice with increasing difficulty and complexity
- Simulations adapted to multiple learning strategies
- Clinical variation built into the sessions
- Control of the environment
- Individualized learning options
- Defined outcomes, benchmarks
- Simulation closely represents practice

Kneebone's evaluation criteria for simulation programs[326]

- Allow for sustained, deliberate practice within a safe environment, ensuring that recently acquired skills are consolidated within a defined curriculum, which assures regular reinforcement.
- Provide access to expert tutors when appropriate, ensuring that such support fades when no longer needed.
- Map onto real-life clinical experience, ensuring that learning supports the experience gained within communities of actual practice.
- Provide a supportive, motivational, and learner-centered milieu, which is conducive to learning.

Assessment

NCME standards: Five sources of validity evidence[327,328]

- Content
- Response process
- Internal structure
- Relationship to other variables
- Consequences

Criteria for good assessment[329]

- Validity or coherence
- Reproducibility or consistency
- Equivalence
- Feasibility
- Educational effect
- Catalytic effect
- Acceptability

Evaluation

Kirkpatrick's four levels of program evaluation[70]

Curriculum development

- Reaction
- Learning
- Behavior
- Results

Grant's ACTION model for evaluating new technologies for learning[330]

- Access
- Cost
- Types of learning
- Integration
- Organization
- Novelty

Continuing medical education

Davis' characteristics of effective (best practice) CME programs[292]

- Needs assessment that can be either subjective (eg, questionnaires) or objective (eg, literature review)
- Focused initiative to meet the needs of the physician
- Interactive educational programs
- Multiple educational strategies
- Multiple sessions
- Time for feedback and practice
- Outcome evaluation

Harden's Crisis Criteria for effective CME[291]

- Convenience
- Relevance
- Individualization
- Self-assessment
- Independent learning
- Systematic

Interprofessional education

Ivey's categorization of interprofessional practices[331]

- Parallel practice
- Coordination
- Consultation
- Collaboration
- Multidisciplinary teams
- Interdisciplinary teams

Parsell and Bligh's elements of interprofessional education[332]

- Relationships
- Collaboration and teamwork
- Roles and responsibilities
- Benefits

MUSC spiral theory[333,334]

- Teamwork: prepare-think-practice
- Transforming ways of knowing: absolute-transitional-independent-contextual
- Ever-increasing acquisition, application, demonstration

Professionalism

Assessment of professionalism[335]

- Evaluations by faculty supervisors
- Nurses and patients
- Peer evaluation

Curriculum development
• Self-evaluation • Standardized patients • Longitudinal observations

CME, continuing medical education; NCME, National Council on Measurement in Education.

CURRICULUM DEVELOPMENT

Using the background medical education theory and key principles to medical education scholarship, the radiation oncology educator can begin curriculum development. The objective of this section is to discuss the educational theory relevant to curriculum development, review curriculum development models, and then explore approaches to curriculum development with application to radiation oncology.

A curriculum can be defined as any planned educational experience.[68] In this context, radiation oncology curriculum examples include a 1-hour lecture on the history of radiation oncology for medical students, a residency training program's annual clinical rotation and didactic lecture schedule, a patient seminar on late effects of radiation oncology, or a national meeting for hands-on brachytherapy simulation and training. The common thread through all of these examples is that the educator has a goal for the curriculum—that is, some type of knowledge transfer.

Curriculum theory proposes three types of curricula in any educational setting (Table 35.5). The first type of curriculum is the "set" or explicit curriculum. The set curriculum is what the educator defines a priori as the instructional plan. A radiation oncology clerkship will have goals and objectives defined for participating medical students to orient them to the experience. The overarching goal of the clerkship is likely "to learn the fundamentals of clinical radiation oncology." A syllabus may be prepared, and the educational strategies employed are chosen to reach the explicit curricular goal.

TABLE 35.5 EDUCATIONAL THEORY'S THREE COEXISTING CURRICULUM TYPES

Type of Curriculum	Radiation Oncology Examples
Set, formal, or explicit curriculum	• Medical student clerkship lecture series • Residency lecture series and rotation schedule • Goals and objectives for society meeting educational session
Hidden or implicit curriculum	• Radiation oncology resident disparages a referring specialty in front of a medical student. • Radiation oncology attending models superb compassion when counseling a patient regarding terminal diagnosis. • Radiation oncology attending belittles a dosimetrist in front of a resident and medical student.
Null curriculum	• Medical school does not include any radiation oncology in their formal curriculum. • Residency program director decides to forgo a formal treatment planning rotation because of training time constraints. • Society does not include a session on palliative radiation because of space constraints at conference center.

The second curriculum in any educational setting is the "hidden" or implicit curriculum. The hidden curriculum is what the learner comes to "know" based on interactions that occur outside formal learning environments.[65] Examples in radiation oncology could include a medical student in a resident workroom overhearing a resident disparaging a referring service or a department choosing not to allocate resident education time to quality and safety or communication skills. The hidden curriculum is often referred to with a negative connotation, but there are positive effects of the hidden curriculum. For example, a resident may observe their attending physician during a particularly compassionate

patient encounter and take away a positive lesson on how to interact with a similar patient in future. Radiation oncology educators must consider their departmental and institutional hidden curriculum when developing a novel set of curriculum. Individual educators may be encouraged to view their behaviors as modeling and note the potential impacts on the hidden curriculum. Areas to consider relating to the hidden curriculum include policy development, evaluation, resource allocation, and institutional slang.[71] These four areas within a radiation oncology department can teach trainees both positive and negative lessons without the trainee ever being exposed to a formal learning environment.

The third type of curriculum is the "null" curriculum, which is defined as what is not taught.[72] The classic example in childhood education is removing art class from a grammar school curriculum, which results in a negative impact on the children by sending a message that art is not important and can, therefore, be neglected. Medical educators within radiation oncology are faced with limited time for education. Thus, during the curriculum planning process, radiation oncology educators must strive for a balance of including material that is important to their learners while not overburdening the learner or institutional resources. Topics that are important to functioning as a radiation oncologist but are often not taught formally during training because of resource constraints include (but are not limited to) treatment planning and plan evaluation, diagnostic radiology interpretation skills, effective communication, collaboration, leadership skills, and career development. The Accreditation Council for Graduate Medical Education (ACGME) permits residency programs to count resident attendance at multidisciplinary tumor boards as adequate training in medical oncology, radiology, and pathology in place of formal clinical rotations.[4] Because of training time constraints, this capitulation is necessary, but it may send a message to U.S. radiation oncology residents that knowledge pertaining to these specialties is less important. This may lead to the long-term detriment of patient care.[73] Radiation oncology itself suffers from the consequences of the null curriculum. Its status as a subspecialty means the formal medical school curriculum frequently does not include radiation oncology material, leading to reduced knowledge of the specialty.[74,75] In graduate medical education (GME), residency training programs outside radiation oncology frequently do not provide formal lectures or didactics pertaining to radiation oncology.[76,77] Radiation oncology educators must carefully consider the educational milieu of the institution and the department when deciding on which educational initiatives to pursue or cut.

Curriculum Development Models

Curriculum development should be a logical and rational process. Often in medical education, curriculum development is a haphazard ordeal or occurs in a reactive, rather than proactive, manner. Multiple curriculum development models have been proposed, such as empirical/analytical/systematic curriculum inquiry, deliberative curriculum inquiry, and reconceptualist curriculum inquiry.[78]

Systematic curriculum inquiry is perhaps the most commonly used medical education curriculum development model. It has been in the literature for more than 60 years, with multiple educators, medical and nonmedical, contributing to its current iteration.[68,79,80] Its six-step, systematic approach helps medical educators ensure critical components necessary for effective curriculum planning are not missed.[68] One criticism of the systematic approach is that it can be a top-down process, with curriculum deans, residency program directors, or clerkship directors dictating curriculum content and structure.

Deliberative curriculum inquiry focuses on the process of curriculum planning, implementation, and evaluation.[81] To be effective, deliberative curriculum inquiry requires a structure for "deliberation."[82] Curriculum stakeholders are given an opportunity to evaluate the curriculum goals and objectives, propose modification to educational methods, and suggest methods for assessment and evaluation. For example, a radiation oncology residency program choosing to employ deliberative curriculum inquiry would create an opportunity for stakeholders within the program (residency, chairperson, program

director, department faculty, institution, and patients) to provide feedback on the program. The ACGME now requires U.S. radiation oncology residency programs to have a program evaluation committee conduct an annual evaluation of the program.[5] Members of the program evaluation committee must include department faculty and residents. To improve the deliberative nature of this process, inclusion of other stakeholders can be considered (eg, patients, institution).

The final curriculum development model is reconceptualist curriculum inquiry.[83] This model of curriculum inquiry aims to explore how the curriculum relates to society. How does the curriculum interact with economic, cultural, and political institutions? An example of reconceptualist curriculum inquiry in radiation oncology is a program director's decision whether to include formal education (eg, a lecture) on health economics in a radiation oncology residency program. By choosing to educate the program's trainees about the economic implications of different radiation treatment modalities, the residency program can have a future societal impact on economic and political institutions.

The systematic, deliberative, and reconceptualist models of curriculum development are not mutually exclusive. Rather, these models can be used simultaneously to achieve the most effective radiation oncology curriculum possible that is properly structured, includes consideration of stakeholder viewpoints, and has potential for societal impact. Further discussion of curriculum development will focus on the systematic model,[68] but implications of the deliberative and reconceptualist models should be considered as well.

Systematic Curriculum Development

Systematic curriculum development for medical education is most clearly defined by the "six-step approach" suggested by Thomas et al[68] as follows: (1) problem identification and general needs assessment, (2) needs assessment of targeted learners, (3) goals and specific objectives, (4) educational strategies, (5) implementation, and (6) evaluation and feedback (Figure 35.6). Although these six steps are presented in a sequential order, in practice, they are often occurring simultaneously. Each step can have effects on or be affected by the other steps. The following discussion focuses on each of the six steps with relevant examples from radiation oncology cited where applicable.

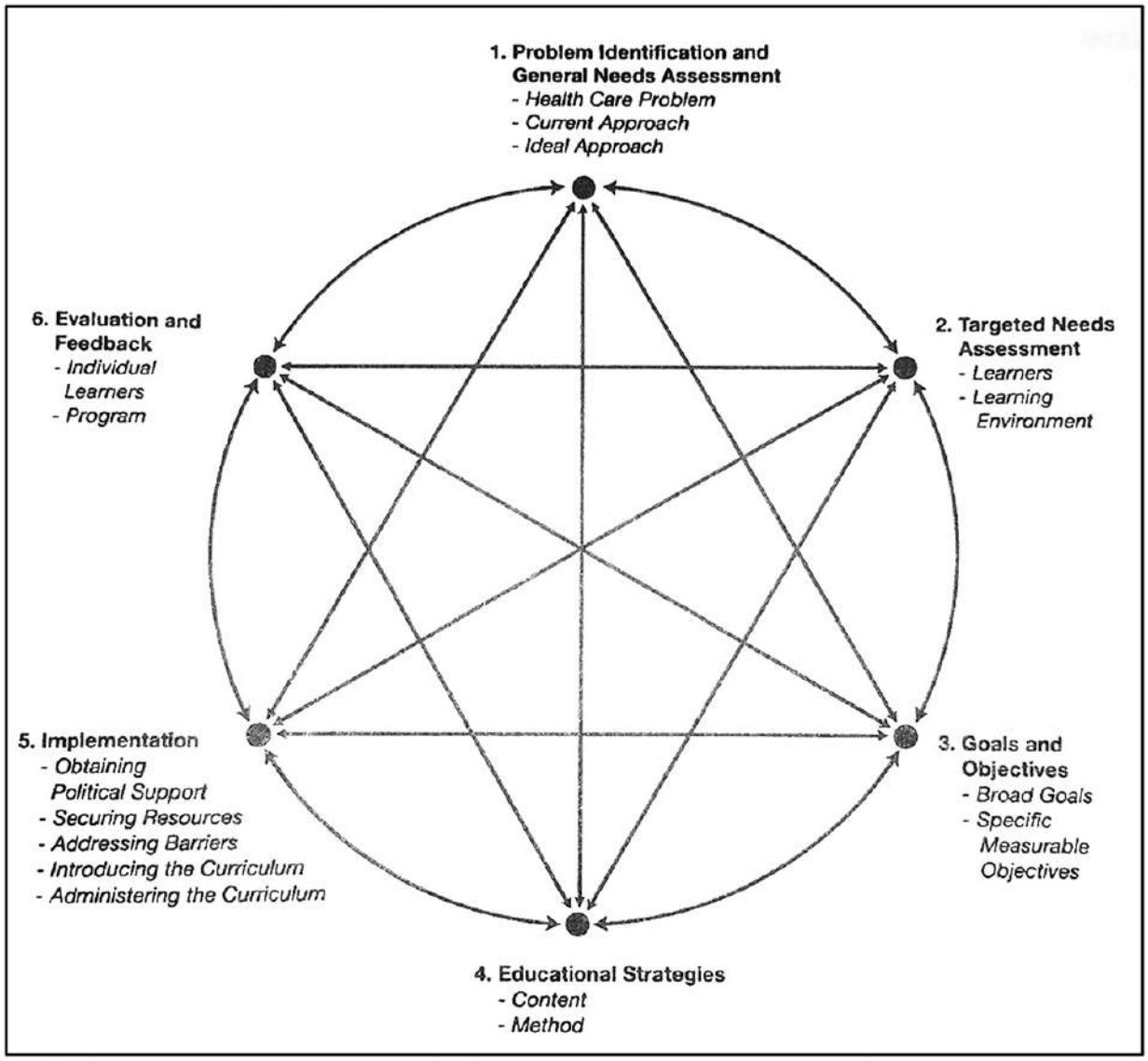


FIGURE 35.6 The six-step approach to systematic curriculum development. (From Thomas PA, Kern DE, Hughes MT, Chen BY, eds. *Curriculum Development for Medical Education: A Six-Step Approach*. 3rd ed. Johns Hopkins University Press; 2016:7, Figure 1. Copyright © 2016 Johns Hopkins University Press. Reprinted with permission of Johns Hopkins University Press.)

Problem Identification and General Needs Assessment

When beginning to develop an educational intervention, an initial problem identification and general needs assessment is done. With respect to radiation oncology, sample problems could include variability in the delineation of radiation target volumes between radiation oncologists[84-87] or lack of exposure to oncology training in medical school curriculum.[88] In either case, once the problem is identified, a general needs assessment is done. This includes determining the current approach to the problem and defining the ideal approach. Often, an educator may identify a problem in their local educational and clinical environment but on review of the literature discovers that another institution or organization is addressing the problem adequately. Rather than develop a new curriculum for the identified problem, the educator can adopt or adapt the existing curriculum to their local needs.

A systematic literature review is an excellent method to identify the current approach to a problem. A systematic literature review may not identify any published approach, in which case there is no curriculum precedent for the educator to follow. Conversely, the systematic review may identify other approaches to the identified problem and thereby provide the educator with a starting point for their curriculum development process. When conducting a medical education systematic review, it is necessary to review resources beyond the usual peer-reviewed literature databases (eg, *MedEdPORTAL*[89]) to ensure approaches to the identified problem are not previously published. Methodology for systematic reviews is defined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[90] and the Institute of Medicine's *Finding What Works in Health Care: Standards for Systematic Reviews*[91] and is beyond the scope of this text. A systematic review of the medical education literature for curriculum development should follow the same rigorous approach used for a systematic review of clinical research.

Subsequent to identifying the current approach to the problem, the ideal approach should be defined. This is an opportunity to incorporate aspects of deliberative and reconceptualist curriculum inquiry. Stakeholders representing the targeted learners (eg, medical students or residents), patients, health care professionals, medical educators, and society can be included in this step of curriculum development to ensure all relevant parties agree with the proposed ideal approach. In the previous examples (ie, variability in contouring and lack of oncology undergraduate education), there would be different stakeholders. The contouring variability example could include residents, medical and physics faculty, and dosimetrists. For the undergraduate oncology education, stakeholders could include medical students, university faculty, teaching faculty, and accreditation bodies. Educators in radiation oncology must also consider accreditation bodies (eg, Liaison Committee on Medical Education, ACGME, Accreditation Council for Continuing Medical Education) and certifying organizations (eg, American Board of Radiology (ABR), the Royal College of Physicians and Surgeons of Canada (RCPSC), Canadian Medical Education Directions for Specialists (CanMEDS), the Royal Australian and New Zealand College of Radiologist, and the Royal College of Radiologists (RCR) in the United Kingdom) when considering the ideal approach to a problem. Training program requirements from these accrediting and certification bodies may direct the ideal approach to an educational problem. New information can be obtained from stakeholders through in-person interviews, focus groups, and questionnaires or surveys. Qualitative and quantitative methods can be used to collect data to define the problem and define goals for the ideal approach to achieve.

By obtaining input from all stakeholders, the educator minimizes the chance of overlooking a key component of the ideal approach to the problem and can begin to generate momentum with the stakeholders for eventual implementation of their new curriculum. The identified differences between the current and ideal approach to a specific health care problem should be the target of any subsequent curriculum development.

Finally, based on the problem identification and general needs assessment, the educator can decide the amount of time and effort to dedicate to curriculum development. If the potential for a positive impact on targeted learners, patients, and society is high, then more time and effort may be devoted to curriculum development. Conversely, if there is a low likelihood of significant impact on learners, patients, or society, less time and effort may be necessary to obtain an acceptable curriculum.

Problem identification and general needs assessments in the radiation oncology literature include surveys identifying a deficiency in medical student knowledge of radiation oncology,[74,75] an analysis of average volume of brachytherapy cases performed by resident volume,[92] studies showing failure of practicing physicians to implement best practices based on high-level evidence,[93,94] or evaluation of critical safety events.[95] These studies identify a problem and indicate a general need for curricular development to solve the problem. However, they do not provide detailed information regarding how best to design the curriculum to solve the problem.

Targeted Needs Assessment

Once the educational problem is identified and the differences between the current and ideal approach are realized, the educator should conduct a targeted needs assessment of the learning environment and learners. In radiation oncology, the targeted learner could be a medical student, resident, attending physician, patient, nurse, dosimetrist, or physicist. The learning environment may be a clerkship, residency program, society meeting, or any other myriad learning environments. The goal of this step in systematic curriculum development is to determine the specific needs of the radiation oncology educators, learners, and environment that differ from the ideal approach identified in the prior step. For example, the physics curriculum proposed by the American Society for Radiation Oncology (ASTRO) for radiation oncology residents[96] may not be feasible in a specific training program's learning environment. Alternatively, the literature reviewed in the general needs assessment may not be current, and educational methods will require updates and modification to be relevant to current learners. A radiation oncology residency program developed in 2002 in Singapore,[97] for instance, may not cover all aspects of radiation oncology training necessary in 2023. In addition, the program was designed to satisfy accreditation requirements of Royal Australian and New Zealand College of Radiologists and may need to be modified if implemented by a program in the United States or Canada because of different accreditation requirements set forth by the ACGME or RCPSC, respectively. However, the design and implementation of the Singapore residency program can provide a starting point for a new residency program followed by a targeted needs assessment within the new program's educational milieu.

Detailed information about the targeted learners and the targeted environment is necessary to develop an effective curriculum. Table 35.6 summarizes characteristics about the targeted learner and environment that are necessary to understand before proceeding further with curriculum development. If the targeted learner is a junior radiation oncology resident, understanding that they have limited or no prior education about contouring a prostate fossa will lead to a different curriculum design compared to that of an attending physician as the targeted learner in a refresher course. Similarly, the resources available within a targeted learning environment dictate how a curriculum is structured. A residency program with a proton center and busy pediatric service will design their resident rotation schedule differently than a training program that does not have a proton center and refers all pediatric cases to an out-of-area proton facility.

TABLE 35.6 CONTENT RELEVANT TO A TARGETED NEEDS ASSESSMENT

Content About Targeted Learners
Expectations regarding the scope of knowledge and skills needed
Previous training and experiences relevant to the curriculum
Already planned training and experiences relevant to the curriculum
Existing characteristics/proficiencies/practices
Cognitive: knowledge, problem-solving abilities
Affective: attitudes, values, beliefs, role expectations
Psychomotor: skills/capabilities (eg, history, physical examinations, procedures, counseling, current behaviors/performance/practices)
Perceived and measured deficiencies and learning needs
Attitudes and motivations of learners to improve performance
Preferences and experiences regarding different learning strategies
Synchronous (educator sets time, such as noon lecture)
Asynchronous (learner decides on learning time, such as with e-learning)
Duration (amount of time the learner think is needed to learn or that they can devote to learning)
Methods (eg, readings, lectures, online learning resources, large and small group discussions, problem-based learning, team-based learning, peer teaching, demonstrations, role-plays/simulations, supervised experience)
Content About Targeted Learning Environment
Related existing curricula

Needs of stakeholders other than the learners (course directors, clerkship directors, program directors, faculty, accrediting bodies, others)
Barriers, enablers, and reinforcing factors that affect learning by the targeted learners
Barriers (eg, time, unavailability, or competition for resources)
Enablers (eg, learning portfolios, electronic medical record reminders)
Reinforcing factors (eg, incentives such as grades, awards, recognition)
Resources (eg, patients and clinical experiences, faculty, role models and mentors, information resources, access to hardware and software technology, audiovisual equipment, simulation center)
Informal and collateral curriculum

From Thomas PA, Kern DE, Hughes MT, Chen BY, eds. *Curriculum Development for Medical Education: A Six-Step Approach*. 3rd ed. Johns Hopkins University Press; 2016:32, Table 3.1. Copyright © 2016 Johns Hopkins University Press. Reprinted with permission of Johns Hopkins University Press.

Given the critical nature of the targeted needs assessment to developing an effective curriculum, methods to obtain the necessary information must be carefully considered. Results of the National Resident Match Program,[98] Association of Residents in Radiation Oncology (ARRO) chief resident survey,[25] and the ASTRO workforce survey[99,100] can provide a starting point for curriculum development. These surveys can provide information on past experiences of targeted learners, work environment, and intrinsic and extrinsic motivation. In addition, these surveys frequently include information on the learning environment in residency programs for GME curriculum development or practice settings for CME curriculum development. An educator must consider how broadly they want their curriculum to be applicable. If the curriculum is developed specifically for a problem identified within their own institution, it may not be applicable to other institutions or educational programs. Thus, reviewing national survey data of training programs[25] and practice environments[100] will inform the radiation oncology educator how they can develop their curriculum in a manner such that it satisfies the needs at their local institution and will be beneficial to other educators in need of a similar curriculum. Table 35.7 summarizes methods commonly employed when conducting a needs assessment of targeted learners.

TABLE 35.7 METHODS FOR NEEDS ASSESSMENT OF TARGETED LEARNERS

Needs Assessment Method	Radiation Oncology Example
Informal discussion or interviews with individual learners, supervisors, or other stakeholders (in-person, over the phone, or by e-mail)	Development of an integrated interdisciplinary oncology elective[189]
Focus group discussions	Focus group discussions with oncologists on patient- and family-centered care[336]
Formal interviews	Interviews of radiation oncology professions regarding uptake of high-precision radiotherapy[63]
Formal questionnaires	Targeted needs assessment for radiation oncology medical student clerkship curriculum[51,106]
Direct observation of targeted learners	Mini-CEX[337]
Pretests of knowledge, attitudes, or skills	Pretest of prostate fossa contouring ability[2]
Audits of current performance	Analysis of brachytherapy procedure volume at U.S. residency programs[92]
Strategic planning sessions for the curriculum	Development of medical school oncology educational goals and objectives[190]

CEX, clinical evaluation exercise.

From Thomas PA, Kern DE, Hughes MT, Chen BY, eds. *Curriculum Development for Medical Education: A Six-Step Approach*. 3rd ed. Johns Hopkins University Press; 2016:37-38, Table 3.2. Copyright © 2016 Johns Hopkins University Press. Reprinted with permission of Johns Hopkins University Press.

Surveys represent the most common method for a radiation oncology targeted needs assessment published in the literature. Numerous resources are available to guide a radiation oncology educator designing a survey or questionnaire for a targeted needs assessment, including resources from the Association for Medical Education in Europe (AMEE)[101,102] and textbooks.[68,103,104] Surveys include interviews, focus groups, and questionnaires. Radiation oncology educators should decide which method best suits the needs of their curriculum development process. Advantages and disadvantages and basic techniques of each method are summarized elsewhere.[68] General considerations when designing a survey include paying careful attention to the goal of the survey (questions should have clear justification for inclusion) and avoiding subjective questions, sensitive questions, or lengthy surveys, as the response rate will decrease with increasing survey length or sensitivity of questions asked. The survey population should be informed of the purpose of the survey and whether responses are confidential. Surveys represent research; therefore, local Institutional Review Board (IRB) approval or exemption should be obtained prior to survey dissemination. A survey should be pilot tested to ensure clarity and understandability.[68] In addition, the pilot data should be analyzed to determine if the data collection format would allow the educator to obtain the desired needs assessment results.

Survey response rate is critical to obtaining representative data. Survey responses can suffer either when the targeted learner does not receive the survey (eg, requesting that a residency program coordinator forward survey invitations on to residents) or when the targeted learner elects not to complete the survey because of length, sensitivity of question topics, unclear questions, or other factors that inadvertently discourage responses. Methods by which to improve survey responses (unit response rate) and question responses (item response rate) are summarized elsewhere.[102]

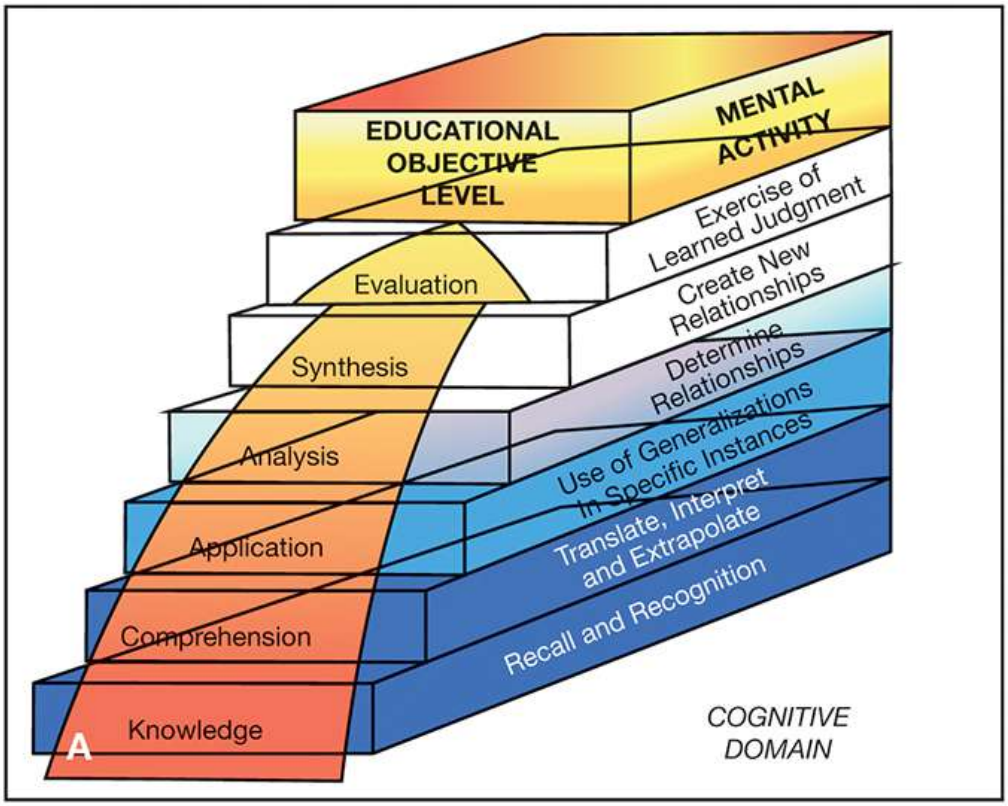
Targeted needs assessments at the undergraduate medical education (UGME), GME, and CME levels are frequently reported in the literature, although many do not identify themselves as such. At the UGME level, targeted needs assessments provide perspective and guidance on radiation oncology education in the general medical school curriculum[74,105] and for radiation oncology clerkships.[51,106] At the GME level, examples of needs assessments include those investigating general residency experiences,[25,107] resident education in intensity-modulated radiation therapy (IMRT),[108] resident knowledge of caring for older patients with cancer,[109] palliative care training,[110,111] brachytherapy experience,[15,92,112] radiation physics education,[113,114] and radiobiology education.[115] Numerous other GME needs assessments for specific educational goals are reported in the literature. Finally, at the CME level, surveys of practicing physicians can inform educators regarding deficiencies in clinical knowledge that should be addressed. An example of a CME-targeted needs assessment is assessing expert consensus on prostate bed delineation for magnetic resonance imaging (MRI)-guided radiotherapy and determining that interobserver variability still exists despite international contouring guidelines and that strategies such as an education program or development of a contouring atlas may lead to diminished variability.[116] Although these studies provide some guidance, it is critical to incorporate alternative methods for the needs assessment, including focused interviews, discussion with multiple stakeholders, and evaluation of available resources.

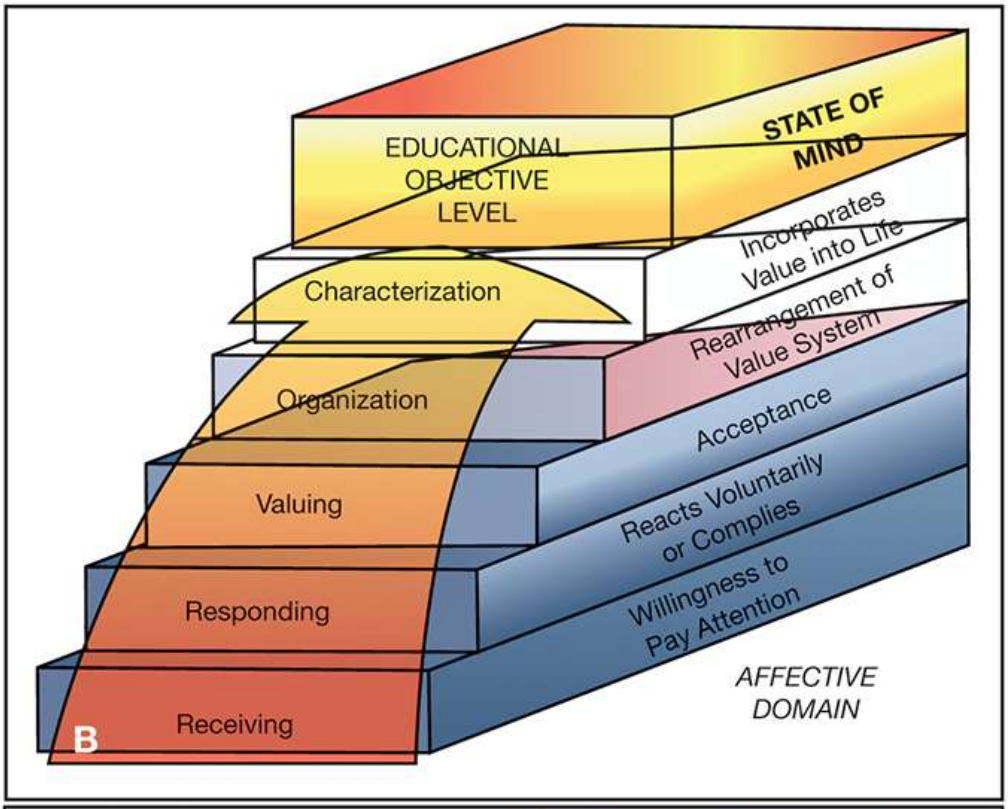
Goals and Objectives

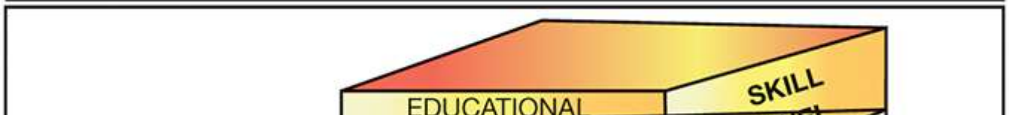
Once the radiation oncology educator has defined the health care problem, performed a general needs assessment, and conducted a targeted needs assessment, they can begin to formulate goals and objectives for the curriculum. Alternatively, the educator may begin the entire curriculum development process with a general goal or specific objective for their targeted learners. Goals and objectives are key to curriculum development because they help guide the choice of curricular content, educational strategies, learner assessment methods, and curriculum evaluation methods and communicate to others what the curriculum addresses and aims to achieve.[68] Curriculum goals are broad and general.

In contrast, curriculum objectives are Specific, Measurable, Attainable, and Relevant and have a Time frame.[117] Specific and measurable objectives help to refine the curriculum content and guide learner assessment and curriculum evaluation methods. Objectives should contain five basic elements: "(a) *Who* (b) *will do* (c) *how much (how well)* (d) *of what* (e) *by when*?"[118] By defining specific measurable objectives, the radiation oncology educator can determine the ideal educational, assessment, and evaluation methods that will demonstrate efficacy of the curriculum.

Learner objectives can be in one of three learning domains: cognitive, affective, or psychomotor. Within the three learning domains, cognitive refers to "knowledge," affective to "attitudinal," and psychomotor to "skill" or "behavioral" objectives.[68] Bloom's taxonomy for the cognitive domain defined six levels of the cognitive domain: knowledge, comprehension, application, analysis, synthesis, and evaluation (Figure 35.7A).[119] The cognitive domain taxonomy was subsequently modified to remembering, understanding, applying, analyzing, evaluating, and creating.[120] One of the modifications included changing the domains to verbs rather than nouns to emphasize the active nature of the learning process. The cognitive taxonomy was further refined to four levels: retrieval of knowledge, comprehension, analysis, and use of knowledge.[121] Taxonomies for the affective domain[122] (Figure 35.7B) and psychomotor domain[123-125] (Figure 35.7C) are also defined in the literature. Another conceptual framework used to define progressive levels of learning objectives is Miller's pyramid of clinical competence, which progresses through four phases: knows, knows how, shows, and does (Figure 35.8).[126,127]


EDUCATIONAL OBJECTIVE LEVEL
MENTAL ACTIVITY
Evaluation
Exercise of Learned Judgment
Synthesis
Create New Relationships
Analysis
Determine Relationships
Application
Use of Generalizations In Specific Instances
Comprehension
Translate, Interpret and Extrapolate
Knowledge
Recall and Recognition
A
COGNITIVE DOMAIN


EDUCATIONAL OBJECTIVE LEVEL
STATE OF MIND
Characterization
Incorporates Value into Life
Organization
Rearrangement of Value System
Valuing
Acceptance
Responding
Reacts Voluntarily or Complies
Receiving
Willingness to Pay Attention
B
AFFECTIVE DOMAIN


SKILL

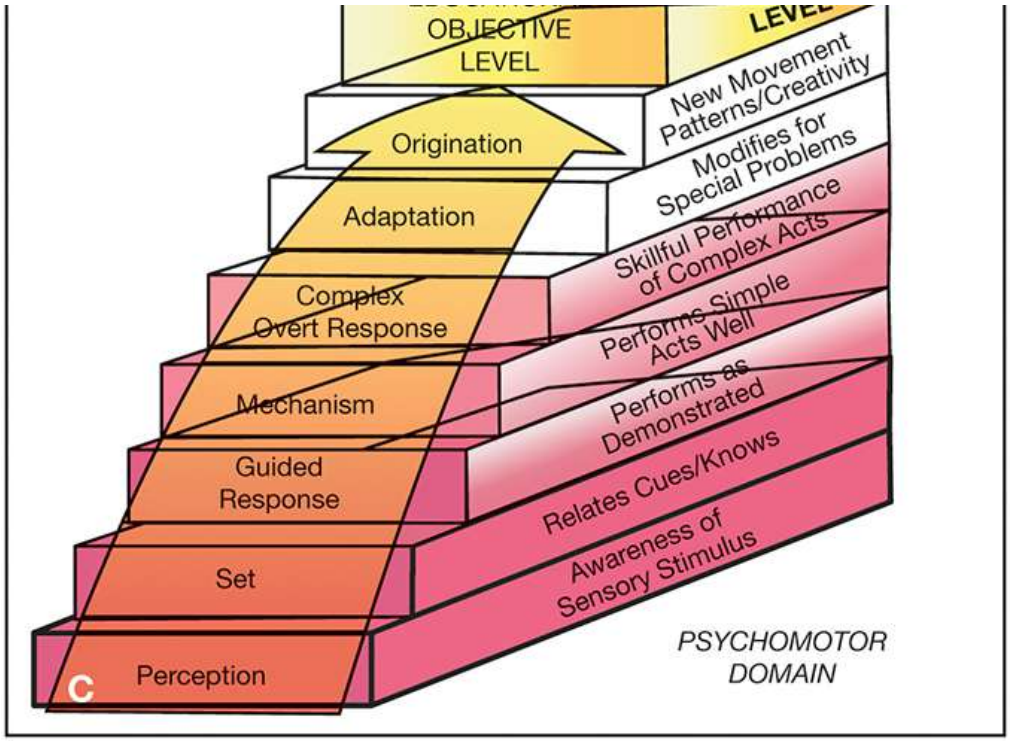


FIGURE 35.7 A-C. Bloom's taxonomy for cognitive, affective, and psychomotor learning domains. (From Federal Aviation Administration. *Aviation Instructor's Handbook*. FAA-H-8083-9. U.S. Department of Transportation, Federal Aviation Administration, Flight Standards Service; 1999.)

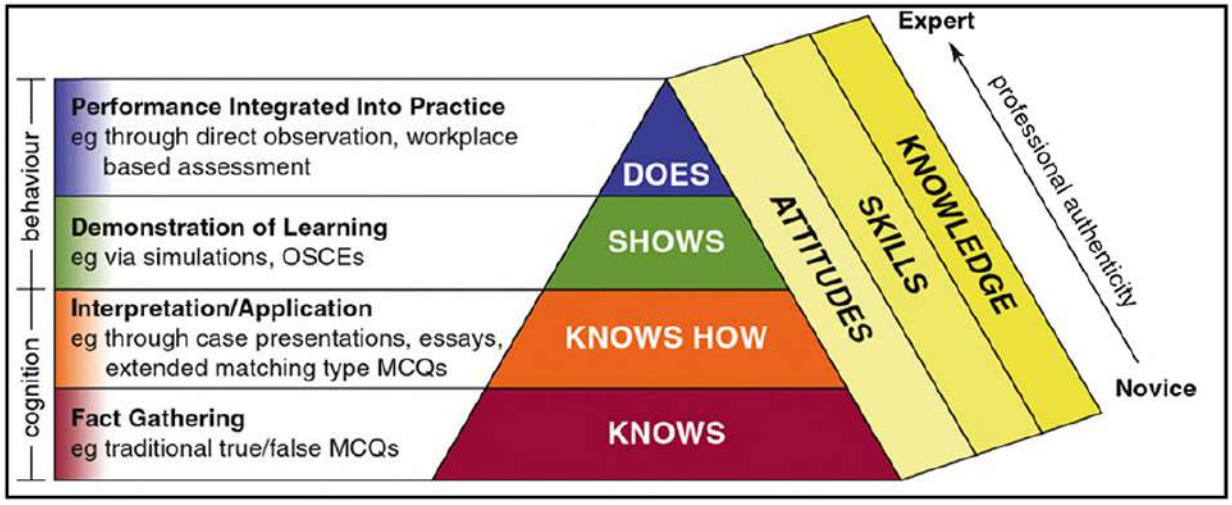


FIGURE 35.8 Miller's pyramid[116] of clinical competence as interpreted by Mehay and Burns. (Adapted with permission from Miller GE. The assessment of clinical skills/competence/performance. *Acad Med*. 1990;65(9 suppl):S63-S67. Copyright © 1990 Association of American Medical Colleges.)

When writing objectives, verbs that are open to fewer interpretations should be used. For example, "to list" or "to demonstrate" is better than "to know" or "be able to." Examples of action verbs that can be used to define objectives for the cognitive, affective, and psychomotor domains can be found in medical education texts.[128] The action verb used in the objective can guide what type of assessment method is used to determine if the learner meets the objective. The radiation oncology educator should

not overlook the critical nature of writing specific and measurable objectives. These represent the keystone of any curriculum. Unfocused, unattainable, or unclear objectives will lead to confusion regarding educational, assessment, and evaluation methods.

Learner objectives are generally written to the highest order expected of the learner. However, the radiation oncology educator needs to consider any enabling objectives at lower levels on the pyramid that provide a foundation for achieving the higher order target objective.[68] In addition to learner objectives, the curriculum designer may also define process objectives in relation to curriculum implementation. Table 35.8 provides examples of learner and related process objectives relevant to radiation oncology. Finally, outcome objectives can be specified that relate to patient or societal outcomes.[68] Demonstrating a positive effect of an educational curriculum on patient or societal health outcomes is the ultimate goal for any medical educator. However, measuring the direct effect of an educational intervention for medical trainees on outcome objectives can be challenging because of the numerous variables that determine health outcomes.

TABLE 35.8 SAMPLE LEARNER AND PROCESS OBJECTIVES FOR RADIATION ONCOLOGY EDUCATION

Domain	Level on Domain Taxonomy	Learner Objective	Process Objective
Cognitive	Remembering	The medical student will correctly identify three radiation emergencies at the end of the lecture.	80% of medical students will correctly identify three radiation emergencies at the end of the lecture.
	Applying	The resident will correctly compute the appropriate number of monitor units to treat an emergency spinal cord compression at the end of the workshop.	100% of residents will correctly compute the appropriate number of monitor units to treat an emergency spinal cord compression at the end of the workshop.
	Evaluating	The radiation oncologist will correctly revise incorrect head and neck target volumes at the end of the interactive contouring workshop.	80% of radiation oncologists will correctly revise incorrect head and neck target volumes at the end of the interactive contouring workshop.
Affective	Receiving	The medical student will acknowledge the importance of using nonmedical jargon with patients at the end of the clerkship.	100% of medical students will acknowledge the importance of using nonmedical jargon with patients at the end of the clerkship.
	Valuing	The resident will demonstrate a willingness to use nonmedical jargon during patient consultations at the end of their first year of clinical training.	100% of residents will demonstrate a willingness to use nonmedical jargon during patient consultations at the end of their first year of clinical training.
	Characterization	The radiation oncologist will modify their discussions with patients to minimize use of medical jargon after completing the communication workshop.	100% of radiation oncologists will modify their discussions with patients to minimize the use of medical jargon after completing the communication workshop.
Psychomotor	Perception	The medical student will correctly identify the bevel side of a brachytherapy needle after observing a permanent prostate implant.	100% of medical students will correctly identify the bevel side of a brachytherapy needle after observing a permanent prostate implant.
	Guided response	The resident will correctly reproduce the attending physician's needle placement technique after a lecture on technique and observing a complete permanent prostate implant.	80% of residents will correctly reproduce the attending physician's needle placement technique after a lecture on technique and observing a complete permanent prostate implant.
	Origination	The brachytherapy fellow will correctly and independently construct a new	100% of brachytherapy fellows will correctly and independently construct

Domain	Level on Domain Taxonomy	Learner Objective	Process Objective
		HDR catheter implant pattern after encountering pubic arch interference by halfway through their 1-y fellowship.	new HDR catheter implant patterns after encountering pubic arch interference by halfway through their 1-y fellowship.

HDR, high-dose rate.

Within the context of educational goals and objectives, competency-based education is gaining popularity. Competency- based education is defined as "an approach to preparing physicians for practice that is fundamentally oriented to graduate outcome abilities … It deemphasizes time-based training and promises greater accountability, flexibility, and learner-centeredness and focuses on the competencies required of learners driven by needs of the health care system."[129]

With respect to radiation oncology competency-based education, national accrediting bodies have developed structured guidelines to assist with defining goals and objectives for program graduates. In the United States, as a component of the Next Accreditation System,[130] the ACGME worked with a number of stakeholder groups, including the ABR, to develop the Radiation Oncology Milestones. The Milestones define competency levels for residents within the six competency domains of Patient Care, Medical Knowledge, Systems-Based Practice, Practice-Based Learning and Improvement, Professionalism, and Interpersonal and Communication Skills.[131] Competency objectives for levels of training are defined within the six domains. These narrative descriptions serve as targets for resident performance throughout their program. Level 1 is the knowledge or skill level expected of a novice or an incoming resident, level 4 is a graduation goal of a final-year resident, and level 5 represents an expert resident whose achievements in that category are above expectation. However, the levels are not meant to correspond with postgraduate year of education, and there is no predetermined timing for a resident to attain a particular level. Residents may also fluctuate throughout their years, such as regression due to overscoring previously, or a particularly difficult or discordant experience for the resident. Recent revisions to Milestones 2.0 also include revisions that preclude using Milestones as a sole assessment in critical situations, such as credentialing or readiness for graduation.[131] The ACGME currently mandates that a program's clinical competency committee assess residents using the Milestone framework semiannually.

Similarly, the RCPSC has developed the CanMEDS framework.[6,132] The CanMEDS competencies include medical expert, communicator, collaborator, leader, health advocate, scholar, and professional. The CanMEDS framework, a product of the Competence by Design (CBD) initiative,[133,134] has been integrated into the Royal College's accreditation standards, specialty training documents, final in-training valuations, exam blueprints, and Maintenance of Certification (MOC) Program. Similar to the ACGME Milestones, there are specific milestones for four levels of residency training, including transition to discipline, foundations of discipline, core of discipline, and transition to practice, as well as entrustable professional activities (EPAs).

Instruction/Educational Strategies

As discussed in the learning theory section, effective learning can be facilitated by addressing preconceptions, building expertise, and developing a metacognitive approach to learning.[135] Learners have prior experiences that shape their attitude and motivation toward learning new knowledge or a new skill. These experiences lead to preconceptions that may need to be addressed prior to engaging the learner. Building expertise requires repeatedly exposing learners to specific conceptual frameworks so they can develop fluency of retrieval known as "automatism."[68] As the learners gain experience, they improve their ability to utilize the specific knowledge or skill until they have achieved expertise. Metacognition refers to the learners' ability to recognize what they know or need to know in a specific

problem-solving situation. This concept is related to the learner's ability for self-reflection.[68] If a curriculum is able to lead learners to identify their preconceptions, build expertise, and improve their metacognition, the curriculum is successful in achieving transformative learning where the learner changes in a meaningful way. Learners may resist this type of change because it challenges their assumptions, beliefs, and values.[68]

Educational strategies for a radiation oncology educational curriculum should match the goals and specific measurable objectives defined previously. Educational strategies refer to both the content and methods by which the goals and objectives will be achieved.[68] A simple method by which to choose the content of a curriculum is to refer to the nouns in the specific measurable objectives. For example, if the objective is "the resident will demonstrate the ability to contour the prostate fossa by the end of the workshop," then the content of the curriculum will focus on the "prostate fossa." Although this seems obvious on the surface, a large curriculum such as that of a clerkship or residency program may have numerous subgoals and specific objectives. There is a risk of bias toward easily implementable and assessable content. If each specific objective is not considered when choosing content and educational strategies, the educator risks omitting content critical to one or more of the specific objectives. To prevent omission of content in a larger educational program with multiple goals and objectives, curriculum mapping can be pursued. A detailed discussion of curriculum mapping is beyond the scope of this text and can be found elsewhere.[68]

Educational methods to relay specific content must also be matched to the learning styles of individual learners. Multiple learning style theories exist in the literature.[136] An example of a learning style conceptual framework is Dunn and Dunn's visual, auditory, kinesthetic, and tactile categorization.[137] It is not usually feasible to create a specific curriculum for each individual learner's preferred learning style. In addition, most learners will learn from multiple different educational strategies. Thus, radiation oncology educators should include multiple educational methods that will allow learners with different learning styles to achieve the learning objective. For example, utilizing only slide-based didactic lectures to teach radiation oncology residents about radiation physics and radiation biology may hinder learners who prefer a problem-based format. When choosing educational methods available, resources must also be considered. The ideal approach identified after the problem identification and general needs assessment may not be feasible based on resources available (time, money, etc).

Commonly used educational methods in relation to radiation oncology include readings, lectures, online learning resources, small group discussion, problem-based learning, peer teaching, real-life supervised clinical experiences, role models, demonstration, simulation, and artificial models. There are other methods less commonly employed in radiation oncology because of restrictive resource requirements for development or implementation, limited numbers of faculty or learners, or lack of knowledge in the radiation oncology educator community of the educational method. These methods include large group discussion, team-based learning, reflection on experience, role-play, standardized patients, audio/video review of the learner, and behavioral/environmental interventions.[68]

Educational methods can be divided based on the domain objectives they aim to achieve. Cognitive objectives may be best achieved through readings, lectures, or discussion; affective objectives through standardized patients, reflection on experience, and role-play; and psychomotor objectives may be best achieved through real-life and supervised clinical experiences, simulation and artificial models, or demonstration with repetition and immediate feedback.

Radiation oncology educators face unique challenges when choosing appropriate educational methods. At the UGME and GME training levels, the number of learners is often small. Medical school clerkships may have one to three students rotating at any given time. Residency training programs also have limited numbers of trainees, often at different training levels. The limited number of trainees translates into limited resources (faculty time, money, space, clinical volume) that can be

dedicated to educational methods. Thus, radiation oncology educators must utilize educational methods that efficiently employ limited resources while achieving the goal and specific objectives of their curriculum.

To overcome the challenge of limited resources, individuals, collaborative groups, societies, and certifying organizations have developed curriculum proposals and specific educational methods to assist individual radiation oncology educators in achieving their local educational goals and objectives. Table 35.9 summarizes selected curricula and educational methods. In addition, educational methods utilized by other medical specialties to teach knowledge and skills that are not specific to radiation oncology (eg, breaking bad news, diagnostic radiology knowledge) should be adopted or adapted by radiation oncology educator so as not to reinvent the wheel.

TABLE 35.9 SELECTED RADIATION ONCOLOGY CURRICULA AND EDUCATIONAL METHODS

Topic	Citation
Medical student oncology curriculum	Tam et al[190] Hirsch[53]
Medical student radiation oncology clerkship curriculum	ROECSG[88]
Radiation oncology residency clinical curriculum	ACGME[5] ESTRO[338] RANZCR[339] RCR[203,340] ROECSG[205]
Radiation oncology residency program physics curriculum	Burmeister[96]
Contouring education	Alfieri[225] Gunther et al[2] Gillespie[52]
Communications	Ju[27]
Treatment planning	Golden et al[196]
Proton therapy physics	Winey[233]
Safety	Abdel-Wahab et al[341]
Brachytherapy	Thaker[28]
Pediatric radiation oncology	Ahern et al[342]
Anatomy	Cabrera[209] Chino[208]
Palliative care curriculum for radiation oncology residency	Garcia et al[343]

ACGME, Accreditation Council for Graduate Medical Education; ESTRO, European Society for Radiotherapy and Oncology; RANZCR, Royal Australian and New Zealand College of Radiologists; RCR, Royal College of Radiologists; ROECSG, Radiation Oncology Education Collaborative Study Group.

Implementation

Once a curriculum is developed with content and educational methods are selected to accomplish the specified goals and objectives, implementation must occur. All too often, well-designed educational interventions are unsuccessful because of barriers encountered during the implementation phase. Consideration of barriers to successful implementation should start at the outset of the curriculum planning process. The general and targeted needs assessment phase of curriculum development is a useful opportunity to begin establishing rapport with stakeholders who will need to provide support for

successful implementation. For example, during the development of a new 1-month international clinical experience for radiation oncology residents, a program director must not only consider stakeholders (eg, the chairman, teaching faculty, GME office, and residents) for a needs assessment but also use the opportunity to develop relations that will be important for successful implementation. For example, if early in the development of the 1-month international clinical experience the residency program director fails to discuss the required funds with the chairman and/or international rotation requirements with the GME office, the resulting decrease in available residents for service coverage or the requirements for an international rotation with the GME office may present insurmountable barriers at the time of implementation. In addition, if the residents themselves were not made aware of the proposed experience prior to an attempt at implementation, they may choose not to participate, thus negating the effort put into the curriculum development.

Resources for successful implementation must be identified and obtained. These include personnel, time, facilities, and funding.[68] Successful implementation requires appropriate resources, and as Figure 35.6 demonstrates, barriers to implementation must be considered during the earlier phases of curriculum development. Table 35.10 provides a checklist that can be used early in the curriculum development process to streamline the implementation phase.

TABLE 35.10 CHECKLIST FOR IMPLEMENTATION

- **Identify resources**
  - Personnel: faculty, audiovisual, computing, information technology, secretarial and other support staff, patients
  - Time: curriculum director, faculty, support staff, learners
  - Facilities: space, clinical sites, clinical equipment, educational equipment, virtual space (servers, content management software)
  - Funding/costs: direct financial costs, hidden or opportunity costs, faculty compensation, costs of scholarship

Obtain support

- ***Internal***
  - From: those with administrative authority (dean's office, hospital administration, department chair, program director, division director, etc), faculty, learners, other stakeholders
  - For: curricular time, personnel, resources, political support
- ***External***
  - From: government, professional societies, philanthropic organizations or foundations, accreditation bodies, other entities (eg, managed care organizations), individual donors
  - For: funding, political support, external requirements, curricular or faculty development resources
- **Develop administrative mechanisms to support the curriculum**
  - Administrative structure: to delineate responsibilities and decision-making
  - Communication
    - Content: rationale; goals and objectives; information about the curriculum, learners, faculty, facilities and equipment, scheduling; changes in the curriculum; evaluation results; etc
    - Mechanisms: websites, social media, memos, meetings, syllabus materials, site visits, reports, etc
    - Operations: preparation and distribution of schedules and curricular materials; collection, collation, and distribution of evaluation data; curricular revisions and changes, etc
    - Scholarship: plans for presenting and publishing about curriculum; human subject protection considerations; IRB approval, if necessary
- **Anticipate and address barriers**
  - Financial and other resources
  - Competing demands
  - People: attitudes, job/role security, power and authority, etc
- **Pilot**
  - Phase-in
  - Full implementation

Plan for curriculum enhancement and maintenance

IRB, Institutional Review Board.

From Thomas PA, Kern DE, Hughes MT, Chen BY, eds. *Curriculum Development for Medical Education: A Six-Step Approach*. 3rd ed. Johns Hopkins University Press; 2016:103, Table 6.1. Copyright © 2016 Johns Hopkins University Press. Reprinted with permission of Johns Hopkins University Press.

Any new or modified educational curriculum represents a change in the status quo, and therefore, radiation oncology educators must become familiar with methods to effect successful change. Kanter's six steps to leading positive change[138] (Table 35.11) and Kotter's eight steps to leading change[139] (Figure 35.9) are two examples of conceptual frameworks that can be employed to garner support from necessary stakeholders and successfully develop and implement a new curriculum or changes to an existing curriculum. One unifying theme in both conceptual frameworks is that to effect change, others must be involved in the process of change. Further discussion of leadership theory[140] and organizational culture[141] is beyond the scope of this text.

TABLE 35.11 KANTER'S SIX STEPS TO LEADING POSITIVE CHANGE

1. Show up
2. Speak up
3. Look up
4. Team up
5. Never give up
6. Lift others up

Kanter RM. TEDx Talk. 2013. https://youtube/owU5aTNPJbs. Copyright © Rosabeth Moss Kanter. Professor Kanter is a Harvard Professor.

FIGURE 35.9 Kotter's eight steps to leading change. (From Kotter JP. *Accelerate: Building Strategic Agility for a Faster-Moving World*. Harvard Business Review Press; 2014. Reprinted by permission of Kotter International.)

Evaluation and Feedback

Per the six-step framework,[68] evaluation and feedback is the final step in curriculum development. Evaluation takes place at both the learner and program levels. In education parlance, "assessment" refers to a test or survey to provide feedback to the learner, whereas "evaluation" refers to methods used to evaluate the educational program. These can include stakeholder surveys, review of aggregate assessment data to determine if the specific and measurable objectives were achieved, and so on. In this section, assessment of the individual learner is referred to as distinct from the evaluation of an educational program, although both are intimately linked.

Learner Assessment

Key to the delivery of any educational intervention is a clear plan for learner assessment. Assessment is defined as "any systematic method of obtaining information from tests and other sources, used to draw inferences about characteristics of people, objects of programs."[142] The purposes of learner assessment are multifold.[143] Many of the educational attributes or traits that educators assess are hypothetical concepts. Assessments allow educators to assign a measure or degree of quantification to such attributes. Assessments aim to document achievement of what was learned or taught, which is helpful to assess the competency of learners and generate learner feedback for areas of improvement. Assessments can also be useful to measure aptitude to gauge learner performance, assign grades or provide ranking, and predict future performances or suitability for certain educational programs (ie, MCAT for admission to medical school). Ultimately, in many settings, assessments are a requirement for accreditation and can inform decisions about the effectiveness of medical education programs and be integral to a programmatic evaluation (see later). To be meaningful, learner assessment must be clearly linked to objectives, define standards for performance, and include measurements that are reliable.

Assessments may be formative or summative. Formative assessments provide the learner with feedback with the intent to allow the learner to identify what they have learned and areas for improvement.[143,144] Formative assessments should occur at multiple defined points throughout a training program or course. In radiation oncology residency programs, formative assessments could include in-house written exams for physics or radiation biology, objective structured clinical examinations (OSCEs) to assess communication skills and end-of-life discussions administered midway through a clerkship rotation in medical school, or annual in-service training exams to assess clinical knowledge. Summative assessments are intended to provide an overall summary of a learner's achievement. They are generally done at the end of a defined curricular period. With respect to radiation oncology, this may include licensing exams at the end of residency, such as those administered by the ABR or RCPSC. Assessments can be "low stakes" and "high stakes." These are often linked, but not always, to formative and summative evaluations, respectively. The consequences of the exam define the stakes of the exam. High-stakes exams have "a serious impact on the examinee," whereas low-stakes exams have significantly lower potential for impact on the trainee.[144,145] Assessments can also be norm referenced (eg, percentile determines performance) or criterion referenced, which are interpreted in the context of specific objectives or learning standards (eg, "Pass/Fail" or "Meets Standard, Standard in Progress, Does not Meet Standard"). The annual in-service training exam is an example of a norm-referenced test, whereas competency-based assessment is usually a criterion-referenced test. Methods to set the pass threshold including the Angoff Method (used for the ABR-certifying exams) are discussed elsewhere.[144]

Assessment Methods

A wide range of assessment methods has been reported in the medical education literature.[68,145,146] Although not an exhaustive list, the following provides a sample of assessment methods. Downing and Yudkowsky[144] propose that there are four major types of assessment methods. Table 35.12 summarizes these methods with examples relevant to radiation oncology. The four groups include written tests, performance tests, clinical observations, and miscellaneous or other forms not classified. Written tests are among the most commonly used forms of assessment. Written tests may include open ended (a.k.a. constructed responses, short or long answer, essay) or closed ended (a.k.a. selected responses, matching, true or false, multiple choice). Closed-ended multiple-choice questions offer the advantage of being easy to administer and grade but may lack the ability to assess diagnostic reasoning. Well-constructed written tests may overcome this problem and allow for more detailed assessments of knowledge and reasoning.[145,147,148]

TABLE 35.12 COMMON ASSESSMENT METHODS AND RELEVANT RADIATION ONCOLOGY EXAMPLES

Assessment Method	Example	Radiation Oncology Example With Relevant Literature if Applicable
Written exam	Multiple-choice exam Essay exam Short-answer exam	• ACR Radiation Oncology In-Training (TXIT) Exam[217] • Pre- and post-test written exams after e-learning module[344] • American Board of Radiology Qualifying Exam • Royal College of Physicians and Surgeons of Canada Radiation Oncology Written Exam
Performance test	OSCE simulation	• Cancer Pain Management OSCE for Medical Students[345] • Standardized Patients to Assess Communication Skills in Radiation Oncology Residents[27] • Prostate or Gynecologic Brachytherapy Insertion Simulation on Phantom
Clinical observation	Structured clinical observation	• Mini-CEX • Direct Observation of Medical Student and Resident in Radiation Oncology Clinic rotations
Miscellaneous	Portfolio review Chart simulation	• Portfolio review to include clinical encounter notes, collection of clinical evaluations, sample of contouring tasks, quality improvement projects

ACR, American College of Radiology; OSCE, objective structured clinical examination.

Performance tests are those assessments that allow for direct observation of the learner. They allow the learner to demonstrate "what they can do."[144] The most common examples are the OSCEs or simulations. An OSCE consists of a series of stations with a distinct focus on a clinical task.[145] Many OSCEs use standardized patients trained to portray a patient and relevant medical scenario.[146] For the purposes of assessment at an OSCE station, an observer will assess the performance of the learner based on a checklist or global rating tool. Although this type of assessment can be constructed to be realistic and reliable, they can be expensive and highly dependent on checklist quality and observer consistency. The term *simulation* refers to a realistic representation of a real-world task.[144] High-fidelity simulations can be used to assess procedural skills or teamwork scenarios. They provide a relatively low-risk environment to assess high-risk and low-frequency scenarios.[149] While simulations can be realistic and provide reliable assessments, they can also be expensive and do not provide a "real-time/real-world" assessment.

Clinical observations are assessments made based on performance in the clinical setting.[144] The clinical performance evaluation or global assessment rating is one of the most common methods utilized during training. The ACGME toolbox distinguishes the global rating from other assessment methods in that "a rater judges the general categories of ability instead of specific skills or behavior and the ratings are completed retrospectively based on general impressions collected over a period of time derived from multiple sources or information."[150] These are easy to carry out for the rater and usually done in real time. There has been considerable literature, however, on the subjectivity of the raters and the variability in the assessments coupled with issues with rating tools.[151]

The final category of assessment includes tools not well positioned in any of the categories above. These include assessment tools such as portfolios, formal oral exams, and bedside oral exams. A portfolio is a purposeful sampling of work to support attestation of meeting a required level of training or competency. Portfolios are combined with self-reflection and allow the learner to demonstrate areas of strengths and potential areas for improvement.[145,152] Portfolios can include a broad sampling of a learner's experiences, including dictations, procedure logs, sample contouring logs, quality improvement projects, and even videos of procedural techniques or consults. Mentoring is integral to

the interpretation of the portfolio. Portfolios can provide a broad sampling to support assessment but can be labor intensive and dependent on faculty development.

The learner should also be positioned to perform accurate and frequent self-assessment. Self-assessment has been cited to yield both noncognitive benefits, such as improvements in morale, motivation, and communication skills, and cognitive benefits, including improvements in knowledge, performance, and self-analysis of performance.[153] Effective implementation of self-assessment would thus enhance professional learners not only to achieve necessary competencies but also to continue to grow and evolve their knowledge, skills, and behaviors as their professions grow and evolve.[6] Self-assessment has been integrated into the ACGME's recommendations for resident evaluation, as self-assessment using the Milestones "will enable residents/fellows to critically evaluate their abilities" and be compared to results from their attendings and supervisors for "more meaningful evaluation."[131]

Selection of Assessment Methods

Numerous resources provide guidance on the selection of specific assessment methods. From a conceptual perspective, the ACGME defined five characteristics integral to an assessment instrument or approach including that the approach should provide valid and reliable data, be feasible, apply to the assessment circumstances, and, finally, provide valuable information.[150] Van Der Vleuten and Schuwirth[154] developed a conceptual model that mirrors these criteria. Their model describes five criteria to help select an appropriate assessment tool. The criteria included are validity (if the assessment measures what it is intended to measure), reliability (does the tool reproducibly measure what it is intended to measure), educational impact (what are the effects of using the tool on learners and the educators), acceptability to learners and faculty, and costs. This model proposes that each of the criteria are weighted depending on the intended purpose of the assessment data and that all factors are multiplied together. For example, if the assessment would be for a certifying exam (eg, ABR-licensing exam), then more weight may be given to reliability and validity as opposed to an in-house physics exam intended to provide the learner with formative feedback where more weight may be given to costs and educational impact. This model is useful to conceptualize that each assessment method has inherent advantages and disadvantages and many factors should be both considered and relatively weighted in choosing a method appropriate to the educational context.

In the context of selecting an assessment method that measures what it is intended to, Miller's pyramid of clinical competence can help provide a framework.[126,144] As discussed previously, Miller's pyramid (see Figure 35.8) progresses through four levels of clinical competence: knows, knows how, shows, and does. It can be useful to map assessment methods to each of these levels. At the base level of "know," a learner may be asked to simply demonstrate factual knowledge of a concept. Here, assessment methods examine the ability of the learner to recite knowledge. Examples of assessment methods include traditional written tests, such as true or false. "Knows how" implies that the learner can use factual knowledge for the purposes of interpretation or application. This level may be assessed by more detailed written tests including short or long written answers or oral exams where the learner is required to illustrate not only their knowledge but also its application. The "shows" level implies an ability to demonstrate learned skills. Assessment methods include simulations or OSCEs. Finally, the "does" level moves the learner's performance into clinical practice. Assessments in this setting take place in the "real world" and include direct observations in a clinical setting and multisource feedback. Figure 35.10 depicts the selection of assessment methods in radiation oncology based on Miller's pyramid.

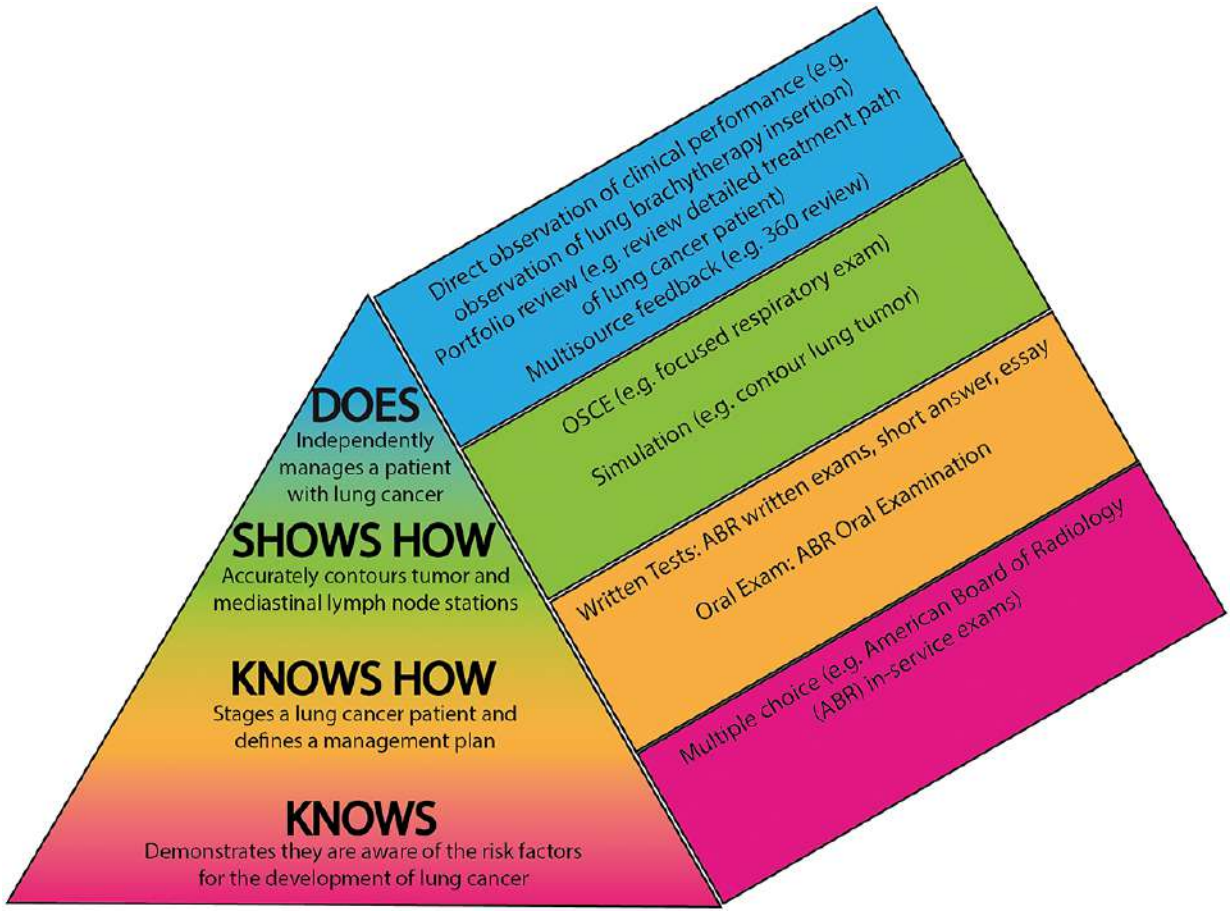


FIGURE 35.10 Miller's pyramid[116] applied to assessment methods in radiation oncology.

Although a multitude of assessment methods exists, the role of the medical educator is to select methods that provide a broad sampling of performance and are reliable, reproducible, and free of bias. No single assessment can give a perfect measure of performance or knowledge, and the application of several methods will provide the most reliable data. Assessment should be mapped to the objectives and instructional methods within a curriculum map (see objectives section).[155,156] A purposeful discussion of assessment methods should happen at the time of curriculum development with the intent of clearly defining what needs to be measured, how this will be measured, who will measure (and how will their skills be developed to support this), and how will the data be used.[145,149] Table 35.13 summarizes some of the practical questions a radiation oncology educator could ask themselves when developing an assessment plan.

TABLE 35.13 PRACTICAL QUESTIONS TO ASK WHEN DEVELOPING AN ASSESSMENT FRAMEWORK

Question	Subset of Questions
What is the goal of assessment?	What is the intended purpose of the assessment data? Are the data meant to be formative or summative?
What are you trying to assess?	Where does the entity being assessed exist on the Miller's pyramid[116]? How best can the learner demonstrate what you are trying to measure (ie, written test or clinical observation)? How many measurements and methods would provide an adequate sampling of the entity to be measured?

Question	Subset of Questions
When will you assess?	How often should assessments take place? If the assessments are formative, what frequency is needed for the learner to improve their performance? Are assessments too frequent and thus not feasible or sustainable?
Who will conduct the assessments?	How will you ensure the assessments are similar and reproducible? Will you need faculty development? How many assessments do different observers need?
Who will manage the assessment data?	Where will the assessment data be kept? Who will collate, distribute, and review the assessment data? How will the security of the assessment data be maintained? How will feedback be given in a timely manner?

Competency and Assessment

As discussed previously in the Goals and Objectives section, medical training is shifting to competency-based frameworks.[129] Within radiation oncology GME, relevant frameworks include the RCPSC CanMEDS framework[6] and ACGME/ABR Radiation Oncology Milestone.[131] In Canada, the RCPSC developed specialty-specific competency frameworks for all specialties including radiation oncology through the CBD project.[133,157] Both the ACGME Milestone Project (Figure 35.11) and the Radiation Oncology Competence by Design define competencies related to the various roles (ie, Communicator, Collaborator, etc) and are specific to the level of training. By the end of a specific level of training, a learner is expected to demonstrate competency through the accomplishment of a number of training level–specific EPAs.[158] An EPA is a clinical task that is demonstrable and typically includes multiple milestones.

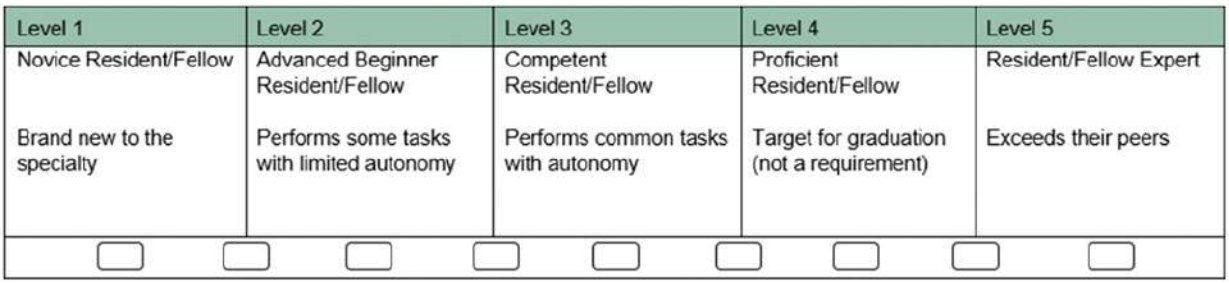


FIGURE 35.11 The Accreditation Council for Graduate Medical Education milestone levels of expectation. (From Edgar L, McLean S, Hogan SO, Hamstra S, Holmboe ES. *The Milestones Guidebook*. Accreditation Council for Graduate Medical Education; 2020. Reprinted with permission of Accreditation Council for Graduate Medical Education.)

Each of the competency-based frameworks in the United States (ACGME) and Canada (CanMEDS) has toolboxes that may help the educator select assessment methods by competency.[159,160] With the evolving competency-based curriculum, there will be changes to these toolboxes, but the foundations will likely remain similar. Although these toolboxes divide assessment methods by competency, it is well established that many of the competencies overlap and their assessment on an individual level is artificial at best. Competencies are not stable through training and develop with experience.[161] The most robust assessment of competencies will rely on features mentioned previously and will include broad, purposeful, and frequent sampling with reliable and reproducible methods. In the context of competency-based assessments, the assessment data can be used both "for learning" and allow self-reflection and to "assess learning" to ensure accountability to training programs and society.[162] Lastly, both the RCPSC and the ACGME mandate the involvement of a clinical competence committee to review competency assessments on a regular basis and help to provide feedback to the learner and the

program. With a shift to competency-based training and assessment, a considerable amount of faculty development will need to occur to ensure that the assessments are performed in a consistent and reliable manner and accomplish the intended outcomes.

Program Evaluation

Program evaluation is a key step in curriculum development. The purposes of evaluation are multifold. Program evaluation can be performed[163,164]:

- to determine the effectiveness of the curriculum for learners
- to document that curricular objectives have been met
- to enable faculty to make changes to improve the program
- to provide data to track program management, evaluate efficiency, and support accountability and dissemination

The following eight practical steps, adapted from the six-step curriculum approach,[68] Fitzpatrick,[165] and AMEE guides,[164,166] are proposed to guide program evaluation:

1. Identify users: As a first step, the stakeholders should be identified. Stakeholders refer to the likely users of the evaluation data. This will often include the learners, the faculty, the curriculum developers, the funders, the university, and the accreditation bodies when appropriate.
2. Determine the purpose of the evaluation: The purpose of the evaluation should be clearly defined. It is here that the approaches to evaluation and the dimensions should be reviewed as discussed earlier. Key questions to ask are as follows: What approach is this evaluation? Will this evaluation be summative or formative? How will the results of this evaluation impact the program, and how will the data specifically be used?
3. Identify resources and select an evaluation team: Resources will need to be allocated to conduct an evaluation. Such resources can include personnel, time, equipment (eg, computers, access to secure databases), and funding. Many medical schools and residency programs may have existing evaluation units, and it can be useful to identify this at the outset. With respect to choosing an evaluation team, it is useful to consider if an evaluation team is best composed of internal or external reviewers. In addition, depending on the approach to evaluation, it may be useful to include participants, faculty, learners, and health care consumers.
4. Determine the evaluation questions: The evaluation questions depend on the approach to the evaluation. With respect to an objective-oriented approach, evaluation should be linked to the process and outcome objectives of a curriculum (see section “Goals and Objectives”). As such, the evaluation will examine the *who will do how much of what* and *when*. It is best when writing program objectives that a lens is given to the evaluation questions to ensure they are in fact measurable and clear. If a participant-oriented approach is taken, evaluation questions could be directed to participants, and the questions asked are related to the perceived effectiveness of the program and the relative strengths and weaknesses.
5. Select an evaluation design: A variety of evaluation approaches can be taken. For the most part, these are dependent on the approach to evaluation and are well summarized elsewhere.[164] Some of the most common evaluation designs relate to an objective approach to document that learning objectives have been met. These can include a post-test design, a pre-/post-test design, or a controlled pre- and post-test design (ie, where an experimental group is exposed to a curricular intervention). As the degree of control increases, the complexity to administer also increases. There are well-known limitations to each design approach.[68]

6. Select a measurement method and relevant instruments to collect data: It is essential that the measurement method be aligned with the questions identified in the evaluation. Similar to the section on assessment, evaluation methods should be chosen to provide reliable and reproducible data that evaluate questions relevant to making appropriate judgments. In part, Kirkpatrick's hierarchy of evaluation[70] (Table 35.14) can help frame the possible methods one might use to evaluate a program examining learner outcomes. At the lowest level of the hierarchy, one could simply evaluate the participation and reaction of learners. One could use rating forms or conduct individual interviews to gain information on the satisfaction of learners (or stakeholders). To demonstrate that learning had taken place, one could examine the results of written or oral exams. With respect to documenting a change in behavior, this would likely be best done in the context of direct observation. Finally, improved patient care could be done through direct observation and performance audits. The most robust evaluation data would be both quantitative and qualitative.

TABLE 35.14 KIRKPATRICK'S HIERARCHY OF EVALUATION[64] IN RELATION TO RADIATION ONCOLOGY EDUCATION

Level 1: Reaction	Are participants satisfied with the educational experience? Example: Medical students rate a clerkship curriculum as useful.[88]
Level 2: Learning	Has learning taken place? Example: Medical students demonstrate improved knowledge on an objective assessment after a single lecture on radiation oncology.[178]
Level 3: Behavior	Is there a measurable change in professional behavior? Example: Learners demonstrate improved contouring accuracy after a teaching intervention.[52]
Level 4: Results	Is there an improvement in patient care? Example: Implementation of a contouring atlas to educate physicians on contour accuracy demonstrates improved tumor control probability and decreased normal tissue complication probability.[346]

7. Collect and analyze the data: The data must be both collected and analyzed. As part of curriculum design, it is essential to define the frequency with which evaluations will be done and how the data will be stored and analyzed. Data may require analysis with both descriptive statistics and qualitative analysis. When established standards are in existence, the data may be compared to these or the literature can be reviewed to relate the experience to other programs or institutions.
8. Dissemination and feedback: The last stage of program evaluation is the act of collating the results and dissemination. Evaluations should be timely and distributed to the relevant stakeholders. It is useful to review the purposes of the evaluation in order to assess who should receive the results and in what format.

Overall, program evaluation is a key component of curriculum development. Table 35.15 provides specific examples of radiation oncology program evaluation.

TABLE 35.15 EXAMPLES OF EDUCATIONAL EVALUATION STUDIES IN RADIATION ONCOLOGY

Study Summary	Evaluation Approaches	Evaluation Methods
Evaluation of a Radiation Safety Initiative for Nurses[347]	Objectives oriented	Pre- and poststudy written tests to assess for changes in knowledge and attitudinal objectives
Evaluation of Theoretical Radiation Oncology Training Programs[26]	Participant oriented	Written user satisfaction surveys
Evaluation of a Contouring Bootcamp[21]	Objectives oriented Participant oriented	Pre- and poststudy written tests Written learner satisfaction surveys

Study Summary	Evaluation Approaches	Evaluation Methods
Longitudinal Study to Assess Adherence to Clinical Pathways[348]	Objectives oriented	Pre- and poststudy written tests using Clinical Performance and Value Vignettes
10-y review of student accomplishments in rapid response radiotherapy program[349]	Objectives oriented/management oriented Participant oriented	Number of first authored papers produced by students in the program Written learner satisfaction surveys

Dissemination

To qualify as scholarship, any curriculum development project must be disseminated to the public.[45] Dissemination of a novel curriculum can help address a health care problem, stimulate change, provide feedback to curriculum developers, increase collaboration, prevent redundant work, and help curriculum developers achieve recognition and academic advancement.[68] Dissemination of a curriculum should be considered during all phases of curriculum development to develop a coherent strategy for dissemination, address ethical and legal issues related to protection of the participants and intellectual property, identify what curriculum material and data will be disseminated, identify the target audience, and identify venues for dissemination.[68] Innovations are more likely to be adopted if there is a perceived relative advantage over existing practice; compatibility with previous experience, beliefs, and values; simplicity of the innovation; trial ability allowing the innovation to be implemented in a stepwise manner; and observability.[167] Ethical and legal issues include consideration of whether local IRB exemption or approval is required prior to disseminating the curriculum. In the United States, many educational projects qualify as "exempt" from IRB review based on Health and Human Services Office for Human Research Protections guidelines for exemption.[168] Projects that are exempted include the following:

Category 1: Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as research on regular and special education instructional strategies or research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods

Category 2: Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior, unless (1) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects, and (2) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation

Radiation oncology educators are encouraged to speak with their institution's IRB representatives to obtain advice on whether IRB exemption or full review is required for an educational project. Professional ramifications for not obtaining proper IRB approval of a scholarship project can be significant.

Consideration of intellectual property issues is also important. Images, figures, and tables used in lectures may be subject to copyright protection. Publishers can be contacted for permissions, or more simply, when developing an educational product, care can be taken to avoid copyrighted materials. In addition, institutions may have copyright protections for patient images or photographs, and the curriculum developer is advised to discuss possible copyright issues with the appropriate institutional representative.

Multiple components of the curriculum development process can be disseminated, including a systematic review performed as a general needs assessment, a survey focus group done as the targeted needs assessment, the curriculum materials themselves including goals and objectives with educational methods (eg, lecture, workshop, small group), and then the assessment and evaluation data. Methods

for dissemination include presentations at national meetings, publication in peer-reviewed journals, and dissemination via the internet (eg, *MedEdPORTAL*[89]). A more detailed discussion of curriculum dissemination strategies is available elsewhere.[68]

CURRICULUM MAINTENANCE, RENEWAL, AND REFORM

Radiation oncology educational programs must adapt and evolve to accommodate changes in accrediting body requirements, learner preferences, turnover of faculty and staff, and changes in clinical practice. In addition, novel systemic therapies and radiation oncology techniques are continually being developed and implemented. As such, training programs must continually address these changes. A seminal paper by Abrahamson[169] describes nine "diseases" of the curriculum. Examples include "carcinoma of the curriculum" characterized by uncontrollable growth of one segment or component of the curriculum; "iatrogenic curriculitis" where the curriculum suffers from excessive tampering or meddling; "curriculum hypertrophy" with an increasingly crowded curriculum due to more and more content crammed into limited educational time; bad teaching leading to "idiopathic curriculitis"; and "curriculum ossification" where the curriculum is "cast in concrete" and is characterized by comments such as "What do you want to change anything for?" or "Well, we've always done it this way." These "diseases," although humorous on the surface, affect many radiation oncology educational programs, including medical school clerkships, residency training programs, educational sessions at society meetings, and CME programs. To prevent or treat Abrahamson diseases of the curriculum, radiation oncology educators should routinely reevaluate their curriculum for deficiencies and areas in need of improvement. A curriculum is never "done" and can be reevaluated utilizing the six-step model[68] or by applying Harden's 10 questions.[80] Without regular reevaluation, radiation oncology educators are at risk for curricular ossification or any of Abrahamson other diseases of the curriculum.

To achieve success when revising or reforming an existing curriculum, methods discussed previously for implementation strategies should be employed. In particular, utilizing a deliberative curriculum development model that includes as many stakeholders as possible will help garner political support for curriculum reform.[170]

CURRENT PRACTICES IN RADIATION ONCOLOGY TRAINING

Having a basic understanding of the principles of medical education can help facilitate the careful development, implementation, and evaluation of a new curriculum and educational scholarship. The following section focuses on the real-world application of medical education principles to UGME, GME, and CME in radiation oncology. This review focuses on the current educational landscape in each setting and identifies areas for potential future educational development and scholarship.

Undergraduate Medical Education in Radiation Oncology

Radiation oncology education as a specific discipline begins during the undergraduate phase of medical training. Students enter medical school with varied experiences and preconceptions about which specialty they plan to pursue. As a small specialty, radiation oncology may be relatively unknown to medical students relative to larger core clerkship specialties (internal medicine, pediatrics, surgery, obstetrics and gynecology, psychiatry, family medicine) or specialties that are commonly portrayed in popular culture (surgery, emergency medicine, etc.). Therefore, radiation oncology educators must work to ensure that the specialty is represented in their institution's core curriculum. In one U.S. needs assessment for radiation oncology education, only 30% of respondents reported receiving a lecture in their medical school on radiation oncology and 1% reported a mandatory radiation oncology educational experience.[51] A survey of students, primary care providers, and

radiation oncology attendings at seven U.S. medical schools demonstrated persistent misconceptions regarding radiation oncology.[105] For example, 23% of the fourth-year medical students and 19% of primary care providers responded that radiation oncologists "push a button to deliver RT every day," indicating a lack of knowledge regarding the daily clinical duties of a radiation oncologist. Similarly, in a survey at two U.S. medical schools, medical students reported increasing comfort regarding their knowledge of medical oncology, surgical oncology, and hospice/palliative care, but not of radiation oncology or survivorship care.[75] A survey of Canadian medical schools demonstrated similar deficiencies in radiation oncology education, with 17% of students reporting no radiation oncology training, a majority reporting no more than 2 hours of radiation oncology teaching, and 19% reporting they were deterred from considering radiation oncology as a career choice because of the lack of knowledge about the specialty.[171] Combined, these data indicate that medical students are not being adequately exposed to clinical aspects of radiation oncology during their core medical school curriculum and are uncomfortable with their radiation oncology knowledge. This deficiency may lead to potential negative consequences. First, students who may otherwise choose radiation oncology as their specialty are not being exposed early and in enough depth in medical school to consider pursuing the specialty. Second, for the majority of students who pursue specialties other than radiation oncology, lack of a basic understanding of the specialty may negatively impact future patient care, including recognizing the need for a radiation oncology consultation, toxicities commonly caused by radiation, or inaccurate counseling on the purpose of radiation within the broader scope of cancer care.

Radiation Oncology Education for All Medical Students

Multiple efforts to develop radiation oncology educational experiences for the general UGME curriculum are reported.[105,171-183] General exposure to radiation oncology can be achieved through development of a preclinical oncology interest group[184] or through tumor board shadowing experience.[183]

Hirsch et al[53,176,178] at Boston University developed a 1.5-hour didactic lecture on radiation oncology during the radiology clerkship. All students at their institution received the lecture. A pre- and postclerkship multiple-choice exam was administered to assess objective knowledge improvement. The average exam score increased, most significantly on the radiation oncology scores (56.5%-71.8% correct, $P < .001$), demonstrating that a single lecture can have a significant impact on knowledge of radiation oncology. The same group has developed the Oncology Education Initiative for preclinical students that includes a radiation oncologist-led oncology education block for the second-year medical students.[185] Students rate the oncology block favorably and specifically report that the oncology block "was effective in contributing to [their] overall medical education."

The group at Thomas Jefferson University has taken a different approach offering an optional 3-week radiation oncology elective during the third-year surgery clerkship.[180,186] Overall objective test scores improved after the rotation (64%-82%) and within the subdomains of clinical (63%-79%), biology (70%-77%), and physics (62%-88%) knowledge (all values $P < .001$).[186] On a follow-up survey, an average of 1.5 years after completion of the elective, improvements in knowledge persisted, with some decay seen for clinical and physics knowledge. Students felt that the elective helped them to understand when to consult a radiation oncologist, identify emergent situations where radiation is needed, and how to take care of patients with cancer, among other benefits.[180] The Department of Radiation Oncology at Thomas Jefferson University has also developed an annual 6-week summer externship during which the student works with the radiation oncology team to perform research and participates in educational activities that provide the student with breadth and depth within the field.[187,188] The program is made further accessible by providing a stipend for the summer program, allowing students who would otherwise need to find paid employment during the break an opportunity to enhance their education without financial burden. At the University of British Columbia, other

approaches have been used to increase medical student exposure to radiation oncology. During the third-year surgery clerkship rotation, only 10% to 15% of medical students partake in radiation oncology electives. As a result, upward of 85% to 90% of graduating medical students receive no clinical exposure to radiation oncology. A targeted needs assessment of learners identified that, relative to other areas of clinical training, medical students felt unprepared to take care of patients with cancer and that supplemental online resources were needed.[189] Based on the six-step method for curriculum development,[68] Ingledew and colleagues developed and implemented a series of online modules, supported by virtual patient vignettes and educational whiteboard videos to provide basic oncology instruction to medical students. User satisfaction surveys demonstrated that medical students completing the modules feel more prepared to deal with oncology in clinical scenarios.[189] The online modules are now being examined for impact on knowledge. The online materials are being utilized throughout Canada and in selected universities in the United States and elsewhere. New modules are being added to meet the objectives of the Canadian Oncology Education Goal and Objectives for medical students.[190]

The aforementioned programs represent methods by which a radiation oncology educator can include a radiation oncology educational experience in their school's core curriculum. Other institutions worldwide report strategies to include radiation oncology in the medical school curriculum.[179,181,191] Radiation oncology primers are available to supplement a course or lecture.[3] Oncology curricula for medical schools have also been proposed that include radiotherapy.[177,190] The primary challenge to implementing radiation oncology education within the core curriculum of a medical school is resource scarcity, in particular student time. Thus, it is critical that the radiation oncology educator utilize the methods discussed earlier to ensure successful implementation within a single institution.

The advent of the COVID-19 global pandemic also spurred the creation of various forms of collaborative, multi-institutional virtual radiation oncology curriculum. Radiation Oncology Virtual Education Rotation (ROVER)[192] was developed as a virtual platform to engage medical students in expert lectures presented as case-based teaching sessions with faculty from various institutions across the United States, facilitating interactive discussions of treatment options and latest research, as well as networking opportunities. Student pre- and postsession surveys demonstrated significant improvement in medical students' understanding of the role of radiation oncology in various disease sites after attending each session ($P < .0001$ for all 10 disease sites).[193] ROVER thus demonstrated its ability to virtually fulfill a need for national medical student education in radiation oncology.

Similarly, the Radiation Oncology Intensive Shadowing Experience (RISE) was created in response to the pandemic to expose medical students underrepresented in medicine (UIM) to the field. The 1-week virtual disease-specific curriculum was developed to incorporate four components: (1) foundational exposure to radiation oncology, (2) didactic teaching, (3) mentorship opportunities, and (4) a capstone experience. The program was initiated at two academic medical centers and created a unique virtual radiation oncology shadowing experience for UIM students to address a critical gap in exposure heightened by the pandemic, with the goal of improving diversity, equity, and inclusion (DEI) in the field.[194] Further details regarding DEI and its intersection with radiation oncology education are discussed later in this chapter.

Education for Students Pursuing a Career in Radiation Oncology

Medical students interested in pursuing a career in radiation oncology represent a different group of learners than the general medical student population. Prior to their first formal rotation in a radiation oncology department, the majority of U.S. medical students spend time in a radiation oncology department shadowing physicians (69%), work in a radiation oncology department conducting research (clinical, translational, or basic science) (60%), or had a lecture on radiation oncology during

the first or second year of medical school (30%). Only 26% report no prior radiation oncology clinical or research experience.[51] However, as mentioned prior, 23% of the fourth-year medical students who have not completed a rotation in radiation oncology still believe that radiation oncologists push a button every day to deliver radiation.[105] Thus, the radiation oncology clerkship is a critical educational experience for students considering radiation oncology as a specialty choice to ensure they understand what their clinical activities and professional responsibilities will entail once they complete residency training. In addition, the clerkship likely represents the student's first significant formal radiation oncology educational experience and is thus the beginning of their radiation oncology training.

The traditional radiation oncology clerkship in the United States and Canada employs the apprenticeship model. Students spend time working with attending and resident physicians in the clinic observing daily clinical activities, including consultations, simulations, treatment planning, contouring, plan review and approval, management of on-treatment patients, and follow-up visits to manage acute and late toxicities. Students report opportunities to participate in clinical care including performing an oncologic history and physical independently without resident or faculty supervision (90%), write or dictate a consult (73%), contour at a planning station for a clinical case (78%), participate in a brachytherapy case (60%), participate in a stereotactic radiosurgery case (57%), participate in a stereotactic body radiation therapy (SBRT) case (49%), and review port films (52%).[51] However, merely participating in these clinical experiences does not mean the medical student is learning the basic background knowledge associated with the experience. For example, participating in a plan review of a base of tongue squamous cell carcinoma being treated with IMRT does not mean the student learns the clinical, radiobiologic, and physics aspects of external beam radiation treatment. Students are encouraged to read primary and secondary literature outside of clinic, but as discussed previously, students will have different learning styles,[136] and thus educational strategies other than clinical observation and outside reading should be incorporated into the clerkship experience.

Students may attend resident-level didactics (clinical, physics, radiation biology) and shadow physicians at tumor boards, but the majority of clerkships did not include formal didactics at the medical student training level.[51,106] This apprenticeship model is not unique to radiation oncology and is frequently used in other subspecialty clerkships where there are limited students at any one time.

These clerkships are also sometimes referred to as "audition rotations", or now more widely known as visiting clerkships, where one of the student's goals for the period is to secure a competitive residency position. There are multiple critiques of the practice of audition rotations. First, visiting clerkships potentially waste valuable educational time during the final year of medical school when the student could be broadening their medical education before focusing on radiation oncology. Second, visiting clerkships outside of the geographic location where the medical student resides require the student to have sufficient funds to travel and pay for room and board during the elective rotation. Therefore, wealthier students may be more likely to take visiting clerkships at novel destinations. Because economic status correlates with race in the United States, selecting students for residency positions based on performance during a visiting audition rotation may discriminate against minority groups. Lastly, visiting clerkships may be difficult to arrange for students with significant home and family responsibilities, thus discriminating against married students or students with children. Residency training programs must be cognizant of the pitfalls of using audition rotations to select future residents and, rather, should holistically evaluate each applicant's medical school performance, letters of recommendation, and personal statement for potential fit with the training program.[195] In a national radiation oncology clerkship needs assessment in the United States, students reported giving a departmental talk on a topic of their choice at 87% of clerkship experiences, whereas 72% of clerkships had no medical student lectures, and 52% of clerkships had no formal lecture, case discussion, or hands-on didactic session at the medical student training level.[106] This disparity suggests

that clerkships may place an emphasis on the audition aspect of the experience rather than the educational experience.

The cessation of in-person "audition rotations" during the COVID-19 pandemic temporarily curbed some of their problematic attributes. Virtual clerkships were developed as part of ROVER, where the emphasis of the experiences was on medical student education and networking opportunities[193] as prospective residency applicants courted the various participating institutions, rather than "auditioning" or "performing." In addition, the ease of engaging with multiple programs virtually lessened the financial and time burden on the student, leading to more equitable opportunities across students of various socioeconomic status. However, with easing restrictions for in-person audition rotations 3 years postpandemic, many of the initial critiques listed above will slowly become relevant again.

Based on the aforementioned data demonstrating a lack of structured didactics for the medical student clerkship, the Radiation Oncology Education Collaborative Study Group (ROECSG) developed a structured, didactic curriculum for the radiation oncology medical student clerkship. Using the six-step model for curriculum development,[68] a series of targeted needs assessments were conducted to determine the target learners' (medical students) needs and preferred learning methods (Figure 35.12).[51,106] Based on these data, a structured, didactic curriculum was developed incorporating three lectures (Introduction to Radiation Oncology, Radiation Biology and Physics, and Simulations/Radiation Emergencies) and a hands-on treatment planning workshop.[196] The needs assessment demonstrated that students want the opportunity to give a lecture to the department (perhaps for the purposes of auditioning for residency) and to give formal case presentations. These activities were not removed from the clerkship but rather supplemented by the addition of the formalized lectures and a treatment planning workshop. The curriculum was piloted at two institutions in 2012[197] and subsequently expanded to 11 academic medical centers in 2013.[88,198] In all, 88 students completed the curriculum in 2013, and subjective evaluation of the curriculum was positive. All lectures and the treatment planning workshop were rated as "quite" to "extremely" useful. Students rated the curriculum as helping them to better understand radiation oncology as a specialty, increase their comfort with their specialty decision, and help the transition to radiation oncology residency.[88] The curriculum subsequently expanded to 22 academic medical centers, with 146 students completing it in 2017. Mean objective multiple-choice question test scores pre- and postcurriculum were 63% and 80%, respectively ($P < .01$). Postscores for students rotating de novo at ROECSG institutions ($n = 30$) were higher compared with prescores for students with 1 or more prior rotations at non-ROECSG institutions ($n = 55$) (77% vs 69%, $P = .01$).[199] This exploratory analysis showing students completing a clerkship at ROECSG institutions perform objectively better when compared with students who completed clerkships at non-ROECSG institutions supports a structured didactic curriculum as a standard component of a radiation oncology clerkship.

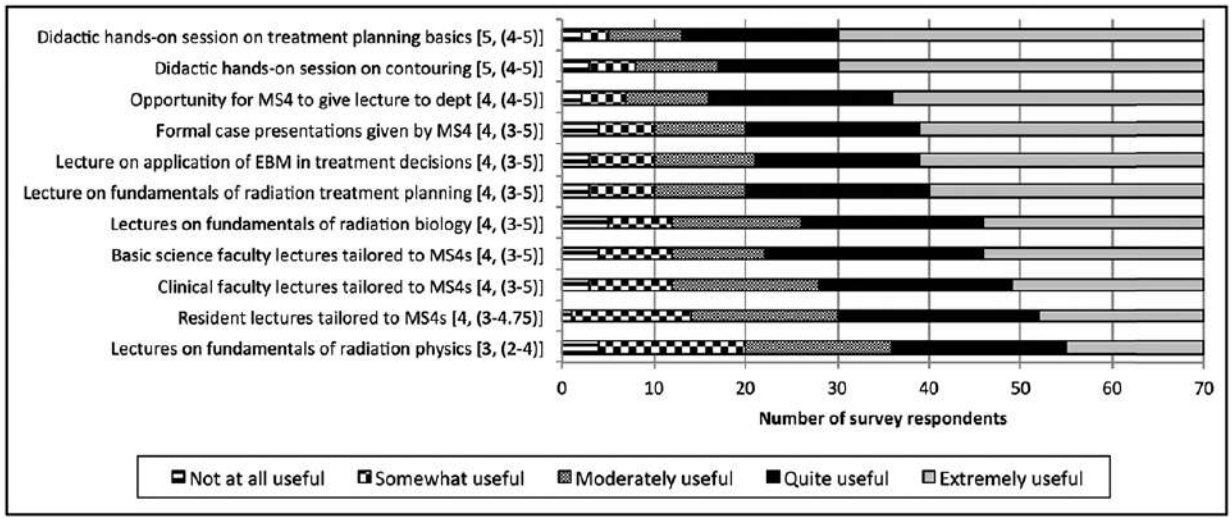


FIGURE 35.12 Survey respondent perspectives on the utility of specific curricular components of an ideal radiation oncology clerkship: median Likert scale (interquartile range). EBM, evidence-based medicine; MS4, fourth-year medical student. (Reprinted from Jagadeesan VS, Raleigh DR, Koshy M, Howard AR, Chmura SJ, Golden DW. A national radiation oncology medical student clerkship survey: didactic curricular components increase confidence in clinical competency. *Int J Radiat Oncol Biol Phys*. 2014;88[1]:51-56. Copyright © 2014 Elsevier. With permission.)

Based on the needs assessment indicating students desired hands-on training for contouring,[51] an additional module was developed that teaches fundamental concepts of atlas-based contouring of the prostate fossa.[200] Using a treatment planning station, students first contoured the prostate fossa on a standardized CT scan with no prior instruction. Utilizing Kolb's experiential learning model[30] (Figure 35.3), this represents the concrete experience. The student then receives a lecture on the CT anatomy of the prostate fossa and how to follow atlas-based instructions for contouring the target volume (reflective observation and abstract conceptualization). The student then repeats the contouring exercise using the atlas and their new knowledge from the lecture (active experimentation and concrete experience). Finally, the student turns on a "gold standard" contour as determined by experts in genitourinary radiation oncology (reflective observation). Students reported subjective improvements in comfort contouring a prostate fossa, ability to find references for contouring, knowledge of CT prostate/pelvis anatomy, and ability to use contouring software tools. In addition, objective analysis of contour accuracy when compared to the gold standard showed significant improvements after the educational intervention.[2]

Formal UGME curriculum development remains nascent in radiation oncology. Implementation of a formal didactic curriculum and hands-on planning and contouring workshops represent methods by which the UGME radiation oncology educator can ensure medical students are making the best career choice while enhancing the students' clinical knowledge to ease the transition to residency training.

Graduate Medical Education in Radiation Oncology

Clinical training in radiation oncology primarily occurs after graduation from medical school. Many countries including the United States,[5] Canada,[132] Australia, New Zealand,[19] and others[18,22-24] train radiation oncologists and medical oncologists as distinct medical specialties. Trainees in these countries complete medical school and a variable amount of non–radiation oncology clinical training followed by 3 to 4 years of full-time radiation oncology clinical training. A small minority of trainees in the United States complete postgraduate fellowships,[201] whereas in Canada, a majority of trainees pursue a postgraduate fellowship.[202] In the United States, these fellowships are not accredited by the ACGME. This discrepancy in fellowship training is likely due to a restricted job market in Canada and

associated difficulty securing employment after residency.[202] In contrast to the radiation oncology–specific training system, clinical oncology trainees in the United Kingdom[203] and other countries train as nonsurgical oncologists and learn to manage both systemic chemotherapy and radiation therapy.

Although certain disease sites, such as pediatric malignancies, and treatment techniques, such as interstitial brachytherapy, have relatively few numbers of cases and are not uniformly geographically distributed, trainees in the United States continue to be certified to treat all disease sites. This raises a dilemma of whether these trainees are adequately prepared to treat rare diseases or use specialized treatment modalities. While, in an ideal training environment, all trainees would see high volumes of rare cases or specialized procedures, analysis of radiation oncology training programs suggests that subspecialty certification in topics such as pediatric radiation oncology, brachytherapy, or particle ion therapy is unlikely in radiation oncology.[204] Despite efforts to find solutions such as modifying accreditation requirements or offering specialized fellowship training, implementing subspecialty training and certification in radiation oncology is currently not feasible. With pediatric radiation, for example, the unequal distribution of cases among residency programs remains a significant hurdle, and attempts to standardize training criteria face practical and regulatory obstacles. Various potential solutions have been proposed, including sending residents to centers with higher pediatric case volumes, restricting pediatric training to specific programs, or assigning specific centers for pediatric training. However, each solution comes with its own set of challenges, such as limited clinical exposure during rotations, scarcity of faculty resources, or resistance from regulatory bodies like the American Board of Medical Specialties. The process of obtaining subspecialty certification entails strict requirements, including the necessity for ACGME-accredited residency programs and a specified duration of training. Despite recognizing the value of subspecialty expertise, the current framework of radiation oncology training and certification is deemed inadequate for accommodating subspecialties such as pediatric radiation oncology in the immediate future. Thus, programs must continue to develop novel training methods including simulation-based education and case-based education to provide sufficient training for rare cases and techniques. U.S. residency program directors also address this problem by allowing residents to train at other centers that see higher volumes of rare cases or use specialized treatment procedures. For example, a residency program housed within a radiation oncology department that does not utilize proton therapy may send their senior residents to a proton center for 2 to 4 weeks of training. By ensuring trainees are competent in the clinical and technical fundamentals of radiation oncology as applied to any disease site or therapeutic technique, training programs will ensure that their graduates are competent to treat rare tumors (eg, pediatric malignancies) or use specialized techniques (eg, interstitial brachytherapy) when required.

CME may also play a pivotal role in the training of radiation oncologists specializing in rare cases. This is discussed in more detail further on in this chapter, in the section on CME.

Regardless of whether trainees focus solely on radiation oncology or learn radiation and medical oncology as in the UK system, during residency, trainees must become competent in all aspects of clinical radiation oncology, including obtaining a focused radiation oncology history and physical, making treatment decisions, simulation, contouring, treatment planning, plan review, and treatment and toxicity management. Residents must learn fundamental scientific knowledge of radiation biology and physics, research methods, and biostatistics. Residents in the United States are assessed semiannually by their department's clinical competency committee using the ACGME Radiation Oncology Milestones,[131] which, as described previously, are divided into the ACGME core competencies, including Patient Care, Medical Knowledge, Systems-Based Practice, Practice-Based Learning and Improvement, Professionalism, and Interpersonal and Communication Skills. In Canada, an almost analogous set of core competencies is represented by the CanMEDS framework and include medical expert, communicator, collaborator, scholar, leader, and health advocate.[6] Finally, residents must be responsible to themselves, their chosen profession, society, and the patient. Based on these

complementary learning goals, a conceptual framework of GME radiation oncology education is presented (Figure 35.13). Educational scholarship related to the clinical care path outlined in this conceptual framework is discussed henceforth.

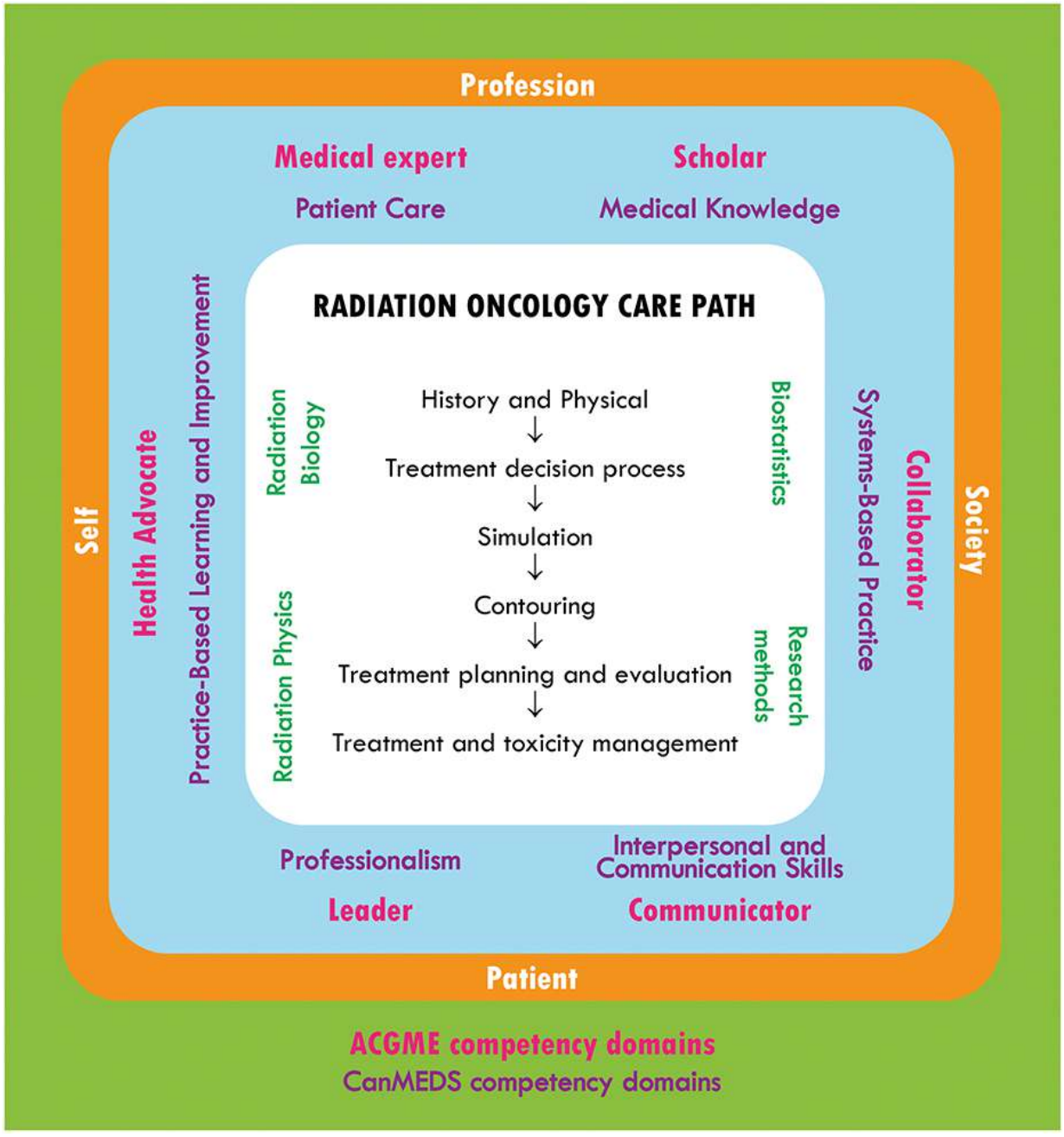


FIGURE 35.13 Conceptual framework for radiation oncology clinical education structured on learner obligations, Accreditation Council for Graduate Medical Education and Canadian Medical Education Directives for Specialists core competencies, fundamental knowledge of physics/radiation biology and research methodology knowledge, and the patient's clinical care path.

Outside accrediting bodies, working groups of stakeholders have also collaborated to develop nationally recognized radiation oncology curriculum. One such group is the ROECSG Core

Curriculum Project Leadership Committee. Competency-based training, as pioneered by CBD[157] as mentioned earlier, aims to direct medical education toward an outcome-based approach as opposed to a chronologic progression through postgraduate years. The cornerstone of competency-based education is the implementation of EPAs, which are "actionable units of work that are completed during clinical care and can be measured and observed" and ensure "meaningful assessment and individualization of education for residents toward ultimate mastery" when compared to more traditional forms of trainee assessment.[205] Given the lack of a current U.S.-specific radiation oncology curricular framework, the ROECSG Core Curriculum Project Leadership Committee recruited appropriate stakeholders in developing and defining content domains, time allocated to each, and radiation oncology EPAs. The resulting framework then underwent rigorous evaluation a Delphi process;[206] the details of the agreed-upon process are beyond the scope of this chapter and can be found in the publication.[205] The final ROECSG consensus curriculum content domains, applied science subdomains, and respective percentage of time allocated, can be found in Table 35.16.

TABLE 35.16 FINAL RADIATION ONCOLOGY EDUCATION COLLABORATIVE STUDY GROUP CONSENSUS CURRICULUM CONTENT DOMAINS, APPLIED SCIENCE SUBDOMAINS, AND PERCENT TIME ALLOCATED

Content Domain/Subdomain	Percentage Time Allocated[a]
Clinical oncology	63
Applied sciences (subdomains below)	16
Professionalism, leadership, and interpersonal communication skills	8
Quality and safety[b]	7
Bioethical and legal issues[b]	2
Diversity, equity, and inclusion[b]	2
Personal wellness	2
Applied Science Subdomains	
Radiotherapy Physics	40
Radiation and Cancer Biology	33
Clinical Research Methods and Biostatistics	27

[a]These content domains should also be integrated within other content domains. This represents additional dedicated curricular hours, independent of other content domains.

[b]Percent time allocated of total residency curricular hours.

Reprinted from Jeans EB, Brower JV, Burmeister JW, et al. Development of a United States radiation oncology curricular framework: a Stakeholder Delphi consensus. *Int J Radiat Oncol Biol Phys*. 2023;115(5):1030-1040. Copyright © 2022 Elsevier. With permission.

Of the 55 initial EPAs, 52 final EPAs met consensus for inclusion, with assigned CBD category; these are listed in Table 35.17. The 52 radiation oncology EPAs are comprehensive in their coverage of all U.S. clinical radiation oncology aspects at present and help to direct training programs on areas of trainee focus for future clinical practice. Trainees can self-assess their progress using an entrustability scale (Table 35.18), a scale that also provides educators and faculty a meaningful framework in which to provide feedback to trainees and to identify opportunities for growth.

TABLE 35.17 FINAL RADIATION ONCOLOGY EDUCATION COLLABORATIVE STUDY GROUP CONSENSUS CURRICULUM UNITED STATES EPAS AND ASSIGNED CBD PHASES

EPA No.	EPA	CBD Category
1	Triaging medically unstable patients	Transition to discipline
2	Establishing a professional relationship with patients, families, and caregivers from diverse backgrounds	Transition to discipline
3	Obtaining a disease site–focused patient history	Transition to discipline
4	Performing basic radiation oncology physical examination techniques (EPA 24)	Transition to discipline
5	Accurately, clearly, and concisely documenting radiation oncology clinical care (EPA 49)	Transition to discipline
6	Assessing patient capacity for medical decision-making	Transition to discipline
7*	Identifying and addressing knowledge deficits during routine patient care (EPA 52)	Transition to discipline
8[a]	Discussing and establishing patients' goals of care to ensure shared decision-making	Foundations of discipline
9	Counseling patients about lifestyle management to reduce long-term cancer risk and improve overall health	Foundations of discipline
10	Recommending and interpreting basic diagnostic studies (EPA 25)	Foundations of discipline
11	Providing evidence-based treatment recommendations for patients with simple radiation oncology clinical presentations (EPA 26)	Foundations of discipline
12	Educating patients, families, and caregivers about the radiation therapy experience and the radiobiologic rationale	Foundations of discipline
13	Presenting an oncologically focused clinical history	Foundations of discipline
14	Determining appropriate simulation techniques and ensuring appropriate execution of simulation for simple cases (EPA 31)	Foundations of discipline
15	Contouring simple target volumes and organs at risk using appropriate imaging modalities (EPA 32)	Foundations of discipline
16	Interpreting a radiation therapy treatment plan (EPA 42, EPA 50)	Foundations of discipline
17	Providing education, counseling, and management for patients regarding common acute and late treatment toxicities (EPA 39)	Foundations of discipline
18	Facilitating communication across professions within a radiation oncology department (EPA 48)	Foundations of discipline
19	Delivering oncologic care with cultural awareness and cultural humility (EPA 46)	Foundations of discipline
20	Delivering bad news and facilitating difficult conversations	Core of discipline
21	Managing appropriate disclosure and care for patients who have experienced a patient safety incident or severe adverse event	Core of discipline
22	Identifying and managing patients who require emergent radiation therapy	Core of discipline
23	Providing appropriate radiation therapy and palliative care for patients at the end of life	Core of discipline
24	Performing advanced radiation oncology examination techniques (EPA 4)	Core of discipline
25	Recommending and interpreting advanced diagnostic studies (EPA 10)	Core of discipline
26	Providing evidence-based treatment recommendations for patients with complex or atypical radiation oncology clinical presentations or complex medical issues (EPA 11)	Core of discipline

EPA No.	EPA	CBD Category
27	Assessing for the use of appropriate local and/or systemic management before, concurrent with, or adjuvant to radiation therapy	Core of discipline
28	Discussing outcomes of different cancers and treatment paradigms with patients, families, and caregivers	Core of discipline
29	Critically appraising evidence including study design, statistical methods, and generalizability as it applies to patient care	Core of discipline
30	Collaborating with other medical disciplines and other health professionals, synthesizing recommendations, and integrating these into the oncology care plan	Core of discipline
31	Determining appropriate simulation techniques and ensuring appropriate execution of simulation for complex or atypical cases (EPA 14)	Core of discipline
32	Contouring complex target volumes and organs at risk using appropriate imaging modalities (EPA 15)	Core of discipline
33	Prescribing target volume doses, selecting dose constraints for organs at risk, and calculating biologic dose conversions	Core of discipline
34	Participating in a radiation therapy quality and safety program (EPA 51)	Core of discipline
35	Reviewing pre-, intra-, and postfraction imaging and recommending appropriate patient shifts	Core of discipline
36	Determining appropriate clinical indications for and treating with unsealed sources	Core of discipline
37	Performing simple brachytherapy procedures	Core of discipline
38	Supervising stereotactic radiation therapy treatments	Core of discipline
39	Providing education, counseling, and management for patients regarding uncommon acute and late treatment toxicities (EPA 17)	Core of discipline
40	Formulating a plan, performing emergency monitor unit calculations, and supervising radiation therapy in an emergency clinical setup	Core of discipline
41	Formulating a long-term oncologic/survivorship care plan for patients	Core of discipline
42	Evaluating a radiation therapy treatment plan (EPA 16, EPA 50)	Core of discipline
46	Advocating for patients to receive appropriate oncologic care, taking into account health disparities and inequities (EPA 19)	Core of discipline
43[a]	Facilitating transfers of care through the health care system	Transition to practice
44	Advocating for appropriate use of radiation therapy as a treatment modality at multidisciplinary tumor board and educating other physicians and allied health professionals about the role of radiation therapy	Transition to practice
45	Performing complex brachytherapy procedures	Transition to practice
47	Identifying bias and harassment in the professional environment and using appropriate mitigation strategies	Transition to practice
48	Managing patient care across professions within a radiation oncology department (EPA 18)	Transition to practice
49	Appropriately documenting to convey management plan to patient and care team and to support billing charges (EPA 5)	Transition to practice
50	Providing feedback on a radiation therapy treatment plan to planning staff or peers (EPA 16, EPA 42)	Transition to practice
51[a]	Identifying and analyzing system-level safety, quality, or resource stewardship concerns in radiation therapy delivery (EPA 34)	Transition to practice
52[a]	Identifying continuing education needs in clinical practice and addressing them with a learning plan (EPA 7)	Transition to practice

EPAs in parentheses are related to the EPA.

CBD, Competence by Design; EPA, entrustable professional activity.

Reprinted from Jeans EB, Brower JV, Burmeister JW, et al. Development of a United States radiation oncology curricular framework: a Stakeholder Delphi consensus. *Int J Radiat Oncol Biol Phys*. 2023;115(5):1030-1040. Copyright © 2022 Elsevier. With permission.

TABLE 35.18 ENTRUSTABILITY SCALE, FINAL RADIATION ONCOLOGY EDUCATION COLLABORATIVE STUDY GROUP CONSENSUS

Level of Entrustment	Resident Role
1	Observe
2	Resident performs EPA with direct supervision.
3	Resident performs EPA with indirect supervision.
4	Resident performs EPA without any supervision.
5	Resident can oversee other residents performing the EPA.

EPA, entrustable professional activity.

Reprinted from Jeans EB, Brower JV, Burmeister JW, et al. Development of a United States radiation oncology curricular framework: a Stakeholder Delphi consensus. *Int J Radiat Oncol Biol Phys*. 2023;115(5):1030-1040. Copyright © 2022 Elsevier. With permission.

This consensus reported the first curricular framework for U.S. clinical radiation oncology training programs and provided a comprehensive set of domains, with appropriate allocation of time, as well as specific EPAs to help guide trainee skill development. Further work is needed to explore its integration into structured radiation oncology residency curricula as well as its implications for assessing the relevance of domains for clinical certification, in addition to its utility as a self-assessment tool.

History and Physical Examination

Trainees entering radiation oncology GME should be competent in obtaining a focused history and physical examination. However, obtaining a history and physical specific for radiation oncology requires further development and refinement of skills developed during medical school and internship. A trainee must learn how to obtain information in the history of the patient that is relevant to radiation oncology, including the complete chronologic oncologic history, family cancer history, past radiation and systemic therapy, history of connective tissue disease or other contraindications for radiation, and other radiation oncology–specific history items. Trainees acquire this skill through clinical observation of attending physicians, feedback on the trainee's case presentations and clinical notes, and lectures on specific disease sites that include a review of relevant history information.

Physical examination is also a skill that is developed during the undergraduate medical training process. Similar to obtaining a history, obtaining a radiation oncology physical examination requires additional skill refinement. For example, trainees must learn to carefully examine the supraclavicular fossa in a patient with cervical cancer and periaortic lymphadenopathy on imaging, whereas patients with anal cancer must be assessed for inguinal lymphadenopathy, and patients with nasopharyngeal squamous cell carcinoma should have a thorough cranial nerve examination. Similar to the patient history, these skills are most commonly taught through faculty clinical observation and lecture format. Endoscopy performed in the clinic is also common; for example, fiberoptic nasolaryngoscopy is typically done on consultation and at follow-up visits for patients with head and neck cancer.[207] These skills can be taught in simulation and honed with practice under supervision during clinical visits.

To perform an appropriate physical examination, anatomic knowledge relevant to oncology is critical.[208] Time spent learning about anatomy is heavily frontloaded in the UGME curriculum with minimal time allotted during residency training, whereas the need for applied anatomy knowledge

increases drastically at the start of residency training (Figure 35.14). To address this need for applied anatomy knowledge, Duke University developed an oncoanatomy course for resident trainees that included a 1-hour didactic session, followed by a 1-hour session in the gross anatomy lab with cadaveric prosections. Implementation of this course demonstrated a significant improvement in objective anatomic knowledge, and residents rated the course as highly effective.[209]

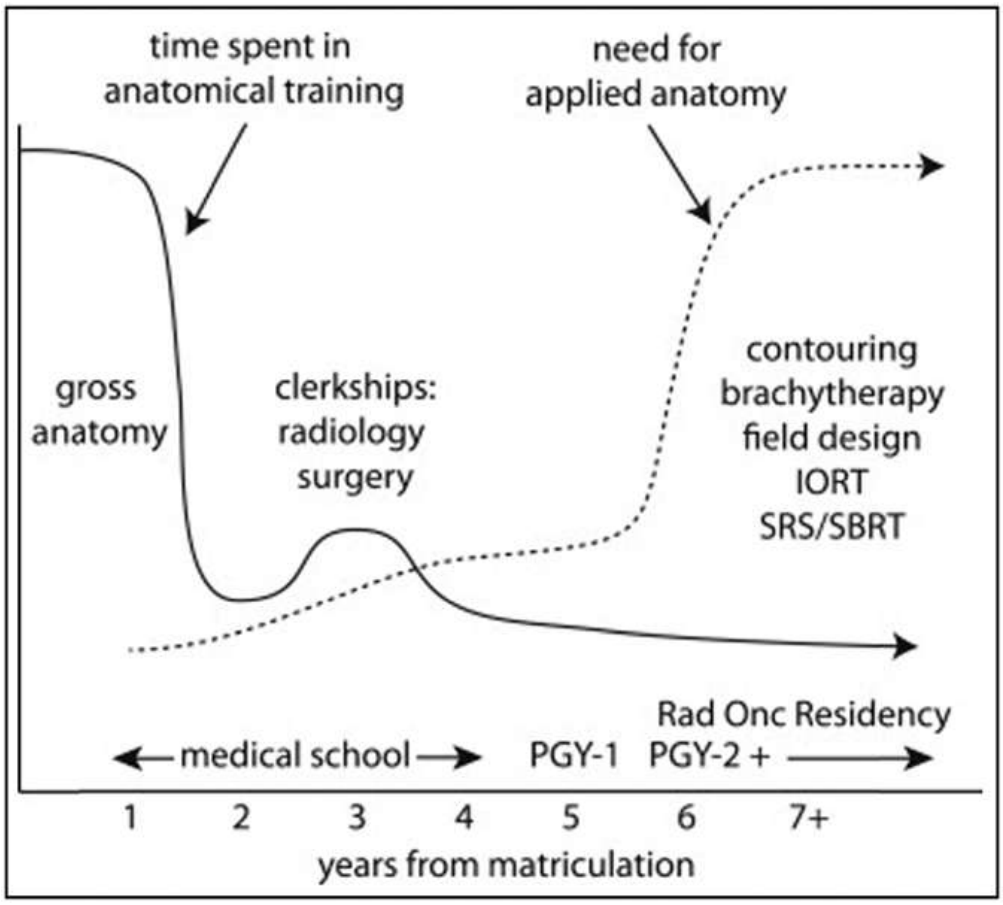


FIGURE 35.14 Schematic of time spent in anatomic instruction and the need to apply knowledge of anatomy for the radiation oncologist in training. There is a large temporal separation between instruction and application. IORT, intraoperative radiation therapy; PGY, postgraduate year; Rad Onc, radiation oncology; SBRT, stereotactic body radiation therapy; SRS, stereotactic radiosurgery. (Reprinted from Chino J, Doyle S, Marks LB. The anatomy of radiation oncology residency training. *Int J Radiat Oncol Biol Phys.* 2014;88[1]:3-4. Copyright © 2014 Elsevier. With permission.)

Communication skills are also necessary during the history and physical process. The University of Pennsylvania developed a novel OSCE with the goal of improving resident skills with regard to breaking bad news.[27] Residents were presented with two case scenarios and given the opportunity to work through the cases with standardized patients. Residents worked through an initial case and then underwent an evaluation by and feedback from the standardized patient, faculty, and residents themselves using the Kalamazoo Essential Elements Communication Checklist – Adapted.[210,211] The residents then completed a second case scenario. Although there was no difference demonstrated in resident performance between scenarios 1 and 2, barriers to developing strong interpersonal relationships were revealed, including perceived lack of empathy, absence of shared decision-making, and use of excessive medical jargon. Resident feedback included the suggestion to allow the resident to review the video recording of the encounter and then repeat the same encounter to try new

wording.[27] An OSCE encounter represents a novel method by which radiation oncology trainees can be taught methods to develop strong interpersonal relationships with their patients at the first clinical encounter.

Clinical Decision-Making

Once the trainee obtains a focused radiation oncology history and physical examination, they must make a treatment decision. Determining a treatment recommendation requires a strong fund of medical knowledge and clinical reasoning skills. Ensuring that graduating trainees obtain the requisite fund of medical knowledge required of a competent radiation oncologist is perhaps the most important role of a residency training program. Without knowledge of treatment guidelines and the primary literature supporting those recommendations, a radiation oncology trainee will have difficulty determining the optimal treatment approach for a specific clinical scenario.

Trainees most commonly learn medical knowledge through a variety of methods, including readings, lectures, online learning resources, peer teaching, and real-life supervised clinical experiences (personal observations of authors). Other teaching methods such as small group discussions and problem-based learning are less commonly employed and represent novel educational methods that may provide trainees with varying learning styles and additional opportunities to assimilate the material. Outside radiation oncology, there is a substantive body of literature on clinical decision-making,[212-215] with recommendations to clearly define critical thinking objectives in a course or curriculum.[216]

Trainee knowledge and clinical decision-making skills for radiation oncology are unique compared to internal medicine, surgery, or other core specialties. However, the same principles for teaching clinical decision-making in these specialties apply to radiation oncology. The most important clinical decision made by the radiation oncologist is whether a patient should receive radiation therapy. The radiation oncologist must evaluate clinical data to determine if radiation therapy is indicated and how best to integrate it with other forms of therapy. However, radiation oncologists also utilize clinical decision-making skills on a daily basis when determining the threshold to order a MRI of the brain in a patient with locally advanced node-positive breast cancer complaining of headaches midway through adjuvant breast radiation, whether a complaint of dysuria during prostate radiation should prompt a urinalysis or if a patient who completed radiation for lung cancer and is complaining of shortness of breath should be started on steroids for possible radiation pneumonitis. Clinical decision-making for radiation oncology trainees is assessed in the United States with formative methods via the American College of Radiology In-Service Exam.[217] Programs in Canada and the United States use internal assessment methods, including case-based skills assessment (colloquially known as “mock oral boards”), case presentations, and faculty feedback. Summative assessment in the United States is through the ABR board exams and through the RCPSC Radiation Oncology Certifying Exams. Studies evaluating methods to teach clinical decision-making specific to radiation oncology, however, are lacking.

Simulation

Subsequent to making a treatment recommendation, the vast majority of radiation oncology patients undergo a radiation therapy simulation scan (eg, CT simulation). Literature regarding formal resident education, specifically regarding the simulation process, is unavailable. Knowledge and skills pertaining to the simulation process are taught via lectures, clinical experience and observation, and informal peer teaching. At the UGME level, a formal lecture regarding the simulation process is included in a structured, didactic curriculum.[88] One study evaluated the efficacy of an educational program for residents on the use of intravenous (IV) contrast media as a component of CT simulation.[218] Resident knowledge regarding the use of IV contrast improved with the intervention,

although this effect was not sustained 1 year afterward. In addition, given the low incidence of IV contrast reactions, the study was unable to demonstrate a clinical effect of the educational intervention. Given the critical nature of the simulation process to the quality of effectiveness of radiation delivery, radiation oncology educators must consider how this is taught and assessed in their local training program.

Contouring

After a patient undergoes simulation, a trainee must be able to accurately and efficiently contour target volumes and adjacent critical structures. "Imaging literacy" for radiation oncologists likely requires collaboration from specialists outside radiation oncology alone.[219] An imaging literacy curriculum was developed using an international two-round Delphi process with four thematic groups of key competencies emerging: imaging fundamentals, clinical application, clinical management, and professional practice.[219] Perhaps the most pertinent competency to the specific technical skill of "contouring" is "delineate on any imaging modality the radiation therapy target and organs at risk in all cancer disease sites and identify targets in 2D, 3D, and 4D image guidance modalities."[219] Radiation oncology educators should review this proposed curriculum to determine where their local program may be deficient.

Multiple educational methods are reported to improve radiologic interpretation skills and contouring skills. Trainee daily clinical activities should include contouring to allow residents to gain a hands-on "concrete" experience per the Kolb experiential learning model.[26] If a program requires trainees to spend significant amounts of time seeing patients in clinic while attending physicians or dosimetrists complete contouring duties, the trainees may graduate deficient in this skill.

To address this curriculum gap, based on a pilot study at a single institution,[220] a two-and-a-half-day National Anatomy and Radiology Contouring Boot Camp was implemented in Canada with significant improvements in knowledge assessment scores and Dice similarity coefficients comparing contour accuracy.[21] In the United States, Memorial Sloan Kettering Cancer Center developed a contouring training module for head and neck cancer, demonstrating improvements in contouring accuracy, although there were still significant deviations in contours indicating a need for repeated exposure and possibly refinement of the curriculum.[221] This is similar to the prostate fossa contouring module developed for medical students.[2] Other contouring educational interventions are also published.[222-225]

Web-based educational methods are also under development. EduCase[226] (access with subscription at EduCase.com) was demonstrated to have a high usability as assessed by resident trainees for head and neck nodal station educational modules.[227] In a randomized study, the use of eContour[228] (access free with registration at eContour.org) compared with any other available contouring materials improved objective assessment of target delineation of the high-risk volume and contralateral parotid gland.[52] Of note, the high-risk volume showed consistently high variability in the Memorial Sloan Kettering study,[221] suggesting that the eContour educational format might further enhance the learning experience. Residents using eContour demonstrated greater knowledge of contour delineation and radiographic anatomy on an objective knowledge assessment, and the mean usability score was high.[52]

Treatment Planning and Treatment Plan Evaluation

Subsequent to accurately delineating contours, a radiation oncology trainee must become proficient in treatment planning and treatment plan evaluation. Working collaboratively with dosimetrists and physicists, the trainee must learn to create a treatment plan, and evaluate treatment plan quality, specifically, to determine when it is not meeting appropriate dosimetric constraints or adequately covering the target volume. Although the treatment plan will nearly always be created by the dosimetrist or physicist in clinical practice, an understanding of how the plan is created, along with the limitations and uncertainties involved, will be exceptionally valuable to the resident when they enter

clinical practice. In the United States, the current ACGME program requirements state that the educational program must include "regularly scheduled didactic sessions" with "instruction in medical physics that includes practical demonstrations of … the use of state-of-the-art treatment planning systems."[5] In the ACGME Radiation Oncology Milestones, each "patient care" milestone includes a competency stating that the resident "critically evaluates treatment plan options."[131] Similarly, the RCR in the United Kingdom calls for "comprehensive teaching of radiotherapy planning … including simulation, virtual simulation, three-dimensional conformal planning, image fusion and IMRT, Volumetric Modulated Arc Therapy (VMAT) and image-guided radiation therapy (IGRT),"[203] and similar content is found in the RCPSC Radiation Oncology Objectives of training documents.[132]

Currently, treatment planning and treatment plan evaluation concepts are taught in the course of regular clinical duties, didactic lectures,[96] and peer-to-peer teaching. The ASTRO physics curriculum developed by the ASTRO Physics Core Curriculum Subcommittee recommends 7 hours dedicated to photon beam characteristics and dosimetry, 2 hours dedicated to electron beam characteristics and dosimetry, 3 hours dedicated to IMRT, and 1 hour dedicated to prescribing, reporting, and evaluating radiation therapy treatment plans.[96] Training programs may include a treatment planning rotation for their residents, but given the competing demands for resident time, most programs do not offer a formal dosimetry rotation.[113] In the recent ARRO chief resident survey, only two-thirds of graduating residents reported receiving adequate experience in treatment planning.[25]

For plan evaluation, the employment of a simple acronym— CB-CHOP—provides a systematic, stepwise approach to analyzing multiple components of treatment plan quality.[229] CB-CHOP stands for *c*ontours, *b*eam arrangements/fields, *c*overage, *h*eterogeneity/*h*ot spots, *o*rgans at risk, and *p*rescription. Given the critical nature of radiation treatment plan evaluation for all modalities (three-dimensional conformal radiation, IMRT, SBRT, radiosurgery, etc), formal educational methods to teach treatment plan evaluation are also necessary. A series of self-directed modules teaching fundamentals of dosimetry and plan evaluation including anteroposterior/posteroanterior (AP/PA) spine, three-field breast, and intensity-modulated radiation was developed at the University of Chicago.[197] These modules provide an opportunity for "active experimentation" within Kolb's experiential learning model.[30] Completion of the modules by the resident physicians was associated with improved resident comfort with AP/PA treatment planning, three-field breast treatment planning, and IMRT planning. Resident understanding of dosimetry concepts including dose grid, beam energy selection, calculation point, iterations, segments, optimization, and ring structure was also significantly improved.[230] Additional structured educational methods to teach and assess competence with treatment planning and dosimetry are needed to ensure that trainees are graduating with the skills necessary to adequately evaluate and constructively critique treatment plans in independent practice. The ASTRO physics curriculum provides an outline for additional dosimetry module development.[96]

Treatment and Toxicity Management

Once a patient begins radiation treatment, the trainee must be proficient in evaluating portal images, volumetric image data and images from other modalities for image-guided radiation, adjusting treatment plans as needed, managing acute toxicity of treatment, and coordinating care with other specialties, including medical oncology and surgical specialties. Similar to other steps in the clinical care path, treatment and toxicity management is primarily taught through a combination of clinical experience, lectures, and reading. Investigations of novel educational methods to teach skills necessary for treatment and toxicity management are limited. A review of methods by which to assess residents' clinical skills proposes the use of OSCEs, standardized patients, and patient management problems in addition to the standard assessment methods of "ward" evaluation, multiple-choice question tests, and oral examinations.[231] An OSCE to teach residents communication skills was developed at the University of Pennsylvania.[27] Two cases representing treatment or toxicity management were

developed, including telling a patient 2 months out from radiation treatment that there is a tumor recurrence and telling the family of an 8-year-old patient that the proton machine is out of commission and the remainder of treatment will be IMRT. Residents received formative feedback from standardized patients and faculty observers. These educational strategies represent novel and effective methods by which to teach radiation oncology trainees about the management of patients receiving radiation and the management of acute and late toxicity, which is essential as toxicities from modern treatments become less common. Further development of teaching material for this component of the care path is needed.

Medical Physics

Medical physics is a key component of training in radiation oncology. The ACGME,[5] RCPSC,[132] and RCR[203] deem medical physics as a required training. According to a recent survey of residency program directors in the United States, 100% of residency programs provide a didactic course in radiation physics,[232] and more than 85% of U.S. residents report adequate formal courses in radiation biology and physics.[25] Didactic lectures represent one of many educational strategies to teach the concepts and knowledge required of a practicing radiation oncologist. Medical physics training for radiation oncology residents in the United States is heterogeneous, with a median of 42 lectures but a range from 10 to 90 per year and only approximately one-third of programs reporting physics rotations.[113] Additional educational strategies should be considered to allow optimal adult learning to occur. Providing an opportunity for hands-on experiences allows for learning in the context of Kolb's experiential learning cycle.[30] Didactic lectures alone cannot accomplish this.

The ASTRO Physics Core Curriculum Subcommittee developed a comprehensive recommended curriculum for medical physics education consisting of 56 hours of didactic sessions.[96] The curriculum also provides recommended references, a set of suggested practical clinical radiation oncology physics modules, and a set of suggested practical modules for radiation therapy treatment planning. The group recommends that training programs ensure residents complete the course at least twice during their training. A detailed physics curriculum for proton therapy is also proposed.[233]

A novel medical physics educational strategy is used at one training program in the United Kingdom where radiation oncology registrars (the equivalent of residents in the United States) spend 6 months completing a medical physics rotation.[234] These trainees continue to spend 1 day per week in clinic to maintain their clinical skills. The goal of the program is that by the end of the 6-month block, the trainee is competent in planning any case with the exception of total-body irradiation. This novel educational strategy utilizing a combination of continued clinical training and hands-on medical physics training could be adapted at other training programs. Importantly, the emphasis on advanced dosimetry over basic physical interactions has become more relevant to clinical practice in the setting of robust modern treatment planning systems.

In the advent of distance learning with the COVID-19 pandemic, trainees have also supplemented their didactic learning with asynchronous virtual tools. These tools, often in the form of free videos, were developed to meet the need for more homogeneous medical physics education across training programs. One such tool, High-Yield Physics (HiPhy),[235] was developed through a multidisciplinary, multi-institutional collaboration and comprises a set of high-yield physics concept videos. Its pilot series reached 154 eligible enrollees across the world. Participants reported improved understanding and confidence applying the knowledge acquired through the videos and improved comprehension of concepts with the use of graphic animation.[236] Similar endeavors include Eric Ford's interactive video series, produced with a textbook supplement "Primer on Radiation Oncology Physics,"[237] which seek to provide radiation oncology and medical physics trainees with a complete and effective introduction to radiation oncology physics. The rapid development of these free and accessible virtual resources

pave the way for incorporation of similar digital tools into the radiation oncology resident's toolbox; this is addressed later in this chapter.

Radiation Biology

Similar to radiation physics, radiation biology is a key component of training in radiation oncology, with the ACGME,[5] RCPSC,[132] and RCR[203] requiring a fundamental understanding of radiobiologic concepts. All U.S. radiation oncology training programs present formal radiation biology courses,[232] with residents reporting sufficient training in radiation biology.[25] A survey of U.S. and Canadian radiation biology educators indicates that many are not completely familiar with relevant radiation biology materials, some do not receive adequate departmental support, and more than 50% are not routinely provided with resident radiation biology performance on the in-training exam.[115] Many residents use the ASTRO radiation biology study guide as a learning resource.[238] In addition, the American College of Radiology in-training exam can be used as a teaching and assessment tool.[239] In recent years, incorporation of mechanisms of systemic therapies, some of which are delivered concurrent with radiation therapy, represents information that is more applicable to daily practice.

Scholarship

Scholarship is a core component of the trainee's educational experience. As noted by the ACGME, "medicine is an art and a science." To train residents to think critically, evaluate literature, incorporate new knowledge, and promote lifelong learning, the program and faculty must foster an environment in which trainees can acquire such skills through active participation in scholarly activities. Prior to completion of the program, residents must complete an investigative project under faculty member supervision. The projects can take a variety of forms, such as biologic laboratory investigation, clinical or translational research, medical physics research, or other research approved by the program director. Investigation into radiation oncology research productivity demonstrated that the amount of designated research time during residency training is the sole independent predictor of productivity as measured through publications.[240] Many U.S. residency programs now offer nonclinical time, which can be used for dedicated research, as part of the program timeline. The amount of nonclinical time varies, but the median nonclinical time across 82 U.S. radiation oncology programs is 10 months, with most programs ranging from 6 to 12 months.[241]

In addition, one unique training pathway available to U.S. radiation oncology residents through the ABR is the Holman Research Pathway (HRP),[242] designed for the trainee who has strong interest and commitment to basic science or clinical research and allows for simultaneous training in both clinical radiation oncology and vigorous research investigation. The goal of the HRP is to thus address the shortage of physician scientist investigators in the field. The trainees who leave this program still complete the 5 standard years of training but have housed within it 18 to 21 months of dedicated research time (21 months with 20% of this time devoted to clinical training; 18 months minimum is required to successfully complete the Pathway).[242] Evaluation of demographic characteristics and research productivity from 2010 to 2019 of HRP graduates has demonstrated its success in training a new cohort of physician investigators through first- or last-author publications, full-time clinical employment after completing residency, grant funding, and lab startup.[243]

Case Logs

One key component of tracking trainees' clinical development and the breadth of their exposure to various clinical case types is through the use of case logs. For example, the ACGME Case Log System is an online database that allows residents to document their clinical experiences while also allowing for the Review Committee for Radiation Oncology a uniform method for verifying clinical

experiences of residents in ACGME-accredited radiation oncology programs.[244] The Review Committee requires residents to log a minimum number of particular case types and procedures; these minimums are not the final target, and residents continue to log cases even after they are met. Meeting the procedural targets is also not the only means by which to evaluate resident competence; rather, they are taken into account with the summative evaluation of residents as detailed earlier.[244]

The minimum case requirements are constantly reevaluated by the ACGME, and new guidelines are published to reflect the changing landscape of disease incidence and use of novel treatment modalities. The most recent case minimums released on July 2023 are listed in Table 35.19. A separate set of case minimums apply for residents who pursue the HRP (Table 35.20).

TABLE 35.19 CASE MINIMUMS FOR NON-HOLMAN PATHWAY RESIDENTS (UPDATED JULY 2023)[5]

Procedural Category	Minimum Number Required	Number of Allowed Observed Cases	Additional Guidance Outlined in the Program Requirements
External beam radiation therapy	450 simulations	NA	No >350 performed in 1 y (detail program requirement).
Bone sarcoma/soft tissue sarcoma	5 simulations	2 simulations	
Breast: postmastectomy	11 simulations	3 simulations	
Central nervous system	19 simulations	5 simulations	
Head and neck subtotal (intact, postoperative, skin)	41 simulations	10 simulations	
Esophagus	5 simulations	2 simulations	
Anorectal (anus, rectum)	10 simulations	3 simulations	
Nonprostate genitourinary (bladder, testes, other)	3 simulations	2 simulations	
Gynecologic subtotal (cervix intact, cervix posthysterectomy, uterus, other)	10 simulations	3 simulations	
Lymphoma (Hodgkin lymphoma and non-Hodgkin lymphoma)	8 simulations	2 simulations	
Non–small cell lung cancer	16 simulations	4 simulations	
Brachytherapy interstitial	7 procedures	NA	
Brachytherapy intracavitary	15 procedures	NA	• 5 must be tandem-based insertions for at least 2 patients. • No >5 should be cylinder insertions.
Pediatric patients	12 patients	NA	Including at least 9 patients with solid tumors
Intracranial stereotactic radiosurgery (SRS-brain)	20 patients	NA	
Stereotactic body radiation therapy (SBRT)	20 patients	NA	To the liver, lung, spine, or other extracranial sites
Radioimmunotherapy, other targeted therapeutic radiopharmaceuticals, or unsealed sources	8 procedures	NA	
I-131	3 procedures	NA	Oral administration of I-131 with administered activity equal to or in excess of 1.22

Procedural Category	Minimum Number Required	Number of Allowed Observed Cases	Additional Guidance Outlined in the Program Requirements
			gigabecquerels (33 mCi)
Parenteral administration	5 cases	NA	Parenteral administration of any alpha emitter, beta emitter, mixed emission, or a photon-emitting radionuclide with a photon energy <150 keV, for which a written directive is required, and/or parenteral administration of any other radionuclide, for which a written directive is required

TABLE 35.20 CASE MINIMUMS FOR HOLMAN PATHWAY RESIDENTS (UPDATED JULY 2023)[5]

Procedural Category	Minimum Number Required	Number of Allowed Observed Cases	Additional Guidance Outlined in the Program Requirements
External beam radiation therapy	350 simulations	NA	No >350 performed in 1 y (detail program requirement).
Bone sarcoma/soft tissue sarcoma	4 simulations	2 simulations	
Breast: postmastectomy	8 simulations	2 simulations	
Central nervous system	14 simulations	4 simulations	
Head and neck subtotal (intact, postoperative, skin)	31 simulations	8 simulations	
Esophagus	4 simulations	2 simulations	
Anorectal (anus, rectum)	8 simulations	2 simulations	
Nonprostate genitourinary (bladder, testes, other)	2 simulations	2 simulations	
Gynecologic subtotal (cervix intact, cervix posthysterectomy, uterus, other)	8 simulations	2 simulations	
Lymphoma (Hodgkin lymphoma and non-Hodgkin lymphoma)	6 simulations	2 simulations	
Non–small cell lung cancer	12 simulations	3 simulations	
Brachytherapy interstitial	7 procedures	NA	
Brachytherapy intracavitary	15 procedures	NA	• 5 must be tandem-based insertions for at least 2 patients. • No >5 should be cylinder insertions.
Pediatric patients	12 patients	NA	Including at least 9 patients with solid tumors
Intracranial stereotactic radiosurgery (SRS-brain)	20 patients	NA	
Stereotactic body radiation therapy (SBRT)	20 patients	NA	To the liver, lung, spine, or other extracranial sites
Radioimmunotherapy, other targeted therapeutic radiopharmaceuticals, or unsealed sources	8 procedures	NA	

Procedural Category	Minimum Number Required	Number of Allowed Observed Cases	Additional Guidance Outlined in the Program Requirements
I-131	3 procedures	NA	Oral administration of I-131 with administered activity equal to or in excess of 1.22 gigabecquerels (33 mCi)
Parenteral administration	5 cases	NA	Parenteral administration of any alpha emitter, beta emitter, mixed emission, or a photon-emitting radionuclide with a photon energy <150 keV, for which a written directive is required, and/or parenteral administration of any other radionuclide, for which a written directive is required

One point to consider is the significance behind the case logs in a resident's readiness for independent practice, especially in the context of programs that may have difficulty fulfilling the required minimums due to low case volume. As mentioned previously, there is ongoing debate regarding the need for subspecialization to ensure residents are able to practice in fields such as pediatric radiation, brachytherapy, or particle ion therapy.[204] For brachytherapy, there is a concerning decline in the number of interstitial cases performed by radiation oncology residents,[245] raising questions about training adequacy. Despite a requirement for minimum case numbers, residents often feel unprepared and advocate for more practical training. Brachytherapy fellowships offer additional training but face challenges, such as a lack of accreditation and program standardization. Workshops and simulation-based residency curricula aim to address training gaps, yet they too have limitations, including time constraints and variability in techniques across institutions.[246,247] Externships at high-volume brachytherapy centers present a promising alternative for senior residents seeking hands-on experience without prolonging their training. Such initiatives hold potential to enhance interest and competency in brachytherapy among residents, ultimately benefiting patient care.[248] In this way, case logs to document completion of hands-on cases performed during externships would allow residents to chronicle their training. However, this will ultimately place a large educational burden on high-volume centers; further efforts will be needed to ensure these designated centers are able to balance training of visiting residents with opportunities for their own native residents and to ensure the administrative aspect of coordinating experiences for a rapid throughput of visitors does not negatively impact the innate function of the program.

Virtual Education and Resources

Although digital resources had existed prior, the COVID-19 pandemic sparked the need for a paradigm shift in radiation oncology education and ushered in rapid integration of virtual education curriculum to support radiation oncologists in training, in addition to aspiring medical students as detailed earlier. Recent review of the landscape of digital resources in radiation oncology has demonstrated the multitude and variety of educational material available.[249] This detailed search, taking into account the credibility of these products, identified 47 free digital education resources, which included online radiation oncology tutorials, podcasts, videos, and slide sets (Table 35.21).

TABLE 35.21 CATEGORIZED LIST OF DIGITAL RADIATION ONCOLOGY RESOURCES (ADAPTED)

Resource Name	Material Covered (Tags Separated by Comma)	Web	iOS App	Android App	Online Video	YouTube Channel	Podcast	File Format (ie, pdf, ppt, csv)	Free or Paid	Membership or Account Required
Contouring and Radiation Planning										
Applied Virtual Anatomy for Radiation Oncology[350]	Contouring and radiation planning	Y	N	N	Y	N	N	Y	Free	Y
ARRO del Regato Webinars[351]	Contouring and radiation planning, general reference	Y	N	N	Y	N	N	N	Free	N
Dosepedia[352]	Contouring and radiation planning	Y	N	N	Y	Y	N	N	Free	N
eContour[228]	Contouring and radiation planning	Y	N	N	N	N	N	N	Free	Y
EduCase[353]	Contouring and radiation planning	Y	N	N	N	N	N	N	Free/paid	Y
I Treat Safely[354]	General reference, contouring	Y	N	N	Y	N	N	Y	Free	Y
IGRT Online[355]	Contouring and radiation planning	Y	N	N	N	N	N	N	Free	Y
Michigan Medicine GI Contouring Atlas[356]	Contouring and radiation planning, case vignettes	Y	N	N	N	N	N	Y	Free	N
NRG/RTOG Oncology Contouring Atlases[357]	Contouring and radiation planning	Y	N	N	N	N	N	Y	Free	N[a]
ProKnow Contouring Accuracy[358]	Contouring and radiation planning	Y	N	N	Y	N	N	Y	Free	Y
Prostadoodle[359]	Contouring and radiation planning	Y	N	N	N	N	N	Y	Free	N
Quality Assurance Review Center/Imaging and Radiation Oncology Core[360]	Contouring and radiation planning	Y	N	N	N	N	N	Y	Free	N

Resource Name	Material Covered (Tags Separated by Comma)	Web	iOS App	Android App	Online Video	YouTube Channel	Podcast	File Format (ie, pdf, ppt, csv)	Free or Paid	Membership or Account Required
Rayos Contra Cancer YouTube[361]	Contouring and radiation planning, brachytherapy, physics, general reference, online video	Y	N	N	Y	Y	N	N	Free	N
Radiobiology/Medical Physics										
ASO distance-learning course[362]	Radiobiology, medical physics	Y	N	N	Y	N	N	Y	Free	Y
ASTRO Radiation Physics[351]	Medical physics, online video	Y	N	N	Y	N	N	Y	Free	N
ASTRO Radiation Biology Lectures[363]	Radiobiology, online video	Y	N	N	Y		N	N	Free	N
EMITEL e-Encyclopaedia of Medical Physics and Multilingual Dictionary of Terms[364]	Medical physics	Y	N	N	N	N	N	N	Free	N
HiPhy Physics[235]	Radiation oncology physics, online video	N	N	N	Y	Y	N	N	Free	N
Primer on Radiation Oncology Physics[237]	Radiation oncology physics	Y	N	N	Y		N	N	Free	N
RSNA Physics Modules[365]	Medical physics	Y	N	N	N	N	N	N	Free	Y
General Radiation Oncology Resources										
Accelerated Education Program[366]	General reference, discussion, contouring	Y	N	N	Y	Y	N	N	Free	N
ARROCase[264]	Case vignettes	Y	N	N	N	N	N	Y	Free	N
ASTRO[367]	General reference	Y	N	N	Y	N	N	Y	Free/Paid	N[a]
Introductory Radiation Oncology	General reference, online video	Y	N	N	Y	Y	N	Y	Free	N

Resource Name	Material Covered (Tags Separated by Comma)	Web	iOS App	Android App	Online Video	YouTube Channel	Podcast	File Format (ie, pdf, ppt, csv)	Free or Paid	Membership or Account Required
Curriculum (IROC)[368]										
Learn Oncology[369]	General reference	Y	N	N	Y	N	Y	N	Free	N
National Cancer Grid[370]	General reference, radiobiology, contouring and radiation planning, medical physics	Y	N	N	Y	N	N	Y	Free	Y
OncologyPro[371]	General reference	Y	N	N	Y	N	N	N	Free	Y
QuadShot News[372]	General reference, discussion	Y	N	N	N	N	N	N	Free	N
Radiation Oncology Education Collaborative Study Group[373]	General reference, statistics, medical physics, radiobiology, introductory curriculum	Y	N	N	Y	Y	N	N	Free	N
Radiation Oncology Virtual Education Rotation[192]	General reference, case vignettes	Y	N	N	Y	N	N	N	Free	N
RSNA Case Collection[374]	Case vignettes	Y	N	N	N	N	N	N	Free	Y
RadOnc Calc[375,376]	General reference, calculator	N	Y	Y	N	N	N	N	Free	Y
RadOnc Tables[377]	General reference, literature review	Y	Y	Y	N	N	N	Y	Free	N[a]
RO Toolbox[378]	General reference, toxicity scales, calculator	N	Y	Y	N	N	N	N	Free	Y
The Med Net[379]	Case vignettes, forum	Y	N	N	N	N	N	N	Free	Y
University of Cincinnati Cancer Center Statistics	Statistics, online video	Y	N	N	Y	Y	N	N	Free	N

Resource Name	Material Covered (Tags Separated by Comma)	Web	iOS App	Android App	Online Video	YouTube Channel	Podcast	File Format (ie, pdf, ppt, csv)	Free or Paid	Membership or Account Required
Seminar Series[380]										
WikiBooks[381]	General reference, literature review	Y	N	N	N	N	N	N	Free	N
Podcasts										
Advances in Radiation Oncology Podcasts[255]	Podcast—General	Y	N	N	N	N	Y	N	Free	N
American College of Radiation Oncology Podcasts[252,382]	Webinars, podcast—General	Y	N	N	Y	Y	Y	N	Free	N[a]
Hormesis[258]	Podcast—Medical physics	Y	N	N	N	N	Y	N	Free	N
Practical Radiation Oncology Podcast[257]	Podcast—General	Y	N	N	N	N	Y	N	Free	N
Rad-Cast[260]	Podcast—General	Y	N	N	N	N	Y	N	Free	N
Radioactive Podcast[383]	Podcast—General	Y	N	N	N	N	Y	N	Free	N
Red Journal Podcasts[256]	Podcast—General	Y	N	N	N	N	Y	N	Free	N
The Accelerators Podcast[261]	Podcast—General	Y	N	N	N	N	Y	N	Free	N
The Fraction[384]	Podcast—General	N	N	N	N	N	Y	N	Free	N
Out of the Gray (Gy) Podcast[259]	Podcast—General	Y	N	N	N	N	Y	N	Free	N
At the Beam[262]	Podcast—General Podcast—Educational	Y	N	N	N	N	Y	N	Free	N

ARRO, Association of Residents in Radiation Oncology; ASO, Applied Sciences of Oncology; ASTRO, American Society for Radiation Oncology; GI, gastrointestinal; IGRT, image-guided radiation therapy; RSNA, Radiological Society of North America; RTOG, Radiation Therapy Oncology Group.

[a]An account is not mandatory, but full access is dependent on account creation.

Adapted from Culbert MM, Brisson RJ, Oladeru OT. The landscape of digital resources in radiation oncology. *Tech Innov Patient Support Radiat Oncol*. 2022;24:19-24. With permission.

As demonstrated, the educators and creators of this content have delved into widely variable vehicles with which to convey information to their audiences. Live webinar sessions were one of the first collaborative efforts early in the pandemic, organized through Radiation Oncology Virtual Education Rotation (ROVER) 2.0, the subsequent iteration of ROVER 1.0. This was designed as a supplementary virtual education curriculum for radiation oncology residents worldwide.[250] The course was conducted through live virtual webinar sessions, structure as complex, ambiguous cases across multiple disease sites. Between October 2020 and June 2021, nine ROVER sessions were held, with 1,487 registered residents completing a presurvey, 786 attending the live case discussion, and 223 completing postsurveys. Those surveyed found learning accessibility to be "very easy" or "easy" (97.5%, n = 119), and a majority rated the ROVER 2.0 virtual sessions to be "valuable" or "very valuable" (99.2%, n = 121).[250] These results demonstrate the feasibility and value in virtual radiation oncology education as a supplement to core residency curricula.

Podcasts have also become a pervasive supplement to core education, with their utility as independent, asynchronous learning tools demonstrated by their popularity—more than 88% of polled U.S. medical residents, parsed by specialty, report listening to medically relevant podcasts.[251] Radiation oncology podcasts have risen in number (Table 35.21), as many pioneering creators stem from professional societies (American College of Radiation Oncology [ACRO],[252] ASTRO,[253] Radiation Research Society[254]) and medical journals (*Advances in Radiation Oncology*,[255] *Red Journal*,[256] *Practical Radiation Oncology*[257]). The scope of these podcasts, however, is broad, ranging from highlights of recent primary research results, to discussion of radiation oncology policy implementation, to advice for early career physicians and personal finance. Other podcasts are focused on medical physics specifically,[258,259] or radiology broadly.[260] Still others involve interviews of leading physicians, scientists, or other radiation oncology personnel, while many highlight recent news and current events within the field.[261] A survey of the range of available series illuminated the need for a podcast specifically targeting radiation oncology education, and thus At the Beam[262] was produced in July 2022, providing case-based workup and management pearls for a broad range of disease sites and pathologies, accompanied by high-yield notes. Of note, the unique perspective of At the Beam stems from its creators' roles as residents themselves; each episode's content is also carefully vetted by field experts. The podcast is open access, free, and catered toward radiation oncology trainees; subsequent analysis of the podcast's performance demonstrated accessibility and portability as its main benefits and found that high engagement for episodes up to 16.4 minutes supports existing data of declining attention spans after 15 to 20 minutes.[263] The podcast was also found to have a broad international reach, with audience members spanning across 53 different countries in 6 different continents. This radiation oncology education–focused podcast thus demonstrates the significance of such modern tools in wide and accessible dissemination of knowledge, and subsequent work will delve into their utility in knowledge retention and efficacy.

More traditional formats for digital education have continued to thrive. Slide decks with case-based learning have been a cornerstone of radiation oncology digital learning. ARROCase,[264] created by the ARRO, is a peer-reviewed, publically accessible educational database with slide decks containing case vignettes and contouring examples, spanning a wide variety of disease sites, for radiation oncology residents. Each case highlights key aspects of case presentation, workup, imaging and laboratory evaluation, treatment option and approaches, contouring guidelines, and follow-up. Similar work has been initiated by resident committee members of the ACRO. The ACRODecks[265] are introductory resources for radiation oncology residents to understand basic principles of oncologic malignancies and to introduce standard treatments to early residents.

Specific materials focusing on contouring, medical physics, and radiobiology have also been developed, as described previously. As vast as the current list of available digital and virtual resources stands, this repertoire of online education will only continue to grow. Further detailed, prospective

investigations into the efficacy, accessibility, sustainability, and durability of each resource will help to inform and guide the continued efforts of educators and content creators.

Continuing Medical Education in Radiation Oncology

For the practicing radiation oncologist, lifelong learning to ensure clinical knowledge and skills are up to date is critical. Perhaps even more so than other areas of medicine, radiation oncology is constantly evolving due to the development of new technologies and treatment techniques, and new treatment paradigms for cancer. The continued maintenance and acquisition of skills in radiation oncology is a complex process, and the implementation of new techniques and maintenance of competency can be challenging.[63] Evidence supporting the efficacy of CME for the maintenance of competency is mixed. Early studies suggested CME has a positive impact on physician performance and patient outcomes.[266] More recent studies failed to demonstrate a significant improvement in patient outcomes for physicians engaging in ongoing maintenance of competency activities.[267,268] A series of Cochrane literature reviews suggest that the impacts of CME may be linked with the type of CME activity, with isolated didactic lectures less effective as compared to interactive sessions, well-planned educational meetings, and quality improvement activities.[269-271] Within radiation oncology, the role for MOC programs administered by certification organizations remains controversial.[272] However, maintaining an up-to-date fund of clinical knowledge and ensuring clinical skills remain current are characteristics of any good physician. In addition, effective education of practicing physicians to drive a change in practice patterns to high-quality and high-value care is needed.[93,94] Thus, programs that educate practicing radiation oncologists are valuable, regardless of whether they are mandated by certifying organizations.

To encourage practicing radiation oncologists to engage in lifelong learning, certifying organizations such as the ABR and RCPSC have established MOC standards. In the United States, the ABR MOC process includes four parts: (1) Professionalism and Professional Standing; (2) Lifelong Learning and Self-Assessment; (3) Assessment of Knowledge, Judgment, and Skills; and (4) Improvement in Medical Practice.[273] Professionalism and Professional Standing requires a license to practice medicine in a jurisdiction in the United States, its territories, or Canada.[274] CME applies most directly to the Lifelong Learning and Self-Assessment and Assessment of Knowledge, Judgment, and Skills components of the ABR's MOC process. Lifelong Learning and Self-Assessment requirements include completing 75 American Medical Association (AMA) Category 1 CME credits every 3 years. Twenty-five of these credits must be SA-CME credits. The general CME credits can be obtained by attending local tumor boards, CME-accredited resident lectures, or any other AMA Category 1 accredited activity. The SA-CME credits can be completed at approved lectures or through journal CME offerings. A by-product of the SA-CME requirement is that residency training programs are now certifying resident didactics for SA-CME to encourage faculty to attend the resident lectures.[275] Assessment of Knowledge, Judgment and Skills requires passing the most recent Online Longitudinal Assessment (OLA) performance evaluation or having passed a Continuing Certification Exam in the previous 5 years. OLA became available to all radiation oncology diplomates in early 2020.[276] It consists of two question opportunities each week, available for 4 weeks to allow flexibility in completion. Once a question is opened, the diplomate is allowed a limited amount of time to answer the question, and they are provided immediate feedback on whether it was answered correctly, with a brief rationale and reference. A passing threshold for OLA is applied when the minimum number of questions, around 200, have been answered. Given only two questions are available a week, and only 52 questions are required a year, it can take a few years to reach the target.[277] Alternatively, the diplomate can opt to take the Continuing Certification Exam, which is a 200-question computer-based exam focusing on clinically relevant applications on all aspects of radiation oncology. However, the

exam is only needed in limited situations and only offered twice a year.[278] Finally, to satisfy the requirement for Improvement in Medical Practice,[279] a practice quality improvement project or other participatory quality improvement activity must be completed every 3 years.

CME requirements in the RCPSC construct are similar to the ABR lifelong learning and self-assessment. CME in Canada represents the culmination of the CBD competence continuum.[133] In contrast to the United States (until recently), in Canada, there is no recertification exam. The RCPSC MOC Program requires radiation oncologists to obtain at least 40 credits per year, at least 400 credits per cycle, with a minimum of 25 credits in each maintenance of competency program section per 5-year cycle. RCPSC maintenance of competency credits fall into one of three program sections: group learning, self-learning, and assessment.[280] More recently, the RCPSC has announced a new phase of high-quality simulation opportunities, and soon simulation education will be embedded into the Continuing Professional Development accreditation process for activities that will satisfy Section 1 and Section 3.[281] The MOC Program thus continues to grow and evolve in supporting the lifelong learning needs of radiation oncology practitioners.

CME activities cover a broad range of educational strategies, including didactic learning, interactive sessions, and practice audit and feedback. These activities often mirror those discussed previously for UGME and GME education. Some of the most commonly recognized CME activities include didactic learning activities at educational meetings (eg, ASTRO, European Society for Radiotherapy and Oncology [ESTRO], and Canadian Association of Radiation Oncology annual society meetings). A variety of interactive activities, including large contouring workshops,[282] provided through national societies, are also used in CME. Many national society meetings include seminars and workshops and allow for the discussion of or dissemination of new techniques. In Europe, the ESTRO School has developed the Fellowship in Anatomic Delineation and Contouring, which incorporates web-based contouring into their educational programs.[282] CME can also be delivered in a small group learning environment, such as weekly tumor boards, simulation-based education, or local grand rounds and lectures.[283,284] Despite the frequency with which such activities are offered, there is a relative paucity of scholarship. Very few publications have robust program evaluation from these CME activities, and the majority evaluate user satisfaction[284] as opposed to change in knowledge or behavior.

Although historically CME was designed to deliver educational content to individual physicians, a primary goal of CME is now systems based or quality improvement.[285] Quality improvement and "audit with feedback" CME programs are becoming more common.[270] Shakespeare et al[286] examined the effects of audit with feedback for practicing radiation oncologist's changes in behavior. Their audit included an assessment of patient charting and radiation plans. Radiation oncologists were provided individualized feedback. The audit with feedback resulted in improvements in some aspects of patient charting and documentation and radiation planning. These effects were retained through time and demonstrated that audit with feedback may be a useful CME exercise. As peer-review and quality assurance programs are developed at radiation oncology centers,[287,288] careful attention should be paid to not only improve consistency and quality in radiation plans[289] but also design programs that allow for continuous practice improvement. By educating individual physicians, CME can drive organizational change and overall improvements in health care delivery. In addition, when deficiencies are noted through the process of peer review, individual or group educational programs may be required, and review of medical education principles previously discussed may be helpful.

CME also plays a pivotal role in the training of radiation oncologists specializing in rare cases, such as pediatric radiation oncology, brachytherapy, and particle ion therapy, even in the absence of a formal fellowship program, as highlighted prior in the section on "Graduate Medical Education". A survey conducted at the 2019 Pediatric Radiation Oncology Society (PROS) Congress shed light on the educational preferences and practices of pediatric radiation oncologists worldwide.[290] The majority of respondents emphasized the importance of postresidency training programs, and while they

advocated for board certification in pediatric radiation oncology, more than 85% of practicing pediatric radiation oncologists did not complete a fellowship. Given these circumstances, pediatric radiation oncologists clearly rely heavily on various educational resources to enhance their knowledge and skills. A significant proportion of respondents reported acquiring knowledge through journals, books, live meetings, and tumor boards, underscoring the importance of continuous learning and collaboration within the professional community. The PROS, serving as a global platform for pediatric radiation oncologists, offers valuable CME opportunities through annual meetings, educational resources on its website, publications, and collaborative efforts aimed at improving pediatric radiation oncology practice worldwide. Despite the challenges and limitations outlined in the survey, the findings provide valuable insights that can inform the development of future educational initiatives and support the ongoing professional development of pediatric radiation oncologists, and similar such practitioners who specialize in rare cases.

In order to develop CME activities, similar to other areas of radiation oncology education, guiding principles and frameworks can help provide valuable perspective. CME activities include a broad range of educational interventions. These can include, among others, didactic programs (eg, lectures and journal clubs with question and answer session), interactive instruction (eg, interactive case discussion, group role-play), audit and feedback, and academic detailing (ie, individual education delivered by a trained professional to education on evidence-based techniques). Harden describes six criteria for effective CME: convenience, relevance, individualization, self-assessment, independent learning, and systematic.[291] The development of effective curriculum for CME programs can be based on the six-step model[68] and enhanced by Davis et al's[292] description of the seven characteristics of effective CME programs: needs assessment, focused initiative, interactive educational programs, multiple educational strategies, multiple sessions, time for feedback and practice, and outcome evaluation. The application of established frameworks to any CME activity or program should allow for robust development, implementation, and evaluation.

Although there is a significant body of literature examining the best practices in development, implementation, and outcomes of CME activities in a variety of other areas in medicine, radiation oncology remains ripe for educational scholarship. Work can be done to improve existing CME curricula and to develop novel CME educational strategies. Potential areas for scholarship include the application of established educational frameworks to CME development and evaluation outcomes linked to changes in knowledge, behavior, and clinical outcomes.

Areas for Further Scholarship in Radiation Oncology Education

Radiation oncology education at the UGME, GME, and CME levels continues to evolve. There remain a myriad of scholarship opportunities to rationally and methodically improve radiation oncology education. Examples include further developing and validating competency frameworks, such as the ACGME Milestones[131] and CanMEDS CBD.[6,160] Development of EPAs also represents an opportunity to move radiation oncology forward, as demonstrated through ROECSG Core Curriculum Project Leadership Committee's proposed curriculum content domains and EPAs.[205,293] Looking beyond the medical profession, there is ample opportunity to develop interprofessional educational activities at all training levels.[294,295]

Simulation-based medical education is being adopted into radiation oncology medical education.[296] There is ample evidence that increasing experience can improve outcomes for brachytherapy[297] and head and neck treatment, particularly in the IMRT era.[86] Reports of decreasing case volume for brachytherapy,[92] reports of limited pediatric cases,[204] and reports from graduating residents of inadequate training in intraoperative radiation, brachytherapy, and proton therapy[25] suggest that development of simulation-based education specific to radiation oncology may provide a solution to

the dilemma of how to safely train residents and assess competency for case scenarios or procedures that are less common or require high technical skill. Many educational reports within radiation oncology represent simulation-based medical education, although they are not identified as such. For example, there are multiple reports of contouring training on a standardized case.[2,52,221,222,227,282] This represents simulation-based education since the trainee is working in a simulated environment with no real-world consequences when making an error, though reports in radiation oncology less often self-identify as simulation-based medical education, with the few examples including brachytherapy training,[28] interprofessional team simulation,[298] and preparation for on-call emergencies.[299] Furthermore, incorporation of virtual and augmented reality in simulated-based education,[300] as well as integration and harnessing of artificial intelligence, are inevitable.[301] Continued work pushing the evolving frontier of clinical radiation oncology will assuredly involve leveraging these tools to enhance trainee education and knowledge.

Equity, Diversity, and Inclusion in Radiation Oncology Education

One area of growing attention but paramount importance is the promotion of equity, diversity, and inclusion (EDI) in health care, and it is critical to integrate these efforts into medical education. Diverse medical teams have been shown to improve patient-physician communication and trust, leading to more equitable patient care;[302,303] buttress innovation and research productivity;[304,305] and reducing physician burnout.[306] Representation impacts the clinical learning environment. In a cohort of 20,000 graduating medical students, White students attending racially diverse medical schools reported being better prepared to care for racial and ethnic minority patients compared to their counterparts at less diverse schools and had stronger attitudes about improving inadequate access to health care.[307] Health systems and medical schools across the United States are increasingly organizing department or institution-level EDI committees and leaders to evaluate their own commitment to equitable medical education, patient care, employment, promotion, and leadership and to develop strategies and initiatives to match the organization's unique needs. While a more detailed and nuanced discussion of EDI in radiation oncology extends beyond the scope of this chapter, highlighted here are ongoing initiatives to promote EDI in radiation oncology education, particularly in the recruitment of medical students into residency programs. Historically, groups underrepresented in the field of radiation oncology include African American, American Indian, Alaska Native, Hispanic American, Native Hawaiian, and Pacific Islander,[308] as well as sexual and gender minorities, such as those identifying as lesbian, gay, bisexual, transgender, queer, intersex, or other.

As discussed previously, the RISE exposes medical students UIM to the field.[194] The program, initiated at two academic medical centers, created a unique virtual radiation oncology shadowing experience for UIM students to address a critical gap in exposure heightened by the COVID-19 pandemic, with the goal of improving DEI in radiation oncology.[194] This 1-week intensive experience was limited to senior UIM medical students. Participants were very satisfied with patient interactions (71%), panel of minority residents/attendings (71%), morning didactics (86%), capstone presentation (86%), and assigned mentors (86%). All students agreed the course was helpful in decision-making regarding what specialty to pursue.[309] Virtual programs like RISE can provide a broad overview of radiation oncology training to a larger cohort of medical students. Conversely, in-person programs targeting a smaller number of participants can provide the depth needed for full immersion in the field's training. One example of this is the UCLA Department of Radiation Oncology's Medical Student Preceptorship Program, which commenced in 2020 with the intended goal of addressing persistent underrepresentation of racial and ethnic minorities in radiation oncology. The program, which supports the accepted students with a stipend, provides a mentored clinical and translational research experience, exposure to clinical radiation oncology practiced at a tertiary academic center,

and career development advice and guidance.[310] Participants in the program have reported firsthand experience as part of a multidisciplinary team, participating in evidence-based decisions in the clinic, and observing firsthand the various stages of workflow, including consultation, simulation, contouring, and review of treatment plans.[311] One such participant was motivated to apply to radiation oncology residency through this program.

Many institutions across the country also seek to offset the financial burden of "audition rotations" or visiting clerkships that may otherwise be inaccessible UCLA offers an Excellence in Medicine Visiting Student Scholarship[312] that provides a stipend to support travel and lodging expenses. Residency programs that offer such financial support for "audition rotations" can begin to offset some of the critiques of these clerkships as detailed earlier in this chapter.

Gender equity in radiation oncology also continues to lag behind other medical specialties.[313] This lack of diversity has been demonstrated at all levels of career, from medical school to department leadership,[314] and manifests as inequity in salary or industry payments,[315] underrepresentation in leadership,[316] and more time and effort invested into career activities by female physicians to accomplish the same levels of recognition as their male counterparts.[317] Many reviews have highlighted the multitude of barriers to gender equity, including unconscious bias, sexual harassment and discrimination, conflicting biologic and professional clocks, and lack of mentorship and/or sponsorship.[318] Crucially, the experiences and barriers facing nonbinary individuals are even further shrouded in the lack of routine or proper demographic documentation and exacerbated by pervasive misgendering in medicine.[319]

Efforts to address the barriers to gender equity have been proposed by Holliday and colleagues and reproduced in Table 35.22.[318] Widely incorporating these strategies into radiation oncology education can begin to shift practices toward diversity, parity, and the evolution of a radiation oncology workforce that more closely resembles the patient population it serves.

TABLE 35.22 EXAMPLES OF BARRIERS AND STRATEGIES TO ADDRESS GENDER EQUITY IN THE RADIATION ONCOLOGY PHYSICIAN WORKFORCE

Barrier	Strategy	Leadership Imperative
Bias	• Unconscious bias training • Blinded resume review • Standardized interviews, adjusting likeability scores	• Hiring and recruitment: • Increase representation of underrepresented groups on recruitment committees • Active recruitment of women and underrepresented minorities
Sexual harassment	• Proactive and enforced policies • Bystander training	• Transform culture: • Create culture that treats women with respect
Salary inequity	• Transparent salary scales • Standardized salary scales • Negotiation training	• Honest assessment of salary inequities at institution
Collisions between biologic and professional clocks	• Generous and transparent maternity leave policies • Support of lactation and integration of work and family responsibilities • On-site childcare options • More flexible tenure timelines • Meetings scheduled during workday to avoid conflict with family responsibilities	• Model practices of inclusion • Implement and support clear policies

Barrier	Strategy	Leadership Imperative
Mentorship	• Increase opportunities for networking and connecting residents and junior faculty with senior faculty	• Create and promote institutional and national career development programs
Exposure	• Debunk misconceptions (eg, lack of patient contact, radiation exposure) through early education of medical students • Include radiation oncology introductory teaching in preclinical curricula	• Connect faculty with medical school opportunities for education, such as guest lectures • Reward faculty for roles in medical school involvement and other diversity initiatives

Reprinted from Holliday EB, Siker M, Chapman CH, et al. Achieving gender equity in the radiation oncology physician workforce. *Adv Radiat Oncol*. 2018;3(4):478-483. With permission.

CONCLUSION

Radiation oncology is a unique field within medicine. Although much of the essential cognitive, affective, and psychomotor knowledge acquired during medical school is useful to a radiation oncology trainee, the knowledge and skills required of a competent and compassionate radiation oncologist are unique and iterative. Curricula to teach this radiation oncology knowledge and skill set must be developed in a logical and rational manner to ensure desired goals and objectives of the learning process are achieved. Furthermore, curricula must be continually updated to meet changes in modern radiation oncology. Meanwhile, the approach to educational programs must reflect changes in information technology, with the potential to increase simulation-based training over traditional didactic lectures and for longitudinal assessments to replace exams performed once every decade. Dissemination of curricular innovations is essential to ensure the radiation oncology educational community is aware of the progress and can further build and improve radiation oncology education while ensuring the educator receives appropriate academic recognition. The radiation oncology profession must place value on medical education scholarship to encourage the advancement of the entire discipline.

Radiation oncology educators must critically evaluate the local, national, and international training milieu and consider disruptive innovation to ensure vigorous and active curriculum revision and renewal. Disruptive innovation is defined in the business sense as follows:

> "Dominant players in most markets focus on sustaining innovations …. That makes a market ripe for upstart companies seeking to introduce disruptive innovations … more convenient products or services."[320]

The concept of disruptive innovation can be applied to radiation oncology education. Current radiation oncology curricula across the globe evolved to satisfy the requirements set forth by accrediting bodies but are not necessarily the most effective and efficient methods for teaching a particular radiation oncology topic or concept. Educational innovations are demonstrated as effective through rigorous curriculum inquiry, learner assessment, and program evaluation and are disseminated have the potential to disrupt the status quo radiation oncology curriculum on a large scale with the ultimate goal of improving the quality of patient care.

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CHAPTER 36

Ethics, Professional Values, and Legal Considerations in Radiation Oncology

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Although progress in medical science has improved the quality and duration of life for some patients with cancer and other serious illnesses, technical expertise alone does not fully account for the upsurge in the societal standing of medical doctors during the past 100 years.[1]

High regard for physicians is contingent on the trust that doctors act unselfishly in a patient's best interests, a role sometimes called moral fiduciary.[2] Essential to this role are medical knowledge and a firm grasp of ethics. Derived from the Greek *ήθοσ* (*ethos*), meaning *character*, ethics refers to the process of applying values and principles in professional interactions and particularly in medical decision-making on behalf of patients. Although not a routine requirement for admission, many medical schools encourage undergraduate applicants to take an introductory course in ethics, and the curriculum of most medical schools now includes coursework in ethics.

To foster an appreciation for the intellectual underpinnings of modern medical ethics, this chapter begins with an overview of scholarly approaches to ethics. Next is a discussion of selected proclamations and codes of ethics published by professional societies, federal commissions, and other authorities as guidelines for medical practice and research. Finally, common practical ethical issues in radiation oncology are addressed, including relevant medicolegal considerations.

CONCEPTUAL APPROACHES USED IN BIOMEDICAL ETHICS

The term *bioethics*, coined in the early 1970s, refers to the academic inquiry and public policy movement addressing the application of science and medicine from a humanistic perspective.[3] Medical ethics may be most

accurately viewed as a branch of bioethics, but the terms are commonly used interchangeably. Among the more influential theoretical approaches that are used in bioethics are *utilitarianism, deontology, casuistry, virtue theory, principlism, and feminism*.

Utilitarianism is based on the premise that, in any situation, the best course of action is the one that produces the maximum net positive value (or least negative value). Utilitarianism can be applied to an individual patient's case or to matters of health policy, in which decisions might be made to achieve the greatest overall benefit for the largest number of people.

Unlike utilitarianism, deontology is an ethical theory based on the morality of actions themselves rather than their net result. Deontology, sometimes called Kantianism in recognition of the influence of Immanuel Kant,[4] calls for consistent standards of behavior at all times, regardless of the consequences. One simple example of the difference between utilitarianism and deontology is the issue of educating patients about their diagnosis, especially if the prognosis is very poor. Whereas a deontologist would always feel obliged to tell the truth even at the risk of causing distress, a utilitarian considers whether telling a patient the complete truth about the disease does or does not really benefit the patient. In daily practice, finding the right balance between purely utilitarian and purely deontologic perspectives in a situation like this one requires consideration of case-specific factors. Respect for the patient's autonomy, for example, is one of the prima facie ethical principles discussed in the next section. Truth-telling is an integral component, and overriding this principle requires justification.

Casuistry is an approach to ethics that emphasizes inductive reasoning based on established precedents, and it is a common practice in both law and medicine. The proper course of action in any individual case is decided by recalling decisions made in prior similar cases. The major weakness of casuistry is the lack of a reference benchmark or settled opinion on novel technologies.

Virtue theory focuses on the character of moral agents, in this case, physicians and other health care providers, focusing less on actions or outcomes. As such, virtue theory captures the way in which correct moral actions occur. For example, it is not only important to tell patients the truth

about their diagnoses, but it is also critical to do so in a compassionate manner. In this case, the virtue is compassion. Accordingly, although virtue is a critical part of assessing moral action, virtues themselves have little guiding force.

Principlism is a system of applied ethics through which core principles ideally govern behavior in the absence of compelling reasons to override them. Principlism can be integrated with the other philosophical approaches already mentioned and serves as a unifying influence.

Feminism concentrates on the concerns of those who are vulnerable and marginalized, as well as categorized unjustly according to particular hierarchies. Frameworks such as structural violence aid in analyzing various practices and policies that perpetuate oppression and injustice. Narrative practice provides a voice to those who may be marginalized on the basis of sex, race, gender, age, disability, susceptibility or presence of stigmatized diseases, imprisonment, health status, and other social categorizations. As such, feminism does not focus solely on women's issues, but on those who are traditionally subject to discrimination.

ETHICAL PRINCIPLES IN BIOMEDICAL ETHICS

A prima facie obligation may be defined as one that is "binding unless overridden or outweighed by competing moral obligations."[4] Four prima facie principles of bioethics are highlighted here: *respect for autonomy, beneficence, nonmaleficence*, and *justice*.

Respect for a patient's autonomy is based on respect for the right to individual liberty. A patient's voluntary decision to seek medical care or comply with referral to a specialist is the starting point of most patient-physician relationships, and competent patients should remain free to forgo therapy or change physicians at any time. The responsibility to respect patients' autonomy is established not only in ethics but also in law. An example is the requirement to obtain a patient's informed consent for proposed medical therapy. In a landmark case involving postmastectomy chest wall radiation therapy, a patient who sustained soft tissue necrosis won a lawsuit against their radiation oncologist for negligence and for lack of proper disclosure regarding possible treatment-related toxicity. The Kansas Supreme Court ruled that doctors should explain "in language as

simple as necessary" the side effects associated with any recommended therapy.[5] Requirements and components for informed consent have since been codified in federal regulations (38 CFR §17.32).

The principle of *beneficence* is intertwined with that of *nonmaleficence*. Some authors have offered nuanced distinctions between the two principles,[4] but the key point is that physicians should act for the benefit of patients and should not harm their patients. Beneficence and nonmaleficence are typically concordant objectives, but sometimes, an intervention that is helpful also entails a high risk of adverse treatment-induced sequelae. For example, administering high-dose morphine to a patient severely dyspneic from an incurable lung malignancy can relieve symptoms but at the same time risks fatally suppressing respiratory drive. Here the quality of remaining life might be improved by a measure that also hastens death. Such an action can sometimes be justified by the principle of double effect, the earliest expression of which is generally attributed to St Thomas Aquinas.[6]

In recent years, a number of states in the United States have enacted the so-called Death with Dignity legislation that permits physicians to prescribe life-ending medications to certain patients with terminal illness when pain or other distress from the illness becomes intolerable to the patient. Generally, there is a stipulation that the patient must be able to self-administer the medication, and there is also a requirement that the patient is competent to make the decision to end their life. Individual hospitals and health systems retain local administrative authority regarding whether these statutes are implemented within the institution and, if so, what specific local regulatory requirements apply.

The principle of justice refers to fairness, typically the equitable distribution of health care resources. Justice-related questions often arise concerning matters of public policy. One specific example is the challenge of determining the means to allocate scarce organs for transplantation. A more global problem faced by all governments is the calculus of distributive justice, which implies that persons ought to be afforded medical care according to their medical needs and the ability of the system to provide.

FORMAL OATHS AND CODES OF ETHICS

There are many published declarations of medical ethics authored by physicians. Not surprisingly, the tone and language of each reflect the social mores and sometimes historical events of the era in which it was composed.

The Physician-Patient Relationship as a Fiduciary Relationship

The physician-patient relationship is a special class of relationship that fits into the broad category of fiduciary relationships, which come with specific ethical and legal obligations beyond those of a normal relationship. As noted in American Jurisprudence:

> *The relation of physician and patient has its foundation on the theory that the former is learned, skilled, and experienced in those subjects about which the latter ordinarily knows little or nothing, but which are of the most vital importance and interest to him, since upon them may depend the health, or even life, of himself or family; therefore the patient must necessarily place great reliance, faith, and confidence in the professional word, advice, and acts of the physician*.[7]

In contrast to the basic duty of care, fiduciaries are held to a much higher standard to act in the best interest of another.[8] Caselaw has clarified additional attributes of such relationships to include power over another (beneficiary), rendering of desirable services requiring special expertise, discretion on the part of the fiduciary to apply that expertise, and a beneficiary who is vulnerable and/or dependent on the fiduciary.[9] Although legal conceptions predate a formal ethical framework, others have developed these frameworks revolving around authority (as evidenced by expert knowledge and skill) and its use for the benefit of the patient, rather than self-interest.[10]

The Hippocratic Oath

> *I will prescribe regimen for the good of my patients according to my ability and my judgment and never do harm to anyone*

The *Corpus Hippocraticum* is a collection of medical treatises dating from around the 5th century BCE, believed to be the work of philosopher-physicians from the Greek island of Cos (Figure 36.1). Contained within the *Corpus* is the well-known oath of Hippocrates, an ancient physician's

pledge of professionalism. Curiously, the oath is inconsistent with some other sections of the *Corpus*, perhaps because it was added later. Comments about abortion and surgery, for example, are at variance with teachings elsewhere in the collected works.[11] Nevertheless, timeless themes are included, and the oath has survived in various modernized versions. The oath is often recited by medical students at the time of graduation—even if its contents are not always well remembered.[12,13]

FIGURE 36.1 Early 19th-century engraving depicting a likeness of Hippocrates, closely resembling images of ancient coins found on the island of Cos bearing his likeness. (Image courtesy of the U.S. National Library of Medicine.)

Percival's Medical Ethics

Hospital physicians and surgeons should minister to the sick, with due impressions of the importance of their office, reflecting that the ease, the health, and the lives of those committed to their charge depend on their skill, attention, and fidelity.

Thomas Percival (1740-1804) (Figure 36.2) published *Medical Ethics* at a time when there was considerable tension among clinicians in his community.[14] In the 1760s, Manchester, England, was a prosperous urban society that comfortably supported public health initiatives, including an infirmary serving as a charity hospital and teaching institution. But as the city grew and became crowded by the 1790s, tensions arose between rival groups in the medical community. Percival was prompted to draft a code of ethics after a contentious dispute about enlarging the infirmary's staff, a threat to the controlling physician faction.[15]

FIGURE 36.2 Thomas Percival (1740-1804). (From Brockbank EM. *Sketches of the Lives and Work of the Honorary Medical Staff of the Manchester Infirmary: From its Foundation in 1752 to 1830 When it Became the Royal Infirmary*. Manchester University Press; 1904.)

Ultimately, *Medical Ethics* provided a template for the codes of ethics adopted by the American Medical Association (AMA) and other societies in the 19th century. Early 20th-century pundits criticized Percival's work as merely a book of medical *etiquette* rather than medical *ethics*. However, revisionist historians have subsequently argued that although Percival focused on interprofessional relationships, he also taught that a physician's duty toward the patient outweighs obligations of civility toward other health care professionals. Furthermore, Percival advanced the enlightened view that indigent patients should receive the same quality of care as affluent patients.[16]

The American Medical Association Code of Ethics

The AMA first adopted a code of ethics at its inaugural meeting in 1847. The initial code was modeled on the work of Percival, but subsequent updates have reflected societal changes and technological progress. The 2016 update begins with an articulation of basic principles[17]:

I. *A physician shall be dedicated to providing competent medical care, with compassion and respect for human dignity and rights*.

II. *A physician shall uphold the standards of professionalism, be honest in all professional interactions, and strive to report physicians deficient in character or competence, or engaging in fraud or deception, to appropriate entities*.

III. *A physician shall respect the law and also recognize a responsibility to seek changes in those requirements, which are contrary to the best interests of the patient*.

IV. *A physician shall respect the rights of patients, colleagues, and other health professionals and shall safeguard patient confidences and privacy within the constraints of the law*.

V. *A physician shall continue to study, apply, and advance scientific knowledge; maintain a commitment to medical education; make*

relevant information available to patients, colleagues, and the public, obtain consultation; and use the talents of other health professionals when indicated.

VI. *A physician shall, in the provision of appropriate patient care, except in emergencies, be free to choose whom to serve, with whom to associate, and the environment in which to provide medical care*.

VII. *A physician shall recognize a responsibility to participate in activities contributing to the improvement of the community and the betterment of public health*.

VIII. *A physician shall, while caring for a patient, regard responsibility to the patient as paramount*.

IX. *A physician shall support access to medical care for all people*.

Among the numerous topics discussed in more detail in the 11 chapters of the code are conflicts of interest in patient care. The AMA code states that "under no circumstances may physicians place their own financial interests above the welfare of their patients. … Treatment or hospitalization that is willfully excessive or inadequate constitutes unethical practice."

The Nuremberg Code and the Declaration of Geneva

During World War II, odious crimes were committed by Nazi physicians who conducted horrific experiments on concentration camp prisoners who were coerced to submit. The Nuremberg Code was a formal response to these World War II–era human rights atrocities disguised as medical experiments.[18] Adopted by the ad hoc court that tried some of the Nazi doctors and medical administrators who conducted these experiments, the Nuremberg Code acknowledges that medical investigations are important and repudiates the defendants' assertions that they had followed contemporary standards of informed consent. For a medical experiment to be morally permissible under the Code, it must meet 10 criteria, paraphrased as follows:

- Voluntary consent of the human subject
- Necessity to yield results helpful to society
- Appropriate design based on knowledge of the disease under study

- Avoidance of unnecessary physical and mental suffering and injury
- Absence of reason to believe that death or disabling injury will occur
- Overall degree of risk in proportion to the nature of the problem to be solved
- Adequate precautions against the possibility of the subject's injury, disability, or death
- Qualified persons conducting the study
- Unrestricted freedom of the subject to end the experiment if they reach the physical or mental state where continuation of the experiment seems impossible
- Willingness of the investigator to discontinue the study at any time if there is reason to believe that continuing the experiment is likely to result in injury or death to the subject

In the aftermath of the war, the international medical community was especially sensitized to the need for universal adherence to high standards of ethical behavior. The Declaration of Geneva was adopted in 1948 by the World Medical Association and has been updated since then. The text includes the physician's vow to ignore "considerations of age, disease or disability, creed, ethnic origin, gender, nationality, political affiliation, race, sexual orientation, or social standing" in the treatment of a patient and to uphold "even under threat … the utmost respect for human life."

Case Study

Despite publicity about the Nuremberg Code and the Geneva Declaration, controversial large-scale, government-sponsored medical studies took place in the years following World War II. Experimentation on the effects of radiation exposure on humans was conducted in the United States during the Cold War, when fears of nuclear warfare prompted inquiry into the carcinogenic and other adverse health effects of environmental exposure to ionizing radiation. In response to public concern about thousands of federally funded studies conducted from the 1940s through 1970s without consent of the subjects, in 1994, President Bill Clinton established the Advisory Committee on Human Radiation Experiments (ACHRE). ACHRE was composed of ethicists, radiation oncologists, and others with relevant

expertise. It was charged with evaluating the experiments' ethical and scientific standards and recommending actions to ensure that any mistakes of the past would not be repeated. ACHRE reviewed all available documentation and also conducted an oral history project in which scientists described prevailing sentiments regarding human research ethics during the era of interest.

ACHRE found that government officials and investigators were in some cases culpable "for not having had policies and practices in place to protect the rights and interests of human subjects who … could not possibly derive direct medical benefit."[19] One example was the observational study of uranium mine workers exposed to radon levels known to be hazardous, without warning and without efforts to reduce the radon levels by ventilating the mines. As a result, lung cancer developed in hundreds of workers, and appropriate compensation was recommended for the individuals affected.

The Belmont Report

In 1972, Jean Heller[20] exposed the injustices of the U.S. Public Health Services (USPHS) Study of Untreated Syphilis in the Negro Male that was conducted in Tuskegee, Alabama. During a 40-year period beginning in the 1930s, 399 indigent African American sharecroppers with syphilis and 200 without syphilis were subjects in a natural history study of the disease. The men mistakenly believed that diagnostic blood tests and lumbar punctures composed treatment for their "bad blood"; when in reality, these were done solely to monitor the course of the infection. Moreover, years later when penicillin was discovered and found to be effective in the treatment of syphilis, it was withheld intentionally from the men. Subsequently, public awareness of the USPHS study likely contributed to enduring reluctance among some members of minoritized groups to participate in clinical trials,[21,22] and the political backlash provoked action by the federal government.

The 1974 National Research Act established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The commission met at the Belmont Conference Center in Maryland to develop ethical guidelines for the conduct of biomedical and

behavioral research. In 1979, the commission published *Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, commonly known as the Belmont Report.[23]

In the Belmont Report, a clear distinction is made between medical research and clinical practice. The term *practice* describes interventions intended "to enhance the well-being of an individual patient … that have a reasonable expectation of success," whereas *research* is "designed to test an hypothesis, permit conclusions to be drawn, and … contribute to generalizable knowledge." Sometimes, a clinician uses good judgment and departs from standard methods for the benefit of an individual patient in special circumstances. However, if major innovations are proposed as a replacement for standard techniques, then a formal investigation should be conducted to assess safety and efficacy. The National Commission embraced a principlist perspective in drafting the report, emphasizing in particular respect for persons, beneficence, and justice. The Belmont Report's definition of respect for persons incorporates respect for autonomy and special concern for individuals with diminished capacity to exercise their autonomy. Involving prisoners in research activity is cited as an example. Although it is inappropriate to deny prisoners the possible benefit of experimental interventions, any direct or indirect pressure on prisoners to participate in clinical studies must be avoided. For instance, a promise of clemency in return for study enrollment is unacceptable. The report also addresses the nature of justice in medical research, emphasizing that the process of selecting subjects for a research study must be carefully examined. Investigators should minimize the chance that socioeconomically disadvantaged groups are represented disproportionately as a result of a vulnerability to manipulation in the health care environment.

The Common Rule

On the heels of the Belmont Report, modern regulations governing human subjects research in the United States were published in 1991 as The Federal Policy for the Protection of Human Subjects (the "Common Rule"). The Department of Health and Human Services regulations lie within 45 CFR part 46. Subpart A encompasses the Common Rule and is recapitulated by 20 federal agencies in their own regulations. Additional subparts

encompass special protections for specific vulnerable populations, including pregnant women, fetuses, neonates (B); prisoners (C); and children (D).[24]

National Electrical Manufacturers Association Code of Ethics

The makers of equipment and software used in the practice of radiation oncology are not required to demonstrate the clinical efficacy of a new device or software through the same sort of clinical testing that is required by the U.S. Food and Drug Administration (FDA) for approval of a new drug or implantable medical device. Rather, most treatment devices are approved after demonstration of safety and substantial equivalence to an approved device that is already commercially available. A company that wishes to sell a new device submits a premarket notification to the FDA at least 90 days before commercial distribution is to begin, in accordance with Section 510(k) of the FDA Modernization Act of 1997. Because devices may be introduced into the market without proof of superiority in any given clinical situation, manufacturers may promote their products to physicians by emphasizing intuitively attractive features that might or might not provide meaningful clinical advantage to patients.

On January 1, 2005, members of the National Electrical Manufacturers Association (NEMA) adopted a code of ethics regarding interactions between makers of medical imaging and treatment equipment and physicians (www.nema.org). Individual sections of the NEMA code address member-sponsored product training and education, support for third-party educational conferences, sales and promotional meetings, arrangements with consultants, gifts, provision of reimbursement and other economic information, charitable donations, and research grants. The guidelines are essentially consistent with the AMA policy on gifts and applicable federal regulations. NEMA members are allowed to support educational conferences and advertise their wares in these venues, and also they may provide educational support for individual customers in the safe use of their products. However, hospitality provided by NEMA members at conferences and meeting should be “modest in value and … subordinate in time and focus to the purpose of the meeting.” When it is necessary to demonstrate

nonportable equipment, members may pay for reasonable travel costs of attendees with a bona fide professional interest, but not for their guests.[25]

COMMON ETHICAL ISSUES IN RADIATION ONCOLOGY

> *Doctors wear a lot of hats these days; besides the usual physician role, we are expected to be a researcher, financial counselor, administrator, gatekeeper, patient advocate in the medicolegal system, ethicist, and Lord knows what else.*
>
> —*Thomas J. Smith*[26]

Financial Relationships With Hospitals and Referring Physicians

Reimbursement for radiation oncology services or other procedure-intensive subspecialties can be a major revenue source for hospitals. At the same time, subspecialists depend on other physicians to refer patients for evaluation and management. These situations can tempt hospital administrators to reward subspecialists for practicing in their facility and might tempt the subspecialists to induce referrals with financial incentives. In either case, a conflict of interests emerges: Treatment recommendations can be influenced not only appropriately by patient-centered beneficence but also inappropriately by the physician's interest in personal gain. In the United States, the Anti-Kickback Statute and the Stark Law make it illegal to engage in such unscrupulous medical business practices. These laws work in tandem with the False Claims Act to deter fraudulent claims to the government, including Medicare and other programs.

The Anti-Kickback Statute (42 USC §1320a-7b) includes both civil penalties and criminal prosecution for acts involving Medicare or state health care programs. Section (b) makes it a felony punishable by a fine up to $25,000 and up to 5 years in prison to solicit or receive "any remuneration (including any kickback, bribe, or rebate) directly or indirectly … in return for referring an individual to a person for … any item or service" reimbursed in whole or in part through Medicare or a state health care program. The Anti-Kickback Statute also bans other fraudulent transactions supported through the same funding sources. As violations come with criminal penalties, proof of improper intent is necessary prior to prosecution. Additional civil penalties include up to a $50,000 fine per

violation and 3 times the value of the kickback (treble damages), as well as *permanent exclusion* from Medicare and other programs; that is, the convicted individual would no longer be able to bill Medicare for any services and their services could no longer be billed by an employer or group practice. Lastly, a conviction also opens liability to the False Claims Act (*infra*).

Named for its leading congressional author, Rep. Pete Stark of California, the Stark Law (42 USC §1395nn; "Limitation on certain physician referrals") bans other misconduct involving Medicare and Medicaid patients. The Stark Law prohibits (1) a physician from referring a patient for a "designated health service" to a clinic or other facility with which the physician or an immediate family member of the physician has a financial relationship and (2) the designated health service from submitting claims for services resulting from prohibited referrals. Unlike the Anti-Kickback Statute, no proof of improper intent is required, and violations are regarded by actions alone under strict liability without any consideration of intent. A detailed discussion of the nuances of the Stark Law is out of scope, but any such conduct blanket illegal on its face unless it falls squarely within one of the dozens of explicit safe harbors (42 CFR §1001.952[a]-[u]). Radiation therapy is considered a designated health service, but it is clarified that a request by a radiation oncologist for radiation therapy is considered integral to the consultation request from the (non–radiation oncologist) referring physician and does not constitute a self-referral per se in most situations. Although sanctions for violations of the numerous Stark Law regulations are civil in nature (in contrast to the criminal penalties of the Anti-Kickback Statute), such violations can also be catastrophic. Each violation currently carries a fine of $15,000 to $100,000 in addition to 3 times the amount claimed (treble damages), as well as the potential from permanent exclusion from the Medicare program. The second piece prohibiting submission of claims stemming from prohibited referrals also opens violators to additional penalties through the False Claims Act (*infra*).

One such safe harbor concerns physician-owned hospitals, which grew in number until 2010, when the Affordable Care Act prohibited both the establishment of any new physician-owned hospitals and the expansion of preexisting ones in Section 6001 (42 USC §1395nn[i]). As an interesting counterpoint, the American Bar Association Model Rules of Professional

Conduct Rule 5.4 explicitly prohibits nonlawyer ownership of any firm or association.[27]

Under the False Claims Act (31 USC §3729), submitting fraudulent claims to the government for reimbursement of health care services is illegal without any consideration of intent. Any person who knowingly presents fraudulent claims to the U.S. government may be fined $5,000 to $10,000 per violation and may be liable for 3 times the amount of any damages (treble damages) sustained by the government. Upcoding (submitting a claim with a code of a higher value than services actually rendered) is a common example of fraudulent behavior under the False Claims Act. Each individual incidence of an upcode is considered an individual violation subject to its own fine and treble damages. Nearly all of these cases are settled, as a judgment for the actual total damages would be catastrophic for nearly all organizations.

Like the Anti-Kickback Statute and Stark Law, the False Claims Act violations may be pursued by the U.S. government. However, it also provides for a unique enforcement mechanism through a "qui tam" action wherein a private citizen functions as a whistleblower (relator) and brings a suit to the government, which can intervene and take the case (31 USC §3730[b]). If successful, the relator is entitled to between 15% and 25% of the recovered proceeds (31 USC §3730[d]), which can be in the hundreds of millions of dollars.[28]

Self-Referral for Radiation Oncology Services

In addition to being considered a designated health service per Stark Law language, radiation therapy is also considered in the category of in-office ancillary service exemptions for Medicare coverage. The implication is that radiation therapy is grouped with a number of less complex services such as simple blood tests or antibiotic injections that a physician might reasonably do in their office for the convenience of rendering a quick diagnosis or managing a simple medical problem on an outpatient basis. Because of this classification for radiation therapy, non–radiation oncologists may own linear accelerators and derive profit from the utilization of this technology on patients referred for treatment. One of the most contentious issues to emerge in recent years is the debate over the legitimacy and ethics of

business arrangements in which non–radiation oncologists own radiotherapy delivery technology and derive profit from self-referring patients for treatment.

In 2013, Jean Mitchell reported a study in *The New England Journal of Medicine* in which patterns of intensity-modulated radiation therapy (IMRT) utilization for prostate cancer were analyzed. Urologists were grouped according to whether they purchased radiotherapy equipment. For those who purchased equipment (the self-referring group), the use of IMRT in the periods before and during ownership was compared. To account for the changing baseline trends in prostate cancer management, the use of IMRT among patients seen by non–self-referring urologists who did not own radiotherapy equipment was also analyzed, and a "difference-in-differences" methodology was employed. It was observed that men treated by self-referring urologists, as compared with men treated by non–self-referring urologists, were significantly more likely to be treated with IMRT rather than less expensive options.[29] Other similarly constructed studies have yielded concordant results.[30,31]

Another concerning area lies in the rapid adoption and use of electronic surface brachytherapy by dermatology practices in the treatment of nonmelanomatous skin cancers. Despite a recommendation from the American Brachytherapy Society to not use this modality outside the auspices of a trial,[32] and a lack of evidence to make a recommendation to use at all from the American Academy of Dermatology,[33] routine clinical use of this modality continues, growing 20-fold over the course of 2 years from 2011 to 2013.[34] Even more concerning are the device manufacturers' billing recommendations to add codes for complex simulation, custom shielding, depth dose calculations, and special procedure for multiple radiation sources *for each fraction delivered*.[34]

Terry Wall[35] offers a perspective on both the legal and ethical aspects of this issue. He points out that advocacy efforts by the American Society for Radiation Oncology (ASTRO) to remove radiation therapy from the list of in-office ancillary service exemptions have been unsuccessful, and there is unlikely to be a legislative resolution. Dr Wall poses the question of whether an individual radiation oncologist who is the potential recipient of a self-referral is "eating fruit from a poisonous tree." He offers guidance for the individual practitioner to ensure that self-referral arrangements put the

patient's interest first, including a mandate to disclose the financial interests to the patient and inform patients of their alternative to receive care elsewhere.

Electronic Recordkeeping and Billing Practices

The principles of respect for autonomy and nonmaleficence oblige confidentiality in physician-patient communications. Publicizing private details of a patient's condition can create social and economic harms for the patient. With the advent of electronic medical records and internet communication, there is a greater need for vigilance in this respect.

The recent passage of the 21st Century Cures Act adds yet another wrinkle in communicating with patients. Among other provisions is one regarding information blocking in electronic medical records (42 USC §300jj-52). Under these provisions, all test results must be automatically released to patients through electronic portals immediately when available. While this serves the principle of respect for autonomy, premature release of results without review by the treating physician or context may at times violate the principle of nonmaleficence. Indeed, a single-institution study of over 5.5 million test results for 44,000 patients revealed a *doubling* in the proportion of test results reviewed by patients before the ordering clinician from 37% to 75% before and after the passage of the Cures Act.[36] Widespread release of pathology and imaging results in an oncology setting without any clinical context may generate unnecessary anxiety.[37]

In the United States, the Health Insurance Portability and Accountability Act of 1996 (HIPAA) empowers the Department of Health and Human Services to codify standards for storage and transmission of an individual patient's health information. Penalties for violations vary in proportion to their severity. In the worst case of wrongful disclosure of information with intent to sell it, a fine of up to $250,000 and a prison term of up to 10 years can be imposed. Of note, this statute does not come with a private cause of action, that is, a private citizen cannot directly sue the responsible party for a breach of information and only the government may bring such actions under HIPAA (see, eg, *Acara v Banks*).[38] However, a more recent case opens the door to an alternate theory of potential private damages under the

14th Amendment,[39] and additional state law claims may provide a private cause of action.[40]

Applications of New Technology

Innovative treatment delivery methods such as stereotactic body radiation therapy for oligometastatic/oligoprogressive disease, proton therapy, adaptive therapy, and other new treatment techniques/indications can be intuitively appealing but cannot be assumed to provide meaningful clinical benefit unless tested properly against existing standard treatment methods. A recent example underscoring this need is the lack of benefit of proton therapy over photon therapy for non–small cell lung cancer in the first randomized trial comparing these modalities.[41] Ideally, it is best that such innovations are tested in formal research protocols in which a clinical problem is identified and the new technology is proposed as a solution so that toxicity and efficacy can be monitored closely. A prospective clinical trial approved and monitored by an institutional review board affords the opportunity to advance knowledge in the field with ethical oversight.[42]

Clinical Trial Conduct

Instances of flagrantly improper clinical research taint the annals of medical history. The USPHS study of syphilis mentioned earlier and the human radiation experiments conducted during the Cold War without the consent of the participants are dark reminders of the need for ethical oversight of research.

Obtaining a participant's informed consent is of paramount importance in conducting most clinical research. Despite the recognized importance of informed consent, precisely how much information should be conveyed to a potential clinical trial participant is debatable. The Belmont Report offers this criterion: "The extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate" in the study. In certain situations, the nature of a study requires that there is incomplete disclosure of information to the participant to sustain the integrity of the study. The Belmont Report condones such research only when "(i) incomplete disclosure is truly necessary to accomplish the goals

of the research, (ii) there are no undisclosed risks to subjects that are more than minimal, and (iii) there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them." The Federal Policy for the Protection of Human Subjects (45 CFR 46) reflects these arguments.

Advances in the biosciences, such as stem cell research, cloning, and manipulations of the human genome, have been associated with contentious public debate. The federal government and professional policies on such matters have sometimes been constructed as a compromise between scientific opportunity and political ideology.[43] Extra safeguards have been imposed in some settings; for example, the federal government requires an extra level of review for gene transfer experiments.[44]

Genetics

The management of some patients with cancer can involve assessment of genetic markers that might predict treatment response and reveal a predisposition to the development of certain cancers among the patient's family members. The National Society of Genetic Counselors has published a guideline concerning genetic cancer risk assessment, counseling, and testing.[45] It is recommended that the process of obtaining informed consent for genetic testing should include, among other considerations, an explanation to the patient of possible implications on the ability to obtain health or disability insurance in the future. In 2008, Congress passed the Genetic Information Nondiscrimination Act (GINA; 42 USC §2000ff), which prohibits discrimination on the basis of genetics and requesting genetic information (1) prior to the manifestation of a disease or disorder and (2) only for the purposes of health insurance and employment. Unfortunately, GINA does not provide any protection for other situations, including other types of insurance or lending. An erratic patchwork of various state laws attempts to fill gaps in various ways, but overall lacks cohesion.[46] Caselaw has also blurred the line of both when disease manifests and what is encompassed in "genetic information."[47] Lawmakers could not foresee the explosion of routine genomic sequencing in the clinical application of precision oncology and the legislative and regulatory

processes lag behind technological advances in this space, potentially leaving patients vulnerable.

Relationships With Industry Sponsors

Incentives from industry representatives to prescribe pharmaceuticals or purchase equipment threaten the fiduciary obligations physicians have to their patients. The AMA Code of Ethics states that physicians should decline cash gifts in any amount from any entity with a financial interest in the physicians' treatment recommendations.[17] The AMA code allows for accepting an in-kind gift that will directly benefit patients and is of minimal value and allows for support for educational programs with certain restrictions.

Advertising items such as patient education pamphlets and anatomic models bearing a sponsor's name are commonly found in radiation oncology clinics.[48] Physicians should be aware of any real or perceived influence on the patient- physician relationships resulting from their tacit compliance with such marketing activities.

Pharmaceutical companies may be prosecuted for kickback schemes or other illegal enticements to physicians, and the civil and criminal penalties paid by the corporations held responsible have ranged up to hundreds of millions of dollars.[49] Brennan et al[50] contend that voluntary self-regulation by physicians, industry, and government is an insufficient safeguard against the conflict of interests nurtured by close relationships between practicing doctors and sellers of pharmaceuticals and medical products. These authors argue that academic medical centers should set an example for the rest of the medical community by establishing policies that forbid gifts to physicians, funds for travel, unjustified consulting fees, participation in speakers' bureaus, and the practice of "ghostwriting" medical articles, among other things. Substantial attention has focused on implementing policies related to these issues.[51,52]

Prasad and Rajkumar[53] recommend a forward-looking strategy of transparency and full disclosure as a means of minimizing the impact of conflict of interest in academic publications and presentations. Their suggestions include excluding authors of reviews, editorials, and practice guidelines from having any financial interest that exceeds a reasonable

threshold[54]; stopping the practice of having professional medical writers funded by industry serve to prepare manuscripts; and open disclosure of the amount of support given to professional organizations by individual industry sponsors. The Physician Payments Sunshine Act was initially enacted as §6002 of the Affordable Care Act and expanded to include other health care providers, like advance practice providers by the SUPPORT ACT (42 USC §1320a-7h). This led to the creation of the Open Payments Program, which publishes all payment data annually in a publically searchable database to promote transparency and accountability.[55] Despite the tracking and disclosure of all these data, other studies continue to demonstrate the ability of these payments to influence physician prescribing practices,[56] even to the point of prescribing nonrecommended and low-value interventions in patients with cancer.[57]

CASE-SPECIFIC DILEMMAS: THE ROLE OF AN ETHICS CONSULTANT OR COMMITTEE

The radiation oncology–related ethical issues discussed thus far relate primarily to general practice and research guidelines. However, individual cases can also pose uncertainties regarding the proper choice of action for a specific patient.

Case Study

A 37-year-old woman undergoes modified radical mastectomy for a pathologic T3N2M0 breast cancer; postoperative chemotherapy and locoregional radiation therapy are recommended. The patient wishes to receive the therapy only if she can periodically interrupt it to alternate with what she calls a "natural herbal" therapy.

In this case, respect for a patient's autonomy conflicts with what is believed to be in the patient's best interests, but a physician cannot ethically abrogate the fiduciary responsibility to a patient simply for reasons of unfamiliarity with alternative medicine or prejudice against its worth.[58] Similar situations may arise when patients do not adhere to standard treatment recommendations because of a particular religious faith or cultural heritage. Although physicians must respect patients' choices, there is no strict obligation for a physician to accept a particular individual as a

patient if de novo, especially if there are foreseeable personal conflicts that might adversely affect the patient-physician relationship, unless the treatment is needed urgently and/or there are no other physicians with the same skills or knowledge to treat the patient. However, terminating an existing relationship requires adequate notice to the patient for the transfer of care and facilitation thereof.

Pediatric oncology also requires special considerations. Parents are the chief decision makers, but sometimes their wishes can seem discordant with the best interests of the child. In a different context, what should be done if the adult children of a patient with a heritable trait for malignancy inquire of the patient's diagnosis, but the patient has instructed the physician not to reveal any information to them? The obligation to patient-physician confidentiality conflicts with a potentially overriding obligation toward the family members who might benefit from guidance toward screening.

In cases such as these in which it is difficult to choose between two defensible courses of action, individuals and committees with experience in clinical medical ethics can provide the expertise needed to sort through the ethical, legal, and social issues involved.[59]

PALLIATIVE MEDICINE

Palliative medicine has become a well-established component of clinical practice, and numerous academic medical centers offer accredited fellowship programs in this field. Palliative medicine places emphasis on symptom management and the goals of care, not only at the end of life but also in the treatment of serious illnesses. An exclusively palliative approach is ethically justified when fully aggressive therapy might be intolerable or futile, but the use of early concurrent palliative care can also be beneficial for patients with metastatic cancer or cancer with high symptom burden who are still receiving aggressive anticancer therapy.

Case Study

A 92-year-old woman presented with stage IVA maxillary sinus cancer. She complained of sinus fullness and a painful 4-cm neck node. Radical radiation therapy to the primary and neck was recommended, and the patient underwent placement of a percutaneous gastric feeding tube and full

dental extraction. Midway through the course of treatment, the patient required a lengthy hospitalization for failure to thrive and severe mucositis.

In retrospect, a less aggressive course of radiation therapy intended to reduce the sinus and neck symptoms would have likely been a better choice for this patient, who was frail and unable to withstand intense treatment. Palliative medicine pays careful attention to a patient's individual needs, quality of life, and a discussion of goals of care. A recent randomized study demonstrated improved quality of life and overall survival when palliative care was given early alongside standard cancer treatment for metastatic lung cancer.[60] In many cases, aggressive symptom management and good communication among patient, family, and provider may result in better quality and, perhaps, quantity of life than would antineoplastic therapy that has little expectation of efficacy but significant risk of morbidity.[61]

ETHICS AND MEDICAL ERRORS

Soon after the discovery of x-rays by Wilhelm Röntgen more than 100 years ago, the first cases of malpractice involving the clinical use of radiation therapy were tried in the U.S. court system.[62] During the early 20th century, severe dermatitis was a frequent plaintiff's complaint—not surprising in view of the physical limitations of the low-energy machines available at the time.

In 1999, the Institute of Medicine published a report on medical errors, elevating the level of public awareness and stimulating inquiry into this topic.[63] One recent study has suggested that medical errors might be the third leading cause of death in the United States.[64]

Physicians are often reluctant to discuss errors. It has been suggested that doctors and patients "harbor deep within themselves the expectation that the physician will be perfect."[65] Other reasons for reticence include uncertainty about whether an event really is an error, concern for the patient's well-being, and fear of litigation.[66] To thread this needle and allow for sincere apologies and expressions of remorse that are not recorded as evidence of negligence, error, or malpractice, many states have enacted the so-called "apology laws," in which expressions of sympathy are inadmissible as evidence of liability in civil court.[67] As of 2021, 39 states, DC, and Guam have such provisions within their state laws.[68]

If a patient has an undesirable treatment outcome, careful review of the case can help distinguish error from untoward but unsurprising occurrence. For example, severe pneumonitis after breast radiation therapy is uncommon, but not necessarily proof of negligence. Concern that disclosing an error causes a patient undue anxiety is contradicted by studies revealing that patients prefer physicians to acknowledge errors[69] and that they might even sue for lack of apology.[70] In cases of alleged or suspected error leading to injury, the institutional risk management service should usually be contacted for advice. However, fear of litigation should be mitigated by the fact that a low overall percentage of patients who suffer negligent injuries actually file malpractice claims.[66] Indeed, Studdert et al[71] demonstrate just how imperfect a vehicle American tort law is to compensate for medical error. In their review of 1,452 closed claims, 3% had no injury and 37% did not involve errors. These with no errors accounted for 13% to 16% of the cost of the entire malpractice system. In contrast, 27% of claims involving injury due to actual error did not receive any compensation. Within radiation oncology, a study examining all cases between 1985 and 2015 found 32 results. The two most common causes of action were excessive radiation (34%) and failure to refer/order appropriate tests (28%). Thirty-four percent of cases resulted in a judgment for the plaintiff (mean amount $4.7 million) and 13% resulted in a settlement (mean amount $1.5 million).[72]

Nondisclosure of error can weaken the trust at the core of the patient-physician relationship. The argument for disclosure is especially strong when there is a specific preventive intervention that might lessen the severity of possible future injury. Nevertheless, the question still remains: Are physicians ethically obliged to disclose an error, even if there is no immediate harm to the patient?

Case Study

A patient with T3N1M0 squamous cell carcinoma of the left retromolar trigone received concurrent cisplatin plus IMRT to the gross disease, with elective coverage of adjacent nodal echelons. The intent was to give 54 Gy to adjacent uninvolved lymph nodes at a rate of 1.8 Gy/day and 66 Gy to the gross disease at a rate of 2.2 Gy/day using a simultaneous integrated

boost technique, with all treatment completed in 30 fractions. After the spinal cord was contoured as an organ at risk, the structure was inadvertently deleted on all planning computed tomography slices below the level of the gross disease. As a result, when the IMRT inverse planning software optimized the dose distribution according to the constraint of limiting the maximum dose to the spinal cord to 50 Gy, the entire cross section of a 6-cm length of cervical spinal cord received the full prescription dose. The error was not detected until 1 week after the patient completed treatment, during a routine quality assurance check.

In this example, no injury has yet occurred, but the patient is at increased risk for radiation myelitis. Although there is currently no available proven preventive measure, if the escalated risk of myelitis is unknown to the patient, they might later undergo misguided management by another physician if symptoms develop. For instance, if the patient develops arm and leg weakness, a magnetic resonance imaging scan showing nonspecific enhancement and edema in the cervical spinal cord might be interpreted as evidence of metastatic intramedullary or epidural tumor rather than radiation change. Unaware of the prior treatment error, the patient would be unable to inform the other physician involved about the high risk for radiation injury. As a result, the patient might be given only minimal supportive care on the assumption of incurable recurrent disease rather than appropriate efforts toward rehabilitation.

Evans and Decker[73] have offered practical suggestions on how to address the issue of a medical error in radiation oncology once the event has been recognized. They advise disclosure for any errors that result in a perceptible clinical effect, change in diagnosis or treatment course, or a chance of future harm. Their two-phase response recommendation involves initial attention to the patient's immediate needs and an apology that avoids giving an impression of defensiveness. Later, after a more thorough analysis of the situation has been completed with the involvement of the hospital's risk management team, a carefully prepared discussion with the patient and other interested parties can occur.

Toward the goal of fostering a culture of safety across the field of radiation oncology and facilitating the identification of preventable systematic errors with different treatment delivery platforms, ASTRO and the American Association of Physicists in Medicine have created a national

Radiation Oncology Incident Learning System.[74] This program allows for anonymous, privacy-protected self-reporting of incidents and near misses. The information can be used locally to inform root cause analysis projects that identify ways of improving patient safety. Industrial engineering–based principles for minimizing errors in a busy radiation oncology clinic are now becoming widely implemented, and entire texts devoted to this topic are available.[75,76]

CONCLUSION

Society's view concerning medical ethics has shifted over time to adapt to the forces of advancing knowledge. Ethical guidelines have sometimes been constructed as formal documents or mandated as law, but no single system comprehensively predicts and resolves all situational dilemmas. The core principles of medical ethics remain essential foundations for the practice of medicine.

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CHAPTER 37

Health Economics and Health Policy

P. Travis Courtney, Ann C. Raldow, Eric M. Chang, and Michael L. Steinberg

The 21st century has been marked by a continued increase in health expenditure in the United States, estimated at 16.7% of the country's gross domestic product (GDP) in 2019 and increased to 18.8% in 2020 during the COVID-19 pandemic followed by a decrease to 17.4% in 2021—the highest ranked in data collected from the Organization for Economic Co-operation and Development (OECD) member countries and nearly twice the OECD average[1] (Figure 37.1). Furthermore, national health spending is only expected to continue its rise in the coming years, with the Centers for Medicare & Medicaid Services (CMS) National Health Expenditures projecting health spending to grow 0.8% points faster than GDP per year over the 2022 to 2031 period, amounting to 19.6% share of GDP by 2031.[2] The cost of cancer care is escalating precipitously, estimated at $24.7 billion in 1987 (in 2007 U.S. dollars) versus $48.1 billion in the 2001 to 2005 period.[3] Although the double-digit growth rates in U.S. cancer expenditures observed prior to the Great Recession began to decline substantially in 2007, associated costs of cancer care are still projected to rise from $183 billion to $246 billion from 2015 to 2030 (in 2020 U.S. dollars), assuming constant incidence, survival, and cost.[4-6]

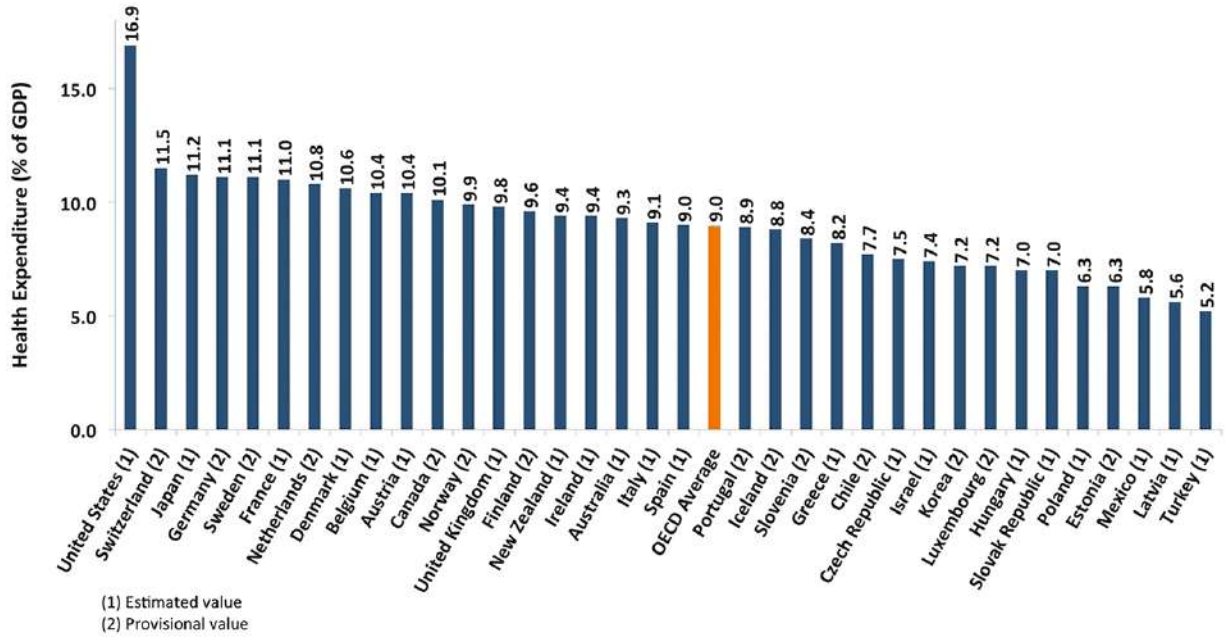

FIGURE 37.1 Health expenditure expressed as a percentage of gross domestic product (GDP) among the Organization for Economic Co-operation and Development (OECD) member countries. (OECD Health Statistics 2021.)

Many factors contribute to this rise in costs, including aging of the population, with anticipated increases in both the number and percentage of older patients and commensurate increases in new diagnoses, magnified by persistence of risk-increasing behaviors and earlier diagnoses via improved cancer screening.[7,8] These demographic factors warrant discussion regarding the allocation and prioritization of resources. Yet, the increasing cost to the individual patient merits further consideration as well. Driven partly by innovation—new advances in systemic therapies, radiotherapy (RT) techniques, surgical devices, and diagnostic tools—these investments pose a particular dilemma, as efforts to cut costs would potentially slow the development of lifesaving medications and technologies. However, in the setting of limited resources, these rising costs are not benign. In 2018, roughly 43% of expenditures in cancer care were publicly funded (33% by Medicare and 10% by Medicaid), and by 2030, more than 70% of cancer diagnoses will be made in persons eligible for Medicare.[7,9,10] Thus, from a societal perspective, we must consider whether our expenditure in cancer care is reasonable when balanced with other priorities in medical care and other areas. Furthermore, substantial out-of-pocket costs directly impact

patients' ability to access medical care and to afford other nonmedical life necessities, with having insurance often not enough to protect patients from the impact of the high costs of treatment.[11] Estimates by the Congressional Budget Office indicate that aging explains less than half of the estimated increase in spending for major health care programs as a share of GDP from 2016 to 2046, with most resulting from rising health care costs per person—indicating that these challenging questions and the need for the transformation of health care delivery will not go away.[12]

In this setting of mounting health care costs, interest in health policy and health economics has flourished in the past decades. Broadly, health policy as a discipline encompasses questions of access, cost, and quality of health care.[13] As a function of health policy, health economics addresses difficult questions regarding the appropriate and efficient allocation of resources in the health care setting as well as the behavior of stakeholders in the face of competing choices for financial resources. In his seminal article, "Uncertainty and the welfare economics of medical care," Kenneth Arrow, often credited with the birth of health care economics, distinguishes between health and other goods, noting that health care, in contrast with other goods and the free market ideal, is marked by uncertainty on behalf of the patient in evaluating the quality of care provided by their physician, leading to asymmetric information.[14] Physicians, serving as agents for their patients, are expected to act in their patients' best interests, though this system, based on trust, permits for misaligned incentives. Moreover, health care is awash in externalities or costs and benefits externally imposed by the purchaser on others not party to the transaction. Given these notable exceptions, it is imperative that health policy ensures symmetric access to quality health care. As defined by Steinberg, ideal health policy should ensure (1) that all patients get all necessary care, (2) that equivocal and nonindicated treatment be excluded, (3) that cost of care be socially responsible, (4) that variation in the quality of care be so small from a technical perspective that does not matter from which facility or provider a patient receives treatment, and (5) that when competition occurs, it should be over the quality of the art of care, such as how patient centered it is and how well staff and physicians communicate with patients.[13]

Radiation oncology, in particular, has been labeled as an outlier in its contribution to health care spending and as such has often been targeted in

policy discussions. Though Medicare's sustainable growth rate (SGR) formula for physician payment was permanently repealed in April 2015, radiation oncology was notable for exceeding its SGR target over the 2003 to 2009 period by nearly 300% expressed as a percentage of 2002 expenditure.[15,16] Between 2000 and 2009, the total Medicare expenditures for external beam RT increased from $256 million to $1.08 billion, mainly owing to reimbursement for intensity-modulated radiation therapy (IMRT).[17] In addition, the code for IMRT demonstrated the fourth highest percent increase of all Medicare codes between 2010 and 2011.[18] However, these disproportionate expenditures subsequently plateaued and even decreased in the following years.[19,20] It should also be noted that although approximately 30% to 50% of all patients diagnosed with cancer will receive some form of RT during their disease course,[21-23] radiation oncology represents only a small percentage of total Medicare spending. In 2017, radiation oncology accounted for just 1.4% of total charges allowed by Medicare, which was generally stable from 2002 (1.2%) and 2012 (1.6%).[19] For comparison, the percentage of Medicare spending on hematology/medical oncology increased from 5.6% to 6.5% in that same time period. A similar pattern was seen in Medicare payments for care at the end of life, in which the average payments per beneficiary between 2016 and 2019 for radiation oncology decreased by approximately 2%, whereas for medical oncology, average payments increased by more than 32%.[24] Furthermore, in 2020, CMS reported that the total spending for radiation oncology services was about $2 billion dollars less than Medicare Part B spending on just three drugs (Rituxan, Opdivo, and Keytruda) that were used in less than half of the number of beneficiaries.[25,26] Despite these trends, the specialty remains the subject of spending scrutiny and has experienced a decline in average Medicare reimbursements of more than 20% over the past decade.[27-29]

Although there are likely multiple underlying causes for the field's disparate, albeit stabilizing and perhaps overstated, contributions to health care spending, including the employment of advanced technologies and the complex teams required for their safe and effective use, they were at least in part secondary to our primarily resource-based payment system, in which hospitals and clinics are reimbursed for discrete elements of care.[30] In this system, there is incentive to maximize billable units, such as by using

advanced treatment modalities when not clinically indicated and by dividing dose over an increased number of fractions—all facilitated by the technological and complex nature of radiation oncology. This engenders further inefficiency as payers invest in the creation of guidelines to restrict payments and providers in turn require significant resources to guarantee appropriate billing. Although radiation oncology's role as a beneficiary of this system could be interpreted as cause for blame, it may also be seen as a charge for leadership by the field in health care reform discussions and in the development and use of modern methods for assessing quality of care and the comparative effectiveness of various treatment modalities.

RT plays a fundamental role in the curative and palliative treatment of cancer. Its continued value in cancer care will depend on the advancement of not only clinical evidence but also health services research. Toward this end, this chapter provides an overview of the value proposition in health care as it relates to radiation oncology, with a focus on modern methods for assessing comparative and cost-effectiveness, including decision analysis and cost-effectiveness analysis. These techniques provide an alternative method for approaching clinical questions not readily answered with standard data analyses and aim to maximize the value of each health care dollar spent. Thus, understanding their employ will be of importance in the establishment of the value of RT in health policy discussions moving forward.

VALUE IN RADIATION ONCOLOGY

Remarkable advances in RT have been made in the past decades, allowing for extraordinary precision in treatment delivery and the attainment of dose escalation paired with decreased morbidity to surrounding normal tissues. In particular, IMRT achieves highly conformal dose distributions using computer-based treatment planning and delivery. The advent of stereotactic body radiation therapy (SBRT) has further provided the ability to deliver large doses of radiation with extreme precision using complex methods of patient immobilization and tumor localization, at times supplanting or offering an alternative definitive treatment to surgery in multiple disease sites. An emerging technology, magnetic resonance imaging (MRI)-guided RT, allows for enhanced soft tissue resolution, beam-on gating, and real-

time online adaptive RT, further enabling the precise delivery of higher doses of radiation safely. Coupled with RT, concomitant advances in oncologic surgery, medical oncology, and diagnostic testing have ushered in an era of personalized medicine, with the promise of more effective, tailored therapy with reduced toxicity. However, historically in cancer care, as in most fields of medicine, doing more for patients has not always equated to improved outcomes. Rising health care spending has not necessarily met with a proportional improvement in outcomes, with the United States ranking 15th out of 42 OECD countries in mortality from cancer per 100,000 persons in 2018 to 2021, despite recent calls for an increased focus on "high-value care" by policy makers, providers, professional societies, payers, and patient groups in the context of health care reform.[31-33] The value proposition in health care is not merely an exercise in cost containment, but it also strives toward a delivery system that incentivizes high-quality, evidence-based, and cost-effective treatments.[34] In this section, we discuss the value proposition as it applies to the specialty of radiation oncology, describing current challenges and future directions in the advancement toward value-based care. Given the many stakeholders involved, it is important to note that the patient's voice is a highly valued component of value-based health care delivery. We, therefore, address these issues with a focus on the patient perspective of high-value care.

Defining Value

To discuss value and the metrics used to measure it, we must first establish a mutual understanding of what is meant by the term *value*.[34] Outside the world of health care, a "good value" can be described as a desirable product or service that can be purchased for a fair price.[35] Definitions of *value* from the Merriam-Webster dictionary center on the fair return in goods, services, or money for something exchanged, with clear parallels in the definition of value as it applies to medicine in terms of relative worth, cost, and quality of care.[36] These issues are reflected in the definitions of value as put forth by multiple governing bodies in health care from around the world, including the European Observatory on Health Systems and Policies, which describes value to include "patient preferences, quality, equity, efficiency,

and product acceptability among a wide range of stakeholders," and the United Kingdom's National Institute for Health and Clinical Excellence (NICE), which defines value as "based on scientific value judgments, including clinical evaluation and an economic evaluation, and social value judgments, including considerations of efficiency and effectiveness."[37,38]

The Value Equation

To unify the often-conflicting goals of the numerous stakeholders in health care delivery, Michael Porter and Elizabeth Olmsted Teisberg established a working definition of value in health care as health outcomes achieved per dollar spent (value = outcomes/cost).[39,40] Outcomes in this equation are specified to include both near-term and longer term health in order to cover the ultimate results of care and are noted to be condition specific and multitiered, with adequate measurement of risk factors and baseline condition to enable for risk adjustment. Costs are defined to include the total costs of the complete cycle of care as opposed to individual services; as Porter notes, narrowly targeted cost containment efforts may not maximize value for the patient, with at times the best approach to increasing value being spending more on some services to reduce the need for others.[40] As both outcomes and costs are dependent on results as opposed to inputs, the challenge in value-based care is to shift focus away from the volume of services as is typical in traditional fee-for-service systems. As described by Porter, "value should always be defined around the customer, and … the creation of value for patients should determine the rewards for all other actors in the system."[40] Recognizing the importance of the patient in the value proposition, Teckie and colleagues, in setting forth a framework for value in the field of radiation oncology, further expanded the numerator toward a more comprehensive definition of quality to include structure and process along with outcomes, in line with the classic Donabedian model[35,41] (Figure 37.2). The Donabedian model is a conceptual framework for evaluating the quality of medical care, in which assessments are drawn from three dimensions of care: structure, process, and outcomes. Structure encompasses the context in which care is delivered, including the physical facility, human resources, organizational characteristics, and, of particular importance in radiation oncology, the equipment and technology. Process

includes all acts of health care delivery, including interactions between the patient and physician and the technical delivery of care. In the Donabedian model, outcomes include not just objective measures, such as survival and functional status, but also subjective measures, such as quality of life and patient satisfaction. By this expanded framework (value = quality/cost), efforts to improve structure, process, and outcomes can all be seen as strides toward improving value.

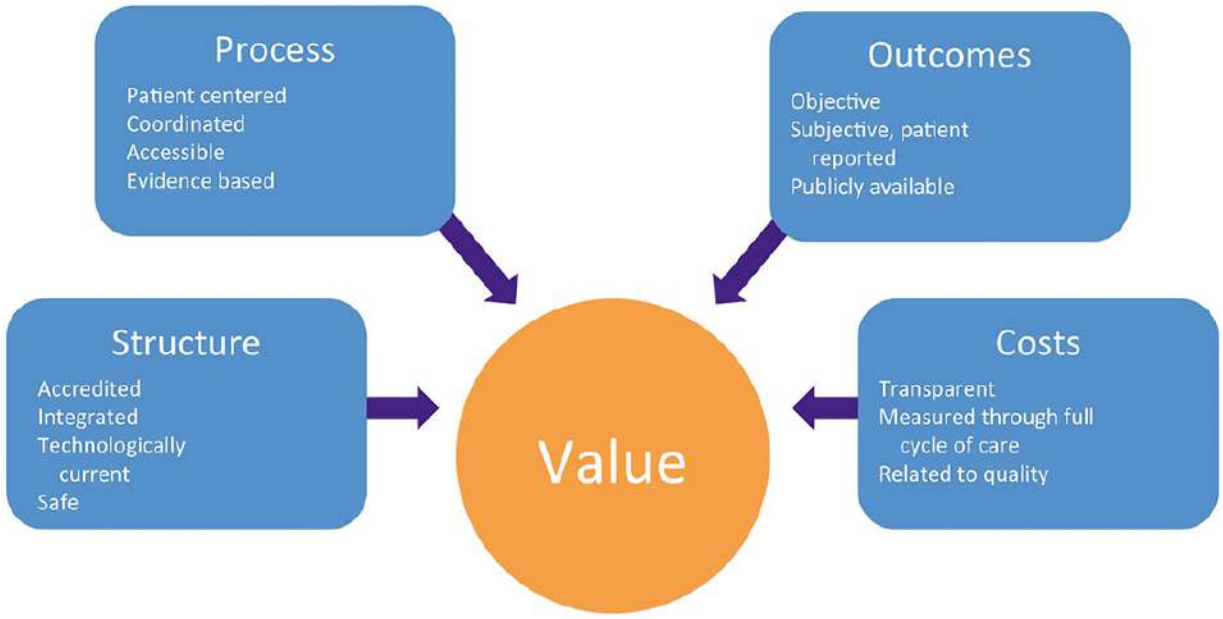

FIGURE 37.2 Components of value as defined by Teckie and colleagues, adapted from the Porter equation including elements from the Donabedian model. (Reprinted with permission from Teckie S, McCloskey SA, Steinberg ML. Value: a framework for radiation oncology. *J Clin Oncol*. 2014;32[26]:2864-2870. Copyright © 2014 by American Society of Clinical Oncology.)

Structure

Donabedian defines structure as "concerned with such things as the adequacy of facilities and equipment; the qualifications of medical staff and their organization; the administrative structure and operations of programs and institutions providing care; fiscal organization and the like."[41] Radiation oncology, as a field, continues to become increasingly complex, with advances in treatment modalities involving multifaceted structural elements requiring multidisciplinary teams and state-of-the-art technology for adequate delivery. This complexity has allowed for wide variation in

structural practices. Although at times this variation is indicated based on an individual patient's needs, critics have noted that deviations may not be associated with increased quality of care, with an opportunity for enhancement of value via standardization.[8] In 2010, the American Society for Radiation Oncology (ASTRO) convened a total of 12 multidisciplinary societies to develop a guidance document describing the elements necessary for the safe delivery of RT. This document, entitled "Safety is No Accident," was published in 2012 and updated in 2019, and sets forth specific requirements for a radiation oncology facility in terms of structure, personnel, and technical process.[42] In 2014, in an effort to expand adoption of these principles and further unify variations in care delivery, ASTRO launched the Accreditation Program for Excellence (APEx), which provides impartial third-party review of practices' personnel, equipment, treatment planning, medical records, patient safety policies, and quality control/quality assessment activities against an established set of performance standards with focus on structure and process elements.[43] Radiation oncology practices (including freestanding single facilities, multisite organizations, and practices that are part of a hospital facility) that apply undergo a process of self-assessment and third-party review against a set of 16 established standards with accreditation granted for 3- or 4-year cycles. The Commission on Cancer and the National Accreditation Program for Breast Centers both accept APEx accreditation as fulfilling the RT component of their accreditation programs, and the U.S. Department of Veterans Affairs (VA) not only accepts APEx as an accrediting body for community-based facilities that treat veterans in the absence of a VA medical center but also awarded APEx a contract to accredit its 41 VA facilities providing radiation oncology services.[44,45] Since its inception, the number of participants has steadily grown. As of February 2025, 406 facilities have obtained APEx practice accreditation, and more are undergoing the painstaking application and accreditation process.[46] Accreditation ideally demonstrates achievement of a threshold level of quality and safety to referring physicians, peers, prospective patients, regulatory agencies, and payers. However, it remains to be seen whether these various stakeholders value accreditation or understand what the evaluation process involves. Moreover, without appropriate economic

incentives to pursue and maintain accreditation, it is unclear how many radiation oncology practices will ultimately elect to participate.

In addition, in 2014, ASTRO and the American Association of Physicists in Medicine (AAPM) launched the Radiation Oncology Incident Learning System (RO-ILS) to further promote safety and quality of care.[47] This system, in which more than 750 facilities in the United States currently participate, establishes a web-based national database of radiation oncology safety incidents. Participating facilities can share events in a secure, nonpunitive environment, which allows for tracking of incidents as well as shared learning for both individual facilities and the field as a whole. The RO-ILS program is free to join because it is supported financially by multiple organizations, including ASTRO, AAPM, the American Society of Radiologic Technologists, and the American Association of Medical Dosimetrists.

Radiation Oncology Equipment Approval

Radiation oncology equipment, such as a linear accelerator, is considered a medical device according to U.S. Food and Drug Administration (FDA) definitions,[48] and thus, its FDA approval process is considerably different than that of medications. The regulatory body overseeing this process is the Centers for Devices and Radiological Health (CDRH), which was established in 1982 under the FDA to ensure the safety and efficacy of medical devices.[49] Medical devices are divided into three classes: Class I devices are low risk, such as stethoscopes or bandages; class II devices are intermediate risk, such as computed tomography (CT) scanners or infusion pumps; and class III devices are high risk and important to supporting health and life, such as pacemakers or artificial heart valves.[50] The majority of radiation oncology equipment is considered class II devices.

The initial steps of obtaining CDRH approval to introduce a new medical device into the market typically include submission of a 510(k) application, which attests that the proposed device is as safe and effective, or "substantially equivalent," to a U.S. legally marketed predicate device.[51,52] A new medical device is considered "substantially equivalent" to the predicate device if the new device has the same intended use and technological characteristics as the predicate device, although a device with

different technological characteristics is considered substantially equivalent if it does not raise questions of safety and efficacy, and data submitted to the CDRH demonstrate that the new device is as safe and effective as the predicate device. As opposed to class III devices, class II devices do not require additional applications beyond the 510(k) to be introduced into the market, such as a Premarket Approval Application that often requires a premarket clinical trial of the proposed device under an Investigational Device Exemption. As such, using the 510k process, the vast majority of new radiation oncology technology does not require a clinical trial showing safety and efficacy prior to being FDA approved. This both reduces the time (510[k] approvals are determined by the CDRH within 90 days) and expenses required to bring new or updated radiation oncology equipment into the market, thereby encouraging continuous innovation and improvement of existing devices, although at times the "improvements" are only incremental.

Despite these potential benefits for the introduction of new medical devices, specifically in radiation oncology systems, concerns have been raised about this process.[53] The data used by the CDRH to evaluate a device's safety and efficacy are solely provided by the device manufacturer, who is understandably incentivized to obtain device approval. In addition, because of the FDA Modernization Act in 1997, the CDRH may outsource 510(k) reviews to third parties,[54] which often have insufficient expertise and/or time to conduct thorough reviews.[55] Furthermore, a 510(k) application is not required for modifications of an already approved device so long as it is not "significantly changed or modified in design, components, method of manufacture, or intended use,"[56] though this decision is also made by the manufacturer. Over time, sequential minor updates to a device can result in the newest version of the device being significantly different from the original predicate device, an effect known as "predicate creep."[57] Consequently, this introduces the possibility for device error and adverse safety events, especially in radiation oncology where new technology is exceedingly complex compared with former versions. As a result, the FDA announced three draft guidances in September 2023 related to the 510(k) process to improve its predictability, consistency, and transparency.[58] Ultimately for the medical device–approval process, a balance must be struck between a timely, relatively inexpensive process that

promotes innovation with thoroughness and appropriate regulatory oversight to ensure the safety and efficacy of the new devices being introduced to the market. Separately, as discussed later, FDA approval of radiation oncology equipment does not guarantee insurance coverage for the new process of care related to a new device, introducing yet another layer of complexity to regulatory processes surrounding radiation oncology device development.

Third-Party Payers

After a new medical device is granted FDA/CDRH approval, its manufacturers may apply for creation of a new Current Procedural Terminology (CPT) code for the service or procedure associated with the device so that it can be incorporated health care payment delivery system. The CPT coding system is managed by the American Medical Association (AMA),[59] and both CMS and commercial insurance companies use this system for the nomenclature used for reimbursement.[60] CPT codes are divided into three categories.[61] Category I CPT codes refer to services and procedures used in routine clinical care. There are several criteria that must be fulfilled for a device to be assigned a category I CPT code, including receipt of FDA approval, distinctness from existing CPT codes, widespread and clinically appropriate consistent use by many physicians across the United States, and demonstration of clinical efficacy in the literature.[62] After obtaining a category I CPT code, the procedure or service is then evaluated by the AMA/Specialty Society Relative Value Scale Update Committee, who determines its valuation in the CMS fee schedule based on the physician work and practice expenses associated with the procedure or service. Category II codes are supplemental codes used only for performance and quality measurement. Category III codes are temporary codes assigned to emerging technology that currently does not meet the criteria for a category I code. Although initially and primarily used for data collection purposes, category III codes may occasionally be used for the payment of the new procedure or service if local Medicare carriers see fit to assign a value and elect payment.

The determination of reimbursement for a new medical device and its associated service or procedure is, therefore, intimately tied to obtaining a

CPT code, and subsequent valuation by CMS is obtained through a complex policy process. Over the years, the level of evidence required for assignment of a category I CPT code has been raised, which has posed challenges for radiation oncology device manufacturers as it is often difficult to initially generate a substantial body of clinical data supporting a new technology because of the high upfront costs associated with radiation oncology technology development and the lack of vendor-based clinical trial infrastructure needed to run evidence producing trials. Even more complicating is that the evidence standards that must be met to obtain category I approval are open to interpretation by various parties in the approval process.[60] Given the challenges surrounding the process of incorporating new medical technology into the health care payment system, particularly in the context of ever-growing U.S. health care spending, health technology assessments (HTAs) have been proposed as a mechanism to improve this process. HTAs provide a framework to systematically and comprehensively assess a new device's impact on the health care system through a variety of data and stakeholder lenses to inform policymaking.[52,63] The data analyzed in an HTA include clinical efficacy and safety outcomes such as progression-free survival and toxicity as well as the cost-benefit and overall economic impact, or in the context of the current chapter, the value proposition, of a new device. It should be noted, however, that the criteria for obtaining a CPT code do not include cost or economic considerations, and this process is thus unable to fully engage the value equation described in earlier sections when evaluating new devices. More broadly, there is a dearth of single, national HTA bodies both in the United States and globally,[63,64] although organizations within the United States, such as the Institute for Clinical and Economic Review, were created to address these concerns and work with major public and private payers to inform coverage criteria.[65] Examples of nationalized HTA programs include the Institute for Quality and Efficiency in Health Care in Germany and the NICE in England and Wales.[66] Going forward, emphasis will continue to be placed on the implementation and uniformization of HTAs in order to address rising health care costs in the United States.

Integration of Care

In the traditional organizational structure of medical care, delivery of care is siloed according to separate medical specialties or departments. However, in the past decades, there has been a shift toward medical practices centered around the patients' perspective of their medical condition integrated across the continuum of care; additionally falling under the realm of structure, this strategy has received attention for promoting high-value care.[67] In the integrated practice unit model, clinical and nonclinical personnel deliver care according to evidence-based care pathways and treatment directives with responsibility for the full cycle of care, including inpatient, outpatient, rehabilitative care, and supporting services, such as nutrition and social work. Importantly, the team measures outcomes, costs, and processes for each patient with feedback mechanisms for refinement of care delivery, economic efficiency, and patient convenience, all relevant to the value proposition. This integration promotes value not only by limiting overuse of tests and procedures but also by increasing use of patient-centered shared decision-making. Specific to oncology, the multidisciplinary clinic model centers a team of multiple specialties, including medical oncologists, radiation oncologists, radiologists, surgical oncologists, and pharmacists, around a specific tumor site.[68] While requiring significant reorganization and reassessment of traditional interactions between subspecialists and ancillary staff, adaptation of these models has been successful at many high-volume centers, with suggestion of both improved outcomes and reduced costs compared to similar community groups.[69,70] For instance, comparison of a consecutive sample of 104 patients with melanoma with localized disease treated in the Michigan community with 104 blindly selected patients treated at the University of Michigan Multidisciplinary Melanoma Clinic during an identical time period matched for Breslow depth and melanoma body site indicated cost savings of $1,600 per patient for patients treated in the multidisciplinary clinic.[69] Via coordination between multiple specialties in complex decision-making, the multidisciplinary model may allow for higher attainment of benchmark measures for quality care in accordance with national practice guidelines. For example, a study of 609 patients with nonmetastatic breast cancer treated in the University of California, Los Angeles, multidisciplinary breast clinic indicated increased appropriate referral rates for genetic testing for family history–based (62% vs 92%) and overall (80% vs 96%) indications

after the inclusion of a genetic counselor in the multidisciplinary clinic.[71] Although limited primarily to observational studies because of difficulty in recruiting patients from practices in which the multidisciplinary model is not standard of care and confounded by parallel improvements in therapies, multiple studies have demonstrated potentially increased survival in patients treated in the multidisciplinary care setting.[72-74] Variations of care for complex patients and for those from underserved backgrounds or rural areas would ideally be minimized in the multidisciplinary setting,[75] and indeed, a study evaluating the impact of a pancreatic cancer multidisciplinary clinic found that disparities in treatment recommendations, surgical outcomes, and overall survival between low and high socioeconomic status patients were eliminated among patients managed within a multidisciplinary care clinic.[76] Cancer learning networks, such as the Canopy Cancer Collective for pancreatic cancer,[77] seek to further improve patient care integration by establishing a network of health care systems in which patient care can be more easily coordinated, while also allowing for the sharing of data and best practices among the involved organizations to improve patient experiences and outcomes.

Alternative Payment Models

Newer coverage models, under the umbrella of the Donabedian definition of structure, offer an opportunity to incentivize value by linking reimbursement to quality metrics as well as encouraging patients to select high-value centers or providers. Traditional fee-for-service reimbursement, in linking payment to the volume of services provided, has been criticized for incentivizing overutilization of care, often without proportionate benefit. The technological focus of radiation oncology, in particular, allows for a surplus of discrete billable units per treatment episode.[30] Pure prospective payment, proposed as an alternative to the traditional fee-for-service payment, reimburses providers a fixed amount independent of the volume of services provided, with the aim of promoting efficiency via incentivizing providers away from costly treatments.[78] However, by shifting the marginal cost of care—and associated financial risk—to providers, pure prospective payment may incentivize providers to select patients with lower risk of complications (“cherry picking”), to provide less care than would best treat

the patient ("stinting on care"), and to avoid treating patients whose optimal treatment involves costly interventions.[78] Thus, the ideal reimbursement system would fall in between these two extremes, with payment linked to value while still allowing for evenly distributed access to high-quality care.[79]

Unfortunately, even with an established definition of value, deriving applicable metrics for quantifying value in oncology remains elusive. Although there are widely accepted measurements of outcomes (eg, prostate-specific antigen progression-free survival in prostate cancer) and toxicities associated with treatment (eg, the Common Terminology Criteria for Adverse Events [CTCAE]), adequately assessing these metrics may require multiple years of follow-up, impractical for adaptation to a reasonable payment cycle. Likewise, it is often difficult to assess whether adverse effects are the result of surgery, chemotherapy, radiation, or something unrelated to treatment.[30] As noted before, linking payment to outcomes metrics without accurate risk adjustment algorithms could also discourage providers from treating sicker patients. Along with this, the rapidly and continually advancing nature of the field makes it challenging to maintain adequate yet up-to-date quality metrics.[80] In the field of medical oncology, the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology, and other national guidelines organizations have put forth frameworks for the evaluation of value, with notable overlap in their attempts to quantify the gradients of benefit associated with drug regimens, toxicity, and quality of life, though formal cost-effectiveness analyses are deemphasized.[81,82] Radiation oncology has been late in the development of its own value metrics, with many measures of quality advanced through more broadly focused organizations. In parallel with the efforts of the AMA Physicians Consortium for Performance Improvement and other similar organizations to develop, implement, and validate quality metrics, the National Quality Forum (NQF)[83] was funded by Congress with the aim of evaluating quality measures for transmission to the CMS for inclusion in eventual value-based penalties and bonuses. ASTRO endeavored to establish a series of best practice guidelines based on evidence and expert review in conjunction with the NQF, such as documentation of pain intensity and care plan and avoidance of overuse of bone scan for staging for low-risk prostate cancer.[84] However, in February

2023, CMS completed a competitive process to determine the entity responsible for the establishment and maintenance of quality measures and did not award the NQF this next phase of work. ASTRO has also worked with the Department of Veterans Affairs National Radiation Oncology Program to develop consensus quality measures in five cancer sites: lung, prostate, rectal, breast, and head and neck.[84,85] These guidelines include a variety of quality measures throughout the radiation oncology care process. For example, documentation of performance status and prior radiation status during the consultation and workup process; ensuring 14 days from simulation to treatment start and peer review of treatment plans during the simulation, planning, and treatment process; and completion of treatment summary during the follow-up process. In addition, in 2013, ASTRO determined a list of five interventions to only be used in specific situations because of proven lack of value as part of the American Board of Internal Medicine Foundation's *Choosing Wisely* initiative[86] (Figure 37.3), and proposed an additional five recommendations the following year.[87] Publication of these guidelines had a variable impact on the practice patterns they sought to address.[88-91] Although admirable steps toward the value proposition, early quality indicators have been criticized for representing little more than enforcers of current standard of care, with persistence of many low-bar measures such as documentation of stage of disease or presence of normal tissue dose constraints, which may or may not directly relate to the actual quality of care. These measures are further debilitated by minimal correlation with reimbursement, without tracking by payers or accrediting bodies, thus effectively having limited impact on patients or society with a call to focus metrics on true gaps in care.[92] Furthermore, care must be taken to ensure adherence to guidelines does not limit patients whose unique clinical situations call for individualized care, slow clinically meaningful advancement if innovation outpaces updates to guidelines, or inadvertently penalize hospitals caring for disadvantaged populations.[30,93]

1	Don't initiate whole-breast radiotherapy as a part of breast conservation therapy in women age ≥50 with early-stage invasive breast cancer without considering shorter treatment schedules.
2	Don't initiate management of low-risk prostate cancer without discussing active surveillance.
3	Don't routinely use extended fractionation schemes (>10 fractions) for palliation of bone metastases.
4	Don't routinely recommend proton beam therapy for prostate cancer outside of a prospective clinical trial or registry.
5	Don't routinely use intensity-modulated radiotherapy (IMRT) to deliver whole-breast radiotherapy as part of breast conservation therapy.

FIGURE 37.3 The American Society for Radiation Oncology's list of five radiation oncology–specific treatments that are commonly ordered but may not always be appropriate as part of the national American Board of Internal Medicine Foundation's *Choosing Wisely* campaign. (Reprinted from Hahn C, Kavanagh B, Bhatnagar A, et al. Choosing wisely: the American Society for Radiation Oncology's top 5 list. *Pract Radiat Oncol*. 2014;4[6]:349-355. Copyright © 2014 American Society for Radiation Oncology. With permission.)

With clear quality metrics still under development, payment reform thus far has mostly occurred in the form of narrow or tiered networks offered by health plans, often based on price or provider relationships with the larger market-dominant entity.[22] However, several alternative payment schemes, such as population-based shared savings arrangements, clinical pathways, and bundles of care and episodes of care payments, have been examined in oncology, accelerated by their inclusion in accountable care organizations (ACOs).[17] In population-based shared savings arrangements, providers are reimbursed via similar fee schedules though are rewarded when their fee-for-service payments are below a predefined target, often via the provider receiving a percentage of the savings. Despite the initial excitement surrounding implementation of these risk-sharing arrangements as elements of oncology-focused ACOs, the anticipated reductions in spending have not been realized.[94,95] It should also be noted that ACO implementation has primarily been within the field of medical oncology, and there is little data directly related to radiation oncology with regard to ACO incentivization. In the clinical pathway approach, best practices are established for each clinical scenario with providers rewarded for adherence with higher fee-for-service payments, bonuses, or other incentives. Providers are expected to adhere to pathways for 60% to 80% scenarios to allow for individualization

of care. This has demonstrated success in reducing treatment variation, drug trend, and hospitalizations in medical oncology; however, its application has been criticized as ill-suited to radiation oncology given the field's anatomic and technologic focus, which allows for potentially larger number of branch points in the decision-making process with a greater role for patient preference in the selection of treatment modality. Lastly, bundled or episodic payment has been described as a middle ground between fee-for-service and pure prospective payment, in which providers are reimbursed upfront based on the expected costs for a clinically defined episode of care, thereby incentivizing efficient use of resources. CMS has devoted significant focus to experiments in episodic payment systems, though with focus in oncology primarily on comprehensive bundles that include medical, surgical, and radiation services as well as the complications of care. Multiple companies have experimented with specialty-specific episodic bundles in radiation oncology with reported improvements in administrative efficiencies, though, in this model, attention to quality measurement will be necessary to ensure implementation actually yields higher value care without incentivizing providers away from high-risk populations. Likewise, to properly incentivize high-value care, bundled payment schemes will likely require context-specific models for different clinical scenarios as well as cost calculations based on updated RT codes that more accurately reflect the current clinical practice.[96]

In July 2015, Turning the Tide Against Cancer, an initiative convened by the American Association for Cancer Research, the Personalized Medicine Coalition, and Feinstein Kean Healthcare to identify policy solutions that will sustain medical innovation while addressing the issue of rising health care costs, held a roundtable consisting of a multidisciplinary group of stakeholders to review key considerations for oncology-focused alternative payment models.[97] Noting reliance on annually calculated spending benchmarks and only intermittently updated episode-of-care definitions, the panel highlighted the importance of having alternative payment models keep pace with emerging science via incentivizing adoption of innovative medicine and technologies that have the potential to improve patient outcomes and make health care more efficient. Toward this end, it stressed the avoidance of unintended barriers to patient access to novel therapies, particularly those that may be expensive in the short term but that may

result in savings in the long term. Given the trend toward more personalized medicine, the roundtable acknowledged that a critical step in this is the coverage of diagnostics that will enable identification of patients who respond best to targeted therapies and thus avoiding the cost of treating patients who will not benefit or will be harmed by adverse effects or delays in initiating more effective treatments. Likewise, the participants suggested that alternative payment models incentivize the physician's ability to appropriately tailor treatment to an individual patient's needs and preferences, furthermore noting that there is no one-size-fits-all model, with the impact of a payment system at times dependent on geographic region, practice characteristics, setting, and other factors. Finally, the panel indicated that alternative payment models should include mechanisms to encourage participation in clinical trials and ongoing postmarket clinical research. Given the potential for models to incentivize patients toward rigorous care protocols or clinical pathways, the panel indicated that care should be taken to make it financially feasible for practices to enroll patients and participate in clinical trials to support continued development of cancer treatment.

Radiation Oncology Alternative Payment Model. Given the concerns surrounding the fee-for-service model and prior history of rising radiation oncology expenditures without improvements in health care quality, Congress sought to create a radiation oncology alternative payment model (RO-APM) for Medicare payment for RT services in 2015.[98] The overall goal of the new model was to transition to a value-based payment system that emphasized high-quality care while also ensuring payment fairness and stability by changing from fee-for-service to prospective, episode-based (ie, bundled) payments based on the patient's cancer site. Payment was to be tied to quality through mechanisms including quality metric performance, clinical data reporting, and patient experience. Multiple stakeholders, including ASTRO, patient advocates, and other relevant interest groups, were going to work in conjunction with CMS to develop this new model; however, the proposed model was ultimately developed solely by CMS, and the associated groups were only able to make comments after the model was published. Moreover, there were several notable concerns with the model.[99] Although voluntary participation was initially proposed in 2017,

the final rule proposed mandatory participation of approximately 30% of all radiation oncologists in the country selected randomly by zip code, much to the dismay of ASTRO. Along with this, payment models were site of service neutral, and payment calculation methodology was flawed, complicated, and challenging for practices to implement. Notably, the implementation of these new burdensome administrative requirements was to take place during the COVID-19 pandemic. In addition, this new model created CMS spending savings through haphazard payment cuts and discount factors, estimated to be $250 million over 5 years, rather than prioritizing patient-centered, value-driven care that would reduce overutilization, among other benefits.

While one of the primary goals of the RO-APM model was to enhance quality of care by linking it to payment, the quality metrics included were limited with only four total: documenting a plan of care for pain, treatment summary communication, screening for depression and follow-up, and advance care planning. As acknowledged in a prior section, it has been difficult to develop quality indicators in radiation oncology, and as such, there exists a dearth of such metrics; however, it was felt that the quality metrics chosen for the RO-APM were not meaningful within radiation oncology and were possibly selected because they were easy to measure rather than reflective of actual quality of care. These metrics were primarily related to documentation, which is not necessarily indicative of higher quality of care, and in the case of depression screening, not generally a part of radiation oncology clinical care. On top of this, there were no relevant outcomes measures included. Other methods for incentivizing quality and value were not a part of this model that was supposedly designed to improve the existing insufficiencies in these areas. For example, missing were initiatives rewarding participation in standardized safety practices or programs, improving patient access and convenience by addressing disparities, or employing evidence-based hypofractionated treatment regimens.

Furthermore, the model did not account for the fact that radiation oncology is a highly technical and innovative field, which is continually evolving from a technologic standpoint. Although these advances are often associated with higher cost, they may also impart improved clinical outcomes. The RO-APM did not have a valid approach to incorporating

new technology into the payment schema. ASTRO, many other stakeholders, and politicians strongly opposed this model. Its implementation was indefinitely delayed by Congressional action in 2022.

In June 2023, ASTRO proposed the Radiation Oncology Case Rate (ROCR) program.[25,100] This model, similar to the CMS RO-APM, proposes a service site-neutral, cancer site-specific, episode- based payment model, with half of the payment being issued prospectively at the beginning of the radiation care process and the remaining half at the end of the treatment course or 90th day of the episode, whichever comes first. Payment is modality agnostic; however, proton therapy and brachytherapy are not included due to their lower utilization and unique cost structure, nor are newer technology and services, such as online adaptive RT. In addition, the ROCR APM seeks to address health care inequities and barriers to care by providing additional payments to facilities who incorporate a transportation screening question from the CMS Accountable Health Communities health-related social needs screening tool[101] into their clinical workflows. It also incentivizes quality through payments tied to accreditation by a credentialing body, such as APEx, and participation in patient safety practices, such as RO-ILS. This new model projects to save $212 million over 5 years. The ROCR model was introduced as bipartisan federal legislation in the U.S. Congress on May 15, 2024, and reintroduced on March 13, 2025 after the federal administration change.[102,103]

Process

Process includes all components of health care delivery, including both the technical processes in how health care is delivered and the interpersonal processes that describe the manner in which care is delivered, with a focus on patient-centered, accessible, and coordinated care.[41] As defined by Donabedian, process can be measured via review of medical records, interviews with patients and providers, and direct observation of health care visits with measurement intrinsically tied to metrics of quality. In a technologically focused specialty such as radiation oncology, the measurement of process goes beyond those components immediately noticeable by patients, such as the quality of the patient-physician interaction and the timeliness of care, to include less tangible components,

such as physician expertise and medical physics quality assurance oversight for treatment planning and delivery.[35] Thus, structural efforts to establish patient-centered and safety-focused process standards, such as the previously mentioned APEx accreditation program, are directly linked with process improvement. The Radiation Therapy Oncology Group (RTOG) cooperative group clinical trials, which specify treatment planning specifics such as contouring guidelines, dose constraints, and planning techniques as enforced by centralized review processes, are another example of process standardization, with evidence suggesting protocol deviations are associated with poorer outcomes.[35] In this light, ASTRO's previously mentioned best practice initiative, which establishes clinical practice guidelines based on the RAND/University of California, Los Angeles, appropriateness criteria, looks beyond defining guidelines to support the indication of radiation to include evidence-based and expert panel–devised assessment of the technical processes underlying the delivery of therapy.[104]

Physician Expertise

Regarding physician expertise, similar to surgical procedures, multiple studies have described the presence of a learning curve in the application of advanced radiation oncology techniques, including IMRT volume delineation, technical IMRT delivery, SBRT,[105] and brachytherapy procedures. For instance, in a single-institution study from the Department of Radiation Oncology at CancerCare Manitoba, the number of patients with prostate cancer treated with I-125 interstitial implant with D90 less than 140 Gy, a metric for the dosimetric quality of the brachytherapy implant, which correlates with decreased biochemical relapse-free survival, declined with increasing experience at the program, with brachytherapy team experience found to be a more important predictive factor of implant quality than size of the prostate.[106] Furthermore, with regard to IMRT, a population-based analysis by Boero and colleagues identified radiation providers from Medicare claims of 6,212 Medicare beneficiaries with head and neck cancer treated between 2000 and 2009 and found that among patients undergoing IMRT, those treated by higher volume providers had increased survival compared with those treated by lower volume providers. Specifically, for every five additional patients treated per provider per year,

the risk of all-cause mortality decreased by 21%.[107] Patients treated by higher volume physicians additionally had decreased head and neck cancer–specific mortality and decreased risk of aspiration pneumonia. Of note, no significant relationship between provider volume and patient survival or toxicity was observed among patients treated with conventional RT. Such results highlight the importance of improved training or novel educational resources for practicing physicians, with a focus on skills-based education, in the establishment of value in radiation oncology, particularly as technology continues to advance at a rapid rate. Other advancements, such as in semiautomated target delineation, knowledge-based planning, and telemedicine, may also assist toward this end without necessitating physician or patient travel.

Telemedicine

Although not a new concept, the implementation of telemedicine or telehealth, which the AMA refers to as "the exchange of medical information from one site to another through electronic communication,"[108] was significantly expedited within the field of radiation oncology, cancer care, and the medical system as a whole as a result of the COVID-19 pandemic. While this expansion was initially the result of infectious precautions and supported by temporary measures from CMS during the public health emergency, the use of telemedicine has persisted, prompting ASCO to endorse standards and practice recommendations for the use of telehealth in oncology.[109] Telemedicine, compared with traditional in-person medicine, offers multiple advantages with respect to the process of medical care and has been identified as a mechanism to increase patient-centered care,[110] even prior to the COVID-19 pandemic.[111] Telehealth increases patient access to and flexibility of care, particularly for vulnerable patients such as those with limited transportation ability or in rural settings,[110,112] which can translate into economic benefits for patients through less missed work and costs associated with in-person visits.[113,114] In addition, multidisciplinary oncology clinics have also incorporated telemedicine,[115,116] and telehealth has been proposed as a way to increase oncology clinical trial accessibility and equitability.[117] Emerging data of patient experiences with telehealth in radiation oncology have found high levels of patient

satisfaction, with significant proportions of patients reporting a preference for telemedicine over in-person visits.[118,119] Similarly, radiation oncologists have reported general satisfaction with and interest in continued use of telemedicine for a significant proportion of patients in their practice.[120-122] Beyond patients and providers, incorporation of telemedicine workflows and work-from-home capability may even confer cost savings to radiation oncology departments.[123]

However, there are some concerns with telemedicine, which must be addressed when considering its future role in health care services. The most obvious is the inability to perform a physical examination, as well as possible challenges establishing a personal connection via telecommunication.[121] This may be balanced by increased patient comfort from attending a health care visit in their own home or other familiar location along with more effective communication from patient friends or family members being able to join visits. Technical difficulties, from both technology and human sources, are also well-known problems, and increased and more widespread use of telecommunication systems for health care services may require additional staff and infrastructure for adequate support.[124,125] Furthermore, recent evaluations of telemedicine have found that it may paradoxically exacerbate health care disparities despite its proposed ability to increase overall access to care.[126-128]

With the end of the COVID-19 public health emergency on May 11, 2023, some of the temporary measures put in place by CMS to encourage widespread adoption of telemedicine may not be continued. These notably include policies related to reimbursement of telehealth services and geographic practice site restrictions.[125,129] There is concern that in the absence of regulatory support, particularly financial, the use of telemedicine will be stifled, and numerous national groups have advocated for its continued backing.[130,131] Given the proposed and already realized benefits of telemedicine, as well as its general acceptance by both patients and providers, support for and optimization of telemedicine should continue so that it remains an option for patients who wish to use it.

Fractionation

The impact of fractionation schedule on the process of RT is considerable. Recent technological advances have allowed for the implementation of hypo- and ultra-hypofractionated treatment courses. Clinical trials in multiple disease sites, such as prostate, breast, and rectum,[132-136] have demonstrated acceptable toxicity and efficacy profiles of these shorter regimens. Under the fee-for-service model, however, there is incentive toward longer fractionation schedules, despite the potential health care system- and patient-level benefits hypofractionated courses can offer. Several economic analyses have found shorter radiation treatment courses to be cost-effective or associated with lower overall costs.[137-141] It should also be considered that while on the per-patient level hypofractionated courses result in lower reimbursement compared with conventionally fractionated courses, total patient throughput can be increased with shorter courses, thus enhancing the value proposition of hypofractionation. Moreover, hypofractionated treatment courses improve patient logistics and financial toxicity, for example, through less missed work, fewer travel expenses, and reduced caregiver burden.[142-144] This may also help to mitigate health care–associated socioeconomic disparities, as increased utilization of hypofractionated RT can improve access to care, treatment compliance, and overall oncologic outcomes in low- and middle-income countries.[145-147] In addition, shorter treatment courses result in less patient travel, which may have a positive environmental impact.[148,149] The ability to hypo- and ultra-hypofractionate radiation treatment relies on continued advancement in treatment precision and accuracy, which improves the therapeutic ratio through tumor dose escalation with simultaneous reduction in dose to surrounding normal tissue. Through this mechanism, newer technologies, such as MRI-guided RT, may further promote the feasibility of shorter fractionation schedules.

Outcomes

Outcomes span all the effects of health care on patients or populations. These include objective outcomes providers and payers have traditionally assessed, such as survival, disease control, functional status, disease recurrence, and complications of treatment. Subjective outcomes, such as patient-reported outcomes, psychosocial ramifications of disease or

treatment, ability to maintain employment status, and patient's understanding of disease, although considered by some as more difficult to assess via traditional scientific methods, are also included and hold equal importance in the value discussion. Of the components in the value equation, the medical community is best at assessing objective outcomes, with wide support for furthering our understanding of the objective impact of particular interventions via high-level clinical research. However, given the expense of such research, there is a need for additional methods to assess objective outcomes at the population level in real-world settings, with multiple specialty-based and multidisciplinary real-time observation registries under development to meet this need.[150-152] The advancement of accurate methods for risk stratification is of particular importance if these outcomes are to be reported on an individual provider level to enhance patient selection of providers or if they are to be connected with reimbursement. This consideration is also relevant for comparisons between treatment modalities, with wider use of multiple research methods for comparative effectiveness in oncology; some of these methods are detailed in this chapter's section on research methods.

The Outcome Measures Hierarchy

As described by Porter, the outcomes for any medical condition can be arranged in a three-tier hierarchy[40] (Figure 37.4). Each tier includes two levels, each described by one or more distinct outcomes dimensions, with success for each dimension measured through specific metrics. In this hierarchy, tier 1 represents the health status achieved or retained, and it includes levels of survival and degree of health or recovery. Specific to cancer care, common metrics in tier 1 include 5-year overall survival and functional status. Tier 2 relates to the recovery process and includes levels of time required to achieve recovery and disutility of care. Common metrics specific to cancer care include time to remission and rates of adverse effects related to the treatment process. Lastly, tier 3 describes the sustainability of health and includes the levels of recurrence of the original disease and associated complications as well as new health issues caused by treatment. Common metrics in cancer include cancer recurrence and incidence of second primary cancers. In this hierarchy schema, tier 1 is generally

considered the most important, with lower tier outcomes dependent on success at higher tiers. However, trade-offs between tiers may exist—such as sacrificing survival benefit in favor of a less morbid treatment modality—and mapping these trade-offs is an important part in furthering innovation in care.

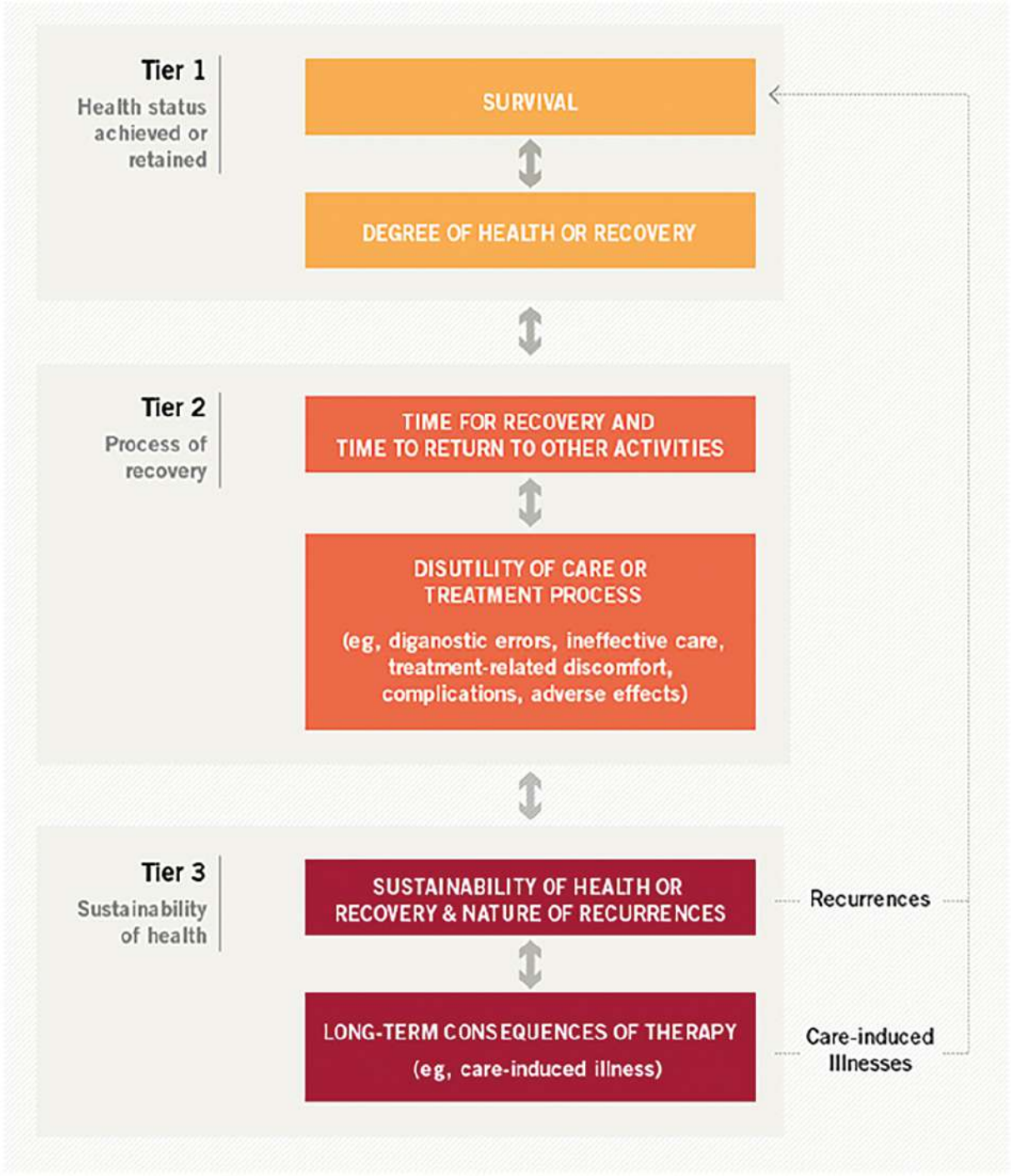

FIGURE 37.4 The outcome measures hierarchy as defined by Porter. (Reproduced with permission from Porter M. *Measure Outcomes & Cost for Every Patient*. Institute for Strategy and Competitiveness; 2012. Copyright © 2012 Michael Porter and the Harvard Business School Institute for Strategy and Competitiveness.)

Patient-Reported Outcomes

The study of subjective outcomes, by comparison, is less mature in its development than traditional clinical research in radiation oncology. While initially falling under the purview of dedicated health services research, patient-reported outcomes are increasingly included in clinical research in oncology, in part spearheaded by the RTOG, which has developed a model for the inclusion of patient-reported outcomes as end points in clinical trials.[153] The FDA provides a broad definition of patient-reported outcomes as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else."[154] With respect to their inclusion in clinical trials, however, patient-reported outcomes typically include health-related quality of life (HRQoL) instruments, with hundreds of validated generic and disease-specific instruments available and radiation oncology–specific instruments currently in development.[155-157] For instance, the National Cancer Institute (NCI) developed a patient-reported outcome measurement system for use in cancer clinical trials, named the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Designed to be used as a companion to the CTCAE, the PRO-CTCAE includes an item library of 124 and 130 items representing 78 and 62 symptomatic toxicities in adult and pediatric patients, respectively, drawn from the CTCAE and has been tested in a consortium of academic- and community-based cancer treatment sites in the NCI-sponsored clinical trial network.[158,159] Application of such HRQoL instruments through patient self-reporting via web-based platforms is a growing area of interest as well. Early prospective trials of these tools have demonstrated their ability to decrease health care usage and improve clinical outcomes, such as HRQoL and even survival.[160-162] Many challenges exist regarding the optimal application of such instruments, including refining the validation process, establishing the clinical meaningfulness of their results, ensuring inclusiveness and equitability,[163] and deciding how to handle missing data; further research to understand their utility in drawing conclusions in the trial setting, such as with regard to dose-limiting toxicity and overall/comparable tolerability, is necessary as well.[164] In the case of patient self-reporting, ensuring appropriate provider follow-up to reported symptoms and adequate patient response rate while minimizing survey fatigue may need to be improved upon.[165] Nevertheless, these tools offer an

opportunity to inform translational and comparative effectiveness research, health care technology assessment, and quality assurance, as well as to quantify value from the patient perspective. Another patient-reported outcome commonly measured is patient satisfaction, which refers to the patient's perception of the quality of care received.[166] Although limited by patients' relative inability to assess the technical quality of their care and inevitable dependence on patients' initial expectations, patient satisfaction remains an important part of the patient experience, and its inclusion in the value proposition reflects the greater shift in mindset in health care toward patient-centered care.

A Patient-Centered Approach to Value

Paralleling the rise of value-based care, patient-centered cancer care has received increasing focus in recent decades, as advocated by the Institute of Medicine (IOM), patient groups, and professional societies.[167] Patient-centered care, as defined by the Picker Institute, describes care that address multiple dimensions of patient care, including patient preference, emotional support, physical comfort, information and communication needs, continuity and transition, care coordination, involvement of family and friends, and access to care.[168] Patient-centered care, while inherently aligned with value-based care via a shared focus on high-quality care, has distinct attributes not typically included in discussions of value, such as patient experience and preference measures as well as conceptions of cost that are payer—as opposed to patient focused[33] (Figure 37.5). Patients themselves appear to intuit these contradictions: In a series of focus groups, interviews, and online surveys of health care consumers undertaken by the American Institutes for Research, respondents in general were unfamiliar with concepts related to evidence-based care, believing medical guidelines to reflect an "inflexible, bargain-basement approach" to treating unique individual patients.[169] Thus, for the transition to value-based care to be accepted and effective on a population level, patients—as recipients, co–decision makers, and co-financiers of this care—will need to be included in the discussion, with patient-centered outcomes, perspectives, and preferences explicitly incorporated into the definitions and metrics of quality and cost.

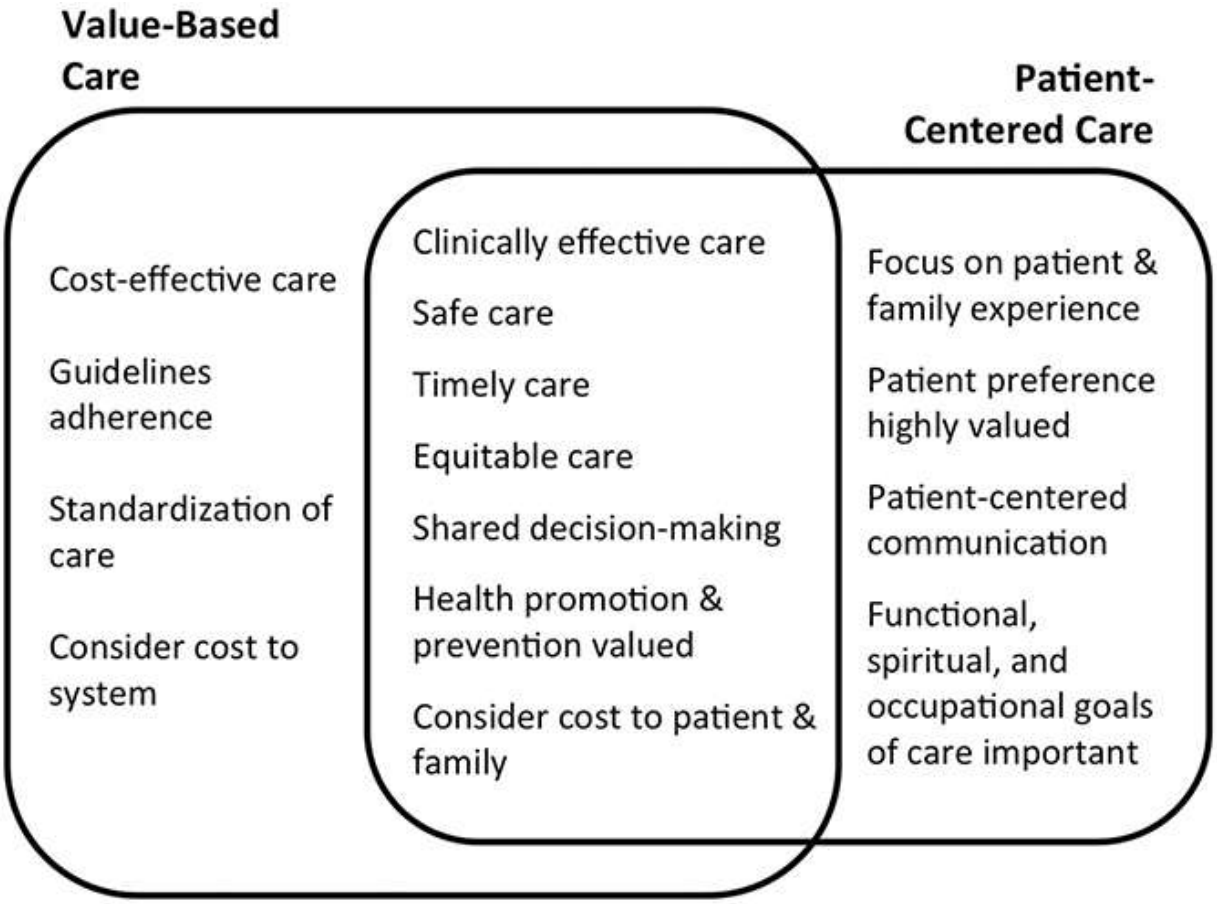

FIGURE 37.5 Attributes of value-based care and patient-centered care. (Adapted by permission from Springer: Tseng EK, Hicks LK. Value based care and patient-centered care: divergent or complementary? *Curr Hematol Malig Rep*. 2016;11[4]:303-310. Copyright © 2016 Springer Science+Business Media New York.)

Aligning Patient-Centered and Value-Based Care

Challenging the alignment of patient-centered and value-based care is the relative inability to assess cost in health care. Under the traditional fee-for-service–based system, although providers and administrators may have knowledge of individual billing charges and the direct costs of running a radiation oncology clinic, it is more difficult to calculate the total cost of care administered at a patient level. Furthermore, in our free market system, the charge for the same procedure can vary widely between providers, with no consistent correlation with the quality or outcome of care.[35] In comparison with how their purchasing decisions are made outside health care, patients are left to make important health care decisions with a relative deficiency of information, unable to assess the real costs or quality of care

offered by different providers; this is exacerbated in a system where the majority of patients are insured by a third party and bear only a small fraction of the total cost of care. Patients thus cannot function as "utility maximizers," choosing products that provide the highest utility for the lowest dollar. This discrepancy in effect removes the market pressure toward high-value care, in part contributing to increased cost, over- and underutilization, and decreased quality in health care. In effort to recreate this market pressure on patients, health plans have responded by increasing cost sharing via higher deductibles and copays. This practice, however, can counteract the achievement of value by preventing patients from pursuing necessary, high-cost sharing treatments, ultimately worsening patients' health and increasing the overall cost of care.

The Financial Burden of Cancer Care

Oncology care, in particular, has been presumed to be relatively shielded from the downward pressure of cost on demand, though evidence suggests that even patients with cancer consider treatment cost in their decision-making, suggesting that the cost of care should receive greater emphasis in assessments of value from a patient perspective.[170] Multiple studies have reinforced the detrimental effect that out-of-pocket costs have on patients' access to medical care as well as ability to pay for other nonmedical life necessities, with a report from the NCI indicating between 33% and 80% of patients with cancer using their savings to finance medical expenses.[35,171,172] In a population-based study from Western Washington State, a cancer diagnosis was associated with a 2.65-times greater likelihood of declaring personal bankruptcy. Upon further analysis, patients with cancer declaring personal bankruptcy additionally demonstrated a 79% greater mortality risk than those who did not.[173] This relationship between extreme financial distress and greater mortality risk is likely multifactorial, partly explained by overall poorer well-being, impaired HRQoL, or subpar quality of care.[174] Likely, further exacerbating the patient's sense of well-being, the burden of financial hardship for cancer care is not borne by the patient alone, with between 2% and 34% of patients borrowing money from friends or family to pay for care.[172] Unfortunately, as multiple forms of cancer are currently incurable with many patients eventually succumbing to disease, at least a

portion of these expenses are likely exhausted on futile care at the end of life. Although the administration of chemotherapy in patients in their last weeks of life has been well documented—indeed, chemotherapy administered the last 2 weeks of life was a previous quality indicator employed by the ASCO Quality Oncology Practice Initiative—evidence indicates that the field of radiation oncology is not immune to potential contributions to futile care, with a population-based study of Surveillance, Epidemiology, and End Results (SEER) Medicare and Texas Cancer Registry Medicare databases indicating an increase in use of advanced RT techniques in patients in the last 30 days of life from 2000 to 2009, with the proportion of patients treated with IMRT increasing from 0% to 6.2% and with stereotactic radiosurgery from 0% to 5.0%.[175-177] Although further research is necessary to determine whether these shifts in practice patterns improve palliative outcomes and to better identify patients who may benefit from advanced techniques in the palliative setting, such as SBRT for bone metastases[178-181] or locally advanced pancreas cancer,[182] consideration should be given toward the potential impact of the cost of these therapies on patients and their families.

Financial Toxicity

There now exists a wealth of evidence describing the deleterious effect of the cost of cancer care on patient well-being, which has led to a push for the inclusion of "financial toxicity," described as the harmful personal financial burden faced by patients receiving cancer treatment, in physicians' discussions with patients of the side effects associated with a particular treatment, with both the IOM and ASCO categorizing cost of care discussions as an essential component of high-quality care.[39,183-185] Additional strategies have been proposed to address financial toxicity, including implementation of screening for financial and health-related social needs (eg, housing and food insecurity, transportation, unemployment, and financial strains)[101]; providing financial literacy, navigation, and assistance to patients; incorporating cost information into treatment decision-making; and reducing low-value care.[186] The aforementioned ROCR APM includes an incentive for incorporating the transportation health-related social needs screening question into clinical

care. Clearly, however, numerous potential obstacles currently preclude effective cost of care discussions between patients and physicians, including uncertainty about the appropriateness of the topic and inability to accurately assess the cost of care.[72] Comprehensive intervention will likely require further research on the measurement of the material, psychological, and behavioral effects of financial toxicity and the identification of potential modifiable risk factors as well as further inclusion of these metrics at a policy level.[73] Composite scores using summary measures of multiple components of financial hardship, such as the Comprehensive Score for Financial Toxicity and Personal Financial Wellness Scale, have been employed in clinical studies as a patient-reported outcome, though results can be difficult to interpret with unclear application to the general population.[63]

Health Equity

Across all disciplines of medicine, inequity in health care results in significantly worse outcomes for socially disadvantaged groups, such as racial or ethnic minorities, people experiencing poverty, or those living in more geographically isolated areas. This is certainly true within the field of radiation oncology, where these disadvantaged populations are less likely to experience appropriate care across the entire cancer spectrum, from screening to treatment to outcomes, due to health care inequity.[187] As defined by the National Academies of Sciences, Engineering, and Medicine Committee on Community-Based Solutions to Promote Health Equity in the United States, health inequities are systematic differences in the opportunities groups have to achieve optimal health.[188] Systemic factors and structural inequities, such as racism and gender inequality, which can span from the individual to the system-wide level, impact social determinants of health, which, in turn, bring about health inequities.[189,190] On the other hand, health equity refers to the concept of all individuals being able to attain their highest level of health without being hindered as a result of their social circumstance. The ultimate outcome of health care inequity is health care disparities, which refers to differences in the receipt of health care and/or health outcomes among different populations.[191,192] Important to the understanding of health care disparities is that they are preventable through

the addressment of societal inequities, social determinants of health, and the subsequent health inequities.[193]

Although attention, albeit perhaps insufficient, had been previously directed toward health equity in radiation oncology, this focus was renewed during the COVID-19 pandemic when health care disparities in general were further amplified and spotlighted.[193] One of the overarching goals of *Healthy People 2030* is eliminating health disparities, achieving health equity, and attaining health literacy, and one of its five core objectives is focused on social determinants of health.[190] Within radiation oncology, the *Red Journal* recently published special issues devoted to Health Equity, Diversity, and Inclusion in which potential mechanisms to analyze and address health inequity in radiation oncology were highlighted, and a call for increased awareness, action, and accountability with regard to health equity was issued.[194,195] While there has been research identifying equal access health care systems as a potential mechanism for advancing health equity,[196,197] this and other broad solutions may currently be politically infeasible. In addition, as the field continues to develop and implement new and innovative treatments, care must be taken to not exacerbate health care inequity and subsequent disparities as the result of differential access to these treatments.[198-200] In addition to the obvious patient-centered benefits associated with improving health equity, strategies to eliminate inequities have also been shown to be cost-effective from a societal perspective.[201]

Value Proposition in Resource-Constrained Countries

Establishing access to RT services remains a challenge in lower income countries because of the resource intensive and expensive nature of RT.[202,203] While the fundamental principles of the value framework described earlier are relevant to all radiation oncology settings, their application can vary depending on the economic status and resource availability of the setting in question. In lower income, resource-constrained countries,[204] the relative weights of each input as well as the overall interpretation of the value proposition conceivably differs from that in higher income countries. In such settings, cost reasonably merits increased consideration as the costs required to establish and expand access to RT services in these countries are high. Yet despite these high upfront expenses, the overall net economic

impact associated with expanding global access to RT services is estimated to be positive, in addition to the positive health impact this would have.[201,205] As in higher income countries, health economic research and costing analyses can play a key role in evaluating the cost component of the value proposition for lower income countries,[206] and efforts to encourage such analyses should be undertaken.

Although providing access to care is an important goal for lower income countries, the quality of the care, the numerator of the value equation, is as equally if not more important in such countries.[207] Among the components that make up quality in the value framework (outcomes, structure, and process), ensuring that a proposed intervention, in this case, RT, can achieve successful outcomes is integral to determining its value in resource-constrained settings. As described earlier, Porter's Outcomes Measures Hierarchy can be used to prioritize multiple clinical outcomes, acknowledging that the outcome tiers may vary on the personal and/or cultural level. Taken together, additional emphasis can be placed on the cost and outcomes elements when assessing the value proposition in radiation oncology in resource-constrained, lower income countries.

Decisional Regret

As previously discussed, the effective measurement of more subjective outcomes in radiation oncology remains an area in need of further research, and their greater inclusion in assessments of value is a critical challenge in the alignment of value-based and patient-centered care.[33] Validated metrics of patient-reported outcomes, in which patients report directly on perceptions of their own health, have been developed and are now more broadly included in clinical trials, providing essential patient-centered data on the impact of interventions; likewise, development of validated instruments to assess patient-reported experience measures, or their perception of their experience with health care delivery, is ongoing. An intriguing example of a validated and well-studied patient-reported outcome with applications to radiation oncology is decisional regret, defined as the negative emotion experienced when we suspect that an alternative course of action would have resulted in a better outcome.[208] Cancer-related decision-making is complex, requiring an understanding of both the medical and

psychosocial impacts of treatment in the context of one's personal values and beliefs; given the complexity and multifactorial nature of these choices, decisional regret offers a broad measure of a patient's treatment experience and quality of life and has been shown to be a more sensitive outcome than patient satisfaction in certain settings. Decisional regret has been identified in multiple cancer sites where RT is commonly used, such as prostate,[209] lung,[210] and breast.[211] In prostate cancer, multiple factors have been associated with treatment regret, including poor HRQoL and global post-treatment quality of life. Interestingly, specific treatment modalities have also been associated with increased post-treatment regret. For example, at the University of California, Los Angeles, a survey of patients with localized prostate cancer treated with IMRT, SBRT, or high-dose rate (HDR) brachytherapy suggested that patients treated with SBRT experienced significantly less treatment regret compared with patients treated with IMRT or HDR.[212] Thus, when comparing modalities—particularly with equivalent long-term survival and comparable toxicity profiles—further understanding of the patient experience is informative in assessing the value of specific medical interventions.

Value in Radiation Oncology: Conclusions

Regardless of the volume of ongoing debate surrounding health care reform, in many ways, the transition to some form of value-based care is inevitable. Enacted in April 2015, the Medicare Access and CHIP Reauthorization Act repealed the SGR to establish the Quality Payment Program to encourage physician participation in APMs that utilize value-based payment; in response to unsustainable rising health care costs, multiple private payers have begun experimenting with APMs already.[30,213] This transition offers an opportunity to serve patients, providers, society, and shareholders alike through better alignment of incentives among stakeholders and reduced administrative costs. Although the recent attempt by CMS to create the RO-APM was unsuccessful, work is already underway to develop a new model, which, among other components, emphasizes value-based care. Whatever method of payment reform ultimately takes ahold will arise from iterative experimentation; radiation oncologists and the patients they treat will be best served by taking an

active role in this collaborative process, both via participation in health care advocacy and contribution to novel health services research.

HEALTH SERVICES RESEARCH

The field of health services research, often referred to as outcomes research, refers to the study of access to care, costs of care, and quality of care. Access to care concerns factors that expedite or hinder the use of medical services. Costs of care include payments by insurers and patients for medical services as well as the cost of lost productivity because of time away from work and decreased wages. As previously discussed, quality of medical care incorporates elements of structure, process, and outcomes. Although there are several methods of analysis relevant to health services research, decision analysis and cost-effectiveness analysis, in particular, are standard techniques used to evaluate and compare medical therapies. As the costs of oncologic care rise, it is vital to evaluate the cost-effectiveness of RT. Cost-effectiveness analyses assess the costs relative to health outcomes for a particular medical intervention. This section explains the theoretical aspects of decision and cost-effectiveness analyses.

Evidence for New Technologies

Prior to further description of decision and cost-effectiveness analyses, it is important to consider the role of health services research and other types of evidence in evaluating new technologies and treatments. The field of radiation oncology is constantly advancing and developing new treatments, though the process of incorporating emerging technology into the standard of care can be prolonged or challenged by the prerequisite of accumulating a sufficient body of supporting evidence. As such, it is imperative to examine the thresholds of evidence a new technology must satisfy so that it may be integrated into the standard of care, as this is intertwined with health care economics and policy. Moreover, emerging technology within radiation oncology often outpaces the evidence demonstrating its benefits to patients, providers, and the health care system, and the need for evidence must be balanced with the opportunity for these stakeholders to experience the advantages of cutting-edge treatments.

When considering the body of evidence needed to support or oppose a new treatment, emphasis is reasonably placed on level I evidence, namely, randomized controlled trials. There are, however, disadvantages with randomized controlled trials, such as feasibility (from resource, time, and ethical standpoints), statistical challenges, and generalizability. For instance, randomized trials often necessitate lengthy follow-up before showing differences between various treatments, and their results may not be available until the therapy itself is out of date. Randomized trials also report the best treatment for the "average person"; patient preferences are not considered. In addition, as described previously, patient-reported outcomes are an important aspect of determining high-value care, and there still exist some challenges with the inclusion and interpretability of these measures in randomized controlled trials. These concerns call into question their role as the predominant and often required source of data for implementing a new treatment.[214,215] While there are known, considerable limitations to observational research, such as selection bias, important conclusions can be drawn from these type of data, particularly in situations when conducting a randomized controlled trial is impractical. Furthermore, methods of research aside from comparative effectiveness, such as decision and cost-effectiveness analyses, might identify benefits or detriments aside from clinical outcomes, which influence a technology's fulfillment of high-value care. It should be noted as well that level I evidence is not required for the creation of a new CPT Category I code. As the field of radiation oncology and its treatments continue to progress, we must consider the quantity and quality of evidence required to implement innovative and potentially higher value technologies.

Decision Analysis

Decision analysis uses a set of mathematical tools designed to determine the most favorable outcome with regard to a particular endpoint, such as overall survival or time without recurrence, for individuals with a given starting situation under many different sets of circumstances, using existing data or assumptions regarding the effectiveness and toxicities of treatments. Decision models can help outline the trade-offs for different treatments in clinical situations when no good evidence is available.

To make a model, a decision tree is created to symbolize the results of clinical choices. The model requires making simplifying assumptions while still being sufficiently complex to correctly illustrate the important aspects of the decision. Figure 37.6 depicts a scenario in which a patient is faced with the treatment dilemma of whether to undergo RT for illness X.[216] Decision nodes are signified by squares in the decision tree, chance nodes by circles, and terminal nodes by triangles.

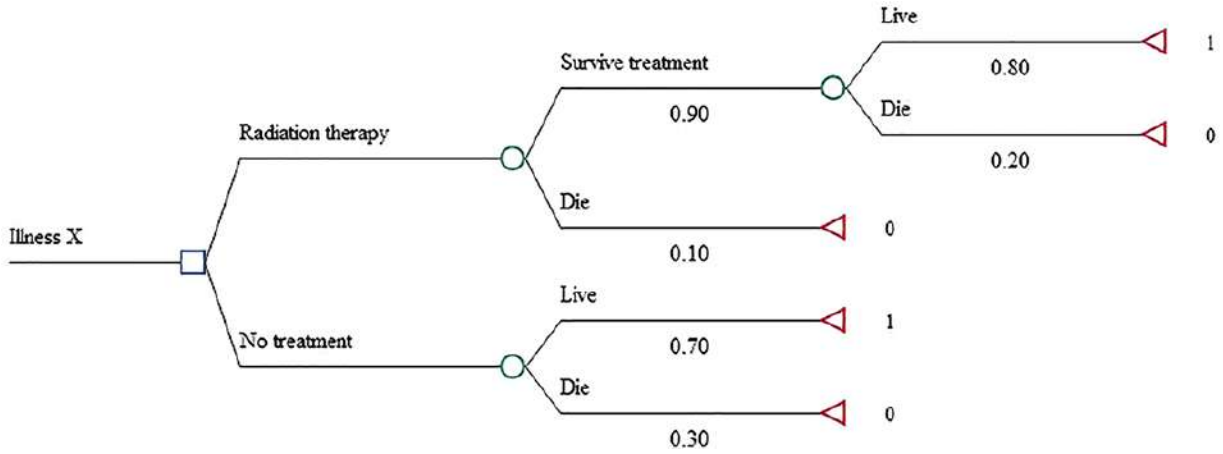

FIGURE 37.6 Decision tree of a patient with illness X. (Reprinted from Sher DJ, Punglia RS. Decision analysis and cost-effectiveness analysis for comparative effectiveness research—a primer. *Semin Radiat Oncol*. 2014;24[1]:14-24. Copyright © 2014 Elsevier. With permission.)

Subsequent to choosing a treatment, there is a chance node after which all potential events are shown as branches. The probability of a particular outcome following a chance node is determined from data from the literature or expert opinion. The probabilities of events at each chance node must add to 1. In Figure 37.6, if the patient with illness X chooses RT, they have a 90% chance of surviving the treatment and a 10% chance of dying from the treatment. If the patient survives the treatment, they then have an 80% chance of remaining alive and a 20% chance of dying. If the patient forgoes treatment, they have a 70% chance of living and a 30% chance of dying.

The terminal nodes depict the final outcomes states of each pathway. Next to each of the terminal nodes is a value associated with that state. In our example, the only two outcome states are living and dying. Being alive

and dead are associated with values of 1 and 0, respectively. When calculating the expected survival rate for RT, we see that if a patient survives treatment, they have an 80% chance of living (outcome of 1) and a 20% chance of dying (outcome of 0). The value at this chance node is calculated by multiplying the probability of the outcome with the associated value, resulting in a value of 0.80. We then substitute the value of 0.80 as the value associated with surviving treatment and multiply this value by its probability of 0.90. The resulting value (0.72) is then combined with that of dying from treatment (outcome of 0 with probability of 0.10), for an expected value of 0.72. The expected survival rate for no treatment is calculated by multiplying the likelihood of living (0.70) with its outcome of 1 and combining that to the product of the likelihood of dying (0.30) and its outcome of 0, to obtain a value of 0.70.

Outcome Values

In our simple example, the outcome value was the likelihood of survival with or without treatment for illness X. However, decision analyses can also model values associated with different health states. A utility is an econometric construct that describes how an individual values a given health state versus death (0) and perfect health (1).[217] The worse the health state, the lower the utility. For instance, experiencing a rectal toxicity may be associated with a utility of 0.7, and living with distant metastasis may be associated with a utility of 0.6. This ability to describe utilities for different outcomes states allows modelers to incorporate side effects of treatments into their model, an important consideration given that many cancer treatments affect a patient's quality of life. The benefit associated with various cancer treatments depends on the trade-offs between the fear and consequences of recurrence versus the inconvenience and potential toxicity of treatment.

Utilities are different from more familiar, descriptive quality-of-life measures as they reflect how a respondent values a state under conditions of *uncertainty*. Although there are several techniques for assessing utilities,[218] the most firmly grounded in expected utility theory is the standard gamble. The standard gamble assesses the utility for a health state by asking how high a risk of death a participant would accept to improve it (Figure 37.7).

The respondent is asked to choose between a certain life in an intermediate health state and a gamble between optimal health and immediate death. The probabilities in the gamble are varied systematically until the respondent feels that the two choices (life in an intermediate health state and the gamble) are equally desirable. At the "point of indifference," the respondent's utility for the health state is given by the probability of optimal health in the gamble. The utility of the health state is given by the probability of perfect health in the gamble such that the respondent is indifferent between the gamble and the certain intermediate outcome.

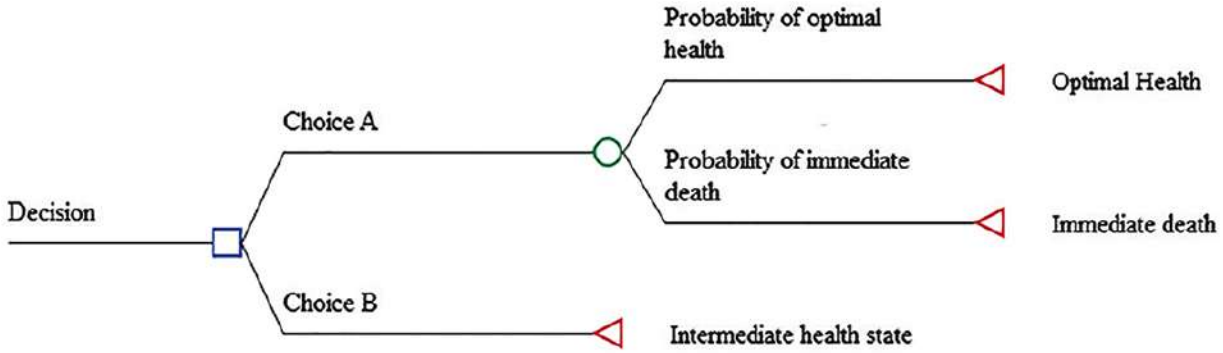

FIGURE 37.7 The standard gamble assesses the utility for a health state by asking how high a risk of death a participant would accept to improve it.

Utilities can also be used to calculate quality-adjusted life-years (QALYs), an index of survival that is adjusted to account for the patient's quality of life during a specific period. The QALY is the standard effectiveness measure.[219] A QALY is determined by multiplying the time spent in a certain health state with the utility associated with that state. For example, 2 years of time spent in a state whose utility is 0.5 would be the equivalent of 1 QALY.

Sensitivity Analysis

The published literature and expert opinion provide the basis for probabilities at the nodes of a decision tree. However, these estimates are often quite uncertain. Sensitivity analyses are, therefore, usually a critical part of decision models. Sensitivity analyses vary a certain parameter (eg, the probability of recurrence of cancer) over the entire plausible range of its

values and then study the effect of varying the parameter on the outcome. Sensitivity analyses provide a measure of the robustness of a conclusion in a similar way to confidence intervals and *P* values in biostatistics. They may also increase the level of confidence by confirming the lack of significant dependence of an outcome on a certain transition parameter. In addition, sensitivity analyses may also identify areas where further research may be valuable by revealing dependence of an outcome measure on the variable studied.[216] One-way sensitivity analyses provide threshold values, and one-way sensitivity analyses of multiple model inputs can be plotted in a Tornado diagram to depict which variables have the greatest impact on the model results.[220] Two- and three-way sensitivity analyses systematically vary two to three parameters simultaneously; the outcomes for each combination of variables can then be assessed.

In the example shown in Figure 37.6, we may not know the likelihood of treatment mortality for illness X. It may also vary by physician or with patient characteristics. In order to determine the optimal treatment strategy for a given treatment mortality, we can conduct a one-way sensitivity analysis. As shown in Figure 37.8, the expected value of RT decreases as the treatment mortality increases. The threshold mortality at which RT and no treatment yield equivalent expected outcomes is 0.125. Below this mortality threshold, RT is associated with the best expected value, but no treatment becomes the optimal strategy above this value.

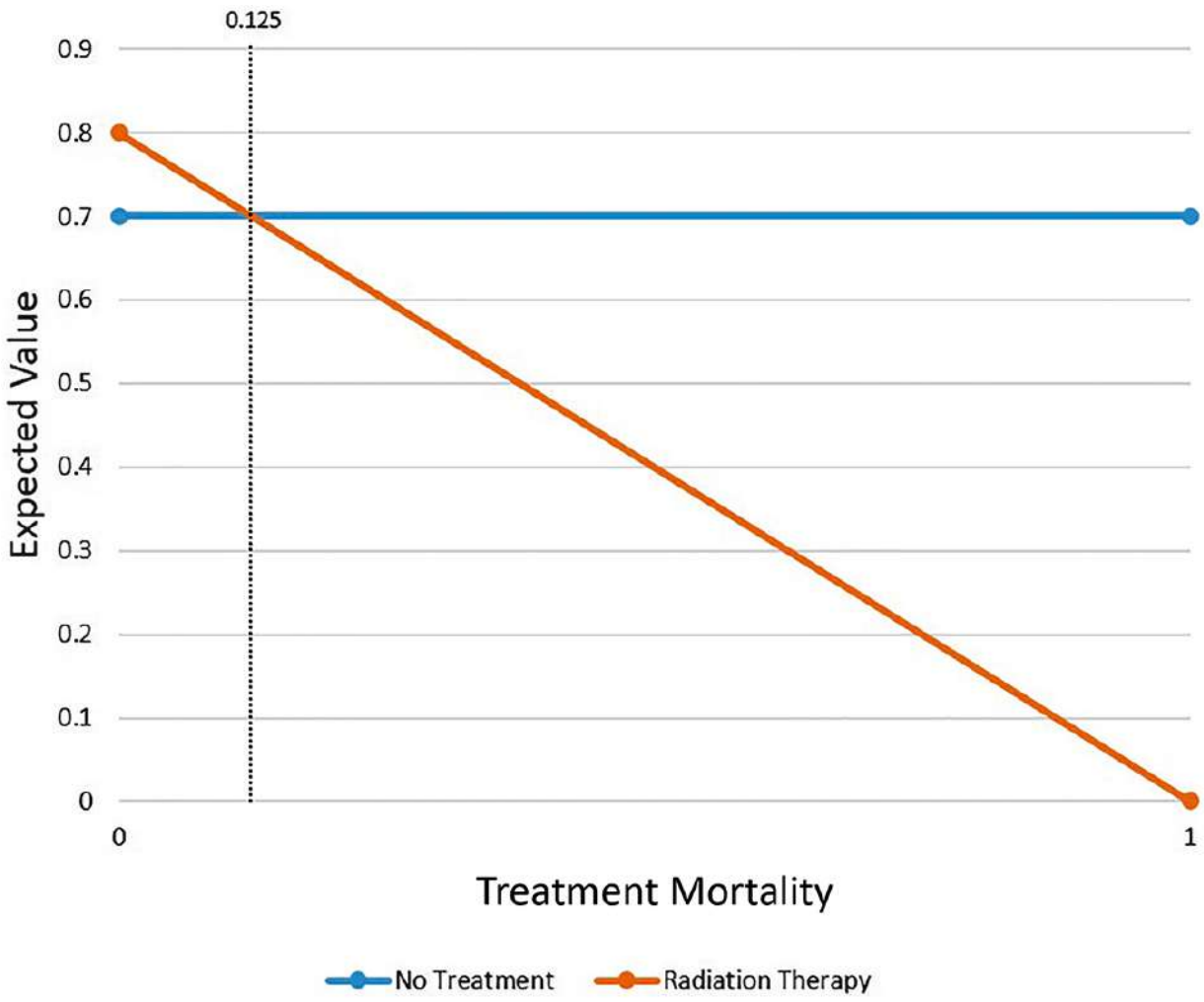

FIGURE 37.8 Sensitivity analysis of mortality from treatment for illness X. (Reprinted from Sher DJ, Punglia RS. Decision analysis and cost-effectiveness analysis for comparative effectiveness research—a primer. *Semin Radiat Oncol*. 2014;24[1]:14-24. Copyright © 2014 Elsevier. With permission.)

Markov Models

Markov models are useful when time needs to be incorporated into a decision model. They allow the study of outcomes by describing events as discrete states. They are particularly helpful in modeling clinical situations where a patient is at risk for a given event over an extended period of time (eg, recurrence of cancer). Markov modeling works by making a number of assumptions. First, a patient is always in one of a finite number of discrete health states. Second, all events are represented as transitions from one state to another. Third, time is divided into equal increments referred to as Markov cycles, which may be days, months, or years depending on the

clinical situation. Fourth, transitions between health states occur only once per cycle. Finally, all patients in a given health state face the same transition probabilities, no matter when they entered that particular health state.[216] Patients start the model in a single health state. As the model cycles, the patients travel through time and may remain in their previous health state or transition to a different health state with a certain transition probability.

Figure 37.9 shows a simplified prostate cancer Markov model.[216] Patients who have completed initial therapy start in the "no-disease" health state. At each cycle, the patients may either remain in the "no-disease" health state, have a finite probability of having a recurrence and transition to the "recurrence" health state, or have a finite probability of dying of causes unrelated to their cancer and transition to the "death" health state. Once in the "recurrence" health state, patients may remain there or with a certain probability die from their recurrent disease and enter the "death" health state. Once the patients enter the "death" health state, they may not exit. (This is an example of an "absorbing" health state.) A type of a Markov model called an absorbing model runs until all patients are in the "death" health state and can be used to calculate residence times in transient states allowing for life expectancy and time spent without recurrence.

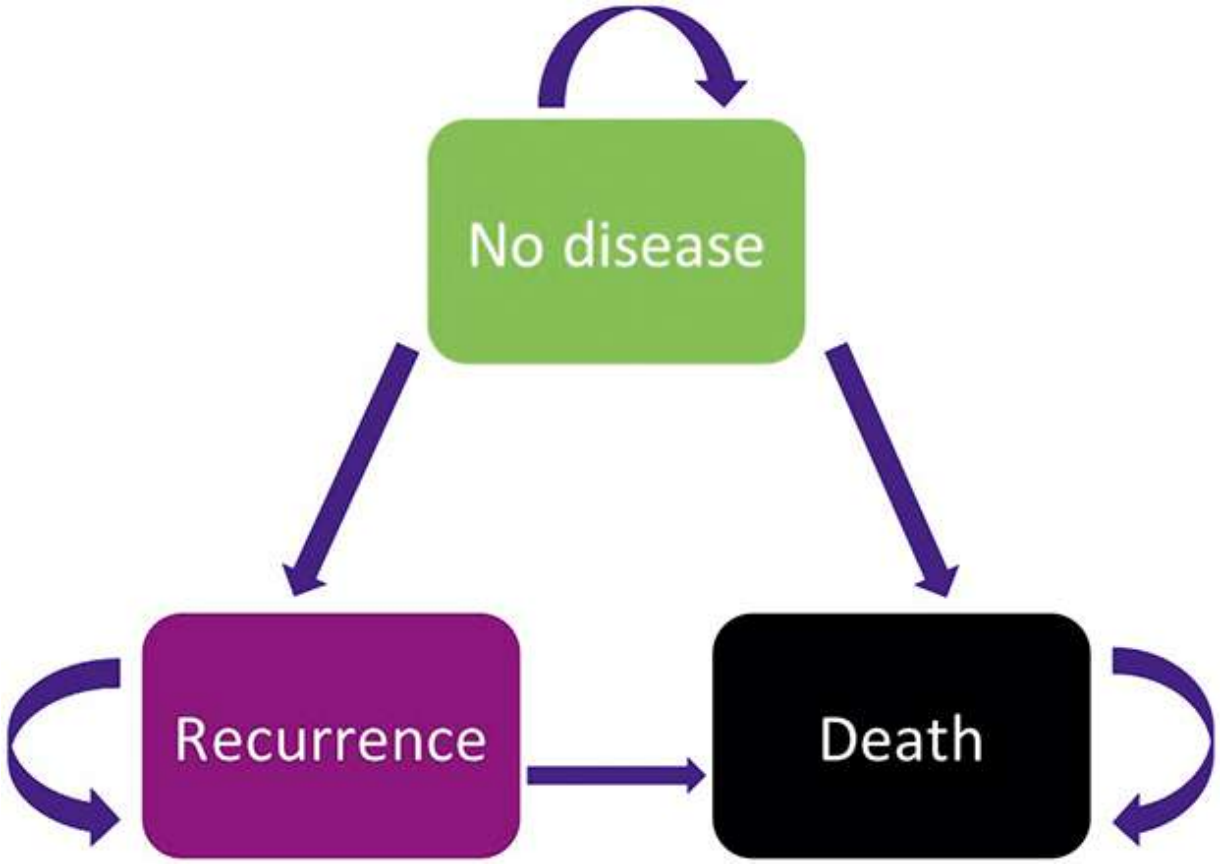

FIGURE 37.9 Markov model with three health states. (Adapted from Sher DJ, Punglia RS. Decision analysis and cost-effectiveness analysis for comparative effectiveness research—a primer. *Semin Radiat Oncol*. 2014;24[1]:14-24. Copyright © 2014 Elsevier. With permission.)

One common method to evaluate a Markov model is the Monte Carlo simulation, where simulated patients enter the model one by one. The computer program then randomly selects a value for a variable in the decision analysis using a probability distribution and tracks the outcome. The process is repeated thousands of times (simulating thousands of patients), and the mean and standard deviation for a result (eg, mean overall survival) are obtained.

Cost-Effectiveness Analysis

Cost-effectiveness analysis is a set of mathematical tools designed to compare the relative costs and benefits of treatment alternatives. The most common type of cost-effectiveness analysis uses a model-based study,

which is nearly identical to a classic decision analysis. A Markov model is created, and QALYs are accumulated over the time scope of the study. Costs are also accumulated during each stage, such that by the end of the analysis, there is a cost and QALY associated with each strategy. One then orders the strategies by effectiveness.

The end result of any cost-effectiveness analysis is reported as an incremental cost-effectiveness ratio (ICER), which is the ratio of the change in costs to incremental benefits of a therapeutic intervention or treatment.[221] The ICER is usually reported as a cost per QALY (eg, $55,000 per QALY). Treatments are considered "cost-effective" or not based on whether the ICER passes a particular threshold, the societal "willingness to pay" (WTP). The amounts $100,000 and $150,000 per QALY are commonly accepted values above which treatments are not considered cost-effective in the United States.[222] A new treatment is said to "dominate" the standard treatment if is more effective and less costly.[221] Model uncertainty and relationship with the WTP threshold can be further assessed through probabilistic sensitivity analysis.[223] In this type of analysis, probability distributions are created for each model variable and then used in a Monte Carlo simulation. Each simulation of the model will "randomly select" a value from each variable's probability distribution to generate thousands of unique ICERs. These data can be plotted on a cost-effectiveness acceptability curve, which graphically demonstrates the probability of an intervention being considered cost-effective at a certain WTP threshold.[224] In the example shown in Figure 37.10, a probabilistic sensitivity analysis was performed on a cost-effectiveness model evaluating the use of stereotactic ablative radiation therapy (SABR) in the treatment of oligometastatic cancer in comparison with the standard of care.[225] As the WTP threshold increases, the probability that SABR will be considered cost-effective (ie, the probability that the ICER will be less than the WTP threshold) increases. This cost-effectiveness analysis example is discussed further in a later section of this chapter.

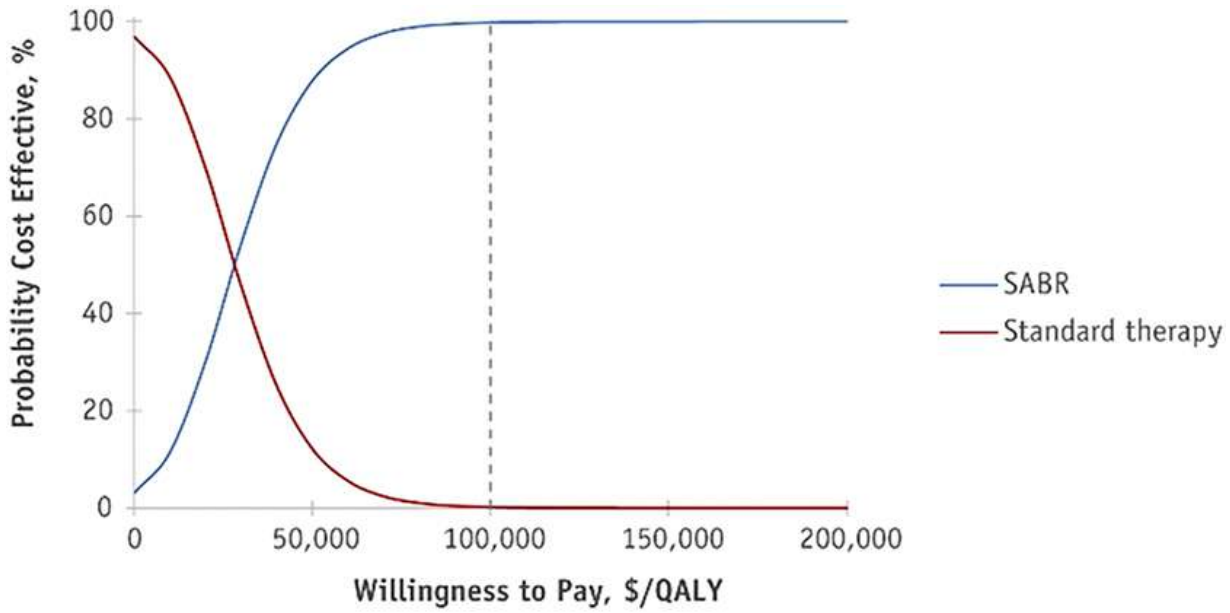

FIGURE 37.10 Probabilistic sensitivity analysis of stereotactic ablative radiation therapy (SABR) compared with standard therapy for oligometastatic cancer. (Adapted from Kumar A, Straka C, Courtney PT, Vitzthum L, Riviere P, Murphy JD. Cost-effectiveness analysis of stereotactic ablative radiation therapy in patients with oligometastatic cancer. *Int J Radiat Oncol Biol Phys*. 2021;109[5]:1185-1194. Copyright © 2020 Elsevier. With permission.)

Costs

Costs included in a cost-effectiveness analysis depend on the perspective of the analysis. In the societal perspective, every cost needs to be measured, including capital expenses and the lost economic productivity of both the patient and caregivers.[221] In the payer perspective, only costs paid by the payer are pertinent. Analyses from the payer perspective primarily take health care reimbursements into account. Costs associated with RT can be divided into fixed costs and variable costs. Fixed costs consist of costs of the facility, physics and engineering maintenance of the machine, and salaried labor.[226] The capital cost of purchasing a linear accelerator or building a proton therapy center makes up a substantial fraction of the fixed costs. The estimated cost of a CT-based linear accelerator is approximately $4 to $5 million, whereas the list price for MRI-based linear accelerators is approximately $8 to $9 million.[227,228] The market price of a proton center is estimated to be on the order of $25 to $200 million.[229-231]

The variable costs of RT vary substantially by radiation treatment modality. They can be broken down into three basic categories: treatment

simulation, treatment planning, and treatment delivery.[226] IMRT and three-dimensional conformal radiation therapy (3D-CRT) simulations involve a CT simulation, which necessitates more effort on the part of physicians, physicists, and therapists than a 2D simulation, which is done using a simple fluoroscopic simulator. Whereas the planning process for a 2D plan involves calculations that can be performed using a calculator, a 3D plan requires more work by the dosimetrist. An IMRT plan is even more complex and, for that reason, more costly. Moreover, quality assurance programs for IMRT plans often entail "dry runs" to guarantee that the planned dose approximates the delivered dose, adding to costs.[232] Because each Lucite compensator is custom-made for each proton patient, compensators used in proton beam therapy (PBT) are more expensive than the wedges used in conventional RT. By the same token, delivering a simple 2D plan is considerably less expensive than a 3D-CRT or IMRT treatment, and PBT is even more expensive (producing protons in a cyclotron is more resource intensive than producing photon from a linear accelerator). In addition, the daily image guidance associated with IMRT incurs additional costs. MRI-guided RT introduces unique costs into these three categories as well. MRI-guided RT employs MRI simulation, often in addition to CT simulation, and its treatment planning is more complex, given the newer technology and workflows. A key innovation of this modality is the improved feasibility and process for online adaptive RT, though this increases overall treatment time and required personnel.

Cost-Effectiveness Questions

Multiple types of questions can be answered within the field of radiation oncology with cost-effectiveness models.[216] For example, what is the cost-effectiveness of using RT, compared to other treatment options, such as surgery, systemic therapy, different RT techniques or regimens, or no treatment at all? In addition, in the setting of multimodal care involving RT, what is the cost-effectiveness of different combined modality regimens?

These questions, particularly regarding RT regimens, have inspired research within the field of prostate cancer, as the explosion of new and expensive technologies such as IMRT and SBRT calls for careful analyses of their cost-effectiveness. For example, Sher and colleagues developed a

Markov model comparing the cost-effectiveness of robotic (R-) and nonrobotic (NR-) SBRT to IMRT for a 65-year-old patient with low-risk prostate cancer from the payer perspective.[233] Their model included the six health states of alive with no evidence of disease, alive with asymptomatic local recurrence, alive with symptomatic local recurrence, alive with distant metastases, death from unrelated causes, and death from prostate cancer. Over time, the patient could also experience toxicity. Patients were allowed to have any combination of sexual, rectal, and urinary toxicities, with the assumption that the development of any toxicity was independent of the others. All toxicities from treatment were assumed to occur within 5 years of therapy; after 5 years, they assumed no new onset of toxicity. Given the lack of robust follow-up, it was assumed that the recurrence risk after SBRT was the same as the recurrence risk after IMRT (an assumption that later proved to be valid).[133,234,235] Each health state was associated with a cost and a utility derived from the published literature. Patients were followed until death. The baseline costs of each RT treatment were defined by the 2012 Medicare payment schedule for hospital-based practice. The total costs of IMRT, NR-SBRT, and R-SBRT were $27,564.21, $10,108.93, and $19,275.41, respectively. Costs after local or distant recurrence were taken from Bayoumi and colleagues, and costs for the management of proctopathy, bladder toxicity, and impotence were extracted from the Institute for Clinical and Economic Review. Quality-adjusted life expectancy after IMRT was slightly higher than after SBRT, because worse toxicity was assumed after SBRT. The ICERs for IMRT over R-SBRT and NR-SBRT were $285,000 and $591,100/QALY, respectively. On sensitivity analysis, SBRT was almost always the cost-effective therapy, in which the ICER for IMRT was generally over $100,000/QALY. Treatment efficacy, rectal toxicity, and impotence and the potential for unforeseen SBRT late effects were the most critical parameters in the model. When including these uncertain parameters in a probabilistic sensitivity analysis, SBRT was still most likely to be cost-effective at a WTP of $100,000/QALY. The authors concluded that SBRT clearly contained more value than IMRT for external beam treatment. One limitation of this study is that although outcomes are well established after IMRT, they are less mature after SBRT, with prospective trials reporting recurrence and toxicity data at relatively short follow-up.[133,234,235]

With the increased use of RT in oligometastatic disease, the cost-effectiveness of this strategy was evaluated by Kumar and colleagues.[225] In this study, the authors created a Markov model comparing SABR with standard-of-care therapy for a 66-year-old patient with oligometastatic cancer, defined as having five or fewer oligometastatic lesions. The model included three health states: alive with stable disease, alive with cancer progression, and death, and patients were followed until death. Patient outcome and toxicity probabilities were derived from the 2019 publication of the SABR-COMET trial.[236] In both alive states, patients could experience treatment-related toxicity within the first 2 years as this was the median follow-up time for the SABR-COMET trial at time of publication. For progression and survival beyond 5 years (the follow-up range the SABR-COMET trial), the probability of death for patients was assumed to follow survival estimates from the SEER database.[237] In addition, sensitivity of the model to this assumption was tested by generating scenarios in which patients were "cured" and their survival followed age-specific mortality rates from United States life tables as well as a scenario in which all patients died after the 5 years of reported trial follow-up. The cost of SABR was calculated from Medicare reimbursement rates for all components of the radiation oncology planning and treatment process for a five-fraction SBRT course. Costs and health utilities were derived from published literature. Given that multiple primary cancer types were included in the SABR-COMET trial, weighted averages based on the proportions of each cancer type in the trial were used for all model inputs when necessary. A WTP threshold of $100,000/QALY was chosen. In the base-case analysis, which was from the health care sector perspective, SABR increased the overall cost of treatment by $54,260, from $405,901 with standard therapy to $460,161 with SABR, as well as increased effectiveness by 1.88 QALYs, corresponding to an ICER of $28,906/QALY, which was considered cost-effective at the WTP threshold used in the study. Similarly, the ICER from the social perspective was also below the WTP threshold at $38,783/QALY. In one-way sensitivity analyses, the model was relatively insensitive to most variables, including the probability of progression and survival when ranged across the 95% confidence intervals for these outcomes reported by the trial. For example, the cost of SABR would have to increase more than 10-fold for this strategy to become cost-ineffective. Probabilistic sensitivity

analysis (Figure 37.10) showed that SABR would be the cost-effective treatment option, with 87.8% and 98.8% of the time at WTP thresholds of $50,000/QALY and $100,000/QALY, respectively. The authors concluded that SABR for oligometastatic cancer was a cost-effective treatment option. The authors acknowledged limitations of their model due to drawing a significant amount of model input data from a single, heterogeneous, phase II trial (SABR-COMET), which notably had updated but overall similar results published after publication of the cost-effectiveness article[238]; however, this is balanced by the fact that the model was relatively insensitive to the variables included.

In another cost-effectiveness study, Chin and colleagues developed a Markov model comparing short-course radiation therapy and total neoadjuvant therapy (SCRT-TNT), consisting of 25 Gy in five daily fractions via 3D or IMRT techniques followed by nine cycles of modified leucovorin calcium, fluorouracil, and oxaliplatin or six cycles of capecitabine and oxaliplatin, versus conventional long-course chemoradiotherapy (LCCRT), consisting of 50.4 Gy in 28 daily fractions with concurrent capecitabine with or without adjuvant chemotherapy for locally advanced rectal cancer.[141] In all cases, patients underwent total mesorectal excision (abdominoperineal resection or low anterior resection). Patients could transition between the five health states of no evidence of disease, resectable locoregional recurrence, unresectable locoregional recurrence, distant metastatic disease, and all-cause death. Patients who experienced resectable locoregional recurrence underwent reirradiation via a hyperfractionated technique of 39 Gy in 26 twice-daily fractions,[239] followed by salvage surgery in a proportion of patients, and patients with unresectable recurrence received palliative capecitabine for 1 year. Outcome and treatment-related toxicity probabilities were obtained from the RAPIDO trial,[134] though the probabilities of transitioning between states after the first cycle (ie, from any locoregional recurrence to metastases or death) were assumed to be the same in each treatment group. Similar to the other cost-effectiveness studies, costs and utilities were derived from the Medicare outpatient payment schedule and published literature. A WTP threshold of $50,000/QALY was chosen. Overall, SCRT-TNT incurred lower costs ($41,355) compared with LCCRT ($54,827) and a higher effectiveness (2.21 QALYs with SCRT vs 2.12 with LCCRT), resulting in a

negative ICER of –$141,256/QALY, indicating that SCRT-TNT "dominated" LCCRT and was overall cost-effective. Sensitivity analyses revealed the model was most sensitive to the probability of transitioning from the no evidence of disease health state to the distant metastasis health state, the probability of low anterior resection as initial treatment, the health utility of being in the no evidence of disease health state after low anterior resection, and the cost of LCCRT and adjuvant chemotherapy, though even if each variable was differed by 25% around the base-case values, SCRT-TNT remained cost-effective. This study, similar to the abovementioned study, was limited by the fact that it drew data primarily from a single phase 3 study (RAPIDO), and furthermore, quality of life and patient-reported outcomes data had not yet been reported for any prospective studies of SCRT-TNT for rectal cancer.

Health Services Research: Conclusions

Although randomized clinical trials are the gold standard for obtaining level I evidence, the dearth of long-term data directing therapeutic choices is one reason to perform decision analysis, which allows assumptions to be made and then varied over a wide range to determine their effects on results. The number of properly constructed cost-effectiveness analyses studying RT reported in the literature is growing; however, the pressing need for additional cost-effectiveness studies within the field of radiation oncology remains. As our treatments become more technical and expensive, it is our responsibility to prove that these treatments lead to benefits (either better survival or improved quality of life) that warrant the increased cost.

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CHAPTER 38

Economic, Gender, and Racial Disparity in Radiation Oncology

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The field of radiation oncology (RO) has evolved rapidly since its inception, incorporating treatment modalities like hypofractionation and stereotactic radiotherapy (RT) aimed at reducing the number of fractions per treatment series. Technological advancements in this field have undoubtedly yielded numerous benefits, including decreased treatment volumes, shorter durations, improved treatment outcomes, and reduced toxicity. However, it is paramount to recognize that these advancements have not consistently resulted in fair and accessible outcomes for all patient populations.[1] Disparities persist within RO, stemming from factors such as race, gender, geographical location, and socioeconomic status (SES). These disparities have had a profound impact on both patients and health care practitioners, exerting far-reaching effects across the entire cancer care continuum.[2] They manifest throughout different stages, ranging from disease burden and associated risks to early detection, diagnosis, and treatment. They significantly affect critical outcomes, such as quality of life, mortality rates, and survival rates, often with social and economic conditions playing a substantial role in driving these disparities.[3] This chapter aims to explore economic, gender, and racial disparities within RO, advocating for health equity by encouraging the effectuation of the highest quality of health in this field for all individuals, particularly focusing on those at the greatest risk of less than optimal health outcomes due to social and economic factors. The reduction of health disparities serves as the metric to gauge advancement toward achieving this goal.[2]

SOCIOECONOMIC STATUS

Definition of Socioeconomic Status

Socioeconomic status (SES) refers to a conceptual framework that categorizes individuals and communities based on various indicators used for codifying a hierarchical structure for social stratification. These indicators often include measures, such as income, education, occupation, that can be reflective of social positioning and offer insights into access to essential material resources such as food, shelter, transportation, education, and health care services, such as RT.[4] Socioeconomic factors play a significant role in influencing cancer risk factors, including tobacco use, inadequate nutrition, physical inactivity, and obesity. In particular, income, education, and health insurance coverage have a direct impact on individuals' ability to access timely and appropriate early detection, treatment, and palliative care for cancer.[3] When understanding the risk, burden, and impact of socioeconomic factors on cancer across the socioeconomic strata, many studies have employed census tract data as a means to designate SES.

The Surveillance, Epidemiology, and End Results (SEER) Program of the U.S. National Cancer Institute (NCI), the preeminent repository on cancer incidence and survival in the United States uses four census tract-level attributes to quantify SES status: SES quintile, two rurality variables, and persistent poverty.[5] The SES quantile is based on the Yost state-based quintile, an index first introduced in 2001 in an effort to investigate SES in breast cancer (BC) incidence among different race and ethnic groups in California.[6] The SES quintile is constructed by first deriving composite SES scores from variables median household income, median house value, median rent, percent below 150% of the poverty line, education index, percent working class, and percent unemployed.[5] Education index, median income, median house value, and median rent correlate positively with high SES, contributing positively to the SES component, whereas the proportion below 150% of the poverty line, percentage of the working class, and percentage unemployed show an inverse relationship with SES, carrying negative loadings. A higher component score indicates a higher SES index.[6] The SES index census tracts are sorted into SES quintiles, ensuring equal populations in each quintile either within a specific state or across the entire United States. The lowest SES group, known as the first quintile, represents the 20th percentile or below, while the highest SES group, the fifth quintile, corresponds to the 80th percentile or above.[5]

The two rurality variables aid in the comparison of cancer incidence and survival disparities between urban and rural areas. The first variable, utilizing the U.S. Department of Agriculture's Rural Urban Commuting Area, classifies areas into two groups: those focused on commuting in urban regions and those not primarily centered on urban commuting. The second variable, the Urban Rural Indicator Code, relies on the Census Bureau's data, categorizing areas into four groups based on the percentage of population living in nonurban regions: all urban (100% urban), mostly urban (≥50% but <100% urban), mostly rural (>0% but <50% urban), and all rural (100% rural) census tracts.[5]

The persistent poverty variable is used to categorize census tracts as persistently poor if at least 20% of the population has lived below the poverty line for around three decades. This dichotomous poverty variable classifies census tracts as either persistently impoverished or nonpersistently impoverished.[5]

Cancer Disparities According to Socioeconomic Status

For all combined cancers for both men and women, the 5-year survival rate is more than 10 percentage points higher for persons who live in affluent census tracts than for persons who live in poorer census tracts.[3] Over the past three decades, there has been a widening of socioeconomic gaps in cancer mortality, particularly pronounced in largely preventable cancers.[7] For instance, women living in economically disadvantaged areas experience double the mortality rate from cervical cancer compared to those in more affluent regions, and men in these areas face mortality rates for lung and liver cancer that are more than 40% higher.[7] Moreover, a higher proportion of colorectal cancer cases diagnosed at an advanced stage are reported among individuals residing in poorer census tracts compared to those in more affluent areas.[3] The American Cancer Society released data on Cancer Statistics 2019; these data were used in Figure 38.1 to illustrate the differences in mortality rates according to SES from 2012 to 2016 according to cancer region. The released statistics show that, when compared to those from more affluent areas, individuals from poorer areas experience disparities in cancer incidence rates. These disparities are most pronounced for uterine cervix, with a relative risk (RR) of 2.00 (1.90-2.10),

liver with RR of 1.37 (1.35-1.40), colorectum with RR of 1.30 (1.28-1.32), lung with RR of 1.28 (1.27-1.29), and prostate with RR of 1.26 (1.23-1.28).[7]

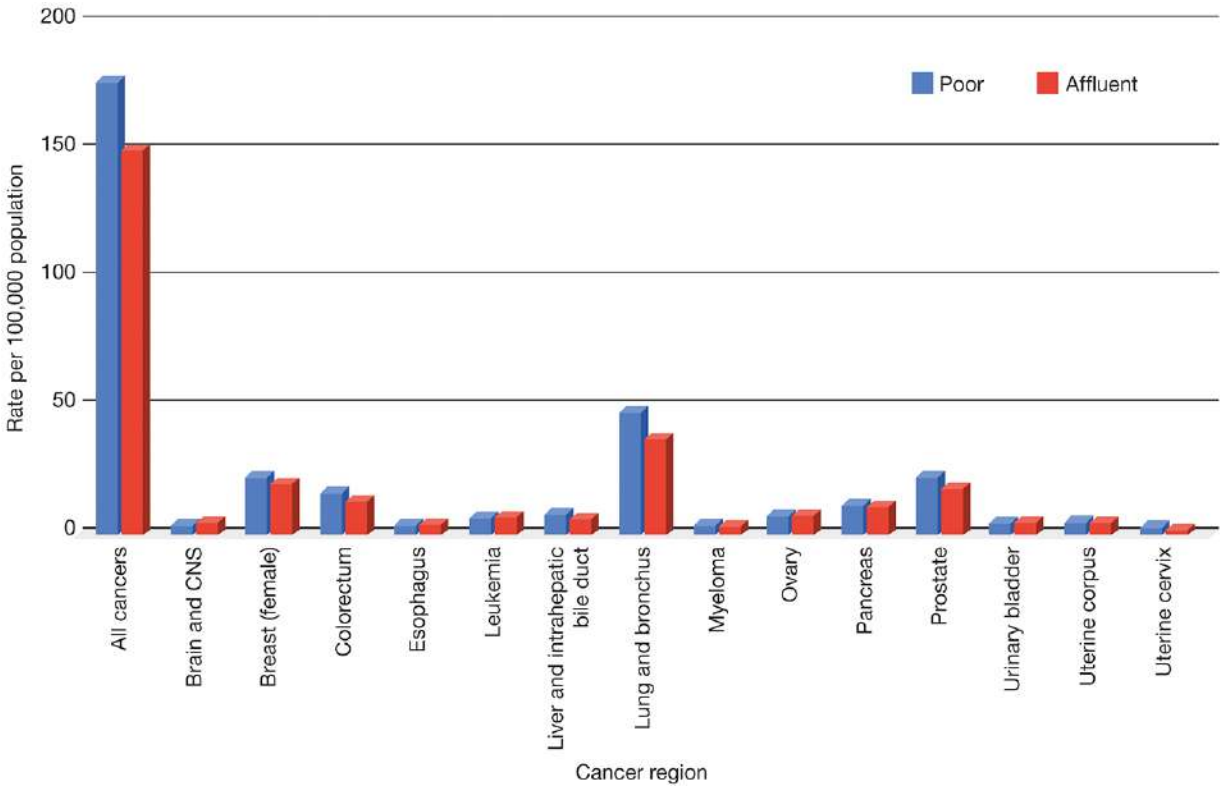

FIGURE 38.1 Cancer mortality rates according to socioeconomic status from 2012 to 2016. CNS, central nervous system. (Data from Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69[1]:7-34.)

These disparities for individuals of disadvantaged SES can potentially be explained by the notion that those of a disadvantaged SES face an elevated likelihood of encountering environmental or behavioral factors that raise their vulnerability to cancer development. They are more susceptible to encountering aggressive tumor characteristics, a greater incidence of coexisting medical conditions, and the presentation of advanced-stage diseases that pose challenges for curative treatments.[2] Moreover, individuals in less affluent census tracts are likely to experience social determinants that increase the risk of certain cancers. For example, poor and minority communities are selectively targeted by the marketing strategies of tobacco companies, may have limited access to fresh foods and healthy nutrition,

and are provided with fewer opportunities for safe recreational physical activity.[3]

These health disparities could potentially be further explained by biologic mechanisms, such as the phenomenon of telomere shortening. After controlling for individual characteristics, including SES at the individual level, research has shown that increasing levels of neighborhood socioeconomic deprivation are associated with shorter leukocyte telomere length (LTL) among a nationally representative sample of adults in the United States.[8,9] Comparing individuals residing in high deprivation neighborhoods to those in areas with lower neighborhood deprivation, it was found that the mean LTL of the former group was approximately 95 base pairs shorter. This reduction in telomere length is equivalent to around 7.5 years of accelerated cellular aging.[10]

Insurance Status Influencing Radiation Oncology Disparities

It is imperative to recognize the importance of health care access in shaping the overall health of a population, two essential aspects emerge as primary concerns: affordability and accessibility. Affordability is associated with health insurance, while accessibility pertains to geographic proximity to health care services.[10] Several studies have shown that compared to patients with cancer with non-Medicaid insurance, patients with Medicaid and no insurance have an elevated risk of death and tend to present with more advanced stages of cancer.[11,12]

A study to evaluate the relationship between insurance status and the use of brachytherapy using a logistic regression model on data collected from the public-use SEER database in patients with prostate cancer (PC), cervical cancer, BC, and endometrial cancer between January 1, 2007, and December 31, 2012, found that patients receiving RT were less likely to receive brachytherapy if they had Medicaid coverage (odds ratio [OR] 0.57, 95% confidence interval [CI] 0.53-0.61, $P < .001$) or lacked insurance coverage (OR 0.50, 95% CI 0.45-0.56, $P < .001$) compared to those with non-Medicaid insurance.[7]

In another study investigating the impact of insurance status on survival rates in patients with Hodgkin lymphoma found that patients with Medicaid or lacking insurance were less likely to receive timely RT and start

chemotherapy and that they were also less frequently treated at academic/research centers (all $P < .01$); even after controlling for other factors, an unfavorable insurance (Medicaid or uninsured) status was associated with a significantly decreased overall survival (hazard ratio [HR], 1.60; 95% CI, 1.34-1.91; $P < .01$).[13]

Yet again, in a study investigating the association of insurance status with detection of early-stage BC, it was determined that when compared with women without insurance or with Medicaid, insured women were slightly older at diagnosis (mean [standard deviation], 53.6 [6.8] vs 53.0 [6.8] years), less likely to receive a diagnosis of locally advanced stage III versus stages I or II BC (11% vs 20%) and more likely to receive a diagnosis of luminal A (HR-positive, ERBB2-negative) BC (69% vs 61%).[12]

While patients covered by Medicaid or lacking insurance face elevated mortality risks, often presenting with more advanced cancer stages and encountering treatment delays, the scenario changes concerning advanced RT, such as intensity-modulated radiation therapy (IMRT). The utilization of advanced RT techniques often requires prior authorization, potentially causing delays in starting treatment.[14] In a study examining the usage of IMRT in patients covered by private insurance versus those covered by Medicaid, significant shifts were observed. Specifically, the findings indicated an increase in the proportion of patients from non-Hispanic Black (NHB) backgrounds covered by Medicaid who received IMRT treatment (from 9.0% to 12.7%). Conversely, there was a decrease in the percentage of patients with private insurance undergoing IMRT treatment (from 37.6% to 32.5%).[15]

African American men face a more than 2-fold increased risk of dying from PC compared to non-Hispanic White men.[16,17] Interestingly, the racial disparity in overall cancer mortality in the United States diminishes after the age of 65, likely attributed to widespread Medicare coverage.[18] In a study evaluating PC-specific mortality in the equal-access Veterans Affairs (VA) health care system, it was found that African American men did not exhibit a higher likelihood of encountering delays in diagnosis or treatment. Second, there was not an increased tendency for African American men to present with more advanced-stage or aggressive forms of the disease. Lastly, African American men with PC did not face a higher mortality rate. In fact, there was a slight but statistically significant decrease in PC-related

mortality among African American men. These positive outcomes for African American men were observed, even though they resided in areas with lower SES.[19] This departure from national trends mirrors similar studies of equitable health systems that have shown no discernible differences in PC outcomes between non-Hispanic White and African American men covered by Medicaid.[20] These findings suggest that access to high-quality medical care plays a pivotal role in establishing racial equity among men diagnosed with PC.

The importance of health care access in shaping public health becomes evident through the critical elements of affordability and accessibility. Studies reveal disparities in cancer outcomes associated with insurance status, notably Medicaid, or with insurance, highlighting heightened risks of mortality, advanced cancer stages at diagnosis, and delays in treatment. However, a notable shift is observed in the context of advanced RT. Specifically, individuals covered by Medicaid displayed an increase in receiving IMRT, whereas those with private insurance demonstrated reduced utilization. In addition, investigations into PC outcomes among African American men exhibited a departure from national norms, indicating no differences in diagnosis delays, disease stages, or mortality rates, even in regions with lower SES within a health care system providing equal access.

Access to Care

Research has highlighted that reduced access to RT is linked to lower utilization of the treatment and poorer cancer-related outcomes.[10] Further, it has been shown that the proximity to the nearest RT facility had a negative association with breast-conserving surgery (BCS), with the OR decreasing by 3% for every 5-mile increase in distance.[21] It is widely accepted that the travel distance to access health care services can impact the type and timing of care received by patients. Patients generally prefer seeking care in close proximity to their homes. RT differs from other cancer treatment methods due to the need for daily visits for a period of up to 7 weeks.[10] This places a significant burden on patients, intensifying travel-related challenges and potentially worsening disparities caused by distance to health care facilities.

The availability of RT depends on the presence of radiation oncologists and linear accelerators, and this can be affected by geographic accessibility. Studies have revealed that radiation oncologists are unevenly distributed across the country, with a higher concentration in academic centers. This geographic maldistribution can create difficulties for patients, particularly when they are required to travel long distances to access cancer care. These travel barriers have been linked to reduced utilization of RT and could potentially result in poorer treatment outcomes for patients[22] (Figure 38.2). Studies have shown that residents of nonmetro (more rural), older, and less insured areas have disproportionately less access to RT and that increased traveling distance to treatment can delay treatment treat times and affect treatment decisions.[21] Further, it has been found that access to RT facility was lower with increasing rurality and worsening area deprivation index.[23]

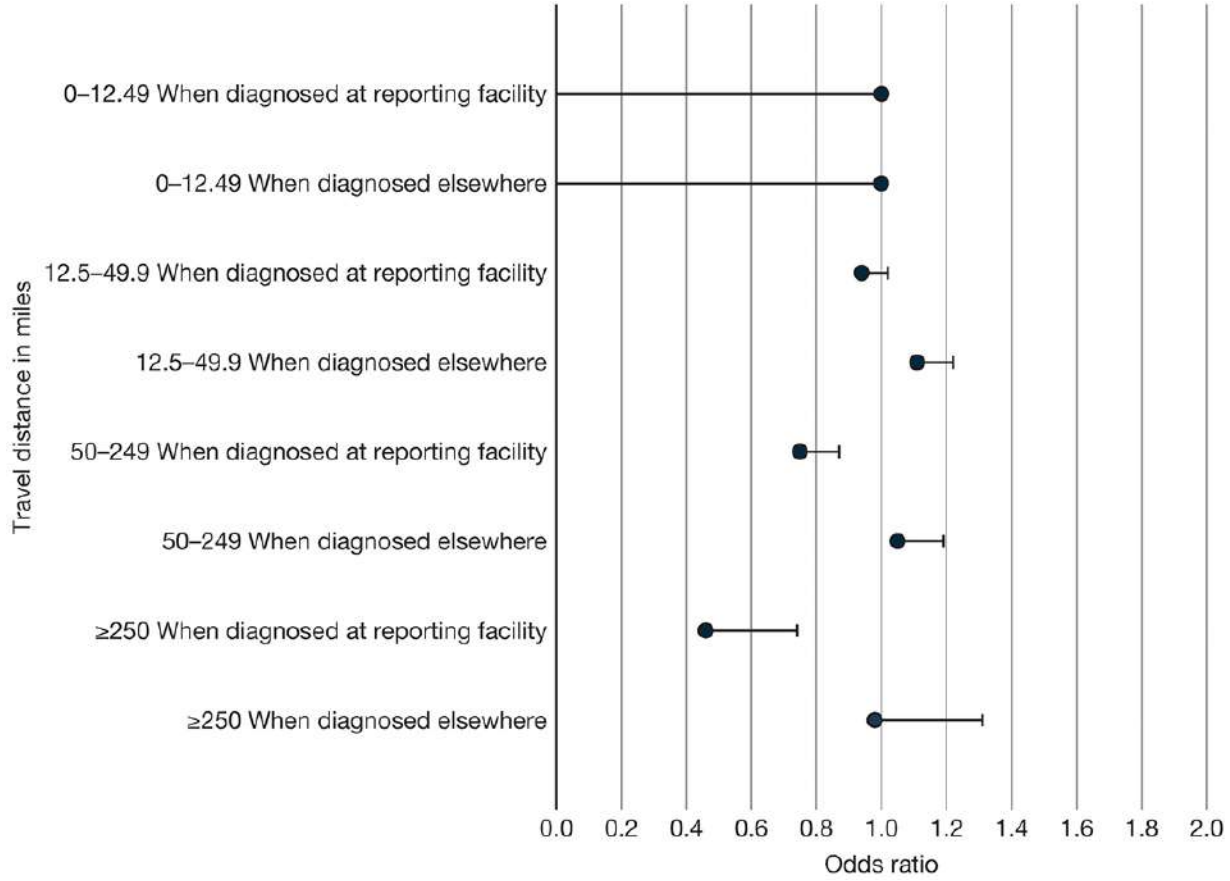

FIGURE 38.2 Likelihood of receipt of radiation therapy among patients with stages II to II rectal cancer based on distance to treatment facility. (Data from Lin CC, Bruinooge SS, Kirkwood MK, et al. Association between geographic access to cancer care and receipt of radiation therapy for rectal cancer. *Int J Radiat Oncol Biol Phys*. 2016;94[4]:719-728.)

Rural residents diagnosed with cancer often face later stage diagnoses and reduced access to treatment, influenced by individual- and community-level socioeconomic disadvantages. Rural residents are more likely to reside in areas that lack grocery stores and fresh produce, which offer limited access to employment opportunities providing health insurance, and lack public infrastructure, such as public transportation and broadband internet, thereby limiting travel options to care for those without vehicles and reducing access to telehealth. Many rural areas are classified as health professional shortage areas, and oncologists are underrepresented in rural areas, in part, due to increased hospital closure rates in rural areas, furthering the reduction in access to care.[24]

Advances in Radiation Oncology ran a four-part series focused on the vulnerable populations within the United States that are most likely to suffer disparities in RT access; this multipart series examined African American, Native American, Hispanic American, and Appalachian patients. The investigation into access to care disparities among African Americans revealed that African American women had lower rates of receiving chemotherapy and RT and experienced significantly higher mortality rates compared to Caucasian women, even after SES adjustments.[25] In addition, a study highlighted an inverse relationship between the distance to RT facilities and the utilization of BCS and RT, with African Americans being 42% less likely than Caucasians to receive BCS plus RT based on an analysis of the Florida Cancer Data System.[10] Furthermore, another study found that African Americans were more reliant on public transportation to reach RT facilities, which took 7 times longer than private vehicle transportation, creating a significant barrier to receiving optimal RT treatment.[26] Consequently, African American women with BC were less likely to undergo adjuvant RT due to increased distance from RT facilities and limited access to private vehicle transportation in comparison to Caucasian women.[27]

The first part of the series further concluded that the type of hospital where patients with BC receive treatment plays a significant role in causing delays in adjuvant RT or chemotherapy for women with stages I to III BC. Hospitals that have a higher probability of treatment delays tend to be smaller, have lower BC surgical volume, are located in rural areas, are not-for-profit, and are less likely to be approved cancer centers by the American

College of Surgeons and are more likely to treat African American women compared to Caucasian women.[27]

The investigation into access to care disparities among Native Americans revealed that American Indians and Alaska Natives are disproportionately diagnosed at more advanced stages of the disease. In recent years, cancer death rates among American Indians demonstrated a steady linear increase; conversely, the rates for Caucasians have seen to decrease linearly. Despite this, there is limited information available on RT access in American Indian and Alaska Native patients.[28]

The investigation into access to care disparities among Hispanic Americans revealed that, similar to African American RT access, Hispanic Americans have restricted access to RT compared to Caucasian patients. Interestingly, they are less likely to experience concurrent disparities in mortality when compared to other underrepresented minorities facing similar challenges.[29]

The last part of the series found that in comparison to the rest of the United States, Appalachians face unique challenges, such as lower education levels, higher poverty rates, and limited health care access. Consequently, the NCI has classified rural populations as special populations due to their elevated risk of cancer and other diseases.[30]

These disparities are also appreciated in the pediatric population. Pediatric patients encounter comparable discrepancies to their adult counterparts concerning access to RT. In a comprehensive study involving 12,000 pediatric patients, it was noted that individuals from neighborhoods characterized by lower median incomes and educational attainment, along with those lacking insurance or covered by Medicaid, face reduced likelihoods of receiving proton RT despite its increased usage in pediatric solid malignancies.[30]

GENDER

Definition

Sex and gender are distinct yet interconnected constructs that influence health and health research. Sex is a complex biologic concept, encompassing anatomy, physiology, genetics, and hormones. On the other hand, gender is a self-identified construct involving gender identity,

expression, and societal and cultural expectations related to specific sex traits. A person's gender identity, such as woman, man, trans man, gender diverse, or nonbinary, may undergo changes over their lifetime and may or may not conform with the cultural expectations of a society based on their biologic sex traits.[31]

Gender Disparities in Cancer Care

Despite advancements in addressing gender-based disparities in human studies, women continue to be underrepresented in cancer trials. For instance, among the 5,157 patients who participated in oncology trials leading to Food and Drug Administration approval of 17 new drugs in 2018, only 38% were women. The underrepresentation of women is evident in various clinical trials sponsored by the NCI, including those focusing on colorectal cancer, lung cancer, and surgical oncology. Even in cancers where females have a higher prevalence, such as lung cancer, melanoma, and pancreatic cancer, they were still underrepresented in therapeutic trials reported in ClinicalTrials.gov from 2003 to 2016, excluding PC and BC trials.[3]

Cancer Disparities in Sexual and Gender Minorities

Over 10.7 million adults in the United States identify as LGBTQ (lesbian, gay, bisexual, transgender, or queer), while at least 500,000 are adult cancer survivors.[32] Research has shown that there are associations between certain types of cancer and the risk of diagnosis or disease-specific mortality among LGBTQ patients.[33]

Sexual minority women experience disparities in cancer prevention, screening, prevalence, and mortality. For example, lesbian women are less likely to initiate human papillomavirus (HPV) vaccination for cervical cancer prevention compared to heterosexual women. In addition, cervical cancer screening rates may be lower in lesbian or bisexual women. Moreover, bisexual women and transgender individuals are less likely than heterosexual women to follow mammography guidelines for BC screening, despite facing a similar disease risk. Despite having similar rates of BC to that of the general population, sexual minority women may have higher BC mortality rates and an increased risk of oropharynx cancer compared to

heterosexual women. Similarly for men who have sex with men, regardless of their HIV status, anal cancer rates are higher than those in the overall U.S. male population.[34]

Approximately 1.3 million adults in the United States identify as transgender, this accounts for about 0.5% of the U.S. adult population.[35] Transgender individuals frequently face several unique challenges to accessing health care, and these challenges have far-reaching implications, affecting everything from cancer diagnosis to treatment, potentially leading to decreased survival rates. Some of these challenges are social in nature, as transgender individuals are nearly 3 times more likely to be unemployed, resulting in higher rates of being uninsured or underinsured. Other barriers experienced by transgender individual are rooted in the absence of appropriate transgender-specific screening guidelines. Despite the lower incidence of PC in transwomen compared to cisgender men, current screening guidelines recommend applying the same standards for PC screening in transwomen as in cisgender men.[32]

RACE AND ETHNICITY

Definitions

The concept of race is defined as a social construct primarily based on the expression of phenotypic genetic traits rather than being grounded in biology. It is widely recognized that there is greater genetic variation within racial groups than between them, leading to significant doubts about using race as a biologic construct to categorize distinct, genetically different population groups. The U.S. Bureau of the Census has underscored the importance of treating race as a social and political construct rather than a biologic one. In the realm of health-related research, the concept of race encompasses both personal identity and group identity aspects, in addition to the more conventional biologic indicators.[33]

The Office of Management and Budget (OMB) provides standards for categorizing race. According to these standards, “White” refers to individuals with origins in Europe, the Middle East, or North Africa. “Black or African American” encompasses individuals with origins in various Black racial groups in Africa. “American Indian or Alaska Native” refers to individuals with origins in the original peoples of North and South America,

including Central America, who maintain tribal affiliation or community attachment. “Asian” includes individuals with origins in the Far East, Southeast Asia, or the Indian subcontinent, such as Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. “Native Hawaiian or Other Pacific Islander” pertains to individuals with origins in the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands. The OMB standards also allow for the reporting of more than one race.[33]

A closely related but distinct construct often intertwined with race is ethnicity. Ethnicity pertains to the sharing of a common culture, including common origins, shared psychological characteristics and attitudes, a common language, religion, and cultural traditions. Discussions on this topic have suggested that one’s race and/or ethnicity should be regarded as affiliations rather than genetic predispositions. Ethnicity can indirectly influence health outcomes by shaping health beliefs, the expression of symptoms, physical functioning, access to health care systems, and medical treatment processes.[33]

Racial Disparities in Radiation Oncology Treatment

In the United States, African Americans bear the highest burden of cancer incidence and mortality. Delays to initiation to treatment and underutilization of RT disproportionately affect race minority patients.[27] When compared to insured non-Hispanic White individuals, racial/ethnic minority group members and those without insurance are at a higher risk of encountering treatment delays and are less likely in some cancers to receive definitive treatment, such as radiation.[34]

A study using data from the National Cancer Database (NCDB) focused on the number of patients with cancer treated with definitive-intent IMRT of 10 primary disease sites (prostate, lung, head and neck, rectum, esophagus, anus, pancreas, stomach, cervix, and uterus) found that the percentage of non-Hispanic White patients facing delays in interval to initiation of treatment (IIT) ranged from 27.4% to 40.4%.[14] In contrast, this percentage varied from 38.4% to 58.9% for Hispanic patients, 38.1% to 57.9% for NHB patients, and 27.3% to 49.1% for Asian patients. Even after adjusting for clinical and sociodemographic factors, Hispanic patients were

notably more prone to experience delayed IIT in 9 out of 10 disease sites. Similarly, NHB patients faced significantly higher odds of experiencing delays in 7 out of 10 disease sites, while Asian patients were significantly more likely to encounter delayed IIT in 8 out of 10 disease sites compared to non-Hispanic White patients. Moreover, when considering primary insurance, non-Hispanic White, Hispanic, and Asian patients with private insurance encountered shorter IIT compared to their counterparts with Medicare. Furthermore, NHB patients with private insurance experienced longer IIT than NHB patients covered by Medicare.[14]

In a retrospective population-based study using the SEER database, researchers focused on 102,486 African American men and non-Hispanic White men diagnosed with localized high-risk PC between 2004 and 2010.[36] The study revealed significant disparities in receiving definitive therapy between African American and White men with high-risk PC. It was found that African American men were notably less likely than White men to receive definitive therapy (81.0% vs 87.4%, $P < .001$). The study further highlighted the disparity in definitive therapy based on race and regional income, showing that African American men in low-income regions were the least likely to receive definitive therapy (75.9%), whereas White men in high-income regions were the most likely (89.6%) (Figure 38.3). In addition, it was determined that African American men in high-income regions were significantly more likely to receive definitive therapy compared to those in low-income regions (87.5% vs 75.9%, $P < .001$). White men in high-income regions were more likely to receive curative therapy than their counterparts in low-income regions, as well as African American men in both high- and low-income regions (89.6% vs 83.6%, 87.5%, and 75.9%; $P < .001$, $P = .004$, and $P < .001$). The analysis, even after adjusting for various factors, including demographics, non–PC deaths within 5 years, and cancer-specific factors, indicated that African American men with high-risk PC were significantly less likely than White men to receive definitive therapy (adjusted OR [AOR] = 0.51; 95% CI: 0.49-0.54; $P < .001$). In addition, individuals from high-income regions had a significantly higher likelihood of receiving definitive therapy compared to those from low-income regions (AOR = 1.19; 95% CI: 1.08-1.32; $P = .001$).[37] When comparing treatment rates for PC in Black and White men, significant disparities can be appreciated as Black men were only half as

likely as White men to receive definitive therapy (surgery or radiation) for their PC. Moreover, Black men whose cancer had spread beyond the prostate were twice as likely as White men not to receive definitive treatment for their cancer (44% compared to 22%). It is important to highlight that when Black men receive the same treatment as White men for the same grade and stage of PC, their survival rates are equivalent.[36]

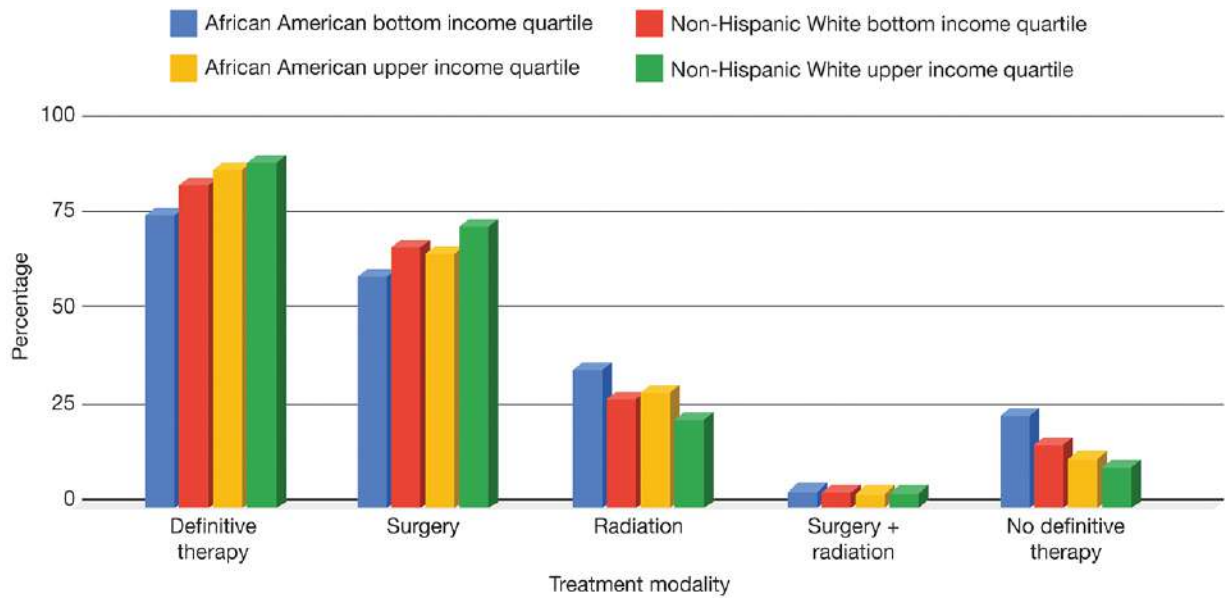

FIGURE 38.3 Receipt of definitive therapy stratified by race and regional income level among men with high-grade prostate cancer. (Data from Zeliadt SB, Potosky AL, Etzioni R, Ramsey SD, Penson DF. Racial disparity in primary and adjuvant treatment for nonmetastatic prostate cancer: SEER-Medicare trends 1991 to 1999. *Urology*. 2004;64[6]:1171-1176.)

Studies additionally have highlighted significant Black-White disparities in PC treatment that persist irrespective of patients' SES or other existing health conditions that might influence treatment decisions. Even after controlling for marital status, age at diagnosis, and geographical region, striking differences were still evident. White men diagnosed with highly aggressive PC were just as likely to receive definitive treatment as White men with moderately aggressive cancer. However, Black men with high-risk cancer were 50% less likely to receive definitive treatment compared to White men with moderately aggressive cancer. This is particularly striking because men diagnosed with poorly differentiated PC face a 2.5 times higher risk of PC-related mortality when lacking nondefinitive treatment.

Interestingly, no disparities between Black and White men were observed in receiving definitive treatment among those diagnosed with low-risk PC. However, among men diagnosed with moderately aggressive cancer, Black men were 36% less likely than their White counterparts to receive definitive treatment.[36,38-41]

Another aspect of the treatment disparities includes treatment completion rates. In a comprehensive national study involving patients who underwent radiation treatment for curable PC and BC, it was found that shorter treatment regimens were associated with decreased instances of treatment noncompletion. Notably, disparities were observed among Black men receiving conventional external-beam radiation therapy (cEBRT), demonstrating higher rates of treatment noncompletion compared to White men. However, this trend was not evident among Black men undergoing stereotactic body radiation therapy (SBRT) or moderately hypofractionated external-beam radiation therapy (mEBRT). Contrarily, no disparities were noted in treatment noncompletion among women with BC. Despite evidence suggesting the benefits of shorter radiation regimens, Black patients consistently received less hypofractionated radiation for PC and BC. A study, using data from the NCDB, showcased a rise in SBRT and mEBRT rates from 2004 to 2017. However, Black patients were less likely than White patients to receive these advanced radiation techniques. Moreover, the study highlighted a significant increase in hypofractionated external-beam radiation therapy (hEBRT) for BC over time, with a notable racial disparity as Black women were less likely to receive hEBRT compared to White women. Even in subgroup analyses, disparities persisted among Black women, both in node-negative and node-positive disease categories. The findings emphasized the lower adoption rates of hypofractionated radiation among Black patients compared to White patients over the study period.[36]

Racial Disparities in Cancer Pain Management

Cancer-related pain is a common challenge for patients undergoing therapy, yet many still do not receive adequate pain relief.[42] Studies have highlighted disparities in pain management, particularly with African American and Hispanic patients being less likely to receive sufficient treatment compared

to non-Hispanic White patients.[43] However, health care systems with equal access, such as the VA Healthcare System and among Black and White Medicare beneficiaries with stage IV BC, demonstrated no racial disparities in pain management. Achieving equity in cancer-related pain management will require maintaining and improving access to appropriate analgesic agents for all patients and addressing racial/ethnic disparities in pain assessment, opioid prescribing, and access to other pain management options.[44]

Racial Disparities in Cancer Survival

Racial disparities in cancer mortality persist, with the highest mortality rates observed among American Indian/Alaska Native populations followed closely by Black communities[45] (Figure 38.4). The death rates in both American Indian/Alaska Native and Black men are significantly higher compared to Asian American/Pacific Islander men and White men. While the Black-White disparity in overall cancer mortality has reduced from its peak in 1993, significant gaps persist. These disparities are rooted in historical wealth inequalities resulting from systemic racism, affecting risk factor exposure and access to equitable cancer prevention, early detection, and treatment across different socioeconomic strata. Even among individuals with higher incomes, Black individuals have lower cancer survival rates than their White counterparts.[36] For instance, within the demographic earning a median annual household income of $75,000 or greater, the 5-year relative cancer survival rate is higher for White individuals (72%) compared to Black individuals (67%).[45]

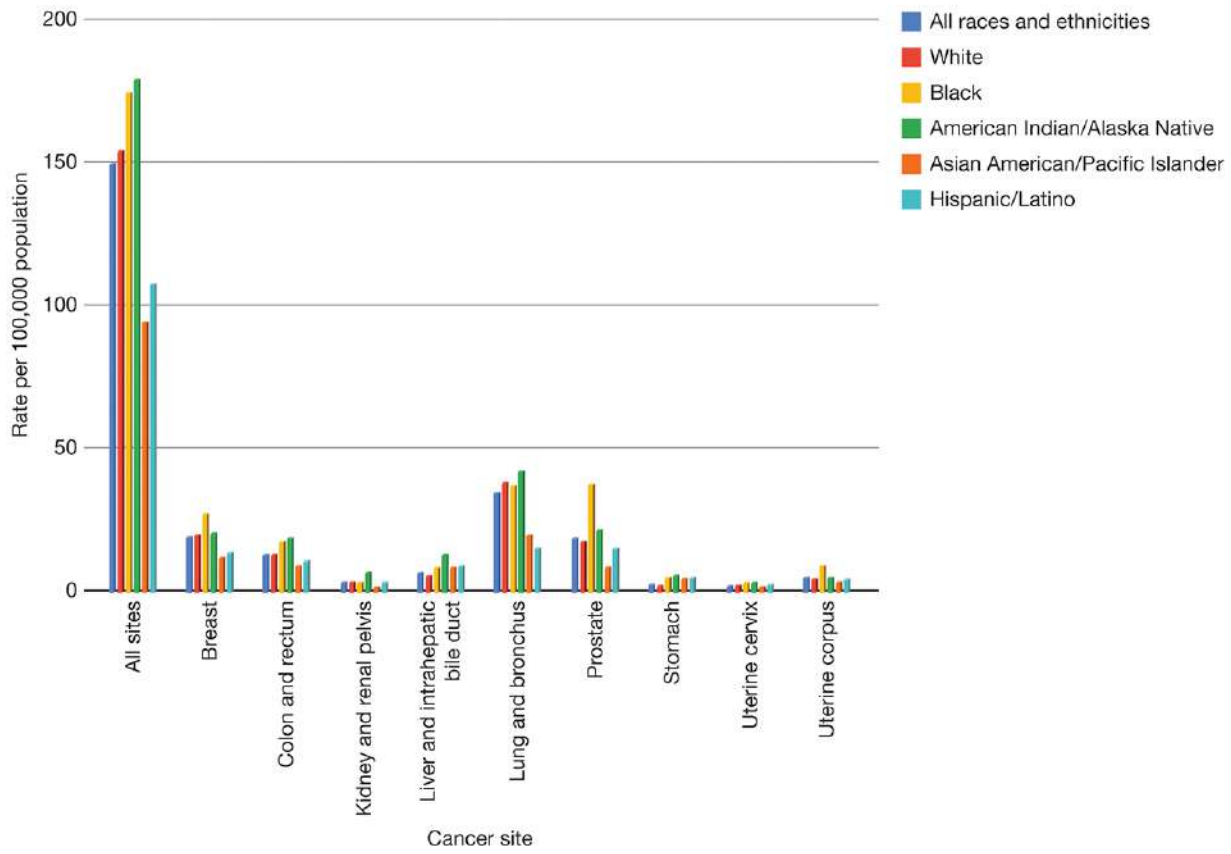

FIGURE 38.4 Mortality rates for select cancers by race and ethnicity, 2016 to 2020. (Data from Islami F, Guerra CE, Minihan A, et al. American Cancer Society's report on the status of cancer disparities in the United States, 2021. *CA Cancer J Clin*. 2022;72[2]:112-143.)

African Americans in the United States face considerable challenges in accessing effective cancer treatments, despite proven benefits demonstrated in randomized controlled trials. Across various cancer types, African Americans often experience higher death rates and shorter survival periods compared to other racial or ethnic groups. Specifically, African American men have an overall cancer death rate 24% higher, while African American women have a 14% higher rate than their Caucasian counterparts. Predominantly, PC (31%), lung (15%), and colorectal (9%) cancers are frequently diagnosed among African American men, while BC (32%), lung (11%), and colorectal (9%) cancers are more common among African American women.[27]

The current 5-year survival rates for BC stages show promising advancements, with rates nearly reaching 100% for stages 0 and I, 93% for stage II, and 72% for stage III. However, these improvements have not been

uniformly experienced across all patient groups. Racial and ethnic minorities, when compared to non-Hispanic White women, tend to receive diagnoses at later cancer stages. This disparity contributes to higher mortality rates, increased treatment-related complications, and reduced overall quality of life among minority populations. Consequently, these groups face a less favorable prognosis, undergo more aggressive treatments, and have a lower quality of life during their survivorship period.[12] In BC cases among African American women, a trend exists for diagnosis at a younger age, aggressive subtypes (such as triple-negative disease), and later stage diagnoses with metastases. These disparities contribute significantly to the overall higher death rates and reduced survival periods among African Americans compared to other racial or ethnic groups in the United States.[27]

In a study aimed to explore how rurality and race/ethnicity intersect in influencing BC outcomes, it was found that NHB and Hispanic women, irrespective of their rural or urban residence, exhibited increased odds of late-stage BC diagnosis, a higher likelihood of not receiving essential BC treatments (such as surgery, RT, and chemotherapy), and an elevated risk of BC-related death compared to Non-Hispanic White women in urban areas. On the other hand, rural and urban Asian and Pacific Islander women generally demonstrated better BC outcomes, experiencing a 10% to 20% reduced risk of BC-related mortality when compared to non-Hispanic White women in urban settings. The disparities observed were notably evident among NHB and Hispanic women, who were less likely to receive crucial treatments, consequently increasing their risks for later stage disease and mortality from BC. The study also noted that after accounting for potential influencing factors, the trends observed in late-stage disease, lack of chemotherapy, radiation, or surgical treatment remained consistent in fully adjusted models, emphasizing the persistent impact of race/ethnicity and treatment disparities on BC outcomes.[46]

INTERSECTIONALITY

Intersectionality acknowledges that individual identities intersect with systems of oppression such as sexism and racism. The overlap of various identities highlights unique experiences that cannot be fully understood by

focusing solely on one aspect of identity. This framework allows for exploration of differences within and among groups and underscores that privilege and oppression are context dependent, meaning an individual may experience privilege in one context while facing disadvantage in another. This nuanced understanding of identity and social systems challenges the simplistic categorization of individuals based on singular identities.[47]

Blacks tended to occupy a socially isolated class characterized by the lowest SES and poorer health outcomes. This underscores how racial disparities in health are closely linked to social forces that group individual characteristics, rather than being solely dictated by independent variations in those characteristics. A study comparing allostatic load among different socioeconomic groups found significant disparities in allostatic load among different socioeconomic groups, particularly emphasizing the contrast between privileged non-Black individuals displaying the lowest allostatic load and SES non-Black individuals exhibiting notably higher allostatic load.[48]

There is a significant interplay between race and regional income, highlighting pronounced treatment disparities among Black and White men based on income levels. Specifically, there are substantial treatment discrepancies between Black and White men in the lower income quintile compared to those in the higher income quintile. Regarding PC mortality, in the lower income quintile, a higher percentage of African American men died from PC compared to White men, while comparable rates were observed between African American and White men in the higher income quintile.[37] Females experience more significant constraints in social stratification compared to males. Being female increases the likelihood of belonging to lower socioeconomic classes.[48]

Moreover, Black individuals, particularly females, experience earlier and more pronounced physiological dysregulation compared to their White counterparts supporting the notion Black women face compounded negative impacts due to both gender and racial discrimination.[48]

Black women, while having lower incidence rates for BC and ovarian cancers compared to non-Hispanic White women, face higher death rates from these cancers and are less likely to participate in clinical trials.[49,50] Hispanic women face a higher risk of infection-related cancers such as cervical cancer, with significantly elevated incidence and death rates

compared to non-Hispanic White women. Limited access to screening and higher rates of HPV infections contribute to these disparities. While Hispanic women are underrepresented in BC, ovarian cancer, and uterine cancer trials, they are adequately represented in cervical cancer trials.[51]

American Indian/Alaska Native women experience cancer as the leading cause of death within their communities. Despite their diverse backgrounds and representation across various tribes and villages, clinical trials often lack representation from these groups. A vast majority of trials lack reporting of American Indian/Alaska Native participants, and the involvement of Native American women in cancer drug trials remains extremely low, reflecting a significant gap in research inclusivity and representation.[35]

SPECIAL CONSIDERATIONS FOR PEDIATRIC CANCERS

Children from racial and ethnic minority backgrounds or lower SES experience disparities in cancer care, resulting in higher relapse rates, lower survival rates, and poorer psychosocial outcomes compared to wealthier, non-Hispanic White counterparts.[52] These disparities extend to the accessibility and delivery of RT. For instance, Black pediatric patients are less likely to receive proton RT, despite being enrolled in national prospective trials with standardized treatment protocols.[53]

Health insurance serves as a critical marker for health care accessibility, playing a significant role in cancer outcomes. Disruptions in health insurance coverage in pediatric patients are linked to reduced access to care. Public or lack of insurance increases the risk of death, particularly with age, across most cancer types. Notably, adolescents/young adults enrolled in Medicaid at diagnosis, especially those previously uninsured, are significantly more likely to be diagnosed with later stage cancer compared to those with private insurance, emphasizing the importance of access to care in the context of health insurance.[52]

CALL FOR INCREASED DIVERSITY AND INCLUSION IN THE FIELD

Many communities, particularly minority groups, hold the hope that some of their own members will address their health care needs. Minority

physicians often feel a sense of responsibility to serve their community, potentially explaining why underrepresented health care professionals are more likely to work in underserved areas.[54] Studies indicate that racially discordant medical interactions tend to be less favorable and effective than those involving individuals of the same race. These cross-racial interactions are notably brief, less focused on the patient's needs, characterized by decreased positive engagement, and lack attempts at building strong rapport. Patients are less involved in decision-making, while physicians dominate the conversation more in such interactions.[55]

There is no observable shift toward increased diversity among female or underrepresented minority trainees over an 8-year span, indicating that the issue of underrepresentation is persisting. Across various levels in RO, females and traditionally underrepresented minority groups, such as Blacks, Hispanics, American Indians, Alaska Natives, Native Hawaiians, and Pacific Islanders, are notably underrepresented compared to their proportions in the wider U.S. population. The representation of females and underrepresented minorities remains lower among RO residents, faculty, and practicing physicians compared to their respective representations among medical school graduates and medical oncology fellows.[54]

Although there is an increase in female representation among RO residents compared to RO practicing physicians, Black, Hispanic, and female representation in RO residents is significantly lower compared to their proportions among medical school graduates (Figure 38.5). Underrepresented minorities collectively constitute 30% of the 2010 U.S. Census, but their representation as RO practicing physicians and faculty is notably lower. Specifically, Blacks, Hispanics, American Indians, Alaska Natives, Native Hawaiians, and Pacific Islanders are significantly underrepresented among RO practicing physicians and faculty compared to the overall U.S. population, indicating their underrepresented status in the field of RO.[54]

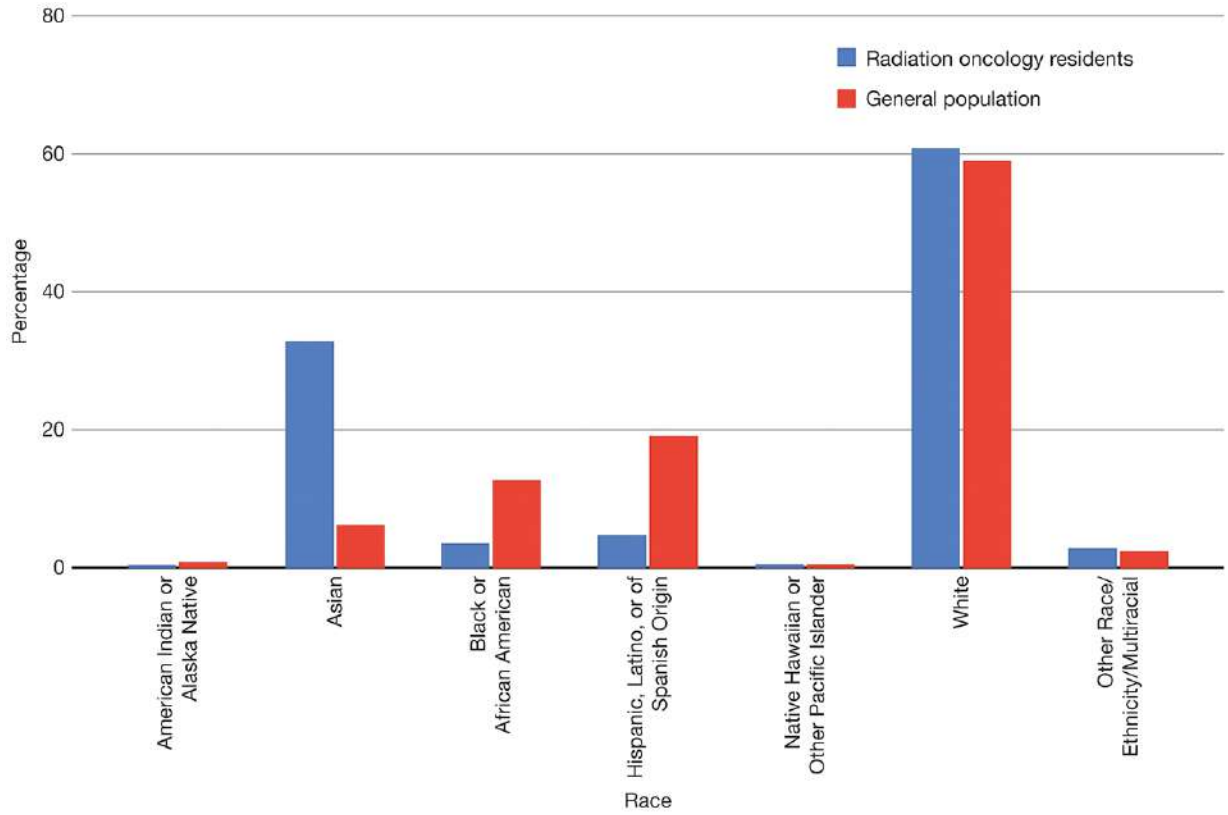

FIGURE 38.5 Active radiation oncology residents by race. (Data from Bitterman DS, Bona K, Laurie F, et al. Race disparities in proton radiotherapy use for cancer treatment in patients enrolled in Children's Oncology Group trials. *JAMA Oncol*. 2020;6[9]:1465-1468.)

CONCLUSION

To address persistent economic, gender, and racial disparities in RO, continuation of shaping effective policies and advocating for social policy changes is needed.[56] Literature suggests that reducing or eliminating disparities in treatable cancer outcomes is achievable when patients receiving definitive radiation have access to high-level and quality care that is comparable.[57] To attain equity in RO, it is essential to acknowledge and incorporate diversity within an inclusive framework. This objective is not solely a cultural aspiration but also brings tangible advantages to health outcomes. It entails ensuring fair treatment and providing equal opportunities for individuals, taking into account differences in gender, age, ethnicity, religion, sexual orientation, identity, socioeconomic background, and disability, particularly within the context of cancer care.[58]

Strategies for reducing cancer health disparities in RO involve interventions at both patient and facility levels. Patient-focused measures include securing financial support for modern radiation technology, building community partnerships, improving transportation options, and addressing financial toxicity. Facility-oriented actions encompass promoting diversity in cancer training, educating faculty and staff on diversity principles, overcoming barriers to clinical trial participation by minorities, and providing research funding to address disparities and enhance health equity.[56]

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SECTION IV

Clinical Radiation Oncology

PART A

Skin

CHAPTER 39

Skin

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The purpose of this chapter is to discuss cutaneous carcinoma, including Merkel cell carcinoma (MCC) and melanoma. Uncommon cutaneous malignancies, such as angiosarcoma and dermatofibrosarcoma protuberans, are addressed elsewhere. Most skin cancers are managed surgically. Because of the functional and/or cosmetic deficits that may occur after surgery for skin cancers of the head and neck, the discussion occasionally focuses on lesions in this area.

Skin cancer is the most common of all malignancies. The American Cancer Society estimates that approximately two million basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs) are diagnosed annually in the United States, although the precise number is unknown because they are not reported.[1] The risk for carcinoma of the skin increases with sun exposure. A low incidence occurs in those with Fitzpatrick skin types V and VI; a corresponding increase occurs in those with Fitzpatrick skin types I and II. The mortality rate is about 1,800 per year, or 0.45%.

Several conditions are associated with carcinoma of the skin, including the following:

- Actinic exposure
- Ionizing radiation
- Scar (eg, burn scar)
- Chronic infection or draining of sinus or fistulous tract (eg, pilonidal sinus)
- Immune disorders
  - Chronic lymphocytic leukemia
  - Solid organ transplant patients
  - Discoid lupus erythematosus
- Chemicals
  - Arsenicals (herbicides, pesticides)
  - Psoralens and ultraviolet light treatment for psoriasis
  - Nitrates
  - Tars, oils, and paraffins
- Hereditary disorders
  - Xeroderma pigmentosum

- Basal cell nevus syndrome
- Albinism
- Congenital epidermolysis bullosa

Melanoma is less common than BCCs and SCCs. Siegel et al[2] estimated that approximately 76,380 melanomas will be diagnosed in the United States in 2016 and that about 10,130 deaths owing to the disease will occur. Dysplastic nevus may increase the risk of developing melanoma.[3]

ANATOMY

Epidermis

The epidermis is thinner in the face than in most portions of the body, measuring approximately 0.04 mm. No consistent change in the thickness of the epidermis occurs with increasing age, and no difference in skin thickness exists between men and women. The layers of the epidermis from superficial to deep are as follows:

- Stratum corneum
- Stratum lucidium
- Stratum granulosum
- Stratum spinosum
- Stratum basale

It is important to know these layers to understand the origin and behavior of a particular type of skin cancer.

Dermis

The dermis, which contains the blood and lymphatic vessels, adnexa, hair follicles, sweat glands, and sebaceous glands, is 1 to 2 mm thick; the dermis of the eyelid is thinner (≤0.6 mm). Beneath the dermis lies the subcutaneous tissue containing the fat and the superficial fascia. No distinct transition occurs from the dermis to the subcutaneous layer.

Lymphatics

No lymphatics exist in the epidermis. A superficial capillary lymphatic plexus lies in the dermis and is without valves.[4] The deep lymphatic trunks in the dermis and subcutaneous tissues have valves. The density of the capillary lymphatics has been noted to be about the same in all areas, except the sole of the foot and palm of the hand, where it is denser. Observation suggests that SCCs and melanomas occurring on the skin of the temple are particularly prone to develop lymphatic metastasis.[5] During the healing of wounds, such as incisions or burns, a regeneration of lymphatic capillaries across the scar occurs, similar to the regrowth of small blood vessels.[3]

The first-echelon lymph nodes for carcinomas of the face and scalp are the superficial network of lymph nodes that form a ring around the top of the neck: submental (level IA), submandibular (level IB), intraparotid or preauricular, postauricular (mastoid), and occipital lymph nodes as well as inconstant facial lymph nodes. The first echelon is highly associated with the exact location of the cancer on the face.

PATHOLOGY

The most common carcinomas of the skin are BCC (65%), SCC (30%), a variant of BCC or SCC, and the adnexal carcinomas. MCC is a rare neuroendocrine malignancy arising in the skin that was first described by Toker[6] in 1972. Verrucous carcinoma, a variant of SCC, occurs most often on the foot and is rare in the head and neck area. Carcinoma in situ (CIS) occurs frequently in the head and neck. Perineural invasion (PNI) is observed in 2% to 3% of patients with BCCs and SCCs.[7]

Noncutaneous carcinomas (eg, renal cell carcinoma) may metastasize to the skin and subcutaneous tissues.

Basal Cell Carcinoma

The common BCC, which arises from the basal layer of the epithelium, may have a variety of growth patterns merged into one another in the same tumor, and the different names applied to the gross and microscopic appearances have clinical implications. The morphea type (sclerosing BCC) shows little surface disease and a marked infiltrating pattern; it is an important subtype because of the higher risk for recurrence. Microcystic BCC is a histologic variant of BCC that exhibits the same natural history as the more common variety. Some lesions will have mixed BCC and SCC (basosquamous cell carcinoma or metatypical BCC). Melanin pigment may be seen on both gross and microscopic examinations of BCC.

Squamous Cell Carcinoma

SCC and its variants (ie, verrucous carcinoma, spindle cell SCC) are similar histologically to SCC occurring in other sites. Most are well differentiated. Evans and Smith[8] identified two categories of spindle cell tumors of skin: one was composed of SCC mixed with a spindle cell component; the other was predominantly spindle cells. The spindle cell component is similar in both groups; mitoses, giant cells, and epithelioid cells may be seen.

Keratoacanthoma

Keratoacanthoma is a benign tumor of the skin that grossly resembles a cystic BCC and microscopically resembles SCC or squamous papilloma. Part of the difficulty in histologic diagnosis is owing to an inadequate biopsy specimen. Ackerman[9] concluded that “the diagnosis of keratoacanthoma can only be made with absolute certainty by biologic behavior in the form of eventual involution.”

Adnexal Carcinoma

Carcinomas may arise from the epithelium of the sweat glands, sebaceous glands, or hair follicles and microscopically resemble the tissue of origin. Carcinoma of the sweat gland can arise from either the eccrine or apocrine glands; however, no reliable histologic criteria exist to differentiate the origin. It is difficult to distinguish between benign tumors and malignant carcinomas of the sweat gland in the absence of metastases. The differential diagnosis includes adenocarcinoma metastatic to skin and BCCs and SCCs with an adenoid cystic growth pattern. They are frequently misdiagnosed at the time of the first biopsy. Malignant trichilemmoma arising from hair follicles is extremely rare.

Microcystic adnexal carcinoma (sclerosing sweat duct carcinoma) is a rare variant of adnexal carcinoma first described in 1982. The lesion usually presents on the upper lip or skin of the periorbital area as an indurated plaque without direct invasion of the overlying epidermis. It often appears as a subcutaneous nodule. It tends to be slow growing and locally invasive.[10-12] Microcystic adnexal carcinoma exhibits a propensity for local recurrence after excision and is associated with PNI; lymph node metastases are rare. The role of radiation therapy (RT) in the treatment of this rare malignancy is undefined.

Merkel Cell Carcinoma

MCC is a small cell neuroendocrine carcinoma arising in the skin. It has been found to be associated with polyomavirus infection. As in neuroendocrine carcinomas arising in other primary sites, MCC produces a neuron-specific enolase and has been found to contain membrane-bound neurosecretory granules within the tumor cell. In the past, the correct diagnosis was often not obtained until an extensive recurrence was noted. MCC was often misdiagnosed as BCC, lymphoma, adnexal carcinoma, or carcinoma metastatic to the skin from another primary site (ie, small cell carcinoma of the lung or medullary carcinoma of the thyroid).[13]

Melanoma

Melanoma arises from melanocytes, which are present in the epidermis as well as in other parts of the body, including the eye and respiratory, gastrointestinal, and genitourinary tracts.

PATTERNS OF SPREAD

The patterns of spread for individual anatomic sites are outlined in section “Selection of Treatment Modality.” Some lesions remain confined to the epidermis (CIS) and may involve a large area of skin. Large in situ lesions occur more often on the trunk; however, small areas of CIS are common on the head and neck.

Basal Cell and Squamous Cell Carcinomas

Both BCC and SCC are usually well differentiated, and most have an indolent growth with distinct margins; a small proportion are poorly differentiated and grow rapidly. BCC occurs more frequently around the central portion of the face, whereas SCC occurs more often on the ears, preauricular and temporal area, scalp, and skin of the neck.

Most lesions remain superficial and invade the adjacent epidermis in a circumferential growth pattern. Invasion of the dermis is usually confined to the superficial (papillary) dermis. Eventually, penetration of the reticular dermis, subcutaneous tissues, and other underlying structures occurs. A few skin carcinomas tend to grow beneath the skin, and the surface lesion gives little indication of their extensive growth; this is more often seen in recurrent tumors. Most early BCCs and SCCs show an orderly invasion of the superficial dermis, which allows successful local therapy. Both BCCs and SCCs invade cartilage and bone, develop PNI, and eventually enter the lymphatics, although the latter is not common. BCC, in particular, has a low incidence of lymphatic involvement unless it is recurrent (0.05%), whereas the incidence of lymph node spread for SCC is estimated to be up to 10% to 20%. As the size and age of the lesion increase, the potential for lymphatic spread increases.

SCCs may develop distant metastases, whereas BCCs rarely produce metastases. BCC tends to be locally invasive and destructive. A variant of BCC known as basosquamous cell carcinoma or metatypical BCC acts more aggressively than BCC and has a propensity for lymphatic spread.

Metatypical BCC is intermediate between BCC and SCC as far as recurrence rates and the risk of metastases.[14]

Spindle cell tumors of the skin have a gross appearance and growth pattern similar to SCCs.

Carcinoma of the Sweat Gland

Carcinoma of the sweat gland occurs with equal frequency in males and females. It predominantly affects older people, although it may occur even in early adulthood. The lesion is generally a subcutaneous nodular mass, which may be solitary or multiple, and the larger lesions may be ulcerated. Carcinoma of the sweat gland most often occurs on the eyelid, face, and scalp. The growth rate varies from indolent to rapid. The tumor may be present for several years with little change and then suddenly begin to enlarge. PNI is frequent. Regional and distant metastases may develop. Scalp lesions are the ones most likely to develop metastases to regional lymph nodes.

Recurrence after excision is frequent, and multiple recurrences are often reported.[15,16] Little information exists on the response to RT.[16] In our limited experience, carcinoma of the sweat gland is sufficiently radioresponsive to justify RT, particularly in association with excision.

The mucin-producing sweat gland adenocarcinoma is a rare tumor. The eyelid is the primary site in about one-half of cases and the face and scalp in another one-fourth of cases. The tumor presents most often in middle-aged men. Wright and Font[17] reported 21 cases that originated on the eyelid. Eight (38%) patients developed one or more local recurrences, one patient died with extensive persistent disease in the face after a 15-year interval, and only one patient had metastasis to the submandibular lymph nodes successfully treated by radical neck dissection.[17] Regional or distant metastasis is a relatively infrequent event for lesions arising in the head and neck area.

Sebaceous Gland Carcinoma

Sebaceous gland carcinoma is rare. It occurs most often on the eyelids, predominantly on the upper lid in older women, although the lower lid and caruncle are also sites of origin; it may occur on other parts of the head and neck skin as well.[18] It is often indolent in its growth; however, it may be locally aggressive and develop regional and distant metastases. Local recurrence is common after excision because the lesions often have significant deep and lateral spread beyond the obvious lesion. Metastasis to regional lymph nodes is reported in about 20% of cases, and a small percentage of patients develop distant metastases.[19] Inadequate treatment often occurs because of incorrect histologic diagnosis.

Keratoacanthoma

Keratoacanthoma benign lesions start as a firm, round skin nodule and grow to 1 to 2 cm in a short time, usually a few weeks. As the lesion matures, the center becomes separate and can be removed, revealing a small crater. The lesion occurs most often in the exposed area of the head and neck. Keratoacanthoma is an unlikely diagnosis for a lesion of the lip vermillion. Typically,

keratoacanthoma is twice as common in men as in women. It occurs most often in patients older than 40 years of age, although it may be seen as early as the second decade of life.

Basal Cell Nevus Syndrome

The basal cell nevus syndrome (aka Gorlin syndrome) is an autosomal dominant disorder with a high level of penetrance but a variable clinical picture. The clinical syndrome may be composed of any or all of the following:

- Multiple BCCs (differing only in their tendency to develop at an early age and on unexposed skin areas)
- Jaw cysts (common)
- Palmar or plantar pits
- Skeletal abnormalities (short fingers, hypertelorism)
- Ectopic calcification
- Eye muscle palsies
- Hamartomas
- Epidermal cysts

The age at onset is frequently in the second or third decade of life, and a family history is often positive for the disorder.[20]

Merkel Cell Carcinoma

MCC occurs primarily in White men between 60 and 80 years of age.[21] The lesion often presents as a painless, raised skin nodule or mass that is red, pink, or blue and may have diffuse margins and is covered with an intact epidermis. Most lesions are 2 cm or smaller at diagnosis.[21] Human polyomavirus is thought to be etiologic in a significant proportion of patients; human polyomavirus DNA in the MCC cells may be associated with an improved prognosis.[21]

MCC displays an aggressive growth pattern. Mojica et al[22] reported on 1,665 patients from the National Cancer Institute's Surveillance Epidemiology and End Results database and observed the following extent of disease at diagnosis: localized, 55%; positive regional nodes, 31%; distant metastases, 6%; and no data, 8%.

Melanoma

Melanoma is more aggressive and prone to metastasize to regional lymph nodes and exhibit hematogenous dissemination compared with BCC and SCC. The likelihood of regional and/or distant metastases is related to the depth of invasion of the primary tumor. The incidence of positive sentinel lymph node biopsies (SLNBs) versus depth of penetration is depicted in Table 39.1.

TABLE 39.1 PRIMARY DEPTH OF INVASION VERSUS SENTINEL LYMPH NODE BIOPSY POSITIVITY

Series	Primary Site	Depth Invasion of (Number of Patients) ≤1 mm	1.01-2.00 mm	2.01-4.00 mm	>4.00 mm
Rousseau et al, 2003,[53] University of Texas MD Anderson Cancer Center	Various	4% (388)	12% (522)	28% (314)	44% (151)
Emery et al, 2007,[54] University of Oregon	Various	2% (41)	13% (85)	20% (35)	27% (11)
Paek et al, 2007,[55] University of Michigan	Various	—	19% (490)	32% (301)	45% (119)
Kruper et al, 2006,[56] University of Pennsylvania	Various	5% (251)	10% (228)	20% (140)	38% (63)
Leong et al, 2006,[57] multicenter study	Head and neck	3% (134)	7% (230)	21% (160)	13% (63)
Berk et al, 2005,[58] Stanford University	Various	0% (45)	18% (115)	19% (64)	16% (32)

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Lymphatic Metastasis

The overall risk of lymphatic metastases is estimated to be up to 10% to 20% for cutaneous SCC of the skin. The risk increases with the size of the lesion, depth of the penetration, histologic grade, and recurrence.

The risk of lymph node metastases from previously untreated BCCs is <1% and is not related to size, depth of penetration, or histologic subtype; the risk increases for recurrent BCCs, especially those with multiple recurrences over several years. Lymph node metastases, however, are seen on rare occasions without a history of recurrence, and an interval of several years may occur between the treatment of the primary lesion and the appearance of involvement in lymph nodes. When they do occur, lymph node metastases are often solitary.

CLINICAL PICTURE

Presenting Symptoms

The common history for BCC or SCC is a slowly enlarging growth on or just beneath the skin surface. Often, a history exists of a sore that will not completely heal. Other symptoms such as bleeding or pain are unusual until the lesion becomes large, and even then symptoms are relatively mild and infrequent. Patients with PNI may complain of paresthesia, especially the sensation of worms crawling under the skin (formication). PNI is usually observed with midface lesions and most often involves cranial nerves V2 and/or VII.[7] Advanced, neglected lesions with bone and cartilage destruction, orbit invasion, and regional metastases may be seen; these advanced lesions often produce few, if any, symptoms, and patients simply delay consulting a physician.

Melanomas usually present as a pigmented skin lesion associated with a change in color, shape, and/or size. Although most probably arise de novo, some may arise in a previously benign nevus. Occasionally, patients present with regional or distant metastases without an apparent primary tumor.

Physical Examination

The site, size, and mobility of the primary lesion are documented. Depending on location, evidence of PNI is assessed as well as any findings that might suggest involvement of underlying bone or cartilage. The regional lymph nodes must be carefully examined, even though they are not often involved. Because of the infrequent appearance of regional lymphatic metastases, and because cases of skin cancer are often not followed diligently, lymph node metastases are frequently missed. Although lymphatic metastases may appear within a few months of the management of the primary lesion, in some cases, many years intervene before the regional lymph nodes become apparent. It is not at all unusual for ≥5 years to intervene between the primary lesion and the appearance of metastases. Patients with chronic lymphocytic leukemia and concomitant skin cancer often have enlarged lymph nodes from both processes and may have elements of SCC and leukemia in the same lymph nodes.

METHODS OF DIAGNOSIS AND STAGING

Biopsy should be performed on the majority of lesions before deciding on treatment. We do not always insist on biopsy for older patients who have a typical skin carcinoma and are to be treated by RT.

Small lesions occurring on the free skin areas (ie, not involving the eyelid, ear, or periorbital areas) can usually undergo biopsy and be treated simultaneously with surgical excision. Larger lesions, or those involving areas where functional or cosmetic deficit might occur from excision, first undergo biopsy with a small incisional biopsy or with a skin punch. Shave biopsies are also often used, except in pigmented lesions where a melanoma is suspected. For the diagnosis and staging of a melanoma, a full-thickness skin biopsy (such as with a punch) is needed. Biopsy with a skin punch should include the subcutaneous fat; punch biopsy is contraindicated when differentiating between keratoacanthoma and SCC because of the small sample size.

The following is a partial list of conditions to be considered in the differential diagnosis of BCC and SCC:

- Senile keratosis
- Keratoacanthoma
- Nonpigmented nevi
- Melanoma
- Cutaneous horn
- Psoriasis
- Lymphoma (mycosis fungoides)
- Soft tissue sarcomas (dermatofibrosarcoma protuberans)
- Hemangiosarcoma
- Metastatic carcinoma
- Adnexal carcinoma of skin
- MCC

Staging

The 2017 American Joint Committee on Cancer (AJCC) systems for SCC of the head and neck and melanoma are depicted in Tables 39.2 and 39.3, respectively.[23] BCC and SCC outside the

head and neck were not included in the AJCC Staging Manual for 2017. Although there is an AJCC staging system for MCC, we prefer the Yiengpruksawan system for this rare entity because of its simplicity: stage I, localized (AJCC stages I and II); stage II, regional lymph node metastases (AJCC stage III); and stage III, distant metastases (AJCC stage IV).[24]

TABLE 39.2 2017 AJCC STAGING SYSTEM FOR SQUAMOUS CELL CARCINOMAS OF THE HEAD AND NECK

Primary Tumor (T)[a]	
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor smaller than 2 cm in greatest dimension
T2	Tumor 2 cm or larger, but smaller than 4 cm in greatest dimension
T3	Tumor 4 cm or larger in maximum dimension of minor bone erosion or perineural invasion or deep invasion[a]
T4	Tumor with gross cortical bone/marrow, skull base invasion, and/or skull base foramen invasion
T4a	Tumor with gross cortical bone/marrow invasion
T4b	Tumor with skull base invasion and/or skull base foramen involvement
Regional Nodes Lymph (N)	
NX	Regional lymph cannot nodes be assessed.
N0	No regional node lymph metastases
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and extranodal extension (ENE)(−)
N2	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−); or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); or in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2a	Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b	Metastasis in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); or metastasis in any node(s) and clinically overt ENE (ENE[+])
N3a	Metastases in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in any node(s) and ENE(+)
Distant Metastasis (M)	
M0	No distant metastases
M1	Distant metastases

Stage	***T***	***N***	***M***
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0

Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IV	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	Any T	N3	M0
	T4	Any N	M0
	Any T	Any N	M1

[a]Deep invasion is defined as invasion beyond the subcutaneous fat or >6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumor); perineural invasion for T3 classification is defined as tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger in caliber, or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression.

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TABLE 39.3 2017 AJCC STAGING SYSTEM FOR MELANOMA

Primary Tumor (T)

T Category	Thickness	Ulceration Status
TX	Primary tumor thickness cannot be assessed (eg, diagnosis by curettage).	
T0	No evidence of primary tumor (eg, unknown primary or completely regressed melanoma)	
Tis	Melanoma in situ	
T1	≤1.0 mm	Unknown or unspecified
T1a	<0.8 mm	Without ulceration
T1b	<0.8 mm 0.8-1.0 mm	With ulceration With or without ulceration
T2	>1.0-2.0 mm	Unknown or unspecified
T2a	>1.0-2.0 mm	Without ulceration1
T2b	>1.0-2.0 mm	With ulceration
T3	>2.0-4.0 mm	Unknown or unspecified
T3a	>2.0-4.0 mm	Without ulceration
T3b	>2.0-4.0 mm	With ulceration
T4	>4.0 mm	Unknown or unspecified
T4a	>4.0 mm	Without ulceration
T4b	>4.0 mm	With ulceration

Regional Lymph Node (N): Extent of regional lymph node and/or lymphatic metastasis

Primary Tumor (T)

T Category	Thickness	Ulceration Status
N Category	Number of tumor-involved regional lymph nodes	Presence of in-transit, satellite, and/or microsatellite metastases
NX	Regional nodes not assessed (eg, SLN biopsy not performed, regional nodes previously removed for another reason) **Exception:** pathological N category is not required for T1 melanomas, use cN.	No
N0	No regional metastases detected	No
N1	One tumor-involved node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	
N1a	One clinically occult (ie, detected by SLN biopsy)	No
N1b	One clinically detected	No
N1c	No regional lymph node disease	Yes
N2	Two or three tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with one tumor-involved node	
N2a	Two or three clinically occult (ie, detected by SLN biopsy)	No
N2b	Two or three, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes
N3	Four or more tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with two or more tumor-involved nodes	
N3a	Four or more clinically occult (ie, detected by SLN biopsy)	No
N3b	Four or more, at least one of which was clinically detected, or presence of any number of matted nodes	No
N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes
Distant Metastasis (M)		
M Category	M Criteria	
	Anatomic Site	LDH Level
M0	No evidence of distant metastasis	Not applicable
M1	Evidence of distant metastasis	See below
M1a	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node	Not recorded or specified
M1a(0)		Not elevated
M1a(1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated

Primary Tumor (T)		
T Category	Thickness	Ulceration Status
M1c(1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)		Normal
M1d(1)		Elevated

Primary Tumor (T)							
T Category	Thickness			Ulceration Status			
Prognostic Stage Groups							
Clinical				***Pathologic***			
When T is …	And N is …	And M is …	Then the clinical stage group is …	When T is …	And N is …	And M is …	Then the clinical stage group is …
Tis	N0	M0	0	Tis	N0	M0	0
T1a	N0	M0	IA	T1a	N0	M0	IA
T1b	N0	M0	IB	T1b	N0	M0	IA
T2a	N0	M0	IB	T2a	N0	M0	IB
T2b	N0	M0	IIA	T2b	N0	M0	IIA
T3a	N0	M0	IIA	T3a	N0	M0	IIA
T3b	N0	M0	IIB	T3b	N0	M0	IIB
T4a	N0	M0	IIB	T4a	N0	M0	IIB
T4b	N0	M0	IIC	T4b	N0	M0	IIC
Any T, Tis	≥N1	M0	III	T0	N1b, N1c	M0	IIIB
Any T	Any N	M1	IV	T0	N2b, N2c, N3b, or N3c	M0	IIC
				T1a/b-T2a	N1a or N2a	M0	IIIA
				T1a/b-T2a	N1b/c or N2b	M0	IIIB
				T2b/T3a	N1a-N2b	M0	IIIB
				T1a-T3a	N2c or N3a/b/c	M0	IIIC
				T3b/T4a	Any N ≥N1	M0	IIIC
				T4b	N1a-N2c	M0	IIIC
				T4b	N3a/b/c	M0	IIID
				Any T, Tis	Any	M1	IV

AJCC, American Joint Committee on Cancer; CNS, central nervous system; LDH, lactate dehydrogenase; SLN, sentinel lymph node.

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Diagnostic Imaging

Computed tomography (CT) and magnetic resonance imaging (MRI) are only necessary in a carefully chosen group of patients being treated for skin cancer. CT is the primary modality for showing bone invasion and nodal metastases, although MRI is often useful in determining muscular or bony invasion in large or neglected lesions and is superior to CT for demonstrating PNI.[25] Positron emission tomography (PET) is useful to detect regional and distant metastases in patients with MCC and melanoma but should be restricted to patients who are found to be node positive.

SELECTION OF TREATMENT MODALITY

Basal Cell and Squamous Cell Carcinomas

The likelihood of cure is similar after surgery or RT for early-stage BCCs and SCCs.[26] Therefore, selection of one modality over another is based on other parameters such as function, cosmesis, age of the patient, convenience, cost, availability of appropriate RT equipment, and the wishes of the patient. Patients with advanced cancers are often best treated with surgery and adjuvant RT if the cancer is resectable and the functional and cosmetic outcomes are acceptable to the patient. It is important to recall that there are newer systemic options, such as immunotherapy, that may be indicated depending on the situation.

Radiotherapy Alone

Small skin cancers located on "free skin," such as the cheek or forehead, may be easily excised and reconstructed with a good cosmetic result and minimal inconvenience; therefore, surgery is usually the treatment of choice for such lesions. It is also desirable to avoid RT in young patients because the late effects of irradiation progress gradually with time and, with very long-term follow-up, may be associated with a suboptimal cosmetic result compared with resection and reconstruction. In contrast, resection of an early-stage skin cancer of the eyelid, external ear, or nose may result in a significant cosmetic deformity and necessitate complex reconstruction that compares unfavorably with RT. This is particularly relevant in the case of older patients who have a limited life expectancy and who are at higher risk for a perioperative complication if the lesion is large and general anesthesia is required. In contrast, small cancers suitable for Mohs excision with local anesthesia are well treated with this technique.

Patients with locally advanced skin cancers present a difficult problem because, although the likelihood of cure may be better with combined RT and surgery in some situations, the cosmetic result is sometimes unacceptable. Patients receive postoperative RT if surgery is indicated and feasible. If surgery is not feasible, the patient is managed with RT alone. Although it might seem that the risk of bone and/or cartilage necrosis would be high after RT for a skin cancer invading these structures, the observed risk of complications is relatively low.[27,28] Exceptions are advanced cancers of the scalp and those overlying the anterior aspect of the tibia where there is little tissue between the skin surface and the bone. Following definitive RT, bone exposure is likely and may progress to an osteoradionecrosis requiring surgical intervention.

Patients with SCC and BCC with incidental PNI have better outcomes after Mohs surgery and postoperative RT compared with RT following a non-Mohs resection.[29] Patients with lesions associated with clinical PNI with gross tumor extending to sites that render complete resection unlikely or unfeasible, such as the cavernous sinus, are treated with RT alone. Subtotal resection does not enhance the likelihood of cure and only increases the morbidity of treatment.

Adjuvant Radiotherapy

Postoperative RT is added after surgery if pathologic examination of the surgical specimen reveals findings indicative of a high risk for local recurrence, such as close or positive margins and/or invasion of nerve, cartilage, or bone. A significant proportion of patients with positive margins after resection of an early-stage skin cancer may never develop a local recurrence. Postoperative RT may be withheld if the lesion is a BCC, the primary site is located on the free skin, the patient is reliable and will return for close follow-up, and if salvage treatment would have a high likelihood of eradicating recurrent tumor with a good cosmetic result. BCCs of the nose, eyelid, or ear and lesions that would have immediate access to major nerve trunks are usually retreated immediately when resection margins are positive. The risk of recurrence is probably greater than for lesions of the free skin, and the consequences of recurrence may be significant. Observation is particularly attractive for the older patient in poor medical conditions who may not live to experience a local recurrence. Metatypical BCCs behave more aggressively than BCCs, and those with positive margins after surgery should be reexcised and/or treated with postoperative RT.

Patients with BCC or SCC and focal incidental PNI involving a small nerve trunk (<0.1 mm) and widely negative margins may be safely observed.[30,31] Otherwise, patients with incidental PNI should be considered for postoperative RT, particularly if the lesion is SCC.

The usual policy for patients with positive margins from SCC is immediate retreatment by either reexcision, RT, or both, depending on the situation. There is evidence that this approach leads to a reduced risk of metastasis and reduced likelihood of death from cancer.

Regional Lymph Node Metastases

Carcinoma of the skin metastatic to the parotid lymph nodes is managed as a high-grade parotid neoplasm, usually with superficial or total parotidectomy followed by postoperative RT.[26,32-34] If only one node is involved and there is no extracapsular extension, it may be safe to withhold RT. However, if the tumor recurs in the parotid area after parotidectomy, the likelihood of salvage is remote.[32] Therefore, it has been our practice to use combined treatment in all patients. If the parotid lymph node metastasis is fixed and thought to be incompletely resectable, the patient is treated with high-dose preoperative RT (6,000-7,000 cGy) followed by parotidectomy. RT alone is used only in patients who are inoperable because of tumor extent or poor medical condition. Patients who have positive parotid nodes and clinically negative cervical nodes may undergo a parotidectomy withholding the neck dissection, followed by postoperative RT to the parotid and the neck with a high likelihood of local-regional control.[35]

Cervical lymph node metastases are managed just as they would be for other carcinomas of the head and neck. Neck dissection alone is adequate treatment if only one node is involved and there is no extracapsular extension. If two or more nodes contain tumor or if extracapsular extension is noted, neck dissection is followed by postoperative RT.

Merkel Cell Carcinoma

The preferred treatment for MCC is resection of the primary tumor with wide surgical margins (2 cm) and sentinel node. Our bias is to treat both the primary site and regional lymphatics with postoperative RT. The dose-fractionation schedule is the same as that employed for SCC. The role of adjuvant chemotherapy is ill defined, but immunotherapy can be considered in all patients with regional disease. Patients who should be considered for adjuvant chemotherapy are those with

positive nodes and/or satellite lesions. Drugs employed are often those used for small cell carcinomas and include etoposide and cisplatin and PD inhibitors.

Melanoma

The preferred treatment for melanoma is resection of the primary lesion with or without sentinel node biopsy. Patients who have lesions with a depth of invasion exceeding 0.8 mm or ulceration and clinically negative nodes should be considered for SLNB. We also consider SLNB for lesions with depth of invasion ≤0.8 mm if there are high-risk features, including regression, invasion into Clark level IV or V, deep margin positive, or young age. Completion lymph node dissection for positive sentinel nodes is no longer considered standard of care as this has shifted to immunotherapy. Fine-needle aspiration should be performed on any grossly positive regional nodes, followed by immunotherapy. An adjunct for patients without gross residual positive nodes, but for high-risk features such as extranodal extension is postoperative RT. Patients with desmoplastic melanoma should be considered for postoperative RT. These patients are usually suitable for surgery alone unless there is extensive PNI associated with a lesion near a named nerve, in which case postoperative RT is considered. Postoperative RT can also be employed to treat the primary site when there are in-transit metastases and the margins are equivocal. Adjuvant postoperative RT is often employed for positive regional nodes. Patients who are at high risk for regional lymph node metastases and are unable to undergo SLNB and/or elective node dissection can be considered for elective nodal irradiation of the first-echelon lymphatics. The dose-fractionation schedule is usually the MD Anderson Cancer Center hypofractionation technique consisting of 3,000 cGy in five fractions over 2.5 weeks with a reduction off of the spinal cord and/or central nervous system (CNS) at 2,400 cGy.[36] Alternatively, conventional fractionation may be employed if late effects and suboptimal cosmesis are a concern.[37] These patients should also be strongly considered for immunotherapy.

Definitive RT using orthovoltage RT or electrons may be employed for older patients with lentigo maligna or lentigo malignant melanoma where excision is not feasible because of cosmesis function and/or medial comorbidities.[38-40] The dose-fractionation schedules are the same as those described for postoperative RT.

TREATMENT TECHNIQUES

Treatment techniques vary for primary lesions and for regional lymph node metastases.

Primary Lesion

RT of the primary lesion is usually accomplished using one of three basic external-beam techniques (orthovoltage RT, electron beam, and high-energy x-rays or photons) or with an interstitial implant either alone or in combination with external-beam techniques (addressed on the next page). Most early skin cancers are managed with orthovoltage RT with beam energies of 100 to 250 kVp. The advantages of this technique, compared with electron beam, are that the maximum dose is at the skin surface; bolus is not required; there is less beam constriction at both the surface and depth so that smaller fields can be used (Figure 39.1); shielding of the eye is easier and more effectively accomplished, particularly if electron energies ≥10 MeV are used (Table 39.4)[41]; it is less expensive; and the likelihood of tumor control may be higher, possibly as a result of increased radiobiologic effectiveness but more likely because of technical problems

that are difficult to overcome when using electrons alone. The disadvantages of orthovoltage x-rays, compared with electron beam, are that there is a higher dose to deeper tissues and to underlying bone and cartilage. The latter problem can be largely eliminated by using heavily filtered orthovoltage beams for tumors involving or overlying cartilage or bone. Another significant problem associated with orthovoltage RT is that most radiation oncology departments do not have an orthovoltage machine, and thus it is unavailable. Electron beam is usually used for lesions of the scalp to reduce the dose to the underlying brain; orthovoltage x-rays are used to treat most other skin cancers. Orthovoltage RT is particularly useful for lesions of the head and neck.

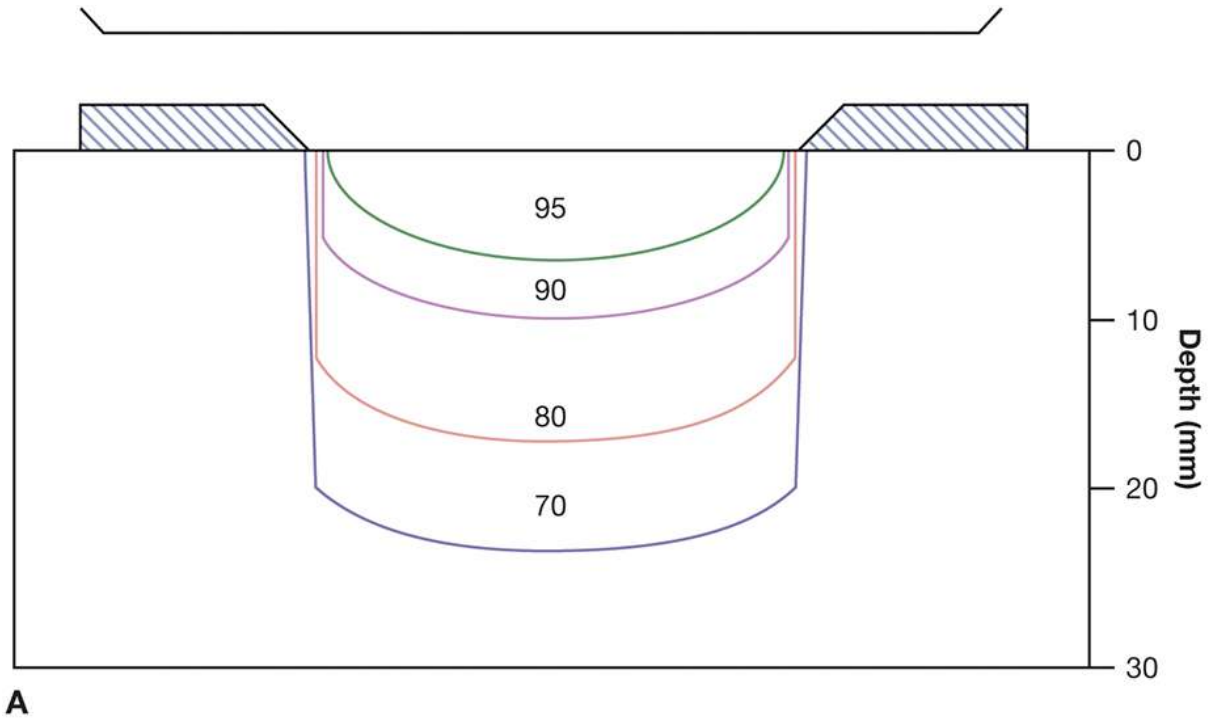
TABLE 39.4 OCULAR PROTECTION: DOSE BENEATH THE EYE SHIELD

		Electron-Beam Energy (MeV)						
Structure (Depth)	**250 kVp x-ray (HVL mm 1.4 Cu)**	**6**	**8**	**10**	**12**	**14**	**17**	**20**
Cornea (1 mm)	10%	18%	37%	64%	75%	93%	98%	102%
Lens (8 mm)	9%	9%	19%	36%	46%	61%	70%	87%
Retina (23 mm)	10%	19%	22%	22%	21%	23%	25%	29%

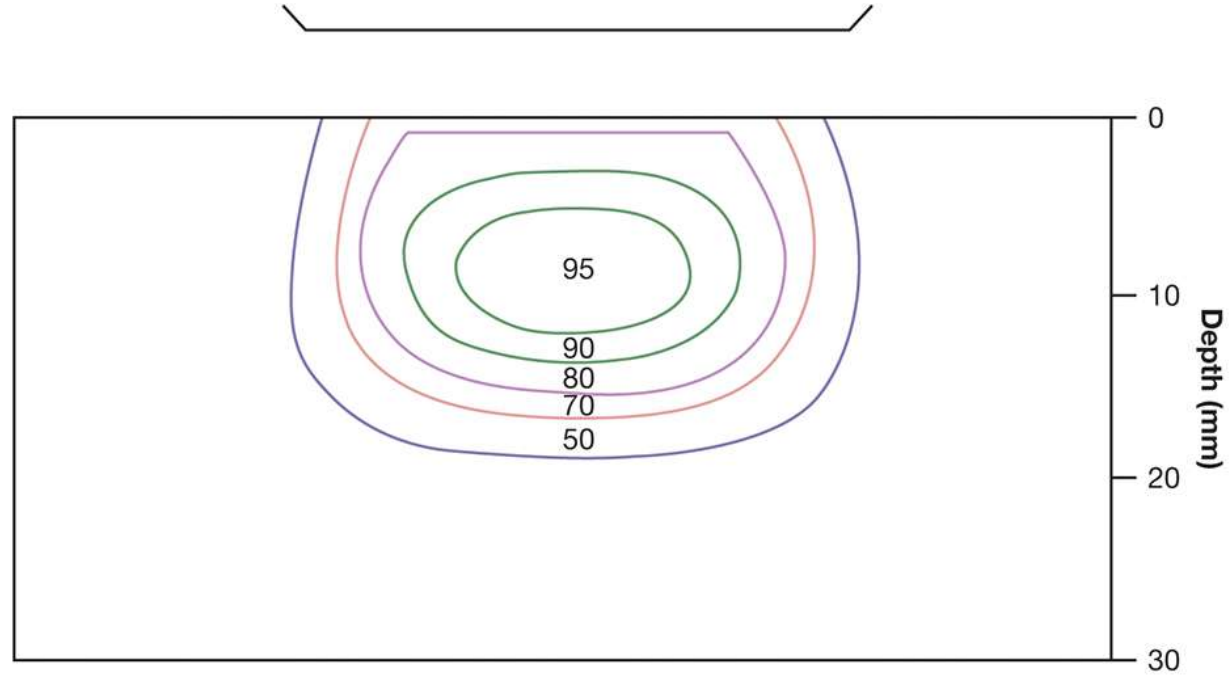
Dose is expressed as a percentage of the dose to D_{max} (depth of maximum dose deposition).

HVL, half-value layer.

Reprinted from Amdur RJ, Kalbaugh KJ, Ewald LM, et al. Radiation therapy for skin cancer near the eye: kilovoltage x-rays versus electrons. *Int J Radiat Oncol Biol Phys*. 1992;23(4):769-779. Copyright © 1992 Elsevier. With permission.



A



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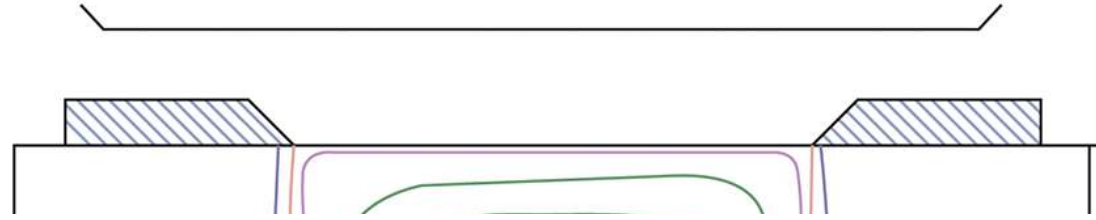

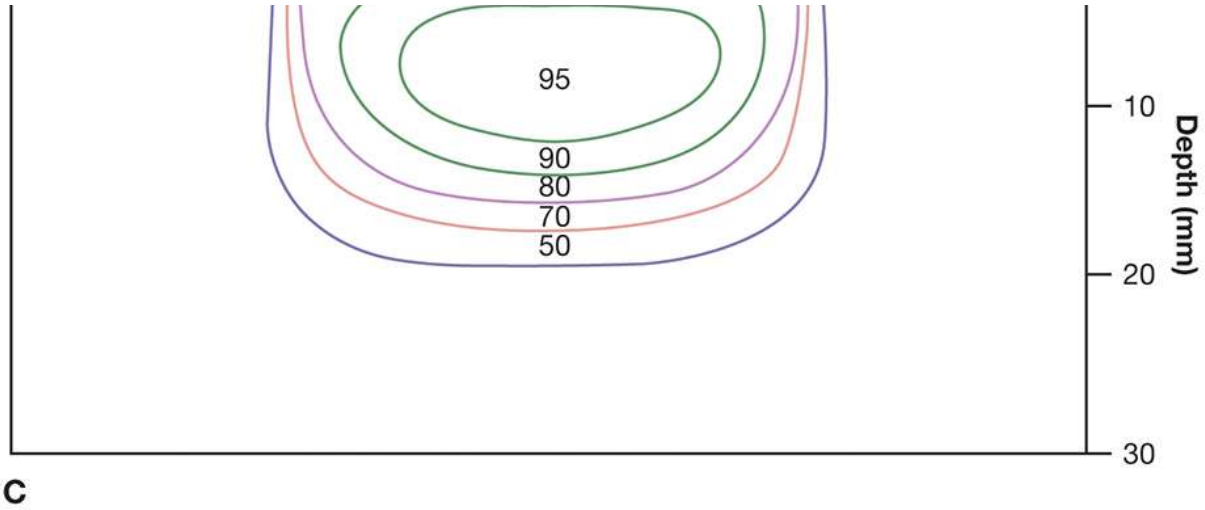

FIGURE 39.1 A. 250-kVp x-rays (half-value layer 1.4 mm Cu) with secondary collimation on the phantom surface. Source-to-surface distance (SSD) = 50 cm; isodose %: 95, 90, 80, 70. B. 6-MeV electron beam with secondary collimation 5 cm above the phantom surface (at the level of the electron cone). Source of collimator distance (SCD) = 95 cm; SSD = 100 cm; isodose %: 95, 90, 80, 70, 50. C. 6-MeV electron beam with tertiary collimation on the phantom surface. SSD = 100 cm; SCD = 100 cm; isodose %: 95, 90, 80, 70, 50.

Before treatment with either electron-beam or orthovoltage x-rays, a customized lead mask is constructed to collimate the beam directly on the skin surface. A 1.0- to 1.5-cm margin is adequate for a well-defined T1 lesion treated with orthovoltage RT. An additional 1 cm is added to the margin when the electron beam is used to account for beam constriction. For larger and/or ill-defined tumors, a 2-cm margin is usually necessary. If the tumor is located near the eye, a gold-plated lead eye shield is placed directly on the anesthetized cornea to minimize the irradiation dose to underlying structures (Figure 39.2). The dose beneath the eye shield is depicted for orthovoltage x-rays and electron beams of various energies in Table 39.4. Isodose distributions for the two techniques are shown in Figure 39.1; note that the dose distribution is better for orthovoltage RT than for electron beam, particularly if a lead mask is not used with the electron beam.

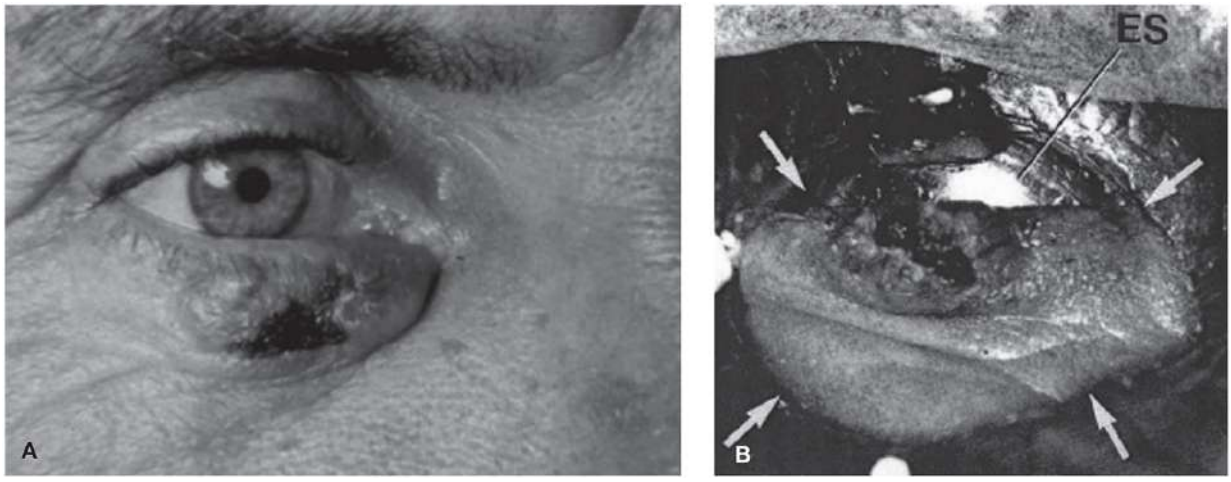

FIGURE 39.2 A. 1- × 1-cm^2 basal cell carcinoma of the midportion of the lower lid. B. Treatment setup that was used to irradiate the patient. Arrows indicate the field edge. ES, eye shield.

Advanced skin cancers that are deeply invasive are often treated with high-energy photons to adequately cover the deep extent of the tumor. Bolus is used to ensure an adequate surface dose. Field arrangement varies with primary site. For example, a wedge-pair technique may be used for lesions involving the external ear, whereas a three-field technique (similar to that used for paranasal sinus cancer) is frequently used for skin cancers with extension proximally along the second division of the fifth cranial nerve. The target volume includes the entire course of the involved nerve, which would include the Gasserian ganglion in this case, to the brainstem. Intensity-modulated radiotherapy (IMRT) may be used in some patients to produce a more conformal dose distribution to reduce the dose to surrounding normal structures. Proton-beam RT may also be used to produce a very conformal dose distribution with steep dose gradients to limit the dose to the visual apparatus and the CNS.[42,43]

The extent of RT fields for patients with PNI varies with the histology and extent of PNI. Patients with BCC or SCC and focal incidental PNI are treated with a wide local field. Those with extensive incidental PNI are treated with fields that include the at-risk nerves to the skull base, particularly if margins are positive or equivocal. The at-risk nerves receive 5,000 to 7,000 cGy depending on the extent of PNI and margin status. Patients with clinical PNI receive definitive RT to fields that include the primary site and involved nerves to the skull base.

The regional lymph nodes are electively irradiated if the suspected risk of subclinical disease exceeds 10% to 15%.[44,45] Patients with SCC and PNI should be considered for elective nodal RT, particularly if the lesion is located on the head or neck.

Dose-fractionation schedules used for irradiation of skin cancers are outlined in Table 39.5. We have recently used twice-daily RT with megavoltage photons or protons at 1.2 Gy per fraction to doses of 744 cGy in a continuous course with a minimum 6-hour interfraction interval for advanced lesions near radiosensitive structures. The suggested maximum doses for short-course orthovoltage RT are listed in Table 39.6.

TABLE 39.5 GUIDELINES FOR SELECTION OF EXTERNAL-BEAM DOSE

Orthovoltage Dose (cGy)[a]	Examples
6,500 over 7 wk	Large untreated lesion with bone/cartilage invasion or large recurrent tumor[b]
6,000 over 7 wk	Large untreated lesion with minimal or suspected bone/cartilage invasion[b]
5,500 over 6 wk	Moderate to large inner canthus, eyelid, nasal, or pinna lesions (20-30 cm^2 area)
5,000 over 4 wk	Small, thin lesion (<1.5 cm) around eye, nose, or ear (10 cm^2 area)
4,500 over 3 wk	Moderate-sized lesion on free[c] skin or postoperative treatment of moderate-sized cancer on free skin with positive margins
4,000 over 2 wk or 3,000 over 1 wk	Small lesions (1 cm) free on skin
The following schemes are used when the late cosmetic result is not important and travel for the patient is difficult:	
4,000 10 in fractions 3,000 or in fractions 5 or 2,000 in 1 fraction	Rapid fractionation produces schemes with a high cure rate for small lesions, although cosmetic may result be less than optimal after 5 y.

[a]Add 10% to dose for supervoltage therapy.

[b]All or a portion of the therapy is given with supervoltage photons and/or electrons.

[c]"Free" refers to not involving the ear, nose, eye, or eyelid.

Reprinted with permission from Mendenhall WM, Million RR, Mancuso AA, et al. Carcinoma of the skin. In: Million RR, Cassisi NJ, eds. *Management of Head and Neck Cancer: A Multidisciplinary Approach*. 2nd ed. J.B. Lippincott; 1994:643-691.

TABLE 39.6 SUGGESTED MAXIMUM SKIN DOSES[A] FOR PALLIATION WITH 250 KVP X-RAYS (BELOW MOIST DESQUAMATION LEVEL FOR THE AVERAGE PATIENT)

Field Size (Area in cm^2)	Total Dose (cGy)						
	1 d (1 Exposure)	2 d (2 Exposures)	4 d (4 Exposures)	5 d (5 Exposures)	2 wk (10 Exposures)	3 wk (15 Exposures)	5 (25 wk Exposures)
Small fields							
10	2,000	2,750	3,500	3,750	5,000	5,500	6,000
50	1,750	2,500	3,250	3,500	4,500	5,000	5,500
Medium fields							
100	1,500	2,000	2,500	2,750	3,750	4,250	5,000
150	1,250	1,750	2,250	2,500	3,250	3,750	4,500
Large fields							
200	1,000	1,500	2,000	2,250	3,000	3,500	4,250
300	Not recommended	Not recommended	Not recommended	2,000	2,750	3,250	4,000

[a]The total doses listed are administered over a treatment course of the indicated length, divided into the indicated number of fractional treatments.

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Parotid Area Lymph Node Metastases

The parotid gland and upper neck are treated with an en face mixed beam of 6-MV x-rays and high-energy electrons (usually 20 MeV), weighted 1.0:0.67 in favor of the electron beam. The electron-beam field is 1 cm larger than the x-ray field to account for the beam constriction of the electrons, except where the field abuts the low-neck field (Figure 39.3). This field arrangement is treated to 4,600 cGy in 23 fractions, specified at a depth of 4 to 5 cm from the skin surface. An anterior field is matched to the lateral mixed-beam field to treat the ipsilateral low neck and is irradiated to 5,000 cGy in 25 fractions, specified at D_{max}.

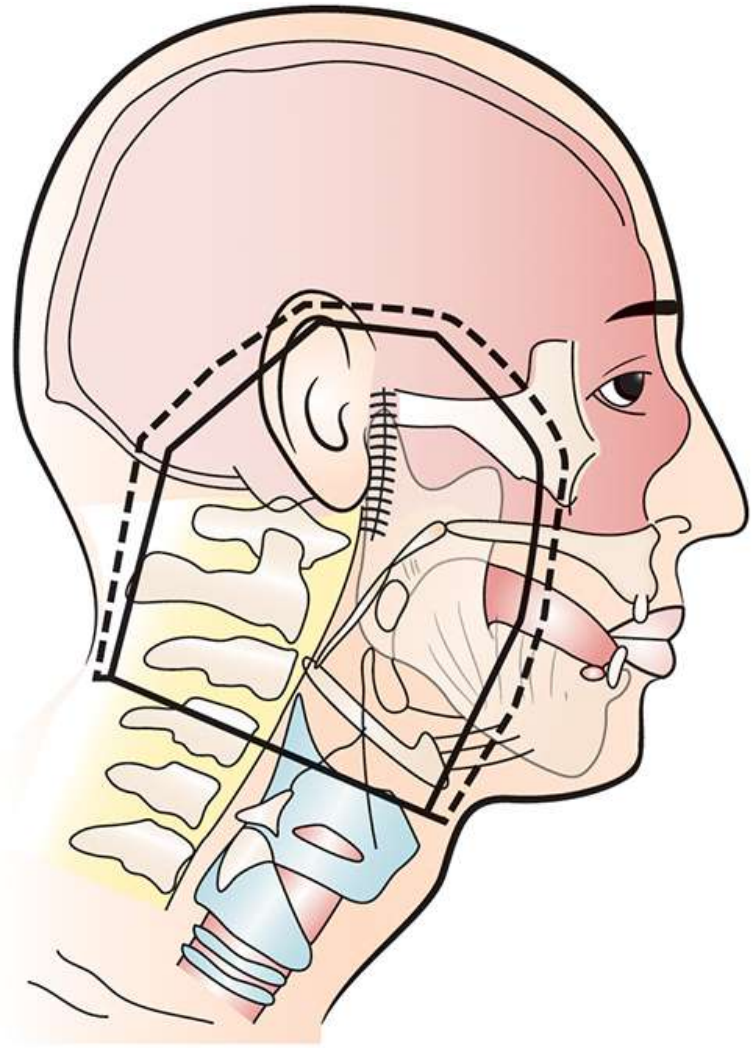

FIGURE 39.3 Typical en face mixed-beam field used in the treatment of parotid node metastases to encompass the entire parotid bed and surgical scar. Patients are treated supine with a face mask made of low-temperature thermal plastic (polycaprolactone) for immobilization and a lead lollipop to decrease the dose to the contralateral salivary gland. A bolus of petrolatum-coated gauze is applied to all scars.

At 4,600-cGy tumor dose, the primary field is reduced off of the spinal cord, and the dose to the tumor bed is boosted with an anteriorly angled 20-MeV electron-beam field or an appositional mixed-beam field with an abutting posterior electron strip. The final dose for patients treated at 200 cGy per fraction with negative margins is 6,000 cGy; with positive margins, 6,600 cGy; and with gross residual disease, 7,000 cGy. If the dose per fraction is reduced to 180 cGy, the total dose is increased by 500 cGy. An alternative to the mixed electron-photon beam is a wedge-pair technique using 4- to 6-MV photon beams. IMRT may also be considered to reduce the dose to the temporal lobe and cerebellum, particularly if the margins are positive and/or tumor involves the deep lobe of the parotid.

Axillary Metastases

Axillary lymph node metastases are irradiated with opposed anterior and posterior portals that include the supraclavicular fossa. The dose-fractionation schedule is 4,500 cGy in 25 fractions

with a reduction and boost depending on margin status.

Ilioinguinal Lymph Node Metastases

Ilioinguinal lymph nodes are usually irradiated with IMRT to reduce the volume of tissue irradiated, particularly small bowel. The femoral and external iliac vessels are contoured on the treatment planning CT, and a 1.5- to 2-cm margin is added to obtain the clinical target volume.

FOLLOW-UP AND MANAGEMENT OF RECURRENCE

After RT, patients are evaluated every 2 to 3 months for the first and second years, every 4 months for the third year, every 6 months for the fourth and fifth years, and annually thereafter. Chest roentgenograms are obtained annually, and follow-up CT, MRI, and/or PET-CT are obtained as needed for patients irradiated for advanced lesions.

Treatment of local-regional recurrences either after RT alone or combined with surgery is usually resection. If a local recurrence is amenable to en bloc surgical resection with frozen section control of the margins, this may be preferable for selected cases. Of note, the frozen section cannot be performed on melanoma due to the requirement for histopathologic staining. Local recurrences after RT may be significantly more extensive than is clinically apparent; thus, wide margins are preferred. Retreatment with RT is rarely indicated because of the high likelihood of complications. The most common scenario for recurrence in the neck nodes is failure in a solitary submandibular location; the success rate of salvage neck dissection is high in this circumstance.

RESULTS

Basal Cell and Squamous Cell Carcinomas

Most series reporting the results of treatment for skin cancer contain a preponderance of early lesions and do not employ a staging system, making it difficult to compare various series and the relative efficacy of different treatment modalities.

Primary Lesion

The likelihood of local control after irradiation for skin carcinomas of various sizes managed at the Mallinckrodt Institute of Radiology is outlined in Table 39.7.[46] The probability of local control is higher for smaller lesions, for BCC compared with SCC, and for previously untreated lesions compared with recurrent cancers. The results of RT using various beam energies are listed in Table 39.8; treatment with orthovoltage irradiation yields local control rates that are as good as, or better than, local control rates yielded by other treatment modalities.[46]

TABLE 39.7 LOCAL TUMOR CONTROL WITH RADIOTHERAPY ACCORDING TO SIZE, CELL TYPE, AND PRESENTATION (FROM MALLINCKRODT INSTITUTE OF RADIOLOGY—339 PATIENTS)

Size	Basal Cell, Previously Untreated	Basal Cell, Recurrent	Squamous Previously Cell, Untreated	Squamous Cell, Recurrent
≤1 cm	64/66 (97%)	22/23 (96%)	11/11 (100%)	10/12 (83%)
1.1-3 cm	71/75 (95%)	27/36 (75%)	19/21 (90%)	7/13 (54%)
3.1-5 cm	11/13 (85%)	7/9 (78%)	7/8 (88%)	6/9 (67%)

Size	Basal Cell, Previously Untreated	Basal Cell, Recurrent	Squamous Previously Cell, Untreated	Squamous Cell, Recurrent
>5 cm	12/13 (92%)	1/2 (50%)	3/5 (60%)	6/11 (55%)
Size not specified	4/4 (100%)	1/1 (100%)	0/1 (0%)	4/6 (67%)
Total	**162/171 (95%)**	**58/71 (82%)**	**40/46 (87%)**	**33/51 (65%)**

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TABLE 39.8 LOCAL CONTROL RATES ACCORDING TO EXTERNAL-BEAM TECHNIQUE (FROM MALLINCKRODT INSTITUTE OF RADIOLOGY—339 PATIENTS)

	Size			
Modality	**≤1 cm (%)**	**1.1-5 cm (%)**	**>5 cm (%)**	**Not Specified (%)**
Basal Cell Carcinoma				
Superficial x-ray	69/71 (97%)	84/90 (93%)	4/4 (100%)	3/3 (100%)
Electron beam	11/12 (92%)	16/22 (73%)	4/5 (80%)	1/1 (100%)
Combination	5/5 (100%)	13/16 (81%)	5/6 (83%)	0/0
Photons (1.2-4 MV)	1/1 (100%)	3/5 (60%)	0/0	1/1 (100%)
Squamous Cell Carcinoma				
Superficial x-ray	12/12 (100%)	10/11 (91%)	1/1 (100%)	0/0
Electron beam	3/4 (75%)	7/10 (70%)	3/4 (75%)	0/1 (0%)
Combination	4/5 (80%)	19/26 (73%)	4/8 (50%)	2/4 (50%)
Photons (1.2-4 MV)	2/2 (100%)	3/4 (75%)	1/3 (33%)	2/2 (100%)

Significance levels: basal cell carcinoma 1.1-5 cm, superficial x-ray (84/90) versus electron beam/combination (29/38), $P = .013$; squamous cell carcinoma ≤1 cm, superficial x-ray (12/12) versus electron beam/combination (7/9), $P = .17$; squamous cell carcinoma 1.1-5 cm, superficial x-ray (10/11) versus electron beam/combination (26/36), $P = .41$.

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Schulte et al[47] reported on 1,113 patients treated with orthovoltage RT for 1,267 skin cancers and followed for a median of 82 months (Table 39.9). Patients were usually treated at 5 Gy per fraction. The incidence of soft tissue necrosis was 6.3%; 83% healed with conservative treatment.[47]

TABLE 39.9 RAW AND CUMULATIVE RECURRENCE RATES OF BASAL CELL AND SQUAMOUS CELL CARCINOMAS AFTER SOFT X-RAY THERAPY

		Recurrence Rates (%)			
			Cumulative After		
Tumor	**Number**	**Raw**	**5 y**	**10 y**	**15 y**
BCCs and SCCs, total[a]	1,267	5.1	4.7	6.9	7.4
BCCs, total	1,019	4.5	4.2	6.1	6.1
T1[b]	615	2.4[c]	3.9	4.7	4.7
T2[b]	366	5.2[c]	4.2	8.6	8.6

		Recurrence Rates (%)			
			Cumulative After		
Tumor	Number	Raw	5 y	10 y	15 y
T3[b]	22	9.1[c]	11.4	11.4	
Previously untreated (primary)	964	4.4	4.2	5.7	5.7
Previously and treated recurrent	55	7.3	4.3	13.2	13.2
SCCs, total	245	6.9	6.0	10.5	12.8
Tis[b]	13	7.7[d]	11.1		
T1[b]	79	1.3[d]	1.7	1.7	1.7
T2[b]	138	8.7[d]	7.4	14.2	19.0
T3[b]	14	21.4[d]	25.9	25.9	
Previously untreated (primary)	233	6.4	5.8	9.6	12.0
Previously and untreated recurrent	12	16.7	30.0	30.0	

BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

[a]Including three patients with combinations of BCCs and SCCs.

[b]Multiple (>1) tumors in the same irradiated field were excluded.

[c]Difference of the raw recurrence rate of BCCs Tis-T3 were statistically significant (X^2, 6.99; $P < .05$).

[d]Differences of the raw recurrence rate of SCCs Tis-T3 were statistically significant (X^2, 9.13; $P < .05$).

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Al-Othman et al[48] reported on 85 patients with 88 clinical T4 SCCs (37), BCCs (41), and metatypical BCCs (10) treated with definitive RT at the University of Florida (Gainesville, FL) between 1964 and 1997. Forty-three lesions were previously untreated, and 45 cancers were recurrent after prior surgery. The 5-year outcomes were as follows: local control, 53%; ultimate local control, 90%; regional control, 93%; ultimate regional control, 100%; distant metastasis-free survival, 95%; cause-specific survival, 76%; and overall survival, 56%. Thirteen (15%) of 85 patients developed a severe treatment-related complication.

Balamucki et al[49] reported on 216 patients treated at the University of Florida for skin carcinomas with incidental (107 patients) or clinical (109 patients) PNI; median follow-up for living patients was 6 years (range, 0.6-2.3 years). One hundred eighty-five patients (86%) had SCCs, and the remainder had BCCs or metatypical BCCs. Patients with incidental PNI were treated with surgery and postoperative RT (99 patients), preoperative RT and surgery (four patients), and RT alone (four patients). Eight patients received adjuvant chemotherapy. Twenty-six (24%) of 107 patients presented with clinically positive nodes. The outcomes for patients treated with incidental PNI are depicted in Table 39.10. Seventeen (16%) of 107 patients developed treatment complications. Patients with clinical PNI were treated with surgery and postoperative RT (58 patients), preoperative RT and surgery (two patients), or RT alone (49 patients). Fifteen (14%) of 109 patients presented with clinically positive nodes. The outcomes for patients treated for clinical PNI are depicted in Table 39.11. Fourteen (23%) of 62 patients who had achieved continuous local control experienced symptomatic improvement in clinical

neuropathic symptoms after treatment. Thirty-nine (36%) of 109 patients developed treatment complications.

TABLE 39.10 OUTCOMES AFTER TREATMENT FOR SKIN CARCINOMA WITH INCIDENTAL PERINEURAL INVASION (107 PATIENTS)

Parameter	5-y Outcome (%)
Local control	80
Ultimate local control	82
Local-regional control	70
Ultimate local-regional control	74
Cause-specific survival	73
Overall survival	55

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TABLE 39.11 OUTCOMES AFTER TREATMENT FOR SKIN CARCINOMA WITH CLINICAL PERINEURAL INVASION (109 PATIENTS)

Parameter	5-y Outcome (%)
Local control	54
Ultimate local control	57
Local-regional control	51
Ultimate local-regional control	56
Cause-specific survival	64
Overall survival	54

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Balamucki et al[50] reported on a subset of these patients and compared their outcomes with radiographic extent of PNI and found that the extent of PNI was inversely related to the likelihood of local control and survival (Table 39.12).

TABLE 39.12 CLINICAL PERINEURAL INVASION: 5-YEAR OUTCOME VERSUS PRETREATMENT RADIOGRAPHIC FINDINGS (45 PATIENTS)

	Radiographic Findings			
5-y Outcome	Imaging Negative (*n* = 11)	Minimal or Moderate Peripheral PNI (*n* = 18)	Central and/or Macroscopic PNI (*n* = 36)	*P*
Local control (%)	81	60	47	.2321
Cause-specific survival (%)	100	58	65	.0815
Overall survival (%)	82	50	52	.2637

PNI, perineural invasion.

Reprinted with permission from Balamucki CJ, DeJesus R, Galloway TJ, et al. Impact of radiographic findings on for prognosis skin cancer with perineural invasion. *Am J Clin Oncol*. 2015;38(3):248-251.

Regional Nodes

Veness et al[32] reported on 167 patients treated at Westmead Hospital (Sydney, Australia) between 1980 and 2000 for cutaneous SCCs metastatic to the parotid and/or cervical nodes. Twenty-one (13%) patients were treated with surgery alone, and the remainder received surgery and adjuvant RT. The median time to recurrence after treatment was 8 months. The 5-year local-regional recurrence and disease-free survival rates were as follows: surgery and RT, 20% and 73%, and surgery alone, 43% and 54%, respectively. Multivariate analysis revealed that multiple positive nodes and treatment with surgery alone were significantly associated with decreased survival.

Hinerman et al[33] reported on 117 patients with 121 clinically positive parotids treated at the University of Florida between 1969 and 2005. Patients were treated with preoperative RT and surgery (17 parotids), surgery and postoperative RT (87 parotids), and RT alone (17 parotids). The 5-year outcomes were as follows: local (parotid) control, 78%; local-regional control, 74%; distant metastasis-free survival, 92%; disease-free survival, 70%; and overall survival, 54%. The 5-year local-regional control rate was 83% after surgery and postoperative RT versus 47% after preoperative RT and surgery or RT alone. Three (3%) patients developed severe complications.

Merkel Cell Carcinoma

Mendenhall et al[51] reported on 59 patients treated with either RT alone (five patients) or combined with surgery (54 patients) at the University of Florida between 1984 and 2015. Fourteen patients received adjuvant chemotherapy. Twenty-five patients had AJCC stage I disease, seven patients had AJCC stage II MCC, and 27 patients had AJCC stage III disease. Median follow-up on survivors was 3.2 years (range, 0.3-20.9 years). Median follow-up for survivors was 6.7 years (range, 1.6-20.9 years). No patient was lost to follow-up. The 5-year outcomes are depicted in Table 39.13. No severe late complications were observed.

TABLE 39.13 MERKEL CELL CARCINOMA 5-YEAR OUTCOMES VERSUS STAGE

Outcomes	Stage 1 (*n* = 24)	Stage II (*n* = 16)	All Patients	*P*-value
Local control (%)	96	87	92	.3240
Regional control (%)	87	65	78	.1587
Local-regional control (%)	87	67	79	.1607
Distant metastasis-free survival (%)	71	37	57	.0073
Cause-specific survival (%)	58	27	45	.0090
Overall survival (%)	48	18	36	.0037

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Melanoma

One of the largest experiences with adjuvant RT for melanoma has been reported by investigators from the MD Anderson Cancer Center (Houston, TX; Table 39.14). Although RT may be used to treat gross disease, this would only occur by default and in mostly palliative situations.

TABLE 39.14 OUTCOMES AFTER SURGERY AND POSTOPERATIVE RADIOTHERAPY AT THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER FOR LYMPH NODE–POSITIVE MELANOMA PATIENTS

Series	Number of Patients	Site	Follow-Up[a]	RC[b]	DMFS[b]	Survival[b]
Ballo et al, 2002[59]	89	Axilla	Median, mo 58 (range, 7-159 mo)	87% (5 y)	49% (5 y)	OS, 50% (5 y)
Ballo et al, 2003[60]	160	Cervical	Median, 78 mo (range, 6-224 mo)	94% (10 y)	43% (10 y)	CSS, 48% (10 y)
Ballo et al, 2004[61]	40	Ilioinguinal	Median, mo 23 (range, 4-107 mo)	74% (3 y)	35% (3 y)	OS, 38% (3 y)

CSS, cause-specific survival; DMFS, distant metastasis-free survival; OS, overall survival; RC, regional control.

[a]Follow-up for surviving patients.

[b]Outcome (interval).

From Mendenhall WM, Amdur RJ, Grobmyer SR, et al. Adjuvant radiotherapy for cutaneous melanoma. *Cancer*. 2008;112(6):1189-1196. Copyright © 2008 American Cancer Society. Reprinted by permission of John Wiley & Sons.

Drescher et al[52] recently reported on 131 patients treated with surgery and postoperative RT with either conventional fractionation (29 patients) or hypofractionation (102 patients); most of those treated with hypofractionated RT received the MD Anderson schedule of 30 Gy in five fractions over 2.5 weeks. The 10-year outcomes were as follows: in-field local control, 87%; local-regional control, 72%; distant metastasis-free survival, 48%; cause-specific survival, 44%; and overall survival, 31%. Six patients experienced late toxicity.

Tsang et al[38] reported on 36 patients treated between 1968 and 1988 with definitive RT for lentigo maligna at the Princess Margaret Hospital (Toronto, Canada) and followed for a median of 6 years. The 5-year local control rate was 86%. Farshad et al[40] reported on 150 patients treated at the University of Zurich with definitive RT for lentigo maligna (93 patients), lentigo maligna melanoma (54 patients), or both (three patients). One hundred one patients were followed for at least 2 years (mean, 8 years); the local control rate was 93%.

CONCLUSION

RT is an effective modality for the primary treatment of skin cancer as well as in the adjuvant setting. It is used to treat the primary skin lesion when resection would result in an unacceptable functional and/or cosmetic outcome as well as in the patient who is medically unsuitable for, or who declines, surgery. Adjuvant RT is usually indicated after surgery for close or positive margins, PNI, bone and/or cartilage involvement, metastatic parotid area lymph nodes, multiple lymph node metastases, and extracapsular extension.

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PART B

Central Nervous System

CHAPTER 40

Primary Intracranial Neoplasms

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ANATOMY

The central nervous system (CNS) is enveloped by three meningeal layers: the *dura mater* (also known as the pachymeninges), the *arachnoid mater*, and the *pia mater*. The pia and arachnoid layers are also referred to as the leptomeninges and within them is the subarachnoid space, which is filled with cerebrospinal fluid (CSF). Dural folds separate the two hemispheres of the cerebrum (falx cerebri) and the cerebrum from the cerebellum and brainstem (tentorium or falx cerebelli). The frontal and parietal lobes are separated by a well-defined sulcus ("central sulcus"). The frontal and temporal lobes are separated by the Sylvian fissure, whereas the parietal and occipital lobes are separated by the calcarine sulcus (Figures 40.1-40.3).

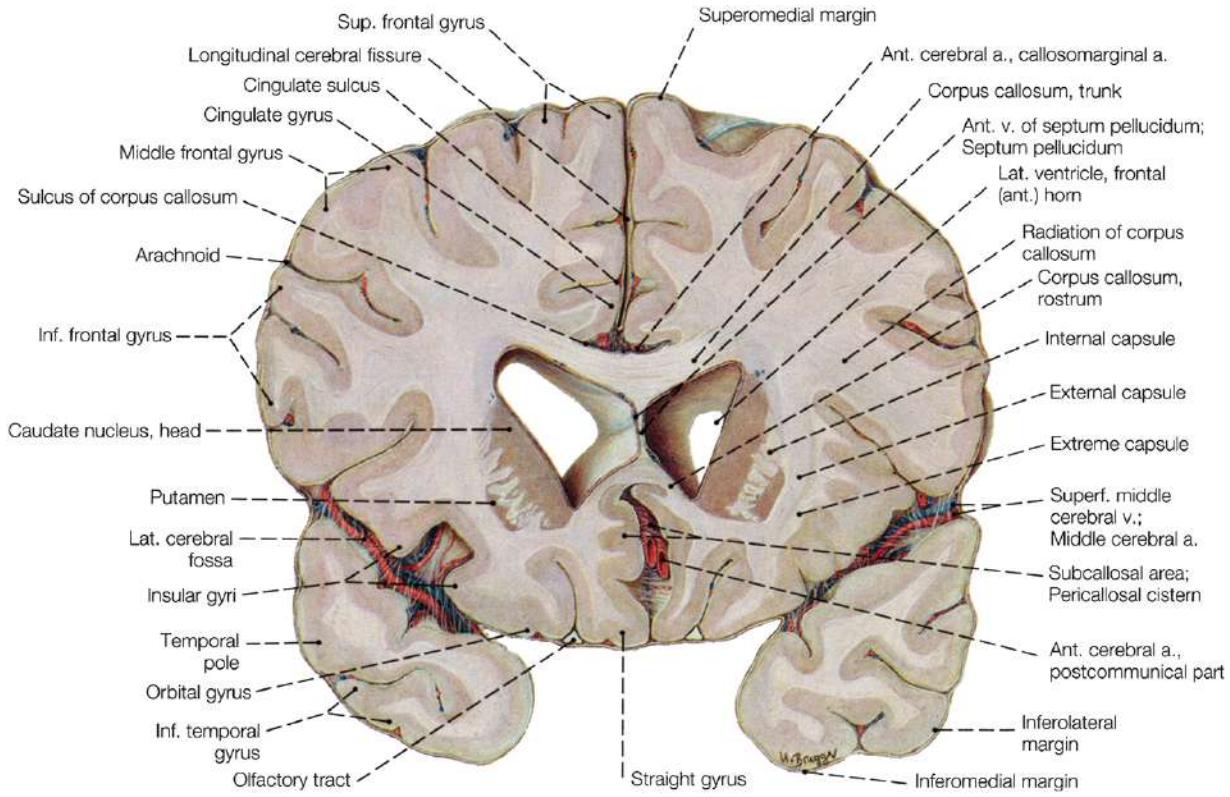

FIGURE 40.1 Coronal section through the telencephalon at the plane of the frontal horn of the lateral ventricle. (Reprinted from Paulsen F, Waschke J. *Sobotta Atlas of Human Anatomy*. 17th ed. Urban & Fischer; 2023, Figure 12.218. Copyright © 2023 Elsevier GmbH Munich. With permission.)

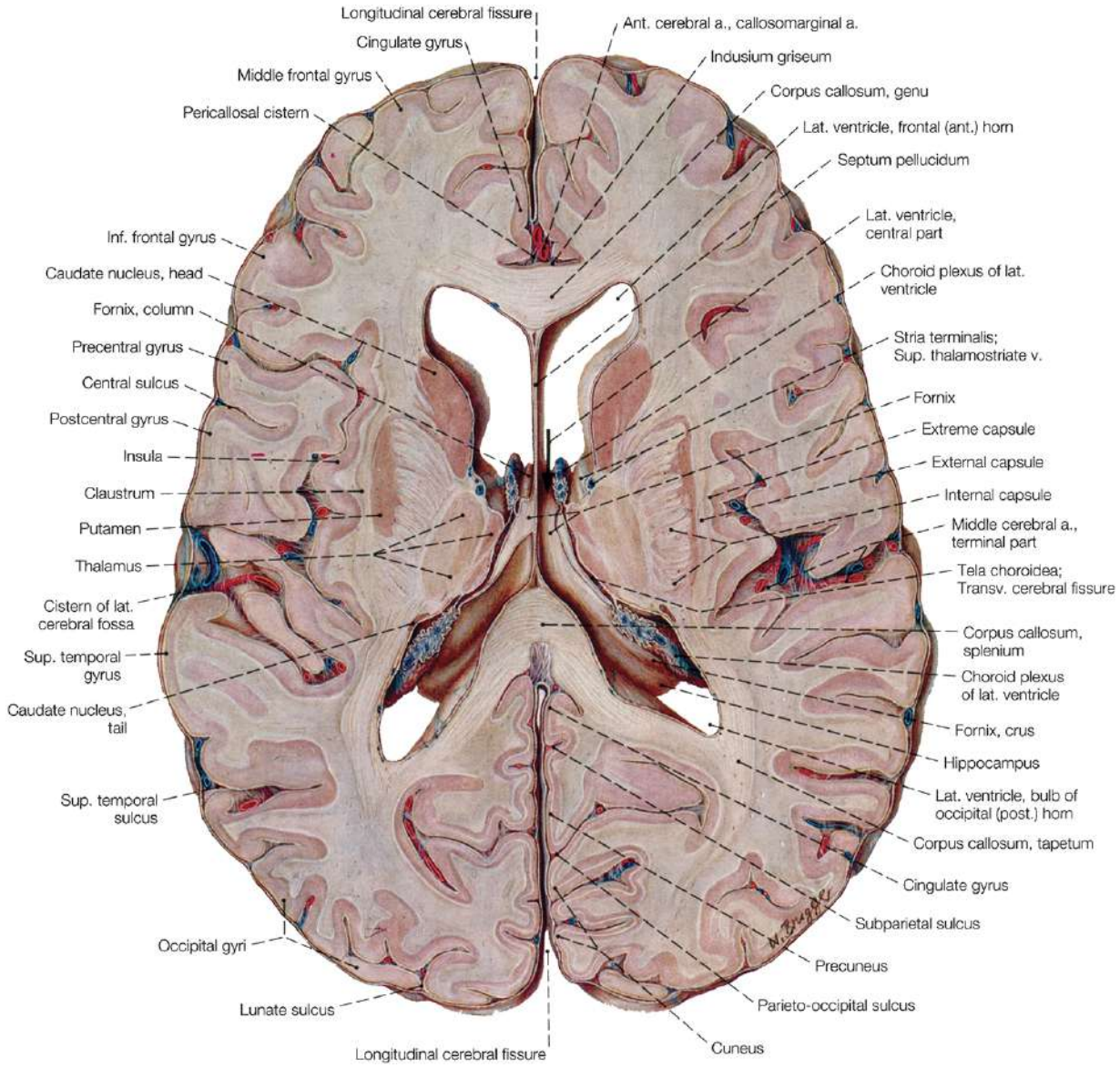

FIGURE 40.2 Transverse section at the level of the floor of the central part of the lateral ventricle. View of the superior surface of the plane of sectioning. (Reprinted from Paulsen F, Waschke J. *Sobotta Atlas of Human Anatomy*. 17th ed. Urban & Fischer; 2023, Figure 12.228. Copyright © 2023 Elsevier GmbH Munich. With permission.)

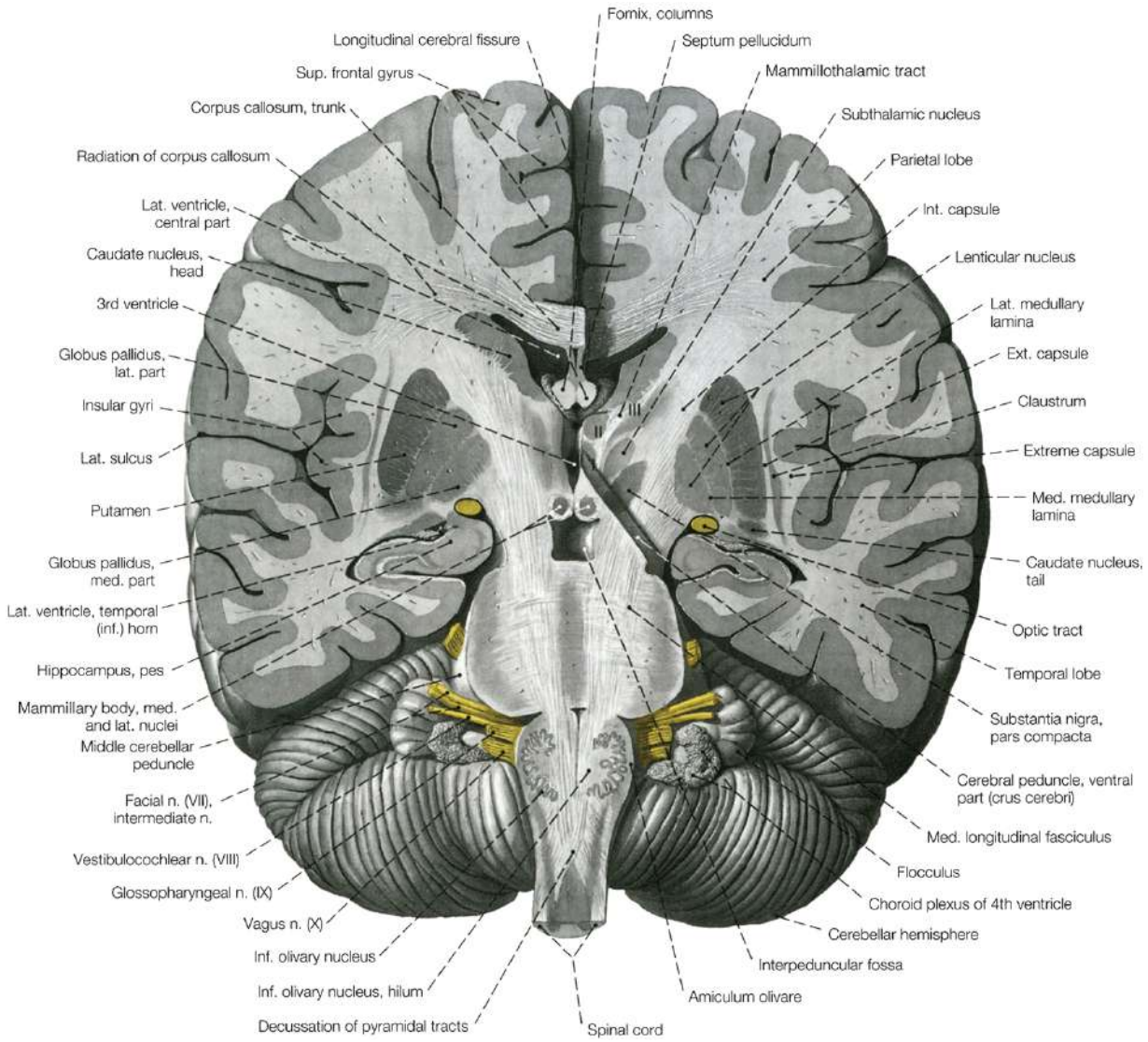

FIGURE 40.3 Section through the telencephalon and brainstem parallel with the cerebral peduncles. View of the posterior surface of the plane of sectioning. On the right side of the figure, the section reaches back to approximately the middle of the cerebral peduncle (oblique section). I to III indicate thalamic nuclei: I, medial nucleus; II, anterior nucleus; III, lateral nucleus. (Reprinted from Paulsen F, Waschke J. *Sobotta Atlas of Human Anatomy*. 17th ed. Urban & Fischer; 2023, Figure 12.194. Copyright © 2023 Elsevier GmbH Munich. With permission.)

The diencephalon consists of the thalamus and the pineal region and is situated between the cerebrum and the mesencephalon, adjacent to the third ventricle. Lateral to the thalamus is the internal capsule, which carries the motor fibers (upper motor neurons) from the cortex en route to the brainstem and spinal cord.

At the tentorial notch, the mesencephalon rides on the upper part of the clivus. Its interior, the tectum, is partially occupied by cranial nerve nuclei (for the oculomotor, trochlear, and proprioceptive portions of the trigeminal nerves). The dorsal plate houses the superior and inferior colliculi, which regulate eye movements and hearing impulses, respectively. The trochlear nerve is the only cranial nerve that exits from this dorsal location.

The pons relays information between the two cerebellar hemispheres and, from the spinal cord to the cerebellum, carries the major ascending and descending pathways between the mesencephalon and the medulla oblongata, and contains the major motor and tactile sensory nuclei for the trigeminal nerve, which emerges from its lateral surface. The border between the pons and the medulla oblongata is noteworthy for the emergence of the abducens, facial, and vestibulocochlear (acoustic) cranial nerves.

The cerebellum develops laterally and posteriorly from the pons and differentiates into the median vermis and the bilateral hemispheres, which are flattened by the sloping tentorium on both sides. Anteriorly, the cerebellum faces the dorsal aspects of the pons and the medulla oblongata (the floor of the fourth ventricle).

The medulla oblongata forms the link between the pons, the spinal cord, and the cerebellum. It houses the majority of the cranial nerve nuclei (abducens, facial, vestibulocochlear, glossopharyngeal, vagal, accessory, and hypoglossal).

CSF is produced by the choroid plexus, which lies in the roofs of the fourth and third ventricles as well as in the medial walls of the central body and inferior horns of the lateral ventricles. The foramina of Monro transmit CSF between the third and lateral ventricles at the superolateral corners of the third ventricle. The aqueduct of Sylvius in the midbrain transmits CSF from the third to the fourth ventricles. It is the narrowest canal of the intracranial nervous system and is, therefore, the most common location of obstruction of flow by compression or tumor deposits, resulting in noncommunicating (obstructive) hydrocephalus. CSF in the fourth ventricle flows out of the ventricular system through the midline foramen of Magendie and the two lateral foramina of Luschka to the subarachnoid space.

CSF resorption back into the venous system occurs at arachnoid (or pacchionian) granulations, special outpouching structures from the arachnoid membrane that enhance fluid movement from the CSF space into the venous sinus system. Scarring from infection or inflammation or clogging of the arachnoid granulations causes increased pressure in the CSF space and communicating hydrocephalus. Recently, the concept of a lymphatic drainage system for the brain has been described (some would say "rediscovered") within the meninges, typically adjacent to dural sinuses.[1] This so-called glial-lymphatic (or "glymphatic") system is thought to provide a mechanism for immunologic cells and macromolecules to traffic between the CNS and the cervical lymph nodes.[2]

EPIDEMIOLOGY

From 2016 to 2020, there were an estimated 450,000 new cases of primary CNS tumors in the United States and 86,000 deaths, for an age-adjusted incidence of approximately 24.83 per 100,000 persons and an average mortality rate of 4.42 per 100,000 persons. The incidence of brain tumors increases with age.[3]

Occupational and environmental exposures have been associated with the development of CNS tumors. Farmers and petrochemical workers have been shown to have a higher incidence of primary brain tumors. A variety of chemical exposures have been linked, as reviewed by Ohgaki and Kleihues.[4] The use of cellular phones has been questioned as a contributing factor to the development of brain tumors. The World Health Organization (WHO) classified radiofrequency electromagnetic fields, such as those emitted by wireless phones, as "possibly carcinogenic to humans" (group 2B) based on limited clinical evidence.[4] Although prior cohort, case-control, and time trend analyses have shown no association between cell phone use and brain tumor risk,[5] subsequent case-control studies have suggested a potential increased risk of glioma, acoustic neuroma, and meningioma among individuals with higher cumulative lifetime cell phone use.[6-12] However, significant concerns with respect to recall and selection biases in most studies prevent a causal association from being concluded.

Prior exposure to ionizing radiation is a known risk factor for the development of primary CNS tumors, particularly meningiomas, but also

gliomas, sarcomas, and other tumor types.[10] There is a 2.3% incidence of primary brain tumors in children treated with prophylactic cranial irradiation for acute leukemia, a 22-fold increase over expected.[13-15]

The development of intracranial malignancy is also associated with several hereditary diseases such as neurofibromatosis types 1 (NF1) and 2 (NF2), von Hippel-Lindau disease, and tuberous sclerosis. Other hereditary associations are with retinoblastoma and Li-Fraumeni syndrome.

NATURAL HISTORY

The natural history of a primary brain neoplasm is determined by its histology, grade, and location. Most adult gliomas spread invasively without forming a natural capsule. They frequently cause edema in surrounding tissue. This edema is usually vasogenic but may be cytotoxic. It is seen best on T2-weighted magnetic resonance imaging (MRI) and is responsible for at least some of the clinical symptoms and signs. The edema is a consequence of altered blood-brain barrier (BBB) permeability. Different tumors cause varying amounts of edema (in descending order, metastases, astrocytomas, meningiomas, and oligodendrogliomas).

Some high-grade neoplasms metastasize by “seeding” the subarachnoid and ventricular spaces. Because of gravity or flow, these metastatic deposits are often present in the caudal portion of the spinal canal. Tumors that have a propensity for CSF spread include medulloblastomas, germ cell tumors, and CNS lymphoma. The exact frequency of CSF spread among other histologies (eg, germ cell tumors, ependymomas) is debated in the literature. Extracranial metastases from primary brain tumors are rare but can occur with medulloblastomas, germinomas, and high-grade astrocytomas.

CLINICAL PRESENTATION

The presenting symptoms of a primary brain tumor are classified as generalized or focal. Headache is more prevalent in patients with fast-growing, high-grade tumors. Seizures are a more common presenting feature in low-grade tumors. Focal neurologic deficits such as weakness, language dysfunction, or sensory loss are more frequent presentations of high-grade tumors. Acute events such as hemorrhage markedly alter the

tempo of symptom onset, regardless of tumor grade. Table 40.1 summarizes common clinical presentations of the more common CNS tumors.

TABLE 40.1 SYMPTOMS, SIGNS, AND DIAGNOSTIC CHARACTERISTICS OF VARIOUS INTRACRANIAL TUMORS

Tumor	Common Symptoms	Common Signs	Imaging Characteristics
Type			
Glioblastoma multiforme	Headache, seizure, unilateral weakness, mental changes	Focal presentation related to tumor location	Enhancing MRI or CT lesion, hypodense interior, often with associated edema
Meningioma	Localized headache	Focal presentation related to tumor location	Enhancing MRI or CT lesion associated with dura
Astrocytoma	Headache, seizure, unilateral weakness, mental changes	Focal presentation related to tumor location	May not enhance on CT or MRI, expansile mass-like T2/FLAIR signal abnormality
Medulloblastoma	Morning headaches, nausea, vomiting	Coordination, increased intracranial pressure (ie, papilledema), abducens and oculomotor nerve deficits	Heterogeneously enhancing on MRI or CT, diffusion restricting on MRI, typical more likely lateral location in adults relative to children
Ependymoma	Morning headaches, nausea, vomiting	Coordination, increased intracranial pressure (ie, papilledema), abducens and oculomotor nerve deficits	Heterogeneous enhancement on MRI or CT with or without calcification
Neurilemoma, schwannoma, neurinomas	Unilateral deafness, vertigo	Ipsilateral acoustic and facial or trigeminal nerve deficits	Homogeneous enhancing mass on MRI or CT, arising from cranial nerve

Tumor	Common Symptoms	Common Signs	Imaging Characteristics
Oligodendroglioma	Insidious headache, mental changes	Focal presentation related to tumor location	Expansile mass-like T2/FLAIR signal abnormality Heterogeneous lesion that may or may not enhance on MRI or CT, frequently with calcification, cystic regions, or hemorrhage
Lymphoma	Focal presentation related to tumor location	Focal presentation related to tumor location	Homogeneous, intense enhancement on MRI, may have a diffuse or “cotton-wool” appearance
Craniopharyngioma	Headache, mental changes, hemiplegia, seizure, vomiting, visual impairment	Cranial nerve deficits (II-VII), endocrine deficits)	Mixed cystic, calcified lesion on MRI and CT, arising from suprasellar region
Location			
Cerebral	Headache, seizure, unilateral weakness, mental changes	Focal presentation related to tumor location	
Cerebellar	Occipital headache	Increased intracranial pressure (ie, papilledema), abducens and oculomotor nerve deficits; coordination	
Brainstem or thalamus	Nausea, vomiting, ataxia	Increased intracranial pressure (ie, papilledema), abducens and	May be seen only on MRI

Tumor	Common Symptoms	Common Signs	Imaging Characteristics
		oculomotor nerve deficits; ataxia	
Optic nerve	Vision loss	Visual field deficit	Uniform enhancement on MRI or CT scan

CT, computed tomography; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.

Because brain parenchyma is anesthetic, headaches associated with brain tumors are due to increased intracranial pressure or to local pressure on sensitive intracranial structures (mainly dura and vessels). Headaches associated with increased intracranial pressure classically occur in the morning. Associated findings may include focal neurologic deficits, behavioral changes, and papilledema. Cushing triad is classically associated with increased intracranial pressure, but the full triad (hypertension, bradycardia, respiratory irregularity) is seen in only one-third of the cases of increased intracranial pressure. Long-standing increases in intracranial pressure may lead to optic atrophy and blindness because of transmission of the pressure to the optic nerves.

DIAGNOSTIC WORKUP

The initial workup of patients with brain tumors must include a complete history and physical examination. Information obtained from relatives and friends is helpful because many tumors cause changes in mentation not appreciated by the patient. In patients with symptoms, signs, or imaging suggestive of systemic dissemination, biopsy confirmation of the primary tumor or at least one of the extracranial metastatic sites is recommended. Solitary brain lesions in adult patients with certain types of known systemic cancer (eg, lung, breast, or colon cancers or melanoma) are far more likely to be a cerebral metastasis than a primary CNS tumor, although this is not always the case.

Imaging Studies

MRI with a gadolinium (Gd)-containing contrast agent is the imaging modality of choice for most CNS tumors. Computed tomography (CT) is generally reserved for those situations in which MRI is contraindicated, such as implanted pacemaker, metal fragment, or paramagnetic surgical clips, or where there is a need to image the extent of calcification or hemorrhage. Classically, the role of positron emission tomography (PET) imaging has been limited by the high baseline uptake of [^{18}F]fludeoxyglucose (^{18}F-FDG) by normal brain, but the advent of novel PET imaging agents is beginning to increase the utilization of this modality, especially ^{18}F-DOTATATE imaging for meningioma.

Magnetic Resonance Imaging

The most useful imaging studies are T1-weighted sagittal images, Gd-enhanced (usually obtained in high-resolution modes such as spoiled gradient recalled echo or Magnetization Prepared – RApid Gradient Echo) and nonenhanced T1 axial images, T2-weighted axial images, and FLAIR (fluid-attenuated inversion recovery) sequences.[16] As is the case with CT contrast agents, Gd-based contrast leaks into parenchyma in areas with BBB breakdown, and the paramagnetic properties of Gd generate hyperintense signal on T1 scans. T1 images are usually better at demonstrating anatomy and areas of contrast enhancement (CE). T2 and FLAIR images are more sensitive for detecting edema and infiltrative tumor. Tumor appearance on T1-weighted MRI is similar to that on CT, although tumor volumes are better delineated on MRI, particularly with low-grade neoplasms that do not demonstrate CE (Figure 40.4). Diffusion-weighted and functional MR also has utility in guiding resection. With the increasing incidence of post-treatment "pseudoprogression," additional specialized diffusion, perfusion, and spectroscopic sequences are being increasingly utilized to distinguish tumor from necrosis or pseudoprogression, and PET imaging may also have some role in this; in the United States, only FDG-PET is approved, but amino acid (FET), FLT, and F-DOPA PET imaging is being evaluated (Figure 40.5).[17] For meningiomas and other CNS tumors harboring somatostatin receptors (SSTRs), SSTR-PET imaging with ligands such as ^{68}Ga-DOTATATE or ^{68}Ga- DOTANOC can be useful to identify tumor margins, particularly in

the skull base where there are other anatomic structures that enhance with MRI-based contrast agents, thereby creating uncertainty as to whether the signal seen on MRI is tumor versus a normally enhancing structure.

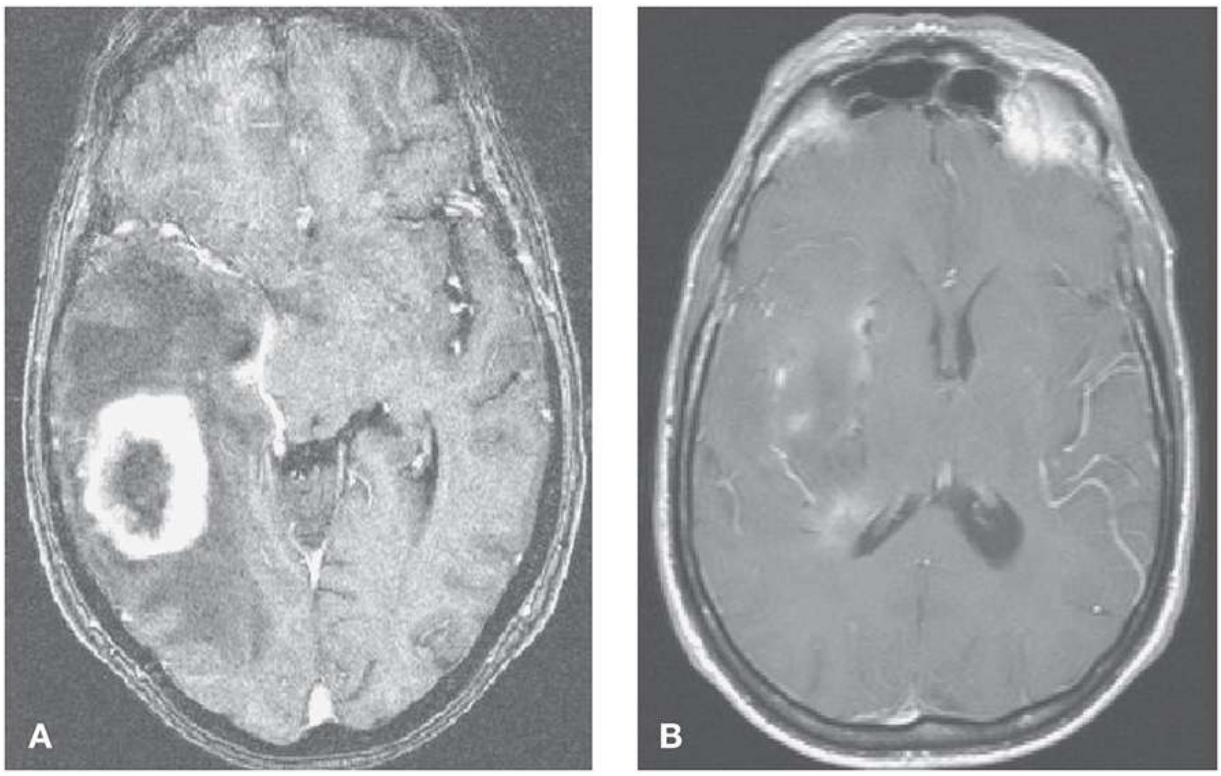

FIGURE 40.4 Magnetic resonance image of the brain showing glioblastoma (A), demonstrating a contrast- enhancing lesion with central necrosis and vasogenic edema, and low-grade glioma (B), illustrating a nonenhancing lesion difficult to delineate from normal parenchyma.

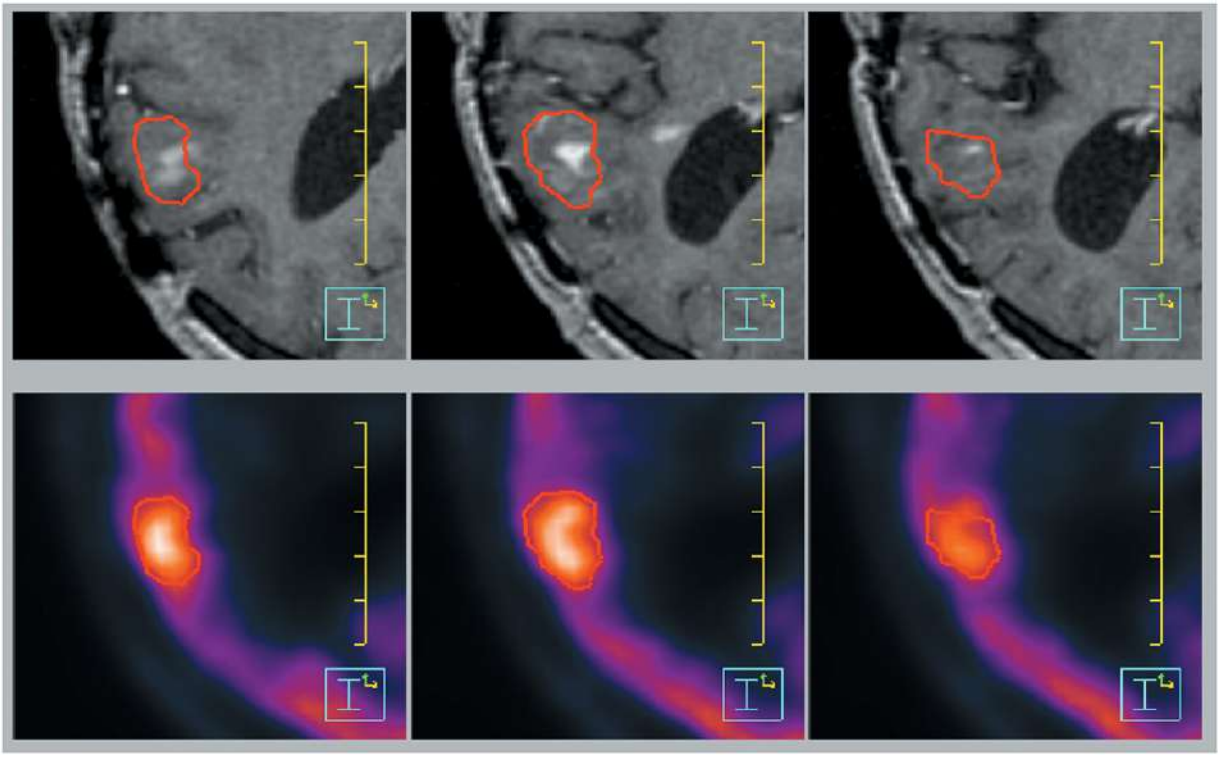

FIGURE 40.5 Oligodendroglioma images using an anatomic imaging technique, contrast-enhanced three-dimensional spoiled gradient recalled echo T1-weighted magnetic resonance image (top row), and a functional imaging technique, fludeoxyglucose positron emission tomography (bottom row). The red contour delineates the extent of increased metabolic activity seen using functional imaging. Looking at the top panel, one can appreciate the fact that if the anatomic image set alone would be used for target definition, it would yield a gross underestimation of the target volume as compared with the functional imaging technique.

Neuraxis Imaging

For neoplasms with a high risk of CSF spread, staging of the neuraxis is essential. Gd-enhanced MRI of the spine is the imaging modality of choice. Ideally, neuraxis imaging should be performed before surgery. In the immediate postoperative period, spinal MRI scans may be difficult to interpret because arachnoiditis and blood products in the CSF can mimic leptomeningeal metastasis. Delayed spinal MRI (>2 weeks after surgery), combined with an increased dose of intravenous (IV) Gd, is a sensitive imaging study to detect leptomeningeal disease.

Histologic Confirmation of Diagnosis

The morbidity of biopsy has decreased significantly with improvements in operative technique and anesthesia, as well as the availability of stereotactic biopsy techniques. Exception might be made in selected patients, such as those patients with known active systemic cancer and multiple lesions that are radiographically consistent with brain metastases, patients with typical clinical and MRI findings of a brainstem glioma or optic nerve meningioma, patients who are human immunodeficiency virus (HIV)-positive with CT or MRI findings consistent with primary CNS lymphoma (PCNSL) and positive Epstein-Barr virus polymerase chain reaction (PCR) in the CSF, or patients with secretory germ cell tumors.

Cerebrospinal Fluid Cytology

CSF cytology is essential for staging tumors with a propensity for CSF spread (eg, medulloblastoma, germ cell tumors, and CNS lymphoma). Sampling of the CSF in the immediate postoperative period may lead to false-positive results, however, and is best done before surgery or more than 2 weeks after surgery, as long as intracranial pressure is not elevated. CSF spread of tumor may be associated with several abnormal CSF findings. These include CSF pressure above 150 mm H_2O at the lumbar level in a laterally positioned patient, elevated protein level (>40 mg/dL in the lumbar cistern), a reduced glucose level (<50 mg/mL), and the finding of tumor cells by cytologic examination. Tumor markers in the CSF may help in making the diagnosis. Emerging assays are being developed and utilized to perform CSF-based cell-free DNA testing as a means of improving the sensitivity of CSF tumor evaluation, as well as providing the assessment of targetable mutations.

Differential Diagnosis

Most adults with new or persistent neurologic findings (focal deficit, increased intracranial pressure, seizures, altered mentation) are investigated using CT or MRI. There are many classical imaging features that help refine the differential diagnosis (Table 40.2).

TABLE 40.2 DIFFERENTIAL DIAGNOSIS OF SPACE-OCCUPYING LESIONS ON COMPUTED TOMOGRAPHY OR MAGNETIC RESONANCE IMAGING

Pathology	Features on CT or MRI
Neoplasm	
Primary	Solitary, no prior cancer, thick nodular CE
Metastatic	Multiple, prior cancer, ++edema, located at gray/white junction
Infectious	
Abscess	Fever, acutely ill, ±systemic infection, cyst cavity with smooth thin walls, CE, and restricted diffusion within cavity
Cerebritis	Fever, acutely ill, ±systemic infection, diffuse T2 change, no CE mass
Meningitis	Diffuse enhancement of meninges on T1-weighted imaging (may simulate leptomeningeal metastases)
Vascular	
Infarct	Gray and white matter involvement, wedge-like vascular distribution associated with restricted diffusion and low ADC signal
Bleeding	Homogeneous, clears quickly, residual hemosiderin ring
Treatment-related necrosis	Central hypodensity, ring CE, edema, >6 mo after radiation therapy or chemotherapy, metabolic scan shows low activity.

ADC, apparent diffusion coefficient; CE, contrast enhancement; CT, computed tomography; MRI, magnetic resonance imaging.

PATHOLOGY

Primary intracranial tumors are of ectodermal and mesodermal origin and arise from the brain, cranial nerves, meninges, pituitary, pineal, and vascular elements. In 2021, the WHO revised its classification system for pathologic subtypes of CNS tumors to combine histology with molecular parameters such as isocitrate dehydrogenase 1 (*IDH1*) mutation, 1p19q codeletion, and H3 K27M mutation for gliomas; RELA fusion for ependymoma; and WNT and sonic hedgehog (SHH) activation for medulloblastoma (Table 40.3).[18] DNA methylation provides a consistent biomarker and indicates the specific tumor cell type from which the tumor cell originates. Machine learning techniques employed to analyze DNA methylation have enabled classification of brain tumors that pose diagnostic challenges due to unusual histopathology or diverse molecular genetic profiles.[19] Guidelines for assigning the grade of malignancy are provided, where applicable.

TABLE 40.3 2021 WHO HISTOLOGIC CLASSIFICATION OF TUMORS OF THE CENTRAL NERVOUS SYSTEM

Gliomas, glioneuronal tumors, and neuronal tumors
Adult-type diffuse gliomas
Astrocytoma, IDH mutant
Oligodendroglioma, IDH mutant, and 1p/19q codeleted
Glioblastoma, IDH wild type
Pediatric-type diffuse low-grade gliomas
Diffuse astrocytoma, *MYB* or *MYBL1* altered
Angiocentric glioma
Polymorphous low-grade neuroepithelial tumor of the young
Diffuse low-grade glioma, MAPK pathway altered
Pediatric-type diffuse high-grade gliomas
Diffuse midline glioma, H3 K27 altered
Diffuse hemispheric glioma, H3 G34 mutant
Diffuse pediatric-type high-grade glioma, H3 wild type and IDH wild type
Infant-type hemispheric glioma
Circumscribed astrocytic gliomas
Pilocytic astrocytoma
High-grade astrocytoma with piloid features
Pleomorphic xanthoastrocytoma
Subependymal giant cell astrocytoma
Chordoid glioma
Astroblastoma, *MN1* altered
Glioneuronal and neuronal tumors
Ganglioglioma
Desmoplastic infantile ganglioglioma/desmoplastic infantile astrocytoma
Dysembryoplastic neuroepithelial tumor
Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters[a]
Papillary glioneuronal tumor
Rosette-forming glioneuronal tumor
Myxoid glioneuronal tumor
Diffuse leptomeningeal glioneuronal tumor
Gangliocytoma
Multinodular and vacuolating neuronal tumor
Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)
Central neurocytoma
Extraventricular neurocytoma
Cerebellar liponeurocytoma
Ependymal tumors
Supratentorial ependymoma
Supratentorial ependymoma, *ZFTA* fusion positive
Supratentorial ependymoma, *YAP1* fusion positive
Posterior fossa ependymoma
Posterior fossa ependymoma, group PFA
Posterior fossa ependymoma, group PFB
Spinal ependymoma

Spinal ependymoma, *MYCN* amplified
Myxopapillary ependymoma
Subependymoma
Choroid plexus tumors
Choroid plexus papilloma
Atypical choroid plexus papilloma
Choroid plexus carcinoma
Embryonal tumors
Medulloblastoma
Medulloblastomas, molecularly defined
Medulloblastoma, WNT activated
Medulloblastoma, SHH activated and *TP53* wild type
Medulloblastoma, SHH activated and *TP53* mutant
Medulloblastoma, non-WNT/non-SHH
Medulloblastomas, histologically defined
Other CNS embryonal tumors
Atypical teratoid/rhabdoid tumor
Cribriform neuroepithelial tumor[a]
Embryonal tumor with multilayered rosettes
CNS neuroblastoma, *FOXR2* activated
CNS tumor with *BCOR* internal tandem duplication
CNS embryonal tumor
Pineal tumors
Pineocytoma
Pineal parenchymal tumor of intermediate differentiation
Pineoblastoma
Papillary tumor of the pineal region
Desmoplastic myxoid tumor of the pineal region, *SMARCB1* mutant
Cranial and paraspinal nerve tumors
Schwannoma
Neurofibroma
Perineurioma
Hybrid nerve sheath tumor
Malignant melanotic nerve sheath tumor
Malignant peripheral nerve sheath tumor
Paraganglioma
Meningiomas
Meningioma
Mesenchymal, nonmeningothelial tumors
Soft tissue tumors
Fibroblastic and myofibroblastic tumors
Solitary fibrous tumor
Vascular tumors
Hemangiomas and vascular malformations
Hemangioblastoma
Skeletal muscle tumors
Rhabdomyosarcoma

Uncertain differentiation
Intracranial mesenchymal tumor, *FET-CREB* fusion positive[a]
CIC-rearranged sarcoma
Primary intracranial sarcoma, *DICER1* mutant
Ewing sarcoma
Chondro-osseous tumors
Chondrogenic tumors
Mesenchymal chondrosarcoma
Chondrosarcoma
Notochordal tumors
Chordoma (including poorly differentiated chordoma)
Melanocytic tumors
Diffuse meningeal melanocytic neoplasms
Meningeal melanocytosis and meningeal melanomatosis
Circumscribed meningeal melanocytic neoplasms
Meningeal melanocytoma and meningeal melanoma
Hematolymphoid tumors
Lymphomas
CNS lymphomas
Primary diffuse large B-cell lymphoma of the CNS
Immunodeficiency-associated CNS lymphoma
Lymphomatoid granulomatosis
Intravascular large B-cell lymphoma
Miscellaneous rare lymphomas in the CNS
MALT lymphoma of the dura
Other low-grade B-cell lymphomas of the CNS
Anaplastic large cell lymphoma (*ALK*+/*ALK*−)
T-cell and NK/T-cell lymphomas
Histiocytic tumors
Erdheim-Chester disease
Rosai-Dorfman disease
Juvenile xanthogranuloma
Langerhans cell histiocytosis
Histiocytic sarcoma
Germ cell tumors
Mature teratoma
Immature teratoma
Teratoma with somatic-type malignancy
Germinoma
Embryonal carcinoma
Yolk sac tumor
Choriocarcinoma
Mixed germ cell tumor
Tumors of the sellar region
Adamantinomatous craniopharyngioma
Papillary craniopharyngioma
Pituicytoma, granular cell tumor of the sellar region, and spindle cell oncocytoma

Pituitary adenoma/PitNET
Pituitary blastoma
Metastases to the CNS
Metastases to the brain and spinal cord parenchyma
Metastases to the meninges

CNS, central nervous system; IDH, isocitrate dehydrogenase; NK, natural killer; PitNET, pituitary neuroendocrine tumor; SHH, sonic hedgehog; WHO, World Health Organization.

[a]Provisional entries, that is, the WHO Working Group felt there was insufficient evidence to recognize these as distinct entities at this time.

From Louis DN, Perry A, Wesseling P, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. *Neuro Oncol*. 2021;23(8):1231-1251. Reproduced by permission of Society for Neuro-Oncology.

GENERAL MANAGEMENT

The medical management of patients with brain tumors includes the management of increased intracranial pressure, seizures, and venous thromboembolic disease.

Cerebral Edema

Glucocorticoids are used to control neurologic signs and symptoms caused by cerebral edema. Lower doses of steroids (eg, 2-4 mg dexamethasone) twice daily (BID) have been shown to be as effective as higher doses, and in fact, based on pharmacokinetic (PK) properties, even once-daily (QD) dosing should be effective. Prolonged steroid use is associated with multiple medical problems; therefore, steroids should be discontinued or tapered to the lowest dose necessary, as soon as possible. Dexamethasone is the most common corticosteroid used for historical reasons and because of minimal mineral-corticoid effects. As with all corticosteroids, a taper is necessary to prevent a rebound in cerebral edema and also to allow the pituitary-adrenal axis to recover. As a means of avoiding or minimizing steroid usage, low-dose bevacizumab and *Boswellia* have also been utilized.[20,21]

Seizures

Patients with seizures require anticonvulsants. Because anticonvulsants such as carbamazepine, phenobarbital, and phenytoin induce hepatic

cytochrome P-450 isoenzymes, which increase the metabolism and clearance of several cancer chemotherapy agents such as paclitaxel and irinotecan,[22] non–enzyme-inducing anticonvulsants, such as levetiracetam, lacosamide, lamotrigine, and pregabalin, are preferred.

Prophylactic anticonvulsant use (in patients who have never experienced a seizure) remains controversial, although practice guidelines from the American Academy of Neurology recommend against their use because of the lack of data.[23]

SURGERY

Surgical procedures can be summarized as biopsy for diagnosis only, resection for cure, surgical debulking for the management of mass effect–related symptoms, CSF diversion procedures to relieve acute symptoms caused by increased intracranial pressure or hydrocephalus, and increasingly reresection to distinguish and manage the effects of progressive tumor from symptomatic necrosis or pseudoprogression. Other roles of surgery include the placement of chemotherapy wafers, brachytherapy devices, and catheters for interstitial drug delivery and for monitoring tumor drug concentrations and/or biologic effects and the procurement of tissue for further therapeutic selection. Complete resection of tumor is associated with a survival advantage for some tumor types.[24] However, for some radiosensitive and/or chemosensitive malignancies such as PCNSL, aggressive resection is unnecessary, and the surgeon's role is limited to providing diagnostic material.

Operative Technique

Ultrasound and CT- and MRI-guidance systems provide surgeons with intraoperative navigation based upon preoperative and/or intraoperative data. In general, these consist of a workstation into which the relevant imaging studies have been loaded, together with infrared or ultrasound detectors that recognize the three-dimensional (3D) orientation and position in space of various tools. Once the patient is registered, the tumor's margins are "visualized" below the scalp so that the surgeon can plan the smallest and safest approach. Resection may be assisted by the use of an intraoperative microscope and guided by the appearance and consistency of

tumor tissue compared with surrounding normal brain. Intraoperative CT, MRI, or ultrasonography can be used to evaluate the completeness of tumor resection. In the case of lesions that are in or near suspected functional cortex, cortical mapping under awake conditions can be performed to localize areas that are critical for motor or speech function. Preoperative functional imaging with functional MRI, diffusion-weighted MRI-based tractography, and/or navigated transcranial motor stimulation are sometimes used as well to localize functional cortex and white matter pathways. Endoscopy can be used to minimize access for resection of intraventricular lesions or pituitary tumors, as well as for reestablishing pathways of CSF flow, for example, in cases of tumors that have obstructed the cerebral aqueduct, thereby avoiding the need for a CSF shunt. In addition to intraoperative image guidance, the use of fluorescent tumor-localizing dyes such as 5-aminolevulinic acid (5-ALA) is approved in both the United States and Europe to enhance the completeness of resection.

Stereotactic biopsy is performed via either frameless or stereotactic frame–based approaches; a CT or MRI is performed, and the data are loaded into an image-guidance system. A target and entry points are selected, and the trajectory is visualized on a workstation. The entry point is located on the patient's scalp, and a small burr hole or twist drill hole is made. The biopsy needle is oriented using the image-guidance system and passed to the appropriate depth, and tissue samples are obtained. Multiple tissue samples may be obtained along the needle tract until the pathologist can provide an intraoperative diagnosis. The volume of tissue removed is insufficient to relieve mass effect, and patients who are symptomatic are better treated by open resection.

A more recently developed stereotactic technique for treating the mass component of brain tumors involves the use of laser interstitial thermal therapy (LITT). Briefly, this approach involves the temporary stereotactic implantation of a cooled laser probe, which can be activated and manipulated within the MRI environment. The laser is used to heat, but not coagulate, adjacent tissue, and it is progressively advanced through the target tissue as the treatment progresses. This approach takes advantage of a previously described relationship between temperature and time, which can be used to predict the likelihood of permanent injury even with relatively small (<10 °C) increases in local tissue temperature. A specialized MRI

technique, called MR thermometry, is used to monitor tissue temperature, and the combination of temperature data with duration of heating is used by the specialized LITT software to create a visual indication on each MRI slice of the probability of tissue death as a result of treatment. LITT for brain tumors was developed initially for the treatment of malignant tumors that would be difficult to access via conventional surgery, and its practice has expanded to include resectable and even benign pathologies. Although the LITT procedure has shown an encouraging safety profile, there have not been any randomized studies to date that have directly compared this approach to conventional surgical treatment.[25]

RADIOTHERAPY

Radiobiologic Considerations Underlying Tissue Injury

The process of radiation injury in the brain is highly complex and dependent on a variety of technical factors including dose, volume, fraction size, and the specific target cell population, as well as secondary mechanisms of expression of injury such as vascular leak causing edema, vascular endothelial loss resulting in hypoxic injury, reactive gliosis, and to date inadequately studied host factors. Some structures (eg, optic chiasm, hypothalamus, lacrimal gland, lenses) appear to be substantially more sensitive to radiation than others. Even focal lesions may result in widespread radiographic and/or functional perturbations. The time course for the manifestation of injury can be highly variable, and the clinical picture is easily confounded with tumor progression. The effect on endothelial cells often becomes manifest as an early T2 signal abnormality on MRI, possibly due to disruption of the BBB and edema formation. Metabolic perturbations observed with PET may reflect oligodendroglial demyelination. Further vascular perturbation and regeneration in response to injury results in an enhancing lesion on imaging. Delayed effects include white matter necrosis and vascular obliteration. The time course can be shortened from several months to a few weeks by increasing the volume of brain irradiated or by increasing the fraction size or total dose.

Historically, late injury from radiotherapy (RT) has been reported as the “tolerance” dose (TD) at either the 5% or 50% risk level at 5 years (TD 5/5 or TD 50/5, respectively). These values for whole-brain fractionated RT at 2

Gy/fraction are 60 and 70 Gy, respectively. With partial-brain irradiation, the corresponding values are 70 and 80 Gy. In the setting of partial-brain fractionated RT with a fraction size less than 2.5 Gy, quantitative analyses of normal tissues effect in the clinic (QUANTEC) have estimated 5% and 10% rates of symptomatic necrosis at 72 and 90 Gy maximum equivalent doses in 2-Gy fractions, respectively.[26]

Treatment Setup

The head should be positioned so that its major axes are parallel with and perpendicular to the central axis incident beam and the treatment table. It may be preferable to fully flex or extend the neck in some patients depending on tumor location and choice of beams, although the use of noncoplanar fields and intensity-modulated radiation therapy (IMRT) techniques makes this less necessary (Figure 40.6).

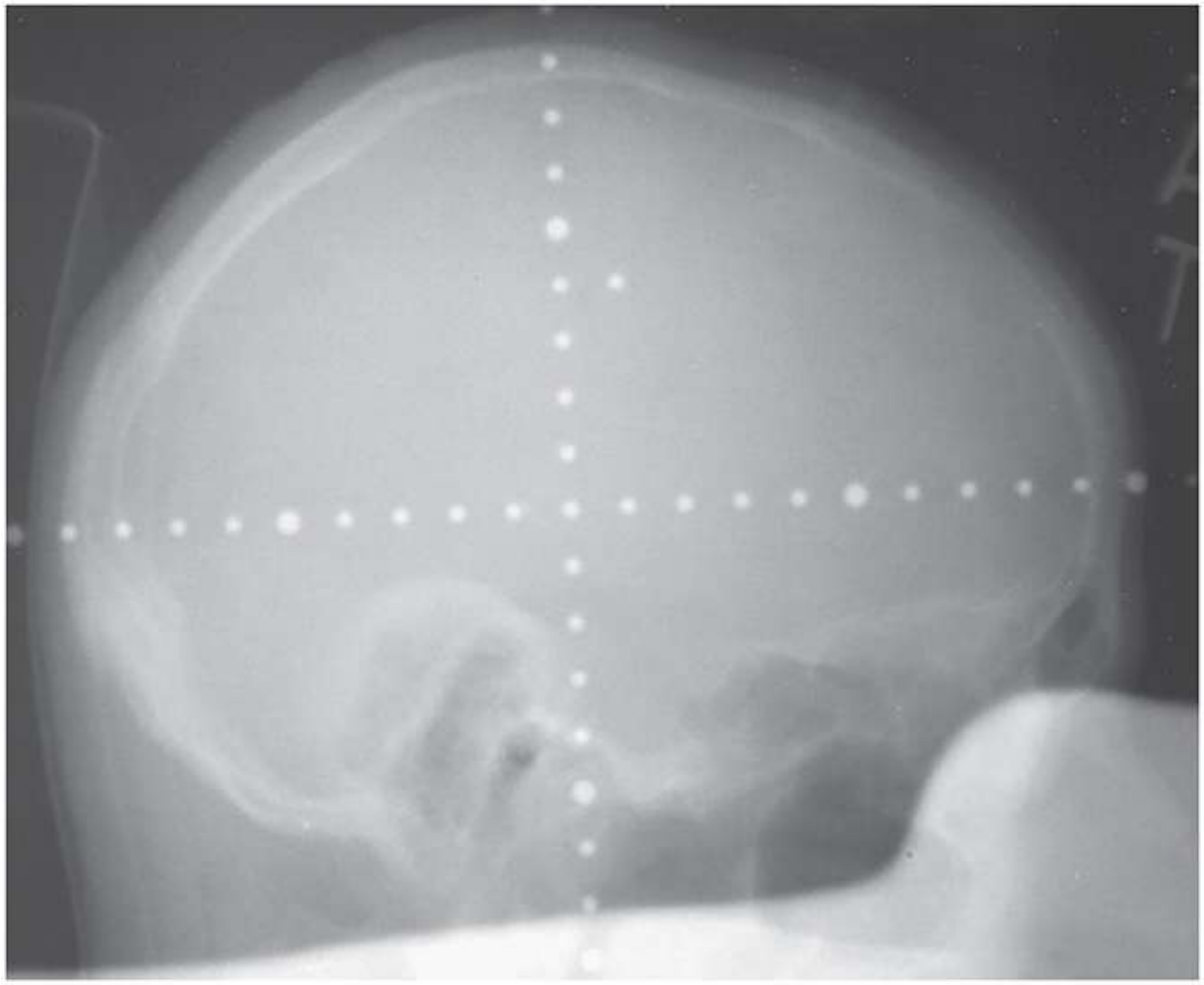

FIGURE 40.6 Lateral portal localization film of whole brain illustrating adequate inclusion of the cribriform plate and the anterior and middle cranial fossae.

Reproducibility of head positioning is achieved using a fixation/immobilization device. Many devices are available for this with reproducibility precision ranging from 1 to 5 mm. Image-guided RT can improve accuracy in delivering RT and reduce margins for setup variability.

Target Volume Definition

Two major factors drive margin selection: the inaccuracy of estimating the clinical target volume (CTV) and the specific dosimetric and setup variability components that are institution specific and determine the planning target volume (PTV).

Common sense and practice dictate that these CTV expansion margins should not traverse anatomically discontiguous structures or include areas unlikely to be infiltrated by tumor. Inclusion of the bony skull is unnecessary unless direct tumor extension is suspected. With some exceptions, "compartmental crossing" to the contralateral hemisphere or, for example, into the posterior fossa or the brainstem for a supratentorial cortical tumor is not necessary, but because many infiltrating gliomas "cross" through the anterior and/or posterior corpus callosal tracts, these should be adequately included in CTV margin selection.

Radiotherapy Techniques

The most commonly employed RT techniques in the management of CNS tumors are partial-brain irradiation, whole-brain radiotherapy (WBRT), craniospinal irradiation (CSI), stereotactic radiosurgery (SRS), fractionated SRS, brachytherapy, and proton therapy. The indications for each of these techniques are discussed under the sections on the individual tumor types. CSI is more frequently used in the management of pediatric CNS tumors and is discussed in detail in Chapters 90.

Whole-Brain Radiotherapy

WBRT is used most often for patients with brain metastases but also for patients with PCNSLs and as a component of CSI.

Conventional WBRT is administered through parallel- opposed lateral portals. The inferior field border should be inferior to the cribriform plate, the middle cranial fossa, and the foramen magnum, all of which should be distinguishable on simulation or portal localization radiographs. When in doubt about tumor coverage or lens sparing for tumors in a subfrontal or middle cranial fossa location, CT-based contouring and planning should be considered. CT-based planning is now the most common approach in the United States, and this allows individualization of beam/machine parameters to ensure adequate coverage.

Incorporation of hippocampal avoidance during WBRT (HA-WBRT) for brain metastases has demonstrated a significant reduction in cognitive toxicity.[27] HA-WBRT requires a thin-slice volumetric postcontrast MRI sequence fused to the treatment planning CT scan. The hippocampal dentate

gyrus should be contoured, and a 5-mm volumetric margin should be generated around the hippocampus to create the HA region.

Craniospinal Irradiation

Traditional CSI techniques utilize opposed lateral cranial fields and one or more posterior spinal fields depending on patient size. The junctioning of noncoplanar fields in the cervical region is potentially hazardous because of the risk of overlap resulting in radiation myelitis. Consequently, great attention needs to be paid to precise immobilization, and a variety of immobilization devices are available for this purpose. Image guidance during RT can help in ensuring day-to-day reproducibility. The prone position permits direct visualization of the light field from the linear accelerator on the patient, thereby allowing daily adjustments of the junctions. However, if anesthesia or sedation is required as may be the case with young children, a supine setup may be considered safer.[28] To avoid the risk of dose overlap, at least two techniques (with numerous variations) are commonly used, and several variations of these have also been reported. In the first, a gap is employed between abutting fields such that the beam edges intersect deep into the spinal cord. This gap could result in a cold spot in a small segment of the spinal cord. If the beam intersection point were raised dorsally, a hot spot would result.

The second technique attempts to avoid this problem using a half-beam technique in which the caudal edge of the brain is matched precisely with the cephalad edge of the abutting spine field without cold or hot spots. This requires collimator angulation and sometimes a couch rotation as well. For both techniques, the use of moving junctions (known as “feathering”) smoothens out any dose inhomogeneity.[29] Several studies have demonstrated that adequate coverage of the subfrontal region and posterior fossa and depth assessment of the cord require CT-based planning. Given the complexity of CSI, we recommend that it be delivered at centers with adequate staff, experience, and expertise.

With sophisticated techniques such as image-guided intensity-modulated helical tomotherapy, volumetric modulated radiotherapy, and intensity-modulated proton therapy (IMPT), it is possible to treat the entire neuraxis in a single setup.[30] Increasingly, proton therapy has been used for CSI with

placement of the finite distal range in the vertebral body, leading to negligent "exit" dose in visceral structures anterior to the spine and maximal sparing of vertebral body–based marrow (Figure 40.7). The recent publication of a randomized phase 2 trial demonstrating a survival advantage with IMPT CSI for leptomeningeal carcinomatosis has increased the utilization of this approach.[31]

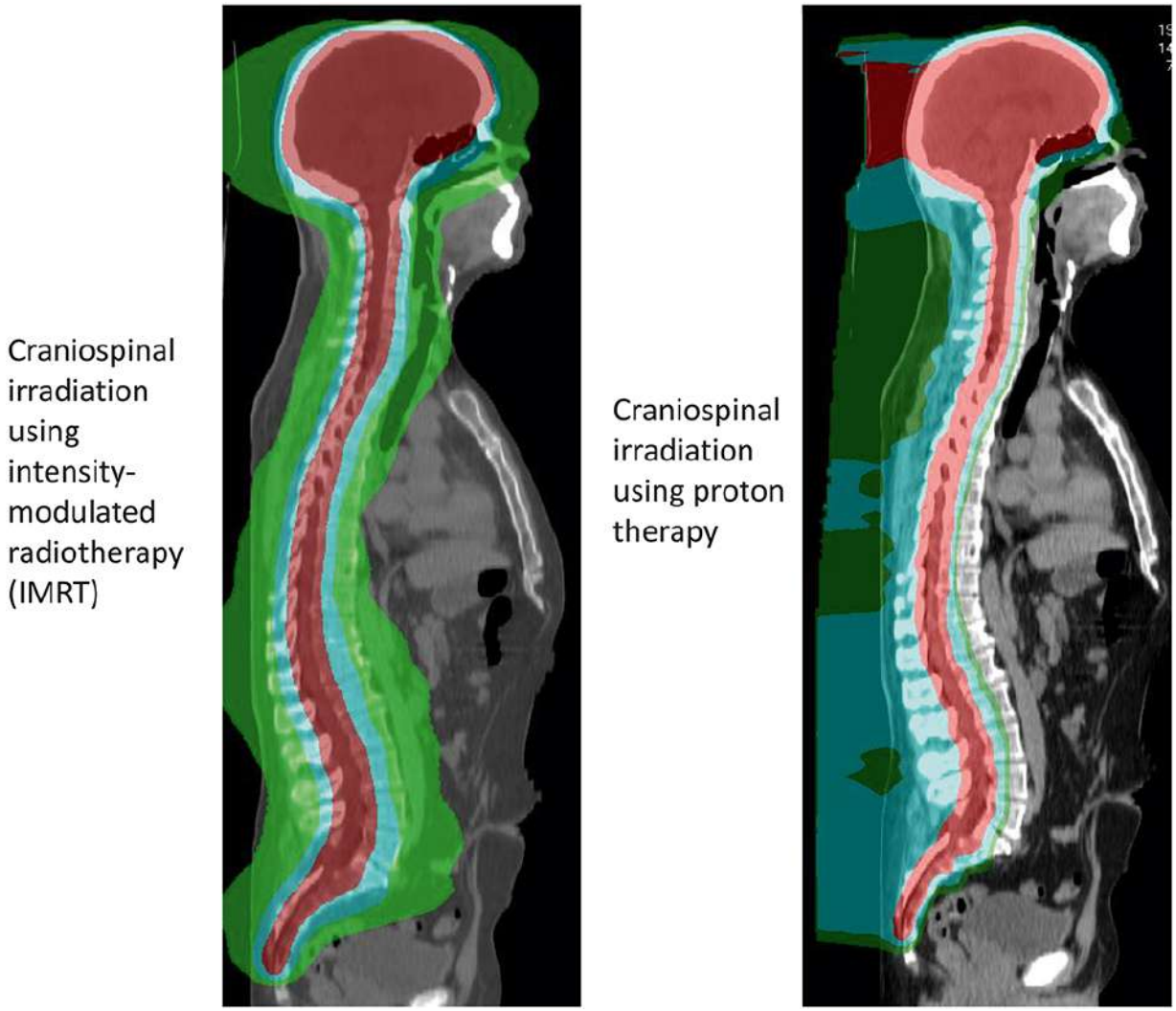

FIGURE 40.7 Comparison of proton therapy to intensity-modulated radiation therapy for craniospinal irradiation demonstrates negligent "exit" dose in visceral structures anterior to the spine and maximal sparing of vertebral body–based marrow achieved with proton therapy.

Stereotactic Radiosurgery

SRS requires a team composed of a radiation oncologist, neurosurgeon, and radiation oncology physicist, in addition to appropriate support staff. SRS can be delivered using a conventional or modified linear accelerator (LINAC) system, a Gamma Knife (Elekta Corp, Stockholm, Sweden), a robotically controlled miniaturized linear accelerator (CyberKnife), a dedicated gyroscopic self-shielded linear accelerator (Zap), or a modified proton system. In LINAC radiosurgery, circular or oval collimators (the so-called "cones") ranging from 4 to 40 mm have historically been used to collimate the treatment beam into a small circular beam, and treatment is delivered using multiple noncoplanar arcs that intersect at a single point to treat an approximately spherical target of less than 4 cm in diameter. Newer miniaturized multileaf collimators allow beam shaping without resorting to the use of externally mounted cones. Techniques incorporate multiple noncoplanar arcs with couch and jaw rotations, which permits a greater portion of the 3D space subtended over the skull to be utilized for beam entry. This approach, sometimes referred to as the "hyperarc technique," allows for better dose conformality and rapid treatment of multiple intracranial lesions, without the need for selecting individual isocenters for each lesion. The legacy Gamma Knife is a fixed beam multisource radiation unit containing 201 cobalt-60 (^{60}Co) sources that are collimated using a helmet with circular apertures ranging from 4 to 18 mm that is focused onto a single-target point. The newer Gamma Knife technology obviates the need for "helmet changes" and can effectively allow IMRT-like dose distributions to be created. For irregularly shaped lesions, treatments delivered using either noncoplanar arcs delivered through a single circular collimator or a single collimator helmet lead to the inclusion of a large amount of normal brain and yield inferior conformality. In these cases, it is advantageous to use multiple circular collimators or collimator helmets placed on different target points (and in the newer versions of the Gamma Knife [Perfexion, Icon, and Esprit], different segments can be treated with different collimator diameters, and differential weighting is also possible) or to consider the use of multileaf collimated beams. The "hyperarc technique" referred earlier also achieves improved dose conformality because of the combination of multiple noncoplanar arcs, the use of a sophisticated multileaf collimator, varying collimator rotations, and multiple couch angles. The newest versions of the Gamma Knife (Icon and Esprit)

incorporate an onboard kV imager capable of generating volumetric CT images that permit frameless and repetitive positioning for fractionated treatments.

The Radiation Therapy Oncology Group (RTOG) study 90-05 established the maximum tolerated dose of single faction SRS to be 24, 18, and 15 Gy for tumors 20 or higher, 21 to 30, and 31 to 40 mm in maximum diameter, respectively, and these and other parameters are frequently used to guide prescription doses.[32] In modern practice, because the number of intracranial lesions treated in one SRS session has increased significantly, there has been a tendency toward decreasing the SRS dose; for example, in a large Japanese study of multiple brain metastases, the SRS dose was decreased to 15 Gy.[33] Such across-the-board dose reductions in other studies have been shown to be associated with reduced local control, especially when WBRT is avoided.[34]

To limit the risk of radionecrosis, recent literature has identified the importance of limiting single-fraction SRS V_{12Gy} to normal brain and intracranial metastatic target volume to 10 mL or less; in situations where this metric cannot be achieved, multifraction SRS is recommended.[26,34,35]

Following surgical resection of brain metastases, postoperative SRS to the surgical cavity has become standard of care based on two prospective trials demonstrating improved surgical bed control with SRS as compared to observation[36] and less neurocognitive toxicity with SRS as compared to conventional WBRT.[37] Currently, as alternatives to postoperative single-fraction SRS, randomized trials are investigating preoperative SRS to reduce the risk of surgical perturbation failure and resultant nodular meningeal disease, and multifraction postoperative SRS to improve local control and reduce rates of radionecrosis. Current single-fraction SRS dosing guidance is from a randomized trial of single-fraction postoperative SRS versus WBRT (N107C/CEC.3) and is supported by existing literature (Table 40.4).[34,37]

TABLE 40.4 RECOMMENDED POSTOPERATIVE CAVITY SINGLE-FRACTION SRS DOSING GUIDANCE

Cavity Volume[a]	Single-Fraction SRS Dose (cGy)
<4.2 cm^3	2,000

Cavity Volume[a]	Single-Fraction SRS Dose (cGy)
≥4.2 to <8.0 cm^3	1,800
≥8.0 to <14.4 cm^3	1,700
≥14.4 to <20.0 cm^3	1,500
≥20.0 to <30.0 cm^3	1,400
≥30.0 to <5.0 cm max	1,200

SRS, stereotactic radiosurgery.

[a]Given the irregular shape of surgical cavities, the total prescribed dose should be based on the surgical cavity volume with a maximum cross-sectional diameter of <5.0 cm.

Reprinted from Gondi V, Bauman G, Bradfield L, et al. Radiation therapy for brain metastases: an ASTRO clinical practice guideline. *Pract Radiat Oncol*. 2022;12(4):265-282. Copyright © 2022 American Society for Radiation Oncology. With permission.

Fractionated Stereotactic Radiosurgery

For lesions larger than 4 cm and/or located in critical regions and/or for situations where single-fraction SRS V_{12Gy} to normal brain and intracranial metastatic target volume exceeds 10 mL,[26,35] the delivery of single-fraction SRS is not desirable because of a high risk of CNS toxicity. Multifraction SRS is a hybrid between conventionally fractionated RT and SRS that combines fractionation with stereotactic localization and targeting techniques. Various systems for multifraction SRS have been developed, with a reported accuracy of 1 to 3 mm. As for SRS, the use of multiple arcs and circular collimators for irregularly shaped lesions leads to the inclusion of a large amount of normal tissue. The use of multiple noncoplanar fixed fields each having a unique entrance and exit pathway will be preferable because of better conformality, as multileaf collimators are almost always used.[38-40] With the Perfexion device, the use of the "Extend" frame permits multifraction SRS as well as targeting of lower cranial lesions. With the incorporation of onboard volumetric imaging, modern LINACS and the most recent version of the Gamma Knife (Icon and Esprit) also permit fractionation, using noninvasive mask fixation systems. The CyberKnife also permits this option using repetitive 2D radiographic imaging incorporated into a sophisticated skull anatomy–based visualization software. There is increasing use of 9 Gy × 3 fractions or 6 Gy × 5 fractions

schedules of multifraction SRS for larger (>3 cm) brain metastases,[34] both to improve the rate and durability of local control and to decrease side effects; an ongoing NRG Oncology randomized trial is prospectively evaluating this approach.

Heavy Charged Particles

Heavy charged particle beams deposit their dose at a depth that depends on their energy over a distance of a few millimeters when the heavy charged particles come to rest, the so-called Bragg peak. To cover a larger volume, the particle beam can be modulated, in effect adding up multiple Bragg peaks. The very sharp dose gradient at the distal edge permits the use of high-dose RT for tumors in critical locations, such as at the clivus and base of the skull, and provides better normal tissue sparing in other situations, especially, for example, in CSI (Figure 40.8).[41,42] Currently, a small number of European and Japanese centers are treating CNS tumors with carbon ions, which putatively have higher linear energy of transfer and presumed superior biologic effect, but mature clinical data are not yet available. There are currently no U.S. centers utilizing these technologies. Neutron-beam irradiation continues to be used in some U.S. centers, but the targeted approach of boron neutron capture therapy, which is rapidly expanding in Asia and Europe, has no U.S. footprint at this time.

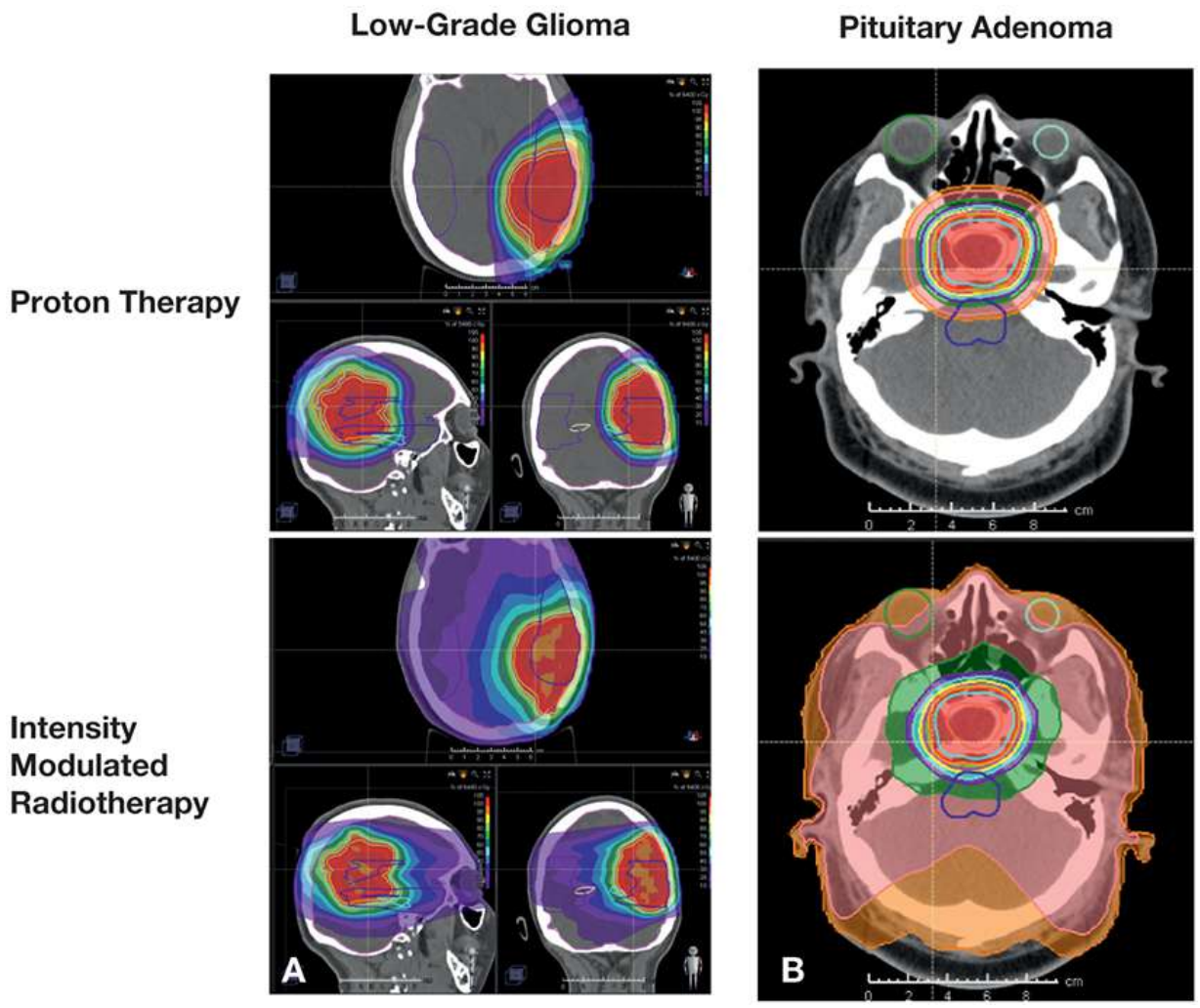

FIGURE 40.8 Comparison of proton therapy to intensity-modulated radiotherapy treatment plans for left temporal oligodendroglioma (A) and nonfunctional pituitary adenoma (B), demonstrating tight target coverage and significant sparing of low-dose radiation exposure to normal tissues throughout the brain in tumor types with favorable prognosis.

Brachytherapy and Radiocolloid Solutions

Selection criteria for brachytherapy include tumor confined to one hemisphere, no transcallosal or subependymal spread, small size (<5-6 cm), well circumscribed on CT or MRI, and accessible location for the implant and often all of the abovementioned combined in the context of a previously irradiated tumor, now locally recurrent, and requiring resection. A balloon-based system, GliaSite, placed into the cavity at the time of surgery has been employed in the treatment of recurrent malignant gliomas whose largest spatial dimension is less than 4 cm and is roughly spherical.[43]

After treatment planning, the balloon is filled with a liquid that contains organically bound iodine-125 (^{125}I) and treatment is completed within 3 to 7 days. Direct infusion of radioimmunoglobulins has been used in primary and recurrent brain gliomas.[44] GammaTile, a newer form of brachytherapy that uses cesium-131 (^{131}Cs) seeds embedded with an absorbable collagen matrix, has been evaluated for its use in selective reirradiation of recurrent brain metastases,[45] meningioma,[46] and glioblastoma (GBM)[47] and is being investigated for upfront surgical cavity irradiation of resected brain metastases in a prospective randomized trial.

CHEMOTHERAPY AND TARGETED AGENTS

Conventional Chemotherapy

Many conventional chemotherapy agents do not adequately penetrate normal or nonenhancing tumor-infiltrated brain, while some drugs, despite having a molecular weight and chemical structure that make them appear capable of crossing the BBB, are actively effluxed out of the brain parenchyma by p-glycoprotein and other active transporter substrates. Even when drug delivery is adequate, most CNS tumors are resistant to most conventional chemotherapeutic agents. Alkylating agents such as BCNU (carmustine) and CCNU (lomustine) have been the most widely studied drugs in CNS tumors. These agents cross the BBB, but prolonged use is difficult because of cumulative myelotoxicity and the dose-related risk of pulmonary fibrosis. Despite radiographic responses in 15% to 40% of patients, the impact on survival is modest at best.

Alkylating chemotherapies, being the only systemic therapy with survival benefit, remain the standard-of-care systemic upfront and salvage therapies for GBM. Temozolomide (TMZ) therapy extended median survival from 12.1 to 14.6 months for newly diagnosed GBM as demonstrated in a randomized, unblinded phase III National Cancer Institute of Canada/European Organisation for Research and Treatment of Cancer (NCIC/EORTC) trial.[48] Most of the survival benefit of TMZ therapy are derived from patients with GBM with O6-methylguanine-DNA methyltransferase (*MGMT)* promoter methylation.[49] Nitrosoureas, in the form of oral (lomustine) or infusion (carmustine), were first approved in 1970 for newly diagnosed gliomas. Carmustine administered via a

surgically implanted, biodegradable polymer (wafer) was also approved for newly diagnosed and recurrent high-grade gliomas (HGGs) because of improved survival (overall survival [OS] 31 vs 23 weeks; hazard ratio [HR] 0.67; *P=0.006*) compared with surgery alone.[50,51] Oral or IV nitrosoureas now largely serve as first-line salvage options for recurrent GBM as endorsed by worldwide guidelines.[52,53] The randomized German CeTeG/NOA-09 trial suggested benefit in combining TMZ with nitrosoureas compared to TMZ alone (median OS [mOS] 48.1 vs 31.4, *P* = .0492; HR = 0.60), specifically for patients with *MGMT* promoter–methylated GBM.[54] Similar benefit was reported in terms of response rates (objective response rate [ORR] 46%) for neoadjuvant carmustine and TMZ in a French trial,[55] and in the ACNS0423 pediatric, single-arm trial of adjuvant TMZ and lomustine for malignant astrocytomas.[56]

Other CNS tumors in which combination regimens are standard of care include PCNSL (high-dose methotrexate with procarbazine/vincristine, or high-dose cytarabine, or TMZ) and medulloblastoma (CCNU, cisplatin, and vincristine or cisplatin and cyclophosphamide and vincristine).

For diffuse low-grade gliomas (LGGs), both TMZ and PCV (procarbazine, CCNU, and vincristine) are effective in newly diagnosed and recurrent diseases. IDH-mutant, 1p/19q- codeleted oligodendrogliomas, and IDH-mutant, noncodeleted astrocytomas are more commonly treated with PCV initially or at recurrence, respectively, whereas IDH wild-type astrocytomas are often treated with TMZ due to the lack of evidence supporting the use of PCV.

There is an urgent unmet need for innovative treatment strategies for infiltrative gliomas. A recent randomized clinical trial of a personalized medicine assay (ChemoID™) guided treatment paradigm compared to physician's choice therapy showed improved survival (mOS 12.5 vs 9 months, *P* = .010; HR: 0.44, *P* = .008).[57] The ChemoID assay tests both the bulk of tumor and the therapy-resistant cancer stem cells (CSCs) from an individual glioma sample for sensitivity to chemotherapy monotherapies or combination regimens listed in the NCCN guidelines. An assay based on assessing the bulk of tumor only (3D Predict) also accurately and prospectively predicted patient-specific responsiveness to TMZ in 17 (85%) of 20 (*P* = .007) patients with newly diagnosed gliomas.[58] OS was significantly longer for "responders" compared to "nonresponders" (mOS

11.6 vs 5.9 months; HR 0.93, $P = .0376$). These chemotherapy sensitivity assays have the potential of enhancing the survival benefit of cytotoxic therapies with minimal, if any, survival benefit in the general GBM population when administered without selectivity.

Direct Delivery of Therapeutic Agents

Methods for circumventing the BBB include implantation of slow-release chemotherapy wafers into a tumor resection cavity;[50,59] pharmacologic, osmotic, or ultrasonic BBB disruption;[60,61] and convection-enhanced drug delivery (CED). CED involves the use of intracerebrally implanted catheters to deliver a drug into the brain parenchyma or tumor, at a slow but continuous rate of flow. Unlike diffusion, in which a drug distributes along an exponentially decaying concentration gradient depending on the size of the molecule, drug distribution by CED is less size dependent, occurs over a larger volume of brain tissue, and results in a more uniform drug concentration within the volume of distribution.[62,63] Large and/or hydrophilic agents that do not cross the BBB are ideal candidates for delivery via CED. Examples of agents used in CED studies include viruses,[64] paclitaxel,[63] topotecan,[65] and a variety of engineered, targeted protein toxins. These toxins are engineered to include a targeting ligand (eg, interleukin-4 [IL-4], IL-13, tumor growth factor-α, transferrin) and a genetically altered bacterial toxin that is effective only when internalized by a cell that expresses the target of the ligand.[66] Two phase III clinical trials have evaluated the use of CED. The PRECISE trial studied CED of IL-13 linked to *Pseudomonas* exotoxin (cintredekin besudotox), as compared to Gliadel wafers in patients with GBM at first recurrence. No difference in OS was observed, but cintredekin besudotox was associated with a higher rate of complications. The TransMID trial evaluated the efficacy of transferrin CRM107 delivered by CED to patients with inoperable recurrent or progressive GBM. The trial was terminated early in 2007 because it was deemed unlikely to meet the prespecified criteria for efficacy. Post hoc analysis of the PRECISE trial indicated that the nonspecialized delivery technology that was used in all of the prior CED studies ("off-the-shelf" single-lumen catheters) could not be placed sufficiently close to target tissue because of concerns about backflow of infusate, or leakage into CSF

spaces that would prevent effective intraparenchymal delivery. These concerns were magnified by the lack of imaging data to verify the extent of delivery in real time. Recently, several specialized, backflow-resistant delivery devices have been introduced into clinical trial, and coinfusion of Gd conjugates, which are visible on MRI, has verified the ability of these devices to produce clinically relevant volumes of distribution. These devices are currently incorporated into new, early-stage therapeutic trials involving CED, and more trials are expected to open over the next few years.

BCNU impregnated in a polymer and made into a wafer has been used for local delivery and placed on the walls of the resection cavity at the time of surgery. The wafer slowly undergoes biodegradation, releasing the active drug. This local delivery system has the advantages of minimal systemic toxicity, no limitation posed by the BBB, and delivery of very high local concentrations of chemotherapy. Studies in GBM have shown the benefit of biodegradable polymers impregnated with carmustine compared to placebo,[67] but not compared to CED.[68]

Recent efforts have sought to use low-intensity pulsed ultrasound with concomitant administration of IV microtubules to open the BBB to enhance the delivery of albumin-bound paclitaxel to the peritumoral brain of patients with recurrent GBM.[69]

Targeted Agents

Molecularly targeted options are expanding rapidly for WHO grade 2 diffuse and WHO grade 1 gliomas, including MEK inhibitor monotherapy or in combination with BRAF inhibitors for BRAF-rearranged and V600E-mutant LGG, respectively.[70-72] mTOR inhibitors also show early efficacy signal for NF1- associated LGG. A double-blind, phase 3 trial recently showed an increased progression-free survival (PFS) of vorasidenib compared to placebo for residual or recurrent grade 2 IDH-mutant glioma with no prior treatment, except surgery.[73] This may be a reasonable alternative to observation in selected patients who wish to defer chemotherapy and/or radiation.

Another targeted strategy successful in gliomas is the use of inhibitors of mTOR for the treatment of subependymal giant cell astrocytomas (SEGAs),

seen in association with tuberous sclerosis. Franz et al prospectively treated 23 patients with a definite diagnosis of tuberous sclerosis and increasing SEGA lesion size with daily everolimus. Twelve (52.2%) patients experienced SEGA volume reductions of 50% or more relative to baseline after 60 months of treatment. The proportion of patients experiencing daily seizures was reduced from 26.9% to 11.1% at 60 months.[74]

Given the high frequency (90%) of BRAF v600E mutations in papillary-subtype craniopharyngiomas, combined inhibition of BRAF (vemurafenib) and MEK (cobimetinib) led to the partial response (PR) in 15 of 16 patients with PFS of 87% at 12 months and 58% at 24 months.[75] The sole patient who did not show response discontinued medical therapy after 8 days due to intolerable toxicity. Case reports have also demonstrated radiographic response to dabrafenib and trametinib.[76-78]

Beyond alkylating chemotherapies, progress in GBM has been elusive. Although no single defining genetic mutation has been identified for gliomas, several key proliferation and survival signaling pathways appear to be important in GBM. The vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), and insulin-like growth factor (IGF) pathways are thought to be particularly relevant in the growth and proliferation of GBM. These pathways are characterized by receptors associated with tyrosine kinase activities and share common mechanisms of pathway activation and intracellular signaling. Overexpression or mutations of receptors and intracellular downstream effectors have been identified in GBM, leading to constitutive activation of signaling pathways, resulting in uncontrolled cellular proliferation, survival, and invasion. The Cancer Genome Atlas Research Network demonstrated that 88% of primary GBMs have deregulation in the receptor tyrosine kinases and downstream RAS or PI3K pathways. Laboratory and clinical trials have focused on targeting these pathways with a variety of agents, including monoclonal antibodies, low-molecular-weight tyrosine kinase inhibitors, and ligand-toxin conjugates.

Bevacizumab, a VEGF-targeted antiangiogenic therapy, failed to yield survival benefit in concurrent U.S. and European phase III randomized, placebo-controlled trials, despite promise in early-phase trials.[79-82] Bevacizumab remains approved in the United States, largely as a steroid-

sparing palliative therapy. Regorafenib, another antiangiogenic agent with dual VEGFR2-TIE2 tyrosine kinase inhibition, is now endorsed by national guidelines based on a randomized phase 2 trial comparing salvage regorafenib with lomustine (mOS 7.4 vs 5.6 months; HR: 0.50; $P = .001$).[83] The most promising molecularly targeted therapy serves less than 5% of patients with GBM with oncogenic mutations, such as BRAF-V600E or NTRK fusions.[70,84]

One-third of GBMs express an aberrant EGF receptor (EGFR) surface receptor, targeted by various small molecule inhibitors, antibodies, and vaccine-mediated approaches. A phase III study of rindopepimut, an EGF receptor variant III (EGFRvIII) peptide conjugated to keyhole limpet hemocyanin failed to improve survival in newly diagnosed GBM in a prospective, randomized, phase III study.[85] Depatuxizumab mafodotin (depatux-m) is an antibody-drug conjugate that preferentially binds cells with EGFR amplification. It is internalized by targeted cells and releases a potent antimicrotubule agent, monomethyl auristatin F. A phase III, prospective, randomized, placebo-controlled trial of depatux-m in newly diagnosed GBM with EGFR amplification demonstrated no OS benefit of depatux-m over placebo but did find statistically significantly longer PFS benefit with depatux-m compared to placebo, a benefit that was greater among the patients with EGFRvIII-mutant or *MGMT*-unmethylated tumors.[86] There was grade 3 to 4 corneal epitheliopathy occurring in 61% of patients treated with depatux-m.[86]

Investigators have studied various adoptive and active immunotherapies in the treatment of GBM. Despite limited success, there has been renewed interest recently with the development of tumor-specific vaccines and the approval of new agents for other solid tumors. The use of an active, tumor-specific immunotherapy is appealing as it could potentially maintain long-term antitumor response while limiting toxicity. In addition to Rindopepimut (EGFRvIII-targeted peptide vaccine), other vaccine strategies in clinical trials include DC Vax (autologous tumor lysate–pulsed dendritic cell vaccine), ICT-107 (dendritic cells prepared from autologous mononuclear cells that are pulsed with six synthetic peptides), and HSPPC-96 (autologous tumor-derived heat shock protein [glycoprotein 96]), and unfortunately, these too, have largely failed. A recent prospective randomized trial replacing TMZ with ipilimumab (anti-cytotoxic T-

lymphocyte antigen 4 [CTLA4]) and nivolumab (anti-programmed death ligand 1 [PD-L1]) for *MGMT* promoter–unmethylated GBM demonstrated no survival benefit.[87] A prospective externally controlled nonrandomized trial adding DC Vax to the standard of care demonstrated favorable OS outcomes in both newly diagnosed and recurrent GBM compared to contemporary, matched external controls who received standard of care alone.[88] Validation of these results in a prospective randomized trial has not been conducted, and DC Vax remains an investigational therapeutic.

Tumor-Treating Fields Therapy

Tumor-treating fields (TTFields) are a novel treatment modality approved for the treatment of either newly diagnosed or recurrent GBM. TTF therapy involves a medical device and transducer arrays to provide targeted delivery of low-intensity, intermediate-frequency, alternating electric fields to produce antimitotic effects selective for rapidly dividing tumor cells with limited toxicity. In the phase 3 EF-14 trial, TTFields plus TMZ provided significantly longer PFS and OS compared with TMZ alone in patients with newly diagnosed GBM after initial chemoradiotherapy. In the phase 3 EF-11 trial, for recurrent GBM, TTFields provided comparable efficacy as investigator's choice systemic therapy, with improved patient-reported quality of life and a lower incidence of serious adverse events.[89] Primary toxicity associated with TTFields is skin irritation generally managed with array relocation and topical treatments, including antibiotics and steroids.

FOLLOW-UP

The follow-up schedule for a patient with brain tumor must be frequent enough to check on side effects and to taper steroids shortly after completion of RT. Periodic MRIs are used to detect tumor recurrence at a stage when further therapy may be contemplated. Assessment of cognitive functioning and quality of life is important, and patients must be monitored for neuroendocrine and ophthalmologic side effects.

SEQUELAE OF TREATMENT

Surgery

With appropriate patient selection, diligent surgical technique, and the use of surgical adjuncts such as speech and/or motor mapping, the rate of complications can be minimized. Even in the best of hands, new temporary neurologic deficits can be seen in 15% or more of patients, although the rate of permanent new deficits is typically now less than 5%.[90] The incidence and types of deficits seen following surgery depend upon the location of the tumor and the deficits present preoperatively. The most common complications associated with surgery are bleeding and infection, particularly in the case of reoperation in a patient who has received prior RT and/or chemotherapy or when chemotherapy wafers are placed into a resection cavity.[91] It has been suggested that the use of linear incisions (as opposed to U-shaped flaps) can help reduce the incidence of incision-related complications, such as infection.[91] Posterior fossa resections, particularly in children with medulloblastoma, may be associated with posterior fossa syndrome (mutism plus bulbar symptoms). Transient perioperative edema, within about 48 hours of surgery, may be responsible for early postoperative neurologic worsening and can often be mitigated with the use of a short course of high-dose steroid therapy.

Patients with postoperative neurologic deterioration require careful clinical assessment, and in most cases, a CT or MRI is required to determine the cause of the deterioration. MRI diffusion-weighted sequences can be used to detect the presence of a new infarct. A high index of suspicion should be maintained for postoperative infection because symptoms may be masked by perioperative steroid use, and the headache and fever associated with craniotomy may obscure the classic signs of meningitis.

Radiotherapy

The response of intracranial tissues to radiation has been classically divided into three phases based on the timing of onset of symptoms: acute, subacute, and late.

Acute Toxicity

Transient worsening of pretreatment deficits may develop during the course of treatment, and further acute toxicities may manifest up to 6 weeks

following completion of irradiation. These symptoms are believed to be the consequence of a transient peritumoral edema and usually respond to a short-term increase or the institution of corticosteroids. Persistent or refractory symptoms may be caused by tumor progression, and repeat imaging while under treatment may be indicated if the clinical condition worsens despite steroids.

General symptoms such as fatigue, headache, and drowsiness may be seen, especially in individuals treated with large brain fields or with CSI. A mild dermatitis that develops in irradiated areas may be treated with topical agents if necessary. Alopecia within the irradiated areas is common and may be permanent with higher total doses. Nausea and vomiting, independent of changes in intracranial pressure, may occur, particularly with posterior fossa or brainstem irradiation. Otitis externa can be seen if the ear is included in the irradiation fields, and serous otitis media also may occur. Patients treated with CSI with photons are at risk for mucositis and esophagitis because of the exit dose from the spinal fields through the oropharynx and mediastinum. Hematologic toxicity may also be seen in these patients because of irradiation of the vertebral bodies, a major depot of bone marrow in adults. These gastrointestinal (GI) and hematologic effects are less severe and less frequent with the use of proton therapy for CSI.[92]

Subacute Toxicity

Subacute or "early-delayed" toxicity that develops during the 6-week to 6-month period following irradiation is attributed to changes in capillary permeability as well as transient demyelination due to damage to oligodendroglial cells. Symptoms, which include headache, somnolence, fatigability, and deterioration of preexisting deficits, usually respond to steroids. The main challenge is to distinguish the clinical and imaging findings from tumor recurrence. The phenomenon of "pseudoprogression" temporally fits within the subacute toxicity time frame.

Late Sequelae

Late sequelae of RT appear from 6 months to many years following treatment and are usually irreversible and progressive. They are thought to

be due to white matter damage from vascular injury, demyelination, and necrosis. The pathophysiology of radiation-induced neurocognitive damage is complex and involves intercellular and intracellular interactions between vasculature and parenchymal cells, particularly oligodendrocytes, which are important for myelination. Oligodendrocyte death occurs either because of direct p53-dependent radiation apoptosis or because of exposure to radiation-induced tumor necrosis factor-α.[93] Postradiation injury to the vasculature involves damage to the endothelium leading to platelet aggregation and thrombus formation, followed by abnormal endothelial proliferation and intraluminal collagen deposition.[93]

The most serious late reaction to RT is radiation necrosis, the incidence and onset of which is radiation dose dependent. Radiation necrosis can mimic recurrent tumor clinically by the reappearance and worsening of initial symptoms and neurologic deficits and radiographically with the development of a progressive, irreversible, enhancing mass with associated edema on imaging. PET, MR spectroscopy, and nuclear and dynamic CT scanning procedures may aid in the differentiation of radiation necrosis from recurrent tumor. The best treatment for symptomatic necrosis is control of symptoms with steroids followed by surgical debulking, although, even after resection, necrosis may progress. Given the central role of capillary leakage to radiation necrosis, bevacizumab, an antibody against VEGF, has been tested clinically as the treatment for radiation necrosis and has shown encouraging results.[94] Other measures include the use of corticosteroids with anticoagulation or hyperbaric oxygen, although randomized trials have not shown these to be useful. In clinical series, LITT has shown utility in treating focal radiation necrosis.[95] Although focal necrosis is usually due to RT alone, diffuse leukoencephalopathy is more commonly associated with the combination of RT and chemotherapy, particularly methotrexate.

Inclusion of the middle ear may result in high-tone hearing loss and vestibular damage, especially in patients who receive cisplatin. Retinopathy or cataract formation may be seen if the eye is in the radiation field. Optic chiasm and nerve injury may manifest as a decrease in visual acuity, visual field changes, or blindness at doses greater than 54 to 60 Gy. Onset of hormone insufficiency from irradiation of the hypothalamic-pituitary axis is variable but may be seen with doses as low as 20 Gy.

Cranial irradiation can produce neuropsychological changes and neurocognitive impairment; other factors such as tumor-related morbidity, as well as the effects of surgery and chemotherapy, may also contribute. Decline in list-learning recall has been observed in prospective clinical trials of therapeutic and prophylactic cranial irradiation.[96,97] These changes are thought to be due in part to interactions between the vasculature and parenchymal cells. Hippocampal-dependent functions of new learning, memory, and spatial information processing appear to be most affected.[98-100] Doses as low as 2 Gy can induce apoptosis in the proliferating cells in the hippocampus.[101] Neuroprotective strategies, including technical approaches of HA using IMRT and pharmacologic approaches using memantine, prevent this neurocognitive toxicity.[101-104]

MANAGEMENT OF INDIVIDUAL TUMORS

Malignant Glioma

Malignant gliomas or HGGs account for approximately half of all primary brain tumors in adults. They are rapidly growing tumors that directly invade the brain parenchyma but almost never metastasize outside the CNS. They present in any age group, although most occur in late adulthood. Prior to the most recent WHO classification, the management of malignant gliomas was approached based on histologically assigned grade, that is, anaplastic gliomas (WHO grade III) and GBM (WHO grade IV). In fact, historical trials included grade III and IV gliomas together, and these are, therefore, described in the section on GBM, as patients with GBM constituted the majority of subjects, whereas anaplastic gliomas are discussed in further detail in the following section. In the new WHO classification, all GBMs by default are wild type for the *IDH* gene, although there are no large clinical trials reported so far that have used this definitional approach. The *IDH*-mutant gliomas are more favorable in terms of prognosis and include the most favorable, that is, those with 1p19q codeletions (oligodendroglioma, either grade 2 or 3 [anaplastic]) or those without (astrocytoma, either grade 2 or 3 [anaplastic]), and yet, there are also *IDH* wild-type astrocytomas that are not definitionally GBM. Given that these are newer categories and no major trials (except for the INDIGO trial) have reported on outcomes using

these definitions, we have provided management strategies using legacy definitions and incorporating IDH status as appropriate.

Glioblastoma

GBM accounts for approximately 75% of all HGGs. The histopathologic features of GBM include nuclear atypia, mitotic activity, vascular proliferation, and necrosis; any three of these suffice to make the diagnosis. GBM is diffusely infiltrative, involving large portions of the brain. MRI characteristically shows vasogenic edema and ring enhancement around central necrotic regions. The current WHO classification requires wild-type IDH for a diagnosis of GBM. In addition, the current classification also includes previous grade 2 and grade 3 astrocytomas with specific molecular characteristics, which would result in these tumors being reclassified as "molecular" GBM; these patients were historically excluded from the majority of trials discussed earlier; as such, a category did not exist when the trials were conducted.

The prognosis for patients with GBM is poor, with a median survival time of approximately at least 18 months in highly selected patients receiving contemporary treatment. Pretreatment patient and tumor characteristics such as age at diagnosis, tumor histology, and Karnofsky performance status (KPS) are the best predictors of outcome. The extent of resection, duration of neurologic symptoms, and radiographic response to treatment have also been suggested as predictors of survival.

Curran et al[105] used nonparametric recursive partitioning analysis (RPA) (a statistical tool that allows for the identifi cation of significant prognostic factors and subsequent classification of patients into groups with similar outcomes) to analyze data from three RTOG trials that included 1,578 patients with malignant gliomas. Age was the most important predictor of survival, with patients younger than 50 faring best; KPS 70 or higher was the next most significant prognostic factor. Taking into account these and other variables, patients could be divided into groups with similar outcomes, with 2-year OS ranging from 4% to 76% and median survival ranging from 2.7 to 58.6 months (Table 40.5). Though developed in patients receiving RT alone, the RPA classification retains prognostic significance in patients treated with RT plus TMZ.[106] More recent studies have integrated

molecular data from *MGMT* promoter methylation status and other novel biomarkers to develop novel risk stratification models.[107]

TABLE 40.5 RADIATION THERAPY ONCOLOGY GROUP RECURSIVE PARTITIONING ANALYSIS OF MALIGNANT GLIOMA

Class	Patient Characteristics	Median Survival (mo)
I, II	Anaplastic astrocytoma	40-60
	Age ≤50 y, normal mental status or age >50 y, KPS >70, symptoms >3 mo	
III, IV	Anaplastic astrocytoma	11-18
	Age ≤50 y, abnormal mental status	
	Age >50 y, symptoms <3 mo	
	Glioblastoma	
	Age <50	
	Age >50 y, KPS ≥70	
V, VI	Glioblastoma	5-9
	Age >50 y, KPS <70 or abnormal mental status	

KPS, Karnofsky performance status.

Molecular Genetics

GBM may arise de novo (primary) or from an LGG that has transformed into a higher grade tumor (secondary). Secondary GBM arises in younger patients and are associated with a more favorable prognosis than those with primary GBM. The more favorable prognosis may be related to the impact of younger age and better performance status of this group. Emerging data suggest that promoter methylation of the *PTEN* gene in LGGs may be causally linked to secondary malignant transformation to GBM. Secondary GBM usually has a mutation in the *IDH1* gene and often have p53 mutations and are no longer classified as GBM.

Treatment

Standard treatment consists of maximal safe surgical resection followed by RT with concurrent TMZ chemotherapy and subsequent adjuvant TMZ

chemotherapy and consideration for application of TTFields. The benefit of surgical resection on survival has been a subject of debate, but over time, a growing body of evidence has supported the concept that survival from GBM relates to the residual disease burden after surgery. Most recently, a Response Assessment in Neuro-Oncology (RANO) group (RANO-resect) performed a volumetric analysis of the impact of extent of resection (and residual disease burden) on survival in over 1000 patients from centers in the United States and Europe. After taking into account demographic and molecular genetic variables known to impact on outcome, the investigators validated the prognostic value of a previously published categorization of extent of resection and showed a substantial difference in survival of patients who could undergo a supramaximal resection versus complete resection, partial resection or biopsy only (mOS 29 vs 19 vs 16 vs 10 months).[24,108] Other approaches including alterations in the delivery of RT, newer chemotherapeutic agents, immunotherapy, and other agents are the subject of ongoing research.

Radiotherapy Target Volume

Randomized trials have demonstrated a clear survival benefit to the use of RT after surgery.[109] Localized irradiation volumes are recommended despite the fact that GBM is usually more widely disseminated. Dandy,[110] for example, identified recurrences in the contralateral hemisphere even after hemispherectomy, showing the phenomenal capability of malignant gliomas to spread along white matter tracts. Such findings as well as autopsy studies[111-113] led to recommendations that the entire intracranial contents should be irradiated. However, Hochberg and Pruitt[114] reported that in 35 patients who had a CT scan within 2 months prior to autopsy, 78% of recurrences of GBM were within 2 cm of the margin of the initial tumor bed and 56% were within 1 cm or less of the volume outlined by the CT scan. These findings were confirmed by Wallner et al[115] who showed that 78% of unifocal tumors (25/32) recurred within 2 cm of the initial tumor volume, defined as the enhancing edge of the tumor on CT scan, and 56% of tumors (18/32) recurred within 1 cm of the initial tumor margin. No unifocal tumor recurred as a multifocal lesion, and large tumors were not more likely to recur farther from the initial tumor margin than smaller tumors.

In a correlative study, Halperin et al[116] reviewed CT scans and pathologic sections of 15 brains of patients with GBM who received minimal or no RT. If radiation treatment portals had been designed to cover the contrast-enhancing volume and peritumoral edema with a 1-cm margin, the portals would have covered histologically identified tumor in only 6 of 11 cases. However, treatment of the contrast-enhancing area and all surrounding edema with a 3-cm margin around the edema would have covered histologically identified tumor in all cases.

Kelly et al[117] reported on 40 patients with intracranial glial neoplasms who underwent CT- and MRI-guided stereotactic serial biopsies. Histologic analysis of 195 biopsy specimens showed that CE most often corresponded to tumor tissue without intervening parenchyma and hypodensity most often corresponded to parenchyma infiltrated by isolated tumor cells, tumor in LGGs, or edema. Isolated tumor cell infiltration extended at least as far as T2 changes on MRI. T2-weighted MRI revealed much larger volumes of infiltrated parenchyma than shown by low attenuation on CT scans.

Therefore, inclusion of all radiographic evidence of tumor and associated edema with generous margins is common practice in the design of treatment portals. The extent of margin expansion remains a relatively poorly studied and controversial area, with considerable variance.[118] With advances in MRI technology, the definition of tumor margins continues to change. For example, Pirzkall et al[119] showed metabolically active tumor extending outside the region defined on T2-weighted MRI in 88% of patients. PET imaging with methionine and/or thymidine may also prove useful.

For some time now, various single-institution reports suggest using smaller and smaller margins, and the rationale is “no reduction in survival observed compared to historic controls.” These reports, being retrospective, of course carry inherent biases. Intriguingly, recent surgical approaches have started moving in a direction opposite to the RT paradigm of margin reduction. Well-conducted analysis reveals that when the surgical resection is extended to remove not only the contrast-enhancing component but also the nonenhancing compartment, survival improves.[120] Such observations should inform radiotherapeutic margin planning.

Radiotherapy Dose

The current "standard approach" delivers a total dose of 59.4 to 60 Gy in 30 to 33 fractions of 1.8 to 2 Gy/fraction, using a "shrinking field" technique. Walker et al[121] performed a dose-response analysis using data from 420 patients treated on Brain Tumor Cooperative Group protocols. Doses ranged from less than 45 to 60 Gy using daily fractions of 1.7 to 2 Gy; only one-third of the patients received less than 60 Gy. A significant improvement in median survival from 28 to 42 weeks in the groups treated with doses of 50 to 60 Gy was found. A Medical Research Council study of 443 patients also showed a significant survival advantage in patients who received 60 Gy compared to those who received 45 Gy (12 vs 9 months; $P = .007$).[122]

For patients with poor pretreatment prognostic factors and a limited expected survival who are not able to tolerate conventional treatment, a shorter course of treatment may provide good palliation. Older patients (>65 years), especially those with poor performance status, have been shown to experience limited post-treatment improvement or rapid neurologic deterioration following conventional RT. Short-course RT, utilizing hypofractionated techniques, some as short as only 1 week, has been tested in older patients, and the results are described later. In Europe and Canada, such hypofractionated schedules are considered "standard" for "older patients" or "poor performance" status patients, and such techniques are also being increasingly utilized in the United States. In one small study, an ultrahypofractionated 5-day regimen was utilized and could possibly be considered for select patients.[123]

Dose Escalation and Altered Fractionation

With the vast majority of tumor recurrences occurring within the previous irradiation field and the poor outcomes associated with standard therapy, regimens designed to deliver a larger dose have been attempted to improve local control and enhance survival.

A benefit for doses greater than 60 Gy either without chemotherapy or with nitrosourea-based chemotherapy has not been demonstrated. The RTOG and Eastern Cooperative Oncology Group (ECOG) randomized 253 patients to either whole-brain irradiation to 60 Gy given in 6 to 7 weeks or

60 Gy plus a 10-Gy boost to a limited volume given in 7 to 8 weeks.[124] There was no benefit for the higher irradiation dose.

Several groups have used hyperfractionated or accelerated regimens as a means to escalate dose, using BID, 3 times daily, and even 4 times daily fractionation.[125,126] Only the study of Shin et al[126-128] showed an improvement in survival using multiple fractions per day compared to one fraction per day. In this study, 81 patients were randomized to 61.4 Gy in 69 fractions of 0.89 Gy given 3 times daily over 4.5 weeks or conventional fractionation to 58 Gy in 30 fractions given QD over 6 weeks. Median survival in the two groups was 39 and 27 weeks, respectively, and the 1-year survival rates were 41% and 20%, respectively ($P < .001$). Others have failed to confirm these results. In a prospective, randomized phase I/II trial, RTOG 83-02 examined dose escalation using BID fractionation in patients with malignant gliomas. Hyperfractionated regimens studied were 64.8, 72.0, 76.8, and 81.6 Gy given in 1.2 Gy fractions BID, and accelerated hyperfractionated regimens were 48 and 54.4 Gy given in 1.6 Gy BID fractions. Patients also received chemotherapy with BCNU. In the final report on all 747 patients, there were no significant differences between the treatment arms with regard to median survival time.[128] A phase III trial compared conventional RT to 60 Gy in 30 daily fractions to hyperfractionated RT to 72 Gy in 60 fractions of 1.2 Gy given BID.[129] No difference in survival was found.

In the contemporary era of concurrent and adjuvant TMZ, escalation of both dose and dose per fraction using IMRT was tested in a prospective phase I/II study. The maximum tolerated dose with TMZ was 75 Gy in 30 fractions (2.5 Gy/fraction). Median survival was 20.1 months, suggesting improved efficacy compared to other contemporary studies. The probability of in-field failure decreased with increasing dose escalation. A prospective randomized trial of this dose fractionation regimen using IMRT demonstrated no OS benefit.[130] The results of this dose fractionation on the same trial using proton therapy are pending.

Dose Escalation Using Radiosurgery

A radiosurgical boost was reported as effective in patients with newly diagnosed malignant glioma in a retrospective analysis of 115 patients

treated at three institutions with a combination of surgery, external beam RT, and LINAC-based radiosurgery on similar institutional protocols.[131] In a prospective randomized trial, Souhami et al[132] compared conventional RT (60 Gy) plus adjuvant BCNU with and without radiosurgery in 203 patients with GBM. At a median follow-up of 61 months, no significant improvement in median survival was observed (13.5 vs 13.6 months). Other trials have explored alternative schedules, without evidence for benefit.

Dose Escalation Using Brachytherapy

Laperriere et al[133] used brachytherapy as a boost to conventional RT in patients with malignant gliomas. Patients were randomized to either external beam RT (50 Gy in 25 fractions) alone (n = 69) or external beam RT plus a temporary stereotactic ^{125}I implant delivering a minimum peripheral tumor dose of 60 Gy (n = 71). Median survival was not significantly different between the two arms (13.8 vs 13.2 months; P = .49).

The results of the Brain Tumor Cooperative Group National Institutes of Health Trial 8701 reported by Selker et al[134] support these findings. In this randomized, prospective trial, 299 patients with newly diagnosed malignant glioma received surgery, external beam RT, and BCNU with or without an interstitial RT boost with ^{125}I. Treatment with an interstitial boost did not prolong survival as compared to conventional treatment.

Dose Escalation Using Proton Therapy

Dose escalation up to 90 cobalt gray equivalent (CGE) with mixed photon and proton-beam irradiation has been tested in two prospective trials.

Fitzek et al[135] reported on a phase II study of 23 patients with newly diagnosed GBM. The 2-year OS was 34% and mOS was 20 months, which compared favorably to historical data. Recurrence was observed in regions treated to 60 to 70 CGE, but only one recurrence was observed in regions treated to 90 CGE. More recently, Mizumoto et al[136] reported on a phase I/II study of 20 patients with supratentorial GBM treated with mixed photon and proton-beam irradiation to 96.6 Gy in 56 BID fractions with concomitant nimustine chemotherapy. MRI-defined T2-enhancing region was treated to 50.4 CGE in 28 daily morning fractions. In daily evening fractions, patients were treated to 23.1 CGE for the first 14 fractions to the

T1-enhancing region plus 1 cm and then 23.1 CGE for the subsequent 14 fractions to the T1-enhancing region only. Median survival was 22 months, and 2-year OS was 45%. Late radiation necrosis was noted in one patient, and late leukoencephalopathy was observed in a second patient. A phase 2 randomized trial comparing photon versus proton RT did not demonstrate improvement in neurocognitive function, a finding not surprising in GBM, but did demonstrate less patient-reported fatigue, a reduction in toxicity and a marked reduction in RT-associated lymphopenia in favor of proton therapy.[137,138] As part of a prospective randomized trial, dose escalation to 75 Gy in 30 fractions using proton therapy is currently under investigation; the trial has completed accrual, but the results are pending.

Radiosensitizers

Studies using radiation modifiers in conjunction with RT to overcome the hypoxia present in malignant gliomas have shown disappointing results. Chang[139] reported on 38 patients treated with hyperbaric oxygen and irradiation using fractionation schedules ranging from 36 Gy given in 3 weeks to 60 Gy given in 6 to 7 weeks and compared them with 42 patients treated with RT alone. An improvement in 18-month survival rate from 10% to 28% and an increase in median survival from 31 to 38 weeks were noted. Perfluorocarbon emulsions, such as Fluosol, which have enormous oxygen-carrying capacity, have been tested as hypoxic sensitizers without significant benefit.[140] Randomized studies failed to show significant improvement with the addition of the hypoxic cell sensitizer misonidazole.[141] Miralbell et al[142] reported the results of EORTC trial examining the addition of carbogen and nicotinamide to overcome the effects of proliferation and hypoxia presumed responsible for radioresistance in GBM. OS was similar in all arms and did not differ from the results of a series using RT alone.

S-phase sensitizer trials using halogenated pyrimidines also failed to improve survival, but contemporary oral prodrug versions are reviving interest in this line of clinical research. The redox-modulating radiosensitizer motexafin gadolinium (MGd) showed encouraging results in a phase I clinical trial[143]; however, the results from a single-arm phase II

trial, RTOG 0513, of MGd and conventional therapy in newly diagnosed GBM showed no survival improvement.[144]

Chemotherapy

The use of cytotoxic chemotherapy for GBM dates back to the 1960s with a controlled study using carmustine.[145] Postsurgical patients were assigned to no further therapy, carmustine alone, radiation alone, and radiation followed by carmustine. At 18 months, 23% of those treated with radiation plus carmustine were still alive as compared to 5% with carmustine or RT alone. The Food and Drug Administration (FDA) approved carmustine and lomustine for the treatment of brain tumors (including GBM) in the 1970s. Subsequent prospective studies failed to demonstrate a survival advantage to carmustine or other cytotoxic chemotherapy for GBM, although two meta-analyses demonstrated a small survival benefit.[146,147]

TMZ is the only chemotherapeutic agent with OS benefit for patients with GBM and anaplastic astrocytoma (AA). TMZ, an oral imidazotetrazine derivative of dacarbazine, is metabolized in vivo to an active agent. Like the nitrosoureas, it alkylates the O^6 position on guanine, producing single-strand DNA breaks. Fatigue, constipation, and nausea are the most common toxicities. While overall well tolerated, TMZ is myelosuppressive in a minority of patients. The FDA approved TMZ for recurrent AA in 1999.[147,148] Approval as adjuvant therapy for GBM was based on a large phase III clinical trial conducted by the EORTC and NCIC[48] that randomized 573 adult patients (ages of 18 to about 70, KPS >70) with newly diagnosed GBM to either radiation alone (total 60 Gy in 30 fractions) or in combination with TMZ. Patients on the experimental arm received TMZ daily at a dose of 75 mg/m^2 during RT due to the expected radiosensitization effect based on preclinical studies, followed by monthly TMZ at a dose of 150 to 200 mg/m^2 for 5 consecutive days in 28-day cycles for six cycles. Survival was improved for those treated with chemoradiation compared to RT alone, specifically mOS was 14.6 months compared to 12.1 months,[48] 2-year survival was 27.2% compared to 10.9%, and 5-year survival was 9.8% compared to 1.9%.[149] Toxicity was acceptable for those treated with TMZ concurrent with RT, including 7% grade 3 or 4 hematologic toxicities.[48]

The benefit of TMZ has also been demonstrated for older patients (age ≥65) with GBM. A randomized phase III trial adding TMZ to hypofractionated RT, followed by monthly adjuvant TMZ improved survival from 7.6 to 9.3 months with combination therapy.[150] PFS was 5.3 versus 3.9 months, 1-year survival rate was 37.8% versus 22.2%, and 2-year survival rate was 10.4% versus 2.8% with radiation plus TMZ versus radiation alone.

Identifying potential predictive laboratory markers aids in selecting candidates for chemotherapy, thus limiting toxicity for patients unlikely to respond to TMZ. Epigenetic silencing of the *MGMT* DNA repair gene by promoter methylation predicts longer survival for patients with malignant glioma treated with alkylating agents.[151] A retrospective analysis of the EORTC/NCIC TMZ study demonstrated a survival benefit for patients treated with TMZ and RT if their tumor contained a methylated *MGMT* promoter (median 21.7 months) as compared to tumors with unmethylated *MGMT* promoters (median 12.7 months).[49] In the NCIC (also known as CCTG)-EORTC trial of older patients with GBM,[150] the *MGMT*-unmethylated group did not achieve a statistically significant benefit in survival from combination RT plus TMZ compared to RT alone, and consequently, modern clinical trials often omit TMZ in the experiment and, occasionally, in the control arm of trials enrolling patients with *MGMT*-unmethylated GBM.

Although the standard adjuvant TMZ dosing is 150 to 200 mg/m^2 for 5 days per 28-day cycle for six cycles, variations in practice include dose intensification and continuing TMZ beyond six cycles despite the lack of OS benefit in randomized trials. An RTOG randomized, phase III trial compared standard adjuvant TMZ with a dose-dense schedule in newly diagnosed GBM (N = 1,173),[152] and 833 patients were randomized to standard RT plus concurrent and standard adjuvant TMZ (150-200 mg/m^2 for 5 days per 28-day cycle) or adjuvant dose-intense TMZ (75-150 mg/m^2 on a 21/28 day schedule). There was no significant difference in mOS (16.6 vs 14.9 months, P = .63) or median PFS (5.5 vs 6.7 months, P = .06). The trial prospectively stratified for *MGMT* methylation status, and no survival benefit with dose-intense therapy was identified in any subgroup. *MGMT* methylation was associated with improved mOS (21.2 vs 14 months, P < .0001), median PFS (8.7 vs 5.7 months, P < .0001), and response (P =

.012). As expected, the dose-intense arm resulted in increased toxicity. Thus, dose intensification of TMZ is not advised for patients with newly diagnosed GBM. A pooled analysis of patient-level data from four randomized trials of newly diagnosed GBM also assessed the benefit of prolonging TMZ beyond six adjuvant cycles, but only demonstrated a slight improvement in PFS (HR 0.80, $P = .03$), particularly in *MGMT*-methylated patients (HR 0.65, $P < .01$).[153] Continuing TMZ beyond six cycles demonstrated no difference in OS in the overall population or in the *MGMT*-methylated subgroup. Thus, neither dose intensification nor prolonged standard adjuvant TMZ is considered standard of care, given the potential for increased toxicity.

A comprehensive review of clinical trials involving RT in combination with radiosensitizing agents on patients diagnosed with GBM analyzed 63 relevant trials published between 1976 and 2021.[154] Despite several approaches of optimizing radiation effectiveness using radiosensitizers, there is no clear evidence of improved patient outcome with putative sensitizers. Tissue selectiveness and penetration of the BBB appear the greatest limitations, shifting the current focus to novel sensitizers and/or alternative delivery methods. Poly(ADP-ribose) polymerase inhibitors, for example, have been explored as putative radiosensitizers and chemosensitizers for their effects on DNA repair mechanisms evidenced in human GBM.[155] All studies have failed to show improved efficacy, including combining veliparib with TMZ and most with RT in children with recurrent CNS tumors,[156] or in children with diffuse intrinsic pontine glioma (DIPG).[157]

In adult patients with recurrent GBM, veliparib added to TMZ showed no improved survival, but worsened myelosuppression was noted,[158] similarly reported in the OPARATIC trial of olaparib combined with TMZ.[159] Even when veliparib was combined with standard 60 Gy irradiation with concurrent and adjuvant TMZ, there was no survival benefit for patients with newly diagnosed GBM.[160] The OLA-TMZ-RTE-01 trial of olaparib with standard chemoradiation for newly diagnosed GBM was deemed tolerable, grade 3 to 4 thrombocytopenia ($n = 4$, 13%) and grade 4 neutropenia ($n = 2$, 7%) as the reported DLTs.[161] The phase II portion is still recruiting with the recommended phase 2 dose of olaparib 100 mg BID on days 1 to 3 every 28 days concurrent with the six adjuvant cycles of TMZ.

The randomized German CeTeG/NOA-09 trial suggested benefit in combining TMZ with nitrosoureas compared to TMZ alone (mOS 48.1 vs 31.4 months, $P = .0492$; HR = 0.60), specifically for patients with *MGMT* promoter–methylated GBM.[54] Similar benefit was reported in terms of response rates (odds ratio 46%) for neoadjuvant carmustine and TMZ in a French trial,[55] and in the ACNS0423 pediatric, single-arm trial of adjuvant TMZ and lomustine for malignant astrocytomas.[56] Alkylating chemotherapies, as the only systemic therapy with survival benefit for GBM, thus remain the standard-of-care systemic upfront and salvage therapies for GBM.

Tumor-Treating Fields

TTFields involve the placement of noninvasive transducer arrays on the scalp and the delivery of low-intensity (1-3 V/cm), intermediate-frequency (100-300 kHz), alternating electric fields to the tumor. TTFields lead to tumor cell kill through their action during two phases of mitosis: (1) during metaphase, by disrupting the formation of the mitotic spindle, and (2) during cytokinesis, by dielectrophoretic dislocation of intracellular constituents resulting in apoptosis.[162] TTFields are most effective when applied in the direction of the division axis of the dividing cell, and therefore, two sequential field directions are applied to tumors using two perpendicular pairs of transducer arrays in order to increase the efficacy of TTFields.[163] Following preclinical studies demonstrating in vitro and in vivo activity in glioma,[164] a prospective randomized trial of TTFields and TMZ versus TMZ alone for newly diagnosed GBM after completion of radiochemotherapy demonstrated no significant difference in patient-reported quality of life with TTFields, except for itchy skin, which was to be expected from transducer arrays.[165]

Long-term results of a prospective randomized trial demonstrated improvement in OS and PFS with the addition of TTFields to conventional treatment involving maximally safe resection and adjuvant chemoradiotherapy for newly diagnosed GBM; mOS improved from 16.0 to 20.9 months.[166] Based on these results, TTFields have been approved for the treatment of recurrent and newly diagnosed GBM by the FDA in the

United States and have obtained a CE mark in Europe for the same indications.

Investigational Approaches

Immunotherapy

Modulation of the immune system is being explored in the setting of GBM through such therapeutic interventions as blocking naturally occurring inhibitory immune checkpoint molecules, adoptive T-cell therapeutics, or vaccine therapy against tumor-specific antigens. Nivolumab, a human immunoglobulin G4 monoclonal antibody targeting programmed cell death protein 1 (PD-1), demonstrated no improvement in OS relative to bevacizumab for recurrent GBM in preliminary results from a phase III trial.[167] Rindopepimut, a peptide vaccine targeting EGFRvIII, has been tested in multicenter trials of newly diagnosed EGFvIII-expressing GBM following gross total resection and conventional RT with concurrent TMZ. Although phase II results demonstrated promising outcomes,[168] a double-blind, randomized phase III trial failed to demonstrate an improvement in OS with the use of rindopepimut.[169] Heat shock protein-peptide complex-96 (HSPPC-96) vaccine is an autologous treatment derived from dendritic cells extracted from the patient's tumor to induce antitumor antibodies, demonstrating no survival benefit when added to bevacizumab for recurrent GBM in preliminary results from a randomized trial. Replacement of TMZ with ipilimumab (anti-CTLA4) and nivolumab (anti–PD-L1) for *MGMT* promoter–unmethylated GBM demonstrated no survival benefit.[87]

Radioimmunotherapy

Radioimmunotherapy using monoclonal antibodies against EGFR tagged with ^{125}I has been evaluated in the treatment of HGGs. In an updated report of one study that included a total of 180 patients with a minimum follow-up of 5 years, median survival was 13.4 months for those with GBM.[170]

Another potential target is tenascin, an extracellular protein overexpressed in malignant gliomas but not found in normal tissue. Radiolabeled monoclonal antibodies to tenascin have been evaluated in phase I or II trials showing activity against newly diagnosed and recurrent malignant gliomas. In a phase II trial by Reardon et al,[171,172] ^{131}I-labeled

murine antitenascin monoclonal antibody was injected directly into the surgical resection cavity in 33 patients with untreated malignant glioma. The patients were subsequently treated with external beam RT and 1 year of alkylator-based chemotherapy. Even after accounting for prognostic factors, median survival (86.7 weeks) was longer than that of historical controls. Treatment-related toxicities were mild; only one patient required reoperation for radionecrosis.

Targeted Therapies

Beyond alkylating chemotherapies, the development of targeted therapies for GBM has been elusive. Bevacizumab, the first antiangiogenic therapy approved for GBM, failed to yield survival benefit in concurrent U.S. and European phase III randomized, placebo-controlled trials, despite promise in early-phase trials.[79-82] Bevacizumab, while still approved in the United States, is largely utilized as a steroid-sparing palliative therapy. Regorafenib is an oral multikinase inhibitor with effects against tumor angiogenesis (VEGFR1-3, TIE2), oncogenesis (*KIT, RET, RAF1, BRAF* genes), tumor microenvironment (PDGFR, FGFR), and tumor immunity (CSF1). Regorafenib is now endorsed by national guidelines at recurrence based on the randomized phase 2 REGOMA trial of salvage regorafenib versus lomustine that showed a mOS of 7.4 versus 5.6 months (HR: 0.50; P = .001).[83]

EGFR gene amplification is seen in approximately 40% to 50% of patients with GBM. EGFR is associated with control of cell growth through autocrine and peregrine effects of growth factors. Inhibitors of EGFR tyrosine kinase, such as gefitinib and erlotinib, and and EGFR antibodies have not been successful to date likely because of mutational resistance mechanisms, limited brain penetration of tyrosine kinase inhibitors, and the presence of multiple signaling bypass opportunities. Clinical trials of vaccine therapy directed against EGFRvIII are discussed earlier. A randomized trial of ABT-414, an antibody-drug conjugate targeting EGFR, added to conventional RT and TMZ for newly diagnosed GBM with EGFR amplification did not demonstrate a survival benefit.

Mutations and loss of the *PTEN* gene are encountered in approximately 70% of patients with GBM. PTEN inhibits signaling through the PI3 kinase

and AKT signaling pathway. Loss of PTEN results in loss of effectiveness of EGFR inhibitors, probably because of constitutive signaling through PI3 kinase, which bypasses any upstream EGFR inhibitor effect. Specific inhibitors, such as CCI-779 and everolimus, are ineffective as single agents. Although preclinical experiments suggest that these agents are potential radiosensitizers,[173-175] a prospective trial of everolimus added to conventional RT and TMZ demonstrated no survival improvement compared to historical controls in newly diagnosed GBM.[176]

Cilengitide, a selective integrin inhibitor that acts on tumor cell motility and impacts tumor interaction with brain microenvironment, demonstrated no improvement in OS when added to conventional RT and TMZ for newly diagnosed *MGMT* promoter–methylated GBM in a large phase III trial.[177]

Neovascularization is a major feature of GBM, and many studies demonstrate that GBM secrete VEGF in abundance. The supporting endothelium strongly expresses receptors for VEGF. Bevacizumab, anti-VEGF antibody, has demonstrated impressive radiographic response rate and reduction in peritumoral edema in multiple phase II trials and is FDA approved for the treatment of recurrent GBM (see later). However, two large phase III randomized clinical trials investigating the addition of bevacizumab to the EORTC/NCIC regimen demonstrated no improvement in OS.[79,80]

The most promising molecularly targeted therapy serves less than 5% of patients with GBM with oncogenic mutations, such as BRAF-V600E or NTRK fusions.[70,84] Combination dabrafenib (150 mg BID) and trametinib (2 mg QD) for adults with *BRAF*V600E mutated was primarily assessed based on ORR by RANO criteria.[70] Best ORR was 26% (95% confidence interval [CI]: 12%-45%) in the intention-to-treat glioma population, 29% (95% CI: 11%-52%) for the GBM subset. Durable responses were noted with five of eight (62.5%) responses ongoing for more than 12 months. Median PFS was 1.9 months (95% CI: 1.7-18.5), while the PFS6 rate was 43% (95% CI: 25%-60%). mOS was 11.7 months (95% CI: 6.4 to not reached), while the OS12 rate was 71% (95% CI: 50%-84%). Toxicities of any grade were observed in 92% of patients with HGGs. Grade 3 or worse adverse events were reported in 31 (53%) patients, mainly fatigue (5 [9%]), decreased neutrophil count (5 [9%]), headache (5 [5%]), and neutropenia (3 [5%]). Larotrectinib is a first-in-class, highly selective tropomyosin receptor kinase

(TRK) inhibitor approved to treat TRK fusion–positive cancer, agnostic to histology. The efficacy and safety of larotrectinib in 33 patients (median age: 8.9 years; range: 1.3-79.0) with TRK fusion–positive primary CNS tumors were evaluated using investigator-assessed ORR.[84] The most common histologies were HGG (*n* = 19) and LGG (*n* = 8). ORR was 30% (95% CI: 16-49) overall. The 12-month rates for duration of response, PFS, and OS were 75% (95% CI: 45-100), 56% (95% CI: 38-74), and 85% (95% CI: 71-99), respectively. Median time to response was 1.9 months (range 1.0-3.8 months). Duration of treatment ranged from 1.2 to 31 or more months. Treatment-related adverse events were reported for 20 patients, with grade 3 to 4 in three patients. No new safety signals were identified. Successful treatment of these driver mutations showcases the promise of molecularly targeted therapies for gliomas.

Treatment of Older Patients

Approximately one-third of patients with GBM are 65 years or above. Older age has been demonstrated to be an important adverse prognostic factor in GBM. In a population-based survey of 3,298 patients with GBM in Ontario,[178] each decade increase in age has been associated with a reduction in OS, with patients older than 70 years having a median survival of 4 to 5 months. In the updated results from the EORTC/NCIC trial, Stupp et al[149] observed a survival advantage to RT with concomitant and adjuvant TMZ compared to RT alone in all age subgroups, including patients older than 60 years.

However, because of concerns over the tolerance of conventional chemoradiotherapy for older patients, particularly those with poor performance status, nonconventional approaches to adjuvant therapy have been tested. A phase III Association of French-Speaking Neuro-Oncologists group trial observed improved median survival (29.1 vs 16.9 weeks) and PFS, but equivalent toxicity, with adjuvant RT to 50 Gy plus supportive care compared to supportive care in patients aged 70 years and above with KPS 70 or higher.[179]

Short-course RT and single-agent TMZ have also been investigated. As described previously, Roa et al observed no difference between standard RT of 60 Gy in 30 fractions or a shorter course of 40 Gy in 15 fractions in

patients with GBM older than 60 years.[180] A more recent European trial compared OS between standard RT (60 Gy in 30 fractions), short-course RT (34 Gy in 10 fractions), and single-agent TMZ in patients older than 60 years.[181] This trial demonstrated inferior median survival with 60 Gy RT versus TMZ in the overall population and inferior median survival with 60 Gy RT versus short-course RT in patients older than 70 years. TMZ was associated with more grade 3 to 4 toxicity. The NOA-08 phase III trial demonstrated noninferior survival but higher grade 3 to 4 toxicity with 1-week-on/1-week-off TMZ compared to RT to 54 to 60 Gy in patients older than 65 years with AA or GBM.[182] These trials also demonstrated that when single-modality therapy is being considered because of poor performance status, tolerability concerns, and so on. TMZ alone is superior to RT for the *MGMT*-methylated patients, but the converse is true for the unmethylated patients.

A Canadian-led phase III trial demonstrated improvement in PFS and OS with the addition of TMZ during and as monthly maintenance doses following short-course RT (40 Gy in 15 fractions) in older (65 years or above) patients with newly diagnosed GBM.[150] Median age of patients was 73 years, and two-thirds were older than 70 years. TMZ prolonged mOS from 7.6 to 9.3 months and increased 1-year survival rate from 22.2% to 37.8%. This survival benefit was most marked in patients with *MGMT* promoter methylation where median survival was extended from 7.7 to 13.5 months, and for the *MGMT*-unmethylated patients, the survival difference did not reach statistical significance. Quality-of-life analyses demonstrated no difference in functional domains but noted more nausea, vomiting, and constipation in patients receiving TMZ. Therefore, in older patients, and poor performance status, in the absence of statistically significant survival improvement, and the increase in toxicity, the use of TMZ for the unmethylated patient needs to be questioned.

Treatment at Recurrence

Although several therapeutic options have been considered for patients with recurrent GBM, none are curative, and therefore, the management goals should be palliative. Hospice referral for palliative care is reasonable for many patients, particularly if they have poor performance status. However,

most patients go on to additional therapy, which may include surgery, reirradiation, additional chemotherapy, and/or a clinical trial. The value of palliative debulking has recently been reexamined by the RANO-resect group. They showed that patients who underwent reresection had a median survival of 11 versus 7 months from time of recurrence and that the benefit was largely restricted to patients who could undergo a resection that left residual enhancing disease of 1 mL or less.[183] Based on an impressive radiographic response rate in two nonrandomized, phase II clinical trials,[48,149] single-agent bevacizumab was approved by the FDA in 2009 for the treatment of recurrent GBM. In a study of 49 patients with GBM, Stupp et al[149] reported ORR of 35%, 6-month PFS of 29%, 3.7-month median PFS, and 7.2-month mOS. Similarly, Stupp et al[48] reported an ORR of 28%, 6-month PFS of 43%, median PFS of 4.2 months, and mOS of 9.2 months in a total of 85 patients. Subsequent randomized trials have shown, however, that bevacizumab does not provide a survival benefit in patients with GBM and that the radiographic "responses" were likely related to the impact that bevacizumab has on microvessel stabilization (thereby reducing enhancement) and reduction of tumor-associated edema.[79,184]

Polymer-based local chemotherapy (carmustine wafers) has been tested in a randomized trial that included 222 patients with recurrent glioma (mostly GBM); survival increased from 44% to 64% at 6 months ($P = .02$) for patients with GBM, and median survival from 23 to 31 weeks.[67] Systemic chemotherapeutic agents have been tested mostly in the context of clinical trials and have been uniformly disappointing, as have targeted agents with the notable exception of EGFR tyrosine kinase inhibitors in patients with recurrent GBM expressing wild-type PTEN and mutant EGFR. Of 26 patients with recurrent GBM treated with EGFR tyrosine kinase inhibitors at the University of California, Los Angeles and who had pretreatment tissue, there were seven responders, while 19 had early progression.[185] Coexpression of mutant EGFR and wild-type PTEN had 86% sensitivity, 89% specificity, and a positive predictive value of 75% for response. The BELOB trial was an open-label phase II trial that randomized patients to single-agent bevacizumab or lomustine versus combination of bevacizumab plus lomustine in recurrent bevacizumab-naïve GBM.[186] This trial demonstrated promising 9-month OS of 59% with combination bevacizumab plus lomustine 90 mg/m^2 relative to single-agent bevacizumab

(38%) or lomustine (43%). During this trial, lomustine administered in combination with bevacizumab required dose reduction from 110 to 90 mg/m^2 because of severe thrombocytopenia. However, subsequent phase III trial of single-agent lomustine 110 mg/m^2 versus combination bevacizumab and lomustine 90 mg/m^2 for recurrent GBM at the time of first progression prolonged PFS but did not confer a survival advantage.[187]

In the treatment of recurrent GBM, a randomized clinical trial found a statistically significant survival benefit with FDA-approved chemotherapy selected using chemosensitivity tumor testing on CSCs (ChemoID) compared to physician-chosen chemotherapy.[57] The survival benefit seen in this trial for recurrent GBM suggests guiding chemotherapy selection using chemosensitivity tumor testing as a strategy for future testing in newly diagnosed GBM.

Repeat RT using one of several different methods (including radiosurgery, brachytherapy, GliaSite balloon brachytherapy, and even repeat external beam photon or proton RT) may be considered for carefully selected patients. Hypofractionated reirradiation with bevacizumab has shown promising results in small single-institutional reports, with surprisingly limited toxicity, attributed to "vascular stabilization and protection" resulting from bevacizumab, and more investigations of this approach are being considered.[188] A prospective randomized trial of hypofractionated reirradiation with bevacizumab compared to bevacizumab alone demonstrated increased 6-month PFS by 25% with relative safety but no effect on OS.[189]

Evidence-Based Treatment Summary

1. Maximal surgical resection is generally recommended to establish pathologic diagnosis, provide tissue for molecular studies, and achieve cytoreduction that may improve neurologic deficits. Increasingly, in the surgical literature, data suggest that a resection should also include the nonenhancing component if feasible and safe.
2. Postoperative RT has been shown to provide a survival advantage in several clinical trials. The typical RT dose is 60 Gy in 6 weeks for younger and prognostically favorable patients. Dose escalation beyond

60 Gy has not proven to be effective; radiation sensitizers have not provided a survival benefit.

3. TMZ, given during and after RT for six cycles, provides a significant survival advantage that is greatest in patients with methylation of the promoter region of the *MGMT* gene. The benefit in the unmethylated population is questionable. Even older patients benefit from this approach. Prolongation beyond 6 months does not enhance survival; neither does dose intensification or chemosensitization strategies.
4. TTFields administered after RT and concomitant with high-dose TMZ also prolong survival.
5. Bevacizumab confers no survival benefit for newly diagnosed GBM but can be an effective salvage therapy at the time of progression, although there are no categorical data demonstrating that it prolongs survival in patients with recurrent GBM. It can also be useful in large tumors with significant cerebral edema by improving neurologic disability and sparing prolonged steroids. The addition of reirradiation improves PFS compared to bevacizumab alone for recurrent GBM.
6. Short-course RT is a reasonable option for older patients or those with poor performance status or transportation limitations.
7. If unimodality therapy is being contemplated (especially in sicker patients, less likely to tolerate combination therapy), TMZ alone for the *MGMT* methylated and RT alone for the *MGMT* unmethylated are reasonable considerations.

World Health Organization Grade 3 Gliomas

Conventional approaches at discussing management utilized grade as a division point to identify different entities. The recent utilization of *IDH* mutation status, and especially the availability of *IDH*-targeted therapeutics, is leading to classification dichotomization, based on the presence or absence of this mutation. Because the majority of the legacy data, with exception of the recently published INDIGO trial, have not used such dichotomization, we continue to present therapeutic strategies as historically developed and driven by grade and separately address the use of *IDH* inhibitors in a latter section.

WHO grade 3 gliomas (see Table 40.3) constitute approximately 25% of HGGs in adults, generally occurring during young to middle adulthood. Histologically, these tumors have increased cellularity, nuclear atypia, and marked mitotic activity, without necrosis or neovascularization. On imaging, anaplastic gliomas may show enhancement and necrosis similar to GBM, although up to one-third of tumors may not enhance.[190] The classification for these gliomas has changed dramatically over the past decade, and some of the older terminology (eg, oligoastrocytoma, "anaplastic") has been dropped in favor of more descriptive terminology that is based upon the molecular genetic makeup of each tumor. Due to the extent of the older terminology in the literature, particularly with respect to clinical trials, we have maintained the use of this language for discussing the historical approaches to the treatment of these tumors.

The prognosis for patients with anaplastic glioma is heavily influenced by a number of molecular genetic factors. Patients with histologically defined anaplastic oligodendroglioma, in general, have a better prognosis. Other prognostic factors include age at diagnosis, mental status, and performance status (see Table 40.5). However, the prognosis of these patients is best defined by molecular factors, such as allelic loss of 1p and 19q and the presence of *IDH1* mutation (see later).

Anaplastic Oligodendroglioma

Anaplastic oligodendroglioma represents 3.5% of all malignant gliomas and 30% of oligodendroglial tumors. They occur predominantly in adults, with median age at diagnosis of 45 to 50 years, approximately 7 to 9 years older than grade II oligodendroglioma; this age difference reasonably corresponds to the average time of tumor "evolution" from grade II to grade III.

Molecular Genetics

Allelic loss of 1p and 19q is thought to be an early genetic alteration in the transformation and progression of oligodendrogliomas. Definitionally, 1p19q codeletion is a prerequisite to label a glial neoplasm and oligodendroglioma as per the current classification, and deletions in 1p and 19q have been associated with longer PFS, OS, and chemo- and radiosensitivity.[191-193]

Therefore, grade 3 (G3) glial neoplasms without this codeletion would be labeled G3 astrocytoma, or, as conventionally referred to, AA. Further, the presence or absence of an *IDH* mutation yields a further subclassification of AA into *IDH* mutated or wild type, with the former having significantly better survival probability and longevity.

The impact of 1p19q codeletion status on outcome has been confirmed in two phase III trials. RTOG 94-02 retrospectively assessed 1p and 19q status in 263 (71%) of 291 enrolled patients with anaplastic oligodendroglioma/oligoastrocytoma randomized to receive chemotherapy with PCV followed by RT or RT alone.[194] Combined loss of 1p and 19q was present in 44% of patients in the PCV plus RT arm and 52% in the RT-alone arm and was more frequent in anaplastic oligodendroglial tumors (76%) than in anaplastic oligoastrocytoma (24%). Combined loss of 1p and 19q resulted in a longer median survival time (14.7 vs 2.6 years [$P < .001$] in patients receiving PCV plus RT; 7.3 vs 2.7 years [$P < .001$] in patients treated with RT alone). In EORTC 26951, 368 patients with anaplastic oligodendroglioma/oligoastrocytoma were randomized to receive RT followed by PCV or RT alone.[195] The presence of 1p or 19q loss was found to be the most important predictor of outcome, with a median survival of 10.3 versus 1.9 years for tumors with or without combined allelic loss of 1p and 19q.

Other molecular factors with clinical implications, as indicated earlier, include somatic mutations in the *IDH1* gene and *MGMT* promoter methylation. *IDH1* mutations have been observed in 55% to 80% of grade II and III gliomas.[196] *IDH* mutations generate an oncometabolite that is believed to be contributory to malignant transformation for precursor cells to gliomas and, therefore, is an early event. Intriguingly, in spite of the fact that the mutation generates the causative oncometabolite, prospective trials of anaplastic gliomas have demonstrated *IDH1* mutations to be a strong positive prognostic factor. In EORTC 26951, *IDH1* mutations were observed in 46% of patients and demonstrated prognostic significance, independent of 1p/19q codeletion, in both arms of the trial for both PFS and OS.[197] In RTOG 9402, *IDH1* mutations were observed in 74% of patients, were associated with longer OS (9.4 vs 5.7 years), and identified patients without 1p19q codeletion who derived an OS benefit from the addition of PCV chemotherapy to RT (5.5 vs 3.3 years).[198] This suggests that both

subgroups, 1p19q codeleted (which almost always harbor *IDH* mutations), and the 1p19q noncodeleted (which now would not be labeled oligodendroglioma), but with *IDH* mutations, should be treated with combination chemoradiotherapy, and the third subset, 1p19q noncodeleted without *IDH* mutations, has the worst prognosis (similar to GBM, and many now qualify for a grade 4 label based on specific molecular alterations) and appears unlikely to derive benefit from the addition of chemotherapy. In both the EORTC and RTOG trials, the longest OS after PCV chemotherapy plus RT was observed in patients whose anaplastic oligodendroglial tumors contained both allelic loss of 1p and 19q and *IDH1* mutation (OS 12.8 years on EORTC trial, 14.7 years on RTOG 9402). *MGMT* promoter methylation has also demonstrated prognostic significance for anaplastic oligodendroglial tumors. However, unlike grade IV astrocytomas (GBM), in which *MGMT* promoter methylation predicts survival benefit from TMZ added to RT, *MGMT* promoter methylation has not shown similar predictive significance for outcome to PCV chemotherapy in anaplastic oligodendroglial tumors.[199] This is to be expected because *MGMT* methylation provides a mechanistic opportunity for TMZ to exert its specific cytotoxicity, and the PCV regimen does not contain TMZ or a drug that creates an identical cytotoxic DNA lesion. A German multicenter phase III trial of upfront RT versus upfront chemotherapy for newly diagnosed anaplastic gliomas observed *IDH1* mutations to be a stronger prognostic factor than either 1p19q codeletion or *MGMT* promoter hypermethylation.[200] The caveat of course is that both *MGMT* promoter hypermethylation and *IDH1* mutations are strongly correlated with 1p19q chromosomal loss.

Treatment

The current standard of care for patients with anaplastic oligodendrogliomas is maximal surgical resection followed by postoperative RT and chemotherapy. The RT target volume includes both the postoperative cavity and any residual enhancing disease, but also the FLAIR or T2 abnormality; unlike the situation with GBM, the postoperative FLAIR abnormality from anaplastic oligodendroglioma (and for that matter low-grade, grade 2 gliomas) most likely represents predominantly residual

tumor with minimal contribution from tumor-associated edema and, therefore, has to be included in the target volume. Indirect support for this comes from the small, but growing body of data regarding supraradical resection of lower grade gliomas, where complete resection of all MR abnormality is associated with longer survival.[201] Although the commonly used RT dose on prospective trials of anaplastic oligodendroglioma is 59.4 Gy, this never took into account molecular variability, and some have proposed that consideration could be made to lower the RT dose to 54 Gy for tumors with favorable prognostic features as outlined earlier, to minimize long-term toxicity (eg, 1p19q codeleted).

Anaplastic oligodendrogliomas are generally thought of as chemosensitive primarily based on high response rates to PCV in several studies. Two large randomized trials, described earlier, have investigated the use of sequential chemoradiotherapy compared to RT alone with chemotherapy reserved for salvage in patients with anaplastic oligodendroglioma and oligoastrocytoma.[194,195] With 11-year follow-up on RTOG 9402, the addition of PCV chemotherapy for four cycles prior to RT did not impact OS for the overall cohort, but did prolong OS for patients with allelic loss of both 1p and 19q from 7.7 to 14.7 years.[194] Among patients without combined allelic loss of 1p and 19q, the addition of PCV chemotherapy prior to RT prolonged survival for patients with *IDH1*-mutated tumors from 3.3 to 5.5 years.[198] With 11-year follow-up, the EORTC trial did observe an OS prolongation with the addition of PCV for six cycles after RT in the overall cohort from 2.6 to 3.5 years, with more benefit observed in tumors with combined allelic loss of 1p and 19q.[195] Therefore, currently, it would be prudent to conclude that in practice, both the 1p19q-codeleted and any *IDH*-mutated (with or without 1p19q codeletion) patients should receive chemoradiotherapy, but the role of combinatorial therapy for the 1p19q-noncodeleted and *IDH* wild-type tumors is questionable.

Because of the significant toxicity associated with PCV, many clinicians now use TMZ, which is much better tolerated. TMZ has produced high response rates in patients with anaplastic oligodendroglioma. Chinot et al[202] administered TMZ to 48 patients with anaplastic oligodendroglioma/oligoastrocytoma who had previously failed PCV chemotherapy. The ORR was 43.8% (complete response [CR] 16.7%, PR

27.1%). Vogelbaum et al[203] reported the results of RTOG 01-31, a phase II trial in which TMZ was given preradiotherapy to patients with newly diagnosed anaplastic oligodendroglioma/oligoastrocytoma. In the 27 patients available for review, the ORR was 33.3% (CR 3.7%, PR 29.6%). The 6-month progression rate was 10.3%. Toxicity was acceptable.

In addition, a recent international retrospective study of over 1,000 adults with anaplastic oligodendroglial tumors observed that combination chemotherapy and RT was associated with longer time to PFS and OS than either modality alone.[204] In cases without 1p19q codeletion, Lassman et al observed that combination chemotherapy and RT was associated with longer time to PFS and OS than either modality alone. In cases with 1p19q codeletion, combination chemotherapy and RT was associated with longer median time to progression compared to either modality alone, but this difference was not associated with a survival advantage. In addition, longer time to progression was observed with PCV, compared to TMZ, in codeleted cases. Therefore, although TMZ is widely used in lieu of PCV, the data supporting this practice are weak at best, and, based on Lassman's retrospective review, possibly deleterious. A North American Intergroup trial is currently enrolling patients in order to compare chemoradiotherapy with either TMZ or PCV for both grade 3 and grade 2 codeleted gliomas (CODEL).

Anaplastic Astrocytoma

Molecular Genetics

AAs are defined by the *IDH* mutation status. AA with *IDH* mutations carries the most favorable prognosis, whereas *IDH* wild-type AA carries the worst prognosis, comparable biologically to GBM.[205]

Treatment

For WHO grade 2 infiltrative gliomas, there is no established standard of care for initial therapy. For *IDH*-mutant diffuse gliomas, 1p/19q-codeleted oligodendrogliomas and, to a lesser degree, *IDH*-mutant astrocytomas, PCV neoadjuvant or adjuvant to definitive radiation or as monotherapy can be used initially or at recurrence.[195,200] *IDH* wild-type astrocytomas are more often treated with TMZ concurrent and adjuvant to radiation and/or as

monotherapy initially or at recurrence, with nitrosourea (BCNU or CCNU) monotherapy or PCV deferred to recurrence.[206] A double-blind, phase 3 trial recently showed increased PFS of vorasidenib (40 mg QD) compared to placebo for residual or recurrent grade 2 *IDH*-mutant glioma who had undergone no previous treatment other than surgery.[73] OS data are pending, and no comparison was made to alkylating chemotherapy and/or RT, yet the PFS was inferior to prior radiation or chemoradiation trial reports. The use of vorasidenib in these high-risk patients, as incomplete resection and/or measurable disease was required, in lieu of upfront chemoradiation remains controversial. Vorasidenib remains an alternative to observation for patients or providers preferring to defer chemotherapy and/or radiation as a salvage strategy.

For *IDH* wild-type diffuse astrocytomas, TMZ is established concurrent and adjuvant to radiation, initial monotherapy, and/or as salvage at recurrence, while nitrosourea (BCNU or CCNU) monotherapy is commonly deferred to recurrence. PCV is not commonly used due to the lack of efficacy in multiple trials.

The current standard of care for patients with AA is maximal surgical resection followed by postoperative RT and chemotherapy. The RT target volume and dose are similar to those for anaplastic oligodendroglioma.

TMZ has shown activity in patients with recurrent AA. In a phase II trial by Yung et al,[148] 162 patients with AA were treated with TMZ (150-200 $mg/m^2/d$ on days 1-5 every 28 days) at the first relapse. The 6-month PFS was 46%, and OS was 13.6 months. The ORR was 35% (CR 8%, PR 27%).

The effectiveness of TMZ was further tested in a phase III trial of non–1p19q-codeleted anaplastic glioma (ie, G3 AA) patients (the CATNON Intergroup trial). This trial randomized patients with newly diagnosed 1p/19q-noncodeleted anaplastic glioma to RT alone, RT with concurrent TMZ 75 mg/m^2 per day, RT followed by adjuvant TMZ of 150 to 200 mg/m^2 given on days 1 to 5 for twelve 4-week cycles, or RT concomitant with daily TMZ and followed by 12 cycles of adjuvant TMZ.[207] The second interim analysis declared futility of concurrent TMZ with no significant difference in mOS between concurrent TMZ (66.9 months, 95% CI: 45.7-82.3 months) and no concurrent TMZ (60.4 months, 95% CI: 45.7-71.5 months). Adjuvant TMZ improved OS (mOS 82.3 months, 95% CI: 67.2-116.6 months) compared with no adjuvant TMZ (mOS 46.9 months, 95%

CI: 37.9-56.9 months) with HR of death for adjuvant TMZ compared to no adjuvant TMZ of 0.64 (95% CI: 0.52-0.79, $P < .0001$).

RTOG 9813 was a phase III trial of RT plus TMZ versus RT plus nitrosourea.[205] This study closed early because of the inability to meet target accrual rate. However, with a median follow-up of 10.1 years, no difference in PFS or OS was observed. However, the RT plus nitrosourea arm experienced more grade 3 or higher toxicity (76% vs 48%) primarily because of myelosuppression, which led to discontinuation of therapy in 27.6% in the nitrosourea arm versus none in the TMZ arm. The trial demonstrated the prognostic benefit of the *IDH1* mutation in AA with *IDH1* mutation–positive patients having longer median survival time than *IDH1* wild-type patients (7.9 vs 2.8 years).

The NOA-04 trial compared radiation with two chemotherapy regimens for anaplastic gliomas, the majority of whom carried a diagnosis of AA.[200] In a 2:1:1 randomization, 318 patients were assigned to partial-brain irradiation alone versus PCV chemotherapy versus TMZ with time-to-treatment failure as the primary end point. Chemotherapy failures were salvaged with RT, and vice versa, and further, TMZ failures were salvaged with PCV and vice versa, almost ensuring that every patient received every therapy at some point. Time-to-treatment failure was similar between each of the arms, as was OS, imputing that the sequence of RT, TMZ, or PCV might not actually matter. This study also helped to establish *IDH1* mutation as an important prognostic factor for AA.

Evidence-Based Treatment Summary

1. Maximal resection is generally associated with more favorable outcomes and is recommended whenever feasible.
2. Molecular characterization of the tumor in terms of combined allelic loss of 1p and 19q and *IDH* mutational analysis carries important prognostic information and is necessary for accurate diagnosis; definitionally, anaplastic oligodendroglioma carries a codeletion of 1p19q.
3. Both AA and anaplastic oligodendroglioma can be either *IDH* wild type or carry a mutation, which imparts a prognostic advantage.

4. Postoperative RT has been shown to provide a survival advantage in several clinical trials, but these trials included patients with both WHO grade III and IV tumors; no trial for only grade III tumors, evaluating RT versus no RT, has been conducted. The RT dose is typically 59.4 to 60 Gy in 6 to 6.5 weeks. Some have proposed that tumors with prognostically favorable molecular features (1p19q codeletion and *IDH* mutation) could be treated to a slightly lower dose of 54 Gy in 6 weeks, given the potential for extended survival with the addition of chemotherapy and the desire to minimize long-term neurotoxicity.
5. In patients with anaplastic oligodendroglioma, the addition of PCV chemotherapy to RT prolongs OS, most notably in patients with combined allelic loss of 1p and 19q, but also in those with *IDH* mutation. Although TMZ is frequently used for these patients, there has been no direct comparison between PCV and TMZ, and limited evidence supports its use.
6. In patients with AA, the addition of adjuvant TMZ after RT provides a survival advantage, and *IDH* retains prognostic significance. The exact role of concurrent TMZ has not been fully defined. Based on the NOA-04 trial, if all three approaches, that is, radiation, TMZ, and PCV are to be used, sequencing may not matter.
7. The role of *IDH* inhibitors in the sequence of therapy remains to be established.

Low-Grade Glioma

LGGs are generally slower growing tumors that are divided into pilocytic and nonpilocytic subtypes. They account for 20% of gliomas and 10% of primary intracranial tumors in adults.

Pilocytic Astrocytoma

Pilocytic astrocytoma, also known as juvenile astrocytoma, corresponds to WHO grade 1. They are more common in children. On imaging, they are well-circumscribed enhancing lesions, often with a cystic component. Tandem duplication of chromosome 7q34 resulting in fusion of the *BRAF*

and *KIAA1549* genes is observed in 60% to 80% of sporadic pilocytic astrocytomas.[208]

Treatment

Pilocytic astrocytomas are more amenable to total resection than other LGGs. Fenestration of the cyst and resection of the mural nodule are usually curative. In tumors in which the wall of the cyst enhances, cystic degeneration is more likely, and resection of the entire cyst is necessary. Complete resection of pilocytic astrocytomas is associated with excellent survival, with the majority (>90%) of patients cured of the tumor; no adjuvant therapy is necessary. Incomplete resection is associated with long-term survival rates of 70% to 80% at 10 years.

The benefit of postoperative RT is unclear. The usual recommendation is for close follow-up following gross or subtotal resection and utilizing RT for tumors that have recurred more than once, or for those with considerable residual disease in a critical location, where even slight progression could result in significant morbidity. The North Central Cancer Treatment Group (NCCTG) 867251 enrolled 20 patients with supratentorial pilocytic astrocytoma on a prospective trial of RT after biopsy (3 patients) or observation after gross (11 patients) or subtotal (6 patients) resection.[209] With a 20-year follow-up, PFS was 95% and OS was 90%, with the cause of death in both patients who died being unrelated to tumor. If RT is indicated, the dose is typically 50 to 54 Gy (1.8-2 Gy fractions). However, there is evidence of improved PFS with RT, and immediate postoperative irradiation may be appropriate in some relatively uncommon cases, depending on the location of the tumor, the extent of residual disease, the feasibility of repeated surgical excision, and availability for follow-up.

The presence of the tandem duplication of chromosome 7q34 resulting in fusion of the *BRAF* and *KIAA1549* genes, observed in 60% to 80% of sporadic pilocytic astrocytomas, has prompted the use of BRAF inhibitors in some of these patients, especially at recurrence, and when other options have been exhausted. Occasional tumor responses have been reported.

For WHO grade 1 gliomas of all histologic and molecular subtypes, including the WHO grade 1 pediatric-like diffuse gliomas, circumscribed astrocytomas, and other glioneuronal tumors as per the 2021 classification,

systemic alkylating or other cytotoxic chemotherapy is reserved for recurrent tumors or malignant transformation. There is no accepted standard of care for salvage systemic chemotherapy, but multiple prospective clinical trials with over 2,000 pediatric patients with LGGs showed efficacy for vincristine and carboplatin, monotherapy with vinblastine, or a combination of thioguanine, procarbazine, CCNU, and vincristine. The typical 5-year PFS for sporadic pediatric LGG ranged from 35% to 45% despite the differing toxicity profiles of the regimens and was higher in patients with NF1-associated LGG (60%-70%). Subsequent progression was common across both sporadic and NF1-associated LGG.[72] Additional options include TMZ, nitrosourea, platinum, vincristine, and etoposide-containing regimens, namely based on approved treatment for infiltrative gliomas.[210] Future trials may help to better personalize therapies in patients with LGG.

Molecularly targeted options for LGGs are in rapid development. Combination dabrafenib and trametinib for *BRAF*V600E-mutated gliomas, such as pilocytic astrocytoma, ganglioglioma/gangliocytoma, or other glioneuronal histologies.[70] The 13 patients in the LGG cohort of the ROAR basket trial had a median follow-up of 32·2 months (interquartile range 25·1-47·8), with 9 patients (69%; 95% CI: 39-91) having an objective response, including 1 CR, 6 PRs, and 2 minor responses. Grade 3 or worse adverse events were reported in 31 (53%) patients, the most common being fatigue (5 [9%]), decreased neutrophil count (5 [9%]), headache (3 [5%]), and neutropenia (3 [5%]). MEK inhibitor monotherapy, such as trametinib and selumetinib, show promising efficacy in BRAF-rearranged (non-V600E mutant) LGGs of various histologies. BRAF inhibitors are contraindicated in BRAF- rearranged LGG due to paradoxical activation of MAPK signaling through increased RAF dimerization.[211] A Pediatric Brain Tumor Consortium phase 2 trial of selumetinib (RP2D of 25 mg/m^2/dose BID) was tolerable and beneficial in children with recurrent or progressive optic pathway and hypothalamic gliomas based on radiographic response and PFS (78% ± 8.5% at 2 years).[212] Visual outcomes also improved in most patients. Notably, visual acuity improved in 4 (21%) of 19 patients and was stable in 13 (68%) of 19 patients, while 5 (26%) of 19 patients had improved and 14 (74%) of 19 patients had stable visual fields. The most common toxicities were grade 1/2 creatine phosphokinase elevation, anemia, diarrhea, headache, nausea/emesis, fatigue, aspartate transaminase

and alanine transferase increase, hypoalbuminemia, and rash. The role of mTOR inhibitors and receptor kinase inhibitors, both as monotherapy and in combination, remains investigational. A Neurofibromatosis Clinical Trials Consortium phase 2 study of daily everolimus in 23 children with median age 9.4 (range: 3.2-21.6) years with recurrent/progressive NF1-associated LGG and prior treatment with carboplatin-containing chemotherapy demonstrated significant clinical benefit, 15 (68%) of 22 enrolled patients showed shrinkage (1 CR, 2 PR) or arrest of tumor growth (12 stable), of which 10 of 15 remained free of progression at a median follow-up of 33 months.[213] Treatment was well tolerated, and none discontinued due to toxicity. Bevacizumab, while approved for recurrent WHO grade 4 GBM, has little role and no clear proven benefit in LGG, but can be used for symptom management from radiation-induced necrosis or transformation to malignant grades. At the time of recurrence, treatment options are limited, with no accepted standard of care and reduced benefit for both *IDH*-mutant and wild-type tumors.[72]

Evidence-Based Treatment Summary

1. Maximal surgical resection, although not tested in a prospective trial, is associated with more favorable outcomes and is recommended whenever feasible. Molecular testing, especially for BRAF, should be conducted, if feasible.
2. Postoperative RT may be considered in patients with incompletely resected tumors, based on risk factors for progression and consequences of progression.
3. Chemotherapy does not have an established role in pilocytic astrocytoma in adults, but BRAF inhibitors are being used in situations where other options have been exhausted.

World Health Organization Grade 2 Gliomas

WHO grade 2 gliomas include those referred to as nonpilocytic or diffusely infiltrating LGGs. They may arise from an astrocytic or an oligodendrocytic lineage. Presentation usually occurs in the third or fourth decade of life, and only a small percentage of patients are younger than 19 or older than 65.

Approximately 80% of patients present with seizures.[214] CT typically demonstrates an ill-defined, diffuse, nonenhancing low-density region, often in the frontal or temporal lobes. Calcifications are commonly seen with oligodendrogliomas. MRI is more sensitive in detecting and defining these lesions, which are hypointense and nonenhancing on T1-weighted images and hyperintense on T2-weighted images. Because these tumors are highly infiltrative, tumor always extend beyond the abnormality observed on imaging. MRI analysis reveals an average growth rate of 5 mm/y.[215]

Histologically, there is increased cellularity compared to normal brain tissue with mild-to-moderate nuclear pleomorphism and no evidence of mitotic activity, vascular proliferative changes, or necrosis. Differentiation from reactive gliosis can be difficult.

Several clinical variables have been found to be of prognostic importance. Pignatti et al[216] performed the most comprehensive of these analyses and constructed a scoring system to identify patients at low and high risk. This study was based on data from two large European phase III trials for LGG designed to examine the dose and timing of postoperative RT, EORTC 22844, and EORTC 22845. Cox regression analysis was used to identify prognostic variables from 322 patients from EORTC 22844 and then validated on 288 patients from EORTC 22845. Multivariable analysis showed that age 40 or above, astrocytoma histology, maximum diameter 6 cm or greater, tumor crossing the midline, and the presence of neurologic deficits negatively impacted survival. A prognostic scoring system was derived: Patients with up to two of these factors were considered low risk (median survival 7.7 years) and patients with three or more as high risk (median survival 3.2 years). However, the data used to identify these prognostic factors predated modern clinical trials evaluating molecular genetics.

Molecular Diagnosis and Prognosis

The distinction between astrocytoma and oligodendroglioma rests on the detection of combined allelic loss of 1p and 19q, which is characteristic of oligodendroglioma, as well as additional genetic aberrations, such as ATRX, TP53, and TERT mutations. 1p19q codeletion is present only with an *IDH1* mutation and is the molecular signature with the most favorable

overall prognosis. The prior tumor subtype of mixed oligoastrocytoma is no longer considered a distinct entity, as the 1p19q-codeleted and *IDH*-mutant grade 2 oligodendroglioma and the *IDH*-mutant grade 2 astrocytoma are considered mutually exclusive subtypes. 1p19q-codeleted and *IDH*-mutant grade 2 oligodendroglioma, when associated with a TERT mutation, carries an mOS of 11 years, whereas *IDH*-mutant grade 2 astrocytoma associated with TP53 mutation and ATRX loss carries a median survival of only 6 to 8 years. LGGs identified as *IDH* wild type show clinical behavior similar to high-grade tumors with poor OS.[217]

In a review of 44 cases of low-grade oligodendrocytic tumors, Sasaki et al[218] considered half of the cases classic oligodendroglioma and the remainder nonclassical oligodendroglioma with more astrocytic features on histopathology. Deletion of 1p was detected in 86% and 27% of these groups, respectively. Response to chemotherapy was assessed at the time of recurrence in 13 patients. Of the 11 who responded to chemotherapy, 10 had a loss of 1p. Both of the nonresponders were found not to have a loss of 1p. A small prospective trial by Hoang-Xuan et al[219] found a similar trend. Loss of 1p with or without loss of 19q, which was detected in 12 of 26 patients with low-grade oligodendrocytic tumors treated with TMZ, was found to have a significant association with response to chemotherapy ($P < .004$).

IDH1 mutations may be predictive of a better prognosis in patients with LGGs, but this marker does not categorically appear to predict response to chemotherapy, with the caveat that the data testing this are dated and sparse.[220] In one prospective trial of RT with or without chemotherapy, the presence of *IDH1* mutation was associated with prolonged median survival from 5.1 years among patients without the mutation to 13.1 years among those with the mutation, when receiving the combined modalities.[221]

Unplanned molecular analyses of EORTC 22033-26033 demonstrated prognostic significance associated with molecular characterization.[222] Median PFS was 62 months for *IDH*-mutated/1p19q-codeleted tumors, 48 months for *IDH*-mutated/1p19q-noncodeleted tumors, and 20 months for *IDH* wild-type tumors. *MGMT* promoter was methylated in all patients with *IDH*-mutated/1p19-codeleted tumors, in 86% of *IDH*-mutated/1p19q-noncodeleted tumors, and 56% of *IDH* wild-type tumors.

Treatment

The clinical course for patients with diffusely infiltrative low-grade tumors is variable, with some patients having long survival even with treatment and others suffering from progressive deterioration despite treatment. In general, early intervention is indicated for almost all patients. Adequate tissue sampling is critical to ensure accurate diagnosis, and maximal surgical resection in this context may be advisable in appropriately selected patients. In younger patients (<40 years) who have undergone complete resection, observation with serial imaging is an option. In those who have undergone a subtotal resection or those with high-risk features, postoperative RT and chemotherapy are recommended, typically 50 to 54 Gy in 1.8 Gy fractions. The INDIGO trial testing an *IDH* inhibitor has introduced yet another possible therapeutic avenue.

Surgery

In practice, most patients undergo surgery at presentation in order to establish the diagnosis and to determine histology, grade, and molecular characteristics that affect treatment. However, even under the best circumstances, total resection with an adequate margin is rarely achieved because of the diffusely infiltrative nature of these tumors and the involvement of eloquent regions. Although controversial, most studies have found total or subtotal (>90%) resection to be associated with improved outcome.[223] Moreover, with the advent of modern MRI and intraoperative electrostimulation in the awake craniotomy setting to assist in identifying critical areas of the brain, resection may be achieved with less morbidity and mortality than in the past.[223,224] Proponents of aggressive resection are also supported by studies that suggest that radical surgery results in more accurate histopathologic diagnosis.[225] In RTOG 98-02, 5-year PFS in 111 good-risk patients, defined as patients younger than 40 years and gross total tumor resection, was 48%.[226] Review of postoperative MRI demonstrated crude recurrence rates of 26%, 68%, and 89% for less than 1, 1 to 2, and greater than 2 cm residual disease, respectively. More recently, some neurosurgeons have advocated for resection of more brain tissue than what appears to be involved on MRI for nonenhancing gliomas, to the extent that does not result in a loss of neurologic function,[227] in other words a

functionally guided resection rather than an anatomic resection. The excellent outcomes in these cases may be related to patient selection (eg, tumor location and tumor volume), and a systematic review did not support the routine use of this surgical approach.[228]

Radiotherapy

Three phase III trials provide the best evidence with respect to the indications for RT as well as the dose (Table 40.6).

TABLE 40.6 PHASE III TRIALS OF PATIENTS WITH LOW-GRADE GLIOMA TREATED WITH RADIOTHERAPY

Study	Treatment Arm	*N*	5-Year Survival (%)
EORTC 22845	Observation[a]	157	66
	54 Gy (30 fractions)	157	68
EORTC 22844	45 Gy (25 fractions)	171	58
	59.4 Gy (33 fractions)	172	59
NCCTG	50.4 (28 fractions)	101	72
RTOG 9802 (Age ≥40 or STR)	64.8 (36 fractions)	102	64
	54 Gy (30 fractions)	128	63
	54 Gy plus PCV	126	72

CCNU, lomustine; EORTC, European Organization for Research and Treatment of Cancer; *N*, number of patients; NCCTG, North Central Cancer Treatment Group; PCV, procarbazine, CCNU, and vincristine; RTOG, Radiation Therapy Oncology Group; TMZ, temozolomide.

[a]Treatment with radiotherapy at progression.

Patients considered favorable by the scoring system introduced by Pignatti et al[216] are typically observed postoperatively and given RT at disease progression or recurrence. This practice is based on the results of a phase III trial by van den Bent et al in EORTC 22845.[229] In this multi-institutional trial, 314 patients with LGGs were randomized to receive postoperative RT to 54 Gy in fractions of 1.8 Gy (n = 157) or RT at progression (n = 157). A significant improvement in median PFS was found with early RT (5.3 vs 3.4 years, $P < .0001$), but there was no difference in median survival (7.4 vs 7.2 years, $P = .872$). It is of note that 65% of the patients in the delayed RT group received RT at progression. Malignant

transformation occurred in 65% to 72% of patients, with no difference between the two groups. Although seizure control was superior in the early RT group, adequate data on quality of life were not obtained. The authors concluded that although early RT may be appropriate in some situations, for example, patients with symptomatic lesions, withholding RT until tumor progression does not jeopardize survival.

For patients given RT postoperatively, the dose has been established by 2 phase III trials. In EORTC 22844, 379 patients were randomized to receive 45 Gy in 5 weeks or 59.4 Gy in 6.6 weeks postoperatively.[230] With a median follow-up of 74 months, OS (58% vs 59%) and PFS (47% vs 50%) were similar in both arms.

In a joint NCCTG, RTOG, and ECOG study, 203 patients were randomized to low-dose RT to 50.4 Gy in 28 fractions (n = 101) or high-dose RT to 64.8 Gy in 36 fractions.[231] There was no significant difference in PFS or OS. Survival at 2 and 5 years was 94% and 72%, respectively, with low-dose RT and 85% and 64% with high-dose RT. Grade 3 to 5 neurotoxicity occurred in 5% of patients in the high-dose cohort and 2.5% of patients in the low-dose cohort.

Consequently, low-dose RT, 50 to 54 Gy in 1.8 Gy fractions, is the standard of care for patients with LGGs. The target volume typically includes a margin of 1 to 2 cm beyond changes demonstrated on traditional MRI sequences. Using FLAIR images, which usually show abnormality beyond any enhancing or nonenhancing tumor, a smaller margin of 0.8 to 1 cm may be used.

However, this concept of dose will likely need to be revisited in light of the fact that it might be possible to decrease dose (to say 45 Gy) in the most favorable subset (1p19q codeleted, *IDH* mutated), but increase it (to say 59.4 Gy) in the most unfavorable subset (*IDH* wild type).

Chemotherapy/Chemoradiotherapy

There is no established standard of care for initial chemotherapy for WHO grade 2, *IDH*-mutant infiltrative gliomas. For *IDH*-mutant diffuse gliomas, 1p/19q-codeleted oligodendrogliomas and, to a lesser degree, *IDH*-mutant astrocytomas, PCV neoadjuvant or adjuvant to definitive radiation or as monotherapy can be used initially or at recurrence.[195,200] *IDH* wild-type

astrocytomas are more often treated with TMZ concurrent and adjuvant to radiation and/or as monotherapy initially or at recurrence, with nitrosourea (BCNU or CCNU) monotherapy or PCV deferred to recurrence.[206]

Multiagent chemotherapy, in particular PCV, appears promising with response rates ranging from 50 to 80% in recurrent and newly diagnosed tumors.[232,233] The publication of mature results from RTOG 9802 has significantly altered the standard of care, as the addition of PCV to RT provided a significant OS advantage.[221] In this phase III trial, 254 unfavorable patients (age ≥40 with subtotal resection or biopsy) were randomized to receive RT alone to 54 Gy in 30 fractions or RT followed by six cycles of standard-dose PCV. With a median follow-up of 11.9 years, mOS was extended from 7.8 years following RT alone to 13.3 years following RT plus chemotherapy, and 10-year OS was increased from 40% with RT alone to 60% following RT plus chemotherapy. The superiority of RT plus chemotherapy to RT alone was observed with all histologic subtypes, although the difference did not reach statistical significance among patients with astrocytoma. Patients with *IDH1*-mutated tumors had longer survival with the addition of chemotherapy to RT. The number of events in patients with *IDH1* wild-type tumors was too small to evaluate treatment effect in this subgroup. Acute grade 3 or 4 toxicity occurred in 67% of patients who received RT plus PCV as compared with 9% of patients who received RT alone.

TMZ has been shown to have activity in phase II trials in newly diagnosed and recurrent LGGs.[219,234-236] RTOG 0424[237] was a phase II study of patients diagnosed with LGG with three or more risk factors for recurrence as established by the aforementioned EORTC Cox regression analysis, reported by Pignatti and colleagues[216]: (1) age 40 years or above, (2) astrocytoma histology, (3) bihemispherical tumor, (4) preoperative tumor diameter 6 cm or larger, and (5) preoperative neurologic function status greater than 1. In this study, patients were treated with RT to 54 Gy in 30 fractions with concurrent and adjuvant TMZ for 12 cycles. With a median follow-up of 4.1 years, 3-year OS was 73%, which was significantly improved relative to the 54% rate derived from the prespecified historical control. Median survival time had not yet been reached. Three-year PFS was 59%. Grade 3 or higher toxicities were increased from 10% to 43% with the addition of TMZ.

Prior to the publication of the mature results of RTOG 9802, a number of efforts to exclude or delay RT in the management of LGG, based on the expectation of equivalent results from the use of TMZ, were undertaken.

EORTC 22033-26033 was a phase III intergroup trial that randomized 477 patients to either dose-dense TMZ (75 mg/m^2 QD for 21 days, repeated every 28 days—one cycle—for maximum of 12 cycles) or RT (50.4 Gy in 28 fractions) with LGG and at least one of the following high-risk features: (1) age 40 or above, (2) progressive disease, (3) tumor size greater than 5 cm, (4) tumor crossing midline, or (5) neurologic symptoms.[222] The primary end point was PFS, with the study powered to demonstrate a prolongation in PFS with the use of dose-dense TMZ as opposed to RT. The study observed no difference in PFS with median PFS of 46 months following RT and 39 months following TMZ. Unplanned analyses demonstrated improved PFS with RT relative to TMZ for *IDH*-mutated, 1p19q-noncodeleted tumors (55 vs 36 months). Other molecular subgroups did not show treatment-related differences, although patient numbers in this unplanned analysis were small. TMZ was associated with higher grade 3 to 4 hematologic toxicity (9% vs <1%) and more grade 3 to 4 infections (3% vs 1%). With a median follow-up of 3 years, no difference between health-related quality of life, assessed using the EORTC patient- reported questionnaires, and cognitive function, as assessed by the Mini-Mental Status Examination, was observed.[238] This trial, at least based on the results available to date, does not support the use of upfront TMZ and deferral of RT for WHO grade II gliomas. Similarly, a prospective single-institution trial of 120 patients with WHO grade II gliomas proactively treated with upfront TMZ, and deferral of RT demonstrated median survival of 9.7 years, considerably inferior to the 13.3 years noted on the chemoradiotherapy arm of RTOG 9802.[239] These data, therefore, should suffice to detract from the practice of RT deferral for these patients, outside the clinical trial context.[222,238]

IDH Inhibitors

The phase 3 INDIGO clinical trial of vorasidenib, an inhibitor of mutant *IDH1* and *IDH2*, demonstrated moderate efficacy in prolonging imaging-based PFS for patients with residual or recurrent grade 2 *IDH*-mutant

glioma who had undergone no previous treatment other than surgery. The median PFS was 27.7 months for patients treated with vorasidenib monotherapy compared to 11.1 months for observation alone. OS data are pending. No comparison was made to alkylating chemotherapy and/or RT, but the reported PFS is inferior to prior radiation or chemoradiation trials. Thus, the use of vorasidenib for high-risk patients, as incomplete resection and/or measurable disease was required, in lieu of upfront chemoradiation remains controversial, yet remains an alternative to observation for patients or providers preferring to defer chemotherapy and/or radiation as a salvage strategy. Until further evidence arises to modify evidence-based recommendations, current data still support the use of adjuvant chemoradiotherapy in high-risk WHO grade 2, *IDH*-mutant glioma.

Evidence-Based Treatment Summary

1. Maximal surgical resection is generally associated with more favorable outcomes and is recommended whenever feasible. Supramaximal resection may be of value for very selected cases.
2. Molecular analysis of resected tumors for 1p19q codeletion, *IDH1* mutation, and *MGMT* promoter methylation, as well as other genetic aberrations such as TP53, TERT, and ATRX, provides important prognostic information that complements known clinical risk factors and may aid in treatment decision-making; these should be obtained whenever feasible.
3. Postoperative RT has not been shown to provide a survival advantage in the only clinical trial testing this question, although PFS and seizure control were superior. The typical RT dose is 45 to 54 Gy; randomized trials do not show a survival advantage with higher doses, but dose tailoring based on molecular features has not been tested and could be considered in future trials. In fact, based on the longevity of patients with favorable features, other attempts to reduce RT-related toxicity should also be considered, and in that vein, NRG Oncology has recently completed accrual to a randomized trial testing protons versus photons for grade 2 gliomas.

4. In a practice-changing phase III trial, the addition of PCV chemotherapy to RT significantly lengthened OS in patients with subtotally resected tumors or whose age was 40 years or above. The addition of TMZ to RT has also improved survival in high-risk tumors relative to historical control data, but these data do not approach level 1. A randomized trial comparing TMZ RT to PCV with RT is underway, and enrollment has almost been completed.
5. The substitution of RT with dose-dense TMZ in high-risk tumors does not provide a PFS benefit, significantly augments hematologic toxicities, and does not impact long-term cognitive functioning or patient-reported quality of life. In *IDH*-mutated/1p19q-noncodeleted tumors, RT is associated with improved PFS relative to dose-dense TMZ. Retrospective comparison to a large multi- institutional experience raises concern about possible survival degradation when RT is deferred.
6. *IDH* inhibitors demonstrate activity as a single agent, delaying progression, compared to observation, but have not been tested against or with other therapeutic modalities such as chemoradiotherapy, and therefore, the precise role in practice remains undefined at present.

Gliomatosis Cerebri

Gliomatosis cerebri is a rare condition with diffuse involvement of multiple parts of the brain (greater than two lobes), frequent bilateral growth, and regular infratentorial extension. This entity has been removed from the 2016 revision of the WHO classification of CNS tumors but is instead considered a special pattern of spread of diffuse glioma subtypes, and therefore, obtaining tissue and performing molecular analysis are strongly recommended.[240] On MRI, there is typically diffuse increased signal on T2-weighted and FLAIR images and low or absent signal in the affected areas on T1-weighted images.

Treatment choices remain limited. Perkins et al[241] reviewed the treatment outcomes of 30 patients with gliomatosis cerebri treated with RT. Transient radiographic improvement or disease stabilization was achieved in 87% of patients with clinical improvement observed in 70%. Patients younger than

40 and those with nonglioblastoma histology had significantly improved OS.

In a French study, 63 patients with gliomatosis cerebri were treated initially with PCV or TMZ.[242] Objective responses were observed in 33% of patients and radiologic responses in 26%, with no significant difference between the two regimens. Median PFS and OS were 16 and 29 months, respectively. Regardless of regimen, patients with an oligodendroglial component had significantly better outcomes in terms of PFS and OS.

A recent German phase II trial treated 35 patients with gliomatosis cerebri with procarbazine and lomustine.[243] Median PFS was 14 months, and mOS was 30 months. Twelve patients received salvage RT at progression. *IDH1* mutation was a strong independent prognostic factor.

A retrospective review of 296 patients with gliomatosis cerebri from the literature (n = 206) and the Association des Neuro-Oncologues d'Expression Francaise (ANOCEF) network (n = 90) demonstrated median survival of 14.5 months.[244] Patients younger than 42, with better KPS, low-grade histology, or oligodendroglial subtype, had better outcomes. The impact of RT on survival remained unclear.

Evidence-Based Treatment Summary

1. Maximal surgical resection is not an achievable goal.
2. RT is considered the standard, but no trials have validated its role. Dose remains ill-defined.
3. The role of chemotherapy remains ill-defined.
4. In the absence of definitive data, our recommendation is, therefore, to treat based on histopathologic and molecular features; one such strategy includes the following:
    a. Nonglioblastoma, *IDH* mutated (grade 2 or 3): Treat all visible tumor to 45 Gy with concurrent and adjuvant TMZ.
    b. Nonglioblastoma, *IDH* wild type (grade 2 or 3): Evaluate for *MGMT* status; if methylated, treat all visible tumor to at least 45 Gy (and consider possible focal boosting to 54-59.4 Gy), with concurrent and adjuvant TMZ; if unmethylated, substitute PCV for TMZ.

c. GBM: If *MGMT* unmethylated, RT alone, and if methylated, TMZ alone; consider adding RT for methylated patients if performance status is high, or there is significant tumor response to TMZ.

Adult Brainstem Glioma

Brainstem gliomas account for 15% of all pediatric brain tumors but can occur in adults.[245] They can be divided into several distinct types. Diffuse midline glioma (DMG) is a narrowly defined but phenotypically and molecularly distinct tumor that is characterized by K27M mutations in the histone H3 gene *HeF3A*, or less commonly in the related *HIST1H3B* gene, occurring primarily in children (but sometimes in adults), with a diffuse growth pattern and midline location (eg, thalamus, brainstem, and spinal cord).[246,247] This entity was newly defined in the 2016 revision to the WHO classification system and includes tumors previously referred to as diffuse intrinsic pontine glioma (DIPG).[240] Although these tumors are associated with poor prognosis, their distinct molecular characteristic provides rationale for future targeted therapies.

DMGs can have diverse imaging appearances, ranging from expansile masses without enhancement or necrosis to peripherally enhancing masses with central necrosis but little surrounding T2/FLAIR abnormality.[248] In contrast, focal, dorsally exophytic, or cervicomedullary tumors can be low grade and have a much better prognosis, especially when found in the context of neurofibromatosis. In addition, enhancement, particularly in a focal lesion, may suggest a juvenile pilocytic astrocytoma rather than an HGG. Although rare, other aggressive tumors such as primitive neuroectodermal tumors and atypical teratoid-rhabdoid tumors can occur in the brainstem.[249,250] Nonneoplastic processes that may be confused with a primary brainstem tumor include neurofibromatosis, demyelinating diseases, arteriovenous malformations, abscess, and encephalitis.

Treatment

Corticosteroids may be necessary to manage neurologic symptoms until treatment is instituted. Patients with hydrocephalus may require placement of a ventriculoperitoneal shunt. The approach to treatment should be based on the type of brainstem glioma as determined by both the clinical

presentation and radiographic findings. Surgery is the treatment of choice for operable lesions (ie, accessible focal tumors, dorsally exophytic and cervicomedullary tumors). For low-grade tumors amenable to surgical resection, as in other LGGs, the role of postoperative RT is controversial, and many would advocate close observation. For unresectable low-grade tumors, RT should be delivered using volumes and doses as for LGGs in other locations.

Involved-field RT is the primary treatment for infiltrating pontine gliomas. The gross tumor volume (GTV) is usually best defined using T2-weighted or FLAIR MRI. A margin of 1 to 1.5 cm is added to create a CTV and further expanded by 0.3 to 0.5 cm to create a PTV. Margins may not need to be uniform in all directions, particularly where bone limits tumor extension. These lesions should be treated with doses on the order of 55.8 to 60 Gy using daily fractions of 1.8 to 2.0 Gy/d. Although RT provides short-term benefits, long-term results have remained dismal. There is no benefit from RT dose escalation. Chemotherapy has no established role. Chapters 90 provides more details as most data on intrinsic pontine gliomas come from pediatric trials.

Fewer data exist with respect to brainstem glioma in adults, but there is some evidence that these tumors may be less aggressive in adults, with OS ranging from 45% to 66% at 2 to 5 years, perhaps because of a greater frequency of more favorable tumor types.[251] Kesari et al[252] published a series of 101 adults with brainstem gliomas and observed 5- and 10-year OS rates of 58% and 41%, respectively. Of the 24 candidate factors, they observed prognostic significance associated with ethnicity, tumor location, age of diagnosis, and tumor grade. In the series from ANOCEF, 48 adult patients with brainstem gliomas were grouped on the basis of their clinical, radiologic, and histologic features.[253] Nearly half had nonenhancing diffusely infiltrative tumors and had symptoms that were present for more than 3 months. Eleven of these 22 patients underwent biopsy, and nine had low-grade histology. Nearly all underwent RT and had a median survival of 7.3 years. A second group of 15 patients who had presented with rapid progression of symptoms and had CE on MRI were described. Fourteen of these patients underwent biopsy and anaplasia was identified in all 14 specimens. Despite RT, the median survival in this group was 11.2 months, which approximates the survival in pediatric series.

Medical therapies for DIPG and H3 K27M DMGs remain limited. Radiation alone, at diagnosis or at recurrence, remains the only effective therapy with survival impact. More than 50% of patients with DIPG succumb within 12 months of diagnosis, and only 1 in 10 survive more than 2 years.[254,255] Enhancing response to standard-of-care RT and/or identifying monotherapies that increase patient survival remain elusive. The driver oncohistone H3 K27M remains untargetable,[247,256] yet exploiting the metabolic and immunologic programs promoted by recurring H3 K27 alterations in primitive oligodendrocyte precursor cells (the cell of origin of DMG) shows early promise.[257,258] Neuronal progenitor cells expressing the oncohistone showed carbohydrate metabolism, particularly glycolysis and tricarboxylic acid (TCA) cycle regulation, as a dominant feature underlying DMG tumor growth.[259] TCA cycle metabolites also dramatically regulate the epigenome, resulting in complex and heterogeneous somatic, epigenetic, and clonal landscapes of DMG.[260-262]

Therapies that address DMG metabolism may help reverse the currently unacceptable survival statistics for patients with DMG. ONC201 (dordaviprone), a first-in-class imipridone, selectively induces apoptosis in cancer cells by ClpP agonism and DRD2 antagonism.[263-265] ClpP normally degrades misfolded proteins in mitochondria, while ONC201 modifies ClpP conformation, promoting excess degradation of specific mitochondrial proteins important for cancer cell viability. DRD2 is a G protein coupled neuroreceptor regulating Ras signaling, while ONC201 antagonizes DRD2, thus inhibiting Ras signaling pathways. ONC201 inhibits TCA cycle and glycolysis, which are key drivers of proliferation in H3 K27M DMG.[266]

An integrated analysis of single-agent ONC201 (dordaviprone) was reported for 50 patients (4 pediatric, 46 adults) with recurrent H3 K27M-mutant DMG in four clinical trials or one expanded access protocol.[267] Eligible patients had measurable disease by RANO-HGG criteria assessed by dual-reader, blinded independent central review. Patients were eligible if performance score was 60 or more and started therapy for progression at 90 days or more from radiation. The ORR by RANO-HGG was 20.0% (95% CI: 10.0-33.7). The median time to response was 8.3 months (range, 1.9-15.9), while the median duration of response was 11.2 months (95% CI: 3.8 to not reached). Performance status improved in 6 (20.6%) of 34 (95% CI: 8.7%-37.9%) evaluable patients. Grade 3 treatment-related treatment-

emergent adverse events (TR-TEAEs) occurred in 20.0% of patients, mainly fatigue (*n* = 5; 10%). No grade 4 TR-TEAEs, deaths, or discontinuations occurred. ONC201 monotherapy was well tolerated and exhibited durable and clinically meaningful efficacy in recurrent H3 K27M-mutant DMG. ONC201 exhibits activity in H3 K27M-mutant gliomas, irrespective of CNS location.[268] A study evaluating the safety and PK of oral ONC201 administered twice weekly on consecutive days (D1D2) in pediatric patients with newly diagnosed DIPG and/or recurrent/refractory H3 K27M glioma was well tolerated without dose-limiting toxicities or grade 3 or higher treatment-related adverse events and associated with greater $AUC_{0\text{-}48}$ compared to once-weekly dosing.[269] The definitive randomized, placebo-controlled, phase 3 ACTION trial (NCT05580562) is assessing single dose weekly and 2-day consecutive weekly compared to placebo in the adjuvant setting, for pediatric and adult patients with non-DIPG, nonspinal, H3 K27M DMG who have not progressed immediately after standard radiation.[270]

A recent semi-systematic review published in December 2023 descriptively summarized 41 clinical trials for DIPG or K27-altered DMG.[271] The main therapeutic strategies under study included chemotherapy, vaccines, adoptive transfer therapy, small molecules, and focused ultrasound. Chemotherapy trials include a phase 2 trial of pomalidomide, next-generation immunomodulatory drug, that broadly affects various molecular and cellular elements within the tumor microenvironment, in turn affecting the concentration of various cytokines that support tumor cell growth.[272] Another phase 1 trial (NCT02992015) of gemcitabine focuses on assessing the intratumoral gemcitabine concentration after systemic treatment after a single IV administration prior to standard-of-care biopsy of radiographically diagnosed DIPG. Vaccine strategies in phase 1-2 trials include three H3 K27M-targeted peptide vaccines monotherapy (NCT04749641, NCT04808245) or in combination with nivolumab (NCT02960230), one PEP-CMV vaccine targeting the CMV (pp65) antigen (NCT05096481), and one rHSC-DIPGVax vaccine targeting neoantigens combined with checkpoint blockers balstilimab and zalifrelimab (NCT04943848). Adoptive transfer chimeric antigen receptor T-cell (CAR-T)-based phase 1 trials include (1) one trial using genetically

modified cells (KIND T cells) for HLA-A*0201–positive patients (NCT05478837), (2) two trials using CAR-T targeting GD2 (NCT05544526, NCT04196413), (3) one trial of B7-H3–specific CAR-T (NCT04185038), and (4) one trial of B7-H3, EGFR806, HER2, and IL-13-Zetakine (Quad) CAR-T (NCT05768880). Non–CAR-T–based adoptive transfer immunotherapy trials include the BRAVO (NCT03396575) and PEACH (NCT04837547) trials. Monoclonal antibody trials include pembrolizumab (anti–PD-1, NCT02359565) and APX005M (anti-CD40, NCT03389802) checkpoint inhibitor monotherapies. The phase 1 AloCELYVIR trial (NCT04758533) represents the only oncolytic virus strategy currently under study.

Aside from the ONC201-based trials now in phase 3 (ACTION, NCT05580562; BIOMEDE, NCT05476939), most small molecules are under study in phase 1-2 trials, including selinexor (selective inhibitor of nuclear export; NCT05099003), abemaciclib (CDK4/6 inhibitor; NCT02644460), ribociclib (CDK4/6 inhibitor) and everolimus (mTOR inhibitor; NCT05843253), vorinostat and temsirolimus (mTOR inhibitors) with or without RT (NCT02420613), CBL0137 (FACT sequestration; NCT04870944), fimepinostat (HDAC and PI3K inhibitor; NCT03893487), panobinostat (HDAC inhibitor; NCT02717455), marizomib (proteasome inhibitor) plus panobinostat (HDAC inhibitor; NCT04341311), OKN-007 (HIF1-α and VEGFR2 expression; NCT05518838), and indoximod (indoleamine 2,3-dioxygenase inhibitor; NCT04049669). Enhanced delivery techniques primarily utilize focused ultrasound for BBB disruption or for sonodynamic therapy (SDT). The phase 1-2 trials focusing on BBB disruption include the commercially available agents panobinostat (NCT04804709), doxorubicin (NCT05615623, NCT05630209), and etoposide (NCT05762419). The phase 1-2 trial of SDT using SONALA-001 (NCT05123534) utilizes noninvasive SDT through MR-guided focused ultrasound to activate protoporphyrin IX (PpIX), a metabolite of the administered IV prodrug ALA, intratumorally through the selective uptake of ALA by tumor cells relative to normal brain cells and local activation using MR-guided SDT. These varied trials highlight the expanding trials and novel medical strategies focused on enhancing the prognosis for DIPG and DMG, beyond the limited benefit radiation offers to date.

Evidence-Based Treatment Summary

1. Surgical resection is indicated for patients with favorable tumor types (based mostly on location) but is not an achievable goal in patients with intrinsic pontine gliomas; however, obtaining tissue is strongly recommended, and molecular testing should be considered.
2. The H3 K27M mutation defines a phenotypically and molecularly distinct tumor, called diffuse midline glioma (DMG), occurring in midline location and associated with an especially poor prognosis; however, this may be a targetable driver mutation. Gliomas with diffuse growth pattern and midline location should be tested for H3 K27M mutation.
3. For DMGs, RT is considered the standard. The addition of chemotherapy remains undefined.

Ependymoma

Ependymoma accounts for only 1.8% of all adult brain tumors.[273] Rosette formation is a hallmark of ependymoma on pathologic specimens. WHO grade I ependymomas include myxopapillary ependymoma, which typically occurs in the spine, and subependymoma.[240] In adults, the subependymomas, which are mostly intracranial, have favorable clinical outcomes. Ependymomas are otherwise divided between WHO grades II and III (anaplastic), with the latter showing increased mitotic activity, tumor necrosis, and microvascular proliferation, suggesting a diagnosis of anaplastic ependymoma. Unlike pediatric ependymomas, which largely arise intracranially, 75% of ependymomas in the adult population arise in the spinal canal. Spinal ependymomas typically present with sensory deficits. Ependymomas may expand locally, extend along ependymal spaces, and, occasionally, disseminate through the CSF. However, the predominant pattern of relapse is local, even when anaplasia is present.[274-279]

Posterior fossa and supratentorial ependymoma are biologically different tumors but are both treated with surgery and RT. In a recent international collaborative study,[280] nine molecular subgroups of ependymoma were identified, three in each anatomic compartment: spine (SP), posterior fossa (PF), and supratentorial (ST) region. In each compartment, one molecular

subgroup of WHO grade I subependymoma (ST-SE, PF-SE, and SP-SE) was observed, occurring in adults only. In the spine, the two other molecular subgroups matched the histopathologic diagnoses of myxopapillary ependymoma (SP-MPE) and WHO grades II and III ependymoma (SP-EPN). In the posterior fossa, the remaining two molecular subtypes were classified as PF-EPN-A and PF-EPN-B. PF-EPN-A occurs primarily in infants and young children (but is observed in 11% of adult patients), and because of its predominately lateral location, it can be difficult to completely resect and thus is associated with high relapse rates.[281] PF-EPN-B occurs primarily in older children and adults and is associated with a more favorable prognosis. More than 70% of supratentorial ependymomas are characterized by fusions between *C11ORF95* and *RELA* genes.[282] Termed ST-EPN-RELA tumors, these ependymomas can occur in both adults and children and are recognized as a distinct molecular entity by the 2016 revision of the WHO classification system. The remaining supratentorial tumors harbor fusions to the oncogene *YAP1* and have a highly favorable prognosis.

Treatment

Maximal surgical resection, including second surgery if necessary, is the initial treatment for ependymoma. Surgery alone may be sufficient in selected patients based on the results of a pediatric series described in Chapters 90. However, the standard of care for most adults is postoperative irradiation. There appears to be a radiation dose response with improved tumor control with doses greater than 50 Gy, and doses of 54 to 59.4 Gy are typically prescribed. Radiation dose for spinal ependymomas can be limited by spinal cord tolerance. At 1.8 to 2 Gy/fraction, the estimated risk of radiation myelopathy is less than 1% at 54 Gy and less than 10% at 61 Gy.[283]

Historically, for posterior fossa tumors, the entire posterior fossa has been irradiated. However, Paulino[284] has shown that the pattern of failure to be “local,” that is, within the tumor bed itself. In nine patients who received RT to the tumor bed plus a 2-cm margin, the two failures in this group were within the tumor bed (ie, there were no failures within the posterior fossa outside the tumor bed). For most patients, a more usual volume now

consists of the tumor bed and any residual disease (GTV) plus an anatomically defined margin of 1 to 1.5 cm to create a CTV. Larger margins may be required in areas of infiltration, and special attention must be paid to areas of spread along the cervical spine because 10% to 30% of the fourth ventricular tumors extend down through the foramen magnum to the upper cervical spine.[278,285] RT field size for spinal ependymomas commonly includes two cranial and two caudal vertebral bodies. Lumbosacral or sacral ependymomas should include coverage of nerve roots, with the caudal border extending to S4/S5 and lateral borders extending to the sacroiliac joints.

In the past, CSI was recommended for patients with high-grade and infratentorial tumors who were believed to be at an increased risk of CSF spread.[276] Modern series document that local recurrence is the primary pattern of failure and that the incidence of isolated spinal relapses is low even among the highest-risk patients, with the majority of spinal failures associated with local recurrences.[274,277] As a result, the current recommendation for patients with ependymomas is limited-field radiation if the spinal MRI scan and CSF cytology are negative. Patients with neuraxis spread (positive MRI or positive CSF cytology) should receive CSI (36 Gy) with boosts to the areas of gross disease and to the primary tumor to total doses of 50 to 59.4 Gy. One exception is spinal myxopapillary ependymomas (WHO grade I), where MR evidence of neuraxis spread can be treated with focal RT, rather than CSI.

Chemotherapy is not effective as primary treatment, thus usually reserved as salvage treatment for patients exhausting surgery and RT options. Randomized trials of chemotherapy in the pediatric population failed to show clinically useful benefit relative to RT,[286] although neoadjuvant chemotherapy in very young children (<3 years, and especially <1 year old) is used to spare or delay RT. In prospective clinical trials, postoperative chemotherapy using combinations of etoposide, vincristine, cyclophosphamide, platinum derivatives, and/or high-dose methotrexate showed a response rate of 40% to 50%.[287-289]

Phase II studies in children with relapsing ependymomas yielded low response rates with either standard- or high-dose chemotherapy (HDC).[290,291] Platinum-based regimens seem superior to nitrosourea-based regimens, in terms of higher response rates, though they failed to show a difference in

terms of PFS and OS.[292,293] Metronomic regimens may yield longer control, specifically oral etoposide or TMZ.[294,295] Targeted agents, such as bevacizumab (with irinotecan or lapatinib), erlotinib, or sunitinib, showed no significant efficacy in unselected populations.[294,296-298] In combination with TMZ, lapatinib showed responses were higher in patients with elevated ErbB2 messenger RNA expression in tumor tissue in a single-arm phase II study in patients with recurrent intracranial and spinal ependymomas.

Results of Treatment

In modern series that utilized mostly local fields for patients with nondisseminated disease, 5-year survival is on the order of 70%.[276,285,299-302]

Several authors have attempted to identify variables associated with improved outcome in adults. Ferrante et al[300] analyzed 20 patients with the fourth ventricle ependymomas. The 5-year survival rate in patients older than 16 years was 60%. The use of postoperative irradiation was associated with a markedly improved 5-year survival of 68% versus 18% without RT ($P = .011$).

Reni et al reported on a series of 70 adult intracranial ependymomas and observed 5-year OS and PFS rates of 67% and 43%, respectively. Older age and supratentorial location were poor prognostic factors, and the use of postoperative RT was associated with improved PFS and a trend toward improved OS.

Metellus et al evaluated 114 adult patients with intracranial ependymoma and observed incomplete resection and supratentorial location to be significant predictors of recurrence and poor survival. For incompletely resected tumors, postoperative RT improved both OS and PFS. In a study of spinal myxopapillary ependymomas from the Rare Cancer Network,[303] the use of postoperative RT was an independent predictor of PFS.

A retrospective study of 23 adult patients with supratentorial ependymomas treated at Columbia-Presbyterian Medical Center with a variety of RT field sizes and doses (including SRS) showed a 5-year survival rate of 100% for hemispheric tumors and 73% for the third ventricular tumors.[302] Of interest, six patients with low-grade tumors did not

receive postoperative irradiation. Five remained free of recurrence during a mean follow-up period of 69 months.

Five-year survival was 62% for a French series of 34 adult patients with ependymoma, 17 of whom had anaplastic histology.[304] Gross total resection was performed in 27 patients. Half of the 34 patients were irradiated; 13 of these received local fields to a mean dose of 56 Gy. Univariable analysis showed that anaplasia and location in the brain parenchyma predicted poor outcome.

Evidence-Based Treatment Summary

1. Maximal surgical resection should be performed when feasible.
2. Postoperative RT is considered the standard, but no prospective trials have validated its role. CSI is used only in patients with disseminated disease.
3. The role of chemotherapy remains to be defined.

Medulloblastoma

Medulloblastoma is a relatively rare tumor in adults with an incidence of 0.5 per 100,000.[273,305] The majority arise in the 20- to 40-year age group. Adult medulloblastomas are more frequently located laterally than those in childhood (50% vs 10%) and are more frequently desmoplastic.[306] In addition, the incidence of severe anaplasia is lower than in the pediatric population.[307] Medulloblastoma is a densely cellular tumor with small, darkly staining ovoid cells with hyperchromatic nuclei and frequent mitoses. Homer Wright rosettes (clustered cells surrounding a central eosinophilic core) are characteristic. CSF dissemination may manifest as positive cytology or macroscopic seeding of the subarachnoid space and is not uncommon. Systemic spread is seen in approximately 5% of patients, mostly in the bone and bone marrow. Shunt procedures have been suggested as a cause, although modern series dispute this.[308]

In children, adverse prognostic factors include male gender and age less than 3 years.[309] Patients with total or near-total resections fare better than those with subtotal resection or biopsy only, and residual tumor greater than 1.5 cm^2 on postoperative scans is an adverse prognostic factor. Patients with

CSF spread have a worse prognosis. Patients are classified as "average risk" if there is less than 1.5 cm^2 residual tumor and no dissemination; patients with greater than 1.5 cm^2 residual and/or dissemination are considered "high risk."

Molecular analyses have identified four distinct subgroups that have now been defined in the 2016 revision to the WHO classification system.[240,310] WNT tumors most frequently occur in late childhood and adolescence, are rarely metastatic, and have a favorable prognosis, regardless of metastatic status. Most WNT tumors display classic medulloblastoma histology and nuclear localization of CTNNB1 (β-catenin), as detected by immunohistochemical staining.[311] Ongoing research has focused on therapeutic de-escalation for this favorable subtype, although prognosis of WNT tumors is worse in adults, relative to pediatric patients.[312] SHH tumors account for most of the infant and adult medulloblastomas and are rare in children. SHH tumors are typically found within the cerebellar hemispheres and have an intermediate prognosis. All nodular desmoplastic medulloblastomas can be characterized as SHH subgroup.[313] Non-WNT and non-SHH tumors are classified as group 3 or 4. Although there can be considerable overlap between these groups, group 3 tumors have characteristically poor prognosis. Group 3 tumors affect mostly infants and children, are rare in adults, commonly present with metastases, and are characterized by MYC amplification. Group 4 tumors can affect patients of all ages.

Treatment

All patients with nondisseminated medulloblastoma should undergo complete resection if feasible. In cases where extension into the brainstem precludes complete resection without significant morbidity, there is no benefit to complete surgical resection as compared to near-total resection.[314]

In general, the treatment guidelines for pediatric medulloblastoma detailed in Chapters 90 should probably be followed. Postoperative RT should begin within 28 to 31 days following surgical resection whenever possible. RT is delivered to the entire craniospinal axis followed by a boost to the tumor bed for average-risk patients and to the posterior fossa and gross metastatic disease for high-risk patients. Although there may be less

concern over long-term toxicity of full-dose CSI in adults as compared with children, adults treated for medulloblastoma with a mean dose to the whole brain of 35 Gy have been shown to have long-term cognitive deficits.[315] It may be reasonable to extrapolate from the pediatric experience and to treat healthy young adults with average-risk disease with reduced-dose CSI (23.4 Gy) as long as appropriate multiagent chemotherapy is administered. For average-risk patients, boost to the tumor bed plus a 1.5-cm margin (as opposed to whole posterior fossa) to 54 Gy is associated with equivalent event-free survival outcomes, although a reduction in CSI to 18 Gy (as opposed to 23.4 Gy) leads to inferior event-free survival.[316] Full-dose CSI (36 Gy) should be delivered in the setting of high-risk disease. This is then followed by a boost to the posterior fossa. Intracranial and spinal metastases should be boosted as well to total doses on the order of 45 to 50 Gy for spinal metastases and 50 to 54 Gy for intracranial metastases. Treatment is usually delivered at 1.8 Gy/d.

The role of adjuvant chemotherapy with lomustine, vincristine, and cisplatin in children with medulloblastoma is well established but remains unclear in adults. A series of 32 adults with medulloblastoma from Germany has shown a nonsignificant trend to prolonged survival with adjuvant chemotherapy.[317] The NOA-07 prospective trial of chemoradiotherapy for adult medulloblastoma demonstrated favorable event-free survival rate of 67%.[318] The ability to complete at least four cycles of adjuvant chemotherapy was dependent on age, with leukopenia being the most common toxicity. The standard regimen of lomustine, vincristine, and cisplatin seems poorly tolerated in adults compared to children.[318,319] To improve tolerance in adults, vincristine dosing frequency is reduced to twice weekly, the maintenance phase limited to six cycles, and/or cisplatin substituted by carboplatin. Other regimens based on cisplatin or carboplatin plus etoposide are also used in adult patients.[320] There are no data supporting HDC/ASCT to further improve outcome in adults with medulloblastoma.

The use of proton therapy has been associated with a meaningful reduction in hematologic and GI toxicity and should be considered when feasible for adult medulloblastoma.[92]

Evidence-Based Treatment Summary

1. Molecular classification has identified four distinct subtypes: WNT, SHH, group 3, and group 4.
2. Maximal surgical resection should be performed, where feasible.
3. Standard treatment consists of postoperative RT to the craniospinal axis followed by a boost to the tumor bed for average-risk disease and to the posterior fossa and any intracranial/spinal metastases for high-risk disease.
4. The use of chemotherapy generally follows the pediatric indications and guidelines.

Primary Central Nervous System Lymphoma

PCNSL is a non-Hodgkin lymphoma that is restricted to the CNS (brain, spinal cord, meninges, and eye) and accounts for less than 3% of primary intracranial malignancies. It occurs in two distinct patient populations: immunocompromised (HIV, post-transplant, etc) and immunocompetent. Immunodeficiency is the only known risk factor. Immunocompetent patients present typically in the sixth and seventh decades of life, whereas immunosuppressed individuals more commonly present in the third and fourth decades of life.

The majority of PCNSLs are B-cell lymphomas of intermediate or high grade that are indistinguishable from high-grade non-Hodgkin lymphomas occurring elsewhere in the body. In immunocompetent patients, PCNSL typically presents with one or multifocal (in 30%) mass lesions primarily located in the frontal lobes, corpus callosum, and deep periventricular brain structures. Although the lesions appear focal, diffuse involvement of the parenchyma is invariably present. As a consequence of this deep localization, patients usually present with cognitive dysfunction or personality change. Other symptoms include headache or focal neurologic dysfunction, such as hemiparesis or hemisensory loss; seizures are rare. Symptoms often progress over weeks to months before a diagnosis is made.

On MRI, PCNSL is hypointense on T1 and hypointense to isointense on T2/FLAIR sequences with variable surrounding edema. There is usually homogeneous enhancement with IV contrast. Ring enhancement is

uncommon, except in immunocompromised patients. The appearance on T2 sequences and lack of central necrosis help differentiate PCNSL from glioma.

Even with the "classic" imaging appearance, histology is essential for diagnosis. If PCNSL is suspected, stereotactic biopsy is the best approach; extensive resection does not improve survival. Corticosteroids should be held at presentation unless absolutely necessary (eg, impending brain herniation) because their "lytic" effect on lymphoma may lead to a false-negative biopsy. Once a diagnosis of PCNSL is established, an extent of disease workup is required. At diagnosis of PCNSL, ocular disease is present in 20% (often misdiagnosed as idiopathic uveitis), and demonstrable leptomeningeal disease is present in 25% (usually asymptomatic until late). A complete staging workup consists of contrast-enhanced brain MR, lumbar puncture (for CSF cytology, flow cytometry, and Epstein-Barr virus PCR), slit-lamp ocular examination (to look for intraocular lymphoma), HIV serology, and contrast-enhanced spine MRI. Systemic staging (body CT, bone marrow biopsy) is rarely positive in patients with typical findings of CNS lymphoma but should be performed if systemic symptoms are present (weight loss, night sweats, and fever).

Age and performance status are the most important prognostic factors. An RPA analysis of 338 patients at Memorial Sloan-Kettering Cancer Center led to the identification of three RPA classes: class I (age <50) was associated with a median survival of 8.5 years; class II (age >50 years and KPS ≥70) 3.2 years; and, class III (age >50 and KPS < 70) 1.1 years.[321] The International Extranodal Lymphoma Study Group evaluated 378 patients and observed age less than 60, ECOG less than 1, elevated lactate dehydrogenase, high CSF protein, and deep regions of the brain as prognostic.[322]

Molecular analyses have identified activating mutations in MYD88 and CD79B in PCNSL, which are important in the Bruton tyrosine kinase (BTK) pathway.[323] BTK integrates B-cell antigen receptor (BCR) and Toll-like receptor (TLR) signaling. Diffuse large B-cell lymphomas (DLBCL), which include PCNSL, frequently harbor mutations in genes encoding members of the BTK pathway. These include the BCR-associated protein CD79B and myeloid differentiation primary response 88 (MYD88), a

cytosolic adapter protein that links IL-1 and TLRs with the nuclear factor κB.

Treatment

The role of surgery is limited to establishing the tissue diagnosis, typically by stereotactic biopsy. Extensive tumor resection offers questionable survival benefit based on a meta-analysis of the extent of surgery.[324] Because PCNSL often responds dramatically to corticosteroid therapy, corticosteroids should be avoided unless absolutely necessary until after tissue is obtained.

PCNSL is exquisitely sensitive to RT and chemotherapy. Although never studied in a prospective manner, WBRT is thought to be more effective than focal RT because of the extensive infiltration of lymphoma throughout the brain. The optimal dose is 45 to 50 Gy, and there is no benefit of adding a boost to the tumor site. With WBRT alone, the median survival is 12 to 18 months and the 5-year survival rate is only 4%.

The standard systemic lymphoma chemotherapy regimens are ineffective for PCNSL, as demonstrated in prospective clinical trials.[325-327] High-dose systemic methotrexate, administered at a high dose (1-8 g/m^2) and at a rapid rate of infusion to overcome the BBB, is the only agent that has demonstrated improved survival over WBRT alone. A randomized phase II study suggested that combination chemotherapy with methotrexate results in superior disease control and survival as compared to single-agent methotrexate.[328] High-dose methotrexate regimens produce adequate levels of drug in the CSF so that direct instillation of chemotherapy (eg, using an Ommaya reservoir) into the CSF is not necessary unless CSF cytology is positive.[329]

WBRT is typically used as postchemotherapy consolidation in patients younger than 60 years, as a salvage strategy for recurrence, or as upfront therapy alone for patients with poor performance status (KPS <40) or renal failure. Patients aged 60 years or above are at high risk of developing treatment-related neurotoxicity following treatment with methotrexate and WBRT; WBRT is often deferred in this subgroup, except for recurrence.

Neurotoxicity after PCNSL treatment is characterized by dementia, ataxia, and urinary incontinence, occurring at a mean of 7 months from

treatment. Both methotrexate and RT can cause this syndrome, and the combination is synergistic. The risk is greatest in patients aged 60 years or above at diagnosis and when methotrexate is administered concurrently or following RT. In one phase II trial, patients aged 60 years or above had a 100% incidence of neurotoxicity at 24 months, whereas those younger than 60 years had a 30% incidence at 96 months.[330]

The commonly used RT schedule for PCNSL in immunocompetent patients is 40 to 45 Gy to the whole brain. The posterior orbits should be included in the whole-brain fields. In patients with ocular involvement, the whole eye can be treated to 30 to 40 Gy, with shielding of the anterior chamber and lacrimal apparatus after this dose. However, most treating physicians reserve the use of ocular RT for failure of intravitreal methotrexate and rituximab. CSI has been advocated for patients with documented CSF involvement. However, intrathecal chemotherapy is preferred because it may be equally efficacious but less toxic with less impact on bone marrow reserve. RT dose reduction, especially in patients responding to chemotherapy, has been tested in a randomized trial and demonstrates a significantly positive impact on PFS, in that addition of low-dose WBRT to chemotherapy improved PFS.[331]

For immunosuppressed patients with PCNSL, modification of the irradiation dose and schedule may be necessary. Patients with poor prognostic features (low KPS, CD4 counts <200, advanced acquired immunodeficiency syndrome [AIDS]) may be treated with an abbreviated course of RT (eg, 36-40 Gy).

Results of Treatment

Unlike non-CNS lymphoma, there appears to be an RT dose response with a threshold between 30 and 50 Gy, with a median of 40 Gy. A study by Bessell et al[332] showed a higher relapse rate and reduced survival rate in patients who received 30.6 Gy WBRT as compared to 45 Gy in patients who had CR to chemotherapy. This was significant for patients younger than 60. However, radiation doses beyond 45 to 50 Gy are associated with a plateau in radiation response. The RTOG conducted a phase II study (RTOG 83-15) to evaluate WBRT as first-line treatment. Median survival was 12 months and recurrence in the brain occurred in 61% of patients,

with more relapses in the 60 Gy region, suggesting no clear dose response over 40 Gy.

The most widely used treatment regimen is based on a phase II study (RTOG 93-10) that treated 102 patients with newly diagnosed PCNSL with five cycles of high-dose methotrexate (2.5 g/m^2), vincristine, and procarbazine followed by 45 Gy WBRT and high-dose cytarabine (3.0 g/m^2) postradiotherapy.[333] Approximately halfway through the study, the dose of WBRT was decreased to 36 Gy delivered by hyperfractionation to those that achieved a CR after preradiotherapy chemotherapy. In all, 58% of patients achieved a CR, and 36% had a PR after preradiotherapy chemotherapy. Median PFS and OS was 24 and 37 months, respectively.

Long-term results with various combination chemotherapy regimens that include IV and intrathecal methotrexate, cranial RT, and IV cytarabine have been encouraging, especially in patients younger than 50 years (5-year survival rate of 60%). In older patients (>50 years), results are poor (5-year survival of rate of <10%) and toxicity is greater with dementia and ataxia in a substantial proportion of patients.[334]

Chemotherapy is also effective without RT or as a means of delaying RT, particularly in patients over age 60 years because of their substantial risk to develop treatment-related neurotoxicity.[335] CRs occur in more than 50% of patients. Single-agent methotrexate using a dose of 8 g/m^2 had a high response rate, but responses were relatively short in duration with a median PFS of approximately 1 year.[336]

Eliminating WBRT from treatment regimens results in higher recurrence incidence but does not translate into an OS detriment. The German PCNSL phase III trial randomized 524 patients to high-dose methotrexate-based chemotherapy with or without WBRT to 45 Gy in 1.5-Gy fractions.[337] The addition of upfront WBRT significantly prolonged PFS, especially among patients who did not achieve a CR following chemotherapy, but no significant OS benefit was noted. In patients with disease less sensitive or insensitive to high-dose methotrexate, WBRT seems more effective than high-dose Ara-C a salvage strategy. The addition of upfront WBRT led to greater impact in patient-reported cognitive functioning and global health status, as well as lower values on Mini-Mental Status Examination.[338]

Current work is focusing on methods to eliminate or reduce the risk of neurotoxicity without compromising long-term disease control. Shah et al[339]

reported a phase II study evaluating the effectiveness and toxicity of reduced-dose WBRT (23.4 Gy) in patients who achieved a CR following methotrexate-based chemotherapy. The estimated 2-year OS and PFS in these 19 patients was 89% and 79%, respectively. At a follow-up of 12 months, none of the patients treated with reduced-dose RT developed treatment-related dementia on neurocognitive studies. This approach was further evaluated in a multicenter phase II study of rituximab, methotrexate, procarbazine, and vincristine (R-MVP) followed by consolidative WBRT to 23.4 Gy in patients who achieve a postchemotherapy CR.[340] Consolidative cytarabine was given after RT. Among 52 patients enrolled, 60% achieved a CR after R-MVP, with a 2-year PFS of 77% and a 3-year OS of 87%. Cognitive assessments demonstrated improvement in executive function and verbal memory after R-MVP with stability of follow-up scores.

In RTOG 1114, 91 patients were randomized to receive R-MPV-A alone or combined with low-dose WBRT (23.4 Gy, 180cGy × 13). Methotrexate was dosed as 3.5 g/m^2 in 2-hour infusions. Radiographic CR rates improved from 76.3% for chemotherapy alone to 92.3% with WBRT consolidation. After a median follow-up of 4.6 years, median PFS was not reached (chemoradiation) versus 2.1 years (chemotherapy), HR = 0.47 (P = .007). The 2-year PFS was 78.7% versus 54%. The OS HR numerically favored chemoradiation but did not reach statistical significance (HR 0.71; P = .33). Comprehensive neuropsychological evaluation showed no differences in cognitive outcomes, with several tests intriguingly favoring chemoradiation, suggesting enhanced tumor control may aid in maintaining cognition.[331]

The use of HDC/ASCT in patients with newly diagnosed PCNSL is another strategy that has been explored as an alternative to WBRT. Available data are limited to a few small, nonrandomized phase 2 studies.[341] In a single-institution study, patients who developed a CR or PR to R-MVP proceed with HDC with thiotepa, cyclophosphamide, and busulfan, followed by ASCT.[342] In transplanted patients, 2-year PFS and OS were 81%. Two clinical trials (NCT00863460) randomized patients to consolidative WBRT versus HDC/ASCT to establish the most effective consolidation strategy.

The International Extranodal Lymphoma Study Group-32 trial was an international randomized phase 2 unblinded study randomizing to methotrexate, cytarabine, thiotepa, and rituximab (MATRix) compared to

other induction combinations. The study also secondarily randomized myeloablative chemotherapy followed by ASCT versus WBRT as consolidation after high-dose methotrexate-based chemoimmunotherapy for 227 patients with newly diagnosed PCNSL (NCT01011920).[343,344] HIV-negative patients (aged 18-70 years) with ECOG status of 0 to 3 received four courses of methotrexate 3.5 g/m^2 on day 1 plus cytarabine 2 g/m^2 BID on days 2 and 3 (group A); or the same combination plus two doses of rituximab 375 mg/m^2 on days −5 and 0 (group B); or the same methotrexate-cytarabine-rituximab combination plus thiotepa 30 mg/m^2 on day 4 (group C), all repeating treatment every 3 weeks. Of the 219 (97%) evaluable, patients treated with rituximab and thiotepa had a complete remission rate of 49% (95% CI: 38%-60%), compared with 23% (14%-31%) of those treated with methotrexate- cytarabine alone (HR 0.46, 95% CI: 0.28-0.74) and 30% (21%-42%) of those treated with methotrexate-cytarabine plus rituximab (0.61, 0.40-0.94). Grade 4 hematologic toxicity was more frequent in patients treated with methotrexate-cytarabine plus rituximab and thiotepa, but infective complications were similar. The most common grade 3-4 adverse events in each arm were neutropenia, thrombocytopenia, anemia, and febrile neutropenia or infections. In all, 13 (6%) patients died of toxicity. MATRix was deemed the most effective induction regimen for patients aged up to 70 years. Patients with responsive or stable disease after induction, with adequate autologous peripheral blood stem cell collection, and without persistent unresolved significant toxicities were further randomized between WBRT started within 4 weeks from the end of induction and carmustine-thiotepa conditioned ASCT (carmustine 400 mg/m^2 on day −6, and thiotepa 5 mg/kg every 12 h on days −5 and −4, followed by reinfusion of autologous peripheral blood stem cells). A permuted block randomized design was adopted for serial randomizations using a computer- generated randomization within each stratum. Of the 122 (54%) of 227 eligible patients, 118 (97%) of 122 were equally randomized to WBRT or ASCT (59 patients in each group). WBRT and ASCT were both effective, with no significant differences in 2-year PFS of 80% (95% CI: 70%-90%) and 69% (59%-79%), respectively (HR = 1.50, 95% CI: 0.83-2.71; P = .17). Grade 4 nonhematologic toxicity was uncommon, but more common with ASCT

than with WBRT. Two toxic deaths (infections) were recorded, both in patients who received ASCT.

Initial and long-term results of the Intergroup ANOCEF- GOELAMS randomized phase II PRECIS study similarly compared WBRT versus HDC (thiotepa-busulfan-cyclophosphamide) plus ASCT consolidation after high-dose methotrexate-based induction chemotherapy for 140 patients aged 60 years or below.[345,346] Both WBRT and ASCT met the predetermined threshold, PFS at 2 years were 63% (95% CI, 49%-81%) and 87% (95% CI, 77%-98%), respectively. Toxicity deaths were recorded in one and five patients after WBRT and ASCT, respectively. Cognitive impairment was observed after WBRT, whereas cognitive functions were preserved or improved after HDC/ASCT. The long-term data (median follow-up, 8 years) showed 8-year event-free survival from random assignment was 67% and 39% in the ASCT and WBRT arms, respectively (P = .03), with a significantly lower risk of relapse after ASCT (HR = 0.13; P < .001). Five and four patients died of ASCT- and WBRT- related toxicities, respectively. The 8-year OS was 69% and 65% in the ASCT and WBRT arms, respectively (not significant), but neurocognition (64% vs 13%, P < .001) was significantly deteriorated after WBRT compared with ASCT at the last follow-up. This study suggested 40 Gy WBRT is less preferable as first line due to increased neurotoxicity and suboptimal PFS, despite similar OS. In practice, the declining interest in WBRT by patients and providers, due to the risks on cognition, has led to increases in HDC/ASCT in select candidates, especially younger, healthier, and higher functioning patients.

Ibrutinib is a first-in-class, oral inhibitor of BTK. Ibrutinib induces death of DLBCL cells with deregulated BCR signaling and has shown promising activity in a variety of B-cell malignancies, with 70% to 90% response rates in patients with chronic lymphocytic leukemia, small lymphocytic lymphoma, mantle cell lymphoma, and Waldenström macroglobulinemia, but only about 25% response rates in relapsed/refractory DLBCL.[347] In a phase 1-2 study, ibrutinib was administered to 20 patients with relapsed or refractory PCNSL or secondary CNS involvement. Patients received ibrutinib at 560 or 840 mg QD in the dose escalation portion of the study and 840 mg QD in the expansion portion. Responses were observed in 15 (75%) of 20 patients; 10 of these had CR. For PCNSL, the response rate was 77%. Ibrutinib CSF concentrations 2 hours postdose were 0.77 ng/mL

(1.7 nM) and 1.95 ng/mL (4.4 nM) in the 560 and 840 mg groups, respectively, demonstrating a dose-dependent increase in CSF penetration, and levels sufficient to induce cell death in CNS lymphoma cells in culture. Upon mutational analysis, many tumors harbored mutations in the BTK pathway, but tumors without such mutations also responded. Ibrutinib, therefore, has substantial activity in patients with relapsed or refractory B-cell lymphoma of the CNS and is being further developed for front-line testing.[348]

Second-generation BTK inhibitors are in clinical testing for PCNSL.[349,350] A single-center retrospective analysis of 14 patients with CNS DLBCL treated with high-dose methotrexate, thiotepa, and second-generation BTK inhibitor orelabrutinib combined with or without rituximab concluded that this PCNSL treatment approach was efficacious and well tolerated. Median follow-up time was 12.8 months. For PCNSL, the CR and overall response rates were 55.6% and 88.9%, respectively. Grade 3 adverse events occurred in five patients (35.7%), were all hematologic, and did not lead to discontinuation of treatment.

In patients with immunosuppression and PCNSL, results are discouraging, although selected patients (non-HIV immunosuppression, favorable prognosis patients with AIDS) may have survival comparable with that of nonimmunosuppressed populations when treated in a standard manner.[351]

Evidence-Based Treatment Summary

1. Surgical resection is not necessary.
2. Avoiding or deferring WBRT results in inferior PFS but without significantly impacting OS. Lower dose WBRT added to aggressive chemotherapy improves radiographic CR rates and PFS. Neurocognitive dysfunction appears to be largely driven by disease recurrence.
3. High-dose systemic methotrexate is the only agent that has demonstrated improved survival over WBRT alone. High-dose methotrexate-based chemotherapy followed by WBRT is the standard treatment for patients younger than 60 years with a good performance status. Patients who achieve CR with high-dose methotrexate-based

chemotherapy should be treated with WBRT to a reduced dose of 23.4 Gy in 1.8-Gy fractions.

4. High-dose methotrexate-based chemotherapy alone with deferred RT may be preferred in older patients because of substantial risk of neurotoxicity associated with combined chemotherapy-RT regimens.
5. WBRT alone should be pursued for patients who are not candidates for chemotherapy.

Meningioma

Meningiomas account for approximately 30% of primary intracranial neoplasms and are the most common benign intracranial tumors in adults.[273] The peak age of incidence is in the sixth and seventh decades, although they may occur at any age. They are more common in women. Typical locations for meningiomas include the cerebral convexities, falx cerebri, tentorium cerebelli, cerebellopontine angle, and sphenoid ridge. Malignant varieties with invasive growth and aggressive behavior occasionally occur.

Grossly, meningiomas are well-circumscribed, firm, tan, or grayish lesions arising from the meninges. Hyperostosis of adjacent bone may be present. Microscopically benign meningiomas usually have a bland whorled appearance with little anaplasia or mitotic activity. Psammoma bodies may be present. Histologic variants (eg, fibrous, transitional, angiomatous) can be identified but are of little prognostic significance. Malignant varieties are identified on the basis of clinical behavior (rapid growth or recurrence, invasiveness) or pathologic features such as microscopic features of malignancy (cellular or nuclear anaplasia, mitotic figures) or specific histologic type (rhabdoid, papillary, anaplastic). The 2007 updated WHO grading criteria incorporate mitotic activity, nuclear-to-cytoplasmic ratio, spontaneous necrosis, brain invasion, and certain meningioma variants to assign grades I through III.[351] Benign meningiomas (~78%-80%) are classified as WHO grade I and associated with slower growth and lower risk of recurrence, atypical meningiomas (20%) WHO grade II with an increased likelihood of aggressive behavior, and anaplastic or malignant gliomas (3%-5%) WHO grade III and associated with high invasiveness and the worst prognosis. The 2016 update to the WHO classification system introduced brain invasion as a criterion that, similar to mitotic count of 4 or

more, can alone suffice for the diagnosis of an atypical WHO grade II meningioma.[240] The 2021 update to the WHO classification system most notably incorporated molecular information, adding *TERT* promotor (*pTERT*) mutation and homozygous deletion of *CDKN2A* and/or *CDKN2B* as grade III criteria, and removed papillary and rhabdoid meningiomas as grade III criteria that previously were present in the WHO 2016 system (Table 40.7).

TABLE 40.7 2021 WHO CLASSIFICATION OF MENINGIOMA[352]

Grade I (Benign)	Grade II (Required for Atypical)	Grade III (Required for Anaplastic/Malignant)
Does not fulfill criteria for grade II or III	Frequent mitoses (4-19 mitotic figures in 10 consecutive HPFs of each 0.16 mm^2, at least 2.5/mm^2) *or* Unequivocal brain invasion (not only perivascular spread or indentation of brain without pial breach) *or* Specific morphologic subtype: Chordoid meningioma, or Clear cell meningioma *or* Three or more of the following: Hypercellularity Small cells with high nuclear-cytoplasmic ratio Prominent nucleoli Sheeting architecture (uninterrupted patternless or sheet-like growth) Foci of spontaneous (noniatrogenic) necrosis	Excessive mitotic index (≥20 mitotic figures in 10 consecutive HPF of each 0.16 mm^2, at least 12.5/mm^2) *or* Frank anaplasia, meaning appearance resembling: Sarcoma Carcinoma, or Melanoma *or* *TERT* promotor (*pTERT*) mutation[a] *or* Homozygous deletion of *CDKN2A* and/or *CDKN2B*[a]

HPF, high-power field; WHO, World Health Organization.

[a]In the 2021 WHO classification, unlike the 2016 WHO classification, papillary and rhabdoid meningiomas have been removed from grade III criteria and can be any grade, and *pTERT* mutation or homozygous deletion of *CDKN2A* and/or *CDKN2B* are new, independent grade III criteria. WHO grades II and III criteria can apply to all meningioma subtypes. However, WHO grade II criteria are necessary for an atypical meningioma diagnosis, and WHO grade III criteria are necessary for an anaplastic (malignant) meningioma diagnosis.

Meningiomas are known to be induced by ionizing radiation, with an average interval to diagnosis of 19 to 35 years, depending on the dose of radiation. They may be multiple, particularly in patients with NF2 and in non-NF2 families with a hereditary predisposition to meningioma.

The most common cytogenetic alteration in meningiomas involves a deletion of chromosome 22. Molecular genetics findings indicate that approximately 50% of meningiomas have allelic losses that involve band q12 on chromosome 22. Allelic losses of chromosomal arms 6q, 9p, 10q, and 14q are seen in both atypical and anaplastic meningiomas. Genetic and cytogenetic alterations accumulate with progression from WHO grade I to WHO grade III lesions. Mutations in the *NF2* gene have been detected in 60% of sporadic meningiomas. The cumulative effect of NF2 mutations or copy number alterations affecting chromosome 22 is the loss of activity/function of a tumor suppressor protein, Merlin (Moesin-ezrin-radixin-like protein) encoded by the gene *NF2*. More recent genomic analysis of meningiomas reveals that in the 40+% of tumors without chromosome 22 loss or NF2 mutation, other somewhat uncommon, but potentially targetable mutations can be identified. In a whole-genome or whole-exome sequencing on 17 meningiomas and focused sequencing on an additional 48 tumors, most meningiomas were found to have "simple genomes," with fewer mutations, rearrangements, and copy number alterations than reported in other CNS tumors in adults. This study confirmed focal *NF2* inactivation in 43% of tumors and found alterations in epigenetic modifiers of NF2 in an additional 8% of tumors. A subset of meningiomas lacking *NF2* alterations harbored recurrent oncogenic mutations in *AKT1* and *SMO* with immunohistochemical evidence of activation of these pathways. These mutations are linked to the potential for identifying targeted therapeutics for some meningiomas.[353] A recent analysis of 274 high-grade meningiomas compared to 456 low-grade meningiomas concluded that high-grade meningiomas actually have a higher mutation burden, but no statistically significant mutated genes other than *NF2* could be identified.[354]

In an analysis of the histologically aggressive variant, rhabdoid meningiomas, designated in the WHO classification as high grade, sequencing of cancer-related genes in 27 meningiomas from 18 patients with rhabdoid features was performed, findings from which led to

specifically evaluating the breast cancer (BRCA)1-associated protein 1 (BAP1) expression by immunohistochemistry in 336 meningiomas. The tumor suppressor gene *BAP1*, a ubiquitin carboxy-terminal hydrolase, was found to be inactivated in a subset of high-grade rhabdoid meningiomas. Patients with BAP1-negative rhabdoid meningiomas had reduced time to recurrence compared with patients with BAP1-retained rhabdoid meningiomas, and a subset of patients with BAP1-deficient rhabdoid meningiomas harbored germline BAP1 mutations, indicating that rhabdoid meningiomas could be a harbinger of the BAP1 cancer predisposition syndrome.[355] These findings are beginning to provide clues toward the goal of identifying actionable mutations in meningioma.

The incidental finding of a meningioma on CT or MRI is not uncommon, particularly in the older patients. Many patients with meningioma are asymptomatic and may remain so for a long time.[356,357] Lesions in the cerebellopontine angle commonly present with symptoms of cranial neuropathy. Cerebral convexity meningioma may present with symptoms of headache or a seizure. Meningiomas of the sphenoid wing or optic nerve may be associated with visual loss. The differential diagnosis of meningioma in the base of the skull or spine includes bone metastasis or primary bone tumors (chondrosarcoma, chordoma, osteosarcoma). In the cerebellopontine angle, acoustic neuromas may resemble meningiomas on imaging.

The near ubiquitous expression of SSTRs on meningiomas has led to interest in developing PET imaging techniques targeting these receptors with somatostatin analogs conjugated to positron emitters, for example, ^{68}Ga-DOTATATE. In a recent RANO publication, ^{68}Ga-DOTATATE PET imaging was encouraged in patients with meningioma, with the expectation that it could impact multiple domains, including confirmation of diagnosis when in doubt, staging in the rare event of distant metastatic disease, support superior definition of targeting, either for resection or RT planning, and potentially for response assessment.[358]

Meningiomas typically grow slowly. In 47 asymptomatic patients with meningioma diagnosed incidentally by MRI, Nakamura et al[359] reported a mean annual growth measured using serial MRI of 14.6% and a mean tumor doubling time of 21.6 years. Higher annual growth rates were seen in young patients and lower annual growth rates in patients with calcification

and hypointense or isointense T2 signals on MRI. The location of the lesion, extent of surgical resection, and histopathologic features of the tumor (benign or malignant) are the most important determinants of prognosis.[360]

After surgery, the average time to recurrence is approximately 4 years. In a review of 38 patients who underwent subtotal resection, the mean diameter increase was 0.37 cm/y and mean tumor doubling time was 8 years.[361]

Treatment

Grade I Meningioma

Patients with asymptomatic lesions may be observed and followed with serial imaging. The treatment of choice for symptomatic or progressive benign meningiomas is complete surgical resection if it can be accomplished with acceptable morbidity. Resection of these typically vascular tumors may be facilitated by preoperative angiography with or without embolization. Even after complete resection, 7% to 12% of these tumors recur at 5 years and 20% to 25% recur at 10 years[362,363] so that follow-up with serial imaging is necessary.

Complete resection of skull-based, cerebellopontine angle, or cavernous sinus meningiomas may be difficult without significant morbidity. Subtotal resections are associated with higher relapse rates of 39% to 47% at 5 years and 60% to 61% at 10 years without adjuvant therapy.[362,363] For these patients, conservative subtotal resection followed by postoperative irradiation may give good local control with less morbidity than an aggressive base of skull resection. An alternative approach for patients who have undergone subtotal resection is follow-up with further surgery, if feasible, and RT delayed to time of recurrence.

In patients with subtotally excised unresectable or recurrent meningiomas, the typical RT dose is 50 to 54 Gy in 25 to 30 fractions over 5 to 6 weeks. The target volume for RT is defined by CT or MRI scan and modified according to the neurosurgeon's description of the location of residual tumor. SSTR-PET imaging with ligands such as ^{68}Ga-DOTATATE or ^{68}Ga-DOTANOC can be useful to identify tumor margins, particularly in the skull base where there are other anatomic structures that enhance with

MRI-based contrast agents, thereby creating uncertainty as to whether the signal seen on MRI is tumor versus a normally enhancing structure.[358] However, this approach has not yet been widely adopted into practice in the United States due to the limited insurance coverage for this type of imaging. The margin expansion for meningiomas is based on the knowledge of direction of spread, especially through neural foramina, bony invasion, dural tails, and so forth. The GTV is the enhancing abnormality on contrast-enhanced MRI. Margin expansions then incorporate setup errors and block margins; these can vary from 0.5 to 1 cm in total depending on the precision of the immobilization and delivery systems. Multiple fields with wedges or rotational fields and 3D conformal techniques are used for maximal sparing of normal brain tissue. IMRT or proton therapy may be helpful in avoiding adjacent surrounding structures.

Postoperative irradiation after less than complete resection improves local control, prolongs the interval to recurrence, and improves survival. In series by Condra et al,[362] subtotal resection with postoperative irradiation had a local control rate of 87% at 15 years compared to 76% following total excision and 30% after subtotal excision (P = .0001). In modern series using MRI and CT localization, 5-year local control is reported to be more than 90%.[364]

Radiosurgery as the sole modality or as postoperative adjuvant therapy may be of interest for selected patients, generally those with smaller tumors. In recent series, 5-year PFS rates are more than 80%.[365-369] In a recent single-institutional study, 85 patients eligible for a potential Simpson grade 1 or 2 resection were treated with SRS (usually because of preference). These patients received SRS either because of radiographic evidence of growth (72%) or due to postoperative recurrence (28%). With a mean follow-up of 69 months, the estimated 2-, 5-, and 10-year local control rates were 99%, 93%, and 93%, respectively, results that compare well with surgical series.[370]

Chemotherapy has not been useful in the treatment of benign meningiomas. Given the high estrogen and progesterone receptor expression on meningiomas, progesterone receptor antagonists have been tested but have not been found beneficial.

Grade II and III Meningiomas

For atypical or malignant meningiomas, the recurrence rate after surgery alone is high (41%-100% at 5 years), even after complete surgical resection,[371] and postoperative irradiation after maximal resection is recommended for all patients. The target volume is more generous than that used for benign meningiomas. The GTV and/or resection bed are typically expanded by 0.5 to 1.0 cm along the dural margin and into brain parenchyma in cases of brain invasion. The recommended dose is on the order of 54 to 59.4 Gy in 30 to 33 fractions for atypical meningioma and 59.4 Gy in 33 fractions for malignant meningioma, although some have reported improved local control with higher doses.[372]

RTOG 0539 enrolled 52 patients into an intermediate-risk cohort comprising WHO grade II tumors with gross total resection (70%) and recurrent WHO grade I tumors (30%) and treated with fractionated RT to 54 Gy.[372] The 3- and 5-year PFS were 92% and 84%, respectively, comparable to PFS estimates following observation of resected WHO grade I meningioma observed in the same trial. In a National Cancer Database analysis, the use of adjuvant RT for subtotally resected WHO grade II meningioma improved OS.[373] In the setting of gross totally resected WHO grade II meningioma, two randomized trials seek to address whether adjuvant RT prolongs PFS and OS.[374]

In a review of 38 patients with malignant meningiomas by Dziuk et al,[371] the use of postoperative RT resulted in superior local control. At 5 years, irradiation following initial resection improved 5-year disease-free survival from 15% to 80% (P = .002). PFS was 57% in patients treated with total resection and RT compared to 28% in patients treated with total resection alone.

Deng et al conducted a prospective phase 2 trial investigating bimodal RT using photons (50 Gy in 25 fractions) with carbon-ion boost involving 18 Gy (relative biologic effectiveness) in 6 fractions for 33 patients with WHO grade 2 meningiomas following subtotal resection. At 3 years, PFS, local PFS, and OS estimates were 80.3%, 86.7%, and 89.8%, respectively.[375]

Systemic therapy has no defined role. Combined chemotherapy with vincristine, adriamycin, and cyclophosphamide has shown some efficacy in

patients with malignant meningiomas.[376]

Unresectable or Recurrent Meningioma

In patients in whom aggressive surgery is not an option, RT may relieve symptoms and decrease the rate of tumor progression.

RT may be useful in the treatment of recurrent meningioma. In a review by Miralbell et al,[377] PFS at 8 years for patients treated with subtotal resection and RT at first recurrence was 78% compared to 11% in patients treated with resection alone ($P = .001$).

Various chemotherapy treatments that have been used in patients with recurrent meningiomas include combined doxorubicin and dacarbazine or ifosfamide and mesna.[378] Long-term, low-dose daily hydroxyurea may have some activity.[379]

Hormonal manipulation, including tamoxifen and the antiprogesterone drug RU486, showed some activity in a SWOG phase II evaluation of tamoxifen in unresectable or refractory meningiomas.[380] However, a subsequent SWOG phase III study of mifepristone for unresectable meningioma was negative.[381]

The EORTC recently reported results from a randomized open-label multicenter comparative phase II trial of trabectedin, which failed to demonstrate sufficient antitumor activity against recurrent grade II or III meningioma to justify further investigation in phase III or as adjuvant therapy for newly diagnosed disease after resection and RT.[382]

The Alliance for Clinical Trials in Oncology is currently conducting a trial of targeted agents selected by the presence of specific mutations in recurrent/progressive meningioma. In this three-arm phase II trial, patients with NF2 would be treated with vismodegib, those with SMO mutations with the focal adhesion kinase (FAK) inhibitor GSK2256098, and those with AKT mutations with a PI3 kinase pathway inhibitor.

Evidence-Based Treatment Summary

1. Small asymptomatic meningiomas in noncritical locations, especially in the older patients or in patients with other comorbidities, can be observed.

2. The goal of surgery is to completely resect the meningioma, with negative margins as patients with WHO grade I completely resected meningiomas have low rates of relapse and can be observed postoperatively.
3. For subtotally resected or unresectable progressive meningioma, RT is frequently used but has not been tested in a prospective clinical trial. Local control appears to be improved with postoperative RT. Both radiosurgery and RT have been used in this context, but have not been directly compared.
4. For grades II and III meningioma, postoperative RT is routinely recommended.
5. Primary RT or radiosurgery could be used for unresectable, progressive meningiomas.
6. Systemic therapy does not have a defined role in meningioma.

Craniopharyngioma

Craniopharyngiomas arise from epithelial remnants of the Rathke pouch and are typically found in the suprasellar region in children or adolescents. They account for less than 5% of all CNS neoplasms in adults. They are slowly growing tumors that often have solid and cystic components, the latter filled with lipoid, cholesterol-laden ("crankcase oil") fluid. Although appearing well encapsulated, craniopharyngiomas typically demonstrate invaginations into adjacent brain and may provoke a vigorous glial reaction.

The cystic nature of craniopharyngiomas is usually evident on CT and MRI and helps distinguish these tumors from other base of skull lesions and pituitary adenomas. The solid portion is often calcified and enhancing, whereas the cystic portion typically demonstrates a thin rim of enhancement. The finding of multiple cysts of varying intensity on T1- and T2-weighted MRI is characteristic of craniopharyngioma.

Intrasellar lesions may compress the pituitary gland and hypothalamus, producing hormonal abnormalities, especially antidiuretic and growth hormone deficits. Prechiasmal lesions may compress the optic pathway, leading to visual field cuts or decreased central visual acuity. Retrochiasmal lesions may grow into the third ventricle and cause hydrocephalus or

compress the optic tracts. Craniopharyngiomas can occasionally reach enormous size and produce neurologic impairment by direct impingement on brain parenchyma. Surgical decompression is the optimal treatment for rapid symptom relief. However, the location, proximity, and adhesiveness of the tumor to adjacent structures often preclude complete resection.

Treatment

A discussion of craniopharyngioma in the pediatric context is provided in Chapters 90. Management options include complete resection, subtotal resection alone, or subtotal resection or biopsy followed by postoperative RT.

Complete surgical resection, which is applicable only to a minority of patients, is associated with local control and long-term survival in 70% to 90% of patients.[383] However, aggressive resection may be associated with significant morbidity, with up to a 10% incidence of perioperative mortality and up to 30% severe morbidity, especially diabetes insipidus or other endocrine deficits, visual impairment, obesity, and memory impairment.

Partial resection or cyst aspiration and biopsy rapidly relieve local compressive symptoms and have less operative morbidity but are associated with eventual tumor progression in most cases. Long-term survival and local control are achieved only in approximately 30% of patients. In contrast to aggressive resections, subtotal resections carry a mortality of about 1%.

With a limited surgical procedure (partial resection or cyst aspiration plus biopsy) followed by RT, local control and survival rates are nearly equivalent to those achieved with complete resection, with survival rates of 89% and 77% at 5 and 10 years, respectively, as compared with 53% to 37% for patients who have had subtotal resection alone. Typically, doses of 50.4 to 54 Gy in 28 to 30 fractions (1.8 Gy) are delivered to the postoperative residual tumor and the borders of preoperative tumor extent with a 1- to 1.5-cm margin depending on the accuracy of the imaging used for planning and the reproducibility of the treatment setup. Reduction of margins to 0.5 cm can be considered when weekly MRI during treatment is used to monitor intratumoral cystic changes. In patients with compressive symptoms, surgical decompression before irradiation is essential because

the tumor typically responds slowly to RT, and radiation-induced edema may worsen compressive symptoms.

With these dose recommendations (ie, 1.8-Gy fractions to 50-54 Gy), the risk of visual impairment is very low (1% and 1.5%). In a retrospective analysis of patients treated with 51.3 to 70 Gy, a higher incidence of radiation-related complications was seen in those who received more than 60 Gy (with an actuarial incidence of optic neuropathy of 30% and brain necrosis of 12.5%), without any concomitant improvement in tumor control.[384]

RT may be given as salvage rather than immediately after subtotal resection. In a series of 76 patients treated at the University of Pennsylvania, long-term survival rates were equivalent.[385] In another series, RT given at recurrence yielded a 10-year PFS rate of more than 70%.[386] Recurrences occur from 3 to 192 months (median 12 months) after subtotal resection so that close surveillance is necessary during the first years following incomplete resection.

Other modalities used in the treatment of craniopharyngioma have included intralesional bleomycin and radioactive colloid instillations for cystic tumors. Radiosurgery may be useful in ablating small residual or recurrent tumors.[387] With radiosurgery, dose to the optic chiasm and nerves must be kept below 8 Gy, estimated to be radiobiologic tolerance for optic neuropathy with single-fraction radiosurgical doses. As a result, radiosurgery use should be restricted to tumors smaller than 3 cm in size and located greater than 3 to 5 mm from the optic apparatus.

Recent genotyping studies have demonstrated that the papillary variant of craniopharyngioma overwhelmingly expresses one or more BRAFV600 mutation(s). In a small, single-center study, 15 of 16 patients treated with the combination of vemurafenib and cobimetinib demonstrated a durable objective response, with median tumor volume recession exceeding 90%. This has led to a larger Alliance trial and the efficacy of this combinatorial regimen will likely impact future sequencing of various therapeutic modalities.[75]

Evidence-Based Treatment Summary

1. Surgical resection is recommended, when feasible.

2. The use of postoperative RT has not been tested in prospective trials but reduces the risk of recurrence and improves survival in incompletely resected tumors. Cyst decompression and biopsy followed by RT may be an acceptable treatment for patients for whom resection is not considered feasible.
3. Intracavitary bleomycin or radiocolloids may be useful in cystic tumors.
4. For papillary craniopharyngioma, dramatic durable responses are obtained with the combination of vemurafenib and cobimetinib, and this therapy is emerging as front line.

Vestibular Schwannoma and Neurofibroma

Neurilemomas, also known as schwannomas and neurinomas, arise from the Schwann cells of the myelin sheath of the peripheral nerves. When occurring close to the eighth cranial nerve, they are also called vestibular schwannomas or acoustic neuromas. These tumors account for approximately 6% of CNS neoplasms in adults. They may be sporadic or associated with NF2, with bilateral vestibular schwannomas being pathognomonic of this disease. Most sporadic vestibular schwannomas are unilateral and occur in the fourth and fifth decades of life. Those arising in patients with NF2 tend to occur in the second or third decade. These tumors grow slowly in a well-circumscribed, expansile manner, displacing adjacent nerves rather than invading them. Most arise from cranial nerve VIII in the medial internal auditory canal. Less commonly, they may arise from other cranial nerves, the trigeminal nerve being the most common alternate site.

Growth in the internal auditory canal gives rise to vestibular and hearing abnormalities in up to 95% of patients. A progressive unilateral sensorineural hearing loss is characteristic. Expansion into the cerebellopontine angle may lead to trigeminal symptoms, and a unilateral absent corneal reflex is an early sign of trigeminal involvement. Large tumors may impinge on the cerebellum and brainstem, leading to ataxia and long tract signs as well as involvement of cranial nerves IX, X, XI, and XII.

Pure tone and speech audiometry are the most useful screening tests. Selective loss of speech discrimination in excess of pure tone loss is particularly suggestive of vestibular schwannoma. Brainstem auditory evoked responses typically demonstrate a slowing of conduction, and

electronystagmography may detect a decrease in caloric response on the ipsilateral side. Thin-slice Gd-enhanced MRI through the cerebellopontine angle is the imaging modality of choice for suspected vestibular schwannoma. Thin-slice, contrast-enhanced, high-resolution CT scan is an acceptable alternative when MRI is not obtainable. An intensely enhancing lesion close to the internal auditory canal is highly suggestive of this diagnosis. Patients with suspected neurofibromatosis should have complete imaging of the craniospinal axis to document other neurilemomas, neurofibromas, and meningiomas that may be present.

Neurofibromas differ from neurilemomas in their cellular composition and growth pattern. Although neurofibromas also arise from peripheral nerves, they are most commonly multiple and associated with NF1. Neurofibromas expand rather than displace the nerve of origin. Histologically, neurofibromas are composed of a hypertrophied mass of fibroblasts and Schwann cells through which run normal neurons. Symptoms are caused primarily through compression of the involved or adjacent nerves.

Treatment

Treatment should offer a high chance of local control as well as preservation of cranial nerve function. Observation alone may be appropriate in patients willing to undergo regular clinical and imaging follow-up and may allow treatment to be deferred for some time. The mainstay of treatment has been microsurgical resection. Retrosigmoid (suboccipital) middle fossa and translabyrinthine approaches offer the possibility of hearing preservation but are associated with higher incidences of seventh nerve damage and postoperative complications. The translabyrinthine approach is associated with low operative morbidity and mortality but sacrifices hearing. At centers with expertise in microsurgical resection, total or near-total resection rates of 90% are routinely obtained with a surgical mortality rate of less than 2%. Anatomic preservation of the facial nerve may be achieved in 90% of patients and functional preservation in more than two-thirds. Preservation of useful hearing is reported in 30% to 50%. In patients in whom a near-total or total resection is achieved, the tumor recurrence rate is less than 10%. In patients in whom a subtotal

resection is achieved, tumor recurrence may occur in one-third to one-half. Adjuvant RT may reduce the rate of recurrence to that of complete resection.

In patients with a medical contraindication to surgery, treatment with external beam irradiation alone is an option. A dose of 50 to 55 Gy in 25 to 30 fractions over 5 to 6 weeks is recommended. Maire et al[388] evaluated 24 patients with stage III and IV cerebellopontine angle schwannomas treated with external irradiation. With a median follow-up of 60 months, there was an 88% tumor control rate with no injuries to the cranial nerve V or VIII.

Radiosurgery may be an alternative to microsurgical resection. The well-circumscribed nature of these tumors, coupled with their typical intense enhancement on MRI, facilitates their localization and treatment using stereotactic techniques. The PFS rate with radiosurgery is nearly 90% at 20 years. Radiosurgical treatment with higher doses yielded high rates of tumor growth arrest (>80%) and tumor shrinkage in up to two-thirds of patients, although facial or trigeminal neuropathy develops in nearly one-third of patients as long as 2 years after therapy. The volume of the lesion is a significant risk factor for complications involving cranial nerve V, VII, or VIII. Temporary enlargement may occur up to 2 years following radiosurgery.[389]

Noren[390] reviewed the results of 669 patients with vestibular schwannoma treated with Gamma Knife radiosurgery between 1969 and 1997. Long-term growth control was achieved in 95%. Facial weakness and/or numbness occurred in approximately one-third of patients during the 1970s but less than 2% in the 1990s. Hearing was preserved in 65% to 70% of patients, although tinnitus was rarely changed by treatment. With dose reduction to 12 to 13 Gy, high rates of tumor control and cranial nerve preservation may be achieved. Flickinger et al[391] reported the results of 313 patients treated with radiosurgery to a median dose of 13 Gy. The actuarial 6-year tumor control rate was 98.6%. The actuarial 6-year rates for the preservation of seventh nerve function, normal fifth nerve function, unchanged hearing level, and useful hearing were 100%, 95.6%, 70.3%, and 78.6%, respectively. Hayhurst et al[392] reported on their clinical series of 200 patients treated with radiosurgery to 12 Gy and observed 5 cm^3 to be the target volume threshold above which adverse treatment effects were more

likely. In addition, they observed a maximum dose threshold of 9 Gy to cranial nerve V as significantly associated with trigeminal neuropathy.

Radiosurgery provides similar local control with less morbidity than surgery for small (<3 cm) unilateral tumors. In a series from the University of Pittsburgh, radiosurgery was found to have improved preservation of facial function ($P < .05$) and hearing ($P < .03$) with decreased associated morbidity ($P < .01$) when compared to surgical resection.[393]

Fractionated RT has been shown to give local control rates of 91% to 97% with similar effects on cranial nerves V and VII.[394-397] However, in one series, fractionated resulted in 2.5-fold greater preservation of hearing compared to radiosurgery.[394] Multifraction SRS may be an option for tumors too large to receive radiosurgery.

Bevacizumab has been used in patients with progressive bilateral vestibular schwannomas associated with NF2, usually in the context of bilateral hearing loss, producing both tumor regression and restoration of hearing in some patients. This has led to this approach being actively investigated at present. Sporadic and NF2-related vestibular schwannomas express VEGF, and bevacizumab binds VEGF with high affinity. In the initial experience reported by Plotkin et al, 10 patients at with NF2 risk for complete hearing loss or brainstem compression were treated with bevacizumab on a compassionate care basis and demonstrated promising results with 6 of 10 patients experiencing 20% or more tumor volume reduction and 4 of 7 patients experiencing significantly improved hearing.[398]

Evidence-Based Treatment Summary

1. Small nonprogressive tumors can be observed.
2. Surgical resection is generally considered the standard of care for symptomatic lesions.
3. Radiosurgery produces outcomes equivalent to surgery, although these modalities have not been prospectively compared.
4. Fractionated RT is being increasingly employed, with institutional reports suggesting a lower incidence of cranial neuropathies than radiosurgery, but this has not been prospectively validated.

5. The role of bevacizumab in NF2-associated progressive bilateral vestibular schwannomas is being explored.

Hemangioblastoma and Hemangiopericytoma

Hemangioblastomas are benign vascular tumors that present during the third and fourth decades of life. They account for 1% to 2% of primary CNS tumors in adults. Most arise in the cerebellum, constituting the most common primary cerebellar tumors in adults. An association with von Hippel-Lindau disease is noted in 10% of patients. Histologically, the tumor consists of closely packed, thin-walled blood vessels in a stroma of large, oval foamy cells. The lesions are intensely enhancing on CT and MRI, and angiography confirms the vascular nature of the lesion. Imaging of the craniospinal axis often documents multiple lesions in patients with von Hippel-Lindau disease. Treatment is surgical, and complete resection is curative. Radiosurgery has also been shown to be useful in patients with unresectable disease but is associated with higher rates of recurrence.[399-401] In von Hippel-Lindau, treatment of symptomatic hemangioblastoma is warranted, but observation of asymptomatic tumors can be considered.[402]

Hemangiopericytoma is a sarcomatous lesion developing from smooth muscle in blood vessels usually along the base of the skull, although intraparenchymal lesions may be seen. In contrast to other primary CNS tumors, hemangiopericytomas commonly develop systemic metastases. There is a 90% 9-year actuarial risk for local failure following surgical resection only. Postoperative RT to total doses of 50 to 60 Gy reduces the risk of recurrence rate and improves OS. Tumor control is dose dependent, with doses greater than 50 Gy associated with superior outcomes. Radiographic response is slow. Radiosurgery has been used for recurrent hemangiopericytomas, with reported local control rates of approximately 80% following treatment.[403]

Evidence-Based Treatment Summary

1. Surgical resection is recommended, when feasible, for both of these diseases.

2. RT is generally reserved for subtotally resected progressive hemangioblastoma, but there are no prospective data.
3. Postoperative RT is recommended for subtotally resected hemangiopericytoma, but there are no prospective data.
4. RT or radiosurgery may be considered for unresectable tumors.

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CHAPTER 41

Fractionated Radiation Therapy and Stereotactic Radiosurgery for Pituitary Adenomas

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ANATOMY

Gross Anatomy and Embryology

The pituitary gland is essential for sustaining life and controls multiple functions in systemic physiologic regulation. It averages an anteroposterior diameter of 8 mm and a transverse diameter of 12 mm. The average weight is approximately 0.5 g, but it almost doubles during pregnancy.[1] It is located within the sella turcica of the sphenoid bone, bounded anteriorly by the sphenoid sinus, laterally by the cavernous sinuses, and superiorly by a dural fold called the diaphragma sellae (Figure 41.1).[1] The superior aspect of the gland is related directly to the arachnoid and pia, and the subarachnoid space then extends below the diaphragma; the optic chiasm is located directly above the hypophysis.[1]

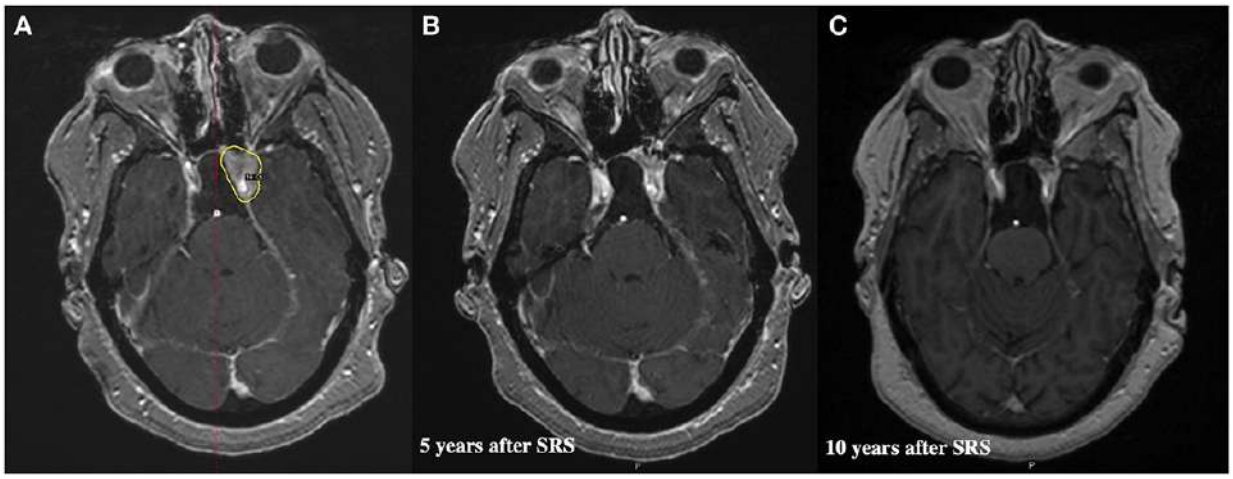

FIGURE 41.1 Illustrative case of a nonfunctioning pituitary neuroendocrine tumor. The tumor was invading the left cavernous sinus with sufficient distance from the optic nerve to allow stereotactic radiosurgery (SRS) in a single fraction. The tumor was treated with 16 Gy at an isodose line of 50% (A, yellow line). The tumor decreased after radiosurgery (B, at 5 years) with a long-term control (C, 10 years after SRS).

The pituitary is divided into two main parts based on embryologic origin: the adenohypophysis (anterior gland), deriving from the oral ectoderm of the Rathke pouch, and the neurohypophysis (posterior gland), deriving from the neural ectoderm.[1] The adenohypophysis encompasses the pars tuberalis, the pars intermedia, and the pars distalis; it constitutes the majority of the total volume of the pituitary gland. The pars tuberalis surrounds the infundibular stem that contains the unmyelinated axons from the hypothalamic nuclei. The pars intermedia forms the border between the pars distalis and the posterior gland; it is mostly nonfunctioning but also contains follicles that produce melanocyte-stimulating hormone (MSH) and endorphins. The pars distalis is the most distal part of the adenohypophysis and secretes the majority of hormones.[1]

Function and Blood Supply

The pituitary gland is connected to the tuber cinereum of the hypothalamus with the infundibulum through the diaphragma sellae. Hypothalamic nerve fibers in the median eminence secrete hypothalamic-releasing hormones into the capillary beds of the infundibulum, and these molecules are transported via the hypothalamohypophyseal portal vessels to the distal parts of the adenohypophysis, inciting the relevant effects. The neurohypophysis main hypothalamic nerve supply is fiber collectively known as the hypothalamohypophysial tract. Glial cells called pituicytes encircle the axons. This tract contains two main sets of fibers: the supraopticohypophysial tract and the tuberohypophysial tract.[1,2]

The pituitary gland is supplied through a number of hypophyseal arteries originating from the internal carotid arteries. The superior hypophyseal artery supplies the anterior lobe, the pituitary stalk, and the optic chiasm. It branches directly from the internal carotid artery or the posterior communicating artery.[1] The inferior hypophyseal artery, the meningohypophyseal trunk, which is a branch of the internal carotid artery, supplies the posterior lobe.[1] The intermediate lobe receives its blood supply from the anastomoses between the anterior and posterior lobe capillaries.[1] The pituitary gland drains into the cavernous sinus, releasing the produced hormones in the systemic circulation.[1] As such, the pituitary gland has a dual circulation; one is composed of arteries and veins, and the other is a portal venous system that links the hypothalamus and the anterior lobe.

The pars distalis area of the anterior pituitary gland produces the following hormones[1]:

- Adrenocorticotropic hormone (ACTH), MSH, and β-endorphin by basophilic-appearing corticotroph cells. The corticotropin-releasing hormone from the hypothalamus cleaves the proopiomelanocortin into ACTH, MSH, and β-endorphins. ACTH stimulates the release of cortisol from the adrenal cortex in conditions of stress.
- Thyroid-stimulating hormone (TSH) from the thyrotroph cells in response to thyrotropin-releasing hormone from the hypothalamus. TSH stimulates the release of T3 and T4 in the thyroid gland.
- Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from basophilic gonadotroph cells in response to the hypothalamic gonadotropin-releasing hormone. In males, LH acts on Leydig cells to stimulate the release of testosterone and FSH acts on Sertoli cells to secrete inhibin B for spermatogenesis. In females, LH initiates steroid production and causes ovulation, while FSH acts on granulosa cells to initiate estrogen production and stimulates follicular development.
- Growth hormone (GH) from acidophilic somatotroph cells in response to GH-releasing hormone. GH has anabolic properties and regulates cell division and protein synthesis.
- Prolactin (PRL) from acidophilic lactotroph cells, which is controlled by the dopamine system via an inhibitory mechanism. It primarily functions to stimulate mammary gland growth and milk production.

The neurohypophysis, despite its name, does not actually produce any hormones; instead, it should be considered a collection of axonal projections from the hypothalamus that store neurosecretions. The posterior gland hormones include[1]:

- Oxytocin that regulates milk ejection during lactation and uterine contraction
- Antidiuretic hormone that controls water content and prevents water depletion by increasing water reabsorption by the kidney tubules

PITUITARY DISORDERS

Pituitary disorders usually manifest by affecting hormone production, either through hypersecretion or through hypopituitarism. Most hypersecretion states are caused by functioning adenomas within the anterior lobe.[1] Functioning pituitary adenomas are usually composed of a single aberrant cell lineage that oversecretes a single hormone. The vast majority of pituitary adenomas are monoclonal in origin, suggesting a single somatic cell.[3] Hypersecretion of the anterior lobe pituitary adenomas results in gigantism, acromegaly, hyperprolactinemia, and Cushing disease.[3] Hypopituitarism may be caused by several destructive processes, such as ischemia (postpartum Sheehan syndrome), inflammatory diseases (granulomatous hypophysitis, lymphocytic hypophysitis, etc), iatrogenic injuries (resection, radiation), trauma, and nonfunctioning tumors

(nonfunctioning pituitary adenoma, and Rathke cleft cyst, craniopharyngioma, metastatic tumor).[1] Hyposecretion of the anterior hormones results in dwarfism, adrenal insufficiency, hypogonadism, and hypothyroidism. A posterior lobe deficiency can cause diabetes insipidus.

Besides endocrine abnormalities, pituitary diseases can cause symptoms through local mass effect on surrounding neurovascular structures. Neurologic signs include visual field defects due to optic chiasm compression, signs of increased intracranial pressure, double vision due to cranial nerve involvement, headache, and nausea.[4]

PITUITARY ADENOMAS

Pituitary tumors can be distinguished between those arising from the anterior lobe (adenohypophyseal) and those arising from the posterior lobe (neurohypophyseal) according to the new World Health Organization (WHO) classification.[5] Pituitary neuroendocrine tumors (PitNETs), usually named pituitary adenoma, are often classified as functioning and nonfunctioning based on pituitary hormone hypersecretion. The PitNETs are then subclassified based on the function of cell type and cell lineage and their related characteristics.[6] Due to their frequency including presence in 0.1% of the population and with an incidence of 3.9 and 7.4 per 100,000 per year, this chapter focuses on PitNETs.[7]

Histopathology and Grading

Approximately half of pituitary adenomas are macroadenomas (>10 mm), and two-thirds are functioning; the most common functioning adenomas are prolactinomas, followed by GH- and ACTH-secreting tumors.[3] Nonfunctioning pituitary adenomas constitute the second most common subtype after prolactinomas.[3] Up until the fourth edition of the 2017 WHO classification and adaptation of cell lineage as the main determining factor of pituitary adenoma classification, their histologic classification relied on pituitary hormone immunohistochemistry and cellular ultrastructural features.[3] Following the fifth edition of the WHO classification, immunohistochemistry (GH, PRL, TSH-β, ACTH, FSH-β, LH-β, and α-subunit of glycoproteins) is necessary for pathologic classification; transcription factors (PIT1, TPIT, and SF1) immunostaining are required when tumors cannot be classified by pituitary hormones alone or in the case of null cell adenomas.[3] The adoption of cell lineage classification is expected to result in a shift of reported PitNET histopathology groups; this is evident especially in the case of null cell tumors that currently represent only 1% to 2% compared to approximately 20% in prior PitNET registries.[3]

The overwhelming majority of PitNETs are benign, exhibiting a low recurrence rate following resection.[4] A few histologic subtypes, including sparsely granulated somatotroph, silent corticotroph, and Crooke cell PitNETs, are perceived as exhibiting a more aggressive clinical behavior; these so-called high-risk types tend to recur, be locally invasive, and be resistant to standard therapies.[8] Primary pituitary carcinomas are quite rare, and the clinical diagnosis requires the occurrence of craniospinal or systemic metastasis.[3]

Pituitary Neuroendocrine Tumors Clinical Presentation and Treatment

Prolactinomas are the most common PitNETs and range from small microadenomas to very large and invasive tumors associated with mass effect symptoms.[3,4] Serum PRL levels are usually correlated with tumor size. Patients presenting with amenorrhea, galactorrhea, loss of libido, and infertility should be evaluated with serum PRL.[4] Mild elevation does not always indicate a PRL-secreting PitNET; head trauma, use of drugs, renal failure, hypothyroidism, and a mass within the stalk disturbing the dopaminergic inhibition can result in a mild elevation of serum PRL.[4] Prolactinomas are usually well controlled with medical therapy, and resection is considered in the setting of refractory to medical management tumors.[9]

GH-secreting tumors are the second most common functional tumors. Children who develop these PitNETs prior to the epiphyses closing develop clinical gigantism, while older children and adults develop acromegaly. These clinical manifestations include enlarged hands and feet; increased bone density; enlarged thyroid, heart, liver, and adrenals; and broadening of the lower face with jaw protrusion.[4] Patients often have accompanying prolactinemia with gonadal dysfunction, hypertension, congestive heart failure, and an increased risk of gastrointestinal cancer.[4] Resection is the primary treatment of GH-secreting PitNETs in most patients, as it

produces immediate GH and insulin-like growth factor-1 (IGF-1) level normalization and provides pathologic characterization.[10] Medications for acromegaly (such as somatostatin receptor ligands, GH receptor antagonists, and dopamine agonists) can be effective and are often recommended for patients with persistent disease following resection; however, they require lifelong treatment, are not always fully effective, and are associated with significant side effects.[10]

ACTH-secreting PitNETs cause Cushing disease due to the chronic hypersecretion of cortisol from adrenal stimulation. Resection remains the first-line treatment of ACTH- secreting PitNETs, as it affords high rate of remission, allows for immediate control of hypercortisolemia and decompression of neural structures, and is associated with low complication rate in high-volume pituitary centers.[11]

Gonadotroph- and thyrotroph-secreting adenomas can occur, but these are much less frequent.[4] Most gonadotroph adenomas are LH- or FSH-producing tumors in middle-aged men and women with ambiguous clinical presentation, usually complaints of infertility and menstrual irregularities.[12] TSH-secreting PitNETs are rare, found in about 1% of patients, and are a rare source of hyperthyroidism.[13]

Radiotherapy (RT) and stereotactic radiosurgery (SRS) are typically used in the management of residual and recurrent PitNETs. Different techniques including SRS, conventional fractionated external beam RT, and proton beam therapy have been used to treat pituitary adenomas.[14]

IONIZING RADIATION TECHNIQUES

Conventional Fractionated External Beam Radiotherapy

Conventional RT uses doses of 1.8 to 2 Gy per fraction for treatment. This modality traditionally demonstrated a reasonable rate of tumor control and endocrine response but a moderate rate of short- to long-term complications.[15] Modern era RT using intensity-modulated RT, volumetric-modulated RT, and multiple beam arcs often allows for better preservation of surrounding organs.[16] The International Commission on Radiation Units and Measurements recommends that treating physicians delineate the volumes of treated targets and organs at risk (OARs).[17] Treatment plan volumes include the gross tumor volume (GTV), which is the visible demonstrable location and extent of the tumor; the clinical target volume (CTV), an expansion of the GTV to account for subclinical malignant disease; and the planning target volume (PTV), which is generated after applying a margin to the CTV to account for treatment uncertainties.[17]

Stereotactic Radiosurgery

SRS aims at delivering a high dose of radiation (overall and per fraction if hypofractionated), with appreciable conformality usually to a small target volume. Historically, SRS was performed using a single fraction, but due to evolution in the technology available, hypofractionated treatment (two to five fractions) using a mask-based approach is now available. Due to its cranial-specific design and its extensive use, Gamma-Knife radiosurgery (Elekta AB, Stockholm) is the most frequently used device in the published literature for SRS-related pituitary adenomas. Other technologies using a linear accelerator based (LINAC) (eg, CyberKnife, Novalis, and ViewRay) are also currently available.

A frame-based or frameless-based approach often with infrared tracking and cone beam computed tomography (CT) allows substantial precision in targeting the lesion and limits the risk of uncompensated movement associated with a mask-based procedure. Due to the high conformality of this technique, little to no margin dose is applied to the target, meaning that the GTV is usually equal to the PTV. SRS was developed, with one of its major goals being to reduce the dose to the surrounding tissue while achieving a high dose to the tumor. This translates to a lower risk of complication while achieving a faster endocrine remission and favorable tumor control rate.

Proton Beam and Other Particle Therapy

Due to their physical properties, proton beam therapy has the capability to improve the sparing of healthy tissue, which is of interest in a highly functional region such as the sellar region. The sharp dose fall-off of the Bragg peak effect needs to be considered when dose planning is performed. For now, due to the relatively limited availability of this technology, proton beam therapy is often reserved to treat larger tumor volume and

for pediatric patients with potentially greater risk for long-term adverse radiation sequelae.[18] Other options for particle- based therapy using linear energy transfer approaches such as with carbon ion therapy are showing promise for skull-based tumors.

Direct comparison of radiation treatment modalities is made difficult by the heterogeneity of published studies. The evaluation of brain and at-risk structure (eg, the normal pituitary gland, cranial nerves, vascular structures, hypothalamus, brainstem, and medial temporal lobes) sparing need longer term follow-up evaluation. The choice of RT modality included the proximity of the tumor to at-risk structure, particularly the optic nerve, the size of the tumor, and the patient characteristics (previous RT, age). The close proximity of the tumor to the optic nerve (often less than 3-5 mm) and a high volume (maximum diameter greater than 2.5-3 cm) could encourage the use of hypofractionation or standard fractionation schemes.

NONFUNCTIONING PITUITARY NEUROENDOCRINE TUMORS

Nonfunctioning PitNETs (NFPitNETs) present mainly with symptoms of mass effect, including optic nerve and cranial nerve compression and/or hormonal dysfunction. The first treatment is often maximal safe resection by a transsphenoidal resection. RT or SRS can then be utilized for residual or recurrent tumor. Alternatively, for patient unable or unwilling an open surgery, RT or SRS can sometimes be proposed as a primary treatment.[19,20]

Conventional RT was the first technique used to treat residual or recurrent lesion, with a local control of up to 90% at 10 years.[21] However, the risk of sequelae has led to a shift in practice toward more selective techniques, such as radiosurgery.[22]

Tumor Control

Tumor control is the primary goal of radiosurgery for NFPitNETs. Multiple studies using single-dose SRS revealed excellent tumor control after treatment, ranging from 93.3% to 100% and 76% to 92% at 5 and 10 years, respectively.[23-30] A recent meta-analysis provided an estimate of 94.0% (95% confidence interval [CI]: 93.0%-96.0%) of tumor control at 5 years and 83.0% (95% CI: 77.0%-88.0%) at 10 years using single-dose SRS[19] (Table 41.1; see Figure 41.1).

TABLE 41.1 MAJOR SERIES FOR NFPITNET TREATED WITH SRS IN A SINGLE FRACTION OR HYPOFRACTIONATED (TWO TO FIVE FRACTIONS)

Study	Technique	Year	*n*	Follow-Up Period (mo)	Median Prescription Dose (Gy)	Tumor Control	Hypopituitarism	New-Onset CN Deficits
Sheehan et al[25,a]	Single-dose GK	2013	512	36	16	98%, 95%, 91%, and 85% at 3, 5, 8, and 10 y, respectively	21%	6.6% from CN II, 2.7% from other CN
Losa et al[26]	Single-dose GK	2017	272	78	15	94.5% and 78.7% at 5 and 10 y, respectively	N/A	N/A
Sun et al[30]	Single-dose GK	2019	204	86	14	97%, 95%, 92%, 92%, and 81% at 3, 5, 8, 10 and 15 y, respectively	18%	7.4% from CN II, with 2.5% without tumor progression
Li et al[28]	Single-dose GK	2021	369	Median 60.8	13	100%, 98%, 97%, 86% and 77% at 1, 3, 5, 10, and 15 y, respectively, respectively	N/A	N/A
Maldar et al[29]	Single-dose GK	2022	109	Median 47	13	93.3%, at 5 y	29.7% at 10 y	1.6% from CN II

Study	Technique	Year	*n*	Follow-Up Period (mo)	Median Prescription Dose (Gy)	Tumor Control	Hypopituitarism	New-Onset CN Deficits
Dumot et al[31]	Single-dose GK	2023	869	44	14	95.5% and 88.8% at 5 and 10 y, respectively	9.9% and 15.3% at 5 and 10 y	1.4% from CN II, 0.7% from other CN
Iwata et al[32,b]	Hypofractionated CyberKnife	2011	100	33	21 Gy/3 fx, 25 Gy/5 fx	98% at 3 y	4%	1%
Liao et al[33]	Hypofractionated Novalis	2014	34 (21 NF)	37	21 Gy/3 fx	100%	N/A	2.9%

Series published after 2013 with 100 patients or more were included for single fraction.

Risk factors reported to be associated with post-SRS progression include cavernous sinus/parasellar invasion,[28,30] larger tumor volumes,[23-25,34] history of ³2 recurrences,[23] and tumor margin doses less than 12[28] or 13 Gy.[35] The recommended prescription doses for nonfunctioning pituitary adenoma single-session SRS range from 13 to 18 Gy and a typical dose is 16 Gy for single-dose radiosurgery.[36]

CN, cranial nerve; fx, fractions; GK, Gamma-Knife; N/A, not available; NF, nonfunctioning; NFPitNET, nonfunctioning pituitary neuroendocrine tumor; SRS, stereotactic radiosurgery.

[a]From a multicenter study.

[b]Linear accelerator series; others were Gamma-Knife.

Hypofractionated radiosurgery using two to five fractions is reported in fewer series with shorter follow-up. NFPitNETs and functioning tumors are frequently reported in the same series.[32,33,37-44] The same meta-analysis previously reported estimated the tumor control at 5 years at 97.0% (95% CI: 93.0%-98.0%).[19] The recommended prescription doses are 21, 20, and 25 Gy in three, four, and five fractions, respectively. Long-term analysis, larger series, and studies on dose selection are needed to evaluate the benefits and risks of a hypofractionated strategy (see Table 41.1). Hypofractionated SRS using a mask-based approach is often preferred for adenomas >3 cm in maximum diameter, for lesions less than 3 mm from the optic nerve and chiasm, and in those with contraindications to, or unwilling to undergo, frame-based SRS.

As an alternative to hypofractionated radiosurgery in three to five fractions, conventional RT with modern RT techniques can be an option for these patients (Table 41.2). Minniti et al[47] reported a series of 68 NFPitNETs of larger than 3 cm treated with RT in 45 Gy per 25 fractions in most of the cases and found a tumor control of 97% at 5 and 91% at 10 years. The rate of new hypopituitarism was 40% at 5 years, with 5.9% of patients developing transient cranial nerve deficits.

TABLE 41.2 MAJOR SERIES REPORTING EXTERNAL BEAM RADIOTHERAPY FOR NFPITNET

Study	Year	Technic	*n*	Follow-Up Period (mo)	Prescription Dose	Tumor Control	Hypopituitarism	New-Onset CN Deficits (%)
Kim et al[45]	2013	6 MV photon beams, 4 arcs in median	76 (54 NF)	81.6	50.4 Gy/28 fx	97.1% at 7 y	48%	0
Kopp et al[46]	2013	Five to six isocentric beam, 6 MV photons, and micro-multileaf collimator	37 (29 NF)	57	50.4 Gy/28 fx (except for eight 45-48 Gy)	91.9% at last f/u	N/A	5
Minniti et al[47]	2015	Five to 10 noncoplanar fixed fields 6 MV linear accelerator	68 (NF)	75	45 Gy/25 fx in 64 and 50.4/28 fx in 4	97% at 5 and 91% at 10 y	26.5%, 40% at 5 y	5.9 (transient)
Barber et al[48]	2016	Five to 13. 6 MV noncoplanar micro-multileaf collimation (Novalis)	75 (54 NF)	47.8	6-30 fx, 24-54 Gy	100%	28.0%	1.5
Plitt et al[43]	2019	CyberKnife 25-28 fractions	53 (41 NF)	33.3	46.7 Gy in 25-28 fx	98.1%	1.9%	0

Series published after 2010 with NFPitNET only and at least 30 patients treated with hypofractionated (3-5 fx) radiation.
CN, cranial nerve; fx, fraction; f/u, follow-up; N/A, not available; NF, nonfunctioning.

Wilson et al[39] compared 51 patients treated with SRS (median dose 14 Gy, single fraction), 67 treated with fractionated stereotactic RT (median dose 50 Gy in 28 fractions), and 53 with conventional RT (median dose 50.4 Gy in 28 fractions) performed from 1971 to 1991, for NFPitNETs. The 5-year probability of tumor control was 100% for SRS, 92.8% for fractionated stereotactic radiation, and 86.9% for conventional RT. Higher visual deficit was reported following conventional RT.

Most of the series with a modern conventional radiation technique included both functional and nonfunctional adenomas, which makes outcomes difficult to evaluate. The outcomes in terms of cognitive function or long-term evaluation compared to other strategies need further study. Ronson et al[49] reported a series of 47 patients treated with proton therapy for both FPitNET and NFPitNET (24 patients). At a median follow-up of 47 months, no tumor progression was reported. In all, 22.8% of patients with functioning tumors achieved endocrine remission. One patient developed temporal lobe necrosis, and 29.7% of the patients developed new hypopituitarism.

Timing of Radiation Therapy and Stereotactic Radiosurgery

The optimal timing of adjuvant RT and SRS after prior resection remains unclear. A recent matched cohort analysis comparing adjuvant SRS in the 6 months after resection to SRS at progression showed a similar tumor control, hypopituitarism, and visual deficit rate in both cases. The median time from resection to new pituitary deficiency was higher in the SRS at progression group.[50] Other studies demonstrated improved tumor control for patients treated during the 6 months after resection.[51,52]

Upfront Stereotactic Radiosurgery

A few studies evaluated the outcomes after upfront SRS before any surgical resection.[34,52,53] Lee et al[52] in a multicentric study reported the outcomes of 41 patients treated with SRS for NFPitNETs of a volume of 2.3 mL (range: 0.2-10.5). The probability of tumor control was 94% at 5 years and 85% at 10 years. In all, 24.4% of the patients had a new or worsened pituitary deficiency. One patient with tumor enlargement had a worsened visual field defect, and one patient had a new oculomotor nerve deficit. Kara et al[34] compared 216 patients treated with adjuvant SRS to 36 patients with primary treatment with no difference in tumor control and post-SRS pituitary deficiency.

Repeat Stereotactic Radiosurgery

Losa et al[26] described the profile of 39 patients with recurrent PitNETs after SRS for both functioning and nonfunctioning adenomas. In 56.4%, the tumor recurrence was considered out of the field of the previous treatment.

Reirradiation has been reported in a small series and can be associated with a mild to moderate rate of complications including temporal lobe necrosis and optic neuropathy in as much as 10% or more patients.[54,55] No precise guidelines on the feasibility of and preferred techniques to use for repeat radiation treatment are available. Prior dose to critical structures, timing of prior radiation, target delineation, and neurologic and endocrine function of the patient at that time should be carefully considered prior to reirradiation.

FUNCTIONING PITUITARY NEUROENDOCRINE TUMORS

FPitNETs are revealed by hypersecretory symptoms in most of the cases. Hypersecretion of ACTH, GH, and PRL are the most common functioning adenoma types. RT or SRS is recommended for failure to achieve endocrine remission after resection and/or medical management or for recurrence of hypersecretion. Pituitary adenoma control of an FPitNET is more often achieved than endocrine remission.[56]

Acromegaly

The differences in remission rates found in the literature could be at least partially explained by differences in estimating endocrine remission. Most of the studies did not use the Cortina acromegaly consensus criteria (random GH <1 ng/mL or nadir GH after an oral glucose tolerance test <0.4 ng/mL and normalization of age- and sex-adjusted IGF-1) to define endocrine remission.[57] In a similar way, comparing the various modalities of radiation delivery is difficult. Conventional RT was the first to demonstrate the efficiency in reducing GH and IGF-1 level.[58] Later, SRS was developed with the aim of reducing complications and is now frequently used to treat patients with persistent or recurrent acromegaly.

Knappe et al[59] described the outcomes of 233 patients treated with fractionated RT (stereotactic, conventional, or conformal) (follow-up: 13.0 ± 8.2 years) and 119 patients treated with single-dose SRS (follow-up: 8.9 ± 5.0). The 10-year remission probability was 48% for fractionated RT and 52% for SRS, with no statistical differences. The mean time to endocrine remission was faster after SRS (2.1 years) compared to fractionated (3 years) treatment. The rate of new pituitary deficiency was not different between groups.

Endocrine remission has been reported between 20.3% and 65% at 5 years after SRS.[60-64]

A multicenter study by Ding et al, published in 2019, reported the outcomes of single-dose SRS for 371 patients. The probability of maintained endocrine remission (defined as normalization of IGF-1 level based on age-matched cohort, off-lowering medication) was 43%, 59%, and 64% at 5, 10, and 15 years after SRS, respectively. The mean time from SRS to endocrine remission was 37.7 ± 32.5 months (Table 41.3).

TABLE 41.3 MAJOR RADIOSURGICAL SERIES FOR ACROMEGALY

Study	Year	*n*	Follow-Up Period (mo)	Definition of Endocrine Remission	Margin Dose (Gy)	Endocrine Remission	Delay From SRS to Endocrine Remission (mo)	Hypopituitarism (%)	New-Onset CN Deficits (%)
Wilson et al[65,a]	2013	86 SRS 10 fractionated (28 fractions in median)	66	GH <2.5 ng/mL Normal age- and gender-matched serum IGF-1 level	20	14% by SRS, 20% by HSRS for GH 18.6% and 50% for IGF-1	N/A	19.8	1.2
Lee et al[60]	2014	136	61.5	Normal age- and gender-matched serum IGF-1 level	25	32%, 65%, 73%, and 83% at 2, 4, 6, and 8 y, respectively	27.5	31.6	2.9
Kong et al[61]	2018	138	85.2	Mean basal GH level of less than 2.5 ng/mL and normal sex- and age-adjusted IGF-1	25	15%, 20.3%, and 44.9% at 3, 5, and 10 y	138	8.6	N/A
Ding et al[62,b]	2019	371	64.5	Normal age- and gender-matched serum IGF-1 level	24.2	51%, 69%, and 74% at 5, 10, and 15 y, respectively	37.7	26	4.3
Uygur et al[64]	2020	110	78	Normal age- and gender-adjusted serum IGF-1 levels, a	23.3	16.4%	26.5	5.4	N/A

Study	Year	*n*	Follow-Up Period (mo)	Definition of Endocrine Remission	Margin Dose (Gy)	Endocrine Remission	Delay From SRS to Endocrine Remission (mo)	Hypopituitarism (%)	New-Onset CN Deficits (%)
				random GH level less than 1 ng/mL, or a nadir GH during glucose tolerance test <0.4 ng/mL					
Knappe et al[59]	2020	233 fractionated, 119 SRS	156 for fractionated, 107 for SRS	Normal or low IGF-1 without suppressive medication	N/A	48% for fractionated, 52% for SRS at 10 y	36 for fractionated, 25.2 for SRS	N/A	N/A

Studies with 100 patients or more and sufficient data were included.

CN, cranial nerve; fx, fractions; GH, growth hormone; HSRS, hypofractionated stereotactic radiosurgery; IGF-1, insulin-like growth factor-1, N/A, not available; SRS, stereotactic radiosurgery.

[a]Linear accelerator.

[b]From multicenter series.

[c]Patients treated with a rotational Gamma-Knife MASEP.

In a meta-analysis of 28 studies involving 1,335 patients, the crude endocrine remission rate was estimated at 44.0% (95% CI: 35.0%-53.0%). The mean margin dose was not associated with endocrine remission in this study.[56] Predictor factors of endocrine remission included temporary cessation of IGF-1–lowering medication,[62] a lower pretreatment IGF-1 index,[66,67] and a higher margin dose.[67] Improvements in radiation modalities and techniques to achieve a higher rate of endocrine remission are under investigation. For example, some studies showed that a higher biologic effective dose could be associated with a higher endocrine remission rate,[67] but this was not confirmed in other studies.[66,68] Compared to nonfunctioning pituitary adenomas, a higher dose to treat acromegaly and achieve endocrine remission is required, and prescription doses are usually between 20 and 25 Gy.

The effect of primary SRS in cases for which there is an operative contraindication or patient refusal of surgery is not fully defined. Only a small series have evaluated this outcome. Gupta et al[69] found 28% of endocrine remission at 5 years in a series of 25 patients. Two studies including a matched analysis showed no differences in endocrine remission rate compared to postresection SRS.[70,71]

Repeat SRS for persistent or recurrent acromegaly after failed SRS was evaluated in 21 patients. The crude endocrine remission rate was 42.9% at a median follow-up of 3.8 years. New cranial nerve deficit occurred in 19.0% of patients.[72]

Gonzales-Virla et al[73] reported a series of 94 patients treated with a LINAC in 20 to 25 fractions with a median dose of 52 Gy, with 61% achieving endocrine remission defined by IGF-1 level at 10 years. Abu Dabrh et al[74] performed a meta-analysis of patients with acromegaly treated with either SRS or conventional fractionated RT and showed no significant differences in the rate of remission rate and hypopituitarism between the two modalities.

The effect of proton therapy in acromegaly was reported in a series of 50 patients. The 5-year probability of endocrine remission was 67%. Endocrine remission occurred in a median of 32 months after the treatment.[75] Iwata et al[76] reported outcomes using three to five fractions CyberKnife radiosurgery in 52 patients and found 17.3% of the patients satisfied the Cortina consensus criteria, with a median follow-up of 60 months. Further studies are required to better define outcomes with the various techniques.

Cushing Disease

In a multicentric study including 278 patients with a mean follow-up of 5.6 years, the rate of endocrine remission was 64% at 10 years post-SRS. Of note, 18% of patients recurred after initial remission. The mean time from SRS to cortisol normalization was 14.5 months. New pituitary deficiency occurred in 25% of patients[77] (Table 41.4).

TABLE 41.4 MAJOR RADIOSURGICAL SERIES FOR CUSHING DISEASE

Study	Year	Radiation Modality	*n*	Follow-Up Period (mo)	Margin Dose (Gy)	Endocrine Remission (%)	Delay of Endocrine Remission (mo)	Hypopituitarism (%)	New-Onset CN Deficits (%)
Devin et al[78]	2004	LINAC	35	42	14.7	49	7.5	40	0
Castinetti et al[79]	2007	GK	40	55	29.5	42.5	22	15	5
Kobayashi[80]	2009	GK	30	64.1	28.7	35	N/A	N/A	N/A
Wan et al[81]	2009	MASEP	68	67	23	27.9	N/A	N/A	N/A
Sheehan et al[25]	2013	GK	96	48	22	70	16.6	36	5.2
Wilson et al[82]	2014	LINAC	36	N/A	20	22.2	N/A	N/A	0
Wattson et al[75,a]	2014	Proton	79	47	20 (all types of functioning adenoma)	54	31	N/A	N/A
Mehta et al[77,b]	2017	GK	278	67.2	23.7	48%, 62%, 64%, and 64% at 2, 5, 10, and 15 y, respectively	14.5	25	3
Abdali et al[83]	2021	SRS (*n* = 34) and FSRS (*n* = 7, 3, or 5) CyberKnife	41	48.8	16	61	14	34	2.4

Series with 30 cases were included.

CN, cranial nerve; FSRS, fractionated stereotactic radiosurgery; N/A, not available; SRS, stereotactic radiosurgery.

[a]Pediatric.

[b]From a multicentric series.

In a meta-analysis of 2021, Mathieu et al[56] reported outcomes from 13 studies including 416 patients. The estimated crude rate for endocrine remission and new hypopituitarism was 48.0% (95% CI: 35.0%-61.0%) and 21.0% (95% CI: 13.0%-31.0%), respectively. Mean margin dose was not associated with outcomes in this study. A margin dose between 20 and 25 Gy in one fraction is generally advised.

For patients with refractory Cushing disease, bilateral adrenalectomy can be proposed for prompt control of hypersecretion in selected cases. Nelson syndrome is a difficult-to-treat condition, characterized by hyperpigmentation, increased ACTH level, and expansion of pituitary adenoma. SRS and proton therapy can be the options to treat Nelson syndrome and allow for a high rate of tumor control and reduction in ACTH level.[75,84,85] A study, including a few number of patients due to the rarity of this condition, suggests that treating patients with SRS before bilateral adrenalectomy is associated with a decreased risk of Nelson syndrome occurrence.[86]

Fewer studies reported outcomes after proton therapy (either single dose or fractionated) for Cushing disease. In a series of 79 patients, the rate of endocrine remission was 67%, with a median time to remission of 32 months.[75] In the same way, the effect of fractionation and proton therapy on outcomes compared to single-session SRS needs further study.

Upfront SRS for Cushing disease was evaluated in 21 patients from a multicentric study. The endocrine remission rate at 5 years was 81%, with a median time of 12.7 months after treatment. The crude risk of hypopituitarism was 23.8%, and 4.7% presented with new cranial nerve deficits.[69]

Repeat SRS for recurrent Cushing disease was evaluated in 20 patients. The rate of durable endocrine remission was 47% at 5 years, with a median time from SRS to remission of 6 months. Ten percent of patients experienced new deficits (transient visual loss in one and permanent diplopia in one).[87]

Prolactinoma

Prolactinomas are more often managed with medical therapy and, in case of failure, by resection. SRS is usually reserved for those who failed the two previous strategies. As such, most of the published prolactinoma studies included a small number of patients who have failed multiple prior treatment approaches.[88-90] Patients with prolactinoma undergoing RT or SRS tend to be a heavily pretreated cohort with appreciable selection bias as compared to other pituitary adenoma cohorts.

A multicentric study evaluated outcomes in a series of 289 patients. The endocrine remission rates were 28%, 41%, and 54% at 3, 5, and 8 years after SRS, respectively. New hypopituitarism occurred in 25% of the patients and a new cranial nerve deficit in 3%, with a median follow-up of 60 months. Tumor progression occurred in 5% of the patients, with a median follow-up of 59 months.

A lower PRL level prior to SRS and an increasing margin dose are associated with better endocrine control.[91] Pan et al[92] in a series of 164 patients showed improved endocrine remission rate if the dose was more than 30 Gy. Typically, a dose between 18 and 25 Gy in a single fraction is delivered to the prolactinoma. Further studies on outcomes with different prescription doses are needed.

In a meta-analysis of 13 studies with 538 patients using Gamma-Knife, LINAC-based SRS, and rotating gamma unit (MASEP), the crude tumor control was 93.0% (95% CI: 90.0%-95.0%) and the endocrine remission was 28.0% (95% CI: 19.0%-39.0%).[56]

Wattson et al[75] reported nine patients treated with proton therapy for a refractory prolactinoma. The remission rate was 38% at 5 years, with an estimated median delay from SRS to remission of 60 months. Further studies on fractionation radiation and proton therapy for prolactinomas are required.

Whole-Sellar Treatment

When the adenoma target on MRI cannot be fully defined for FPitNETs, a whole-sellar treatment can be performed. Lee et al,[93] in a series of 64 patients with acromegaly (n = 22), Cushing (n = 20), and prolactinoma (n = 2), the probability of endocrine remission was 54%, 78%, and 87% at 2, 4, and 6 years post-SRS, respectively. New hypopituitarism was 43.5%, with a median endocrine follow-up of 41 months. Inevitable, such a whole-sellar approach will deliver more radiation to the normal pituitary gland and stalk. Durankus et al[94] in a series of nine patients with Cushing disease found similar results. The high rate of hypopituitarism found in these two studies was not confirmed in two comparative studies on Cushing disease and acromegaly.[95,96]

Temporary Cessation of Pituitary Adenoma Suppressive Medications

Some studies have shown evidence of cessation of pituitary adenoma suppressive medications at the time of SRS to be a predictor of endocrine remission.[62,79,97] This effect is not always reported[85,91,98] or maintained at long term.[99] Therefore, it is generally reasonable to stop such medications 4 to 12 weeks prior to SRS so as to improve the response of the adenoma to ionizing radiation. Discussion with the endocrinologist is recommended to ensure that the temporary cessation is prudent.[56]

TOXICITY

Hypopituitarism

The most common complication of radiation is the occurrence of new pituitary hormone deficiency. This rate of hypopituitarism after RT and SRS increases with time. A multicentric study including both NFPitNETs and

FPitNETs (1,023 patients with 410 NFPitNETs) found a probability of new hypopituitarism of 7.8%, 16.2%, 22.4%, 27.5%, and 31.3% at 1, 3, 5, 7, and 10 years, respectively. New diabetes insipidus was reported in 1.1% of patients in this study.[100] The thyroid axis followed by the corticotroph or gonadotroph hormones was the most frequently involved.[100]

The risk factors that increase the risk for hypopituitarism are male sex,[101] increasing age,[102] prior RT,[25] suprasellar extension,[103] small gland volume,[101] poor visualization of the pituitary gland,[104] high dose to the tumor margin,[25,101,103] lower isodose line,[100] higher dose to the pituitary stalk,[102] and a greater distance from the center of the target to the center of the pituitary gland (>4 mm).[105]

Graffeo et al[101] suggested that reducing the mean dose to the gland <11 Gy in one fraction may help decrease the occurrence of new pituitary deficiency. However, this should not compromised the coverage of the tumor.

Cranial Nerve Deficits

Cranial nerve deficit after SRS most frequently involved the optic nerve followed by other cranial nerve in proximity (eg, III, IV, V, and VI). Most of the studies reported in Tables 41.1 to 41.4 noted a cranial nerve palsy rate of approximately 1% to 5%. Some deficits occurred in the context of tumor progression,[30] and the rate without documented adenoma progression has been reported between 1.6% and 2.9%.[23,25]

Cranial nerve II is highly sensitive to ionizing radiation, whereas the dose tolerance to the cranial nerves in the cavernous sinus is usually higher.[106] For patients without prior RT, the maximum point dose to the optic apparatus to keep the risk of optic nerve neuropathy below 1% is approximately <10 Gy in a single dose, 20 Gy in three fractions, and 25 Gy in five fractions. The choice of RT technique should take these constraints into account to lower the risk of an optic nerve deficit.[107] Relevant to OAR constraints for pituitary RT/radiosurgery are available in Table 41.5.[108]

TABLE 41.5 ORGAN AT RISK RADIATION DOSE CONSTRAINTS

	Radiation Dose Constraints			
OAR	**Conventional Fractionation**	**Single-Fraction SRS**	**Three-Fraction SRS**	**Five-Fraction SRS**
Optic pathway	$D_{0.035\ cm^3} < 55$ Gy	$D_{0.035\ cm^3} < 10$ Gy (mandatory) $D_{0.035\ cm^3} < 8$ Gy (optimal)	$D_{0.035\ cm^3} < 20$ Gy (mandatory) $D_{0.035\ cm^3} < 15$ Gy (optimal) $V_{10.5\ Gy} < 0.5\ cm^3$	$D_{0.035\ cm^3} < 25$ Gy (mandatory) $D_{0.035\ cm^3} < 22.5$ Gy (optimal) $V_{12.5Gy} < 0.5\ cm^3$
	$D_{0.035\ cm^3} < 54$ Gy $D_{1\text{-}10\ cm^3} < 59$ Gy	$D_{0.035\ cm^3} < 15$ Gy (mandatory) $D_{0.035\ cm^3} < 10$ Gy (optimal)	$D_{0.035\ cm^3} < 23.1$ Gy (mandatory) $D_{0.035\ cm^3} < 18$ Gy (optimal)	$D_{0.035\ cm^3} < 1$ Gy (mandatory) $D_{0.035\ cm^3} < 23$ Gy (optimal)
Pituitary gland	$D_{0.035\ cm^3} < 50$ Gy	$D_{MEAN} < 9$ Gy		
Temporal lobe	$D_{0.035\ cm^3} < 65$ Gy $D_{1\ cm^3} < 60$ Gy (mandatory)			

OAR, organ at risk; SRS, stereotactic radiosurgery.

Data from Bisello S, Cilla S, Benini A, et al. Dose-volume Constraints fOr oRganS At risk In Radiotherapy (CORSAIR): an "all-in-one" multicenter-multidisciplinary practical summary. *Curr Oncol*. 2022;29(10):7021-7050.

Long-Term Tumor Occurrence

The long-term risk of new tumor (benign and malignant) after conventional RT was estimated in a recent study of Hamblin et al[109] for patients treated for PitNET and craniopharyngioma. The probability of new tumor at 20 years was 4% (2.0%-6.0%) for the irradiated group, which was significantly higher than the 2.1% (1.1%-3.1%) probability in the control group.

In a SRS study involving a nonmalignant condition treated with SRS with 641 PitNETs, the risk of malignant transformation was estimated at 2.26 per 100,000 patient-years (95% CI:0.11-11.17) for radiosurgery-associated intracranial malignancy.[110]

Vascular Stenosis and Stroke After Prior Ionizing Radiation

Due to the frequency of cavernous sinus involvement, the treatment plan does not necessarily spare the internal carotid artery. Stenosis of the internal carotid artery after SRS has been reported, with an incidence of 0.70 per 1,000 patient-years (0.12-2.33) for FPitNET and NFPitNET.[111] Milanese et al[112] found one patient with a stroke due to carotid occlusion among 36 treated with conventional RT. The incidence of carotid stenosis and stroke was not reported for proton beam RT, so no comparison between modality can be performed.

Sims-Williams found no excess stroke compared to age- and sex-matched cohort for a series of patients with acromegaly treated with SRS, with a mean follow-up of 134 months.[113] Rim et al[15] in a small series using external beam RT reported a high rate of vascular complications (5%), suggesting that proton beam therapy can confer some sparing advantage for risk structures.

CONCLUSION

RT and SRS are important tools to manage patients with both NFPitNETs and FPitNETs. Long-term adenoma control is achieved in most patients with pituitary adenomas. A moderate rate of patients with functioning adenoma patients achieves endocrine remission. Hypopituitarism remains the most common complication following radiation to treat a pituitary adenoma; with timely diagnosis and hormonal replacement, this complication is a manageable one. Other complications such as cranial nerve dysfunction, cerebrovascular stenosis and stroke, and radiation-induced neoplasia are fortunately quite rare. The field is evolving with the aim of optimizing tumor control, endocrine remission, and minimizing side effects.

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CHAPTER 42

Primary Base of Skull Tumors

Mark W. McDonald

ANATOMY

The skull base is a complex anatomic interface between the intracranial contents and the disparate extracranial compartments, including the paranasal sinuses, middle and inner ear, upper parapharyngeal space, and posterior neck and spine.[1] The skull base may be considered in three parts: anterior, central (or middle), and posterior (Figure 42.1). The petrous temporal bone is sometimes described as the posterolateral skull base and engages both the central and posterior skull base. Table 42.1 lists key skull base foramina or structures and their associated neurovascular structures, illustrated in Figure 42.2.

TABLE 42.1 KEY SKULL BASE FORAMINA/SPACES AND TRAVERSING NEUROVASCULAR STRUCTURES

Skull Base Location	Foramen or Space	Traversing Nerve/Neural Structure	Traversing Vessel
Anterior	Cribriform plate	Olfactory (CN I)	
	Optic canal	Optic (CN II)	Ophthalmic artery
Central	Superior orbital fissure	Ophthalmic (CN V1) Oculomotor (CN III) Trochlear (CN IV) Abducens (CN VI)	Superior ophthalmic vein
	Foramen rotundum	Maxillary (CN V2)	
	Foramen ovale	Mandibular (CN V3)	Accessory meningeal artery
	Foramen spinosum	Meningeal branch of mandibular nerve	Middle meningeal artery
	Vidian (pterygoid) canal	Vidian nerve	Vidian artery
	Meckel cave (aka trigeminal cave)	Trigeminal nerve ganglion (aka gasserian ganglion)	
	Dorello's canal	Abducens (CN VI) on way to cavernous sinus	
Posterior/posterolateral	Facial nerve (fallopian) canal	Facial (CN VII)	
	Internal auditory canal	Facial (CN VII) Vestibulocochlear (CN VIII)	Labyrinthine artery
	Foramen lacerum	Vidian nerve leaves its anterior aspect	Artery of pterygoid canal Emissary veins (carotid artery is immediately superior)
	Jugular foramen	Glossopharyngeal (CN IX) Vagus (CN X)	Meningeal branch of ascending pharyngeal artery Inferior petrosal sinus

Skull Base Location	Foramen or Space	Traversing Nerve/Neural Structure	Traversing Vessel
		Exit of spinal accessory nerve (XI)	Jugular bulb
	Foramen magnum	Medulla oblongata Entrance of spinal component of CN IX	Vertebral arteries Anterior and posterior spinal arteries
	Hypoglossal canal	Hypoglossal (CN XII)	

CN, cranial nerve.

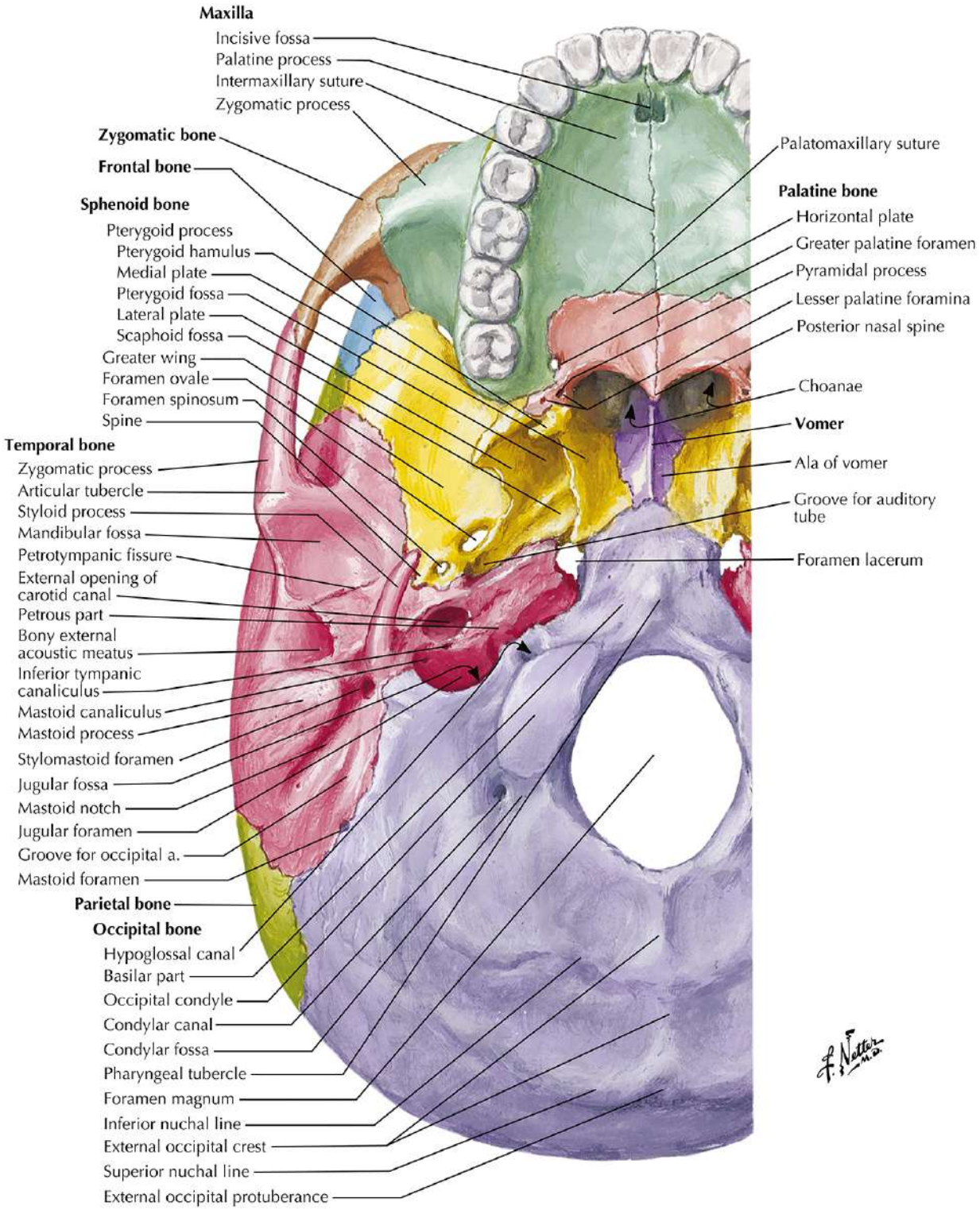

FIGURE 42.1 Anatomy of the skull base. Bones of the cranial base: superior view. (Reprinted from Netter FH. *Netter Atlas of Human Anatomy: Classic Regional Approach*. 8th ed. Elsevier; 2023. Plate 32. Copyright © 2023 Elsevier. With permission.)

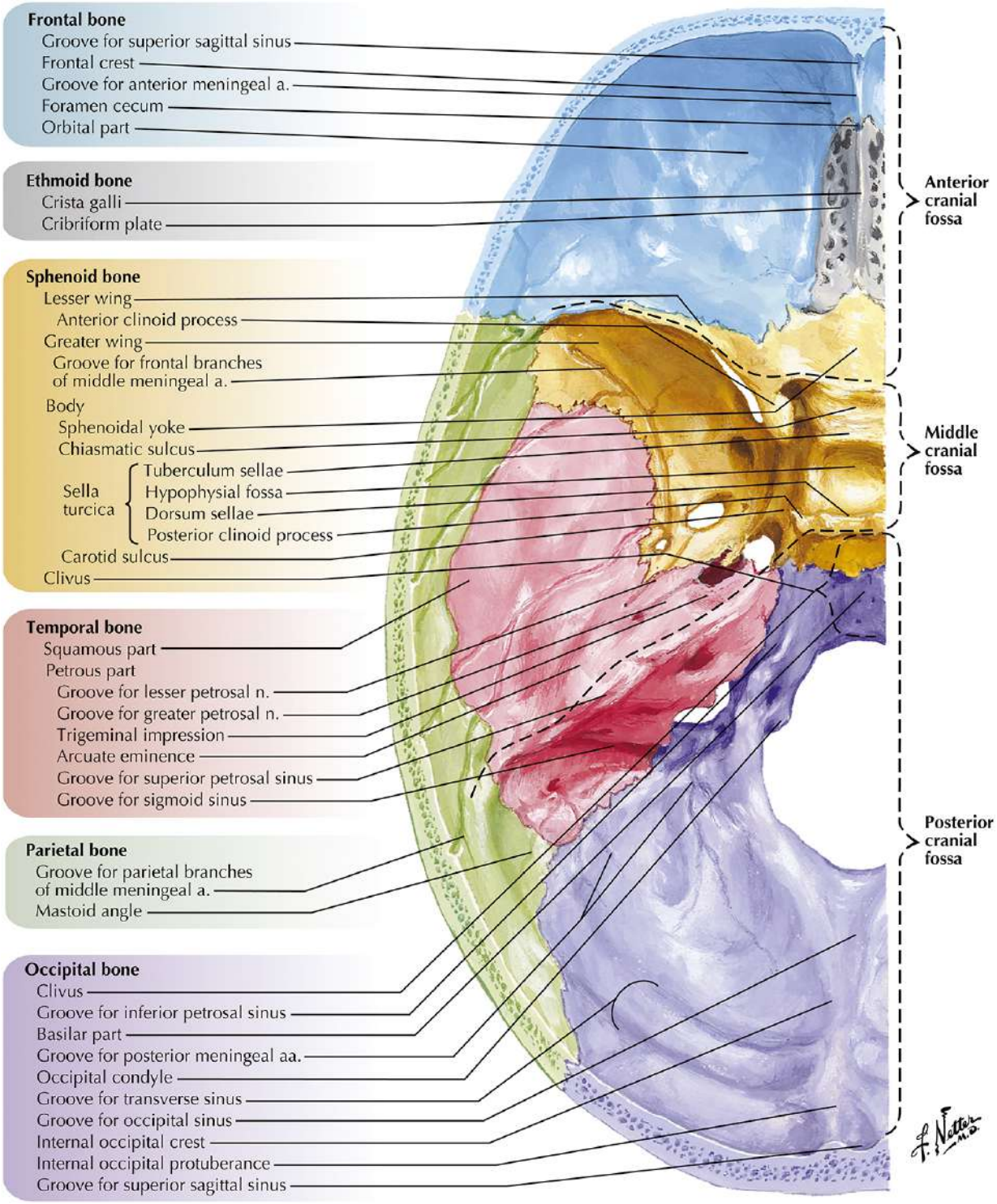

FIGURE 42.2 Skull base *foramina*. Foramina and canals of the cranial base: superior view. (Reprinted from *Netter FH. Netter Atlas of Human Anatomy: Classic Regional Approach*. 8th ed. Elsevier; 2023. Plate 34. Copyright © 2023 Elsevier. With permission.)

The anterior skull base interfaces with the orbit and sinonasal compartment. It is formed by the orbital plates of the frontal bone, the cribriform plate (cranial nerve [CN] I) and crista galli

of the ethmoid bone, and the planum sphenoidale and lesser wings of the sphenoid bone. The lesser wings of the sphenoid form the roof of the orbital apex and boundaries of the optic canals (CN II) and mark the division between the anterior and central skull base.

The middle or central skull base corresponds to the middle cranial fossa, pterygopalatine, and infratemporal fossae. Formed by the sphenoid and temporal bones, the central skull base contains the sella turcica (pituitary), clinoid processes, superior (sphenoid) portion of the clivus bone, and greater wings of the sphenoid. Paramedian to the central skull base are the cavernous sinuses containing CN III to CN VI and the cavernous portion of the internal carotid artery (ICA), and the temporal lobes of the brain. Foramen rotundum (V2), foramen ovale (V3), and foramen spinosum (meningeal branch of V3) traverse through the greater wings of the sphenoid. The petrous apex of the temporal bone forms the boundary between the central and posterior skull base, with the anterosuperior portion of the petrous apex forming the floor of the middle cranial fossa. At the superomedial aspect of the petrous apex is the petroclival junction, site of foramen lacerum, a predominantly fibrocartilaginous synchondrosis of the temporal bone with the occipital component of the clivus and the most common origin site for skull base chondrosarcoma.[2,3]

The posterior skull base is formed by the temporal, sphenoid, and occipital bones, with the posterosuperior portion of the petrous apex forming the anterior wall of the posterior cranial fossa. It contains the cerebellopontine angle, internal auditory meatus (CN VII, CN VIII), jugular foramen (CN IX, CN X, CN XI), hypoglossal canal (CN XII), and the foramen magnum (medulla, spinal component of CN XI, vertebral arteries, and anterior and posterior spinal arteries).

The clivus is formed from the sphenoid and occipital bones and bridges the central and posterior skull base. It may be conceptually divided into three levels (Figure 42.3). The superior (sphenoid) portion contains the dorsum sella and the posterior clinoids. At the caudal margin, the abducens nerve passes through Dorello's canal and marks the transition from the superior and middle clivus.[4]

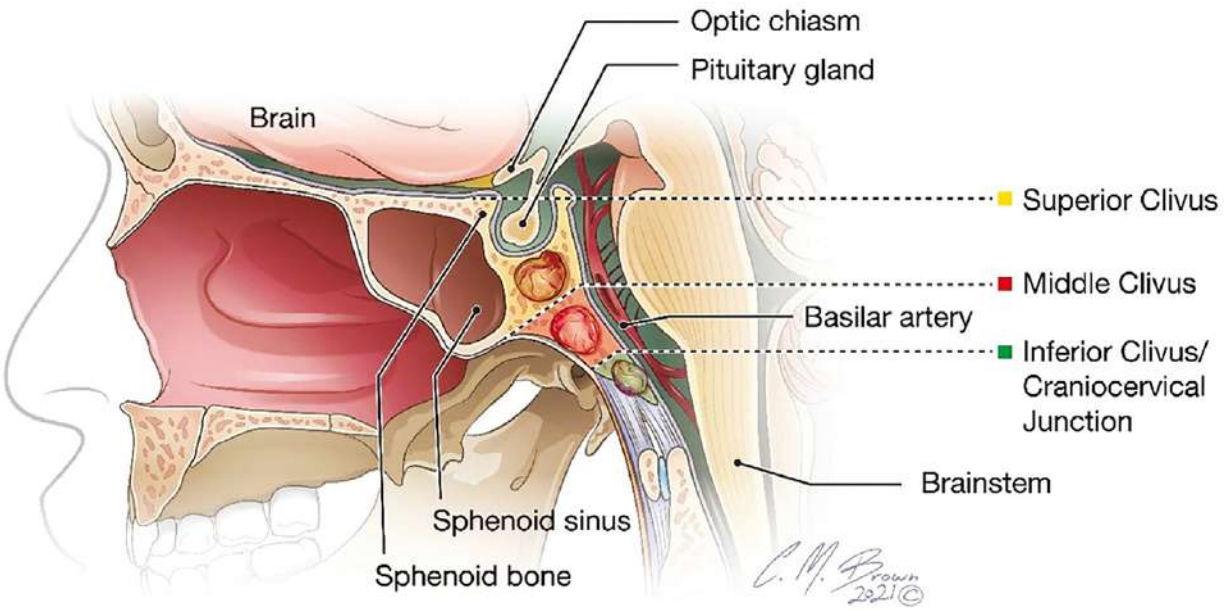

FIGURE 42.3 Illustration of the clivus. (Reprinted from Rao D, Stein R, Jenson M, Patel J, Fiester P. Imaging review of the endoscopic operative corridor for clivus lesions. *Curr Probl Diagn Radiol*. 2023;52[1]:66-76. Copyright © 2022 Elsevier. With permission.)

The middle (sphenoid) clivus extends from the sellar floor to the sphenoid body, with the lateral borders being the paraclival ICAs, foramen lacerum, and petroclival fissure. Middle clival lesions are most directly accessible and more likely to obtain a gross total resection via endonasal surgical approaches.[4]

The inferior (nasopharyngeal) clivus consists of the occipital portion of the clivus from the roof of the nasal choana to the foramen magnum. Lesions here are most difficult to access endonasally.

Paragangliomas arise along sympathetic or parasympathetic ganglia (Figure 42.4). In the past, paragangliomas have been called *chemodectomas* or *glomus tumors*, which are imprecise terms to be avoided.[5] Most head and neck paragangliomas are parasympathetic and arise, in order of frequency, at the carotid body, jugular, vagal, or tympanic sites.[6] Taken together, carotid body and jugular paragangliomas comprise about 80% of all head and neck paragangliomas.[7]

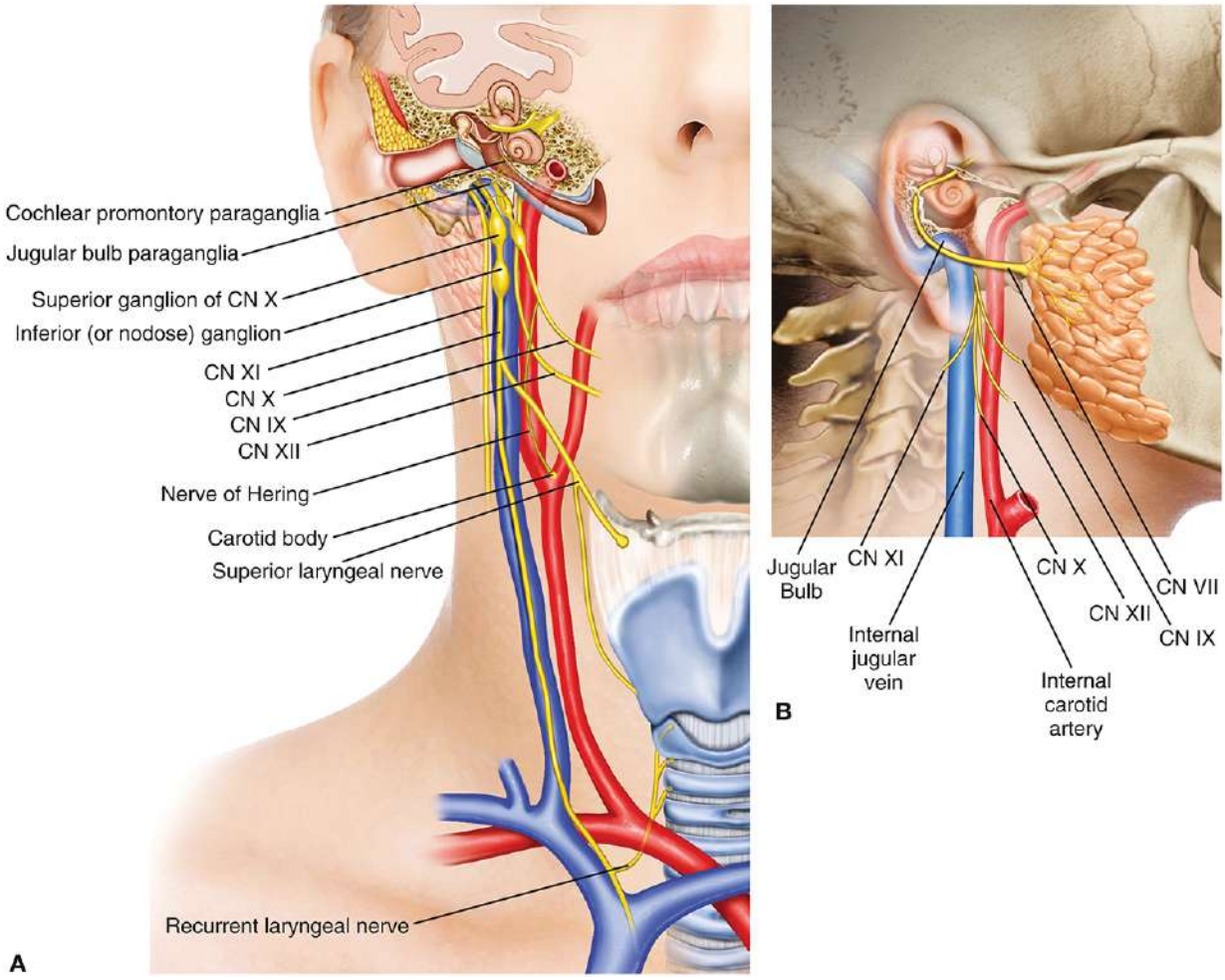

FIGURE 42.4 Anatomy relevant to head and neck paragangliomas. Anatomic site of origin of head and neck paragangliomas, in frontal (A) and lateral (B) views. CN, cranial nerve. (Reprinted from Verlicchi A, Nicolato A, Valvassori L, et al. Head and neck paragangliomas. In: Winn HR, ed. *Youmans and Winn Neurological Surgery*. 8th ed. Elsevier; 2023:1376, Figure 181.1. Copyright © 2023 Elsevier. With permission.)

Carotid body paragangliomas arise at the carotid bifurcation, at the plexus formed by the carotid sinus branch of the vagal nerve, and rami from the glossopharyngeal nerve and cervical sympathetic trunk.

Jugular paragangliomas arise at the superior ganglion of the vagal nerve at the jugular foramen. The jugular foramen is formed by the petrous portion of the temporal bone and the jugular process of the occipital bone, medial to the stylomastoid foramen, lateral to foramen magnum and the hypoglossal canal, and posterior to the carotid canal.

Vagal paragangliomas represent just 5% of head and neck paragangliomas and arise from the inferior ganglia of the vagal nerve (the ganglion nodosum), superior and medial to the carotid bifurcation and below the skull base.[5] Larger vagal tumors extending to the jugular foramen become indistinguishable from jugular paragangliomas with inferior extension.

Tympanic paraganglioma arises at the cochlear promontory, site of the tympanic plexus with the tympanic nerve (a branch of the glossopharyngeal nerve), and sympathetic branches from the internal carotid plexus. Jugulotympanic paragangliomas involve both sites or may be used as a catchall term for tumors of either location.

GENERAL PATHOLOGY

Many pathologies may involve the skull base. The anterior skull base is most commonly involved by direct extension of sinonasal malignancies or hematogenous metastases from other malignancies.[8,9] Sellar tumors including pituitary adenomas and craniopharyngiomas are discussed elsewhere. In the posterior skull base, the most prevalent pathologies include vestibular schwannomas and meningiomas, while perineural tumor spread may also be seen. Central skull base pathology can include perineural tumor spread from nasopharyngeal cancers, adenoid cystic carcinoma, and both cutaneous and mucosal squamous cell carcinomas.

Fibrous dysplasia is a mesenchymal disorder of bone that often involves the skull or facial bones. It may be an isolated finding or a part of McCune-Albright syndrome when accompanied by various endocrine abnormalities.[10] Most lesions are asymptomatic, incidentally detected, and managed with observation, while symptomatic patients may be treated with bisphosphonates.[11] While fibrous dysplasia can usually be diagnosed by computed tomography (CT), its appearance on magnetic resonance imaging (MRI) can mimic tumor with significant enhancement, and clinicians may be further mislead by avidity on positron emission tomography/CT (PET/CT).[12] The most common and easily recognized presentation of fibrous dysplasia is expanded bone with a ground-glass (pagetoid) appearance of both dense and radiolucent areas on CT.[2] Approximately a quarter of cases have a homogeneously dense (sclerotic) appearance on CT while a cystic (lytic) pattern is seen in a minority of presentations, with an expansile cystic lucency with a fluid or soft tissue appearing center surrounded by a dense bony shell.[13]

Skull base osteomyelitis, typically a bacterial or fungal infection from the sinonasal cavity or middle ear, can cause extensive bone and cartilaginous destruction, which may mimic an aggressive malignant process. Affected patients typically have an antecedent history of infection, surgery, or trauma, with patients who are diabetic and immunocompromised patients at greater risk.[14]

CHORDOMA

Pathology

Chordoma is a malignant mesenchymal tumor of bone. Chordomas are thought to arise from the remnant or ectopic notochord tissue,[15] and the diagnosis is confirmed by expression of brachyury, a notochord cell lineage transcription factor encoded by the *TBXT* gene.[16] Other common immunohistochemistry characteristics of chordoma include positive cytokeratin, epithelial membrane antigen (EMA), and S100 protein.[17] The histology of chordoma is notable for an abundant extracellular matrix with “physaliphorous” bubbly tumor cells, which may be found in solid masses or as cords and nests within a mucinous tumor matrix.[18] Mitotic figures are typically rare or absent.

The pathogenesis of chordoma has not been elucidated, but they may exist on a continuum of notochord remnant lesions. The notochord is a key structure in embryonic development as the precursor of the vertebrate nervous system.[19] While notochordal degeneration is typically complete by 10 weeks of gestation, persistent notochordal tissue may be found in the vertebral bodies of infants and children and rarely in middle-aged adults.[20]

Benign notochordal cell tumors (BNCTs), or *rests*, have previously been termed *ecchordosis physaliphora*, particularly when arising in the clivus. BNCTs appear to have a greater incidence than chordoma. In one study of 916 patients undergoing thin-slice CT and MRI for a variety of

indications, lesions with imaging characteristics consistent with BNCTs were incidentally detected in seven patients (crude incidence 0.76%).[21] While there are no agreed-upon features that distinguish radiographic BNCTs from chordoma, BNCTs are typically small (<2 cm) lesions without bony erosion, often arise on a filiform bony stalk or remain intraosseous, and are most often asymptomatic, although prepontine lesions may lead to compressive symptoms or a cerebrospinal fluid (CSF) leak.[21,22]

The difficulty in distinguishing between BNCTs and chordoma on both imaging and histologic examination suggests a link between them.[23-25] Proposed criteria for intervention of benign-appearing apparent notochordal lesions include symptomatic lesions, tumors >3 cm in size, atypical imaging characteristics (bony erosion, local invasion, or contrast enhancement), any appreciable growth on serial imaging, and patient preference.[24]

The subtypes of chordoma include conventional, chondroid, dedifferentiated, and poorly differentiated. In the National Cancer Database (NCDB) and Surveillance, Epidemiology, and End Results (SEER) data sets, the great majority of cases are conventional, with chondroid comprising 10% of cases, dedifferentiated ≤1%, and poorly differentiated not separately reported.[26]

Chondroid chordomas have a more hyaline-appearing matrix with cells that look similar to chondrocytes and may be confused with chondrosarcomas.[18] Chordomas are distinguished by positive brachyury staining and immunopositivity for cytokeratin and EMA, which are negative in chondrosarcoma.[27] The variant of chondroid chordoma does not appear to have any prognostic significance. In isolated series, the chondroid chordoma subtype has been variably reported to have a lower[28] or higher[29,30] likelihood of recurrence, while more studies[31-33] have found no difference. There was no statistically significant difference and not much numerical difference between survival outcomes for conventional and chondroid chordoma in NCDB and SEER data sets.[26]

Poorly differentiated chordomas, which occur more commonly in children, have a loss of *INI1* from isolated deletion of the *SMARCB1* gene and can be differentiated from other SMARCB1-deficient tumors such as atypical teratoid/rhabdoid tumor by brachyury expression and a distinct DNA methylation profile.[34,35] Dedifferentiated chordomas have a biphasic morphology with sarcomatous components. Both dedifferentiated and poorly differentiated chordomas have an aggressive clinical course and notably poor prognosis compared to conventional and chondroid chordoma.[36]

Epidemiology and Risk Factors

An analysis from the SEER database suggests that chordoma is the most common histology of malignant bone tumor arising in the head and neck in both adults and children.[37] The annual percentage change of age-adjusted incidence of malignant bone tumors of the head and neck between the years 2000 and 2019 was 1.52.

Chordomas arise at a median age of 58 with a male predominance (1.6:1) and are also more common in White patients.[26,38] There are no known exposures associated with an increased risk of developing chordoma.

Most chordomas are thought to represent sporadic malignant degeneration of notochord rests along the axial skeleton. The *TBXT* gene (previously known as the *T* gene), which is located on chromosome 6q27 and encodes brachyury, appears implicated in the pathogenesis of

chordoma.[39] The common *TBXT* gene rs2305089 variant is associated with a significant increased risk of sporadic chordoma in a White population,[40] but not in an Asian population.[41] A limited number of cases of familial chordoma have been reported, with a pedigree suggestive of an autosomal dominant inheritance with incomplete penetrance.[42] *TBXT* gene duplication is associated with susceptibility to familial chordoma[43] but rare or nonexistent in sporadic cases.[38,39] In young children, chordoma may occur within the setting of tuberous sclerosis.[44]

Retrospective evaluations have alternately associated female[45] and male sex[46] with a higher risk of disease progression and death. In multivariate analysis of NCDB and SEER data sets, there was no apparent difference in survival between men and women, nor by race.[26] Patients younger than 60 years had a decreased risk of mortality. Increasing tumor size, vascular encasement (ICA, basilar artery, or vertebral arteries), brainstem displacement, and prior site surgery or radiotherapy are correlated with lesser extent of resection, greater postoperative complications, higher tumor recurrence, and inferior survival.[47] In a multivariate analysis of 170 patients with skull base chordoma, avidly enhancing tumors with relatively less T2 hyperintensity were associated with a higher risk of progression (hazard ratio 1.88) than less enhancing more T2 hyperintense tumors.[29] A study of 174 patients with clival chordoma identified a radiomic score from preoperative multiparametric MRI features, which, together with gross total resection, was predictive of progression-free survival (PFS).[48]

Tumors with a Ki67 proliferation index ≥5% and homozygous 9p21 deletions appear to be associated with a more aggressive clinical course and shorter survival.[49,50] A larger study of 105 clival chordoma cases identified homozygous 9p21 deletions and 1p36 deletions as independent prognostic factors for PFS.[51]

Natural History

There are few data on the natural history of untreated chordoma. A series of 19 patients with skull base chordoma with serial imaging over a mean of 22 months prior to surgery was reported.[52] Compared to baseline MRI, the measured tumor volume increased by a mean of 8% per month for an absolute volume increase of 0.8 cm^3 per month (standard deviation ±0.7 cm^3). Their data showed that smaller tumors grew at a faster rate than larger tumors, consistent with a sigmoidal or Gompertzian model of growth in which the tumor growth fraction decreases exponentially as tumors enlarge.[53]

Skull base chordomas are primarily spread by direct tumor extension with local destruction. Tumors may extend superiorly to involve the sellar/suprasellar region displacing or encasing the pituitary or optic apparatus, laterally to involve the cavernous sinus or middle cranial fossa, posteriorly to involve the prepontine cistern with potential brainstem compression or, sometimes, invagination, and anteriorly into the sphenoid sinus or prevertebral soft tissues, the latter sometimes being substantially involved. Chordomas may have different degrees of dural involvement from dense adhesion to frank penetration, which is associated with a poorer prognosis.[54]

Local recurrence is the predominant pattern of failure for skull base chordomas. Maintenance of local tumor control is a prognostic factor for distant disease-free survival.[55] In the Paul Scherrer Institute (PSI; Villigen, Switzerland) experience, the 7-year distant metastasis-free survival was 92%, with all cases of distant disease seen in patients experiencing local failures.[56] Surgical seeding in the operative approach occurred in 12 (5.7%) of 210 patients in one series.[57]

Clinical Presentation

The most common presenting symptom in adults is a CN palsy.[58] CN VI (abducens) is most often affected with resultant diplopia. Most patients also note headaches, which may have been long-standing and progressive. CN V may be affected with tumor in the cavernous sinus, and lower CNs may be affected by disease involving the inferior clivus. Rhinorrhea from spontaneous CSF leak and compressive optic neuropathy are rare presentations.[59,60] Among children, ear pain, headaches, and diplopia are the most common presenting symptoms.[61] Clival chordomas are sometimes found incidentally on imaging obtained after trauma or for other reasons.

Diagnostic Workup

Initial evaluation should include both a skull base protocol MRI and CT. To screen for metastatic or multifocal chordoma, an MRI of the remainder of the spinal axis is recommended in guidelines[62] and a CT of the chest, abdomen, and pelvis is used for systemic staging. MRI of the spinal axis may also identify presumed benign notochord remnant tumors, which should be observed for growth. Chordoma has variable uptake on ^{18}F-fluorodeoxyglucose PET/CT, and its role in chordoma is poorly defined. In a series of 23 patients with chordoma (only one clival) undergoing PET/CT, the mean maximum standardized uptake value (SUVmax) was 5.8, and PET features did not correlate with MRI features.[63] The incidence of metastatic disease at presentation is low, but not well defined. A systematic review of published cases of metastatic chordoma identified the lungs and other spine bones as being the most common sites of distant metastases.[64] Cervical lymph node involvement may occasionally be seen and may be associated with cases with more significant prevertebral soft tissue involvement.

For many patients with skull base chordomas, the pathologic diagnosis (or at least confirmation of malignancy) is made intraoperatively during the definitive surgery. A biopsy is typically only considered when definitive surgery is not contemplated, or there is diagnostic uncertainty (eg, concern for clival metastasis, nasopharyngeal cancer, or other conditions for which radical surgery would rarely be indicated).

Imaging

Both CT and MRI are indicated in the evaluation of skull base pathology. CT is useful for evaluating cortical bone erosion and osseous changes, identifying tumoral calcifications, and for surgical planning. Permeative or erosive bone changes are suggestive of a more aggressive, rapidly proliferative process or infection, while bone expansion or remodeling with smooth cortical thinning is suggestive of a slow-growing process.[65] MRI provides optimal evaluation of soft tissue, perineural spread, dural, and marrow involvement. T1-weighted MRI sequences without gadolinium contrast and without fat saturation are recommended to identify tumor involvement in the marrow.[66] Dedicated skull base MRI protocols are required as routine MRI brain sequences can easily miss or mischaracterize skull base pathologies.[2] Recommended sequences include thin-slice T1 precontrast imaging *without* fat suppression, T2 sequences with fat suppression, and T1 postcontrast with fat suppression.[2]

On MRI, chordomas are typically intermediate or low signal on T1 sequences, with small foci of intrinsic T1 hyperintensity corresponding to intratumoral hemorrhage or mucous.[67] More than half of clival chordomas have no or mild contrast enhancement.[68] If enhancing, chordomas may

have heterogeneous contrast enhancement from minimal to moderate (Figure 42.5). Chordomas are typically T2 hyperintense. These characteristics are shared with skull base chondrosarcomas. A higher apparent diffusion coefficient value on MRI may help distinguish chondrosarcoma from chordoma,[69] and a multiparametric MRI radiomics analysis also showed good discrimination between the histologies.[70]

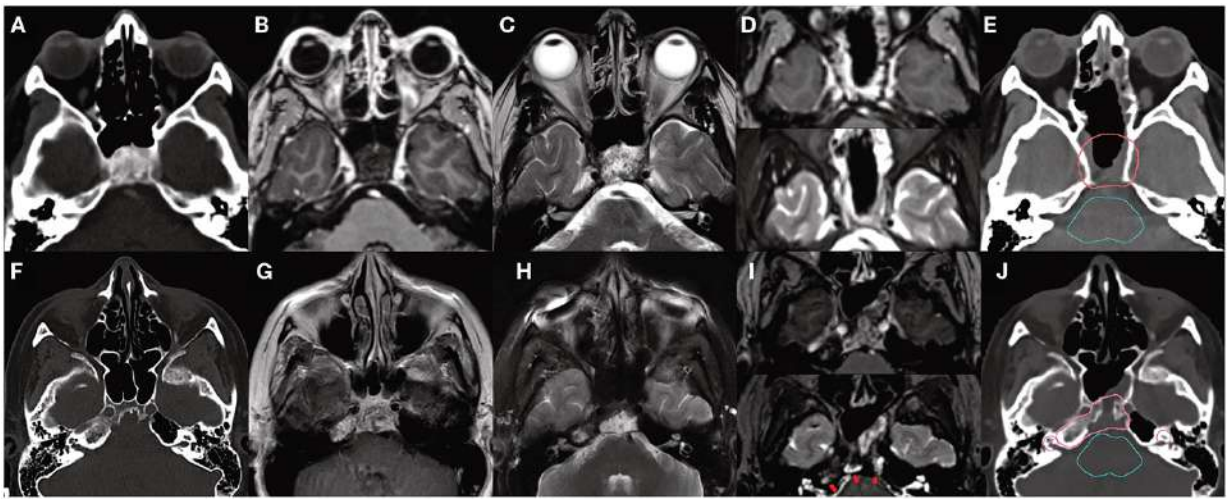

FIGURE 42.5 Variation in contrast enhancement patterns in clival chordomas. In first patient, an expansile ground-glass superior clival mass is on shown on computed tomography (CT) (A), with minimal T1 postcontrast enhancement (B), and T2 hyperintensity (C). Postoperative magnetic resonance imaging (MRI) (T1 postcontrast and T2; D) showed no residual tumor. E. Radiation treatment planning CT with the high-dose clinical target volume (74 Gy) in pink covering the primary tumor bed. In a different patient, a lytic expansile lesion involved the clivus and right petrous apex on CT (F) with heterogeneous T1 postcontrast enhancement (G) and T2 hyperintensity (H). Postoperative MRI (T1 postcontrast and T2; I) showed residual T2 hyperintense disease (red lines) in the right petrous apex and margins of the central clival resection. J. Radiation treatment planning CT with the high-dose clinical target volume (74 Gy) in pink covering the primary tumor bed and residual disease.

Staging

In the American Joint Committee on Cancer (AJCC) eighth edition staging system for primary tumors of bone of the skull and face, T1 tumors are those ≤8 cm in greatest dimension, which applies to nearly all skull base chordomas. The prognostic and therapeutic relevance of current AJCC staging is, therefore limited.

General Management

Patients with skull base chordomas should be evaluated by an experienced skull base surgical team for aggressive efforts at maximal surgical resection in an effort to achieve gross total resection. More than one surgery and more than one surgical approach may be required to achieve maximal tumor debulking. Postoperative radiotherapy is recommended for the majority of patients.

A suggested algorithm for management is presented in Figure 42.6.

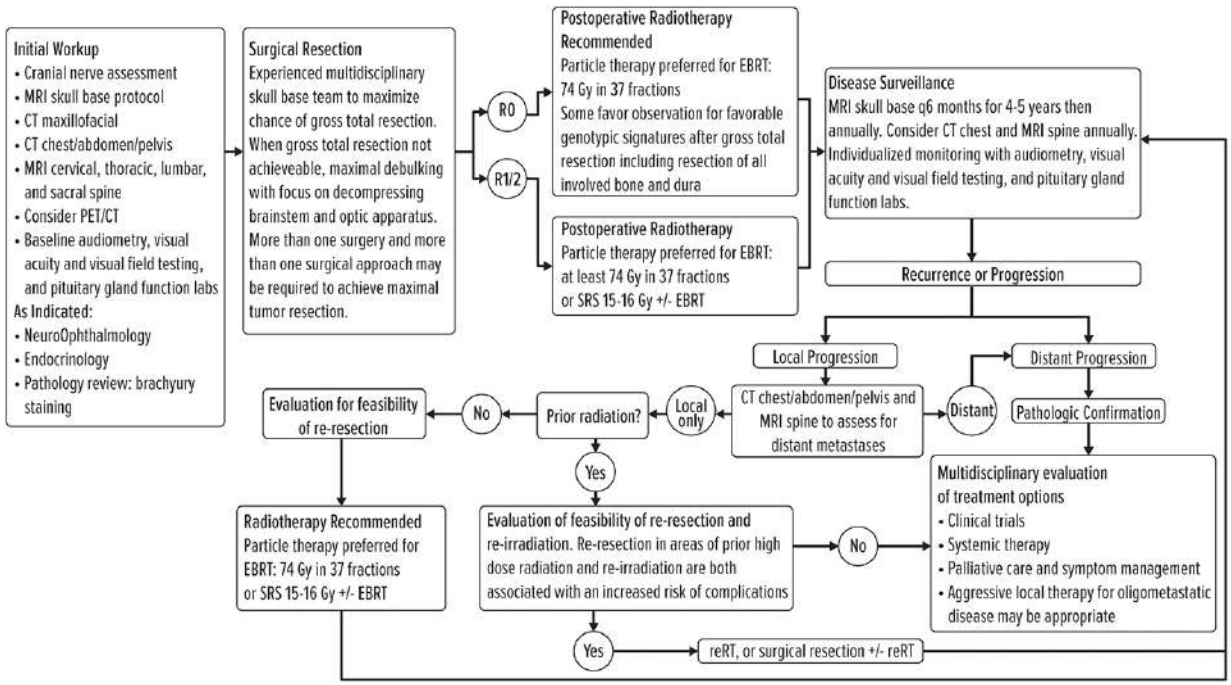

FIGURE 42.6 Suggested algorithm for skull base chordoma. CT, computed tomography; EBRT, external beam radiation therapy; MRI, magnetic resonance imaging; PET, positron emission tomography; q, every; RT, radiation therapy; SRS, stereotactic radiosurgery.

Surgery

An endoscopic transnasal transclival approach provides a direct corridor to the clivus without interposing major neurovascular structures and has become the mainstay for surgical resection of many clival lesions.[71] A variety of transcranial approaches may be selected or combined with an endoscopic approach based on the location of the tumor and experience of the surgeon.

The goal is maximal safe surgical resection. The chordoma tumor matrix is typically mucinous or gelatinous and more readily removed, while the outer layer is more fibrous and may be adherent to neurovascular structures.[72] Gross total resection is consistently associated with more favorable outcomes than a lesser extent of resection.[57,73,74] When a gross total resection is not achievable, maximal tumor debulking appears beneficial. A study of patients with skull base chordoma undergoing surgery and postoperative proton therapy found a residual tumor volume >20 cm^3 was associated with a higher risk of progression.[30] A larger chordoma tumor volume was associated with brainstem compression, which necessitates some compromise in target volume coverage by high-dose radiotherapy. A study of 195 patients with skull base chordoma identified a postoperative tumor volume >4.9 cm^3 was associated with a higher risk of progression.[75]

The extent of tumor resection achieved is greater and the complications fewer, with increasing operative volume and duration of skull base surgical experience and access to specialized tools and techniques.[76-78] Because skull base tumors are rare, surgical expertise is difficult to accrue and maintain outside high-volume centers with the associated interdisciplinary team and resources required for a successful skull base program.[79,80] Patients should be evaluated by an experienced skull base surgical team to explore all options to achieve maximal resection prior to radiotherapy, particularly for skull base chordoma.

Based on the long natural history of chordoma, some practices have favored observation following gross total resection, reserving radiotherapy for salvage therapy of recurrent disease. However, there are data to support adjuvant radiotherapy, regardless of the extent of resection, described below.

Principles of Radiation Therapy

In a series of 284 patients with skull base chordoma undergoing surgery, planned postoperative radiotherapy was associated with improved PFS and chordoma-specific survival compared to observation or when radiotherapy was delivered for recurrent disease.[81] The apparent benefit of postoperative radiotherapy was also seen in patients undergoing gross total resection of disease. In another series with multivariate analysis of 210 patients with skull base chordoma undergoing surgery, both non–gross total resection and omission of postoperative radiation therapy were associated with inferior PFS.[57] The best outcomes were observed in those undergoing both gross total resection and postoperative proton-based radiotherapy. Many studies have found salvage surgical interventions at the time of recurrence are less likely to achieve gross total resection and that radiotherapy is most effective in the setting of the least burden of residual disease, and so patients receiving salvage (rather than adjuvant) radiotherapy are more likely to have a larger volume of disease and unfavorable tumor geometry in relationship to critical organs at risk (OARs).

The team at the University of Pittsburgh have proposed a genotypic risk stratification to guide patient management based on the percentage of tumor cells with 1p36 and 9p21 chromosomal deletions on fluorescence in situ hybridization.[82] In their experience with 152 patients with clival chordomas, patients could be stratified into three risk groups. Group A patients (deletions of 1p36 <15% and 9p21 <4%) had the best prognosis with a 5-year PFS of ~85%. Group A tumors were more often asymptomatic smaller tumors in younger patients, with a less invasive phenotype more easily amenable to gross total resection. Group C (deletions of 1p36 >15% and 9p21 >25%) had the worst prognosis with a mean PFS of 16 months. Group B represented all other combinations and had a 5-year PFS of ~40%. All groups benefited from gross total resection compared to lesser surgeries. Following gross total resection, there was no apparent difference in PFS with the addition of postoperative radiation for group A or group B. Postoperative radiation was associated with improved PFS after subtotal resection in group B and for all patients in group C, regardless of the extent of resection. This management approach has not yet been externally validated, and as the authors note, less radical resections performed elsewhere that might still be considered gross total resection may not yield the same results.

Radiation Techniques

Treatment Modalities and Dose

A position paper sponsored by the Chordoma Foundation recommends postoperative particle therapy–based radiation for skull base chordoma after both gross total and subtotal resection.[62] A dose of at least 74 Gy (relative biologic effectiveness [RBE]) in 37 fractions was recommended, regardless of the extent of resection.

Outcomes with lower dose radiation are poor. Conventionally fractionated radiotherapy to 60 Gy after subtotal resection or biopsy yielded a 5-year PFS of 25% in a series of 18 patients.[83] An NCDB analysis in skull base chordoma found that among patients receiving radiation, doses

>60 Gy were associated with improved overall survival.[84] A separate NCDB analysis including chordoma of all sites found that proton beam therapy and doses >65 Gy were associated with improved overall survival.[85]

Kim and colleagues compiled skull base chordoma outcomes from a published series using photon, photon plus proton, proton, and carbon ion therapy to evaluate a dose-response relationship to local control.[86] Converting the varied fractionation schedules used in each study to an equivalent dose in 2 Gy fractions (EQD2) with an α/β of 3, their model estimates that a dose of 74 Gy (RBE) in 37 fractions would yield a 5-year local control rate of 82%, while a dose of 79 Gy (RBE) would be required to reach 90%.

Gamma Knife data also support a dose response, suggesting that a marginal dose of 15 or 16 Gy is desired. Koga and colleagues reported progression in all six patients with skull base chordoma treated with a median marginal dose of 12 Gy compared to no progression in four patients who received a marginal dose of at least 16 Gy.[87] Echoing the poor results of lower dose treatment, a separate series of 53 patients with skull base chordoma treated to a mean marginal dose of 13.5 Gy reported a 5-year PFS of 18%.[88] Multi-institutional data found improved local control following Gamma Knife with a marginal dose ≥15 Gy.[89]

The bulk of the clinical outcomes data for skull base chordomas are from patients managed with proton therapy, and the results appear superior to both stereotactic radiosurgery (SRS) and those managed with modern photon techniques even at higher doses.[57,90,91] A series of 57 patients with chordoma (n = 15 base of skull) treated with intensity-modulated radiation therapy (IMRT) to a median dose of 70 Gy in 35 fractions reported a 5-year local control of 47%.[92] A series of 24 patients with skull base chordoma treated with image-guided IMRT to a median dose of 76 Gy after biopsy (n = 1), subtotal (n = 15), or gross total (n = 8) resection reported a 5-year local control of 65%.[93] A series of 19 patients with clival chordoma treated with CyberKnife to a median dose of 37.5 Gy in 5 fractions reported a 5-year local control of 60%.[94] The North American Gamma Knife Consortium reported on 71 patients with skull base chordoma treated at six centers to a median marginal dose of 15 Gy.[89] The 5-year "treated tumor" control rate was 66% whereas the skull base tumor control rate was 58% due to recurrences outside the treated volume.

In contrast, the PSI experience using pencil beam scanning proton therapy in the treatment of 151 patients with skull base chordoma reported a 5-year local control of 81%.[95] At 7 years, the local control estimate was 71% and overall survival was 73%.[56] A systematic review of 16 studies including 752 patients treated with proton therapy for skull base chordoma to a mean dose of 74 Gy (RBE) reported a 5-year weighted average local control of 77% and overall survival of 80%.[96]

The team at Massachusetts General Hospital have also reported long-term follow-up on 204 children treated for clival chordoma over a 40-year period. The median age at treatment was 11 years. Patients were treated with surgery followed by a median dose of 76.7 Gy (RBE) with either protons alone or combined photon and proton treatment. The 20-year PFS and overall survival were both 64%.[61] Poorly differentiated chordomas were present in 9% and associated with worse outcomes.

Target Volume Definition

Detection of residual tumor on immediate and early postoperative imaging is challenging due to anticipated imaging changes from granulation tissue, blood, packing material, and fat grafting.[97]

By contouring the extent of the gross disease prior to surgical intervention on preoperative imaging, one can more readily recognize areas of concern for residual disease after surgery. Residual tumor is most often identified at the deep margin of the resection as well as posterior and lateral to critical structures, such as the ICA (eg, cavernous sinus). Tumor in the inferior clivus and occipital condyles is challenging to access for complete resection.[98,99] In addition, residual tumor may be identified in the prevertebral soft tissue or as residual involved bone (eg, posterior clinoids or occipital condyles). Diffusion-weighted imaging (DWI) appears to improve the detection of residual and recurrent disease with high signal on trace DWI sequences.[100] As always, consultation with the surgical team is essential to understand areas of greatest concern and to provide clinical context to observed radiographic findings after surgery.

There are limited available guidelines for contour delineation in skull base chordoma. Available recommendations from the European Society for Radiotherapy and Oncology Advisory Committee on Radiation Oncology Practice[101] and the Chordoma Foundation[62] are summarized in Table 42.2. Given the high risk for residual microscopic disease at the margins of the resection, patients treated with fractionated therapy typically receive high-dose radiotherapy to a large volume encompassing the preoperative tumor bed. Conversely, patients treated with SRS typically receive high-dose radiotherapy to a substantially smaller volume, typically the apparent residual tumor with a 1 to 2 mm planning target volume (PTV) expansion depending on the radiosurgery platform. Investigators from the Mayo Clinic evaluated the relationship of tumor recurrence to the prescription isodose line of treatment in eight patients with skull base chordoma who experienced a skull base recurrence after Gamma Knife.[102] Only two were in field, while 6/8 were either marginal (falling within the 20%-40% isodose line) or remote (outside the 20%-30% isodose line). These and other experiences[89] suggest that the larger volume treated with fractionated high-dose radiotherapy is associated with improved skull base tumor control. An example case is shown in Figure 42.7.

TABLE 42.2 SKULL BASE CONTOURING GUIDELINES

	ESTRO ACROP for Chordoma and Chondrosarcoma[101]	Chordoma Foundation Position Paper[62]
CTV1	Typically includes preoperative tumor volume with an anisotropic margin of 10-20 mm plus the residual tumor and surgical resection margins. Include posterior portion of residual sphenoid sinus for those who underwent transsphenoidal surgery	Encompass all volumes at risk for microscopic disease, including areas of preoperative tumor extension. Include prevertebral long muscles if they are infiltrated
CTV2	Residual tumor plus 5-10 mm expansion modified to natural barriers to tumor growth, plus the resection margins at higher risk of residual disease	Encompass any residual microscopic disease in the tumor bed after surgery, followed, in some cases, by a third volume (CTV3) to any sites of residual gross disease
Do not include	Previously compressed normal structures that have reexpanded after surgery, peritumoral edema, surgical tract	Inclusion of the entire surgical access path in CTV1 remains controversial. Inclusion of the retropharyngeal space in the target volume definition as a possible site of recurrence remains controversial

CTV, clinical target volume.

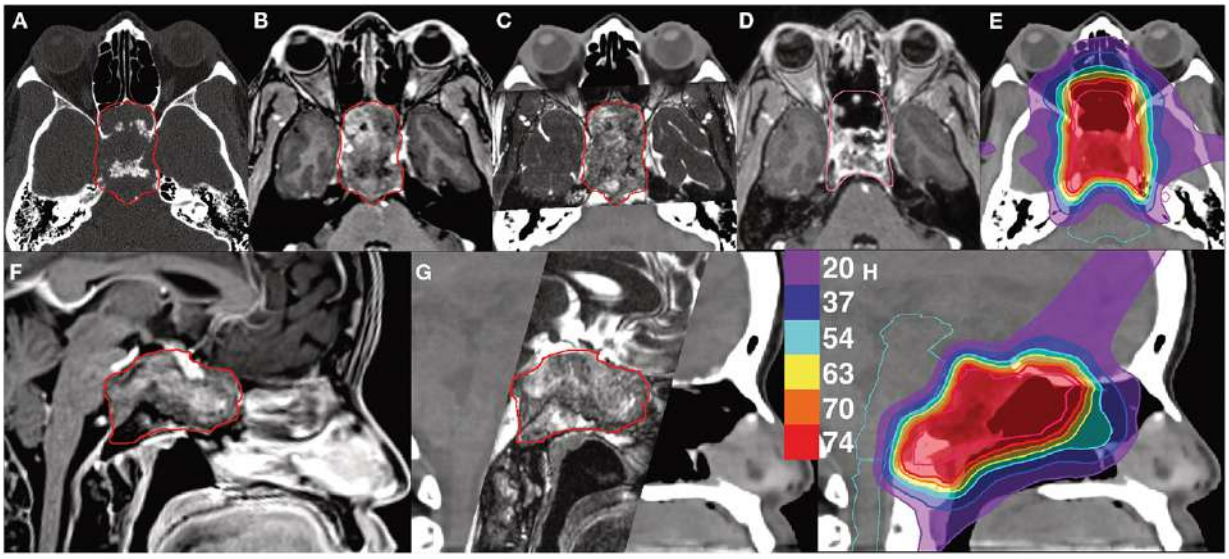

FIGURE 42.7 Example of chordoma of the skull base. This patient in their early 60s presented with headaches. A-C,F,G. Tumor volume is outlined in red on preoperative axial computed tomography (A) and axial and sagittal T1 postcontrast (B,D) and T2 (C,E) magnetic resonance imaging (MRI); a large clival tumor with prepontine, bilateral cavernous sinus, and sphenoid sinus extension, abutting the brainstem and optic chiasm. An endoscopic transnasal transclival resection was performed. DF. T1 postcontrast MRI at the time of radiation planning with a clival defect and enhancement related to right-sided nasal septal flap and abdominal fat graft. There was no apparent residual tumor. The high-dose clinical target volume to receive 74 Gy (relative biologic effectiveness) is shown in pink. GE,H. Proton radiation treatment plan.

Response Assessment and Surveillance

Following radiotherapy, the expected outcome is no growth of residual tumor or no recurrence of disease. During a course of fractioned radiotherapy, chordomas may experience a transient increase in tumor volume, presumably due to tumor necrosis and edema.[86] This is perhaps more relevant in patients with spine or sacral chordomas being treated with definitive radiotherapy and less frequently an issue for skull base chordomas. Sacral and spine chordomas treated nonoperatively often have some volumetric tumor response to the extraosseous soft tissue component of disease after high-dose radiotherapy.

There are few data to guide recommendations on surveillance imaging. The Chordoma Foundation position paper recommends an MRI every 6 months in the first 5 years and then annually through 15 years post-treatment with no specific recommendations for distant surveillance.[62] The group at MD Anderson Cancer Center reported on 91 patients with skull base chordoma in surveillance for a mean follow-up time of 79 months during which time 34 had experienced disease progression.[103] About half of recurrences occurred in the first 5 years and about one-third occurred more than 10 years after treatment, highlighting the importance of long-term follow-up. Pulmonary metastases and leptomeningeal spread were the two most common patterns of distant disease in their experience. Every instance of distant recurrence was preceded by an initial local recurrence. Based on their observed patterns of failure and timeline, they recommended both a CT of the chest/abdomen/pelvis and an MRI of the spine every 6 months in the first year and then annually to screen for distant disease. Compared to alternate published surveillance protocols, the authors noted their approach would reduce the time to diagnosis of recurrence (assuming patients lacked symptoms, which may have prompted earlier imaging).

Systemic Therapy

There are currently no systemic therapies approved for a chordoma indication. Chordomas often express a variety of potentially actionable targets, including c-KIT, epidermal growth factor receptor (EGFR), vascular endothelial growth factor, platelet-derived growth factor receptors, and HER2/neu. A genomic mapping of genetic dependencies in chordoma has been published, with preclinical data suggesting promising efficacy of small-molecule inhibitors of Src homology-2 domain-containing phosphatase 2 (SHP2).[104] Previous clinical results with targeted therapies have been modest. A phase II trial of imatinib in 56 patients with progressive locally advanced or metastatic chordoma reported a median time to progression of 9 months and a median overall survival of 35 months.[105] A phase II trial of sorafenib in 27 patients with progressive locally advanced or metastatic chordoma reported a 1-year PFS of 73% and overall survival of 86.5%.[106] Lapatinib was evaluated in a small phase II trial with only modest activity,[107] while case reports have reported the activity of other EGFR inhibitors.[108] A double-blind randomized trial in patients with locally advanced unresectable chordoma used radiotherapy with either a placebo or novel brachyury vaccine.[109] The trial closed early after treatment of 24 patients as there appeared to be no synergistic antitumor effects of the vaccine with radiotherapy. Nevertheless, the *TBXT* gene, which encodes brachyury, remains an attractive therapeutic target for chordoma, and other vaccine trials are underway. Immunotherapy has shown promise with some data to suggest that programmed death-ligand 1–negative chordoma may still benefit from immune checkpoint inhibitors.[110]

CHONDROSARCOMA

Pathology

Chondrosarcomas are mesenchymal tumors with cartilaginous differentiation. Skull base chondrosarcomas arise from the rests of chondrocytes within the synchondroses of the basilar skull bones.[111] The majority (80%-90%) of chondrosarcomas are "conventional," with a three-tier grading system based on degrees of atypia, cellularity, and mitotic activity.[112] Grade 1 chondrosarcomas are similar in appearance to normal cartilage or the appearance of benign enchondroma but with a permeative pattern of infiltration in which normal bone trabeculae are surrounded by neoplastic cartilage.[18] Skull base chondrosarcomas are most often conventional and grade 1 or 2.[16] More than 85% of skull base chondrosarcomas harbor *IDH1 or IDH2* mutations, most commonly $IDH1^{R132C}$.[113] The nonconventional chondrosarcoma histologies include mesenchymal, dedifferentiated, and clear cell. Mesenchymal chondrosarcoma is a rare small round blue cell histology,[114] which is more commonly seen in young adults and associated with a worse prognosis.[115] Dedifferentiated chondrosarcomas are very aggressive tumors with a poor prognosis.[116] Clear cell chondrosarcomas are low grade and occur primarily at an epiphyseal location in long bones.[117]

Epidemiology and Risk Factors

Chondrosarcomas are the second most common primary malignancies of bone after osteosarcoma,[118] but occurrence at the skull base is rare. Data on skull base chondrosarcoma from the NCDB suggest a median age of 51 years old with a near-equal prevalence by sex (55% male) and most cases (85%) occurring in non-Hispanic White patients.[119]

Extracranial chondrosarcoma has been reported as a rare secondary malignancy after radiation therapy for lung cancer, cervical cancer, Hodgkin lymphoma, and total body irradiation, among others,[120-123] and maxillary sinus chondrosarcomas have been reported after radiation for retinoblastoma.[124]

The majority of chondrosarcomas are thought to represent sporadic malignant degeneration of rests of chondrocytes along the spheno-petro-clival junction.[111] Ollier disease and Maffucci syndrome, caused by somatic mosaic mutations of *IDH1* and *IDH2*,[125] are both characterized by multiple enchondromas with an increased risk of developing chondrosarcoma[126] and low-grade gliomas.[127] About 1% of skull base chondrosarcomas arise in the setting of Ollier disease or Maffucci syndrome.[128]

Younger age is associated with a more favorable prognosis.[129-131] Conventional histology and grade 1 chondrosarcomas are associated with the best outcomes. Grade 1 and 2 chondrosarcomas appear to have nearly identical outcomes, while grade 3 histology was associated with a 33% recurrence rate, though not statistically significant, perhaps because of small numbers.[132] The extent of tumor resection for skull base chondrosarcomas appears less predictive of outcomes when adequate postoperative radiotherapy is given. The rate of tumor recurrence or progression is comparable after gross total resection and subtotal resection when patients receive postoperative radiotherapy.[132] For skull base chondrosarcomas, tumor within the cavernous sinus adherent to the ICA or CNs is the most common reason for a subtotal resection.[3]

Natural History

Many patients have a long antecedent history of slowly progressive symptoms before presentation, suggestive of a slow growth rate. Skull base chondrosarcomas spread by direct tumor extension with local destruction. There are very few data on the natural history of untreated skull base chondrosarcomas. A case report of a young patient with a radiographic diagnosis consistent with a chondrosarcoma observed with serial MRIs over 10 years noted varied growth rates, initially rather rapid followed by a prolonged period of stability without intervention.[133] Some have argued that we may be misinterpreting these sometimes prolonged periods of tumor stability as signs of efficacy of radiotherapy rather than simply the indolent course of the disease.[134]

Clinical Presentation

As with chordoma, patients with chondrosarcoma typically present with symptoms from tumor mass effect on adjacent neurovascular structures.[67] Diplopia and headaches are common presenting symptoms, with CN VI and CN V most commonly affected.[128] Hearing loss, dizziness, facial nerve dysfunction, trigeminal dysesthesias, and other cranial neuropathies may be seen depending on the extent of the disease. Fewer than 10% are asymptomatic and discovered incidentally.[128]

Diagnostic Workup

As with skull base chordomas, initial evaluation should include both a skull base protocol MRI and CT. Prior to establishing the histologic diagnosis, many patients will have undergone additional imaging workup to rule out a potential bone metastasis of unknown primary, but if

not already obtained, a CT of the chest may be obtained to evaluate for pulmonary metastatic disease and serve as a baseline. Metastatic disease is rarely identified at presentation of skull base chondrosarcoma— less than 2% in an NCDB analysis[135]—and subsequent development of extracranial metastases is very rare, observed in just 0.5% of patients in a systematic review.[128] This contrasts with extremity or extracranial chondrosarcomas, where 7% to 11% of patients may present with pulmonary metastatic disease.[136-138] In these patients with extracranial chondrosarcoma, factors associated with the development of pulmonary metastatic disease include dedifferentiated or high-grade histology, presence of lymph node metastases, large tumor size (>8.6 cm), and locally recurrent disease.[136] The incidence of osseous metastatic disease in extracranial conventional chondrosarcoma is very low (<1%), suggesting no role for routine skeletal imaging.[138]

As with skull base chordoma, the pathologic diagnosis is often made intraoperatively during the definitive surgery. A biopsy is typically only considered when definitive surgery is not contemplated, or there is diagnostic uncertainty (eg, concern for clival metastasis, nasopharyngeal cancer, or other conditions for which radical surgery would rarely be indicated).

Imaging

Chondrosarcomas share similar imaging characteristics to chordomas as previously outlined. Chondrosarcomas are more likely to be lateralized or paramedian in location.

Staging

As with chordomas, the AJCC staging is of limited prognostic or therapeutic value for skull base chondrosarcomas. Essentially, all will be ≤8 cm in greatest dimension and, therefore, T1.

General Management

Patients with skull base chondrosarcomas should be evaluated by an experienced skull base surgical team for maximal safe surgical resection while minimizing the risks of iatrogenic toxicity. Gross total resection is less common. When an R0 resection is not achievable, maximal tumor debulking should focus on decompressing the brainstem and optic apparatus to optimize the ability of radiation therapy to cover residual disease. More than one surgery and more than one surgical approach may be required to decompress critical OARs. Radiotherapy is a recommended adjuvant therapy for the majority of patients.

A suggested algorithm for management is presented in Figure 42.8.

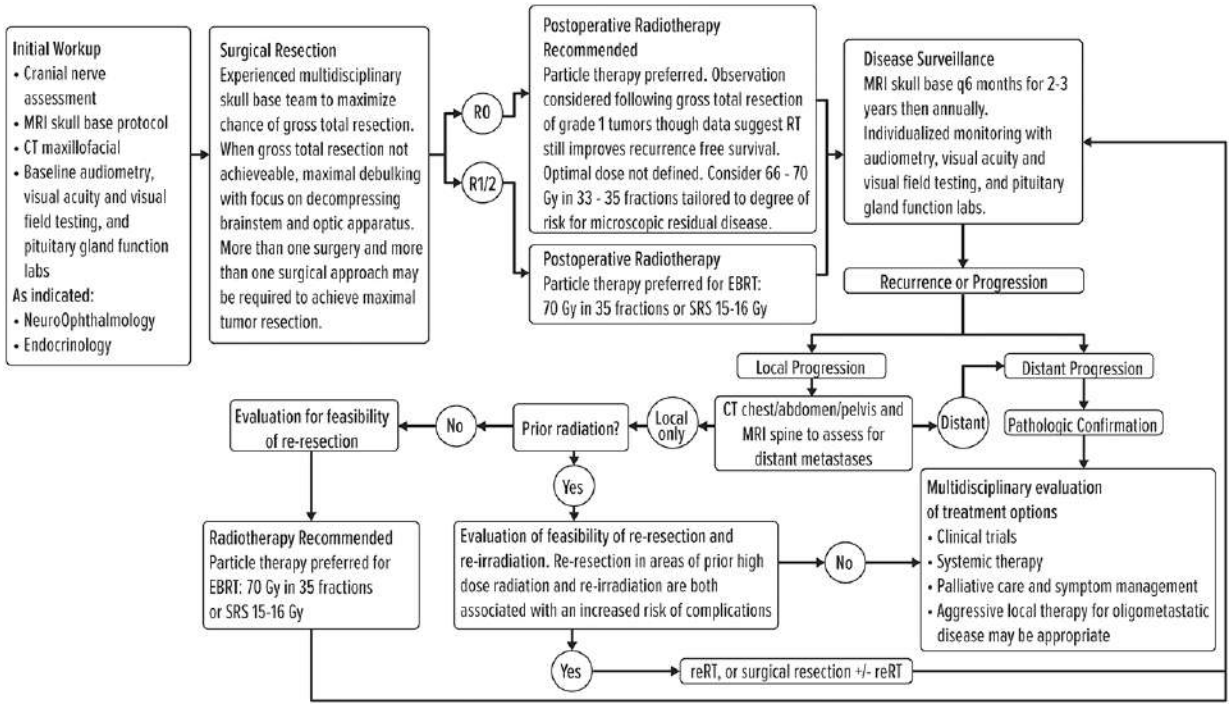

FIGURE 42.8 Suggested algorithm for chondrosarcoma of the skull base. CT, computed tomography; EBRT, external beam radiation therapy; MRI, magnetic resonance imaging; PET, positron emission tomography; q, every; RT, radiation therapy; SRS, stereotactic radiosurgery.

Surgery

As with chordomas, mucinous portions of chondrosarcoma tumors are more readily removed, while the outer layer may be adherent to neurovascular structures.[3] For mesenchymal and dedifferentiated chondrosarcomas, which are rare at the skull base, gross total resection is associated with improved PFS.[139] For conventional grade 1 to 2 chondrosarcomas adherent to critical neurovascular structures, leaving a moderate volume of residual disease to minimize risks has no apparent decrement in outcome when patients receive adequate postoperative radiotherapy. An NCDB analysis of patients with skull base chondrosarcoma undergoing combined surgery and radiation therapy found no difference in survival following subtotal versus complete surgical resection, although surgical cohorts fared better than radiotherapy alone.[135]

Data on 77 patients with skull base chondrosarcoma managed with subtotal resection and proton therapy at PSI found a tumor volume >25 cm^3 was associated with a higher risk of local recurrence.[131] The only local failures were in patients with tumors abutting or compressing the brainstem or optic apparatus. Optimizing the tumor geometry by decompressing the brainstem and optic apparatus is needed for the best outcomes in skull base chondrosarcoma and to mitigate radiation- induced toxicities to these critical structures.[128]

Based on the indolent growth rate of conventional chondrosarcomas, some have favored observation following gross total resection, reserving radiotherapy for salvage therapy of recurrent disease. However, there are data to support adjuvant radiotherapy, regardless of the extent of resection, described below.

Principles of Radiation Therapy

In a systematic review and meta-analysis including 560 patients with skull base chondrosarcoma, the best outcomes were observed in those treated with combined surgery and radiation therapy, with a 5-year freedom from recurrence/progression of 91%.[132] For those treated with surgery alone, the 5-year recurrence was 44%. Furthermore, even for the minority of patients undergoing gross total resection, postoperative radiation was associated with a statistically significant benefit in recurrence-free survival, suggesting a role for radiotherapy regardless of the extent of surgical resection. In an NCDB analysis of 718 patients with skull base chondrosarcoma, receipt of proton-based radiotherapy and a dose ≥60 Gy (RBE) was associated with improved overall survival compared to photon-based radiotherapy.[135]

Radiation Techniques

Treatment Modalities and Dose

An NCDB analysis that evaluated chondrosarcoma at all body sites evaluated the association of both radiation dose and technique with outcomes.[140] Patients treated with proton therapy had the highest 5-year survival, with both proton therapy and SRS associated with a statistically significant higher survival than IMRT. Those treated with >60 Gy had a statistically significant higher survival than those receiving 40 to 60 Gy, which, in turn, was associated with better survival than those receiving palliative (<40 Gy) radiation.

A multi-institutional analysis of 251 patients with skull base chondrosarcoma treated at PSI or the Centre de Protonthérapie in Orsay, France (CPO) to a median dose of 70 Gy (RBE) reported a 7-year failure-free survival of 93%.[141] In a separate report of the 77 patients treated at PSI with pencil beam scanning proton therapy for residual or progressive skull base chondrosarcomas, the crude rate of adverse radiation effects was 7.8% (three patients with hearing loss, two radiation necrosis, one optic neuropathy), with toxicity correlated with higher radiation dose.[131] The authors proposed a prospective trial to evaluate modest-dose de-escalation, reserving 70 Gy (RBE) for older patients with tumors abutting the brainstem or optic apparatus, using 64 Gy (RBE) in young (eg, ≤45 years) patients with small tumors not abutting OARs, and 68 Gy (RBE) for the remainder of patients.

The group at the Heidelberg Ion Beam Therapy Center reported on 101 patients with skull base chondrosarcoma treated with carbon ion therapy (n = 79) or proton therapy (n = 22).[142] Those treated with carbon ion therapy received a median dose of 60 Gy (RBE) in 20 fractions, while those treated with proton therapy received a median dose of 70 Gy (RBE) in 35 fractions. With a median follow-up time of 40 months, there was no statistically significant difference in the 5-year local control between carbon ion therapy (90.5%) and proton therapy (100%).

For SRS, there is also evidence for radiation dose response, suggesting a marginal dose of 15 to 16 Gy in a single fraction is optimal. In a multicenter series of 51 patients receiving Gamma Knife for residual or recurrence skull base chondrosarcoma (median tumor volume 8 cm^3), Kawashima and colleagues reported the best results in patients receiving ≥16 Gy with a 5- and 10-year local control of 83%.[143] Those receiving <15 Gy had a 5-year local control of about 50%. The North American Gamma Knife Consortium reported a multicenter study of 46 patients undergoing SRS for skull base chondrosarcoma who also had a median tumor volume of 8 cm^3.[144] The 22 patients with no prior history of radiation who received a marginal dose ≥15 Gy enjoyed 100% local control at 10 years compared to 47% with a marginal dose <15 Gy. The

rate of adverse radiation effects in those without prior radiotherapy was 7% (two instances of radiation necrosis, one cranial neuropathy).

Fewer data are available for IMRT in skull base chondrosarcoma. Sahgal and colleagues reported on 18 patients with skull base chondrosarcoma treated to a median dose of 70 Gy in 35 fractions with image-guided IMRT.[93] The 5-year local control rate was 88%.

Target Volume Definition

Available recommendations from the European Society for Radiotherapy and Oncology Advisory Committee on Radiation Oncology Practice[101] and the Chordoma Foundation[62] are summarized in Table 42.2. An example case is shown in Figure 42.9. There are few data on patterns of failure in skull base chondrosarcoma, which could inform an appropriate target volume. The high tumor control rates achieved with radiosurgery suggest that more limited margins are adequate for skull base chondrosarcoma. An analysis of patterns of failure from PSI included 5 patients with skull base chondrosarcoma and 30 patients with chordoma.[145] The majority of recurrences were localized to areas of compromised dose coverage to meet brainstem or optic chiasm constraints. The gross tumor volume (GTV) receiving <66 Gy (RBE) was associated with local failure on multivariate analysis. When the volume of GTV receiving <66 Gy was >3 cc, the 5-year local control was 86% versus 97% when <3 cc of GTV was underdosed.

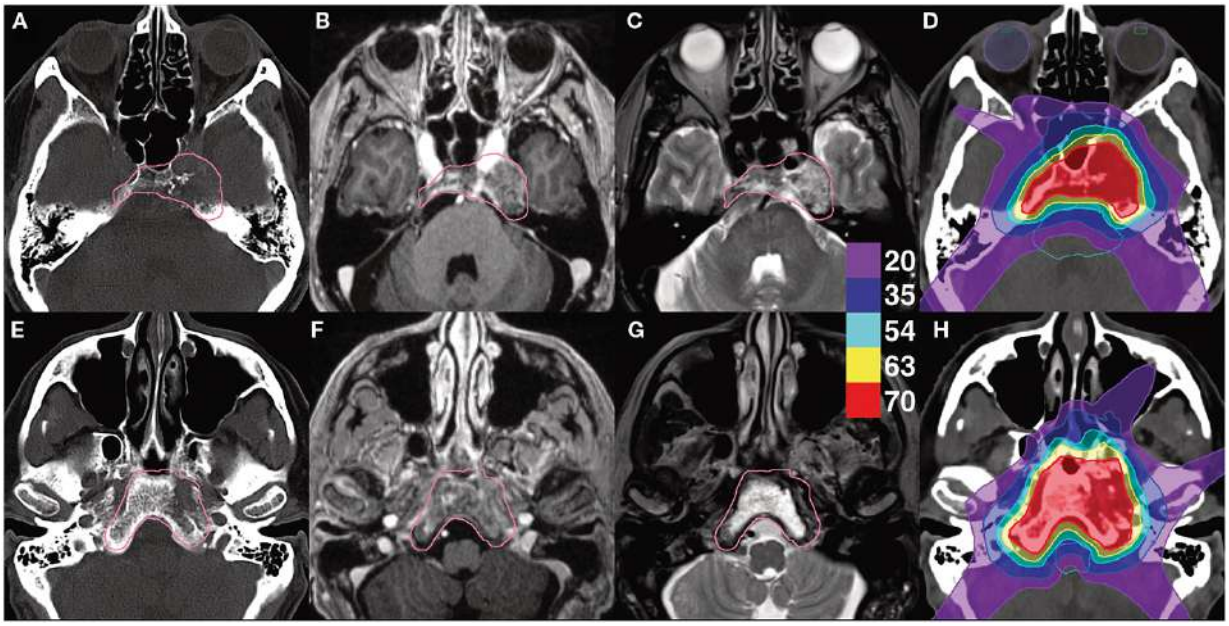

FIGURE 42.9 Examples of chondrosarcoma of the skull base. The high-dose clinical target volume in pink is overlaid on all images. This patient *in their* mid-70s presented with abrupt onset of vertiginous symptoms and initial computed tomography (A,B) and magnetic resonance imaging (MRI) showed an infiltrative clival mass eroding the left petroclival synchondrosis. A retromastoid suboccipital craniotomy was performed, which minimally decompressed the tumor. T1 postcontrast (C,D) and T2 (E,F) MRIs from the time of radiation planning with residual tumor extending to the left cavernous sinus. G,H. Proton radiation treatment plan to 70 Gy (relative biologic effectiveness) in 35 fractions. Follow-up imaging over the next 3 years showed interval decrease in contrast enhancement, especially of the extraosseous component of disease with no change in the tumor volume.

Response Assessment and Surveillance

Following radiotherapy, the expected outcome is no growth of residual tumor or no recurrence of disease. A systematic review included 247 patients with radiographic response assessment after radiotherapy, of whom 27% were noted to have reduced tumor volumes and 58% stable treated tumor.[128]

There are few data to guide recommendations on surveillance imaging. A skull base protocol MRI every 6 months in the first 2 to 3 years after treatment followed by annual imaging is one approach. Long-term follow-up is recommended, given the long natural history of this disease. Given the extremely low risk of developing distant disease, routine extracranial surveillance imaging does not appear indicated.

Systemic Therapy

Chemotherapy has poor activity and limited role in conventional chondrosarcoma, and trials of targeted agents have not yet been effective.[146] Mesenchymal chondrosarcoma may be managed like Ewing sarcoma with similar chemotherapy and multimodal therapy.[147] Dedifferentiated chondrosarcomas may be managed similarly to osteosarcoma.[146]

PARAGANGLIOMA

Pathology

Paragangliomas are malignant neuroendocrine tumors arising at sites of sympathetic or parasympathetic paraganglia. The histology of paragangliomas is notable for a so-called Zellballen growth pattern of polygonal or spindle cells arranged in nests surrounded by a fibrovascular stroma.[148] In the 2022 World Health Organization classification, all paragangliomas are considered malignant neoplasms with variable metastatic potential.[149] Paragangliomas have in the past been considered benign neoplasms, but there are no histologic differences or pathologic criteria to differentiate “malignant” from “benign” paragangliomas. Histologically, all paragangliomas may demonstrate cellular pleomorphism, mitotic figures, occasional necrosis, and local invasion of adjacent bone and soft tissue. All paragangliomas have metastatic potential so paragangliomas should be categorized as metastatic or nonmetastatic rather than using the term *benign* or *malignant*.[150] It is also challenging to differentiate potential sites of metastatic disease from synchronous or asynchronous multifocal paraganglioma. Because of the wide distribution of paraganglia in normal organs, paragangliomas arising in diverse organs including the liver and lungs may represent separate sites of disease rather than hematogenous metastases. In general, because lymph nodes and bone do not harbor paraganglia, involvement of these areas is clearly consistent with metastatic disease.[149]

Epidemiology and Risk Factors

The incidence of paraganglioma (inclusive of pheochromocytomas) is estimated between 4 and 8 per million per year.[151-153] The incidence appears to have increased over time as more incidental tumors are detected on imaging.[151,154] Only about 3% of extraadrenal paragangliomas arise in the head and neck.[155] The median age at presentation is around 50 years old, notably younger in those diagnosed with genetic causes and older in those with sporadic tumors.[154] Head

and neck paragangliomas are 2 to 3 times more common in women than in men.[155] It is unclear whether there is any variation in incidence by race or ethnicity.

Carotid body paragangliomas appear to be more common in patients in a chronic hypoxic state, for example, those living at extreme altitude, smoking, or with conditions like pulmonary fibrosis or emphysema.[156] In contrast to those arising at low altitude, paragangliomas in high-altitude populations appear to have a markedly stronger female predominance and lower rates of bilaterality or family history,[157] and the growth rate appears to be significantly faster.[158] Conversely, it has been posited that the more indolent natural history of paragangliomas in the Netherlands may be due in part to the country's low elevation, with many living near or below sea level.[159,160] Several of the genetic abnormalities associated with paraganglioma cause upregulation of the hypoxia- inducible factor signaling pathway despite normal blood oxygen levels, creating a pseudo-hypoxic state impacting cellular migration and proliferation, apoptosis, angiogenesis, and other processes implicated in tumorigenesis.[161,162]

Germline predisposing mutations are identified in about 40% of patients with paragangliomas, and somatic mutations are seen in about one-third of sporadic cases.[162] There are four autosomal dominant paraganglioma syndromes, PGL1 to PGL4, associated with mutations in the succinate dehydrogenase (*SDH*) complex. PGL1 syndrome involves *SDHD* mutations. It appears to be the most common mutation associated with head and neck paragangliomas[163] and has a favorable prognosis with a low risk of metastases (3%-5%) but a 60% rate of multifocal tumors and 50% to 60% risk of pheochromocytomas or thoracoabdominal paragangliomas.[6] PGL2 involves *SHDAF2* mutations and is notable for young age of onset, high frequency of multifocal disease, and very rare metastases.[164] PGL3 involves *SDHC* mutations and is also associated with multifocal disease and rare metastases.[162] PGL4 involves mutations of the *SDHB* gene. About 25% of patients with *SDHB* mutations have synchronous primaries at presentation, and a similar percentage have pheochromocytomas. The lifetime incidence of metastatic disease is as high as 40%.[165] *SDHB* mutations are associated with shorter survival in patients with metastatic disease.[166] *SDHB* mutations also have a higher incidence for developing other malignancies, including gastrointestinal stromal tumor, renal cell carcinomas, breast carcinomas, and papillary thyroid carcinomas.[162] Multiple endocrine neoplasia type 2, neurofibromatosis type 1, and von Hippel-Lindau diseases are associated with pheochromocytomas and less commonly with head and neck paragangliomas.[6,162]

A combined SEER and The Cancer Genome Atlas analysis of pheochromocytomas and paragangliomas identified younger age, female sex, aortic or carotid body tumors, and complete surgical resection as factors associated with a more favorable prognosis.[167]

Natural History

Head and neck paragangliomas are typically slow-growing tumors. In a series of 39 patients with head and neck paragangliomas, which were initially observed for a median of 2 years, 44% experienced tumor growth, with an estimated tumor doubling time of 5.7 years.[168] A larger series of 48 patients with head and neck paragangliomas under observation for an average of 4.2 years observed that 60% experienced a volume increase >20%, with a median growth rate of 1 mm per year and a median doubling time of 4.2 years.[169] A proportion of patients experience no measurable growth on serial imaging, at least initially. In one series of temporal bone paragangliomas with observation beyond 5 years, five of 11 had no demonstrable growth.[170] It is

important to note that patients under observation may develop new CN deficits without radiographic progression.[171] The growth rate of paragangliomas is also unpredictable. Some patients may experience a period of rapid tumor growth.[172]

Clinical Presentation

Carotid body paragangliomas generally present with a nontender and usually asymptomatic neck mass. On examination, a rubbery mass is palpable anterior to the sternocleidomastoid muscle. Though often a subtle finding, the tumor may be noted to be mobile in the horizontal plane but fixed in the vertical plane due to attachment to the carotid—the so-called Fontaine sign.[173] Large tumors may cause some degree of dysphagia or odynophagia from mass effect, as well as affect adjacent lower CNs with resultant dysphagia or hoarseness.

Vagal paragangliomas also typically present with a painless neck mass with associated hoarseness or dysphagia from lower CN involvement. Jugular paragangliomas commonly present with hoarseness or other lower CN palsies and may also cause pulsatile tinnitus or sudden hearing loss.

Tympanic paragangliomas often present with pulsatile tinnitus and unilateral hearing loss, initially conductive from mass obstruction or involvement of the tympanic membrane and later sensorineural or mixed hearing loss from involvement of the otic capsule, inferior cochlear vein, or direct involvement of CN VIII.[174] Otoscopy reveals a classic red or purple-red mass visible behind the tympanic membrane. More advanced disease may protrude as a friable mass in the external auditory canal. Patients may develop facial nerve weakness or palsy as the tumor erodes into the nearby facial nerve (fallopian) canal of the petrous temporal bone.

Patients with secretory paragangliomas may have hypertension, episodes of tachycardia, sweating, anxiety, diarrhea, orthostatic hypotension, or hyperglycemia.[150] Patients with secretory paraganglioma may be asymptomatic yet still at risk for cardiovascular toxicity from unrecognized and untreated catecholamine secretion. Secretory paragangliomas are associated with a high incidence of secondary diabetes mellitus ranging from mild insulin resistance to profound insulin deficiency.[175]

Diagnostic Workup

Paragangliomas are nearly always an initial radiographic diagnosis. Biopsy is not recommended due to the risk of life-threatening complications from percutaneous biopsy of these highly vascular tumors.[176] When a tumor is radiographically consistent with paraganglioma, pathologic confirmation is not required before radiotherapy.

Multiple clinical practice guidelines recommend that all patients with paragangliomas have plasma metanephrine levels measured at presentation.[150,177,178] It is often said that only about 5% of head and neck paragangliomas are metabolically active, but under-ascertainment is likely, given inconsistent awareness and screening practices. In a series of 182 patients with head and neck paraganglioma, 9% had hyperadrenergic clinical symptoms and/or laboratory normetanephrine values ≥2-fold normal reference values, and an additional 9% had less pronounced aberrations in plasma metanephrines without symptoms.[179] Elevated plasma metanephrines may also indicate the presence of a synchronous pheochromocytoma or thoracoabdominal paraganglioma.

Patients with secretory paragangliomas require medical management with α-blockers for 7 to 14 days before surgery to reduce the risk of intraoperative hemodynamic instability.[150] Following surgery on secretory tumors, annual metanephrine testing is recommended, which may help detect recurrence or metastasis, while those with nonsecreting tumors do not require continued biochemical surveillance unless they have a known genetic variant placing them at risk for future primary paragangliomas or if they were to develop signs or symptoms of secretory disease.[150] While most patients with secretory tumors are managed with surgery, if the patient is treated with radiotherapy, plasma metanephrines may be checked every 6 months to assess biochemical response to therapy and for the detection of tumor progression or potential metastasis. Patients with persistently elevated metanephrines require ongoing medical management to reduce the risk of cardiovascular toxicity from excess catecholamine secretion.

Contrast-enhanced MRI is used to image the primary site, while a high-resolution temporal bone or skull base CT is also necessary to evaluate the extent of tympanic and jugular paragangliomas. Either a whole-body MRI (skull base to kidneys) or DOTATATE PET/CT is recommended in all patients to screen for synchronous primaries or metastatic disease.[177] DOTATATE PET/CT has greater sensitivity than MRI or CT for the detection of multifocal or metastatic disease.[5] Genetic counseling should be offered to all patients, regardless of age at presentation or family history.[150,177,178]

Imaging

Paragangliomas are avidly enhancing on both CT and MRI due to their high vascularity. They are typically T1 isointense and T2 hyperintense. Internal flow voids are characteristic, sometimes described as a "salt and pepper" appearance. On both T1- and T2-weighted sequences, areas of high blood flow velocity result in multiple punctate or serpiginous areas of signal loss (the "pepper") amidst the background of contrast enhancement of the tumor (the "salt").[180] Areas of slow flow or subacute hemorrhage also yield hyperintense "salt" foci.[181] A salt and pepper appearance may not be seen in smaller tumors, especially those <1 cm in size.[182] Jugular paraganglioma typically features a moth-eaten appearance of the jugular foramen and mastoid bone on CT. CT is necessary to define the relationship of tympanic paragangliomas with osseous structures of the middle ear. Carotid body paragangliomas cause a splaying of the internal and external carotid artery, yielding a "Lyre sign" on conventional, CT, or MR angiography.[180]

Staging

The AJCC eighth edition staging for neuroendocrine tumors excludes head and neck paragangliomas.

For carotid body tumors, the Shamblin classification system (Figure 42.10) is based on the tumor relationship to the carotid arteries. As originally proposed, it is an intraoperative assessment, with group I being localized and more easily excised, group II adherent and partially surrounding carotid vessels, and group III intimately surrounding the carotid vessels.[183]

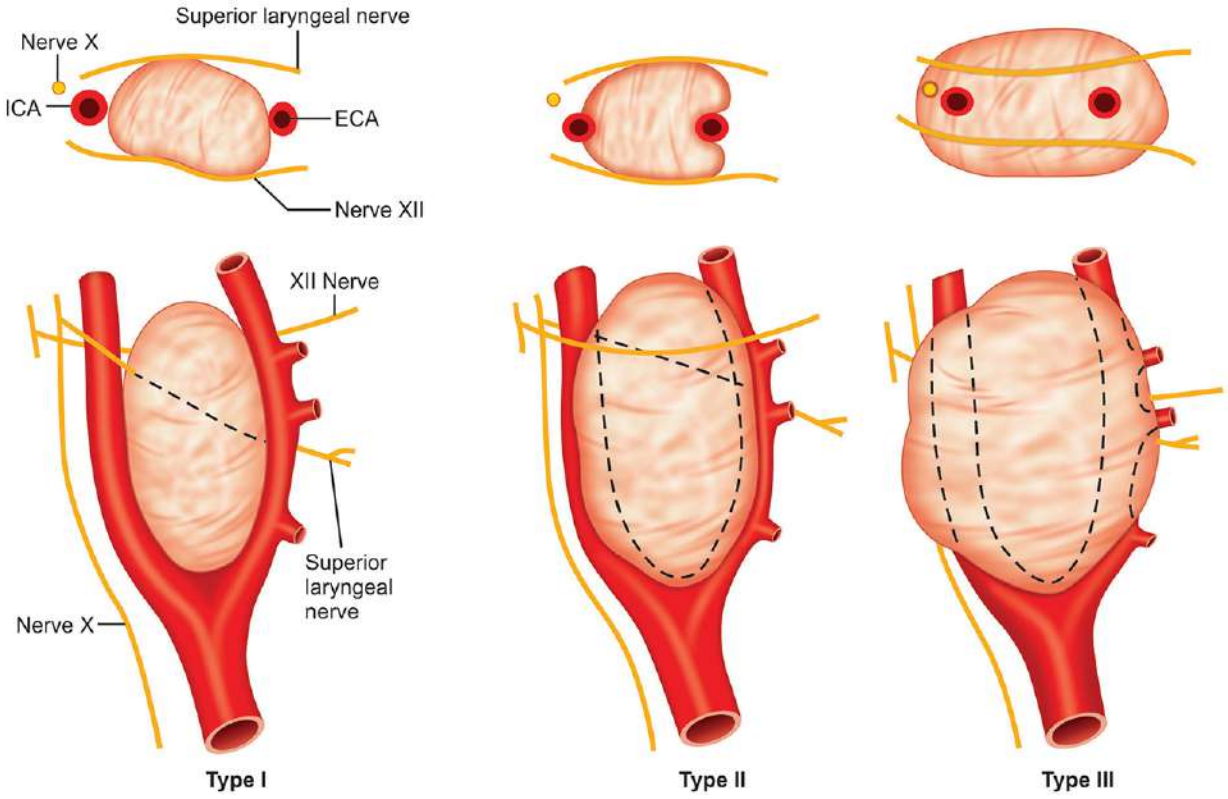

FIGURE 42.10 Illustration of the Shamblin classification of carotid body paragangliomas. ECA, external carotid artery; ICA, internal carotid artery. (Used with permission of Jaypee Brothers Medical Publishers from Myers EN. Management of tumors of the parapharyngeal space. In: De Souza C, ed. *Otorhinolaryngology: Head and Neck Surgery*. 2nd ed. Jaypee Brothers Medical Publishers; 2019:488; permission conveyed through Copyright Clearance Center.)

For tympanic and jugulotympanic paragangliomas, the Fisch and Mattox classification system (Table 42.3) describes the extent of the tumor.[184]

TABLE 42.3 FISCH AND MATTOX CLASSIFICATION SYSTEM FOR JUGULAR PARAGANGLIOMAS

Class	Extent
A	Tumors confined to the middle ear (tympanic paraganglioma)
B	Tumors limited to tympanomastoid area without bony destruction of the infralabyrinthine compartment of the temporal bone
C1	Tumors involving the jugular foramen and jugular bulb with limited involvement of the carotid canal
C2	Tumors involving the vertical portion of the carotid canal
C3	Tumors involving the horizontal portion of carotid canal
C4	Tumors involving foramen lacerum and cavernous sinus
De1/2	Intracranial extradural extension <2 cm or >2cm
Di1/2/3	Intracranial intradural extension <2 cm, 2-4 cm, or >4 cm

Note that D is not a separate class but a modifier of class C tumors. For example, a tumor may be described as C3Di2.

Modified with permission from Sivalingam S, Konishi M, Shin SH, Lope Ahmed RA, Piazza P, Sanna M. Surgical management of tympanojugular paragangliomas with intradural extension, with a proposed revision of the Fisch

classification. *Audiol Neurootol*. 2012;17(4):243-255. Copyright © 2012 Karger Publishers, Basel, Switzerland.

General Management

Multidisciplinary patient care will consider the patient's age, comorbidities, and preferences and the size, extent, and growth rate of the tumor to develop a plan to control the tumor while minimizing the risks of iatrogenic toxicities (eg, CN dysfunction). For many patients, an initial "wait-and-scan" approach is favored. Typical indications for early intervention include small carotid body and tympanic paragangliomas amenable to surgery with minimal iatrogenic risk, patients with significant brainstem compression, conductive hearing loss, pulsatile tinnitus, facial nerve weakness, secretory tumors, evidence of metastatic disease, those with rapid growth, or patient choice.

A suggested algorithm for management is presented in Figure 42.11.

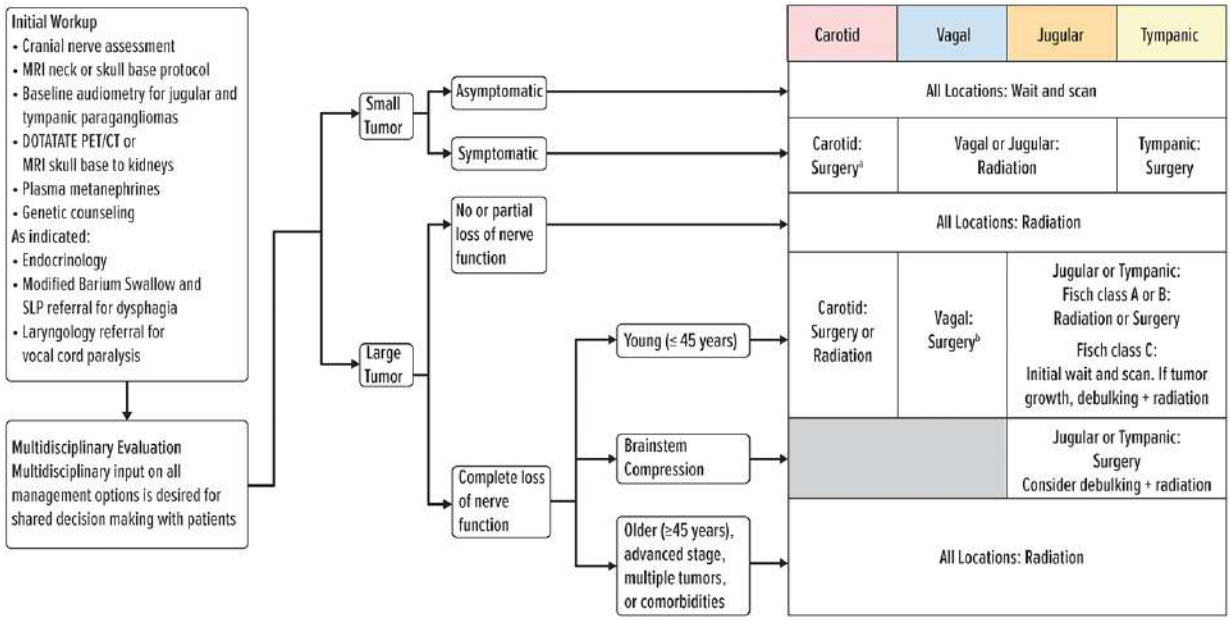

FIGURE 42.11 Suggested algorithm for *paragangliomas*. [a]For bilateral carotid body paragangliomas, consider surgery on one side and observation or radiotherapy for the contralateral side. [b]Caution that patients with deficits may retain residual tone and worsening of function may occur after surgical intervention; surgery for bilateral vagal paraganglioma is typically contraindicated. CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography. (Adapted from Verlicchi A, Nicolato A, Valvassori L, et al. Head and neck paragangliomas. In: Winn HR, ed. *Youmans and Winn Neurological Surgery*. 8th ed. Elsevier; 2023:1395. Copyright © 2023 Elsevier. With permission.)

Surgery

The role of surgery is significantly influenced by the age and comorbidities of the patient, location of the tumor, symptoms from secretory tumors or mass effect, existing CN deficits, and the risk of inducing new or worsening CN deficits. Improvements in surgical technique have significantly reduced the risk of perioperative stroke and mortality, but postoperative CN deficits remain common, developing in 40% or more.[185]

Shamblin group I carotid body paragangliomas and those <5 cm are typically amenable to resection with a modest risk of morbidity and high chance of tumor control.[155] Using cross-

sectional imaging, it can be difficult to distinguish between group I and II tumors, but group III may be recognized by the loss of a tumor to carotid adventitia interface, greater angle of contact with or encasement of the carotid vessels, and larger tumor maximal diameter.[186] Group II and III tumors and larger tumors (>3.2 cm) are associated with a higher risk of intraoperative and early postoperative neurovascular complications.[187] In a multivariate analysis of 184 patients undergoing surgery for 200 carotid body paragangliomas, tumors with a maximal diameter ≥5 cm and Shamblin group III were both associated with a higher risk of permanent CN dysfunction.[188] Patients with bilateral tumors may be considered for a staged surgical approach to avoid the risk of iatrogenic bilateral deficits. However, patients undergoing bilateral resection of carotid body paragangliomas are at increased risk of loss of carotid baroreceptor feedback with resultant hypertension and hemodynamic instability.[155] For that reason, some favor observation or radiation therapy to the contralateral tumor.

Surgical resection of vagal paragangliomas essentially always requires sacrifice of the vagal nerve,[155,189,190] with 60% reported to have an additional lower CN deficit after surgery.[191] Patients with bilateral vagal tumors or who may have a preexisting contralateral deficit of CN X or CN XII are typically not appropriate candidates for surgery as the development of bilateral deficits can lead to profound dysfunction requiring a tracheostomy and g-tube dependence.[190] Small asymptomatic tumors are typically observed, especially if bilateral. Growing or symptomatic tumors are typically irradiated.[192]

For jugulotympanic paragangliomas, the great majority of Fisch class A and B tympanic tumors are amenable to complete surgical resection while a subtotal resection is more likely in class C patients who may considered for planned conservative decompressive surgery with or without postoperative radiotherapy or primary radiotherapy.[193,194] A systematic review including 382 patients with jugulotympanic paragangliomas found class A and B tumors managed with surgery had a <1% risk of CN damage, which increased to 71% to 74% with class C tumors.[195]

In a meta-analysis, surgery for jugular foramen paragangliomas was associated with an approximately 60% rate of new lower CN deficits after a complete excision.[196] Gross total resection of tympanic and jugulotympanic paragangliomas is also associated with a high rate of hearing loss and facial nerve paresis or paralysis.[196] Proposed indications for surgery in these tumors include young age, secreting tumors, significant intracranial mass effect, tumor progression after radiotherapy, and cases with a perceived low risk of iatrogenic CN injury.[155]

While surgical intent is typically complete resection, in some instances, a subtotal resection may be warranted. For example, in a jugulotympanic tumor, resection of the tympanic portion can improve symptoms such as conductive hearing loss or pulsatile tinnitus, leaving the jugular fossa and/or intracranial extent of disease for observation or radiation therapy.[155] Preoperative embolization is commonly used before surgery of vagal and jugular paragangliomas.

When surgical intervention results in lower CN deficits, younger patients are more likely to be rehabilitated while older patients are more likely to experience chronic dysphagia.[171,197] In older patients, an argument is made for observation based on the idea that lower CN dysfunction from tumor is slowly progressive and often incomplete, allowing time for better physiologic adaptation.

Preexisting CN dysfunction does not obviate the functional risks of surgical intervention. Patients may retain (easily underappreciated) partial function or compensatory function, which, if lost, would meaningfully worsen their swallow and/or speech. Table 42.4 outlines common

nerve deficits and functional impairments from paraganglioma tumor involvement or surgical sequela.

TABLE 42.4 NEUROVASCULAR STRUCTURES AND IMPAIRMENTS THAT MAY RESULT FROM PROGRESSIVE TUMOR OR INTERVENTIONS IN HEAD AND NECK PARAGANGLIOMAS

Neurovascular Structure	Relevant Location	Component/Function	Functional Impairment	Intervention
Glossopharyngeal nerve (CN IX)	Jugular foramen and parapharyngeal space	Motor function to stylopharyngeus muscle	Palatal elevation	Swallow therapy
		Sensory function, afferent feedback from base of tongue and lateral pharyngeal wall	Dysphagia, loss of gag reflex	Swallow therapy, direct food to contralateral sensate pharynx
	Adjacent parasympathetic fibers depart CN IX at jugular foramen, pass through tympanic plexus to otic ganglion	Parasympathetic innervation of parotid gland	Temporary decrease in parotid salivary flow	Generally self-limited
Vagal nerve (CN X)	Superior vagal ganglion at jugular foramen or ganglion nodosum in carotid space	Sensory function from larynx and lateral pharyngeal wall	Aspiration, dysphagia	Swallow therapy
		Motor function of larynx	True vocal fold paralysis	Vocal fold injection/medialization
		Parasympathetic innervation of gastrointestinal viscera	Gastroesophageal dysmotility, gastroesophageal reflux, persistent nausea/vomiting	Motility/prokinetic agents, reflux medications
	Pharyngeal branch departs ganglion nodosum and passes between internal and external carotid, enters pharynx at upper border of middle constrictor	Motor function of palate	Unilateral palatal paralysis with velopharyngeal incompetence/nasal regurgitation	Swallow therapy; delayed surgery to create unilateral palatal adhesion to posterior pharyngeal wall
		Motor function of pharynx	Unilateral pharyngeal constrictor paralysis with aspiration	Swallow therapy, head positioning during swallow
Spinal accessory nerve (XI)	Exits jugular foramen, passes over internal jugular vein through sternocleidomastoid to trapezius	Motor function of sternocleidomastoid and trapezius muscles	Shoulder drop or weakness from loss of trapezius, can cause severe pain	Intraoperative grafting, physical therapy for shoulder strengthening
Hypoglossal nerve (XII)	Hypoglossal foramen, shares fibers with CN X at ganglion nodosum in carotid space, runs superficial to	Motor function of extrinsic and intrinsic muscles of tongue (excepting palatoglossus)	Dysphagia, food lodged on paralyzed side	Swallow therapy

Neurovascular Structure	Relevant Location	Component/Function	Functional Impairment	Intervention
	external carotid artery			
Cervical sympathetic chain	Superior cervical ganglion deep to internal carotid artery	Distribution to skin, pharyngeal plexus, ascending sympathetic plexus along internal carotid	Horner syndrome (ptosis, miosis, anhidrosis)	May have oculoplastic surgery for ptosis
		Sympathetic innervation of parotid gland	First bite syndrome—painful cramp or spasm in parotid area with the first bite of food	Avoid tart and bitter foods, may treat with carbamazepine
Carotid baroreceptors	Carotid body, carotid sinus to the glossopharyngeal nerve	Autonomic nervous system, cardiovascular equilibrium	Orthostatic hypotension, hypertension, paroxysmal tachycardia	Medical management; eg, clonidine, β -blockers

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Principles of Radiation Therapy

Meta-analyses of treatment outcomes for jugular paragangliomas provide a compelling rationale for radiotherapy when local control measures are indicated (Table 42.5). In a 2011 study, compared to gross total resection, radiotherapy was associated with a higher rate of tumor control and a markedly lower rate of new lower CN deficits.[196] A larger study in 2023 found lower rates of toxicity with both modalities, but the toxicity profile still favored radiotherapy.[198] Suarez and colleagues performed a meta-analysis of a series including both jugular and vagal paragangliomas.[172] The mean rate of tumor control for jugular paragangliomas managed with radiotherapy was higher than in those managed with surgery (91.5% vs 78.2%, $P = .002$) with fewer major complications (11.4% vs 28.2%, $P = .003$). There was no difference in the mean rate of tumor control across series with fractionated therapy ($n = 461$, 89%) and SRS ($n = 254$, 94%, $P = .32$).

TABLE 42.5 POOLED ESTIMATES OF OUTCOMES FOR JUGULAR PARAGANGLIOMAS IN TWO META-ANALYSES

					New Cranial Nerve Deficits (%)				
Study	Treatment	# pts	Mean *f/u*	Tumor Control (%)	CN VII	CN IX	CN X	CN XI	CN XII
Ivan et al[196]	Gross total resection	351	88 mo	86	–	38	26	40	18
	SRS	339	71 mo	95	–	9.7	9.7	12	8.7
Campbell et al[198]	Surgery	2,215	–[a]	85	27	20	21	13	12
	SRS	1,283	–	93	4	1	3	<1	1

CN, cranial nerve; SRS, stereotactic radiosurgery.

[a]Follow-up duration inconsistently reported and, therefore, not reported or analyzed; however, authors considered >2 years to represent long-term follow-up.

Quality of life was measured in a small series of 42 head and neck paragangliomas in 30 patients: 14 treated with radiotherapy alone and 16 with surgery followed by radiotherapy.[199] Patients treated with definitive radiotherapy reported better overall quality of life, and those treated with combined modality therapy reported statistically significant worse symptoms of trismus and difficulty speaking. Volumetric analysis in 15 patients showed about 40% tumor regression at 2 and 3 years after radiotherapy. While stable disease is the definition of local control after radiotherapy, tumor response is underappreciated. Many authors who have performed volumetric analysis have observed tumor regression over time after radiotherapy, ranging from about 20% to 40% volume decrease.[200-203]

Tinnitus and conductive hearing loss are the symptoms most likely to improve with radiotherapy. Existing neurologic impairments from tumors are least likely to improve with radiotherapy.

Radiation Techniques

Treatment Modalities and Dose

Paragangliomas have typically been managed with a moderate dose of radiotherapy with excellent local control outcomes. For fractionated therapy, 45 Gy in 25 fractions provides excellent control with fewer risks of iatrogenic toxicities. For hypofractionated stereotactic radiotherapy, 25 Gy in 5 fractions or 21 Gy in 3 fractions is efficacious, and for SRS, a dose of 15 Gy appears optimal. The selection of radiation treatment modalities and fractionation is based on tumor size, proximity to critical normal structures, patient preference, and availability of advanced treatment modalities.

The University of Florida published long-term outcomes of conventionally fractionated radiotherapy in 176 head and neck paragangliomas in 149 patients, of whom 83% received 45 Gy in 25 fractions. The 15-year rate of local control was 95%, with no moderate or severe complications, no secondary malignancies, and no malignant transformations observed.[204] Princess Margaret Hospital published results using moderately hypofractionated radiation to 35 Gy in 15 fractions in 45 patients with jugulotympanic paragangliomas with ~93% tumor control at a median follow-up of 10 years.[205] A total of five studies and two abstracts have reported outcomes in 107 patients with head and neck paragangliomas treated with proton therapy with local control rates of 97 to 100%.[200,202,206-209] In a systematic review, there was some suggestion that tumor regression and symptom improvement may be greater with proton than photon radiotherapy.[210]

Hypofractionated stereotactic radiotherapy results were reported in a series of 34 jugulotympanic or carotid body paragangliomas treated to a median of 25 Gy in 5 fractions (prescribed at a mean isodose of 83%). At a median follow-up time of 66 months, 97% maintained local control.[211] A radiographic partial response was observed in 59% and 45% had symptom improvement, with a 7% rate of late toxicity—one grade 1 (asymptomatic) cerebellar radionecrosis and one facial nerve weakness.

A systematic review and meta-analysis of SRS in head and neck paragangliomas identified a median marginal dose of 15 Gy in 1 fraction was required to achieve a local control rate ≥90%.[212]

Metastatic sites of disease also respond to moderate-dose radiotherapy. In a retrospective review of 41 patients treated to 107 metastatic sites from paraganglioma or pheochromocytoma, when evaluating the biologic effective dose (BED) using an α/β ratio of 10, the 5-year local control was 91% for a BED ≥53 Gy_{10} versus 62% for a BED <53 Gy_{10} ($P = .001$).[213] Nearly all (94%) symptomatic patients experienced some symptom improvement.

Target Volume Definition

For paraganglioma, the GTV is typically well defined on contrast-enhanced CT and using a co-registered MRI where tumor is T2 hyperintense and avidly enhancing on T1 postcontrast imaging. The CT should be used to include adjacent areas of osseous erosion and bone involvement. For fractionated therapy, previous versions of the UK Royal College of Radiologists' clinical practice guidelines recommended a minimum expansion of 0.5 cm from the GTV to create a clinical target volume (CTV), plus additional expansion for setup uncertainties to create the PTV.[214] This is consistent with the total GTV to PTV expansion of 1 cm used in several series.[200,215,216] Current UK guidelines note that no margin from GTV to CTV is required but caution against margins that are too tight that could lead to marginal misses.[214] Some patients experience transient or variable tumoral swelling during a course of fractionated radiotherapy.[217] Given the moderate doses employed for paraganglioma in fractionated therapy, using this more generous margin to reduce the risk of a marginal miss is unlikely to be associated with a significant increase in morbidity. For SRS, the CTV is the same as GTV, and a 1- to 2-mm margin is applied to create the PTV depending on uncertainties inherent in the radiosurgery platform.

Systemic Therapy

A number of systemic therapies are available for patients with metastatic paraganglioma and/or pheochromocytoma. In a systematic review, cytotoxic chemotherapy with cyclophosphamide, vincristine, and dacarbazine achieved a partial response in 37% and a complete response in 4%.[218] Temozolomide and sunitinib are second-line therapies.[219] A similar rate of partial response in excess catecholamine secretion was also observed. A number of radiopharmaceuticals have been used, including ^{131}I-metaiodobenzylguanidine and peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE.[220] Additional promising radiopharmaceuticals are under investigation.[221]

RADIATION DOSE CONSTRAINTS

The location of skull base targets in proximity to multiple critical normal structures makes radiotherapy planning a challenge. One must balance a desire to maximize target volume coverage, which appears critical to achieving tumor control, particularly for chordomas,[30,222,223] with the desire to maintain a reasonable level of iatrogenic risk. There is considerable variability in the reported literature on radiation dose constraints for challenging skull base tumors, but a common theme is that the radiation dose constraints are pushed higher than are commonly used in other scenarios. Using overly conservative dose constraints risks, compromising target volume coverage and disease control outcomes.

The European Particle Therapy Network (EPTN)[224] and the Chordoma Foundation position paper[62] have both outlined recommendations that are summarized in Table 42.6. The EPTN

constraints are based on calculating the BED to OARs using α/β ratios and converting to an EQD2. For example, a single-treatment plan that delivers a nominal dose of 63 Gy to the surface of the brainstem ($\alpha/\beta = 2$) over 37 fractions (~1.7 Gy per fraction) equates to an EQD2 of 58.32. When a sequential planning technique is used for the boost, the dose per fraction to OARs may vary between phases of the plan, requiring that the EQD2 be calculated separately in each plan and summed.

TABLE 42.6 DOSE CONSTRAINTS FOR SKULL BASE CHORDOMAS AND CHONDROSARCOMAS

	European Particle Therapy Network Consensus[224]			Chordoma Foundation Position Paper[62]	
Organ at Risk	α/β Ratio	Dose Constraint in EQD2	Toxicity End Point	Dose Constraint in Gy (RBE) for Standard Fractionation	Toxicity End Point
Cervical spinal cord	NR	NR	NR	$D_{surface}$ <67 D_{center} <55	Any clinical symptoms
Temporal lobe	NR	NR	NR	$D_{2\%}$ <71	Radiation necrosis visible on MRI
Brain	2	V_{60} ≤3 cc	Symptomatic brain necrosis		
Brainstem	2	$D_{surface\ 0.03cc}$ ≤60 $D_{interior\ 0.03cc}$ ≤54	Radiation necrosis	$D_{surface}$ <63 D_{center} <50	Any measurable toxicity
Chiasm and optic nerves (considered separately)	2	$D_{0.03cc}$ ≤55	Optic neuropathy	$D_{2\%}$ <60	Vision loss
Cochlea	3	D_{mean} ≤45	Hearing loss		
Cochlea	3	D_{mean} ≤32	Tinnitus		
Hippocampus	2	$D_{40\%}$ ≤7.3	Memory loss		
Lacrimal gland	3	D_{mean} ≤25	Keratoconjunctivitis		
Lens	1	$D_{0.03cc}$ ≤10	Cataract		
Pituitary	2	D_{mean} ≤45	Panhypopituitarism		
Pituitary	2	D_{mean} ≤20	Growth hormone deficiency		
Retina	3	$D_{0.03cc}$ ≤45	Vision loss		
Skin	2	$D_{0.03cc}$ ≤25	Permanent alopecia		

MRI, magnetic resonance imaging; NR, not reported; RBE, relative biologic effectiveness.

TOXICITIES OF RADIATION

Acute Toxicity

For these primary skull base malignancies, acute side effects of irradiation are typically modest.[225] Fatigue is common. Patients may experience odynophagia toward the end of

treatment depending on the inferior extent of the disease and target volumes, for example, when tumors involve the craniocervical junction and/or infiltrate the prevertebral muscles. Nausea may be seen when there is a meaningful dose to the area postrema or dorsal vagal complex of the brainstem. When disease extends laterally in the temporal bone, adjacent temporary epilation and alopecia may be seen.

If radiotherapy dose passes through the eyes, many patients will report blue flashing lights, which have previously been ascribed to direct retinal stimulation but appear to be production of Cherenkov light emission within the vitreous humor.[226]

Patients often have sinus congestion and nasal complaints after endoscopic sinus surgery, which may be exacerbated during radiotherapy. The flow of mucous within the paranasal sinuses complex depends on adequate mucous production and ciliary function, ostial patency, temperature, and humidity.[227] Endoscopic skull base surgery is associated with short-term sinonasal inflammation and impairment in sinonasal-related quality of life[228] and long-term smell impairment, increased incidence of posterior nasal discharge, and longer mucociliary clearance time.[229] High-dose radiation to paranasal sinus mucosa can lead to depletion of goblet cells and irreversible loss of cilia, which can result in nasal epithelial atrophy and chronic rhinosinusitis.[230]

Late Sequelae

If seen, most serious toxicities are late. In a systematic review including 818 irradiated patients with skull base chondrosarcomas, the most common late radiotherapy toxicities included hypopituitarism (15%), hearing loss (7%), radiation necrosis (4%), CN neuropathies (2%), and osteoradionecrosis (1%).[128] The profile is similar for chordomas. In a series of 112 patients treated with high-dose proton therapy, the most common late toxicities were hypopituitarism (17%), hearing loss (5%), symptomatic radiation necrosis (5%), and vision loss (<3%).[225] In a series of 204 pediatric patients with skull base chordoma irradiated with proton or mixed proton-photon therapy, the most common late toxicities were endocrine abnormalities and auditory toxicities including recurrent otitis and hearing loss.[61] Radiographic-only brainstem changes and temporal lobe changes were observed in 2% each.

Radiation Optic Neuropathy

Radiation-induced optic neuropathy (RION) is an irreversible vascular injury to the optic nerve or chiasm with subsequent demyelination. Patients typically develop abrupt and painless loss of vision, often with a long latency from radiation. In one study, the mean latency to RION was 31 months.[231] MRI at the time of onset typically shows discrete enhancement of the affected optic nerve, often with expansion and high T2 signal in the enhancing segment.[232] Pathology of optic nerves with RION shows ischemic demyelination, reactive astrocytosis, endothelial hyperplasia, obliterative endarteritis, and fibrinoid necrosis.[233]

A multi-institutional analysis from PSI and CPO evaluated the risk of RION in 289 patients irradiated for skull base chordoma or chondrosarcoma.[234] All patients had received a minimum dose of 45 Gy (RBE) to the optic apparatus and had a median follow-up time of 5.6 years. The median maximum dose to the optic apparatus was about 60 Gy (RBE), with a range of 45 to 76 Gy (RBE). Twelve patients developed any-grade RION for a crude incidence of 4.2%. No

radiation dose metrics were associated with the risk of RION, but advancing age and hypertension were associated with an increased risk on univariate analysis.

The University of Florida analyzed the risk of vision loss after high-dose radiotherapy for skull base chordoma or chondrosarcoma in a series of 148 patients.[235] All patients had received a minimum dose of 30 Gy (RBE) to the optic apparatus and had a median follow-up time of 4.1 years. The 5-year incidence of vision loss was 2%. There were no instances of vision loss observed when the maximum dose was <60 Gy (RBE) and a 3.6% crude incidence rate when the maximum dose was >60 Gy (RBE). The presence of multiple medical comorbidities was associated with the risk of vision loss on univariate analysis.

Radiation Necrosis

Given the high dose required for adequate disease control of skull base chordomas, and to a lesser extent chondrosarcoma, radiation-induced parenchymal brain imaging changes are seen relatively frequently during MRI surveillance. Parenchymal brain radiation necrosis can vary from minor imaging findings to devastating and life-threatening symptomatic necrosis.

The Quantitative Analysis of Normal Tissue Effects in the Clinic review suggests that partial brain irradiation to 72 Gy in standard fractionation is associated with a 5% risk of symptomatic radiation necrosis but provides no specific guidance on volume constraints.[236] One study found that the risk of radiation necrosis increased sharply when the absolute volume of temporal lobe receiving 60 Gy exceeded 5.5 cm^3 or the volume receiving 70 Gy exceeded 1.7 cm^3.[237] International guidelines for radiation planning in nasopharyngeal cancer suggest a planning goal that the temporal lobe dose to 0.03 cm^3 be restricted to ≤70 Gy with a maximum acceptable constraint of 72 Gy.[238] In radioresistant tumors such as chordomas that involve the cavernous sinus or otherwise abut parenchymal brain, these constraints cannot be met while adequately covering tumor.

Asymptomatic MRI changes can cause diagnostic confusion and concern for tumor recurrence, brain metastases, or glioma. Correlating the MRI findings with the prior radiation treatment plan can improve the assessment of probable radiation necrosis. MRI with perfusion or spectroscopy (depending on the size and location of the abnormality) can help distinguish radiation necrosis from tumor. Asymptomatic radiation edema or necrosis may be treated with pentoxifylline and vitamin E in an effort to improve or stabilize the process, hoping to avoid progression to symptomatic necrosis. The combination (typically pentoxifylline 400 mg with vitamin E 400 IU twice daily) is thought to improve oxygenation to tissues by reducing blood viscosity and increasing deformability of erythrocytes, to reduce cytokine-mediated inflammation, and to reduce oxidative damage by scavenging free radicals, among other effects.[239] The combination has shown some promise in the brain.[240] For patients with symptomatic radiation necrosis, dexamethasone provides short-term relief without addressing the underlying pathophysiology. Bevacizumab has been shown to improve symptoms and imaging findings in two small randomized controlled trials.[241,242] For those with contraindications to bevacizumab, hyperbaric oxygen can provide clinical and radiologic improvement or stability.[243]

Brainstem necrosis is of special concern. The University of Florida reported on the incidence of brainstem toxicity in 163 patients treated with high-dose radiotherapy for skull base tumors with a median follow-up time of 4 years.[244] All patients had received a minimum of 45 Gy (RBE) to the brainstem, with a median D0.03cc of 63.5 Gy (RBE) and median *D*max of 65.7 Gy

(RBE). The 5-year incidence of grade ≥2 brainstem toxicity was 1.3%. These and other experiences support the clinical safety of the higher dose constraints employed for skull base malignancies requiring high-dose radiotherapy.

Radiation Ototoxicity

Otologic complaints and complications are relatively common in skull base tumors from both tumor and treatment effect.[245] Hearing may be compromised by radiation-induced mucosal inflammation leading to mastoid effusion, radiation neuropathy of the vestibulocochlear nerve, or fibrosis, atrophy, or ossification of the inner ear. Patients may develop frequent inner ear infections, sensorineural and/or conductive hearing loss, otorrhea, otalgia, tinnitus, vertigo, or perforation of the tympanic membrane. A mean radiation dose >30 Gy dose to the mastoid air cells and posterior nasopharynx is associated with an increased risk of post-treatment mastoid air cell opacification.[246] Myringotomy can be performed to treat effusions and preserve hearing.[245]

Radiation-induced sensorineural hearing loss is associated with an increasing mean radiation dose to the cochlea.[247] Because no threshold dose has been established, the dose to the cochlea should be kept as low as possible. A ≥10 dB change in hearing on pure tone audiometry is considered clinically significant. A mean cochlear dose of 45 Gy is associated with about a 19-dB decrement in high-frequency hearing loss.[248] Unfortunately for tumors involving the petrous apex in close proximity to the cochlea, it is not always possible to spare both cochlea, and patients should be counseled on a significant risk of progressive hearing loss on the affected side after treatment.

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CHAPTER 43

Spinal Canal Tumors

Nikhil Rammohan, Clifford G. Robinson, Jeff M. Michalski, and Jiayi Huang

Tumors of the spinal cord and cauda equina account for approximately 3% of primary central nervous system (CNS) tumors overall and 4% in children.[1] Spinal canal tumors are classified by the World Health Organization (WHO) according to histologic types. Clinically, they are also characterized by their location relative to the protective layers of the spinal cord as extradural, intradural–extramedullary, or intramedullary (Figure 43.1). Intramedullary lesions arise from the intrinsic substance of the spinal cord. Histologically, intramedullary spinal cord neoplasms include gliomas such as astrocytoma, ependymoma, and oligodendroglioma. Intradural-extramedullary tumors arise from the connective tissues, blood vessels, or coverings adjacent to the cord or cauda equina. Common histologies include nerve sheath tumor, meningioma, and ependymoma. Extradural tumors are most commonly metastatic, although primary tumors in this compartment may occur as well. Primary extradural tumors arising from the vertebral bodies may include benign tumors such as osteoid osteoma, osteoblastoma, and aneurysmal bone cysts, or malignant tumors such as plasmacytoma or myeloma, chordoma or chondrosarcoma, osteosarcoma, and Ewing sarcoma. Other primary extradural tumors arising outside the vertebral body include epidural hemangiomas, lipomas, extradural meningiomas, nerve sheath tumors, and lymphomas.

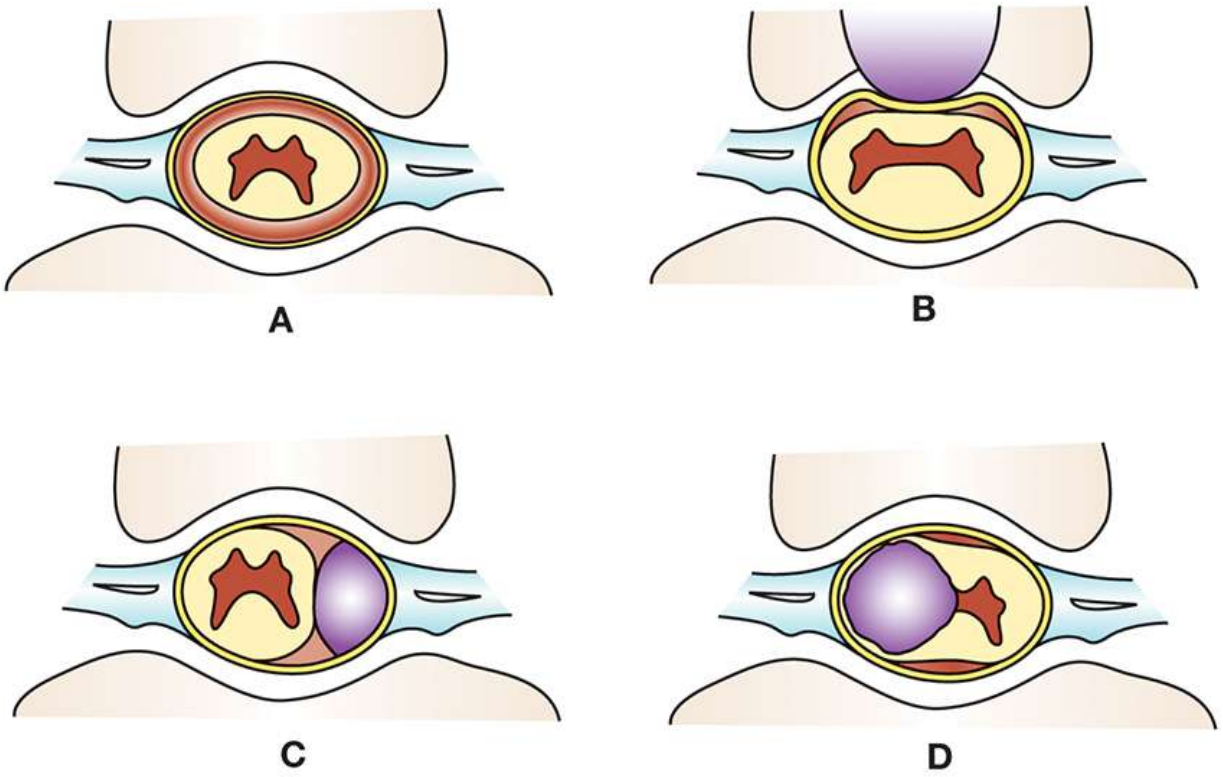


FIGURE 43.1 Neoplasms affecting the spinal cord. A. Normal transverse spine. The spinal cord is enveloped by the pia, arachnoid, and dura mater, which are housed in the spinal canal and surrounded by ligaments supporting the vertebral bony structures. The subarachnoid space contains cerebrospinal fluid (*brown*). B. Transverse spine with extradural mass. An extradural mass (eg, metastasis) from the vertebral body is compressing the dural sac and the spinal cord from the anterior direction. The subarachnoid space becomes obliterated at that level, causing a myelographic block. C. Transverse spine with an intradural-extramedullary mass. The mass, typically a meningioma or nerve sheath tumor, is compressing the spinal cord and roots in the dural sac, causing a myelographic block with a laterally displaced cord and, at times, producing a capping contour of contrast border. D. Transverse spine with intramedullary mass. An intramedullary mass (astrocytoma or ependymoma) is infiltrating and expanding the spinal cord within the dural sac, causing a myelographic block.

Radiation therapy is an important modality in the management of both primary and metastatic tumors involving the spinal canal. This chapter focuses primarily on the management of primary spinal cord tumors. Primary extradural tumors are usually managed in a manner similar to histopathologically identical tumors arising at other locations and are not discussed here in detail. The management of metastatic tumors involving the spinal canal is discussed in Chapters 102.

ANATOMY

Spinal Cord

The spinal cord is a slender cylinder composed of functional segments corresponding to 31 pairs of spinal nerves: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 1 coccygeal. In contrast to the brain, the white matter of the spinal cord is located in the periphery and surrounds the central gray matter. The gray matter contains the cell bodies of sensory, motor, and autonomic neurons. On cross section, the gray matter is a butterfly-shaped region with anterior horns controlling motor function, lateral horns (in the thoracic and upper lumbar region) controlling autonomic functions, and posterior horns involved in sensation. The white matter contains the axonal elements of neurons that transmit impulses to and from the brain. As in the brain, the axons of the spinal cord white matter possess a myelin sheath formed by the cytoplasmic extension of glial cells. Schwann cells sheath the spinal nerves that enter and exit the spinal cord. The spinal cord is organized into somatotopically distinct regions (Figure 43.2). The lateral and anterior spinal cord white matter contains the nerve tracts that are involved with fine motor control and tone, including the corticospinal tracts. The spinocerebellar tracts transmit muscle stretch and tone sensation from the extremities to the cerebellum. The lateral spinal thalamic tract is located laterally near the spinal cord surface and carries ascending crossed pain fibers to the thalamus. The dorsal columns transmit fine touch and positional sensation from the extremities to the brain. Because of its serial organization, injury to the spinal cord results in characteristic neurologic findings that depend on the location of the insult.

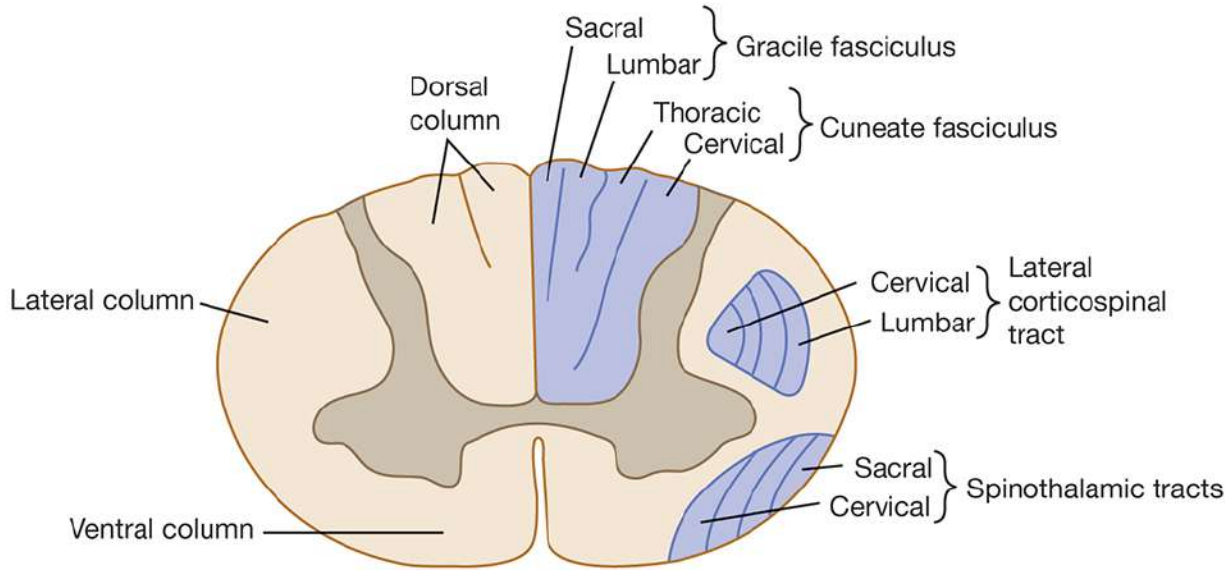


FIGURE 43.2 Somatotopic organization of the cervical spinal cord in transection. (Reprinted with permission from Waxman SG. *Clinical Neuroanatomy*. 30th ed. McGraw-Hill; 2024:54, Figure 5-15. Copyright © 2024 by McGraw-Hill LLC.)

The spinal cord is surrounded by the meninges, which are composed (from outer to inner) of the dura mater, arachnoid, and pia mater. The pia mater covers the spinal cord and its blood vessels. This layer condenses laterally into approximately 20 pair of dentate ligaments, which suspend the cord to the dura mater. The dura mater forms a dense, fibrous barrier between the bony spinal canal and the spinal cord. The dural sac ends inferiorly at S2-3, but the dura continues with the filum terminale down to the coccyx. The arachnoid mater resides between the dura mater and the pia mater. The arachnoid encloses the subarachnoid space filled with cerebrospinal fluid (CSF). The subarachnoid space follows the arachnoid down to the end of the dural sac.

The growth of the vertebral column during childhood takes place at a rate and extent greater than that of the spinal cord itself. By adulthood, the spinal cord is nearly 25 cm shorter than the vertebral column and ends near the level of the L1 vertebral body. Because of this differential growth, the exit level of each pair of spinal nerves in the spinal cord is usually higher than the corresponding vertebral body level. For example, in adults, the C8 nerve root leaves the cord at the C6 vertebral body, the T6 nerve at the T3 vertebral level, and the T12 nerve at the T9 vertebral level. All of the lumbar nerves exit the spinal cord from vertebral levels T10 through T12,

and all of the sacral nerves exit the spinal cord near the L1 vertebral level. The lower lumbar, sacral, and coccygeal nerves form the cauda equina, the collection of nerves that fills the thecal sac below L1. At its most caudal extent, the cord tapers to a thin segment, the conus medullaris. It is tethered to the coccyx by the filum terminale, a dense thread of pia mater.

Spinal Canal

The posterior body surfaces and neural arches of the vertebrae form the vertebral foramina, which in continuity form the spinal canal. Vertebral foramina are triangular in the lumbar and cervical regions, where the cord is mostly mobile, and round in the thoracic region. The spinal canal is lined with ligaments, including the posterior longitudinal ligament on its anterior wall, the flaval ligaments between adjacent arches, and the interspinous ligaments between the spinous processes. At each vertebral level, a spinous process protrudes from the posterior aspect of the neural arch, and transverse processes extend from the lateral edges of each arch. The laminae are those portions of the neural arch between the spinous and transverse processes, and the pedicles lie between the transverse processes and the body. At the intersection between the laminae and pedicles are superior and inferior paired articular facets. The superior articular facets are synovial joints that articulate with the inferior articular facets of the vertebra immediately above. The paired pedicles of each vertebra are notched at their superior and inferior edges such that the notches from two contiguous vertebra form an intervertebral foramen, through which the spinal nerve courses.

EPIDEMIOLOGY

Based on population data, 22% of primary spinal tumors are malignant and 78% nonmalignant (62% benign and 16% with borderline behavior).[2] The most common sites are the spinal cord (60%), followed by the spinal meninges (36%), and the cauda equina (4%). Incidence appears to increase with advancing age, peaking at the seventh decade of life. Age-adjusted incidence rates are 0.76 per 100,000 persons for nonmalignant tumors and 0.22 per 100,000 persons for malignant tumors. The frequency of nonmalignant cases is higher for females (60%), whereas malignant cases

are equally distributed by sex. Age-adjusted rates appear to be higher in Caucasian race and non-Hispanic ethnicity.[2] In adults, the most common histology types are meningioma (37.6%), nerve sheath tumor (23.1%), ependymoma (20.5%), and astrocytoma (4.2%). In children, the most common histology types are astrocytoma (31.4%), ependymoma (21.6%), oligodendroglioma (16.8%), nerve sheath tumor (13.3%), and meningioma (7.4%) (Table 43.1).[1]

TABLE 43.1 PRIMARY SPINAL CANAL TUMORS OF ADULTS AND CHILDREN: TYPES, LOCATIONS, AND FREQUENCIES

	Type	Location	Frequency (%)
Adults	Meningioma	Intradural-extramedullary	39.9
	Nerve sheath tumor	Intradural-extramedullary	30.5
	Ependymal tumors	Intramedullary or intradural-extramedullary	16.0
	Astrocytoma and other gliomas	Intramedullary	2.1
	Mesenchymal tumors	Intramedullary	3.8
	Others	—	7.6
Children	Astrocytoma and other gliomas	Intramedullary	28.1
	Ependymal tumors	Intramedullary or intradural-extramedullary	16.5
	Nerve sheath tumor	Intradural-extramedullary	17.6
	Meningioma	Intradural-extramedullary	4.6
	Mesenchymal tumors	Intramedullary	14.7
	Others	—	16.3

Based on Central Brain Tumor Registry of the United States (CBTRUS) statistical report from 2016 to 2020.

NATURAL HISTORY

Primary spinal tumors have the capacity to cause significant neurologic morbidity. Intramedullary tumors produce neurologic damage by local

invasion or cystic compression of the cord, whereas extramedullary lesions compress, stretch, or distort the cord or the spinal nerves. Primary spinal cord tumors may be focal or relatively localized in some patients but may involve nearly the entire length of the cord in others. Local tumor progression is the dominant form of treatment failure of spinal cord tumors, though leptomeningeal dissemination may occur rarely.[3,4] Spread to lymph nodes is not typically seen with spinal canal tumors. Extraneural spread is rare, occurring with an overall incidence of approximately 1%, though this risk appears to be higher than cerebral tumors.[5] The major causes of death in patients with spinal canal tumors are complications of paraplegia or quadriplegia, such as infection or respiratory compromise.

CLINICAL PRESENTATION

Pain is the most common presenting symptom, affecting approximately 72% of patients.[6] Often, the pain is localized to the region of involvement and may be present well before the patient manifests localizing neurologic signs. Radicular pain, a result of pressure on nerve roots, reflects the distribution of the involved root and indicates that conduction is intact. Numbness replacing pain is a more advanced sign that indicates compromise of spinal nerve or nerve tract conduction. Extramedullary tumors can cause distention of the dura with severe pain in the region of the tumor that is characteristically aggravated by recumbency because of venous congestion. Thus, pain is often worse at night. Movement or the Valsalva maneuver also may worsen pain.

Other symptoms of CNS involvement include weakness (55% of patients), sensory deficits (39%), and sphincter dysfunction (15%).[6] Low-grade tumors generally have a more prolonged duration of symptoms than high-grade tumors. Bladder and bowel dysfunction as presenting symptoms are relatively uncommon except for tumors that involve the conus medullaris and filum terminale.

Tumors involving the lumbosacral spine present with a cauda equina nerve root compression syndrome. Patients may have radicular pain in the anterior (L4), lateral (L5), or posterior (S1) thigh with corresponding paresthesias followed by muscle wasting of the glutei, hamstrings, or tibialis anterior muscles. Saddle anesthesia, absent ankle reflexes (S1), or

plantar (S2) responses may be present. Impotence and loss of anal or bulbar cavernous reflexes also may occur.

DIAGNOSTIC WORKUP

History and Physical Findings

Table 43.2 shows the diagnostic workup for primary tumors of the spinal cord. A meticulous and accurate patient history and physical examination are critical aspects of the initial assessment and can often localize suspected spinal tumors. The neurologic examination should concentrate on testing motor and sensory functions and reflexes. The differential diagnosis of a patient with a spinal cord tumor may include syringomyelia, multiple sclerosis, amyotrophic lateral sclerosis, diabetic neuropathy, viral myelitis, or paraneoplastic syndromes.

TABLE 43.2 DIAGNOSTIC WORKUP FOR PRIMARY SPINAL CORD TUMORS

General
History
Physical examination
Complete neurologic examination
Diagnostic Imaging Studies
Plain radiography
Magnetic resonance imaging (MRI) of the entire spine
MRI of the brain (consider for high-grade ependymomas or astrocytomas)
Myelography with computed tomography (if MRI is contraindicated)
Laboratory Studies
Cerebrospinal cytology (consider if clinical or radiologic suspicion of leptomeningeal disease)

A cutaneous sensory level may be definable, although the level of cord injury will be a few segments higher than the superior level of sensory loss because of pathway crossing characteristics. Loss of pain and heat and cold sensation below a specific dermatomal level indicates compromise of the spinothalamic pathway in the lateral columns. Impaired posture, gait, and coordination and loss of vibration sense indicate compromise of the posterior spinocerebellar pathways or the posterior columns.

At the level of the lesion, flaccid weakness and loss of tendon reflexes may occur. Below the lesion, the same signs are noticed in acute stages, but spastic paralysis and hyperactive tendon reflexes plus an upward Babinski

toe sign ensue in subacute and chronic stages. These findings are consistent with lower and upper motor neuron involvement, respectively. The signs and symptoms of neurologic dysfunction may be asymmetric. In some cases, a classic Brown-Séquard syndrome may be present with ipsilateral loss of motor function and fine touch sensation and contralateral loss of pain and temperature sensation below the level of the lesion.

Autonomic reflexes (eg, sweating) are frequently increased below the level of the lesion and may encompass the whole body if the lesion is cervical. Sweating disappears at the level of the compressed cord. Disruption of urinary and bowel function usually occurs later than sensory and motor dysfunction. Early loss of bladder function, saddle anesthesia, and later pain characterize neoplasms of the conus medullaris and filum terminale.[7]

Radiographic Studies

Although plain films are not typically used as the principal imaging modality for the evaluation of suspected spinal canal tumors, abnormalities can be detected from increased intracanal pressure, including erosion of vertebral pedicles, enlargement of the anteroposterior diameter of the bony canal, or scalloping of the posterior wall of the vertebral bodies. Calcification may be seen in extramedullary tumors, especially meningiomas, and, less frequently, in nerve sheath tumors. Changes are more likely to be detected on plain radiographs in children than in adults, such as kyphoscoliosis or scalloping of the vertebral bodies.[8,9]

Myelography, once considered the standard examination in evaluation of the spinal cord and canal, is now used principally in patients who are unable to undergo magnetic resonance imaging (MRI) because of the presence of implanted ferromagnetic materials or for whom images at the level of concern are distorted by the presence of surgical hardware. In this situation, computed tomography (CT) scanning combined with myelography will give better spatial resolution. CT myelography may be particularly beneficial as part of radiotherapy treatment planning in the postoperative setting, where the spinal cord may be obscured by artifact on the MRI.[10]

Computed Tomography

CT is most helpful in evaluating the spine for extradural pathologic processes. Bone tumors or paraspinal soft tissue masses that secondarily involve the spinal cord (eg, dumbbell tumors) can be imaged with contrast-enhanced CT scans. Nerve sheath tumors can enlarge the intervertebral foramina or spinal canal and cause smooth erosion of bone. Meningiomas are occasionally calcified. Both of these neoplasms are partially outlined by CSF and produce extramedullary deformity by displacement of the spinal cord.[11]

Magnetic Resonance Imaging

MRI has replaced myelography and CT as the imaging study of choice in evaluation of tumors of the spinal canal. Sagittal and axial images give a three-dimensional (3D) appreciation of the patient's anatomy and help plan therapy. The various signal characteristics of the CSF—white and gray matter, bone and bone marrow, fat, and flowing blood—all facilitate the interpretation of the study. Some cystic tumors, vascular lesions, or lipomas can be diagnosed based on their characteristic signals on T1- and T2-weighted images without contrast injection. Intravenous gadolinium-containing contrast agent administration improves the sensitivity of MRI by enhancing the solid component of intramedullary tumors and differentiating them from surrounding edema or syrinx cavities (Figures 43.3 and 43.4). Unlike low-grade gliomas in the brain, nearly all spinal cord gliomas, regardless of grade, enhance with gadolinium contrast agents. Sagittal T1-weighted images usually localize intramedullary mass neoplasms along with adjacent cysts. Intradural-extramedullary lesions also show enhancement on T1-weighted images after administration of contrast. The use of contrast also increases the sensitivity of detecting leptomeningeal metastases.[12]

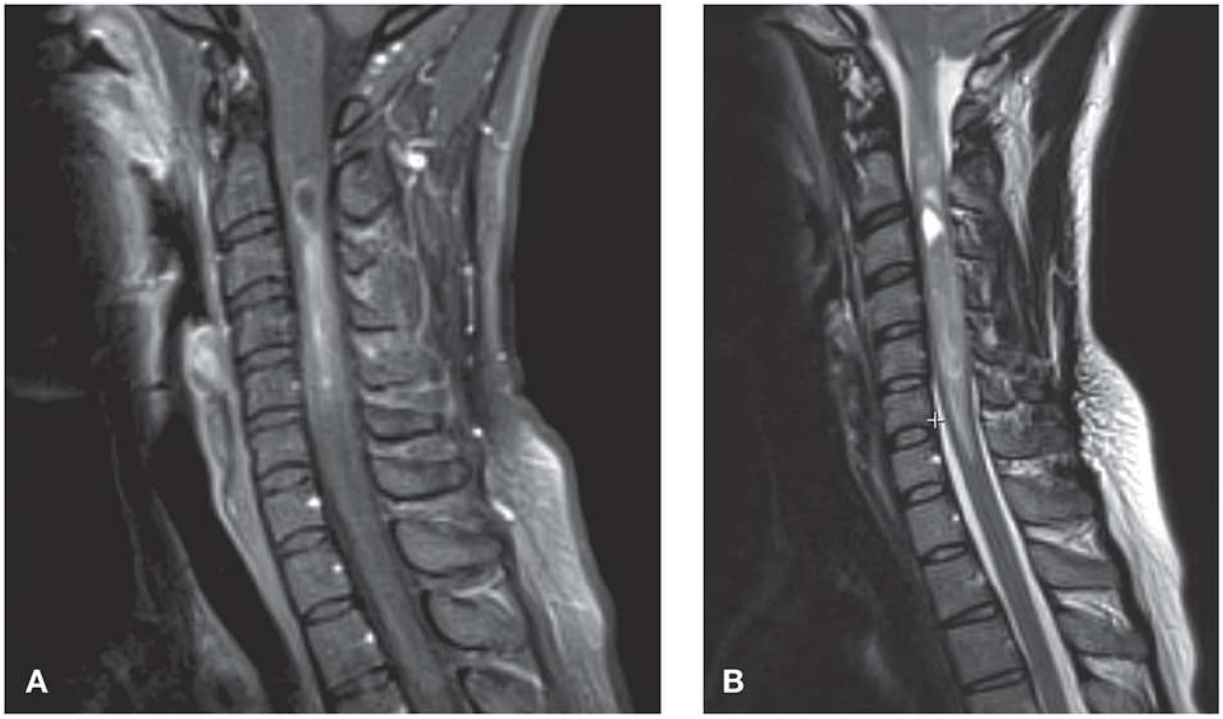


FIGURE 43.3 Sagittal magnetic resonance imaging scans of a 30-year-old woman with a low-grade astrocytoma involving the cervical spine. A. T1-weighted image demonstrates an intramedullary lesion that expands the cord from the level of the craniocervical junction to the level of C7. The enhancing component extends from mid C2 to C5, and there is an associated cystic component at the cranial aspect of the lesion. B. T2-weighted image demonstrates T2 hyperintensity within the lesion suggestive of edema and hypointensity suggestive of blood products.

FIGURE 43.4 Sagittal magnetic resonance imaging scans of a 12-year-old male with a myxopapillary ependymoma involving the lumbar spine. A. T1-weighed image demonstrates a homogeneously enhancing intradural-extramedullary mass at the level of L1. B. T2-weighted image demonstrates hyperintensity of the mass. (Courtesy of Aseem Sharma, MD, Mallinckrodt Institute of Radiology.)

MRI of the brain should be performed in patients with high-grade ependymomas or astrocytomas to exclude the possibility of neuraxis seeding or the presence of an intracranial primary tumor.

Cerebrospinal Fluid

A patient suspected of having a spinal canal neoplasm should not be subjected to a lumbar puncture before MRI. Symptoms may be exacerbated

after a spinal tap because of shifting of the spinal cord and incarceration before the tumor can be localized adequately. The CSF usually has increased protein levels and may exhibit xanthochromia, especially with extradural compression conditions, but lower values can be found in cases of intramedullary disease and with compression in the cervical region.[7] The incidence of leptomeningeal spread in patients with primary spinal cord glioma is low overall but is substantially more common with malignant tumors. Of note, two recently recognized entities have significantly higher risk of leptomeningeal dissemination: glioblastoma with primitive neuronal component and diffuse leptomeningeal glioneuronal tumors.[13,14] Cytologic examination of the CSF is not done routinely but may be considered in the presence of clinical or radiologic suspicion.

Tissue Diagnosis

Suspected primary tumors of the spinal cord and spinal canal should be pathologically confirmed whenever possible. Strong consideration should also be given to biopsy of any presumed metastatic tumors if they are the first site of disease recurrence after successful management of a previous malignant primary tumor. In rare circumstances in which emergency radiation therapy is indicated to relieve spinal cord compression in the absence of a confirmed cancer diagnosis, a patient should be made aware of the consequences of treatment in the absence of a definitive diagnosis, including the inability to tailor therapy based on histology and possible delay of appropriate treatment for nonmalignant etiologies.

PATHOLOGIC CLASSIFICATION

The current comprehensive classification system of spinal tumors was published by the WHO in 2007 and recently updated in 2021 to incorporate many molecular markers to establish histology types. The WHO classification groups CNS neoplasms by the tumor histology and provides a grading system to predict prognosis and guide therapy.[15,16] Tumor types include neuroepithelial (ie, astrocytoma, ependymoma, ganglioglioma), nerve sheath (ie, schwannoma, neurofibroma), meningioma, lymphoma, germ cell, and metastatic tumors. Clinically, spinal tumors are also

characterized by their location as extradural, intradural-extramedullary, or intramedullary.

Intramedullary Tumors

Intramedullary spinal tumors constitute approximately 20% to 30% of all primary spinal tumors, and approximately 80% are glial in origin, of which ependymoma is the most common histology (60%-70%) followed by astrocytoma (30%-40%).[17] Ependymomas are derived from glial cells similar to those lining the ventricular system and can be either intramedullary or intradural-extramedullary. The 2021 WHO classification defines ependymomas according to a combination of histopathologic and molecular features as well as anatomic sites, dividing them into molecular groups across the supratentorial, posterior fossa, and spinal compartments. Spinal ependymal tumors now include the following entities: spinal ependymoma (grade 2 or 3), MYCN-amplified spinal ependymoma (grade 2 or 3), myxopapillary ependymoma (grade 2), and subependymoma (grade 1).[18] For more information on spinal ependymoma in children, refer to Chapters 90.

In contrast to intracranial astrocytoma, most spinal cord astrocytomas are low grade (WHO grade 1 or 2), including 75% in adults and 85% to 90% in children.[6,19,20] Juvenile pilocytic astrocytomas (grade 1) in particular, as in other locations in the CNS, are not infiltrative in nature. Recognition of this feature, along with advances in surgical techniques and intraoperative monitoring, has led neurosurgeons to manage these tumors with more radical resections. However, diffuse astrocytomas (grades 2-3) or H3 K27-altered diffuse midline glioma (grade 4) is infiltrative, and complete resection carries a significant risk of neurologic disability. In these cases, a subtotal resection or biopsy may be the only safe surgical option.[21-23] A discriminating feature of intramedullary spinal cord tumors is the presence or absence of a syrinx. Syringes associated with spinal cord astrocytoma occur in 20% to 40% of patients. Syringes can span the entire length of the cord, although they tend to favor more rostrally located tumors, as well as favoring the more rostral portion of the tumor itself.[24] In certain instances, a syrinx may even extend into the medulla, producing an obstructive

hydrocephalus.[25] The syrinx itself can be responsible for significant neurologic deficit.

For more information on spinal astrocytomas in children, refer to Chapters 90. A variety of vascular neoplasms can arise from within the spinal cord, including arteriovenous malformations, hemangiomas, and hemangioblastomas. Approximately one-third of hemangioblastomas are associated with von Hippel-Lindau disease. These are benign neoplasms that are usually well circumscribed and amenable to surgery.[26] Unresectable or recurrent hemangioblastomas may be treated with stereotactic radiosurgery (SRS).[27]

Intradural-Extramedullary Tumors

Most intradural-extramedullary neoplasms are meningiomas, nerve sheath tumors, or extramedullary ependymomas such as myxopapillary ependymomas. They are usually amenable to complete surgical excision.

Meningiomas are usually benign, slow-growing, well-encapsulated neoplasms that are easily separated from the spinal cord; most can be completely excised, and they rarely recur. They may arise anywhere within the intradural space but are most commonly found in the cervicothoracic region and are uncommon in the lumbar region and rare in the sacrum. Spinal meningioma occurs more frequently in females. The peak incidence is between the sixth and eighth decades of life. The duration of symptoms before diagnosis is typically between 12 and 24 months, with longer duration as an independent predictor for a lack of improvement after surgery.[28]

Nerve sheath tumors arise from the Schwann cell, the cell responsible for insulating peripheral nerves and contributing to impulse conduction. Nerve sheath tumors have been called neurofibroma, schwannoma, neuroma, and neurilemmoma in the past. More recently, a distinction between neurofibroma and schwannoma has been made. Although both tumors arise from Schwann cells, certain gross, microscopic, and clinical features help distinguish the two. Growing evidence also suggests that they arise via distinct pathogenic mechanisms.[29,30] Neurofibromas typically encase involved nerve roots, whereas schwannomas commonly displace the nerve roots because of their asymmetric growth. The plexiform neurofibroma is

associated with type 1 neurofibromatosis, and the presence of multiple tumors helps establish the diagnosis of this genetic condition. In contrast, schwannoma is associated with type 2 neurofibromatosis. Patients with type 1 neurofibromatosis may be at risk for malignant tumor transformation following radiotherapy.[31,32] Nerve sheath tumors are usually solitary and may occur in any section of the spinal canal. They are evenly distributed in the cervical, thoracic, and lumbar regions; they are least common in the sacrum. They occur in men and women with equal frequency and are most commonly diagnosed in the fourth through sixth decades of life. Most of these tumors are completely intradural, although 10% to 15% may have an extradural component as well (the so-called dumbbell tumors). Most nerve sheath tumors are benign, well-encapsulated lesions that are amenable to total surgical excision. The rare malignant nerve sheath tumors have a natural history similar to soft tissue sarcomas, and they should be treated as such.[33,34]

Miscellaneous Neoplasms

Unusual intradural-extramedullary tumors include lipomas, dermoids, and epidermoid tumors. They are typically benign and amenable to complete resection. Even if incompletely excised, recurrences are usually slow.

Extradural Tumors

Most extradural tumors are metastatic, and the presentation and management of these is discussed in Chapters 102. A variety of primary bone and soft tissue tumors may arise from an extradural location and involve the spinal canal. Bone tumors include osteosarcoma, chordomas, chondrosarcoma, and Ewing sarcoma. Soft tissue tumors include soft tissue sarcomas, including malignant nerve sheath tumors, lymphomas, and neuroblastomas. These tumors and their management are discussed in Chapters 85 (lymphoma), 92 (neuroblastoma), 94 (soft tissue sarcoma), 95 (osteosarcoma/chordoma), and 96 (Ewing tumor).

PROGNOSTIC FACTORS

The major prognostic factors in patients with primary spinal canal tumors are tumor type and grade, tumor extent and location, patient age, and presenting neurologic function. Treatment-related factors that influence the outcome include tumor resectability and the use of radiation therapy for certain tumor types. Many of these factors are interdependent. For example, ependymomas occur most frequently in the distal spinal canal and are more often resectable than astrocytic tumors.

Milano et al analyzed 664 patients with spinal cord astrocytomas and 1,057 patients with spinal cord ependymomas using the Surveillance, Epidemiology, and End Results database. In this largest study to date on prognostic factors for long-term outcome, lower grade, younger age, and surgical resection were associated with significantly better overall survival and cause-specific survival for both astrocytomas and ependymomas. Radiotherapy was associated with worse cause-specific survival, but this is likely because of adverse selection bias. The 5-year overall survival of grades 1, 2, 3, and 4 astrocytomas was 82%, 70%, 28%, and 14%, and the 5-year cause-specific survival was 89%, 77%, 36%, and 20%, respectively. The 5-year overall survival of grades 1, 2, and 3 ependymomas was 92%, 97%, and 58% and the 5-year cause-specific survival was 100%, 98%, and 64%, respectively.[35] Weber et al analyzed the long-term outcomes of 183 patients with spinal myxopapillary ependymomas from a pooled database of the Rare Cancer Network and the MD Anderson Cancer Center and reported 10-year overall survival of 92% and 10-year progression-free survival of 61%. Tumor recurrence occurred in 32% of patients, and 85% of the recurrences were local. On multivariate analysis, older age (≥36), adjuvant radiation therapy, and gross total resection were associated with improved local control and progression-free survival.[36]

Several investigators have reported that patients with cervical spinal tumors have a worse survival and neurologic outcome than patients with more caudal tumors.[37-40] Guidetti et al stated that patients with cervical lesions had a higher surgical risk and complication rate, which made thorough resection of tumors in this location difficult and sometimes inadvisable.[40] In a series of 62 patients with exclusively intramedullary ependymomas, patients with high cervical presentations (above C5) accounted for four of six postoperative deaths because of apneic respiratory complications.[38] In the Mallinckrodt Institute of Radiology experience,

Garcia reported that the primary tumor location was the most important prognostic feature. It was suggested that a greater concentration of function per unit volume of the upper spinal cord compared with that of the cauda equina accounted for the worst neurologic outcome and survival in patients with rostral tumors.[39] In these studies, tumors affecting the cervical spinal cord were more likely to be astrocytomas, and tumors in the caudal spinal cord, filum terminale, or cauda equina were more likely to be ependymomas. The anatomic dependence of various tumor types may also contribute to the better prognosis seen in patients with tumors of the lower spinal canal.

Extensive involvement of the spinal cord with an ependymoma is associated with a worse outcome. Linstadt et al reported a 93% 10-year disease-specific survival rate with localized ependymoma compared with 50% for patients with diffuse tumors.[41] Extensive tumors have a 50% local failure rate after surgery and radiation therapy, compared with only 20% for limited disease (one to three vertebral body segments).[42] However, the extent of disease has not been a prognostic factor in other series.[43]

Neurologic function at diagnosis is an important clinical prognostic factor. In general, the fewer the symptoms and the better the neurologic function at presentation, the greater the likelihood the tumor will be controlled with fewer long-term adverse neurologic sequelae. Poor neurologic function in patients with spinal cord tumors is often attributable to the disease process and a prolonged delay in diagnosis rather than the effect of surgery or radiation therapy.[38,40,44]

GENERAL MANAGEMENT

Figure 43.5 is a treatment algorithm for intradural masses confirmed by MRI or CT.

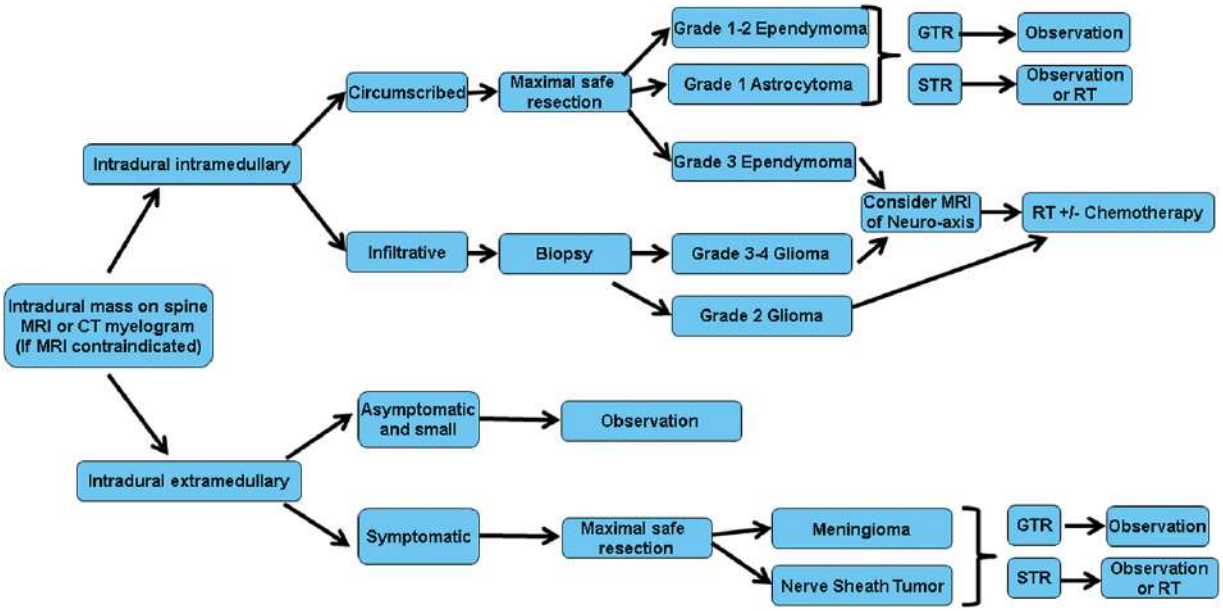


FIGURE 43.5 Intradural tumor treatment algorithm. CT, computed tomography; GTR, gross tumor resection; MRI, magnetic resonance imaging; RT, radiotherapy; STR, subtotal resection.

SURGICAL MANAGEMENT

Intramedullary Tumors

Intramedullary tumors, most of which are astrocytomas and ependymomas, present a surgical challenge. Complete surgical excision is the treatment of choice if it can be achieved without compromising neurologic function. Ependymomas are more frequently amenable to gross total excision than are astrocytomas.[21,40] Myxopapillary ependymomas most commonly involve the cauda equina and are less aggressive than other ependymomas, though they have been reported to seed the CSF.[45-49] Encapsulated myxopapillary tumors of the cauda equina are frequently amenable to complete en bloc excision, and the recurrence rate is very low. Unencapsulated or adherent tumors are often removed piecemeal and are associated with a high local recurrence rate after surgery alone, and adjuvant radiation therapy should be considered.[42,49-51]

Complete resection of intramedullary tumors with preservation of neurologic function was not possible until 1940, when Greenwood introduced the bipolar coagulation forceps. Since then, other technological advancements have emerged, including the dissecting microscope, intraoperative ultrasound, ultrasonic aspirator, contact laser scalpel, and

intraoperative neurophysiologic monitoring. These modern surgical techniques have increased the complete resectability of intramedullary tumors while minimizing neurologic injury.[52-55]

Intraoperative ultrasonography is used to localize the lesion, define its extent, and assess the progress of tumor resection.[56] The ultrasonic aspirator allows removal of tissue fragments from within 1 mm of the vibrating tip, permitting dissection immediately adjacent to vital neural tissue.[57] The contact laser scalpel only delivers thermal energy to tissue upon direct contact, and the laser beam resides entirely within a coated sapphire crystal probe tip. It provides precise dissection of tumor with little mechanical or thermal injury to normal spinal cord parenchyma.[58]

Intraoperative neurophysiologic monitoring is considered standard of care for resection of intramedullary tumors. It is dependent on two key components: somatosensory-evoked potentials (SEPs) and motor-evoked potentials (MEPs). SEPs are monitored continuously during the incision of the dorsal midline of the spinal cord to avoid injuring the dorsal column, as the cord anatomy is often distorted by the tumor. MEPs are monitored once the surgeon starts to dissect the tumor to avoid irreversible damage to the corticospinal tract. MEPs should be monitored using a combination of epidural electrodes (D waves) and signals from limb muscle. Typically, a decrement of 50% or more of D-wave amplitude is considered a major indication to stop surgery.[59] Sala et al reported that the use of intraoperative neurophysiologic monitoring during resection of intramedullary tumors significantly improved long-term ambulatory status as compared to historical controls.[60]

The risk of paralysis after surgery is <1% of patients with minimal or no preoperative neurologic deficits but may be much higher for those who present with more substantial deficits. Approximately one-third of patients will develop temporary motor deficits after surgery, and most will have at least some postoperative deterioration in neurologic status.[61,62] If complete excision of low-grade spinal cord tumors is achieved, the local recurrence rate is low and prognosis is excellent without additional adjuvant therapy. In patients who recur, tumor regrowth is often slow and second resection may be possible.[22,63-65]

Intradural-Extramedullary Tumors

The treatment of choice for most tumors in this location is maximal surgical excision with preservation of neurologic function. Most benign nerve sheath tumors can be completely resected with low risk of recurrence. In contrast, complete resection of malignant peripheral nerve sheath tumor is difficult, and local recurrence is high and typically occurs between 7 and 15 months after surgery. For spinal meningioma, local recurrence is low after Simpson grade I resection but can be as high as 30% after Simpson grade II resection with an average time of 12 years after surgery. Thus, Simpson grade I resection is preferred for spinal meningioma if attainable.[66-68]

CHEMOTHERAPY

The reported use of chemotherapy for primary spinal canal tumors is limited. Outside a clinical trial, chemotherapy is often reserved for patients with progression of disease following surgery and radiotherapy with no other treatment options. Combined with the low incidence of the disease, most studies are retrospective with very few patients, which limits any definitive conclusion regarding their efficacy. The use of chemotherapy for spinal canal tumors is often extrapolated based on the experience for intracranial tumors. However, such assumption requires further validation as the underlying oncogenesis and biologic pathways may be different between the two entities.[69]

Platinum and etoposide are generally considered the most active agents for ependymomas. In the setting of recurrent ependymoma, platinum-based chemotherapy has been shown to produce higher response rates than nitrosourea-based chemotherapy, but most patients in the studies had intracranial ependymomas.[70,71] In a prospective phase II study, 10 consecutive patients with recurrent cellular spinal cord ependymomas were treated with oral etoposide. Two patients had partial responses, and five patients had stable disease. The median overall survival was 17.5 months.[72]

Temozolomide is an attractive agent for primary spinal cord glioma, given its success in treating intracranial astrocytoma.[73] Kim et al reported their experience of treating two patients with primary spinal cord glioblastoma multiforme with concurrent radiotherapy and temozolomide followed by adjuvant temozolomide. The two patients survived 12 and 16

months, respectively, in contrast with a median survival time of 9 months in other reports.[74] Chamberlain reported a series of 22 patients with recurrent WHO grade II glioma treated with temozolomide. Overall, there were 18% partial response and 55% with stable disease. The median survival was 23 months, and progression-free survival at 2 years was 27%.[75]

For young children, especially those <3 years of age, there is an even greater interest in identifying effective and minimally toxic chemotherapy to delay or eliminate radiation therapy. There are two prospective cooperative group trials that have included children with primary spinal cord astrocytomas. In one clinical trial conducted by the French Society of Pediatric Oncology, eight children with unresectable or recurrent intramedullary low-grade gliomas were treated with a planned 16-month course of carboplatin, procarbazine, vincristine, cyclophosphamide, etoposide, and cisplatin. Seven of the patients had a clinical or radiographic response to the chemotherapy. Five of the patients remained progression free, with a follow-up ranging from 16 to 59 months.[76] In the Children's Cancer Group 945 trial, 13 children with high-grade astrocytic spinal cord neoplasms were assigned to receive two cycles of "8-drugs-in-1-day" chemotherapy before radiation therapy, then eight additional cycles thereafter. At 5 years, 46% of the children had no progression and 54% were alive. The authors argued that more intensive therapy was necessary.[77] Mora et al reported a small but thought-provoking study of three infants with spinal cord astrocytomas (WHO grade 2 or 3) treated with irinotecan and cisplatin. All three infants had subtotal resection and progressed on conventional carboplatin-based chemotherapy. After switching to irinotecan and cisplatin, all three patients had remarkable radiologic and clinical response. At the time of the last follow-up, they had remained in remission at 12, 20, and 48 months after diagnosis. The authors hypothesized that irinotecan and cisplatin may provide synergistic effect without overlapping toxicities.[78] A recent phase II Children's Oncology Group clinical trial (COG-ACNS0423) treated pediatric patients with high-grade glioma with adjuvant radiation and concurrent temozolomide followed by additional temozolomide and lomustine chemotherapy, which included 5% of spinal high-grade astrocytomas. The study demonstrated improved event-free survival and overall survival as compared to historical controls of similar regimen without lomustine.[79]

RADIATION THERAPY

There are currently no randomized controlled trials to guide the role of radiation therapy for primary spinal canal tumors. Clinical use of postoperative radiation therapy is generally guided by patterns of failure and the prevailing attitude of many radiation centers.[80] Patients with completely resected low-grade astrocytomas and ependymomas typically have an excellent prognosis, with local failure rates of <10% without additional therapy.[68,81-83] Most centers do not advocate routine use of adjuvant radiation therapy in this setting, but long-term follow-up is indicated as late failures can occur.

In contrast, adjuvant radiation therapy after incomplete resection or piecemeal excision of low-grade ependymomas and astrocytomas is supported by retrospective analyses. Guidetti et al first reported a beneficial outcome in patients receiving radiation therapy after an incomplete excision of an ependymoma.[40] Piecemeal removal of ependymoma in the region of the conus medullaris, cauda equina, and filum terminale (most commonly myxopapillary ependymoma) has high local failure rate ranging from 20% to 43%. Adjuvant radiation therapy in these patients after piecemeal excision produces a similar local recurrence rate equal to that of patients undergoing gross total resection.[42,49,51,84] The long-term outcome of 183 spinal myxopapillary ependymomas from Weber et al showed adjuvant radiation therapy improved 10-year progression-free survival from <40% to 70%. The authors advocated more liberal use of adjuvant radiation therapy for patients with myxopapillary ependymoma with subtotal resection, piecemeal resection, or questionable gross total resection.[36] In a multi-institutional series, adjuvant radiation therapy significantly improved progression-free survival in the 40 patients with low- and intermediate-grade astrocytomas.[21] After adjuvant radiotherapy, the cumulative incidence of local failure ranges from approximately 20% for low-grade ependymoma to 40% for low-grade astrocytoma.[80]

Nonetheless, there are clinical circumstances in which careful follow-up after incomplete resection is appropriate, with a second surgery or radiation therapy considered at the time of progression or recurrence. Radiation therapy of the spine in a child may produce a spinal deformity (ie, scoliosis or kyphosis) because of retardation of bone growth from damage to

epiphyseal plates of the vertebral bodies as well as soft tissue fibrosis and contracture.[85] Most spinal cord tumors in young children are either low-grade astrocytomas or well-differentiated ependymomas that have a very low growth rate. Delaying radiation therapy until recurrence or tumor progression may allow the child to grow at a normal rate for several years before receiving radiation therapy. Constantini et al reported a series of 164 patients younger than 21 years of age treated with radical surgery alone without adjuvant radiotherapy. Gross total resection or subtotal resection was achieved in 77% and 20% of patients, respectively. The 3-month neurologic function was 60% stable, 16% improved, and 24% deteriorated compared with preoperative function. The 5-year progression-free survival rate for low-grade and high-grade tumors was 78% and 30%, respectively.[86]

The prognosis of high-grade astrocytomas and ependymomas is dismal, and multimodality treatment is recommended, ideally on a clinical trial. Adjuvant radiation therapy is routinely recommended, regardless of the extent of resection. The role of concurrent and adjuvant chemotherapy for high-grade intramedullary astrocytoma remains inconclusive as discussed earlier. Despite aggressive treatments, few patients with high-grade astrocytomas survive beyond 2 years.[80,87] As with intracranial high-grade glioma, novel therapies beyond traditional radiotherapy and cytotoxic chemotherapy are desperately needed.

Relapse can occur years after treatment and is predominantly local. In a series of 37 spinal ependymomas treated with adjuvant radiotherapy, more than 50% of failures developed 5 years after diagnosis, and the extent of surgical resection correlated with time to progression.[88] These findings were confirmed in another series of patients with spinal myxopapillary ependymoma, where Chao et al reported a median time to recurrence of 7.7 years.[89]

The prognosis is excellent for most patients with intradural-extramedullary tumors, which rarely recur after total excision. However, subtotally resected meningiomas may recur late after surgery.[90] Some investigators have advocated postoperative radiation therapy using either conventional fractionated external-beam radiotherapy or SRS.[91,92] Data supporting the routine use of radiation therapy in the management of patients with nerve sheath tumors, vascular malformations, lipomas, hemangiomas, teratomas, and dermoids are limited.

Radiation Therapy Techniques

Target Volume

Historically, it had been recommended that superior and inferior field borders encompass two vertebral bodies above and below a tumor defined by myelography, with the width of the field approximated between the tips of the lateral processes of the vertebral bodies. With the advancement of CT simulation and MRI fusion, the gross tumor volume (GTV) can be more accurately defined and smaller margins may be used. For low-grade astrocytomas or ependymomas, a clinical target volume (CTV) margin of 0.5 to 1 cm is appropriate. The CTV should encompass the preoperative GTV plus any associated intratumoral cysts. It is not necessary to include an intramedullary syrinx that extends above or below the primary tumor unless there is radiographic or surgical evidence of tumor extension to these regions. Planning treatment volume (PTV) margins of 0.5 cm or less may be used to account for setup error, with smaller PTV margins necessitating adequate patient immobilization and optimal daily localization techniques (orthogonal kilovoltage imaging, cone-beam CT, etc).

High-grade astrocytomas and ependymomas can be more infiltrative, and a larger CTV margin of at least 1.5 cm craniocaudally should be used. Merchant et al described a diffuse failure pattern in children with high-grade gliomas shortly after completing radiation therapy, suggesting that the tumor was not adequately covered in the irradiated volume and the need for larger CTV margins of 1.5 cm.[93] The intervertebral foramina should be included within the CTV if tumor extension is suspected.

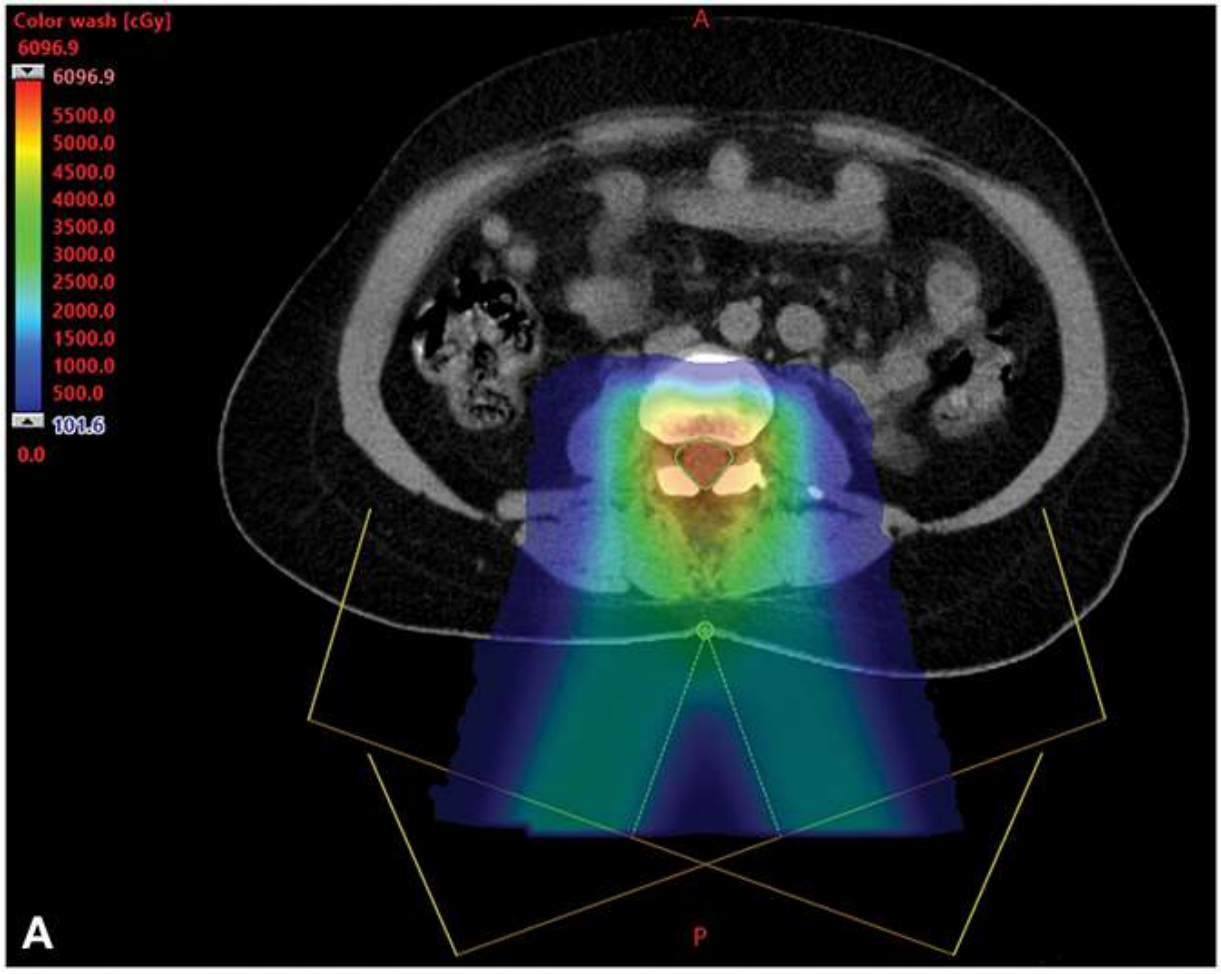
For myxopapillary ependymomas involving the conus, a 1.5-cm CTV margin cephalad and caudad to the GTV is used, but not beyond the thecal sac, which is typically at the level of S2-3. If the cauda equina is involved, the CTV should extend inferiorly to encompass the entire thecal sac, with the volume widened at the sacroiliac joints to ensure adequate coverage of the meningeal sleeves in the intervertebral foramina. Failure to adequately encompass the thecal sac has been associated with an increased rate of treatment failure.[84]

Craniospinal or spinal axis irradiation is usually not indicated in the treatment of most spinal cord tumors; local failure accounts for most tumor recurrences.[21,39,41,42,82] However, neuraxis dissemination may be seen in

patients with anaplastic ependymomas,[94] malignant astrocytomas,[95,96] and myxopapillary ependymomas.[46,47] Craniospinal irradiation may be considered if there is evidence of leptomeningeal dissemination.

Radiation Technique

The majority of primary tumors of the spinal canal are now treated with intensity-modulated radiation therapy (IMRT) methods, which reduce normal tissue dose and improve target dose conformality compared to conventional 3D-field arrangements. For younger patients, techniques utilizing proton beam radiation therapy are preferred to reduce dose to organs at risk even further and minimize secondary malignancy risk (Figure 43.6).[97]


Color wash [cGy]
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0.0
A
A
P

FIGURE 43.6 Treatment planning for spinal cord tumors. This is a 67-year-old woman with a history of spinal ependymoma who underwent gross total resection and had subsequent disease progression treated with intensity-modulated proton therapy (IMPT), 54 GyE in 30

fractions to lower thoracic to upper sacral spine with protons. The clinical target volume is shown in green outline. A. Axial view showing the arrangement of the two posterior oblique proton beams. B. Sagittal view more clearly delineating the superoinferior extent of the target. Note the target conformality with IMPT and limited exit dose anteriorly into the bowel.

Radiation Dose

Low-grade astrocytomas and ependymomas should be irradiated to a total dose of 50.4 Gy, given in 1.8 Gy daily fractions. High-grade ependymomas or astrocytomas can be treated to a dose of 54 Gy with 1.8 Gy daily fractions.[80] Limited dose-response data exist for spinal cord tumors. In the Mallinckrodt series of 37 patients with primary spinal cord tumors, local control and survival were significantly better for those who received 40 Gy or higher.[39] Shaw et al reported that the local failure rate of ependymomas was 35% in patients receiving 50 Gy or less compared with only 20% in patients receiving more than 50 Gy.[42] However, doses beyond 50.4 Gy have not been shown to improve local control or survival.[41,96,98] In patients with evidence of CSF dissemination, craniospinal irradiation should be considered. Typical doses to the craniospinal axis range from 36 to 39.6 Gy, with a boost to sites of gross tumor to 50.4 to 54 Gy.

Stereotactic Radiosurgery

SRS provides the ability to deliver highly conformal, high-dose radiation in such a manner as to mitigate normal tissue injury while escalating dose to the target volume. Most spine SRS reports to date have focused on its use in the management of metastatic disease to the spine. In a recent review, Hsu et al found local control rates in excess of 80% in most series, with significant pain improvement in 43% to 97%.[99]

A few reports have also detailed spine SRS in the management of patients with intradural tumors. In the largest series reported to date, Gerszten et al treated 73 patients with benign intradural spinal tumors (meningioma, schwannoma, neurofibroma) using CyberKnife (Accuray Inc) spine SRS to doses ranging from 16 to 30 Gy in one to five fractions. At a median of 37 months follow-up, the local control rate was 98% and pain improved in 70% of meningiomas, 50% of schwannomas, and 0% of neurofibromas. Three patients developed radiotherapy-related spinal cord toxicity 5 to 13 months after treatment.[91] Overall radiographic response

rates for benign intradural tumors in the series reported to date range from 28% to 39%.[99]

Investigators from Stanford University have reported their experience treating spinal cord ependymomas and hemangioblastomas using spine SRS delivered with the CyberKnife system (Figure 43.7). In the earliest report, seven patients with 10 intramedullary spinal tumors (seven hemangioblastomas, three ependymomas) received spine SRS to a dose of 18 to 25 Gy in one to three fractions.[27] At a mean follow-up of 12 months, one ependymoma and two hemangioblastomas were smaller on follow-up imaging, with the remainder stable. No significant treatment-related complications were reported. In a follow-up study, Daly et al reported a 3-year actuarial control rate for 27 spinal hemangioblastomas treated with spine SRS to 18 to 25 Gy in two to three sessions. One patient developed a grade 2 foot drop 4 months after SRS, and two patients developed grade 1 sensory deficits.[100]

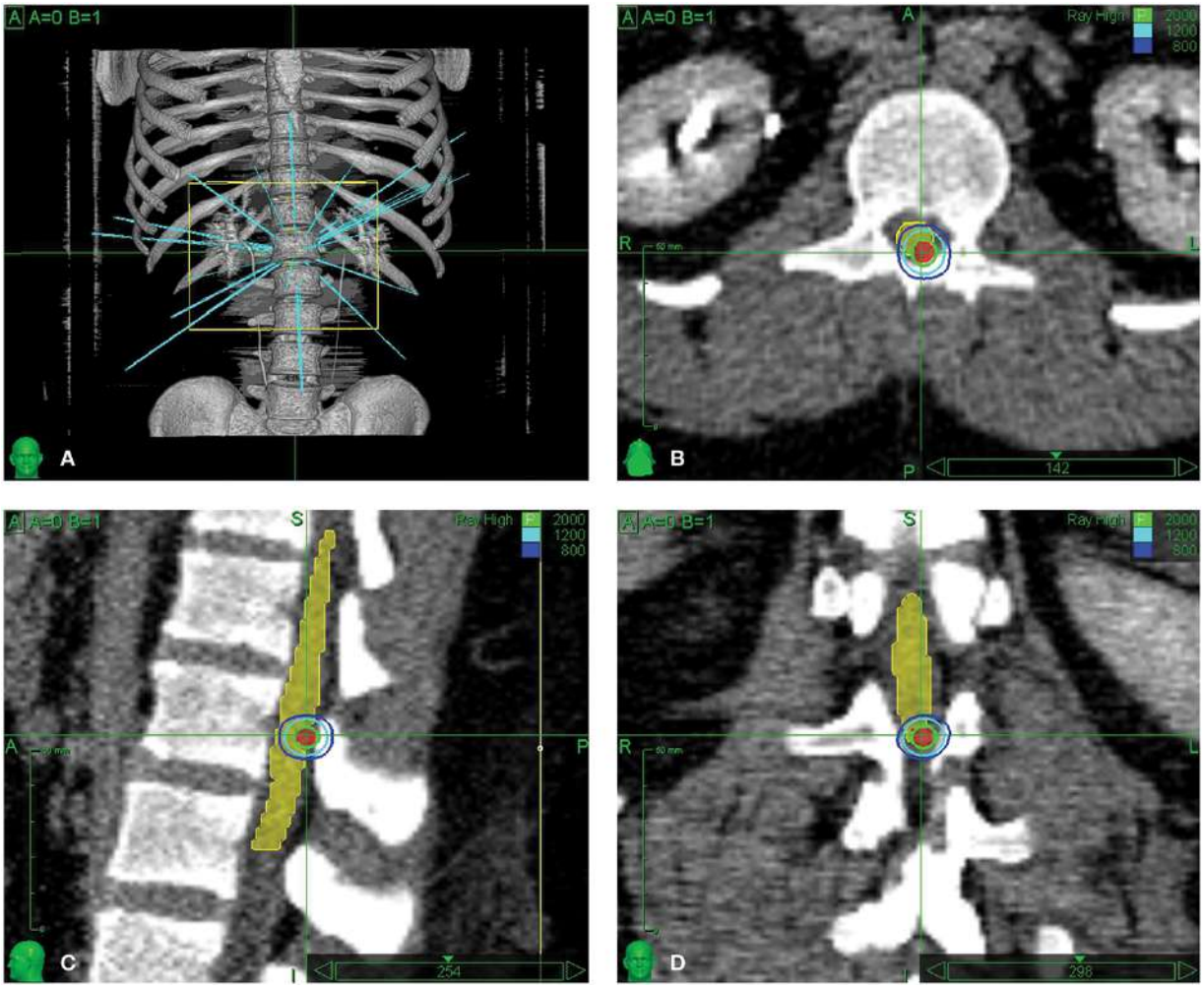

FIGURE 43.7 Stereotactic radiosurgery for an L1 hemangioblastoma. A single dose of 20 Gy was delivered with CyberKnife using 87 noncoplanar beams as shown in *blue*. As is typical of treatment delivery with this unit, the plan is nonisocentric. Gross tumor volume is shown in *solid red*, spinal cord in *solid yellow*. *Green line*, prescription dose of 20 Gy; *light blue line*, 12 Gy; *dark blue line*, 8 Gy. A. Three-dimensional representation of select noncoplanar beam paths. B. Axial isodose display reveals a sharp dose gradient between the prescription dose and the 12 and 8 Gy isodose lines. C. Sagittal isodose display. D. Coronal isodose display. (Courtesy of Scott Soltys, MD, and Megan Daly, MD, Stanford University Department of Radiation Oncology, Stanford, CA.)

Early results of spine SRS for intradural-extramedullary or intramedullary lesions are promising, and with the rapidly increasing availability of extracranial radiosurgery devices, SRS for these patients will no doubt increase in utilization. However, with such few reports and limited follow-up to date, caution certainly seems warranted, given the potential for

late toxicity in these patients with high rates of long-term survival. Issues related to spinal cord tolerance after spine SRS are discussed below.

Proton Therapy

Proton therapy is a form of particle radiation that provides very conformal radiation therapy with a lower integral dose than other forms of photon radiation therapy.[101] Due to its unique physical property, it can spare low-dose exposure to the normal tissues distal to the proton beam, which theoretically should translate to reduction of late toxicities, such as secondary malignancy and cardiac disease, especially for young adults or pediatric patients.[102-104] Amsbaugh et al reported a prospective case series of seven pediatric patients with spinal ependymomas treated with proton therapy (ranging from 45 to 54 cobalt gray equivalents). They showed proton therapy was well tolerated and dramatically reduced dose to all normal tissues anterior to the vertebral bodies as compared to photon therapy. After relatively short median follow-up of 26 months, local control, event-free survival, and overall survival were all 100%, and there was no grade 3 toxicity.[105] However, due to the relative rarity of the primary spinal tumors and the required long-term follow-up for end points such as secondary malignancy and cardiac disease, sufficient clinical data to support or refute the benefit of proton therapy for spinal tumors will unlikely to emerge in the near future. Individualized decision based on tumor location, patient age, and access to proton therapy will be required to consider treatment for proton therapy.

Spinal Cord Tolerance

A reversible myelopathy can occur within 2 to 6 months after radiation therapy. L'Hermitte sign, characterized by shock-like sensations radiating to the hands and feet when the neck is flexed, is the classic finding. It is believed that this phenomenon is related to transient demyelination of the treated length of the spinal cord.[106,107] This syndrome usually lasts a few weeks, and no therapy is required. It is not associated with chronic progressive myelitis.

Chronic, progressive, or delayed myelopathy can occur months to years after radiation therapy. The latency period of chronic myelopathy has been

reported to be bimodal, with peaks of incidence occurring at 13 and 29 months. The early peak may correspond to white matter injury with subsequent demyelination, and the latter peak may correspond to microvascular injury. Permanent myelopathy is characterized by progressive motor weakness, paresthesias, and loss of pain or temperature sensation. Patients ultimately lose bowel and bladder control and experience complete sensory and motor function loss.[108] Diagnosis of radiation myelopathy requires that the dominant neurologic abnormality be localized to a segment irradiated and other causes have been ruled out. MRI may assist in the diagnosis, with cord edema frequently being present in the early delayed phase. Within 8 months of the onset of symptoms, the T1-weighted images may show low intensity in the region of spinal cord injury, whereas the T2 image shows high intensity. The lesion may enhance with contrast. Late changes in patients with permanent delayed myelopathy may include atrophy.[109] Even with modern imaging, it may be difficult to determine whether neurologic deficits after radiotherapy are related to tumor progression or treatment-induced myelopathy.

The occurrence of chronic progressive myelopathy depends on the total dose, fraction size, volume, and region irradiated. Historically, the spinal cord has been limited to maximum doses of 45 to 50 Gy with fractionation schedules of 1.8 to 2 Gy/day. These estimates came from an era of inexact dose estimation with a bias toward reporting injury in highly selected populations.[110,111] More recently, data have been published from institutions that have treated large groups of patients in a systematic and reliable manner. The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) initiative comprehensively reviewed modern radiotherapy toxicity data and published guidelines on spinal cord tolerance.[112] For conventional external-beam radiation therapy at 1.8 to 2 Gy/day, a dose of 50, 60, and 69 Gy is associated with a 0.2%, 6%, and 50% rate of myelopathy, respectively. However, pediatric patients and patients receiving potentially neurotoxic chemotherapy may have decreased spinal cord tolerance, with reports of myelopathy at dose of 50 Gy or less.[113-115]

Dose-volume data for myelopathy after spine SRS are evolving. In a multi-institutional review of 1,075 patients treated with spine SRS principally for metastatic disease, the rate of spinal cord toxicity was 0.6%.[116] Data from the QUANTEC initiative indicate that the rate of

myelopathy will be <1%, with the maximum dose to the spinal cord limited to the equivalent of 13 Gy in a single fraction or 20 Gy in three fractions.[112] The most commonly employed dose constraint for single fraction SRS is to keep <10% of the spinal cord (defined as 3-6 mm above and below the target volume) to <10 Gy.[99] Intriguing data from investigators at Stanford University utilizing SRS for spinal hemangioblastoma suggest that spinal cord tolerance may be higher than predicted by conventional modeling.[100,117] Maximum cord dose delivered in two to three sessions in their series was an average of 22.7 Gy (range, 17.8-30.9 Gy) to small volumes, with only 1 of 24 treatments resulting in myelopathy. Such a phenomenon may at least in part be explained by preclinical experiments suggesting a dramatic length and partial volume effect to spinal cord tolerance after radiation. For example, in one animal study, the ED50 (dose at which 50% of animals developed limb paralysis) for single fraction full-thickness radiation to the spinal cord was 20.4 Gy for a 20-mm cord length, compared with 53.7 Gy for 4-mm and 87.8 Gy for 2-mm cord lengths.[118]

Both animal and human studies have demonstrated that irradiated spinal cord may recover at least partially over time. Animal experiments of reirradiation using Rhesus monkeys estimated cord recovery of 76%, 85%, and 100% at 1, 2, and 3 years, respectively.[119,120] In human studies, where reirradiation is at least 6 months after the initial radiation course, essentially no cases of myelopathy were observed when the cumulative 2-Gy equivalent doses are 60 Gy or less.[112,121]

CONCLUSION

Spinal canal tumors are relatively rare and consist of diverse histologic entities. Surgery remains the primary treatment modality, aided by gradual advances in neurosurgical techniques. Adjuvant IMRT is generally considered for incomplete resection, recurrent tumors, or high-grade tumors. New radiotherapy techniques such as proton beam therapy or SRS have shown promising potential to improve the therapeutic ratio. The role of chemotherapy is not clearly defined and is often extrapolated from intracranial counterparts. Continued long-term follow-up of clinical outcomes and innovation of novel approaches are essential for improving the management of spinal canal tumors.

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PART C

Head and Neck

CHAPTER 44

Adult Tumors of the Eye and Orbit

Shervin Tabrizi and Helen A. Shih

Primary tumors of the eye and orbit are rare. The American Cancer Society estimates that in 2024, there were be 3,320 new cases with 560 deaths from primary eye cancers.[1] Male-to-female incidence is similar. In adults, uveal melanoma is the most common primary intraocular cancer, followed by lymphoma. Metastases, or secondary intraocular tumors, are more common than primary tumors and typically come from breast or lung cancers.[2] Numerous other tumors such as optic pathway glioma, conjunctival tumors, and eyelid carcinomas also occur in the orbit. Radiation therapy (RT) is effective in the treatment of many of these tumors, can be delivered externally or by brachytherapy depending on the clinical situation, and can be used exclusively or in combination with other treatments, such as surgery and chemotherapy. A variety of external-beam RT (EBRT) techniques, including photon techniques such as intensity-modulated radiation therapy (IMRT), stereotactic radiotherapy (SRT), and proton therapy, have key roles in the management of these tumors, given the anatomic proximity of critical structures in this location. This chapter outlines the most relevant benign and malignant conditions of the eye and orbit in adults, with an emphasis on radiotherapeutic management. Because cancers originating in the eye require significant radiation dose for their control, exposure of normal tissue is often inevitable, with possible late toxicities that warrant close monitoring, multidisciplinary care, and an ongoing need for interventions to mitigate these toxicities.[3]

ANATOMY

The eye is not an exact sphere but rather a fused two-piece unit. The smaller, more curved anterior unit is the cornea and is linked to the larger unit called the sclera. The transparent corneal segment is typically about 8 mm in radius. The sclera constitutes the remainder of the globe, with a radius of approximately 12 mm. The cornea and sclera are connected by the limbus. The area opposite the pupil, the fundus, shows the characteristic pale optic disc or papilla, where vessels enter and optic nerve fibers exit the eye. Dimensions of the globe differ among adults by only 1-2 mm. The vertical measure, generally less than the horizontal distance, is about 24 mm in adults. The eye is made up of three coats or tunics, enclosing three transparent structures (Figure 44.1). The outermost layer is composed of the cornea and sclera. The middle layer consists of the choroid, ciliary body, and iris, collectively known as the uvea. The innermost is the retina, which receives blood supply from the vessels of the choroid as well as the retinal vessels. The lens is suspended centrally to the ciliary body by the suspensory ligament, made up of fine transparent fibers.

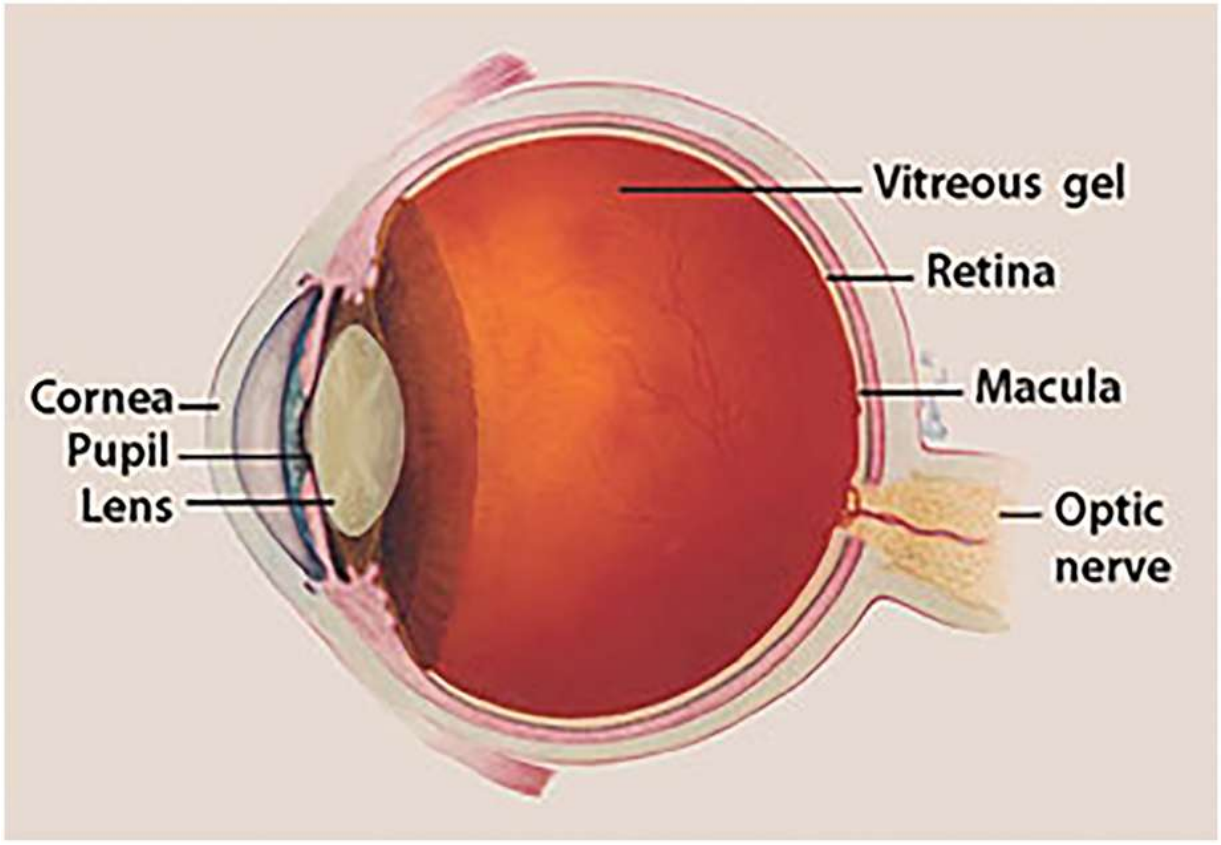

FIGURE 44.1 Normal eye anatomy. (Courtesy of National Eye Institute, National Institutes of Health (NEI/NIH).)

RADIATION TOLERANCE OF OCULAR STRUCTURES

Eyelid

Acute radiosensitivity of eyelid skin is comparable to the skin at other sites, and loss of eyelashes may occur at doses as low as 20 Gy using standard fractionation.[4] Late effects can include telangiectasia and atrophy. Xerophthalmia can result from doses as low as 24 to 26 Gy and may be the result of dysfunction of either the meibomian glands, lacrimal acinar cells, or both.[5] Significant xerophthalmia can cause corneal desiccation and pain. It is generally believed that smaller fraction sizes, longer treatment schedules, and smaller volumes will reduce late effects, but this must be weighed against the potential for ocular trauma if using shielding on a daily basis.[6] Optimum management of eyelid toxicity includes cleanliness, dressings for moist desquamation, healing time, and artificial tears to mitigate meibomian gland dysfunction.

Conjunctiva

Acute conjunctivitis is common with doses ≥30 Gy, and superimposed occasional bacterial or rarely viral infections may occur.[7] Conjunctivitis can be reduced by treating with an open eye with megavoltage equipment if the clinical situation permits. Treatment of acute conjunctivitis includes artificial tears to relieve symptoms and treatment of an underlying infection when indicated.

Lacrimal System

The lacrimal gland system includes the main lacrimal glands, accessory lacrimal glands, and the lacrimal duct system. Symptoms of dryness can occur if any of these structures receive radiation. The most concerning late effect is "dry eye syndrome," where patients can experience tearing, redness, discharge, foreign body sensation, blurred vision, and photophobia. Moderate-dose orbital RT (30-45 Gy) can cause dry eye syndrome 4 to 11 years after treatment, whereas higher doses (>57 Gy) can produce it in 9 to 10 months.[8] Lacrimal shielding should be used if it does not compromise tumor control. Similarly, if clinically feasible, shielding the accessory lacrimal glands may reduce toxicity if the main gland is irradiated. IMRT can help minimize risks of RT-induced xerophthalmia, and prophylactic nasolacrimal duct intubation with silicone tubing may be considered in high-risk patients.[9,10] Treatments available for RT-induced xerophthalmia include topical lubricants, moist chamber goggles, punctual occlusion with plugs, or tarsorrhaphy.

Cornea

Although RT can directly injure the cornea, most acute corneal toxicity results from loss of the tear film with secondary keratitis sicca. Punctate epithelial erosions are common after conventionally fractionated RT doses of 30 to 50 Gy.[11] They typically subside within several weeks but can persist for years. At higher doses, corneal edema (40-50 Gy) or perforation (60 Gy) may occur, causing pain, tearing, foreign body sensation, or reduced vision. Corneal toxicity can be reduced by using megavoltage equipment to reduce the surface dose or by using careful RT planning to minimize corneal

irradiation so long as tumor dose is not compromised. Commercially available eye shields may also be used, particularly for electron beam RT.[12] There are little published data on the management of corneal toxicity from RT. Close ophthalmologic follow-up is recommended, and topical treatment with steroids or antibiotics can be administered when indicated.

Iris

The iris is relatively radioresistant, and acute iritis is rare. Persistent iritis, with symptoms such as pain, red eye, and blurred vision, has been observed after hypofractionated RT doses of 30 to 40 Gy and after doses ≥70 Gy given with conventional fractionation.[13] A challenging late effect of the iris is neovascular glaucoma, where patients may present with ocular pain, headache, photophobia, decreased vision, and redness.[14] Risk factors include higher radiation dose, diabetes, vitreous hemorrhage, and retinal detachment. Whenever possible, techniques that spare the anterior chamber should be adopted. The primary treatments for iritis and neovascular glaucoma are topical steroids and cycloplegic drops, respectively. Laser panretinal photocoagulation or peripheral cryotherapy may prevent or delay the progression of glaucoma if performed early in the course of glaucoma development. However, in many cases, more aggressive intervention such as trabeculectomy may be required. Occasionally, progression to a blind, painful eye may necessitate enucleation. Intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy appears to be a promising option for the management of iris neovascularization associated with neovascular glaucoma.[15]

Lens

RT can lead to accelerated cataract formation, even at low dose, with the risk dependent on age at the time of treatment, total dose, and fractionation.[16,17] Hall estimated a 50% risk of cataract for 1-Gy exposure to the lens during childhood.[16] In adults, higher doses are associated with radiation-induced cataract: After 2.5 to 6.5 Gy, there is a 33% risk of progressive cataract with a latent period of 8 years, whereas after 6.51 to 11.5 Gy, there is a 66% risk with a latent period of 4 years.[17] Cataract risk can be reduced by using customized lens shields and lens-sparing

techniques or by using more fractionated RT schedules. IMRT may be used to reduce cataract risk by reducing overall lens dose. The corrective treatment for RT-induced cataract is surgery, which yields excellent results.

Retina

Radiation retinopathy is a late effect of RT that typically presents 6 months to 3 years after treatment, although cases have been reported as far as 15 years after therapy.[18] Patients may be asymptomatic or may complain of floaters or reduced visual acuity. Clinical signs include microaneurysms, telangiectasia, hard exudates, cotton-wool spots, and neovascularization. The threshold dose for retinal damage is 30 to 35 Gy. In a Cochrane database review of RT for macular degeneration, no retinopathy or optic nerve damage was reported in 1,154 patients treated with doses up to 24 Gy.[19] The risk of retinopathy increases dramatically when doses exceed 50 Gy using standard fractionation.[20] Incidence and severity also increase with coexistent diabetic retinopathy, hypertension, collagen vascular disease, simultaneous chemotherapy, and pregnancy.[21] The pathophysiology of radiation retinopathy is believed to involve radiation-induced loss of endothelial cells, leading to vascular closure, downstream ischemia, and vascular incompetence.[22] Several treatment options, including laser photocoagulation, intravitreal steroids, and anti-VEGF therapy, have been described, but currently, there is no standardized treatment approach for the management of radiation retinopathy. Local photocoagulation may delay progression of retinopathy and improve symptoms.[23-25] Intravitreal triamcinolone may reduce edema and improve vision in the short term, but with limited benefit to long-term vision outcomes.[26,27] Off-label intravitreal anti-VEGF therapy has been tested in several retrospective and prospective studies, which have confirmed tolerability and suggested benefits in reducing macular edema and potentially improving visual outcome. However, significant variability persists in reported outcomes of response to anti-VEGF therapy, and the optimal timing of initiation of therapy and dosing schedule remains a topic of ongoing investigation.[28-34]

Optic Nerve

Like the retina, the optic nerve manifests toxicity months or years after RT, with a peak incidence at 18 months.[35] Radiation-induced optic neuropathy (RION) has a variable presentation and is related to the nerve fibers most affected, usually causing visual field defects. In a review by investigators from the Mayo Clinic, the risk of RION was almost zero with conventionally fractionated doses ≤50 Gy and still rare with maximum dose <55 Gy. The risk of RION increases from 3% to 7% at 55 to 60 Gy and is substantial (>7%-20%) at doses >60 Gy.[36] Parsons and colleagues,[37] in a series of 131 patients (215 optic nerves) treated with RT for extracranial head and neck tumors, found no RION in nerves that received <59 Gy. Fraction size was of primary importance: In cases where >60 Gy was received, fraction size was more important than total dose in producing RION. The 15-year actuarial risk was 11% when the fraction size was <1.9 Gy compared with 47% when the fraction size was >1.9 Gy. A significant exception in the development of RION appears to exist for patients treated for pituitary tumors, where toxicity has been reported at doses as low as 46 Gy in 1.8-Gy fractions.[36] Similar relatively low risk of RION was seen with proton therapy in a retrospective series of 514 patients with cranial base chordomas or chondrosarcomas treated with mixed proton and photon therapy, with <1% rate of RION among 124 patients with optic nerves receiving <59 Gy (relative biological effectiveness [RBE]) versus 5.8% occurrence among 390 patients with optic nerves receiving ≥60 Gy (RBE).[38] Because there is no known effective therapy for RION, dose-sophisticated treatment planning should be implemented to minimize volume, total dose, and, especially, dose per fraction to the optic nerve.

MANAGEMENT OF BENIGN OCULAR DISEASES

Pterygium

Pterygium is a benign growth of fibrovascular tissue on the conjunctiva that can cause irritation, erythema of the cornea, and, in advanced cases, vision obstruction. The exact cause of pterygium is unknown, but it is associated with excessive exposure to wind, sunlight, or sand. It has also been postulated that ultraviolet light exposure may increase the risk of pterygium.[39] At present, no reliable medical treatment exists to reduce or even prevent pterygium progression. If symptoms are severe, the only

definitive treatment is surgical removal. Without adjuvant treatment, surgical resection alone carries recurrence rates of 20% to 80%.[39] Therefore, adjunctive measures are recommended, which can be broadly classified as medical methods, β-irradiation, and surgical methods. Intraoperative and postoperative mitomycin C are the most commonly used medical adjuncts, reducing recurrence rates to 3% to 37%.[40] However, topical chemotherapy is not commonly used out of concern for late complications, including scleral sclerosis, infectious scleritis, perforation, and endophthalmitis, all with consequences that can impair vision.[41] β-Irradiation has a historical role in the management of pterygium. In a prospective randomized study, 96 eyes with primary pterygium received β-irradiation with strontium-90 after resection or sham irradiation.[39] Local control was 93.2% for the irradiated group versus 33.3% for the sham radiation group. Like topical chemotherapy, however, β-irradiation has generally been abandoned due to the risk of sight-threatening complications, such as scleral necrosis, infectious scleritis, corneal perforation, and endophthalmitis.[42] Thus, this therapy is of historic interest. Surgical adjuvant therapy is the mainstay of management for primary and recurrent pterygium. Currently, conjunctival autografting is generally regarded as the procedure of choice because of its efficacy and long-term safety, with recurrence rates of 2% to 39% without the attendant sight-threatening complications of topical chemotherapy or β-irradiation.[43]

Choroidal Hemangiomas

Choroidal hemangiomas are benign vascular tumors of the choroid. Although probably congenital in all cases, they are frequently undetected until after the second decade of life and can have a wide range of clinical features and treatment options.[44] These tumors are characterized as either circumscribed or diffuse. Most circumscribed choroidal hemangiomas are noted first when they produce visual symptoms caused by accumulation of serous subretinal fluid, degenerative changes in the macula, or both. In contrast to circumscribed choroidal hemangiomas, the diffuse variety is larger and associated with Sturge-Weber syndrome, a neurologic disorder marked by a distinctive port-wine stain on the forehead, scalp, or around the eye. This stain is a birthmark caused by an overabundance of capillaries

near the surface of the skin. Blood vessels on the same side of the brain as the stain may also be affected. Diffuse tumors are usually diagnosed in young patients either because of the examination of the fundus prompted by a facial hemangioma (port-wine stain) or because of the visual impairment secondary to serous retinal detachment or hyperopic amblyopia (Figure 44.2). The clinical course of either form of choroidal hemangioma is highly variable, with visual impairment ranging from none to total blindness. Neither variety of choroidal hemangioma metastasizes or transforms to malignancy. Therefore, the primary indication for treatment is to prevent loss of visual acuity.

FIGURE 44.2 Diffuse choroidal hemangioma with exudative retinal detachment. (Reprinted from Kubicka-Trząska A, Kobylarz J, Romanowska-Dixon B. Ruthenium-106 plaque therapy for diffuse choroidal hemangioma in Sturge-Weber syndrome. *Case Rep Ophthalmol Med*. 2011;2011:785686. http://creativecommons.org/licenses/by/3.0/.)

Treatment options include laser photocoagulation, thermo therapy, photodynamic therapy, and RT. Photocoagulation is beneficial for circumscribed lesions, but diffuse lesions have a high recurrence rate and retinal damage is possible.[44] Low- to moderate-dose radiation using lens-sparing external-beam photon irradiation, episcleral plaque therapy, and proton beam therapy have all been used in the treatment of choroidal hemangioma.[45] Total doses of 18 to 30 Gy delivered in 10 to 18 fractions of external-beam photon RT can result in the partial flattening of the hemangioma, resorption of subretinal fluid, and reattachment of the retina within 6 to 12 months.[46] Heimann et al[46] reported no recurrence of subretinal fluid with a mean follow-up of 3.6 years. In another series with a follow-up of 66 months, Kivela et al[47] found that subretinal fluid had reaccumulated in only 1 of 12 patients treated, thus demonstrating response durability. In a series of 53 patients treated with IMRT to a mean dose of 21.6 Gy (range 21.6-42 Gy), Wang et al[48] reported resolution of subretinal fluid in all patients and resolution of exudative retinal detachment in 76.7% of patients. In very advanced cases with retinal detachment, a higher dose of 36 Gy in 1.8 Gy fractions appears to be efficacious, but larger series with longer follow-up are needed to reliably assess response durability and delayed side effects, including retinopathy and cataract formation.[46,47] Lens-sparing techniques, including three-dimensional conformal RT (3D-CRT) with computed tomography (CT) planning, should be considered to reduce the incidence of cataract formation.[49] Brachytherapy has also been used for choroidal hemangioma treatment, particularly for circumscribed lesions. This treatment usually achieves resolution of subretinal fluid and reattachment of the retina with preservation of pretreatment visual acuity.[50] Radiation dose varies with the isotope, but in a study using iodine-125 with target dose of 48 Gy to the apex of the lesion, tumor regression was noted in 8/8 cases treated.[50] Proton therapy can also be considered for choroidal hemangioma. On long-term follow-up in a series of 71 cases with circumscribed choroidal hemangioma treated with 20 Gy (RBE), retinal reattachment occurred in all cases, and a completely flat scar was obtained in 91.5%.[51] The main complications during the surveillance period were cataracts (28%) and radiation-induced maculopathy (8%). No cases of eyelid complications or neurovascular glaucoma were observed.

Capillary Hemangioma

Capillary hemangiomas are benign endothelial cell neoplasms that rarely occur on the eyelids or skin of the orbit. Retinal capillary hemangiomas may represent a component of the von Hippel-Lindau syndrome, and lesions of the face that occupy the distribution of the trigeminal nerve can be a component of Sturge-Weber syndrome. The natural history of these lesions is usually spontaneous regression over 3 to 4 years, making conservative management the treatment of choice.[52] Occasionally, however, lesions may be large enough to obstruct vision and amblyopia may occur. Treatment options then include corticosteroids, interferon α-2a, laser therapy, embolization, immunomodulators, surgery, and systemic propranolol.[53] Because of these many alternatives, RT in the management of capillary hemangiomas is primarily of historical interest, with original studies showing that doses in the 16 to 20 Gy range provide effective local control.[54]

Orbital Pseudotumor

Orbital pseudotumor is a rare inflammatory process that affects the soft tissue components of the orbit. Clinically, it presents in the fourth and fifth decades of life with signs and symptoms including proptosis, swelling, increased orbital pressure, and restricted ocular motion.[55] The diagnosis is based on history, imaging of the orbit, and pathologic examination of tissue in accessible lesions. Characteristic imaging features include extraocular muscle enlargement, optic nerve thickening, and inflammation of retrobulbar adipose tissue. Treatment options for orbital pseudotumor include corticosteroids, EBRT, immunotherapy, chemotherapy, and surgery. Corticosteroids are typically used as primary treatment.[56] RT is usually reserved for cases that are refractory to corticosteroid treatment. Matthiesen and colleagues[57] described 20 orbits treated with a median dose of 20 Gy and, at follow-up of 16.5 months, found improved symptoms and/or reduction of corticosteroid dose in 87.5%, with 56% able to discontinue steroid treatment completely. A systematic review of 19 studies with 241 patients reported significant heterogeneity in dose among studies, with a median total dose of 20 Gy (range 4-36 Gy), with response rates of 74% to 100%, and a median recurrence rate of 10%.[58] Based on these observations,

radiation appears to achieve durable control in orbital pseudotumor and is an effective strategy in patients who respond poorly to medical treatment.

Thyroid Eye Disease

Thyroid eye disease (TED), frequently termed *Graves ophthalmopathy*, is part of an autoimmune process that can affect the orbital and periorbital tissue, the thyroid gland, and, rarely, the pretibial skin or digits (thyroid acropathy).[59] Although the term *thyroid ophthalmopathy* is more general, the disease process is specifically an orbitopathy in which the orbital and periocular soft tissues are primarily affected with secondary effects on the eye. TED may compromise a patient's vision by causing diplopia, decreased ocular motion, exposure keratitis, or optic neuropathy. A variety of treatments exist, including thyroid hormone regulation, corticosteroids, EBRT, or surgical decompression.[60]

RT with moderate doses has historically been used in cases refractory to medical therapy, which are a minority of TED cases.[61] Abboud et al[62] reported symptom improvement in 87% of cases with doses of 20 Gy using standard fractionation. Numerous randomized controlled trials have tested orbital RT for TED, with heterogeneity among studies with respect to severity of TED on trial entry, radiation dose and fractionation, and inconsistent use of concurrent corticosteroids.[63-71] A further limitation of many of the randomized controlled trials is that they did not involve patients with sight-threatening ophthalmopathy and could not assess the role of radiation in this important subset.[72] Mourits et al[67] randomized 59 patients to either 20 Gy in 10 fractions to both orbits or sham RT and found improved globe motility and elevation, but no difference in change in lid fissure, soft tissue swelling, proptosis, or clinical activity score (a measure of disease activity and propensity to progress). The authors concluded that RT should be used only for motility impairment. Gorman et al[71] randomized 42 subjects to orbit RT to one orbit and sham RT to the other followed by the reverse therapy 6 months later. No clinically or statistically significant differences were observed at 6 months. At 12 months, muscle volume and proptosis were slightly improved in the orbit that was first irradiated. Prummel et al[70] conducted a trial where 88 patients with mild TED were randomly assigned to bilateral RT or sham RT. Radiation was effective in

improving motility and decreasing severe diplopia, but no differences in health-related quality of life were detected, although lack of complete quality of life data on 58% of subjects resulted in low power to detect a difference.

Retrospective studies suggest that RT may be effective for treating or preventing compressive optic neuropathy (CON). Shams and colleagues[73] compared 144 patients with TED who received steroids alone to 105 patients who received orbital RT and steroids. At an average follow-up of 3.2 years, the rate of CON was 17% in the steroid only group and 0% in the steroids and RT group. Gold and colleagues[74] reported on 104 patients with active TED and CON who received a steroid taper and RT and found that 94% did not require urgent decompression surgery. RT may also enable successful tapering or elimination of steroids in patients with TED.[75,76]

A 2022 report by the American Academy of Ophthalmology on the role of orbital radiation for TED concluded that despite a lack of definitive randomized data, the best available evidence currently suggests that orbital RT with or without steroids is effective in preventing CON, improving motility restriction, decreasing the clinical activity of TED, and potentially reducing steroid dose.[72] Orbital RT could therefore be considered for patients with TED, especially those with CON, those who are refractory to steroids, and those unable to reduce their steroid dose. Orbital RT is generally well tolerated, common side effects including dry eyes and cataracts.[76-79] Serious complications such as keratitis and retinopathy have been reported but are rare.[77,80] Radiation technique for TED usually involves treatment of both orbits with parallel-opposed lateral beams with low-energy (6-MV) photons, with 20 Gy in 10 fractions as a typical dose. A downward 5° tilt or use of half-beam block should be used to avoid direct irradiation of the contralateral lens.

Neovascular Age-Related Macular Degeneration

Neovascular age-related macular degeneration (nAMD) is a common condition affecting 8% of adults globally and is a leading cause of blindness.[81] The treatment for nAMD is long-term, repeated intravitreal injections of anti-VEGF therapy, but due to the costs and risks associated with long-term anti-VEGF therapy, there is interest in alternative treatments

to reduce the number of injections. RT has been tested as an approach to mitigate nAMD. The INTREPID study was a phase 2 double-masked, sham-controlled randomized trial of 230 patients treated with 16 Gy, 24 Gy, or sham SRT. SRT resulted in a 29% reduction in anti-VEGF therapy injections in the year following SRT.[82] The STAR trial was a large, multicenter follow-up trial that randomized 411 patients to 16-Gy SRT or sham SRT in a 2:1 ratio. On follow-up after 96 weeks, SRT was associated with a 22% reduction in the number of ranibizumab injections, reduction in macular central subfield thickness (due to less subretinal fluid), noninferior visual outcomes, and a higher rate of retinal microvascular abnormalities (35% vs 12%).[83] SRT could therefore be a viable option to reduce the need for anti-VEGF injections in nAMD.

Optic Nerve Sheath Meningioma

Optic nerve sheath meningiomas (ONSMs) are rare, usually benign, tumors that arise from the optic nerve sheath, represent 1% to 2% of all meningiomas, and are the second most common optic nerve tumor after optic nerve gliomas.[84] Patients typically present with slow and progressive vision loss.[85] Diagnosis can usually be made with contrast-enhanced magnetic resonance imaging, precluding the need for a surgical biopsy.[86] Without treatment, vision loss can progress in most patients, although close observation could be considered an initial strategy in asymptomatic patients.[85,86] RT is an effective treatment modality for preserving vision and preventing disease progression. In a series of 64 patients with ONSM managed with observation, surgery, RT alone, or combined surgery and RT, RT alone was associated with the best visual outcome and was the only group without a statistically significant decrease in vision over a mean follow-up of 150 months.[87] Surgery (with or without RT) was associated with a complication rate of >60% versus 33.3% with RT alone.[87] Conformal techniques for RT, such as IMRT or SRT, should be considered to minimize the risk of long-term toxicity in this patient population with an excellent prognosis. A dose of 50.4 to 54 Gy in conventional fractionation, below the tolerance of the optic nerve, is typically used.[88] Ratnayake et al[89] reported on long-term outcomes of 26 patients with ONSM treated with SRT to a median dose of 50.4 Gy in 28 fractions. At a median follow-up of 68

months, local control was 100% and visual acuity improved or remained stable in 77% of patients. Late toxicities included grade 1 dry eye in 12% of patients. One patient developed late grade 3 radiation retinopathy treated with an intravitreal VEGF inhibitor.[89] A systematic review and meta-analysis of 39 studies (736 eyes) evaluating the use of RT for ONSM found a local control rate of 97% with a mean follow-up at 46 months. IMRT, SRT, and proton therapy were associated with lower rates of complications compared to 3D-CRT.[88]

OCULAR AND ORBITAL MALIGNANT TUMORS

Ocular Metastases

Tumor metastases to the eye are more common than primary ocular tumors, with the uvea representing the most common site affected.[90] Shields and colleagues[2] described a comprehensive series of ocular metastases and found that within the uvea, 88% of metastases are to the choroid (Figure 44.3), followed by metastases to the iris (9%) and ciliary body (2%). This difference is hypothesized to reflect blood supply, which heavily favors the choroid as compared to the iris and ciliary body. The most common primary cancer sites for uveal metastasis in males were lung (40%), gastrointestinal (9%), and prostate (6%). The primary site was unknown at the time of presentation in 29% of males. In females, the most common sites were breast (68%) and lung (12%). Metastases can be either unilateral or bilateral. In a study of 264 patients with uveal metastases from breast cancer reported by Demirci and colleagues,[91] 62% of patients had unilateral metastasis at presentation. Patients with breast cancer metastatic to the uvea have survival rates of 65% at 1 year, 35% at 3 years, and 24% at 5 years.

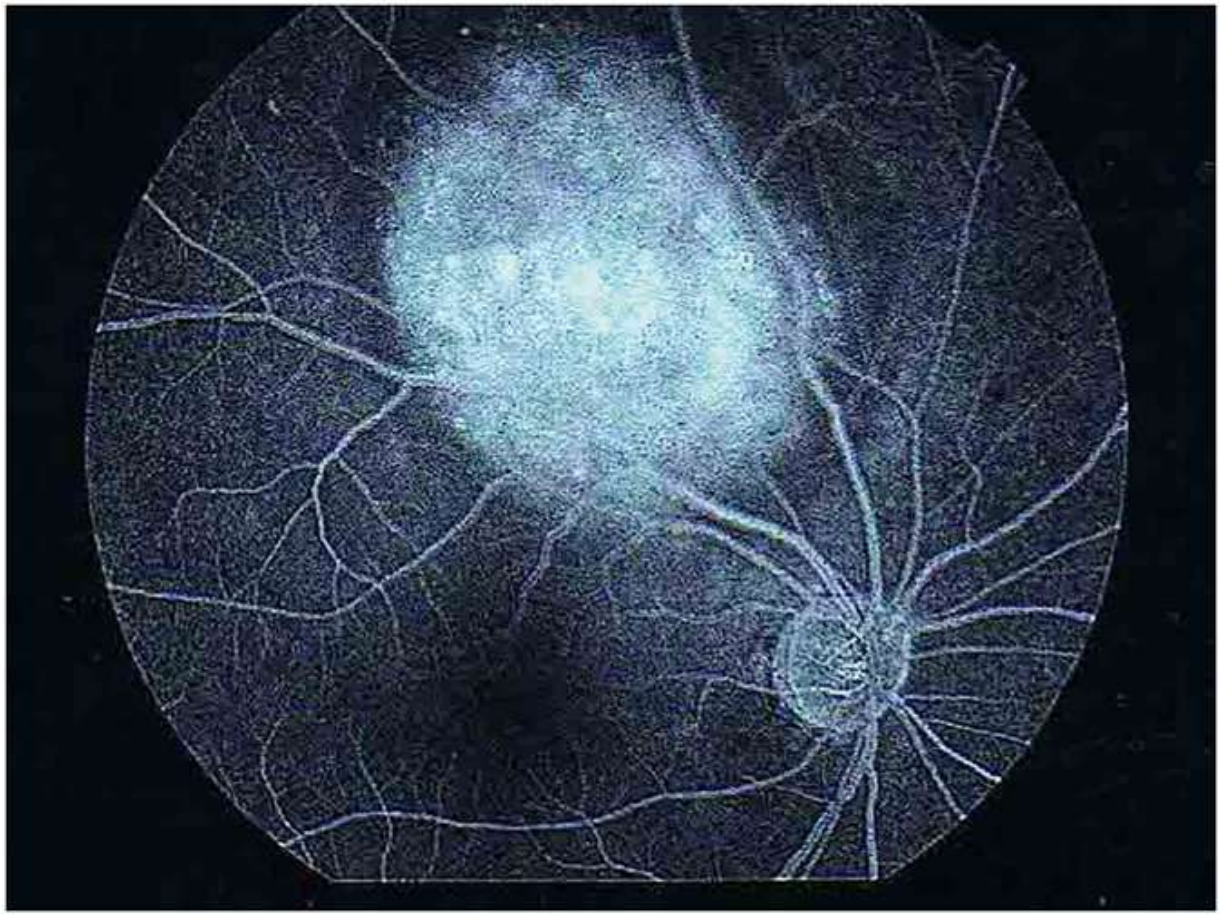

FIGURE 44.3 Fundus fluorescein angiography of choroidal metastasis from non–small cell lung cancer showing hyperfluorescence from the surface of the choroidal tumor in its late phase with the accumulation of subretinal fluid. (Reprinted from Singh A, Singh P, Sahni K, Shukla P, Shukla V, Pant NK. Non-small cell lung cancer presenting with choroidal metastasis as first sign and showing good response to chemotherapy alone: a case report. *J Med Case Rep*. 2010;4:185. http://creativecommons.org/licenses/by/2.0.)

Numerous treatment options exist for choroidal metastases, including systemic chemotherapy, hormonal therapy, EBRT, brachytherapy, and photodynamic therapy. Individualized treatment should be considered, taking into account disease extent and life expectancy, with the primary goal of maintaining visual acuity and quality of life. As systemic treatments for metastatic cancers improve, clinicians may be more frequently faced with the treatment of symptomatic choroidal metastases. For cases with multifocal or diffuse presentations, EBRT has been effective with doses in the range of 20 to 40 Gy. Rosset described 58 patients (88 eyes) treated with EBRT with a median dose of 35.5 Gy (range 20-53 Gy) in 10 to 30

fractions.[92] Various techniques were used, and lens sparing was achieved whenever possible. Visual acuity improved in 62% of patients, with significantly better results when doses >35.5 Gy were used. Complications included three cataracts, retinopathy in a single patient who underwent a biopsy, and one case of glaucoma from subretinal hemorrhage. In cases of unilateral disease undergoing bilateral radiation, the authors noted no cases of new contralateral lesions but did describe new contralateral lesions in three of 26 patients when unilateral technique was used. Although they recommended bilateral irradiation even for unilateral disease (Figure 44.4), unilateral treatment is favored with modern techniques that can easily avoid the contralateral side and make retreatment feasible if necessary. Kamran and colleagues[93] reported on a hypofractionated approach with proton beam irradiation in 77 patients (99 eyes) treated with a median dose of 20 Gy (RBE) in two fractions at Massachusetts General Hospital/Mass Eye and Ear. Tumor regression was observed in 100% of eyes, and local control was 94%. The rate of radiation vasculopathy, decreased visual acuity, or both was 46% at 6 months and 73% at 1 year. All six eyes with local recurrence were successfully retreated with the same regimen.

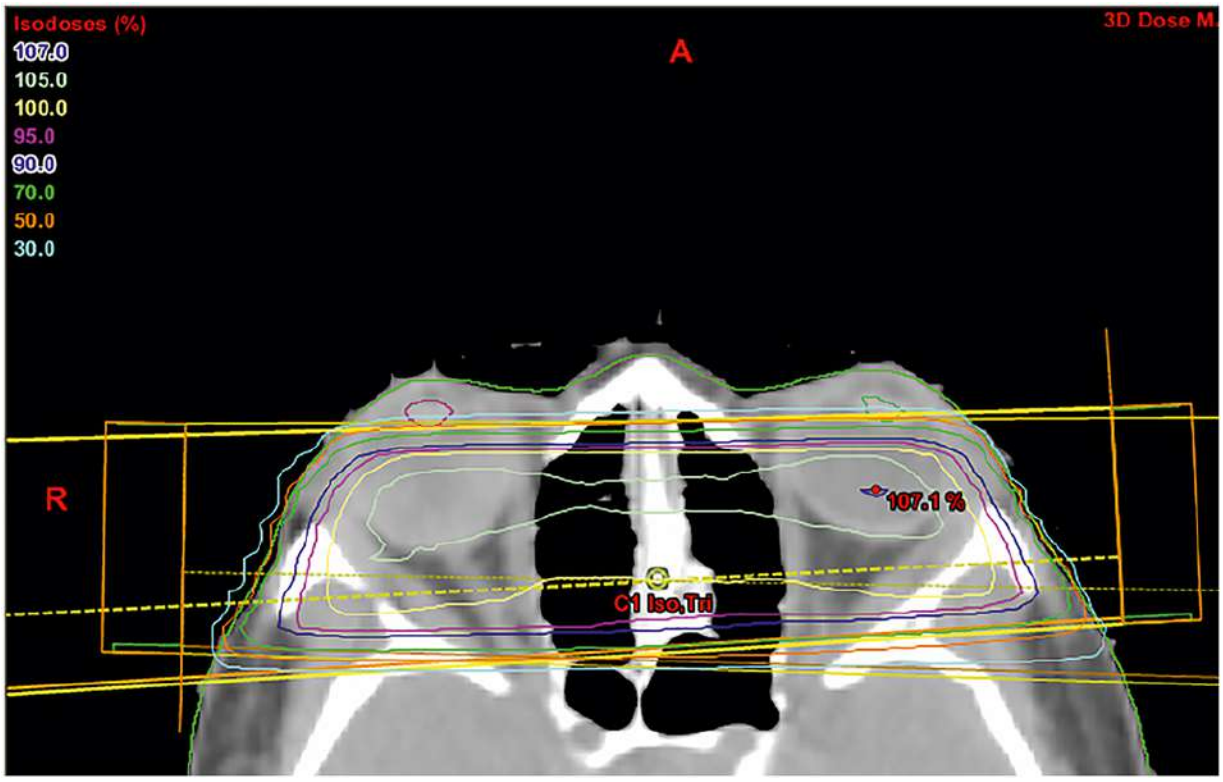

FIGURE 44.4 Bilateral radiation therapy for uveal metastases in a patient with widely metastatic lung cancer.

Plaque brachytherapy is usually reserved for solitary metastases. This modality offers precise, controlled radiation delivery to the eye over 3 to 4 days of treatment, an important consideration in uveal metastases because many patients have limited survival expectancy. Clinical factors to consider for plaque brachytherapy include the size and thickness of the lesion and the distance of the lesion from the optic nerve and fovea. Investigators from the Wills Eye Hospital studied 36 patients who received plaque brachytherapy as either primary or salvage treatment (after EBRT) for uveal metastases.[94] The mean duration of treatment was 86 hours, and mean doses to the apex and base of the tumor were 68.8 and 235.6 Gy, respectively. Tumor regression was documented in 94% of cases with a median follow-up of 11 months. Five of six cases where plaque brachytherapy was used after suboptimal response to EBRT were successfully salvaged. Complications from plaque brachytherapy are similar to those of EBRT, including dry eyes, radiation retinopathy, papillopathy, and cataracts. The investigators concluded that plaque brachytherapy is an effective, time-

efficient method for the treatment of selected solitary uveal metastases. Thus, both EBRT and plaque brachytherapy are effective therapies for uveal metastases, with the optimal treatment depending on the extent of intraocular disease, symptoms, and overall condition and prognosis of the patient. Close collaboration of ophthalmologists, radiation oncologists, and medical oncologists is imperative to tailor an appropriate treatment strategy for each patient.

Uveal Melanoma

Uveal melanomas represent <5% of all malignant melanomas, with an annual incidence of approximately five to six per million.[95-97] These tumors may arise from any of the three parts of the uvea and are sometimes referred to by their location, such as iris melanoma (Figure 44.5), ciliary body melanoma, or choroidal melanoma (Figure 44.6). True iris melanomas, originating from within the iris as opposed to originating elsewhere and invading the iris, are distinct in their etiology and prognosis, such that the other tumors are often referred to collectively as "posterior uveal melanomas." Incidence of uveal melanoma varies by race and ethnicity and is highest in the non-Hispanic White population.[98] Several epidemiologic and environmental risk factors have been associated with uveal melanoma, including fair skin, light eye color, increased tendency to sunburn, cumulative intense sun exposure, use of sunlamps, welding, and commercial cooking.[99-101] A study from the United Kingdom showed that 45% of patients were asymptomatic when their tumor was detected.[102] Advances in diagnostic techniques such as binocular indirect ophthalmoscopy, angiography, and B-scan ultrasonography have aided ocular oncologists in the evaluation and management of patients with uveal melanoma.[103]

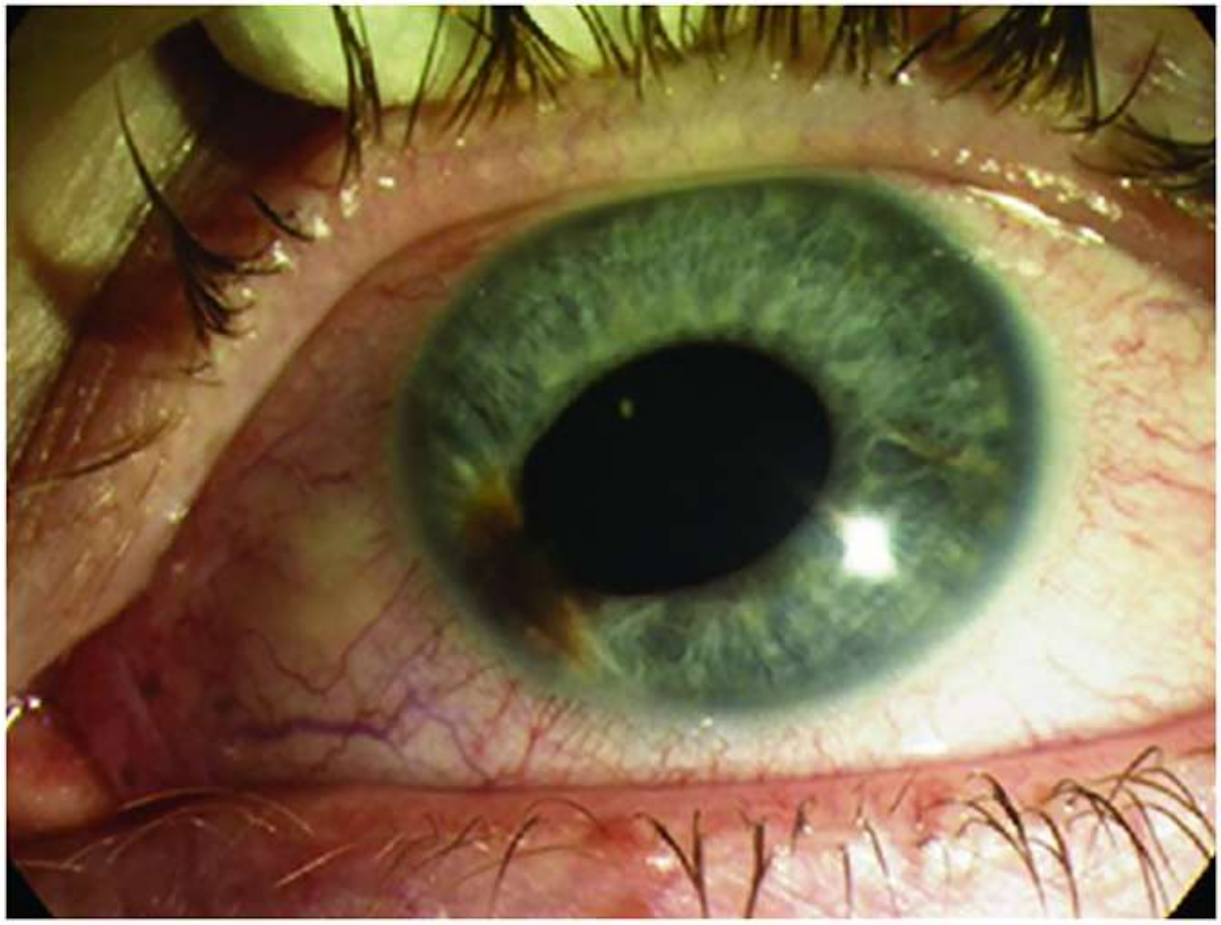

FIGURE 44.5 Iris melanoma located at the inferonasal aspect of the eye. (Reprinted from Papastefanou VP, Cohen VM. Uveal melanoma. *J Skin Cancer*. 2011;2011:573974. http://creativecommons.org/licenses/by/3.0/.)

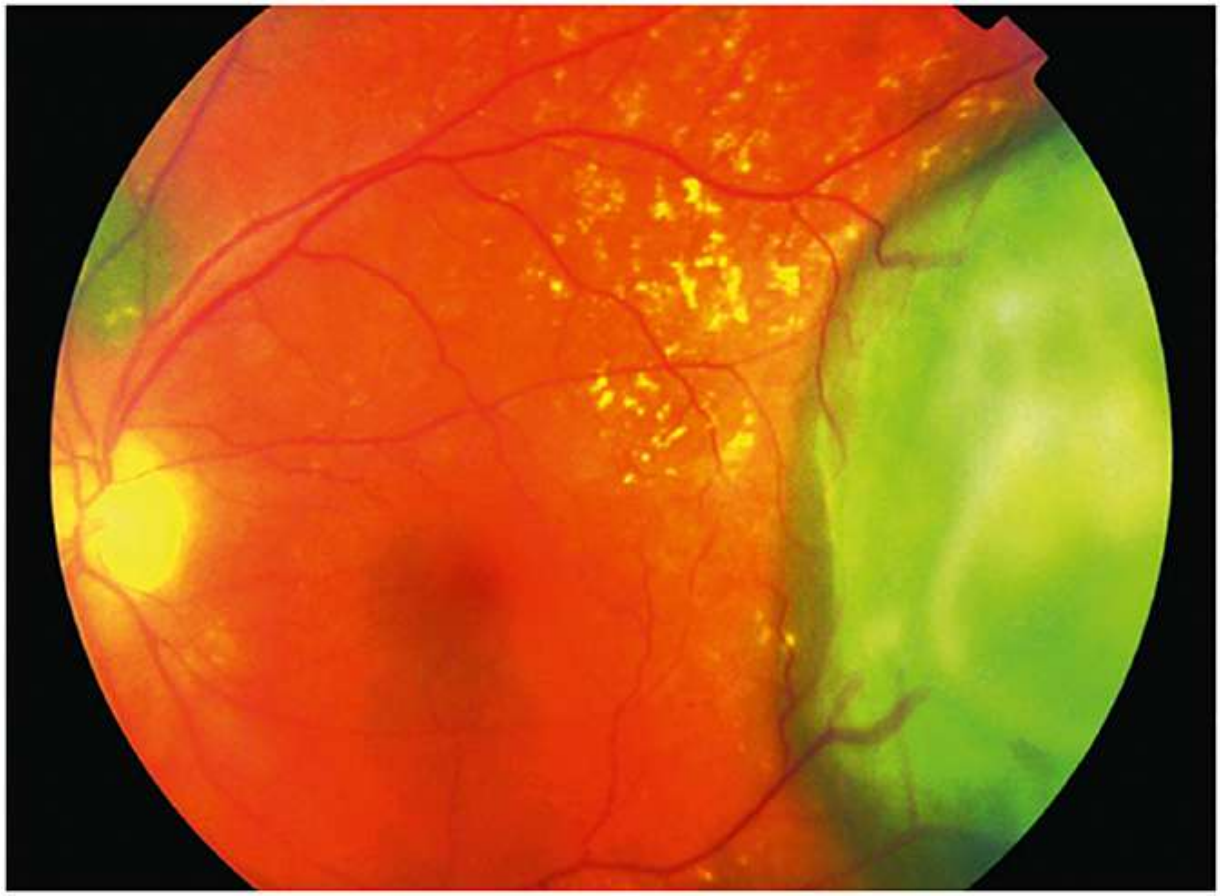

FIGURE 44.6 Typical choroidal melanoma with associated nonrhegmatogenous retinal detachment. (Reprinted from Papastefanou VP, Cohen VM. Uveal melanoma. *J Skin Cancer*. 2011;2011:573974. http://creativecommons.org/licenses/by/3.0/.)

Uveal melanomas are distinct from the more common cutaneous melanomas. Almost all uveal melanomas and most choroidal nevi have a mutation in a *GNA* family gene, such as *GNAQ* and *GNA11*.[104-106] Molecular characterization has led to the identification of subsets of uveal melanoma based on mutations, gene expression profiles (GEP), and other features. The Cancer Genome Atlas identified four subsets of uveal melanoma, characterized by distinct genetic and gene expression features and the presence or absence of inflammation.[107] Subsets A and B correspond to a favorable prognosis, GEP class 1, and gain of chromosome 6p, whereas subsets C and D correspond to a poor prognosis, GEP class 2, chromosome 3 monosomy, and chromosome 8q amplification (Table 44.1).[108,109] Commercially available tests can distinguish GEP class 1 versus class 2 tumors, and more recent versions further divide class 1 tumors into class 1A

and class 1B. The 5-year risk of metastasis is 2%, 21%, and 72% for GEP class 1A, class 1B, and class 2 tumors, respectively.[110-112] The 10-year risk of uveal melanoma metastasis was 25% in a series of 8,033 eyes, with significant variation based on tumor thickness (12% for 0-3.0 mm, 26% for 3.1-8.0 mm, 49% for >8.0 mm).[113] Risk of metastatic relapse appears to continue to rise with longer follow-up beyond 10 years.[114] Liver is the most common site of spread, and overall survival after the development of metastases is approximately 1 year.[115,116] Tebentafusp, a bispecific protein that binds the CD3 T-cell receptor and gp100 displayed on HLA-A*02:01, has demonstrated a survival benefit of 27% versus 18% at 3 years in patients with metastatic uveal melanoma who carry the HLA-A*02:01 allele.[117] But systemic therapy options are otherwise limited, and there is a need for more efficacious and widely applicable treatments.

TABLE 44.1 CHARACTERISTICS OF SUBSETS OF UVEAL MELANOMA

Subset	GEP Class	Chromosome 3	Chromosome 8q	Chromosome 6p	Metastatic Potential
A	Class 1	No change	No change	Partial or total gain	Low
B	Class 1	No change	Partial gain	Gain	Intermediate
C	Class 2	Monosomy	3 or more copies	No change	High
D	Class 2	Monosomy	3 or more copies	No change	High

Adapted by permission from *Nature*: Jager MJ, Shields CL, Cebulla CM, et al. Uveal melanoma. *Nat Rev Dis Primers*. 2020;6(1):24. Copyright © 2020 Springer Nature.

Several local treatment options exist for uveal melanoma. Most patients are treated with the goal of eradication of disease and long-term survival. Local tumor recurrence is associated with increased mortality.[118] Factors predictive of local recurrence include epithelioid cell type, large tumor size, and posterior tumor extension.[119] When possible, curative treatment should be sought with the goals of preserving the eye and preserving as much vision as possible with acceptable cosmesis. In patients with known metastatic disease, the main objective is to preserve vision and remove any threat of the eye becoming painful within the patient's life expectancy.

Many factors influence treatment selection, including tumor characteristics (size, location, and extent), secondary effects (such as the risk of cataracts), concurrent ocular disease (such as diabetic retinopathy), the patient's general health and life expectancy, and the cost and duration of the treatment.[120] In cases where preserving the eye and maintaining some useful vision are feasible, organ preservation therapy should be considered. RT, delivered either externally or by brachytherapy, has been instrumental as an organ-preserving modality in the primary management of uveal melanoma.

Observation

Indeterminate pigmented choroidal nevi are typically observed without treatment until growth is documented. The probability of malignancy can be estimated according to tumor thickness, serous retinal detachment, orange pigment, and symptoms.[121] Patients and clinicians can then make a combined decision on when to commence therapy after discussion of risks and benefits. The annual risk of malignant transformation of choroidal nevi is reported at approximately 1 in 9,000.[122]

Enucleation

Enucleation was traditionally the standard of care for choroidal melanoma since the late 19th century, but its effectiveness in improving survival has never been clearly demonstrated.[123] A study from the Helsinki University Hospital looked at the long-term prognosis of patients treated by enucleation between 1962 and 1981 and found death was attributable to melanoma in 61% of cases.[114] They also reported that cause-specific mortality (CSM) increased with longer follow-up. The 5-, 15-, 25-, and 35-year CSM was 31%, 45%, 49%, and 52%, respectively, thus illustrating that a substantial number of patients die of metastatic disease more than 5 years after enucleation. The desire to improve survival and preserve vision stimulated the development of alternative, organ-preserving therapies for uveal melanoma. Still, enucleation is required in a subset of patients, typically because the tumor is too extensive at presentation. General guidelines for enucleation include large tumor size (tumor diameter >20 mm; thickness >12 mm); involvement of the optic nerve; invasion of more

than 30% of the iris, ciliary body, or angle; retinal perforation; or poor general health of the patient.[120]

Endoresection

Transretinal endoresection is controversial, mainly because of fears of seeding tumor cells, but has been advocated for juxtapapillary tumors up to 10 mm in diameter.[121] The operation involves vitrectomy, tumor removal with a vitrector either via a retinotomy or after lifting a retinal flap, fluid-air exchange to drain any subretinal fluid, endolaser photocoagulation to destroy any residual tumor in the sclera and to achieve retinopexy, air-silicone exchange, and, if possible, adjunctive brachytherapy.[124] Given the seemingly heightened risk of tumor seeding with endoresection, some investigators have recommended preoperative stereotactic radiation, but this practice is similarly controversial.[125] Endoresection carries an approximately 10% risk of local recurrence, which can arise from microscopic disease in the scleral bed or at the margins of resection.[124]

Transscleral Resection

Transscleral local resection (exoresection) has been promoted for tumors >6 mm thick in patients highly motivated to retain vision and in patients with severe exudative retinal detachment after RT.[120] The procedure carries substantial operative risk. Choroidectomy and cyclochoroidectomy, for example, require hypotensive anesthesia with systolic blood pressure lowered to approximately 40 mm Hg.[126] The operation involves the preparation of a lamellar scleral flap, ocular decompression by limited pars plana vitrectomy, resection of the tumor together with the deep scleral lamella, suturing of the scleral flap, intraocular injection of balanced salt solution, and adjunctive brachytherapy either at the end of the operation or several weeks later. This procedure has approximately 30% incidence of local relapse when performed exclusively, but this probability declines to approximately 10% when perioperative brachytherapy is delivered.[127]

Transpupillary Thermotherapy

Transpupillary thermotherapy (TTT) is a procedure in which 1-minute applications of 3-mm spots of low-energy diode laser are administered to

the tumor and the surrounding choroid.[128] The objective is not immediate thermoablation but rather heating the tumor by only a few degrees so that following treatment, tumor regression occurs slowly, often resulting in a white scar. A study of 391 patients treated with TTT reported a 5-year local recurrence rate of 29%, with higher recurrence rates for tumors with more high-risk features, suggesting that careful patient selection is critical for utilizing this technique.[129] TTT should be considered only for small and flat pigmented choroidal lesions with only a few risk factors. Some advocates of TTT recommend combined brachytherapy with TTT. Yarovoy and colleagues[130] reported improved tumor regression and recurrence-free survival with similar complication rates when TTT was used with brachytherapy compared with brachytherapy alone. By contrast, Marinkovic and colleagues[131] did not find better control rates with the combination of brachytherapy and TTT, but did find more rapid vision loss with combination therapy.

Plaque Brachytherapy

Plaque brachytherapy is a mainstay of treatment in many centers, with iodine-125 (I-125) and ruthenium-106 (Ru-106) being the most common isotopes, although palladium-103 (Pd-103) has also been used effectively.[132] I-125 emits γ rays, which have a range sufficient for tumors up to 8 to 10 mm thick, whereas Ru-106 delivers β particles that have a more limited range, which is suitable for tumors <5 mm thick. Historically, the general objective with all plaques was to deliver approximately 80 Gy to the tumor apex by fixing the plaque in the exact location of the tumor (Figures 44.7 and 44.8). However, some data suggest lower doses may be sufficient for tumor control with less toxicity. Perez and colleagues[133] examined 190 cases treated between 1988 and 2010 and analyzed outcome with respect to apical dose. Local control and overall survival did not differ according to dose quartile (<69, 69-81, 81-89, >89 Gy). However, visual acuity and radiation complications increased with increasing dose, and the authors concluded that doses as low as 69 Gy may be appropriate for uveal melanoma. Dedicated computer modeling has been developed for RT planning to create a 3D model of the eye and determine the appropriate treatment time and estimated dose to the optic nerve, macula, and lens.[134] Juxtapapillary tumors

approximating or overhanging the optic disc present a dosimetric challenge but may be treated with brachytherapy. Sagoo and associates[135] reported on 141 such patients treated with plaque brachytherapy. In 126 eyes, the plaque utilized a notched design, which created an elliptical dose distribution with a median dose of 85 Gy. Local control was 90%, and metastases developed in 13%. Visual acuity was generally poor, with 77% having a final acuity of 20/200 or worse. Given the alternative of enucleation, however, this technique represents a reasonable treatment choice.

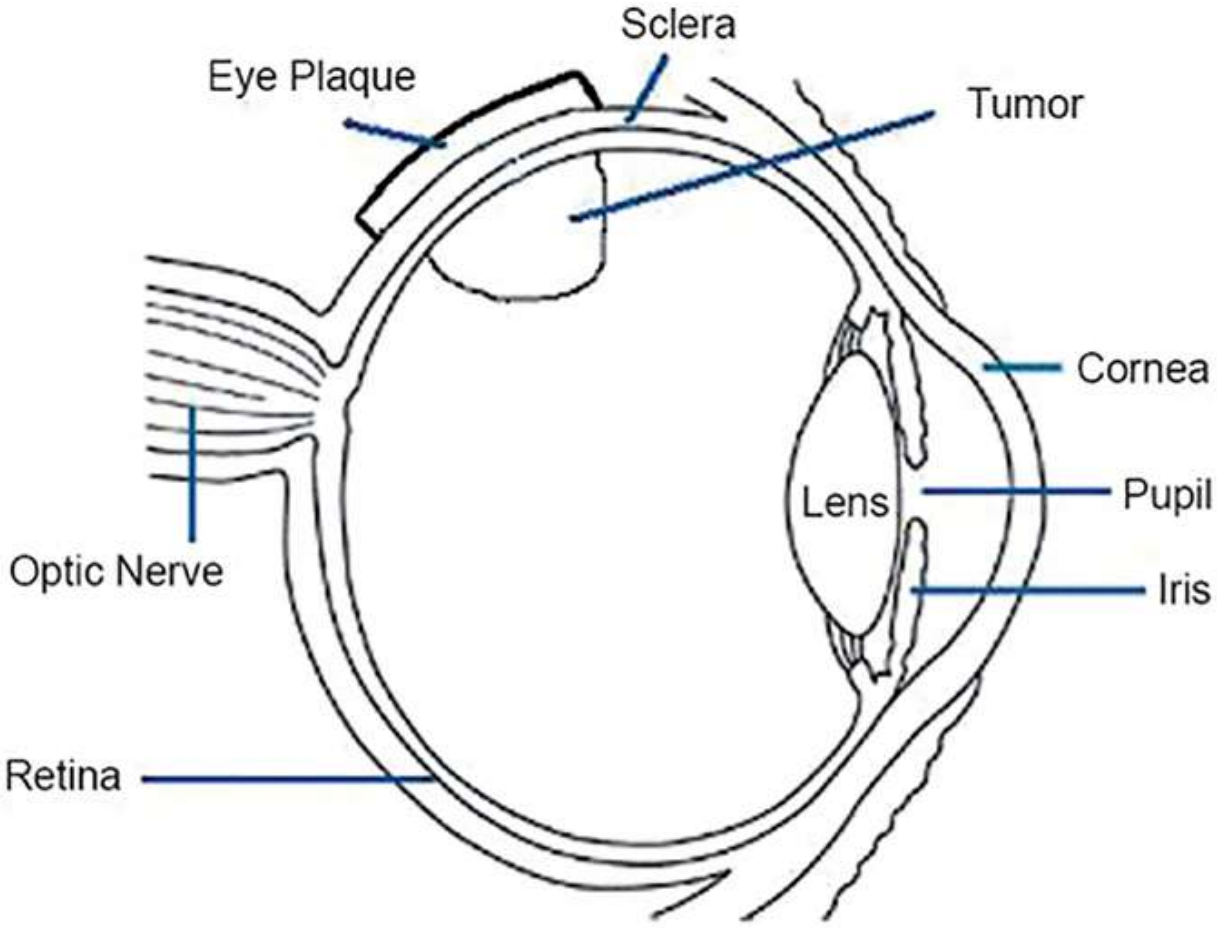

FIGURE 44.7 Eye anatomy and plaque placement in the location of tumor. (Reprinted with permission from Chaudhari S, Deshpande S, Anand V, et al. Dosimetry and treatment planning of Occu-Prosta I-125 seeds for intraocular lesions. *J Med Phys*. 2008;33[1]:14-18. Copyright © 2008 *Journal of Medical Physics*.)

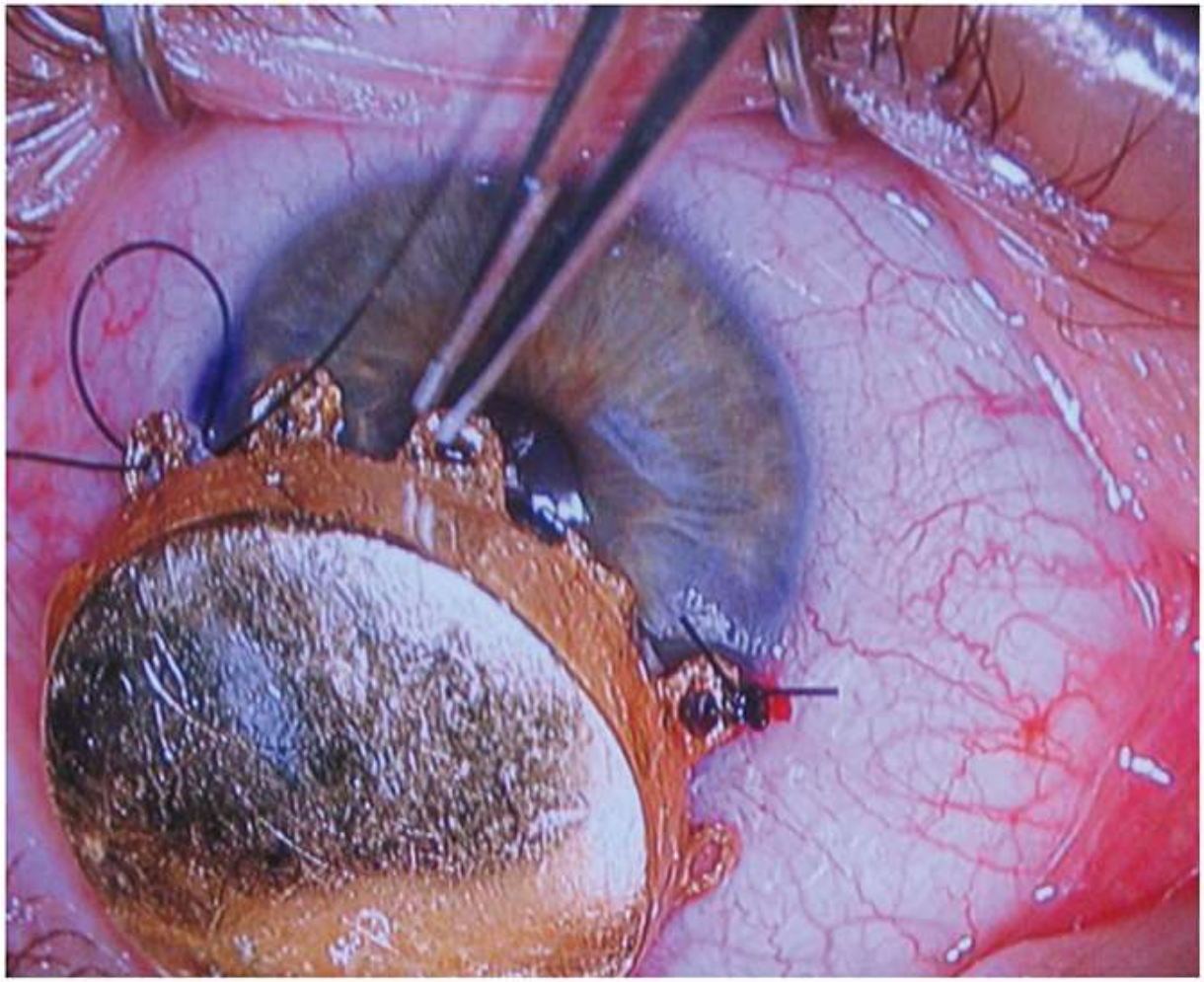

FIGURE 44.8 Plaque brachytherapy for melanoma of the iris. (From Khan MK, Khan N, Almasan A, Macklis R. Future of radiation therapy for malignant melanoma in an era of newer, more effective biological agents. *Onco Targets Ther*. 2011;4:137-148. Reprinted by permission of Informa UK Limited, trading Taylor & Francis Group. https://www.tandfonline.com)

The largest prospective experience of patients treated with plaque brachytherapy was conducted by the Collaborative Ocular Melanoma Study (COMS) group. From 1986 to 2003, COMS conducted two multicenter trials of brachytherapy with I-125 versus enucleation in selected patients with choroidal melanoma. Long-term results were subsequently published in COMS Report 28 in 2006, which evaluated 1,317 patients.[136] Eligible patients had unilateral choroidal melanoma with an apical height of 2.5 to 10 mm and a maximum basal tumor diameter (MBTD) of 16 mm. Patients whose tumors were contiguous with the optic disc were ineligible, as were

patients with metastases from melanoma or another malignancy. Patients were followed for 5 to 15 years. Within 12 years after enrollment, 471 (36%) of 1,317 patients died. Overall, CSM at 5 and 10 years for both treatment arms was 19% and 35%, respectively. Cumulative all-cause mortality was 43% in the I-125 arm and 41% in the enucleation arm, indicating that with long-term follow-up, there was no survival difference between plaque brachytherapy and enucleation. Age >60 years and MBTD >11 mm were the primary predictors of time to death. Local control was excellent in the COMS series, with only 12.5% of patients requiring salvage enucleation.[137]

Visual acuity after plaque brachytherapy depends on a number of factors. Shields et al[138] reported the outcome of 1,106 patients with baseline visual acuity of 20/100 or better who underwent brachytherapy for uveal melanoma and found that 34% of patients had poor visual acuity at 5 years and 68% at 10 years, defined as 20/200 to no light perception. Factors adversely affecting visual acuity were age >60 years, poor vision at baseline, tumor thickness >8 mm, proximity to the foveola of <5 mm, recurrent tumor, subretinal fluid, and history of diabetes or hypertension. The best results were obtained in eyes with small tumors outside a radius of 5 mm from the optic disc and foveola. The 2014 American Brachytherapy Society consensus guidelines on plaque brachytherapy for uveal melanoma determined that brachytherapy is appropriate for the majority of uveal melanomas.[139] Exceptions include tumors with >5 mm of extraocular extension, basal diameters that exceed the limits of brachytherapy applicators, patients with blind and painful eyes, and patients with no light perception.

Proton Beam Therapy

Proton beam therapy is often used to treat uveal melanoma and offers advantages for the treatment of tumors that extend close to or are contiguous with the optic disc, referred to as parapapillary and peripapillary tumors, respectively.[140] Because of the dosimetric properties of protons, which deliver a homogeneous dose to the tumor with a sharp field edge, a high tumor dose can be delivered with relative sparing of the optic nerve. In a dosimetric comparison of proton therapy versus I-125 plaque

brachytherapy, proton therapy provided better dose sparing of the fovea for most tumor locations and sizes, except for large, nasally located tumors, where brachytherapy enabled better sparing of the fovea.[141] The decision to use proton therapy over other forms of external-beam radiation often depends on the availability of treatment facilities. In a large survey of ocular proton therapy centers by The Particle Therapy Cooperative Oncology Group, the most common dose and fractionation used for proton therapy of uveal melanoma was 60 Gy (RBE) in four fractions over a week, utilized at seven of 10 surveyed centers.[142] Other dose and fractionation schemes were comparable in total dose and number of fractions and included 70 Gy (RBE) in five fractions, 58.4 Gy (RBE) in four fractions, and 56 Gy (RBE) in four fractions.

One of the largest experiences in proton beam therapy for uveal melanoma is from Massachusetts General Hospital/Mass Eye and Ear.[143] Treatment planning involves intraoperative examination by transillumination, and the edges of the tumor are delineated by four tantalum rings sutured to the sclera. For visible iridociliary tumors, surgery is not performed, and a light-field clinical setup is utilized. Radiation planning is done with the EyePlan treatment planning software and a geometric eye model to define the beam aperture and range modulation needed to adequately encompass the tumor with a 3-mm margin to allow for motion during treatment, setup error, and possible microscopic extension.[144] Patients receive a total dose of 70 Gy (RBE), delivered in 5 consecutive days.[143] For tumors ≤15 mm in largest diameter and ≤5 mm in thickness that are located within 1 disc diameter of the optic nerve or fovea, a reduced dose of 50 Gy (RBE) in five fractions is used with comparable rates of local control.[145] Long-term follow-up in a series of 573 patients with peripapillary and parapapillary uveal melanomas with a median surveillance of 96.3 months demonstrated low rates of local recurrence, with 5- and 10-year local recurrence of 3.3% and 6%, respectively.[140] Similarly, high rates of local control have been observed in a larger series from the same institution.[146] Enucleation rates were 13.3% and 17.1% at 5 and 10 years after treatment, respectively. Of 450 patients with baseline visual acuity of 20/200 or better, two-thirds had visual acuity <20/200 on long-term follow-up, although 56% could count fingers. The most common complications were radiation maculopathy and/or papillopathy. By 3 years, the cumulative

rate of both complications was 49%, and by 10 years increased to 61% for papillopathy and 68% for maculopathy. The visual outcome after proton therapy depends on the height of the tumor and its location relative to the fovea and optic nerve.[143] Anterior segment complications, such as rubeosis iridis and neovascular glaucoma, occur less frequently, with each occurring in approximately 15% of cases at 5 years after radiation.[147] These results indicate that although visual acuity is compromised with proton therapy, particularly in patients with juxtapapillary lesions, some preservation is possible and eye conservation is likely with low rates of local recurrence.

Stereotactic Radiotherapy

Stereotactic radiation can be delivered by linear accelerator (LINAC) or by specialized devices for focused radiation such as the Leksell gamma knife. Because gamma knife treatment is usually done in a single fraction, the term *radiosurgery* is applied, whereas for LINAC-based treatment, single-fraction or multifraction treatments are possible. Gamma knife radiosurgery (GKRS) for uveal melanoma was introduced in 1998 by investigators at the Indiana University School of Medicine.[148] Nineteen patients with uveal melanoma were treated to a dose of 40 Gy prescribed to the 50% isodose line. With a median follow-up of 40 months, 3- and 5-year overall survival rates were 86% and 55%, respectively. The 3- and 5-year tumor control rates were both 94%. Six (32%) of the 19 treated patients developed distant metastasis 31 to 75 months after GKRS. Out of the 19 patients treated, two had improved, four had stable, and 13 had worse vision in the treated eye. Similar results were reported in a larger series of 78 patients from investigators in Milan.[149] The dose was adjusted over the treatment period: seven patients received 50 Gy to the 50% isodose line (1994-1995), 21 patients received 40 Gy to the 50% isodose line (1995-1999), and 47 patients received 35 Gy to the 50% isodose line (2000-2006). Local tumor control was achieved in 91.0% of patients, and the eye retention rate was 89.7%. A significant relative reduction of visual acuity was observed during follow-up, most commonly because of exudative retinopathy (33.3%), neovascular glaucoma (18.7%), radiation retinopathy (13.5%), and vitreous hemorrhage (10.4%). In a retrospective comparison of 85 patients treated with GKRS (35 Gy to 50% isodose, 39 months average follow-up) versus

106 patients treated with proton therapy (58.4 Gy [RBE] in four fractions, 34 months average follow-up), local control rates were similar at 98% and 95% for GKRS and proton therapy, respectively.[150] GKRS was associated with more deterioration of vision (65% losing more than three lines of Snellen acuity compared to 45% with proton therapy), with 33% of GKRS and 54% of proton therapy patients retaining visual acuity of 6/60 or better.

In an effort to reduce the complications of single-fraction stereotactic radiosurgery, fractionated SRT has also been investigated. Muller and colleagues conducted a prospective study on 102 patients with uveal melanoma treated with fractionated SRT between 1999 and 2007.[151] Patients had uveal melanoma of the choroid or ciliary body with a tumor thickness <12 mm and diameter <16 mm with no metastases. The SRT technique, like GKRS, utilized a fixed immobilization system, and a dose of 50 Gy was delivered in five equal fractions on 5 consecutive days using 6-MV photons with stereotactic arcs. With a median follow-up of 32 months, local control was achieved in 96% of patients. Fifteen enucleations were performed 2 to 85 months after radiation, and best corrected visual acuity (defined as 20/x while using glasses if needed) decreased from a mean of 0.26 at diagnosis to 0.16 at 3 months after irradiation and declined to 0.03 at 4 years after therapy. Deterioration of visual acuity was in part related to complications. Grades 3 to 4 neurovascular glaucoma occurred in nine patients, eight of which required enucleation. In these nine patients, tumors were not anteriorly located, nor did they receive a high dose to the ciliary body, as one might expect, but were associated with grade 3 retinopathy. The authors hypothesized that the physical reaction of ischemic retinopathy might also affect vessels in the ciliary body. Thirteen (13%) patients developed grade 3 or 4 optic neuropathy, which was associated with posterior tumors and optic nerve dose, which was limited to 4 Gy/fraction. Grade 3 cataracts occurred in 10 (10%) patients and were managed by extraction and lens implantation. Cataract formation was dose related, with a median dose of 5 Gy/fraction to the lens causing cataract in 50% of cases. The authors concluded that although local control was excellent, the number of secondary enucleations was substantial, particularly from neovascular glaucoma.

Intraocular Lymphoma

Intraocular lymphomas consist of vitreoretinal lymphomas (VRLs) and choroidal lymphomas. Primary VRL is an uncommon clinical manifestation of non-Hodgkin lymphoma (NHL), which arises in the retina or the vitreous humor.[152] It usually develops in patients in the fifth and sixth decades of life as chronic, relapsing, and steroid-resistant uveitis and vitritis. Patients often complain of blurred vision, a painless loss of vision, and floaters. Primary VRL is generally considered a subtype of primary central nervous system lymphoma (PCNSL) based on frequent co-occurrence with PCNSL and similar clinical behavior. Primary VRL progresses to intracranial involvement in 60% to 85% of cases.[153] Historically, primary VRL has been difficult to diagnose, often taking several years from the onset of symptoms to establishing a diagnosis, which likely contributed to suboptimal outcomes in many cases.[154] Given the tumor's rarity, the optimal treatment of primary VRL is unclear. RT has been used with durable control after 35 to 45 Gy given exclusively to both eyes in the absence of central nervous system disease.[155] However, concerns of CNS relapse have led investigators to use chemotherapy as initial treatment and radiation as a consolidative therapy.[156,157] Methotrexate and cytosine arabinoside are most commonly used, given their ability to cross the blood-ocular barrier.

Primary choroidal lymphomas are usually low-grade B-cell lymphomas with similar features to other extranodal marginal-zone lymphomas.[158] EBRT can be used for primary choroidal lymphomas, with a typical dose of 30 Gy in conventional fractionation associated with high rates of local control and low risk of systemic spread.[159-161] Systemic therapy with rituximab can also be considered.[162] Intraocular lymphoma secondary to disseminated systemic disease also typically involves the choroid. The most common subtype for secondary choroidal lymphoma is diffuse large B-cell lymphoma.[158]

Orbital Tumors

Adult Optic Pathway Glioma

Optic pathway gliomas, with or without contiguous involvement of the hypothalamus, have an incidence of approximately 1 in 100,000, with 90% presenting in the first two decades of life.[163] Pediatric optic pathway gliomas are typically low-grade, benign entities that are sporadic or

associated with neurofibromatosis type 1 and can require long-term follow-up into adulthood.[164,165] By contrast, optic pathway gliomas that are diagnosed in adults are often higher grade (WHO grade III or grade IV) and have an aggressive disease course.[166] Adult malignant optic pathway glioma was first described by Hoyt et al[167] in 1973. Given the rarity of the disease, most published literature on this disease consists of case reports or small case series. Malignant optic pathway gliomas can mimic optic neuritis on initial presentation and typically present with rapidly progressive unilateral vision loss, which often spreads to bilateral blindness.[168,169] The treatment approach consists of RT and chemotherapy, similar to other high-grade gliomas. Outcomes remain poor, with overall survival of less than 1 year.[168]

Primary Orbital Lymphoma

Orbital NHLs account for only 0.01% of NHL and are typically B-cell lymphomas.[170] Depending on the stage and grade of disease, observation, first-line chemotherapy, and chemotherapy followed by RT are treatment options. RT is generally the treatment of choice for NHL localized to the orbit.[171] Local control rates of 90% to 100% can be achieved using doses of 30 to 36 Gy.[172] Historically, radiation was delivered with an anterior portal prescribed to the orbital apex or by wedged anterior and lateral fields. Late effects from these techniques include cataract formation, lens ulceration, glaucoma, and lacrimal impairment.[170] More recently, investigators have described the use of IMRT in orbital lymphoma to reduce dose to the contralateral orbit, lacrimal gland, and lens (Figure 44.9).[173]

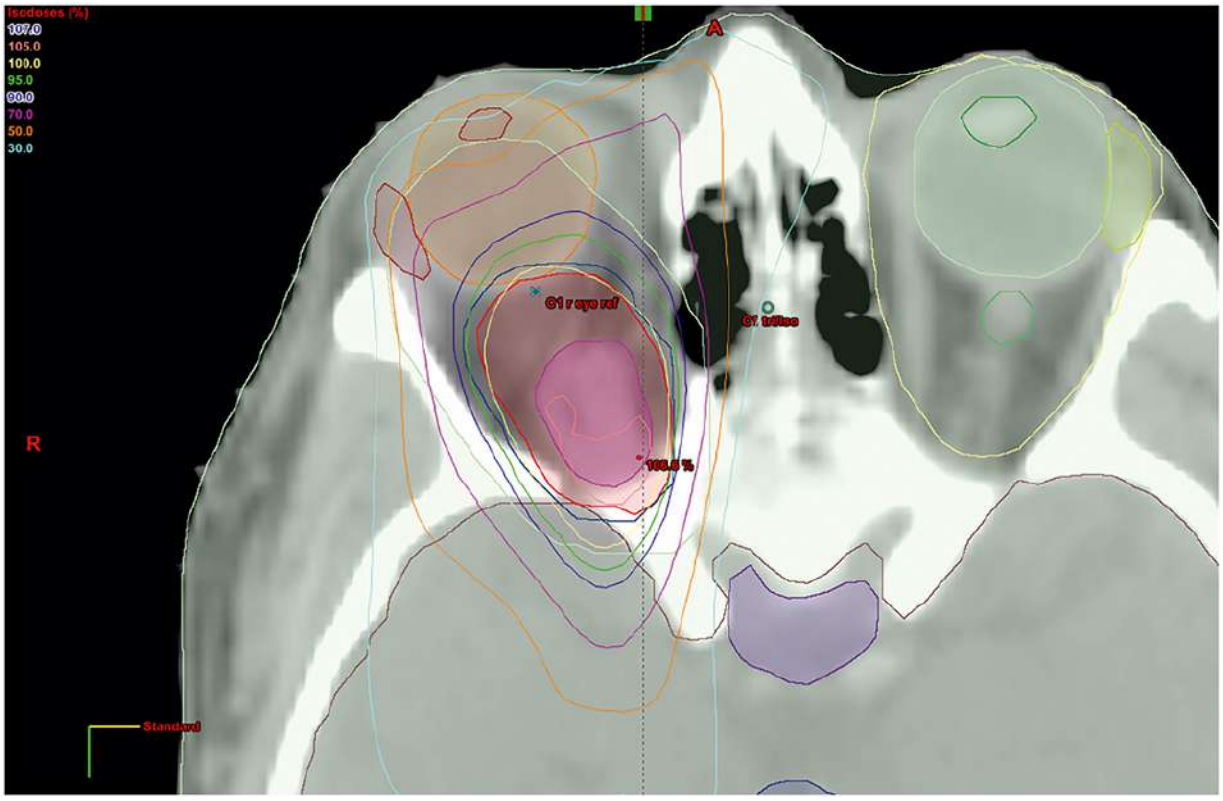

FIGURE 44.9 Primary orbital lymphoma treated with intensity-modulated radiation therapy illustrating sparing of lens, lacrimal gland, and contralateral orbit.

Conjunctival Tumors

Conjunctival tumors comprise a variety of conditions, from benign papilloma to malignant lesions such as squamous cell carcinoma (SCC). Radiotherapeutic management of these tumors is related to the histologic type. Mucosa-associated lymphoid tissue (MALT) lymphoma, for example, has been effectively managed with exclusive RT, with local control rates approaching 100%.[174] In a series of patients with MALT lymphoma of the ocular adnexa that included 37 patients with conjunctival disease, Hashimoto and colleagues[175] reported local control rates of 100% with a median dose of 30.6 Gy. Electron beam therapy was frequently used with eye lens shielding when possible, depending on the extent of disease (Figure 44.10). Treatment options for SCC include excision with or without adjuvant cryotherapy or topical chemotherapy, whereas advanced cases may require orbital exenteration.[176] RT has been used in the primary, adjuvant, and salvage settings with a variety of methods, including photon, proton, and electron beam therapy.[177,178] Most frequently, however, radiation is used

in patients with relapsed disease. The treatment volume typically includes gross tumor with margins of approximately 1 cm and doses of approximately 60 Gy, as in cases of SCC at other sites.[179]

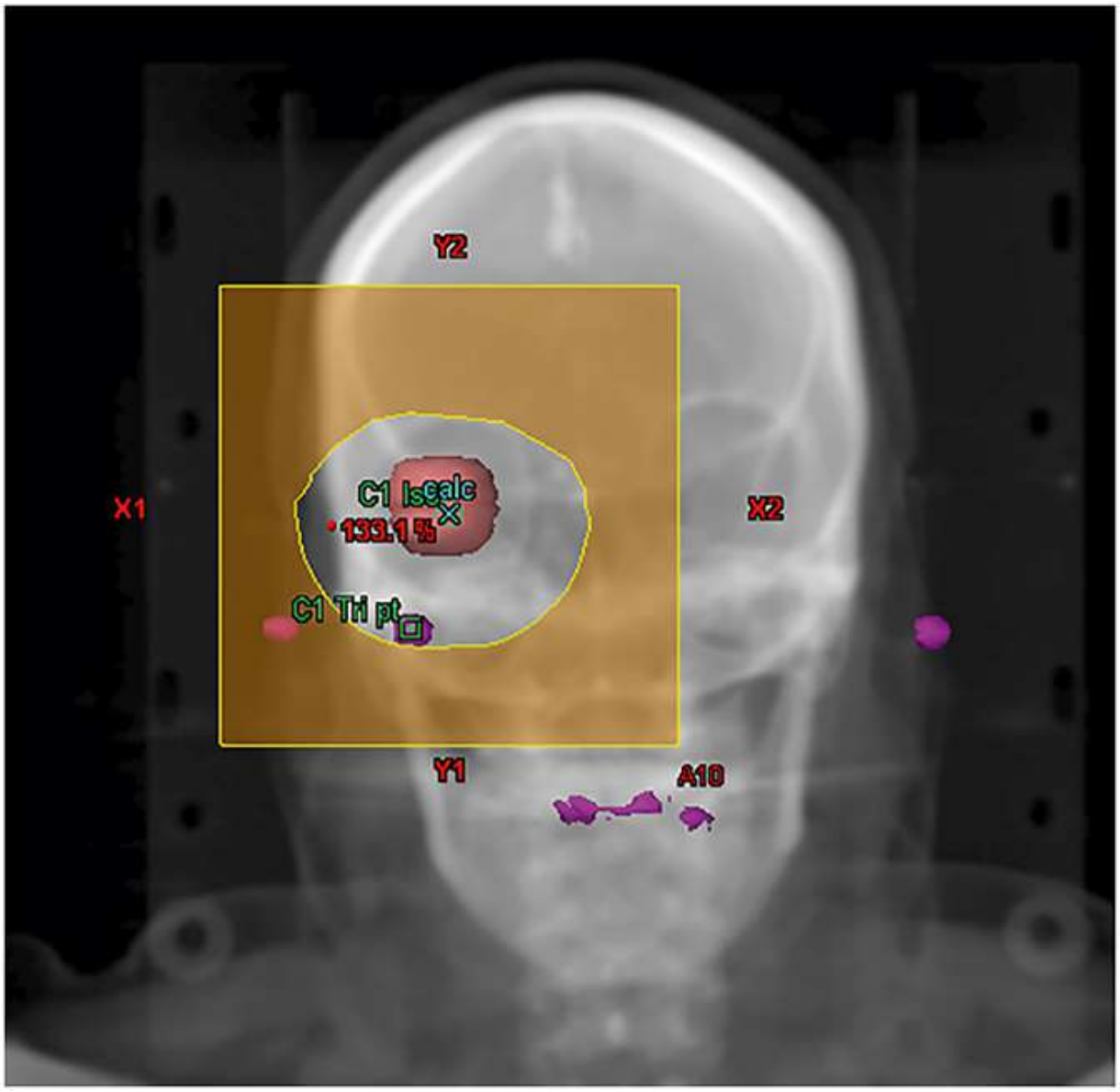

FIGURE 44.10 Electron beam therapy for mucosa-associated lymphoid tissue lymphoma of the conjunctiva. The patient received 30.6 Gy using 9-MeV electrons. Lens shielding was not used because of the extent of disease at presentation.

Sebaceous Carcinoma of the Eyelid

Sebaceous gland adenocarcinoma occurs in the periorbital area, usually in the eyelid.[180] It can exhibit aggressive local behavior and can metastasize to regional lymph nodes and distant organs. Older individuals tend to be affected, but it occurs with greater frequency and at an earlier age in patients with hereditary retinoblastoma treated with radiation.[181] The main systemic association is Muir-Torre syndrome, an autosomal dominant condition characterized by a greater frequency of sebaceous adenoma, sebaceous carcinoma, keratoacanthoma, and gastrointestinal malignancies.[182] The most common pattern of metastasis of eyelid sebaceous carcinoma is through the lymphatic channels to regional lymph nodes. Historically, regional node metastasis occurred in about 30% of cases, but metastases have become less frequent in recent years.[183] Tumors that originate in the upper eyelid tend to metastasize to preauricular and parotid nodes. Tumors of the lower eyelid region can metastasize to submandibular and cervical nodes. Until recently, orbital exenteration was believed to be the only reasonable option in the management of sebaceous carcinoma that involved most of the conjunctiva and invaded the orbit. However, local excision with adjuvant therapies, such as topical chemotherapy or cryotherapy, is becoming more common.[184,185] EBRT, with doses of approximately 60 Gy, is rarely used for primary treatment but should be considered for patients with adverse features such as regional lymph node involvement or recurrent disease.[186]

Periorbital Skin Cancers

Skin cancers of the eyelid and periorbital skin include most frequently basal cell carcinoma (BCC) and SCC, but also rare histologies such as Merkel cell carcinoma (MCC).[187] For small BCC and SCC, single modality treatment with surgery or RT results in good local control, but RT is frequently used due to cosmetic concerns. For more advanced tumors or more aggressive histologies, such as MCC, combined surgery and RT are typically recommended. Low-energy electron beam therapy or orthovoltage irradiation is useful in this setting and can be delivered with an eye shield. RT for skin tumors requires doses of 60 Gy or more for definitive treatment using standard fractionation, but altered fraction can be employed to shorten treatment duration and minimize ocular trauma of shield placement.

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CHAPTER 45

Ear

Geoffrey Sedor, Luqman Dad, and Tony J. C. Wang

ANATOMY

The external, middle, and inner components of the ear develop from the three embryonic layers: ectoderm, mesoderm, and endoderm.

The external ear consists of the auricle or pinna, the external auditory meatus (canal), and the tympanic membrane (Figure 45.1). The auricle is composed of elastic cartilage covered with skin. The external auditory meatus connects the tympanic membrane to the exterior and is approximately 2.4-cm long. The outer third is cartilaginous, and the inner two-thirds is bony and slightly narrower. The external auditory canal (EAC) is anterior to the mastoid process and posterior to the parotid gland at the temporomandibular joint (TMJ). The inferior border of the canal lies near the jugular bulb and the facial nerve as it descends through the stylomastoid foramen. The skin lining the auditory canal is continuous with that of the auricle, and in the outer one-thirds of the canal, it contains hair follicles and sebaceous and ceruminous glands. The tympanic membrane, made of multiple layers of squamous epithelium, separates the auditory canal from the middle ear.

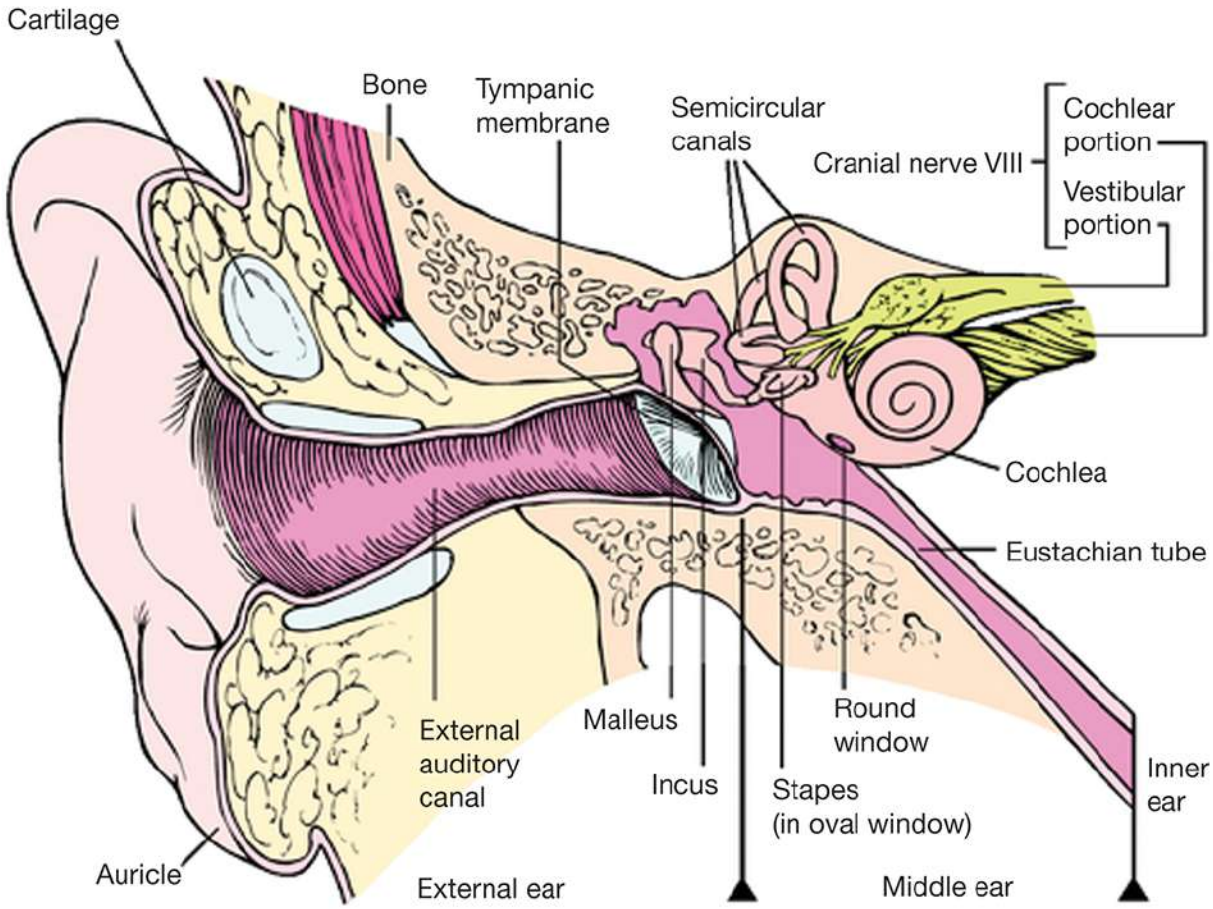


FIGURE 45.1 Ear anatomy.

The middle ear houses the auditory ossicles and the tympanic cavity and opens into the eustachian tube to communicate with the pharynx. The middle ear cavity is lined with a mucoperiosteal membrane, and the eustachian tube is lined with stratified columnar epithelium and has numerous mucous glands in two-thirds of the tube closer to the pharynx. The overall length of the eustachian tube is 3.5 cm.[1]

The inner or internal ear lies in the petrous portion of the temporal bone and consists of the bony labyrinth and the membranous labyrinth. The membranous labyrinth, which holds the organ of hearing, is housed within the bony labyrinth. The cochlea, which is responsible for hearing, and the vestibule, which is responsible for balance, are part of the inner ear.

Blood supply to the auricle and the EAC comes from branches of the posterior auricular artery and the superficial temporal artery, which arise from the external carotid artery. Blood is supplied to the middle ear region

by branches of ascending pharyngeal artery, the middle meningeal artery, and the artery of the pterygoid canal. The inner ear is supplied by the internal auditory artery, which is a branch of the basilar artery, and the anterior inferior cerebellar artery.

The nerves innervating the ear include cranial nerves V, VIII, IX, and X. The eighth cranial nerve or vestibulocochlear nerve is responsible for auditory and vestibular functions. It exits from the brainstem between the pons and the medulla and follows the internal acoustic meatus.

For the external ear, lymphatic vessels of the tragus and the anterior external portion of the auricle drain into the superficial parotid lymph nodes. The posterior and superior aspects of the auricle drain into the retroauricular lymph nodes, and the lobule drains into the superficial cervical group of lymph nodes. Lymphatics from the middle ear and the mastoid antrum pass into the parotid nodes and into the upper deep cervical lymph nodes. The lymphatics in the middle ear and eustachian tube are rather sparse, and the inner ear has no lymphatics.

EPIDEMIOLOGY

Malignant disease of the auricle is common (accounts for 6% of all skin cancers), but cancers of the middle ear and EAC are rare, with an incidence of approximately 1 per million people.[2-4] Tumors of the external ear are most often cutaneous malignancies and may be related to sun exposure.[5,6] Other predisposing factors described, although their significance is in question, are otorrhea, chronic eczema, chronic dermatologic conditions, and chronic ulcerations from trauma.[7]

Tumors of the external ear most commonly occur in patients 60 to 70 years of age; tumors of the middle ear and the mastoid are more common in patients 40 to 60 years of age.[8,9] More women than men have middle ear tumors, but more men have tumors of the external ear.[10,11]

CLINICAL PRESENTATION

External Ear

Basal cell carcinomas are more common than squamous cell carcinomas (SCCs) in the external ear, with a ratio of 1.3:1.[8] They present as small

ulcerations, mostly on the helix.[12,13] For SCCs, lymph node metastases occur in approximately 10% to 15%.[14] The common sites of lymph node metastases in order of frequency are the parotid gland, the upper deep cervical chain, and the postauricular nodes.[9,14] The rate of regional metastasis is higher in advanced disease and may involve the level 5 cervical lymph node group.[15]

External Auditory Canal

Most patients present with symptomatic lesions of the EAC. Pruritus and pain are common. Swelling behind the ear, decreased hearing, and facial paralysis are seen in advanced cases. Spread of the tumor into the lymphatic regions is more common than spread to other areas of the ear (~20%).[16,17] Tumors arising in the cartilaginous portion of the canal invade the cartilaginous walls and spread into the bony canal areas. However, those arising in the bony canal have a more effective barrier (preventing spread) and therefore progress predominantly along the main axis of the canal, eventually invading the middle ear or the cartilaginous part of the canal. The local spreading route is depicted in Figure 45.2. Distant metastases are rare.

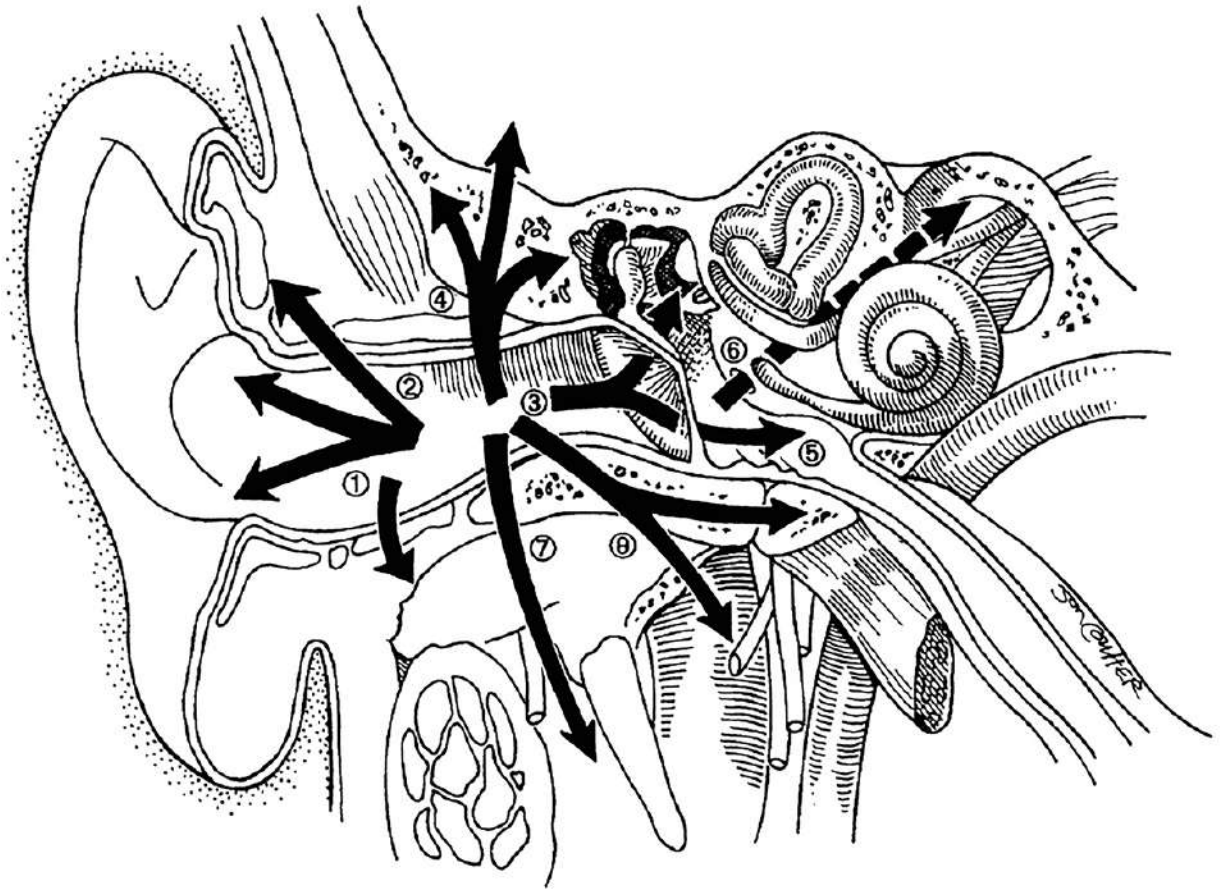


FIGURE 45.2 Coronal anatomy of pathways of spread of primary cancer of the EAC. Cancer can spread (1) anteriorly through the cartilaginous canal into the parotid gland, (2) through the concha into the postauricular sulcus, (3) through the tympanic membrane into the middle ear, (4) posteriorly into the mastoid, (5) into the anterior mesotympanum to the carotid artery and eustachian tube, (6) into the inner ear through the round window or otic capsule, (7) along the extratemporal facial nerve into the infratemporal fossa, and (8) inferomedially into the jugular fossa, carotid artery, and lower cranial nerves. (Reprinted with permission from Moody SA, Hirsch BE, Myers EN. Squamous cell carcinoma of the external auditory canal: an evaluation of a staging system. *Am J Otol*. 2000;21[4]:582-588.)

DIAGNOSTIC WORKUP

Table 45.1 summarizes workup and diagnostic procedures. A history and physical examination, including otoscopy and a careful lymph node exam, should be performed. Neurologic exam findings of cranial nerve deficits may be an indication of advanced disease. A baseline audiology testing should be performed before any treatment.

TABLE 45.1 DIAGNOSTIC EVALUATION FOR CARCINOMA OF THE EAR

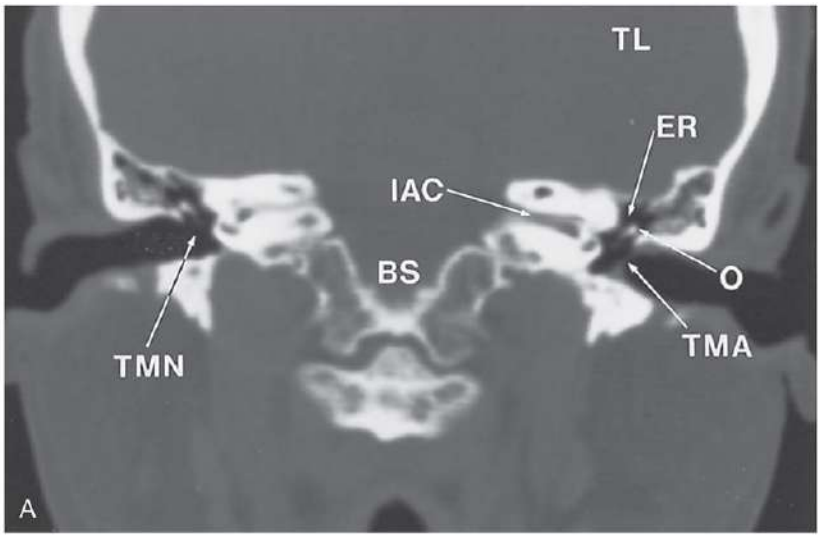
History
Physical examination
- Otoscopy
- Neurologic examination for cranial nerve function
- Careful assessment of regional lymph nodes

Laboratory tests
- Complete blood count
- Blood chemistry

Radiographic studies
- High-resolution computed tomography (standard)
- Magnetic resonance imaging (selected patients)
- Arteriography (optional)

Biopsy
- Other studies
- Audiology testing

Both multidetector computed tomography (CT) and magnetic resonance imaging (MRI) play an important role in visualizing tumors of the ear.[18] CT can show abnormal soft tissue, soft tissue enhancement, and distortion of the normal tissue planes. Most importantly, when evaluating EAC tumors, CT can provide an accurate prediction of bone erosion, such as wall of the EAC, middle ear, TMJ, carotid artery canal, and jugular fossa and thus can help to determine the extension and the operability of tumors (Figure 45.3).[19-21] Sometimes, MRI can differentiate the tumor from mastoiditis and cholesteatomas and provide excellent delineation of soft tissue tumor margins, muscle infiltration, intracranial extension, dural or cerebral involvement, and vessel encasement.[21,22] Except in selected cases, angiography and jugular venography have also been abandoned in favor of CT.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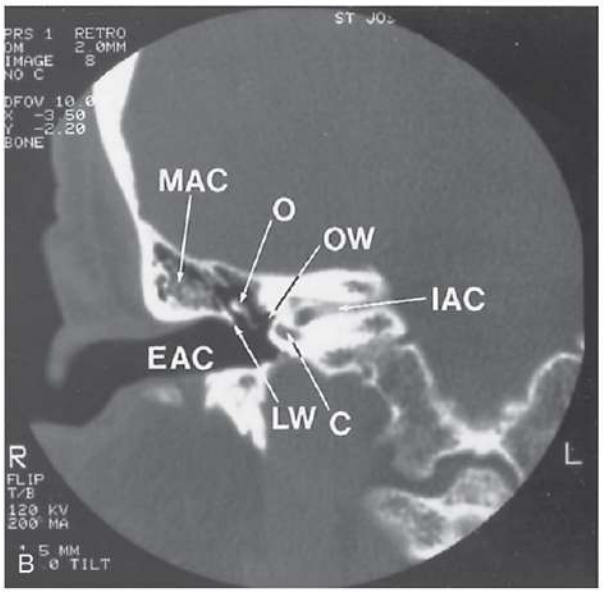
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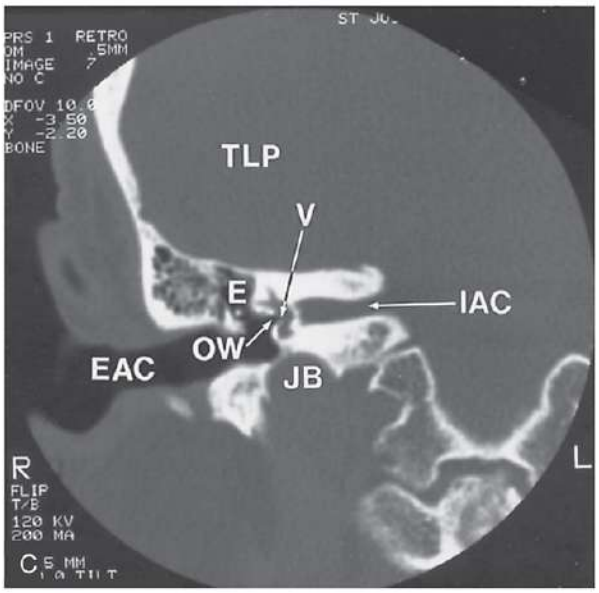
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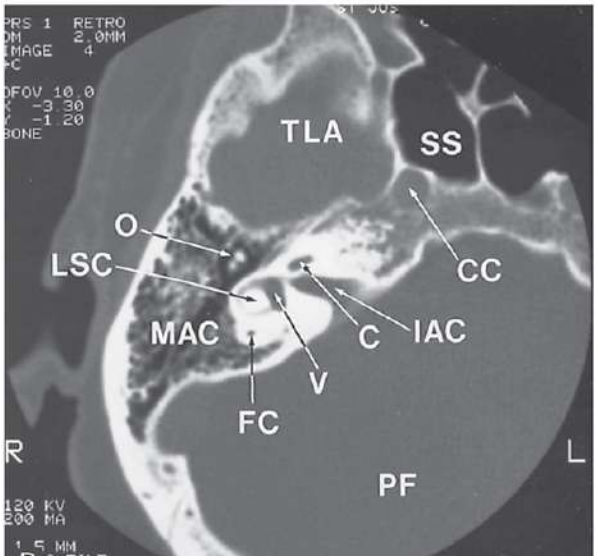
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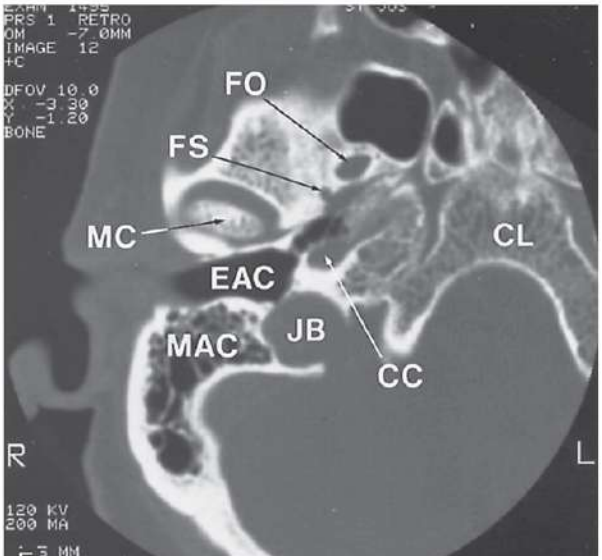
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FIGURE 45.3 Normal anatomy of the ear. A-C. Coronal sections. D, E. Transverse sections. BS, brainstem; C, cochlea; CC, carotid canal; CL, clivus; E, epitympanum; EAC, external auditory canal; ER, epitympanic recess; FC, facial canal; FO, foramen ovale; FS, foramen spinosum; IAC, internal auditory canal; JB, jugular bulb; LSC, lateral semicircular canal; LW, lateral wall, epitympanic recess (scutum); MAC, mastoid air cells; MC, mandibular condyle; O, ossicles; OW, oval window; PF, posterior fossa; SS, sphenoid sinus; TLA, temporal lobe, anterior portion; TLP, temporal lobe, posterior portion; TMA, tympanic membrane, abnormally thickened; TMN, tympanic membrane, normal appearance; V, vestibule. (Courtesy of Robert Gresick, MD, DePaul Health Center, St. Louis, MO.)

Diagnosis is always established by biopsy and occasionally by aspiration of the exudative material or by surgical exploration. A bone scan may be done to determine the changes in the temporal bone around the tumor, but it provides very nonspecific information and is not a recommended method of evaluation.

PATHOLOGIC CLASSIFICATION

Approximately 85% of the tumors involving the auditory canal, middle ear, and mastoid area are SCCs. Infrequently, basal cell carcinomas, adenocarcinomas, adenoid cystic carcinomas, and melanomas are seen.[23] Even rarer are sarcomas, specifically embryonic rhabdomyosarcomas. Ceruminous gland tumors and papillomas rarely arise in the auditory canal.[7,23,24] Carcinoid tumors of the middle ear are rare, and only 50 cases have been reported in the literature.[25,26] Endolymphatic sac tumors or aggressive papillary middle ear tumors are distinct from middle ear adenomas and act aggressively. They are characterized by slow growth but extensive local invasion and bone destruction.[27,28]

PROGNOSTIC FACTORS

Lesions of the external ear are usually more easily controlled than lesions of the middle ear or mastoid. External ear lesions are usually diagnosed earlier; they are mostly cutaneous, and adequate surgery or radiation therapy is usually effective.[3,9,29] Presence of large lesions involving the middle ear, especially those extending into the temporal bone or soft tissue, is a poor prognostic sign and makes treatment more difficult.[2,30,31] There does not appear to be a correlation between tumor differentiation, positive

margins, or perineural disease and survival, although they may serve as a predictor for local control in tumors involving the temporal bone.[30,32,33] Seventh cranial nerve palsy associated with middle ear tumors indicates poor survival as shown in pooled-data survival analysis and has been adopted into the staging system. Spread of tumors to the lymph nodes usually indicates a poor prognosis because this is often a late event in the natural history of the disease.[17,32,34] Nomogram for predicting overall survival and cause-specific survival in patients with middle ear cancer has been proposed using Surveillance, Epidemiology, and End Results database.[35]

STAGING

The eighth edition of the American Joint Committee on Cancer staging manual[36] includes the external ear in its staging system under *Cutaneous Squamous Cell Carcinoma and Other Cutaneous Carcinomas* (Table 45.2). A group from the University of Pittsburgh proposed a staging system for SCC of the EAC and temporal bone, which was updated in 2002.[17,37-39] The primary tumor stage is determined by the level of bony erosion, size, and involvement of the middle ear. Lymph node disease is considered an advanced stage with poor prognosis. This staging system has often been cited in the literature (Table 45.3).[2,17,34,38,40-46]

TABLE 45.2 THE AMERICAN JOINT COMMITTEE ON CANCER AND INTERNATIONAL UNION AGAINST CANCER STAGING SYSTEM FOR EAR CANCER

Stage	Staging Criteria
T Category	
Tx	Primary tumor cannot be assessed.
Tis	Carcinoma in situ
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor >2 cm, but ≤4 cm in greatest dimension
T3	Tumor >4 cm in maximum dimension or minor bone erosion or perineural invasion or deep invasion[a]
T4a	Tumor with gross cortical bone/marrow invasion
T4b	Tumor with skull base invasion and/or skull base foramen involvement

Stage	Staging Criteria		
N Category			
Nx	Regional lymph nodes cannot be assessed.		
N0	No regional lymph node metastases		
N1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension and ENE(−)		
N2a	Metastasis in a single ipsilateral node >3 cm but not >6 cm in greatest dimension and ENE(−)		
N2b	Metastases in multiple ipsilateral nodes, none >6 cm in greatest dimension and ENE(−)		
N2c	Metastases in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(−)		
N3a	Metastasis in a lymph node >6 cm in greatest dimension and ENE(−)		
N3b	Metastasis in any node(s) and ENE(+)		
M Category			
M0	No distant metastasis		
M1	Distant metastasis		
Stage Grouping			
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IV	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T any	N3	M0
	T4	N any	M0
	T any	N any	M1

ENE, extracapsular nodal extension.

[a]Deep invasion is defined as invasion beyond the subcutaneous fat or larger than 6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumor); perineural invasion for T3 classification is defined as tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger in caliber, or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression.

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TABLE 45.3 PITTSBURGH TUMOR STAGING SYSTEM (MODIFIED)

Stage	CT or Pathology Findings
T1	Tumor limited to the EAC without bony erosion or evidence of soft tissue involvement
T2	Tumor with limited EAC bone erosion (not full thickness) or limited (<0.5 cm) soft tissue involvement
T3	Tumor eroding the osseous EAC (full thickness) with limited (<0.5 cm) soft tissue involvement, or tumor involving the middle ear and/or mastoid
T4	Tumor eroding the cochlea, petrous apex, medial wall of the middle ear, carotid canal, jugular foramen, or dura, or with extensive soft tissue involvement (>0.5 cm), such as involvement of TMJ or styloid process, or evidence of facial paresis

CT, computed tomography; EAC, external auditory canal; TMJ, temporomandibular joint.

Reprinted with permission from Cristalli G, Manciocco V, Pichi B, et al. Treatment and outcome of advanced external auditory canal and middle ear squamous cell carcinoma. *J Craniofac Surg*. 2009;20(3):816-821.

GENERAL MANAGEMENT

External Ear

Tumors of the external ear are most often treated with limited surgery or external radiation therapy. Treatment in the early stages with irradiation is usually in the form of megavoltage electron beam therapy or orthovoltage.[47,48] Most radiation techniques have been fairly successful in the treatment of lesions in this area, with local control rates of 80% to 97%.[3,49-51] Caccialanza et al[3] reported a 5-year cure rate of 78% with a mean follow-up of 2.4 years for 115 carcinomas of the pinna treated with definitive kilovoltage radiation to a total dose of 45 to 70 Gy, in 2.5- to 5-Gy fractions given 2 to 3 times per week. Surgery is beneficial if the lesion has invaded the cartilage of the ear or extends medially into the auditory

canal. If SCC of the external ear is treated with surgery alone, there is a recurrence rate of 14% to 19%.[9,52] Mohs surgery is another option, with reported local recurrence rates of 5% to 7%.[29,53] Advanced lesions involving a significant portion of the ear canal are managed with a combination of irradiation and surgery. Palmer and Snell[54] describe the use of radical soft tissue and subtotal temporal bone excision with deltopectoral flap coverage for extensive tumors of the auricular area.

Treatment of draining lymphatics is normally not required for early stages of external ear tumors.[13] Afzelius et al[12] indicate that lesions larger than 4 cm and those with cartilage invasion have an increased risk of nodal spread; they recommend prophylactic neck dissection.[55] Most investigators do not agree with this approach because the overall chance of lymph node involvement in tumors of the external ear is only 16%. Osborne et al[56] reported that parotidectomy may be unnecessary in the management of advanced auricular carcinoma without clinically positive parotid disease.

Interstitial irradiation using afterloading ^{192}Ir, particularly for tumors smaller than 4 cm, is also an effective method of treatment, affording excellent local control with good cosmesis[51] (Table 45.4).

TABLE 45.4 TREATMENT OF CARCINOMA OF THE EXTERNAL EAR

Result	Modality	
	Surgery	Irradiation
Cure at 3 y[57]	330/358 (92%)[a]	141/174 (81%)
Cure at 5 y[3]		(78%)
Local control at 2 y[29,50]	82/87 (94%)[b]	60/62 (97%)
Local control at 2 y[48]		(86%)[c]
Local control at 4 y[51]		60/61 (99%)
Local control at 5 y[49]		128/138 (93%)
Local control at 5 y[48]		(79%)[c]

[a]Results given as number of successful outcomes/patient population.

[b]Treatment by Mohs micrographic surgery.

[c]Included advanced primary tumors.

External Ear Canal and Middle Ear

Radical surgery followed by postoperative radiation therapy is an acceptable method of treatment for more advanced lesions of the EAC and lesions in the middle ear and mastoid.[31,44,58] Pfreundner et al[31] recommended a postoperative radiotherapy dose of 54 to 60 Gy for patients with negative margins. Positive margins warrant higher doses of 66 Gy because of higher recurrence rates. Except for tumors detected early, neither modality alone is considered optimal; a combination of the two produces the best results.

Lesions of the outer part of the auditory canal require local excision with at least a 1-cm margin between the lesion and the tympanic membrane if there is no radiographic evidence of invasion of the mastoid. Surgery for tumors of the auditory canal is performed through a U-shaped incision with elevation of the flap from below. A split-thickness skin graft is usually required to cover the deficit along the auditory canal.

When the tumor involves the bony auditory canal and impinges on the tympanic membrane but does not involve the middle ear or the mastoid, a partial temporal bone resection may be necessary; in this procedure, the auditory canal, tympanic membrane, malleus, and incus are removed along with the TMJ, and the defect is grafted with a split-thickness skin graft. Postoperative radiation may be indicated, depending on margin status.

Middle Ear and Temporal Bone

In the management of temporal bone tumors originating from the middle ear and mastoid area, surgical options include subtotal temporal bone resection, total temporal resection, lateral temporal resection, or mastoidectomy. Complete resection with clear margins may be difficult to achieve, given that important structures reside around the temporal bone.[40,55,59-61] Postoperative radiation therapy is recommended and increases local tumor control.[31,40,62] In studies that suggest limited benefit of postoperative irradiation, the results may be related to the extent of the tumor.[63] Given that total and subtotal temporal bone resection can result in significant morbidity, some investigators favor limited surgery with postoperative or perioperative radiation, or even definitive radiotherapy in early or unresectable lesions.[62,64,65] Stereotactic ablative radiotherapy may represent a new treatment option for organ preservation. A study used 37.5

Gy/3 fractions or 40 Gy/5 fractions radiotherapy as a first-line treatment, resulting in 3-year overall survival rates: 69% for T1/2, 79% for T3 (95% CI, 47-93), and 0% for T4 disease with limited toxicities.[66] Murai et al reported their experience in treating unresectable locally advanced SCC of the EAC and middle ear with carbon ion therapy. The 3-year local control was 54%.[67] Chemotherapy has been used in tumors of the ear. The common regimen includes cisplatin, docetaxel, and mitomycin via intravenous or intra-arterial routes.[68,69] A meta-analysis suggested that preoperative chemoradiotherapy (CRT) followed by surgery may improve the survival of patients with SCC of EAC and that definitive CRT may be equivalent to surgical resection.[70] However, additional trials are necessary to determine efficacy because there was no controlled trial in this meta-analysis.

RADIATION THERAPY TECHNIQUES

Tumors involving the pinna can be treated with megavoltage electrons or with superficial or orthovoltage irradiation. The fields can be round or polygonal, drawn around the tumor to spare surrounding normal tissues. For small, superficial tumors, margins of 1 cm are adequate (Figure 45.4). However, more extensive lesions require larger fields, which may encompass the entire pinna or external canal and require 2- to 3-cm margins around the clinically apparent tumor.[71] Lesions involving the pinna must be treated with slow fractionation (1.8-2 Gy daily) to prevent cartilage necrosis. Doses of 66 Gy over a period of 6.5 weeks are required to achieve adequate tumor control.

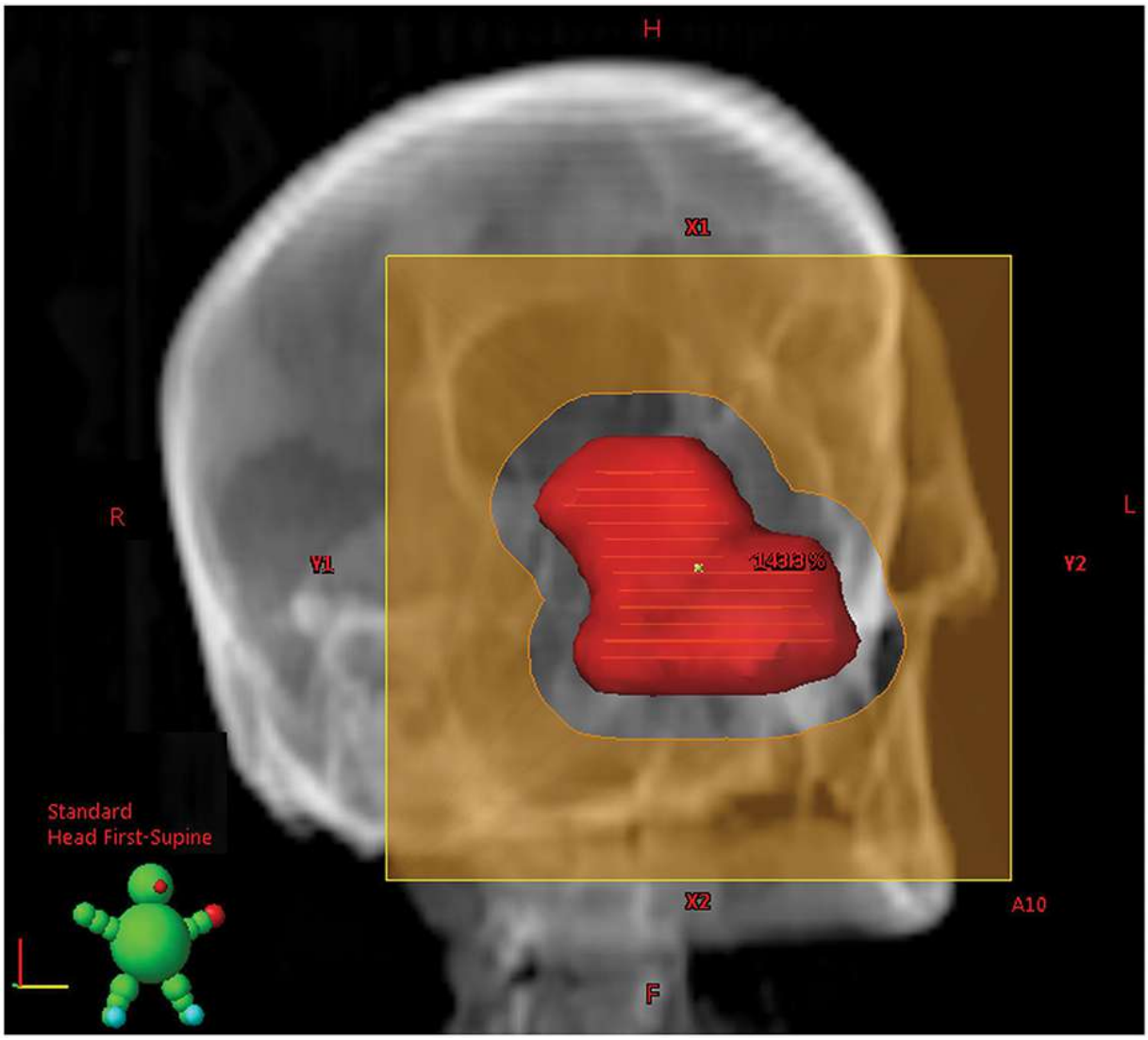

FIGURE 45.4 Example of beam's eye view of the target volume and electron aperture cutout. (Reprinted from Michiels S, Mangelschots B, Roover R, Devroye C, Depuydt T. Production of patient-specific electron beam aperture cut-outs using a low-cost, multi-purpose 3D printer. *J Appl Clin Med Phys*. 2018;19[5]:756-760. http://creativecommons.org/licenses/by/4.0/.)

Large lesions of the EAC are treated with radiation or in combination with surgery; the field should encompass the entire ear and temporal bone with an adequate margin (3 cm). The volume treated should include the ipsilateral preauricular, postauricular, and subdigastric lymph nodes. Treating lymphatics beyond the jugulodigastric area is usually not necessary.

The use of intensity-modulated radiotherapy (IMRT) can help improve target coverage and spare normal critical structures. Careful understanding of lymphatic drainage and tumor extension is crucial for target delineation and to avoid geographic misses. Pretreatment CT, MRI, or positron emission tomography-computed tomography scans should be reviewed along with any operative or pathology reports.

In the definitive treatment of advanced EAC or middle ear cancers, gross target volume (GTV) should include the clinical and radiographic gross disease (Figure 45.5). Clinical target volume 1 (CTV1) should encompass the GTV with a 0.3- to 0.5-cm margin to a dose of 66-70 Gy at 2 Gy per fraction. CTV2 should include CTV1 with a margin of 0.5 to 0.7 cm, as well as the preauricular nodes, postauricular nodes, ipsilateral upper cervical neck (level II), and parotid gland, receiving a dose of 63 Gy at 1.8 Gy per fraction. A CTV3 can be considered for some patients with more advanced and aggressive tumors for treatment of the ipsilateral middle and lower neck (levels III and IV) and contralateral upper neck (level II) to a dose of 56 Gy at 1.6 Gy per fraction. Planning target volumes are created with a margin of 3 to 5 mm around the CTVs.

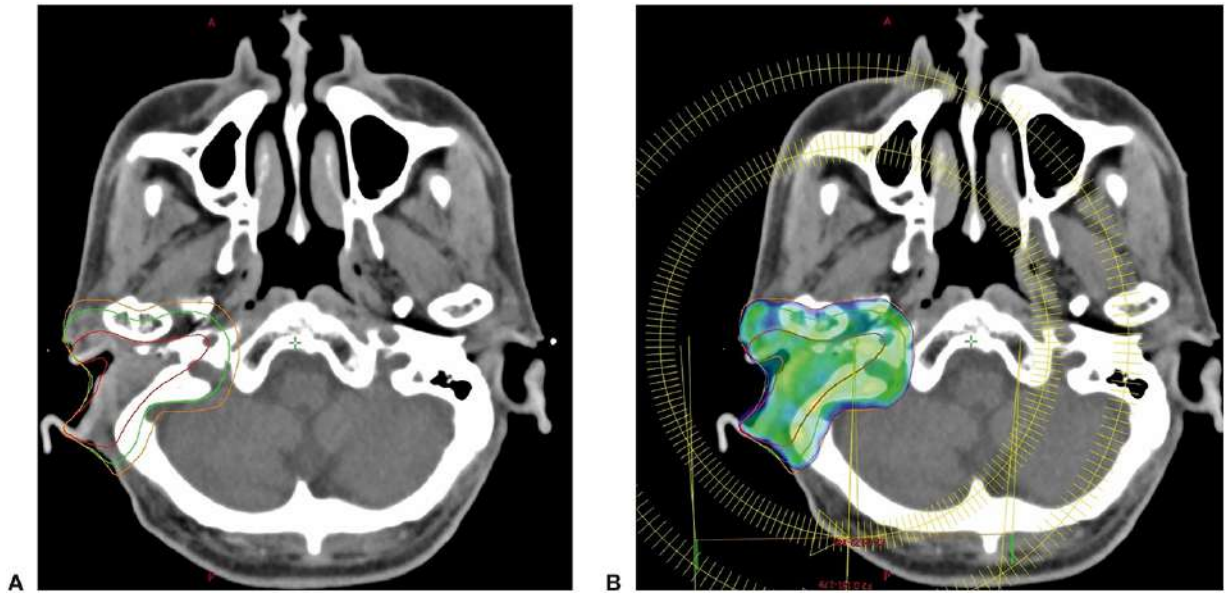

FIGURE 45.5 A. Treatment plan for external auditory canal squamous cell carcinoma: gross target volume is in red, high-risk clinical target volume (CTV1) is in green, and planning target volume is in orange. B. Dose color wash of two full-arc volumetric modulated arc therapy plans.

Chen et al[62] described the target volumes for postoperative IMRT of the EAC and middle ear. In the postoperative setting, CTV1 includes the original tumor region, surgical bed, soft tissue invasion, areas with positive residual disease, or positive margins to a dose of 60 to 66 Gy at 2 Gy per fraction. CTV2 includes CTV1 with a margin of 0.5 to 0.7 cm, depending on the anatomy, and the ipsilateral upper neck (level II), including the parotid region, to a dose of 54 to 60 Gy at 1.8 Gy per fraction. In some patients, CTV3 is included to cover the ipsilateral middle to low neck (levels III and IV) with or without the contralateral upper neck (level II) to a dose of 50 to 54 Gy at 1.6 Gy per fraction. Plans should be optimized to cover 95% of the planning target volume with 100% of the prescribed dose. In this case series, marginal failure occurred at the preauricular space and glenoid fossa of the TMJ. Caution should be taken to cover the area.

Extremely advanced tumors that are unresectable should be treated with high-energy ipsilateral electron beam therapy (16 to 20 MeV) alone or mixed with photons (4 to 6 MV), wedge pair (superior inferiorly angled beams) techniques using low-energy photons, or IMRT. IMRT is a reasonable option if nodal coverage is indicated. Doses of 60 to 70 Gy over 6 to 7 weeks are required. Doses higher than this may produce osteoradionecrosis of the temporal bone. If various types of radiation therapy beams are available, individualized treatment plans should be devised[72] (Figure 45.6). Most patients receiving radiation therapy to the middle ear and temporal bone regions benefit from immobilization devices such as the Aquaplast system. When electron beam radiation therapy is administered, using a water bolus in the EAC and concha may reduce the auricular complications.

FIGURE 45.6 Computerized isodose distribution for treatment of a middle ear tumor using a combination of photons and electrons. (From Foley H, Hopley S, Brown E, Bernard A, Foote M. Conformal orbit sparing radiation therapy: a treatment option for advanced skin cancer of the parotid and ear region. *J Med Radiat Sci*. 2016;63[3]:186-194. Reprinted by permission of John Wiley & Sons.)

Palliative Radiation Therapy

Radiation therapy offers significant palliation in recurrent or advanced disease. Pain relief is reported in 61% of patients with tumors of the auditory canal and middle ear.[73] Recurrences developing after previous irradiation may be retreated with low-dose radiation therapy and hope for control of tumor in approximately 20% of patients.[74] When a small-volume local recurrence occurs after previous radiation therapy, fractionated high-dose rate treatment may be considered.

RESULTS OF THERAPY

The series of patients reported from several institutions is small. Results of treatment with various modalities are shown in Table 45.5. In more extensive lesions, combinations of surgery and irradiation have yielded satisfactory results. Overall 5-year survival rates with combination therapy for tumors involving the middle ear and EAC range from 40% to 60%, whereas patients with early-stage tumors achieve a 70% 5-year survival rate with no evidence of disease.

TABLE 45.5 RESULTS OF TREATMENT OF CARCINOMA OF THE EXTERNAL AUDITORY CANAL AND MIDDLE EAR

Author	Time Span	Published	Number	Result
Osu et al[77]	2001-2021	2022	15	3-y OS: 73%
Katano et al[78]	2001-2019	2021	34	5-y OS: S + RT: 66.7%; RT: 45.1%
Nagano et al[79]	2003-2016	2019	21	2-y OS: 62%
Choi et al[64]	1990-2013	2017	32	5-y OS: 57%
Gandhi et al[80]	2001-2012	2016	43	5-y OS: 30%
Morita et al[81]	1997-2015	2016	57	5-y OS: T1/2 OP: 100%; RT: 81.3%. T3/4 CRT: 52.1%; OP + CRT: 55.6%
Ihler et al[82]	1997-2013	2015	36	5-y OS: 59.4%
Takenaka et al[83]	2006-2013[a]	2015	752	5-y OS: 57%
Xie et al[84]	2004-2012	2015	41	2-y OS: 56.9%
Shen et al[85]	1983-2011	2014	247	5-y OS: 47.4%
Leong et al[86]	2001-2012	2013	35	5-y OS: 48.6%
Prabhu et al[58]	1976-2003	2009	30	5-y OS: 74%

Author	Time Span	Published	Number	Result
Madsen et al[2]	1992-2001	2008	68	5-y OS: 44%
Ogawa et al[44]	1984-2005	2007	87	5-y OS: 55%
Pemberton et al[87]	1965-1988	2006	123	5-y LC: 56%
Nakagawa et al[70]	1998-2004	2006	25	For T1/2, 3-y OS: 100% For T3, 5-y OS: 80% For T4, 5-y OS: 35%
Sarkar et al[88]	1987-1996	2005	41	2-y OS: OP + RT: 85%; RT: 19%
Hashi et al[89]	1980-1998	2000	20	5-y OS: 59%

CRT, chemoradiotherapy; LC, local control; OP, operation; OS, overall survival; RT, radiation therapy; S, surgery.

[a]Meta-analysis, for published year.

Data from a multi-institutional series (Figure 45.7) indicate that there is a negative association between disease-free survival and the extent of disease using the University of Pittsburgh staging system.[44] These data also provide evidence of the success of combined surgery and postoperative irradiation for malignancies of the temporal bone.[75,76]

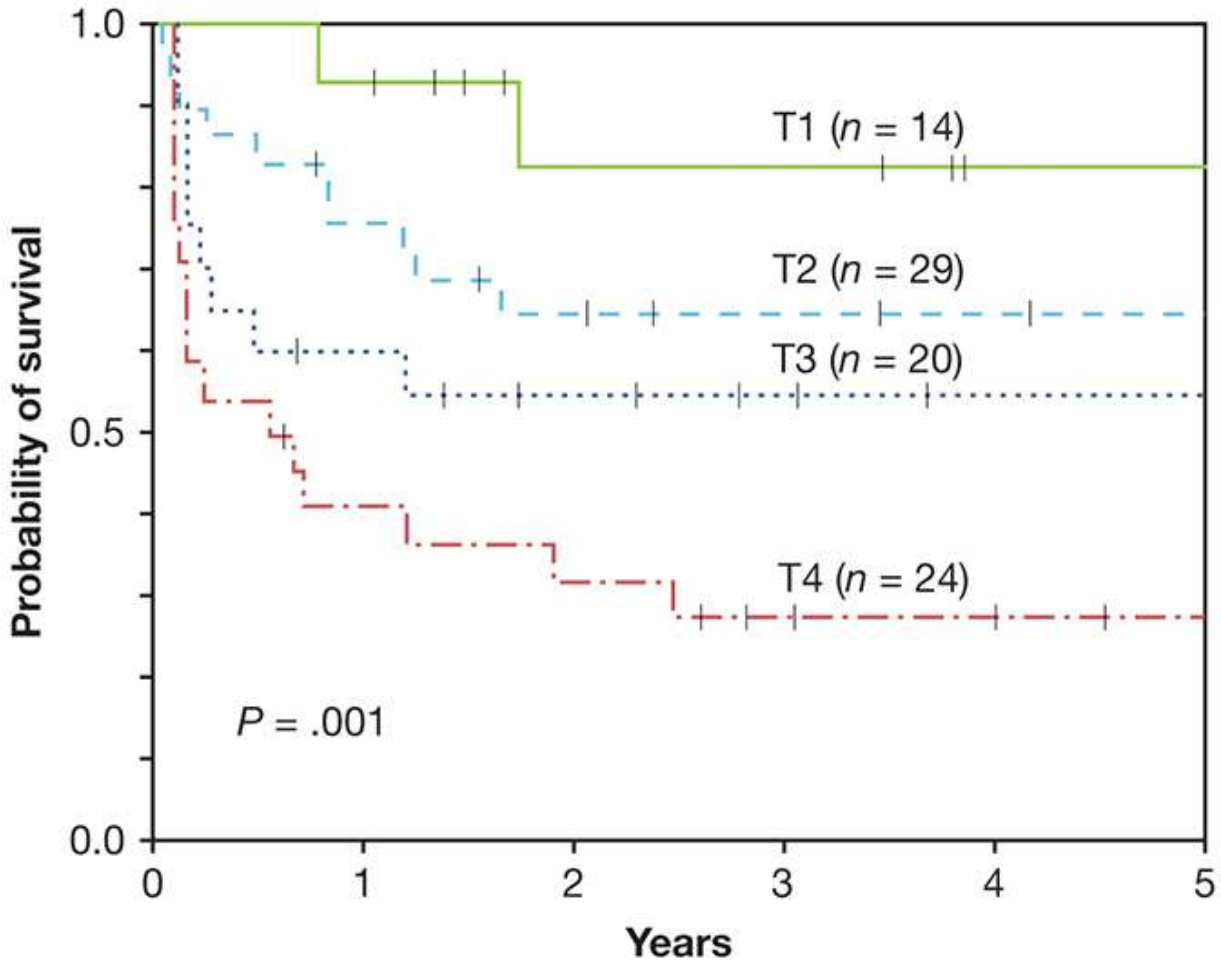

FIGURE 45.7 Data from patients with tumors of middle ear and EAC from a multi-institutional series demonstrate the association between disease-free survival and extent of disease using the University of Pittsburgh staging system. (Reprinted from Ogawa K, Nakamura K, Hatano K, et al. Treatment and prognosis of squamous cell carcinoma of the external auditory canal and middle ear: a multi-institutional retrospective review of 87 patients. *Int J Radiat Oncol Biol Phys*. 2007;68[5]:1326-1334. Copyright © 2007 Elsevier. With permission.)

NORMAL TISSUE COMPLICATIONS

Organs at risk should include the brainstem, spinal cord, cochlea, eye, optic nerve, chiasm, lens, larynx, oral cavity, parotid glands, and temporal bone. Normal tissue constraints are given in Table 45.5.

For conventionally fractionated radiation therapy, the mean dose to the cochlea should be limited to less than or equal to 45 Gy, or more conservatively to 35 Gy, to reduce sensorineural hearing loss.[90] Modeling of some of the sensorineural hearing loss data from the Quantitative Analysis

of Normal Tissue Effects in the Clinic studies is presented in Figure 45.8. The phenomenologic binomial equation of Zaider and Amols was used.[91] Chen et al[92] noted that hearing loss at a given radiation dose increased as frequency of the sound increased. The data are reasonably represented by theoretical curves with a characteristic dose (parameter α_2) of about 10 Gy (Table 45.6).

TABLE 45.6 NORMAL TISSUE DOSE CONSTRAINTS

Structure	Constraints
Brainstem	Maximum <60 Gy
Spinal cord	Maximum <45 Gy
Cochlea	Mean dose <45 Gy
Optic nerve	Maximum <55 Gy
Optic chiasm	Maximum <55 Gy
Lens	Maximum <10 Gy
Larynx	Mean dose <44 Gy; maximum <66 Gy
Oral cavity	Mean dose <35 Gy
Parotid gland	Combined parotid glands mean dose <25 Gy or spare one parotid gland mean dose <20 Gy
Temporal bone	Limit to <70 Gy to reduce osteoradionecrosis chance

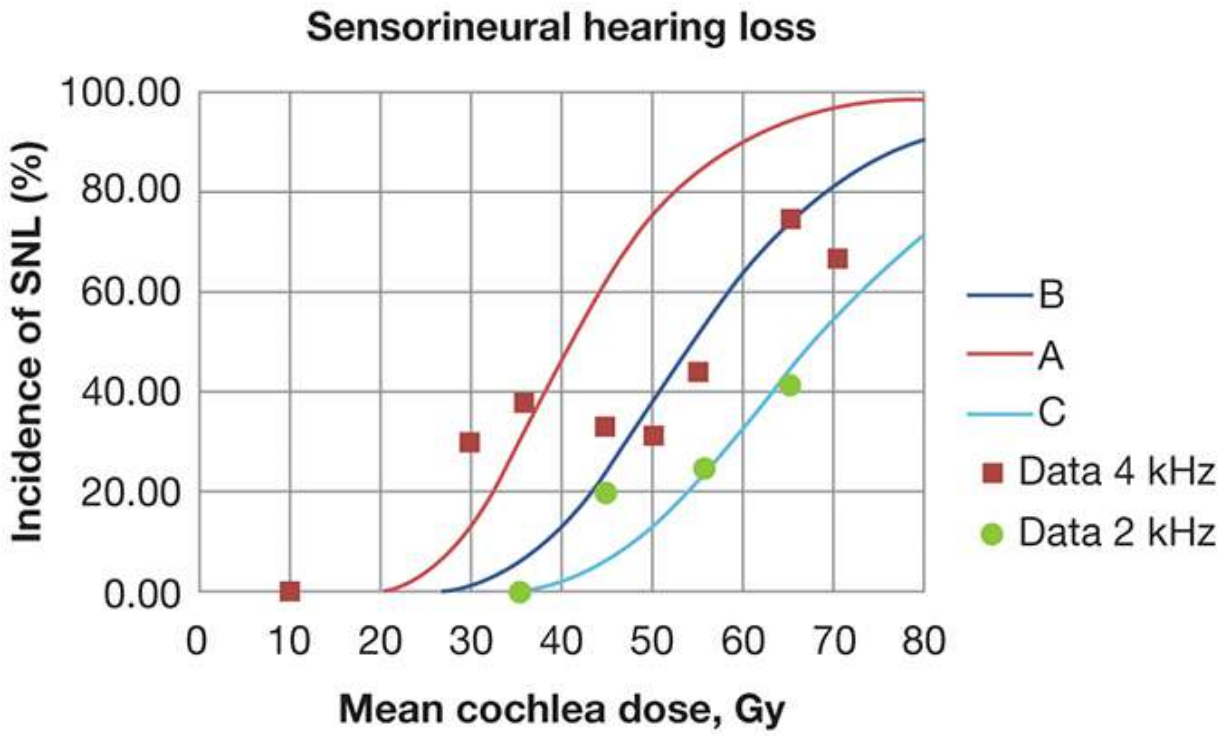

FIGURE 45.8 Modeling of the quantitative analysis of normal tissue effects in the clinic sensorineural hearing loss data using the phenomenologic binomial equation of Zaider and Amols.[91] Data for 2 kHz are shown as circles and those for 4 kHz as squares. All points are taken from Figure 1a, b of Bhandare et al.[90] Theoretical curves use a simple two-parameter variant of the nested exponential equation of Zaider and Amols[91]: $P(D) = 100 \exp[-\alpha_1 \exp(-\alpha_2 D)]$. The three curves are drawn with $\alpha_1 = 40$; the central curve has $1/\alpha_2 = 13.3$ Gy (B), and the outer curves are for $1/\alpha_2$ = (A), 10 Gy and (C), 16 Gy. SNL, sensorineural hearing loss.[94] (Reprinted with permission from Burri RJ. Ear. In: Chao KSC, Perez CA, Brady LW, eds. *Radiation Oncology: Management Decisions*. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2011:203-209.)

A relationship between mean dose to the cochlea and hearing loss was established by Schuette et al[93] in a retrospective cohort of patients with head and neck cancer treated with radiation therapy and/or cisplatin, finding an increase in pure tone average at 1, 2, and 4 kHz of 0.92 dB for every 10 Gy of mean dose to the cochlea.

SEQUELAE OF TREATMENT

Possible sequelae with surgery are hemorrhage, infection, loss of facial nerve function, and, rarely, carotid artery thrombosis. Occasionally, vertigo is reported after temporal bone resection. Vertigo may last for 2 weeks, and

a period of unsteadiness may last for a few months. Permanent deafness usually occurs on the operated side.

Radiation therapy sequelae include cartilage necrosis of the EAC and osteoradionecrosis of temporal bone.[13,95] Very rarely, secondary infections and meningitis are reported.[11] Due to the proximity of the brainstem and medulla oblongata, it is extremely difficult to deliver a high dose of irradiation to the temporal bone without a significant risk of injury to these structures. An overall 10% incidence of bone necrosis can be expected after administration of 60 to 65 Gy.

Reconstruction may be pursued after initial surgery, which may utilize autologous grafts or prosthetics. While radiation is known to cause fibrosis and bone demineralization, there has been no association found between adjuvant radiation therapy and osseointegrated implant complications.[96-98] Based on a large meta-analysis by Huang et al,[99] the dose delivered to the cochlea, radiotherapy technique (three- dimensional conformation), tumor type, concurrent chemotherapy, and the age of the radiotherapy population are all linked to radiation-induced ototoxicity.

After external ear lesions are treated with interstitial irradiation, there is a 4% incidence of late cutaneous and cartilage necrosis. Risk of necrosis increases for lesions larger than 4 cm.[51] Most patients can experience acute grade 2 and 3 skin toxicities with postoperative IMRT.[62] Following definitive or postoperative radiation, there is a 30% incidence of xerostomia.[58]

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CHAPTER 46

Locally Advanced Squamous Carcinoma of the Head and Neck

Jessica W. Lee, Jessica L. Geiger, and David M. Brizel

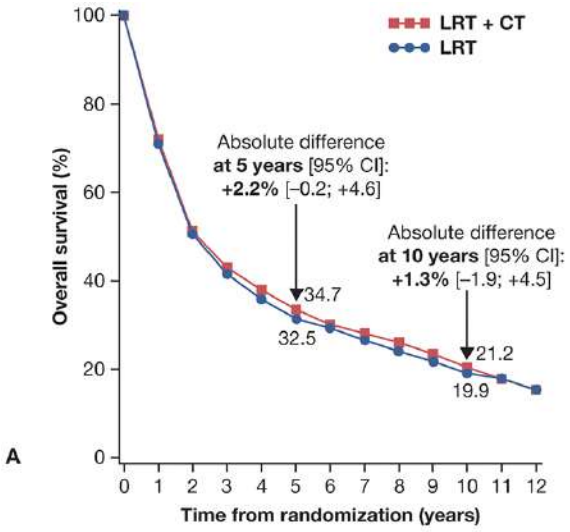
In the United States, an estimated 66,920 patients were diagnosed with head and neck cancer in 2023, with over 900,000 new diagnoses worldwide.[1,2] Locally advanced, nonmetastatic disease comprises about 60% of this population. Locoregional failure remains the predominant recurrence pattern, and most fatalities result from uncontrolled locoregional disease.

Historically, radiation therapy (RT) alone was the standard nonsurgical therapy for locally advanced disease, with dose fractionation evolving from daily treatment to hyperfractionation and accelerated fractionation regimens.[3-6] A meta-analysis of 11,423 patients on 33 trials from 1970 to 2010 (Meta-analysis of Radiotherapy in squamous cell Carcinomas of Head and neck) found that altered fractionation resulted in a 3.1% and 1.2% absolute improvement in overall survival (OS) at 5 and 10 years, respectively.[7,8] Nonetheless, even the most effective RT-alone regimens result in local control rates of 50% to 70% and disease-free survival (DFS) rates of 30% to 40%.

This circumstance stimulated the investigation of treatments combining chemotherapy and radiation (CRT). Landmark trials from the Veterans Affairs Laryngeal Cancer Study Group and the European Organization for the Research and Treatment of Cancer (EORTC) investigated larynx preservation with sequential chemotherapy and RT in locally advanced larynx and hypopharynx cancer, respectively. Both randomized patients to induction cisplatin (CDDP) and 5-fluorouracil (5-FU) followed by RT versus laryngectomy and postoperative RT and demonstrated that larynx preservation could be achieved without compromising OS.[9,10]

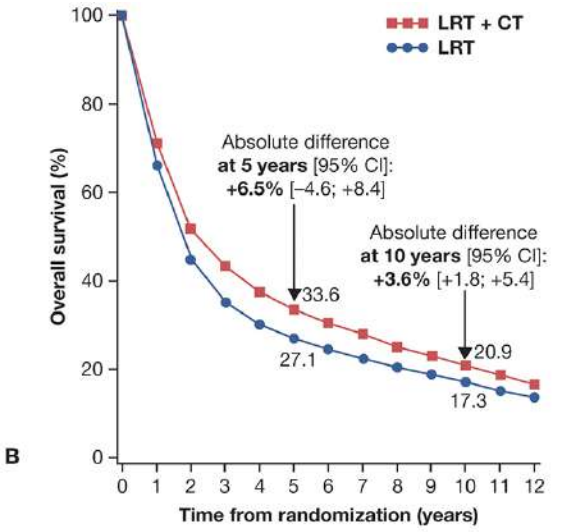
Subsequently, numerous randomized trials have demonstrated the superiority of CRT over RT alone in locally advanced, nonmetastatic head

and neck squamous cell carcinoma (HNSCC). A meta-analysis of 19,805 patients from 107 trials conducted from 1965 to 2016 (Meta-Analysis of Chemotherapy on Head and Neck Cancer [MACH-NC]) demonstrated that the addition of concurrent chemotherapy to RT resulted in a 6.5% and 3.6% absolute improvement in OS at 5 and 10 years, respectively[11,12] (Figure 46.1B). This benefit was greatest with the use of platinum-containing chemotherapy and predominantly attributable to improved locoregional control, with no significant difference seen in distant metastases and benefits decreasing with increasing patient age (Figure 46.2).



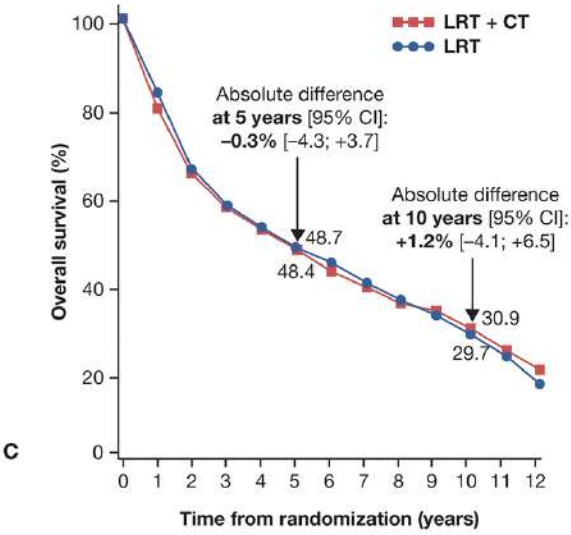
Number of deaths/person-years

	Years 0–2	Years 2–5	Years 5–10	Years 10+
LRT + CT	1657/4981	492/3573	150/1560	28/206
LRT	1683/4917	526/3396	127/1480	29/226



Number of deaths/person-years

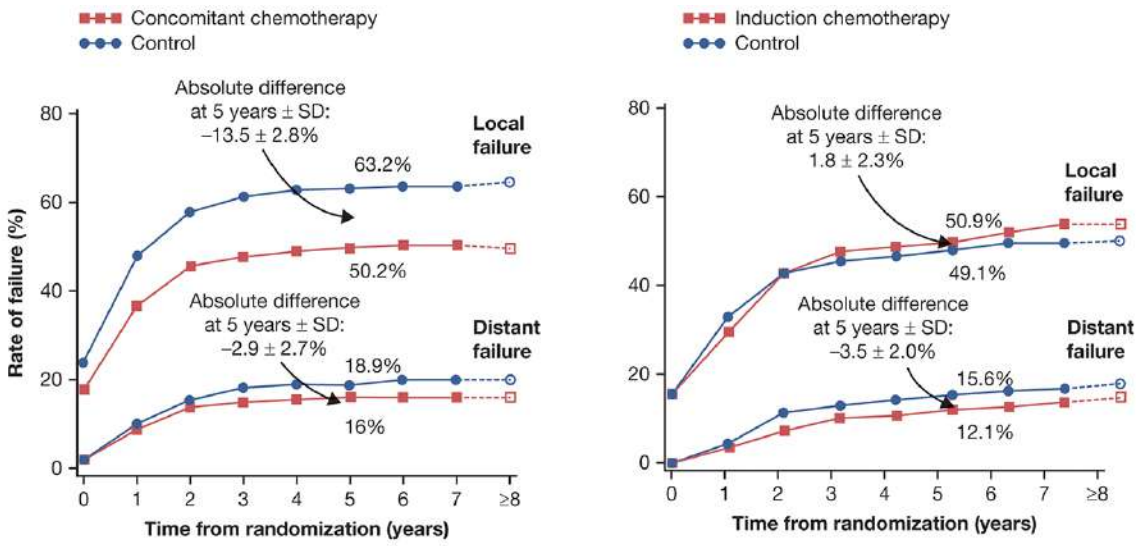
	Years 0–2	Years 2–5	Years 5–10	Years 10+
LRT + CT	2454/7420	851/5629	407/4315	171/1513
LRT	2819/6981	800/4520	316/3507	126/1116



Number of deaths/person-years

	Years 0–2	Years 2–5	Years 5–10	Years 10+
LRT + CT	473/22399	187/1828	87/951	30/150
LRT	490/23744	209/1956	100/1085	29/126

FIGURE 46.1 Data from the Meta-Analysis of Chemotherapy in Head and Neck Cancer trial demonstrating that adding concurrent chemotherapy to radiotherapy provides a significant improvement in survival while induction and adjuvant chemotherapy do not. A. Induction chemotherapy. B. Concurrent chemotherapy. C. Adjuvant chemotherapy. CT, chemotherapy; LRT, local radiotherapy.



Local failure and distant failure/person-years by period

	Years 0–2	Years 3–5	Years ≥6	Years 0–2	Years 3–5	Years ≥6
Local failure						
Control	493/1,648	22/406	2/165	497/2,627	38/1,073	10/684
Chemotherapy	373/1,837	20/603	1/240	519/2,749	58/1,142	22/751
Distant failure						
Control	82/1,756	8/416	1/166	90/2,788	18/1,116	8/711
Chemotherapy	83/1,915	6/616	0/241	62/2,929	23/1,204	9/773

FIGURE 46.2 Data from the Meta-Analysis of Chemotherapy in Head and Neck Cancer trial illustrating that the major therapeutic benefit of platinum-based chemotherapy results from an improvement in locoregional disease control when the drugs are given concurrently with radiotherapy. No significant improvement occurs with induction chemotherapy followed by radiotherapy.

The benefit of combined chemotherapy and RT is chiefly seen with concurrent delivery, which represents a biologically attractive approach as some chemotherapeutic agents may both radiosensitize cells and provide additive cytotoxicity. Direct comparisons of concurrent CRT versus induction chemotherapy with RT alone are few, but confirm that concurrent is superior.[13-15] Radiation Therapy Oncology Group (RTOG) 9111 was a three-arm trial of induction CDDP followed by RT alone versus concurrent CRT with CDDP versus RT alone in larynx cancer. Concurrent therapy constituted the most effective means of larynx preservation and provided the best disease control, albeit without a statistically significant survival benefit. The MACH-NC meta-analysis of this trial and others found that concurrent versus induction chemotherapy was associated with a 5-year absolute OS benefit of 6.2%, and generally, the addition of induction or

adjuvant chemotherapy to RT conferred no survival benefit[12] (see Figure 46.1).

Certain issues must be considered when evaluating randomized trials of CRT for advanced head and neck cancer. The first consideration relates to the effectiveness of the RT-alone control arm. Specifically, does it represent optimal single-modality treatment? If the CRT regimen is more effective than RT alone but the RT is suboptimal, then it is difficult to accurately gauge whether the combined modality regimen represents a true improvement in therapy. The second consideration concerns the toxicity of CRT itself. Typically, both acute and late toxicities from CRT are greater than from RT alone.[16-18]

Acute mucositis constitutes the most significant impediment to the timely delivery of concurrent CRT. Supportive care for mucositis and acute xerostomia, dysgeusia, and dermatitis includes oral rinses, saliva substitutes, topical moisturizers, and wound and pain management. Support for swallowing function from speech-language pathologists, as preventive therapy and after treatment, is a necessity. Still, up to about one-third of patients require enteral feeding tubes and hospitalization.[19-21] As prolongation of total treatment time adversely affects the success of RT, a major challenge has been developing regimens that integrate chemotherapy and RT but do not excessively increase total treatment time.[22-24] A thorough understanding of toxicity is mandatory, as avoidance of the functional morbidity associated with surgery in advanced head and neck cancer is one of the main reasons for using concurrent CRT in the first place.

Apart from supportive care, strategies for toxicity reduction include pharmacologic intervention with radioprotectors, reducing dose to normal tissues, and de-intensifying therapy by reducing target doses or volumes. Previously, a phase III trial published in 2000 demonstrated that administering the intravenous radioprotector amifostine prior to daily head and neck RT reduced acute and late xerostomia without compromising disease control or survival.[25] Subsequently, other randomized trials demonstrated that compared to older three-dimensional conformal RT (3D-CRT), intensity- modulated radiation therapy (IMRT) improved dosimetric sparing of parotid glands and reduced acute and late xerostomia, also without compromising clinical outcomes.[26] More recently, proton therapy has shown promising improvements in dosimetric normal tissue sparing and

toxicity in several retrospective studies in HNSCC.[27,28] Ongoing phase II trials are comparing protons to IMRT in unilateral neck RT (NCT02923570), oropharyngeal cancer (NCT01893307), and nasopharyngeal cancer (NPC) (NCT04528394), among others.

Late sequelae following RT include xerostomia, dysphagia, mandibular osteoradionecrosis, trismus, hearing loss, hypothyroidism, and accelerated carotid artery stenosis.[17,19,29] Prophylactic management with dental evaluation and thyroid labs following neck irradiation is standard of care, and the role of ultrasound screening for carotid artery stenosis has also been investigated.[30-32] Other therapeutic interventions include cholinergic agents to stimulate saliva flow, swallowing rehabilitation, and hyperbaric oxygen therapy for late tissue necrosis.[29] Aggressive lymphedema management by certified therapists is often required.[33] Patient-reported health-related quality of life (QoL) is also worse with concurrent chemotherapy but improved with IMRT compared to 3D-CRT. Health-related QoL often but not always recovers to baseline within 1 year, with certain symptoms such as xerostomia prone to persisting.[34] The severity and complexity of acute and late toxicities associated with head and neck CRT highlight the critical role of oncologists, nurses, dietitians, speech and physical therapists, social workers, and other multidisciplinary team members in optimizing patient care and QoL.

HISTORICAL DEVELOPMENT OF RADIATION AND CONCURRENT CHEMOTHERAPY

CRT may be administered in synchronous or alternating schemes. Synchronous administration results in the delivery of RT and chemotherapy on the same day. Typically, chemotherapy will be given for 1 day or more at the initiation of RT and then repeated in the same manner several weeks later. Alternating regimens usually sandwich RT and chemotherapy around one another. Radiation and drugs are, therefore, not necessarily, given on the same days. In such a scheme, chemotherapy would be given during the first week of treatment with RT following in subsequent week(s) before chemotherapy is given again.

Synchronous Radiation and Single-Agent Chemotherapy

Synchronous treatment is completed more quickly than alternating treatment. It is, therefore, preferable from a theoretical standpoint in terms of addressing the issue of accelerated repopulation, albeit at the expense of increased acute side effects. Early randomized trials used conventionally fractionated RT with single-agent chemotherapy. These studies are summarized in Table 46.1. The experimental arms of RTOG 9003,[3] EORTC 22791,[5] and DAHANCA 6-7[6] are included to provide a basis for comparison with optimal regimens of RT alone.

TABLE 46.1 RANDOMIZED TRIALS OF ONCE-DAILY IRRADIATION AND CONCURRENT CHEMOTHERAPY IN ADVANCED HEAD AND NECK CANCER

Institution	*N*	Radiotherapy	Chemotherapy	Outcome RT vs RT + CCT	Comments
RTOG 9003 Accelerated fractionation	268	72 Gy/42 d	None	LC: 54% DFS: 39% S: 51%	
Hyperfractionation	263	81 Gy/49 d	None	LC: 54% DFS: 38% S: 54%	
DAHANCA 6-7	1,476	70 Gy/39 d	None	LC: 76% DFS: 73%	
EORTC 22791	356	80.5 Gy/47 d	None	LC: 59%	
NCOG	104	70 Gy (1.8 Gy/d)	Bleo 5 mg^2/wk weeks 1-7; synchronous	LC: 35% vs 70%; *P* = .001 DFS: 15% vs 31%; *P* = 0.04 S: 24% vs 43%; *P* = .11	RT+CCT → ↑ acute toxicity, but RT not delayed
EORTC	224	64 Gy (1.8-2.0 Gy/d)	Bleo 15 mg^2/wk weeks 1-5; synchronous	DFS: 22% vs 23%; *P* = NS	RT+CCT → ↑ acute toxicity with RT delayed in 30%

Institution	*N*	Radiotherapy	Chemotherapy	Outcome RT vs RT + CCT	Comments
				S: 23% vs 22%; *P* = NS	
Christie Hospital	313	50-55 Gy (3.3 Gy/d)	MTX 100 mg/m^2 d 0, 14; synchronous	LC: 50% vs 70%; *P* = .02 S: 37% vs 47%; *P* = .07	Statistically significant benefit in LC and S for oropharynx
NCI Canada	175	66 Gy (2.0 Gy/d)	5-FU 1,200 mg/m^2 d 1-3 and 15-17; synchronous	DFS: 30% vs 50%; *P* = .06 S: 50% vs 63%; *P* = .08	Placebo-controlled trial
Yale University	195	68 Gy (1.8-2.0 Gy/d)	MMC 15 mg/m^2 d 5, 43; synchronous	LC: 54% vs 76%; *P* = .003 S: 42% vs 48%; *P* = NS	Predominantly post-op series 1° RT in 74 patients Benefit unclear in this patient group
Cleveland Clinic	100	66-72 Gy (1.8-2.0 Gy/d)	5-FU 1,000 mg/m^2 CI CDDP 20 mg/m^2 CI Days 1-4 and 22-25; synchronous	LC: 34% vs 42%; *P* = .004 S: 48% vs 50%; *P* = NS	RT+CCT ↑ toxicity but RT not delayed LC means survival with 1° site organ preservation.
Princess Margaret Hospital	209	50 Gy (2.5 Gy/d)	MMC 10 mg/m^2 5-FU 1,000 mg/m^2 CI Days 1-4 and 43-46; synchronous	LC: ~40% vs ~40% S: ~40% vs ~40%	RT only: continuous course RT+CTT: 4-wk break after 25 Gy
NICR Italy	157	RT/CCT: 60 Gy RT: 66 Gy	5-FU 200 mg/m^2 bolus CDDP 20 mg/m^2 bolus	LC: 32% vs 64%; *P* = .04 DFS: 9% vs 21%;	Unresectable disease RT+CCT: RT on weeks 2, 3, 5, 6, 8, and 9

Institution	*N*	Radiotherapy	Chemotherapy	Outcome RT vs RT + CCT	Comments
			Days 1-5, 22-26, 43-47, and 64-68; alternating	*P* = .008 S: 10% vs 24%; *P* = .01	RT only: ≥2-wk delay in >30%
GORTEC 94-01	226	70 Gy (2 Gy/d)	Carboplatin (CBDCA) 70 mg/m^2 5-FU 600 mg/m^2/d CI	LC: 25% vs 48%; *P* = .002 DFS: 15% vs 27%; *P* = .01 S: 16% vs 22%; *P* = .05	Significantly increased acute and late toxicity with RT/CCT
Intergroup Nasopharynx	193	70 Gy (2 Gy/d)	CDDP 100 mg/m^2 Days 1, 22, and 43 Post-RT CDDP/5-FU	DFS: 24% vs 69%; *P* < .001 S: 47% vs 78%; *P* = .005	Early trial closure

5-FU, 5-fluorouracil; Bleo, bleomycin; CDDP, cisplatin; CI, continuous infusion; DFS, disease-free survival; EORTC, European Organization for the Research and Treatment of Cancer; LC, local control; MMC, mitomycin-C; MTX, methotrexate; NCI, National Cancer Institute; NCOG, Northern California Oncology Group; NICR, National Institute for Cancer Research.; NS, not significant; RT/CCT, radiotherapy and concurrent chemotherapy; RTOG, Radiation Therapy Oncology Group; S, survival.

Both the Northern California Oncology Group (NCOG) and the EORTC tested radiation and synchronous bleomycin against RT alone.[35,36] Acute toxicity was worse in the combined modality arm in both trials, but the outcomes were quite different with respect to efficacy. The EORTC trial showed no improvement in DFS or OS, while the RT/bleomycin combination in the NCOG program led to a statistically significant doubling of locoregional control and DFS, as well as a near-significant improvement in OS from 24% to 43%.

Differences in study design and execution may explain the discrepancy between outcomes in the EORTC and NCOG trials. Fractionation was similar in the two studies, but patients in the EORTC trial received 15 mg of bleomycin twice weekly during the first 5 weeks of RT for a total dose of 150 mg, whereas the NCOG patients received 5 mg twice weekly for a total dose of 70 mg. Acute mucosal and skin toxicity was worse in the RT/bleomycin arm in both trials. Toxicity significantly prolonged the RT delivery time in 30% of the combined modality patients in the EORTC trial, but not in any of the RT-alone patients. This prolongation of treatment time and associated tumor repopulation in such a large proportion of patients may have negated any benefit accrued from the use of concurrent therapy. There were no differences in overall treatment time between the two treatment arms in the NCOG trial. An important lesson from these two studies is that the dose administration schedules of concurrent chemotherapy must be carefully designed so that toxicity does not adversely affect overall treatment compliance.

The Christie Hospital in Great Britain evaluated RT and 100 mg/m^2 of single-agent methotrexate (MTX) given at the commencement of and after 2 weeks of a 3-week course of treatment.[37] Most of the 313 patients in this protocol received 50 to 55 Gy in 15 or 16 fractions. Mucositis was significantly greater in the patients receiving MTX, but there was no difference in long-term toxicity. The addition of MTX increased local control from 50% to 70% (P = .02) and OS from 37% to 47% (P = .07). The greatest benefit was seen in patients with oropharyngeal primary tumors who constituted one-third of the study population. Local control with RT/MTX was 78% versus 38% with RT alone (P = .002) in this patient subset. OS was 25% with RT alone and 50% with RT/MTX (P = .009). Unfortunately, the data from this trial are not generally applicable to current clinical practice because of the large radiation fraction sizes that were used.

5-FU has been used in conjunction with RT more frequently than any other chemotherapeutic agent. Lo et al[38] reported the first study to show a significant improvement in local control and OS with the addition of bolus 5-FU to RT in oral cavity SCC. Browman et al[39] compared RT and continuous infusion 5-FU against RT alone in a placebo-controlled randomized trial sponsored by the National Cancer Institute of Canada. All 175 patients received 66 Gy in 2-Gy fractions. 5-FU was given at 1,200

mg/m^2/d for the first 3 days of the first and third weeks of irradiation. Confluent mucositis was more frequent in the 5-FU arm than in the placebo arm (32% vs 11%; P = .001), as was weight loss >15% from pretreatment baseline (41% vs 11%; P < .0001). This increased acute toxicity did not prolong the delivery of RT in the RT/5-FU arm relative to the RT/placebo arm. Two-year DFS and OS were 30% and 50% for RT/placebo patients and 50% and 63% for RT/5-FU patients (P = .06 and .08), respectively.

The relative radioresistance of hypoxic cells in vitro is well understood.[40] Clinically, the existence of hypoxia in both head and neck primary tumors and metastatic lymph nodes has been described, and its adverse impact on the prognosis of patients treated with RT has been demonstrated.[41,42] Investigators from Yale University designed their treatment strategy around this principle. They treated 195 patients in two randomized trials with mitomycin-C (MMC). This agent is predominantly metabolized in and preferentially cytotoxic to hypoxic cells. The Yale treatment program consisted of 68 Gy ± MMC on days 1 and 43 of RT. Local control was improved with the addition of MMC from 54% to 76% (P = .003). OS improved from 42% to 48%, but this was not statistically significant. Most patients in these trials received adjuvant postoperative or preoperative irradiation, however. Only 74 (38%) received definitive, primary RT, and the benefit from the addition of MMC in this subset is unclear.[43]

Synchronous Radiation and Multiagent Chemotherapy

CDDP is a radiosensitizing chemotherapy frequently combined with radiation, too.[44] The combination of CDDP and 5-FU is also one of the most active cytotoxic drug combinations against HNSCC. Consequently, investigators have incorporated both into a variety of concurrent treatment strategies.

A prospective multicenter trial from the University of Munich randomized 298 patients with unresectable stages III to IV HNSCC to twice-daily (bid) RT with or without concurrent CDDP, 5-FU, and leucovorin.[45] RT was three cycles of 23.4 Gy at 1.8 Gy bid to 70.2 Gy total, and treatment breaks were scheduled on days 12 to 21 and 34 to 43. Chemotherapy was three cycles of CDDP 60 mg/m^2, bolus 5-FU 350 mg/m^2 then continuous infusion 350 mg/m^2/d × 4 days, and bolus leucovorin 50

mg/m^2 then continuous infusion 100 mg/m^2/d × 4 days on days 2, 22, and 44 with RT. CRT doubled both 3-year local control (36% vs 17%; $P < .004$) and OS (48% vs 24%; $P < .0003$). CRT also increased acute grade 3 to 4 mucositis (38% vs 16%; $P < .001$), though no difference in serious late toxicity was seen.

A phase III trial from the Cleveland Clinic randomized 100 patients with stages III to IV nonnasopharyngeal HNSCC to RT alone (66-72 Gy in 1.8-2 Gy/fraction) versus CRT with concurrent CDDP (20 mg/m^2/d × 4 days) and continuous infusion 5-FU (1,000 mg/m^2/d × 4 days) on weeks 1 and 4.[46] The main objective of this study was primary site organ preservation, with response assessment after ~55 Gy and surgical salvage pursued after 3 to 6 weeks recovery in patients with persistent or progressive disease. Five-year OS with primary site preservation was increased with CRT versus RT (42% vs 34%; $P = .004$), although there was no significant difference in OS. CRT versus RT was also associated with increased acute toxicity, particularly weight loss and feeding tube requirement (58% vs 32%; $P < .01$).

MMC and 5-FU were used in a trial from Princess Margaret Hospital of 209 patients with locally advanced larynx or hypopharynx SCC, which randomized patients to RT alone or split-course RT with concurrent chemotherapy.[47] RT alone was 2.5 Gy/d to 50 Gy in 28 days, and split-course RT included a planned 4-week break after 25 Gy, resulting in the same dose over a total time of 56 days. Two cycles of bolus MMC (10 mg/m^2) and continuous infusion 5-FU (1,000 mg/m^2/d × 4 days) were given on days 1 and 43. The intent of the treatment break was to maintain comparable levels of acute toxicity in the two treatment arms. Acute toxicity was, in fact, equivalent in the two groups. Unfortunately, however, there was no difference in 4-year local control (~40%) or OS (~40%).

The Princess Margaret trial raises an important question: Can one quantify the contribution provided by concurrent chemotherapy in terms of the delivery of an equivalent dose of irradiation? Approximately 0.6 Gy/d is necessary to compensate for the tumor repopulation that transpires with each day of prolongation of standard course RT.[23] Thus, the total dose in the Princess Margaret Hospital CRT arm would have needed 67 Gy [(2.5 Gy × 20) + (0.6 Gy/d × 28 days)] to be isoeffective with the 50 Gy continuous course RT-alone arm. The equivalent efficacy of the two treatments in this trial suggests that chemotherapy compensated for the tumor repopulation

that occurred during the treatment break. Thus, one could argue that the chemotherapy was equivalent to approximately 17 Gy of additional irradiation. There can be no doubt as to the inferiority of the split-course fractionation scheme in this trial had it been delivered without chemotherapy and compared directly to the continuous course RT regimen. Conversely, if CRT had been given with continuous course RT, it would quite probably have been more efficacious than the RT-alone regimen.

A Spanish three-arm randomized trial (N = 859) provides additional information that is pertinent to the estimation of the radiotherapeutic dose equivalent provided by the delivery of concurrent chemotherapy.[48] Patients were assigned to receive one of the following regimens:

(a) 2 Gy/d to 60 Gy/42 days,

(b) 1.1 Gy bid to 70.4 Gy/44 days, or

(c) 2 Gy/d to 60 Gy/42 days with concurrent bolus 5-FU 250 mg/m^2 given every other day.

Progression-free survival (PFS) and OS were significantly worse in arm A as compared with arms B and C, as one would expect. Arms B and C were equally efficacious. Not accounting for the different fractionation in arms B and C and the unconventional administration of chemotherapy, it is still clear that the addition of 5-FU was comparable to dose escalation of approximately 10 Gy. A modeling analysis of phase III trials comparing CRT with RT only suggests that concurrent chemotherapy provides the equivalent of a 10- to 12-Gy dose escalation.[49]

Neither the Princess Margaret nor the Spanish trial delivered maximally intensive RT in their respective control arms. The rationale for treatment intensification with the addition of concurrent chemotherapy as opposed to simple RT dose escalation is weak in such a context. The situation may be dramatically different, however, when the RT-alone arm is maximally intensive such as in RTOG 9003 or EORTC 22791. Dose escalations of 10 to 12 Gy are not possible with accelerated regimens that already deliver 72 Gy in 6 weeks or with hyperfractionated regimens delivering 79 Gy in 7 weeks (see section “Radiation Fractionation Scheme”). Concurrent chemotherapy, however, can be added to modified fractionation regimens ≥70 Gy.

Alternating Radiotherapy and Chemotherapy

Alternating therapy produces less acute mucosal toxicity than synchronous therapy but may prolong the overall treatment time by several weeks. Although longer treatment times adversely affect efficacy in programs of standard RT alone due to tumor repopulation, the significance of overall treatment time (for RT) in a continuous course of alternating RT and chemotherapy is controversial. Some investigators have suggested that the usual time-dose relationships do not apply.[50]

The National Institute for Cancer Research in Italy conducted a phase III trial comparing RT with alternating RT and chemotherapy in 157 patients with unresectable HNSCC.[51,52] The RT arm was designed to give 70 Gy/7 weeks via standard fractionation. The combined therapy arm scheduled chemotherapy on weeks 1, 4, 7, and 10 and radiation (60 Gy) on weeks 2 to 3, 5 to 6, and 8 to 9. Each 2-week cycle of radiation consisted of 20 Gy/10 fractions. Each cycle of chemotherapy included 5 days of bolus CDDP (20 mg/m^2/d) and bolus 5-FU (200 mg/m^2/day). The incidence of grades 3 to 4 mucositis (18%-19%) was the same in both treatment groups. However, RT treatment delays occurred more often in the RT-alone patients: 32% with a 1-week prolongation and 25% with a ≥2-week prolongation. The corresponding delays in the combined modality treatment group were 11% and 15%. The median dose of RT delivered in the combined modality treatment group matched the planned dose of 60 Gy, but it was only 62 Gy in the RT-alone group. Five-year actuarial survival was significantly better in the combined modality treatment patients (24% vs 10%; P = .01), as were DFS (21% vs 9%; P = .008) and local control (64% vs 32%; P = .04).

Given the similar levels of acute toxicity, it is unclear why treatment times were prolonged and total doses reduced so extensively in the RT-only patients. Better protocol compliance in the control arm might well have changed the outcome of this trial. There are no other randomized trials of RT and alternating chemotherapy. Further randomized trials of alternating therapy will be necessary to determine its true value because the deficiencies of the National Institute for Cancer Research study prevent definitive conclusions.

Despite its drawbacks, the Italian study, like the Princess Margaret Hospital trial, strongly reinforces the idea that in some settings,

chemotherapy counteracts tumor repopulation during treatment. The total RT treatment time was prolonged in the combined modality arms in both studies. The fundamental difference between these two trials is that patients received no treatment during the RT break in the Princess Margaret Hospital trial and the patients in the Italian trial received chemotherapy during each interruption of RT.

CONTEMPORARY RANDOMIZED TRIALS OF RADIOTHERAPY AND CONCURRENT CHEMOTHERAPY

Curative Intent Treatment

Based on promising phase I to II trials of concurrent CRT, the French cooperative group initiated GORTEC 94-01 to evaluate conventionally fractionated RT with or without concurrent chemotherapy. This phase III trial randomized 226 patients with stages III to IV oropharyngeal cancer to RT alone (70 Gy in 2 Gy/fraction) versus CRT with concurrent carboplatin (70 mg/m^2/d × 4 days) and continuous infusion 5-FU (600 mg/m^2/d × 4 days) on weeks 1, 4, and 7.[18,53] CRT versus RT was associated with improved 5-year locoregional control (48% vs 25%; P = .002), DFS (27% vs 15%; P = .01), and OS (22% vs 16%; P = .05). Improved efficacy with CRT was accompanied by a significant increase in acute grades 3 to 4 mucositis from 39% to 71% (P = .005) and hematologic toxicity, with one treatment-related death from febrile neutropenia and sepsis. Grades 3 to 4 late toxicity numerically higher with CRT versus RT, though not statistically significant (56% vs 30%; P = .12).

An Intergroup phase III trial also demonstrated the efficacy of conventionally fractionated RT with concurrent platinum chemotherapy, although this study closed early due to slow accrual, with 271 of 362 planned patients analyzable.[54] Patients with unresectable oral cavity, oropharynx, larynx, and hypopharynx primaries were randomized to three arms, all of which received a total of 70 Gy in 2 Gy/fraction daily: RT alone versus CRT with concurrent CDDP (100 mg/m^2 on days 1, 22, and 42) versus split-course CRT with a break after 30 Gy to allow for potential resection and three cycles of CDDP (75 mg/m^2) and continuous infusion 5-FU (1,000 mg/m^2/d × 4 days) every 4 weeks. Compared to RT alone, CRT with daily RT and CDDP had improved 3-year OS (37% vs 23%; P = .014),

while split-course CRT did not (27%). Grade 3 or higher toxicity was higher with daily CRT versus RT alone (89% vs 52%; $P < .0001$) and with split-course CRT versus RT alone (77% vs 52%; $P < .001$).

In locally advanced NPC, the Intergroup 0099 trial demonstrated a survival benefit with combined concurrent and adjuvant chemotherapy compared to RT alone.[55] One hundred and ninety-three patients were randomized to 70 Gy in 1.8 to 2 Gy/fraction daily RT alone versus the same RT with concurrent CDDP (100 mg/m^2 on days 1, 22, and 42) and three cycles of adjuvant CDDP (80 mg/m^2) and continuous infusion 5-FU (1,000 mg/m^2/d × 4 days) every 4 weeks. The trial was terminated early when an interim analysis demonstrated improved OS with the combined modality regimen. Concurrent and adjuvant CRT versus RT alone was associated with improved 3-year PFS (69% vs 24%; $P < .001$) and 3-year OS (78% vs 47%; $P = .005$). CRT was also associated with increased grades 3 to 4 leukopenia and vomiting ($P < .05$), and 73% of CRT patients completed treatment as planned, compared to 91% of the RT-alone patients. Table 46.1 summarizes the data from the trials of conventionally fractionated irradiation and concurrent chemotherapy.

One must not only ask whether CRT is more effective than conventionally fractionated RT but also whether it is superior to hyperfractionated or accelerated fractionation regimens, as these represent the most efficacious single-modality treatment strategies. A prospective randomized trial from Duke University was one of the first to provide insight into this issue.[56] Patients with locally advanced HNSCC were randomized to hyperfractionated irradiation alone versus split-course hyperfractionation with concurrent CDDP and 5-FU. Patients in the RT-alone arm received 1.25 Gy bid continuous course to 75 Gy in 6 weeks, whereas patients on the CRT arm received 1.25 Gy bid split course to 70 Gy in 7 weeks. Chemotherapy was given during weeks 1 and 6 of irradiation (CDDP 12 mg/m^2/d × 5 days and continuous infusion 5-FU 600 mg/m^2/d × 5 days).

The time-dose aspects of the RT in the combined modality arm are similar to those of the previously discussed trials. The time-dose characteristics of the RT in the control arm were similar to certain aspects of both the concurrent boost arm (decreased treatment time) and the hyperfractionation arm (increased total dose) of RTOG 9003. Most

importantly, these characteristics made the RT more intensive in the control arm than in the experimental CRT arm. This study design was intentional because the primary objective of the trial was to determine whether a lower dose of RT with concurrent chemotherapy would be superior to maximally intensive/effective RT alone. This trial enrolled 116 patients, with 54% presenting with unresectable disease and approximately 46% of primaries located in the oropharynx. Locoregional control was 70% versus 44% (P = .006), favoring the combined modality patients. An unpublished update of the 5-year survival revealed superiority in the combined modality patients (42% vs 27%; P = .04) (Figure 46.3). Grade 3 mucositis was seen in approximately 75% of the patients in both arms, the main difference being that the mean time to resolution of mucositis was 50% longer in the patients receiving radiation and concurrent chemotherapy (6 vs 4 weeks).

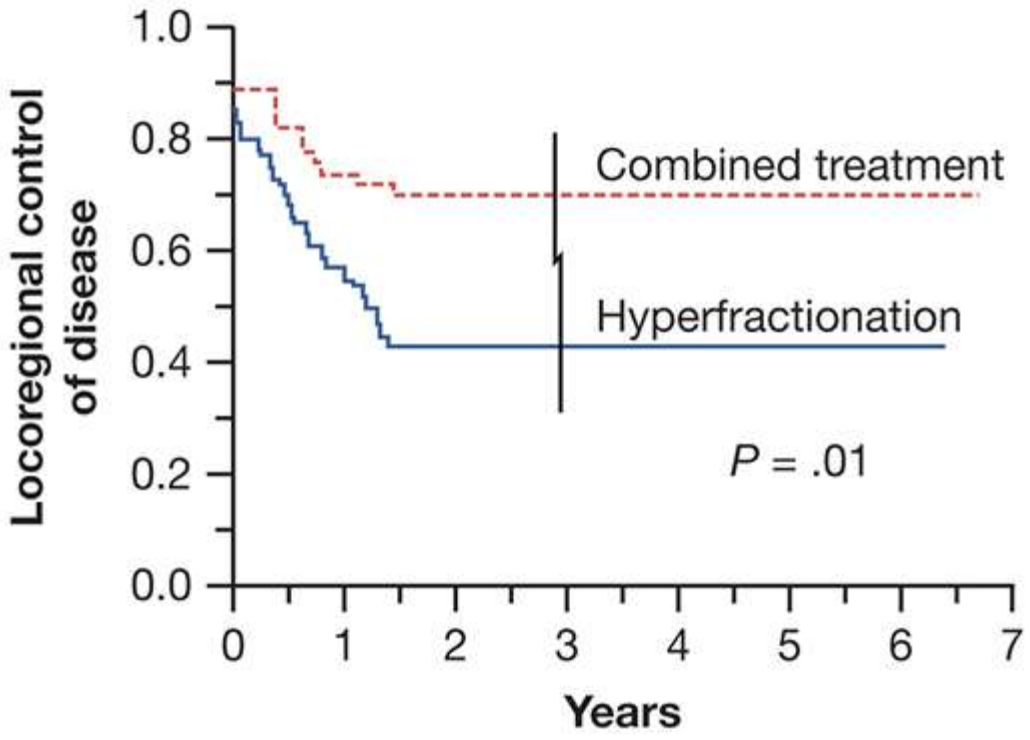


FIGURE 46.3 Five-year locoregional control in the Duke University randomized trial of continuous course accelerated hyperfractionation (44%) versus split-course accelerated hyperfractionation and concurrent cisplatin/5-fluorouracil (P = .01). Extended follow-up has demonstrated that the survival benefit of combined modality treatment is also statistically significant.

The German Cancer Society 95-06 trial also confirmed that CRT is superior to maximally intensive single-modality irradiation.[16] Three hundred and eighty-four patients, 93% of whom had either stage III or IV oropharyngeal or hypopharyngeal primaries, were enrolled. As in the Duke trial, the total dose of RT delivered in the CRT arm was lower than that in the RT control arm. RT patients received 77.6 Gy in 6 weeks (14 Gy at 2 Gy/fraction daily, then 63.6 Gy at 1.4 Gy bid), and CRT patients received 70.6 Gy in 6 weeks (30 Gy at 2 Gy/fraction daily, then 40.6 Gy at 1.4 Gy bid). Chemotherapy consisted of MXC (10 mg/m^2) on days 5 and 35 and 5-FU given as a single bolus of 350 mg/m^2 and a 5-day continuous infusion of 600 mg/m^2/d. Two-year survival was significantly better in the combined modality arm (54% vs 45%; P = .05), as was locoregional control (61% vs 45%; P = .001). Acute and chronic toxicity were equivalent in the two treatment populations.

Jeremic et al evaluated hyperfractionated irradiation (1.1 Gy bid to 77 Gy) with or without concurrent low-dose daily CDDP (6 mg/m^2) in stage III/IV patients.[57] This trial enrolled 130 patients, with approximately one-third of the primaries located in the oropharynx, 59% with T3-T4 primaries, and 80% with nodal involvement. Five-year locoregional control (50% vs 36%; P = .04), PFS (46% vs 25%; P = .007), and OS (46% vs 25%; P = .007) (Figure 46.4) were all significantly improved with the addition of concurrent chemotherapy. Of note, the distant metastasis-free survival was also improved in the concurrent therapy patients (86% vs 57%; P = .01).

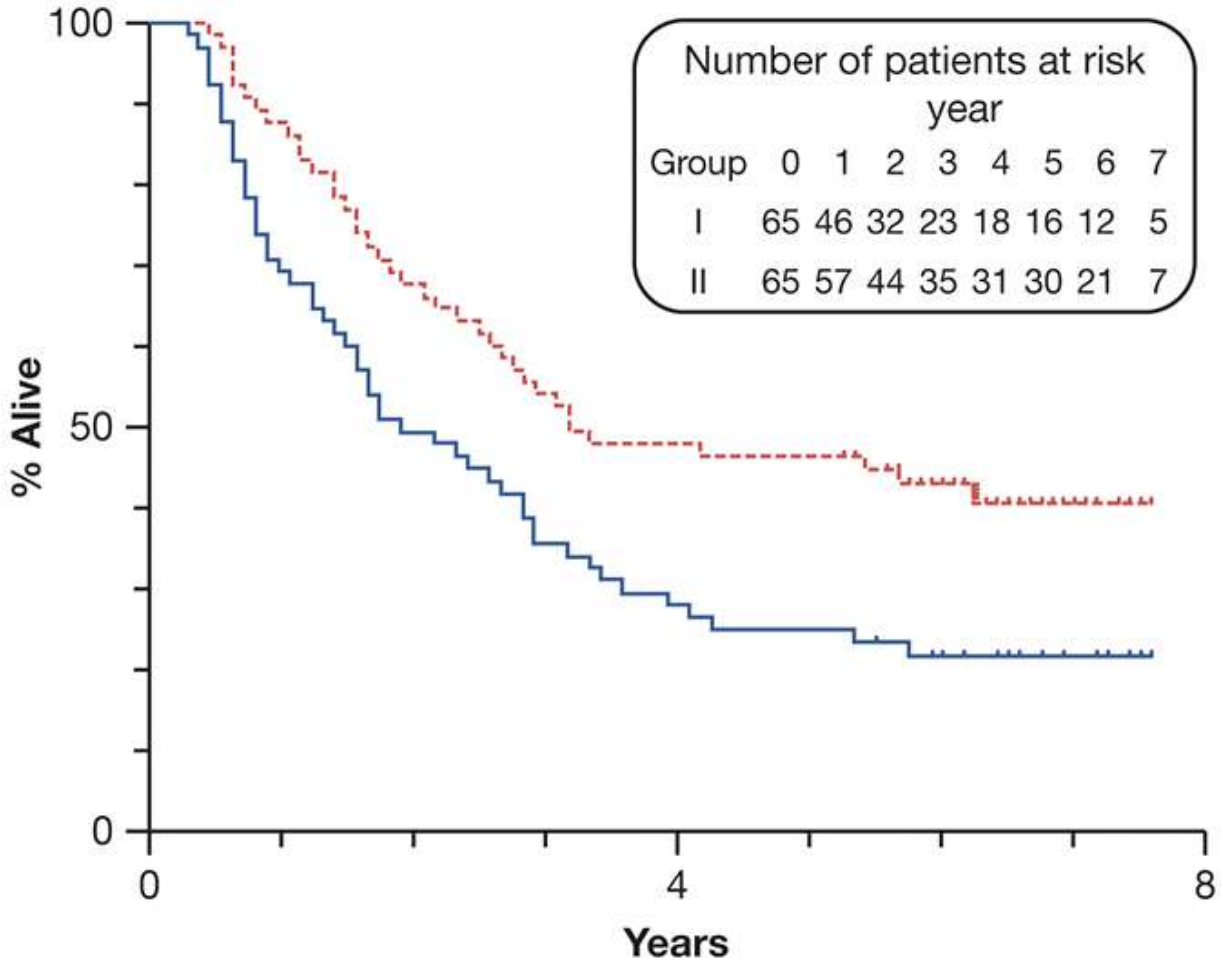


FIGURE 46.4 Five-year survival in the Yugoslavian trial of hyperfractionated irradiation alone (25%) or with daily low-dose concurrent cisplatin (46%) (P = .007).

A French cooperative group (FNLCC-GORTEC) tested a related concept in 163 patients with technically unresectable carcinomas of the oropharynx and hypopharynx.[58] RT was administered at 1.2 Gy bid to a total dose of 80.4 Gy/46 days to oropharyngeal primary tumors and 75.6 Gy/44 days to hypopharyngeal primary tumors. The experimental arm received the same RT and concurrent CDDP (100 mg/m^2) on days 1, 22, and 43 of RT. Three 5-day cycles of continuous infusion 5-FU were also administered. The first cycle was 750 mg/m^2/d and the second and third cycles were 430 mg/m^2/d. Three-year DFS favored the concurrent chemoradiation arm (48% vs 25%; P = .002), as did OS (38% vs 20%; P = .04). Post hoc subset analyses demonstrated that the larger (and statistically significant) benefit was confined to the patients with oropharyngeal carcinomas. However, the trial

was not designed to compare treatment efficacy in these two different primary sites of origin.

A three-arm randomized trial from the University of Vienna compared conventionally fractionated RT (70 Gy in 2 Gy/fraction daily) against continuous hyperfractionated accelerated RT with and without MXC (Vienna-Continuous Hyperfractionated Accelerated Radiation Therapy [V-CHART] + MMC and V-CHART, respectively).[59] RT was given as an initial 2.5-Gy fraction followed by 1.65 Gy bid to a total dose of 55.3 Gy in 17 days. MMC was given as a 20 mg/m^2 bolus on day 5 of RT. Of the 239 patients enrolled, 85% had T3/4 primary tumors, and 79% had nodal involvement.

Three-year actuarial locoregional control was 48% for V-CHART + MMC versus 32% for V-CHART and 31% for conventional fractionation (CF) (P = .05 and .03, respectively). Survival including death from all causes was also improved to 41% in the V-CHART + MMC arm as compared with 31% for V-CHART and 24% for CF (P = .03).

The incidence of confluent mucositis was 90% in both experimental arms as compared with 33% in the CF arm. The median time to complete resolution of mucositis was 6 to 7 weeks in all three arms. Grades 3 to 4 hematologic toxicity, primarily thrombocytopenia, developed in 20% of the V-CHART + MMC patients. Table 46.2 summarizes the data from the trials that used modified fractionation and concurrent chemotherapy and includes the RTOG 9003 and EORTC 22791 data as a point of reference for optimally delivered RT alone.

TABLE 46.2 RANDOMIZED TRIALS OF ACCELERATED OR HYPERFRACTIONATED RADIOTHERAPY AND CONCURRENT CHEMOTHERAPY IN ADVANCED HEAD AND NECK CANCER

Institution	*N*	Radiotherapy	Chemotherapy	Outcome RT vs RT+CCT	Comments
RTOG 9003 Accelerated fractionation and conc. boost	268	72 Gy/42 d 1.8 Gy q day and 1.5 Gy concurrent boost	None	LC: 54% DFS: 39% S: 51%	

Institution	*N*	Radiotherapy	Chemotherapy	Outcome RT vs RT+CCT	Comments
RTOG 9003 Hyperfractionation	263	81 Gy/49 d 1.2 Gy bid	None	LC: 54% DFS: 38% S: 54%	
University of Munich	298	70.2 Gy/51 d 1.8 Gy bid in both arms 23.4 Gy × 3 cycles 10-d split between cycles	5-FU 350 mg/m^2 bolus on day 2 5-FU 350 mg/m^2/d × 4 CI Leucovorin 50 mg/m^2 bolus on day 2 Leucovorin 100 mg/m^2/d × 4 CI CDDP 60 mg/m^2 × 1 Days 2-5, 22-25, 44-47	LC: 17% vs 36%; *P* = .01 S: 24% vs 48%; *P* < .0003	Unresectable disease
University of Vienna	239	55 Gy/2.5 wk for V-CHART ± MMC 70 Gy/7 wk CF control	MMC 20 mg/m^2 on day 5	LC: 32% vs 48%; *P* = .05 S: 31% vs 49%; *P* = .03	V-CHART vs V-CHART+MMC
Yugoslavian Cooperative	130	77 Gy/49 d in both arms 1.1 Gy bid	CDDP 6 mg/m^2/d	LC: 36% vs 50%; *P* = .04 DFS: 25% vs 46%; *P* = .007 S: 25% vs 46%; *P* = .007	Daily chemotherapy

Institution	*N*	Radiotherapy	Chemotherapy	Outcome RT vs RT+CCT	Comments
Charité University, Berlin	384	RT/CT: 70.6 Gy/6 wk RT: 77.6 Gy/6 wk	MMC 10 mg/m^2 d 5,36 5-FU 350 mg/m^2 bolus 5-FU 600 mg/m^2 5 d CI	LC: 45% vs 61%; *P* = .001 S: 24% vs 29%; *P* = .009	
Duke University	116	RT/CCT: 70 Gy/48 d (1-wk break @ 40 Gy) RT: 74 Gy/42 d (continuous course) 1.25 Gy bid both arms	5-FU 600 mg/m^2/d CI CDDP 12 mg/m^2/d bolus Days 1-5 and 36-40	LC: 44% vs 70%; *P* = .007 DFS: 41% vs 61%; *P* = .06 S: 34% vs 55%; *P* = .04	Acute and chronic toxicity comparable between RT and RT+CCT
FNLCC-GORTEC	163	80 Gy/47 d (oropharynx) 76 Gy/44 d (hypopharynx)	80 Gy/47 d CDDP 100 mg/m^2 on days 1, 22, and 43 5-FU 750 mg/m^2 × 5 d cycle 1 and 430 mg/m^2 × 5 d cycles 2 and 3	LC: DFS: 25% vs 48%; *P* = .002 S: 20% vs 38%; *P* = .04	All patients with unresectable disease
Swiss Cooperative Group	224	74.4 Gy/44 d 1.2 Gy bid	74 Gy/40 d 1.2 Gy bid CDDP 20 mg/m^2/d Two 5-d cycles	LC: 33% vs 51%; *P* = .04 DFS: 24% vs 27%; *P* > .10 S: 32% vs	

Institution	*N*	Radiotherapy	Chemotherapy	Outcome RT vs RT+CCT	Comments
				46%; *P* = .15	

5-FU, 5-fluorouracil; bid, twice-daily; CDDP, cisplatin; CF, conventional fractionation.; CI, continuous infusion; DFS, disease-free survival; LC, local controls; MMC, mitomycin-C; RT/CCT, radiotherapy and concurrent chemotherapy; RTOG, Radiation Therapy Oncology Group; S, survival; V-CHART, Vienna-Continuous Hyperfractionated Accelerated Radiation Therapy.

Adjuvant Postoperative Irradiation

The role of chemotherapy for patients receiving primary resection and postoperative irradiation has been studied less extensively than in the definitive irradiation setting. The National Cancer Institute Head and Neck Contracts Program[60] conducted a three-arm trial that evaluated the addition of one cycle of preoperative CDDP and bleomycin with or without six cycles of sequential CDDP (80 mg/m^2) maintenance chemotherapy after surgery and postoperative irradiation. The control arm consisted of surgery and postoperative irradiation alone. This trial enrolled 443 patients and demonstrated no benefit with respect to locoregional control or survival from the addition of chemotherapy. Nearly half of the patients who were randomized to receive maintenance chemotherapy never received it. Despite this flaw in study execution, the incidence of distant metastases as the site of first relapse was 9% in the patients assigned to maintenance chemotherapy as opposed to 19% in those who were not (P = .02).

Intergroup Study 0034 readdressed the issue of postoperative chemotherapy in a trial that randomized patients after surgery to three 21-day cycles of sequential CDDP (100 mg/m^2) and infusion 5-FU (1,000 mg/m^2/d × 5 days), followed by 50 to 60 Gy versus 50 to 60 Gy alone with no chemotherapy.[61] Again, there was no significant improvement in locoregional control or OS associated with the use of chemotherapy, but the incidence of distant metastases was reduced from 30% to 20% (P = .02).

In contrast to the use of sequential postoperative RT and chemotherapy, EORTC 22931 enrolled 334 patients with pT3-T4 disease (except pT3N0 larynx) with negative margins, pT1-T2 with pN2-N3 disease or risk factors

(extranodal spread, positive margins, perineural involvement, or vascular tumor embolism), or oral cavity or oropharyngeal tumors with level IV-V nodes. Patients were randomized to postoperative RT alone 66 Gy in 2 Gy/fraction daily versus the same RT with CDDP (100 mg/m^2 on days 1, 22, and 43).[62] Two-thirds of patients in the combined modality arm received all three cycles of chemotherapy. With a median follow-up of 5 years, chemotherapy significantly increased 5-year PFS from 36% to 47% (P = .04) and 5-year OS from 40% to 53% (P = .02). Acute grade 3 or high mucositis was significantly higher in the concurrent treatment arm (41% vs 21%; P = .001).

RTOG 9501 enrolled 459 patients with postoperative oral cavity, oropharynx, larynx, or hypopharynx SCC with ≥2 nodes involved, extracapsular extension (ECE), or positive margins.[63,64] Patients were randomized to postoperative RT alone 60 Gy in 2 Gy/fraction daily with or without a 6 Gy boost versus the same RT with the same CDDP used on EORTC 22931. Sixty-one percent of patients in the concurrent therapy arm received all three cycles of chemotherapy. With a median follow-up of 4 years, chemotherapy significant improved 2-year local-regional control from 72% to 82% (P = .01), with only eight local or regional recurrences occurring beyond the 2-year point. Initially, DFS also favored concurrent chemotherapy, although on long-term 10-year follow-up, RT versus CRT showed no significant difference in local-regional failure DFS (28.8% vs 22.3%; P = .1), DFS (19.1% vs 20.1%; P = .25), or OS (27.0% vs 29.1%; P = .31). Acute toxicity grade 3 or higher toxicity was increased with chemotherapy, with RT versus CRT (34% vs 77%; P < .001), but late toxicity was similar (17% vs 21%; P = .29).

A comparative analysis of the pooled data from these two studies ECE and/or microscopically involved surgical margins were the only risk factors for which the addition of chemotherapy to postoperative radiation was significant.[65] Patients with ≥2 nodes without ECE as their only risk factor did not benefit from the addition of chemotherapy. A trend in benefit to the addition of chemotherapy was seen in patients with stage III to IV diseases, perineural invasion (PNI), lymphovascular space invasion (LVI), and oral cavity or oropharyngeal tumors with level IV-V nodes. As such, concurrent chemoradiotherapy remains the standard of care for adjuvant therapy in patients with locally advanced HNSCC and the presence of ECE and/or

positive surgical margins. While long-term follow-up of RTOG 9501 found no significant outcome differences in analysis of all randomized patients, a subgroup analysis of patients with positive surgical margins and/or ECE demonstrated improved local-regional control and DFS with the addition of chemotherapy, further supporting these findings as poor risk factors in this disease.[64] Despite these recommendations, a retrospective analysis of the National Cancer Database identified a subset of patients with negative surgical margins and no ECE who still received adjuvant CRT.[66] Survival benefits of CRT versus RT alone increased in patients with multiple positive lymph nodes, despite the findings of the EORTC and RTOG studies, highlighting the need for ongoing evaluation into other poor risk factors for disease recurrence.

PRINCIPLES FOR THE CHOICE OF CONCURRENT TREATMENT REGIMENS

Three general statements can summarize the previously reviewed randomized trials:

1. RT with concurrent chemotherapy is more efficacious than conventionally fractionated RT alone in advanced head and neck cancer.
2. Concurrent therapy appears to be more effective than maximally intensive single-modality RT administered via a modified fractionation regimen.
3. Acute and late toxicity are increased with the use of concurrent chemotherapy.

No consensus exists, however, regarding either the optimal radiation dose fractionation scheme or the optimal scheduling of chemotherapy in these concurrent regimens. These controversies pose a decision-making dilemma to the physician when it is time to devise a treatment plan. Below, each component of concurrent treatment regimens is discussed to guide the selection process.

Radiation Fractionation Scheme

One rational approach to the choice of radiation dose fractionation within the context of concurrent chemotherapy would start with the selection of an optimal single-modality therapy and a definition of both its clinical efficacy and toxicity. Different dose fractionation schemes in concurrent treatment programs could then be normalized to one another using the biologically equivalent dose (BED) concept[67]: BED = $nd[1 + d/(\alpha/\beta)]$, where n = number of fractions delivered, d = dose per fraction, and α/β = 10 for tumors and acute responding normal tissues and 2 for late responding tissues. The intent of this normalization process is to allow a comparison of different treatment programs to identify those having a favorable profile in terms of maximizing the probability of tumor control while minimizing the risk of late toxicity. Kasibhatla et al evaluated prospective trials of CRT in order to estimate the radiotherapeutic dose equivalence of the concurrent chemotherapy.[49] They concluded that, with respect to the tumor, the administration of concurrent chemotherapy was equivalent to the delivery of an additional 10 to 12 Gy. Subsequently, Lee and Eisbruch estimated that concurrent chemotherapy was equivalent to the delivery of an additional 8 Gy when the development of acute mucositis was used as the end point.[68]

Whether modified fractionation irradiation and concurrent chemotherapy is superior to conventionally fractionated irradiation and concurrent chemotherapy was addressed in RTOG 0129.[69] Both RT and chemotherapy constituted experimental variables in this trial. This trial randomized 743 patients with stages III to IV oral cavity, oropharynx, hypopharynx, or larynx carcinoma to accelerated fractionation with concomitant boost (72 Gy in 42 fractions with 1.8 Gy/fraction daily and 1.5 Gy/ fraction boost as second treatment the last 12 days per RTOG 9003) and concurrent CDDP (100 mg/m^2 triweekly for two cycles) or conventionally fractionated RT (70 Gy in 2 Gy/fraction daily) and concurrent CDDP (100 mg/m^2 triweekly for two cycles for 3 cycles). No differences were observed in local-regional failure, PFS, distant metastases, or OS; 8-year OS was 48% in both arms. The findings show that one can compensate for the elimination of the third dose of CDDP by the more intensive radiation schedule. It should also be pointed out that on the conventionally fractionated arm, only 69% of patients could tolerate all three cycles of CDDP, a common occurrence with the use of high-dose CDDP. Outcome was also the same in the

conventionally fractionated arm patients who received two versus three cycles of CDDP.

Concurrent Chemotherapy Regimens

Concurrent CDDP with 100 mg/m^2 bolus dosing every 3 weeks on days 1, 22, and 43 of RT has historically been the standard based on multiple phase III randomized trials.[14,54,62,63,70] This schedule was originally developed in induction chemotherapy trials and later incorporated into concurrent chemotherapy regimens. However, smaller, more frequent chemotherapy doses may be preferable to bolus administration on two counts. Smaller individual doses may also reduce morbidity without compromising efficacy, which is especially critical as compliance is often limited with bolus administration. More frequent administration could provide radiosensitizing chemotherapy during a larger proportion of the RT course. Only around two-thirds of patients complete all three cycles.[62,63] RTOG 0129 and other studies have suggested that 200 mg/m^2 of CDDP concurrent with radiation is required to achieve maximal benefit when used concomitantly with radiation.[71]

Weekly CDDP regimens have been increasingly favored, in large part, because of their reduced toxicity and ease of administration. Recent prospective randomized trials have compared weekly versus triweekly regimens, mostly in the postoperative setting. In a phase III randomized trial from India, 300 patients with nonnasopharyngeal HNSCC received 60 to 70 Gy CRT with CDDP either every 3 weeks (100 mg/m^2 on days 1, 22, and 43) or weekly (30 mg/m^2).[72] 87.3% of enrolled patients had an oral cavity primary, with 93% receiving CRT in the adjuvant setting. In the triweekly arm, the median cumulative dose was 300 mg/m^2, although 56 of 150 patients received two instead of three cycles of CDDP. In the weekly arm, the median cumulative CDDP dose was 210 mg/m^2. Two-year locoregional control was higher with triweekly versus weekly CDDP (73.1% vs 58.5%; P = .014). There was also a trend toward improved survival with triweekly CDDP, and there was no difference in pattern of failure between the two arms. Acute severe toxicity was also higher with triweekly versus weekly CDDP (84.6% vs 71.6%; P = .006), although there was no difference in feeding tube placement or chronic toxicity. In updated

results presented at ASCO 2022, the triweekly versus weekly regimen remained more efficacious with 5-year locoregional control 55.2% versus 48.2%.[73]

In the phase II/III JCOG1008 trial, 261 postoperative patients with HNSCC receiving 66 Gy CRT were randomized to triweekly CDDP (100 mg/m^2 on days 1, 22, and 43) or weekly CDDP (40 mg/m^2).[74] The median cumulative dose of CDDP was 280 mg/m^2 in the triweekly arm and 239 mg/m^2 in the weekly arm. Survival was noninferior in the weekly arm; 2- and 3-year survival was 74.2% and 59.1% with triweekly CDDP and 77.7% and 71.6% with weekly CDDP, respectively. Grade 3 or higher neutropenia, infection, renal impairment, and hearing impairment were higher with triweekly CDDP. The discrepancy between this trial and the prior Indian trial may be due, in part, to the higher cumulative dose achieved in the weekly arm on this trial.

In the ConCERT trial, 278 patients with nonnasopharyngeal HNSCC receiving 70-Gy concurrent CRT in the definitive setting were randomized to triweekly CDDP (100 mg/m^2) versus weekly CDDP (40 mg/m^2). In all, 59.6% of patients had an oropharynx primary. In results presented at ASCO 2022, weekly CDDP was noninferior and associated with lower rates of acute grades 3 to 4 toxicity, including fewer hospitalizations and treatment breaks.[75] Two-year locoregional control was 57.69% versus 61.53% with triweekly versus weekly CDDP. An ongoing phase II/III trial, NRG HN009 (NCT05050162), is randomizing participants with oropharynx, larynx, hypopharynx, or human papillomavirus (HPV)-positive unknown primaries to triweekly CDDP (100 mg/m^2) versus weekly CDDP (40 mg/m^2), with an estimated enrollment of 464 participants.

In NPC, recent phase III trials of induction chemotherapy and sequential CRT have all used concurrent triweekly CDDP (80-100 mg/m^2 × 2-3 cycles).[76-79] Prior to these trials, one multicenter randomized phase II trial, KCSG-HN10-02, did compare concurrent triweekly CDDP (100 mg/m^2 on days 1, 22, and 43) versus weekly CDDP (40 mg/m^2) in 109 patients, with all patients receiving three cycles of adjuvant CDDP 80 mg/m^2 and 5-FU 1,000 mg/m^2/d every 3 weeks.[80] Three-year PFS was similar with triweekly versus weekly CDDP (63.8% vs 64.9%; P = .074), and grades 3 to 4 toxicity was also similar (39.3% vs 47.2%; P = .443).

ChiCTR-TRC-12001979 was the first phase III trial randomizing 510 patients with nonkeratinizing NPC to concurrent triweekly CDDP (100 mg/m^2 × 2 cycles) versus weekly CDDP (40 mg/m^2 × 6 weeks), with no induction or adjuvant chemotherapy given.[81] Three-year failure-free survival was similar with triweekly versus weekly regimens (85.4% vs 85.6%; $P > .99$), with acute grades 3 to 4 toxicity was lower with triweekly CDDP (55.8% vs 66.3%; $P = .015$). The median cumulative CDDP dose was also slightly lower in the triweekly vs weekly group (200 mg/m^2 vs 220 mg/m^2).

Phase III trials comparing of platinum-based and non– platinum-based concurrent treatment regimens are almost nonexistent, and the relative benefit of concurrent platinum versus fluorouracil or taxane therapy is unknown. Meta- analysis data have suggested that fluorouracil or CDDP regimens are more successful than carboplatin- or mitomycin-based treatments[82] and that concurrent platinum monotherapy is better than nonplatinum monotherapy.[11] In a single small phase III trial, a weekly paclitaxel concurrent regimen appeared equivalent to a weekly CDDP concurrent schedule.[83] Overall, however, the data must be considered limited and not definitive.

Most concurrent chemotherapy regimens use a single agent, an approach that, in general, suboptimally exploits the potential systemic benefits of this modality. In most other diseases, multiagent chemotherapy has been considered a better approach in controlling distant disease. In head and neck cancer, multiagent induction chemotherapy regimens have clearly demonstrated an impact on distant metastases, a benefit observed both from single trials and in a large meta-analysis.[11] This same meta-analysis demonstrated a significant but less pronounced impact on distant metastases from concurrent treatment schedules. However, no survival difference has been identified when comparing concurrent single-agent platinum regimens and concurrent multiagent schedules.

Radiation has also been administered in conjunction with concurrent high-dose intra-arterial CDDP. This approach has the hypothetical advantage of allowing selective delivery of chemotherapy to the tumor while sparing uninvolved organs and allowing for the administration of intravenous sodium thiosulfate, a systemic CDDP-neutralizing agent designed to protect the kidneys. Although the procedure proved technically

challenging, a phase II multi-institutional trial proved feasible.[84] However, a phase III trial comparing concurrent radiation and intra-arterial versus intravenous CDDP revealed no benefit,[85] and this mode of administration is not recommended.

The two most widely used CDDP administration schedules are 100 mg/m^2 every 3 weeks and 40 mg/m^2 once weekly. Equipoise exists regarding the relative efficacy of these different approaches. NRG-HN009 is an ongoing randomized phase III trial that is designed to answer this question (NCT05050162). Limited evidence suggests that CDDP may be more effective than carboplatin.[86] Taxanes are also active agents against HNSCC but have not been studied extensively as components of CRT regimens. The ongoing trial RTOG 1216 is a three-arm study comparing postoperative CRT with standard CDDP versus docetaxel-cetuximab versus CDDP-atezolizumab (NCT01810913).

Induction Chemotherapy and Sequential Chemoradiation

The use of induction chemotherapy for locoregionally advanced HNSCC is an attractive treatment option. The dramatic tumor shrinkage seen in previously untreated patients after CDDP-based chemotherapy regimens suggests that an improvement in locoregional control and even survival should also result. Multiple phase III clinical trials in nonnasopharyngeal HNSCC, however, have failed to demonstrate any reproducible impact from induction treatment schedules on overall outcome. The MACH-NC identified a marginal survival benefit with fluorouracil and platin induction chemotherapy with RT compared to RT alone, but this survival improvement was dwarfed by that obtained with the use of concurrent CRT regimens.[11,12]

Induction trials including the landmark Veterans Affairs (VA) larynx trial, however, have demonstrated a reduction in distant metastases compared to nonchemotherapy regimens.[9] The absence of impact on OS in this trial and others reflects the historically limited importance of distant metastases in the natural history of this disease. However, as locoregional control improved with concurrent CRT, distant metastases emerged as a more frequent cause of treatment failure, prompting renewed interest in induction chemotherapy.[87] Phase III randomized trials in locally advanced

nonnasopharyngeal HNSCC including TAX 323 and TAX 324 demonstrated the superiority of three-drug taxane, cisplatin, and fluorouracil (TPF) regimens when compared to cisplatin and fluorouracil (PF) alone[88-91] (Table 46.3). In these studies, successful induction was followed by definitive RT or CRT. TAX 323 randomized 358 patients with stages III to IV HNSCC to induction TPF versus PF followed by conventionally fractionated 66 to 70 Gy or accelerated/hyperfractionated 70 to 74 Gy RT alone, with 7% to 8% of patients discontinuing chemotherapy due to progression.89 TAX 324 randomized 501 patients with stages III to IV HNSCC to induction TPF versus PF followed by 70 to 74 Gy conventionally fractioned RT with concurrent weekly carboplatin area under the curve of 1.5, with 7% to 13% of patients discontinuing chemotherapy due to progression.[90] Long-term follow-up of both TAX 323 and TAX 324 confirmed significantly improved PFS and OS with TPF, with similar late toxicities.[92,93] A meta-analysis of these studies also found the taxane-containing induction regimens to be superior to platinum-fluorouracil alone.[94]

TABLE 46.3 TAXANE, CISPLATIN, AND FLUOROURACIL (TPF) VERSUS CISPLATIN AND FLUOROURACIL (PF) INDUCTION CHEMOTHERAPY: RANDOMIZED TRIALS

	Hitt et al[88]	Vermorken et al[89]	Posner et al[90]	Pointreau et al[91]
Taxane	**Paclitaxel**	**Docetaxel**	**Docetaxel**	**Docetaxel**
Definitive Treatment	**Variable**	**Radiation**	**Radiation/Weekly Carboplatin**	**Variable**
Response rate				
PF	68%	54%	64%	59%
TPF	80%	68%	72%	80%
P value	<.001	.006	.07	.002
Survival	2 y	3 y	3 y	3 y
PF	54%	26%	48%	60%
TPF	67%	37%	62%	60%
P value	.06	.02	.002	.57

The above studies established TPF as the preferred induction regimen but did not establish induction chemotherapy followed by concurrent CRT, also known as sequential chemoradiation, as the standard of care. The phase III trials PARADIGM and DeCIDE randomized stages III to IV nonnasopharyngeal HNSCC to induction TPF followed by concurrent CRT versus CRT alone.[95,96] PARADIGM compared three cycles of induction TPF followed by concurrent CRT with docetaxel or carboplatin versus CRT with two cycles of CDDP 100 mg/m^2; RT was accelerated with concomitant boost to 72 Gy in 6 weeks, except for patients with a favorable response to induction, who received conventionally fractionated 70 Gy with carboplatin. DeCIDE compared two cycles of induction TPF followed by concurrent CRT with 74 to 75 Gy RT bid and concurrent docetaxel, fluorouracil, and hydroxyurea versus the same CRT alone. Both PARADIGM and DeCIDE closed early after enrolling 145 and 285 patients, respectively, due to slow accrual. In PARADIGM, 56 of 69 who initiated induction completed CRT, while 66 of 72 who initiated CRT alone completed treatment. In DeCIDE, 122 of 136 who initiated induction completed CRT, while 130 of 133 in the CRT alone completed treatment. Neither trial observed a significant difference in the primary end point of OS or secondary end points of PFS (PARADIGM) or recurrence-free survival and distant failure-free survival (DeCIDE), though both were underpowered due to early termination. It is important to recognize that the treatment-related mortality rate was nearly 5% in both of these trials, which may have offset the effect of improved local-regional and distant control on OS. A meta-analysis of induction chemotherapy followed by concurrent CRT versus CRT alone revealed decreased distant metastasis rate with induction chemotherapy; however, there were no statistically significant differences in OS, PFS, overall response rate, or locoregional recurrence rate.[97]

Nonetheless, there are several situations where induction chemotherapy may have a role. In the organ preservation setting, induction chemotherapy has been investigated as a selection tool, with responders approached nonoperatively with RT, while nonresponders may be considered for surgery. This strategy is also grounded in part on historical studies demonstrating correlation between CDDP response and radiation response in untreated HNSCC.[98]

Using this paradigm, induction chemotherapy appears to be an acceptable strategy in the larynx preservation setting. The landmark RTOG 9111 trial in stages III to IV larynx SCC compared up to three cycles of induction PPF followed by RT alone in responders and surgery and postoperative RT in nonresponders versus concurrent CRT with single-agent triweekly CDDP versus RT alone. Five hundred and twenty patients were enrolled.[15] In the induction arm, around 85% of patients had a partial or complete response (CR) at the primary site after two cycles of induction PF, the same as the 85% seen in the VA larynx study. At 10 years, the primary end point of laryngectomy-free survival was similar between the induction chemotherapy and concurrent CRT arms (28.9% and 23.5%, respectively), but lower in the RT-alone arm (17.2%). Comparing the chemotherapy arms, although laryngeal preservation and locoregional control were superior in the concurrent CRT arm compared to the induction arm, distant metastatic control was equivalent. OS was not significantly different between the induction chemotherapy versus concurrent CRT versus RT-alone arms (38.8% vs 27.5% vs 31.5%).

Another trial from the University of Michigan (UMC 9520) used a single cycle of induction PF for subsequent treatment selection in stages III to IV larynx SCC. This phase II trial enrolled 97 patients.[99] In all, 75% of patients had a >50% response after a single cycle of induction chemotherapy and subsequently received concurrent CRT with triweekly CDDP (with two additional cycles of adjuvant chemotherapy), while most of the remaining patients underwent laryngectomy, with larynx preservation ultimately possible in 70% of the cohort. Importantly, there was no difference in OS in patients requiring laryngectomy due to failure to respond to induction chemotherapy versus those who did respond.

TPF is now the preferred induction regimen, though its increased side effects make compliance difficult with the full chemoradiation treatment package. On the phase II TREMPLIN trial, 153 patients with stages III to IV larynx/hypopharynx SCC received three cycles of induction TPF. In all, 85% had ≥50% response at the primary tumor. Responders received RT and were randomized to concurrent triweekly CDDP or cetuximab, while nonresponders underwent surgery. However, following induction therapy, just 43% and 71% of responders in the concurrent CDDP and cetuximab

arms, respectively, were able to complete the full protocol due to substantial acute toxicity.[100]

The evidence for induction chemotherapy as a predictive tool in oropharyngeal and oral cavity cancer is much more limited. The Southwest Oncology Group conducted a phase II trial in base of tongue or hypopharyngeal cancer, enrolling 59 participants who received two cycles of induction PF.[101] In all, 81% of the 37 base of tongue patients had a >50% response at the primary site and received concurrent CRT with triweekly CDDP. One of the four base of tongue nonresponders refused salvage surgery. Three-year PFS with organ preservation was 62% for the base of tongue. The University of Pennsylvania also conducted a phase II trial in resectable stages III to IV oropharyngeal cancer, enrolling 53 participants who received two cycles of induction carboplatin and paclitaxel.[102] In all, 89% of patients had a ≥50% response in the primary tumor and received concurrent CRT with weekly paclitaxel. Three of the six nonresponders refused surgery. The 3-year locoregional control was 82%, and the overall rate of organ preservation was 77%. Given the high rate of response to induction chemotherapy and the low compliance with salvage surgery, the use of induction chemotherapy for treatment selection is questionable, especially compared to upfront nonoperative or operative management.

The UMC conducted multiple single-arm phase II trials using induction chemotherapy for treatment selection in oropharynx cancer.[103] One of these was UMCC 9921, which enrolled 66 patients with stages III to IV oropharyngeal cancer who received one cycle of CDDP or carboplatin with fluorouracil.[104] In all, 81% had a >50% response in the primary tumor and received concurrent CRT with triweekly CDDP or carboplatin and adjuvant paclitaxel, with organ preservation achieved in 73% of patients. In this trial, high-risk HPV copy number was also positively associated with induction chemotherapy response and survival.

The relegation of induction chemotherapy to a purely predictive tool is disquieting to both medical and radiation oncologists. Induction adds significant cost and toxicity, especially when sequenced with concurrent chemoradiation. Compliance rates for an entire course of treatment with these regimens are only 65% to 70% in the most experienced hands.[88,105] It should provide an additional survival benefit or an improvement in distant

metastatic disease control. Other less toxic predictive "biomarkers" than responsiveness to induction chemotherapy might emerge in the future.

In NPC, nonoperative management is standard. Given challenges in tolerating adjuvant chemotherapy after concurrent CRT, several recent trials from China have examined induction chemotherapy instead, with several demonstrating a survival benefit.

A multi-institutional phase III trial randomized 241 patients with stages III to IVB NPC (except T3-T4N0) to induction docetaxel (60 mg/m^2), CDDP (60 mg/m^2), and continuous infusion 5-FU (600 mg/m^2/d × 5 days) every 3 weeks for three cycles, followed by concurrent CRT with three cycles of triweekly CDDP (100 mg/m^2) versus CRT alone.[76] Induction TPF versus CRT alone was associated with improved 3-year failure-free survival (80% vs 72%; P = .034). A second trial randomized 476 patients with stages III to IVB (except T3N0-1) NPC to induction CDDP (80 mg/m^2) and continuous infusion 5-FU (800 mg/m^2/d × 5 days) every 3 weeks for two cycles, followed by concurrent CRT with three cycles of triweekly CDDP (80 mg/m^2) versus CRT alone.[106] Induction PF versus CRT alone was associated with higher 5-year DFS (73.4% vs 63.1%; P = .007), 5-year distant metastasis-free survival rate (82.8% vs 73.1%; P = .014), and 5-year survival (80.8% vs 76.8%; P = .040).[77] In addition to induction TPF and PF, induction gemcitabine and CDDP have also demonstrated a survival benefit.[78] A third phase III trial randomized 480 patients with stages III to IVB NPC (except N0) to induction gemcitabine (1 g/m^2 on days 1 and 8) and CDDP (80 mg/m^2 on day 1) every 3 weeks for three cycles, followed by concurrent CRT with CDDP (100 mg/m^2 on days 1, 22, and 43) versus CRT alone. Compliance was excellent. In the induction arm, over 90% of patients received all induction chemotherapy and CRT with two to three cycles of concurrent CDDP, while in the CRT-alone arm, over 95% of patients received CRT with two to three cycles of concurrent CDDP. Induction gemcitabine and CDDP versus CRT alone significantly improved 3-year recurrence-free survival (85.3% vs 76.5%), 3-year distant recurrence-free survival (91.1% vs 84.4%), and 3-year survival (94.6% vs 90.3%). Both TPF and gemcitabine/CDDP are considered preferred regimens for induction chemotherapy treatment paradigms in locoregionally advanced NPC.[30]

These trials support a preferred strategy of induction chemotherapy and concurrent CRT for locally advanced nasopharyngeal cancer; CRT followed by adjuvant chemotherapy remains somewhat controversial. The ongoing phase II/III NRG-HN001 trial (NCT02135042) is investigating whether circulating Epstein-Barr virus (EBV) DNA may be used as a biomarker to identify patients who benefit from adjuvant chemotherapy. On this trial, patients with stages II to IVB nonmetastatic NPC with detectable pretreatment plasma EBV DNA will undergo conventionally fractioned RT with weekly CDDP (40 mg/m^2), with post-treatment EBV DNA assessed within 1 week after CRT. Patients with detectable post-treatment EBV DNA are randomized (phase II) to adjuvant gemcitabine and paclitaxel versus control CDDP and 5-FU, whereas patients with undetectable post-treatment EBV DNA are randomized (phase III) to observation versus control CDDP and 5-FU with a primary end point of PFS.

Radiotherapy and Molecularly Targeted Agents

Understanding the molecular basis of HNSCC has spurred interest in therapies targeting genetic mutations and aberrantly expressed proteins in HNSCC. Potential targets include epidermal growth factor receptor (EGFR), MET, and Notch transmembrane receptors and their downstream prosurvival PI3K, JAK/STAT, and Ras signaling pathways.[107] EGFR is upregulated in approximately 90% of patients with HNSCC and has been associated with a poor prognosis.[108-110] Cetuximab, a monoclonal antibody targeting EGFR, was the only Food and Drug Administration–approved targeted therapy available for HNSCC until the recent advent of immune checkpoint inhibitors, which are discussed separately. Of note, cetuximab is associated with rare hypersensitivity reactions that can result in anaphylaxis during initial infusion. Rates of grades 3 to 4 hypersensitivity reaction as high as 22% have been reported in North Carolina and Tennessee.[111] Hypersensitivity is likely mediated by immunoglobulin E antibodies directed against the oligosaccharide galactose-α-1,3-galactose, which is present on the cetuximab heavy chain; these pretreatment antibodies were found to be higher in patients from the southeastern United states.[112]

In 2006, Bonner and colleagues reported the results of IMCL-9815, a phase III randomized trial comparing RT alone or RT with weekly

cetuximab (400 mg/m^2 loading dose 1 week prior to RT followed by 250 mg/m^2 weekly during RT) in stages III to IV oropharynx, hypopharynx, and larynx SCC.[113] In all, 424 patients were enrolled. Cetuximab significantly increased OS when compared to RT alone, with a 2010 updated analysis reporting improved median OS from 29 to 49 months (P = .018) and improved 5-year OS from 36% to 46%.[114] Acute grade 3 or higher toxicity was generally similar between the two groups, including around 52% to 56% with mucositis. The two notable exceptions were higher rates of acneiform rash and infusion reactions with cetuximab. Around 17% of cetuximab-treated patients developed a grade 3 or higher acneiform rash. Grade 2 or higher acneiform rash was also associated with improved survival in cetuximab-treated patients, compared to grade 1 or no rash. An unplanned subgroup analysis found that cetuximab was more beneficial in patients with oropharynx cancers, smaller primary tumors, younger age, and higher performance status, initially suggestive of HPV association. However, a subsequent analysis found no interaction between cetuximab and HPV status.[115]

The control arm of the above trial was RT alone, which does not constitute optimal therapy for locally advanced disease. RTOG 0522 investigated whether cetuximab would be beneficial when added to chemoradiation. This phase III trial randomized 891 patients with stages III to IV oropharynx, hypopharynx, and larynx SCC to CRT without or with concurrent cetuximab. Accelerated RT (72 Gy in 42 fractions over 6 weeks or 70 Gy in 35 fractions over 6 weeks) and CDDP 100 mg/m^2 on days 1 and 22 were used in both arms. Addition of cetuximab increased treatment interruptions and mucositis and had no effect on 3-year PFS or OS or distant metastases. The absence of any benefit with cetuximab in RTOG 0522 contrasts with a phase III trial of untreated recurrent or metastatic HNSCC, where cetuximab significantly improved OS when added to CDDP or carboplatin and fluorouracil.[116]

Subsequently, multiple phase III trials have compared concurrent CDDP versus cetuximab with RT, largely in patients with HPV-associated oropharyngeal SCC (OPSCC), and found that cetuximab results in inferior OS compared to CDDP with no reduction in acute toxicities. RTOG 1016 randomized 987 patients with HPV-positive OPSCC to accelerated RT 70 Gy in 35 fractions over 6 weeks with concurrent CDDP 100 mg/m^2 on days

1 and 22 or concurrent cetuximab.[117] At 5 years, cetuximab versus CDDP was associated with inferior PFS (67.3% vs 78.5%, $P = .0002$), inferior OS (77.9% vs 84.6%, $P = .0163$), and higher locoregional failure (17.3% vs 9.9%, $P = .0005$). Rates of distant metastases and acute and late toxicity were similar between the two groups. The De-ESCALaTE HPV trial randomized 334 patients with HPV-positive low risk (smoking history 0-10 pack-years) OPSCC to conventionally fractionated RT 70 Gy with concurrent CDDP 100 mg/m^2 on days 1, 22, and 43 or concurrent cetuximab.[118] At 2 years, cetuximab versus CDDP was associated with higher recurrence (16.1% vs 6.0%, $P = .0007$) and inferior OS (89.4% vs 97.5%, $P = .001$). The ARTSCAN III trial randomized 291 patients with stages III to IV oropharynx, hypopharynx, or larynx SCC to daily fractionated RT with concurrent weekly CDDP 40 mg/m^2 or cetuximab. RT was conventionally fractionated to 68 Gy, with T3-T4 tumors undergoing a second randomization to 68 Gy versus 73.1 Gy. Eighty-five percent of patients had oropharynx primaries, and 89% of those oropharyngeal primaries were HPV positive. Unplanned interim analysis after 298 patients had been randomized demonstrated that cetuximab versus CDDP was associated with higher 3-year locoregional failure (23% vs 9%, $P = .0036$); 3-year OS was 78% versus 88% ($P = .086$), and distant metastases were similar. Dose escalation for T3-T4 tumors showed no benefit. Lastly, TROG 12.01 randomized 189 patients with stages III to IV HPV-positive OPSCC to conventionally fractionated RT with weekly CDDP 40 mg/m^2 or concurrent cetuximab, with no difference in the primary end point of symptom severity. Three-year failure-free survival was also inferior with cetuximab (80% vs 93%, $P = .015$). Together, these trials confirmed that concurrent CDDP remains the standard of care.

Another monoclonal anti-EGFR antibody, panitumumab, has also been investigated in HNSCC though has no role currently in therapy. In a phase III Canadian study, patients with locoregionally advanced SCC of the oral cavity, oropharynx, larynx, or hypopharynx were randomized to conventionally fractionated 70 Gy RT with CDDP 100 mg/m^2 on days 1, 22, and 43 versus accelerated RT 70 Gy in 35 fractions over 6 weeks with panitumumab 9 mg/kg every 3 weeks on days 7, 15, and 36 of RT.[119] No survival differences between the two groups were demonstrated. However, the study design was flawed, including no distinction of HPV-related

oropharynx tumors and low event rate. Furthermore, unlike cetuximab, panitumumab added to cytotoxic chemotherapy in the metastatic setting does not improve survival compared with chemotherapy alone.[120]

Apart from EGFR, molecularly targeted agents directed at tumor hypoxia have also been investigated in HNSCC. Hypoxia and dysregulated vasculature are common features of solid tumors. In HNSCC, overexpression of hypoxia-inducible factors is related to vascular endothelial growth factor (VEGF) expression, increased microvessel density, and reduced local control and OS after chemoradiation.[121] VEGF expression has also been associated with a 1.88-fold increased risk of death at 2 years in a meta-analysis of 1,002 patients with HNSCC.[122] Multiple studies assessing hypoxia by other means, including tumor oxygen tension or imaging with hypoxic radiotracers, have further cemented the correlation between hypoxia and reduced local control and survival following RT.[41,42,56,123]

Several therapeutic approaches directed at tumor hypoxia have been investigated in locally advanced HNSCC with limited success. Tirapazamine is a prodrug reduced to a cytotoxic free radical under hypoxic conditions and also sensitizes hypoxic cells to CDDP.[124] The randomized phase III TROG 02.02 (HeadSTART) trial of 861 patients with stages III to IV HNSCC found that adding tirapazamine to standard chemoradiation with CDDP had no effect on locoregional control, OS, or QoL.[125] However, a quarter of patients had noncompliant radiation plans, and a subset analysis of 693 patients who received at least 60 Gy to gross disease demonstrated a nonsignificant improvement in locoregional failure with tirapazamine.[126] Phase I/II trials have demonstrated that adding bevacizumab, a VEGF-A inhibitor, to CRT in HNSCC appears to be generally safe and feasible, although increased rates of hemorrhage and tissue necrosis have been reported, and one trial was terminated early due to reduced locoregional control with bevacizumab.[127-132] Several of these trials incorporated both bevacizumab and EGFR inhibitors such as erlotinib or cetuximab, as EGFR is one of many growth factors driving VEGF expression. In a phase III trial in recurrent or metastatic HNSCC, bevacizumab not only improved PFS when added to platinum-containing chemotherapy doublet but also increased treatment-related hemorrhage and deaths, with no improvement in OS.[133]

DEVELOPMENTAL ASPECTS OF COMBINED MODALITY THERAPY

De-escalation in Human Papillomavirus–Positive Disease

A landmark retrospective analysis of RTOG 0129 established HPV-positive oropharyngeal cancer as a distinct entity.[134] In a cohort of 323 patients, tumors positive for HPV DNA or p16 expression had significantly improved prognosis. At 3 years, HPV-positive versus HPV-negative OPSCC had PFS of 73.7% versus 43.4% ($P < .001$) and OS of 82.4% versus 57.1% ($P < .001$). Recursive partitioning analysis identified HPV status and smoking pack-years (≤10 vs >10) as the first and second major determinants, respectively, of OS and identified low-, intermediate-, and high-risk groups with 3-year OS of 93%, 70.8%, and 46.2%. Low risk was defined as HPV positive and ≤10 pack-years or HPV positive, >10 pack-years, and American Joint Committee on Cancer (AJCC) fifth edition stage N0-N2a disease. High risk was defined as HPV negative and >10 pack-years or HPV negative, ≤10 pack-years, and T4 disease; intermediate risk was in between. Subsequent analyses confirmed the prognostic and predictive importance of HPV status. HPV-positive versus HPV-negative disease demonstrated similar time to progression (~8 months) and patterns of failure, but significantly improved survival after first progression (2-year OS 54.6% vs 27.6%, $P < .001$).[135,136]

With the increased overall life expectancy and rising incidence of HPV-positive OPSCC, there has been significant interest in reducing treatment toxicities while maintaining excellent prognosis.[137] Approaches include using induction chemotherapy for risk stratification and de-escalating adjuvant or definitive chemoradiation.

ECOG-ACRIN E1308 investigated induction chemotherapy in 80 patients with HPV-positive AJCC seventh edition stages III to IV OPSCC. Patients received three cycles of CDDP, paclitaxel, and cetuximab followed by RT with concurrent cetuximab.[138] In all, 54 Gy in 27 fractions was given for a clinical CR at the primary site, while 69.3 Gy in 33 fractions was given for <CR. Fifty-one patients with a CR receiving 54 Gy with cetuximab had 2-year PFS and OS of 80% and 94%, respectively. One challenge to interpreting the data from this trial is that patients who had a CR at the primary site but <CR in the neck would have had the neck

boosted to 69.3 Gy, and the additional dose received by the primary site was not reported.

Another trial from University of California, Los Angeles enrolled 45 patients with HPV-positive stages III to IV OPSCC who received two cycles of induction carboplatin and paclitaxel followed by concurrent CRT with paclitaxel.[139] In this, 54 Gy in 27 fractions was given for a CR or partial response, while 60 Gy in 30 fractions was given for a less than partial response. Two-year PFS was 92%. While reduced dose RT was associated with reduced toxicity, it is unclear whether using induction chemotherapy for risk stratification represents true de-intensification. Recently, other means of risk stratification including serum and imaging biomarkers have been explored and are addressed below.

In the postoperative setting, ECOG-ACRIN E3311 enrolled 495 patients with HPV-positive AJCC seventh edition stages III to IVA OPSCC following transoral surgery and neck dissection.[140] Thirty-eight patients with low-risk disease (pT1-T2 N0-N1 and no risk factors) were observed, with a 2-year PFS of 96.9%. Two hundred and nine patients with intermediate-risk disease (close <3 mm margins, ≤1 mm ENE, 2-4 lymph nodes involved, PNI, or LVI) were randomized to reduced dose 50 Gy or standard dose 60 Gy, with similar 2-year PFS of 94.9% and 96.0%, respectively. One hundred and thirteen patients with high-risk disease (positive margins or >1 mm ENE or ≥5 lymph nodes involved) received 66 Gy with concurrent weekly CDDP 40 mg/m^2, with a 2-year PFS of 90.7%. Importantly, nearly one-third of patients received trimodality therapy on E3311, highlighting the need for careful patient selection.

A conceptually similar risk-stratified postoperative trial, PATHOS, is ongoing (NCT02215265). Another phase II trial from the Mayo Clinic, MC1273, enrolled patients with HPV-positive AJCC seventh edition stages III to IV OPSCC and ≤10 pack-year smoking history who underwent surgery with negative margins and at least one intermediate-risk factor (≥T3, ≥N2a, PNI, or LVI) or any ENE.[141] Thirty-six intermediate-risk patients received 30 Gy in 1.5 Gy fractions bid to the primary site and neck with concurrent docetaxel 15 mg/m^2 on days 1 and 8. Forty-three patients with any ENE received the same, with a simultaneous integrated boost to 36 Gy in 1.8 Gy fractions to lymph node levels with ENE. Two-year locoregional control was 96.2%, PFS was 91.1%, and OS was 98.7%.

Results from MC1675, a phase III trial randomizing patients 2:1 to the de-escalated paradigm above versus standard 60 Gy with or without weekly CDDP 40 mg/m^2, were presented at 2021 American Society for Radiation Oncology annual meeting.[142] De-escalated versus standard adjuvant therapy achieved similar 2-year locoregional control (95.5% vs 97.9%), PFS (86.5% vs 95.1%), and OS (96.1% vs 97.0%), with the notable exception of patients with pN2 disease and ENE, where 2-year PFS was lower with de-escalated versus standard therapy (42.9% vs 100%).

In the definitive RT setting, two different de-intensified regimens were assessed on NRG HN002, a phase II trial enrolling patients with HPV-positive OPSCC with AJCC seventh edition stage T1-T2 N1-N2b M0 or T3 N0-N2b M0 disease and ≤10 pack-year smoking history.[143] Three hundred and six patients were randomized to two parallel arms: concurrent CRT with 60 Gy in 6 weeks with weekly CDDP 40 mg/m^2 or accelerated RT alone with 60 Gy in 5 weeks. The primary end point was 2-year PFS superior to a historical control of 85%. The CRT arm achieved this standard (90.5%; P = .04), while the accelerated RT-alone arm did not (87.6%; P = .23). Thus, the concurrent 60-Gy CRT arm is one of three arms on HN005 (NCT03952585), an ongoing randomized phase II/III in patients with HPV-positive OPSCC with AJCC eighth edition stage T1-T2 N1 M0 or T3 N0-N1 M0 disease and ≤10 pack-year smoking history. The other two arms are accelerated RT 70 Gy in 6 weeks with concurrent CDDP (100 mg/m^2 on days 1 and 22) and accelerated RT 60 Gy in 5 weeks with concurrent nivolumab (starting 1 week prior to RT, 240 mg/m^2 every 2 weeks for six cycles). After phase II interim futility analysis, the 60-Gy CRT arm was closed as the prespecified noninferiority threshold was not reached.

Two multi-institutional phase II trials from the University of North Carolina and University of Florida have also investigated de-intensified definitive CRT, enrolling patients with AJCC seventh edition stage T0-T3 N0-N2c M0 HPV-positive OPSCC and either ≤10 pack-year smoking history or ≤30 pack-years and abstinent for 5 years. Patients received a de-intensified regimen of 60 Gy with weekly CDDP 30 mg/m^2. The first trial enrolled 44 patients, with patients assessed by primary site biopsy and dissection of initially involved nodes within 6 to 14 weeks post-treatment.[144,145] In all, 86% achieved a pathologic CR, and 3-year PFS and OS were 100%. The second trial enrolled 114 patients, and the patients

were assessed with standard post-treatment PET rather than surgery, with 2-year PFS and OS of 86% and 95%, respectively.[146] Thirty-four percent of patients required a temporary feeding tube, and no grade 3 or higher late toxicity was observed.

In the future, serum and imaging biomarkers may also be useful to select patients suitable for treatment de-escalation. Circulating tumor DNA (ctDNA) of high-risk HPV subtypes demonstrates high sensitivity and specificity for HPV-positive OPSCC at diagnosis and during post-treatment surveillance.[147] The relationship between ctDNA clearance kinetics during definitive radiation and clinical outcomes is an area of active investigation in HPV-positive OPSCC. For instance, one study from the UMC found that low pretreatment ctDNA with early increase at week 2 was associated with improved clinical outcomes, while studies from the University of North Carolina and Osaka University reported that ctDNA clearance at week 4 was associated with improved disease control.[148-150] Several ongoing phase II trials are using ctDNA clearance, largely at week 4, to select patients suitable for treatment de-escalation (eg, NCT04900623, NCT05268614, NCT03215719). Imaging biomarkers have also been investigated, including glucose metabolism parameters on ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) and hypoxia on ^{18}F-fluoromisonidazole (FMISO) PET.[151,152] Ongoing phase II trials are using metabolic response or absence of hypoxia on intratreatment FDG-PET or FMISO-PET, respectively, as biomarkers to identify patients suitable for de-escalated chemoradiation in HPV-positive OPSCC (eg, NCT04667585, NCT03323463).

Overall, several themes emerge from the de-escalation trials above. A sizeable fraction of patients in these trials received induction chemotherapy in addition to roughly 6 weeks of radiation, often with concurrent chemotherapy, or upfront surgery in addition to 6 weeks of chemoradiation. Arguably, neither of these represents meaningful treatment de-intensification. On the other hand, in the setting of definitive concurrent chemoradiation, caution is warranted as reducing, replacing, or omitting cytotoxic chemotherapy may result in inferior clinical outcomes, as evidenced by the results of RTOG 1016.[117] Improved upfront risk stratification of HPV-positive disease is needed, potentially with serum or imaging biomarkers, to better identify patients suitable for modest or

aggressive treatment de-intensification. Currently, in the absence of level I evidence for de-intensification, 70 Gy with concurrent CDDP remains the standard of care for nonoperative management of patients with HPV-positive and HPV-negative.[30]

Immunotherapy

Immune checkpoint inhibitors such as antibodies directed against programmed cell death 1 (PD-1) or programmed death ligand 1 (PD-L1) represent promising modalities of treatment since HNSCC is seen as an immunosuppressive disease. In recurrent or metastatic HNSCC, KEYNOTE-048 randomized 882 participants to first-line therapy with the PD-1 inhibitor pembrolizumab alone versus pembrolizumab with platinum and 5-FU versus cetuximab with platinum and fluorouracil.[153] Pembrolizumab with chemotherapy improved OS compared to cetuximab with chemotherapy across all arms, regardless of PD-L1 positivity. Pembrolizumab alone also improved OS over cetuximab with chemotherapy in patients with PD-L1 positivity (combined positive score [CPS] ≥1). In platinum-refractory recurrent or metastatic HNSCC, CheckMate 141 randomized 361 patients to the PD-1 inhibitor nivolumab versus standard single-agent systemic therapy and demonstrated an OS benefit with nivolumab.[154] Given this success, immunotherapy has also been assessed in locally advanced HNSCC in operative and nonoperative management.

In the preoperative setting, immunotherapy has demonstrated limited success in early-phase trials. CheckMate 358 was a multicohort phase I/II trial that included 52 patients with AJCC seventh edition stages III to IV resectable HNSCC. Neoadjuvant nivolumab 240 mg on days 1 and 15 was given prior to surgery on day 29, and while no pathologic CRs were observed, pathologic regression was seen in 23.5% of HPV-positive and 5.9% of HPV-negative tumors.[155] A phase II trial from the University of Cincinnati enrolled 92 patients with resectable locally advanced HNSCC and either cT3-T4 disease, ≥2 lymph nodes involved, and/or clinical ENE.[156] Patients received neoadjuvant and adjuvant pembrolizumab 200 mg for seven doses total. Compared to historical control, pembrolizumab improved DFS only in intermediate-risk patients without positive margins

and without ENE. In the postoperative setting, multiple ongoing phase III trials including IMvoke010 (NCT03452137), IMSTAR-HN (NCT03700905), NIVOPOSTOP (NCT03576417), RTOG 1216 (NCT01810913), and MK-3475-689 (NCT03765918) are investigating the addition of immune checkpoint inhibitors to standard adjuvant therapy.

In nonoperative management of locally advanced nonnasopharyngeal HNSCC, several phase III trials have failed to demonstrate any benefit for adding immunotherapy to standard CRT with 70 Gy and concurrent triweekly CDDP 100 mg/m^2. JAVELIN Head and Neck 100 randomized 697 patients receiving standard CRT with concurrent CDDP to either avelumab, a PD-L1 inhibitor, 10 mg/kg every 2 weeks for 12 months versus placebo.[157] The primary end point of median PFS was not reached in either arm but appeared to favor the placebo group. The similar GORTEC-REACH trial randomized 707 patients receiving standard CRT with concurrent CDDP or, if ineligible for CDDP, concurrent cetuximab to either avelumab 10 mg/kg every 2 weeks for 12 months or standard therapy alone.[158,159] Interim analysis presented at the 2021 European Society for Medical Oncology (ESMO) Congress showed that in patients receiving CDDP, the 1-year PFS rate was 64% with avelumab versus 73% with standard therapy, which crossed the futility boundary. In patients receiving cetuximab, avelumab did significantly reduce distant metastases (hazard ratio [HR] = 0.31, P = .007), but otherwise no significant improvement in PFS was seen. KEYNOTE-412 studied pembrolizumab, randomizing 804 patients receiving standard CRT to pembrolizumab 200 mg every 3 weeks for 17 doses versus placebo. In results presented at ESMO 2022, pembrolizumab was associated with a trend toward improved event-free survival (HR = 0.83, P = .0429), which did not meet the superiority threshold. Benefit was larger in patients with high PD-L1 expression (CPS >20) but remained nonsignificant. The final results of GORTEC-REACH and KEYNOTE-412 have not yet been published. In locally advanced nasopharyngeal SCC, several ongoing phase III trials are assessing the addition of immunotherapy to standard induction chemotherapy and concurrent CRT (eg, NCT04453826, NCT03700476, NCT04557020).

Disease and treatment-related factors may explain immunotherapy's absence of benefit in HNSCC chemoradiation trials such as JAVELIN and KEYNOTE. PD-L1 expression and tumor mutational burden (TMB) are

predictive biomarkers for immunotherapy response, and selection of patients with high mutation burden or PD-L1 expression may be necessary to realize a benefit with PD-1/PD-L1 inhibitors. However, in locally advanced non–small cell lung cancer (NSCLC), which has a similar rate of PD-L1 positivity and TMB to HNSCC, immunotherapy did improve survival when added to chemoradiation in unselected patients.[160,161] Patterns of failure may contribute to this discrepancy, as immune checkpoint inhibitors may have more of an impact on the distant metastases more common in NSCLC rather than the locoregional failures common in HNSCC.[162] Elective nodal irradiation, which is standard of care in HNSCC but not in NSCLC due to locoregional patterns of failure, may also hinder the process of T-cell priming by antigen-presenting cells, which occurs in lymph nodes. One analogous situation would be locally advanced cervical cancer, where elective nodal irradiation with CDDP-based chemoradiation is also standard, as in HNSCC. In the phase III CALLA trial, addition of immunotherapy to standard CRT in locally advanced cervical cancer did not show any significant improvement in PFS in results presented at the 2022 International Gynecologic Cancer Society meeting.[163] Overall, locally advanced HNSCC remains a challenging disease to eradicate, and thus far, immunotherapy has not demonstrated any benefit when added to standard CRT.

SUMMARY

Historic trials have demonstrated the superiority of altered fractionation as opposed to conventional once-daily fractionation in locally advanced head and neck cancer. Altered fractionation RT has, in turn, been superseded by conventionally fractionated RT with concurrent chemotherapy for locally advanced disease. Current standard of care remains RT with concurrent CDDP. In general, adding induction chemotherapy, adjuvant chemotherapy, targeted therapy, and, more recently, immunotherapy to the chemoradiation paradigm has shown limited success, although induction chemotherapy has demonstrated a survival benefit in locally advanced NPC.

The increased acute and late toxicity that results from combining these multiple modalities pose immediate challenges. These include the need for effective strategies in toxicity prophylaxis and management, as well as the

need to develop criteria for a priori selection of patients who may benefit from treatment de-escalation while not compromising disease control. Recent and ongoing studies de-intensifying chemoradiation in patients with HPV-positive oropharyngeal cancer have been promising. Incorporating serum and functional imaging biomarkers to disease site and stage-specific therapy is another area of active investigation. These efforts will allow for the optimal integration of RT, chemotherapy, biologically targeted therapy, and immunotherapy for those patients requiring combined modality therapy.

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CHAPTER 47

Nasopharynx

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ANATOMY

The nasopharynx is a cuboidal chamber, slightly broader in the transverse dimension than the anterior-posterior dimension (Figure 47.1). Anteriorly, it is continuous with the nasal cavity via the posterior choanae, whereas inferiorly, it communicates with the oropharynx. The roof of the nasopharynx is formed by the basilar portion of the sphenoid and occipital bones and the floor by the superior surface of the soft palate and nasopharyngeal isthmus. The lateral walls of the nasopharynx contain the pharyngotympanic tube (*eustachian tube*) openings, which are bounded by a prominence known as the *torus tubarius*. The *torus* is formed by the cartilage of the pharyngotympanic tube elevating the mucous membrane of the lateral nasopharynx. Posterior to the *torus* is the pharyngeal recess otherwise known as the *fossa of Rosenmüller*. The lateral walls, including the pharyngeal recess (fossa of Rosenmüller), are the most common origin of nasopharyngeal malignancies. The posterior wall of the nasopharynx contains the superior pharyngeal constrictor muscle, pharyngobasilar fascia, and buccopharyngeal fascia.

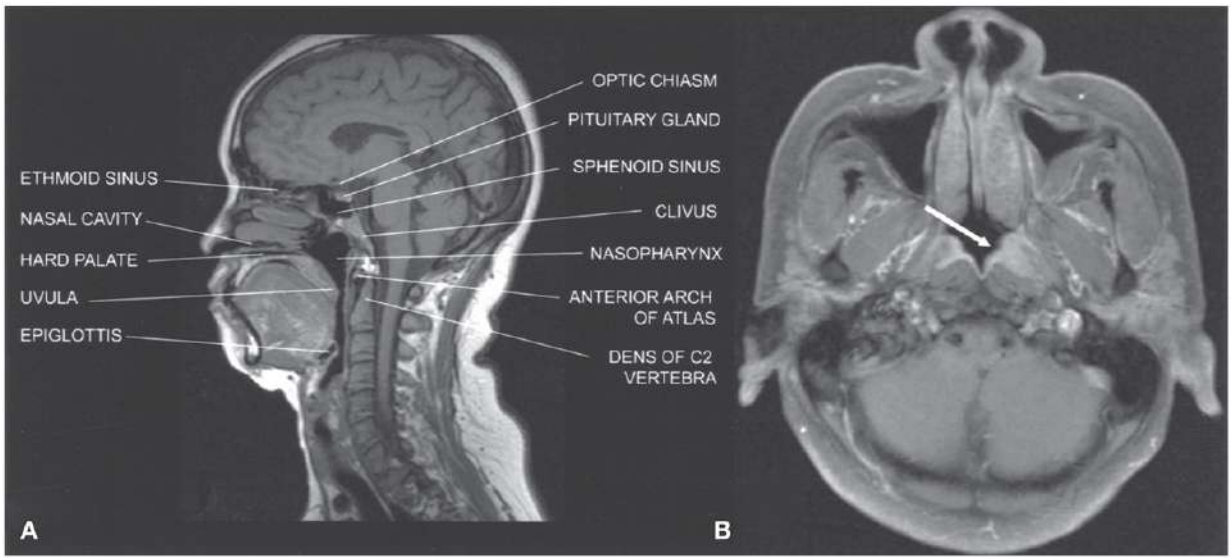

FIGURE 47.1 A. Midsagittal magnetic resonance image (MRI) of the head showing the nasopharynx and related structures. B. Axial contrast-enhanced MRI showing a small tumor in the left fossa of Rosenmüller (arrow) and normal structures in the rest of the nasopharynx.

The superior pharyngeal constrictor only extends superiorly to the skull base in the midline, and laterally, the pharyngobasilar fascia serves to attach the constrictor muscle to the base of the skull at the basiocciput and petrous portion of the temporal bone. This lateral area of muscular deficiency is otherwise known as the *sinus of Morgagni*, through which the pharyngotympanic tube and levator veli palatini pass. The pharyngobasilar fascia is continuous with the foramen lacerum and is in close proximity to the foramen ovale, foramen spinosum, jugular foramen, hypoglossal canal, and carotid space. The proximity of these foramina to the *sinus of Morgagni* assumes importance in the consideration of intracranial extension (Figure 47.2). A summary of the various foramina located in the base of skull is presented in Table 47.1.

TABLE 47.1 FORAMINA OF THE BASE OF THE SKULL AND ASSOCIATED ANATOMIC STRUCTURES

Foramen/Fissure	Cranial Nerve	Other Structures
Cribriform plate	Olfactory nerve (I)	Anterior ethmoidal nerve
Optic foramen	Optic nerve (II)	Ophthalmic artery
Superior orbital fissure	Oculomotor (III), trochlear (IV), ophthalmic division of trigeminal (V_1) nerve, abducens (VI) nerves	Ophthalmic vein, orbital branch of middle meningeal and recurrent branch of lacrimal arteries, sympathetic plexus, filaments from carotid plexus
Foramen rotundum	Maxillary division of trigeminal (V_2) nerve	
Foramen ovale	Mandibular division of trigeminal (V_3) nerve	Accessory meningeal artery, lesser superficial petrosal nerve
Foramen lacerum		Internal carotid, sympathetic carotid plexus, vidian nerve, meningeal branch of ascending pharyngeal artery, emissary vein
Foramen spinosum	Recurrent branch of V_3 nerve	Middle meningeal artery and vein
Stylomastoid foramen	Facial (VII) nerve	
Internal acoustic meatus	Auditory (VIII) nerve	Internal auditory artery
Jugular foramen	Glossopharyngeal (IX), vagus (X), spinal accessory (XI) nerves	Inferior petrosal sinus, transverse sinus, meningeal branches from occipital and ascending pharyngeal arteries
Hypoglossal canal	Hypoglossal (XII) nerve	Meningeal branch of ascending pharyngeal artery
Foramen magnum		Spinal cord, spinal accessory nerve, vertebral vessels, anterior and posterior spinal vessels

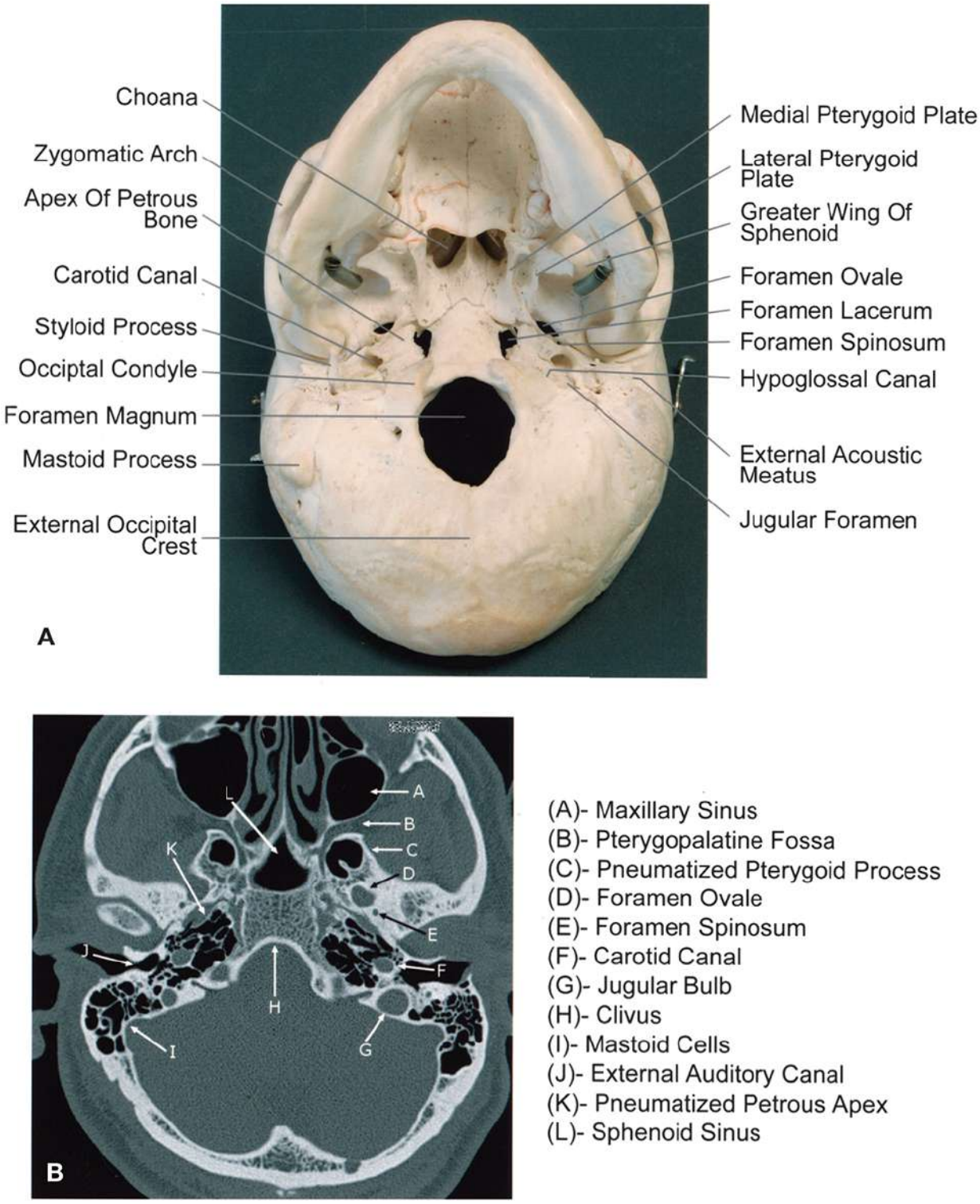

FIGURE 47.2 A. Basal view of skull illustrating the foramina of the base of the skull and the occupying structures. B. Axial computed tomography scan illustrating the bony anatomy.

The afferent innervation of the nasopharynx anterior to the pharyngotympanic tube orifice is provided by the maxillary division of the trigeminal nerve (V_2) and, posterior to the tubal orifice, the glossopharyngeal nerve. Motor supply is via the pharyngeal branches of the glossopharyngeal nerve, vagus nerve, and sympathetic fibers

from the superior cervical ganglion. The arterial supply of the nasopharynx is provided by the ascending pharyngeal artery, sphenopalatine artery, and the artery of the pterygoid canal. Venous drainage is provided by the pharyngeal plexus that drains into the internal jugular veins directly or via communication with the pterygoid plexus.

EPIDEMIOLOGY AND ETIOLOGY

Nasopharyngeal carcinoma (NPC) is an uncommon cancer in most parts of the world. The age-adjusted incidence rate (per 100,000 people per year) among men ranges from below 1 in the United States and Japan to 5.4 in Algeria; 5.8 in the Philippines; 11.0 in Singapore; 17.2 among Eskimos, Indians, and Aleuts in Alaska to 25 in Southern China.[1-4]

A bimodal age distribution is observed in low-risk populations. The first peak incidence arises between 15 and 25 years of age, with the second peak at 50 and 59 years of age.[5-7] In high-risk populations, the peak incidence occurs in the fourth and fifth decades of life.[5] Both genders have a similar age distribution; however, the male-to-female incidence ratio is 2:1 to 3:1.[8]

This distinct racial and geographical distribution of NPC suggests a multifactorial cause. Current epidemiologic and experimental data identify at least three important etiologic factors[1]: genetic,[2] environmental, and[3] viral.

The high incidence of NPC among Southern Chinese and populations of Southern Chinese descent suggests a component of genetic susceptibility. A genome-wide association study of NPC found three susceptibility loci[9] and confirmed a linkage study that found a gene closely linked to the human leukocyte antigen (HLA) locus conferred a greatly increased risk of this disease.[10] In addition, several HLA haplotypes, including A2, B46, and B17, are associated with an increased risk of developing NPC.[11,12]

The high consumption of salted fish in Southern China has been implicated as an important environmental factor.[13-16] Dimethylnitrosamine, a carcinogen found in salted fish, has been shown to induce carcinoma in the upper respiratory tract in rats.[14] Other potential environmental etiologic factors that have been associated with NPC include alcohol consumption and exposure to dust, fumes, formaldehyde, and cigarette smoke,[17,18] although definitive conclusion has been elusive. Descendants of Chinese who have migrated from endemic areas to Western countries show progressively lower risk, but their incidence remains higher than the indigenous populations.[19-21] Buell[19] observed that American-born second-generation Chinese had a lower risk than the Asian-born first generation, whereas Whites born in Southeast Asia had an increased risk compared to American-born Whites. Dickson and Flores[21] reported that the incidence rate in Chinese who were natively born in China was 20.5, compared with 1.3 for Chinese and 0.2 for Whites born in Canada. Taken together, environmental factors appear to play a role in the etiology of NPC.

Epstein-Barr virus (EBV) has been associated with NPC, especially the nonkeratinizing type, irrespective of ethnic or geographic origin.[22] Premalignant lesions of nasopharyngeal epithelium show increased levels of EBV, suggesting that EBV infection may influence the early stages of tumorigenesis in NPC.[23] Detection of a single form of EBV DNA in tumors suggests that clonal expansion from an initial EBV-infected and, ultimately, EBV-transformed cell is likely. EBV's tumorigenic potential is due to a set of latent genes, latent membrane proteins (LMP1, LMP2A, and LMP2B), and EBV-determined nuclear antigens (EBNA1 and EBNA2), which are the proteins predominantly expressed in NPC.[24] LMP1 is the principal oncogene with evidence that the C-terminal activating regions of the protein activate a variety of signaling pathways, including mitogen-activated protein kinases, phosphoinositol-3-kinase, nuclear factor κB, and epidermal growth factor receptor (EGFR).[25,26] LMP1 is also required for cell immortalization and is present in 80% to 90% of NPC tumors.[27] This mounting evidence highlights the likely etiologic role for EBV in NPC.

NATURAL HISTORY

Local Extension

A summary of structures locally infiltrated by NPC at diagnosis is provided in Table 47.2.

TABLE 47.2 STRUCTURES LOCALLY INFILTRATED BY NASOPHARYNGEAL CARCINOMA AT DIAGNOSIS

Structures Involved	Frequency (%)
Adjacent soft tissue	
Nasal cavity	87

Structures Involved	Frequency (%)
Parapharyngeal space, carotid space	68
Pterygoid muscle (medial, lateral)	48
Oropharyngeal wall, soft palate	21
Prevertebral muscle	19
Bony erosion/paranasal sinus	
Clivus	41
Sphenoid bone, foramina lacerum, ovale, rotundum	38
Pterygoid plate(s), pterygomaxillary fissure, pterygopalatine fossa	27
Petrous bone, petro-occipital fissure	19
Ethmoid sinus	6
Maxillary antrum	4
Jugular foramen, hypoglossal canal	4
Pituitary fossa/gland	3
Extensive/intracranial extension	
Cavernous sinus	16
Infratemporal fossa	9
Orbit, orbital fissure(s)	4
Cerebrum, meninges, cisterns	4
Hypopharynx	2

Based on magnetic resonance imaging of 308 patients from Pamela Youde Nethersole Eastern Hospital, Hong Kong.
Reprinted with permission from Barnes L, Eveson JW, Reichart P, Sidransky D. *Pathology and Genetics of Head and Neck Tumours. World Health Organization Classification of Tumours*. Vol 9. IARC Press; 2005.

Anterior

Anteriorly, it is common for the extension and infiltration of tumor into the nasal fossa. Invasion of the lateral wall of the nasal fossa can lead to involvement and destruction of the pterygoid plates. Beyond these structures, though less common, is invasion of the posterior ethmoid and maxillary sinuses. In advanced disease, infiltration of the orbital apex (typically through the inferior orbital fissure) can occur.

Superior and Posterior

Superiorly, tumors can directly invade the base of skull, the sphenoid sinus, and the clivus. The foramen lacerum, positioned directly above the pharyngeal recess (*Rosenmuller Fossa*), is a vulnerable spot through which the tumor may enter the cavernous sinus and the middle cranial fossa to invade cranial nerves II to VI (Figure 47.3). Figure 47.4 demonstrates involvement of the trigeminal cave (*Meckel cave*) and the maxillary branch of the trigeminal nerve (V_2). The foramen ovale also allows access for tumor to invade the middle cranial fossa, in addition to the petrous portion of the temporal bone, and the cavernous sinus. Posteriorly, invasion of the prevertebral (longus capitis) muscles is commonly seen.

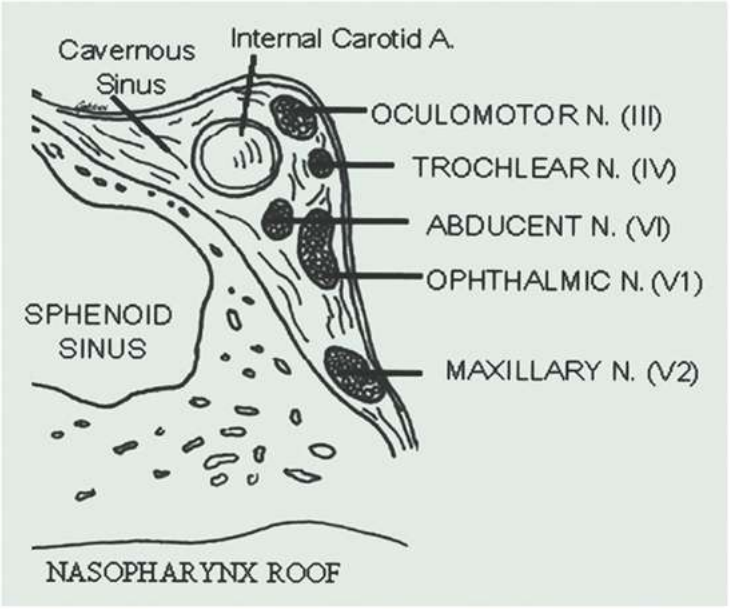

FIGURE 47.3 Coronal section through the sphenoid sinus and roof of the nasopharynx showing the relative positions of the cranial nerves III to VI. (Reprinted with permission from Chao KSC. *Practical Essentials of Intensity-Modulated Radiation Therapy*. Lippincott Williams & Wilkins; 2005:138.)

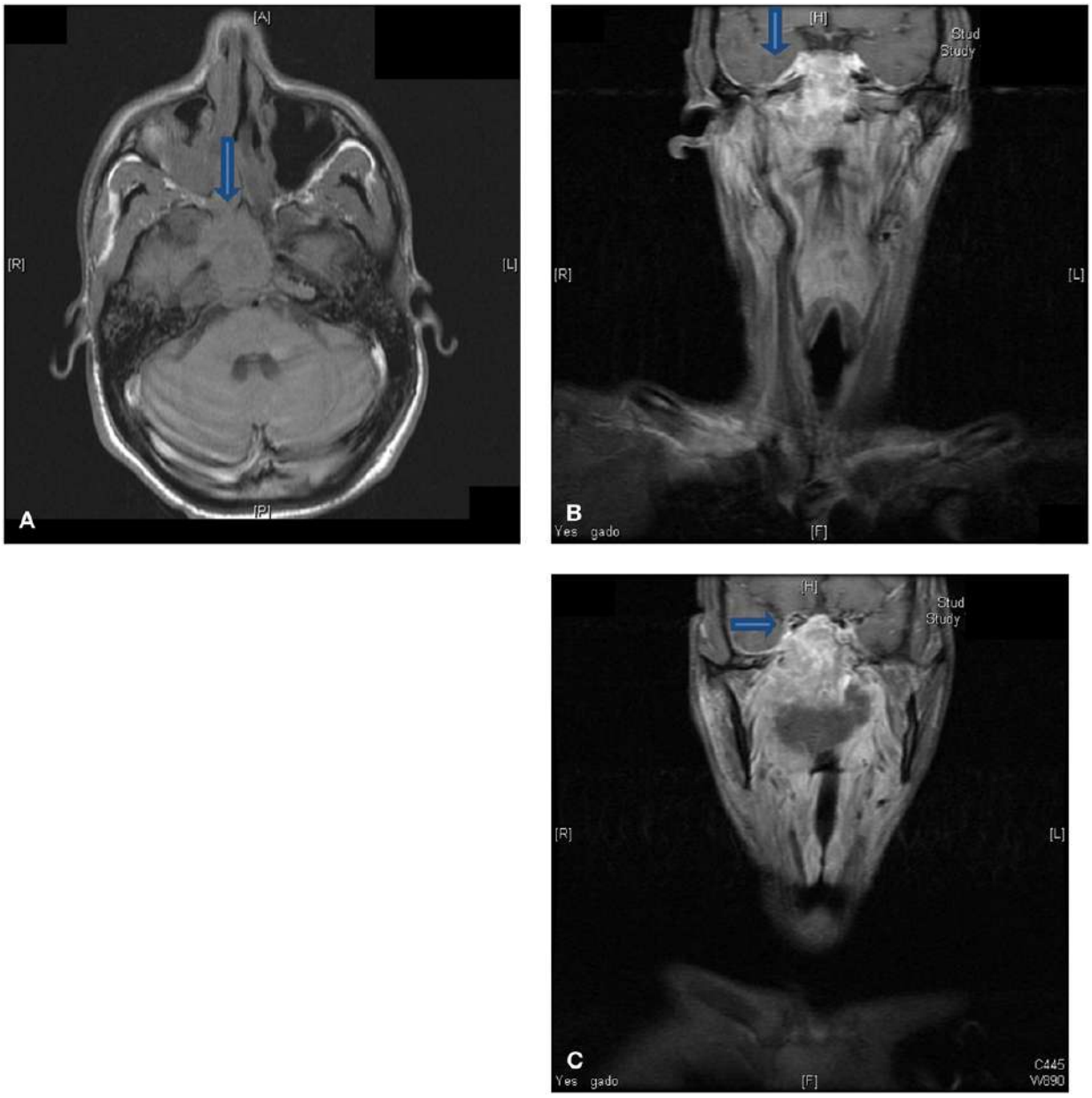

FIGURE 47.4 A. Axial T1-weighted magnetic resonance image (MRI) demonstrating involvement of the maxillary branch of the trigeminal nerve by nasopharyngeal carcinoma (V_2) (*arrow*). B. Coronal contrast-enhanced MRI showing involvement of the trigeminal cave (aka Meckel cave) by nasopharyngeal carcinoma (*arrow*). C. Coronal contrast-enhanced MRI showing involvement of the maxillary branch of the trigeminal nerve by nasopharyngeal carcinoma (V_2) (*arrow*).

Inferior

Extension inferiorly to the oropharynx is not unlikely, with potential involvement of the tonsillar pillars, the tonsillar fossa, and the lateral and posterior oropharyngeal walls. In advanced disease, invasion of the C1 vertebra posteriorly and inferiorly can occur. Direct invasion of the soft palate is uncommon.

Lateral

Lateral extension occurs early with involvement of the lateral parapharyngeal space along with invasion of the levator and tensor veli palatini muscles (Figure 47.5). In advanced disease, invasion of the pterygoid muscles can occur. Direct extension of the tumor or lateral retropharyngeal lymph node metastasis in the parapharyngeal space may lead to invasion or compression of cranial nerves IX to XI as they transpire the jugular foramen, cranial nerve

XII as it emerges from the hypoglossal canal, and the cervical sympathetic nerves. Direct invasion or compression of the internal carotid artery can occur in advanced disease (Figure 47.6). Tumor can directly invade the middle ear through the pharyngotympanic (eustachian tube).

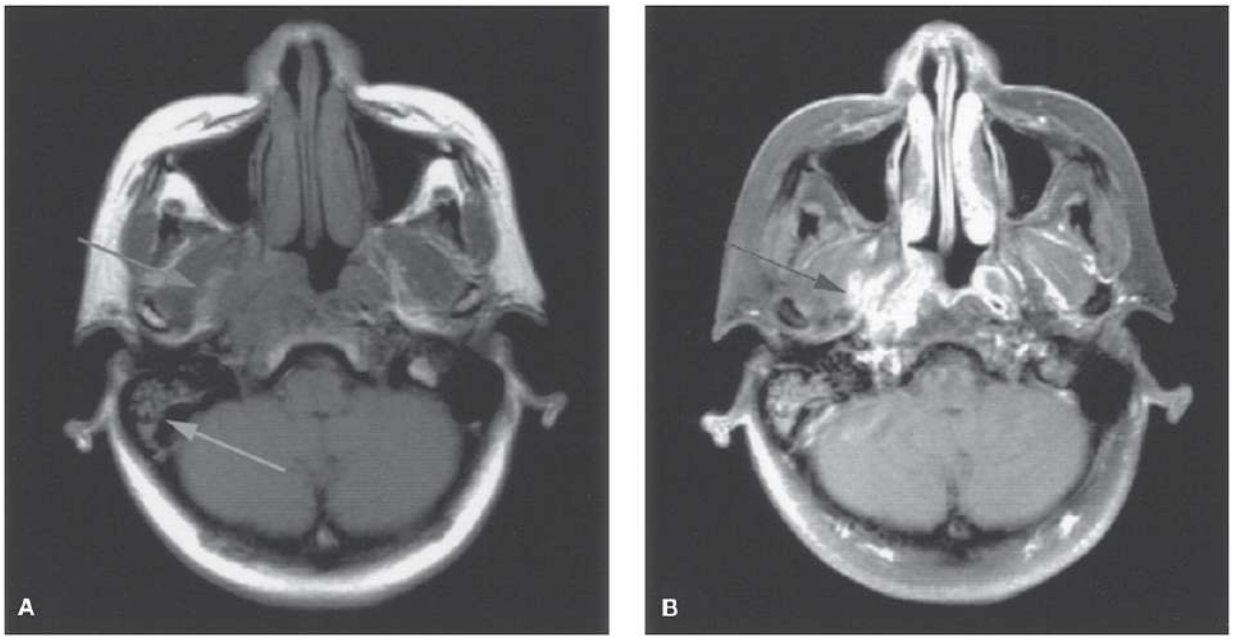

FIGURE 47.5 A. Axial T1-weighted magnetic resonance image (MRI) showing tumor infiltration of the right parapharyngeal space (*left arrow*). Note the resultant serous otitis media (*right arrow*). B. Axial contrast-enhanced MRI showing enhanced tumor involving the parapharyngeal space and medial pterygoid muscles (*arrow*).

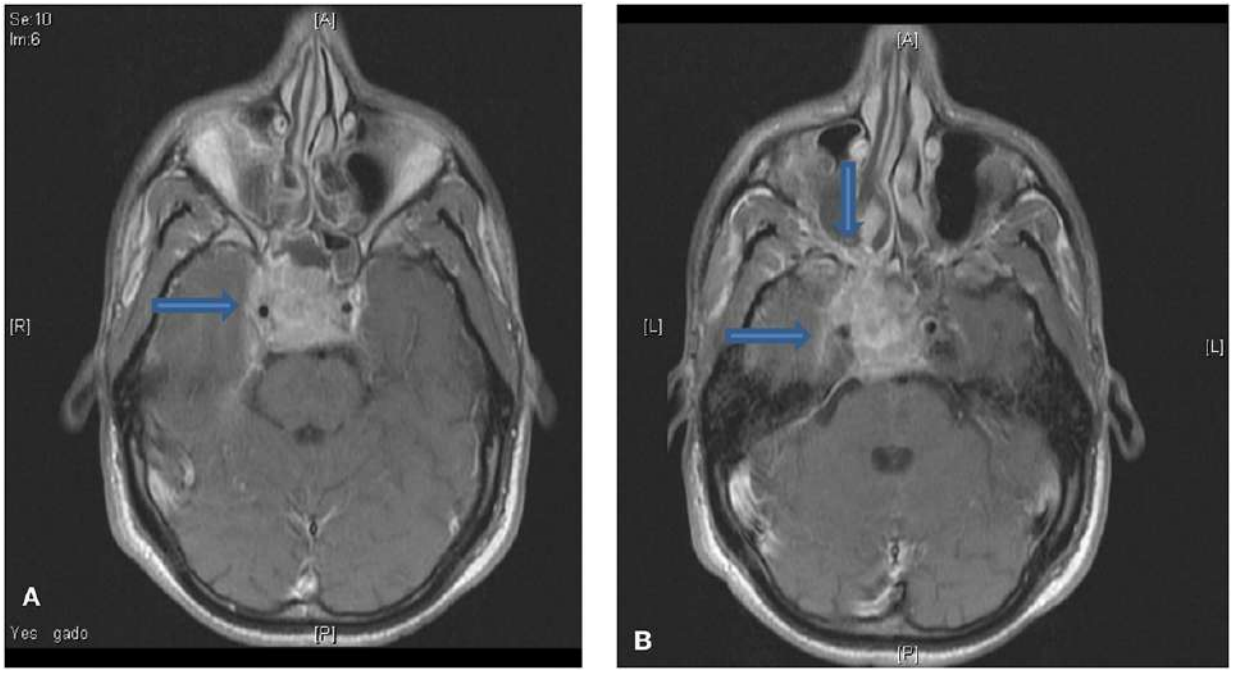

FIGURE 47.6 A. Axial contrast-enhanced magnetic resonance image (MRI) demonstrating involvement of the cavernous sinus by nasopharyngeal carcinoma. B. Axial contrast-enhanced MRI showing invasion of the pterygopalatine fossa (*vertical arrow*) with spread to cavernous sinus (*horizontal arrow*).

Lymphatic Spread

The nasopharynx is composed of a vast avalvular lymph capillary network that exists in the mucous membrane leading to frequent involvement of regional neck nodes (Figure 47.7). Up to 85% to 90% of cases present with lymphatic spread to the ipsilateral nodes.[28-30] Bilateral spread is present in approximately 50% of cases. The distribution of NPC-involved nodes at diagnosis is shown in Figure 47.8. An anatomic and radiographic study that directly examined lymphatic vasculature concluded that there are two major lymph collectors of the nasopharynx (Figure 47.7B).[31] One lymph collector runs along the lateral side of the pharyngeal wall, whereas the second runs more posteriorly. The lateral lymph collector empties into multiple first-tier nodes, which include the lateral pharyngeal node, the jugulodigastric/subdigastric node, and the third, fourth, and fifth nodes of the retropharyngeal group.[31] The posterior lymph collector empties into the first node (*node of Rouvière*) of the retropharyngeal group (Figure 47.9). This direct study is corroborated clinically by frequent observation of lateral and retropharyngeal lymph node involvement by magnetic resonance image (MRI) of computed tomography (CT) scans, even though they remain impalpable. Metastasis to the jugulodigastric and superior-posterior cervical nodes is also common. From these first-tier nodes, further metastatic spread to the midjugular, lower jugular, and posterior cervical and supraclavicular nodes can develop. Seldom, submental and occipital nodes can be involved secondary to lymphatic obstruction caused by widespread cervical lymphadenopathy. Mediastinal lymph nodes and, occasionally, axillary nodes may be involved with the presence of supraclavicular lymphadenopathy.

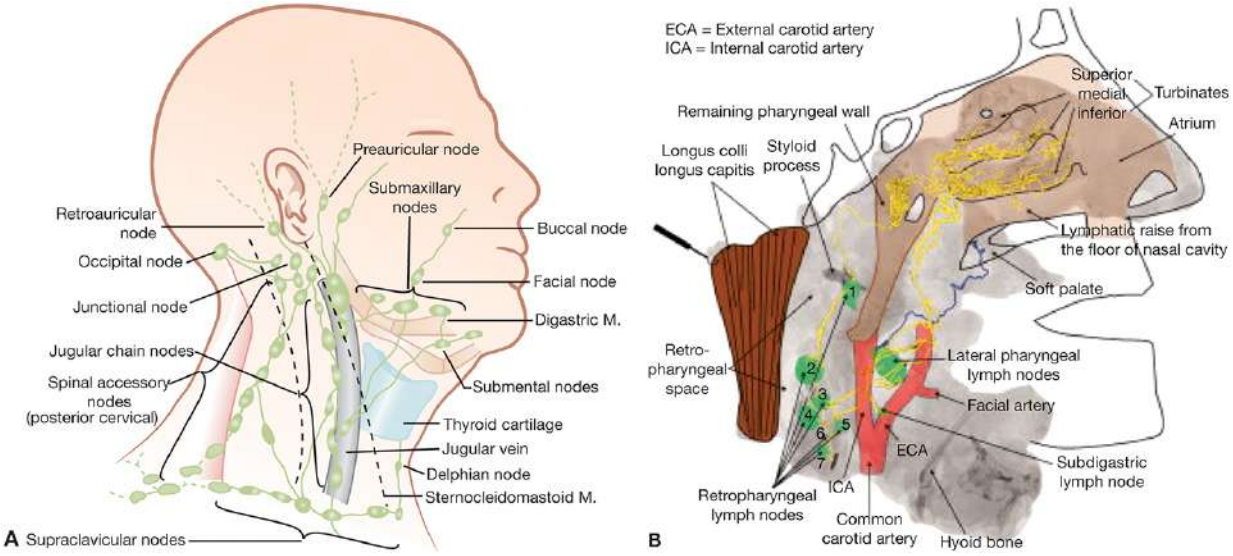

FIGURE 47.7 A. Pathways for lymphatic spread of nasopharyngeal carcinoma. (A. Redrawn from Rouvière H. *Anatomie Des Lymphatiques de L'homme*. Masson; 1932:10.) B. Two major lymph collectors of the nasopharynx: (a) lateral lymph collector and (b) posterior lymph collector. *Yellow* indicates lymphatic vessels from the nasal cavity. *Blue* indicates lymphatic vessels from soft palate. *Green* indicates lymph nodes. Retropharyngeal nodes are numbered. *Red* indicates carotid artery. *Dark brown* indicates longus muscles. *Light brown* indicates remaining pharyngeal and nasal wall. (B. From Pan WR, Suami H, Corlett RJ, Ashton MW. Lymphatic drainage of the nasal fossae and nasopharynx: preliminary anatomical and radiological study with clinical implications. *Head Neck*. 2009;31[1]:52-57. Copyright © 2008 Wiley Periodicals. Reprinted by permission of John Wiley & Sons.)

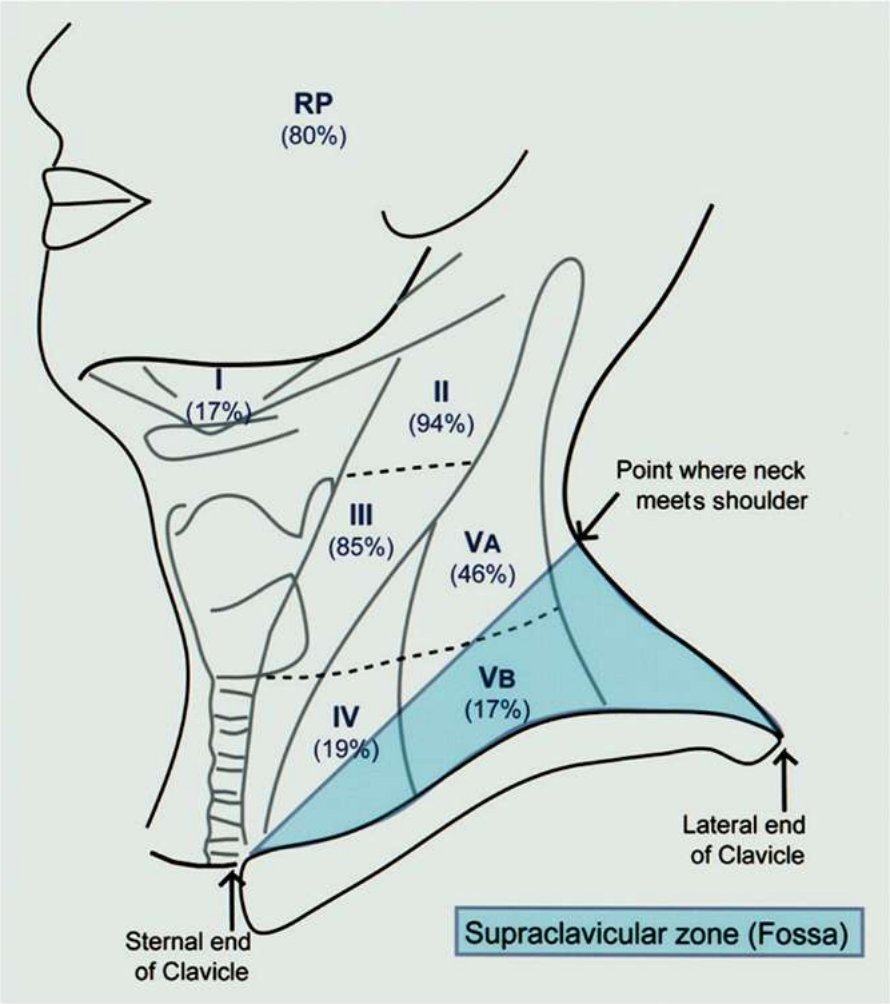

FIGURE 47.8 Two examples of coronal magnetic resonance images showing bilateral cervical lymphadenopathy. There is orderly downward lymphatic spread toward the supraclavicular fossa.

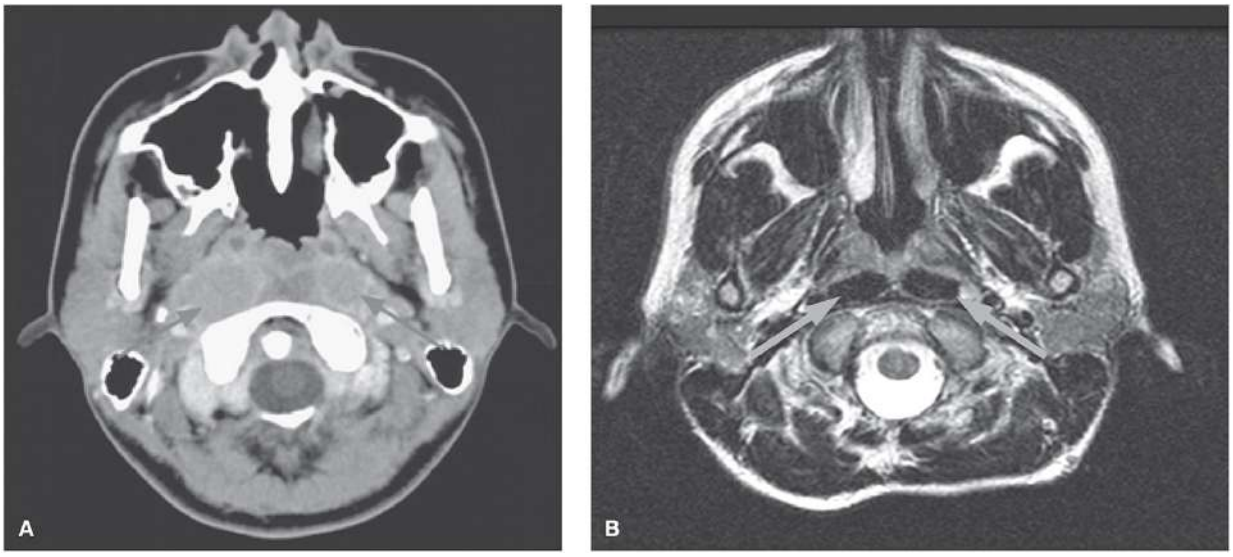

FIGURE 47.9 A. Axial contrast-enhanced computed tomography scan showing involvement of bilateral retropharyngeal lymph nodes (*arrows*) by nasopharyngeal carcinoma. B. Axial T2-weighted magnetic resonance image showing involvement of bilateral retropharyngeal lymph nodes (*arrows*) by nasopharyngeal carcinoma.

Hematogenous Dissemination

Distant metastasis is present in 3% to 6% of the cases at presentation and may occur in 18% to 50% of cases during the disease course.[32-36] The rate of distant metastasis is highest in patients with advanced neck node metastasis,[28,37,38] especially with low-neck involvement.[39,40] The bone is the most common distant metastatic site followed by the lungs and liver,[41] with lung metastasis being associated with better prognosis than other sites. Brain and skin metastases rarely occur.[42,43]

CLINICAL PRESENTATION

NPC presents in patients with symptoms in one or more of the following three categories: (1) neck masses, usually appearing in the upper neck; (2) presence of tumor mass in the nasopharynx (epistaxis, nasal obstruction and discharge); or (3) skull base erosion and palsy of cranial nerves V and VI because of tumor extension superiorly (headache, diplopia, facial pain, and numbness).

The frequency of various presenting symptoms and signs is summarized in Table 47.3. A neck mass is the most common presenting symptom, followed by nasal and aural symptoms. The physical signs commonly present at diagnosis are enlarged neck node(s) and, less often, cranial nerve palsy. The cranial nerves V and VI are frequently involved, whereas cranial nerves I, VII, and VIII are rarely involved (Table 47.4).[30,44]

TABLE 47.3 SYMPTOMS AND PHYSICAL SIGNS OF NASOPHARYNGEAL CARCINOMA AT PRESENTATION

Symptom/Sign	Chao and Perez[45] (*n* = 164) (%)	Lee et al[30] (*n* = 4,768) (%)
Neck mass	66	76
Enlarged neck node(s)		75
Nasal (discharge, bleeding, obstruction)	>37	73
Aural (tinnitus, hearing impairment)	41	62
Headache	40	35
Cranial nerve palsy	23	20
Neurologic symptoms		
Ophthalmic (diplopia, squint)		11
Facial numbness		8
Slurring of speech		2

Symptom/Sign	Chao and Perez[45] (*n* = 164) (%)	Lee et al[30] (*n* = 4,768) (%)
Sore throat	16	
Weight loss		7
Trismus		3
Distant metastases		3
Dermatomyositis		1

TABLE 47.4 INCIDENCE OF CRANIAL NERVE INVOLVEMENT BY NASOPHARYNGEAL CARCINOMA AT DIAGNOSIS

Cranial Nerve	Chao and Perez[45] (*N* = 164) (%)	Chan et al[46] (*N* = 722) (%)
I	—	—
II	1.3	0.8
III	3.5	1.3
IV	2.4	0.6
V	7.8	V_1, 3.5; V_2, 5.8%; V_3, 3.9
VI	13.3	5.1
VII	3.6	0.1
VIII	4.8	—
IX-XII	IX, 2; X, 5.4; XI, 1.3; XII, 4.8	2.4

Cervical lymphadenopathy is present in up to 87% of patients.[47] Typically, a mass is observable in the upper posterior neck and palpable beneath the superior portion of the sternocleidomastoid muscle close to the mastoid process. This is caused by metastasis to the parapharyngeal nodes or superior-posterior cervical nodes of the spinal accessory chain.

DIAGNOSTIC AND STAGING WORKUP

Diagnosis of NPC is made by biopsy of the primary tumor. This can typically be performed with local anesthesia in an outpatient setting. Biopsy by direct visualization with general anesthesia may be necessary for diagnosis when the tumor is not visible or when the patient cannot cooperate. Not uncommonly, the tumor is submucosal and not visible. For suspicious cases of a nasopharyngeal primary tumor with lack of visible tumor, random biopsies of the most commonly involved sites are warranted: pharyngeal recess (*fossa of Rosenmüller*) on each of the lateral walls and superior-posterior wall of the nasopharynx. Fine-needle aspiration (FNA) of a suspicious neck mass may establish the presence of metastatic NPC in the regional lymphatics. This may be performed prior to the biopsy of the nasopharynx when the primary tumor is not clinically detectable.

Table 47.5 lists the pretreatment diagnostic evaluations and staging evaluations that are generally recommended for NPC.

TABLE 47.5 RECOMMENDED PRETREATMENT DIAGNOSTIC EVALUATIONS FOR NASOPHARYNGEAL CARCINOMA

General
Medical history
Physical examination
Palpation of neck node (record size, laterality, and lowest extent of enlarged nodes)
Testing of cranial nerve (including assessment of vision and hearing functions)
Exclusion of gross signs of distant metastases
Fiberoptic endoscopy examination
Nasopharyngoscopy and biopsies
± Panendoscopy
Otologic assessment
Inspection of tympanic membranes (as clinically indicated)

General
Baseline audiologic testing (preferable)
Laboratory studies
Complete blood count
Liver function tests
Urinalysis
EBV-specific serologic tests
Immunoglobulin A (IgA)
Antiviral capsule antigen (VCA) titers
Serum EBV DNA levels
Radiographic studies
Assessment of locoregional extent (imaging of the nasopharynx, paranasal sinuses, base of skull, nasal cavity, and neck)
Magnetic resonance imaging (study of choice)
Computed tomography (acceptable alternative)
Chest radiograph (posterior-anterior and lateral)
Additional metastatic workup if clinically indicated or N3 disease
Positron emission tomography (study of choice)
Computed tomography of the chest and abdomen
In patients with abnormal LFTs or clinical suspicion of lung or liver metastasis
Bone scan
In patients with advanced locoregional disease, symptoms suggestive of bone metastasis, or an elevated serum alkaline phosphatase

EBV, Epstein-Barr virus; LFT, liver function test.

Complete physical examination should include thorough palpation of the neck, cranial nerve examination, percussion and auscultation of the chest, palpation of the abdomen for possible liver involvement, and percussion of the spine and bones for possible bone metastasis. CT and MRI of the head and neck are useful in the evaluation of tumor erosion into the bony structures of the base of skull along with retropharyngeal and cervical lymphadenopathy. However, MRI is the preferred imaging technique in the staging evaluation of NPC.[48-50] The current American Joint Committee on Cancer (AJCC) T classification requires a search for tumor invasion into the soft tissue (eg, parapharyngeal space) and bony structures. MRI may be necessary for proper staging because CT has limitations in accurately defining tumor extension into these regions[51] and MRI was used[52] for the study that informed the updated 2017 AJCC system. MRI is superior to CT in delineating muscle and soft tissue involvement and examination of the skull base.[51,53,54] When utilizing MRI, thin slices (3 mm) should be used for accurate staging (Figure 47.10). Thicker slices (eg, ≥5 mm) risk misdiagnosis of what may be a higher T-stage disease.

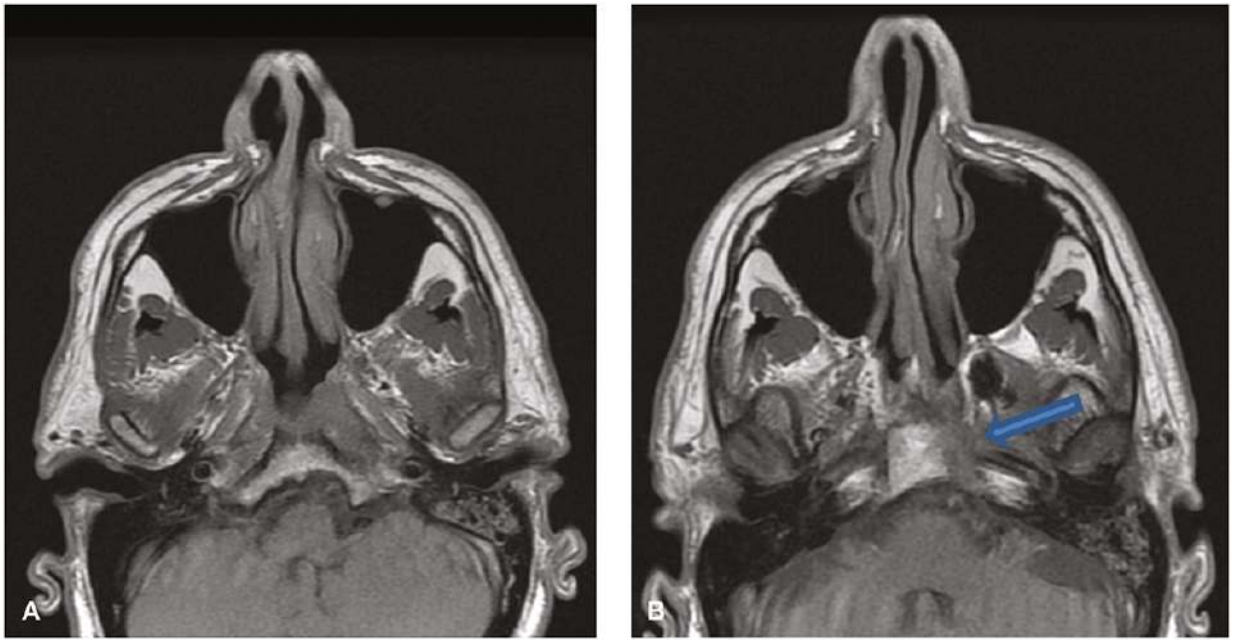

FIGURE 47.10 A. Axial T1-weighted magnetic resonance image (MRI) with 5-mm slices. B. Axial T1 MRI with 3-mm slices, skull base invasion (*arrow*) upstaged this tumor from T1 to T3.

Ng et al[55] compared MRI and CT in assessing the extent of disease. The study found a significantly higher sensitivity of MRI for skull base involvement (60% vs 40%), intracranial involvement (57% vs 36%), retropharyngeal node (58% vs 21%), and tumor infiltration of prevertebral muscles (ie, longus colli muscles) (51% vs 22%) compared to CT. By MRI, T staging was modified in 27% of patients, with 22% being upstaged and 4% being downstaged.

MRI and CT scans can detect lymph node metastasis that may not be clinically evident on physical examination.[56] According to a study by Van den Brekel et al,[57] lymph node metastasis is commonly recommended to be radiologically defined by the presence of central necrosis, extracapsular spread, shortest axial diameter ≥10 mm (11 mm for the jugulodigastric node and 5 mm for the retropharyngeal node), or a cluster of ≥3 lymph nodes that are borderline in size.

Detailed evaluation of nodal enlargement by palpation and imaging should consist of the size and location of the node, unilateral/bilateral involvement, and assessment of supraclavicular fossa involvement. Figure 47.8 defines the anatomic boundaries of the supraclavicular fossa, and Figure 47.11 demonstrates an example of bilateral cervical lymph node involvement seen by radiologic studies.

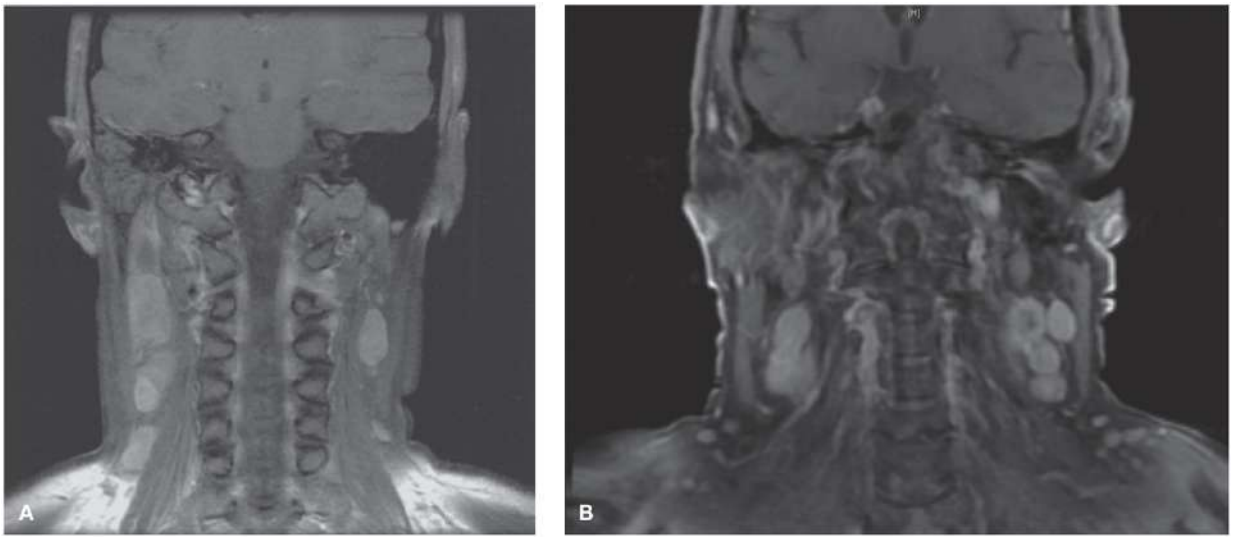

FIGURE 47.11 Two examples of coronal magnetic resonance images showing bilateral cervical lymphadenopathy. There is orderly downward lymphatic spread toward the supraclavicular fossa.

A complete search for distant metastasis is recommended for patients with advanced locoregional disease (eg, N3 disease) or patients with suspicious clinical or laboratory findings. Positron emission tomography (PET)/CT scanning (Figure 47.12) is now commonly utilized in place of conventional staging by CT, bone scans, and ultrasound and appears to be at least as sensitive. Chang et al[58] demonstrated that [^{18}F]fluorodeoxyglucose (FDG)-PET was superior to conventional workup (ie, chest x-ray, isotope bone scan, and abdominal ultrasound) in the detection of distant metastases, where 12% of patients were upstaged to stage IVC. PET, in the study, offered a sensitivity and specificity of 100% and 90.1%, respectively. However, large comparative studies of these various staging modalities have yet to be reported.[58-60]

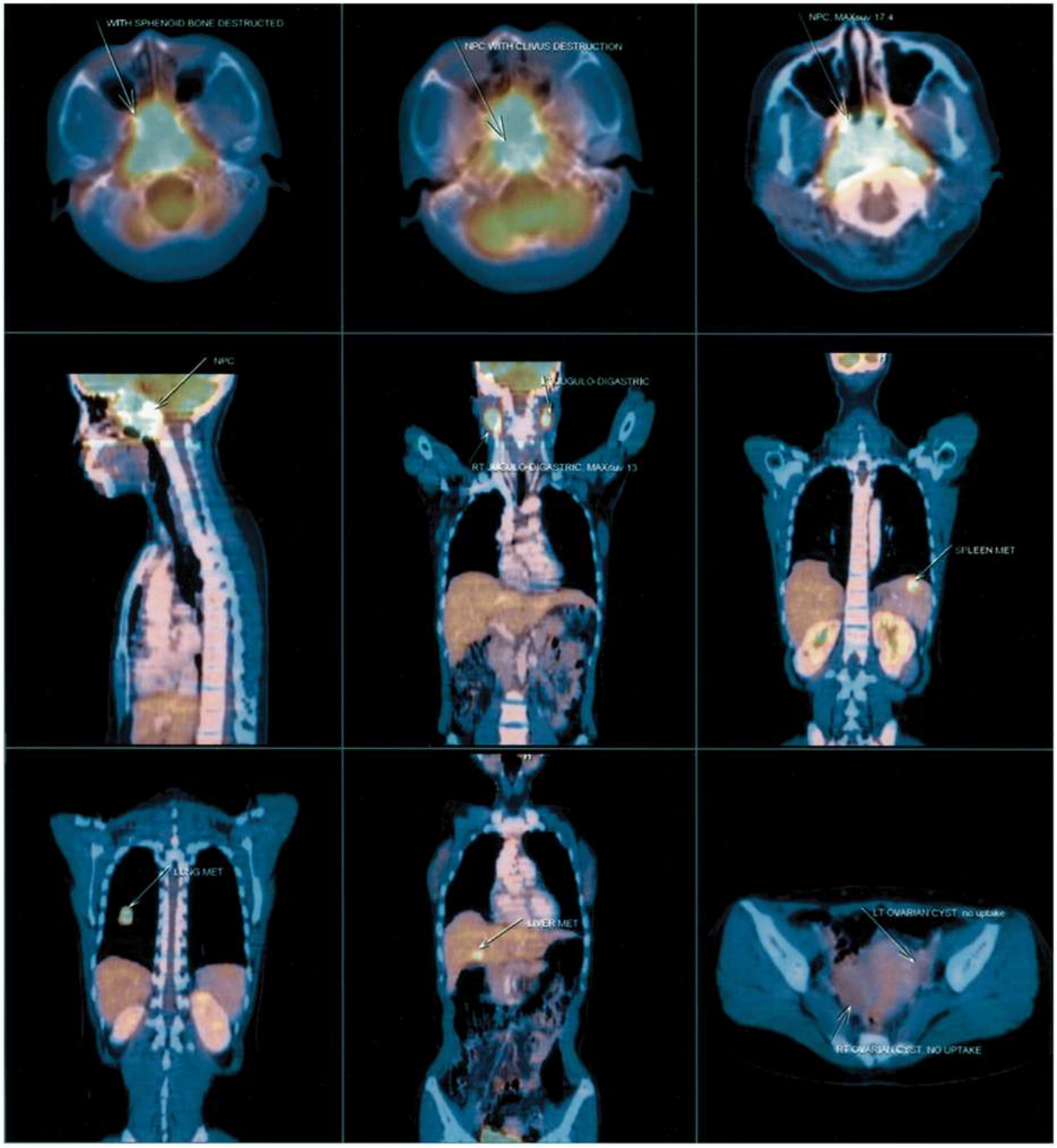

FIGURE 47.12 Positron emission tomography coupled with computed tomography (PET-CT) for a patient with nasopharyngeal carcinoma. Physical examination and biochemistry did not show any sign suggestive of distant metastases. X-ray of the chest was normal. PET-CT revealed multiple distant metastases in the lung, liver, and spleen, in addition to extensive local infiltration and bilateral cervical lymph nodes. (Reprinted with permission from Chan J, Bray F, McCarron P, et al. Nasopharyngeal carcinoma. In: Barnes L, Eveson JW, Reichart P, Sidransky D, eds. *Pathology and Genetics of Head and Neck Tumours. World Health Organization Classification of Tumours*. Vol 9. 3rd ed. IARC Press; 2005. Copyright © Dr. A. W. M. Lee.)

The intimate association of EBV with NPC, independent of geographic and ethnic background, has provided clinicians with a tumor marker for disease diagnosis. Immunoglobulin A (IgA) antiviral capsid antigen (VCA) and IgG anti-early antigen (EA) antibodies are both sensitive for diagnosing NPC; however, IgA anti-VCA has better specificity.[61] More than 90% of untreated patients with NPC from California, East Africa, and Hong Kong have elevated IgA antibody titers.[62-64] Elevated IgA anti-VCA and IgG anti-EA antibody titers are typically associated with nonkeratinizing carcinoma (both the differentiated and undifferentiated histologic subtypes). Neel et al[65]

reported 82% and 86% of patients with nonkeratinizing carcinoma had elevated IgA anti-VCA and IgG anti-EA antibody titers, respectively, in contrast with only 16% and 35%, respectively, in patients with the keratinizing histologic type. IgA anti-VCA antibodies may serve as a screening test in high-risk patients as it can be found elevated in patients months before the onset of symptoms.[66,67] A baseline test of plasma EBV DNA may be useful for prognosis, and levels over time can be utilized as surveillance in a post-treatment setting.[68,69]

STAGING SYSTEM

Various staging systems have been devised to predict prognosis and guide treatment strategy for patients with NPC.[70-73] The AJCC, Union for International Cancer Control (UICC), and Ho staging systems are the most commonly used systems in the English literature. The AJCC and UICC systems are virtually identical in their 2002 version, and this continues in the 2010 and 2017 updates. Each system has particular limitations; however, they continually evolve and build upon each other's experience. Table 47.6 displays the 2017 AJCC staging system currently in use.[74]

TABLE 47.6 AJCC STAGING OF NASOPHARYNGEAL CANCER, 2017

Stage	Staging Criteria		
T category			
TX	Primary tumor cannot be assessed.		
T0	No evidence of primary tumor		
T1	Tumor confined to the nasopharynx or extension to oropharynx and/or nasal cavity without parapharyngeal involvement		
T2	Tumor with extension to parapharyngeal space and/or adjacent soft tissue involvement (medial pterygoid, lateral pterygoid, prevertebral muscles)		
T3	Tumor with infiltration of bony structures at skull base, cervical vertebra, pterygoid structures, and/or paranasal sinuses		
T4	Tumor with intracranial extension; involvement of cranial nerves, hypopharynx, orbit, and parotid gland; and/or extensive soft tissue infiltration beyond the lateral surface of the lateral pterygoid muscle		
N category			
NX	Regional lymph nodes cannot be assessed.		
N0	No regional lymph node metastasis		
N1	Unilateral metastasis in cervical lymph node(s) and/or unilateral or bilateral metastasis in retropharyngeal lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage		
N2	Bilateral metastasis in cervical lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage		
N3	Unilateral or bilateral metastasis in cervical lymph node(s), larger than 6 cm in greatest dimension, and/or extension below the caudal border of cricoid cartilage. Metastasis in lymph node(s) >6 cm		
M category			
M0	No distant metastasis		
M1	Distant metastasis		
Stage grouping			
0	Tis	N0	M0
I	T1	N0	M0
II	T1, T0	N1	M0
	T2	N0	M0
	T2	N1	M0
III	T1, T0	N2	M0
	T2	N2	M0
	T3	N0	M0
	T3	N1	M0
	T3	N2	M0
IVA	T4	N0	M0

Stage	Staging Criteria		
	T4	N1	M0
	T4	N2	M0
	Any T	N3	M0
IVB	Any T	Any N	M1

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It is important to understand changes to the staging system over time for interpretation of older studies, which use prior classifications. The designation "T0" has been added for an EBV-positive unknown primary with cervical lymph node involvement. Tumors confined to the nasopharynx have similar outcomes to tumors that extend to the nasal cavity and oropharynx.[21,75] From the 2002 to 2010 system (Tables 47.7 and 47.8, respectively), T2a was, therefore, downstaged to T1, which is defined as tumor confined to the nasopharynx or tumor that extends to the nasal cavity and/or oropharynx. Tumors with parapharyngeal involvement were classified as T2 in the 2010 system and were no longer subdivided as T2b. Tumors with parapharyngeal space involvement are at higher risk for local and regional recurrence, as well as a high rate of distant metastasis.[76] Now, in the 2017 version, adjacent muscle involvement (including medial pterygoid, lateral pterygoid, and prevertebral muscle) is now designated as T2. Cranial nerve involvement has been shown to carry a worse prognosis than skull base involvement[28,39,77,78]; as such, T3 disease includes involvement of the bony structures of the skull base, whereas T4 includes involvement of the cranial nerves. The previous T4 criteria of extension to the "masticator space" or "infratemporal fossa" have been replaced in the 2017 by a specific description of soft tissue involvement "beyond the lateral surface of the lateral pterygoid muscle, parotid gland" to avoid ambiguity.

TABLE 47.7 AJCC STAGING OF NASOPHARYNGEAL CANCER, 2002

Stage	Staging Criteria
T category	
TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor confined to the nasopharynx
T2	Tumor extends to adjacent soft tissues: Nasal cavity,[a] oropharynx[b]
	T2a. Tumor without parapharyngeal extension[c]
	T2b. Tumor with parapharyngeal extension
T3	Tumor involves bony structures and/or paranasal sinuses.
T4	Tumor with intracranial extension, involvement of cranial nerves, hypopharynx, orbit, infratemporal fossa,[d] or masticator space[d]
N category	
NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis
N1	Unilateral metastasis in lymph node(s), ≤6 cm in greatest dimension, above the supraclavicular fossa
N2	Bilateral metastasis in lymph node(s), ≤6 cm in greatest dimension, above the supraclavicular fossa
N3	Metastasis in lymph node(s)
	N3a. >6 cm in dimension
	N3b. Extension to the supraclavicular fossa[e]
M category	
MX	Distant metastasis cannot be assessed.
M0	No distant metastasis
M1	Distant metastasis

Stage	Staging Criteria		
Stage grouping			
0	Tis	N0	M0
I	T1	N0	M0
IIA	T2a	N0	M0
IIB	T1	N1	M0
	T2a	N1	M0
	T2b	N0	M0
	T2b	N1	M0
III	T1	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N0	M0
	T3	N1	M0
	T3	N2	M0
Stage IVA	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1

[a]Nasal cavity: Anterior extension beyond the posterior margins of the choanal orifices.

[b]Oropharynx: Inferior extension beyond the level of the free border of the soft palate. The junction at C1/C2 level is recommended as a more consistent radiologic landmark.[79]

[c]Parapharyngeal extension: Posterior-lateral infiltration beyond the pharyngobasilar fascia.

[d]Masticator space and infratemporal fossa: Extension beyond the anterior surface of the lateral pterygoid muscle, or lateral extension beyond the posterior-lateral wall of the maxillary antrum, and the pterygomaxillary fissure.

[e]Supraclavicular fossa: Triangular region defined by the superior margin of the sternal end of the clavicle, the superior margin of the lateral end of the clavicle, and the point where the neck meets the shoulder.

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TABLE 47.8 AJCC STAGING OF NASOPHARYNGEAL CANCER, 2010

Stage	Staging Criteria
T category	
TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor confined to the nasopharynx or tumor extends to the nasal cavity[a] and/or oropharynx[b] without parapharyngeal extension[c]
T2	Tumor with parapharyngeal extension[c]
T3	Tumor involves bony structures of skull base and/or paranasal sinuses.
T4	Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, and orbit or with extension to the infratemporal fossa/masticator space[d]
N category	
NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis

Stage	Staging Criteria		
N1	Unilateral metastasis in cervical lymph node(s), ≤6 cm in greatest dimension, above the supraclavicular fossa, and/or unilateral or bilateral retropharyngeal lymph node(s), ≤6 cm in greatest dimension		
N2	Bilateral metastasis in cervical lymph node(s), ≤6 cm in greatest dimension, above the supraclavicular fossa[e,f]		
N3	Metastasis in lymph node(s)[e] >6 cm and/or to supraclavicular fossa[f]		
	N3a. >6 cm in dimension		
	N3b. Extension to the supraclavicular fossa[f]		
M category			
M0	No distant metastasis		
M1	Distant metastasis		
Stage grouping			
0	Tis	N0	M0
I	T1	N0	M0
II	T1	N1	M0
	T2	N0	M0
	T2	N1	M0
III	T1	N2	M0
	T2	N2	M0
	T3	N0	M0
	T3	N1	M0
	T3	N2	M0
IVA	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IVB	Any T	N3	M0
IVC	Any T	Any N	M1

[a]Nasal cavity: Anterior extension beyond the posterior margins of the choanal orifices.

[b]Oropharynx: Inferior extension beyond the level of the free border of the soft palate. The junction at C1/C2 level is recommended as a more consistent radiologic landmark.[79]

[c]Parapharyngeal extension: Posterior-lateral infiltration beyond the pharyngobasilar fascia.

[d]Masticator space and infratemporal fossa: Extension beyond the anterior surface of the lateral pterygoid muscle, or lateral extension beyond the posterior-lateral wall of the maxillary antrum, and the pterygomaxillary fissure.

[e]Midline nodes are considered ipsilateral nodes.

[f]Supraclavicular fossa: Triangular region defined by the superior margin of the sternal end of the clavicle, the superior margin of the lateral end of the clavicle, and the point where the neck meets the shoulder.

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NPC has a unique pattern of nodal spread as compared to other sites in the head and neck region, which is reflected in the nodal staging classification. Retropharyngeal nodes are the first echelon of nodal metastases,[80] and retropharyngeal lymph node involvement independent of laterality and without cervical lymph node involvement was defined as N1 beginning in the 2010 system. Spread to the low-neck correlates strongly with the development of distant metastasis.[39,40] The previous N3b criterion of supraclavicular fossa extension was changed to lower neck involvement (as defined by nodal extension below the caudal border of the cricoid cartilage) in the 2017 update. In addition, N3a and N3b have been merged into a single N3 category. Lastly, the previous substages IVA (T4 N0-2 M0) and IVB (any T N3 M0) are now merged to form IVA, whereas the previous IVC (any T any N M1) is now staged as IVB.

These modifications to the staging classifications will require continued examination to determine if they improve prognostic accuracy.

PATHOLOGIC CLASSIFICATION

The vast majority of malignant nasopharyngeal tumors are carcinoma (80%-99%), with the remainder of these lesions (about 5%) being lymphomas.[81] Other rare malignant tumors of the nasopharynx include adenocarcinoma, plasmacytoma, melanoma, and sarcomas. Regarding NPC, the most current World Health Organization (WHO) pathologic classification, released in 2017,[82] includes three major types (Figure 47.13). Keratinizing squamous cell carcinoma is distinguished by the presence of keratin pearls or intracellular keratin. Nonkeratinizing carcinoma is characterized by the complete absence of keratin formation and is further subdivided into differentiated and undifferentiated subtypes. The third type is known as basaloid squamous cell carcinoma[83] and is composed of closely packed small tumor cells that form a lobular and, at times, palisading pattern along with focal squamous carcinoma elements. Basaloid squamous cell carcinoma is quite rare, with a frequency of less than 0.2%[46] (Figure 47.13). The nonkeratinizing type has a strong association with EBV positivity.[84] The keratinizing type may have a correlation with human papillomavirus (HPV); however, the small sample size of these studies requires continued investigation.[85]

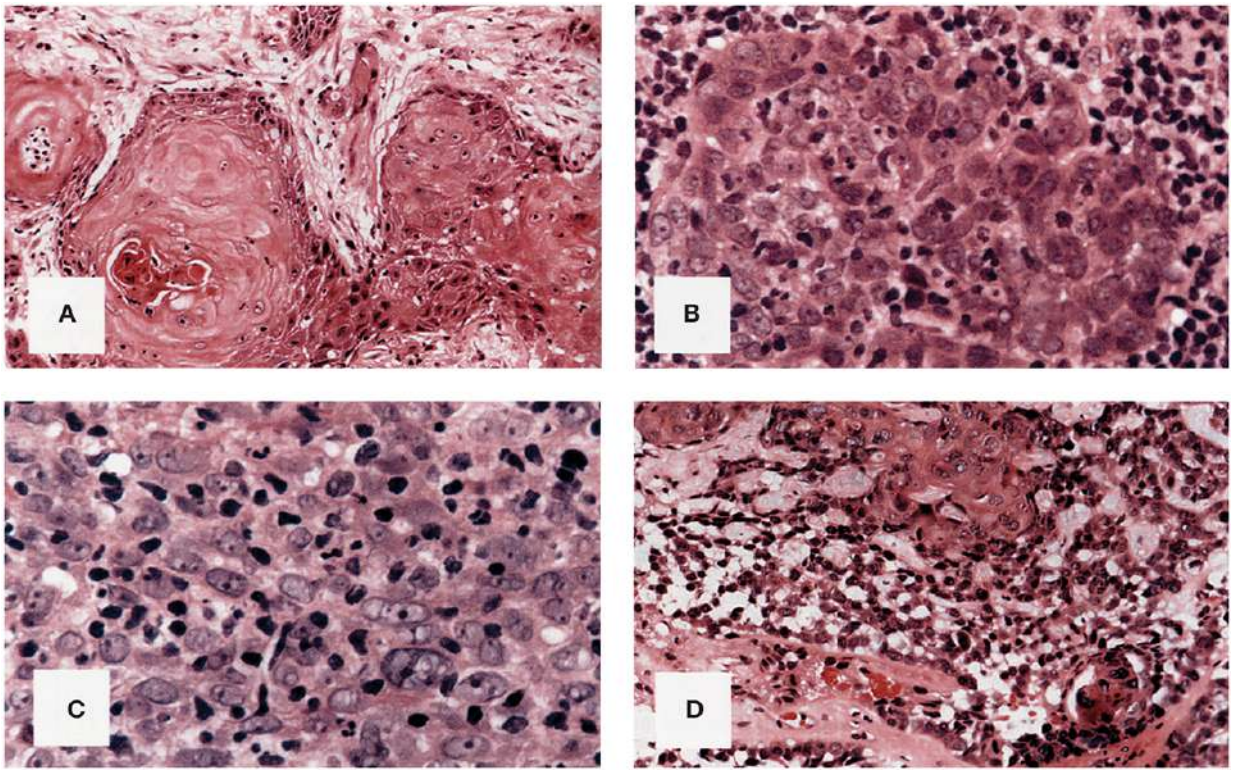

FIGURE 47.13 Photomicrographs of nasopharyngeal carcinoma. A. Keratinizing squamous cell carcinoma. B. Nonkeratinizing carcinoma, differentiated subtype. C. Nonkeratinizing carcinoma, undifferentiated subtype. D. Basaloid squamous cell carcinoma. (Reprinted with permission from Chan J, Bray F, McCarron P, et al. Nasopharyngeal carcinoma. In: Barnes L, Eveson JW, Reichart P, Sidransky D, eds. *Pathology and Genetics of Head and Neck Tumours. World Health Organization Classification of Tumours*. Vol 9. 3rd ed. IARC Press; 2005. Copyright © Dr. J. K. C. Chan.)

The histologic differences between these three types are by no means distinct. Lesions can share intermediate features, and some may be histologic hybrids. Lymphoepithelioma or lymphoepithelial carcinoma is considered a morphologic variant of undifferentiated carcinoma in which many lymphocytes are found among the tumor cells. Geography, race, and national origin affect the distribution of the WHO histologic types (Table 47.9). The frequency of nonkeratinizing carcinoma varies from 99% in Hong Kong to 75% in the United States.[46]

TABLE 47.9 FREQUENCY OF DIFFERENT HISTOLOGIC SUBTYPES OF NASOPHARYNGEAL CARCINOMA

	High Incidence Population (%): Hong Kong	Intermediate Population (%): Tunisia	Low Incidence Population (%): The United States
Keratinizing squamous cell carcinoma	1	8	25
Nonkeratinizing carcinoma	99	92	75
Undifferentiated	92	76	NA
Differentiated	7	16	NA
Basaloid squamous carcinoma	<0.2	NA	NA

NA, not available.

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Of note, the former WHO classification remains quite commonly used and classifies the three histologic types as (a) squamous cell carcinoma, (b) nonkeratinizing carcinoma, and (c) undifferentiated carcinoma.[70] This leads to unnecessary confusion with the new WHO classification as the former classification has been used in the majority of, albeit older, studies.

PROGNOSTIC FACTORS

The extent of local invasion, regional lymphatic spread, and distant metastasis, as reflected by the TNM staging, is the most important prognostic factor. In general, advanced T category is associated with worse local control and overall survival (OS); advanced N category predicts increased risk of distant metastasis and worse survival. The presence of distant metastasis (M1) upon presentation usually indicates poor prognosis, and treatment has conventionally been palliative in nature. A summary of the patterns of failure and survival rate for the different stages can be found in the "Results of Treatment" section.

The association of bone erosion, cranial nerve palsy, and lower nodal level with poorer survival is largely undisputed.[86-89] However, the prognostic significance of parapharyngeal extension has been a topic of controversy. In a study of 364 patients, Chua et al[90] showed that greater tumor extension as defined by extension to the prestyloid space or extension to the anterior part of the masticator space was associated with a worse local failure-free rate (L-FFR of 72% vs 86%) and lower distant failure-free rate (D-FFR of 68% vs 87%) compared to tumors with no extension or extension only to the retrostyloid space. Other investigators have reported similar significant findings.[76,88,91-93] Cheng et al[94] found parapharyngeal space extension to be the key factor in distant metastasis, even in N1 and N2 NPC.

However, Teo et al[87] did not find parapharyngeal space involvement to be an independent significant prognosticator in a study of 903 patients. Au et al,[95] using the AJCC/UICC definition of extension beyond the pharyngobasilar fascia in a study of 1,294 patients, also found that parapharyngeal extension was not a significant factor upon multivariate analysis.

These contradictory findings may be attributed to varying definitions of parapharyngeal space and incidence in the different series,[76,87,88,91] prompting some to advocate for consideration of the degree of parapharyngeal space extension in future staging systems.[93] In addition, suboptimal imaging by CT and conflation with retropharyngeal node enlargement likely contribute to the debate.[96,97]

Nevertheless, the 2010 AJCC staging system (Table 47.8) downgraded involvement of the oropharynx and/or nasal cavity without parapharyngeal extension from T2a to T1 while designating the presence of parapharyngeal extension to be the sole determinant of T2 classification. This was in light of recent multiple large retrospective studies that found no significant difference in disease failure hazard ratios (HRs) between former AJCC 2002 T2a and T1.[94,98-100]

In the current 2017 AJCC staging system,[74] further refinement to T2 stage has been defined. Soft tissue involvement of the medial and lateral pterygoid muscles was downstaged to T2 (from T4 in the 2010 AJCC system), based on a large analysis of 1,609 patients who all were staged by MRI and received intensity-modulated radiation therapy (IMRT).[52]

Another prognostic factor to consider is the gross volume of the primary tumor (GTV-P). Although it is highly correlated to T stage, considerable variability in tumor volume exists within the same T stage, and evidence

increasingly suggests that tumor volume as an independent significant factor can better predict prognosis than T category as specified by both AJCC/UICC and Ho staging systems[101-105] (Figure 47.14).

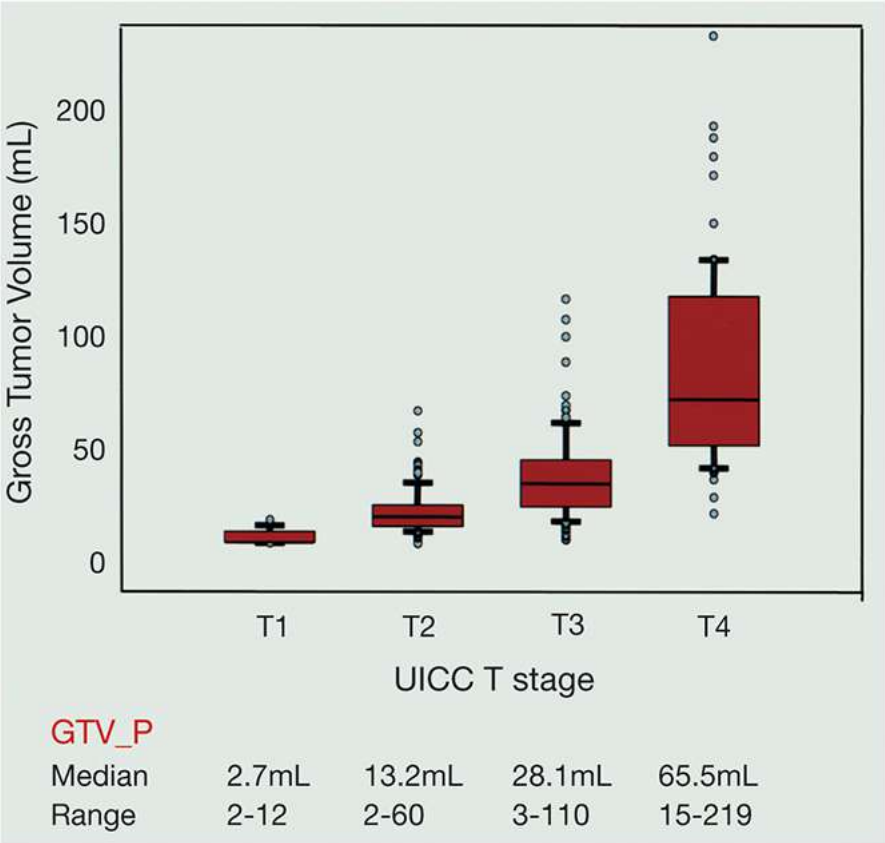

FIGURE 47.14 The correlation between T category and gross volume of primary tumor (GTV-P). UICC, International Union Against Cancer. (Modified from Sze WM, Lee AW, Yau TK, et al. Primary tumor volume of nasopharyngeal carcinoma: prognostic significance for local control. Int *J Radiat Oncol Biol Phys*. 2004;59[1]:21-27. Copyright © 2004 Elsevier. With permission.)

In a study of 308 patients staged with MRI, Sze et al[103] showed that those with GTV-P <15 cm^3 had significantly higher L-FFR than those with ≥15 cm^3 (97% vs 82% at 3 years; $P < .01$). Multivariate analysis confirmed GTV-P to be a strong significant factor independent of T category by 1997 AJCC/UICC fifth edition; the risk of local failure increased by 1% for every 1 cm^3 increase in volume. A similar observation between GTV and clinical outcomes has been observed in other head and neck tumors, including oropharyngeal cancers.[106] Further study is required to determine how tumor volume may be optimally incorporated into future staging systems.

Most series have found significantly better prognosis for females and younger patients.[86,95,107] In 759 patients, Sham and Choy[86] showed a higher 5-year survival rate in females compared with males (45% vs 28%) and in patients younger than 40 years of age versus those older than 40 (50% vs 40%, $P = .002$). However, they did not find age to significantly affect the 10-year survival rate. Multivariate analysis of 1,294 patients by Au et al[95] also showed worse cancer-specific death rates in males (HR = 1.28, $P = .02$) and patients older than 50 years (HR = 1.79, $P < .001$).

Although not all studies have found histology to be an independent prognostic factor,[28,108] many have found nonkeratinizing and undifferentiated carcinomas (formerly known as lymphoepitheliomas) to be more radiosensitive and offer better prognosis than keratinizing squamous cell carcinoma.[32,109,110] Of note, regarding ethnicity as a prognostic factor, a study by Corry et al[111] showed no prognostic difference between ethnic Asian and non-Asian patients with nonkeratinizing carcinoma.

Epstein-Barr Virus, Human Papillomavirus, and Other Biomarkers

Because of the association of EBV with NPC, various anti-EBV antibodies have long been studied for their potential as biomarkers. Although some studies have shown that elevated level of serum anti-EBV antibodies could indicate the presence[64,112,113] of disease, others have shown anti-EBV antibody titers to have little value for post-treatment surveillance.[65,114,115] The prognostic value of such titers prior to treatment has also been controversial. Although Xu et al[116] found that high EBV DNAase–specific neutralizing antibody at diagnosis predicted significantly worse event-free (EFS) and OS, others found that a number of antibodies (VCA-IgG, VCA-IgA, EA-IgG, EA-IgA, EBNA-IgG, EBNA-IgA) could not predict prognosis.[113,117,118]

Circulating cell-free DNA of EBV in the plasma of patients with NPC is a significant prognostic marker and has been found to be superior to serum anti-EBV antibodies.[118] Lo et al[119] showed that plasma EBV DNA had high sensitivity (96%) and specificity (93%) for detecting NPC, whereas Ma et al[120] showed that circulating EBV DNA levels correlated significantly with tumor burden. Studies by Lo et al[121] and Lin et al[68] found that high pretreatment levels were associated with advanced stages and poor prognosis. Meanwhile, Leung et al[69] showed that pretreatment plasma EBV DNA load was an independent prognostic factor for OS in 376 patients and could be used to segregate early-stage patients into poor- and high-risk subgroups. Thus, pretreatment EBV DNA assays have the potential to complement TNM staging in guiding treatment.

The ability of post-treatment EBV DNA to prognosticate outcomes has also been studied. Le et al[122] found no correlation between pretreatment EBV DNA levels and survival; they did find post-treatment levels to be a strong significant predictor of outcome; patients with no detectable EBV DNA had a 2-year OS rate of 94% versus 55% for patients with detectable post-treatment levels ($P < .002$).

Other studies have also consistently reported that patients with elevated post-treatment EBV DNA load have had higher risk of tumor recurrence.[68-125] Using multivariate analysis to compare various prognostic factors for NPC, Lin et al[126] found that the combined EBV DNA load (pretreatment and 1-week post-treatment) was the single most significant factor.

The ability of post-treatment EBV DNA to influence decisions regarding adjuvant therapy is currently being investigated in the NRG Oncology cooperative group HN001 trial (NCT02135042). This phase II randomized/phase III trial offers differing treatment regimens to patients with stages IIB to IVB NPC on the basis of post-chemoradiotherapy (CRT) EBV DNA levels. The hypothesis is that post-treatment EBV DNA can be used to risk-stratify patients following a course of definitive concurrent CRT. In this way, it could serve as a biomarker potentially identifying those at the highest risk for recurrence and most likely to benefit from adjuvant chemotherapy. Therefore, in the phase III cohort, patients with undetectable post-CRT EBV DNA will be randomized to observation alone versus standard adjuvant chemotherapy consisting of cisplatin and 5-fluorouracil (5-FU). The primary end point for this portion of the trial is OS with the hypothesis that observation will be noninferior to adjuvant chemotherapy. Patients with detectable post-CRT EBV DNA are randomized in the phase II portion of the trial to standard adjuvant chemotherapy or a non–cross-resistant, experimental doublet consisting of paclitaxel and gemcitabine with the hypothesis that experimental chemotherapy will be associated with superior progression-free survival (PFS). The outcomes of this trial may allow for the creation of individualized treatment recommendations using post-CRT EBV DNA as a guide.

Both Wang et al[127] and An et al[128] demonstrated that the clearance rate of plasma EBV DNA during the first month of salvage chemotherapy could predict tumor response and OS in patients with metastatic/recurrent NPC; undetectable levels after the first cycle indicated significant better survival. These data suggest that early evaluation of plasma EBV DNA can offer oncologists timely insight for potential alterations in the therapeutic regimen for patients with a slow clearance rate. In addition, Wang et al[129] prospectively monitored the plasma EBV DNA of 245 patients with NPC in clinical remission with assays every 3 to 6 months and found the plasma EBV DNA assay to have much greater sensitivity, specificity, and accuracy than FDG-PET in predicting relapse, suggesting its utility for post-treatment surveillance.

HPV-associated oropharyngeal carcinomas are now recognized as a separate subtype in the 2017 version of AJCC.[74,130] However, the implications of HPV to NPC with respect to etiology, prognosis, and treatment are unclear. Stenmark et al[131] reported on a 61-patient cohort from the Midwestern United States where 30% of patients were HPV positive/EBV negative. The patient outcomes in OS, PFS, and locoregional control (LRC) were worse in this HPV-positive/EBV-negative subgroup, when compared to EBV-positive tumors. Lin et al[132] evaluated NPC cases from southern China ($n = 86$) and Stanford, California, USA ($n = 108$), where no HPV-positive cases were detected in the Chinese cohort, whereas 5 of 11 EBV-negative cases in the Stanford cohort harbored HPV as confirmed by polymerase chain reaction. Of note, these 11 EBV-negative patients had a trend toward worse survival. Dogan et al[133] reported on a case series of 90 patients with NPC where six patients with confirmed

nasopharyngeal origin were HPV positive. These HPV-positive patients had a similar OS to EBV-positive NPC, whereas EBV/HPV-negative NPC had worse OS. Because of these conflicting studies and limited patient numbers, future work will be required to determine the prognostic significance of HPV positivity in NPC.

As with other head and neck squamous cell carcinomas, EGFR is commonly expressed in patients with NPC. Chua et al[134] found expression of EFGR in 89% of patients, in which overexpression was associated with significantly poorer disease-specific survival. Others have reported similar findings of prognostic significance.[25,135,136] Ma et al[135] performed multivariate analysis on several biomarkers in 78 patients, including microvessel density, Ki67 antigen, p53 oncoprotein, HER2, and EGFR, and found EGFR to be the only independent prognostic factor.

The study by Hui et al[137] showed that 58% of patients with NPC had expression of hypoxia-inducible factor 1-alpha (HIF-1α), 57% had carbonic anhydrase IX (CA IX), and 60% had vascular endothelial growth factor (VEGF). Those with positive hypoxic profile (high expression of HIF-1α and CA IX) had a worse PFS (P = .04); those with both positive hypoxic and angiogenic profile (high VEGF) were strongly associated with worse PFS (P = .0095). Multiple other studies have also shown that overexpression of these markers, particularly VEGF, is associated with poorer survival.[138-140]

Other biologic factors that might have prognostic significance include E-cadherin and β-catenin,[141] c-erbB2,[142] p53,[143] NM23-HI,[144,145] and interleukin-10.[146] Further validation of these potential biomarkers is needed.

TREATMENT STRATEGY

Because of the anatomic location, proximity to critical structures, surgical exposure, and tumor resection with sufficient margins have been very challenging.[147] Primary surgical intervention was rare after the 1950s for these reasons, with surgical interventions employed mainly for biopsy to gain histologic confirmation and salvage therapy for persistent or recurrent cancer. Primary treatment since has typically employed either radiation therapy (RT) alone and, more recently, in combination with chemotherapy.

Radiation Therapy

To achieve the best therapeutic ratio, every single step in the RT procedures (localization of gross tumor and target volumes, immobilization, optimization of dose fractionation, determination of treatment techniques, and precision in RT delivery) is important.

For planning, the patient should be set up in a supine position with head extended for adequate separation between the primary tumor/retropharyngeal nodes and the upper neck nodes. The tip of the uvula and the base of the occiput should be on a parallel plane to the beam axis. The patient is immobilized with a thermoplastic mask covering the head-to-shoulder region (Figure 47.15). For patients to be treated by conventional two-dimensional (2D) technique, a mouth bite is useful to minimize the dose to the oral cavity with enlarged neck nodes to be marked with wire before imaging.

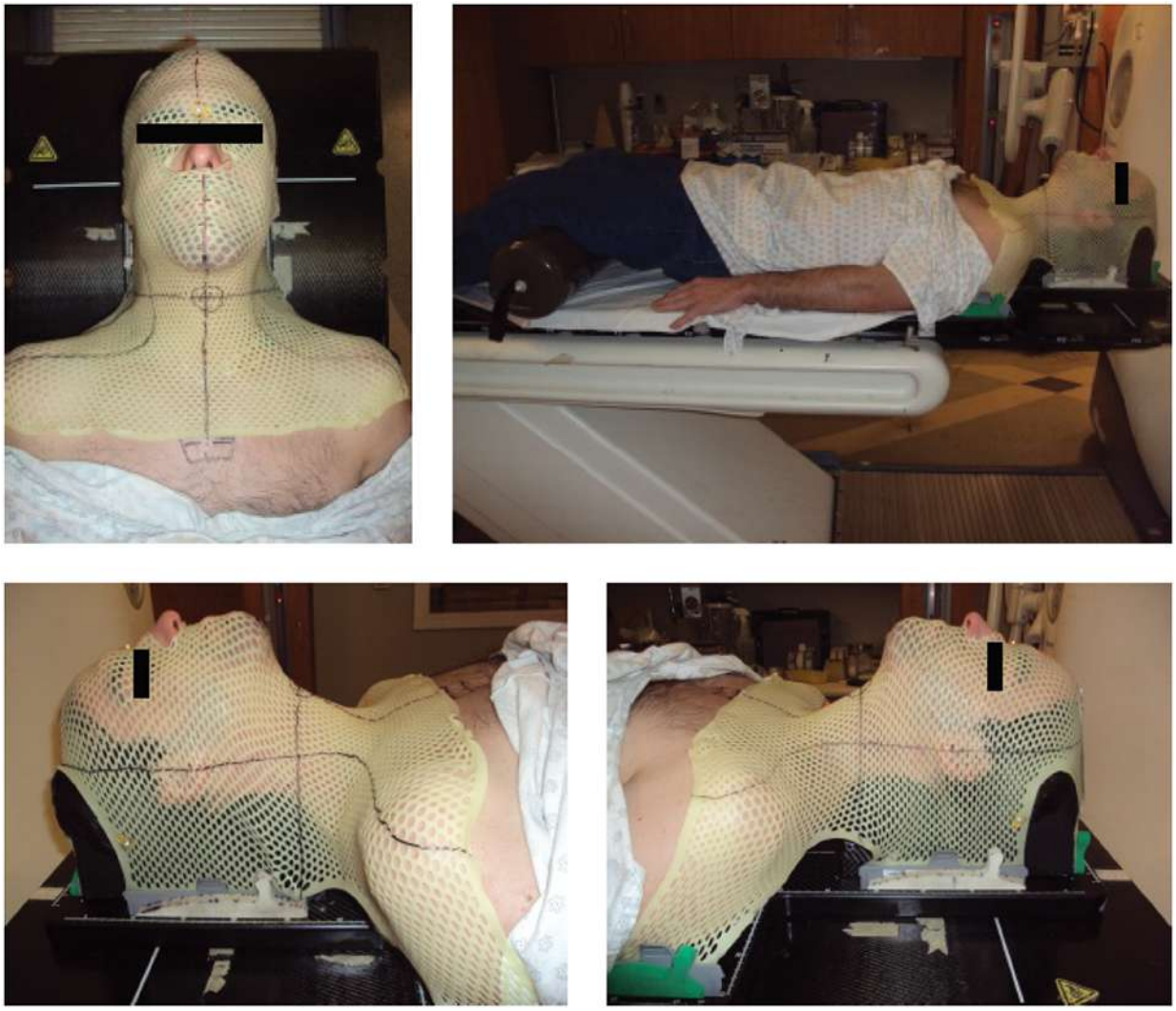

FIGURE 47.15 Immobilization of a patient in a customized thermoplastic mask covering the whole head-to-shoulder region.

Dose, Time, and Fractionation

A significant dose-response has been observed in the majority of retrospective studies, based on patients irradiated with 2D techniques. Marks et al[148] and Vikram et al[149] showed that local control was significantly improved in patients who received >67 Gy to the tumor target. Perez et al[28] observed that patients with T1-2 tumors had a local tumor control rate of 100% for those given >70 Gy, compared with 80% for those treated with 66 to 70 Gy. However, local control for patients with T3-4 tumors remained below 55%, even with a total dose >70 Gy. Similar findings were reported by Mesic et al,[150] where ≥70 Gy achieved better local control for T1-2 tumors compared with 60 Gy (94% vs 76%), but higher doses or larger fields did not significantly improve outcomes in T3-4 tumors. These observations suggest that, besides consideration of the prescribed dose, the problem of sufficient coverage has to be overcome for advanced tumors.

Lee et al[151] reported a study of 1,008 patients with T1 tumors irradiated by four different fractionation schedules and demonstrated that total dose was the most important radiation factor (P = .01). Dose fraction did not affect local control; however, it was a significant risk factor for temporal lobe necrosis (TLN).[152,153] Therefore, a fractional dose of >2 Gy should be avoided[154] (see section "Sequelae of Treatment").

The impact of the time factor is more contentious. A randomized study by Marcial et al,[155] where 62 patients were treated with split-course irradiation (30 Gy in 10 fractions over 2 weeks, then a 3-week rest period, and followed by an additional 30 Gy in 10 fractions) compared with 59 patients with 66 Gy in 33 fractions in 6.5 to 7

weeks, demonstrated no significant difference in 5-year local control (86% vs 80%), nodal control (86% vs 78%), or disease-free survival (40% vs 30%).

However, Vikram et al[149] observed that patients with interruption of RT for ≥21 days had significantly poorer local tumor control than patients without interruptions (34% vs 67%). Similar findings have been subsequently reported,[156,157] with the general consensus that prolongation is likely to be detrimental, even for nonkeratinizing NPC.

In general, the prescription recommended for NPC is to a total dose of about 70 Gy over 7 weeks to the gross tumor along with 50 to 60 Gy for elective treatment of potential risk sites.

Tumor Target Volumes

The GTV should encompass the primary nasopharyngeal tumor, gross retropharyngeal lymphadenopathy, and gross nodal disease as determined by clinical, endoscopic, and radiologic examinations. Lymph nodes ≥1 cm or with evidence of central necrosis are considered gross nodal disease. For patients given induction chemotherapy, it is recommended that the targets be determined by the prechemotherapy extent.

Prophylactic neck radiation is usually recommended in N0 patients because of the high incidence of occult neck node involvement. Lee et al[36] found patients with a clinically negative neck who underwent elective neck irradiation had a significantly lower nodal recurrence rate than those untreated (11% vs 40%). In addition, even with successful salvage by subsequent treatment, patients with nodal recurrence had a significantly greater incidence of distant metastases than those without recurrence (21% vs 6%).

The clinical target volume (CTV) includes the GTV, regions of microscopic disease, and potential infiltrative spread. Different centers may have different philosophies in defining the margins and dose level. For example, Table 47.10 shows the delineation criteria for the various CTVs currently employed at Memorial Sloan Kettering Cancer Center (MSKCC). A gross disease CTV (CTV_{70}) is defined as the GTV plus an additional margin of 5 mm to 1 cm surrounding all gross diseases. The margin may be decreased to as small as 1 mm in critical regions near the brainstem or spinal cord. The high-risk subclinical CTV ($CTV_{50\text{-}59.4}$) encompasses the GTV including all potential areas of microscopic spread of disease. This volume should include at a minimum the entire nasopharynx, retropharyngeal lymph nodal regions, clivus, skull base, pterygoid fossae, parapharyngeal space, sphenoid sinus, posterior fourth to third of the nasal cavity, and posterior fourth to third of the maxillary sinuses. This $CTV_{50\text{-}59.4}$ should also include lymph nodal groups that are at risk of potential microscopic disease spread: bilateral upper deep jugular (junctional, parapharyngeal), submandibular, subdigastric (jugulodigastric), midjugular, posterior cervical, and retropharyngeal lymph nodes. In patients with clinically N0 neck, it is not necessary to include level I nodal regions. It is reasonable to omit elective nodal irradiation for the uninvolved low neck (IV and Vb) based on prospective data from Tang et al.[158]

TABLE 47.10 EXAMPLE OF GUIDELINE ON ANATOMIC STRUCTURES/BOUNDARIES FOR DELINEATING CLINICAL TARGET VOLUMES (CTV) FOR INTENSITY-MODULATED RADIATION THERAPY

	Delineation of CTV	
CTV	**Structures**	**Anatomic Boundaries**
CTV_{70}	GTV + ≥5 mm margin (can be reduced to as low as 1 mm for tumors in close proximity to critical structures/neurologic structures)[a]	
$CTV_{50\text{-}59.4}$	CTV_{70} + ≥5 mm margin (as low as 1 mm when close to critical structures)[a]	
	Entire nasopharynx	5-10 mm from mucosal surface of nasopharynx
		Anterior: Junction with nasal choana
		Lateral: Medial border of parapharyngeal space
		Caudal: Caudal border of C1 vertebra
	Base of skull	Posterior: Anterior 1/2-2/3 of clivus (entire clivus, if involved)
		Lateral: Lateral border of foramen ovale
	Parapharyngeal spaces	Lateral: Lateral border of styloid processes
	Inferior sphenoid sinus	Cranial: Lower half of sphenoid sinus (in T3-T4 disease,

	Delineation of CTV	
CTV	**Structures**	**Anatomic Boundaries**
		include entire sphenoid sinus)
	Posterior nasal cavity	Anterior: Posterior fourth to third of nasal cavity
	Posterior maxillary sinuses	Anterior: Posterior fourth to third of maxillary sinuses (to ensure pterygopalatine fossae coverage)
	Cavernous sinus, include high-risk patients (T3, T4 bulky disease involving roof of nasopharynx)	
	High-risk nodal levels (include all bilaterally)	a. Upper deep jugular (junctional, parapharyngeal) b. Submandibular (level I)[b] c. Subdigastric (jugulodigastric) (level II) d. Midjugular (level III) e. Low jugular and supraclavicular (level IV)[c] f. Posterior cervical (level V)[c] g. Retropharyngeal

Based on guideline currently used at Memorial Sloan Kettering Cancer Center and detailed in RTOG 0615.

GTV, gross tumor volume (all gross primary tumor and involved lymph nodes); PTV, planning target volume (CTV + 3- to 5-mm margin).

Total dose prescription at:

PTV_{70}: 70 Gy in 35 fractions (2 Gy per fraction) or 70 Gy in 33 fractions (2.12 Gy per fraction).

$PTV_{50\text{-}59.4}$: 50 Gy in 25 fractions (2 Gy per fraction) or 59.4 Gy in 33 fractions (1.8 Gy per fraction).

[a]CTV margins may also be limited to exclude the bone *not* at risk for subclinical disease or air.

[b]Bilateral IB lymph nodes can be spared if patient is node negative. The treatment of level IB may result in the delivery of clinically significant radiation doses to normal structures, such as the floor of the mouth, mandible, and upper pharyngeal mucosa above the hyoid. At the discretion of the treating radiation oncologist, level IB may also be spared or limited to the anterior border of the submandibular gland in low-risk node-positive patients. Patients presenting with isolated retropharyngeal nodes or isolated level IV nodes are considered low risk for level IB involvement. Treatment of level IB should be considered in node-negative patients with extensive involvement of the hard palate, nasal cavity, or maxillary antrum.

[c]Uninvolved low neck (IV and Vb) can be spared at the discretion of the treating radiation oncologist.

The planning target volume (PTV) is defined as the CTV including a circumferential margin of typically 3 to 5 mm to all the CTVs to account for setup errors and potential patient motion. The PTV margin may be decreased to as small as 1 mm in regions near-critical normal structures, such as the brainstem or spinal cord.

Conventional Two-Dimensional Treatment Techniques

One of the most common RT approaches employed is composed of two phases.[159] Phase I consists of large lateral opposing faciocervical fields that encompass the primary tumor and the upper neck nodes in one volume, with a matching lower anterior cervical field for the lower cervical lymphatics. Phase II is used after 40 Gy to limit the dose to the spinal cord. This three-field technique includes lateral opposing facial fields coupled with anterior facial field for the primary tumor. Typical treatment fields and radiologic landmarks are shown in Figure 47.16. Shrinking treatment fields by cone down after 50 to 60 Gy should be done, when possible, to increase protection of critical structures.

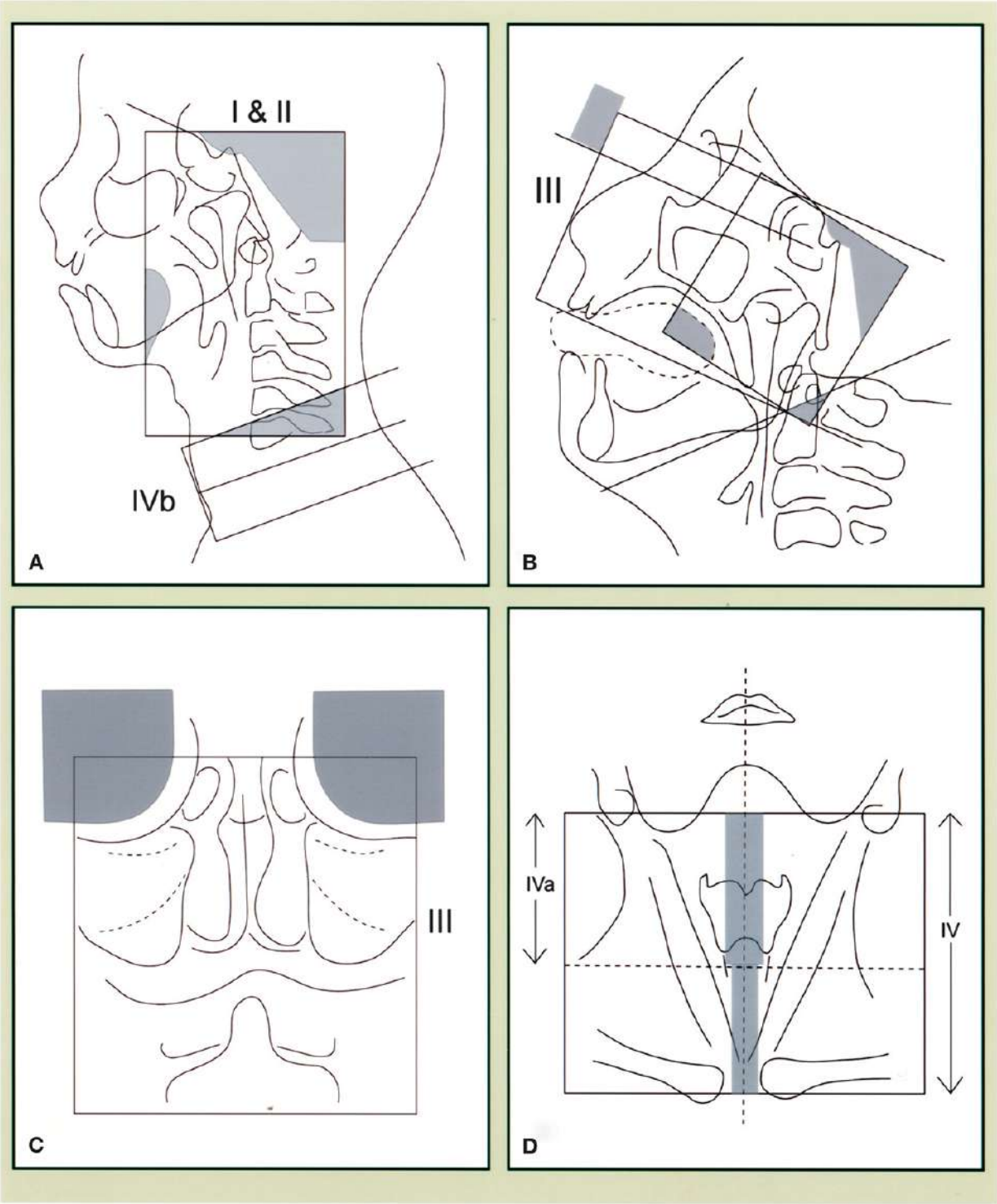

FIGURE 47.16 Conventional two-dimensional radiotherapy using Ho's technique. A. Phase I, lateral-opposed faciocervical fields (I-II) and lower anterior cervical field (IVb). B. Phase II, sagittal view showing lateral-opposed facial fields and noncoplanar anterior facial field (III). C. Coronal view of anterior facial field (III). D. Anterior cervical field for whole neck (IV).

The three-field technique in phase II allows the dose to be minimized to the temporomandibular joints and the bilateral temporal lobes. However, coverage may not be sufficient for tumors with extensive posterior-lateral

extension to the parapharyngeal spaces or caudal extension to the oropharynx. To remedy this deficit, an additional dose is delivered by a posterior-lateral field with avoidance of neurologic structures.[160]

Three-Dimensional Conformal Treatment Techniques

NPC presents most typically as a concave tumor allowing for computerized 3D treatment plans to be an important technical advance for improved radiation delivery. Several investigators have designed multifield conformal plans, including the seven-field technique used at MSKCC (The United States)[161] and the "boomerang" technique used at Peter MacCallum Cancer Center (Australia).[162] When compared to conventional 2D plans, 3D planning demonstrated better tumor dose coverage while decreasing normal tissue dose in several studies.[87,163,164]

Leibel et al[165] from MSKCC demonstrated that the target volume underdosed at the 95% isodose level was lowered with 3D plans when compared with 2D plans (7% vs 22%). On average, the mean tumor dose increased to 13%, leading to an estimation that tumor control would increase by 15%. However, a subsequent study in which 68 patients received this technique for a boost of 19.8 to 25.2 Gy following phase I conventional 2D treatment for 50.4 Gy to a total dose of 70.2 to 75.6 Gy did not show significant improvement; the 5-year L-FFR was 77%, and late toxicity grade ≥3 was 25%.[161]

More encouraging results were obtained by Jen et al,[166] who compared 72 patients treated with 3D conformal technique with 108 patients treated with 2D technique. A significant improvement in 3-year L-FFR for T4 (86% vs 47%), and EFS for both stage III (80% vs 56%) and stage IV (82% vs 33%), was observed. Furthermore, the incidence of xerostomia at 3 years was significantly less with 3D conformal treatment (69.2% vs 98.0%), although for most other late toxicities, little difference was seen.

Intensity-Modulated Radiation Therapy Techniques

IMRT has supplanted conventional RT in the treatment of NPC in an increasing number of institutions throughout the world. The intensity of the radiation beams can be modulated to deliver a high dose to the tumor with a superior target volume coverage while significantly limiting the dose to surrounding normal tissues.[167-172] Following the initial publication[173] and the subsequent update on IMRT for NPC from the University of California, San Francisco (UCSF),[171] several other institutions have utilized IMRT with similar excellent treatment outcomes.[174-180]

Another point of interest is the possibility of biologic enhancement by simultaneous modulated accelerated radiation therapy (SMART), also known as dose painting, as a new way of delivering an accelerated fractionation (AF) schedule, a concept that was first reported by Butler et al[181] for the treatment of other head and neck cancers with IMRT.

These differing methods and dose fractionation regimens for IMRT are being investigated by different groups. Table 47.11 summarizes the key features along with the reported results. The majority of the patients in these series received additional chemotherapy and/or enhanced RT with boosts or AF. All reported encouraging early results with local control in excess of 90% at 2 to 4 years.

TABLE 47.11 INTENSITY-MODULATED RADIATION THERAPY FOR NASOPHARYNGEAL CARCINOMA: METHODS AND RESULTS BY DIFFERENT CENTERS

	UCSF[171,182]	MSKCC[174]	PWH[176]	SYS[183]	QMH[175]	QMH[184]	CUHK[185]	NCCS[186]	PYNEH[187]
Number of patients	118	74	63	104	50	50	865	195	193
Patient characteristics									
Treatment period	1995-2003	1998-2004	2000-2002	2001-2004	2000-2002	2000-2004	2001-2008	2002-2005	2005-2007
T category	All	All	All	All	T1-T2	T3-T4	All	All	All
Intensity-modulated RT									
PTV-G									
Margin around GTV (mm)	—	5-10	2	—	—	—	—	3-5	5-8
Total dose (Gy)	70	70.2	66	64-70	68-70	76	68	66-70	70
Dose per fraction (Gy)	2.12	2.34	2	2.33-2.56	2-2.06	2.17	2	2-2.12	2.12
Additional treatment									

	UCSF[171,182]	MSKCC[174]	PWH[176]	SYS[183]	QMH[175]	QMH[184]	CUHK[185]	NCCS[186]	PYNEH[187]
Accelerated fractionation	—	80%	—	—	—	—	—	—	62%
Boost	22% ICB		32% ICB 24% 3D	—	—	—	—	10% ICB	—
Chemotherapy (%)	90	93	30	23	0	68	65	>57	84
Median follow-up (mo)	30	35	29	19	14	25	40	36.5	30
Tumor control									
Time point (y)	4	3	3	3	2	2	5	3	2
Local-FFR (%)	96	91	92	99	100	96	90.4	89.6	95
Nodal-FFR (%)	98	93	98	99	94	—	—	—	96
Distant-FFR (%)	72	78	79	88	94	94	84	89.2	90
Overall survival (%)	74	83	90	86	NR	92	83	94.3	92
Late toxicities									
Xerostomia (grade ≥2) (%)	2[a] (2 y)	32 (1 y)	23 (2 y)	—	—	—	—	—	—
Deafness (grade >2) (%)	7[a]	>15	15	—	—	42	—	—	—
Fibrosis (grade >2) (%)	—	—	11	—	—	14	—	—	—
Dysphagia (grade >2) (%)	1[a]	—	5	—	—	—	—	—	—
Hypopituitarism (%)	—	0	23	—	—	—	—	—	—
Osteonecrosis (%)	0.8	0	2	—	—	—	—	—	—
Temporal lobe necrosis (%)	0.8	0	3	—	—	4	—	—	—
Carotid pseudoaneurysm/epistaxis (%)	0.8[a]	—	—	—	—	4	—	—	—

3D, three-dimensional conformal boost; FFR, failure-free rate; GTV, gross tumor volume; ICB, intracavitary brachytherapy; MSKCC, Memorial Sloan Kettering Cancer Center (the United States); NR, not reported; PTV-G, planning target volume for gross tumor; PWH, Prince of Wales Hospital (Hong Kong); QMH, Queen Mary Hospital (Hong Kong); RT, radiation therapy; SYS, Sun Yat-sen Cancer Center (China); UCSF, University of California, San Francisco (the United States).

[a]Based on data reported by Lee N, Xia P, Quivey JM, et al. Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience. *Int J Radiat Oncol Biol Phys*. 2002;53(1):12-22.

At the UCSF, patients were typically prescribed 70 Gy to the $PTV_{gross\ disease}$ and involved lymph nodes in 2.12 to 2.25 Gy fractions, whereas the $PTV_{high\text{-}risk\ subclinical}$ were prescribed 59.4 Gy in 1.8 fractions, and a clinical negative neck ($PTV_{low\text{-}risk\ subclinical}$) received 54 Gy at 1.64 Gy fractions all in conventional once-daily (QD) fractions.[171,182] Bucci et al[182] reported the updated results of 118 patients, which confirmed excellent LRC of 96%. Yet, distant failure remained high (28%) despite broad use of concurrent-adjuvant CRT. OS was 74% at 4 years.

At MSKCC, Wolden et al[174] reported their initial experience with 74 patients, where 59 were treated with AF using the concomitant boost method and 15 by the SMART method/dose painting. For the SMART cohort, a total dose of 70.2 Gy at 2.34 Gy/fraction was given to the gross disease, and the "microscopic" PTV received 54 Gy at 1.8 Gy/fraction. There was a trend, but no statistically significant improvement in 3-year L-FFR than for patients treated by 3D conformal boost (91% vs 79%, $P = .11$). Updated results by Setton et al[188] on 177 patients confirmed excellent rates of disease control (92% 3-year and 83% 5-year local control) and survival (87% 3-year and 75% 5-year OS) with this technique. Additional dose escalation by SMART boost in 50 patients with T3 and T4 tumors was reported by Kwong et al[184] from Queen Mary Hospital (Hong Kong). They sought to deliver a total dose of 76 Gy at 2.17 Gy/fraction to the gross tumor. The early result for LRC was excellent (96% at 2 years); however, serious late toxicities were observed, including 4% of patients having a life- threatening hemorrhage from carotid artery pseudoaneurysm and another 4% developing TLN with a median follow-up of 2.1 years.

Two different IMRT approaches are currently being utilized by different centers[1]: an extended whole-field (EWF) IMRT technique, in which the total target volume is encompassed in the IMRT plan, or[2] a split-field (SF) IMRT technique, in which the target volumes superior to the vocal cords are treated with an IMRT plan and the lower neck nodes are treated with a conventional low anterior neck field.[189-191] Discussions among practitioners on

which IMRT technique is best have been persistent. Concerns of potential failures at the SF matchline because of potential underdosing, or even complications resulting from overdosing, have caused many centers to implement EWF IMRT, even when no clinically involved neck nodes are evident in the matchline region. These concerns may be caused by the treatment delivery system that is used at centers where a perfect match between the IMRT fields and the low anterior neck field is not possible. However, with a EWF technique, an unnecessary dose of radiation is delivered to the normal glottic larynx.[192] Whereas with the SF IMRT technique, the dose to the vocal cords is minimal because of shielding by a midline Cerrobend block or the multileaf collimator (MLC). At the moment, no IMRT matchline failures or complications have been reported with the SF IMRT technique.[173]

Figures 47.17 and 47.18 show examples of MSKCC IMRT plans delivered with the dynamic MLC system using a sliding window technique to patients with early and advanced disease, respectively. A total dose of 70 Gy at 2.12 Gy/fraction to the $PTV_{gross\ disease}$ and 59.4 Gy to the $PTV_{high\text{-}risk\ subclinical}$ is given over 33 QD fractions (Table 47.10). For the low neck, if SF IMRT is used, a dose of 50.4 Gy at 1.8 Gy/fraction/day is generally prescribed. However, if the low neck is included in the IMRT fields and is considered at low risk for nodal involvement, the $PTV_{low\text{-}risk\ subclinical}$ typically receives 54 Gy at 1.64 Gy/fraction/d.

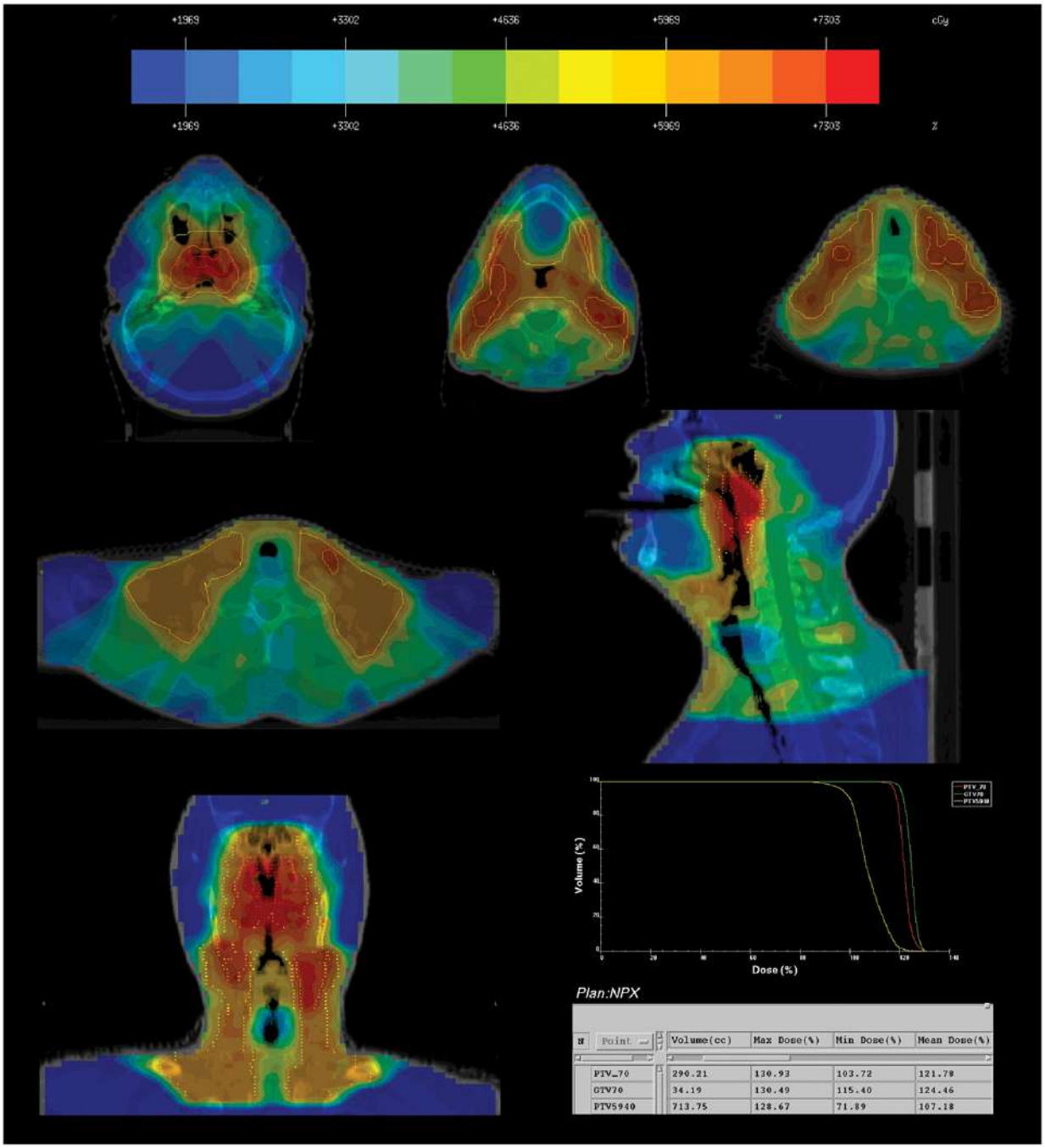

FIGURE 47.17 Intensity-modulated radiation therapy for a patient with T2N2M0 nasopharyngeal carcinoma treated at Memorial Sloan Kettering Cancer Center showing delineation of gross tumor targets (GTV) and planning target volumes (PTV) for 70 and 54 Gy, the dose distribution, and the dose-volume histogram (DVH) for GTV, PTV_{70}, and $PTV_{59.4}$.

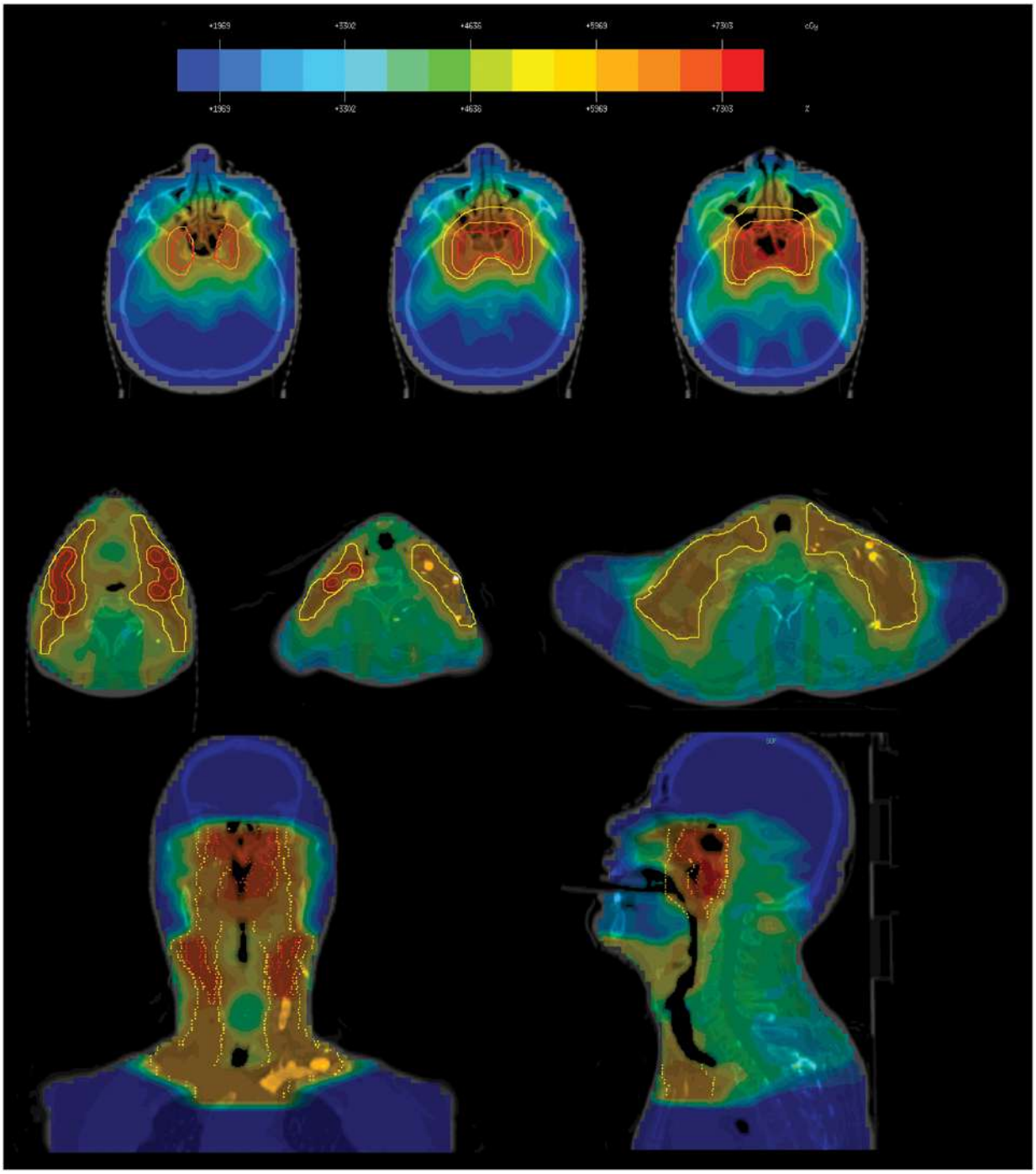

FIGURE 47.18 Intensity-modulated radiation therapy for a patient with T4N2M0 nasopharyngeal carcinoma treated at Memorial Sloan Kettering Cancer Center showing delineation of gross tumor (GTV) and planning target volumes (PTV) for 70 and 54 Gy, and the dose distribution.

Inverse planning involves the appropriate specification of normal tissue dose constraints. It is important to note that overstrigent use of normal tissue constraints might result in inadequate cover of tumor targets; therefore, optimal balance is essential. Different dose-constraint guidelines have been suggested.[193,194] An example of dose-constraint guidelines is provided in Table 47.12, which displays the guidelines presently used at MSKCC.

TABLE 47.12 INTENSITY-MODULATED RADIATION THERAPY FOR NASOPHARYNGEAL CARCINOMA: AN EXAMPLE OF NORMAL

TISSUE DOSE CONSTRAINTS	
Structures	**Constraints**
Critical Structures	
Brainstem	Max <5 Gy or 1% of PTV cannot exceed 60 Gy.
Optic nerves	Max <54 Gy or 1% of PTV cannot exceed 60 Gy.
Optic chiasm	Max <54 Gy or 1% of PTV cannot exceed 60 Gy.
Spinal cord	Max <45 Gy or 1 mL of the PTV cannot exceed 50 Gy.
Mandible and temporomandibular joint	Max <70 Gy or 1 mL of the PTV cannot exceed 75 Gy.
Brachial plexus	Max <66 Gy
Temporal lobes	Max <60 Gy or 1% of PTV cannot exceed 65 Gy.
Other Normal Structures	
Oral cavity	Mean <40 Gy
Parotid gland	Mean ≤26 Gy (should be achieved in at least one gland) or at least 20 mL of the combined volume of both parotid glands will receive <20 Gy or at least 50% of the gland will receive <30 Gy (should be achieved in at least one gland)
Cochlea	V55 <5%
Eyes	Mean <35 Gy, max <50 Gy
Lens	Max <25 Gy
Glottic larynx	Mean <45 Gy
Esophagus, postcricoid pharynx	Mean <45 Gy

Based on guidelines presently used at Memorial Sloan Kettering Cancer Center.
PTV, planning target volume.

Dose Escalation

Excellent local tumor control has been reported by delivering an additional boost to patients with early disease treated by conventional 2D technique.

Brachytherapy

The most commonly used method is brachytherapy. Intracavitary insertions[195-203] or interstitial implants[204-207] have been used in T1 to T3 NPCs as a boost treatment following external beam radiation therapy (EBRT) or in the treatment of recurrent disease, either alone or in combination with EBRT. Brachytherapy is not suitable for the treatment of tumors with intracranial extension because of the rapid reduction of dose as distance from the radioactive source increases. Since the advent of IMRT as primary RT for NPC and with its demonstration of excellent local control, the use of brachytherapy as a boost treatment following definitive IMRT has dramatically declined. Multiple applicators and techniques have been developed for the delivery of intracavitary brachytherapy.[197-199,201,203-208] In the past, intracavitary brachytherapy was delivered using low-dose rate (LDR) techniques. However, currently, remote afterloading and fractionated high-dose rate (HDR) techniques are more commonly used (Figure 47.19).[208]

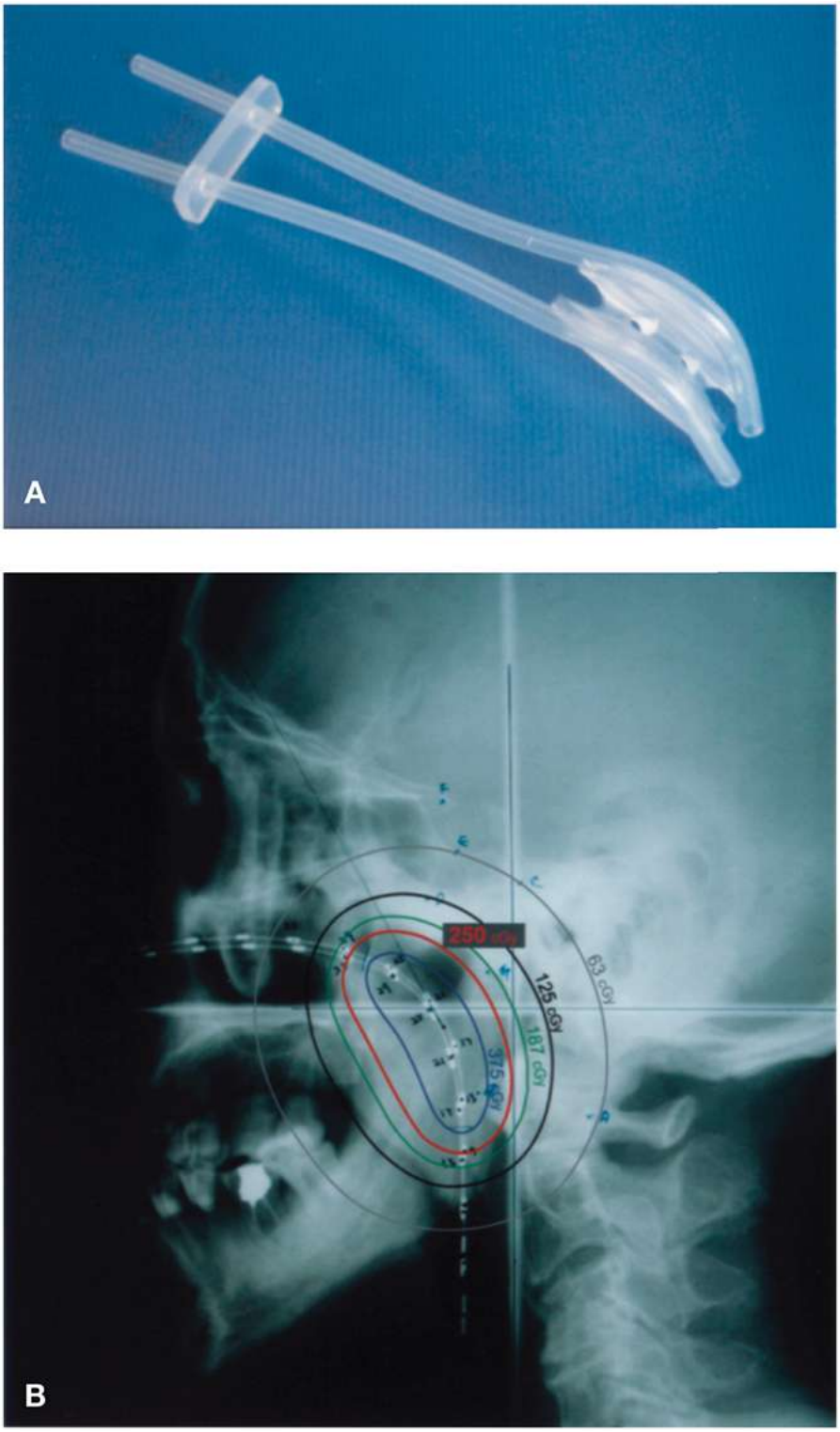

FIGURE 47.19 Endocavitary brachytherapy for nasopharyngeal carcinoma. A. The Rotterdam nasopharyngeal applicator. B. The simulator check film showing the position of the radioactive sources and the dose distribution.

Table 47.13 summarizes reports on the use of brachytherapy as a boost for dose escalation. Most studies demonstrated that local control up to 90% to 95% could be achieved for T1-2 tumors without excessive late damages. A retrospective comparison by Wang[198] from Massachusetts General Hospital (the United States)

reported that for T1 and T2 patients who received a 10- to 15 Gy, LDR brachytherapy boost after 60 to 64 Gy by EBRT had a 5-year L-FFR of 90% versus 54%, with $P = .001$ for patients receiving EBRT alone to 65 to 70 Gy. A similar study by Teo et al,[209] where delivery of 18 to 24 Gy in three fractions by HDR brachytherapy, showed a significant improvement of the 5-year L-FFR of 95% compared with a 90% 5-year L-FFR for EBRT-only patients ($P = .016$).

TABLE 47.13 ADJUVANT BRACHYTHERAPY BOOST FOR PRIMARY TREATMENT OF NASOPHARYNGEAL CARCINOMA

			Brachytherapy			Local Control		
Author	**T Category[a]**	**External RT Dose (Gy)**	**Modality**	**Dose (Gy)**	**Fraction**	**Day**	**Year**	**Rate (%)**
Chang et al[210]	T1	65-68 65-68 68-72	HDR-ICB HDR-ICB Control	5-11 15-16.5 —	1-2 3	1-8 15	5	94 80 vs 74 ($P = .01$)
Lee et al[200]	T1-3	54-72	HDR-ICB or LDR-ICB	5-7 10-54	2	1	5	89
Levendag et al[196]	T1-2a T2b	60 70	HDR-ICB HDR-ICB	15 11	5 2	3	5	92
Lu et al[211]	T1-2	66	HDR-ICB	10	2	8	2	94
Ng et al[212]	T1-4	43-70	HDR-ICB	6-15	2-5	2-5	5	96
Ozyar et al[213]	T1-4	59-71 59-74	HDR-ICB Control	12 —	3	3	5	86 vs 94 ($P = .23$)
Ren et al[214]	T2b	60 68	HDR-ICB Control	12-20 —	1	1	5	98 vs 80 ($P = .012$)
Syed et al[207]	T1-4	50-60	ICB + interstitial	33-37	1	3	5	93
Teo et al[209]	T1-2a	60-71 60-71	HDR-ICB Control	18-24 —	3	15	5	95 vs 90 ($P = .17$)
Vikram[215]	T1-4	60-66	Interstitial	160 in 1 y			5	96
Wang[198]	T1-2	60-64 65-70	LDR-ICB Control	7-10 —	1	1	5	91 vs 60 ($P < .01$)

HDR, high-dose rate; ICB, intracavitary brachytherapy; LDR, low-dose rate; NR, not reported; RT, radiotherapy.

[a]By 2002 AJCC sixth edition or 1997 AJCC fifth edition.

However, a report by Ozyar et al[213] of patients with T1 to T4 tumors treated with HDR brachytherapy boost of 12 Gy in three fractions did not show improvement over EBRT alone (3-year L-FFR: 86% vs 94%; $P = .23$). More recently, a prospective trial by the International Atomic Energy Agency studied 275 patients with locoregionally advanced NPC disease (TNM stage III or M0 stage IV) who were all treated by induction chemotherapy followed by concurrent CRT to 70 Gy; then one randomized arm received a brachytherapy boost of 11 Gy LDR or three fractions of 3 Gy HDR. With a median follow-up of 29 months, the authors reported no additional benefit of brachytherapy boost compared with CRT alone toward 3-year OS (63.3% vs 62.9%, $P = .742$), locoregional-FFR (54.4% vs 60.5%, $P = .647$), or distant metastasis-free survival (52.6% vs 59.8%, $P = .496$).[216]

One major limitation of brachytherapy is that the dose delivered is adequate only for superficial nonbulky tumors. Furthermore, optimal positioning of the applicators depends on both the individual clinician's skill and the patient's anatomic features.

Stereotactic Radiosurgery

Stereotactic radiosurgery or fractionated RT allows for precise delivery of highly conformal RT with a rapid dose falloff and provides an alternative for dose escalation. Hara et al[217] reported a study of 82 patients with T1 to T4 tumors showing excellent 5-year L-FFR of 98% after receiving a median stereotactic RT (SRT) boost of 12 Gy (range, 7-15 Gy) following EBRT to 66 Gy. However, despite the addition of concurrent chemotherapy in 76% of the patients, the distant failure rate was 32% and OS was 69%. With a median follow-up of 40.7 months for living patients, 12.1% of patients developed radiographic TLN (only 2.4% were symptomatic with seizures) and 3.6% developed retinopathy. The risk was especially high in patients with T4 tumors.

Altered Fractionation

Over the past few decades, studies have been conducted to explore the role of altered fractionation regimens in head and neck cancers, along with NPCs. Hyperfractionation, AF, and a combination of which were explored in conjunction with concurrent chemotherapy.

Sanchiz et al[218] conducted a large randomized trial examining twice-daily (BID) versus QD irradiation for head and neck cancer including tumors of the nasopharynx. Eight hundred fifty-nine patients with advanced head and neck cancers (T3-T4, N0-3, M0 by UICC staging), which included 92 patients with NPC, were randomly assigned to QD irradiation (group A), BID irradiation (group B), or QD irradiation with concurrent 5-FU chemotherapy (group C). Groups B and C showed a significant improvement in median duration of response and OS when compared to group A. No significant differences were seen between groups B and C.

The first randomized trial on AF for NPC by Teo et al[219] used an uncommon schedule of 2.5 Gy/fraction QD for eight fractions before randomization to an experimental arm using 1.6 Gy BID for an additional 32 fractions versus a control arm treated with 2.5 Gy QD for another 16 fractions. The trial was terminated early because of excessive neurologic toxicities in the AF arm (49% vs 23%). For this series of 159 patients (62% with T1-2 tumors), the AF arm did not achieve a significant improvement in tumor control (5-year L-FFR, 89% vs 85%). Jen et al[220] reported on 222 patients where 76 patients received hyperfractionated RT at 1.2 Gy/fraction BID and 12 patients received accelerated-hyperfractionated RT at 1.6 Gy BID to a median dose of 80 Gy for these BID RT groups. The remaining 134 patients are treated by conventional QD fractionation to a median dose of 70 Gy. The patients treated by BID fractionation did not demonstrate a statistically significant difference in 5-year L-FFR when compared to QD fractionation (T1-3, 93% vs 86%; T4, 44% vs 37%). The 1.2 Gy/fraction regimen did not cause excessive toxicity; however, patients treated with 1.6 Gy/fraction had a 27% incidence of TLN.[221] See section "Sequelae of Treatment" for more details regarding the influence of dose fractionation on brain necrosis.

To minimize the risk of late damage, the more moderate AF schedule of the Danish Head and Neck Cancer Study Group 6 to 7 Trials using 2 Gy/fraction, six fractions per week[222] of 1,476 patients with head and neck cancer, of which 435 had pharyngeal tumors, including the nasopharynx, demonstrated AF resulted in significantly improved 5-year L-FFR (76% vs 64% for six and five fractions, $P = .0001$) and disease-specific survival (73% vs 66%, for six and five fractions, $P = .01$), but not for OS. This same fractionation schedule was tested retrospectively for NPC by Lee et al.[223] They reported for patients irradiated to a total dose of 66 Gy with 2D technique when on an AF schedule had significantly higher L-FFR than those treated with conventional five fractions per week. The benefit was significant particularly for T3-4 tumors (87% vs 62%; $P < .01$), and multivariate analyses confirmed that fractionation was an independent prognostic factor for overall progression (AF group, HR = 0.63, 95% confidence interval [CI], 0.41-0.98; $P = .04$). In addition, no significant increase in late toxicity was observed at 3 years (20% vs 15%).

This schedule was then used in the subsequent NPC-9902 trial initiated by the HKNPCSG,[224] which aimed to assess the therapeutic benefit of AF and/or concurrent-adjuvant CRT, that randomized 189 patients with locally advanced NPC (T3-T4, N0-1, M0) to four arms[1]: conventional fractionation (CF) alone,[2] AF (six fractions/week) alone,[3] CF with concurrent chemotherapy, and[5] AF with concurrent chemotherapy. Preliminary results with a median follow-up of 2.9 years showed that AF per se did not demonstrate a significant improvement in EFS when compared with CF (AF vs CF: HR 0.68, 95% CI 0.37-1.25, $P = .22$). However, AF combined with CRT (arm 4) achieved a strongly significant improvement when compared with CF alone (EFS: 94% vs 70%, $P = .008$) but without an improvement in OS. A significant increase in acute and late toxicity in the AF combined with CRT arm was also noted.

From these and other experiences with altered fractionation schedules in the treatment of NPC, in addition to other head and neck cancers, it has been concluded that both total dose and overall treatment time are important factors in determining outcomes.[225] With the increasing use of IMRT, dose escalation—to allow ample dose delivery to the gross and subclinical disease—has become achievable without associated changes in rates of toxicity, considerably improving the therapeutic ratio of concurrent chemoradiation and causing the above fractionation schemes to fall out of favor.

Chemotherapy

NPC is generally regarded to be a highly chemosensitive disease. Although RT alone is the standard treatment for stage I NPC, concurrent CRT with or without adjuvant chemotherapy is the current standard for locally advanced disease (stages III-VB) based on multiple randomized controlled trials and meta-analyses (Table 47.14). Although

there is less evidence for CRT in intermediate-stage (2010 AJCC stage II) disease, it is currently recommended that such patients be treated with CRT in light of pooled data from two phase III trials[226,227] and a more recent phase III trial from Chen et al.[228] In more detail, Chen and colleagues[228] demonstrated that Chinese stage II (equiv. to AJCC II-III; only 13% of the study patients were AJCC 2010 stage III) patients with NPC who received concurrent CRT had a superior 5-year OS compared to those treated with radiation alone (94.5% vs 85.8%, P = .007) with improved distant control (94.8% vs 83.9%, P = .007). Multivariate analyses found that the number of chemotherapy cycles was the only independent factor associated with improved OS, PFS, and distant control. With the addition of chemotherapy, an increase in acute side effects was observed, but no significant increase in late effects was reported.

TABLE 47.14 RANDOMIZED PROSPECTIVE TRIALS WITH CONCURRENT CHEMORADIOTHERAPY

Author	Year	Patients (*N*)	Control Arm	Radiotherapy Dose (Gy)	Experimental Arm (Chemotherapy)			Time Point (year)	Tumor Control (%)[a]		
					Induction	Concurrent	Adjuvant		LRC	DMFS	OS
Concurrent ± adjuvant chemoradiotherapy (phase III trials)											
Al-Sarraf[229]	1998	193	RT	70	—	P	PF	5	NR	NR	63 vs 37
Lin[230]	2003	284	RT	70-74	—	PF	—	5	89 vs 73	79 vs 70	72 vs 54
Kwong[231]	2004	222	RT	52.5-68	—	U	PF/VBM	3	80 vs 72	85 vs 71	87 vs 77
Chan[232]	2005	350	RT	66	—	P	—	5	NR	NR	70 vs 59
Wee[233]	2005	221	RT	70	—	P	PF	5	NR	83 vs 63	67 vs 49
Zhang[234]	2005	115	RT	70-74	—	O	—	2	NR	92 vs 80	100 vs 77
Chen[b,58]	2008	316	RT	70	—	P	PF	2	98 vs 92	87 vs 79	90 vs 80
Lee[236]	2010	348	RT	70	—	P	PF	5	88 vs 78	74 vs 68	68 v. 64
Lee[237]	2011	189	RT	70	—	P	PF	5	81(C)-90(A) vs 85(C)-75(A)	75(C)-95(A) vs 75(C)-74(A)	78(C)-85(A vs 66(C,A)
Chenb[228]	2011	230	RT	68-70	—	P	—	5	93 vs 91	95 vs 84	86 vs 95
Induction-concurrent chemoradiotherapy (phase II trials)											
Hui[238]	2009	65	CCRT	66	DP	P	—	2	NR	NR	95 vs 86
Fountzilas[239]	2012	141	CCRT	66-70	PET	P	—	3	NR	NR	72 vs 67

A, accelerated fractionation; C, conventional fractionation; CCRT, concurrent chemoradiotherapy; D, docetaxel; DMFS, distant metastasis-free survival; E, epirubicin; F, fluorouracil; LRC, locoregional control rate; M, methotrexate; NR, not reported; O, oxaliplatin; OS, overall survival; P, cisplatin; RT, radiotherapy alone; T, paclitaxel; U, uracil and tegafur; V, vincristine.

[a]Experimental arm versus control arm.

[b]Stage II by Chinese 1992 staging system (equivalent to stages II and III by AJCC seventh edition), 13% of patients were AJCC stage III.

Concurrent Chemoradiotherapy

The landmark Intergroup 0099 trial was the first to document a significant survival benefit for CRT versus RT alone.[229] This trial randomized 147 patients with locally advanced NPC to either RT alone or CRT, at centers located in the United States. Chemotherapy consisted of concurrent cisplatin (CDDP; 100 mg/m^2 on days 1, 22, and 43), followed by three cycles of adjuvant CDDP (80 mg/m^2 on day 1) and 5-FU (1,000 mg/m^2/d on days 1-4) every 4 weeks. RT was delivered in 1.8 to 2 Gy fractions to a total dose of 70 Gy. The trial was closed early because of a significant OS benefit in favor of CRT (78% vs 47% at 3 years). A 5-year update confirmed PFS (58% vs 29%) and OS (67% vs 37%) in favor of CRT. Reactions to these findings were initially tempered by several limitations of the trial. Results achieved in the RT arm were much poorer than those generally obtained at centers treating endemic NPC. Outcomes in the CRT arm were in fact more consistent with outcomes obtained in endemic areas using RT alone. Another concern was that 24% of the enrolled patients had disease of keratinizing histology, and it was unknown whether the same benefit would be seen in endemic areas with predominantly undifferentiated disease.

Subsequent trials confirmed the benefit of concurrent CDDP-based chemotherapy in endemic populations. Wee et al[233] reported the results of 221 stage III to IVB patients from Singapore randomized to receive either RT alone or CRT. Chemotherapy consisted of a slightly modified version of the Intergroup regimen: CDDP (25 mg/m^2 on days 1-4) for three cycles every 3 weeks, followed by adjuvant CDDP (20 mg/m^2 on days 1-4) and 5-FU (1,000 mg/m^2/d on days 1-4) for three cycles. RT was delivered to a dose of 70 Gy in 2-Gy fractions. Three-year OS for the CRT and RT arms was 85% and 65%, respectively (P = .006). CRT reduced the incidence of distant metastasis by 17% at 2 years (P = .003).

Langendijk et al[240] performed a meta-analysis of 10 trials that randomized patients with NPC to conventional RT or CRT. The 10 studies included four neoadjuvant trials,[241-244] three concurrent (± adjuvant) trials,[229,230,245] two adjuvant trials,[246,247] and one neoadjuvant + adjuvant trial.[248] The authors found a pooled HR for death of 0.82, with an absolute survival benefit of 4% at 5 years. Subgroup analysis revealed that the OS benefit was only significant for those patients receiving concurrent chemotherapy, with an HR for death of 0.48 and absolute survival benefit of 20% at 5 years. Analysis of the neoadjuvant chemotherapy trials found a significant reduction in locoregional recurrence and distant metastasis, but no OS benefit.

These results, in combination with results from a second meta-analysis[249] and the Singapore trial, reported by Wee et al,[233] confirmed CRT as the standard approach in stages III, IVA, and IVB NPC. At many centers, the standard course of chemotherapy has been based on the U.S. Intergroup regimen, which consisted of concurrent high-dose CDDP (100 mg/m^2 × 3 cycles) and adjuvant CDDP/5-FU for three cycles. This regimen is associated with significant acute and late toxicities, and patient compliance is frequently difficult to achieve. In the Intergroup 0099 trial, for example, only 63% completed all three cycles of concurrent chemotherapy, and only 55% were able to receive all three courses of adjuvant therapy.[229] As a result, weekly CDDP has been adopted by many institutions, especially for patients with poor nutritional status.[250] In a phase III trial, comparing CRT versus RT alone in 350 patients with locally advanced disease, Chan et al[232] demonstrated good efficacy and tolerability for a regimen consisting of weekly CDDP (40 mg/m^2). Seventy-eight percent of patients in the CRT arm received at least four cycles of CDDP, and CRT was associated with a statistically significant survival benefit after adjusting for age and disease stage. A more recent randomized study by Chen et al[251] confirmed that OS and LRC of weekly CRT were superior to RT alone with weekly CDDP, though it did observe greater acute (63% vs 32%) and late (33% vs 26%) toxicity in the CRT arm. In addition, a retrospective comparative study by Jades et al[252] found similar clinical outcomes and toxicity profiles between concurrent weekly CDDP and the every 3 weeks schedule. Ultimately, whether weekly CDDP is equivalent to the every 3 weeks Intergroup regimen remains to be directly evaluated in a randomized manner.

Other Chemotherapy Agents

Weekly oxaliplatin (70 mg/m^2) has been demonstrated to have good tolerability and efficacy, albeit in the setting of a small phase III trial of 115 patients randomized to CRT or RT alone.[234] Carboplatin has also been employed as a substitute to high-dose CDDP, with comparable efficacy, in a noninferiority trial reported by Chitapanarux et al.[253] Two hundred and six patients were randomized to either concurrent high-dose CDDP and adjuvant CDDP/5-FU or concurrent weekly carboplatin and adjuvant carboplatin/5-FU. The trial had 80% power to detect an HR for death of 1.25 at 3 years. No significant difference in disease-free survival or OS was seen at a median follow-up of 26 months. Disease-free survival was 59.6% and 64.7% (P = .522) for the carboplatin and CDDP arms, respectively.

Cetuximab to target EGFR (EGFR overexpression is observed in >80% of patients with NPC) has been examined in a phase II trial with optimistic findings.[254] The 2-year rates of OS, locoregional PFS, distant metastasis-free survival, and PFS were 89.9%, 93.0%, 82.8%, and 86.5%, respectively. Bevacizumab, to exploit the angiogenesis pathway (VEGF is overexpressed in about two-thirds of NPC patients), has been studied in a phase II trial where the agent was added to the standard CRT schedule and demonstrated promising results.[255] Lee et al[255] reported, with a median follow-up of 2.5 years, a 2-year OS, locoregional PFS, distant metastasis-free survival, and PFS of 90.9%, 83.7%, 90.8%, and 74.7%, respectively.

Adjuvant Chemotherapy

Although good efficacy and tolerability have been shown for select alternative regimens, the greatest body of evidence for concurrent CRT has been with the CDDP-based U.S. Intergroup regimen of concurrent plus adjuvant chemotherapy. Nevertheless, it is unknown whether the adjuvant chemotherapy component of the U.S. Intergroup regimen contributed to its survival benefit. Randomized trials comparing RT alone to RT plus adjuvant

chemotherapy have all been negative to date.[247,248] Moreover, there are data to suggest a survival benefit for concurrent CRT without adjuvant chemotherapy.[230,232] Lastly, compliance with adjuvant chemotherapy can be especially difficult, as patients are recovering from the acute effects of CRT. In 2011, Chen et al[256] reported a randomized trial that compared concurrent CRT to concurrent CRT plus adjuvant chemotherapy (CDDP/5-FU) in 508 patients. With a median follow-up of 38 months, there were fewer failures at any site in the concurrent CRT plus adjuvant chemotherapy group versus the CRT group only (14% vs 16%); however, this difference was not statistically significant (P = .13). It is important to note that this trial was not designed as a noninferiority trial against the standard. In addition, compliance was an issue in this study, where about 18% of patients randomized to the adjuvant arm did not receive adjuvant chemotherapy.[256]

Two recently published studies from Sun Yat-sen University in China have found adjuvant capecitabine to be an efficacious and well-tolerated alternative to CDDP-based regimens.[257,258] The first study included 406 patients with stage III to IVA NPC and reported an improvement in the 3-year failure-free survival (FFS) (85.3% vs 75.7%, P = .0023) with the administration of 1 year of oral metronomic capecitabine following standard CRT. In this study, grade 3 or 4 adverse events were higher (17% vs 6%) in the adjuvant chemotherapy arm.[257] The second study included 180 patients with stage III to IVb NPC and reported that adjuvant capecitabine improved the 5-year FFS (78.5% vs 65.9%, P = .03) compared to CRT alone.[258] The adjuvant chemotherapy compliance rate was 79%.

In light of the above data, adjuvant chemotherapy, using either CDDP-based regimen or capecitabine, should be considered in patients with stage III to IV NPC who did not receive induction chemotherapy. Given concerns regarding the toxicities and tolerability of adjuvant systemic therapy, the final treatment decision should be individualized based on an analysis of the potential benefits versus risks. In this patient population, a biomarker such as post-treatment EBV DNA to help stratify patients for treatment with adjuvant chemotherapy versus observation would be extremely valuable. As discussed earlier, this is currently being investigated in the NRG Oncology HN001 trial, which randomizes patients with undetectable post-CRT EBV DNA to observation versus adjuvant chemotherapy consisting of cisplatin and 5-FU.

Neoadjuvant Chemotherapy

Several recent prospective phase III studies have demonstrated improved survival with neoadjuvant chemotherapy using a variety of systemic regimens.[259,260,261] In a phase III study of 480 patients with locoregionally advanced NPC, the regimen of three cycles of induction cisplatin and gemcitabine was shown to improve 3-year recurrence-free survival (85.3% vs 76.5%, HR 0.51; 95% CI 0.34-0.77) and 3-year OS (94.6% vs 90.3%, HR 0.43; 95% CI, 0.24-0.77) compared to CRT alone.[259] In another multicenter phase III study conducted by Sun Yat-sen University, 480 patients with stage III to IVB NPC were randomized to cisplatin chemoradiation with or without docetaxel, cisplatin, and fluorouracil induction therapy.[260] With a median follow-up of 45 months, patients treated with induction chemotherapy had significantly improved 3-year FFS (80% vs 72%, P = .034), OS (92% vs 86%, P = .029), and distant FFS (90% vs 83%, P = .031). Overall toxicity was higher in the induction arm, with 73% versus 54% of patients in the CRT alone arm experiencing a grade 3 or 4 adverse event (P < .0001). In a third multicenter trial reported by Cao et al,[261] 476 patients were randomized to cisplatin chemoradiation with or without cisplatin and fluorouracil induction therapy. Patients treated with induction chemotherapy had significantly higher 3-year disease-free survival (82.0% vs 74.1%, P = .028) with a strong trend for improved 3-year distant FFS (86.0% vs 82.0%, P = .056); however, there was no difference in OS, and toxicity was significantly increased during concurrent chemoradiation in patients who received induction. Figure 47.20 demonstrates the potential value of induction chemotherapy in tumor control.

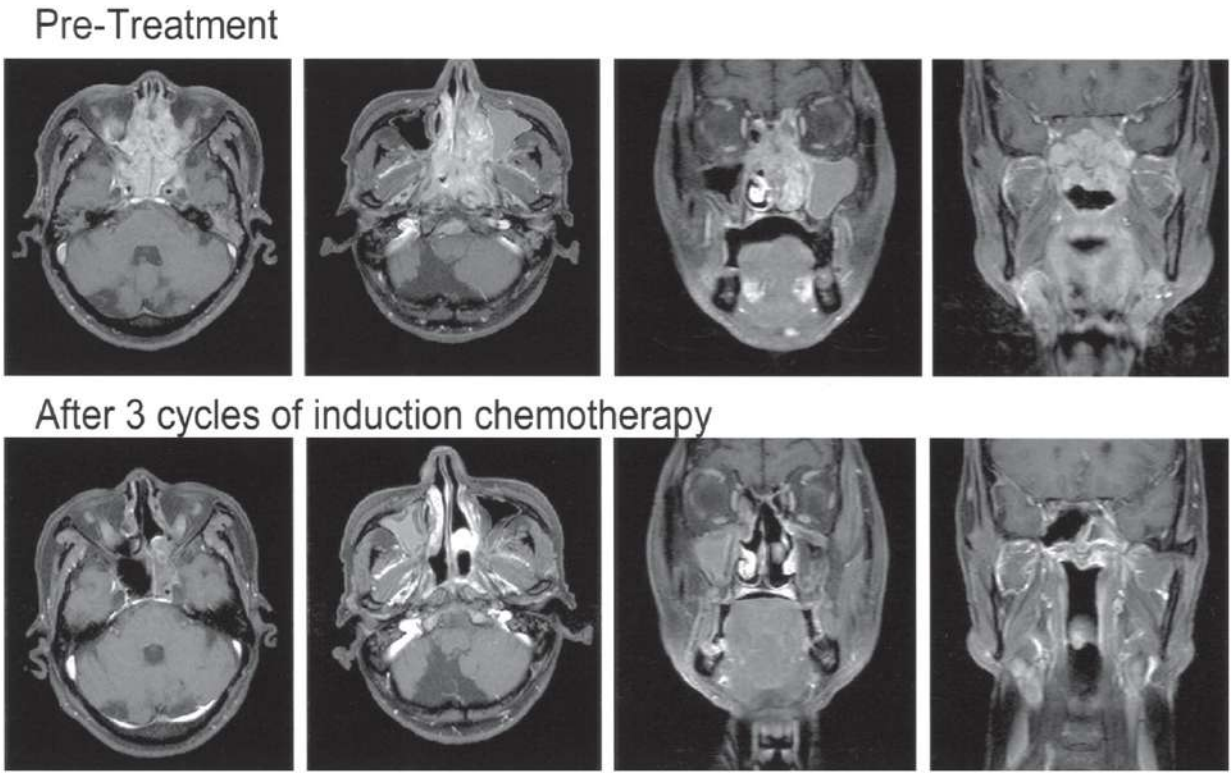

FIGURE 47.20 Magnetic resonance imaging showing shrinkage of primary tumor by induction chemotherapy using cisplatin and 5-fluorouracil before proceeding to concurrent cisplatin and radiotherapy. (Reprinted from Lee AW, Lau KY, Hung WM, et al. Potential improvement of tumor control probability by induction chemotherapy for advanced nasopharyngeal carcinoma. *Radiother Oncol*. 2008;87[2]:204-210. Copyright © 2008 Elsevier Ireland Ltd. With permission.)

The preliminary results of a phase III trial, organized by the Hong Kong Nasopharyngeal Cancer Study Group (NPC-0501), were reported. This study by Lee et al[262] randomized 706 patients to one of three arms: (1) CDDP/5-FU induction chemotherapy plus concurrent CDDP-RT, (2) concurrent CDDP-RT plus adjuvant CDDP/5-FU, or (3) CDDP/capecitabine induction chemotherapy plus concurrent CDDP-RT. In addition, patients in each of these three arms were randomized to either conventional or accelerated RT. Because of the multiarmed design, patient numbers were limited in each of the six arms. Overall, the benefit of induction chemotherapy with respect to OS remains uncertain; however, the capecitabine induction arm demonstrated an improved toxicity profile that may inform future studies.

RECURRENT/METASTATIC NASOPHARYNGEAL CARCINOMA

Because long-term survival can be achieved for a substantial proportion of patients with early locoregional recurrence, aggressive salvage treatment is usually advocated. Several approaches can be used successfully, including surgery, brachytherapy, and EBRT. In the reirradiation setting, a recently reported phase III randomized trial from Sun Yat-sen University reported that 65 Gy in 54 fractions, given BID, yielded better 3-year OS (74.6% vs 55.0%, $P = .014$) and led to lower rates of grade 3 or worse radiation-induced toxicity (34% vs 57%, $P = .023$) compared to standard fractionation (60 Gy in 27 daily fractions).[263]

In the recurrent metastatic setting, combination chemotherapy regimens such as cisplatin and gemcitabine have traditionally been used as first-line therapy. However, the recently published phase III JUPITER-02 trial demonstrated that the addition of toripalimab, a humanized immunoglobulin-G4K monoclonal antibody targeting programmed cell death protein 1, significantly improved median PFS (11.7 vs 8.0 months, $P = .0003$) compared to gemcitabine and cisplatin chemotherapy alone.[264]

For patients with symptomatic metastatic disease, palliation with RT is generally recommended. In addition, in the de novo metastatic setting, You et al[265] demonstrated a 2-year OS benefit (76.4% vs 54.5%, $P = .004$) with the addition of consolidative locoregional RT to patients who have at least a partial response to upfront chemotherapy.

Early Detection and Diagnosis

Although progress in surgical and reconstructive techniques and RT delivery methods has led to improvements in the control rate for primary treatment of NPC, local failure remains a problem for patients with advanced T category. Distinction should be made between persistent disease (tumors that do not completely regress following primary treatment) and recurrent disease (tumors that reemerge after initial complete regression) because the prognoses and therapeutic considerations are different, with better survival and control rates for persistent disease.[266]

As tumors regress at different rates following RT, one difficult decision is when to consider residual tumors as genuine persistence and proceed with salvage treatment. In one prospective study by Kwong et al,[267] serial biopsies of the nasopharynx were performed on 803 patients after RT treatment to observe the time course of histologic remission for NPC and determine its prognostic significance. The 5-year L-FFR was 82% for patients who achieved early histologic remission (<5 weeks) and 77% for those with delayed remission (5-<12 weeks), but only 40% for those with persistent disease at 12 weeks, despite subsequent salvage treatment.[267] Thus, although delayed histologic remission was not a poor prognostic factor, positive biopsies beyond 12 weeks did indicate poor prognosis. The optimal time for intervention remains uncertain, but because it is important to avoid both unnecessary overtreatment and excessive delay in treatment, the authors recommended an observation period of 10 weeks before additional treatment.[267]

Early detection of locoregional failure is crucial for a better chance of salvage, and regular follow-up after completion of primary treatment is recommended. Frequently used methods include manual palpation, rigid nasopharyngeal endoscopy and nasopharyngeal biopsies, imaging techniques (eg, CT and MRI), and serologic tests (eg, anti-EBV titers, plasma EBV DNA levels).

Nasopharyngoscopy is more sensitive than CT and MRI in detecting tumor persistence/recurrence and is the preferred method for initial screening.[268,269] If a patient presents with suspicious endoscopic findings or elevated anti-EBV titers, a nasopharyngeal biopsy is performed to confirm the diagnosis. CT or MRI is performed upon a confirmed diagnosis to delineate the tumor extent.[270] Although MRI has limitations in separating tumor recurrence from radiation fibrosis,[271] it is superior to CT in demonstrating the extent of soft tissue tumors, as well as identifying submucosal infiltration, marrow infiltration in the skull base, perineural invasion, and intracranial spread.[268,272,273]

Technetium-99m methoxyisobutylisonitrile single-photon emission computed tomography may be a useful tool for differentiating persistent or recurrent tumor from radiation fibrosis[274] and was shown by Kostakoglu et al[275] to be superior to MRI performed at 3 to 6 months post-RT in diagnosing complete response. The advent of FDG-PET is another valuable development. FDG-PET and MRI were compared in 67 patients with NPC 4 to 70 months after completion of RT and found FDG-PET superior to MRI in all aspects in the detection of local recurrence, with increased sensitivity (100% vs 62%) and specificity (93% vs 44%).[276] It may also contribute useful information to questionable findings on MRI.[277,278]

Paraneoplastic syndrome (PNS) can signal a silent neoplasm and may precede the clinical manifestation itself of persistent or recurrent NPC. PNS can follow the course of the tumor and can sometimes be used to diagnose recurrence and monitor its evolution, with the most common dermatologic manifestation being dermatomyositis and the syndrome of inappropriate antidiuretic hormone secretion being a common endocrinologic presentation.[279]

Circulating cell-free DNA of EBV may be another useful tool for early detection of treatment failure. A longitudinal study by Lo et al[121] showed that elevation of EBV DNA levels was noted in patients with relapse up to 6 months before detectable clinical disease. In addition, EBV DNA copy number has been shown to predict margin status postsalvage nasopharyngectomy. Wei et al[280] reported that in patients with early recurrent NPC with elevated EBV DNA copies, surgical resection reduced the copy number of EBV DNA postoperatively and that negative surgical margins are associated with zero EBV DNA copies postoperatively.

The incorporation of plasma EBV DNA measurements as screening prior to PET in detecting post-treatment failures of NPC has been investigated. In a prospective study by Wang et al,[129] 245 patients with NPC in remission were monitored prospectively via plasma EBV DNA assay every 3 to 6 months, where 36 patients with abnormal EBV DNA tests and 5 patients with clinical suggestion signs of recurrence, but undetectable EBV DNA levels, underwent FDG-PET scans. Elevated EBV DNA levels correctly predicted all 36 recurrences, whereas the 5 patients who presented with clinical signs suggestive of recurrent disease but with undetectable EBV DNA levels did not have recurrent disease. The authors concluded that plasma EBV DNA appears to be a useful biomarker for post-treatment surveillance in NPC.

Meanwhile, the clearance rate of plasma EBV DNA during the first month of chemotherapy has also been found to predict tumor response and patient survival in 30 patients with recurrent NPC and may have the potential as an early prognostic marker to help guide salvage treatment.[127]

Additional Radiation for Persistent Disease

Excellent results have been reported when using brachytherapy for locally persistent disease after a full course of EBRT (Table 47.15, part A), with 5-year L-FFR in the range of 87% to 95% for patients with initial T1 tumors (AJCC 2002 T1-2a).[209,266,281-283] Preliminary evidence suggests that patients with disease persisting from initial T2 tumors (AJCC 2002 T2b) could also be effectively treated by brachytherapy.[284]

TABLE 47.15 RESULTS OF LOCALLY PERSISTENT/RECURRENT NASOPHARYNGEAL CARCINOMA TREATED WITH BRACHYTHERAPY

			Brachytherapy			Local Control	
Author	T Category	Modality	Dose (Gy)	Fraction	Day	Time (y)	Rate (%)
Part A. Local persistence							
Kwong et al[266]	T1	Interstitial gold grain	60			5	87
Law et al[281]	T1-2a	Iridium mold	40			5	90
Leung et al[282]	T1-2	HDR-ICB	22.5-24	3	15	5	95
Leung et al[284]	T2b	HDR-ICB	22.5-24	3	15	5	97
Zheng et al[283]	T1	HDR-ICB	15-30	5-6	15-18	5	100
	T2	HDR-ICB	15-30	5-6	15-18		90
Part B. Local recurrence							
Kwong et al[266]	rT1	Interstitial gold grain	60			5	63
Law et al[281]	rT1-2a	Iridium mold	50-55[a]			5	89
Leung et al[285]	rT1-2	EBRT + HDR-ICB	50 + 14.8[a]	3	15	3	72

EBRT, external beam radiotherapy; HDR-ICB, high-dose rate intracavitary brachytherapy.

[a]Median dose.

SRT is a valuable alternative for delivering additional EBRT. Yau et al[286] studied 755 patients with T1-4 tumors and found that 7% had positive biopsies 8 weeks after completion of primary RT. Twenty-one patients were treated with fractionated SRT to a median dose of 15 Gy and achieved a 3-year L-FFR of 82%, which was similar to the corresponding L-FFR of 86% in the complete responders and was significantly better than the corresponding L-FFR of 71% in 24 patients treated with HDR brachytherapy to a median dose of 20 Gy.

Reirradiation for Recurrent Disease

Various RT modalities are used to treat recurrent NPC, including intracavitary brachytherapy, external beam irradiation, interstitial implantation, particle beam RT, and stereotactic radiosurgery (Table 47.16).[197,202,203,205,206,287] IMRT has also been used with excellent preliminary results, with control rates of up to 100% for rT1-3.[288]

TABLE 47.16 RESULTS ON REIRRADIATION FOR LOCAL RECURRENCE OF NASOPHARYNGEAL CARCINOMA

Author	Year	*N*	Reirradiation Technique	Time (y)	Treatment Outcome (Actuarial Rate)		Major Late Toxicity (Cumulative Incidence)	
					Local Control (%)	Survival (%)	Overall (%)	Brain Necrosis (%)
Fu et al[289]	1975	39	All 2D	5	26	41	23	NR
Yan et al[290]	1983	219[a]	All 2D	5	18	>29	>12	
Wang[197]	1987	51	All 2D	5	NR	33	6	2

Author	Year	*N*	Reirradiation Technique	Time (y)	Treatment Outcome (Actuarial Rate)		Major Late Toxicity (Cumulative Incidence)	
					Local Control (%)	Survival (%)	Overall (%)	Brain Necrosis (%)
Pryzant et al[203]	1992	53	All 2D	5	35	18	NR	NR
Lee et al[291]	1997	654	All 2D	5	rT1: 35 rT2: 28 rT3-4: 11	16	26	3
Teo et al[292]	1998	123	All 2D	5	5	rT1: 43 rT2: 31 rT3-4: 16	rT1: 63 rT2: 48 rT3-4: 31	NR
Chua et al[293]	1998	97	All 2D	5	NR	rT1-2: 57 rT3: 42 rT4: 17	NR	16
Leung et al[285]	2000	91	All 2D	5	38	30	57	27
Chang et al[294]	2000	186	81% 2D, 19% 3D	3	NR	rT1: 39 rT2: 24 rT3: 28 rT4: 4	2D: 23 3D: 9	2D: 14 3D: 0
Zheng et al[295]	2005	86	All 3D	5	rT1: 92 rT2: 81 rT3: 68 rT4: 41	rT1: 70 rT2: 52 rT3: 32 rT4: 10	49	16
Lu et al[296]	2004	49	IMRT	3/4	100	NR	NR	NR
Chua et al[288]	2005	31	IMRT	1	rT1-3: 10% rT4: 35	63	19	7
Koutcher et al[297]	2010	29	83% IMRT, 4% 2D, 13% 3D	5	52	60	31	17
Ozyigit et al[298]	2011	51	47% SBRT, 53% 3D	2	rT1-2: 75 rT3-4: 54	rT1-2: 85 rT3-4: 46	3D: 48 SBRT: 21	3D: 19 SBRT: 4
Qiu et al[299]	2011	70	IMRT	2	66	67	36	NR
You et al	2023	144	IMRT	3	Hyperfractionation: 51 Standard fractionation: 54	Hyperfractionation: 75 Standard fractionation: 55	Hyperfractionation Grade 3 or higher: 34 Standard fractionation Grade 3 or higher: 57	Hyperfractionation Grade 3 or higher: 10 Standard fractionation Grade 3 or higher: 26

2D, conventional two-dimensional external radiotherapy and/or brachytherapy; 3D, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiation therapy; SBRT, stereotactic body radiation therapy.

[a]Patients with regional relapse included.

The most important prognostic factors are the TNM stage of the tumor at the time of recurrence and reirradiation dose. Thorough restaging, including metastatic workup, is necessary. A study of 891 patients with local recurrence from 1976 to 1985 by Lee et al[300] showed that only 32% of reirradiated patients achieved local salvage, with 54% developing regional and/or distant failure. Most series using conventional 2D technique showed that doses ≥60 Gy were associated with better outcome.[197,203,291,292] For IMRT, 60 to 70 Gy is recommended, taking into account factors such as previous radiation amount, overlap between previously treated area and target for reirradiation, interval between RT courses, tumor bulk, and whether concurrent chemotherapy will be given.[301]

Lee et al[302] retrospectively compared the symptomatic late toxicity rate in 487 patients with two courses of EBRT versus 3,635 patients with one course and found that the major determinant of late complications was the severity of damage during the initial course and that the sum of total biologic dose tolerated (BED-∑) was higher than expected with a single-course treatment (BED-1). This suggested partial recovery of normal tissue (especially in patients reirradiated after 2 years or more) and higher tolerance for reirradiation when primary treatment was

given with better sparing of normal tissues. Assuming an α/β ratio of 3 Gy, the BED-$\sum$ that incurred 20% toxicity at 5 years was 129% that of BED-1.

Brachytherapy has been widely used for the treatment of recurrent NPC (Table 47.15, part B) and can be used effectively on its own for early-stage recurrent NPC.[266,281] Using interstitial implants with radioactive gold grains, Kwong et al[266] reported a 5-year L-FFR of 63%; complications included headache (28%), palatal fistula (19%), and mucosal necrosis (16%). Law et al[281] achieved excellent local salvage up to 89% using iridium mold, but the complication rate was 53%.

The combination of brachytherapy and EBRT is useful, particularly when conventional 2D technique is used. Lee et al[291] showed that patients reirradiated by combined modalities had an improved 5-year L-FFR of 45% compared with 32% by EBRT alone and 29% by brachytherapy alone. The superiority of the combined method has been supported by other studies.[197,203,285,289] A study from MSKCC associated combined modality treatment (CMT), consisting of EBRT followed by brachytherapy, achieved similar L-FFR with previous historical series. CMT also demonstrated fewer late grade 3 or higher events compared with patients receiving EBRT alone (8% vs 73%).[297]

Stereotactic radiosurgery or fractionated SRT is another useful tool for retreatment of local recurrence, as it allows for rapid falloff of radiation dose outside tumor volume and near surrounding critical structures and can be used either alone for smaller lesions or in combination with EBRT for larger ones. Control rates ranging from 53% to 86% have been reported.[303-306] For advanced recurrence with extension beyond the nasopharynx, this method offers better dose coverage than brachytherapy. A higher salvage rate from adding stereotactic radiation as a boost after EBRT has been reported.[294,304,307] Although most series reported a low risk of complications, massive hemorrhage with potential fatal outcome has been described.[304] Radiosurgery should thus be avoided when there is direct tumor encasement of the carotid artery or when a high cumulative dose has already been delivered. Fractionated SRT has shown improved late toxicity profile compared to 3D conformal RT[298] and single-dose radiosurgery[308] and may also give better local control rates compared with single-fraction radiosurgery.[309]

Advances in imaging technology and RT techniques have made it possible to reduce target volume without jeopardizing local control, reducing complication rates. Table 47.17 summarizes the treatment outcome and severe late complications by external beam reirradiation. Past series using 2D technique achieved 5-year survival rates in the range of 16% to 63%, and the incidence of TLN ranged from 2% to 27%. The use of 3D conformal RT showed improving results. In one study by Chang et al,[294] none of the patients reirradiated by 3D technique developed TLN compared with 14% of those reirradiated by 2D technique. Zheng et al[295] reported a 5-year local salvage rate of 71% from 3D technique, but the actuarial rate of late toxicities (grade 4) was still as high as 49%.

TABLE 47.17 INCIDENCE OF LATE TOXICITY FOLLOWING RADIATION WITH CONVENTIONAL TECHNIQUE (WITHOUT CONCURRENT CHEMOTHERAPY) FOR NASOPHARYNGEAL CARCINOMA

Severe Late Complication	Sanguineti et al[29] (*N* = 378)	Chao and Perez[45] (*N* = 164)	Lee et al[40] (*N* = 4,527)	Yeh et al[310] (*N* = 849)	Leung et al[311] (*N* = 880)[a]
Period	1954-1992	1956-1991	1976-1985	1983-1998	1990-1998
Radiotherapy					
Total dose (Gy)	61-70	56-69	65[b]	68-76	62.5-66[b]
Dose per fraction (Gy)	NR	1.8-2	2.5-4.2	1.8	2-2.5
Altered fractionation (%)	8	Nil	Nil	Nil	Nil
Sequential chemotherapy (%)	Nil	Nil	8	Nil	20
Overall incidence (%)					
Grading of toxicity	≥3	≥3	≥2	≥1	?
Crude rate	30.4	14	30.8	NR	16.5
Actuarial rate	19 (10 y)	NR	60 (10 y)	NR	14 (5 y)
Treatment mortality (%)	3.2	3	1.4	NR	0.9
Types of complications (%)					
Temporal lobe necrosis	1.1	1.2	3	6[c]	1.1
Brainstem encephalopathy/myelopathy	2.4		1		
Cranial neuropathy	4.5		5.3	3.3	6.8

Severe Late Complication	Sanguineti et al[29] (*N* = 378)	Chao and Perez[45] (*N* = 164)	Lee et al[40] (*N* = 4,527)	Yeh et al[310] (*N* = 849)	Leung et al[311] (*N* = 880)[a]
Endocrine dysfunction	7.9		3.5		8.6
Severe epistaxis		1.2	0.6		0.3
Carotid rupture		0.6			
Hearing loss	2.6		8.2	54[c]	
Persistent otitis			2.5	32[c]	
Trismus	2.9	0.6	5.1	12[c]	0.7
Bone damage[d]	2.6	2.4	0.4		
Eyeball damage[e]			0.2		
Soft tissue necrosis/fistula	1.1	1.8	0.4		0.5
Pharynx stricture/dysphagia		4.2		6[c]	
Soft tissue fibrosis	4.2		15.9	25[c]	1.4
Persistent lymphedema	0.5	0.6	0.1		
Radiation-induced malignancy			<0.1		

NR, not reported.

[a]Patients with one course of radiotherapy.

[b]Median dose equivalent to 2 Gy/fraction.

[c]Five-year actuarial rate.

[d]Bone necrosis, fracture, or osteomyelitis.

[e]Cataract, retinitis, corneal ulcer.

The use of IMRT for reirradiation has shown very encouraging short-term results. Using IMRT to deliver 68 to 70 Gy, Lu et al[296] reported 100% salvage rate without any severe late complications in a series of 49 patients with a median follow-up of 9 months. Using IMRT to a median dose of 54 Gy in 31 patients (with or without induction chemotherapy and stereotactic boost), Chua et al[288] reported a 1-year control rate of 100% for rT1-T3 and 35% for rT4, with late complications (> grade 3) of 25% (at 1 year). Using a median dose of 70 Gy in 70 patients, Qiu et al[299] reported a locoregional salvage rate of 66% with a similar toxicity rate at 2 years. Although rT staging did not predict the control rate, original T classification remained a significant adverse prognostic factor and may serve as a strong marker for the underlying locally aggressive biology of the original disease. Longer follow-up is needed to better evaluate treatment results and sequelae resulting from IMRT.

As another alternative, proton beam therapy (PBT) allows for the delivery of RT dose distributions that are typically more conformal than can be achieved with IMRT. This is due to the physical properties of the proton beam that result in maximal dose delivery at a narrow specified depth in the tissue, a phenomenon known as the Bragg peak. Because of the increased precision, PBT is especially useful in the setting of reirradiation, where it is critically important to minimize overlap of radiation fields from multiple treatments, particularly for the dose to surrounding sensitive organs, such as the cranial nerves and brain. An analysis of DVHs from patients who underwent reirradiation with PBT for recurrent NPC found that patients with optimal dose coverage of target volumes experienced significantly improved outcomes (OS of 83% for optimal coverage, 17% for suboptimal coverage), highlighting the importance of high-quality RT for producing good outcomes in the recurrent setting.[312]

A multi-institutional study that included 92 patients who underwent reirradiation with PBT for multiple types of recurrent HNC found a favorable toxicity profile compared to historical controls of patients retreated with photon techniques.[313] This included a low risk of grade 3+ dermatitis (8.7%) and dysphagia (7.1%). Furthermore, locoregional failure was found to be only 25% at 1 year. However, two deaths occurred as a result of bleeding events, reflecting the increased risk of serious vascular toxicity with a second course of RT. In all cases, the risks of toxicities associated with retreatment must be weighed against the risk of uncontrolled tumor progression that is usually associated with significant morbidity and impairment in quality of life.

CRT may also improve treatment outcome for recurrent NPC in certain patients, and most recent salvage radiation series have included cisplatin-based chemotherapy for advanced-stage disease.[288,297,299,314] Using gemcitabine and cisplatin as induction chemotherapy followed by reirradiation with IMRT in 20 patients (95%

rT3-4), Chua et al[288] reported a 1-year local salvage rate of 75%. In a study of 35 patients (66% rT3-4), Poon et al[314] reported a 1-year EFS of 42% by CDDP followed by adjuvant chemotherapy with cisplatin and 5-FU. However, although concomitant chemoirradiation is increasingly used to treat primary NPC, it remains uncertain whether concomitant chemoirradiation is appropriate for retreatment of purely local recurrences (rT1-2), because of high rates of toxicity and potential complications.

Surgical Treatment

For patients with persistent nodal disease, radical neck dissection is the preferred treatment for persistent or recurrent lymph node involvement in the neck when there is no distant metastasis[315] and may achieve a 5-year nodal control rate of 66% and disease-free survival rate of 37%.[316] In cases with extension of disease beyond lymph nodes into nearby structures, additional afterloading brachytherapy to tumor bed may improve local control.[317]

Surgical management at the primary site is hampered by difficulties in obtaining adequate exposure and obtaining adequate surgical margins.[147,318-320] Various approaches have been employed, including an infratemporal approach from the lateral aspect[321]; transpalatal, transmaxillary, and transcervical approaches from the inferior aspect[320,322]; and an anterior-lateral approach.[323] More recently, minimally invasive techniques, such as a transnasal approach and an endoscopic approach, have also been employed successfully.[324] Although controversial, salvage surgery by nasopharyngectomy can be a viable option in certain patients in which the disease is localized in the nasopharynx, with acceptable results reported for rT1-3 tumors.[274] Wei et al[325] reported a 5-year control rate of 62% and 5-year disease-free survival rate of 49% in 60 patients who received curative resections. Typically, all patients with recurrence have undergone prior radical RT, thereby associated complications of trismus and palatal fistula being common; however, the mortalities associated with these surgical procedures are low.

Recurrent NPC is frequently located in the pharyngeal recess on the lateral wall. Access to this region is crucial for complete tumor extirpation. Wei and Sham[326] advocated the anterior-lateral approach or maxillary swing approach for localized recurrence in the nasopharynx. After facial incisions and the necessary osteotomies, the maxilla bone is swung laterally while remaining attached to the anterior cheek flap as one osteocutaneous entity (Figures 47.21 and 47.22). The nasopharynx with the tumor and its surrounding area including the paranasopharyngeal region are then widely exposed for resection. Upon completion of nasopharyngectomy, the maxilla is replaced and attached to the remainder of the facial skeleton with miniplates.

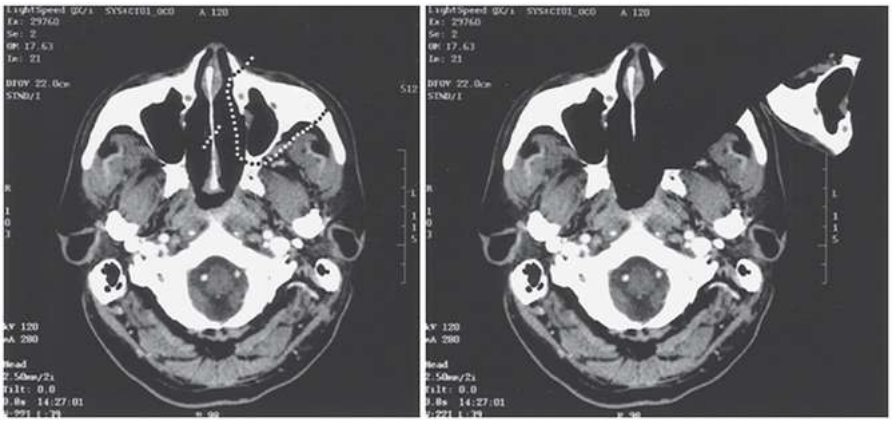

FIGURE 47.21 A. Computed tomography shows planned osteotomies of the maxilla and the posterior part of the nasal septum (broken line). B. The maxilla is swung laterally while still attached to the anterior cheek flap.

FIGURE 47.22 The left maxilla is swung laterally, exposing the nasopharynx (arrow).

Wei et al[323] reported 161 patients with salvage nasopharyngectomy employing this approach performed at Queen Mary Hospital (Hong Kong) for recurrent NPC following primary treatment by radical RT. Twelve patients had prior brachytherapy as a salvage procedure. All patients were recurrent stage T1, with 78% of these patients achieving negative tumor resection margins, confirmed by frozen section, with the remaining patients demonstrating microscopic tumor at the internal carotid artery or the skull base during surgery, making further complete resection unattainable. All patients recovered from this anterior-lateral approach and were discharged. Regarding treatment-associated morbidities, trismus of varying grades was present in 60% and palatal fistula in 25% of patients. Recent modification of the palatal incision has eliminated the problem of palatal fistula.[327]

Satisfactory long-term results can be achieved when persistent/recurrent tumor is completely resected. Several recent surgical series reported LRC and OS rates of 40% to 72% and 30% to 54%, respectively.[324,328-330] Postoperative reirradiation is recommended for patients with positive surgical margins and/or advanced disease[325,331,332] and may be beneficial even when surgical margins are negative.[274]

For recurrent tumors, margin status, adjuvant treatment type, and parapharyngeal space involvement were significant prognostic factors for local control, whereas dura or brain involvement, local recurrence, and adjuvant treatment type predicted survival.[324] Preoperative EBV DNA levels and PET-CT can assist in predicting the

outcome of salvage nasopharyngectomy, and PET-CT may predict the presence of extracapsular spread of metastatic lymph nodes.[333]

RESULTS OF TREATMENT

Specific results of various treatments are mentioned in the previous respective sections. This section focuses on summarizing these results.

The local and regional control rates in select conventional RT series are listed in Tables 47.18 and 47.19. Control of the primary lesion using conventional RT varied with the T classification (Table 47.18), ranging from 64% to 97% for T1 lesions, 54% to 94% for T2 lesions, 34% to 100% for T3 lesions, and 40% to 71% for T4 lesions.[28,32,33,149,150,334,335] Dose escalation with intracavitary brachytherapy if using non-IMRT treatment techniques[198] has been shown to improve local control. Stereotactic radiosurgery boost after EBRT (both conventional and IMRT) has also shown improved local control.[336,337] Nonkeratinizing squamous cell carcinoma (both differentiated and undifferentiated subtypes) had improved local control rates when compared to keratinizing squamous cell carcinoma in T2 to T3 lesions, but not in T1 or T4 lesions.[28,229,240]

TABLE 47.18 LOCAL TUMOR CONTROL AFTER CONVENTIONAL RADIATION THERAPY

Author	Year	5-Y Local Control Rate by T Stage[a] (%)			
		T1	T2	T3	T4
Hoppe[33]	1976	87	94	68	44
Mesic[150]	1981	97	84	73	71
Chu[32]	1984	76	79	37	55
Vikram[149]	1985		74	100[b]	63
Wang[334]	1990	76	54	34	42
		67[c]	84[c]	78[c]	52[c]
Perez[28]	1992	85[d]	75[d]	67[d]	40[d]
Bailet[335]	1992	64		61	

T, primary tumor stage.

[a]By 1992 AJCC T stage.

[b]With only three patients in this group.

[c]Treated by twice-daily accelerated fractionation.

[d]10-Year actuarial rate.

TABLE 47.19 NODAL CONTROL AFTER CONVENTIONAL RADIATION THERAPY

Author	Year	5-Y Nodal Control Rate by N Stage[a] (%)			
		N0	N1	N2	N3
Hoppe[33]	1976	96	92	87	89
Mesic[150]	1981	100	90	88	82
Perez[28]	1992	82[b]	86[b]	78[b]	

N, regional lymph node stage.

[a]By 1992 AJCC N stage.

[b]10-Year actuarial rate.

Excellent nodal control rates in the neck have been demonstrated by conventional RT even after involvement of extensive cervical lymph node metastasis (Table 47.19). The neck nodal control rates ranged from 82% to 100% for N0, 86% to 92% for N1, and 78% to 89% for N2 to N3 disease.[28,33,150] Five-year survival rates ranged from 36% to 58% (Table 47.20).[28,32,33,150,334,335,338]

TABLE 47.20 OVERALL SURVIVAL AFTER CONVENTIONAL RADIATION THERAPY

Author	Year	Patients (*n*)	5-Y Survival Rate (%)	Analysis
Hoppe[33]	1976	82	57	Actuarial
Mesic[150]	1981	251	52	Actuarial disease free
Chu[32]	1984	80	36	Actuarial
Vikram[149]	1985	107	56	Actuarial[a]
Wang[334]	1990	185	43	Absolute
Bailet[335]	1992	103	58	Actuarial

OS, overall survival.

[a]Estimated from survival curve.

The 5-year survival rate with conventional non-IMRT radiotherapy correlated with the T stage, as well as with the N stage (Table 47.21), being 60% to 76% for T1, 48% to 68% for T2, 27% to 55% for T3, and 0% to 29% for T4 lesions[33,334] and 42% to 78% for N0, 27% to 70% for N1, and 32% to 52% for N2 to N3 disease. When nodes in the lower neck and/or the supraclavicular fossa are involved, prognosis is poor.

TABLE 47.21 OVERALL SURVIVAL BY T AND N STAGE[A] AFTER CONVENTIONAL RADIATION THERAPY

		5-Y Local Control Rate by T Stage[a] (%)				5-Y Survival Rate by N Stage[a] (%)			
Author	Year	T1	T2	T3	T4	N0	N1	N2	N3
Hoppe[33]	1976	76[b]	68[b]	55[b]	0[b]	78[b]	70[b]	42[b]	39[b]
Chu[32]	1984					42[c]	27[c]	52[c]	27[c]
Wang[334]	1990	60[d]	48[d]	27[d]	29[d]	60[d]	42[d]		32[d]

N, regional lymph node stage; T, primary tumor stage.

[a]By 1992 AJCC T and N stage.

[b]Actuarial disease-free survival.

[c]Actuarial survival.

[d]Absolute survival.

Contemporary series with IMRT demonstrated excellent local and regional control was achieved in 97% and 98% of the patients treated at UCSF, respectively.[171] An update of the UCSF experience continued to show excellent local control of approximately 96%.[182] Subsequently, several other institutions also recently published their results, which further demonstrate excellent local control rates ranging from 82% to 100% and regional control rates ranging from 91% to 98% (Table 47.22).[154,174-176,184,186-188,254,255,339-347]

TABLE 47.22 RESULTS FROM CONTEMPORARY IMRT SERIES WITH OR WITHOUT CHEMOTHERAPY

Study	Year	Stage	N	Median Follow-Up (months)	Timepoint (years)	Local Control Rate (%)	Regional Control Rate (%)	Distant Metastasis-Free Rate (%)	OS (%)
Lee et al[171] (UCSF)	2002	All	67	31	4	97	98	66	88
Kwong et al[175] (Hong Kong)	2004	T1 N0-1[a]	33	24	3	100	92	100	100
Kam[176] (Hong Kong)	2004	All	63	29	3	92	98	79	90
Wolden et al[174] (MSKCC)	2006	All	74	35	3	91	93	78	83
Kwong et al[184] (Hong Kong)	2006	III-IVB[a]	50	25	2	96	NA	94	92
Lee et al[339] (MSKCC)	2009	All	68	31	2	93	91	85	80

Study	Year	Stage	N	Median Follow-Up (months)	Timepoint (years)	Local Control Rate (%)	Regional Control Rate (%)	Distant Metastasis-Free Rate (%)	OS (%)
Tham et al[186] (Singapore)	2009	All	195	37	3	90	NA	89	94
Lin et al[340] (China)	2009	II-IV[a]	323	30	3	95	98	90	90
Wong et al[348] (China)	2010	All	175	34	3	94	93	87	87
Lin et al[341] (China)	2010	IIB-IVB[a]	370	31	3	95	97	86	89
Kam et al[342] (Hong Kong)	2010	All	231	59	6	82	91	75	66
Ng et al[187] (Hong Kong)	2011	All	193	30	2	95	96	90	92
Xiao et al[343] (China)	2011	III-IVA[a]	81	54	5	95	NA	NA	75
Bakst et al[154] (MSKCC)	2011	II-IVB[a]	25	33	3	91	91	91	89
Xiayun et al[344] (China)	2011	IIB-IVB[b]	54	30	3	95	98	86	88
Ma et al[254] (Hong Kong)	2011	III-IVB[b]	30	32	2	93	93	93	90
Lee et al[255] (MSKCC)	2011	IIB-IVB[c]	42	30	2	NA	NA	91	91
Su et al[345] (China)	2012	I-IIB[b]	198	51	5	97	98	98	NA
Sun et al[346] (China)	2014	I-IVB[b]	868	50	5	92	96	85	NA
Setton et al[188] (MSKCC)	2016	I-IVB[c]	177	52	5	83	91	83	74
Wu et al[347] (China)	2017	I-IVB[c]	614	113	10	89	96	80	73

IMRT, intensity-modulated radiation therapy; M, distant metastasis stage; MSKCC, Memorial Sloan Kettering Cancer Center; N, regional lymph node stage; NA, not available; NPC, nasopharyngeal carcinoma; T, primary tumor stage; UCSF, University of California, San Francisco.

[a]By 1997 AJCC stage.

[b]By 2002 AJCC stage.

[c]By 2010 AJCC stage.

The RTOG conducted a phase II trial using IMRT+/− chemotherapy in the treatment of NPC where patients with ≥T2 (ie, ≥T2b by AJCC 2002) and/or node-positive disease also received concurrent CDDP followed by adjuvant CDDP and 5-FU chemotherapies. The results showed that a multi-institutional setting can reproduce the excellent results (local control rate of 92.3%) observed from single-institution studies.[339] This reproducibility of excellent LRC rates in a multi-institutional trial, along with several single-institution studies, with IMRT is encouraging; however, distant metastases remain a therapeutic challenge despite extensive use of chemotherapy. The distant recurrence rate ranges from 10% to 15% at 2 years[187,339] and 4-year rates are as high as 34% (Table 47.22).[171] Novel systemic therapies or regimens are needed for improved distant control and OS of this disease.

SEQUELAE OF TREATMENT

Overall Incidence and Types

Because of the anatomic proximity of the nasopharynx to critical structures, and the need for high radiation doses and adequate field coverage, the risks of radiation-induced toxicities are substantial. The overall complication rate from conventional treatment ranged from 31% to 66%, with severe sequelae including TLN, hearing loss, xerostomia, neck fibrosis, cranial nerve dysfunction, endocrine dysfunction, soft tissue necrosis, osteonecrosis, and

transverse radiation myelitis.[29,33,40] The diagnosis of irradiation injury can be difficult, as other possible causes (tumor recurrence in particular) must be excluded.

The toxicity results of five major series using conventional irradiation for NPC are summarized in Table 47.23.

TABLE 47.23 INCIDENCE OF LATE TOXICITY FOLLOWING RADIATION WITH CONVENTIONAL TECHNIQUE (WITHOUT CONCURRENT CHEMOTHERAPY) FOR NASOPHARYNGEAL CARCINOMA

Severe Late Complication	Sanguineti et al[29] (*N* = 378)	Chao and Perez[45] (*N* = 164)	Lee et al[40] (*N* = 4,527)	Yeh et al[310] (*N* = 849)	Leung et al[311] (*N* = 880)[a]
Period	1954-1992	1956-1991	1976-1985	1983-1998	1990-1998
Radiotherapy					
Total dose (Gy)	61-70	56-69	65[b]	68-76	62.5-66[b]
Dose per fraction (Gy)	NR	1.8-2	2.5-4.2	1.8	2-2.5
Altered fractionation (%)	8	Nil	Nil	Nil	Nil
Sequential chemotherapy (%)	Nil	Nil	8	Nil	20
Overall incidence (%)					
Grading of toxicity	≥3	≥3	≥2	≥1	?
Crude rate	30.4	14	30.8	NR	16.5
Actuarial rate	19 (10 y)	NR	60 (10 y)	NR	14 (5 y)
Treatment mortality (%)	3.2	3	1.4	NR	0.9
Types of complications (%)					
Temporal lobe necrosis	1.1	1.2	3	6[c]	1.1
Brainstem encephalopathy/myelopathy	2.4		1		
Cranial neuropathy	4.5		5.3	3.3	6.8
Endocrine dysfunction	7.9		3.5		8.6
Severe epistaxis		1.2	0.6		0.3
Carotid rupture		0.6			
Hearing loss	2.6		8.2	54[c]	
Persistent otitis			2.5	32[c]	
Trismus	2.9	0.6	5.1	12[c]	0.7
Bone damage[d]	2.6	2.4	0.4		
Eyeball damage[e]			0.2		
Soft tissue necrosis/fistula	1.1	1.8	0.4		0.5
Pharynx stricture/dysphagia		4.2		6[c]	
Soft tissue fibrosis	4.2		15.9	25[c]	1.4
Persistent lymphedema	0.5	0.6	0.1		
Radiation-induced malignancy			<0.1		

NR, not reported.

[a]Patients with one course of radiotherapy.

[b]Median dose equivalent to 2 Gy/fraction.

[c]Five-year actuarial rate.

[d]Bone necrosis, fracture, or osteomyelitis.

[e]Cataract, retinitis, corneal ulcer.

The series of 378 patients treated at MDACC during 1954 to 1992 showed an actuarial frequency rate in grade ≥4 toxicity of 16%, 19%, and 29% at 5, 10, and 20 years, respectively.[29] Despite the use of higher radiation doses, Sanguineti et al[29] showed a reduction in the 10-year actuarial rate of severe toxicity from 14% in 1954 to 1971 to 5% in 1983 to 1992. Other investigators have reported similar findings.

The decreased rates of complications over time were likely due to the use of newer oblique and opposed lateral field techniques instead of single central field, custom blocking, and image-guided (CT) treatment planning.[29]

Because of the extremely narrow therapeutic treatment margin of NPC, maximum conformity and precision in RT delivery are crucial for minimizing the risk of late damage. The emergence of IMRT is a major advance for improving physical dose distribution and has increased the potential for protecting normal tissues. Studies on patients treated with IMRT thus far have shown substantial sparing of salivary function,[171,175,176] whereas other benefits will require longer follow-up to confirm.

The improved conformity offered by IMRT has led to attempts at dose escalation in order to achieve better tumor coverage for patients with extensive locoregional infiltration. However, studies have shown that dose escalation together with concurrent chemotherapy may lead to severe toxicities.[184,349] Furthermore, extensive use of concurrent CRT independent from incorporation of dose escalation has been shown to significantly increase toxicities (grade ≥3) compared to RT alone.[224,229,233,235,236,350,351]

Temporal Lobe Necrosis

TLN is perhaps the most troublesome complication. Studies on patients with NPC treated with conventional 2D-RT found that TLN accounted for up to 65% of all irradiation-induced deaths; large fractions (>2 Gy) and overacceleration of treatment schedule greatly increased risk, with incidence as high as 33%.[40,152,153]

Diagnosis of TLN was often difficult and thus delayed. In Lee et al's examination of 102 patients with late TLN following conventional 2D-RT,[352] only 31% presented with classic symptoms of TLN (hallucinations, absence attacks, déjà vu), whereas 14% had headaches, confusion, convulsions, or hemiparesis. Thirty-nine percent had vague symptoms of dizziness, poor memory, or sudden changes in behavior, whereas 16% were asymptomatic.

TLN remains a serious concern in patients treated with IMRT, with incidence of 3% to 4% being reported for schedules of 70 Gy at 2.12 Gy/fraction,[182] 66 to 74 Gy at 2 Gy/fraction,[176] and 76 Gy at 2.17 Gy/fraction.[184] Series using larger fractions (70.2 at 2.34 Gy/fraction and 68 Gy at 2.27 Gy/fraction) had incidence rates as high as 12% to 14%.[154,343] According to Bakst et al,[154] a prospective trial of hypofractionated dose-painting IMRT using 2.34-Gy fractions to deliver a total dose of 70.2 Gy had favorable disease control and survival outcomes; however, 12% of treated patients developed TLN, with the conclusion that large fractional doses should be avoided to prevent infield brain radiation necrosis.

Cranial Neuropathy

Cranial nerves IX through XII, particularly XII, are the most frequently impaired by radiation.[40,311,353] This is related to marked radiation fibrosis, especially in patients who receive an additional boost dose to the parapharyngeal space. Common symptoms include slurring of speech, twitching of neck muscles, and/or dysphagia. In a study of 31 patients with NPC with post-RT dysphagia, Wu et al[354] found that 77% aspirated after the act of swallowing, raising concerns of fatal aspiration pneumonia.

Cranial nerve VI is also frequently affected, particularly in patients with TLN, whereas isolated palsy of branches of cranial nerve V is less common.[40] Optic neuropathy is rare with careful attention to the RT technique and should be considered when treating lesions with base of skull involvement.[355] The possibility of intracranial recurrence may confound the diagnosis of radiation injury, and exclusion of recurrence is necessary.

Oral Complications

Xerostomia is an almost universal complication from treatment with conventional RT and may lead to dental caries. Jen et al[356] showed that the salivary flow dropped by half with a dose of 7.2 Gy, reached the nadir after 36 Gy, and then further dropped after completion of RT without recovery during the following 2 years.

However, Lee at al[171] reported marked recovery of salivary function in patients treated with parotid-sparing IMRT (mean parotid dose, 34 Gy); the rate of grade 2 xerostomia decreased from 64% at 3 months to 2.4% at 2 years. Randomized trials comparing 2D-RT and IMRT in patients with T1-2 tumors have confirmed IMRT's advantage in this regard.[357,358] Nevertheless, it is important to rule out tumor invasion of the parotid gland prior to parotid-sparing IMRT, as recurrences have been reported. Cannon and Lee[359] concluded that PET alone may be insufficient for the detection of intraparotid lymph node involvement in patients with multilevel nodal disease, including disease in level II nodes. Even with negative PET findings, these patients may require additional evaluation of any benign-appearing parotid nodules before parotid-sparing IMRT by FNA or CT-guided biopsy.

Dental sequelae frequently accompany xerostomia. In a series of 1,758 patients, 2.7% developed osteoradionecrosis at the maxilla and 1.7% at the mandible. Tong et al[360] reported a 29% complication rate in patients who had post-RT extraction of posterior maxillary teeth, with 10.5% developing osteonecrosis. Prophylactic fluoride treatment should be employed to prevent dental decay, and decayed teeth should be extracted prior to RT to reduce this risk.[360,361]

Aural Toxicity

Hearing loss has always been a common radiation sequela, and the increasing use of cisplatin-based concurrent CRT has resulted in deafness rates as high as 42%.[362]

Sensorineural hearing loss (SNHL), particularly in the high-frequency range, was found in at least 30% of patients assessed with audiograms following RT, with higher rates in patients treated by concurrent CRT.[40,363-365] The primary determinant of high-frequency SNHL is mean cochlea dose, which should be kept below 48 Gy to minimize damage.[40,363-365] Because of the location of the primary tumor in the nasopharynx, pharyngotympanic tube (*eustachian tube*) damage resulting in otitis media is difficult to avoid. However, lowering the dose to the external auditory canal and mastoid air cells can reduce the incidence and severity of acute external otitis and chronic serous otitis media, respectively.

Carotid Artery Injury

Carotid stenosis is a potentially fatal complication reported in patients who undergo irradiation of the head and neck region. Interval from RT was a significant independent predictor for severe carotid stenosis. Some have advocated for routine duplex ultrasound screening for high-risk patients (older than 60 years, smoking, hypertension, hypercholesterolemia, cerebrovascular symptoms).[366,367] Severe cases may require carotid endarterectomy or endoplasty.

Massive bleeding from ruptured pseudoaneurysms at the petrous portion of the internal carotid has been reported following IMRT with dose escalation.[184,368] Urgent diagnosis and intervention with endovascular occlusion or stenting may be needed to prevent fatal consequences. Other concerns include severe telangiectasia and hypervascularization in the internal maxillary artery territory, for which emergency embolization may be considered.

Endocrine Dysfunction

The most common endocrine sequelae are amenorrhea and/or galactorrhea from hyperprolactinemia in female patients and followed by hypothyroidism and hypoadrenalism.

Lee et al[40] observed symptomatic hypothalamic-pituitary dysfunction in 5% of patients, with a median latency of 5 years, whereas a longitudinal study by Lam et al[369] with detailed endocrine assessment found a 5-year incidence of 62%, with dysfunction detected as early as 1 year following RT.[370] The deficiency of releasing of inhibitory factors indicated that the hypothalamus is the primary location of damage.[371,372] As many of these dysfunctions may be corrected pharmacologically, routine evaluation of hypothalamic, pituitary, and thyroid function should be considered in the follow-up examination of long-term survivors.

Shielding may help lessen endocrine dysfunction when using 2D technique.[373] The need for maximum conformity to protect normal tissues during RT is paramount.

Second Malignancies

Radiation-induced malignancy is rare, with an incidence of 0.04% and latency period >10 years. The most common histologic types are maxillary osteosarcoma[374] and soft tissue sarcoma.[80] Surgery presents the only chance of cure, but the prognosis is often poor. Although second primary head and neck cancer is relatively uncommon for patients with NPC, Teo et al[375] reported an excessive incidence rate of tongue cancer at 0.13% per patient-year. The possibility of radiation carcinogenesis cannot be excluded.

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CHAPTER 48

Cancer of the Nasal Cavity and Paranasal Sinuses

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ANATOMY

Nasal Cavity

The nasal cavity extends from the hard palate inferiorly to the base of the skull superiorly. It is above and behind the vestibule and is defined anteriorly by the transition from the skin to mucous membrane and posteriorly by the choanae, which opens directly into the nasopharynx.[1] The nasal cavity consists of four subsites: the nasal vestibule, the lateral walls, the floor, and the septum.

The *nasal vestibule* is the triangular space located inside the aperture of the nostril as a slight dilation that extends as a small recess toward the apex of the nose. It is defined laterally by the alae; medially by the membranous septum, the distal end of the cartilaginous septum, and columella; and inferiorly by the adjacent floor of the nasal cavity. It is lined by the skin containing hairs and sebaceous glands; therefore, tumors at this location are often those that arise from the skin, usually squamous cell cancers,[2] but may occasionally be basal cell carcinoma,[3] sebaceous carcinoma,[4] melanoma,[5,6] or non-Hodgkin lymphoma.[7,8]

The *lateral walls* correspond with the medial walls of the maxillary sinuses and consist of thin bony structures that have three shell-shaped projections (superior, middle, and inferior conchae or turbinates) into the nasal cavity. The *floor* extends from the vestibule to the nasopharynx above the hard palate of the maxilla. The *septum* divides the nasal cavity into right and left halves.

Paranasal Sinuses

The paranasal sinuses are named according to the bones in which they are located: the ethmoid, maxilla, sphenoid, and frontal.

Ethmoid Sinuses

The ethmoid sinuses are composed of several small cavities, the ethmoid air cells, within the ethmoid labyrinth located below the anterior cranial fossa and between the nasal cavity and the orbit. They are separated from the orbital cavity by a thin, porous bone, the *lamina papyracea*, and from the anterior cranial fossa by a portion of the frontal bone, the *fovea ethmoidalis*. They are in close proximity to the optic nerves laterally and the optic chiasm posteriorly. The ethmoid sinuses are divided into anterior, middle, and posterior groups of air cells. The middle ethmoid cells open directly into the middle meatus. The anterior cells may drain indirectly into the middle meatus via the infundibulum. The posterior cells open directly into the superior meatus.

Maxillary Sinuses

The maxillary sinuses, the largest of the paranasal sinuses, are pyramid-shaped cavities located in the maxillae. The lateral walls of the nasal cavity form the base and the roofs correspond to the orbital floors, which contain the infraorbital canals. The floors of the maxillary sinuses are composed of the alveolar processes. The apices extend toward and frequently into the zygomatic bones. Secretions drain by mucociliary action into the middle meatus via the hiatus semilunaris through an aperture near the roof of the maxillary sinus. Ohngren line is a theoretical plane dividing each maxillary sinus into the suprastructure and infrastructure; it is defined by connecting the medial canthus with the angle of the mandible.

Sphenoid Sinus and Frontal Sinuses

The sphenoid bone forms a midline inner cavity that communicates with the nasal cavity through an aperture in its anterior wall. It is directly apposed superiorly to the pituitary gland and optic chiasm, laterally to the cavernous sinuses, anteriorly to the ethmoid sinuses and nasal cavity, and inferiorly to the nasopharynx. The paired, typically asymmetric frontal sinuses are located between the inner and outer tables of the frontal bone. They are anterior to the anterior cranial fossa, superior to the sphenoid and ethmoid sinuses, and superomedial to the orbits. They usually communicate with the middle meatus of the nasal cavity.

EPIDEMIOLOGY

Cancers of the nasal cavity and paranasal sinuses are relatively uncommon. Fewer than 7,500 cases are diagnosed each year in the United States, with an incidence of 0.556 per 100,000.[9] Cancers of the maxillary sinus are twice as common as those of the nasal cavity; cancers of the ethmoid, frontal, and sphenoid sinuses are extremely rare. They generally develop after the age of 40 years, except for esthesioneuroblastoma (ENB), which has a unique bimodal age distribution[10] and occurs twice as often in men than in women.[11] These tumors are most common in Japan and South Africa.

The etiologic factors vary by tumor type and location. Adenocarcinomas of the nasal cavity and ethmoid sinus have been reported to occur more frequently in carpenters and sawmill workers who are exposed to wood dust.[12,13] Synthetic wood, binding agents, and glues may also be involved as cocarcinogens.[14] Squamous cell carcinomas (SCCs) of the nasal cavity have been seen more often in nickel workers.[15] Maxillary sinus carcinomas have been associated with radioactive thorium-containing contrast material (thorotrast) used for radiographic visualization of the maxillary sinuses in the past. Occupational exposure to the production of chromium, mustard gas, isopropyl alcohol, and radium also may increase the risk of sinonasal carcinomas.

Cigarette smoking is reported to increase the risk of nasal cancer, with a doubling of risk among those who smoked heavily or long term and a reduction in risk after long-term cessation. After adjustment for smoking, a significant dose-response relationship has also been noted between alcohol consumption and risk of nasal cancer.[16]

NATURAL HISTORY

Nasal Vestibule

Nasal vestibule carcinomas can spread by direct invasion of the upper lip, gingivolabial sulcus, premaxilla (early events), or nasal cavity (late events), as shown in Figure 48.1. Vertical invasion may result in septal (membranous or cartilaginous) perforation or alar cartilage destruction. Lymphatic spread from nasal vestibule carcinomas is usually to the ipsilateral facial (buccinator and mandibular) and submandibular nodes. Large lesions extending across the midline may spread to the contralateral

facial or submandibular nodes. The incidence of nodal metastasis at diagnosis is approximately 5%.[17,18] Without elective nodal treatment, approximately 15% of patients develop nodal relapse. Hematogenous metastases are rare.

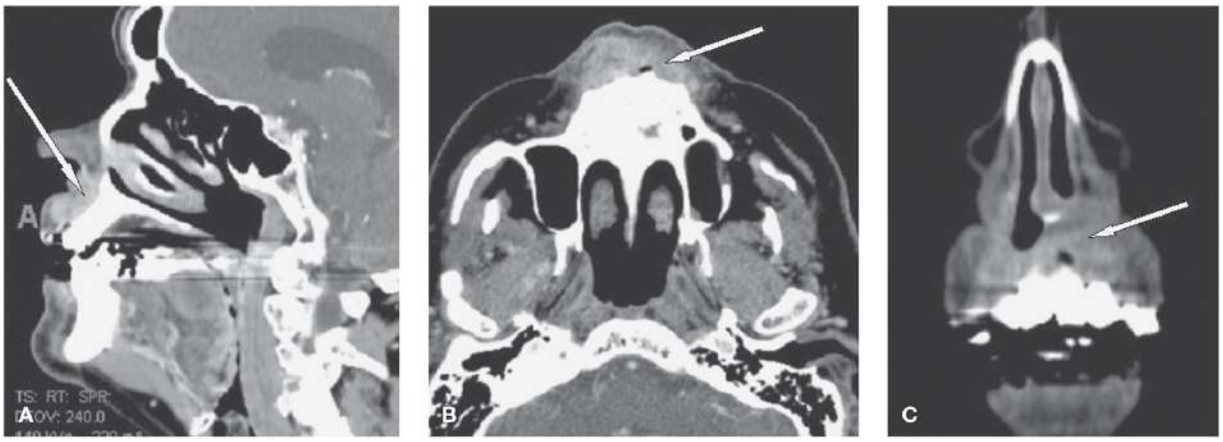

FIGURE 48.1 Computed tomography scans of a nasal vestibule squamous cell carcinoma that has spread by direct invasion of the upper lip (*arrow* in A) and gingivolabial sulcus and premaxilla (*arrow* in B and C).

Nasal Cavity and Ethmoid Sinuses

The pattern of contiguous spread of carcinomas varies with the location of the primary lesion. Tumors arising in the upper nasal cavity and ethmoid cells can extend to the orbit through the thin lamina papyracea and to the anterior cranial fossa via the cribriform plate, or they may grow through the nasal bone to the subcutaneous tissue and skin. Lateral wall primaries invade the maxillary antrum, ethmoid cells, orbit, pterygopalatine fossa, and nasopharynx. Primaries of the floor and lower septum may invade the palate and maxillary antrum. Perineural extension (typically involving branches of the trigeminal nerve) is seen most often with adenoid cystic carcinomas.

Lymphatic spread of nasal cavity primaries is uncommon, although spread to retropharyngeal and cervical lymph nodes is possible. In a series of 51 patients reported by the University of Texas MD Anderson Cancer Center, only one patient had palpable subdigastric nodes at diagnosis. Of the 36 patients who did not receive elective lymphatic irradiation, two (6%) experienced subdigastric nodal relapse.[19]

The risk of nodal involvement in patients with cancer of the nasal cavity and paranasal sinuses has not been well defined and may vary depending on the histologic subtype. Current decision-making on whether to cover specific nodal regions is based on interpretation of single-institution retrospective analyses.

Ahn[20] in a review of the Surveillance, Epidemiology, and End Results (SEER) database from 2004 to 2009 identified 1,811 patients who had local and nodal staging information, with paranasal sinus cancer as their first cancer diagnosis, defined histology (squamous, melanoma, adenocarcinoma, sinonasal undifferentiated, and ENB), and defined primary site. Of all the patients examined with information on local and nodal extent, 1,578 (87.1%) patients had no gross nodal involvement at presentation.

On presentation, level 1 was involved in 5.1%, level 2 in 6.7%, level 3 in 1.8%, level 4 in 1.2%, level 5 in 1.1%, retropharyngeal nodes in 0.7%, parotid nodes in 0.6%, and facial nodes in 0.2% of all patients. Isolated skip metastases to level 3 or 4 occurred in 0.7% of patients. On presentation, at least 2.5% presented with bilateral or contralateral disease. In patients with SCC of the nasal cavity, there was a clear gradation in nodal risk among patients with T1 versus T4 disease (4% vs 23%, $P < .001$); this was not evident in patients with melanoma of the nasal cavity, who had a 5% to 10% risk of nodal involvement regardless of local extension. Local extension of SCC of the maxillary sinus did not predict nodal involvement in a significant manner, although T1 tumors showed an 11% risk of nodal involvement compared to 21% to 24% for T2+ disease. SCC, small cell, and sinonasal undifferentiated (SNUC) carcinoma had higher rates of nodal dissemination at presentation (14.4%, 19.1%, and 25.3%, respectively), compared to adenocarcinoma, ENB, and melanoma (7.1%, 8.7%, 5.8%, respectively). Although confounded by stage and histology, maxillary sinus carries the highest risk (20.6%), followed by frontal/sphenoid (15.4%), ethmoid (11.9%), and nasal cavity (8.5%, $P < .001$).

The issue of appropriate radiation volumes in the treatment of these patients has not been entirely elucidated, although the data suggest that in some with potential higher nodal involvement, it is advisable to electively irradiate regions at risk. However, as noted by Ahn,[20] in the absence of gross

neck disease, the low neck and retropharyngeal nodes do not need to be treated.

Hematogenous dissemination is rare. In the MD Anderson Cancer Center series, for example, distant metastasis to the bone, brain, or liver occurred in only 4 of 51 patients.[21]

The olfactory region is the site of origin of ENB and, occasionally, adenocarcinomas. ENB constitutes approximately only 3% of all intranasal neoplasms. About 250 cases have been reported between 1924 and 1990.[21] The tumor is typically composed of round, oval, or fusiform cells containing neurofibrils with pseudorosette formation and diffusely increased microvascularity.[22]

ENB may be mistaken for any other "small round cell tumor," that is, a group of aggressive malignant tumors composed of small and monotonous undifferentiated cells that include Ewing sarcoma, peripheral primitive neuroectodermal tumor (also known as extraskeletal Ewing), rhabdomyosarcoma, lymphoma, small cell carcinoma (undifferentiated or neuroendocrine), and mesenchymal chondrosarcoma. The clinical presentations of these entities often overlap, but clinicopathologic features and immunohistochemical staining may help in distinguishing among them.

The route of contiguous spread of ENB is similar to that of ethmoid carcinomas. Lymph node involvement and distant metastasis are uncommon at diagnosis.[23,24]

Maxillary Sinuses

The pattern of spread of maxillary sinus cancers varies with the site of origin. Suprastructure tumors extend into the nasal cavity, ethmoid cells, orbit, pterygopalatine fossa, infratemporal fossa, and base of the skull (Figure 48.2A-C). Invasion of these structures gives lesions of the suprastructure a poorer prognosis. Their treatment is also associated with greater morbidity as a consequence of craniofacial resection or radiation of intracranial and ocular structures. Infrastructure tumors often infiltrate the palate, alveolar process, gingivobuccal sulcus, soft tissue of the cheek, nasal cavity, masseter muscle, pterygopalatine space, and pterygoid fossa (Figure 48.2D-J).

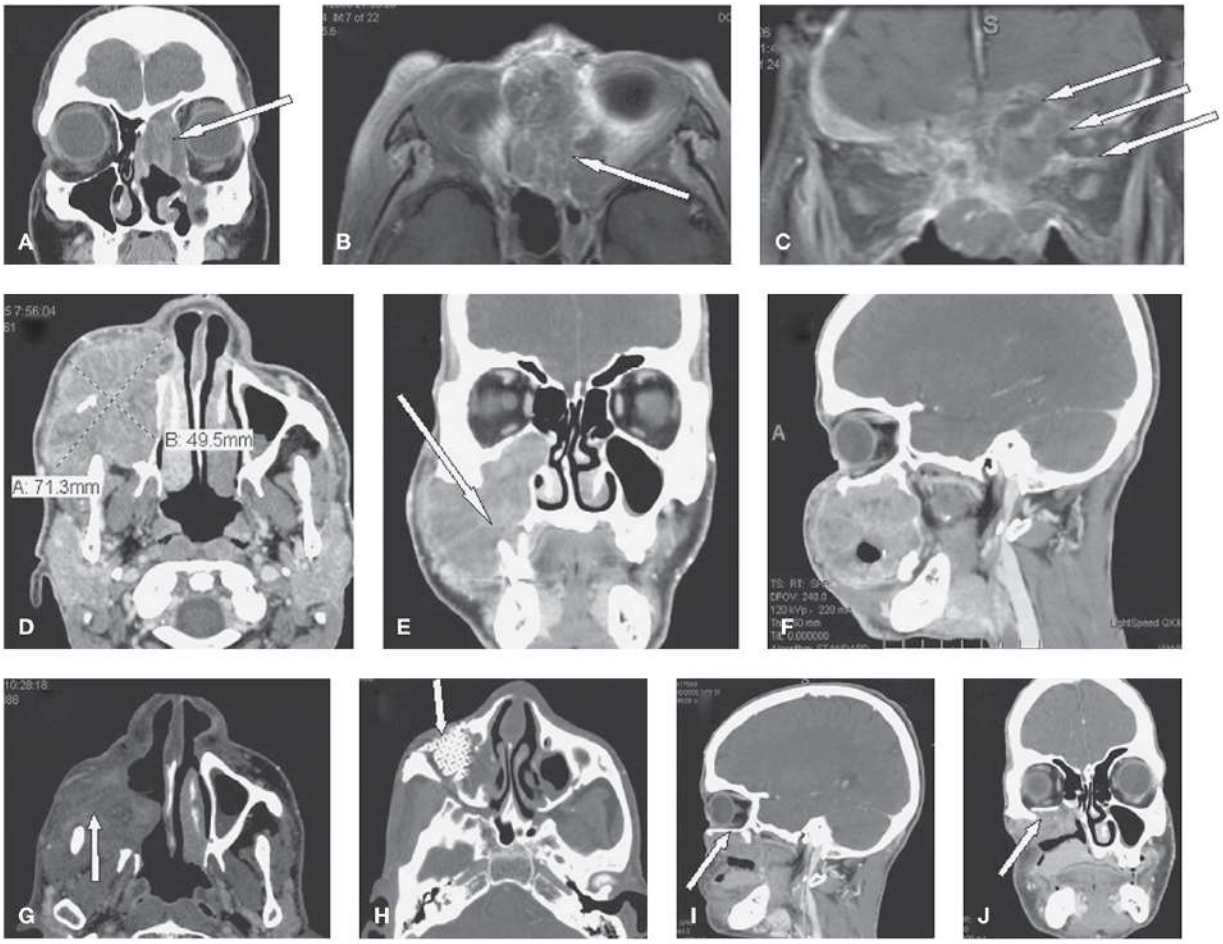

FIGURE 48.2 The pattern of spread of maxillary sinus cancers. A-C. Suprastructure tumors are shown, with *arrows* indicating the involvement of the nasal cavity and ethmoid cells (A), the orbit (B), and the base of the skull (C). D-J. Advanced tumor is shown, with *arrows* indicating alveolar process destruction with loosening of a tooth (E) and abutment of the orbital floor without frank intraorbital invasion (F). The patient had a maxillectomy and orbital floor resection with an anterior-lateral thigh flap (*arrow* in G), and titanium mesh reconstruction of the orbital floor (H-J).

The maxillary sinuses are believed to have a limited lymphatic supply[25] and a correspondingly low incidence of lymphadenopathy at diagnosis.[26,27] Only 6 (8%) of the 73 patients in the MD Anderson Cancer Center series had palpable lymphadenopathy at diagnosis. The incidence of nodal spread, however, varies with the histologic type (17%, or 5/29 patients with SCC or poorly differentiated carcinomas, vs 4%, or 1/27 for patients with adenocarcinoma, adenoid cystic carcinoma, or mucoepidermoid carcinoma). The incidence of subclinical disease, as reflected in the rate of nodal relapse in patients who did not receive elective neck treatment, also

varies with histologic type (38%, or 9/24 patients with SCC or poorly differentiated carcinomas, vs 8%, or 2/26 patients with adenocarcinoma, adenoid cystic carcinoma, or mucoepidermoid carcinoma). The cumulative incidence of nodal involvement (gross and microscopic) for patients with SCC and poorly differentiated carcinomas is about 30%. The risk of regional recurrence after treatment is 20% to 30% or higher, depending on the extent of disease and elective neck treatment.[28] Ipsilateral subdigastric and submandibular nodes are most often involved. Hematogenous spread is uncommon.

CLINICAL PRESENTATION

Nasal Vestibule

Carcinomas of the nasal vestibule usually present as asymptomatic plaques or nodules, often with crusting and scabbing. Advanced lesions may extend beyond the vestibule and may cause pain, bleeding, or ulceration. Large ulcerated lesions may become infected, leading to severe tenderness that requires anesthesia for complete clinical assessment.

Nasal Cavity

Nasal cavity tumors present with symptoms and signs of nasal polyps (eg, chronic unilateral discharge, ulcer, obstruction, anterior headache, and intermittent epistaxis), hence delaying the diagnosis. Additional symptoms and signs develop as the lesion enlarges: medial orbital mass, proptosis, expansion of the nasal bridge, diplopia resulting from invasion of the orbit, epiphora because of obstruction of the nasolacrimal duct, anomaly of smell or anosmia from involvement of the olfactory region, or frontal headache because of extension through the cribriform plate.

The common presenting symptoms of ENBs are nasal obstruction and epistaxis. Spaulding et al[29] found that anosmia could precede diagnosis by many years. Other symptoms are related to contiguous disease extension into the orbit (proptosis, visual field defects, orbital pain, epiphora), paranasal sinuses (medial canthus mass, facial swelling), or anterior cranial fossa (headache) or are due to inappropriate antidiuretic hormone secretion.[29]

Ethmoid Sinuses

The presenting symptoms and signs of ethmoid sinus tumors are central or facial headaches and referred pain to the nasal or retrobulbar region, a subcutaneous mass at the inner canthus, nasal obstruction and discharge, diplopia, and proptosis. In one study of 34 patients with ethmoid sinus cancers treated at MD Anderson Cancer Center between 1969 and 1993,[30] nasal cavity symptoms (nasal obstruction, epistaxis, discharge) were reported in 25 (74%) patients, orbital symptoms (diplopia, orbital pain, vision loss, proptosis, inner canthus mass, tearing) in 12 (35%), headache in 6 (18%), and hyposmia or anosmia in 5 (15%).

Maxillary Sinuses

Maxillary sinus cancers are usually diagnosed at advanced stages. Symptoms and signs are facial swelling, pain, or paresthesia of the cheek induced by disease extension to the premaxillary region, epistaxis, nasal discharge and obstruction related to tumor spread to the nasal cavity, ill-fitting dentures, alveolar or palatal mass, unhealed tooth socket after extraction from spread to the oral cavity, and proptosis, diplopia, impaired vision, or orbital pain because of orbital invasion.[31]

DIAGNOSTIC WORKUP

The recommended pretreatment physical, diagnostic, and staging evaluations are listed in Table 48.1.

TABLE 48.1 PRETREATMENT EVALUATION FOR TUMORS OF THE NASAL CAVITY AND PARANASAL SINUSES

General	Complete History and Physical Examination
	Fiberoptic endoscopic examination with biopsies
Radiographic	Computed tomography (CT)/positron emission tomography (PET)/magnetic resonance imaging (MRI) of the primary site and neck
Laboratory	Complete blood count
Others	Dental evaluation with extractions/restorations as needed
	Baseline ophthalmologic examination
	Baseline speech and swallowing assessment if surgery is planned

Physical Examination

Inspection and palpation of the orbits, nasal and oral cavities, and nasopharynx can provide preliminary determination of tumor extent. Bimanual palpation is important in assessing contiguous extension of nasal vestibule lesions and in identifying buccinator and submandibular nodal involvement. Careful examination of cranial nerves is required. Fiberoptic nasal endoscopy after mucosal decongestion and topical analgesia allows assessment of local extent and facilitates biopsy of tumor involving the nasal cavity or nasopharynx.

Radiographic Evaluation

Imaging has a crucial role in the staging of sinonasal tumors. Magnetic resonance imaging (MRI) and computed tomography (CT) scans are complementary.[32] MRI is superior at detecting direct intracranial or perineural or leptomeningeal spread.[33] T2-weighted MRI can be helpful in distinguishing tumor (low signal) from obstructed secretions (bright).[34] CT is superior for detecting early cortical bone erosion or extension through the cribriform plate or orbital walls.

MRI, especially T1 weighted with gadolinium contrast, may be used as a supplement or alternative to CT scanning. CT provides the best information about the tumor and its local invasion into surrounding bone structures. MRI allows an estimate of tumor spread into surrounding soft tissue areas, such as the anterior cranial fossa and the retromaxillary space. Bone scintigraphy scan is useful in detecting distant metastases.

The expansile tendency of olfactory neuroblastoma is characterized by bowing of the sinus walls. The destructive aspect is manifested as tumor replacing the turbinates, septum, and sinus walls with extension into contiguous areas. The density or signal and enhancement characteristics are nonspecific of olfactory neuroblastoma.

Certain features provide clues as to the nature of the tumors in this region. Slowly progressive lesions tend to deform instead of destroy bony structures. Intermediate-grade tumors can cause sclerosis of the adjacent bone. Lymphomas tend to permeate the bone without frank destruction, and carcinomas and sarcomas infiltrate and destroy adjacent bone.

Biopsy

Transnasal biopsy is preferred for tumors arising from or extending into the nasal cavity or nasopharynx. Some paranasal sinus tumors may be more easily sampled using transoral procedures or an open Caldwell-Luc approach.

Laboratory Studies

Complete blood counts and serum chemistries can be used to screen for the presence of distant metastases. Abnormalities of these tests can be further investigated as necessary.

STAGING

The eighth edition of the *American Joint Committee on Cancer's (AJCC) Cancer Staging Manual* tumor-node-metastasis (TNM) classification includes staging for cancers of the maxillary sinus, the ethmoid sinus, and the nasal cavity.[35] Significant updates from the sixth edition affect classifications of T4 lesions and hence stage IV disease. Specifically, T4 lesions are now considered either T4a (moderately advanced local disease) or T4b (very advanced local disease), which leads to stratification of stage IV disease as either IVA (moderately advanced local or regional disease), IVB (very advanced local or regional disease), or IVC (distant metastatic disease). Definitions of anatomic stage prognostic groupings and TNM classifications are given in Table 48.2.

TABLE 48.2 2017 AMERICAN JOINT COMMITTEE ON CANCER STAGING SYSTEM FOR CANCER OF THE NASAL CAVITY AND PARANASAL SINUSES

Definitions of TNM	
Primary Tumor (T)	
TX	Primary tumor cannot be assessed.
Tis	Carcinoma in situ
Maxillary Sinus	
T1	Tumor limited to maxillary sinus mucosa with no erosion or destruction of the bone
T2	Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of

Definitions of TNM

	maxillary sinus and pterygoid plates
T3	Tumor invades any of the following: the bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of the orbit, pterygoid fossa, ethmoid sinuses.
T4a	Moderately advanced local disease
	Tumor invades anterior orbital contents, skin of the cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses.
T4b	Very advanced local disease
	Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V2), nasopharynx, or clivus.

Nasal Cavity and Ethmoid Sinus

T1	Tumor restricted to any one subsite, with or without bony invasion
T2	Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion
T3	Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate.
T4a	Moderately advanced local disease
	Tumor invades any of the following: anterior orbital contents, skin of the nose or cheeks, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses.
T4b	Very advanced local disease
	Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than (V2), nasopharynx, or clivus.

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension, ENE neg
N2	Metastasis in a single ipsilateral lymph node, >3 cm but not >6 cm in greatest dimension, or in multiple ipsilateral lymph nodes or contralateral lymph nodes, none >6 cm in greatest dimension and ENE neg
N2a	Metastasis in a single ipsilateral lymph node, >3 cm but not >6 cm in greatest dimension and ENE neg

Definitions of TNM			
N2b	Metastasis in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE neg		
N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE neg		
N3a	Metastasis in a lymph node >6 cm in greatest dimension and ENE neg		
N3b	Metastasis in any node(s) with clinically overt ENE (ENE positive)		
Distant Metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic Stage/Prognostic Groups			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3T1T2T3	N0N1N1N1	M0M0M0M0
Stage IVA	T4aT4aT1T2T3T4a	N0N2N2N2N2N2	M0M0M0M0M0M0
Stage IVB	T4bAny T	Any NN3	M0M0
	Any T	Any N	M1

ENE, extranodal extension.

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PATHOLOGIC CLASSIFICATION

Most nasal vestibule cancers are SCCs; the remaining tumors are basal cell or adnexal carcinomas. Most cancers of the nasal cavity and paranasal sinuses are also SCCs, although minor salivary gland neoplasms (adenocarcinoma, adenoid cystic carcinoma, and mucoepidermoid carcinoma) account for 10% to 15% of lesions in these locations.

Melanoma accounts for 5% to 10% of nasal cavity malignancies but is rare in the paranasal sinuses. Neuroendocrine carcinomas of the sinonasal region (including small cell carcinoma, ENB, and SNUCs), lymphomas, sarcomas, and plasmacytomas are even less common.

PROGNOSTIC FACTORS

Patient-specific factors (primarily prognostic for survival) include age and performance status. Disease-specific factors (primarily prognostic for locoregional control) include location, histology, locoregional extent (reflected in the TNM stage), and perineural invasion. Extensive local disease involving the nasopharynx, base of the skull, or cavernous sinuses markedly increases surgical morbidity as well as the risk of subtotal surgical excision. Tumor extension into the orbit may require enucleation, but minimal invasion of the floor or medial wall may be dealt with through resection and reconstruction, sparing the globe.

GENERAL MANAGEMENT

Nasal Vestibule Tumors

Nasal vestibule tumors can be treated definitively with surgery, primary radiation therapy (RT), or postoperative (adjuvant) RT when indicated because of tumor size or positive surgical findings. For small superficial tumors, standard treatment approaches are surgery or primary RT. Depending on the location and size of the primary tumor, radiation can be delivered as external beam RT, brachytherapy, or a combination of the two. Primary RT may be preferable for nasal vestibule carcinoma for better cosmetic outcome, although surgery can yield high control rates with excellent cosmetic results for selected small superficial tumors. Adjuvant radiation is indicated for cases involving positive surgical margins, positive lymph nodes, or perineural invasion. Cartilaginous invasion is not a contraindication for RT because fractionated treatment carries a low risk of necrosis.[36] For large invasive tumors with extensive tissue destruction and distortion, the combination of surgery and RT, with the radiation given either before or after surgery, is the mainstay of treatment. However, some clinicians favor primary radiation with salvage surgery for this situation.[37]

Cosmesis can be enhanced by having experienced prosthodontists design aesthetically satisfactory custom-made nasal prostheses after radical surgery. Patients who are older or who have poor performance status can be treated with RT alone. No role for systemic chemotherapy has been established for tumors of this type.

Nasal Fossa Tumors

Either surgery or primary RT can produce similarly high control rates for early-stage nasal fossa lesions. The choice of treatment modality is generally guided by the size and location of the tumor as well as the anticipated cosmetic outcome. Posterior nasal septum lesions or locally advanced lesions are generally treated surgically, but small anterior-inferior septal lesions (≤1.5 cm) can be treated effectively with interstitial brachytherapy (iridium-192 [^{192}Ir] implant). For lateral wall lesions extending to the nasal ala, primary external beam RT may produce the best cosmetic results.

Paranasal Sinus Tumors

Surgery can produce excellent control rates for T1 and T2 tumors and is generally the mainstay of treatment. The combination of surgery and postoperative RT is the treatment of choice for patients with more advanced but resectable SCC tumors who are medically fit to undergo surgery.[38] For SNUC tumors, response to induction chemotherapy (IC) guides chemoradiation strategies for complete (CR) or partial response (PR) and surgery followed by adjuvant therapy for nonresponders.[39] Maxillary sinus and ethmoid sinus tumors often present as locally advanced disease (large T3 or T4) and are commonly managed with surgery and postoperative RT. Ethmoid sinus carcinomas can be treated with radiation alone or with concurrent chemotherapy to avoid structural or functional deficits. Surgery generally involves medial maxillectomy and en bloc ethmoidectomy; a craniofacial approach is required if tumor extends superiorly to the ethmoid roof or olfactory region.[40,41] Primary RT, with or without concurrent chemotherapy, can be considered for patients who are not fit to undergo surgery owing to significant comorbid conditions or poor performance status or for patients who decline radical surgery.[42]

Early ENB lesions involving the ethmoids with little or no bony destruction or nerve invasion can be treated adequately by high-energy (photon, proton, or electron) RT with good cosmetic and functional results. Those with more extensive local disease benefit from surgery and adjuvant irradiation, although some have advocated against combined surgery and RT because of complications. Patients with locally advanced disease or high-grade tumors should receive aggressive treatment with combined modalities, such as surgery, RT, and chemotherapy. Elective nodal irradiation is not generally recommended for Kadish stages A and B because the incidence of nodal relapse is less than 15%. Distant metastasis is uncommon (10%) even among patients presenting with locally advanced disease.

CHEMOTHERAPY: NEOADJUVANT AND CONCOMITANT

Neoadjuvant chemotherapy (ie, chemotherapy given before surgery) can reduce tumor volumes, which may allow a less extensive surgical resection than would be possible otherwise.[39] Similarly, chemotherapy given before primary RT can also reduce tumor volumes and facilitate RT planning by increasing the distance between tumor borders and critical organ structures, such as the brain, chiasm, optic nerve, or spinal cord. Investigations are ongoing to determine whether the response (or lack of same) to neoadjuvant chemotherapy can help in the choice of definitive treatment. For example, if neoadjuvant chemotherapy produces a CR, then primary RT, with or without chemotherapy, can be considered; a less than CR would prompt surgical excision of the lesion followed by adjuvant RT.[43]

The optimal treatment strategy for patients with orbital encroachment of sinonasal cancer is controversial. Organ (orbital) preservation with neoadjuvant therapy may determine if patients require an orbital exenteration for locally advanced sinonasal cancer. Yusuf et al[44] reported on 20 patients determined by a multidisciplinary team to require an orbital exenteration as part of definitive treatment of their sinonasal cancer. Neoadjuvant treatment consisted of concurrent chemoradiation therapy (CRT) in all patients aside from two who refused chemotherapy and underwent RT alone. Six patients received primary surgery followed by adjuvant CRT. Five patients (36%) receiving neoadjuvant therapy had

complete disease response at the time of surgery. Fourteen patients underwent orbital preservation (OP). With a median time of follow-up of 18.8 months, actuarial exenteration-free survival was 62% at 2 years for patients undergoing OP. No patients receiving neoadjuvant therapy required an immediate post-treatment orbital exenteration; however, one patient required salvage orbital exenteration when they experienced local failure 35 months after treatment. At 2 years, there were no significant differences in locoregional control (75% vs 60%, $P = .997$), progression-free survival (40% vs 36%, $P = .493$), or overall survival (OS) (40% vs 58%, $P = .815$) between patients receiving OP or upfront surgery ($P = .815$). On multivariate analysis, tumor site predicted for locoregional control (maxillary, 86%; nasal cavity, 80%; ethmoid sinus, 40%; $P = .050$). Treatment was well tolerated in both groups. One patient treated with OP experienced grade 3 radiation-related toxicity, developing dysphagia, which improved with medical management. However, one patient developed renal failure following the first dose of cisplatin and subsequently died before completion of treatment.

Concurrent CRT can also be used for patients with medical conditions that preclude surgery if those patients have good performance status. Depending on the patient's performance status and renal function, single-agent cisplatin or carboplatin can be used concurrently with external beam radiation for locally advanced, unresectable SCC. Neoadjuvant chemotherapy or concurrent chemoradiation with etoposide and cisplatin or carboplatin can be used to treat SNUC, neuroendocrine carcinoma, or small cell carcinoma. Chemotherapy is not used routinely for ENB, and its role in the management of this disease is under investigation. Chemotherapy may have a role in the management of Kadish stage C disease, and although responses to chemotherapy have been reported, they are usually of limited duration.[45] Concurrent chemotherapy during radiation may be considered for inoperable cases.

PALLIATION

Symptoms of incurable sinonasal cancer are particularly distressing. Multidisciplinary input is required even for very advanced cases, as palliation may involve limited surgery, RT, chemotherapy, investigational

studies, or best supportive care. The morbidity of each modality must be balanced with the potential benefits in symptom control and improved quality of life. Particular attention is required to address the control of pain and discomfort as a first priority, and the impact of disfigurement and dysfunction, which is often present.

Chemotherapy can be given as single-agent therapy in investigational settings. If RT is given, large doses per fraction are usually given to reduce the duration of treatment. However, if concurrent chemotherapy is added, treatment with 2-Gy fractions should be considered to avoid severe acute effects. Radiation or chemotherapy is often effective in reducing tumor bulk and relieving symptoms associated with disfiguring masses, proptosis, discomfort or neuropathic pain, headache, epistaxis or other bleeding, nasal obstruction or discharge, and trismus.

RADIATION THERAPY TECHNIQUES

Tumors of the Nasal Cavity

Nasal Vestibule Tumors

Target Volumes

For small, well-differentiated lesions that are less than 1.5 cm in diameter, small fields with a 1- to 2-cm margin are appropriate. The initial target volume for all poorly differentiated tumors and well-differentiated primary tumors larger than 1.5 cm without palpable lymphadenopathy should include both nasal vestibules with at least 2- to 3-cm margins around the primary tumor (wider margins for infiltrative tumor) as well as bilateral facial, submandibular, and subdigastric nodes. When lymph node involvement is present at diagnosis, the lower neck is also irradiated. For larger nasal vestibule lesions, the lower half of the nose and the upper lip are treated as well as the regional lymphatics, including the facial lymphatics and upper neck nodes. For postoperative RT, the initial target volume includes the operative bed plus a 1- to 1.5-cm margin and the elective nodal regions.

Treatment Techniques

External Beam Radiation. Thin superficial nasal vestibule lesions can be treated with orthovoltage x-rays or electrons with skin bolus, whereas thicker lesions are generally treated with electrons, photons, or protons. In definitive therapy, the target volume is treated to a dose of 66 to 70 Gy, with a small reduction in the treatment fields after 50 Gy to boost the dose to the gross disease. For patients presenting with palpable neck adenopathy, the entire neck is treated with at least a subclinical dose of 50 Gy, and the gross disease plus a 1- to 2-cm margin is then treated with an additional 16 to 20 Gy. A technique for external beam irradiation using electrons is illustrated in Figure 48.3. The patient lies supine, immobilized with the neck slightly flexed by using a custom mask to align the anterior surface of the maxilla parallel with the top of the couch. For larger nasal vestibule lesions, the lower half of the nose and the upper lip are treated with an anterior appositional field using 20-MeV electrons and 6-MV photons weighted 4 to 1. Skin collimation is used to minimize scatter irradiation to the eye and reduce the penumbra of the beam and reduce the field size required. Custom beeswax bolus material is prepared to allow a relatively flat surface contour onto which the electron beam is incident, avoiding inhomogeneity because of oblique incidence and surface irregularity. A bolus is also used to fill the nares to avoid the dose perturbation from the air cavity with electron beams. In photon treatments, the bolus is removed to spare the skin unless the overlying skin is involved. An intraoral Cerrobend-containing stent is used to displace the tongue posteriorly and partially shield the upper alveolar ridge. In proton treatments, bolus material is not required and an aperture is used instead of skin collimation to minimize scatter irradiation to the eye and reduce penumbra of the beam.

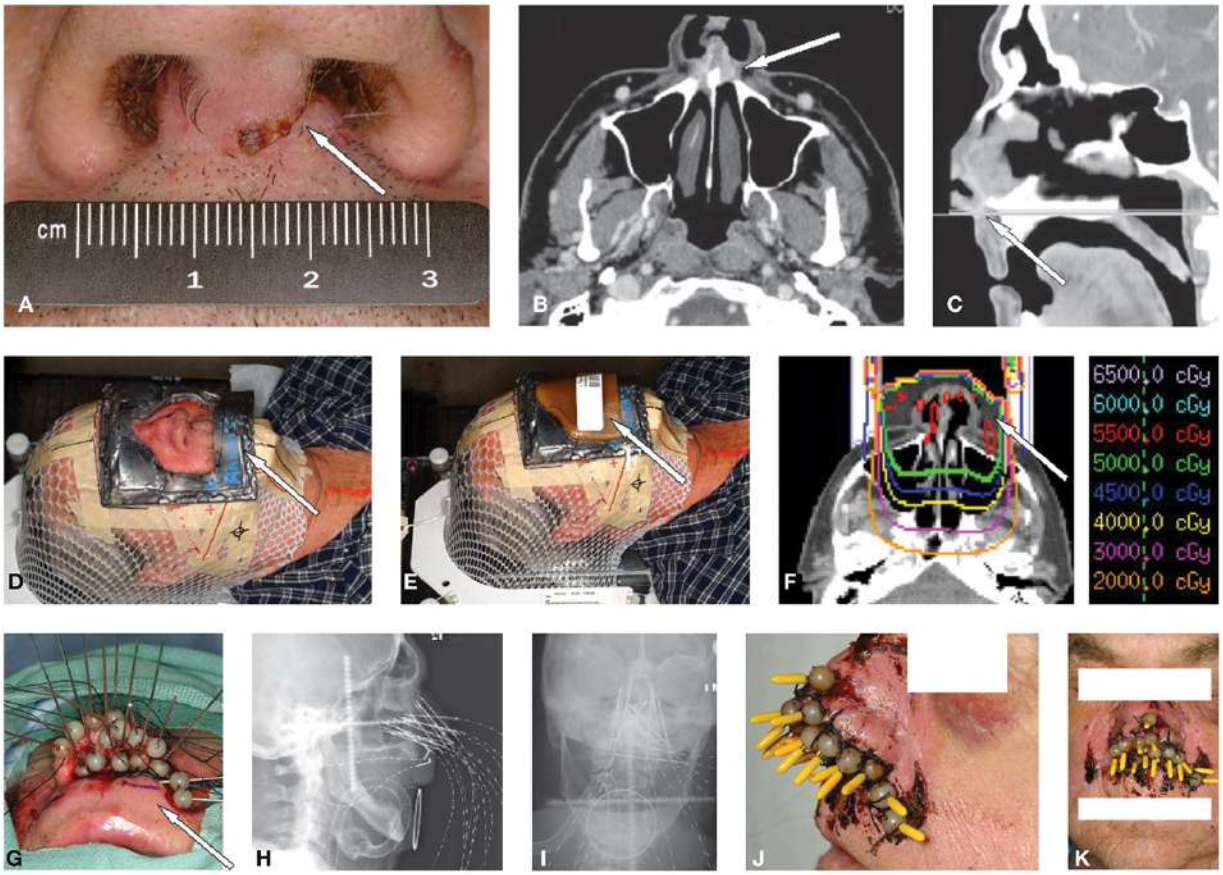

FIGURE 48.3 Nasal vestibule squamous cell carcinoma. A. *Arrows* indicate tumor expanding the columella. B and C. *Arrows* indicate invasion downward into the upper gingivobuccal sulcus on computed tomography (CT) imaging. D. *Arrow* shows setup for electron-beam phase of therapy with custom lead skin collimation in situ. E. *Arrow* shows the beeswax bolus in situ. F. Dosimetry to 50 Gy resulting from an appositional electron beam with beeswax bolus (*arrow*) to compensate for surface obliquity. The primary tumor, facial, and level II nodes were treated with 50 Gy. This was followed by 25 Gy administered by an interstitial low-dose rate iridium needle implant at 0.55 Gy/h. G. Dummy wires are inserted into each hollow tube. Each tube has a ball anchor at the distal end of the needles, which is pushed snugly against the skin and sutured to the skin. Note the placement of transverse "moustache" needles. H and I. Orthogonal x-ray (anterior-posterior, lateral) films taken to document the placement of the needles. CT-based planning was performed. J and K. Live sources in situ.

When indicated, the right and left facial lymphatics are irradiated with appositional fields; these require an approximately 15° gantry rotation to the respective side with 6-MeV electron fields, each abutting the appositional primary lesion portal and the upper neck fields. The medial border is matched to the lateral border of the anterior primary field. The anterior border extends down from the oral commissure to the middle of the

horizontal ramus of the mandible, whereas the posterior border extends from the upper edge of the anterior field to just above the angle of the mandible. The inferior border splits the horizontal ramus of the mandible and is matched to the upper neck field. The junctions are moved twice during the course of treatment to reduce dose heterogeneity. The submandibular and subdigastric nodes are treated with lateral parallel-opposed photon fields. For patients with involved nodes, these upper neck fields are matched inferiorly to an anterior portal treating the middle and lower neck nodes.

For definitive treatment, the external beam radiation schedule for lesions up to 1.5 cm in diameter for which a combination of electrons and photons is used is typically 50 Gy in 25 fractions followed by a boost of 10 to 16 Gy in 5 to 8 fractions (prescribed at the 90% isodose line). Larger lesions to be treated by external beam radiation alone receive 50 Gy in 25 fractions plus a boost of 16 to 20 Gy in 8 to 10 fractions. The schedule for elective nodal irradiation is 50 Gy in 25 fractions. Palpable nodes are given a boost to a total dose of 66 to 70 Gy in 33 to 35 fractions, depending on the size. For postoperative treatment, the volume is reduced off the undissected nodal regions after 50 Gy (25 fractions) to deliver an additional 6 Gy to the surgical bed. At 56 Gy, a final "cone down" is done to include a 4-Gy dose to the preoperative tumor bed, for a total dose of 60 Gy. If the excision was limited or positive margins are present, the final cone-down dose is 10 Gy for a total dose of 66 Gy.

Brachytherapy. Brachytherapy for small lesions is accomplished by using a ^{192}Ir wire implant or, in selected cases, by using an intracavitary ^{192}Ir mold. Hollow needles for afterloading are inserted under general anesthesia, which allows good exposure of the tumor and protects the airway in the event of bleeding from the vascular Kiesselbach plexus on the anterior nasal septum or from posterior hemorrhages originating from larger vessels near the sphenopalatine artery, behind the middle turbinate. Implantation of a T2 SCC of the columella is shown in Figure 48.3. The recommended doses for low-dose rate brachytherapy have evolved empirically and range from 60 to 65 Gy delivered during 5 to 7 days.

Brachytherapy can be used instead of an external beam boost for patients with T1 or T2 nasal vestibule tumors after initial larger field RT. After

delivery of 50 Gy, the patient is assessed, and if the tumor volume has been substantially reduced, a boost of 20 to 25 Gy may be administered in about 2 days by using low-dose rate brachytherapy.

High-dose rate brachytherapy has also been used to deliver the boost. A custom mold of the nasal vestibule is fabricated, and tumor is marked in the mold. Two to four plastic tubes are inserted into the mold alongside the tumor at 1-cm intervals. For tumors of the lateral part of the vestibule, two catheters are placed on the inner aspect of the nasal vestibule. For medially localized tumors, catheters are placed on both sides of the vestibule. After external beam radiation to 50 Gy in 5 weeks, high-dose rate brachytherapy is delivered in week 6. The dose is typically 3 Gy per fraction, given twice a day, to a total dose of 18 Gy specifically at the center of the tumor. With a median overall treatment time (external beam radiation plus brachytherapy) of 36 days, this technique has been reported to yield 2-year local control rates of 86% and ultimate locoregional control rates of 100%.[46]

Nasal Fossa Tumors

Target Volume

The technique for primary or postoperative external beam irradiation of nasal cavity tumors depends on the depth of the neoplasm. For tumors located less than 3.5 or 4.0 cm from the skin of the apex of the nose, electrons can be used, as 20-MeV electrons will provide coverage up to 5 cm in depth. A margin of at least 1 cm deep to the posterior edge must be included in the full-dose volume. The technique is as previously described for nasal vestibule carcinoma. CT-based treatment planning is necessary for accurate target localization and dose calculation.

Intensity-modulated radiation therapy (IMRT) with either photons or protons are recommended for tumors of the nasal cavity in which the target volume is more than 5 cm deep or for tumors of the ethmoid sinus[47] (Figure 48.4). This technique delivers the desired dose to the target volume while minimizing the dose to critical organs, such as the cornea, lens, lacrimal glands, retina, optic nerve, optic chiasm, brain, and brainstem. For postoperative RT, the primary clinical target volume (CTV) descriptions are given in Table 48.3. The CTV_1 consists of the primary tumor bed with a 1.0- to 1.5-cm margin. A boost subvolume consisting of high-risk regions

(sites of positive margins, gross macroscopic residual tumor) to be treated to higher doses may be outlined. The CTV_2 includes the entire operative bed. For ethmoid sinus tumors, this might include the frontal sinus, maxillary sinus, and sphenoid sinus. The bony orbit is part of the operative bed when orbital exenteration is performed because of tumor invasion. For lesions involving the ethmoid sinuses or olfactory region, the CTV should also include the cribriform plate. A third CTV may be delineated to encompass the tract of cranial nerve V2 to the foramen rotundum if perineural invasion is present. For primary RT given as IMRT, the CTV_1, consisting of the gross tumor volume plus a margin of 1 to 2 cm, receives the full dose of 66 to 70 Gy. For patients receiving neoadjuvant chemotherapy, target volume definition is based on the extent of disease before chemotherapy.

TABLE 48.3 TARGET VOLUMES FOR INTENSITY-MODULATED RADIATION THERAPY OF SINONASAL CANCERS

Target	Description	Dose (33-35 Fractions) (Gy)
Primary Radiation Therapy		
GTV	GTV (= prechemotherapy volume)	66-70
CTV_1 (primary CTV)	GTV + 1.0-1.5 cm	66-70
CTV_2 (intermediate-dose CTV)	Primary CTV + 1.0-1.5 cm	59-63
CTV_3 (elective CTV)	Nodal volumes, nerve tract, and base of skull margin	54-57
Postoperative Radiation Therapy		
CTV_{HR} (high-risk CTV)	Sites of suspected positive margins, gross macroscopic residual tumor, extracapsular nodal disease	66-70[a]
CTV_1 (primary CTV)	Primary tumor bed with 1.0-1.5-cm margin	60
CTV_2 (intermediate-dose CTV)	Surgical bed	57
CTV_3 (low-dose CTV)	Trigeminal nerve perineural invasion is present, additional skull base margin, elective nodal volume if indicated	54

CTV, clinical target volume; GTV, gross tumor volume.

[a]70 Gy may be given by adding a second boost plan or increasing the number of fractions to 35.

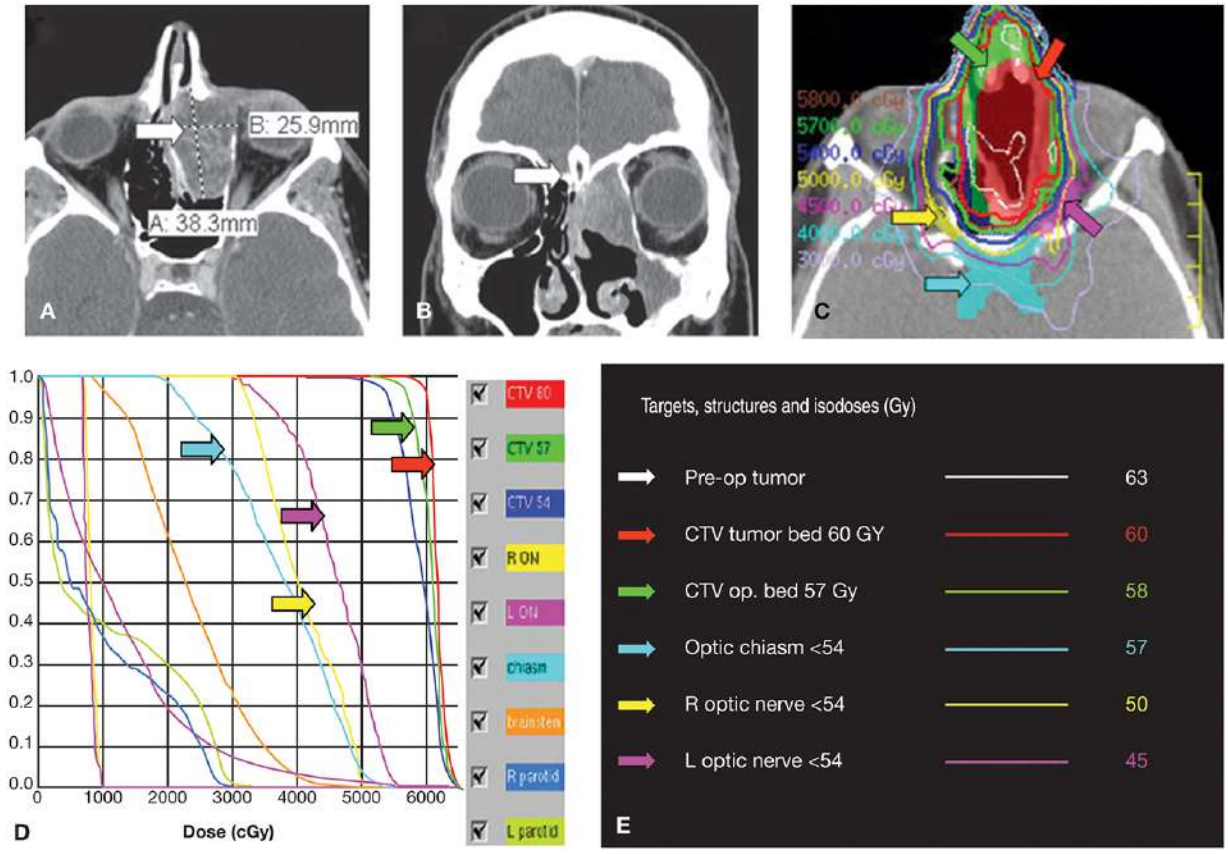

FIGURE 48.4 Intensity-modulated radiotherapy for adjuvant radiotherapy for an adenoid cystic carcinoma of the ethmoid sinus, anterior skull base, nasal cavity, and medial orbit following endoscopic anterior-posterior ethmoidectomy with resection of tumor, left maxillary antrostomy with disease removal, bilateral sphenoidotomy, and frontal sinusotomy with anterior approach to the anterior skull base including a left lateral rhinotomy and medial maxillectomy and extradural resection of anterior cranial base. A and B. Preoperative computed tomography scans with tumor indicated by *white arrow*. C. Transverse section at the level of the orbit that shows sharp dose gradient at the interface of the clinical target volume (CTV) and the optic nerves and chiasm. D and E. Cumulative dose-volume (*y*-axis) histogram.

For three-dimensional (3D) conformal RT, the initial target volume for postoperative radiation consists of the surgical bed with 1- or 2-cm margins, depending on the surgical pathology findings and the proximity of critical structures. The boost volume consists of areas at greatest risk of recurrence,

such as close or positive resection margins or regions of perineural invasion, with 1- to 2-cm margins.

For small anterior-inferior septal lesions, brachytherapy can be accomplished by using a single-plane implant of the lesion with 2 cm margins. Elective neck irradiation is not given routinely even for patients with large tumors or early-stage Kadish A or B ENB.

Setup and Field Arrangement

For target volumes less than 5 cm deep, an electron technique similar to that described for nasal vestibule carcinomas is used. Treatment devices include lead skin collimation to obtain a sharp penumbra as well as bolus material in the nasal cavity, in postoperative defects, and on skin scars. An intraoral stent is used to depress the tongue, provide a patent airway, and aid in immobilization. Tungsten internal eye shields may be used if the target volume approaches the orbits (see Figure 48.3).

For 3D conformal therapy or IMRT, the patient is immobilized in a supine position with the head positioned such that the hard palate is perpendicular to the treatment couch. Scars are marked with thin radio-opaque wires, bolus, and other devices are positioned, and transverse CT images are obtained from the vertex to the upper mediastinum. For IMRT, rigid immobilization is necessary, including the use of special head and shoulder thermoplastic masks that extend down to the upper thorax. The shoulders can be additionally depressed and fixed by using wrist straps tethered to a footboard. Target volumes are delineated as previously described.

For IMRT, multiple gantry angles are used based on beam optimization algorithms. An example of a 10-field noncoplanar arrangement with two vertex beams is shown in Figure 48.4. The beam angle selections are based on the same principles as for 3D conformal therapy:

1. Preference for the shortest path to the target
2. Avoidance of direct irradiation of the critical structures (eg, avoid beam entry through the contralateral eye after ipsilateral exenteration)
3. Use of as large a beam separation as possible

Inverse planning is usually done, and multiple iterations may be necessary to ensure that the following are accomplished:

1. Targets are covered.
2. Normal tissue constraints are respected.
3. Dose is relatively homogeneous.

Dose calculations should include heterogeneity corrections because of the significant amounts of air and bone in the sinuses. Radiation oncologists must work closely with physicists and dosimetrists. It is important to realize that the criteria for accepting or rejecting the plan may not be evident from the dose-volume histogram.

For 3D conformal RT, anterior oblique wedge-pair photon fields are appropriate for lesions located in the anterior lower half of the nasal cavity. Opposed-lateral fields can be used to treat tumors at the posterior part of the nasal fossa, provided the ethmoid cells are not involved. The optic pathway can be excluded from the radiation fields with this setup. For primaries of the upper nasal cavity and ethmoidal air cells, a three-field setup allows coverage of the ethmoid cells while sparing the optic apparatus. CT-based treatment planning is necessary to select beam and wedge angles (usually 45°-60°) and the relative loading of the fields, as well as to evaluate the dose to critical structures, such as the brain, brainstem, and optic structures.

Proton beam therapy techniques for treating nasal fossa tumors are rapidly evolving and include both passive scattering and discrete spot scanning beams. Theoretically, the advantage of proton therapy (PT) derives from the unique physical properties of protons that allow deposition of most of the particle's energy at the end of its range. Descriptions of the various techniques by which PT can be delivered are beyond the scope of this chapter. Nevertheless, with optimization of dosimetry, the conformality and heterogeneity within the target volumes provided by PT should be equivalent to what can be achieved with either electron or photon therapy, with the added advantage of minimizing the unnecessary dose or "dose bath" from IMRT to the surrounding normal tissue structures.

Greenwalt et al[48] reported on seven adult patients with primary mucosal nasal cavity,[4] ethmoid sinus, and maxillary antrum melanoma treated with external beam PT. Six patients underwent gross total resection before PT,

and one patient underwent a biopsy of unresectable disease from intracranial extension. In the postoperative setting, PT was initiated at a median of 53 days after surgery. The primary target volume was defined as the surgical bed plus a margin for microscopic disease and setup uncertainties. The median PT dose to the primary high-risk planning target volume was 74.4 Gy (relative biologic effectiveness [RBE]) (range, 69.6-74.4). Six patients were treated with elective nodal radiation to the neck to a median dose of 50 Gy (range, 48-50). None of the patients had neoadjuvant, concurrent, or adjuvant chemotherapy. Median follow-up was 1.4 years from the end of PT (range, 0.5-6.6 years). The cause-specific survival and OS rates were equivalent at 83% at 1 year and 67% at 1.5 years. Three patients died of metastatic disease, all died within 25 months of completing PT. One patient who was treated with 69.6 Gy (RBE) recurred locally at 2 months after completing PT and died of distant disease. The locoregional control rates at 1 and 1.5 years were both 86%, whereas the freedom from distant metastases rate was 71% at 1 and 1.5 years. One patient experienced grade 2 epiphora and grade 4 visual toxicity, leading to loss of useful vision in the treated eye. One patient with brain necrosis was found to have developed brain metastases requiring steroids following PT. Two patients reported grade 2 sinusitis, one patient had a grade 2 oral cavity fistula, and one patient reported grade 2 sensorineural hearing loss. No contralateral visual complications occurred.

Radiation Therapy Dose Fractionation Schedule

The dose schedule for low-dose rate brachytherapy is 60 to 65 Gy during 5 to 7 days. The external beam regimen for primary RT is 50 Gy in 25 fractions followed by a boost of 16 to 20 Gy in 8 to 10 fractions, depending on the size of the lesion. Postoperative RT consists of 50 Gy to elective tissue, 56 Gy to the operative bed, and 60 Gy to the tumor bed, with an optional boost to close or positive surgical margins, all given at 2 Gy per fraction. Dose regimens for intensity-modulated therapy, whether with photons or protons, are summarized in Table 48.3.

Tumors of the Paranasal Sinuses

Target Volume

Because maxillary cancers are usually diagnosed at a locally advanced stage and surgery is the primary therapy, most patients receive postoperative RT. Delineation of target volumes is based on physical examination, pretreatment imaging, intraoperative findings (tumor extension relative to critical structures such as orbital wall, cribriform plate, cranial nerve foramina, and ease of resection), and pathologic findings (such as positive margin or perineural invasion).

For photon-based treatment delivery, IMRT is the preferred treatment method as it generally yields better dose distribution in terms of both tumor coverage and sparing of normal tissues than can be achieved with 3D conformal RT.[47,49]

Jeong et al[50] compared in 10 patients volumetric modulated arc therapy (VMAT) and noncoplanar IMRT for nasal cavity and paranasal sinus cancer with regard to the coverage of planning target volume (PTV) and the sparing of organs at risk (OARs). Planning objectives were (a) to deliver 60 Gy in 30 fractions to 95% of PTV; (b) to ensure maximum dose (D_{max}) of optic nerves, optic chiasm, and brainstem to be less than 50 Gy, eyes to less than 40 Gy, and lenses to less than 10 Gy and the mean dose (D_{mean}) of parotid glands to less than 25 Gy; and (c) to reduce doses of OARs as much as possible without compromising coverage of PTV.

VMAT plan and each of noncoplanar IMRT (7-, 11-, and 15-beam) plans were evaluated by heterogeneity index (HI) and conformity index (CI) of the PTV, D_{max}, and D_{mean} of the OARs, treatment delivery time, and monitor units (MUs). The HI of PTV was defined as D5% to D95%/D_{mean}, where D5% and D95% are the minimum doses delivered 5% and 95% of the PTV, respectively. The CI of PTV was defined as VTV/VPTV, where VTV is the treatment volume enclosed by the prescribed 60-Gy isodose surface and VPTV is the volume of the PTV. The HI and CI of VMAT plan were better than each of 7-, 11-, 15-beam noncoplanar IMRT plans (mean HI, 0.07 vs 0.10 vs 0.09 and 0.10, $P = .004$, $P = .012$, and $P = .005$; mean CI, 1.05 vs 1.13 vs 1.10 and 1.10, $P = .002$, $P = .008$, and $P = .016$). In OAR-sparing effects, VMAT and each of noncoplanar IMRT (7-, 11-, and 15-beam) plans showed equivalent sparing effects for bilateral optic nerves, optic chiasm, brainstem, and bilateral parotid glands. For the eyes and lenses, VMAT achieved equivalent or better sparing effects when compared with each of

noncoplanar IMRT plans. For bilateral lacrimal glands, which did not apply constraint during planning, each of the noncoplanar IMRT plans showed better D_{max} and D_{mean} than VMAT. VMAT showed lower MUs and reduced treatment delivery time when compared with noncoplanar IMRT plans. The authors concluded that in the patients with nasal cavity or paranasal sinus cancer, VMAT provided better homogeneity and conformity for PTV than each of 7-, 11-, and 15-beam noncoplanar IMRT plans while achieving equal or better OAR-sparing effects and using fewer MUs and lower treatment delivery times.

PT and intensity-modulated proton therapy (IMPT)[51] may offer additional advantages over IMRT in terms of further reducing the dose to normal tissues while achieving equivalent doses to the target volume. The CTV_1 consists of the primary tumor bed with 1.0- to 1.5-cm margin of normal tissue. The CTV_2 encompasses the operative bed, including the bony orbit after orbital exenteration and the ethmoid, frontal, or sphenoid sinuses if explored during surgery. A third CTV may be delineated to encompass the tract of cranial nerve V2 to the foramen rotundum if perineural invasion is present. A CTV for high-risk areas (CTV_{HR}; see Table 48.3) may also be outlined to cover, for example, gross macroscopic residual tumor or positive margins to which a higher dose may be delivered.

Radiation Therapy Dose Prescriptions

For primary RT using IMRT, VMAT, or IMPT, the prescription doses are 66 to 70 Gy to the gross tumor volume (the prechemotherapy volume for those receiving systemic treatment), plus a 1- to 1.5-cm margin of normal-appearing tissue (CTV_1), 59 to 63 Gy to other secondary CTVs such as the rest of the involved sinus and wider region around the primary target, and 54 to 57 Gy to the tracts of nerves (if perineural invasion is present) and to elective nodal regions. An example of an IMRT plan for primary definitive RT of a T4N0 SCC is shown in Figure 48.5.

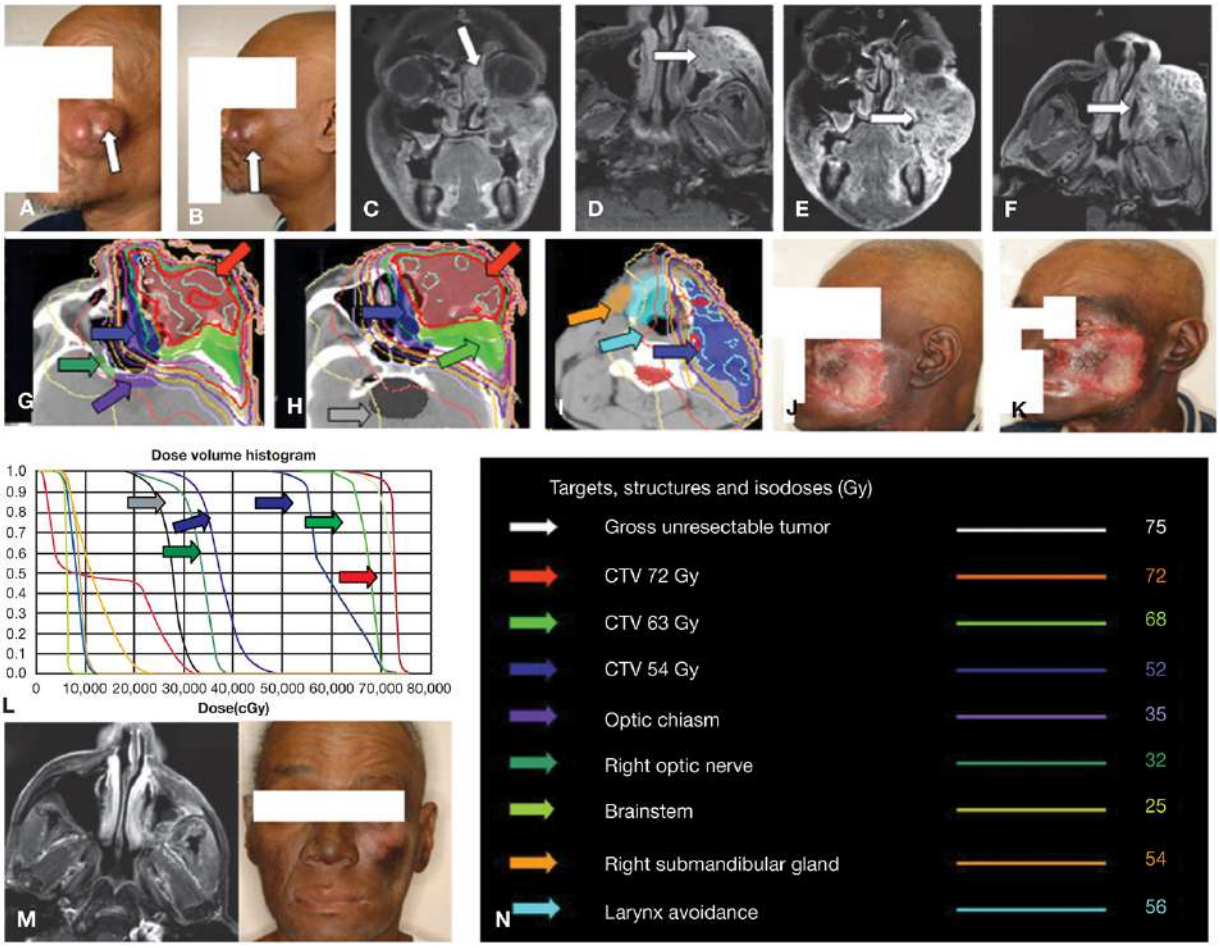

FIGURE 48.5 Intensity-modulated radiotherapy (IMRT) for definitive radiotherapy for T4N0 squamous cell carcinoma of the maxillary sinus. A and B. Pretreatment photographs showing the skin of cheek involvement. C and D. Magnetic resonance imaging (MRI) scans with tumor indicated by *white arrow*. E and F. MRIs following induction chemotherapy showed progressive disease involving the left maxilla, left nasoethmoid region, extending inferiorly into the premaxillary soft tissues. G-I. IMRT plan with sections showing coverage of the target volumes. The patient was treated using concomitant boost fractionation. The primary plan delivered 57 Gy and a concomitant boost plan administered an additional 15 Gy. G and H also show avoidance of the normal tissues, as listed in the key and illustrated further in the cumulative dose-volume histogram in (L). J and K. The skin reaction during the final week of radiotherapy. M and N. MRI and patient photo at follow-up, showing healed skin with hyperpigmentation. The tumor was in complete remission at the last visit 7 months after therapy. CTV, clinical target volume.

For postoperative RT using a 3D conformal technique, the initial target volume consists of the operative bed with 1- to 2-cm margins. The boost field consists of the primary tumor bed and areas at higher risk of recurrence, such as positive resection margins or perineural invasion.

Radiation is administered to the neck after node dissection if multiple nodes are involved or extracapsular extension is present. Elective radiation of ipsilateral submandibular and subdigastric nodes is given for patients with SCC or poorly differentiated carcinoma. An example of an intensity-modulated proton plan for postoperative RT is shown in Figure 48.6.

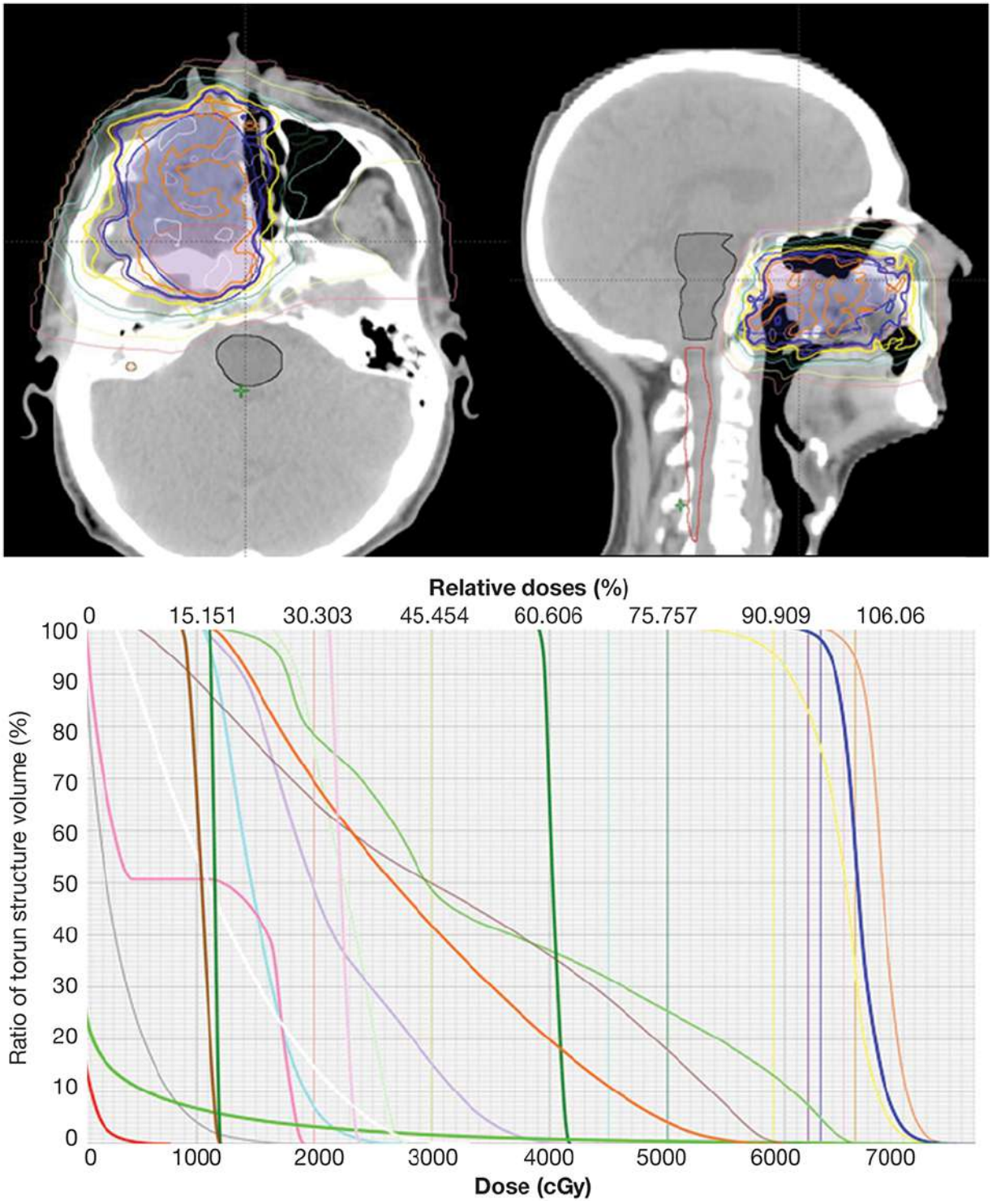

FIGURE 48.6 Proton therapy for recurrent adenoid cystic carcinoma (ACC) of the right hard palate. The patient had a palatectomy with radial forearm free flap reconstruction followed by postoperative external beam radiation therapy with intensity-modulated radiation therapy to 60 Gy in 30 fractions. One year later, the ACC recurred with enhancement in right V1 and V2, involvement of the right cavernous sinus, and an enhancing mass in the infratemporal fossa and pterygopalatine fossa. Salvage surgery involved a right total maxillectomy with

orbital preservation, pterygomaxillary space dissection and resection, and an extracranial dissection of Vidian nerve and cranial nerve 5, V2. With evidence of skull base and cavernous sinus involvement after surgery, he was treated with postoperative chemoradiation with intensity-modulated proton therapy (IMPT) and cisplatin to a dose of 66 Gy (RBE) in 33 fractions. No evidence of disease was present at 6 months after salvage therapy. The figure represents the axial, sagittal, and dose-volume histogram (DVH) of the IMPT plan. (DVH for the IMPT plan, from *left* to *right* on the graph: *red*, spinal cord; *green*, whole brain; *black*, brainstem; *pink*, left parotid; *white*, left eye; *brown*, right cochlea; *dark green*, left lens; *sky blue*, right parotid; *brown*, oral cavity; *violet*, optic chiasm; *red*, right eye; *green*, mandible; *light green*, left optic nerve; *soft pink*, right lens; *dark green*, right optic nerve; *yellow*, clinical target volume [CTV] or CTV_3; *blue*, CTV_2; *orange*, CTV_1.)

Setup and Field Arrangement

Patients undergoing treatment of paranasal tumors are immobilized in a supine position with the head slightly hyperextended to bring the floor of the orbit parallel to the axis of the anterior field. An intraoral stent is used to open the mouth and depress the tongue out of the radiation field. After palatectomy, the stent can be designed to hold a water-filled balloon to obliterate the large air cavity in the surgical defect to improve dose homogeneity. An orbital exenteration defect can also be filled directly with a water-filled balloon to decrease the dose delivered to the temporal lobe. Marking of the lateral canthi, oral commissures, external auditory canals, and external scars facilitates target volume delineation. The planning CT scan should include the entire head to allow the use of vertex beams. The principles of target delineation and plan evaluation for IMRT of maxillary sinus cancer are the same as those described for nasal cavity and ethmoid tumors.

For 3D conformal radiation, a three-field technique consisting of anterior and right and left lateral fields is used for tumors involving the suprastructure or extending to the roof of the nasal cavity and ethmoid cells. The lateral fields may have a 5° posterior tilt and 60° wedges. The relative loading varies from 1:0.15:0.15 to 1:0.07:0.07 depending on the tumor location and photon energy. For the initial target volume, the superior border of the anterior portal is above the crista galli to encompass the ethmoids and, in the absence of orbital invasion, at the lower edge of the cornea to cover the orbital floor. The inferior border is 1 cm below the floor of the sinus, and the medial border is 1 to 2 cm (or more if necessary) across the midline to cover contralateral ethmoidal extension. The lateral

border is 1 cm beyond the apex of the sinus or falling off the skin. The superior border of the lateral portals follows the floor of the anterior cranial fossa, the anterior border is behind the lateral bony canthus parallel to the slope of the face, the posterior border covers the pterygoid plates, and the inferior border corresponds to that of the anterior portal. The boost volume encompasses the tumor bed while sparing the optic pathway.

Anterior and ipsilateral wedge-pair (usually 45° wedges) photon fields are used for tumors of the infrastructure with no extension into the orbit or ethmoids. If necessary, the lateral portal can have a 5° inferior tilt to avoid beam divergence into the contralateral eye. Lateral-opposed photon fields are preferred for tumors of the infrastructure spreading across the midline through the hard palate. If necessary, the fields can be slightly angled (5° inferior tilt from the ipsilateral side and 5° superior tilt from the contralateral side) to avoid irradiating the contralateral eye. The use of a half beam with the isocenter placed at the level of the orbital floor and the upper half of the fields shielded further reduces exposure of the eyes by beam divergence.

The eyes and the optic pathway are of particular concern. With 3D conformal/IMRT/VMAT/IMPT techniques, the cornea can generally be shielded or a planned avoidance structure (to avoid keratitis) in patients with limited involvement of the medial or inferior orbital wall. If the tumor invades the orbital cavity without necessitating orbital exenteration, care should be taken to avoid irradiating the lacrimal gland to prevent xerophthalmia. It is important to keep the dose to the contralateral optic nerve as well as the optic chiasm below 54 Gy in 27 fractions to prevent bilateral blindness.

Treatment of the Neck

For squamous and undifferentiated carcinoma, elective neck irradiation is recommended. Ipsilateral upper neck treatment can be delivered using a lateral appositional electron field (usually 12 MeV). With conventional radiation techniques, careful matching is required to prevent hot or cold spots. The superior border of the field slopes up from the horizontal ramus of the mandible anteriorly to match the inferior border of the primary portal posteriorly, leaving a small triangle over the cheek untreated. The anterior

border is just behind the oral commissure, the posterior border is at the mastoid process, and the inferior border is at the thyroid notch (above the arytenoids). The nodal volume can also be covered by using IMRT with sparing of the parotid gland. Alternatively, the primary tumor bed and the upper neck can be treated with IMRT with the isocenter above the arytenoids and matched to a separate unmodulated lower neck field. This allows the laryngeal structures to be spared by using a larynx block.

If the maxillary sinus is being treated with conventional non-IMRT techniques, the central axes of the primary (sinus) fields and the opposed lateral upper neck fields all are placed in the plane of the inferior border of the maxillary fields (ie, usually 1 cm below the floor of the maxillary sinus). An independent collimator jaw is used to shield the caudal half of the maxillary fields and the cephalad half of the neck field. The junction between the primary and the neck fields can be moved during the course of treatment to reduce dose heterogeneity in this region. Portals are reduced after 42 Gy, and treatment to the posterior neck continues with abutting electron fields to the desired dose. The middle and lower neck are irradiated with an anterior appositional photon field matched to the inferior border of the opposed-lateral upper neck fields.

Dose Fractionation Schedule

Table 48.3 summarizes the dose regimens for IMRT/IMPT. With 3D conformal techniques, the dose for postoperative RT at 2 Gy per fraction is 50 Gy for elective nodal treatment, 56 Gy to the operative bed, 60 Gy to the tumor bed if resection margins are negative, and 66 Gy if margins are positive. For primary RT, the total dose to the primary tumor at 2 Gy per fraction is 66 to 70 Gy. The contralateral optic nerve and chiasm are excluded from the field after a dose of 50 to 54 Gy. When the tumor invades structures adjacent to the optic chiasm, a dose of up to 60 Gy to the chiasm may be acceptable because of the higher probability of control and the relatively low risk of visual impairment,[37] after clear discussion with the patient.

FOLLOW-UP AND RECURRENCES

Salvage is possible for some persistent or recurrent lesions. In particular, recurrent cancers of the nasal vestibule remain curable with salvage surgery after primary radiation or occasionally with salvage radiation after primary surgery. Regional recurrences can be treated successfully with neck dissection with or without postoperative radiation depending on the pathologic features. Treatment options are limited for tumors that recur after combined modality therapy, although a few highly selected patients may qualify for reirradiation with curative intent. Cumulative doses of radiation to neural tissues (spinal cord, brainstem, brain, optic structures) are the main limitation to reirradiation.

Most oncologists recommend a second baseline physical examination together with CT, MRI, or positron emission tomography with CT for patients with nasal cavity or paranasal sinus tumors at 3 months after treatment. Common practice is to repeat clinical examination and imaging when indicated every 4 months for the first 3 years after treatment, every 6 months for the fourth and fifth years after treatment, and annually thereafter. In addition to monitoring possible tumor recurrence, these follow-up visits are critical for identifying and managing side effects of treatment.

RESULTS OF TREATMENT

The results of treatment have improved from the 1960s through the 1990s, with OS rates increasing progressively from 33% ± 18% in the 1960s to 42% ± 15% in the 1970s, 54% ± 15% in the 1980s, and 56% ± 13% in the 1990s ($P < .001$).[52] In a systematic review of published series spanning 40 years, Dulguerov et al[53] demonstrated progressive improvements in outcome for all treatment modalities (surgery, surgery with radiation, and radiation). However, a more recent review of the experience at the University of California, San Francisco, showed no significant differences in 5-year OS rates or local control rates by a decade of treatment (1960s-2000s; OS, 46%-56%; local control 55%-62%) or by radiation technique (conventional, 3D conformal, or IMRT; OS 47%-57%; local control 59%-65%). However, the incidence of severe (grade 3 or 4) side effects declined significantly over time from 50% in the 1960s to 16% in the 2000s.[54]

For patients with SNUC, multimodality approach to treatment is necessary to achieve optimal disease-specific survival (DSS) and OS (Figure 48.7). IC response is used as a guide for treatment optimization at the UT MD Anderson Cancer Center. For patients with PR or CR to IC, 5-year DSS was 81% with chemoradiation therapy and 54% after surgery and postoperative radiation or chemoradiation. For patients not achieving a PR with IC, 5-year DSS was 39% in patients treated with surgery plus radiation or chemoradiation and 0% in patients treated with chemoradiation alone.[39]

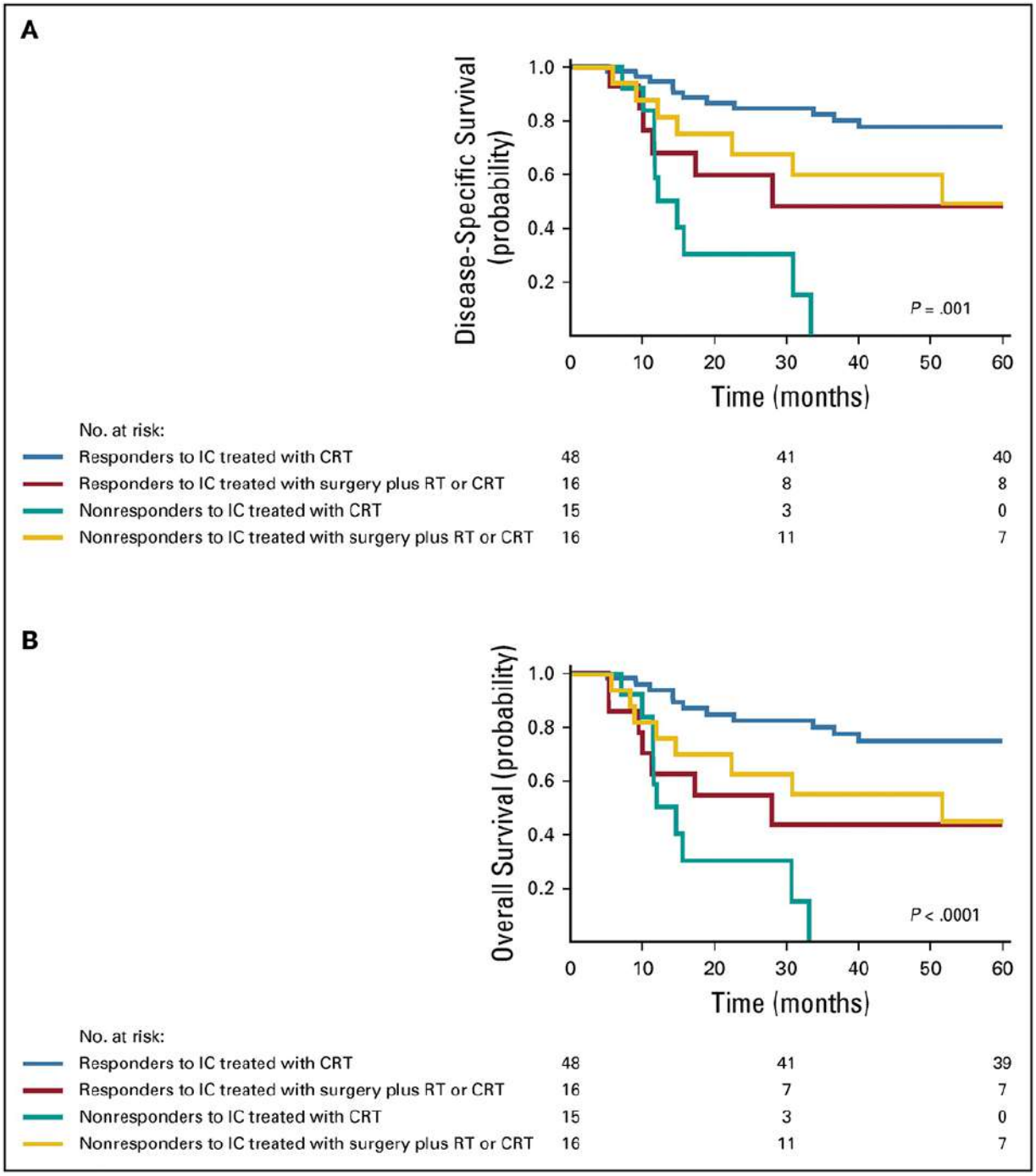

FIGURE 48.7 Survival outcomes according to definitive locoregional treatment by response to induction chemotherapy (IC). Disease-specific (A) and overall (B) survival in patients who responded to IC and were treated subsequently with concurrent chemoradiation therapy (CRT; blue) or surgery followed by radiotherapy (RT) or concurrent CRT (red), and in patients who did not respond to IC and were treated subsequently with concurrent CRT (green) and surgery followed by RT or concurrent CRT (orange). (Reprinted with permission from Amit M, Abdelmeguid AS, Watcherporn T, et al. Induction chemotherapy response as a guide for treatment optimization in sinonasal undifferentiated carcinoma. *J Clin Oncol*. 2019;37[6]:504-512. Copyright © 2019 by American Society of Clinical Oncology.)

Tumors of the Nasal Cavity

Nasal Vestibule Tumors

Findings from several retrospective studies of RT for nasal vestibule tumors suggest that either brachytherapy or external beam RT can produce cure rates of up to 90% for small (<2 cm) lesions (Table 48.4).[2,3,17,18,55-64] For 2- to 4-cm lesions, external beam radiation can control 70% to 80% of tumors. Although nodal spread of disease is relatively rare for lesions smaller than 2 cm, up to 40% of patients with larger primary tumors have metastases to the cervical nodes at presentation. With the use of appropriate radiation techniques and fractionation schedules, severe and late complications after RT are uncommon (see Table 48.4).

TABLE 48.4 LOCAL AND REGIONAL CONTROL RATES OF NASAL VESTIBULE CARCINOMAS TREATED BY DEFINITIVE RADIOTHERAPY

Series	Patients	Local Control	Regional Control	Comments/Complications
MD Anderson 1967-1984[56]	32	BT: 11/11 controlled	Small lesions, no ENI: 11/11	Osteonecrosis, epistaxis: 1 patient each
		EB: 20/21 (95%) controlled	Large lesions, no ENI: 5/9 (56%)	
			Large lesions, ENI: 12/12 (100%)	
Princess Margaret Hospital 1958-1983[18]	54	<2 cm (*n* = 34): 97% ≥2 cm (*n* = 16) + size not reported (*n* = 6): 57%	No ENI: 51/54 (94%)	Osteonecrosis, 2 patients; nasal stenosis, 2 patients; massive epistaxis, 1 patient
Daniel den Hoed Cancer Center, Rotterdam 1968-1978[58]	32	EB, <1.5 cm, 72% (5 y); >1.5 cm, 50% (5 y)	Data not available	External beam radiotherapy hypofractionated (2.5-3 Gy/fraction)
		Dose <54 Gy, 37%; >54 Gy,		

Series	Patients	Local Control	Regional Control	Comments/Complications
		82%		
VU University, Amsterdam[45]	56	Overall at 2 y: 79% (ultimate at 5 y after salvage, 95%) <1.5 cm (*n* = 32): 83% (ultimate, 94%) ≥1.5 cm (*n* = 24): 74% (ultimate, 96%)	Routine ENI to the mustache region 2-y control rate: 87% (6/7 neck relapses were salvaged) 5-y ultimate control rate: 97%	Rhinorrhea: 45%; nasal dryness 39%; epistaxis 15%; adhesions 4% Skin necrosis: 3 patients (all in IDR BT group) Sarcoma in the nasal vestibule: 1 patient
University of Florida 1970-1995[61]	564	Overall at 5 y: 87% EB: 60/71 (86%) Surgery and EB: 8/8 (100%) (ultimate LC: 94%)	T1-T2: 39/43 (91%) T4: 30/36 (83%) N0 LC: 87% (ultimate, 97%) N0/no ENI: 47/54 (87%) (ultimate neck control, 97%)	Soft tissue necrosis: 15 patients Severe complications: 3 patients
Queens Medical Centre, Nottingham, UK[57]	23	EB only: 8/13 Surgery only: 8/10	Not reported	Radionecrosis: 1 patient
DAHANCA, Denmark[55]	174	5-y locoregional control: 67% T1: 79% T2: 54% T3: 35%	No ENI: 89%	Not reported
Queensland Radium Institute, Australia[61]	28	Surgery and EB: 4/6 (66%) EB: 13/22 (59%)	Surgery and EB: 57% EB: 86%	Septal necrosis, 2 patients; nasobuccoalveolar fistula and fistula, 1 patient each

Series	Patients	Local Control	Regional Control	Comments/Complications
French Groupe Europeen de Curietherapie[2]	1676	Skin of the nose and nasal vestibule carcinoma treated by BT or EB (ortho- or megavoltage) Overall LC = 93% (FU ≥2 y); <2 cm, 96%; 2-3.9 cm, 88%; ≥4 cm, 81% LC of nose skin: 94% LC of vestibule: 75% LC for previously untreated tumors: 95% vs 88% for recurrent tumors		
Daniel den Hoed Cancer Center, Rotterdam[59]	64	Local relapse-free survival: 92% at 5 y T1: 89% T2: 100%		Not reported

BT, brachytherapy; EB, external beam; ENI, elective nodal irradiation; FU, follow-up; IDR, intermediate-dose rate; LC, local control; RT, radiotherapy.

An analysis by the Groupe Europeen de Curietherapie of 1,676 carcinomas of the skin of the nose and nasal vestibule treated by brachytherapy or external beam irradiation revealed an overall local control rate of 93%.[3] Local control depended on tumor size (<2 cm, 96%; 2-3.9 cm, 88%; ≥4 cm, 81%), tumor site (external surface, 94%; vestibule, 75%), and status (new, 95%; recurrent, 88%). Local control was independent of histology for tumors <4 cm, but for those >4 cm, basal cell carcinomas

were more often controlled than were SCCs. Complications were rare (necrosis, 2%). The local control rate with surgery was approximately 90%.

Nasal Fossa Tumors

Documentation of treatment outcomes for nasal fossa tumors, like nasal vestibule tumors, comes mostly from retrospective studies.[19,65,66] Results are best for lesions confined to the nasal septum, which are generally small and well controlled with primary RT. Locoregional control rates range from 60% to 85%, and the rate of isolated regional recurrence for patients who did not receive elective nodal irradiation is approximately 5%. The most common complications after RT are soft tissue necrosis, visual impairment, and nasal stenosis, seen in 5% to 11% of patients (Table 48.5).[19,63-65] Ang et al[19] at MD Anderson Cancer Center reported better primary disease control and survival rates for patients with tumors located in the septum (86%) versus patients with tumors on the lateral wall or floor of the nasal fossa (68%). In that study, no patients with nasal septum carcinomas who underwent elective nodal irradiation had nodal relapses, whereas two of eight patients who did not undergo nodal irradiation experienced recurrence in the ipsilateral subdigastric nodes. Distant metastasis was more common among patients with lateral wall and floor disease, and ultimately, survival rates were best among patients with nasal septum tumors. However, other groups[65] found no differences in results for tumors at various sites within the nasal cavity. Results of the treatment for early-stage tumors are excellent after either RT or surgery.

TABLE 48.5 TREATMENT OUTCOMES FOR NASAL FOSSA TUMORS

Series	Patients	Treatments	Survival Rates at 5 Y	Late Complications
MD Anderson 1969-1985[19]	45	RT alone: 18 patients RT+ surgery: 2 patients Surgery + RT: 25 patients Median time to relapse: 9 mo	Overall: 75% Disease specific: 83%	Radiation-induced blindness: 2 patients Surgical blindness: 2 patients Maxilla necrosis: 3 patients Nasal stenosis: 2 patients

Series	Patients	Treatments	Survival Rates at 5 Y	Late Complications
				Septal perforation: 1 patient Severe dental decay: 1 patient
Roswell Memorial Park Institute 1942-1964[63]	57	RT alone: 30 patients Surgery alone: 13 patients Surgery + RT: 14 patients	Crude overall: 56% Disease free: 56%	Not reported
University of Puerto Rico 1976[64]	40	RT alone: 34 patients Surgery alone: 6 patients	Overall: 56%	Not reported
Mallinckrodt Institute of Radiology 1969-1984[65]	56	RT alone: 28 patients RT + surgery: 18 patients Surgery + RT: 10 patients	Overall: 52%	Soft tissue necrosis: 2 patients Cataract: 1 patient Nasal synechiae: 1 patient Severe otitis media: 2 patients Hemorrhage (fatal): 2 patients Optic neuropathy: 1 patient Brain necrosis: 1 patient

RT, radiation therapy.

An analysis of 783 patients with nasal cavity cancer included in the SEER database from 1988 through 1998[66] revealed SCC to be the most common tumor type (49.3%), followed by ENB (13.2%). More than half of the cases presented with a small primary tumor (T1), and only 5% had positive nodes at diagnosis. Overall mean survival time was 57 months, and the 5-year survival rate was 40.3%. On multivariate analysis, male sex, increasing age, T status, N status, and poorer tumor grade all adversely affected survival ($P < .05$). RT, given to 50.5% of patients, also independently predicted poorer survival ($P = .03$), probably because those patients had had poor prognostic features, such as perineural invasion,

positive margins, or poor performance status (medically unfit for surgery).[66] Five-year survival rates also correlated with the extent of tumor dedifferentiation, being 75.3%, 61.9%, 47.6%, and 36.8% for well-, moderately, poorly, and undifferentiated cancers, respectively.

Esthesioneuroblastoma

Either surgery or primary RT as single-modality therapy can produce locoregional control rates exceeding 90% for tumors that are confined to the nasal cavity (Kadish stage A).[9] Single-modality therapy has also been used for lesions involving the nasal cavity and one or more paranasal sinuses (stage B), as has surgery followed by adjuvant RT. However, the optimal therapy for stage B lesions is not clear because of the heterogeneity of these tumors. Disease that extends beyond the nasal cavity and paranasal sinuses (stage C) seems to be best treated with a combination of surgery and radiation, and the role of chemotherapy, if any, is being investigated. Elective nodal irradiation is not generally recommended because the incidence of nodal relapse is less than 15%. Distant metastasis is uncommon (10%) even among patients presenting with locally advanced disease. Among 783 nasal cavity cancers identified from the SEER database, 103 (13.2%) were ENBs; the median survival time for patients with these tumors was 88 months, and the overall 5-year survival rate was 63.6%.[66] Tables 48.6[67-72] and 48.7[10] summarize the results of treatment. The prognosis for patients with stage A disease is excellent. Overall, 30% of patients with stage B tumors died of the disease. About 60% of patients with stage C tumors died of the disease, primarily because of failure to control the primary tumor. As noted earlier, distant metastasis is uncommon (10%) even in locoregionally advanced disease.

TABLE 48.6 OVERALL TREATMENT RESULTS OF ESTHESIONEUROBLASTOMA

Series	Patients	Local Control	Regional Control and Survival	Comments/Complications
MD Anderson 1982-2002[67]	31	5 y: 96.2%	5 y: 91.3% 5-y OS: 93.1% DM: 0%	

Series	Patients	Local Control	Regional Control and Survival	Comments/Complications
UCLA 1970-1990[68]	26	Overall: 18/26 (69%) S alone: 1/7 (14%) RT alone: 2/5 (40%) S + RT: 10/12 (83%)	4/26 (15%) patients had nodal disease (at presentation or after initial therapy) 5-y CSS: 74% 5-y RFS: 58%	Postoperative cerebrospinal fluid leak, epiphora, radiation retinopathy (3/17 patients)
Mayo Clinic 1951-1990[69]	49	5 y: 65% (all patients) S alone: 73% S + RT: 86%	3/49 (6%) had N1 at presentation and 8/46 (17%) had regional relapse (7/8 with concurrent local failure) 5-y DFS and OS: 55% and 69% (all patients)	Osteonecrosis of trephine bone plate (4 patients)
U Virginia 1959-1991[70]	40	Overall: 30/40 (75%) controlled	4/40 (10%) clinically N1 at presentation and 4/36 (11%) developed regional relapse 5-y OS: 78%	—
U Virginia Health System, 1976-2004 treated with a standardized protocol[71]	50	17 patients (34%) developed recurrent disease, which was locoregional in 12 patients	5-y DFS: 86.5% Possibility for surgical salvage	—

Series	Patients	Local Control	Regional Control and Survival	Comments/Complications
Hospital do Cancer Instituto Nacional de Cancer, Rio de Janeiro, Brazil 1983-2000[72]	36	S + RT, 18; RT only, 14; S only, 1 RT; and chemotherapy, 2	5- and 10-y DFS: 46% and 24% 5- and 10-y OS: 55% and 46% N+ and DM adversely affected prognosis (P < .001 and P = .01, respectively)	Kadish classification best predicted disease-free survival

CSS, cause-specific survival; DFS, disease-free survival; DM, distant metastases; OS, overall survival; RFS, relapse-free survival; RT, radiation therapy; S, surgery.

[a]Kadish A or B received preoperative RT followed by craniofacial resection; Kadish stage C disease was treated with preoperative chemotherapy and RT followed by a craniofacial resection.

TABLE 48.7 PATTERN OF FAILURE AND RESULTS OF SALVAGE TREATMENT OF ESTHESIONEUROBLASTOMA BY STAGE AND TREATMENT

Kadish Stage	Therapy	Local Control	Nodal Relapse	Salvage by Subsequent RT or S	Distant Metastasis	Died of Disease
A (n = 24)	RT	3/5	1/5	3/3	0/5	0/5
	S	5/9	1/9	4/4	0/9	0/9
	S + RT	9/10	2/10	2/2	1/10	1/10
	All	17/24 (71%)	4/24 (17%)	9/9	1/24 (4%)	1/24 (4%)
B (n = 33)	RT	6/7	2/7	0/1	0/7	3/7
	S	3/6	0/6	1/2	0/6	2/6
	S + RT	15/20	1/20	3/4	3/20	5/20
	All	24/33 (73%)	3/33 (9%)	4/7	3/33 (9%)	10/33 (30%)

Kadish Stage	Therapy	Local Control	Nodal Relapse	Salvage by Subsequent RT or S	Distant Metastasis	Died of Disease
C (*n* = 21)	RT	2/5	2/7	0/0	1/5	4/5
	S	1/1	0/6	0/0	0/1	0/1
	S + RT	9/15	1/20	1/1	1/15	8/15
	All	12/21 (57%)	3/33 (9%)	1/1	2/21 (10%)	12/21 (57%)

RT, radiotherapy; S, surgery.
Data from Elkon D, Hightower SI, Lim ML, Cantrell RW, Constable WC. Esthesioneuroblastoma. *Cancer*. 1979;44(3):1087-1094.

Spaulding et al[29] reported results for 25 patients treated at the University of Virginia Medical Center from 1959 through 1986 who were followed for 2 years after therapy. Treatment approaches had gradually evolved during that period, with progressive introduction of craniofacial resections, complex field megavoltage radiation, and, for stage C disease, the addition of chemotherapy. Therefore, patients were assigned to two groups, based on treatment era, for comparative analysis. Although this series is relatively small, it revealed two interesting findings on this rare disease: First, that extensive craniofacial resection does not seem to confer a major advantage over wide local excision for patients with stage B lesions, and second, that the addition of chemotherapy to craniofacial resection and RT for patients with stage C tumors may yield higher DSS rates.

A larger series of 72 patients with sinonasal neuroendocrine tumors treated at MD Anderson Cancer Center between 1982 and 2002[67] included a spectrum of histologies: ENB (31 patients), SNUC (16 patients), neuroendocrine carcinoma (18 patients), and small cell carcinoma (7 patients). The OS rates at 5 years were 93.1% for patients with ENB, 62.5% for those with SNUC, 64.2% for neuroendocrine carcinoma, and 28.6% for small cell carcinoma (P = .0029; log-rank test). The local control rates at 5 years also were superior for patients with ENB (96.2%) compared with patients who had SNUC (78.6%), neuroendocrine carcinoma (72.6%), or small cell carcinoma (66.7%) (P = .04). The corresponding regional failure rates at 5 years were 8.7% for patients with ENB, 15.6% for SNUC, 12.9%

for neuroendocrine carcinoma, and 44.4% for small cell carcinoma, and distant metastasis rates were 0% for ENB, 25.4% for SNUC, 14.1% for neuroendocrine carcinoma, and 75.0% for small cell carcinoma. Moreover, local therapy alone produced excellent local and distant control rates for ENB. Among eight patients treated for ENB since 2000 with surgery and adjuvant IMRT to 60 Gy (one with stage B disease and seven with stage C [five of whom had intracranial extension]), there were no local recurrences, and one nodal recurrence was salvaged surgically. All eight patients were alive with no evidence of disease at the last follow-up. Institutional experience outcomes from several institutions are reported in Table 48.6.[67-72]

Ozsahin et al[24] described the results of treatment in 13 European and North American centers for 77 patients with olfactory neuroblastomas, 11 with Kadish stage A, 29 with stage B, and 37 with stage C; 56 patients had surgery, 44 with total tumor excision. All but 5 patients received RT (50% with 3D CRT) and 21 had chemotherapy. With a median follow-up of 72 months, locoregional tumor control was 62%, disease-free survival 57%, and OS 64%. Patients having total tumor resection or receiving greater than 54 Gy had better OS than those treated with lower doses. Six of the patients treated with RT (56-70 Gy) developed grade 3 or 4 late complications (five osteonecrosis and one retinopathy).

Madani et al[73] published a report on 84 patients (73 with primary and 11 with local recurrent sinonasal tumors), 9 of which were ENB, treated with IMRT (median dose of 70 Gy in 35 fractions). Mean D50 to the optic chiasm was 37.2 Gy, to ipsilateral optic nerve 49.4 Gy, to contralateral optic nerve 47.1 Gy, and to the retina 37.7 and 28.4 Gy.

Multimodality management has been correlated with improved outcomes.[74]

Modesto et al[75] described their experience in 43 patients with ENB, two groups, one of 26 and the other of 17 patients treated at separate institutions. Five patients had stage A at diagnosis (confined to the nasal cavity), 13 stage B (tumor extending into the paranasal sinuses), 16 stage C (beyond the paranasal sinuses), and 9 stage D (cervical lymph node involvement) according to the modified Kadish classification. Neoadjuvant platinum-based chemotherapy was administered to 24 patients, leading to a 70.8% response rate (6 CR and 11 PR). A total of 31 (72%) patients were treated by surgery; 39 (90.6%) underwent RT. Among them, 11 (28.2%)

patients were treated using IMRT. Median dose was 64 Gy (range 30-70 Gy). Twelve patients (28%) received bilateral cervical lymph node irradiation (LNI) (median dose 57 Gy, range 50-66 Gy). Twelve patients (21%) received platinum-based CRT. After a median follow-up of 77 months, the 5-year OS was 65% and the 5-year progression-free survival was 58%.Twelve patients (28%) developed locoregional relapse. The major prognostic factor was the modified Kadish stage with 3-year survival rates of 100% for Kadish A to B versus 48% for stage C and 22% for stage D. After adjustment for tumor stage, neither neoadjuvant chemotherapy nor LNI seemed predictive for locoregional tumor control or survival. Protons have been used sparingly in the treatment of some of these patients. Nakamura et al[76] reported on 42 patients with ENB treated with PT and 26% receiving chemotherapy. With a median follow-up time of 69 months, the 5-year OS and progression-free survival were 100% and 80% for Kadish A, 86% and 65% for Kadish B, and 76% and 39% for Kadish C, respectively. Dagan et al[77] reported on 84 adult patients without metastases receiving primary (13%) or adjuvant (87%) treatment with PT for sinonasal cancers, of which 23%[20] were olfactory neuroblastomas. Advanced stage (T3 in 25% and T4 in 69%) and high-grade histology (51%) were common. Surgical procedures included endoscopic resection alone (45%), endoscopic resection with craniotomy (12%), or open resection (30%). Gross residual disease was present in 26% of patients. Most patients received hyperfractionated PT (1.2-Gy RBE twice daily, 99%) and chemotherapy (75%). The median PT dose was 73.8 Gy (RBE), with 85% of patients receiving more than 70 Gy. The median follow-up was 2.4 years for all patients and 2.7 years for living patients. Local tumor control (LC), neck control, freedom from distant metastasis, disease- free survival, cause-specific survival, and OS rates were 83%, 94%, 73%, 63%, 70%, and 68%, respectively, at 3 years. The 3-year LC rate was 61% for primary RT and 59% for patients with gross disease. Late toxicity occurred in 24% of patients (with grade 3 or higher unilateral vision loss in 2%). Akimoto et al[78] reported on 339 patients with non–squamous cell cancer in the head and neck, of which 63 were olfactory neuroblastomas, treated with protons. The median follow-up was 64 months. OS, progression-free survival, and local control rate of all patients at 5 years were 61.2%, 36.8%, and 71.2%, respectively, and OS and local control rate were 86.2% and 79.0% in

olfactory neuroblastomas. Among all patients, 254 (75%) were not suited for photon RT because doses to OARs exceeded tolerance dose in the evaluation of dose-volume histogram. However, OS at 5 years of these patients was 65.5%. Regarding treatment morbidity, 34 (10%) patients developed grade 3 or 4 late toxicities, such as brain injuries and neuropathy. None experienced grade 5 toxicities.

Tumors of the Paranasal Sinuses

Five-year outcomes from studies reported since 1998 continue to illustrate that local control after treatment of paranasal sinus tumors remains problematic[79-86] (Table 48.8). For patients with carcinoma of the maxillary sinuses, the combination of surgery and radiation yields 5-year local control and survival rates ranging from 44% to 80%. These rates are better than those achieved with either surgery or RT alone. For RT alone, the 5-year local control rates range from 22% to 39%, and the 5-year OS rates from 22% to 40%. Findings from a large multicenter retrospective analysis of 418 patients with ethmoid sinus adenocarcinoma indicated that the size of the lesion (T4), the extent of nodal involvement (N+), and the presence of brain extension were the most significant prognostic factors for OS.[87] Although the authors concluded that surgery followed by postoperative RT remains the treatment of choice, they did note that 51% of the patients developed recurrences, 74% of which were local.

TABLE 48.8 OUTCOME OF PATIENTS WITH LOCALLY ADVANCED CANCER OF THE PARANASAL SINUSES TREATED WITH COMBINED SURGERY AND RADIATION THERAPY

Study (Reference)	Year	Patients	5-Y Survival (%)	Local Recurrence (%)	Distant Metastasis (%)
A. Results from Surgery and Conventional Radiation Therapy					
Lavertu et al[79]	1989	54	38	52	–
Spiro et al[80]	1989	105	38	49	15
Zaharia et al[81]	1989	149	36	43	–
Paulino et al[50]	1998	48	47	46	17

Study (Reference)	Year	Patients	5-Y Survival (%)	Local Recurrence (%)	Distant Metastasis (%)
Le et al[82]	1999	97	34	54	34
Myers et al[83]	2002	141	52	56	33
Jiang et al[31]	1991	67[a]	53[b]	24	27
Katz et al[84]	2002	31		21	
Blanco et al[85]	2004	106	27	42	29
Dirix et al[46]	2007	127	54	47	20
Bristol et al[86]	2007	90 G1 (1969-1991) 56 G2 (>1991-2002)			
B. Results from Surgery and Intensity-Modulated Radiation Therapy					
Duthoy et al[88]	2005	39	2-y OS: 68 4-y OS: 59	2-y: 27 4-y: 32	–
Ahamad et al (unpublished)[c]	2005	53	Crude: 88.6	Crude: 15.12-y: 204-y: 25	20.7
Daly et al[66]	2007	36	45	2-y: 38	
Hoppe et al[89]	2008	37	80	2-y: 25	
Madani et al[73]	2009	84	58.5	41.5	18
Dirix et al[46]	2010	40	89	2-y: 24	
C. Side Effects of Combined Surgery and Radiation Therapy in Patients with Paranasal Sinus Cancer					
Vestibulocochlear			Vestibular dysfunction, persistent otitis, tinnitus, hearing impairment		
Ophthalmologic (lacrimal gland, eyes, lens, optic nerves, and chiasm)			Retinopathy, xerophthalmia, keratopathy, cataracts, visual impairment		
Neurologic (brain, brainstem, spinal cord, temporal lobe)			Neurocognitive impairment, cranial neuropathy, myelopathy, brain necrosis		
Endocrine (pituitary gland, hypothalamus, thyroid gland if neck is irradiated)			Multiple endocrine dysfunction: hyperprolactinemia, syndromes associated		

Study (Reference)	Year	Patients	5-Y Survival (%)	Local Recurrence (%)	Distant Metastasis (%)
			with decreased GH, FSH, LH, T4, TSH, ACTH, and their downstream hormones		
Oral (major salivary glands, oral mucosa, mandible, and temporomandibular joint)			Xerostomia, dental caries, dysgeusia, mandible exposure, necrosis, and trismus		
Connective tissue complications (oral cavity, soft palate musculature, pharynx, larynx, skin and subcutaneous tissues, skull bones)			Soft tissue necrosis, skin changes, persistent lymphedema, subcutaneous fibrosis, cartilage necrosis, nasal dryness, choanal stenosis, swallowing and voice dysfunction, bone necrosis		

ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; OS, overall survival; TSH, thyroid-stimulating hormone.

[a]Patients with node-negative disease.

[b]Five-year relapse-free survival.

[c]Patients treated at MD Anderson Cancer Center with intensity-modulated radiation therapy.

A 1991 review of outcomes after treatment of 73 patients with maxillary sinus carcinomas at MD Anderson Cancer Center reported 5-year local and regional control rates according to pathologic T category as follows: for T1 and T2 tumors, 91% local and 71% regional control; for T3, 77% local and 80% regional; and for T4, 65% local and 93% regional.[31] Five-year regional control rates according to N category were 84% for N0 disease and 82% for N1 or N2 disease. The most common histologic subtypes were SCC (48%) and adenoid cystic carcinoma (27%); 5-year local and regional control rates were 62% (local) and 86% (regional) for squamous cell tumors and 82% (local) and 94% (regional) for adenoid tumors. Perineural invasion and nodal disease at presentation were poor prognostic factors. An update of this report published in 2007[79] showed that increasing the radiation portals to cover the skull base for patients with perineural invasion reduced the risk of local recurrence and that adding elective nodal irradiation for patients with squamous or undifferentiated tumors improved the rates of nodal control, distant metastasis, and recurrence-free survival.

The extent of neuroendocrine differentiation of sinonasal carcinomas also influences the patterns of failure. In one study, the 5-year actuarial rates of local, regional, and distant failure according to tumor histology were as

follows: ENB 4% local failure, 9% regional failure, and 0% distant failure; neuroendocrine carcinoma 27% local, 13% regional, and 12% distant; SNUC 21% local, 16% regional, and 25% distant; and small cell carcinoma 33% local failure, 44% regional failure, and 75% distant failure.[67]

IMRT has emerged as the standard of care for tumors of the paranasal sinuses with low toxicity and high local control rates.[47,73,88-91] Madani et al[73] reported the largest series to date, in which 105 patients (most of whom [56%] had ethmoid sinus tumors) were treated with IMRT. At a median follow-up time of 40 months, the 5-year actuarial local control and OS rates were 70.7% and 58.5%, respectively. In multivariate analysis, invasion of the cribriform plate was found to predict worse local control ($P < .001$) and lower OS ($P < .001$).

The role of PT using passive scattering and IMPT in the management of sinonasal malignancies is rapidly evolving and may be preferred to IMRT when dose-limiting structures may be compromised with definitive doses.[51] Resto et al[92] reported on 102 patients with various histologies receiving surgery and postoperative PT. With a median follow-up of 61 months, the 5-year local control and OS were 95% and 90% for complete resection, 82% and 53% for partial resection, and 87% and 49% for biopsy only, respectively. Toxicity was not reported. Russo et al[93] reported on 54 patients with SCC treated with PT of which 69% had surgery and 39% had chemotherapy. The 5-year local regional control rate and OS were 73% and 47%, respectively. Wound site complications (eg, fistulas) occurred most commonly with nine grade 3 and six grade 4 complications. Zenda et al[94] reported on 90 patients with various histologies of which 18% had surgery and 12% had chemotherapy. With a median follow-up of 57 months, the 5-year OS and progression- free survival rates were 64% and 44%, respectively. Linton et al[95] reported on 26 patients with adenoid cystic carcinoma of which 77% had surgery and 23% were treated with protons alone. The 2-year local control and OS were 95% and 93%, respectively. There were 17 (19%) late grade 3 and 6 (7%) late grade 4 toxicities including two patients with encephalomyelitis infection and four patients with an optic nerve disorder. Takagi et al[96] reported on 40 patients treated with definitive PT alone for adenoid cystic carcinoma tumors, and with a median follow-up of 38 months, the 5-year local control, progression-free survival, and OS were 76%, 30%, and 63%, respectively. There were 36

grade 3 or higher events in 21 (26%) patients. High-grade toxicities included osteoradionecrosis, vision loss, and nasopharyngeal ulcers, resulting in three grade 5 toxicities.

Dagan et al[97] described their experience in 84 patients treated with PT involving sinonasal sites: nasal/ethmoid (67), maxillary (15), and frontal or sphenoid (2). Histologies included SCC (22), adenoid cystic carcinoma (14), olfactory neuroblastoma (23), adenocarcinoma (8), SNUC (7), neuroendocrine carcinoma (4), mucoepidermoid carcinoma (3), and other histologies (3). Thirty-eight patients had intracranial tumors, and 31 had orbital invasion. Eleven patients were treated after biopsy alone, nine after subtotal resection, and two for recurrence after gross total resection. Twenty-two (26%) had gross tumor at the time of PT. Median PT dose was 73.8 CGE (range, 56.8-74.4 CGE) at 1.2 CGE/fraction twice daily with elective nodal therapy. Sixty-six (78%) of patients were treated to the neck electively. Sixty-three patients (75%) received chemotherapy (mostly concurrent low-dose weekly cisplatin). The median follow-up was 2.4 years (range, 0.4-6.7 years) for all patients and 2.7 years for living patients (range, 0.6-6.7 years). Three-year local control and nodal control rates were 83% and 94%, respectively. Freedom from distant mets was 73.2%, cause-specific survival was 70%, and OS was 68%. Grade 3 to 5 toxicities occurred in 24% of patients, with one fatal central nervous system necrosis.

Truong et al[98] described their experience with 20 patients with primary sphenoid malignancy who received proton beam to a median dose of 76 CGE with a median follow-up of 27 months. The 2-year local control, regional control, and freedom from distant metastasis rates were 86%, 86%, and 50%, respectively.

Patel et al[99] performed a meta-analysis summarizing the retrospective data of various histologies and performed comparative effective analysis between charged particle and photon therapy. The median follow-up time was approximately 40 months for both groups, and the pooled OS (relative risk 1.51, 95% confidence interval 1.14-1.99; P = .0003) and disease-free survival (1.93, 95% confidence interval 1.36-2.75, P = .0003) was higher at 5 years for charged particle than for photon therapy.

Future Directions in Radiation Therapy

IMRT has improved the cancer care in external beam RT for sinonasal malignancies.[47,80-83] Proton beam therapy confers further benefits for nasal and paranasal sinus tumors, and investigators at MD Anderson Cancer Center and others have demonstrated the clinical feasibility of IMPT for this purpose (Figure 48.6).[100] The additional advantages of this technique over photon-based IMRT are its ability to limit the low-dose radiation received by adjacent critical OAR structures and allow escalation of dose to the target volume. Well-designed clinical trials in cooperative group setting will be necessary to provide the evidence required for the widespread adoption of PT over IMRT for these rare malignancies. Finally, further improvements in the local control of sinonasal malignancies will require incorporating systemic agents as neoadjuvant or concurrent therapy. Again, the rarity of sinonasal cancer will most likely require international cooperative group trials to facilitate timely analyses of outcomes and design of future trials.

SEQUELAE OF TREATMENT

Soft Tissue and Bone

The formation of nasal cavity synechiae (fibrous mucosal bands causing airway stenosis) can be prevented by intermittent dilation of the nasal passages with a petroleum-coated cotton swab until mucositis has resolved. Dry mucous membranes can be managed symptomatically with saline nasal spray. Soft tissue or cartilage necrosis is uncommon after therapy, at an estimated incidence of 5% to 10%.[27,70]

Eyes and Optic Pathway

Chronic keratitis and iritis (dry eye syndrome) can develop after RT if tumor extension to the orbital cavity mandates irradiation of the lacrimal gland to doses of more than 30 to 40 Gy.[101,102] Without lacrimal irradiation, fewer than 20% of patients treated with up to 55 Gy to the cornea develop chronic corneal injury. The risk of cataract formation at 5 years is approximately 5% after doses of up to 10 Gy to the lenses using conventional fractionation; this risk increases to 50% at 5 years after 18 Gy.

Radiation retinopathy generally occurs within 18 months to 5 years after treatment.[103] It is rare after doses of less than 45 Gy, but the incidence increases to about 50% after doses of 45 to 55 Gy.[101,102] Optic neuropathy tends to develop between 2 and 4 years after RT, but it has been reported as late as 14 years after treatment. The reported incidence of optic neuropathy is less than 5% after 50 to 60 Gy but increases to around 30% for doses of 61 to 78 Gy. Factors that influence the risk of radiation-induced optic neuropathy were reported in 2006 for 273 patients treated between 1964 and 2000 in whom the radiation fields included the optic nerves or chiasm.[104] The likelihood of developing optic neuropathy was primarily influenced by the total dose, but fraction size was marginally significant. The 5-year rates of freedom from optic neuropathy were 95% for doses 63 Gy or fewer treated once daily, 98% for doses 63 Gy or fewer treated twice daily, 78% for doses greater than 63 Gy treated once daily, and 91% for doses greater than 63 Gy treated twice daily. On multivariate analysis, the risk of optic neuropathy was found to correlate with increasing total dose (P = .0047) and possibly with increasing patient age (P = .091), once-daily versus twice-daily fractionation (P = .068), and overall treatment time (P = .097). When the target volumes include the optic pathway, special attention must be paid to hot spots and dose per fraction to avoid optic neuropathies.

Optimizing the technique for paranasal sinus tumors is crucial so that the radiation dose to the optic apparatus is limited to the greatest extent possible to minimize the risk of complications. Investigators at the University of Florida, reviewing 464 patients treated from 1964 through 2001,[105] reported a 20% incidence of ipsilateral radiation retinopathy at 5 and 10 years after conventional or 3D RT. In that study, patients were deemed functionally blind when visual acuity dropped to 20/100 on the Snellen chart, and neovascularization (rubeosis iridis or neovascular glaucoma) was coincident with radiation retinopathy. The use of IMRT has been shown to limit the doses of the optic apparatus without compromising local control. Indeed, Chen et al[54] reported findings for 127 patients treated between 1960 and 2005 with a variety of RT techniques that had evolved over that period, namely, conventional, 3D conformal, and IMRT. They concluded that the incidence of severe (grade $\geq$ 3) complications depended on the radiation treatment technique used: 54% for conventional therapy, 22% for 3D conformal therapy, and 13% for IMRT. Specifically, the

incidence of grade 3 or 4 late ocular toxicity decreased from 20% with conventional techniques to 0% with IMRT, whereas grade 3 or 4 late auditory toxicity decreased from 15% with conventional to 4% with IMRT ($P < .001$).[54] Moreover, to date, no radiation-induced blindness has been reported among the collective experience, with 308 patients treated with IMRT as either definitive or postoperative therapy for nasal and paranasal malignancies.[47,54,65,73,88,90,91,106]

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* Deceased.

CHAPTER 49

Salivary Glands

Neil Panjwani, Pattana Wangaryattawanich, Brittany Barber, Lauren Shih, Christina P. Rodriguez, and Upendra Parvathaneni

The salivary glands consist of the three large, paired major glands—parotid, submandibular, and sublingual (Figure 49.1)—and many smaller, minor glands located throughout the upper aerodigestive tract. Salivary gland malignancies are rare and make up only approximately 0.4% of all cancers and account for less than 5% of the annual incidence of head and neck malignancies in the United States. The international variation in the incidence is between 0.4 and 2.6 in 100,000 per year, with a mean of approximately 1.2 in 100,000.[1] In the United States, the incidence of major salivary gland cancer increased from 1977 till 2009 from 1.0 to 1.6 in 100,000, mainly seen for the smaller tumors due to raised awareness and improved detection with modern imaging techniques.[2]

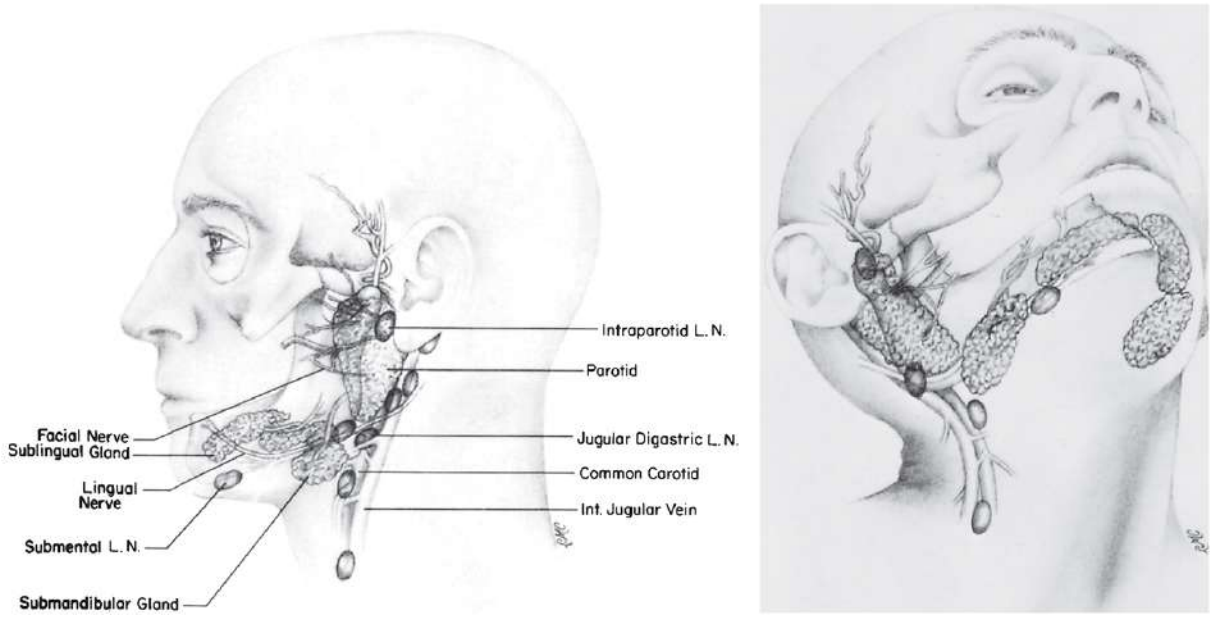

FIGURE 49.1 Anatomy of salivary glands.

ANATOMY

Major Salivary Glands

Parotid Gland

The parotid gland can be divided into two lobes—a superficial or lateral lobe and a deep lobe – by the plane of the facial nerve (VII) running through the gland. The main trunk of the VII exits the stylomastoid foramen, giving off branches to the posterior belly of the digastric muscle, then branches within the parenchyma of the gland. Typically, it divides into an upper temporofacial division and a lower cervicofacial division at the pes anserinus, located approximately 1 to 2 cm from the stylomastoid foramen. The upper division further branches into main temporal, zygomatic, and buccal branches, and the lower division divides into marginal mandibular and cervical branches. VII enters the deep surface of the gland as a single trunk, passing posterolateral to the styloid process in the retromandibular region and anastomoses with the auriculotemporal (ATN) branch of the trigeminal nerve's mandibular division (V3). It usually leaves the gland as five or more branches, emerging at the anterior, upper, and lower borders of the gland. VII runs superficial to the main blood vessels that traverse the gland but is interwoven within the glandular tissue and its ducts with the main lower trunk running between the superficial and deep lobe in the retromandibular location, an identifiable landmark on a contrast computed tomography (CT) scan. Thus, removal of all or part of the parotid gland demands meticulous dissection, if the nerve is to be spared. Notorious variation in branching patterns and cross-innervation exists within the gland, and as such, identification of the nerve during surgery is paramount to both minimizing morbidity and noting gross nerve invasion, which may alter the extent of resection thereafter.[3]

The parotid gland does not have a well-defined capsule, and its edges can be amorphous on imaging (especially CT scan), necessitating the use of established anatomic landmarks for radiotherapy (RT) planning. It is located superficial to and partly behind the ramus of the mandible, with the accessory glands covering the masseter muscle along the parotid duct and the lower zygomatic and upper buccal branches of VII. Superficially, it overlaps the posterior part of the muscle and largely fills the space between the ramus of the mandible and the anterior border of the

sternocleidomastoid muscle. One or more isthmi that wrap around the branches of VII connect the superficial and deep lobes of the gland.

The parotid gland contains an extensive lymphatic capillary plexus, many aggregates of lymphocytic cells, and numerous intraglandular lymph nodes in the superficial lobe (Figure 49.2). Lymphatics drain from more lateral areas on the face, and forehead, including parts of the eyelids, diagonally downward and posterior toward the parotid gland, as do the lymphatics from the anterior frontotemporal region of the scalp. Associated with the gland, both superficially and more deeply, are parotid lymph nodes. These drain downward along the retromandibular vein to empty in part into the superficial lymphatics and nodes along the lateral surface of the sternocleidomastoid muscle and in part into upper level 2 nodes of the deep cervical chain. Skin lesions of the face and scalp drain to the superficial parotid lymph nodes and are hence potentially amenable to treatment with electrons. Rarely, nasopharynx cancers that present with a heavy nodal burden have been known to involve the deep parotid nodes. Lymphatics from the anterior parietal region of the scalp drain partly to the superficial parotid nodes in front of the ear (preauricular nodes) and partly to the superficial nodes behind the ear (retroauricular nodes from the posterior scalp), which, in turn, drain into the upper deep cervical nodes.[4]

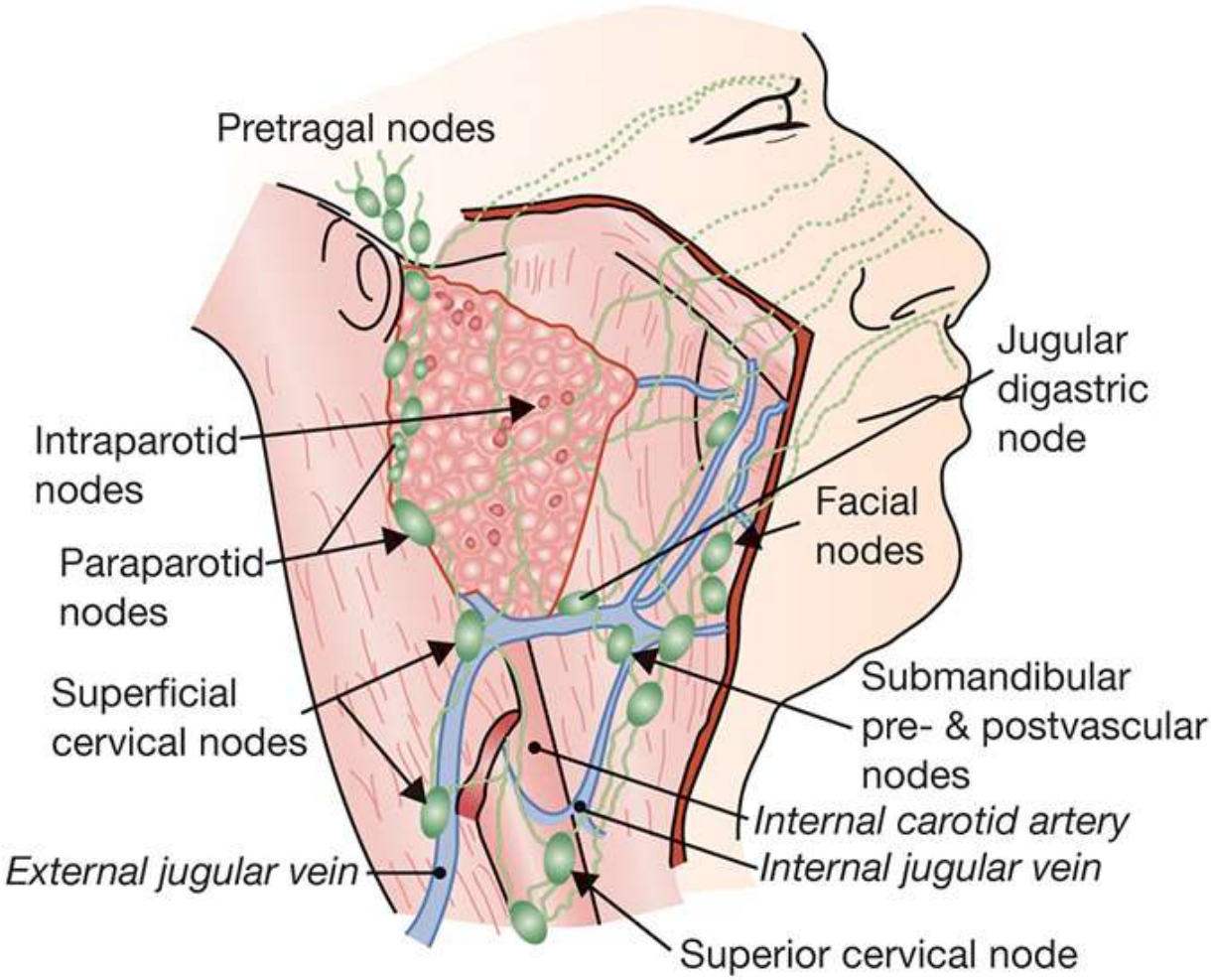

FIGURE 49.2 Lymph node distribution in and around the parotid gland.

Submandibular Gland

The submandibular gland (SMG) is well encapsulated and largely fills the triangle between the two bellies of the digastric and the lower border of the mandible and extends upward deep to the mandible. The SMG has a larger superficial part, or body, and a smaller deep process. The superficial component lies on the lower surface of the mylohyoid and deep process behind the muscle against the lateral surface of the extrinsic muscle of the tongue, the hyoglossus. The superficial part is adjacent and medial to the level 1B (submandibular) lymph nodes. The deep process of the SMG lies between the lingual nerve above and the hypoglossal nerve below.[5] Bimanual palpation with one finger in the floor of the mouth and one under

the edge of the mandible facilitates clinical detection of masses in this gland.

Unlike the parotid gland, there are no lymph nodes within the SMG itself. In other words, there will not be a cancer spread to the SMG from a draining primary site, for example, from the oral cavity or anterior nasal cavity, rather, nodal spread from primary sites is to the level 1B lymph nodes that lie adjacent to the SMG in close proximity. Hence, sparing of the SMG is possible, while treating 1B lymph nodes to elective doses (45-54 Gy) with highly conformal techniques such as proton therapy that has minimal exit dose beyond the Bragg peak. A cancer of the SMG has to originate from the gland itself, or be the result of direct infiltration (not via lymphatic spread) from an abutting structure, for example, the floor of the mouth or tongue. From the lateral and superior portions of the gland, lymph flows to the prevascular or preglandular submandibular lymph nodes. The posterior portion of the gland gives rise to one or two lymphatic trunks, which follow the facial artery and go directly to the anterior subdigastric nodes of the internal jugular chain.[6] The level 1B nodes overlying the SMG, followed by the subdigastric and high midjugular level 2 lymph nodes, are those involved in nodal metastases from a primary malignancy of the SMG. This gland is closely associated with the cranial nerve (CN) XII, marginal mandibular nerve branch of VII, and lingual nerve (V3). A dissection of this gland and level 1B lymph nodes usually leaves the patient with a (temporary) paresis of the marginal mandibular nerve with a lip droop and a functional consequence of dribbling while consuming liquids.

Sublingual Gland

This smallest of the three major salivary glands, along with many minor salivary glands, lies between the mucous membrane of the floor of the mouth above and the mylohyoid muscle below, the mandible laterally, and the genioglossus muscles of the tongue medially. This is a rare site for malignant neoplasms; they are difficult to distinguish from cancer of the floor of the mouth accounting for fewer than 2% of all reported cases of salivary gland tumors.[1,7] The sublingual gland drains either to the 1B lymph nodes or more posterior into the deep internal jugular chain level 2 nodes between the digastric and omohyoid muscles. Rarely, the lymphatics of the

sublingual gland drain into a submental (level 1A) node or supraomohyoid level 3 jugular node.

Minor Salivary Glands

Minor salivary glands are widely distributed in the upper aerodigestive tract, palate, buccal mucosa, base of tongue, pharynx, larynx, trachea, lip, gingiva, floor of mouth, paranasal sinuses, nasal cavity, and nasopharynx.

EPIDEMIOLOGY

Seventy percent of all salivary tumors arise in the parotid gland, 8% in the SMG, and 22% in the minor salivary glands.[7] The proportion of malignant tumors increases from parotid gland (25%) to SMG (43%) to minor salivary glands (65%).[7,8] There is a preponderance of benign tumors in women; malignant tumors exhibit an equal sex distribution.[1] Patients with benign tumors are younger (mean age, 46 years) compared with those with malignant tumors (mean age, 54 years), with a trend to an older age for SMG and minor salivary gland locations.[7] Two to three percent of salivary neoplasms occur in children, in whom half of the tumors are malignant.[9] Two-thirds of the cancers are located in the major salivary glands (parotid gland 53%, SMG 12%, sublingual 1.5%), and one-third in the minor salivary glands, predominantly in the oral cavity.[1] The tumors in children are mostly less advanced, and a 95% 5-year survival is reached.[9]

Etiologic factors are not clearly defined. Nutrition may be a factor because Eskimos in the Arctic, who have a low intake of vitamins A and C, have a high incidence. Cigarette smoking and alcohol consumption are in general not related to salivary gland cancers,[10] except Warthin tumors. In a study by de Ru et al,[11] patients with a Warthin tumor had a smoking history of 97%; their mean age at the time of operation was 11 years higher compared to the pleomorphic adenoma group. Irradiation can also be a cause, as evidenced by the increased incidence of survivors of the atomic bombs dropped on Hiroshima and Nagasaki.[12] Saku et al[12] studied salivary gland tumors in atomic bomb survivors of Hiroshima and Nagasaki. Two-thirds of all cases were parotid, and the remainder was equally distributed between SMG and minor salivary glands. Mucoepidermoid cancer (MEC) and Warthin tumor (benign) were particularly elevated compared with

nonexposed persons and disproportionately high at high radiation doses. The incidence of subsequent salivary gland cancer after radiation in childhood is increased compared to the general population.[13] There is a dose-response relationship with an excess relative risk of 0.27 to 0.36 per Gy.[14] The majority of these tumors are MECs[13]; however, less than 1% of salivary gland tumors may be caused by former irradiation.[15]

Workers in various occupations experience an increased risk of salivary gland cancer.[16] For women employed as hairdressers or working in beauty shops, a significantly elevated risk was observed in a study by Swanson and Burns.[17]

Women with salivary gland cancer may have a 2.5 elevated breast cancer risk.[18] After treatment for salivary gland cancer, an increased risk for subsequent cancer of the oral cavity (hazard ratio [HR] 3.5), thyroid (HR 2.7), lung and kidney cancer (HR 1.7), and second salivary gland cancer (HR 10), especially after acinic cell cancer (HR 31), is seen. For adenoid cystic cancer (ADCC), the risk of developing nasopharyngeal is increased with a factor of 17.[19]

NATURAL HISTORY

Local invasion is the initial route of the spread of malignant tumors of the salivary glands, depending on the location and histologic type. For parotid tumors, this may result in fixation to structures in around 20% of cases.[20] Skin invasion is more often seen in parotid tumors (8%-10%), compared with submandibular tumors (3%).[21,22]

Approximately 18% to 25% of patients with a malignant parotid salivary gland tumor present with facial palsy from nerve invasion, often misdiagnosed over the years as idiosyncratic Bell palsy.[7,20,22,23] Perineural tumor spread (PNTS) is well recognized with ADCC, salivary duct carcinoma (SDC), high-grade MEC, and squamous and undifferentiated cancers. Regional nodal spread and distant metastases are common among the higher grade malignancies.

A detailed study of the Dutch Head and Neck Oncology Group (NWHHT) concerning patients with a salivary gland malignancy found an overall incidence of clinically positive nodes of 14% and clinically occult, pathologically positive nodes in an additional 11% of patients.[21] This

percentage depends on the number of neck dissections performed, the tumor location, histology, and T-stage. The number of elective neck dissections performed varies between the tumor locations. Stennert et al[24] performed a neck dissection in all malignant *parotid* tumors and found 53% unilateral positive nodes and 0% contralateral nodes. In selected patients in other studies, the percentage of positive nodes varied between 20%[25] and 38%.[26] In the large National Cancer Database study of 22,653 parotid cases, positive nodes were found in 24% and occult nodes in 10%.[27] Three out of four involved lymph nodes in early parotid malignancies (21% occult nodes) were localized in the intraparotid nodes by Stenner et al.[28] Resection of *submandibular* tumors is combined with a (partial) neck dissection in most cases. Pathologic neck nodes may be seen in up to 42% of cases.[26] The risk of positive lymph nodes in *minor salivary gland* cancer depends on four prognostic factors: male gender, T3-T4, pharyngeal site, and histology (high-grade MEC and high-grade adenocarcinoma). Based on these factors, a scoring system from 0 to 4 was developed by Lloyd et al.[29] The risk of positive nodes in minor salivary gland cancer is less than 10% for scores 0 to 1, 17% for score 2, 41% for score 3, and 70% for score 4. Salivary gland tumors arising in the oral cavity produce an incidence of cervical node metastases of less than 10%.[8,26,30] In nasopharyngeal salivary gland tumors, a risk of around 20% has been shown.[31] In general, the risk of positive findings in the neck including *all salivary gland malignancies* may be based on a combination of T-stage, tumor localization, and histology. An example of a rating scale to estimate the risk of positive neck nodes, based on the tumor location, T-stage, and histologic type, is shown in Table 49.1. The highest risk is seen for squamous cell carcinoma, undifferentiated cancer, and SDC.[26,32] There is an intermediate risk for MEC and a low risk for acinic cell, ADCC, and carcinoma ex pleomorphic adenoma.[26] A 15% risk is found for T1 tumors, 26% for T2, and 33% for T3-T4.[26]

TABLE 49.1 RISK ESTIMATION (%) FOR POSITIVE NECK NODES

Summation: *T* Score + Histologic Type Score	Parotid Gland	Submandibular Gland	Oral Cavity	Other Locations
2	4	0	4	0
3	12	33	13	29

Summation: *T* Score + Histologic Type Score	Parotid Gland	Submandibular Gland	Oral Cavity	Other Locations
4	25	57	19	56
5	33	60	–	–
6	38	50	–	–

T1 = 1; T2 = 2; T3-T4 = 3; acinic/adenoid cystic/carcinoma ex pleomorphic adenoma = 1; mucoepidermoid = 2; squamous/undifferentiated = 3.

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The overall distant metastases are encountered in 3% to 4% of patients at presentation and in 33% after 10 years.[21,23] They are fairly common with ADCC, SDC, high-grade MEC, and undifferentiated carcinomas; in the case of ADCC, they may occur quite late in the course of the disease, without recurrence of the primary tumor.[21,33,34] Distant metastases are primarily to the lung, bone, and, occasionally, the liver.[21] Reported incidence of distant metastases in patients with ADCC after 10 years of follow-up is around 40%.[21,34,35] Five years after the diagnosis of distant metastases of ADCC and acinic cell cancer, more than one-third of the patients are still alive; 10% are alive after 10 years. An update of the survival data of the NWHHT study after the diagnosis of distant metastases of salivary gland cancer is shown in Figure 49.3.

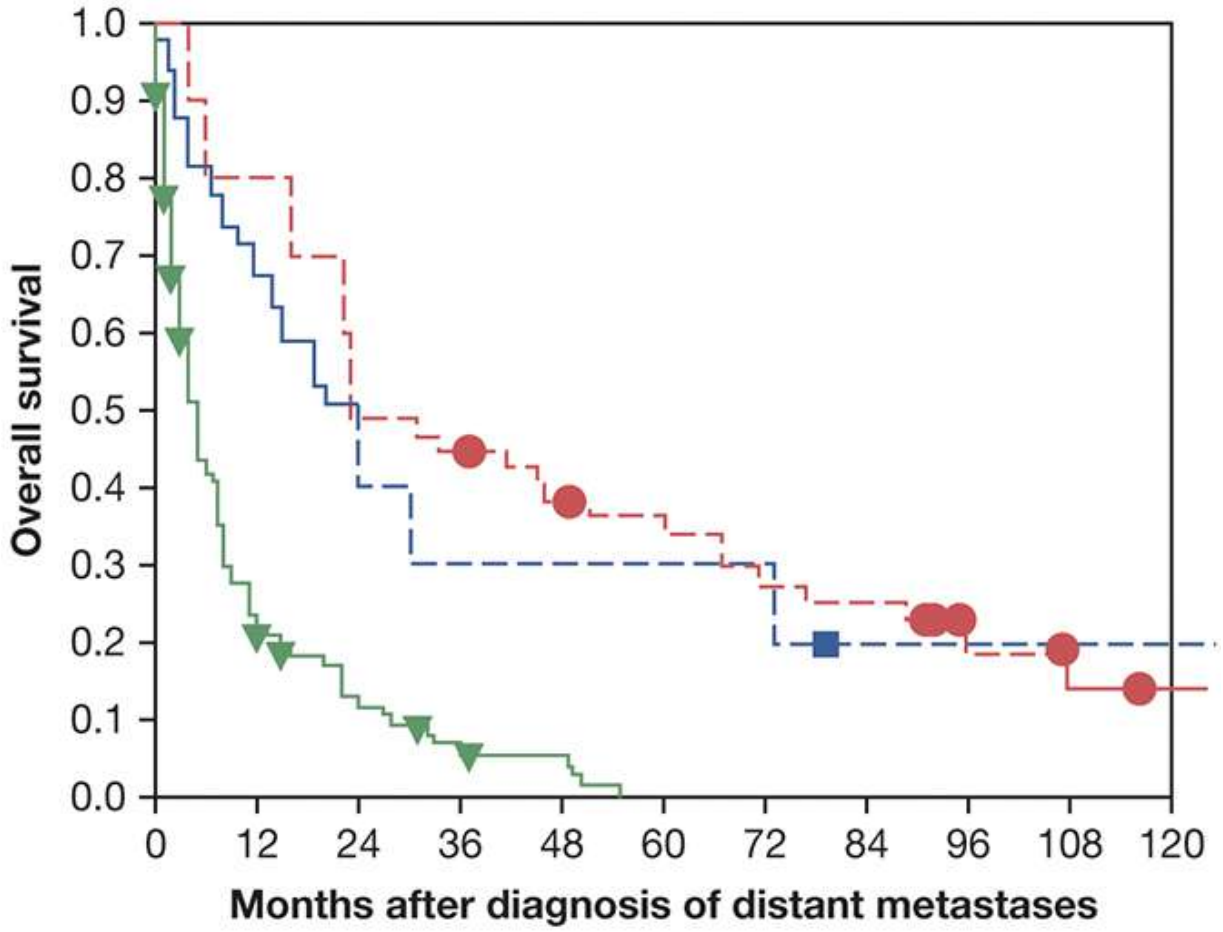


FIGURE 49.3 Survival after diagnosis of distant metastases depending on histology, update of the nationwide Dutch study. (●) adenoid cystic carcinoma[36]; (■) acinic cell carcinoma[12]; and (▲) others[37] ($P < .001$). (From Terhaard CHJ, Lubsen H, Van der Tweel I, et al. Salivary gland carcinoma: independent prognostic factors for locoregional control, distant metastases, and overall survival: results of the Dutch head and neck oncology cooperative group. *Head Neck*. 2004;26[8]:681-693. Copyright © 2004 Wiley Periodicals. Reprinted by permission of John Wiley & Sons.)

CLINICAL PRESENTATION

Clinical presentation of salivary gland malignancies can range dramatically from indolent asymptomatic masses present for several years or rapidly enlarging painful masses, with or without CN palsies, and/or neck lymph nodal masses. Three of four parotid masses are benign.[7] Patients most often have a painless, rapidly enlarging mass, often present for years before a sudden change in its indolent growth pattern prompts the patient to seek medical attention. Duration of clinical symptoms before diagnosis may last more than 10 years.[7,21] For malignant tumors, the median duration of

clinical symptoms generally is shorter (3-6 months)[21,38] compared to that of benign tumors, although, for some minor salivary gland tumors, median periods of 2 years have been reported.[30]

Pain and CN involvement is more frequently associated with malignant disease.[7] Although as many as one-third of parotid cancers may have involvement of VII, only 10% to 20% of patients complain of pain.[7,20,21] Often, these patients are managed unsuccessfully for a Bell palsy for a number of years before a scan is obtained that reveals a parotid malignancy. Pain and/or trismus may appear with the involvement of deeper structures and muscles of mastication (masseter, temporalis, and pterygoid muscles). Depending on the size and location, patients can present with salivary gland obstruction, pain, inflammation, and postprandial swelling, which can lead clinicians to a diagnosis of sialadenitis, rather than malignancy. Sialadenitis can be secondary to obstruction by salivary gland neoplasms, which can delay diagnosis if cross-sectional imaging is not arranged. Thus, clinicians must consider malignancy in any evaluation of salivary gland swelling with pain. A thorough examination of the parotid gland involves palpation of the gland over the face and neck, assessment of the overlying skin, bimanual palpation of the buccal space including Stensen duct, examination of the oropharynx and nasopharynx, and a thorough evaluation of facial nerve function and symmetry. The adjacent parapharyngeal space is divided into a prestyloid (anterolateral) and poststyloid (posteromedial) compartment by a fascial layer extending from the styloid process to the tensor veli palatini. Tumors of the parotid may involve the base of skull and cause intractable pain and paralysis of various CNs, especially VII (facial asymmetry) and ATN (paresthesia in the preauricular region). Deep lobe malignancies can be present as a submucosal mass bulging into the oropharynx, masquerading a tonsillar mass, or into the nasopharynx that obstructs the eustachian tube, causing otalgia and the sensation of a “blocked ear.” CN neuropathies may be present in deep lobe tumors that extend into the poststyloid compartment alongside CN IX, CN X, CN XI, and CN XII. Extension into the infratemporal fossa may cause trismus by invasion of the pterygoid muscles.

SMG and sublingual gland malignancies are present in close proximity to the lingual (V3) and hypoglossal (XII) nerves and thus, depending on the histology, may present with palsy of these nerves. Bimanual palpation of

the SMG should be performed to evaluate the extent of the tumor and invasion of adjacent structures, including the mandible, floor of mouth mucosa, skin, and mylohyoid. Asymptomatic swelling of the floor of the mouth is the primary presentation in sublingual salivary gland cancer, and SMG, with pain and ipsilateral tongue numbness (V3) or tongue asymmetry, deviation and fasciculations (XII), and weakness of the lower lip, suggests marginal mandibular nerve (VII) involvement as symptoms of advanced disease.[39]

The signs and symptoms associated with tumors of the minor salivary glands vary because of their diverse locations. The distribution of presenting sites and risk of malignancy for 380 cases of intraoral minor salivary gland tumors is shown in Table 49.2.[40] A painless lump is the most common presenting symptom. Almost all extraoral minor salivary gland tumors are malignant.[7] Extraoral minor salivary gland tumors are most frequently seen in the nasal cavity (52%), followed by the larynx (18%), the oropharynx (14%) mostly localized in the tongue base, nasopharynx (8%), and ethmoid (8%).[7] For tumors arising in the nasal cavity or sinuses, facial pain is the most common presenting symptom, followed by nasal obstruction. Laryngeal primary tumors most frequently cause hoarseness or voice change.

TABLE 49.2 DISTRIBUTION OF PRESENTING SITES OF INTRAORAL MINOR SALIVARY GLAND TUMORS

Site	Number of Patients (%)	Percentage Malignant
Palate	206 (54)	43
Upper lip	64 (17)	9
Buccal mucosa	54 (14)	37
Retromolar region	20 (5)	95
Lower lip	18 (5)	56
Floor of mouth	13 (3)	69
Tongue	5 (1)	60
Total	380	41

Adapted from Buchner A, Merrell PW, Carpenter WM. Relative frequency of intra-oral minor salivary gland tumors: a study of 380 cases from northern California and comparison to

reports from other parts of the world. *J Oral Pathol Med*. 2007;36(4):207-214. Copyright © 2007 Blackwell Munksgaard. Reprinted by permission of John Wiley & Sons.

Clinical features suggesting a malignant salivary gland tumor are rapid growth rate, pain, PNTS with CN palsies, childhood occurrence, skin involvement, and cervical adenopathy.

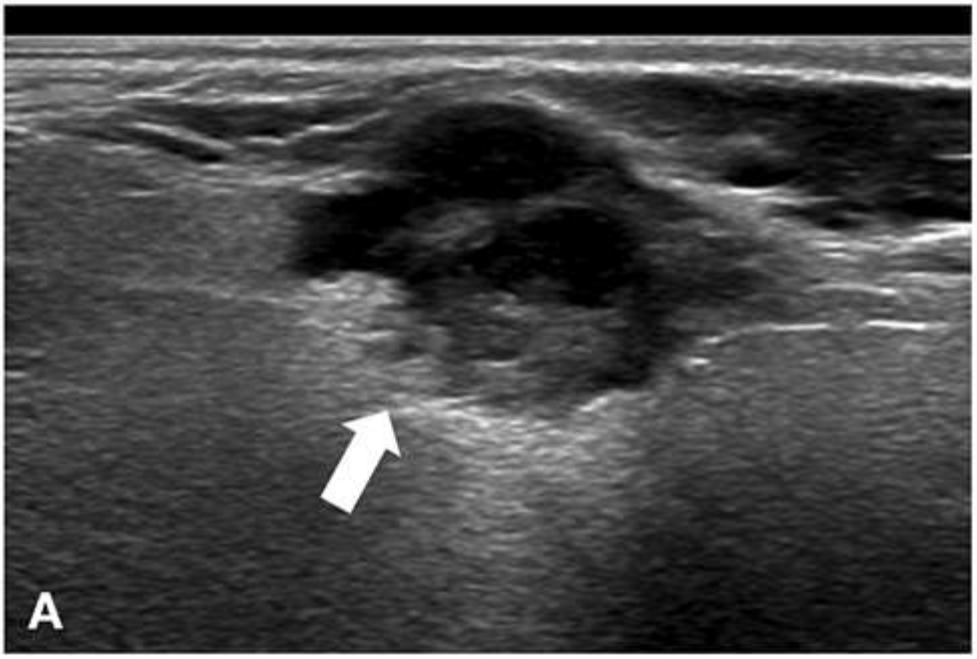
DIAGNOSTIC WORKUP AND STAGING

Major Salivary Glands

The diagnostic workup of major salivary gland tumors includes a careful history and physical examination, with particular attention to signs of local fixation, regional adenopathy, and PNTS.

For superficial lesions of the parotid gland, the SMG, and sublingual gland and evaluation of the cervical lymph nodes, ultrasound (US) is the first diagnostic step, combined with fine-needle aspiration biopsy (FNAB), although one is justified to proceed directly to a resection if there are imaging features consistent with a malignant tumor. Radiologic examination plays a pivotal role in the comprehensive assessment of patients with salivary gland tumors. These imaging modalities provide crucial information regarding tumor localization, extent, number (single vs multiple), and potential regional or distant metastases, aiding in accurate diagnosis and treatment planning.[41] The available imaging techniques include US, CT, magnetic resonance imaging (MRI), and ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography/CT (PET/CT).[42-45] US is commonly employed as the initial imaging tool for evaluating superficial palpable lumps in the head and neck region, including the major salivary glands. Its wide availability, safety, and ease of use make it a preferred choice. In addition, it offers high-resolution imaging of accessible superficial lesions and can be effectively used for imaging-guided tissue biopsies, utilizing either FNAB or core-needle biopsy (Figure 49.4).[42] In US, signs of malignancy are ill-defined borders with heterogeneous architecture, internal necrosis, and cystic changes.[46] Benign salivary tumors are well defined and hypoechoic. However, the effectiveness of US is dependent on the operator, and it has limitations in assessing deeply located or bone-obscured lesions, such as deep parotid lesions or minor salivary

gland tumors. Furthermore, US is not optimal for assessing the full extent of tumors, including bone invasion, PNTS, and regional metastases. In such cases, CT and/or MRI are more appropriate for complete tumor staging.[42,43]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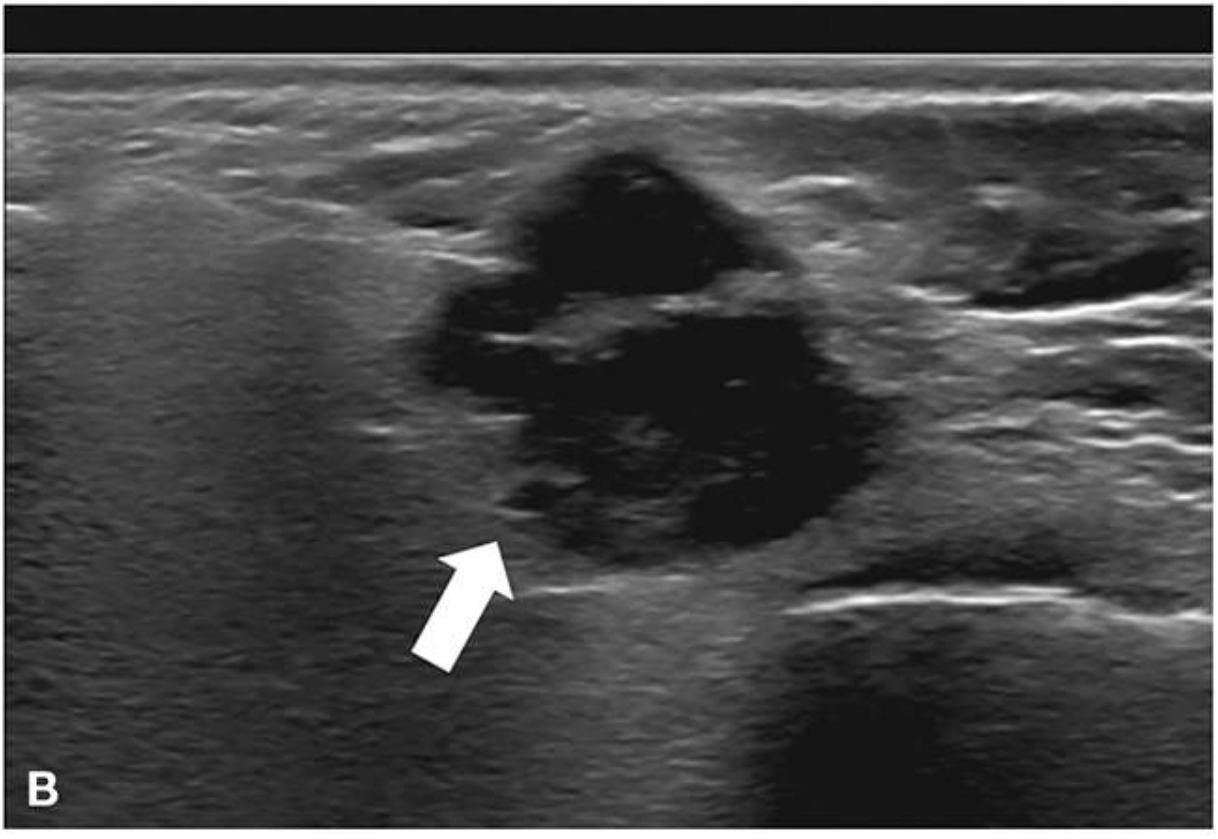
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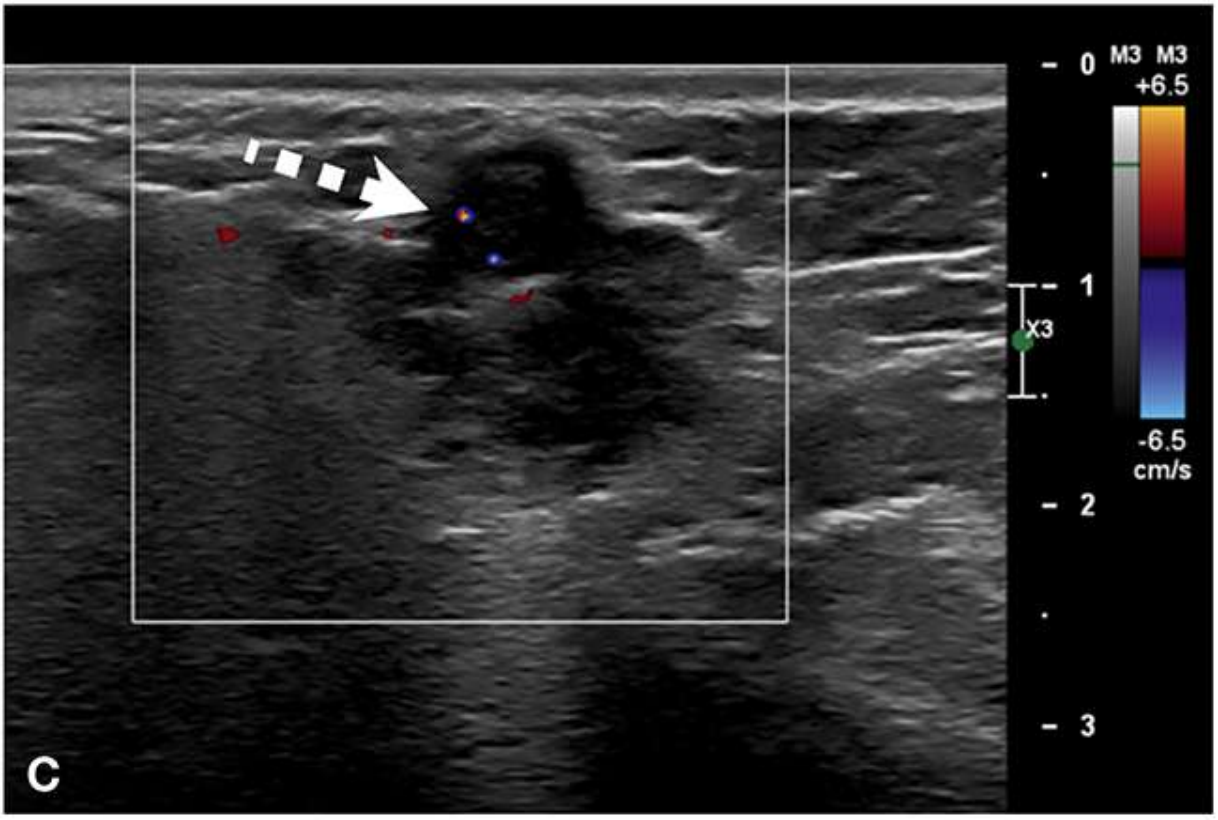
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FIGURE 49.4 Mucoepidermoid carcinoma (MEC) of the right parotid. A 29-year-old woman presents with palpable lump over the right parotid area. Longitudinal (A) and transverse (B) ultrasound show a mixed iso- and hypoechoic mass with irregular margins centered in the superficial right parotid (arrows). C. Ultrasound with color flow demonstrates mild increased internal vascularity within the mass (arrow). D. Ultrasound-guided core-needle biopsy was subsequently performed, with the final pathology showing MEC.

CT and MRI are indispensable imaging modalities for evaluating salivary gland tumors, as they offer detailed cross-sectional images that provide valuable insights into the size, shape, and involvement of tumors with surrounding structures.[43] MRI is superior to CT, especially when malignancy is suspected, based on the excellent soft tissue contrast (Figure 49.5). When feasible, both CT and MRI should be performed with intravenous (IV) contrast to fully characterize tumors and thoroughly assess the extent of primary tumors and metastatic disease. The advantages of CT include its rapid acquisition time and wide availability in most health care

institutions, making it a practical choice for initial assessment. In addition, CT can provide valuable information about the integrity of bony structures, particularly the cortical bones (Figure 49.6). Detection of cortical erosion or destruction is possible with CT, aiding in the evaluation of tumor involvement with adjacent bone structures. On the other hand, MRI with contrast excels in offering exceptional soft tissue visualization and precise anatomical details, making it particularly valuable in identifying tumor boundaries. MRI is highly effective in assessing potential PNTS, a crucial factor in determining the extent of the disease and planning appropriate treatment strategies, especially for ADCC, SDC, squamous and undifferentiated carcinomas, and high-grade MEC (Figures 49.7 and 49.8).[47] The tumor extension along VII (stylomastoid foramen and temporal bone), the CNV3 (ATN and foramen ovale), or, less commonly, nerve V2 (foramen rotundum) as seen in tumors of the deep parotid lobe involving the pterygopalatine fossa may be visualized by T1-weighted images.[48] This is of special importance for the delineation of these nerves in case of postoperative radiotherapy (PORT) and definitive RT for extensive PNTS (Figure 49.9), involving V3 and VII. The imaging characteristics of salivary gland tumors can vary based on their histologic types and tumor grading.[49,50] However, there is a challenge in using imaging to reliably distinguish between benign and malignant salivary gland tumors. In many cases, low-grade malignancies exhibit well-defined margins that can resemble those of benign tumors (Figure 49.10). Conversely, high-grade malignancies frequently display infiltrative margins on imaging.[50] T1-weighted images are excellent for assessing the margins, extension into the deep tissues, and patterns of infiltration because the (fatty) background of the gland is hyperintensive. With T1-weighted gadolinium series, tumor infiltration and heterogeneous enhancement may be visualized, as seen in high-grade tumors.[46] With fat-suppressed T2-weighted images, the fluid content of a tumor is visualized. In general, benign tumors are hyperintensive, and malignant tumors show intermediate or low intensity at T2-weighted MRIs. Researchers have explored advanced imaging techniques, such as diffusion-weighted imaging and dynamic contrast-enhanced MR perfusion, to improve the differentiation between benign and malignant salivary gland tumors.[51-54] Despite these efforts, the precise role of these techniques in enhancing diagnostic accuracy still requires validation.

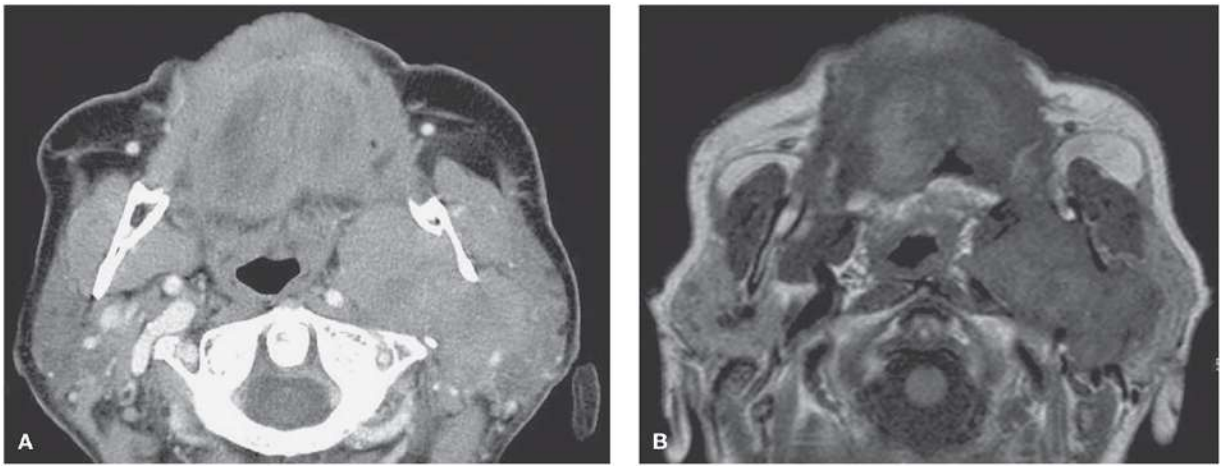

FIGURE 49.5 A patient with acinic cell cancer of the left parotid gland. A. Axial contrast-enhanced computed tomography image. B. T1-weighted magnetic resonance image. Both images show an infiltrating soft tissue mass involving the deep and superficial lobe. The tumor has widened the left stylomandibular tunnel, with infiltration in the pterygoid musculature. The left internal carotid artery is displaced medially. (Courtesy of Dr F.A. Pameyer, Radiologist, University Medical Center Utrecht.)

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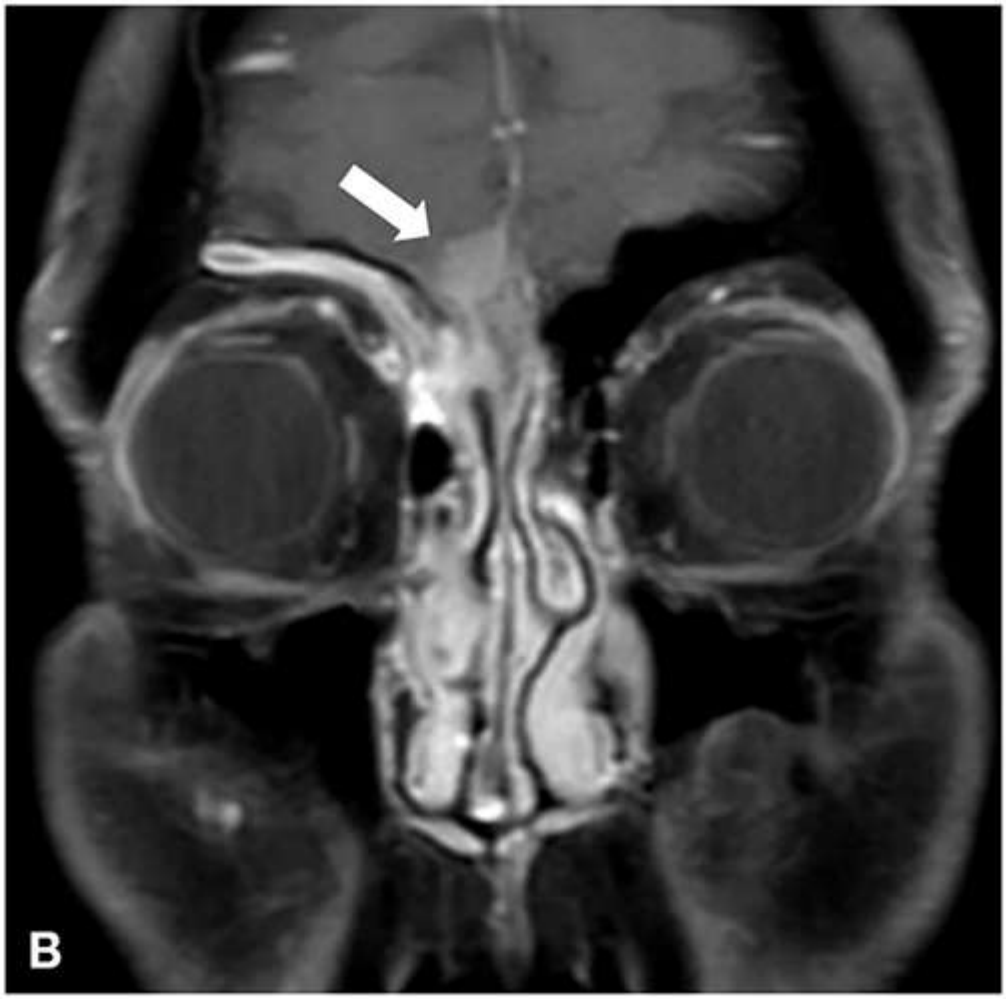
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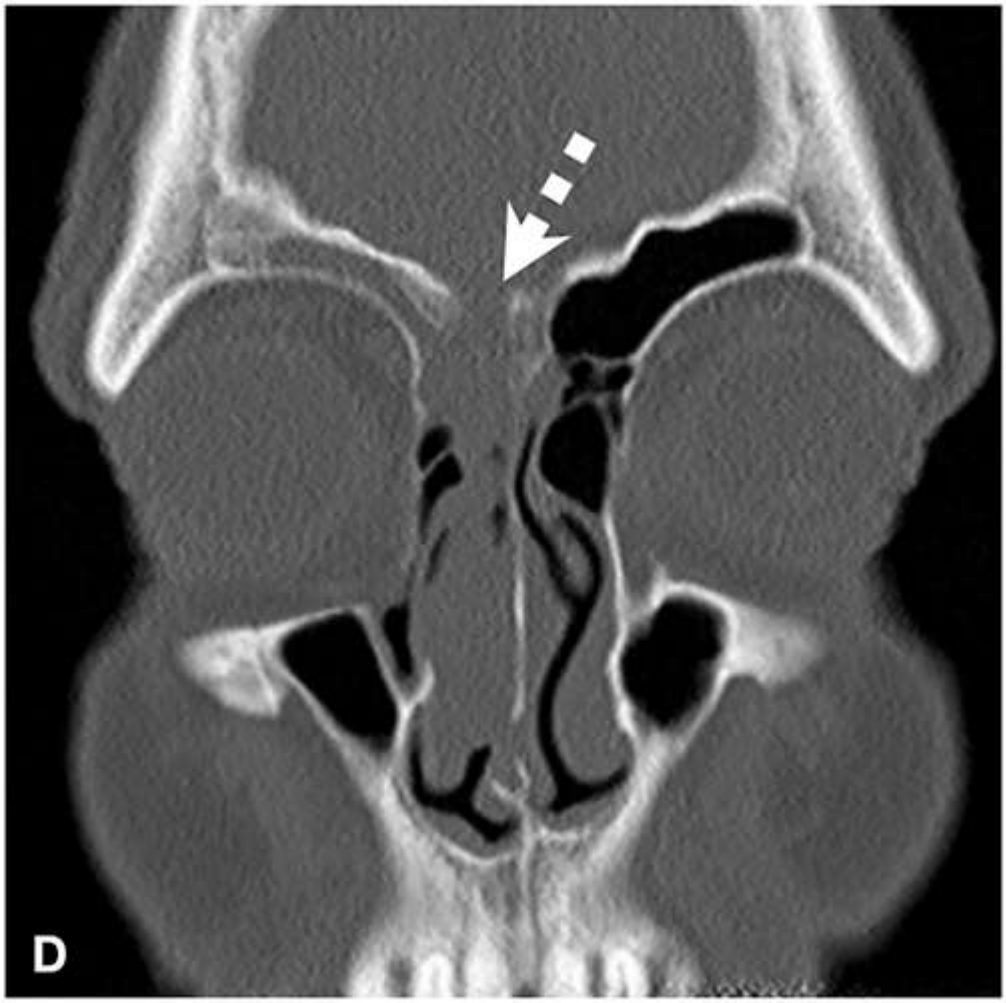

FIGURE 49.6 Adenoid cystic carcinoma of sinonasal cavity. A 50-year-old man presents with epistaxis. Axial (A) and coronal (B) contrast-enhanced, fat-suppressed, T1-weighted images show an infiltrative enhancing tumor centered in the right anterior ethmoid sinus invading the adjacent skull base and extending into the anterior cranial fossa (arrows). Axial (C) and coronal (D) computed tomography images in bone window demonstrate evidence of bone erosion and destruction at the right anterior ethmoid sinus and the right cribriform plate (arrows).

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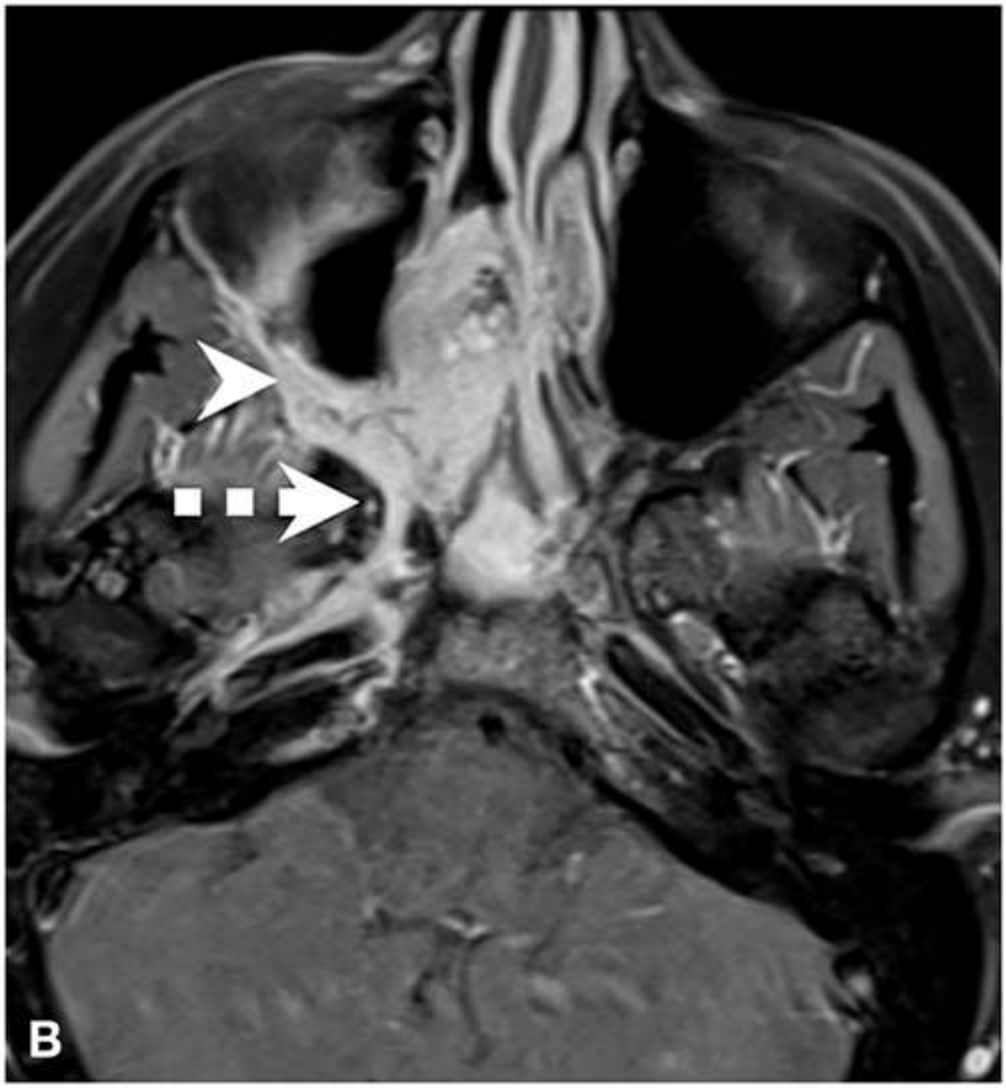
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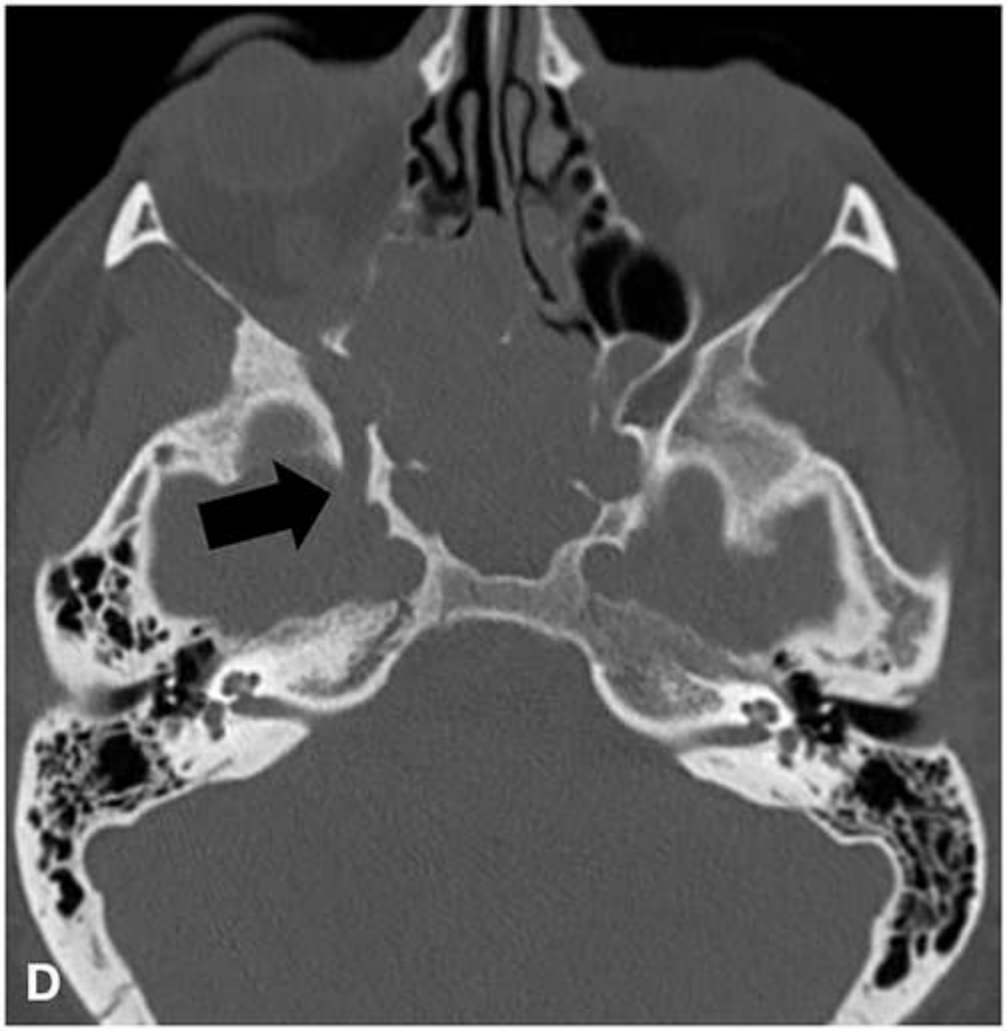
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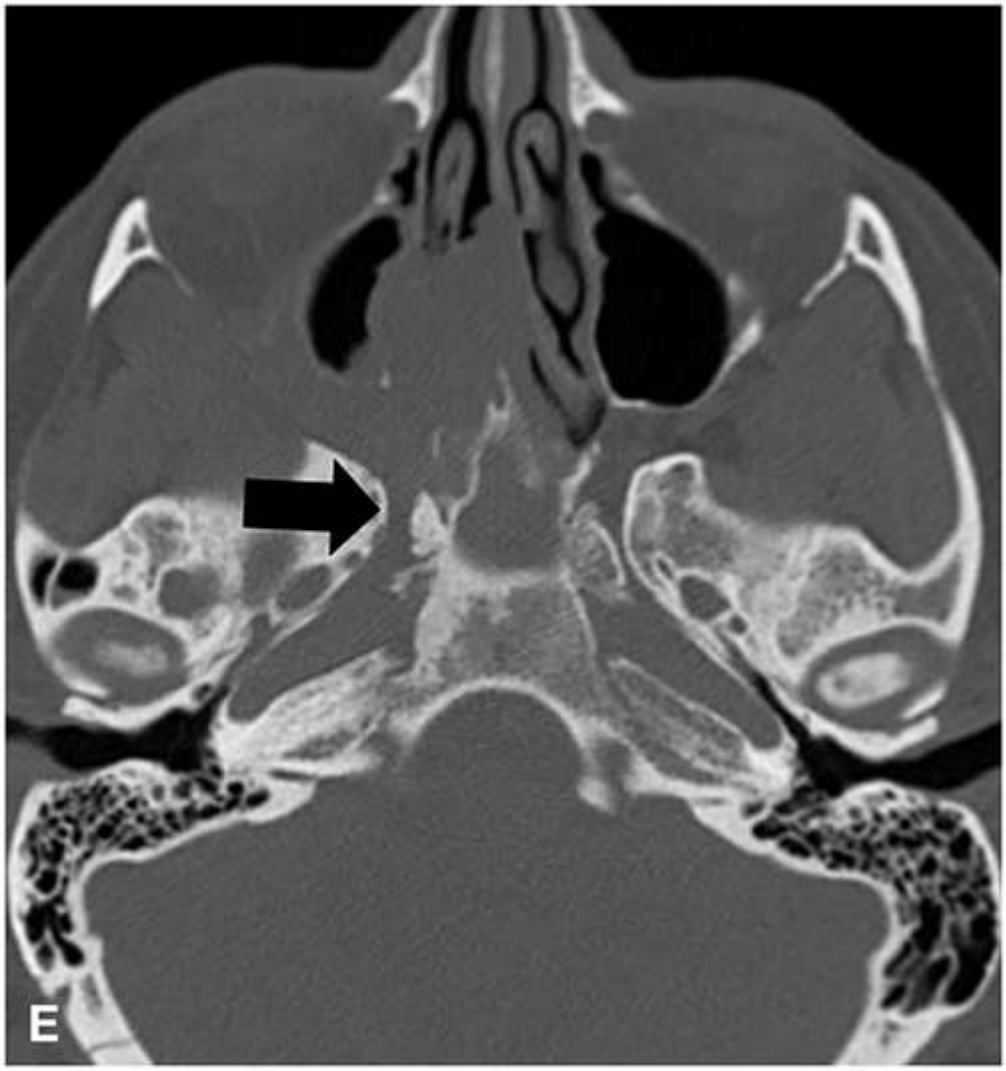
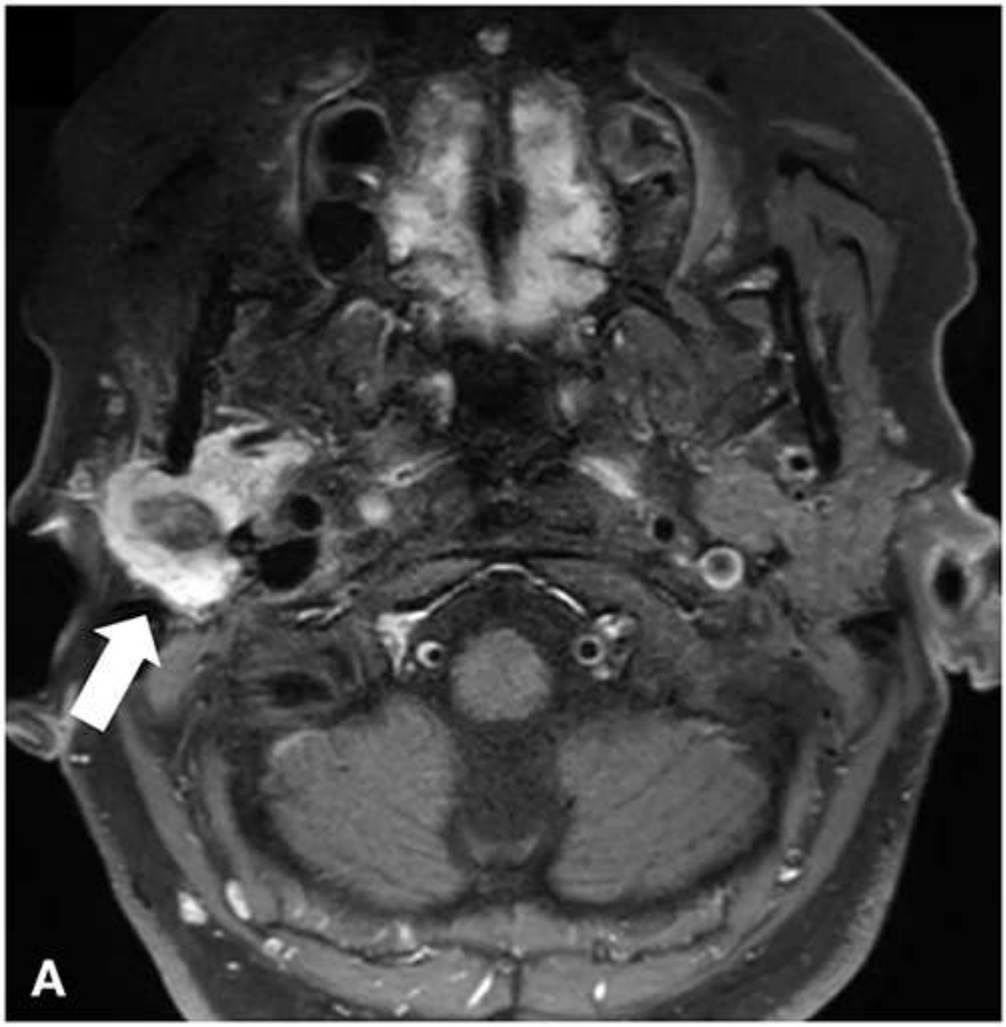


FIGURE 49.7 Adenoid cystic carcinoma (ADCC) with perineural tumor spread (PNTS) along the trigeminal nerve (V). A 38-year-old woman with locally advanced ADCC of the nasopharynx. Axial (A, B) and coronal (C) contrast-enhanced, fat-suppressed, T1-weighted images show a large infiltrative enhancing mass extensively involving the sphenoid and ethmoid sinuses, with PNTS into the pterygopalatine fossa (arrowheads in A and B), foramen rotundum (solid arrows in A and C), and vidian canal (dashed arrows in B and C). Axial computed tomography images in the bone window (D, E) show enlargement of the right foramen rotundum and vidian canal secondary to PNTS (arrows).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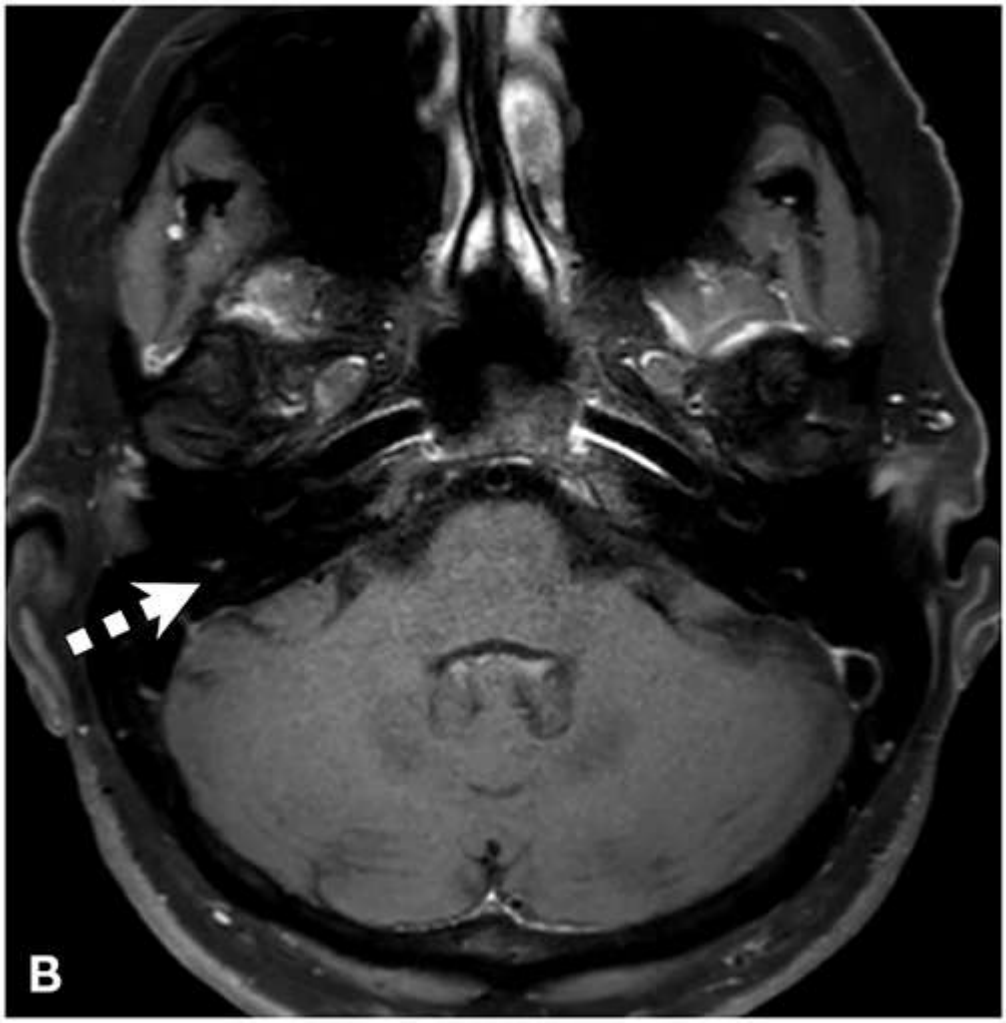
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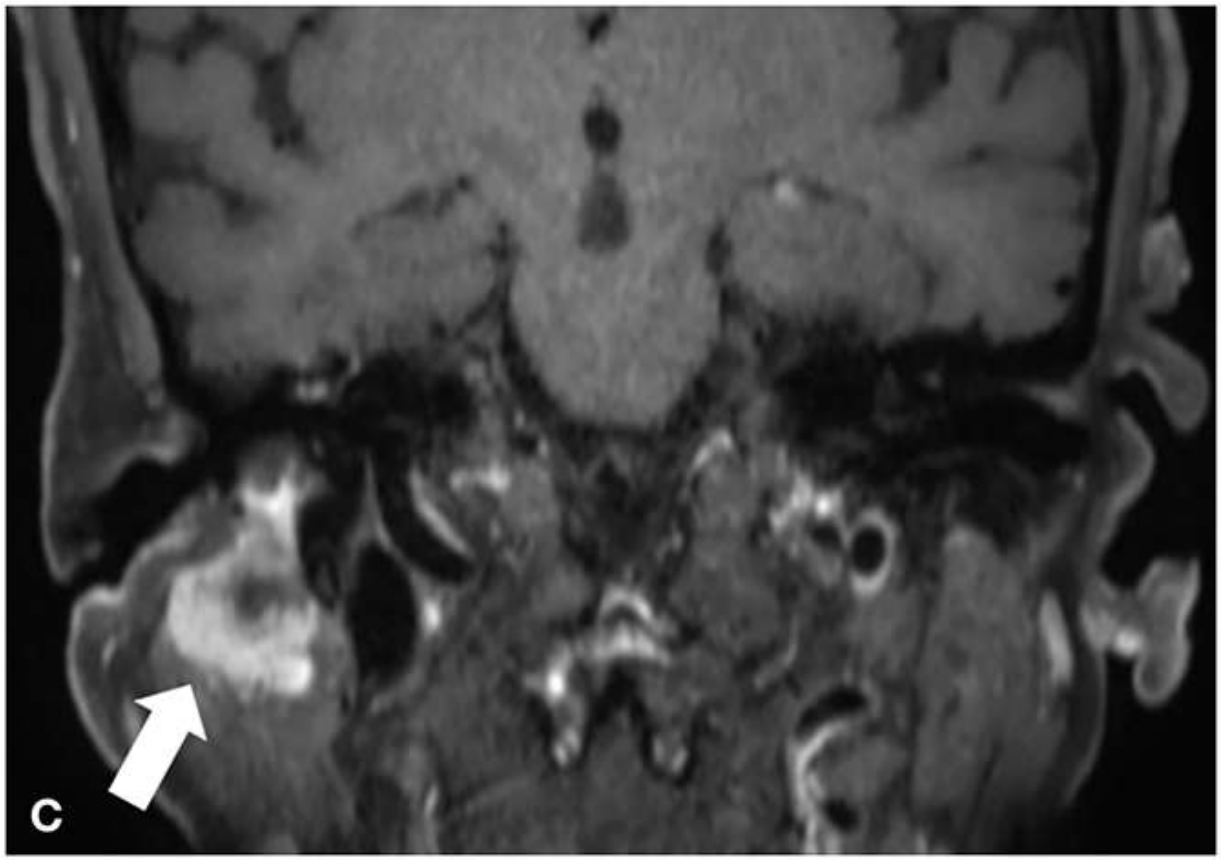
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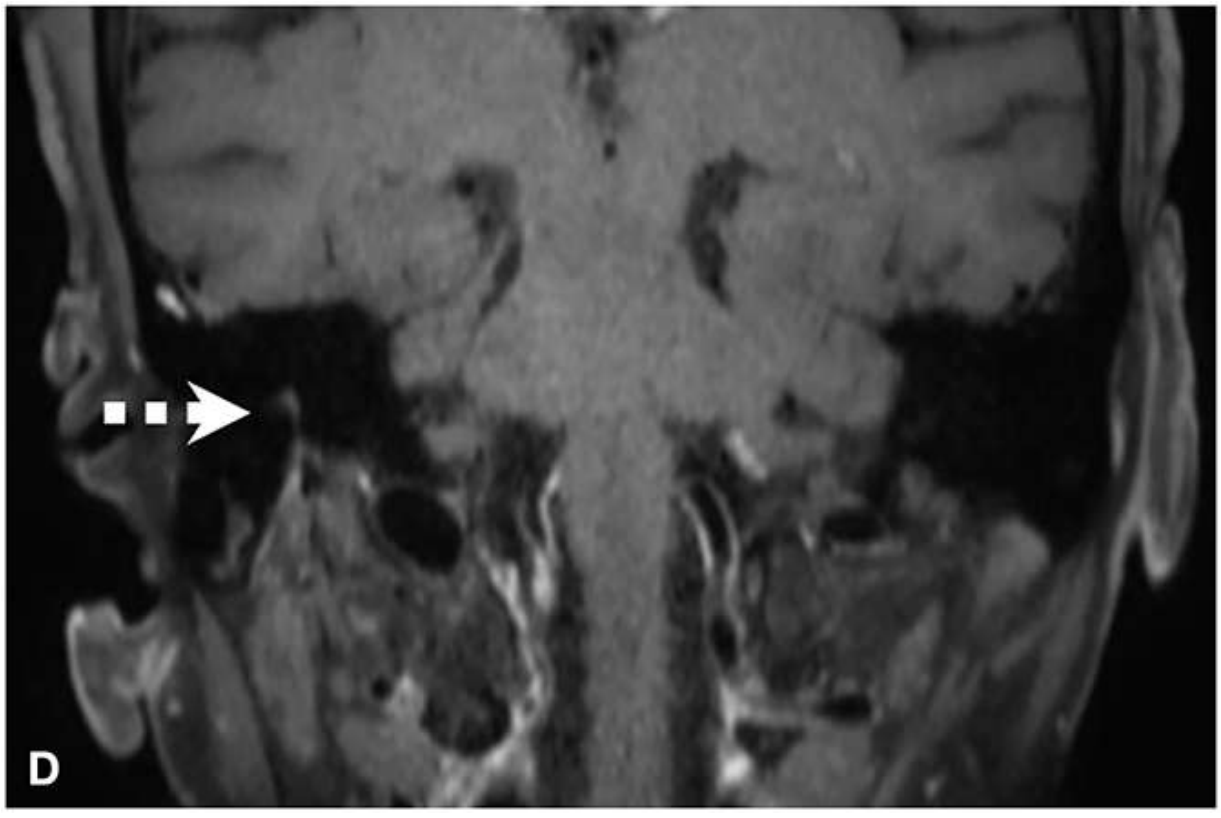
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FIGURE 49.8 Adenoid cystic carcinoma with perineural tumor spread (PNTS) along the facial nerve (VII). A 64-year-old woman presents with a palpable lump over the right parotid area and right facial palsy. Axial (A, B) and coronal (C, D) contrast-enhanced, fat-suppressed, T1-weighted images demonstrate a large infiltrative enhancing tumor involving the superficial and deep right parotid (arrows in A and C). There is subtle asymmetric thickening and enhancement of the mastoid segment of the right facial nerve (arrows in B and D), suspicious for PNTS. Perineural invasion was subsequently confirmed by histopathologic examination.

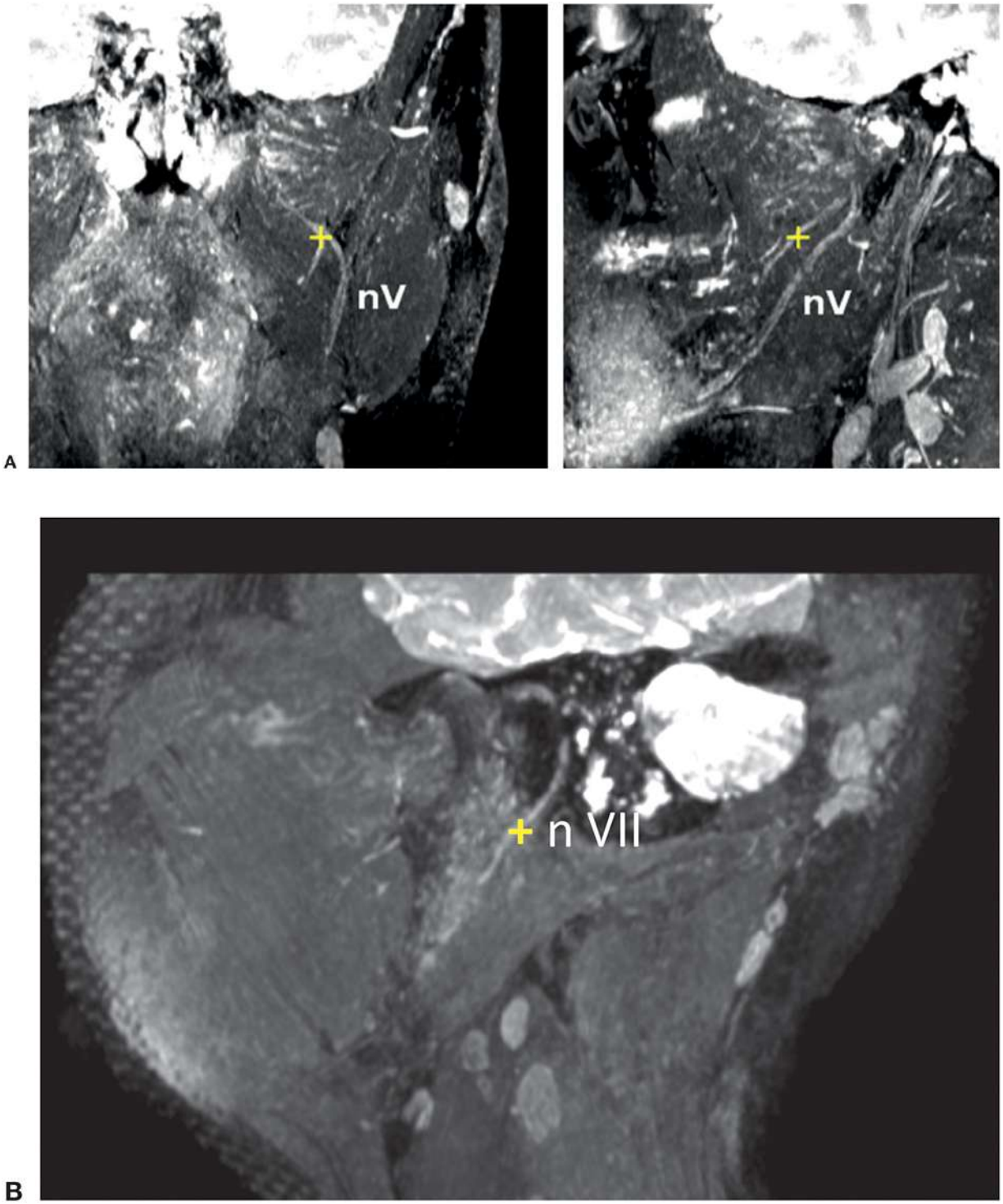

FIGURE 49.9 Three-dimensional magnetic resonance imaging, T2-fast field echo with binomial radiofrequency pulses for water-selective excitation: (A) nerve V (nV) and (B) nerve VII (nVII).

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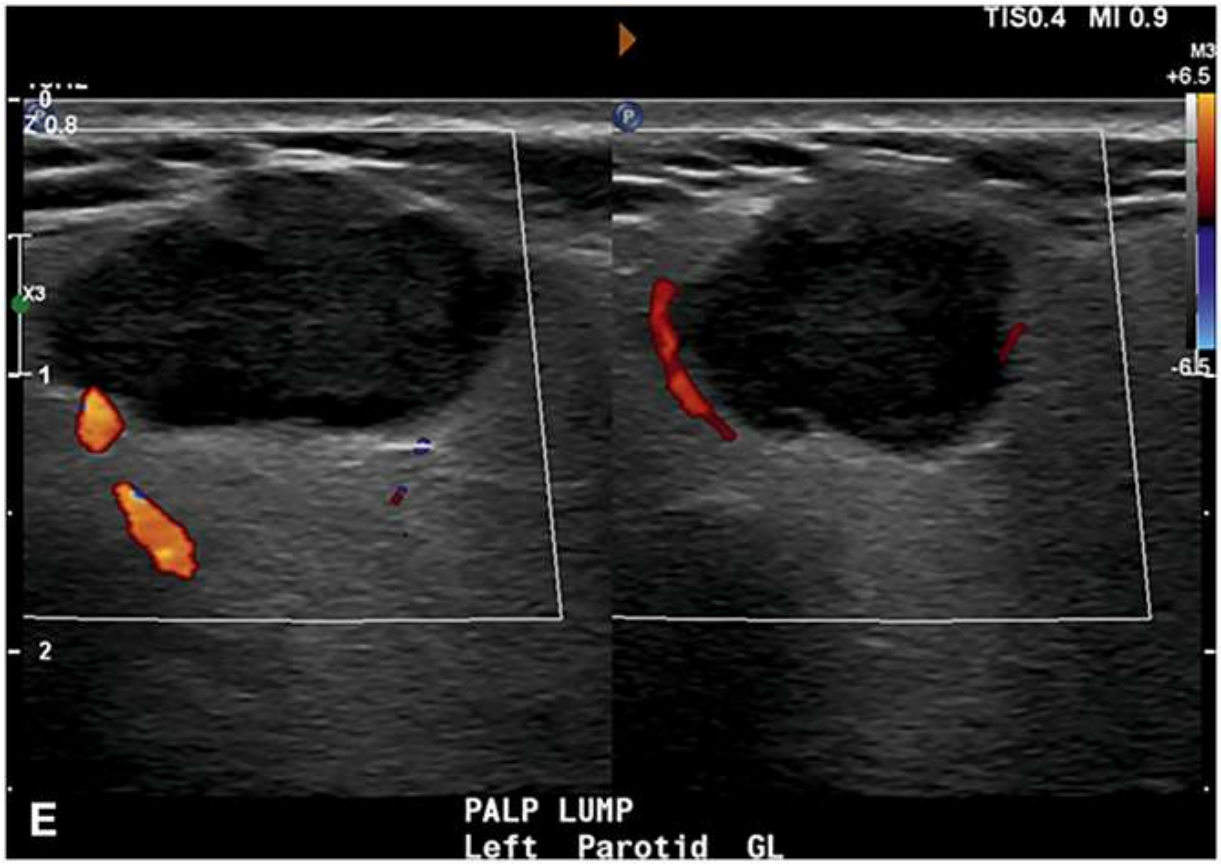

FIGURE 49.10 Low-grade mucoepidermoid carcinoma (MEC). A 31-year-old woman with low-grade MEC presents with a painless palpable lump over the left parotid area. Axial T1 weighted (A) and T2 weighted with fat suppression (B) and axial (C) and coronal (D) contrast-enhanced T1 weighted with fat suppression demonstrate a small well-circumscribed enhancing mass in the left superficial parotid, mimicking benign salivary gland tumors such as pleomorphic adenoma. E. Corresponding parotid ultrasound with color-flow Doppler I age shows mild vascularity surrounding the lesion.

^{18}F-FDG PET/CT scans combine functional and anatomic information, offering valuable data on metabolic activity and assisting in the detection of distant metastases. It is of value for tumor staging and surveillance, especially in patients with advanced-stage or high-grade salivary gland malignancies (Figure 49.11).[44,45,55] The current American Society of Clinical Oncology guideline recommends obtaining PET/CT in patients with advanced-stage high-grade salivary gland malignancies.[41] However, when it comes to distinguishing between benign and malignant salivary gland tumors, PET/CT has limitations due to the overlapping metabolic activities of these tumors.[44] For instance, certain benign salivary gland tumors, notably Warthin tumor and pleomorphic adenoma, can exhibit

hypermetabolic activity with increased FDG uptake, resembling high-grade salivary gland malignancies (Figure 49.12). In contrast, some low-grade salivary gland malignancies such as acinic cell carcinoma and low-grade MEC tumor might not display elevated FDG uptake.[45] Therefore, the definitive diagnosis of salivary gland tumors still relies on histopathologic examination.

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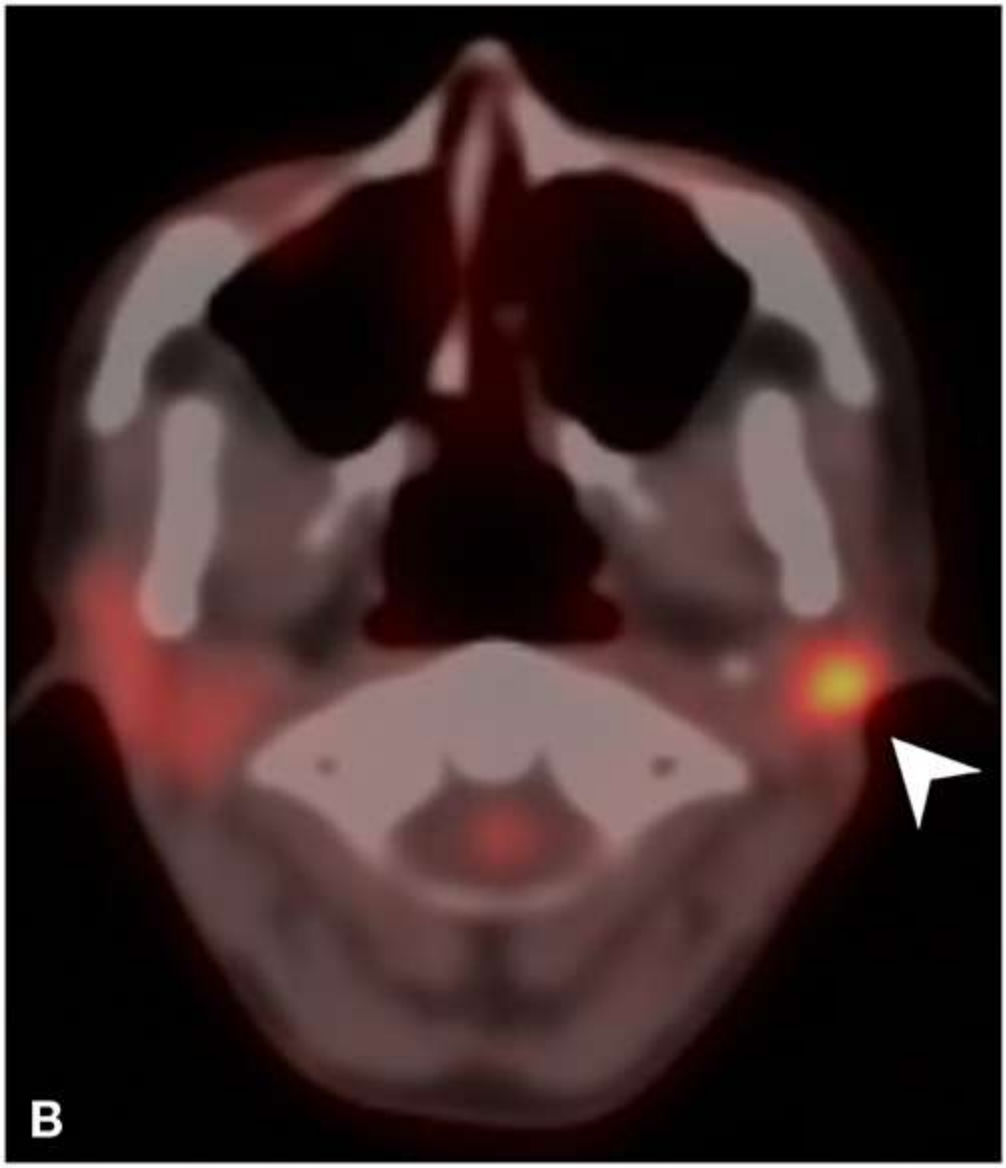
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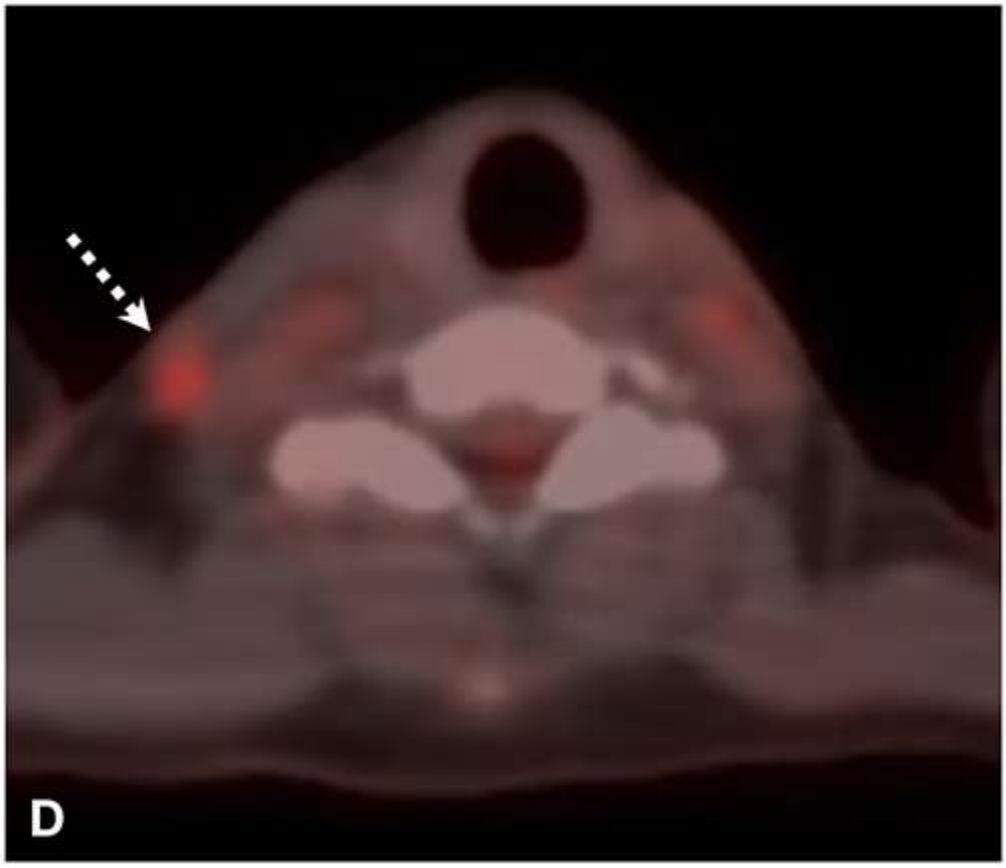
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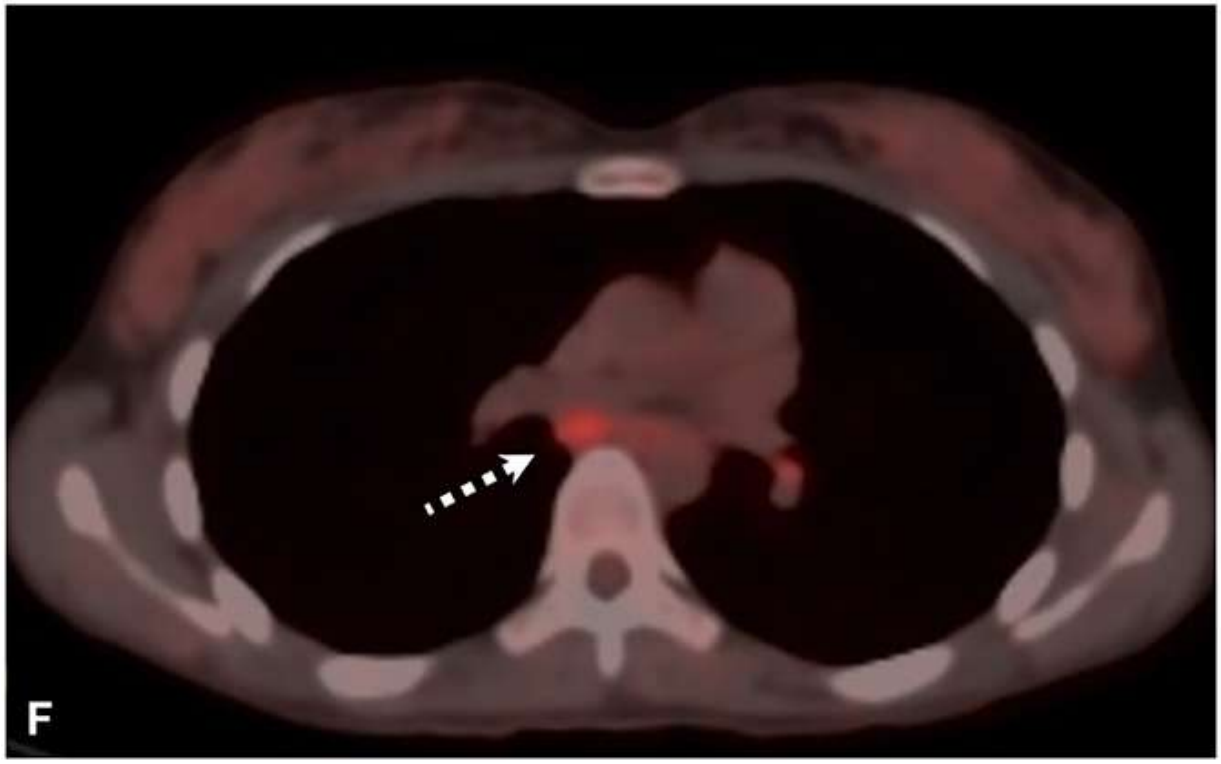
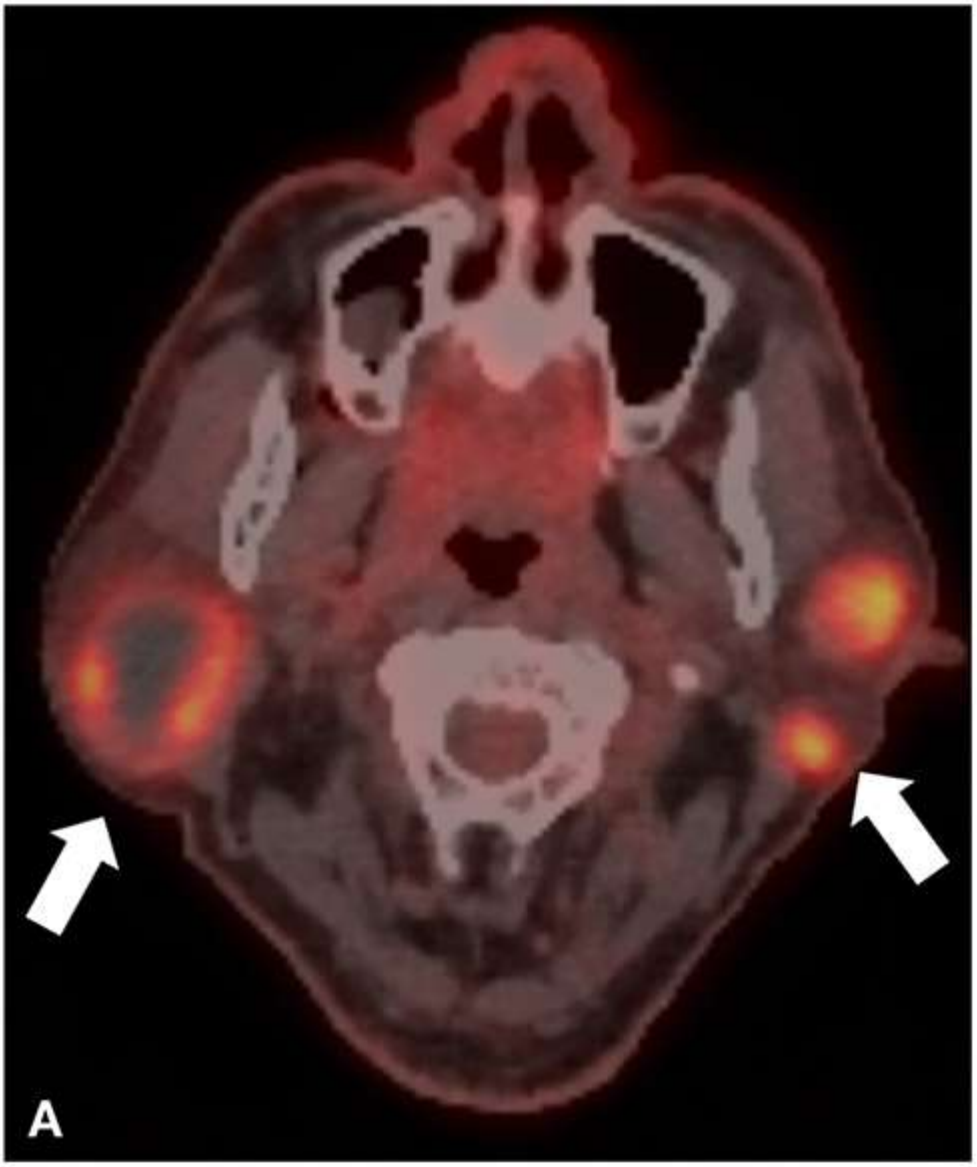


FIGURE 49.11 Metastatic mucoepidermoid carcinoma (MEC). A 27-year-old woman with recurrent high-grade MEC of the left parotid, status post left parotidectomy, and adjuvant radiation therapy. A. Axial contrast-enhanced, fat-suppressed, T1-weighted image shows an enhancing infiltrative tumor in the left parotidectomy bed (arrow). B-F. Axial fused positron emission tomography/computed tomography images demonstrate fluorodeoxyglucose (FDG)-avid recurrent tumor in the left parotid (arrowhead in B) and multiple FDG-avid lymph nodes in both sides of the neck (arrows in C and D) as well as in the right hilar and the subcarinal regions (arrows in E and F, respectively), consistent with widespread metastatic lymphadenopathy.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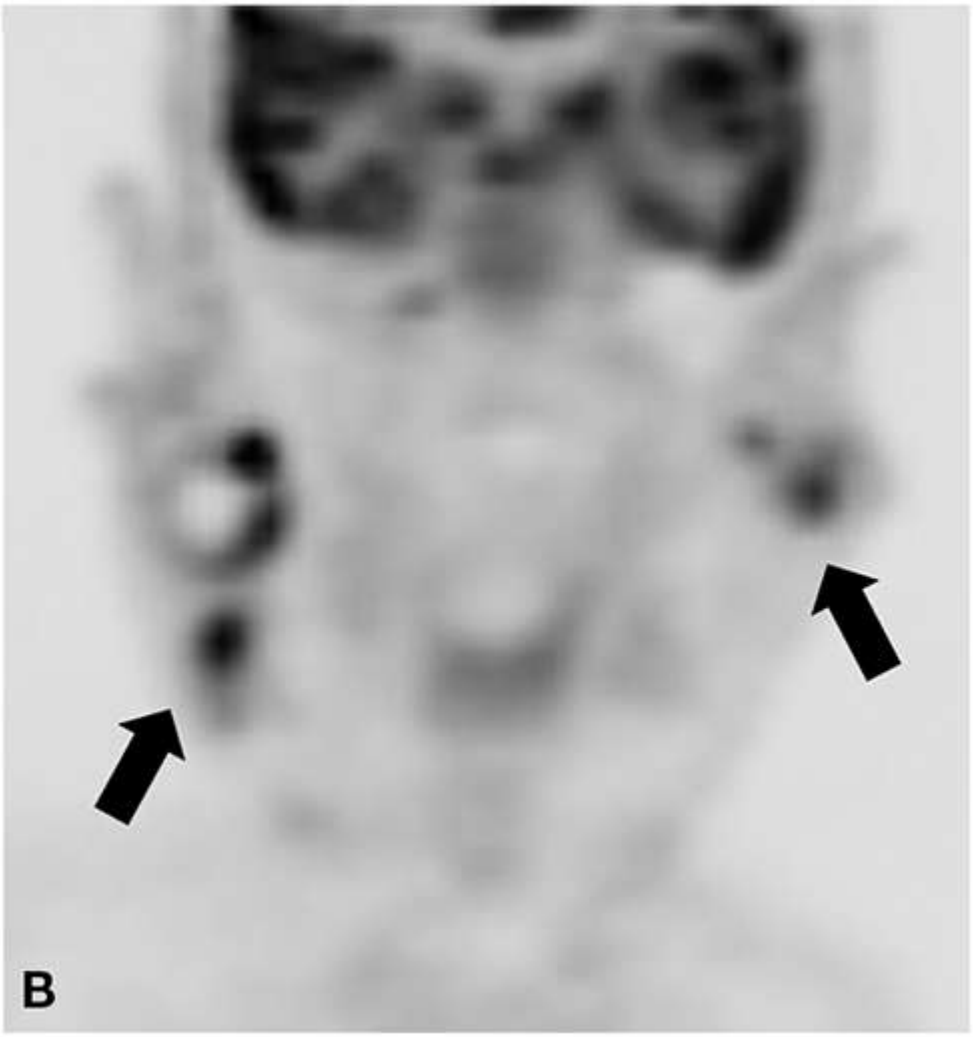
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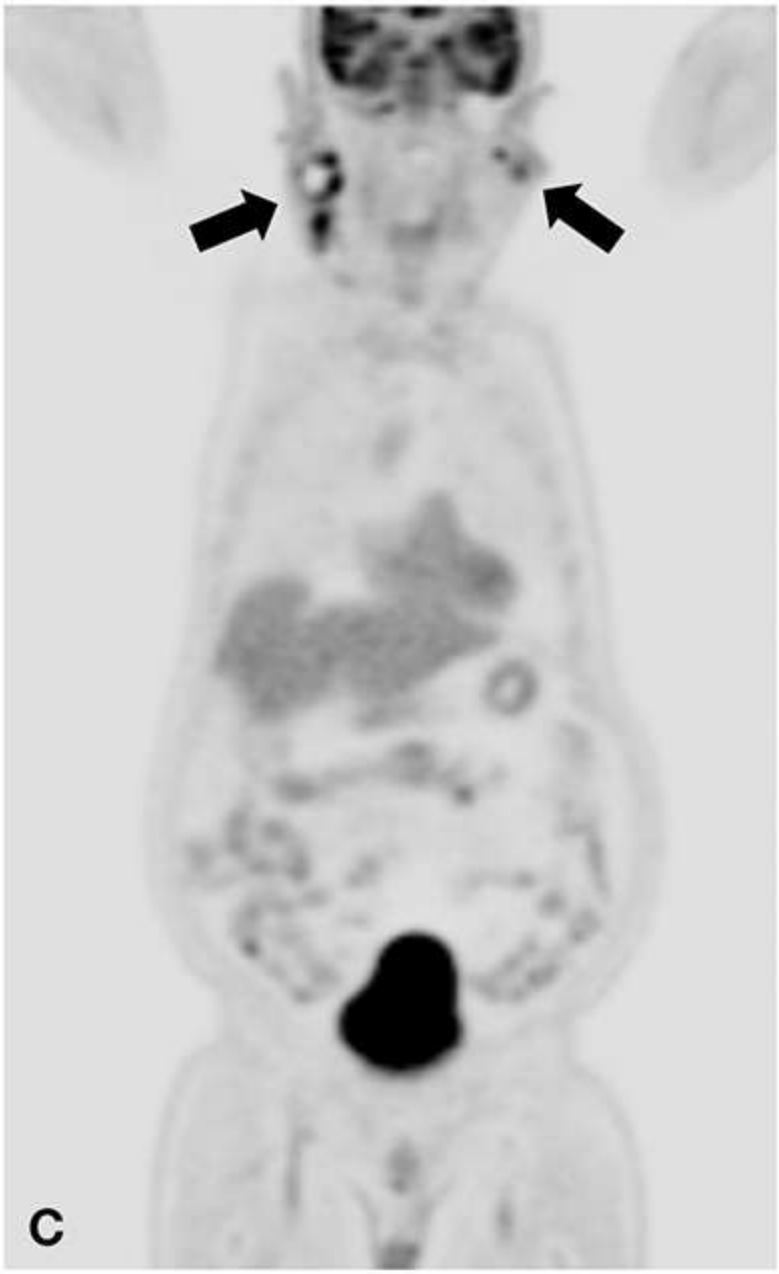

FIGURE 49.12 Warthin tumor (aka papillary cystadenoma lymphomatosum). A 75-year-old man with a history of smoking. Positron emission tomography/computed tomography (PET/CT) was performed for evaluation of progressively enlarging lung mass. Axial fused PET/CT (A) and coronal PET images with maximum intensity projection (B, C) demonstrate multiple fluorodeoxyglucose-avid masses in the bilateral parotid glands (arrows). Note cystic change with central photopenia within the dominant right parotid mass. Warthin tumor was histologically confirmed with tissue biopsy.

The eighth edition of the manual of the American Joint Committee on Cancer and the eighth edition of the classification system of the

International Union Against Cancer are identical for major salivary glands[56] (Table 49.3). They are based on size; tumor extension; nodal size, number, and location; and, a change from the seventh edition, extranodal extension. Relative survival rates for major salivary gland cancer according to stage are shown in Figure 49.13.

TABLE 49.3 UICC CANCER STAGING SYSTEM FOR MAJOR SALIVARY GLAND CANCER (PAROTID, SUBMANDIBULAR, SUBLINGUAL), EIGHTH EDITION

Primary Tumor (T)			
T1	≤2 cm without extraparenchymal extension[a]		
T2	>2-4 cm without extraparenchymal extension		
T3	>4 cm and/or extraparenchymal extension[a]		
T4a	Invasion skin and/or mandible and/or ear canal and/or facial nerve		
T4b	Invasion skull base and/or pterygoid plates and/or carotid artery		
Regional Lymph Nodes (N)			
N0	No regional lymph node metastasis		
N1	Ipsilateral single lymph node, ≤3 cm, without ENE		
N2a	Single ipsilateral lymph node >3 cm but <6 cm, without ENE		
N2b	Multiple ipsilateral lymph nodes, none >6 cm, without ENE		
N2c	Bilateral or contralateral lymph nodes, none >6 cm, without ENE		
N3a	Lymph node >6 cm, without ENE		
N3b	Single or multiple nodes with ENE		
Distant Metastases (M)			
MX	Presence of distant metastasis cannot be assessed.		
M0	No distant metastasis		
M1	Distant metastasis		
Stage Grouping			
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1, T2, T3	N1	M0

IVA	T1, T2, T3	N2	M0
	T4a	N0, N1, N2	M0
IVB	T4b	Any N	M0
	Any T	N3	M0
IVC	Any T	Any N	M1

ENE, extranodal extension; UICC, Union for International Cancer Control.

[a]Extraparenchymal extension is clinical or macroscopic evidence of invasion of soft tissues. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes.

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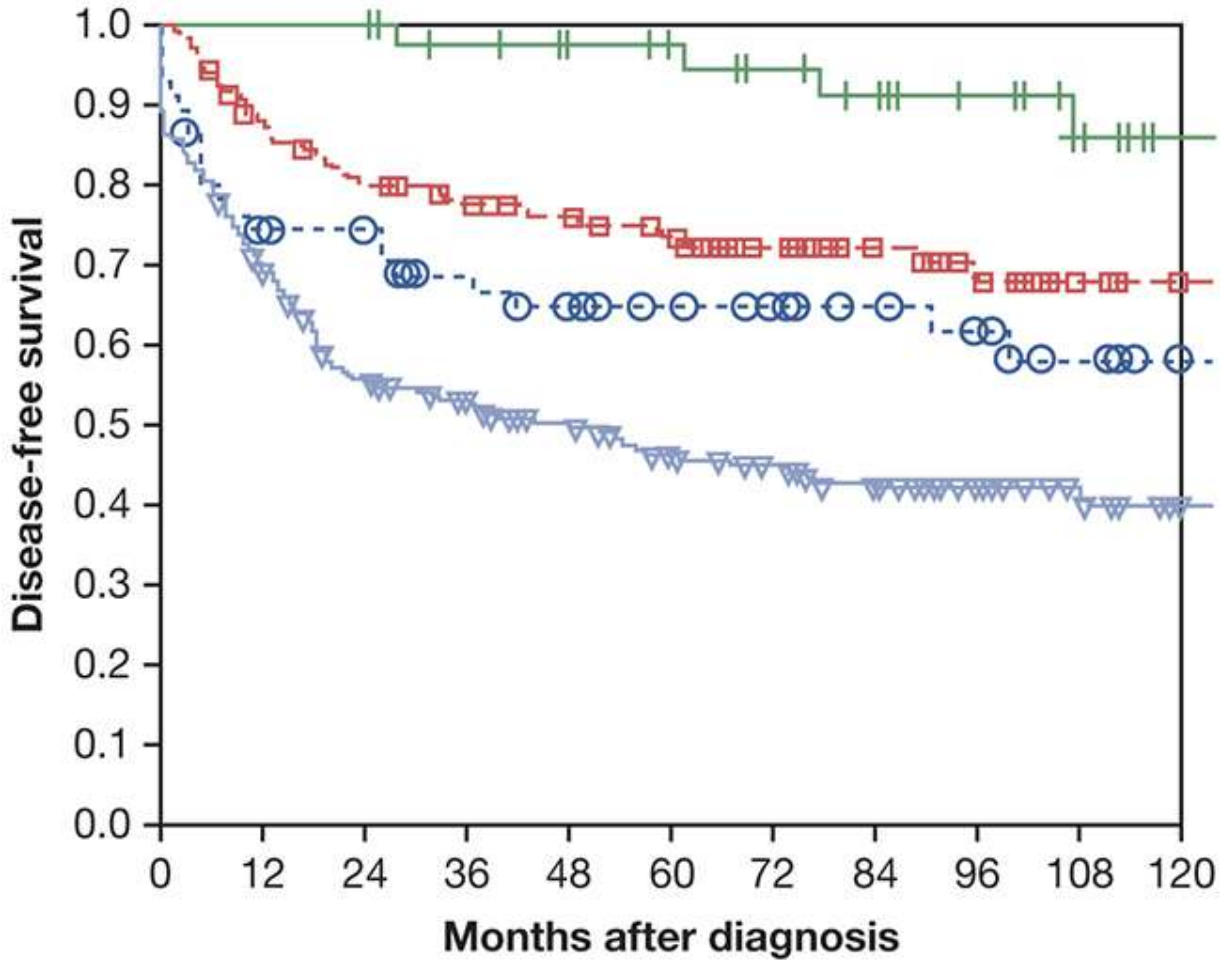

FIGURE 49.13 Disease-free survival for major salivary glands according to the 2002 classification of the American Joint Committee on Cancer. Results of the nationwide Dutch study: +, stage I; □, stage II; ○, stage III; and ∇, stage IV.

Minor Salivary Glands

Various radiographic studies may be used, including plain films, to ascertain bone erosion in advanced lesions, although CT is best to detect bone invasion and nodal involvement, and MRI for soft tissue infiltration and PNTS. CT and MRI scans may be used to evaluate depth, contiguous involvement, and the retropharyngeal nodes. US may be used to examine the neck nodes and is operator dependent. PET can be helpful for overall staging. The definitive diagnostic procedure is an excisional biopsy, particularly if malignancy is clinically suspected. Unplanned incisional biopsies should be avoided, and fine-needle biopsies are impractical because of the polymorphism of most malignant salivary gland tumors.

A formal staging system has not been developed for minor gland tumors. The same staging system of minor salivary glands for squamous cell carcinoma in sites other than the parotid gland or SMG may be used.[56]

PATHOLOGIC CLASSIFICATION

Salivary glands are composed of acinar-ductal units with acinar cells on the inside of the acinar units and ductal epithelial cells on the inside of the striated and excretory ducts. Myoepithelial cells are located in the outside of acini and intercalated and striated ducts. Basal (reserve) cells are found on the outside of the excretory ducts.[57] Carcinomas may arise from all these cell types, either separately or combined. The histologic classification of these salivary gland tumors is very demanding for the head and neck pathologist. In 1991, the World Health Organization (WHO) classification for salivary gland tumors of 1972 was expanded from 7 to 20 subtypes. Various types of carcinomas were distinguished based on precise histologic definitions, prognosis, and treatment, discussed more in detail by Seifert and Sobin.[58] In 2005, the WHO classification of malignant salivary gland tumors was extended. Again, 24 subtypes were specified[56] (Table 49.4). Classification may be difficult, as shown in a reevaluation of 101 intraoral salivary gland tumors by experienced pathologists; major disagreement was seen in 8, and there was minor disagreement in 33.[59]

TABLE 49.4 WHO CLASSIFICATION OF TUMORS OF SALIVARY GLANDS

Malignant tumors

Mucoepidermoid carcinoma

Adenoid cystic carcinoma

Acinic cell carcinoma

Polymorphous adenocarcinoma

Clear cell carcinoma

Basal cell carcinoma

Intraductal carcinoma

Adenocarcinoma, NOS

Salivary duct carcinoma

Myoepithelial carcinoma

Epithelial-myoepithelial carcinoma

Carcinoma ex pleomorphic adenoma

Secretory carcinoma

Sebaceous adenocarcinoma

Carcinosarcoma

Poorly differentiated carcinoma

- Undifferentiated carcinoma
- Large cell neuroendocrine carcinoma
- Small cell neuroendocrine carcinoma

Lymphoepithelial carcinoma

Squamous cell carcinoma

Oncocytic carcinoma

Uncertain malignant potential

- Sialoblastoma

Benign tumors

Pleomorphic adenoma

Myoepithelioma

Basal cell adenoma

Malignant tumors
Warthin tumor
Oncocytoma
Lymphadenoma
Cystadenoma
Sialadenoma
Ductal papillomas
Sebaceous adenoma
Canalicular adenoma and other ductal adenomas
Non-neoplastic epithelial lesions
Sclerosing polycystic adenosis
Nodular oncocytic hyperplasia
Lymphoepithelial sialadenitis
Intercalated duct hyperplasia
Benign soft tissue lesions
Hemangioma
Lipoma/sialolipoma
Nodular fasciitis
Hematolymphoid tumors
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)

WHO: World Health Organization; NOS: not otherwise specified.
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Most salivary gland subtypes are very rare. The percentage of the histologic subtypes varies from series to series and from the localization of the tumor (Figure 49.14). In 666 patients with a salivary gland carcinoma in a study performed in the Netherlands, for which the pathology was revised, ADCC was most frequently diagnosed (27%), followed by MEC (16%), acinic cell carcinoma (14%), carcinoma ex pleomorphic adenoma (8%), undifferentiated carcinoma (7%), SDC and adenocarcinoma not otherwise

specified (both 6%), polymorphic low-grade adenocarcinoma (PLGA) and squamous cell carcinoma (both 5%), and epithelial-myoepithelial carcinoma in 2%. In this large study, all other subtypes were rarely or not at all diagnosed.[21]

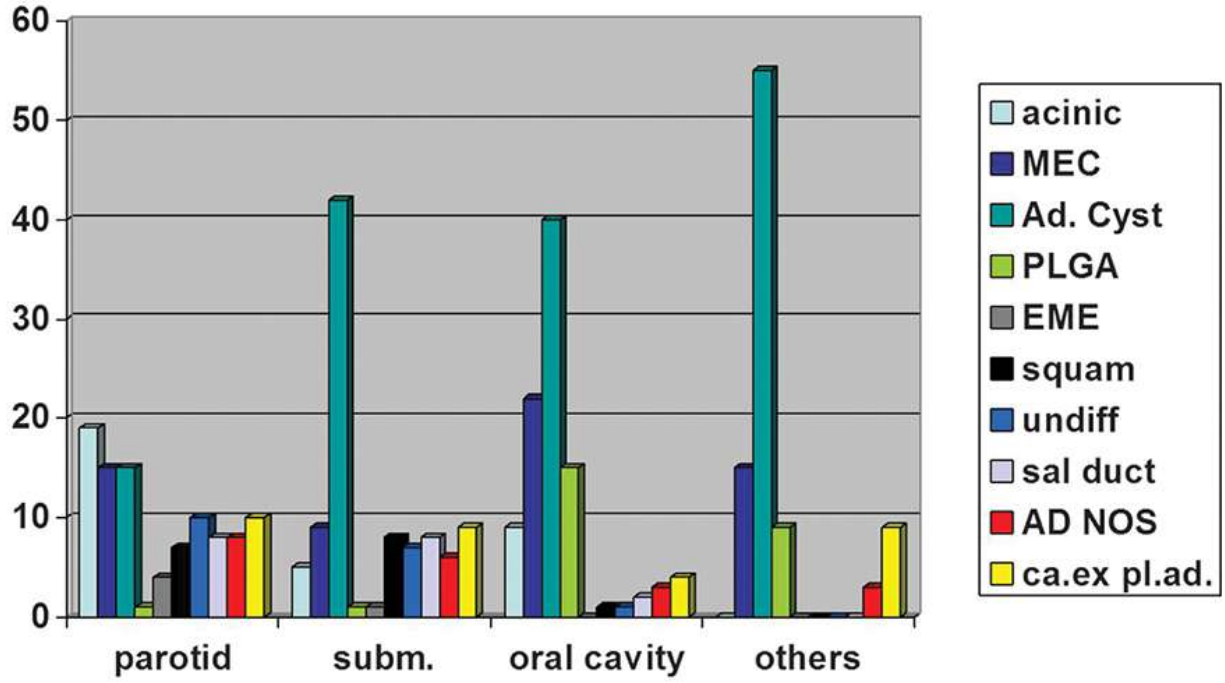


FIGURE 49.14 Distribution of various cell types (%) in series from the Dutch study, depending on site. Ad. Cyst, adenoid cystic; AD NOS, adenocarcinoma not otherwise specified; ca. ex pl. ad., carcinoma ex pleomorphic adenoma; EME, epithelial-myoepithelial carcinoma; MEC, mucoepidermoid cancer; PLGA, polymorph low-grade adenocarcinoma; sal duct, salivary duct carcinoma; squam, squamous cell carcinoma; subm, submandibular. undiff, undifferentiated.

Salivary gland carcinomas may be graded from low to high based on malignant potential, particularly for MEC. However, there is a disparity for grading, even among experienced pathologists.[60] Low- and intermediate-grade MEC, PLGA, epithelial-myoepithelial, cribriform and tubular ADCC, and acinic cell carcinomas comprise a group of low-to-moderate malignancy; high-grade MEC, malignant mixed, solid component and high-grade ADCC, undifferentiated carcinoma, and SDCs represent more high-grade primary malignancies.[60]

ADCC is the most common in minor salivary glands, followed by the SMG.[8,21,36,61,62] Perineural invasion and local and distant (usually lung)

recurrences are common in ADCC.[62-64] Indolent presentation and delayed recurrences are common and warrant a long-term follow-up program (>10 years). The ADCC variety has a tubular pattern that has been associated with the best prognosis, a cribriform pattern with an intermediate prognosis, and a solid pattern with the worst prognosis.[65]

In parotid tumors in children and adults, the most common malignant subtype is MEC.[9,66-68] MEC contains squamous cells, mucus-producing cells, and cells of intermediate type. Several grading criteria and cell cycle–based Ki 67 proliferation index of MEC have been published.[57] *Acinic cell* cancer derives from cells of the terminal ducts and intercalated ducts. An extensive update of the literature is published by Vander Poorten et al.[69] Most tumors (86%) are located in the parotid gland.[69] Like in MEC, Ki 67 proliferation index is a prognostic factor for disease-free survival.[57] *Carcinoma ex pleomorphic adenoma* may be localized in all salivary glands, although the majority is found in the parotid gland. In the development of carcinoma ex pleomorphic adenoma, a progressive loss of heterozygosity of chromosomes 8q, 12G, and 17P is seen.[70] The prognosis is poor with a high risk of distant metastases.[21] *Undifferentiated and squamous cell carcinoma* are mainly localized in the parotid gland. The prevalence of comorbidity for patients with squamous cell carcinoma of the salivary gland is comparable to other head and neck cancers, whereas the prevalence of comorbidity in all other malignant salivary gland cancer subtypes is significantly less.[71] Also, patients with squamous cell carcinoma of the salivary glands are mostly older.[1] So, squamous cell carcinomas of the salivary gland may be a different entity among salivary gland cancers and are most likely secondary, that is, regional nodal metastases to the intraparotid lymph nodes (especially superficial parotid) from a skin cancer of the face or scalp rather than a primary salivary gland malignancy. Similarly, melanomas and Merkel cell carcinomas of the parotid gland are very likely secondary from skin primary tumors. The PLGA, SDC, and epithelial-myoepithelial carcinoma are the most common new subtypes of the WHO 1991 classification. *PLGA* is a solid, ovoid, nonencapsulated mass with a highly variable growth pattern (Figure 49.15A). Most are located in the palate and are slowly growing tumors, and 80% are stage I/II. The prognosis is generally good, with a tendency to local and seldom regional recurrences or distant metastases.[72] SDC resembles ductal breast

cancer morphologically (Figure 49.15B). They derive from excretory duct cells. They are usually located in the parotid gland and are highly aggressive.[73,74] They are frequently positive for androgen receptors and positive for HER2/neu protein.[74] However, the gene amplification is seen in less than 50% of the cases.[57] There is also a low-grade subtype, resembling breast atypical ductal hyperplasia and low-grade ductal carcinoma in situ. The prognosis is excellent.[75] *Epithelial-myoepithelial carcinoma* is mainly localized in the parotid gland. The tumors are composed of myoepithelial cells, surrounded by epithelial-lined ducts, resembling intercalated ducts. It is a low-grade tumor, and all 14 patients of the Dutch study remained disease free. However, local recurrences may be encountered.[76] *Myoepithelial carcinomas* have exclusive myoepithelial differentiation. They are commonly seen in the parotid gland and the palate. Differentiation with other salivary gland cancers may be difficult. The prognosis is poor, with a 5-year disease-free survival of 40%.[77] *Basal cell adenocarcinoma* is a low-grade tumor, predominantly seen in the parotid gland, with a high risk on local recurrence but a low risk for regional recurrences or distant metastases.[78] *Malignant oncocytoma* is a high-grade malignant tumor, characterized by oncocytes, with necrosis, perineural spread, vascular invasion, and a high risk for cervical lymph nodes.[79] Most tumors are found in the parotid gland or SMG. Positive resection margins are a major source of poor overall survival.[79] *Salivary gland cystadenocarcinoma* is a low-grade tumor, predominantly localized in the parotid gland. It has an excellent prognosis.[80] *Mucinous adenocarcinoma* is a high-grade malignancy from the palate and floor of mouth, with a high risk for neck node and distant metastases.[81] Sebaceous carcinoma is mainly localized in the parotid gland and is a slow-growing, low-grade tumor.[82] In 2017, four new entities were described by Skálová et al.[83] *Mammary analog secretory carcinoma* (MASC), mostly a low-grade tumor, in the past was mainly classified as acinic cell carcinoma. They have specific chromosomal translocations and molecular and immunohistochemical findings.[84] Most cases are seen in the parotid gland and oral cavity. *Cribriform adenocarcinoma* mimics PLGA and is primarily seen in the tongue. It is a very rare tumor, with a high risk on positive cervical lymph nodes. *Sclerosing polycystic adenosis adenoma* involves the parotid gland and is, although benign, associated with a high risk of local recurrence after

surgery. Finally, a new myoepithelioma variant is the *mucinous (secretory) myoepithelioma*, with a benign to low-grade malignant behavior. It is a very rare subtype mainly seen in the minor salivary glands.

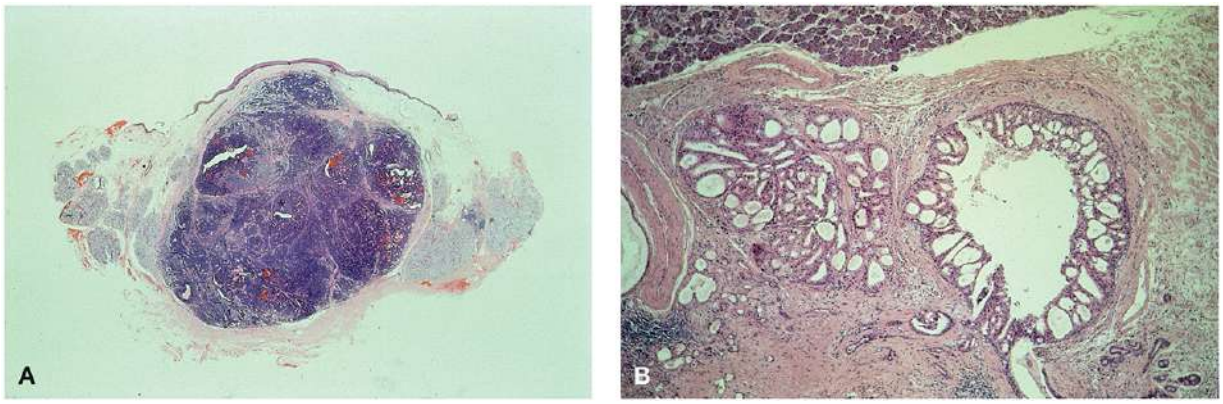


FIGURE 49.15 Examples of polymorphous low-grade adenocarcinoma (A) and salivary duct carcinoma (B). (Courtesy of Prof. Dr P. Slootweg, pathologist, Radboud University Medical Center, Nijmegen Netherlands.)

Based on the high morphologic diversity of salivary gland carcinomas, the differential diagnosis is a challenging task for the pathologist. Molecular testing may serve as a powerful diagnostic tool.[84]

PROGNOSTIC FACTORS

A number of prognostic variables have been studied in the management of salivary gland cancer. In these studies, multivariate analyses have been performed, considering locoregional control, distant metastases, and survival. Results of studies with sufficient number of patients and follow-up have been summarized in Table 49.5. Local control and overall survival are influenced by site, favoring tumors of the oral cavity.[21] T- and N-stages are independent variables for locoregional control, distant metastases, and survival, regardless of site.[8,21,23,34,66,67,85-91] As may be concluded from Table 49.5 in almost all studies, histologic subtype is not an independent prognostic factor for locoregional control but plays a role in risk on distant metastases and overall survival.[21] The added prognostic value of cytology and/or histologic subtype in salivary carcinoma is limited, largely because of the combined prognostic value of other prognostic factors, such as tumor size, N- and M-classification, and comorbidity.[92] Histologic subtypes may

be divided into low- and high-grade tumors, although a bit subjective. Grading is associated with the risk of recurrence and overall survival.[23,88] Comorbidity is associated with overall survival, but not with disease-free survival.[71]

TABLE 49.5 PROGNOSTIC FACTORS FOR SALIVARY GLAND CANCER—SELECTION OF MULTIVARIATE ANALYZED STUDIES

Study (by Name of First Author)	*N*	Locoregional Control	Distant Meta-Analyses	Survival
General				
Terhaard[21,71]	565	L: T, site, bone inv. R: N VII dysfunction, N L + R: Margin, therapy[a]	Gender, T, N, skin, histology, perineural inv.	OS: Gender, age, T, skin inv., bone inv., comorbidity
Holtzman[85] Bjorndal[64] Chen, adenoid cystic[86] Chen, S alone[103]	291 871 140 207	L: T, therapy[b] L + R: Stage, therapy[b] L + R: Stage, margin, vasc. invasion, grade L + R: T4, perineural inv., major nerve involvement, therapy[a] L + R: pN+, grade, margin, T3-T4	Stage	DFS + OS: Stage, clinical nerve invasion, therapy[a] OS: Age, latency, stage, margin, vasc. invasion
Major				
Yun Li[88] (SEER)	4,218			OS + DFS: Age, gender, grade, site (par > subm.), T, N, therapy[a]
Parotid				
Spiro[68]	470			OS: Stage, age, histology, site
Bhattacharryya[66] Vander Poorten[22]	903 237			OS: Age, T, N, extraglandular extension

Study (by Name of First Author)	*N*	Locoregional Control	Distant Meta-Analyses	Survival
				DFS: Age, pain, T, N, perineural + skin inv., N VII dysfunction
Poulsen[87]	209	L: Age, N, margin, grade		
Submandibular				
Bhattachatyya[36]	370			OS: Age, grade
Storey[61]	83	Grade, histology, margin, early years		DS: Early years
Minor				
Jones[8] Lopes[30] Beckhardt[38] Parsons[110] Zeidan[37] (SEER)	103 128 116 95 2,222	L: T, N R: Stage N, histology, bone invasion Histology L: Stage, therapy[a]		OS: T, general condition DFS: Stage, therapy[a] DFS: Grade, T, margin DFS: Stage, therapy[a] OS: Gender, T, N, therapy[a]

DFS, disease-free survival; inv., invasion; L, local; OS, overall survival; R, regional; RT, radiation therapy; S, surgery; SEER, Surveillance, Epidemiology, and End Results; SG, salivary glands.

[a]S + RT > S.

[b]S + RT> RT.

Oncogene expression has been evaluated in the search for additional prognostic factors. In a review, Stenman et al discussed the diagnostics and therapeutic importance of new biologic markers for salivary gland cancer.[93] Overexpression of HER2/neu is related to aggressiveness, distant metastases, and poor survival in salivary gland cancer,[94] especially in SDC.[95] It also has been similarly associated with poor prognosis in carcinomas of the breast, ovary, and endometrium. High Ki 67 nuclear antigen and p53 tumor suppressor expression may be related to poor prognosis. In a study of Finland, comparing both markers, only Ki 67 expression was an independent prognostic factor for overall survival.[96]

Another molecular feature studied in relationship to prognosis was the DNA content in ADCCs. DNA aneuploidy is correlated with the solid type and poor prognosis.[65]

Major Salivary Glands

The survival of patients with submandibular cancers is inferior to that with parotid cancers according to a study by Spiro et al.[68] Extraglandular extension[66,67] and skin invasion[22,89,97] in parotid cancers result in decreased disease-free survival. More advanced age was found to be a negative prognostic factor for locoregional control in some studies[20,32,90] and for disease-free and overall survival in most studies.[22,66,68,89,91] Impairment of the function of the facial nerve is a known prognostic factor, influencing not only locoregional control[7,21,97] but also disease-free survival.[89,91,97,98] Pain at presentation may be associated with reduced disease-free survival.[89] Perineural invasion and pain are closely related; however, perineural growth, not pain, in some studies, is an independent prognostic factor for distant metastases[21] or disease-free survival.[67,86,99]

The importance of histologic subtype for major salivary gland cancer varies in published studies. In most studies, histologic types are subdivided into low and high grade. The main prognostic significance of grading relates to disease-free survival.[66,23] In the large Surveillance, Epidemiology, and End Results (SEER) database of major salivary gland carcinomas, higher grade was associated with higher stage and is an independent prognostic factor for overall survival in stages II to IV.[100] The best prognosis is seen for acinic cell and low-grade MEC[21,69] and the worst for undifferentiated[21,97] and squamous cell cancer.[21,68] At the Netherlands Cancer Institute, a prognostic score for patients with parotid carcinoma was developed and validated.[22,89] The preoperative prognostic score was based on a weighted combination of prognostic factors (age, pain, clinical T- and N-stages, skin invasion, and facial nerve dysfunction); histology and grading were not incorporated. Four subgroups were formed with markedly different prognoses. In the postoperative score, perineural invasion and positive surgical margins were also included. In ADCC, named major nerve involvement is a prognostic factor; however, this may not be true for microscopic invasion only.[101] Intraneural invasion is a more predominant

prognostic factor than perineural invasion.[102] Positive or close surgical margins result in an increase in local recurrence rate.[21,23,61,87,103] RT in addition to surgery improves locoregional control in patients with adverse prognostic factors.[20,26,86,88,97,104,105] Improvement of overall survival by PORT has been shown in data from the National Cancer Database[106] and even in early-stage ADCC.[107] In a matched-pair analysis of PORT, improved overall survival was found in stage III and IV major salivary glands.[108]

Minor Salivary Glands

Tumors located in the larynx or nasal cavity/paranasal sinus have significant lower cause-specific survival compared to location in the oral cavity.[109,110] The poorest prognosis is associated with ADCC.[30,37] Stage, base of skull involvement, and bone invasion are risk factors for locoregional recurrence and survival in minor salivary gland cancers.[8,30,37] Locoregional control may be improved by adding PORT.[37]

GENERAL MANAGEMENT

The general management of salivary gland malignancies in most patients includes surgical excision followed by PORT for unfavorable prognostic factors (Table 49.6). PORT to enhance local control is recommended for T3-T4 tumors, close or incomplete resection, bone involvement, perineural invasion, high-grade cancer, recurrent cancer, and neck node lymph metastases.[21,38,61,67,90,97,103] Elective neck RT prevents nodal relapses; however, it is in general not indicated for acinic cell and other low-grade carcinomas or ADCC.[111] According to Chen et al, study for carcinoma ex pleomorphic adenoma and ADCC, surgery and PORT are the standards.[86,105] Concurrent PORT plus platinum- and/or paclitaxel-based chemoradiotherapy for high-risk patients (nodal involvement, microscopic positive margins, T3-T4, perineural involvement) have been postulated to improve locoregional control rates. However, in the published data, the number of patients is small, the follow-up is short, the acute toxicity is more severe, and there is little proof that concurrent postoperative chemoradiotherapy is superior to PORT alone and is not indicated.[112,113] For advanced, inoperable, and recurrent salivary gland cancers, high linear energy transfer (LET) RT such as primary neutron therapy (NRT)[114] may

lead to superior local control rates, compared with primary photon therapy, without clear evidence of improved survival rates[115] Another treatment option in these cases is carbon ions, with the advantage of a higher relative biologic effectiveness (RBE) on tumor similar to NRT.[116] High local control rates may be achieved with primary treatment with carbon ions in ADCC.[117] In Table 49.6, indications for RT in salivary gland cancer are summarized.

TABLE 49.6 INDICATIONS FOR RADIOTHERAPY: SALIVARY GLAND CANCER

Local PORT	Regional PORT	Primary RT (≥70 Gy)	High LET RT Consider If Available
AJCC stage T3-T4	pN_+ (60 Gy)	Med. inoperable	R2 resection
High grade	ENE (66 Gy)	Funct. inoperable	Primary RT: T4
Perineural invasion	Elective (Table 49.1) 50 Gy	Irresectable	Reirradiation
Close res. (1-5 mm) (60 Gy)		Recurrent	
Incomplete res. (66 Gy)			

AJCC, American Joint Committee on Cancer; ENE, extranodal extension; Funct., functional; LES, low energy transfer; Med., medical; PORT, postoperative radiotherapy; Res., resection; RT, radiotherapy.

Major Salivary Glands

Surgical technique depends on the location and extent of primary disease and regional adenopathy.

Parotid Tumors

Superficial parotidectomy is generally sufficient for low-grade tumors with a well-defined capsule. Partial deep lobe dissection may be required for larger tumors extending between the upper and lower divisions of the facial nerve or deep to the mandible beneath the pes anserinus. A total parotidectomy involves removing the entire parotid gland both superficial and deep to the facial nerve and is typically indicated for high-grade tumors with extension to the deep lobe, those with suspected intraglandular lymphadenopathy, or tumors originating within the deep lobe.

Preoperatively, surgeons must be prepared to sacrifice the facial nerve and plan reconstruction accordingly when there is facial asymmetry in the presence of known malignancy or when there is obvious PNTS on preoperative imaging. If the preoperative examination and diagnostic evaluation reveal a fully intact VII, all attempts should be made to preserve it during surgery, except in the case of gross invasion encountered intraoperatively.[41]

Preservation of VII, at least partially, followed by PORT is the preferable treatment unless VII is already involved by tumor.[118] Aggressive surgery does not improve disease-free survival in the absence of nerve involvement. A decrease in extended surgery, resulting in a decrease in sacrifice of VII, has been shown in the course of years.[68] Cable facial nerve grafting with the greater auricular or sural nerve graft decreases the incidence of facial palsy postoperatively, especially if branches and not the main trunk are involved.[119] PORT has no negative effect on facial nerve function.[119] When there is nerve involvement, resection should proceed until proximal and distal facial nerve margins are negative, which may require mastoidectomy in order to transect the nerve proximal to invasion. Failure to do so is associated with an increased incidence of locoregional recurrence.[120]

Advanced tumors may invade into adjacent structures, including the overlying skin, muscle (masseter, sternocleidomastoid, pterygoid, or temporalis), bone (mandible, styloid, mastoid), and vasculature (external or internal carotid artery). Resectability should be determined by a careful review of the preoperative imaging and multidisciplinary tumor board review. In particular, careful consideration of potential encasement of the internal carotid artery should be reviewed in advanced malignancies. A multi-subspecialty approach (head and neck surgeon, reconstructive surgeon, radiation oncologist) may be necessary to optimize resection and reconstruction versus consideration of primary RT, especially with high LET particle beam RT (ie, NRT or carbon ion, if available) in all salivary gland origin malignancies. If a salvage surgical approach (in case of RT failure) and its morbidity are not going to be significantly different versus upfront surgery, an initial nonsurgical approach could be justified, with the caveat that postirradiation surgery could perhaps have greater perioperative complications. Multidisciplinary tumor board discussion between the

surgeon and radiation oncologist is essential and may also influence PORT fields.

It is well established that a clinically positive neck should be addressed with a neck dissection, followed by PORT.[26] The risk of occult nodal disease depends on T-stage and histologic type.[26,110] High-grade salivary histopathologies have a 49% risk of occult lymph nodal metastases compared to low- or intermediate-grade tumors.[121] High-risk histologies include high-grade MEC, adenocarcinoma NOS, carcinoma ex pleomorphic adenoma, SDC, squamous cell carcinoma, undifferentiated carcinoma, or any other tumor with high-grade transformation; have been shown to have a higher risk of occult metastases; and are typically treated with neck dissection at the time of resection of the primary.[32,121-126]

As shown in the scoring system in Table 49.1, the decision to treat the neck for parotid tumors will be indicated by a score of at least 4.[26] When local prognostic factors indicate PORT, no elective neck dissection has to be performed; the neck nodes could be electively irradiated without compromising regional control.[24,127] Parotid tumors with facial nerve involvement are associated with frequent occult neck nodes. Elective neck treatment is also indicated for all high-grade cancers. Elective neural treatment to the proximal origin of the involved nerve is indicated to all tumors with overt PNTS.[127] Specific levels of elective neck dissection or neck irradiation for occult metastases are dependent upon the site of disease. For parotid tumors, level IB-IV is generally recommended.[121] Involvement of level I for parotid tumors is an independent risk factor for disease-free survival.[128] For submandibular and sublingual malignancies, neck dissection of levels I to III is sufficient.[129]

The first echelon neck nodes in parotid salivary gland cancer are the intraparotideal,[28,130] followed by level IB-IV nodes.[111,130] Level IA and V nodes are only involved if other levels, especially level IB, are positive.[130] Contralateral neck nodes are generally not at risk. There is no indication for elective neck dissection or neck irradiation for T1 acinic and other low-grade tumors or ADCC (Table 49.1).[26,61,111]

Submandibular and Sublingual Gland Tumors

In most cases, elective neck dissection of levels I to III combined with a local resection is performed for submandibular tumors. SMG excision is generally uncomplicated due to the fascial capsule around the gland, which limits spread. Advanced tumors can, however, invade the adjacent mandible, lingual nerve (V3), XII, and marginal mandibular (VII) nerves. Similarly, sublingual gland malignancies necessitate a wide local excision of the floor of mouth mucosa and may require partial resection of the tongue musculature, mylohyoid, mandibular periosteum, and lingual nerve. Occasionally, a marginal or segmental mandibulectomy is necessary and requires osseocutaneous free flap reconstruction.

Minor Salivary Glands

Minor salivary gland malignancies may arise in a wide variety of locations, and site-specific surgery approaches are necessary. ADCC is the predominant histologic subtype in minor salivary gland cancer. Surgical resection is typically indicated for tumors arising in the palate, tongue, floor of mouth, oral cavity, or oropharynx, as surgical exposure is readily available and postoperative morbidity is acceptable. However, tumors arising in the nasopharynx, posterior nasal cavity, or sphenoid region may be less resectable.[131] Primary RT has been used in surgically inaccessible sites or combined with surgery because of locally aggressive tumor behavior and the occurrence of incomplete resection.[21,38,131]

The indication of elective neck treatment may depend on a prognostic index (scores 0-4) using four clinicopathologic factors associated with increased risk on positive nodes: male gender, stage T3/T4, pharyngeal location, and high grade.[29] For a score greater than 2, elective treatment of the neck nodes is indicated. The risk of occult neck disease is largest for oral cavity or oropharyngeal localizations. When PORT is indicated, it is advisable to treat the ipsilateral neck nodes as dictated by the location of the primary site and its draining lymph nodes.[132] Patients with ADCC can have a long natural history with late recurrences,[131] and consideration should be given to careful surgical reconstruction and rehabilitation because even patients who are not cured can live many years before dying of disease (Figure 49.3).[21] Occasionally, a patient may present after simple excision of a lesion, and the pathologic examination shows ADCC. If reexcision would

cause significant functional or cosmetic sequelae, RT alone may be used, and in terms of optimizing for the best probability of local control, particle beam RT such as NRT or carbon ions would be the treatment of choice, if available.[115] However, a planned simple excision is not recommended as the initial management of these tumors because of the potential for a significant volume of residual disease. Surgery alone may be used to treat early-stage hard palate lesions without evidence of positive margins, perineural spread, or bone invasion; simple excision must be avoided.[39]

RADIATION THERAPY TECHNIQUES

Pleomorphic Adenoma

The pleomorphic adenoma (benign mixed tumor) is histologically benign, occurs frequently in a relatively young population, and comprises 65% to 75% of all parotid epithelial tumors.[68] Standard therapy has been conservative (superficial) parotidectomy, with recurrence rates of about up to 6.5% after 2 years.[133-135] Simple excision results in a high recurrence rate of around 25% as focal capsular exposure occurs in virtually all cases.[136] Besides, local recurrence is more frequently encountered in younger patients and positive resection margins.[133,135] Indications for postoperative irradiation may include microscopically positive margins after surgical resection and large, deep-seated lesions that may not allow complete surgical excision with adequate margins or would require sacrificing the facial nerve and spillage during surgery. The risk of malignant transformation in a large Dutch study was only 0.15%; however, in recurrent cases, it is 3.2%.[135] The mean delay between surgery and the first recurrence was 7 years and only 2 years for the second recurrence. The risk of facial nerve paresis increases after repeated surgery.[136] Most recurrent pleomorphic adenomas are multinodular.[137] In a review of Witt et al, local control after surgery for recurrence was 63% after surgery alone and 91% after surgery with PORT.[137] RT may decrease the risk of a recurrence in case of multinodular recurrence only, not for uninodular disease.[138] The entire parotid area should be irradiated with a dose of 50 to 60 Gy in 5 to 6 weeks. In Figure 49.16, an example of a large, multicystic pleomorphic adenoma is shown, with a close safety margin and spillage during parotidectomy; PORT was indicated.

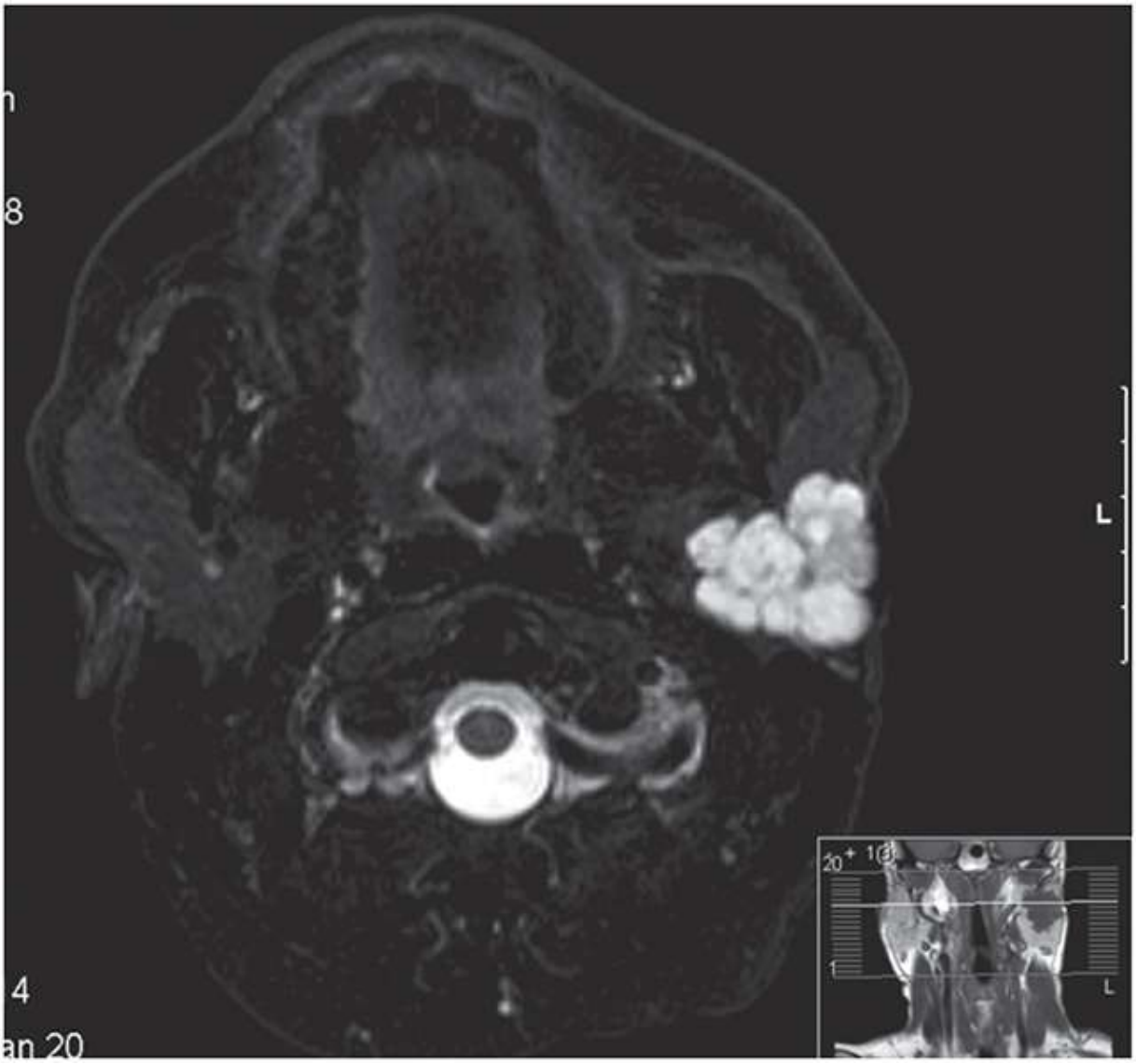


FIGURE 49.16 Multicystic pleomorphic adenoma, T2 STIR, transversal slice.

Parotid Gland

The volume of PORT is determined by pathologic findings, such as perineural invasion of a major nerve, lymph node involvement, and grade of the tumor. Typically, the entire ipsilateral preoperative parotid gland bed is delineated on the postoperative CT scan performed in a custom-made head and neck mold.[67,139] The delineation of the clinical target volumes will be individualized based on the extent and grade of the disease and surgery performed.[67] For example, in case of an aggressive tumor of the deep lobe, the parapharyngeal space and the infratemporal fossa have to be electively

covered. Although it is good practice to include the entire surgical bed, it is not necessary to treat the entire scar to full skin dose because only 1% of the patients have a scar failure.[89] For skin-invading tumors, a bolus over the scar is required. In tumors with named perineural invasion (eg, ADCC), especially in case of intraneural invasion,[101] the nerve provides a route to the base of skull. So, it is important to electively cover the entire CN pathways from the parotid up to the nerve origin at the base of the skull.[101] For perineural invasion, PORT with a dose of 50 Gy, including the base of skull, decreased the local recurrence rate from 15% with surgery alone to 5% with combined surgery and PORT in a study by Chen et al.[140] Focal microscopic perineural invasion only is not an indication for routine inclusion of the entire nerve pathway, although it would be prudent to cover the nerve foramina at the skull base, for example, the stylomastoid foramen and/or the mastoid segment of VII up to the distal genu, while sparing the cochlea, and the foramen ovale in case of ATN without including a large volume of the temporal lobe of brain. A clear relationship between dose and local control has only been found by Chen et al; a dose of 60 Gy or higher resulted in significantly higher local control rates for occult disease, and a dose of at least 60 Gy PORT is recommended[25,86,100,139] and at least 66 Gy (33 fractions) for high-risk patients with positive margins (<1 mm) and extensive PNTS.[67]

The ipsilateral neck is treated after a neck dissection has been performed for positive nodes; levels I to V should be included.[26] There is no indication for bilateral elective neck treatment.[24,28,111] The recommended PORT dose for positive nodes is at least 60 Gy (30 fractions) and 66 Gy for extranodal disease.[26] Elective irradiation of the neck should be considered for advanced T-stage, certain histologic subtypes (Table 49.1), facial nerve dysfunction at presentation, and recurrent disease. The intraparotid nodes should be included by treating the entire parotid bed in node-positive cancers.[28,129] In high-risk parotid cancer, level 1B-IV should be electively included.[26,28,127,141] A dose of around 46 to 50 Gy is recommended.[26,67]

Three basic conventional PORT approaches are widely used, depending on available equipment: three-dimensional conformal radiation therapy (3DCRT) planning procedure, electron/photon mixed technique, and intensity-modulated radiation therapy/volumetric modulated arc therapy (IMRT/VMAT) planning. The first involves unilateral anterior and posterior

oblique-wedged pair fields using 60Co or 4- to 6-MV photons (Figure 49.17A). Typical field boundaries to treat the parotid bed are the zygomatic arch superiorly, the anterior border of masseter muscle anteriorly to cover the parotid duct and accessory gland along the duct, just behind the mastoid process posteriorly, and the posterior belly of the digastric muscle near hyoid bone inferiorly.[105] These may have to be altered (enlarged) if elective treatment of lymph nodes or nerve pathways is indicated. A slight inferior angulation of the beams avoids an exit dose through the contralateral eye. A simpler technique uses homolateral fields with 12- to 16-MeV electrons in combination with photons.[77,142] Usually, 80% of the dose is delivered with electrons and 20% with 60Co or 4- to 6-MV photons to spare the opposite salivary gland, reduce mucositis, and decrease the skin reaction produced by electrons (Figure 49.17B). Yaparpalvi et al[142] compared nine conventional treatment techniques. Ipsilateral wedge pair technique with 6-MV photons, wedged anterior-posterior and posterior-anterior and supplemented by a lateral 6-MV beam, and mixed beam using 6-MV photons and 16-MeV electrons (1:4 weighted) were the most optimal, considering dose homogeneity within the target and dose to normal tissues. Electron beam (9-12 MeV) and tangential photon fields are effective conventional techniques for sparing the underlying spinal cord (< 45 Gy) and the contralateral parotid gland in elective neck RT. Conventional techniques do not allow for tissue heterogeneity (air cavity, dense bones, and tissues); underdose and overdose may be seen. However, this would not preclude efficacious PORT, where resources are scarce. Modern RT with conformal techniques like IMRT/VMAT should be the treatment of choice where available, due to superior dose homogeneity and target coverage while sparing organs at risk (OARs), especially the ipsilateral cochlea.

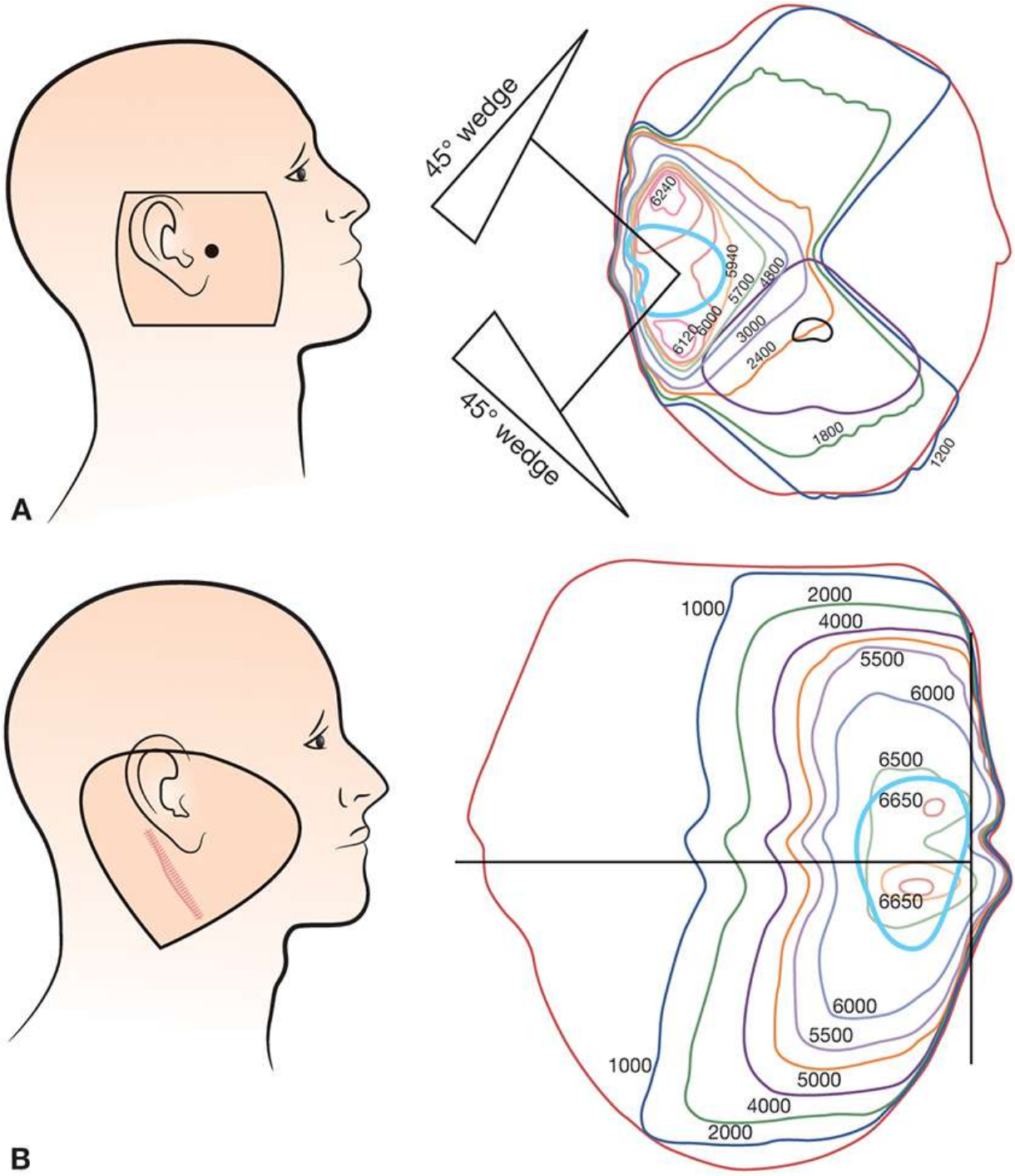


FIGURE 49.17 Conventional radiotherapy for parotid cancer. A. Unilateral wedge arrangement and isodose distribution using wedged pair. B. Ipsilateral 16-MeV electrons plus 60Co (4:1) electron beam field.

After outlining of the target volumes and critical normal tissues on the planning CT scan, a more conformal plan by the use of geometrically

shaped beams of uniform intensity may be reached.[139] More normal tissue may be spared with this technique.[139,143] In case of named perineural invasion, athin cut MRI, ideally in the treatment position, can be used to delineate the CNs be used to delineate the CNs (Figure 49.9). IMRT/VMAT can produce conformal dose distributions and steep dose gradients. Five- to seven-field inverse IMRT allows excellent coverage of the tumor with sparing of the mandible, cochlea, spinal cord, brain, temporal lobe, and oropharynx,[144] compared with 3DCRT. Especially the dose to the cochlea and eustachian tube should be limited to 45 to 50 Gy.[145,146] Compared to 3DCRT, IMRT may spare the inner ear better.[147] In the National Cancer Database, 5-year overall survival for major salivary gland treated postoperatively with IMRT or 3DCRT was, respectively, 84.7% and 80.7% (P = .06).[107] Figure 49.18 shows a comparison of 3DCRT and IMRT planning for a PORT plan for a parotid cancer, without named nerve involvement, treated with a dose of 66 Gy. The mean dose to the mastoid, meatus acusticus externus, and contralateral parotid gland was 53 and 43, 57 and 51, and 1 and 9 Gy, for 3DCRT and IMRT, respectively. The maximum dose to the cochlea was 39 and 32 Gy, respectively. In Figure 49.19, a patient with a recurrent adenocarcinoma of the parotid gland with named perineural involvement, for which a total parotidectomy was performed, is shown. The resection was incomplete. The involved facial nerve was delineated based on MRI (Figure 49.9B). A unilateral IMRT technique was used.

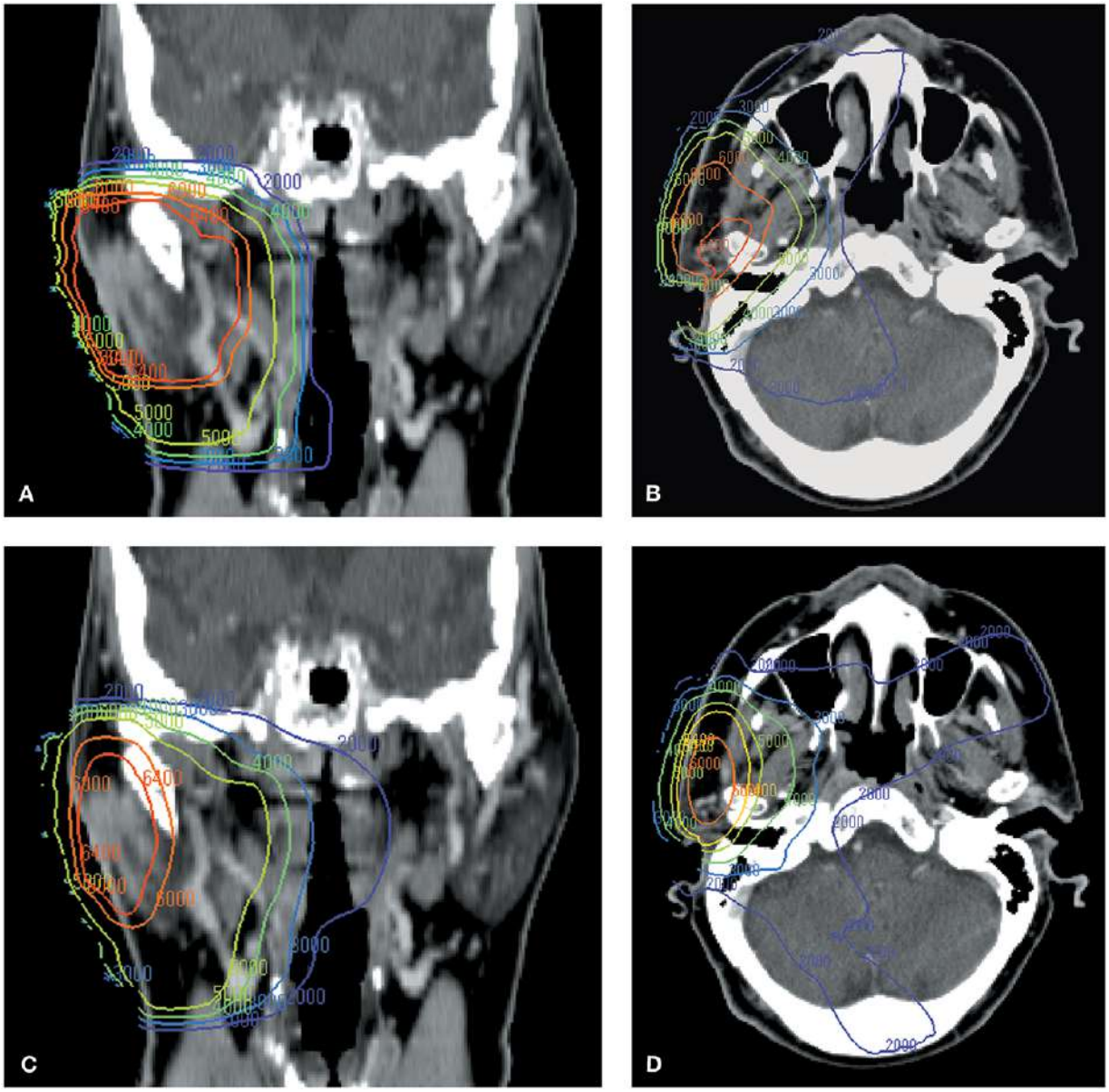
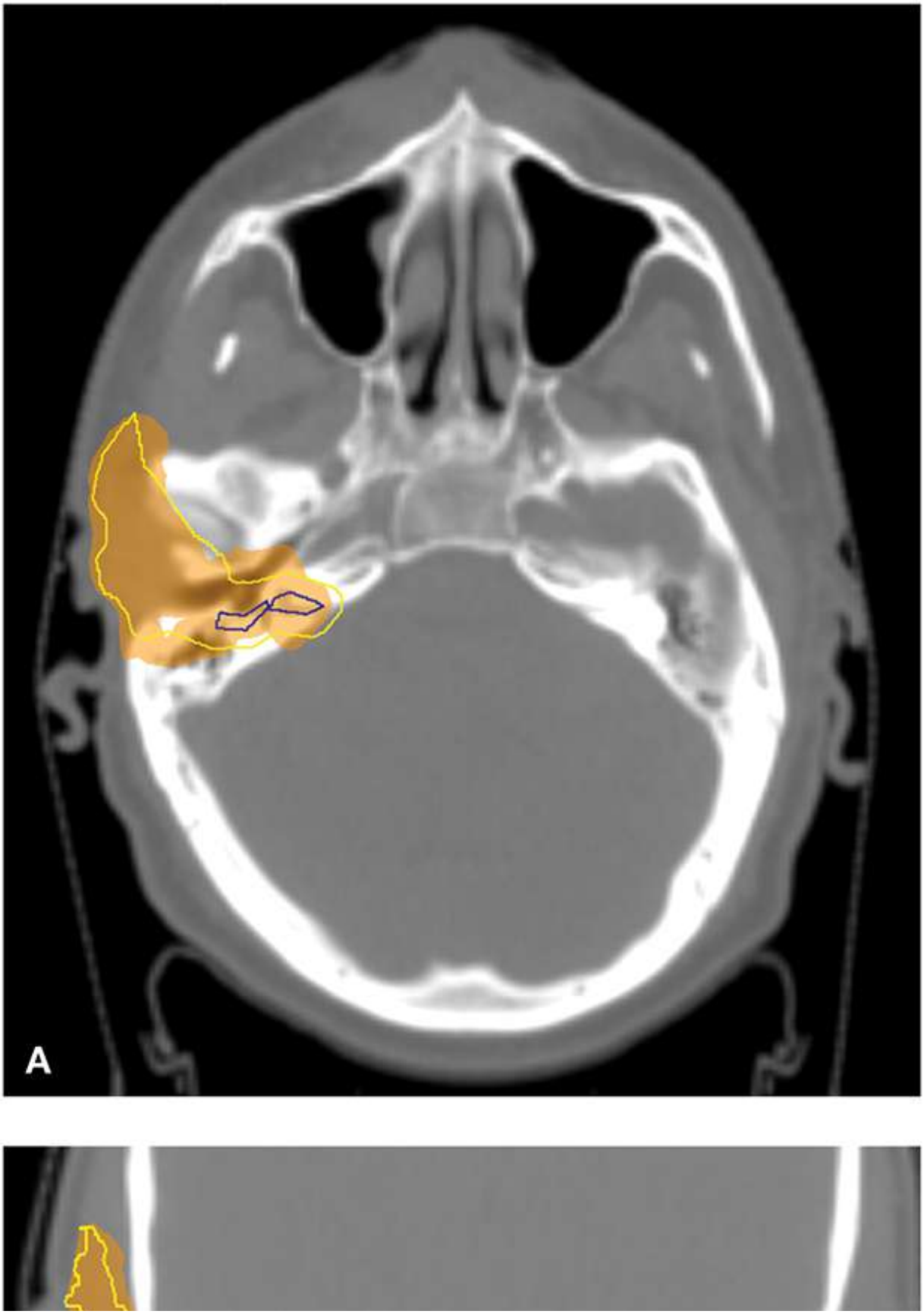


FIGURE 49.18 Postoperative radiation therapy of a parotid cancer, microscopically incomplete resected. Coronal (A and C) and transversal (B and D) dose distribution for three-dimensional conformal radiation therapy (25 × 2 Gy primary field, 8 × 2 Gy boost) (A and B) and intensity-modulated radiation therapy (inverse, 7 fields and 39 segments; simultaneously moderated accelerated radiotherapy [SMART]: 33 × 1.6 Gy primary field, 33 × 2 Gy boost) (C and D).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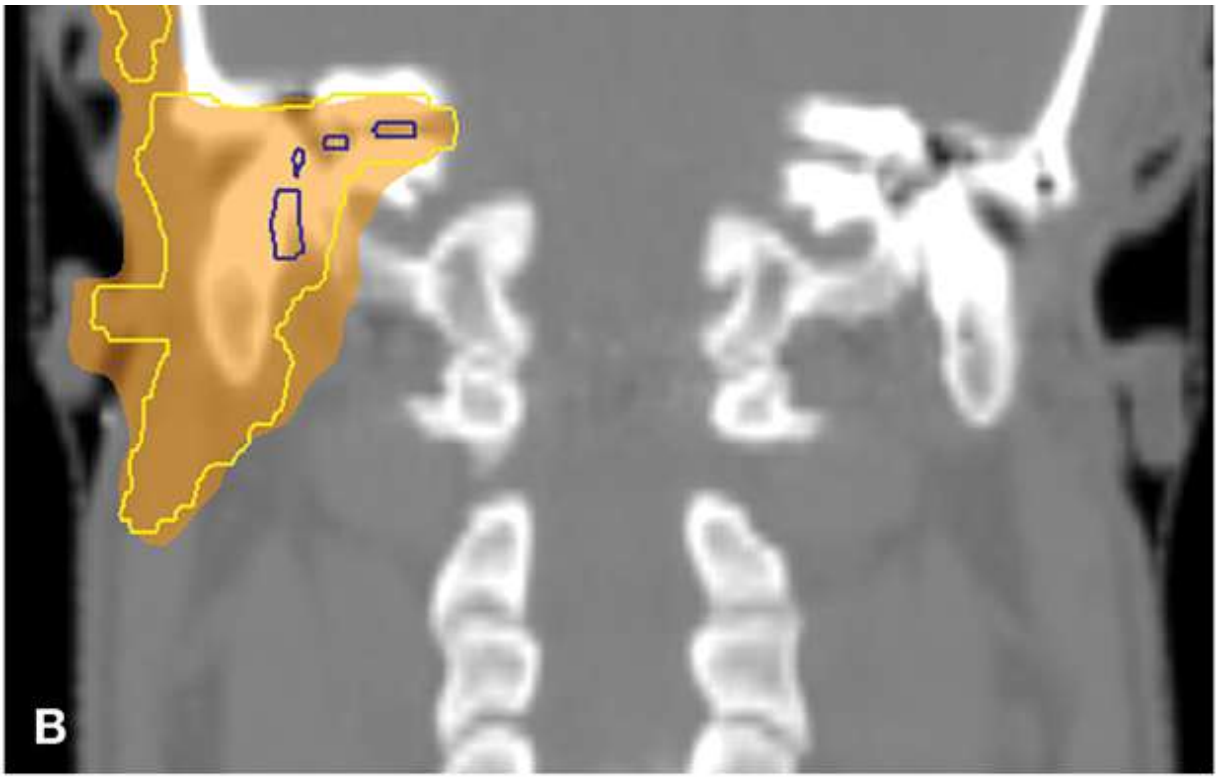
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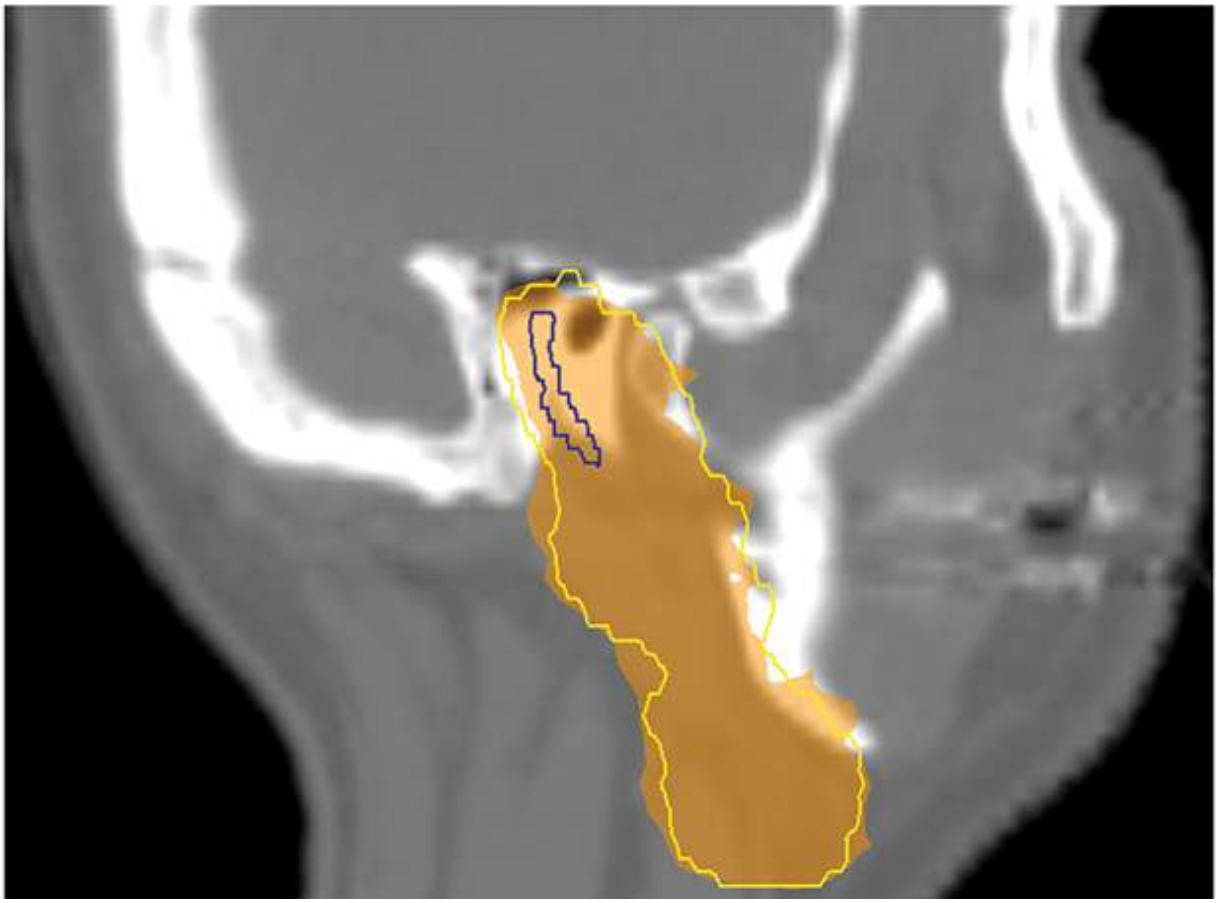


FIGURE 49.19 Recurrent adenocarcinoma of the parotid gland with named nerve involvement (nVII, in blue), delineated on the base of magnetic resonance imaging (Figure 49.9B). A unilateral intensity-modulated radiation therapy technique was used, in yellow 50-Gy isodose (boost not shown): transversal (A), coronal (B), and sagittal (C) planes.

Submandibular Gland

Except for small acinic cell, other low-grade tumors, and ADCC (see Table 49.1), the neck node level IB-IV[141] should be irradiated electively, following the indications outlined for parotid tumors; technical considerations are similar. Bilateral fields may be required for tumor extension toward the midline, although they should be set up to spare the contralateral salivary glands. Five-year locoregional control was significantly higher for a dose of more than 56 Gy in a study by Mallik et al.[148] If there is named perineural invasion of a major nerve, a tumor dose of 60 to 66 Gy in 6 to 6.5 weeks is recommended with the highest dose (66-72 Gy) to the grossly identifiable nerve involvement (per MRI), and electively the nerve path to the base of skull should be treated. For ADCC of the SMG with only focal microscopic perineural invasion, an attempt to encompass the base of the skull near the foramen ovale would require a significant change in the treatment volume and may not be warranted because of potential morbidity of including the entire ipsilateral parotid gland and the low rate of relapse at that site.[131] Sparing of the parotid while electively treating up to the inferior alveolar nerve foramen of the mandibular ramus is adequate. An example of 3DCRT for a T2 ADCC of the SMG is shown in Figure 49.20.

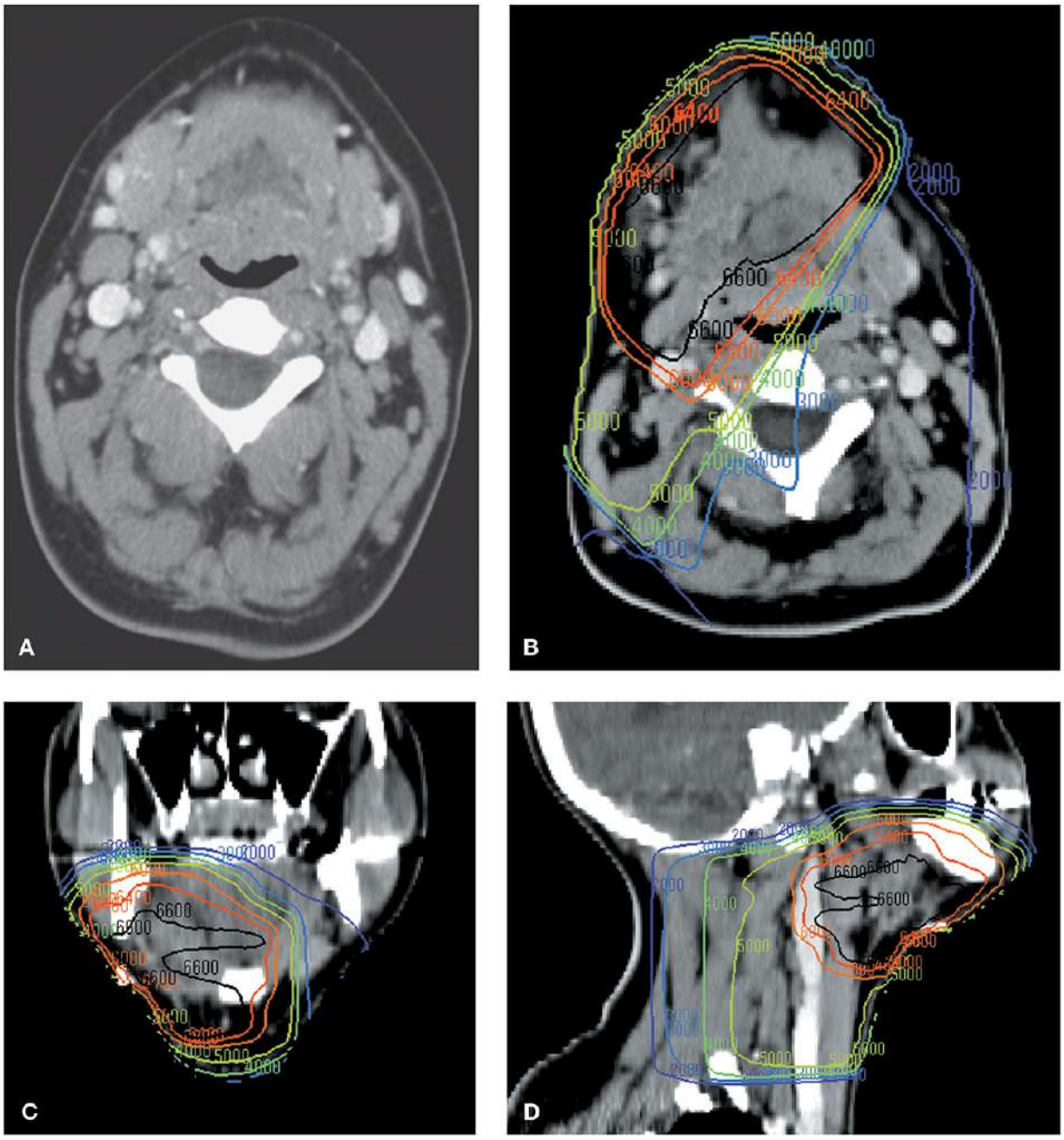


FIGURE 49.20 Dose distribution for a T2N0 adenoid cystic cancer of the right submandibular gland. Computed tomography performed before microscopically incomplete local excision (A). Three-dimensional conformal radiation therapy, three fields (one right and two left oblique): 25 × 2 Gy, 5 × weekly primary tumor and level I to III nodes, 8 × 2 Gy boost; transversal (B), coronal (C), and sagittal (D) planes. Mean dose to contralateral submandibular gland is 27 Gy.

Sublingual Gland

These tumors are mostly malignant and mostly ADCC, and most patients present with advanced disease and high grade but with a relatively lower risk of positive neck nodes. Aggressive surgery is required, with PORT in almost all cases,[39,149] with elective treatment of levels I to III.[140] In case of named nerve involvement, the lingual and/or XII nerve should be included in the RT portals.

Minor Salivary Glands

The RT technique for treating minor salivary gland tumors depends on the involved location and two additional considerations. First, when a named branch of a CN is involved by ADCC, the nerve pathways to the base of the skull should be electively treated. Second, for tumors of the paranasal sinuses, the base of the skull is electively included because of its proximity to the tumor bed. In case of ADCC with perineural invasion, IMRT may reduce the high-dose volume, compared to conventional bilateral opposed fields; Figure 49.21 shows an example for a patient with a minor salivary gland cancer of the palate. IMRT is a useful strategy for irradiating minor salivary gland sites such as the ethmoid sinuses while sparing the optic pathways.[150]

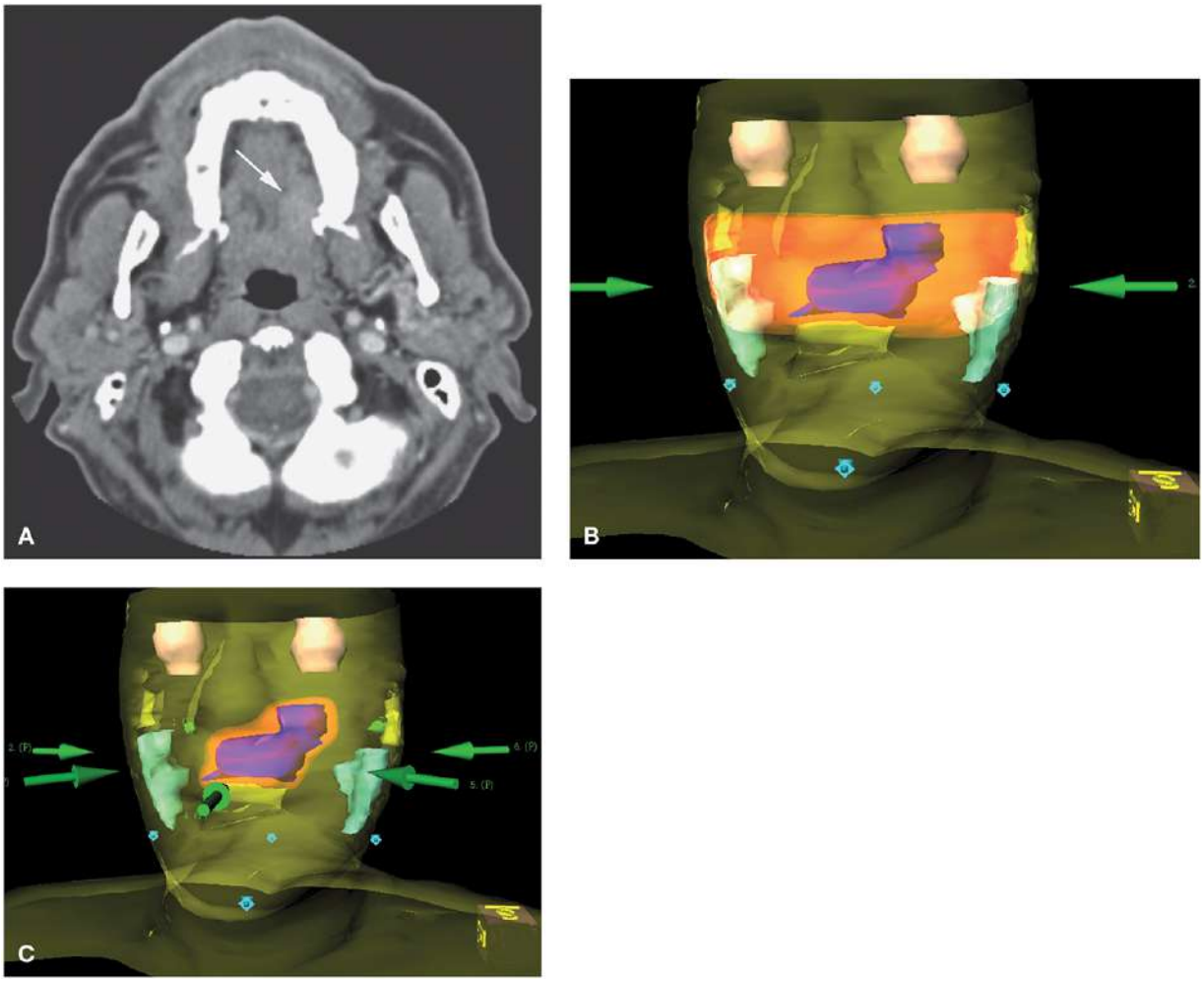


FIGURE 49.21 T2NO adenoid cystic cancer of the palate with major perineural invasion. Computed tomography performed before local excision (A, arrow: tumor); target includes right palatinus major nerve until base of skull. Dose distribution (25 × 2 Gy primary field) in transversal planes; conventional bilateral opposed fields (B); intensity-modulated radiation therapy (7 fields, 40 segments) (C); 95% isodose of 50 Gy in red.

Also, because the incidence of lymph node metastases is usually lower for ADCC than that for squamous cell carcinomas of similar size, the RT fields are rarely extended to cover nodal regions for N0 cancers. Indications for elective treatment of the neck nodes may depend on a scoring system.[26,29] Typically, for male patients with a T_3/T_4 N_0, pharyngeal site tumor neck nodes should be treated prophylactically.[131] In minor salivary gland cancers of the oral cavity, elective radiation of the neck nodes is indicated only for high-grade cancers. PORT is indicated after resection of metastatic neck lymphadenopathy.

For patients receiving PORT after surgical resection, a dose of 60 to 63 Gy is given for close margins and 66 Gy for microscopically positive margins. For gross residual disease after surgery or for lesions treated with RT alone, a total dose of 70 Gy is recommended at 2 Gy per fraction, although NRT or carbon ion should be used if available for optimal outcomes. Elective dose to the relevant nodal levels is in the range of 46 to 50 Gy.[26,131,151]

RESULTS OF THERAPY

Surgery Plus or Minus Postoperative Radiotherapy

Tables 49.7 to 49.9 list local control rates and 5- and 10-year survival rates for several series reporting the surgical, RT, and combination treatment of carcinomas of the major and minor salivary glands. Little adverse effect of delay between surgery and PORT may be predicted for what are, in general, slow-growing salivary gland cancers. In three studies, one concerning submandibular cancer,[61] one for minor salivary gland,[131] and another for ADCC,[86] impaired locoregional control rates were seen for a delay of more than 6 weeks, which was not confirmed in the Dutch study.[26] The prognosis for children with a malignant salivary gland cancer (mostly MEC of the parotid gland) is excellent, with a 5-year overall survival of more than 90%.[9] Most are treated with surgery alone because of the possible risk of radiation-induced malignancies.

TABLE 49.7 RESULTS OF STANDARD THERAPY FOR CANCER OF THE PAROTID

Study (by Name of First Author)	Number of Patients	Treatment	% 5-Y Survival	% 10-Y Survival	% Local Control
Bhattacharyya[66]	903	S ± R	67	50	NA
Spiro[7]	623	S	55	47	61
Terhaard[21]	37	S	67	61	51 (10 y)
	254	S + R	65	51	88 (10 y)
Garden[67]	166	S + R	78	60	90 (10 y)
North[97]	19	S	59	NA	74
	50	S + R	75	NA	98

Study (by Name of First Author)	Number of Patients	Treatment	% 5-Y Survival	% 10-Y Survival	% Local Control
Poulsen[87]	209	S + R	71	65	76
Renehan[104]	37	S	77	63	57 (locoreg.)
	66	S + R	78	67	85 (locoreg.)
Pohar[20]	56	S	65	50	63 (locoreg.)
Chen (carc, ex pl. ad.)[105]	91	S + R	55	40	89 (locoreg.)
	23	S	44	NA	49 (5-y)
	40	S + R	59	NA	75 (5-y)

ad, adenoma; carc, carcinoma; locoreg., locoregional; NA, not available; pl., pleomorphic; R, irradiation; S, surgery.

TABLE 49.8 RESULTS OF STANDARD THERAPY FOR CANCER OF THE SUBMANDIBULAR GLANDS

Study (by Name of First Author)	Number of Patients	Treatment	% 5-Y Survival	% 10-Y Survival	% Local Control
Spiro[7]	129	S	31	22	40 (loreg.)
Terhaard[21]	68	S + R	57	45	91 (10 y)
Storey[61]	83	S + R	60 (DFS)	53 (DFS)	88 (loreg.)
Bhattacharyya[36]	370	S ± R	60	NA	NA
Mallik[148]	39	S + RT			
	25	RT ≤ 56 Gy	59 (DFS)	NA	59 (loreg.)
	14	RT > 56 Gy	77 (FDS)	NA	100 (loreg.)

DFS, disease-free survival; loreg., locoregional; NA, not available; R, irradiation; RT, radiation therapy; S, surgery.

TABLE 49.9 RESULTS OF STANDARD THERAPY FOR MINOR SALIVARY GLANDS

Study (by Name of First Author)/Site	Number of Patients	Treatment	% 5-Y Survival	% 10-Y Survival	% Local Control
Spiro[7]	526	S	48	37	35 (locoreg.)
Garden[131]	160	S + R	81	65	88 (15 y)

Study (by Name of First Author)/Site	Number of Patients	Treatment	% 5-Y Survival	% 10-Y Survival	% Local Control
Terhaard[21] (oral cavity)	67	S	87	76	91
	54	S + R	85	72	98
Lopes[30] (oral cavity)	59	S	86	83	90 (locoreg.)
	32	S + R	88	56	78 (locoreg.)
	15	R	46	–	13 (locoreg.)
Beckhardt[38] (palate)	79	S	90 (DSS)	80 (DSS)	NA
	35	S + R	87 (DSS)	83 (DSS)	NA
Ali[63] (adenoid cystic, 59 minor)	28	S			42 (10 y)
	58	S + R			90 (10 y)
Salgado[151]	98	S + R	82	58	81 (10 y)
Zeidan[37]	90	S + R	76	63	88 (10 y)

DSS, disease-specific survival; locoreg., locoregional; NA, not available; R, irradiation; S, surgery.

Long-term follow-up is recommended because failures may appear after 5 years, especially for minor salivary gland tumors and ADCC.[8,21,23,86] Recurrent tumors in general are more difficult to control than are primary ones, so initially optimized locoregional control rates should be the goal. Because of high rates of local failure of approximately 40% for parotid gland, 60% for SMG, and 65% for minor salivary glands with surgery alone,[7] many institutions have advocated PORT especially to reduce the incidence of local failure. Local tumor control appears to be improved by the combination of surgery and PORT, although randomized controlled trials have not been performed. Evidence in favor of PORT is based on retrospective studies and matched-pair analyses. In the matched-pair study by Armstrong et al,[108] PORT significantly improved locoregional control (from 17% to 51% for stages III-IV), not for stages I and II major salivary gland cancer. Locoregional control for patients with positive nodes increased from 40% to 69%. In most studies, an imbalance in prognostic factors is seen comparing surgery alone with combined therapy, favorable surgery alone. Despite this imbalance, locoregional control with combined surgery and PORT is superior to surgery alone for patients with negative

prognostic factors, irrespective of site.[21,26,61,63,85,86,88,105,108,148] This was also shown for low-grade salivary gland cancer.[152] In the nationwide Dutch study, the relative risk for surgery alone, compared with combined treatment, was 9.7 for local recurrence and 2.3 for regional recurrence.[26] PORT is particularly effective if there are close (<5 mm) or microscopic positive resection margins, enhancing local control from around 50% to 80% to 95%.[26,86,87,118] Comparable results are noted for T3-T4 tumors and pathologically confirmed bone and perineural invasion.[26,63,85,148] For ADCC with perineural invasion, PORT increased 10-year local control rates from 30% to 80% in a study by Chen et al.[86] However, for a T1 or T2 low-grade tumor that was completely resected with no bone, lymph node, or perineural invasion, surgery alone will result in more than 90% 10-year local control rate and PORT is not indicated.[26]

Treatment results may also depend on histopathologic status. However, after review, histologic type may change, even among experienced pathologists. In general, the best prognosis is shown for *acinic cell* and low- to intermediate-grade MEC, with a 15% risk of distant metastases after 10 years and a 10-year locoregional control rate of around 85%. Ten-year overall survival is around 80% and 65%, respectively.[7,21,36,69] PORT is indicated for the high-grade group.[21,69] *Squamous cell* and *undifferentiated* tumors have been associated with a 10-year overall survival of 35% or less, caused by a high risk of distant metastases and locoregional recurrence of 35% and 50%, respectively.[7,21,87] PORT is indicated in all cases to improve locoregional control. The intermediate-risk group consists of *cancer ex pleomorphic adenoma and* ADCC. Distant failure after 10 years is around 35% after initial staging with CT scan.[21,34,105] Although the risk of nodal recurrence is low (5%-10%), local recurrence and neural pathway recurrence are diagnosed more often (20%-50%) in ADCC. PORT is indicated in almost all cases. In cancer ex pleomorphic adenoma, 5-year local control rates were 75% and 49% for yes or no PORT, respectively, in a study by Chen et al.[105] A precipitous decrease in relapse-free survival is noted among 5 (around 70%), 10 (around 50%), and 15 years (around 45%) for patients with ADCC, which are well known for late recurrences.[21,63,86] Significant improvement was reported in local control for ADCC with combined surgery and PORT in several studies,[64,86,103,104] regardless of site.

Local tumor control rates with combined modality therapy for these tumors approach 85% to 90% at 10 years.

In the WHO classification of 1991, among others, three new subtypes were described that are diagnosed relatively frequently. *PLGA* is situated predominantly in the palate. The vast majority is cured with a wide local excision, without a need for elective treatment of the neck. In the large SEER database, the 10-year disease-specific survival was more than 95%, and only 20% of the patients were treated with PORT.[72] SDC is a very aggressive disease, predominantly arising in the parotid gland. PORT is indicated in all cases. Most patients die of distant disease, despite often successful locoregional combined therapy. PORT improves locoregional control.[73,74] Because of a high percentage of distant metastases, 5-year survival is only around 30%.[73] The prognosis correlates with HER2/neu receptor status. HER2/neu overexpression correlates with decreased disease-specific survival.[74] *Epithelial-myoepithelial* cancers have a very favorable outcome, with the risk of distant metastases below 5% and a disease-free survival of more than 80% after 10 years. However, local recurrences may be seen in one out of three; PORT is indicated in case of incomplete margin, tumor necrosis, lymphatic invasion, and myoepithelial anaplasia.[76] In *basal cell adenocarcinoma*, PORT may increase overall survival for T3-T4 cases.[78]

Minor salivary gland tumors of the oral cavity have a more favorable prognosis than paranasal sinus tumors (maxillary and ethmoid sinus and nasal cavity), possibly due to dosimetric limitations of 3DCRT and initial extent of involvement at presentation.[131] Patients with hard palate lesions tend to be diagnosed when they have small asymptomatic disease, which is easily detected on physical examination. On the other hand, paranasal sinus tumors usually do not cause symptoms until they are locally advanced. The surgical approach for these tumors is more difficult, with a greater chance for leaving behind residual disease, leading to higher recurrence rates. A combined approach with surgery and PORT is recommended, with 10-year local control rates around 85% (see Table 49.9).[37,131,151]

Primary Radiotherapy

The poor results for salivary gland cancer with RT alone in several series have been attributed to the use of primary RT for patients with locally advanced lesions or distant metastases at presentation, who were essentially treated for palliation. In addition, margin-negative surgery as a sole modality is effective only in favorable low-grade histology with an operable presentation in a healthy patient. This imbalance effectively biases the outcomes in favor of surgery over primary RT. Locoregional control rates after conventional photon or electron therapy (low LET RT) are around 25%.[112,115] Ten-year locoregional control depended on T-stage in a series of the University of Florida, 72% and 20% for T1-T3 and T4, respectively.[85] For treatment with photons with curative intent, a clear dose-response relationship has been described.[26,153] A dose of at least 66 to 70 Gy should be adapted, resulting in a 5-year local control of 50% to 70%, although late recurrence was observed. The generally slow rate of regression of advanced salivary gland tumors and inadequate results with conventional RT have made them a logical target for alternative approaches, such as high LET particles (NRT and carbon ions), due to the superior RBE.

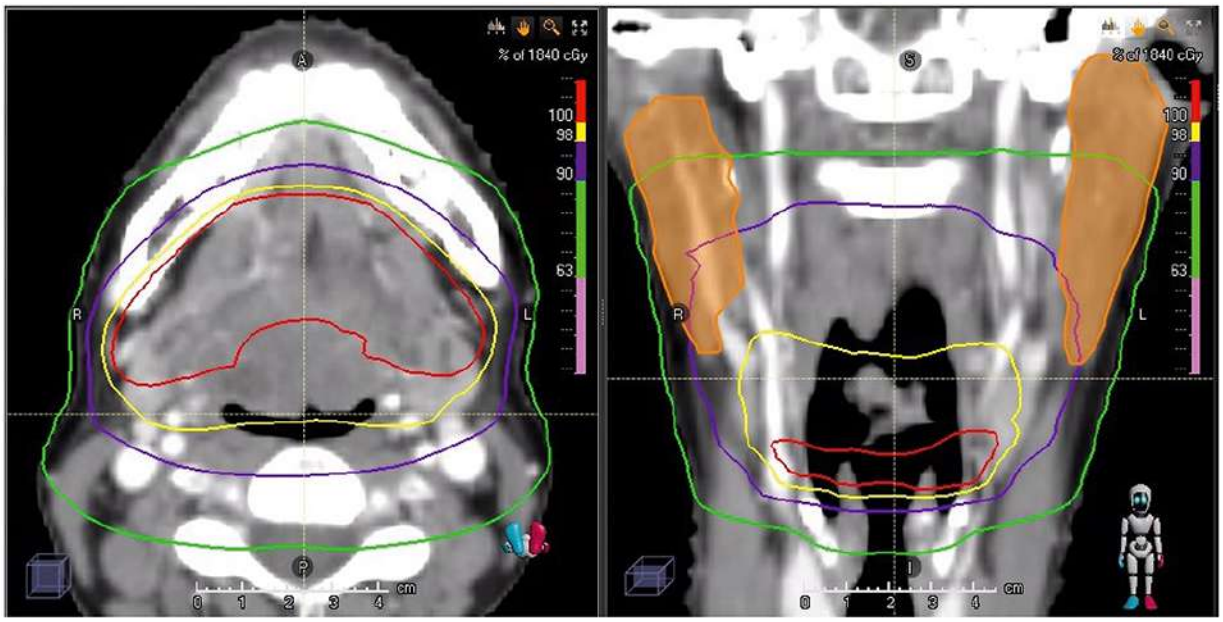
Particle Therapy

Patients with inoperable primary or recurrent major or minor salivary glands were included in the RTOG-MRC randomized phase III clinical trial.[115] Patients were randomized between 70 Gy for 7.5 weeks or 55 Gy for 4 weeks of photon therapy (x-ray radiation therapy [XRT] = low LET) and high LET fast NRT (16.5-22 nGy in 12 fractions over 4 weeks). The study had to be stopped because of ethical issues raised by a statistically significant difference (2- to 3-fold in favor of NRT) in 2-year locoregional control, after the inclusion of only 32 patients during a planned interim analysis. The review board prohibited further accrual of patients to the randomized study, given the magnitude of the efficacy in favor of NRT. The 10-year locoregional control was 17% after XRT and 56% after NRT.[115] However, there was no statistically significant improvement in survival (15% vs 25%), perhaps due to delayed onset of distant metastatic disease among survivors following the successful local treatment, as well as the small number of patients analyzed.[115] Late morbidity was somewhat higher for NRT, given the technical limitations of primitive NRT equipment

available at the majority of centers that participated in this study. For example, most lacked a multileaf collimated beam, couch rotation, and an isocentric gantry, which were available only at select centers. Primary NRT in salivary gland disease is reserved for macroscopically residual disease after surgery (R2) and unresectable tumors with local control rates far superior to conventional XRT. Stannard et al have published results of 335 patients treated with NRT.[114] The 5-year locoregional control was 80% after R2 resection, 55% for unresected cases, and 40% for irresectable cases. The risk of late grade 3 to 4 morbidity was 20%. Douglas et al performed a retrospective review of 279 patients treated at the University of Washington with fast NRT for salivary gland cancers, 263 of which had gross disease at the time of treatment. The 6-year cancer-specific survival and locoregional control were 67% and 59%, respectively, and grades 3 to 4 toxicity was 10%.[154] In small retrospective studies, modern XRT has been suggested to have similar efficacy as NRT but with less toxicity. Spratt et al performed a retrospective review of 27 patients with unresectable salivary cancer treated with XRT to a median dose of 70 Gy with IMRT or 3DCRT. Of these, 18 patients received chemotherapy. The 5-year locoregional control was 47%, which appears to compare favorably to the NRT arm of RTOG-MRC study.[115,155] However, interstudy comparisons are limited by the tumor stage heterogeneity and are fraught with selection bias, as well as other well-known inherent limitations of retrospective analyses.

Fundamentally, the x-ray beam and the neutron beam used in the RTOG-MRC study have not changed since their discovery. However, highly conformal techniques such as IMRT/VMAT have become the standard of care by conforming radiation around organs at risk to significantly reduce toxicity. The efficacy of XRT using modern techniques could only be possibly improved through superior targeting in situations that were previously limited by the historical XRT techniques, such as PNTS via CNs to the skull base and middle cranial fossa. Salivary gland cancers in general are well known to be relatively chemorefractory. Logically, combining XRT with an ineffective chemotherapy is not expected to improve the efficacy of XRT, and this was demonstrated in a large retrospective study of over 2,000 patients utilizing a national database.[112] The argument that modern XRT techniques such as IMRT/VMAT combined with chemotherapy could be as effective as NRT remains to be tested. Given the evidence from the RTOG-

MRC study, NRT (and other high LET modalities such as carbon ion) is the proven standard for superior local control in cases of unresectable salivary gland tumors.[115] Recent technical advances at the University of Washington have enabled the clinical implementation of intensity-modulated neutron therapy (IMNT) to leverage the therapeutic advantage of NRT while limiting dose and, therefore, toxicity to adjacent OARs as compared to historical 3D conformal NRT (Figure 49.22).[156]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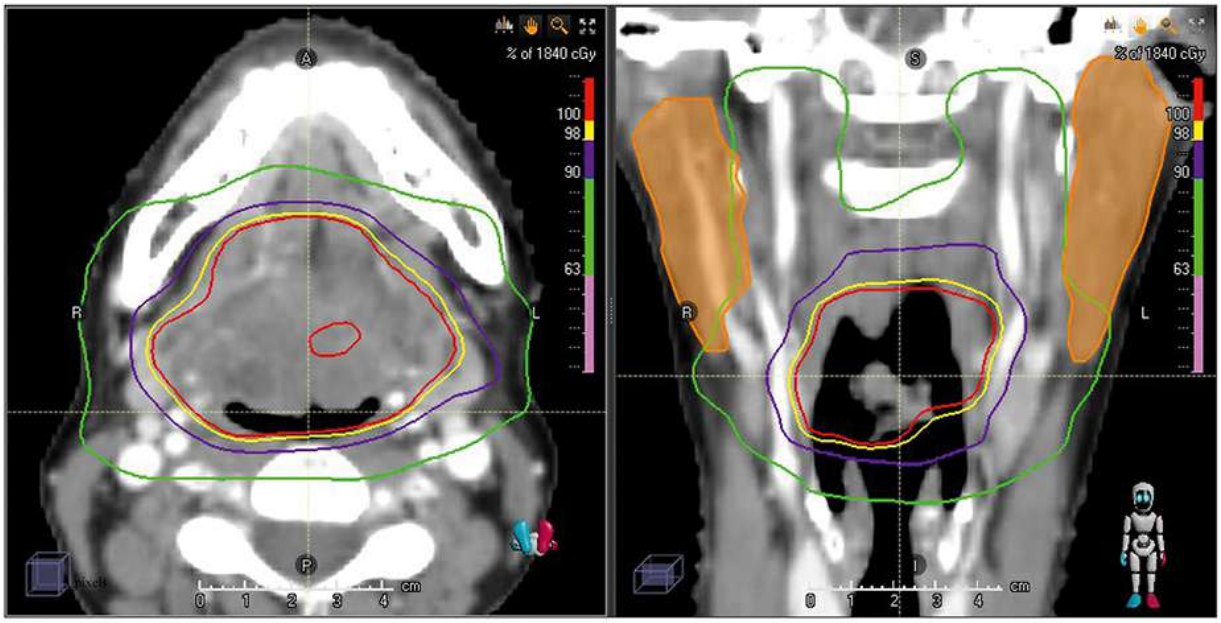
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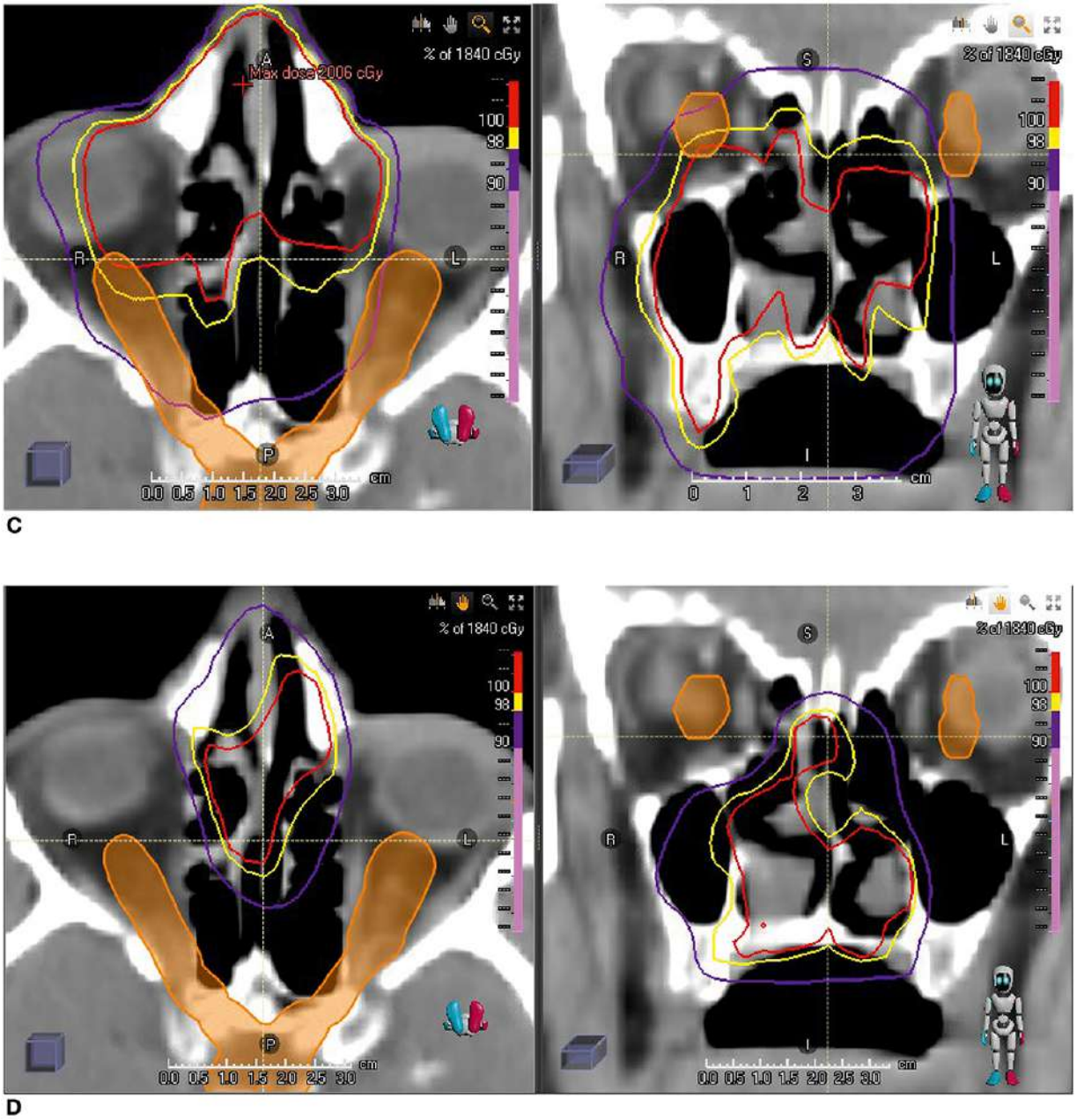

FIGURE 49.22 Three-dimensional (3D) fast neutron radiotherapy (NRT) plan (A) compared with intensity-modulated neutron radiotherapy (IMNT) plan (B) for a patient with advanced tongue base adenoid cystic carcinoma. Parotid gland (orange color wash) sparing is seen (green isodose line), while maintaining target cover (red isodose line). IMNT (C) versus 3D plan NRT (D) for postoperative sinonasal mucoepidermoid cancer. Optic nerves (orange color wash) being spared by IMNT (purple isodose line) while maintaining target cover (yellow isodose line). (Reproduced from Anderson AC, Stewart RD, Sponseller PD, et al. Intensity-modulated neutron therapy (IMNT) for head and neck cancer: early toxicity outcomes. *Int J Radiat Oncol Biol Phys*. 2023;117[2 suppl]:e561-e562.)

Treating disease involving the base of skull, such as cavernous sinus and Meckel's cave in the middle cranial fossa with historical 3DNRT was previously limited by dose to the adjacent temporal lobe of brain that is more sensitive to high LET therapy. Given this greater sensitivity of brain and neural structures to NRT, the dose to the targets adjacent to the brain (with cavernous sinus, Meckel cave, and/or middle cranial fossa involvement) was limited to two-thirds of the total prescribed dose, and as a result, excess skull base failures were noted. In an effort to improve results for tumors invading the base of skull, several new techniques were developed. A combination of NRT with a gamma knife stereotactic radiosurgical boost has been used for tumors invading the base of skull.[157] Compared to a historical control group, treated with NRT only, in 34 patients treated with combined NRT and gamma knife, the actuarial local control rate at 40 months was 82% versus 39% for the control group. Complication grades were equal.[157]

Alternatively, a proton beam (PBT) boost allows for a highly conformal and fractionated course that may be less damaging to the brain than a single high-dose gamma knife treatment and is superior for larger and irregular targets that are underdosed by NRT at the skull base.[158] However, with the recent availability of IMNT (since the fall of 2022), the vast majority of cases receive the entire prescribed dose with NRT and do not require a boost dose either through gamma knife or PBT.

Carbon ions have the theoretical advantage of higher biologic effectiveness similar to other high LET RT such as NRT, however, with a more precise targeting capability than historical 3D conformal NRT. In Heidelberg, 309 advanced ADCC, 60% T4, and 37% paranasal location were treated with a combination of photons (median 50 Gy) and carbon ions (median 24 GyE).[159,160] Five-year local control for R1 (29%), R2 resection (44%), and inoperable tumors (28%) were ±80%, 56%, and 51%, respectively. Toxicity was moderate. In a subset of R2 resection and inoperable cases (>90% T4, paranasal, parotid gland with base of skull invasion, nasopharynx), combined IMRT with carbon ion boost (n = 58) was compared with IMRT only (n = 37). Although not randomized, 5-year local control with carbon ion boost was significantly better (60% vs 40%).[160] In a series from Japan, primary carbon ion therapy (n = 40) was compared with primary PBT (n = 40) for advanced ADCC. Local control

after 5 years for T4 and inoperable cases was equal (68%) for both treatment options.[117] However, the incidence of late grade 3 or more late complications in their study was high (61% for protons and 39% for carbon ions) and dose dependent (>72 GyE).[117] Because of the favorable Bragg peak effect, PBT may be used to decrease toxicity, especially in the cases of completely resected tumors where PORT may be indicated. Given the lower dose to OARs, acute toxicity was lower in a retrospective study comparing protons with photons in pediatric salivary gland tumors.[161] However, in terms of efficacy, proton beam is also a low LET beam like XRT, although it has approximately 10% higher biologic effectiveness than XRT. The magnitude of biologic superiority (local control) of NRT is more than 3-fold compared to the XRT as per the RTOG-MRC study.[115] The main drawback with high LET RT consideration is the limited availability of these centers, with IMNT available at only one site in the world (University of Washington, Seattle) and a limited number of carbon ion facilities in Europe and Asia. Data concerning PBT for salivary gland cancer are scarce, and there is no comparative study versus NRT.

In conclusion, carbon ions or NRT should be taken into account, if available, for unresectable, residual, or recurrent salivary gland tumors.[115] Despite high locoregional control, historically, late toxicity was of concern with older NRT techniques that are no longer in operation. Despite the lack of published data, modern conformal high LET techniques such as IMNT are expected to maintain high local control while minimizing toxicity to adjacent OARs.

SYSTEMIC THERAPY

The rarity of salivary gland neoplasms and their localized nature provides limited opportunities for conducting randomized trials of systemic therapy. Most published studies are limited to small, single-arm trials and generally include different histologic subtypes; the heterogeneous natural history of disease within salivary neoplasms makes the determination of standard-of-care therapy challenging.

For *curative-intent* treatment of localized disease, patients are treated definitively with surgery and/or radiation, and the role of systemic chemotherapy is not established in this setting. While some small case

series and retrospective studies have suggested a benefit for postoperative concurrent chemoradiation, there is no consensus on its routine use outside a clinical trial at this time.[162,163] A retrospective study utilizing the National Cancer Database analyzing more than 2,000 patients who underwent resection of major salivary gland cancer with at least one high-risk feature (T3-T4 stage, N1-N3 stage, positive surgical margins) demonstrated that patients who received adjuvant chemoradiation had inferior overall survival compared to patients who underwent adjuvant radiation alone in a multivariate analysis.[112] The role of adjuvant chemoradiation is being investigated prospectively in the completed randomized phase II/III clinical trial, RTOG 1008 (NCT01220583), comparing radiation with chemoradiation using weekly cisplatin in high-risk patients following surgical resection.[164] In Europe, GORTEC 2016-02 (NCT02998385) is a similarly designed trial that includes both high-risk resected salivary gland and nasal minor salivary gland carcinomas and is expected to shed light on this unanswered clinical question.[165]

For patients with recurrent or metastatic salivary gland tumors, systemic therapy is given with *palliative intent*. Given the indolent nature of some salivary gland neoplasms, the decision to start systemic therapy should be individualized. In general, systemic therapy can be considered in patients with symptomatic disease not amenable to local therapy or with tumor growth that may compromise organ function. In select patients, such as those who are asymptomatic with low-volume indolent disease such as ADCC, observation may be appropriate. There is not currently a preferred treatment regimen or consensus standard-of-care first-line therapy that demonstrates significant survival advantage in this setting; there are no randomized data demonstrating the benefit of preventive treatment compared to best supportive care.

Some conventional chemotherapy agents have demonstrated activity in advanced salivary gland tumors, mainly in small phase II trials or case series, including cisplatin, paclitaxel, vinorelbine, epirubicin, mitoxantrone, and methotrexate.[166,167] A small phase II trial of 36 patients comparing vinorelbine and cisplatin with vinorelbine showed higher response rate (44% vs 20%) with combination therapy.[168] A phase II study of 32 patients were treated with gemcitabine and cisplatin (or carboplatin if prespecified contraindications to cisplatin were met) showed a response rate of 24%,

which fell below the prespecified trial criteria to be declared active.[169] In both trials, multiple tumor histology types were included. A phase II trial of single agent paclitaxel conducted by the Eastern Cooperative Oncology Group treated 45 patients, with 8 partial responses seen among patients with mucoepidermoid or adenocarcinoma histology for a response rate of 26%; however, no responses were seen for patients with ADCC.[170] The combination of carboplatin and paclitaxel was studied in 14 patients, with 2 (14%) patients demonstrating a partial response.[171] Overall, these prospective experiences are small and characterized by histologic heterogeneity and modest rates of objective responses. Although these studies often report high rates of disease stabilization, it can be difficult to discern whether this observation is attributable to drug activity or the inclusion of relatively indolent disease subsets.

More recently, molecularly targeted agents have been shown to be active in a select group of salivary gland cancers treated in the palliative setting. These approaches warrant additional and ongoing study in salivary neoplasms, especially given limited success with conventional chemotherapy. Lenvatinib, a multitargeted tyrosine kinase inhibitor, has been evaluated in two phase II trials for ADCC, demonstrating modest efficacy with partial responses seen in 11.5% and 15.6% of patients treated (three and five patients, respectively).[172,173] Toxicity necessitating dose reductions or treatment discontinuation was relatively common in both studies.

Next-generation sequencing and immunohistochemical biomarker testing can be considered to evaluate potential eligibility for other targeted therapies in advanced/metastatic salivary gland cancers. Many advanced salivary gland tumors are androgen receptor positive and may benefit from androgen deprivation therapy, such as leuprolide and bicalutamide, enzalutamide, and abiraterone.[174-176] In salivary gland neoplasms that overexpress HER2, small series or basket clinical trials have demonstrated activity with anti-HER2 agents including trastuzumab (either alone or in combination, such as trastuzumab and docetaxel), ado-trastuzumab emtansine, fam-trastuzumab deruxtecan, and combined pertuzumab and trastuzumab[177-181] The role of ado-trastuzumab emtansine is similarly being evaluated in patients previously treated with a prior HER2-targeted therapy.[182,183]

In the rare situation that salivary gland cancers harbor *NTRK* gene fusions (such as in MASC), *BRAF* V600E mutations, or *RET* gene fusions, oral tyrosine kinase inhibitors targeting these alterations can be considered. The Food and Drug Administration (FDA) has approved larotrectinib and entrectinib for the treatment of patients with *NTRK* gene fusion–positive tumors, with phase I/II studies of these agents showing high objective response rates in patients with *NTRK* gene fusion–positive cancers.[184-186] In addition, the FDA has approved the combination dabrafenib/trametinib for all advanced *BRAF* V600E–mutated tumors. Selpercatinib similarly has FDA approval in all advanced *RET* gene fusion–positive solid tumors, with ongoing evaluation in the LIBRETTO-001 trial (NCT03157128) for non–lung or thyroid solid tumors.[187]

Finally, based on the results of the KEYNOTE-158 trial, patients with either previously treated tumor mutational burden high (TMB-H) or microsatellite instability high (MSI-H)/deficient mismatch repair (dMMR) advanced salivary gland cancer are eligible to receive pembrolizumab. This trial included three patients with salivary gland cancer and TMB-H and two patients with MSI-H/dMMR.[188,189]

While the number of targeted agents is increasing rapidly, ongoing evaluation of these approaches warrants further study to evaluate the efficacy, risks, and benefits to inform appropriate patient selection and use.

SEQUELAE OF TREATMENT

The most notable complication of the treatment of parotid malignancies is facial nerve paralysis, which is often caused by the initial or repeated surgical procedure. However, various series have shown that sacrifice of VII is rarely necessary, unless the nerve is directly involved by tumor, particularly when PORT is given.[68,87] When sacrifice of VII is required, nerve grafting and PORT achieve comparable nerve function compared with unirradiated graft despite more negative prognostic factors.[118] Other postoperative sequelae, such as salivary fistulae, “first-bite” syndrome—where the patient experiences pain and/or jaw stiffness with only the first bite of their food—and neuromas of the greater auricular nerve, are sometimes seen. Frey syndrome (ie, gustatory sweating) may occur in a few patients after parotid surgery, but it is rarely bothersome.[90]

Partial xerostomia after irradiation of the parotid gland is frequently observed and may be permanent. Trismus may result from RT-induced fibrosis of the temporomandibular joint or the masseter and other muscles or mastication. It usually occurs when there is extensive tumor infiltration of the muscles of mastication and when high doses are given.

RT to the parotid gland may result in complications along the auditory system. Late toxicity, external canal stenosis, dryness, skin atrophy, and chronic otitis externa, resulting in conductive hearing loss, although rare, may be seen. Chronic otitis media has been documented in 35% to 40%, because of damage to the muscles of the eustachian tube. This may lead to conductive hearing loss, and repeated myringotomies may be indicated.[190,191] Radiation-induced hearing loss mostly is caused by progressive endothelial damage to the vascularization of the inner ear. This will cause sensorineural hearing loss, cognitive impairment, and, at the end, decrease quality of life. However, most hearing loss is seen above 4,000 Hz; for daily use, normal frequency ranges from 1,000 to 3,000 Hz. In a prospective study of patients treated for head and neck cancer, a 10 dB or greater hearing loss 2 years after RT was seen in 40% for 8,000 Hz and in 50% for 3,000 Hz.[146] A threshold of 45 Gy was seen at 2,000 Hz or greater, also depending on age and baseline hearing loss.[146] In published results, the mean threshold dose for the cochlea and eustachian tube for sensorineural hearing loss varies between 40 and 50 Gy.[145,146,191] The latency is around 1.5 to 2 years. After this time, hearing loss stabilizes. The risk of sensorineural hearing loss depends on the RT technique. From 2D conventional to 3DCRT, the mean dose to the cochlea may decrease from above 50 Gy to around 40 Gy,[139,144] and further improvement is noted with the use of IMRT.[139,147] No dose-response relationship has been published for vestibular damage.[191]

Garden et al[131] reported complications of RT in 51 of 160 patients receiving PORT with *2D* RT for minor salivary gland tumors. The most common complication was decreased hearing in 26 patients, 20 of whom had myringotomies or myringotomy tubes placed for serous otitis media. Bone necrosis or exposure was observed in several patients; however, this complication has been seen infrequently during the past decade with improved RT techniques and treatment of multiple, as opposed to single fields per day. Complications to the eyes or optic pathways were diagnosed

in patients with paranasal sinus primary tumors. At least six cases of contralateral optic atrophy occurred.[131] Other eye complications included dry eye syndrome, nasolacrimal duct obstruction, cataract, retinopathy, and perforated globe.[131] To reduce the incidence of bilateral blindness, the dose to the optic chiasm and contralateral optic nerve is limited to 54 Gy. In patients with extensive tumor involvement of the orbit, it may be preferable to remove the eye surgically rather than to subject the entire orbit to high doses. Radiation-induced injury to the visual pathway is dose dependent. None of the patients receiving a dose of less than 50 Gy develop optic neuropathy or chiasm injury, whereas the 10-year actuarial incidence of optic nerve chiasm injury is 5% and 30% for patients receiving 50 to 60 and 61 to 78 Gy, respectively.[192]

RT of tumors of the pharynx, and less frequently the oral cavity, may result in permanent complaints of xerostomia. In the largest published series, the mean dose to the parotid glands relative to a 50% risk of 1-year xerostomia was 39 Gy, and no threshold was seen.[193] A mean dose beneath 20 Gy is preferable to reach a low risk on xerostomia.[193] This serious late complication may be significantly reduced by the use of IMRT.[194] Data on quality of life are scarce. In a prospectively scored small series of 36 patients treated for parotid carcinoma with PORT, quality of life deteriorated during treatment and returned to almost baseline levels from 6 weeks to 1 year after RT.[195] In general, the risk of late toxicity is much lower using modern radiation techniques like IMRT and VMAT compared to 2D or 3D RT. Based on dose-response models for OARs, PBT may be preferred in some cases, depending on the estimated lower risk at late toxicity without compromising efficacy.[196]

TREATMENT OF RECURRENCE

Retreatment usually involves additional surgery, if feasible, and PORT in previously irradiated patients (Figure 49.23). In the retreatment of parotid neoplasms, preserving facial nerve function and obtaining local control are more difficult than for the initial tumor. Therapy consisting of surgery with PORT has demonstrated enhanced local control, and sacrifice of VII may be necessary less often if this combination is used. In certain histologic subtypes (eg, ADCC), retreatment of locally recurrent disease yields

prolonged survival. Aggressive local therapy for recurrent disease is indicated if the probability of long-term survival is high, as in the case of ADCC. Fractionated stereotactic reirradiation, with a dose of 5 times 6 Gy, resulted in a 50% locoregional control in a study by Karam et al.[197] Reirradiation is not advised within 1 year after the first course of RT and not for large tumor volumes.[197] PBT is a strong consideration in most cases of reirradiation, especially if "in-field" control could be achieved by prior XRT for a number of years and is now limited by the lack of the precision provided by the Bragg peak effect advantage inherent to PBT. For a central "in-field" failure, reirradiation with PBT would be necessary only in cases in which IMRT/VMAT plan could not spare critical structures located away from the target—in particular, tumors that are abutting OARs that are built in "series" and hence are "dose dependent" and "volume independent." Thus, optic nerves, optic chiasm, brainstem, and spinal cord will not meaningfully benefit from PBT. In this situation, a full dose to the target volume would also deliver the same dose to the abutting interface region of the OAR, regardless of the modality. And any underdosing to the target (to spare the OAR) would result in underdosing the target, regardless of the modality. It is in the "volume-sensitive" structures built in "parallel"—such as brain, cerebellum, oral mucosa, and salivary glands—that PBT could be superior to IMRT/VMAT in reducing mean dose (due to the reduced unnecessary irradiation beyond the Bragg peak) in the intermediate- (<50% of prescribed dose) to low-dose ranges. Multimodality treatment may be beneficial for recurrence disease of the minor salivary gland, if initial tumor classification is $T_{1\text{-}2.}$[198] For unresectable recurrences that have previously received low LET RT (x-rays, PBT), high LET RT such as NRT or carbon ions should be considered, if available.

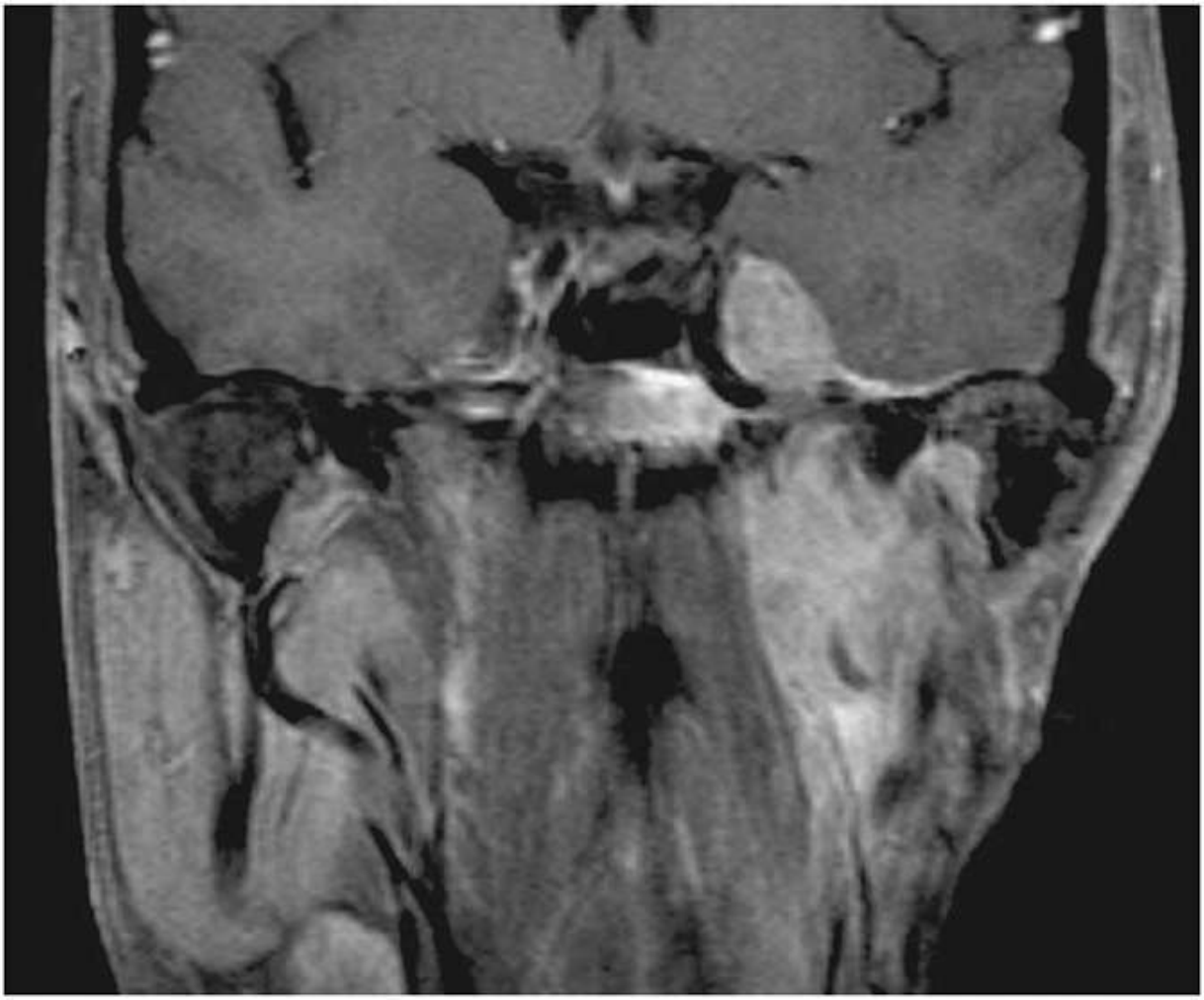

FIGURE 49.23 Coronal fat-suppressed contrast-enhanced magnetic resonance image shows a recurrence of squamous cell cancer of the parotid gland after total parotidectomy. The tumor is centered in the left masticator space with perineural spread along the nV3. Retrograde perineural spread of tumor through foramen ovale on the left side. (Courtesy of Dr F.A. Pameyer, Radiologist, University Medical Center Utrecht, Netherlands.)

Chemotherapy also has been used for recurrent disease.[167,168] However, in view of its significant toxicity and modest response rates in a population that may have recurrent yet indolent progressive disease, trials of aggressive cytotoxic therapy are recommended only on carefully drafted protocols. In the future, molecular target agents may be tested in selected recurrent salivary gland cancers.

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CHAPTER 50

Oral Cavity

Irini Yacoub and Nancy Y. Lee

GENERAL PRINCIPLES

The management of squamous cell carcinoma (SCC) of the lip and oral cavity is primarily surgical, with adjuvant treatment based on stage and postoperative pathologic findings. Reconstructive microsurgery has acceptable functional outcomes,[1] as well as improved oncologic outcomes;[2] thus, organ-preserving approaches have largely grown out of favor in North America. Nevertheless, definitive radiotherapy may be a treatment option for patients who are not candidates for surgery because of medical reasons or who refuse surgery. A multidisciplinary approach is paramount in the evaluation and management of patients with oral cavity cancer. A team of health care providers including head and neck surgical oncology, radiation and medical oncology, plastic surgery, nursing, dentistry, dietary, speech pathology, and social work should evaluate the patient before treatment is delivered. Multidisciplinary evaluation prior to treatment disposition helps to ensure that broad consensus treatment recommendations are made and that interdisciplinary coordination of care is facilitated. Once treatment has been completed, the multidisciplinary team should provide follow-up to the patient to ensure early detection of recurrent disease and adequate management of treatment sequelae.

INCIDENCE, EPIDEMIOLOGY, AND ETIOLOGY

Oral cancer is the 13th most common cancer worldwide[3] and 8th in the United States, with an estimated 54,540 adults (4% of all cancers) in the United States diagnosed in 2023.[4] The National Cancer Institute estimates of oral cavity and pharynx cancers contribute to 2% of all cancer deaths.[5] The estimated 5-year survival for all stages is 68.5%, whereas survival for cancer localized to the primary site is 86.6%.[5] According to the National

Cancer Institute, age-adjusted death rates have been rising on average 0.4% each year over 2011 to 2020.[5] Oral cavity cancer is more common in men than women, particularly among those with a history of alcohol or tobacco use.[5]

Approximately 747,316 newly documented instances of lip, oral cavity, and pharyngeal cancer were reported globally in 2020, an age-standardized rate (ASR) of 8.1 new cases per 100,000 individuals. Melanesia had the highest occurrence with an ASR of 19.8 per 100,000 individuals, followed by South-Central Asia (13.5), Central and Eastern Europe (10.3), Western Europe (10.0), and Australia and New Zealand (10.0). Countries with the lowest ASR included Central America (2.0), Western Africa (3.1), Western Asia (3.7), Northern Africa (3.9), and Eastern Africa (4.3). Males had a significantly higher incidence rate (12.2) compared to females (4.3), nearly triple the occurrence. The incidence of lip, oral cavity, and pharyngeal cancer increased with age, peaking among individuals aged 70 to 85 years and above (37.8). Lip and oral cavity malignancy had the highest incidence, followed by pharynx.[6] Finally, lip and oral cavity had the highest mortality, followed by pharyngeal and salivary gland.[6] The incidence of oral cavity cancer seems to be decreasing in many parts of the world, mirroring the overall decline in tobacco use since 1990.[7]

The epidemiology of oral cancer strongly reflects exposure to certain environmental agents, particularly tobacco and alcohol. Smoking is identified as an independent risk factor in 80% to 90% of patients who present with cancer of the oral cavity.[8,9] Tobacco users have a 5- to 25-fold higher risk of oral cavity and oropharyngeal cancer.[10] The combined use of alcohol and tobacco may have a synergistic effect on carcinogenesis.[10] International Head and Neck Epidemiology Consortium pooled analysis data demonstrate a greater than multiplicative joint effect between tobacco and alcohol on head and neck cancer risk, which is most pronounced in carcinoma of the pharynx and oral cavity.[11] Cessation of smoking and alcohol are associated with a decline in the risk of cancer of the oral cavity.[9,12] In India, Sri Lanka, and Taiwan, the habit of chewing betel nut leaves rolled with lime and tobacco (mixture known as “pan”), which results in prolonged carcinogen exposure to the oral mucosa, is thought to be the leading cause of oral cancer.[13,14]

Ultraviolet radiation has been associated with carcinoma of the lip.[15] Around 90% arise from the lower lip.[16] While the human papillomavirus (HPV) is a well-established risk factor for oropharyngeal malignancy,[17] its role in the incidence of oral cavity malignancy is less significant.[18] Certain syndromes such as xeroderma pigmentosum, Li-Fraumeni, ataxia telangiectasia, Bloom syndrome, and Fanconi anemia have been associated with a predisposition to oral cancer.[19,20]

Overall, there has been a declining trend in the overall incidence of oral cavity squamous cell carcinoma (OCSCC) over the past 30 years. However, Surveillance, Epidemiology, and End Results data suggest an increasing incidence of oral tongue carcinoma in young White individuals aged 18 to 44 years, which is most pronounced among young White women.[21-23] The increase in oral cavity malignancy among this group, despite decreasing tobacco and alcohol consumption worldwide,[24,25] suggests an unknown or yet identified risk factor in this specific population.

In patients with cancer of the oral cavity, the risk of developing a second primary cancer is well recognized and associated with worse prognosis and higher risk of treatment failure in patients with early-stage disease.[26,27] Schwartz et al demonstrated a 22% 5-year probability of a second head and neck cancer in 851 treated patients.[27] Modifiable risk factors, such as smoking cessation, may decrease the risk of oral cavity malignancy. Oral cancer risk decreases by about 35% in the first 4 years of cessation, with a reduction of about 80% by 20 years.[28] For those who quit smoking beyond 20 years, the risk parallels that of never-smokers; a similar effect is seen with stopping the use of alcohol.[29] Therefore, continued efforts toward tobacco and alcohol cessation are a central strategy in the management of patients with oral SCC.[29]

ANATOMY

The oral cavity is composed of the lips, oral tongue, floor of the mouth, retromolar trigone, alveolar ridge, buccal mucosa, and hard palate (Figures 50.1-50.3). The anterior boundary of the oral cavity is the skin-vermilion junction. The superior portion of the oral cavity extends posteriorly to the junction between the hard and soft palate, whereas the inferior portion

extends to the circumvallate papillae. The specific anatomic subsites of this region are noted below.

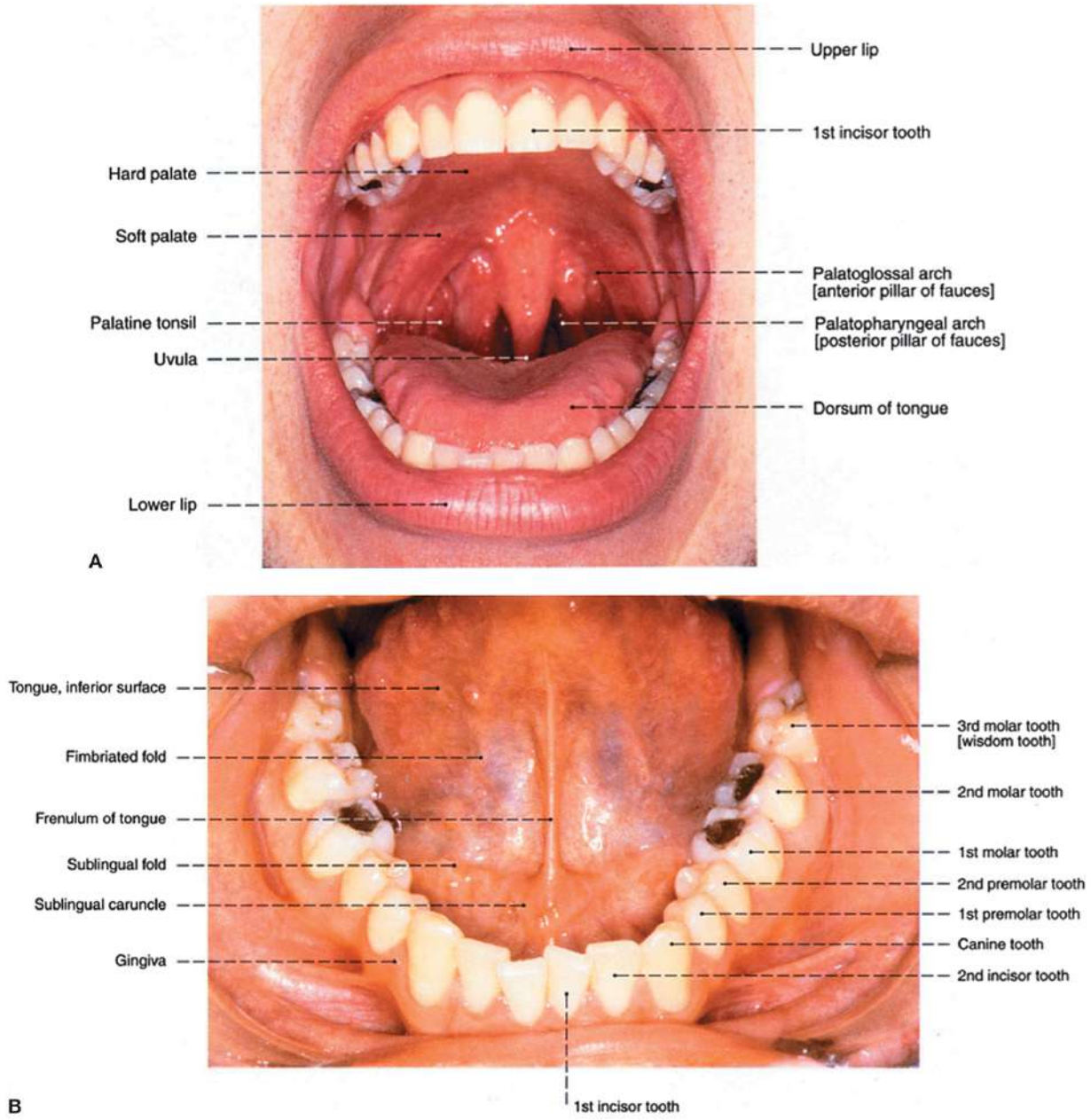

FIGURE 50.1 A. Oral cavity surface anatomy. B. Floor of the mouth surface anatomy. (Reprinted from Paulsen F, Waschke J. *Sobotta Atlas of Human Anatomy*. 17th ed. Urban & Fischer; 2023, Figure 8.193. Copyright © 2023 Elsevier GmbH Munich. With permission.)

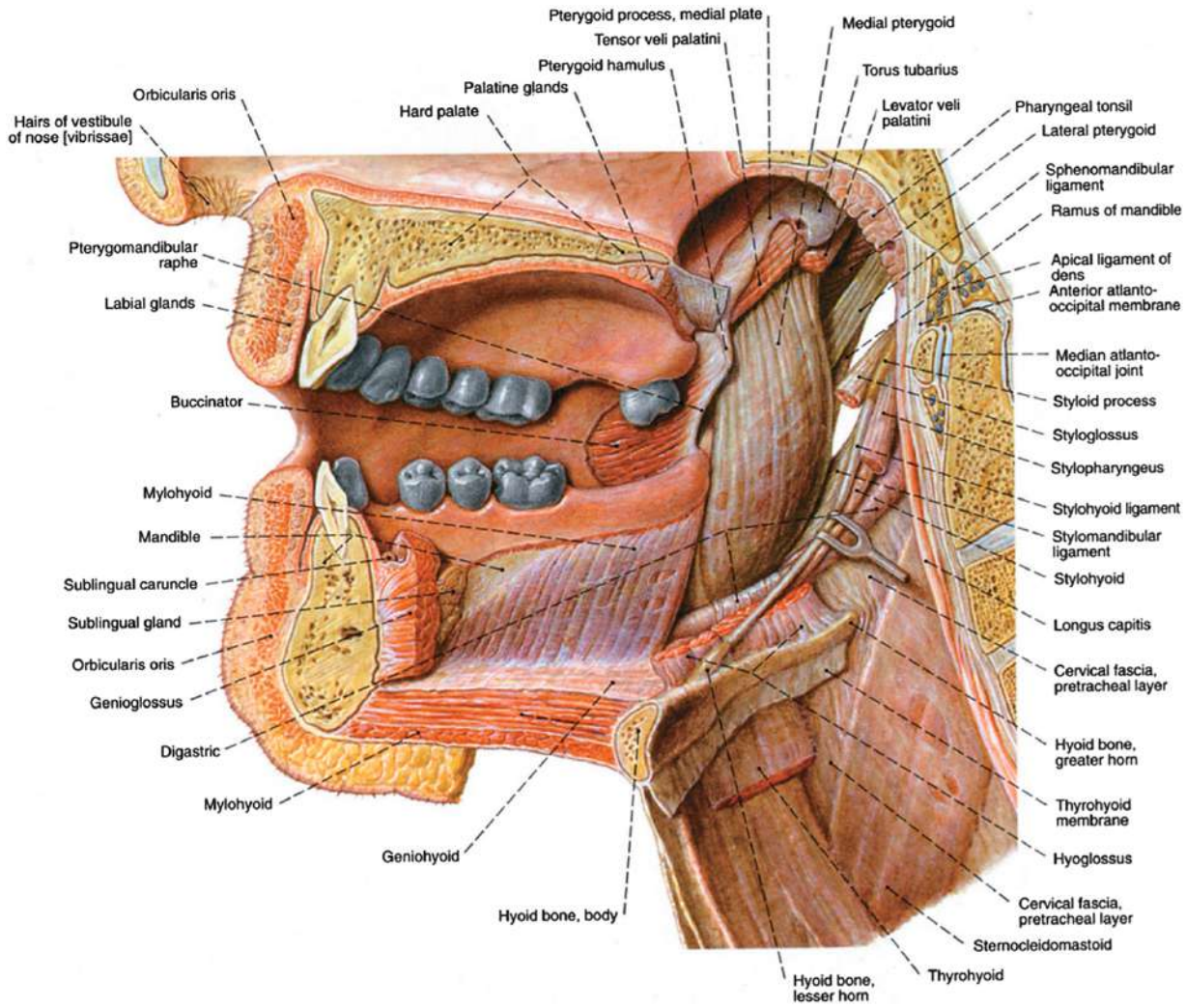

FIGURE 50.2 Oral cavity; paramedian section depicting regional anatomy. (Reprinted from Paulsen F, Waschke J. *Sobotta Atlas of Human Anatomy*. 17th ed. Urban & Fischer; 2023, Figure 8.130. Copyright © 2023 Elsevier GmbH Munich. With permission.)

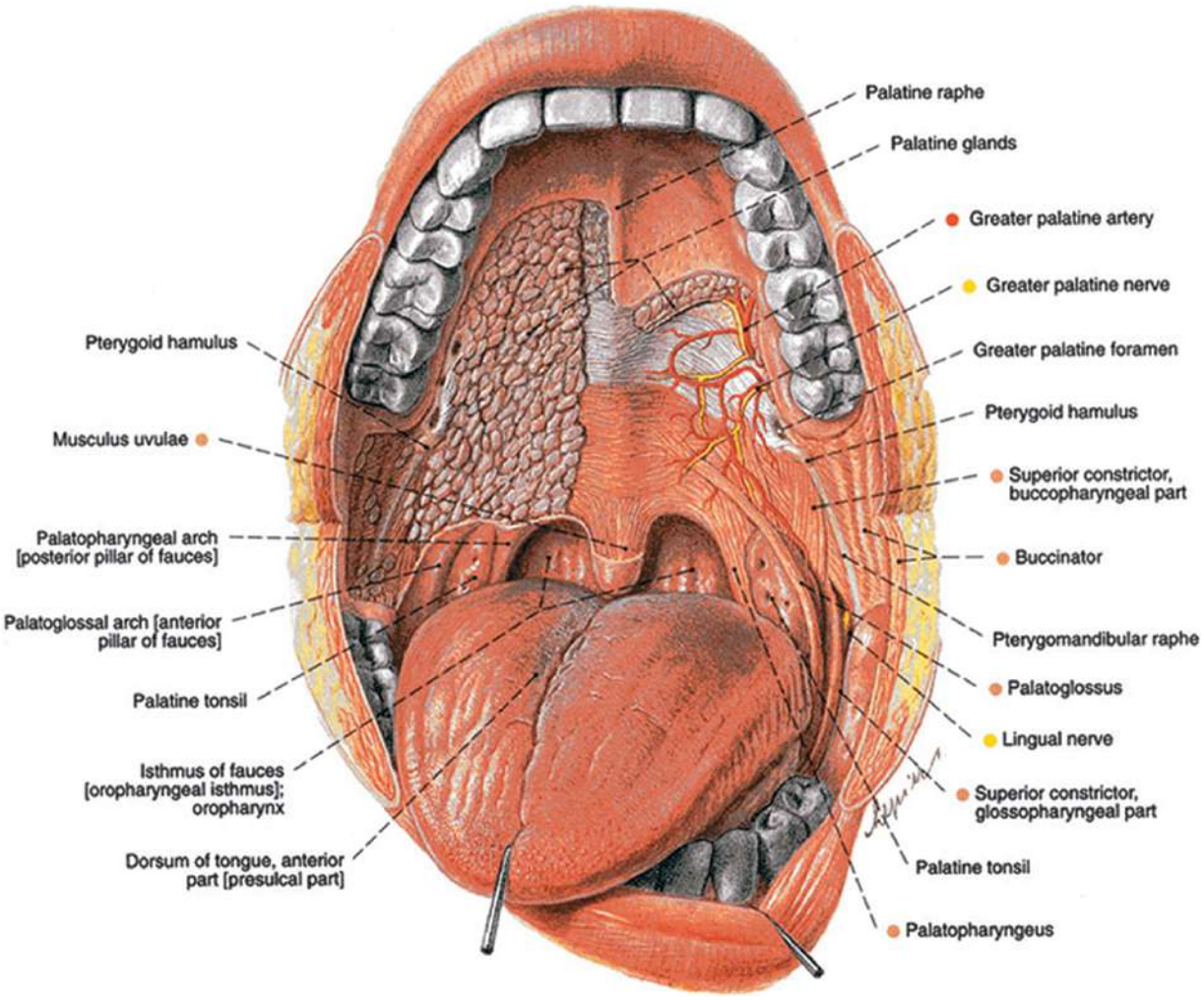

FIGURE 50.3 Oral cavity illustration depicting regional anatomy. (Reprinted from Paulsen F, Waschke J. *Sobotta Atlas of Human Anatomy*. 17th ed. Urban & Fischer; 2023, Figure 8.162. Copyright © 2023 Elsevier GmbH Munich. With permission.)

Lip

The lips begin at the junction of the vermilion border with the skin and form the anterior aspect of the oral vestibule. The lips are composed of the vermilion surface, which is the portion of the lip that comes in contact with the opposing lip. The lips are well defined into an upper and lower. The primary motor control of the lips is provided by the buccal and mandibular branches of the facial nerve. Most tumors of the lip arise at the vermillion border and can invade adjacent skin, whereas lesions near the gingivobuccal sulcus may invade the alveolar ridges.[30] Lymphatic drainage of the upper

and lower lip is primarily to the submental and submandibular group, with some to the preauricular nodes.[31,32]

Oral Tongue

The anterior two-thirds of the tongue is mobile and considered part of the oral cavity. The oral tongue extends anteriorly from the circumvallate papillae to the undersurface of the tongue at the junction of the floor of the mouth. The fibrous septum divides the tongue into right and left halves. The oral tongue can be demarcated into four anatomic areas: the tip, lateral borders, dorsal surface, and undersurface (ventral surface). There are six pairs of muscles that form the oral tongue. Three of these muscles are extrinsic, whereas the other three are intrinsic. The extrinsic muscles include the genioglossus, hyoglossus, and styloglossus. The intrinsic muscles include the lingual, vertical, and transverse muscles. The former primarily move the body of the tongue, whereas the latter alter the shape and conformation of the tongue during speech and swallowing. The blood supply to the tongue is primarily via the lingual artery, tonsillar branch of the facial artery, and the ascending pharyngeal artery with primary drainage by the internal jugular vein. General sensation of the anterior two-thirds of the tongue is supplied by the lingual nerve. Excluding the circumvallate papillae, taste fibers from the anterior two-thirds of the tongue run in the chorda tympani branch of the facial nerve; the glossopharyngeal nerve provides sensation and taste to the posterior third of the tongue and circumvallate papillae. The oral tongue is the most commonly involved in oral cavity sites. These tumors may spread to involve the muscles of the tongue, floor of the mouth, or mandible.[30] Primary sentinel lymph nodes for the anterior tongue are submental lymph nodes, submandibular lymph nodes, and jugulo-omohyoid lymph nodes. The lateral and middle tongue drain into submandibular, jugulodigastric, and thyroid lymph nodes. The root of the tongue drains into the jugulodigastric lymph nodes. The tongue drains into the bilateral neck. The lateral tongue has pathways that can skip directly to level IV.[32-34]

Floor of the Mouth

The floor of the mouth is a semilunar space extending from the lower alveolar ridge to the undersurface of the tongue. The floor of the mouth overlies the mylohyoid and hyoglossus muscles. The posterior boundary of the floor of the mouth is the base of the anterior tonsillar pillar. This region is divided into right and left by the frenulum of the tongue and contains the ostia of the submandibular and sublingual salivary glands. A sling formed by the mylohyoid muscles medially supports the anterior floor of the mouth, and the hyoglossus supports the posterior floor of the mouth. The lingual and hypoglossal nerves are lateral to the hyoglossus, whereas the lingual artery is medial to the hyoglossus. Innervation of the floor of the mouth is provided by the lingual nerve. Tumors of the floor of the mouth may spread laterally into the mandible, superiorly into the tongue, or posteriorly into the base of tongue.[30] The floor of the mouth drains into bilateral levels I to III.[32]

Hard Palate

The hard palate extends from the inner surface of the superior alveolar ridge to the posterior edge of the palatine bone. This is a semilunar area between the superior alveolar ridge and the mucous membrane covering the palatine process of the maxillary palatine bones. Tumors of the hard palate may invade the greater palatine nerves, along cranial nerve V2, and into the base of skull through the foramen rotundum.[30] The hard palate drains into the submandibular nodes and levels I to III.[35]

Alveolar Ridge

The alveolar ridges include the alveolar processes of the maxilla and mandible and the overlying mucosa. The mucosal covering of the lower alveolar ridge extends from the line of attachment of mucosa in the buccal gutter to the line of free mucosa of the floor of the mouth. The lower alveolar ridge extends to the ascending ramus of the mandible posteriorly. The superior alveolar ridge mucosa extends from the line of attachment of mucosa in the upper gingival buccal gutter to the junction of the hard palate. The posterior margin is the upper end of the pterygopalatine arch. Carcinomas of the alveolar ridge invade bone early. Lower ridge malignancies may invade the mandibular canal and inferior alveolar nerve.[30]

Retromolar Trigone

The retromolar trigone is the triangular area overlying the ascending ramus of the mandible. The base of the triangle is formed by the posterior most molar, and the apex lies at the maxillary tuberosity. Tumors of the retromolar trigone tend to invade bone early.[30] The retromolar trigone drains into levels I to III.[32]

Buccal Mucosa

The buccal mucosa includes the mucosal surfaces of the cheek and lips from the line of contact of the opposing lips to the pterygomandibular raphe posteriorly. This extends to the line of attachment of the mucosa of the upper and lower alveolar ridge superiorly and inferiorly. Innervation is supplied by the buccal nerve, a branch of the mandibular nerve. Buccal mucosa tumors may invade the buccinator muscle, fat, or subcutaneous tissue.[30] The buccal mucosa most commonly metastasizes to level I nodes.[32]

Nodal Levels

The neck is traditionally divided into five primary nodal levels (ie, levels I-V) plus the retropharyngeal nodes that are relevant to the staging and management of oral cavity carcinoma. The level VI nodal station is not discussed in this section because it is rarely pertinent for oral cavity cancer. The classification of neck nodal regions, initially popularized by Robbins et al,[36] has served as a surgical reference system based on visible landmarks. Over the years, there have been several revisions regarding the proposed boundaries of nodal stations in the neck, with refinements to include radiologic landmarks.[37,38] Gregoire et al[39,40] published consensus guidelines for the computed tomography (CT)-based delineation of nodal levels in the node-negative neck that were revised in 2014 to serve as a guide in the practice of radiation oncology. In the following discussion, we incorporate radiographic landmarks and anatomic considerations from these guidelines (where relevant) alongside traditional surgical anatomic landmarks.

Level I

Level I includes the submental (Ia) and submandibular (Ib) triangles. Level Ia is limited anteriorly by the mandibular symphysis, posteriorly by the

body of the hyoid bone, and cranially by the geniohyoid muscle. The medial border is virtual because this region continues to the contralateral Ia station. Level Ib is located within the space bounded by the inner table of the mandible laterally, the digastric muscle medially, the mandibular symphysis anteriorly, and the submandibular gland posteriorly.

Level II

Level II includes the upper jugular chain lymph nodes from the base of the skull to the carotid bifurcation (surgical landmark) or the caudal body of the hyoid bone (clinical landmark); this nodal station extends from the posterior edge of the submandibular gland anteriorly to the posterior border of the sternocleidomastoid posteriorly. The level II nodal region is further subdivided into IIa and IIb. The vertical plane defined by the spinal accessory nerve (surgical landmark) or the posterior edge of the internal jugular vein (radiographic landmark) defines each subdivision within this level; level IIa lies anterior whereas IIb lies posterior to this plane.

Robbins et al[36] initially defined the cranial limit of level II as the base of the skull. However, from a practical standpoint, during surgical management of the neck, the cranial border of level II is taken as the insertion of the posterior belly of the digastric into the mastoid.[40] It was later proposed that the bottom edge of C1 serve as the radiographic landmark for defining the cranial border of level II in the node-negative neck.[40] Consequently, the retrostyloid space is considered the cranial continuation of level II from C1 to the skull base.[39,40]

Level III

Level III is the caudal extension of level II. It includes the midjugular nodes, of which the surgical landmarks extend from the carotid bifurcation to the omohyoid muscle inferiorly, the sternohyoid medially, and the posterior aspect of the sternocleidomastoid posteriorly. The corresponding radiographic landmarks are the caudal edge of the hyoid bone superiorly and the caudal edge of the cricoid cartilage inferiorly.

Level IV

Level IV includes the inferior jugular nodes located around the inferior third of the internal jugular vein. Level IV is bounded by the omohyoid muscle superiorly, the clavicle inferiorly, and the posterior aspect of the sternocleidomastoid posteriorly.

Level V

Level V includes nodes in the posterior triangle, which are located posterior to the sternocleidomastoid muscle. This space is bordered by the base of the skull superiorly, clavicle inferiorly, and posterior aspect of the sternocleidomastoid anteriorly. The uppermost part of level V is generally thought to belong to the occipital nodal region.[39] Therefore, from a practical standpoint, the radiographic cranial border of level V has been accepted as a horizontal plane crossing the cranial edge of the hyoid bone.[40] From a surgical perspective, level V is further subdivided into Va and Vb, and the caudal edge of the cricoid arch is the anatomic landmark denoting this subdivision (Vb lies below this boundary).

Retropharyngeal Nodes

The retropharyngeal space, which contains the retropharyngeal nodes, extends from the skull base (cranially) to the hyoid bone (caudally). The anterior boundary of the retropharyngeal space is the pharyngeal constrictor muscles, and the posterior boundary is the prevertebral fascia. The retropharyngeal nodes are further divided into medial and lateral groups. The lateral retropharyngeal nodes lie medial to the carotid artery and lateral to the longus capitis and longus colli muscles, whereas the medial group consists of one or two nodes intercalated along the midline lymphatics.

MOLECULAR BIOLOGY

In parallel to the Fearon and Vogelstein model describing the genetic basis of colon cancer,[41] there are a series of specific genetic events that precede the development of oral SCC.[42] Cancer progression models describe several steps that occur during tumor development: Oncogenes become activated and tumor suppressor genes become deactivated, and a series of these alterations are required for carcinogenesis. In the oral mucosa, this genetic progression is reflected histologically by the transformation from normal

mucosa to dysplastic epithelium and ultimately to frankly invasive SCC. Data to support this model come from studies that reveal genetic alterations in histologically normal tissues and in premalignant lesions, including loss of heterozygosity at chromosomes 3p14 and 9p21. Furthermore, mutations in the region of chromosome 17p13, which encompasses the tumor suppressor gene *TP53*, are among the early events that contribute to malignant transformation. Indeed, biopsies of normal mucosa from patients with upper aerodigestive tract carcinomas frequently harbor *TP53* mutations.

Comprehensive studies of whole-genome sequencing, gene copy number analysis, and messenger RNA and protein expression of head and neck SCC have been performed and have helped to provide an unbiased characterization of the genomic alterations seen in this disease.[43-46] Known tumor suppressor genes and oncogenes were found to be mutated, including *TP53, PIK3CA, PTEN, HRAS*, and *CDKN2A*. It was observed that HPV-positive tumors had a reduction in mutation rate of at least 50% relative to smoking-associated tumors. Moreover, they were inversely correlated with *TP53* mutations, suggesting that HPV-positive tumors are genomically distinct. However, very few oral cavity tumors (~4%) appear to be driven by high-risk HPV.[47]

The first genomic analyses have identified loss-of-function mutations in *NOTCH1* that suggest that *NOTCH* may act as a tumor suppressor gene in head and neck cancers rather than as an oncogene, as it had been identified in other malignancies.[48] The Cancer Genome Atlas published results validating the initially identified genomic findings in head and neck cancers.[43] Subset analysis of patients with oral cancer has found that reduced copy number alterations and activating mutations in *HRAS* or *PIK3CA* are associated with improved clinical outcomes.

The use of whole-exome sequencing has also been applied to evaluate genomic alterations in younger, nonsmoking patients, and this analysis surprisingly found no significant difference in mutation frequencies, types of mutations, or copy number between younger and older patients with oral tongue cancers.[45] Smoking was seen to have a minimal effect on genomic changes. *FAT1* and *TP53* mutations were not significantly increased in the younger cohort and may represent a novel area of study. Although the genomic characterization has allowed clinicians to better understand the

molecular alterations underlying the development of oral cancers, the majority of known mutations represent nontargetable tumor suppressor genes. Therefore, further studies of these alterations as potential prognostic and predictive biomarkers and synthetic lethality approaches are needed to fully realize the immense potential of assessment of the genomic alterations in the tumor of an individual patient with oral cancer.

More recent analyses have focused on recurrent and metastatic head and neck cancers that suggest the potential for precision approaches to treating these advanced tumors with more than 20% showing "actionable" mutations.[49] Liquid biopsy approaches analyzing tissue fluids including saliva and blood also hold tremendous promise in the early detection of recurrence of oral cancers.[50] Furthermore, immunoprofiling of squamous cancers of the head and neck inclusive of oral cavity tumors indicates that immune-oncologic approaches to treating these tumors should be considered in future clinical investigations.[51]

NATURAL HISTORY AND PATTERNS OF SPREAD

Premalignant Lesions

Leukoplakia

Leukoplakia and erythroplakia are gross clinical descriptors that do not always correspond directly to specific pathologic entities.[19,52] The World Health Organization defines leukoplakia as a white patch or plaque that cannot be rubbed off or characterized clinically or pathologically as any other disease[52] (Figure 50.4). Leukoplakia is not related to the presence or absence of dysplasia; however, it is the most common precursor of cancer of the oral cavity. Leukoplakia is primarily a clinical entity, with certain key pathologic features. These features include hyperkeratosis and acanthosis. Leukoplakia may begin as a thin gray or gray/white plaque that may appear translucent, is sometimes fissured or wrinkled, and typically soft and flat. They frequently have sharply demarcated borders but occasionally blend gradually into normal surrounding mucosa.

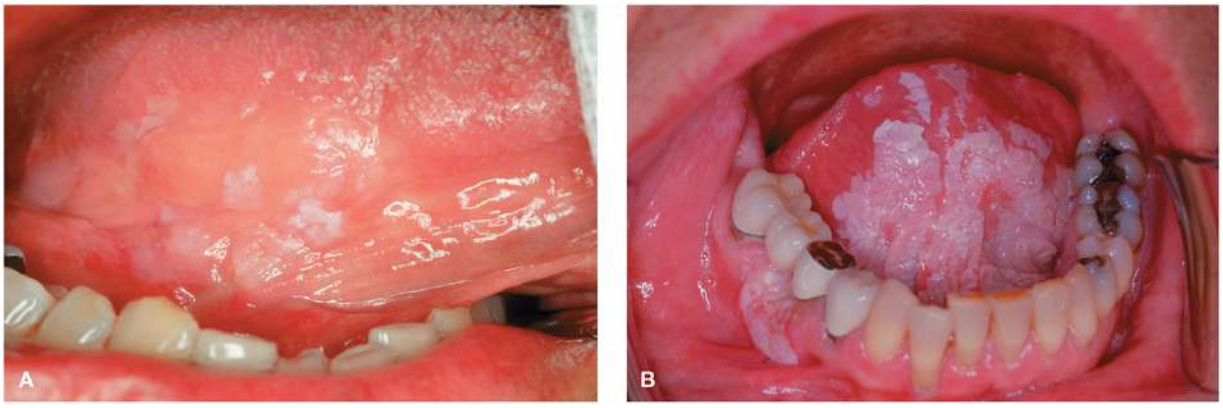

FIGURE 50.4 A. Superficial patches of leukoplakia involving the lateral and ventral surface of the oral tongue. B. Extensive leukoplakia involving the ventral oral tongue, floor of the mouth, and mandibular alveolus.

Homogeneous leukoplakia is a uniform white lesion that is prevalent in the buccal mucosa; it is the most common variety of leukoplakia and has a low malignant potential. Conversely, high-risk oral leukoplakia demonstrates abnormal orientation of cells, nuclear hyperchromatism, increased mitosis, and nuclear cytoplasmic ratio.[19] Clinically, these lesions are nonhomogeneous, nodular, speckled, or verrucous, with central ulceration or erosion.[52] Follow-up studies demonstrate that between <1% and 18% of oral leukoplakias develop into oral cancer, with the latter clinical subtype conferring a higher risk of malignant transformation.[53,54]

Leukoplakia may regress spontaneously without therapy. A baseline biopsy may be performed to establish diagnosis and rule out malignant transformation. Leukoplakia with clinically or histologically aggressive features, demonstrating dysplasia, should be excised. Reported recurrence rates after surgical resection ranges from 0% to 35%.[55] However, there is no good evidence that treatment of oral leukoplakia may prevent the development of oral cancer.[56]

Erythroplakia

Erythroplakia describes a chronic, red, generally asymptomatic lesion or patch on the mucosal surface that cannot be attributed to a traumatic, vascular, or inflammatory cause. Erythroplakia, like leukoplakia, is a clinical diagnosis of exclusion that requires the clinician to rule out all other erythematous oral lesions.[57] However, erythroplakia is associated with a

higher risk of malignant transformation than leukoplakia. Transformation rates are considered to be the highest among all precancerous oral lesions and conditions.[58] Histopathologically, it has been documented that in homogeneous oral erythroplakia, 51% showed invasive carcinoma, 40% carcinoma in situ, and 9% mild or moderate dysplasia.[58] The treatment of choice for erythroplakia is surgical excision.

Oral Submucous Fibrosis

The term describes a generalized fibrosis of the oral cavity tissues resulting in marked rigidity and trismus. At early stages, these premalignant lesions are characterized by blanching of the mucosa with a marble-like appearance. At more advanced stages, palpable fibrous bands become evident around the buccal mucosa and the mouth opening. Once oral submucous fibrosis reaches advanced stages, approximately 25% of cases biopsied demonstrate epithelial dysplasia in addition to subepithelial alterations.[10] Oral submucous fibrosis is associated with the use of betel quid (with or without tobacco) or pan masala.[10] In India, it is estimated that as many as 5 million individuals are afflicted with oral submucous fibrosis.[10]

Oral Cavity Cancer

Relative Distribution

The most common subsite for OCSCC (excluding the lip) is the oral tongue.[59] In a review of 3,308 cases of oral cavity cancer treated at the University of Texas MD Anderson Cancer Center between 1970 and 1999, 32% involved the oral tongue.[19] The floor of the mouth is the second most common subsite where oral cavity carcinomas may arise. Carcinoma of the alveolar ridge accounts for approximately 10% of oral cavity carcinomas. SCC of the retromolar trigone and hard palate is rare. Similarly, carcinoma of the buccal mucosa is rare in the United States but is the most common carcinoma of the oral cavity in Southeast Asia because of the widespread use of betel nut.[19]

Patterns of Spread

Local Spread

Carcinoma from distinct anatomic subsites may exhibit different tendencies for spread based on natural anatomic barriers and location. For instance, the majority of lip cancers are local growths that do not invade deeply into the tissues of the oral cavity or mandible.[60] However, a select few lip carcinomas may be deeply invasive with perineural involvement, posterior spread to involve cortical bone, extension to the inferior alveolar nerve, or spread to the skin of the face.[59] SCC of the floor of the mouth can secondarily involve the ventral tongue, extend along the lingual nerve and submandibular duct, or invade the cortex of the mandible. Tumors in this location can invade deeply, involving the muscles of the floor of the mouth. There is an anatomic gap between the mylohyoid and hyoglossus muscles through which a carcinoma can gain access to submandibular and sublingual areas. Carcinomas of the alveolar ridge and retromolar trigone tend to invade bone early. Tumors of the inferior alveolar ridge may access the mandibular canal and the inferior alveolar nerve, whereas tumors of the superior alveolar ridge may pass into the maxillary antrum or floor of the nose. Infiltrating lesions of the buccal mucosa can invade the buccinator muscle, extend to the buccal fat pad, and invade the subcutaneous tissue. The hard palate has a relatively dense mucoperiosteum that is relatively resistant to tumor invasion. However, the primary and secondary palates are fused at the incisive fossa, where tumors can gain access into the nasal cavity. The greater palatine foramina can allow tumors to spread posteriorly and enter the pterygopalatine fossa and skull base.

Lymphatic Metastases

The oral cavity has an extensive group of lymphatics that manifest a fairly predictable lymph node drainage pattern based on location (subsite) within the oral cavity[59] (Table 50.1).

TABLE 50.1 RELATIVE INVOLVEMENT OF LYMPH NODE REGIONS BY ORAL CAVITY SUBSITE

	Percentage Involved			
	Submaxillary	**Submental**	**Upper Jugular**	**Midjugular**
Oral tongue	18	9	73	18

	Percentage Involved			
	Submaxillary	Submental	Upper Jugular	Midjugular
FOM	64	7	43	0
RMT	25	0	63	12.5

FOM, floor of mouth; RMT, retromolar trigone.

From Byers RM, Wolf PF, Ballantyne AJ. Rationale for elective modified neck dissection. *Head Neck Surg*. 1988;10(3):160-167. Copyright © 1988 Wiley-Liss, Inc., A Wiley Company. Reprinted by permission of John Wiley & Sons, Inc.

The lymphatic nodal stations most commonly involved include levels I to IV.[61,62] Site-specific metastases have been previously mentioned above, for each subsite. The retrostyloid space is potentially at risk for involvement by metastatic disease when upper level II nodes are grossly positive.[39] The medial retropharyngeal nodes are rarely a site of metastases in head and neck SCC.[63] The lateral retropharyngeal nodes generally at risk in primary carcinoma of the nasopharynx and oropharynx are rarely involved in oral cavity cancer unless there is oropharyngeal involvement or a significant nodal burden.[64-66] The lymphatic drainage pattern to the upper and lower lip is distinct. The principal lymphatic drainage of the upper lip is to preauricular, periparotid, submental, and submandibular lymph nodes, which secondarily drain into deep jugular lymph nodes. The medial portion of the lower lip drains primarily to the submental lymph nodes, whereas the lateral portion drains into the submandibular triangle.[67]

A classic study by Lindberg[68] demonstrated that the superior deep jugular nodes are most frequently involved by cancers of the oral cavity. The anterior portion of the tongue drains into the submental nodes (level Ia), and the lateral portion drains into the submandibular (level Ib) and deep jugular nodes (level II). The posterior oral tongue drains into the upper jugulodigastric group of lymph nodes (level II). The lymphatics of the oral tongue also have extensive communication across the midline; thus, carcinomas of the oral tongue can metastasize bilaterally. Studies suggest that some carcinomas of the lateral oral tongue may metastasize to level IV lymph nodes without involving level I, II, or III.[69] This implies that there may be separate lymphatic channels draining from the oral tongue directly to level IV nodes, allowing for apparent “skip metastases.”

Dye injection studies have shown that the floor of the mouth has superficial and deep lymphatic drainage systems.[69] The superficial system crosses randomly in the midline and drains into both the ipsilateral and contralateral submandibular lymph nodes. The deep lymphatic system is thought to penetrate the periosteum and drains into the submandibular and upper jugular lymph nodes. Lymphatics from the buccal mucosa drain into the periparotid, submental, and submandibular nodes. Tumors of the alveolar ridge may drain into the submental and submandibular triangles, upper deep jugular, and retropharyngeal lymph nodes. Tumors of the inferior alveolus are more likely to metastasize to the neck than tumors of the superior alveolus. The main lymphatic drainage from the retromolar trigone is into the superior deep jugular lymph nodes; however, there may be some drainage into periparotid and retropharyngeal lymph nodes. Lymphatics in the hard palate are few, but drainage is into submandibular, superior deep jugular, and retropharyngeal nodes.

The risk of neck metastases depends on several factors, including the site and size of the primary tumor. Overall, for patients with OCSCC, cervical metastases occur in approximately 30% of cases.[70] The rate of neck metastases for carcinoma of the lip is approximately 10%.[71] SCC of the oral tongue carries a higher risk of nodal metastases, the frequency ranging from 15% to 75%, depending on the size and depth of the primary lesion.[68,72] Approximately 25% of patients with carcinoma of the oral cavity will have occult nodal metastases, and 3% of patients will have contralateral metastases.[68,72] Contralateral metastases are more common in tumors that approach or cross the midline. Early tumors of the floor of the mouth have approximately a 12% to 30% incidence of occult nodal metastases depending on the thickness of the lesion, whereas larger lesions can have an incidence of nearly 50%.[73] Approximately 15% to 20% of upper alveolar ridge tumors will involve the neck at presentation; the risk of occult metastases in a clinically negative neck is approximately 15% to 20%.[68] The incidence of neck metastases in lower alveolar ridge tumors is higher than for tumors of the upper alveolar ridge.[68] For cancers of the buccal mucosa, the incidence of positive cervical lymph nodes at diagnosis is 10% to 30%; the incidence of pathologically positive nodes in a clinically negative neck is about 15%. Similar rates of occult metastases occur for SCC of the retromolar trigone; however, patients tend to present with more advanced

disease, resulting in a somewhat higher rate of regional metastases.[74] The incidence of lymph node involvement from carcinoma of the hard palate is low, approximately 15%.[60,75]

Distant Metastases

Distant metastasis occurs in approximately 15% to 20% of patients who eventually die of their disease.[76] The risk of distant metastases increases with the degree of lymph node involvement. Patients with recurrent disease are also at higher risk for distant metastases.[77] Patients without clinically appreciable neck disease rarely fail distantly after treatment. In general terms, with respect to head and neck cancer, 66% of distant metastases are to the lungs, 22% to the bones, and 9.5% to the liver.[78] On rare occasions, the oral cavity will serve as a site for distant metastasis from another anatomic primary tumor site.[59]

PATHOLOGIC CLASSIFICATION

The predominant histopathologic type of cancer in the oral cavity is SCC. There are several variants of SCC, including basaloid and verrucous carcinoma. Basaloid SCC is believed to have a worse prognosis than traditional SCC. In a retrospective comparison between basaloid SCC and traditional poorly differentiated SCC, the former had a higher incidence of advanced disease at presentation, distant metastases, and poorer overall survival (OS) rate.[79] Verrucous carcinoma is a less common variant of SCC. It is generally considered a low-grade malignancy with low metastatic potential and good overall prognosis, although often with challenges for local control in elderly patients.[19] For most cases, adjuvant radiation and elective neck dissection (END) are not indicated. Sarcomatoid carcinomas can be found in the oral cavity and larynx. This variant of SCC carries a poor prognosis with a mean survival of approximately 2 years.[80]

Less than 10% of neoplasms of the oral cavity have nonsquamous histology. Most of these are minor salivary gland tumors, which tend to arise in the hard palate. Adenoid cystic carcinoma accounts for approximately 30% to 40% of minor salivary gland cancers of the oral cavity.[81] Other histologies that can occur in the oral cavity include adenocarcinomas, melanoma, ameloblastoma, lymphoma, and Kaposi

sarcoma.[59] Approximately 50% of acquired immunodeficiency syndrome–related cases of Kaposi sarcoma have oral cavity involvement.[82] Most lymphomas in the head and neck arise in Waldeyer ring (tonsil, base of the tongue, and nasopharynx). Only 2% of all lymphomas are found in the oral cavity.[83] Fortunately, melanoma of the oral cavity is very rare and represents only 0.2% to 8% of all melanomas.[84] Mucosal melanomas generally have a worse prognosis than cutaneous melanomas.[85]

CLINICAL PRESENTATION

The oral cavity is an anatomic region that is readily accessible to visual inspection and palpation. Despite this fact, many patients with oral cavity tumors present with advanced-stage disease as initial symptoms may be vague and painless. Tumors of the oral tongue often present as small ulcers and gradually invade the musculature of the tongue. Advanced lesions may be either ulcerative or exophytic and are usually quite evident. Some cancers of the oral tongue are painful even in their early stages. Cervical metastases occur early in the natural history of the disease, with 30% to 40% of patients harboring cervical lymph node metastases at diagnosis. SCCs of the oral tongue most often arise along the lateral borders of the tongue[19] (Figure 50.5).

FIGURE 50.5 T2N0M0 squamous cell carcinoma involving the right lateral oral tongue.

Lesions of the floor of the mouth are often infiltrative and may invade bone, the muscles of the floor of the mouth, and the tongue. The frenulum is frequently a site of involvement. Clinical fixation of the tumor to the mandible suggests periosteal involvement, which may occur early.

Tumors of the alveolar ridge may present with pain while chewing, loose teeth, or ill-fitting dentures in edentulous patients. These cancers often arise in edentulous areas or along the free margin of the mandibular alveolus[86] (Figures 50.6 and 50.7). Anesthesia of the lower lip and teeth may indicate involvement of the mandibular canal and inferior alveolar nerve.[87] Tumors of the lip may abut the mandible and require imaging to evaluate the integrity of the mandible.[88]

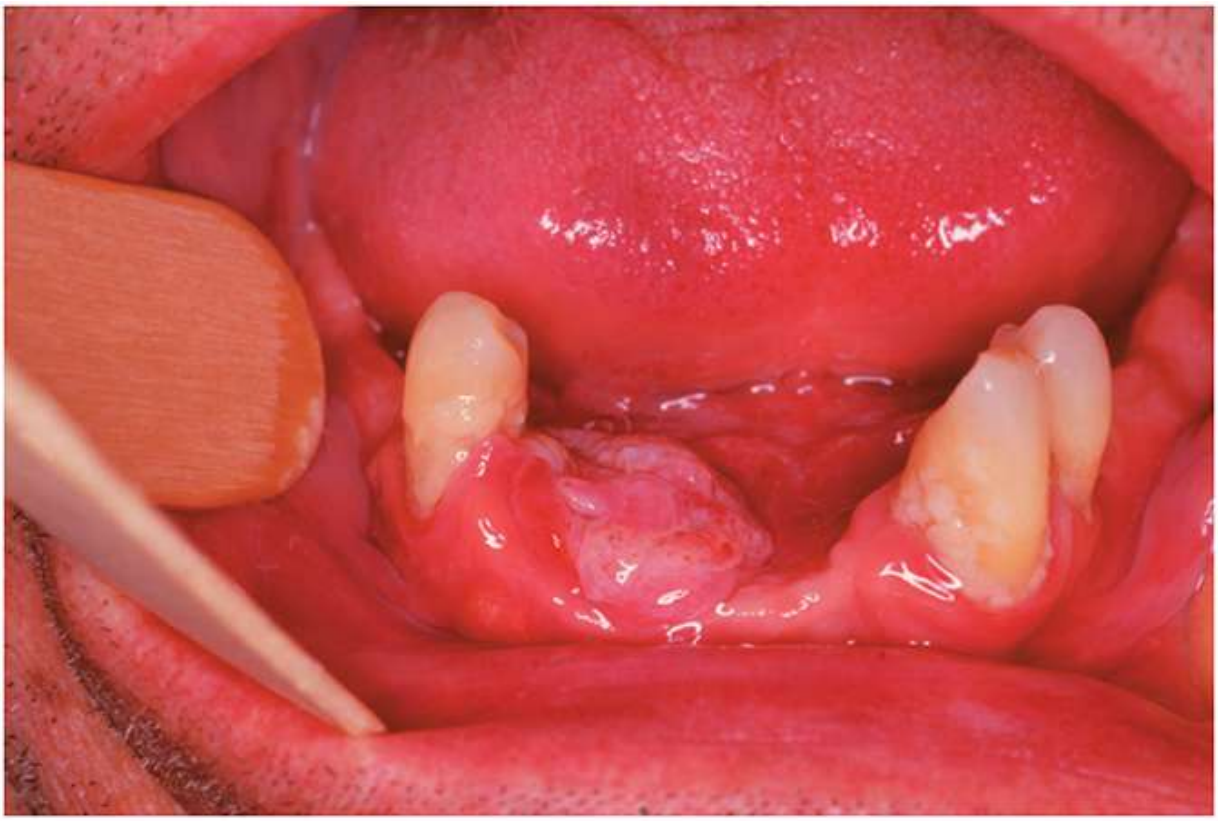

FIGURE 50.6 T1N0M0 squamous cell carcinoma of the mandibular alveolus. No evidence of bone invasion identified on panorex or computed tomography imaging.

FIGURE 50.7 Squamous cell carcinoma involving the mandibular alveolus and buccogingival space.

Tumors involving the retromolar trigone region may present with an exophytic growth pattern and limited involvement of underlying bone (Figure 50.8), or they may infiltrate cortical bone and spread along regional tissue planes to involve the pterygoid complex and parapharyngeal space. These latter lesions often induce trismus early in the clinical course.

FIGURE 50.8 Exophytic T3 carcinoma involving the right retromolar trigone, anterior tonsillar pillar, and proximal soft palate with minimal infiltration into the right base of the tongue.

Carcinoma of the buccal mucosa is rarely symptomatic early in its course. Lesions may be papillary or erosive and located near the dental occlusal line. These tumors are often relatively asymptotic and, therefore, seldom come to medical attention as T1 lesions. Often, these tumors manifest associated leukoplakia.[89] Multiple primary sites and local recurrence are also common. These tumors most frequently arise adjacent to the lower molars along the occlusal line of the teeth.

Carcinoma of the hard palate is often painless, and the sole presenting symptom may be an irregularity in the mucosa or ill-fitting dentures. Other presenting symptoms include nonhealing ulcers of the hard palate, intermittent bleeding, and pain.[90]

DIAGNOSTIC EVALUATION

Patients with oral cavity cancer should undergo a comprehensive history and physical examination. Detailed visual and digital examinations are particularly important for oral cavity tumors. A biopsy of lesions in question should be obtained as well as a thorough dental assessment. CT scans, panoramic radiographs, magnetic resonance imaging (MRI), and other imaging studies may also be important for accurate staging of the tumor and in treatment planning.

The history of present illness should address the following issues: tobacco and alcohol use; dysphagia; odynophagia; pain; trismus; difficulties with speech; hoarseness; loose teeth; ill-fitting dentures; hypoesthesia of the face, lips, or mandible; weight loss; and malnutrition. Otalgia suggests involvement of the ninth or tenth cranial nerve; facial numbness may suggest involvement of the fifth cranial nerve. Hypoesthesia usually results from perineural invasion (PNI), often from penetration of the mandible and perineural spread along the inferior alveolar nerve. The presence of trismus may indicate extension into the pterygoid musculature, signifying locally advanced disease. Other symptoms include a persistent ulcer, bleeding, drooling, or respiratory distress. A patient's comorbid illnesses must also be considered in designing the overall treatment strategy.

A detailed examination of the head and neck should be performed, with particular focus on the oral cavity and oropharynx. This usually begins with a full inspection of the oral cavity, including thorough inspection of the teeth. Palpation of the oral cavity can help assess bony involvement, tongue fixation, and depth of involvement. Deviation or fixation of the tongue suggests involvement of extrinsic muscles of the tongue. Bimanual palpation can help assess the depth of tumor invasion into musculature of the tongue and floor of the mouth. A thorough palpation of the neck is important to assess regional nodal disease.

Imaging can complement the physical examination in determining the extent of disease. A chest x-ray should be performed to exclude lung metastases or a second primary cancer. CT is the modality most commonly used to determine the extent of soft tissue and bony involvement and occult disease in the neck (Figure 50.9). CT may be used to determine the extent of invasion into the deep musculature of the tongue and adjacent structures. Moreover, CT is a valuable modality for visualizing invasion of the mandible, palate, and pterygopalatine fossa. If CT scanning is not available,

then panoramic radiographs can be used to demonstrate mandibular invasion. MRI may be used in case of contrast allergy or a lesion that is not well visualized on CT. For instance, MRI may be used if a patient has significant dental artifact that obscures visualization of the primary tumor on CT. MRI provides excellent definition of tumor involving the tongue and is a good modality for evaluating the possibility of perineural spread. Ultrasound may be used to screen for enlarged lymph nodes that are not clinically detectable. In experienced hands, the accuracy of ultrasound when combined with fine-needle aspiration may be superior to CT or MRI for staging the neck.[91]

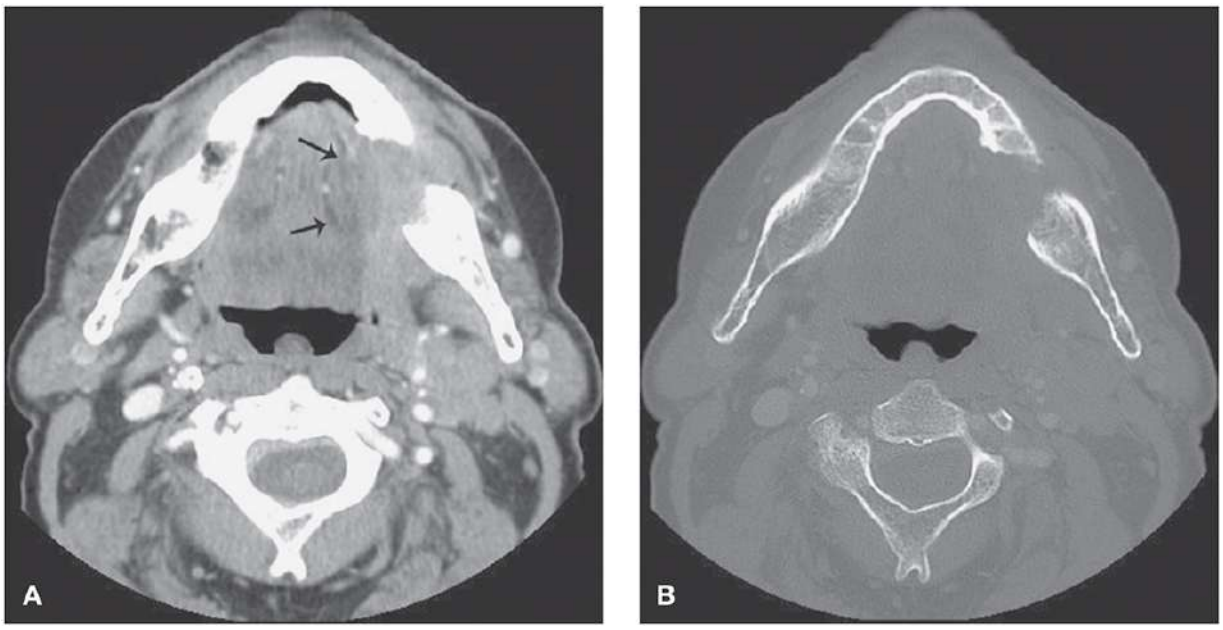

FIGURE 50.9 A. Transverse computed tomography (CT) image with contrast depicting infiltrative squamous cell carcinoma of the left lateral oral tongue and floor of the mouth with associated bone destruction (arrows). There is posterior tumor extension to involve the retromolar trigone and tonsillar complex. B. Corresponding CT bone window views demonstrating destruction of the mandibular body.

Positron emission tomography (PET) and PET/CT have been used increasingly in head and neck cancer evaluation for staging disease in the neck, evaluation of perineural and skull base involvement, identification of distant metastases, and detection of recurrence. In the initial staging, the use of PET/CT may assist with the determination of the depth of invasion, which is routinely determined pathologically.[92] In addition, several studies

suggest that PET is more sensitive and specific in evaluating lymphatic metastases compared to CT and MRI.[93,94] PET/CT may improve the anatomic localization of abnormalities identified on PET and decrease the number of equivocal PET findings.[95] Liao et al[96] prospectively evaluated 473 patients with OCSCC and reported a sensitivity of 77.7% and a specificity of 58% for PET/CT after histopathologic correlation of nodal metastases to the neck. Linz et al, demonstrated a negative predictive value (NPV) for PET/CT of 93% in a prospective study evaluating 150 patients with OCSCC.[97] Pentenero et al[98] report an accuracy of 66.7%, a specificity of 76.9%, and an NPV of 83.3% for staging of the neck with PET/CT. Despite the improved overall accuracy, clinical application of PET/CT is limited by the suboptimal detection of small metastases. Therefore, the decision to pursue a neck dissection should not be based solely on PET/CT findings.

Reports have indicated that the overall sensitivity and specificity of PET may be superior to CT and MRI for evaluating persistent or recurrent disease, particularly in patients who have received previous radiotherapy.[99,100] The accuracy of PET in detecting disease recurrence or persistence may be influenced by the time post-treatment when images are acquired. It is recommended that a PET scan not be performed until 8 to 12 weeks post-treatment to minimize the risk of both false-negative and false-positive interpretations.[101-104] Postoperative PET/CT may also improve the detection of early recurrent disease. A disease by Yu et al analyzed the charts of 391 patients treated for oral malignancy, of which 237 underwent PET/CT planning and 154 were planned with CT only. Patients screened with postoperative PET/CT were more likely to be diagnosed with early recurrence compared to those who received CT only and were more likely to undergo treatment intensification. The authors also showed postoperative PET/CT was associated with improved disease-free survival (DFS) and OS for patients with intermediate-risk features (T3-4, node positivity, lymphovascular invasion, PNI, tumor thickness >5 mm, and close surgical margins).[105]

STAGING

The American Joint Committee on Cancer (AJCC) has established a staging system for cancer of the oral cavity. The staging guidelines apply to all forms of carcinoma and are based on the eighth edition of the AJCC Staging Manual (Table 50.2).[106] Nonepithelial malignancies and melanoma of the lip and oral cavity are not included in the staging system. There are several pertinent changes from prior editions of the AJCC Staging Manual: (a) clinical and pathologic depth of invasion are now used in indicating the T category, (b) extrinsic tongue muscle involvement is no longer denoted as T4, (c) separate N staging categories are now present for patients treated with and without neck dissection, and (d) the presence of extranodal extension (ENE) is introduced as a descriptor of HPV-negative SCC.[106]

TABLE 50.2 STAGING OF ORAL CAVITY CARCINOMA (INCLUDING MUCOSA OF THE LIP)

Definition of Primary Tumor

T Category	**T Criteria**
TX	Primary tumor cannot be assessed.
Tis	Carcinoma in situ
T1	Tumor ≤2 cm in greatest dimension, ≤5 mm depth of invasion (DOI)
T2	Tumor ≤2 cm in greatest dimension, DOI >5 mm, *or* tumor >2 cm, and ≤4 cm, with ≤10 mm of DOI
T3	Tumor >2 cm and ≤4 cm, with DOI >10 mm or tumor >4 cm, with DOI ≤10 mm
T4	Moderately advanced or very advanced local disease
T4a	Tumor >4 cm with DOI >10 mm or tumor invades adjacent structures only (eg, through cortical bone of the mandible or maxilla, or involves the maxillary sinus or skin of the face)
T4b	Tumor invades masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery.
Definition of Regional Lymph Node (N)	
Clinical N (cN)	
N Category	**N Criteria**
Nx	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastases

Definition of Primary Tumor

N1	Metastases in a single ipsilateral lymph node, ≤3 cm in greatest dimension, ENE (−)
N2	Metastases in a single ipsilateral lymph node >3 cm, but ≤6 cm in greatest dimension and ENE (−); in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE (−); *or* in bilateral or contralateral lymph nodes, ≤6 cm in greatest dimension and ENE (−)
N2a	Metastases in a single ipsilateral lymph node >3 cm, but ≤6 cm in greatest dimension and ENE (−)
N2b	Metastases in multiple ipsilateral lymph nodes, ≤6 cm in greatest dimension, and ENE (−)
N2c	Metastases in bilateral or contralateral lymph nodes ≤6 cm in greatest dimension and ENE (−)
N3	Metastases in a lymph node >6 cm in greatest dimension and ENE (−) *or* in any node with clinically overt ENE (+)
N3a	Metastases in a lymph node >6 cm in greatest dimension and ENE (−)
N3b	Metastases in any lymph node(s) and clinically over ECE (+)

Definition of Regional Lymph Node (N)

Pathologic N (pN)

N Category	**N Criteria**
Nx	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastases
N1	Metastases in a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE (−)
N2	Metastases in a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE (+); >3 but ≤6 cm in greatest dimension and ENE (−); in multiple ipsilateral lymph nodes, ≤6 cm in greatest dimension and ENE (−); *or* in bilateral or contralateral lymph nodes, ≤6 cm in greatest dimension and ENE (−)
N2a	Metastases in a single ipsilateral or contralateral lymph node ≤3 cm in greatest dimension and ENE (+), *or* in a single ipsilateral lymph node, >3 but ≤6 cm in greatest dimension and ENE (−)
N2b	Metastases in multiple ipsilateral lymph nodes ≤6 cm in greatest dimension and ENE (−)
N2c	Metastases in bilateral or contralateral lymph nodes ≤6 cm in greatest dimension and ENE (−)

Definition of Primary Tumor

N3	Metastases in a lymph node >6 cm in greatest dimension and ENE (−); in a single ipsilateral lymph node, >3 cm in greatest dimension and ECE (+); *or* multiple ipsilateral, contralateral, or bilateral lymph nodes, any with ENE (+)
N3a	Metastases in a lymph node >6 cm in greatest dimension and ENE (−)
N3b	Metastases in a single ipsilateral lymph node >3 cm in greatest dimension and ECE (+), *or* in multiple ipsilateral, contralateral, bilateral lymph nodes, any with ENE (+)

Note. A designation of "U" or "L" may be used for any N category to indicate metastases above or below the lower border of the cricoid, respectively. Similarly, clinical or pathologic extranodal extension (ENE) should be recorded as ENE (−) or ENE (+).

AJCC Eighth Edition Prognostic Stage Groups

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1, T2	N1	M0
	T3	N0, N1	M0
Stage IVA	T1, T2, T3	N2	M0
	T4a	N0, N1, N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

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GENERAL MANAGEMENT

Surgical resection, radiation, chemotherapy, or combined modality approaches are classic treatment options that have been employed for patients with cancer of the oral cavity. The choice of treatment modality, either singly or in combination, depends on the stage and size of the tumor and relevant patient factors, such as toxicity, performance status, comorbid disease, and convenience. The overall health and functional status of the patient are important determinants in choosing between surgical and nonsurgical approaches.

Surgery is the mainstay of treatment for lesions of the oral cavity.[107] Surgical resection is expeditious, effective, and often associated with modest morbidity and good functional outcome, particularly for patients with small- to moderate-sized lesions. Definitive radiation therapy can be considered for patients with early-stage disease who either are not surgical candidates or refuse surgical management. For patients with advanced lesions of the oral cavity, a combined modality approach is generally recommended. In patients with high-risk pathologic features including nodal extracapsular extension and positive resection margins, the addition of concurrent chemotherapy during the postoperative radiation treatment course may further augment tumor control rates, provided the chemotherapy can be tolerated.[108-111]

PRINCIPLES OF SURGERY

All patients with oral cavity carcinoma should be evaluated by a head and neck surgical oncologist. In patients who are not surgical candidates, definitive high-dose radiation has been associated with higher rates of osteoradionecrosis (ORN) and inferior control rates, particularly in the setting of more advanced disease, highlighting the role of surgery as optimal management.[112-115] The primary objectives of surgery are complete resection of the primary tumor with negative margins and staging and treatment of the regional lymphatics. Margin status is one of the most important variables associated with survival, as locoregional control is significantly improved with margins of 0.5 cm or greater, relative to margins of <0.5 cm (36% vs 18%).[108,109,116]

Surgical Management of the Primary Tumor

In treating cancer of the oral tongue, it is best to obtain adequate margins during initial resection. Data from the National Cancer Database (NCDB) have demonstrated worse OS, by a reduction of survival of 13%, compared to negative margins.[117] The outcome of intraoperative positive margins followed by immediate repeat resection revised to negative margins is associated with worse survival compared to negative margins achieved with initial resection (31% vs 49%).[118] Several strategies are being developed to enhance the ability of surgeons to detect margins intraoperatively. However,

these remain largely experimental and are yet not being used in routine clinical practice.[119-121] Although surgeons and pathologists agree on the quantified distances for free margins, pathologic findings of margin status can be misclassified because of tissue shrinkage, inaccurate sampling, and improper orientation.[122] Although shrinkage is unavoidable, accurate assessment of all margins can be performed from the main specimen, as opposed to sampling from the tumor bed. How the surgeon takes the margins is also extremely important, and it is recommended that the margins be taken from the tumor specimen rather from the tumor bed, as the latter is associated with higher risks of local recurrence.[123] Furthermore, proper orientation of the specimen and communication with the pathologist are vital to assessing accurate margin status.

The ability to obtain clear, three-dimensional margins is the most important factor in selecting the surgical approach, and this is typically guided by the size and location of the tumor as well as factors related to the patient's dentition as well as the presence or absence of trismus. Most often, lesions of the anterior or lateral oral tongue and floor of the mouth can be resected transorally; however, in cases with significant posterior extent and/or in patients with trismus and/or obstructive dentition, a visor flap with lingual release—sometimes referred to as a pull-through or lip-splitting incision with mandibulotomy—may be required for optimal resection. The visor flap is an approach that avoids a facial incision and is associated with lower rates of oral incompetence and fistula.[124] Buccal resections can often be performed with a transoral approach or with a lip-split incision to allow adequate exposure for mandibular or maxillary resection. Retromolar trigone resections often require mandibulectomy because of the posterior extent and increased rate of bone invasion. The introduction of transoral robotic surgery offers a novel approach for resecting more posterior tumors without mandibulotomy.

Transoral resection is often used for excision of floor of the mouth tumors, and these excisions often involve marginal or segmental mandibulectomy because the presence of mandibular invasion is associated with worsened local control. The decision on whether to perform a marginal versus a segmental resection is based on the preoperative assessment of invasion of the periosteum and cortex.[125] However, this type of assessment remains a challenge because results of preoperative physical examination

are predictive of bone invasion only two-thirds of the time. This can be enhanced using imaging that has excellent specificity despite limitations in assessment of microscopic invasion.[126] For the management of small tumors with periosteal involvement, marginal mandibulectomy is associated with outcomes equivalent to those of segmental mandibulectomy. The major indications for segmental mandibulectomy include preoperative or intraoperative findings of bone invasion, tooth loss with low mandibular bone height, and bone that has previously been irradiated. In cases in which both a mandibulotomy and marginal mandibulectomy are contemplated, the risk of postradiation ORN is high and should be considered with caution.[127] Transoral resection can often be employed to resect lesions of the hard palate and maxillary alveolar ridge, though larger tumors that extend into the paranasal sinuses, masticator space, or infratemporal fossa and may require a facial incision to improve access.

Surgical Management of the Neck

The relatively high rate of cervical nodal metastasis associated with oral cavity cancers warrants management of the neck in the vast majority of patients with oral tongue, floor of the mouth, buccal, and retromolar trigone tumors. The selection of type and extent of neck dissection is dependent on whether the patient is clinically node negative based on physical examination and imaging; in clinically node-negative patients, a neck dissection is considered elective. In contrast, patients with nodes that are palpable or detected on imaging require a therapeutic neck dissection. Although neck dissection is a safe procedure, it is not without morbidity; shoulder dysfunction, iatrogenic cranial nerve injuries, and vascular insult remain significant complications of neck dissection.

Therapeutic neck dissection in clinically positive disease is a well-established treatment strategy, and the extent of dissection recommended in this setting has decreased considerably over the past several decades. In the early 1900s, radical en bloc resections according to the surgical oncologic principles advanced by Dr William Halsted were recommended. Over the intervening years, these relatively morbid operations have largely been replaced by more selective approaches to involve only the nodal basins with expected metastasis with preservation of uninvolved nonlymphatic

structures, including the internal jugular vein, sternocleidomastoid muscle, and spinal accessory nerve. The contemporary practice of these more limited procedures has been supported, with data demonstrating that regional control and survival rates do not decrease with more selective approaches, particularly when adjuvant therapies are used to manage microscopic residual disease in high-risk patients.[100]

Koyfman et al recently published guidelines on the management of the neck in oral cavity malignancies. For patients with cT2 to cT4 disease with a clinically negative neck, who are treated with curative intent, an ipsilateral neck dissection should be performed.[128] For patients with a clinically negative neck, the dissection should include levels Ia, Ib, II, and III, and at least 18 nodes should be removed.[128] For patients whose preoperative examination reveals a cN-positive neck, a selective neck dissection at levels I to IV or I to V is recommended. In these cases, positive pathologic nodes are found in more than 75%, with 15.8% having skip metastasis to level III or IV, without involvement of level I or II.[33,59,69,129] The use of radical and modified neck dissections is typically reserved for patients with advanced nodal disease (N3), disease extending into level V, or invading critical structures in the neck. In addition, contralateral neck dissection should be performed in patients with a clinically node-positive neck.[128] In patients with advanced disease of the oral tongue, lip, or mandible, tumor crossing midline, and floor of the mouth involvement, bilateral neck dissection may be required.[130,131]

For patients with cT1 disease and cN0 neck, an ipsilateral neck dissection should be performed.[128] The decision to proceed to END is based on a >20% probability of occult nodal disease being present for patients with early-stage tumors that are clinically node negative (cN0).[132] END can be therapeutic if no positive nodes are found at pathologic review, and it can provide important staging information to guide decision about the need for adjuvant therapy in patients found to have pN-positive disease with or without ENE. The depth of tumor invasion has been reported to be the best predictor for regional metastasis in the cN0 neck. Nevertheless, cutoffs for the extent of depth of invasion for which neck dissection is recommended remain ill-defined. A meta-analysis identified a depth of 4 mm from the mucosal surface in oral tongue cancers as the cutoff most frequently cited as an indication for END, based on an NPV of 95.5%.[133] Other analyses have

shown that the depth of invasion >4 mm is associated with an increased risk of occult metastasis and late cervical recurrences.[134-136] In floor of the mouth tumors, a depth of invasion >1.5 mm is associated with 33% occult regional metastasis, whereas in buccal carcinomas, tumors of the maxillary alveolar ridge, and tumors of the hard palate, depth has not been extensively studied, and occult metastases are rare, occurring in 9% of patients and most often associated with T4 tumors.[137,138] Therefore, END is not indicated for early-stage buccal, maxillary alveolar ridge, or hard palate cancers in cN0 cases. In addition to the depth of invasion, growth type, number of mitoses, PNI, lymphovascular invasion, and poorly differentiated and infiltrative growth patterns are associated with metastasis.[136,138] There is no clear consensus regarding which of these risk factors necessitate END. Once the decision to proceed with END is made, the literature supports dissection of at least the supraomohyoid neck, including levels I to III. The notable exception is cancer of the oral tongue, for which extension to remove level IV can be considered because of the occasional identification of skip metastases, which are difficult to salvage.[69] The need to extend a neck dissection to include level IIB has been questioned because dissection of this nodal level requires dissection of spinal accessory nerve, which, in turn, is associated with greater morbidity. The results of several prospective studies support the exclusion of level IIB in ENDs for patients with oral cavity cancer as the incidence of nodes with occult regional disease is 11.1% in cN0 patients.[139] If dissection is not feasible, elective radiation to a dose of 50 to 56 Gy may be efficacious.[128]

Given that as many as 70% of END are found to have no pathologic lymph nodes at pathologic review and neck dissection can be both morbid and costly, alternatives to END have been explored, and these include observation, elective radiation, or sentinel lymph node biopsy (SLNB). There have been several prospective studies performed to evaluate observation versus END, with one study demonstrating a survival benefit with END.[140] The rate of nodal recurrence in the observation arms in that study performed in Brazil was 41.7% compared with 15% in the END arm. Although successful salvage was higher with observation than with END (57% vs 16%), 66% fewer salvage attempts occurred in the END groups. Because the node-related mortality is higher with observation than with

END (22% vs 10%), END has been the standard of care for most patients with oral cavity cancers.[141]

In a recent landmark study, D'Cruz and colleagues at Tata Memorial Hospital in Mumbai evaluated 500 patients with early-stage OCSCC who were randomly assigned to undergo END versus observation with therapeutic neck dissection to evaluate survival differences between treatment options.[142] The unadjusted improvement in OS for END was 12.5% (END vs observation with TND, 80% vs 67.5%), and this result was confirmed after the investigators adjusted for other covariates (hazard ratio [HR], 0.63; $P < .001$). Although no difference was observed in the cohorts when patients had pN0 disease (HR, 1.2; $P = .54$), among pN-positive cases, significant improvement in survival was noted in the END cohort (HR, 0.52; $P = .008$). In addition, data from this study confirmed that depth >3 mm was a significant independent predictor of regional metastasis (HR, 2.17; $P < .001$). There was no difference observed for OS when patients with tumor depth <3 mm were compared across the two cohorts ($P = .12$); however, the study was not powered to definitively address this issue.[142] Overall, this study's results support the practice of END for early-stage N0 OCSCC and confirm that depth is an important variable in the decision between END or observation and therapeutic neck dissection.

Another option for managing the clinically node-negative neck is SLNB, which is a less invasive approach used to accurately identify occult metastasis in early-stage oral cancer. SLNB is based on the principle that cancer spreads first to a primary echelon lymph node known as the "sentinel node" that can be readily identified and meticulously evaluated for microscopic disease. This minimally invasive technique to stage regional lymph nodes is well established in melanoma and breast cancer and allows for a more systematic and accurate pathologic assessment of regional lymph nodes for metastasis without the morbidity of END. There have been several multi-institutional prospective studies that have been performed to assess the efficacy of SLNB in oral SCC. In a trial completed in Europe, sentinel lymph nodes were identified in 93% of patients with a low false-negative rate.[143] In a study performed in North America (ClinicalTrials.gov identifier: NCT00042926), SLNB was found to have a 96% NPV overall in cancers of the oral tongue.[144] Hasegawa et al conducted a multi-institutional study of patients with T1-2 node–negative disease with ≥4 mm depth of

invasion randomized to sentinel node versus neck dissection. Metastases-positive nodes were observed in 24.8% and 33.6% of patents in the dissection and sentinel biopsy group, respectively (P = .19), without a survival disadvantage, but with improved neck functionality in patients in the sentinel node group.[145] Similar results were shown by Garrel and colleagues who reported a neck node recurrence-free survival of 89.6% versus 90.7% in the neck dissection and sentinel node arm.[146]

A meta-analysis showed a pooled NPV of 96% in early-stage oral cavity tumors, with no difference in regional recurrence between SLNB and END (6.7% and 6%, respectively). The accuracy and consistent NPV found in most studies indicate that SLNB offers an excellent alternative to END in cN0 patients with early oral squamous cancers. Although this approach has become a standard of care for the management of the cN0 neck in patient with oral cavity cancer in Europe, its use in the United States has been much more limited. Factors that might explain the slow adaptation of SLNB in this country include the steep learning curve, the additional preoperative workup required, and the need for an experienced multidisciplinary team. There is no level I evidence yet available regarding survival equivalency with END.

Reconstruction

The oral cavity is a complex site made up of several structures critical for speech, swallowing, and appearance, and successful rehabilitation of these functions in patients who have undergone oral cancer extirpative surgery involves meticulous anatomic restoration post-resection. A successful, reconstruction should attempt to address all three of these functions, and it must be tailored to the site of the defect. Patients with advanced-stage disease are often best reconstructed with microvascular free tissue transfer, which has become standard in head and neck reconstruction and has improved both oncologic and functional outcomes.[1] In the case of oral tongue reconstruction, which is critical to restoring function, the major goals of reconstruction are to allow obliteration of the oral cavity to minimize dead space, to maintain premaxillary contact for articulation and the oral phase of swallowing, and to optimize the mobility of the tip of the tongue to maximize tongue sweep. Postoperative measures of tongue

protrusion and elevation have helped to identify objective targets for favorable speech and swallowing outcomes.[147] Also, for total glossectomy, the volume and convexity of the flap are critical to the achievement of optimal functional outcomes.[148]

For patients with oral cancers requiring mandibulectomy, mandibular reconstruction with bone ensures the best outcomes for speech, swallowing, and cosmesis and also helps to maintain symmetric temporomandibular joint articulation, enabling mouth opening and maintenance of an occlusal plane for chewing. The major cosmetic goals of mandibular reconstruction include providing facial height and projection to prevent the "Andy Gump" deformity.[149] Reconstruction of maxillary and hard palate reconstruction can provide oronasal separation as well as a surface necessary for premaxillary contact and obliteration during the oral phase of swallowing. Although prosthetic palatal obturation can also help achieve these objections, the choice between prosthetic obturation and free tissue is based on the size of the defect, the location, and the number of remaining teeth.[150] The major goals for reconstruction of the floor of the mouth include separation of the oral cavity from the neck and provision of soft tissue bulk between the ventral tongue and the mandible that prevents tethering of the tongue as well as provision of a platform for tongue elevation and protrusion. Major objectives of buccal reconstruction include resurfacing the cheek with prevention of cicatricial scarring and trismus. As swallowing function is well established as one of the most important factors associated with improved quality of life, oral cavity reconstruction and swallowing therapy under the guidance of an experienced speech pathologist are the critical elements in the successful functional rehabilitation after oral cavity cancer resection.

PRINCIPLES OF RADIATION THERAPY

Primary Radiation Therapy

Surgery is the primary treatment modality for oral cavity malignancy. When using radiation alone as the primary management, it is important to consider that the bony structures of the mandible and maxilla may impact the transmission of ionizing radiation. For early-stage disease, a combined approach including both external beam radiation and interstitial

brachytherapy is often recommended for optimal outcome. Thus, a course of radiation can require several weeks of daily therapy followed by an interstitial implant. The normal tissue toxicity risks of xerostomia, dental and gum injury, and occasional ORN may render radiation therapy a less attractive option for single modality treatment of patients who are candidates for surgery. For locally advanced disease, definitive radiation or chemoradiation is not advised in patients who are candidates for surgery.

Historically, sites commonly treated with single modality radiation include the lip, floor of the mouth, and oral tongue.[151,152] Early work indicates that the success rate of radiotherapy is higher if some or all of the treatment is administered with brachytherapy.[153,154] Decroix and Ghossein[155] reported outcomes in 602 patients with cancer of the oral tongue treated with radium implantation or implantation plus external beam radiation. In this series, recurrence at the primary site or at the primary site and neck was 14% and 22% for T1 and T2 lesions, respectively. The Royal Marsden Hospital reported local control rates of 90% at 5 years for T1 and T2 tumors treated with interstitial radiation with or without external beam radiation.[156] Pernot et al[157] reported local control rates of 96% for T1, 85% for T2, and 64% for T3 lesions of the oral cavity treated with brachytherapy and neck dissection. In this series, locoregional control rates were 83%, 70%, and 44%, respectively. Retrospective studies suggest that control rates at the primary site of early oral cavity lesions treated with either brachytherapy alone or a combination of brachytherapy plus external beam radiation range from approximately 70% to >95%.[155-158] For tumors that either involve the mandible or are immediately adjacent to it, definitive radiotherapy is contraindicated because it compromises control and increases the risk of ORN.

Intraoral cone, like interstitial brachytherapy, is a localized radiation therapy technique that has been used to boost the dose to the primary tumor in the oral cavity. Institutions with significant experience with this technique have reported results that rival those obtained by interstitial brachytherapy.[159,160] Either technique for boosting the primary tumor has resulted in improved outcomes compared to high-dose radiation therapy alone.[160,161] In general, external beam radiation therapy followed by either technique is preferable to radiation therapy alone. As with all specialized procedures, the skill and experience of the radiation oncologist are of

critical importance to the successful delivery and outcome of interstitial radiation or intraoral cone therapy.

It is difficult to compare radiation alone to surgery using retrospective analyses as patients who receive radiation alone are at baseline poor surgical candidates and/or with very invasive unresectable or morbid disease. The outcomes for advanced lesions of the oral cavity (T3 and T4) are less than satisfactory with either surgery or radiation alone. Membreno et al conducted a systematic review evaluating the outcomes of primary radiation with or without chemotherapy. Radiotherapy showed less favorable outcomes compared to surgery including lower OS and progression-free survival, with higher feeding tube dependency in the radiotherapy alone group.[162] In most advanced-stage cancers, single modality therapy is inferior to combined modality therapy.[154,163,164] Adjuvant radiation therapy can be delivered preoperatively or postoperatively.[159,163] Although each strategy has potential advantages and disadvantages, postoperative radiation therapy is generally preferred. Postoperative radiation treatment carries the advantage of no delay in the implementation of surgical resection and complete pathologic staging of the tumor. However, it must be borne in mind that postoperative wound complications may delay the implementation of radiation therapy.

Adjuvant Radiation

Although surgery has emerged as the preferred initial treatment approach for the majority of patients with tumors of the oral cavity, adjuvant radiation is commonly recommended to enhance the likelihood of locoregional tumor control. Robertson et al[165] conducted a phase III study in the United Kingdom of 350 patients with T2-T4/N0-N2 oral cavity or oropharyngeal cancers comparing surgery and postoperative radiation versus radiation alone. Because a difference in survival was identified, the study was closed early. The authors found that after 23 months, OS, cause-specific survival, and local control were all improved in the surgery plus radiation arm. Traditionally, indications for postoperative radiation therapy include multiple cervical metastases, positive or close margins, extracapsular extension, PNI, advanced T stage, and mandibular bone involvement. A phase III study conducted at the University of Texas MD Anderson Cancer

Center established the relative prognostic significance of clusters of two or more clinicopathologic features.[166] The adverse clinicopathologic features in this study included (a) close or positive margins, (b) nerve involvement, (c) ≥2 positive lymph nodes, (d) largest node >3 cm, (e) treatment delay >6 weeks, and (f) Zubrod performance status ≥2. This landmark trial demonstrated several now well-established management recommendations: Dose of ≤54 Gy postoperatively was associated with higher primary failure rates compared to ≥57.6 Gy, ≥63 Gy is necessary for ENE, and the presence of ENE as the only factor independently predictive of locoregional recurrence. Moreover, the authors concluded that escalation of dose beyond 63 Gy (in 1.8 Gy per fraction) to sites of increased risk did not yield improved locoregional control. Koyfman et al recently published American Society of Clinical Oncology (ASCO) guidelines on the adjuvant management of patients with oral cavity malignancy. For patients with pathologically negative neck, or a single node that does not have ENE, adjuvant neck radiation is not typically recommended unless there are indications to radiate from the primary characteristics, including PNI, lymphovascular space invasion, or a T3/T4 tumor.[128] For patients with pN1 disease who did not undergo a high-quality neck dissection, adjuvant neck radiation is also recommended.[128]

It is well established that head and neck tumors are rapidly proliferating. Several retrospective series have demonstrated an association between diminished outcomes and a delay beyond 6 weeks in initiating postoperative radiation.[167-169] A multi-institutional prospective study by Ang et al demonstrated that the total treatment time from the completion of surgery to the completion of radiation may affect the likelihood of ultimate disease control.[170] This study illustrated the impact of overall treatment time on 5-year locoregional control: Patients with overall times <11 weeks demonstrated a locoregional control rate of 76%, compared to 62% for 11 to 13 weeks, and 38% for times beyond 13 weeks. An observation study of 25,216 patients from the NCDB demonstrated a time from surgery to radiation of 42 days or less was associated with improved survival compared with 50 days or longer.[171] Hence, it is recommended that adjuvant radiation proceed as soon as surgical wounds are well healed, optimally 4 to 6 weeks after completion of surgery.

There has been significant interest in the use of intensified radiation fractionation schedules to counter rapid tumor cell repopulation as a means of improving outcomes in patients with head and neck cancer treated with radiation. Altered fractionation regimens such as hyperfractionation or accelerated fractionation have been considered for patients being treated with radiation alone, as this approach has been demonstrated to improve the likelihood of locoregional tumor control in the definitive setting.[172] Overgaard demonstrated an accelerated schedule of 6 days per week was associated with significantly higher OS compared to 5 days a week.[173] However, the use of altered fractionation in the postoperative setting has not been resolved. Ang et al reported a trend toward higher locoregional control and survival with a concomitant boost schedule compared to a standard fractionation schedule.[170] However, in a subsequent study, Sanguineti et al[174] demonstrated no benefit for accelerated fractionation, except in patients for whom postoperative radiation was delayed.

There has been recent interest in postoperative chemoradiation for patients with high-risk pathologic features. The results of two randomized trials suggest that postoperative chemoradiation may be beneficial for improving locoregional control and DFS among selected patients with specific high-risk features.[108,109] The impact of chemoradiotherapy appears to be most pronounced in patients with ENE and/or microscopically involved surgical margins.[109,110]

Radiation Techniques

General Considerations

Historically, carcinoma of the oral cavity has been treated with opposed lateral fields, using either two-dimensional or three-dimensional (CT-based) techniques. However, since the emergence of intensity-modulated radiation therapy (IMRT) at the turn of the millennium, there has been a dramatic shift in the radiotherapeutic management of head and neck cancer. Since that time, IMRT has gained widespread adoption and has become the de facto standard in the management of carcinoma of the head and neck.[114,175] The major driver for this dramatic shift away from conventional techniques has been the potential for normal tissue sparing and consequent

improvement in functional outcomes, particularly in the realms of salivary function and dysphagia.

With respect to oral cavity cancer, the improvements in conformality afforded by IMRT have opened the opportunity to mitigate damage to major salivary glands (xerostomia), the mandible (ORN), and the pharyngeal structures (dysphagia).[63,176-180] However, it is important to bear in mind that there are instances in which IMRT may not provide significant additional benefit in the treatment of oral cavity cancer and conventional techniques may be fully adequate. It is also valuable to consider that practitioner and treating center experience may be important indicators of potential outcomes when IMRT is utilized in the treatment of patients with head and neck cancer.[181,182]

Each institution should select appropriate oral cavity cases for treatment with IMRT. For instance, patients with T1/T2N0 carcinoma of the floor of the mouth or alveolar ridge who have undergone surgical staging of the neck may not benefit from IMRT because the bulk of both parotid glands can be excluded from opposed lateral portals (Figure 50.10). Ideal candidates for IMRT include patients with T1/T4 primary lesions with ipsilateral neck disease. In patients who have ipsilateral positive neck nodes, IMRT may allow dose limitation to the contralateral parotid gland without compromising treatment results.[183] In patients with bilateral neck disease, it may be difficult to effectively spare the parotid glands, particularly when superior level II cervical lymph nodes are involved, because of the coverage of the retrostyloid space in this setting.[184]

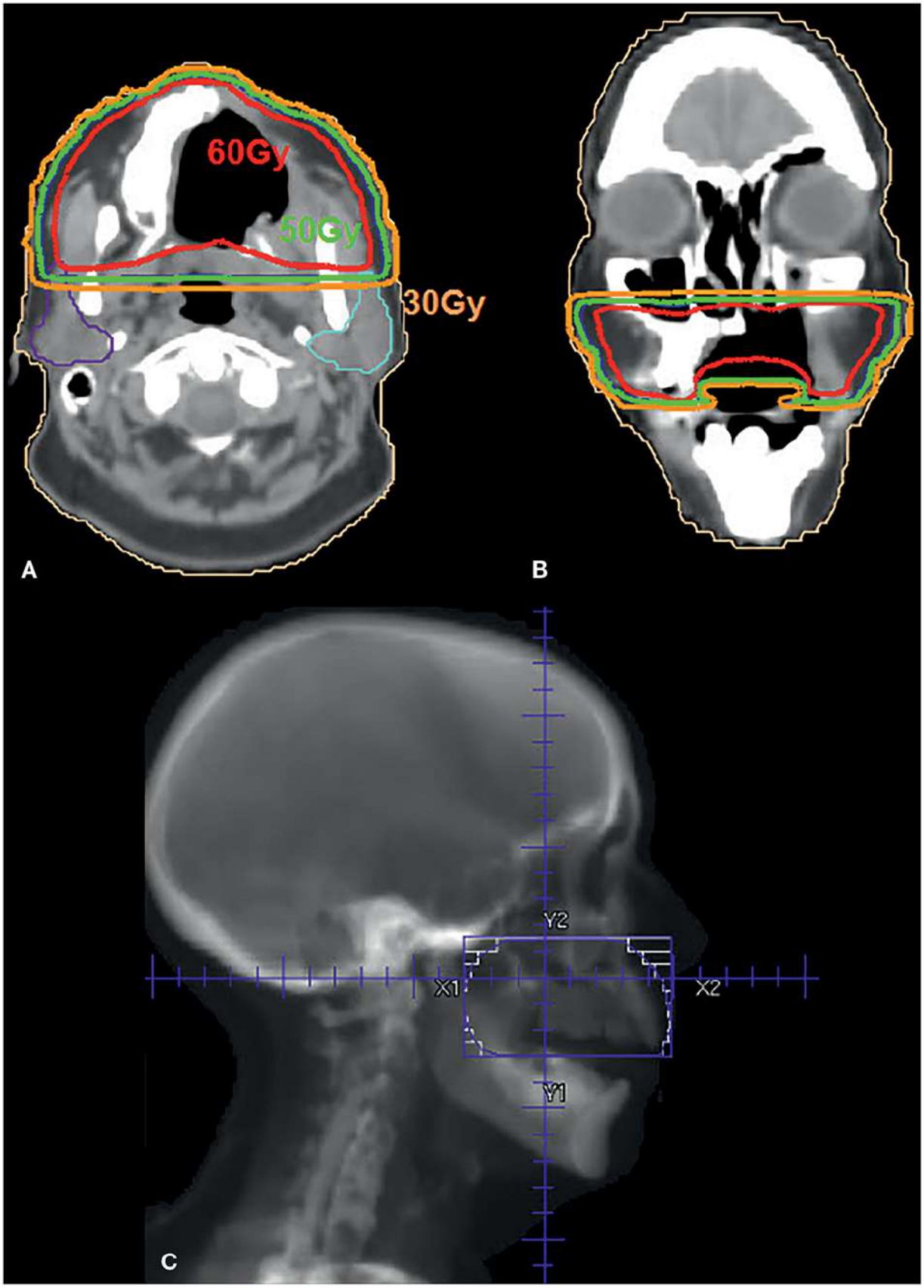
60Gy
50Gy
30Gy
A
B
Y2
X1
X2
Y1
C

FIGURE 50.10 T4N0M0 squamous cell carcinoma of the maxillary alveolar ridge in a patient who underwent left infrastructure maxillectomy and left selective neck dissection. The figure illustrates postoperative conventional radiation field design with opposed laterals to cover the maxilla and operative bed at risk. Treatment of the neck was omitted in lieu of a negative neck dissection. A and B. Relevant isodose lines. C. Right lateral digitally reconstructed radiograph of the field. The parotid tissue is nearly completely spared by this field arrangement.

Intensity-Modulated Radiation Therapy

The use of more conformal techniques may be associated with a unique set of potential pitfalls. Whereas treatment planning with two-dimensional or three-dimensional techniques does not universally mandate careful interpretation of cross-sectional imaging and attention to anatomic detail, IMRT requires precise target volume delineation. If a target volume is not included within the clinical target volume (CTV), it may receive a subtherapeutic dose of radiation and thus portend marginal recurrence. The quality of conformal radiation therapy is significantly associated with outcomes in the treatment of head and neck cancer.[181,182,185]

Most cases of oral cavity cancer will be treated postoperatively. It is important to consider that neck dissection tends to disrupt the anatomic landmarks defining borders between nodal levels. The task of distinguishing the primary tumor resection bed and adjacent neck dissection poses a significant challenge in target volume design. Gregoire et al[39,184] proposed guidelines for target volume delineation in the postoperative patient that are available as a reference. The authors encourage the reader to review these guidelines as they consider more selective coverage of nodal regions during target volume delineation. These guidelines serve in part as the basis for the recommendations presented in this section. Treatment considerations for each oral cavity subsite are presented in the section "Subsite-Specific Treatment and Results."

The discussion to follow is relevant to target volume design in the postoperative setting. Figure 50.11 illustrates relevant target volumes for a typical postoperative oral cavity case. Figures 50.12 and 50.13 provide examples of special considerations for patients with positive margins/ENE and ipsilateral treatment, respectively. There are three classes of CTVs that can be defined based on the practice of a range of North American institutions and cooperative group guidelines.[39,40,64,184,186,187]

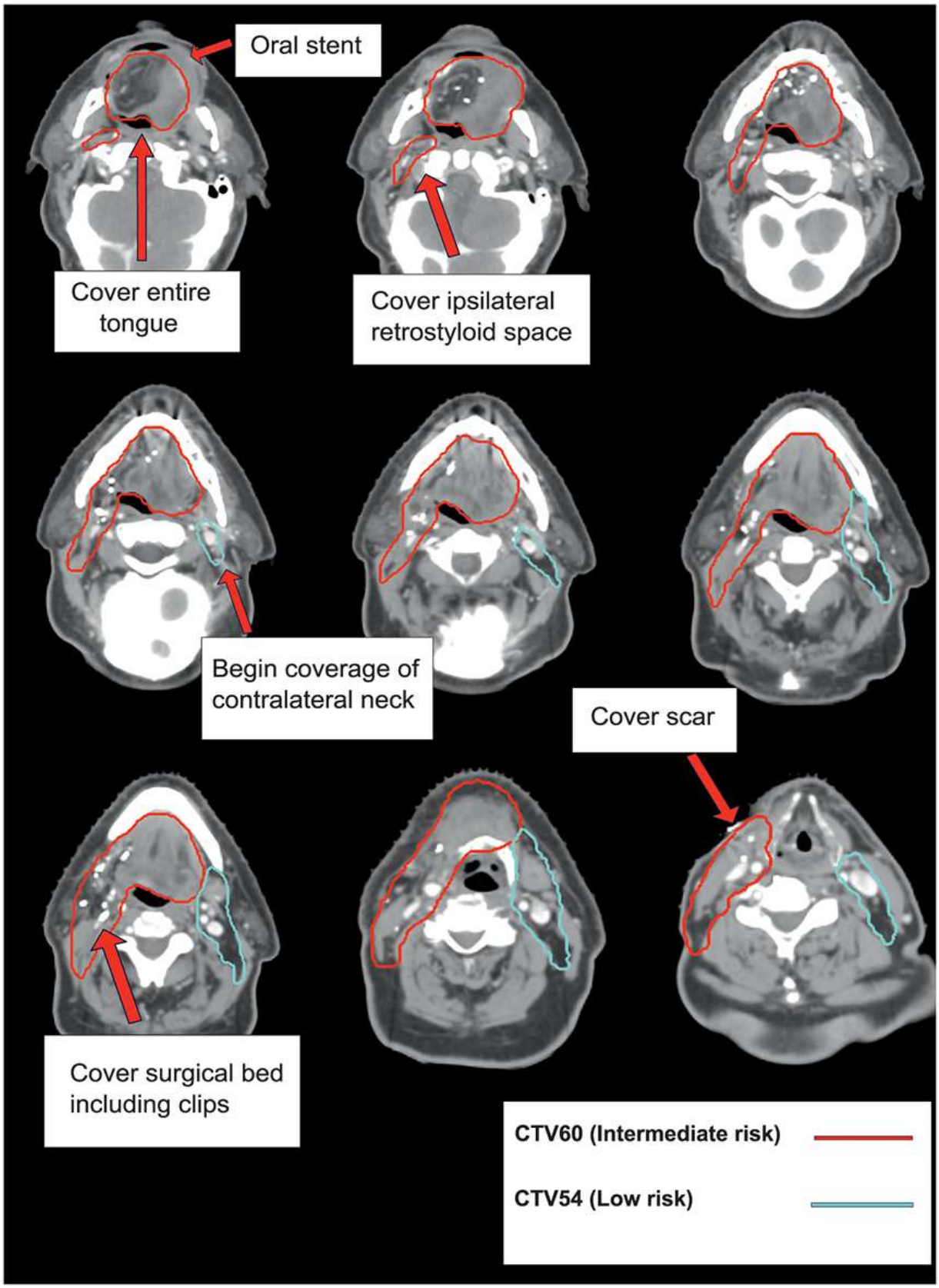
Oral stent
Cover entire tongue
Cover ipsilateral retrostyloid space
Begin coverage of contralateral neck
Cover scar
Cover surgical bed including clips
CTV60 (Intermediate risk)
CTV54 (Low risk)

FIGURE 50.11 T3N1M0 squamous cell carcinoma of the right oral tongue. The patient underwent right hemiglossectomy, including resection of the floor of the mouth, and right selective neck dissection. The tumor was 3 cm in size, with a depth of invasion of 1.3 cm, and 1/46 lymph nodes with evidence of carcinoma (no evidence of elective neck dissection). Adjuvant treatment was delivered with radiation therapy alone using intensity-modulated radiation therapy with the intent of maximizing coverage to regions at risk while sparing salivary glands and pharyngeal tissues. Note that the ipsilateral retrostyloid space and entire tongue, intraoral free flap, and dissected neck are included in CTV_{60}. The cranial extent of CTV_{54} in the contralateral neck is the bottom edge of the body of C1. The retropharyngeal nodes are not covered in this setting to allow sparing of the pharyngeal structures.

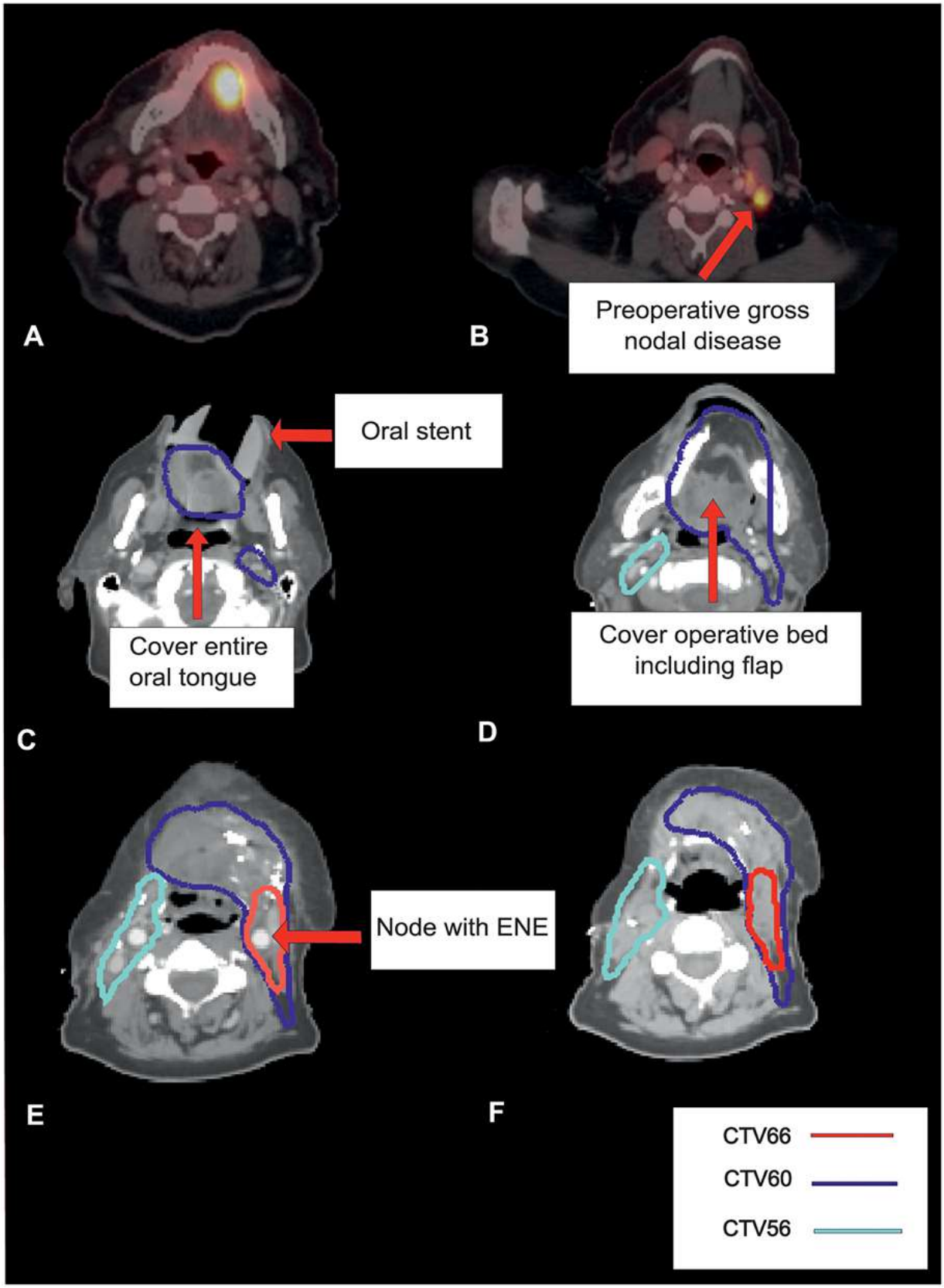
A
B
Preoperative gross nodal disease
Oral stent
Cover entire oral tongue
C
D
Cover operative bed including flap
Node with ENE
E
F
CTV66
CTV60
CTV56

FIGURE 50.12 T4N3bM0 squamous cell carcinoma of the floor of the mouth with evidence of elective neck dissection (ENE) treated on RTOG protocol 1216 (ClinicalTrials.gov identifier: NCT01810913). The patient underwent left mandibulectomy, composite resection of the floor of the mouth, left hemiglossectomy, and neck dissection. The final pathology demonstrated 3 cm primary lesion, with 6/55 lymph nodes positive for carcinoma, and ENE in a lymph node at left level II. The treatment was delivered with intensity-modulated radiation therapy using a simultaneous integrated boost concurrently with chemotherapy. The neck region with evidence of ENE received 66 Gy in 2.2 Gy per fraction, whereas the primary site, free flap, and ipsilateral neck received 60 Gy in 2.0 Gy per fraction. The contralateral neck received 56 Gy in 1.87 Gy per fraction. A and B. Preoperative positron emission tomography showing primary and nodal disease. C-F. Postoperative target volume delineation.

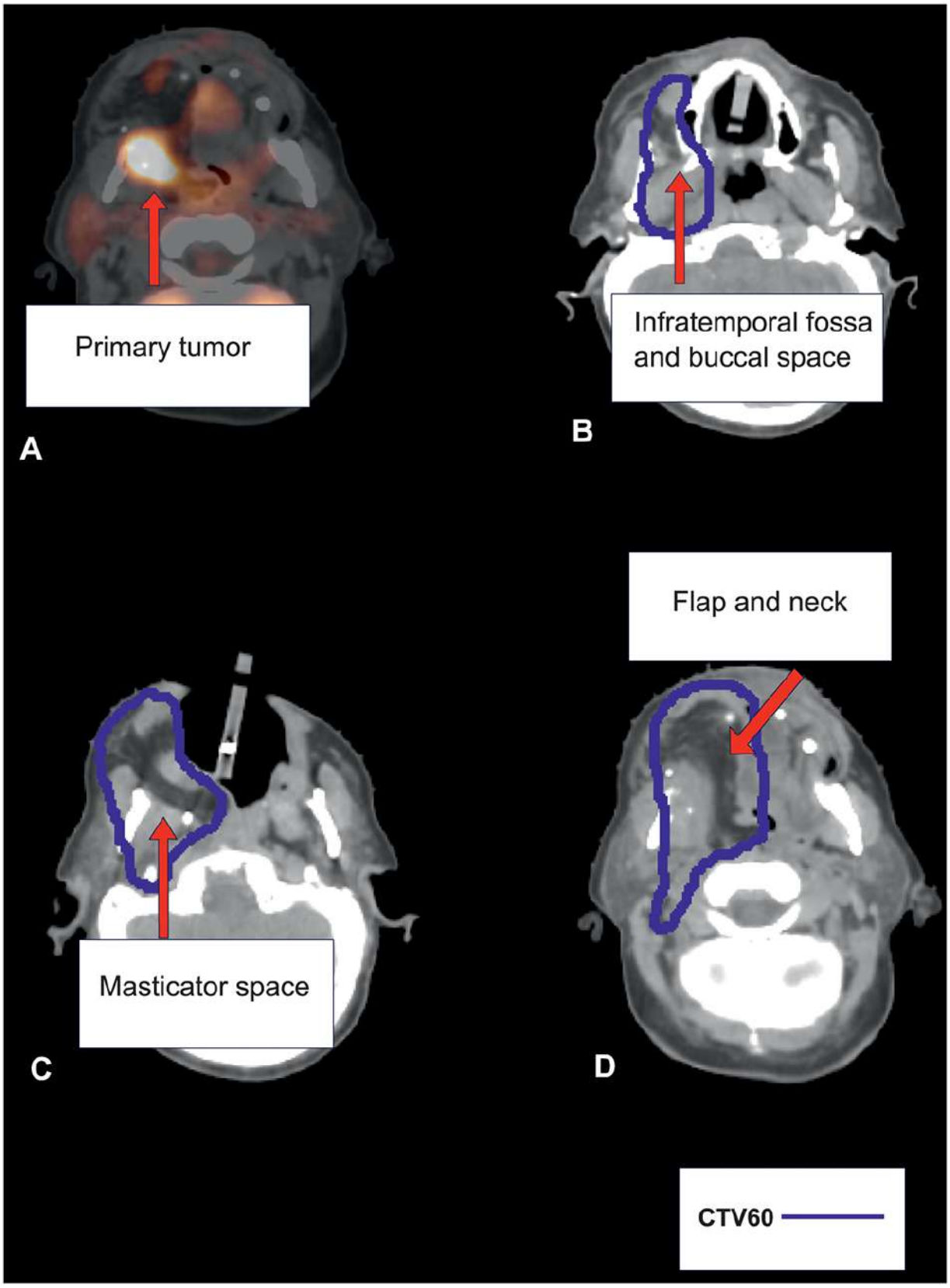
Primary tumor
A
Infratemporal fossa and buccal space
B
Masticator space
C
Flap and neck
D
CTV60

FIGURE 50.13 T2N1M0 squamous cell carcinoma of the right retromolar trigone. The patient underwent composite resection of the right retromolar trigone, buccal mucosa, maxilla, and right neck dissection, followed by anterolateral thigh free flap reconstruction of the defect. A. Preoperative positron emission tomography showing disease at the primary site. B-D. Postoperative target volume delineation of the surgical bed, masticator space, infratemporal fossa, free flap, and ipsilateral neck.

- The GTV_{70} is defined as all areas of gross disease as can be seen on CT, MRI, PET, and physical examination, including all nodes measuring >1 cm, containing a necrotic center, or fluorodeoxyglucose avid on PET imaging. An expansion on this volume will yield the CTV_{70}.[30]
- The high-risk CTV (CTV_{66}) is defined as the volume harboring ENE or a positive margin. The CTV_{66} 66 Gy can be delivered as either a simultaneous integrated boost (SIB) (2.2 Gy per fraction over 30 fractions) or a sequential boost.
- The intermediate-risk CTV (CTV_{60}) is defined as the volume that includes the primary tumor bed (based on preoperative imaging, physical examination, and operative findings) plus regions of grossly involved adenopathy. The target volume should include the entire primary surgical bed and the pathologically positive hemineck; this frequently requires coverage of nodal levels I, IIa-b, III, and IV for most cases. It is recommended that CTV_{60} receives 60 Gy in 2.0 Gy per fraction.
- The low-risk CTV ($CTV_{54\text{-}56}$) usually includes the prophylactically treated neck felt to have a low risk of harboring microscopic disease (eg, the uninvolved low or contralateral neck) and should receive 54 to 56 Gy as a SIB in 1.8 to 1.87 Gy per fraction.
- For patients with oral tongue or floor of mouth tumors approaching midline, who received ipsilateral neck dissection and are at high risk of contralateral nodal involvement, bilateral neck radiation should be administered.[128]

It is common practice for the radiation oncologist to consider selective coverage of the neck and retropharyngeal nodes in order to limit dose to critical organs at risk. This generally involves limiting cranial coverage of

the level II neck to the level of C1 in the N0 neck to spare the parotid gland and the upper pharyngeal structures.[64,177,178,184,188] This is an accepted standard in the N0 neck, which may potentially be extended to patients with small N1 disease.[64,184,189] Marginal recurrences near the base of the skull, above this cranial border of level II, have been reported in the node-positive neck.[183] The retrostyloid space represents the cranial extension of level II to the skull base. In cases where involvement of upper level II with one or more lymph nodes is evident, it is suggested that the retrostyloid space be included in the intermediate-risk target volume (ie, CTV_{60}) (see Figure 50.11).[184] In addition to this principle, there are several target volume design details specific to the postsurgical patient with head and neck cancer that should be considered.

- When a metastatic lymph node abuts or infiltrates muscle (most commonly the sternocleidomastoid or paraspinal musculature), it is recommended that the muscle be included in CTV_{60}, at least for the invaded nodal station (Figure 50.12).[184]
- When a metastatic node lies at the boundary with a nodal level that was not intended to be part of the intermediate-risk CTV, it is recommended that CTV_{60} be extended to encompass this adjacent level.[184]
- If level IV or Vb is involved, it is suggested that CTV_{60} be extended to include the supraclavicular fossa.[184]
- In the event of flap reconstruction of the oral cavity or neck, it is recommended that the entire flap be considered for inclusion in the IMRT field (either CTV_{60} or $CTV_{54–56}$ based on physician discretion), particularly if there is evidence of ENE.[190]
- In the case of extensive perineural spread, it is recommended that the proximal course of the involved nerves be included in the treatment field to the level of the infratemporal fossa or skull base.[191]

Conventional Radiotherapy

For the treatment of oral cavity cancer with either two- dimensional or three-dimensional techniques, the oral cavity tumor bed and upper echelon lymph nodes are included within the initial lateral fields (Figure 50.14). The

upper border of the field is positioned to provide a 1.5- to 2.0-cm border on the tumor bed in an attempt to partially spare parotid glands and hard palate without compromising coverage of the tumor bed and regional lymphatics. The inferior border of the field resides at approximately the thyroid notch, just above the true vocal cords. The posterior border is set at the midvertebral body level if level V nodal coverage is not required. The nodal volume should include levels Ia to Ib, II, and III. For patients with more advanced neck disease or positive level V lymph nodes, where the posterior chain requires radiation, the initial fields should be set behind the C1 vertebral body spinous process. The portals are then reduced at approximately 45 Gy to spare high dose to the spinal cord. If patients harbor cervical lymph node metastases, or high-risk disease, then the lower neck will also be treated. In this case, half-beam–blocked anteroposterior (AP) or opposed AP/posteroanterior (PA) fields can be matched to the inferior border of the opposed lateral fields at the level of the thyroid notch. An anterior larynx block is used, which protects not only the central larynx from unnecessary radiation dose but also against spinal cord overdose because of a three-field overlap.

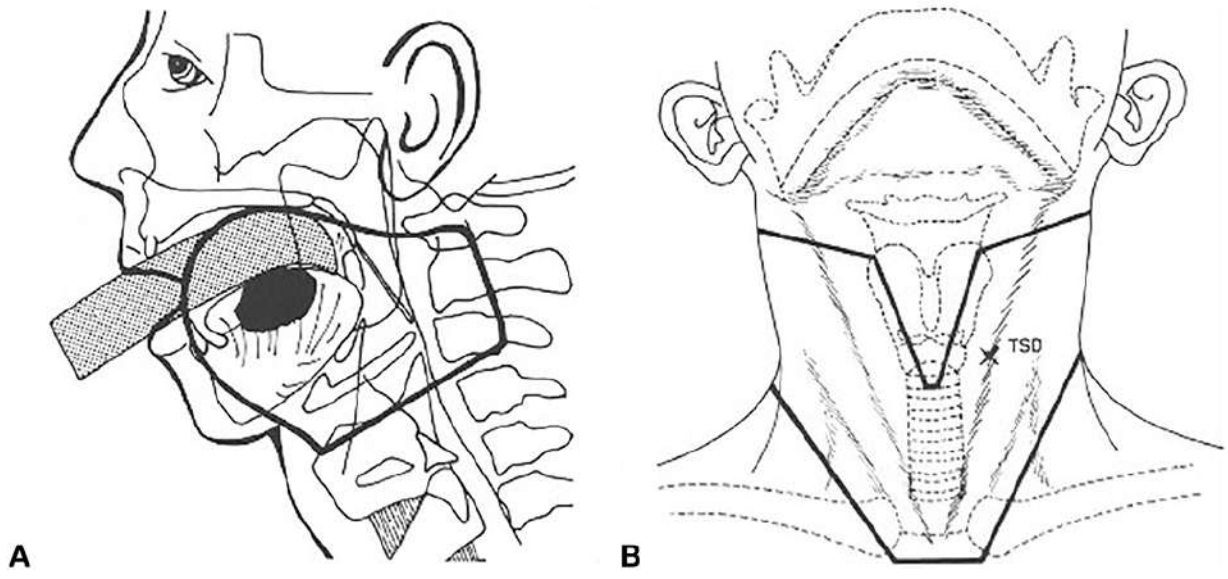

FIGURE 50.14 A. Illustration of field design for treatment of carcinoma of the oral tongue with an N0 neck. B. Illustration of field design for treatment of the neck for elective bilateral neck irradiation. (Reprinted with permission from Million RR, Cassisi NJ, eds. *Management of Head and Neck Cancer: A Multidisciplinary Approach*. 2nd ed. J.B. Lippincott; 1994.)

Dose and Fractionation

When postoperative radiation is used for oral cavity cancer, the most common dose fractionation in the United States is 1.8 to 2.0 Gy/day. The authors generally recommend 2.0 Gy daily fractions. Dissected tissues that harbored the original tumor should generally receive dose on the order of 60 Gy. However, for close or positive microscopic margins or ENE, either an SIB to 66 Gy (eg, 2.2 Gy per fraction over 30 fractions) or a sequential 6.0 Gy localized boost should be considered. In the former scenario, the SIB volume should be kept small to minimize normal tissue complications (see Figure 50.12). If there is gross residual disease, either further surgical resection or focal boosting up to 70 Gy may be necessary. Regions of somewhat lesser risk (ie, clinically or pathologically uninvolved necks) should receive dose on the order of 54 to 56 Gy if treatment is delivered with an SIB.

When definitive radiation is used for oral cavity cancer, boosting the primary tumor with either interstitial implantation, submental, or intraoral cone therapy can result in increased tumor control and decreased complications, particularly ORN.[130] When external beam radiation therapy is used as the sole treatment modality, even small lesions that cannot be excised or treated with brachytherapy require doses in the range of 66 Gy in 2.0 Gy fractions for reliable control. For larger tumors, local control rates are generally unacceptable, even with the utilization of IMRT.[114,115] In patients who are unable to receive necessary chemotherapy, a hyperfractionated regimen or an extra fraction a week should be considered.[172,173] This has been demonstrated in the Meta-Analysis of Radiotherapy in squamous cell carcinomas of Head and Neck, which showed hyperfractionated regimens, along with concomitant chemoradiation, are associated with improved outcomes.[192]

Lower doses to the elective neck may be acceptable in patients treated with definitive radiation. Nevens et al[193] demonstrated an equivalent rate of local failure (14.1% vs 14.4%) in the 40 Gy compared to 50 Gy arm, with a trend toward less dysphagia at 6 and 24 months, and reduced salivary gland toxicity, although oral cavity cancers represented only 9% to 11% of patients in each arm in this study.

Simulation and Treatment Considerations

The patient should undergo simulation in the supine position with the neck extended. A thermoplastic mask is generally used to immobilize patients during simulation and treatment. Shoulder immobilization is important during this process, which is accomplished by using either a three-/four-point Aquaplast mask along with a shoulder immobilization device or a five-point mask that also encompasses the shoulders. For most oral cavity simulations, a bite block should be used to depress the tongue away from the hard palate; some institutions use a cork and tongue blade or a custom intraoral stent[194] for this purpose (Figure 50.15).

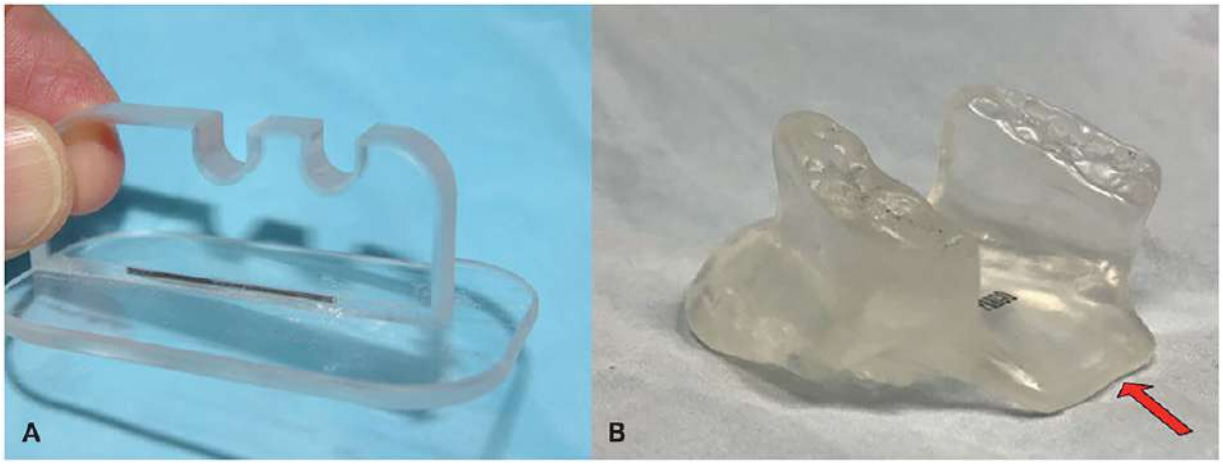

FIGURE 50.15 A. Lucite oral cavity mouthpiece fabricated at the University of Wisconsin for patients with oral cavity carcinomas. Upper dentition or maxillary alveolus links to U-shaped notch, and tongue rests beneath smooth undersurface of mouthpiece. Note embedded solder wire in mouthpiece floor to facilitate visualization of tongue positioning at the time of simulation and beam design. B. Custom acrylic mouth-opening and tongue-depressing stent utilized at several centers for the treatment of oral cavity carcinoma. The posterior edge (red arrow) helps to immobilize the tongue, whereas the superior ridges allow the maxillary teeth to rest and secure the stent in place.

CT simulation should be performed using a slice thickness of ≤3 mm, and intravenous contrast should be utilized in patients who have adequate renal function. The addition of contrast dye during simulation facilitates target volume delineation. The CT acquired during simulation should extend from the top of the head to the carina. During the treatment planning process, the planning treatment volume (PTV) for each region at risk should receive 95% of the prescription dose, and efforts should be made to spare

critical structures at risk. Table 50.3 lists normal tissue dose constraints for IMRT treatment planning.

TABLE 50.3 NORMAL TISSUE DOSE-VOLUME CONSTRAINTS[A]

Organ at Risk (OAR)	Dose-Volume Constraint
Spinal cord (+*5 mm*)	Dose to 0.03 mL ≤ 48 Gy
Brain stem (+*3 mm*)	Dose to 0.03 mL ≤ 52 Gy
Parotid glands	(a) Mean dose to single gland ≤ 26 Gy
	(b) *20 mL* of combined volume of both parotids <20 Gy
	(c) *50% single gland <30 Gy*
OAR pharynx	(a) *Dose to 33%* ≤ 50 Gy
	(b) *Mean dose ≤ 45 Gy*
	(c) Dose to 15% ≤ *60 Gy*
Glottic/supraglottic larynx	Mean dose ≤ 44 Gy
Cochlea	Max dose <35 Gy
Optic apparatus	Max dose <54 Gy
Brachial plexus	Max dose <66 Gy

IMRT, intensity-modulated radiation therapy.

[a]Dose-volume constraints for IMRT planning adapted based on Qualitative Analysis of Normal Tissue Effects in the Clinic recommendations,[195-198] practice standards, and Radiation Therapy Oncology Group protocol guidelines (RTOG 0920, ClinicalTrials.gov identifier, NCT00956007; and RTOG 1216, ClinicalTrials.gov identifier, NCT01810913).

IMRT may be more sensitive to intertreatment setup variations than conventional radiation therapy.[199] Daily imaging and strict immobilization protocols may decrease setup error and improve the fidelity of treatment delivery.[199-201] It is recommended that institutions use daily image-guided radiation therapy (IGRT) to enhance the setup reproducibility of IMRT treatment delivery. This may be accomplished with several IGRT techniques, including orthogonal kilovoltage films, kilovoltage cone beam CT, or megavoltage CT imaging. With the use of IGRT techniques, PTV expansions on the CTV may be limited to 2 to 5 mm. However, larger margins may be necessary for target volumes subject to significant interfraction variability; examples include the tongue in the absence of an

intraoral stent, a large flap in the oral cavity or neck, and some cases where there is significant shoulder motion and the low neck must be included in an extended IMRT field.[202] For these circumstances, a CTV-PTV expansion margin of 10 mm or greater may be necessary.

The delivery of a single IMRT plan throughout the course of treatment provides better dose conformality compared to the delivery of several consecutive (sequential) plans.[203] In the absence of low-lying cervical adenopathy, the low anterior neck can be treated with a single AP field or AP/PA fields matched to an upper IMRT field. The advantage of this split-field technique, compared to treating the low neck with an extended IMRT field, lies in the ability to decrease the mean dose to the larynx and inferior pharyngeal constrictors.[204]

Prior to the initiation of head and neck radiation, a careful oral and dental evaluation, including a panoramic radiograph, should be performed. Dentition in poor condition should be identified and considered for extraction to minimize the subsequent risk of ORN. Specifically, those teeth that will reside within the high-dose radiation volume that demonstrate significant periodontal disease, advanced caries, or abscess formation or are otherwise in a state of disrepair should be extracted. In addition, impacted teeth, unopposed teeth, and teeth that could potentially oppose a segment of a resected jawbone should be considered for extraction if they are anticipated to reside within the high-dose radiation treatment volume. Extraction of marginal teeth should also be considered in patients who are deemed unable to maintain adequate oral hygiene.

Radiation can induce several chronic effects in the oral cavity that warrant routine surveillance. Radiation can impair bone healing and diminish the capacity for successful recovery following trauma or oral surgery. For this reason, elective oral surgical procedures including extractions must be very carefully considered after radiation. Escalation of dental caries deriving from xerostomia following radiation is well recognized (Figure 50.16). Radiation of the major salivary glands changes the nature of salivary secretions,[60] which can increase the accumulation of plaque and debris and reduce salivary pH and the buffering ability of saliva.[205] This creates an environment in the oral cavity, which predisposes patients to caries. During a course of radiation to the oral cavity, simple techniques such as the use of custom molds or wax to absorb electron

backscatter can diminish hot spot mucositis from dental fillings and improve treatment tolerance.[59] Attention to oral hygiene with frequent dental follow-up examinations and cleanings, daily fluoride therapy (Figure 50.17), flossing, and brushing should be an integral component of the education and postradiation care of patients who undergo radiation to the oral cavity.

FIGURE 50.16 Advanced dental caries in a patient with profound radiation xerostomia and lack of attention to dental hygiene over many years following treatment.

FIGURE 50.17 Custom-designed fluoride carrier trays to facilitate daily fluoride application to existing dentition.

Proton Radiation

Proton beam therapy is increasingly used in the management of head and neck malignancy due to its ability to spare nearby critical organs. Although there are yet no randomized data comparing photons to protons in the management of oral malignancies, several retrospective analyses have reported favorable dosimetric profiles using intensity-modulated proton therapy.[206,207] Particularly in the recurrent setting, the use of proton radiation has demonstrated impressive local control rates as high as 77% at 1 year.[208] A systematic review on the use of proton radiation for oral and oropharyngeal carcinoma demonstrated improved acute toxicity profiles compared to photon therapy.[209]

Brachytherapy

Historically, brachytherapy has played an important role in the treatment of oral cavity carcinoma. Brachytherapy has been used to boost the primary

site in the oral cavity before or following external beam radiation (Figure 50.18). This technique has also been used as a sole modality in the treatment of selected (early-stage) tumors of the oral cavity with good results.[157,158,210] When brachytherapy is used as a sole treatment modality, doses of 65 to 75 Gy are commonly prescribed over 6 to 7 days. Traditionally, radiation has been delivered using low-dose rates of 0.4 to 0.6 Gy/hour to the target volume.[211,212] However, there has been recent interest in high-dose rate (HDR) (Figure 50.19) and pulsed dose rate techniques,[213,214] although there is no compelling evidence that these techniques are superior to traditional low-dose rate radiation in the treatment of head and neck cancer. There have been several dose and fractionation schedules published for HDR brachytherapy in the treatment of oral cavity cancer.[215-218] Although the American Brachytherapy Society has not provided a consensus as to optimal dose and fractionation,[219] there is concern regarding the potential morbidity with fraction sizes ≥6.0 Gy in this setting.[219,220]

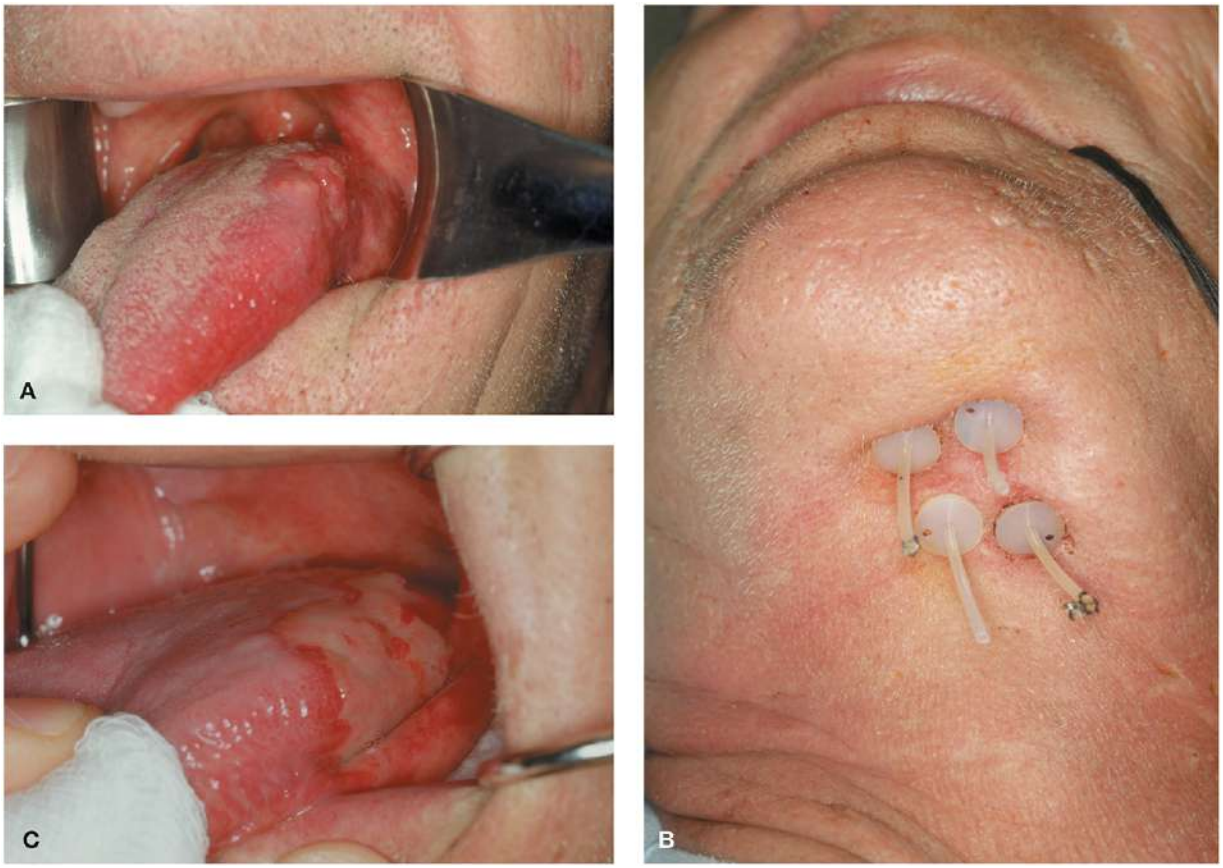

FIGURE 50.18 A. T2N0M0 squamous cell carcinoma involving the left lateral oral tongue. B. Submental view of interstitial implantation catheters housing ^{192}Ir seeds for delivery of 25-Gy tumor boost following external beam radiation of 50 Gy. C. Implantation bed mucositis conforming to the tumor distribution 7 days following 25-Gy implant boost.

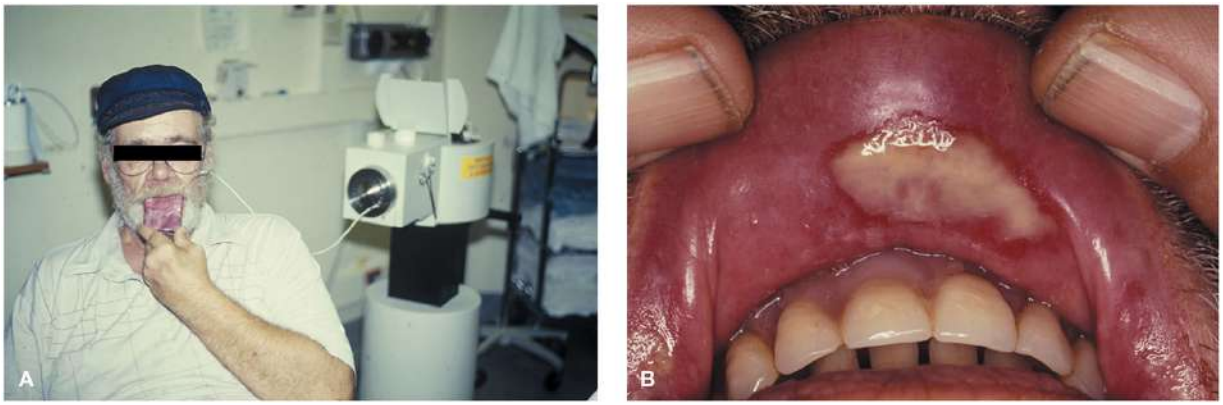

FIGURE 50.19 A. Patient undergoing high-dose rate (HDR) brachytherapy for superficial T1 upper lip squamous cell carcinoma (buccal surface) using a single interstitial catheter for source delivery. B. Focal mucositis 1 week following completion of HDR brachytherapy treatment course.

Many techniques for brachytherapy in the oral cavity have been described.[221] Brachytherapy can be accomplished with either rigid cesium needles or iridium-192 (^{192}Ir) sources afterloaded into angiocaths. The most common technique is afterloading with ^{192}Ir.[179] Guide needles can be inserted either freehand or with the aid of a custom template to help maintain optimal source spacing.

Depending on the size of the lesion, a single plane, double plane, or volume implant can be used to cover the tumor with a 1-cm margin. For tumors <1 cm in thickness, single-plane implants are adequate. Surface mold radiation can also be considered for small tumors <1 cm depth or superficial lesions of the lip, hard palate, lower gingiva, and floor of the mouth. However, when lesions exceed 2.5 cm, it is difficult to avoid significant cold spots in the implant volume. For this reason, it is recommended that for lesions larger than 2.5 cm, part of the treatment is given with external beam radiation to supplement the dose to the cold spots. In this setting, a combined treatment plan typically gives 50 Gy over 5 weeks with external beam radiation followed by 30 Gy with a brachytherapy implant. What must be borne in mind is that as tumors get too close to the mandible or are large in volume, the risk of ORN increases.[222]

Over the past decade or more, stepwise improvements in reconstructive surgery techniques have diminished the practice frequency of brachytherapy in the treatment of oral cavity carcinoma. In addition, a diminishing percentage of radiation oncologists remain highly skilled and experienced with the requisite implant techniques. Nevertheless, in experienced hands, the expert use of brachytherapy can provide excellent tumor control and high-quality cosmetic and functional results. An example of the use of HDR interstitial brachytherapy for a patient with advanced T2N0 lower lip cancer is illustrated in Figure 50.20. Similar comments parallel the use of intraoral cone radiation treatment described further in the section below.

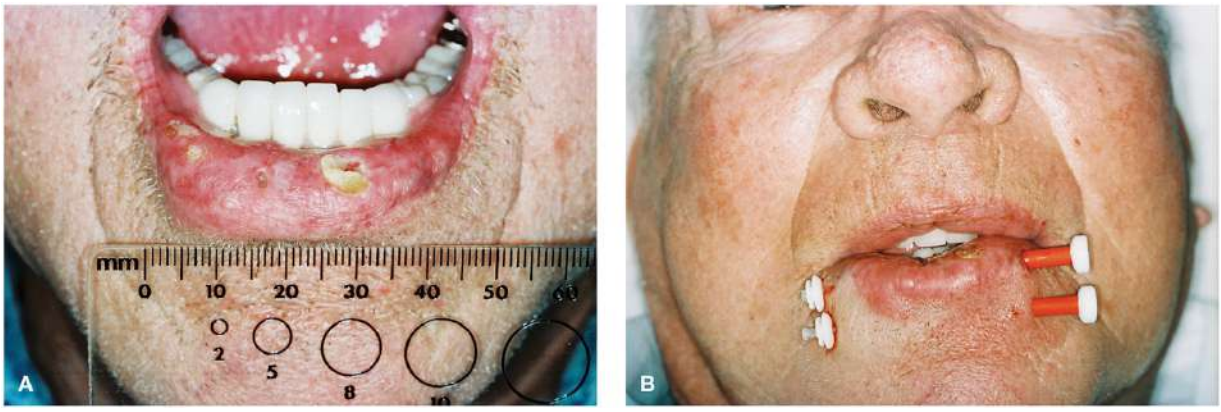

FIGURE 50.20 A. Infiltrative T2N0 squamous cell carcinoma of the lower lip measuring 3.5 cm × 1.2 cm × 1.2 cm. B. Interstitial iridium-192 implant performed (two catheters) for high-dose rate brachytherapy delivery over 11 elapsed days as sole treatment. The patient remains with no evidence of disease at 6 years with excellent cosmetic and functional status.

Intraoral Cone

The intraoral cone is another delivery tool to enable boosting of radiation dose to sites within the oral cavity while avoiding direct dose to the mandible (Figure 50.21). This technique is generally best suited for anterior oral cavity lesions in edentulous patients. However, palatal arch sites can be targeted with the intraoral cone as well. Treatment with intraoral cone involves either 100 to 250 kilovolt (peak) (kvp) x-rays or electron beams in the 6 to 12 MeV range.[159,160] Lesions up to 3 cm are amenable to treatment with intraoral cone as long as they are accessible. Intraoral cone therapy requires careful daily positioning and verification by the physician. For this purpose, the device is equipped with a periscope to visualize the lesion. The cone abuts the mucosa and is centered directly over the lesion. Intraoral cone treatment should take place prior to external beam radiation so that the lesion can be adequately visualized. A major advantage of cone therapy is that it is highly focal to the tumor bed but noninvasive. Hence, when available, for suitable lesions, it may be preferred to brachytherapy. However, as noted for brachytherapy delivery, operator experience and dedication are essential to optimize outcome.

FIGURE 50.21 A. Intraoral cone boost technique at the University of Wisconsin for focal delivery of electron beam radiation. The electron cone is mounted directly to the accelerator gantry with a sideview periscope enabling direct vision and positioning for daily treatment. B. Focal mucositis involving the distal oral tongue following treatment of a 1-cm tumor in this location with intraoral cone technique.

PRINCIPLES OF SYSTEMIC THERAPY

Over the decades, the role of chemotherapy has advanced from use only in the recurrent or metastatic setting to use in the definitive treatment setting. The advantage of systemic therapy was explored by the meta-analysis of chemotherapy in head and neck cancer (MACH-NC).[223,224] The study included pooled data from randomized trials of patients with a diagnosis of oral cavity, oropharynx, hypopharynx, and larynx cancer who received chemotherapy in the induction, concurrent, or adjuvant setting.[223] Although the trials included in this analysis vary with respect to radiation dose, fractionation schedule, and chemotherapy regimen, they have in common a randomized comparison between radiotherapy and radiotherapy plus chemotherapy. The updated MACH-NC report of 93 randomized trials identifies an absolute survival benefit of 4.5% at 5 years with the addition of chemotherapy, which is mainly driven by the effect of concurrent chemoradiation (6.5% at 5 years).[223] However, patients with oral cavity comprised only 21% of the patient population in the pooled analysis.[112] The ASCO guidelines on the management of the neck in oral cavity malignancy recommend the use of chemotherapy with radiation in patients with ENE.[128] The currently accepted chemotherapy regimen is cisplatin 100 mg/m^2 delivered every 3 weeks. The use of lower dose cisplatin (30-40 mg/m^2) has been studied, but not in the adjuvant setting.[225] Due to a lack of phase III

data in the adjuvant setting, high-dose cisplatin should be used unless there is a medical contraindication.

Several studies have focused on the use of chemoradiation in patients with high-risk pathologic features following initial surgery. Cooper et al[108] reported the results of RTOG 9501 comparing radiation alone (60-66 Gy) to chemoradiation (same radiation dose plus three cycles of 100 mg/m^2 cisplatin) in patients with head and neck carcinoma demonstrating high-risk features after gross total resection. High-risk disease was defined as any or all of the following: two or more involved lymph nodes, extracapsular extension of nodal disease (ENE), and microscopically involved resection margins. This study demonstrated a benefit in locoregional control and DFS for the chemoradiation arm, but no OS benefit was appreciated. A parallel study, EORTC 2931, reported by Bernier et al[109] randomized patients to essentially equivalent treatment arms following head and neck cancer surgery. Eligibility criteria included patients with pathologic T3 or T4 disease (except T3/N0), patients with any T-stage disease with two or more involved lymph nodes, or patients with T1/T2 and N0/N1 disease with unfavorable pathologic findings (ENE, positive margins, perineural involvement, or vascular embolism). Local control, progression-free survival, and OS were superior for patients in the chemoradiation arm. In a subsequent comparative analysis using pooled data from these two studies, ENE and/or microscopically involved surgical margins were the risk factors for which the impact concurrent chemoradiation was significant.[110] There was a trend favoring concurrent chemoradiation in the subset of patients with stage III to IV diseases, vascular embolism, perineural infiltration, and/or positive lymph nodes at levels IV and V with oral cavity or oropharyngeal primaries.[110] The subset of patients with two or more involved lymph nodes, without evidence of ENE, did not appear to benefit from chemotherapy in this analysis.

Laskar and colleagues also evaluated the role of adjuvant therapy in patients with adverse prognostic features including ECE, ≥2 nodes, involved margins, extensive soft tissue infiltration and/or skin infiltration requiring major reconstruction, PNI, or lymphovascular embolization. Patients were randomized to standard 60 Gy given 5 days a week, or concurrent chemoradiation with weekly cisplatin, or a third arm with radiation delivered six fractions per week. The authors did not find a

difference between the three arms in terms of locoregional control or DFS. There was no benefit to intensification with either modality in patients with a single adverse factor, although a benefit was seen in patients with a combination of high-risk features for example, T3 to T4 primary with N2 to N3 nodes along with ECE.[226] These studies suggest that the addition of chemoradiation following surgery should be considered in patients with high-risk head and neck cancer features who are able to tolerate treatment.

Neoadjuvant systemic therapy is generally not recommended in the standard management of resectable OCSCC. In the case of technically unresectable OCSCC, the concept of neoadjuvant chemotherapy as a means of downstaging disease in order to enable surgical resection has been explored.[227] In a study by Chaukar et al, the authors randomized 68 patients with stage T2 to T4 oral cavity cancer necessitating resection of the mandible for paramandibular disease in the absence of radiologic or clinical evidence of bone erosion to either upfront surgery or two cycles of docetaxel, cisplatin, and fluorouracil every 3 weeks. The authors did not demonstrate any compromise in outcomes, with 47% of patients achieving mandibular preservation.[228] The engagement of an experienced head and neck surgical oncologist to explore the technical feasibility of resection is paramount due to the potential of disease progression and the consequent risk of compromising the potential for resection in borderline patients. Generally, in this context, a combination of docetaxel, cisplatin, and 5-fluorouracil (5-FU) is the preferred induction regimen for clinically fit patients[184] with reported response rates of 17% to 50%.[227] However, it is important to consider that the inherent toxicity of these regimens may compromise the ability to deliver local therapy.[229-231]

The use of molecular targeted therapies has steadily advanced in the field of head and neck oncology. Cetuximab is a monoclonal antibody against the epidermal growth factor receptor that has been approved for the management of locally advanced, recurrent, or metastatic head and neck SCC.[229,232] In the context of locally advanced head and neck SCC, Bonner et al reported the results of a multinational study demonstrating the superiority of cetuximab plus radiation to radiation alone.[233] However, this study did not include patients with OCSCC. The RTOG launched a study (RTOG 0920) to evaluate the impact of cetuximab in the postoperative treatment for intermediate-risk disease. The study defines intermediate-risk disease as

PNI, lymphovascular space invasion, close margins, T3/T4a disease, T2 disease with >5 mm thickness, and single lymph node >3 cm or ≥2 or lymph nodes <6 cm without ENE. After an R0 resection, patients are randomized to either radiation or cetuximab plus radiation. A parallel study (RTOG 1216, ClinicalTrials.gov identifier: NCT01810913) was launched to explore the benefit of cetuximab and docetaxel compared to standard platinum-based chemotherapy in the setting of patients with high-risk disease (ENE or positive margins). Over two-thirds of patients in RTOG 0920 had oral cavity cancer. At a median follow-up of 7.2 years, OS was not improved with cetuximab, although DFS was improved.[234] The results of RTOG 1216 are awaiting publication.

Neoadjuvant Immunotherapy

Novel approaches are needed to improve outcomes in patients with oral cavity malignancy who continue to have moderate outcomes. In recent years, the use of immunotherapy for head and neck SCC has increased substantially. There are numerous trials evaluating immunotherapy in the neoadjuvant, definitive, and salvage setting. In a randomized phase 2 trial of neoadjuvant nivolumab and nivolumab plus ipilimumab in untreated oral cavity cancer, 53% and 69% had pathologic downstaging, respectively.[235]

Uppaluri et al published in their phase III trial of neoadjuvant and adjuvant pembrolizumab in resectable, locally advanced, non–HPV-related head and neck cancer.[236] Thirty-six patients were enrolled. One-year relapse rate was 17% in patients with high-risk pathology (lower than the historical rate of 35%), including ENE and/or positive margins. In addition, eight (22%) patients experienced pathologic tumor response ≥50% with necrosis, debris, and giant cell/histiocytes. However, no patients experienced a pathologic complete response.[236] This trial provides the rationale for trial KN689, an ongoing phase 3 trial of perioperative pembrolizumab (NCT03765918).

PROGNOSTIC AND PREDICTIVE FACTORS

The most significant prognostic factor for outcome in oral cavity carcinoma is the presence of cervical metastases.[237] In patients with positive cervical metastases, the 5-year survival is reduced by approximately 50% compared

to those without cervical metastases.[238] The prognosis diminishes further when patients harbor multiple levels of nodal involvement or ENE. In a retrospective review, Myers et al[237] found that 5-year disease-specific and OS rates for pathologically N0 patients were 88% and 75%, respectively; these decreased to 65% and 50%, respectively, if patients were node positive but without evidence of ENE. Patients who were node positive with evidence of ENE had 5-year disease-specific and OS rates of 48% and 30%, respectively.

Several histopathologic factors in the primary lesion are associated with adverse prognosis. Tumor thickness and depth of invasion have been shown to confer a higher risk of regional metastases.[19] PNI has been correlated with cervical lymph node metastases, extracapsular extension, and diminished survival.[239-241] Microvascular invasion has also been correlated significantly with cervical lymph node metastases.[241,242] However, lymphatic invasion has not been correlated significantly with cervical lymph node invasion.[19] The prognostic significance of grade has also been evaluated.[203] Because of the wide variation in pathologic interpretation, it is difficult to discern the independent value of histologic grading as a prognostic or predictive value.[19]

SURVEILLANCE

The major goals of surveillance include early diagnosis of recurrence and second primary tumors and management of the ongoing sequelae of head and neck cancer treatment. It is advisable that follow-up be conducted by the multidisciplinary team that provided oncologic management to the patient.[243,244] National guidelines recommend a history and physical examination, including a complete head and neck examination with fiberoptic examination, about every 3 months for the first year following treatment. Follow-up may be spaced out to every 6 months after the first year if there is low suspicion for disease recurrence.[245] All patients who have completed radiation treatment for oral cavity cancer should undergo routine head and neck examination, imaging, and dental evaluation. Dreizen et al also showed that caries development may be prevented by daily use of a gel containing 1% sodium fluoride.[246] In addition, it is recommended that the follow-up protocol include an assessment of thyroid function (thyroid-

stimulating hormone level) every 6 to 12 months. Radiation-induced hypothyroidism is detected over the subsequent years in 20% to 25% of patients who undergo neck irradiation.[247,248] Smoking and alcohol cessation, as well as screening for lung cancer in clinically indicated patients, are also important components of an ongoing follow-up program for all patients with head and neck cancer.[249]

SUBSITE-SPECIFIC TREATMENT AND RESULTS

Lip

The treatment approach for lip cancer is driven by the stage of disease and the expected functional outcome. Surgery is generally the preferred treatment modality for early-stage carcinoma of the lip, although radiation therapy is an option for local tumor control. Although the local control of T1 and T2 squamous cancers of the lip is excellent with surgical resection, disruption of the oral sphincter provided by the orbicularis muscle can lead to oral incompetence if not properly reconstructed. Therefore, several reconstructive methods have been developed to help preserve oral sphincteric function, even following large excisions for T3 and T4 lesions. For these larger lesions, surgery followed by radiotherapy remains a standard therapy (Figure 53.2). One possible exception is a superficial cancer that occupies most of the lip, which is best managed with primary radiation therapy because of the potential functional and cosmetic implications of primary surgery.

The successful surgical management of lip cancers includes the eradication of the primary tumor with free margins with preservation of the oral sphincteric function of the lip. For small lesions, excision with primary closure can be highly effective in achieving both of these objectives, whereas resection of larger legions can often require complex local flap repairs to attain satisfactory oncologic, cosmetic, and functional outcomes. SLNB can also prove to be useful in the management of patients with node-negative lip cancers, but further clinical investigation in this area is needed.

When primary radiotherapy is used to treat lip cancer, the target volume should include the primary tumor plus a 1.5- to 2.0-cm margin. For early-stage lesions, photons in the orthovoltage range (100-200 keV) or electrons may be used. The electron energy should be chosen based on the thickness

of the lesion (commonly 6-9 MeV). Efforts should be made to shield the underlying gum, dentition, and mandible as appropriate. This can be accomplished with the use of oral shields or Cerrobend stents. The recommended dose is 50 Gy in 4.5 to 5 weeks for smaller lesions and 60 Gy in 5 to 6 weeks for larger lesions. Some institutions have used an approach where external beam radiation is given to approximately 40 to 50 Gy followed by a brachytherapy boost; however, small- to intermediate-stage lesions can be treated by primary brachytherapy alone (Figure 50.18).

An important consideration in managing lip cancer is the risk of regional metastatic disease. Generally, the risk of regional lymph node metastatic disease for T1 and T2 cancers of the lip is lower than for stage-matched tumors of other oral cavity sites. Thus, END is recommended for patients with T3 and T4 carcinomas of the lip; however, it may not be warranted for all T1 and T2 lesions. Some institutions have used a "moustache field" for elective irradiation of the perifacial lymphatics (~50 Gy) for more advanced upper lip lesions.[250]

Oral Tongue

Although primary radiation therapy and surgery are potential treatment options for early-stage carcinoma of the oral tongue, the preferred treatment for most oral tongue cancers in the United States is primary surgery.[19] Surgical resection and reconstruction as appropriate is generally preferred for medically operable patients. Postoperative radiation therapy is recommended for patients with large primary tumors (T3, T4), close or positive surgical margins, evidence of perineural spread, multiple positive nodes, or ENE.[250] Postoperative chemoradiation should be considered for patients with adverse risk factors who are able to tolerate combined modality treatment.[108-111] Primary radiotherapy techniques can be used for patients who refuse or are unable to tolerate surgery.

Surgical approaches to oral tongue cancers can be either transoral, transcervical, or via mandibulectomy to obtain the exposure necessary to achieve adequate margins. Partial glossectomy is the most common procedure performed for oral tongue cancers, and the extent of resection depends on the size and growth pattern of the tumor, as some lesions are relatively infiltrative, while others may be more exophytic. Because the

tongue is essentially composed of skeletal muscle covered by mucosa, the tissue is extremely elastic, and wide margins are encouraged at the onset of resection to avoid retraction of muscle fibers with microscopic tumor cells that could serve as a source of local recurrence.

Total glossectomy may be indicated for extensive tumors or those that involve the intrinsic tongue musculature. Total glossectomy, even with reconstruction, can result in difficulty with deglutition and maintenance of an adequate airway. Aspiration may be a chronic problem; thus, laryngectomy may be necessary in some cases. However, properly selected patients with adequate postoperative rehabilitation can be treated with total glossectomy without laryngectomy. If the larynx is preserved, laryngeal suspension and palatal augmentation may help with the rehabilitative efforts.

Tumor size and depth of invasion are currently the most reliable indicators for predicting cervical metastases in patients with oral tongue SCC. Because of the high risk of nodal metastases, the neck should be addressed with either surgery or radiation in all but the earliest tumors of the oral tongue. Patients with small oral tongue cancers should be considered for neck therapy, particularly if the primary tumor exhibits extension onto the floor of the mouth or if there is increased tumor thickness. Treatment of the clinically negative neck is most often accomplished by supraomohyoid neck dissection. END appears to result in better overall cancer outcome than observation. Potential pitfalls of observation include a salvage rate of only one-third for patients who do not undergo END along with resection of the oral cavity primary.

Superficial T1 lesions can be treated with brachytherapy alone. Commonly, ^{192}Ir temporary implants are used to deliver 50 to 60 Gy with dose rates of 40 to 60 cGy/hour. However, HDR techniques can also be considered. For infiltrating T1 or T2 lesions, a combined approach using external beam and a brachytherapy or intraoral cone boost should be considered. More advanced lesions should be treated with an approach combining surgery and radiation therapy. In patients treated with IMRT, the intermediate-risk CTV (see “Intensity-Modulated Radiation Therapy” section) should include the intrinsic and extrinsic muscles of the tongue, the floor of the mouth, base of the tongue, glossotonsillar sulcus, and the anterior tonsillar pillar (Figure 50.11). The adjacent dissected neck should

also be included in this volume. Patients with advanced lesions and high-risk disease (particularly with multiple positive nodes) should receive radiation treatment to the bilateral necks. In patients with early-stage disease close to midline or patients with well-lateralized disease that is deeply invasive (>4 mm), both sides of the neck should be considered for treatment. For patients with a clinically and radiographically N0 neck, with well-lateralized and superficial disease (<4 mm invasion), 50 to 54 Gy should be considered for the ipsilateral neck as elective nodal irradiation. The appropriate draining lymphatics (usually levels I-IV unilaterally or bilaterally) should be included in the low- to intermediate-risk CTV (Figure 50.11 and Table 50.1). Ipsilateral versus bilateral neck treatment has also been evaluated. A study of a collaborative database of 176 patients with pathologic stage T1-T2N0-N2b SCC of the oral tongue and floor of mouth treated with surgery and unilateral neck dissection demonstrated an ipsilateral and bilateral/contralateral failure rate of 11.9% and 3.6%, respectively. The authors concluded in well-lateralized pathologic T-stage with contralateral node-negative neck, unilateral treatment is associated with low contralateral neck failures.[251]

Floor of the Mouth

Surgery is usually preferred in patients who are medically operable because proximity of the tumor to the mandible confers a significant risk of radiation-induced ulceration and ORN. Small lesions of the floor of the mouth are most commonly resected transorally. The surgical defect can be left to heal by granulation or reconstructed with a split-thickness skin graft or local flap. Advanced stage of floor of the mouth cancers is usually managed by a combination of surgery and radiation or chemoradiation.

In the surgical management of floor of the mouth cancer, special attention should be paid to mandibular invasion. A cancer that appears to involve only the periosteum or that only superficially invades the mandible can be removed via a transoral or transcervical approach in which a marginal mandibulectomy is performed. However, segmental mandibulectomy may be necessary for patients with a limited mandibular height when there is no direct bone invasion, because marginal mandibulectomy may leave these patients with insufficient bone, placing

them at high risk for radionecrosis or pathologic fracture. A full-thickness segmental resection may be necessary if there is frank bone invasion. For advanced cancers, resection of the anterior arch of the mandible may be necessary. Defects of the anterior segment of the mandible require reconstruction with bone, usually with a free fibular or iliac crest graft.

Management of the neck is similar to that for other tumors of the oral cavity. Patients with lesions <2 mm thick with no adverse pathologic factors and a clinically and radiographically negative neck may be observed after primary resection and observation. Otherwise, most N0 patients should receive either selective neck dissection or radiation therapy. Patients with advanced lesions and high-risk disease (particularly with multiple positive nodes) should receive radiation treatment to bilateral necks.

Small (T1 and T2) lesions may be treated with a combination of external beam radiation and boost with interstitial implant or intraoral cone. For lesions that are very close to the mandible, brachytherapy is contraindicated because of the risk of ORN. Infiltrative lesions that are tethered to the mandible and advanced lesions following surgical resection should receive postoperative radiation. Target volume design considerations for postoperative treatment are similar to that for oral tongue carcinoma. In cases where IMRT is used, the intermediate-risk CTV (see "Intensity-Modulated Radiation Therapy" section) should include genioglossus and geniohyoid muscles bilaterally, the sublingual and submandibular glands ipsilaterally (bilaterally if the tumor is midline), adjoining alveolar ridge and mandible, the muscles at the root of tongue, and the dissected necks.[189] Because of the close proximity of floor of the mouth lesions to the midline, treatment of both sides of the neck should be considered. The low- to intermediate- risk CTV (see "Intensity-Modulated Radiation Therapy" section) should include the appropriate electively treated necks (Figure 50.12 and Table 50.1). Another important consideration is the presence of gross PNI of the branches of the inferior alveolar nerve. In the event of extensive perineural involvement, coverage of the mandibular canal to the infratemporal fossa should be considered.[191]

Cases of floor of the mouth carcinoma in which there is no indication for neck irradiation (eg, a T4N0M0 primary with early mandibular involvement and a negative bilateral neck dissection) may be good candidates for treatment with conventional techniques. In this setting, opposing lateral

fields may be used to encompass the oral cavity tumor bed (including the mandible, floor of the mouth, and oral tongue); this volume is commonly treated to 50 to 54 Gy. High-risk areas (primary surgical bed, close margins, perineural spread) may receive additional boost treatment up to 60 to 66 Gy.

Hard Palate and Upper Alveolar Ridge

Tumors of the hard palate are quite rare, accounting for only 0.5% of all oral cancers in the United States. Most carcinomas manifest as a granular superficial ulceration of the hard palate. Initial growth tends to be superficial, although these tumors can extend through the periosteum of bone into regions adjacent to the oral cavity, such as the paranasal sinuses and floor of the nose. Surgery is the preferred modality for the treatment of this subsite.

Wide local excision may be adequate to obtain surgical margins. However, infrastructure maxillectomy may in some cases be necessary. For tumors that extensively involve the adjacent bony and soft tissue structures, a total maxillectomy, with or without orbital exenteration, may be required. A defect in the maxilla results in the lack of oral/nasal separation that can impair the ability to speak and swallow effectively. An obturator with or without a skin graft is the most common method used to restore oral/nasal separation. The obturator is commonly fabricated from a synthetic polymer and provides oronasal separation that can yield improved speech and swallowing function. Regional pedicled flaps and free tissue transfers may provide alternatives to obturation. One consideration in the reconstruction of palatal defects with nonremovable flaps is that they can mask local recurrences that can be more readily identified in patients whose defects are obturated.

Postoperative radiation therapy should be delivered when there are adverse features, that is, close/positive margins, perineural extension, vascular invasion, high-grade histology, multiple positive nodes, or ENE. The radiation field should encompass the entire surgical bed. In many cases, it may be feasible to treat with opposed lateral fields to cover the volume at risk (Figure 50.10). However, for well-lateralized lesions of the upper alveolar ridge, ipsilateral radiation with a wedge pair may be adequate. Conformal treatment techniques, including IMRT, can also be used to tailor

the radiation coverage to the high-risk tissue bed, draining lymphatics, surgical flap, and routes of perineural spread along V2 as deemed appropriate.

Elective treatment of the neck is controversial for hard palate region tumors. Although some series have shown lower rates of occult metastases for palatal tumors when compared to other oral cavity sites, preoperative imaging should be performed to evaluate for the presence of metastases to the retropharyngeal nodes because these are difficult to evaluate on clinical examination and are at some risk for spread from primary palatal tumors. Elective treatment of the clinically negative neck should be considered in high-grade tumors or lesions that present with advanced T stage.

Retromolar Trigone

SCC of the retromolar trigone is uncommon, and the true incidence is difficult to determine because these cancers often involve both the retromolar trigone and adjacent sites, thereby making it difficult in some cases to identify the original tumor epicenter. Cancers of the retromolar trigone may be advanced at presentation because only a thin layer of soft tissue overlies the bone in this region and invasion of the underlying bone may occur early. In addition, there are multiple pathways for spread from this site, including the buccal mucosa, tonsillar fossa, glossopharyngeal sulcus, floor of the mouth, base of the tongue, hard and soft palate, masticator space, and maxillary tuberosity. As patients tend to present with advanced disease of the retromolar trigone, many have regional metastases at the time of presentation.

The treatment of carcinoma of the retromolar trigone has been controversial.[252] Traditionally, surgery and radiation have been felt to be comparable modalities of treatment. However, recent reports suggest that surgery with adjuvant or neoadjuvant radiotherapy may be associated with better outcomes compared to radiation alone.[253,254] Although early-stage T1 and T2 cancers may be treated equally effectively with surgery or radiation, the probability of ORN is likely higher with definitive radiation.[252] Stage III and IV lesions commonly require combined surgery and radiation. The resection of advanced cancer of the retromolar trigone usually requires a composite resection of soft tissue and bone. Transoral robotic surgery can

be helpful in the management of smaller tumors in the retromolar trigone.[255] A limiting factor for the achievement of adequate surgical resection margins for tumors in this area includes extension of tumor posterosuperiorly into the pterygopalatine fossa and/or the base of the skull.

Well-lateralized lesions of the retromolar trigone can be treated by ipsilateral treatment using mixed beam techniques or angled wedge techniques. In the case of more extensive lesions that require free flap reconstruction, IMRT may be beneficial to aid in covering the postoperative tumor bed and neck (Figure 53.15). For extensive tumors of the retromolar trigone (or those with evidence of perineural spread), the infratemporal fossa should be included in the CTV. Treatment of the contralateral neck is at the discretion of the treating physician. In considering treatment options for carcinoma of the retromolar trigone, it is important to consider that some HPV+ tonsil tumors can largely involve the retromolar trigone and are ideally managed with nonsurgical treatment, highlighting the importance of testing tumors in this area for the presence of high-risk HPV subtypes.

Buccal Mucosa

Verrucous carcinoma accounts for <5% of all oral cavity carcinomas, occurs most often in the buccal mucosa, has a more favorable prognosis, and is considered a low-grade malignancy. Surgical resection remains the preferred mode of treatment for primary lesions of the buccal mucosa. Adjuvant radiation treatment is usually not indicated in the setting of completely excised verrucous carcinoma of the buccal mucosa. Because verrucous carcinomas rarely metastasize, END is often not indicated for patients with this disease. Careful pathology review with clinical correlation is important in the categorization of verrucous carcinomas, as this diagnosis can influence subsequent treatment recommendations.

SCC of the buccal mucosa can be an especially aggressive cancer of the oral cavity, as buccal cancers have multiple potential routes of spread to adjacent areas in the head and neck. Posteriorly, they can extend to involve the pterygoid muscles, and superiorly, they can grow to involve the alveolar ridge, palate, or maxillary sinus. The majority of patients have cancer that extends beyond the buccal mucosa. Metastasis to the cervical lymph nodes most commonly affects the submandibular nodes.

Transoral resection is preferred and is most convenient for small lesions of the buccal mucosa. Tumors approximating the gingiva should be resected with the gingiva and periosteum as an additional deep margin, whereas those that involve the periosteum should be resected with an additional deep margin of bone provided by a marginal mandibulectomy. Cancers that directly invade bone should be resected with a segment of bone. Larger tumors (T3 or T4) may require surgery combined with radiation therapy or chemoradiotherapy.

When considering target volume delineation for carcinoma of the buccal mucosa, it is important to be comprehensive in covering the inner cheek and entire buccal mucosa. The CTV should extend from the orbital rim (superiorly) to the retromolar trigone (posteriorly). Moreover, in the event of extensive disease (ie, T3/T4 or N2/N3) that is treated postoperatively, the masticator space and infratemporal fossa should be covered within the CTV. As is the case with retromolar trigone carcinoma, treatment of the contralateral neck is at the discretion of the treating physician.

MANAGEMENT OF RECURRENT DISEASE

The recurrence rates after treatment of cancer of the oral cavity are approximately 30%, with local recurrence being the most common.[256] Unfortunately, the survival after salvage treatment remains quite poor at 20% to 30%.[217] The appropriate management of recurrent oral cavity cancer depends largely on the extent of disease, the prior therapy administered, and whether the recurrences are local, regional, or both. The disease-free interval between initial treatment and recurrence is among the most important factors associated with survival after salvage surgery, and a disease-free interval of more than 10 months is significantly associated with improved survival.[256] Although surgery and chemoradiotherapy have similar outcomes in the case of early recurrences, surgical salvage has been found to be superior to chemoradiotherapy for late recurrence (84.4% vs 52% 5-year disease-specific survival).[256] In the case of small recurrences at the primary site in patients whose index therapy was surgical excision only, further excision with postoperative radiotherapy is often recommended. For larger recurrences in patients who received radiation as part of their initial management, the rate of surgical salvage is quite low. In some cases, further

resection may be considered for palliation or curative treatment attempt, particularly in the setting of a clinical trial. Systemic therapy, reirradiation, and palliative care are other options for this group of patients, and the risks and benefits of each should be discussed with the individual patient.

If there is distant disease recurrence, systemic therapy approaches will likely assume primary importance. A combination of docetaxel, cisplatin, and 5-FU or a platinum doublet (plus a taxane or 5-FU) combined with cetuximab are commonly used regimens for first-line treatment.[229,257] Immunomodulating agents targeting the programmed death -1 receptor and its ligand represent novel and promising strategies in the treatment of metastatic and recurrent SCC of the head and neck.[258,259] In a phase III trial enrolling patients with platinum-refractory disease, about 50% of whom had oral cavity cancer, nivolumab improved OS from 5.1 to 7.5 months.[258] These agents have demonstrated a survival advantage compared to standard single-agent chemotherapy in the setting of platinum-refractory head and neck SCC.[258] The use of cetuximab may also play an important role in the recurrent or metastatic setting. In the phase III trial evaluating cetuximab plus platinum-based chemotherapy in patients with recurrent or metastatic SCC of the head and neck (where 20% of patients had oral cavity malignancy), the addition of cetuximab resulted in an OS improvement of 10.1 months compared to chemotherapy alone.[260] Ongoing concepts being investigated include combining these agents with standard cetuximab-containing regimens.[261]

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CHAPTER 51

Oropharynx

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The incidence of oropharyngeal cancer (OPC) is rising, a phenomenon largely attributable to human papillomavirus (HPV). HPV-associated OPC carries a significantly more favorable prognosis than HPV-negative disease, regardless of the chosen treatment modality. The recognition that HPV-associated OPC is a distinct pathologic and clinical entity has led to significant multidisciplinary interest in redefining and tailoring treatment paradigms for OPC based on HPV status.

In general, appropriate treatment strategies should focus on maintaining high cure rates while minimizing long-term, treatment-induced functional morbidity. Early-stage OPC is best managed with single-modality therapy, namely, radiation therapy (RT) or surgery, with the choice based upon anticipated post-therapy morbidity. Treatment of locoregionally advanced OPC typically involves multiple treatment modalities. The most common definitive strategies are either concurrent chemoradiation (CRT) or surgery followed by adjuvant RT with or without chemotherapy, based on pathologic risk factors.

Innovative approaches to surgery and RT, as well as the incorporation of novel systemic therapies, are currently under investigation with the intent to maximize the therapeutic index for both HPV-associated and non–HPV-associated OPCs. Transoral surgical techniques including laser and robotic resection have the potential to reduce morbidity. Advances in RT allow for optimized dose delivery to the primary tumor and involved nodes while sparing normal tissues, particularly the major salivary glands and pharyngeal constrictor muscles. The use of immune-modulating agents has improved outcomes in patients with metastatic and recurrent OPC, establishing these agents as an integral component of OPC therapy. Incorporation of immunotherapy into definitive treatment is an area of active investigation.

EPIDEMIOLOGY

Despite the variable incidence of OPC worldwide due to differences in behavioral and environmental risk factors, the international burden of OPC is projected to increase by 2030. Most OPC diagnoses around the world, particularly in developing nations, are associated with major risk factors of tobacco consumption and/or excessive ingestion of alcohol.[1] In the United States, there are about 55,000 newly diagnosed cases of OPC annually.[2,3] The annual percentage change of OPC incidence rates in the United States is generally higher for men than for women (5.4:1), and particularly high for non-Hispanic White men in the sixth decade of life.[3] These incidence rates have steadily increased since the 1980s; however, in contrast to much of the world, this is due to a 225% increase in

HPV-associated OPC. In fact, approximately 70% of newly diagnosed OPCs in the United States are HPV associated, while non–HPV-associated OPC has declined by at least 50% over the same time period, correlating with an overall decrease in tobacco consumption among the U.S. population.[4]

HUMAN PAPILLOMAVIRUS–ASSOCIATED OROPHARYNGEAL CANCER

Human Papillomavirus

HPV is a circular, double-stranded DNA virus that infects epithelial tissues. It was found to be associated with cervical cancer in 1983[5] and was subsequently established as a significant human carcinogen in 1995.[6] Over 200 HPV subtypes have been identified to date, and they are classified as high risk or low risk based upon epidemiologic associations with cervical cancer in case-control studies.[7] HPV16 is identified in >90% of all HPV-associated OPCs, while HPV18, HPV33, and HPV35 are associated with the majority of the remainder.[8] Infection with HPV16 confers an approximate 14-fold increase in the risk of developing OPC.[9]

See Chapters 2 for details on HPV-associated tumorigenesis. In brief, the HPV genome notably encodes two oncoproteins, E6 and E7, which inhibit the tumor suppressors p53 and Rb, resulting in dysregulation of the G1/S and G2/M checkpoints.[10] Although E6 and E7 oncoprotein function is necessary for the development of an HPV-associated malignancy, it is not sufficient, highlighting that yet undefined genetic events are required for malignant transformation.[11]

A number of different techniques are used to detect HPV in OPC biopsy specimens. The ability to reliably detect HPV E6/E7 messenger RNA in clinical specimens would be ideal. However, this approach is clinically impractical because it is very difficult to detect viral RNA in cytologic fluid and paraffin-embedded tissues. The gold standard is thus the detection of HPV DNA via polymerase chain reaction (PCR) or in situ hybridization (ISH). PCR is a technique with high sensitivity but low specificity, as cross-contamination or transcriptionally inactive DNA can confound results. ISH involves the use of oligonucleotide probes designed to anneal to complementary strands of HPV DNA within the tumor specimen. Advantages of ISH include localization of DNA within the tumor specimen and identification of even a sole viral copy.[12] A consequence of HPV E7-mediated Rb inhibition is induction of demethylases, resulting in overexpression of $p16^{INK4A}$ (p16), an upstream tumor suppressor that functions as a cyclin-dependent kinase inhibitor.[13] Immunohistochemistry (IHC) staining for p16 is regarded as a highly sensitive surrogate for HPV status and is frequently utilized in clinical practice without the need for confirmatory studies. Indeed, p16 IHC is the preferred assay to guide American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) eighth edition staging, and tumor p16 status alone is often sufficient to define patient eligibility for inclusion in clinical trials. However, there is up to a 20% discordance rate between HPV ISH and p16 IHC results, which is likely attributable to a number of factors, including infection with non-HPV16 subtypes (which some assays do not cover),

undetectably low viral copy numbers, and/or true biologic discordance.[14] Patients with discordant p16 and HPV testing have been shown to have a significantly worse prognosis than patients with concordant (p16-positive/HPV-positive) OPC, albeit still better prognosis than p16-negative/HPV-negative OPC. There is ongoing discussion regarding whether additional biomarker confirmation beyond p16 IHC should be mandatory for patients enrolling in clinical trials in which therapeutic de-escalation is contingent on HPV status.[15]

Clinical Characteristics of Human Papillomavirus–Associated Oropharyngeal Cancer

HPV-associated OPC is more likely to occur in males than in females (3:1), particularly non-Hispanic White males.[3] The latency period between exposure to HPV and diagnosis of HPV-associated OPC is typically greater than 10 years[16]; however, patients with HPV-associated OPC are still on average 5 to 10 years younger than patients with non–HPV-associated OPC. Patients with HPV-associated OPC are also more likely to be married, college educated, and have a median income >$55,000. The use of marijuana additionally elevates the odds of developing HPV-associated OPC.[17] Analogous to cervical cancers, certain sexual behaviors have been associated with an increased risk of developing HPV-associated OPC. These include a higher number of vaginal or oral sex partners, infrequent condom use, and early age of first intercourse.[18] While the majority of patients with HPV-associated OPC are nonsmokers, tobacco use is an independent prognostic factor, with studies demonstrating a positive correlation between disease progression, death, and smoking history.[19,20] Whether there is a synergism between exposure to HPV, tobacco, and/or alcohol in terms of increased risk of developing HPV-associated OPC is a matter of ongoing controversy.

HPV-associated OPCs are characterized frequently as poorly differentiated, nonkeratinizing, or basaloid upon histopathologic examination.[21] HPV-associated and non–HPV-associated OPCs also differ in regard to molecular alterations. HPV-associated OPCs are associated with wild-type p53, upregulation of p16, and infrequent amplification of cyclin D, whereas the converse is true for non–HPV-associated OPCs. A subset of patients with HPV-associated OPC with more extensive smoking histories have tumors more likely to exhibit *TP53* mutations, higher epidermal growth factor receptor (EGFR) and Bcl-xL expression, and tend to have oncologic outcomes similar to those of patients with non–HPV-associated OPC.[10]

Response of Human Papillomavirus–Associated Oropharyngeal Cancer to Standard Therapy

In general, patients with HPV-associated OPC have significantly better treatment response and survival outcomes than patients with non–HPV-associated OPC.[22,23] A reanalysis of RTOG 0129, a randomized study comparing cisplatin administered with either accelerated concomitant boost RT or conventionally fractionated RT, revealed that HPV status was

independently associated with improved outcomes. Three-year overall survival (OS) was 82% in patients with HPV-associated OPC compared to 54% in patients with non–HPV-associated OPC. Even after adjustment for age, tumor and nodal stage, treatment assignment, and tobacco use, HPV status independently predicted for improved survival (hazard ratio [HR] = 0.42, 95% confidence interval [CI] = 0.27-0.66). In addition, locoregional progression (13.6% vs 24.8%) and progression-free survival (PFS) (71.8% vs 50.4%) were significantly improved in patients with HPV-positive disease. Other large cooperative group studies have demonstrated similar findings.[23,24] It is important to realize that the prognostic significance of HPV is independent of the utilized CRT platform and additionally applies to treatment with RT alone[25] or surgery.[26]

ANATOMY

The oropharynx is contiguous with the oral cavity anteriorly, the larynx and hypopharynx posterior/inferiorly, and the nasopharynx superiorly. Four main subregions compose the oropharynx: the tonsil, base of tongue, pharyngeal wall, and soft palate. The tonsillar region contains the anterior and posterior tonsillar pillars and the palatine tonsil. The base of tongue comprises the posterior third of the tongue. The main sensory innervation of the base of tongue is via the glossopharyngeal nerve (cranial nerve [CN] IX), with a small portion supplied by the internal laryngeal nerve (CN X). The soft palate is a fibromuscular structure, the muscles of which are innervated by branches of CN V2, CN IX, CN X, as well as sympathetic branches of the superior cervical ganglion. Sensory innervation of the soft palate is via CN IX. See Chapters 30 for further detail.

The oropharynx contributes to many key functions, including degustation, respiration, and speech. Advanced tumors arising in the oropharynx can infiltrate muscles and nerves, significantly impeding these functions. A major goal of successful therapy is to limit long-term functional morbidity.

ROUTES OF SPREAD

The primary routes of dissemination of OPC include direct extension and lymphatic drainage, with hematogenous spread being less common. OPCs have a predilection for submucosal extension, often visualized as raised erythematous regions without distinct borders or ulceration. This can best be appreciated by direct visualization rather than on radiographic imaging.

Lymphatic Spread of Oropharyngeal Cancer

The lymphatic drainage of the oropharynx and the neck was first described by Rouvière in 1938[27] and has since been elucidated by others.[28] Nodal groups are classified by the level system[29] and defined by surgical, anatomic, and radiologic landmarks. Recently, this system (levels I-VI) was refined with the addition of sublevels (Ia/Ib, IIa/IIb, and Va/Vb), also incorporating radiologically defined landmarks (as shown in Table 51.1).[30] The most common location for regional lymph node (LN) metastasis from OPC is ipsilaterally in

level II. The probability of regional metastasis is related to the size and location of the primary tumor within the oropharynx. Subsequent lymphatic spread typically proceeds in a systematic manner through the draining LN stations with only rare isolated skip metastases (0.3%).[31] Tumors encroaching midline or involving the posterior pharyngeal wall notably exhibit a higher propensity for bilateral lymphadenopathy.[32]

TABLE 51.1 RADIOGRAPHIC BOUNDARIES OF NECK NODE LEVELS

Level	Cranial	Caudal	Anterior	Posterior	Lateral	Medial
Ia	Geniohyoid m, plane tangent to basilar edge of mandible	Plane tangent to body of hyoid bone	Symphysis menti, platysma m	Body of hyoid bone	Medial edge of anterior belly of digastric m	NA
Ib	Mylohyoid m, cranial edge of submandibular gland	Plane through central part of hyoid bone	Symphysis menti, platysma m	Posterior edge of submandibular gland	Inner side of mandible, platysma m, skin	Lateral edge of ant. belly of digastric m
II	Caudal edge of lateral process of C1	Caudal edge of body of hyoid bone	Posterior edge of submandibular gland; ICA; posterior edge of posterior belly of digastric m	Posterior edge of SCM	Medial edge of SCM m	Medial edge of ICA, paraspinal m
III	Caudal edge of body of hyoid bone	Caudal edge of cricoid cartilage	Posterolateral edge of sternohyoid m; anterior edge of SCM m	Posterior edge of SCM m	Medial edge of SCM m	Int. edge of ICA, paraspinal m
IV	Caudal edge of cricoid cartilage	2 cm cranial to sternoclavicular joint	Anteromedial edge of SCM m	Posterior edge of SCM m	Medial edge of SCM m	Medial edge of ICA, paraspinal m
V	Cranial edge of body of hyoid bone	CT slice including transverse cervical vessels	Posterior edge of SCM m	Anterior border of trapezius m	Platysma m, skin	Paraspinal m
VI	Caudal edge of body of thyroid cartilage	Sternal manubrium	Skin, platysma m	Separation between trachea and esophagus	Medial edge of SCM, thyroid gland, skin	NA
RP	Base of skull	Cranial edge of body of hyoid bone	Fascia under pharyngeal mucosa	Prevertebral m	Medial edge of ICA	Midline

CT, computed tomography; ICA, internal carotid artery; m, muscle; NA, not applicable; RP, retropharyngeal; SCM, sternocleidomastoid muscle.

The extent of occult pathologic LN involvement in patients undergoing elective neck dissection[33] has helped to guide not only the scope of selective neck dissection but also standardized contouring atlases, which aid in delineating appropriate elective RT volumes.[34-35]

Distant Metastatic Spread of Oropharyngeal Cancer

Distant metastatic spread of OPC is relatively uncommon, affecting approximately 15% of patients during the course of their disease.[36] The most common locations for distant metastatic spread are the lung parenchyma,[36] followed by bone and liver. Distant metastases are more common in patients presenting with locoregionally advanced or recurrent tumors, with the risk increasing with the primary tumor stage and the extent of cervical lymphadenopathy.[37] Extranodal extension (ENE), lower cervical lymphadenopathy (level IV), and lymphovascular invasion (LVI) have also been associated with increased rates of distant metastasis.[38]

CLINICAL PRESENTATION

OPCs present with a constellation of symptoms, dependent upon the location of the primary tumor, invasion of nearby organs, and extent of nodal disease. Often, patients present with an asymptomatic neck mass, which is usually mobile, firm, and nontender. A fixed mass can be indicative of ENE and invasion into surrounding structures. Some patients complain of deep-seated otalgia within the auditory canal. This is mediated via irritation of branches of CN IX with referral via the petrosal ganglion to the tympanic nerve of Jacobson. Regurgitation of foods can occur with tumor invasion of the soft palate and resultant inhibition of its ability to elevate during swallowing. Trismus is seen with more advanced tumors and reflects tumor invasion of the pterygoid fossa and/or musculature. Odynophagia and dysphagia are other common presenting symptoms that occur with tumor invasion of the pharyngeal musculature or obstruction by pathologic lymphadenopathy and can result in aspiration, decreased oral intake, and weight loss. Based on initial presenting symptoms and clinical status, baseline evaluation by a multidisciplinary supportive care team inclusive of a swallowing specialist, dietician, and dentist/oral surgeon prior to initiation of treatment may be advised.

DIAGNOSTIC EVALUATION

Physical Examination

A complete examination of all accessible mucosal surfaces within the head and neck should be performed in any patient with a known or suspected diagnosis of OPC. This process serves not only to characterize the extent of the primary tumor and optimal biopsy sites but also to evaluate for synchronous malignancies in the upper aerodigestive tract,

given the relatively high incidence of such, particularly in patients with a significant smoking history. Physical examination should be systematic and reproducible. Following examination of the oral cavity, where particular attention should be directed to dental health (if RT is indicated, necessary extractions should ideally be completed at least 2 weeks prior to the start of treatment), one should closely examine the anterior tonsillar pillars, tonsillar fossae, posterior tonsillar pillars, and soft palate. Proper exposure can be achieved with either gloved index fingers or simultaneous use of two disposable tongue depressors. Palpation of the tonsillar fossa and the base of tongue should be performed since these locations can harbor occult primary tumors. Palpation of the base of tongue should be at the end of the examination due to its propensity to trigger the gag reflex. Direct visualization should be followed by fiberoptic examination for optimal inspection of the base of tongue, posterior-inferior tonsils, and vallecula, as well as evaluation for disease extension to laryngeal and hypopharyngeal sites. Fiberoptic examinations should be recorded and compared to assess response during the course of therapy.

OPCs often appear as ulcerated masses with associated erythema, neovascularization, and mucositis. Tenderness, evidence of recent bleeding, obstruction of the airway, skin invasion, alteration of gag reflex, and extent of trismus (measured from upper to lower incisors) should be documented. Bulging of the parapharyngeal space should also be noted, as this could represent retropharyngeal lymphadenopathy.

Careful examination of the neck is also important for staging and management. The neck should gently be turned to the side being examined in order to relax the sternocleidomastoid muscle, which, in turn, facilitates the detection of smaller LNs. Lymphadenopathy should be documented in terms of neck level, size, firmness, degree of fixation, and whether there is skin involvement/ulceration.

Biopsy of the primary site should be performed. Adequate exposure for in-office biopsies of the proximal oropharynx is usually achievable. Posterior oropharyngeal tumors are often biopsied under general anesthesia in the operating room, typically as part of a comprehensive examination and endoscopic evaluation (laryngoscopy, bronchoscopy, and esophagoscopy). Tumor HPV status should be assessed, typically via p16 IHC, as discussed previously. Fine-needle aspiration (FNA) specimens obtained from cervical lymphadenopathy may not be sufficient for HPV testing. If FNA specimens are nondiagnostic, oftentimes in the setting of cystic or necrotic tissue, then core needle biopsy can be performed.

Computed Tomography

Computed tomography (CT) imaging of the head and neck with intravenous contrast should be performed for all patients with newly diagnosed OPC in order to assess the extent of the primary tumor and to determine the presence of cervical LN metastases. Scan slice thickness <5 mm is necessary to optimize the detection of smaller pathologically involved LNs and to provide the best anatomic delineation of both primary and nodal diseases. Radiographically concerning LNs are enlarged (>1 cm in any axis) with no apparent fatty hilum, contrast enhancing, and/or partially necrotic. Primary tumors

appear as contrast-enhancing masses, often distorting normal anatomic relationships. LN and primary tumor size should be measured in cephalad-caudad as well as axial dimensions in order to accurately stage patients. Dental artifact may obscure visualization, requiring further scanning with an adjusted head position or the use of metal artifact–reducing reconstruction algorithms. Thoracic CT should be performed routinely (either alone or in combination with a positron emission tomography [PET] scan) to assess for pulmonary metastases in patients with N2 or greater nodal disease, lower neck nodal involvement, and/or advanced primary tumors.

Positron Emission Tomography

^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT imaging incorporating tumor physiology in conjunction with anatomic information is routinely recommended for the initial staging of patients with OPC. From a practical standpoint, PET-based imaging can sensitively assess not only the locoregional burden of disease but also the presence of distant metastases. See Chapters 30 for further detail. Clinical status and knowledge of prior procedures are critical to PET interpretation, as recent biopsies and infections can lead to nononcologic hypermetabolic activity.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) can be a useful imaging tool for oropharyngeal squamous cell carcinoma (OPSCC), particularly when there is concern for CN involvement and/or tumor impingement on the skull base. Squamous cell carcinoma appears hypointense in T1-weighted images and hyperintense in T2-weighted images. The ability of MRI to differentiate tumor from soft tissue is particularly useful when determination of the extent of base of tongue or oral tongue invasion is necessary. In addition, MRI is useful in patients with compromised renal function who are unable to receive iodinated contrast agents. See Chapters 30 for further detail.

PATHOLOGIC CLASSIFICATION

Squamous cell carcinomas are the most common histologic subtype, comprising >95% of all OPCs. Uncommonly, minor salivary gland tumors and mesenchymal tumors can affect this region. Given the proportionally high content of lymphoid tissue in the region within Waldeyer ring, malignant Hodgkin and non-Hodgkin lymphomas can also arise in this region. This chapter discusses only squamous cell and related (poorly differentiated and lymphoepithelioma) histologic subtypes.

STAGING

OPC staging was revised in the AJCC/UICC eighth edition to reflect the significant differences in prognosis between HPV-associated and non–HPV-associated disease.[39] Clinical staging is based on all available history, physical examination, endoscopic, and

radiographic data. For both HPV-associated and non–HPV-associated OPSCCs, the size and extent of the primary tumor define the T stage, with T1 being <2 cm, T2 >2 cm but ≤4 cm, and T3 >4 cm. For non–HPV-associated primaries, T4a describes tumors invading the larynx, extrinsic muscles of the tongue, medial pterygoid, hard palate, or mandible. T4b describes tumors encasing the carotid artery or invading the lateral pterygoid, pterygoid plates, lateral nasopharynx, or skull base. For HPV-associated (p16-positive) primaries, T4 disease is more simply classified as tumor invasion of the larynx, extrinsic muscles of the tongue, medial pterygoid, hard palate, mandible, or beyond. Clinical nodal staging for HPV-associated disease is also simplified. N0 signifies the absence of lymphadenopathy; N1 is one or more ipsilateral LNs <6 cm, N2 is contralateral or bilateral LNs <6 cm, and N3 is defined as LN(s) >6 cm. The resultant clinical stage grouping of HPV-associated OPSCC is as follows: Clinical stage I now comprises T0-2N0-1; stage II is now T0-2N2 or T3N0-2; and stage III is composed of T0-4N3 or T4N0-2. Pathologic LN staging is also simplified to equate pN1 with ≤4 LNs and pN2 with >4 involved nodes. The resultant pathologic stage grouping of HPV-associated OPSCC is as follows: Stage I includes T0-2N0-1; stage II is T0-2N2 or T3-4N0-1; and stage III is composed of T3-4N2. Both clinical and pathologic stage IV are limited to patients with distant metastatic disease (M1) (Tables 51.2-51.4).

TABLE 51.2 AJCC/UICC EIGHTH EDITION TNM STAGING SYSTEM FOR HPV-MEDIATED (P16-POSITIVE) OROPHARYNGEAL CANCER

Primary Tumor (T)	
T0	No primary identified
T1	Tumor 2 cm or smaller in greatest dimension
T2	Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3	Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced local disease; tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond
Clinical Regional Lymph Nodes (cN)	
NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis
N1	One or more ipsilateral lymph nodes, none larger than 6 cm
N2	Contralateral or bilateral lymph nodes, none larger than 6 cm
N3	Lymph node(s) larger than 6 cm
Pathologic Regional Lymph Nodes (pN)	
NX	Regional lymph nodes cannot be assessed.
pN0	No regional lymph node metastasis
pN1	Metastasis in four or fewer lymph nodes
pN2	Metastasis in more than four lymph nodes
Distant Metastasis (M)	

M0	No distant metastasis present
M1	Distant metastasis present

AJCC, American Joint Committee on Cancer; HPV, human papillomavirus; UICC, Union for International Cancer Control.
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TABLE 51.3 AJCC/UICC EIGHTH EDITION CLINICAL STAGE GROUPING FOR HPV-ASSOCIATED (P16-POSITIVE) OROPHARYNGEAL CANCER

	T0	T1	T2	T3	T4
N0	N/A	I	I	II	III
N1	I	I	I	II	III
N2	II	II	II	II	III
N3	III	III	III	III	III
M1	IV	IV	IV	IV	IV

AJCC, American Joint Committee on Cancer; HPV, human papillomavirus; UICC, Union for International Cancer Control.
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TABLE 51.4 AJCC/UICC EIGHTH EDITION PATHOLOGIC STAGE GROUPING FOR HPV-ASSOCIATED (P16-POSITIVE) OROPHARYNGEAL CANCER

	T0	T1	T2	T3	T4
N0	NA	I	I	II	II
N1	I	I	I	II	II
N2	II	II	II	III	III
M1	IV	IV	IV	IV	IV

AJCC, American Joint Committee on Cancer; HPV, human papillomavirus; UICC, Union for International Cancer Control.
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For non–HPV-associated (p16-negative) tumors, the staging is similar to the prior AJCC/UICC seventh edition aside from factoring in ENE. Primary tumor staging is as above. For clinically staged OPSCCs without ENE, N0 indicates no clinical or radiographic evidence of pathologic lymphadenopathy; N1 indicates a single LN <3 cm in the ipsilateral neck; N2a indicates a single LN >3 cm and <6 cm in the ipsilateral neck; N2b indicates multiple ipsilateral cervical LNs, all <6 cm in size; and N2c indicates bilateral cervical LNs, all <6 cm. N3 is now divided into two subcategories: N3a indicates

the presence of at least one LN >6 cm, while N3b indicates overt clinical evidence of ENE, irrespective of LN number, size, or laterality (Tables 51.5 and 51.6).

TABLE 51.5 AJCC/UICC EIGHTH EDITION TNM STAGING SYSTEM FOR P16-NEGATIVE OROPHARYNGEAL CANCER

Primary Tumor (T)

TX	Primary tumor cannot be assessed.
Tis	Carcinoma in situ
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor >2 cm but not >4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced or very advanced local disease
T4a	Moderately advanced local disease Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible.[a]
T4b	Very advanced local disease Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery.

Clinical Regional Lymph Nodes (cN)

NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension and ENE negative
N2	Metastasis in a single ipsilateral node >3 cm but not >6 cm in greatest dimension and ENE negative; *or* metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE negative; *or* in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE negative
N2a	Metastasis in a single ipsilateral node >3 cm but not >6 cm in greatest dimension and ENE negative
N2b	Metastasis in multiple ipsilateral nodes, none >6 cm in greatest dimension and ENE negative
N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE negative
N3	Metastasis in a lymph node >6 cm in greatest dimension and ENE negative; *or* metastasis in any node(s) and clinically overt ENE positive
N3a	Metastasis in a lymph node >6 cm in greatest dimension and ENE negative
N3b	Metastasis in any node(s) and clinically overt ENE positive

Pathologic Regional Lymph Nodes (pN)

NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension and ENE negative
N2	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension and ENE positive; *or* >3 cm but not >6 cm in greatest dimension and ENE negative; *or* metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE negative; or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE

	negative
N2a	Metastasis in single ipsilateral or contralateral node ≤3 cm in greatest dimension and ENE positive; *or* a single ipsilateral node >3 cm but not >6 cm in greatest dimension and ENE negative
N2b	Metastasis in multiple ipsilateral nodes, none >6 cm in greatest dimension and ENE negative
N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE negative
N3	Metastasis in a lymph node >6 cm in greatest dimension and ENE negative; *or* in a single ipsilateral node >3 cm in greatest dimension and ENE positive; *or* multiple ipsilateral, contralateral or bilateral nodes, any with ENE positive
N3a	Metastasis in a lymph node >6 cm in greatest dimension and ENE negative
N3b	Metastasis in a single ipsilateral node >3 cm in greatest dimension and ENE positive *or* multiple ipsilateral, contralateral, or bilateral nodes, any with ENE positive
Distant Metastasis (M)	
M0	No distant metastasis present
M1	Distant metastasis present

AJCC, American Joint Committee on Cancer; ENE, extranodal extension; UICC, Union for International Cancer Control.

[a]Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx.

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TABLE 51.6 AJCC/UICC EIGHTH EDITION STAGE GROUPING FOR P16-NEGATIVE OROPHARYNGEAL CANCER

	T1	T2	T3	T4a	T4b
N0	I	II	III	IVA	IVB
N1	III	III	III	IVA	IVB
N2	IVA	IVA	IVA	IVA	IVB
N3	IVB	IVB	IVB	IVB	IVB
M1	IVC	IVC	IVC	IVC	IVC

AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control.

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For p16-negative pathologically staged nodal disease, the eighth edition now classifies a single LN (ipsilateral or contralateral) <3 cm with ENE as N2a, while either a single pathologic LN >3 cm with ENE or multiple LNs with ENE is N3b. The presence of distant metastatic disease is classified as M1. The stage grouping for p16-negative OPSCC is unchanged from prior editions. Stage I comprises T1N0 disease, and stage II comprises T2N0 disease. Stage III includes patients with T3N0-1 or T1-T2N1. Stage IV is divided into three subgroups. Stage IVa includes patients with T4aN0-2a-c and T1-3N2a-c disease.

Stage IVb defines patients with technically unresectable disease, including patients with an extensive primary tumor (T4b, any N) or extensive lymphadenopathy (any T, N3). Stage IVc includes patients with distant metastases (M1).

MANAGEMENT STRATEGIES

Functional organ preservation with minimal toxicity is the management goal for all patients with OPC. Based on AJCC stage, patients are usually divided into two different treatment groups to help guide therapy decisions: early stage and locoregionally advanced. Those with stage I and II diseases are typically considered early stage, while others are considered to have locoregionally advanced disease. For all subsites, early-stage tumors are usually well controlled with a single local treatment modality, namely, RT or surgery. This paradigm is in flux for HPV-associated disease as some presentations that would have been considered locoregionally advanced based on AJCC seventh edition, for example, T1N1 or T2N1, are classified as early stage in AJCC eighth edition staging. Ultimately, treatment modality selection should be based on the primary tumor size, extent of local spread, and involved subsites. Small tumors of the tonsil and small exophytic tumors of the base of tongue can typically be managed surgically with a favorable toxicity profile, whereas the morbidity of surgery for tumors involving the soft palate is less favorable, resulting in a preference for primary RT for these tumors. For locoregionally advanced disease, two appropriate treatment strategies are used: either surgery followed by RT with or without chemotherapy based on pathologic risk factors or RT, usually with concurrent chemotherapy.

SURGICAL TECHNIQUES, APPROACHES, AND RESULTS

Neck Dissection

Cervical LN dissections, otherwise known as neck dissections, can be both diagnostic and therapeutic for pathologic lymphadenopathy. Modern nomenclature classifies neck dissections as either comprehensive, with removal of all nodal groups (I-V), or selective, with removal of only the nodal groups felt to be at high risk of pathologic involvement based on patterns of spread. Comprehensive dissections are typically recommended for patients with evidence of advanced nodal disease, whereas selective dissections are usually recommended for patients who are clinically node negative or have minimal nodal disease.[40,41] For patients with OPSCC, selective neck dissections typically target the nodes in levels II and IV, and sometimes V; this practice results in removal/identification of all pathologic lymphadenopathy in >90% of clinically node-negative patients.[31,42] The extent of the tumor and lymphatic drainage patterns of the anatomic subsite determine whether ipsilateral or bilateral neck selective dissection is indicated.

Base of Tongue

Surgery plays a limited role in the management of large and/or midline base of tongue tumors, given the inherent morbidity of a near-total or total glossectomy.[43] For select,

well-lateralized or polypoid base of tongue tumors with minimal associated cervical lymphadenopathy, a partial glossectomy can be performed. Given the high propensity for occult microscopic nodal involvement, bilateral cervical LN dissection is recommended. Base of tongue tumors in close proximity to the laryngeal apparatus, such as those arising in the vallecula, often require a supraglottic or total laryngectomy to achieve adequate margins of resection. Traditional surgical approaches for base of tongue tumors include the midline mandibulotomy (splitting the lip, mandible, and oral tongue midline), the lateral mandibulotomy (dividing the mandible near the angle and approaching the base of tongue from the side), and the floor drop procedure (elevating the inner periosteum from the mandible from angle to angle which releases the entire floor of mouth and oral tongue into the neck exposing the base of tongue). These approaches have largely been replaced by transoral robotic surgery (TORS), as discussed below.

Tonsil Cancers

For small (<1 cm) early-stage tonsil cancers confined to the anterior pillar, a wide local excision can achieve adequate tumor-free margins, whereas tumors involving the palatine tonsil often require a radical tonsillectomy. For both of these situations, the tonsil is approached transorally with primary closure. Larger tumors with extension onto the tongue, mandible, or into surrounding tissue often require a composite resection, usually including resection of the tonsil, tonsillar fossa, pillars, a portion of the soft palate, tongue, and mandible. For tumors not adjacent or adherent to the mandible, a midline mandibulotomy approach is used. For tumors adherent to the mandible, a partial mandibulectomy is used. Defects are often closed with a myocutaneous flap. Complications from surgery depend on the extent of resection, with impairment in swallowing possible with removal of part of the tongue or soft palate. Certain patients with well-lateralized, small tonsil primaries can be managed with ipsilateral neck dissection.

Soft Palate Cancers

Surgical resection is rarely recommended as initial therapy for soft palate tumors. Resection of the soft palate is often associated with significant reflux into the nasopharynx during swallowing, even with the use of custom prostheses. In addition, due to the midline location, primary disease can spread to the bilateral cervical and retropharyngeal LNs, with frequency high enough to require elective treatment. When surgery is performed, the tumors are approached transorally, and a full-thickness wide local resection is performed when tumors are limited to the soft palate. A more extensive composite resection is required if disease extends to surrounding structures. Flaps or prostheses are used to preserve velopharyngeal competence. Nasal speech is also often a consequence.

Minimally Invasive Transoral Surgical Approaches

Minimally invasive transoral surgical approaches, such as transoral laser microsurgery (TLM) and TORS, which were previously only routinely used as an alternative to open surgical procedures in the setting of limited tonsillar resections, are now increasingly being utilized in the United States for a diverse array of patients with OPC.[44] Indeed, a systematic review and meta-analysis, inclusive of a randomized controlled trial, has demonstrated that TORS results in improved peri- and postoperative outcomes as well as decreased local recurrences, when compared to open operations for patients with head and neck squamous cell carcinoma (HNSCC).[45] Importantly, candidates for minimally invasive surgical procedures should be carefully selected to minimize the necessity of multimodal treatment (ie, adjuvant RT/CRT), which is associated with increased late toxicity.

Transoral Laser Microsurgery

TLM makes use of a laser to excise tumor. Small series report favorable outcomes for select patients with stage I to IV OPSCC treated with TLM with or without neck dissection, followed by adjuvant RT or CRT.[46-49] Positive margin rates are variable (3%-24%) and differ based on the primary site (eg, more common when operating on base of tongue tumors). Notable complications include postoperative hemorrhage (5%-10%) and temporary tracheostomy placement (17%-30%). The latter is often needed for exposure, airway control, and/or aspiration management following extensive resection. High rates of locoregional control (LRC) following this procedure have been reported, primarily for stage I and II patients (87%-100%); for stage III and IV patients, local recurrence is more common (20%-30%). Swallowing outcomes are favorable, with series reporting most patients tolerating a normal diet postoperatively.[46,49]

Transoral Robotic Surgery

The use of a computer-aided interaction between the surgeon and the patient is commonly referred to as “robotic” surgery. The most common robotic surgical system, the da Vinci Surgical system, is composed of three surgical instruments and a binocular endoscope controlled by robotic arms and inserted under direct or endoscopic guidance by the surgeon from a patient-side apparatus. The surgeon controls the instruments from a console separated from the patient. The operative environment is visualized virtually, in a 3D environment created via a computer, which links the environment provided by the binocular endoscope to the position of the instruments. The surgeon’s movements are translated into micromovements of the instruments. The advantages of this system include motion scaling, which can increase precision, as well as reduce hand tremor and fatigue. When the system is used for transoral surgeries, an assistant is often positioned by the patient’s head.

There have only been two prospective randomized trials comparing RT to TORS in the treatment of patients with OPC that have published results to date. ORATOR was a phase II randomized trial that enrolled 68 patients with T1-2N0-2 OPC from multiple hospitals in Canada and Australia and randomized them to primary RT/CRT versus TORS and neck

dissection with or without adjuvant RT/CRT based on pathologic risk factors. The primary outcome was swallowing-related quality of life (QoL). Notably, 88% of patients had p16-positive disease. The investigators found that swallowing-related QoL outcomes were significantly improved in the primary RT cohort at 1 year post-treatment. However, the difference did not appear to be clinically meaningful, and the differences between the two arms became less pronounced with longer follow-up. The risk of postoperative hemorrhage in the TORS arm was higher than expected, with four grade 2 or higher events, including one grade 4 and one grade 5 event. In light of this, the trial was modified to mandate elective temporary tracheostomy for patients undergoing TORS. PFS and OS were similar between the two arms.[50,51] ORATOR2 was an international phase II study randomizing patients with T1-2N0-2 HPV-related OPC to primary RT/CRT (de-escalated dose of 60 Gy) versus transoral surgery (TLM or TORS) plus neck dissection with or without adjuvant RT/CRT based on pathologic risk factors. The trial was terminated early after accrual of 61 patients due to an unacceptable number of grade 5 toxicities in the transoral surgery arm, most notably two treatment-related deaths (attributed to postoperative hemorrhage and spondylodiscitis).[52] Thus, while the current data show that RT and transoral surgical approaches may result in comparable oncologic and QoL outcomes for patients with early stage, primarily p16-positive OPC, the spectra of toxicities differ and there appears to be a significant risk of upfront treatment-related mortality with transoral surgery, which should warrant caution particularly at institutions without significant experience with this technique. There are other ongoing randomized phase II/III trials comparing primary RT to transoral surgery approaches (SCOPE, BEST OF) that will provide further data to guide management of these patients. In the meantime, careful multidisciplinary evaluation factoring in institutional experience is essential to determine the appropriate treatment modality.

ADJUVANT THERAPY FOLLOWING DEFINITIVE SURGICAL RESECTION

Following surgical resection of OPC, pathologic features including advanced primary T stage (T3 or T4), LVI, perineural invasion (PNI), positive margin, multiple pathologically involved cervical LNs, and ENE place patients at increased risk for locoregional recurrence.[53] In these cases, postoperative radiotherapy (PORT) has been shown to reduce the risk of locoregional relapse and is thus typically recommended.[54,55] The time interval between surgical resection and initiation of PORT has been shown to significantly impact patient outcomes and should ideally be ≤6 weeks.[56]

Adjuvant Chemoradiotherapy for Oropharyngeal Cancer

The addition of cisplatin-based chemotherapy to PORT has been compared to PORT alone for medically fit patients with HNSCC with high-risk pathologic features in a number of randomized studies,[57-61] the majority of which have demonstrated statistically significant[57-59] improvements in LRC and disease-free survival (DFS) with the addition of chemotherapy to PORT. Two of these studies also demonstrated statistically significant

improvements in OS with chemotherapy plus PORT versus PORT alone.[57,58] Two seminal randomized phase III trials are described here. RTOG 9501 randomized patients with pathologic features of two or more involved nodes, ENE, and/or positive margins to PORT versus PORT plus bolus cisplatin 100 mg/m^2 every 3 weeks, and EORTC 22931 randomized to similar arms, but also included patients with other high-risk features such as PNI, vascular tumor embolism, and/or nodal involvement in levels IV to V from an oral cavity or oropharyngeal primary. Notably, a significant portion of patients in these studies had OPC (EORTC 30%, RTOG 43%).[57,60,61] A pooled comparative analysis of patients in these two trials revealed that the presence of ENE and/or positive surgical margins were the only risk factors for which the addition of bolus cisplatin to PORT significantly improved oncologic outcomes.[62] An unplanned subset analysis from the reported long-term follow-up outcomes of RTOG 9501 supported this conclusion, with improved LRC, DFS, and cause-specific survival noted only in the subset of patients with ENE and/or positive margins.[61] Adjuvant PORT plus chemotherapy is thus currently recommended primarily for patients with OPC with ENE and/or positive surgical margins. Given the increased toxicity associated with the addition of chemotherapy, patient performance status should always be factored into decision-making.

Concurrent Chemotherapy Regimens for Adjuvant Chemoradiotherapy

The optimal chemotherapy regimen to be delivered concurrently with PORT is unknown. Regimens of 100 mg/m^2 bolus cisplatin every 3 weeks,[57,60,61] 50 mg/m^2 cisplatin weekly,[58] and 20 mg/m^2 cisplatin/600 mg/m^2 5-fluorouracil (5-FU) on d1-5 and d29-33[59] have all been utilized in randomized studies investigating PORT alone versus chemotherapy plus PORT. A randomized comparison of weekly cisplatin (40 mg/m^2) versus bolus cisplatin (100 mg/m^2 every 3 weeks) in patients receiving postoperative CRT for high-risk locally advanced HNSCC (14% OPC) was recently conducted, with results demonstrating noninferiority of the weekly cisplatin regimen in terms of OS. Patients in the weekly cisplatin arm also demonstrated significantly decreased frequency of grade 3+ neutropenia, infection, renal toxicity, and ototoxicity.[63] Weekly cisplatin at a dose of 40 mg/m^2 is thus a reasonable alternative regimen to bolus cisplatin for patients who require adjuvant CRT.

RTOG 0234 was a phase II trial that randomized patients with stage III and IV HNSCC (39% OPC) with high-risk postoperative features (positive margin, ENE, and/or at least two pathologically involved cervical nodes) to PORT (60 Gy) with cetuximab (400 mg/m^2 loading dose, followed by 250 mg/m^2 weekly) and weekly docetaxel (15 mg/m^2) versus PORT with cetuximab and weekly cisplatin (30 mg/m^2). Patients who received the docetaxel regimen had higher 2-year OS (79% vs 69%) and 2-year DFS (66% vs 57%).[64] RTOG 1216 is an ongoing randomized phase II/III trial designed to determine if there is an OS benefit for patients with high-risk non–HPV-associated HNSCC treated with the combination of cetuximab and docetaxel versus cisplatin alone (40 mg/m^2 weekly) or the combination of programmed death-ligand 1 (PD-L1) inhibitor atezolizumab and cisplatin versus cisplatin alone, all in the setting of adjuvant PORT. In summary, based on the

available data, many consider bolus cisplatin 100 mg/m^2 every 3 weeks to be the standard chemotherapy regimen to be used concurrently with PORT in patients with high-risk OPC (ENE and/or positive margins), based primarily on RTOG 9501 and EORTC 22931. However, weekly cisplatin can be considered based on randomized noninferiority data and is being increasingly used in the standard arm in clinical trials. For cisplatin-ineligible patients, the combination of docetaxel and cetuximab can be considered, though further confirmatory data are pending.

Adjuvant Radiation Therapy Dose

The optimal dose for PORT is also not well studied. An early dose-finding randomized trial established the efficacy of 57.6 Gy in 1.8 Gy daily fractions to the tumor bed, with a boost to 63 Gy to areas at high risk (ie, nodal regions with ENE), without clear benefit to further dose escalation.[65,66] Most randomized studies demonstrating the benefit of concurrent chemotherapy with PORT used conventionally fractionated RT, namely, 60 to 66 Gy in 2 Gy daily fractions, to high-risk areas (primary tumor bed with positive margin, or nodal regions with ENE). In three of the four studies, doses >65 Gy were delivered to high-risk areas.[57-59] The fourth study, RTOG 9501, allowed a dose of 60 Gy with an optional 6 Gy boost; however, only 13% of patients received this optional boost.[60,61] Accelerated PORT has been studied in randomized trials, which consistently showed no OS benefit as well as significantly increased toxicity with acceleration; thus, this approach is not recommended.[67,68] Based on the available data, doses between 60 to 66 Gy in 2 Gy daily fractions to high-risk areas and 50 to 54 Gy in 1.8 to 2 Gy daily fractions to low-risk areas are considered most appropriate. For patients with HPV-associated OPC, this paradigm is shifting, and it may be appropriate to de-escalate RT dose to a total of 50 Gy in 2 Gy daily fractions for select patients as discussed in the section “Deintensification.”

Postoperative Radiotherapy Treatment Volume

The typical treatment volume used in PORT for HNSCC includes the bilateral neck and the primary tumor bed.[69] However, it is unclear whether both the neck and primary always need to be included in the PORT volume. In those with completely resected primary OPC with negative margins whose sole indication for PORT is pathologic cervical adenopathy, some would direct therapy only to the neck. In addition, for well-lateralized primary tumors, patterns of progression would suggest that PORT to the ipsilateral neck only may be appropriate.[70] For patients with a positive margin as the sole indication for treatment in the setting of a comprehensive neck surgery without pathologically involved cervical LNs, some would direct treatment to the primary resection bed only; indeed, there are phase II trial data in support of this practice, though this trial was limited by its relatively small size.[71]

DEFINITIVE RADIATION THERAPY

For early-stage OPC (stage I, and select stage II patients[72]), the use of RT as a single modality is associated with good outcomes and functional preservation.[73] There are additionally chemotherapy-ineligible patients with more locally advanced disease, for whom RT alone must be considered. Although there is no consensus on the optimal dose fractionation schedule for patients with OPC receiving RT alone, randomized data[74-76] and meta-analyses[77,78] support an OS benefit with the use of accelerated or hyperfractionated RT. Therefore, for patients with OPC who are treated with RT alone, consideration should be given to altered RT fractionation.

Hyperfractionated Radiation therapy

The benefit of hyperfractionated RT for patients with OPC was clearly demonstrated in EORTC 22791, in which patients with T2-3N0-1 nonbase of tongue OPC were randomized to conventionally fractionated RT at 70 Gy (2 Gy/d) or to 80.5 Gy hyperfractionated at 1.15 Gy twice daily. Hyperfractionated RT was associated with a statistically significant improvement in LRC (5-year, 59% vs 40%) without an increase in long-term toxicity. In addition, there was a trend toward improved OS (P = .06), particularly in stage III patients.[76,79] RTOG 9003 was a four-arm phase III randomized study comparing two accelerated fractionation regimens and a hyperfractionation regimen to conventionally fractionated RT for patients with stage II and IV HNSCC (~60% with OPC). Long-term follow-up of this trial confirmed that hyperfractionation (81.6 Gy/68 twice-daily fractions) was associated with significantly improved LRC and OS, compared to standard fractionation. There was additionally no difference in grade 3 or higher late toxicities among the study arms.[74]

Accelerated Radiation Therapy

Accelerated RT has also been shown to benefit patients with OPC but may depend upon the exact regimen used. For example, a randomized study that enrolled primarily patients with OPC compared an accelerated regimen of 66 to 70 Gy delivered in 2 Gy daily fractions 6 days per week to the same dose delivered 5 days per week and demonstrated improved LRC (42% vs 30%, P = .004), DFS (50% vs 40%, P = .03), and a trend toward improved OS (35% vs 28%, P = .07) with the accelerated regimen.[75] Of note, accelerated fractionation improved local control for patients with p16-positive (HR: 0.56 [0.33-0.96]) and p16-negative OPC (HR: 0.77 [0.60-0.99]).[80] EORTC 22851 compared 1.6 Gy thrice daily to 72 Gy versus 1.8 to 2 Gy daily to 70 Gy over 7 to 8 weeks in patients with locally advanced HNSCC. Patients receiving accelerated fractionation had significantly improved 5-year LRC; however, both acute and late toxicities were increased with the regimen, drawing into question its utility.[81] In addition, another study investigating an accelerated regimen of 1.8 Gy twice daily to 59.4 Gy compared to 2 Gy daily to 70 Gy in patients with stage III/IV HNSCC found no benefit in terms of LRC or OS for the accelerated regimen.[82] It is unknown if the lack of benefit seen was due to the regimen used or the eligibility criteria, as the benefit for acceleration in some randomized studies was less

significant for those with stage IV disease, as well as for patients with a larger nodal disease burden.[83]

Accelerated Versus Hyperfractionated Radiation Therapy

The Meta-Analysis of Radiotherapy in squamous cell Carcinomas of Head and Neck (MARCH) collaborative group pooled 15 randomized studies with a total of 6,515 patients with locally advanced disease (44% with OPC), comparing conventionally fractionated RT to either accelerated RT or hyperfractionated RT. Altered fractionation RT regimens were associated with a 3.4% absolute improvement in 5-year OS. Heterogeneity in patients included in accelerated and hyperfractionated trials obscures ideal direct comparison; however, hyperfractionated RT resulted in an 8.1% absolute improvement in OS at 5 years, compared to a 2% absolute benefit with accelerated RT.[78] An updated analysis in 2017 including data from 33 trials reported a 1.2% absolute benefit in 10-year OS with altered fractionation RT, with the benefit seemingly limited to those receiving hyperfractionated RT (10-year OS benefit of 3.9%; HR 0.83, 95% CI, 0.74-0.92).[84] Given the heterogeneity of the data as well as the logistical challenges associated with delivering altered fractionation regimens, there is no consensus on the optimal fractionation in the setting of definitive RT alone in the treatment of patients with OPC.

Hypofractionated Radiation Therapy

Hypofractionated RT has been investigated in the definitive treatment of OPC. Princess Margaret Hospital published their single-institution experience of treating over 2,000 patients with HNSCC, the majority of whom had OPC, with either hypofractionated RT (60 Gy/25 fractions), accelerated RT (70 Gy/35 fractions over 6 weeks), or CRT. The rates of 3-year locoregional and distant control for patients with both HPV-related and HPV-negative early-stage disease (per AJCC eighth edition) were comparable, regardless of the RT regimen utilized. Hypofractionated RT also appeared to be well tolerated. The authors thus concluded that hypofractionated RT could be considered in the definitive treatment of such patients, with obvious limitations of this study including its nonrandomized nature.[85] This approach is rather attractive given the shorter treatment timeframe, while also avoiding twice-daily treatments. Further investigation is needed to determine the optimal role for this approach, namely, by continuing to quantify both comparative efficacy and associated late toxicities.

Stereotactic body radiotherapy (SBRT) is a technique used to deliver ablative doses of external beam RT in five or fewer fractions with high accuracy and has increasingly been adopted in the definitive treatment of various malignancies, such as inoperable early-stage non–small cell lung cancer.[86] There is currently a lack of evidence to support utilization of SBRT as a primary treatment option for patients with OPC,[87] although this is an area of active investigation.

CONCURRENT CHEMORADIOTHERAPY FOR LOCOREGIONALLY ADVANCED OROPHARYNGEAL CANCER

For patients with locoregionally advanced OPC, concurrent CRT is the standard treatment. Resection when possible is generally not recommended, given the associated morbidity. In addition, adjuvant CRT is frequently necessary for these patients if surgical resection is pursued with similar morbidity to definitive CRT. Comparisons of outcomes of patients treated with RT with or without neck dissection versus surgery with or without adjuvant RT revealed higher complication rates associated with surgery.[43] With the advent of transoral and robotic surgical techniques, these findings are being reconsidered. However, as discussed above, recent trials have not demonstrated a benefit to minimally invasive surgery over definitive RT/CRT for patients with OPC.[50,52]

Evidence for Concurrent Chemoradiotherapy

The use of concurrent CRT for most patients with stage III and IV (nonmetastatic) OPC is based on the results of the meta-analysis of head and neck cancer, which demonstrated a 6.2% absolute improvement in 5-year OS with the use of concurrent CRT compared to RT alone.[88] This OS benefit was also observed specifically in the OPC subgroup of 5,872 patients (HR: 0.78, 95% CI: 0.72-0.85, $P < .0001$).[89] A benefit to cisplatin-containing and poly-chemotherapy regimens was noted, as was decreasing benefit of the addition of chemotherapy with increasing age. The updated MARCH meta-analysis additionally compared altered fractionation RT alone to conventionally fractionated CRT in patients with stage III and IV HNSCC and demonstrated that CRT resulted in significantly improved 10-year OS.[84]

Level I evidence from multiple randomized studies restricted to patients with OPC additionally supports the use of concurrent CRT for stage III/IV disease.[90,91] The Groupe d'Oncologie Radiothérapie Tête et Cou (GORTEC) compared conventional RT (2 Gy daily to 70 Gy) to RT plus three cycles of carboplatin/5-FU. A total of 222 patients (113 assigned to RT alone and 109 assigned to combined treatment) were eligible for analysis. With a median follow-up of 5.5 years, absolute 5-year OS was significantly higher in the combined modality arm (15.8% with RT alone vs 22.4% with CRT). Five-year LRC was also significantly improved with concomitant therapy (24.7% vs 47.6%, $P = .002$).[92]

Acute Toxicity of Chemoradiotherapy

For patients with OPC, a course of concurrent CRT is a life-changing event given the associated toxicities, including fatigue, nausea, emesis, thickened secretions, xerostomia, mucositis, dysphagia, odynophagia, alopecia, dermatitis, anemia, neutropenia, hoarseness, Lhermitte syndrome, and infection. Mucositis, defined as acute inflammation of the mucous membranes in the throat and mouth, is one of the most common acute toxicities of CRT, affecting approximately 70% of patients. Mucositis contributes significantly to malnutrition, dehydration, treatment breaks, hospitalization, and feeding tube placement. It is typically managed by topical (diphenhydramine-lidocaine-antacid mouthwash,

doxepin mouthwash[93]) and oral analgesics (pregabalin,[94] gabapentin[95]), although opioids are frequently necessary. Novel therapeutics to combat severe mucositis are under investigation. One promising agent is avasopasem manganese, a small molecule superoxide dismutase mimetic proposed to selectively radio-protect normal tissues. Two trials, which enrolled a total of 678 patients with locally advanced HNSCC receiving CRT, randomized patients to placebo versus avasopasem and demonstrated clinically meaningful reductions in oral mucositis (severity, incidence, duration) with the addition of avasopasem.[96,97] Dysphagia is also a significant acute complication and can contribute to poor nutritional status as well as aspiration and resultant infection. Early therapeutic intervention should be promoted and involves swallowing exercises designed to strengthen the pharyngeal musculature.[98] Patients should undergo nutritional evaluation before, during, and after treatment, particularly those who lose 5% of their body weight over 1 month. Reactive, as opposed to prophylactic, feeding tube placement is generally preferred for patients with OPC, and various guidelines and criteria can help inform clinical decision-making in this regard. Prophylactic feeding tube placement should still be considered in high-risk patients, such as those with severe pretreatment weight loss and dysphagia with significant aspiration risk.[99]

Late Toxicity of Chemoradiotherapy

Late toxicities of CRT for patients with OPC can also be quite significant and can include dysphagia, fibrosis, osteoradionecrosis, trismus, xerostomia, dental caries, feeding tube dependence, and neuritis. With modern IMRT and supportive care, grade 3 or higher late toxicities afflict roughly 20% of patients with OPC.[100] Chronic feeding tube dependence afflicts 3% to 4% of patients with OPSCC, and late cranial neuropathies can affect 4% to 5% of patients.[101,102] Lymphedema and neck fibrosis are common and can be mitigated by occupational therapy and custom compression devices. Given the increased risk for dental and oral complications, patients should be evaluated by an experienced dentist at least 2 times per year, with consultation with the treating radiation oncologist prior to any planned extractions. Pilocarpine is approved by the U.S. Food and Drug Administration as a sialagogue and can be prescribed to aid in the treatment of RT-induced xerostomia, to supplement other strategies involving salivary substitutes, dietary modification, as well as increased hydration.[103] Fluoride treatments can help reduce caries and sensitivity.[104] Trismus can be prevented and managed with custom exercises and devices. Notably, a long-term report of patients with HPV-associated OPC treated with CRT demonstrated that development of additional late toxicities beyond those present at 2 years post-CRT was rare. Furthermore, long-term QoL in all domains was similar to that seen before treatment.[105]

Alternative Concurrent Chemoradiotherapy Regimens

Bolus cisplatin at 100 mg/m^2 every 3 weeks is often cited as a standard concurrent chemotherapy regimen due to its lengthy track record in randomized trials. However, the

toxicity of bolus cisplatin has motivated evaluation of alternative regimens. Multiple randomized studies that compared RT alone to concurrent CRT using nonbolus cisplatin schedules including daily cisplatin (6 mg/m^2/d),[106] weekly cisplatin (40 mg/m^2),[107] or cisplatin (20 mg/m^2/d) on days 1 to 5 repeated every 3 weeks[108] have demonstrated comparable outcomes. Weekly cisplatin is of particular interest, given its increased tolerability and relative ease of administration. Although a recent systematic review and meta-analysis demonstrated comparable survival outcomes and toxicity in patients treated with RT with weekly cisplatin versus bolus cisplatin,[109] there are overall more high-level data in support of utilization of bolus cisplatin. Further evidence should come from an ongoing phase II/III trial through NRG (NCT05050162), which is randomizing patients with locally advanced HNSCC to RT plus weekly versus bolus cisplatin and notably has separate study arms for patients with HPV-associated OPC.

For patients who are not eligible to receive cisplatin based on medical comorbidities or performance status, there is no standard of care cytotoxic radiosensitizer. (Cetuximab is discussed in the targeted therapy section.) The aforementioned GORTEC randomized study demonstrated an OS advantage using a carboplatin/5-FU regimen specifically chosen to avoid cisplatin-related tinnitus, renal dysfunction, and emesis, although this regimen can notably result in significant mucosal toxicity. The combination of carboplatin and paclitaxel has also been trialed in a single-arm study.[110] Nonrandomized data support the use of single-agent carboplatin, specifically in place of cetuximab, for cisplatin-ineligible patients with locally advanced OPC, although selection bias is a limitation of these studies.[111,112] In addition, a recent phase II/III study randomized 356 cisplatin-ineligible patients with locally advanced HNSCC to RT alone versus RT plus concurrent docetaxel and showed significantly higher 2-year DFS (42% vs 30.3%, P = .002) and 2-year OS (50.8% vs 41.7%, P = .035) with the addition of docetaxel.[113] Any of these regimens are acceptable choices for cisplatin-ineligible patients, although the best evidence is for carboplatin/5-FU. As discussed above, if patients have locoregionally advanced OPC and are not eligible to receive any systemic therapy, then consideration for altered fractionation RT should be given. Concurrent use of targeted agents is discussed below.

Concurrent Chemotherapy and Accelerated Radiation Therapy

Two randomized studies have shown that there is no benefit to accelerated RT over conventionally fractionated RT when delivered with concurrent platinum-based chemotherapy. GORTEC 99-02 randomized patients with locoregionally advanced HNSCC to either very accelerated RT (64.8 Gy in 1.8 Gy twice-daily fractions), conventionally fractionated RT (70 Gy over 7 weeks) with concurrent carboplatin and 5-FU, or accelerated RT (70 Gy delivered in 2 Gy daily fractions to 40 Gy, then 1.5 Gy twice daily) with concurrent carboplatin and 5-FU. Outcomes in both CRT arms were similar and were superior to very accelerated RT alone, with lower rates of acute toxicity and percutaneous gastrostomy tube placement during therapy and at 5 years post-treatment.[114] RTOG 0129 randomized patients with locally advanced disease (60% with

OPC) to accelerated concomitant boost RT (72 Gy) with two cycles of bolus cisplatin (100 mg/m^2) versus conventionally fractionated RT (70 Gy over 7 weeks) with three cycles of bolus cisplatin (100 mg/m^2). Again, there was no benefit to accelerated CRT in terms of 8-year OS (accelerated 47.6% vs conventional 47.7%), locoregional progression (36.7% vs 38.5%), or grade 3 to 5 toxicity (37.9% vs 36.5%).[115] Either RT fractionation approach can thus be considered for patients with locally advanced OPC receiving concurrent systemic therapy.

Induction Chemotherapy Prior to Definitive Local Therapy

The utility of induction chemotherapy as a means to reduce the risk of distant failure and improve survival for patients with locoregionally advanced OPC was an area of active study, particularly given that the rising use of definitive CRT reduced the competing risk of locoregional failure and that the primary pattern of progression was distant metastases.[116] However, mature results from multiple randomized studies did not demonstrate significant improvement in PFS or OS with induction chemotherapy followed by concurrent CRT, and in fact reported increased associated toxicity.[117-119] Induction chemotherapy is thus not routinely recommended in the treatment of patients with nonmetastatic OPC but could be considered if there is an unavoidable delay in initiating CRT, or for rapidly growing tumors, and those adjacent to critical normal structures limiting the ability to deliver curative-intent radiation doses. Early-phase induction chemotherapy studies in the patient population with HPV-positive OPC are discussed in the section “Deintensification.”

Targeted Agents and Radiation Therapy

EGFR is commonly overexpressed in HNSCC and was thus identified as a molecular target for therapy. A randomized study compared RT (70-76.8 Gy) with weekly cetuximab, an EGFR inhibitor (loading dose of 400 mg/m^2 followed by 250 mg/m^2), to RT alone for patients with locoregionally advanced HNSCC (60% OPC). The combination therapy was found to improve LRC, DFS, and OS, independent of tumor p16 status.[120] Based on these data, it was hypothesized that the combination of cetuximab plus RT could be, at the very least, an option for cisplatin-ineligible patients and potentially even a new standard of care/less toxic regimen allowing for deintensification of treatment for HPV-associated OPC. However, data from multiple phase III randomized trials comparing cetuximab plus RT to cisplatin plus RT for mostly HPV-associated locally advanced OPC have demonstrated not only the inferiority of concurrent cetuximab to cisplatin in terms of survival and recurrence outcomes but also a lack of benefit in terms of reduced treatment-related toxicity.[100,121-123] See the section “Deintensification” for further discussion. Cetuximab should also notably be avoided in specific regions (particularly the Southeastern United States) where severe anaphylactic reactions mediated by an immunoglobulin E response to the galactose-α-1,3-galactose oligosaccharide found on the Fab portion of the cetuximab heavy chain are seen.[124] Although cetuximab has been shown

to be inferior to cisplatin in the definitive treatment setting, it remains an option for cisplatin- or otherwise chemotherapy-ineligible patients in certain geographical areas, as it has been shown to be superior to definitive RT alone.

Immune checkpoint inhibitors, which target programmed death-1 (PD-1) and PD-L1, have been evaluated in combination with RT in the definitive treatment of OPC. NRG HN004 was a phase II/III trial that randomized cisplatin-ineligible patients with locally advanced HNSCC to RT plus cetuximab versus RT plus durvalumab, a PD-L1 inhibitor. Patients with favorable-risk HPV-associated OPC were notably excluded. The study enrolled 190 patients but was closed after planned interim futility analysis due to higher rates of locoregional failure in the durvalumab arm, with no signal toward improved PFS.[125] The phase II PembroRad trial randomized 133 cisplatin-eligible patients with locally advanced HNSCC (majority with OPC) to pembrolizumab plus RT versus cetuximab plus RT and demonstrated no difference in survival outcomes between the arms, though notably less toxicity in the pembrolizumab arm.[126] Further investigation into the combination of immunotherapy and RT in the definitive treatment setting is necessary prior to integration into routine clinical practice.

Additional novel targeted agents, such as DNA-dependent protein kinase inhibitors, antagonists of inhibitor of apoptosis proteins, and second mitochondria-derived activator of caspases mimetics, have been and are being actively investigated in clinical trials in both the cisplatin-eligible and cisplatin- ineligible patient populations. These therapies have not yet been integrated into the standard of care.[127,128]

Targeted Agents in Combination With Cytotoxins and Radiation Therapy

Patients with OPC comprised 70% of those enrolled onto RTOG 0522, which compared two concurrent cycles of 100 mg/m^2 cisplatin and accelerated RT to 72 Gy with or without cetuximab. The combination of cisplatin, cetuximab, and RT did not improve LRC, DFS, or OS and was associated with increased toxicity.[129] The phase III GORTEC 2007-01 trial compared cetuximab and RT to carboplatin/5-FU plus cetuximab and RT for patients with locally advanced HNSCC (>60% OPC) and demonstrated significantly improved PFS and LRC rates at 3 years with the addition of chemotherapy. However, toxicity was increased with chemotherapy, and there was no difference in OS. No differences in outcome were seen as a function of HPV status for either of these trials. Based on these data, the addition of cetuximab to CRT in the treatment of locally advanced OPSCC is not recommended.[130]

The phase III JAVELIN Head and Neck 100 study randomized 697 patients with locally advanced HNSCC (majority with OPC) to standard CRT (70 Gy with bolus cisplatin) plus concurrent and adjuvant avelumab versus placebo. The addition of the PD-L1 inhibitor avelumab failed to improve PFS compared to placebo (HR 1.21, 95% CI 0.93-1.57, favoring placebo, P = .92). This finding was independent of HPV status.[131] KEYNOTE-412 is a similar phase III study randomizing patients with locally advanced HNSCC to CRT plus pembrolizumab versus CRT plus placebo.[132] Preliminary unpublished findings have not demonstrated a statistically significant benefit to pembrolizumab in terms of event-free survival. These findings highlight that more research into the optimal

integration of immunotherapy and other targeted agents into the definitive treatment of patients with locally advanced OPC is necessary prior to adopting them as standard therapy.

DEFINITIVE RADIATION THERAPY SIMULATION, TREATMENT PLANNING, AND TECHNIQUES

Radiation Therapy Simulation

Patients should undergo CT-based simulation to allow for optimal RT planning. Low osmolar iodinated contrast should be administered to optimize the distinction between vascular structures and LNs. Patients are positioned supine with neck gently extended, with a rigid head-holder cradling the posterior calvarium. The shoulders should be positioned as caudally as possible to allow adequate exposure of the neck. This can be achieved with either shoulder-pulls, other commercially available devices, or a combination of the two. Tongue immobilization can be useful for patients with pathologic involvement of the oral tongue. Bite-blocks are also useful as they often elevate the hard palate with its minor salivary glands. Dental amalgam can obscure the quality of the images; CT artifact–reducing algorithms can assist in this regard, as can custom dental trays or putty molds.

The head should be immobilized with a thermoplastic mask. Care should be taken to ensure that the mask is tight enough around the nose, chin, and forehead to inhibit movement. Images should be taken from above the calvarium to the carina to ensure appropriate volumes can be drawn. CT slice thickness should be no greater than 3 mm. The addition of metabolic imaging and MRI has been found to be complementary for gross tumor volume (GTV) delineation.[133]

Radiation Therapy Volumes

Definitive RT volumes for patients with OPC are based on ICRU 50. The GTV includes all known primary and cervical LN tumor extension based on clinical, endoscopic, and imaging findings. The GTV is usually expanded to include a margin for microscopic extension, forming the clinical target volume (CTV). Current international consensus guidelines specify an expansion of 5 mm from the GTV to form the high-risk CTV_primary and 10 mm to form the low-risk CTV_primary. Other anatomic areas at risk for occult microscopic spread based on the tumor location and extent are usually encompassed in the low-risk CTV_primary.[35]

Consensus guidelines for contouring the clinically node-negative neck have been published and endorsed by international head and neck cancer cooperative groups.[134] These guidelines are clinically useful aids for delineating specific nodal treatment volumes. Levels II to IV in the clinically node-negative neck would typically be covered in the low-risk CTV for patients with OPC. Similar guidelines have been proposed for clinically node-positive and postoperative patients.[69,135] A 3- to 5-mm margin on the nodal GTV, depending on the extent of adjacent structure involvement, is sufficient for the high-

risk nodal CTV. Specific recommendations for node-positive patients include coverage of the supraclavicular fossa for patients with level IV or Vb lymphadenopathy, coverage of the retrostyloid space for patients with level II lymphadenopathy, coverage of the retropharyngeal nodes in the setting of high level II lymphadenopathy and/or primary tumors extending into the nasopharynx or pterygoid region, and CTV coverage of the entire thickness of muscles invaded by pathologic lymphadenopathy. Pathologic lymphadenopathy spanning adjacent levels should trigger inclusion of the full extent of both levels in the CTV. One nodal region beyond those pathologically involved is typically included in the low-risk volume. For example, a patient with pathologic lymphadenopathy in level II would have level IB included in the low-risk treatment volume.

CTVs are expanded to account for organ motion and setup uncertainty ideally based on institution-specific data in order to form the planning target volume (PTV). For patients with OPC, movement of the base of tongue, which can be significant particularly with swallowing, should be considered when determining an appropriate PTV margin. The expansion from CTV to PTV should also account for imaging methods used to assess daily setup. In general, if more frequent image guidance is performed, less margin should be needed for setup uncertainty. A 3- to 5-mm CTV to PTV expansion, if frequent kilovolt image or cone-beam CT guidance is utilized, is relatively standard practice.[136] Representative contours for a patient with locoregionally advanced OPSCC are shown in Figure 51.1.

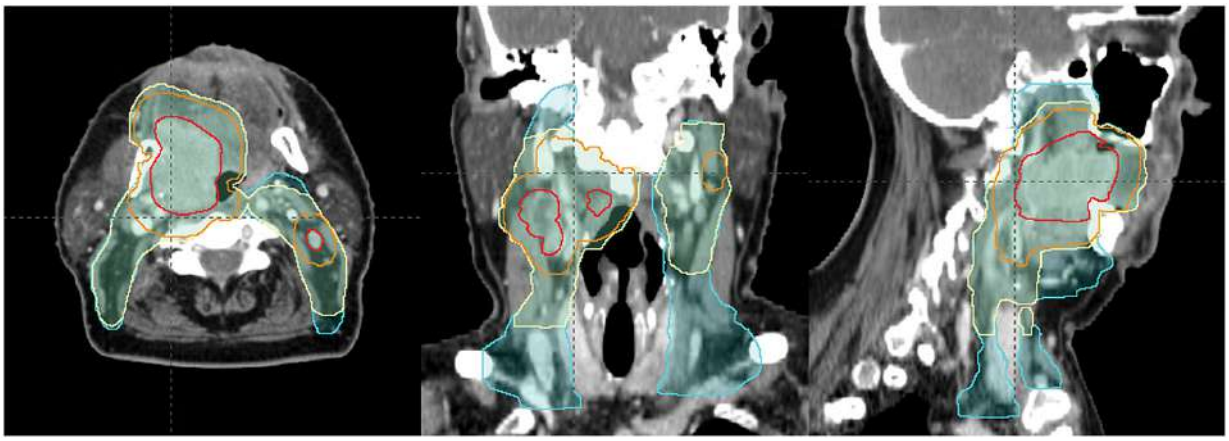

FIGURE 51.1 Representative computed tomography (CT)-based contours for a patient with cT4N2M0 human papillomavirus–related squamous cell carcinoma of the right oropharynx. Axial (left), coronal (middle), and sagittal (right) images of contrast-enhanced neck CT for radiation planning with gross tumor volume in red, low-risk planning target volume (PTV) in cyan, intermediate-risk PTV in yellow, and high-risk PTV in orange.

Indications for Ipsilateral Radiation Therapy

For well-lateralized early-stage tonsillar cancers with no involvement of the base of tongue and minimal involvement of the soft palate (>1 cm margin between the medial extent of tumor and midline), the contralateral neck can be excluded from the CTV, which

will significantly limit the exposure of the contralateral parotid, submandibular gland, and pharyngeal musculature.[32] Patients with contralateral cervical LN involvement usually have extensive involvement of ipsilateral cervical LNs[137] or tumors approaching or crossing the midline. Surgical series also demonstrate that the risk of contralateral cervical LN involvement correlates with primary tumor size and is thus more common in T3/T4 tumors.[138,139] An analysis of patients with mostly T1-2 (79%) and N0-1 (88%) tonsillar cancer who underwent resection of their primary tumors often with ipsilateral LN dissection showed that only 5% of patients progressed in the contralateral neck.[140]

A large series of patients undergoing definitive RT to a tonsil primary and only the ipsilateral neck demonstrated 0% progression in the contralateral neck in patients with T1 tumors and only 1% to 2% progression in those with T2 tumors. In the few patients with T3 tumors, contralateral nodal progression was 3% to 10%.[141,142] Further analysis of these series shows that contralateral nodal progression was associated with both base of tongue and soft palate involvement (13%), T3 stage (10%), and specifically involvement of the midline of the soft palate (16.5%). Thus, omission of RT to the contralateral neck in select patients with well-lateralized T1-2N0-1 tonsillar cancers should be strongly considered. Importantly, these excellent outcomes appear to be independent of tumor HPV status.[143]

Studies evaluating the role of ipsilateral treatment in the context of N2b disease and concurrent CRT are relatively sparse. An analysis of patients with tonsil cancer treated at MD Anderson Cancer Center from 1970 to 2007 included only 3 patients who received concurrent systemic therapy for N2b disease. In these patients, there was no contralateral neck progression.[144] An analysis of 20 patients with locoregionally advanced tonsillar cancer with N2b nodal disease, 18 of whom received concurrent CRT, demonstrated high rates of primary and nodal disease control along with a low risk of contralateral nodal progression. A caveat to this study is that all patients were staged with PET/CT and most patients underwent resection of the primary (80%) and/or neck dissection (70%).[145] Another retrospective analysis that included 41 patients undergoing ipsilateral RT for tonsillar cancer with N2b disease (88% receiving concurrent CRT and 98% staged by PET/CT) reported no contralateral neck recurrences.[146] At this time, omission of RT to the contralateral neck remains controversial in the setting of N2b or more advanced nodal disease for well-lateralized tonsillar cancer.[147]

Intensity-Modulated Radiation Therapy

IMRT has been widely adopted for the treatment of HNSCC,[148] due to its ability to minimize normal organ exposure to RT. This is particularly important for patients with OPC as pharyngeal constrictor dose and parotid dose are associated with dysphagia[149] and xerostomia,[150] respectively.

The impact of IMRT on reduction of xerostomia has been established by numerous phase II and III trials. One notable phase III randomized trial is PARSPORT, in which patients with T1-4N0-3 HNSCC (without disease involving the parotid glands) who were recommended to receive either definitive or adjuvant RT without concurrent chemotherapy were randomized 1:1 to receive either conventional RT (parallel-opposed

3D technique) or IMRT. The primary end point was the proportion of patients with grade 2 or worse xerostomia at 12 months, assessed via the late effects of normal tissues (LENT SOMA) scale.[150] Six centers in the United Kingdom recruited 94 patients (47 in each arm). Eighty-five percent of participants had OPC. IMRT significantly reduced the mean RT dose to the ipsilateral (47.6 vs 61 Gy) and contralateral (25.4 vs 61 Gy) parotid glands ($P < .0001$). At 12 months, only 38% of patients treated with IMRT had grade 2+ xerostomia compared to 74% in the conventional RT arm, independent of other treatment and clinical characteristics. Locoregional progression and OS were similar between the two arms. Other trials have reported a similar magnitude of reduction in late xerostomia with IMRT when concurrent chemotherapy is administered as well.[151] Ongoing cooperative group trials recommend limiting the mean dose to the parotids to ≤26 Gy. Furthermore, the mean dose to the submandibular gland is recommended to be limited to ≤39 Gy.

Large retrospective studies have demonstrated significant associations between treatment with IMRT and shorter duration of treatment-related feeding tube use.[152] Many studies have attempted to correlate dosimetric parameters with functional swallowing consequences following RT or CRT. Consensus on dosimetric parameters does not exist as the studies to date have all been retrospective and their findings are not completely concordant. In general, dose to the larynx and pharyngeal constrictors should be as low as possible to limit the risks of aspiration, feeding tube dependence, and stricture.

Intensity-Modulated Radiation Therapy Treatment Strategies

With the advent of IMRT, a simultaneous integrated boost (SIB) technique, whereby different doses are delivered to different targets simultaneously within the same treatment fraction, was investigated in the treatment of patients with OPC. This technique is intended to increase the specificity of tumor RT, decreasing dose to normal tissues. There can be greater heterogeneity of the dose distribution, resulting in larger hot spots. The alternative technique is sequential boost IMRT, whereby typically two plans are created, a low-dose plan that encompasses elective volumes and a high-dose plan that boosts gross disease with margin. The boost plan is typically delivered sequentially, after completion of the initial lower dose plan. In general, when treating definitively with conventionally fractionated RT, a sequential boost IMRT course involves 44 to 50 Gy in 2 Gy daily fractions to the elective lower risk volume, followed by a 20 to 26 Gy boost to the high-risk volume, to allow for a total dose of 70 Gy to gross disease. An SIB plan allows for delivery of a similar biologically effective dose (BED) to gross disease, while utilizing a range of alternative doses per fraction to elective volumes (typically 54-63 Gy as 1.6-1.8 Gy per fraction). A meta-analysis of seven trials inclusive of 1,049 patients with HNSCC demonstrated no differences in survival outcomes or grade 3 or higher toxicity in patients treated with definitive SIB-IMRT versus sequential boost IMRT plans.[153] Either of these IMRT techniques is thus appropriate, and the use depends on provider/institutional experience and preference.

Proton Beam Radiation Therapy

The use of proton beam therapy (PBT) in the definitive or adjuvant treatment of HNSCC is an area of active clinical investigation, with the relevant literature currently consisting primarily of small institutional reports and nonrandomized studies. Given its unique dosimetric characteristics, PBT is hypothesized to minimize dose to normal structures without compromising target coverage, thereby maintaining oncologic outcomes while limiting toxicity when compared to IMRT. Preliminary data are generally supportive of this hypothesis. A case-matched control analysis of patients with OPC demonstrated significantly lower doses to the oral cavity, hard palate, larynx, mandible, and esophagus in PBT plans compared to IMRT plans.[154] Various single-institution series have demonstrated decreased changes in taste and appetite, mucositis, pain, and narcotic requirements in the subacute treatment-recovery phase, as well as decreased feeding tube dependency, hospitalizations, late xerostomia, and severe weight loss in patients with OPC treated with PBT in comparison to patients treated with IMRT.[155-158] In addition, single-institution noncomparative prospective studies have demonstrated encouraging survival rates and disease control in patients with OPC treated with PBT, in both the definitive and adjuvant settings.[159,160] Currently, institutions with significant experience with PBT may consider its use for particularly challenging OPC cases when it is difficult to meet normal tissue constraints with IMRT. However, routine utilization is limited pending high-level data regarding its efficacy in comparison to IMRT. Results from prospective studies, such as a phase II/III trial at MD Anderson Cancer Center randomizing patients with stage III and IVB OPSCC to definitive PBT- versus IMRT-based CRT (NCT01893307), will help guide future management.

DEINTENSIFICATION OF THERAPY FOR PATIENTS WITH HUMAN PAPILLOMAVIRUS–POSITIVE OROPHARYNGEAL CANCER

Given the generally superior outcomes of patients with HPV-associated OPC, in combination with the potential for significant acute and late treatment-related toxicity, strategies to deintensify curative-intent treatment for patients with both early-stage and locoregionally advanced disease while maintaining favorable oncologic outcomes are being actively evaluated. Some studies have identified higher risk subgroups who may be less amenable to deintensification, given overall poorer oncologic outcomes, such as patients with a significant smoking history or patients with very advanced disease (T4, N3, matted lymphadenopathy).[161-164] With these few exceptions, many patients with HPV-associated OPC are considered potential candidates for treatment deintensification. In this regard, many different approaches have been investigated in the prospective arena with selected studies in Table 51.7.

TABLE 51.7 SUMMARY OF SELECTED RANDOMIZED THERAPEUTIC DE-ESCALATION TRIALS FOR P16-POSITIVE OROPHARYNGEAL CANCER

Trial	Patient Population[a]	*N*	Treatment Groups	Key Results
RTOG 1016[100]	cT1-T2N2a-N3M0 or cT3-T4N0-N3M0; age ≥ 18; Zubrod PS 0-1; p16+ IHC	849	Accelerated RT (70 Gy/35 fx in 6 wk) with concurrent cetuximab vs concurrent bolus cisplatin	• 5-y PFS: 63.7% (cetuximab) vs 78.4% (cisplatin); HR 1.72 (95% CI 1.29-2.29; *P* = .0002) • 5-y OS: 77.9% (cetuximab) vs 84.6% (cisplatin); HR 1.45 (1one-sided 95% upper CI 1.94; *P* = .5056 for noninferiority; one-sided log-rank *P* = .0163); failed to meet noninferiority criteria
De-ESCALaTE HPV[121]	cT3N0M0-T4N0M0 or cT1N1M0-T4N3M0; <10 pack-year smoking history; age >18; ECOG PS 0-1; p16+ IHC	334	RT (70 Gy/35 fx in 7 wk) with concurrent bolus cisplatin vs cetuximab	• 2-y recurrence: 6.0% (cisplatin) vs 16.1% (cetuximab); HR 3.4 (95% CI 1.6-7.2 *P* = .0007) • 2-y OS: 97.5% (cisplatin) vs 89.4% (cetuximab); HR 5.0 (95% CI 1.7-14.7; *P* = .0012)
TROG 12.01[122]	Stage III (excluding cT1-2N1) or stage IV (excluding T4 and/or N3 and/or N2b-c if >10 pack-year smoking history); age ≥18; ECOG PFS 0-1; p16+ IHC	189	RT (70 Gy/35 fx in 7 wk) with concurrent cisplatin (40 mg/m^2 weekly) vs cetuximab	• 3-y PFS: 93% (cisplatin) vs 80 (cetuximab); HR 3.0 (95% CI 1.2-7.7; *P* = .015) 3-y OS: 98% (cisplatin) vs 96% (cetuximab); HR 2.3 (95% CI 0.4-12.7; *P* = .32)
NRG HN002[165]	cT1-2N1-N2bM0 or cT3N0-N2bM0; ≤10 pack-year smoking history; age ≥18; Zubrod PFS 0-1; p16+ IHC	306	RT (60 Gy/30 fx in 6 wk) with concurrent weekly cisplatin (CRT) vs accelerated RT alone (60 Gy/30 fx in 5 wk)	• 2-y PFS: 90.5% (CRT) vs 87.6% (accelerated RT alone); HR 0.67 (95% CI 0.36-1.24; *P* = .20); null hypothesis of 2-y PFS ≤85% rejected • 2-y LRF: 3.3% (CRT) vs 9.5% (accelerated RT alone); HR 0.39 (95% CI 0.17-0.90; *P* = .02) • 2-y OS: 96.7% (CRT) vs 97.3% (accelerated RT alone); HR 0.95 (95% CI 0.31-2.95; *P* = .93)
ECOG-ACRIN 3311[166]	Stage III-IVA with cT1-T2 p16+ OPC amenable to TORS; age ≥18; ECOG PS 0-1; p16+ IHC	395	• Low risk: observation, no adjuvant RT • Intermediate risk (margins <3 mm, N1-N2 with ≤1 mm ENE, ≤4 LN involved): randomized to 50 Gy/25 fx (5 wk) vs.	• Low-risk 2-y PFS: 96.9% (90% CI 91.9%-100%) • Intermediate-risk 2-y PFS: 94.9% (90% CI 91.3%-98.2%) (50 Gy) vs 96.0% (90% CI 92.8%-99.3%) (60 Gy)

Trial	Patient Population[a]	*N*	Treatment Groups	Key Results
			60 Gy/25 fx (6 wk), not powered for comparison • High risk: adjuvant RT (66 Gy) with weekly cisplatin	• High-risk 2-y PFS: 90.7% (90% CI 86.2%-95.4%) • Low-risk 2-y OS: 100% • Intermediate-risk 2-y OS: 99% (90% CI 93%-100%) (50 Gy) vs 98.1% (90% CI 95.9%-100%) (60 Gy) • High-risk 2-y OS: 96.3% (90% CI 93.3%-99.3%)

CI, confidence interval; CRT, chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; ENE, extranodal extension; fx, fractions; HR, hazard ratio; IHC, immunohistochemical; LN, lymph node; LRF, locoregional failure; OPC, oropharyngeal cancer; OS, overall survival; PFS, progression-free survival; PS, performance status; RT, radiation therapy; TORS, transoral robotic surgery.

[a]All staging based on AJCC seventh edition.

One approach to deintensification, given the toxicity of cisplatin, has been to investigate alternative concurrent systemic therapy agents. Three randomized phase III trials have shown that RT with concurrent cetuximab is inferior to RT with concurrent cisplatin in the treatment of HPV-associated OPC. RTOG 1016 was a noninferiority trial that randomized 846 patients with locally advanced HPV-associated OPC to accelerated RT (70 Gy/35 fractions over 6 weeks) with concurrent cetuximab versus bolus cisplatin. The cetuximab arm not only failed to meet the criteria for noninferiority based on 5-year OS (77.9% for cetuximab vs 84.6% for cisplatin) but also had significantly worse PFS and locoregional failure rates.[100] The phase III De-ESCALaTE HPV trial randomized 334 patients with low-risk (nonsmokers or patients with <10 pack-year history) HPV-associated OPC to RT (70 Gy in 35 fractions, once daily) plus bolus cisplatin versus RT plus weekly cetuximab. Patients in the cetuximab arm had significantly lower 2-year OS (89.4% vs 97.5%, HR 5.0, $P = .001$) and higher 2-year recurrence rates (16.1% vs 6.0%, HR 3.4, $P = .0007$) and additionally did not experience reduced toxicity.[121] The TROG 12.01 trial randomized 189 patients with low-risk HPV- associated OPC to RT (70 Gy in 35 fractions, once daily) plus weekly cisplatin versus RT plus weekly cetuximab. This trial similarly demonstrated that patients receiving cetuximab had inferior failure-free survival (80% vs 93% at 3 years, $P = .015$), with no benefit in terms of reduced toxicity.[122] Cetuximab should thus not be utilized for the purpose of deintensification in the treatment of cisplatin-eligible patients with HPV-associated OPC. Nivolumab is being investigated as an alternate agent in NRG HN005, as discussed below.

Another approach under investigation is response-adapted therapy. ECOG 1308 was a single-arm study that investigated de-escalation of RT dose based on response to induction chemotherapy. Patients with a complete response to induction chemotherapy (three cycles of cisplatin, paclitaxel, and cetuximab) received 54 Gy with concurrent cetuximab and those with a partial response received 69.3 Gy with concurrent cetuximab. Patients treated with the lower dose of 54 Gy had 2-year PFS and OS rates of 80% and 93%, respectively.[167] CCRO-022 was a single-arm phase II trial with a similar study design,

namely, modifying definitive RT dose based on response to an induction chemotherapy regimen, in this case carboplatin and paclitaxel. Complete or partial responders (55%) received 54 Gy with concurrent paclitaxel and nonresponders received 60 Gy, with high 2-year PFS of 92% in the cohort.[168] Others have deintensified therapy in patients with a favorable response to induction chemotherapy by significantly shrinking or eliminating elective nodal RT volumes. In one study, following an induction regimen consisting of cisplatin, paclitaxel, and cetuximab ± everolimus, patients with >50% reduction in the sum of tumor diameters were classified as having a "good response" (GR). These patients were prescribed standard-dose CRT to gross disease only, while those with a response not meeting the predefined threshold ("nonresponse" [NR]) received standard-dose CRT to gross disease as well as the next elective nodal station at risk. There was a trend toward improved PFS in patients with GR versus NR (86% vs 68.7%, P = .086).[169] Among patients with HPV-related OPC with GR, 2-year PFS and OS were 93.1% and 92.1%, respectively, indicating that this is a potentially promising treatment strategy pending further investigation. Another phase II trial enrolling patients treated with TORS and neck dissection omitted primary site coverage for patients with favorable pathologic features, targeting only the at-risk neck, and reported excellent LRC and survival rates at 2 years, as well as promisingly low toxicity rates.[170] There are ongoing investigations into deintensification of RT dose based on mid-treatment imaging biomarkers as well, with one phase II study de- escalating patients with early-stage p16-positive OPC from 70 Gy/35 fractions to 54 Gy/27 fractions if certain interim FDG-PET parameters[171] were met. Initial acute toxicity data were promising, and we await further data on associated oncologic outcomes from this study and others utilizing novel functional imaging platforms.[172,173]

Another de-escalation strategy is simply reducing RT and/or chemotherapy dose in the setting of concurrent CRT. In a single-arm phase II study, patients with intact cT0-T3N0-N2c HPV-associated OPC were treated with definitive intent to 60 Gy with concurrent weekly cisplatin (30 mg/m^2). The primary end point was a pathologic complete response (pCR) rate, measured based on mandatory post-CRT biopsy of the primary site as well as dissection of involved LN levels, irrespective of imaging response. Remarkably, 86% of patients (37/43) had a pCR, and toxicities were decreased compared to historical controls.[174] In addition, 3-year LRC was 100%, and 3-year OS was 95%.[175] Given that a major critique of this trial was that confirmatory neck dissection could have been therapeutic, another single-arm phase II trial was initiated, testing the same de-escalation regimen of 60 Gy/6 weeks with concurrent weekly low-dose cisplatin, with a primary end point of 2-year PFS. One hundred and fourteen patients were enrolled, with excellent 2-year PFS of 86%.[176] NRG HN002 was a randomized phase II trial evaluating the efficacy of reduced-dose RT with weekly cisplatin versus accelerated reduced-dose RT without cisplatin (60 Gy/6 weeks with cisplatin vs 60 Gy/5 weeks, with 6 fractions per week RT alone) for patients with T1-2N1-N2b, or T3N0-N2b p16-positive OPC, per AJCC seventh edition staging, and a minimal smoking history (≤10 pack-years). In all, 306 patients were randomized, and the prespecified thresholds for the primary end points of 2-year PFS and swallowing function at 1 year were met by patients in the CRT arm, despite higher

associated rates of grade 3+ acute toxicity.[165] NRG HN005 was subsequently planned, randomizing a similar patient population with OPC to 70 Gy/6 weeks with bolus cisplatin versus 60 Gy/6 weeks with bolus cisplatin (winning arm of HN002) versus 60 Gy/5 weeks with concurrent nivolumab, again with co-primary end points of PFS and swallowing function. Based on the results of a scheduled interim futility analysis, experimental arm 2 (60 Gy with cisplatin) was closed due to not meeting the noninferiority threshold. Accrual to the other two arms is ongoing. Pending further randomized clinical trial data, it is not advisable to consider de-escalation of RT dose in the definitive setting for patients with p16-positive OPC unless they are enrolled in a clinical trial.

As discussed previously, minimally invasive surgical techniques such as TORS are being used increasingly for OPC. There is interest in the utilization of TORS specifically to facilitate deintensification of adjuvant RT dose. ECOG-ACRIN 3311 was a phase II study in which patients with stage III and IVa HPV-associated OPC underwent TORS followed by risk-adapted adjuvant therapy based on pathologic risk assessment. If patients met the following eligibility criteria, they were considered "intermediate risk" and randomized to 50 Gy versus 60 Gy of adjuvant RT without chemotherapy: close margins (<3 mm), N1-N2 with ≤1 mm ENE, up to four positive nodes. There were additional nonrandomized arms in the study: In the "low-risk" arm, patients with T1-T2 disease resected with negative margins (>3 mm) and N0-N1 disease without ENE were observed without further treatment. In the "high-risk" arm, patients with positive margins, >1 mm ENE, and/or >4 pathologically involved LNs received 66 Gy with concurrent weekly cisplatin (40 mg/m^2). The patients were additionally stratified based on a smoking history. The primary end point was 2-year PFS, and the investigators reported rates of 94.9% versus 96.0% for patients receiving reduced-dose (n = 100) versus standard-dose PORT (n = 108). An exploratory comparison indicated that PFS did not differ significantly between these arms, though the study was not powered for this comparison.[166] Notably, 31% of patients enrolled on this study required adjuvant CRT based on high-risk pathologic features, highlighting the importance of careful patient selection for TORS in order to avoid trimodality therapy. A phase III comparison of transoral surgery plus reduced-dose adjuvant RT versus definitive CRT for this patient population is planned.

MC1273 was a phase II trial that investigated aggressive adjuvant RT dose deintensification from 60 to 66 to 30 to 36 Gy for patients with HPV-associated OPC. Eligible patients had AJCC seventh edition stage III and IV disease and a smoking history of ≤10 pack-years. Patients had to undergo margin-clearing surgery and either a high-risk pathologic feature (ENE) or one or more intermediate-risk factors such as PNI, LVI, two or more positive LNs, ≥T3 primary tumor, or >3 cm LN. Patients without ENE received 30 Gy in 1.5 Gy fractions twice daily to the primary site and dissected and elective nodal volumes with concurrent docetaxel, while patients with ENE received an additional SIB of 36 Gy in 1.8 Gy fractions only to the nodal level with ENE. Eighty patients were enrolled, and LRF was 0% at 2 years post-treatment for patients without ENE versus 7% for patients with ENE.[177] A follow-up phase III study (NCT02908477) is underway.

While data are promising with several different approaches, therapeutic deintensification for patients with HPV-associated OPSCC remains experimental and should not be routinely considered off-trial pending results from randomized phase III trials.

POST-TREATMENT MANAGEMENT AND SURVEILLANCE

Following definitive therapy for OPC, patients should undergo routine clinical evaluation. Current guidelines recommend examination every 1 to 3 months for the first year post-therapy, every 2 to 6 months in the second year post-therapy, every 4 to 8 months in years 3 to 5 post-therapy, and annually thereafter. The frequency of follow-up within the first 2 years after completion of therapy coincides with the likelihood of recurrence within that interval. Given that a common side effect of RT to the neck is hypothyroidism, thyroid-stimulating hormone should be evaluated every 6 to 12 months in patients who have received RT to the bilateral neck. In addition, RT to the neck is associated with an increased risk of carotid artery stenosis and stroke; thus, routine carotid artery ultrasound screening for certain high-risk patients should be considered.[178,179] Speech/swallow and nutritional evaluation should be initiated or continued as clinically indicated, and smoking and alcohol consumption should be queried and addressed as needed as well.

Patients with node-positive and/or locoregionally advanced OPC should undergo imaging to assess treatment response 3 to 4 months after completion of treatment. A radiographic complete response on contrast-enhanced neck CT, defined as nonenhancing, nonnecrotic nodal tissue <1.5 cm, is associated with excellent long-term disease control in the neck, and no further therapy is needed.[180] Surveillance CT imaging of the primary site does not add additional information to physical/fiberoptic examination and should not be routinely performed.[181]

PET/CT is often the sole imaging modality utilized following the completion of RT or CRT. A prospective study by Porceddu et al helped to clarify the role of ^{18}F-FDG-PET–guided management following definitive RT/CRT for patients with node-positive HNSCC. Per the study protocol, 112 node-positive patients, based on pretreatment PET/CT (74% with OPC), underwent PET/CT approximately 12 weeks post-therapy. The results revealed that a negative PET scan at 12 weeks post-RT/CRT was associated with no isolated nodal progression, independent of the presence of residual CT abnormalities in the neck.[182] The negative predictive value (NPV) of PET was 98.1% (95% CI, 93.2%-99.8%) compared to 96.8% for CT (95% CI, 88.8%-99.6%). More importantly, however, false-positive readings were seen in only 1.8% of PET scans compared to 38% of diagnostic CT scans, resulting in a positive predictive value (PPV) of 77.8% for PET/CT and 14% for CT. When the analysis was restricted to p16-positive patients, the results were similar, with NPV of 98.2% (95% CI, 90.4%-100%) and PPV of 66.7% (95% CI, 9.4%-99.2%) for PET. Long-term follow-up of these patients demonstrated that PET-directed management resulted in >90% of patients being spared a neck dissection (previously standard of care), with only one patient experiencing a neck recurrence following initial metabolic resolution.[183] A randomized study has since been reported

comparing the utility of post-CRT PET/CT-based neck surveillance versus planned neck dissection in patients with N2 or N3 nodal disease. The trial accrued 564 patients (282 in each arm), 84% of whom had OPC with 75% of tumors tested being p16 positive. Patients assigned to the PET/CT-based neck surveillance arm had 2-year OS of 84.9% (95% CI, 80.7%-89.1%) compared to 81.5% (95% CI, 76.9%-86.3%) in the planned neck dissection group. Furthermore, there were no differences in 2-year LRC: 91.9% (95% CI, 88.5%-95.35) in the surveillance group and 91.4% (95% CI, 87.8%-95.0%) in the planned neck dissection group.[184] Finally, PET/CT-based surveillance was more cost-effective overall, with estimated savings of $2,190 per patient. This is an important consideration, given the substantial financial toxicity burden experienced by patients with OPC undergoing definitive treatment.[185] Given these data, PET/CT-guided management after definitive RT-based treatment should be the standard approach, with observation after a complete clinical response, repeat PET/CT in 4 to 6 weeks after equivocal findings, and consideration of salvage surgical resection if concern for residual FDG-avid disease. Notably, multiple prospective studies have determined that the presence of residual FDG activity can be difficult to interpret when PET/CT is obtained earlier than 12 weeks post-treatment, with treatment-related inflammation resulting in higher rates of false positivity. Therefore, careful timing of post-treatment imaging evaluation is paramount.[186] There is no clear evidence to support continued routine imaging surveillance in patients with a complete clinical response on post-treatment PET/CT; further imaging during the follow-up interval is prompted based on clinical concern and/or physical examination findings, as patients with clinically detected recurrence have been shown to have similar survival outcomes as patients with recurrences detected by subsequent surveillance imaging.[187]

Quantifying levels of plasma circulating tumor DNA (ctDNA), including circulating tumor HPV DNA (ctHPV DNA) for HPV-related disease, is a novel approach to sensitive detection of minimal residual disease and/or recurrences. Prospective studies have demonstrated high PPV and NPV for ctHPV DNA-based surveillance, with the potential for early identification of disease recurrence in patients with HPV-associated OPSCC.[188,189] While ctDNA-based surveillance is currently not standard of care, this is an area of active investigation.

TREATMENT OF RECURRENT AND METASTATIC OROPHARYNGEAL CANCER

Systemic Therapy for Recurrent and Metastatic Oropharyngeal Cancer

For many years, the standard systemic therapy for patients with recurrent or metastatic OPC was platinum-based chemotherapy. Single-agent cisplatin (100 mg/m2) has been shown to improve OS compared to best supportive care.[190] Cisplatin was also shown to be superior to single-agent methotrexate.[191] Multiple randomized studies investigated combination cisplatin-based regimens. The combination of cisplatin (100 mg/m^2) with 5-FU (1000 mg/m^2/d) demonstrated improved response rates (32% vs 17%), but not improved median survival (5.7 months) over cisplatin alone.[192] For OPC specifically, a

planned subset analysis of a phase III trial comparing cisplatin and pemetrexed to cisplatin and placebo demonstrated that patients receiving the combination regimen had improved OS (9.9 vs 6.1 months, $P = .002$) and improved PFS (4 vs 3.4 months $P = .047$).[193] The addition of EGFR inhibitors to platinum-based chemotherapy was shown in the phase III EXTREME study to improve OS (7.4 months with bolus cisplatin/5-FU or carboplatin/5-FU vs 10.1 months with the combination of platinum, 5-FU, and cetuximab); notably, a large proportion of enrolled patients had recurrent or metastatic OPC.[194] Immune checkpoint inhibitors have significantly altered the landscape for patients with recurrent and metastatic HNSCC. KEYNOTE-048 was a phase III study randomizing 882 patients with previously untreated recurrent or metastatic HNSCC (majority with OPC) to pembrolizumab alone, pembrolizumab plus chemotherapy (platinum and 5-FU), or cetuximab plus chemotherapy (per the EXTREME study). The study demonstrated improved OS with pembrolizumab plus chemotherapy versus the winning EXTREME arm (13 vs 10.7 months, $P = .003$), establishing this regimen as an appropriate first-line treatment for patients with recurrent or metastatic OPSCC. The results also supported the use of pembrolizumab monotherapy in the first-line setting for patients with PD-L1–positive tumors, based on an OS benefit in that subgroup when compared to the EXTREME arm.[195] The OS benefits of pembrolizumab with or without chemotherapy over cetuximab with chemotherapy notably persisted with long-term (4-year) follow-up.[196]

In the platinum-refractory setting, immune checkpoint inhibitors are also standard options for patients with recurrent and metastatic HNSCC. The CheckMate 141 study randomized 361 patients (35.5% with pharyngeal cancers) to nivolumab 3 mg/kg every 2 weeks or the investigator's choice of 40 to 60 mg/m^2 methotrexate, 30 to 40 mg/m^2 docetaxel, or 250 mg/m^2 weekly cetuximab after a loading dose of 400 mg/m2. Patients treated with nivolumab had significantly longer median survival (7.5 vs 5.1 months) and 1-year OS (36% vs 16.6%). In an exploratory analysis, p16-positive patients who received nivolumab had longer median survival as well (9.1 vs 4.4 months, HR 0.56, 95% CI: 0.32-0.99).[197] The phase III KEYNOTE-040 trial additionally randomized 495 patients with platinum-refractory recurrent or metastatic HNSCC to receive pembrolizumab or investigator's choice systemic therapy (methotrexate, docetaxel, or cetuximab) and demonstrated significantly improved OS in the pembrolizumab arm (8.4 vs 6.9 months, HR 0.80, $P = .016$). The results stratified based on tumor PD-L1 status revealed that the OS benefit is limited to patients with PD-L1–positive tumors.[198] Either nivolumab or pembrolizumab is thus first-line option for patients with platinum-refractory recurrent or metastatic OPC.

Reirradiation for Recurrent or Second Primary Disease

For the subgroup of patients with recurrent locoregionally confined OPC, surgical resection is recommended, although this is feasible only in a small proportion of patients.[199] Following surgery[200] in those with high-risk pathologic features or in those who are not surgical candidates,[201] a second course of full-dose CRT has been shown to result in long-term survival in approximately 20% of patients. Patients who are able to

undergo surgery prior to reirradiation and chemotherapy-naïve patients who are treated with more intensive regimens of CRT have improved outcomes. Due to the high risk of significant normal tissue toxicity (including up to a 15% risk of fatal carotid artery rupture), patients undergoing a second course of conventionally fractionated CRT should be managed at experienced centers.[202] It is unknown if a repeat course of conventionally fractionated CRT is superior to chemotherapy alone for these patients, as a phase III comparison of these modalities failed to accrue. The ongoing phase II ECOG-ACRIN 3191 study, randomizing patients with resected recurrent/second primary HNSCC with high-risk features to repeat conventionally fractionated CRT (60 Gy/30 fractions IMRT or PBT with weekly cisplatin or carboplatin) versus pembrolizumab alone will help to elucidate the benefit of local therapy in addition to modern systemic agents. This trial initially included a third arm of pembrolizumab with conventionally fractionated RT that was closed in 2023.

Stereotactic Body Radiotherapy

There are more robust data supporting the use of SBRT in the reirradiation setting of locoregionally recurrent disease than in the initial definitive treatment setting, though prospective data are still limited. This treatment approach is attractive because it entails a much shorter course compared to repeat full-dose CRT and the potential for less treatment-related toxicity. An early phase I dose escalation trial demonstrated no grade 3 or higher dose-limiting toxicities in 25 patients with previously irradiated HNSCC (24% with OPC) treated with doses up to 44 Gy/5 fractions over 2 weeks. The median time to disease progression was 4 months, and median OS was 6 months.[203] Two phase II trials[204,205] treated patients with recurrent or new primary HNSCC (most with OPC) in a previously irradiated area with SBRT (36-44 Gy/5-6 fractions over 1-2 weeks) and concurrent cetuximab. They reported low rates of grade 3 or higher acute and late toxicities, with a median OS of 10-12 months. Other trials are investigating the use of SBRT with concurrent immunotherapy[206] and/or other targeted agents in the treatment of patients with previously irradiated disease.[207] Reirradiation with SBRT is still overall associated with a relatively high risk of fatal carotid artery rupture. Factors associated with the risk of carotid artery rupture include ≥180 degrees of carotid invasion by tumor, as well as a high maximum carotid dose.[208] Overall, SBRT is a reasonable treatment option for patients with previously irradiated, recurrent OPC, but the decision to treat must be highly individualized, taking into account the location and extent of the recurrent tumor, the interval from the previous course of RT, as well as institutional expertise.

Proton Beam Therapy

As discussed previously, the unique dosimetry of PBT can result in decreased dose to normal tissues, with the Bragg peak allowing for steep dose gradients. There has thus been significant interest in utilizing PBT for reirradiation of HNSCC in an effort to reduce treatment-related toxicity. To date, only retrospective data on definitive PBT reirradiation exist, with high rates of LRC and OS, though again a significant risk of acute and late

grade 3 or higher toxicities, including grade 5 bleeding events.[209,210] An ongoing phase II trial (NCT03164460) is randomizing patients with unresectable previously irradiated recurrent or second primary HNSCC to treatment with SBRT or PBT, with a primary end point of toxicity.

Brachytherapy

Brachytherapy, the application of radioactive materials in close proximity to tumors, was primarily utilized in the pre-IMRT, preconcurrent CRT era as a means to deliver a tumoricidal dose to gross disease while minimizing dose to the mandible. The advent of improved RT planning and delivery techniques, in addition to the recognition that osteoradionecrosis secondary to brachytherapy is significantly underreported, has corresponded to a major decrease in the utilization of brachytherapy for OPC and the resultant limited availability of expertise. There are a few scenarios for which brachytherapy for OPC could be considered, namely, for recurrent disease or in other settings necessitating a highly conformal dose to a target with a very limited extent.[211]

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CHAPTER 52

Hypopharynx

Matthew E. Witek, Jonathan P. Giurintano, Nitika Tripathi, and Paul M. Harari

Hypopharynx cancers are uncommon head and neck (H&N) malignancies with an annual incidence of approximately 3,000 cases per year comprising nearly 3% of all H&N cancers in the United States.[1] Hypopharynx cancer carries one of the poorest prognoses of all H&N subsites owing to patients often presenting with locally advanced disease as well as a high propensity for the development of distant metastases. Hypopharynx cancer is strongly associated with cigarette smoking, and patients diagnosed with this disease often carry significant medical comorbidities that can complicate the successful delivery of aggressive cancer therapy. Multidisciplinary management of patients with hypopharynx cancer requires the collaborative effort of H&N surgeons, radiation oncologists, medical oncologists, radiologists, pathologists, speech and swallow therapists, nutritionists, nurses, and social workers. Advances in surgical and radiation technology techniques have made organ and function preservation more amenable for selected patients with early-stage disease. Treatment of locally advanced disease has increasingly involved nonsurgical approaches with combined radiation and chemotherapy. However, laryngopharyngectomy with neck dissection and risk-adapted adjuvant therapy remains an established approach for motivated patients with very advanced disease. Notwithstanding improvements in radiotherapy (RT) and surgical techniques, new systemic agents, and supportive measures, overall survival remains poor. Future efforts to develop prognostic and predictive biomarkers to guide clinical decision-making and novel systemic agents to improve disease control are needed.

ANATOMY

The hypopharynx, sometimes referred to as the laryngopharynx, is contiguous superiorly with the oropharynx and inferiorly with the cervical esophagus (Figure 52.1). As general landmarks, the superior border of the hypopharynx is demarcated by the hyoid bone and the inferior border by the cricoid cartilage. With regard to cancer diagnosis and staging, there are three primary anatomic subsites within the hypopharynx: the bilateral pyriform sinuses, the postcricoid region, and the posterior pharyngeal wall.

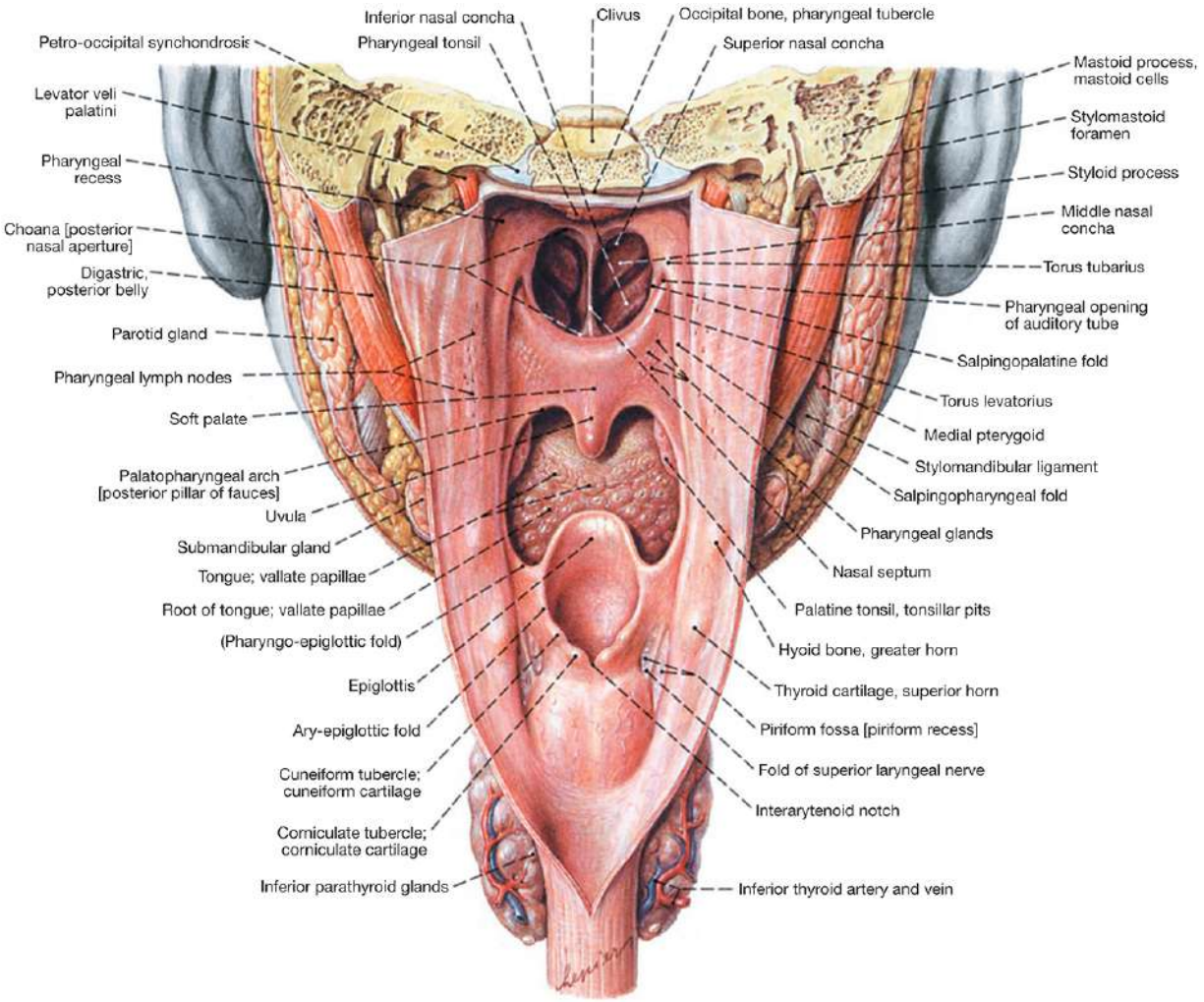


FIGURE 52.1 Posterior view of the hypopharynx shows the relationship of the pyriform sinus, pharyngeal wall, and postcricoid region within the head and neck. (Reprinted from Paulsen F, Waschke J. *Sobotta Atlas of Human Anatomy*. 17th ed. Urban & Fischer; 2023, Figure 11.23. Copyright © 2023 Elsevier GmbH Munich. With permission.)

The pyriform sinuses are essentially inverted pyramids with the medial, lateral, and anterior walls narrowing inferiorly to form the apices. Posteriorly, the pyriform sinuses are open and contiguous with the pharyngeal walls. Superiorly, the sinuses are surrounded by the thyrohyoid membrane through which passes the internal branch of the superior laryngeal nerve. Tumor involvement of the sensory branches of this nerve can result in referred otalgia. The postcricoid region is composed of the mucosa overlying the cricoid cartilage, with the arytenoid and esophageal mucosa forming the superior and inferior borders, respectively. The posterior pharyngeal wall predominantly comprises the squamous mucosa covering the middle and inferior pharyngeal constrictor muscles and is separated from the prevertebral fascia by the retropharyngeal space. Typically, the mucosa lining the pharyngeal wall is <1 cm in thickness and provides a minimal barrier to direct tumor infiltration. The posterior pharyngeal wall is contiguous with the lateral wall of the pyriform sinus (Figure 52.2).

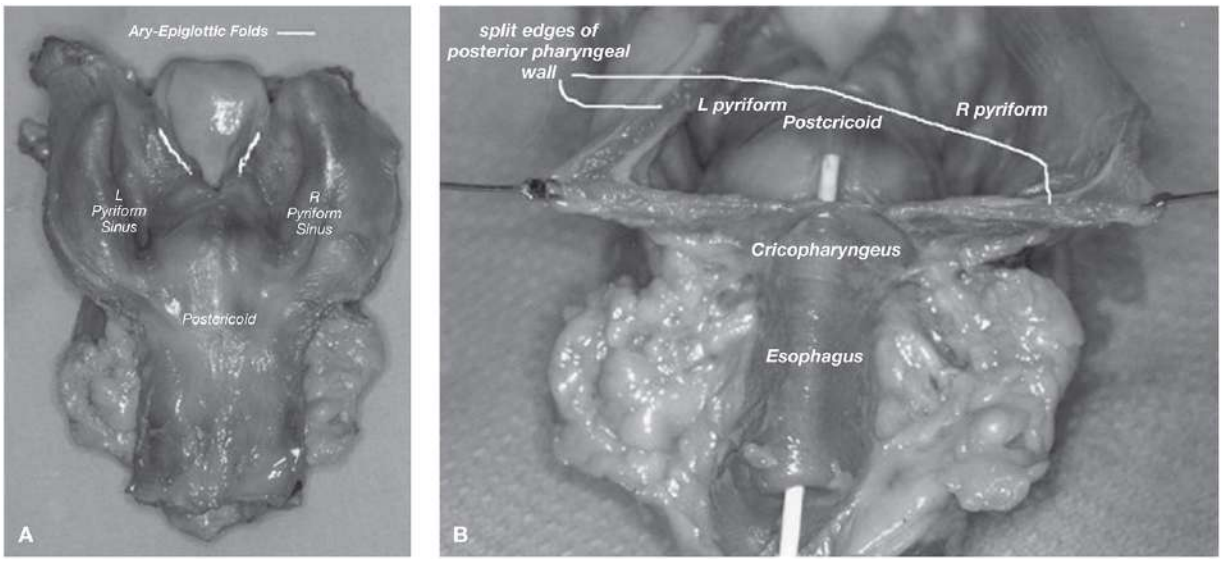


FIGURE 52.2 A. Posterior view of resected larynx and hypopharynx specimen afforded by incision through the posterior pharyngeal wall, cricopharyngeus, and cervical esophagus in the posterior midline. The aryepiglottic folds (marked) and arytenoids separate the pyriform sinuses (hypopharynx) from the larynx. B. The three primary anatomic subsites (posterior pharyngeal wall, postcricoid region, and pyriform sinuses) are revealed in this posterior view of the hypopharynx with the posterior pharyngeal wall incised.

Sensory innervation of the hypopharynx is provided by the internal branch of the superior laryngeal nerve as well as fibers deriving from the glossopharyngeal nerve. The recurrent laryngeal nerve and the pharyngeal plexus provide the primary motor supply. The arterial supply of the hypopharynx is derived primarily from branches of the external carotid artery: superior thyroid arteries, ascending pharyngeal arteries, and lingual arteries.

There is a rich network of lymphatics within the hypopharynx that drains directly through the thyrohyoid membrane and into the jugulodigastric lymph nodes, most commonly involving the subdigastric node. In addition, there may be direct drainage into the spinal accessory nodes. Tumors involving the posterior pharyngeal wall can also drain to the retropharyngeal nodes, including the most cephalad retropharyngeal nodes of Rouvière.

EPIDEMIOLOGY AND ETIOLOGY

Hypopharynx cancers are relatively uncommon. In the United States, the annual incidence is approximately 3,000 cases per year, accounting for nearly 7% of the upper aerodigestive tract.[2] Approximately three-fourths of hypopharyngeal cancers occur in men, with a mean age of 62 years.[3] Over 90% of patients with hypopharynx cancer report past cigarette use.[4] Alcohol appears to potentiate the carcinogenic effects of tobacco. In addition, alcohol consumption at medium to high levels for a long period of time can increase the likelihood of hypopharynx cancer in nonsmoking patients.[5] The index hypopharynx cancer often occurs within a field of diseased mucosa characterized by high-grade dysplasia. This “field cancerization” reflects widespread mucosal exposure to carcinogens and is responsible for the high rate of synchronous and metachronous primary tumors identified in patients with hypopharynx cancer. Successful counseling with particular emphasis on smoking cessation can enhance treatment tolerance and diminish the risk of developing subsequent cancers of the upper aerodigestive tract. Patients with occupational exposure to coal dust, steel dust, iron compounds, and fumes have also shown an increased risk for developing hypopharynx cancer.[6,7] Overall, the incidence of hypopharynx cancer has shown some gradual decline in the United States. From 1975 to 2001, the incidence

decreased by approximately 35%, perhaps as a result of smoking cessation efforts.[8] Human papillomavirus (HPV) infection is well established as a risk factor for the development of squamous cell carcinoma (SCC) of the gynecologic tract, particularly the uterine cervix. The relation between HPV and H&N cancer is now becoming much better appreciated, particularly for cancers of the oropharynx, where it may approach 60% to 70% in some series. Studies have demonstrated that approximately 20% to 25% of patients with hypopharynx cancer test positive for HPV DNA,[9,10] and seropositivity for antibodies against the HPV-16 E6 and E7 antibodies has been associated with a significantly elevated risk of hypopharyngeal cancer. The clinical implications of the presence of HPV in hypopharynx cancer are yet to be defined.

There is a recognized increased risk of developing cancers of the postcricoid region for patients with Plummer-Vinson syndrome, characterized by iron deficiency anemia, hypopharyngeal webs, weight loss, and dysphagia.[11] Favorable changes in the epidemiology of hypopharynx cancer have resulted from changes in nutrition. The addition of iron to flour has made Plummer-Vinson syndrome quite rare in the upper Midwestern United States and Scandinavian countries where it was formerly more common. An associated decrease in hypopharynx cancer involving the postcricoid region has followed.

PROGNOSTIC FACTORS

Several prognostic factors have been identified for patients with hypopharynx cancer. Age, particularly older than 70 years, has been identified as an unfavorable predictor of outcome.[11] This may simply reflect the diminished likelihood of older patients to successfully tolerate the aggressive therapy approaches required for locoregionally advanced cancers of the H&N. Women have been found to achieve somewhat improved outcomes compared to men, although this may in part be a manifestation of earlier stage disease at diagnosis.[12,13] In addition, tumor location has an impact on outcome, with cancers of the pyriform sinus generally faring better than those arising in the postcricoid or posterior pharyngeal wall regions.[12,13] As a whole, patients with hypopharynx cancer fare poorly in comparison with patients harboring tumors from other H&N sites (Figures

52.3 and 52.4).[14] To a lesser extent, tobacco, alcohol, medical comorbidities, and dietary factors may also have an impact on outcome.[15,16]

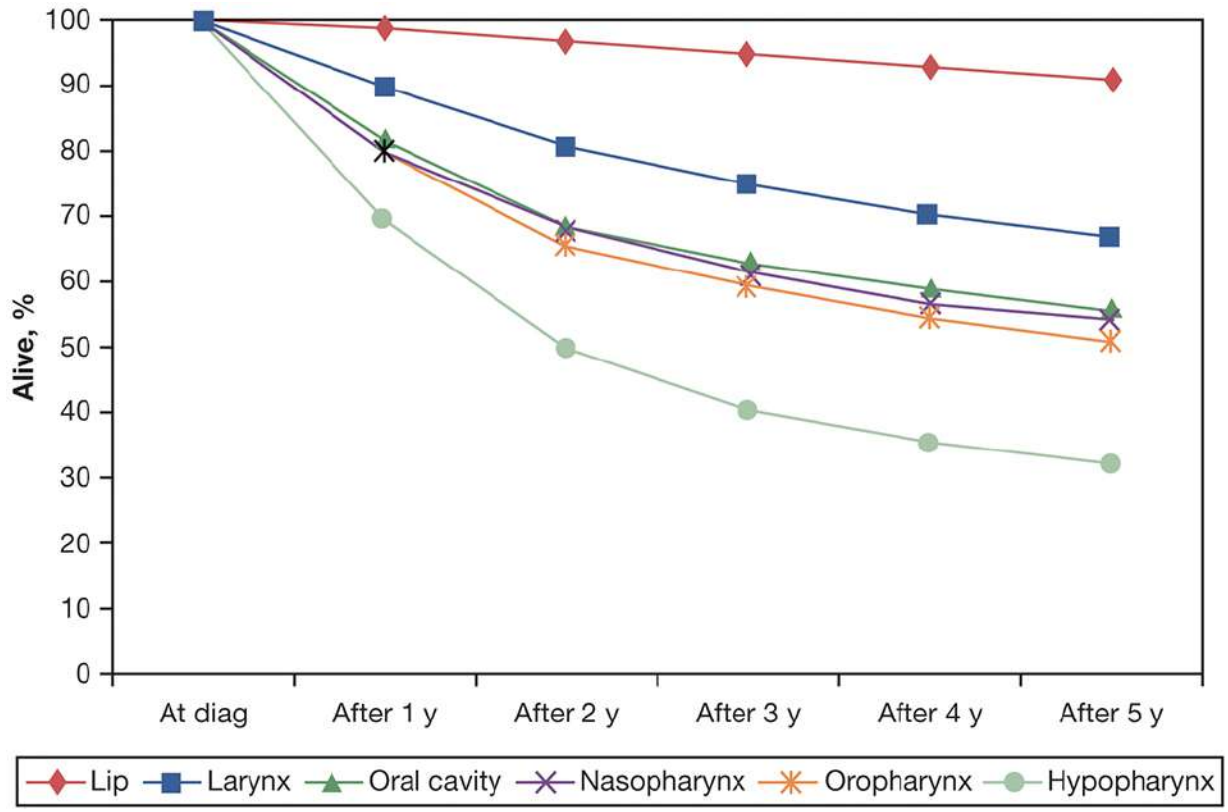
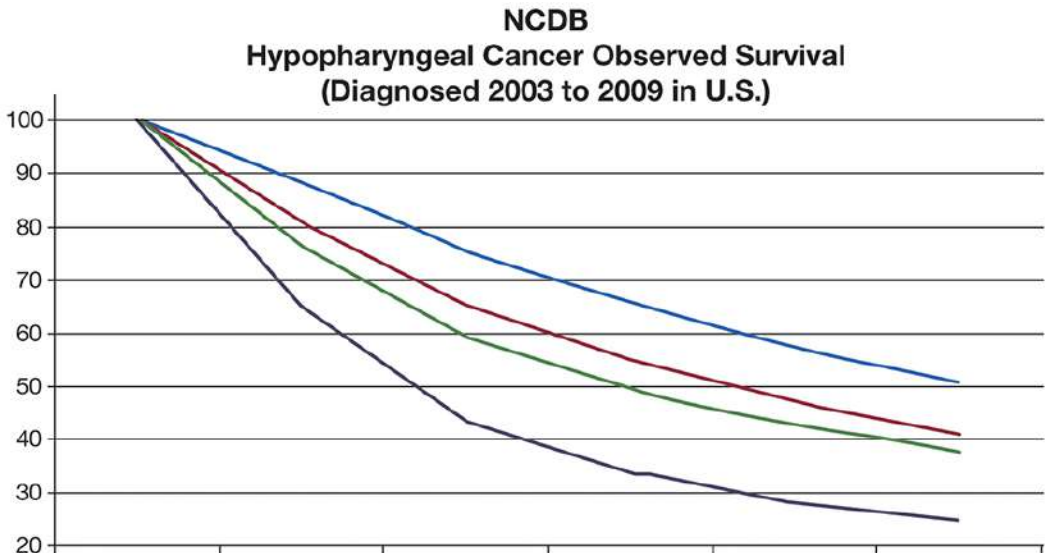


FIGURE 52.3 Five-year survival by mucosal site for head and neck cancers from 1990 to 1999 cases. (From Cooper JS, Porter K, Mallin K, et al. National Cancer Database report on cancer of the head and neck: 10-year update. *Head Neck*. 2009;31[6]:748-758. Copyright © 2009 Wiley Periodicals, Inc. Reprinted by permission of John Wiley & Sons, Inc.)



	DX	1 Year	2 Year	3 Year	4 Year	5 Year
Stage I n=360	100	88.7	75.3	65.8	57.4	50.9
Stage II n=870	100	81	65.6	55.1	47.1	41.1
Stage III n=1,827	100	76.9	59.3	49.7	42.8	37.8
Stage IV n=5,764	100	65.2	43.5	33.8	28.5	25.1

FIGURE 52.4 Observed survival for hypopharyngeal cancer in the United States is calculated for new cases identified in the National Cancer Database (NCDB) as an Aggregate Report from all Commission on Cancer hospitals (1233 programs) from 2003 to 2009 and includes all pathologic types and the selected anatomic sites: C129, C130, C131, C132, C138, and C139. Staging according to the sixth edition of the *AJCC Cancer Staging Handbook*. (From National Cancer Data Base. Commission on cancer. American College of Surgeons. National Cancer Database [NCDB] survival reports. Accessed April 17, 2017. https://m.facs.org/NCDB.SurvivalDS/app/index.html?guid=8989f6dc-9809-4603-8571-7b63548ee64e, with permission from the National Cancer Data Base.)

Biologic factors have been investigated for their potential role in hypopharyngeal cancer. The presence of p53 gene mutations has been associated with bulkier tumors and younger patients along with higher expression of the epidermal growth factor receptor (EGFR). However, p53 has not shown correlation with multiple primary tumors, tumor grade, or DNA ploidy.[17,18] Further, there are conflicting data regarding the prognostic significance of EGFR expression for patients with hypopharyngeal cancer.[19] Some studies suggest EGFR overexpression portends a worse prognosis for patients undergoing (chemo)radiotherapy, but not for patients treated with primary surgical resection.[20,21]

STAGING

The primary staging system for hypopharynx cancer is the American Joint Committee on Cancer's (AJCC) 2016 eighth edition of the *AJCC Cancer Staging Handbook* and is based on a combination of clinical and radiographic data (Table 52.1).[22] There were no significant changes made between the seventh and eighth editions regarding primary tumor criteria (T-stage) and clinical stage groupings. However, in the eighth edition, the nodal group staging now incorporates extranodal extension (ENE), which constitutes N3b disease, regardless of nodal size or laterality. There were no changes to hypopharynx cancer made in the AJCC ninth edition. Although AJCC staging is a very useful tool to broadly group similar cancer types, it should not be used as a blueprint for management. Patient factors, including age, comorbid medical conditions, and motivation for organ preservation, are beyond the scope of the staging system but nevertheless represent important factors for consideration with each individual patient.

TABLE 52.1 AMERICAN JOINT COMMITTEE ON CANCER 2010 T STAGING FOR HYPOPHARYNX CANCER

T Stage	Description
T1	Limited to 1 subsite of the hypopharynx and ≤2 cm in greatest dimension
T2	Tumor invades more than 1 subsite of the hypopharynx or an adjacent site, or measures >2 cm but ≤4 cm in greatest diameter without fixation of hemilarynx
T3	Tumor measures >4 cm in greatest dimension or with fixation of hemilarynx or with extension to the esophagus
T4a	Invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, or central compartment soft tissue, which includes prelaryngeal strap muscles and subcutaneous fat
T4b	Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures

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PATTERNS OF SPREAD

Local Extension

It is sometimes difficult to definitively assign tumor origin to a specific subsite in the hypopharynx when the tumor overlaps more than one subsite. Of the hypopharynx cancer cases recorded in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database between 2000 and 2008, 83% of tumors with a known subsite arose in the pyriform sinus. An additional 9% arose from the posterior pharyngeal wall, and 4% originated in the postcricoid region.[5] Because of the high propensity for advanced primary disease as well as regional nodal involvement, the majority of patients with hypopharynx cancer present with stages III and IV disease. In a retrospective study from Washington University, 87% of patients with cancers of the pyriform sinus and 82% of patients with posterior pharyngeal wall tumors presented with stage III or IV disease.[23]

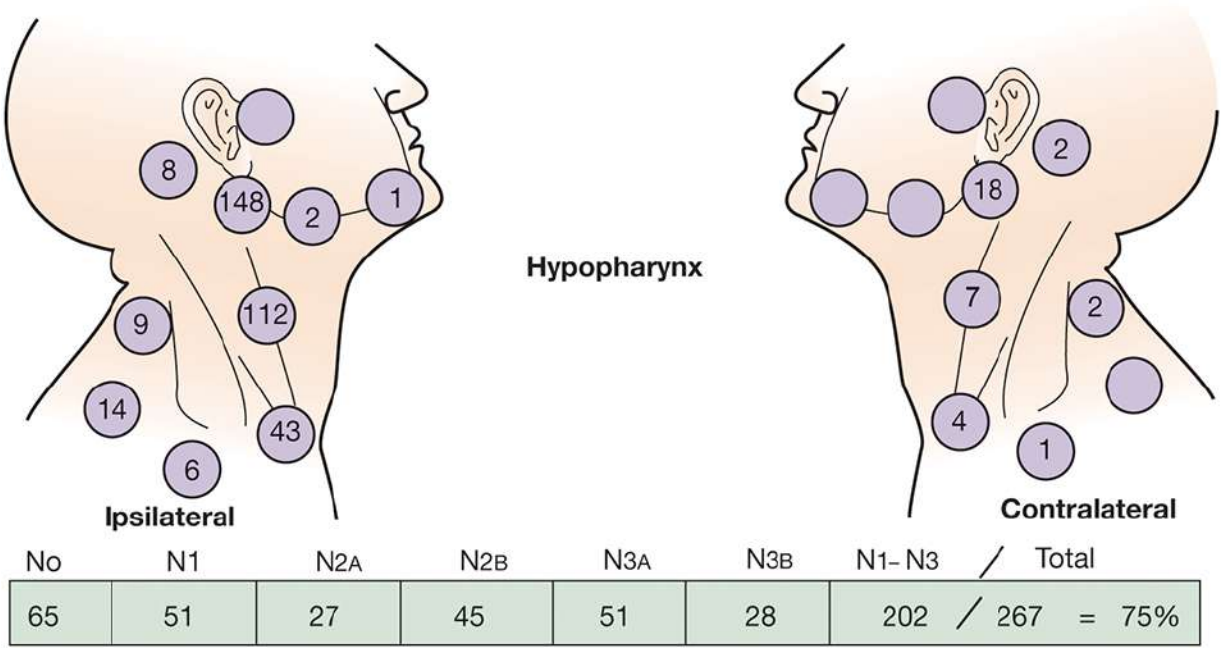
Cancers arising from the pyriform sinus may spread superiorly to involve the aryepiglottic folds and arytenoids and invade the paraglottic and preepiglottic space. Lateral tumor extension can involve portions of the thyroid cartilage, allowing entry into the lateral compartment of the neck. High-resolution computed tomography (CT) or magnetic resonance imaging (MRI) is often useful for optimal assessment regarding the extent of tumor invasion. For tumors arising from the medial wall, the most common site of involvement for pyriform sinus tumors, there is a likelihood of tumor involvement of intrinsic muscles of the larynx, resulting in vocal cord fixation. Inferior tumor extension beyond the apex can involve the thyroid gland.

Cancers arising within the postcricoid region can extend circumferentially to involve the cricoid cartilage or anteriorly to involve the larynx with resultant vocal cord fixation. Tumor involvement of the recurrent laryngeal nerve can also precipitate vocal cord fixation. Primary postcricoid tumors are often quite extensive and can involve the pyriform sinus, trachea, or esophagus. As a result, these tumors generally carry a worse prognosis in comparison to tumors from other subsites of the hypopharynx.[13] Nodal spread to the paratracheal nodes and inferior deep cervical nodes is not uncommon. Tumors arising from the posterior pharyngeal wall can extend to involve the oropharynx superiorly, the cervical esophagus inferiorly, and the prevertebral fascia and retropharyngeal space posteriorly.

Many cancers of the hypopharynx have a propensity for submucosal spread. It can, therefore, be difficult to accurately quantify the full microscopic extent of disease. This is particularly true for cancers of the posterior pharyngeal wall and postcricoid regions. Careful study through serial sectioning of surgical specimens has identified that 60% of hypopharynx cancers demonstrate subclinical spread with a range of 10 mm superiorly, 25 mm medially, 20 mm laterally, and 20 mm inferiorly.[24] This extensive pattern of tumor infiltration can present considerable challenge in the effort to achieve clear surgical margins or full dosimetric coverage with RT.

Regional Disease

Because of the rich lymphatic drainage of the hypopharynx, more than 50% of patients will manifest clinically positive cervical lymph nodes at the time of diagnosis, and ultimately, 65% to 80% of patients will have nodal involvement, as 30% to 40% of N0 necks harbor micrometastatic disease when electively dissected.[25] Jugular chain nodes, levels II to IV, as well as retropharyngeal nodes are all at high risk of harboring regional metastases in patients with hypopharynx cancer. Postcricoid tumors may also spread directly to pre- and paratracheal nodal basins. In light of cross-draining lymphatics, there is a significant risk of bilateral cervical node metastasis (Figure 52.5).[26,27]



No	N1	N2A	N2B	N3A	N3B	N1–N3 / Total
65	51	27	45	51	28	202 / 267 = 75%

FIGURE 52.5 Nodal distribution patterns for a series of 267 patients with hypopharynx cancer as summarized by admission records at the MD Anderson Cancer Center. (From Lindberg R. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. *Cancer*. 1972;29[6]:1446-1449. Copyright © 1972 American Cancer Society. Reprinted by permission of John Wiley & Sons, Inc.)

Distant Metastases

The most common site for distant metastasis to develop in patients with cancer of the hypopharynx is the lung. Previously, approximately one-quarter of patients diagnosed with hypopharynx cancer presented with distant metastases, although this incidence in more recent reports is estimated at approximately 16%.[28] For those patients not rendered free of locoregional disease following initial therapy, the incidence of distant metastases increases notably with the length of time following initial treatment.[29,30]

Field Cancerization

Carcinogens can induce dysplastic changes throughout the mucosa of the upper aerodigestive tract, leading to an increased risk for field cancerization that enhances the likelihood of synchronous or metachronous secondary primary tumors. Approximately 7% of patients with hypopharynx cancer will manifest a second primary tumor at initial diagnosis, and between 10%

and 20% will develop a secondary primary tumor over time. In fact, this second tumor risk is a significant cause of mortality in patients who survive more than 2 years following initial treatment.[4]

CLINICAL PRESENTATION

In light of the nonspecific nature of early symptoms, the majority of patients with cancers of the hypopharynx present with advanced local or regional disease. Frequently, there is a delay between presentation and diagnosis as patients are often managed for presumed infectious or gastrointestinal etiology. The majority of symptoms are related to local tumor spread, including dysphagia and odynophagia. There may be frank pharyngeal obstruction, invasion of constrictor muscles, prevertebral space invasion, or strap muscle invasion. Common presenting signs and symptoms include dysphagia, sore throat, hoarseness, weight loss >10 pounds, and neck mass. The majority of patients present with more than one of these signs and symptoms.[31] Roughly, 25% of patients will present with clinical stage III disease and 50% with clinical stage IV disease; however, reflux symptoms can be a common presentation leading to diagnosis of stage I or II hypopharyngeal tumors.[4] Selected patients may first come to medical attention with complaints of unilateral ear pain (referred to as otalgia) due to tumor involvement of the visceral sensory nerves of the pharynx.

Pretreatment Evaluation and Staging Workup

A comprehensive workup for patients with cancers of the hypopharynx should include a detailed history focusing on the duration of symptoms, amount of weight loss, the presence of otalgia, changes in voice quality, and degree of dysphagia. A previous history of another upper aerodigestive tract malignancy and a history of tobacco smoking are commonly associated. The physical examination should include direct and indirect visualization of the full laryngopharyngeal axis with particular attention to the size, location, and anatomic positioning of the primary tumor as well as the mobility status of the true vocal cords. Dentition and oral health should be assessed. If the patient presents with cervical adenopathy, the size, number, location, texture, and mobility of these nodes should be documented.

Although cervical adenopathy associated with hypopharynx cancer may be analyzed with fine-needle aspiration (FNA) biopsy, there is little value in this approach, because most patients will receive advanced radiographic imaging to further define the nodal involvement. On rare occasions, FNA may be useful to help distinguish other coexisting causes of lymphadenopathy, such as lymphoma. Most patients will undergo a direct laryngoscopy under general anesthesia in conjunction with esophagoscopy. This panendoscopy allows not only biopsy confirmation of the primary tumor site but also mapping of the extent of the tumor as well as the ability to survey for synchronous primary tumors (Figure 52.6A). The use of transnasal fiberoptic techniques makes it possible for a panendoscopy to be done for selected patients without anesthesia in the clinic setting.

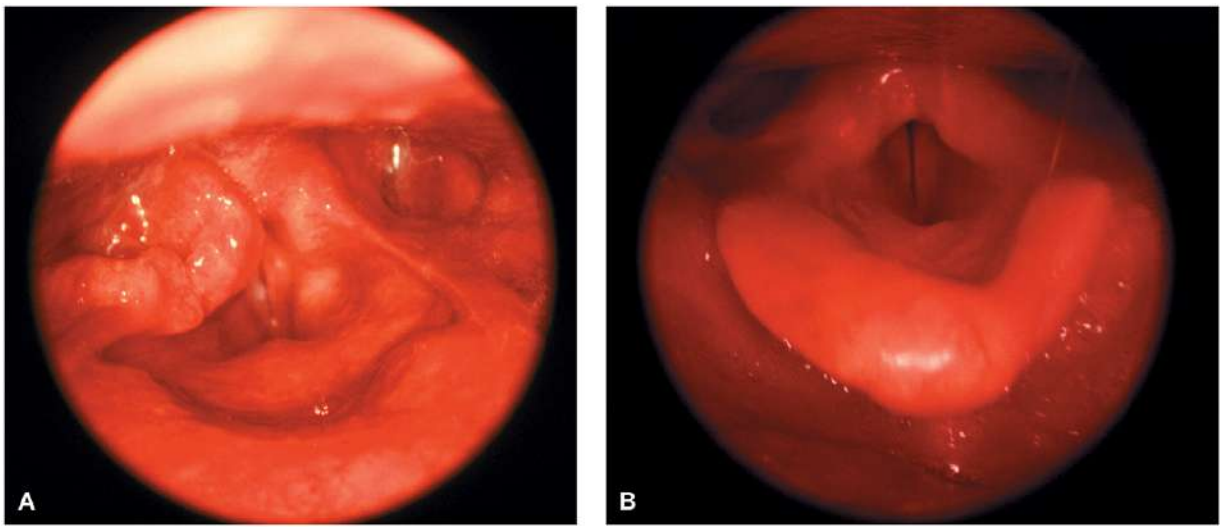


FIGURE 52.6 A. Outpatient clinic photograph taken through a rigid endoscope mounted with a 35-mm camera of a newly diagnosed exophytic T2 tumor arising from the right pyriform sinus with involvement of the adjacent aryepiglottic fold. There was no compromise of vocal cord mobility, and clinical staging of the primary lesion was T2. B. Photographic examination 1 year following 70-Gy radiation and concurrent cisplatin chemotherapy with complete tumor regression and excellent functional status of the laryngopharynx. Note mild-to-moderate mucosal edema of supraglottic structures following high-dose radiation.

In addition to panendoscopy, patients should undergo either high-resolution CT with contrast or MRI extending from the skull base to below the clavicle to help assess the extent of the primary tumor and to quantitatively and qualitatively assess cervical adenopathy (Figures 52.7

and 52.8).[27] Although a chest x-ray has traditionally been used to assess for the presence of pulmonary metastasis, 18-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) imaging (with accompanying CT for co-registration) is increasingly used to assess the extent of regional adenopathy and to survey for the presence of distant metastasis. FDG-PET is a valuable adjunct to CT or MRI in the radiation treatment planning process, particularly for patients treated with conformal intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), or tomotherapy techniques. Di Martino et al[31] compared CT, PET, color-coded duplex sonography, palpation, and panendoscopy in assessment of tumor and nodal status. Schwartz et al[32] examined the standardized uptake value (SUV) of primary and nodal metastasis in patients with H&N cancer and their relationship to clinical outcome. A primary tumor SUV >9.0 was associated with a significantly lower local recurrence-free survival and disease-free survival. However, there was no correlation between nodal SUV and clinical outcome.

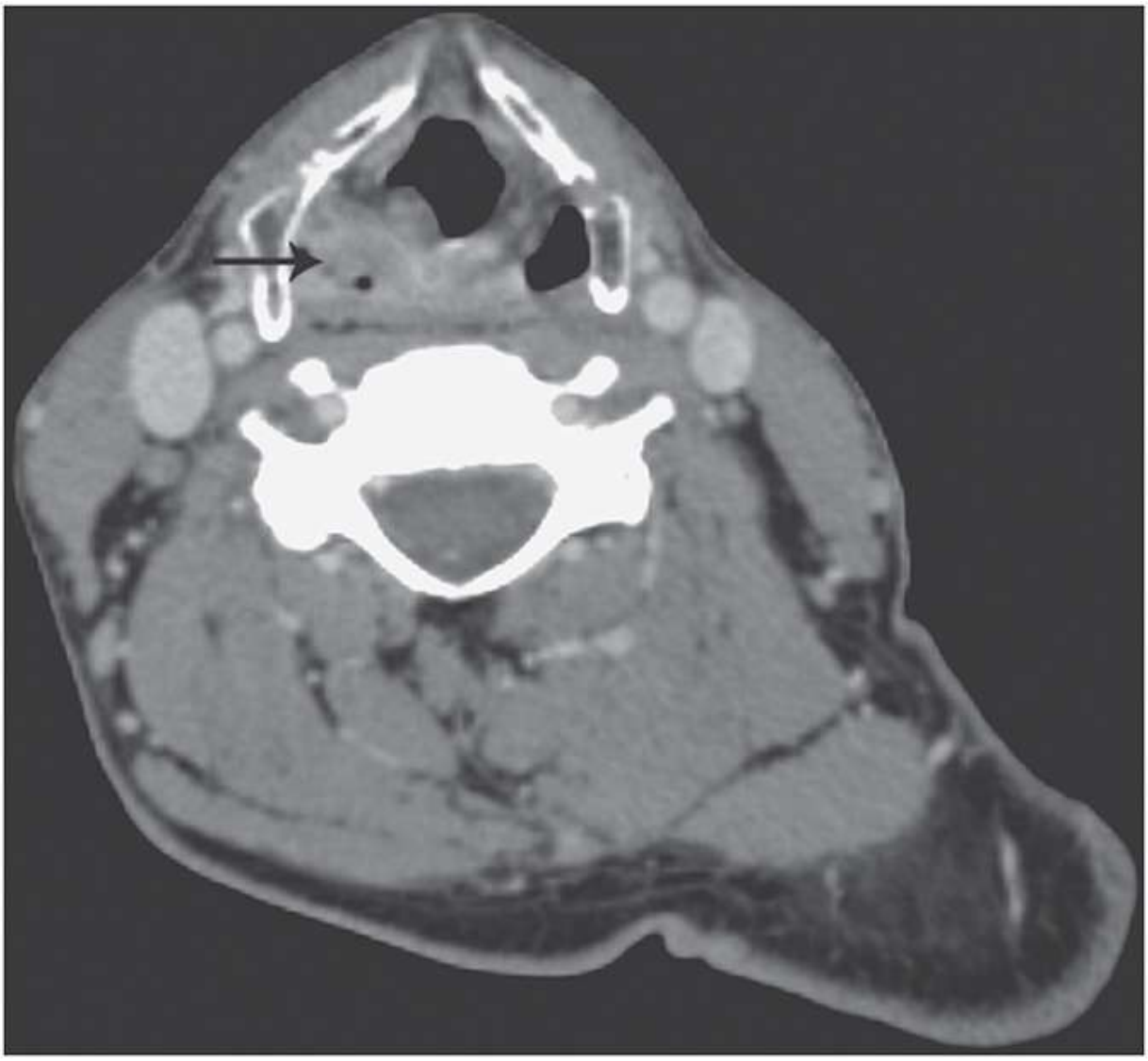


FIGURE 52.7 Axial computed tomography image from the same case as in Figure 52.6 depicting the T2 hypopharynx tumor involving the right pyriform sinus.

FIGURE 52.8 Axial gadolinium-enhanced T1-weighted magnetic resonance image scan with fat saturation depicting metastatic lateral retropharyngeal node with evidence of central necrosis and peripheral enhancement.

A recent prospective multicenter study of 233 patients with H&N SCC (including 46 hypopharyngeal cancers) highlighted the potential impact of PET imaging on H&N SCC management.[33] TNM staging and therapeutic decisions were first determined based on conventional workup and then physicians were unblinded to FDG-PET data and asked to restage the patients and reanalyze their therapeutic decisions. PET and conventional

workup revealed discordant TNM staging in 100 (43%) patients. PET was deemed significantly more accurate than conventional staging and improved the staging in 20% of patients. Incorporation of PET data ultimately impacted management in 32 (13.7%) patients (Table 52.2), supporting the use of FDG-PET in H&N SCC staging.

TABLE 52.2 IMPACT OF FDG-PET ON STAGING AND MANAGEMENT FOLLOWING CONVENTIONAL WORKUP

End Point	Impact of FDG-PET on 233 Patients
Discordant TNM stage	100 (43%)
PET accurately upstaged	30 (13%)
PET accurately downstaged	17 (7.3%)
PET inaccurately changed stage	13 (5.6%)
No confirmed gold standard TNM	40 (17%)
Impact on Patient Management[a]	
Low	188 (80.7%)
Medium	12 (5.2%)
High	20 (8.6%)

FDG, fluorodeoxyglucose; PET, positron emission tomography; TNM, tumor-node-metastasis classification.

[a]Impact ratings: low, treatment modality and delivery unchanged; medium, change within the same treatment modality (planned procedure, dose, or mode of administration changed); high, change in treatment intent or treatment modality (eg, curative to palliation, surgery to chemoradiation).

Derived from Lonneux M, Hamoir M, Reychler H, et al. Positron emission tomography with [18F]fluorodeoxyglucose improves staging and patient management in patients with head and neck squamous cell carcinoma: a multicenter prospective study. *J Clin Oncol*. 2010;28(7):1190-1195.

Many patients with hypopharynx cancer present with concurrent medical and social comorbidities that require consideration before initiating cancer-directed therapy. Commonly, there is a progressive history of dysphagia and odynophagia with associated weight loss. Whether these patients are treated with surgical or nonsurgical approaches, a gastrostomy tube may need to be considered as a temporary measure. It is important to optimize or at least stabilize the patient's nutritional status prior to initiating definitive therapy.

It is valuable for patients with hypopharynx cancer to undergo evaluation by a speech and swallow therapist to determine the degree of dysfunction prior to therapy. This may be done as a bedside study of swallowing capacity, a fiberoptic endoscopic evaluation of swallowing, or (usually preferably) through the more definitive fluoroscopic barium swallow study. This modified barium swallow study is called a cookie swallow, video pharyngogram, or oropharyngeal motility study and is most commonly done with a speech pathologist in attendance. If objective swallowing dysfunction is present, patients may be taught adaptive techniques to improve the effectiveness and safety of their oral intake. In addition, close follow-up with the same speech and swallow therapist is highly desirable during and after therapy to maximize the patient's long-term functional capabilities.

Because many patients with hypopharynx cancer have an active history of alcohol and tobacco use, it is important to counsel accordingly and encourage all patients to take advantage of methods and programs to facilitate smoking and alcohol cessation. All patients should undergo comprehensive dental evaluation and cleaning as well as basic education regarding oral hygiene. For patients treated with conventional RT techniques, there is a significant likelihood of long-term xerostomia that can promote dental decay. If existing dentition is in poor condition, dental extractions should be considered prior to therapy, particularly for teeth that will reside within the high-dose radiation region. Typically, 10 to 14 days are required following dental extractions to allow for healing prior to the initiation of RT. Custom fluoride carrier trays should be fabricated and discussed for long-term use in an effort to diminish the rate of dental decay for patients with chronic xerostomia.

Finally, many patients with hypopharynx cancer will have social issues, including lack of family support, financial limitations, transportation issues, poor nutrition, and hygiene habits that may hamper their ability to successfully receive adequate care. Often, the involvement of a case manager or social worker is of central importance to assist patients who require support both during and following cancer therapy.

PATHOLOGIC CLASSIFICATION

In SEER data from 2000 to 2008, 93.9% of hypopharynx cancers were SCC, with lymphoma, sarcoma, adenocarcinoma, and adenoid cystic carcinoma each accounting for approximately 0.5% of cases.[5] Similarly, the National Cancer Database (NCDB) Benchmark Reports evaluated 17,654 cases of hypopharyngeal cancer in the United States between the years 2000 and 2008. Over 90% of cases were SCC.[34]

Management

For patients presenting with early-stage, resectable disease, voice-preserving surgery and definitive RT alone are viable and acceptable treatment options. The vast majority of patients, however, present with stage III or IV disease and warrant multimodality treatment. Prior SEER database revealed a gradual trend away from primary surgery and toward definitive radiation without a decrement in overall survival.[35] These data suggested that primary radiation exhibited improved survival compared to surgery alone, but that combined surgery with radiation offered a survival benefit over either single modality. The use of chemotherapy in this study was unknown. Further, radiation was recorded as either received or did not receive with no mention of radiation dose raising the possibility that patients received palliative rather than curative-intent radiation doses. An updated SEER database analysis using data from 2004 to 2015 comparing more modern approaches of hypopharynx management suggested improved overall survival with surgery and adjuvant chemoradiation therapy versus chemoradiation.[3] Despite sophisticated statistical analyses, similar limitations still exist. For example, radiation dose is not specified and disease characteristics between treatment cohorts were different. Fifteen percent of patients in the chemoradiation arm had overall stage IVB disease, often uncurable, while the surgical arm included only 6%. Conversely, patients undergoing surgery were more likely to have cT4 disease compared to those receiving upfront chemoradiation. Recent results from the analysis of NCDB are similar to those proposed in the SEER analyses. After careful statistical modeling, surgery and adjuvant therapy were superior in survival compared to upfront chemoradiotherapy. However, despite less favorable disease characteristics in the surgical arm, patient selection bias has to be considered as only 12% (n = 706 of 6,055)

of patients included in the study underwent surgery.[36] Though nonrandomized, these studies provide real-world survival data estimating the overall survival risk for patients motivated to pursue the preservation of native laryngopharyngeal function through definitive chemoradiation therapy (Table 52.3).

TABLE 52.3 GENERAL TREATMENT RECOMMENDATIONS BASED ON HYPOPHARYNX TUMOR STAGE

Stage I	Radiation alone or voice preservation surgery if feasible
Stage II	Radiation alone
Stages III and IV with functional laryngopharynx	Concurrent chemoradiation followed by selective neck dissection
Stages III and IV with dysfunctional laryngopharynx[a]	Laryngopharyngectomy with adjuvant RT or CRT

CRT, chemoradiation therapy; RT, radiation therapy.

[a]Patients with bulky, destructive tumors that severely compromise the airway or destroy cartilage, bone, and deep soft tissue are often best served with immediate laryngopharyngectomy and postoperative radiation or chemoradiation.

Primary Surgery

T1 and T2 Tumors

Contemporary indications for primary surgical management of patients with early cancers of the hypopharynx include those with a history of previous H&N radiation, those in whom organ conservation approaches are deemed possible, and those who refuse radiation. Even for patients with hypopharynx cancer who will receive nonoperative treatment approaches, it remains critical for the H&N surgeon to remain actively involved. The role of the surgeon in these cases may include endoscopic biopsy with detailed assessment of tumor extent, methods to secure the airway (tracheotomy or laser debulking), and methods to ensure adequate nutrition (gastrostomy). The surgeon will also play a vital role in multidisciplinary oncologic follow-up after nonoperative treatment.

Selected T1 and T2 hypopharynx cancers may lend themselves to surgical excision. These favorable subsites include the upper pyriform sinus

and the posterior pharyngeal wall. Traditional conservation surgery for early-stage hypopharyngeal cancers consisted of an open supraglottic partial laryngectomy encompassing the aryepiglottic fold, extending the field of resection to include part of the arytenoids, the base of the tongue, and the upper pyriform sinus if necessary. With the advent of fiberoptic lasers, small cancers isolated to the posterior pharyngeal wall may be removed by endoscopic laser resection, utilizing a microscope-mounted laser delivery system or laser handpieces to precisely incise the mucosa and coagulate small vessels. Whereas minimally invasive endoscopic approaches often allow for early swallowing, if an open approach is employed, then dysphagia requiring nothing by mouth status is common in the postoperative period and temporary tracheotomy placement may be necessary, especially if reconstruction of the posterior wall is affected with an adynamic and insensate free flap. Relative contraindications to organ conservation surgery for hypopharynx cancers include cartilage invasion, vocal fold fixation (involvement of the paraglottic space), involvement of preepiglottic space, postcricoid invasion, deep pyriform sinus invasion, and extension beyond the larynx.

Innovations with free flap reconstruction have allowed retention of speech, swallowing, and breathing functions of the larynx despite extensive resection by way of a hemilaryngopharyngectomy. The temporoparietal flap and radial forearm free flap coupled with rigid cartilaginous support have been employed to retain function in patients with hypopharynx cancers without extension to the postcricoid region or apex of the pyriform sinus.[37]

In recent years, advancements in organ preservation surgery have included the use of transoral laser microsurgery (TLM) and transoral robotic surgery (TORS). For selected cases, these approaches can achieve oncologic tumor removal while limiting normal tissue disruption, thereby potentially avoiding tracheostomy and the use of feeding tubes.[38-41] This approach may involve concurrent or delayed neck dissection following transoral resection of the primary lesion (to allow for final margin assessment). The necks in some T1N0 patients may be observed with close interval follow-up CT scans. Adjuvant (chemo)radiotherapy is utilized in the majority of patients using this approach (see section “Postoperative Radiotherapy” for indications) and should generally encompass the primary tumor site as well as bilateral necks and supraclavicular fossae. Recent

results have demonstrated that appropriately selected T1 or T2 lesions can achieve negative margins by TLM or TORS.[39] Oncologic outcomes appear similar to open surgical approaches using this technique and are likely accompanied by lower rates of permanent gastrostomy tube or tracheostomy placement (Table 52.4).

TABLE 52.4 FIVE-YEAR ONCOLOGIC OUTCOMES FOR TRANSORAL MICROLASER SURGERY FOR T1 OR T2 HYPOPHARYNGEAL TUMORS

Study (Reference)	T-Stage	N	Node (+) (%)	LC (%)	DSS (%)	OS (%)	Permanent Gastrostomies (%)	Permanent Tracheostomies (%)
Martin et al[40]	pT1	20	62	84	NR	68 (stages I-II)	3.5[a]	3.5[a]
	pT2	48		70	NR			
Karatzanis et al[39]	pT1	45	56	90	78	NR	0	0
	pT2	74	64	83	70	NR	4	2.5

DSS, disease-specific survival; LC, local control; NR, not reported; OS, 5-year overall survival.

[a]Entire cohort, including T3 and T4 patients.

TORS is currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of benign and malignant tumors classified as T1 and T2, as well as benign base of tongue resection procedures. Compared to TLM, which relies on visualization of the hypopharynx with a microscope or endoscope aimed through specialized laryngoscopes, TORS has the advantage of better visualization with a three-dimensional magnified camera, the option to utilized angled endoscopes, and manipulation using "wristed" instruments, which provide the means to resect tumor en bloc. There currently exist three iterations of the da Vinci (Intuitive Surgical Inc, Sunnyvale, CA, USA) surgical robot: two multiport (MP) models, the Si and Xi, and the single port (SP) model. Whereas the MP models offered a rigid 0- or 30-degree endoscope to be used with either two or three rigid working arms, the SP robotic system employs a flexible endoscope and working arms, which are deployed through an SP. Addressing the

limitations of the MP models, including the rigid orientation of the ports and large instrument size, the SP model was developed to increase maneuverability in narrow, hard-to-access spaces (such as the hypopharynx), allowing for improved visualization in the piriform sinuses and postcricoid region and more facile use of instrumentation.[42] Traditionally, dissection is performed with a grasping instrument and monopolar cautery; however, flexible fiberoptic CO_2 laser delivery may also be utilized via the robotic instrument cart.[43] These instruments provide the means to achieve oncologic tumor removal while limiting tissue disruption, thereby avoiding tracheostomy and feeding tubes in many cases. Neck dissection can be done concurrently or in a staged manner; when neck dissection is performed, the ipsilateral superior thyroid artery is routinely ligated as it exits the external carotid artery so as to inhibit blood flow through the superior laryngeal artery, which reliably arises from the posterior aspect of the pharyngoepiglottic fold origin.[42,44]

Early studies demonstrate oncologic outcomes similar to open approaches, and a more recent study suggests that TORS may improve survival for selected patients compared to TLM and primary radiation for T1 and T2 tumors of the hypopharynx.[45,46] Finegersh et al showed that TORS hypopharyngectomy was shown to have a significantly decreased rate of positive margins compared to TLM (13% compared to 32%), and numerous studies have shown that patients undergoing TORS experience reduced postoperative morbidity and quicker recovery compared to open conservation surgery.[46-48] Existing literature supports the efficacy and safety of TORS in treating early-stage hypopharyngeal cancer and continues to demonstrate the ability to achieve negative margins in the hypopharynx for select T1 and T2 lesions, preserving the larynx and, in some cases, avoiding tracheostomy. The majority of patients in these recent series have functional swallow and voice outcomes as well.[49,50]

While TORS represents an excellent treatment option, there do exist limitations and contraindications to its use in early-stage hypopharyngeal cancers. The main limitations in TORS are determining whether the tumor is safely resectable and the ability to gain adequate exposure to visualize the extent of the tumor. Certain anatomic features, including trismus, the presence of mandibular tori, retrognathia, and a severely acute angle of the

mandibular parasymphysis, may limit transoral exposure of the hypopharynx, even with the SP robot. Contraindications to TORS include retropharyngeal course of the carotid artery, invasion of the pyriform sinus apex, vocal fold fixation, and invasion of the thyroid cartilage inner perichondrium.[42] As the technology evolves and surgeons build experience with these procedures, additional data will emerge to describe long-term outcome results for patients with early-stage hypopharyngeal cancers.[51]

T3 or T4 Resectable Tumors

Favorable T3 hypopharynx cancers that present in the upper aspect of the pyriform sinus and allow full extirpation by either an extended supraglottic laryngectomy or extended vertical partial laryngopharyngectomy with free flap reconstruction are infrequent. However, most T3 and T4 hypopharynx cancers that are treated surgically will require total laryngectomy with efforts to preserve a posterior strip of the hypopharynx spanning the oropharynx to the esophagus. This preserved posterior wall of the hypopharynx may be tubed and closed on itself in selected cases. In the past, it was common practice to accept primary reconstruction of this segment as adequate for swallowing if closure over a nasogastric tube was possible. However, with the proliferation of regional and free tissue reconstruction options, primary closure has been discouraged for cases with less than a 3- to 3.5-cm width of posterior pharyngeal wall mucosa to tube on itself. Most commonly, superior swallowing results when the anterior and lateral walls of the remaining hypopharynx are reconstructed with a pedicled or free flap.

For more bulky tumors of the hypopharynx, total laryngopharyngectomy, removal of the larynx, and the entire hypopharynx are required. This procedure creates a gap between the oropharynx and the esophagus that must be reconstructed. Historically, total circumferential laryngopharyngectomy defects were repaired with a gastric pull-up procedure, mobilizing the stomach and esophagus and pulling the stomach upward into the neck, or with a staged regional flap reconstruction, such as the Wookey flap.[52,53] With the advent of the pectoralis major myocutaneous flap, the use of the tubed pectoralis flap was pursued, though this can be technically difficult to tube in certain patients due to the bulk of fat and

muscle underlying the skin paddle. With the advent of microvascular reconstruction, the free jejunum flap and tubed free gastro-omental flap were initially popularized, though the lower morbidity, easier-to-harvest fasciocutaneous flaps, particularly the anterolateral thigh free flap and radial forearm free flap, have emerged as the predominant reconstructive methods in recent years.[54]

While microvascular techniques have seen significant advancements in recent decades, resulting in decreased operative times and increased free flap survival rates, reconstruction of total circumferential pharyngeal defects remains a challenge with numerous potential complications, including risk of free flap failure, pharyngocutaneous fistulae, and pharyngoesophageal stricture.[54]

Palliative Surgery

For patients with incurable, metastatic disease at presentation, or with symptomatic local recurrence not amenable to curative salvage therapy attempts, surgery can play an important role in palliation. If aspiration of secretions (despite nothing by mouth status and enteral feedings) persists, laryngopharyngectomy may afford a reasonable option to discuss with the patient and family members. Similarly, complete stenosis of the pharynx or upper esophagus due to tumor (or following treatment) may leave a patient with the constant need for suctioning their own secretions. In selected patients, laryngopharyngectomy with gastric pull-up may be a reasonable palliative option. Finally, gastric feeding tube placement can be considered for patients who do not wish to pursue palliative RT or surgery.

Postoperative Radiation Therapy

Most advanced hypopharynx cancers that are treated with initial surgical resection have unfavorable features that warrant the addition of postoperative RT in an effort to enhance locoregional control rates. Classic indications for postoperative radiation include T3 to T4 primary tumors, close or positive microscopic margins, cartilage or bony invasion, lymphovascular space invasion, extensive perineural invasion, more than one metastatic lymph node, or the presence of ENE. IMRT and VMAT are commonly used to enable sufficient conformal coverage of the tumor bed,

flap, and bilateral nodal regions at risk while reducing dose to adjacent organs.[55] Commonly used doses include 63 to 66 Gy in 30 to 33 fractions to areas harboring microscopic residual disease at the primary site or in regions previously containing lymph nodes with ENE. A dose of 60 Gy typically covers the tumor bed and nodal regions without positive surgical margins or ENE. Elective doses of 50 to 56 Gy are typically prescribed to elective nodal regions. Although less common, conventional therapy approaches using shrinking field techniques are adequate if more advanced conformal technologies are not available. Proton therapy can be considered in the postoperative setting, especially in patients previously treated with RT for a prior H&N cancer to avoid overdosing the spinal cord and other critical organs.[56] The Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) have evaluated the role of concurrent chemotherapy along with postoperative radiation in prospective randomized trials. Eligibility criteria in the RTOG trial included patients with two or more positive nodes, ENE, or microscopically positive margins. All patients received either 60 Gy alone or with concurrent cisplatin 100 mg/m^2 every 3 weeks. This trial demonstrated an improvement in locoregional control and disease-free survival for patients who received concurrent chemoradiotherapy. However, no significant benefit in absolute survival was confirmed.[57] The EORTC conducted a similar trial that included patients with stage III (except T3N0 larynx), stage IV, and patients with stage I or II with positive margins, lymphovascular invasion, and perineural invasion. All patients received either 66 Gy alone or with cisplatin at 100 mg/m^2 every 3 weeks. This trial demonstrated a significant improvement in progression-free survival and overall survival with the addition of chemotherapy.[58] A subsequently published post hoc analysis of the combined data from these trials suggested that patients with ENE and positive margins were most likely to benefit from the addition of chemotherapy, whereas those with two or more involved lymph nodes without ENE as their only risk factor did not appear to benefit from the addition of chemotherapy.[59]

Although the studies above identify that the addition of cisplatin chemotherapy to postoperative radiation can improve tumor control outcome for specific categories of high-risk patients, it is clear that this modest benefit comes at the expense of additional toxicity. Careful clinical

judgment regarding the selection of patients most likely to tolerate and thereby benefit from this approach is warranted. A recently updated meta-analysis demonstrated similar modest benefit from the addition of concurrent chemotherapy in the postoperative setting as compared to the definitive setting. However, this analysis showed that patients older than 70 years of age derive little to no benefit from the addition of systemic chemotherapy to radiation in H&N cancer.[60] Despite the lack of benefit of concurrent chemoradiation therapy in the postoperative setting for patients over 70 years of age in prior systematic analyses, additional factors, especially performance status and extent of comorbidities, should be considered in a multidisciplinary manner to finalize management. The inadvertent introduction of treatment breaks during the adjuvant radiation course can easily compromise the potential benefits of the combined modality therapy in this setting. Cooperative group studies aimed at improving clinical outcomes and minimizing toxicities using non–cisplatin-based therapies are ongoing (NCT01810913).

Definitive Radiation Therapy

T1 and T2 Tumors

Curative RT is generally the preferred treatment option for patients with T1 or T2 hypopharynx tumors (see Table 52.3). This approach affords good potential for organ preservation without compromise in clinical outcome. A classic course of RT for hypopharynx cancer lasts 6 to 7 weeks, with treatment delivered 5 days per week. A review of published clinical results of definitive RT for H&N cancer suggests a significant loss of local control with prolongation of overall radiation treatment time; therefore, interruptions in treatment once underway should be avoided whenever possible.[61,62]

IMRT/VMAT are commonly used; however, conventional treatment involving a shrinking field technique that initiates with opposed lateral fields encompassing the primary tumor and upper neck lymphatics with a matched anterior field to complete treatment of the lower neck are valid approaches (Figure 52.9; Table 52.5). One of the most common worldwide fractionation regimens involves the delivery of 2-Gy daily fractions to 70 Gy over 7 weeks. Because of the high likelihood of subclinical nodal

metastases even in the clinically N0 neck, patients traditionally receive comprehensive radiation to encompass nodal regions from the skull base to the clavicle. Because of the varying thicknesses of the H&N, custom compensators or wedges should be used for the lateral fields to improve dose homogeneity. Shrinking field techniques to spare direct spinal cord dose after approximately 45 Gy, as well as final mucosal reductions after 54 to 60 Gy, are often appropriate with posterior neck boosting, with electrons to supplement posterior chain nodal dosing without excessive dose to the spinal cord.

TABLE 52.5 GENERAL ANATOMIC LANDMARKS FOR FIELD DESIGN USING CONVENTIONAL HEAD AND NECK RADIOTHERAPY FOR HYPOPHARYNX CANCER

Border	Description
Superior	Include base of skull
Posterior	Behind vertebral spinous processes (or further if required to cover metastatic cervical lymph nodes)
Inferior	Lower aspect of cricoid cartilage unless extensive caudal tumor extension
Anterior	Flash skin at level of thyroid cartilage

For T1 lesions, classic dose is 66 to 70 Gy in 2-Gy daily fractions. For T2 to T4 lesions, consider altered fractionation regimens or concurrent cisplatin-based chemotherapy, particularly for patients over 70 years of age. Gross disease should generally receive 70 Gy with concurrent chemotherapy.

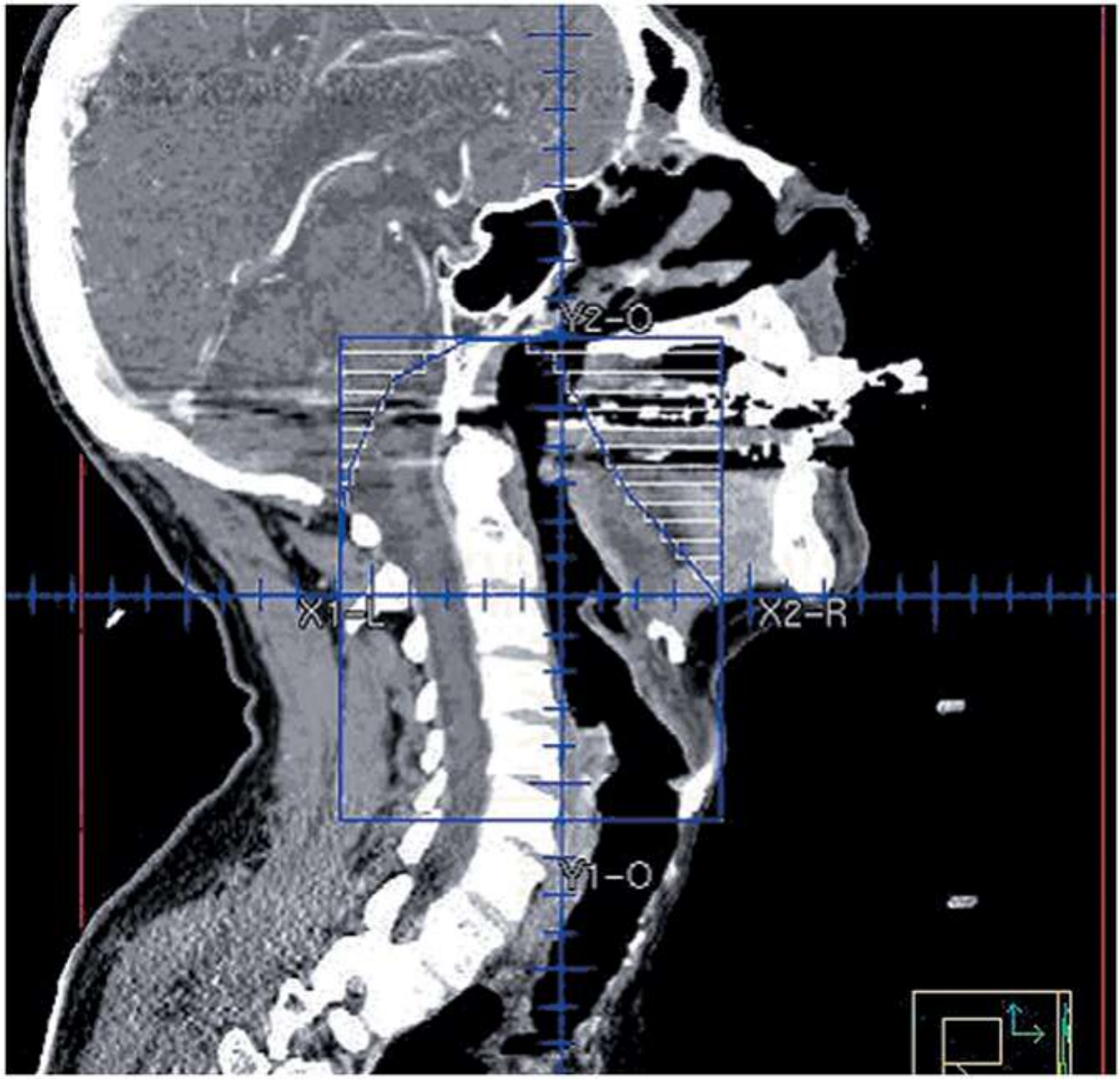


FIGURE 52.9 Digitally reconstructed radiograph depicting a classic lateral field designed to encompass the T2 pyriform sinus cancer from Figures 52.6 and 52.7 plus bilateral cervical lymphatics from skull base to cricoid, with a matching anterior low neck field to extend the lymphatic coverage to the level of the clavicle.

SCCs of the H&N are rapidly proliferating tumors. There has been significant interest over the past several decades in the use of intensified radiation fractionation schedules to counter rapid tumor cell repopulation as a means of improving outcomes in patients with H&N cancer treated with radiation alone. Altered fractionation techniques, including hyperfractionation (eg, 1.1-1.4 Gy twice daily) and accelerated fractionation

(eg, 6 fraction per week or concomitant boost regimens), have demonstrated improved locoregional control rates for patients with H&N cancer.[63-65] A meta-analysis examined 15 trials that compared conventional fractionation to altered fractionation, either hyperfractionation or accelerated fractionation. This meta-analysis demonstrated a small but statistically significant survival benefit of 3.4% at 5 years with altered fractionation. The benefit was higher with hyperfractionation compared to accelerated fractionation and was more pronounced for patients younger than age 50 (Figure 52.10).[66]

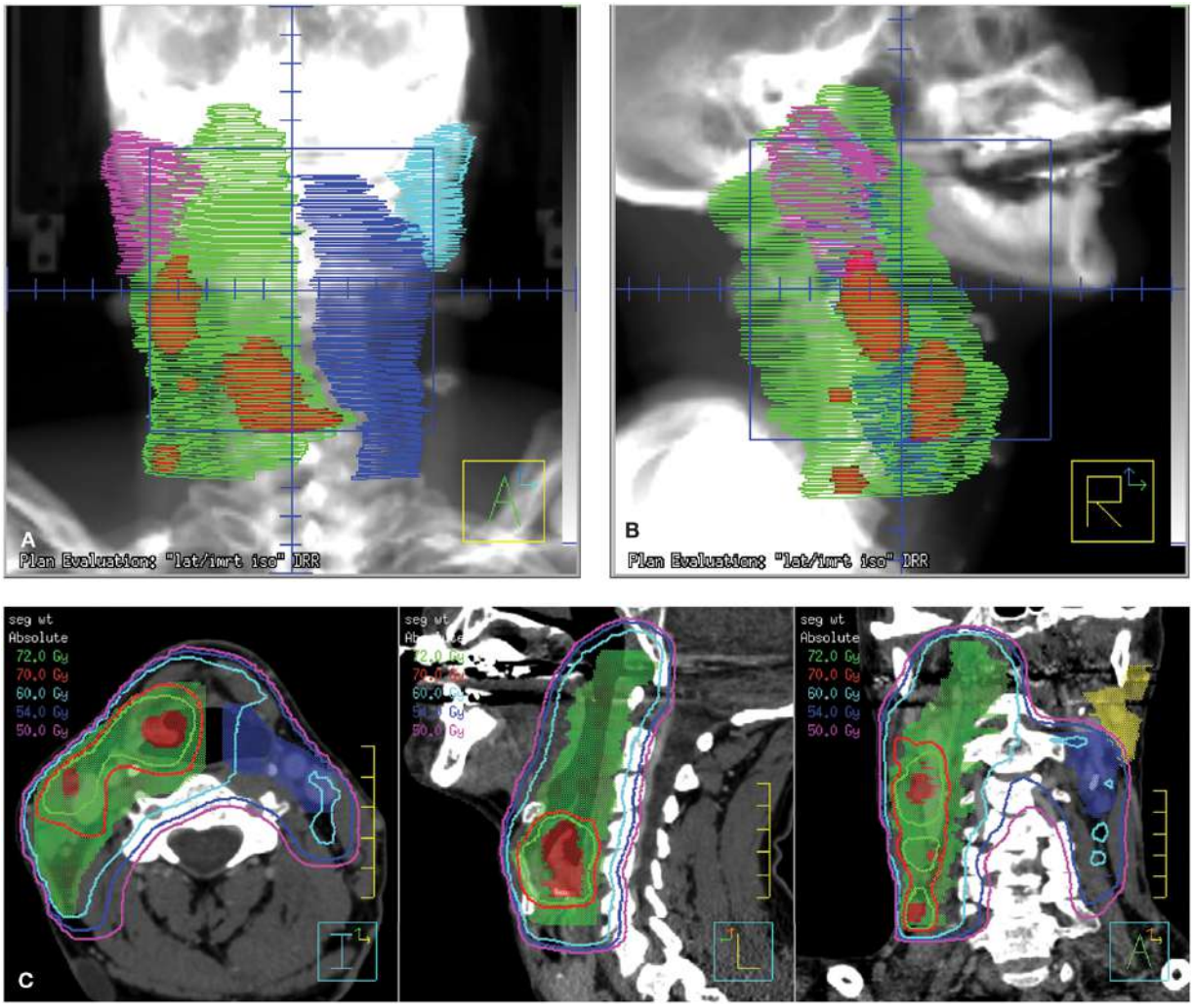


FIGURE 52.10 Beam's eye projections of intensity-modulated radiation therapy target contours for a patient with T2N2bM0 tumor of the right pyriform sinus (same case as depicted in Figures 52.6, 52.7, and 52.9). A and B. Depict anterior and lateral projections highlighting the GTV (red, 70 Gy), high-risk CTV1 (green, 60 Gy), low-risk CTV2 (blue, 54 Gy), and bilateral parotid glands. C. Demonstrates transverse, sagittal, and coronal treatment planning images depicting head and neck intensity-modulated radiation therapy isodose distributions for the same patient. The left parotid gland received a mean dose of 22 Gy. CTV, clinical target volume; GTV, gross tumor volume.

Early T-stage hypopharynx patients with N0 or N1 neck disease can be considered for treatment with either radiation alone or concurrent radiation plus chemotherapy. In this setting, gross disease should receive 70 Gy and the contralateral neck (N0) should receive 50 to 54 Gy. With T1N0 lesions, patients may achieve 5-year disease-specific survival (DSS) on the order of

90%, whereas T2N0 lesions may achieve DSS above 70% (Tables 52.6 and 52.7).[67-71]

TABLE 52.6 LOCAL CONTROL FOR CARCINOMA OF THE POSTERIOR PHARYNGEAL WALL TREATED WITH RADIATION ALONE

	Local Control After Radiation Therapy		Ultimate Local Control After Salvage	
Stage	**2-Year (%)**	**5-Year (%)**	**2-Year (%)**	**5-Year (%)**
T1	100	100	100	100
T2	79	74	86	81
T3	59	49	66	66
T4	36	36	36	36

Adapted from Fein DA, Mendenhall WM, Parsons JT, Stringer SP, Cassisi NJ, Million RR. Pharyngeal wall carcinoma treated with radiotherapy: impact of treatment technique and fractionation. *Int J Radiat Oncol Biol Phys*. 1993;26(5):751-757. Copyright © 1993 Elsevier. With permission.

TABLE 52.7 CAUSE-SPECIFIC AND OVERALL SURVIVAL FOR CARCINOMA OF THE PYRIFORM SINUS TREATED WITH RADIATION ALONE

Stage	5-Year Cause-Specific Survival (%)	5-Year Overall Survival (%)
I	96	57
II		61
III	62	41
IVa	49	29
IVb	33	25

Data from Amdur RJ, Mendenhall WM, Stringer SP, Villaret DB, Cassisi NJ. Organ preservation with radiotherapy for T1-T2 carcinoma of the pyriform sinus. *Head Neck*. 2001;23(5):353-362.

T3 and T4 Tumors

There are several reasons why patients with hypopharynx cancer who are technically resectable may not undergo primary surgery. These include age (eg, patients over 70-80 years old), the presence of significant medical comorbidities, or patient unwillingness to accept total laryngectomy. Curative-intent radiation or chemoradiation is often pursued in these

settings. Conventional RT commonly involves a shrinking three-field technique to deliver approximately 70 Gy in 2-Gy daily fractions to areas of gross disease and 50 to 60 Gy to areas of microscopic disease. If patients are scheduled to undergo postradiotherapy neck dissection, then gross nodal disease can be limited to 60 to 63 Gy. If patients are not candidates for postradiotherapy neck dissection, then gross nodal disease should be carried to 70 Gy. Altered fractionation regimens such as hyperfractionation or accelerated fractionation should be considered for patients being treated with radiation alone, given the overall survival benefit observed with these approaches over standard fractionation in meta-analysis.[66]

In patients with adequate performance status, concurrent chemoradiation strategies using platinum-based chemotherapy should be considered. The updated meta-analysis to examine the benefit of chemotherapy in advanced H&N cancer confirms a significant survival advantage for the use of concomitant chemotherapy (6.5%), with the effect of single-agent platin significantly higher than other monochemotherapies.[60] However, this meta-analysis also confirms a steadily decreasing benefit for the use of chemotherapy with advancing patient age, such that no advantage is observed for patients over 70 years of age. This same loss of statistical benefit for patients over 70 years of age is also observed for the outcome gains derived from altered fractionation over conventional fractionation.[66] Therefore, once-daily radiation regimens without concurrent chemotherapy may be quite reasonable for patients with hypopharynx cancer over 70 years of age or for those patients with modest performance status.

Another alternative to concomitant chemotherapy or accelerated fractionation is the more recent introduction of molecularly targeted therapies in the treatment of patients with H&N cancer. The most mature clinical data set in H&N cancer involves the use of EGFR inhibitors, such as cetuximab (monoclonal antibody against the EGFR). An international phase III trial comparing high-dose radiation alone versus radiation plus cetuximab in patients with advanced H&N cancer confirmed a locoregional control improvement (10% at 5 years) and overall survival advantage (10% at 5 years) with the addition of cetuximab.[72,73] A relatively small subset of patients with hypopharynx cancer was enrolled in this study of 424 patients, and this subset did not demonstrate a clear advantage with the use of the EGFR inhibitor treatment. Ongoing trials to examine the potential value of

adding cetuximab to concurrent chemoradiation approaches in advanced H&N cancer are in progress in both the definitive and high-risk postoperative settings.

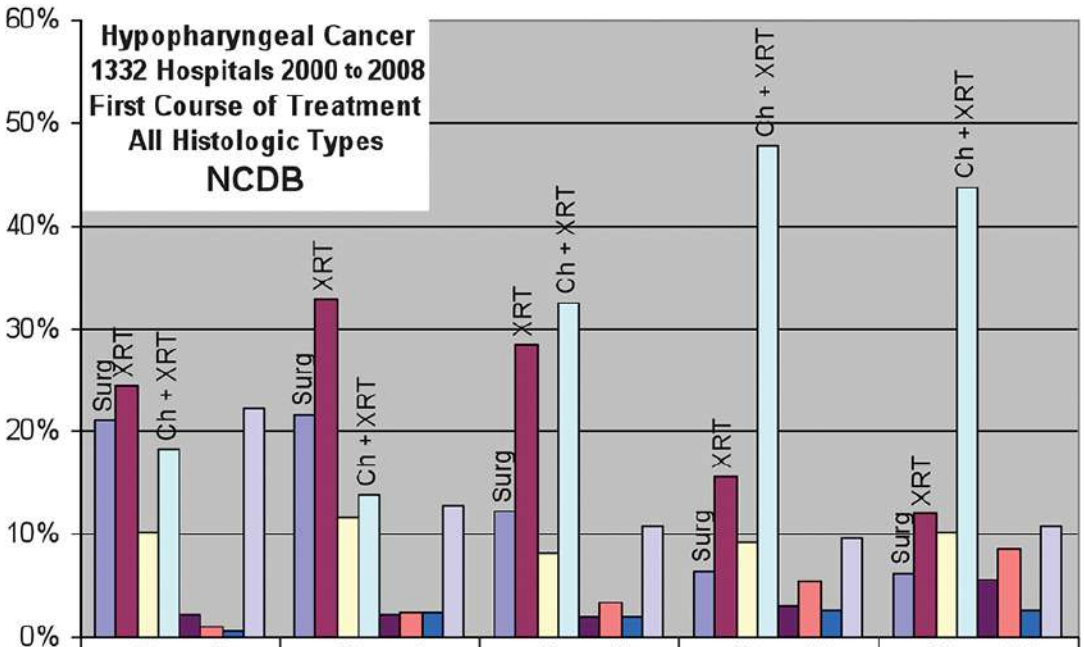
Management of hypopharynx cancer has gradually evolved over the past decades to reflect the steady advancement of nonsurgical therapy. Data from the NCDB Benchmark Reports addressing 16,136 cases diagnosed in 2000 to 2008 reveal the combination of radiation and chemotherapy to be the most common initial treatment overall for stage II (32.6%), stage III (47.8%), and stage IV (43.8%) disease (Figure 52.11).[34] Over 50% of stage III and stage IV cases received initial treatment with chemotherapy in some form—either alone or in combination with radiation or surgery. Radiation as a single-modality therapy was the most common initial treatment for stage I hypopharynx cancer (24.4%), followed by surgery alone (21.0%) as the next most common. It has been reported that approximately 35% to 45% of patients with advanced hypopharyngeal tumors treated with concurrent chemoradiotherapy utilizing IMRT can be expected to live 5 years, with laryngeal preservation in approximately two-thirds of survivors (Table 52.8).[74-76] These survival rates from single institutions utilizing IMRT should be interpreted cautiously in light of less favorable outcomes identified through a cross-sectional analysis of patients diagnosed with hypopharyngeal cancer in the United States in 2003. Review of the NCDB data identified 5-year observed survival for the majority of hypopharyngeal cancers (stage IV) to be only 19.8% (see Figure 52.4).[16]

TABLE 52.8 ONCOLOGIC OUTCOMES FOR PATIENTS UNDERGOING CONCURRENT CHEMORADIOTHERAPY AND INTENSITY-MODULATED RADIATION THERAPY FOR ADVANCED HYPOPHARYNGEAL CANCERS

Study (Reference)	Total Patients in Study (*n*)	Stage	# of Patients per Stage (%)	Larynx Preservation Rate (%)	5-Year OS (%)
Huang et al[77]	33	II	2 (6)	67	44
		III	5 (15)		
		IV	26 (79)		
Liu et al[78]	27	II	5 (19)	63	35
		III	4 (15)		

Study (Reference)	Total Patients in Study (*n*)	Stage	# of Patients per Stage (%)	Larynx Preservation Rate (%)	5-Year OS (%)
		IV	18 (66)		

OS, overall survival.



	Stage 0 (N=176)	Stage I (N=1020	Stage II (N=1849)	Stage III (N=3288)	Stage IV (N=9803)
Surg	21%	21.60%	12.30%	6.50%	6.20%
XRT	24.40%	33%	28.40%	15.60%	12%
S + XRT	10.20%	11.60%	8.30%	9.30%	10.20%
Ch + XRT	18.20%	13.80%	32.60%	47.80%	43.80%
Ch	2.30%	2.30%	2.10%	3%	5.70%
S + Ch + XRT	1.10%	2.50%	3.40%	5.40%	8.60%
Other	0.60%	2.40%	2.10%	2.70%	2.70%
None	22.20%	12.80%	10.90%	9.60%	10.90%

FIGURE 52.11 The stage-specific first course of treatment for hypopharyngeal cancer in the United States from Commission on Cancer–accredited cancer programs from 2000 to 2008 is presented with unknown stage excluded. Ch, chemotherapy; NCDB, National Cancer Database; S, surgery; XRT, radiotherapy. (From National Cancer Data Base. Commission on cancer. American College of Surgeons. Benchmark Reports. http://cromwell.facs.org/BMarks/BMPub/Ver10/bm_reports.cfm, with permission from the National Cancer Data Base.)

Induction Chemotherapy and Sequential (Chemo)radiation

Recently, there has been renewed interest in the concept of induction chemotherapy approaches for patients with locoregionally advanced H&N cancer. In an effort to examine the potential for organ preservation in patients with advanced cancers of the hypopharynx, the EORTC conducted a randomized trial for patients with tumors that would require total laryngectomy as the surgical approach. This trial randomly allocated patients to induction chemotherapy with cisplatin and 5-5-fluorouracil (5-FU), followed by definitive radiation versus primary surgical resection and postoperative radiation. With a median follow-up of 10 years, this trial demonstrated no significant difference in 5- or 10-year overall survival or progression-free survival. Of note, two-thirds of living patients in the chemoradiotherapy arm were able to retain their larynx.[79] More recently, the introduction of taxane-containing regimens has been demonstrated to improve outcomes in patients receiving induction chemotherapy. Three randomized trials have been reported that compare induction 5-FU and cisplatin versus 5-FU, cisplatin, plus a taxane. The EORTC study (TAX-323) randomized patients with locoregionally advanced, unresectable disease to induction cisplatin and fluorouracil (PF) versus induction docetaxel, cisplatin, and fluorouracil (TPF), followed by definitive radiation alone.[74] Treatment with TPF improved the median overall survival from 14.5 to 18.8 months, with a 27% reduction in the risk of death. Similar results were noted in TAX-324, which utilized similar induction chemotherapy arms (TPF vs PF), followed by concurrent chemoradiotherapy with carboplatin.[75] Five-year survival in the TPF arm was 52% versus 42% receiving PF, while no increased rates of gastric feeding tubes or tracheostomies were noted between groups. A subgroup analysis of patients with larynx and hypopharynx cancer demonstrated improved survival in these patients, as well as higher rates of laryngectomy-free survival.[76]

In addition to enhanced survival outcomes, a recent randomized French study demonstrated that TPF induction chemotherapy (compared to PF induction) results in superior tumor response rates (80% vs 59%) as assessed by laryngoscopy and CT or MRI.[80] Those with response to induction chemotherapy were treated with organ-preserving

(chemo)radiotherapy, whereas nonresponders underwent laryngectomy and postoperative (chemo)radiation. The higher response rates in the TPF arm translated into higher rates of laryngeal preservation (70% vs 57% at 3 years), without a decrease in overall survival (60% at 3 years in both arms). Despite the superiority of TPF chemotherapy than PF, concerns about tolerance of postinduction chemoradiotherapy led to the TREMPLIN trial, which compared induction TPF followed by comprehensive H&N RT with either concurrent cisplatin or cetuximab.[81] Indeed, treatment compliance was challenging following completion of TPF, with only 43% of patients receiving full-dose systemic therapy on the cisplatin arm and 71% on the cetuximab arm. Patients receiving concurrent cisplatin or cetuximab had similar clinical outcomes with regard to larynx preservation at 3 months (95% and 93%, respectively), larynx function preservation (87% and 82%, respectively), and overall survival at 18 months (92% and 89%, respectively). These aggressive treatment approaches certainly warrant consideration for H&N subsites such as hypopharynx where organ preservation is desirable and overall outcomes are generally poor. Patients with good performance status, no contraindications to taxanes or platins, a high tumor burden and/or advanced nodal disease may be optimal candidates for this approach.[82] Nevertheless, these strategies are toxic and costly, and prospective data support equivalent survival outcomes for patients treated with a 7-week course of concurrent chemoradiotherapy alone.[83] Therefore, careful assessment of tumor control, survival, and long-term functional outcome dovetailed with quality-of-life (QoL) evaluation are important to place these regimens in best perspective for patients with advanced H&N cancer.

Postradiotherapy Neck Dissection

Patients with hypopharynx cancer also require careful evaluation regarding regional nodal metastases. For N0 or N1 patients treated with primary radiation or chemoradiation approaches, adjuvant neck dissection is generally unnecessary. However, for patients presenting with N2 or N3 neck disease, careful evaluation of tumor response in the neck is important to help gauge the potential value of adjuvant neck dissection following radiation or chemoradiation. An increasing number of reports suggest that

detailed imaging of the neck 12 weeks postradiation with FDG-PET can serve as a valuable guide to help select those patients warranting adjuvant neck dissection. One such study from the University of Iowa assessed the value of a postradiation FDG-PET to help select those patients who might benefit most from subsequent neck dissection. For complete clinical responders, the Iowa study concluded that FDG-PET in this setting has a very high negative predictive value. The authors suggest that FDG-PET may be a valuable tool to help determine which patients should undergo adjuvant neck dissection versus observation following the completion of H&N radiation or (chemo)radiotherapy.[84] In a multi-institutional study comparing PET-CT surveillance versus neck dissection, at a median follow-up of 36 months, PET-CT–guided surveillance resulted in fewer neck dissections than the planned neck dissection cohort without impacting overall survival.[85] It should be noted that patients with hypopharynx cancer only comprised 10% of the total patient population. Despite these emerging data, many institutions mandate adjuvant neck dissection for all patients presenting with N2 or N3 neck disease in an effort to maximize regional disease control.[86-88] Both approaches are readily defendable at present. If neck dissection is performed, this provides an opportunity for the surgeon to reassess the primary tumor site under anesthesia with directed biopsy if suspicious for residual disease. If residual disease at the primary site is highly suspected or confirmed by biopsy several months following completion of radiation or chemoradiation, this will prompt consideration regarding the feasibility and advisability of salvage surgery options.

Palliative Radiotherapy

The management of patients with unresectable locoregional disease without distant metastases is dependent on patient performance status. A patient with a good performance status may be offered definitive RT, concurrent chemoradiotherapy, or induction chemotherapy with sequential (chemo)radiotherapy, as discussed above. However, patients with poor performance status who are not considered candidates for aggressive radiation or chemoradiation approaches should be managed with palliative intent. This may include short-course radiation regimens such as 4 to 5 Gy in 5 fractions over 1 to 2 weeks with consideration of the same scheme 3

weeks later if the regimen is tolerated and a favorable response is achieved. A recent study suggests using a 3.7-Gy fraction twice daily × 2 consecutive days for three cycles every 2 to 3 weeks, as described in RTOG-85-02, may have similar palliative efficacy with less toxicity as compared to other palliative regimens.[89] Other approaches described include 50 Gy in 16 fractions[90] and 30 Gy in 5 fractions, 2 fractions per week.[91] Systemic chemotherapy alone can be considered, although, for poor performance status patients, best supportive care with medical therapy and airway control may also be appropriate.

Palliative Chemotherapy

As many as one-quarter of patients with hypopharynx cancer will develop metastatic disease at some point in their clinical course. In this setting, treatment is palliative and should be delivered to maximize or help maintain QoL. If patients are having difficulty with local pain, bleeding, or swallowing, palliative short-course RT can be delivered, as described above. Surgery may also provide a reasonable palliative option for selected patients who have incurable disease but significant symptoms related to their localized disease, as described above. Many patients in this setting will benefit from narcotic analgesics for pain management.

Patients with adequate or good performance status should be considered for palliative chemotherapy. Median overall survival for patients with metastatic disease is 6 to 10 months.[92] Single-agent cisplatin is usually the first regimen, as it has been shown to improve overall survival.[93] Combinations of cytotoxic chemotherapies have demonstrated improved response rates over cisplatin alone, but have not improved survival and are accompanied by increased toxicity[94] and, therefore, are uncommonly utilized. However, recent randomized studies have shown efficacy of the anti-EGFR monoclonal antibody cetuximab. In combination with cisplatin as first-line treatment, cetuximab improved overall survival from 7.4 to 10.1 months over cisplatin alone.[92] As second-line therapy in patients who have progressed through platinum-based chemotherapy, cetuximab also has demonstrable activity as either monotherapy[95] or in combination with platinum-based chemotherapy.[96]

COMPLICATIONS

Surgery

The complications from surgery generally fall within the confines of bleeding, infection, reaction to the anesthesia, and damage to structures around or in the field of surgery. The damage to the laryngopharynx that occurs in the course of removing those tissues involved by cancer necessarily interferes with key laryngeal functions: breathing, swallowing, and speaking.

If an effort is made to preserve laryngeal function, some compromise may be required. A long-term tracheotomy, nothing by mouth status with the use of gastrostomy feedings, and significant dysphonia are not uncommon for patients with hypopharynx cancer treated with conservation laryngeal surgery. These same complications may attend the more comprehensive laryngopharyngectomy as well. Stenosis of the neopharynx, difficulty with alaryngeal speech, and stomal stenosis may compromise the same functions ordinarily ascribed to the larynx. For all open surgical approaches, the risk of a salivary fistula is greatest for those patients previously treated with radiation. More recent literature has advocated for the use of either pedicled or free tissue reconstruction in all cases of salvage laryngectomy when feasible, with meta-analysis showing incidence of pharyngocutaneous fistula at 37% in salvage laryngectomy with primary closure compared to 19% after flap closure ($P < .01$).[97] Although salivary fistulas are rare with endoscopic approaches, they have occurred in cases requiring aggressive laser resection.

Radiation Therapy

During a course of H&N RT, there are predictable side effects that are experienced by the majority of patients: mucositis, fatigue, loss of taste acuity, radiation dermatitis, and xerostomia. Typically, patients will begin to experience mucositis during the third week of RT. This initially manifests as mucosal blanching within the treatment field but can progress to patchy or confluent mucositis. Initially, patients can be treated with an over-the-counter pain reliever, but once patients develop grade II or III mucositis, they will commonly require narcotic analgesics for adequate pain control. The combination of dysphagia and mucositis can result in significant

nutritional compromise, necessitating intravenous hydration and parenteral nutritional supplementation. Nausea associated with treatment can also further complicate the nutritional status. These acute toxicities can become particularly pronounced in the setting of intensified radiation fractionation schedules or combined chemoradiotherapy. Patients may require prophylactic antiemetics. In patients receiving concurrent RT and platinum-based chemotherapy, there is clear potential for myelosuppression; therefore, blood counts should be monitored regularly. Signs or symptoms of infection should be addressed promptly. Finally, xerostomia can become problematic during the course of radiation. Ultimately, patients can be reassured that most of these side effects, with the exception of xerostomia, are temporary and will resolve several weeks to months following completion of therapy.

As noted, one of the acute side effects of RT that can become permanent is xerostomia. Chemical and physical modifiers of the radiation response have been utilized to reduce long-term xerostomia. The free radical scavenger amifostine has the potential to reduce radiation effects on normal tissues if administered just prior to each radiation fraction. A randomized phase III trial demonstrated a reduction in the severity of the acute and chronic grade 2 or higher xerostomia in patients who received amifostine during RT.[98] Dose-limiting toxicities commonly include hypotension and nausea. There has been concern over possible tumor-protective effects of amifostine, but a recent meta-analysis does not suggest this.[99] However, data supporting the use of amifostine to reduce xerostomia have been generated in the setting of conventional radiation, and the magnitude of benefit on xerostomia of parotid-sparing IMRT appears greater than that of amifostine.[55,100] Therefore, the ultimate value of amifostine in patients with advanced H&N cancer, especially in the setting of IMRT, has been called into question.[101] Currently, there is no universal standard recommendation across treatment centers for the use of this radioprotector.

In some cases, patients with hypopharynx cancer who complete a course of RT will be noted to have persistent laryngeal edema on subsequent follow-up visits. Although in the early post-treatment phase (in fact up to 24 months), significant or newfound edema should raise suspicion regarding the possibility of persistent or recurrent disease. The majority of patients who receive high-dose radiation across major segments of the larynx and

hypopharynx will manifest some degree of edema, mucosal congestion, and eventual fibrosis (see Figure 52.6B). Generally, this collateral damage is a tolerable chronic toxicity with modest impact on patient QoL. However, in approximately 10% to 15% of patients, this edema is severe enough to cause significant airway and swallow function compromise requiring tracheostomy. Rarely, more significant complications such as osteoradionecrosis (ORN) of the cervical spine may occur. In this setting, patients can present with persistent neck pain prompting imaging and biopsy. Most cases can be managed conservatively; however, progression to serious complications including epidural abscess, radiculopathy, and myelopathy has been described. Once neurologic symptoms emerge, they can progress rapidly, indicating the need to maintain vigilance in patients with cervical spine ORN.[102-104]

LONG-TERM FOLLOW-UP

Regardless of whether patients undergo primary surgery or RT, there is value in close post-treatment surveillance by H&N surgeon and radiation oncologist in a multidisciplinary manner. Follow-up care is designed initially to survey for recurrence. As duration from time of intervention to clinic visits lengthen, the focus shifts to surveillance for second primaries (ie, lung), to address morbidity from treatment, and to provide generalized support.

Although there are limited data to guide surveillance, commonly, during the first 6 months after treatment, patients should be followed every 4 to 6 weeks with clinical examination, including fiberoptic nasopharyngoscopy. Recommended guidelines include a follow-up visit every 1 to 3 months during the first year, every 2 to 4 months for the second year, every 4 to 6 months for years 3 through 5, and every 6 to 12 months thereafter. In addition, if the patient received comprehensive H&N radiation, the serum thyroid-stimulating hormone level should be measured every 6 to 12 months. Imaging evaluation of the neck, most commonly with CT or MRI scan, is obtained at 3- to 6-month intervals during the first 2 years or as indicated based on clinical findings. Functional imaging with ^{18}FDG-PET can sometimes prove valuable to help differentiate post-treatment fibrosis from persistent or recurrent disease.

A study by Hermans et al[105] examined findings on CT scan of the neck 3 to 4 months following completion of RT for patients with larynx or hypopharynx cancer to examine correlation with long-term outcome. The authors suggest that in patients achieving complete radiographic resolution of all pretreatment disease, the likelihood of subsequent local failure is very small. These patients might, therefore, undergo routine clinical examination, with repeat imaging reserved for instances where the clinical examination becomes suspicious for recurrence. For patients who achieved <50% reduction in tumor volume or retained a mass 1 cm or larger on the post-treatment imaging study, the likelihood of local failure was 100% and 30%, respectively. In these patients, repeat CT at 3 to 4 months, FDG-PET, or biopsy is, therefore, recommended. Preliminary reports indicate that the results of the first post-RT FDG-PET scan may be a strong predictor of developing locoregional disease recurrence.

In the post-treatment setting of patients with hypopharynx cancer, the involvement of an experienced H&N radiologist is highly desirable for optimal interpretation of imaging results. Soft tissue changes following ablative surgery and reconstruction, or following high-dose radiation or chemoradiation with resultant edema and fibrosis, can be very difficult to differentiate from tumor, particularly for the inexperienced reader.

MANAGEMENT OF RECURRENCE

After completion of treatment, patients should be followed closely for signs of recurrent or persistent disease. If recurrence is suspected, this should be confirmed by biopsy. If biopsy is confirmatory, then the patient should undergo complete restaging to assess the extent of disease. In the setting of local or regional disease alone, patients treated with initial radiation or chemoradiation can be considered for surgical salvage therapy. Although salvage surgery following comprehensive H&N radiation and chemotherapy presents several resection and reconstructive healing challenges for the surgeon, selected patients may still derive long-term benefit from this approach. Select patients with low-volume localized disease may be candidates for TLM for recurrent disease following radiation.[106] Recurrent patients who initially received comprehensive H&N radiation have traditionally not been considered good candidates for repeat

high-dose radiation in light of normal tissue tolerances. However, two recent prospective RTOG studies have demonstrated that reirradiation to the H&N is feasible.[107,108] With the advent of highly conformal radiation delivery techniques, selected patients may benefit from reirradiation approaches in conjunction with systemic chemotherapy.[109] A retrospective study from Memorial Sloan-Kettering Cancer Center has suggested that IMRT is beneficial for local control in this setting,[110] and a recent prospective trial of reirradiation utilizing IMRT suggests long-term disease control can be achieved in select patients with tolerable toxicity.[111] The use of stereotactic body radiosurgery is becoming more common in the management of patients with H&N cancer who manifest locoregional recurrence. Recent data suggest that patients with laryngeal and hypopharyngeal primaries exhibit significantly more late toxicities compared to those with oral cavity and oropharyngeal primaries, likely related to cartilage in the retreatment region. Therefore, careful consideration should be given to patient performance status, preexisting organ dysfunction, and goals of care prior to delivering ablative doses of RT in the laryngopharynx.[112] Many patients with recurrent disease, however, are not good candidates for aggressive surgery or salvage RT and are best served with systemic chemotherapy or best supportive care approaches.

QUALITY OF LIFE

Assessment of parameters, including functional status, organ preservation, treatment cost, and patient assessment of QoL, plays an increasingly important role in the evaluation of overall treatment efficacy. For patients with larynx and hypopharynx cancer, a focus of contemporary clinical investigation has been the study of treatments designed to preserve laryngeal function for patients traditionally treated with total laryngectomy. A frequently cited but somewhat controversial study by McNeil et al[113] employed a questionnaire administered to healthy individuals and concluded that some might forgo total laryngectomy in favor of alternative therapy, even if this choice diminished their ultimate chance for cure. A more recent report by El-Deiry et al[114] evaluated long-term QoL in a matched pair analysis comparing the surgical and nonsurgical treatment of patients with advanced H&N cancer involving the oropharynx,

hypopharynx, and larynx. Although patients in the surgery arm demonstrated worse speech outcomes than those treated with chemoradiation, this difference did not carry over to the overall QoL score. These investigators concluded that, although it seems reasonable that organ preservation (nonsurgical) treatment will uniformly result in a higher QoL, the complexities of human adjustment and multitude of potential treatment effects render this assumption invalid for many patients. Alternatively, a study from the Medical University of South Carolina compared swallow-related QoL after surgery or RT for H&N cancer using a dysphagia symptom survey, the MD Anderson Dysphagia Inventory (MDADI). They found significantly better scores on the emotional and functional components of the MDADI for patients undergoing chemoradiation compared to those undergoing surgery followed by radiation.[115] There have been relatively few prospective assessments of QoL following treatment for H&N cancer. In a subset of locally advanced patients requiring radical surgery, such as total laryngectomy and partial pharyngectomy, the functional deficits are predictable. However, for patients undergoing organ preservation with either radiation alone or in combination with chemotherapy, it can be difficult to assess the true extent and quality of organ preservation. Regardless of the primary treatment approach, these patients often require long-term speech, swallow, and dental rehabilitation. A study from Meyer et al[116] retrospectively assessed speech intelligibility and QoL in survivors of H&N cancer. A total of 64 patients were enrolled; 31 underwent RT alone, 5 underwent surgery alone, and 28 received both. All patients underwent comprehensive subjective and objective testing of speech function and QoL. They found significant subjective and objective deficits in speech and QoL, even 5 years after completion of therapy. Terrell et al[117] reported the results of a self-administered health survey of 570 patients at a Veterans' Administration hospital that demonstrated that the single most notable event having a negative impact on QoL was placement of a feeding tube. This was followed by medical comorbid conditions, presence of a tracheotomy tube, chemotherapy, and neck dissection.

A prospective study on QoL utilizing the EORTC QLQ-C30 and QLQ-H&N35 questionnaires was conducted in Sweden on 357 patients. This study found that QoL issues were significantly associated with the site of origin, with stage at diagnosis being the most important predictor. In

addition, patients with hypopharynx cancer exhibited the poorest QoL.[118] Similarly, another study prospectively examining swallow function in patients with H&N cancer demonstrated that worse swallowing was associated with hypopharyngeal tumor sites.[119] Although the use of IMRT can have a significant impact on xerostomia and QoL measures in patients with H&N cancer,[120,121] the intimate approximation of hypopharyngeal tumors to pharyngeal constrictor musculature does not allow for sparing of these structures vital to long-term swallow function, likely contributing to the poorer QoL of patients with hypopharynx cancer in comparison to patients with other H&N cancer.[122]

CONCLUSION

Patients with cancers of the hypopharynx commonly present with advanced disease associated with varying degrees of compromise in speech or swallow function. Many patients with hypopharynx cancer also carry significant medical and social comorbidities. Typically, small T1 or T2 lesions can be managed with either primary radiation or surgery, with similar clinical outcome. For intermediate-stage disease that would require laryngopharyngectomy for the surgical approach, an increasingly preferred treatment option is combined chemoradiation. For bulky hypopharynx tumors with significant airway compromise, laryngeal distortion, and cartilage destruction, it is generally best to proceed with definitive surgery with postoperative radiation or chemoradiation.

Despite an aggressive approach in the overall management of patients with hypopharynx cancer, ultimate cure rates remain quite poor. There are relatively few early-stage patients; and for many advanced-stage patients, it is difficult to achieve long-term control. Even for those patients with excellent response to therapy, there exists a continuous risk for the development of second malignancies, particularly of the upper aerodigestive track with long-term follow-up. Post-treatment patients often require aggressive speech and swallow therapy to maximize their functional outcome. There is significant interest in the incorporation of molecularly targeted therapies in combination with traditional cytotoxic therapy and radiation in an effort to improve outcomes.

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CHAPTER 53

Laryngeal Cancer

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ANATOMY

The larynx is divided into the supraglottis, glottis, and subglottis. The supraglottis consists of the epiglottis, false vocal cords, ventricles, aryepiglottic folds, and arytenoids. The glottis includes the floor of the ventricle, interarytenoid area, true vocal cords, and the anterior commissure. The subglottis is located below the vocal cords (Figures 53.1 and 53.2).[1]

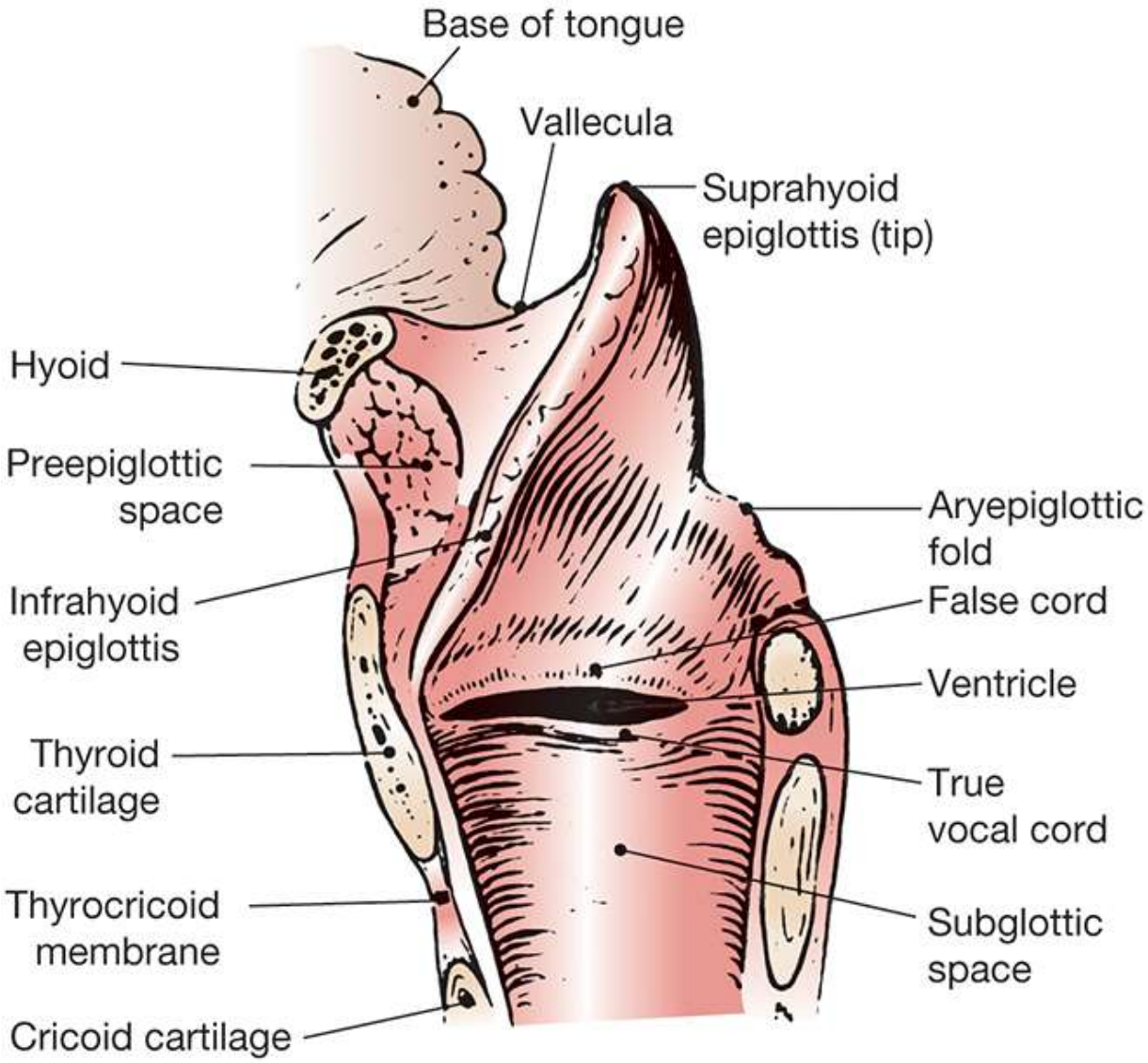


FIGURE 53.1 Diagrammatic sagittal section of the larynx. (Reprinted from Paulsen F, Waschke J. *Sobotta Atlas of Human Anatomy*. 17th ed. Urban & Fischer; 2023, Figure 11.49. Copyright © 2023 Elsevier GmbH Munich. With permission.)

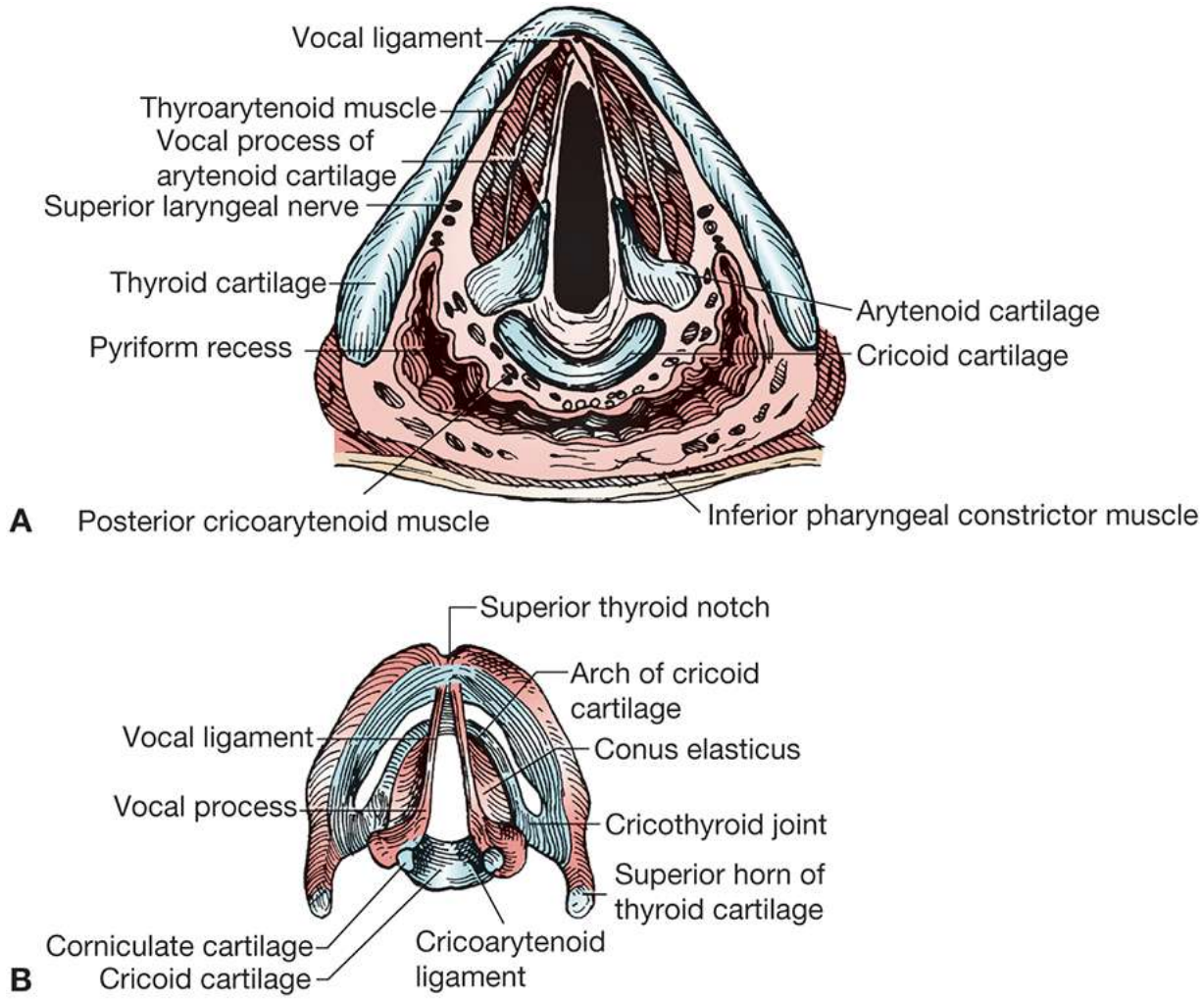


FIGURE 53.2 A. Cross section of the larynx at the level of the vocal cords. B. Framework of the larynx. (Reprinted from Paulsen F, Waschke J. *Sobotta Atlas of Human Anatomy*. 17th ed. Urban & Fischer; 2023, Figures 11.63 and 11.40. Copyright © 2023 Elsevier GmbH Munich. With permission.)

The axial line of demarcation between the glottic and supraglottic larynx is the apex of the ventricle. The demarcation between the glottis and the subglottis is ill-defined, but the subglottis is considered to extend from a point 5 mm below the free margin of the vocal cord to the inferior border of the cricoid cartilage or 10 mm below the apex of the ventricle.

The vocal cords vary from 3 to 5 mm in thickness and terminate posteriorly with their attachment to the vocal process or the arytenoid cartilage. The posterior commissure is the mucosa between the arytenoids (interarytenoid area).

The shell of the larynx is formed by the hyoid bone, thyroid cartilage, and cricoid cartilage; the cricoid cartilage is the only complete ring of the upper airway. The more mobile interior framework is composed of the heart-shaped epiglottis and the arytenoid, corniculate, and cuneiform cartilages. The corniculate and cuneiform cartilages produce small, rounded bulges at the posterior end of each aryepiglottic fold.

The thyroid and the cricoid cartilage and a portion of the arytenoid cartilage are hyaline cartilage and may ossify with age, particularly in men. The epiglottis is elastic cartilage; ossification does not occur, and even focal calcification is rare.[2]

The external laryngeal framework is linked together by the thyrohyoid, the cricothyroid, and the cricotracheal ligaments or membranes (Figures 53.3 and 53.4).[1]

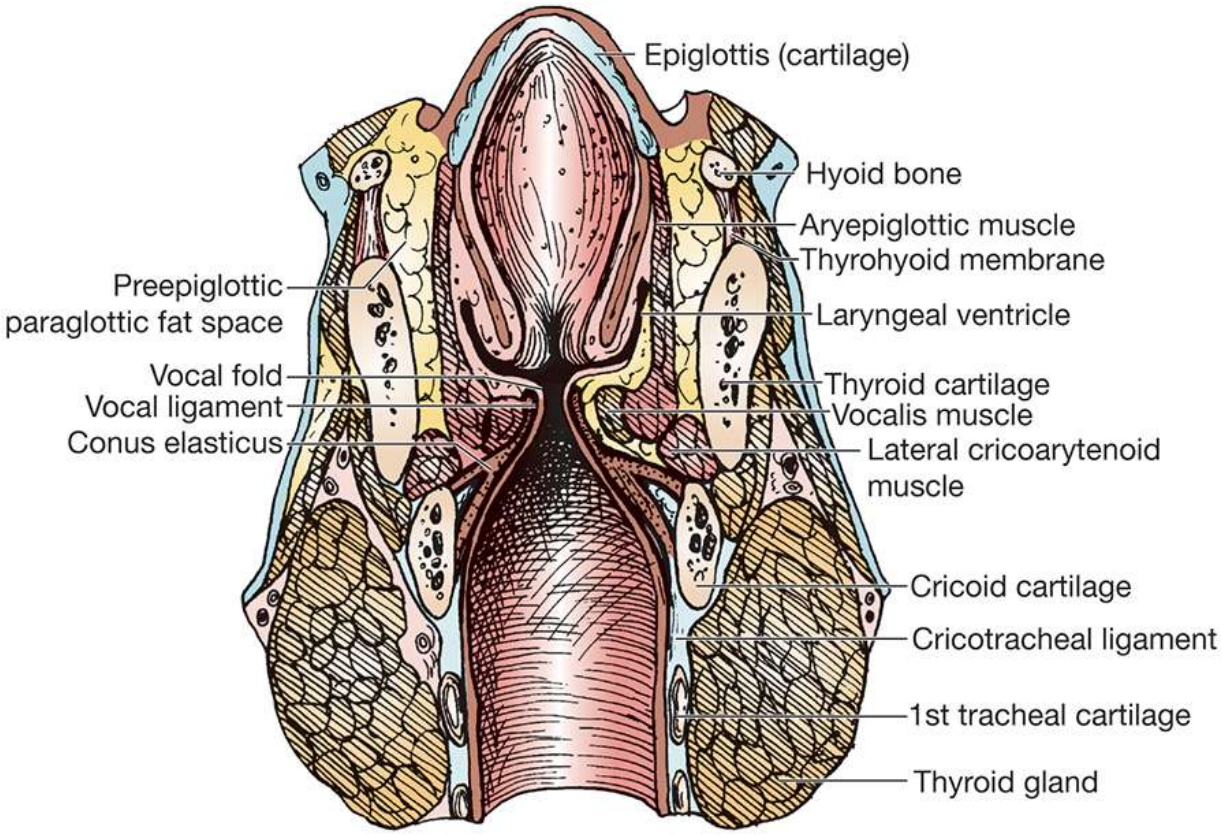


FIGURE 53.3 Diagram of the coronal view of the larynx. (Reprinted from Paulsen F, Waschke J. *Sobotta Atlas of Human Anatomy*. 17th ed. Urban & Fischer; 2023, Figure 11.66. Copyright © 2023 Elsevier GmbH Munich. With permission.)

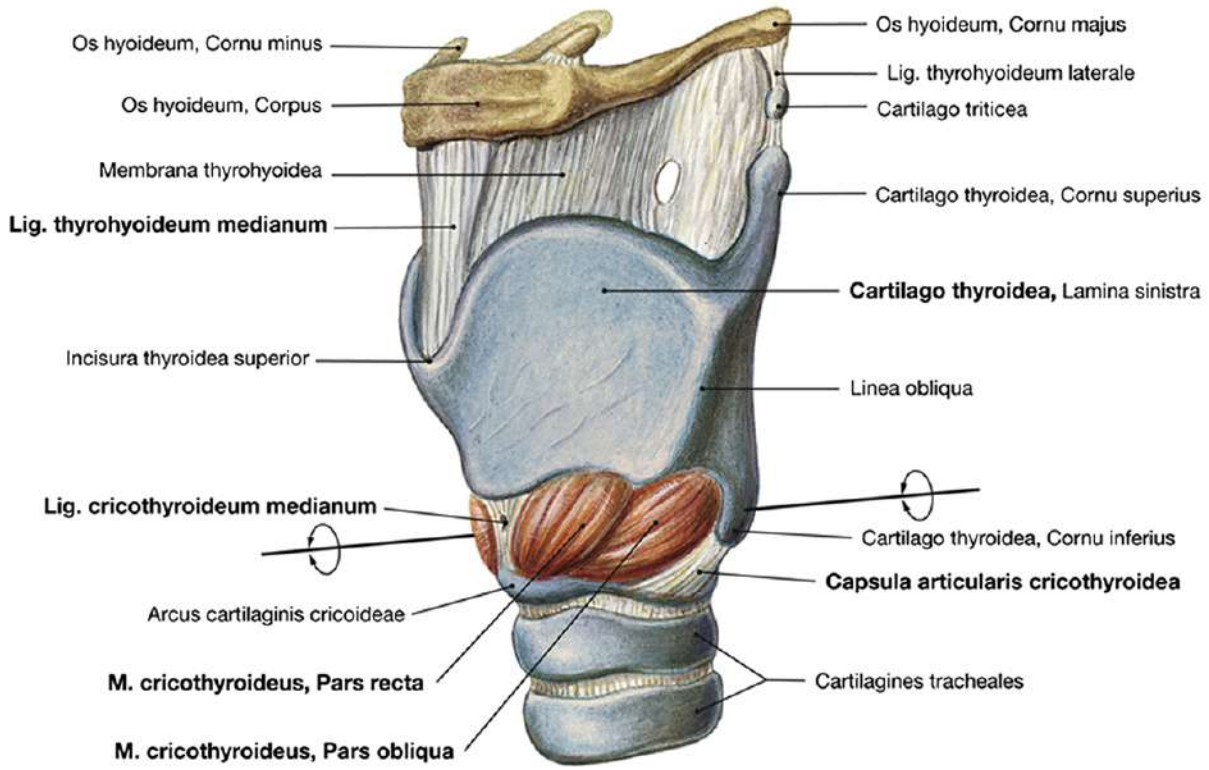


FIGURE 53.4 External view of the larynx. (Reprinted from Paulsen F, Waschke J. *Sobotta Atlas of Human Anatomy*. 17th ed. Urban & Fischer; 2023, Figure 11.41. Copyright © 2023 Elsevier GmbH Munich. With permission.)

The epiglottis is joined superiorly to the hyoid bone by the hyoepiglottic ligament. The epiglottis is joined to the thyroid cartilage by the thyroepiglottic ligament at a point just below the thyroid notch and above the anterior commissure. This area of attachment is the *petiole* of the epiglottis. The arrangement of the ligaments that connect the cricoid and arytenoid cartilages and form the vocal ligaments is shown in Figure 53.2B.[1] The conus elasticus (cricovocal ligament) is the lower portion of the elastic membrane that connects the inferior framework. It connects the upper surface of the cricoid, the vocal process of the arytenoid, and the lower thyroid cartilage; its free border is thickened into the vocal ligament. The quadrangular membrane is the upper portion of the elastic membrane that connects the superior framework. It connects the false vocal cords, aryepiglottic folds, and the epiglottis.

The vocal ligaments and thyroarytenoid/vocalis muscle complex attach to the vocal process of the arytenoid posteriorly and the thyroid cartilage

anteriorly. The intrinsic muscles of the larynx, which primarily control the movement of the cords, are presented in Figures 53.2 and 53.3.[1] The extrinsic muscles are concerned primarily with swallowing. The cricothyroid muscle draws the larynx anteriorly and inferiorly when contracting. The consequence is increased vocal cord tension, leading to increased pitch of the voice. It is innervated by the external branch of the superior laryngeal nerve (Figure 53.4).[1] The intrinsic muscles of the larynx are innervated by the recurrent laryngeal nerve.

The preepiglottic and paraglottic fat spaces are essentially one contiguous space lying between the external framework of the thyroid cartilage and hyoid bone and the inner framework of the epiglottis and intrinsic muscles. Lam and Wong[3] showed that there are thin membranous septa between the paraglottic and preepiglottic spaces, which produce a barrier to tumor spread to a limited degree. The space is traversed by blood and lymphatic vessels as well as nerves. Because few capillary lymphatics arise in this area, invasion of the fat space seldom leads to lymph node metastases. The fat space is limited by the conus elasticus inferiorly; the thyroid ala, thyrohyoid membrane, quadrangular membrane, and hyoid bone anterolaterally; the hyoepiglottic ligament superiorly; and the fascia of the intrinsic muscles medially. Posteriorly, it is adjacent to the anterior wall of the pyriform sinus.

The laryngeal surface of the epiglottis and the free margin of the vocal cords are squamous epithelium, and the remaining mucosa is usually pseudostratified ciliated columnar epithelium. Beneath the epithelium of the free edge of the vocal cord is the lamina propria, which can be divided into three layers. There is no true submucosal layer along the free margin of the vocal fold.[4] The laryngeal arteries are branches of the superior and inferior thyroid arteries.

The supraglottic structures have a rich capillary lymphatic plexus; the trunks pass through the preepiglottic space and the thyrohyoid membrane and terminate mainly in the jugulodigastric (level II) lymph nodes; a few drain to the middle internal jugular chain (level III) lymph nodes.

There are essentially no capillary lymphatics of the true vocal cords; as a result, lymphatic spread from glottic cancer occurs only if tumor extends to supraglottic or subglottic areas.

The subglottic area has relatively few capillary lymphatics. The lymphatic trunks pass through the cricothyroid membrane to the pretracheal (Delphian) lymph nodes in the region of the thyroid isthmus. The subglottic area also drains posteriorly through the cricotracheal membrane, with some trunks going to the paratracheal (level VI) lymph nodes and others continuing to the inferior jugular (level IV) chain.

EPIDEMIOLOGY AND RISK FACTORS

Cancer of the larynx represents about 2% of the total cancer burden and accounts for 0.3% of all cancer deaths. It is the second most common head and neck mucosal cancer. In 2023, in the United States, there will be approximately 12,380 new cases of cancer of the larynx (9,900 men and 2,480 women) and about 3,820 deaths from laryngeal cancer.[5] Based on 1973-1998 U.S. data, at diagnosis, about 51% of the cases remain localized, 29% have regional spread, and 15% have distant metastases.[6] The ratio of glottic to supraglottic carcinoma is approximately 2:1.

Cancer of the larynx is strongly related to cigarette smoking. The risk of tobacco-related cancers of the upper alimentary and respiratory tracts declines among former smokers after 5 years and is said to approach the risk of nonsmokers after 10 years of abstention.[7] The role of alcohol in provoking laryngeal cancer remains unclear.[8] Some evidence exists that heavy marijuana smoking may be associated with laryngeal cancer in young patients.

PATTERNS OF SPREAD

Local Spread

Although supraglottic and glottic lesions tend to remain confined to their original compartments, there is no anatomic barrier to growth from one area to the next. Glottic lesions tend to be slow growing, but as they increase in size, they extend to the supraglottic and subglottic areas. Supraglottic lesions do not often start near the vocal cords. Involvement of the cords on their external epithelial surface is a late phenomenon, but submucosal extension by way of the paraglottic space occurs earlier.

The fat space is an important avenue of submucosal tumor spread for infrahyoid epiglottis, false cord, and true vocal cord lesions. As the false cord and the true vocal cord lesions penetrate anteriorly and laterally, they quickly encounter the tough perichondrium of the thyroid cartilage and may eventually be shunted by the conus elasticus (lateral cricothyroid membrane) out of the larynx via the cricothyroid space. Thyroid cartilage invasion usually occurs in the ossified section of the cartilage, commonly in the region of the anterior commissure tendon or the junction of the anterior one-fourth and the posterior three-fourths of the thyroid lamina.[9]

Fixation of the vocal cord from laryngeal cancer is usually caused by invasion or destruction of the vocal cord muscle, invasion of the cricoarytenoid muscle or joint, or, rarely, invasion of the recurrent laryngeal nerve. Perineural spread is uncommon.

Supraglottic Larynx

Suprahyoid Epiglottis

A lesion of the suprahyoid epiglottis may produce a large exophytic mass with little tendency to destroy cartilage or spread to adjacent structures. Other lesions may infiltrate the tip and destroy cartilage. The destructive lesions tend to invade the vallecula and preepiglottic space, the lateral pharyngeal walls, and the remainder of the supraglottic larynx.

Infrahyoid Epiglottis

Lesions of the infrahyoid epiglottis tend to produce irregular tumor nodules and simultaneously invade the porous epiglottic cartilage and thyroepiglottic ligament into the preepiglottic fat space and extend toward the vallecula and base of the tongue. The thick hyoepiglottic ligament is an effective tumor barrier. However, the tumor may present in the vallecula and base of the tongue without involving the suprahyoid epiglottis.

Lesions of the infrahyoid epiglottis grow circumferentially to involve the false cords, aryepiglottic folds, medial wall of the pyriform sinus, and the pharyngoepiglottic folds. Invasion of the anterior commissure and cords and anterior subglottic extension usually occur only in advanced lesions. Infrahyoid epiglottic lesions that extend onto or below the vocal cords are at high risk for thyroid cartilage invasion, even if the cords are mobile.[10]

False Cord

Early false cord carcinomas, which are usually submucosal with little exophytic component, are difficult to delineate accurately. They involve the paraglottic fat space early in their development and may spread a considerable distance beneath the mucosa without producing physical signs. These carcinomas extend to the perichondrium of the thyroid cartilage quite early, but cartilage invasion is a late phenomenon. Extension to the lower portion of the infrahyoid epiglottis and invasion of the preepiglottic space are common. Submucosal extension involves the true vocal cord, which may appear normal. Vocal cord invasion is often associated with thyroid cartilage invasion. Submucosal extension to the medial wall of the pyriform sinus occurs early.

Aryepiglottic Fold/Arytenoid

Early lesions of the aryepiglottic fold/arytenoid are usually exophytic. It may be difficult to decide whether the lesion started on the medial wall of the pyriform sinus or on the aryepiglottic fold. As the lesions enlarge, they extend to adjacent sites and eventually cause fixation of the larynx, which is usually a result of involvement of the cricoarytenoid muscle or joint or, rarely, invasion of the recurrent laryngeal nerve. Computed tomography (CT) may distinguish the cause of fixation. Advanced lesions invade the thyroid, epiglottic, and cricoid cartilages and eventually invade the pyriform sinus and postcricoid area.

Glottic Larynx

Most lesions of the true vocal cord begin on the free margin and upper surface of the cord. When diagnosed, about two-thirds are confined to the cords, usually one cord. The anterior portion of the cord is the most common site. Anterior commissure involvement, which is common, is said to occur when no tumor-free cord can be seen anteriorly; if the lesion crosses to the opposite cord, anterior commissure invasion is certain. Small lesions isolated to the anterior commissure account for only 1% to 2% of cases. Extension to the posterior commissure is uncommon, occurring only in advanced lesions.

Tumors at the anterior commissure may extend anteriorly via the anterior commissure tendon (Broyles ligament)[11] into the thyroid cartilage. Kirchner,[12] using whole-organ sections, showed that such extension is unusual unless the tumor extends off the vocal cord onto the base of the infrahyoid epiglottis and suggested that the tendon serves as more of a barrier than an avenue of tumor spread. Early subglottic extension is also associated with involvement of the anterior commissure, and tumor may grow through the cricothyroid membrane.

Lesions that arise on the posterior half of the vocal cord tend to extend along the submucosa toward the medial side of the vocal process and invade the cricoarytenoid joint and posterior commissure; this spread is difficult to appreciate by clinical examination.

Subglottic extension may occur by simple mucosal surface growth, but it more commonly occurs by submucosal penetration beneath the conus elasticus. One centimeter of subglottic extension anteriorly or 4 to 5 mm of subglottic extension posteriorly brings the border of the tumor to the upper margin of the cricoid, exceeding the anatomic limits for conventional hemilaryngectomy. Lesions may spread beneath the epithelium along the length of the vocal cord within Reinke space.[13]

As vocal cord lesions enlarge, they extend to the false cord, vocal process of the arytenoid, and subglottis. Infiltrative lesions invade the vocal ligament and muscle and eventually reach the paraglottic space and the perichondrium of the thyroid cartilage. Advanced glottic lesions eventually penetrate through the thyroid cartilage or via the cricothyroid space to enter the neck, where they may invade the thyroid gland. Lesions involving the anterior commissure often exit the larynx via the cricothyroid membrane after they extend subglottically.[13]

A fixed cord that is associated with a lesion having <1 cm of subglottic extension and no false cord involvement does not ordinarily indicate invasion of the thyroid cartilage.[12] If the false cord is also involved, cartilage invasion is likely.

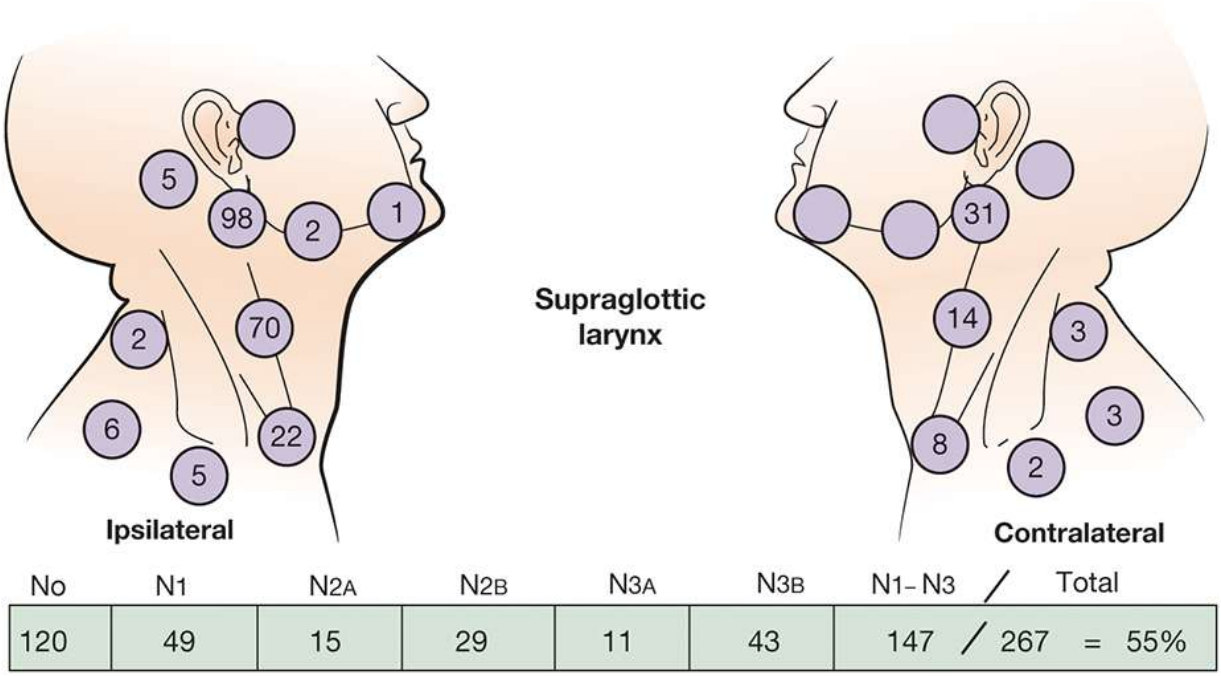
Subglottic Larynx

Subglottic cancers are rare.[14] Most involve the inferior surface of the vocal cords by the time they are diagnosed, so it is difficult to know whether the

tumor started on the undersurface of the vocal cord or in the true subglottic larynx. Because early diagnosis is uncommon, most lesions are bilateral or circumferential at discovery. They involve the cricoid cartilages in the early stage because there is no intervening muscle layer. Partial or complete fixation of one or both cords is common; misdiagnosis or diagnostic delay is frequent.

Lymphatic Spread

The location and stage of neck nodes detected on admission for previously untreated patients with squamous cell carcinoma of the supraglottic larynx are given in Figure 53.5.[15] The disease spreads mainly to the level II nodes. The level Ib nodes are rarely involved, and there is only a small risk of level V lymph node involvement. The incidence of clinically positive nodes is 55% at the time of diagnosis; 16% are bilateral.[15] Elective neck dissection shows pathologically positive nodes in at least 16% of cases; observation of initially node-negative necks eventually identifies the appearance of positive nodes in 33% of cases.[16,17] Spread to the pyriform sinus, vallecula, and base of the tongue increases the risk of lymph node metastases. The risk of late-appearing contralateral lymph node metastasis is 37% if the ipsilateral neck is pathologically positive, but the risk is unrelated to whether the nodes in the ipsilateral neck were palpable before neck dissection.



No	N1	N2A	N2B	N3A	N3B	N1–N3 / Total
120	49	15	29	11	43	147 / 267 = 55%

FIGURE 53.5 Nodal distribution on admission, MD Anderson Cancer Center, 1948-1965. (From Lindberg R. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. *Cancer*. 1972;29[6]:1446-1449. Copyright © 1972 American Cancer Society. Reprinted by permission of John Wiley & Sons.)

The incidence of clinically positive lymph nodes at diagnosis for vocal cord carcinoma approaches zero for T1 lesions and is ≤6% for T2 lesions.[18] The incidence of neck metastases increases to 20% to 30% for T3 and T4 lesions. Glottic spread is typically associated with metastasis to the level II nodes. Anterior commissure and anterior subglottic invasion are also associated with involvement of the midline pretracheal lymph node (level VI).

Lederman[19] reported a 10% incidence of positive lymph nodes in 73 patients with subglottic carcinoma.

CLINICAL PRESENTATION

Carcinoma arising on the true vocal cords produces hoarseness at a very early stage. Odynophagia, otalgia, pain localized to the thyroid cartilage, and airway obstruction are features of advanced lesions.

Hoarseness is not a prominent symptom of cancer of the supraglottis until the lesion becomes extensive. Odynophagia, usually mild, is the most frequent initial symptom, often described as a sore throat. Some patients report a sensation of a "lump in the throat." Pain is referred to the ear by way of Arnold branch of the vagus nerve. A neck mass may be the first sign of a supraglottic cancer. Late symptoms include weight loss, halitosis, dysphagia, and aspiration.

DIAGNOSTIC WORKUP

Physical Examination

Flexible fiberoptic endoscopes provide the best view of the larynx, hypopharynx, and posterior oropharynx. The scope is inserted through the nasal passage and passed over the nasopharyngeal side of the soft palate to provide a "bird's-eye" view of the larynx. The mucosal surfaces of the base of tongue, posterior pharyngeal wall, vallecula, hypopharynx, supraglottis, glottis, and subglottis are examined. Vocal cord mobility is determined by asking the patient to say "ee" (adduction) and sniff in (abduction). Subtle distinctions between paresis and paralysis may require multiple examinations or stroboscopy.

Ulceration of the infrahyoid epiglottis or fullness of the vallecula is an indirect sign of preepiglottic space invasion. Palpation of diffuse, firm fullness above the thyroid notch with widening of the space between the hyoid and the thyroid cartilages signifies invasion of the preepiglottic space. The preepiglottic fat space is a low-density area on the CT scan, and changes resulting from tumor invasion are easily seen.

Postcricoid extension may be suspected when the laryngeal click disappears on physical examination. Postcricoid tumor may cause the thyroid cartilage to protrude anteriorly, producing a fullness of the neck. Invasion of the thyroid cartilage remains a difficult clinical diagnosis. Localized pain or tenderness to palpation or a small bulge over one ala of the thyroid cartilage is suggestive.

Radiographic Studies

CT scan with contrast enhancement is often the method of choice for studying the larynx (Figure 53.6).[20] The CT scan should be performed before biopsy so that abnormalities that may be caused by the biopsy are not confused with tumor. CT is preferred to magnetic resonance (MR) imaging because the longer scanning time for MR results in motion artifact.[21] CT slices 1 to 2 mm thick are obtained at 1- to 2-mm intervals through the larynx and at 3-mm intervals for the remainder of the study. Thinner sections (1-2 mm through the larynx) facilitate high-quality multiplanar reformations. The gantry is angled so that the scan slices are parallel to the plane of the true vocal cords. It is also necessary to obtain a CT scan of the entire neck to detect positive, nonpalpable lymph nodes. Positive retropharyngeal nodes may be present at diagnosis in patients with laryngeal cancer who have advanced neck disease.[22] Retropharyngeal adenopathy will not be apparent on physical examination but is usually appreciated on CT scan. Contrast enhancement helps to outline the blood vessels and the thyroid gland. Tumor is often enhanced, probably because of reactive inflammatory changes.

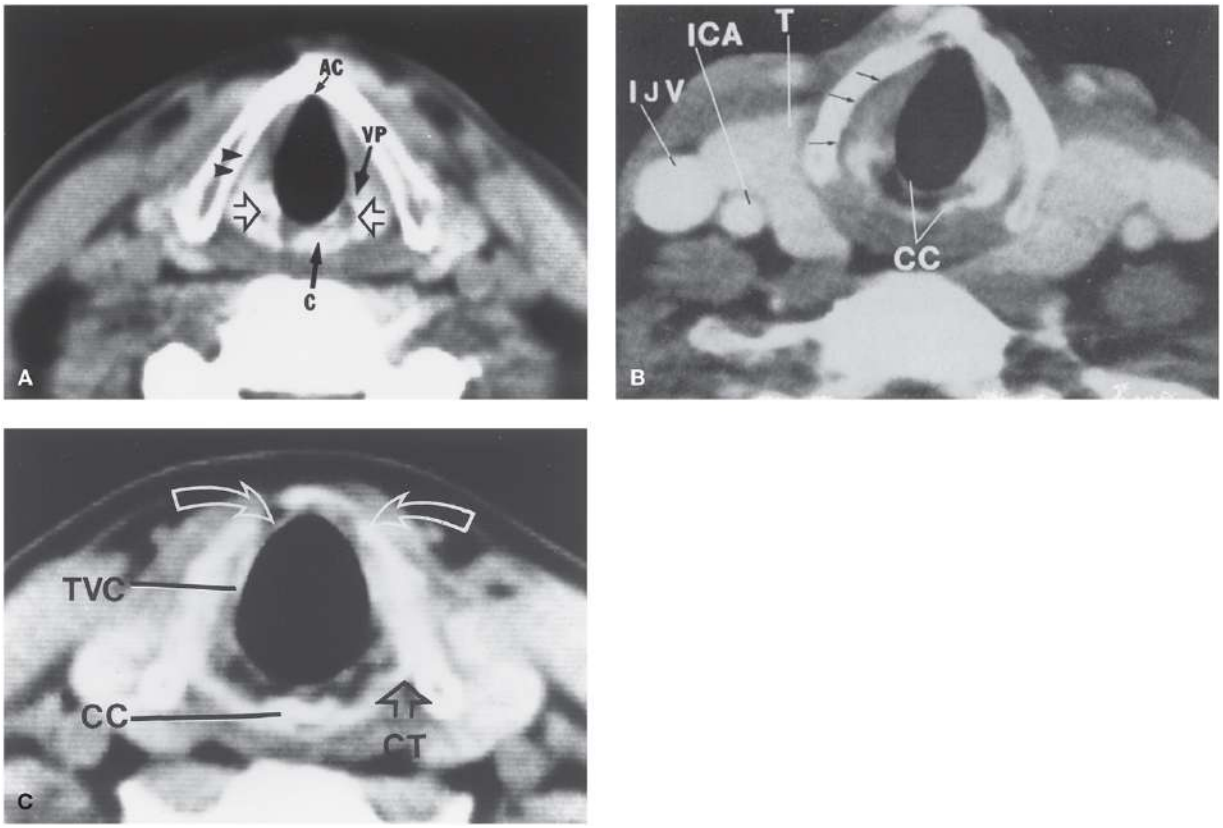


FIGURE 53.6 A. Normal computed tomography anatomy of the midplane of the true vocal cords. Open arrows indicate arytenoid cartilages. The top of the cricoid cartilage (C) is partially visualized at this level. The vocal process of the left arytenoid cartilage is demonstrated. A narrow, low-density plane is seen between the right true vocal cord and the thyroid lamina (arrowheads); this is the inferior part of the paraglottic fat space. Note the complete lack of tissue at the anterior commissure. Any tissue here density should be considered abnormal. B. Normal computed tomography anatomy just below the midplane of the vocal cords. Arrows indicate low-density lower paraglottic fat space. The fibrofatty tissue in this space facilitates separation of the vocal cord and the adjacent thyroid lamina. If this clear space is maintained in the face of the thyroid lamina irregularity adjacent to the tumor, the lamina abnormality can be attributed to uneven calcification rather than tumor destruction. The posterior portion (lamina) of the cricoid cartilage (CC) is seen. The outer and inner cortex of the cartilage is calcified; an intervening marrow space has a lower density. The vertical height of the lamina is 2 to 3 cm. There is incomplete calcification of the thyroid cartilage anteriorly. C. Normal computed tomography anatomy 5 mm below the free margin of the true vocal cord. The vocal cord appears thin because of abduction during scanning. There is incomplete bilateral paramedian calcification and thinning of the thyroid lamina (arrows). Notice the normal lack of tissue density between the airway and the anterior arch of the thyroid cartilage. CT, cricothyroid joint; ICA, internal carotid artery; IJV, internal jugular vein; T, thyroid gland. (Reprinted with permission from Million RR, Cassisi NJ. Larynx. In: Million RR, Cassisi NJ, eds. *Management of Head and Neck Cancer: A Multidisciplinary Approach*. J.B. Lippincott; 1984:315-364.)

The value of MR imaging includes defining subtle exolaryngeal spread or early cartilage destruction as well as the extent of tracheal invasion and esophageal invasion. Sagittal MR may also be useful in detecting early invasion of the base of the tongue.

Vocal Cord Carcinoma

Although the CT scan does not show minimal mucosal lesions and is generally not helpful for well-defined, easily visualized T1, or early T2 vocal cord carcinomas, it is almost always obtained. CT is excellent for determining subglottic extension and is often used in selected T1 and most T2 lesions for this reason alone. CT scanning is useful in the diagnosis of moderately advanced and advanced lesions; it is excellent for demonstrating extension outside the larynx into the soft tissues of the neck and has the potential for determining thyroid or cricoid cartilage invasion, which tends to occur at the edges of the cartilage rather than on the faces. Early cartilage involvement is difficult to detect with axial scans, but it may be demonstrated by coronal or sagittal scanning techniques. If the low-density plane of the paraglottic space is intact, cartilage is probably not invaded by tumor.

Archer et al[23] correlated CT findings with the incidence of cartilage or bone invasion on whole-organ sections. For 12 of 14 patients with pathologic evidence of cartilage invasion, the average diameter of the tumor in two dimensions was >16 mm, and the lesion was located below the top of the arytenoid. Lesions in which the maximum diameter lay above the top of the arytenoid had a low incidence of cartilage invasion.[23]

Supraglottic Carcinoma

The CT scan provides an excellent means for viewing the preepiglottic and paraglottic fat spaces. Soft tissue extension into the neck or base of the tongue can also be seen. The CT scan is also useful for determining extension to the subglottis.[2]

Diagnostic procedures for laryngeal cancer at the University of Florida are summarized in Table 53.1.[24] A CT scan is usually performed for all patients; MR is obtained in a small subset of patients with questionable findings on CT. Positron emission tomography (PET) is not routinely

obtained; although it may be useful to evaluate suspicious lymph nodes, it would change the treatment. Chest CT is usually obtained to detect pulmonary metastases, particularly in patients with positive cervical nodes. It may also be useful to identify the occasional synchronous lung cancer. Direct laryngoscopy and biopsy with frozen section are usually performed with the patient under general anesthesia. The ventricles, subglottis, apex of the pyriform sinus, and postcricoid area must be carefully examined because these areas are not consistently seen by indirect examinations. Fiberoptic telescopes (0° and 30°) are introduced through the laryngoscope for inspection of these areas. A generous biopsy specimen is taken from the obvious lesion; additional biopsy specimens may be obtained from suspicious areas and from areas grossly involved. The mucosa of the margin of the cord may be stripped to provide adequate tissue if the lesion is distributed superficially along the cord and is not obviously a carcinoma.

TABLE 53.1 DIAGNOSTIC WORKUP FOR CARCINOMA OF THE LARYNX

General
History
Physical examination
Indirect laryngoscopy
Direct laryngoscopy
Biopsies
Radiographic studies
Chest x-ray films
Computed tomography with contrast enhancement (before biopsy) RT
Magnetic resonance imaging (selected cases)

RT, radiotherapy.

From Mendenhall WM, Parsons JT, Mancuso AA, et al. Larynx. In: Perez CA, Brady LW, eds. *Principles and Practice Radiation of Oncology*. 4th ed. Lippincott-Raven; 1998:1094-1116.

STAGING

The 2017 American Joint Committee on Cancer (AJCC)[25] staging system for laryngeal primary cancer is listed in Table 53.2. T2 glottic cancers are stratified into those with normal (T2A) and impaired (T2B) vocal cord mobility. For lesions arising in the supraglottis, the sites of origin include false cords, aryepiglottic folds, suprahyoid epiglottis, infrahyoid epiglottis, pharyngoepiglottic folds, and arytenoids. Only in the early T stages can one identify the specific site of origin with certainty. As the lesion enlarges, the site of origin is often an educated guess based on the location of the greatest tumor bulk/density. The major difference between the 1998 and 2010 staging systems is that a glottic cancer that invades the paraglottic space is upstaged to T3 in the latter system, even with mobile vocal cords, resulting in significant stage migration.[26] In addition, T4 has been stratified into T4A and T4B, based on resectability.

TABLE 53.2 STAGING OF LARYNGEAL CANCER

Supraglottis	
TX	Primary tumor cannot be assessed.
Tis	Carcinoma in situ
T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (eg, mucosa of base of the tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx.
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following area: postcricoid space, preepiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage.
T4	Moderately advanced or very advanced
T4a	Moderately advanced local disease; tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus).
T4b	Very advanced local disease; tumor invades prevertebral space, encases carotid artery, invades or mediastinal structures.
Glottis	
TX	Primary tumor cannot be assessed.
Tis	Carcinoma in situ

Supraglottis

T1	Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
T1a	Tumor limited one to vocal cord
T1b	Tumor both involving vocal cords
T2	Tumor extends supraglottis and/or subglottis and/or with impaired vocal cord mobility.
T3	Tumor limited to the larynx with vocal cord fixation and/or invasion of paraglottic space and/or inner cortex of thyroid cartilage
T4	Moderately advanced or very advanced
T4a	Moderately advanced local disease; tumor invades through the outer cortex of the thyroid cartilage and/or invades beyond tissues beyond the larynx (eg, trachea, cricoid cartilage, soft tissues of neck including deep extrinsic muscle the of tongue, strap muscles, thyroid, or esophagus).
T4b	Very advanced local disease; tumor invades prevertebral space, encases carotid artery, invades or mediastinal structures.

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PATHOLOGIC CLASSIFICATION

Nearly all malignant tumors of the larynx arise from the surface epithelium and, therefore, are squamous cell carcinoma or one of its variants.

Carcinoma in situ occurs frequently on the vocal cords. Differentiating among dysplasia, carcinoma in situ, squamous cell carcinoma with microinvasion, and true invasive carcinoma is a problem that the pathologist and the clinician frequently confront.

Most vocal cord carcinomas are well or moderately well differentiated. In a few cases, an apparent carcinoma and sarcoma occur together, but most of these are actually a spindle cell carcinoma (ie, squamous cell carcinoma with a spindle cell stromal reaction).

Verrucous carcinoma occurs in 1% to 2% of patients with carcinoma of the vocal cord. The histologic diagnosis is difficult and must correlate with the gross appearance of the lesion.

Small cell neuroendocrine carcinoma is rarely diagnosed in the supraglottic larynx, but it should be recognized because of its biologic

potential for rapid growth, early dissemination, and responsiveness to chemotherapy.[27,28]

Minor salivary gland tumors arise from the mucous glands in the supraglottic and subglottic larynx, but they are rare.[29] Even rarer are paragangliomas, carcinoids, soft tissue sarcomas, malignant lymphomas, and plasmacytomas. Benign chondromas and osteochondromas are reported, but their malignant counterparts are rare.

PROGNOSTIC FACTORS

The extent of the primary lesion and neck disease are the major determinants of prognosis. The likelihood of local control is determined primarily by T stage; there are conflicting data pertaining to a possible inverse relationship between N stage and local control. The likelihood of local-regional control is affected primarily by the overall AJCC stage, which accounts for both T stage and N stage. AJCC stage and N stage are the major determinants of cause-specific survival. Primary tumor volume predicts for local control and survival for patients with advanced glottic carcinomas treated with curative-intent radiotherapy (RT) and chemotherapy.[30] In addition, within each N stage, patients with positive nodes in the low neck below the level of the thyroid notch tend to have a lower cause-specific survival rate than those with disease confined to the upper neck. Human papillomavirus status may be a prognostic factor for patients with advanced laryngeal treated with chemoradiation.[31] In general, women tend to have a better prognosis than men.

TREATMENT OF VOCAL CORD CARCINOMA

Selection of Treatment Modality

In treating vocal cord carcinoma, the goal is cure with the best functional result and the least risk of a serious complication. Patients may be considered to be in an early group if the chance of cure with larynx preservation is high, a moderately advanced group if the likelihood of local control is 60% to 70% but the chance of cure is still good, and an advanced group if the chance of cure is moderate and the likelihood of laryngeal preservation is relatively low.[32] The early group may be treated initially by

RT or, in selected cases, by transoral laser microsurgery (TLM) or transoral robotic surgery (TORS).[33] The moderately advanced group may be treated with either RT with laryngectomy reserved for relapse or by total laryngectomy with or without adjuvant postoperative RT. The obvious advantage of the former strategy, which is used at the University of Florida, is that there is a fairly good chance that the larynx will be preserved.[34-36] Although some patients may be rehabilitated with a tracheoesophageal puncture after laryngectomy, only about 20% of patients use this device long term, and the majority use an electrolarynx.[37] The advanced group is treated with total laryngectomy and neck dissection with or without adjuvant RT or by RT and adjuvant chemotherapy.[38] Data suggest that if patients whose tumors show a partial or complete response to two to three cycles of neoadjuvant chemotherapy are then given high-dose RT, the cure rates are comparable with those obtained with initial total laryngectomy.[39] Another less expensive and less toxic method to select patients likely to be cured by RT alone is to calculate the primary tumor volume on pretreatment CT or MR. Data indicate that primary tumor volume is inversely related to the probability of local control after irradiation.[40,41] Recent data indicate that whereas induction chemotherapy probably does not improve the likelihood of local-regional control and survival, concomitant chemotherapy and RT result in an improved likelihood of cure compared with RT alone.[42-44] There is a subset of patients with high-volume (>3.5 mL), unfavorable, advanced cancers who may be cured by chemoradiation but have a useless larynx and permanent tracheostomy and/or gastrostomy.[40] These patients are best treated with a total laryngectomy, neck dissection, and postoperative RT.[45]

Carcinoma in Situ

Lesions diagnosed as carcinoma in situ can be treated with TLM. However, it is difficult to exclude the possibility of microinvasion on these specimens. Recurrence is frequent if the patient continues to smoke and the cord may become thickened and the voice hoarse with repeated treatments.

Early RT for carcinoma in situ often means a better chance of preserving a good voice, especially since many patients with this diagnosis eventually receive this treatment.[42]

Many patients with a diagnosis of carcinoma in situ have obvious lesions that probably contain invasive carcinoma. We have often proceeded with RT rather than put the patient through a repeated biopsy procedure.

Early Vocal Cord Carcinoma

In many centers, RT is the initial treatment prescribed for T1 and T2 lesions, with surgery reserved for salvage after RT failure.[18,46,47] However, TLM and TORS have shown comparable cure rates with the possibility of using RT for recurrences.[46,48,49] Supracricoid laryngectomy, as reported by Laccourreye et al,[50] is a procedure designed to remove moderate-sized cancers involving the supraglottic and glottic larynx. The larynx may be removed with preservation of the cricoid and the arytenoid with its neurovascular innervation; the defect is closed by approximating the base of the tongue to the remaining larynx. The oncologic and functional results of this procedure in selected patients are reported to be excellent. TLM may also provide high cure rates for select patients with small, well-defined lesions limited to the mid one-third of one true cord.[51-55] A small subset of TLM surgeons successfully use this technique for moderately advanced cancers.[46] The major advantage of RT compared with partial laryngectomy is better quality of the voice. The advantages of surgical treatments include avoidance of RT, single treatment, and cost-effectiveness. However, if voice quality is important for the patient, surgery should be avoided. Open partial laryngectomy finds its major use as salvage surgery in suitable cases after RT failure. Even if the patient has a local recurrence after salvage partial laryngectomy, there is a third chance with total laryngectomy, which may still be successful.

Verrucous lesions have the reputation of being unresponsive to RT and, in some instances, converting into invasive, often anaplastic, metastasizing lesions. Partial laryngectomy is recommended for early verrucous carcinoma of the glottis, but RT is recommended if the alternative is total laryngectomy. We have observed typical verrucous lesions that have disappeared with RT and not recurred. O'Sullivan et al[56] also made this observation. In addition, a variety of tumors that recur after unsuccessful treatment (with surgery, RT, and/or chemotherapy) are more likely to exhibit more aggressive behavior.

Moderately Advanced Vocal Cord Cancer

Fixed-cord lesions (T3) may be subdivided into relatively favorable or unfavorable lesions. Patients with unfavorable lesions usually have extensive bilateral disease with a compromised airway and are considered to be in the advanced group. Patients with favorable T3 lesions have disease confined mostly to one side of the larynx, have a good airway, and are reliable for follow-up. Some degree of supraglottic and subglottic extension usually exists. The extent of disease and tumor volume (≤3.5-4 mL), in particular, are related to the likelihood of control after RT.[40]

The patient with a favorable lesion is advised of the alternatives of RT with surgical salvage or immediate total laryngectomy. Recent data suggest that the likelihood of local- regional control is better after some altered fractionation schedules compared with conventional once-daily RT.[44,57] Follow-up examinations are recommended every 4 to 6 weeks for the first year, every 6 to 8 weeks for the second year, every 3 months for the third year, every 6 months for the fourth and fifth years, and annually thereafter. The patient must understand that total laryngectomy may be recommended purely on clinical grounds without biopsy-proven recurrence and that the risk of laryngeal osteochondronecrosis is about 5%.

Evaluation of cord mobility after 50.4 Gy or at the end of RT has not been helpful in predicting local control.[41] Some patients in whom the vocal cord remained fixed have had local tumor control of the disease for 2 years or longer after RT.

The major difficulty in using RT for the more advanced lesions is distinguishing radiation edema from local recurrence during follow-up examinations.[58] Progressive laryngeal edema, persistent throat pain, or fixation of a previously mobile vocal cord frequently signifies recurrent disease in the larynx, although a few patients with these findings remain disease-free with long-term follow-up.

Extended hemilaryngectomy has been used by a few surgeons in the treatment of well-lateralized fixed-cord lesions. A permanent tracheostomy is usually required because a portion of the cricoid is resected, but a useful voice may be retained.[59]

Advanced Vocal Cord Carcinoma

Advanced lesions usually show extensive subglottic and supraglottic extension, bilateral glottic involvement, and invasion of the thyroid, cricoid, and/or arytenoid cartilages.[9,23] The airway is compromised, necessitating a tracheostomy at the time of direct laryngoscopy in approximately 30% of patients. Clinically positive lymph nodes are found in about 25% to 30% of patients.

The mainstay of treatment is total laryngectomy, with or without adjuvant RT. The most frequent sites of local failure after total laryngectomy are the tracheal stoma, the base of the tongue, the neck lymph nodes, and/or or soft tissues of the neck. If the neck is clinically negative before surgery and if postoperative RT is planned, neck dissection may be withheld, and RT may be used to treat both sides of the neck.[60] However, in practice, most surgeons prefer to perform elective bilateral selective (levels II-IV) neck dissections in conjunction with a total laryngectomy for T3 N0 or T4 N0 laryngeal cancer, even if postoperative RT is planned. If the lymph nodes are clinically positive, a therapeutic neck dissection is performed at the time of laryngectomy.

The indications for postoperative RT include close or positive margins, significant subglottic extension (1 cm or more), cartilage invasion, perineural invasion, lymphovascular space invasion, extension of the primary tumor into the soft tissues of the neck, multiple positive neck nodes, and extracapsular extension.[61,62] Preoperative RT is indicated for patients who have fixed neck nodes, have had an emergency tracheotomy through tumor, or have direct extension of tumor involving the skin.

Definitive RT is prescribed for the patient who refuses total laryngectomy or is medically unsuitable for major surgery.

As previously stated, there is evidence that two to three cycles of induction chemotherapy followed by RT in patients obtaining at least a partial response may provide a moderate likelihood of larynx preservation without compromising cure.[39] Data suggest that concomitant chemotherapy and RT are more efficacious than RT alone or induction chemotherapy followed by RT.[42,43] The optimal combination of concomitant chemotherapy and irradiation is unclear.[44]

A randomized intergroup trial (Radiation Therapy Oncology Group [RTOG] 91-11) compared three treatment arms: arm A, three cycles of induction cisplatin and fluorouracil followed by RT in complete and partial

responders; arm B, RT and concomitant cisplatin (100 mg/m^2 on days 1, 22, and 43 of RT); and arm C, once-daily RT (70 Gy in 35 fractions over 7 weeks) alone.[42] Five hundred forty-seven patients were randomized and followed for a median of 3.8 years; 518 patients were evaluable. The rates of larynx preservation were as follows: arm A, 72%; arm B, 84%; and arm C, 67%. The rates of larynx presentation were significantly improved for arm B; there was no significant difference between arms A and C. The 5-year survival rates were similar for the three treatment groups: arm A, 55%; arm B, 54%; and arm C, 56%. The likelihood of developing distant metastases was lower for the two groups of patients who received adjuvant chemotherapy.

Surgical Treatment

Cordectomy is an excision of the vocal cord and may be performed by a TLM or TORS approach or externally by a thyrotomy. Its use is usually confined to small lesions of the middle one-third of the cord. After cordectomy, a pseudocord is formed, and the patient has a useful, if somewhat harsh, voice.

Vertical partial laryngectomy (ie, hemilaryngectomy) allows removal of limited cord lesions with preservation of voice. One entire cord with as much as one-third of the opposite cord with the adjacent thyroid cartilage is the maximum cordal involvement suitable for surgery in men; women have a smaller larynx, and usually only one vocal cord may be removed without compromising the airway. Partial fixation of one cord is not a contraindication to hemilaryngectomy; a few surgeons perform a hemilaryngectomy for selected fixed-cord lesions. The maximum subglottic extension suitable for hemilaryngectomy is 8 to 9 mm anteriorly and 5 mm posteriorly; this limit is necessary to preserve the integrity of the cricoid. Tumor extension to the epiglottis, false cord, or both arytenoids is a contraindication to hemilaryngectomy.

Supracricoid partial laryngectomy is used for selected T2 and T3 glottic carcinomas and entails removal of both true and false cords and the entire thyroid cartilage. The cricoid is sutured to the epiglottis and hyoid (cricohyoidoepiglottopexy).

Total laryngectomy with or without neck dissection is the operation of choice for advanced lesions and as a salvage procedure for RT failures in lesions that are not suitable for conservation surgery. The entire larynx is removed, and the pharynx is reconstructed. A permanent tracheostomy is required. Speech may be reconstituted with a prosthesis or with an electrolarynx. One hundred four (63%) of 166 patients entered into the surgery and postoperative irradiation arm of the Veterans Affairs Laryngeal Cancer Study Group randomized trial were evaluable for voice rehabilitation at 2 years after treatment.[63] Ninety-six patients had undergone a total laryngectomy and communicated as follows: tracheoesophageal, 27 (28%); esophageal, 5 (5%); artificial larynx, 47 (50%); nonvocal, 7 (7%); and no data, 10 (10%).[63] One hundred seventy-three patients underwent total laryngectomy and postoperative RT at the University of Florida, and 69 patients were evaluable for 5 years or longer.[37] Voice rehabilitation was accomplished as follows: tracheoesophageal, 19%; electrolarynx, 57%; esophageal, 3%; nonvocal, 14%; and no data, 7%.

Radiation Therapy Technique

RT for T1 or T2 vocal cord cancer is delivered by small portals covering only the primary lesion.[47] The cervical lymph node chain is not electively treated. For T1 lesions, RT portals extend from the thyroid notch superiorly to the inferior border of the cricoid and fall off anteriorly. The posterior border depends on the posterior extension of the tumor.[21] For T2 tumors, the field is extended depending on the anatomic distribution of the tumor. The field size ranges from 4×4 cm^2 to 5×5 cm^2 (plus an additional 1.0 cm of "flash" anteriorly) and is occasionally 6×6 cm^2 for a large T2 lesion. Portals larger than this increase the risk of edema without improving the cure rate. Intensity-modulated RT (IMRT) may be considered for T1-T2 glottic cancers to reduce the dose to carotid arteries.[47] The potential advantages of this technique must be weighed against the potential increased likelihood of a marginal miss.

A commonly used dose fractionation schedule at many institutions is 66 Gy for T1 lesions and 70 Gy for T2 cancers, given in 2-Gy fractions. Evidence suggests that increasing the dose per fraction may improve the likelihood of local control.[64-68] Ample data suggest that 1.8 Gy once daily

results in significantly lower local control rates compared with 2.0 Gy once daily.[65] Yamazaki et al[69] reported a prospective trial in which patients with T1 N0 squamous cell carcinoma of the glottic larynx were randomized to definitive RT at 2.0 or 2.25 Gy per fraction. The 5-year local control rates were 77% after 2.0 Gy per fraction and 92% after Gy per fraction (P = .004); there was no difference in either acute or late toxicity. Patients with T1 or T2 vocal cord cancer treated with once-a-day fractionation at the University of Florida are irradiated with 2.25-Gy fractions; the dose fractionation schemes used are as follows: Tis-T2 A, 63.0 Gy in 28 fractions, and T2B, 65.25 Gy in 29 fractions. Concomitant weekly cisplatin 30 ng/M^2 is considered for patients with T2 B cancers.

At the University of Florida, patients are treated in the supine position; the field borders for a patient with a T1 N0 cancer are depicted in Figure 53.7.[21] A three-field technique, using 4- or 6-MV x-rays, is used to deliver approximately 95% of the dose through opposed lateral wedged fields weighted to the side of the lesion; the remaining dose is delivered by an anterior field shifted 0.5 cm toward the side of the lesion (Figure 53.8).[21] The tumor dose is usually specified at the 95% normalized isodose line.

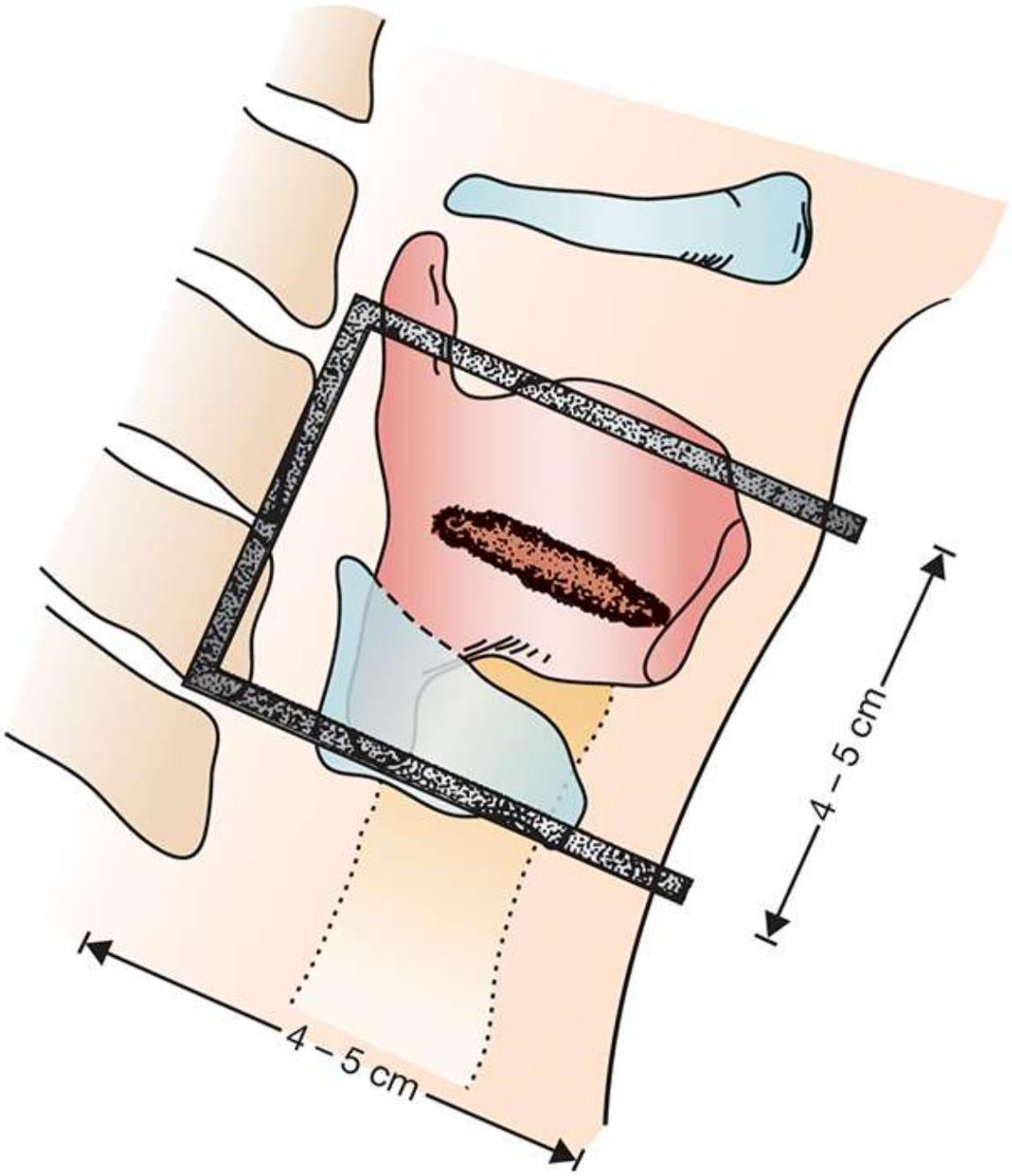

FIGURE 53.7 Treatment portal for early glottic carcinoma. The top border is adjusted according to the lesion. The middle of the thyroid notch is the landmark for very early lesions, and the top of the notch is the marker for larger lesions or those with minimal supraglottic extension. The posterior border is 1 cm posterior to the back edge of the thyroid cartilage if the lesion is confined to the anterior two-thirds of the vocal cord; if the posterior one-third of the vocal cord is involved, the posterior border is placed 1.0 to 1.5 cm behind the cartilage. The inferior border is placed at the bottom of the cricoid cartilage if there is no subglottic extension. (Reprinted with permission from Million RR, Cassisi NJ. Larynx. In: Million RR, Cassisi NJ, eds. *Management of Head and Neck Cancer: A Multidisciplinary Approach*. 2nd ed. J.B. Lippincott; 1994:431-497.)

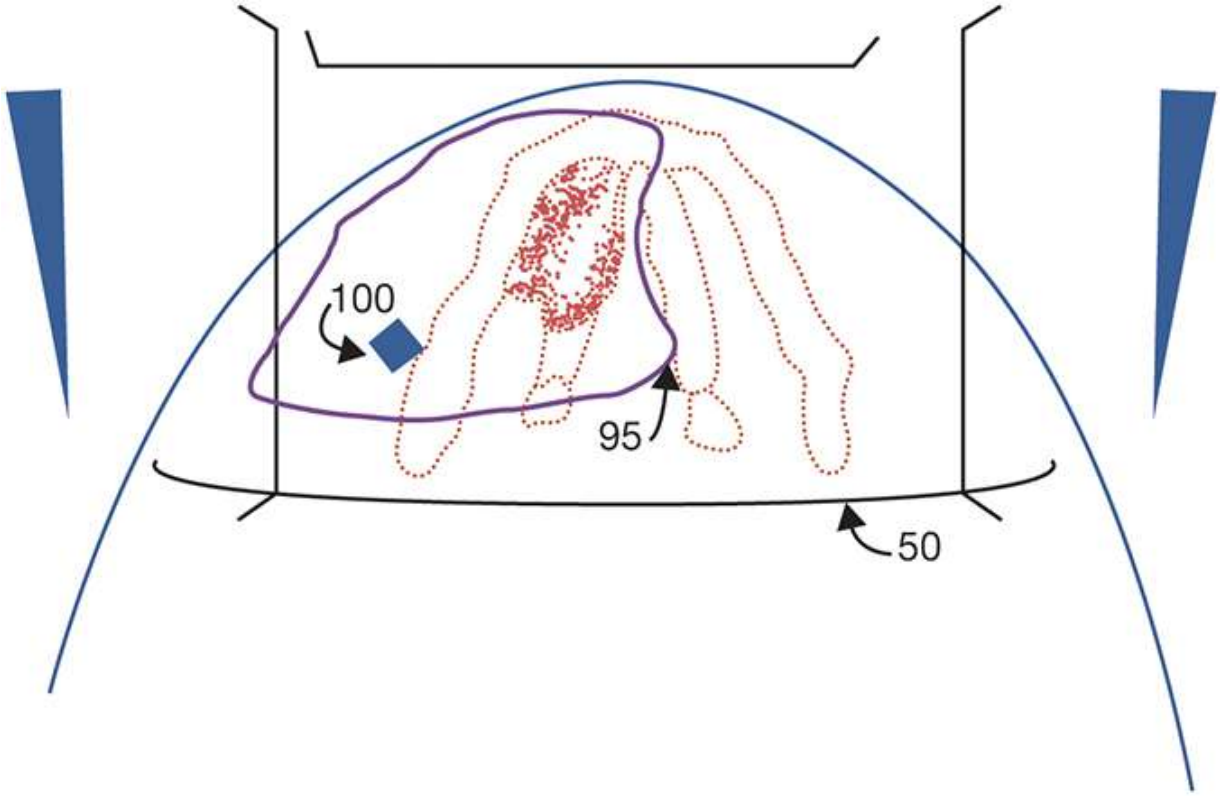

FIGURE 53.8 Normalized isodose distribution for three-field technique for the treatment of a tumor involving the anterior two-thirds of one true vocal cord. The dose is specified at the 95% isodose line. (Reprinted with permission from Million RR, Cassisi NJ. Larynx. In: Million RR, Cassisi NJ, eds. *Management of Head and Neck Cancer: A Multidisciplinary Approach*. 2nd ed. J.B. Lippincott; 1994:431-497.)

RT of T3 and T4 lesions requires larger portals, which include the levels II and III lymph nodes (Figure 53.9).[20,70] The level IV lymph nodes are included in a separate low neck portal. Patients treated at the University of Florida are irradiated in a continuous course twice daily at 1.2 Gy per fraction to a total dose of 74.4 Gy. The portals are reduced after 50.4 Gy in 42 fractions; the reduced portals cover only the primary lesion.

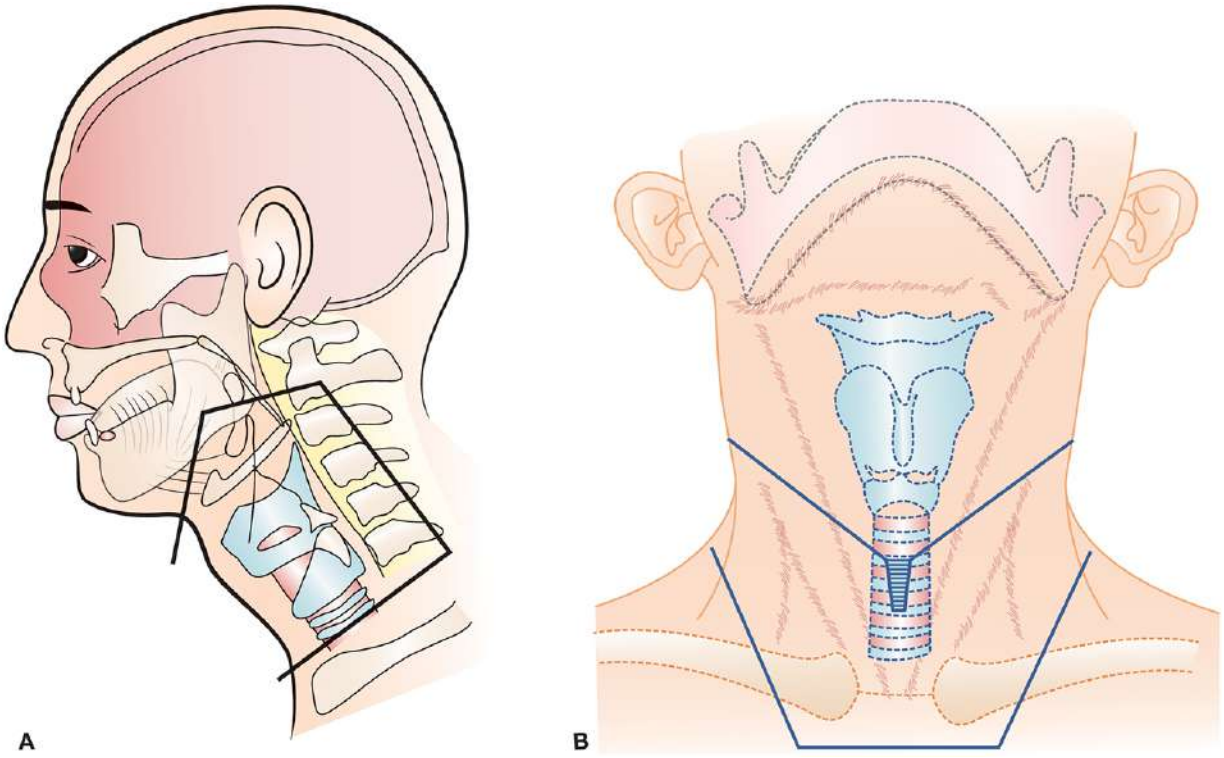

FIGURE 53.9 A. Radiation treatment technique for carcinoma of glottic larynx, stage T3-T4 N0. The patient is treated supine, and the field is shaped with Lipowitz metal. Anteriorly, the field is allowed to fall off. The entire preepiglottic space is included by encompassing the hyoid bone and epiglottis. The superior border (just above the angle of the mandible) includes the jugulodigastric lymph nodes. Posteriorly, a portion of the spinal cord must be included within the field to ensure adequate coverage of the midjugular lymph nodes; spinal accessory lymph nodes themselves are at little risk of involvement. The lower border is slanted to facilitate matching with the low neck field and to reduce the length of spinal cord in the high-dose field. The inferior border is placed at the bottom of the cricoid cartilage if the patient has no subglottic spread; in the presence of subglottic extension, the inferior border must be lowered according to the disease extent. B. Example of a low neck portal for T3 N0 glottic carcinoma. The main nodes at risk are the low jugular and lateral paratracheal. The Delphian node would be in the primary portal. A very narrow and short midline shield is used. (A. From Parsons JT, Mendenhall WM, Mancuso AA, Cassisi NJ, Stringer SP, Million RR. Twice-a-day radiotherapy for T3 squamous cell carcinoma of the glottic larynx. *Head Neck*. 1989;11(2):123-128. Copyright © 1989 Wiley Periodicals, A Wiley Company. Reprinted by permission of John Wiley & Sons. B. Reprinted with permission from Million RR, Cassisi NJ, Mancuso AA, et al. Management of the neck for squamous cell carcinoma. In: Million RR, Cassisi NJ, eds. *Management of Head and Neck Cancer: A Multidisciplinary Approach*. 2nd ed. J.B. Lippincott; 1994:75-143.)

IMRT is used if there is a clear advantage associated with this technique. Disadvantages associated with IMRT include increased dose inhomogeneity, increased total body dose, and increased labor and

expense.[71] The most common indications for IMRT for laryngeal cancers would be the occasional patients with a node-positive T3-T4 cancer, where the retropharyngeal nodes would be electively irradiated and the dose to the contralateral parotid gland reduced, and/or a difficult low match between the lateral fields used to treat the primary site and upper neck and the anterior low neck field in a patient with a short neck and large shoulders. In the latter instance, IMRT could be used to encompass the entire target volume and avoid the problem of field junctioning entirely. IMRT is especially useful for patients with extensive subglottic invasion, where achieving an adequate inferior margin with conventional lateral portals may not be possible.

Evidence from both retrospective and randomized trials points to improved therapeutic ratios with altered fractionation schedules.[44] Given that RT is effective treatment for head and neck primary squamous cell carcinoma, it should not be surprising that higher doses of RT given more intensively would be more effective at providing tumor control. Because most observers have noted no increase in late toxicity with the various regimens, it generally is concluded that these schedules yield an improved therapeutic ratio. A recently updated RTOG 90-03 trial reported on 1,073 patients who were randomly selected to receive one of four fractionation schedules[57,72,73]:

1. Standard fractionation: 2 Gy per fraction, once a day, 5 days a week, to a total dose of 70 Gy in 35 fractions over 7 weeks
2. Hyperfractionation: 1.2 Gy per fraction, twice daily (≥6 hours apart), 5 days a week, to a total dose of 81.6 Gy in 68 fractions over 7 weeks
3. Accelerated fractionation with split: 1.6 Gy per fraction, twice daily (≥6 hours apart), 5 days a week, to a total dose of 67.2 Gy in 42 fractions over 6 weeks, including a 2-week rest after 38.4 Gy
4. Accelerated fractionation with concomitant boost: 1.8 Gy per fraction, once a day, 5 days a week to a large field, plus 1.5 Gy per fraction once a day to a boost field given 6 hours or more after treatment of the large field for the last 12 treatments days, to a total dose of 72 Gy in 42 fractions over 6 weeks

The 5-year local-regional failure rates were as follows: standard fractionation, 59%; hyperfractionation, 51%; accelerated split course, 58%; and concomitant boost, 52%. Both the hyperfractionation and concomitant schedules boost yielded local-regional control rates that were significantly better than those with standard fractionation. There was a trend toward improved overall survival with hyperfractionation, but no difference in cause-specific survival. Acute toxicity was increased with all three altered fractionation schedules; there was a modest increase in late effects with the concomitant boost schedule.

The treatment technique used for postoperative RT after total laryngectomy is depicted in Figure 53.10.[61] The treatment technique for preoperative RT is essentially the same as that used for RT alone. Alternatively, IMRT may be employed for the indications discussed previously.

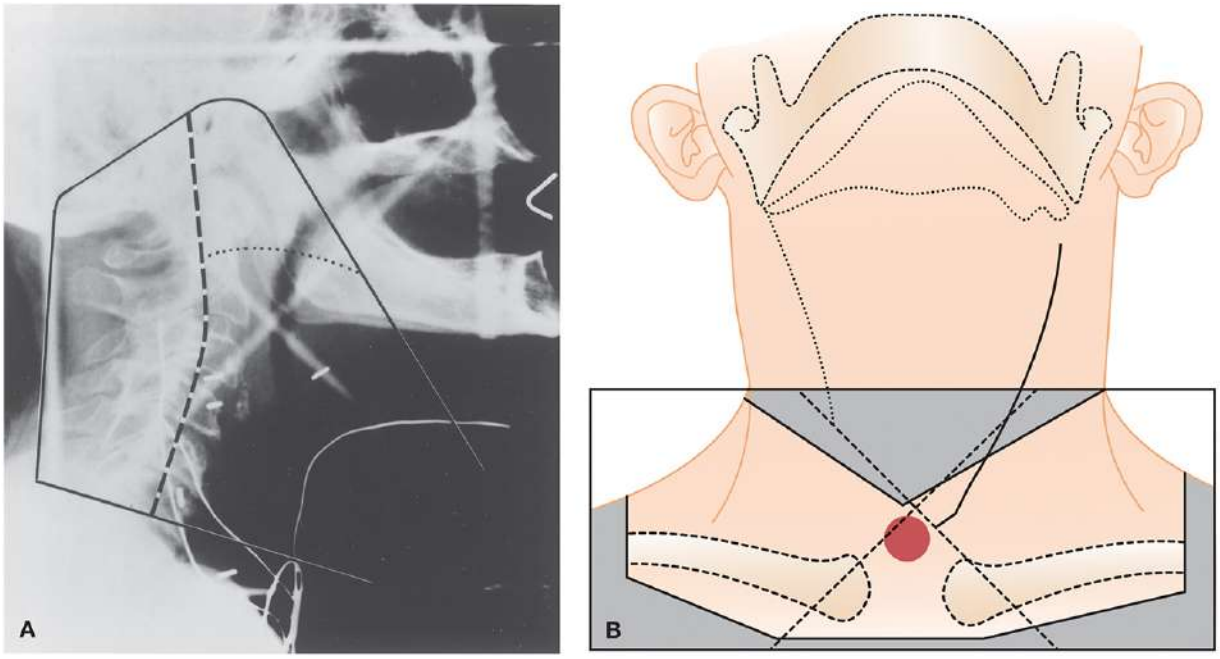

FIGURE 53.10 A. Typical simulation film for postoperative treatment of advanced cancer of the laryngopharynx. If the neck is pathologically negative, the superior field border is lowered to 2 cm above the angle of the mandible. The initial "off-cord" reduction (50 Gy) (broken line) and the final reduction (dotted line) are indicated. Wires mark the surgical scars and stoma. The slanting line used on the lower border reduces the length of spinal cord treated by the primary field, allows better caudal coverage of the mucosal surfaces while simultaneously bypassing the shoulders, and facilitates matching of the low neck field. B. Schematic diagram of the low neck field. The rectangle (solid line) represents the light field. The shaded areas represent the blocked portions of the field (stacked lead blocks). The superior border of the neck field is the inferior border of the primary field. The actual line is treated only in the primary field. The upper border of the low neck field assumes a V shape. In the midline of the patient, the apex of the V generally is at or close to the central axis (broken lines) so that the portal that treats the spinal cord is not divergent in its upper portion and diverges away from the primary fields in its lower portion. At the junction of the three fields, a short (2-3 cm) segment of spinal cord remains untreated by any of the three fields. (Reprinted from Amdur RJ, Parsons JT, Mendenhall WM, Million RR, Stringer SP, Cassisi NJ. Postoperative irradiation for squamous cell carcinoma of the head and neck: an analysis of treatment results and complications. *Int J Radiat Oncol Biol Phys*. 1989;16(1):25-36. Copyright © 1989 Elsevier. With permission.)

Treatment of Recurrence

Most recurrences appear within 18 months, but late recurrences may appear after 5 years. The latter are likely second primary malignancies. The risk of metastatic disease in lymph nodes increases with local recurrence.[18]

Recurrence After Radiation Therapy

With careful follow-up, recurrence is sometimes detected before the patient notices a return of hoarseness. There is often minimal lymphedema for 1 to 2 months after RT, which usually subsides or stabilizes. An increase in edema, particularly if associated with hoarseness or pain, suggests recurrence, even if there is no obvious tumor. Fixation of a previously mobile vocal cord usually implies local recurrence, but we have occasionally observed a patient who has experienced a fixed cord with an otherwise normal-appearing larynx and who has not shown evidence of recurrence.

It may be difficult to diagnose recurrence if the tumor is submucosal. Generous, deep biopsies are required. If recurrence is strongly suspected, laryngectomy may rarely be advised without biopsy-confirmed evidence of recurrence. PET may be useful to distinguish recurrent tumor from necrosis.

RT failures may be salvaged by cordectomy, hemilaryngectomy, supracricoid partial laryngectomy, or total laryngectomy. Biller et al[74] reported a 78% salvage rate by hemilaryngectomy for 18 selected patients in whom RT failed; total laryngectomy was eventually required in two patients. Only two patients died of cancer. These investigators offered guidelines for using hemilaryngectomy: contralateral vocal cord is normal, arytenoid is not involved, subglottic extension does not exceed 5 mm, and vocal cord is not fixed. In our experience, 14 patients irradiated for T1 or T2 vocal cord cancers underwent a hemilaryngectomy after local recurrence, and 8 were successfully salvaged.[18]

Recurrence After Surgery

The rate of salvage by RT for recurrences or new tumors that appear after initial treatment by hemilaryngectomy is about 50%. Lee et al[75] reported seven successes among 12 patients; one lesion was later controlled by total laryngectomy. Total laryngectomy can be used successfully to treat hemilaryngectomy failures not suitable for RT. RT rarely cures patients with recurrence in the neck or stoma after total laryngectomy.

TREATMENT OF SUPRAGLOTTIC LARYNX CARCINOMA

Selection of Treatment Modality

Patients with supraglottic laryngeal carcinoma may be considered to be in an early or favorable group suitable for RT or conservation laryngectomy or an unfavorable group often requiring total laryngectomy.

Early and Moderately Advanced Supraglottic Lesions

Treatment of the primary lesion for the early group is by RT or supraglottic laryngectomy, with or without adjuvant RT.[76] TLM or TORS[77] is effective in experienced hands for small, selected lesions.[52] Total laryngectomy is rarely indicated as the initial treatment for this group of patients and is reserved for treatment failures. RT and supraglottic laryngectomy are highly successful modes of therapy for early lesions.[76]

The decision to use RT or supraglottic laryngectomy depends on several factors, including the anatomic extent of the tumor, medical condition of the patient, philosophy of the attending physician(s), and inclination of the patient and family. Overall, about 80% of patients are treated initially by RT. Approximately half of the patients seen in our clinic whose lesions are technically suitable for a supraglottic laryngectomy are not suitable for medical reasons (eg, inadequate pulmonary status or other major medical problems); these patients are treated with RT.

Analysis of local control by anatomic site within the supraglottic larynx shows no obvious differences in local control by RT for similarly staged lesions. Invasion of the preepiglottic space is not a contraindication to supraglottic laryngectomy or RT. Primary tumor volume based on pretreatment CT is inversely related to local tumor control after RT.[40] A large, bulky (>6 mL) infiltrative lesion, especially one with extensive preepiglottic space invasion, is a common reason to select supraglottic laryngectomy.

The status of the neck often determines the selection of treatment of the primary lesion. Patients with clinically negative neck nodes have a high risk for occult neck disease and may be treated by RT or supraglottic laryngectomy and bilateral selective neck dissections (levels II-IV).

If a patient has an early-stage primary lesion but advanced neck disease (N2b or N3), combined treatment is frequently necessary to control the neck disease.[38] In these cases, the primary lesion is usually treated by definitive RT, with surgery added to the treatment of the involved neck

site(s). If the same patient were treated with supraglottic laryngectomy, neck dissection, and postoperative RT, the portals would unnecessarily cover the primary site and the neck. If the patient has early, resectable neck disease (N1 or N2a) and surgery is elected for the primary site, postoperative RT is added only because of unexpected findings (eg, positive margins, multiple positive nodes, or extracapsular extension). We prefer to avoid routine high-dose preoperative or postoperative RT in conjunction with a supraglottic laryngectomy because the lymphedema of the remaining larynx may be considerable, although it eventually subsides. However, Lee et al[78] from the MD Anderson Cancer Center reported excellent results with combined supraglottic laryngectomy and postoperative RT for moderately advanced lesions.

Advanced Supraglottic Lesions

Although a subset of these patients may be suitable for a supraglottic or supracricoid laryngectomy, total laryngectomy is the main surgical option. Selected advanced lesions, especially those that are mainly exophytic, may be treated by RT and concomitant chemotherapy,[43] with total laryngectomy reserved for RT failures.

For patients whose primary lesion is to be treated by a total or partial laryngectomy and who have resectable neck disease, surgery is the initial treatment, and postoperative RT is added if needed. If the neck disease is unresectable, preoperative RT is used. The indications for preoperative and postoperative RT have been previously outlined.

Surgical Treatment

Supraglottic Laryngectomy

Supraglottic laryngectomy is voice-sparing surgery that can be used successfully for selected lesions involving the epiglottis, a single arytenoid, the aryepiglottic fold, or the false vocal cord. This can be performed via TLM or TORS.[33] Extension of the tumor to the true vocal cord, the anterior commissure, or both arytenoids, fixation of the vocal cord, or thyroid or cricoid cartilage invasion precludes supraglottic laryngectomy. The supraglottic laryngectomy may be extended to include the base of the tongue if one lingual artery is preserved.

All patients have difficulty swallowing, with a tendency to aspirate immediately after surgery, but almost all learn to swallow again in a short time; motivation and the amount of tissue removed are key factors in learning to swallow again. Preoperatively, adequate pulmonary reserve is evaluated by blood gas determinations, function tests, chest roentgenography, and a work test involving walking the patient up two flights of stairs to determine tolerance to pulmonary stress. The voice quality is generally normal after supraglottic laryngectomy.

Supracricoid Laryngectomy

This procedure is an option for lesions extending from the supraglottis into one or both vocal cords. However, vocal cord fixation is a relative contraindication. At least one arytenoid must be preserved for successful decannulation and phonation. Extension to the cricoid and thyroid cartilage destruction also preclude its use. Phonation and respiratory function are reconstituted by approximating the cricoid to the hyoid (cricohyoidopexy).

Wide-Field Total Laryngectomy

Total laryngectomy is performed as previously described.

Radiation Therapy

The primary lesion and both sides of the neck are treated with opposed lateral portals; wedges are used to compensate for the contour of the neck (Figure 53.11).[21] The lower neck nodes are irradiated through a separate anterior portal. IMRT may be employed to spare one or both parotids and to avoid a low match line in the occasional patient with a short neck and large shoulders. We currently use either hyperfractionation or simultaneous integrated boost. The latter schedule delivers 70 Gy in 35 fractions over 30 treatment days in 6 weeks with 1 twice-daily fraction during the last 5 weeks (with a minimum 6-hour interfraction interval). The high-risk clinical target volume (CTV) encompasses the gross disease, the intermediate-risk CTV receives 63 Gy at 1.8 Gy per fraction, and the standard-risk CTV receives 56 Gy at 1.65 Gy per fraction.

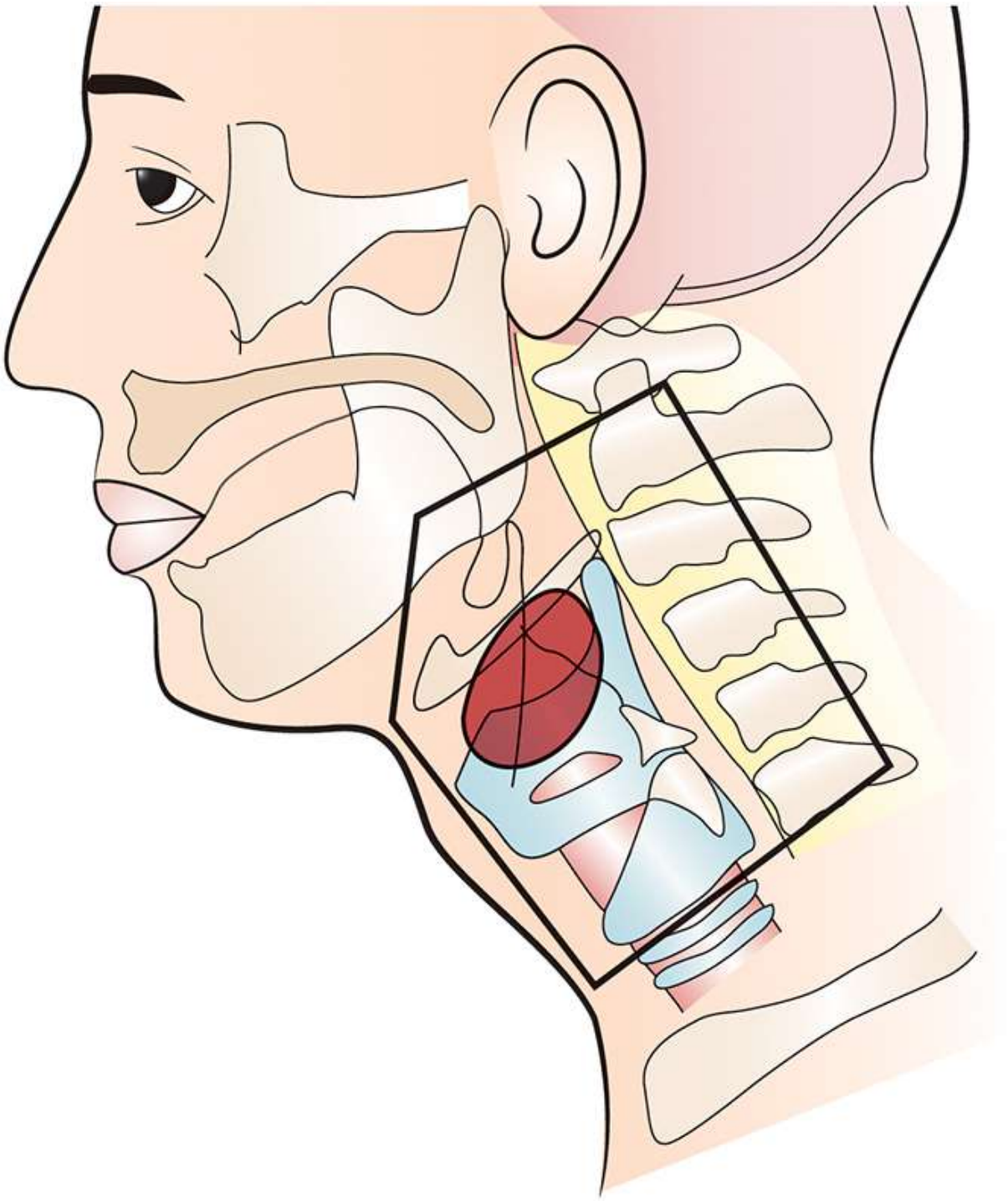

FIGURE 53.11 Example of the portal for a lesion of the lower epiglottis or false vocal cord and a clinically negative neck. The subdigastric nodes are included, but not the junctional nodes. Depending on the anatomy and tumor extent, the anterior border may fall off (ie, "flash") or a small strip of skin may be shielded. (Reprinted with permission from Million RR, Cassisi NJ, Mancuso AA, et al. Management of the neck for squamous cell carcinoma. In: Million RR, Cassisi NJ, eds. *Management of Head and Neck Cancer: A Multidisciplinary Approach*. 2nd ed. J.B. Lippincott; 1994:75-143.)

In the case of clinically positive nodes, an electron beam portal may be used to increase the dose to the posterior cervical nodes after the fields are reduced to avoid the spinal cord at 45 Gy if parallel opposed fields are employed. CT is obtained 4 weeks after completing RT, and a neck dissection is added if the residual cancer in the nodes is believed to exceed 5%; otherwise, the patient is observed, and a CT is repeated in 3 months.[38] Alternatively, a PET-CT is obtained at 3 months, and a neck dissection is added if persistent positive nodes are observed.

Patients experience a sore throat, loss of taste, and moderate dryness during RT. Edema of the arytenoids may occur and give a sensation of a lump in the throat. Tracheostomy is rarely necessary, even for bulky lesions.

Edema of the larynx may persist for several months to a year. Patients who continue to smoke heighten the side effects of dryness, dysphagia, and hoarseness.

Preoperative and Postoperative Treatment Technique

If total laryngectomy is required and the lesion is resectable, postoperative RT is preferred because there is no evidence that preoperative RT produces any better local-regional control or survival rates than surgery and postoperative RT. Irradiation is added for close or positive margins, invasion of soft tissues of the neck, significant subglottic extension (1 cm or more), thyroid cartilage invasion, multiple positive nodes, and extracapsular extension. The high-risk areas are usually the base of the tongue and the neck.

The dose for postoperative RT as a function of known residual disease is as follows: negative margins, 60 Gy in 30 fractions; microscopically positive margins, 66 Gy in 33 fractions; and gross residual disease, 70 Gy in 35 fractions. All patients are treated with a continuous course, one fraction per day, 5 days per week. The lower neck is treated with doses of 50 Gy in 25 fractions at D_{max}. If there is subglottic extension, the dose to the stoma is boosted with electrons (usually 10-14 MeV) for an additional 10 Gy in five fractions. The treatment technique is shown in Figure 53.10.[61] If postoperative RT is added after supraglottic laryngectomy, dose is lowered to 55.8 Gy given in 1.8-Gy fractions. This dose produces acceptable rates of local control and laryngeal edema.[78]

The treatment technique used for preoperative RT is essentially the same as that used for patients treated with RT alone, using doses of 50 to 60 Gy at 1.8 to 2.0 Gy per fraction. Thereafter, the dose is boosted to areas of unresectable disease (usually the neck) to total doses ranging from 66 to 70 Gy.

Treatment of Recurrence

Failures after supraglottic laryngectomy or RT can frequently be controlled by further treatment; therefore, recognition of recurrence should be vigorously pursued.[76] Salvage of patients with recurrence after combined total laryngectomy and RT is uncommon. Stomal recurrences are occasionally controlled by RT or surgery; however, the average lifespan after stomal recurrence is 6.3 months.[79]

RESULTS OF TREATMENT

Vocal Cord Cancer

The local control and survival rates after treatment of early-stage glottic carcinoma are depicted in Tables 53.3 to 53.6.[46] Mendenhall et al[80] recently reported on 50 patients treated at the University of Florida with definitive RT for carcinoma in situ and observed the following 5-year outcomes: local control, 91%; ultimate local control with larynx preservation, 93%; and ultimate local-regional control, 100%. Chera et al[47] reported on 585 patients at the University of Florida for T1-T2 N0 glottic carcinoma and observed the following 5-year local control rates: T1 A1, 95%; T1 B, 94%; T2 A, 81%; and T2 B, 74%. The local control and survival rates are similar for transoral laser excision, open partial laryngectomy, and RT. Larynx preservation rates are also comparable. Voice quality depends on the amount of tissue removed with partial laryngectomy and is probably similar for patients with limited lesions treated with laser to those undergoing RT and poorer for patients undergoing open partial laryngectomy.[46]

TABLE 53.3 LOCAL CONTROL OF LARYNGEAL CANCER AFTER TRANSORAL LASER EXCISION

Institution	Follow-Up[a]	Number of Patients	Stage	Local Control (%)	Local With Control Larynx Preservation (%)	Ultimate Local Control (%) (Interval)
University of Göttingen[52]	Median, 78 mo	159	pTis-pT2	94	99	—
University of Kiel[97]	Mean, 40 mo	8	pTis	100	—	—
		88	pT1a	92	—	—
		10	pT1b	80	—	—
		8	pT2	88	—	—
		114	pTis-pT2	—	96	—
University of Brescia[98]	Mean, 76 mo	21	pTis	81	—	95[b] (5 y)
		96	pT1	82	—	87[b] (5 y)
		23	pT2	74	—	91[b] (5 y)
		140	pTis-pT2	80	97	—
Washington University[99]	Minimum, 3 y	61	T1	77	90	98
University of Naples[100]	Minimum, 5 y	321	T1	82[b]	89[c]	—
		158	T2	60[b]	–67[c]	—
La Sapienza University[101]	Minimum, 3 y	12	Tis	100	100	—
		120	T1a	94	100	—
		24	T1b	91	100	—
Tata Memorial Hospital[102]	Minimum, 18 mo	52	T1a	90	94	—
		17	T1b	65	88	—
		13	T2	77	92	—

[a]Follow-up period for the total number of patients.

[b]Ultimate local control with laser treatment alone.

[c]Local-regional control rate.

From Mendenhall WM, Werning JW, Hinerman RW, Amdur RJ, Villaret DB. Management of T1-T2 glottic carcinomas. *Cancer*. 2004;100(9):1786-1792. Copyright © 2004 American Cancer Society. Reprinted by permission of John Wiley & Sons.

TABLE 53.4 LOCAL CONTROL OF LARYNGEAL CANCER AFTER OPEN PARTIAL LARYNGECTOMY

Institution	Follow-Up	Number of Patients	Stage	Local Control (%) (Interval)	Local Control With Larynx Preservation (%)	Ultimate Control Local (%)
Universitaire Timone[103]	NS	62	T1	100	100	
		65	T2	92	92	—
Hôpital Saint Charles[104]	Minimum, 3 y	18	T1a	100	—	—
		40	T1b	95	—	—
		23	T2a	83	—	—
Mayo Clinic[105]	Median, 6.6 y	159	Tis-T1	93 (5 y)	94	100
Hôpital Laënnec[106]	Minimum, 3 y	295	T1	89	—	—
		90	T2a	74	—	—
		31	T2b	68	—	—
		416	T1-T2b	84	—	97
Washington University[99]	Minimum, 3 y	404	T1	92	93	99
Washington University[107]	Minimum, 5 y	71	T2	93	93	99

NS, nonsignificant.

From Mendenhall WM, Werning JW, Hinerman RW, Amdur RJ, Villaret DB. Management of T1-T2 glottic carcinomas. *Cancer*. 2004;100(9):1786-1792. Copyright © 2004 American Cancer Society. Reprinted by permission of John Wiley & Sons.

TABLE 53.5 LOCAL CONTROL OF LARYNGEAL CANCER AFTER RADIOTHERAPY

Institution	Follow-Up[a]	Number of Patients	Stage	Local Control (%) (Interval)	Local Control With Preservation Larynx (%) (Interval)	Ultimate Local Control (%) (Interval)
University of Florida[18]	Minimum, 2 y	230	T1a	94 (5 y)	95 (5 y)	98 (5 y)
	Median, 9.9 y	61	T1b	93 (5 y)	95 (5 y)	98 (5 y)
		146	T2a	80 (5 y)	82 (5 y)	96 (5 y)
		82	T2b	72 (5 y)	76 (5 y)	96 (5 y)
Massachusetts General Hospital[108]	NS	665	T1	93 (5 y)	—	—
		145	T2a	77 (5 y)	—	—
		92	T2b	71 (5 y)	—	—
University of California, San Francisco[109]	Median, 9.7 y	315	T1	85 (5 y)	—	96[b] (5 y)
		83	T2	70 (5 y)	—	91[b] (5 y)
Princess Margaret Hospital[110]	Median, 6.8 y	403	T1a	91 (5 y)	—	—
		46	T1b	82 (5 y)	—	—
		286	T2	69 (5 y)	—	—
MD Anderson Hospital[111]	Median, 6.8 y	114	T2a	74 (5 y)	—	—
		116	T2b	70 (5 y)	—	—
		230	T2	72 (5 y)	—	91 (5 y)

NS, nonsignificant.

[a]Follow-up period for the total number of patients.

[b]Local-regional control rate.

From Mendenhall WM, Werning JW, Hinerman RW, Amdur RJ, Villaret DB. Management of T1-T2 glottic carcinomas. *Cancer*. 2004;100(9):1786-1792. Copyright © 2004 American Cancer Society. Reprinted by permission of John Wiley & Sons.

TABLE 53.6 LARYNGEAL CANCER SURVIVAL DATA

Institution	Treatment	Follow-Up	Number of Patients	Stage	Cause-Specific Survival (%) (Interval)	Absolute Survival (%) (Interval)
Washington University[99]	Laser	Minimum, 3 y	61	T1	95 (5 y)	84 (5 y)
University of Göttingen[52]	Laser	Median, 6.5 y	159	pTis-T2	100 (5 y)	87 (5 y)
University of Brescia[98]	Laser	Mean, 6.3 y	140	pTis-T2	98 (5 y)	93 (5 y)
Washington University[99]	OPL	Minimum, 3 y	404	T1	97 (5 y)	84 (5 y)
Mayo Clinic[105]	OPL	Median, 6.6 y	159	Tis-T1	—	84 (5 y)
Washington University[107]	OPL	Minimum, 5 y	71	T2	—	−92 (5 y)
University of Florida[18]	RT	Minimum, 2 y	230	T1a	98 (5 y)	82 (5 y)
		Median, 9.9 y	61	T1b	98 (5 y)	79 (5 y)
			146	T2a	95 (5 y)	77 (5 y)
			82	T2b	90 (5 y)	77 (5 y)
University of California San Francisco[109]	RT	Median, 9.7 y	315	T1	96 (10 y)	65 (10 y)
			83	T2	91 (10 y)	63 (10 y)
Massachusetts General Hospital[108]	RT	NS	665	T1	98 (5 y)	—
			145	T2a	92 (5 y)	—
			92	T2b	84 (5 y)	—
MD Anderson Hospital[111]	RT	Median, 6.8 y	230	T2	92 (5 y)	73 (5 y)

OPL, open partial laryngectomy; NS, nonsignificant; RT, radiotherapy.

From Mendenhall WM, Werning JW, Hinerman RW, Amdur RJ, Villaret DB. Management of T1-T2 glottic carcinomas. *Cancer*. 2004;100(9):1786-1792. Copyright © 2004 American Cancer Society. Reprinted by permission of John Wiley & Sons.

Foote et al[81] reported on 81 patients who underwent laryngectomy for T3 cancers at the Mayo Clinic between 1970 and 1981. Seventy-five patients underwent a total laryngectomy and six underwent a near-total laryngectomy; 53 patients received a neck dissection. No patient underwent adjuvant irradiation or chemotherapy. The 5-year rates of local-regional control, cause-specific survival, and absolute survival were 74%, 74%, and 54%, respectively. The results of definitive RT patients with T3 glottic carcinoma are depicted in Table 53.7[70] and are similar to the surgical outcomes reported by Foote et al.[81]

TABLE 53.7 STAGE T3 GLOTTIC CARCINOMA TREATED WITH IRRADIATION ALONE (NO CHEMOTHERAPY)

Investigator	Institution	Number of Patients	Minimum Follow-Up (y)	Local Control (%)	Ultimate Control After Surgery Salvage (%)
Harwood et al[112]	Princess Margaret (Toronto)	112	3	51	77
Wang[113]	Massachusetts General (Boston)	70	4	36	57
Fletcher[114]	MD Anderson (Houston)	17	2	77	No data
Skolyszewski and Reinfuss[115]	15 European Centers	91	3	50	No data
Stewart et al[116]	Manchester (England)	67	10	57	67
Mills[117]	Cape Town, South Africa	18	2	44	78
Mendenhall et al[41]	University Florida of (Gainesville)	75	2	63	86

Modified from Parsons JT, Mendenhall WM, Mancuso AA, Cassisi NJ, Stringer SP, Million RR. Twice-a-day radiotherapy for T3 squamous cell carcinoma of the glottic larynx. *Head Neck*. 1989;11(2):123-128. Copyright © 1989 Wiley Periodicals, A Wiley Company. Reprinted by permission of John Wiley & Sons.

The survival and control rates of patients with T3 fixed-cord lesions treated at the University of Florida are presented in Table 53.8.[82] There was no relationship between subsequent local control and whether the vocal cord remained fixed or became mobile during irradiation. The incidence of severe complications, including those after the initial treatment and any later salvage procedures, was 15% after RT alone and 15% after surgery alone or combined with adjuvant irradiation. The vocal quality varied from fair to nearly normal. Hinerman et al[34] recently reported an update on the University of Florida experience treating fixed-cord T3 glottic cancers with definitive RT and reported a 5-year local control rate after RT of 63%.

TABLE 53.8 T3 GLOTTIC CARCINOMA TREATED AT THE UNIVERSITY OF FLORIDA, 1965-1988: 5-YEAR RESULTS

Parameter	Radiotherapy Alone (53 Patients)	Surgery With or Without (65 Adjuvant Radiotherapy Patients)
Local-regional control (%)	62	75
Ultimate control local-regional (%)	84	82
Absolute survival (%)	55	45
Cause-specific survival (%)	75	71

Data from Mendenhall WM, Parsons JT, Stringer SP, Cassisi NJ, Million RR. Stage T3 squamous cell carcinoma of the glottic larynx: a comparison of laryngectomy and irradiation. *Int J Radiat Oncol Biol Phys*. 1992;23(4):725-732.

The results of treatment of T4 vocal cord carcinoma in four surgical series and two radiotherapy series are summarized in Table 53.9.[64] Hinerman et al[34] observed an 81% 5-year local control rate in 22 selected patients with favorable T4 cancers treated with definitive RT at the University of Florida.

TABLE 53.9 TREATMENT OF STAGE T4 GLOTTIC CARCINOMAS

Investigator	Tumor Stage	Number of Patients	Method of Treatment	Results: Evidence No of Disease
Jesse[118]	T4 N0-N+	48	Laryngectomy	54% at 4 y
Ogura et al[119]	T4 N0	11	Laryngectomy	45% at 3 y
Skolnik et al[120]	T4 N0	7	Laryngectomy	30% at 5 y
Vermund[121]	T4 N0	31	Laryngectomy	35% at 5 y
Stewart and Jackson[122]	T4 N0	13	Radiotherapy with for surgery salvage	38% at 5 y
Harwood et al[64]	T4 N0	56	Radiotherapy surgery with for salvage	49% at 5 y[a]

[a]Life-table method; uncorrected for deaths from intercurrent disease.

Modified from Harwood AR, Beale FA, Cummings BJ, Keane TJ, Payne D, Rider WD. T4nomo glottic cancer: an analysis of dose-time volume factors. *Int J Radiat Oncol Biol Phys*. 1981;7(11):1507-1512. Copyright © 1981 Elsevier. With permission.

Parsons et al[83] reviewed the literature and reported a local control rate of 62% in a series of 87 patients treated with RT alone for T4 glottic carcinoma.

Supraglottic Cancer

The proportion of patients suitable for a supraglottic laryngectomy is depicted in Table 53.10.[76] Depending on the referral patterns, a modest subset of patients is suitable for this operation. The extent of neck disease for patients treated with either surgery or RT is shown in Table 53.11.[76] In general, patients treated with supraglottic laryngectomy appropriately have earlier stage neck disease and would be anticipated to have a lower risk of distant failure and improved survival. The local control rates after transoral laser, RT, and supraglottic laryngectomy are summarized in Tables 53.12 to 53.14.[76] In general, the local control rates after transoral laser excision are fairly good for patients with T1-T2 tumors and tend to deteriorate for those with more advanced disease. The local control rate for patients selected for supraglottic laryngectomy is excellent. However, the incidence of severe

complications tends to be higher after supraglottic laryngectomy compared with RT and transoral laser excision (Table 53.15).[76,84]

TABLE 53.10 PROPORTION OF PATIENTS SUITABLE FOR SUPRAGLOTTIC LARYNGECTOMY

Series	Number of Patients	Number (%) Supraglottic With Laryngectomy
Ogura et al, 1975[123]	263	177 (67)
Lutz et al, 1990[124]	202	72 (36)
Lee et al, 1990[78]	404	60 (15)
Weems et al, 1987[125]	195	30 (15)
Gregor et al, 1996[126]	89	26 (29)
Spriano et al, 1997[127]	257	38 (14)

Some values were estimated as closely as possible to fit the table format if the information was not specifically stated in the cited reference.

From Hinerman RW, Mendenhall WM, Amdur RJ, Stringer SP, Villaret DB, Robbins KT. Carcinoma of the supraglottic larynx: treatment results with radiotherapy alone or with planned neck dissection. *Head Neck*. 2002;24(5):456-467. Copyright © 2002 Wiley Periodicals. Reprinted by permission of John Wiley & Sons.

TABLE 53.11 SUPRAGLOTTIC CARCINOMA: EXTENT OF NECK DISEASE VERSUS TREATMENT

Series	Treatment	Number of Patients	Extent Neck of Disease
Bocca, 1991[128]	SGL	537	94% N0-N1
Isaacs et al, 1998[129]	SGL	39	74% N0-N1
Ogura et al, 1975[123]	SGL	177	77% N0
Davis et al, 1991[130]	Laser	14	93% N0
Zeitels et al, 1994[131]	Laser	45	100% N0
Rudert et al, 1999[132]	Laser	34	82% N0-N1
Ghossein et al, 1974[133]	Radiation	203	53% N0
Hinerman et al, 2002[76]	Radiation	274	54% N0

Some values were estimated as closely as possible to fit the table format if the information was not specifically stated in the cited reference.

SGL, supraglottic laryngectomy.

From Hinerman RW, Mendenhall WM, Amdur RJ, Stringer SP, Villaret DB, Robbins KT. Carcinoma of the supraglottic larynx: treatment results with radiotherapy alone or with planned neck dissection. *Head Neck*. 2002;24(5):456-467. Copyright © 2002 Wiley Periodicals. Reprinted by permission of John Wiley & Sons.

TABLE 53.12 SUPRAGLOTTIC CANCER: LOCAL CONTROL AFTER TRANSORAL LASER EXCISION

Series	Staging	Number of Patients	Percentage Patients of T1 with or T2 Tumors	Local Control (%)			
				T1	*T2*	*T3*	*T4*
Davis et al, 1991[130]	P	14 R	57	100	100	50	—
Steiner,[a] 1993[52]	P	81 R	72	—	76	77	100
Zeitels et al, 1994[131]	ND	22	100	100	100	—	—
Zeitels et al, 1994[131]	ND	23 R	65	100	92	63	—
Csanády et al, 1999[134]	ND	23	100	70[b]	—	—	
Rudert et al, 1999[132]	P	34 R	50	100	75	78	38

Some values were estimated as closely as possible to fit the table format if the information was not specifically stated in the cited reference.

ND, type of staging not provided; P, pathologic staging; R, plus or minus radiotherapy.

[a]Fifty-one glottic and 30 supraglottic.

[b]Overall local control rate for T1 and T2.

From Hinerman RW, Mendenhall WM, Amdur RJ, Stringer SP, Villaret DB, Robbins KT. Carcinoma of the supraglottic larynx: treatment results with radiotherapy alone or with planned neck dissection. *Head Neck*. 2002;24(5):456-467. Copyright © 2002 Wiley Periodicals. Reprinted by permission of John Wiley & Sons.

TABLE 53.13 SUPRAGLOTTIC CANCER: LOCAL CONTROL AFTER RADIOTHERAPY

Series	Institution	Number of Patients	Local Control (%)			
			T1	*T2*	*T3*	*T4*
Fletcher and Hamberger, 1974[135]	MD Anderson Hospital	173	88	79	62	47
Ghossein et al, 1974[133]	Foundation Curie	203	94	73	46[a]	52
Wang and Montgomery, 1991[136]	Massachusetts General Hospital	229 qd	73	60	54	26
		209 bid	89	89	71	91
Nakfoor et al, 1998[137]	Massachusetts General Hospital	164	96	86	76	43
Sykes et al, 2000[138]	Christie Hospital	331[b]	92[c]	81[c]	67[c]	73[c]
Hinerman et al, 2002[76]	University of Florida[d]	274	100	86	62	62

Some values were estimated as closely as possible to fit the table format if the information was not specifically stated in the cited reference. bid, twice daily; qd, everyday.

[a]All had cord fixation.

[b]All N0.

[c]After 17 were salvaged by total laryngectomies.

[d]1998 American Joint Committee on Cancer staging.

From Hinerman RW, Mendenhall WM, Amdur RJ, Stringer SP, Villaret DB, Robbins KT. Carcinoma of the supraglottic larynx: treatment results with radiotherapy alone or with planned neck dissection. *Head Neck*. 2002;24(5):456-467. Copyright © 2002 Wiley Periodicals. Reprinted by permission of John Wiley & Sons.

TABLE 53.14 LOCAL CONTROL AFTER SUPRAGLOTTIC LARYNGECTOMY

Series	Institution	Number of Patients	Patients With T1 and T2 Tumors (%)	Local Control (%)			
				T1	*T2*	*T3*	*T4*
Ogura et al, 1975[123]	Washington University	177	78		94[a]		
Bocca, 1991[128]	Milan University						
Stage I		47	100	94			
Stage II		252	100		82		
Stage III		205	53		80[b]		

Series	Institution	Number of Patients	Patients With T1 and T2 Tumors (%)	Local Control (%)			
				T1	*T2*	*T3*	*T4*
Stage IV		33	70		67[c]		
Lee et al, 1990[78]	MD Anderson Cancer Center	60	58	100	100	100	100
DeSanto, 1990[139]	Mayo Clinic	70	100	100	100		
Steiniger et al, 1997[140]	Albany Medical College	29	83		97[a]		
Spriano et al, 1997[127]	Varese, Italy	54	100	96[d]			
Burstein and Calcaterra, 1985[141]	University of California, Los Angeles	40	58	100[d]		85	94
Isaacs et al, 1998[129]	University of Florida	33	76	100[d]		78	71
Lutz et al, 1990[124]	University of Pittsburgh	72	No data			99[d]	

Some values were estimated as closely as possible to fit the table format if the information was not specifically stated in the cited reference. T stages were not specified.

[a]Overall local control rate for T1-T4.

[b]Overall local control rate for T1-T3.

[c]Overall local control rate for T2-T3.

[d]Overall local control rate for T1-T2.

From Hinerman RW, Mendenhall WM, Amdur RJ, Stringer SP, Villaret DB, Robbins KT. Carcinoma of the supraglottic larynx: treatment results with radiotherapy alone or with planned neck dissection. *Head Neck*. 2002;24(5):456-467. Copyright © 2002 Wiley Periodicals. Reprinted by permission of John Wiley & Sons.

TABLE 53.15 SUPRAGLOTTIC CANCER: SEVERE COMPLICATIONS ACCORDING TO TREATMENT MODALITY

Series	Institution	Severe Complications
Radiotherapy		
Fletcher and Hamberger, 1974[135]	MD Anderson Cancer Center	10/173 (6%)

Series	Institution	Severe Complications
Ghossein et al, 1974[133]	Fondation Curie	8/117 (7%)
Nakfoor et al, 1998[137]	Massachusetts General Hospital	12/169 (7%)
Sykes et al, 2000[138]	Christie Hospital	7/331 (2%)
Hinerman et al, 2002[76]	University of Florida	12/274 (4%)
Supraglottic Laryngectomy		
Lee et al, 1990[78]	MD Cancer Anderson Center	9/63 (14%)
Isaacs et al, 1998[129]	University of Florida	14/34 (41%)
Burstein and Calcaterra, 1985[141]	University California, Los Angeles	14/41 (34%)
Steiniger et al, 1997[140]	Albany Medical College	12/29 (41%)
Spriano et al, 1997[127]	Varese, Italy	13/54 (24%)
Gall et al, 1977[95]	Washington University	20/133 (15%)
Weber et al, 1993[142]	University of Pittsburgh	12/69 (17%)
Beckhardt et al, 1994[143]	University of Wisconsin	15/50 (30%)
Transoral Laser Excision		
Rudert et al, 1999[132]	University Kiel, Germany	3/34 (9%)
Zeitels et al, 1994[131]	Massachusetts and Eye Ear Infirmary	2/45 (4%)
Steiner,[a] 1993[52]	University Göttingen, Germany	7/240 (3%)
Davis et al, 1991[130]	University Utah, Salt Lake City	0/14 (0%)
Csanády et al, 1999[134]	Albert Gyorgyi Szent Medical University, Szeged, Hungary	0/23 (0%)

Some values were estimated as closely as possible to fit the table format if the information was not specifically stated in the cited reference.

[a]Includes patients with glottic cancer.

From Hinerman RW, Mendenhall WM, Amdur RJ, Stringer SP, Villaret DB, Robbins KT. Carcinoma of the supraglottic larynx: treatment results with radiotherapy alone or with planned neck dissection. *Head Neck*. 2002;24(5):456-467. Copyright © 2002 Wiley Periodicals. Reprinted by permission of John Wiley & Sons.

LARYNGECTOMY VERSUS ORGAN PRESERVATION

Treatment of advanced laryngeal cancer carries significant morbidity with deteriorations in quality of life. Thus, many centers and patients have elected to pursue organ preservation strategies. The first major breakthrough in organ preservation came with the Department of Veterans Affairs Laryngeal Cancer Study Group Trial ("The VA Trial").[39] Stage III and IV patients were randomized to total laryngectomy followed by RT versus RT or induction chemotherapy + RT. The conclusion was that induction chemotherapy + RT produced equivalent survival to total laryngectomy + RT. In 2003, the RTOG 91-11 study randomized patients to organ preservation modalities and found that concurrent chemotherapy and RT (CCRT) produced superior survival outcomes. Following these studies, the employment of CCRT for advanced laryngeal cancer has risen significantly.

In 2006, Hoffman et al[85] used the National Cancer Database and found that of all cancers in the United States, laryngeal cancer is the only one with a declining survival rate. While early-stage cancer maintains high survival outcomes, patients with advanced disease have a declining lifespan. This pattern coincides with the trend of increased use of organ preservation and decreased use of total laryngectomy for advanced laryngeal cancers.

Over the past 15 years, there has been great interest in reexamining the optimal treatment for advanced laryngeal cancers. In 2007, Chen and Halpern[86] analyzed 10,590 patients from the late 1990s and found that total laryngectomy had superior survival outcomes compared to RT or CCRT. In 2009, Gourin et al[87] analyzed a population of patients treated between 1985 and 2002 and found that patients with stage IV disease had improved 5-year survival compared to organ preservation. In 2012, Dziegielewski et al[88] performed a population-based analysis of survival from 1998 to 2008 and found that T3 and T4a laryngeal cancers treated with total laryngectomy + RT had improved overall and disease-free survival. The 5-year survival rates for T3 cancers treated with total laryngectomy + RT, RT, and chemoradiotherapy (CRT) were 70%, 18%, and 52%, respectively. For T4a disease, these figures were 49%, 5%, and 16%. In 2014, Megwalu and Sikora[89] found similar survival outcomes using the Surveillance, Epidemiology, and End Results database to analyze 5,394 patients with

stage III and stage IV laryngeal carcinomas treated between 1992 and 2009. Disease-specific survival rates for surgically treated patients at 2 and 5 years were 70% and 64% versus organ preservation strategies, which yielded rates of 55% and 51%. Multivariate analysis, accounting for the year of diagnosis, stage, age, sex, subsite, race, and marital status, continued to show improved disease-specific and overall survival for patients receiving primary surgery.

Since the initial VA trial, advanced laryngeal cancer survival outcomes have deteriorated, prompting debate on whether the results of the trial can be widely applied to all advanced laryngeal cancer.[90] Population-based studies have shown that treatment strategies need to be tailored to the patient and that T stage is a better determinant of survival than the overall stage.[87,88] It has become widely accepted that the majority of patients with T4a cancer will experience better survival and functional outcomes when treated with laryngectomy versus organ preservation.[87-89] However, the debate over which T3 tumors can be optimally treated with CRT continues.[91]

FOLLOW-UP POLICY

Follow-up of patients with early lesions is planned for every 4 to 8 weeks for 2 years, every 3 months for the third year, every 6 months for years 4 and 5, and then annually for life.

Follow-up of patients with vocal cord or supraglottic larynx lesions treated by RT or conservative surgery is almost more important than the treatment itself because early detection of recurrence usually results in salvage that may include cure with voice preservation.

If recurrence is suspected but the biopsy is negative, patients are reexamined at 2- to 4-week intervals until the matter is settled. The value of follow-up CT scans for detecting early local recurrence is investigational.

Wagenfeld et al[92] studied 740 cases of glottic larynx cancer treated from 1965 to 1974 to determine the incidence of second respiratory tract malignancies. There was a minimum follow-up of 5 years. There were 48 second respiratory tract malignancies, although only 14 were expected. Twenty-five were in the lung, and 23 were scattered among other head and neck sites. Only 7 of the 23 second head and neck primary lesions resulted

in death; these second lesions were frequently diagnosed in an early stage during routine follow-up for the glottic lesion.

Because the risk of a lethal lung primary lesion is nearly as great as that of dying of an early glottic carcinoma, it makes sense to obtain annual chest roentgenograms. Approximately 50% of patients who receive moderate- to high-dose RT to the entire thyroid gland will develop hypothyroidism within 5 years, and so thyroid functions are checked every 6 to 12 months and thyroid replacement is initiated if the thyroid-stimulating hormone level begins to rise.[93]

SEQUELAE OF TREATMENT

Surgical Sequelae

Neel et al[94] reported a 26% incidence of nonfatal complications for cordectomy. Immediate postoperative complications included atelectasis and pneumonia, severe subcutaneous emphysema in the neck, bleeding from the tracheotomy site or larynx, wound complications, and airway obstruction requiring tracheotomy. Late complications included granulation tissue that had to be removed by direct laryngoscopy to exclude recurrences, extrusion of cartilage, laryngeal stenosis, and obstructing laryngeal web.

The postoperative complications and sequelae of hemilaryngectomy include chondritis, wound slough, inadequate glottic closure, and anterior commissure webs.[95] The complications associated with supraglottic laryngectomy and total laryngectomy for supraglottic carcinomas include fistula (8%), carotid artery exposure or blowout (3%-5%), infection or wound sloughing (3%-7%), and fatal complications (3%).[95] The risk of complication increased if tumor margins were involved by tumor; there was no change in risk associated with age, sex, race, laryngeal site, stage of primary tumor, size of primary tumor, use of low-dose preoperative RT, or status of the positive nodes.

The incidence of complications after treatment of supraglottic carcinoma is given in Table 53.15.[76]

Radiation Therapy Sequelae

The acute reactions from the treatment of early vocal cord cancer using a tumor dose of 2.25 Gy per day to administer a total dose 63 Gy (4- or 6-MV photons, five fractions per week) are relatively mild. During the first 2 to 3 weeks, the voice may improve as the tumor regresses. The voice generally becomes hoarse again because of RT-induced changes, even though the tumor continues to regress. A mild sore throat develops beginning at the end of the second week, but medication is usually not required. The voice begins to improve approximately 3 weeks after completion of treatment, usually reaching a plateau in 2 to 3 months. Patients with extensive lesions often recover a normal voice, although not as frequently as those with small tumors.

Edema of the larynx is the most common sequela after RT for glottic or supraglottic lesions. The rate of clearance of the edema is related to the RT dose, volume of tissue irradiated, addition of a neck dissection, continued use of alcohol and tobacco, and size and extent of the original lesion. Edema may be accentuated by a neck dissection and may require 6 to 12 months to subside.

Soft tissue necrosis leading to chondritis occurs in <1% of patients, usually in those who continue to smoke. Soft tissue and cartilage necroses mimic recurrence, with hoarseness, pain, and edema; a laryngectomy may be recommended as a last resort for fear of recurrent cancer, even though biopsy specimens show only necrosis.

Corticosteroids such as dexamethasone (Decadron) have been used to reduce RT-induced edema after recurrence has been ruled out by biopsy. If ulceration and pain occur, administration of an antibiotic such as tetracycline may help. Of 519 patients with T1 N0 or T2 N0 vocal cord cancer treated at the University of Florida, 5 (1%) experienced severe complications,[18] including total laryngectomy for a suspected local recurrence (1 patient), permanent tracheostomy for edema (3 patients), and a pharyngocutaneous fistula after a salvage total laryngectomy (1 patient).

In patients irradiated for supraglottic carcinoma, sore throat persists 1 to 2 months after completion of treatment. There is an associated dry mouth from RT of the salivary and parotid glands, a loss of taste, and a sensation of a lump in the throat. It is unusual for patients to require a tracheotomy before RT unless severe lymphedema develops at the time of direct laryngoscopy and biopsy. However, in patients who have recovered from

the direct laryngoscopy and biopsy without obstruction, a tracheotomy has rarely been required during a fractionated course of RT.

Patients treated twice a day with 1.2-Gy fractions (continuous- course technique) to a total dose of 74.4 Gy usually have more brisk acute reactions than those treated once a day with 2-Gy fractions. Approximately 30% treated with twice-a-day RT require temporary gastrostomy feeding tubes because they have difficulty in swallowing.[96]

Examples of acute chondritis requiring discontinuation of treatment have not been seen, although most epiglottic lesions exhibit cartilage invasion.

The epiglottis, both suprahyoid and infrahyoid portions, remains thicker than normal for long periods of time, but this is not often associated with difficulty in swallowing, respiratory obstruction, or aspiration. The patient is cautioned to eat and drink slowly until the edema resolves. The false cord and arytenoids may develop some edema.

Lesions of the suprahyoid epiglottis frequently destroy the tip of the epiglottis, and it may require some time for the exposed cartilage to heal. Successful RT of infrahyoid epiglottis tumors is not associated with a high rate of necrosis, even though most of these lesions penetrate the porous epiglottic cartilage.

The incidence of severe late complications in 274 patients treated with RT alone or combined with neck dissection at the University of Florida was 4%.[76]

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CHAPTER 54

Unusual Nonepithelial Tumors of the Head and Neck

Adam L. Holtzman and Daniel M. Trifiletti

PARAGANGLIOMAS

Anatomy

Paragangliomas (PGs), previously called glomus tumors, are neuroendocrine tumors (NETs) found in the peripheral nervous system. Whereas adrenal tumors are referred to as pheochromocytomas, extra-adrenal tumors are termed *paragangliomas* and are commonly found in the head and neck (H&N). They are often located in the jugular bulb and along the tympanic (Jacobson) and auricular (Arnold) branches of the tenth nerve in the middle ear or in other anatomic sites (Figure 54.1). Depending on the location, PGs are classified as tympanic (middle ear), jugular, carotid, or vagal or designated as originating from other locations, such as the larynx, adventitia of thoracic aorta, abdominal aorta, or the surface of the lungs (Figure 54.2).[1]

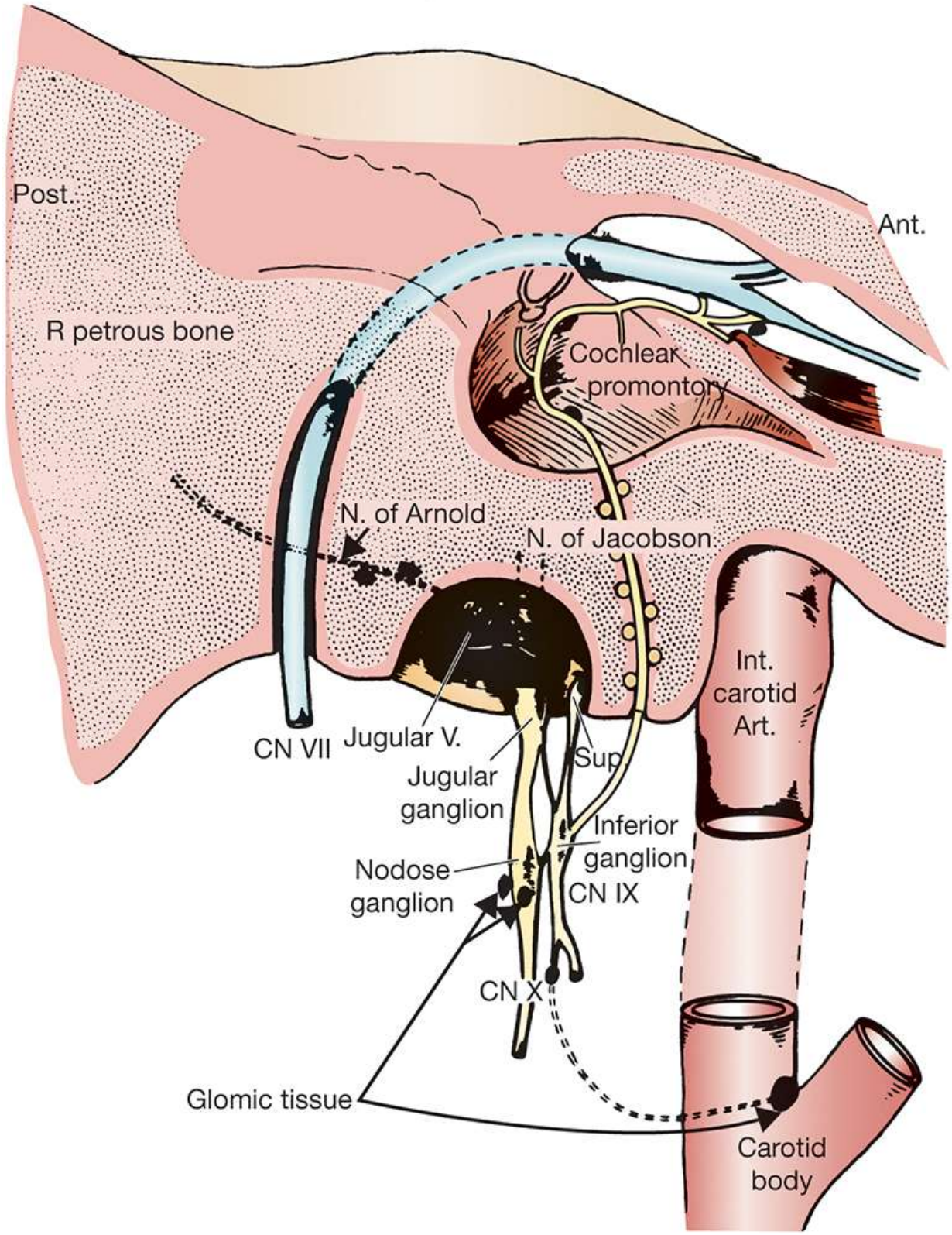

FIGURE 54.1 Anatomy of the region of jugular paragangliomas. CN, cranial nerve. (From Hatfield PM, James AE, Schulz MD. Chemodectomas of the glomus jugulare. *Cancer*. 1972;30[5]:1164-1168. Copyright © 1972 American *Cancer* Society. Reprinted by permission of John Wiley & Sons.)

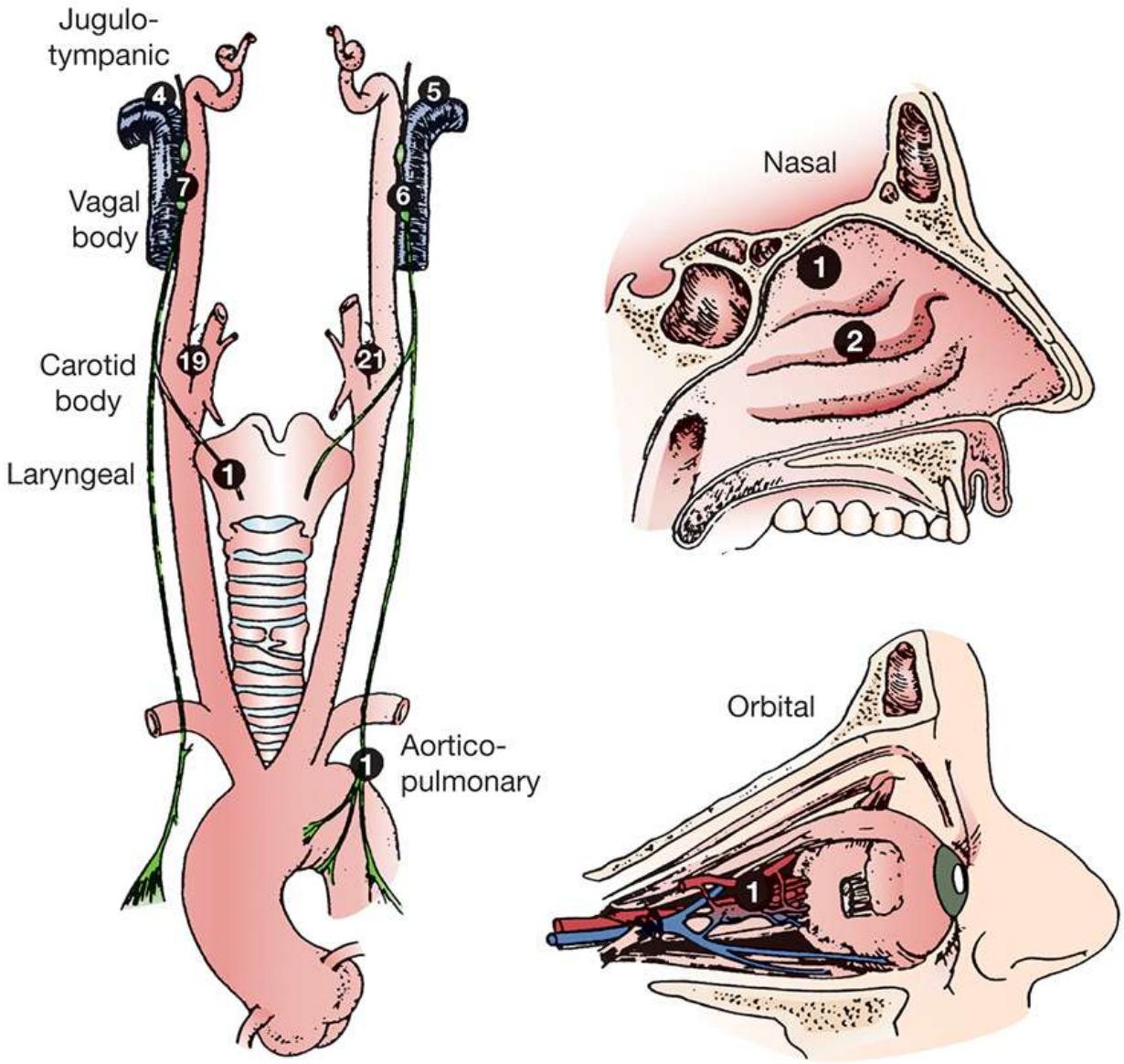

FIGURE 54.2 Distribution of paragangliomas of the head and neck region. Laterality was not specified in three patients with carotid body paragangliomas. The diagram does not include one left carotid body paraganglioma that was found incidentally at autopsy and a left vagal body paraganglioma that presented in a patient who had two other paragangliomas. (From Lack EE, Cubilla AL, Woodruff JM, Farr HW. Paragangliomas of the head and neck region: a clinical study of 69 patients. *Cancer*. 1977;39[2]:397-409. Copyright © 1977 American Cancer Society. Reprinted by permission of John Wiley & Sons.)

Ninety-five percent of PGs of the H&N are nonchromaffin, nonsecretory benign tumors. Clinically, they are divided into benign and, very rarely, malignant neoplasms. Malignancy, in contrast to most other tumors, is defined by clinical behavior such as the development of metastases, rather than from histologic evaluation.[2] The incidence can vary based on tumor location, with up to 15% of the carotid body and vagal lesions being malignant.[3,4]

PGs consist of large epithelioid (smooth muscle) cells with fine granular cytoplasm embedded in a rich capillary network and fibrous stroma with reticulin fibers, which derive from embryonic neural crest cells. Although histologically benign, they may extend along the lumen of the vein to regional lymph nodes, but rarely to distant sites. These tissues are responsive to changes in oxygen and carbon dioxide tensions and pH.

Epidemiology

The mean age at diagnosis has been reported to be 45 years for carotid body tumors and 52 years for tympanic PG.[5] These tumors occur 3 or 4 times more frequently in women than in men, suggesting a possible estrogen influence.[3,5,6] PG tumors may be familial; they occur in multiple sites in 10% to 20% of patients.[7] Incidence may be influenced by hereditary syndromes, including Paraganglioma Syndromes 1 to 5 (PGL1-5), Multiple Endocrine Neoplasia Type 2 (MEN2), and Neurofibromatosis Type 1 (NF1).

Recent advances in genetics identified three loci associated with hereditary PGs, and genetic screening may detect affected patients.[8] Multiple PGs of the H&N are rare, with an incidence of 10% of all patients, but in familial cases, it increases up to 35% to 50%. In the H&N region, while several susceptibility genes have been identified, they are most commonly caused by the *SDHD* gene and present with bilateral carotid body tumors or carotid body tumors associated with tympanic-jugular tumors.[7]

Clinical Presentation

PGs may arise along the nerve roots. In the middle ear, they may initially cause earache or discomfort. As they expand, eventually, they produce pulsatile tinnitus, hearing loss, and, in later stages, cranial nerve paralysis resulting from invasion of the base of the skull in 10% to 15% of patients. If the tumor invades the middle cranial fossa, symptoms may include temporoparietal headache, retro-orbital pain, proptosis, and paresis of cranial nerves V and VI. If the posterior fossa is involved, symptoms may include occipital headache, ataxia, and paresis of cranial nerves V to VII, IX, and XII; invasion of the jugular foramen causes paralysis of nerves IX to XI. Carotid body PG usually presents as a painless, slowly growing mass in the upper neck. Occasionally, the mass may be pulsatile and may have an associated thrill or bruit. As it enlarges, the mass may extend into the parapharyngeal space and be visible on examination of the oropharynx.

Diagnostic Workup

Diagnostic evaluation for PGs is outlined in Table 54.1. In the majority of tympanic PGs, physical examination demonstrates a red, vascular middle ear mass, although, occasionally, it may be bluish or white (the latter resembling a cholesteatoma).[5] Figure 54.3 demonstrates an example of the clinical and radiographic appearance of a tympanic PG. Audiography may demonstrate conductive hearing loss in the ear involved by tumor as noted in 33 of 49 patients evaluated by Larson et al[5]; 4 of 33 patients with conductive deficits also exhibited tympanic pulsations. Examination of the neck may occasionally

demonstrate a mass in the neck that may be pulsatile or have a bruit or regional lymph node metastases, although exceedingly rare.

TABLE 54.1 DIAGNOSTIC WORKUP FOR HEAD AND NECK PARAGANGLIOMA

General
Clinical history
General physical examination
Ear, nose, and throat examination
Radiographic Studies
Computed tomography scan (with contrast) to define tumor extent and possible central nervous system involvement)
Magnetic resonance imaging with gadolinium
Arteriography to determine bilateral involvement and collateral cerebral blood flow (optional)
Jugular phlebography (optional)
Laboratory Studies
Complete blood cell count
Blood chemistry profile
Urinalysis (optional)
Special Tests
Audiograms to establish baseline hearing loss
Histologic staining to determine the presence of catecholamines

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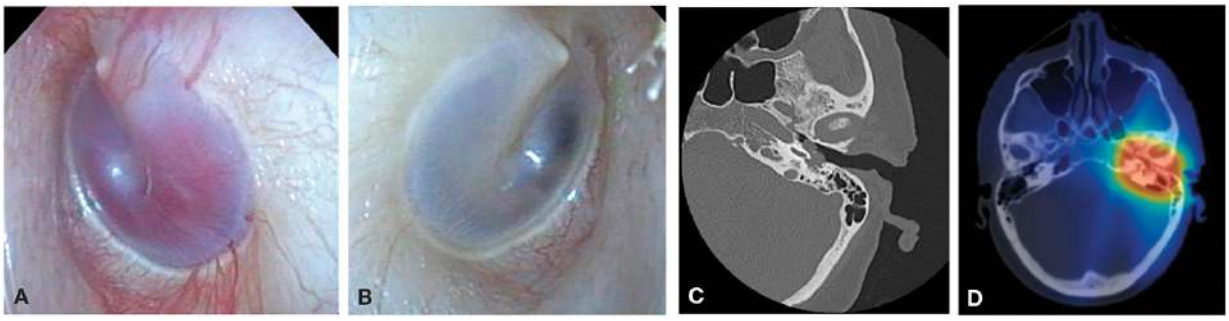
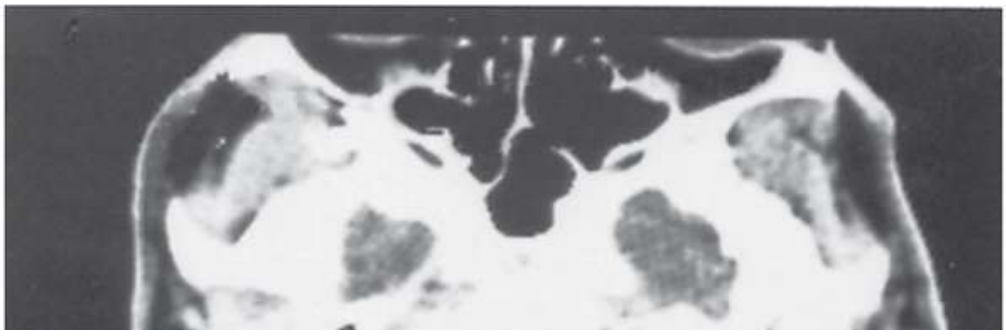


FIGURE 54.3 A. Tympanic paraganglioma involving the left middle ear with the left tympanic membrane demonstrating a bulging, pulsatile, purple-red mass. B. As compared to the right ear of the same patient serving as a normal examination control. C. The tumor within the left ear canal is shown on high-resolution, bone-windowed computed tomography. D. Representative intensity-modulated radiation therapy plan fused to a color wash dose distribution being treated to 45 Gy at 1.8 Gy per treatment.

High-resolution computed tomography (CT) with contrast has a degree of sensitivity and specificity to diagnose this tumor when located in the middle ear or jugular bulb; masses as small as 3 mm have been demonstrated. Tumor enhancement is similar to that of

the temporalis muscle (Figure 54.4).[5] In 46 patients with glomus tympanicum, there were no instances of local bony erosion; instead, the tumors engulfed the ossicular chain, bulged or protruded through the tympanic membrane, filled the middle ear, or extended into the eustachian tube orifice or aditus ad antrum. This pattern is in contrast to cholesteatomas or even other malignancies such as endolymphatic sac tumors (ELSTs), which typically destroy adjacent bony landmarks, including the ossicles, and progressively erode the petrous bones as they enlarge.[5] Distinction from ELST, while rare and less than 300 cases reported in the literature, is important as this locally aggressive malignancy (Figure 54.5) necessitates carcinoma-type dosing of 66 Gy or higher to gross disease to achieve durable tumor control.[9]

A



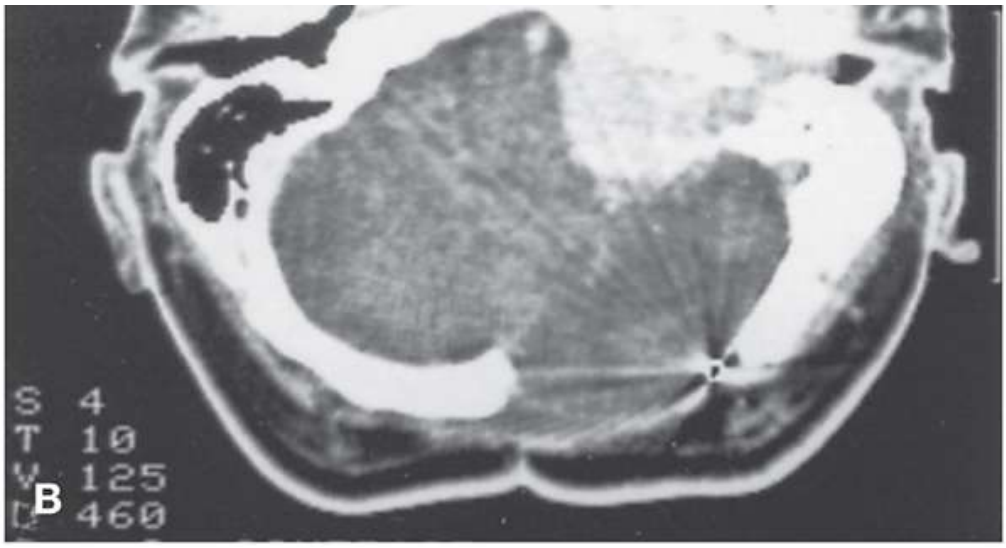


FIGURE 54.4 A. Late-phase arteriogram illustrating large jugular paraganglioma with extension into the neck. B. Computed tomography scan with contrast enhancement showing intracranial component of lesion.

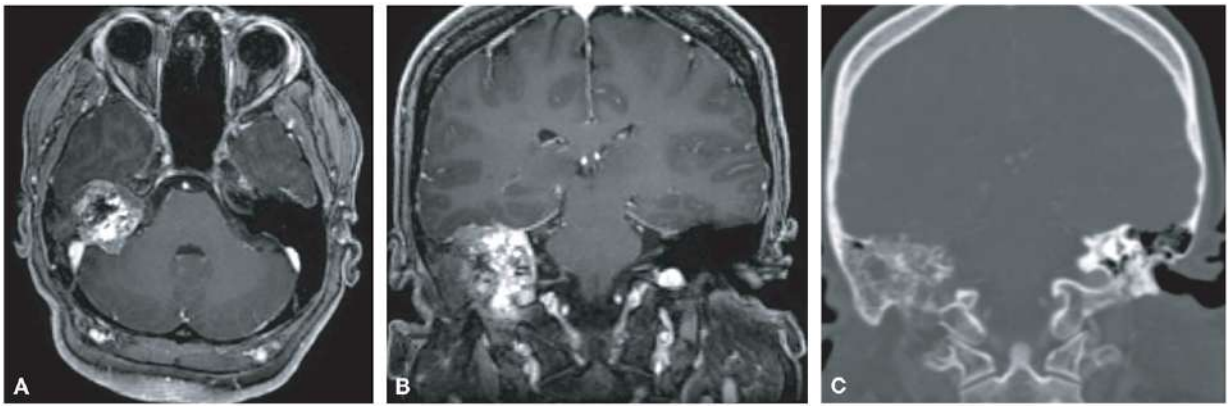


FIGURE 54.5 Axial (A) and coronal (B) T1-weighted three-dimensional magnetic resonance imaging (MRI) fused to coronal computed tomography (CT) of the head (C) with bone windowing demonstrating an endolymphatic sac tumor (ELST). Less common in jugulotympanic paragangliomas, ELST is associated with osseous erosion including involvement of the semicircular canals and jugular plate as shown by CT. MRI demonstrates a lobular enhancing mass arising from the right mastoid and petrous temporal bone with peripheral areas of intrinsic T1 hyperintensity. There is an extension through the tegmen mastoideum superiorly, jugular plate laterally, into the right internal auditory canal and cerebellopontine angle medially, and slightly through the right mastoid bone and base of skull inferiorly. (Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

Magnification angiography is a sensitive and specific means of detecting tympanic PGs. This procedure is performed after high-resolution thin-section CT scan (with contrast material), only when there is a question regarding the nature of the lesion or the location of the carotid canal. Findings include a hypervascular middle ear mass that first appears in the middle to late arterial phase, persists through the capillary phase, and quickly disappears in the venous phase without demonstrably early draining veins. Diagnosis is made clinically and radiographically, and treatment with radiotherapy (RT) without a

tissue diagnosis is accepted practice. Biopsy of an aberrant internal carotid artery can result in major neurologic sequelae or death.

Vogl et al[10] reported on 40 patients with PGs of the skull; diagnostic interpretations were correlated with histologic examination, digital subtraction angiography, CT, and clinical follow-up. Sixteen of 18 proven tumors were detected with spin-echo images alone. Although four high-flying jugular bulbs were misinterpreted as tumors because of similar signal intensity, combined evaluation allowed differentiation between tumor and sinusal blood flow in all cases.

Drapé et al[11] described magnetic resonance imaging (MRI) findings in 31 patients with a clinical suspicion of PG; gadoterate meglumine was injected into 19 patients. Twenty-seven of 28 pathologically confirmed PGs were detected with MRI; a peripheral capsule was present in most tumors. The investigators were able to differentiate three subtypes of PGs (vascular, solid, and myxoid) on the basis of relaxation times and enhancement characteristics. Multidetector CT angiography was found to be more accurate in the diagnosis of six PGs, with enhancement in the arterial phase, when compared with MRI.[12]

As PGs show high levels of somatostatin receptor (SSTR) subtypes 2 and 5, fluorine-(^{18}F)-octreotate positron emission tomography (PET) may be useful for diagnostic purposes in a semiquantitative manner and for improving target volume delineation in RT planning. Astner et al[13] noted that preliminary findings with two different PET tracers for SSTR imaging have been reported: Gallium-68 (^{68}Ga)-DOTATOC (DOTA-D-Phe(1)-Tyr(3)-octreotide [somatostatin analog]) PET was shown to detect SSTR expressing tumors with high sensitivity and specificity. A second PET tracer, Gluc-Lys(^{18})F-TOCA, allows fast, high-contrast imaging of SSTR-positive tumors with superior biokinetics and diagnostic performance as compared with indium-111 (^{111}In)-diethylenetriamine pentaacetic acid-octreotide and—as far as can be determined from the literature—comparable to[14] Ga-DOTATOC.[15-17]

Cytochemical techniques demonstrate increased levels of serotonin, epinephrine, and norepinephrine in normal tissue of the carotid body. Histologic staining techniques, including chromaffin and argentaffin reactions, identify patients with hormonally active tumors. This is important because the PGs may coexist with a pheochromocytoma, which requires special preoperative preparation of the patient. Biopsy of PGs should be avoided as they can result in severe hemorrhage.

Staging

The prognosis of these tumors is closely related to the anatomic location and the volume of the lesion, which is reflected in the Glasscock-Jackson classification,[18] and an alternative system proposed by McCabe and Fletcher[14] is presented in Table 54.2.

TABLE 54.2 MODIFICATION OF MCCABE AND FLETCHER CLASSIFICATION OF PARAGANGLIOMA

Group I: Tympanic Tumors
Absence of bone destruction on x-rays of the mastoid bone and jugular fossa

Absence of facial nerve weakness
Intact eighth nerve with conductive deafness only
Intact jugular foramen nerves (cranial nerves IX, X, and XI)
Group II: Tympanomastoid Tumors
X-ray evidence of bone destruction confined to the mastoid bone and not involving the petrous bone
Normal or paretic seventh nerve
Intact jugular foramen nerves
No evidence of involvement of the superior bulb of the jugular vein on retrograde venogram
Group III: Petrosal and Extrapetrosal Tumors
Destruction of the petrous bone, jugular fossa, and/or occipital bone on x-rays
Positive findings on retrograde jugulography
Evidence of destruction of the petrous or occipital bones on carotid arteriogram
Jugular foramen syndrome (paresis of cranial nerve IX, X, or XI)
Presence of metastasis

Reprinted from Wang ML, Hussey DH, Doornbos JF, Vigliotti AP, Wen BC. Chemodectoma of the temporal bone: a comparison of surgical and radiotherapeutic results. *Int J Radiat Oncol Biol Phys*. 1988;14(4):643-648. Copyright © 1988 Elsevier. With permission.

General Management

Li et al[15] published a historical perspective of various treatment modalities used to treat PGs over the past 60 years.

Surgery

Surgery is generally selected for small tumors that can be completely excised. Tympanic PGs are particularly well managed with excision via tympanotomy or mastoidectomy. Percutaneous embolization of a low-viscosity silicone polymer has been used, frequently as preoperative preparation of the tumor embolization of feeding vessels allows meticulous microsurgery with virtually complete hemostasis.

Surgical treatment of a PG arising in the jugular bulb, however, often consists of piece-by-piece removal accompanied by significant intraoperative bleeding with damage to adjacent neurovascular structures and requires more complex surgical approaches involving the base of the skull. Preoperative embolization via a transarterial approach has proved beneficial but is often limited by vascular anatomy and unfavorable locations. Abud et al[16] reported experience with preoperative devascularization using direct puncture and intralesional injection of cyanoacrylate (acrylic glue) under fluoroscopic guidance in nine patients with H&N PGs. Ozyer et al[17] performed devascularization with intralesional injection of *N*-butyl cyanoacrylate (seven carotid and three jugular PGs). The tumors were subsequently surgically removed.

The local tumor control rate with surgery alone (SA) is only about 60%, and there is a significant risk of morbidity, particularly cranial nerve injury and bleeding based on the location and extent of the tumor.

In a retrospective review of all skull base surgery cases treated at Baylor University, 175 jugulotympanic PGs and 9 (5.1%) malignant cases were identified.[2] The 5-year survival rate was 72%.

Radiation Therapy

RT is frequently used in the treatment of PGs, particularly for those in the tympanic and jugular bulb locations where gross total removal may result in significant morbidity, including cranial nerve dysfunction or risk of hemorrhage. Tumors with destruction of the petrous bone, jugular fossa, or occipital bone or patients with jugular foramen syndrome are more reliably managed with irradiation.[5,6,19,20] While in the past there were questions on the effectiveness of RT in the treatment of PG because of histologic sections, obtained even many years after irradiation, it is possible to find chromophilic cells remaining in the tumor.[18] Suit and Gallager,[21] however, demonstrated in a murine mammary carcinoma model that morphologically intact cells may have lost their reproductive ability after irradiation, which is the ultimate end point of cell killing. Furthermore, it is extremely unusual to observe clinical regrowth of a glomus tumor after irradiation, even if they do not regress completely as is common in most benign diseases treated with RT. Mendenhall et al,[4,22] updated the University of Florida experience in a total of 149 patients with 176 benign PGs treated with curative-intent RT. The 15-year overall local control (LC) was 95% with a median dose of 45 Gy in 25 treatments. No patient developed a moderate or severe complication, including radiation-induced second tumors or malignant transformation of the benign PG demonstrating the long-term efficacy and safety of RT.

Radiation Therapy Techniques

RT techniques are determined by the resectability, patient symptoms, location, and extent of the tumor.[20,23,24] Treatment is given at the rate of 1.8 to 2 Gy per day with five treatments per week for a total tumor dose of 45 to 50.4 Gy in 5 weeks or 12.5 to 15 Gy in a single fraction with stereotactic-ablative radiotherapy (SABR). Image-guided (IG), intensity-modulated radiation therapy (IMRT) is a highly desirable technique to treat these tumors, with a representative isodose dose distribution for single fraction SABR (Figure 54.6). Table 54.3 summarizes the doses of irradiation recommended by several investigators and the probability of tumor control for each.[20,24,25] Of note, there is no convincing evidence that dose escalation above 50 Gy improves tumor control for benign PG.[4,22]

TABLE 54.3 LOCAL CONTROL WITH RADIATION THERAPY FOR TEMPORAL BONE PARAGANGLIOMA OF THE TEMPORAL BONE (TYMPANIC AND JUGULAR)[24,26]

Institution (Reference)	Local Control	Nominal Dosage Schedule
Princess Margaret Hospital[20]	42/45[a]	35 Gy/3 wk

Institution (Reference)	Local Control	Nominal Dosage Schedule
Queen Elizabeth Hospital, Birmingham[27]	19/20[b]	45-50 Gy/4-5 wk
University of Washington[28]	10/13	8-65 Gy/4-7 wk
Rotterdamsch Radio-Therapeutisch Instituut, Netherlands[29]	19/19	40-60 Gy/4-6 wk
University of Minnesota[30]	13/14	30-60 Gy/3.5-7.5 wk
University of Virginia[31]	14/17	40-50 Gy/4-5 wk
Total	117/128 (91%)	

[a]Two patients listed as failures were salvaged with further treatments.

[b]One patient listed as a failure was salvaged with further radiation therapy.

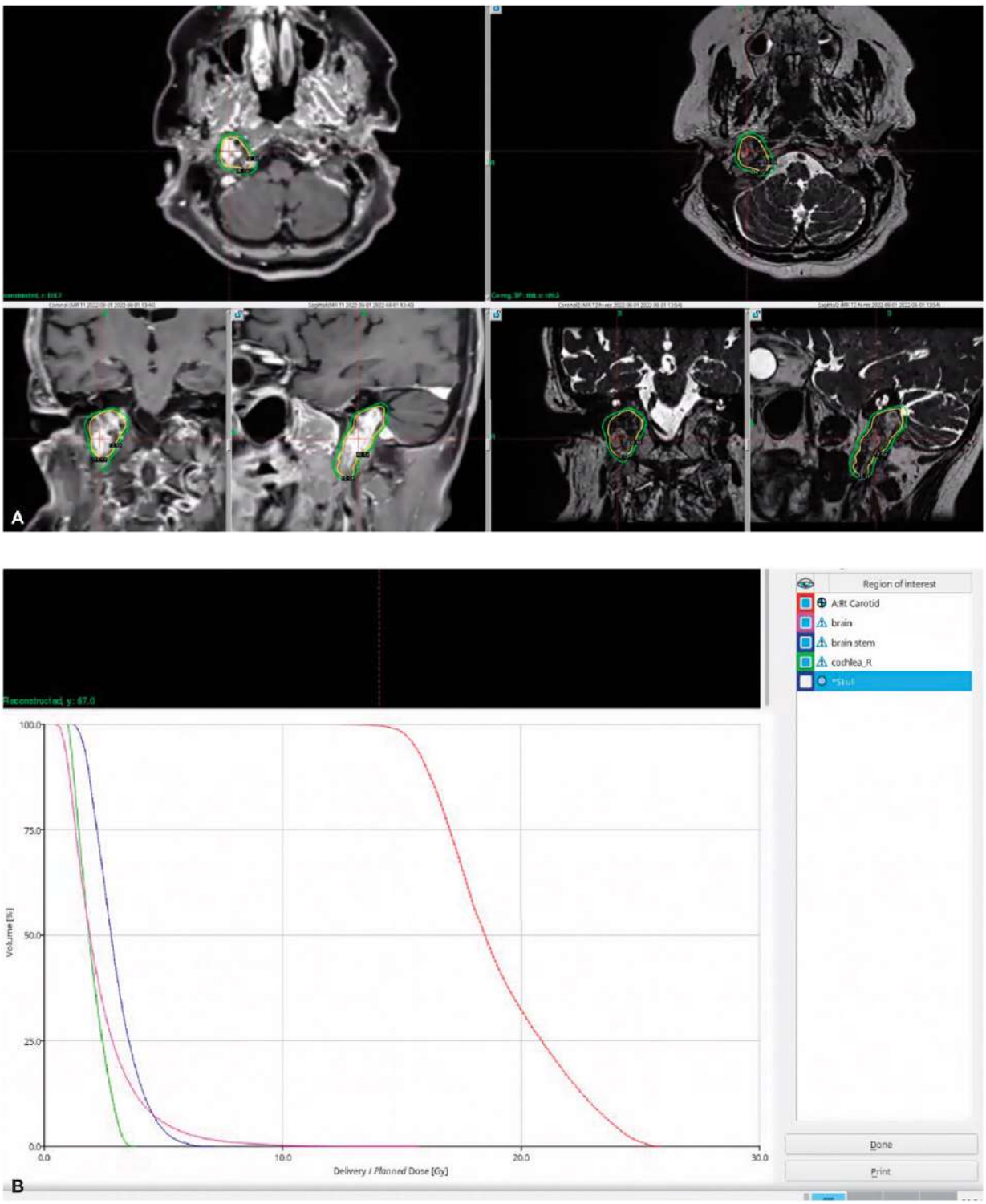


FIGURE 54.6 A. T1- and T2-weighted magnetic resonance images showing the dose distribution with stereotactic radiation therapy (radiosurgery) for right jugulotympanic paraganglioma. This patient received 15 Gy in 1 treatment with Gamma Knife, with the yellow line representing the 100% isodose line. B. In the dose-volume histogram, the red line represents the coverage of the gross tumor volume, the green line shows the cochlea, and the purple line shows the dose to the brainstem. (Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

van Hulsteijn et al[25] performed a meta-analysis of 283 jugulotympanic PGs in 276 patients. Pooled regression proportions for initial, combined, and salvage treatment were, respectively, 21%, 33%, and 52% in radiosurgery studies and 4%, 0%, and 64% in external beam RT studies. Pooled LC proportions for RT as initial, combined, and salvage treatment ranged from 79% to 100%.

RT for jugulotympanic PGs results in excellent local tumor control. The effects of RT on regression of tumor volume remained ambiguous, although the data suggest that complete regression can be achieved in some patients.

Leber et al[32] reported on 13 patients with PGs treated with radiosurgery in 6, because of recurrences after surgical removal. Histology was not available in seven patients; diagnosis was made from neuroradiologic features only. With a mean follow-up of 42 months (range 14-72 months), there was no tumor progression and no clinical deterioration in any patient; 64% of the patients had improvement of symptoms, and in 36%, the volume of the lesion decreased in size. There was no radiation-related morbidity. There have been an increasing number of reports of PG <3 cm treated with SABR, with tumor control over 80% and relatively minimal morbidity. The mean single dose is about 16 Gy (range 13-20 Gy).[33-38]

A report on fractionated stereotactic irradiation (6-MV x-rays) of 17 patients has been published, with a dose of 57 Gy.[39] Pollock[40] reported on 42 glomus tumors (19 primary treatment and 23 recurrences after initial surgery) treated with Gamma Knife (Elekta Corp, Stockholm) stereotactic radiation (12-24 Gy single dose at 50% isodose, depending on tumor size). Twelve lesions (31%) decreased in size, and 26 were unchanged. The most common complication was hearing loss (19%). Wegner et al[41] treated 18 patients with carotid or jugular lesions with fractionated stereotactic CyberKnife (Accuray). Fifteen (83%) patients had single jugular tumors, and three patients had bilateral jugular tumors. Ten tumors were previously untreated, and eight were persistent after previous surgical resection. The median prescribed dose was 20 Gy in three fractions (range: 16-25 Gy in 1-5 fractions). The median prescription coverage of the tumor was 93.6% (range: 83%-98.72%). Median follow-up was 22 months. All the patients were alive at the time of the last follow-up with imaging available for review. The tumor was stable in 17 patients and decreased in size in one patient—yielding an LC rate of 100%. No patients experienced any new or worsening treatment-related neurologic deficits.

Results of Therapy

The postirradiation change in tumor size is slow, with an increase in proliferative and perivascular fibrosis and minimal alterations in the chief epithelial cells. Histologic evaluation of tumor cell viability is not reliable.[21] Despite the persistence of tumor both clinically and angiographically, amelioration of symptoms, absence of disease progression, and occasional return of cranial nerve function have been reported. Sixteen patients were treated for tympanic PGs tumors at Washington University.[3] In five patients, initial treatment consisted of irradiation alone, and all were tumor free at the last follow-up (4.5 years in one patient) or at death. Seven of eight patients irradiated for surgical recurrence

were free of disease 4.5 to 19 years after irradiation. The remaining four patients were treated preoperatively or postoperatively; only one had recurrence and was salvaged surgically and tumor free 10 years later. Of six patients with glomus jugulare lesions treated with irradiation, two with extensive lesions died of their disease, whereas the glomus tumor was controlled in four, including two patients with intracranial extension. Irradiation doses ranged from 46 to 52 Gy, with 86% to 100% tumor control with doses over 46 Gy and 50% (two of four) with doses below 46 Gy.

Wang et al[26] reported on 32 patients with tympanic PGs; 13 are treated with SA, 15 with irradiation alone, and 4 with a combination of both modalities. The initial tumor control rate was 46% with SA; ultimately 84% of patients were tumor free after salvage with additional surgery. Although 78% survived 10 years, 31% developed complications. Of the patients treated with irradiation, 84% had initial local tumor control; 77% survived 10 years, and only 11% developed complications. The doses of irradiation used were slightly higher than those reported by others (mean 58.3 Gy). However, no improvement in tumor control was noted with higher doses. Complications occurred in two patients receiving 66 Gy.

Zabel et al[42] described results in 22 patients with large PGs of the skull base (8 after primary surgery and 4 after embolization), treated with fractionated stereotactic irradiation (median total dose 57 Gy with median fraction dose 1.8 Gy). With a median follow-up of 5.7 years, 5- and 10-year actuarial tumor control was 90%, with 7 (32%) patients having a partial response and 13 patients with (59%) stable tumors. No patient developed new neurologic deficit.

Powell et al[19] reported on 84 patients with PGs of the H&N, 46 of which were either jugular or tympanic locations, treated with irradiation alone (45-50 Gy in 25 fractions). LC of the lesion was 73% at 5 years. Thirty patients were treated with surgery after irradiation with no recurrences (median follow-up of 9 years). Four patients, treated with SA, developed recurrences by 7 years. Four carotid body and vagal tumors treated with irradiation were locally controlled at 1, 2, 8, and 11 years, respectively. In 13 patients treated with SA, the 15-year LC rate was 54%.

Hinerman et al[43,44] updated a previous report with 104 patients who had 121 PGs of the temporal bone, carotid bone, or vagal treated with RT alone in 104 patients or subtotal resection with or without RT (17 tumors). There were six tumor recurrences, with a local tumor control of 95%. No severe treatment complications were noted. As aforementioned, Gilbo[4] and Mendenhall et al[22] updated the series in 2014 and 2019, showing continued high control even at 15 years after therapy.

Ivan et al[45] published a meta-analysis based on 869 patients in 46 studies reported with PGs, with follow-up ranging from 6 to 256 months. The tumor control rates were, for subtotal resection 69%, gross tumor resection (GTR) 86%, subtotal resection and radiosurgery 71%, and stereotactic radiosurgery (SRS) alone 95%. Post-treatment cranial nerve deficit was observed in 26% to 40% of patients treated with GTR and in about 10% of the SRS group. Guss et al[46] reported on a meta-analysis of 19 studies (335 patients) with glomus tumors treated with stereotactic radiotherapy (SRT) (radiosurgery), eight

publications with a median follow-up of 36 months; tumor control (unchanged or reduced tumor volume) was 95% to 96%, with various RT techniques.

In 29 patients with postsurgical recurrent PGs (16 jugular, 7 carotid, 5 tympanic, and 1 thyroid), Elshaikh et al[47] reported a 5-year tumor control of 100% in 12 treated with RT and 62% in 17 treated surgically.

Cheesman and Kelly[48] emphasized the importance of evaluating preoperatively the swallowing function of patients with jugular PGs undergoing surgery, as it is common for these patients to develop postsurgical dysphagia.

The results of primary treatment for temporal bone PGs are summarized in Table 54.4.

TABLE 54.4 TEMPORAL BONE PARAGANGLIOMA: LOCAL CONTROL AFTER RADIATION THERAPY ALONE OR RADIATION THERAPY AND SURGERY

Author (Reference)	Number of Patients	Local Control (%)	Follow-Up (Year)
Larner et al[49]	15	93 (RT alone)	Median, 16.2
Powell et al[19]	46	90 (RT alone)	Median, 9
Wang et al[26]	19	84 (RT ± surgery)	5-35
Konefal et al[3]	23	83 (RT ± surgery)	Mean, 10.5
Pryzant et al[50]	19	95 (RT ± surgery)	Mean, 11
Cole and Beiler[51]	30	97 (RT alone)	3-27
Boyle et al[52]	9	100 (RT alone)	1-12
Schild et al[53]	8	100 (RT ± surgery)	Median, 7.5
de Jong et al[54]	38	89 (RT ± surgery)	Median, 11.5
Hinerman et al[44]	53	93 (RT ± surgery)	Mean, 15

RT, radiation therapy.

From Hinerman RW, Mendenhall WM, Amdur RJ, Stringer SP, Antonelli PJ, Cassisi NJ. Definitive radiotherapy in the management of chemodectomas arising in the temporal bone, carotid body, and glomus vagale. *Head Neck*. 2001;23(5):363-371. Copyright © 2001 John Wiley & Sons. Reprinted by permission of John Wiley & Sons.

The initial results of treatment for carotid body or vagal PGs are summarized in Table 54.5. Complications were rare in patients treated with PG of the H&N.

TABLE 54.5 CAROTID BODY/VAGAL PARAGANGLIOMA: RADIATION THERAPY ALONE OR RADIATION THERAPY AFTER SURGERY

Author (Reference)	Number of Patients	Local Control (%)	Follow-Up (Year)
Valdagni and Amichetti[55]	7	100 (RT ± subtotal resection)	1-19
Verniers et al[56]	22	100 (RT ± subtotal resection	Mean, 10
Powell et al[19]	4	100 (RT alone)	Median, 9
Schild et al[53]	2	100 (subtotal resection + RT)	Median, 7.5

Author (Reference)	Number of Patients	Local Control (%)	Follow-Up (Year)
Cole and Beiler[51]	30[a]	97 (RT alone)	3-27
Hinerman et al[44]	18	96 (RT ± resection)	Mean, 9

RT, radiation therapy.

[a]Jugular and vagal paraganglioma.

From Hinerman RW, Mendenhall WM, Amdur RJ, Stringer SP, Antonelli PJ, Cassisi NJ. Definitive radiotherapy in the management of chemodectomas arising in the temporal bone, carotid body, and glomus vagale. *Head Neck*. 2001;23(5):363-371. Copyright © 2001 John Wiley & Sons. Reprinted by permission of John Wiley & Sons.

SOLITARY FIBROUS TUMORS

Solitary fibrous tumors (SFTs), also termed *hemangiopericytomas* (HPCs) when they refer to lesions within the central nervous system (CNS), are mesenchymal, nonmeningothelial soft tissue neoplasms that account for 3% to 5% of all soft tissue sarcomas and 1% of all vascular tumors. Lesions of the H&N were also previously described as giant cell angiofibromas and orbital fibrous histiocytoma (OFH), which are all now recognized within the spectrum of SFT.[57] Approximately 15% to 30% of all SFTs occur in the H&N, and of these, approximately 5% occur in the sinonasal area. While vagal PGs originate within the first 2 cm of the extracranial stretch of the vagus nerve and are associated with the inferior ganglion,[58] SFTs are believed to originate from the pericytes of Zimmerman extravascular cells, morphologically resembling smooth muscle, found around the capillaries or from primitive mesenchymal cells. The function of the pericyte is uncertain but is believed to provide mechanical support for the capillaries having contractile function.[59]

SFTs of the H&N are uncommon. Lesions previously diagnosed in the H&N as HPCs, giant cell angiofibromas, and OFHs are now recognized as within the expanded spectrum of SFTs.

Epidemiology

SFTs represent approximately 1% of all vascular neoplasms; it occurs in both genders with equal frequency and is found primarily in adults. In the H&N, the most common sites are the nasal cavity and the paranasal sinuses and, less frequently, the orbital region, the parotid gland, and the neck.[60-62] HPCs represent 3% to 4% of all meningeal and <1% of CNS tumors.

Pathology

SFTs are composed of a proliferation of tightly packed pericytes around thin-walled endothelial-lined vascular channels, ranging from capillary-sized vessels to large, gaping sinusoidal spaces.[63] The tumor has a tendency to grow slowly and invade locally into adjacent structures.[60,64] Although they are always well circumscribed and partially or completely surrounded by a pseudocapsule, benign tumors may be difficult to differentiate

from malignant tumors. However, prominent mitoses (>4 per high-power field), foci of necrosis, and increased cellularity are suggestive of malignancy; the definitive sign is local recurrence or development of metastases. In general, tumors of the CNS, lower extremity, and mediastinum tend to be more malignant, with local recurrence occurring in up to 50% of cases.[63]

Kowalski and Paulino[65] reviewed 12 cases of SFTs. The mitotic index per 10 high-power fields varied from 0 or 1 to 15. Proliferation indices using MIB-1 (Ki-67) ranged from 2.6% to 52.5%. Clinical follow-up showed three cases with recurrence all possessing proliferation indices of approximately 10%, indicating a more aggressive subset of SFTs. Vuorinen et al[66] found proliferation index to be a poor predictor of prognosis for intracranial HPC.

Clinical Presentation

Soft tissue SFT is a firm, painless, slowly expanding mass that is often nodular and well localized. The skin overlying the mass does not have any discoloration or redness to indicate its vascular origin because the capillaries are emptied of the blood by compression of massive numbers of pericytes surrounding them.[63] In the H&N, the tumor may constitute a polypoid, soft gray or red mass that grows slowly and may cause nasal obstruction. Epistaxis and nasal obstruction are common symptoms. Orbital SFTs account for 3% of orbital malignancies and most frequently occur with painless proptosis.[67] SFT rarely originates in the lacrimal sac. When present, however, it occurs in a younger age group than that of other locations.[68]

HPC may occur intracranially. When it arises in the brain, it is a solid mass attached to the meninges that grossly resembles a meningioma. These intracranial HPCs carry a high risk of local failure (80%), as well as a higher potential for dissemination. Meningeal HPCs almost always recur, despite seemingly complete removal, because of infiltrative properties of HPC cells and not just higher proliferation potential. The mean time for local recurrence is 75 months.[69] For more specifics regarding intracranial HPC, refer to Chapters 40.

The incidence of metastasis, which depends on the site of origin, can be 50% to 80%. Late metastases occurring 10 years after diagnosis are not uncommon.

On CT imaging, the SFT appears as a well-circumscribed, homogeneously and intensely enhancing mass. On MRI, the mass is isointense to slightly hyperintense to muscle on T1- and T2-weighted imaging. Multiple, branching flow voids are typically seen within the tumor on both T1- and T2-weighted images. On T2-weighted imaging, the punctate black flow voids in cross section within the relatively bright tumor, creating a characteristic "salt-and-pepper" appearance in tumors >2 cm in diameter. In addition, flow voids of large feeding arteries are seen at the periphery of the mass. Angiography demonstrates the characteristic appearance of a vascular tumor, with large feeding arteries, intense tumor stain, and early draining veins.[58] On arteriography, according to Yaghmai,[70] SFT is the only vascular tumor that has radially arranged or spiderlike branching vessels around and inside the tumor and a long-standing, well-demarcated tumor stain. Intracranial tumors typically

have arterial blood supply from both meningeal and cerebral connections, with one to three main feeders supplying many small corkscrew-like vessels.[69] The most distinctive and constant feature of this tumor is its hypervascularity, which may be demonstrated with contrast-enhanced CT.[61] Intracranially, the diffusely enhancing tumor may closely resemble a meningioma on CT. However, some CT signs may suggest HPC rather than meningioma, such as a lack of calcification, scarce surrounding edema, and ringlike enhancement. Both CT and MRI scans are of special value in the delineation of the full extent of the tumor.

General Management

Complete surgical resection, if possible, combined with preoperative embolization of the tumor, is the treatment of choice. More extensive surgery is required in tumors that show features of malignancy. Many patients undergo surgical treatment after embolization of the feeding artery(ies).

For incompletely resected tumors, postoperative RT is used.[71,72] The role of chemotherapy in this tumor is not well determined; a few reports have described partial tumor regression in some lesions treated with cytotoxic agents. Doxorubicin, either alone or in combination drug regimens, is the most effective agent for metastatic SFT, producing complete and partial remissions in 50% of cases. Other drugs prescribed when metastasis occurs are cyclophosphamide, dacarbazine, vincristine, and actinomycin D.[73] Park et al[74] reported on 14 patients with soft tissue HPC treated with temozolomide 150 mg/m^2 orally on days 1 to 7 and days 15 to 21 and bevacizumab 5 mg/kg intravenously on days 8 and 22, repeated at 28-day intervals. The median follow-up period was 34 months. Eleven (79%) patients achieved a partial response, with a median time to response of 2.5 months. Estimated median progression-free survival (PFS) was 9.7 months, with a 6-month progression-free rate of 78.6%. The most frequently observed toxic effect was myelosuppression.

Radiation Therapy Techniques

The role of RT alone in the management of SFT is controversial. The main role of irradiation is as an adjuvant after complete excision of the lesion or postoperatively for minimal residual disease.[62,75,76] The tumor has been considered relatively radioresistant. Preoperative doses of 45 to 50 Gy and postoperative doses of 50 to 65 Gy at 1.8 to 2 Gy per treatment are indicated for local tumor control based on the extent of resection and if residual disease is present.[71,72]

The fields of irradiation should be wide to encompass the tumor bed with a margin of at least 3 to 5 cm edited to boundaries of anatomic tumor spread similar to those used in the treatment of other soft tissue sarcomas discussed in the ensuing section near the end of this chapter.

Results of Therapy

Billings et al[77] reported on 10 patients with SFT of the H&N: 7 tumors arose from soft tissue sites and 3 from the mucosa. All patients underwent wide excision of the primary lesion with a local recurrence rate of 40%. Three patients developed metastatic lung disease 0 to 8 years after initial diagnosis. Each patient who developed metastatic disease had abundant mitoses on pathologic review compared with rare or absent mitoses in the lesions that took a more benign course.

Spitz et al[62] published a report on 36 patients with SFT. The median follow-up was 57 months. Twenty-eight (78%) patients underwent complete and potentially curative resection. Of the nine (32%) patients who had local recurrences, four (44%) had epidural tumors and three (33%) had retroperitoneal tumors, but none had extremity tumors. Ten patients had recurrences at distant sites. Of the 13 patients who experienced any form of disease recurrence, four had recurrences after a disease-free interval of more than 5 years. The 5-year actuarial survival rate for the entire group of 36 patients was 71%.

Carew et al[78] reviewed the records of 12 patients with SFT: 5 had high- or intermediate-grade lesions and 7 had low-grade lesions. Nine patients were treated with curative intent; they underwent a variety of surgical resections dictated by the tumor location and size. Four patients received postoperative RT, to a median dose of 60 Gy, for positive surgical margins (two patients), high-grade histology (one patient), or a recurrent lesion (one patient). The 5-year overall survival (OS) rate for patients treated surgically was 87.5%. A single mortality occurred in a patient with a recurrent high-grade lesion who failed at local, regional, and distant sites.

Staples et al[79] reported on 12 patients with localized SFT, 7 treated with SA (only 1 had long-term tumor control and 2 were salvaged with RT), 4 with resection and postoperative irradiation (all with long-term tumor control), and 1 with surgery and chemotherapy. Local tumor control was achieved at all sites treated with doses >55 Gy. Mitotic activity was not a reliable predictor of biologic behavior.

Shaigany et al[80] reported on a study of the Surveillance, Epidemiology, and End Results (SEER) database (1973-2012) encompassing 121 cases of SFT of the H&N and compared results with 510 of other body sites. H&N SFTs were most commonly located in the connective and soft tissue (18.4%), followed by the nasal cavity and paranasal sinuses (8.5%). H&N sites were smaller than other extracranial locations and more likely to be of lower histologic grade, and the primary treatment modality was SA for 95.8% of cases. The 5-, 10-, and 20-year disease-specific survival (DSS) for were 84.0%, 79.4%, and 69.4%, respectively. Higher histologic grade and the presence of distant metastases were poor prognostic factors. Adjuvant radiotherapy (ART) did not appear to confer a survival benefit.

Bishop et al[71] reviewed the outcomes of 31 patients treated for SFT with surgery and RT. The most common sites of involvement included the H&N (n = 9, 29%), trunk (n = 10, 32%), and lower extremities (n = 9, 29%). Nearly half the cases were treated with postoperative RT (45%) to a median dose of 58 Gy, and the other half received preoperative therapy. The 5-year rates of LC and distant metastatic-free survival were 100% and 92%, accordingly. There were no regional failures.

BASE OF SKULL CHORDOMA

Anatomy

Chordomas are rare neoplasms of the axial skeleton that arise from the remnant of the primitive notochord (chorda dorsalis). About 50% arise in the sacrococcygeal area; 35% arise from the skull base, where they typically involve the clivus, and the remaining 15% occur in the midline along the path of the notochord, primarily involving the vertebrae of the mobile spine.[81]

Epidemiology

Chordomas are more common in patients in their 50s and 60s but can occur in all age groups. In children and young adults, the prognosis and long-term survival appear to be better than in older patients. No risk factors have been identified. Male predominance is reported at a 2:1 to 3:1 ratio.

Natural History

Although slowly growing, chordomas are locally invasive, destroying bone and infiltrating soft tissues. The lethality of these tumors rests on their critical location, aggressive local behavior, and extremely high local recurrence rate. The incidence of metastasis, which has been reported to be as high as 25%, may be related to the long clinical history and identification of high-grade variants. The lungs are the most common site for distant disease (>50%), followed by the liver and bone. Factors associated with the development of metastatic disease include age <25 years and local recurrence at the primary site. Lymphatic spread is uncommon.[82]

Pathology

Chordoma is a soft, lobulated tumor that may have areas of hemorrhage, cystic changes, or calcification. It is frequently encapsulated but may be nonencapsulated or pseudoencapsulated. Histologically, it is composed of cords or masses of large cells (physaliferous cells) with typical vacuoles and granules of glycogen in the cytoplasm and abundant intercellular mucoid material. Usually, there are few mitotic cells.[83] Pathologic variants include conventional, dedifferentiated, and poorly differentiated histology. Chondroid is a subtype of conventional, and dedifferentiated may have a high-grade sarcomatous component and occur more commonly at sites of previously treated chordoma.[84] Poorly differentiated tumors tend to occur more commonly in younger patients and are characterized by the loss of INI1 (SMARCB1). It is associated with higher local and distant progression and may be more responsive to chemotherapy.[85] Brachyury expression has been shown to be a histologic marker for chordoma. Gene duplication has been shown to confer increased susceptibility to familial chordoma.[86] Aside from the previously mentioned histologic variants, the prognostic factors that most influence the choice of treatment are the tumor location and local extent of disease.

Clinical Presentation

Regarding the skull base, chordomas tend to originate midline from along the spheno-occipital synchondrosis where the basisphenoid and basiocciput bones joined to form the clivus. This contrasts with chondrosarcomas that occur paramedian along the petroclival cartilage-producing cells in areas of enchondral ossification of the temporal bone.[81] Figure 54.7 shows an example schematic of a sagittal rendering of the clivus. Clinical symptoms vary with the location and extent of the tumor. In the head, extension may be intracranial or extracranial, into the sphenoid sinus, nasopharynx, clivus, and sellar and parasellar areas, with a resultant mass effect. In chordomas of the spheno-occipital region, the most common presenting symptom is headache. Other presentations include symptoms of pituitary insufficiency, nasal stuffiness, bitemporal hemianopia, diplopia, and other cranial nerve deficits. Volpe et al[87] reviewed the clinical features of 48 patients with chordoma and 49 patients with low-grade chondrosarcoma of the skull base. Twenty-five (52%) patients with chordoma and 24 (49%) patients with chondrosarcoma had ocular symptoms (diplopia or visual impairment) as the initial manifestation of the disease. Of the 59 patients (both groups) with diplopia, it was initially intermittent in 25 (42%). Headache and diplopia from abducens nerve palsy occurred in 22 (46%) patients with chordoma and 23 (47%) with chondrosarcoma. While often grouped together for largely historic purposes, these are two distinct clinical entities and should be demarcated as such for clinical and research purposes.

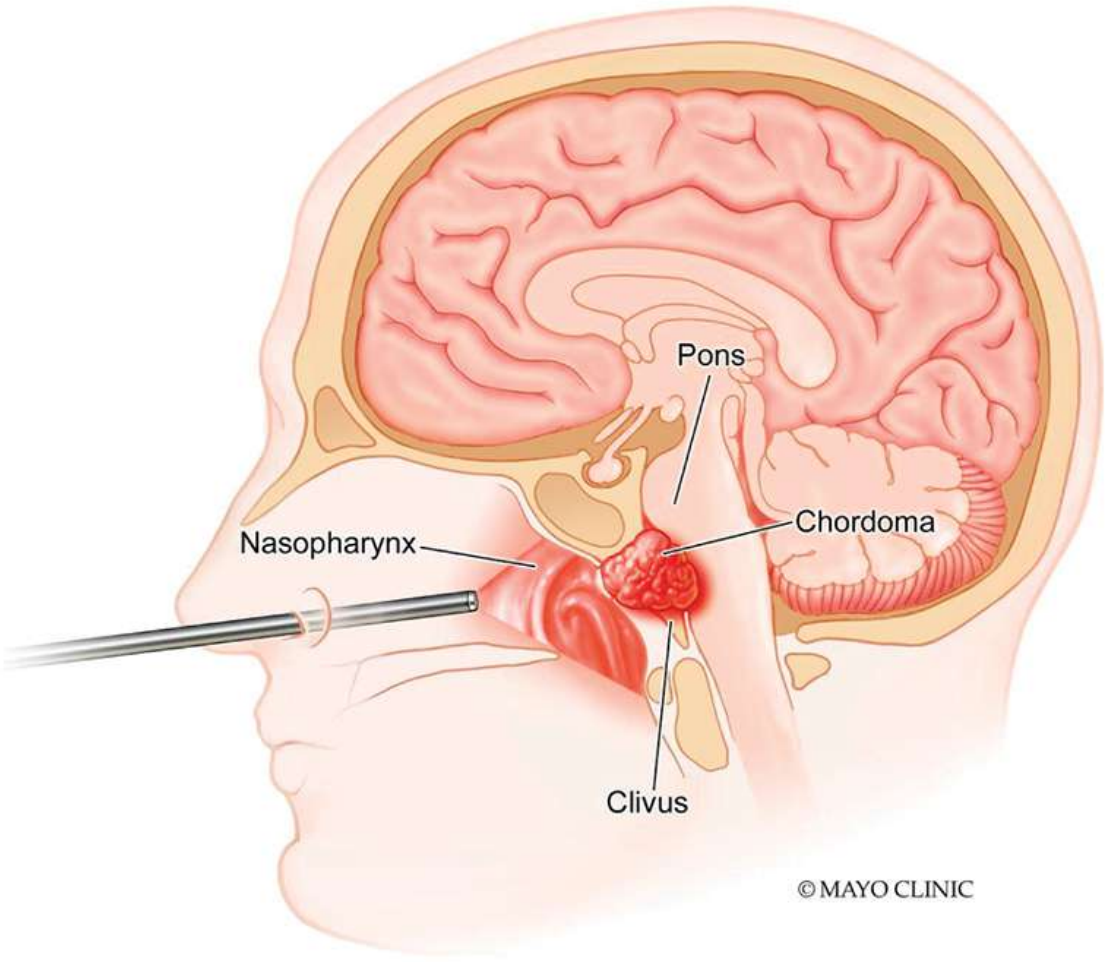


FIGURE 54.7 Sagittal anatomic rendering of the clivus. From a surgical standpoint, the clivus is divided into three anatomic divisions. There are slight differences in the description of the boundaries based on surgical techniques and authors. Simply, they are divided into the upper, middle, and lower clivus, which is demarcated by the floor of the sella and the sphenoid. This separates into a sellar, sphenoidal, and nasopharyngeal division. Tumors such as the one represented in the image are referred to as craniocervical junction chordomas because it involves the lower one-third of the clivus. (Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

Diagnostic Workup

The diagnostic workup varies with the primary location of disease. Most patients have significant bony destruction, intracranial, and soft tissue extension; hence, CT and MRI are necessary for proper diagnosis and management decisions (Table 54.6).[81,88,89] In most cases, the soft tissue component is much more extensive than initially appreciated, and a CT scan and MRI with contrast enhancement can identify these findings. High-resolution bone CT can help demonstrate bony destruction and intratumoral calcification.[89] MRI with high-resolution T2-weighted sequences with steady-state sequences is essential for treatment planning. Figure 54.8 shows an axial T2 MRI preoperatively and

postoperatively and highlights the importance of 3D T2-weighted imaging for treatment planning of chordoma.

TABLE 54.6 DIAGNOSTIC WORKUP FOR SKULL BASE AND SINONASAL TUMORS

General
History
Physical examination
Radiologic studies
Preoperative and postoperative high-resolution computed tomography scan/magnetic resonance imaging
Chest imaging (computed tomography of the chest and/or PET-CT)
Laboratory studies
Complete blood cell count
Chemistry
Special studies
Endocrinologic profile (clivus)
Visual evaluations (clivus)
Audiologic assessment (temporal bone)

Based on Kuan EC, Wang EW, Adappa ND, et al. International consensus statement on allergy and rhinology: sinonasal tumors. *Int Forum Allergy Rhinol*. 2024;14(2):149-608.

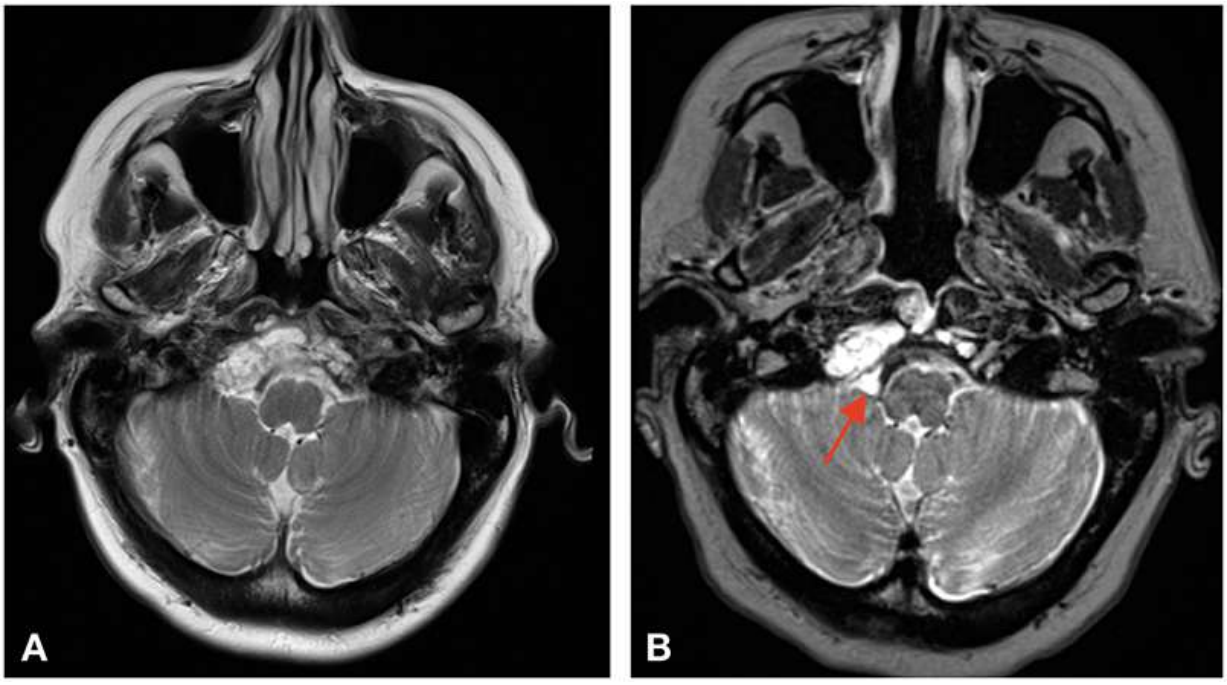


FIGURE 54.8 Chordoma of the clivus showing preoperative and postoperative T2-weighted magnetic resonance images (MRIs). A. A low-resolution preoperative MRI. B. A high-resolution, fusion planning MRI used for radiation treatment planning. Not only is the residual tumor in the bilateral occipital condyles more easily determined, but there is also a small focus of residual tumor near the brainstem that abuts the V1 segment of the vertebral artery (red arrow), which was not definitively distinguishable without the improved resolution. (Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

Reliable signs of chordoma of the skull base are posterior extension to the pontine cistern; a lobulated, “honeycomb” appearance after gadolinium; the swollen appearance of the bone in the early stages; bone erosion on CT; and frequent extension to critical structures such as the circle of Willis, cavernous sinuses, and brainstem.[90]

General Management

Because of their surgical inaccessibility and relative resistance to RT, clival chordomas represent a formidable therapeutic challenge. The general management of the patient is dictated by the anatomic location of the tumor and the direction and extent of spread. Upfront maximal safe resection is the primary treatment option.[81] The exception is in poorly differentiated subtypes, in which some groups propose upfront chemotherapy, followed by RT and/or surgery based on response.[85] Most modern surgical techniques include anterior endoscopic endonasal approaches (EEAs). Open craniotomy is typically reserved for staged resections in combination with EEA such as when or if the primary is not entirely accessible to an endonasal approach because of the location or extent of disease. Because of the high incidence of local recurrence, combined surgical excision and irradiation is frequently used. Figure 54.9 shows an example of a craniocervical junction chordoma, which is often a difficult location to achieve gross total resection. While erlotinib is used in the palliative setting, no effective chemotherapeutic agent or combination of drugs has been identified. The development of systemic therapies including immunotherapy, tyrosine kinase inhibitors, brachyury vaccines, and enhancer of zeste homolog 2 inhibitors such as tazemetostat are currently in the investigational stage.[91]

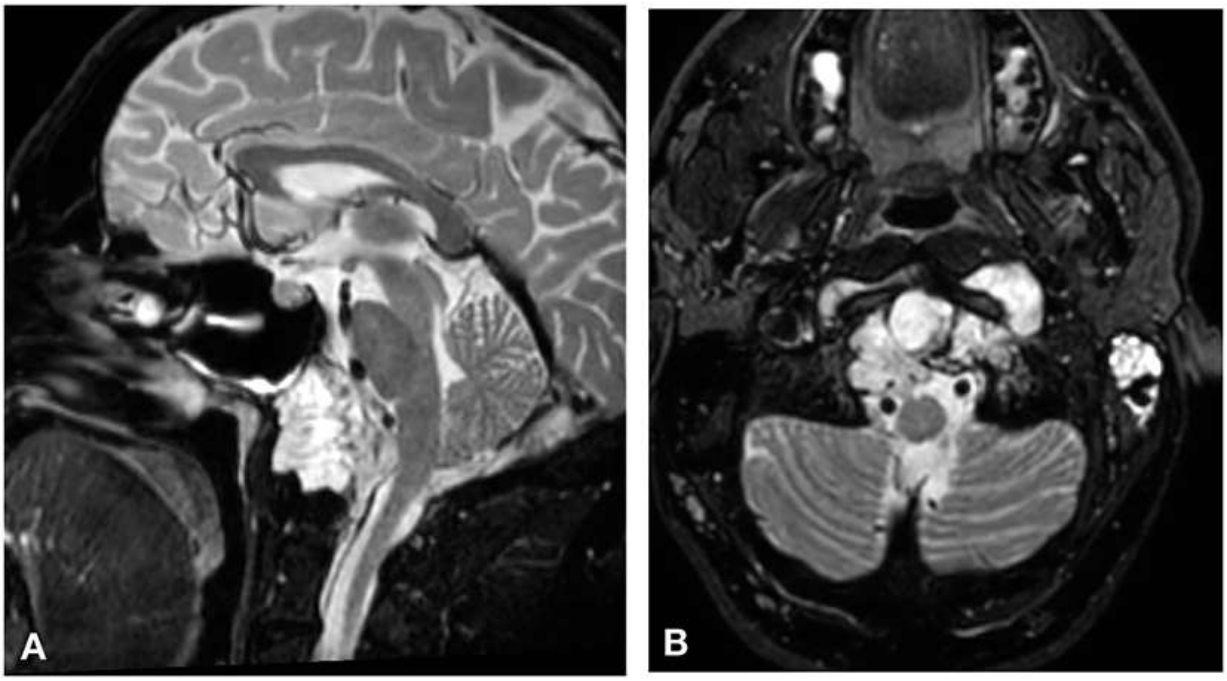


FIGURE 54.9 Sagittal (A) and axial (B) T2-weighted magnetic resonance imaging showing a T2 bright craniocervical junction chordoma. This tumor involves lower one-third of the clivus. Tumors of this area often present in a tent-like manner with both a prevertebral and posterior dural component draping over the dens. Chordomas of this location have the lowest rates of gross total resection compared to sphenoidal and sellar clival lesions and higher local recurrence rates. (Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

Radiation Therapy Techniques

Irradiation techniques vary considerably, depending on the location of the tumor along the craniospinal axis; however, highly conformal techniques with both photons or protons have become a mainstay in therapy. Precision RT planning, using CT and MRI, is required because high doses of external beam RT are needed.

The tumor usually surrounds the brainstem, optic apparatus, and spinal cord and infiltrates vertebral bones. For skull base tumors, IMRT, radiosurgery, and proton therapy (PT) are used. In the treatment of chordomas surrounding the spinal cord, PT can provide high-dose homogeneity and planning target volume (PTV) coverage. In addition to maximal safe resection, tumor decompression and removal can provide optimal target dosimetry to allow for safe dose escalation around sensitive organs at risk (OARs) (Figure 54.10). Dose levels are typically prescribed using a sequential boost with an initial volume to 50 to 60 GyRBE (Gy radiobiologic equivalent) and a boost to 70 to 74 GyRBE or higher based on the extent of resection.[81,92-97] Example target definitions and OAR dose constraints are also provided in Table 54.7. PTV expansions are based on specific institutional guidelines but are typically 2 to 3 mm with thermoplastic immobilization and daily image guidance. Of note, these OAR constraints provided were used for series with adult patients. Pediatric patients have more stringent guidelines for dose constraints and recommendations to follow institutional or cooperative group protocols for those cases.[72,96]

Treatment to high doses should be conducted at high-volume centers with experience with dose escalation, given the associated risks of CNS necrosis.[98,99] For skull base chondrosarcoma, target coverage is typically compromised to meet more conservative dose constraints of the brainstem and optics as studies show no difference in ultimate tumor control.

TABLE 54.7 SUMMARY TREATMENT VOLUME DEFINITIONS AND ORGAN AT RISK DOSE CONSTRAINTS FOR ADULTS WITH SKULL BASE CHORDOMA

ICRU-62 Volume	Dose	Definition
GTV		Gross residual and/or tumor bed
CTV low	50-60 GyRBE at 1.8/2 GyRBE	GTV expanded for preoperative and high-risk subclinical extent of disease
CTV high	>70 GyRBE at 1.8/2 GyRBE	GTV
PTV	CTV plus 3 mm based on institutional practice and daily CBCT image guidance	

Organ	Dose constraint (GyRBE)
Brainstem D (0.1 mL)	<55, 64
Brainstem core[a] D (0.1 mL)	<50, 60
Spinal cord D (0.1 mL)	<50, 55
Optic chiasm D (0.1 mL)	<55, 60
Optic nerves D (0.1 mL)	<55, 60
Retina D (0.1 mL)	<50 Gy
Cochlea (D_{max})	<36, 45
Temporal lobe (V20)	<10%
Temporal lobe (V60)	<6 mL
Temporal lobe (V70)	<1.5 mL
Hippocampus (mean)	<5, 20
Pituitary gland (mean)	<30

Mayo Clinic Florida target volume definition and dose constraints for skull base tumors in adult patients (age >22 years). The listed constraints represent two dose levels; this represents primary and secondary priorities. The constraints for the optic chiasm and optic nerve, retina and brainstem, the secondary constraints represent absolute, hard constraints with few exceptions. Note that these constraints may differ significantly from pediatric constraints and are best conducted at high-volume skull base centers.

CBCT, cone-beam CT; CTV, clinical tumor volume; D(0.1 mL), maximum dose to 0.1 mL; D_{max}, maximum dose; GTV, gross tumor volume; PTV, planning tumor volume.

[a]Brainstem core is a 3-mm anisotropic subtraction structure 3 mm in all directions, except superior and inferior.

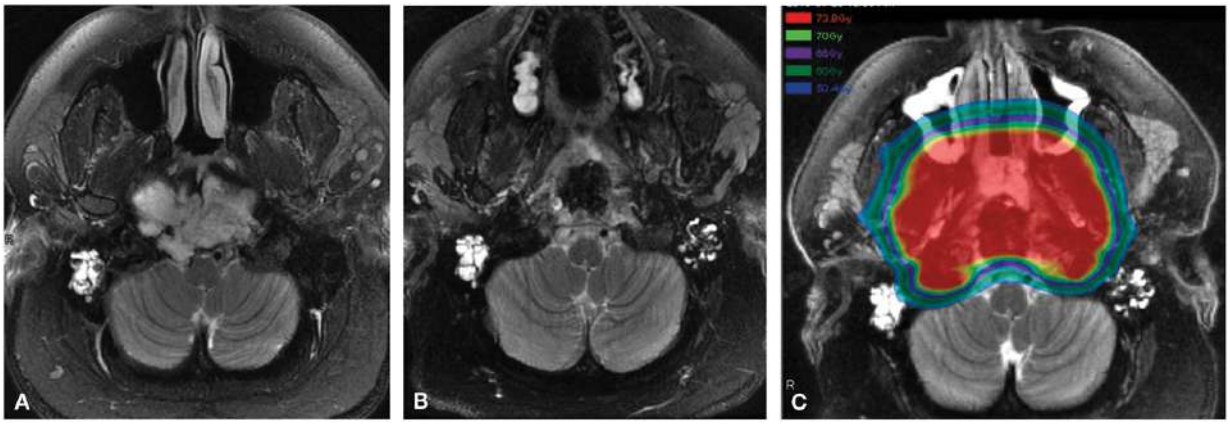


FIGURE 54.10 Axial T2-weighted magnetic resonance imaging showing preoperative (A), postoperative (B), and fused color wash (C) dose distribution of a near-totally resected clival chordoma. Preoperatively, there was gross tumor abutting the brainstem, and by decompressing the tumor via an endoscopic endonasal technique, this created a 2- to 3-mm space between the brainstem and the postoperative resection bed. This allowed for full-dose escalation to 73.8 GyRBE to be delivered in the adjuvant setting with proton therapy without compromising target coverage at the interface between a critical organ at risk. (Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

Of note, one issue when planning for chordomas that involve the spine includes the introduction of titanium hardware often used for spinal stabilization. This may cause significant image artifacts on image registration, target delineation, and dose calculation. More recently, carbon fiber–reinforced polyetheretherketone low-density implantable material has been used to improve robustness for treatment planning with particle therapy (Figure 54.11).[100]

FIGURE 54.11 A. Cervical-thoracic spinal chordoma showing axial magnetic resonance imaging (MRI) on presentation with cord compression. B. The postoperative hardware is shown on sagittal computed tomography (CT). Because it is carbon fiber, low-density material, there is little image artifact. Not only does this improve treatment plan robustness for planning with particle therapy, but also as shown greatly reduces CT- and MRI-based artifact. This improves visualization of the tumor bed and avoidance structurs, such as the spinal cord, that are often being treated to their normal tissue tolerance. C. Postoperative radiotherapy following decompressive surgery showing the planning target volume (lime green) being treated using a mixed proton-photon in a 2:1 ratio technique to a total dose of 75.6 GyRBE. (Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

Because of the slow proliferative nature of chordomas, high linear energy transfer (LET) may prove useful in their management, as discussed later.

Results of Therapy

Photons

Although survival in some patients with chordoma may be long term, the salient feature of this unusual neoplasm is local recurrence with eventual death. The course may be indolent, with multiple treatments for recurrences, but the overall 5-year disease-free survival rate is <10% to 20%. Catton et al[101] analyzed the long-term results of treatment for patients with chordoma of the sacrum, base of the skull, and mobile spine treated predominantly with postoperative photon irradiation. In 20 base of skull chordomas, most of them were irradiated with conventionally fractionated radiation to a median dose of 50 Gy in 25 fractions for 5 weeks (range 25-50 Gy), and the median survival was 62 months (range 4-240 months) from diagnosis with no difference between clival and nonclival presentations. There was no survival advantage to patients receiving radiation doses >50 Gy (median 60 Gy) compared with lower doses <50 Gy (median 40 Gy). Hyperfractionation regimens did not influence the degree or duration of symptomatic response or PFS. Median survival after retreatment was 18 months. Of note, modern series now treat patients to doses of 70 Gy or higher in the primary and adjuvant setting for residual disease.

Forsyth et al[102] reported on 51 patients with intracranial chordomas (19 classified as chondroid) treated surgically (biopsy in 11 patients and subtotal removal or greater in 40); 39 patients received postoperative irradiation. At the time of the analysis, 17 patients were alive. The 5- and 10-year survival rates were 51% and 35%, respectively; 5-year survival was 36% for biopsy patients and 55% for those who had resection. Patients who underwent postoperative irradiation tended to have longer disease-free survival times.

Gay et al[103] analyzed the outcome of 46 patients with cranial base chordomas and 14 with chondrosarcomas after extensive surgical resection, with 50% of them treated previously and 20% received postoperative irradiation. Nine patients with chordomas and two with chondrosarcomas died during the postoperative follow-up period. The 5-year recurrence-free survival (RFS) for all patients was 76%. Chondrosarcomas had a better prognosis than chordomas (5-year RFS of 90% and 65%, respectively; $P = .09$). Patients who had undergone previous surgery had a greater risk of recurrence than did those who had not undergone previous surgery (5-year RFS rates of 64% and 93%, respectively; $P < .05$). Those with total or near-total resection had a better 5-year RFS rate (84%) than did patients with partial or subtotal resection (64%; $P < .05$). Postoperative leakage of cerebrospinal fluid was the most frequent complication (30% of patients) and was found to increase the risk of permanent disability. Patients who had undergone previous irradiation had a greater risk of death in the postoperative period (within 3 months of operation) and during follow-up.

Tai et al[104] reviewed the results of irradiation combined with surgery, irradiation alone, and SA in 159 patients reported in the literature. An analysis of the optimal biologically equivalent dose was performed using the linear-quadratic formula on 47 patients. With conventional photon irradiation, no dose-response relationship was shown. Survival improved in patients undergoing surgery followed by irradiation.

Keisch et al[105] reported on 21 patients with chordoma treated at the authors' medical center: 5 had clival tumors, 2 had nasopharyngeal tumors, and 1 had a lumbar spine tumor. Nine patients were treated with SA, eight had subtotal resection and postoperative irradiation, and four received irradiation alone after biopsy. The 5- and 10-year actuarial survivals were significantly better in patients treated with SA or surgery and irradiation than in those treated with RT alone (52%, 32%, and 0%, respectively; $P = .02$). Disease-free survival of patients with base of skull tumors was not significantly different among the treatment groups.

Kim et al[106] reported 14 clivus chordomas undergoing postoperative IMRT simultaneous integrated boost (SIB). Total and near-total resections were achieved in 11 (78.6%) patients and partial in 2 (14.3%) patients, and 1 (7.1%) patient received RT for recurrent tumor after total resection. A moderate hypofractionation schedule was used: Doses to PTV1, PTV2, and PTV3 were 3.9, 3.15, and 2.8 Gy through 15 fractions for the first two patients, and the rest received 2.5, 2.2, and 1.8 Gy through 25 fractions, respectively. The biologically equivalent dose in 2-Gy fractions (EQD2) was 65 to 68 Gy for PTV1, 52 to 56 Gy for PTV2, and 44.3 to 44.8 Gy for PTV3. The median follow-up was 41 months. Eight patients were free of disease for a median of 42.5 months (range 23-91 months), four patients had stable disease for a median of 60.5 months, and 1 patient showed partial response for 38 months after RT. Estimated 5-year PFS and OS rates were 92.9%. IMRT-SIB was well tolerated without lasting toxicity.

Debus et al[107] reported on 45 patients treated for chordoma or chondrosarcoma with postoperative fractionated 3D SRT. The median dose at isocenter was 66.6 Gy for chordomas and 64.9 Gy for chondrosarcomas. All chondrosarcomas achieved and maintained local tumor and recurrence-free status at 5 years of follow-up. LC rate of chordomas at 5 years was 50%, and survival was 82%. Clinically significant late toxicity developed in only one patient.

Den et al[108] described a multi-institutional study of 31 patients, of whom 28 with clivus chordoma or chondrosarcoma, treated with various photon techniques (single-dose stereotactic, fractionated 3D chemoradiation therapy [CRT], IMRT). The median fractionated total dose was 65 Gy. Actuarial 3-year local tumor control was 68%, and OS was 63%. Patients receiving 65 Gy or a higher dose had a 5-year tumor control of 78% and OS of 90%. No grade 2 or greater toxicity was observed.

Muthukumar et al[109] published a report on 15 patients with skull base chordoma and chondrosarcoma treated with SRT (13 had previous surgical resection). The median minimum marginal tumor single dose was 18 Gy (12-20 Gy), and the number of isocenters ranged from 1 to 10 (average, 4). Dose to the optic nerve or chiasm was ≤9 Gy. With a median follow-up of 40 months, eight patients had clinical improvement, three were stable, and four had died. No significant morbidity was noted.

Sahgal et al[110] reviewed 24 patients treated with skull base chordoma with IG-IMRT to a median dose of 76 Gy at 2 Gy per treatment. The 5-year OS and LC rates were 85.6% and 65.3%, respectively. Radiation toxicities were limited despite treating to high doses to the optic chiasm, nerves, and brainstem.

Particle Therapy

Successful results have also been demonstrated with surgical resection followed by high-dose particle irradiation.[111] A representative summary of studies evaluating PT for skull base chordoma in adult patients is shown in Table 54.8. Berson et al[112] described 45 patients with chordomas or chondrosarcomas at the base of the skull or cervical spine treated by subtotal resection and postoperative irradiation. Twenty-three patients were treated definitively by charged particles, 13 patients with photons and particles, and 9 were treated for recurrent disease. Doses ranged from 36 to 80 Gy equivalent (GyE). There appeared to be significant benefit for patients with smaller tumor volumes (80% vs 33% actuarial survival rate at 5 years). Patients treated for primary disease had a 78% actuarial local tumor control at 2 years versus 33% for recurrent disease.

TABLE 54.8 LITERATURE SUMMARY OF REPRESENTATIVE PROTON THERAPY STUDIES FOR SKULL BASE CHORDOMA

Author (Reference)	Patients (*n*)	Median Dose (GyRBE)	Follow-Up Median (Years)	Local Control
Munzenrider et al[113]	169	NR (66-83)	Median 3.4 (0-21)	5 y, 73% 10 y, 54%
Hug et al[114]	33	Mean 70.7 (64.8-79.2)	Mean 2.8 (0.5-6)	3 y, 67% 5 y, 59%
Weber et al[95]	71	Mean 72.5 (range NR)	Mean 4.2 (0-15)	7 y, 71%
Demizu et al[115]	53	Median 70 (range NR)	Median 4.4 (0.5-11)	5 y, 74%
Fung et al[116]	100	Median 72 (68.4-73.8)	Median 5 (1-10)	5 y, 75%
Holtzman et al[92]	91	Median 73.8 (69.6-75.6)	Median 3.7 (0-10)	4 y, 76%

NR, not reported.

Austin et al[117] evaluated 141 patients with chordoma and chondrosarcoma of the base of skull and cervical spine treated with proton and photon irradiation. The local disease was controlled in 111 patients. They reviewed 26 patients who had recurrent disease (21 nonchondroid chordomas, 2 chondroid chordomas, and 3 chondrosarcomas). The prescribed doses ranged from 67 to 72 GyRBE. Approximately 25% (6/26) of the cases failed in the prescribed dose region. More than half (15/26) failed in regions where tumor dose was limited by normal tissue constraints. Approximately 10% of the patients recurred in the surgical pathway, and 10% were judged to be marginal misses. Overall, 75% of the patients failed in regions receiving less than the prescribed dose. All tumors that failed in the high-dose region had recurrences (10/26) and larger tumors (average volume of 102 mL) than those with base of skull disease (16/115), with an average volume of 63 mL.

O'Connell et al[118] reported on 62 patients with base of skull chordomas treated with proton beam irradiation (65-73.5 GyE); 29 patients (19 women and 10 men) experienced local failure, and 14 women (48%) and 7 men (21%) died of disease. On histologic analysis, the presence of >10% necrosis, prominent nucleoli, and tumor >70 mm were

significant predictors of short-term DSS. Chondroid chordoma and conventional chordomas had equivalent outcomes.

Fagundes et al[119] reviewed the Massachusetts General Hospital experience with 204 patients treated for chordoma of the base of the skull or cervical spine. Sixty-three (31%) patients had treatment failures, which were local in 60 (29%) patients and the only site of failure in 49 patients. Two patients had regional lymph node relapse, and three developed surgical pathway recurrence. Thirteen patients relapsed in distant sites (especially lungs and bones). The 5-year actuarial survival rate after any relapse was 7%. Terahara et al[120] reported on 132 patients with skull base chordoma treated with combined photon and proton irradiation; in 115 patients, dose-volume data and follow-up were available. The prescribed doses ranged from 66.6 to 79.2 GyRBE (median 68.9 GyRBE). Dose to the optic structures (optic nerves and chiasm), the brainstem surface, and the brainstem center was limited to 60, 64, and 53 GyRBE, respectively. Local failure developed in 42 of 115 patients, with the actuarial local tumor control rates at 5 and 10 years being 59% and 44%, respectively. In a Cox multivariate analysis, the model's equivalent uniform dose suggested that the probability of recurrence of skull base chordomas depends on gender, target volume, and target dose inhomogeneity; equivalent uniform dose was shown to be a useful parameter to evaluate dose distribution for the target volume.

Hug et al[114] analyzed efficacy of fractionated proton RT for 33 skull base chordomas and 25 chondrosarcomas. Following various surgical procedures, residual tumor was present in 91% of patients; 59% demonstrated brainstem involvement. Target doses ranged from 64.8 to 79.2 GyRBE (mean 70.7 GyRBE). The range of follow-up was 7 to 75 months (mean 33 months). In 10 (17%) patients, the treatment failed locally, resulting in LC rates of 92% (23/25 patients) for chondrosarcomas and 76% (25/33 patients) for chordomas. All tumors with volumes of ≤25 mL remained locally controlled compared with 56% of tumors >25 mL (P = .02). Of patients without brainstem involvement, 94% did not experience recurrence, whereas with brainstem involvement (and dose reduction because of brainstem tolerance constraints), the tumor control rate was 53% (P = .04). Actuarial 5-year survival rates were 100% for patients with chondrosarcoma and 79% for patients with chordoma. Grade 3 and 4 late toxicities were observed in four (7%) patients and were symptomatic in three (5%).

Ares et al[121] treated 42 patients with chordomas and 22 with chondrosarcomas of the skull base using spot scanning protons (median doses 73.5 and 68.4 Gy, respectively, at 1.8-2.0 GyRBE). With a median follow-up of 38 months, 5-year tumor control was 81% and 94% and OS 100% and 91%, respectively. Late toxicity consisted of one grade 3 and one grade 4 unilateral optic neuropathy and two patients with grade 3 CNS necrosis. No patient experienced brainstem toxicity.

Noël et al[122] reported on 49 chordomas and 18 chondrosarcomas treated with high-energy photons (two-thirds of dose) and 201-MeV protons (one-third of dose). The median total dose was 67 GyRBE (60-70 GyRBE). With a median follow-up of 32 months, 3-year local tumor control was 71% for chordomas and 85% for chondrosarcomas and 4-year OS was 88% and 75%, respectively. Fourteen tumors (21%) failed locally.

Weber et al[95] reported on 71 patients with chordoma who received pencil-beam scanning PT at a typical dose of 74 GyRBE. The estimated 7-year LC and OS rates were 70.9% and 81.7%, accordingly. On multivariate analysis, optic apparatus and/or brainstem compression, histology, and GTV were independent prognostic factors for LC and OS.

Holtzman et al[92] reported on 112 patients treated with PT to a median dose of 73.8 GyRBE. At 5 years after RT, the actuarial OS, DSS, and LC rates were 78% (n = 87), 83% (n = 93), and 74% (n = 83), respectively. LC and DSS by resection status were 95% versus 70% (P = .28) and 100% versus 80% (P = .06) for gross total versus subtotal, resection or biopsy alone.

Indelicato et al[96] reviewed 29 patients treated with passively scattered PT, the majority of which involved the base of skull or cervical spine to a median dose of 73.8 GyRBE. The 5-year LC, PFS, and OS were 85%, 82%, and 86%, respectively. Excluding three patients with dedifferentiated/not otherwise specified chordoma, the 5-year LC rate increased to 92%. Serious grade 3 or higher toxicity included three patients with hardware failure or related infection requiring revision surgery; however, no patient experienced CNS toxicity including brainstem injury, myelopathy, vision loss, or hearing loss after radiation.

In a prospective trial of 20 patients treated with PT with chordoma/chondrosarcoma published by Baumann et al, 3-year LC was 86%, with two patients with acute grade 3 toxicity (fatigue) and one patient with late grade 3 toxicity (osteoradionecrosis).[123]

In the largest pediatric chordoma study to date, Ioakeim-Ioannidou et al[94] reviewed 204 pediatric patients with base of skull tumors treated with proton-based RT to a median dose of 76.7 GyRBE to GTV. Ten- and 20-year OS and PFS rates were 78% and 69% and 64% and 64%, respectively. Multivariable actuarial analyses showed poorly differentiated subtype, radiographical progression prior to RT, larger treatment volume, and lower clivus location to be prognostic factors for worse OS, PFS, and LC. RT late toxicity was acceptable with 12% of patients with late toxicities, including 2% who developed second malignancy.

Tobert et al[124] reviewed impact of proton-based RT following surgery for 67 patients with spinal or sacral chordoma. Stratified by if patients received >70 GyRBE, OS was greater for the patients who received 70 Gy or higher (5-year OS 82% vs 63%, P = .001).

Palm et al[98] reviewed 715 patients with chordoma treated with PT or conventional RT from the National Cancer Database (NCDB) patients. In patients with chordoma, PT was associated with improved OS at 5 years in a multivariate analysis (100% vs 34.1%; P = .031), and a high dose for chordoma was significant for improved OS in a univariate analysis with both definitive (79.0% vs 54.1%; P = .027) and perioperative (83.3% vs 77.4%; P = .007).

Benk et al[125] described results in 18 children with base of skull or cervical spine chordomas who received fractionated high-dose postoperative irradiation using mixed photon and 160-MeV proton beams. Median tumor dose was 69 GyRBE, with a 1.8-GyRBE daily fraction. With a median follow-up of 72 months, the 5-year survival was 68%, and the 5-year disease-free survival rate was 63%. Patients with cervical spine

chordomas had a worse survival rate than did those with base of skull lesions (P = .008). Treatment-related morbidity was acceptable: Two cases of growth hormone deficit corrected by hormone replacement, one temporal lobe necrosis and one fibrosis of the temporalis muscle, improved after surgery.

A report on PT for base of skull chordoma published by the Royal College of Radiologists[126] concluded that outcome after proton irradiation is superior to that reported for conventional photon irradiation; however, a Cochrane library review[97] noted that there is a lack of published evidence to confirm a clinical difference between modalities. In summary, RT schedules involving a mixed regimens of either and including both protons and photons have achieved an approximately 60% to 80% local tumor control rate at 5 years and 50% to 60% at 10 years.

Recently, heavy particles have been used to treat some of these patients.[111,112,127] While PT has the ability to reduce low and moderate doses of RT, both proton and photon modalities are limited in the potential to biologically intensify therapy beyond physical dose deposition alone (Figure 54.12). Because carbon exhibits a higher LET than photons and protons, this leads to a higher RBE, where damage caused by carbon ions is clustered in the DNA, overwhelming the cellular repair systems.[128] Ongoing studies regarding LET optimization with protons are underway, both protons and photons are considered low LET. A representative summary of studies evaluating carbon ion RT (CIRT) for skull base chordoma is shown in Table 54.9.

TABLE 54.9 CARBON ION RADIOTHERAPY LITERATURE SUMMARY FOR SKULL BASE CHORDOMA

Author, Reference, Institution	LOE/Study Design	Number of Patients	Median Total Dose and/or Dose Range, GyE	Total Fractions	Median Follow-Up, Months (Range)	Local Control Rate	Overall Survival Rate	Grade 3+ Toxicity or Other QoL Outcome
Lu et al,[129] MCR	2/systematic review	389	48-74	16-37	NA	1, 5, and 10 y, 99%, 80%, and 56%	1, 5, and 10 y, 100%, 94%, and 78%	The incidence of early and late toxicity (gr ≥3) ranged from 0% to 4% across all study groups.
Iannalfi et al,[130] CNAO	3/prospective phase 2 + prospective registry cohort	65	70.4	16	49 (6-87)	3 and 5 y, 77% and 71% for carbon	3 and 5 y, 90% and 82%	Acute: None Late: gr 4 eye, 2 pts; gr 3 nervous system disorder, 3 pts. All 3 cases of G4 toxicity were expected: in

Author, Reference, Institution	LOE/Study Design	Number of Patients	Median Total Dose and/or Dose Range, GyE	Total Fractions	Median Follow-Up, Months (Range)	Local Control Rate	Overall Survival Rate	Grade 3+ Toxicity or Other QoL Outcome
								2 pts, the optic nerve was very close to the GTV (causing visual field deficit at the baseline); in a third case, the pt was affected by preexistent unilateral important hearing deficit.
Mizoe et al,[131] NIRS	3/prospective trial (pilot, phase 1/2, phase 2)	33	48.0-60.8	16	53 (8-129)	5 and 10 y, 85.1% and 63.8%	5 and 10 y, 87.7% and 67%	Acute: None Late: None
Schulz-Ertner et al,[132] GSI	3/prospective phase 1/2	96	60 (60-70)	20	31 (3-91)	3 and 5 y, 80.6% and 70.0%	3 and 5 y, 91.8% and 88.5%	Acute: gr 3 mucositis, 3 pts Late: gr 3 optic nerve neuropathy, 4.1%; necrosis fat problem, 1 pt
Mattke et al,[127] GSI	4/retrospective	111	66	22	49 (41-54)	3 and 5 y, 80% and 65% for carbon	3 and 5 y, 91% and 83% for carbon	Acute: None Late: No gr 4
Koto et al,[133] NIRS	4/retrospective (prospectively enrolled)	34	60	16	108 (9-175)	5 and 9 y, 76.9% and 69.2%	5 and 9 y, 93.5% and 77.4%	Acute: gr 3 mucositis, 1 pt Late: gr 3 mucosal ulcer, 1 pt; gr 4 ipsilateral optic nerve injuries, 2 pts; gr 5

Author, Reference, Institution	LOE/Study Design	Number of Patients	Median Total Dose and/or Dose Range, GyE	Total Fractions	Median Follow-Up, Months (Range)	Local Control Rate	Overall Survival Rate	Grade 3+ Toxicity or Other QoL Outcome
								mucosal ulcer, 1 pt
Takagi et al,[134] HIBMC	4/retrospective	13	57.6-74.0	16-37	56	5 and 8 y, 85% and 71%	5 and 8 y, 86% and 76%	Acute: None Late: gr 3: brain necrosis, 2 pts; optic nerve disorder, 1 pt; nervous system disorders, 2 pts; middle ear inflammation, 1 pt; gr 4: pharyngeal hemorrhage, 1 pt
Uhl et al,[135] GSI	4/retrospective	155	75	20	72 (12-165)	3, 5, and 10 y, 82%, 72%, and 54%	3, 5, and 10 y, 95%, 85%, and 75%	Not graded: At 10 y: headache, dizziness, fatigue, xerostomia, double vision, visual deficits, hearing deficits, and cranial nerve deficits

ACTH, adrenocorticotropic hormone; CAS, Chinese Academy of Sciences; CNAO, National Center of Oncological Hadrontherapy (Italy); GH, growth hormone; gr, grade; GSI, German Ion Research Center (Heidelberg); GyE, gray equivalents; HIBMC, Hyogo Ion Beam Medical Center (Japan); LOE, level of evidence; MCR, Mayo Clinic Rochester; NA, not applicable; NIRS, National Institute of Radiological Sciences (Japan); NR, not reported; ORN, osteoradionecrosis; pts, patients; SNHL, sensorineural hearing loss; SPHIC, Shanghai Proton and Heavy Ion Center.

Reprinted from Holtzman AL, Seidensaal K, Iannalfi A, et al. Carbon ion radiotherapy: an evidence-based review and summary recommendations of clinical outcomes for skull-base chordomas and chondrosarcomas. *Cancers (Basel)*. 2023;15(20):5021. http://creativecommons.org/licenses/by/4.0/.

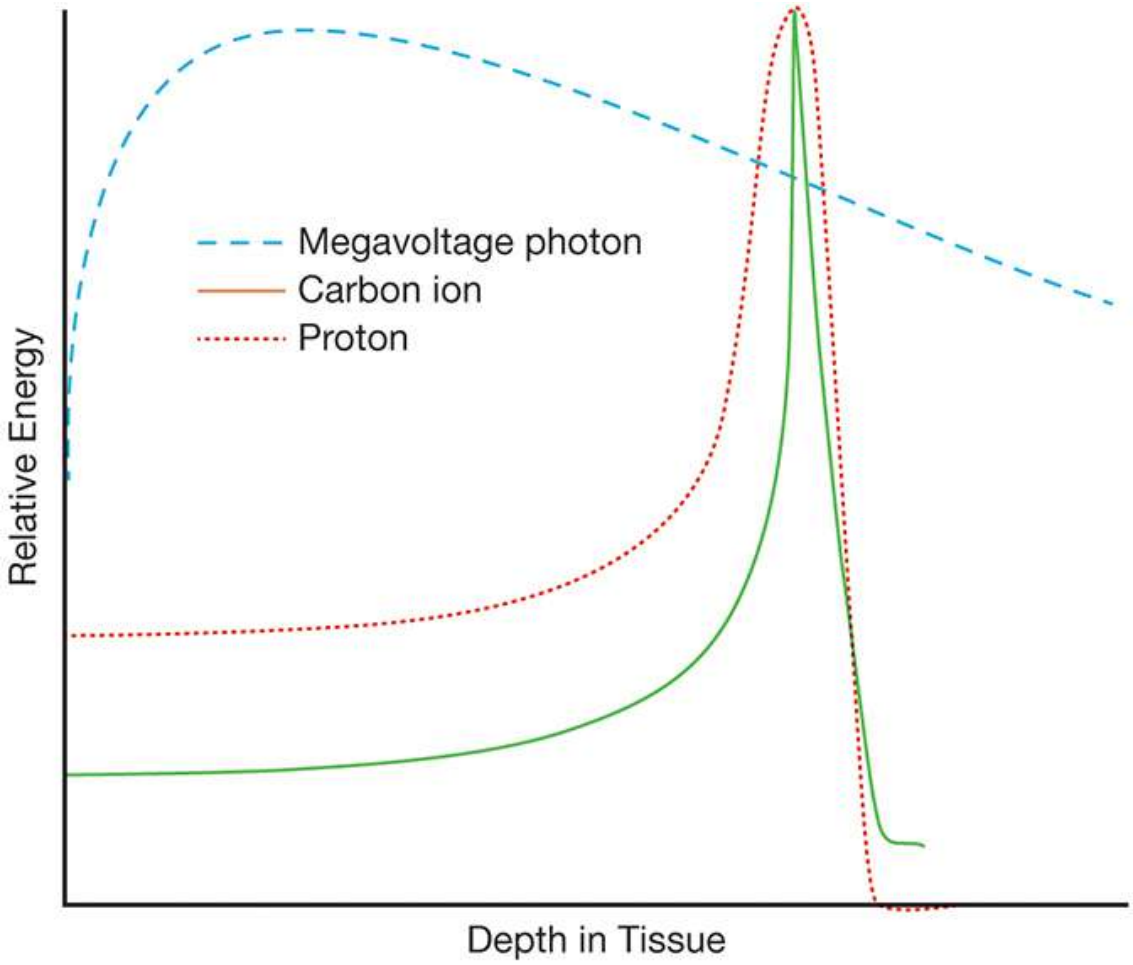


FIGURE 54.12 Dose deposition at depth for 6-MV photons, protons, and carbon ions. Carbon ions exhibit a characteristic energy distribution in depth, known as the "Bragg peak," where low levels of energy are deposited in tissues proximal to the target, and the majority of energy is released in the target. Distal tissues receive little energy, although, unlike protons, there is energy deposited distally due to nuclear fragmentation. (Reprinted from Malouff TD, Mahajan A, Krishnan S, Beltran C, Seneviratne DS, Trifiletti DM. Carbon ion therapy: a modern review of an emerging technology. *Front Oncol*. 2020;10:82. http://creativecommons.org/licenses/by/4.0/.)

Hasegawa et al[136] reported on 54 patients with skull base or paracervical tumors (31 with chordomas) treated with carbon ions (escalating doses from 48 to 60.8 GyE in 16 fractions over 4 weeks). In the 31 patients with chordoma, 5-year local tumor control and OS were 78% and 85%, respectively. Patients were divided into two groups: a low-dose group (n = 10) irradiated with doses ranging from 48 to 57.8 GyE and a high-dose group (n = 21) irradiated with 60.8 GyE. The 5-year local tumor control was 60% for the low-dose group and 93% for the high-dose group, and the OS was 90% and 84%, respectively. One late grade 2 brain sequela was noted in a patient treated with 60.8 GyE.

Likewise, Schulz-Ertner et al[121] treated 24 chordomas and 13 chondrosarcomas with 3D planning carbon ions (median dose 60 GyE). With a mean follow-up of 13 months, local tumor control at 2 years was 90%. PFS was 83% for chordomas and 100% for chondrosarcomas. No significant toxicity was observed.

Mattke et al[127] reviewed the outcomes of patients treated with either carbon or PT for skull base chordoma. With a median follow-up over 4 years, no significant differences between protons and carbon ions were observed regarding LC, OS, or overall toxicity. The 5-year LC rates were 61% for protons and 65% for carbon.

Holtzman et al[137] performed a systematic review that reviewed the quality of evidence and identified 24 papers published on skull base chordoma treated with CIRT. Two systematic reviews were identified. Lu et al reported the LC incidence at 1-, 5-, and 10 years following carbon therapy were 99%, 80%, and 56%, respectively.[129] The incidence of severe early and late toxicity ranged from 0% to 4% across all study groups. Dong et al identified nearly 900 patients with skull base sarcomas who received CIRT, 526 had chordoma, and 255 had chondrosarcoma. The LC rate at 5 and 10 years in these studies was 74.3% and 64.7%, respectively. The incidence of acute grade 3 toxicity was 3.2% to 3.8%, and late grade 4 was 2.1% to 8.0%.[138]

Sequelae of Treatment

While highly conformal external beam RT has been used to mitigate acute and late effects following therapy, in patients treated with high irradiation doses, there is an increasing probability of sequelae, including brain damage (Figure 54.13A), brainstem (Figure 54.13B) and spinal cord injury, optic pathway toxicity (Figure 54.13C), bone or soft tissue necrosis, and xerostomia.[139]

FIGURE 54.13 Representative toxicities following high-dose complications from radiotherapy. A. Left temporal radionecrosis as shown on T1-weighted magnetic resonance imaging (MRI) with contrast (red arrow). B. T1-weighted brain MRI showing axial slice illustrating enhancement in the right pons consistent with clinically asymptomatic brainstem necrosis (red arrow). C. Bilateral enhancement on coronal brain MRI showing bilateral optic nerve enhancement (red arrows). This patient developed bilateral grade 4 vision loss. (Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

Regarding the temporal lobe, several groups have evaluated clinical outcomes following PT. McDonald et al[140] in 2014 published the outcomes on 66 patients with skull base tumors treated with uniform scanning 3D conformal PT to a median dose of 75.6 GyRBE. The 3-year estimate of any grade temporal lobe radiation necrosis was 12.4%, and they illustrated that only the dose-volume relationship was associated with the risk of radiation necrosis. They modeled a 15% 3-year risk of any grade temporal lobe radiation necrosis

when the absolute volume of a temporal lobe receiving 60 GyRBE exceeded 5.5 cm^3, or V70 >1.7 cm^3. In regard to the clinical implications and determination of RBE and LET for PT, this is still a debate. Clinical evidence shows that the RBE for protons may in fact be higher than as reported as 1.1. While the incidence of temporal lobe epilepsy and grade 3 complications are rare, more work into RBE optimization and understanding its clinical effects is ongoing. Zhang et al reviewed 566 patients treated with double-scattering PT or IMRT. The reported dose tolerance at D1% was 58.6 Gy for protons and 69.1 Gy for photons, with the calculated RBE for temporal lobe enhancement being 1.18.[141]

Schröder et al[142] evaluated nearly 300 patients with a median radiologic follow-up of over 4.5 years. They showed that not only clinical dose but also age, V40Gy, hypertension, and dose to at least 1 mL (D1cc) in the temporal lobe were associated with grade 2 necrosis or greater. This was cross-valuated and used to develop an age * prescription-dose * D1cc (Gy) * hypertension patient-wise model to predict the risk of radionecrosis following PT.

In patients receiving high-dose PT for clivus tumors, Slater et al[143] observed a 26% incidence of endocrine abnormalities at 3 years and 37% at 5 years, with hypothyroidism being the most frequent sequela. The dose to the pituitary in patients with abnormalities ranged from 63.1 to 67.7 GyE.

Weber et al[95] reviewed in a series of 222 patients with skull base chordoma and chondrosarcoma treated to a median dose of 72.5 GyRBE with pencil-beam PT. In total, there were 25 events (≥grade 3 toxicity): 5 (25%) patients with grade 3 unilateral optic neuropathy, 2 (8%) patients with grade 4 bilateral optic neuropathy, 13 (56%) patients with grade 3 temporal lobe necrosis, 1 (8%) with cerebellum brain parenchyma grade 3 necrosis, 1 (8%) patient with a grade 4 spinal cord necrosis, and 3 (12%) patients with grade 3 unilateral hearing loss. Of note, no patient experienced brainstem toxicity nor grade 5 toxicity or treatment-related secondary malignancies were observed. The estimated 5- and 7-year high-grade (≥grade 3 toxicity) toxicity-free survival was 87.2 (95% confidence interval [CI] 82.4-92.3). A summary of brainstem toxicity is provided in Table 54.10.

TABLE 54.10 REPRESENTATIVE LITERATURE SUMMARY OF BRAINSTEM NECROSIS IN SKULL BASE TUMOR SERIES

Author (Reference)	Size (n)	Follow-Up	Brainstem Dose (GyRBE)	Brainstem Complications
Holtzman et al[144]	163	Median—47 mo	D(0.03 mL) 63.5 D_{max} 65.7	1.3% grade 2+
Weber et al[95]	222	Mean—50 mo	NR Mean prescribed dose 72.5	No events
Sahgal et al[110a]	42	Median—36 mo	D_{max} 67.6	1 brainstem glioma
Feuvret et al[145]	159	Median—77 mo	D_{max} <64	1 brainstem glioma
Debus et al[146]	367	Mean—42.5 mo	D_{max} 63	4% grade 2+

All series included used proton-based techniques with the one noted exception.

[a]Intensity-modulated radiotherapy.
D(0.03 mL), maximum dose to 0.03 mL; D_{max}, maximum dose; NR, not reported.

Chhabra et al[93] reported the clinical outcomes and toxicities of 100 patients treated with PT for chordoma on the proton collaborative group prospective registry to a median dose of 74 GyRBE. Acute grade 3 toxicity consisted of common pain (n = 3), radiation dermatitis (n = 2), fatigue (n = 1), insomnia (n = 1), and dizziness (n = 1). No grade ≥ 4 acute toxicities were reported nor grade ≥ 3 late toxicities.

It has been well reported that pediatric patients are more sensitive to brainstem toxicity following RT as compared to adult patients and are treated to lower dose threshold.[96,147] Haas-Kogan et al[148] reviewed the outcomes of symptomatic brainstem toxicity from the three largest U.S. pediatric proton centers as part of a National Cancer Institute workshop on PT for children. The overall incidence of toxicity was 2.4% and the actuarial rate of grade ≥2 brainstem toxicity was successfully reduced from 12.7% to 0% at one center after adopting modified radiation guidelines, which included reducing the brainstem goals to D(0.1 mL) to <56.6 GyRBE, D(10%) <55.4 and D(50%) <52.4.[147] Guidelines for treatment planning and current consensus brainstem constraints for PT were presented from each group and note they are more conservative than what is currently being used for adult patients with skull base tumors. Note that these OAR constraints differ substantially from that provided in Table 54.7 for adult practice patterns from Mayo Clinic Florida.

ESTHESIONEUROBLASTOMA

Esthesioneuroblastoma (ENB), also referred to as olfactory neuroblastoma (ONB), was first described by Berger and Luc.[149] They are thought to arise in the olfactory receptors in the nasal mucosa or the cribriform plate of the ethmoid bone. The olfactory nerves perforate grooves in the ethmoid bone in the cribriform plate and continue into the subarachnoid spaces, accounting for the high incidence of intracranial extension.[149]

Epidemiology

ENB constitutes 3% of all endonasal neoplasms and 0.3% of all upper aerodigestive tract malignancies, and over 1,000 cases have been reported in the world literature.[149] There appears to be a slight male predominance, and 80% of patients in SEER database from 1973 to 2014 were White.[150] The age distribution was unimodal, with ENB most frequently occurring in the fifth to sixth decades of life. Only 8% of all ONBs are diagnosed prior to 25 years of age.

Natural History

Although others thought that ENB was of ectodermal origin, most observers believe the tumor to be of neuroectodermal origin in the olfactory epithelium.[149] Most of these tumors occur high in the nasal cavity or in the lateral wall adjacent to the ethmoid. The tumor may spread to the opposite ethmoid bone, superiorly to the frontal sinus and anterior cranial

fossa; posteriorly to the sphenoid sinus, nasopharynx, and base of the skull; laterally to the orbits, forward to the frontonasal angle; or inferiorly to the nasal cavity and antrum (Figure 54.14). Lymphatic spread may be to the subdigastric, posterior cervical, submaxillary, or preauricular nodes, as well as to the nodes of Rouvière. The exact incidence of distant metastases is uncertain; it has been stated to be as high as 50%, but this rate is influenced by the use of chemotherapy in high-risk patients.

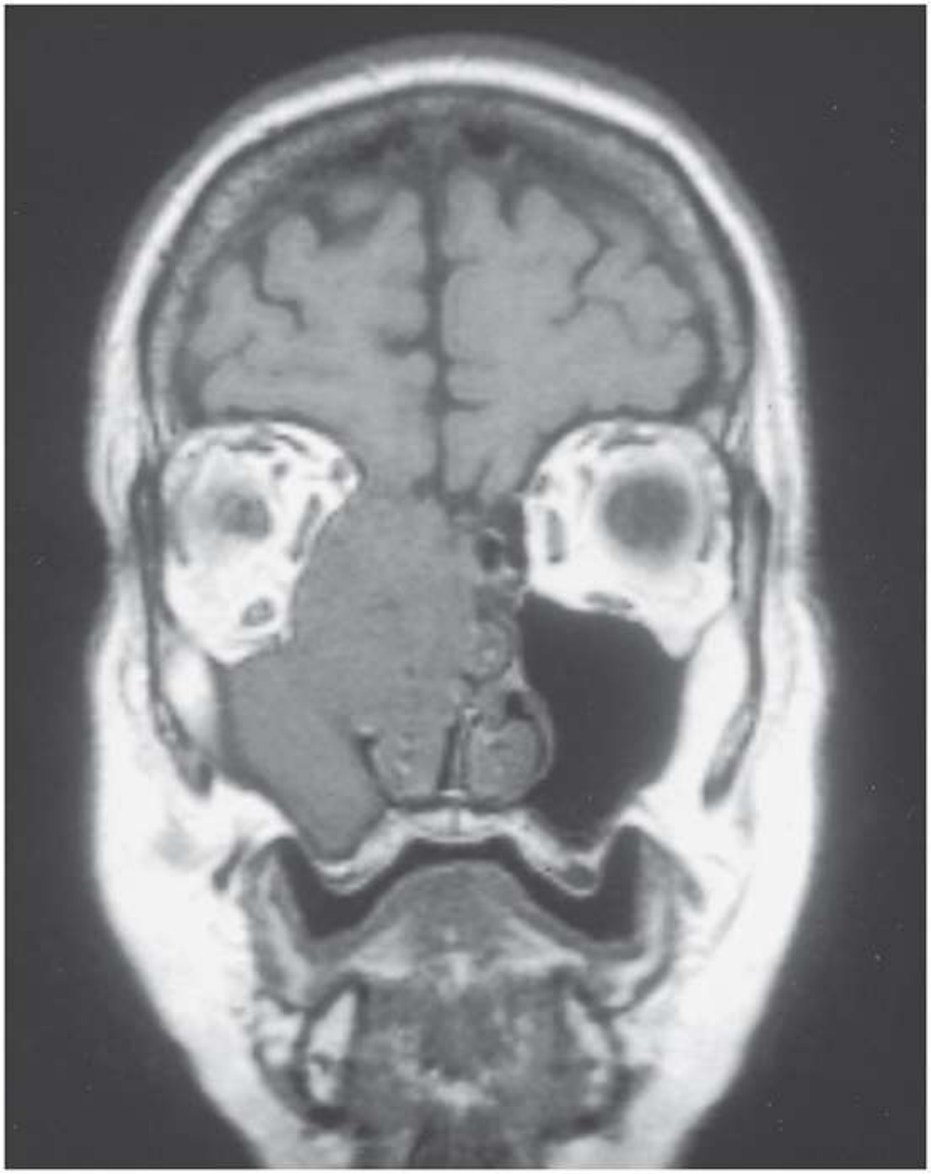


FIGURE 54.14 Coronal magnetic resonance imaging scan showing a large soft tissue mass and bone destruction in the right ethmoidal maxillary sinuses and nasal cavity secondary to extensive (Kadish stage C) esthesioneuroblastoma.

Clinical Presentation

These tumors tend to be friable and bleed easily. The most common clinical symptoms are epistaxis and nasal blockage. Patients may also have local pain or headache, visual disturbances, rhinorrhea, tearing, proptosis, or swelling in the cheek.[151] The symptoms may be associated with a mass in the neck.

Diagnostic Workup and Staging

Physical examination may show the inferior aspect of a polypoid friable mass in the nasal cavity. Ocular findings or a mass in the nasopharynx may be present. With early lesions, CT or MRI may show only nonspecific opacification, soft tissue swelling, and, occasionally, bone destruction.[152] Octreotide is a somatostatin analog that, when coupled to a radioisotope, produces a scintigraphic image of NETs expressing somatostatin type 2 receptors. Octreotide scintigraphy may be useful in confirming the preoperative diagnosis of certain H&N NETs, such as PGs, Merkel cell carcinomas, medullary thyroid carcinomas, and ENBs. Bustillo et al[153] carried out a retrospective study that compared the results of octreotide scintigraphy with the histopathologic diagnosis in 74 patients with H&N NETs. Of the 60 patients undergoing evaluation for suspected PG, octreotide scintigraphy was correctly positive in 36 of 37 patients with PG and correctly negative in 19 of 23 patients who did not exhibit PG (sensitivity of 97% and a specificity of 82%). There were 14 patients in the nonparaganglioma group. Octreotide scintigraphy detected or diagnosed locoregional recurrences in two with ENB.

Table 54.6 outlines the suggested diagnostic workup. CT provides the best information about the tumor and its local invasion into surrounding bone structures.[154] MRI allows an estimate of tumor spread into surrounding soft tissue areas, such as the anterior cranial fossa and the retromaxillary space. PET-CT (preferred) or bone scintigraphy scan is useful in detecting distant metastases.

The expansile tendency of ONB is characterized by bowing of the sinus walls. The destructive aspect is manifested as tumor replacing the turbinates, septum, and sinus walls with extension into contiguous areas (Figures 54.14 and 54.15). The density or signal and enhancement characteristics are nonspecific of ONB.

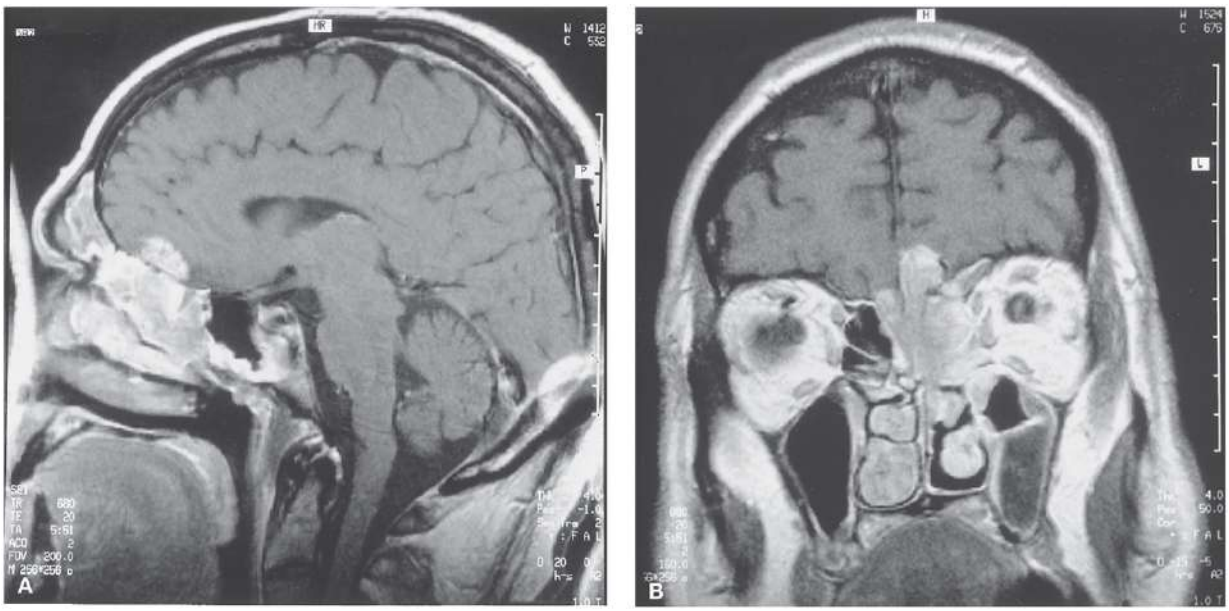


FIGURE 54.15 Sagittal (A) and coronal (B) views of preoperative magnetic resonance imaging of a 56-year-old patient who was initially seen with a Kadish stage C tumor involving left nasal cavity and extending intracranially. (From Chao KSC, Kaplan C, Simpson JR, et al. Esthesioneuroblastoma: the impact of treatment modality. *Head Neck*. 2001;23[9]:749-757. Copyright © 2001 John Wiley & Sons, Inc. Reprinted by permission of John Wiley & Sons, Inc.)

Although dopamine β-hydroxylase and catecholamines are produced by these tumors, their measurements or vanillylmandelic acid excretion levels have not proven clinically useful.

A staging system has been proposed by Kadish et al[151] (Table 54.11).

TABLE 54.11 KADISH SYSTEM FOR STAGING OF ESTHESIONEUROBLASTOMA

Stage	Characteristic
A	Disease confined to the nasal cavity
B	Disease confined to the nasal cavity and one or more paranasal sinuses
C	Disease extending beyond the nasal cavity or paranasal sinuses; includes involvement of the orbit, base of the skull or intracranial cavity, cervical lymph nodes
D	Distant metastatic sites

From Kadish S, Goodman M, Wang CC. Olfactory neuroblastoma: a clinical analysis of 17 cases. *Cancer.* 1976;37(3):1571-1576.

Pathologic Features and Prognostic Factors

ENBs are polypoid, frequently reddish, soft, and vascular tumors with neuroblasts and neurocytes. ENBs contain epithelial components serving as a supporting stroma and have a nerve component that corresponds to the olfactory cells. Rosettes are the main feature, consisting of several rows of cells arranged around the central area.[149] ENBs may be confused with lymphoma or anaplastic carcinoma and have diffuse, regular distribution.

ENBs contain many fibrils, which fill the central space of the rosette (called a pseudorosette). It has been suggested that the presence of chromaffin granules indicates a derivative from primitive neural crest cells. ENB must be distinguished from other poorly differentiated neoplasms, including sinonasal undifferentiated carcinoma (SNUC), which is derived from the Schneiderian epithelium. SNUC lacks rosettes and intercellular fibrils.[155]

Extension of the primary tumor based on the Kadish staging system[151] has been identified as the most important determinant of treatment outcome, although this was not confirmed by Chao et al[156] High-grade tumors had worse outcome in the reports from the Mayo Clinic and the University of California, Los Angeles (UCLA).[157]

Argiris et al[158] found that in 16 patients with ENB, 11 of whom had Kadish stage C and 8 (50%) had brain involvement at presentation. Craniofacial resection was performed in 13 (81%) patients; 14 received either preoperative or postoperative therapy (RT in 11 and chemotherapy in 4). The actuarial 5-year survival was 60% and disease-free survival 33%, with a median follow-up of 4.3 years. The first site of failure was locoregional alone in 10 of 12 patients who progressed, and in 6 patients involved the brain or the meninges. Two patients were successfully salvaged.

Hyams[159] proposed a histologic grading system for ENB in which grade I tumors have an excellent prognosis and grade IV tumors are uniformly fatal. The Hyams grading system predated advanced craniofacial techniques, extensive use of immunohistochemistry, and the recognition of SNUC as a distinct entity. Miyamoto et al[160] in a retrospective review of 12 patients with ENB and 14 with SNUC, used the Kadish clinical stage and Hyams histopathologic system. Kadish staging was available for 26 patients (2 patients with stage A tumors; 7 with stage B, and 17 with stage C). Of the eight evaluable patients with Kadish stage A or B tumors, six remained disease free for more than 2 years compared with only five of seven Kadish stage C tumors. Slides were available for Hyams grading in 21 patients (2 patients with grade I tumors, 4 with grade II, 4 with grade III, and 11 with grade IV). They concluded that both the Hyams grading and the Kadish staging system can be used as independent predictors of outcome. Papadaki et al[161] analyzed 18 formalin-fixed paraffin-embedded ONB specimens (12 primary tumors and 6 recurrences or metastases) from 14 patients and concluded that p53 point mutation does not play an important role in the initial development of ONB; however, p53 wild-type hyperexpression may occur in subsets, show local aggressive behavior, and have a tendency for recurrence.

Choby et al[162] performed a multicenter, case-control study incorporating Hyams grade into the existing staging systems. A total of 256 patients were included. They found that adding this variable to known ONB staging systems was better able to estimate disease progression. In fact, the novel Kadish staging system, patients with stage VI disease were nearly 7 times as likely to experience disease progression as patients with stage I disease.

General Management

Surgery alone (SA) (including endoscopic technique) appears to be adequate treatment for small, low-grade tumors in which negative surgical margins can be obtained. A complete resection with preservation of neurovascular structures is achievable by either EEA or craniofacial approaches. Endoscopic endonasal techniques have gained in use because of the reduced postoperative hospital stays, minimally invasive technique, and reduced complication rates with comparable oncologic outcomes for the appropriate patient population.[163] Those with more extensive local-regional disease benefit from surgery and adjuvant irradiation. Patients with locally advanced disease or high-grade tumors should receive aggressive treatment with combined modalities, such as surgery, RT, and chemotherapy.[154,164]

Dias et al[165] reported on 35 patients with ENB treated with GTR through a transfacial approach with postoperative RT in 11 patients, craniofacial resection and postoperative RT in 7, exclusive RT in 14, craniofacial resection alone in 1, and a combination of chemotherapy and RT in two patients. RT median dose was 48 Gy. Craniofacial resection plus postoperative RT provided a better 5-year disease-free survival rate (86%) compared with the other therapies ($P = .05$). The 5-year DSS rate was 64% and 43% for the low- and high-grade tumors, respectively ($P = .20$). At 5 and 10 years, disease-free survival was 46% and 24%, respectively, and OS was 55% and 46%, respectively.

Monroe et al[166] described treatment results in 22 patients who received RT for ENB. The modified Kadish stage was stage A in 1 patient, stage B in 4 patients, stage C in 15 patients, and stage D in 2 patients. Treatment modalities included primary RT in 6 patients, preoperative RT in 1 patient, postoperative RT after craniofacial resection in 12 patients, and salvage RT in 3 patients treated for recurrence after surgery. Elective neck RT was performed in 11 of 20 patients (2 patients had cervical metastases at presentation for RT). Rates of local tumor control, cause-specific survival (CSS), and absolute survival at 5 years were 59%, 54%, and 48%, respectively. The CSS rate at 5 years was lower after primary RT (17%) than after craniofacial resection and postoperative RT (56%). Cervical metastases occurred in 6 (27%) of 22 patients. No neck recurrences occurred in 11 patients treated with elective neck RT compared with four neck recurrences in 9 (44%) patients not receiving elective neck RT ($P = .02$). Their data and review of the current literature suggest a higher cervical failure rate than previously recognized; elective neck RT seems to correlate with improved nodal tumor control and should be considered in the treatment of ENB.

Gruber et al[167] described 28 patients with ENB treated with RT (median dose 60 Gy). In 13 patients, total tumor resection (recommended by the authors) was performed. Chemotherapy (cisplatin, etoposide, cyclophosphamide, and vincristine) combined with RT was used in five patients. With a median follow-up of 68 months, 54% of the patients were free of local tumor progression (51% at 10 years). Disease-free survival at 10 years was 25%.

Ozsahin et al[168] described the results of treatment in 13 European and North American centers for 77 patients with ONB, 11 with Kadish stage A, 29 with stage B, and 37 with stage C; 56 patients had surgery, 44 with total tumor excision. All but 5 patients received

RT (50% with 3DCRT) and 21 had chemotherapy. With a median follow-up of 72 months, locoregional tumor control (LRC) was 62%, disease-free survival 57%, and OS 64%. Patients having total tumor resection or receiving ≥54 Gy had better OS than those treated with lower doses. Six of the patients treated with RT (56-70 Gy) developed grade 3 or 4 late complications (five osteonecrosis and one retinopathy).

Sperry et al[169] treated 30 patients with ENB (70% with Kadish stage C) with surgery in 27 (52% craniofacial resection), combined with postoperative RT in 75.9% and chemoradiation in 23%. Local tumor failure at 5 years was 43.6%, and regional failure was 15.7%. The 5-year disease-free survival was 40.7% and OS was 80%.

Madani et al[170] published a report on 84 patients (73 with primary and 11 with local recurrent) sinonasal tumors, 9 of which were ENB, treated with IMRT (median dose 70 Gy in 35 fractions). Mean D50 was 37.2 Gy to the optic chiasm, 49.4 Gy to ipsilateral optic nerve, 47.1 Gy to contralateral optic nerve, and 37.7 and 28.4 Gy to the retina.

Sharrett et al[171] described treatment results in 75 patients with H&N ENB. The median follow-up was 105 months (range 6-539). The majority of the patients were men (64%), with a median age of 50.7 years at the time of diagnosis. A total of 77% had advanced-stage disease (Kadish stage C). All patients received RT; 88% was postoperative and 12% was definitive. The median RT dose was 60 Gy (range 42-70). Twenty (26.6%) patients received chemotherapy. The 5- and 10-year LC rates were 96% and 93%, whereas the 5- and 10-year LRC were 87% and 68%, respectively. Ninety-three percent of patients were free from distant metastasis at 5-year follow-up and 81% at 10 years. Half of the total recurrences were after a 5-year follow-up. The 5- and 10-year OS rates were 87% and 74%; the 5- and 10-year DSS were 93% and 84%, respectively. On univariate analysis, younger age was associated with better RFS, DSS, and OS. On multivariate analysis, younger age was the only independent prognostic factor for improved RFS ($P = .03$), DSS ($P < .0001$), and OS ($P < .0001$). The authors recommend surgery followed by postoperative RT and chemotherapy for advanced ENB.

Modesto et al[172] described their experience in 43 patients with biopsy-proven ENB, in two groups one of 26 and the other of 17 patients treated at separate institutions. Five patients had stage A at diagnosis (confined to nasal cavity), 13 stage B (tumor extending into paranasal sinuses), 16 stage C (beyond the paranasal sinuses), and 9 stage D (cervical lymph node involvement) according to the modified Kadish classification. Neoadjuvant platinum-based chemotherapy was administered to 24 patients, leading to a 70.8% response rate (6 complete and 11 partial). A total of 31 (72%) patients were treated by surgery, and 39 (90.6%) underwent RT. Among them, 11 (28.2%) patients were treated using IMRT. The median dose was 64 Gy (range 30-70 Gy). Twelve (28%) patients received bilateral cervical lymph node irradiation (LNI) (median dose 57 Gy, range 50-66 Gy). Nine (21%) patients received platinum-based concomitant CRT. Three patients received platinum-based adjuvant chemotherapy. After a median follow-up of 77 months, the 5-year OS was 65% and the 5-year PFS 58%. Twelve (28%) patients developed locoregional relapse, mostly within the first 2 years (five locally, two regionally, and five both locally and regionally). The major prognostic factor was the modified Kadish stage

with 3-year survival rates of 100% for Kadish A-B versus 48% for stage C and 22% for stage D. After adjustment for tumor stage, neither neoadjuvant chemotherapy nor LNI seemed predictive for LRC or survival. Interestingly among initial stage B and C patients (N = 29), two of them (7%) presented an isolated cervical lymph node relapse, and none occurred among patients previously treated by elective or adjuvant LNI.

Because of the tumor location, good prognosis, and generally younger age at diagnosis, PT has become increasingly utilized for the treatment of ENB. Nishimura et al[173] reported on 14 patients with ONB treated with proton beam (65 GyRBE in 2.5-GyRBE fractions) and 6 patients combined with surgery, sometimes combined with chemotherapy. With a median follow-up of 40 months, 5-year local PFS was 84%, disease-free survival 71%, and OS 93%.

Dagan et al[174] reported on 84 adult patients without metastases receiving primary (13%) or adjuvant (87%) treatment with PT for sinonasal cancers, of which 23% were ONB. Advanced stage (T3 in 25% and T4 in 69%) and high-grade histology (51%) were common. Surgical procedures included endoscopic resection alone (45%), endoscopic resection with craniotomy (12%), or open resection (30%). Gross residual disease was present in 26% of patients. Most patients received hyperfractionated PT (1.2 GyRBE) twice daily, 99%) and chemotherapy (75%). The median PT dose was 73.8 GyRBE, with 85% of patients receiving more than 70 Gy. The median follow-up was 2.4 years for all patients and 2.7 years for living patients. Local tumor control, neck control, freedom from distant metastasis, disease-free survival, CSS, and OS rates were 83%, 94%, 73%, 63%, 70%, and 68%, respectively, at 3 years. The 3-year LC rate was 61% for primary RT and 59% for patients with gross disease. Late toxicity occurred in 24% of patients (with grade 3 or higher unilateral vision loss in 2%).

Akimoto et al[175] reported on 339 patients with nonsquamous cell cancer in the H&N, of which 63 were ONBs, treated with protons. The median follow-up was 64 months. OS, PFS, and LC rate for all patients at 5 years were 61.2%, 36.8%, and 71.2%, respectively, and OS and LC were 86.2% and 79.0% for ONBs, respectively. Among all patients, 254 (75%) were not suited for photon RT because doses to OARs exceeded tolerance dose in the evaluation of dose-volume histogram. However, OS at 5 years of these patients was 65.5%. Regarding treatment morbidity, 34 (10%) patients developed grade 3 or 4 late toxicities, such as brain injuries and neuropathy. None experienced grade 5 toxicities.

Suefuji et al[176] reviewed outcomes following CIRT in a subanalysis of the Japan Carbon-Ion Radiation Oncology Study Group (J-CROS). Twenty-one patients with T4 ENBs treated with CIRT were retrospectively reviewed. With a median follow-up period of 39 months, the 3-year OS and LC rates were 88.4% and 83.0%, respectively. Grade 4 late toxicity was observed in three patients, including ipsilateral optic nerve disorder (n = 2) and ipsilateral retinopathy (n = 1).

Chemotherapy for ENB consists of platinum-based regimens in combination with cyclophosphamide, vincristine, and, occasionally, doxorubicin. It is usually used with surgery and/or RT and most commonly for the treatment of locally advanced disease, high-grade tumors, patients with recurrence, younger patients, or neoadjuvantly for those

deemed to be inoperable.[149,177] Brisson et al[177] reviewed the 636 patients from the SEER registry, of which 195 of whom received chemotherapy. They showed that with propensity score matching and inverse probability of treatment weighting, there was inferior OS and CSS for patients who received chemotherapy compared to those who did not. On subgroup analysis, those patients who did not undergo surgery and were treated with chemotherapy and/or RT (hazard ratio [HR] 0.3, $P < .001$) had the most impact. Because of the nature of retrospective SEER registry studies, it is difficult to eliminate selection bias from those who received a trimodality therapy but also suggests that patients who are considered nonsurgical candidates may benefit from the addition of chemotherapy.

Elective Neck Treatment

Recurrence is frequent and occurs in 40% to 50% of cases with long intervals to relapse, which can occur over 5 years from the initial therapy.[178] Although the sites of metastases are widely variable and often atypical, Beitler et al[156] found cervical node metastasis to be as frequent as local recurrence. Davis and Weissler[179] compiled a retrospective review of patients and found that the cumulative cervical metastasis rate reached 27% (55/207 patients). Noh et al,[180] in a report of 19 patients with ENB treated with combinations of surgery, RT, and/or chemotherapy, noted that 4 patients with high-risk factors received elective neck RT (45-70 Gy). There were no cervical node failures in 5 patients with Kadish stages A and B, 3 of 10 in patients with Kadish stage C treated surgically, and 0 in 9 receiving chemotherapy.

Peacock et al[181] reported on 53 patients with ENB in the H&N; 42 (79%) underwent craniofacial resection as the definitive surgical treatment, 28 (53%) patients underwent surgery and ART (ART group) to the primary site only, and 25 (47%) SA as treatment for the primary site (SA group). The median follow-up was 84.5 months for the ART group and 93 months for the SA group. Following initial treatment, the 5-year actuarial survival was 89% for the ART patients and 75% for the SA patients; the 5-year local RFS was 89% for the ART patients and 63% for the SA group. The 5-year cervical lymph node metastasis-free survival was 80% for the ART patients and 75% for the SA patients. Among the 18 patients with delayed cervical lymph node metastases, 10 underwent salvage neck surgery and RT, 5 had SA, and 3 did not have surgery or RT, because of distant metastases or other comorbidities. Four patients recurred in the neck following salvage treatment. With a median follow-up time of 31 months, the 2-year RFS estimate was 85% versus 74% following salvage treatment. Thus, the 5-year delayed cervical lymph node metastasis rate in patients with ENB and a clinically N0 neck undergoing local treatment is 23%. The delayed lymph node metastases were effectively salvaged in the majority of patients. The authors proposed that patients with ENB and a clinically N0 neck should not undergo elective neck RT as part of their initial treatment in order to avoid acute and late toxicity.

Ni et al[178] reviewed long-term outcomes of 143 who underwent salvage therapy for ENB at the Mayo Clinic. This series included approximately one-third of patients who had regional recurrences. Salvage therapy for the entire cohort was shown to be effective as

subsequent 5-year OS was 63%. Subsequent recurrences were not infrequent, however, and tended to occur at shortened intervals compared to initial disease progression.

Jiang et al[182] reviewed 71 patients from MD Anderson Cancer Center to evaluate the role of elective nodal irradiation (ENI) in clinically N0 patients. With a median follow-up of over 6.5 years, among N0 patients, 11 patients without ENI developed isolated neck recurrences. None of these 13 patients who received ENI recurred regionally. While ENI was associated with significantly improved regional nodal control at 5 years (100% for ENI vs 82%, $P < .001$), there was no difference in OS or disease-free survival. The authors concluded that although ENI significantly reduces the risk of cervical nodal recurrence in patients with clinically N0 necks, this did not translate to a survival benefit.

Yin et al[183] published a retrospective analysis of 116 patients with naïve ENB treated in China. According to the Kadish stage classification, 20% (23 patients) presented with stage B and 79% (92 patients) with stage C. Thirty-two patients showed cervical lymph node metastasis in the initial staging. Among 84 patients with N0 disease, the management of neck in 80 patients with Kadish stage B/C was available, with treatment modalities consisting of primary RT in 27 patients, preoperative RT in 10, postoperative RT in 40, and SA in 3. Fifty patients were treated with ENI and 30 without any prophylactic neck treatment. Thirty-two of 116 (28%) patients were N positive at the time of initial diagnosis, most frequently involving the level II lymph nodes (81%), followed by level IB (53%), level III (28%), and the retropharyngeal nodes (RPNs) (25%). Rates of OS, disease-free survival, and regional relapse-free survival at 5 years were 77%, 71%, and 98%, respectively, for patients treated with ENI, compared with 62%, 50%, and 75% for those without neck treatment. The regional failure rate was 2% for patients with ENI compared with 23% without neck treatment, and distant failure rates were 20% in the ENI group versus 27% in the untreated neck group. Neck recurrence occurred in 7 of 30 patients who were without neck treatment, all relapsed in level IB or level II. The authors concluded that the treatment target of ENI should at least cover the bilateral upper and middle neck, namely, level IB-III and RPNs.

As noted, because of the low incidence of cervical lymph node metastasis (≤10%) in early-stage ENB, elective irradiation of the neck or a dissection is not indicated. However, in patients with Kadish stage C disease, the cervical metastatic rate climbed to 44% (25/57 patients). As stated previously, Monroe et al[166] observed cervical node metastasis in 6 (27%) of 22 patients. In 11 patients treated with elective neck RT, no recurrences were noted, in contrast to 4 (44%) of 9 patients not receiving elective neck RT. Thus, with advanced-stage disease, cervical nodes may be initially managed by irradiation, radical neck dissection, or a combination of both. Zanation et al[184] recommend salvage of neck metastases occurring 6 months or more after treatment of the primary site to be treated with combined surgery and RT. They showed a clear disease-free survival advantage (59% vs 14%) in patients with combined modality therapy versus single modality in the salvage setting.

Hollen et al reviewed 26 patients with untreated nasal cavity ENB at the University of Florida.[185] For patients with Kadish stages B and C, ultimate neck control was 100% at 5

years for patients who received ENI versus 69% among those not receiving ENI ($P < .05$).

In summary, the risk of subclinical disease is high, with regional recurrence rates approaching 30% to 40% at 10 years from initial therapy for high-grade tumors (Kadish stages B and C). ENI is an effective therapy for reducing nodal relapse to less than 5%; however, given the additional acute and late toxicity with prophylactic irradiation, controversy exists over the optimal treatment strategy and sequencing as multiple studies show that salvage of isolated nodal relapse is highly effective and may not lead to differences in OS compared to upfront ENI.

Radiation Therapy Techniques

Treatment techniques are similar to those described for the treatment of paranasal sinuses (see Chapters 48). When combined therapy is used, preoperative doses of 45 Gy and postoperative doses of 50 to 60 Gy are indicated, depending on the status of the surgical margins. Doses of 65 to 70 Gy are delivered with irradiation alone in patients with inoperable or subtotally resected tumors at 1.8 to 2.0 Gy per treatment.[154,157,174] Contrast-enhanced CT or MRI scans before initiation of treatment are crucial to demarcate the extension of the tumor and delineation of normal anatomy.[186] Because of the proximity of ENB to the optic nerves, the optic chasm, and the brainstem, the precision of treatment setup, target volume definition, and dose homogeneity dictate tumor control and the sequelae of treatment. High doses per fraction (exceeding 2 Gy) increase the possibility of late sequelae, such as blindness and bone and brain necrosis. Some institutions use hyperfractionation 1.2 Gy twice daily when treating tumors adjacent to the optic apparatus.[154,187] IMRT and particle therapy, including both proton and heavy ions, provide excellent outcomes for the treatment of ENB (Figure 54.16). Special attention should be directed to reduce unnecessary irradiation to ocular structures, including optic nerve(s) and chiasma. While not indicated for all cases as previously discussed, when delivered ENI should include the primary nodal echelon, which includes levels 1B and II and the retropharyngeal lymph nodes.

FIGURE 54.16 Representative proton therapy plan covering the primary site and lymph node volumes to a total dose of 54 GyRBE with proton therapy. This technique minimizes the dose to developing brain tissue, cochlea, and oral cavity. PTV, planning target volume. (From Drescher NR, Indelicato DJ, Dagan R, et al. Outcomes following proton therapy for pediatric esthesioneuroblastoma. *Pediatr Blood Cancer*. 2024;71[2]:e30793. Copyright © 2023 Wiley Periodicals LLC. Reprinted by permission of John Wiley & Sons.)

Of note, attention to be made to the CTV extension along the dural, in particular for tumors with intracranial extension. Yu et al[188] reviewed 38 patients from a single-institutional retrospective series. Over half of the patients had intracranial extension at diagnosis. The dura was the most commonly involved site of relapse, and the 8-year dural disease-free survival was 57% versus 90% (P = .017) with and without intracranial extension. After dural recurrence, the median survival time was 42 months; however, salvage treatments were effective in rare cases of isolated low-volume recurrence.

Results of Therapy

Surgery and Irradiation

Platek et al,[189] in an analysis of SEER data (1973-2005) of 135 cases of ONB, noted that 59% of the patients were treated with surgery and RT, 23% with surgery only, 12% with RT only, and 6% with neither. No data on chemotherapy administration were available. The 5-year survival with surgery plus RT was 66%, with surgery only 51%, with RT only 26%, and with other therapy 34% (P = .003).

RT is an important component in the management of ENB, but the optimal sequence when integrated with surgery is unknown. Eden et al[190] observed no significant difference in survival whether preoperative or postoperative irradiation was given, but suggested improved local tumor control with preoperative irradiation. Technical factors may have contributed to a higher incidence of postoperative RT failures because three of five postoperative cases received <50 Gy; all three patients were treated with a single anterior field, which gives less homogeneous dose distribution throughout the treatment volume.

Foote et al[157] updated the experience of the Mayo Clinic. Seventeen patients had disease confined to the nasal cavity or paranasal sinuses (Kadish stages A and B), and 32 patients had more advanced disease. Treatment included either gross total resection alone or combined with RT. The 5-year actuarial survival, disease-free survival, and local tumor control rates were 69.1%, 54.8%, and 65.3%, respectively. Local tumor control was improved in patients who received postoperative irradiation (55.5 Gy), even after complete tumor resection.

Levine et al[191] conducted a retrospective review of 35 patients; 6% of them presented with cervical metastasis, and ultimately 25.7% developed cervical metastases. Fourteen percent of the patients had a local recurrence at an average of 6 years after diagnosis, and in 37%, at least one episode of metastatic disease occurred. The disease-free survival was 80.4% at 8 years. CNS complications occurred in 25.7% of patients, orbital complications in 22.9%, systemic post-treatment problems in 20%, and chemotoxic sequelae in 18%.

Eriksen et al[192] carried out a retrospective review of 13 patients with ENB (Kadish stage A 1 patient, stage B 5 patients, and stage C 7 patients). The 5-year disease-free survival was 51%. Forty-six percent of the patients experienced relapse, and despite intensive salvage therapy, median survival after recurrence was only 12 months.

Chao et al[193] reported on 25 patients with ENB (Kadish stage A in 3 patients, stage B in 13 patients, C in 8 patients, and modified D in 1 cervical nodal metastasis patient); 17 patients were treated with surgery and RT, 6 with irradiation alone, and 2 with surgery only. Eight patients received neoadjuvant chemotherapy. The median follow-up was 8 years. The 5-year actuarial OS, disease-free survival, and local tumor control rates were 66.3%, 56.3%, and 73%, respectively. Kadish stage was not a significant prognosticator for local tumor control or disease-free survival. Five-year local tumor control was 87.4% for combined surgery with RT and 51.2% for irradiation alone. Two patients with Kadish stages A and B disease underwent surgical resection alone; both failed locally. In contrast, only three of nine patients with Kadish stage A or B disease who received ART had a local recurrence. With ART, the surgical margin status did not influence local tumor control.

Chemotherapy and Irradiation

Eden et al[190] described results in 16 patients with stage A or B disease and 24 patients with stage C disease treated with irradiation (median dose 50 Gy) and surgery for stage A and B diseases, with the addition of chemotherapy (cyclophosphamide and vincristine) for stage C disease. Actuarial survival rates at 5 and 10 years were 78% and 71%, respectively. Locoregional failure developed in 15 of 40 patients; 68% of the failures were locoregional (including the brain, neck, facial bone, and sinus). They had no recurrences at the primary tumor bed; all recurrences were either outside the irradiation field or at distant sites.

Preoperative neoadjuvant therapy may provide a valuable complement to radical resection if there is expected high morbidity with surgery.[194]

Konuthula et al[195] analyzed 90 patients with Kadish stages C and D ENB in the NCDB, with 55% treated with definitive radiation (RT) (median dose 59.4 Gy) and 45% receiving chemotherapy. The mean follow-up was 57.1 months. There was no difference in 5-year

survival between the patients who received RT and those treated with RT and chemotherapy (74.8% vs 64.4%). There was also no difference in survival between whether a clinically node-negative neck was treated with RT (72.9% vs 67.0%).

Sequelae of Treatment

Treatment sequelae depend on the dose of irradiation and the location and extent of disease. Reported severe toxicities that can occur when treating sinonasal tumors include bone necrosis, brain necrosis or abscess, blindness, or painful eye reactions requiring enucleation. This is because of the sensitive adjacent normal tissues and the extensive surgeries and high doses indicated. Some studies note that the risk of severe grade 3+ toxicity regardless of radiation modality approaches one-quarter of patients.[154,196] A summary of studies evaluating late visual impairment is shown in Table 54.12.

TABLE 54.12 STUDIES REPORTING TREATMENT OUTCOME AND LATE GRADE 3 VISUAL IMPAIRMENT AFTER CONFORMAL RADIOTHERAPY THERAPY FOR SINONASAL TUMORS

Author (Reference)	Number of Patients	Treatment	Median Dose (Gy)	Follow-Up (Months)	Local Control (Year)	Overall Survival	Grade 3 Visual Morbidity
Claus et al[197]	32	IMRT+/−S	70	15	NR	80% (1 y)	0
De Leo et al[198]	148	PT	73.8	49	85% (4)	89% (4)	5
Duthoy et al[199]	39	IMRT+S	70	31	68% (4)	59% (4 y)	2
Combs et al[200]	46	IMRT+/−S	64	16	81% (2)	90% (2 y)	0
Hoppe et al[201]	30	IMRT+S	60	23	NR	NR	0
Daly et al[202]	36	IMRT+/−S	70	39	58% (5)	45% (5 y)	0
Dirix et al[203]	25	IMRT+S	60	27	81% (2)	88% (2 y)	0
Madani et al[170]	84	IMRT+/−S	70	40	70% (5)	58.5% (5 y)	1
Li et al[204]	514	PT based	70	58			22

IMRT, intensity-modulated radiation therapy; NR, no report; PT, proton therapy; S, surgery.

Modified from Madani I, Bonte K, Vakaet L, Boterberg T, De Neve W. Intensity-modulated radiotherapy for sinonasal tumors: Ghent University Hospital update. *Int J Radiat Oncol Biol Phys*. 2009;73(2):424-432. Copyright © 2009 Elsevier. With permission.

Simon et al,[205] in 13 patients with olfactory ENB treated with surgery and RT, noted that one patient lost vision as a result of glaucoma and radiation retinopathy after 67.3 Gy in 34 fractions. One patient treated with 61.8 Gy in 34 fractions developed a visual field defect and optic atrophy and also had a nasal cutaneous fistula. One patient sustained intraoperative rupture of the ocular globe and subconjunctival hemorrhage.

Lucas Jr et al[206] reported on a small series of pediatric patients treated with proton RT. Four patients developed radiation- related late toxicities, including endocrine dysfunction, two cases of grade 2 retinopathy, and one case of grade 3 optic neuropathy.

Drescher et al[164] described the outcomes of 15 pediatric patients treated with PT. Serious late toxicity included major reconstructive surgery (n = 2), symptomatic retinopathy (n = 3), cataracts requiring intervention (n = 2), chronic otitis media requiring antibiotics (n = 2), chronic keratoconjunctivitis requiring antibiotics (n = 2), hypothyroidism requiring hormone replacement (n = 2), and in-field basal cell skin cancer (n = 1).

NASOPHARYNGEAL ANGIOFIBROMA

Epidemiology

Juvenile nasopharyngeal angiofibroma (JNPAF) is found more frequently in young pubertal boys; it has been shown to contain androgen receptors[207] and, occasionally, to regress with estrogen therapy. Hwang et al,[208] in 24 nasopharyngeal angiofibromas, detected androgen receptors in 18 (75%) of 24 cases, whereas only two (8.3%) were positive for progesterone. None of the 24 cases was positive for antibodies to estrogen.

The tumor is believed to originate from the posterior-lateral wall of the nasal cavity where the sphenoidal process of the palatine bone meets the horizontal ala of the vomer and the roof of the pterygoid process because it is always involved.[209] Other investigators agree, because the involution of tumor after irradiation usually occurs in this direction.[210]

JNPAF comprises <0.05% of H&N tumors. Patient's age at presentation ranges from 9 to 30 years, with a median of 15 years. Females comprise <4% of the total cases.[211]

Clinical Presentation and Pathology

Symptoms usually occur 2 to 48 months before diagnosis. The most common complaints are nasal obstruction or epistaxis, followed by nasal voice or discharge, cheek swelling, proptosis, diplopia, hearing loss, and headaches.[212] Nasopharyngeal angiofibroma may initially extend into the nasal fossae and maxillary antrum and push the soft palate downward and then through the pterygopalatine fossa and superoanteriorly through the inferior orbital fissure or laterally through the pterygomaxillary fissure to the cheek and temporal regions.[211]

Beham et al,[184] in a study of 32 cases of JNPAF, noted that most of the tumor vessels, which lacked elastic laminae, were characterized by vascular walls of irregular thickness and variable muscle content. In places, endothelial cells were separated from the stroma by only a single attenuated layer of contractile cells; in some more fibrotic hyaline areas, the stromal cells displayed reactivity for smooth muscle actin. The irregularity of the vascular walls, together with the lack of elastic laminae and stromal fibers, explains the pronounced tendency for hemorrhage in these lesions.

Differential diagnosis includes fibrosarcoma, rhabdomyosarcoma (RMS), chronic sinusitis, arteriovenous malformation, lymphangioma, neurofibroma, pleomorphic adenoma, lymphoma, pyogenic granuloma, polyps, and hemangioma.

Diagnostic Workup

After the history and physical examination, CT scans or MRI with and without contrast should be obtained. Characteristic findings are a mass in the posterior nasal or pterygopalatine fossa and bone erosion in the sphenopalatine foramen and extension to the pterygoid plate. The pattern of enhancement in this highly vascular tumor is diagnostic, and many investigators believe carotid angiograms are unnecessary after CT diagnosis of the lesion, unless embolization, which is also controversial, is contemplated. CT scans are especially helpful in regions involving thin bony structures (paranasal sinuses, orbits) and MRI to evaluate the nasopharynx and parapharyngeal space, including special resolution of soft and nervous tissues and intracranial extension.[186,209,211]

Seventy-two patients with JNPAF were evaluated with CT or MRI.[186] Origin of the tumor was in the pterygopalatine fossa at the aperture of the pterygoid (vidian) canal. The tumor extended posteriorly along the pterygoid canal, with invasion of the cancellous bone of the pterygoid base and greater wing of the sphenoid in 60% of the patients. The inability to remove the tumor in toto was principally due to deep invasion of the sphenoid; 93% of recurrences occurred with this type of tumor extension.

Biopsies are not indicated in all patients because of the potential for severe hemorrhage. It is important to perform a biopsy of the lesion when the clinical picture (sex, age, location, and behavior of the lesion) is not consistent with JNPAF because some lesions have proven to be sarcomas or chronic sinusitis.[209] While rare, cases of fibrosarcoma have been reported in patients in their 40s.[213]

Staging and Prognostic Factors

Staging schemes have been proposed by Chandler et al,[209] a radiographic staging system by Sessions et al,[210] and a more detailed anatomic system by Radkowski et al[214] In a retrospective review of 44 cases of JNPAF, invasion of the skull affected two-thirds of the patients, and the rate of recurrence was 27.5%.[215] Extensions to the infratemporal fossa, sphenoid sinus, base of pterygoids and clivus, the cavernous sinus (medial), foramen lacerum, and anterior fossa were correlated with more frequent recurrence.[216]

General Management

Optimum management of these patients remains controversial, and the decision of whether surgery or RT should be used depends, in part, on the initial extent of the disease. In patients with extracranial tumors,[215] surgery is the treatment of choice and yields near-zero mortality or any long-term morbidity.[217] Tumor extension to the posterior infratemporal fossa or intracranially is associated with a higher risk of recurrence.[218]

Residual tumor in symptom-free patients should be kept under surveillance by repeated CT scanning, because involution may occur. For patients with recurrent, unresectable tumor with symptoms or progression, RT may be used if further surgical resection is either highly morbid or technically not feasible.[211,212,217] When there is intracranial tumor extension (seen in about 20% of patients), the risk of surgically related death increases.

Some investigators consider preoperative intra-arterial tumor vessel embolization at the time of diagnostic bilateral carotid angiography, claiming a decrease in operative bleeding.[219] Salvage with embolization of polyvinyl alcohol has been described.[220] Others have reported anecdotal evidence of partial regression with the use of estrogens, believed to be the result of feedback inhibition of the pituitary's production of gonadotropin-releasing hormone.

Although RT is equally effective in extracranial tumors, the low but existing risk of secondary malignancies should limit its use to the more advanced tumors only, such as those involving the orbital apex or the base of the skull in which curative resection with low morbidity is unlikely.[211] In the experience of Cummings et al[212] covering 20 years, only two radiation-related malignancies were noted (one skin, one thyroid).

Radiation Therapy Techniques

Conformal techniques are recommended with either IMRT or PT. Because of the young age of the patient and excellent survival, techniques to reduce integral dose such as protons should be considered when available. Positive microscopic margins or history or recurrence in the setting of radiographic complete resection are not indications for RT. CTV is defined as the entire pterygopalatine fossa and inferior orbital fissure on the ipsilateral side plus 5 to 10 mm expansion of the GTV in all directions edited to anatomic boundaries of tumor spread (Figure 54.17). The recommended tumor dose ranges from 30 to 36 Gy at 1.8 to 2 Gy per treatment. Doses of 36 Gy provide approximately 90% tumor control. Focal boosts to 40 to 50 Gy in 20 to 28 fractions in 5 weeks can be considered to areas of gross residual tumor for select cases.[211] Target definitions and treatment approaches used at the Mayo Clinic Florida are summarized in Table 54.13.

TABLE 54.13 TREATMENT OPTIONS FOR THE MANAGEMENT OF JUVENILE NASOPHARYNGEAL ANGIOFIBROMA

Indication for RT	Visible tumor on CT or MR scans in a situation where curative resection with low morbidity is unlikely
RT dose	36 Gy at 1.8 Gy per treatment. May consider boosting gross tumor to 40-45 Gy in selected cases for patients > than age 18 y and no gross tumor abutting the optic apparatus
RT technique	In most cases, photon-based IMRT; can consider proton therapy to reduce integral dose
GTV	Visible tumor on CT and MRI
CTV	CTV = the entire pterygopalatine fossa and inferior orbital fissure on the ipsilateral side plus 10 mm expansion from the GTV edited for barriers to tumor spread. There is no elective nodal irradiation.
PTV	CTV plus 3 mm based on institutional practice and daily CBCT image guidance

Current treatment practice at the Mayo Clinic Florida.

CBCT, cone-beam computed tomography; CTV, clinical tumor volume; D(0.1 mL), maximum dose to 0.1 mL; D_{max}, maximum dose; GTV, gross tumor volume; IMRT, intensity-modulated RT; MRI, magnetic resonance imaging; PTV, planning tumor volume; RT, radiation therapy.

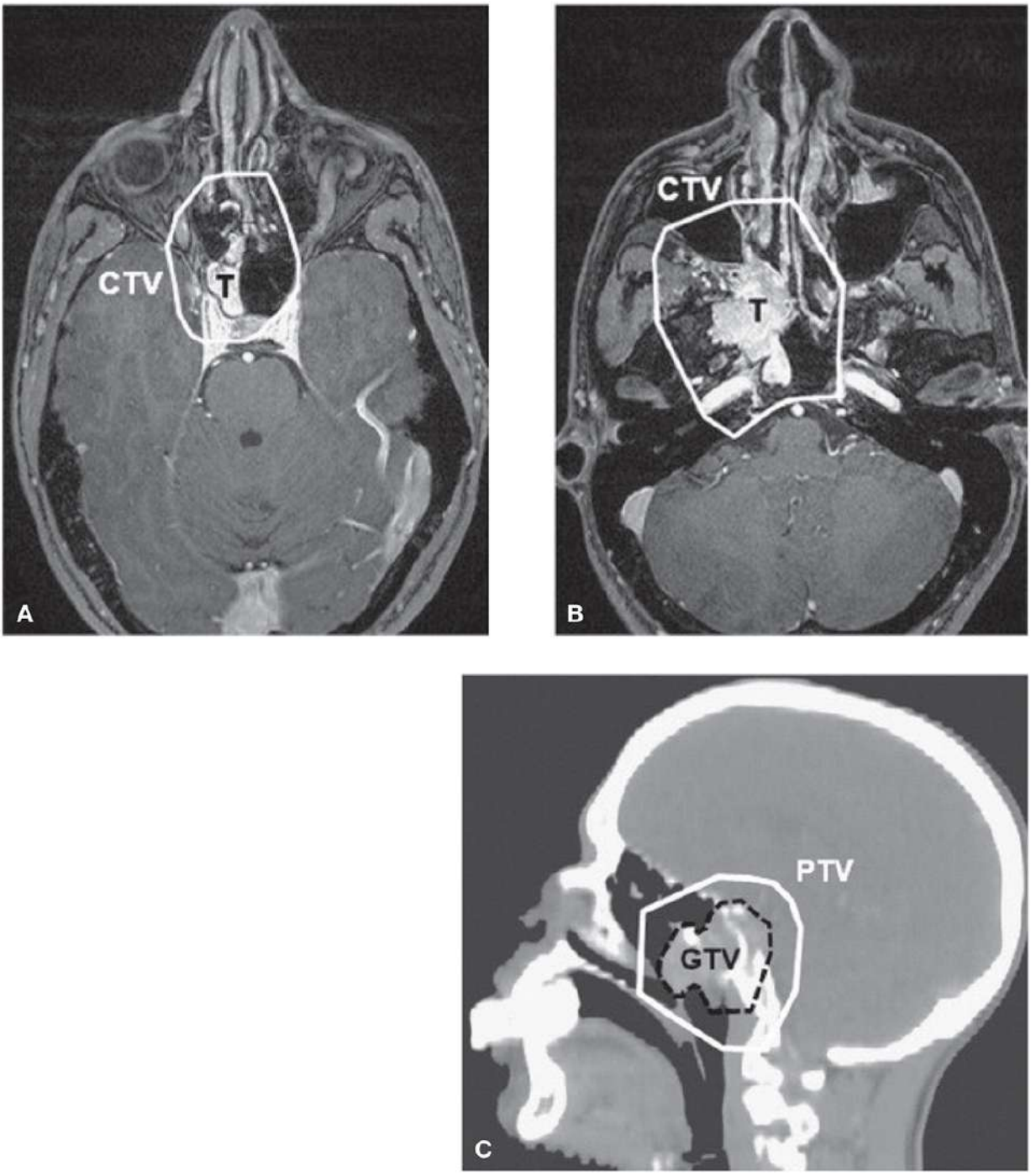


FIGURE 54.17 (A and B) The contrast-enhanced, T1-weighted magnetic resonance scan fused to simulation computed tomography (CT) scan (C). In A and B, the tumor is bright white, indicating that it is highly vascular. In (A), the tumor (T) involves the right side of the sphenoid sinus and the posterior portion of the inferior orbital fissure and nasal cavity. In (B), the tumor (T) epicenter is in the pterygomaxillary fossa and the tumor involves the medial portion of the infratemporal fossa and the posterior portion of the nasal cavity. The white line in (A and B) is the CTV, which puts a margin of a least 1 cm on the gross tumor volume (GTV) in areas where there is no barrier to tumor spread. When tumor involves a portion of the sphenoid sinus, we cover the entire sinus in the CTV. **C** is the midline sagittal reconstruction CT image showing the GTV and PTV (CTV + 1 mm). CTV, clinical tumor volume; PTV, planning target volume. (Reprinted from Amdur RJ, Yeung AR, Fitzgerald BM, Mancuso AA, Werning JW, Mendenhall WM. Radiotherapy for juvenile nasopharyngeal

angiofibroma. *Pract Radiat Oncol*. 2011;1[4]:271-278. Copyright © 2011 American Society for Radiation Oncology. With permission.)

The advantages of IMRT for the treatment of extensive or recurrent JNPAF were described in three patients on whom the tumor affected the base of the skull, pterygopalatine, infratemporal fossae, posterior orbit, and nasopharynx.[219] Tumor dose varied from 34 to 45 Gy. Chakraborty et al[221] treated eight patients with IMRT for stage III tumors (median dose 39.6 Gy). LC at 2 years was 87.5%, and toxicity was minimal (persistent rhinitis in one patient). Significant sparing of the surrounding OARs was obtained. No grade 3/4 toxicities were experienced.

Results of Therapy

In a surgical report, 18 patients were treated with gross tumor excision; two cases with intracranial involvement required a combined neurosurgical-otolaryngologic approach.[222] Recurrent intracranial disease was detected by MRI in three patients, who were treated with 35-, 36-, and 45-Gy external beam irradiation. Extracranial tumor recurrences were reexcised in seven patients. All patients (followed up with serial MRI) are living without evidence of active disease.

Cummings et al[212] treated 42 patients primarily with irradiation and 13 for postsurgical failures; all except six had biopsies. Nine had stage IV disease according to Chandler's staging system. Dose was 30 to 35 Gy in 14 to 16 fractions over a 3-week period. Follow-up ranged from 3 to 26 years. The control rate was 80% and was equivalent for all dose ranges. Of 11 recurrences, 8 were controlled by a second course of irradiation and 3 by surgery. These tumors regress slowly, with 50% still present at 12 months. At 24 months, 23% of tumors were still present, and half of those recurred. Of the complete responders, only 1 of 33 had a recurrence.

At the Mallinckrodt Institute of Radiology, Fields et al[223] reviewed the authors' experience with 13 patients: 11 surgical failures and 2 primarily treated with irradiation. Intracranial extension was noted in 38% of patients. Follow-up ranged from 40 to 173 months. Doses ranged from 36 to 52 Gy, with a median of 48 Gy (1.8-2 Gy per fraction, 5 days a week). The control rate was 85%; patients failing irradiation were salvaged with embolization. Late morbidity was primarily xerostomia and dental decay.

Ungkanont et al[224] described results in 20 patients treated before 1974 and 23 treated between 1975 and 1993: 31 had surgery (18 with preoperative embolization), 3 had irradiation, 7 received chemotherapy (4 combined with surgery), and 2 were observed. Disease-free survival was 67%; 28% of patients survived with residual tumor, and 4.6% died of surgical complications. Roche et al[225] treated 15 patients with JNPAF with various maxillofacial surgical resections, combined with Gamma Knife radiosurgery in 2 patients and external RT in 4 patients. With a median follow-up of 108 months, 12 patients were tumor free and 2 had no progression. All patients had normal or near-normal quality of life.

Tumor regression usually occurs slowly after either irradiation[212] or chemotherapy[226]; therefore, the presence of tumor up to 2 years after treatment is not an invariable sign of failure unless it is symptomatic or progressing. McAfee et al[227] treated 22 patients with JNPAF with definitive RT (30-36 Gy); with a median follow-up of 12.7 years, 20 (91%) patients had tumor control. The two patients failing were salvaged with surgery. No major treatment morbidity was noted. Kasper et al,[228] in nine patients treated with RT (30-35 Gy), observed 25% to 50% initial tumor regression within 1 year. Eventually, seven of the patients had complete clinical tumor regression, but on CT or MRI, only two of seven had no residual disease.

The management of large JNPAF with intracranial extension is complex. In 18 patients with JNPAF, preoperative MRI, embolization of feeding branches from the external carotid artery, and attempted complete resection were used in seven patients with intracranial disease[222]; serial MRI scans were used for follow-up. Intracranial disease that was persistent or recurrent and demonstrated subsequent growth was irradiated (35-45 Gy) or reexcised.

Wiatrak et al[229] reported on three patients with extensive intracranial extension treated primarily with RT doses of 36.6, 40.0, and 50.4 Gy, respectively, without surgical tumor resection. Although there was no complete resolution of the tumors, significant improvement of symptoms was obtained without serious sequelae.

Ochoa-Carrillo et al[230] reported on 31 patients treated with surgery or RT. Surgery was the treatment chosen in patients with stage II and III diseases, whereas RT was the treatment in stage IV, but it had low effectiveness, indicating the need to carefully investigate the value of surgical approaches in these tumors. RT (30-55 Gy) was administered to 16 patients: seven with stage III persistent or recurrent tumor, and eight patients as initial treatment for stage IV disease. The disease-free interval of patients with stage III and IV diseases was 80.3% and 19%, respectively, after 36 months of follow-up.

Tranbahuy et al[231] reported on seven patients with juvenile angiofibroma who underwent direct tumoral embolization. This technique induced marked devascularization and necrosis of the tumor. No neurologic sequelae were encountered.

Goepfert et al[226] reported on five patients with aggressive nasopharyngeal angiofibromas recurrent after extracranial resection and irradiation who were treated with chemotherapy. Doxorubicin (60 mg/m^2 intravenous push for 1 day) and dacarbazine (250 mg/m^2 intravenous drip for 5 days) were given, with courses being repeated every 3 to 4 weeks. In a second regimen, vincristine, dactinomycin, and cyclophosphamide were administered at usual doses. Excellent tumor regression was noted in all patients. Patients were disease free at 2, 3, 6, and 10 years.

Amdur et al[211] reported the outcomes of 24 patients treated with RT. The standard dose in the first half of the series was 30 Gy in 22 treatments (1.43 Gy/treatment), but was increased to 35 to 36 Gy at 1.8 Gy/treatment because increased recurrences with the lower dosing regimen. Elective nodal coverage was omitted and all recurrences were at the primary site within 5 years of completing therapy. While LC was 77% with those who received <32 Gy versus 91% with those treated with 35 to 36 Gy. All recurrences

following RT were successfully salvaged with surgery, and no patient had a significant growth abnormality or second tumor.

Sequelae of Therapy

Most investigators agree that surgical morbidity and mortality increase with intracranial extension of the tumor. The most common RT sequelae include delayed growth secondary to hypopituitarism and decreased bone maturation.[232]

Malignant degeneration in JNPAF undergoing RT has been occasionally reported,[233,234] and there are several documented cases of radiation-induced sarcomas in these patients.[212,235] Spagnolo et al[235] reported on four patients treated with irradiation who later developed sarcoma. Cummings et al[212] reported two neoplasms developing 13 and 14 years after irradiation; one was a basal cell carcinoma and the other metastatic thyroid carcinoma. Both patients are alive without disease. Two patients developed cataracts.

Mucosal Melanomas

Primary mucosal melanomas (MMs) of the H&N area constitute 2% to 8% of the cases seen each year in the United States.[236] They compose approximately 1% of all melanomas and about half arise in the H&N. They occur more commonly in countries such as Japan, where MM is found in 22% to 32% of patients with malignant melanoma. Most occur in the fifth to seventh decades of life; they are extremely rare in the first two decades (0.6% of MMs).[237] A review by Batsakis[238] of 204 MMs showed 56.4% to be from the upper respiratory tract and 44% from the oral cavity and pharynx. Nasal cavity or paranasal tumors comprise <1% of malignant melanomas and 2% to 9% of H&N melanomas.[239] Pigmentation may precede the lesion in up to 28% of patients for more than 1 year.[240] In the oral cavity, the most common location is the hard palate (up to 80%), followed in order of decreasing frequency by the upper gingiva and lower gingiva.

Diagnostic Workup

Summary diagnostic workup is found in Table 54.6.

An excisional biopsy should be performed when feasible with incisional or punch biopsy an acceptable alternative.[241] Batsakis[238] found that one-third of these lesions were amelanotic, and Hoki et al[239] noted that 25% were amelanotic.

Metastatic melanoma to the mucosa of the H&N area is less common. It can be differentiated from primary tumors by the presence of normal tissue between subepidermal tumor and the basal layer of melanocytes.[238] PET-CT should be used to identify metastases because of its high sensitivity in detecting both regional lymph node involvement and distant metastatic spread.

Management and Results of Therapy

Primary management is surgical resection. Because some have shown over one-third of patients may have associated adjacent pigmentation, some investigators recommend prophylactic excision of all adjacent melanocytic nevi. Results with irradiation are comparable with those of surgical series, with most patients having distant progression. Because of the poor survival of these patients because of distant metastases and not locoregional failure, primary RT with salvage surgery is an alternative for MMs of the H&N.[242] ENI is not indicated in all patients, as only few develop nodal metastasis.[243]

In a review of the Japanese literature, Umeda et al[244] found a local tumor control rate for stage I and II diseases of 58% (7/12) in surgically treated patients with oral melanomas and a minimum follow-up of 3 years. Similar rates of failure have been reported, even with radical en bloc excisions (20%-42%). Because the main cause of treatment failure is distant metastases and because almost no patient has clinically evident nodal metastases at presentation, an elective neck node dissection is not consistently recommended. This subject is still controversial, as 30% to 60% of patients may later develop nodal disease.[245]

Harwood and Cummings[246] treated 12 cases and added 12 cases from the literature for a total of 24 patients and 25 lesions. Local tumor control was achieved in 11 of 24 (9-54 months' follow-up). Six of seven tumors treated with 4-Gy fractions or larger were controlled, versus 5 of 18 treated with smaller fractions. Saigal et al[243] treated 17 patients with MMs (sinonasal tract in 11, oral cavity in 6) with surgery (16 combined with RT) and 1 with RT. Seven patients received adjuvant immunotherapy. With a median follow-up of 35.2 months, local tumor control at 5 years was 81%, disease-free survival 44.5%, and OS 51.5%.

Krengli et al[247] reported on 74 patients with upper aerodigestive tract MMs (31 nasal and 12 oral), 17 treated with SA, 42 with surgery and RT (median dose 60 Gy, 2-Gy fractions), 11 with RT alone, and 4 with chemoimmunotherapy. At 3 years, the local recurrence was 43% with SA and 29% with surgery plus RT. Grade 3 mucositis was noted in nine patients.

Kingdom and Kaplan[248] described results in 13 patients with MM of the nasal cavity and paranasal sinuses treated with surgical resection. Eight had microscopically negative margins. Seven patients received postoperative irradiation (30-62 Gy). The neck was treated in three patients with doses of 30 to 50 Gy. The local tumor recurrence rate was 85% (11/13), with a mean interval from primary tumor treatment to recurrence of 16 months. Metastatic neck disease developed in two patients and distant metastases in four. Patients receiving postoperative irradiation had increased disease-free interval and prolonged survival. Negative surgical margins were not predictive of a more favorable outcome. The investigators recommend resection of tumor with negative margins and postoperative irradiation for the treatment of all patients with mucosal malignant melanoma.

Zenda et al[249] treated 14 patients with H&N MMs using protons (60 Gy in 15 fractions, 3 fractions per week). With a median follow-up of 36.7 months, the 3-year local tumor control was 85.7% and OS 58%. The most frequent failure site was the cervical nodes (six patients). Two patients developed late decreased visual acuity.

Immunotherapy

Actionable mutations in melanoma including KIT mutations, TRK fusions, and BRAF mutations are under investigation. Checkpoint inhibitors have become a mainstay in therapy for cutaneous melanoma. Their role in MM is uncertain and not well studied, and both the indications and sequencing with surgery and radiation are still under investigation.[250]

D'Angelo et al[251] performed a pooled analysis of 889 patients who received immunotherapy, of which 86 (10%) had MM. Of those who received nivolumab monotherapy, the median PFS was 3.0 months, and objective response rates were 23.3%. Median PFS in patients treated with nivolumab combined with ipilimumab was 5.9 months with objective response rates of 37.1%. The incidence of grade 3 or 4 treatment-related adverse events rates was similar between the mucosal and cutaneous cohorts and roughly 4-fold higher for combination therapy as compared to monotherapy.

Lechner et al[252] performed an international multicenter retrospective analysis of 505 sinonasal MM cases from 11 international institutions. There was a statistically significant survival benefit for patients who received ART, compared with those who underwent SA (HR = 0.74) and immune checkpoint blockade for the management of recurrent or persistent disease, with or without distant metastasis, conferred longer survival (HR = 0.50, $P = .04$).

Abiri et al[253] reviewed over 1,900 cases of MM in the NCDB. Surgery with immunotherapy was associated with greater OS than SA (HR 0.672; $P = .036$). Surgery and immunotherapy (HR 0.425; $P = .024$) and combination with RT (HR 0.594; $P = .045$) were associated with superior OS than surgery with radiation.

Heavy Particles

Three prospective analyses[254-256] have been conducted on MM treated with CIRT. Patients have generally been treated with 16 fractions to a dose of 57.6 to 70.4 GyE with 2-year LC rates of 80% to 90%, with acceptable anticipated toxicity based on the extent and location of the primary tumor. A representative literature summary is included in Table 54.14.

TABLE 54.14 REPRESENTATIVE LITERATURE SUMMARY OF OUTCOMES FOLLOWING CARBON THERAPY FOR MUCOSAL MELANOMA

Author (Reference)	Number of Patients	Median Total Dose or Dose Range (GyE)	Total Fractions	Median Follow-Up, Months	Local Control Rate	Overall Survival Rate	Grade 3+ Toxicity or Other QoL Outcome
Yanagi et al[256]	72	52.8-64.0	16	49	5 y, 84.1%	3 and 5 y, 46.1% and 27.0%	Acute: None Late: None
Jingu et al[254]	37	57.6	16	19	1 and 3 y,	1 and 3 y, 88.2%	Acute: NR Late: NR

Author (Reference)	Number of Patients	Median Total Dose or Dose Range (GyE)	Total Fractions	Median Follow-Up, Months	Local Control Rate	Overall Survival Rate	Grade 3+ Toxicity or Other QoL Outcome
					90.6% and 65.3%	and 88.1%	
Takayasu et al[255]	21	57.6-64.0	16	16	3 y, 92.3%	3 y, 49.2%	Acute: gr 3 mucositis, 2 pts (10%); thrombocytopenia, 1 (5%) pts, leukopenia, 5 (24%) pts Late: None
Koto et al[237]	260	57.6	16	22	2 and 5 y, 83.9% and 72.3%	1 and 2 y, 96% and 62%	Late: gr 3, 27 pts; gr 4, ipsilateral blindness, 5 pts; mucosal ulcer, 1 pt; 2nd malignant disease in irradiated volume, 1 pt
Demizu et al[257]	29	65 or 70.2	26	14	1 and 2 y, 95% and 59%	1 and 2 y, 96% and 62%	Acute: gr 3 mucositis, 18, gr 3 dermatitis, 7 Late: gr 3, periodontal disease, 1 pt; gr 4, nasal bleeding, 1 pt
Hayashi et al[258]	21	54.0 (40.0-64.0)	8-16	27	2 y, 40.5%	2 y, 59.6%	Analyzed patients with recurrent disease Toxicities reported for entire cohort of 48 pts Acute: gr 3 acute toxicities, 5 (10.4%) pts Late: gr 3+, 18 (37.5%) pts, including gr 5 CNS necrosis, 1 pt

CNS, central nervous system; gr, grade; pt, patient; QoL, quality of life.

Yanagi et al[256] reported on 72 patients at Chiba who received doses from 52.8 to 64 GyE over 16 fractions in 4 weeks. With a median follow-up of 49.2 (range, 16.8-108.5) months, the 5-year LC rate was 84.1% and the 3- and 5-year OS rates were 46.1% and 27.0%, respectively. No acute or late toxicities of grade 3 or higher were reported. A 2011 analysis from Jingu et al[254] reviewed 37 patients who received a total 57.6 GyE over 16 fractions. After a median follow-up of 19 months, the 3-year LC, distant metastasis-free survival, and OS rates were 65.3%, 37.6%, and 88.1%, respectively. Toxicities were not reported. MRI minimum apparent diffusion coefficient was a prognostic factor for survival.

More recently, in 2019, Takayasu et al[255] from Gunma published their prospective experience treating 21 patients with MM of the H&N to doses between 57.6 and 64.0 GyE over 16 fractions. After a median follow-up of 15.5 months, the 3-year LC, PFS, and OS rates were 92.3%, 37.0%, and 49.2%, respectively. Regarding serious toxicities, eight

patients developed either grade 3 mucositis (2 patients; 10%), thrombocytopenia (1 patient; 5%), or leukopenia (5 patients; 24%). No patient developed a serious (grade 3 or higher) late toxicity.

Several other retrospective outcomes studies in the treatment of MM with carbon ion therapy were published between 2014 and 2019.[237,257,258] The most recent multicenter study from the J-CROS—which includes investigators from NIRS, Hyogo, Gunma, and HIMAT—is an update of patients reported in earlier series. In this 2017 multicenter study of various H&N histologies, multicenter study from the J-CROS, but this one focused on MM patients alone, Koto et al[237] reported on 206 patients treated with a total 57.6 GyE over 16 fractions. With a median follow-up of 22 months (range, 1-132), the authors reported 5-year LC, PFS, and OS rates of 72.3%, 27.2%, and 44.6%, respectively. A total of 27 grade 3 toxicities and 7 grade 4 toxicities were reported, including ipsilateral blindness (n = 5), mucosal ulcer (n = 1), and a second malignancy in the irradiated volume (n = 1). No late toxicities of grade 3 or higher were reported.

SARCOMAS OF THE HEAD AND NECK

Natural History

Sarcomas account for <1% of malignant neoplasms in the H&N. The histology is complex and requires immunochemical analysis, including angiosarcoma, chondrosarcoma, hemangiosarcoma, leiomyosarcoma, liposarcoma, malignant fibrous sarcoma, neurofibrosarcoma, osteosarcoma, RMS, malignant schwannoma, and synovial sarcoma. Fibrosarcoma, angiosarcoma, leiomyosarcoma, and RMS are the most common types, but this varies in published reports. Distribution of these sarcomas was 33% in the scalp or face, 26% in the orbit or paranasal sinuses, 14% arising from upper aerodigestive tract including the larynx, and 27% in the neck. Synovial sarcomas are rare soft tissue malignancies in the H&N region, accounting for 3% to 5% of H&N tumors. Histologic, immunohistochemical, and characteristic chromosomal translocation findings are necessary for diagnosis. The poor prognosis of this sarcoma justifies radical surgery with postoperative radiation.[259-261]

Radiation-induced sarcoma of the H&N is a rare long-term complication of treatment. The rarity of this tumor is reflected in the very few series reported in the English language medical literature.[262,263] When they do occur, most appear at least 10 years following RT. There is a possibility of a postirradiation sarcoma whenever a suspicious lesion is seen, regardless of the amount of time that has passed since RT was administered. The original pathology should be reexamined to ensure that the original tumor was diagnosed correctly.

The incidence of radiation-induced sarcomas of the H&N is, however, likely to increase due to progressive aging of the population combined with improved survival in patients with H&N cancer. This problem can be extremely challenging, and the overall outlook has been reported to be very bleak. Patel et al[262] reviewed 69 cases reported in the English medical literature since 1966 and pooled this information with their experience in treatment of 10 patients. This group was compared for survival with 124 patients with a diagnosis of H&N sarcoma registered on the Head and Neck Sarcoma database at the

Royal Marsden Hospital. There was no site prediction for radiation-induced sarcoma of the H&N, but malignant fibrous histiocytoma was the most common pathologic diagnosis. The period of latency between initial RT and diagnosis ranged from 9 to 45 years, with a median of 17 years. Surgery was the mainstay of treatment, and follow-up ranged from 6 months to 15 years with a median of 48 months. The actuarial 5-year disease-free survival rate in these patients was 60%.

Clinical Presentation and Diagnostic Workup

Clinical presentation varies with the primary site of disease. Tumors arising from the aerodigestive tract usually present with nasal bleeding, a palpable mass in the neck, or difficulty in swallowing or breathing. In tumors arising from the base of the skull or the nerve sheath, cranial nerve deficit is the most common presentation. Diagnostic workup follows that of soft tissue sarcomas of other sites in the body. With early lesions, radiographs or CT may show only nonspecific opacification, soft tissue swelling, and, occasionally, bone destruction. Table 54.6 outlines the suggested diagnostic workup. MRI, especially with gadolinium contrast, may be used as a supplement or alternative to CT scanning.[262,264] A CT scan of the chest is indicated to complete the staging workup to assess for distant metastasis.

The American Joint Committee on Cancer staging system for soft tissue sarcomas is based on histologic grade, the tumor size and depth, and the presence of distant or nodal metastases. The staging system applies to all H&N soft tissue sarcoma subtypes, with the exception of angiosarcoma, RMS of the embryonal and alveolar subtype, Kaposi sarcoma, and dermatofibrosarcoma protuberans.[265]

Prognostic Factors

Prognostic factors for predicting local recurrence or disease-free survival include anatomic site, treatment modality, tumor histology and grade, tumor size, extension of disease, lymph node metastasis, and surgical margins.[266-268]

A report from Royal Marsden Hospital showed anatomic location and treatment modality to be independent prognostic factors for local recurrence; tumors of the head had a better local RFS than did those of the neck.[267] Patients treated with a combination of surgery and RT had a better RFS than did those treated with surgery or irradiation alone. The only significant independent prognostic factor for OS was the implementation of definitive surgery versus biopsy. In the abovementioned report, the prognostic impact of tumor stage and grade did not reach statistical significance. In contrast, Tran et al[269] reported that 90% of patients with low-grade tumors were free of disease versus only 16% with high-grade lesions.

Bentz et al[270] reviewed 111 patients with H&N sarcoma; median duration of follow-up was 51 months; the actuarial 5-year relapse-free survival, DSS, and OS were 55%, 52%, and 44%, respectively. By multivariate analysis, size and grade significantly influenced all survivals, whereas margin status additionally influenced relapse-free survival.

In 109 soft tissue sarcomas of all sites, a French study demonstrated that quality of the surgery was one of the most important variables for predicting local recurrences. Tumor size, surgical margins, presence of tumor necrosis, and adequacy of the excision correlated with metastasis-free survival.[271]

General Management

Surgery is the preferred initial treatment modality for sarcomas; however, it is often difficult to achieve complete resection of the tumor, and a high recurrence rate has been observed with SA.[272] Extracapsular enucleation of the tumor results in 90% local recurrence because of the presence of microscopic pseudopodia, which tend to grow through the pseudocapsule into the surrounding tissue, and the presence of skipped lesions some distance from the main tumor mass. Pathologic analysis of the surgical bed often discloses microscopic extension of tumor. Farhood et al,[273] in a review of 176 cases of adult H&N sarcomas, reported that the pathologic margins of surgical specimens obtained by wide local excision were positive in >50% of cases. This resulted in inferior OS for sarcomas of the H&N when compared with extremity sarcomas.[274] Wide local excision, with a 5-cm margin around the pseudocapsule in extremity sarcomas, is associated with better outcome, although approximately 20% will have local recurrence. The criteria for surgical resection are impractical for H&N sarcomas because of anatomic limitations[275]; wide local excision is rarely possible because the tumors extend beyond the confines of origin and in the proximity of vital neurovascular structures. Some retrospective studies have suggested improved local tumor control when combined surgery and external irradiation are used. In 130 patients with soft tissue sarcomas of the H&N treated with SA at Royal Marsden Hospital, the overall 5-year survival was 50%; local tumor control was only 47%, and local recurrence was the cause of death in 63% of cases. Patients treated with combined modality treatment (surgery and irradiation) had less extensive surgery, yet local RFS was longer.[267]

Synovial sarcoma in the H&N is rare. In a report of 36 patients, Al-Daraji et al[276] noted there was a predilection for the parotid and the temporal regions, and nine involved skeletal muscle. Of 29 patients followed for a median of 14 years after surgical treatment, 11 were alive and tumor free.

A multidisciplinary discussion before the initiation of treatment is required to formulate the best approach for radiation delivery, surgical technique, and mode of reconstruction.

Radiation Therapy

RT, by external beam or brachytherapy, plays an important adjunctive role in disease management, especially for tumors where en bloc resection with negative margin is not possible.[277] Chemotherapy regimens are available for soft tissue neoplasms, primarily designed to improve local tumor control.[278]

A systematic review of RT trials was performed by the Swedish Council of Technology Assessment in Health Care.[279] This synthesis of the literature on RT for soft tissue

sarcomas is based on data from five randomized trials. Moreover, data from 6 prospective studies, 25 retrospective studies, and 3 other articles were used. In total, 39 scientific articles were included, involving 4,579 patients. The results were compared with those of a similar overview from 1996, which included 3,344 patients. There was evidence that ART improves local tumor control in combination with conservation surgery with negative, marginal, or minimal microscopic positive surgical margins. There are still insufficient data to establish that preoperative RT is favorable compared to postoperative RT in patients presenting primarily with large tumors. The preoperative setting results in more wound complications; however, this rate may be lower when compared to historic rates from extremity soft tissue sarcoma.[280] There is also no randomized study comparing external beam RT and brachytherapy.

Radiation Therapy Techniques

General principles for RT of H&N sarcomas are similar to those of soft tissue sarcomas. Complete coverage of the surgical bed and scar with adequate margins (2-5 cm) is required.[277] However, because of the proximity of critical and radiosensitive organs (eyes, spinal cord, brainstem), highly conformal techniques such as IMRT or particles are indicated to avoid seriously compromising target coverage to meet normal tissue constraints. Techniques similar to those used in epithelial tumors of the H&N can be applied to sarcomas. In general, 50 to 60 Gy is needed for postoperative adjuvant irradiation, and an additional 10- to 15-Gy boost is recommended if the surgical margins are close (≤3 mm) or involved by tumor. Some institutions prefer preoperative irradiation of 45 to 50 Gy. Special attention should be directed to limiting the dose to critical structures. The use of highly conformal radiation techniques such as particle therapy or IMRT (Figure 54.18) allows for optimization of target coverage and sparing of OARs. Target definitions and treatment approaches are summarized in Table 54.15 for patients with soft tissue sarcomas of the H&N. This table does not apply to those with RMS, Ewing sarcoma, and angiosarcoma, nor does it include bone tumors such as chordoma, chondrosarcoma, or osteosarcoma. For those, refer other sections within this chapter and text.

TABLE 54.15 TREATMENT OPTIONS FOR POSTOPERATIVE RADIOTHERAPY FOLLOWING GROSS TOTAL RESECTION OF ADULT SOFT TISSUE SARCOMA[A] OF THE HEAD AND NECK

Indication for RT	Preoperative: Consider preoperative for deep, bulky, or high-grade tumors. In addition, in situations when the tumor is abutting critical organs at risk or if there is uncertainty over expected surgical margins Postoperative: High grade AND >5 cm, R1/R2 resection (low or high grade), scenarios where surgical salvage of local recurrence will not be possible or high risk of morbidity
Preoperative RT dose	Prescription dose 50 Gy in 25 treatments
Postoperative RT dose	R0 resection: 60-64 Gy (1.8-2.0 Gy per fraction) R1 or R2 resection: 66-70 Gy (1.8-2.0 Gy per fraction) We do not currently hypofractionate for head and neck sarcomas, but early clinical investigations are ongoing.

ENI	No ENI: Node negative or when adding ENI significantly increases the risk of acute toxicity or a late complication. Yes ENI: This is rare and only considered in cases of positive nodes or histologies at high risk for nodal spread. ENI dose: 50 Gy at 2 Gy per fraction. In patients with a positive node, we include the area of positive adenopathy in the high-risk target volume and boost to approximately 60 Gy.
RT technique	In most cases, photon-based IMRT; can consider proton therapy to reduce integral dose
GTV	Fuse T1 contrast and T2 sequences from MRI (preferable in treatment position) to treatment planning scan. Define GTV by visible tumor on CT and MRI.
CTV	Resection bed plus 1-2 cm edited for anatomic boundaries to tumor spread
PTV	CTV plus 3 mm based on institutional practice and daily CBCT image guidance

Current clinical practice at the Mayo Clinic Florida for soft tissue sarcoma.

CBCT, cone-beam computed tomography; CTV, clinical tumor volume; ENI, elective nodal irradiation; GTV, gross tumor volume; IMRT, intensity-modulated radiotherapy; PTV, planning tumor volume; R0, margin negative; R1, margin microscopically positive; R2, gross residual tumor.

[a]Soft tissue histologies other than rhabdomyosarcoma, Ewing sarcoma, and angiosarcoma. This does not include bone sarcomas, such as chordoma, chondrosarcoma, and osteosarcoma.

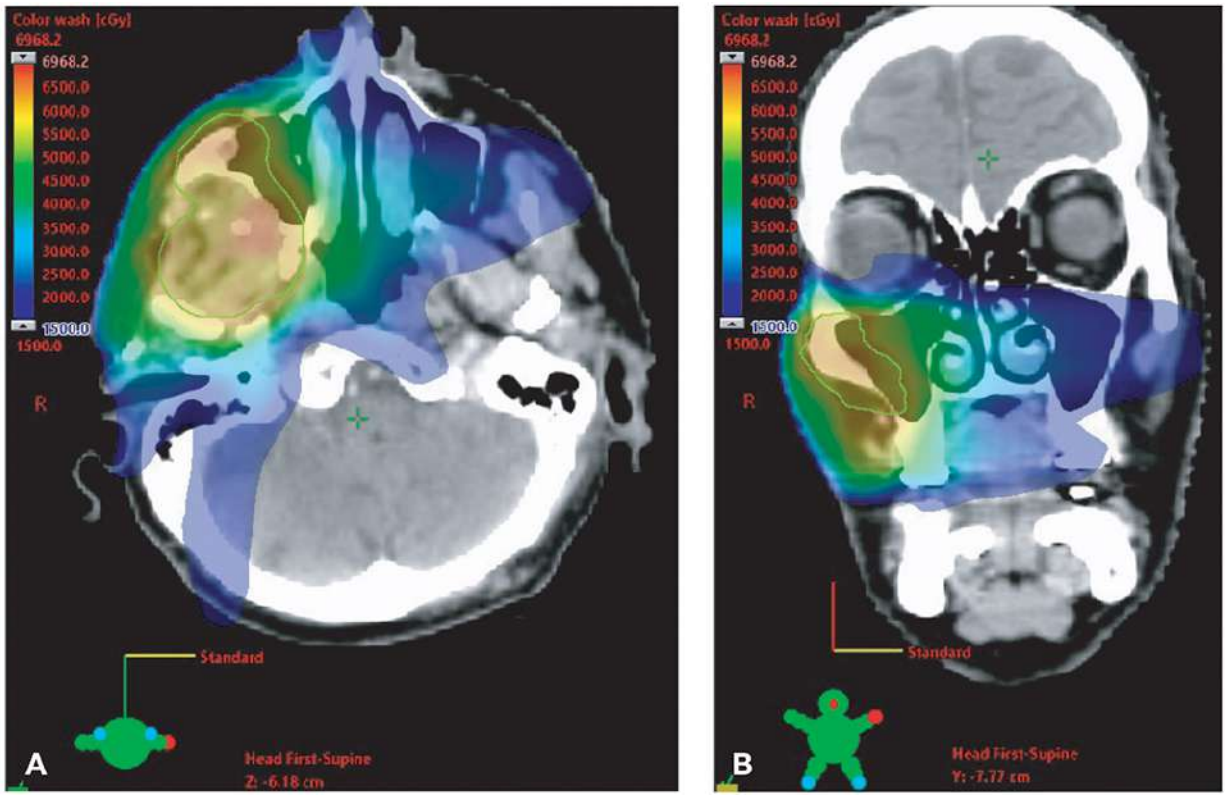


FIGURE 54.18 Representative intensity-modulated radiotherapy (IMRT) plan showing an axial (A) and coronal (B) color wash dose distribution from a computed tomography planning scan of a right maxillary sinus solitary fibrous tumor being treated postoperatively to 60 Gy. The planning target volume is shown in green. Highly conformal techniques such as IMRT allow for reduction in dose to the optic apparatus. (Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

Results of Therapy

Because of the propensity for sarcomas to invade the surrounding tissues, complete surgical clearance may be difficult. In a series from UCLA, attempted en bloc resection left residual tumor at the surgical margins in 52 of 127 patients.[269] The incidence of local recurrence was high (60%) with SA.

In a retrospective report of 73 patients with sarcomas of the H&N treated at Princess Margaret Hospital, the 5-year CSS was 62%, with a local recurrence rate of 41% and a distant metastasis rate of 31%.[264] Extension to adjacent structures, high-grade tumor, and tumor >10 cm were associated with poor survival. Gross residual tumor after surgery was also associated with a high local recurrence rate (75%) despite the addition of RT. Patients with clear surgical margins or only microscopic involvement fared much more favorably and had a similar local tumor control rate (74% and 70%, respectively), provided adjuvant irradiation was given. Because of the difficulty in obtaining wide surgical margins, 68% of the patients died as a result of uncontrolled local disease. These data substantiate the importance of surgical margins as well as the contribution of adjuvant irradiation.[144]

Colville et al[275] reported on 41 male and 19 female patients treated with H&N soft tissue sarcomas, with an overall 5-year survival of 60%. Twenty-five patients had SA, 20 had surgery and pre- or postoperative RT, and 15 received nonsurgical treatment. With a mean follow-up of almost 4 years, the 5-year local tumor control was 56% in the surgical group and 40% in the nonsurgical group (more advanced and aggressive tumors). The 5-year survival was 70% and 40%.

Penel et al[281] recorded their experience with 28 adult H&N soft tissue sarcomas. The most common subtype was RMS (seven cases). Twenty-two patients presented with previous inadequate resection performed elsewhere before admission. Nineteen patients had surgery (complete resection in 13 cases). Associated treatments were neoadjuvant chemotherapy, adjuvant chemotherapy, and postoperative RT in 4, 3, and 10 cases, respectively. The 2-year OS rate was 56%. Wolden et al[282] treated 28 patients with H&N RMS using IMRT (50-55 Gy in 1.8 Gy fractions) combined with chemotherapy. With a median follow-up of 24 months, local tumor control was 95% and 3-year survival 100%. McDonald et al[283] treated 20 children with RMS in the H&N with IMRT (median dose 50.4 Gy, 1.8 per fraction). With a median follow-up of 29 months, the 3-year local tumor control was 100% and survival 76%.

Pandey et al[284] reported on 22 cases of H&N sarcomas (the neck, lower jaw, tongue, cheek, scalp, and maxilla were the most common sites affected). None of the patients had palpable neck nodes or distant metastasis at presentation. All the patients were treated with primary surgical resection, followed by adjuvant treatment in 14 cases (63.6%). After a median follow-up of 14.5 months, two patients died, six developed local recurrence, four developed metastatic disease, and another patient developed a second primary sarcoma. The overall 5-year survival was 80%, whereas the 5-year disease-free survival rate was 24.1%.

Barker et al[285] published a review of 44 patients with nonmetastatic soft tissue sarcoma in the H&N. The most common tumor histologies included malignant fibrous histiocytoma

(15 patients), angiosarcoma (9 patients), fibrosarcoma (6 patients), and leiomyosarcoma (6 patients). The median OS for all patients was 79 months. The actuarial 5-year local tumor control was 55% and was highly correlated with the extent of surgical excision: 25% for subtotal resection or debulking, 65% for wide local excision, and 100% for radical excision. Local tumor control at 5 years was 60% for patients treated with both surgery and RT, 54% for SA, and 43% for radiation alone. ART significantly improved the LC rates (from 25% to 54%) for patients with close (<2 mm) or positive surgical margins. Of 14 patients with locoregional failure in whom salvage was attempted, 9 (64%) were rendered disease free.

Moalikyar et al[286] reported on 40 patients with H&N sarcomas, histologies including undifferentiated pleomorphic sarcoma (9), fibrosarcoma (6), chondrosarcoma (6), angiosarcoma (5), spindle cell sarcoma (3), osteosarcoma (3), and others (7). Tumor sites were the scalp or skin (11), mandible or temporomandibular joint (9), skull base or paranasal sinuses (9), neck (6), or upper airways (6). Histologic grade was low for 13, intermediate for 5, high for 17, and unavailable for 5. All patients underwent gross total tumor resection: 22 (57%) treated with SA, whereas 18 (43%) patients received surgery and postoperative RT. At a median follow-up of 14.9 months, the 2-year OS, LRC, and distant metastasis control were 68%, 73%, and 74%, respectively. Positive margins significantly reduced both 2-year LRC (52% vs 84%; $P = .01$) and OS (42% vs 81%; $P = .004$). The addition of ART did not improve 2-year LC (70% vs 77%; $P > .05$) or OS (58% vs 79%; $P > .05$). However, among the subgroup of patients with positive margins, the use of RT improved 2-year OS (73% vs 0%; $P = .03$) without an associated LC benefit. Similarly, improved 2-year OS was identified for high-grade tumors treated with RT (73% vs 0%; $P = .03$) with no associated LC benefit. Sarcomas of the skull base or paranasal sinuses demonstrated significantly worse 2-year LC (28% vs 86%; $P = .0002$) and OS (0% vs 83%; $P = .001$) than other evaluated subsites.

Huang et al[287] extracted data from 1,525 patients from the SEER database with diagnosis of H&N sarcoma treated between 1973 and 2010. Selected patients had no prior malignancies and no distant metastatic disease. The most common histology was fibrohistiocytic tumors (18.6%), followed by unspecified sarcomas (15.5%), blood vessel tumors (14.0%), liposarcomas (12.1%), and leiomyosarcomas (11.6%). Most tumors were nonspecifically coded as connective tissue of the head, face, and neck (60.3%). After that, the most common site was the skin/scalp (19.6%), followed by nasal cavity/paranasal sinus (4.6%) and oral cavity (3.9%). Of the cohort, 576 (37.8%) patients received RT in addition to surgery.

With a median follow-up of 48 months, the 5-, 10-, and 15-year OS rates were 64%, 49%, and 42%, respectively. The median OS in patients treated with surgery and RT was 82 months, which was inferior to that of 139 months in patients with surgery only ($P < .001$). Multivariate analyses showed that age >60, regional stage, high grade, and tumor size >5 cm were factors associated with worse survival. RT seemed to improve OS, but that result was not statistically significant (HR 0.90, $P = .247$).

Further analyses showed that patients with high-grade tumors had an improved OS by RT (HR 0.78, $P = .017$). The median survival was 59 months in patients with RT versus 45 months in those patients without RT. There was no significant difference in OS among patients with low-grade tumors by RT.

Brandmaier et al[288] also analyzed the SEER database for local H&N cancers diagnosed between 1990 and 2011 that included an array of 12 sarcoma subtypes totaling 1,046 patients. Tumor size and staging data were limited. For all patients with H&N sarcoma, the SA cohort had a 5-year OS of 65.4% compared to 53.3% for patients receiving surgery and ART ($P = .0009$). The 5-year CSS in the surgery cohort was 82.4% compared to 64% in patients receiving surgery and ART ($P < .0001$). Age >75 years was a negative prognostic factor for CSS, relative to age 20 to 39, with an HR of 1.61 ($P = .033$). High-grade histology was also a negative prognostic factor for CSS; grade 3 tumors had an HR of 8.0 relative to grade 1 ($P < .0001$). Among patients with grade 3 sarcomas, those receiving SA had a 5-year OS of 48.2% versus 43.7% for those receiving surgery and RT ($P = .81$).

Among a smaller subset of stage T1N0 grade 3 sarcomas, the 5-year OS for SA was 61.1% versus 51.6% for surgery and RT ($P = .89$). The CSS for the two groups was 77.5% and 71.6%, respectively ($P = .99$).

The authors hypothesized that ART could be beneficial for grade 3 H&N sarcomas, regardless of tumor stage or margin status.

Mahmoud et al[289] using the NCDB evaluated RT utilization pattern and outcome of adjuvant therapies in 2,096 patients with nonmetastatic H&N sarcomas diagnosed between 2004 and 2012, who underwent tumor resection. Chi-square test assessed the cohort that included 1,366 males and 730 females with a median age of 62 years (range: 18-90). Fibromatous sarcoma (20%) and high grades (36%) were the most common histology and grade, respectively. RT delivery was significantly more frequent in high-grade, large tumors with positive surgical margins. At a median follow-up of 36 months, RT use did not impact survival nor did CT, which was delivered in 260 patients. Restricting the survival analysis to 752 high-grade patients, the 5-year OS improved from 43% to 54%, with RT delivery reducing mortality HR by 36% ($P < .001$).

Their analysis showed that ART may improve survival in high-grade H&N sarcomas and that chemotherapy may not be beneficial.

Reported results of treatment of soft tissue sarcomas are summarized in Table 54.16.

TABLE 54.16 TREATMENT RESULTS OF ADULT SOFT TISSUE SARCOMAS OF THE HEAD AND NECK

			5-Y Actuarial Rates	
Author (Reference)	**Number of Patients**	**Modalities**	**Local Control (%)**	**Survival (%)**
Greager et al[290]	48	S, R, C	—	Disease free: 54
Farhood et al[273]	176	S, R, C	—	Overall: 55
McKenna et al[291]	16	S, R, C	75	Disease free: 63

Author (Reference)	Number of Patients	Modalities	5-Y Actuarial Rates	
			Local Control (%)	Survival (%)
Eeles et al[267]	103[a]	S, R, C	47	Overall: 50
LeVay et al[264]	52	S, R, C	59	Cause specific: 63
Tran et al[269]	164	S, R, C	41	Overall: 66
Willers et al[292]	57	S, R, C	60	Overall: 66
Colville et al[275]	60	S, R, C	50	60

C, chemotherapy; R, radiation therapy; S, surgery.

[a]Series based on adults and children, excluding angiosarcomas.

Particles

Because of the dosimetric and potential biologic enhanced effects with particle therapy, protons or heavy ions have been more commonly used for H&N bone and soft tissue sarcomas. Hug et al[293] reported on 27 patients treated at Massachusetts General Hospital in Boston (18 primary and 9 recurrent sarcomas of the H&N close or abutting critical structures with 160-MeV protons; mean dose 68.5 GyE in 2.1-GyE fractions). Local recurrence was seen in eight (29%) patients and regional recurrence in six (22%) patients. Tumor grade had a significant impact on outcome. One patient developed Lhermitte sign and another hypothyroidism.

Jingu et al[294] described results in 27 patients with H&N unresectable bone and soft tissue sarcomas, treated with carbon ions (57.6, 64.0, or 70.4 GyE in 16 fractions). The 3-year local tumor control was 91.6% and survival 72%. Therapy was well tolerated. A comparison with historical results showed that local tumor control rate with 70.4 GyE was significantly higher than that with 57.6 or 64.0 GyE (3-year, 91.8% vs 23.6%, $P < .0001$). Furthermore, the OS with 70.4 GyE tended to be higher than that with 57.6 or 64.0 GyE (3-year, 74.1% vs 42.9%, $P = .09$).

Tumor Characteristics and Prognosis

Several series have shown that tumor grade and size dictate the outcome of patients with H&N sarcomas, such as leiomyosarcoma, RMS, and malignant fibrous sarcoma.[261,267,268,271] Farhood et al,[273] in a review of 176 adult H&N sarcomas, found that only 20% of the patients with high-grade tumors were alive 10 years after treatment, compared with 88% of patients with low-grade tumors.

Some series have reported that chondrosarcoma is not a radiosensitive tumor and that RT has no role in its treatment. However, modern reports have demonstrated efficacy of high-dose RT for patients with this histology. Hasegwa et al[295] performed a retrospective analysis of 32 patients with grade I or II skull base chondrosarcoma treated at the Mayo Clinic. Fourteen (44%) underwent upfront RT, whereas 18 (56%) were followed with serial MRI alone. Of the patients who received upfront ART, the 5-, 10-, and 15-year

cumulative freedom was 100%, 100%, and 67%, in those who received RT as compared to 64%, 64%, and 64%, respectively, in those who underwent upfront surveillance. While RT reduced the risk of early recurrence, this was not statistically significant (P = .250) and many of these patients were salvaged as the 10-year DSS was 95% with no difference between either cohort (P = .50).

Weber at el.[95] reviewed the outcomes from 151 patients treated with proton-based therapy for skull base chondrosarcoma. The 7-year LC rate was 93.6%. Figure 54.19 shows an example illustration of preoperative and postoperative chondrosarcoma status post near-total resection who received postoperative pencil-beam PT.

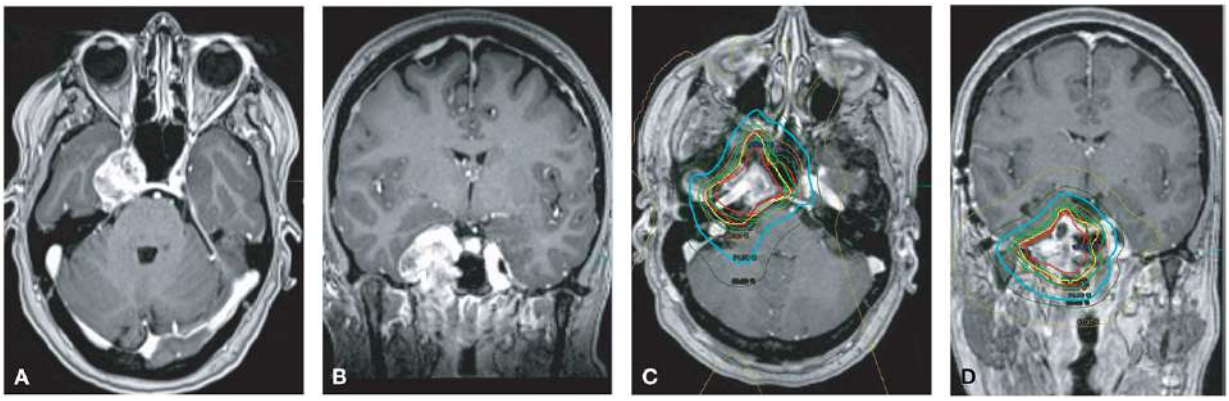


FIGURE 54.19 Preoperative T1-weighted magnetic resonance imaging (MRI) with contrast axial (A) and coronal (B) sequences showing a right petroclival chondrosarcoma. This patient underwent a near-total gross resection and received 70.2 GyRBE using a three-field pencil-beam scanning proton technique showing axial (C) and coronal (D) planning MRI co-registered to the planning computed tomography simulation. The planning target volume is shown in red. (Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

Catanzano et al[296] reviewed 427 patients with a histologic diagnosis of chondrosarcoma in the NCDB. They found that 680 received a form of RT (13%). The multivariate proportional hazards analysis controlling for various patient, tumor, and treatment variables, including RT dose and modality, demonstrated that while overall RT was not associated with improved survival (HR 0.96, 95% CI 0.76-1.20), when examining just the patient cohort with positive surgical margins, RT trended toward improved survival (HR 0.81, 95% CI 0.58-1.13). When comparing advanced and conventional RT modalities, advanced RT was associated with significantly decreased mortality (HR 0.55, 95% CI 0.38-0.80). Modern advanced conformal RT may present a treatment option for certain patients, particularly in selected high-risk patients, particularly those with residual disease or a high risk of morbidity from recurrence related to either the tumor's location or the salvage intervention.

Osteogenic sarcoma of the H&N has a pattern of recurrence different from similar tumors elsewhere in the body. H&N osteosarcomas are usually high grade; they have a very high incidence of local recurrence but a lower risk of distant metastases. Several studies have used adjuvant irradiation and chemotherapy, which commonly results in

improved LRC and survival. Tran et al[269] reported a 73% 5-year survival rate in patients with osteogenic sarcoma of the H&N treated with high-dose preoperative irradiation followed by wide surgical excision.

Chemotherapy

The role of either routine preoperative or adjuvant chemotherapy to improve disease-free survival in sarcoma of the H&N is controversial. There are notable exceptions such as with synovial sarcoma, RMS, Ewing sarcoma, mesenchymal chondrosarcoma, osteosarcoma, and some cases of poorly differentiate chordoma where chemotherapy has demonstrated efficacy. Unlike with soft tissue sarcomas of the extremities, in which distant metastasis is the most common cause of death, the majority of deaths in sarcomas of the H&N are associated with local failure. Approximately half of the distant metastases were detected after local recurrence occurred.[264] Chemotherapy did not appear to affect local tumor control. With the noted exceptions, adjuvant chemotherapy for H&N sarcomas should be given only in a clinical trial setting.[85,278]

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CHAPTER 55

Neck Cancer, Including Carcinoma of Unknown Primary

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ANATOMY

The locations of the various lymph node groups in the head and neck are shown in Figure 55.1.[1] Under normal conditions, the right and left lymphatic networks do not shunt from one side to the other.[2] The following discussion focuses on mucosal squamous cell carcinomas (SCCs) unless otherwise specified.

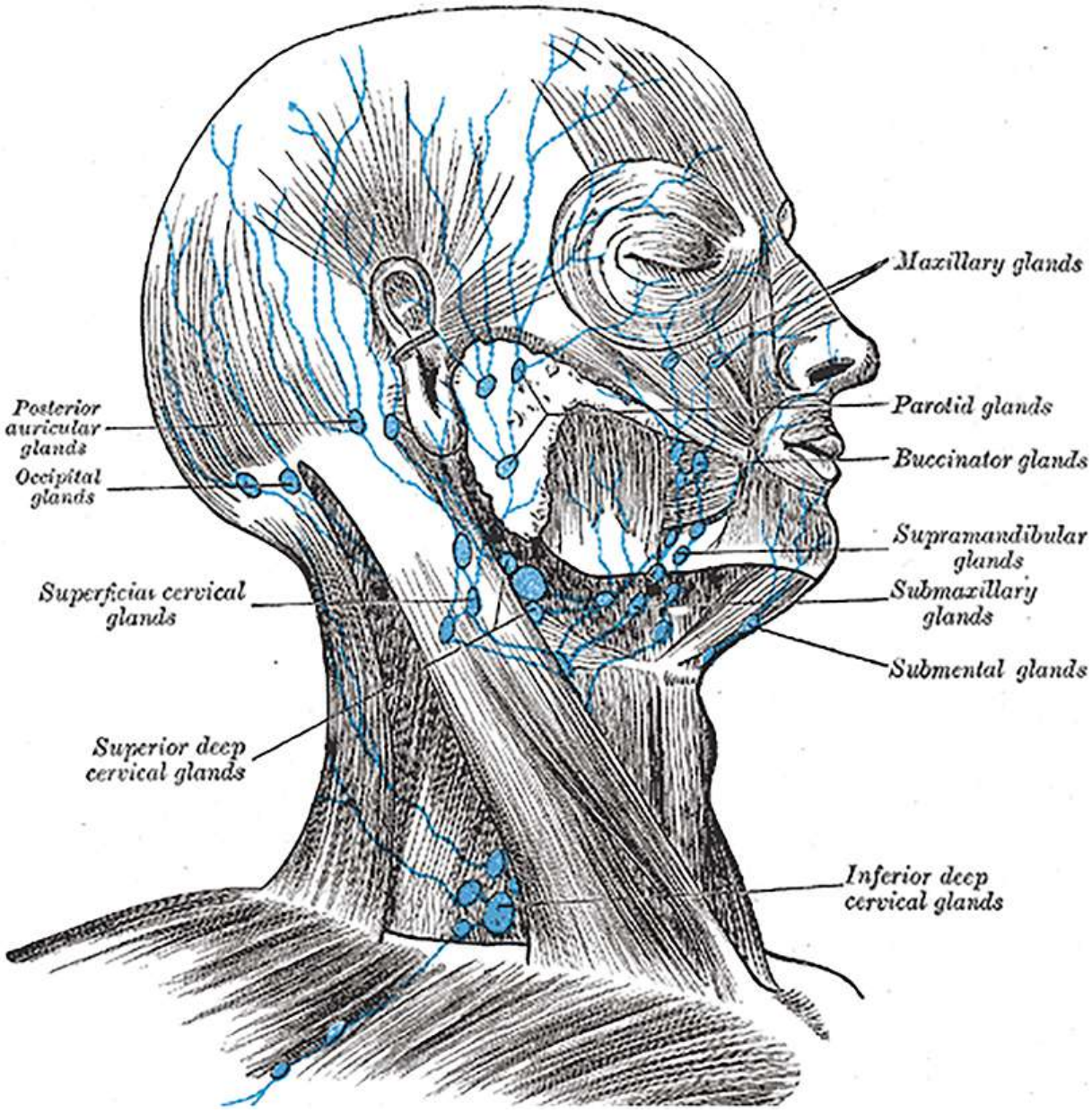

FIGURE 55.1 Arrangement of lymph nodes in the head and neck. (Redrawn from Rouvière H. *Anatomie Des Lymphatiques de L'homme*. Masson; 1932:10.)

The internal jugular chain (IJC) lymph nodes lie adjacent to the internal jugular vein and extend from the skull base to the clavicle. The most superior group of lymph nodes in this chain lies near the base of the skull in the posterior aspect of the lateral pharyngeal space and is often referred to as the parapharyngeal or junctional lymph nodes. These lymph nodes lie deep in the sternocleidomastoid muscle, the posterior belly of the digastric muscle, and the tail of the parotid gland. The remaining IJC lymph nodes

are artificially divided into the subdigastric, middle jugular, and lower jugular groups.

The spinal accessory chain (SAC) lymph nodes are distributed along the course of cranial nerve XI. The superior nodes of the SAC blend with the upper IJC nodes. The supraclavicular lymph nodes merge laterally with the SAC lymph nodes and medially with the lower IJC lymph nodes.

There are typically three to six submandibular lymph nodes. They may be either preglandular or postglandular; there are no lymph nodes in the substance of the submandibular gland. Adjacent to these nodes are also the perifacial lymph nodes, which lie next to the facial artery and vein around the marginal mandibular nerve. The submental lymph nodes lie in the midline between the anterior bellies of the digastric muscles, anterior and superior to the hyoid bone, and superficial to the mylohyoid muscle. There are typically one to three nodes in this area. The lateral retropharyngeal lymph nodes lie within the retropharyngeal space, which is bounded anteriorly by the pharyngeal constrictor muscles, superiorly by the skull base, and posteriorly by the prevertebral fascia. They are usually found at the level of the C1 and C2 vertebral bodies but may be found as inferiorly as C3. The medial retropharyngeal nodes are small, inconstant intercalated nodes that are located near the midline and empty into the lateral retropharyngeal lymph nodes.

The neck nodes are divided into levels as follows: level I, submental (IA) and submandibular (IB) nodes; level II, upper internal jugular nodes, from the skull base to the level of the hyoid bone divided by the spinal accessory nerve into levels IIa (anterior to the nerve) and IIb (posterior to the nerve); level III, middle internal jugular nodes, from the level of the hyoid bone to the omohyoid muscle; level IV, inferior internal jugular nodes, from the level of the omohyoid muscle to the clavicle; level V, divided by the spinal accessory nerve into levels Va (superior to the nerve) and Vb (inferior to the nerve); and level VI, central neck nodes, bounded by the hyoid bone, the sternum, and the common carotid arteries. Included in level VI are the paratracheal, pretracheal, precricoid (Delphian), and tracheoesophageal groove nodes.[3]

NATURAL HISTORY

The risk of lymph node metastases is influenced by the location of the primary tumor, histologic differentiation, size of the lesion, and the availability of capillary lymphatics.[4-7] The estimated risk of subclinical disease in the clinically negative neck as a function of the primary site and tumor (T) stage is shown in Table 55.1.[4] Previously unirradiated recurrent lesions have a higher risk of lymphatic involvement than untreated lesions. Moreover, their spread is less predictable. Previous irradiation of the lymphatics likely reduces the risk of lymph node metastases.

TABLE 55.1 DEFINITION OF RISK GROUPS

Group	Estimated Risk of Subclinical Neck Disease (%)	Stage	Site
I: Low risk	<20	T1	Floor of mouth, retromolar gingiva, trigone, palate, buccal hard mucosa
II: Intermediate risk	20-30	T1	Oral tongue, soft palate, pharyngeal wall, supraglottic larynx, tonsil
		T2	Floor mouth, oral of retromolar tongue, gingiva, trigone, hard palate, buccal mucosa
III: High risk	>30	T1-4	Nasopharynx, pyriform sinus, base of tongue
		T2-4	Soft palate, pharyngeal wall, supraglottic larynx, tonsil
		T3-4	Flour of mouth, oral retromolar tongue, trigone, gingiva, hard palate, buccal mucosa

Reprinted from Mendenhall WM, Million RR. Elective neck irradiation for squamous cell carcinoma of the head and neck: analysis of time–dose factors and causes of failure. *Int J Radiat Oncol Biol Phys*. 1986;12(5):741-746. Copyright © 1986 Elsevier. With permission.

The relative incidence of clinically positive lymph nodes in the neck by anatomic site and T stage is shown in Table 55.2.[5] The most commonly involved lymph nodes in the head and neck are the level II lymph nodes, followed by the level III lymph nodes. Lesions that are well lateralized almost always spread first to the ipsilateral neck nodes. Lesions on or near

the midline as well as lateralized base of the tongue and nasopharyngeal lesions may spread to both sides of the neck.

TABLE 55.2 CLINICALLY DETECTED NODAL METASTASES ON ADMISSION CORRELATED WITH T STAGE

Primary Site	T Stage	N0 (%)	N1 (%)	N2-3 (%)
Oral tongue[a]	T1	86	10	4
	T2	70	19	11
	T3	52	16	31
	T4	24	10	66
Floor of mouth[a]	T1	89	9	2
	T2	71	18	10
	T3	56	20	24
	T4	46	10	43
Retromolar trigone/anterior tonsillar pillar[b]	T1	88	2	9
	T2	62	18	20
	T3	46	21	33
	T4	32	18	50
Soft palate[b]	T1	92	0	8
	T2	64	12	24
	T3	35	26	39
	T4	33	11	56
Tonsillar fossa[b]	T1	30	41	30
	T2	32	14	54
	T3	30	18	52
	T4	10	13	76
Base of tongue[b]	T1	30	15	55
	T2	29	14	56
	T3	26	23	52
	T4	16	8	76

Primary Site	T Stage	N0 (%)	N1 (%)	N2-3 (%)
Oropharyngeal walls[b]	T1	75	0	25
	T2	70	10	20
	T3	33	22	44
	T4	24	24	52
Supraglottic larynx[c]	T1	61	10	29
	T2	58	16	26
	T3	16	25	40
	T4	26	18	41
Hypopharynx[d]	T1	37	21	42
	T2	30	20	49
	T3	21	26	54
	T4	26	15	58
Nasopharynx[e]	T1	8	11	82
	T2	16	12	72
	T3	12	9	80
	T4	17	6	78

Data are those of 2,044 patients, MD Anderson Hospital, Houston, TX, 1948-1965.

[a]T stage defined by Lindberg.[5]

[b]T stage defined by Fletcher et al.

[c]T stage defined by Fletcher et al.

[d]T stage defined by MacComb et al.

[e]T stage defined by Chen and Fletcher.

Modified from Lindberg R. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. *Cancer*. 1972;29(6):1446-1449.

Patients who have clinically positive lymph nodes on the ipsilateral side of the neck may be at risk for contralateral lymph node spread if the metastatic masses produce significant obstruction of the lymphatic trunks. In addition, patients who have undergone previous surgery on one side of the neck develop shunting of lymph across the submental region to the opposite side of the neck. When contralateral lymph node metastases occur,

the level II lymph nodes are most frequently involved, followed by the level III and level IV lymph node groups.

As tumor grows within a lymph node, the node becomes indurated and more rounded and enlarges. Tumor eventually extends through the capsule of the lymph node and invades the surrounding structures. Extension to neurovascular bundles is common and may produce a mass that is fixed to palpation. The incidence of tumor involvement and the likelihood of capsular penetration as a function of lymph node size are shown in Table 55.3.[6]

TABLE 55.3 RELATIONSHIP BETWEEN NODE SIZE, THE PRESENCE OF TUMOR IN THE NODE, AND CAPSULAR PENETRATION IN 519 NODES

	Size of Node (cm)				
	1	2	3	4	≥5
Number of nodes	177	183	84	17	58
Percentage positive	33	62	81	88	100
Percentage positive capsular with penetration	14	26	49	71	76

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Modified from Richard JM, Sancho-Garnier H, Micheau C, Saravane D, Cachin Y. Prognostic factors in cervical lymph node metastasis in upper respiratory and digestive tract carcinomas: study of 1,713 cases during a 15-year period. *Laryngoscope*. 1987;97(1):97-101. Copyright © 1987 The Triological Society. Reprinted by permission of John Wiley & Sons.

The risk of lateral retropharyngeal lymph node involvement is related to the primary site and neck stage[7]; the medial retropharyngeal nodes are almost never the site of metastatic disease. The incidence of positive retropharyngeal nodes based on pretreatment computed tomography (CT) and, in selected cases, magnetic resonance imaging (MRI) is shown in Table 55.4.[7]

TABLE 55.4 INCIDENCE OF POSITIVE RETROPHARYNGEAL NODES FOR VARIOUS PRIMARY SITES AND CLINICAL NECK STAGES (794 TUMORS)

	Clinical Neck Stage		
Primary Site	**N0 Neck (%)**	**N+ Neck[a] (%)**	**Overall (%)**
Nasopharynx	2/5 (40)	12/14 (86)	74
Pharyngeal wall	6/37 (16)	12/56 (21)	19
Soft palate	1/21 (5)	6/32 (19)	13
Tonsillar region	2/56 (4)	14/120 (12)	9
Pyriform or sinus postcricoid area	0/55 (0)	7/81 (9)	5
Base of tongue	0/31 (0)	5/90 (6)	4
Supraglottic larynx	0/87 (0)	4/109 (4)	2

[a]N+ are neck nodes clinically involved (stages N1-3B).

From McLaughlin MP, Mendenhall WM, Mancuso AA, et al. Retropharyngeal adenopathy as a predictor of outcome in squamous cell carcinoma of the head and neck. *Head Neck*. 1995;17(3):190-198. Copyright © 1995 Wiley Periodicals, A Wiley Company. Reprinted by permission of John Wiley & Sons.

DIAGNOSTIC WORKUP

Physical Examination

The patient is examined in the sitting position, the examiner behind the patient with one hand on the occiput to flex the patient's head forward and the other hand on the side of the neck to be examined. To examine the IJC lymph nodes, which lie deep to the sternocleidomastoid muscle along the internal jugular vein, place the thumb and index finger around the sternocleidomastoid muscle in the form of a "C" and then gently proceed from the sternal notch to the angle of the mandible. Both sides of the neck should not be examined simultaneously. The level Ib and level Ia nodes may be evaluated by direct palpation of these areas as well as by a bimanual examination with the index finger placed on the floor of the mouth.[8]

The following features of metastatic lymph nodes should be recorded: anatomic location, size, consistency, mobility, and clinical impression as to whether the node is involved with cancer.

Radiographic Evaluation

CT, MRI, fluorodeoxyglucose-positron emission tomography (FDG-PET), and ultrasound may be used to evaluate cervical metastatic disease.[9] At the University of Florida, CT remains the primary method of examination of most carcinomas arising in the upper aerodigestive tract and the regional lymphatics. MRI is the primary study only in patients with nasopharyngeal malignancies. MRI may also be used in patients who are allergic to intravenous contrast medium. Ultrasound has been used mainly in Europe to evaluate the cervical nodes. FDG-PET may be used to evaluate equivocal suspicious lymph nodes if the results of the scan would alter the treatment plan. Positive nodes <1 cm will not be reliably detected on a PET scan. FDG-PET remains unproven with regard to improving accuracy rates over those available with properly performed and interpreted CT.

Small metastases may be seen as lucent foci in normal-sized nodes. Such metastases have been identified and surgically confirmed in nodes as small as 6 to 8 mm; however, most subclinical disease in normal-sized nodes remains undetected on CT. FDG-PET has a marginal capability to improve CT in detecting the subclinical disease in small (<1 cm) nodes.

Lucent foci in normal-sized nodes must be differentiated from hilar fat or volume-averaging artifacts. As the metastasis grows, the node becomes more spherical than elliptical. Areas of necrosis are almost always present in nodal metastases larger than 2 cm. As the metastasis enlarges, the capsule of the node becomes hyperemic and is seen radiographically as contrast-enhanced rim. When the capsule becomes indistinct and irregular along its outer margin, it is highly suggestive early of capsular penetration. Continued growth causes obliteration of the fat planes surrounding the nodes. Finally, no clear plane of normal tissue lies between the mass and the adjacent structures, at which point the clinician usually notes fixation (Figure 55.2). Penetration of the prevertebral fascia and fixation to the scalene muscles are uncommon in untreated patients. Largely necrotic nodes may be negative on FDG-PET examinations.

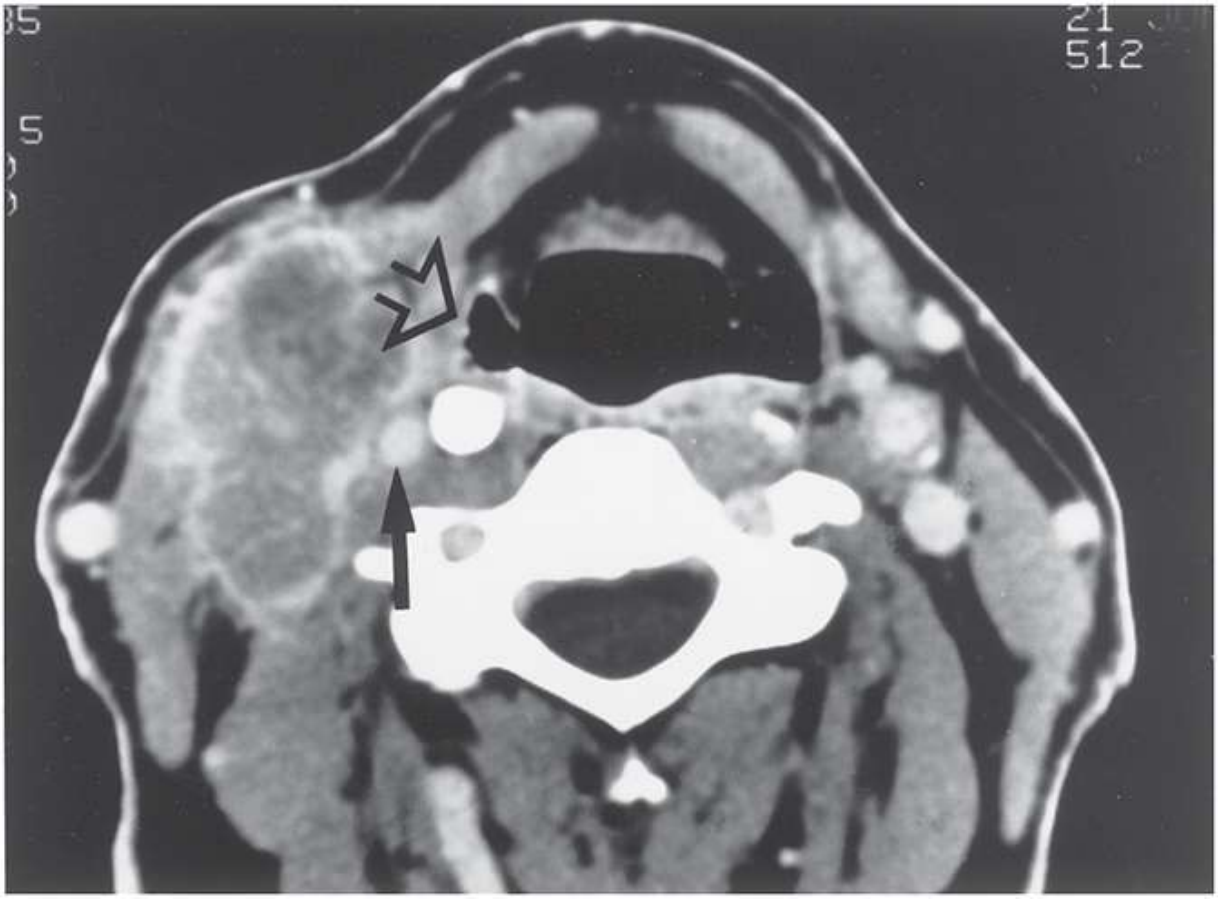

FIGURE 55.2 T1 squamous cell carcinoma of the lateral wall of the right pyriform sinus (open arrow) and a fixed N3B neck node that abuts but does not surround the carotid artery (solid arrow).

If a node shows evidence of capsular penetration and envelops more than 50% of the circumference of the carotid artery, clinical evidence of fixation to the artery is likely. Ultrasound and MRI may prove useful in evaluating tumor extension to the carotid, as suggested by CT. MRI tends to be better at excluding extension to the neurovascular bundle when it is suspected on CT, whereas ultrasound can help show invasion of the vessel wall, thus confirming focal extension to the artery.

STAGING

The staging systems shown in Table 55.5 are those of the American Joint Committee on Cancer (AJCC).[10] Because all University of Florida data presented in this chapter were analyzed using the 1983 AJCC staging

system,[11] both the 1983 and 2017 systems are outlined in Table 55.5. Stage N3C in the 1983 system is rare and should alert the clinician to search for another primary lesion. The 2017 AJCC staging system classifies bilateral or contralateral nodes not more than 6 cm in diameter as N2C; N3 is defined as a metastasis in a lymph node more than 6 cm in diameter.[10] The AJCC nodal staging system for head and neck cancer has not changed appreciably since the 1997 edition. The AJCC nodal staging for nasopharyngeal carcinoma differs from other head and neck primary sites and will be discussed in the chapter devoted to that topic.

TABLE 55.5 1983 AND 2017 AMERICAN JOINT COMMITTEE ON CANCER STAGING FOR NECK LYMPH NODES

Stage	Definition
1983 Stage	
NX	Nodes cannot be assessed.
N0	No clinically positive nodes
N1	Single clinically positive homolateral node 3 cm or less in diameter
N2	Single clinically positive homolateral node more than 3 cm but not >6 cm in diameter or multiple clinically positive homolateral nodes, none >6 cm in diameter
N2A	Single clinically positive homolateral node >3 cm but not >6 cm in diameter
N2B	Multiple clinically positive homolateral nodes, none >6 cm in diameter
N3A	Clinically positive homolateral node(s), one >6 cm in diameter
N3B	Bilateral clinically positive nodes (in this situation, each side of the should neck staged be separately N3B) (ie, left, N23; right, N1)
N3C	Contralateral node(s) clinically positive only
2017 Stage	
NX	Regional lymph nodes cannot be assessed.
N0	No lymph regional node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and extranodal extension (ENE)(−)
N2	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−); or metastases in multiple ipsilateral nodes,

Stage	Definition
	none larger than 6 cm in greatest dimension and ENE(−); or in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension, ENE(−)
N2a	Metastasis in single ipsilateral or contralateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b	Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastasis bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); or metastases in a single ipsilateral node ENE(+) or multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in a single ipsilateral node ENE(+) or multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+)

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SURGERY

Historically, surgical treatment of neck lymphatics involved radical neck dissection. This involves the removal of lymph nodes in levels I to V along with the spinal accessory nerve, sternocleidomastoid muscle, and internal jugular vein. This is seldom performed today, as many studies have demonstrated that structures not involved by cancer in the neck can be preserved without sacrificing survival. The only indication to remove nonlymphatic structures in the neck (nerves, muscles, internal jugular vein, etc) is the direct involvement of the structure by a cancerous node.

Modified radical neck dissection, or functional neck dissection, involves the removal of lymph nodes in levels I to V with preservation of at least one of the following structures: spinal accessory nerve, sternocleidomastoid muscle, or internal jugular vein. This approach is used when the nodal burden is advanced with high-risk spread to level V or invasion of nonlymphatic structures.

The most commonly performed surgical neck treatment of neck lymphatics is now the selective neck dissection. This approach involves

preserving all nonlymphatic structures and only removing the high-risk lymphatic levels. The advantage of this approach is that it maintains function, minimizes morbidity, and does not compromise oncologic treatment. The levels to be removed are determined by the site of cancer. Levels I to III are addressed for oral cavity cancers. Levels II to IV are included for the treatment of oropharyngeal, laryngeal, and hypopharyngeal cancers. If nodes suspicious for metastases are encountered in areas outside the planned neck dissection, the selective neck dissection should be converted to a modified radical neck dissection.

Bilateral neck dissections may be performed simultaneously or separately (staged) in patients with bilateral neck disease as long as one internal jugular vein can be preserved. If both the internal jugular veins need to be sacrificed, at least one should be reconstructed with a vein graft (eg, saphenous vein or femoral vein). If both the internal jugular veins are left sacrificed, the patient is at high risk of cerebral edema, extreme facial edema, and, potentially, blindness.

Complications of Neck Dissection

Complications of neck dissection include hematoma; seroma; lymphedema; wound infection; wound dehiscence; skin flap necrosis; chyle leak; damage to cranial nerves V, VII, X, XI, and XII; internal jugular vein rupture; and carotid rupture. The incidence of complications is higher when neck dissection is combined with resection of the primary lesion or when it follows a course of radiation therapy (RT). The postoperative mortality rate for unilateral neck dissection after RT was 3% for patients treated between 1964 and 1982.[12] This figure is now <1%.

The incidence of postoperative complications in a series of patients treated with RT to the primary lesion and neck followed by unilateral or bilateral neck dissection(s) is shown in Tables 55.6[12] and 5.7.[13] Two of 10 patients undergoing a staged bilateral neck dissection experienced a moderately severe complication compared with 4 of 40 patients undergoing a simultaneous bilateral neck dissection. None of the 10 patients who underwent a staged bilateral neck dissection experienced a severe complication, compared with 6 of 40 (15%) patients who underwent a simultaneous bilateral neck dissection ($P = .24$).[13]

TABLE 55.6 POSTOPERATIVE COMPLICATIONS OF UNILATERAL NECK DISSECTION AFTER IRRADIATION TO THE PRIMARY LESION AND NECK (143 PATIENTS)

Complications	Number of Complications	Number of Second Operations to Repair Complication	Death
Salivary fistula	1	0	0
Wound breakdown	23	15	0
Bleeding	2	1	1
Pneumonia	2	0	1
Orocutaneous fistula	1	1	0
Lymphatic fistula	2	0	0
Pulmonary embolus	1	0	0
Cardiovascular problem	2	0	1
Sepsis	1	0	1
Total complications	35[a]	17	4[b]
Incidence (%)	33/143 (23)	17/143 (12)	4/143 (3)

[a]Thirty-five complications in 33 patients.

[b]Deaths occurred 6, 7, 8, and 35 days after surgery.

Reprinted from Mendenhall WM, Million RR, Cassisi NJ. Squamous cell carcinoma of the head and neck treated with radiation therapy: the role of neck dissection for clinically positive neck nodes. *Int J Radiat Oncol Biol Phys*. 1986;12(5):733-740. Copyright © 1986 Elsevier. With permission.

TABLE 55.7 COMPLICATIONS AFTER RADIATION THERAPY FOLLOWED BY A BILATERAL NECK DISSECTION (*N* = 50 PATIENTS)

Severity	Complication	Number of Patients
Moderate	Wound breakdown	2
	Bleeding	1
	Laryngeal edema	2
	Chyle fistula	1
Severe	Wound breakdown	4
	Fatal cardiac arrest	1

Severity	Complication	Number of Patients
	Fatal acute laryngeal edema	1

Reprinted from Somerset JD, Mendenhall WM, Amdur RJ, Villaret DB, Stringer SP. Planned postradiotherapy bilateral neck dissection for head and neck cancer. *Am J Otolaryngol*. 2001;22(6):383-386. Copyright © 2001 Elsevier. With permission.

Taylor et al[14] analyzed the incidence of moderate (2+) and severe (3+) wound complications in a series of 205 patients who underwent a planned unilateral neck dissection after RT at the University of Florida. RT was given once daily in 123 patients, twice daily in 80 patients, and with both techniques in the remaining 2 patients. The incidence of wound complications increased with total dose and dose per fraction (Figure 55.3).

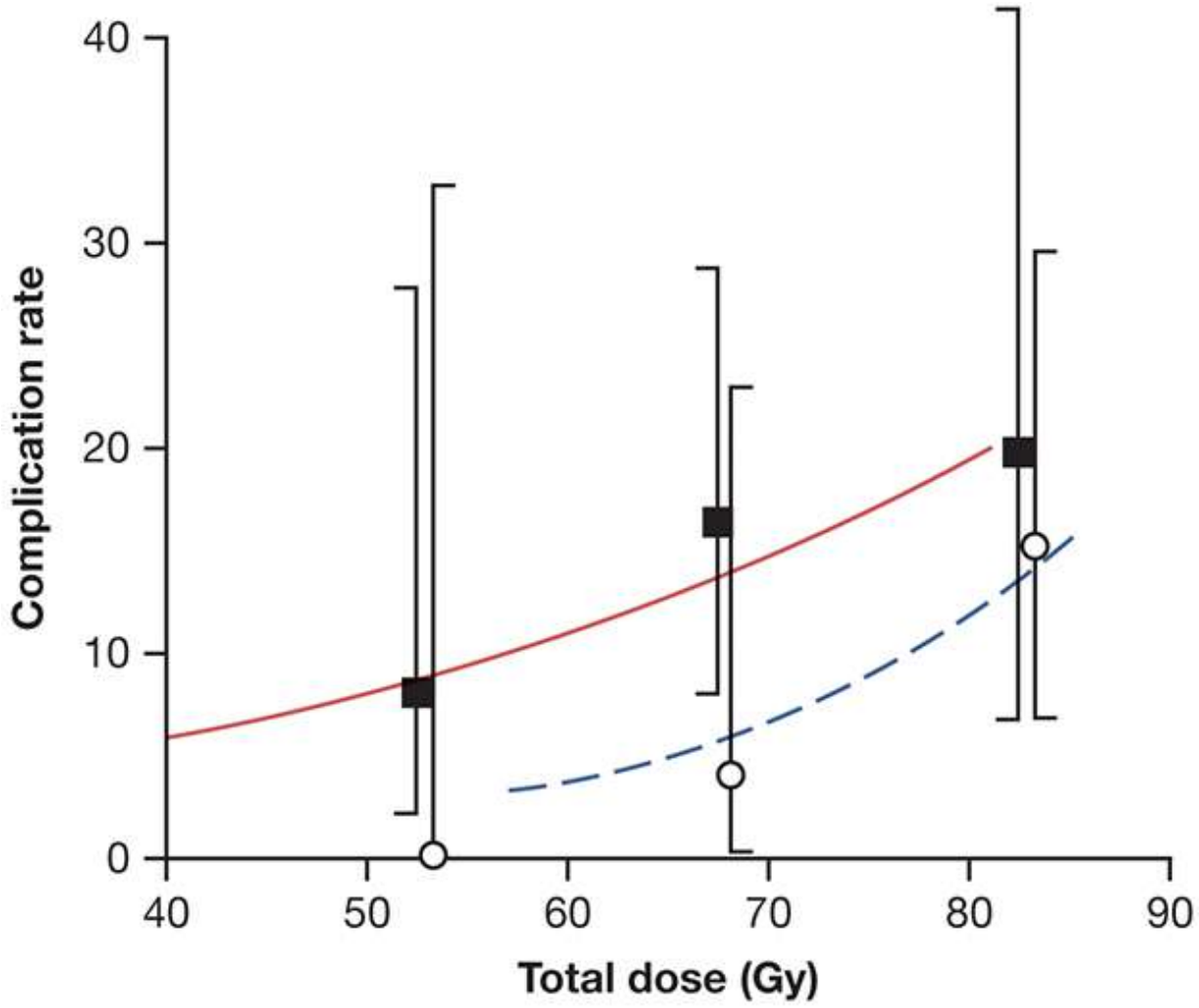

FIGURE 55.3 Complication rate (2+ or 3+) versus total dose. Separate analysis for once a day (filled square, solid curve) and twice a day (circle, dashed curve). Data are plotted at the midpoints of the range 45 to 60, 60 to 70, and 75 to 90 Gy. Error bars denote 95% confidence intervals. The curves are the results of separate logistic regression analysis. (Reprinted from Taylor JM, Mendenhall WM, Parsons JT, Lavey RS. The influence of dose and time on wound complications following post-radiation neck dissection. *Int J Radiat Oncol Biol Phys*. 1992;23[1]:41-46. Copyright © 1992 Elsevier. With permission.)

RADIATION THERAPY

RT may be used in the treatment of cervical lymph node metastases as elective treatment when there are no palpable lymph nodes, as the only treatment for clinically positive lymph nodes,[15] or as preoperative or postoperative treatment in combination with neck dissection for clinically positive lymph nodes.[16]

The regional lymph nodes are considered in the treatment planning of the primary lesion. With clinically negative neck nodes, treatment planning depends on the estimated risk of subclinical disease in the nodes. With clinically positive lymph nodes, the plan is influenced by the number of lymph nodes, size, and location.

Elective Radiation Therapy of Cervical Lymph Nodes When the Primary Tumor Is Treated by Radiation Therapy

Factors that influence the decision to irradiate the neck electively are site and size of the primary lesion, histologic grade, difficulty in neck examination, relative morbidity for adding lymph node coverage, likelihood of the patients returning for follow-up examinations, and suitability of the patient for a neck dissection if the tumor appears in the neck at a later date. Patients in whom the primary lesion is to be treated by RT, who have clinically negative nodes, and in whom the risk of subclinical disease is 15% to 20% or greater receive elective neck irradiation to a minimum dose equivalent to 45 to 50 Gy over 4.5 to 5 weeks (see Table 55.1). Patients with lesions arising in the lip, nasal vestibule, nasal cavity, or paranasal sinuses have a low risk of subclinical neck disease, and the neck is not treated electively unless the lesion is recurrent, advanced, or poorly differentiated. Similarly, the risk of occult neck disease is essentially 0% for T1 and 1.7% for T2 glottic carcinomas, and elective neck RT is not indicated.[17,18]

The lateral treatment portals used to encompass cancers in the oropharynx, supraglottic larynx, and hypopharynx include the upper jugular and often the midjugular chain lymph nodes. RT portals used for primary lesions of the oral cavity, nasopharynx, glottis, nasal cavity, and paranasal sinuses must be enlarged to include the lymph nodes. The treatment portals for irradiation of the cervical lymph nodes must be designed in such a way as to minimize additional mucosal irradiation. A common error in irradiating oropharyngeal and nasopharyngeal cancers is to enlarge the lateral (primary) portals inferiorly to unnecessarily include all of the larynx in the lateral portals (Figure 55.4).[19] Because the midneck is smaller in circumference than the upper neck, the total dose and dose per fraction are higher in the larynx than along the central axis of the beam, leading to

double trouble. Although a field junction through a positive node(s) may be avoided with intensity-modulated radiation therapy (IMRT), the larynx still receives a substantially higher dose compared with a separate anterior low neck portal with a midline laryngeal block junctioned at the thyroid notch (Figures 55.5 to 55.7).[20] Treating an unnecessarily large field increases the acute and late effects of RT and, by increasing the risk of an unplanned split, reduces the probability of disease control.[19,20]

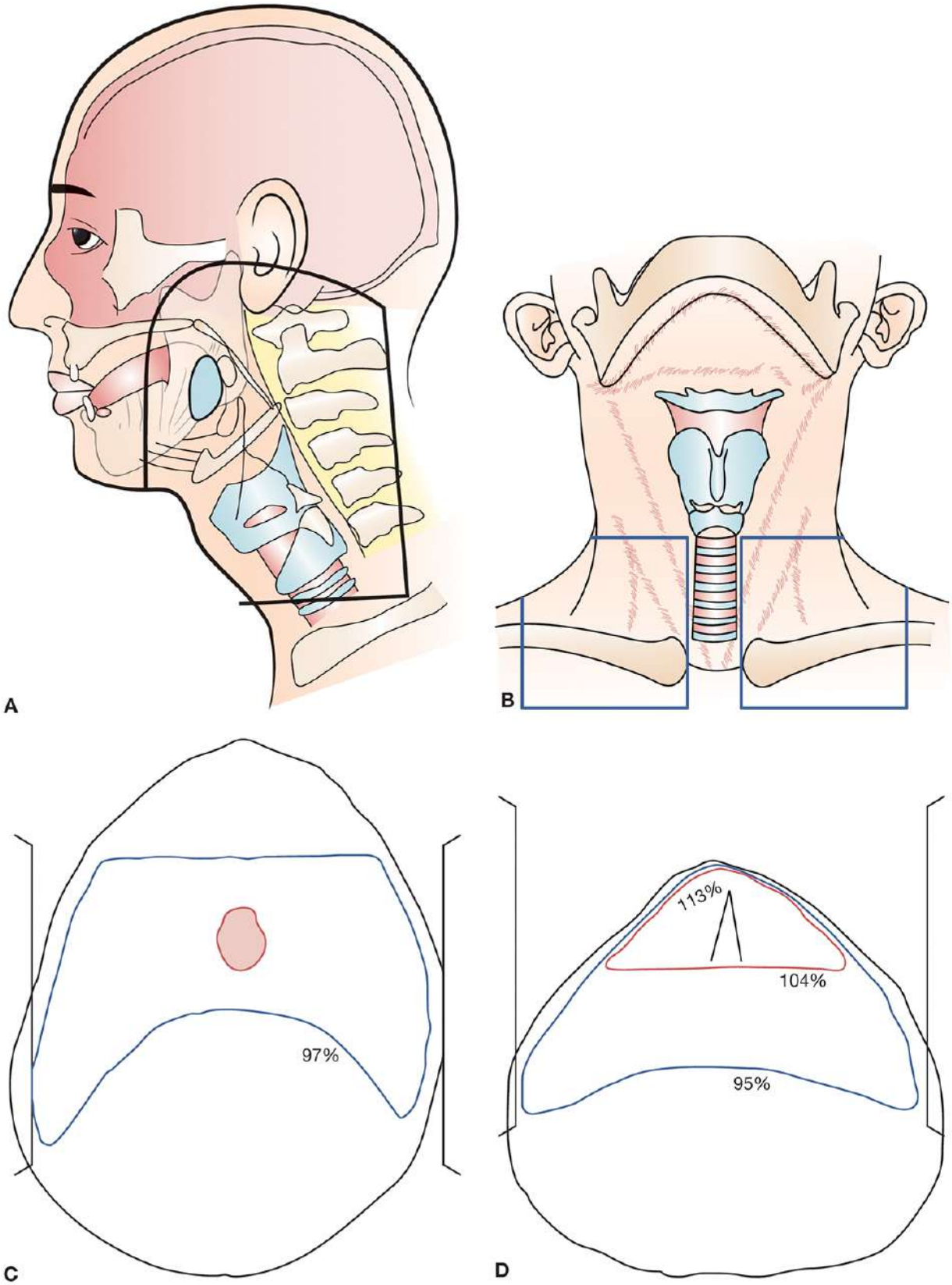
A
B
97%
C
113%
104%
95%
D

FIGURE 55.4 Carcinoma of the base of the tongue: large radiation portals. A. Parallel-opposed lateral portals include the primary lesion, larynx, hypopharynx, most of the cervical spinal cord, and the upper portion of the trachea and cervical esophagus. Treatment through this portal tangentially irradiates the skin of the anterior neck unnecessarily. If an anterior field is not used to irradiate the low neck, the inferior border of the lateral field may be placed near the clavicle (dashed line). B. Anterior low neck portal. The wide midline tracheal block partially shields the low internal jugular lymph nodes, which are located adjacent to the trachea. The supraclavicular lymph nodes, which are less likely to be involved with tumor than the low jugular nodes, are adequately covered. C. Central axis dosimetry at the level of the base of tongue primary lesion. The contours were obtained from a RANDO phantom using parallel cobalt-60 fields weighted equally. The base of tongue tumor is outlined, and the tumor dose is specified at 97% of the maximum dose. D. Off-axis contour through the larynx. The minimum dose to the entire larynx is 104% of the maximum dose specified at the central axis, and the maximum dose on this off-axis contour is 113%. If the base of tongue tumor dose is specified as 50 Gy at 2 Gy per fraction, the minimum larynx dose is 53.61 Gy at 2.14 Gy per fraction, and the maximum larynx dose is 58.25 Gy at 2.33 Gy per fraction. If the tumor dose is specified as 60 Gy at 2 Gy per fraction, the minimum larynx dose is 64.33 Gy at 2.14 Gy per fraction, and the maximum larynx dose is 69.9 Gy at 2.33 Gy per fraction. (Reprinted from Mendenhall WM, Parsons JT, Million RR. Unnecessary irradiation of the normal larynx. *Int J Radiat Oncol Biol Phys*. 1990;18[6]:1531-1533. Copyright © 1990 Elsevier. With permission.)

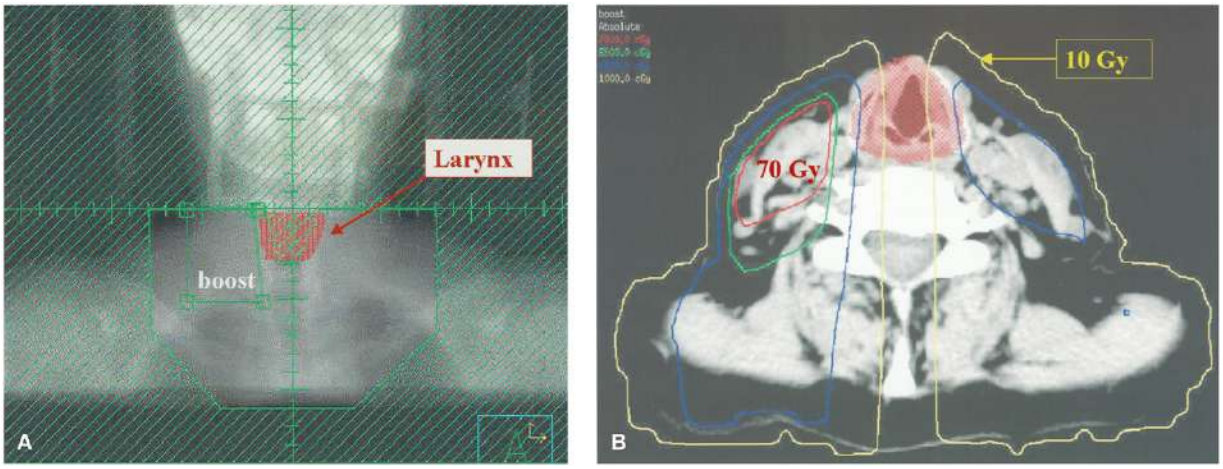

FIGURE 55.5 Laryngeal dose in a model patient with a stage T2N2b carcinoma of the tonsil with positive nodes on the right side at the level of the larynx. The primary site is irradiated with either intensity-modulated radiation therapy or lateral opposed fields. The cervical lymphatics inferior to the primary site fields are treated with an anterior low neck field. A. Digitally reconstructed radiograph of the low neck fields. The larynx was contoured and appears as a red color-wash structure. The larynx is shielded with a narrow midline block that does not cover the entire width of the larynx. In this model patient, the entire low neck field received 50 Gy and then the field size was reduced to boost the positive nodes on the right of the larynx to 70 Gy. Irradiation was given with a 6-MV photon beam with source to axis distance of 100 cm. B. Axial dose distribution at the level of the true vocal cords showing that the dose to the central portion of the larynx is extremely low when the larynx is shielded in the anterior low neck field. (From Amdur RJ, Li JG, Liu C, Hinerman RW, Mendenhall WM. Unnecessary laryngeal irradiation in the IMRT era. *Head Neck*. 2004;26[3]:257-264. Copyright © 2004 Wiley Periodicals. Reprinted by permission of John Wiley & Sons.)

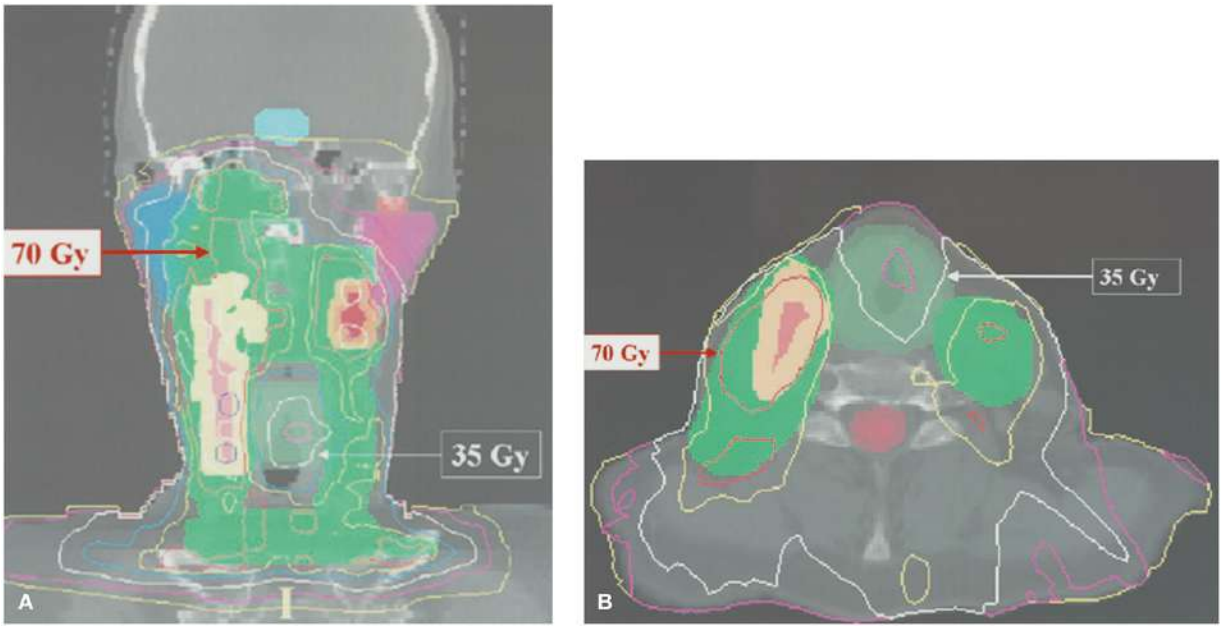

FIGURE 55.6 Dose distribution using intensity-modulated radiation therapy as described in the text to treat the model patient with a stage T2N2b carcinoma of the tonsil with positive nodes on the right side at the level of the larynx. The plan was optimized to minimize the dose to the larynx while delivering 70 Gy to gross disease and 59.4 Gy to areas at risk for subclinical disease. A. Coronal projection near the middle of the larynx. B. Axial projection at the level of the true vocal cords. A comparison of Figures 55.5B and 55.6B shows that sparing of the central portion of the larynx is shielded in an anterior low neck field. (From Amdur RJ, Li JG, Liu C, Hinerman RW, Mendenhall WM. Unnecessary laryngeal irradiation in the IMRT era. *Head Neck*. 2004;26[3]:257-264. Copyright © 2004 Wiley Periodicals. Reprinted by permission of John Wiley & Sons.)

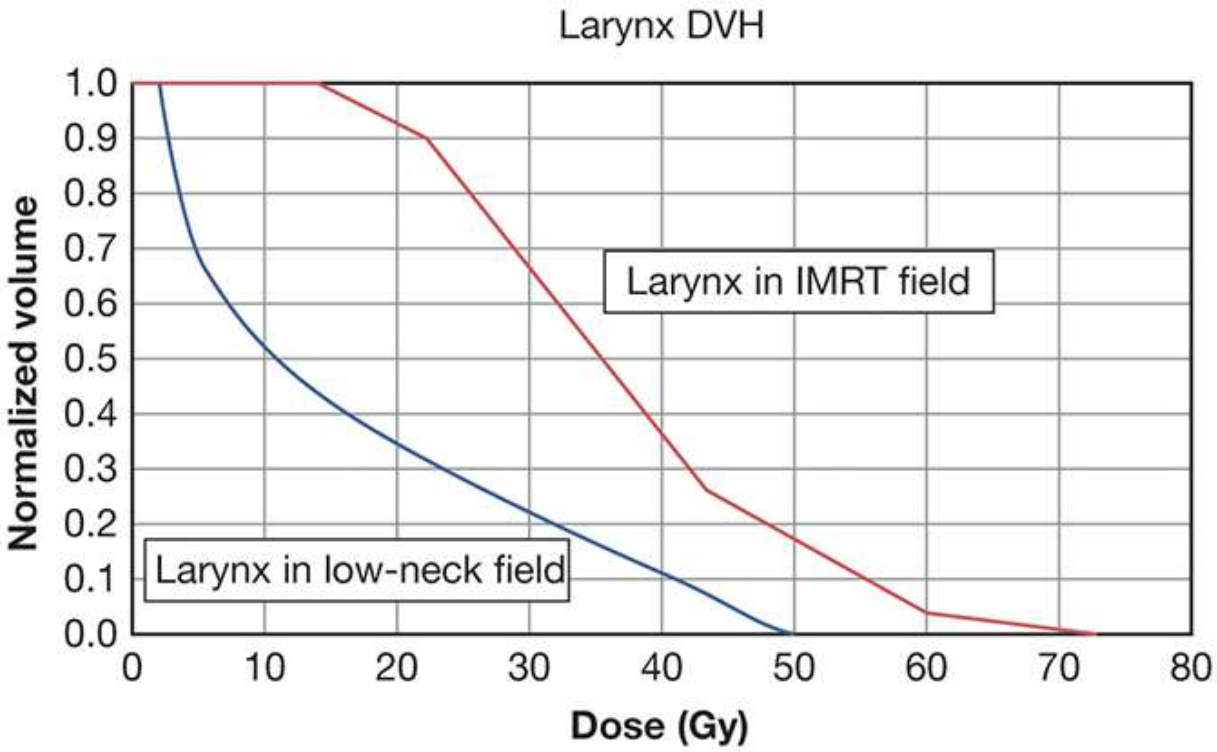

FIGURE 55.7 Dose-volume histogram (DVH) of the larynx for the model patient described in Figures 55.5 and 55.6. The red line is the DVH when the larynx is included in the intensity-modulated ration therapy (IMRT) fields shown in Figure 55.6. The blue line is the DVH when the larynx is shielded in the anterior low neck field shown in Figure 55.5. There is a major difference in the portion of the larynx that receives an extremely low dose. For example, when the larynx is included in the IMRT fields, the entire larynx receives more than 10 Gy, whereas when the larynx is shielded in the low neck field, approximately 45% of the larynx receives <10 Gy. (From Amdur RJ, Li JG, Liu C, Hinerman RW, Mendenhall WM. Unnecessary laryngeal irradiation in the IMRT era. *Head Neck*. 2004;26[3]:257-264. Copyright © 2004 Wiley Periodicals. Reprinted by permission of John Wiley & Sons.)

IMRT may be used to treat patients if there is a goal that can be achieved to reduce the toxicity of irradiation. These goals are usually parotid sparing to reduce the risk of long-term xerostomia, avoiding a low neck match in patients with a low-lying larynx, and improved coverage of the poststyloid parapharyngeal space in patients with nasopharyngeal cancer.[21] If one or more of these goals cannot be achieved, the patients may be better off being treated with conventional RT because of the disadvantages of IMRT, which include increased risk of a marginal miss, less homogeneous dose distribution, and increased cost and complexity.[21]

Elective neck irradiation for early oral cavity lesions includes the level Ib and level II lymph nodes. The level III and level IV lymph nodes are treated

as well by using a narrow anterior field. For primary lesions located in the oropharynx, nasopharynx, supraglottic larynx, and hypopharynx, the lower neck nodes are also routinely included. The low neck is treated with a single anterior field (Figure 55.8). A tapered midline larynx or trachea shield is added to protect the spinal cord, the larynx, and the pharynx. For primary lesions lying below the thyroid notch, a small midline tracheal block 1-cm wide is placed in the low neck field, to shield the trachea, esophagus, and spinal cord.

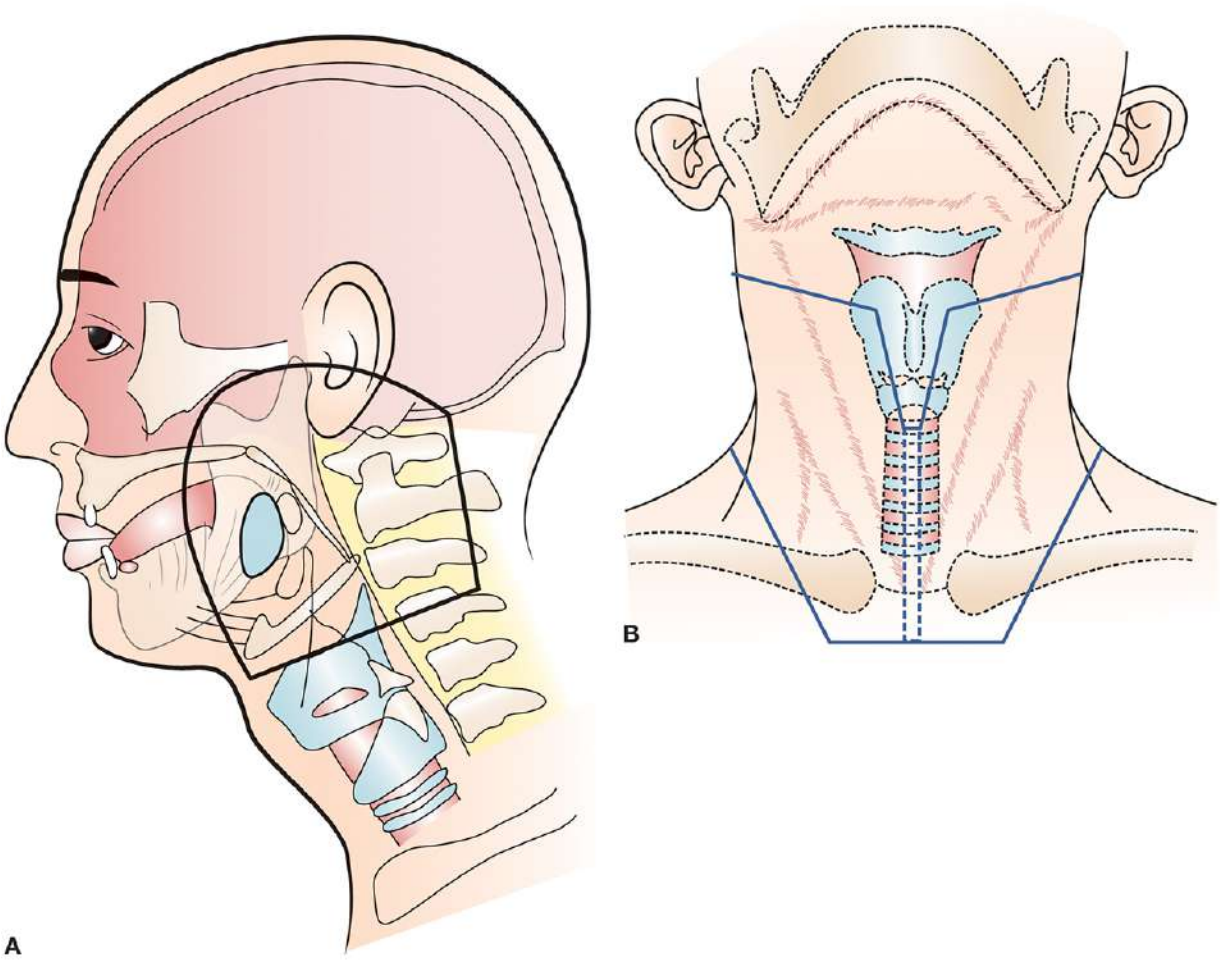

FIGURE 55.8 Lateral and anterior fields are used to irradiate a patient with a carcinoma limited to the base of tongue. A. Parallel-opposed fields include the primary lesion with a 2- to 3-cm inferior margin. The lower border of the field is placed at the thyroid notch and slants superiorly as the junction line proceeds posteriorly as the junction line proceeds posteriorly. This substantially reduces the amount of mucosa larynx and spinal cord included in the primary treatment portals. B. En face low neck portal with tapered midline larynx and tapered midline larynx block. It is not necessary to treat the supraclavicular fossa unless clinically positive nodes are found in that particular hemineck. A 5-mm midline tracheal block may be placed in the low neck portal (dashed line). (Reprinted from Mendenhall WM, Parsons JT, Million RR. Unnecessary irradiation of the normal larynx. *Int J Radiat Oncol Biol Phys*. 1990;18[6]:1531-1533. Copyright © 1990 Elsevier. With permission.)

Treatment of Clinically Positive Cervical Lymph Nodes When the Primary Tumor Is Treated by Radiation Therapy

The dose required to control a clinically positive lymph depends on the size of the lymph node[15,22] and whether concomitant chemotherapy is

administered. Relatively recent data suggest that advanced disease has a better chance of cure after altered fractionation or concomitant chemotherapy.[23] Patients treated at the authors' institution routinely receive hyperfractionation or simultaneous integrated boost (SIB) combined with weekly cisplatin 30 mg/m^2. SIB consists of 70 Gy in 35 fractions over 30 treatment days in 6 weeks with one twice-daily fraction during the last 6 weeks with a minimum 6-hour interfraction interval. The high-risk planning treatment volume (PTV) receives 70 Gy at 2 Gy per fraction, intermediate-risk PTV receives 63 Gy at 1.8 Gy per fraction, and the standard-risk PTV receives 56 Gy at 1.6 Gy per fraction. Positive nodes receive approximately 70 to 74 Gy, regardless of the size or rate of regression.

The decision to add a neck dissection after RT for multiple unilateral positive nodes or bilateral lymph node disease is individualized and is based on the diameter of the largest node, node fixation, and number of clinically positive nodes in the neck. If clinically positive lymph nodes disappear completely during RT, the likelihood of control by RT alone is improved and a neck dissection may be withheld.[24-27] Peters et al[28] reported on 100 node-positive patients with SCC of the oropharynx treated with concomitant boost RT between 1984 and 1993 at the MD Anderson Cancer Center (Houston, TX). Sixty-two patients had a complete response (CR) in the neck and received no further therapy. Three (5%) patients subsequently developed an isolated recurrence in the neck, and four (6%) patients developed a recurrence in the neck in conjunction with other sites of relapse. The 2-year neck disease control rates did not vary significantly with pretreatment nodal size: ≤3 cm, 87%; and >3 cm, 85%. The incidence of subcutaneous fibrosis was similar following RT alone compared with another group of patients who underwent a neck dissection in addition to RT. Johnson et al[29] reported on 81 patients with node-positive stages III and IV SCC of the head and neck treated with concomitant boost accelerated hyperfractionated RT at the Medical College of Virginia (Richmond). Fifty-eight (72%) patients had a CR in the neck and were followed; three (5%) patients subsequently developed an isolated recurrence in the neck and one additional patient developed recurrent cancer in the neck and in the primary site. The 3-year neck disease control rates were 94% for nodes ≤3 cm compared with 86% for those >3 cm.

Both of these series of patients received aggressive altered fractionated RT, and it is unclear whether these data can be broadly extrapolated to patients with head and neck cancer from a variety of head and neck primary sites that are treated less aggressively. It is also unclear whether the addition of concomitant chemotherapy results in a lower likelihood of needing a neck dissection. However, multiple subsequent studies evaluating neck control rates either after RT alone or combined with chemotherapy suggest that the likelihood of an isolated failure in the neck is low if there is a CR after treatment.[16,30-34]

The authors' policy at the University of Florida has changed to the extent that we now evaluate patients with clinically positive nodes with a CT 4 weeks after RT or a PET-CT at 3 months and withhold neck dissection in the subset of patients with a CR thought to have ≤5% risk of residual disease.[35-42] Liauw et al[38] evaluated a series of 550 patients treated with definitive RT at the University of Florida between 1990 and 2002; 341 (62%) patients underwent a post-RT planned neck dissection. CT images obtained at approximately 4 weeks post-RT were reviewed for 211 patients; radiographic complete response (rCR) was defined as no nodes >1.5 cm and no focal abnormalities such as focal lucency, enhancement, or calcification.[32] The outcomes are depicted in Table 55.8. Thirty-two patients had an rCR and were followed and did not undergo a neck dissection; the neck control rate was 97%. Recent data published by Yeung et al[35] suggest that for those who have a partial response to RT, neck dissection may be safely limited to only those levels that remain suspicious after RT. Post-RT selective neck dissection likely results in improved quality of life.[43] PET-CT is obtained 3 months after completion of RT to minimize the risk of a false-positive scan; those with a negative PET-CT are followed, the remainder undergo a neck dissection. Goenka et al[41] reported on 302 patients with node-positive oropharyngeal SCCs treated with IMRT and concomitant chemotherapy at the Memorial Sloan Kettering Cancer Center between 2002 and 2009. Patients underwent a PET-CT following treatment to assess response. A clinical and rCR was observed in 260 (86.1%) patients and were observed. The neck control rate was 97.7%. Three of four patients who recurred in the neck were successfully salvaged. Patients who underwent a neck dissection had the following rates of pathologically visible tumor: PET-CT positive, 52%; and PET-CT negative, 25%.

Mehanna et al[42] reported on a prospective trial where 564 node-positive patients were randomized to chemoradiation followed by PET-CT and either planned neck dissection (282 patients) or observation in the event of a CR (282 patients). Patients in the latter group underwent fewer neck dissections: the 2-year survival rates were comparable.

TABLE 55.8 PREDICTIVE VALUE OF POSTRADIOTHERAPY COMPUTED TOMOGRAPHY FINDINGS AT 4 WEEKS IN THE HEMINECK CORRELATED TO NECK DISSECTION PATHOLOGY (*N* = 193 HEMINECKS)

	NPV		PPV	
Findings	**Number/Total Number**	**Percent**	**Number/Total Number**	**Percent**
Any lymph node >1.5 cm	85/118	72	24/75	32
Any lymph node with focal lucency	49/57	86	49/136	36
Any focally abnormal lymph node[a]	75/98	77	34/95	36
Any lymph with node enhancement	111/147	76	21/46	46
Any lymph with node calcification	102/144	71	15/49	31
Two or more focally abnormal lymph nodes[a]	90/113	80	34/80	43
Any lymph node >1.5 cm and any focally abnormal lymph node	32/34	94	55/159	35

NPV, negative predictive value; PPV, positive predictive value.

[a]Focally abnormal lymph nodes equal grade 3 or 4 focal lucency, focal enhancement, or focal calcification.

Reprinted with permission from Liauw SL, Mancuso AA, Amdur RJ, et al. Postradiotherapy neck dissection for lymph node-positive head and neck cancer: the use of computed tomography to manage the neck. *J Clin Oncol*. 2006;24(9):1421-1427. Copyright © 2006 by American Society of Clinical Oncology.

If a neck dissection is planned to follow RT in patients with clinically positive lymph nodes, the preoperative dose varies with the size and location of the lymph node, fixation, and response to RT. Preoperative doses

of 50 Gy are sufficient for mobile lymph nodes 3 to 4 cm in size, but 60 Gy or more is recommended for 5- to 6-cm nodes and for fixed nodes. Lymph nodes measuring 7 to 8 cm are almost always fixed to adjacent structures and often require doses of 70 to 75 Gy for the surgeon to achieve a complete resection. If the lymph node lies behind the plane of the spinal cord, electrons may be used to boost the dose after the primary fields have been reduced off the spinal cord after 45 to 50 Gy.[12] Alternatively, IMRT may be employed. Patients in whom the decision is made to add a neck dissection after completion of RT receive full-dose irradiation to the clinically positive neck nodes because the decision depends on the response to RT.

Another technique commonly used for boosting the dose to the neck mass after spinal cord tolerance has been reached, and the treatment to the primary lesion has been completed is opposed anterior and posterior fields with wedges. The final dose to the neck node (not to the entire neck) may be 70 to 80 Gy without exceeding the spinal cord tolerance (Figure 55.9). The anterior and posterior wedge-pair technique is preferable to an appositional electron boost field because high energy electron beams increase the skin and mucosal dose.

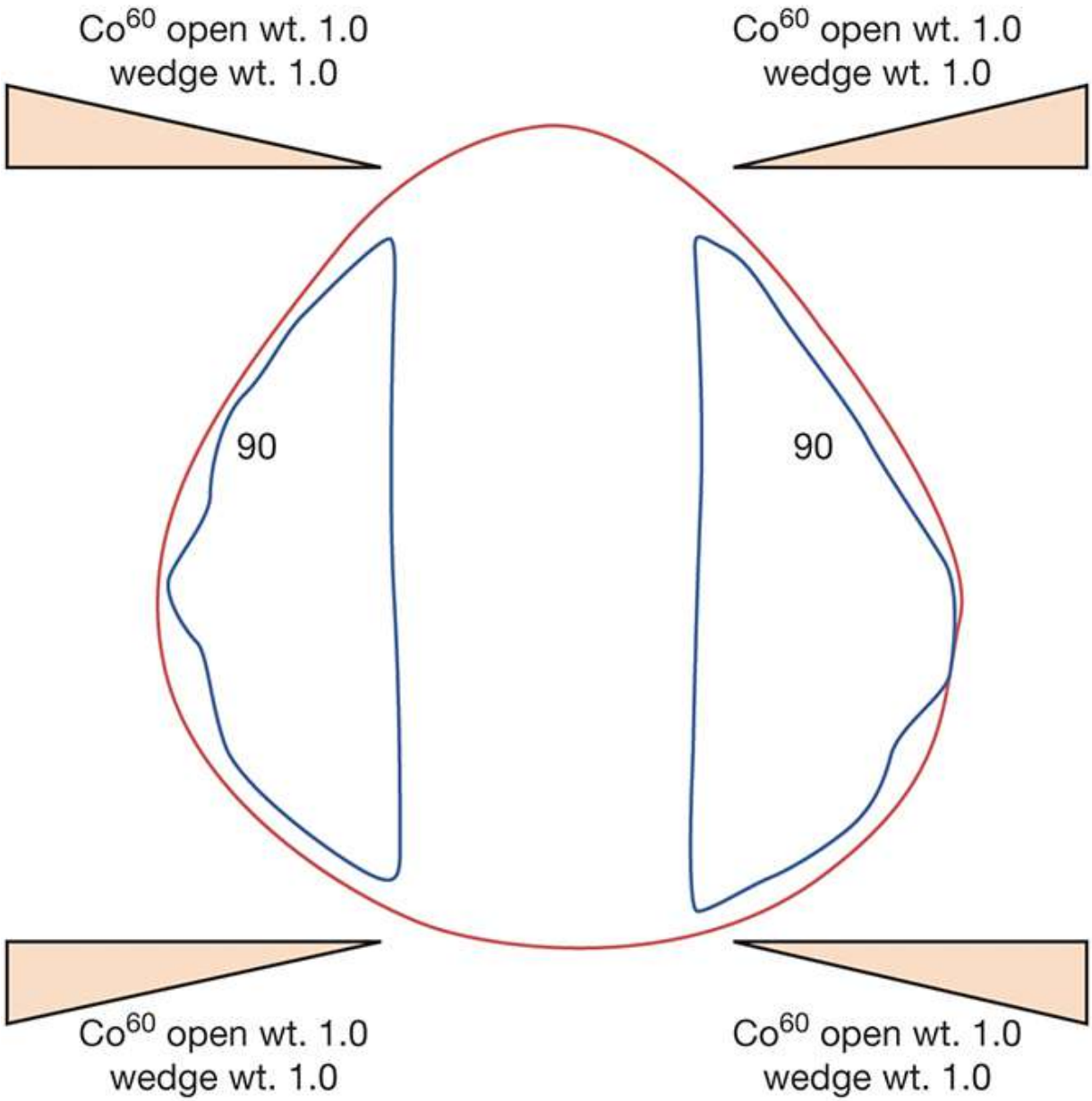

FIGURE 55.9 Dose distribution for anterior and posterior wedge cobalt-60 portals, both fields weighted 1.0.

When the cervical lymph nodes are located superficially, sometimes within 1 cm from the skin or fixed to it, treatment with high energy photon beams (≥6 MV) may underdose these nodes. Treatment should be initiated with cobalt-60 or 4-MV x-rays for the initial 45 to 50 Gy, after which a higher energy photon beam can be used to continue RT of the primary tumor if the neck nodes are clinically negative or if a neck dissection is planned to follow RT (Figure 55.10). Parallel-opposed 6-MV x-ray beams

may adequately treat the upper neck nodes included in the primary treatment fields; however, the supraclavicular nodes in the en face low neck field may be underdosed with a 6-MV beam in very thin patients. Although electrons alone may be used to treat cervical nodes, it is preferable to combine them with photons because of the high surface dose with high electron energies. The use of both 20-MeV electrons and 17-MV x-rays is compared with treatment by 20-MeV electrons alone in a patient with a lateralized lesion of the oropharynx (Figure 55.11).[44] The addition of the 17-MV x-rays to the 20-MeV electrons decreases the surface dose while still adequately irradiating the cervical nodes that are within the primary field. The addition of the x-ray beam also produces a dose distribution that is less affected by bone than that from the electron beam alone.

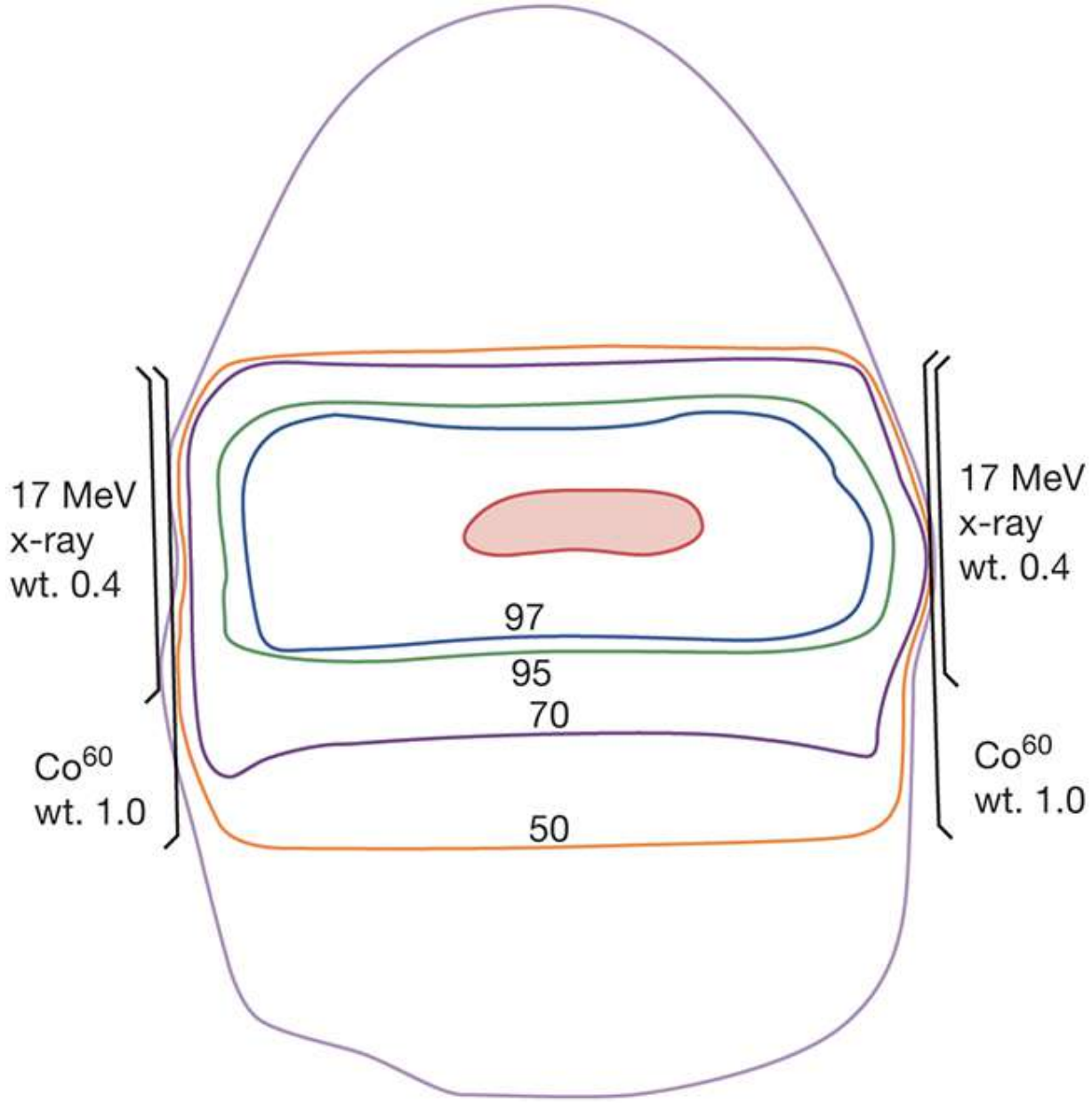

FIGURE 55.10 Dose distribution for parallel-opposed cobalt-60 portals, each weighted 1.0, with reduced 17-MV x-ray portals, each weighted 0.4.

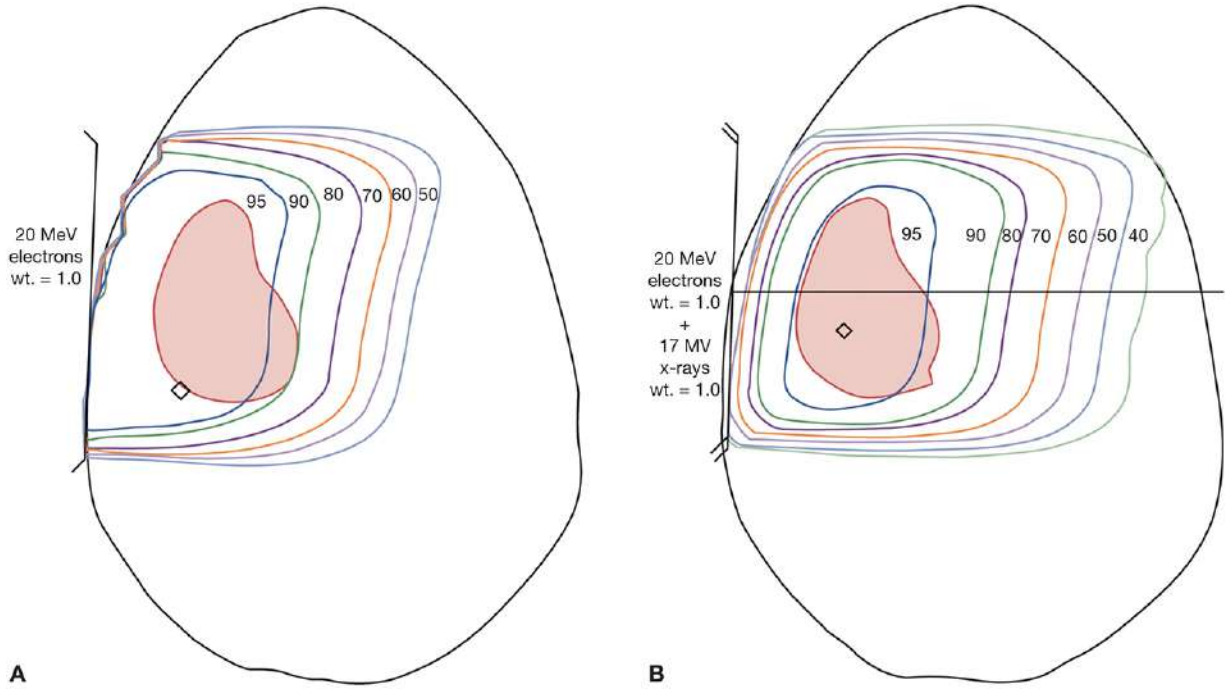

FIGURE 55.11 A. Dose distribution for 20-MeV electrons, field size 8.5 cm by 8.5 cm, SSD 100 cm. B. Dose distribution for 20-MeV electrons, field size 8.5 cm by 8.5 cm, and 17-MV x-rays, field size 7 cm by 7 cm, SSD 100 cm for both. The given doses are weighted 1 to 1. The addition of the 17-MV x-ray beam reduces the surface dose and gives a dose distribution that is affected less by bone. SSD, source to skin distance. (Reprinted with permission from Bova FJ. Treatment planning for irradiation of head and neck cancer. In: Million RR, Cassisi NJ, eds. *Management of Head and Neck Cancer: A Multidisciplinary Approach*. 2nd ed. J.B. Lippincott; 1994:306.)

Large lymph nodes may not show much regression during the course of RT but often show significant regression from completion of treatment to the time the patient returns for neck dissection, usually after 4 to 6 weeks. The mass frequently has a thick capsule that facilitates its removal at the time of neck dissection.

Patients with bilateral neck disease require individualized treatment planning jointly by the radiation oncologist and the surgeon. If the disease is minimal on one side, RT alone may be used to control the disease on that side of the neck, and a neck dissection may be used on the side with more disease. If a major bilateral disease is present, bilateral neck dissection should follow RT.

Complications of Neck Irradiation

The complications of neck irradiation include subcutaneous fibrosis and lymphedema of the larynx and submentum. The latter complications may be minimized by sparing an anterior strip of skin when designing the parallel-opposed lateral portals used to encompass the primary lesion. The probability of complications is directly related to the radiation dose with little, if any, morbidity observed with the doses used for elective radiation therapy of the neck.

Complications of neck treatment in patients who receive RT in conjunction with resection of the primary lesion and a neck dissection are essentially the same as those occurring after neck dissection. However, they occur with an increased incidence depending on the RT dose and extent of surgery.

Treatment of the Neck After Incisional or Excisional Biopsy

Open biopsy of a clinically positive neck node before definitive treatment potentially spills tumor cells along tissue planes that may not be removed with a radical neck dissection. McGuirt and McCabe[45] reported that incisional or excisional biopsy of positive neck nodes before definitive surgery increased the risk of neck failure and worsened the prognosis for patients with SCC of the head and neck. Parsons et al[46] reported their experience with incisional or excisional biopsy of positive neck nodes followed by RT as the initial step in the treatment of the patient; these data were updated by Mack et al.[47] After excisional biopsy of a single lymph node, RT alone to the primary lesion and to the neck resulted in a 95% rate of neck control.[47] If residual disease remained in the neck after biopsy, RT followed by neck dissection was more successful than RT alone for controlling neck disease (Table 55.9).

TABLE 55.9 EFFECT OF NECK NODE BIOPSY ON 5-YEAR RATE OF NECK CONTROL (660 HEMINECKS)

	No Neck Biopsy		Neck Biopsy		
Hemineck Stage	Number of Heminecks	Probability of Hemineck Control (%)	Number of Heminecks	Probability Hemineck of Control (%)	Significance of Difference Between Curves
N1	253	87 ± 3	12	100	*P* = .22
N2A	53	73 ± 8	15	93 ± 6	*P* = .18
N2B	218	78 ± 3	23	72 ± 11	*P* = .86
N3A	69	54 ± 7	17	81 ± 10	*P* = .30

From Ellis ER, Mendenhall WM, Rao PV, et al. Incisional or excisional neck-node biopsy before definitive radiotherapy, alone or followed by neck dissection. *Head Neck*. 1991;13(3):177-183. Copyright © 1991 Wiley Periodicals, A Wiley Company. Reprinted by permission of John Wiley & Sons.

If the primary lesion is to be treated surgically, the patient's neck is typically treated with a completion neck dissection followed by RT. If the primary lesion is to be treated with RT, the patient is treated with RT. If there is no palpable disease remaining in the neck after excisional biopsy of a positive node, the neck may be treated with RT alone. If an incisional biopsy of the node has been performed (leaving gross disease) or if other positive nodes remain after an excisional neck node biopsy, a completion neck dissection is performed with removal of skin over the biopsy site as well as any other structures involved by cancer. RT follows the surgical procedure. The dose of RT preceding a neck dissection depends on the amount of gross disease in the neck and the degree of fixation.[1]

TREATMENT OF THE NECK AFTER SURGERY

Patients treated surgically generally undergo resection of the primary cancer and a unilateral or bilateral neck dissection depending on the location and extent of the primary and presence and extent of positive neck nodes. Indications for postoperative RT include positive or close (<5 mm) margins, initially positive margins with negative separately submitted margins, extracapsular extension, multiple positive nodes, lymphovascular space invasion, perineural invasion, bone or cartilage invasion, extension into the soft tissues of the neck, invasion of the apex of the pyriform sinus, and

subglottic extension of 1 cm or more. The highest risk indications are positive margins and extracapsular extension and require the addition of concomitant cisplatin during the course of postoperative RT. Because of the risk of increased radioresistance due to tumor cells being in potentially hypoxic tissues, the minimum dose is 60 Gy at 2 Gy per once-daily fraction. Areas at higher risk may be boosted to doses in the range of 66 to 70 Gy. Alternatively, patients at particularly high risk may be treated with hyperfractionation at 1.2 Gy per twice-daily fraction to doses up to 74.4 or 70 Gy in 35 fractions over 6 weeks treating twice daily once weekly for the last 5 weeks of RT. Consideration may be given to treating the primary site alone if the neck nodes are pathologically negative. Postoperative RT is not employed for the sole indication to electively treat the clinically negative neck in lieu of a neck dissection. Patients with a clinically negative neck who will require postoperative RT may forego a neck dissection and the neck irradiated in conjunction with the primary site.

RESULTS OF TREATMENT

Clinically Negative Nodes

Elective neck dissection and elective neck irradiation are equally effective in controlling subclinical disease. The decision whether to use surgery or RT for the purpose of electively treating the neck nodes depends on the method used to treat the primary lesion. Patients with a relatively early primary lesion and clinically negative nodes should be treated with one modality. Patients whose primary lesion is treated surgically may undergo an elective neck dissection, and those whose primary lesion is to be treated with RT should be considered for elective neck irradiation. Patients who develop a local recurrence on a metachronous second primary after RT for an SCC with a cN0 neck in whom the neck has been irradiated may be treated with surgery to the primary site alone and the neck observed because the likelihood of subclinical disease in the cervical lymphatics is <10%.[48,49]

The results of elective neck irradiation at the University of Florida for patients with SCC of the head and neck in whom the primary lesion was controlled are shown in Table 55.10.[4,50] Patients were divided into three risk categories based on the estimated risk of subclinical disease in the neck as follows: group I, low risk (<20% likelihood of occult disease); group II,

moderate risk (20%-30% risk of occult disease); and group III, high risk (more than 30% likelihood of occult disease). There were six neck failures (21%) in 28 patients who did not receive elective neck irradiation and eight neck failures (5%) in 162 patients who received elective neck irradiation. Of the eight failures in patients receiving elective neck irradiation, two occurred within the irradiation fields, one at the field margin, and five in out-of-field areas. No correlation was found between the rate of tumor control in the first-echelon lymph nodes and the irradiation dose for doses ranging from 40 to 55 Gy or greater.[4] Only one failure occurred in the first-echelon lymph nodes, and this was after 48 Gy in 25 fractions using continuous-course irradiation.[4] The low neck, defined as that part of the neck located below the treatment portals used to treat the primary lesion, received either 50 Gy in 25 fractions or 40.5 Gy in 15 fractions, specified at D_{max} (0.5 cm depth). Both dose fractionation protocols were equally effective in sterilizing subclinical disease in the low neck.[51] Elective neck irradiation is equally efficacious for SCC arising from various head and neck primary sites.

TABLE 55.10 CONTROL OF DISEASE IN THE CLINICALLY NEGATIVE NECK WITH ELECTIVE NECK IRRADIATION (NUMBER CONTROLLED/NUMBER TREATED)

Risk Group	No ENI (%)	Partial ENI (%)	Total ENI (%)
I (<20%)	13/15 (87)	16/17 (94)	1/1 (100)
II (20%-30%)	6/9 (67)	34/38 (89)	10/11 (91)
III (>30%)	3/4 (75)	32/33 (97)	61/62 (98)

ENI, elective neck irradiation.

Reprinted from Mendenhall WM, Million RR. Elective neck irradiation for squamous cell carcinoma of the head and neck: analysis of time-dose factors and causes of failure. *Int J Radiat Oncol Biol Phys*. 1986;12(5):741-746. Copyright © 1986 Elsevier. With permission.

In patients in whom primary failure occurs in addition to failure in the clinically negative nodes, the chances of surgical salvage are poor. In patients in whom the primary lesion is controlled and in whom failure develops in the initially negative neck, the chances of salvage with neck dissection are approximately 60%.

Although elective neck irradiation significantly reduces the risk of neck recurrence, there is no definite evidence that it improves survival. It would be necessary to conduct a large randomized trial to detect a survival difference, if one exists. Another problem is that the first-echelon lymph nodes are often included in the treatment portals used to treat the primary lesion so that it is often impossible to avoid at least partial elective neck irradiation. Therefore, such a trial would have to be restricted to primary sites where the portals would have to be enlarged to electively irradiate the neck or to patients treated with elective neck dissection rather than elective neck irradiation. Vandenbrouck et al[52] and Fakih et al[53] have conducted randomized trials comparing elective neck dissection with no elective neck treatment for patients with oral cavity carcinoma and oral tongue cancer, respectively. No survival advantage was noted for patients undergoing elective neck dissection in either study. However, because of the small number of patients in both trials, it is likely that even if a survival difference existed, it would have been missed. Subsequently, a randomized trial was conducted at the Tata Memorial Hospital (Mumbai) where 596 patients with T1-T1 N0 SCCs of the oral cavity were randomized to resection of the primary and observation of the neck or to resection of the primary and elective neck dissection. Those in the latter group had significantly improved overall survival at 3 years (80% vs 68%; $P = .01$).[54]

Dearnaley et al[55] reported on a series of 148 patients treated with an interstitial implant, either alone or combined with external-beam RT, for cancer of the tongue or floor of the mouth. Of 131 patients with negative neck nodes at diagnosis, 59 (45%) received elective neck irradiation to a dose of 40 Gy or greater. A multivariate analysis showed that elective neck irradiation significantly improved survival and reduced the risk of dying of cancer. Piedbois et al[56] reported a series of 233 patients with T1-2N0 carcinoma of the oral cavity treated with interstitial iridium brachytherapy: 123 patients received no elective neck treatment, and 110 patients underwent elective neck dissection. Patients who received an elective neck dissection tended to have more advanced primary lesions. Although the ultimate rates of neck control were similar, a multivariate analysis showed that elective neck dissection was significantly associated with improved survival.

Clinically Positive Nodes

The incidence of treatment failure in the neck by N stage and treatment category has been reported by the MD Anderson Cancer Center (Table 55.11) and the University of Florida (Table 55.12 and Figure 55.13).[57,58] In patients in whom the neck is treated with combined modalities, RT precedes surgery when the primary site is to be treated with irradiation or when the node is incompletely resectable. Surgery precedes RT when the primary site is to be treated operatively and the nodes are resectable.

TABLE 55.11 FAILURE OF INITIAL IPSILATERAL NECK TREATMENT: 596 PATIENTS WITH CARCINOMA OF THE TONSILLAR FOSSA, BASE OF TONGUE, SUPRAGLOTTIC LARYNX, OR HYPOPHARYNX

	N0							
Treatment[a]	No Treatment	Partial Treatment	Complete Treatment	N1 (%)	N2A (%)	N2B (%)	N3A (%)	N3B (%)
Irradiation								
		15%	2%	15	27	27	38	34
Surgery	55% (16/29)	35%	7%	11	8	23	42	41
Combined		1/5	0/6	0	0	0	23	25

[a]MD Anderson Cancer Center data; patients treated 1948-1967.

Modified from Barkley HT Jr, Fletcher GH, Jesse RH, Lindberg RD. Management of cervical lymph node metastases in squamous cell carcinoma of the tonsillar fossa, base of tongue, supraglottic larynx, and hypopharynx. *Am J Surg*. 1972;124(4):462-467. Copyright © 1972 Elsevier. With permission.

TABLE 55.12 FIVE-YEAR RATE OF NECK CONTROL BY 1983 AJCC STAGE AND TREATMENT (459 PATIENTS; 593 HEMINECKS)

	Irradiation Alone		Irradiation + Neck Dissection		
Stage	Number Heminecks	Control (%)	Number Heminecks	Control (%)	Significance
N1	215	86	38	93	$P = .28$
N2A	29	79	24	68	$P = .6$
N2B	138	70	80	91	$P < .01$
N3A	29	33	40	69	$P < .01$

AJCC, American Joint Committee on Cancer.
Excludes 67 heminecks on which incisional or excisional biopsy was done before treatment.
University of Florida data; patients treated October 1964 to October 1985; analysis December 1988 by Eric R. Ellis, MD.

TABLE 55.13 CERVICAL METASTASIS APPEARING IN THE CONTRALATERAL N0 NECK: 596 PATIENTS WITH THE CARCINOMA OF TONSILLAR FOSSA, BASE OF TONGUE, SUPRAGLOTTIC LARYNX, OR HYPOPHARYNX

	Stage				
Treatment[a]	N0 (%)	N1 (%)	N2A (%)	N2B (%)	N3A (%)
Irradiation	4	2	9	7	0
Surgery	25	17	23	43	33
Combined	0	0	0	11	0

[a]MD Anderson Hospital data; patients treated 1948-1967.
Adapted from Barkley HT Jr, Fletcher GH, Jesse RH, Lindberg RD. Management of cervical lymph node metastases in squamous cell carcinoma of the tonsillar fossa, base of tongue, supraglottic larynx, and hypopharynx. *Am J Surg*. 1972;124(4):462-467. Copyright © 1972 Elsevier. With permission.

When the initial treatment is surgery, a neck dissection is sufficient treatment for patients with a single positive lymph node <3 cm unless there is extracapsular spread of disease. RT may be added for control of subclinical disease in the contralateral side of the neck (Table 55.14).[57] The presence of multiple positive nodes in the surgical specimen is an indication for postoperative RT of the neck, especially when positive nodes are found at more than one level.[6,59,60]

TABLE 55.14 LYMPH NODE DISEASE CONTROL BY RADIATION TREATMENT TECHNIQUE (NUMBER CONTROLLED/NUMBER TREATED)

Node Size (cm)	Continuous Course (%)	Split Course (%)	Excluded[a]	Total (%)
<1.0	5/5	2/2	1/1	8/8
1.0	29/35 (83)	19/23 (85)	3/4	51/62 (82)
1.5-2.0	43/49 (88)	20/24 (83)	5/9	68/82 (83)
2.5-3.0	14/19 (74)	10/18 (56)	0/3	24/40 (60)
3.5-6.0	14/20 (70)	10/17 (59)	0/1	24/38 (63)

Node Size (cm)	Continuous Course (%)	Split Course (%)	Excluded[a]	Total (%)
≥7.0	0/2	0/5	0/1	0/8

[a]Less than 50 Gy for nodes equal to 1.0 cm and <55 Gy for nodes equal to 1.5 cm.
Modified from Mendenhall WM, Million RR, Bova FJ. Analysis of time-dose factors in clinically positive neck nodes treated with irradiation alone in squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys*. 1984;10(5):639-643. Copyright © 1984 Elsevier. With permission.

Olsen et al[61] reported a series of 284 patients who underwent neck dissection at the Mayo Clinic for pathologic stages N1 and N2 SCC of the head and neck; no patient received adjuvant therapy. Neck recurrence-free survival rates at 5 years were as follows: N1, 76%; N2, 60%; and overall, 69%. A multivariate analysis showed that four or more positive nodes (P = .005), invasion of lymphatic or vascular spaces (P = .003), invasion of soft tissue (P = .0008), and a desmoplastic stromal pattern (P = .0001) were significantly associated with an increased risk of recurrence in the neck.[61]

The postoperative dose prescribed is usually 60 Gy in 30 fractions to 65 Gy in 35 fractions over 6 to 7 weeks for patients with negative margins; higher doses may be prescribed when residual disease is present in the neck.[59,62,63] If RT is to be added after surgery, it is usually initiated within 4 to 6 weeks after the operation, although it has been reported that a delay to 10 weeks is not associated with an increased risk of neck failure.[59]

The rate of control for neck nodes treated with RT alone as a function of node size, treatment scheme, and dose is shown in Table 55.14. RT alone is sufficient for patients with N1 (up to 2 cm) disease as long as the fraction size (2 Gy) and the total dose are sufficient.[36] RT followed by neck dissection has provided better rates of disease control than RT alone for patients with more advanced neck disease. The rate of neck disease control for patients treated with twice-daily RT, alone or followed by neck dissection, is shown in Figure 55.12 and shows a significant improvement in the control rates when neck dissection was added in selected cases.[64,65] As shown in a multivariate analysis by Ellis et al,[66] the addition of neck dissection after RT is independently related to a significantly decreased risk of disease-specific death. At least 50 Gy should be given preoperatively to the lymph nodes, although doses vary according to the size and degree of fixation of the lymph node. For example, large, fixed lymph nodes require

70 to 75 Gy of preoperative RT (Table 55.15). The likelihood of disease control in each side of the neck treated with irradiation and neck dissection is decreased when the node is fixed before treatment or when residual tumor is found in the pathologic specimen (Tables 55.16 and 55.17).[12] No difference is seen in the rate of control as a function of the interval between RT and neck dissection when comparing patients who have surgery within 6 weeks with those who have neck dissection more than 6 weeks after RT.[12] If a local recurrence occurs, prior combined treatment of the neck does not diminish the chance of successful surgical salvage of the patient.[67] The likelihood of disease control at the primary site was not found to be related to neck stage at diagnosis in patients treated with RT alone or followed by neck dissection at the University of Florida[68]; this finding is different from what others have reported.[69]

TABLE 55.15 CERVICAL LYMPH NODE DISEASE CONTROL WITH RADIATION THERAPY FOLLOWED BY NECK DISSECTION, WITH PRIMARY LESION TREATED INITIALLY BY RADIATION THERAPY (NUMBER CONTROLLED/NUMBER TREATED)

	Minimum Node Dose (Gy)			
Minimum Node Diameter (cm)	**<50**	**50–50.99**	**60–69.99**	**≥70**
<3	5/5	1/2	5/5	3/3
3-4	6/8	10/14	9/9	5/7
5-6	4/7	5/5	7/8	4/4
7-8	2/3	2/4	4/6	3/4
≥9	No data	1/1	2/4	0/1

University of Florida data; patients treated 1964-1982; analysis 1984 by W.M. Mendenhall, MD. Ninety-one patients were treated with once-a-day fractionation, continuous- or split-course technique (100 heminecks).

Reprinted from Mendenhall WM, Million RR, Cassisi NJ. Squamous cell carcinoma of the head and neck treated with radiation therapy: the role of neck dissection for clinically positive neck nodes. *Int J Radiat Oncol Biol Phys*. 1986;12(5):733-740. Copyright © 1986 Elsevier. With permission.

TABLE 55.16 CONTROL OF DISEASE IN THE NECK AS A FUNCTION OF NODE MOBILITY (109 PATIENTS; 121 HEMINECKS)

Size (cm)	Proportion of Nodes Fixed (%)	Number Heminecks Controlled/Number Treated	
		Mobile or Tethered (%)	Fixed (%)
<3	1/23 (4)	19/22 (86)	1/1 (100)
3-4	4/44 (9)	33/40 (83)	2/4 (50)
5-6	9/27 (33)	17/18 (94)	6/9 (67)
7-8	10/21 (48)	8/11 (73)	5/10 (50)
≥9	3/6 (50)	2/3 (67)	1/3 (33)

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TABLE 55.17 NECK DISEASE CONTROL AS A FUNCTION OF PATHOLOGIC FINDINGS IN THE NECK DISSECTION SPECIMEN (108 PATIENTS; 120 EVALUABLE HEMINECKS)

Size (cm)	Number Heminecks Controlled/Number Treated		
	Proportion With Specimens Positive (%)	Negative Specimen (%)	Positive Specimen (%)
<3	10/23 (43)	13/13 (100)	7/10 (70)
3-4	22/43 (51)	20/21 (95)	14/22 (64)
5-6	10/27 (37)	17/17 (100)	6/10 (60)
7-8	12/21 (57)	8/9 (89)	5/12 (42)
≥9	4/6 (67)	2/2 (100)	1/4 (25)

One patient was excluded because data were unavailable.

Reprinted from Mendenhall WM, Million RR, Cassisi NJ. Squamous cell carcinoma of the head and neck treated with radiation therapy: the role of neck dissection for clinically positive neck nodes. *Int J Radiat Oncol Biol Phys*. 1986;12(5):733-740. Copyright © 1986 Elsevier. With permission.

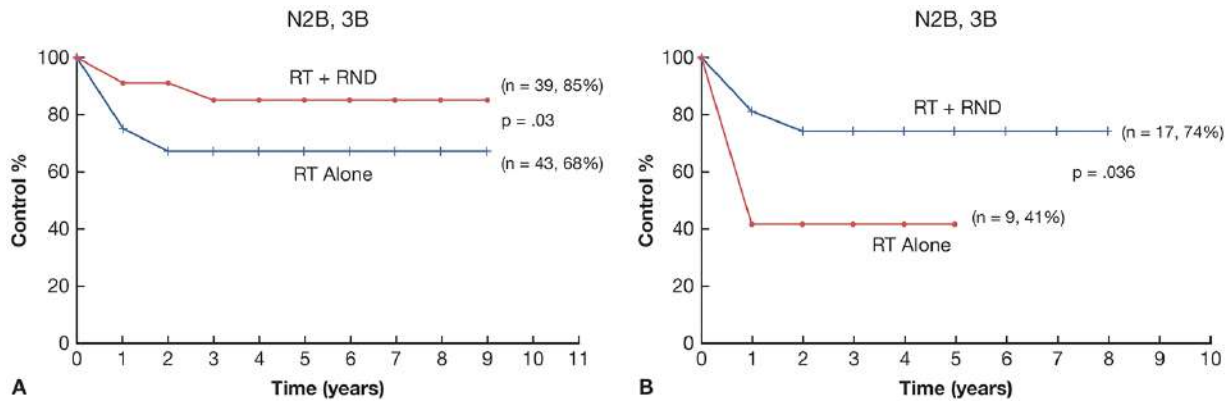

FIGURE 55.12 Rate of neck disease control (life table method[83]) for patients treated with twice-daily irradiation alone or combined with neck dissection (radiotherapy [RT] plus residual neck dissection [RND]) for clinically positive neck nodes. A. N2B, N3B. B. N2A, N3A. (From Parsons JT, Mendenhall WM, Cassisi NJ, Stringer SP, Million RR. Neck dissection after twice-a-day radiotherapy: morbidity and recurrence rates. *Head Neck*. 1989;11[5]:400-404. Copyright © 1989 Wiley Periodicals, A Wiley Company. Reprinted by permission of John Wiley & Sons.)

Results After Incisional or Excisional Biopsy

Patients who have undergone an incisional or excisional biopsy of a metastatic lymph node before referral do not have an increased risk of neck failure or a decreased cure rate if RT is the next step in treatment.[46] The likelihood of control and the cure rate are probably diminished if an operation without prior RT follows an incisional or excisional biopsy of a metastatic neck node because of the risk that the biopsy procedure disseminated tumor cells into tissues not removed by neck dissection.[45]

Ellis et al[66] reported on 508 patients with 660 positive heminecks treated at the University of Florida with RT alone or followed by a planned neck dissection. Pretreatment node biopsy did not influence the outcome when RT was the next step in treatment (see Table 55.9).[66] The results of the forward stepwise log-rank tests of prognostic factors for predicting time to recurrence are shown in Table 55.18.[66]

TABLE 55.18 PROGNOSTIC FACTORS, IN ORDER OF THEIR IMPORTANCE, FOR PREDICTING THE TIME TO OCCURRENCE OF VARIOUS EVENTS

Event	Rank Order	Factor	Level of Significance
Recurrence in neck (*n* = 660 heminecks)	1	Increasing *N* stage	*P* = .0001
	2	Treatment neck of with RT alone	*P* = .0001
	3	Fixed nodes	*P* = .0001
	4	T stage[a]	*P* = .0350
Death with disease present (*n* = 508 patients)	1	Recurrence above clavicles	*P* = .0001
	2	Increasing *N* stage	*P* = .0003
	3	Fixed nodes	*P* = .0053
	4	Treatment of with neck RT alone	*P* = .0121
For occurrence of distant metastasis (*n* = 508 patients)	1	Recurrence above clavicles	*P* = .0001
	2	Increasing *N* stage	*P* = .0003
	3	Fixed nodes	*P* = .0704
	4	Nodes below thyroid notch	*P* = .1023

RT, radiation therapy.

[a]This factor is thought to be correlated with the censoring pattern.

From Ellis ER, Mendenhall WM, Rao PV, et al. Incisional or excisional neck-node biopsy before definitive radiotherapy, alone or followed by neck dissection. *Head Neck*. 1991;13(3):177-183. Copyright © 1991 Wiley Periodicals, A Wiley Company. Reprinted by permission of John Wiley & Sons.

Zenga et al[70] reported on 45 patients from 1998 to 2012 who underwent open biopsy for human papillomavirus (HPV)-positive oropharyngeal cancer. All patients underwent definitive surgical treatment. Disease-specific survival was 98% versus 99% in a control group who did not undergo an open biopsy. Only 7% of the open biopsy group were found to have dermal metastases in the excised skin. It is known that hypoxic tissues, such as a scar, are increasingly resistant to RT. Thus, excision of the biopsied area along with a neck dissection will improve the efficacy of adjuvant RT. This study questions the idea that previous open biopsy

adversely affects patient outcomes in this subset of patients. Neck dissection is an effective primary treatment for previously violated neck nodes. However, an adjuvant dose of RT with 60 to 70 Gy is needed to minimize recurrence rates.

CERVICAL LYMPH NODE METASTASIS WITH UNKNOWN PRIMARY TUMOR

In a small percentage of patients with enlarged cervical lymph nodes, the primary lesion cannot be found, even after extensive evaluation.[71-73] Patients with enlarged lymph nodes in the upper neck have a good prognosis when treated aggressively, compared with those with enlarged lymph nodes in the low IJC or supraclavicular fossa. The latter patients are more likely to have primary lesions located below the clavicles, which carry a much worse prognosis. The majority of patients have either SCC or poorly differentiated carcinoma. Those with adenocarcinoma almost always have a primary lesion below the clavicles, although, if the nodes are located in the upper neck, one must exclude a salivary gland, thyroid, or parathyroid primary tumor. This section deals with patients presenting with SCC or poorly differentiated carcinoma in the upper or middle neck.

Patients should be evaluated with a thorough physical examination, including careful evaluation of the head and neck. A needle biopsy of the lymph node should be performed. After chest roentgenography, a CT or MRI of the head and neck is obtained to detect an unknown primary lesion arising from the mucosa of the head and neck. It is unclear whether FDG-PET scans may identify primary lesions that would not otherwise be identifiable.[74] The available data suggest that some patients will benefit from these studies. Direct laryngoscopy and examination under anesthesia are performed with directed biopsies of the nasopharynx, tonsils, base of the tongue, and pyriform sinuses, and of any abnormalities noted on CT or MRI or suspicious mucosal lesions noted at laryngoscopy. Patients with adequate lymphoid tissue in their tonsillar fossae should undergo at least an ipsilateral tonsillectomy. The likelihood of bilateral tonsillar carcinomas is probably less than 5% and may prompt some surgeons to perform bilateral tonsillectomy. If a contralateral tonsillar malignancy is missed and the patient is treated with an ipsilateral field arrangement for an ipsilateral

tonsillar cancer, salvage treatment would probably be compromised. The diagnostic evaluation for the patient with cervical metastasis from an unknown head and neck primary lesion is summarized in Table 55.19. The results of a diagnostic evaluation for an unknown primary site in 236 patients at the University of Florida are depicted in Table 55.20.[75] Overall, 132 primary sites were discovered in 126 (53%) patients and were most often located in the oropharynx: tonsillar fossa, 59 (45%); base of the tongue, 58 (44%); pyriform sinus, 10 (8%); pharyngeal wall, 3 (2%); and supraglottic larynx, 1 (1%).[75]

TABLE 55.19 DIAGNOSTIC WORKUP FOR CERVICAL LYMPH NODE METASTASES: UNKNOWN PRIMARY TUMOR

General
History
Physical examination
Careful examination of neck and supraclavicular regions
Examination oral of cavity, pharynx, and larynx (indirect laryngectomy)
Radiographic Studies
Chest roentgenogram
Computed tomography or magnetic resonance imaging of head and neck (special attention to nasopharynx, pharynx, and larynx)
Laboratory Studies
Complete cell blood count
Blood chemistry profile
Direct and Laryngoscopy-Directed Biopsies
Nasopharynx, tonsils, base of tongue, pyriform and sinuses, any suspicious abnormal or mucosal areas
Fine-needle aspirate or core needle biopsy of the cervical node
Tonsillectomy

TABLE 55.20 DETECTION OF PRIMARY SITE VERSUS PATIENT GROUP

Patient Group	Biopsy-Proven Primary of Patients Site/Number (%)
PE−/RAD−	21/72 (29.2)

Patient Group	Biopsy-Proven Primary of Patients Site/Number (%)
PE−/RAD+	51/82 (62.2)
PE+/RAD−	15/25 (60.0)
PE+/RAD+	39/57 (68.4)
Total	126/236 (53.4)

PE−, physical examination negative; PE+, physical examination suspicious, but not definitely positive; RAD−, radiologic examination negative; RAD+, radiologic examination (computed tomography and/or magnetic resonance imaging) suspicious, not definitively positive.

From Cianchetti M, Mancuso AA, Amdur RJ, et al. Diagnostic evaluation of squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck primary site. *Laryngoscope*. 2009;119(12):2348-2354. Copyright © 2009 The American Laryngological, Rhinological, and Otological Society. Reprinted by permission of John Wiley & Sons.

Some patients may be cured with treatment directed only to the involved area of the neck[76]; however, the authors usually irradiate the nasopharynx and oropharynx as well as both sides of the neck. The hypopharynx and larynx were irradiated as well until 1997 when it was decided to eliminate them because they are rarely the site of the primary cancer and because irradiation of these sites significantly increases the morbidity of treatment. It is not necessary to irradiate the oral cavity unless the patient has submandibular adenopathy, in which case the authors either do a neck dissection and observe the patient or irradiate the oral cavity and oropharynx and not the nasopharynx. Patients are treated with parallel-opposed fields at 1.8 Gy per fraction to a midline dose of 64.8 Gy with a reduction of the spinal cord at 45 Gy tumor dose (Figure 55.13). An alternative is to use IMRT to spare the contralateral parotid gland in patients with ipsilateral neck nodes. The lower neck is treated through a separate en face anterior field. IMRT may be used if patients have unilateral neck disease to reduce the dose to the contralateral parotid.

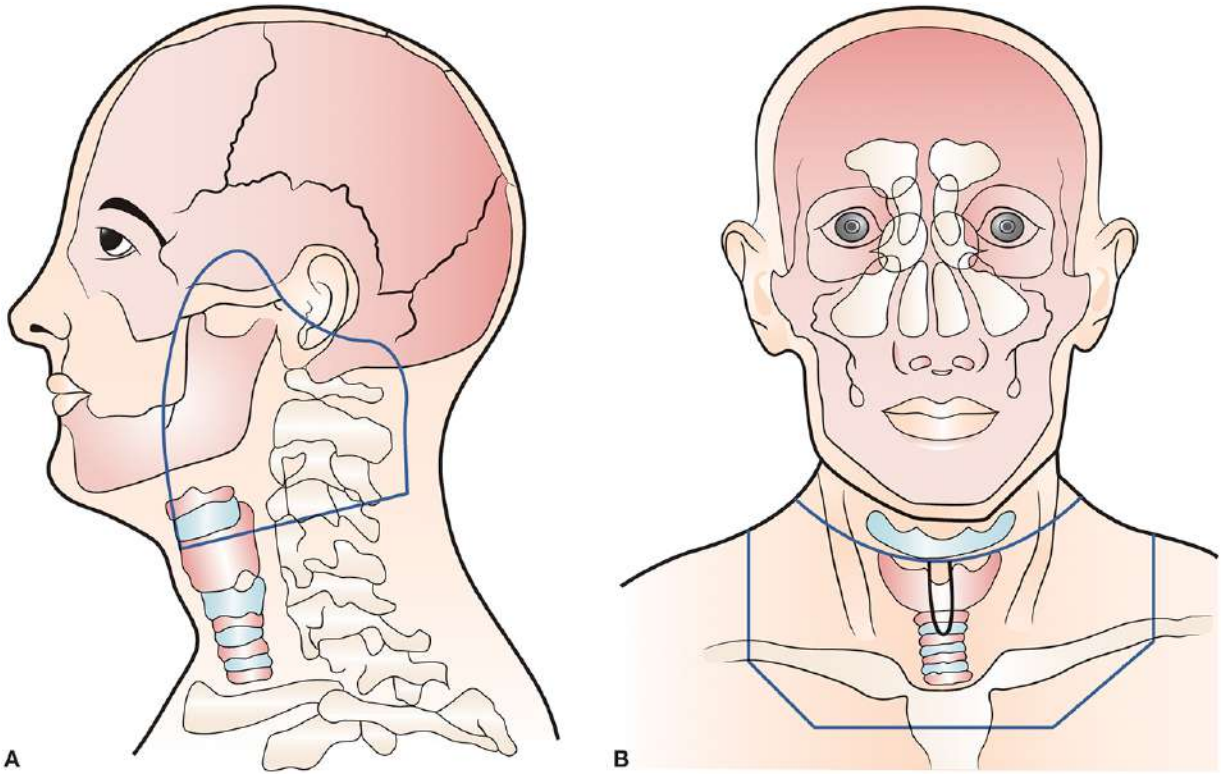

FIGURE 55.13 Radiation therapy portals used starting from 1997 to treat head and neck mucosal sites and upper cervical lymph nodes (A) and lower cervical and supraclavicular lymph nodes (B). The inferior border for lateral portals is placed at the superior anterior border of the thyroid cartilage, shielding the hypopharynx and larynx. (Reprinted from Erkal HS, Mendenhall WM, Amdur RJ, Villaret DB, Stringer SP. Squamous cell carcinomas metastatic to cervical lymph nodes from an unknown head-and-neck mucosal site treated with radiation therapy alone or in combination with neck dissection. *Int J Radiat Oncol Biol Phys*. 2001;50[1]:55-63. Copyright © 2001 Elsevier. With permission.)

Erkal et al[72] reported on patients 126 with treated curative intent at the University of Florida between 1964 and 1997 with follow-up for at least 2 years. RT was delivered to head and neck mucosal sites and both sides of the neck in 119 patients and to the neck alone in 7 patients. Twelve (10%) patients developed SCC in a head and neck mucosal site at 0.5 to 10.9 years (median, 1.8 years) after treatment. The 5-year results were as follows: head and neck mucosal failure, 13%; neck node control, 78%; distant metastases, 14%; absolute survival, 47%; and cause-specific survival, 67%. Wallace et al[77] reported a combined series of 179 patients treated at the University of Florida (139 patients) and the University of Wisconsin (40 patients). The 5-year mucosal control rate was 92%; the head and neck mucosa was irradiated in 174 (97%) patients. For the subset of 28 patients where the

mucosal RT was limited to the nasopharynx and oropharynx, the 5-year mucosal control rate was 100%. De Leo et al[78] subsequently reported on 50 patients treated with the larynx-sparing technique described above between 1997 and 2019 at the authors' institution; none of these patients developed a head and neck mucosal SCC after receiving RT.

Colletier et al[79] reported on 136 patients treated with neck dissection followed by RT to head and neck mucosal sites and bilateral lymph nodes. Six percent of patients developed carcinomas in head and neck mucosal sites within RT portals, and 4% of patients developed carcinomas in head and neck mucosal sites outside the RT portals. The absolute survival rate at 5 years was 60%. The authors recommended RT to head and neck mucosal sites. Reddy and Marks[80] reported on 16 patients with RT to ipsilateral lymph nodes and 36 patients with RT to head and neck mucosal sites and bilateral lymph nodes. The authors concluded that RT reduced the rate of developing carcinomas in head and neck mucosal sites. For patients with no RT to head and neck mucosal sites, the rate of developing carcinomas in head and neck mucosal sites was 46% and the absolute survival rate at 5 years was 47%. For patients treated with RT to head and neck mucosal sites, the rates were 8% and 53%, respectively. Grau et al[81] reported on 273 patients treated with curative intent at five cancer centers in Denmark between 1975 and 1995 with surgery alone (23 patients), RT to the ipsilateral neck either alone or combined with surgery (26 patients), and RT to the neck and head and neck mucosa either alone or combined with surgery (224 patients). The ipsilateral oropharynx unintentionally received some RT in patients treated to the ipsilateral neck alone, depending on the treatment technique. The 5-year rates of freedom from failure in the head and neck mucosa were as follows: surgery alone, 45%; RT with or without surgery to the ipsilateral neck, 77%; and RT to the head and neck mucosa with or without surgery, 87%. The oropharynx, particularly the base of the tongue, was the most common location of mucosal site failure.

The incidence of subsequent mucosal primary lesions was compared by Erkal et al[82] for 1,112 patients with a known primary site (oropharynx, hypopharynx, and supraglottis) and a series of 126 patients treated for an unknown primary site at the University of Florida. The incidence of subsequent mucosal head and neck cancer was similar for both groups, suggesting either that mucosal irradiation significantly reduced the risk of

primary site failure or that patients with unknown primary sites have a much lower risk of a second primary head and neck cancer developing subsequently (Figure 55.14).[72]

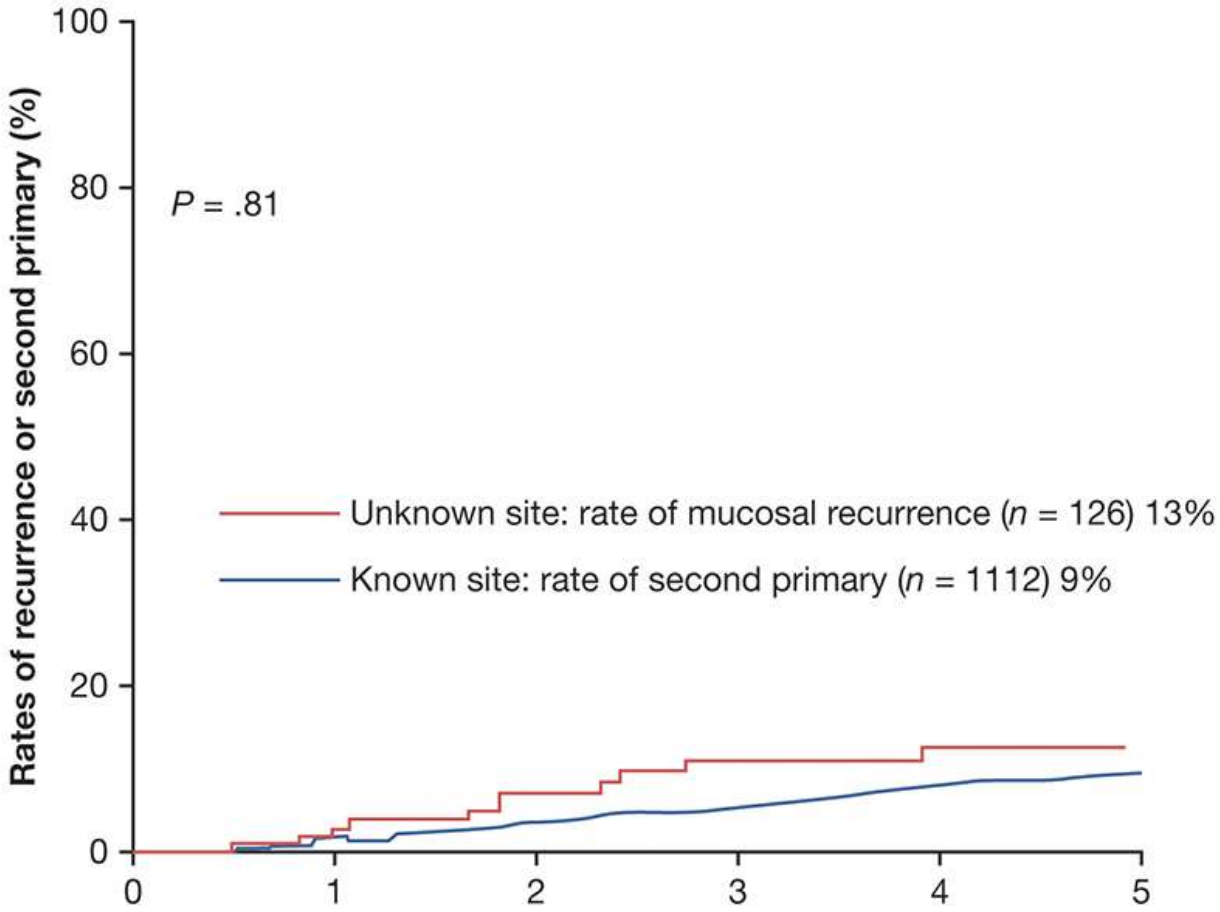

FIGURE 55.14 The rate of developing carcinomas in head and neck mucosal sites for patients treated for carcinomas with an unknown head and neck mucosal site compared to the rate of developing metachronous carcinomas in head and neck mucosal sites for patients treated for carcinomas with a known head and neck mucosal site. (Reprinted from Erkal HS, Mendenhall WM, Amdur RJ, Villaret DB, Stringer SP. Squamous cell carcinomas metastatic to cervical lymph nodes from an unknown head-and-neck mucosal site treated with radiation therapy alone or in combination with neck dissection. *Int J Radiat Oncol Biol Phys*. 2001;50[1]:55-63. Copyright © 2001 Elsevier. With permission.)

A subset of patients presenting with SCC metastatic to the neck nodes from an unknown head and neck primary site are treated with palliative intent because of the poor medical condition, extensive nodal involvement, or distant metastases at presentation. Treatment of the neck depends on the extent and location of the adenopathy. Forty of 166 (24%) patients were

treated palliatively at the University of Florida between 1964 and 1997.[83] Treatment was delivered to the neck alone to a dose of 30 Gy in 10 fractions over 2 weeks or 20 Gy in 2 fractions with a 1-week interfraction interval. The nodal response rate was 65%, and the symptomatic response rate was 57% at 1 year. The 1-year absolute and cause-specific survival rates were 25%.

The main complications of RT for patients treated for an unknown head and neck primary tumor are xerostomia, dysphagia, and neck fibrosis. The complications of treatment of the neck, which have been discussed previously, depend on whether chemotherapy and/or neck dissection is added.[83]

An alternative approach to carcinoma of unknown primary of the neck involves transoral surgery: transoral robotic surgery (TORS) or transoral laser microsurgery (TLM). The TORS approach involves using the surgical robot to access difficult-to-reach areas of the oropharynx to take more thorough directed biopsies. With the robot, the surgeon performs bilateral tonsillectomy/extended tonsillectomy as well as lingual tonsillectomy/base of tongue shaves. Moreover, if a primary is found on inspection or frozen section, the surgeon may perform a resection at the same time. Typically, a selective neck dissection (levels II-IV) is performed in conjunction with the TORS procedure. Durmus et al[84] reported on the initial experience of this method at the Ohio State University. In 77% of patients, the primary site was identified; 76% of tumors were found in the palatine tonsils and 24% in the base of the tongue. Seventy-seven percent of these patients underwent complete resection with negative margins. Adjuvant treatment was delivered as indicated, with 59% of patients able to avoid chemotherapy. Other studies have demonstrated similar results, with the primary being found in 72% to 90% of cases versus 25% to 57% of cases using traditional biopsy techniques.[85] Kang et al summarized the TORS approach for carcinoma of unknown primary (Figure 55.15).

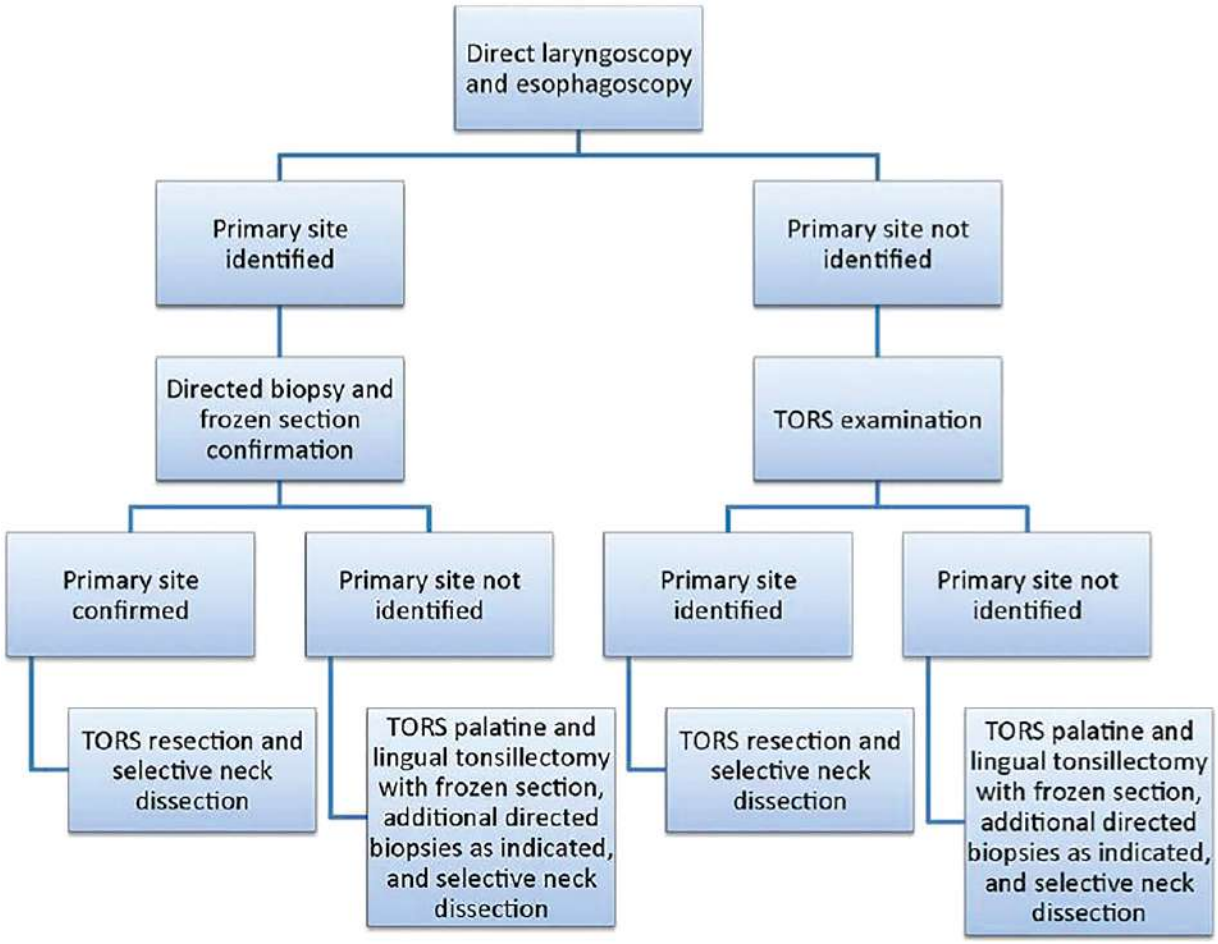

FIGURE 55.15 Treatment paradigm for carcinoma of unknown primary metastatic to cervical lymph nodes. TORS, transoral robotic surgery. (From Kang SY, Dziegielewski PT, Old MO, Ozer E. Transoral robotic surgery for carcinoma of unknown primary in the head and neck. *J Surg Oncol*. 2015;112[7]:697-701. Copyright © 2015 Wiley Periodicals. Reprinted by permission of John Wiley & Sons.)

Another transoral technique, TLM, utilizes a laser instead of the electrocautery of the TORS approach. Graboyes et al[86] reported the largest series of carcinoma of unknown primary worked up and treated with TLM. Eighty-nine percent of patients had the primary site identified. The approach also involves palatine tonsillectomy and base of the tongue resections as well as selective neck dissection. Twenty-six percent of patients who were treated with the TLM approach managed to avoid RT altogether.

There are several advantages to identifying the primary site in patients presenting with carcinoma of unknown primary of the neck. When the

primary site is elucidated, RT can be tailored to a smaller field and lower dose, thus reducing the morbidity of RT. Some have contended that conventional RT for carcinoma of unknown primary, when the primary site is not found, can lead to grade 3 dysphagia in 50% of patients.[87] This has not been our experience when the targeted mucosal sites are limited to the oropharynx.[71,77] If the primary site is completely resected, adjuvant treatment may be avoided or deintensified. However, because the majority of these patients have an oropharyngeal primary, it is likely that the HPV-positive nonsmokers could safely have their treatment deintensified without respecting the primary site. Functional outcomes for this approach are excellent with a 4.5% gastrostomy rate at 1 year and return of quality of life to pretreatment baseline or better.[85] Perhaps even more significant is the potential survival advantage provided when the primary site is identified and treated appropriately.[86,88-90]

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CHAPTER 56

Thyroid Cancer

Robert J. Amdur and Roi Dagan

BASIC THYROID ANATOMY AND PHYSIOLOGY

Gross Anatomy

The thyroid gland is located in the central anterior neck at the cervical-thoracic junction (Figure 56.1). The bulk of the gland is located immediately anterior and inferior to the thyroid cartilage. It has two lateral lobes connected by a central isthmus. Approximately 50% of individuals have a pyramidal lobe that extends superiorly from the central aspect of the gland, which is a remnant of the gland's embryologic origin, the thyroglossal duct. The average adult thyroid gland measures approximately 5×5 cm^2 and weighs 10 to 20 g.

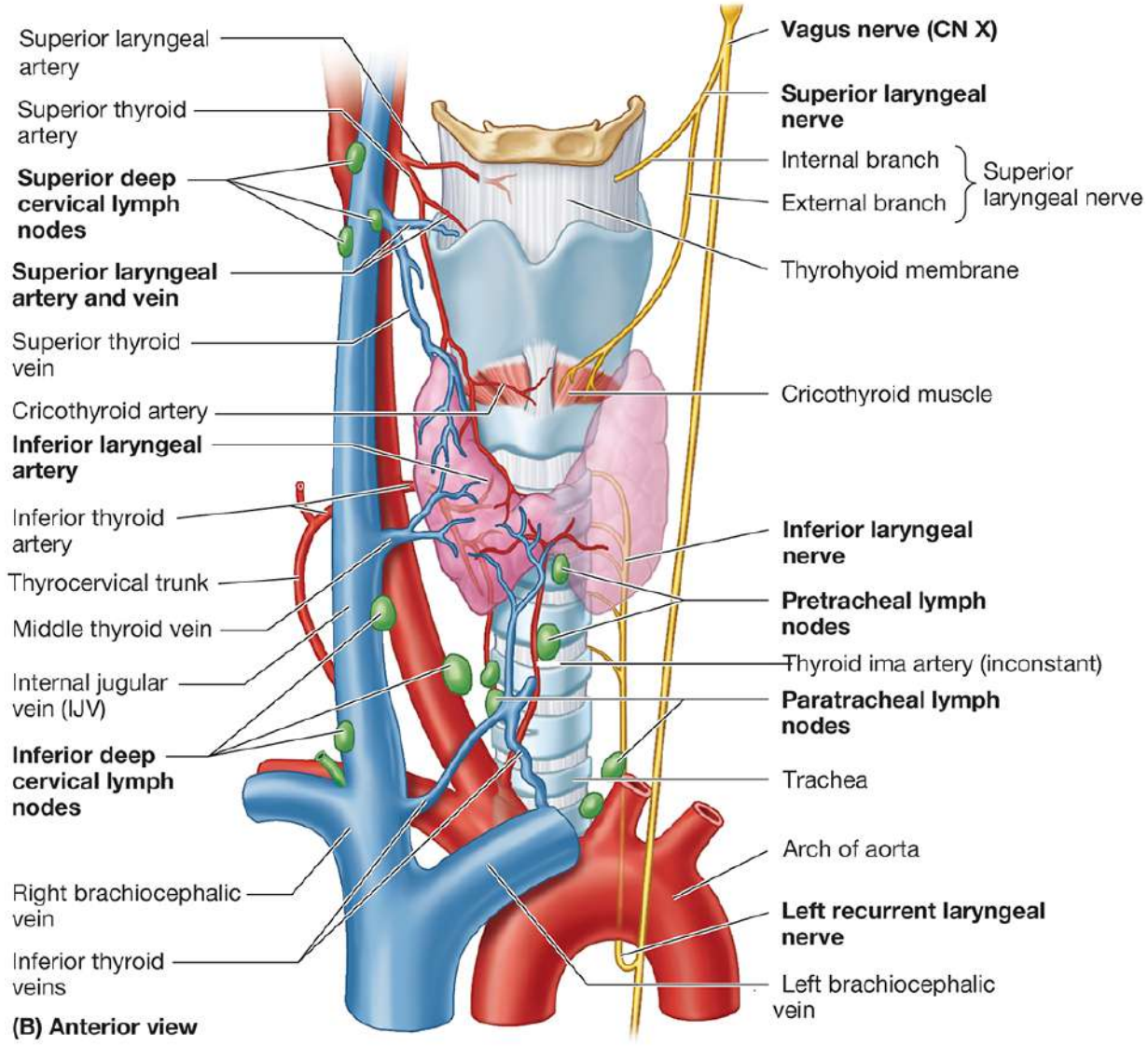

FIGURE 56.1 Anatomic location of the thyroid gland relative to the larynx, major vessels, and draining lymphatics. (Reprinted with permission from Agur AMR, Dalley AF. *Moore's Essential Clinical Anatomy*. 7th ed. Wolters Kluwer; 2024:620.)

The location of the gland in the central neck and its relation to critical structures explain the presenting symptoms of advanced neoplastic processes arising from the thyroid as well as potential complications of thyroid surgery and radiotherapy (Figure 56.2). The lateral lobes extend superiorly to the level of the midthyroid cartilage overlying the larynx and inferiorly to the sixth tracheal ring. The gland wraps around 75% of the tracheal circumference, posteriorly encroaching on the esophagus. The lateral extent is just medial to the common carotid arteries. The recurrent laryngeal nerves, sympathetic trunks, vagus, and phrenic nerves are all found immediately posterior to the gland, and the gland is

anteriorly bound by the strap muscles. Parathyroid glands are located posterior to the thyroid gland and vary in location and number.

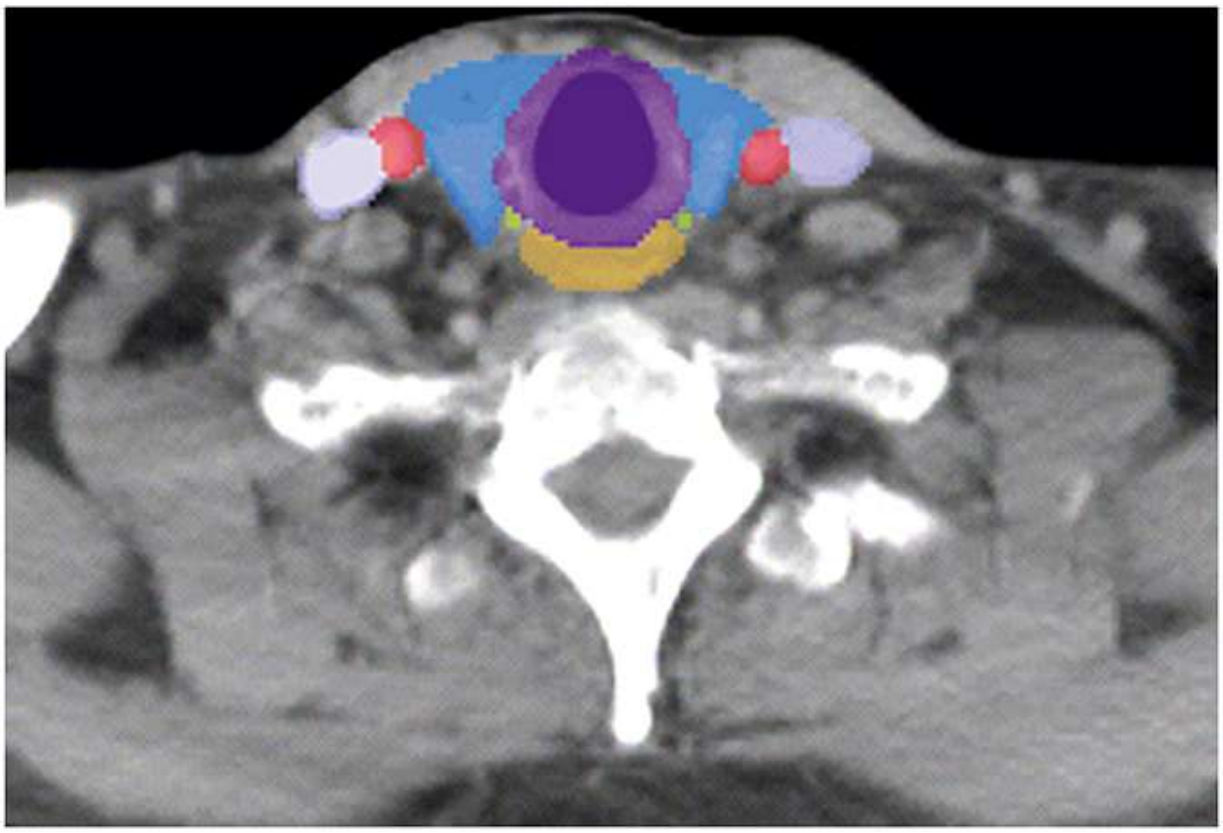

FIGURE 56.2 Anatomy of the thyroid gland. Contrast-enhanced axial computed tomography slice at the level of the bottom of the cricoid cartilage (purple) showing the position of the thyroid gland (blue) relative to the esophagus (orange), carotid arteries (red), jugular vein (lavender), and the approximate position of the recurrent laryngeal nerves (yellow green).

Vasculature and Lymphatics

The arterial blood supply to the thyroid gland is provided by the paired superior thyroid arteries (branches of the external carotid arteries) and inferior thyroid arteries (branches of the thyrocervical trunk from the subclavian arteries). Venous blood drains via the paired superior and middle thyroid veins to the internal jugular veins and from the inferior thyroid veins to the subclavian and innominate veins. There is a dense lymphatic network draining the gland in multiple directions, and bilateral involvement of lymph node metastases is common. According to the American Joint Committee on Cancer's (AJCC) eighth edition of the *AJCC Cancer Staging Manual*, the first-echelon nodes for thyroid cancer metastases are located in level 6 (the central or "visceral" compartment) between

the hyoid bone and the thoracic inlet.[1] Specifically, these are the paralaryngeal, paratracheal, and prelaryngeal (Delphian) nodes. Second-echelon nodal spread is to the mid- and lower cervical nodes (levels 3 and 4), supraclavicular nodes, upper mediastinal nodes (level 7), and, to a lesser extent, the upper cervical nodes (level 2). Level 1 (submental and submandibular) lymph nodes are rarely involved.

Spread of thyroid cancer to the retropharyngeal nodes is unusual, but we see positive retropharyngeal nodes in patients with many positive nodes in the lateral cervical stations and with advanced-stage disease at the primary site. With thyroid cancer, the positive retropharyngeal nodes are often in the more inferior portion of the station (Figure 56.3).

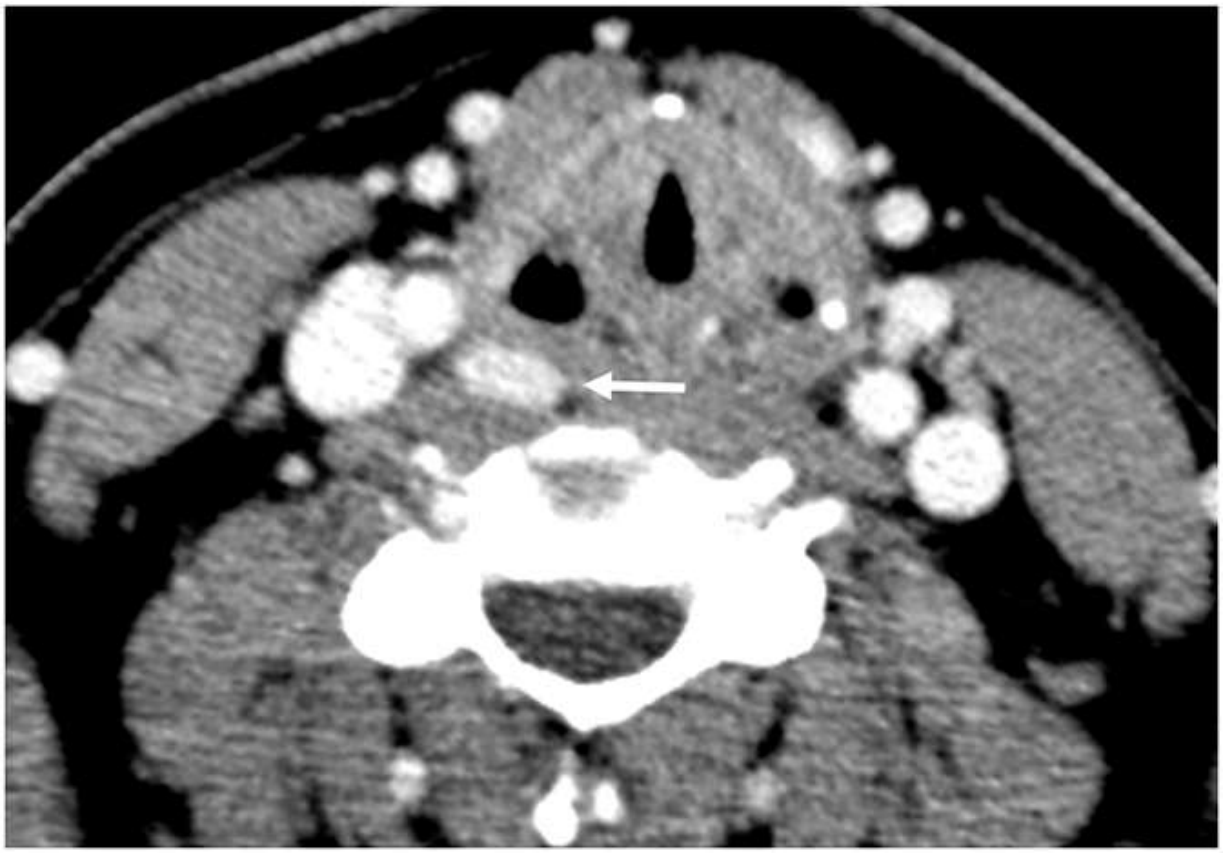

FIGURE 56.3 Axial computed tomography image with intravenous contrast at the level of the false vocal cords in a patient with papillary thyroid cancer. The arrow points to a retropharyngeal node. Metastatic cancer in this node explains the avid enhancement from iodinated contrast.

Microscopic Anatomy

Microscopically, the normal thyroid gland consists of numerous lobules comprising individual follicles forming the structural and functional unit of the

gland (Figure 56.4). The supporting stroma and vasculature are intertwined around the follicles. Each follicle consists of a single layer of cuboidal surface epithelium comprising thyroid follicular cells surrounding a central lumen-containing colloid, a substance rich in thyroglobulin (Tg). Separate from the follicular epithelium are the parafollicular cells, or C cells, which are neural crest–derived cells containing granules of calcitonin. The thyroid gland is incompletely surrounded by a connective tissue capsule.

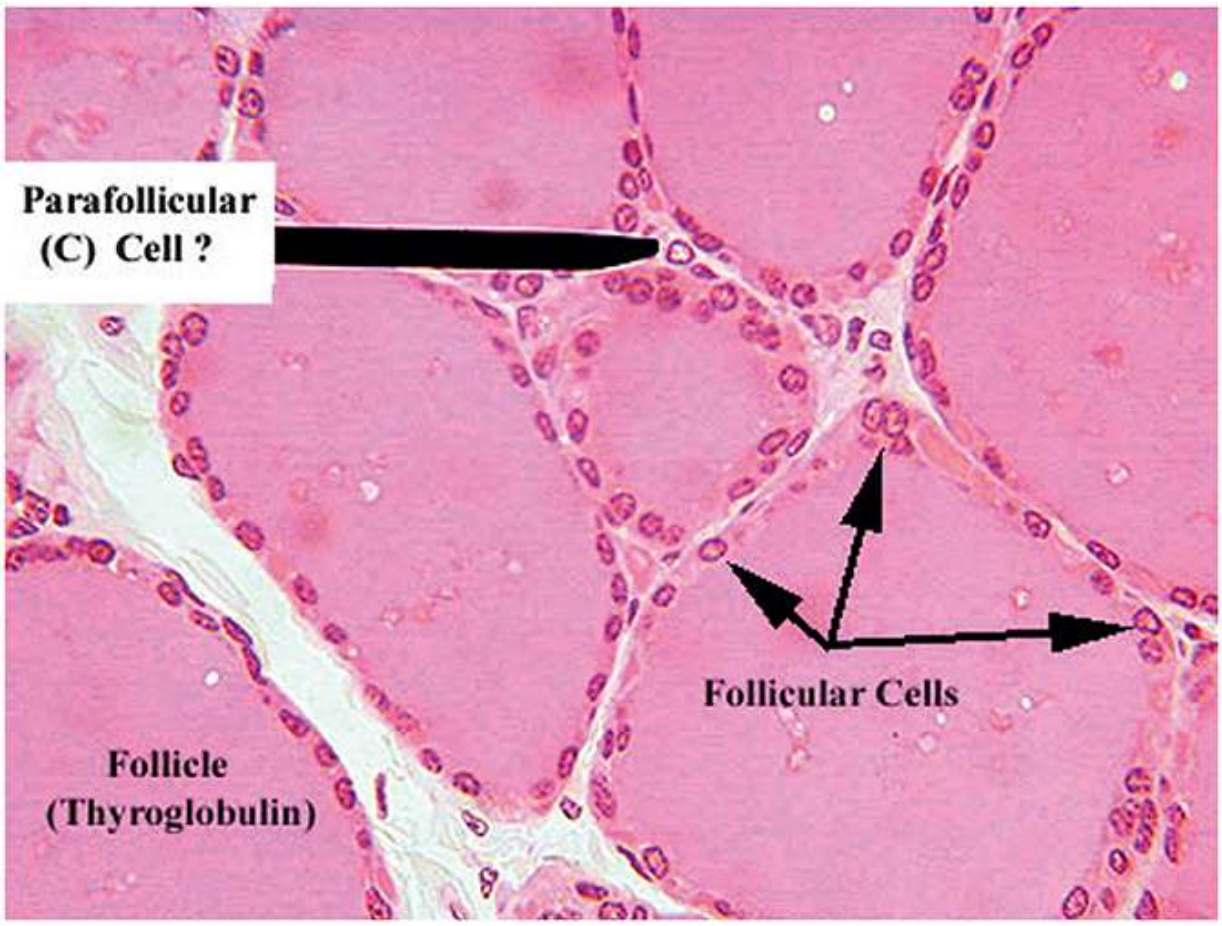

FIGURE 56.4 Thyroid follicle. Thyroid follicular cells produce thyroglobulin and thyroid hormone. Thyroid cells, which are normally located in the thyroid follicles and in perifollicular regions, synthesize and secrete calcitonin. (Reprinted by permission from Springer: Mazzaferri EL, Amdur RJ. Thyroid and parathyroid physiology. In: Amdur RJ, Mazzaferri EL, eds. *Essentials of Thyroid Cancer Management (Cancer Treatment and Research)*. Springer; 2005:7-17. Copyright © 2005 Springer Science+Business Media.)

Physiology

The primary physiologic role of the thyroid gland is the production of thyroid hormone, which plays an important role in metabolic homeostasis. A secondary

role is the production of calcitonin, a hormone involved in calcium homeostasis. The follicular cells of the thyroid gland synthesize and secrete Tg and thyroid hormone in two biologically active forms, thyroxine (3,5,3′,5′-iodothyronine or T_4) and triiodothyronine (3,5,3′-iodothyronine or T_3). It is useful to consider T_4 as the storage and transport form of thyroid hormone and T_3 as the metabolically active form. Most circulating thyroid hormone is bound to thyroxine-binding globulin. In peripheral tissues, where thyroid hormone executes its endocrine function, T_4 is rapidly converted to the more active form T_3 by the action of T_4 monodeiodinase. T_3 is transported to the nucleus where it binds to specific nuclear receptors and interacts with regulatory genes, influencing their expression. The gene products ultimately increase the cell's basal metabolic rate, protein synthesis, catecholamine effects, and growth of long bones and play an essential role in metabolism of proteins, fats, and carbohydrates. Thyroid hormone exerts its endocrine function on virtually all cells in the body.

Iodine is a critical component of thyroid hormone and is essential for thyroid function. The recommended daily intake is 150 μg, and at least 50 μg of daily intake is necessary to prevent deficiency, resulting in a goiter. The follicular cells of the thyroid gland possess a unique ability to actively uptake and concentrate iodine. The sodium iodine symporter (NaIS) actively transports sodium and iodine against an electrochemical gradient across the cell membrane in an energy-dependent fashion. This transmembrane protein is stimulated by thyroid-stimulating hormone (TSH or thyrotropin), which is synthesized in the anterior pituitary. Functional NaIS is present on malignant follicular cells seen in multiple variants of differentiated thyroid cancer (DTC). The unique ability to concentrate iodine within these malignant cells makes radioactive iodine (RAI), such as iodine-131 (I-131), a potent targeted therapy. The central role of TSH in driving the internalization of iodine within follicular thyroid cells is exploited in preparation for I-131. To increase the efficacy of I-131 therapy, T_4 deprivation, a low-iodine diet, and administration of recombinant human TSH (rhTSH) can be used to increase the effects of TSH on follicular thyroid cells (see the section on preparing patients for I-131). NaIS is also present in the parotid glands, breast tissues, gastric mucosa, and nasolacrimal ducts, placing them at risk for injury from I-131 therapy.

Upon entering the follicular cells, iodine is transported across the apical membrane and oxidized to a form that binds to tyrosyl residues of Tg, a large (660 kDa) glycoprotein synthesized by the follicular cells. Iodinated Tg becomes the main component of the intraluminal colloid stores of the thyroid follicles. T_3

and T_4 are synthesized by the coupling of iodinated tyrosine. They remain attached to the Tg until leaving the gland. TSH stimulation results in endocytosis of colloid droplets from the lumen into the follicular cells where it is hydrolyzed and releases Tg, T_4, and, to a lesser degree, T_3 into the circulation. Malignant differentiated follicular cells retain this function. Thus, serum Tg becomes a unique tumor marker after thyroidectomy and thyroid remnant ablation.

A feedback loop between the thyroid, pituitary, and hypothalamus regulates thyroid hormone synthesis and secretion. Thyrotropin-releasing hormone (TRH) is synthesized in the hypothalamus, and its primary function is to increase the secretion of TSH in the pituitary. Both T_3 and T_4 in turn inhibit TRH release and TSH secretion.

CLASSIFICATIONS OF THYROID CANCER

Correct pathologic classification of thyroid carcinoma is fundamental to the appropriate clinical management of the malignancy.[2] A system of classification that the authors find useful for clinical practice is shown in Table 56.1 and discussed below. The cell of origin, cytologic features, and growth morphology determine the pathologic classification. All carcinomas of the thyroid gland are derived from the follicular epithelium, except medullary thyroid carcinoma (MTC), which is derived from the parafollicular C cells. Capsular invasion is important in the pathologic diagnosis of certain thyroid carcinomas. The diagnosis of papillary thyroid carcinoma (PTC) is entirely predicated on the presence of diagnostic nuclear features and does not require invasive growth, while follicular carcinoma (FC) requires the presence of capsular or vascular invasion. Other rarely encountered malignant neoplasms of the thyroid gland include thyroid lymphoma and sarcomas. These two entities are not discussed in this chapter and are better evaluated and managed under paradigms detailed in the chapters on lymphoma and sarcoma.

TABLE 56.1 CLASSIFICATION OF THYROID CANCER BY CELL OF ORIGIN

Follicular epithelial cell
Well-differentiated thyroid cancer (DTC)
Papillary thyroid carcinoma (PTC)
Classic
Follicular variant
Oncocytic variant
Unfavorable variants
Diffuse sclerosing
Tall cell

Columnar cell
Hobnail
Follicular thyroid carcinoma (FTC)
Classic
Hürthle cell (oncocytic) carcinoma
Poorly differentiated thyroid cancer (PDTC): insular carcinoma
Undifferentiated thyroid cancer: anaplastic carcinoma

Parafollicular C cell

Medullary carcinoma

Differentiated (Follicular-Derived) Thyroid Carcinoma

The two major subgroups comprising DTC are PTC and FC.[2] They are distinguished mainly by cytologic features: In PTC, cytology is diagnostic of malignancy, whereas in FC, the diagnosis of malignancy requires evidence of tumor invasion through the tumor (not the thyroid) capsule. It is for this reason that PTC is usually diagnosed by fine-needle aspiration (FNA), but diagnosis of FC usually requires at least a lobectomy.

Papillary Thyroid Carcinoma

The distinguishing features of PTC include nuclear enlargement, hypochromasia, intranuclear cytoplasmic inclusions (nuclear pseudoinclusions), nuclear grooves, and distinct nucleoli. After formalin fixation, nuclei may appear pale, optically clear, and resemble "Orphan Annie's eyes." PTC is strongly lymphotropic, and multicentric disease within the parenchyma of the gland is often present secondary to early lymphatic spread. All PTC stain strongly for Tg.[3-5]

In its classic variant, PTC has a tumor architecture comprising branching papillae with fibrovascular cores. The follicular variant of PTC differs from the classic variant by its follicular growth pattern; however, it retains the nuclear features diagnostic of PTC. The oncocytic variant of PTC has the morphology of oncocytomas elsewhere in the body with abundant pink cytoplasm. From the clinical standpoint, the distinction between classic, follicular, and oncocytic subtypes of PTC is not important because they are treated the same way and have similar prognoses. The unfavorable variants of PTC have a worse prognosis than the above three subtypes.

Diffuse sclerosing is a rare form of PTC, with histologic features of extensive sclerosis, lymphocytic infiltrate, and psammoma bodies. A greater percentage of patients with diffuse sclerosing PTC present with extrathyroidal extension or distant metastases. Likewise, tall cell, columnar, and hobnail variants are commonly associated with poor prognostic features, such as advanced age, large

tumor size, aggressive histologic features with early invasion, and distant metastases. The distinguishing feature of tall cell PTC is that at least 70% of the carcinoma is composed of cells that are at least twice as tall as they are wide because of abundant cellular cytoplasm. Columnar and hobnail cell variants are rare. These carcinomas histologically show striking nuclear stratification, usually with papillary architecture. However, the usual nuclear features of PTCs may be absent; therefore, some pathologists prefer to classify columnar and hobnail cell variants as poorly differentiated carcinomas.

Follicular Carcinoma

FC, like PTC, is a DTC of follicular cell origin. This malignant thyroid neoplasm lacks the cytologic features of PTC. These carcinomas show evidence of thyroid follicle formation and are usually well circumscribed with a defined tumor capsule.[2] They are grossly indistinguishable from follicular adenomas. The diagnosis of FC is dependent on the presence of one of two histologic features: (a) tumor invasion through the entire tumor capsule or (b) tumor invasion into a blood vessel located in the tumor capsule or immediately outside the tumor capsule. Minimally invasive forms of FC may present a pathologic challenge and often require serial sectioning to find evidence of capsular or vascular invasion, while widely invasive forms of FC are obviously invasive tumors on both gross and microscopic evaluation.

Hürthle Cell (Oncocytic) Carcinoma

The more general term for Hürthle cell carcinoma is oncocytic carcinoma of the thyroid (not to be confused with the oncocytic variant of PTC). Some references classify Hürthle cell carcinoma as a subtype of follicular thyroid cancer, but more recent molecular studies suggest it is a separate entity.[2,6]

Hürthle cells are large and contain abundant granular eosinophilic cytoplasm. Hürthle cells may be seen in both benign and other non-Hürthle cell malignant neoplastic lesions; however, at least 75% of the tumor must be composed of Hürthle cells to designate it Hürthle cell carcinoma. Similar to FC, Hürthle cell carcinoma requires the presence of capsular or vascular invasion to classify it as a malignant neoplasm.

Poorly Differentiated Thyroid Carcinoma (Insular Carcinoma)

These follicular epithelial cell–derived tumors are intermediate between DTC and undifferentiated, or anaplastic, thyroid cancer (ATC). Both their histologic

appearance and biologic behavior are more aggressive than DTC.[2] They tend to be widely invasive, and many will extend beyond the gland. Insular carcinoma is characterized by tumor cells that are arranged in discrete nests separated by a fibrous stroma. Microscopically, they are usually solid with some evidence of follicle formation. Mitoses and necrosis are often present. The presence of more differentiated areas of tumor admixed with insular carcinoma suggests that the latter represents "dedifferentiated" tumors.

Undifferentiated Thyroid Carcinoma (Anaplastic Carcinoma)

ATC is the most aggressive form of thyroid carcinoma. Most patients are diagnosed at the age of 65 years or above.[2,7] ATC originates from the thyroid follicular epithelium but shows little to no evidence of histologic differentiation. This tumor is defined as much by its clinical behavior as its histologic appearance. When diagnosed, most ATCs are widely invasive, replacing most if not all of the normal-appearing gland, and freely infiltrate the perithyroidal tissues. They are usually accompanied by bulky metastatic lymphadenopathy and distant metastatic spread. Gross pathologic evaluation is characterized by widely infiltrative disease with areas of necrosis and hemorrhage. Various microscopic patterns have been described, including small cell, spindle cell, giant cell, squamoid, or pleomorphic. They are hypothesized to be lesions that have dedifferentiated from more benign differentiated follicular neoplasms.

Medullary Thyroid Carcinoma

MTC does not originate from the follicular epithelial cells, but from the parafollicular C cells, which are neural crest–derived cells whose function is to produce calcitonin. Cases are seen sporadically (80%) or in association with familial multiple endocrine neoplasia (MEN IIa, MEN IIb, and pure familial MTC) syndromes. Multifocal and bilateral MTCs are usually seen in patients with MEN, but, otherwise, familial and sporadic MTCs are indistinguishable. Grossly, these tumors are well circumscribed and nonencapsulated. Microscopically, tumors can have different appearances, including patterns that mimic other types of thyroid tumors. The most common pattern is of solid growth or nests similar to insular carcinoma. Amyloid, which is present in approximately 80% of cases, is a characteristic feature of MTC. Calcitonin stains are usually positive and specific for MTC, but up to 20% of cases may not stain for calcitonin; therefore, other neuroendocrine markers such as chromogranin may be useful.

Classification Based on the Capacity to Concentrate Iodine

Different pathologic classes of thyroid carcinoma concentrate iodine to various degrees. This characteristic is central to management decisions because the ability to concentrate iodine presents a useful therapeutic target. Table 56.2 presents a classification system that categorizes cancers based on whether they always concentrate iodine, infrequently concentrate iodine, or never concentrate iodine. Papillary carcinoma and FC (with the exception of the more aggressive variants) usually concentrate iodine. The follicular variant of papillary cancer has the same avidity for iodine as papillary cancer with classic morphology. Therefore, from the treatment standpoint, the distinction between these types of DTCs is not important. The aggressive variants of papillary carcinoma and Hürthle cell carcinoma can concentrate iodine, but to a lesser degree than the classic morphologies. In fact, there is often no measurable iodine uptake in metastases of these tumors. Anaplastic and medullary cancers never concentrate iodine to a clinically useful degree.

TABLE 56.2 CLASSIFICATION OF THYROID CANCER BASED ON THE ABILITY TO CONCENTRATE IODINE

Usually concentrate iodine to a degree that may be curative
Papillary thyroid carcinoma
Classic
Follicular variant
Oncocytic variant
Follicular thyroid carcinoma
Classic
Often do NOT concentrate iodine to a degree that is curative
Unfavorable variants of papillary thyroid carcinoma
Diffuse sclerosing
Tall cell
Columnar cell
Hobnail
Hürthle cell (oncocytic) carcinoma
Rarely concentrate iodine to a degree that is curative
Poorly differentiated thyroid carcinoma: insular carcinoma
Never concentrate iodine to a degree that is curative
Anaplastic carcinoma
Medullary carcinoma

EPIDEMIOLOGY OF THYROID CANCER

The most recent report of thyroid cancer incidence using the Surveillance, Epidemiology, and End Results database was published in 2017 with data from 1974 to 2013.[8]

DTC accounted for about 90% of total thyroid cancer cases, with 90% of these being papillary carcinoma. The approximate distribution of thyroid cancer cases by sex, race, and histology was as follows: female, 75%; White, 80%; papillary, 84%; follicular, 11%; medullary, 2%; and anaplastic, 1%. Distribution by age was <20 years, 2%; 20 to 39 years, 31%; 40 to 59 years, 42%; 60 to 79 years, 22%; and ≥80 years, 3%.

Between 1974 and 2013, the incidence of thyroid cancer tripled, from ~4.5 to 14.4 per 100,000 individuals with almost the entire increase attributable to PTC. These findings are explained by the fact that the large increase in thyroid cancer diagnosis is from the detection of early-stage tumor on neck ultrasound (US) and other imaging studies. The extent of cancer at diagnosis was distributed as follows: localized, 59; regional, 33%; and distant, 5%.

Radiation-Induced Thyroid Cancer

Exposure to ionizing radiation is an established risk factor for thyroid nodules and cancer. Well-recognized data come from survivors of atomic bombs in Hiroshima and Nagasaki and the nuclear reactor accident in Chernobyl.[9-15] A recent analysis of the 59,687 atomic bomb survivors in the Life Span Study demonstrated a total of 24.5% of cases of thyroid cancer in this cohort were attributed to radiation exposure with a strong dose response.[13] Women and young children appeared to be most susceptible. An estimated additional 1,000 cases of thyroid cancer throughout Europe have been attributed to the Chernobyl accident.[15] An increased risk of thyroid cancer has also been attributed to exposure to therapeutic radiation in children treated for Hodgkin lymphoma, tinea capitis, enlarged tonsils, and enlarged thymus.[16-18] Radiation-induced thyroid cancer is pathologically indistinguishable from spontaneous forms of the disease and is not associated with more aggressive biology or poorer prognosis.[19-22]

Familial Medullary Thyroid Carcinoma

Twenty-five percent of cases of MTCs are hereditary. All patients with MTC should be screened for familial disease, and genetic testing is considered the standard of care for all first-degree relatives of patients with newly diagnosed MTC. Heritable forms of MTC are associated with the familial MEN syndromes

(MEN IIa, MEN IIb, and pure familial MTC) and have their own unique epidemiology. These disorders are inherited in an autosomal dominant manner due to a germline point mutation in the *RET* gene on chromosome 10q11.2. Men and women are affected equally, given the pattern of inheritance. These patients typically present with bilateral and multifocal tumors compared to sporadic forms of MTC. The aggressiveness and age of onset of familial MTC differ depending on the specific genetic mutation. Prophylactic thyroidectomies are increasingly being performed on patients at risk for developing MTC.[23]

CLINICAL MANIFESTATIONS OF THYROID CANCER

The most common presentation of thyroid cancer is an asymptomatic thyroid nodule found incidentally by the patient, clinicians, or on an imaging study performed for other reasons.[24,25]

Alternatively, locally advanced thyroid cancer presents with symptoms from involvement of the critical structures intimately associated with the thyroid gland, massive cervical lymphadenopathy, or metastatic disease. These patients present with symptoms such as hoarseness from tumor compression of the recurrent laryngeal nerve, airway compromise, dysphagia or respiratory symptoms, and pain and weight loss resulting from metastatic dissemination.

DIAGNOSTIC EVALUATION OF THYROID CANCER

Laboratory Studies

All patients with thyroid nodules should undergo a serum TSH in addition to basic metabolic, renal, and liver function tests and a complete blood count. Other lab tests, such as Tg, T_3, and T_4, are commonly obtained but are rarely useful in the initial management of thyroid cancer. Serum calcitonin can be measured during the initial evaluation of patients with MTC and is essential during follow-up for these patients.

Ultrasound and Ultrasound-Guided Fine-Needle Aspiration

Neck US with Doppler and US-FNA are the standard diagnostic approaches for evaluating thyroid nodules, both palpable and incidentally detected on imaging. US-FNA has several benefits in the evaluation of thyroid nodules over other means of obtaining a tissue diagnosis: (1) the technique is minimally invasive and is usually performed as an outpatient procedure; (2) the operator can visually verify that the biopsy needle is in the nodule(s) of suspicion; and (3) it allows for

evaluation of nonpalpable nodules and, in the setting of cystic lesions, lowers the rate of inadequate specimens. Cervical US is also an important staging tool because it is effective in identifying lymph node metastases and extrathyroid extension.[26-30]

Computed Tomography and Magnetic Resonance Imaging

Computed tomography (CT) and magnetic resonance imaging (MRI) commonly detect otherwise clinically occult thyroid nodules. Malignancy is likely with either imaging technique when there are findings of a mass with extrathyroidal extension, lymph node metastases, or both. In this setting, the studies are useful in presurgical planning by establishing the extent of extraglandular tumor and helping the surgeon determine the need for extended neck dissections (Figures 56.5 and 56.6). MRI is superior to CT for establishing the local extent of a known cancer, because it will more clearly show esophageal or tracheal invasion (Figure 56.6).[31] MRI is indicated in the presence of hoarseness, stridor, dysphagia, or other clinical signs of locally extensive thyroid cancer that cannot be adequately assessed by US.

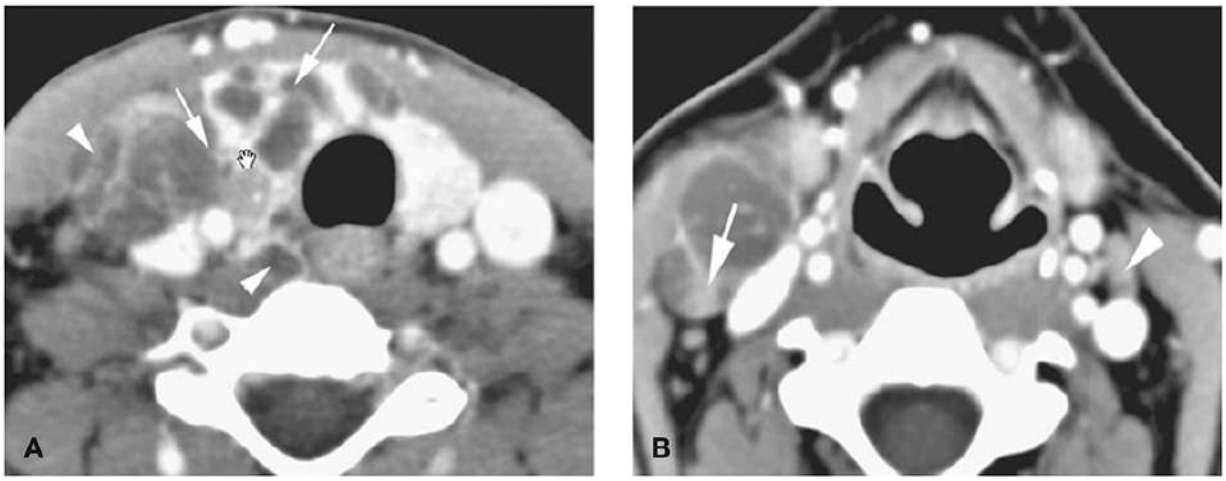

FIGURE 56.5 A patient presenting with a neck mass. A. Computed tomography image showing the mass to be due to a primary papillary thyroid carcinoma coming into contact with a related level 4 metastatic lymph node (arrows). The lymph node at level 4 and in the tracheoesophageal groove is shown by the arrowheads. B. A section more superiorly shows level 3 adenopathy that is multicystic in a pattern typical but not necessarily diagnostic of papillary thyroid carcinoma. There is upper level 4 cystic adenopathy with an enhancing mural nodule (arrow)—a morphology suggesting of thyroid carcinoma. A contralateral enhancing positive node with a focal low-density defect (arrowhead) is also present. (Reprinted with permission from Mancuso AA, Mendenhall WM, Vaysberg M. Thyroid: nodules and malignant tumors. In: Mancuso AA, ed. *Head and Neck Radiology*. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010:1457-1481.)

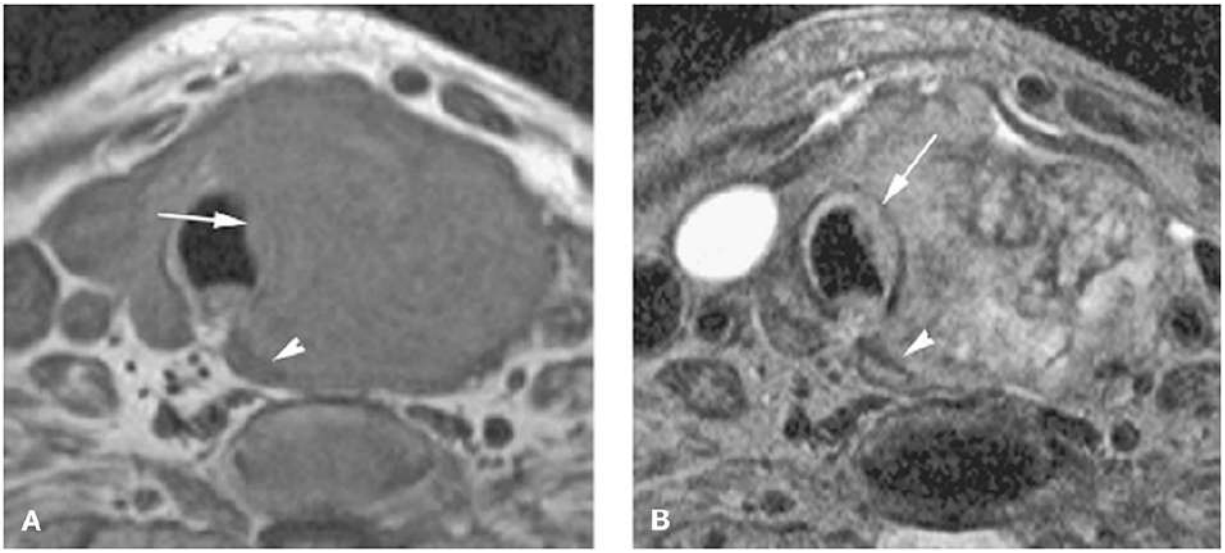

FIGURE 56.6 A patient demonstrating the value of magnetic resonance in the detection of invasion of the trachea and cervical esophagus, especially as it pertains to treatment planning. This patient has anaplastic carcinoma of the thyroid gland. In (A), T1-weighted images show distortion of the trachea (arrow) and esophagus (arrowhead), but it is difficult to determine whether invasion is present. In (B), the T2-weighted image shows obvious growth of tumor replacing the normal signal of cartilage of the trachea with growth on both sides of the cartilage (arrow) as well as replacement of the normal muscular wall signal of the cervical esophagus (arrowhead), indicating esophageal wall invasion. (Reprinted with permission from Mancuso AA, Mendenhall WM, Vaysberg M. Thyroid: nodules and malignant tumors. In: Mancuso AA, ed. *Head and Neck Radiology*. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010:1457-1481.)

A major downside to CT is that useful imaging of the neck requires contrast enhancement, which can interfere with subsequent I-131 therapy. Because of their high concentration of iodine, CT contrast agents can seriously compromise the effectiveness of therapeutic I-131. When patients receiving iodinated contrast agents require I-131, therapy should be delayed in order to achieve adequate efficacy. In selected cases, a noncontrasted CT of the chest may be indicated to evaluate the presence of mediastinal and lung metastases, but, generally speaking, it is not necessary to perform a CT before primary therapy of most DTCs.

Nuclear Medicine Studies

The four major nuclear medicine studies related to thyroid cancer evaluation with iodine isotopes are radioactive iodine uptake (RAIU), thyroid scan, diagnostic whole-body scan (DxWBS), and post-treatment whole-body scan (RxWBS). Table 56.3 summarizes the characteristics of each of these studies.

TABLE 56.3 NUCLEAR IMAGING STUDIES USED IN THE MANAGEMENT OF DIFFERENTIATED THYROID CARCINOMAS

Study	Isotope	Diagnostics	Results	Purpose	Comment
Radioactive uptake (RAIU) study	Usually I-123 (200-400 μCi)	Counts are measured over the low neck 2-24 h after administration.	Not an image but a number. Normal findings after near-total thyroidectomy are 0.5%-3%.	Quantifies the ability of thyroid tissue and cancer to concentrate iodine and estimates the amount of remaining normal and malignant tissue. RAIU is required by federal regulation before outpatient therapy with I-131.	Performed the week before I-131 administration when prepared with T_4 deprivation and on the day of the second injection when prepared with rhTSH
Diagnostic whole-body scan (DxWBS)	I-131 (1-3 mCi) or I-123 (1.5-3 mCi)	The entire body is imaged with a gamma camera ~3 d after I-131 administration.	Records images of the distribution of radioactive iodine throughout the entire body	To detect residual cancer or normal thyroid tissue	Patients should be prepared with a low-iodine diet and TSH elevation. The value of this study is controversial. We do not use this study to plan treatment or monitor cancer status.
Post-treatment whole-body scan (RxWBS)	I-131, 30-250 mCi (therapeutic dose range)	Same as DxWBS but performed ~7 d after I-131 administration	Same as DxWBS	After remnant ablation, it documents the quality of treatment and identifies unsuspected nodal and	False positives are the only downside and their impact is mitigated when interpreted in the appropriate

Study	Isotope	Diagnostics	Results	Purpose	Comment
				distant metastases. When normal thyroid tissue has been previously ablated, it identifies cancer that is I-131 avid.	clinical context.
Thyroid scan	I-123, I-131, or Tc-99	Same basic procedures as RAIU, but the thyroid is imaged with a gamma camera.	Results are an image of the thyroid.	Used in the evaluation of thyroid nodules to determine if the nodule is functional (ie, “hot” or “cold”)	Thyroid scan is included in this table so that it is not confused with RAIU or whole-body scans. Thyroid scans are not used to plan cancer treatment or post-treatment surveillance.

rhTSH, recombinant human thyroid-stimulating hormone; TSH, thyroid-stimulating hormone.

RAIU tests are used to quantify the RAI-concentrating ability of remnant thyroid tissue after thyroidectomy. This value is required by federal regulation for outpatient I-131 therapy.

Thyroid scans produce images of the thyroid’s ability to concentrate iodine and have a historical use in the evaluation of thyroid nodules, characterizing them as functional (“hot”) or nonfunctional (“cold”). The authors do not use thyroid scans in the workup or management of patients with thyroid cancer.

The typical DxWBS involves a total body image several days after administering approximately 3 mCi of I-131 or I-123. The current value of a DxWBS in thyroid cancer management is controversial. Some experts use a DxWBS to determine the therapeutic dose of I-131 in a patient being treated for thyroid cancer. Some experts use a DxWBS as part of the surveillance program following initial treatment. A comprehensive discussion of the issues related to DxWBS is beyond the scope of this chapter. The main arguments against doing

DxWBS are low sensitivity, stunning of residual cancer cells, and unnecessary radiation exposure. The bottom line is that reasonable people will disagree about the role of DxWBS in thyroid cancer management. The authors do not use DxWBS to stage or monitor patients with thyroid cancer and have not ordered a DxWBS in over 5 years.

An RxWBS should be done in every patient who receives a therapeutic dose of I-131. The optimal interval between administration and scan in most patients is approximately 7 days. The primary purpose of an RxWBS is to detect gross residual disease in the regional lymphatics or in distant sites and to determine if known disease concentrates iodine.

Fluorodeoxyglucose-positron emission tomography (FDG-PET) is another nuclear medicine study that is commonly used to detect metastatic disease, but the predictive value of PET in thyroid cancer is controversial.[32,33]

TSH stimulation increases the accuracy of FDG-PET in most types of DTC. A prospective trial comparing FDG-PET studies during thyroid hormone suppression to studies after administration of rhTSH showed increased detection of occult metastases in the stimulated studies.[34] Some insurers will not reimburse for FDG-PET for thyroid cancer without prior documentation of follicular-derived thyroid cancer with a suppressed or stimulated Tg over 10 ng/mL and a negative DxWBS.[35]

OUTCOME AND PROGNOSTIC FACTORS

The AJCC staging system documents the major prognostic factors that determine disease-specific survival after diagnosis of thyroid cancer (Table 56.4 and Figure 56.7). There are major differences in the staging system from prior versions and from the many prognostic models from other groups. The remainder of this subsection discusses some of the issues that deserve additional explanation.

TABLE 56.4 AMERICAN JOINT COMMITTEE ON CANCER (AJCC) EIGHTH EDITION (2017) TNM STAGING SYSTEM FOR THYROID CANCER

Papillary, follicular, poorly differentiated, Hürthle cell, and anaplastic thyroid carcinoma

Primary tumor (T)	
TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor
T1	Tumor ≤2 cm in greatest dimension limited to the thyroid
T1a	Tumor ≤1 cm in greatest dimension limited to thyroid
T1b	Tumor >1 cm but ≤2 cm in greatest dimension limited to the thyroid

Papillary, follicular, poorly differentiated, Hürthle cell, and anaplastic thyroid carcinoma

T2	Tumor >2 cm but ≤4 cm in greatest dimension limited to the thyroid
T3	Tumor >4 cm limited to the thyroid, or gross extrathyroidal extension invading only strap muscles
T3a	Tumor >4 cm limited to the thyroid
T3b	Gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid, or omohyoid muscles) from a tumor of any size
T4	Includes gross extrathyroidal extension
T4a	Gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve from a tumor of any size
T4b	Gross extrathyroidal extension invading prevertebral fascia or encasing the carotid artery or mediastinal vessels from a tumor of any size
Regional lymph node (N)	
NX	Regional lymph nodes cannot be assessed.
N0	No evidence of locoregional lymph node metastasis
N0a	One or more cytologically or histologically confirmed benign lymph nodes
N0b	No radiologic or clinical evidence of locoregional lymph node metastasis
N1	Metastasis to regional nodes
N1a	Metastasis to level VI or VII (pretracheal, paratracheal, or prelaryngeal/Delphian, or upper mediastinal) lymph nodes. This can be unilateral or bilateral disease.
N1b	Metastasis to unilateral, bilateral, or contralateral lateral neck lymph nodes (level I, II, III, IV, or V) or retropharyngeal lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Prognostic stage groups

Differentiated

When age at diagnosis is …	And T is …	And N is …	And M is …	Then the stage group is …
<55 y	Any T	Any N	M0	I
	Any T	Any N	M1	II
≥55 y	T1	N0/NX	M0	I
	T1	N1	M0	II
	T2	N0/NX	M0	I

Papillary, follicular, poorly differentiated, Hürthle cell, and anaplastic thyroid carcinoma

	T2	N1	M0	II
	T3a/T3b	Any N	M0	II
	T4a	Any N	M0	III
	T4b	Any N	M0	IVA
	Any T	Any N	M1	IVB
Anaplastic				
When T is …	**And N is …**	**And M is …**		**Then the stage group is …**
T1-T3a	N0/NX	M0		IVA
T1-T3a	N1	M0		IVB
T3b	Any N	M0		IVB
T4	Any N	M0		IVB
Any T	Any N	M1		IVC

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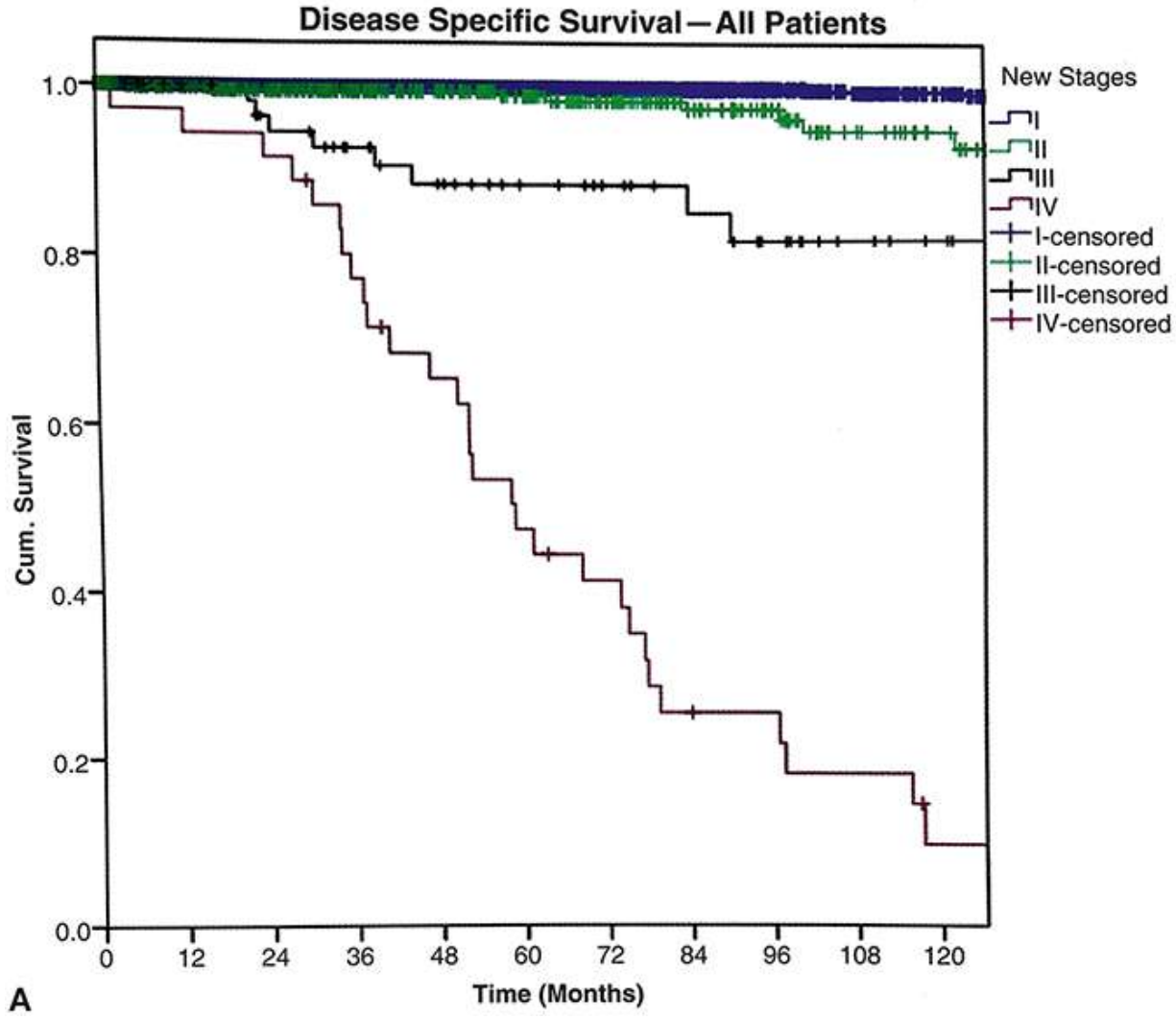
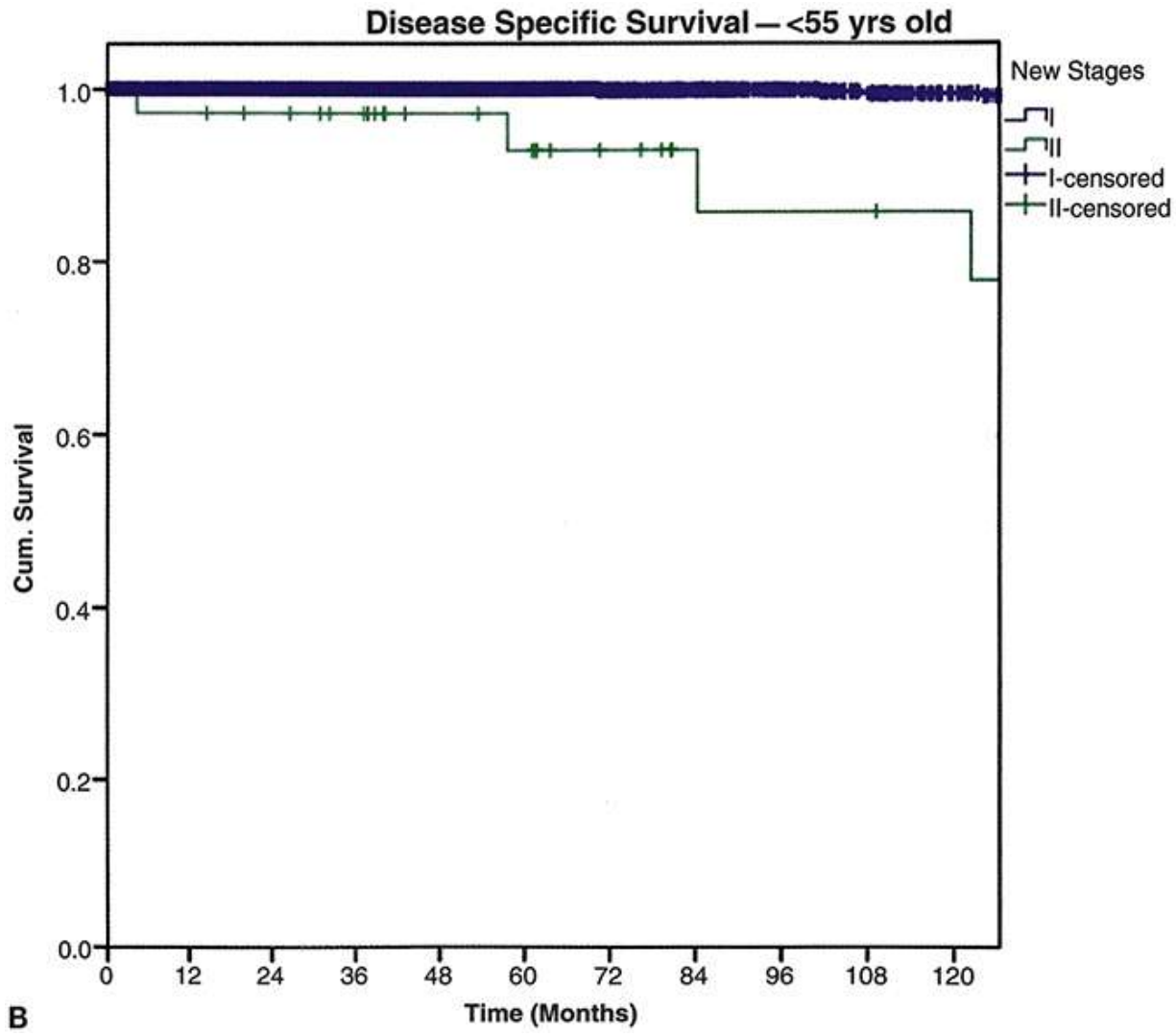

Disease Specific Survival—All Patients
New Stages
I
II
III
IV
I-censored
II-censored
III-censored
IV-censored
Cum. Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
72
84
96
108
120
Time (Months)

A


Disease Specific Survival — <55 yrs old
New Stages
I
II
I-censored
II-censored
Cum. Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
72
84
96
108
120
Time (Months)

B

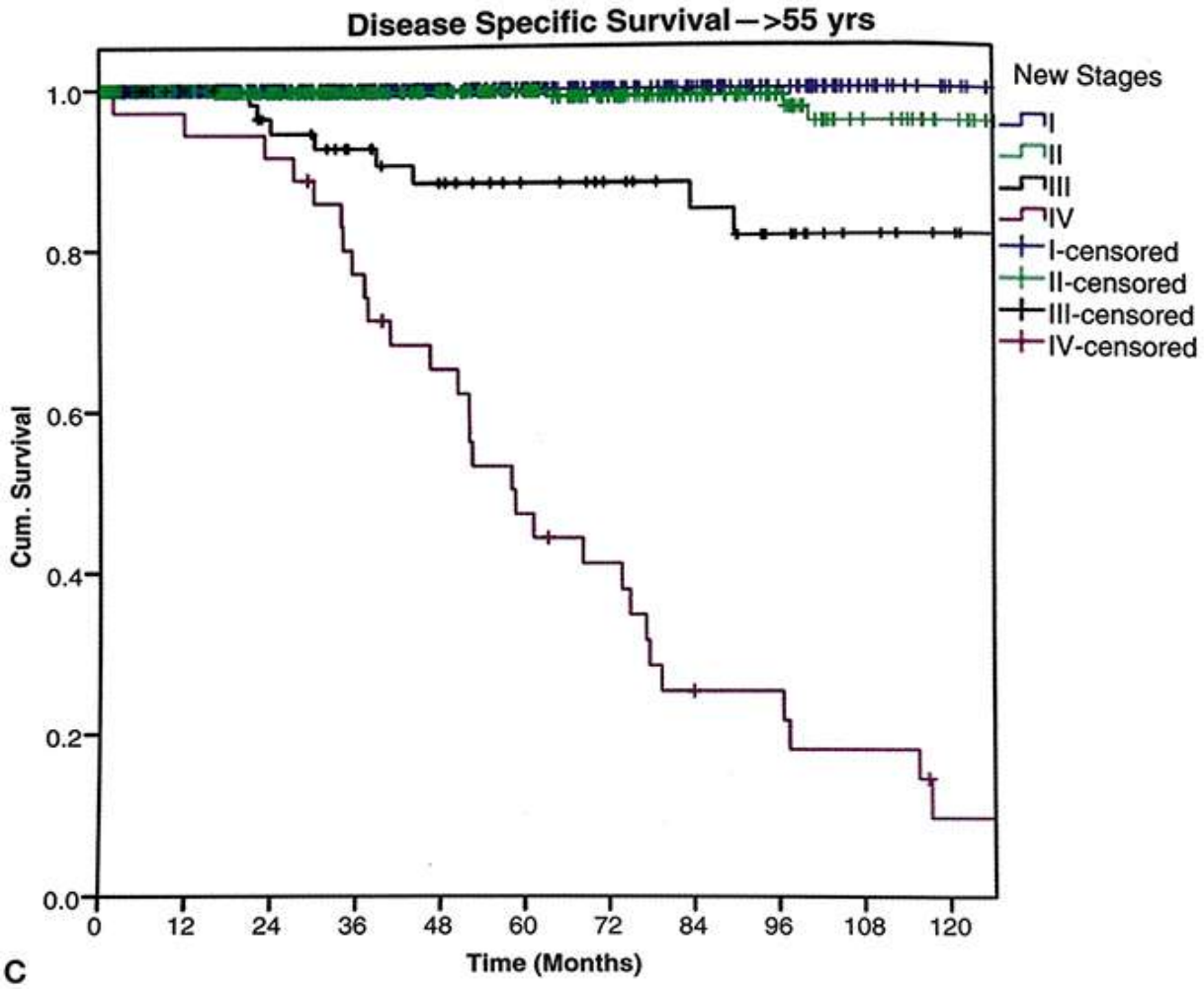


FIGURE 56.7 Disease-specific survival (death from thyroid cancer) using the eighth edition of the American Joint Committee on Cancer staging system for all patients (A), patients age <55 years (B), and patients age >55 years (C).

Recurrence Versus Survival

Many discussions of treatment for thyroid cancer are controversial. A major reason for disagreement is an inability to agree on the outcome end point. The major options are as follows: overall survival (an event is death from any cause), disease-specific survival (an event is death from thyroid cancer), relapse-free survival (an event is cancer recurrence), and local-regional control (an event is cancer recurrence in the thyroid bed or regional neck nodes).

Most types of thyroid cancer have an indolent growth rate such that patients live many years with uncontrolled tumor. An additional complicating factor is that DTC shares with prostate cancer the feature of exhibiting a highly specific serum marker of tumor activity. Serum Tg level is to DTC what prostate-specific

antigen is to prostate cancer. Therefore, with most forms of thyroid cancer, there is also the debate about biochemical versus clinical evidence of cancer control.

Most major studies of outcome of thyroid cancer use either overall or disease-specific survival as the outcome end point. The major limitation of these survival end points is that they do not reflect the morbidity from tumor recurrence that does not cause death. Psychological stress from living with recurrent cancer or uncertainty about cancer cure is substantial,[36,37] and there is physical morbidity that comes from additional diagnostic testing and salvage therapy. This limitation runs through almost every major debate about thyroid cancer treatment because the difference between recurrence and survival results is usually large. Figure 56.8 shows the key figure from a classic study demonstrating this concept.

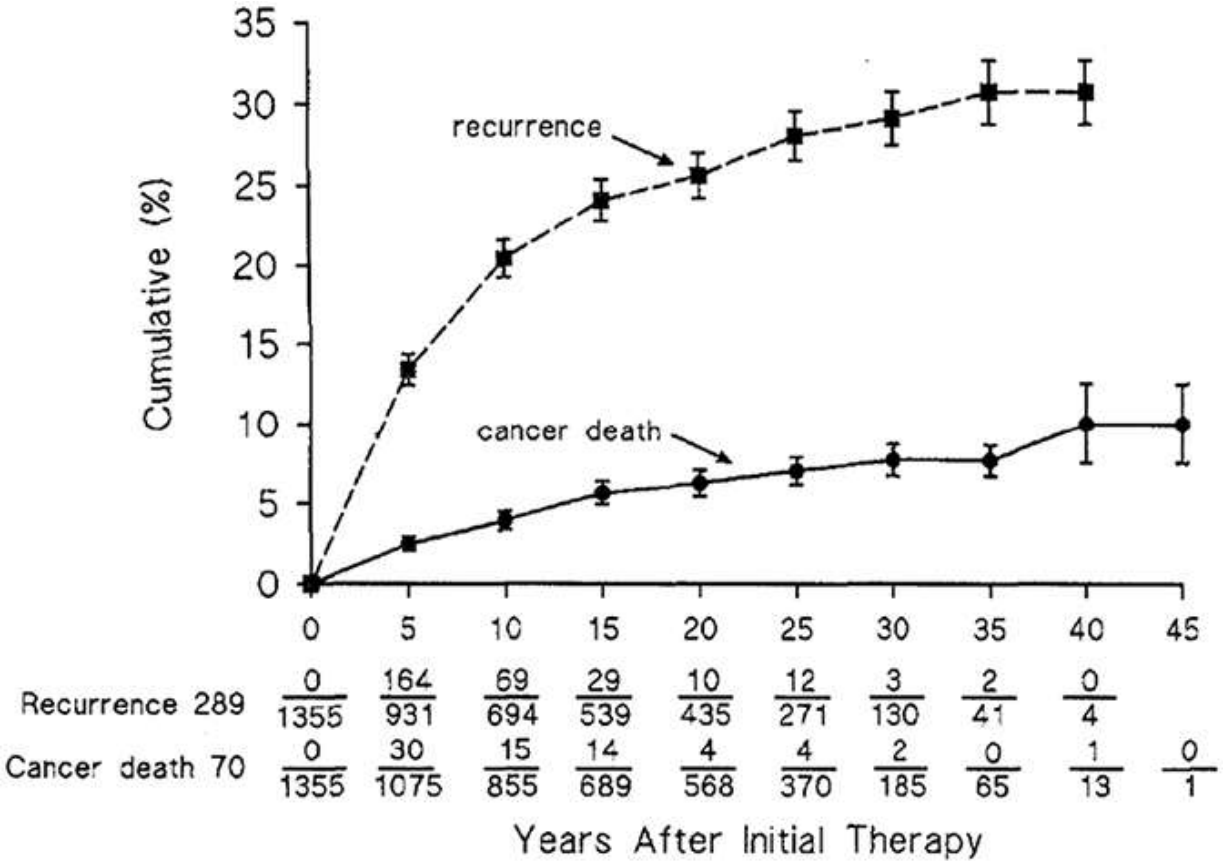


FIGURE 56.8 Tumor recurrence and cancer deaths in 1,355 patients treated for follicular and papillary thyroid carcinoma. (Reprinted from Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med*. 1994;97[5]:418-428. Copyright © 1994 Elsevier. With permission.)

In this chapter, we do not present specific studies related to a treatment recommendation in a specific situation. Summarizing specific studies would

make this chapter unacceptably long, and it would not end with definitive answers. For this reason, our approach is to list the major guideline references (Table 56.5) and summarize their opinions in some of the major treatment situations. These major guidelines contain a long list of references of the specific studies that inform the discussion topic.

TABLE 56.5 CONSENSUS GUIDELINES FOR THE MANAGEMENT OF THYROID CANCER

Organization	Reference
American Thyroid Association: DTC in Adults	Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2016;26(1):1-133.
American Thyroid Association: DTC in Children	Francis GL, Waguespack SG, Bauer AJ, et al. Management guidelines for children with thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2015;25(7):716-759.
American Thyroid Association: Medullary Carcinoma	Wells SA Jr, Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. *Thyroid*. 2015;25(6):567-610.
American Head and Neck Society: EBRT for DTC	Kiess AP, Agrawal N, Brierley JD, et al. External-beam radiotherapy for differentiated thyroid cancer local-regional control: a statement of the American Head and Neck Society. *Head Neck*. 2016;38(4):493-498.
American Head and Neck Society: Recurrent Thyroid Cancer	Scharpf J, Tuttle M, Wong R, et al. Comprehensive management of recurrent thyroid cancer: an American Head and Neck Society consensus statement: AHNS consensus statement. *Head Neck*. 2016;38(12):1862-1869.
American Head and Neck Society: Management DTC	Shindo ML, Caruana SM, Kandil E, et al. Management of invasive well-differentiated thyroid cancer: an American Head and Neck Society consensus statement. AHNS consensus statement. *Head Neck*. 2014;36(10):1379-1390.
American Head and Neck Society: Central Neck Dissection for DTC	Agrawal N, Evasovich MR, Kandil E, et al. Indications and extent of central neck dissection for papillary thyroid cancer: an American Head and Neck Society consensus statement. *Head Neck*. 2017;39(7):1269-1279.
American Thyroid Association: Anaplastic Carcinoma	Smallridge RC, Ain KB, Asa SL, et al. American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. *Thyroid*. 2012;22(11):1104-1139.

DTC, differentiated thyroid cancer; EBRT, external-beam radiation therapy.

Age

Age is a major prognostic variable in the AJCC staging systems. The current AJCC system dichotomizes staging based on age under 55 years versus 55 years and above. Age is a major factor in all outcome studies because of the consistent finding that younger patients do better than older patients, especially those in the older adult age groups. Of course, the prognostic effect of age is really a continuous variable, but it is more useful for treatment decisions to force a dichotomous breakpoint. But, the major limitation of this approach to age is that it ignores the data that young children (<12 years old) do worse than young adults.[38] The explanation for this difference may be that young children present with more advanced-stage disease at diagnosis, frequently with distant metastases.[39,40]

Unfavorable Variants of Papillary Thyroid Cancer

The most important prognostic factor for disease recurrence and cancer mortality is the histologic classification. Survival following diagnosis is long for most stages of papillary and follicular thyroid cancer with classic histology. The term *unfavorable variant* usually refers to subtypes of papillary carcinoma called tall cell, hobnail, or diffuse sclerosing. Most studies show that the prognosis of an unfavorable variant is substantially worse than with classic histology of a similar stage.[41,42] Note that follicular variant PTC is not unfavorable, meaning that the prognosis is similar for a given stage of follicular variant PTV and classic histology PTC.

Hürthle Cell Carcinoma

There is major disagreement about the prognosis of Hürthle cell carcinoma relative to other forms of DTC such that some authors recommend a separate staging system. A summary of this debate is beyond the scope of this chapter. A paper from our group summarizes the main issues and presents our data on the subject.[43]

Positive Surgical Margin

A positive surgical margin is an important prognostic factor in most cancer situations. But microscopic margin status is not a factor in the American Thyroid Association (ATA) treatment guidelines. Data on the independent significance of a microscopic positive margin in DTC are scarce. Some studies suggest that a positive margin warrants more aggressive treatment,[44] but the most respected study on this subject concludes that a positive margin does not affect the

recurrence rate following standard treatment.[45] As with many other debates in thyroid cancer, the studies evaluate different end points. In the Memorial Sloan Kettering series, the end point is clinical recurrence (visible tumor recurrence) without discussion of biochemical recurrence data.[45] Our view is that a microscopically positive margin should be taken into account such that we are reluctant to recommend observation, regardless of other factors.

Number of Positive Lymph Nodes

The prognostic importance of positive neck nodes from DTC has been a major controversy for decades. The AJCC staging system reflects the conclusion that the distinction between no positive nodes and at least one positive node has some importance, but stage does not change based on the number of positive nodes (see Table 56.4). In patients with positive nodes, guidelines from the ATA do not change treatment recommendations based on node number.

Our opinion is that these guidelines undervalue the significance of many positive nodes in predicting outcome and making treatment decisions. Multiple studies show that multiple positive nodes constitute a powerful negative prognostic factor. A publication from our group summarizes published data on this subject.[46] We take the number of positive nodes into account when making treatment decisions (Table 56.6).

TABLE 56.6 EMPIRIC I-131 DOSING FOR TREATMENT OF DIFFERENTIATED THYROID CANCER FROM THE UNIVERSITY OF FLORIDA DEPARTMENT OF RADIATION ONCOLOGY

Adjuvant treatment soon after total thyroidectomy (No prior I-131 treatment and no visible tumor)	
Observation[a] (No I-131 treatment)	**All must be present:** pT1-2, pN0-1a, M0 ≤3 positive nodes No extranodal extension Negative margin Postop Tg[b] <1.0 ng/mL
30 mCi	All other scenarios
100 mCi	**If any are present:** pT3b ≥4 positive nodes ENE that is not extensive[c] Positive margin and postop Tg[b] ≥1.0 ng/mL
200 mCi	**If any are present:** pT4 Extensive ENE[c]

M1 (with the exception of large-volume disease)

For recurrent tumor based only on serum thyroglobulin level (no visible disease) following at least one prior I-131 treatment

Observation without additional I-131 is always a reasonable option.
We recommend observation when life expectancy unrelated to thyroid cancer is <5 y or when the risk of additional I-131 treatment is high: renal insufficiency, peripheral blood count deficiency, or substantial dry eye from prior I-131 treatment.
Our usual dose when treating recurrent tumor based only on serum thyroglobulin level is 100 mCi.

Other situations of recurrent tumor following at least one prior I-131 treatment

The range of scenarios in the category is wide: distant metastasis, small-volume unresectable disease in the neck, and gross total resection of neck disease with a high risk of recurrence based on pathologic findings: positive margin, soft tissue invasion, multiple positive nodes, and extranodal extension.
We usually do not give I-131 treatment in this setting when the risk of I-131 treatment is high (major renal insufficiency, peripheral blood count deficiency, or dry eye problems).
When we treat with I-131 in this setting, our usual dose is 100-200 mCi.

There are differences between these guidelines and those of the American Thyroid Association.

[a]Observation is always reasonable, and we explain this as part of the discussion of treatment options.

[b]Serum thyroglobulin (Tg) value obtained ≥6 weeks after thyroidectomy with any level of thyroid-stimulating hormone. The 1.0-ng/mL Tg threshold is only applicable in the absence of anti-thyroglobulin antibodies.

[c]Extranodal extension (ENE) of tumor beyond the node capsule. We do not have a definition of "extensive" in this setting.

From 8th edition (2017) of the AJCC staging system.[1]

Extranodal Extension

Extranodal extension of metastatic tumor is an important prognostic factor in most types of cancer. In thyroid cancer, this factor is not included in the AJCC staging system nor in the factors that determine treatment in the ATA guidelines. However, there is evidence that extranodal extension predicts a higher recurrence rate in patients with DTC.[47] We take extranodal extension into account when making treatment decisions (see Table 56.6).

Distant Metastases

A unique feature of thyroid cancer is that patients with extensive distant metastases from DTC may be cured with I-131 therapy and most experience long-term survival.[48] Treatment of distant metastases depends on the specific situation, and the scenarios vary so greatly that further discussion is beyond the

scope of this chapter. The consensus guidelines listed in Table 56.5 address the treatment of distant metastases across various situations.

SURGICAL MANAGEMENT OF THYROID CANCER

Surgery is the primary treatment of localized thyroid cancer of all histologies. A total thyroidectomy is the preferred oncologic procedure, but the consensus guidelines listed in Table 56.5 describe scenarios where lobectomy is acceptable.

It is critical to understand that even a total thyroidectomy leaves residual thyroid tissue that will have major implications for subsequent therapy and disease monitoring. The clearest evidence of residual thyroid tissue after total thyroidectomy is seen in postoperative I-131 thyroid studies, which nearly always show uptake in the region of the thyroid bed. The presence of residual thyroid tissue in this setting is not a sign of incomplete surgery, but a matter of practicality. The ligament connecting the posterior surface of the thyroid capsule to the trachea harbors microscopic nests of thyroid tissue and is rarely completely resected in order to reduce the risk of tracheal injury. Second, the recurrent laryngeal nerve is embedded in thyroid tissue at the point where the nerve enters the larynx, and it is not possible to remove all of this thyroid tissue without injuring the nerve and compromising voice quality and laryngeal function.

Several important complications can arise from thyroidectomy. The most common are recurrent laryngeal nerve injury (temporary 30% and permanent 2%) and hypoparathyroidism (temporary 5% and permanent 0.5%).[49]

Neck Dissection in Differentiated Thyroid Cancer

As with squamous cell carcinomas, a modified radical neck dissection is done for thyroid cancer when there is a visible or palpably positive node. However, elective neck dissection (removal of lymphatic regions at risk for subclinical disease) is generally not performed for DTC, unlike primary surgery for most other head and neck cancers. Despite a high incidence of subclinical lymph node involvement in even small DTCs, elective neck dissection is not included in the initial surgical approach because the results without neck dissection have been good.[50]

An ongoing controversy is the role of central (level 6) node dissection as part of the thyroidectomy procedure. The consensus guidelines listed in Table 56.5 summarize this controversy. In our opinion, thorough dissection of the central compartment is not necessary in the absence of clinically suspicious nodes at the time of surgery.

MANAGEMENT OF DIFFERENTIATED THYROID CANCER WITH RADIOACTIVE IODINE

Bioconcentration of Radioactive Iodine

I-131 for DTC is one of the most successful targeted therapy in oncology. The iodine-concentrating capacity of benign and neoplastic thyroid tissue makes most thyroid carcinomas amenable to I-131 therapy. I-131 is taken up by thyroid tissue, including DTC of follicular epithelial origin, at a rate 6.6 times more than most tissues in the body. The biologic half-life in extrathyroidal tissue is 12 days compared to 80 days for thyroid tissue (Table 56.7).

TABLE 56.7 PHYSICAL, BIOLOGIC, AND EFFECTIVE HALF-LIVES ($T_{½}$) OF I-131

Tissue	Physical $t_{½}$	Biologic $t_{½}$	Effective $t_{½}$
Thyroid	8 d	80 d	7.3 d
Extrathyroidal	8 d	12 d	8 h

Radioactive Decay of Iodine-131

I-131 is produced from the fission of uranium atoms during the operation of nuclear reactors or in the detonation of nuclear bombs. I-131 decays by negatron emission (β-minus decay) to xenon-131 (Xe-131). A neutron from the I-131 nucleus converts to a proton, and an electron (β particle) is emitted from the nucleus. This first transition results in a β particle with a range of energies from 250 to 800 keV. These β particles are the reason I-131 is able to deliver targeted cytotoxicity. Because electrons of this energy range will deposit their energy within a millimeter, only the cells taking up the I-131 are affected.

In the second decay step, unstable Xe-131 decays to stable xenon, releasing a photon with an energy of 364 keV. This product is therapeutically undesirable, because the photon will travel far from the source where iodine is concentrated. It contributes very little cytotoxicity to thyroid cancer cells and increases the total body dose; however, it is this photon emission that makes iodine useful for diagnostic imaging.

Goals of Radioactive Iodine Therapy for Differentiated Thyroid Cancer

Broadly speaking, the two basic purposes of adjuvant I-131 are (a) thyroid remnant ablation and (b) adjuvant therapy for residual microscopic disease. Ablation of the remaining thyroid tissue facilitates the use of serum Tg as a very

sensitive and specific marker for disease persistence after primary therapy. I-131 may increase the chance of cancer cure by destroying cancer cells remaining in the operative bed, occult lymph node metastases, and distant metastases.

Dose of Radioactive Iodine (I-131) to Treat Differentiated Thyroid Cancer

There are two main approaches to selecting the dose of I-131 for remnant ablation or treatment of known residual DTC: empiric and dosimetric. With the empiric method, all patients with the same disease risk factors get the same dose. With the empiric method, patients undergo tests of iodine metabolism to customize the dose based on individual physiology. It is beyond the scope of this chapter to discuss the many dosimetric approaches that have been described in the literature. The bottom line is that today most experts recommend empiric dosing in the absence of renal insufficiency or multiple prior I-131 treatments.

Table 56.6 summarizes the indications and dose of I-131 that we currently use in our program. There are differences between these guidelines and those of the major published guidelines.

Preparing Patients for Iodine-131 Treatment

Appropriate preparation for I-131 therapy is critical to obtaining the optimal desired effect of therapy, whether for remnant ablation or adjuvant therapy residual disease. There are many elements to consider when deciding how thorough to be. Table 56.8 summarizes how we prepare patients in our program. These factors are discussed in detail in the consensus guidelines from the ATA.

TABLE 56.8 PREPARATION OF PATIENTS FOR I-131: GUIDELINES FROM THE UNIVERSITY OF FLORIDA DEPARTMENT OF RADIATION ONCOLOGY

Component	Description	Comments
Low-iodine diet	A diet that is low in iodine (≤50 μg/d) for 2 wk before, and 2 d after, I-131 administration. Diet instructions are available at www.thyca.org.	The purpose of a low-iodine diet is to deplete the total body iodine stores to a degree that maximizes the uptake of I-131 by thyroid tissue and thyroid cancer.[70,71]
Intravenous iodinated contrast exposure	Iodine contrast, as used with computed tomography (CT) scans, results in a large amount of iodine stored in interstitial tissues.	In patients who have received intravenous iodinated contrast within 3 mo of the planned date of therapeutic I-131 administration, we measure the urine iodine level 1-2 wk

Component	Description	Comments
		before the planned date of administration (see below).
Urinary iodine measurement	Total body iodine level is determined by the amount of iodine in the urine. The gold standard is a 24-h urine specimen, but we use a spot urine sample because it is more convenient for the patient.	Ideally, urine iodine is ≤50 μg/L before cancer treatment with I-131. When we suspect inadequate iodine depletion, we measure urine iodine 1-2 wk before the planned date of I-131 administration, on day ≥7 of a low-iodine diet. If the urine iodine is ≤150 μg/L, we administer I-131 as planned. If the level is higher, we delay administration, with the patient on a low-iodine diet for as long as we think it will take to adequately deplete total body iodine stores. It is ideal to recheck the urine iodine concentration, but we do not do this when the initial value was <300 μg/L.
rhTSH instead of T_4 deprivation	rhTSH 0.9-mg intramuscular injection twice (2 d and 1 d) before I-131 administration	Compared to T_4 deprivation, rhTSH injections avoid the problems of hypothyroidism and result in less total body radiation exposure but may decrease the potency of I-131 cancer treatment. Also, the cost of rhTSH may not be covered by the patient's insurance. We use rhTSH in all adults when the patient can afford the cost. We do not use rhTSH in children as it is not FDA approved in children and because children tolerate hypothyroidism better than adults do.
T_4 deprivation instead of rhTSH	Stop all thyroid hormone (usually levothyroxine, T_4) replacement for as long as it takes to raise the TSH level to ≥30 μU/mL by the day of I-131 administration. Ideally, pretreatment testing and the administration date should be scheduled well in advance. For this reason, our standard program is to stop thyroid hormone replacement 6 wk before the planned date of I-131 administration because TSH is almost always >30 μU/mL after ~5	Compared to rhTSH, T_4 deprivation may make I-131 treatment more effective because hypothyroidism decreases urinary excretion of I-131 and thus increases biologic half-life. Another advantage of T_4 deprivation is that it does not have the cost of rhTSH injections. But, T_4 deprivation causes the physiologic problems of hypothyroidism and results in a higher total body radiation dose. We use T_4 deprivation, instead of rhTSH, in adults who cannot afford rhTSH. We use T_4 deprivation in all

Component	Description	Comments
	wk of deprivation when we check it 5-10 d before the planned date of administration.	children because rhTSH is not FDA approved in children and because children tolerate hypothyroidism better than adults do.
Lithium	The recommended dose of lithium carbonate is ~20 mg/kg/d (usually 300 mg 3 times a day) for 7 d, beginning 5 d before I-131 administration. At this dose, serum lithium concentration should be measured on day 4 and/or 5 (therapeutic range 0.6-1.2 mEq/L). We have found it difficult to get serum lithium results back in a timely manner. For this reason, in standard-size patients, we often use an empiric dose of 300 mg twice a day and do not check serum levels.	Lithium increases radiation dose in target tissue by increasing iodine retention time preferentially in normal and malignant thyroid cells.[72,73] We use lithium in most patients who do not have a published contraindication, including psychiatric problems, dementia, seizure disorder, cardiac arrhythmia, renal insufficiency, hepatic impairment, hypo- or hypernatremia, and any of these medications: diuretic, antidepressant, nonsteroidal anti-inflammatory drugs, seizure medication, and calcium channel blockers. In patients who are at high risk for tumor recurrence, we often stop contraindicated medications for the week of lithium treatment or administer lithium without stopping the medication.
Stopping T_4 for 4 d with the rhTSH program	Discontinue thyroid hormone replacement 3 d prior to, and the day of, I-131 administration in patients prepared with rhTSH injections.	Thyroid hormones contain iodine. Stopping thyroid hormone replacement for a short time before I-131 administration may increase the efficacy of treatment by augmenting the low-iodine diet.[74] We stop T_4 for 4 d in all patients prepared with rhTSH injections.
Scopolamine	Scopolamine transdermal patch of 0.33 mg/24 h. Apply patch behind your ear as soon as you get up in the morning on the day of I-131 administration. Remove the patch 48-72 h later. Dispense 1 patch. No refills.	Scopolamine is an antimuscarinic that decreases stimulation of the salivary glands. Less salivary stimulation may decrease iodine uptake and thus decrease radiation dose to the salivary glands from I-131 therapy. We use scopolamine in all patients without major contraindications such as angle-closure glaucoma, pyloric obstruction, or serious dementia.
Sour candy	Do NOT eat sour candy for ~3 d after I-131 administration.	Some programs recommend sucking on sour candy during the first few days after I-131 administration. The

Component	Description	Comments
		idea behind sour candy is that stimulating salivary production "washes" iodine out of the saliva glands. One of the few studies on this issue suggested that sour candy INCREASES the radiation dose to the saliva glands.[75] For this reason, we give the patient instructions to NOT chew gum, suck on any type of candy, or eat spicy food for 3 d after I-131 administration.
T_3 during T_4 deprivation	Triiodothyronine (T_3, liothyronine sodium) 25 µg orally twice a day starting the day of discontinuation of T_4, and stopping 2 wk before the day of I-131 administration	T_3 has a much shorter half-life than T_4. The idea behind administering T_3 is to decrease the fatigue and other symptoms of T_4 deprivation. We do not use T_3 because a formal study failed to show a quality of life benefit.[76]
Diagnostic whole-body scan (DxWBS)	Total body image ~3 d after administration of I-131 (1-3 mCi) or I-123 (1.5-3 mCi) with TSH ≥30 µU/mL	Some experts use this study to determine the therapeutic dose of I-131. We do not perform this study.

FDA, U.S. Food and Drug Administration; T_3, 3,5,3′-iodothyronine; T_4, 3,5,3′,5′-iodothyronine; TSH, thyroid-stimulating hormone.

Outpatient Management of Iodine-131

Grigsby et al[51] described the pattern of radiation exposure in 65 household members of 30 patients treated with I-131. The mean dose to family members was well below regulatory standards at 0.24 mSv, and the maximum dose was 1.11 mSv. The Nuclear Regulatory Commission (NRC) has issued guidance on the release of patients following I-131 treatment for thyroid cancer, and a copy of all material related to the issue can be found on the NRC website. Major recommendations were issued in 1997 (NRC Regulatory Guide 8.39) and have largely remained in place. Several minor subsequent recommendations have been issued, most recently in early 2011 under 10 CFR 35.75.[52] Overall, the recommendations are intended to keep the exposure to the public "as low as reasonably achievable."

Risks of I-131 Therapy

A therapeutic dose of I-131 exposes all tissues in the body to ionizing radiation. For this reason, I-131 may damage any tissue in the body and may cause the formation of all types of benign and malignant tumors. The risk of toxicity from I-131 treatment for thyroid cancer depends on the administered dose, the patient's physiology related to iodine metabolism, the sensitivity of the patient to ionizing radiation, tumor burden, tumor location, and the ability of tumor cells to concentrate iodine.

A discussion of all possible acute and late toxicities that have been reported following I-131 treatment will not be useful to most clinicians. Table 56.9 is a version of the consent document that we use to explain the main side effects and complications of I-131 therapy.

TABLE 56.9 SIDE EFFECTS AND RISKS OF I-131 THERAPY: CONSENT DOCUMENT LANGUAGE FROM THE UNIVERSITY OF FLORIDA DEPARTMENT OF RADIATION ONCOLOGY

The most common temporary side effects from I-131 treatment

Swelling of the saliva glands or neck: It is common to experience mild pain and swelling of the saliva glands that are located near the jawbone. This discomfort usually goes away in 3-5 d.

Taste change: It is common to experience a change in the way food tastes. Taste usually returns to normal within 3 wk after taking I-131.

Nausea: Some patients have nausea—possibly with vomiting—for 1-3 d after taking I-131. Take the nausea medication that we give you as often as you need it.

The main serious and permanent problems that may occur after I-131 treatment

Decrease in saliva and tears causing dry mouth, tooth decay (cavities), and dry eyes:
The risk of these problems depends mainly on I-131 dose and the status of your saliva and tear glands.

Bone marrow damage causing infection, bleeding, and problems from anemia:
The risk of these problems depends mainly on I-131 dose and the status of your bone marrow.

I-131 can cause cancer to develop in the future:
We will try to estimate the risk of cancer from I-131 is your situation.
A publication with a formula is second primary malignancies patients with in thyroid cancer.
A website for cancer risk calculation is https://radiationcalculators.cancer.gov/radrat

Damage to testicles or ovaries: I-131 therapy may cause early menopause if you are a woman and impotence and other problems if you are a man. The chance that you could get these problems depends on your age and dose of I-131.
I-131 therapy may decrease your fertility or ability to produce a normal baby. You should definitely not get pregnant if you are a woman, or get a woman pregnant if you are a man, for at least 6 mo after I-131 therapy.

To decrease the chance of problems, do these things:

Do not wear contact lenses for 3 d after receiving I-131.

Stay well hydrated for 3 d after taking I-131: Drink enough fluid so that you need to urinate every few hours. This will decrease radiation exposure to your saliva glands, bladder, and other organs.

Have at least one bowel movement each day for 3 d after taking I-131: Eat prunes or take a laxative, such as Dulcolax 15 mg, as needed.

Avoid things that stimulate saliva production for 3 d after taking I-131: Do not chew gum, use smokeless tobacco, or suck on candy.

EXTERNAL-BEAM RADIOTHERAPY FOR THYROID CANCER

Indications for External-Beam Radiotherapy for Differentiated Thyroid Cancer

There are no randomized control trials defining the indications for external-beam radiotherapy (EBRT) in thyroid cancer. The European Multicentre Study on Differentiated Thyroid Cancer trial was planned as a prospective multicenter trial to evaluate the benefit of adjuvant EBRT in locally advanced DTC. Patients with pT4 disease with or without lymph node metastases and no known distant metastases who underwent total thyroidectomy, I-131, and TSH suppression were to be randomized to EBRT or observation. The trial closed prematurely, however, as only 16% of patients consented to be randomized to EBRT. The trial was converted to a prospective cohort study, and subsequent results failed to define the role of EBRT in this population.[53-55] Therefore, recommendations for EBRT are based on institutional retrospective experiences. Table 56.10 summarizes indications for EBRT from our department and the major consensus guideline publications.

TABLE 56.10 INDICATIONS FOR EXTERNAL-BEAM RADIOTHERAPY FOR DIFFERENTIATED THYROID CANCER

Age	University of Florida	ATA Guidelines[35]	AHNS Guidelines[56]
Age ≤18 y	Painful metastases or impending normal tissue damage from a growing tumor not amenable to other treatment	No child-specific guidelines	No child-specific guidelines
Age >18 y with visible, unresectable neck disease	Most situations where surgery is not able to remove all visible tumors with acceptable morbidity, but age is a factor.	Recommendation 71 [C22]: EBRT is considered for local-regional recurrence that is not surgically resectable,	EBRT is recommended for patients with gross residual or unresectable local-regional disease, except for patients <45 y old with limited gross

Age	University of Florida	ATA Guidelines[35]	AHNS Guidelines[56]
	Due to the increased risk of complications from EBRT in young patients, we usually treat small-volume (<2 cm^3), unresectable residual tumor in the neck in patients <55 y old with I-131 without EBRT if the patient is I-131 naive. We do not use EBRT if I-131 may be curative or elevated Tg is the only sign of disease.	particularly in patients with no evidence of distant disease.	disease that is I-131 avid.
Age >18 y: *Adjuvant treatment soon after thyroidectomy*	Most cases with stage T_4 primary tumors or nodal metastases with extensive extranodal extension, but age is a factor. We often do not give adjuvant EBRT in patients <55 y old with risk factors for microscopic residual tumor. We do not use EBRT if I-131 may be curative or elevated Tg is the only sign of disease.	There is no role for routine adjuvant EBRT to the neck in patients with DTC after initial complete surgical removal of the tumor.	EBRT should not be used routinely as adjuvant therapy after complete resection of gross disease.
Age >18 y: *After gross total resection of recurrence following initial therapy*	Same as for adjuvant EBRT after thyroidectomy	No guidelines in the absence of unresectable disease	After complete resection, EBRT may be considered in select patients older than 45 y old with a high likelihood of microscopic residual disease and a low likelihood of responding to I-131. This scenario may occur in the setting of gross extrathyroidal extension or with revision surgery for

Age	University of Florida	ATA Guidelines[35]	AHNS Guidelines[56]
			persistent or recurrent disease.

AHNS, American Head and Neck Society; ATA, American Thyroid Association; DTC, differentiated thyroid cancer; EBRT, external-beam radiotherapy.

External-Beam Radiotherapy Technique

Techniques for treating metastatic disease will vary by site, tumor burden, and clinical circumstances; therefore, this chapter only discusses the technique used for treating the primary site and nodal regions.

CT simulation is used for treatment planning with patients positioned supine with arms at their side and the neck extended such that the mandible is at 90° with respect to the treatment couch. An Aquaplast (WFR/Aquaplast Corporation) mask, custom head holder, and shoulder straps are used to immobilize the head and neck and to depress the level of the shoulders. Bolus material should be applied over scars on the neck. Intravenous contrast may be helpful in defining target volumes and normal tissue structures, but this is contraindicated if I-131 is being considered within the next 3 months. Axial CT images are acquired from above the skull base to the middle of the chest. Although not necessary, preoperative image sets may be fused to treatment planning CT scans to aid in target definitions. Historically, conventional anterior- posterior/posterior-anterior or lateral fields have been described to treat thyroid cancer, often requiring custom bolus materials to ensure homogeneous dose distributions. Because the target volume straddles the level of the shoulder and, in nearly all cases, contains concavities with envaginated critical normal tissues, we treat all thyroid cancer cases with intensity-modulated radiotherapy (IMRT). We do not routinely bolus neck scars because the tangential beams in the IMRT plan deliver a high dose to the skin of the low neck.

External-Beam Radiotherapy Dose and Target Guidelines

Table 56.11 lists the major publications from the modern era with dose and target volume information related to EBRT with curative intent for thyroid cancer. Table 56.12 summarizes the guidelines that we use.

TABLE 56.11 MAJOR PUBLICATIONS WITH DOSE AND TARGET INFORMATION FOR EXTERNAL-BEAM RADIOTHERAPY TO THE NECK FOR DIFFERENTIATED THYROID CANCER

Organization	Reference
American Head and Neck Society	Kiess AP, Agrawal N, Brierley JD, et al. External-beam radiotherapy for differentiated thyroid cancer local-regional control: a statement of the American Head and Neck Society. *Head Neck*. 2016;38(4):493-498.
National Cancer Center, Korea	Lee EK, Lee YJ, Jung YS, et al. Postoperative simultaneous integrated boost-intensity modulated radiation therapy for patients with locoregionally advanced papillary thyroid carcinoma: preliminary results of a phase II trial and propensity score analysis. *J Clin Endocrinol Metab*. 2015;100(3):1009-1017.
Memorial Sloan Kettering Cancer Center	Romesser PB, Sherman EJ, Shaha AR, et al. External beam radiotherapy with or without concurrent chemotherapy in advanced or recurrent non-anaplastic non-medullary thyroid cancer. *J Surg Oncol*. 2014;110(4):375-382.
MD Anderson Cancer Center	Schwartz DL, Lobo MJ, Ang KK, et al. Postoperative external beam radiotherapy for differentiated thyroid cancer: outcomes and morbidity with conformal treatment. *Int J Radiat Oncol Biol Phys*. 2009;74(4):1083-1091.

TABLE 56.12 EXTERNAL-BEAM RADIOTHERAPY NECK TARGET VOLUME AND DOSE GUIDELINES FOR THYROID CANCER FROM THE UNIVERSITY OF FLORIDA

Standard fractionation with moderate risk of recurrence: 60/54 Gy prescriptions

We use this program when our indication for EBRT is met and there is NO evidence of visible residual tumor, extranodal extension of tumor, or surgical margin <0.5 cm.
CTV 60 Gy at 2 Gy = Postoperative areas thought to be at high risk for recurrence. These include areas where recurrent tumor was resected plus a 1-cm margin edited for anatomic boundaries to tumor spread, and dissected nodal stations with pathologically positive nodes.
CTV 54 Gy at 1.8 Gy = Undissected nodal stations that we judge to be at >10% risk of recurrence
PTVs = CTV + 0.3 cm

Standard fractionation with high risk of recurrence: 70/63/56 Gy prescriptions

We use this program when our indication for EBRT is met and there is visible residual tumor, extranodal extension of tumor, or surgical margin <0.5 cm.
CTV 70 Gy at 2 Gy = Visible residual tumor and/or postoperative areas with close margin or extranodal extension, plus a 1-cm margin edited for anatomic boundaries
to tumor spread
CTV 63 Gy at 1.8 Gy = Dissected nodal stations with pathologically positive nodes
CTV 56 Gy at 1.6 Gy = Undissected nodal stations that we judge to be at >10% risk of recurrence
PTV = CTV + 0.3 cm

Stereotactic body radiation therapy (SBRT)

We use neck SBRT for small-volume (<2 cm^3) visible disease in situations where we judge the risk of treating a larger volume to be unacceptable. We do not have criteria for choosing the 50 vs 35 Gy schedules.
A single target volume: CTV = GTV, PTV = CTV + 0.2 cm
Dose to 95% of PTV = 50 Gy at 5 Gy (10 treatments) or 35 Gy at 7 Gy (5 treatments)

EBRT, external-beam radiotherapy; CTV, clinical target volume; GTV, gross total volume; PTV, planning target volume.

Sequencing of External-Beam Radiotherapy and I-131 Treatment

When there are indications for both EBRT and I-131 treatment, there is the question of sequencing. There is no high-quality study specific to this question. In the words of the American Head and Neck Society Consensus guidelines, "There is no consensus on the optimal sequence of EBRT and I-131."[56]

The argument for starting with EBRT is that it often minimizes delay to starting adjuvant treatment. The argument for starting with I-131 is concern that EBRT will "stun" cancer cells in a way that decreases uptake of I-131.

We individualize the decision based on the projected delay to administering I-131 treatment and the likelihood that I-131 treatment will increase the chance of cure. In most cases, we deliver EBRT first.

THYROID-STIMULATING HORMONE SUPPRESSION FOR DIFFERENTIATED THYROID CANCER

A common practice in the management of DTC is administration of supratherapeutic doses of T_4 in an effort to drive the TSH below detectable limits (<0.1 mIU/L), thereby decreasing stimulation of residual benign and malignant follicular- derived thyroid cells. There is in vitro evidence that TSH-receptor stimulation is sufficient to initiate thyroid tumorigenesis.[57] A large retrospective series of patients with DTC with 30 years of follow-up showed that, compared with no adjunctive therapy, treatment with TSH suppression with T_4 resulted in a 50% reduction in cancer deaths (6% vs 12%).[58] Another study showed that the degree of TSH suppression (TSH ≤0.05 mIU/L vs ≥1 mIU/L) was associated with improved relapse-free survival.[59]

A major limitation to TSH suppression is the associated toxicity as these patients experience subclinical and even overt thyrotoxicosis. As such, these patients are prone to bone demineralization and cardiac abnormalities, including tachyarrhythmia, conduction abnormalities, increased contractility, ventricular hypertrophy, systolic and diastolic dysfunction, and even cardiac death.[60] Nevertheless, a meta-analysis with over 4,000 patients with DTC demonstrated that the relative risk of major adverse clinical events was 0.73 ($P < .05$) favoring a "likely" or "questionable" benefit to TSH suppression in 15 of 17 trials.[61] The authors concluded that TSH suppression is justified following initial therapy for DTC. The authors recommend TSH suppression to just below 0.1 mU/L for

patients with high-risk thyroid cancer, while maintaining the TSH at or slightly below the lower limit of normal (0.1-0.5 mU/L) in patients at low risk of recurring.

CHEMOTHERAPY AND TARGETED AGENTS FOR DIFFERENTIATED THYROID CARCINOMA

There are two settings where chemotherapy or targeted systemic therapy is indicated: adjuvant treatment or treatment for recurrent or metastatic disease for which surgery, EBRT, or I-131 treatment is not a reasonable option.

The ATA's statement summarizes the view of most experts regarding the adjuvant situation: "RECOMMENDATION 61: There is no role for routine systemic adjuvant therapy in patients with DTC (beyond I-131 and/or TSH suppressive therapy using [levothyroxine])."[35]

There is no standard treatment for DTC that is not likely to respond to surgery or radiation therapy. Traditional systemic cytotoxic therapies have no significant role because of poor response rates.[62] Recent advances in targeted therapeutics have opened new doors for effective systemic therapy for recurrent or metastatic disease that is unresponsive to I-131. Most of the agents currently under investigation target specific pathways involved in cellular proliferation through inhibition of tyrosine kinase receptors and angiogenesis through inhibition of vascular endothelial growth factor receptors. This is a rapidly evolving area. Section C41 of the ATA guidelines summarizes the status of this issue as of late 2015.[35]

MANAGEMENT OF MEDULLARY THYROID CARCINOMA

All patients with MTC should be tested for *RET* mutations, including sporadic cases. Genetic screening and testing are also indicated. Similar to follicular epithelial-derived DTC, the initial primary management of localized MTC is total thyroidectomy, which is the only completely effective therapy. Central neck dissection should be performed in all cases, and compartment-oriented lateral neck dissection is indicated when clinically involved. There is no role for adjuvant I-131 therapy. All patients should be followed with serum calcitonin levels as this presents a sensitive and specific marker for the extent of residual disease.

MTC is uncommon, and most of the time it behaves as an indolent disease where long survival with uncontrolled tumor is common. For these reasons, there

are few studies on the role of EBRT. The American Head and Neck Society consensus document is currently the best summary of this issue.[23]

Traditional cytotoxic systemic therapies have been ineffective in the management of metastatic or recurrent MTC; however, recent advances in therapies targeting the *RET*-tyrosine kinase receptors have shown promising preclinical and early clinical results.[63-67]

MANAGEMENT OF ANAPLASTIC THYROID CARCINOMA

The ATA guidelines explain the major issues and relevant literature related to the diagnosis and treatment of ATC.[68]

Complete surgical excision should be the goal of initial therapy, when feasible. However, surgery should be avoided when complete excision is not possible as debulking does not improve outcomes. There is no therapeutic role for I-131.

The great majority of patients with ATC present with poor performance status and locally advanced disease such that gross total resection is not possible. For this reason, the goal of treatment in most ATC cases is palliation.

Patients with good performance status and no evidence of distant metastases should be offered aggressive treatment with maximum safe resection and EBRT, with or without concurrent chemotherapy. There is no consensus on the EBRT fractionation program, but a recent study of the National Cancer Database showed that survival was better when the EBRT total dose was 60 to 75 Gy as compared to lower doses.[69] In our program, we usually use the 70/63/56 Gy program described in Table 56.12.

The most aggressive approach is to combine EBRT with chemotherapy involving a taxane, anthracycline, platin, or a combination of all. In our program, we rarely use chemotherapy with EBRT for ATC due to the high toxicity of combination therapy in this setting.

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PART D

Thorax

CHAPTER 57

Lung Cancer

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EPIDEMIOLOGY

In 2020, lung cancer accounted for 11.4% (2.2 million) of the total cases of cancer worldwide. In the United States, lung cancer is the second most common cancer and the most common cause of cancer-related death in both men and women. The American Cancer Society projects 238,340 people being diagnosed with lung cancer in 2023 and 127,070 deaths.[1] A similar number of people in the United States die from lung cancer as from breast, prostate, and colorectal cancers combined. The incidence and mortality rates for men began to drop around 1990, and a slight drop in the incidence and mortality rates has only recently been observed for women. The lag in the trend of declining lung cancer rates in women compared with men reflects historical differences in cigarette smoking between the sexes; cigarette smoking in women peaked about 20 years later than in men. Sex, racial, and sociodemographic disparities exist in the incidence and mortality for lung cancer with rates highest in men, particularly those residing in counties with low income and education level, and particularly in African Americans.

Voluntary or involuntary cigarette exposure accounts for 80% to 90% of all cases of lung cancer. Indoor radon exposure is now considered the second leading cause of lung cancer in the United States. Other known risk factors for lung cancer include exposure to occupational and environmental carcinogens, such as asbestos, arsenic, and polycyclic aromatic hydrocarbons.

ANATOMY

The lungs are situated on each side of the mediastinum, which contains the heart, trachea, esophagus, and great vessels. The lungs are conical in shape with an apex projecting upward into the neck for approximately 2 to 3 cm above the clavicle, a base sitting on the diaphragm, a costal surface along the chest wall, and a mediastinal surface that is molded to the heart and other mediastinal structures. Visceral pleura covers the lungs, and parietal pleura covers the inside of the chest cavity. The lungs are freely suspended but are rooted to the mediastinum by the structures emerging from the hilum.

The lungs are divided into distinct lobes—three lobes within the right lung and two lobes and the lingula within the left lung. The right lung is divided into the upper, middle, and lower lobes by the oblique (major) and horizontal (minor) fissures. The oblique fissure runs forward and downward from approximately the level of the fifth thoracic vertebral body to the diaphragm, dividing the lungs into upper and lower lobes. The horizontal fissure separates the right middle from the right upper lobe, fanning out forward and laterally from the hilum. The middle lobe is thus a small, triangular lobe bounded by the horizontal and oblique fissures and actually rests on the diaphragm. The left lung is divided by only the oblique fissure into two lobes—the upper and lower lobes. The lingula, located in the left upper lobe, is homologous to the right middle lobe and also touches the diaphragm.

The trachea bifurcates at the carina, which lies at the junction between the manubrium and body of the sternum, into the right and left main bronchi. Each main bronchus divides into lobar bronchi, each supplying a lobe of the lung. Although the lingula is in the left upper lobe, the lingular bronchus is considered by many a

lobar bronchus. Each lobar bronchus divides into smaller bronchi that form the bronchopulmonary segments. These segments are pyramidal in shape, with an apex toward the lung root and a base at the pleural surface. Structures entering each bronchopulmonary segment (ie, bronchus and artery) tend to lie centrally. Structures leaving the segment (ie, veins and lymphatics) lie in the periphery of the segment within the connective tissue that separates the segments. Segmental bronchi divide into bronchioles, continue to branch, and eventually form the alveoli, where blood-gas exchange occurs.

The main lymphatic drainage for each bronchopulmonary segment follows the vasculature and airways toward the hilum, where it ultimately drains into the mediastinum. However, the rich network of lymphatics within the thorax leads to complex variability in drainage patterns.

The International Association for the Study of Lung Cancer (IASLC) developed a lymph node map that reconciles differences among older maps and provides precise anatomic definitions for all lymph node stations.[2] The IASLC lymph node map has been endorsed by the American Joint Committee on Cancer (AJCC) and incorporated into the staging manual. The IASLC lymph node map designates 14 lymph node levels compartmentalized into intrapulmonary, hilar, and mediastinal zones that have prognostic implications and are utilized in common clinical practice.

CLINICAL PRESENTATION AND PATTERNS OF SPREAD

Signs and symptoms of lung cancer directly reflect the patient's local, regional, or distant pattern of spread. Lung cancer spreads locally by direct extension of the primary tumor, regionally via involvement of the thoracic lymphatics, and distantly via invasion into vascular channels leading to hematogenous spread. From cases registered to the Surveillance, Epidemiology, and End Results (SEER) program (https://seer.cancer.gov/statfacts/html/lungb.html), ~20% of lung cancers are localized to the primary site at initial diagnosis, ~20% have regional lymph node involvement and/or direct extension of the primary cancer outside the lung, and more than 50% present with distant metastases (and ~5% are with unknown/unrecorded stage). Small cell lung cancer (SCLC) has a greater propensity to present in more advanced stages.

Intrathoracic Spread

There is a wide range of symptoms attributable to intrathoracic mass effects from lung cancer. Tumor invading or compressing the airways accounts for common symptoms of cough and dyspnea, with more extensive airway invasion resulting in possible stridor or hemoptysis. Dyspnea may also arise from atelectasis, post– obstructive pneumonia, or a pleural or pericardial effusion. Potentially life-threatening hemoptysis can result from tumor eroding into blood vessels. Patients can experience pain from tumor invasion or spread into the mediastinum, parietal pleura, or chest wall. A central primary tumor or mediastinal lymph node can impinge upon the recurrent laryngeal nerve (either along its course under the aortic arch on the left or in the supraclavicular region on the right), which can cause hoarseness. Phrenic nerve impingement may initially produce hiccups, and progressive damage can produce unilateral paralysis of the diaphragm with shortness of breath. See the section "Superior Vena Cava Syndrome" for more details.

Obstruction of the superior vena cava (SVC) from primary tumor or mediastinal lymphadenopathy commonly causes a sensation of fullness in the head and dyspnea. Physical findings include jugular venous distension and, occasionally, swelling of the face and arms.

Primary tumors arising within the superior sulcus may produce the classic Pancoast syndrome (more common with non–small cell lung cancer [NSCLC] vs SCLC) manifested by shoulder pain, Horner syndrome, and brachial plexopathy. See the section "Superior Sulcus Tumors and Pancoast Syndrome" for more details.

Distant Extrathoracic Spread

Contralateral lung, liver, bone, adrenals, and brain are the most frequent sites of distant disease; however, lung cancer can spread to any part of the body and cause symptoms from tumor mass effect or alterations in the microenvironment around the metastatic site (which may contribute to metastasis-related bony pain). For some metastatic sites, such as adrenal or liver, symptoms are not common, particularly in the setting of nonbulky disease. For other sites, such as the eloquent brain, metastases (even of relatively small size) can

result in debilitating symptoms. Brain metastases can also cause generalized symptoms of headache, nausea, or seizure, though could also be asymptomatic in some patients.

Paraneoplastic Syndromes

Paraneoplastic syndromes are characterized by specific signs and symptoms that are likely mediated by humoral factors secreted by tumor cells or by an immune response against the tumor. These uncommon syndromes often resolve with treatment of the cancer, though could persist and require ongoing management. Examples of paraneoplastic syndrome are discussed in the subsequent section.

Cushing Syndrome

Ectopic production of adrenocorticotropic hormone (ACTH) can cause Cushing syndrome. Typical signs and symptoms include muscle weakness, weight loss, hypertension, hirsutism, osteoporosis, hypokalemic alkalosis, and hyperglycemia. Cushing syndrome is relatively common in patients with SCLC or carcinoid tumors.

Syndrome of Inappropriate Antidiuretic Hormone Secretion

The syndrome of inappropriate antidiuretic hormone (SIADH) secretion results in hyponatremia. Approximately 10% of patients who have SCLC exhibit SIADH, and SCLC accounts for approximately 75% of all SIADH. Symptoms include headache, muscle cramps, anorexia, and decreased urine output. If left untreated, cerebral edema can develop, leading to mental status changes, coma, seizures, and respiratory arrest.

Hypercalcemia

Hypercalcemia in patients with lung cancer may be attributable to the secretion of a parathyroid hormone–related protein, calcitriol, or other cytokines, including osteoclast-activating factors. In one study of 1,149 consecutive lung cancers, 6% of patients had hypercalcemia.[3] Among those with hypercalcemia, squamous cell carcinoma, adenocarcinoma, and SCLC were responsible for 51%, 22%, and 15% of cases, respectively. Symptoms of hypercalcemia include anorexia, nausea, vomiting, constipation, lethargy, polyuria, polydipsia, and dehydration. Renal failure, confusion, and coma are late manifestations.

Lambert-Eaton Myasthenic Syndrome

Lambert-Eaton myasthenic syndrome (LEMS) is an autoimmune disorder characterized by muscle weakness of the limbs that improves with repeated testing, in contrast to myasthenia gravis, which worsens with repetition. Proximal muscles are predominantly affected, and patients complain of difficulty climbing stairs and rising from a sitting position. Approximately 3% of patients with SCLC exhibit LEMS, and SCLC accounts for approximately 60% of all LEMS.[4] The neurologic symptoms of LEMS precede the diagnosis of SCLC in more than 80% of cases, often by months or years.

Hypertrophic Osteoarthropathy

Hypertrophic pulmonary osteoarthropathy (HPO), most frequently associated with adenocarcinoma, is defined by clubbing and periosteal proliferation of the tubular bones. HPO is further characterized by a symmetrical, painful arthropathy that usually involves the ankles, knees, wrists, and elbows. A radiograph of the long bones shows characteristic periosteal new bone formation. A bone scan or positron emission tomography (PET) typically demonstrates diffuse uptake by the long bones.

SCREENING, DIAGNOSTIC STAGING, AND WORKUP

Screening for Lung Cancer

Given the high mortality rate of lung cancer and that the majority of patients are diagnosed with advanced stage, identifying lung cancer at an earlier stage has the potential to improve outcomes. While screening trials

involving chest x-rays and/or sputum sampling failed to demonstrate a survival benefit, early trials of spiral computed tomography (CT) in lung cancer screening were promising[5] and set the groundwork for the landmark National Lung Screening Trial (NLST).[6] From 2002 to 2004, 53,454 participants between 55 and 74 years of age, with a history of cigarette smoking of at least 30 pack-years and not having quit smoking more than 15 years ago, were randomly assigned to three annual screenings with either low-dose CT (n = 26,722) or standard chest x-ray (n = 26,732). Screening with low-dose helical CT scans had a 20% relative reduction in risk of death caused by lung cancer (P = .004) and a 6.7% relative reduction in all-cause mortality (P = .02). A 2019 update of the NLST showed that with longer follow-up, the number needed to screen to prevent one lung cancer death remained unchanged, with similar rates of lung cancer incidence in both arms.[7] Similarly in the NELSON trial, patients between the ages of 50 and 74 years and who currently smoke or quit less than 10 years ago were randomly assigned to undergo CT screening at T0 (baseline), year 1, year 3, and year 5.5 or no screening.[8] Screening reduced lung cancer mortality by 24% (95% confidence interval [CI] 0.61-0.94; P = .01). As of 2021, the U.S. Preventive Services Task Force recommends "annual screening for lung cancer with LDCT in adults aged 50 to 80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years."[9] The 2023 guideline from the American Cancer Society is the same except years since quitting is no longer an eligibility factor for people who formerly smoked.[10]

Diagnostic Workup

Outside of diagnosing lung cancer after an abnormal screening CT scan, or after an incidental finding during the workup of another problem (ie, cardiac arrest, chronic obstructive pulmonary disease exacerbation, or pneumonia), lung cancer is generally diagnosed when working up new symptoms (described earlier) and signs (ie, abnormal physical examination), particularly in patients with significant smoking history. An abnormal chest x-ray, showing a mass, obstruction or atelectasis, is often one of the first diagnostic findings of lung cancer. Nevertheless, all patients with suspected lung cancer (with or without an abnormal chest x-ray) should undergo a contrast-enhanced CT scan of the chest and upper abdomen to include the entire liver and adrenal glands. Suspicious CT findings warrant consideration of PET/CT imaging to optimally assess for the likelihood of lung cancer, although PET/CT scans are often performed only after pathologic diagnosis of lung cancer to better characterize the extent of extracranial disease.

While the sensitivity and specificity of PET in assessing mediastinal nodal metastasis is markedly superior to CT,[11] the potential for false positives and false negatives (particularly with smaller lymph nodes 16) necessitate lymph node tissue sampling (when feasible).

Percutaneous fine-needle aspiration (FNA) has long been used to obtain tissue for pathologic diagnosis of lung cancer. The U.S. guidance (ie, for supraclavicular lymph nodes or pleural effusions) or CT guidance (ie, for lung, liver, adrenal, or bone sites) is used to increase the diagnostic yield. For CT-guided lung biopsy, there is a ~25% risk of pneumothorax, though most resolve without intervention; only approximately 5% require a chest tube. A negative biopsy cannot rule out malignancy unless another benign diagnosis can clearly be established. Fiberoptic bronchoscopy enables visualization of the tracheobronchial tree and obtaining cytologic brushings and washings and biopsy of visible lesions. Navigational bronchoscopy utilizes a virtual map of the bronchial tree that is generated from a high-resolution CT imaging to potentially target lesions not accessible with standard bronchoscopy and may increase the diagnostic yield. For some peripheral lesions, navigational bronchoscopic biopsy and CT-guided percutaneous biopsy may both be feasible, and the decision-making on the optimal approach should involve a multidisciplinary discussion.

Fiberoptic endoscopy techniques can also be combined with ultrasound to aid in targeting mediastinal and hilar lymph nodes to biopsy. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) can readily sample paratracheal (lymph node levels 2 and 4), subcarinal (level 7), or hilar lymph node stations (level 10). A prospective study comparing EBUS-TBNA with PET/CT scans revealed an accuracy of 98% and a sensitivity and specificity of 92% and 100%, respectively.[12] An esophageal approach known as transesophageal endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) can perform the same function, especially the sampling of mediastinal nodes that are posterior or inferior, such as the retrotracheal (lymph node station 3p), subcarinal (level 7), paraesophageal (level 8), and pulmonary ligament lymph nodes (level 9).

In skilled hands, mediastinoscopy remains the most accurate technique to assess upper and lower paratracheal (lymph node stations 2 and 4), prevascular (station 3a), retrotracheal (station 3p), subcarinal (station 7), and hilar lymph nodes (station 7), particularly for normal-sized nodes. Lymph nodes within the aortopulmonary window (lymph node station 5) and along the ascending aorta (station 6) are not accessible by standard mediastinoscopy techniques; however, they can be evaluated by anterior mediastinotomy (also known as the Chamberlain procedure) or video-assisted thoracoscopic techniques. Although considered the gold standard, mediastinoscopy does have a false-negative rate of approximately 10%. Furthermore, less invasive techniques such as EBUS-TBNA or EUS-FNA are often favored. Mediastinoscopy should be considered in situations where less invasive techniques are nondiagnostic. It is reasonable to forgo invasive staging of the mediastinum in patients with clinical stage I peripheral disease, particularly those with PET-positive primary tumors but no mediastinal uptake and no obviously enlarged nodes on CT.

Video-assisted thoracoscopy can also be used to reach mediastinal nodes not accessible by standard mediastinoscopy, EBUS-TBNA, or EUS-FNA techniques.

STAGING

Definitions of tumor, node, metastasis (TNM) for the eighth edition of the *AJCC Cancer Staging Manual* are shown in Table 57.1. The stage groupings are shown in Table 57.2.

TABLE 57.1 AJCC STAGING OF LUNG CANCER, EIGHTH EDITION

Tx	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy.
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (ie, not in the main bronchus)
T1mi	Minimally invasive adenocarcinoma: adenocarcinoma (≤3 cm in greatest dimension) with a predominantly lepidic pattern and ≤5 mm invasion in greatest dimension
T1a	Tumor is ≤1 cm in greatest dimension.
T1b	Tumor >1 cm but ≤2 cm in greatest dimension
T1c	Tumor >2 cm but ≤3 cm in greatest dimension
T2	Tumor >3 cm but ≤5 cm or having any of the following features: involves the main bronchus but without involvement of the carina; invades the visceral pleura; or associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung
T2a	Tumor >3 cm but ≤4 cm in greatest dimension
T2b	Tumor >4 cm but ≤5 cm in greatest dimension
T3	Tumor >5 cm but ≤7 cm in greatest dimension or directly invading any of the following: parietal pleura, chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium, or separate tumor nodule(s) in the same lobe as the primary
T4	Tumor >7 cm or tumor of any size that invades diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; separate tumor nodule(s) in an ipsilateral lobe different from that of the primary
N0	No regional lymph node involvement
N1	Involvement of ipsilateral intrapulmonary, or peribronchial, hilar lymph nodes
N2	Involvement of mediastinal or subcarinal lymph nodes
N3	Involvement of contralateral mediastinal or hilar lymph nodes. Involvement of ipsilateral or contralateral scalene or supraclavicular nodes
M0	No distant metastasis
M1	Distant metastasis present
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion
M1b	Single extrathoracic metastasis

M1c	Multiple extrathoracic metastases in one or several organs

AJCC, American Joint Committee on Cancer.

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TABLE 57.2 PROGNOSTIC STAGE GROUPING: TNM SUBSETS, EIGHTH EDITION

Stage	Tumor	Node	Metastasis
Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA1	T1(mi)	N0	M0
	T1a	N0	M0
Stage IA2	T1b	N0	M0
Stage IA3	T1c	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
Stage IIB	T1a-c	N1	M0
	T2a	N1	M0
	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a-c	N2	M0
	T2a-b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	T1a-c	N3	M0
	T2a-b	N3	M0
	T3	N2	M0
	T4	N2	M0
Stage IIIC	T3	N3	M0
	T4	N3	M0
Stage IVA	Any T	Any N	M1a
	Any T	Any N	M1b
Stage IVB	Any T	Any N	M1c

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PATHOLOGIC CLASSIFICATION

The four major classifications of lung cancer include (a) squamous cell carcinoma, (b) adenocarcinoma, (c) small cell carcinoma, and (d) large cell carcinoma. Historically, the most important histologic information to guide treatment for lung cancer was distinguishing between non–small cell and small cell carcinoma. However, in recent decades, specific systemic regimens (discussed later) have been shown to be more or less efficacious for certain lung cancer subtypes. Moreover, among patients with squamous cell carcinoma and adenocarcinoma, specific mutations can determine if there are molecular characteristics (ie, specific mutations) that can optimally guide therapy (targeted therapy is discussed in more detail later). Molecular testing can be performed from the sampled tissue, or from serum or blood (ie, liquid biopsy). The 2021 World

Health Organization (WHO) Classification of Lung Tumors has placed a greater emphasis on molecular characteristics.[13]

Prognostic and Predictive Factors

Prognostic factors, such as TNM stage, are those that predict clinical outcome independent of therapy, and predictive factors are those that predict response to a particular therapeutic regimen. The past decade has seen significant advances in our understanding of tumor-related prognostic and predictive factors. With the advent of novel immunotherapies and targeted systemic therapies specific for molecular subtypes of NSCLC (discussed later in the chapter), a subset of patients (even with metastatic disease) can experience prolonged progression-free survival (PFS) and overall survival (OS). Thus, having a "targetable" mutation predicts response to specific targeted agents. Objective assessment of performance status (ie, Karnofsky or Eastern Cooperative Oncology Group [ECOG] scales), and whether a patient experienced significant weight loss (generally >5%) in the 6 months preceding diagnosis have been shown in large trials to be among the factors most predictive of survival (along with TNM stage).[14] In addition, age, sex, and marital status have been shown to be prognostic for survival in a number of studies. Movsas et al[15] reported that baseline quality of life (QoL), as quantified by validated instruments, superseded performance status, age, sex, and other classic prognostic indicators for survival in a prospectively collected data set in patients enrolled on a Radiation Therapy Oncology Group (RTOG) clinical trial, suggesting that baseline QoL may be one of the most important predictors of long-term survival.

GENERAL MANAGEMENT OF NON–SMALL CELL LUNG CANCER

The management of NSCLC presents a formidable challenge. Oncologists must not only account for the stage and extent of disease spread at the time of diagnosis but also carefully weigh the impact of baseline pulmonary functional status and comorbidities on the patient's ability to tolerate treatment. NSCLC is an aggressive tumor of a vital organ that is poorly functioning at baseline in the majority of patients. Therefore, the final therapeutic approach must be tailored to the individual. The treatment principles presented in this section should be viewed as guidelines and not as a cookbook for the management of this disease.

For patients with stage I disease, the standard of care for patients who are surgical candidates is complete surgical resection with the possible addition of adjuvant chemotherapy for those patients who present with stage IB and high-risk disease, although there is significant controversy. For patients with stage I disease who are medically inoperable, stereotactic body radiation therapy (SBRT), also known as stereotactic ablative radiotherapy (SABR), is the standard of care. There are several trials investigating the use of immunotherapy for these patients.

For stage II, patients who are operable may be treated with surgery upfront followed by adjuvant chemotherapy and immunotherapy or with neoadjuvant perioperative chemoimmunotherapy; this is an area of active investigation. Patients who are inoperable may be treated as stage III if they have node-positive disease (N1) or stage I if they have node-negative disease (T2b or T3). Stage II is relatively uncommon and should be managed in a multidisciplinary setting.

For patients with stage III disease, a significant amount of controversy exists regarding optimal management. For select patients with stage III disease at diagnosis who are candidates for surgical resection, neoadjuvant chemoimmunotherapy or chemoradiotherapy is often used. For patients with unresectable stage III disease, the standard approach is concurrent chemoradiotherapy followed by adjuvant immunotherapy for fit patients or sequential chemotherapy and radiotherapy (RT) for patients who cannot tolerate concurrent treatment.

For patients with stage IV disease without significant local presenting symptoms or need for urgent radiation, systemic therapy is the standard initial treatment approach. When significant local presenting symptoms requiring radiation are present—SVC obstruction, hemoptysis, or cord compression—palliative RT can precede systemic therapy. A detailed discussion of the goals of care with consideration of early referral to hospice should be part of the initial treatment approach. Early introduction of palliative care into the standard

treatment paradigm in this setting not only improves QoL and reduces inappropriate hospitalization at the end of life but may also improve survival.[16]

In the next two sections, we divide the management for NSCLC into early and locally advanced stages. Early stage includes T1 to T2 N0 tumors, although some studies could include T3 tumors by size criteria, that is, 7 cm or less. Locally advanced stages include node-positive and large tumors T3 to T4.

MANAGEMENT OF EARLY-STAGE NON–SMALL CELL LUNG CANCER (T1 TO T2N0)

Preoperative Assessment

Patient selection is critical when an operative approach is being considered for the management of NSCLC. This includes an assessment of the clinical extent of disease, the predicted postresection pulmonary reserve of the patient, and preoperative cardiac clearance for the intended surgical procedure. Although there are no strict guidelines for operability, traditionally, patients are considered to be suitable for resection if their predicted postoperative forced expiratory volume in 1 second (FEV_1) is more than 60% and diffusing capacity for carbon monoxide more than 60%.[17] Patients who do not meet those criteria should undergo additional testing, including exercise test, or ventilation-perfusion imaging to determine the regional variance in pulmonary function, including the potential loss of functional lung tissue within the planned area of excision.

Resection for Early-Stage Lung Cancer

The standard of care for a patient with early-stage, node-negative lung cancer is surgical resection through either a lobectomy or pneumonectomy with mediastinal lymph node dissection. A trial from the Lung Cancer Study Group randomized 276 patients with T1N0 NSCLC to lobectomy versus limited surgical resection (either wedge resection or segmentectomy). In 1995, they reported a 17% risk of local recurrence with limited resection versus 6% with lobectomy ($P = .008$).[18] However, a nonrandomized trial by Okada et al[19] suggested sublobar resection did not confer worse local control versus lobectomy and afforded better postoperative lung function in appropriately selected patients with early-stage NSCLC. More recently, a pair of phase III trials established that sublobar resection has a role in small peripheral tumors. The Japanese Clinical Oncology Group (JCOG) 0802 trial randomized 1,106 patients with 2 cm peripheral NSCLC or less to lobectomy or segmentectomy, with segmentectomy improving 5-year OS from 91.1% to 94.3% in spite of having more locoregional recurrences (10.5% vs 5.4%).[20] The Cancer and Leukemia Group B (CALGB) 140503 trial randomized 697 patients with peripherally located, early stage (≤2 cm), with intraoperative confirmation of node-negative NSCLC.[21] With a median follow-up of 7 years, the disease-free survival (DFS) and OS were not significantly different between the groups, while lung function (specifically FEV_1 and forced vital capacity) was worse after lobectomy. Sublobar resection can be considered for small, peripheral, node-negative lung tumors.

Radiation for Early-Stage Lung Cancer

There appears to be no role for adjuvant RT after sublobar resection of early-stage NSCLC with negative surgical margins. The American College of Surgeons Oncology Group Z4032 study analyzed 222 patients who underwent sublobar resection as they were objectively deemed to be at high risk for lobectomy for early-stage (≤3 cm) NSCLC and were randomized to undergo or not undergo adjuvant intraoperative brachytherapy.[22] With a median follow-up of more than 4 years, the local recurrence and OS rates were similar between the two groups. Among 14 patients who were found to have positive margins at the staple line, the hazard ratio (HR) for local recurrence was 0.22 ($P = .24$) (an unplanned analysis) with brachytherapy. While not based on level 1 data, patients with positive surgical margins after sublobar resection or lobectomy are generally offered adjuvant RT to the staple lines or high-risk areas (if identified with staples by the thoracic surgeon). Gross residual disease should be treated with curative intent (depending on pathologic staging and sites of disease) if feasible.

Historically, early-stage NSCLC was treated with conventional fractionation to doses on the order of 70 Gy. Dose escalation trial allows safe delivery of doses up to 102.9 Gy to small peripheral tumors.[23] Based on fundamental radiobiologic principles, Fletcher[24] predicted that using conventional fraction sizes of 1.8 to 2

Gy, doses of 100 Gy or higher might be required for the sterilization of most NSCLC tumors. These doses are not routinely achievable with conventionally fractionated RT in the patient who is medically inoperable without excessive toxicity.

SBRT refers to the delivery of large doses of radiation to a small treatment volume, usually employing multiple beams, using a small number of fractions (usually five fractions or less). Application of SBRT in lung cancer was impractical until advanced imaging treatment delivery techniques were developed (Figure 57.1). Cancer control and survival outcomes from phase I and II studies of SBRT (discussed later) were markedly superior to conventionally fractionated radiation, although it was not clear how much benefit was derived from more modern cancer staging and treatment planning approaches. Thus, the Scandinavian SPACE study randomized 102 patients from 2007 to 2011 to SBRT (15 Gy × 3) versus conventionally fractionated RT (2 Gy × 35) and found similar PFS, OS, and local control.[25] The TROG 0902 CHISEL randomized 101 patients (21-01 randomization) from 2009 to 2015 to SBRT (18 Gy × 3 or 12 Gy × 4) versus conventionally fractionated RT (2 Gy × 30-33 or 2.5 Gy × 20).[26] While OS, PFS, and QoL were greater with SBRT, these differences were not significant. Notable differences between the CHISEL and SPACE studies include the dose fractionation used, use of PET staging (all patients in CHISEL, 65% in SPACE), performance status (ECOG ≤1 in CHISEL vs 24% in SPACE with ECOG >1), and use of four-dimensional (4D) CT and cone-beam CT (CBCT) (required for CHISEL and only used at few sites in SPACE).

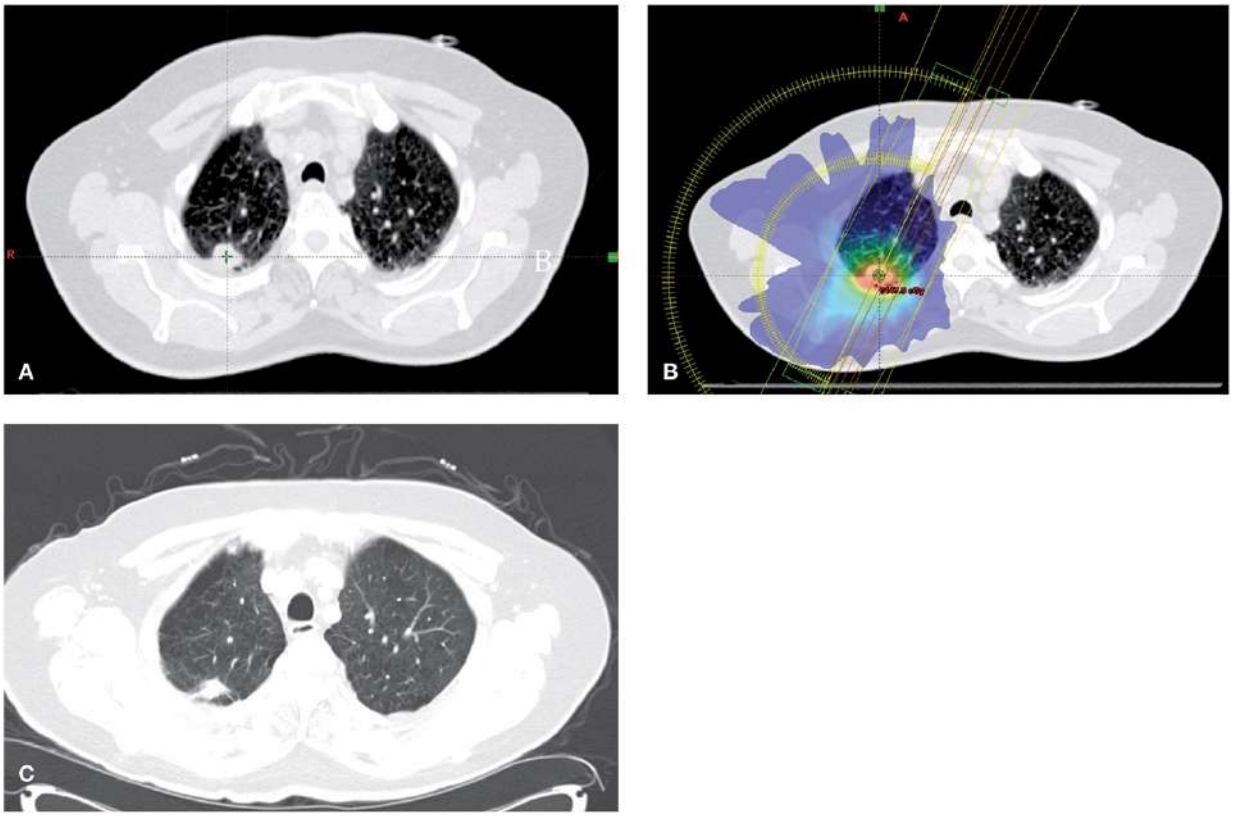

FIGURE 57.1 Stereotactic body radiation therapy (SBRT) in stage I non–small cell lung carcinoma (NSCLC). The patient was diagnosed as having T1N0M0 right upper lobe NSCLC and was treated with SBRT. A. Pretreatment tumor volume. B. Treatment plan with dose color-wash. C. Computed tomography showing response 6 weeks after treatment.

The CHISEL and SPACE studies were preceded by promising phase I and II data (discussed later) in patients with early-stage NSCLC who are medically inoperable or who opted against resection (Table 57.3). The phase I (n = 37 patients) and phase II (n = 70 patients) studies, from Indiana University, of three-fraction SBRT for early-stage NSCLC, established the excellent local control (~88% at 3-year) and survival outcomes after SBRT. Notably, their analyses also established the increased risks of high grade and fatal toxicity using

such an SBRT approach for targets within the 2 cm zone of the proximal bronchial tree.[27] The phase II RTOG 0236, which followed from these studies, demonstrated more than 90% 5-year tumor control and median survival of ~4 years after SBRT of 60 Gy in three fractions among 55 evaluable patients with peripheral early-stage NSCLC.[28,29] The RTOG 0915 phase III noninferiority study compared 34 Gy × 1 versus 12 Gy × 4 for peripheral early-stage NSCLC and showed no significant difference in rates of tumor control, OS, or adverse events.[30]

TABLE 57.3 PROSPECTIVE TRIAL OUTCOMES FOR PATIENTS WITH EARLY-STAGE NON–SMALL CELL LUNG CANCER RECEIVING STEREOTACTIC BODY RADIATION THERAPY

Authors (Years Enrolled)	Patients	Dose (Gy)	T Stage	3-y Local Control (%)	3-y Lobar Control (%)	3-y Overall Survival (%)
SBRT trials in inoperable patients						
Baumann et al (2003-2005)[265]	57	15 Gy × 3 to 67%	T1-T2	92	—	60
Fakiris et al (2002-2004)[266]	70	T1: 20 Gy × 3 to 80% T2: 22 Gy × 3 to 80%	T1-T2	88	—	43
RTOG 0236 (2004-2006)[29]	55	18 Gy × 3 to PTV edge	T1-T2	98	91	56
JCOG 0403 (2004-2008)[31]	100	12 Gy × 4 to isocenter	T1	87	—	60
RTOG 0813 (2009-2013)[41]	38 33	11.5 Gy ×5 to 60%-90% 12.0 Gy ×5 to 60%-90%	T1-2 central	—	87 85	52 54
RTOG 0914 (2009-2011)[30]	39 45	34 Gy ×1 to 60%-90% 12 Gy ×4 to 60%-90%	T1-2 peripheral	89 (5 y) 93 (5 y)	— —	55[a] 65[a]
SBRT trials in operable patients						
JCOG 0403 (2004-2008)[31]	64	12 Gy × 4 to isocenter	T1N0M0	85	—	77
RTOG 0618 (2007-2010)[32]	33	18 Gy × 3 to PTV edge	T1-2 ≤ 5 cm	96	96	75[a]
STARS-ROSEL (2008-2013)[37]	58	Peripheral: 18 Gy × 3 Central: 12.5 Gy × 4	T1-T2a ≤ 4 cm	—	96	95
Revised STARS (2015-2017)[38]	80	Peripheral: 18 Gy × 3 Central: 12.5 Gy × 4, SIB 60 Gy	T1	99	94	91

PTV, planning target volume; SBRT, stereotactic body radiation therapy; SIB, simultaneous integrated boost; —, not reported.

[a]Estimated from overall survival figures.

While SBRT is the standard of care for early-stage NSCLC in patients not fit for surgery, its use in operable patients is much more controversial. The JCOG 0403[31] phase II nonrandomized trial showed 3-year OS of 60% and 77% in the inoperable (n = 64) and operable cohorts (n = 100), respectively. Thirty-one percent of deaths were attributed to lung cancer among inoperable patients, whereas 50% were attributed in the operable cohort. The RTOG 0618 phase II study of operable patients reported favorable local control (n = 1 in-field recurrence), 4-year DFS (57%), and 4-year OS (56%) after SBRT in 26 evaluable patients with medically operable early-stage (≤5 cm) NSCLC. Four patients (15%) developed SBRT-related grade 3 adverse events, and there were no grade 4 and 5 adverse events.[32] In response to these promising results, multiple prospective randomized trials comparing SBRT with surgery in resectable early-stage NSCLC were launched,[33-36] but failed to accrue enough patients and were subsequently closed. A pooled analysis from two of these trials (STARS and ROSEL) compared outcomes among 31 patients with stage I NSCLC 4 cm or less who underwent SABR versus 27 who underwent resection.[37] The median follow-up was 40.2 months for the SABR

group and 35.4 months for the surgery group. Estimated OS at 3 years was 95% (95% CI 85-100) in the SABR group compared with 79% (64-97) in the surgery group (HR 0.14, 95% CI 0.017-1.190, log-rank P = .037). Recurrence-free survival at 3 years was 86% (95% CI 74-100) in the SABR group and 80% (65-97) in the surgery group (HR 0.69, 95% CI 0.21-2.29, log-rank P = .54). A separate Revised STARS cohort[38] with 80 operable patients (no overlap with prior STARS) with tumors 3 cm or less and median 5.1 years of follow-up showed 5-year OS of 87% and 5-year PFS of 77%. Chang et al[38] posit several reasons for the improved survival of the patients in the Revised STARS cohort compared to RTOG 0618 in that they were younger, had smaller tumors, had better pulmonary function, were treated with modern SBRT technique, and overwhelmingly received EBUS, which was performed in 90% of the patients.

While based on a small pooled randomized and nonrandomized experiences, these data suggest that SBRT may be a viable noninvasive option for selected patients with early-stage operable NSCLC, particularly in those who may be at increased risk from surgical resection (Table 57.3). Data from the currently enrolling VALOR (NCT02984761) and STABLE-MATES (NCT02468024) trials will prove better comparative data.

It is challenging to treat early-stage NSCLC that is central (within 2 cm of the proximal bronchial tree) or ultracentral (with various definitions[39] but generally with gross tumor volume [GTV] or planning target volume [PTV] overlapping the proximal bronchial tree other mediastinal structures[40]) in location. The phase I and II RTOG 0813 enrolled 120 patients (100 evaluable for efficacy and 89 evaluable for toxicity) who received five-fraction SBRT for central early-stage NSCLC (with only 17% having ultracentral tumors defined as PTV overlap with mediastinal and/or pericardial pleura).[41] The maximum tolerated dose was 12 Gy × 5, with 7.2% experiencing dose-limiting toxicity. The HILUS study[42] enrolled 65 patients treated with an eight-fraction 56 Gy SBRT course with early-stage lung NSCLC located 1 cm from the proximal bronchial tree. Due to excessive risks of toxicity, the author concludes that the 7 Gy × 8 regimen should not be used for tumors within 1 cm of the main bronchi and trachea, and for other patients, the maximum dose (to 0.2 cc) to the main bronchi and trachea should be less than 70 to 80 Gy equivalent dose in 2-Gy fractions. From a follow-up pooled analysis of Expanded HILUS[43] (HILUS study participants plus patients added retrospectively), 3-year local control and OS rates were 84% and 40%, respectively. Thirty (13%) of 230 patients developed fatal five toxicity, of which bronchopulmonary bleeding occurred in 20. Significant factors associated with fatal hemoptysis and fatal toxicity included tumor compression of the tracheobronchial tree and maximum dose to the mainstem bronchi or bronchus intermedius, while the largest diameter of the gross target volume was not significant. In a separate analysis of 127 patients (mostly treated with eight-fraction SBRT), tumor location 1 cm or less from the trachea or main bronchi was a significant predictor of severe toxicity.[44] The SUNSET study reported less than 7% risks of grade 3 to 5 toxicity after 7.5 Gy × 8 for well-selected (no endobronchial obstruction) ultracentral (nonnodal) lung tumors for which the protocol required less than 120% maximum dose.[45]

The HyTEC report pooled data from 46 studies of SBRT for early-stage NSCLC, which allowed for modeling tumor control probabilities with respect to prescribed dose at the PTV periphery. For T1 to T2N0 NSCLC, the authors recommended 43 ± 1 Gy in three fractions, 47 ± 1 Gy in four fractions, and 50 ± 1 Gy in five fractions to "achieve the maximal local control rate."[46] With respect to SBRT treatment planning, dose heterogeneity with steep dose gradients minimizes the volume of normal tissue exposed to high doses and allows for high maximal doses (ie, 125%-150% of prescribed dose) within the target, which has been shown to correlate with better tumor control.[47] In treatment planning, particularly with central lesions, it is often advisable to underdose the target to meet normal tissue constraints[39,48]

Due to the success of immune checkpoint inhibitors (ICIs) in metastatic and locally advanced NSCLC, several trials are looking at incorporating immunotherapy into earlier stages. The MD Anderson I-SABR[49] phase 2 trial randomized 141 patients with stage I and IIA or recurrent NSCLC to SABR with or without concurrent and adjuvant nivolumab. At 33-month follow-up, immunotherapy improved 4-year event-free survival (EFS) from 53% to 77% (per protocol HR 0.38, P = .0056) at the cost of 15% immunologic grade 3 adverse events (no grade 3 pneumonitis). Many other trials are ongoing (KEYNOTE 867, SWOG/NRG S1914, NRG PACIFIC 4/RTOG 3515, ASTEROID).

MANAGEMENT OF LOCALLY ADVANCED NON–SMALL CELL LUNG CANCER

Operable Stage III Non–Small Cell Lung Cancer

Considerable controversy exists regarding the role of surgery in stage III NSCLC. In the 1960s and 1970s, patients with documented N2 disease were generally regarded as incurable and referred for nonoperative approaches. Martini et al[50] reported the outcome of 1,598 patients who underwent surgical resection, 706 of whom had mediastinal nodal involvement. Of these, 151 patients underwent complete surgical resection with mediastinal node dissection. Survival in patients with clinical stage I or II (pathologic N2) was favorable at 50% at 3 years. Survival in patients with obvious clinical N2 disease was extremely poor at 8% at 3 years. Martini et al[50] stated: "Very few patients with gross mediastinal nodal involvement benefit from resection. We believe that this group of patients should not be considered for thoracotomy unless innovative forms of treatment can be offered." Beyond gross mediastinal nodal involvement, multistation N2 disease and subcarinal nodal involvement are also shown in multiple series to be portend to poor outcomes.[51,52]

Based on these and similar results with surgical resection alone in stage III disease, neoadjuvant approaches were explored to facilitate surgical resection. However, significant controversy still exists regarding the role of surgical resection in stage III disease. A European Organisation for Research and Treatment of Cancer (EORTC) phase III trial randomized patients with biopsy-proven N2 disease who responded to induction chemotherapy to either resection or RT. Both arms showed similar median and 5-year OS for patients randomly assigned to resection versus RT at 16.4 versus 17.5 months and 15.7% versus 14%.[53]

Neoadjuvant (Induction) Therapy

Preoperative Systemic Therapy

With the advent of immunotherapy, the role of perioperative systemic therapy has been rekindled. The use of immunotherapy upfront has the theoretical advantage of a high neoantigen burden and an intact anatomy with improved draining lymph nodes that could result in better and more efficient antigen presentation and, therefore, priming of a more tumor-specific T cell.[54] Historically, studies of neoadjuvant cytotoxic chemotherapy were underpowered as these closed early as the adjuvant studies that accrued more rapidly demonstrated a survival advantage. A meta-analysis of 15 trials demonstrated an OS benefit of 5% at 5 years for neoadjuvant chemotherapy over surgery alone, which is similar to the benefit of the more traditional adjuvant treatment.[55] Neoadjuvant treatment has the potential advantage of facilitating a surgical procedure to abate the need for a more extensive resection, a higher probability of completion of planned systemic therapy, and providing prognostic information as the degree of pathologic response is associated with an improved outcome.

Several placebo-controlled phase 3 trials—CheckMate 816,[56] KEYNOTE 671,[57] and AEGEAN[58]—comparing induction chemotherapy with and without immunotherapy have been reported (Table 57.4). These studies have several differences, and as of this writing, there is neither a clearly defined optimal strategy nor is there a preferred ICI or a preferred chemotherapy backbone. Logistical challenges remain an important factor to consider; most of these trials excluded patients with the most common oncogene-driven lung cancer (epidermal growth factor receptor [EGFR] mutations and anaplastic lymphoma kinase [ALK] alterations) because these patients are less likely to benefit from immunotherapy. This point entails the need to have a presurgical histologic diagnosis with enough tissue to establish the presence of these abnormalities. The genetic testing turnaround time and often scant tissue available are frequent barriers to a timely initiation of neoadjuvant treatment. When faced with the decision to offer neoadjuvant treatment, the clinician and their patients also need to consider the chemoresistant nature of this disease. Neoadjuvant chemoimmunotherapy can lead to a response that prevents the need for a pneumonectomy, but this is not the goal of treatment, and therefore, patients should only be offered this strategy if the patient is likely to have a complete surgical resection even if there is no significant response.

TABLE 57.4 PHASE III TRIALS OF PERIOPERATIVE CHEMOIMMUNOCHEMOTHERAPY

Study	Population	Intervention	Control	Adjuvant Treatment	Primary End Point	Surgery	pCR	EFS	OS
CheckMate 816[56]	Stage IB-IIIA resectable NSCLC	Three cycles of nivolumab + chemotherapy	Chemotherapy alone	None dictated	EFS and pCR	83.2% vs 75.4%	24% vs 2.2%	31.6 vs 20.8 (HR 0.63; 97.38% CI 0.43-0.91)	NR vs NR (HR 0.57; 99.67% CI 0.30-1.07)
KEYNOTE 671[57]	Stage II, IIIA, or resectable IIIB	Four cycles of pembrolizumab + chemotherapy	Placebo + chemotherapy	Pembrolizumab for 1 year	EFS and OS	82.1% vs 79.4%	18.1% vs 4%	NR vs 17 (HR 0.58; 95% CI 0.46-0.72)	NR vs 45.5 (HR 0.72; 95% CI 0.56-0.93)
AEGEAN[58]	Stage II, IIIA, or resectable IIIB	Four cycles of durvalumab + chemotherapy	Placebo + chemotherapy	Durvalumab for 1 year	EFS and pCR	77.6% vs 76.6%	17.2% vs 4.3%	NR vs 25.9 (HR 0.68; 95% CI 0.53-0.88)	Not reported
CheckMate 77T		Four cycles of nivolumab + chemotherapy	Placebo + chemotherapy	Nivolumab for 1 year	EFS	78% vs 77%	25.3% vs 4.7%	NR vs 18.4 (HR 0.58; 95% CI 0.42-0.81)	Not reported

CI, confidence interval; EFS, event-free survival; HR, hazard ratio; NSCLC, non–small cell lung cancer; NR, not reached; OS, overall survival; pCR, pathologic complete response.

Preoperative Chemoradiotherapy

The rationale for preoperative chemoradiotherapy is that surgical resection after chemoradiotherapy will optimize local control, thereby improving clinical outcomes in locally advanced disease. A phase II trial by the Southwest Oncology Group (SWOG) of induction chemoradiotherapy followed by surgical resection in 126 patients with stage IIIA/IIIB disease showed a promising 3-year survival of 26%.[59] Motivated by these results, an intergroup randomized phase III trial was initiated to determine the value of adding surgery to chemoradiotherapy in stage III disease with a primary end point of OS. Patients with stage T1 to 3 with pathologic proof of N2 NSCLC involvement (eg, biopsy) who were deemed to be potentially technically resectable were randomly assigned to concurrent induction chemoradiation to 45 Gy followed by surgery or the same induction chemoradiation with completion to 61 Gy.[60] The median OS was 23.6 months in the trimodality arm and 22.2 months in the bimodality group ($P = .24$). For those with pN0 status at thoracotomy, the median OS was 34.4 months. The median PFS was better in the trimodality arm (12.8 vs 10.5 months, $P = .017$). An unplanned, exploratory analysis suggested that patients who underwent lobectomy in the trimodality arm had improved survival compared to matched patients receiving chemoradiotherapy. One of the most important findings from this trial was the significant toxicity of right-sided pneumonectomy after induction chemoradiotherapy. Among the 29 patients who underwent a right pneumonectomy, there were 11 postoperative deaths (38%).[61] Overall, this trial did not demonstrate a survival benefit for the addition of surgery to chemoradiotherapy in patients with stage IIIA NSCLC.

Two phase III trials examined whether adding neoadjuvant radiation to induction chemotherapy would benefit PFS. The phase III German Lung Cancer Cooperative Group trial compared neoadjuvant chemotherapy, surgery, and postoperative radiation, versus neoadjuvant chemotherapy, twice-daily (BID) chemoradiation followed by surgery and a further radiation if positive margins.[62] Mediastinal downstaging

(46% vs 29%) and pathologic response (60% vs 20%) favored the neoadjuvant chemoradiation arm, but median PFS was no different at around 10 months. The SAKK 16/00 trial had a simpler design comparing induction platinum doublet chemotherapy to sequential platinum doublet followed by 44 Gy in 22 fractions. Similarly to the German trial, the median EFS was around 12 months in both arms.[63]

In conclusion, the role of neoadjuvant chemoradiotherapy in stage III NSCLC remains unclear, especially now in the era of preoperative chemoimmunotherapy, with induction chemotherapy preferred to neoadjuvant chemoradiation about 2:1 by institutions.[64]

Adjuvant Therapy

Postoperative Systemic Therapy

The strongest evidence for the use of adjuvant chemotherapy in patients with NSCLC comes from two meta-analyses. The 2008 Lung Adjuvant Cisplatin Evaluation meta-analysis, which pooled data from five large trials involving 4,584 patients, focused on the effectiveness of postoperative cisplatin-based chemotherapy in NSCLC.[65] The results showed an overall HR of death of 0.89 (95% CI 0.82-0.96) with chemotherapy, corresponding to 5-year absolute survival benefit of 5.4%. The benefit was seen in patients with stage II (HR 0.83, 95% CI 0.73-0.95) and IIIA disease (HR 0.83, 95% CI 0.72-0.94). For patients with stage IA, no study has found a positive effect of adjuvant treatment. For those patients with stage IB, the benefit was marginal and not statistically significant (HR 0.93, 95% CI 0.78-1.10). To determine whether adjuvant chemotherapy improves survival for stage IB, the CALGB 9633 randomized patients with pT2N0 NSCLC to observation or adjuvant chemotherapy. OS was similar in both arms with HR 0.83 (95% CI 0.64-1.08).[66] Subset analysis for tumors larger than 4 cm in diameter showed a benefit with HR 0.69 (95% CI 0.48-0.9). Adjuvant chemotherapy in these patients remains an area of controversy and should only be offered in select cases after a careful discussion of risks and benefits. The 2015 Cochrane meta-analysis by the Non-Small Cell Lung Cancer Collaborative Group analyzed individual patient data from 26 randomized clinical trials, involving 8,447 patients. The analysis demonstrated clear evidence of a benefit of adding chemotherapy after surgery (HR 0.86, 95% CI 0.81-0.92), with an absolute survival increase of 4% at 5 years.[67]

More recently, postoperative immunotherapy has been studied with both pembrolizumab and atezolizumab after chemotherapy found to be beneficial. The IMpower010 study was an open-label study of 1,005 patients with stage IB (tumors ≥4 cm) to IIIA NSCLC after mandatory platinum-based adjuvant chemotherapy who were randomized to atezolizumab versus best supportive care (BSC). The analysis followed a prespecified step that demonstrated that initial improvement in DFS compared to BSC alone. In patients with stage II to IIIA whose tumors had a programmed death-ligand 1 (PD-L1) staining of 1% or greater, the DFS was not reached in the investigational arm and was 35.3 months in those treated with BSC, HR for DFS was 0.66 (95% CI 0.50-0.88). Subset analyses showed that the greatest magnitude of DFS improvement was seen in patients with PD-L1 50% or greater, in whom an HR for DFS was 0.43 (95% CI 0.27%-0.68%) over BSC.[68] A final OS analysis is still pending at the time of this writing. Prespecified exploratory analyses published currently show showed an OS improvement in favor of atezolizumab in the stage II to IIIA PD-L1 50% population or greater (stratified HR 0.43, 95% CI 0.24-0.78).[69]

The KEYNOTE-091 (PEARLS) trial was a triple-blind adjuvant study of 1,177 patients with completely respected stage IB (tumors ≥4 cm) to IIIA NSCLC who were randomized to adjuvant pembrolizumab versus placebo. An interim analysis showed an improvement in median DFS from 42 to 53.6 months (HR 0.76, 95% CI 0.63-0.91, $P = .0014$). In contrast to the IMpower010 study, no benefit in DFS was seen in the PD-L1 tumor proportion score more than 50% population (HR 0.82, 95% CI 0.57-1.18).[70]

The percentage of patients with grade 3 adverse events or greater was 22% in IMpower010 and 34% in PEARLS. The rate of discontinuation of immunotherapy for adverse events was 18.2 and 22% in IMpower010 and PEARLS, respectively.

Patients with driver oncogenes were included in both adjuvant immunotherapy studies. Currently, however, we know that the value of immunotherapy in this patient population is small, and in contrast, patients may benefit from the use of adjuvant tyrosine kinase inhibitors (TKIs). The ADAURA study was a placebo-controlled trial for patients with resected NSCLC that harbored a deletion 19 or an L858R EGFR mutation.[71] In all, 682 patients with resected stage IB to IIIA disease were randomly assigned to receive 3 years of

adjuvant osimertinib or placebo after optional chemotherapy. The primary end point of the study was DFS, which was markedly improved in the experimental arm with overall HR of 0.18 (95% CI 0.10-0.33). The 5-year OS was 88% for those randomized to osimertinib versus 78% for those on placebo (HR 0.49; 95.03% CI 0.34-0.70). The OS benefit was consistent among subgroups, though a larger benefit was seen for those patients who had stage IIIA disease (HR 0.37, 95% Cl 0.20-0.64). This study has been heavily criticized because crossover to osimertinib—a therapy known to be markedly superior to its alternatives—was not mandated at the time of disease relapse, and therefore, only 38.5% of patients on the control arm whose disease had relapsed ever received osimertinib.[72] Despite this limitation, adjuvant osimertinib is the current standard of care for patients who present with these EGFR abnormalities. In patients with alteration in ALK, the ALINA study randomized 257 patients with resected stage IB to IIIA to either 2 years of alectinib or up to four cycles of adjuvant chemotherapy. A preliminary analysis showed a significant DFS benefit was seen in patients randomized to alectinib in both stage II to IIIA (HR 0.24, 95% CI 0.13-0.45) and intention-to-treat (ITT) populations (HR 0.24, 95% CI 0.13-0.43).[73]

It is unknown if these results can be extrapolated to other patients with rarer oncogene-driven mutations and it is unlikely that phase 3 results will ever be conducted in these subgroups given its rarity.

Postoperative Radiotherapy

The predominant pattern of intrathoracic failure after surgical resection is along the surgical stump or in the mediastinal nodes. Concern over locoregional failure led to investigations of postoperative radiotherapy (PORT) in completely resected stages II and IIIA NSCLC to reduce local recurrence.[74] The role of PORT has historically been controversial. In the Medical Research Council PORT meta-analysis, PORT was associated with a decrease in survival for patients with pN1 disease (attributed to excessive morbidity) and no difference in pN2.[75] Subsequent studies found support for PORT in pN2 disease. A SEER analysis of stage II/III resected NSCLC showed that PORT was associated with an improved 5-year OS for pN2 patients (27% vs 20%) but reduced OS for pN0 and pN1 patients.[76] A subset analysis of the Adjuvant Navelbine International Trialist Association trial[77] showed that in patients with pN2 disease, PORT was associated with improved median survival in both the chemotherapy (23.8 vs 47.4 months) and observation arm (median survival 12.7 vs 22.7 months). In contrast, PORT for pN1 was associated with improved survival only if no chemotherapy was given and worse survival if chemotherapy was given.

The hypothesis of PORT-benefiting pN2 disease was investigated in the European Lung Adjuvant Radiotherapy trial (LungART) and the Chinese PORT-C phase III trials. In LungART,[78] 501 patients (90% of those who currently smoke or formerly smoked) with pN2 disease after complete resection and nodal exploration were randomized to observation or PORT 54 Gy; 89% of PORT patients were treated with 3D conformal technique and 96% of patients received chemotherapy. In both arms, 3-year DFS and OS were similar at around 45% and 68%, respectively. While PORT was associated with a 50% decrease in mediastinal relapse, it was also associated with increased death, particularly cardiopulmonary deaths (8% vs 0%). In PORT-C,[79] 394 patients (45% of those who currently smoke or formerly smoked) with pN2 disease after complete resection and four cycles of platinum doublet chemotherapy were randomized to observation or PORT 50 Gy; 89% of PORT patients were treated with intensity-modulated radiotherapy (IMRT). Three-year OS was around 80% in both arms and 3-year DFS was also not statistically different at 40.5% with PORT and 32.7% with observation, though after preplanned analysis (stratified by the number of detected and positive lymph nodes), a statistically significant difference was found.

With two phase III trials in disparate populations both negative for the addition of PORT for pN2 disease, adjuvant radiation is not routinely recommended in patients with positive nodes following a *complete resection* and who are candidates for systemic therapy. Recent analyses suggest an association between increased heart dose and survival after PORT.[80] Further investigations into cardiopulmonary cause of death and the role for advanced radiation techniques are expected.

Postoperative Chemoradiotherapy

The ECOG 3590 randomized 488 patients with stage II and IIIA NSCLC and negative margins after surgery to RT either with or without four cycles of chemotherapy. RT in both arms consisted of 50.4 Gy in 28

fractions. There was no difference in local recurrence or survival between the two arms.[81] In current practice, concurrent chemoradiation is typically recommended in the adjuvant setting if gross disease was left behind at surgery, and variably recommended if microscopic disease was left behind at surgery.

Inoperable Stage III Non–Small Cell Lung Cancer

The current standard of care for inoperable stage III NSCLC is concurrent chemoradiation and adjuvant immunotherapy. Current trials are looking at incorporating immunotherapy earlier in treatment. The evolution of arriving at the current standard of care has been a fairy linear processing, starting from radiation alone in the 1980s, to the incorporation of sequential chemotherapy in the 1990s, to concurrent chemoradiation in the 2000s, and to sequential immunotherapy in the 2010s, and finally to the open question of concurrent immunotherapy in the 2020s.

Radiotherapy Alone

Most patients with inoperable locally advanced NSCLC will receive definitive thoracic RT as a part of their treatment strategy. Kubota et al[82] performed a randomized phase II trial in stage III NSCLC comparing chemotherapy with or without RT that showed an increase in 3-year survival from 3% to 29% with radiation. At present, definitive thoracic RT is part of the standard therapeutic approach for patients with unresectable locally advanced NSCLC. However, because of high local failure rates and the significant toxicity associated with this treatment, investigations have been performed to determine the optimal dose, treatment volume, and integration with chemotherapy.

Dose and Fractionation With Radiotherapy Alone

The RTOG 7301 phase III trial compared 40 (including with a split course), 50, and 60 Gy, delivered with conventional fractionation. The 60-Gy arm had the lowest local failure at 35% and was established as the standard of care.[83,84]

Motivated by these results, the RTOG moved to explore methods of escalating radiation dose while maintaining the therapeutic ratio through altered fractionation schedules. RTOG 8311 was a randomized phase I/II trial that compared doses from 60.0 to 79.2 Gy using 1.2 Gy fractions delivered BID. No significant differences in the toxicity were found, although in a subset analysis of good performance status patients, there was a dose response identified for survival that plateaued at 69.6 Gy, which became the standard altered fractionation regimen for subsequent RTOG trials.[85]

The progression of 2D to 3D conformal radiotherapy (CRT) in the early 1990s allowed increased conformal dose around the tumor. Bradley et al[86] demonstrated by multivariate analysis that GTV was strongly predictive of OS and cause-specific survival, suggesting that large-volume disease might require escalated doses of RT, if feasible. Rengan et al[87] found that even in patients with large stage III tumor volumes, local failures were reduced when treated to 64 Gy or more.

Starting in the early 2000s, multiple trials attempted to find maximum tolerated doses for hypofractionated radiation (ie, >2.0 Gy per fraction). A University of Wisconsin phase I dose escalation trial for 25 fractions evaluated doses from 57 to 85.5 Gy using IMRT.[88] Based upon their protocol-defined criteria, 63.25 Gy in 25 fractions was the maximally tolerated dose. Higher doses had concerning rates of grade 4 to 5 toxicities related to central and perihilar structures, such as the proximal bronchial tree.

A UT-Southwestern (UTSW) phase I dose escalation trial for 15 fractions evaluated doses from 50 to 60 Gy, with all arms being well tolerated and no association between fraction size and toxicity.[89] In a subsequent UTSW trial, patients were randomized to 60 Gy in 15 or 30 fractions to determine if the hypofractionated course would yield superior 1-year OS. No statistically significant difference was found in survival or toxicity outcomes.[90]

Taken together, these data suggest that dose escalation can be achieved safely in locally advanced NSCLC via novel hypofractionation and treatment delivery approaches. However, caution should be employed when considering hypofractionated regimens beyond 60 Gy per 15 fractions, particularly in ultracentral locations.

Volume of Radiation With Definitive Radiotherapy: Involved-Field Versus Elective Nodal Irradiation in Inoperable Stage III Non–Small Cell Lung Cancer

In the era of 2D RT for NSCLC, it was customary to include the elective nodal basin in the radiation portals for any patient receiving curative-intent RT, regardless of stage. There is ample evidence that the elective nodal basins can be safely omitted in stage I NSCLC in patients who have undergone modern clinical staging.[28,86] Although ^{18}FDG-PET/CT has become an indispensable tool for noninvasive staging of the mediastinum, studies have shown that FDG-PET may carry up to a 25% false-negative rate in lymph nodes less than 1 cm in the short axis.[11,91]

Motivated by this concern, several studies have examined the rate of elective nodal failure in patients treated with involved-field radiotherapy (IFRT) and have shown this to be a relatively rare event of less than 5% to 10%.[92,93] In the only prospective study of elective nodal irradiation (ENI) versus IFRT, Yuan et al[94] compared IFRT 68 to 74 Gy versus ENI 60 to 64 Gy, showing an increase in 2- and 5-year local control with IFRT of 8% and 15%, respectively (only statistically significant at the 5-year time point). In addition, Yuan et al demonstrated an improved OS rate at 2 years with IFRT (39.4% vs 25.6%, P = .048) and higher pneumonitis rates in patients treated with ENI (29% vs 17%, P = .044). Although interesting, this study has been criticized for the imbalances in the radiation dose delivered and lung V_{20} between the two arms. In a single-institution retrospective cohort comparison of patients receiving definitive 3DCRT for locally advanced NSCLC, Fernandes et al[95] analyzed 108 consecutive patients treated with either ENI (median dose 63.6 Gy) or IFRT (69.9 Gy). In a multivariable logistic regression analysis, the IFRT cohort had a lower risk of high-grade esophagitis (odds ratio [OR] 0.31, P = .036).

The incorporation of routine PET/CT for staging led to a phase 2 noninferiority trial PET-Plan/ARO-2009-09, which sought to determine whether planning using PET/CT could allow reduced target volumes. The trial randomized patients to chemoradiation planned using PET alone (PET-directed) compared to conventional planning (using PET, CT-size criteria, and ENI). The PET-directed arm mean dose was 67.3 Gy compared to 65.3 Gy for the conventional arm. One-year locoregional progression was noninferior in the PET-directed arm in both the per-protocol and ITT analysis, ranging from 14% to 17% compared to 29% to 30% in the conventional target arm. Invasive mediastinal sampling was per the treating physician.[96]

These studies support that IFRT can be employed in patients with locally advanced NSCLC without risk of significant compromise in clinical outcome and with possibly decreased side effects.

Combined Modality

Induction Chemotherapy

In locally advanced NSCLC, the dominant pattern of failure in these patients was through distant dissemination in about 75% to 80% of patients.[84] To address the issue of whether adding induction chemotherapy to radiation would improve survival in locally advanced disease, multiple phase III trials looked at adding induction chemotherapy before radiation regimens. CALGB 8433 randomized 155 patients with unresectable stage III NSCLC with excellent performance status and showed that chemotherapy increased median survival from 9.6 to 13.7 months (P = .0066).[97] Subsequently, RTOG 8808 randomized 490 patients and showed an improved median survival of 13.8 months with induction chemotherapy compared to 11.4 months with standard RT and 12.3 months with hyperfractionated RT (P = .03).[98] A similar Gustave-Roussy trial with more intense induction chemotherapy did show decreased distant metastases though the improvement in OS did not reach statistical significance (2-year OS 21% vs 14%).[99] Overall, these trials established the role of chemotherapy, in addition to radiation, in the management of unresectable stage III NSCLC (Table 57.5).

TABLE 57.5 SEQUENTIAL CHEMOTHERAPY VERSUS RADIATION THERAPY ALONE FOR LOCALLY ADVANCED NON–SMALL CELL LUNG CANCER

Author	RT (Gy)	CT	Sequence	Number of Patients	Median Survival (mo)	Overall Survival (%)			
						1 Year	2 Year	3 Year	5 Year
Le Chevalier et al[267]	65	—	—	177	10	41	14	4	—
	65	VCPC	CT → RT → CT	176	12	51	21	12	—
RTOG 8808[98]	60	—	—	149	11.4	46	19	6	5
	60	PV	CT → RT	151	13.2	60	32	15	8
	69.6 BID	—	—	152	12.0	51	24	13	6
CALGB 8433[97]	60	—	—	77	9.7	40	13	11	7
	60	PV	CT → RT	79	13.8	55	26	23	19

CT, chemotherapy; PV, cisplatin, vinblastine; RT, radiation therapy; VCPC, vindesine, cyclophosphamide, cisplatin, lomustine.

Concurrent Chemoradiotherapy

To determine the efficacy of chemotherapy radiosensitization, the EORTC performed a phase III randomized trial comparing concurrent cisplatin-based chemoradiation to RT alone. They demonstrated a clear survival benefit to chemotherapy radiosensitization that was attributed to improvement in local control, given no difference in distant metastases.[100] A Cochrane meta-analysis of 19 randomized studies and 2,728 patients compared concurrent chemoradiation with definitive radiation.[101] Concurrent chemotherapy improved the overall risk of death (HR 0.71) and overall PFS (HR 0.69) at the expense of increased acute toxicity, especially severe esophagitis with concurrent treatment (relative risk [RR] 4.96).

Concurrent Versus Sequential Chemoradiotherapy

Initial phase II trials suggested that concurrent chemoradiotherapy—with response rates of 75% to 85%—might be more effective than sequential chemoradiotherapy,[102,103] which was subsequently confirmed in phase III trials. Furuse et al[104] performed a phase III trial comparing concurrent chemoradiotherapy with mitomycin, vindesine, and cisplatin given at systemic doses to sequential chemotherapy and RT, showing improved survival with the concurrent approach (median survival of 16.5 vs 13.3 months and 5-year survival of 15.8% vs 8.9%). RTOG 9410 compared two different concurrent regimens (cisplatin and vinblastine with conventional RT, arm 1, or cisplatin and oral etoposide with hyperfractionated RT, arm 2) to a "standard" sequential regimen of cisplatin and vinblastine followed by conventional RT (arm 3). Comparing arm 1 to arm 3 (as per the study design), median survival times improved significantly (17 vs 14.6 months), as did 5-year survival (15% vs 10%) with an increase in acute grade 3 through grade 5 nonhematologic toxicities.[105] The survival in arm 2 was not significantly better than arm 1, although this intensive regimen was associated with much higher esophageal toxicity. A meta-analysis of six trials by Auperin et al[106] showed a significant benefit to concurrent over sequential chemotherapy and RT with an absolute increase in 3-year OS of 5.7% (from 18.1% to 23.8%) and in 3-year PFS of 2.9% (from 13.1% to 16.0%). Concurrent chemoradiotherapy decreased locoregional progression (34.1% to 28.1% at 3 years), although not distant progression. Again, this improvement in locoregional control came at the expense of greater acute toxicity for patients receiving concurrent chemoradiotherapy, with an increase in acute esophageal toxicity (grades 3 and 4) from 4% to 18% with an RR of 4.9 ($P < .001$).

Because of the increased toxicity with concurrent chemoradiation, especially acute esophagitis, there can be treatment delays that have been found to be detrimental in terms of radiobiologic efficacy.[107] Meta-analysis of RTOG trials with concurrent chemoradiation demonstrated that on multivariable analysis, there was a 2% decrease in OS for each additional day beyond 5 days from the planned end of treatment.[108] Appropriate patient selection and maneuvers to minimize toxicity are increasingly important to minimize the likelihood of treatment delays that can compromise the efficacy of concurrent therapy.

In summary, these studies established concurrent over sequential chemoradiotherapy as the standard approach for patients with good performance status and minimal weight loss, at the expense of greater toxicity to the patient, especially esophagitis.

Cytotoxic Platforms for Concurrent Chemoradiotherapy in Locally Advanced Non–Small Cell Lung Cancer

Several chemotherapy regimens that pair cisplatin or carboplatin with etoposide, vinorelbine, mitomycin, vindesine, irinotecan, paclitaxel, docetaxel, and pemetrexed have each been studied; unfortunately, few head-to-head trials comparing these agents have been conducted. There is no single regimen that could be considered standard. In North America, the most common prescribed regimens are either cisplatin and etoposide (EP) at systemic doses or carboplatin and paclitaxel administered weekly during RT. Unlike limited SCLC, where cisplatin is dosed at 60 mg/m^2 every 3 weeks and etoposide at 80 to 120 mg/m^2 daily × 3 both during and after radiation,[109] an alternative dose and schedule is generally used. There are abundant data from the SWOG and RTOG for a schedule that was ultimately phase III tested in RTOG 9309 and later by the Hoosier Oncology Group: specifically, cisplatin 50 mg/m^2 days 1 and 8, 29 and 36; and etoposide 50 mg/m^2 intravenously days 1 through 5 and days 19 through 33.[59,61,110] This schedule, while inconvenient, is tried and tested and generally safe. The carboplatin-paclitaxel regimen is administered weekly during radiation with a carboplatin dose of area under the curve (AUC) of 2 and paclitaxel at 40 to 50 mg/m^2. Prior to the era of immunotherapy after radiation was completed, two more cycles were administered 3 weeks apart using a higher (systemic) dosage of both agents (carboplatin AUC 6 and paclitaxel 200 mg/m^2). Given its favorable toxicity profile and superiority to gemcitabine in combination with cisplatin in advanced nonsquamous NSCLC, pemetrexed has been widely adopted in the metastatic setting, The PROCLAIM study randomized patients with stage III nonsquamous histologies to either EP or cisplatin with pemetrexed during definitive thoracic radiation.[111] After 598 patients were enrolled, the study was stopped early because of futility; no difference was observed between the two arms with respect to OS (26.8 vs 25 months, HR = 0.98, 95% CI 0.79-1.20, P = .83), median PFS (11.4 vs 9.8 months, HR, 0.86, 95% CI 0.71-1.04, P = .13), and response rates (35.9% vs 33%, P = .45). The only clear toxicity difference was a higher incidence of neutropenia for patients treated with EP (54.8% vs 44.5%, $P \leq .05$).

Given the lack of evidence for a “best” or preferred regimen, clinicians and patients need to decide which chemotherapy to choose based on other considerations, including histology (pemetrexed only useful for patients with nonsquamous histology), potential toxicities (eg, kidney injury for cisplatin, neuropathy for paclitaxel), and cost. It is important to remember that only patients who are treated with cisplatin-based regimens receive adequate systemic doses of chemotherapy. Although weekly carboplatin and paclitaxel are useful as a radiosensitizer, the doses of chemotherapy are unlikely to eradicate micrometastatic disease and are, therefore, likely inferior systemic treatment.

In patients who will receive high lung V_{20} (percentage of normal lung that will receive ≥20 Gy) more than 35% or in those with borderline pulmonary function or other comorbidities, many clinicians consider administration of chemotherapy first for two or even three cycles, followed by radiation alone or concurrent chemoradiation if there has been sufficient tumor shrinkage to allow a more reasonable RT treatment field. In those with minimal or no tumor shrinkage using this approach, some investigators omit concurrent chemotherapy during radiation to avoid untoward toxicity, proceeding with radiation alone. These patients are often much more symptomatic than those with smaller volume tumors, with postobstructive symptoms including wheezing, pneumonitis, and hypoxia, and often have compromised performance status. However, the one study to isolate the role of induction therapy prior to concurrent chemoradiation with paclitaxel and carboplatin failed to show a survival advantage compared to concurrent chemoradiation alone.[112]

Toxicity mitigation is another major challenge that has been inadequately addressed. Both acute esophagitis and long-term pneumonitis and pulmonary fibrosis are common complications of combined modality therapy. A meta-analysis demonstrated a 6-fold increase in short-term esophagitis, grade 3, or worse (18% vs 3%) in those receiving concurrent chemoradiation as opposed to asynchronous or sequential chemotherapy and radiation.[106] Randomized trials evaluating amifostine as an esophageal protectant failed to show a significant reduction in esophagitis rates.[113,114] Advances in technologies including proton therapy (PT) may help reduce

the severity and duration of acute and late esophageal and pulmonary effects. This is currently under investigation.

Immunotherapy After Radiation

The addition of immunotherapy to the treatment of lung cancer has been one of the most important developments in the treatment of this disease in the past decade. Immunotherapy using ICIs has changed the paradigm of treatment of lung cancer and many other malignancies. A detailed explanation of ICI is outside the scope of this review, and readers of this chapter are referred to many excellent reviews on this topic.

The PACIFIC trial was a phase 3, randomized, double-blind, placebo-controlled trial that demonstrated that the addition of a PD-L1 ICI after chemotherapy and radiation dramatically improved OS.[115] Seven hundred and thirteen patients who had not progressed after concurrent chemoradiotherapy were randomly assigned on a 2:1 ratio to receive either durvalumab or a placebo for 12 months. The final analysis of the trial showed that patients who received durvalumab had an improvement in PFS (median 16.8 vs 5.6 m, HR 0.52, 95% CI 0.42-0.65) and OS with a median of 47.5 versus 29.1 months with placebo (HR 0.72, 95% CI 0.59-0.89).[115] In exploratory analysis, the PFS and OS benefit was seen across all levels of expression of PD-L1, with the exception of OS in patients who had a negative expression of PD-L1 where the HR for OS was 1.15 (95% CI 0.75-1.75). In the United States, the use of durvalumab is approved by the Food and Drug Administration, independent of PD-L1 expression, whereas the European Medicine Agency approved it only in patients with a PD-L1 1% or greater. Immune-mediated adverse events of any grade were reported in 24.2% of patients treated with durvalumab. These were grade 3 or greater in 3.4% of patients with pneumonitis being the most common one.[116] For patients who are not candidates for concurrent chemoradiation, the PACIFIC-6 study was a trial that demonstrated that patients treated with sequential chemotherapy and radiation experience a comparable safety profile and an improved efficacy compared to historical controls treated without immunotherapy.[117] These trials included patients with mutation-driven NSCLC in very small numbers. The use of adjuvant immunotherapy in this subpopulation is currently a matter of controversy, as patients with advanced EGFR-mutated cancers have not shown to benefit from immunotherapy in phase 3 trials.[118] Furthermore, there is concern that starting a TKI shortly after the use of an ICI may increase the risk of TKI-associated pneumonitis. Therefore, the use of immunotherapy for patients with EGFR and ALK abnormalities is currently not recommended, though whether this applies to other driver mutations is a matter of intense debate and controversy.

Targeted Agents in Locally Advanced Disease

Identifying oncogene-driven NSCLC has led to the development of targeted therapy. This treatment has revolutionized the treatment and outcome of patients who have NSCLC that are driven by molecular abnormalities. Prior to the identification of molecular abnormalities, the use of targeted therapy with or after chemoradiation in all patients with NSCLC was not successful[119,120] and even detrimental as was in the case of the use of gefitinib, a TKI, which we now know is effective only in patients with EGFR mutations.[121] These studies underscore the need for biomarker designed clinical trials.

Unfortunately, the study of use of targeted agents in patients with molecularly driven NSCLC treated with chemoradiation has been proven extremely difficult. In patients with EGFR mutations, early-phase studies have proven the safety and preliminary efficacy of adding EGFR TKI to radiation.[122,123] RTOG 1306/Alliance 31101 aimed to compare standard chemoradiation versus induction erlotinib or crizotinib for 12 weeks followed by chemoradiation; this study was terminated because of poor accrual after 59 of 234 patients were accrued. The LAURA study (NCT03521154) is a global randomized study that evaluates if the addition of osimertinib after chemoradiation improves PFS compared to placebo in patients with stage III NSCLC with EGFR mutations.

For patients with other driver mutations, there is currently no data to guide us on whether targeted therapy should be added after chemoradiation.

Dose Escalation With Concurrent Chemoradiotherapy

Although concurrent chemoradiotherapy has emerged as the standard therapeutic approach for fit patients with unresectable locally advanced disease, suboptimal locoregional control necessitated investigations into dose escalation. Although phase II trials showed promise in dose escalation with concurrent chemotherapy,[124,125] RTOG 0617 showed a detriment to 74 Gy compared with 60 Gy, and 60 Gy remains the standard dose in stage III NSCLC treatment. RTOG 0617 was a 2 × 2 phase III trial of 544 patients to simultaneously examine the question of 60 versus 74 Gy concurrent chemoradiation with or without cetuximab in inoperable stage III NSCLC. At a median follow-up of 5.1 years, median survival was 28.7 months for patients who received standard-dose radiation and 20.3 months for those who received high dose (HR 1.35, 95% CI 1.08-1.69; $P = .0072$). Cetuximab did not improve survival and added severe toxicity (grade ≥3, 87.3% vs 71.2%, $P < .0001$). Both the radiation dose and cetuximab results crossed protocol-specified futility boundaries. There were no statistical differences in overall grade 3 toxic effects or greater between RT groups, though if esophagitis and dysphagia were combined, high-dose group experienced more of these toxicities (20.8% vs 7.3%, $P < .0001$). There were more treatment-related deaths in the high-dose radiation group (nine vs three patients). There were no differences in grade 3 pulmonary events or greater between treatment groups. Multivariable analyses in the RTOG 0617 reports[119,126] and related publications[127] have suggested that heart volume exposure (eg, V_5, V_{40}) are prognostic for survival. Multiple modeling efforts have attempted to define cardiac substructure-specific constraints, which is an area of active investigation.[128,129]

Superior Sulcus Tumors and Pancoast Syndrome

Superior sulcus tumors (SSTs) were first described in 1838 and the characteristic accompanying neurologic symptoms in 1932 by Dr Henry Pancoast. SSTs account for less than 5% of all lung cancer.[130] The most common symptom among patients with SST is pain in the shoulder attributable to direct invasion of the parietal pleura, vertebral body, ribs, or brachial plexus (Figure 57.2). Pain radiating down the ulnar aspect past the elbow indicates T1 nerve root involvement, whereas pain in the fourth and fifth digits indicates involvement of the C8 nerve root. There may be weakness or atrophy of the intrinsic muscles of the hand. Involvement of the stellate ganglion may manifest as Horner syndrome: the triad of ptosis, miosis, and hemifacial anhidrosis. Irritation or compression of the adjacent sympathetic chain may cause ipsilateral flushing and sweating of the face or reflex sympathetic dystrophy, a regional syndrome of burning neuropathic pain. Pancoast syndrome is a constellation of signs and symptoms, including shoulder/arm pain, Horner syndrome, and unilateral upper extremity weakness.

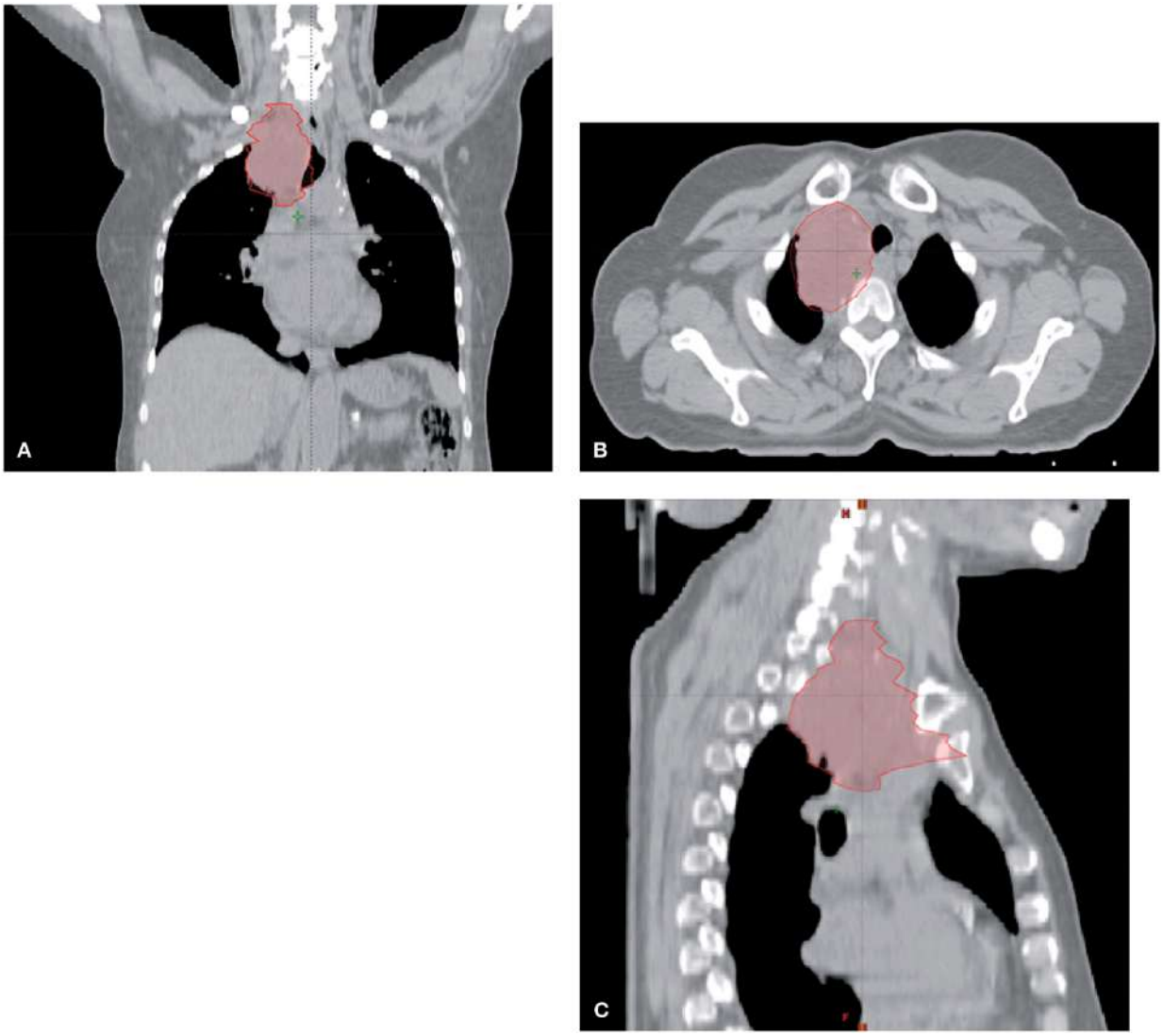

FIGURE 57.2 A 51-year-old person who has smoked formerly presented with right shoulder pain and right-sided Horner syndrome and was found to have an adenocarcinoma in the right superior sulcus. A. Coronal view with gross tumor volume (GTV) contoured. B. An axial view with GTV contoured. A 4-cm tumor is seen invading the mediastinum with displacement of the trachea. He underwent a staging evaluation including mediastinoscopy and was staged as T4N0M0. C. Sagittal view with GTV contoured showing vertebral body impingement. The patient was treated with radiotherapy with concurrent cisplatin and etoposide to 50 Gy and underwent resection with negative margins.

Determining the feasibility of resection is a critical decision point in the management of NSCLC SSTs. Because of the apical location of the tumor, invasion of the brachial plexus, vertebral bodies, and subclavian vessels is not uncommon and may preclude surgical resection as an option, magnetic resonance imaging (MRI) is recommended for determining involvement of these structures.

Multimodality Therapy for Superior Sulcus Tumors

SWOG 9416/Intergroup 0160 included 110 patients with T3 to 4, N0 to 1 SSTs. All patients were treated with neoadjuvant concurrent chemoradiation (45 Gy in 25 fractions with two cycles of cisplatin/etoposide), followed by surgery within 3 to 5 weeks, and then two further cycles of chemotherapy.[131] Eighty-eight patients (80%) underwent surgery, and 83 (76%) had complete resection. The 5-year OS was 44%. Sixty-one resected patients (56%) had a pathologic complete response to induction therapy, and their 5-year survival was

significantly better at 54%. The JCOG 9806 trial showed similar results with 76% of patients undergoing surgery and 5-year OS 56%.[132]

Patients with unresectable localized SSTs and those with stage III disease and bulky N2 (or N3) lymph nodes should be treated with definitive chemotherapy and radiation.[133,134] A retrospective analysis from the Netherlands examined the outcome of 49 patients with stage II or III SST who received 66 Gy with daily cisplatin (6 mg/m^2).[135] Nineteen patients had sufficient response to undergo resection, and in these patients, there was a 53% pathologic complete response rate. The 5-year OS was 18% in patients who received chemoradiotherapy and 33% in patients who were able to undergo surgery.

CURRENT RADIOTHERAPY TECHNIQUES AND FUTURE DIRECTIONS

The treatment of lung cancer presents unique challenges from the technical perspective, due to the combination of breathing motion, significant tissue heterogeneity, and, in some cases, the need for frequent treatment adaptation. All these challenges become even more severe when complex treatment techniques are used, such as SBRT or PT.

The developments of the past 10 to 15 years led to a large-scale availability of tools and techniques for adequate management of these technical difficulties. There are indications that the introduction of improvements such as adaptive therapy and daily alignment on tumor based on CBCT imaging had a measurable clinical impact.[136] SBRT has become the standard of care in inoperable stage I NSCLC, thanks to excellent results in local control and low toxicity.[137] At the same time, techniques such as SBRT require a high level of confidence in the accuracy of the overall treatment workflow,[138] and ensuring a high technical quality of treatments at a large scale is challenging. For instance, it has been shown that it is possible to generate lung SBRT plans that fulfill internal quality assurance criteria but are associated with an expected inferior outcome.[139]

Imaging for Treatment Planning

Accuracy in this phase of treatment preparation is crucial, as uncertainties in representing either the patient anatomy or the tissue density will in principle result in systematic errors. CT is the key imaging method to generate a 3D model of the patient's anatomy for treatment planning. The reproducibility of patient positioning should be maximized, which in the case of patients with lung cancer means achieving two goals:

1. Finding a good balance between patient comfort, so that the position can be maintained during the treatment sessions, and reproducibility, so that after imaging the patient position can be adjusted via small translations and/or rotations of the couch
2. Facilitating inter- and intrafraction regularity of breathing in terms of both motion amplitude and relation between external references (eg, the patient surface) and internal anatomy

The patient is typically scanned with both arms above the head, to maximize the degrees of freedom in choosing beam directions, and the scan should encompass the whole-lung volume, including the costophrenic recesses.

Several methods are available to describe the breathing motion in an image data set that will be then used in treatment planning.[140] The most common imaging approach is the respiratory correlated 4DCT, which represents the breathing motion in the region of interest via multiple intrinsically registered 3D data sets (typically 10). 4DCT helps inform a decision about the motion management approach, which is typically considered for patients with a target motion of more than 5 mm.[140] The 4DCT is also used to generate additional data sets for contouring and/or dose planning, such as the average, mid-ventilation,[141] and maximum intensity projection. These data sets retain some information about the breathing motion but are not associated with the computational burden of a 10-phase 4DCT. For treatments in free breathing, the most common data set for planning is the average CT, where the Hounsfield Unit value for each voxel is the average across the breathing cycle.

Systems for motion mitigation should be considered in case of large motion amplitude, with the caveat that for some of them, for example, breath-hold, reproducibility, and patient compliance may be an issue.

Target Definition and Planning Techniques

Gross Tumor Volume

Clinical macroscopic disease is defined as the GTV. The GTV in the patient with lung cancer is usually derived from a treatment planning CT or PET/CT obtained during quiet respiration. Intravenous contrast is usually not required for identification of the primary tumor unless it is located adjacent to the hilum or mediastinum. European Society for Radiotherapy and Oncology guidelines[142] recommend the preset lung window setting (W = 1,600, L = −1,600) to delineate tumors surrounded by lung parenchyma and the preset mediastinum window setting (W = 400, L = 20) to delineate lymph nodes and tumors invading the mediastinum. A PET/CT within 3 weeks of starting radiation is recommended to avoid stage migration with increasing time to treatment. Intravenous contrast may be valuable in identifying nodal disease. On CT, a short-axis diameter 1 cm or more is often employed for identification of pathologically involved nodes. However, this cutoff is unsatisfactory, having a relatively poor sensitivity of approximately 60% for correctly identifying nodal disease. Meta-analyses suggest that FDG-PET/CT sensitivity and specificity are around 80% and 90%, respectively, compared to CT at around 60% and 80%, respectively.[11,143] The gold standard for the identification of mediastinal nodal disease is through invasive staging. When feasible, the mediastinum should be pathologically staged through either cervical or mediastinoscopy EBUS-TBNA; this information should be incorporated into delineating the nodal GTV. Current studies investing incorporating systematic prechemoradiation nodal sampling suggest that EBUS-TBNA for treatment planning can decrease organ at risk doses as well improve coverage of PET-occult nodal disease.[144,145]

Clinical Target Volume

The clinical target volume (CTV) represents a volumetric expansion of the GTV to encompass microscopic disease. For the primary tumor, pathologically derived correlative data have shown that a 7- to 9-mm margin would encompass all microscopic disease in 90% to 95% of lung adenocarcinomas, whereas a 4- to 6-mm margin would be sufficient in 90% to 95% of lung squamous cell carcinomas.[146,147] A study by Meynard et al[148] using modern pathology techniques recommend primary tumor expansions of 7 and 4 mm margins for adenocarcinoma and squamous cell carcinoma, respectively. For nodal disease, surgical series have shown that a 3-mm margin will encompass 95% of the microscopic extranodal extension of disease in lymph nodes less than 2 cm. However, larger margins may be required for lymph nodes more than 2 cm.[149]

Planning Target Volume

In x-ray RT, geometrical uncertainties are taken into account during planning via the definition of a PTV, which is an expansion of the GTV/CTV with appropriate margins.[150] Planning margins should be defined for each treatment protocol considering these aspects: frequency of imaging for positioning (eg, daily vs weekly), type of imaging and alignment (eg, 2D projections and “bone match” vs 4D CBCT and “tumor match”), and motion management approach (eg, free breathing vs breath-hold). While the same positioning margins should be used for a population of patients treated with the same immobilization systems and imaging/alignment protocol, the margin for breathing motion should be defined at the level of the individual patient.

These additional issues should be considered while defining margins in lung cancer treatment:

1. Any choice of imaging method and volume definition is associated with uncertainties and trade-offs: For instance, the 4DCT is based on a few breathing cycles on a single day, which may not be fully representative of the intra- or even interfraction breathing motion.
2. Commonly used “margin recipes” can also incorporate breathing motion.[151] If one considers the breathing motion as a potentially source of systematic and random errors, the benefit of a 4DCT with respect to a 3DCT is even more evident, as it allows to remove the systematic uncertainty due to the periodic breathing motion. This will lead to a significant reduction in the margin needed to compensate for this component of the breathing motion. One the other hand, the breathing motion baseline may change, and this should be considered a source of systematic error.[141]
3. The margin depends also on the beam penumbra, which is shallower in the lung than in higher density tissue, and the PTV approach assumes that the motion of the CTV will not affect the PTV dose (“static

dose cloud approximation"). When the PTV encompasses a volume with significant tissue heterogeneities, the question of whether the PTV dose metrics are representative of the dose to the moving CTV does not have a simple answer. For instance, a study investigating the influence of GTV motion on SBRT dose distributions found that the dose to the moving GTV was closer to the dose of the static GTV and internal target volume (ITV) than to the PTV dose.[152] This resulted because the GTV had a higher density than the surrounding tissue and the dose distribution was essentially moving together with the GTV.

A detailed analysis of this aspects, in particular in the initial clinical implementation of complex techniques, will help define appropriate treatment margins and fully appreciate what improvements in the treatment workflow will contribute the most to margin reduction.[153]

The most common approach do define a margin for breathing motion in clinical practice is to use the 4DCT to define an ITV, which is the volume encompassed by the GTV/CTV throughout the breathing cycle (Figure 57.3).[154] This is the most expedient way to include a margin for breathing motion. This contour is then transferred to a 3D data set, typically the average CT, and planning is performed on a PTV defined as ITV plus an additional margin for setup error. The main disadvantage of the ITV is that it is a conservative approach with respect to target coverage that is ensured at the expense of a higher dose than strictly needed to healthy tissues in its proximity. By comparison, an analysis of 297 lung SBRT patients treated with a mid-ventilation–based PTV margin estimated that an ITV + 5 mm expansion would have resulted in a bigger PTV for 47% of the patients.[155] These two margin approaches have not been directly compared in the clinic, and they are both associated with high local control and low toxicity.

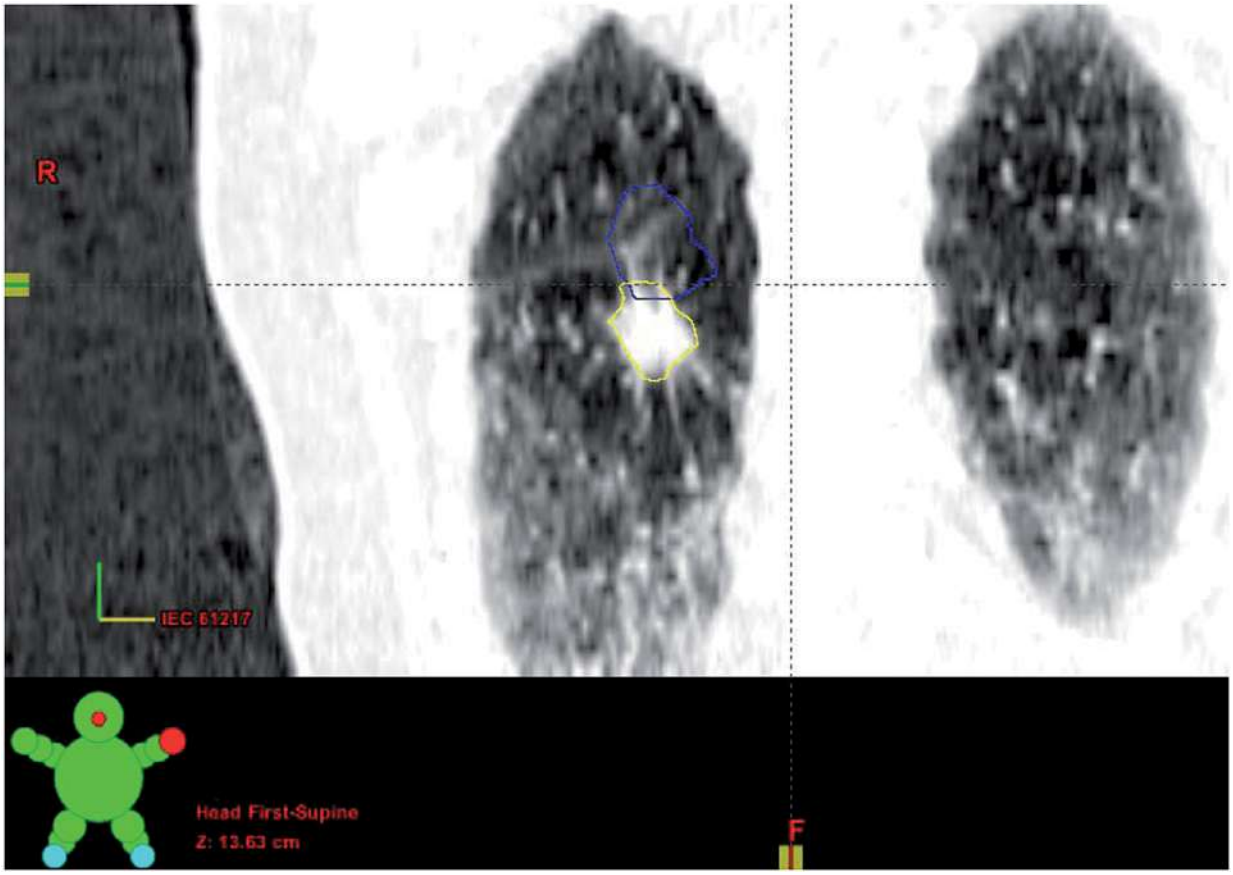

FIGURE 57.3 Tumor motion during a patient's normal respiratory cycle. The yellow wireframe shows the tumor position at full inspiration. The blue wireframe shows the tumor position at full expiration.

In some treatment planning software, it is possible to include the full 4D data set in treatment plan optimization, thus removing the need of a margin for the periodic breathing motion. This method also has the advantage of explicitly considering the dose perturbation due to breathing motion in the optimization process. However, this advanced planning approach also has disadvantages (eg, it is computationally more intensive and delineated contours should be available for all phases), and it is not the norm in clinical practice.

Treatment Planning

According to the tumor volume, shape, and location; the dose prescription; and the available beam technology, lung cancer is treated with techniques ranging from 3DCRT to static IMRT and volumetric-modulated arc therapy (VMAT).

3DCRT can be used to generate clinically acceptable dose distributions when the target volume has a regular shape, and the dose conformity requirements are not stringent. However, the quality of 3DCRT dose distribution drops significantly with large and/or irregularly shaped targets, where techniques using intensity modulation should be preferred.[156-158]

The first application of intensity-modulated treatments in lung relied on static field IMRT. Over the years, VMAT became the technique of choice for most patients, as it is typically associated with the same quality of dose distribution and a significantly lower beam delivery time.[159] The combination of VMAT and flattening filter free beams allows for an even faster delivery,[160] which positively affects patient comfort and reduces intrafraction motion.

Due to the radiation sensitivity of healthy lung tissue at low doses, the balance between dose conformality and normal tissue sparing may lead to different solutions in lung according to the specific clinical scenario. For instance, if the lung is the only dose-limiting organ, fewer beam directions, or narrower arcs, should be preferred: This approach will be associated with a lower lung volume receiving low-intermediate doses between 5 and 20 Gy, and it may be worth the cost of a slightly worse conformity. On the other hand, there are situations where the dose conformity should be maximized, for example, because a high dose is prescribed and the esophagus is adjacent to the target volume: This will in general lead to a plan with several beams, or broader arcs, that will result in a good conformity but also with a larger lung volume receiving a nonzero dose.

In intensity-modulated techniques, it is possible that the lung volume receiving low doses will be larger than in 3DCRT, due the increase in number of beams and in Monitor Units,[161] due to the presence of many small segments. This is not an inevitable consequence of using IMRT, which can generate lung dose distributions at least as good as 3DCRT in the low-dose region,[162] but rather the results of specific planning approaches. It is, therefore, important to carefully "drive" the optimization process in the desired direction, for example, by properly selecting the beam geometry, avoiding strict constraints on target dose uniformity, and limiting the contribution of small segments to the total dose. Generating a plan where most of the dose is delivered with larger segments will also reduce the dosimetric impact of interplay (see later).

Another aspect that should be considered with intensity-modulated techniques is the so-called interplay effect, that is, the interaction between the time structure of beam delivery via multiple segments and the breathing motion. This effect can, in principle, cause both "cold spots" in the target and "hot spots" in healthy tissues. Extensive literature data suggest that interplay is not a primary concern in conventional fractionation. In fact, given the significant random component of the phenomenon,[163] estimated dosimetric impact is limited to 1% to 2% over the treatment course. Dose perturbations may become more prominent in SBRT and when fast beam delivery with a flattening free filter is considered, though most studies suggest that the interplay effect is still not associated with a significant dose deterioration.[162] In selected critical cases, it would be useful to estimate the interplay effect for a specific plan and breathing pattern, but this feature is unavailable in most treatment planning systems.

Lung RT is challenging from the point of view of dose calculation due to the presence of multiple transitions between tissues of significantly different densities. This heterogeneity causes a lack of charged particle equilibrium and a dose "build up" or "build down"[164] that cannot be accurately modeled with simple algorithms. The scenario becomes even more complex in highly conformal techniques and SBRT, when small fields shaped by multileaf collimators are applied, thus requiring an accurate modeling of the beam upstream

of the patient surface. It has been shown that pencil-beam dose calculation algorithms may lead to clinically significant differences with respect to more accurate methods, not only in SBRT[165-168] but even with simple 3DCRT techniques.[169] Dose calculation algorithms such as convolution/superposition or Monte Carlo[170] should be used for all lung RT treatments and are a must for complex techniques.[138]

Readers are encouraged to reference dose constraints from QUANTEC for 3D radiation planning,[171] published trial protocols for IMRT planning,[126] and HyTEC for SBRT planning.[172]

Image Guidance, Treatment Monitoring, and Treatment Adaptation

Image guidance systems are essential to ensure reproducibility in patient positioning and thus allowing for smaller margins. Daily megavoltage or kilovoltage planar imaging can be used, but volumetric CBCT is necessary in case of highly conformal techniques or small margins, as it increases the setup accuracy[173] and it allows to move from a positioning based on bone anatomy to a "tumor match." If available, a 4DCBCT should be preferred, as there are indications that it reduces the interobserver variability in patient alignment.[174] When the target volume is composed by a primary tumor in the lung and lymph nodes in the mediastinum, their motion is in general different (eg, more motion in a lower lobe tumor and less motion in a superior paratracheal node). Consequently, the setup strategy may favor accuracy in one part of the target over the other, and this could be reflected in the planning margins.

Surface guidance is an additional imaging method based on nonionizing radiation that cannot replace a CBCT but can be used for patient prepositioning before imaging, patient monitoring during treatment, and providing a beam-triggering signal.[175]

Breath-hold and beam gating are treatment options for patients with large breathing motion, even though the theoretical advantages should be weighed against the additional uncertainties associated with these methods: Breath-hold reduces tumor motion and may lead to better normal tissue sparing, but reproducibility issues have been reported[176]; the vast majority of gating approaches rely on a surrogate breathing signal (eg, the patient surface), whose relation with the internal anatomy can vary.[140]

Lung cancer treatments are also affected by interfraction anatomy changes (eg, in tumor volume, or in the anatomy of the lung) that may benefit from treatment adaptation. The proportion of patients requiring adaptation depends on factors such as the fractionation schedule, applied margin, the positioning protocol, and the minimum dose difference that triggers replanning. As a consequence, different institutions may report rate of replanning as different as 7%[177] vs 27%.[178] A commonly reported obstacle to the widespread use of adaptive therapy are limited human resources and technical limitations.[179] RT equipment designed to facilitate adaptive protocols is becoming increasingly available, and this will likely lead to an increase in treatment adaptation also in lung cancer. The ARTIA-lung randomized trial is investigating whether daily adaptation may decrease toxicity in locally advanced lung cancer (NCT05488626).

Physics Aspects of Particle Therapy for Lung Cancer

Protons and heavier ions have a dose depth deposition characterized by a peak followed by a very sharp dose falloff. This makes them an interesting option for RT in general and for lung cancer. The main dosimetric benefit of PT in lung cancer is a lower dose to the lungs, heart (including substructures), and esophagus, even though the extent of sparing depends on several factors, including the beam delivery technique (Figure 57.4). Scattering techniques are not always superior to x-ray techniques (XRT), and this may be one of the reasons why in a clinical trial comparing IMRT and PT delivered with scattered beams (NCT0915005), the proton arm was not associated with better dose distributions in the lung.[180] Pencil-beam scanning (PBS) has superior dose shaping capabilities to both passive scattering and IMRT, and this translates into better dose distributions in both planning studies and clinical practice.[181]

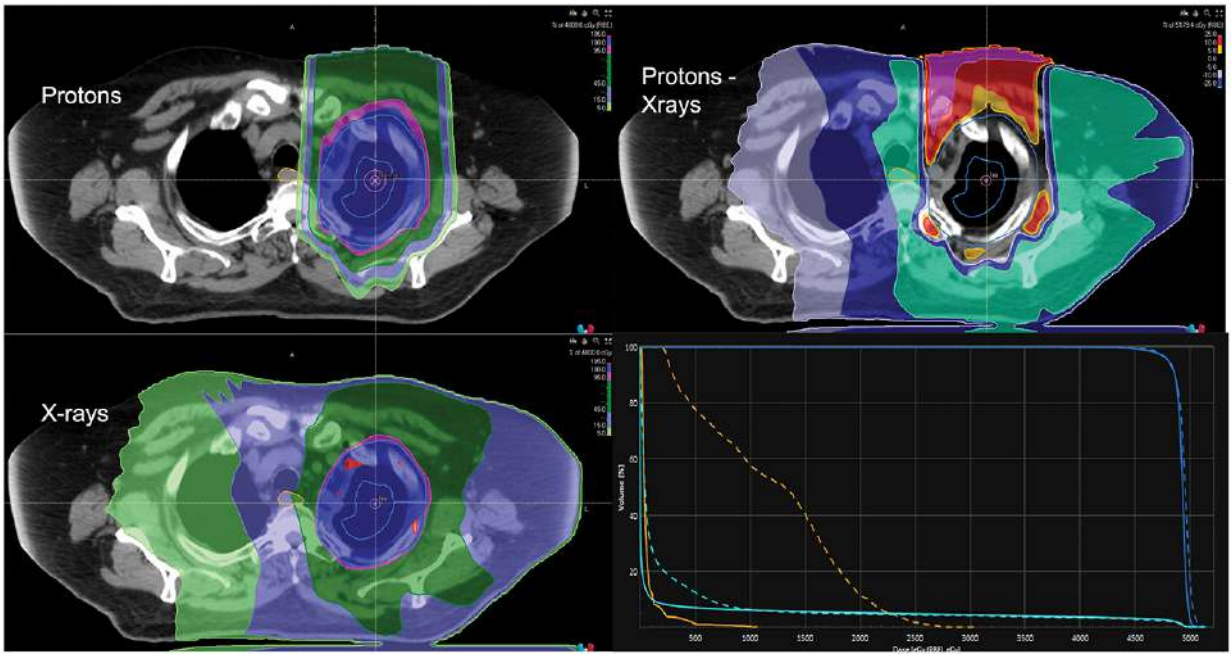

FIGURE 57.4 Comparison between a proton and a photon plan. The isodose levels correspond to 105%, 100%, 95%, 45%, 15%, and 5% of the prescribed dose. The dose differences are shown as the percentage of the prescription dose. Dose-volume histograms are shown for the planning target volume (darker blue), esophagus (orange), and lung (light blue). Solid and dashed lines are for the proton and the photon plan, respectively.

The very localized dose deposition of heavier charged particles is at the same time a strength and a potential weakness, as particle therapy dose distributions are in general more sensitive than XRT to uncertainties, such as patient positioning and breathing motion.[182] This sensitivity, combined with higher costs and reduced availability, means that only a small fraction of patients with lung cancer are treated with PT.

The increased sensitivity of proton dose distributions to intra- and interfraction changes in anatomy has two specific consequences in lung cancer treatment:

1. Treatment adaptation is more often necessary in PT than in XRT. In the NCT0915005 trial at MD Anderson, 29% of patients treated with PT needed plan adaptation versus 12% of those treated with IMXT.[183] A planning study suggested that up to 60% of the patients need treatment adaptation when PBS is used.[184] It is, therefore, recommended that patients with lung cancer treated with PT receive CT scans during the treatment course at regular intervals, for example, once a week, to verify the consistency between the planned and delivered dose.
2. The management of breathing motion is in general more critical than in XRT. The AAPM Task Group Report 290 on respiratory motion management in particle therapy[185] provides a detailed guideline on this topic. While some clinical scenarios (eg, a non-SBRT dose prescription combined with moderate breathing motion) can be safely planned on an average CT and treated in free breathing, more challenging situations require dedicated planning and delivery approaches. A robust optimization approach that considers not only setup and range error but also the breathing motion via multiple phases of the 4DCT should be the preferred approach. When this is not possible, an evaluation of the dose perturbation due to breathing motion should be performed, such as by recalculating the dose on all breathing phases. When possible, the time structure of PBS delivery should also be considered in plan evaluation, to assess the impact of interplay effects.

Pencil-beam dose calculation algorithms are inadequate for lung PT,[186] and Monte Carlo or methods of equivalent accuracy should be used in both plan optimization and final dose calculation.

For a systematic discussion of PBS treatments for thoracic tumors, the reader is referred to The Particle Therapy Cooperative Group consensus guidelines.[187]

METASTATIC NON–SMALL CELL LUNG CANCER

Basic Systemic Therapy Precepts

The treatment of metastatic NSCLC has continued to evolve. By the early 1990s, it was clear that platinum-based chemotherapy could prolong survival, improve symptom control, and yield superior QoL compared with BSC.[188] Over the past decade, the main advances in the treatment of patients with metastatic NSCLC have been the discovery of mutation-driven malignancies in a subset of patients, the advent of immunotherapy, and also active investigations into whether ablative doses of radiation can improve survival in patients with limited metastatic disease burden at the time of diagnosis or progression (Figure 57.5).

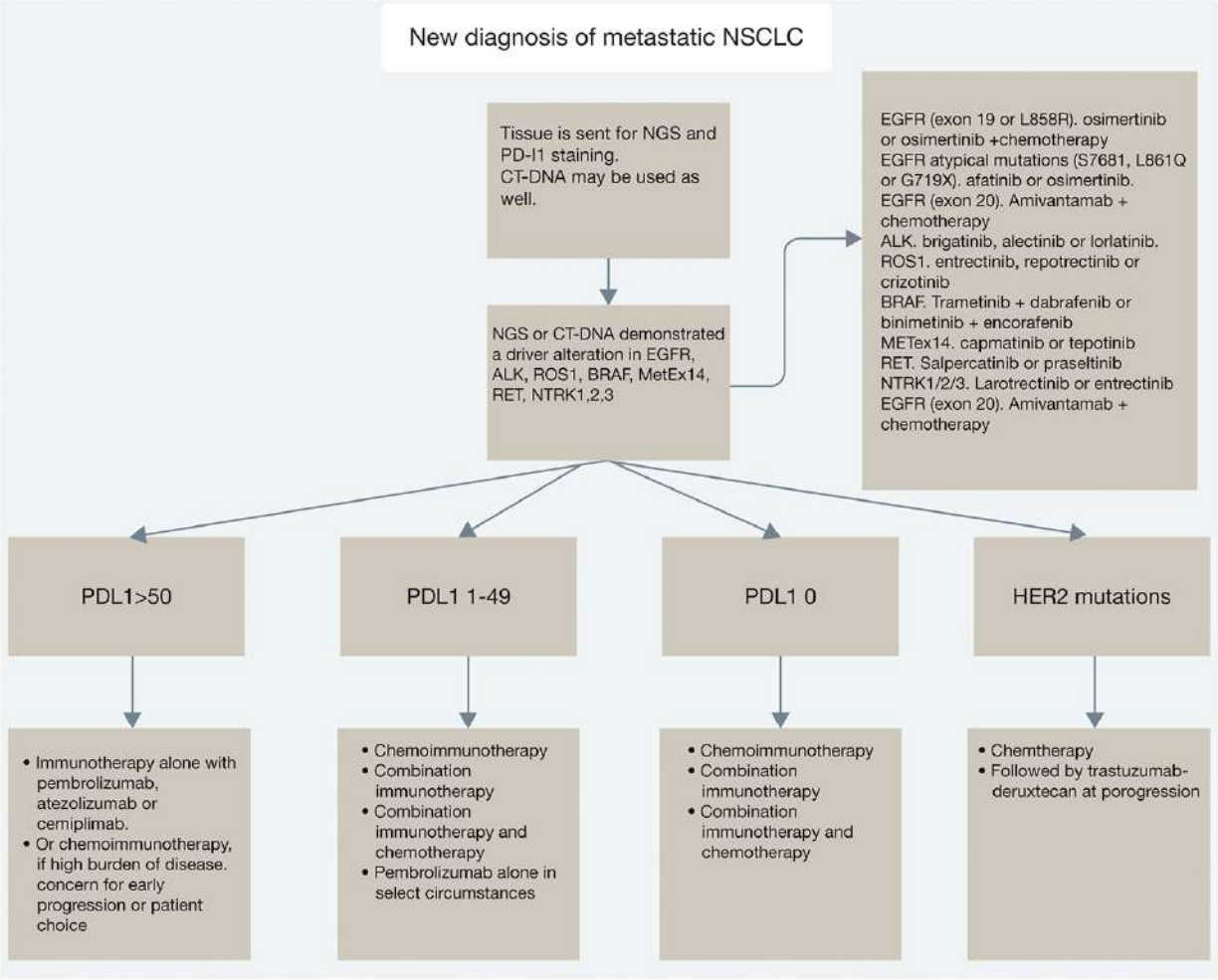

FIGURE 57.5 Molecular biomarker workup for a new diagnosis of metastatic non–small cell lung cancer (NSCLC) to decide on first-line systemic therapy. CT, computed tomography; EGFR, epidermal growth factor receptor; NGS, next-generation sequencing; PD-L1, programmed death-ligand 1.

Immunotherapy

Immunotherapy in the form of ICIs has dramatically changed the treatment paradigm for patients with a variety of malignancies. In NSCLC, treatment with PD-L1 inhibitors was first approved in patients with progressive disease after first-line chemotherapy; several trials demonstrated an improved outcome comparing ICI versus standard second-line chemotherapy (Table 57.6).[189,190]

TABLE 57.6 PHASE III TRIALS OF IMMUNOTHERAPY IN METASTATIC NON–SMALL CELL LUNG CANCER

Study	Intervention	Control	Population	ORR	PFS (mo)	OS (mo)
First-line PD-L1 monotherapy						
KEYNOTE 24[268]	Pembrolizumab	Doublet platinum chemotherapy	All NSCLC with a PD-L1 > 50%	46.1% vs 31.1%	7.7 vs 5.5 (HR 0.50; 95% CI 0.39-0.65)	26.3 vs 13.4 (HR 0.62; 95% CI 0.48-0.81)
KEYNOTE 042[191]	Pembrolizumab	Doublet platinum chemotherapy	All NSCLC with a PD-L1 > 1%	27.3% vs 26.7%	5.6 vs 6.8 (HR 0.79; 95% CI 0.70-0.89)	16.4 vs 12.1 (HR 0.79; 95% CI 0.70-0.89)
IMpower110[269]	Atezolizumab	Doublet platinum chemotherapy	All NSCLC with a PD-L1 > 1%	31.4% vs 32.1%	5.8 vs 5.6 (HR 0.72; 95% CI 0.60-0.86)	18.9 vs 14.1 (HR 0.85; 95% CI 0.69-1.04)
EMPOWER-Lung[193]	Cemiplimab	Doublet platinum chemotherapy	All NSCLC with a PD-L1 > 50%	46% vs 21%	8.1 vs 5.3 (HR 0.51; 95% CI 0.42-0.62)	26.1 vs 13.3 (HR 0.57; 95% CI 0.46-0.71)
First-line immunotherapy and chemotherapy						
KEYNOTE 189[195]	Pembrolizumab, carboplatin, and pemetrexed	Carboplatin and pemetrexed	Non-SCC	48.3% vs 19.9%	9 vs 4.9 (HR 0.50; 95% CI 0.42-0.60)	22 vs 10.6 (HR 0.60; 95% CI 0.50-0.72)
KEYNOTE 407[270]	Pembrolizumab, carboplatin, and taxane	Carboplatin and taxane	SCC	62.6% vs 38.4%	8 vs 5.1(HR 0.57; 95% CI 0.47-0.69)	17.1 vs 11.6 (HR, 0.71; 95% CI 0.58-0.88)
IMpower150[271]	Atezolizumab, carboplatin, paclitaxel, bevacizumab	Carboplatin, paclitaxel, bevacizumab	Non-SCC	63.5% vs 48%	8.4 vs 6.8 (HR 0.57; 95% CI 0.48-0.67)	19.5 vs 14.7 (HR 0.80; 95% CI 0.67-0.95)
Combination immunotherapy						
CheckMate 227[272]	Nivolumab, ipilimumab	Doublet platinum chemotherapy	All histologies <1% PD-L1	27.3% vs 23.1%	5.1 vs 4.7 (0.75; 95% CI 0.59-0.95)	17.4 vs 12.2 (HR 0.65; 95% CI 0.52-0.81)
			All histologies >1% PD-L1	35.9% vs 30%	5.1 vs 5.6 (0.79; 95% CI 0.67-0.94)	17.1 vs 14.9 (HR 0.77; 95% CI 0.66-0.91)
Combination immunotherapy and chemotherapy						
CheckMate 9LA[273]	Nivolumab, ipilimumab, doublet platinum chemotherapy	Doublet platinum chemotherapy	All histologies	38% vs 25%	6.4 vs 5.3 (HR 0.70; 95% CI 0.59-0.83)	15.8 vs 11 (HR 0.75; 95% CI 0.63-0.88)
POSEIDON[274]	Durvalumab, tremelimumab, doublet platinum chemotherapy	Doublet platinum chemotherapy	All histologies	38.8% vs 24.4%	6.2 vs 4.8 (HR 0.72; 95% CI 0.60-0.86)	14 vs 11.7 (HR 0.77; 95% CI 0.65-0.92)

CI, confidence interval; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; NSCLC, non–small cell lung cancer; NR, not reached; SCC, squamous cell cancer.

Subsequent studies focused on patients with treatment-naïve metastatic disease. In patients with high PD-L1 expression and no driver mutation, pembrolizumab, atezolizumab, and cemiplimab have demonstrated superior efficacy over chemotherapy alone.[191-194] Several programmed cell death protein 1 and PD-L1 inhibitors have also been paired with chemotherapy and demonstrated superior outcomes compared to patients treated with chemotherapy alone.[195-198] The choice in the first line of ICI alone, ICI with chemotherapy, or

combination immunotherapy is a complex decision that involves goals of care, willingness to accept toxicity risks, and a patient's support system. In patients without driver mutations (except for KRAS mutations) and PD-L1 expression greater than 50% with limited disease burden, ICI alone is an appropriate treatment that reduces the incidence of side effects compared to using chemoimmunotherapy. In patients with PD-L1 low tumors (0% to 49%), the preferred treatment option is chemoimmunotherapy or combination immunotherapy. ICI alone in patients with PD-L1 1% to 49% is likely inferior, although it is an acceptable option for patients who want to avoid adverse events from chemotherapy.

Molecular Determinants of Therapy

Another major advancement in the management of patients with metastatic NSCLC is the discovery that a fraction of patients with mostly adenocarcinomas has a driver genetic abnormality. Pharmacologically inhibiting this abnormality with targeted treatment is now the standard of care for these patients.

Epidermal Growth Factor Receptor

EGFR-activating mutations are found in approximately 10% to 15% patients with of lung cancer, with the most common mutations being exon 19 deletion or exon 21 L858R mutations. The activating mutations can be inhibited by TKI, which results in a decrease in the cancer burden.[199] The first-generation TKIs erlotinib and gefitinib were proven to be more effective than chemotherapy in several clinical trials. OS was not found to be different in the majority of this trials, likely because of crossover to an EGFR TKI in the majority of patients randomized to chemotherapy.[200,201] Second- and third-generation TKIs such as osimertinib were designed to address the development of a resistance mutation T790M, which impairs the binding of these TKIs to the EGFR. A phase III study compared osimertinib to either erlotinib or gefitinib, and this demonstrated improved efficacy, PFS, and OS for osimertinib.[202] Patients with EGFR mutations commonly have brain metastasis at presentation, and osimertinib also showed a higher central nervous system (CNS) response rate and CNS-specific PFS compared to the older TKIs. Recent trials have tested the hypothesis of whether adding chemotherapy to osimertinib is beneficial compared to osimertinib alone.[203] As of this writing, the results have showed an improvement in PFS at the cost of adverse events, and whether this will affect OS or if there is a specific population who benefits more (the presence of brain metastasis, higher burden of disease) to inform this more aggressive approach is a topic of controversy.[204]

ALK

ALK positivity defines a distinct molecular subset of NSCLC (3%-7%). Crizotinib was the first agent approved for ALK mutations, but PFS was short, and it had limited activity in patients with CNS metastasis. Currently, alectinib,[205] brigatinib,[206] and lorlatinib[207] have been shown to be superior to crizotinib and are the standard of care for these patients.

ROS1

The translocation between *ROS1* and other genes, the most common of which is *CD74*, occurs in 1% to 2% of NSCLC.[208] These fusions lead to the constitutive activation of *ROS1*. This activation can be inhibited with crizotinib,[209] entrectinib,[210] or reprotectinib.[211] Given the low incidence of ROS1 abnormalities, these agents have been approved based on open-label phase 2 studies. Crizotinib has low CNS activity; therefore, entrectinib and repotrectinib are preferred agents.

BRAF

BRAF can also act as an oncogenic driver in the presence of an activating mutation, the most common one of which is V600E, observed in 1% to 2% of lung adenocarcinomas.[212] In patients with this disease, inhibition of only the BRAF pathway is effective but leads to acquired resistance, most commonly through a bypass signaling via MEK, another protein in the same pathway. By combining a BRAF inhibitor with an MEK inhibitor, the pathway is blocked at two different points, which can overcome or delay the development of resistance. Encorafenib and binimetinib[213] have been approved for this disease.

Other Driver Mutations

Many targeted drugs are actively being investigated in the clinical trial testing. When feasible, patients with metastatic NSCLC should undergo molecular testing via a broad, panel-based approach, usually by next-generation sequencing. Other targetable mutations at this time include KRAS, MET exon 14, RET, HER2, and NTRK1/2/3.

Role of Radiation in Oligometastatic/Oligoprogressive Non–Small Cell Lung Cancer

Although survival for patients with metastatic NSCLC remains poor with 5-year OS of less than 10%, there is a subset of patients who have better prognosis and may benefit from aggressive local therapy, though identifying this subset has remained challenging. One subgroup that has consistently shown superior outcome is patients with limited systemic disease burden (oligometastatic disease), and this has been incorporated into the AJCC eighth edition staging system, with M1b being patients with a single site of extrathoracic metastasis. The exact definition of oligometastatic is still evolving and varies based on studies. An international analysis of 757 patients with NSCLC with one to five synchronous or metachronous metastases and a controlled primary (treated with curative-intent local therapy including surgery, SBRT, curative dose radiation, or some combination) showed 5-year OS of 29.4% for the entire population, with 5-year OS of 47.8% for the best risk group on recursive partitioning analysis in patients with metachronous disease, and 5-year OS of 13.8% in the worst risk group for patients with synchronous metastases and N1/N2 disease.[214] Beyond treating the primary lung tumor, aggressive radiation may also have a role in managing the oligometastatic sites. A multicenter, phase II trial randomized patients with synchronous metastatic NSCLC with three or fewer metastatic lesions after first-line systemic therapy to either local consolidative therapy (LCT) to all sites of disease +/− maintenance treatment or maintenance treatment alone.[215] LCT included surgery or radiation, and radiation was given with curative intent when possible. The study was terminated early after randomization of 49 patients due to improved median PFS in the LCT group. On long-term follow-up, the PFS benefit was durable at 42.2 months (95% CI 7.4-23.1 m) in LCT group versus 4.4 months (95% CI 2.2-8.3 m) in the maintenance group (P = .017). A similar randomized phase II trial with 29 patients with oligometastatic NSCLC from UTSW published a year later showed a similar improvement in PFS with aggressive radiation.[216] SABR-COMET was a randomized phase II trial of SABR versus standard of care that included patients with mixed histologies—including NSCLC—and one to five oligometastases with a controlled primary. Aggressive radiation improved OS and PFS compared to standard of care,[217] leading follow-up phase III trials (NCT03862911, NCT03721341). The SINDAS trial asked a similar question in patients with EGFR-mutated NSCLC, comparing TKI only against TKI plus radiation, showing an improvement in OS with addition of radiation.[218]

As systemic therapies improve, there is also a category of patients with “oligoprogressive” disease, who may have many sites of metastasis that are all responding to systemic therapy but one or a few sites of disease that are progressing. In this scenario, aggressive RT, such as with SBRT, to the sites of oligoprogressive disease can give patients more time on the targeted agent before having to switch systemic therapies. In published series of patients on erlotinib or crizotinib with four or fewer sites of extracranial progressive disease, ablative local therapy such as SBRT to the oligoprogressive sites can provide an additional 6 months or more of PFS on the same targeted agent.[219,220] The CURB trial was a phase II randomized trial of SBRT versus standard of care in patients with metastatic breast cancer or NSCLC who were oligoprogressive on first-line systemic therapy, with oligoprogression defined as five or less progressive lesions on PET/CT or CT.[221] The study was closed to accrual with 106 patients, before reaching the targeted sample size, after the primary efficacy end point was met during a preplanned interim analysis. For the 59 patients with NSCLC, median PFS improved from 2.2 to 10.0 months with SBRT, and the time to new systemic therapy was 11.0 months.

Conclusion

These are very exciting times for the treatment of metastatic NSCLC as significant advances have become available that are dramatically changing the paradigm of how we treat this disease. Systemic therapy options

are increasingly personalized for patients based on their cancer's molecular targets and biomarkers. As systemic therapies improve, there may also be an increasing role for local therapy in providing durable disease control.

PALLIATIVE RADIOTHERAPY

Given the propensity of lung cancer for locoregional recurrence and/or distant metastatic disease, RT plays an important role in the palliation of symptomatic disease in many patients with lung cancer. The most common sites of disease that require palliative RT include the thorax, bone, and brain. Intrathoracic disease and bone metastasis will be covered here. The reader is referred to Chapters 16, 101, and 102 for radiosurgery, palliation of brain metastases, and palliation of spine metastases, respectively, in the management of CNS metastases from lung cancer.

Palliation of Intrathoracic Disease

Symptoms from progression of intrathoracic lung cancer that may benefit from a course of palliative RT include cough, hemoptysis, chest wall pain, SVC syndrome, dyspnea from airway obstruction, and hoarseness from involvement of the recurrent laryngeal nerve. For intrathoracic disease, higher doses of radiation with biologic effectiveness dose greater than 35 Gy_{10} (eg, 30 Gy in 10 fractions) are recommended by meta-analyses[222] and ASTRO 2011 guidelines.[223] A 2018 update to ASTRO guidelines recommends the use of concurrent chemotherapy for patients with stage III NSCLC who are not suitable for curative therapy but have ECOG PS 0-2 with a life expectancy of at least 3 months.[224]

Endobronchial brachytherapy may provide relief for patients with endobronchial lesions causing obstruction or hemoptysis. With improvements in radiation technique and the ability to increase the therapeutic ratio through fractionation, external beam radiation is generally preferred to brachytherapy, though it may be reasonable to consider if an obstruction fails external beam radiation. The lesion to be treated should be visible by bronchoscopy and generally located in the trachea, mainstem, or lower lobe bronchi. This procedure requires the combined efforts of an interventional pulmonologist and brachytherapist. The pulmonologist performs fiberoptic bronchoscopy, placing an afterloading catheter within the airway adjacent to the tumor under direct visualization. In a retrospective study from MD Anderson Cancer Center involving 175 patients with lung cancer who received high-dose rate brachytherapy for metastatic or locally recurrent lung cancer, 115 (66%) patients demonstrated symptomatic improvement.[225]

Superior Vena Cava Syndrome

Lung cancer is the most common cause of SVC syndrome and accounts for approximately 80% of cases at diagnosis. If the SVC becomes obstructed because of an extrinsic mass, blood returns to the heart through collateral vessels to the azygos vein or inferior vena cava. Venous collaterals dilate over weeks so that the upper body venous pressure and resulting edema of the arm and face decrease over time. The severity of the symptoms is, therefore, attributable not only to the degree of SVC narrowing but also to the rapidity with which it develops. The characteristic signs include cyanosis, plethora, distention of subcutaneous veins, and edema of the head, neck, and arm. Patients may report dyspnea or cough. Rarely, severe and acute obstruction can result in cerebral edema or laryngeal stridor. The clinical course may be exacerbated by the development of a thrombus or the simultaneous tumor mass effect on the bronchi or heart.

Traditionally, SVC syndrome was viewed as a medical emergency. Accumulating experience, however, demonstrates that the course of SVC is rarely life-threatening.[226] Immediate intervention is warranted when the symptoms are life-threatening (eg, cerebral edema leading to altered mental status, stridor, or clinically significant hemodynamic compromise). Intravascular stenting provides the most immediate relief and can be accomplished even when there is complete obstruction. In the absence of life-threatening symptoms, the patient should be appropriately staged and biopsied and the underlying malignancy treated in a manner appropriate for its stage and presentation. The majority of patients with SVC syndrome attributed to SCLC will respond to systemic therapy and should start this as soon as the diagnosis is confirmed (see the section "Small Cell Lung Carcinoma"). For limited-stage SCLC, radiation can be added starting with cycle 2, which

also has the advantage of treating a smaller, postchemotherapy volume. Patients with NSCLC and SVC syndrome are less likely to respond to chemotherapy; thus, the threshold for starting radiation or placing an endovascular stent should be lower.

SMALL CELL LUNG CARCINOMA

In the United States in 2023, approximately 33,000 patients were diagnosed with SCLC, constituting approximately 14% of all lung cancer diagnoses. Over the past several decades, the proportion of SCLC among all lung cancer histologies has been decreasing, perhaps because of smoking cessation and the proliferation of low-tar cigarettes. Although there has been a modest but statistically significant improvement in 2- and 5-year survival in both limited- and extensive-stage diseases in recent decades, the outcomes are still extremely poor, particularly since the majority (approximately two-thirds) of patients present with extensive-stage disease with an expected 5-year survival of only 3%.

Pathology

The establishment of a firm pathologic diagnosis distinguishing SCLC from NSCLC variants such as carcinoma with neuroendocrine features and carcinoid is extremely important in this disease, as it can have a significant impact on management and clinical outcome. Histologically, SCLC is one of the small, round, blue cell tumors (along with neuroblastoma, rhabdomyosarcoma, Merkel cell carcinoma, etc) with scant cytoplasm and indistinct nucleoli. Cells are often molded together, and crush artifact is commonly noted after needle biopsy but is not pathognomonic. Almost all SCLC samples are immunoreactive to keratin and epithelial membrane antigen, and approximately 80% express thyroid transcription factor-1.[227] The majority of tumors will stain for neuroendocrine markers, including synaptophysin, neuron-specific chromogranin A, enolase, and CD56. Immunohistochemistry alone, however, cannot distinguish SCLC from small cell cancer of nonthoracic origin or from NSCLC with neuroendocrine differentiation. The WHO recognizes that SCLC can occur in a pure type or mixed with NSCLC in up to 30% of cases.

Prognostic Factors in Small Cell Lung Cancer

The most clinically important prognostic factor in SCLC is stage (limited vs extensive), with 5-year survival of approximately 30% for patients with local disease versus 3% for those with extensive disease.[1] Other clinical factors consistently reported to correlate with improved survival include good performance status, female gender, and normal lactate dehydrogenase levels at baseline.[228]

Staging Workup

As in patients with NSCLC, patients with SCLC should undergo a timely and efficient history, physical examination, and laboratory and radiographic evaluation. The history and physical should be performed with particular attention to signs and symptoms of paraneoplastic syndromes, including SIADH and elevated ACTH. Laboratory evaluation should include a complete blood count and comprehensive chemistry panel. Radiographic studies should include a CT scan of the chest and abdomen with intravenous contrast, with PET/CT for suspected limited-stage disease. All patients with SCLC, regardless of stage, should undergo a brain MRI with gadolinium or a head CT with contrast to evaluate for brain metastases. A diagnostic thoracentesis should be performed for any identified pleural effusion to determine the presence of malignant cells. The TNM staging system adopted by the AJCC is applicable to both NSCLC and SCLC. Most historical studies classified patients as having limited or extensive disease based on the 1973 Veteran Administration Lung Group staging scheme.[229] In this system, limited stage is defined as disease confined to the ipsilateral hemithorax, which can be safely encompassed within a tolerable radiation portal. Virtually all studies in limited disease exclude malignant pleural effusions due to the significant risk of pulmonary toxicity in a high-risk patient population with little chance of cure.

Clinical Presentation and Paraneoplastic Syndromes

Paraneoplastic syndromes are commonly encountered in lung cancer; however, the spectrum of paraneoplastic syndromes in SCLC is distinct from that observed in NSCLC. Neurologic paraneoplastic syndromes are more commonly encountered in SCLC and are thought to be primarily autoimmune in nature. LEMS is seen in 3% of all patients with SCLC at presentation and is characterized by proximal muscle weakness that improves with continued activity. This syndrome occurs when autoantibodies are generated against voltage-gated calcium channel receptors on the presynaptic membrane, impeding release of acetylcholine into the neuromuscular junction and resulting in muscular weakness. A wide variety of other rare autoimmune neurologic paraneoplastic syndromes have been described in SCLC, including encephalomyelitis, cerebellar degeneration, and retinopathy. SCLC can also elaborate hormonally active peptides including ACTH and vasopressin leading to Cushing syndrome and SIADH, respectively. Although SCLC is the most common tumor associated with SIADH, only 10% of patients meet the clinical criteria for SIADH. Similarly, only 5% of patients with SCLC present with Cushing syndrome. Despite the fact that paraneoplastic syndromes may lead to early identification and diagnosis of SCLC, some of these syndromes, such as Cushing, have been associated with poorer survival.[230] Treatment of the cancer will often, although not always, ameliorate the paraneoplastic syndromes.

General Therapeutic Precepts

Early-stage (ie, T1-2, N0) SCLC is diagnosed in less than 5% of incident cases. For these patients, definitive surgical resection is a potential therapeutic option. In a population-based study, lobectomy without adjuvant radiation was associated with an approximately 50% OS.[231] Given the propensity for early nodal dissemination with SCLC, invasive staging of the mediastinum should be performed prior to surgical resection. For patients who are medically inoperable, SABR could be used in place of surgery for early-stage, node-negative disease, with some clinical data showing efficacy.[232] After surgical resection or SABR, the primary mode of failure for these patients is distant dissemination. Therefore, adjuvant chemotherapy is recommended for all patients, even if node negative. Postoperative radiation is recommended if positive margins or nodal involvement is found at resection.

The majority of patients present with evidence of nodal or distant dissemination at the time of diagnosis. Multiagent chemotherapy, usually a platinum-based combination, is an essential part of therapy for these patients. For patients with limited-stage disease, the addition of thoracic radiation significantly improves survival and, therefore, is an integral of part their treatment regimen.[233-235] For patients with extensive- stage disease, first-line therapy now includes multiagent chemotherapy plus PD-L1 ICIs. In the preimmunotherapy era, consolidative thoracic radiation was found to be potentially beneficial for select good performance status patients who have complete resolution of their extrathoracic tumor burden after chemotherapy, to reduce the risk of intrathoracic failure.[236,237] The role of thoracic radiation is less certain in the era of immunotherapy for extensive-stage SCLC. Prophylactic cranial irradiation (PCI) is still a standard of care after systemic therapy for patients with SCLC, as this has been shown to provide a significant improvement in absolute survival for these patients.[238,239] However, the trials showing a benefit to PCI were conducted without routine MRI imaging, and there is also evidence PCI might not be beneficial for patients with no brain mets on MRI.[240] MRI brain surveillance is also an acceptable practice in place of PCI.

Chemotherapy for Limited-Stage Disease

EP for four cycles is the most common chemotherapy regimen used for limited-stage SCLC and has the most published clinical evidence.[109,241] For patients not eligible to receive cisplatin, there is clinical evidence that carboplatin can be used with similar rates of disease response and survival.[242] Cisplatin is associated with higher rates of nephropathy, neuropathy, hearing loss, and nausea/emesis, but carboplatin is associated with higher risks of myelosuppression.

Radiation Timing for Limited-Stage Disease

A randomized trial by the JCOG evaluated concurrent versus sequential chemotherapy and thoracic radiation in patients with limited-stage SCLC.[243] All patients received 45 Gy in 1.5-Gy fractions BID and were randomized to receive four cycles of cisplatin (80 mg/m^2 on day 1) and etoposide (100 mg/m^2 days 1, 2, and

3) every 4 weeks concurrent with RT (beginning day 2) or every 3 weeks sequentially before RT. Patients treated concurrently had longer median survival compared to patients treated sequentially: 27 versus 20 months. A meta- analysis by De Ruysscher et al[244] that included more than 2,300 patients from nine randomized trials evaluated the timing of RT when given concurrently with multiagent chemotherapy. When all trials were pooled together, "earlier or shorter" RT did not have a significant impact on OS compared with "later or longer" RT (HR 0.99, 95% CI 0.91-1.08, P = .78). However, if looking at trials with similar chemotherapy compliance rates between the arms, results were in favor of earlier radiation (OS HR 0.79, 95% CI 0.69-0.91). It is recommended to start radiation with cycle 1 or 2 of chemotherapy, unless radiation fields are very large at diagnosis, and more tumor shrinkage could significantly decrease radiation treatment toxicity.

Radiation Dose and Fractionation for Limited-Stage Disease

The optimal dose and fractionation scheme for concurrent chemoradiation for limited-stage SCLC is an area of active investigation. SCLC is highly radiosensitive, suggesting that hyperfractionation could be employed to reduce late normal tissue toxicity. It also has a high proliferative rate, arguing for accelerated treatment to counteract repopulation. Between 1989 and 1992, 417 patients were enrolled in a randomized, intergroup trial of concurrent accelerated hyperfractionated RT versus standard daily RT in patients with limited-stage SCLC.[109] All patients received four cycles of cisplatin (60 mg/m^2 on day 1) and etoposide (120 mg/m^2 on days 1, 2, and 3), and RT began with cycle 1. In the once-daily arm, patients received 45 Gy in 1.8-Gy fractions over 5 weeks. In the BID arm, patients received 45 Gy in 1.5-Gy fractions over 3 weeks. Patients who achieved a complete response were offered PCI. OS was significantly higher in the BID arm (26% vs 16% at 5 years), and local recurrence was significantly lower (36% vs 52%). There was a significant increase in grade 3 acute esophagitis (26% vs 11%) in the BID arm, with no difference in late toxicity.

Since the two arms of the abovementioned Turrisi trial do not have the same biologic equivalence, there has been immense interest on whether a BID radiation regimen would be superior to a daily regimen to a higher dose (ie, 60-70 Gy). The Concurrent Once-daily Versus Twice-daily Radiotherapy trial enrolled 547 patients between 2008 and 2013 at 88 centers worldwide, randomizing patients with limited-stage disease to 45 Gy BID or 66 Gy once daily.[245] The 2-year OS was not significantly different (56% for BID, 51% for once daily), and the rate of grade 3 or greater esophagitis was 19% in both arms. CALGB 30610/RTOG 0538 compared 45 Gy in 30 fractions over 3 weeks versus 70 Gy in 35 fractions.[246] A third arm was closed, which administered 61.2 Gy in 5 weeks per RTOG 0239. All patients received concurrent EP, and RT begins with cycle 1 or cycle 2. OS did not significantly differ between treatment arms (P = .594). Median OS was 28.5 months (95% CI 25.4-34.5) for 45-Gy BID compared with 30.1 months (95% CI 24.4-37.2) for 70-Gy once-daily RT. Grade 3+ esophageal toxicity was 16% in the 45-Gy BID arm and 17.5% in the 70-Gy once-daily arm. Rates of grade 3 dyspnea were low, 4% (12 patients) on the BID arm and 7% (21 patients) on the once-daily arm, and the only case of grade 4 dyspnea reported was on the BID arm. Both trials concluded that once-daily radiation is an acceptable alternative to BID radiation, although BID is still standard of care.

The high intrathoracic relapse rate observed in limited-stage SCLC after radiation had led to continued interest in dose escalation. Choi et al[247] conducted a phase I dose escalation study with both BID and once-daily arms. In the BID arm, 45 Gy in 30 fractions over 3 weeks was the maximum tolerated dose. In the once-daily arm, the dose was escalated to the maximum of 70 Gy in 35 fractions over 7 weeks without dose-limiting toxicity. More recently, Gronberg et al[248] investigated whether BID radiation to 60 Gy in 40 fractions improves survival over 45 Gy in 30 fractions. This randomized, phase 2 trial was done at 22 public hospitals in Norway, Denmark, and Sweden. All patients received chemotherapy and started radiation around cycle 2. Between 2014 and 2018, 170 patients were randomized. At 2 years, OS was 66% versus 39% favoring the 60 Gy group (OR 3.09, 95% CI 1.62-5.89; P = .0005). Overall, there was no difference in toxic effects between the 60-Gy group and the 45-Gy group. These results are encouraging and would benefit from additional clinical testing.

Radiotherapy Techniques for Limited-Stage Disease

There have been immense technological advances in the radiation treatment of lung cancer. While most of the clinical data are in NSCLC, SCLC could derive similar clinical benefits. Early-stage, node-negative SCLC

can be treated with SABR, following similar principles as NSCLC.[232,249] IMRT is increasingly used for node-positive lung cancer, with data in NSCLC suggesting superior clinical outcomes over 3D conformal radiation.[127] There are also small clinical series with proton radiation showing safety and efficacy.[250,251] Advanced technologies should be deployed as appropriate to deliver a high dose to the target and minimize dose to the normal tissues.

Radiotherapy Volume for Limited-Stage Disease

Limited-stage SCLC is frequently bulky at presentation, requiring large treatment fields to encompass all sites of intrathoracic disease. Therefore, induction chemotherapy has been employed to achieve cytoreduction of disease prior to initiation of thoracic RT. This approach raises the concern of potentially increasing the risk of marginal treatment failure if the postchemotherapy volume alone is included in the radiation portal. To address this question, the SWOG conducted a randomized study, enrolling 191 patients who had a partial response or stable disease after 6 weeks of induction chemotherapy. They were randomized to receive RT (48 Gy split course) to either the preinduction or postinduction volume.[252] There was no difference in local recurrence rates: 32% in the preinduction versus 28% in the postinduction arm. Careful retrospective studies of patients treated with preinduction or postinduction thoracic RT show that local failure is not significantly higher if smaller fields are used. Furthermore, most intrathoracic failures occur in the smaller postchemotherapy radiation field, arguing, as in locally advanced NSCLC, against the use of ENI.[253,254] Recent clinical trials in limited-stage disease have targeted gross disease, with some including the ipsilateral hilum regardless of involvement.[245,246]

Radiotherapy for Extensive-Stage Disease

Systemic therapy is the essential element in the treatment of patients with extensive-stage SCLC with good performance status; however, thoracic RT may play a role in selected patients. Based on the observation that patients have high rates of thoracic relapse after systemic therapy alone, a single-institution prospective randomized trial was undertaken in Yugoslavia.[236] In this trial, 209 patients with extensive disease were enrolled and treated with three cycles of EP. Of those, 110 patients who had a partial response in the chest and a complete response outside the chest were randomized to receive thoracic radiation with concurrent carboplatin and etoposide, followed by two cycles of EP, versus four further cycles of EP alone. All eligible patients received PCI. The thoracic radiation was delivered in 54 Gy in 36 fractions over 12 days. At 5 years, the OS was higher in the arm that featured thoracic radiation: 9% versus 4%.

Similarly in the chemotherapy era, the Dutch CREST trial tested 30-Gy thoracic radiation after platinum/etoposide in patients who had any response to chemotherapy.[237] Thoracic radiation was associated with a 2-year OS benefit (13% vs 3%, $P = .004$), but not a 1-year OS benefit, which was the primary end point of the study. After stratifying for intrathoracic disease after chemotherapy in a subsequent analysis, a significant difference in OS was seen in the 434 of 495 patients who had residual disease after chemotherapy (33% vs 26% at 1 year, 12% vs 3% at 2 years, $P = .044$).[255] Both of the abovementioned trials were conducted without immunotherapy as part of the systemic regimen, which is now standard of care in extensive-stage SCLC, and the benefit of thoracic radiation in this patient population is uncertain.

Beyond thoracic radiation, RTOG 0937 was a randomized phase II study in patients with metastatic SCLC with one to four extrathoracic sites of disease (excluding brain metastasis); patients were randomized to receive 45 Gy in 15 fractions to all sites of disease followed by PCI, versus PCI alone, after chemotherapy. The trial was closed for futility after an interim analysis of 86 patients.[256] With a median follow-up of 9 months, there was no significant difference in 1-year OS: 60% for PCI versus 51% for PCI and RT to thoracic and metastatic sites. There are ongoing studies to evaluate the role of thoracic and extrathoracic radiation in patients with extensive- stage disease, in the era of chemoimmunotherapy.

Prophylactic Cranial Irradiation and Radiation for Brain Metastasis

Brain metastases are present at diagnosis in approximately 20% of patients with SCLC. The brain is also a frequent site of failure after chemotherapy for extensive disease or chemoradiotherapy for limited-stage disease. Several randomized trials have addressed the value of PCI following a response to initial therapy and

have consistently demonstrated a decrease in the incidence of brain metastases. A meta-analysis reported the results of 987 patients treated in seven randomized trials enrolling between 1977 and 1995,[238] with 85% limited-stage patients and 15% extensive. All were randomized to either PCI or observation following a response to chemotherapy, and brain imaging was not required prior to PCI. At 3 years, PCI was found to significantly decrease the incidence of brain metastases (59% vs 33%) and significantly improve OS (21% vs 15%).

PCI in extensive-stage SCLC was studied in an EORTC trial,[239] randomizing 286 patients to either PCI or observation after any response to four to six cycles of chemotherapy. Brain imaging was not required prior to PCI. The 1-year cumulative incidence of brain metastases was significantly decreased in the PCI arm at 15% versus 40%, and 1-year OS was significantly increased in the PCI arm at 27% versus 13%. A similar Japanese randomized trial did not replicate these results; the trial was terminated after enrollment of 163 patients when an interim futility analysis determined that no benefit was possible. Patients were randomized after any response to chemotherapy, but unlike the EORTC study, brain imaging was done before enrollment. The median OS was not significantly different between the two arms with a trend toward worse survival in the PCI arm: 11.6 months for patients who received PCI versus 13.7 months for those who did not (HR 1.27, CI 0.96-1.68, $P = .094$).[240] Thus, the role of PCI in extensive-stage SCLC remains an ongoing controversy.

To help define the optimal dose and fractionation for PCI, an intergroup trial randomized patients with limited-stage SCLC who had achieved a complete response to chemoradiotherapy to standard dose, 25 Gy in 10 daily fractions, or high dose, 36 Gy in either 18 daily fractions or 24 BID fractions.[257] A total of 720 patients were randomized; at 2 years, the cumulative incidence of brain metastases was not significantly different between the two arms: 29% in the standard-dose arm versus 23% for high dose. There was poorer 2-year OS in the high-dose arm: 42% versus 36%. Patients enrolled in this trial participated in baseline and follow-up neuropsychological test batteries along with QoL assessments. Wolfson et al[258] reported an increased incidence of chronic neurotoxicity at 12 months after PCI in the 36-Gy cohort ($P = .02$). Taken together, these results establish 2.5 Gy in 10 fractions as the current preferred regimen to deliver PCI.

For patients with brain metastases, the standard of care therapy is whole-brain radiation to 30 Gy in 10 fractions. Studies have looked at the use of memantine and hippocampal avoidance (HA) radiation to decrease neurotoxicity from treatment with conflicting results. NRG CC001 randomized 518 patients with brain metastases from 2015 to 2018 to HA whole-brain radiation therapy (HA-WBRT) plus memantine or WBRT plus memantine. Risk of cognitive failure was significantly lower after HA-WBRT (adjusted HR 0.74, 95% CI 0.58-0.95; $P = .02$), with no difference in intracranial PFS and OS.[259] Patients on this trial did not have SCLC, but there has been extrapolation into the small cell patient population. Conflicting results regarding HA have been seen with PCI. PREMER is a phase III trial that randomized 150 patients with SCLC to PCI or HA-PCI.[260] The primary objective was delayed free recall at 3 months, which was better in the HA-PCI arm (5.8%) compared with the PCI arm (23.5%; OR 5, 95% CI 1.57-15.86; $P = .003$). The incidence of brain metastases, OS, and QoL were not significantly different. However, Belderbos et al[261] reported that in a multicenter, randomized phase 3 trial of 168 patients with SCLC, standard PCI versus HA-PCI of 25 Gy in 10 fractions did not find a lower probability of cognitive decline in patients with SCLC receiving HA-PCI compared with conventional PCI. No increase in brain metastases at 2 years was observed in the HA-PCI arm. NRG CC003 randomized 392 patients with SCLC to PCI or HA-PCI (25 Gy in 10 fractions) and also did not show a clear benefit to neuroprotection with HA-PCI.

Due to concerns of neurotoxicity, there has been increasing interest in stereotactic radiosurgery (SRS) for brain mets from SCLC. While the standard of care is still WBRT, there are now clinical reports of SRS for small cell brain mets, with favorable cranial control and survival.[262,263]

Systemic Therapy for Extensive-Stage Disease

For decades, in patients with adequate performance status, chemotherapy was the cornerstone of treatment for extensive- stage SCLC. Cisplatin or carboplatin plus etoposide was the recommended regimen.[242] This changed in 2018 with the results from IMpower133,[264] a double-blind, placebo-controlled, phase 3 trial to evaluate atezolizumab plus carboplatin and etoposide in patients with extensive-stage SCLC. Atezolizumab improved median OS from 10.3 to 12.3 months (HR 0.70, 95% CI 0.54-0.91; $P = .007$). In 2019, the

CASPIAN trial reported for patients with extensive-stage disease randomized to durvalumab plus EP; durvalumab plus tremelimumab plus EP; or EP alone, durvalumab plus EP was associated with a significant improvement in OS (HR 0.73, 95% CI 0·59-0.91; $P = .0047$) over EP alone. The current standard of care first-line systemic therapy for extensive-stage SCLC is now chemoimmunotherapy.

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CHAPTER 58

Mediastinum and Trachea

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MEDIASTINAL TUMORS

The mediastinum is a trapezoidal structure in the center of the thoracic cavity. It is bound by the sternum anteriorly, the vertebral column posteriorly, and the lungs and pleural laterally (Figure 58.1). The diaphragm forms the floor of the mediastinum, while the thoracic outlet at the first thoracic vertebra, its rib, and the manubrium form the roof.[1] Conceptually, it is helpful to divide the mediastinum into anterior, middle, and posterior compartments, but no anatomic barriers specifically separate these regions.[2-4] The anterior mediastinum is the space anterior to the pericardium and great vessels and is occupied by the thymus, lymph nodes, and small vessels, including branches from the internal thoracic chain. The middle mediastinum is composed of the heart, proximal great vessels, central airway structures, and lymph nodes. The International Thymic Malignancy Interest Group (ITMIG) have codified these anatomic boundaries into a series of computed tomography (CT)-based radiographic standards for aiding clinical diagnosis and research.[5]

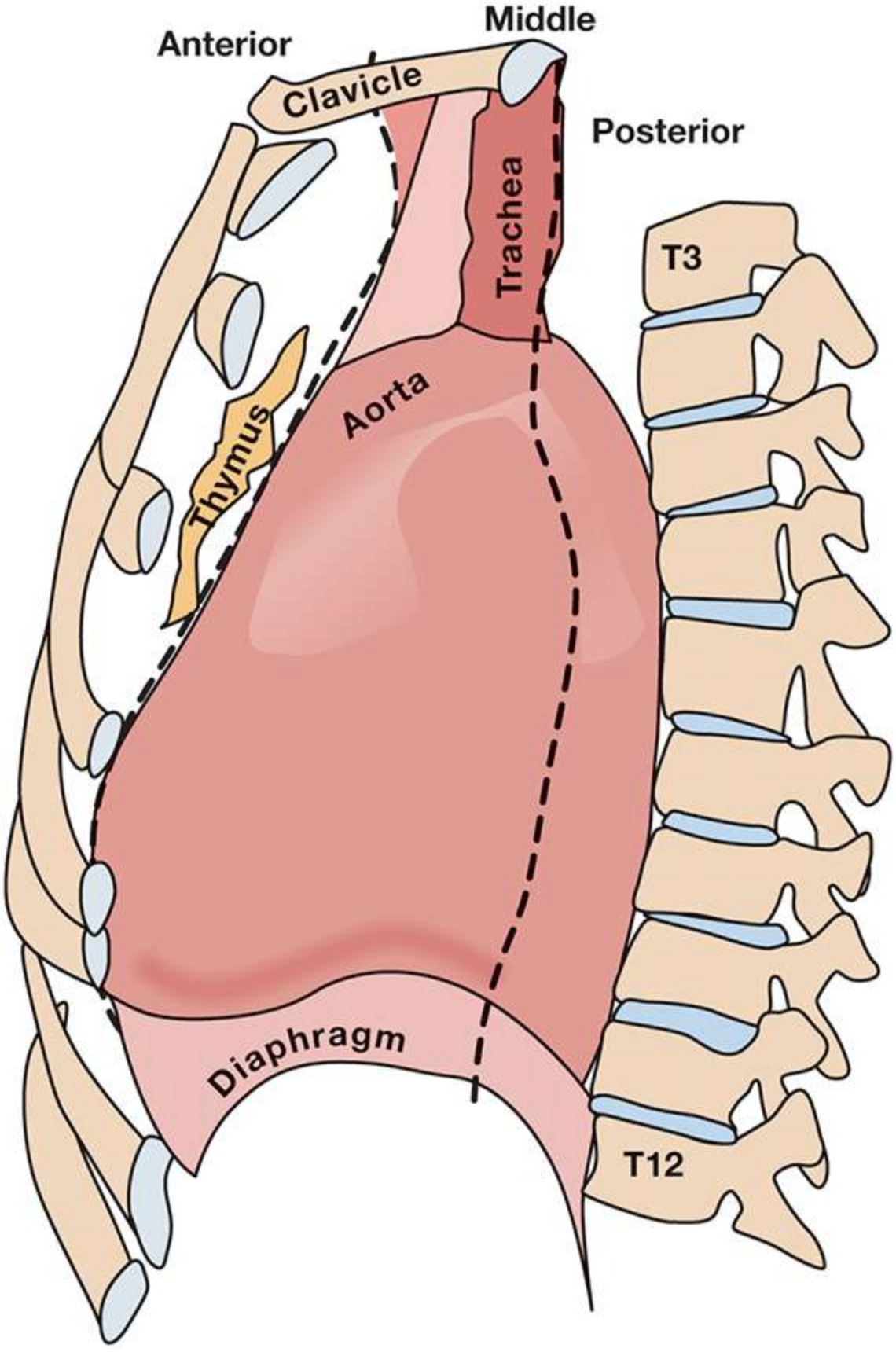
Anterior
Middle
Clavicle
Posterior
Trachea
T3
Thymus
Aorta
Diaphragm
T12

FIGURE 58.1 Anatomy of the mediastinum.

Tracheal anatomy is depicted in Figure 58.2. The posterior mediastinum is posterior to the heart and great vessels and contains the sympathetic chain ganglia, vagus nerve, thoracic duct, and esophagus. Given the number of structures within the mediastinum, it is not surprising that a heterogeneous group of malignancies can arise in this location. Thymic, neurogenic, germinal, and mesenchymal tissues may all give rise to neoplasms. The malignancies that occur within the various compartments in the mediastinum are listed in Table 58.1.

TABLE 58.1 HISTOLOGIES OF TUMORS APPEARING IN THE VARIOUS COMPARTMENTS OF THE MEDIASTINUM

Anterior (Anterosuperior)	Middle	Posterior
Thymic tumors	Lymphomas	Lymphomas
Thymomas	Cysts	Neurogenic tumors
Thymic carcinomas	Bronchogenic	Peripheral nerves
Thymic cysts	Foregut	Malignant peripheral nerve sheath tumors
Carcinoids	Pericardial	Schwannomas
Thymolipomas	Thoracic duct	Neurosarcomas
Lymphomas	Meningoceles	Sympathetic ganglia
Hodgkin disease	Mesenchymal tumors	Ganglioneuroblastomas
Non-Hodgkin lymphomas	Tracheal tumors	Ganglioneuromas
Undifferentiated	Carcinomas	Neuroblastomas
Germ cell tumors	Cardiac and pericardial tumors	Paraganglia
Seminomas	Hernias	Paragangliomas
Nonseminomas	Hiatal	Mesenchymal tumors
Embryonal carcinomas	Morgagni	Endocrine tumors
Choriocarcinomas	Vascular tumors	Esophageal tumors and cysts
Mixed germ cell tumors	Ascending aortic	Hiatal hernias
Teratomas (dermoid cysts)	Transverse arch	Lateral thoracic meningoceles
Endocrine tumors	Descending aortic	
Parathyroid adenomas	Great vessels	
Thyroid tumors	Lymphadenopathy	
Mesenchymal tumors	Inflammatory	
Amyloid tumors	Granulomatous	
Castleman disease	Sarcoidosis	
Chordomas		
Extramedullary hematopoiesis		
Fibromas, fibrosarcomas, malignant fibrous histiocytoma		

Anterior (Anterosuperior)	Middle	Posterior
Hemangiomas, hemangioendotheliomas, hemangiopericytomas		
Intrathoracic meningioma		
Lipomas, liposarcomas		
Leiomyomas, leiomyosarcomas, leiomyoblastomas		
Lymphangiomas, lymphangiosarcoma, lymphangiomyomatosis		
Mesotheliomas		
Mesenchymomas		
Myxomas		
Rhabdomyosarcomas, rhabdomyomas		
Xanthogranulomas		
Morgagni hernias		

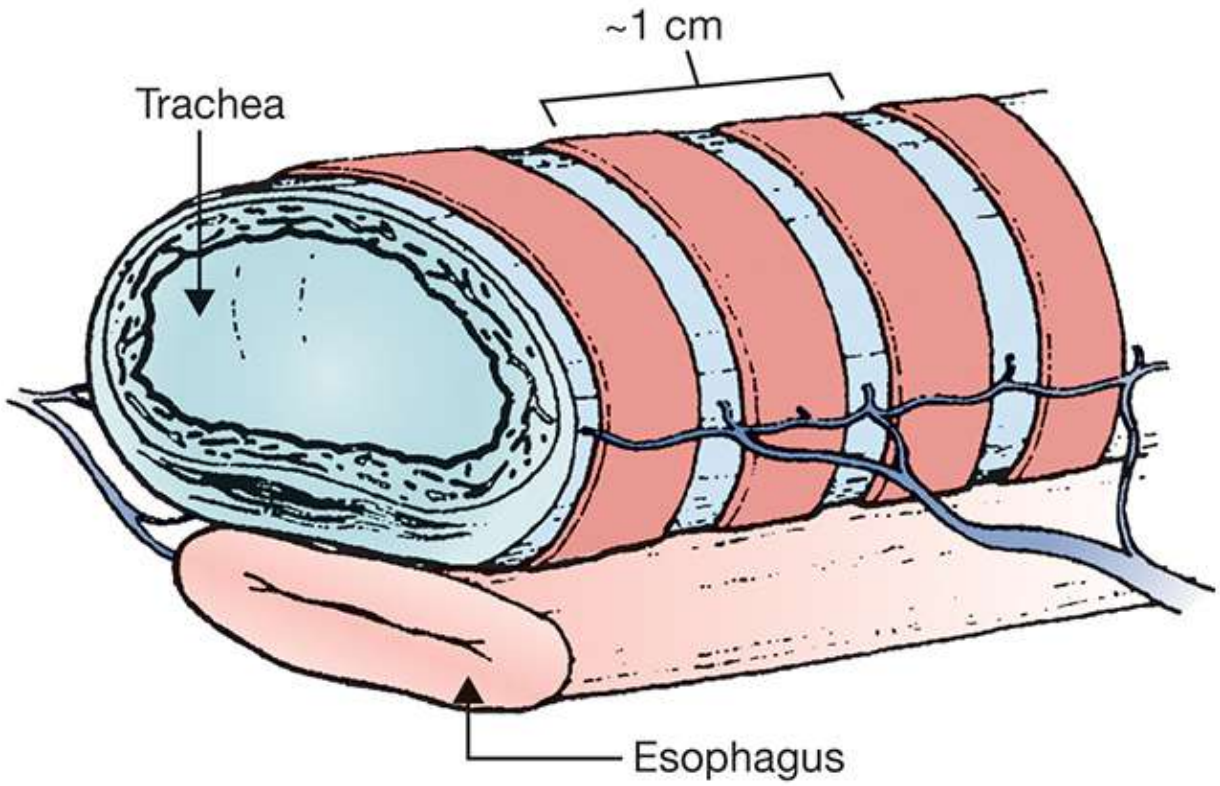

FIGURE 58.2 Representative schema of the trachea. Note the lateral longitudinal anastomotic artery running parallel to the organ and the intercartilaginous branches feeding each tracheal segment. The trachea resides in close proximity to the esophagus.

Incidence of Primary Mediastinal Tumors

Lymphomas represent the most common type of anterior mediastinal tumor and are discussed in a separate chapter. The malignancy with the next highest incidence—tumors of thymic origin—are rare and represent about 0.2% to 1.5% of all malignancies.[6] Thymic carcinomas are especially rare and account for only 0.06% of all thymic neoplasms.[7] The frequency and prevalence of primary mediastinal tumors seem to be increasing over time.[8-11] Adults generally develop thymic tumors and lymphomas, but they can also develop germ cell tumors and carcinomas.[11,12] Neurogenic tumors disproportionately develop in children.[9,13,14]

THYMOMAS

The thymus gland is an irregular lobulated lymphoepithelial organ in the anterior mediastinum. Embryologically, the thymus is derived from the endoderm of the lower portion of the third pharyngeal pouch and involutes during adulthood, gradually being replaced by adipose tissue. Its blood supply is from the internal mammary arteries, and its venous return drains to the innominate and internal thoracic veins. Its lymphatics drain into the lower cervical, internal mammary, and hilar lymph nodes.

The vast majority of thymic tumors are thymomas, 90% of which are found in the anterosuperior mediastinum; other variants occur in the middle and posterior mediastinum or neck.[15] Thymomas are epithelial tumors associated with an exuberant lymphoid component composed of immature cortical thymocytes. Although lymphomas, carcinoid tumors, and germ cell tumors can all arise within the thymus, only thymomas, thymic carcinomas, and thymolipomas arise from true thymic elements.

Epidemiology

Thymomas are exceedingly rare. The Surveillance, Epidemiology, and End Results (SEER) project reported the thymoma incidence in the United States to be 0.13 to 0.15 per 100,000 person-years.[16,17] For patients with associated myasthenia gravis, the peak age is in the fourth decade, whereas for patients without myasthenia gravis, the peak age is in the seventh decade or later.[17-23] According to the SEER data, the incidence of thymoma

increases into the eighth decade of age and then decreases.[24] Thymomas are more common in men than in women (P = .007) and are most common among Asians/Pacific Islanders (0.49/100,000 person-years).

Thymomas represent 20% of all mediastinal tumors in adults[4,12,25,26] and 15% in pediatric populations.[15] Furthermore, they are the most common tumor of the anterior mediastinum, accounting for about 30% of all such masses.[9-11,15,27,28] Though a precise causative factor has not been identified, associations of thymomas with Epstein-Barr virus, lymphoepitheliomas, radiation exposure, and cytogenetic abnormalities have been suggested.[29-35]

Natural History

Thymomas are generally characterized by an indolent growth pattern that can be locally invasive. The vast majority of thymomas are cytologically bland tumors, and approximately half of them are noninvasive.[11,23,36-46] Roughly one-third of thymomas are asymptomatic and found incidentally on the lateral component of chest x-rays.[42,43,47] Of the symptomatic thymomas, about 40% of cases present with symptoms relating to impingement of nerves and/or vessels by the intrathoracic mass, ranging from cough, chest pain, dyspnea, hoarseness, superior vena cava obstruction, and even tumor hemorrhage.[48] The remainder of symptomatic patients present with one of several paraneoplastic syndromes, the most common of which are myasthenia gravis, benign cytopenias, hypogammaglobulinemia, and polymyositis.[18,21,49-52]

Myasthenia gravis has the highest incidence among the par athymic syndromes and occurs in approximately 45% of patients with thymomas, with the reported prevalence in studies involving more than 100 patients ranging from 10% to 67%.[19,20,22,23,53,54] Conversely, only 10% to 15% of patients with myasthenia gravis have a thymoma; 60% of patients with myasthenia will have thymic lymphoid hyperplasia, and roughly 25% will have a normal thymus.[20,55-58] Thymectomy results in clinical improvement in most cases even when the thymus is normal.[59]

Myasthenia gravis is characterized by the presence of antibodies that react to nicotinic acetylcholine receptors in muscle and disrupt transmission at the neuromuscular junction or mediate receptor internalization.[55] The cardinal features are weakness and fatigability of skeletal muscles, with

most patients first experiencing fatigue in the ocular muscles followed by ptosis and diplopia, and later developing generalized weakness. More severe cases involve the proximal limb girdle muscles, and, in the worst cases, respiration can be limited.[60-62]

Other systemic symptoms occur in 5% to 10% of patients with thymomas as part of a constellation of autoimmune disorders. Souadjian and associates, in reviewing more than 500 cases of thymoma, noted that 71% were associated with systemic disease.[52] These include erythroid and neutrophil hypoplasia, pancytopenia, Cushing syndrome, DiGeorge syndrome, carcinoid syndrome, Lambert-Eaton syndrome, pernicious anemia, nephrotic syndrome, syndrome of inappropriate antidiuretic hormone hypersecretion, Whipple disease, lupus erythematosus, pemphigus, myotonic dystrophy, scleroderma, polymyositis, polyneuritis, myocarditis polyarthropathy, myotonic dystrophy, Sjögren syndrome, Addison disease, panhypopituitarism, sarcoidosis, hypogammaglobulinemia, ulcerative colitis, rheumatoid arthritis, Hashimoto thyroiditis, hyperthyroidism, hyperparathyroidism, and thyroid carcinoma.[15,63-66] Other miscellaneous diseases include hypertrophic osteoarthropathy and chronic mucocutaneous candidiasis.[65]

Several studies have also reported an excess risk of developing a second primary malignancy of approximately 15% among patients with thymoma, which is a reason why these patients mandate indefinite post-treatment surveillance.[49,50,52,67-69] An aberrant immune system is postulated to be a mechanism for the development of these metachronous malignancies.[70] The highest excess risk of subsequent malignancy appears to be for non-Hodgkin lymphoma, but thymoma patients are also at risk for upper foregut digestive system malignancies and soft tissue sarcomas.[24] Patients with higher grade and advanced-stage tumors seem to have the highest risk of metachronous extrathymic malignancies.[70]

The vast majority of thymomas are indolent, but if the tumors spread, they most commonly implant on regional pleural surfaces (the so-called “drop metastases”), which can progress to malignant pleural effusions.[18,71] Other mechanisms for metastases are uncommon for this histology. The rate of lymphogenous metastasis in a large database of 1,093 patients with thymomas was 1.8%, with 90% of positive lymph nodes located in the

anterior mediastinum.[72] Only rarely do thymomas spread hematogenously, though metastases have been reported in the liver, lung, and bone.[73]

Diagnosis

The radiographic presence of an anterior mediastinal mass is suggestive of a thymic tumor as these histologies account for the majority of masses in this location (see Table 58.1).[11] A clinical diagnosis of thymoma can sometimes be made based on the presence of an anterior mediastinal mass in conjunction with clear evidence of a parathymic syndrome, such as myasthenia. The absence of symptoms suggestive of lymphoma (fevers, weight loss, adenopathy) or tell-tale radiographic findings for rare histologies such as teratoma are further clues suggestive of a thymic malignancy.

Nonetheless, histologic confirmation is usually required to establish a definitive diagnosis. Biopsy can be performed via a fine-needle aspiration, bronchoscopy, mediastinoscopy, video-assisted thoracoscopy (VATS), or open biopsy. Historically, biopsies were assumed to be relatively contraindicated because of a concern for tumor spillage into the pleural space when the capsule was breached.[74,75] However, no cases of seeding of a needle tract or the biopsy site have been reported in recent series, and only three recurrences in thoracotomy scars have been reported.[76,77] In fact, multivariate analysis in one series of 136 patients being treated for thymomas showed better survival among patients who underwent biopsy before surgery ($P = .056$).[50] Therefore, many centers routinely obtain biopsy samples of anterior mediastinal tumors for histologic assessment.[20,49,76,78-81]

When thymoma is suspected or confirmed, the diagnostic workup begins with a careful evaluation of myasthenia gravis. Routine blood work for commonly associated syndromes should be done, with serum α-fetoprotein and β-human chorionic gonadotropin in men to rule out a germ cell tumor.[82] In addition to laboratory studies, imaging is a hallmark of thymoma diagnosis and treatment planning.

Plain film chest x-rays were historically the main diagnostic modality for identifying and measuring thymic tumors. Thymomas tend to appear as ovoid, smooth, and unilateral mass occupying the space between the thoracic inlet and the cardiophrenic angle.[83] More advanced presentations

may present an irregular border between the mediastinum and the lung, suggesting lung invasion, or elevation of the diaphragm if the phrenic nerve has been infiltrated.

Contrast-enhanced CT is the most common technique for visualization of thymomas and other anterior mediastinal masses.[45,84-86] Magnetic resonance imaging (MRI) can provide more detail when needed, delineating the musculoskeletal anatomy and neurovascular structures of the mediastinum.[87-89] MRI may also improve sensitivity for defining the soft tissue extent of the mass in addition to providing information regarding tumor grade and invasiveness beyond that which can be gleaned from CT. Common features indicative of a high-grade tumor include low T2-signal foci within the mass, the presence of mediastinal lymphadenopathy, an incomplete capsule, and/or inhomogeneous enhancement (Figure 58.3).[90,91]

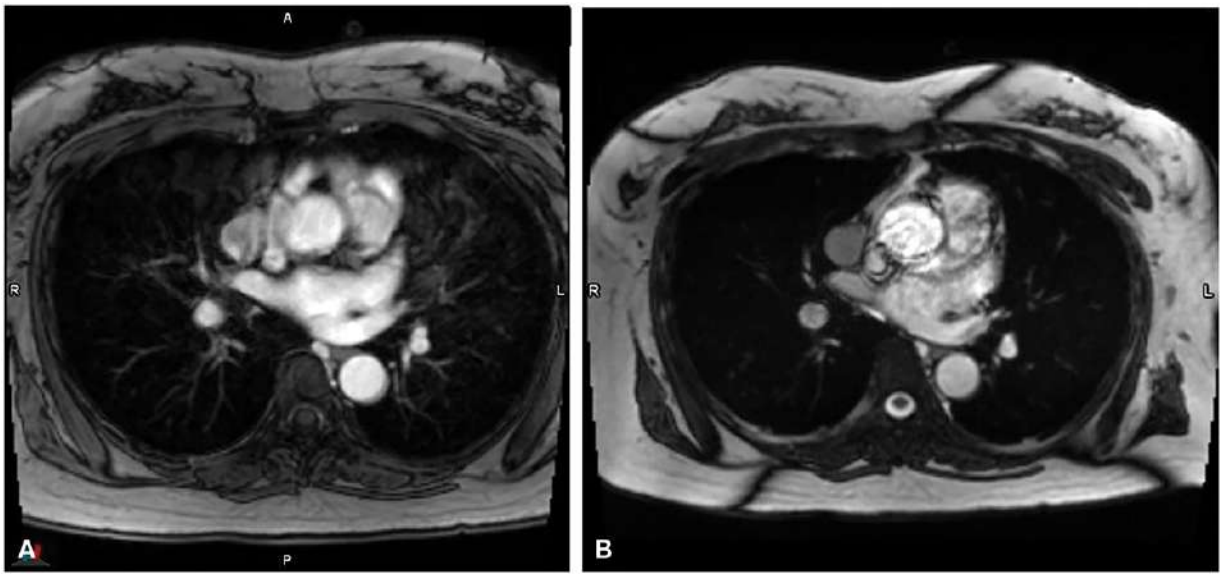

FIGURE 58.3 Magnetic resonance imaging of the chest for a patient with type AB thymoma. A. The lesion shows rapid enhancement on T1 postcontrast image. B. The lesion is T2 hyperintense compared with muscle on T2-weighted series.

The use of ^{18}F-fluorodeoxyglucose positron emission tomography (PET) is expanding for visualizing several types of malignancies, including thymoma. In the mediastinum, the results of PET can be confounded by the physiologic uptake of fluorodeoxyglucose by the thymus in children and young adults.[92-95] Nevertheless, this imaging modality has continued to

show promise for disease detection and for evaluating prognosis. Recent studies have shown that not only can PET improve the sensitivity of diagnosis, but it also can be helpful for establishing the grade of the disease and for distinguishing thymoma from thymic carcinoma, as the latter tends to have significantly higher metabolic activity.[96-100] In terms of distinguishing between lower and higher risk thymomas, maximum standardized uptake value may lack sensitivity, though some emerging data suggest that homogeneously distributed uptake is more characteristic of lower risk thymomas (types A, AB, and B1).[101]

In one provocative study in which 49 patients with thymic tumors underwent PET imaging, the rate of fluorodeoxyglucose uptake was compared with the expression of several biologic markers, including GLUT1, GLUT3, HIF-1α, vascular endothelial growth factor (VEGF), microvessel density, CD31 and CD34, p53, and bcl-2. The authors found a direct correlation between fluorodeoxyglucose uptake on PET and expression of GLUT1, HIF-1α, VEGF, and p53 as well as microvessel density, and several of these markers also correlated with tumor grade.[102] Predicting the presence of HIF-1α may also be germane to therapeutic strategies that seek to match radiation dose to the presence of hypoxia and its associated radioresistance in the tumor microenvironment.[101]

These findings are important because they imply that metabolic response may be a viable marker for measuring treatment efficacy. Figure 58.4 demonstrates PET findings from a patient with locally advanced thymoma treated with trimodality therapy. Indium 111-octreotide, carbon-11 methionine, and gallium-67 citrate, two other nuclear medicine agents, have also been reported to show some activity for thymic malignancies, but utilization of these modalities has been limited by their lack of sensitivity in distinguishing benign conditions such as thymic hyperplasia from frank neoplasia.[83,103]

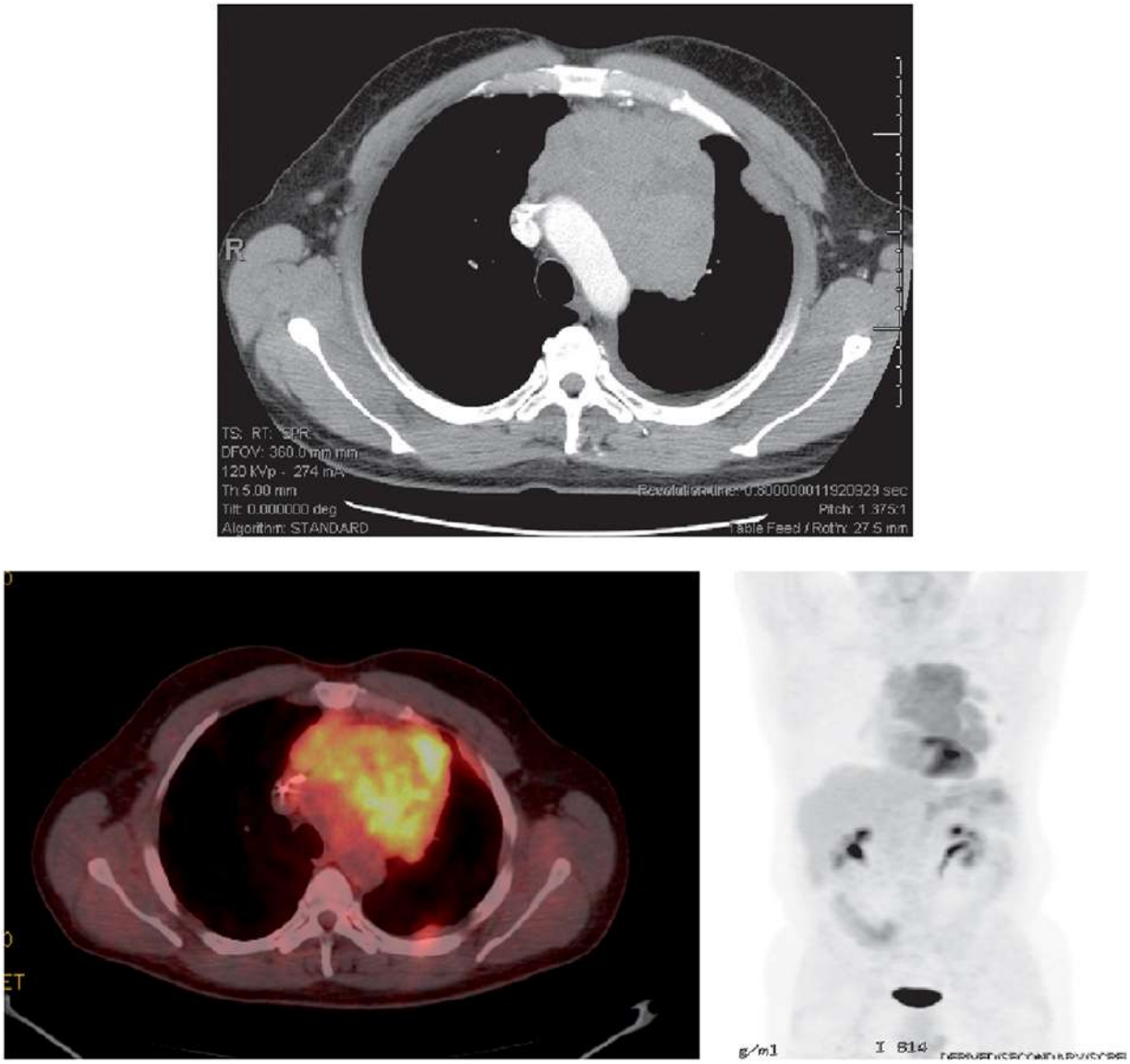

FIGURE 58.4 Positron emission tomography (PET) scanning in thymic malignancies. PET imaging has been shown to aid in delineating the extent of disease and assessing for metastases.

Pathologic Classification

The varied appearances and the frequent absence of classic malignant features have made thymomas challenging to classify pathologically. Disagreements on the prognostic importance of certain pathologic features have led to multiple proposed classification systems (Table 58.2). Indeed, even simple terminology such as “invasive versus noninvasive” or “benign versus malignant” has not accurately captured clinical behavior.

Recurrences and metastases after resection have been reported in all large series,[19,20,104-106] regardless of disease stage or histologic subtype.[18-20,22,23,44,49,50,105-113] Ultimately, even bland-appearing, noninvasive thymomas have the fundamental characteristics of a malignant tumor in their ability to recur and metastasize.

TABLE 58.2 THYMOMA CLASSIFICATION SYSTEMS

Bernatz et al[114]	Muller-Hermelink and Kirchner[115]	Suster and Moran[711]	WHO[123]
Spindle cell	Medullary	Thymoma, well differentiated	Type A
–	Mixed		Type AB
–	Predominantly cortical		Type B1
Lymphocyte rich	Cortical		Type B2
Lymphoepithelial			
Epithelial rich	Well-differentiated thymic carcinoma	Atypical thymoma	Type B3
–	High-grade thymic carcinoma	Thymic carcinoma	Type C

WHO, World Health Organization.

A historical perspective of thymoma classification systems is illustrative of the challenges of pathologic classification for thymoma. The earliest system, proposed by Bernatz, identified four categories based on the predominant cell type: lymphocytic, epithelial, mixed, and spindle cell.[114] In practice, this classification system is poorly correlated with clinical prognosis. Verley and Hollman later also identified four categories: spindle or oval, lymphocyte rich, differentiated epithelial cell rich, and undifferentiated epithelial.[105] The first three types are cytologically bland, whereas the fourth category includes pleomorphic tumors with high numbers of mitoses and atypia, which are also considered thymic carcinoma. Unfortunately, this categorization also did not correlate well with prognosis.

A third classification system based on work by Muller-Hermelink and associates based classification on the different subsets of epithelial cells found in the thymus: cortical, medullary, mixed cortical and medullary, and

well differentiated.[115] Although this system was widely used, again no consistent correlation between epithelial cell morphology and clinical prognosis has been validated.[116] Although some associations have been found, such as cortical thymomas behaving more aggressively and being more often associated with myasthenia gravis, several multivariate analyses have shown that the Muller-Hermelink classification system is not an independent predictor of survival, casting doubt on the link between this histologic classification and prognosis.[18,21,78-80,105,109,116-120] Another confounder for these classification schemes is that they do not consistently correlate with other schemes.[116] Concordance rates for thymomas classified independently by a panel of pathologists were often as low as 35% within one system, although two small studies demonstrated 78% concordance when using the Muller-Hermelink classification system.[121,122] The poor correlation between the histopathology of thymomas and their potential for aggressive malignant behavior or systemic syndromes underlines the need for a consistent and predictive classification system,[45] The current system—the World Health Organization (WHO) classification—represents an important step in this direction, though further refinement that perhaps includes a molecular component will likely be required.

The WHO classification, first proposed in 1999 and currently in its fifth iteration as of 2021, is similar to the Muller-Hermelink system but recognizes six different types of thymic tumors (A, AB, B1, B2, B3, C; see Table 58.2).[123-125] Type A tumors are composed of neoplastic oval or spindle-shaped epithelial cells without atypia or lymphocytes. Type AB is similar to type A, but with foci of lymphocytes. Type B tumors consist of plump epithelioid cells that can be subdivided into three subtypes defined by increasing proportions of epithelial cells and increasing atypia. Type B1 tumors resemble normal thymic cortex with areas similar to thymic medulla. Type B2 tumors have scattered neoplastic epithelial cells with vesicular nuclei and distinct nucleoli among a heavy population of lymphocytes; perivascular spaces are prominent, and a palisading effect of tumor cells along the perivascular spaces may be present. Type B3 is composed of predominantly round or polygonal epithelial cells exhibiting mild atypia admixed with a minor component of lymphocytes; thus, this type resembles what others have described as well-differentiated thymic carcinoma. Thymic carcinomas are designated type C tumors and have

cytologic atypia and a cytoarchitecture resembling carcinoma that is distinctively unlike normal thymus tissue.[126]

Concordance rates among different pathologists using the WHO system were reported to be 90% and 95% in two independent studies.[127,128] The most clinically distinct subtypes are type B3, formerly known as well-differentiated thymic carcinoma, and type C, thymic carcinomas. The clinical characteristics associated with the other WHO subtypes still vary considerably, but the WHO system at least seems to correlate well with Masaoka stage (Table 58.3) in studies in which patients were analyzed with the WHO system.[126] The vast majority of type A and AB tumors are Masaoka stage I or II, and the B subtypes tend to resemble the higher Masaoka stages.[126]

TABLE 58.3 MASAOKA STAGING SYSTEM FOR THYMOMAS

Stage		Description
I		Macroscopically completely encapsulated, with no microscopic capsular invasion
II	a	Macroscopic invasion into surrounding mediastinal fatty tissue or mediastinal pleura
	b	Microscopic invasion into the capsule
III		Macroscopic invasion into surrounding organs
IV	a	Pleural or pericardial implants/dissemination
	b	Lymphagenous or hematogenous metastases

Adapted from Masaoka A, Monden Y, Nakahara K, Tanioka T. Follow-up study of thymomas with special reference to their clinical stages. *Cancer*. 1981;48(11):2485-2492. Copyright © 1981 American Cancer Society. Reprinted by permission of John Wiley & Sons.

With regard to prognosis, the WHO system has been found to have independent prognostic value for disease-specific survival, with only two small studies indicating that stage was the only prognostic variable.[126] Most of the prognostic value of the WHO classification is attributable to type C having distinctly worse survival,[129-131] but even studies that excluded type C could demonstrate WHO type as having independent prognostic value.[131,132]

More recent pathologic studies have provided intriguing insights into prognostic histologic features. In one such study by Shim and colleagues

that involved assessing the effect of stromal lymphocytic infiltration in thymic carcinoma,[133] patients with low levels of $CD4^+$ lymphocytes and $CD20^+$ lymphocytes within the tumor stroma were found to have lower survival rates, and various combinations of $CD4^+$, $CD8^+$, and $CD20^+$ cells were particularly predictive of worse survival outcomes. These authors concluded that these lymphocytes may work together to suppress cancer progression and that combinations of them may be useful for stratifying patients in terms of long-term prognosis.[133]

Molecular Characterization

During the past several years, pathologic classification systems for several thoracic malignancies have been refined by the incorporation of molecular markers, including expression of subtype-specific markers at the RNA/protein level and identification of somatic mutational alterations in tumor DNA. These findings have tried to bridge the gaps between the histology of normal cortical and medullary epithelium and the genetic alterations present in tumors, and these efforts remain a work in progress with room for ongoing improvement.[134] Inspired by the efforts to identify targeted therapies in other nonthymic malignancies, several studies have shown elevated expression of the epidermal growth factor receptor (EGFR) in large percentages of thymic malignancies, similar to what is observed among non–small cell lung cancer (NSCLC) and other epithelial cancers.[135-138] However, increased EGFR expression in thymoma is rarely associated with accompanying mutations,[139-141] and targeted EGFR inhibitors have not shown consistent improvements in thymic tumor response or disease control rates.[142-144] Other signaling pathways that often show overexpression are the VEGF,[145] IGF-1R,[146] and KIT pathways,[147,148] although, again in most circumstances, the overexpression takes place mainly in thymic carcinomas rather than thymomas. Beyond expression targets with therapeutic relevance, a recent study has identified frequent POU2F3 expression in thymic carcinoma with squamous differentiation.[149] POU2F3 has recently emerged as a molecular subtype of small cell lung cancer and may represent a dependency for tumor growth.[150]

Patterns of somatic mutational alterations have been well defined with array-based comparative genome hybridization and next-generation

sequencing. Two major findings have been described, largely in a mutually exclusive manner. For patients with type A and AB thymomas, point mutations in general transcription factor II-I are present in upward of 80% of cases and associated with improved overall survival.[151,152] The mutations are missense variants (p.L424H) that are unique to thymoma and not observed in other malignancies, thought to alter expression of transcriptional targets though ultimately incompletely understood. Type A and AB thymomas are also associated with expression of a large microRNA cluster on chromosome 19 associated with the PI3K pathway with unclear therapeutic relevance.[153] By contrast, copy number alterations are frequently observed in B-subtype thymomas and thymic carcinoma.[154] Alterations are typically low-level gains without amplifications. Some alterations are shared between thymoma and thymic carcinoma (such as 1q gain, 3p loss, and 6 loss), while others can demonstrate a mutually exclusive relationship between histologies (such as 7p or 7q gain in thymoma and 8q24 gain and 16q loss in thymic carcinoma).

These historical findings have been validated in a project from the Cancer Genome Atlas Project to molecularly subtype thymic epithelial tumors using a data set of 120 patients using multi-omic approaches incorporating DNA mutational analysis, messenger RNA (mRNA) expression, and somatic copy number alterations.[155] This tour de force analysis identified four distinct molecular subtypes that largely reflected the known WHO subtypes. The first two were characterized, respectively, by G2F2I mutation or mRNA clusters associated with T-cell signaling expression. The next two subtypes were characterized by the presence or absence of chromosomal stability based upon somatic copy number. These subtypes were associated with disease-free and overall survival. As in other malignancies like breast cancer, the identification of molecular subtypes holds promise for novel strategies in the identification of targeted therapies, though no efforts have been successful to date.

Staging

The most commonly used staging system for thymomas was published by Masaoka and associates in 1981 (Table 58.3).[107,156] Staging is based on the extent of either macroscopic or microscopic invasion into structures

including the thymoma capsule and surrounding mediastinal structures at the time of surgery. Other groups have tried to improve upon the Masaoka system. For example, the French Groupe d'Etudes des Tumeurs Thymiques classification (Table 58.4) incorporates completeness of resection, which may be of prognostic value but does not allow patients to be compared independent of treatment factors.[157]

TABLE 58.4 GROUPE D'ETUDES DES TUMEURS THYMIQUES (GETT) THYMOMA STAGING SYSTEM

Stage		Description
I	a	Encapsulated tumor, completely resected
	b	Macroscopically encapsulated tumor, completely resected Surgeon suspects mediastinal adhesions and potential capsular invasion.
II		Invasive tumor, completely resected
III	a	Invasive tumor, subtotal resection
	b	Invasive tumor, biopsy only
IV	a	Distant pleural implants or supraclavicular metastasis
	b	Distant metastasis

From Gamondes JP, Balawi A, Greenland T, et al. Seventeen years of surgical treatment of thymoma: factors influencing survival. *Eur J Cardiothorac Surg*. 1991;5(3):124-131. Reproduced by permission of European Journal of Cardio-Thoracic Surgery.

It is a testament to the robustness of Masaoka classification system that it has persisted nearly unchanged for 30 years. But despite its popularity, areas of ambiguity have persisted, especially with regard to the Masaoka system's tendency to incorporate both clinical and pathologic data. For instance, some clinicians have questioned the precision with which one can assess that a "tumor is adherent to but not breaking through mediastinal pleura." After all, the mediastinal pleura is not typically in the pathologic specimen.[158] Therefore, a group headed by the ITMIG proposed a new staging classification in 2013 based upon TNM staging principles.[159] The T-stage—which still drives staging does not distinguish between encapsulated and unencapsulated tumors. Staging is broken down as the presence or absence of microscopic invasion into mediastinal fat (T1a), invasion into mediastinal pleura (T1b), pericardium (T2), "more resectable" organs (T3),

and “less or unresectable” organs (T4).[160] Although it remains to be seen whether this staging system can provide better prognostic information above historical staging systems, at the very least, it provides a standard template for communication among physicians and for the design of collaborative trials, an essential contribution by the staging system for the investigation of a rare disease like thymoma. There are challenges in using the new TNM staging system to make decisions regarding the need for adjuvant radiation therapy as the data on the role for adjuvant radiation therapy are predominantly based on the Masaoka staging system. Table 58.5 is a helpful tool to extrapolate Masaoka staging system[156] to the TNM staging system in order to help with making recommendations for adjuvant therapy.[161]

TABLE 58.5 COMPARISON BETWEEN THE MODIFIED MASAOKA STAGING SYSTEM AND TNM-BASED STAGING SYSTEM FOR THYMIC EPITHELIAL TUMORS INCLUDED IN THE AJCC EIGHTH EDITION CANCER STAGING MANUAL

Descriptors	Modified Masaoka Clinical Staging of Thymoma[156]	Eighth Edition of the AJCC Staging System[159,160]
Encapsulation	I—Macroscopically and microscopically completely encapsulated	T1a—Encapsulated or unencapsulated, with or without extension into mediastinal fat
Involvement beyond capsule	IIA—Microscopic transcapsular invasion	T1a—Encapsulated or unencapsulated, with or without extension into mediastinal fat
	IIB—Macroscopic invasion into surrounding fatty tissue or grossly adherent to but not through mediastinal pleura or pericardium	T1b—Involvement of mediastinal pleura
Involvement of pleura, pericardium, great vessels, or neighboring organs	III—Macroscopic invasion into neighboring organs (ie, pericardium, great vessels, or lung)	T2—Involvement of pericardium T3—Involvement of lung, brachiocephalic vein, superior vena cava, chest wall, phrenic nerve, chest wall, hilar (extrapericardial) pulmonary vessels T4—Involvement of aorta, arch vessels, main pulmonary artery,

Descriptors	Modified Masaoka Clinical Staging of Thymoma[156]	Eighth Edition of the AJCC Staging System[159,160]
		myocardium, trachea, or esophagus
Nodal involvement	IVB—Lymphogenous or hematogenous metastasis	N0—No nodal involvement
		N1—Anterior (perithymic) nodes
		N2—Deep intrathoracic or cervical nodes
Metastatic spread	IVA—Pleural or pericardial dissemination	M0—No metastatic disease
	IVB—Lymphogenous or hematogenous metastasis	M1a—Separate pleural or pericardial nodule(s)
		M1b—Pulmonary intraparenchymal nodule or distant organ metastasis

AJCC, American Joint Committee on Cancer.

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Prognostic Factors

The two factors that have consistently demonstrated prognostic value in multivariate analyses in large studies are tumor invasiveness (ie, disease stage) and completeness of resection.[18,19,21,22,36-38,43,49,50,78,104,107,162-165] Disease stage has proved important for prognosis in every large study.[18-20,22,23,44,49,50,104,107,166] Mean overall survival rates at 15 years are 78% for those with stage I disease, 73% stage II, 30% stage III, and 8% for stage IV disease (Table 58.6).[19] At 10 years, mean disease-free survival rates are 92% for those with stage I disease, 87% stage II, 60% stage III, and 35% for stage IV (recurrence rates are summarized in Table 58.7).[19,22,104,117,165]

TABLE 58.6 OVERALL SURVIVAL RATES FOR PATIENTS WITH THYMOMAS AT 5 AND 10 YEARS

Study	Institution	Study Years	n	%R0	5-Y Survival				10-Y Survival			
					I	II	III	IV	I	II	III	IV
Kondo and Monden[53]	JACS	1990-1994	924	92	100	98	89	71	100	98	78	47
Regnard et al[712]	ML, Paris	1955-1993	307	85	89	87	68	66	80	78	47	30
Maggi et al[20]	Torino	Before 1991	241	88	89	71	72	59	87	60	64	40
Rena et al[131]	Torino	1988-2000	175	84	100	100	100	100	100	100	85	–
Zhu et al[713]	Fudan, Shanghai	1989-2002	175	89	100	96	78	57	–	–	–	–
Nakahara et al[23]	Osaka	Before 1988	141	80	100	92	88	47	100	84	77	47
Wilkins et al[50]	Johns Hopkins	1957-1997	136	68	84	66	63	40	75	50	44	40
Rea et al[714]	Padua	1970-2001	132	82	93	93	60	36	84	82	51	0
Blumberg et al[49]	MSKCC	1949-1993	118	73	95	70	50	100	86	54	26	0
Quintanilla-Martinez et al[117]	MGH	Before 1994	116	94	100	100	70	70	100	100	60	0
Pan et al[21]	Taipei	1961-1991	112	80	94	85	63	41	87	69	58	22
Elert et al[184]	Wurzburg	1957-1988	102	–	83	90	46	–	–	–	–	–

JACS, Japanese Association for Chest Surgery; MGH, Massachusetts General Hospital; ML, Marie Lannelongue Hospital, Le Plessis-Robinson, France; MSKCC, Memorial Sloan Kettering Cancer Center; R_0, complete resection.

TABLE 58.7 RECURRENCE RATES OF THYMOMAS

Study	Institution	Study Years	n	% Receiving R0	% Receiving Chemo	% Receiving RT	5-Y Recurrence Rates by Stage I	II	III	IVa
Kondo and Monden[53]	JACS institutions	1990-1994	862	100	12	32	1	4	28	34
Regnard et al[712]	ML, Paris	1955-1993	307	85	few	half	4	7	16	58
Maggi et al[20]	Torino	Before 1991	241	88	7	12	2	13	30	25
Wright et al[715]	MGH	1972-2003	179	90	–	–	0	0	22	41
Rena et al[131]	Torino	1988-2000	178	84	13	43	1.6	8.6	28	40
Zhu et al[713]	Fudan, Shanghai	1989-2002	175	80	14	97	4	2.4	43	57
Cowen et al[27]	FNCLCC	1979-1990	149	42	100	50	0	7	23	25
Wilkins et al[46]	Johns Hopkins	1957-1997	136	68	7	37	8	10	24	0
Blumberg et al[49]	MSKCC	1949-1993	118	73	32	58	4	21	47	80
Ruffini et al[106]	Torino	1974-1993	114	100	–	25	5	10	30	33

FNCLCC, Federation Nationale des Centres de Lutte Contre le Cancer; JACS, Japanese Association for Chest Surgery; MGH, Massachusetts General Hospital; ML, Marie Lannelongue Hospital, Le Plessis-Robinson, France; MSKCC, Memorial Sloan Kettering Cancer Center; R_o, complete resection; RT, radiation therapy.

The extent of resection is the other major factor consistently identified as being prognostic in thymic malignancies.[19,49,50,167-169] Patients for whom complete (R_0) resections can be done have significantly better survival than do those with R_1 or R_2 resections.[107,170] R_0 resections are almost always possible for stage I tumors, but resectability rates decrease on average to 50% for stage III tumors.[20,23,44,107]

As mentioned previously, the WHO histology classification was found to be independently associated with prognosis. Major studies reporting

analyses of stage, histology, and resection status as independent predictors of survival in thymic tumors are summarized in Table 58.8. Other potential prognostic factors are tumor size and the presence of symptoms.[18,49,109] Interestingly, although bulky tumor size was classically defined in terms of a 10-cm threshold, a more recent publication of 154 consecutive patients with thymic epithelial tumors treated in the modern era (2000-2014) demonstrated that a size greater than 4 cm was associated with worse relapse-free survival, even among patients with stage I disease.[171] With regard to symptoms, older series reported that patients with parathymic syndromes such as myasthenia gravis and other autoimmune diseases fared worse than those without such syndromes,[46,49,165] but this finding has not been replicated in newer series.[19,22,23,50,79,80,107,109,163,172-174] Indeed, some studies have found survival to be better for patients with myasthenia gravis,[20,50,175] perhaps because of earlier detection of thymomas.[49,176-178] A study published in 2005 indicated that myasthenia gravis, present in 25% of 1,089 patients from Japan,[54] did not affect 5-year overall survival rates among patients with stage III disease. For patients with stage IV disease, 5-year overall survival rates were 85.1% for patients with myasthenia gravis versus 63.9% for patients without. R_0 resection was accomplished in a significantly higher proportion of patients with myasthenia gravis (60%) than those without it (38%).

TABLE 58.8 RESULTS OF MULTIVARIATE ANALYSES OF FACTORS PREDICTING THYMOMA-SPECIFIC SURVIVAL

				Histology	Stage	R_0
Study	**Institution**	**Study Years**	**n**	***P* Value**		
Okamura et al[716]	Osaka	1957-2000	273	.05	.0001	NS
Rieker et al[717]	Heidelberg	1967-1998	218	<.0024	<.001	–
Wright et al[715]	MGH	1972-2003	179	.004	.002	NS
Rena et al[131;a]	Torino	1988-2000	178	.014	.012	.0001
Park et al[128;b]	Yonsei	1992-2002	150	.019	<.001	0.47
Rea et al[714;b]	Padua	1970-2001	132	.0001	.003	NS
Kondo et al[718;b]	Tokushima	1973-2001	100	NS	.04	<.05

MGH, Massachusetts General Hospital; NS, not statistically significant; R_0, complete resection.

[a]Type C excluded.

[b]Overall survival instead of disease-free survival.

Another potential prognostic factor is patient age. Patients older than 30 to 40 years may have a better prognosis than younger patients.[18,78,165] Thymomas in children seem to follow a more malignant course than those in adults.[179] Fortunately, malignant thymomas in children are extremely rare.[180]

General Management

The number of treatment modalities that have shown activity for thymoma are numerous and include surgery, radiation, cytotoxic chemotherapy, immunotherapy, and targeted agents. The optimal utilization and sequencing of these treatments is not well defined by randomized prospective trials. Therefore, treatment selection for these tumors can be daunting. The ITMIG, therefore, advocates that patients with thymic epithelial tumors are best served in a setting in which multimodality consultation can occur prior to initiation of treatment.[181] The authors agree that multidisciplinary consultation is critical to achieve best outcomes.[182]

Surgery

Surgical resection is the mainstay of treatment for thymomas. A complete en bloc surgical resection (R_0) remains the treatment of choice for all thymomas, regardless of invasiveness, except in rare, advanced cases with extensive intrathoracic or extrathoracic metastasis. Fortunately, the vast majority (90%-95%) of thymomas are localized.[183] Operative mortality rates average 2.5% (range 0.7%-4.9%).[18-20,23,44,49,104,184] Resectability rates for stage I thymomas should approximate 100%, but those rates vary widely for higher stage thymomas: 43% to 100% (mean 85%) for stage II, 0% to 89% (mean 47%) for stage III, and 0% to 78% (mean 26%) for stage IV.[104]

Because the completeness of resection is such an important prognostic factor, an aggressive surgical approach is justified to remove as much of the lesion as possible at surgery. If residual microscopic disease is suspected of

being present (an R_1 operation), metallic clips should be placed to help delineate the radiation field. Whether subtotal resections are beneficial is controversial, with some authors demonstrating better survival when debulking takes place before adjuvant radiation therapy[20,23,53,107,108,165] and others finding no benefit from debulking over biopsy alone.[19,20,23,49,78,157,165,175,185] One large study found significant differences in 5-year survival rates among patients undergoing subtotal resection versus biopsy only (64% vs 36%) but little difference in 10-year survival rates, suggesting that any benefit may be only in intermediate- term survival.[53] Resection for thymomas should include a lymph node dissection, including dissection of the deep thymic region (N2) lymph nodes for more advanced tumors.[186]

Traditional surgical techniques for patients with stage I thymic tumors produce 5-year survival rates in excess of 90%, with survival rates decreasing slightly at 10 years,[20,23,66] and with local recurrence rates of less than 5%. For stages II and III disease, recurrence rates after surgery alone range from 10% to 47%. In a study of more than 100 patients previously treated for thymoma, causes of death were as follows: 38% were related to thymoma (range 19%-58%), 9% to postoperative causes (range 2%-19%), 22% to myasthenia gravis (range 16%-27%), 9% to other autoimmune diseases (range 2%-19%), and 29% to unrelated causes (including other cancers) (range 8%-47%).[18-20,22,23,44,50,105,108,117,165] Recurrence rates are summarized in Table 58.7.

The use of minimally invasive techniques including VATS thymectomy and robotic thymectomy has come into use over the past decade. Video-assisted techniques are generally accepted for benign conditions of the thymus, but their appropriateness in oncologic settings is a matter of active investigation. A Japanese center reported on using this procedure to treat 35 patients with clinical stage I thymoma from 1998 to 2009.[187] The authors reported the technique to be safe, with no perioperative deaths and three minor complications. Disease in 20 of the 35 patients was upstaged to Masaoka stage II or III at the time of surgery. At an average follow-up time of 65 months, one patient had experienced recurrence in the bilateral lung.[187] Similarly, a Polish group reported on 24 patients operated on for thymoma with VATS, which resulted in no operative mortality and one

bleeding complication.[188] Finally, a Chinese center reported on comparative outcomes between 15 patients with early-stage thymoma with myasthenia gravis treated with VATS and 18 patients treated with the trans-sternal technique. The VATS patients achieved similar perioperative morbidity and significantly better neurologic outcomes, although the authors noted that selection bias may have influenced the latter finding as the open sternotomy patients had, on average, more advanced tumors.[189]

Despite this promising safety profile, it is an open question whether the oncologic outcomes will be the same as open procedures. Nakagiri et al compared 45 patients with early-stage thymoma who underwent VATS thymectomy with 29 patients who underwent open sternotomy.[190] They noted that all three cases of pleural recurrence occurred in the VATS group. Their conclusion was that VATS was oncologically feasible but that the technique should be favored for patients for whom en bloc resection is likely; special caution should be exercised for large or cystic tumors, for which the risk of capsular injury and tumor spillage is high.

Robotic surgical techniques have also become an accepted approach at specialized centers. The potential advantages of robotic techniques include increased rates of preserved pulmonary function, improved cosmesis, and higher rates of patient compliance because of the minimally invasive nature of the surgery.[191] The improved visualization and versatility of the robotic technique may allow for increased radicality of thymectomies by allowing surgeons to achieve resections in challenging anatomies such as patients with tumor located between the aorta and innominate vein or in those with encasement of the left phrenic nerve.[192]

Several institutions have explored the use of robotics in thymectomy, and a few studies have been published. Rückert et al demonstrated the feasibility of this technique for patients undergoing thymectomy for myasthenia gravis.[193] That same group of investigators then published a retrospective cohort study comparing robotic and nonrobotic thoracoscopic thymectomy and found that rates of remission of myasthenia gravis were actually higher for patients who had received a robotic thymectomy; the authors attributed this finding to the potential for improved mediastinal dissection with the robotic technique.[194] A survey of the utilization of robotic techniques published in 2013 revealed that nearly 3,500 robotic

thymectomy cases had been performed at approximately 100 centers worldwide.

Finally, surgeons have recently asked whether patients with early-stage thymoma and no evidence of myasthenia may be served by thymomectomy (removal of the tumor alone, akin to a wide local excision) rather than complete thymectomy. Tseng et al reported on a cohort of 95 patients treated at a Taiwanese center between 2002 and 2011.[195] Forty two patients underwent thymomectomy, while 53 underwent complete thymectomy. As expected, patients undergoing thymomectomy had lower morbidity and shorter hospitalizations. Intriguingly, after a median follow-up of 57 months, neither the rate of tumor recurrences nor myasthenia neurologic outcomes were significantly different in the two groups. A separate retrospective series of thymomectomy with or without extended thymectomy for patients with stage I or II thymomas did not report a difference in tumor recurrence rates with a more limited resection.[196] As these are nonrandomized retrospective studies with limited patient numbers and length of follow-up, the results should be interpreted with caution. Nevertheless, minimizing not just surgical technique, but also the surgical target itself, is a compelling subject for further inquiry.

The appropriate use of these newer surgical techniques and surgical paradigms will clearly evolve as more evidence is collected on their safety and oncologic efficacy. Publication of long-term outcomes and development of clinical trials, whenever possible, will be critical for defining the role of these novel approaches in the spectrum of thymic malignancies.

Patterns of Failure

The pattern of failure in the overwhelming majority of thymomas is locoregional: 81% of recurrences are local, 9% are distant, and 11% are both.[18,19,44,49,105,106] Figure 58.5 demonstrates that, although recurrences in a radiation field are rare, a significant number of intrathoracic recurrences are observed along pleural surfaces.[197]

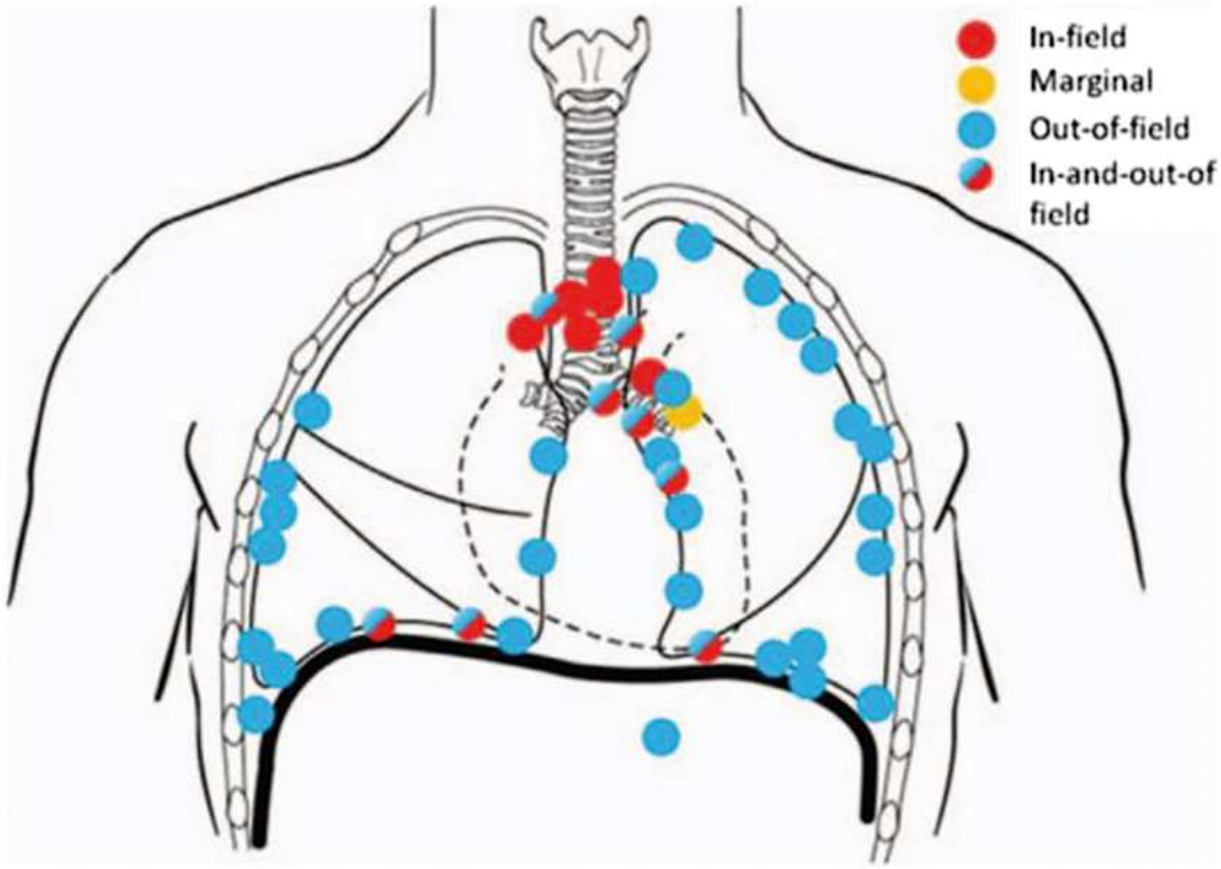

FIGURE 58.5 Graphical illustration of failure patterns following radiotherapy for stages II to IV thymoma. (Reprinted from Rimner A, Gomez DR, Wu AJ, et al. Failure patterns relative to radiation treatment fields for stage II-IV thymoma. *J Thorac Oncol*. 2014;9[3]:403-409. Copyright © 2014 International Association for the Study of Lung Cancer. With permission.)

Most recurrences arise within 3 to 7 years,[18-20,49,50,106] but recurrence has been documented as late as 32 years after the initial resection.[44,56,173,198,199] Given the tendency for late recurrences, patients require at least two decades of follow-up after potentially curative therapy.

If technically feasible, the traditional recommendation for recurrence has been surgery and adjuvant radiation.[77,106,200] Most recurrences (50%-75%) are operable, and of those that are operable, the reported rates of a successful R_0 resection range from 45% to 71%.[49,77,104,106,201] Patients with a recurrence after an R_0 resection generally experience acceptable short- and long-term results,[77,200] with 10-year actuarial survival rates ranging from 53% to 72%[77,104,106,202]; 10-year survival rates after an incomplete resection, by contrast, range from 0% to 35%.[19,77,104,106,202]

Despite the historical tendency to reresect operable recurrences, some emerging data suggest that this recommendation for reresection should be tempered by the high rate of additional recurrences. In one study from Memorial Sloan Kettering Cancer Center, of 25 patients who experienced recurrent disease after initial resection, 11 (44%) had disease that was amenable to reresection. In that same study, 50% of patients undergoing surgery for recurrent disease had an R_0 resection, but 82% of these patients still experienced a second recurrence. The authors concluded that "despite the historical enthusiasm for re-resection … reoperation should be considered only in selected patients."[203]

When recurrent disease is unresectable, radiation and chemotherapy have been used with modest results: 5-year overall survival rates reportedly range from 25% to 50%, with poorer longer term survival.[20,49,104,106,201,204]

Radiation Therapy

Adjuvant Radiation After Complete Resection

Recurrence rates for stage I thymomas after an R_0 resection are so low that radiation is considered unlikely to offer improvement.[205] More commonly, radiation therapy is offered as an adjuvant treatment for patients with resected stage II and III thymomas or those with incompletely resected tumors. However, patterns of care studies demonstrate significant controversy around these indications; some centers recommend adjuvant radiation for all patients,[23,108] others recommending adjuvant radiation for stage II and III thymomas,[19,66,81,157,165] and still others recommending radiation only after an incomplete resection.[53,157,165] The reason for this diversity of opinions is that the evidence regarding adjuvant radiation is retrospective, and, because of the rarity of thymoma, studies span many decades. Nonetheless, because disease stage and completeness of resection are such important prognostic factors, analyses of adjuvant radiation have tended to focus on these factors.

For completely resected stage II thymoma, studies have been mixed with regard to local control benefit of adjuvant radiotherapy, with some studies showing trends toward better local control after adjuvant radiation, others finding no difference in recurrence rates, and one series reporting worse results with adjuvant radiation.[53,106,206-209] A report by Chang et al of patients

with completely resected stage II or III thymoma demonstrated similar overall survival rates but improved disease- free survival rates with adjuvant radiation therapy (93% with radiation vs 70% without).[206] In counterpoint, Berman and associates found that the local recurrence rate among 74 patients after complete resection for stage II disease was only 3% and was not affected by receipt of adjuvant radiation.[207] Utsumi et al reported similar findings in a study of patients with stage I or II completely resected disease.[208] Finally, a SEER analysis of 901 patients showed no clear benefit from adjuvant radiation for patients with completely resected disease.[209] Some studies have sought to fine-tune the pathologic indications for adjuvant radiotherapy in stage II disease with additional high-risk features beyond capsular invasion. For instance, Haniuda and colleagues found that patients with fibrous adhesion to the mediastinal pleura without microscopic invasion benefited the most from postoperative therapy[210]: Recurrence rates among patients with such adhesion were 36.4% versus 0% among those without adhesion.

Similar to the literature for stage II disease, there are mixed findings in the literature regarding the role of adjuvant radiation after R_0 resection for stage III thymoma. Traditionally, the literature has consisted of small retrospective studies showing excellent local control after radiation but unclear survival benefit with conflicting results. An illustrative example of a positive result in terms of local control is an early study by Urgesi and colleagues, who reported no in-field recurrences and only three out-of-field recurrences among a cohort of 33 stages III and IVa patients treated with surgery and radiation.[163] Similarly, Ogawa reported on 103 patients with stages I to IV thymoma treated with postoperative radiation and found a 100% in-field control rate.[211] And yet the impact of local control benefit on survival outcomes has not been borne out in some single-institution studies. For instance, Shen and colleagues reported on 83 patients with completely resected stage II and stage III thymic epithelial tumors and found no survival benefit to adjuvant radiation in this group.[212]

Studies using large population-based databases to assess the role of postoperative radiotherapy have reported mixed results. The Japanese Association for Research on the Thymus Database Study published its findings on postoperative radiotherapy for stages II to III thymoma in 2015

using the records of 2,835 registered patients. In multivariate analysis comparing those who either did or did not receive adjuvant radiation, the study found no benefit to radiotherapy for either relapse-free survival or overall survival.[213] Furthermore, subgroup exploratory analysis failed to identify factors among the stage III patients that could reliably predict a benefit to adjuvant radiation.

In contrast to the Japanese study, three population-based analyses found an association with adjuvant radiation with improved outcomes. Weksler et al reviewed the outcomes of 798 patients with stage III thymoma in the SEER database. In multivariate analysis, postoperative radiation therapy after surgery was associated with improved disease-free survival, but not with overall survival.[214] Jackson and colleagues reported on a population cohort of 4,056 patients in the National Cancer Database with all stages of thymoma and found that adjuvant radiation was associated with improved overall survival after adjustment for other clinical factors. Subgroup analysis found that this benefit was most pronounced in patients with stages IIB to III disease and with positive margin.[215] Lastly, an analysis of 1,263 patients in the ITMIG database who had undergone complete resection of a stage II or III thymoma found a 7% improvement in the 10-year overall survival among those given postoperative radiotherapy (86% vs 79%, P = .002).[216] Furthermore, the association of radiotherapy with overall survival was significant after multivariate adjustment.

The dose-response relationship is also a matter of contr oversy in the literature. Harnath and colleagues found that doses in excess of 50 Gy were associated with improved disease- free and overall survival among 27 patients diagnosed with thymic epithelial tumors and treated with adjuvant radiation. However, Fan et al reviewed the cases of 53 patients who underwent complete resection of stage III thymoma followed by radiation (range 28-60 Gy) and found to clear dose-response relationship.[217]

Even if local control is achieved, it is not evident that distant or regional recurrences or overall survival are clearly impacted by adjuvant radiation.[49,53,218-220] The North American thoracic intergroup of the National Clinical Trials Network proposed a randomized clinical trial for thymoma to further clarify the role of postoperative radiotherapy for resectable disease (as well as the impact of neoadjuvant or induction systemic therapy for unresectable or borderline thymoma), but CTEP ultimately rejected the

proposal as not being of sufficient priority for investment of NCI resources to support such an effort. Until a randomized controlled trial rigorously addresses the controversy around postoperative radiotherapy for completely resected tumors, we recommend that treatment for stage II or III disease should be made on an individual basis and should consider risk factors such as frank pleural or pericardial invasion, tumor grade, and comorbid conditions.

Decisions on the use of postoperative radiotherapy also need to carefully consider the potential long-term toxicities of radiotherapy in this population. Due to the location of the thymectomy bed extending over the heart, there can be significant exposure of the heart and cardiac substructures, including the left main and left anterior descending artery. The impact of cardiac adverse events on outcomes has been well documented in NSCLC[221,222] and breast cancer.[223]

We, therefore, strongly recommend that proposed treatment strategies be discussed in a multidisciplinary setting before the final recommendation is made. Ultimately, the evidence for adjuvant is limited by its largely retrospective character; a strong emphasis on designing and completing randomized controlled trials[224] (NCT02633553, NCT02014805) is needed to settle the role of adjuvant radiation in more definitive manner. For incompletely resected tumors, radiotherapy is often considered to be an important adjunctive treatment for addressing residual disease. Although rigorous prospective evidence is unavailable for this clinical scenario, retrospective analyses have observed very low rates of mediastinal failure among patients with gross residual disease treated with adjuvant radiation.[39,163,225]

Radiation as Neoadjuvant Therapy

Radiation has been proposed as a neoadjuvant strategy to reduce tumor burden and improve resectability, especially for cases involving gross invasion of critical structures.[36,110,166,226-230] Response rates of up to 80% have been reported, and a theoretical decrease in the potential for tumor seeding during surgery has been proposed as well.[20,39,165,226] The rates of R_0 resections after neoadjuvant radiation for stage III thymoma can be as high as 53% to 75%,[110,230] which are favorable compared with the typical 50%

rate of R_0 resections of stage III thymomas.[19,22,23,39,49,81,107,157] Ten-year survival rates do not seem to be better after preoperative radiation, but to date, studies evaluating this approach have been small.[110,229,230] For patients recommended to receive neoadjuvant (preoperative) radiotherapy, the authors recommend consideration of platinum-based radiosensitizing chemotherapy.

Radiation as Definitive Therapy

Radiation therapy alone has been used for patients who cannot undergo surgery because of medical conditions, or those for whom surgical resection is not possible, with modest results. Arakawa and associates reported that 7 of 12 patients presenting with unresectable tumors treated with primary radiation therapy were still alive at follow-up times ranging from 1 to 5 years.[231] Ciernik and associates reported a 5-year survival rate of 87% for a small group of patients with stages III and IV disease who underwent radiation without resection,[225] and Jackson and colleagues found 10-year survival rates of 44% for patients who received radiation after biopsies or incomplete resections.[232] As for the use of radiation for recurrent disease, Urgesi and others reported on comparative outcomes of 21 patients with intrathoracic recurrences, of whom 11 were able to undergo resection/debulking and 10 were treated with radiotherapy alone.[201] The 7-year survival rate of 70% was similar for those treated with radiation alone and for those treated with surgery and adjuvant therapy. The standard dose for definitive radiotherapy ranges from 60 to 70 Gy in 2 Gy fractions, largely extrapolating from the principles of radiotherapy for NSCLC. Improvements in radiotherapy planning and treatment delivery have also increased interest in the use of hypofractionated radiotherapy with image guidance, including stereotactic body radiation therapy, to decrease the time under treatment while minimizing potential short and long-term toxicities. A single-institution prospective study of SBRT[233] in this population included 32 patients with thymoma or thymic carcinoma. In all, 56.3% of patients had IVA or IVB disease. The response rate was 96.9%, median progression-free survival (PFS) was 28 months, and local control rate was 81.25%. Treatment was well tolerated. Although combined modality therapy is often still prioritized for patients with unresectable thymoma,

these improvements in treatment planning and delivery provide an intriguing potential management option for selected patients.

Chemotherapy

Platinum-based chemotherapies serve as the backbone for combination regimens typically used in the first-line setting. Preferred regimens combine cisplatin and adriamycin, either in combination with cyclophosphamide or cyclophosphamide and vincristine. For patients with underlying cardiac risk factors where an anthracycline may be contraindicated, cisplatin/etoposide and carboplatin/paclitaxel are other acceptable regimens. Thymomas can be chemotherapy with overall response rates greater than 50%.[69,174,234-242] However, duration of response is often limited with median responses ranging from 12 to 18 months. Whether chemotherapy influences long-term survival is more difficult to assess. In one retrospective analysis of 90 patients, chemotherapy reduced the rates of metastases to the lung, pleura, or other sites by half (17% vs 38%, $P < .05$). All of those patients were high risk with stage III or IV tumors treated with radiation and partial or no resection.[165] Another study reported a nonsignificant trend toward better disease-free survival from the addition of chemotherapy.[185]

As is true for the literature on the effects of radiation, most of the series describing the use of chemotherapy are small, single-arm studies with approximately 20 patients owing to disease rarity. The absence of randomized control arms limits direct comparisons, exacerbating the typical caveats associated with cross-trial comparisons. The accepted primary end point for efficacy is overall response rate, which is not a validated surrogate for overall survival or PFS, typically accepted as gold standard for outcomes in systemic therapies. In addition, some studies of systemic chemotherapies predate the implementation of the current WHO guidelines for tumor subtyping, applying histologic classifications no longer in use. Most importantly, no retrospective studies have been able to describe any prognostic biomarkers for the likelihood of response to platinum-based chemotherapy regimens, preventing any efforts to stratify regimen selection on a patient-by-patient basis.

The most promising use of chemotherapy is in the neoadjuvant setting. Like preoperative radiation, chemotherapy seems to render tumors more

suitable for complete resection. An early investigation suggested that neoadjuvant chemotherapy was associated with improved survival for patients with stage III or IVa thymomas.[178] This hypothesis was more rigorously tested in a phase II prospective trial by Park et al: 27 patients with radiographic evidence of stage III or IV thymic malignancies were enrolled (9 were thymoma and 18 were thymic carcinoma).[243] After induction therapy with docetaxel/cisplatin, 19 of the 27 patients underwent surgery and 15 among the 19 achieved a complete resection, which represents 55.6% of the intent-to-treat population. Overall survival at 4 years were 92.9% and 62.2% among those who did and did not achieve complete resection, respectively, though statistical significance was not achieved (possibly as a result of the small numbers involved). This study serves as evidence that tumor resectability can potentially be improved with a course of systemic chemotherapy.

Aside from cytotoxic agents, cytostatic agents can also be beneficial, often with a more tolerable side-effect profile. This is best exemplified with somatostatin analogs (eg, octreotide) and high-dose corticosteroids.[244,245] In one prospective study, two courses of glucocorticoid therapy before surgery led to a 47% response rate among 17 patients with resectable thymomas.[246] This therapy seems to work by exploiting the ability of corticosteroids to induce apoptosis in $CD4^+$ $CD8^+$ immature thymocytes. Another prospective study by the Eastern Cooperative Oncology Group enrolled 42 patients with unresectable, advanced thymic malignancies for whom octreotide scans were positive. Patients were treated with octreotide with or without prednisone. Two patients had complete responses and ten had partial responses, which led the investigators to conclude that octreotide alone had modest activity and that prednisone improved the overall response rate.[247] Similar cytostatic agents include pemetrexed[248] and everolimus.[249] Though overall response rates were only 25% and 9.4%, respectively, disease control rates of 75% and 94%, and median PFS remained 12.1 and 16.6 months, respectively. For prednisone, octreotide, and everolimus, treatment may provide an additional immunosuppressive benefit in patients with paraneoplastic disease.

Targeted therapies, which seek to take advantage of aberrations in signaling pathways, have been investigated in small series for thymic malignancies. Early studies have focused on c-KIT, EGFR, IGF-1R, and

VEGF angiogenesis and histone deacetylation pathways.[141,250,251] Phase I/II trials with agents targeting receptors in these pathways, like those with EGFR- and IGF-1R–targeted agents, have been largely disappointing.[252,253]

Ultimately, a better understanding of tumor biology coupled with studies involving larger numbers of patients is necessary to advance targeted therapies in thymoma.

Immunotherapies are an intriguing therapeutic modality in thymoma, given the role of the normal thymus in promoting immunologic self-tolerance and frequent association with clinical paraneoplastic syndromes including myasthenia gravis. Two studies have evaluated the anti-programmed cell death protein 1/programmed death ligand 1 (PD-1/PD-L1) immune checkpoint inhibitors pembrolizumab[254] and avelumab[255] in a limited number of patients. While both studies featured response rates greater than 25%, clinical responses were invariably associated with grade 3 and 4 immune-related adverse events. Most concerning were the frequent associations with immune-related myocarditis causing complete heart block in two patients. These results may reflect the primed state for antigen cross-presentation and elicitation of adaptive immune responses. To this point, similar associations with paraneoplastic syndromes were seen in the phase 2 study of the IGF-1R inhibitor cixutumumab.[256] Current guidance is to avoid immune checkpoint blockade in thymoma outside the clinical trial setting.

Combined Modality Therapy

Some evidence exists to suggest that multimodality treatment can improve both resectability and long-term survival among patients with stage III or IV thymomas; typical combinations include neoadjuvant chemotherapy followed by surgery and postoperative radiation, chemotherapy, or both. Prospective trials of preoperative combination chemotherapy have been undertaken at several institutions[78,239,241,243,257,258]; the regimens in all cases included cisplatin with some combination of cyclophosphamide, doxorubicin, vincristine, prednisone, or epirubicin. Reported response rates to these regimens range from 62% to 100% (Table 58.9); R_0 resections were possible in 57% to 82% of cases; and pathologic complete response rates ranged from 4% to 31%. Overall survival rates at 5 years (57%-95%) were quite favorable for unresectable stage III or IV thymoma.[78,239,241,257,259] In

many of these studies, most if not all patients received postoperative radiation (Table 58.9), and the results seem superior to historical results from patients who underwent surgical resection alone. In summary, multimodality therapy consisting of preoperative combination cisplatin-based chemotherapy followed by surgery and postoperative radiation can produce excellent results. Although anthracycline-based chemotherapy is preferred for induction chemotherapy, for those patients who cannot tolerate anthracycline- based chemotherapy, induction chemoradiation with cisplatin and etoposide may be a reasonable alternative as determined by two prospective pilot studies by Korst et al[260] and Tamiya et al,[261] in which all patients were able to undergo resection.

TABLE 58.9 OUTCOMES AFTER COMBINED MODALITY THERAPY FOR THYMOMAS

Study	Institution	*n*	Pre-op Chemo	Adjuvant Therapy	% Response	% R_0	% pCR	% 5-Y Survival
Lucchi et al[178]	Pisa	36	Csiplatin, vp, epi	RT and chemo	67	78	6	65 (est)
Venuta et al[78]	Rome	25	Cisplatin, vp, epi	RT and chemo	–	80	4	80
Kim et al[241]	MD Anderson	22	Cyclo, doxo, cisplatin, pred	RT and chemo	77	82	18	95
Rea et al[239]	Padua	16	Cyclo, doxo, cisplatin, vin	RT or chemo	100	69	31	57
Yokoi et al[719]	Tochigi	17	Cyclo, doxo, pred	RT and chemo	93	12	7	81
Kunitoh et al[258]	JCOG	23	Cisplatin, vin, doxo, vp	RT	62	69	14	85
Park et al[243]	Seoul	27	Docetaxel, cisplatin	RT, chemo, or both	63	79	NR	79.4 (4 y OS)

cyclo, cyclophosphamide; doxo, doxorubicin; epi, epirubicin; pCR, pathologic complete response; pred, prednisone; R_0, complete resection; vin, vincristine; vp, etoposide.

Modest results have also been obtained from the combination of chemotherapy plus definitive radiation therapy for unresectable thymoma. A prospective intergroup study[234] reported a 5-year survival rate of 52.5% for 26 patients (96% Masaoka stage III), who were treated with cisplatin, doxorubicin, and cyclophosphamide followed by radiation therapy using a two-dimensional (2D) radiation technique to 54 Gy in 1.8 Gy/fraction from 1983 to 1995 for patients with unresectable thymomas. The median survival time was 93 months. A more recent prospective phase 2 study by Fan et al[262] reported a 5-year survival rate of 56% for 56 patients (75% Masaoka stage IVB) who were treated with definitive concurrent chemoradiation with cisplatin, etoposide, and 60 Gy in 2 Gy/fraction using intensity-modulated radiation therapy (IMRT) with an objective response rate of 85.7%. Next-generation studies in this patient population will likely test a hypofractionated approach.

Radiation Therapy Dose

Radiation doses given for thymoma have ranged from 30 to 70 Gy, most often given in standard 1.8- to 2.0-Gy fractions. Typical postoperative doses are 45 to 50 Gy, with higher doses for positive surgical margins (54 Gy) or gross disease (60-70 Gy). Dose-response effects have been difficult to determine owing to the retrospective nature of most published studies; one study did not identify a dose response,[263] but two others did.[185,264] One systematic review[265] failed to identify optimal doses in the postoperative and definitive settings due to the paucity and heterogeneity of published data.

Radiation Targets

The radiation approach and targets is dependent on the intent of treatment. Full descriptions of radiation therapy definitions, reporting guidelines, and targets and techniques for thymic malignancies are detailed in two papers by Gomez et al and developed with the ITMIG.[266,267] As radiation planning techniques have evolved, the trend in treating thymic tumors, like NSCLC, has been toward the use of involved-field techniques. Because thymomas do not routinely spread via the lymphatic system, the draining nodal distributions do not need to be included in the radiation fields.[106] In general,

neoadjuvant or definitive radiation therapy is delivered a clinical tumor volume consisting of the entire extent of gross disease as visualized on imaging with a further clinical tumor margin (1-2 cm) to account for microscopic infiltration. Extending the clinical tumor margin into the lung parenchyma is generally unnecessary.

When radiation is to be given as adjuvant therapy, the radiation treatment fields are designed to treat any residual gross disease and the surgical bed. This region is defined based on the pretreatment images, with the field generally encompassing the surgical field that can be defined by the placement of surgical clips and preoperative imaging that delineates the superior-inferior extent of disease before treatment. Again, a clinical tumor margin is added to account for infiltration beyond the area previously occupied by gross tumor.

It is highly advisable to review the treatment volumes for adjuvant radiotherapy with the operating surgeon to ensure that all areas of concern for recurrence are addressed. Likewise, the surgeon can aid the radiation oncologist by placing radio-opaque clips at the time of surgery to help define the tumor bed and other areas of interest. It is especially critical to mark in this way regions known to harbor an unresected positive margin based on frozen section or wherever there is a high expectation of margin positivity on permanent section.

There is evidence that these principles of delineation lead to good interobserver consensus; an investigation by Holliday and colleagues sought to measure interobserver variability by comparing contours among seven radiation oncologists given a pilot data set for a preoperative and postoperative case.[268] Their results showed exceptional agreement in the preoperative contours, although lower agreement was observed in the postoperative setting, further highlighting the benefit of multidisciplinary involvement that includes the surgeon for these cases.

Thymic tumors have a propensity to spread to the pleura. Radiation can be directed at pleural targets for palliation and to prolong disease control in select cases. A phase II study by Wang et al[269] treated patients with unresectable pleural metastases that progressed on chemotherapy with IMRT to 30 to 50 Gy in 2 Gy/fractions. This regimen was safe when one course of radiation was delivered and the control rates were higher with 50 Gy. Unfortunately, 93.5% of patients developed out-of-field failures,

indicating that only targeting areas of known pleural metastases is not sufficient in preventing future progression. In theory, hemithoracic intensity-modulated pleural radiation (IMPRINT) could be beneficial in thymic malignancies because of their tendency for drop metastases along the pleural surfaces. This technique has been assessed in several studies. In one such study, Sugie et al[270] reported findings from 60 patients with stages I to IV invasive thymoma, 48 of whom had been treated with fields limited to the mediastinum to a dose of 30 to 64 Gy and the other 12 given hemithoracic radiation therapy to a dose of 11.2 to 16 Gy. Although the toxicity of the extended-field (hemithoracic) radiation was acceptable and seemed to produce modest improvements in pleural dissemination rates, no differences were found in overall survival between the two techniques.[271] Other small studies have also tested hemithoracic radiation to doses of 15 to 20 Gy, and some have had promising results.[272-274] However, these studies were small and primarily retrospective. Ultimately, the dose that can be delivered safely in hemithoracic therapy is probably not sufficient for controlling microscopic disease, which typically requires 40 to 45 Gy. However, conformal techniques such as IMRT and proton therapy may allow further dose escalation as being studied in current investigations (ClinicalTrials.gov Identifier: NCT05354570).

Radiation Modalities and Simulation Techniques

CT-based treatment planning is essential for targeting the tumor and for accurate dosimetry of critical structures. In the modern era, 4D techniques or deep inspiratory breath-hold (DIBH) to manage respiratory motion are also helpful for ensuring coverage of the target as well as optimizing avoidance of organs at risk. As is true for all thoracic and mediastinal tumors, the major critical structures include the spinal cord; lung parenchyma; the heart and associated substructures, including the pericardium, cardiac chambers, and coronary arteries; esophagus; bronchus; and trachea. The guidelines to be followed to minimize dose to these structures are the same as those used in the treatment of lung cancer. Table 58.10 lists common dose constraints for radiation therapy, with or without chemotherapy, for mediastinal malignancies. These constraints were derived from a Quantitative Analysis of Normal Tissue Effects in the Clinic

Consensus analysis published in 2010.[275-278] Any deviations from these dose constraints should be reviewed in a radiation quality assurance setting and discussed with the patient before treatment is begun.

TABLE 58.10 STANDARD-DOSE CONSTRAINTS USED IN RADIATION THERAPY FOR THORACIC MALIGNANCIES

Organ at Risk	RT Alone	Chemo and RT	Chemo and RT Before Surgery
Spinal cord	D_{max} <45 Gy	D_{max} <45 Gy	D_{max} <45 Gy
Lung	Mean dose ≤ 20 Gy V_{20} ≤ 40%	Mean dose ≤ 20 Gy V_{20} ≤ 35% V_{10} ≤ 45% V_5 ≤ 65%	Mean dose ≤ 20 Gy V_{20} ≤ 30% V_{10} ≤ 40% V_5 ≤ 55%
Heart	V_{30} ≤ 45% Mean dose <26 Gy	V_{30} ≤ 45% Mean dose <26 Gy	V_{30} ≤ 45% Mean dose <26 Gy
Esophagus	D_{max} ≤ 80 Gy V_{70} < 20% V_{50} < 50% Mean dose<34 Gy	D_{max} ≤ 80 Gy V_{70} < 20% V_{50} < 40% Mean dose <34 Gy	D_{max} ≤ 80 Gy V_{70} < 20% V_{50} < 40% Mean dose <34 Gy
Kidney	20 Gy < 32% of bilateral kidney	20 Gy < 32% of bilateral kidney	20 Gy < 32% of bilateral kidney
Liver	V_{30} ≤ 40% Mean dose <30 Gy	V_{30} ≤ 40% Mean dose <30 Gy	V_{30} ≤ 40% Mean dose <30 Gy

D_{max} = maximum dose; V_x = percent volume of organ receiving *x* dose.

From Marks LB, Bentzen SM, Deasy JO, et al. Radiation dose-volume effects in the lung. *Int J Radiat Oncol Biol Phys*. 2010;76(3 suppl):S70-S76.

Major advances in radiation delivery over the past decade have led to great improvements in both the conformality and therapeutic ratio of radiation for thoracic malignancies. IMRT has been shown to allow the dose to normal structures to be reduced relative to that from 3D conformal radiation and to allow accurate target localization.[279-285] Indeed, a recent study of 496 patients with locally advanced, unresectable NSCLC demonstrated that the more advanced technique (4D CT with IMRT) led to lower rates of high-grade radiation pneumonitis and better overall survival compared with 3D simulation and 3D conformal therapy.[286] Although

similar comparisons for thymic malignancies have not been done because of the rarity of this disease as well as the paucity of respiratory movement of the superior anterior mediastinum, the same principles would be expected to apply, given the mediastinal location of these tumors and hence their close proximity to the lungs, heart, and esophagus.

Another treatment modality, proton beam therapy, has shown promise for reducing the dose to normal structures while maintaining adequate doses to the tumor target in NSCLC.[279,287-294] Indeed, the dose distribution properties of proton therapy, specifically the "Bragg peak" that minimizes dose distal to the tumor, are well suited for anteriorly located thymic tumors. Proton therapy has been shown to produce greatly reduced doses to critical structures in mediastinal lymphoma, which often presents in the same anterior location as thymic malignancies, compared with photon-based techniques.[295] Vogel and colleagues tested this hypothesis by comparing double-scattered proton beam plans to IMRT plans for 22 consecutive patients requiring treatment for thymic malignancies. They confirmed that proton beam therapy resulted in statistically significant reductions in dose to the heart, lungs, left ventricle, and spinal cord and that the baseline risk of major cardiac events was increased by 135% after IMRT and 74% after proton therapy ($P = .04$).[296] This same group as well as Mercado et al[297] published the first clinical results with proton therapy for patients with thymic malignancies, revealing low toxicity rates and acceptable recurrence rates. As these studies are small and either retrospective or from prospective registry data, further investigation via rigorous, prospective clinical trials will be essential in determining if the dosimetric benefits of proton beam therapy (Figure 58.6) translate to clinical benefits.

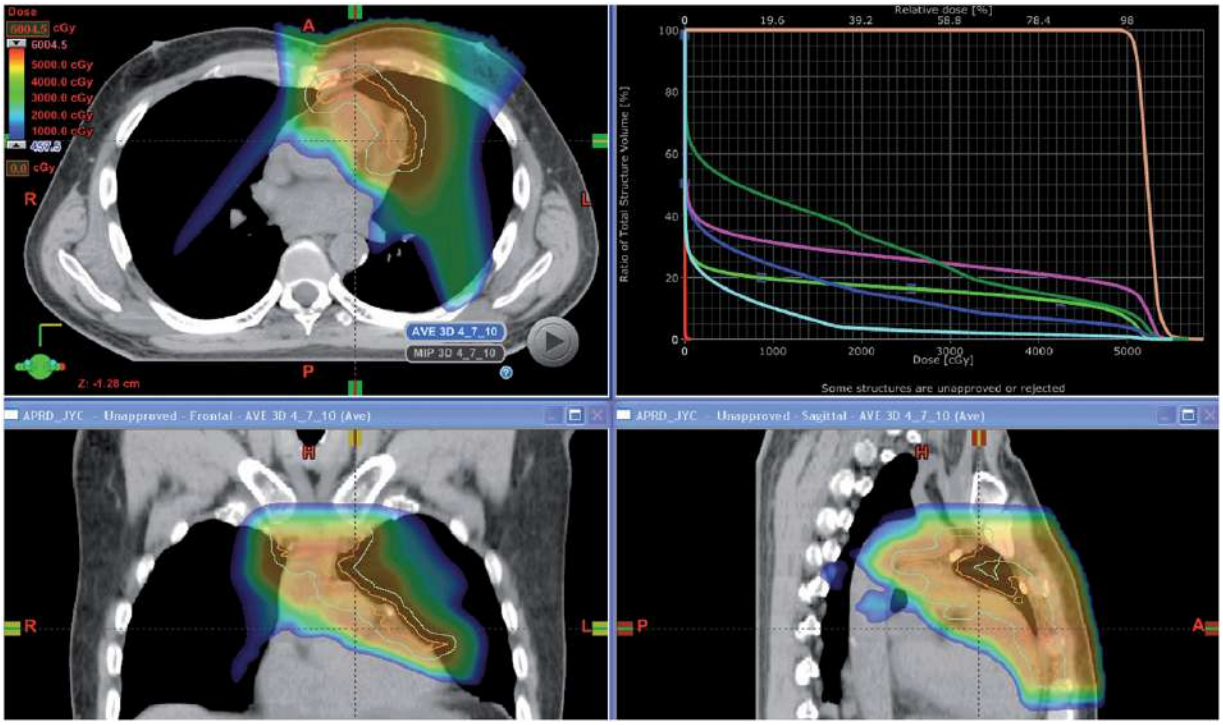

FIGURE 58.6 Axial, sagittal, and coronal views of a typical proton plan for postoperative treatment of thymoma. Surrounding structures including the lungs, heart, and esophagus have significantly diminished radiation exposure with this approach, as illustrated in the dose-volume histogram.

Regardless of treatment modality, we recommend that all treatment simulations for patients with thymic tumors take place while the patients are supine, and well immobilized with their arms above their head, to maximize the number of potential beam arrangements. We recommend that 4D CT scans be obtained at the time of simulation to assess the motion of the tumor during respiration. If 4D CT scanning is not available, we recommend either a slow helical scan to encompass all phases of the breathing cycle or that CT images be obtained at full inspiration (DIBH) and expiration to assess the extremes of respiratory motion.

THYMIC CARCINOMA

Natural History and Diagnosis

Thymic carcinomas are considerably less common than thymomas. Like thymomas, thymic carcinomas are thought to arise from the thymic epithelium and typically appear in the anterosuperior mediastinum. The

clinical behavior of thymic carcinoma is quite different from that of thymoma; they are generally more aggressive and have a higher propensity for capsular invasion, pleural involvement, and extrathoracic metastatic proliferation. Because of these features, thymic carcinoma often presents as advanced disease, and its 5-year survival rates are much poorer than for thymomas.[53,298,299]

Clinically, thymic carcinoma can present as cough, dyspnea, pleuritic chest pain, phrenic nerve palsy, or superior vena cava syndrome.[298,300,301] Associated paraneoplastic syndromes have been observed occasionally, though these are less commonly seen compared to thymoma.[301-303] CT scans often demonstrate an irregular mass with necrotic, cystic, or calcified regions.[300,304-306] In about 80% of cases, thymic carcinoma shows radiographic evidence of invasion into adjacent structures in the mediastinum, and mediastinal lymphadenopathy is evident at presentation in about 40%.[301,307-309] Distant metastases to regional lymphatics, bone, liver, kidney, and lung are also common clinical features.[301,310-312] Therefore, bone scanning, MRI, PET with 18F-flourodeoxyglucose or 11C-labeled methionine, and single-photon emission computed tomography have been used for both staging and evaluation of response to therapy.[92,313-316]

Historically, thymic carcinomas have been classified as type C thymic tumors in the WHO classification, and disease staging is often done with the Masaoka clinical staging system for thymomas and now with the official TNM staging system.[107,317] Most thymic carcinomas are undifferentiated high-grade lesions with anaplasia and marked cellular atypia, lacking the histologic features of a normal thymus[318]; others may be of adenocarcinomatous, sarcomatous, squamous, basaloid, mucoepidermoid, or lymphoepithelial-like histology.[300,319,320] Some thymic carcinomas are associated with multilocular thymic cysts, which are acquired lesions of the thymic gland associated with an inflammatory reaction. Recent studies have demonstrated the importance of thorough sampling of thymic cysts to rule out underlying carcinoma.[321]

Because histologic grade is one of the most significant indicators of prognosis, a revised histologic classification has been proposed that broadly divides thymic carcinomas into high-grade or low-grade lesions.[322] Tumors in the low-grade histologic group are characterized by a relatively favorable clinical course and a low incidence of local recurrence and metastasis.[323-325]

High-grade variants of thymic carcinoma are more lethal, with frequent metastases to regional lymph nodes, bone, liver, and lung.[306,326] In a recent study by Gao et al[327] of 127 patients with thymic carcinoma treated with complete surgical resection and adjuvant radiation therapy, the most common sites of failure were distant/nodal (32.3%), pleural (22%), and local (15%).

In addition to grade, extent of surgical resection, Masaoka stage, TNM stage, and receipt of adjuvant therapy are also associated with improved survival[328-331]; interestingly, the specific histology of thymic carcinoma, just as in thymoma, does not appear to reliably confer an impact on survival. Stage IVb patients with lymph node–only metastases may have better outcomes than those with distant metastatic disease at presentation, a result that may be driven by the possibility of curative resection in some of these patients.[332]

General Management

Owing to the paucity of prospective data with this rare tumor, the ideal therapeutic regimen is unknown. Current management strategies borrow from the principles of treating NSCLC. Thus, an aggressive multimodality approach is often employed, which includes the consideration of primary surgical resection, neoadjuvant or adjuvant cisplatin-based chemotherapy, and postoperative radiation therapy.

Although incomplete resection does not necessarily preclude long-term survival if multimodality platinum-based therapy is used,[333] complete resection is nevertheless the cornerstone of treatment.[328-331] The recently published American Radium Society (ARS) Appropriate Use Criteria[334] for thymic carcinomas recommended against the use of minimally invasive thymectomy for thymic carcinoma due to the infiltrative nature of these tumors. Reflecting multiple other single- institution studies, Takeda and colleagues observed a median survival time of 57 months for patients with completely resected thymic carcinomas versus 13 incomplete resection.[335] A multi-institutional study of patients with thymic carcinoma showed that the 5-year survival rates of total resection, subtotal resection, and inoperable groups were 67%, 30%, and 24%, respectively.[53] Likewise, a large series of 1,042 cases from the combined European Society of Thoracic Surgeons

(ESTS) and ITMIG databases reported overall survival rates for R0, R1, and R2 groups were 70%, 55%, and 42%, respectively.[330] In light of this consistent finding in multiple data sets, complete resection of the primary tumor is a fundamental recommendation.

The routine addition of lymph node dissection is more controversial, though it has merited attention because of the higher rate at which thymic carcinomas spread to regional lymph nodes in comparison to thymomas. Park et al retrospectively reviewed 37 patients with thymic carcinoma who were divided into four groups: no node dissection, N0 by limited dissection, N0 by extensive dissection, and N1 by dissection of any type.[336] Among the 29 patients who underwent node dissections, 6 (20.7%) were found to harbor nodal metastases. Furthermore, patients who underwent no dissection or node negative after limited dissection had outcomes that were inferior to those who were node negative after an extensive dissection. These results suggest that an extensive dissection may impart more accurate staging and better prognostic information. Though this intriguing study requires confirmation in larger investigations, it raises an intriguing hypothesis that routine lymph node dissection may improve outcomes either by the therapeutic effect of completely excising gross disease or by providing better guidance for necessary adjuvant therapies.

The role of radiotherapy for thymic carcinoma is not well defined, again owing to the rarity of the disease and the absence of prospective clinical trials. Although radiotherapy should be considered in all cases of thymic carcinoma, there is limited evidence that omission in completely resected, early-stage disease may be feasible. A small investigation of four patients fitting this characterization who were treated with radical surgery alone found that all four were alive and free from relapse at a median follow-up of 72 months (range, 12-167 months).[337]

Most single-institution retrospective studies have reported on outcomes withed adjuvant radiation therapy, typically to a dose of 40 to 70 Gy delivered in standard fractionation (1.8- to 2.0-Gy fractions).[263,324,335,338-341] In one such series of 26 patients treated with surgery and postoperative radiation without chemotherapy, Hsu and associates observed a 5-year overall survival rate of 77% for all patients,[341] 82% for patients with completely resected tumors, and 66% for those with subtotally resected tumors. The 5-year local control rate was 91% with a median radiation dose

of 60 Gy. In another study of 40 patients given either surgery and adjuvant radiation or definitive radiation therapy with or without chemotherapy, Ogawa and associates reported complete resections in 16 patients; moreover, no local recurrences were observed among the patients with complete resection who had received adjuvant radiation of at least 50 Gy.[324] Kondo and colleagues observed no survival benefit from adding adjuvant radiation to surgical resection in a retrospective multi-institutional study of 186 patients, although the authors did note that the retrospective nature of the study and its small subgroup sizes precluded any definitive conclusions.[53]

Investigators of the ESTS database reported on 229 patients treated with thymic carcinoma between 1999 and 2010. Compared to patients receiving surgery alone, a significant survival advantage was observed among patients receiving surgery and postoperative radiotherapy. Ahmad and colleagues went further to study the combined ESTS and ITMIG databases to create a cohort of 1,042 thymic carcinomas, 60% of whom received adjuvant radiotherapy. In their multivariable analysis, attaining R0 resection and administration of radiotherapy were the only variables associated with prolonged overall survival (hazard ratio for radiotherapy, 0.45).[330]

In aggregate, these studies seem to indicate that local control is improved with radiation and that a survival benefit may also accrue. The quality of the evidence, however, is limited by its retrospective nature and vulnerability to selection bias. As is true for all mediastinal tumors, better knowledge will depend on conducting randomized clinical trials. The formation of international collaborations such as the ESTS and the ITMIG is reassuring developments, as they will likely underpin the design and completion of such trials. The ARS Appropriate Use Criteria recommend against the use of elective nodal irradiation when treating thymic carcinoma definitively or adjuvantly after surgical resection. In addition, the panel[334] recommended the use of proton therapy or IMRT for thymic carcinoma to maximize radiation conformity and reduce radiation exposure to the heart and lungs.

The use of adjuvant cisplatin-based chemotherapy has shown significantly beneficial effects in several studies.[234,342,343] In one such study, Nakamura and associates treated 10 patients with unresectable thymic carcinoma with platinum-based protocols, with or without radiation therapy, and observed a median survival time of 11 months.[343] Yoh and others

reported excellent preliminary results (ie, a 42% response rate) from the use of weekly cisplatin, vincristine, doxorubicin, and etoposide for the treatment of advanced tumors.[344] Other studies have shown favorable responses from various combinations of cisplatin, etoposide, ifosfamide, doxorubicin, nedaplatin, cyclophosphamide, and vincristine.[234,235,342-346] Finally, although data are limited, some centers advocate combined chemoradiation in select circumstances for thymic carcinoma, particularly after R1 or R2 resections.[347]

Molecular pathways may provide a new avenue for treatment. Exploratory studies have shown the association of thymic carcinoma with certain mutations (VEGF,[145] IGF-1R,[146] and KIT pathways).[147,148,348] These approaches have struggled to obtain validation in larger cohorts of patients.[349] High expression of KIT at the immunohistochemical (IHC) level in the absence of frequent activating point mutations may explain increased responses to the multikinase-targeted inhibitors sunitinib[350] and lenvatinib,[351] with overall response rates upward of 26% and 40% and PFS of 7.2 and 9.3 months, respectively. The greatest improvement in systemic therapies for thymic carcinoma has come with immune checkpoint blockade. Two phase 2 studies have demonstrated overall response rates in the 20% to 25% range, all in patients with a tumor PD-L1 IHC staining of greater than 50%.[254,352] Responses may last for several years, but the vast majority of patients will experience recurrence and may respond to rechallenge.[353] As in thymoma, immune-related adverse events can be a series and often follow a similar clinical spectrum with myositis/myasthenia gravis/myocarditis overlap.

Because of the rarity of thymic carcinoma, few treatment recommendations can be made; however, it seems clear that for patients with resectable disease, complete surgical resection is the preferred initial therapeutic intervention.[53,104,335,354,355] For patients with unresectable lesions, neoadjuvant chemotherapy, with or without thoracic radiotherapy, seems reasonable. Ultimately, after complete resection, the most important prognostic factors are the initial disease stage and tumor grade. Five-year survival rates for patients with higher disease stage and higher grade neoplasms range from 15% to 20%, whereas for patients with low-grade, localized disease those rates can range from 80% to 90%.[322,326] The addition

of adjuvant therapies for patients with poor prognostic factors should be made on an individual basis in the context of a multidisciplinary review.

THYMIC CARCINOID

Thymic carcinoid (neuroendocrine) tumors of the thymus are very rare, accounting for less than 5% of all neoplasms of the anterior mediastinum. They originate from normal thymic Kulchitsky cells, which belong to the amine-precursor-uptake-and-decarboxylation group.[356] Thymic carcinoid tumors are often confused with thymomas because of similarities in their clinical behavior. Most patients with thymic carcinoids are men aged 30 to 50 years; the male-to-female ratio is 3 to 1.[357] Roughly half of thyroid carcinoids are associated with endocrine disorders such as MEN-1 (multiple endocrine neoplasia type 1) or secondary Cushing syndrome.[358-360]

Thymic carcinoids can present with symptoms related to compression of normal structures (chest pain, dyspnea, cough, hoarseness, superior vena cava syndrome)[356,361] or with no symptoms.[360] These tumors are best evaluated by CT or MRI for visualizing local invasion of the surrounding structures (pericardium, great vessels, pleura, sternum) and metastases within or outside the thorax. Most thymic carcinoids detected in radiographic studies are already advanced, commonly metastasizing to regional lymph nodes. Metastases are present in up to 40% to70% of patients within 8 years of the initial diagnosis,[362,363] which may explain the poor prognosis associated with these tumors.

The Masaoka staging system for thymoma has been used for staging thymic carcinoids.[107,357] The WHO system classifies the pathology of thymic carcinoids into typical carcinoid, atypical carcinoid, large cell neuroendocrine carcinoma, or small cell carcinoma,[123,124] and a system proposed by Klemm and Moran classifies these tumors as well differentiated (low grade), moderately differentiated (intermediate grade), or poorly differentiated (high grade).[364] Notably, neither grading nor other histologic variables have shown a consistent association with prognosis.[357]

Complete surgical resection is the preferred method of treatment, although recurrence is common. Incomplete resections followed by adjuvant radiation, chemotherapy, or both seem to provide some benefit without increasing morbidity or mortality.[360,362,365,366] Distant metastases to

bone, liver, or skin occur in 30% to 40% of cases.[367] Despite aggressive treatment, the prognosis in most cases is poor. According to one report, the overall 5-year survival rate was 31%, and all 14 patients expired within 9 years.[361] A more recent analysis of 205 patients from the combined ESTS and ITMIG databases was more reassuring with a reported 5-year survival rate of 68%, although this result should be tempered by the observation that 39% of patients experienced recurrence in this time frame.[363] Similar to the other thymic malignancies, overall survival was influenced primarily by the Masaoka stage and completeness of resection. Neither chemotherapy nor radiotherapy showed statistical significance with regard to overall survival benefit. Thymic carcinoids associated with MEN-1 are especially lethal; in one study, the 5-year survival rate for patients with thymic carcinoids without associated endocrinopathy was about 70% but was only 35% for those with an endocrinopathy.[360,361,368]

OTHER RARE TUMORS OF THE THYMUS

Thymoliposarcoma was first described by Havlicek and Rosai in 1984.[369] This rare and distinctive entity is considered the malignant counterpart of thymolipoma. Thymoliposarcomas have appeared in adults aged 36 to 77 years, with a slight female predominance. Unlike its thymolipoma counterpart, thymoliposarcoma is not associated with myasthenia gravis. It grows by expansion and has a relatively low risk of distant metastasis in the absence of histologic dedifferentiation. Complete surgical resection or subtotal resection with adjuvant radiation therapy has been used for local control.[369,370]

MALIGNANT MEDIASTINAL GERM CELL TUMORS

Epidemiology

Primary extragonadal germ cell tumors account for 2% to 5% of all germ cell tumors.[371,372] About two-thirds of these tumors occur in the anterior mediastinum,[373-375] making the mediastinum the most common site of primary extragonadal germ cell tumors among young adults, mostly male.[376] Similar to gonadal sites, these can include teratomas, seminomatous tumors, and nonseminomatous tumors; the former is the most common mediastinal

germ cell tumor.[377] Benign teratomas arise from germ cell elements, but they are not included in this discussion because they are not malignant and surgical resection is often curative (immature teratomas are rare and aggressive with poorer outcomes). Germ cell tumors contribute about 10% of all malignant mediastinal tumors and about 2% of mediastinal neoplasms.[378] In a pooled analysis of 341 patients with mediastinal germ cell tumors treated at 11 cancer centers over a 20-year period, the median age of presentation was 33 years for seminomatous tumors and 28 years for nonseminomatous tumors.[379,380]

Primary extragonadal germ cell tumors have several observed associations. Klinefelter syndrome has been documented in patients with mediastinal germ cell tumors, but not in patients with testicular germ cell tumors.[381-384] In one study, up to 20% of patients with mediastinal germ cell tumors were found to have the Klinefelter karyotype (47,XXY).[385,386] Several unusual malignant processes are associated with nonseminomatous germ cell tumors, including hematologic malignancies such as acute myeloid leukemia, acute nonlymphocytic leukemia, acute megakaryocytic leukemia, myelodysplastic syndrome, and malignant histiocytosis.[386-390]

Natural History

Primary extragonadal germ cell tumors arise along midline structures of the body extending from the pineal gland, through the mediastinum and retroperitoneum, to the presacral areas. The origin of these primary extragonadal germ cell tumors remains controversial,[391-393] but presumably, they arise from germ cells that migrate along the urogenital ridge during embryonic development.[386,394] Because the embryologic urogenital ridge extends from C-6 to L-4, malignant transformation of displaced germ cells can give rise to primary germ cell tumors outside the gonads.

Because primary gonadal germ cell tumors can spread to the retroperitoneum and mediastinum,[374,386] the diagnostic workup must be thorough to avoid overlooking an occult gonadal primary. Although primary mediastinal germ cell tumors have the same morphologic and histologic appearance as those of the testes, primary germ cell tumors of the mediastinum are more aggressive and have a poorer prognosis.[395-397]

Primary mediastinal seminomatous germ cell tumors are sensitive to radiation and chemotherapy, but nonseminomatous tumors are less vulnerable to treatment and are considered poor-risk diseases in all staging systems.[397,398] Such tumors are often invasive at the time of diagnosis, and approximately half of such tumors will present with distant metastases, most often to the lung.[379] TP53 mutations are also associated with reduced overall survival.[399]

Tumor markers can aid in the diagnosis of mediastinal germ cell tumors; serum α-fetoprotein levels are elevated in 75% of patients (median, 2,500 ng/mL) at diagnosis, and β-human chorionic gonadotropin and lactate dehydrogenase levels are elevated in about 50% of patients at presentation.[379] Pure seminomatous histologies are less likely to be associated with biomarker elevation, although occasionally a modest rise in β-human chorionic gonadotropin can be observed.

Clinical Presentation

As is true for other mediastinal tumors, local symptoms are usually caused by tumor compression or invasion of adjacent structures. Primary extragonadal germ cell tumors present with clinical symptoms in many cases,[400] with dyspnea (25%), chest pain (23%), cough (17%), fever (13%), weight loss (11%), vena cava occlusion syndrome, and fatigue/weakness (6% each) being the most common.[379,401,402] These tumors may be asymptomatic in other cases,[403] with incidental diagnosis.[404,405] Roughly one-third of seminomatous mediastinal germ cell tumors present with metastases at diagnosis. The cervical lymph nodes are enlarged in about 25% of such cases, but abdominal lymphadenopathy has also been present. Distant metastases from nonseminomatous germ cell tumors are even more common, with rates of 85% to 90% in prior series but in more recent series about 50% at diagnosis.[379,406-409]

Diagnostic Workup

Mediastinal germ cell tumors are usually readily detected on chest x-rays, with most masses noted in the anterosuperior mediastinum. CT scans of the chest, abdomen, and pelvis are essential to evaluate the mass and to screen for metastases and lymphadenopathy. A careful physical examination and

testicular sonography should be performed to rule out an occult primary gonadal tumor. As mentioned earlier, tumor marker assessment can be helpful for diagnosis, evaluating treatment efficacy, and surveillance.[11,410-412] Thus, the determination of baseline tumor marker levels both before treatment is begun and after treatment is completed is essential.

The initial diagnosis of mediastinal germ cell tumors is usually reached through a combination of findings from CT, radiography, sonography, and tumor marker measurements. Whether PET or MRI has a place in the management of these tumors is unclear. In some instances, the tumor marker findings are sufficient to classify the lesion as an extragonadal nonseminomatous germ cell tumor without histologic confirmation, but false-positive β-human chorionic gonadotropin levels have been reported.[413,414] Histopathologic analysis can often be done easily via fine-needle aspiration and cytologic staining for tumor markers. Biopsy samples should be obtained whenever possible because both the choice of treatment and prognosis depend greatly on histology.[413,414]

Prognostic Factors

The most important prognostic factor for mediastinal germ cell tumors is histologic type. Seminomas are highly curable, but nonseminomatous germ cell tumors, despite advances in therapy, are associated with poor PFS and overall survival. The presence of metastases with tumors of either histologic type is also associated with adverse PFS and overall survival. In nonseminomatous tumors, elevated β-human chorionic gonadotropin levels are associated with inferior overall survival.[379] Nomograms have been developed to aid in prognostication.[415]

General Management

Seminomatous Tumors

Seminomas are quite sensitive to both radiation therapy and chemotherapy, and thus, all patients with tumors of seminomatous histology should be treated with curative intent, even in the presence of metastatic disease. The choice of treatment has evolved with the development of cisplatin-based

chemotherapy regimens, and most patients should be initially treated with systemic chemotherapy.[416]

Historically, mediastinal seminomatous tumors (like all mediastinal tumors) were treated surgically.[386,417] Complete radical resection can be considered in some cases if it is technically feasible and if the patients do not want radiation or chemotherapy. Definitive radiation replaced surgical resection for localized mediastinal seminomatous germ cell tumors, with long-term survival rates of 60% to 80% achieved even for those with bulky tumors.[372,386,389,417] Before the advent of platinum-based chemotherapy, radiation therapy had the advantage of being more tolerable and less toxic, and relapses could be effectively treated with systemic chemotherapy.[372] However, cisplatin-based chemotherapy has eclipsed radiation; in an early application of this approach, Einhorn and colleagues at the University of Indiana reported a complete response rate of 63% lasting a median duration of 18 months for 19 patients with disseminated seminoma treated with cisplatin-based chemotherapy.[418] In more modern series, the response to primary systemic chemotherapy is favorable for 92% of patients, and 5-year overall survival rates exceeding 90% are standard.[419,420]

Residual radiographic abnormalities after the completion of chemotherapy for bulky mediastinal seminomas are not uncommon, but the management strategy in such cases is still controversial. In the vast majority (80%-90%) of such cases, the residual masses represent dense fibrosis with no viable tumor.[386,421-423] Some clinicians have advocated surgical resection or biopsy of all postchemotherapy masses larger than 3 cm,[87,422-424] and others recommend close follow-up in such cases, with early intervention if the mass enlarges on chest x-ray or CT scan and resection, radiation, or salvage chemotherapy reserved for progressive disease.[386,389,423,425] Whether PET is useful for predicting viable tumor is debatable and under investigation.[426,427] Even though seminomas are extremely sensitive to radiation therapy, radiation therapy delivered to residual masses after chemotherapy has not shown a significant benefit.

Circumstances in which radiation may be appropriate include patients who refuse chemotherapy, in whom chemotherapy is contraindicated, or who likely harbor viable residual disease after chemotherapy based upon highly suspicious imaging findings or pathologic confirmation. Radiation doses and treatment techniques for mediastinal seminomatous germ cell

tumors have varied.[428-433] Doses as low as 30 Gy and as high as 50 Gy have been recommended.[378,430] Given the absence of unambiguous clinical trial guidance, radiation dose should be adjusted based on the size of the lesion, the history of chemotherapy exposure, and the clinical circumstance. Because the disease is infiltrative and susceptible to nodal involvement, the entire mediastinum was traditionally encompassed with anteroposterior-posteroanterior fields with CT guidance. In the prechemotherapy era, the use of smaller portals was associated with marginal relapses,[429] and in fact the clinical target volume for definitive radiation alone often electively covered the supraclavicular, cervical and para- aortic lymph nodes.[411,428,431,434] Extrapolating from the experience with prophylactic treatment of para-aortic nodes in testicular seminomas, one could assume that the contiguous lymphatic drainage sites for a mediastinal primary could be treated effectively with 20 Gy with minimal morbidity.[435]

In conclusion, cisplatin-based combination chemotherapy can consistently produce 5-year overall survival rates in excess of 90% for mediastinal seminomas. However, for selected patients, definitive radiation therapy has produced local tumor control rates of 89% to 100% and long-term survival rates of 60% to 80%.[378,386,429,431,436]

Nonseminomatous Germ Cell Tumors

The primary treatment for nonseminomatous germ cell tumor is intensive cisplatin-based chemotherapy, but surgical resection of all residual masses after first-line chemotherapy is recommended whenever technically possible, either as a one-stage or as a sequential procedure.[437-440] Chemotherapy regimens should include either cisplatin and etoposide or cisplatin, etoposide, and bleomycin. Patients whose tumors respond well to initial chemotherapy followed by complete resection of any residual mass can have excellent outcomes, but the outcome for patients who do not respond to primary therapy is poor, as salvage therapy is rarely effective.[397]

The role of radiation therapy in nonseminomatous germ cell tumors is not clear. Radiation may be useful for unresectable residual masses, given the relatively high rate of persistent viable tumor and the poor success rates of salvage therapy. Nonseminomatous germ cell tumors are in fact radiosensitive, but they require higher doses than seminomatous tumors.

Akin to other solid tumors, doses of 60 Gy or more may be necessary to achieve disease control.[441]

Before the cisplatin-based chemotherapy era, fewer than 5% of patients with mediastinal nonseminomatous germ cell tumors survived.[411] Since that time, long-term disease-free survival rates have varied from 45% to 72% in studies using cisplatin-based combination chemotherapy followed by surgery.[379,397,442] Several salvage regimens have been used for disease that progresses during or after initial chemotherapy, but unfortunately, long-term survival rates for patients with relapsed mediastinal germ cell tumors are less than 10%.[379,397,443,444] Thus, surgical resection and even radiation therapy may be appropriate in select cases to augment chemotherapy or as an alternative treatment modality when no further chemotherapy is available. As with other disease sites, there is intense interest in the use of immune-modulatory agents in the management of these tumors.[445]

MEDIASTINAL MESENCHYMAL TUMORS

Epidemiology

True mediastinal mesenchymal lesions are exceedingly rare tumors. Retrospective series suggest that 2% to 8% of all mediastinal lesions are primary mesenchymal tumors; extrapolation of these values puts the estimated incidence at approximately 0.1 to 0.2 per million.[11,446-448] More than half of mediastinal mesenchymal tumors are vascular or lymphatic in origin, with the rest composed of unusual histologic variants.[449] The age predilection depends on the specific histologic subtype.[49,405,446-448,450]

Clinical Presentation and Workup

Mesenchymal lesions can arise in any of the three mediastinal compartments. Mesenchymal tumors that present in children seem to be more malignant than those presenting in adults.[450,451]

Mediastinal mesenchymal lesions can reach impressively large sizes before detection, typically presenting with symptoms such as chest pain and dyspnea. At least one series suggests that symptomatic presentation is a harbinger of malignant character, with 80% of patients with malignant disease presenting with symptoms versus 44% of patients with benign

masses.[11] An accurate histopathologic diagnosis is critical.[450] Tissue for these analyses can be obtained via mediastinoscopic biopsy, fine-needle aspiration, or endoscopy. Disease can be staged according to the American Joint Committee on Cancer staging system for soft tissue tumors.

Tumors of Adipose Tissue

Lipomas are the most common adult benign tumor; however, mediastinal lipomas are rare, representing 1.6% to 2.3% of all mediastinal tumors.[449,452-454] Mediastinal lesions can occur either in isolation or multiples and may mimic cardiomegaly or pleural effusion on a chest x-ray. They are usually well circumscribed and encapsulated but can grow to a large size before detection.[455,456] For example, a lipoma 40 cm × 25 cm × 15 cm in size and 3.78 kg in weight has been reported.[457] Though these tumors can be quite large and cause significant compressive symptoms [458-460] gross total resection is almost always curative.[13,461-464] Technically, lipomas are considered "benign" tumors, but those that are growing or causing symptoms should be referred for surgical resection.

In contrast to lipomas, liposarcomas consist of immature fat cells with malignant histology and behavior. The fifth WHO Classification of Tumors of Soft Tissue and Bone divided liposarcoma into five clinicopathologic and genetic subtypes: well-differentiated liposarcoma (WDLS)/atypical lipomatous tumor (ALT), de-differentiated liposarcoma, myxoid/round cell liposarcoma, pleomorphic liposarcoma, and myxoid pleomorphic liposarcoma.[465] WDLS/ALT and de-differentiated liposarcoma account for 50% to 60% of all liposarcomas. All the subtypes can arise in the mediastinum. WDLS/ALT is low-grade malignancy that mostly arises in the extremities, inguinal region, and retroperitoneum. De-differentiated liposarcomas are WDLS containing a nonlipogenic sarcomatous component that could be low or high grade. These tumors often arise in the retroperitoneum, followed by the extremities. Myxoid liposarcomas represent for nearly 20% to 30% of the liposarcomas. These tumors are the least common types of liposarcomas in adults but are common in children; also, these are the least common types of liposarcoma arising in the mediastinum. Pleomorphic liposarcomas account for less than 5% of liposarcoma. These are typically high-grade, poorly differentiated tumors,

which most commonly occur in the extremities. Myxoid pleomorphic liposarcomas are rare and aggressive tumors. Retrospective studies have supported the WHO classification.[466-468]

Distinguishing lipomas from liposarcomas can be difficult histologically; liposarcomas are distinguished by size heterogeneity, hyperchromatic nuclei, and eosinophilic cytoplasm.[469] Primary mediastinal liposarcomas often appear in the posterior portion of the mediastinum. Anterior mediastinal liposarcomas are possible albeit rare.[470] Tumors often appear to be encapsulated and well circumscribed, even when invasion is present (Figure 58.7), giving rise to the term "pseudocapsule." In one historical review, survival times for patients with well-circumscribed lesions ranged from 3 to 17 years, whereas patients with grossly invasive tumors died within 2 years.[471] As is true for all sarcomas, the prognosis depends on the histologic grade.[472,473]

FIGURE 58.7 Computed tomography scan (left) and intraoperative photograph (right) of a primary mediastinal liposarcoma filling right thoracic cavity. The recommended treatment for this malignancy is aggressive surgical resection with adjuvant radiation therapy and consideration of systemic therapy. (From Wiedemann D, Schistek R, Gassner E, Antretter H. Mediastinal liposarcoma. *J Card Surg*. 2011;26[2]:162-164. Copyright © 2010 Wiley Periodicals. Reprinted by permission of John Wiley & Sons.).

Like other sarcomas, optimal treatment consists of surgical resection and adjuvant radiation therapy.[441,474] ALT is more indolent, and a marginal resection technique should be employed to minimize surgical morbidity. For

ALT/WDLS, if en bloc resection with negative margins is achieved, radiotherapy is not indicated.[475] In one report that reviewed 91 patients with ALT/WDLS, positive surgical margins were associated with a higher risk of local progression, suggesting that reresection or adjuvant radiotherapy could be considered for patients with positive surgical margins.[476] For example, in one series, patients with positive margins received a 14 to 20 Gy boost to the high-risk area. For myxoid liposarcoma, a dose reduction to 36 Gy can be considered.[477]

Tumors of Lymph Tissue

Tumors arising from the vascular or lymphatic components of the mediastinum make up the bulk of the remaining mediastinal mesenchymal lesions.[446-448] Lymphangiomas and hemangiomas are morphologically similar under light microscopy, and the presence of red blood cells or chyle within the tumor lumen often serves as a primary diagnostic aid.[461] Localized lymphangiomas are rare; less than 1% are located only in the mediastinum. More commonly, these are located in the neck, and approximately 10% have mediastinal extension.[478] A cystic lymphangioma is illustrated in Figure 58.8.[479]

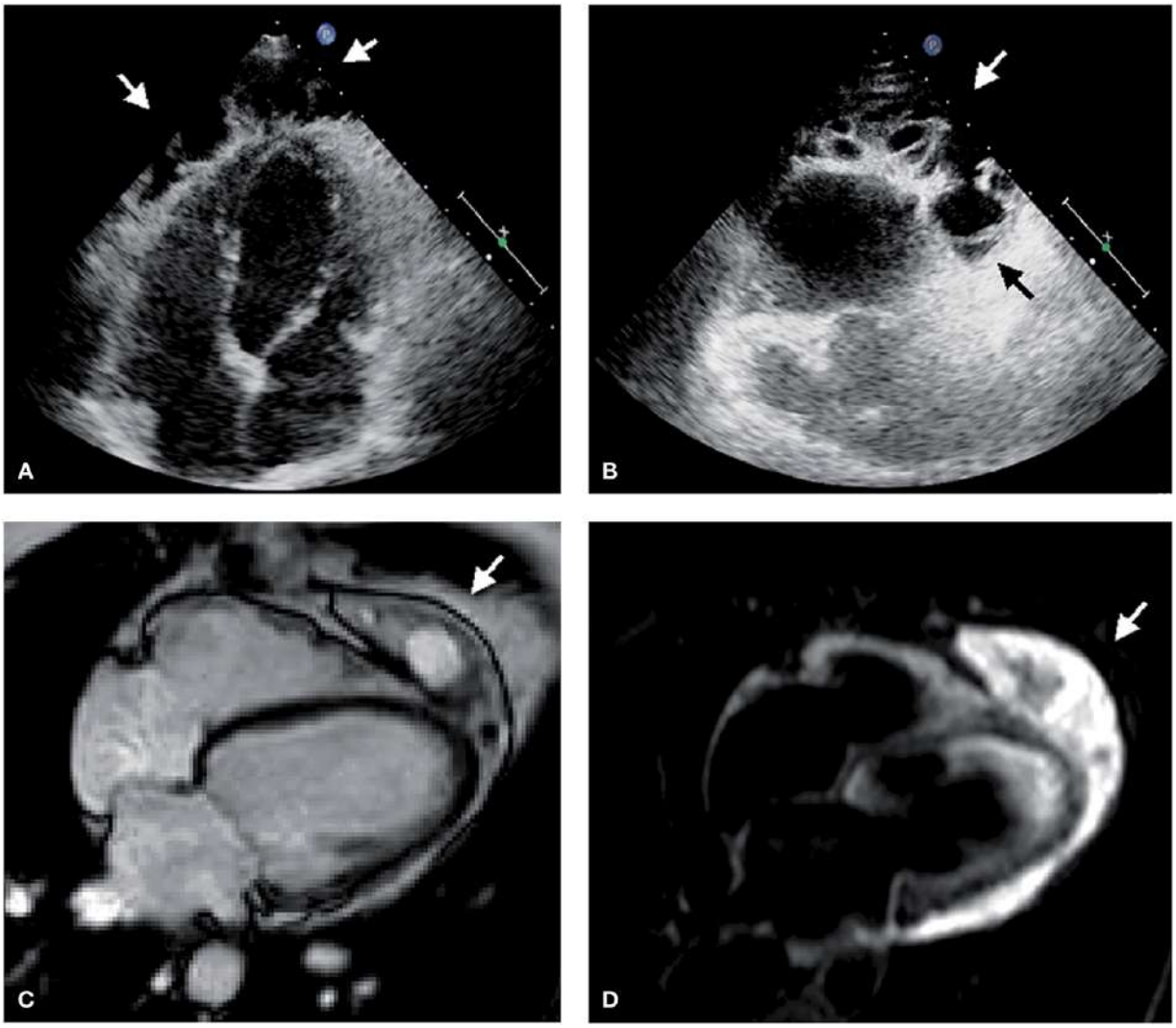

FIGURE 58.8 Echocardiographs (top) and cardiac magnetic resonance images (bottom) of mediastinal lymphangioma. The patient presented with palpitations and was found to have a cystic lymphangioma surrounding both ventricles from the apex to the left atrioventricular groove. The arrows are pointing to the tumor. (Reprinted from Conte G, Aldrovandi A, Reverberi C, Cademartiri F, Ardissino D. Mediastinal cystic lymphangioma. *J Am Coll Cardiol*. 2011;57[16]:e207. Copyright © 2011 American College of Cardiology Foundation. With permission.)

Lymphangiomatosis, which is characterized by synchronous widespread lymphangiomas, is a rare benign condition and accounts for 0.7% to 4.5% of mediastinal tumors. The majority of patients (~90%) have tumors in the neck and axilla and present by the age of 2 years.[480,481] By contrast, pure mediastinal-type tumors are rare and usually not discovered until adulthood

due to the relative lack of associated symptoms.[482] Younger age and mediastinal or pulmonary involvement carry a poor prognosis.[461,483-491]

Lymphangiosarcoma seems to be a malignant variant of lymphangiomas and should be treated like other soft tissue sarcomas, with the optimal treatment being full extirpation.[492] In the largest reported retrospective series of 25 patients with mediastinal and cervicomediastinal lymphangiomas, survival rates were excellent after surgical resection alone, and only one patient died of a complication from lymphangioma.[493] Lesions arising from the low thoracic duct with symptomatic chylothorax have a higher risk of recurrence after surgical resection. Low-dose adjuvant radiotherapy of 15 to 20 Gy in 10 to 12 fractions following surgery was reported to be effective in preventing recurrence in patients with refractory symptoms.[494]

Tumors of Vascular Tissue

Mediastinal mesenchymal lesions of endothelial origin include hemangiomas, hemangioendotheliomas, and hemangiopericytomas. Many of these tumors have an indolent course, but hemangiopericytomas are notable for having both malignant and benign presentations. Malignant hemangiopericytomas have high rates of metastasis at presentation. Hemangiomas can be capillary or cavernous; cavernous hemangiomas (ie, angiomyomas or hamartomas) are distinguished from capillary hemangiomas by the presence of smooth muscle. Hemangiomas and hemangioendotheliomas are typically well circumscribed. Hemangioendotheliomas contain the hallmark cytoplasmic Weibel-Palade bodies.[495,496]

Hemangiopericytomas arise from the capillary pericytes of Zimmerman.[497] Although most are indolent, recurrence and metastases have been observed many years after resection.[498] Retrospective studies suggest that high mitotic rates and proliferative indices may portend malignant behavior.[499,500] Nevertheless, long-term survival is still possible with aggressive treatment of metastatic disease.[501] Surgery remains the mainstay of therapy and is often curative.[502] Because of their benign nature, hemangiomas or hemangioendotheliomas should not be treated with radiation.[502] An endoscopic approach has been proposed for several types of

intrathoracic tumors including benign hemangiomas and should be explored further.[503] Radiation remains an option for incompletely resected hemangiopericytomas.

Miscellaneous Mediastinal Mesenchymal Lesions

A mélange of other mediastinal mesenchymal lesions have been reported, usually of musculoskeletal or connective tissue origin, with the former typically appearing within the posterior mediastinum and the latter typically appearing in the anterior mediastinum.[449,484,504] These lesions have been treated with surgical excision and, occasionally, postoperative radiation therapy, depending on the histology and clinical presentation.[446-449,505-509]

MEDIASTINAL NEUROGENIC TUMORS

Epidemiology

Neurogenic tumors of the thorax are generally classified by their neural cell of origin, including tumors of the nerve sheath (schwannomas and neurofibromas), autonomic ganglion (ganglioneuromas and neuroblastomas), and paraganglion (paragangliomas and pheochromocytomas). Most neurogenic lesions arise in the posterior mediastinum. Indeed, they are the most common cause of a posterior mediastinal mass and account for roughly one quarter to one-third of all mediastinal neoplasms[9,11,510-512]

Neurogenic neoplasms are rare, with an incidence of 0.5 per million in adults.[11] Neuroblastoma, an aggressive variant of neurogenic tumors, occurs primarily in children[513] and appears in the mediastinum in about 20% of cases. This condition is covered in the pediatric malignancy section of this book. Neuroblastomas are more common in male Caucasians, whereas other malignant neurogenic tumors occur at equal rates in both sexes.[514-516]

Paragangliomas are rare tumors that arise from extra- adrenal paraganglia and can be either functional (catecholamine secreting) or nonfunctional.[517,518] Most of these tumors are benign and surgical resection is usually curative, but about 10% of patients are reported to have malignant tumors[519] and germline mutations are suggested to have an association with

this. The higher rate of malignancy is reported to be associated with SDHB germline mutations[520,521]

The most common neurogenic tumors in adults are benign schwannomas and neurofibromas, often presenting in the setting of neurofibromatosis type 1 (NF-1), an autosomal dominant neurocutaneous disorder, with an estimated birth incidence of 1 in 2,500.[499] Individuals affected with NF-1 are at increased risk of developing both benign and malignant tumors. The most common benign tumor in individuals with NF-1 is neurofibroma, a heterogeneous benign peripheral nerve sheath tumor.[522,523] Neurofibromas can occur as discrete focal cutaneous or subcutaneous growths, as intraforaminal spinal tumors, or as plexiform tumors. Plexiform neurofibromas are composed of the same cell types as dermal neurofibromas but have an expanded extracellular matrix and a rich vascular supply.[524] In one study of 125 patients with NF-1, plexiform neurofibromas were clinically visible in 32%.[525] Schwannomas often originate from the intercostal or sympathetic nerves and can become quite large before being detected.[461] Surgery is the mainstay of treatment, but the possibility of achieving an R0 resection depends on the extent of locoregional disease. Few local recurrences are reported, and long-term local control rates are nearly 100%.[511,514,526-529] In adults, most malignant mediastinal neurogenic tumors are malignant peripheral nerve sheath tumors (MPNSTs). Individuals with NF-1 carry a heightened risk of developing MPNSTs, with a lifetime risk of almost 7.5% to 15%.[530,531] Because most NF-1–associated MPNSTs arise within preexisting plexiform neurofibromas, individuals with NF-1 and plexiform neurofibromas warrant increased surveillance. For MPNSTs, adjuvant irradiation to a dose of 60 Gy or more or brachytherapy is reported to show improved local control of disease.[532]

With regard to anatomic origin, it is reported that MPNSTs were located in the trunk in 40% to 51% of the patients studied.[516] Patients with NF-1 were 22-27% of the patients had NF-1. The median age at presentation of the MPNST tends to be younger in patients with NF-1[487,533]

Natural History and General Management

In up to 80% of cases, mediastinal neurogenic tumors present as an asymptomatic, incidentally found mass (Figures 58.9 and 58.10). In some cases, these masses can grow slowly enough to involve nearly the entire hemithorax before detection.[515,534,535] Large or rapidly growing lesions can cause chest pain and nerve dysfunction (including Horner syndrome) from compression.[536] Proximal organs such as the vagus or phrenic nerves, esophagus, trachea, and cardiac chambers may be involved by direct extension or via the nerve sheath.[537-545] Local invasion and bony destruction are common.[546] Distant metastases were reported to present in 26% of patients at diagnosis.[547,548] Because MPNSTs are difficult to detect before they infiltrate nearby structures (making surgery difficult) and metastasize, the prognosis is poor.[549] Malignant triton tumors, an extremely rare subtype of MPNSTs, have aggressive biologic behavior and, therefore, the prognosis is very poor.[550]

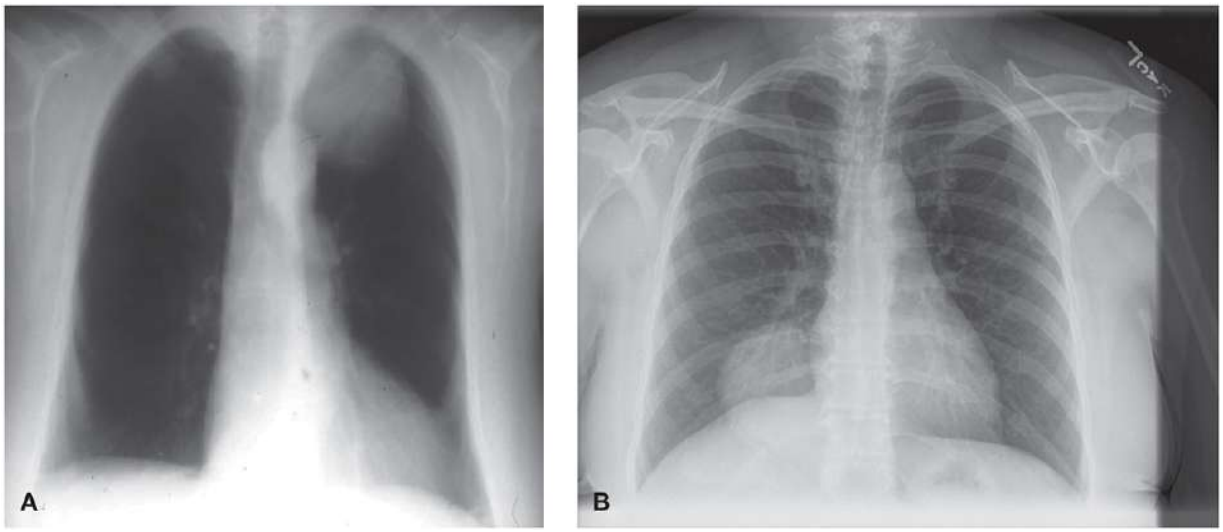

FIGURE 58.9 Posteroanterior chest radiographs of (A) a mediastinal schwannoma and (B) a mediastinal neurofibroma. (Courtesy of Steve Primack, MD.)

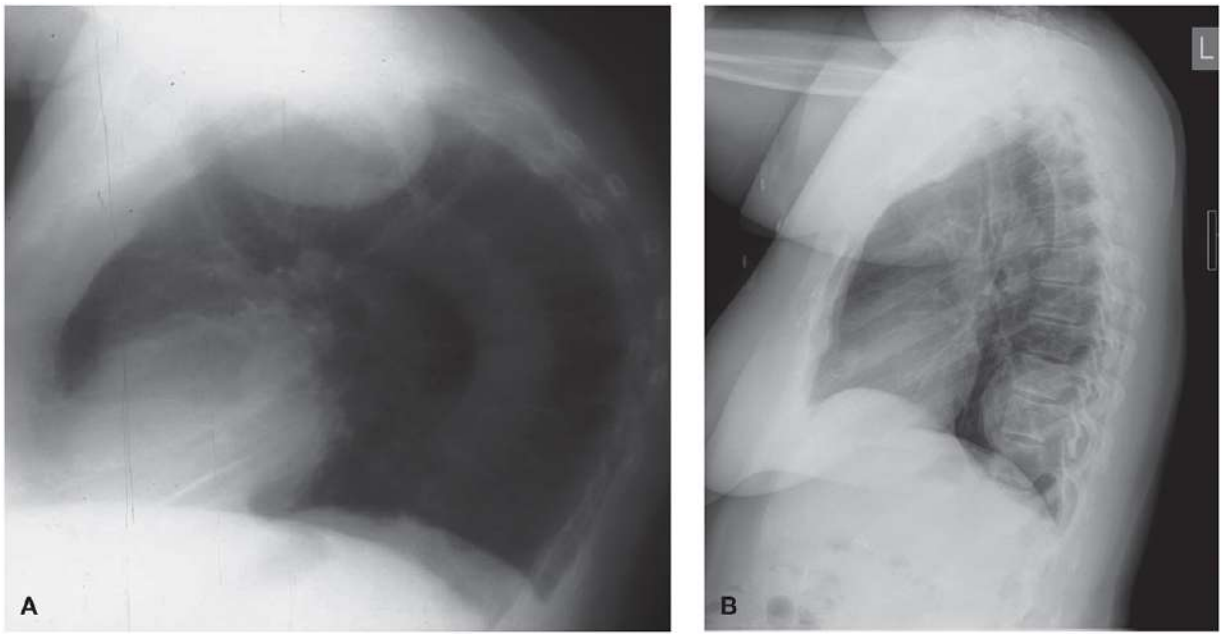

FIGURE 58.10 Panel A, Lateral chest radiograph of a mediastinal schwannoma. (Courtesy of Steve Primack, MD.) Panel B, posteroanterior chest radiograph of a mediastinal neurofibroma. (Courtesy of Steve Primack, MD.)

Management of malignant mediastinal neurogenic tumors requires a multidisciplinary approach similar to the management of adult soft tissue sarcomas. High-resolution CT (Figure 58.11) is essential, as is MRI (Figure 58.12), to evaluate the neural and spinal anatomy if involvement is suspected.[551] A definitive pathologic diagnosis is often reached after surgical intervention[552]; examples of histologic slides of a schwannoma and a neurofibroma are shown in Figures 58.13 and 58.14, respectively. Histologic examination often reveals nuclear atypia, mitotic figures, cellularity, typical Antoni A and B areas, and tumor necrosis; these findings, in combination with positive IHC staining for S-100 protein and negative staining for smooth muscle markers such as desmin, are suggestive of a nerve sheath origin. Of these features, the factor most reliably correlated with malignancy is a mitotic figure of 5 or more in 50 high-power fields.

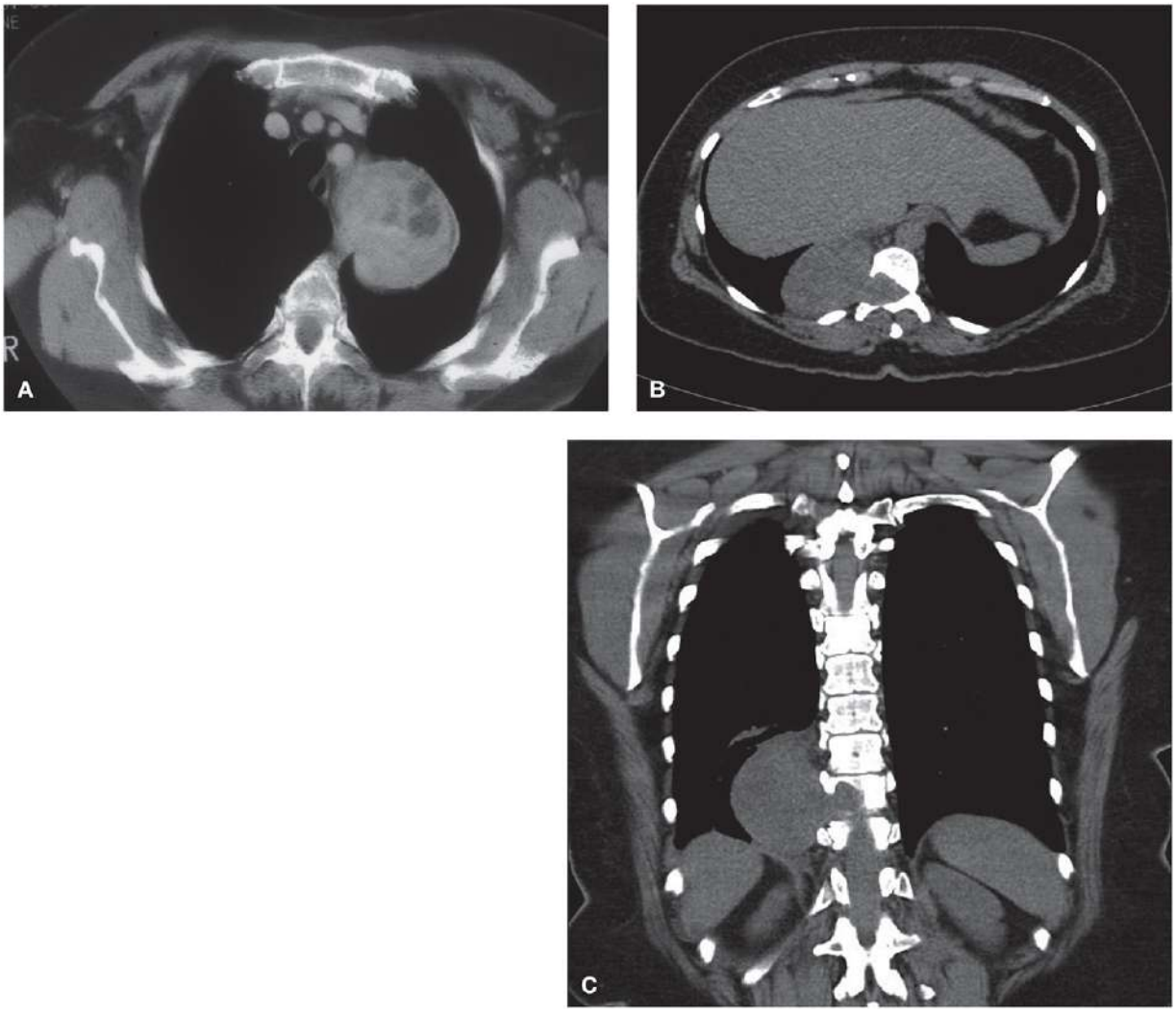

FIGURE 58.11 Axial computed tomography (CT) scans of (A) a mediastinal schwannoma involving the sympathetic chain and (B) a mediastinal neurofibroma. Panel C, Coronal CT scan of a mediastinal neurofibroma. (Courtesy of Steve Primack, MD.)

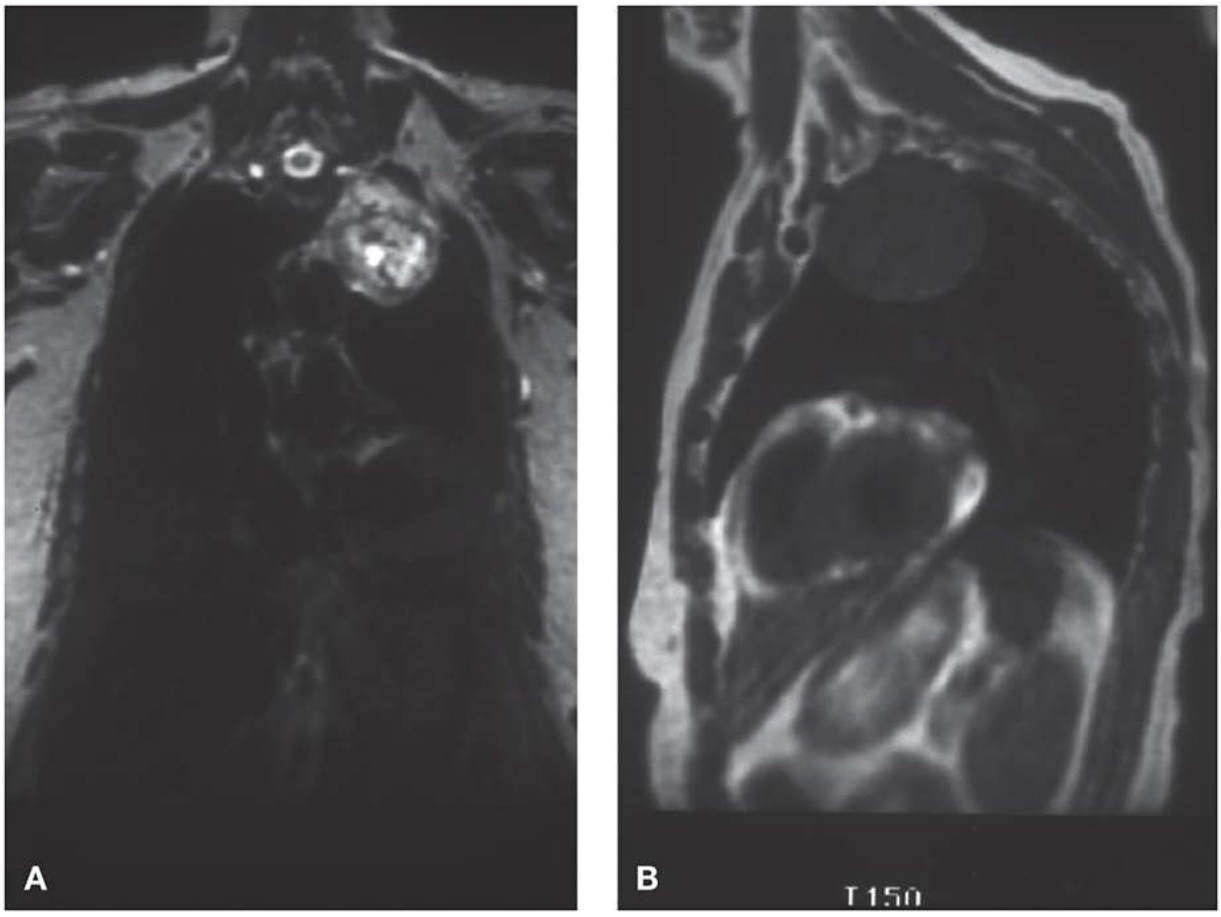

FIGURE 58.12 Coronal (A) and sagittal (B) magnetic resonance images of a mediastinal schwannoma involving the sympathetic chain. (Courtesy of Steve Primack, MD.)

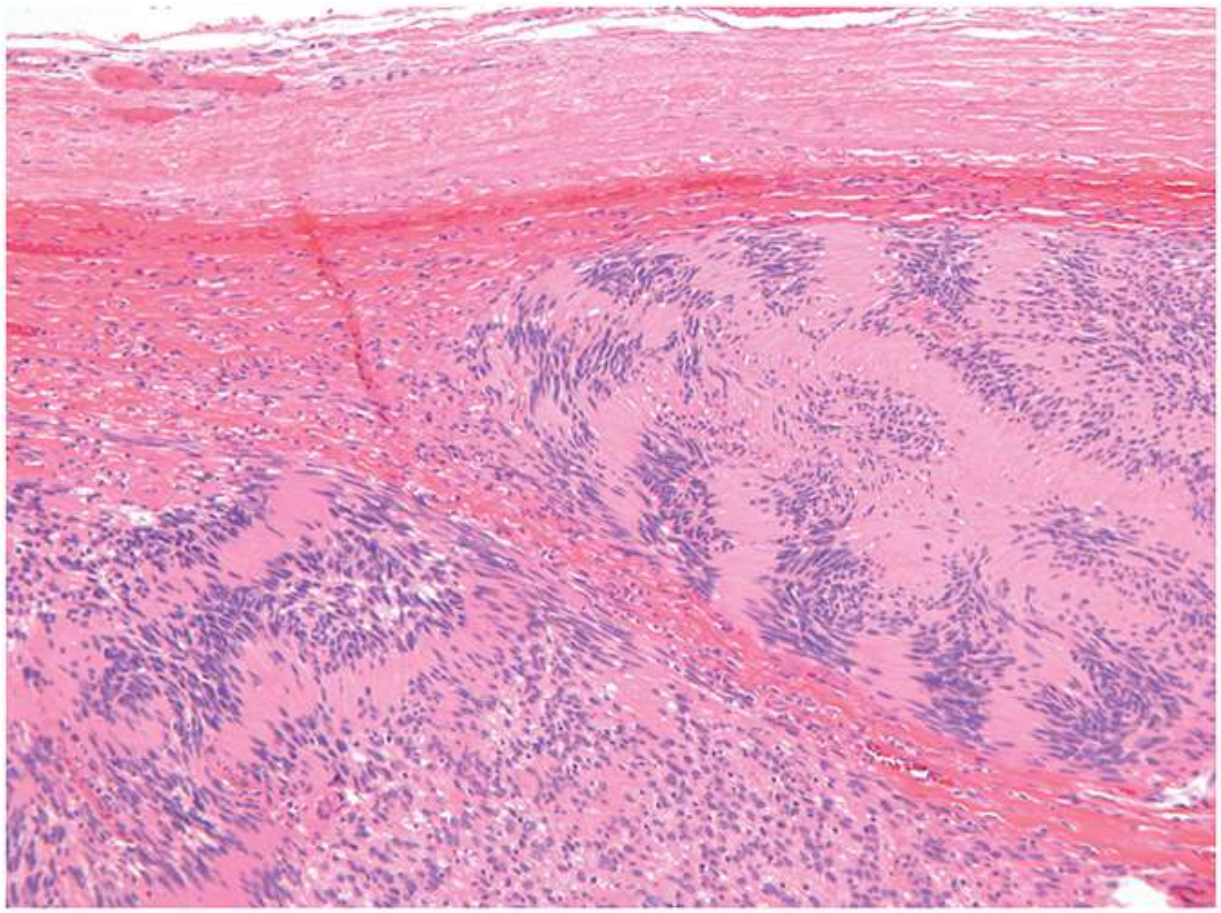

FIGURE 58.13 Hematoxylin-and-eosin–stained section of a schwannoma shows a circumscribed and encapsulated neoplasm composed of low-grade spindled and wavy Schwann cells with alternating palisaded cellular and stroma-rich areas (Verocay bodies) with nonpalisaded cellular foci (Antoni A areas) and hypocellular foci (Antoni B areas) (original magnification 100×). (Courtesy of David Sauer, MD.)

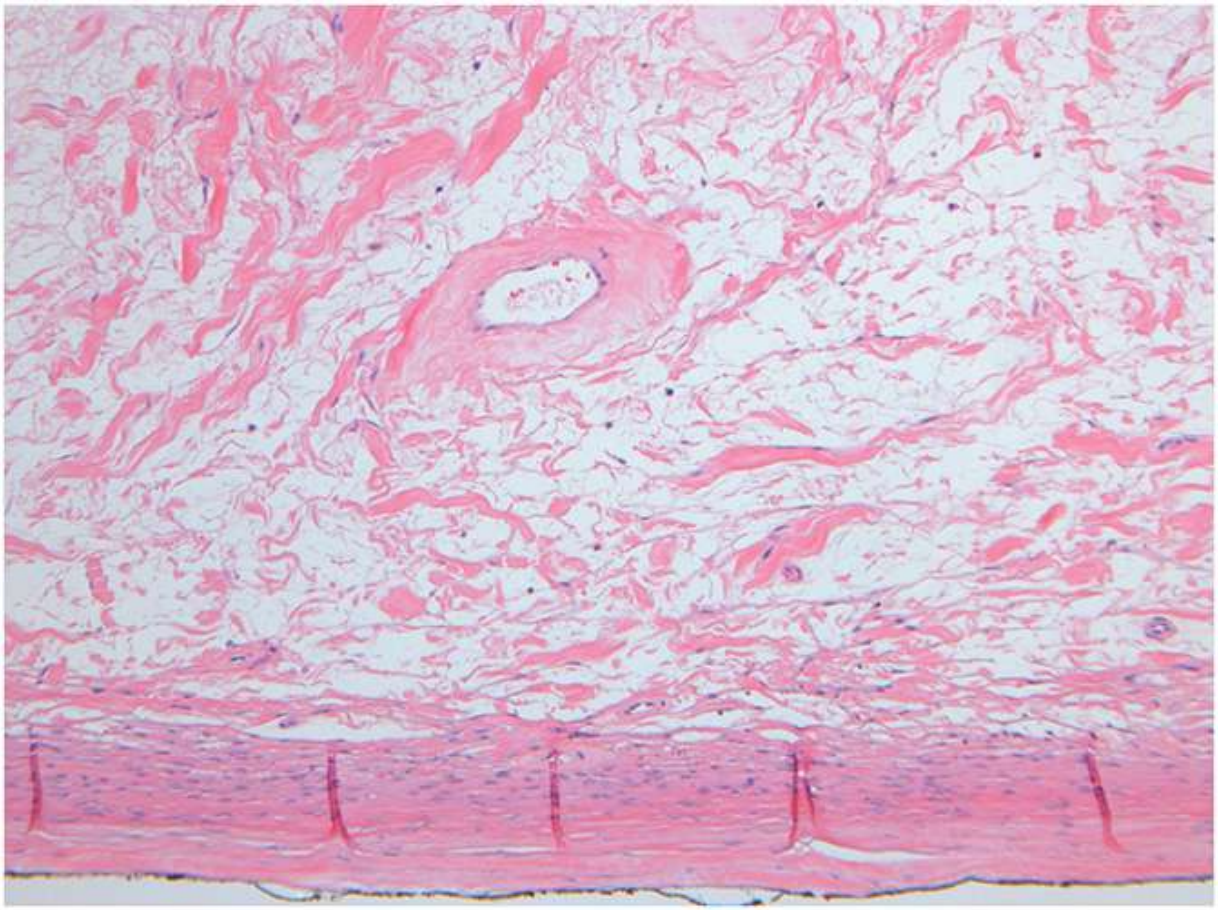

FIGURE 58.14 Hematoxylin-and-eosin–stained section of a neurofibroma shows a circumscribed and encapsulated neoplasm composed of a disorganized proliferation of low-grade spindled fibroblastic and Schwann cells within a myomatous and collagenous stroma (fibrils resembling shredded carrots). Scattered background mast cells and entrapped axons are also present (original magnification 100×). (Courtesy of David Sauer, MD.)

Surgical resection is the mainstay of therapy. An R0 resection should be attempted but is often difficult for mediastinal tumors because of impingement on surrounding structures and, in the case of neurofibromas, the risk of drastic neurologic deficits. Advances in surgical technique, including minimally invasive approaches such as VATS surgery, are available but should be undertaken only by experienced thoracic surgeons.[553-555]

As is true for the treatment of soft tissue sarcomas, radiation appears to improve local control for MPNSTs when combined with surgery. One series reported on 134 patients with MPNSTs treated at the Mayo Clinic between 1975 and 1993.[532] Only 25 of those patients had mediastinal tumors, a

resection with a negative margin was possible for 68%, which was an improvement over a historical series showing an R0/R1 rate of only 55% for mediastinal MPNSTs.[556] About half of the patients received radiation as a part of initial treatment, and the median cumulative radiation dose, including external beam irradiation, brachytherapy, and intraoperative radiation therapy, was 60 Gy. At 5 years, the overall survival rate was 52% and the local tumor control rate was 51% for the entire group of patients.

Prognostic factors for overall survival found to be significant in multivariate analyses were surgical margin status and history of radiation. Prognostic factors for local control were surgical margin status, radiation dose, and the use of intraoperative radiation or brachytherapy. The use of radiation with a dose of 60 Gy or higher as a part of the initial treatment showed statistically significant improvement of local control, whose rates were improved from 50% to 87% at 3 years and from 50% to 73% at 5 years (P = .021), but regarding overall survival, there was not statistically significant improvement.

Other evidence supporting the use of radiation after surgery for MPNSTs comes from a review of 205 patients with localized MPNSTs at all body sites treated over a 25-year period at the Istituto Nazionale per lo Studio e la Cura dei Tumori in Milan, Italy.[516] That study reported a disease-specific mortality rate of 53% at 10 years for the patients with tumors in the trunk. Of these, 44% of the patients had received radiation therapy. Variables found to be significant in multivariate analyses for survival included tumor site (head and neck or trunk tumor location has higher disease-specific mortality), tumor size (>12 cm), surgical margin status, and the use of adjuvant radiation (P = .016). Eventual distant metastasis development was seen in 42% of patients, the vast majority of which were pulmonary.

Planning and delivery of external beam radiation therapy for MPNSTs is facilitated with the use of modern approaches, including 3D conformal radiation, IMRT, and image-guided radiation using onboard imaging approaches. Patients with these tumors, which are complicated to manage, should be treated at centers with extensive multidisciplinary experience in thoracic and paraspinal neoplasms. Radiation treatment after surgery for microscopic disease should be given at a minimum dose of 60 Gy in 30 fractions, similar to the adjuvant dose given in other soft tissue sarcomas. Given the close proximity of the posterior mediastinum to the spinal cord,

careful attention should be paid to immobilization and the use of image guidance techniques. Although placing the patient in the prone position may reduce the distance from the localization points to the treatment volume, the patient must be able to rest comfortably in the same position throughout the treatments. Daily onboard imaging with stereoscopic guidance can ensure daily accuracy. IMRT is often necessary to provide a concave dose distribution around the spinal cord. In cases of gross residual disease, higher doses may be beneficial but can be challenging to deliver, given the constraints on exposure of normal tissues.

For patients with unresectable disease, radiation can be delivered either alone or with chemotherapeutic agents that are typically used for soft tissue sarcomas. Few agents are effective for MPNSTs, and treatment regimens usually include doxorubicin or ifosfamide.[557] Finally, significant progress has been made in recent years in elucidating the molecular genetics and biology of MPNSTs, especially in patients with NF-1. A variety of genetic alterations have been reported in MPNSTs, but it is yet unclear whether any of them are causally related to tumorigenesis or can be exploited for treatment effect.[558] As is true for the treatment of soft tissue sarcomas, radiation appears to improve local control for MPNSTs when combined with surgery. The findings from 134 patients with MPNSTs treated at the Mayo Clinic between 1975 and 1993.[532] Only 25 of those patients had mediastinal tumors, a resection with a negative margin was possible for 68%, which was an improvement over a historical series showing an R0/R1 rate of only 55% for mediastinal MPNSTs.[556] About half of the patients received radiation as a part of initial treatment, and the median cumulative radiation dose, including external beam irradiation, brachytherapy, and intraoperative radiation therapy, was 60 Gy. At 5 years, the overall survival rate was 52% and the local tumor control rate was 51% for the entire group of patients.

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TRACHEAL CARCINOMAS

Tracheal neoplasms are quite rare, contributing to fewer than 0.5% of all tumors.[559] Most of the information available to date is derived from pooled

population-based data sets or single-institution series involving a variety of treatment regimens. Review of the largely retrospective data has revealed several patterns: First, surgical resection is the cornerstone of therapy; second, local recurrence is a major pattern of failure resulting in morbidity and mortality; and third, adjuvant radiation seems to have some positive effect on outcomes.

Demographics

Primary tracheal malignancy is exceedingly uncommon, accounting for approximately 0.1% to 0.4% of all diagnosed malignancies.[560] Epidemiologic data from the SEER project estimate an incidence of 0.2 per 100,000 persons in the United States; the true incidence of tracheal carcinomas is likely even lower.[38] Traditionally, adenoid cystic carcinomas (formerly known as cylindromas) were considered the most common tracheal neoplasms, but recent reports suggest that the most prevalent histology worldwide is squamous cell carcinoma (60%-90%).[561] Other less common histologies include neuroendocrine tumors (glomus tumors, granular cell carcinomas, and small cell carcinoma),[562-566] sarcomas (chondrosarcoma and myxofibrosarcoma),[567,568] and glandular tumors (acinic cell carcinoma).

Tracheal cancer affects roughly twice as many men as women; estimates of incidence from the SEER database are 0.2 per 100,000 for men and 0.1 per 100,000 for women.[569] The male-to-female ratio is 23:1 for squamous cancer but is closer to 1:1 for adenoid cystic carcinomas.[570] Although squamous cell carcinoma is associated with tobacco exposure, data are mixed regarding the association of tobacco with adenoid cystic carcinoma.[571] Squamous cell variants typically present during the sixth decade of life, whereas adenoid cystic carcinomas seem to present at younger ages. Other histologies include carcinoid, carcinosarcoma, granular cell tumor, hemangioma, neurogenic tumors, chondroma, and chondrosarcoma.[572-618]

Anatomy

The trachea is a fibrocartilaginous tube connecting the larynx superiorly and the mainstem bronchi inferiorly. The esophagus, thyroid, parathyroid,

and trachea are derived from the same out-pouching of the embryonic foregut; the lungs arise from terminal tracheal buds.

In adults, the trachea is 12 cm long; its diameter is slightly larger in men (2.3 cm) than in women (2.0 cm). In cross section, the organ is "C" or "U" shaped. The upper border lies around the sixth or seventh cervical vertebra, and the lower border around the fourth (full expiration) or sixth (full inspiration) thoracic vertebra. Each centimeter of trachea contains about two cartilaginous rings. The posterior aspect of the trachea is membranous and is intimately associated with the esophagus. Three branches of the inferior thyroid artery supply blood to the upper half of the trachea and connect to the superior thyroid artery, which contributes small vessels that run from the tracheal wall adjacent to the thyroid isthmus. The bronchial arteries supply blood to the lower trachea and carina. Arterial branches interdigitate between each cartilaginous ring (see Figure 58.2).

Natural History

Tracheal carcinomas can present with a variety of symptoms, including cough, dyspnea, dysphagia, and hemoptysis.[600,619] Tracheal tumors tend to be evenly distributed between upper, mid-, and lower trachea.[620] Yang and colleagues reported cough to be the most common symptom (present in 72% of patients), followed by dyspnea (66%), stridor (39%), hemoptysis (39%), and dysphonia (31%).[621] Adenoid cystic carcinomas in particular are often first mistaken for asthma, which is often treated as such until "refractory" obstructive symptoms are evaluated with bronchoscopy, typically after numerous "normal" chest radiographs.[618,619,622-631] Hemoptysis is more likely to be the presenting symptom of squamous cell carcinoma,[621,632] and dysphagia is considered an ominous sign.[633] In one study of nonadenoid cystic/nonsquamous tracheal tumors, benign tumors presented with dyspnea, whereas malignant tumors were associated with hemoptysis.[575]

In 40% to 50% of cases, adenoid cystic carcinomas are diagnosed with metastases,[634] but survival is relatively long despite the presence of such metastases.[632,635-638] In one series, the median survival time for such patients was 37 months,[570] and the median reported survival from the time of diagnosis was approximately 5 years.[561,621] When these tumors spread, they

almost always do so in distant nodes rather than in the locoregional paratracheal lymph nodes. Local recurrence is the predominant form of treatment failure and can appear 10 or more years after treatment.[639-641]

Unlike adenoid cystic carcinoma, squamous cell carcinoma has a much more aggressive course, with reported median survival times of only 6 to 12 months depending on resectability.[19,632,633,637,642-647] The disease often presents with local extension via paratracheal lymph nodes (in ~30% of cases) and distant metastases.[648]

The clinical course and natural history of other pathologic variants of tracheal tumors are difficult to accurately characterize because of the scarcity of reported findings. Adenocarcinomas and sarcomas are thought to have poor prognoses.[575,611,613,617,649-662] Granular cell tumor, carcinoid, lymphoma, leiomyoma, and small cell carcinoma all have variable prognoses, yet they seem to be less aggressive than the squamous carcinomas, adenocarcinomas, or sarcomas.[575]

Staging and Prognostic Factors

No system for staging tracheal neoplasms has been universally accepted or adopted. One staging system proposed by Licht and colleagues does not seem to have predictable prognostic value.[47] In some studies, lymph node involvement does not seem to have a significant adverse effect on prognosis,[19,621,648] although an epidemiologic analysis showed an association between nodal status and survival outcomes.[663] The size and location of the tumor seem to be important because of the extent of surgical resection necessary to remove the tumor and higher postoperative mortality associated with carinal resection.[622,663,664]

In 2004, Bhattacharyya proposed a staging system, wherein stage I is defined as T1N0 disease, stage II as T2N0, stage III as T3N0, and stage IV as T4N0 or any N1 disease (Table 58.11).[663] A similar system, with minor modifications, was used by Webb and colleagues in evaluating the experience at MD Anderson Cancer Center.[561] Subsequently, Macchiarini proposed a more elaborate staging model that draws from experience with other thoracic malignancies.[559] In 2022, Piórek et al proposed a simplified TNM classification where both T and N classifications correlated with survival in patients treated surgically, whereas only T-stage correlates with

survival for patients treated palliatively. This difference is likely owing to a high likelihood of morbidity and mortality from local versus systemic symptoms[665] (Table 58.10). However, at this time, it remains to be seen which system will be broadly implemented by clinicians or validated with large-scale clinical data sets.

TABLE 58.11 STAGING SYSTEMS FOR TRACHEAL CARCINOMA

Bhattacharyya Staging System[626]

Primary Tumor (T)		
T1	Primary tumor confined to the trachea; size <2 cm	
T2	Primary tumor confined to the trachea; size >2 cm	
T3	Spread outside the trachea but not to adjacent organs or structures[a]	
T4	Spread to adjacent organs or structures[a]	
Tx	Unknown or cannot be assessed	
Regional Lymph Nodes (N)		
N0	No evidence of regional nodal disease	
N1	Positive regional nodal disease	
Nx	Unknown or cannot be assessed	
Anatomic Stage/Prognostic Groups		
Stage		
I	T1	N0
II	T2	N0
III	T3	N0
IV	Any	N1
IV	T4	Any
Macchiarini Staging System[559]		
Primary Tumor (T)		
Tx	Cannot be assessed	
Tis	Any tumor without invasion	
T1a	<3 cm limited to mucosa	
T1b	≥3 cm limited to mucosa	

Bhattacharyya Staging System[626]

T2	Any tumor that invades cartilage or adventitia		
T3	Any tumor that invades trachea or larynx		
T4a	Any tumor that invades carina or main bronchus		
T4b	Any tumor that invades neighboring structures		
Regional Lymph Nodes (N)			
Nx	Regional lymph nodes cannot be assessed		
N0	No evidence of node metastasis		
N1	Local nodes positive (N1a < 3 cm; N1b ≥ 3 cm)		
Upper third	Highest mediastinal nodes; upper paratracheal nodes, prevascular and retrotracheal		
Middle third	Upper paratracheal nodes; prevascular and retrotracheal; lower paratracheal nodes; para-aortic nodes (ascending aorta or phrenic)		
Lower third	Upper paratracheal nodes; prevascular and retrotracheal; subaortic nodes (aortopulmonalis window)		
N1A	1-3 positive nodes in upper third		
N1B	>3 positive nodes in upper third		
N2	Regional nodes positive		
Upper third	Lower paratracheal nodes; subaortic nodes (aortopulmonalis window)		
Middle third	Highest mediastinal nodes; subaortic nodes (aortopulmonalis window)		
Lower third	Upper paratracheal nodes; pulmonary ligament		
Distant Metastasis (M)			
Mx	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Metastasis to nodes other than N1 and N2		
M2	Distant metastasis (eg, lung)		
Anatomic Stage/Prognostic Groups			
Stage			
0	Tis	N0	M0

Bhattacharyya Staging System[626]

Ia	T1a	N0	M0
Ib	T1b-2	N0	M0
IIa	T1b-2	N1	M0
IIb	T1b-2	N2	M0
IIIa	T3	N0	M0
IIIb	T3	N1-2	M0
IVa	Any	N1-2	M1
IVb	Any	N1-2	M2

[a]The MD Anderson system denotes "arising from but extending outside of trachea" as T3 disease and does not use T4.[477]

Bhattacharyya Staging System from Bhattacharyya N. Contemporary staging and prognosis for primary tracheal malignancies: a population-based analysis. *Otolaryngol Head Neck Surg*. 2004;131(5):639-642. Copyright © 2004 American Association of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF). Reprinted by permission of John Wiley & Sons; Macchiarini Staging System reprinted from Macchiarini P. Primary tracheal tumours. *Lancet Oncol*. 2006;7(1):83-91. Copyright © 2006 Elsevier. With permission.

In addition to clinical staging, molecular genetic analysis may prove important in future characterization and treatment of tracheal cancers. Kieran reported a single case of tracheal adenoid cystic carcinoma with NOTCH1 mutations successfully treated with nirogacestat, an experimental NOTCH1 inhibitor.[666]

General Management

Bronchoscopy is essential for the diagnosis of tracheal malignancies and for preoperative surgical planning.[619,667-669] In an acute respiratory compromise, rigid bronchoscopy (see Figure 58.2) may be indicated to "core out" the tracheal neoplasm.[622,670,671] In one series of 56 patients reported by Mathisen and Grillo, rigid bronchoscopy led to improved airway symptoms in 90% of cases, with 5% experiencing mild, easily controlled bleeding.[672] Photodynamic therapy may hold promise as a means of local treatment for palliation of symptoms or definitive management of superficial early lesions.[673] Esophagoscopy is suggested for all patients to rule out esophageal invasion. A CT scan of the chest is indicated to aid in the

evaluation of tumor extension, resectability, involvement of lymph nodes, and pulmonary metastases,[600,619,669,674-678] and coronal reconstruction can be helpful to evaluate tracheal wall thickening and extraluminal extension.[679] Virtual bronchoscopy can be useful to get a complete characterization of tracheal and tumor anatomy to facilitate surgical planning.[680]

Treatment Approaches

Resectability is universally associated with lower mortality in reported series[19,637,667,681] and as such is the initial strategy for most tracheal primaries.[559,646,648,667,675,682-684] Resection rates vary, however, by institutional and national practice, from 10% to over 65% based on the above-cited studies. Historic registry data from the Netherlands demonstrated a resection rate of 12%[642]; however, a recent update[685] suggests that 24% underwent resection in 2000 to 2005 (vs 58% who received radiotherapy). Contraindications to resection depend in large part on the preference of the surgeon; for example, Pearson recommends tracheal resection for at least some patients with adenoid cystic carcinoma with low-burden pulmonary metastases, yet many would consider such cases unresectable.[570,634,686] Regardless, many tracheal carcinomas are either improperly classified (eg, nontracheal primaries with tracheal extension) or systematically undertreated surgically.[685]

Most patients undergoing surgery have a median sternotomy and cervical collar excision, although extensive subglottic or high tracheal disease may require cervical exenteration with mediastinal tracheostomy.[634,640,648] Margins may of necessity be compromised to ensure a functioning airway. Technical advances in surgical procedures such as complete mobilization of the right hilar ligament, detachment/implantation of the left hilum, mobilization of the cervical trachea, and techniques for carinal resection/reconstruction and intrapericardial dissection have improved the likelihood of an R_0 resection.[342,664,681,687] Other surgical techniques like VATS are also reported in a limited number of cases.[688,689] Gaissert and colleagues reported improvements in both complete resection rates (from 68% to 82%) and in-hospital mortality (declining from 21% to 3%) with the increasing use of such techniques over a 40-year period.[636,682]

After resection, postoperative radiation is usually recommended.[561,636,637,667,668,671,682] Pathologic features such as completeness of resection, involvement of the thyroid gland, and lymphatic invasion have clearly been shown to have prognostic value,[690] and postoperative radiotherapy is routinely recommended for all patients at many institutions.[561,690] Preoperative radiotherapy has also been attempted, but fewer reports of this experience have been published. In aggregate, several small retrospective series seem to show a benefit for adjuvant radiation (Table 58.12). Chow and colleagues found that patients who underwent resection plus adjuvant radiation had a median survival time of 61 versus 16 months for those who received only surgery.[691] Regnand and others found that 31 patients who had had a complete resection with adjuvant radiation had seemingly better 5-year survival rates than did 27 patients without adjuvant radiation (74% vs 53%), but this apparent difference was not statistically significant.[19]

TABLE 58.12 RESULTS OF RESECTION WITH ADJUVANT IRRADIATION FOR PRIMARY TRACHEAL CARCINOMA

Study and Reference	Histology	Treatment	Median Survival Times or Rates
Grillo and Mathisen[637]	Squamous (*n* = 70) Adenoid cystic (*n* = 80)	Surgery ± RT[a] RT Surgery ± RT[a] RT	34 mo 10 mo 118 mo 28 mo
Licht et al[47]	–	Surgery alone (*n* = 6) RT alone (*n* = 35) Laser/cautery ± RT (*n* = 24) RT + chemo (*n* = 2)	48% (5-y actuarial) 7% 28% 0%
Chow et al[691]	–	Surgery alone (*n* = 5) RT alone (*n* = 12) Surgery + RT (*n* = 5)	16 mo 26 mo 61 mo
Regnard et al[19]	–	R_0 + RT (*n* = 31) R_0 (*n* = 27) $R_{1,2}$ + RT (*n* = 15) $R_{1,2}$ (*n* = 6)	74% (5-y actuarial) 53% (*P* = NS) 47% 0% (*P* < .05)

Study and Reference	Histology	Treatment	Median Survival Times or Rates
Maziak et al[570]	Adenoid cystic (*n* = 35)	R_0 ± RT (*n* = 14)[a] $R_{1,2}$ + RT (*n* = 15) RT alone (*n* = 6)	9.8 y 7.5 y 6.2 y
Wang et al[692]	Adenoid cystic (*n* = 191)	R_0 (*n* = 45) R_0 + RT (*n* = 26) R_1 + RT (*n* = 58) R_1 alone (*n* = 13) RT alone (*n* = 23)	198 mo (surgically treated patients) 92 mo (nonsurgically treated patients)

R_0, complete resection; $R_{1,2}$, incomplete resection; RT, radiation therapy.

[a]A minority of these patients received surgery alone.

Postoperative radiation seems to be effective for incompletely resected disease as well, with 5-year survival rates of 45% for such patients versus 0% for patients who did not receive radiation ($P < .05$).[19] Webb and colleagues, describing the experience at MD Anderson, demonstrated a statistically significant improvement in survival for patients given adjuvant radiotherapy rather than chemoradiation; however, no difference in survival was found between adjuvant radiotherapy and surgery alone.[561] In the largest series reported to date, 191 patients consecutively treated at the National Cancer Center, China, Wang and colleagues used postoperative radiation therapy for positive margins and salvage radiation therapy after local failure. In their series radiation, therapy has significant impact in both settings, with disease-free survival of 55 and 31 months, respectively, after the use of radiation therapy.[692] The results of studies of definitive therapy for tracheal tumors are summarized in Table 58.13.

TABLE 58.13 RETROSPECTIVE SERIES EXAMINING RADIOTHERAPY ALONE FOR PRIMARY TRACHEAL CARCINOMA

Study	Histology	Treatment	Local Control	Survival
Schraube et al[645]	Squamous (*n* = 11)	46-60 Gy RT + 15-20 Gy HDR	6/11	31 mo median
Cheung[720]	Squamous (*n* = 20)	40-60 Gy 40-60 Gy		5 mo median 12 mo median

Study	Histology	Treatment	Local Control	Survival
	Adenoid cystic (*n* = 4)			
Fields et al[694]	Squamous (*n* = 17) Adenoid cystic (*n* = 1)	>60 Gy 40-60 Gy <40 Gy >60 Gy	5/6 1/7 0/4 1/1	25% at 5 y (*n* = 18)
Rostom and Morgan[721]	Squamous (*n* = 28) Adenoid cystic (*n* = 3)	60-70 Gy <60 Gy 50-70 Gy	16/24 0/4	11% (4-y actuarial) 67% at 4 y
Makarewicz and Mross[695]		60 Gy RT + 6-12 Gy HDR (*n* = 8) 40-60 Gy RT (*n* = 3) <40 Gy (*n* = 12)	6/8 1/3 0/12	9.5 mo median (*n* = 23)
Fuwa et al[698]		RT + LDR (*n* = 4) (80-128 Gy)[a]	3/4	75% at 3 y
Zeng et al[706]	Squamous (*n* = 18) Adenoid cystic (*n* = 6)	60-70 Gy	9/18 5/6	33.3% at 5 y
Je et al[722]	Adenoid cystic (*n* = 9)	RT (*n* = 3) RT + HDR BT boos (*n* = 6)	0/3 3/6	66.7% at 5 y 22.2% at 10 y

HDR, high-dose rate; LDR, low-dose rate; RT, radiotherapy.

[a]One treatment-related death in patient receiving 60 Gy RT + 53 Gy LDR Ir-192.

Radiation has also been used as monotherapy for unresectable tumors and is the only independent risk factor for survival in these patients.[693] Results are best when doses have exceeded 60 Gy.[643,694,695] Mornex and associates found that the 5-year survival rate decreased from 12% for those receiving at least 56 Gy to 5% for those receiving lower doses.[696] However, Chow and others caution against giving doses higher than 60 Gy, as three of six patients in their study given doses in excess of 60 Gy had severe complications requiring surgical intervention, for example, tracheoesophageal fistula, esophageal stricture, and severe tracheal

crusting,[691] whereas none of the six patients treated with less than 60 Gy in that study had late side effects. Other authors have corroborated the concern of high doses contributing to the risk of complications.[697] Still, Chow and colleagues noted significantly better local control among patients who received greater than 50 Gy as adjuvant therapy and greater than 60 Gy as definitive therapy.[691] By way of comparison, Fuwa and colleagues reported reasonable results with a novel endoluminal-centering catheter; the median dose delivered to the group as a whole was 91 Gy (given as external beam radiation with low-dose rate 192Ir brachytherapy). Only one treatment-related death was reported 1 year after therapy in a patient who had received a total dose of 113 Gy.[698] Harms and colleagues, using median doses of 60 Gy delivered by external beam radiation plus 15- to 18-Gy brachytherapy boosts, reported minimal rates of severe (grade 3-4) toxicity (8% of 25 patients).[699] Exploratory studies of fast neutrons for locally advanced adenoid cystic carcinomas have been reported; in the University of Washington experience with endoluminal brachytherapy, fast neutrons were considered feasible and toxicity acceptable.[700] A summary of the experience with radiation as monotherapy for primary tracheal neoplasms is given in Table 58.11.

Combined chemoradiotherapy without resection has been attempted at some institutions, usually for nonsquamous tumors, with mixed results.[561,632,701,702] In general, patients with squamous cell carcinoma have fared poorly, and those with small cell carcinoma or lymphoma have done better.[47,561,621,703]

Radiation Techniques

No evidence is available to suggest that adjuvant radiation therapy is not beneficial in tracheal malignancies; however, any postoperative radiation should not be begun before 30 to 45 days after surgery to allow sufficient wound healing. Modern CT-based 3D conformal or intensity-modulated radiation techniques should be used. Case reports and small series using proton therapy[704] and carbon ion therapy[705] are also reported. Aggressive treatment is warranted to prevent airway obstruction, even when the intent is palliative.[696] External beam doses should be about 60 Gy for fully resected disease,[561] with a boost considered for squamous cell lesions with

high-risk features.[690] In a series of 32 patients treated for tracheal cancers reported by Zeng and colleagues in 2020, higher boost doses, up to 68 Gy, resulted in improvement in PFS compared to patients getting lower or no boost dose (5-year PFS 44% vs 13%). They did not observe increases in grade 3 or higher toxicity. Radiation therapy techniques included 2D, 3D, and IMRT.[706]

An intraluminal boost technique allows the dose to be increased (and, theoretically, local control to be increased as well) with minimal added acute or late side effects.[645,691,699,707-709] Standard constraints on organs at risk should be observed in all cases.[275,276,278,710] Intraluminal brachytherapy is also useful for palliative treatment. Skowronek and colleagues, in a study of patients treated with 10 to 30 Gy in one to three fractions, found that high-dose brachytherapy as monotherapy led to prolonged survival and improved quality of life.[709] In patients with locally extensive disease, the gravest complication of radiation therapy is the development of a tracheoesophageal fistula, which can be difficult if not impossible to avoid. For patients with emergent airway obstruction, rigid bronchoscopy should be performed instead of urgent radiotherapy.

The role of elective nodal irradiation for tracheal carcinoma is uncertain. As mentioned earlier, nodal status does not seem to have prognostic significance; even cervical adenopathy was not associated with poorer outcome.[621] Given the low proclivity for lymphatic spread of adenoid cystic carcinomas, the choice to avoid elective nodal irradiation for this variant is certainly reasonable. Because local recurrence is the major factor influencing survival, nodal and regional failure patterns are not a main concern. Yet if mediastinal or cervical nodes are seen on radiographic or pathologic examination, or if worrisome pathologic risk features[690] are discovered at surgery, radiation to these regions should be considered.

CONCLUSION

Primary tracheal cancer is quite rare and, in most cases, is of squamous or adenoid cystic histology. The optimal management strategy for these tumors seems to be a combined modality approach incorporating surgical resection and postoperative radiation. For localized disease, the role of chemotherapy, either alone or concurrent with radiation, is unknown.

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CHAPTER 59

Esophageal Cancer

Brian G. Czito and Christopher G. Willett

Less than 20% of patients diagnosed with esophageal cancer are cured, with approximately half of patients presenting with unresectable or metastatic disease. This chapter reviews the natural history and treatment of esophageal cancer, including anatomy, risk factors, patterns of spread and recurrence, staging, results of current therapeutic approaches, radiation planning techniques, toxicity data, and future treatment strategies.

ANATOMY

The esophagus is a thin-walled, hollow tube approximately 25 cm in length. It is lined with stratified keratinized squamous epithelium, extending from the cricopharyngeus muscle at the level of the cricoid cartilage superiorly to the gastroesophageal (GE) junction inferiorly. The lower one-third (5-10 cm) of the esophagus may contain glandular elements. Replacement of the stratified squamous epithelium with columnar epithelium is referred to as Barrett esophagus, often occurring in the lower one-third. The Z line refers to the endoscopically visible junction of the squamous and glandular epithelium. The esophageal wall is composed of three layers: the mucosa, submucosa, and muscularis propria (Figure 59.1). The mucosal layer contains the epithelium, lamina propria, and muscularis mucosae. The epithelium is separated from the lamina propria by a basement membrane. In the portion of the esophagus containing columnar-type epithelium, the muscularis mucosae may consist of two layers. The mucosa may be divided into distinct layers, including M1 (epithelium), M2 (lamina propria), and M3 (muscularis mucosae). Similarly, the submucosal layer may be divided into inner (SM1), middle (SM2), and outer (SM3) layers. The muscularis propria consists of a circular inner layer and longitudinal outer layer. The adventitia (periesophageal connective tissue) lies directly on the muscularis propria.[1] No serosa is present, facilitating extraesophageal spread of disease.

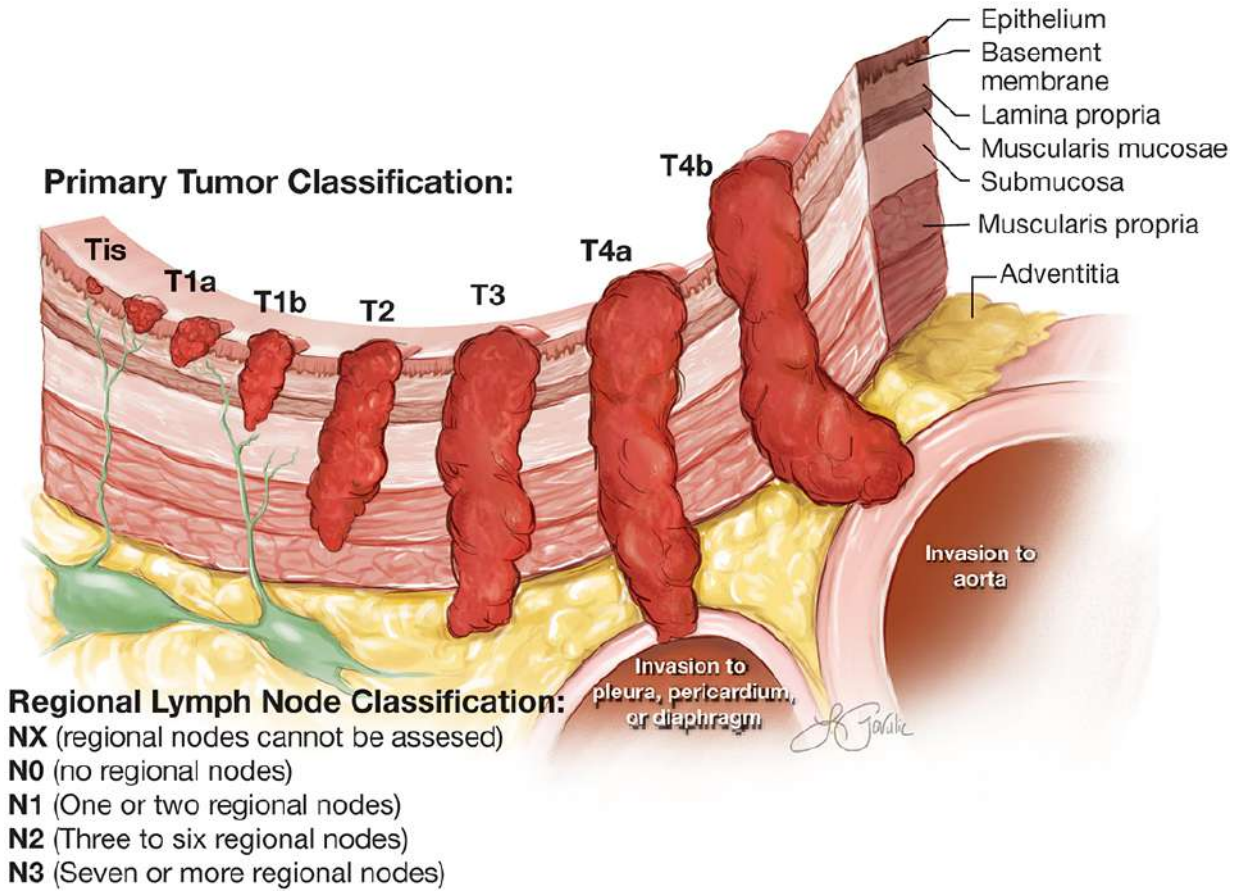


FIGURE 59.1 Diagram of esophageal wall. (Reprinted with permission from American College of Surgeons, Hunt KK, Katz MHG, Veeramachaneni N. In: Alliance for Clinical Trials in Oncology, ed. *Operative Standards for Cancer Surgery: Vol 2: Thyroid, Gastric, Rectum, Esophagus, Melanoma*. Wolters Kluwer; 2019:313.)

Although somewhat arbitrary, the esophagus is frequently divided into cervical and thoracic components. The most recent American Joint Committee on Cancer (AJCC) report divides the esophagus into four regions: cervical, upper thoracic, midthoracic, and lower thoracic (Figure 59.2).[1] The cervical esophagus lies within the neck and begins at the cricopharyngeus muscle (approximately the C7 level or 15 cm from the incisors) and extends to the thoracic inlet (at approximately the T3 level or at ~20 cm from the incisors [the level of the suprasternal notch]). The thoracic esophagus extends from approximately the level of T3 (beginning at about 20 cm) to T10 or T11.[1,2] The upper thoracic esophagus is bordered superiorly by the thoracic inlet and inferiorly by the lower border of the azygos vein, extending from approximately 20 to 25 cm. Radiographically, tumors in this location would be located between the sternal notch and azygos vein. The middle thoracic esophagus extends from the lower border of the azygos vein to the inferior pulmonary veins, extending from approximately 25 to 30 cm. The lower thoracic esophagus extends from the inferior pulmonary veins to the stomach and is inclusive of the GE junction, typically extending from approximately 30 to 40

cm. Endoscopically, the GE junction is often defined as the point where the first gastric fold is encountered, although this may be a “theoretical” landmark. The location of the GE junction can be accurately defined histologically as the squamocolumnar junction. In the most recent AJCC staging system, cancers with an epicenter in the lower thoracic esophagus or GE junction or within the proximal 2 cm of the stomach (ie, cardia) and extending up to the GE junction or esophagus are staged as an adenocarcinoma of the esophagus. If the epicenter is more than 2 cm distal to the GE junction, these are classified as stomach cancers. Useful landmarks in reference to endoscopy include the carina (~25 cm from the incisors) and GE junction (~40 cm from the incisors).

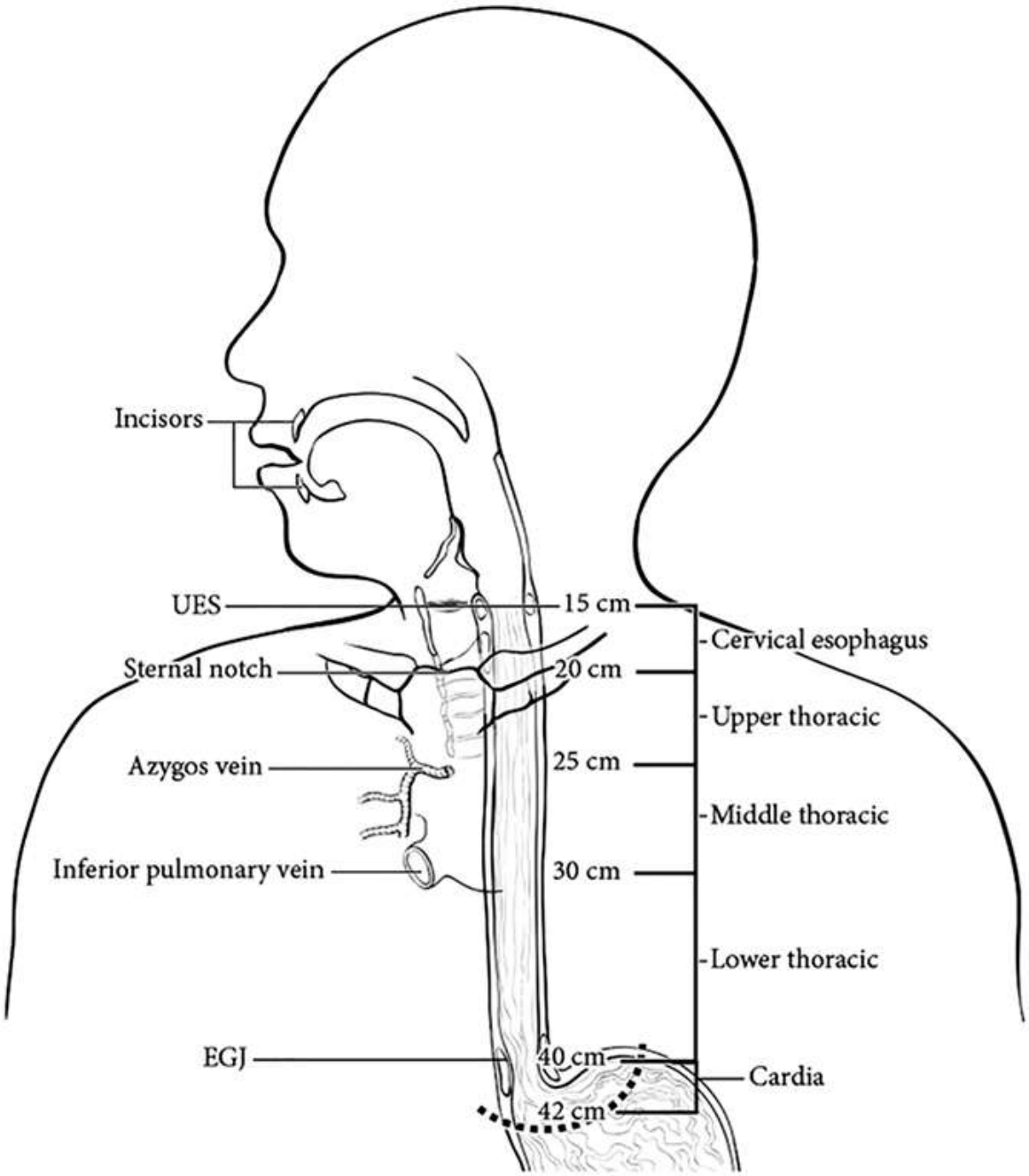
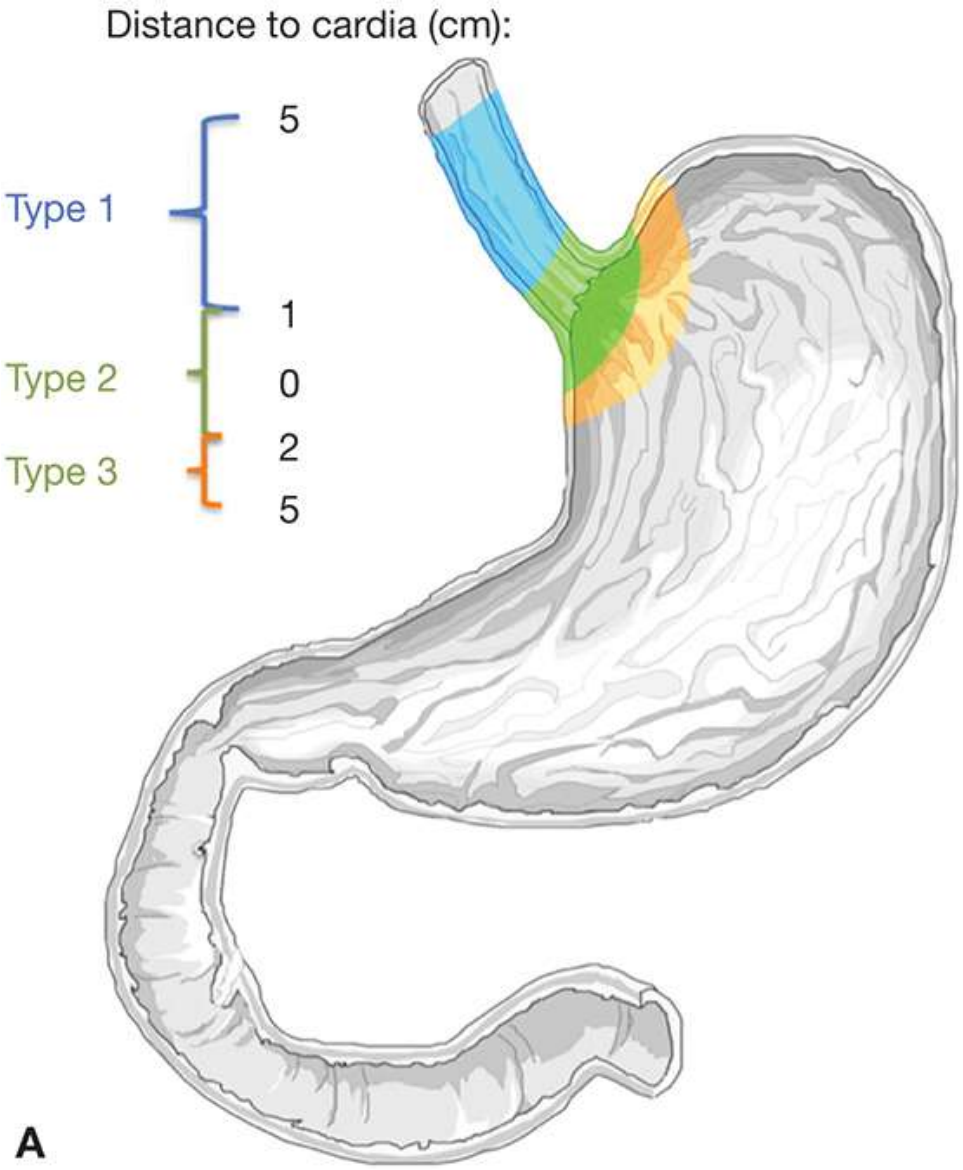


FIGURE 59.2 Anatomy of the esophagus. Note the lengths of various segments of the esophagus as measured from the upper central incisors. EGJ, esophagogastric junction; LES, lower esophageal sphincter; UES, upper esophageal sphincter. (From Rice TW, Gress DM, Patil DT, Hofstetter WL, Kelsen DP, Blackstone EH. Cancer of the esophagus and esophagogastric junction—major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017;67(4):304-317. Copyright © 2017 American Cancer Society. Reprinted by permission of John Wiley & Sons, Inc.)

Rudiger Siewert et al[3,4] characterized cancer *involving the GE junction* according to the location of the tumor (Figure 59.3). If the tumor center is located from more than 1

cm up to 5 cm above the GE junction (Z line), the tumor is classified as a type I adenocarcinoma of the distal esophagus. If the tumor center is located within 1 cm cephalad to 2 cm caudad to the GE junction, it is classified as type II. If the tumor center is located more than 2 cm below the GE junction, the tumor is classified as type III. Only Siewert type I/II tumors would be staged as esophageal cancer in the most recent AJCC staging system. However, locally advanced/bulky tumors can make it difficult to accurately distinguish where tumors originated in relationship to the GE junction.


Distance to cardia (cm):
5
Type 1
1
Type 2
0
2
Type 3
5
A

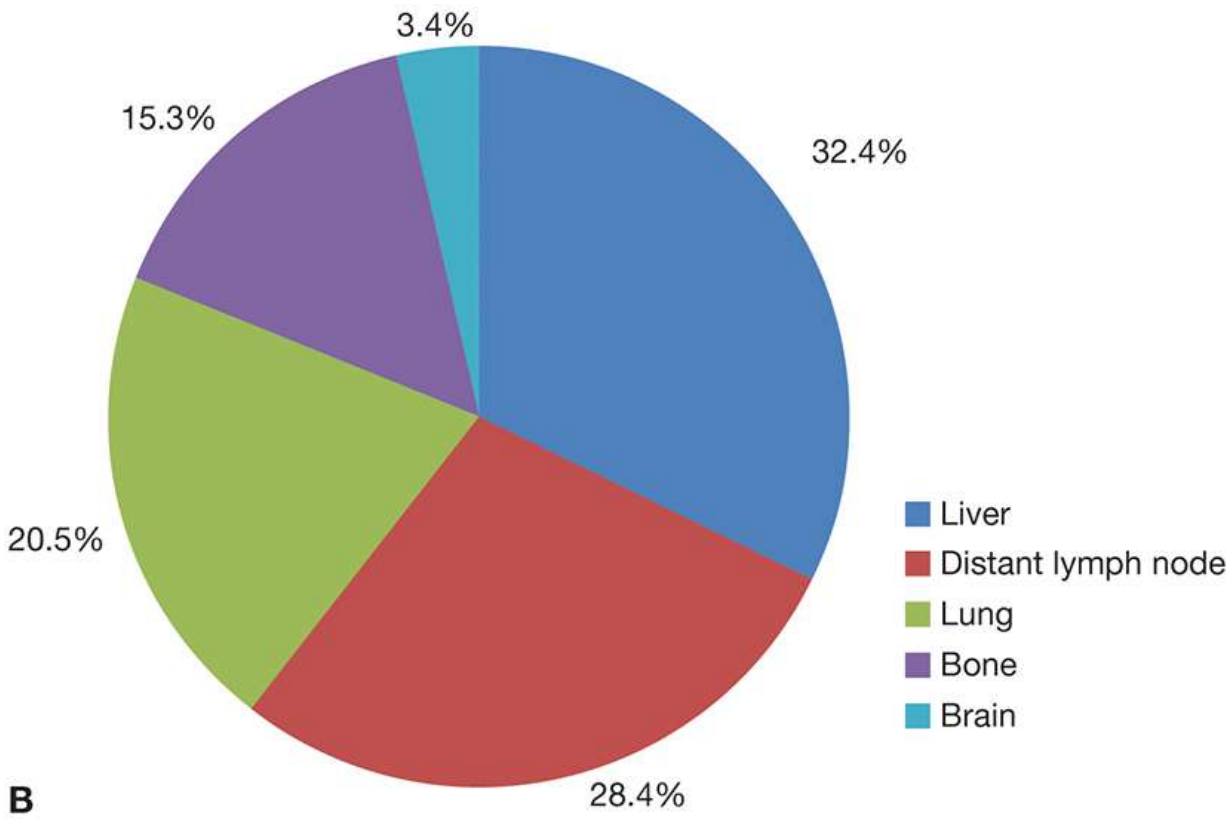


FIGURE 59.3 A. Siewert classification of the gastroesophageal junction cancers according to the location of the tumor. (Reprinted from Matzinger O, Gerber E, Bernstein Z, et al. EORTC-ROG expert opinion: radiotherapy volume and treatment guidelines for neoadjuvant radiation of adenocarcinomas of the gastroesophageal junction and the stomach. *Radiother Oncol*. 2009;92[2]:164-175. Copyright © 2009 Elsevier Ireland Ltd. With permission.) B. The distribution of 2,043 sites of distant metastases in 1,440 patients with esophageal cancer. (Adapted from Wu SG, Zhang WW, Sun JY, Li FY, Lin Q, He ZY. Patterns of distant metastasis between histological types in esophageal cancer. *Front Oncol*. 2018;8:302. http://creativecommons.org/licenses/by/4.0/.)

Lymphatic Drainage

The esophagus has an extensive, longitudinal interconnecting system of lymphatics. The esophageal lymphatic network is primarily located within the submucosa (Figure 59.4); however, channels are also present within the lamina propria, facilitating spread of even superficial cancers of the esophagus involving the mucosa. In addition to these longitudinal lymphatics, intramural lymphatics may traverse the muscularis propria, facilitating tumor spread to regional lymphatic channels and paraesophageal nodes. Supporting this, autopsy series have demonstrated a high incidence of directly draining channels extending from the submucosa lymphatics into the thoracic duct, facilitating systemic spread. Lymph can travel the entire length of the esophagus before draining into lymph nodes,[2] and thus, the entire esophagus is at potential risk for lymphatic involvement. Up to 8 cm or more of "normal" tissue can exist between gross tumor and micrometastases "skip areas" secondary to this extensive lymphatic network.[5] In

addition, as many as 71% of frozen tissue sections scored as margin negative by conventional histopathology show involvement by lymphatic micrometastases with immunohistochemistry.[6] Lymphatics of the esophagus drain into nodes that usually follow arteries, including the inferior thyroid artery, the bronchial and esophageal arteries, and the left gastric artery (celiac axis).[7]

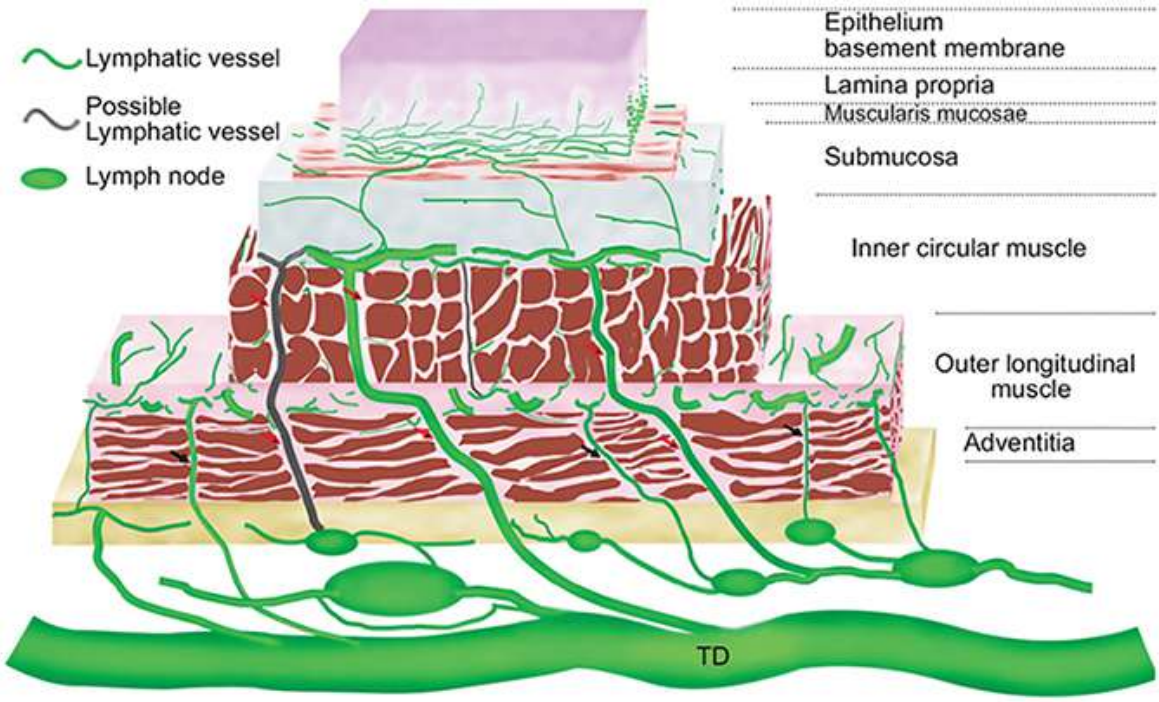


FIGURE 59.4 Lymphatics are found in virtually all layers of the esophagus except epithelium and basement membrane, primarily running longitudinally in the lamina propria and submucosa and more radially in the intermuscular space. More superficial lymphatics generally connect to the submucosa, which can subsequently drain directly to the thoracic duct or regional lymph nodes (including paraesophageal). Similarly, there can be direct lymphatic drainage to the intermuscular lymphatic plexus within the muscularis propria. Adventitial lymphatics can also drain to local regional lymphatics as well as the thoracic duct. (From Wang Y, Zhu L, Xia W, Wang F. Anatomy of lymphatic drainage of the esophagus and lymph node metastasis of thoracic esophageal cancer. *Cancer Manag Res*. 2018;10:6295-6303. Reprinted by permission of Informa UK Limited, trading Taylor & Francis Group. https://www.tandfonline.com)

EPIDEMIOLOGY AND RISK FACTORS

Esophageal carcinoma accounts for approximately 6% of all gastrointestinal malignancies. In 2025, there will be an estimated 22,070 new patients diagnosed with esophageal cancer in the United States and 16,250 deaths. Worldwide, in 2020, an estimated 604,000 esophageal cancer cases and 544,000 deaths occurred. Five-year survival worldwide for esophageal cancer ranges from 15% to 25%.[8] Most cases occur in males, at a rate of 4:1 relative to females.[9-11]

The incidence of esophageal carcinoma varies according to geography. Most cases of esophageal cancer occur in less developed countries. Nearly 80% of cases and deaths

occur in Asia. Worldwide, squamous cell carcinoma accounts for 90% of all disease. In contrast, adenocarcinoma is more common in developed countries.[8] The highest incidence of esophageal cancer occurs in Linxian, China, Russia, and the Caspian region of Iran. The incidence in these regions is 100/100,000 persons. What is often referred to as the "esophageal cancer belt" extends from northern Iran through the Central Asian republics to north-central China. In areas such as northern France, Kazakhstan, and South Africa, the incidence can be as high as 50 to 99/100,000. Although the reasons for the geographic discrepancy are unknown, some reports have linked the arid climate and alkaline soil with these high-risk areas, as well as the ingestion of nitrosamines, and inversely to the consumption of riboflavin, nicotinic acid, magnesium, and zinc.[12,13] In the United States, the incidence rate among males is less than 5 per 100,000. Over the last 20 years, there has been an increase in the incidence of adenocarcinoma at a rate of 5% to 10% per year.[14] In 1987, adenocarcinoma was reported to represent 34% and 12% of esophageal cancers in White men and women versus 3% and 1% for African American men and women, respectively.[14] As of 1998, esophageal adenocarcinoma accounted for almost 55% of all diagnosed cases in White men, and in the United States, the rates of adenocarcinoma now exceed those of squamous cell carcinoma, accounting for 80% of esophageal cancers in the United States.[8] African American men are more frequently diagnosed with squamous cell carcinoma.[14-16]

Important risk factors for esophageal cancer include sex, race, alcohol consumption, smoking, obesity, economic and social status, and dietary (tea and coffee consumption, low consumption of fruits and vegetables, and micronutrients) and genetic factors.[17,18] In North America and Western Europe, alcohol use and tobacco use are the major risk factors for squamous cell carcinoma, accounting for 80% to 90% of cases.[19] Reports have described the relative risk of esophageal cancer by the amount of alcohol and tobacco consumed, including a relative risk of 155:1 when consuming more than 30 g/day of tobacco along with 121 g/day of alcohol.[20]

Diets low in fruits, vegetables, and animal products result in marginal deficiencies in vitamins and trace elements and are associated with the development of squamous cell carcinoma.[21] Patients with Plummer-Vinson (Paterson-Kelly) syndrome, a condition characterized by iron deficiency anemia and low riboflavin levels, are at an increased risk for oral cavity, hypopharyngeal, and esophageal cancer. In addition, dietary intake of nitrosamines, nitrosamides, and *N*-nitroso compounds and exposure to polyaromatic hydrocarbons have been implicated in esophageal carcinoma. Examples of nitrate-rich foods include pickled vegetables, alcoholic beverages, cured meats, and fish. Betel quid chewing in Taiwan and India has been implicated as a potential cause as well.[22-24] Thermal irritation from consumption of hot beverages, soup, and food and physical irritation due to loss of teeth (poor oral hygiene) have been implicated in some studies. The role of human papillomavirus 16 and 18 has been linked to squamous cell carcinoma in some geographic areas although these results are inconsistent.[24]

Other risk factors associated with esophageal carcinoma include achalasia and tylosis. Achalasia of long duration (25 years) is associated with a 5% incidence of squamous cell carcinoma.[25,26] Patients with tylosis (hyperkeratosis of the palms and soles and papilloma of the esophagus) have a reported 38% risk in developing esophageal cancer at a mean age of 45 years.[27] In addition, carcinoma of the esophagus occurs in 2% to 4% of patients with head and neck cancer.

Risk factors leading to the development of adenocarcinoma of the esophagus are increasingly understood. Most esophageal adenocarcinomas tend to arise from the metaplastic columnar-lined epithelium known as Barrett esophagus.[28] Severe and long-standing GE reflux disease has clearly been shown to be a significant risk factor for Barrett esophagus, which may lead to adenocarcinoma. It has been estimated that patients with long-standing severe reflux have a 44-fold risk of developing adenocarcinoma.[29] Tobacco use is a more moderate risk factor for adenocarcinoma development. Smokers appear to have a 2- to 3-fold greater risk for developing esophageal adenocarcinoma than do nonsmokers.[30,31] The relative risk of esophageal adenocarcinoma persists even after three decades following smoking cessation, in contrast to a significant decline in similar patients with squamous cell carcinoma.[32] Obesity has also been linked to a 3- to 4-fold risk of adenocarcinoma, possibly because of an increased risk of reflux.[33] This is particularly pertinent to central obesity (visceral fat).[34] It has been estimated that a middle-aged patient with Barrett esophagus has a 10% to 15% risk of developing esophageal adenocarcinoma during their lifetime, although other reports have suggested this risk may be overstated.[35]

Although many risk factors are associated with esophageal carcinoma, few studies have demonstrated a causal relationship leading to pathogenesis. Montesano et al[36] reported possible genetic abnormalities involved in the genesis of esophageal cancer. In addition, possible differences in mechanisms of pathogenesis for squamous cell carcinoma and adenocarcinoma were described. Genetic abnormalities in squamous cell carcinoma include p53 mutations and multiple allelic losses at 3p and 9q, with amplification of cyclin D1 and epidermal growth factor receptor (EGFR). These mutations lead to cell hyperplasia, low- and high-grade dysplasia, and, ultimately, squamous cell carcinoma. In contrast, genetic abnormalities in adenocarcinoma include overexpression of p53; multiple allelic losses at 17p, 5q, and 13q; and amplification and overexpression of EGFR and human epidermal growth factor receptor 2 (HER-2). These abnormalities may be involved in the stepwise development of Barrett esophagus, dysplasia, and, ultimately, adenocarcinoma. These differences suggest that squamous cell carcinoma and adenocarcinoma have different series of genetic mutations as etiologies, but these abnormalities occur in 23% to 94% of tumors studied. Whole exome sequencing has identified mutations in p53 and the cyclin-dependent kinase inhibitor CDKN2, as well as multiple other known tumor-associated genes, in both adenocarcinoma and squamous cell carcinoma. Next-generation sequencing has identified frequent genomic alterations of CCND1 and SOX2 and/or *TP53* genes in

esophageal squamous cell carcinoma (more akin to squamous cell carcinomas of the head and neck), whereas esophageal adenocarcinomas more closely resemble chromosomally unstable variants of gastric cancer.[37,38]

NATURAL HISTORY AND PATTERNS OF SPREAD

Squamous cell carcinoma is characterized by extensive local growth and proclivity to lymph node metastases. Because the esophagus has no covering serosa, direct invasion of contiguous structures may occur early. Lesions in the upper esophagus can impinge on or invade the recurrent laryngeal nerves, carotid arteries, and trachea. If extraesophageal extension occurs in the mediastinum, tracheoesophageal or bronchoesophageal fistula may occur. Tumors in the lower one-third of the esophagus can invade the aorta or pericardium, resulting in mediastinitis, massive hemorrhage, or empyema.

A review correlating the incidence of lymph node metastases with depth of penetration revealed that 18% of patients with spread to the submucosa had lymph node involvement.[39] For T1 lesions, the reported incidence of nodal spread is 10% to 21%, although this may be higher or lower depending on depth of involvement; for T1a disease, lymph node metastases rates range from approximately 7% to 9%, and T1b 28% to 38%. Increasing tumor size as well as differentiation, lymphovascular invasion, and location may influence these rates.[40] For T2 lesions, this rises to 33% to 69%.[41-44] The location of involved lymph nodes is influenced by the origin of the primary tumor. At autopsy, lymph node metastases are found in approximately 70% of patients.[45-47] In patients with cervical lesions, lymph node metastases to the abdominal lymph nodes are rare. Distant metastasis can occur at almost any site. In a series of 1,470 patients with both adenocarcinoma and squamous cell carcinoma, common sites of distant metastases included liver, distant lymph nodes, lung, bone, and less commonly the brain. Patients with adenocarcinoma were more likely to experience brain and liver metastases, although patients with squamous cell carcinoma were more likely to develop lung metastases (Figure 59.5; see Figure 59.3B).[48]

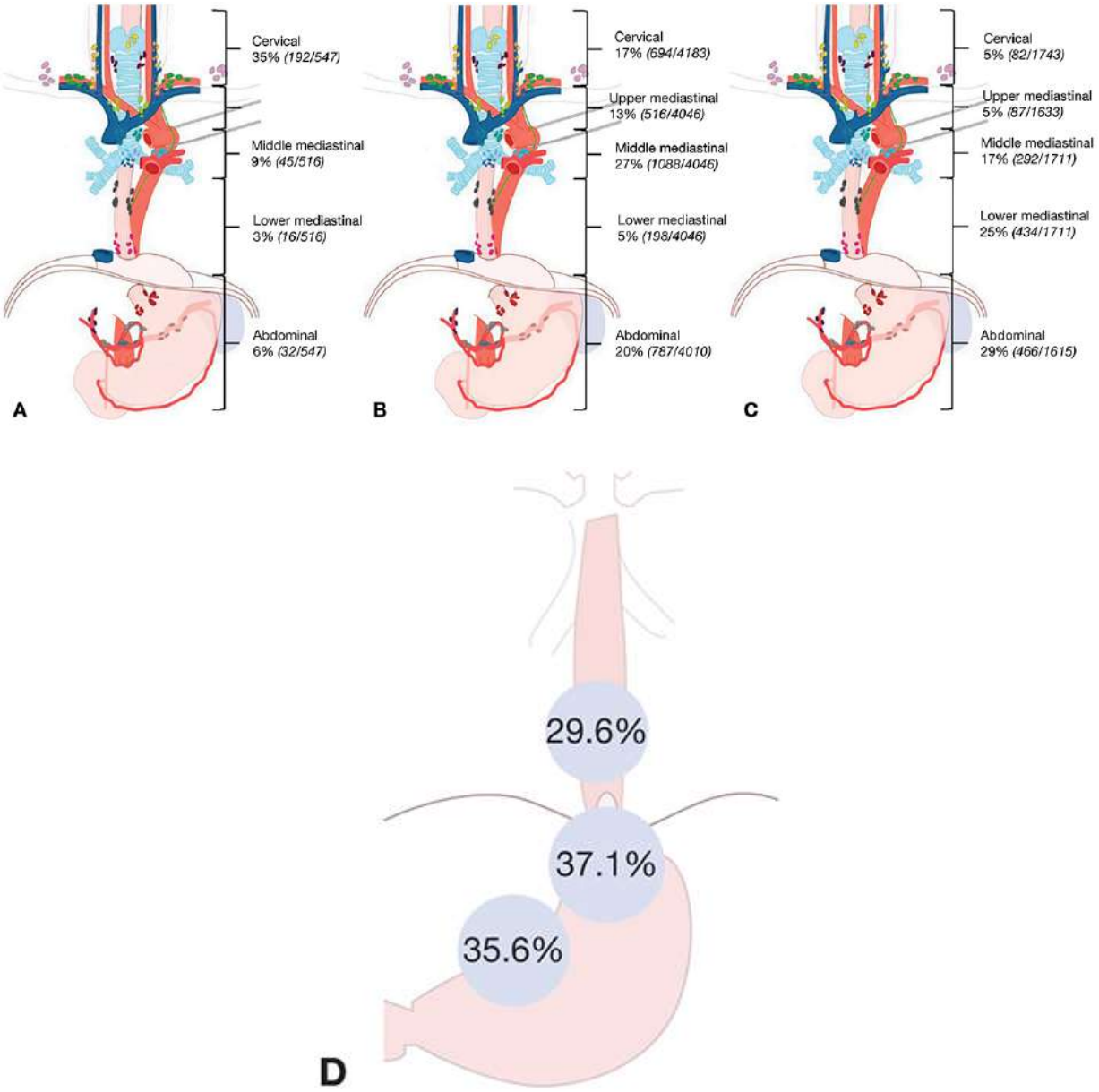


FIGURE 59.5 Prevalence of lymph node metastases per tumor location in patients with squamous cell carcinoma: upper esophageal tumor (A), middle upper thoracic esophageal tumor (B), and distal thoracic esophageal tumor (C). Data are presented as percentage of patients with lymph node metastases in this region. D. Pattern of nodal distribution in 132 patients undergoing resection only for esophageal adenocarcinoma. (A-C. Reprinted from Hagens ERC, van Berge Henegouwen MI, Gisbertz SS. Distribution of lymph node metastases in esophageal carcinoma patients undergoing upfront surgery: a systematic review. *Cancers (Basel)*. 2020;12[6]:1592. http://creativecommons.org/licenses/by/4.0/. D: Adapted by permission from Springer: Castoro C, Scarpa M, Cagol M, et al. Nodal metastasis from locally advanced esophageal cancer: how neoadjuvant therapy modifies their frequency and distribution. *Ann Surg Oncol*. 2011;18[13]:3743-3754. Copyright © 2011 Society of Surgical Oncology.

A review of 1,077 patients with squamous cell carcinoma of the thoracic esophagus undergoing esophagectomy further characterized patterns of nodal spread. Primary disease was located in the upper (5%), middle (63%), and lower (32%) thoracic

esophagus. In total, 47% of patients had lymph node metastases. On multivariate analysis, T stage, tumoral length, and degree of differentiation significantly correlated with incidence of lymph node metastases. In approximately 6% of cases, skip metastasis (distant lymph node metastases without regional lymph node metastasis) occurred, usually in patients with poorly differentiated, large, and deeply invasive tumors. Of involved nodes, 37% were macroscopically involved versus 63% microscopically involved, indicating that most lymph node metastases would be below the resolution of detection using contemporary imaging tools. Lymph node involvement was grouped into five categories: cervical, thoracic upper mediastinum, thoracic middle mediastinum, thoracic lower mediastinum, and abdominal lymph nodes.[49] A similar study of 1,893 patients with thoracic squamous cell carcinoma from China mapped patterns of lymph node metastases by primary tumor location, with similar patterns of spread. In this study, independent prognostic factors for lymph node metastases included tumor length, differentiation, and depth of invasion. The authors recommended treating nodal basins according to clinicopathologic factors, including enlargement of fields of patients with adverse histologic features, demonstrating similar rates of spread compared to the previously described series.[50] A systemic review of lymph node metastases in patients undergoing upfront surgery encompassing 8,952 patients similarly demonstrated that both squamous cell carcinoma and adenocarcinoma histologies can metastasize to cervical, thoracic, and abdominal lymph node stations, regardless of primary tumor location, although prevalence was significantly influenced by primary tumor site.

For lower esophageal and GE junctional adenocarcinomas, approximately 70% of patients will have nodal metastases at presentation. In one series of Italian investigators of 132 patients with adenocarcinoma undergoing surgery alone, common sites of metastases included periesophageal (30%), paracardial (37%), perigastric (36%), and celiac axis (14%) (see Figure 59.5D). This is influenced by tumoral depth of penetration, with nearly all T3 and T4 lesions exhibiting metastases in surgical series. Pathologic resection data have demonstrated rates of lymphatic involvement for lower esophageal and GE junctional tumors of 45%, 85%, and 100% for T2, T3, and T4 tumors, respectively (Figure 59.6).[42] In patients with lower esophageal cancer, involvement of both mediastinal and abdominal lymph nodes is common (Figure 59.7).[42] The primary direction for lymphatic flow for the lower esophagus is toward the abdomen. According to the classification by Siewert, nodal metastases are often seen in the mediastinum and abdomen for type I tumors, whereas type III tumors metastasize almost exclusively inferiorly, toward the celiac axis. Type II tumors are intermediate, preferentially spreading inferiorly and less frequently into the mediastinum. The primary value of the Siewert classification is in guiding appropriate surgery (ie, type I tumors are generally treated with esophagectomy and mediastinal lymph node resection, while types II and III are approached through the abdomen), although it may be useful in radiation field design as well.[3] Generally speaking, the incidence of abdominal nodal

involvement increases as one proceeds distally in the esophagus to the GE junction. For patients with tumors arising from the GE junction, mediastinal involvement is less common. Nodal metastases above the level of the carina are rare in lower esophageal and junctional tumors.[51] In addition, histologic analyses of lower esophagus and GE junction adenocarcinoma specimens suggest that many patients without nodal involvement on conventional histopathology actually have involvement when assessed by immunohistochemistry.[52]

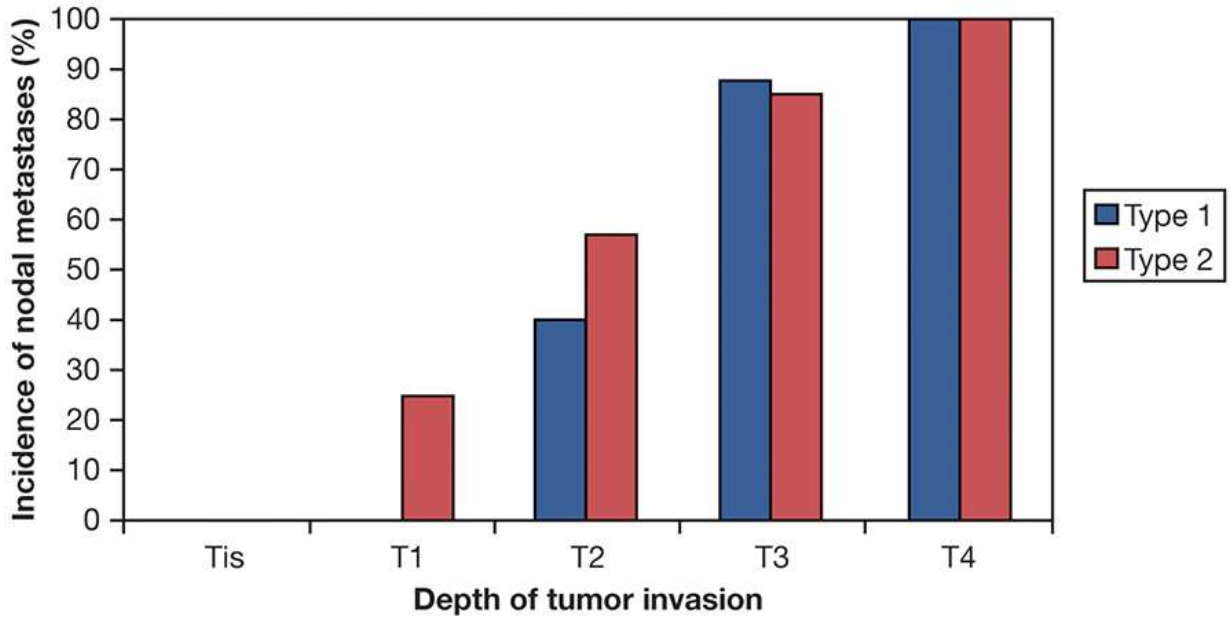


FIGURE 59.6 The incidence of nodal metastases related to depth of tumor invasion for adenocarcinoma. (Reprinted from Dresner SM, Lamb PJ, Bennett MK, Hayes N, Griffin SM. The pattern of metastatic lymph node dissemination from adenocarcinoma of the esophagogastric junction. *Surgery*. 2001;129[1]:103-109. Copyright © 2001 Elsevier. With permission.)

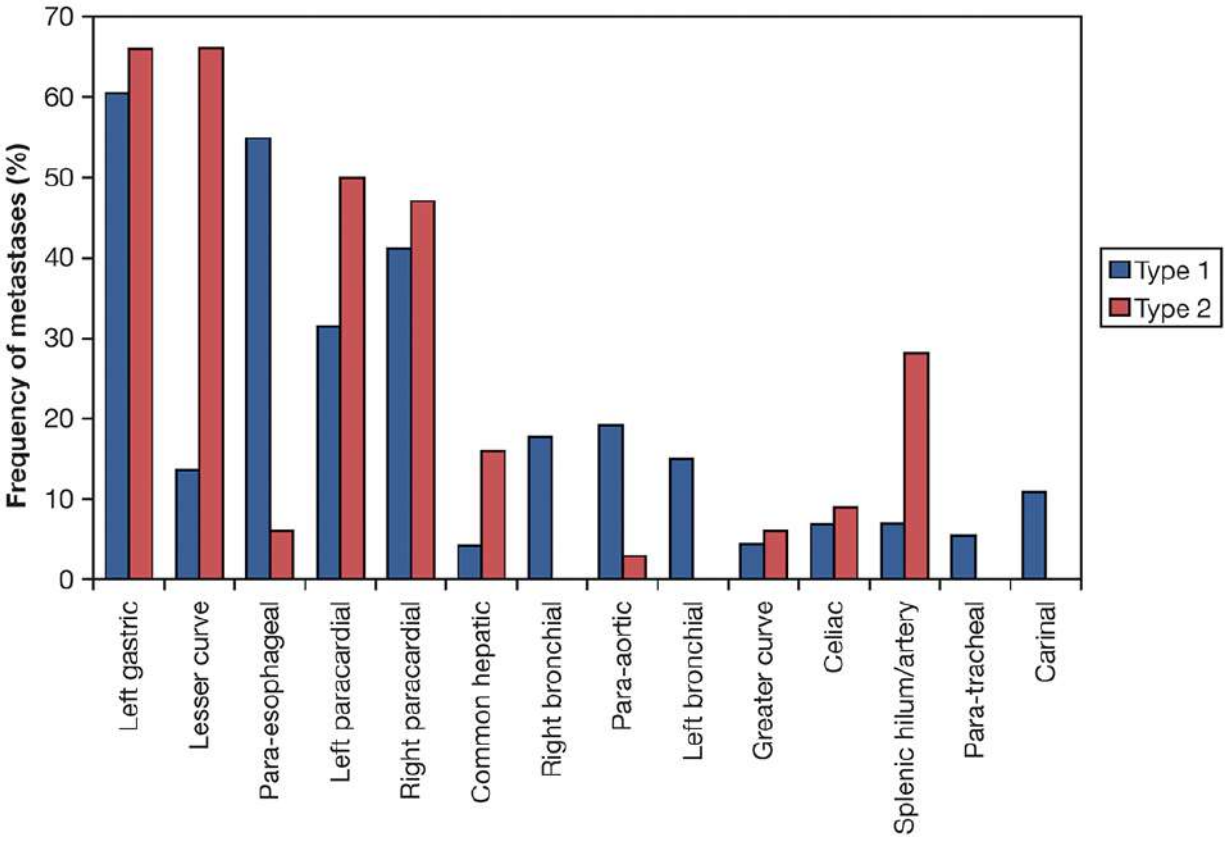
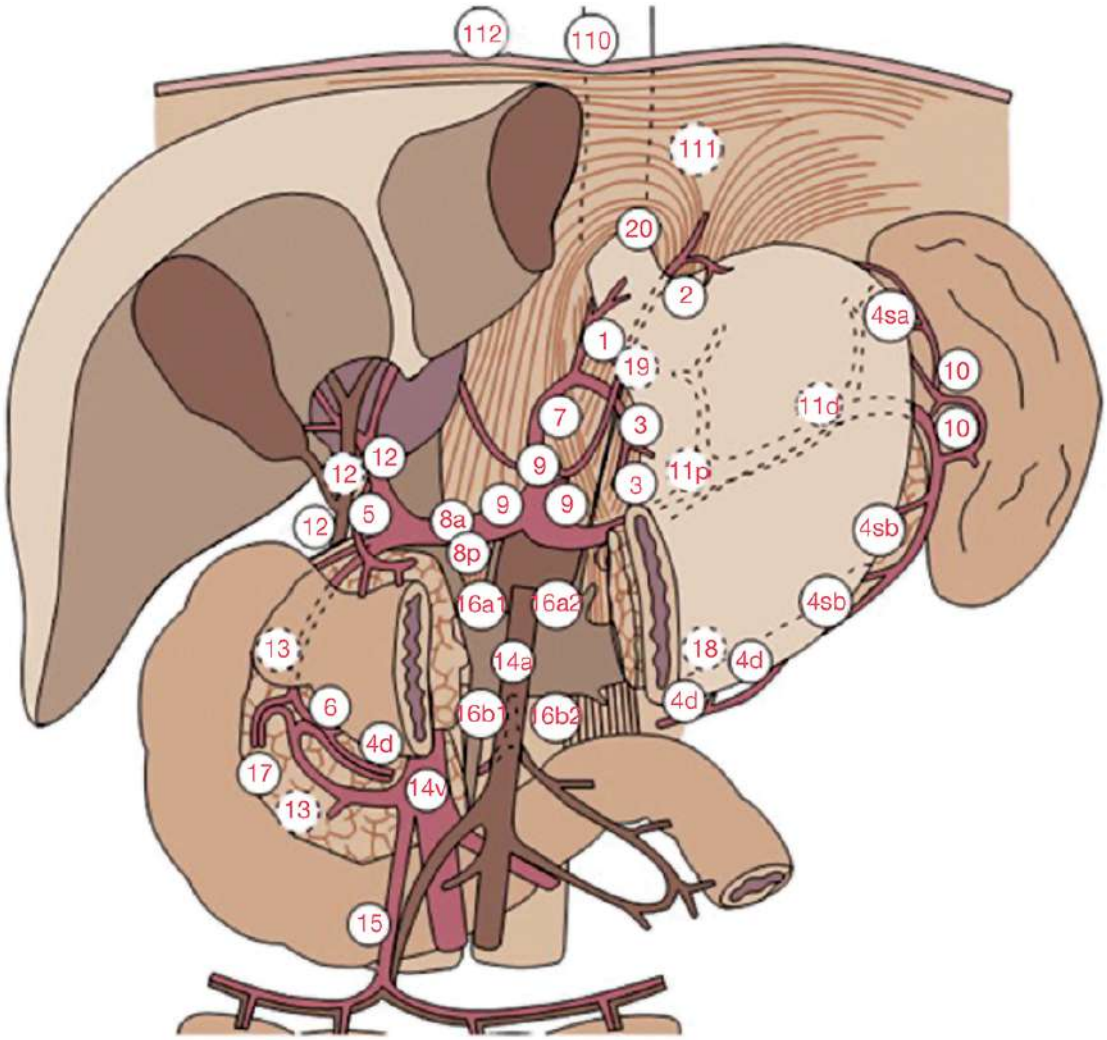


FIGURE 59.7 Distribution of nodal metastases by frequency of site involved for adenocarcinoma. (Reprinted from Dresner SM, Lamb PJ, Bennett MK, Hayes N, Griffin SM. The pattern of metastatic lymph node dissemination from adenocarcinoma of the esophagogastric junction. *Surgery*. 2001;129[1]:103-109. Copyright © 2001 Elsevier. With permission.)

Extensive nodal mapping has been performed by Japanese investigators, who have devised the Japanese Gastric Cancer Association Classification (Figure 59.8).[53] Using this system of nodal classification, investigators from Erlangen evaluated 326 patients with esophagogastric junction adenocarcinoma (AEG) undergoing primary resection. Tumors were stratified as AEG type I (distal esophagus), II (gastric cardia), and III (subcardia). Note that there was significant overlap in the majority of tumors for all stages, with an overall incidence of lymph node metastasis of 71%. In T1 patients, only 17% exhibited lymph node metastasis, whereas 78%, 86%, and 90% of T2, T3, and T4, respectively, had involved nodes. Figure 59.9 shows varying patterns of nodal spread based on T stage as well as AEG location. Additional generalizations from this study include that lymph vascular invasion was highly predictive of nodal spread and that proximal extension of type II and III tumors into the distal esophagus (particularly beyond the Z line) predicted an increasing incidence of paraesophageal lymph node involvement.[54]



No. 1	Right paracardial LN
No. 2	Left paracardial LN
No. 3	LN along the lesser curvature
No. 4sa	LN along the short gastric vessels
No. 4sb	LN along the left gastroepiploic vessels
No. 4d	LN along the right gastroepiploic vessels
No. 5	Suprapyloric LN
No. 6	Infrapyloric LN
No. 7	LN along the left gastric artery
No. 8a	LN along the common hepatic artery (Anterosuperior group)
No. 8p	LN along the common hepatic artery (Posterior group)
No. 9	LN around the celiac artery
No. 10	LN at the splenic hilum
No. 11p	LN along the proximal splenic artery
No. 11d	LN along the distal splenic artery
No. 12a	LN in the hepatoduodenal ligament (along the hepatic artery)
No. 12b	LN in the hepatoduodenal ligament (along the bile duct)
No. 12p	LN in the hepatoduodenal ligament (behind the portal vein)
No. 13	LN on the posterior surface of the pancreatic head
No. 14v	LN along the superior mesenteric vein
No. 14a	LN along the superior mesenteric artery
No. 15	LN along the middle colic vessels
No. 16a1	LN in the aortic hiatus
No. 16a2	LN around the abdominal aorta (from the upper margin of the celiac trunk to the lower margin of the left renal vein)
No. 16b1	LN around the abdominal aorta (from the lower margin of the left renal vein to the upper margin of the inferior mesenteric artery)
No. 16b2	LN around the abdominal aorta (from the upper margin of the inferior mesenteric artery to the aortic bifurcation)
No. 17	LN on the anterior surface of the pancreatic head
No. 18	LN along the inferior margin of the pancreas
No. 19	Infradiaphragmatic LN
No. 20	LN in the esophageal hiatus of the diaphragm
No. 110	Paraesophageal LN in the lower thorax
No. 111	Supradiaphragmatic LN
No. 112	Posterior mediastinal LN

FIGURE 59.8 Locations of lymph node (LN) stations. (Reprinted from Matzinger O, Gerber E, Bernstein Z, et al. EORTC-ROG expert opinion: radiotherapy volume and treatment guidelines for neoadjuvant radiation of adenocarcinomas of the gastroesophageal junction and the stomach. *Radiother Oncol*. 2009;92[2]:164-175. Copyright © 2009 Elsevier Ireland Ltd. With permission.)

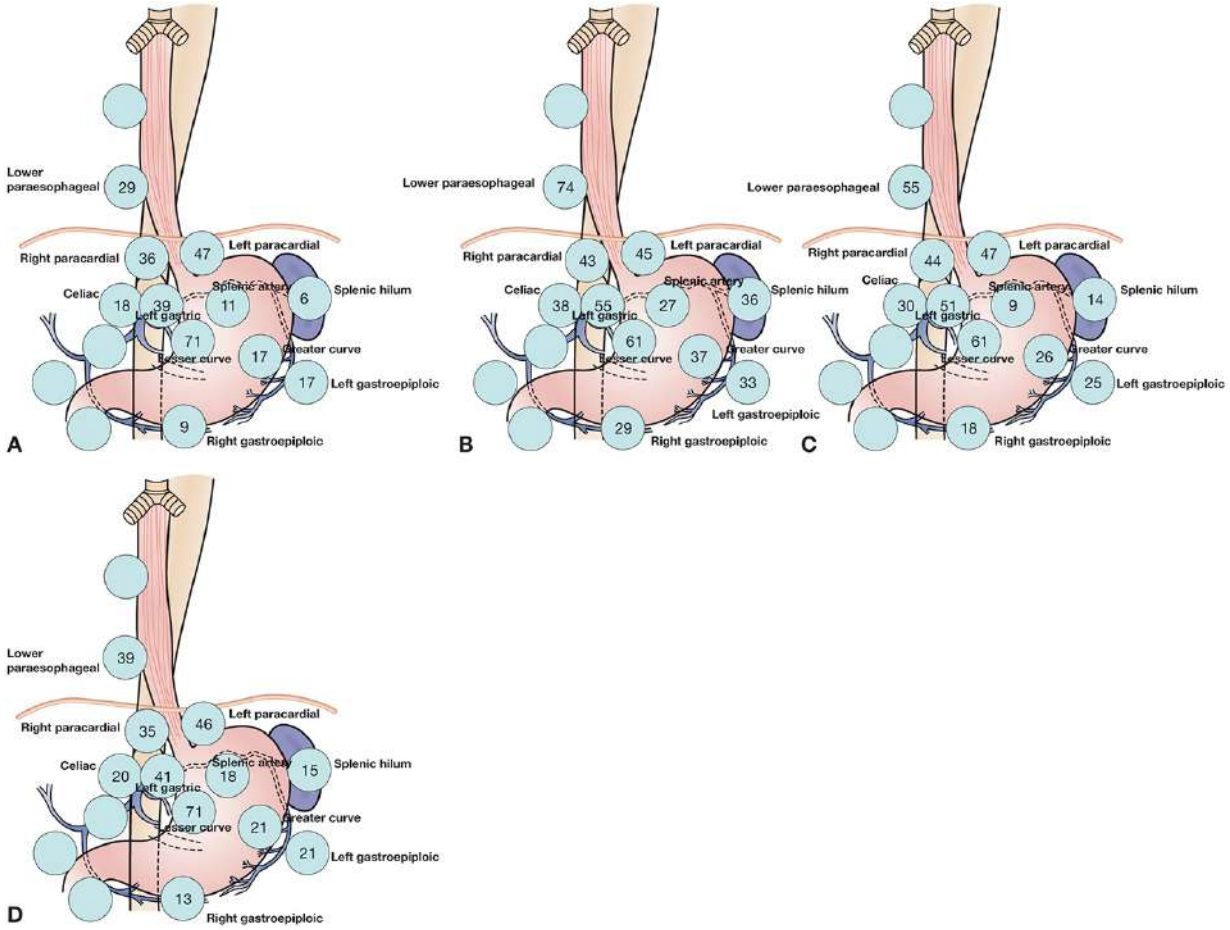


FIGURE 59.9 A. Frequency percent of nodal involvement for T2 tumors. B. Frequency percent of nodal involvement for T3 to T4 tumors. C. Frequency percent of nodal involvement for AEG type I tumors. D. Frequency percent of nodal involvement for AEG type II/III tumors. AEG, esophagogastric junction adenocarcinoma. (Based on data from Meier I, Merkel S, Papadopoulos T, et al. Adenocarcinoma of the esophagogastric junction: the pattern of metastatic lymph node dissemination as a rationale for elective lymphatic target volume definition. *Int J Radiat Oncol Biol Phys*. 2008;70:1408-1417.)

LOCAL FAILURE

In an older series at the University of Pennsylvania and Fox Chase Cancer Center of patients with adenocarcinoma of the esophagus and GE junction treated with surgery alone, the locoregional recurrence rate was 77%.[55] In contemporary randomized trials, local failure rates with surgery alone range from 29% to 45%.[56-59] Similarly, data from contemporary randomized trials of esophageal cancer using "definitive" chemoradiation also indicate that local failure is a major cause of failure, with approximately 50% of patients failing locally (Table 59.1). In a study of 239 patients receiving definitive

chemoradiotherapy, 50% presented with local failure, 48% distant failure, and 31% no failure. Of local failures, 90% were within the gross tumor volume (GTV), whereas clinical target volume (CTV) and planning target volume (PTV) failures were seen in only 23% and 12%, respectively.[60] In many trials, patterns of failure are reported as first site of recurrence. This fact, along with infrequent post-therapy imaging and inability to detect subclinical recurrences, likely leads to underestimates of local recurrence rates. These data clearly emphasize the need for improvements in local treatment modalities.

TABLE 59.1 LOCAL FAILURE RATES FROM RANDOMIZED TRIALS EVALUATING CHEMORADIATION ALONE IN ESOPHAGEAL CANCER

	Dose (Gy)	Local Failure (Crude) (%)	Local Failure (2-Y) (%)
RTOG 85-01[65]	50	45	47
INT 0123[66]	50	55	52
INT 0123[66]	64	50	56
German[67]	. 60	51	58
SCOPE[68]	50	40	NS

INT, Intergroup; RTOG, Radiation Therapy Oncology Group.

CLINICAL PRESENTATION

Symptoms of esophageal cancer often start 3 to 4 months before diagnosis. Location of the primary tumor in the esophagus may influence presenting symptoms. Dysphagia is seen in more than 90% of patients regardless of location. Odynophagia is present in up to 50% of patients.[61] Weight loss is common, with 40% to 70% of patients reporting a loss of more than 5% of total body weight. This extent of weight loss has been associated with a worse prognosis. Less frequent symptoms may include vague chest and upper abdominal pain, hoarseness, cough, and glossopharyngeal neuralgia.[62]

Advanced lesions can produce signs and symptoms due to tumor invasion into local structures. Hematemesis, hemoptysis, melena, dyspnea, and persistent cough secondary to tracheoesophageal or bronchoesophageal fistula may occur. Compression or invasion of the left recurrent laryngeal nerve or the phrenic nerves can cause dysphonia or hemidiaphragm paralysis. Superior vena cava syndrome and Horner syndrome can also occur from more advanced lesions. Pleural effusion and exsanguination resulting from aortic communication may also be rarely seen.[61] Abdominal and back pain may occur with celiac axis nodal involvement with lower esophageal tumors.

DIAGNOSTIC WORKUP

After a thorough history and physical examination, all patients with suspected esophageal cancer should have a workup similar to that outlined in Table 59.2. Attention

should be paid to cervical and supraclavicular lymph nodes. Basic blood counts and a metabolic panel with liver function tests should be obtained.

TABLE 59.2 DIAGNOSTIC WORKUP FOR ESOPHAGEAL CANCER

Multidisciplinary evaluation (surgical, radiation, and medical oncology)
History and physical
Complete blood count and chemistry profile
Upper gastrointestinal endoscopy and biopsy
Chest, abdomen, and pelvic computed tomography (CT) with intravenous and/or oral contrast (combined positron emission tomography [PET]-CT optimal)
PET evaluation (combined PET-CT optimal)
Endoscopic ultrasound, with fine-needle aspiration if indicated (if no evidence of distant metastases)
Bronchoscopy if tumor is located at or above the carina or there is suspected airway involvement
Nutritional assessment and consideration of feeding tube (nasogastric or feeding jejunostomy) in selected situations

Although the esophagogram may be used to define lesion extent, endoscopy is the best tool to diagnose and define the extent of the lesion. During flexible endoscopy, biopsies and/or brushings should be taken of the primary site and suspicious areas harboring satellites or submucosal spread. In addition, accurate endoscopic measurement and characterization of tumor and GE junction in relation to the incisors facilitate radiation treatment planning, as may the strategic placement of radiopaque fiducials at the superior and inferior extent of the primary lesion. Examination with panendoscopy of the oral cavity, pharynx, larynx, and tracheobronchial tree may also be performed at the time of esophagoscopy in patients with squamous cell carcinomas, given the high incidence of second tumors in the head and neck and upper airway.[2] In addition, bronchoscopy should generally be performed in patients with proximal malignancies to evaluate for the presence of tracheal, carinal, or bronchial invasion, particularly for patients with tumors abutting these structures on computed tomography (CT). CT of the thorax and abdomen is critical to identify metastases to the lung, liver, upper abdominal nodes, or adrenals; additionally, the primary tumor can usually be appreciated as well as enlarged regional lymph nodes. However, CT may not adequately assess periesophageal lymph node involvement or accurately define the true extent of the primary tumor.[63,64] Conventional CT scan can accurately determine resectability in only 65% to 85% of cases. Furthermore, CT accurately predicts T stage in approximately 70% of cases and nodal involvement in only 50% to 70% of cases.[69-71] Pelvic CT may be performed as clinically indicated.

To more accurately assess periesophageal and celiac lymph node involvement and transmural extent of disease, endoscopic ultrasonography (EUS) should be performed. EUS provides accuracy rates of 85% to 90% for tumor invasion (T stage) and 75% to 80% for lymph node metastases when matched to surgical pathology.[72-75] A meta-

analysis in nearly 3,000 patients with squamous cell carcinoma concluded that EUS had good diagnostic accuracy for squamous cell carcinoma, albeit with better performance in substaging T1 disease (Ta1 and T1b), as well as T4 tumors, with overall T-staging and N-staging accuracy of 71% and 79%, respectively.[76] However, the accuracy of endoscopic ultrasound following neoadjuvant therapy is significantly less, ranging from 27% to 48% for T staging and 38% to 71% for N staging. This is possibly due to the failure to discriminate tumor from postradiation inflammation and fibrosis.[77-79] Illustrating the potential limitations associated with contemporary staging techniques, in one series of 102 patients with clinically staged (by positron emission tomography [PET], EUS, and/or CT) T2-3 N0 tumors receiving induction chemotherapy alone, 60% of patients were found to have metastatic nodal disease.[80]

Surgical staging procedures, including thoracoscopy, mediastinoscopy, and laparoscopy, may provide additional staging information and are considered in selected patients at some institutions.[81] Laparoscopy would primarily be used for tumors at the GE junction.

Patients with significant obstruction and inability to maintain their weight may require placement of a feeding tube. If surgery is planned, gastric tube placement is generally avoided, given that the stomach will ultimately serve as the “neoesophagus” following resection and a feeding jejunostomy tube may be placed.

PET has proven to be a valuable staging tool in patients with esophageal cancer. The addition of PET to standard staging studies such as CT can improve the accuracy of detecting stage III and stage IV disease by 23% and 18%, respectively.[82,83] Overall, it is estimated that PET will detect distant metastatic disease in approximately 20% of patients who are considered to have locoregional disease only by CT. However, PET also appears to have a lower accuracy in detecting local nodal disease compared to CT alone or in combination with endoscopic ultrasound. Of importance, some series suggest that PET can be used to predict response to therapy, with PET “responders” experiencing significantly improved outcomes compared to “nonresponders.”[84] However, in one pooled analysis, the sensitivity of PET in detecting pathologic complete response following treatment was 0.62, and pooled specificity 0.73, with the authors concluding that current imaging modalities (including PET) are insufficiently accurate to identify complete responders.[85] In addition, PET has been used to predict response to treatment early during the treatment course. The phase II CALGB 0803 study included early response assessment during treatment using PET as a biomarker to individualize therapy, allowing initial chemotherapy-alone nonresponders to cross over to an alternate chemotherapy regimen during radiation. This strategy indicated improved pathologic complete response rates in early PET nonresponders who crossed over, as well as portending improved outcomes in patients responsive to induction therapy.[86] In this study, 257 patients with locally advanced esophageal and GE junction cancers were randomized to induction chemotherapy with modified FOLFOX-6 or carboplatin/paclitaxel. PET scan was subsequently obtained and patients who responded

(≥35% decrease in standard uptake value [SUV]) continued on with the same chemotherapy during chemoradiation, while nonresponders switched to the alternate chemotherapy. Pathologic complete response rates were 40% in the PET responders after FOLFOX who continued on with such, and 18% for nonresponders who crossed over. In comparison, pathologic complete response rate was 14% for the carboplatin/paclitaxel responders and 20% for nonresponders who crossed over to FOLFOX. However, in this trial pathologic complete response did not seem to accurately predict overall survival. Thus far, the ability of intermittent (on treatment) PET to assess early outcomes during combined modality, to date, has not reliably correlated between interim findings on PET parameters and pathologic complete response and/or clinical outcome.[87] This has led to ongoing investigation of early treatment response as measured by PET as a surrogate for therapeutic efficacy and clinical outcomes, with potential subsequent therapy modification based on early response.[88]

STAGING SYSTEMS

Esophageal staging can be based on pathologic or clinical criteria. Pathologic staging is performed after invasive procedures, including esophagectomy, mediastinotomy, or thoracotomy. Clinical staging is often employed with "definitive" and neoadjuvant chemoradiation approaches and is less accurate. With the combination of CT, PET, and EUS, clinical staging closely correlates with pathologic stage. Note that the most recent AJCC staging system takes into consideration tumor type and grade, as well as involved number of lymph nodes (Table 59.3; Figures 59.10 and 59.11).

TABLE 59.3 AMERICAN JOINT COMMITTEE ON CANCER 2017 ESOPHAGEAL CANCER STAGING SYSTEM (8TH EDITION)

Category	Criteria
T category	
TX	Tumor cannot be assessed.
T0	No evidence of primary tumor
Tis	High-grade dysplasia, defined as malignant cells confined by the basement membrane
T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
T1a[a]	Tumor invades the lamina propria or muscularis mucosae
T1b[a]	Tumor invades the submucosa
T2	Tumor invades the muscularis propria
T3	Tumor invades the adventitia
T4	Tumor invades adjacent structures
T4a[a]	Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum

Category	Criteria
T4b[a]	Tumor invades other adjacent structures, such as the aorta, vertebral body, or trachea
N category	
NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis
N1	Metastasis in 1-2 regional lymph nodes
N2	Metastasis in 3-6 regional lymph nodes
N3	Metastasis in ≥7 regional lymph nodes
M category	
M0	No distant metastasis
M1	Distant metastasis
Adenocarcinoma G category	
GX	Differentiation cannot be assessed.
G1	Well differentiated, with .95% of the tumor composed of well-formed glands
G2	Moderately differentiated, with 50%-95% of the tumor showing gland formation
G3[b]	Poorly differentiated, with tumors composed of nest and sheets of cells with <50% of the tumor demonstrating glandular formation
Squamous cell carcinoma G category	
GX	Differentiation cannot be assessed.
G1	Well differentiated, with prominent keratinization with pearl formation and a minor component of nonkeratinizing basal-like cells, tumor cells arranged in sheets, and mitotic counts low
G2	Moderately differentiated, with variable histologic features ranging from parakeratotic to poorly keratinizing lesions and pearl formation generally absent
G3[c]	Poorly differentiated, consisting predominantly of basal-like cells forming large and small nests with frequent central necrosis and with the nests consisting of sheets or pavement-like arrangements of tumor cells that are occasionally punctuated by small numbers of parakeratotic or keratinizing cells
Squamous cell carcinoma L category[d]	
LX	Location unknown
Upper	Cervical esophagus to lower border of the azygos vein
Middle	Lower border of the azygos vein to lower border of the inferior pulmonary vein
Lower	Lower border of the inferior pulmonary vein to the stomach, including the esophagogastric junction

[a]Subcategories.

[b]If further testing of “undifferentiated” cancers reveals a glandular component, categorize as adenocarcinoma G3.

[c]If further testing of “undifferentiated” cancers reveals squamous cell component or if after further testing they remain undifferentiated, categorize as squamous cell carcinoma G3.

[d]Location is defined by epicenter of esophageal tumor.

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cTNM Adenocarcinoma

	N0	N1	N2	N3	M1
Tis	0				
T1		I	IIA	IVA	IVA	IVB
T2		IIB	III	IVA	IVA	IVB
T3		III	III	IVA	IVA	IVB
T4a		III	III	IVA	IVA	IVB
T4b		IVA	IVA	IVA	IVA	IVB

A

cTNM Squamous Cell Carcinoma

	N0	N1	N2	N3	M1
Tis	0				
T1		I	I	III	IVA	IVB
T2		II	II	III	IVA	IVB
T3		II	III	III	IVA	IVB
T4a		IVA	IVA	IVA	IVA	IVB
T4b		IVA	IVA	IVA	IVA	IVB

B

pTNM Adenocarcinoma

		N0	N1	N2	N3	M1
Tis		0				
T1a	G1	IA	IIB	IIIA	IVA	IVB
	G2	IB				
	G3	IC				
T1b	G1	IB	IIB	IIIA	IVA	IVB
	G2	IB				
	G3	IC				
T2	G1	IC	IIIA	IIIB	IVA	IVB
	G2	IIA				
	G3	IIA				
T3		IIB	IIIB	IIIB	IVA	IVB
T4a		IIIB	IIIB	IVA	IVA	IVB
T4b		IVA	IVA	IVA	IVA	IVB

C

pTNM Squamous Cell Carcinoma

		N0		N1	N2	N3	M1
		L	U/M				
Tis		0					
T1a	G1	IA	IA	IIB	IIIA	IVA	IVB
	G2-3	IB	IB				
T1b		IB		IIB	IIIA	IVA	IVB
T2	G1	IB	IB	IIIA	IIIB	IVA	IVB
	G2-3	IIA	IIA				
T3	G1	IIA	IIA	IIIB	IIIB	IVA	IVB
	G2-3	IIA	IIB				
T4a		IIIB		IIIB	IVA	IVA	IVB
T4b		IVA		IVA	IVA	IVA	IVB

D

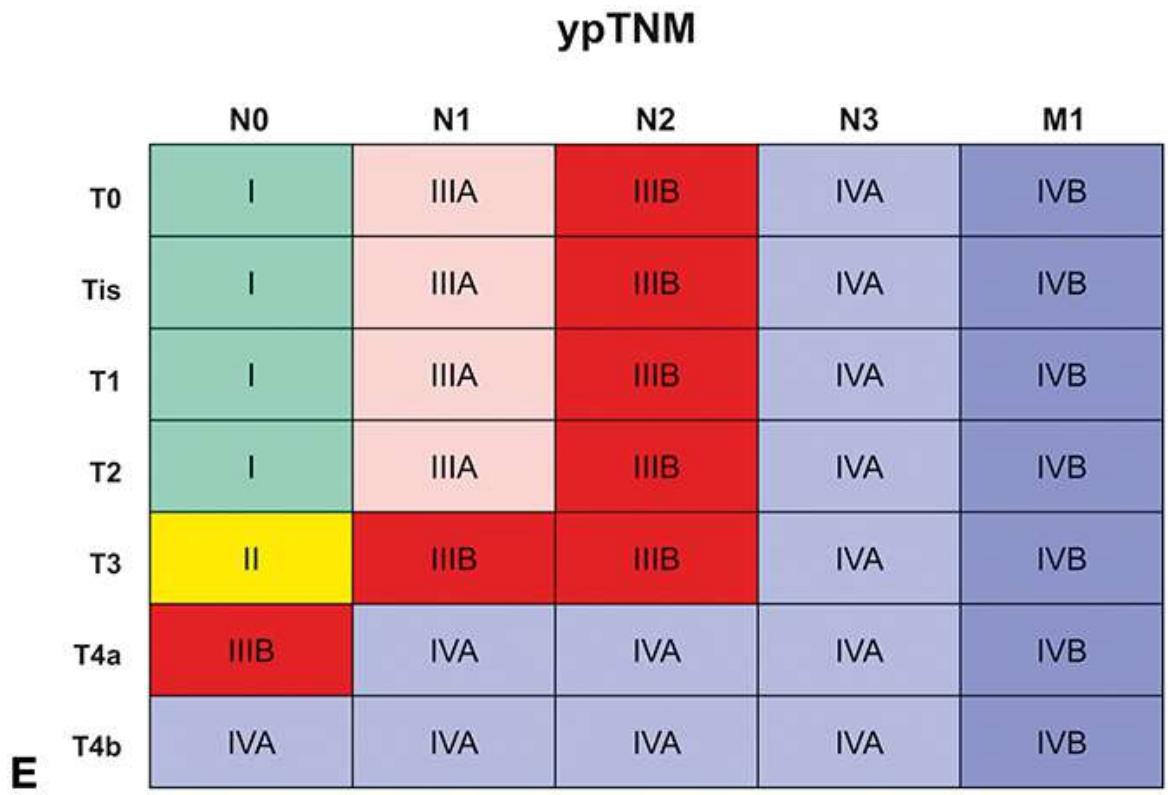


FIGURE 59.10 Clinical stage groups (cTNM): adenocarcinoma (A) and squamous cell carcinoma (B). Pathologic stage groups (pTNM): adenocarcinoma (C). and squamous cell carcinoma (D). Postneoadjuvant pathologic stage groups (ypTNM): adenocarcinoma and squamous cell carcinoma (E). (Reprinted from Rice TW, Ishwaran H, Ferguson MK, Blackstone EH, Goldstraw P. Cancer of the esophagus and esophagogastric junction: an eighth edition staging primer. *J Thorac Oncol*. 2017;12[1]:36-42. Copyright © 2016 International Association for the Study of Lung Cancer. With permission.)

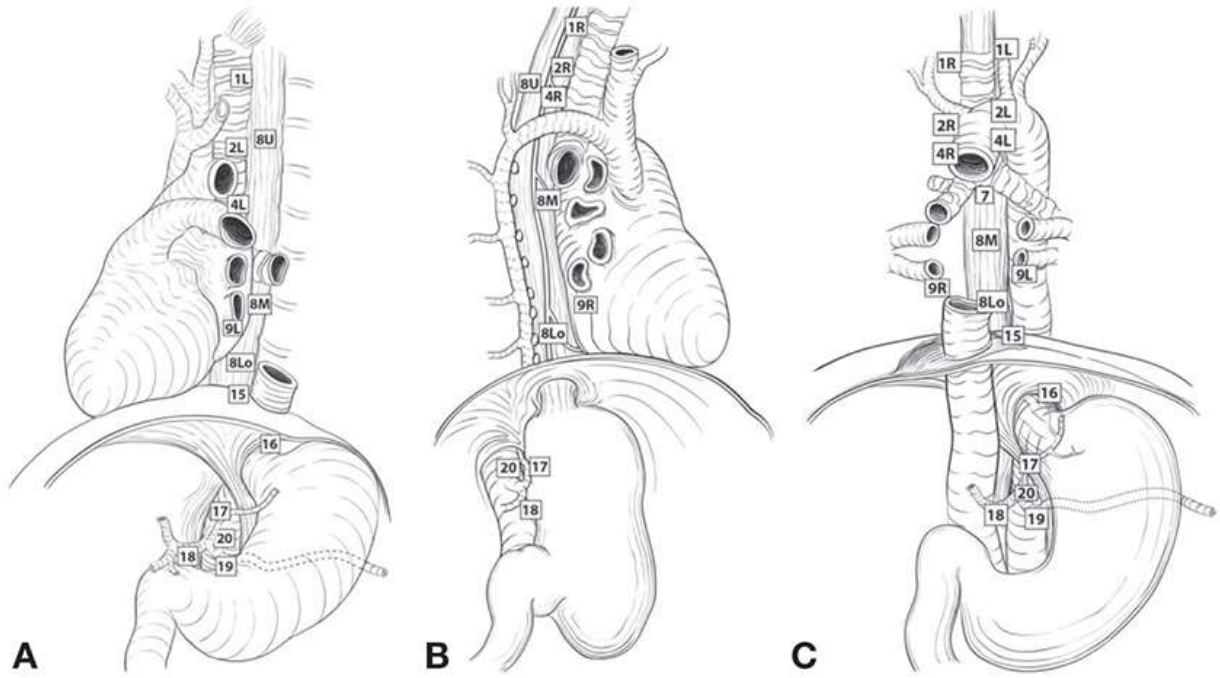


FIGURE 59.11 Lymph node maps for esophageal cancer. Regional lymph node stations for staging esophageal cancer from the left (A), right (B), and anterior (C). 1R, right lower cervical paratracheal nodes, between the supraclavicular paratracheal space and apex of the lung; 1L, left lower cervical paratracheal nodes, between the supraclavicular paratracheal space and apex of the lung; 2R, right upper paratracheal nodes, between the intersection of the caudal margin of the brachiocephalic artery with the trachea and apex of the lung; 2L, left upper paratracheal nodes, between the top of the aortic arch and apex of the lung; 4R, right lower paratracheal nodes, between the intersection of the caudal margin of the brachiocephalic artery with the trachea and cephalic border of the azygos vein; 4L, left lower paratracheal nodes, between the top of the aortic arch and the carina; 7, subcarinal nodes, caudal to the carina of the trachea; 8U, upper thoracic paraesophageal lymph nodes, from the apex of the lung to the tracheal bifurcation; 8M, middle thoracic paraesophageal lymph nodes, from the tracheal bifurcation to the caudal margin of the inferior pulmonary vein; 8Lo, lower thoracic paraesophageal lymph nodes, from the caudal margin of the inferior pulmonary vein to the esophagogastric junction; 9R, pulmonary ligament nodes, within the right inferior pulmonary ligament; 9L, pulmonary ligament nodes, within the left inferior pulmonary ligament; 15, diaphragmatic nodes, lying on the dome of the diaphragm and adjacent to or behind its crura; 16, paracardial nodes, immediately adjacent to the gastroesophageal junction; 17, left gastric nodes, along the course of the left gastric artery; 18, common hepatic nodes, immediately on the proximal common hepatic artery; 19, splenic nodes, immediately on the proximal splenic artery; 20, celiac nodes, at the base of the celiac artery. Cervical periesophageal level VI and level VII lymph nodes are named as per the head and neck map. (From Rice TW, Gress DM, Patil DT, Hofstetter WL, Kelsen DP, Blackstone EH. Cancer of the esophagus and esophagogastric junction—major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA *Cancer J Clin*. 2017;67(4):304-317. Copyright © 2017 American Cancer Society. Reprinted by permission of John Wiley & Sons, Inc.)

PATHOLOGIC CLASSIFICATION

Squamous cell carcinoma and adenocarcinoma constitute 95% of all esophageal tumors, although other rare histologic subtypes are occasionally seen.[89] Immunohistochemical staining may be required in poorly or undifferentiated cancers to differentiate between squamous cell and adenocarcinoma. An updated World Health Organization classification of esophageal cancers is given in Table 59.4.

TABLE 59.4 PATHOLOGIC CLASSIFICATION OF MALIGNANT ESOPHAGEAL TUMORS

Epithelial tumors
Squamous cell carcinoma
Variants of squamous cell carcinoma
Basaloid squamous cell carcinoma
Squamous cell carcinoma with sarcomatoid features
Undifferentiated carcinoma
Spindle cell carcinoma
Pseudosarcoma and carcinosarcoma
Verrucous carcinoma
In situ carcinoma
Adenocarcinoma
Adenoacanthoma
Adenoid cystic carcinoma (cylindroma)
Mucoepidermoid carcinoma
Adenosquamous carcinoma
Carcinoid
Small cell carcinoma
Nonepithelial tumors
Sarcoma, 13 variants reported, most common is leiomyosarcoma.
Malignant melanoma
Myoblastoma
Choriocarcinoma
Lymphoma

Given that there has been a rise in adenocarcinoma compared to squamous cell carcinoma, examinations of outcomes by histology have been performed. Some series have reported that patients with squamous cell carcinomas have improved survival,[90] whereas others have suggested that patients with adenocarcinoma have an improved survival[91] and some others report no survival differences. Overall, there can be no direct comparison until randomized studies are done with stratification based on histology.

Pseudosarcoma is a variant of a poorly differentiated squamous cell carcinoma with spindle-shaped cells in the stroma resembling fibroblasts. Verrucous carcinoma is a well-differentiated, papillary variant of squamous cell carcinoma.[2] Squamous cell carcinoma in situ is rarely seen in the United States and should be distinguished from dysplasia.[92-94]

Adenocarcinoma may arise from foci of ectopic gastric mucosa or intrinsic esophageal glands. However, as described previously, it is believed that the vast

majority arise from Barrett esophagus. If a focus of squamous cell metaplasia is found in an adenocarcinoma, the tumor may be referred to as an adenoacanthoma.[95]

Adenoid cystic carcinomas are rare, with an incidence of 0.75%. Patients with this malignancy present around the sixth decade of life and have a poor median survival.[96] Mucoepidermoid tumors (adenosquamous carcinomas) are more aggressive and carry a poor prognosis.[97] The incidence of small cell carcinoma is approximately 2%. Patients with these malignancies often present in the sixth to eighth decades of life, and the lesion is usually located in the middle to lower esophagus in males.[98,99] These are believed to originate in the argyrophilic cells in the esophagus and may produce paraneoplastic syndromes, such as antidiuretic hormone secretion and hypercalcemia.[100] The clinical course of small cell carcinoma is similar to that of small cell carcinoma of the lung and may be responsive to chemotherapy and radiation therapy.[97,99]

Nonepithelial tumors of the esophagus are rare. Among these, leiomyosarcomas are the most common. Twenty-five percent of patients with this tumor present with metastases.[101-103] Histologically, these tumors have interlacing bundles of spindle-shaped cells. Less aggressive forms have fewer mitotic figures and less anaplasia. Prognosis has been reported to be more favorable than that of squamous cell carcinoma.[97] In patients with Kaposi sarcoma, gastrointestinal involvement of the esophagus can be seen.[104]

Malignant melanoma is rare and can occur as a primary esophageal tumor or as a metastasis. These lesions are usually large and often covered by intact squamous mucosa with focal areas of ulceration. Spread is usually submucosal. Mean survival is approximately 7 months.[105,106] Lymphoma constitutes approximately 1% of esophageal malignancies. It is usually associated with direct extension from other organs, although primary esophageal lymphoma has been reported.[107]

PROGNOSTIC FACTORS

According to the Union Internationale Contre le Cancer/AJCC seventh-edition staging system, R-status, age, and histologic subtype were independent prognostic factors of survival, whereas tumor grade and site were not.[108] It should be recalled that these data consider patients treated with surgery alone and as such do not apply to patients receiving chemotherapy or radiotherapy. A study published by Nomura et al[109] evaluating 301 patients treated with chemoradiotherapy showed that T stage, M stage, and gender were prognostic factors in multivariate analysis.

In addition to stage, other factors portend outcome. Tumor length/size may also impact outcome. In a study of 582 patients undergoing surgical resection as primary treatment, tumoral length adversely affected survival, with 5-year survival rates of 77%, 48%, 38%, and 23% for tumor lengths of 1, 2, 3, or more than 3 cm, respectively ($P <$ .001).[110] Of note, length was not prognostic if patients were N+ or M+. Similarly, in patients with adenocarcinoma, 5-year survival rates have been shown to be significantly higher for patients with tumors 2 cm or less compared to those with tumors more than 2

cm.[111] Another study of 1,553 patients with squamous cell carcinoma of the esophagus determined that tumor size, grade, lymphadenopathy, stage, and family history were prognostic following esophagectomy.[112]

In another large study from the Mayo Clinic, clinicopathologic factors that affected prognosis included T and N status, tumor grade, age .76 years, extracapsular lymph node extension, and the absence of chemotherapy or radiotherapy; anatomic location did not influence survival.[113] In addition, weight loss and low overall performance status also indicate poor prognosis.[114] Deep ulceration of the tumor, sinus tract formation, and fistula formation are other poor prognostic factors.[61]

Obtaining uninvolved pathologic margins at resection is of significant importance with regard to long-term outcome. An Intergroup study (discussed later) evaluating chemotherapy preceding and following esophagectomy showed that outcomes were similar in patients undergoing R1 resection (positive microscopic margins) or R2 resection (gross residual disease) or patients not undergoing resection at all. Only patients undergoing R0 resection (uninvolved margins) had a substantial chance of long-term disease-free survival.[115] A meta-analysis of 17 studies found that major pathologic response following neoadjuvant therapy in patients with GE cancer was predictive of survival.[116] Another meta-analysis of 13 series showed that perineural invasion is an adverse prognostic biomarker in esophageal cancer, often associated with more advanced stage and poor differentiation.[117] A patterns-of-care survey examined the outcomes of patients with adenocarcinoma and squamous cell carcinoma of the esophagus between 1996 and 1999. Patients were treated with radiation therapy across 59 institutions. On multivariate analysis, significant improvements in survival were seen in patients treated at centers with 500 or more patients with new cancers compared to centers seeing less than 500 patients (hazard ratio [HR] 1.32; $P = .03$).[118]

GENERAL MANAGEMENT

Treatment for esophageal carcinoma is characterized as either curative or palliative. According to one historical study,[119] only 20% of patients present with cancer of the esophagus that is truly localized to the esophagus, indicating that at the time of diagnosis, approximately 80% of patients have either locally advanced or distant disease. Figure 59.12 is a treatment algorithm for newly diagnosed esophageal cancer.

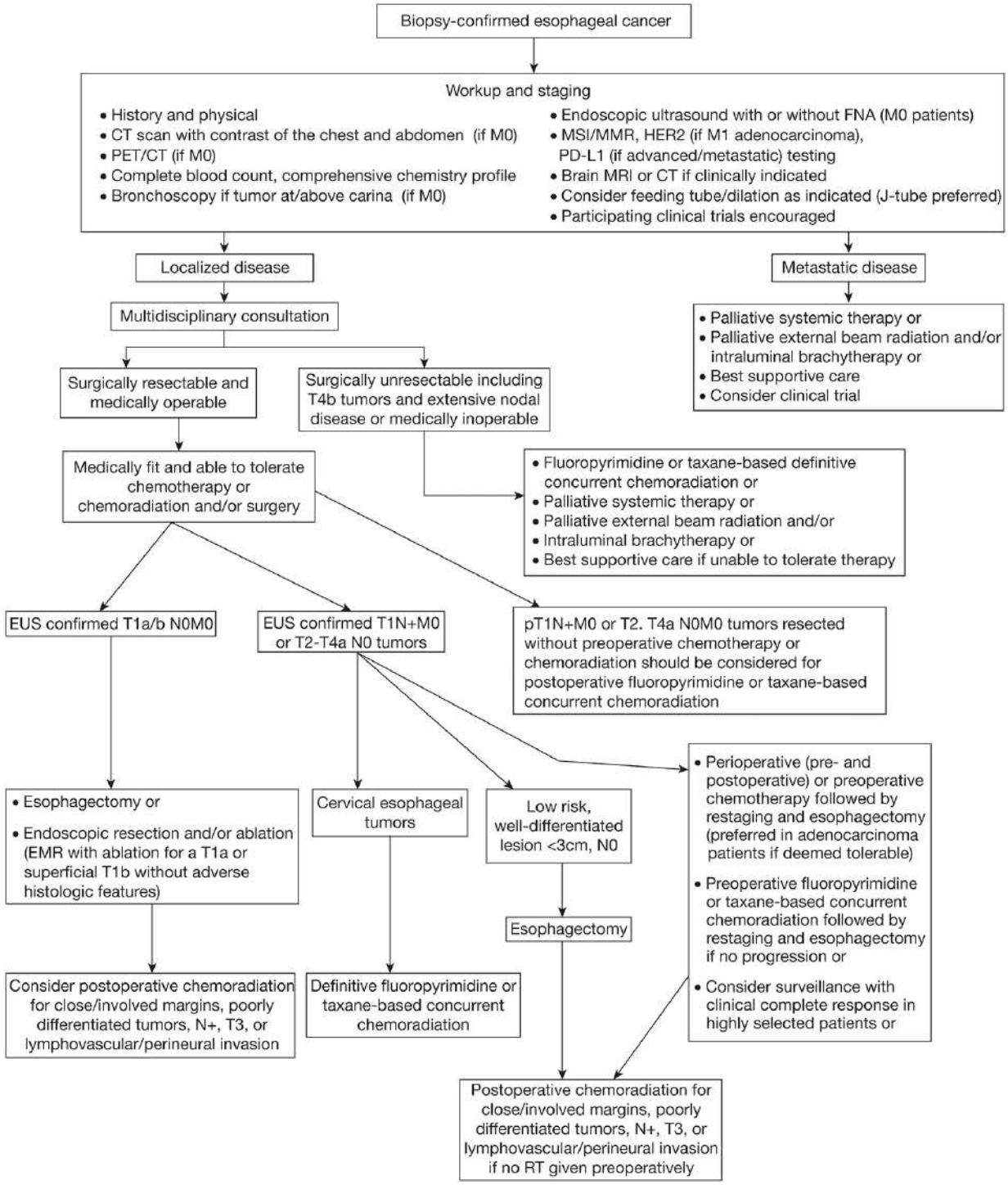


FIGURE 59.12 Treatment algorithm for newly diagnosed esophageal cancer. Treatment approaches are based in location and stage of the tumor, as well as surgical resectability and medical comorbidities of the patient. CT, computed tomography; EMR, endoscopic mucosal resection; EUS, endoscopic ultrasound; FNA, fine-needle aspiration; HER2, human epidermal growth factor receptor 2; MRI, magnetic resonance imaging; MSI/MMR, microsatellite instability/DNA mismatch repair deficiency; PD-L1, programmed death ligand-1; PET, positron emission tomography; RT, radiation therapy.

Surgery With Curative Intent

Surgery of the thoracic esophagus usually requires a subtotal or total esophagectomy and is usually undertaken for lesions of the middle to lower one-third of the thoracic esophagus and GE junction. Patients with stage I to III tumors are often considered for potentially curative resection; however, aortic, tracheal, heart, or great vessel invasion may preclude resection. Esophagectomy may be accomplished by a number of techniques, including a transhiatal esophagectomy, right thoracotomy with laparotomy with intrathoracic anastomosis (Ivor Lewis esophagogastrectomy), right thoracotomy with laparotomy with cervical anastomosis (McKeown or "three-hole" esophagogastrectomy), and left thoracoabdominal, transhiatal, or radical esophagectomy via open or laparoscopic approaches. Each technique has its advantages and disadvantages. In general, advantages of the transthoracic approach include better visualization with access and resection of the upper two-thirds of the esophagus and mediastinal lymph nodes. One potential advantage of the McKeown approach is a cervical anastomosis, which may allow for easier management of anastomotic leaks. Alternatively, the transhiatal approach has less morbidity than does thoracotomy (including respiratory compromise) with easier access to anastomotic leaks. However, a recent randomized trial evaluating intrathoracic versus cervical anastomosis following total or high-grade minimally invasive esophagectomy revealed leakage rates of 12.3% for intrathoracic versus 34.1% for cervical anastomoses, with less severe complications and lower recurrent nerve palsy rates after Ivor Lewis surgery, indicating that intrathoracic anastomosis resulted in better outcomes for patients treated with transthoracic minimally invasive esophagectomy or mid to distal esophageal or GE junction cancers.[120] In any instance, achievement of negative margins at resection has been reported to be a significant prognostic factor and should be the goal of esophageal resection. Exemplifying this, in a study of 500 patients undergoing transthoracic resection, patients undergoing margin-negative resection had a 5-year survival rate of 29% versus no 5-year survivors in patients with involved margins.[121]

Ivor Lewis esophagectomy is the classic approach to expose midesophageal lesions. A left thoracotomy procedure exposes lesions of the GE junction. Transhiatal esophagectomy is performed without a thoracotomy and is useful in lower esophageal lesions, although direct visualization and dissection of varying mediastinal lymph nodes cannot be achieved. An emerging treatment option in addition to the above techniques is the use of minimally invasive esophagectomy, which can include laparoscopy-assisted, thoracoscopic, or more limited thoracotomy. Minimally invasive techniques, including robotic approaches, are being increasingly applied to esophageal cancer. A hybrid minimally invasive esophagectomy (consisting of laparoscopic abdominal phase of gastric mobilization) with an open right thoracotomy may have a lower incidence of intraoperative/postoperative pulmonary complications and tumor spillage compared to an open approach, with a potential improvement in overall and disease-free survival.[122] Despite this, even at specialized centers, postoperative morbidity remains high, with

overall complication rate of 50% to 60% and with 1- and 3-month mortality rates reported to be less than 2% and less than 6%, respectively.[123] The optimal surgical approach is unknown and remains a topic of ongoing investigation.

Laparotomy or laparoscopy can be performed before neoadjuvant therapy or concurrently with esophagectomy to rule out peritoneal-based disease below the diaphragm, particularly in more advanced adenocarcinomas of the GE junction. Multiple reconstruction options are available following definitive surgery; esophagogastrostomy is the most widely used, using the stomach as a conduit to replace the esophagus. Patients with significant obstruction and inability to maintain their weight often require placement of feeding jejunostomy. If surgery is planned, gastric tube placement is generally avoided, given that the stomach will ultimately serve as the "neoesophagus" following resection, with feeding jejunostomy often preferred. Colon interposition, preferably with the left colon, can also be used; however, this approach is generally reserved for patients who have previously undergone gastric surgery or other procedures that have devascularized the stomach. Similarly, jejunal interposition may be utilized.

Squamous cell carcinoma of the cervical esophagus presents a difficult management situation. Proximal esophageal tumors less than 5 cm from the cricopharyngeus are generally treated with definitive chemoradiotherapy. If surgery is performed, resection of portions of the pharynx, the entire larynx, the thyroid gland, and the proximal esophagus is often required. Radical neck dissections are also carried out.[61] Because of the significant morbidity and loss of organ function with surgery, chemoradiation alone has been frequently employed. The survival probability with definitive chemoradiotherapy is similar, without the major functional impairments, morbidity, and mortality associated with surgery.[124] The optimum time to surgery following neoadjuvant therapy remains a topic of investigation, although delaying surgery from the traditional 4 to 6 weeks to greater than 12 weeks might improve tumor response to neoadjuvant therapy and thereby facilitate radical resection. This remains a topic of investigation.

Curative Combination Therapy

In the treatment of patients with esophageal cancer, an approach of radiation therapy with concurrent chemotherapy, with or without surgery, is frequently adopted. Multiagent chemotherapy with cisplatin and 5-fluorouracil (5-FU) has been used historically, although other combinations (eg, paclitaxel and carboplatin; 5-FU with oxaliplatin) are now commonly utilized. Additional combinations of novel systemic agents (that also act as radiosensitizers) with radiation therapy are under investigation.

Palliative Treatment

Palliative treatment is frequently used for the relief of symptoms of esophageal carcinoma, especially dysphagia.[125] Surgical palliation involves resection and reconstruction, if possible, removing the bulk of the disease, potentially preventing abscess and fistula formation, as well as bleeding. Substernal bypass with the colon or entire stomach has also been carried out.[125] However, given the poor prognosis in patients with advanced disease and morbidity associated with resection, a surgical approach is rarely adopted and should be avoided in patients who can be managed with nonsurgical modalities.

Endoscopic dilation is a reasonable alternative. When the lumen of the esophagus is dilated to 15 mm, dysphagia is often no longer experienced. Repeat dilation is often required.[61] Esophageal stenting with either conventional plastic stents or metallic self-expanding stents can also be used to maintain patency.[126]

Palliative irradiation is frequently used to control the primary disease, as well as distant metastases. Resolution of symptoms, especially pain and dysphagia, can be accomplished in up to 87% of patients. Palliative treatment regimens range from 20 Gy over 1 week[62] to 50 Gy over 5 weeks. Laser ablation with or without intraluminal brachytherapy can be used. The addition of three fractions of 7 Gy each can improve the stenosis-free interval and prevent obstruction.[126]

RADIATION THERAPY TECHNIQUES

Simulation

When patients are simulated, the radiation oncologist should know the extent of disease based on imaging (barium swallow, CT, PET, magnetic resonance imaging [MRI]), as well as on endoscopy. CT simulation is appropriate for treatment planning. During simulation, the patient is positioned, straightened, and immobilized on the simulation table. An immobilization device (eg, wing board, alpha cradle, body fix, or Vac-Lok on indexed wing board) is used to minimize variation in daily setup. Arms are generally placed overhead and knee support placed underneath the legs. Palpable neck disease should be marked with a radiopaque wire. The administration of oral contrast to delineate the esophagus is generally used and helps define the extent of mucosal irregularity, whereas small-bowel contrast can help identify any bowel in the field. For GE junctional tumors (particularly with significant gastric involvement), it may be advisable to have the patient come in with an empty stomach. Fasting prior to simulation and treatment each day may allow for greater reproducibility of treatment. In contrast, simulation without fasting and delivery of oral contrast may allow for planning in a “worst-case” scenario, with the patient later instructed to fast prior to treatment delivery. For cervical and upper thoracic lesions, an immobilization mask may assist in creating a reproducible position. Some authors have also advocated that midesophageal primaries be simulated in prone position to maximize distance between the target volumes and spinal cord. The patient is placed on the CT simulator in the treatment

position, and a scan of the entire area of interest with margin is obtained. At a minimum, 3- to 5-mm slices should be used, allowing accurate tumor characterization, as well as improved quality of digitally reconstructed radiographs. If patients lose more than 10% of their body weight during therapy, consideration should be given to repeat CT planning. Intravenous contrast is generally used to delineate mediastinal and abdominal vascular nodal basins, including the celiac axis and to allow the radiation oncologist to discern normal vasculature from other adjacent normal structures, and potential adenopathy. The tumor and vital structures are then outlined on each slice on the treatment planning system. The use of respiratory gating or breath-hold techniques may help to reduce target motion with respiration and, therefore, avoid normal-tissue irradiation associated with larger margins used in free-breathing approaches, particularly for lower esophageal cancers. Additional techniques to minimize physiologic motion include abdominal compression devices. Four-dimensional CT scan may be appropriate to assess tumoral motion, facilitating appropriate margin placement on the target volumes, particularly in lower esophageal tumors and/or diseases involving the stomach.

Treatment Planning

Target Design

In the design of radiation fields for esophageal cancer, it is important to define varying target volumes, including gross disease as well as potential areas of subclinical involvement (ie, the GTVs and CTVs, respectively). Definition of GTV is based on multiple studies, including endoscopic descriptions (from both esophagogastroduodenoscopy [EGD] and EUS). The proximal and distal aspects of the tumor should be standardly defined by the gastroenterologist based on distance from the incisors, as well as relationship to varying landmarks as measured from the incisors (eg, the GE junction). The radiation oncologist is able to use these measurements to help correlate with disease extent visualized on planning CT scan, using varying anatomic landmarks (eg, the GE junction, which is frequently located ~40 cm from the incisors in many patients), as well as carina (which is frequently located at ~25 cm in most patients) to help more accurately define the GTV. Additionally, endoscopists may place radiopaque fiducial markers at the superior and inferior extent of the primary tumor to help facilitate disease extent. Esophageal wall thickening correlating to the GTV can frequently be visualized on diagnostic and radiation planning CT. Similarly, EUS appears to be the most reliable test in detecting lymphadenopathy related to nodal spread. As in EGD, the endoscopist should be encouraged to accurately define not only the primary disease extent on EUS as measured by distances from the incisors but also depth of penetration and potential involvement of adjacent structures, which can also be used to help guide GTV delineation. Similarly, EUS may detect lymph nodes that may not be easily appreciated on CT or PET imaging, and the endoscopist should describe the size as well as the location (eg, distance from incisors, relationship to adjacent

mediastinal structures) of these, further facilitating accurate definition of potentially involved lymph nodes, either adjacent to or well removed from the primary tumor itself. In addition, radiographic areas of lymphadenopathy should similarly be included in the GTV.

Although the utility of PET in esophageal cancer staging primarily lies in its ability to detect distant metastases not fully appreciated on CT imaging (and thereby alter treatment approach of these patients),[127,128] diagnostic PET-CT has more recently been integrated into radiation planning of patients with esophageal cancer and definition of GTV. Generally, gross disease as defined on PET is characterized by a SUV of more than 2 to 2.5.[129] Generally speaking, PET-avid nodes should be included within the GTV volume. In a study from Fox Chase Cancer Center, the mean GTV length as determined by PET-CT closely correlated with endoscopy findings.[74] Another study from Australian investigators reported that CT-alone-based definition of GTV excluded PET-avid disease in the majority of patients, resulting in a potential geographic miss of disease in a significant minority of patients.[130] Similarly, the fusion of CT-PET has been shown to prompt GTV and PTV modification in the majority of patients.[131] Another analysis of PET-CT-based (as compared to CT-alone) radiotherapy planning of patients with esophageal cancer indicated a reduction of intraobserver and interobserver variability in GTV delineation.[132] However, another study compared the planning of patients with CT-alone treatment followed by adjustment based on PET findings. Although PET scan influenced GTV volume in half of the patients, no locoregional recurrences were seen following CT-based radiotherapy that could have been prevented by the addition of PET.[133]

Finally, although the routine use of fluoroscopic barium swallow in esophageal cancer has decreased, this study may still be useful to the radiation oncologist for field design. A study by Chinese investigators suggested that, as compared to CT, endoscopy with barium swallow more accurately defines the true length of middle and lower esophageal tumors, although CT appeared to better determine this for tumors located at the GE junction.[134]

In summary, accurate definition of primary and nodal gross disease is paramount in radiation planning for esophageal cancer. It is important to rely on all diagnostic studies, including barium swallow (when available), EGD, EUS, CT, MRI, as well as PET scan.

The identification of potential direct and nodal pathways for spread of subclinical disease (ie, CTV definition) in esophageal cancer is also of paramount importance. These areas vary significantly, depending on the site of origin of disease, making esophageal cancer planning somewhat complex. In terms of direct disease extension along the esophagus itself, varying reports have assessed the histologic findings at primary esophagectomy to determine subclinical extent of disease. One prospective analysis of 66 resection specimens showed that placement of a 3-cm margin proximally and distally on the primary tumor would cover microscopic disease extension in 94% of squamous cell carcinomas. Similarly, in GE junctional carcinomas, a 3-cm proximal

margin included subclinical disease extension in 100% of patients and 5 cm distally covered 94% of subclinical spread.[135]

As described previously, the esophagus is characterized by a rich submucosal network of lymphatics that facilitates early lymph nodal spread of disease, even for superficial esophageal cancers. The appropriate cranial and caudal margins remain a matter of debate in the treatment of esophageal cancer. Historically, very large fields were treated, encompassing potential pathways and lymphatic spread from the thoracic inlet down to the celiac axis region; however, such fields are potentially fraught with treatment-related toxicity and may be difficult for patients to tolerate, particularly in the context of concurrent chemotherapy delivery. Most contemporary radiation trials used margins of 3 to 5 cm cranially and caudally on the GTV, along with an approximate 2-cm radial margin. With disease located at or above the carina (or middle/upper one-third of the esophagus in some instances), many of these trials recommended fields inclusive of the supraclavicular lymph node basins, whereas celiac axis nodal basin coverage was recommended for disease of the distal esophagus.[135] However, the appropriate field size for patients with esophageal cancer remains controversial, particularly the role of elective nodal irradiation.

Even the concept of what constitutes "involved field" and "extended field" can vary between series. Comparative series have yielded conflicting results to this effect, although recent reviews have suggested that elective nodal irradiation appears to prevent or delay regional nodal relapse. However, its impact on survival in these patients remains less clear, with a higher incidence of esophageal and lung toxicities in the latter.[136] Analysis of a randomized trial from China of patients with squamous cell carcinoma treated with definitive chemoradiation with either paclitaxel plus 5-FU or cisplatin with 5-FU utilized an involved field–alone approach. Elective nodal failure (defined as failure in an unirradiated area not seen pretreatment) as well as "extensive" nodal region (described as anywhere from the bilateral upper neck down through the celiac region) was seen in 8.5% and 11.6% of patients, respectively. The authors concluded that an involved field can achieve low rates of isolated nodal failure and satisfactory survival outcomes and elective nodal irradiation may be unnecessary.[137] This remains a topic of ongoing study and randomized studies are needed. Further description of lymph node basin coverage follows.

Field Design

Historically, the treatment of very proximal (cervical) esophageal cancers has been challenging. Because of the changing contour from the neck to the thoracic inlet, treatment of lesions in the upper one-third of the esophagus may present a difficult technical problem. Lesions in the upper cervical or postcricoid esophagus are often treated from the laryngopharynx to the carina, depending on extent of disease. Supraclavicular and superior mediastinal nodes are irradiated electively. Using older/conventional methods, this was achieved with lateral parallel opposed or oblique

portals to the primary tumor and a single anterior field for the supraclavicular and superior mediastinal nodes.[114] Another historical technique treated lesions in this region by means of a four-field box approach, using a wax bolus to build up the lack of tissue above the shoulders, acting as a compensator. A high-energy beam (.15 MV) is used, and both sides of the neck are treated prophylactically. Other methods of treating lesions at the thoracic inlet include 140-degree arc rotations, anterior wedged pairs, and three- or four-field techniques using posterior oblique portals combined with a single anterior portal or anteroposterior-posteroanterior (AP/PA) fields.[114] Using three-dimensional (3D) approaches, varying techniques have been implemented, including treatment of the primary tumor and lymph nodes using an AP/PA approach to 39.6 to 41.4 Gy at 1.8 Gy/fraction, followed by a left or right opposed oblique pair to bring the total dose to 50.4 Gy, thereby limiting the spinal cord dose. This technique will generally exclude the supraclavicular fossa, and a separate electron field is often added, treating to a depth of 2 to 3 cm, depending upon individual anatomy. In modern field design, intensity-modulated radiation therapy (IMRT)–based planning has facilitated the treatment of upper esophageal lesions and is our preferred method for treating these tumors (Figure 59.13). Strict normal-tissue constraints, including normal lung and spinal cord, are important considerations in using these techniques (discussed later).

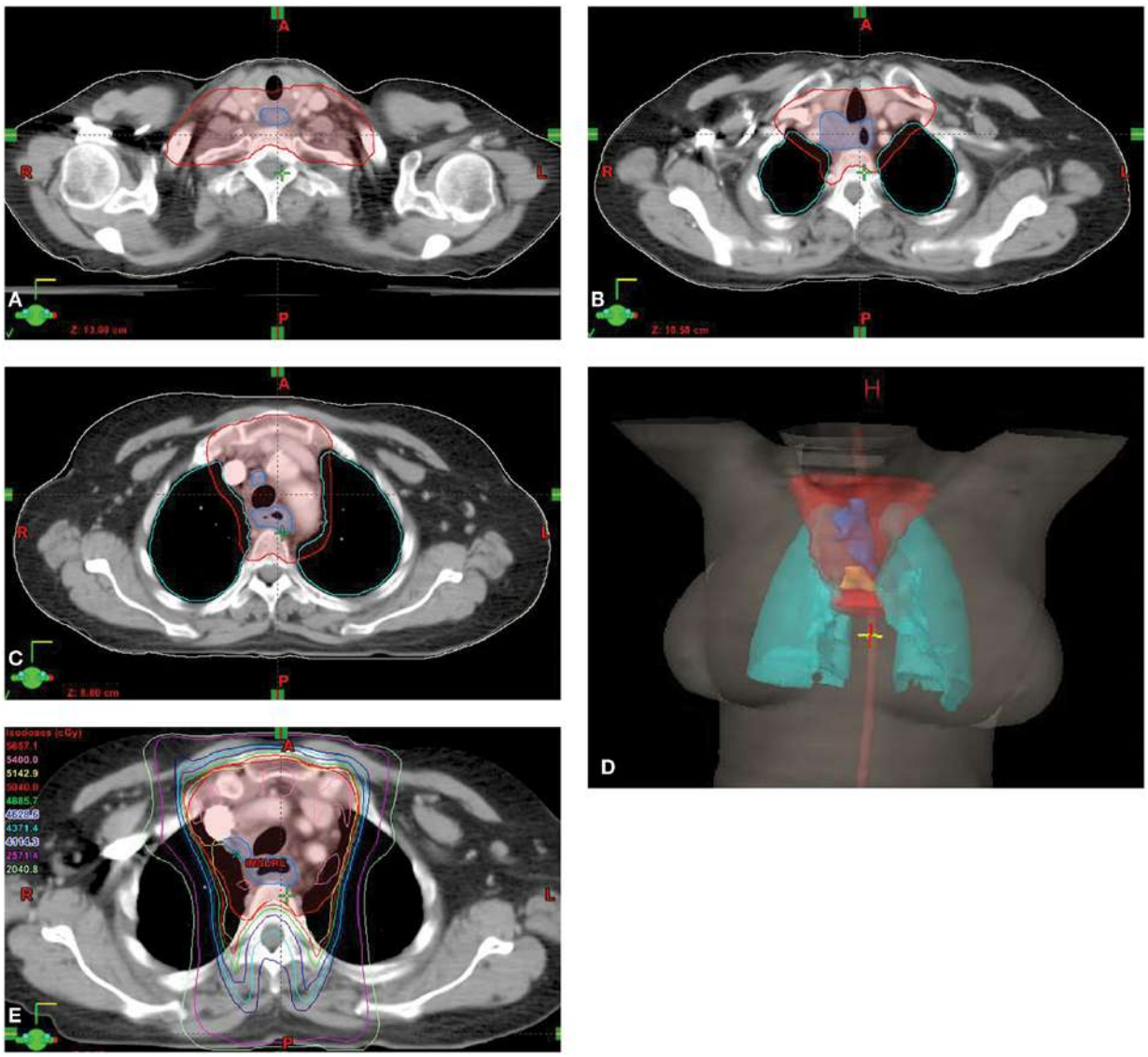
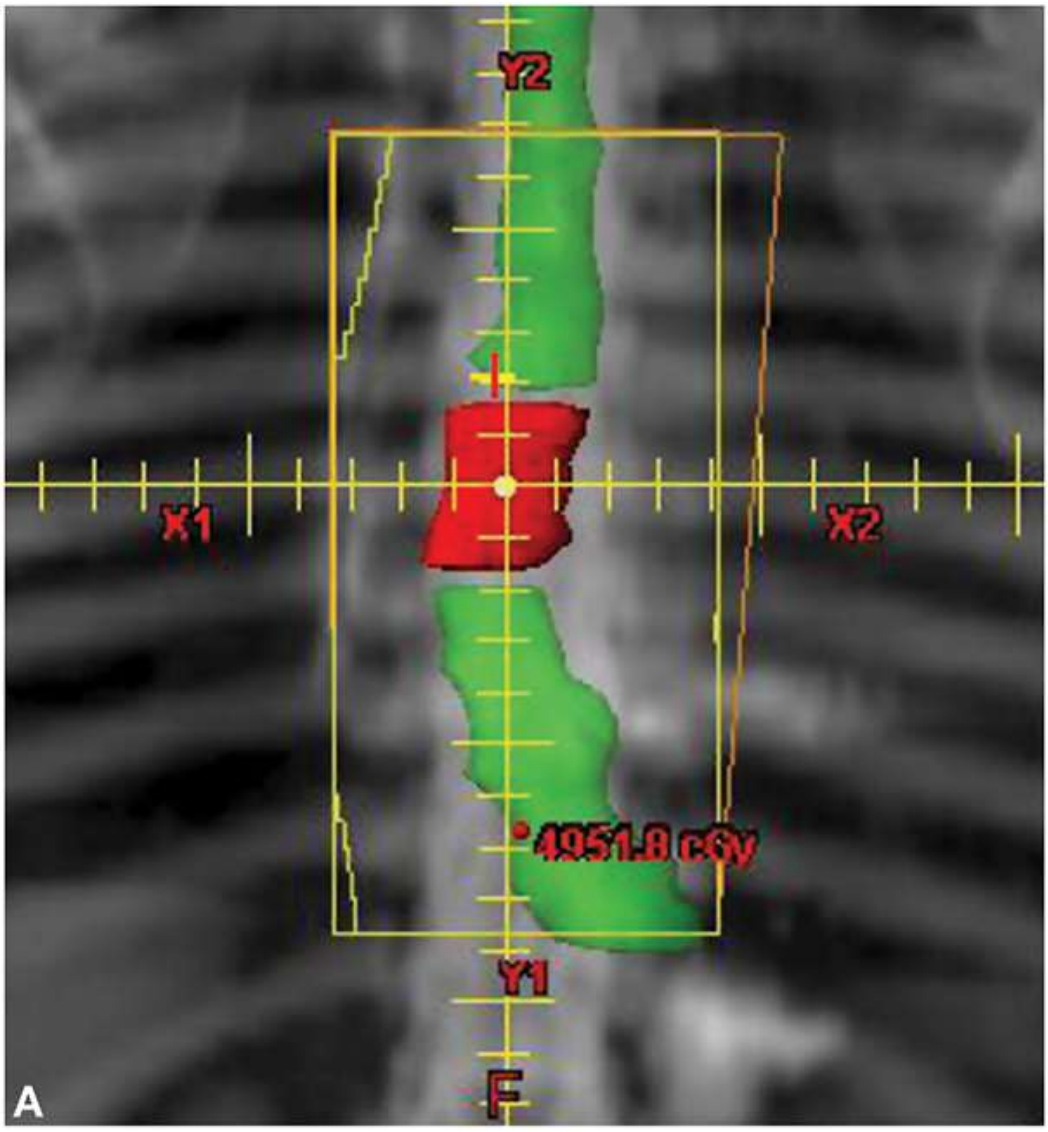


FIGURE 59.13 A-C. Examples of planning target volume (PTV) in a 62-year-old woman with a cT3 N1 squamous cell carcinoma of cervical esophagus. Gross tumor volume (GTV), blue volume; PTV, red volume. D. Three-dimensional reconstruction of PTV from above the patient. Carina, yellow; GTV, dark blue; lungs, light blue; PTV, red; spinal cord, brown. E. Isodose curves of this patient treated with a nine-field intensity-modulated radiation therapy plan. Note that beams are primarily anteriorly oriented. (Courtesy of Rodney Hood, CMD.)

Based on the previously described and other pathologic patterns of spread data in squamous cell carcinoma of the esophagus, general guidelines in terms of field design can be made as follows: for cervical and upper thoracic squamous cell carcinoma, the CTV should generally include nodal basins extending from the lower cervical and supraclavicular region superiorly to the subcarinal lymph node basin inferiorly, inclusive of the upper paraesophageal lymph nodes (Figure 59.14A). For lower esophageal squamous cell carcinomas, lymph node basins from the subcarinal region superiorly to the left gastric and common hepatic artery/celiac lymph nodal basins

inferiorly should generally be included (described further later in this chapter). In a small series of patients without celiac radiation coverage, six (10%) had celiac nodal failure, portending a worse prognosis. The authors concluded that although overt celiac failure only occurred in 1 of 10 patients, the lack of effective salvage in treatments may justify treatment of this basin in patients with distal esophageal cancer.[138] For tumors of the middle esophagus, we recommend individual field design according to clinical scenarios, with a more complete coverage of paraesophageal mediastinal lymph nodes, particularly in patients with a good performance status (Figure 59.14B,C).[48] These are general guidelines, and all plans should be individualized based on available imaging and endoscopic findings.


Y2
X1
X2
4951.8 cGy
Y1
F
A

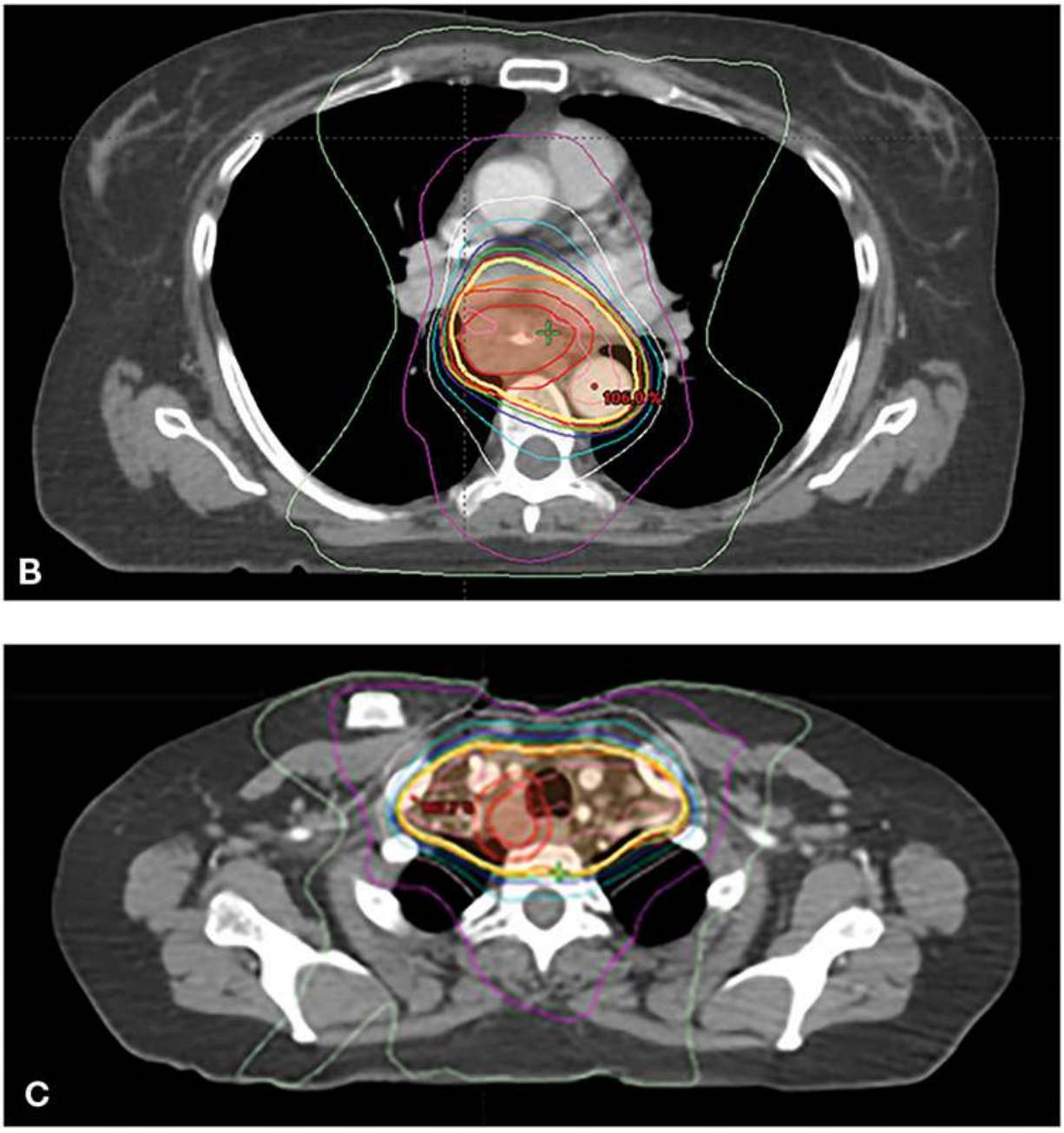


FIGURE 59.14 A. Example field for a midesophageal squamous cell carcinoma. Note that the field is inclusive of adjacent mediastinal/paraesophageal nodes, with approximately 5-cm margin superiorly on the gross tumor volume (GTV), as well as slightly larger margin on the inferior aspect of the GTV based on concern of previously unappreciated spread at the time of endoscopy. B. This 56-year-old woman had a midesophageal squamous cell carcinoma with upper mediastinal involvement. Using a simultaneous integrated boost (SIB) technique (low-dose planning target volume in orange, 45 Gy in 25 fractions; higher dose planning target volume red, with central GTV in red, 50 Gy/25 fractions). C. Upper mediastinal nodal involvement is seen utilizing SIB technique.

In field design, potential nodal involvement (and therefore target volumes) based on nodal size is problematic, given that some reports demonstrated that less than 15% of

metastatic nodes are more than 1 cm and that average size differences between involved and uninvolved nodes are frequently not significantly different.[139] In addition, fluorodeoxyglucose-PET scanning has an estimated sensitivity of only 67% of detecting nodal metastases.[9] Even endoscopic ultrasound, generally considered the most sensitive test for detecting lymph node metastases, is only able to detect such disease in approximately 75% of patients.[140] Therefore, it is not appropriate to rely exclusively on varying imaging modalities to define areas of subclinical spread for esophageal cancer, realizing that patterns-of-spread data are important in determining radiation field design.

The design of radiation fields for the treatment of adenocarcinoma of the esophagus is similar to that of lower thoracic squamous cell carcinomas but deserves special mention. Periesophageal lymph nodes are generally included in all patients. Given that lymph node involvement is clearly associated with depth of tumor penetration (T stage) and the fact that most patients in the United States and Europe presenting with GE junctional carcinoma will have more advanced disease, inclusion of celiac lymph basins for adenocarcinoma of the distal esophagus/GE junction is usually indicated, although it remains an area of controversy. Based on the previously described patterns of spread data from Erlangen and others, specific considerations include the following: Lymph vascular invasion is highly predictive of nodal spread. Proximal extension of tumors (particularly beyond the Z line into the distal esophagus for type II and III tumors) predicts an increasing incidence of paraesophageal lymph node involvement. Based on an estimated nodal incidence cutoff of 20% for inclusion, specific considerations include the following:

- The lower paraesophageal, paracardial, lesser curvature, and left gastric artery nodes should be included in the CTV.
- The presence of lymph vascular invasion predicts a nodal positivity rate of more than 20% in the left and right gastroepiploic, greater curvature, celiac trunk, and splenic hilar regions.
- In T3 to T4 disease, the gastroepiploic, greater curvature, celiac trunk, splenic hilar, splenic artery, and common hepatic artery should be included.
- High-grade tumors should also include the left gastroepiploic, greater curvature, and celiac trunk nodes in CT design.
- Larger and more deeply penetrating tumors should also include the splenic artery and splenic hilar nodes, as well as those along the greater curvature.
- Tumors extending above the diaphragm and those extending more than 1.5 cm beyond the Z line should include the mid paraesophageal nodes, potentially treating up to the carina. Of note, significant involvement of the distal esophagus by GE junctional tumors (.1.5 cm beyond the Z line) should potentially lead to inclusion of not only lower but also middle paraesophageal nodes based on patterns of spread.

However, treating these more extensive fields must be weighed against potential side effects of increased irradiation of normal tissue.

In summary, middle and lower paraesophageal nodes should be included in patients with T2 to T4 type I and T2 to T4 type II tumors extending more than 1.5 cm above the Z line and patients with T3 to T4 type II tumors. The splenic hilar and artery nodes are considered "sparable" in T2 tumors, notably type I.[54]

Although, historically, two-dimensional-based radiation planning has been carried out primarily using anatomic landmarks such as bone and carina, as well as fluoroscopic barium swallow, to determine field borders, contemporary treatment using CT-based planning allows improved visualization of both target and nontarget structures, along with 3D reconstruction and creation of a "beam's-eye" view of varying fields, allowing improved conformity around target structures and improvements in normal-tissue sparing. Because volumetric data can be obtained by CT scans, dose-volume histogram data can also be generated. A variety of 3D techniques are being used and are described later.

Potential beam orientations for the treatment of thoracic esophageal and GE junction tumors (again defined as tumors involving the GE junction with an epicenter within 5 cm proximal or distal to the GE junction) include an initial AP/PA approach followed by AP/right posterior oblique (RPO)/left posterior oblique (LPO) fields with or without boost, an initial AP/PA approach followed by right anterior oblique (RAO)/LPO fields with or without boost, and a three-field technique (AP/PA with left lateral or oblique field). One potential approach in lesions of the thoracic esophagus or GE junction is to use initial AP/PA/RAO/LPO fields, with boost fields using laterally oriented beams. The inferior margin of the initial fields includes the GE junction and, for lower or middle one-third lesions, the celiac axis nodal basins (generally located at the level of T12 and identifiable on CT), as well as gastrohepatic ligament. Initial fields are often treated to a dose of 45 Gy, taking care to avoid as much of the heart as reasonably possible while continuing to minimize the kidney volume in the radiation field, inclusive of the above nodal basins. Reduced fields encompassing gross disease with an approximate 2-cm margin through oblique or lateral fields may then be used for an additional 5.4 Gy. Doses usually do not exceed 50 Gy, and lower doses (eg, 41.4 Gy) may be appropriate (discussed later).

A margin of 5 cm above and below the GTV is generally recommended to cover subclinical submucosal/nodal disease, as well as an approximate 2.0- to 2.5-cm radial margin, although individual margins are case dependent. Because it is imperative to account for daily setup uncertainty as well as physiologic internal organ motion (secondary to respiration, peristalsis, cardiac motion, etc), additional margin must be added to a CTV, particularly to the more mobile distal esophagus. The internal target volume (ITV) has been used to account for physiologic motion of the target volume, which is included in the PTV. Varying reports analyzing esophageal motion have shown average anterior and posterior motion ranges from 0.1 to 4 mm, lateral motion from 0.3

to 4.2 mm, and superior-to-inferior motion from 3.7 to 10 mm.[142] An analysis evaluating interfraction esophageal motion in the right-left and AP direction showed average right-left motion of 1.8 ± 5.1 mm (favoring leftward movement) and average AP motion of 0.6 ± 4.8 mm (favoring posterior movement), with an average absolute motion of 4.2 mm or less in the right-left and AP directions. The authors concluded that 12-mm left, 10-mm posterior, and 9-mm anterior margins are appropriate.[141] Some authors have recommended defining 1-cm radial, 1.5-cm distal, and 1-cm proximal margins from CTV to ITV if target motion data are not available. Image-guided radiation therapy, including cone beam CT, may also be useful in localizing tumor and establishing physiologic variability between daily treatments.

Figures 59.15 and 59.16 show general recommendations for elective target nodal station coverage in a patient with a type I GE junctional tumor with accompanying example field/volumes. Figure 59.17 shows general recommendations for elective target nodal station coverage in a patient with a type II GE junctional tumor. Nodal basins are similar to type I tumors with the exception of inclusion of nodal basins along the splenic artery course. Figures 59.18 and 59.19 show general recommendations for elective target nodal station coverage in a patient with a type III GE junctional tumor with accompanying example fields. Note that in type III tumors, there is less emphasis on more proximal (lower mediastinal) nodes and more comprehensive coverage of the splenic artery course, including splenic hilum. Figure 59.20 shows examples of varying nodal locations on axial CT images.

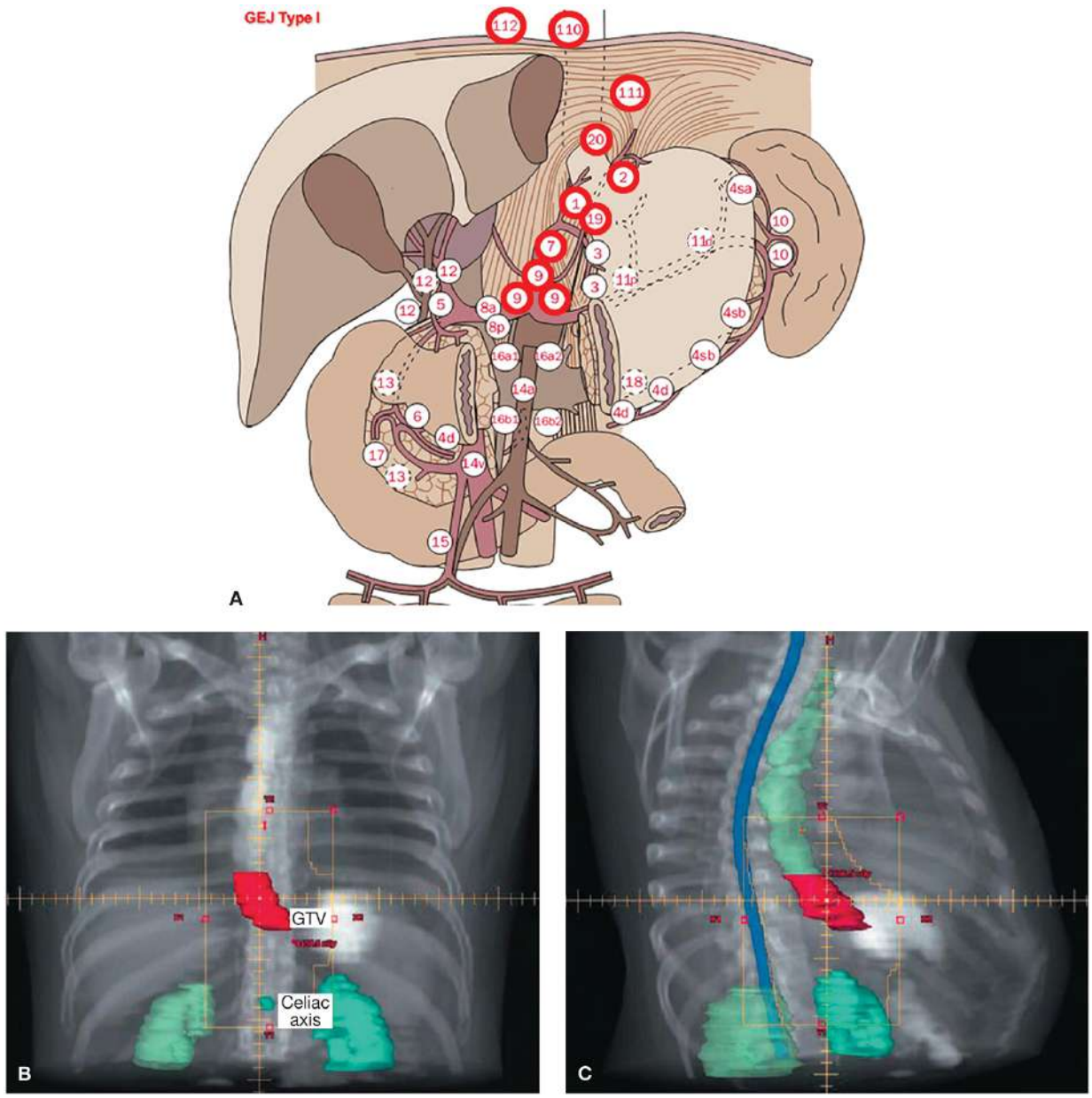
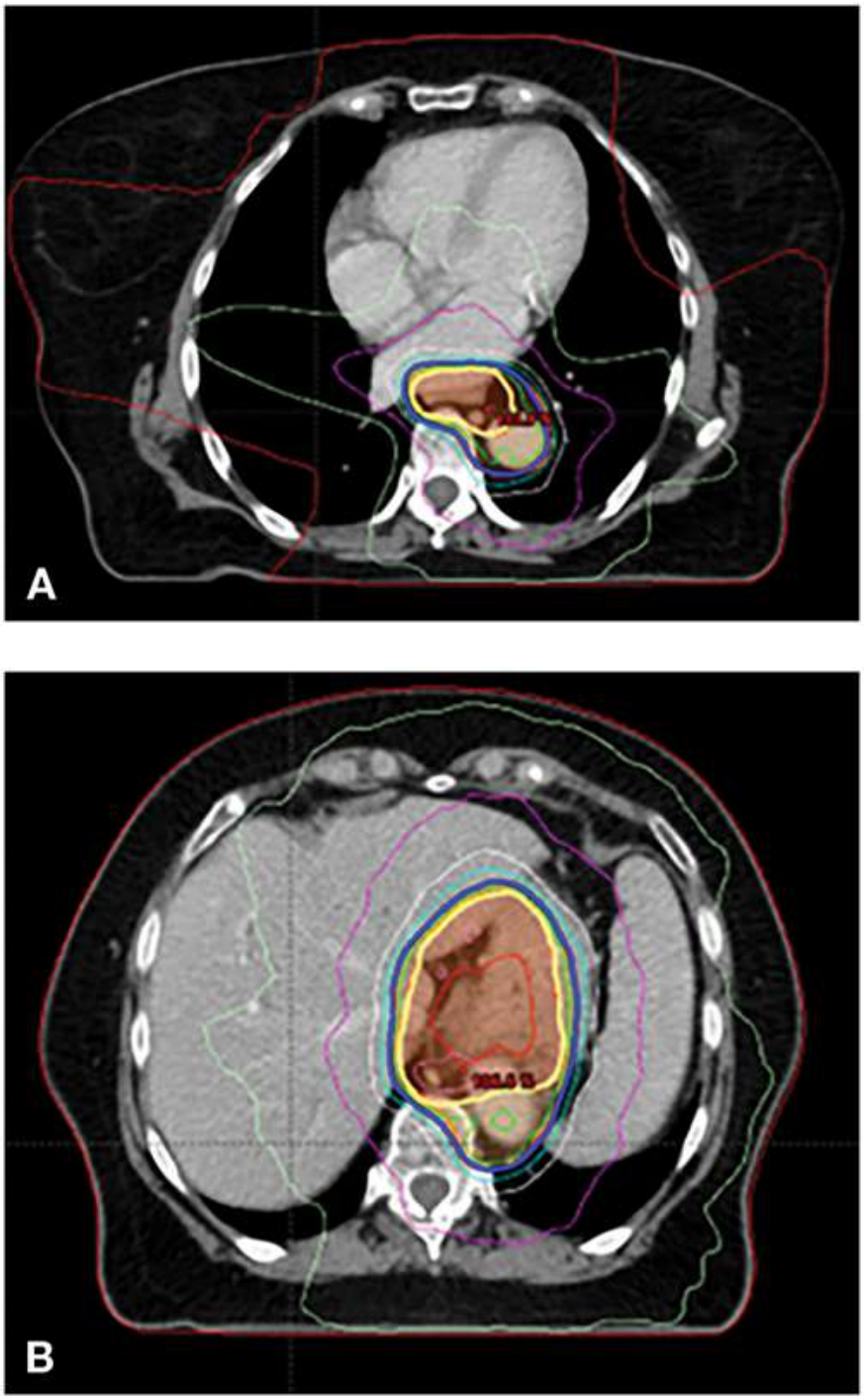


FIGURE 59.15 A. Recommended nodal basins to be included for type I gastroesophageal junctional (GEJ) tumors based on Japanese Gastric Cancer Association lymph node stations. (Reprinted from Matzinger O, Gerber E, Bernstein Z, et al. EORTC-ROG expert opinion: radiotherapy volume and treatment guidelines for neoadjuvant radiation of adenocarcinomas of the gastroesophageal junction and the stomach. *Radiother Oncol*. 2009;92[2]:164-175. Copyright © 2009 Elsevier Ireland Ltd. With permission.) B. Example field for a type I GEJ adenocarcinoma. GTV, gross tumor volume. C. Example oblique field for a type I GEJ tumor, inclusive of the above nodal basins.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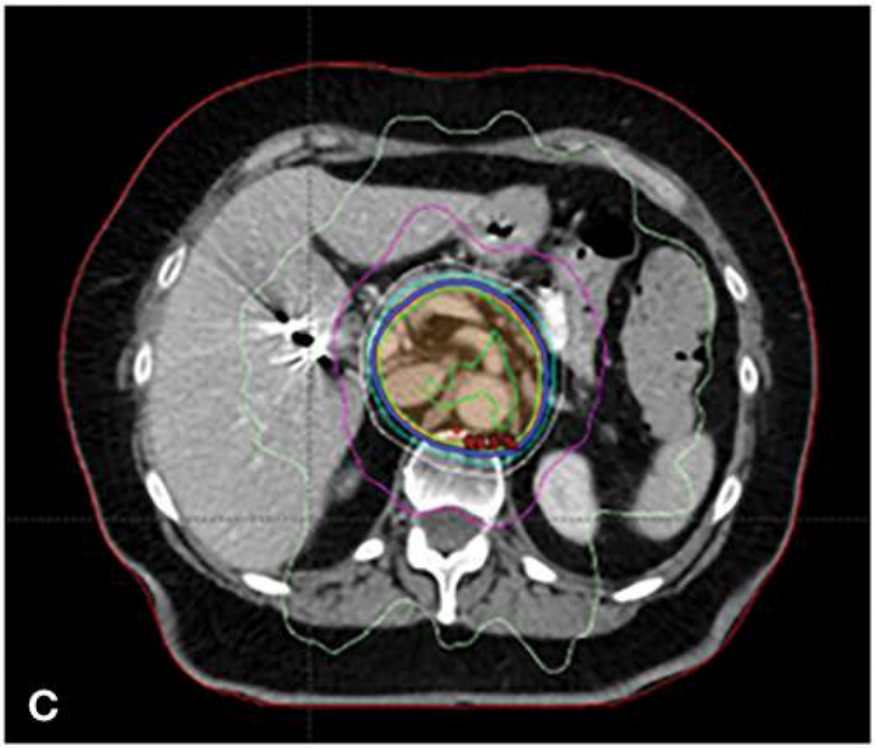


FIGURE 59.16 A. Intensity-modulated radiation therapy (IMRT) treatment of patient with a type I tumor utilizing a simultaneous integrated boost (SIB) technique, 45 and 50 Gy, respectively, in 25 fractions illustrated by the yellow and blue isodose lines, respectively; upper aspect of planning target volume. B. Level of the primary tumor. C. Level of celiac axis.

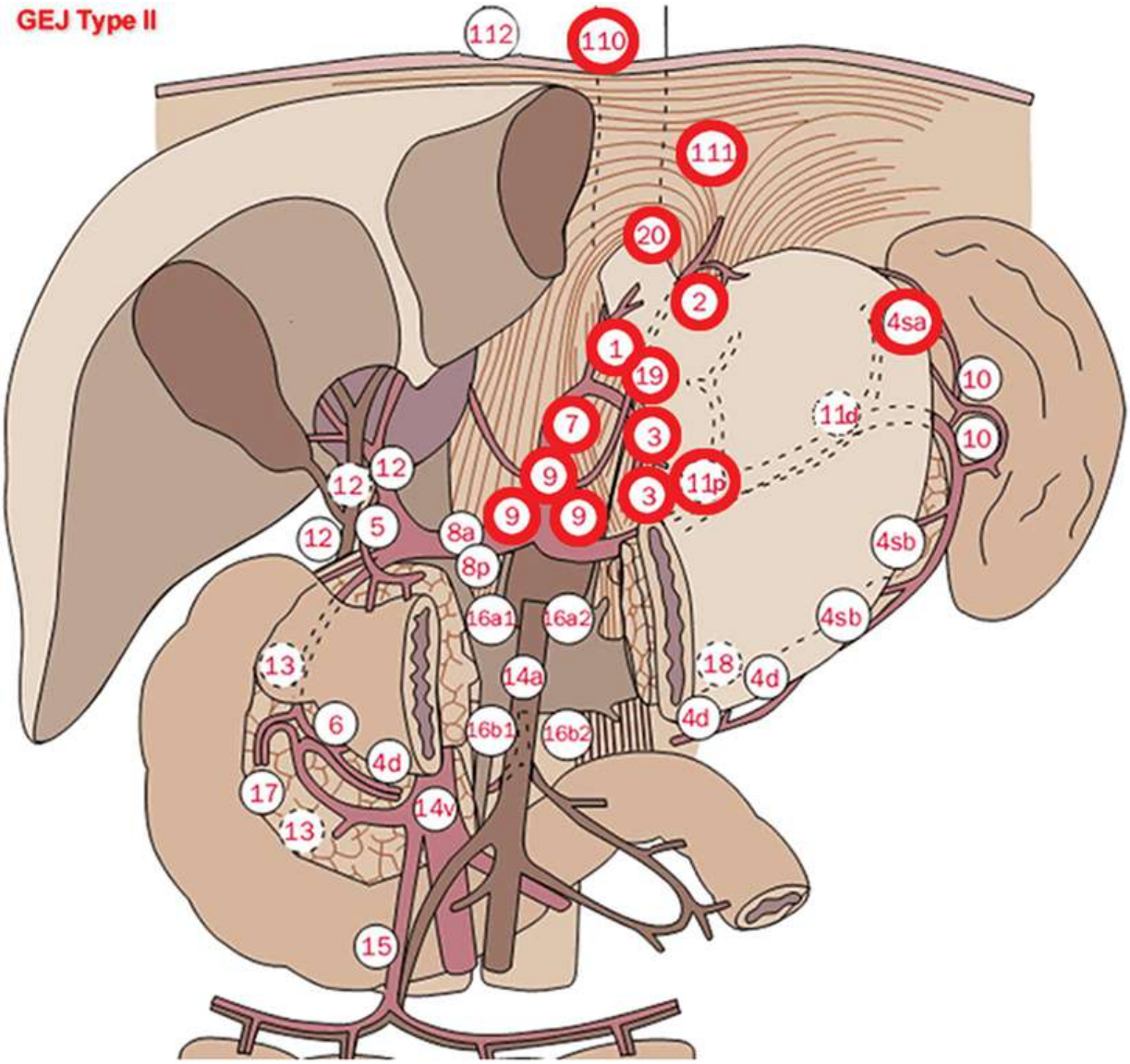


FIGURE 59.17 Recommended nodal basins to be included for type II gastroesophageal junctional (GEJ) tumors based on Japanese Gastric Cancer Association lymph node stations. (Reprinted from Matzinger O, Gerber E, Bernstein Z, et al. EORTC-ROG expert opinion: radiotherapy volume and treatment guidelines for neoadjuvant radiation of adenocarcinomas of the gastroesophageal junction and the stomach. *Radiother Oncol*. 2009;92[2]:164-175. Copyright © 2009 Elsevier Ireland Ltd. With permission.)

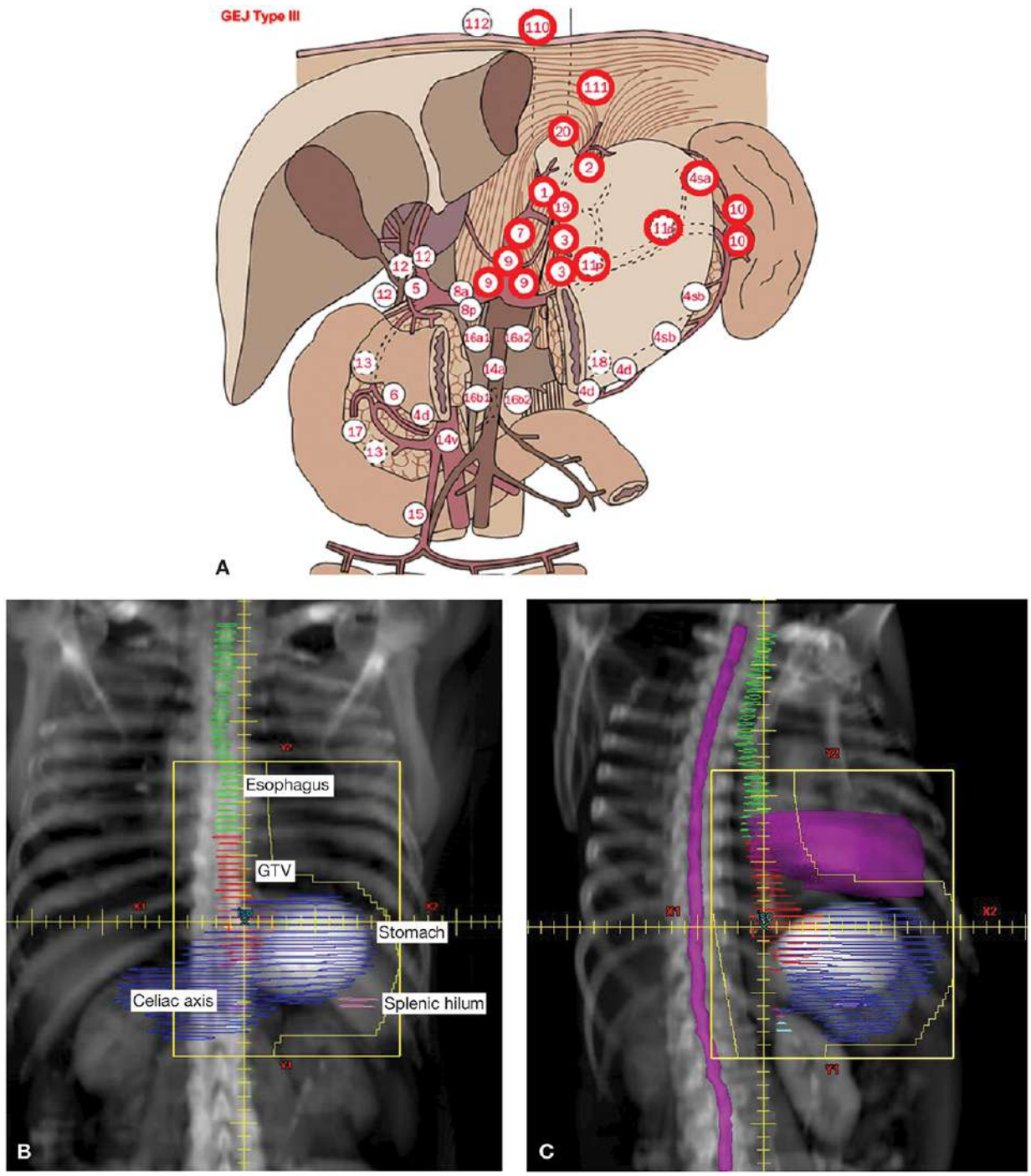


FIGURE 59.18 A. Recommended nodal basins to be included for type III gastroesophageal junctional (GEJ) tumors based on Japanese Gastric Cancer Association lymph node stations. (Reprinted from Matzinger O, Gerber E, Bernstein Z, et al. EORTC-ROG expert opinion: radiotherapy volume and treatment guidelines for neoadjuvant radiation of adenocarcinomas of the gastroesophageal junction and the stomach. *Radiother Oncol*. 2009;92[2]:164-175. Copyright © 2009 Elsevier Ireland Ltd. With permission.) B. Example field for a type III GEJ adenocarcinoma. GTV, gross tumor volume. C. Example oblique field for a type III GEJ tumor, inclusive of the above nodal basins.

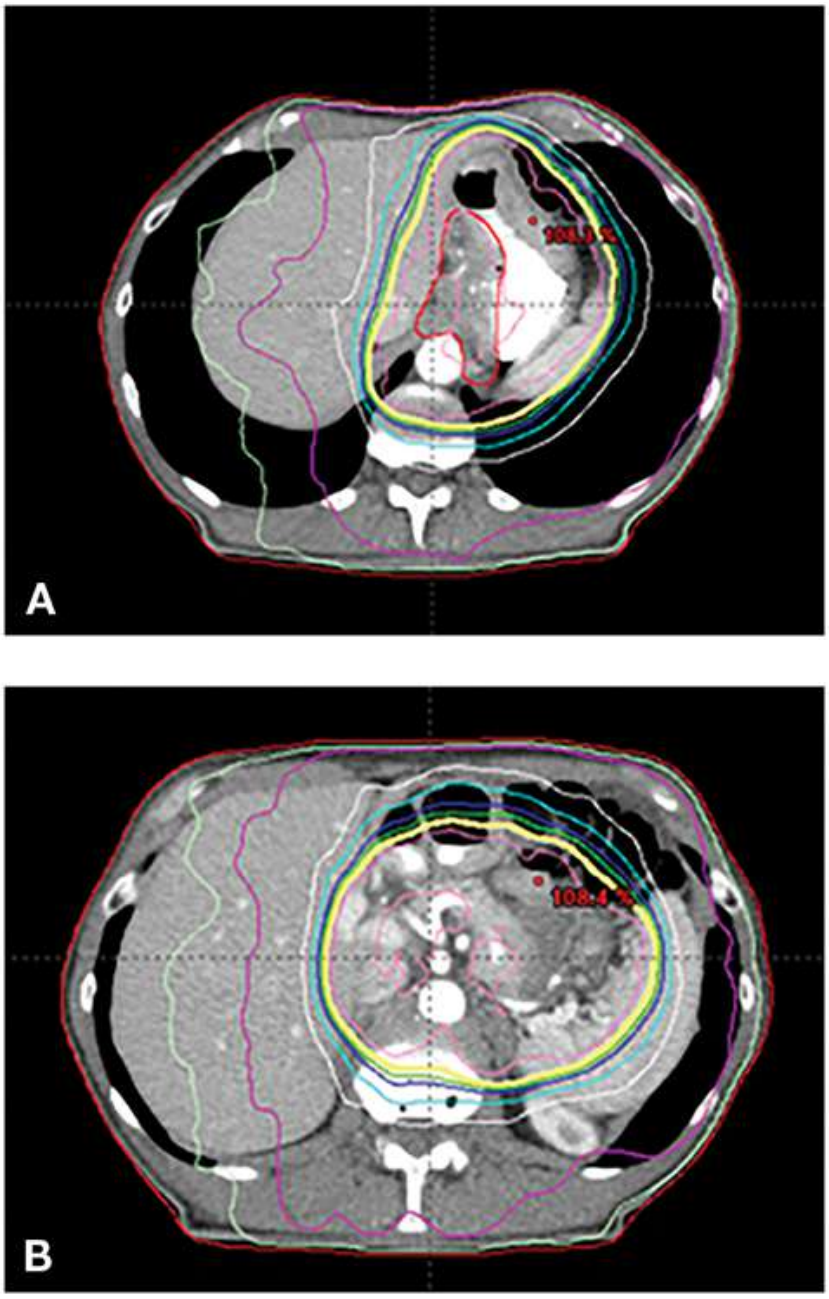
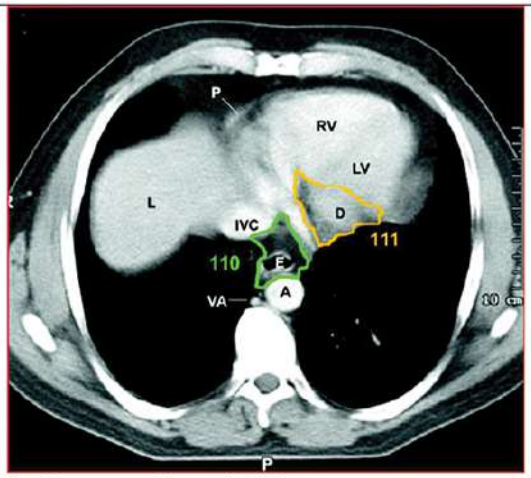
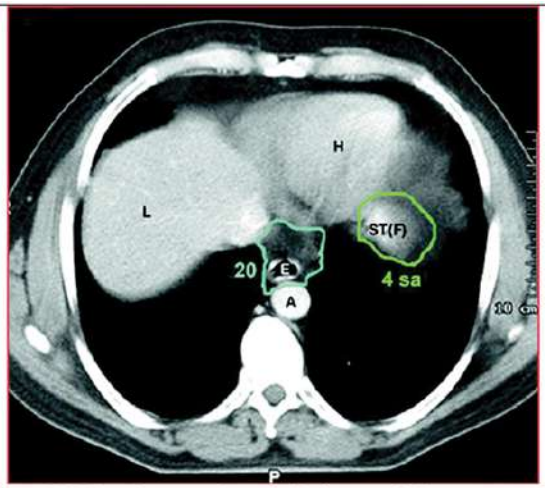


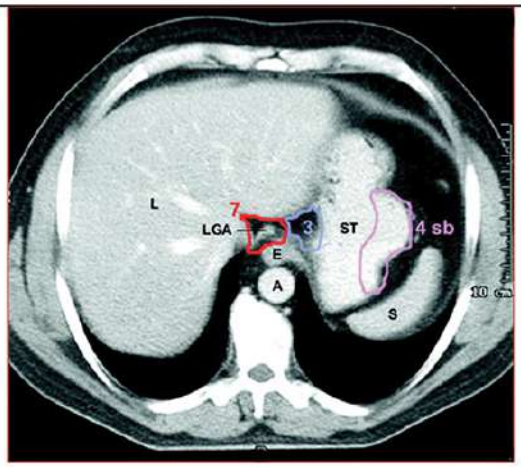
FIGURE 59.19 A. A 72-year-old man with type III gastroesophageal junction cancer, at the level of primary tumor (45 Gy) isodose line in yellow, gross tumor volume in red. B. Level of celiac axis.



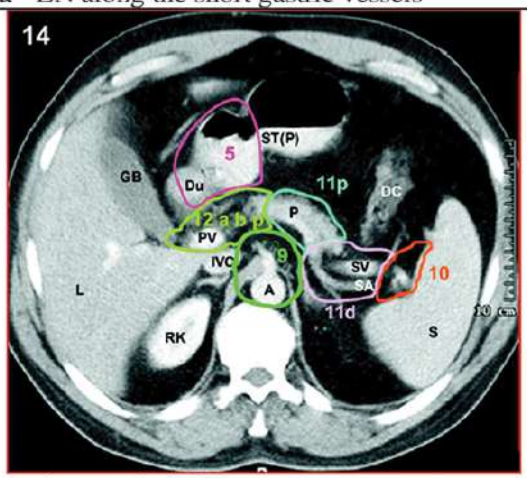
110 - Paraoesophageal LN
111 - Supradiaphragmatic LN



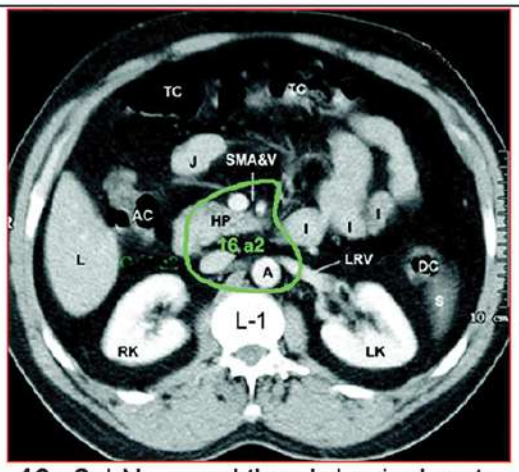
20 - LN in the esophageal hiatus of the diaphragm
4sa - LN along the short gastric vessels



3 - LN along the lesser curvature
4sb - LN along the left gastroepiploic vessels
7 - LN along the left gastric artery



5 - Suprapyloric LN,
9 - LN around the celiac artery
10 - LN at the splenic hilum
11p - LN along the proximal splenic artery
11d - LN along the distal splenic artery
12 a, b, p - LN in the hepatoduodenal ligament



16 a2 LN around the abdominal aorta

LEGEND:

A – Aorta; AC – Ascending Colon; D - Diaphragm; DC – Descending Colon; Du – Duodenum; E – Esophagus; GB – GallBladder; I – Ilium; H – Heart; J – Jejunum; IVC – Inferior Cava Vein; L – Liver; L-1 – First Lumbar Vertebra; LK – Left Kidney, LRV – Left Renal Vein; LV – Left Ventricle; P – Pancreas; PV – Portal Vein; RGA – Right Gastric Artery; RK – Right Kidney; RV – Right Ventricle; S – Spleen; SA – Splenic Artery; SMA&V – Superior Mesenteric Artery and Vein; SV – Splenic Vein; ST – Stomach; ST(F) – Stomach Fundus; ST(P) – Stomach Pylorus; TC - Transverse Colon; VA – Azygos Vein

FIGURE 59.20 Examples of lymph node stations on corresponding computed tomography slices. (Reprinted from Matzinger O, Gerber E, Bernstein Z, et al. EORTC-ROG expert opinion: radiotherapy volume and treatment guidelines for neoadjuvant radiation of adenocarcinomas of the gastroesophageal junction and the stomach. *Radiother Oncol*. 2009;92[2]:164-175. Copyright © 2009 Elsevier Ireland Ltd. With permission.)

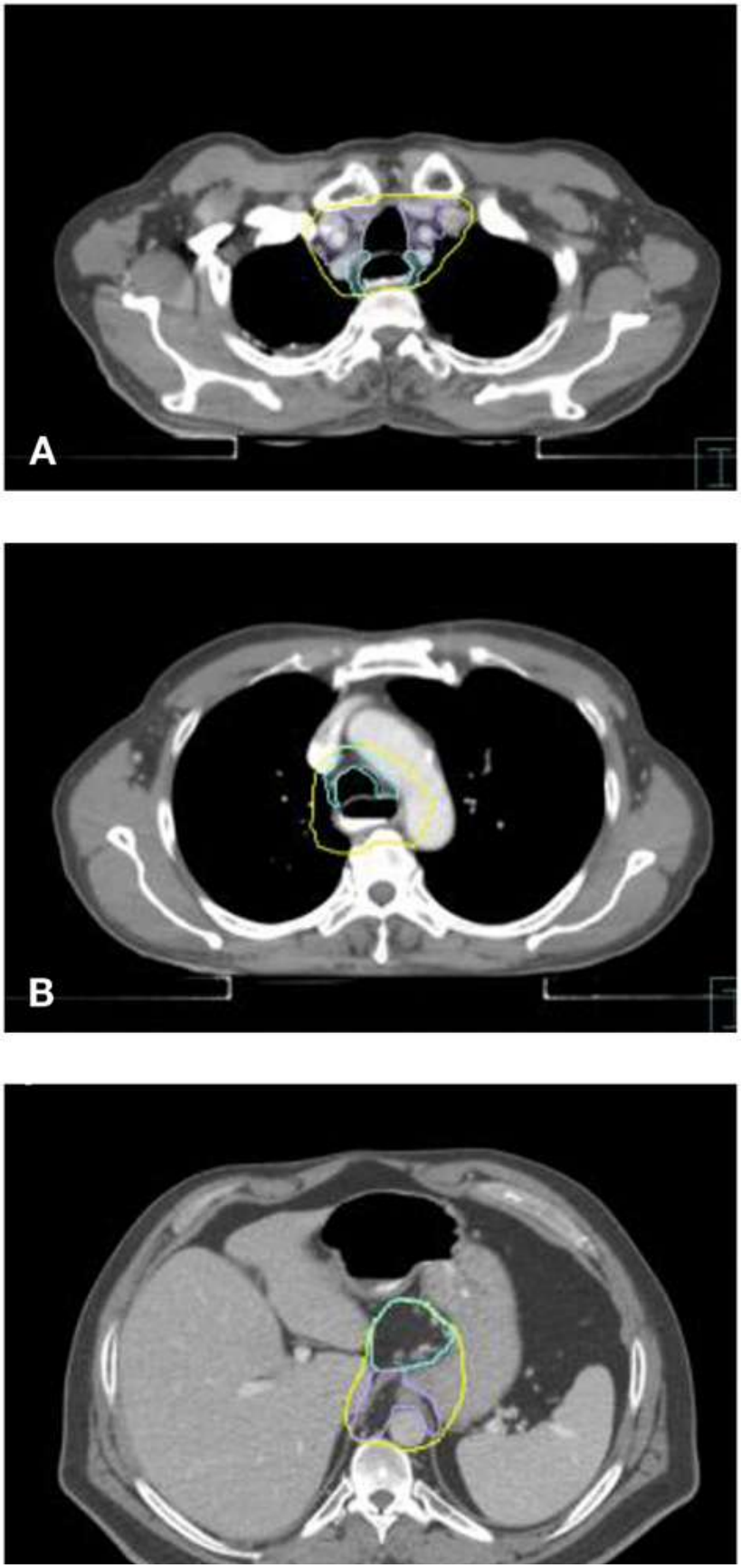
Another potential treatment planning approach for thoracic esophageal cancer is the use of IMRT. IMRT also uses CT-based planning, again allowing 3D reconstruction of varying structures. However, IMRT differs from 3D planning through the delivery of radiation dose by partitioning a radiation field into multiple smaller fields of varying shapes and sizes, varying the dose intensity between each area. This is carried out with either dynamic IMRT (in which collimating leaves move in and out of the radiation beam path during treatment) or "step-and-shoot" IMRT (in which the leaves change the radiation field shape while the beam is turned off). Either method is particularly effective at conforming radiation dose to the target structures while avoiding dose to normal tissue. Radiation oncologists must determine which structures are most critical and weigh their importance during the treatment planning process. Of importance, the greater the number of "avoidance" normal structures, the more difficult it is to meet all dose constraints. IMRT uses "inverse planning," in which an intended prescription dose is placed on target volumes and dose constraints are placed on normal-tissue structures. Thereafter, computer software algorithms allow design of unconventional treatment fields that would not otherwise be possible with standard planning methods. Radiation oncologists and medical physicists critically evaluate numerous plans until dose constraints are satisfactorily met. The result should be a series of radiation doses that closely conform to the target volumes while minimizing dose to normal tissues. Similarly, volumetric arc therapy (VMAT) also utilizes IMRT delivery, while the gantry is actively rotating during treatment. Dosimetric comparisons of IMRT versus 3D conformal therapy in cervical esophageal cancer have demonstrated superior target volume coverage and conformality with decreased normal-tissue dose.[142] A potential disadvantage of IMRT is the possibility of delivering low doses of radiation therapy to normal-tissue areas that might not normally be irradiated using 2D or 3D techniques. The influence of this on toxicity (eg, low-dose pulmonary irradiation and development of postoperative pulmonary complications, circulating lymphocytes) remains uncertain. Another potential disadvantage of IMRT is possible dose inhomogeneity, leading to potential hot spots in normal organs. Because IMRT requires precise target definition, the potential for marginal miss increases and careful target delineation is of paramount importance. With setup uncertainty, physiologic organ motion must be considered to ensure accurate and reproducible setup, including the use of immobilization devices, possible respiratory gating/breath-hold techniques, etc. Generally, high-energy photons

(4-18 MV) are recommended when using 3D conformal or IMRT therapy, potentially facilitating a reduction of the integral lung dose.

Another approach to treating esophageal cancer is utilization of proton therapy, which is a particle-based therapy that utilizes the unique nature of protons to distribute their energy over a relatively limited range (so-called Bragg peak), thereby further sparing adjacent normal organs. A multi-institutional experience of 580 patients treated across three academic centers compared patients receiving 3D versus IMRT and proton beam therapy. Advanced treatment technologies (IMRT and proton beam) were associated with significantly reduced rates of postoperative complications and length of stay. The authors indicated prospective randomized data will be needed to validate these results.[143] A phase IIB trial by Lin et al randomized 107 patients with esophageal cancer to receive proton beam radiation therapy (n = 46) versus IMRT (n = 61) to a dose of 51.4 Gy in 28 fractions. The primary end point, defined as total toxicity burden, was found to be 2.3 times higher for IMRT versus proton beam therapy, and postoperative complication rate 7.6 times higher for IMRT versus proton beam radiation therapy, although 3-year progression-free survival (51%) and overall survival (45%) rates were similar for both arms. The authors concluded that proton beam therapy reduced the risk and severity of adverse effects compared with IMRT while maintaining similar disease-related outcomes.[144] Long-term toxicity and efficacy outcomes of proton beam versus IMRT are being evaluated in the ongoing NRG-GI006 phase III randomized trial. Additionally, in a registry-based study of patients older than 65 years comparing 3D versus IMRT treatment, IMRT was not associated with esophageal cancer–specific mortality or pulmonary mortality, but was with improved all-cause mortality, including cardiac and other cause mortality.[145] Similarly, in an analysis of the Radiation Therapy Oncology Group (RTOG) 0617 trial randomizing patients with non–small cell lung cancer to receive concurrent carboplatin and paclitaxel with or without cetuximab with a second randomization to 60 versus 74 Gy, no benefit was seen in terms of radiation dose escalation. On secondary analysis, however, IMRT was associated with less grade 3 or more pneumonitis (7.9% vs 3.5%; P = .039), lower heart doses (P < .05), and lower heart V_{40} doses, with the heart V_{40} significantly associated with overall survival (P < .05). Additionally, the lung V_{20} dose was also associated with increased grade 3 or more pneumonitis risk on multivariable analysis (P = .026), with the authors concluding IMRT was associated with lower rates of severe pneumonitis and cardiac doses.[146,147]

An expert panel has published contouring guidelines for esophageal and GE junction CTV volumes for IMRT planning. Examples of consensus CTV are illustrated in Figure 59.21. Delineation of the proximal border of the CTV was described as 3 to 4 cm above the proximal edge of the GTV, or 1 cm above any grossly involved periesophageal nodes, oriented along the esophageal mucosa and not a simple geometric expansion. For proximal tumors, the upper border was not extended beyond the level of the cricoid cartilage unless disease presence precludes such. For proximal or midesophageal tumors, the distal border for CTV creation was described as 3 to 4 cm below the

proximal edge of the GTV, again oriented along the esophagus. For lower tumors, what is described as at least a 2-cm margin along clinically involved gastric mucosa was recommended if treating definitively, or if treating to lower, preoperative-intent doses (≤45 Gy), a 4-cm or greater gastric margin was felt appropriate, particularly with significant gastric extension. CTV radial margin was described as at least 1 cm in all directions on GTV, with a 1-cm radial margin from the outer esophageal wall to encompass periesophageal lymph nodes, with a limit of 5 mm into cardiac tissue, including the pericardium. For more distal tumors involving or approaching the GE junction, the CTV was described as being extended inferiorly to the level of the celiac axis origin, bounded by the lateral aspect of the vertebral body on the right and 0.5 to 1 cm beyond the lateral aspect of the aorta on the left, vertebral body posteriorly and pancreatic body anteriorly. Periaortic and gastrohepatic (sometimes classified as lesser curve or left gastric) lymph nodes were deemed appropriate for inclusion. Examples of CTVs are shown in Figures 59.22 to 59.24. Inclusion of some or all nodes in the splenic hilum and greater curvature region was felt potentially appropriate for Siewert type II GE junction tumors depending on clinical and pathologic features. For tumors above the level of the carina, inclusion of the bilateral supraclavicular nodal basins was recommended. PTV delineation was created by adding 0.5 to 1 cm to the CTV in all directions (which is essentially equivalent to the traditional practice of placing the field border 5 cm above and below the GTV).[148]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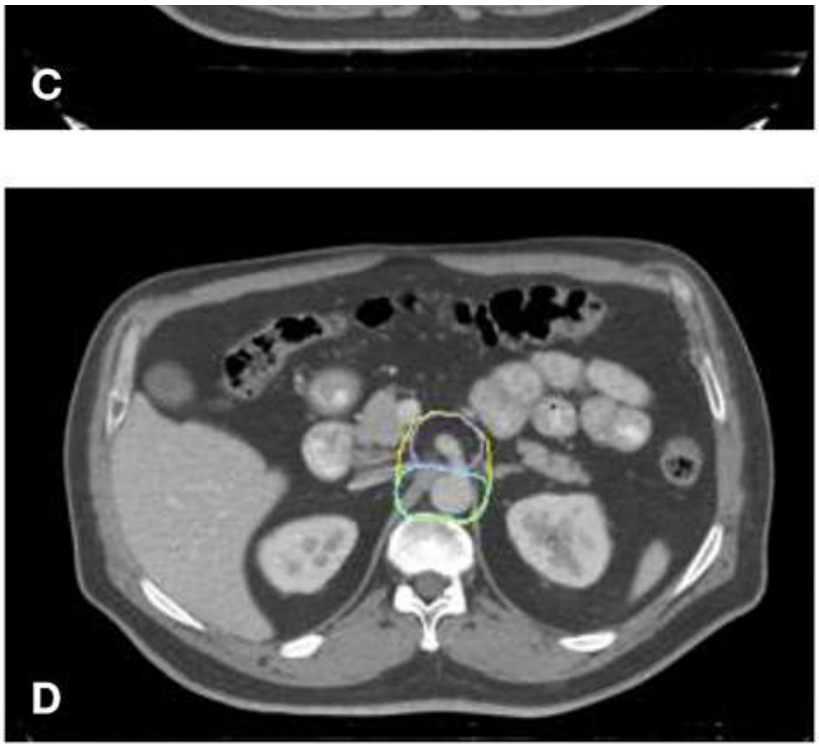

FIGURE 59.21 Examples of consensus clinical target volume (CTV) contours encompassing defined nodal regions. A. CTV contour (yellow) encompasses level 3 retrotracheal (blue) and level 2 upper paratracheal (purple) nodes. B. CTV encompasses level 4 lower paratracheal (blue) and level 8 periesophageal nodes. C. CTV encompasses lesser curvature/gastrohepatic ligament (blue) and paracardial (purple) nodes. D. CTV encompasses para-aortic (blue) and celiac (purple) nodes. (Reprinted from Wu AJ, Bosch WR, Chang DT, et al. Expert consensus contouring guidelines for intensity modulated radiation therapy in esophageal and gastroesophageal junction cancer. *Int J Radiat Oncol Biol Phys*. 2015;92[4]:911-920. Copyright © 2015 Elsevier. With permission.)

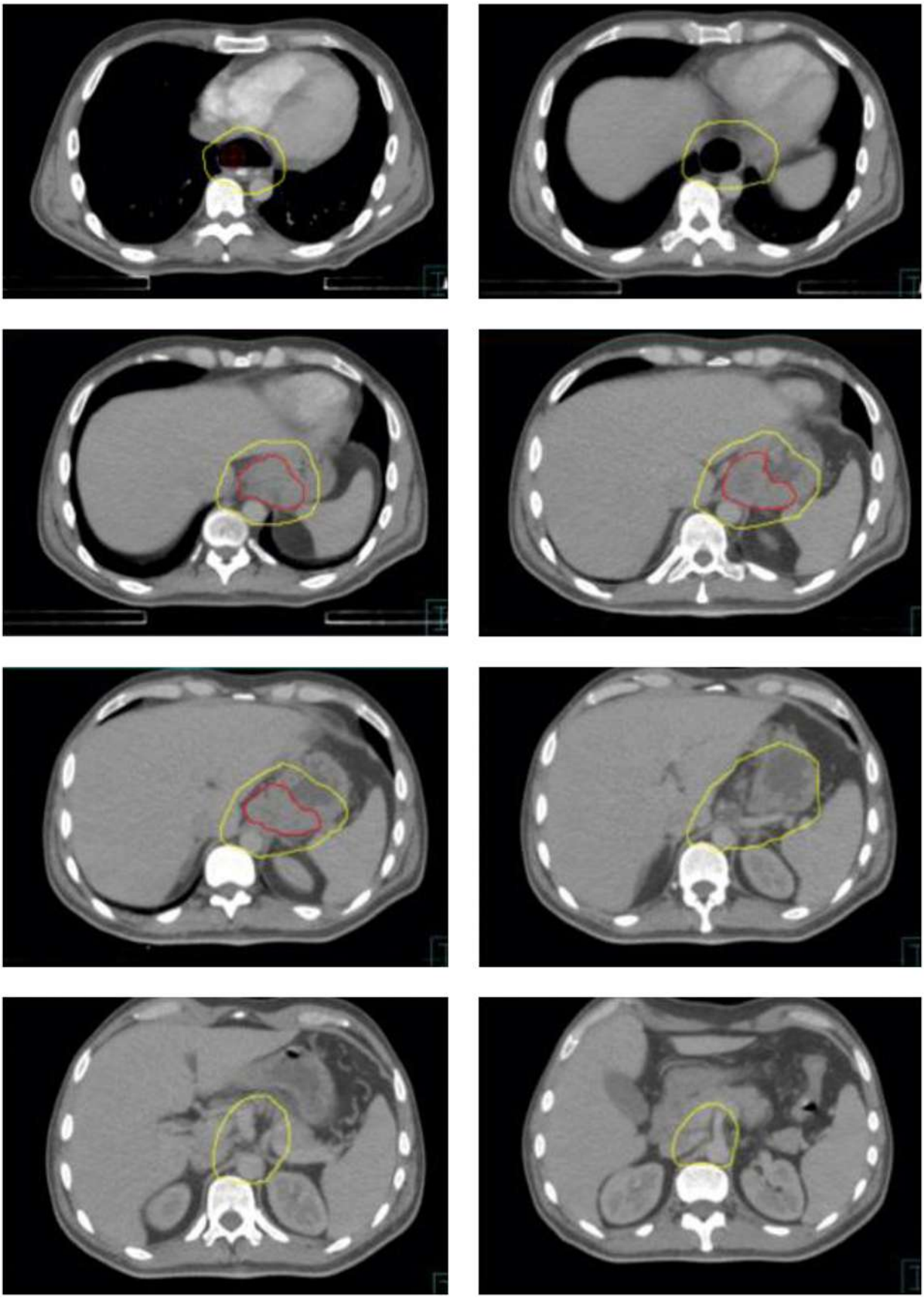

FIGURE 59.22 Consensus clinical target volume contours for T3N0, Siewert II gastroesophageal junction cancer, gross tumor volume in red.

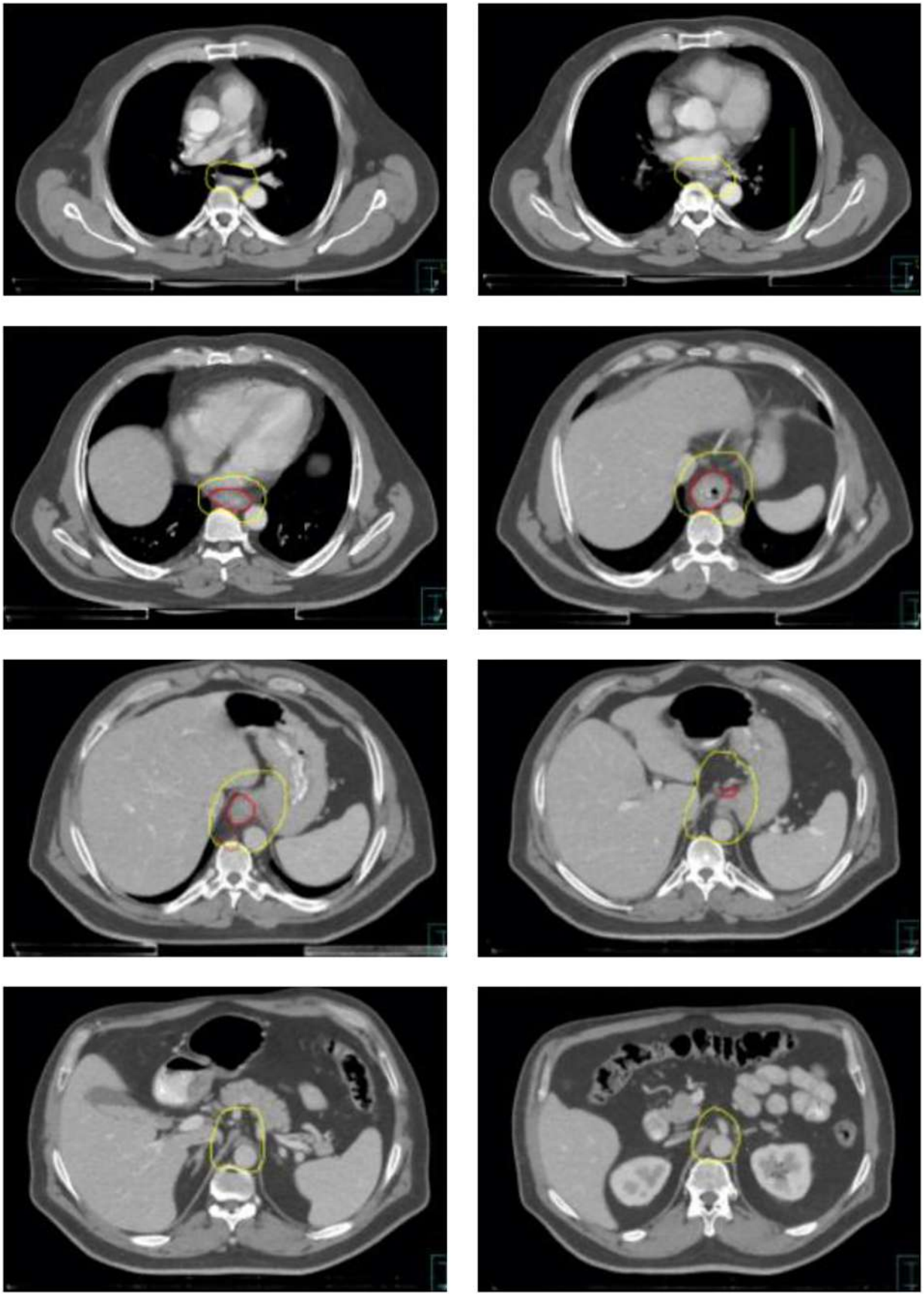

FIGURE 59.23 Consensus clinical target volume contours for T3N1 distal esophageal cancer.

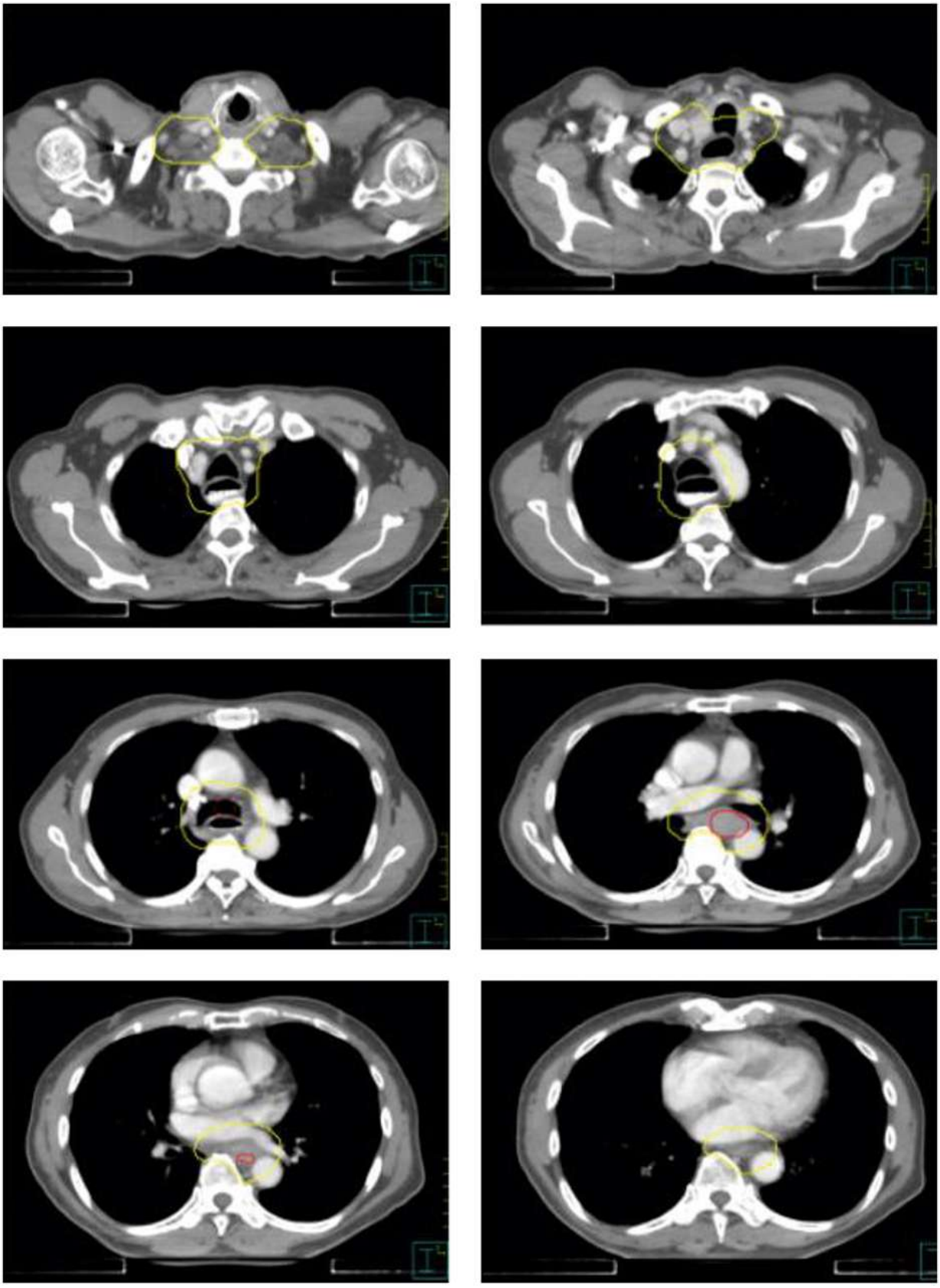

FIGURE 59.24 Consensus clinical target volume contours for T3N1 proximal esophageal cancer.

Dose Constraints

In radiation therapy planning of esophageal cancer, normal-tissue tolerance should always be considered. The spinal cord dose is generally limited to 45 Gy using 1.8-Gy fractions (and potentially less when delivered with novel systemic agents). Efforts to minimize radiation to the heart (in particular the left ventricle in lower esophageal/GE junction lesions) should be made. Adopting an off-heart approach using oblique orientations (including right anterior and left posterior, described earlier) is one potential way of achieving this, although multiple approaches exist, including IMRT-based techniques. Similarly, efforts to minimize dose to normal pulmonary tissues should be made, based on data suggesting that the volume of irradiated lung may correspond to postoperative complications and worsened pulmonary function (described later). Advanced radiation techniques including IMRT are frequently utilized.

Accurate delineation of adjacent organs, including the lungs, liver, kidneys, heart, and spinal cord, is important. Varying dose-volume normal-organ constraints have been suggested, including achieving a lung V_{20} of less than 20%, limiting more than 2,300 cm^3 of normal lung tissue to less than 5 Gy, and using mean lung dose of less than 18 Gy. Similarly, a V_{10} of 60% or less has been proposed to reduce the incidence of postoperative pulmonary complications. Historically, heart dose constraints have included maintaining one-third, two-thirds, and total heart volumes of less than 45, 40, and 30 Gy, respectively. Recommended heart constraints include keeping less than 30% of the cardiac volume to a total dose of 40 Gy and less than 50% receiving 25 Gy, minimizing dose to the left ventricle, although with careful and advanced treatment planning, significant improvement upon these constraints can often be achieved. In the setting of potentially significant volumes of the heart in the radiation field, consideration of respiratory gating and/or breath-hold techniques can be made. For lower esophageal and GE cancers, it is recommended that at least 70% of one physiologically functioning kidney receive a total dose of less than 20 Gy and that, collectively, no more than 50% of the combined functional renal volume should receive more than 20 Gy.[53] One should also consider the possibility of impaired kidney function in the context of varying comorbidities, using nuclear medicine renal studies to assess individual renal function in such situations or where significant volumes of kidneys are anticipated to be within the radiation field. Generally, 70% of the liver parenchyma should be kept to a dose of less than 30 Gy. Many of these constraints can be achieved with 3D planning with appropriate and careful design of shielding blocks/multileaf collimation and dose-volume histogram analysis, as well as potential improvement in these parameters with the use of IMRT. Examples of normal tissue constraints for esophageal cancer planning are listed in Table 59.5.

TABLE 59.5 INTERNATIONAL CONSENSUS OF CLASSIFICATION OF BR PDAC BASED ON ANATOMICAL DEFINITION USING CT IMAGINGS INCLUDING CORONAL AND SAGITTAL SECTIONS

Resectable: R	• SMV/PV: no tumor contact or unilateral narrowing

	• SMA, CA, CHA: no tumor contact
Borderline resectable: BR	Subclassified according to SMV/PV involvement alone or arterial invasion
BR-PV (SMV/PV involvement alone)	• SMV/PV: tumor contact 180° or greater or bilateral narrowing/occlusion, not exceeding the inferior border of the duodenum. • SMA, CA, CHA: no tumor contact/invasion
BR-A (arterial involvement)	• SMA, CA: tumor contact of less than 180° without showing deformity/stenosis • CHA: tumor contact without showing tumor contact of the PHA and/or CA (The involvement of the aorta is categorized as unresectable. Presence of variant arterial anatomy is not taken into consideration.)
Unresectable: UR	Subclassified according to the status of distant metastasis
Locally advanced: LA	• SMV/PV: bilateral narrowing/occlusion, exceeding the inferior border of the duodenum • SMA, CA: tumor contact/invasion of 180 or more degree[a] • CHA: tumor contact/invasion showing tumor contact/invasion of the PHA and/or CA • AO: tumor contact or invasion
Metastatic: M	Distant metastasis[b]

CA, celiac artery; CHA, common hepatic artery; PHA, proper hepatic artery; PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein.

[a]In the cases with CA invasion of 180° or more without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a distal pancreatectomy with en bloc celiac axis resection (DP-CAR), some members prefer these criteria to be in the BR-A category.

[b]Including macroscopic para-aortic and extra-abdominal lymph node metastasis.

Reproduced from Isaji S, Mizuno S, Windsor JA, et al. International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. *Pancreatology*. 2018;18(1):2-11.

Doses of Radiation

Because locoregional failure is common after conventional chemoradiation, investigators have evaluated dose escalation techniques. Varying series using doses beyond 50 Gy have shown local control rates ranging from approximately 77% to 88%.[148,149] However, Minsky et al[66,150] reported the results of a randomized trial in which 236 patients with clinical stage T1 to T4, N0/1, M0 squamous cell, or adenocarcinoma of the esophagus were selected for nonsurgical therapy. Patients were randomized to receive 64.8 versus 50.4 Gy, both with concurrent 5-FU and cisplatin chemotherapy. Patients with cervical, mid, or distal esophageal cancer were eligible, with the exception of those with tumors within 2 cm of the GE junction, with approximately 85% of patients with squamous cell histology. This study was closed after interim analysis showed no probability of superiority in the high-dose arm. No significant difference in median survival (13 vs 18.1 months), 2-year survival (31% vs 40%), or locoregional failure/persistence of disease (56% vs 52%) was seen between the high-dose and standard-dose arms. Eleven treatment-related deaths occurred in the high-dose arm

compared with 2 in the standard-dose arm, with 7 of the 11 high-dose arm deaths occurring in patients who received 50.4 Gy or less. The authors performed a separate survival analysis including only patients receiving the assigned radiation dose. Despite this, no survival advantage was noted in the high-dose arm. These authors concluded that higher radiation doses did not increase survival or locoregional control and that the standard radiation dose for patients treated with concurrent 5-FU and cisplatin chemotherapy is 50.4 Gy. Based on these data, standard dose of radiation therapy for esophageal cancer is usually 50 to 50.4 Gy at 1.8 to 2 Gy per fraction, including delivery of similar doses in the definitive, adjuvant (45-50 Gy), or neoadjuvant (41.4-50 Gy) settings. Nonetheless, critics of this trial argue that older radiation techniques were used and that dose escalation should be evaluated using modern techniques. In addition to the above, the Dutch ART-DECO phase III trial randomized 260 patients with T2 to T4, N0 to N3 inoperable esophageal cancer to receive either 50.4 Gy in 28 fractions or dose-escalated 61.6 Gy in 28 fractions using a simultaneous integrated boost technique, both with weekly carboplatin and paclitaxel delivery. At a median follow-up of 50 months, 3-year overall survival was 42% versus 39% (P = .22) with no difference in 3-year local progression presurvival (52% vs 59%; P = .08), including when stratified by histology. Grade 4 and higher toxicity rates were similar between the two groups (17% vs 24%; P = .15).[151] Similarly, the French CONCORDE randomized phase III trial enrolled 160 patients with inoperable esophageal cancer to receive 40 Gy elective nodal irradiation followed by a 10 Gy boost versus dose-escalated 26 Gy boost, using IMRT/VMAT techniques, with concurrent FOLFOX-4 chemotherapy for three cycles followed by three cycles of adjuvant chemotherapy. Preliminary results at a median follow-up of 35.3 months showed no difference in overall (median 25.2 vs 23.5 months; P = .4) or local progression-free survival (median 16.2 vs 18.4 months; P = .88) or difference in grade 3 or higher toxicity (29.5% vs 29.3%).[153] Another trial from China randomized 319 patients with squamous cell carcinoma to receive conventional fractionated 60 vs 50 Gy to the tumor and regional lymph nodes. Concurrent weekly docetaxel and cisplatin were utilized, with two cycles of consolidation chemotherapy. The 60 Gy arm had similar survival outcomes but a higher severe pneumonitis rate compared with the 50 Gy arm. The authors concluded 50 Gy should be considered as the recommended dose in combined-modality therapy (CMT) for patients with squamous cell carcinoma.[152] The UK SCOPE-2 study is a four-arm trial comparing carboplatin/paclitaxel versus cisplatin-/capecitabine-based chemoradiation, with a second randomization to standard versus high-dose radiation therapy (50 vs 60 Gy, both in 25 fractions). Patients will receive a lead-in of chemotherapy and then be further randomized based on intratreatment PET analyses. Finally, a Chinese study is comparing a regimen of 50 Gy in 25 fractions with concurrent cisplatin and 5-FU (CF) versus a simultaneous integrated boost treatment to a total of 66 Gy in 30 fractions with concurrent CF in patients with nonoperable squamous cell carcinoma.

Brachytherapy

In addition to external beam radiation therapy (EBRT), intracavitary therapy can be used with curative or palliative intent. Brachytherapy has also been used as a dose escalation tool in addition to EBRT. The advantage of brachytherapy centers on exploitation of the inverse-square law and quick dose falloff, thus sparing surrounding tissues from radiation while providing focal dose escalation. The radioactive source of choice is usually 192Ir. High-dose-rate (HDR) techniques can deliver 100 to 400 Gy/hour, allowing treatment to be given in 5 to 10 minutes.

With brachytherapy, an afterloading catheter is introduced through the nose into the esophagus to the primary tumor site under fluoroscopic guidance. This is often performed with the patient on the simulation table. Contrast may be used to define the tumor site. CT scan can also be used to discern tumor location. After localization films are taken and dosimetry is generated, the catheter is then attached to a remote afterloader through a guide cable and the 192Ir source inserted through remote control. Doses of 5 to 20 Gy are usually delivered to a depth of 1 cm from the center of the catheter. Dose can be shaped and modified through the use of dwell times.

RESULTS OF THERAPY

The best survival results have been reported in patients who have esophageal tumors that are truly localized. Survival rates range from 25% to more than 35% at 5 years, and these results have been attained using an array of treatment approaches. Problems arise in comparisons of various modalities, however, because of patient selection factors. A historical review of the Princess Margaret Hospital data[154] supported the concept that extent of tumor, rather than therapy, is the most important factor influencing survival. They found a significant correlation between T stage and response to treatment: T1 lesions showed a 100% response rate, whereas T2 and T3 lesions had response rates of 68% and 58%, respectively. Not unexpectedly, they also found differences in survival according to T stage, M stage, and overall stage. Almost 20% of patients with stage I disease were alive at 3.5 years, whereas only 11% of patients with stage II disease were alive after the same interval, and all patients with stage III disease died by approximately 1.5 years following therapy.

Surgery Alone

Surgery remains a benchmark to which other modalities are compared. Surgery removes the tumor, a length of normal esophagus, and lymph nodes. Although multiple techniques exist for the resection of esophageal cancer, no one surgical approach has clearly been shown to be superior with regard to complications or outcomes. Proponents of more extended resection (including transthoracic approaches) have advocated that such procedures result in a superior nodal clearance and therefore offer a more complete "oncologic" resection. A trial from the Netherlands randomized 220 patients with

esophageal adenocarcinoma to transhiatal esophagectomy alone or transthoracic esophagectomy with extended lymph node dissection. Patients undergoing transhiatal resection experienced significantly fewer pulmonary complications and chylous leaks, as well as significantly reduced ventilator dependence and intensive care unit and hospital stays. At a median 4.7-year follow-up, no significant difference in locoregional recurrence was seen between the two groups (32% transhiatal vs 31% transthoracic). Furthermore, no significant differences were seen in median disease-free survival (1.4 vs 1.7 years; $P = .15$) or median overall survival (1.8 vs 2.0 years; $P = .38$). However, there did appear to be a nonsignificant trend favoring the transthoracic approach in improved disease-free survival (5 years, 27% vs 39%) and overall survival (5 years, 29% vs 39%). The authors concluded that a transhiatal approach was associated with less morbidity relative to transthoracic surgery, with no apparent survival advantage with either technique, although a trend toward improved survival with a transthoracic approach was seen with longer follow-up.[56] Updated 5-year survival results were 34% versus 36%, respectively.[155] In contrast, a randomized trial from Japan comparing transhiatal to left thoracoabdominal approaches in patients with esophagogastric junction cancers demonstrated different outcomes. Both groups underwent total gastrectomy and splenectomy with extensive nodal dissection. Ten-year survival was 37% for the transhiatal approach versus 24% for the thoracoabdominal approach ($P = .06$). The authors concluded left thoracoabdominal resection should be avoided in patients with esophagogastric junction or gastric cardia tumors.[156]

In summary, none of the surgical approaches to localized esophageal cancer has clearly been shown to be superior with regard to complications or outcomes, and no one standard surgical approach exists for esophageal cancer resection.

After resection alone, however, locoregional relapse is a common mode of failure. Contemporary randomized trials with surgery-alone arms have reported locoregional failure rates of 32% to 45%.[56,57,115,156] It should be remembered that patterns of failure reports often describe the first site of failure only and may include only patients undergoing R_0 resection, potentially underreporting the true incidence of locoregional recurrence. These and other data suggest that even with modern surgical techniques, locoregional persistence of disease after resection remains a major problem. Prospective, randomized trials using surgery alone in the treatment of esophageal cancer have reported 3-year survival rates ranging from 6% to 48%, with more favorable rates likely reflecting inclusion of patients with earlier-stage disease[58,157-160] (Table 59.6). Given these high rates of relapse and poor long-term survival, the integration of adjuvant or neoadjuvant chemoradiation approaches into the treatment of esophageal cancer is rational and indicated.

TABLE 59.6 COMPARISON OF SURGICAL ARMS IN RANDOMIZED STUDIES

Trial	Year	Patients (Total)	Patients (Surgical)	Median Survival (mo)	2-Y Survival (%)	3-Y Survival (%)
Walsh et al[158]	1996	110	55	11	26	6
Urba et al[57]	2001	100	50	18	NA	15
Bosset et al[160]	1997	282	139	19	40	35
Kelsen et al[115]	1998	440	227	16	37	23
MRC[159]	2002	802	402	13	34	NA
Burmeister et al[161]	2005	256	128	19	NA	31
van Hagen et al[162]	2015	368	188	24	50	44
Mariette et al[58]	2014	195	97	41	NA	34

MRC, Medical Research Council Oesophageal Cancer Working Group; NA, not applicable.

Radiation Therapy Alone

A trial from China randomized 269 patients to either surgery alone or radiation therapy alone. Surgery entailed esophagectomy while radiation field varied by location of the primary tumor. Patients received 50 to 50.4 Gy of daily treatment, followed by reduced fields receiving 1.5 Gy BID to a cumulative dose of 68.4 to 71 Gy. The 1-, 3-, and 5-year overall survival rates in the surgery-alone group were 93%, 62%, and 37% versus 89%, 56%, and 35%, respectively. The authors concluded survival might be equivalent between these arms.[163] However, in most series, radiation therapy alone has been usually delivered when lesions are deemed inoperable because of tumor extent or medical contraindications and/or palliative treatment is indicated. Patients receiving radiation as a sole treatment modality have a median survival of 6 to 12 months and 5-year survival of less than 10%.

A historical review analyzing 49 series involving more than 8,400 patients treated primarily with radiation therapy alone found overall survival rates at 1, 2, and 5 years to be 18%, 8%, and 6%, respectively.[164] Hancock and Glatstein[124] reviewed 9,511 patients and found only 5.8% were alive at 5 years. Okawa et al[165] reported 5-year survival rates by stage. For patients with stage I disease, the 5-year survival rate was 20%; stage II, 10%; stage III, 3%; and stage IV, 0%. Overall, the 5-year survival rate was 9%. For cervical esophageal lesions treated with radiation alone, the cure rates were comparable with those in patients treated with surgery alone. Lederman[166] treated 263 patients with radiation therapy alone and reported 3- and 5-year survival rates of 11% and 7%, respectively. In a more contemporary series, an Intergroup randomized study (discussed later) comparing combined chemotherapy with 5-FU and cisplatin with radiotherapy (50 Gy) versus radiotherapy only (64 Gy) showed that 3-year actuarial survival with

radiotherapy alone was 0%. These and other data suggest that treatment with radiation therapy alone for patients with esophageal cancer is palliative in most patients.

Preoperative Radiation Therapy

The use of preoperative radiation therapy has potential biologic and physical advantages, including increased resectability of tumors, increased tumor radioresponsiveness secondary to improved tumor oxygenation, a theoretical decreased likelihood of dissemination at the time of surgery, and avoidance of surgery in patients with rapidly progressive disease.

There are multiple, largely historical randomized studies comparing preoperative irradiation followed by surgery with surgery alone. These studies demonstrate no clinical benefit to the use of preoperative radiation therapy alone (Table 59.7). Launois et al[167] reported delivering 40 Gy over 8 to 12 days with surgery 8 days later versus surgery alone. Resection rates were similar—70% and 58% for preoperative irradiation and for surgery alone, respectively. The 5-year survival rate after resection was 11.5% for those treated with surgery alone, compared with 9.5% for those treated with irradiation and surgery. The second randomized study, published by the European Organisation for Research and Treatment of Cancer (EORTC), used 33 Gy over 12 days.[168] There was no significant difference in survival between those receiving preoperative irradiation and those receiving surgery alone. Arnott et al[169] reported on 176 patients, 86 of whom were treated with esophagectomy alone versus 90 who were treated with preoperative radiation therapy. Preoperative radiation therapy was delivered with 4-MV photons using opposed fields, delivering 20 Gy at 2 Gy/fraction. Resectability and local failure were not reported. Patients receiving low-dose radiation therapy did not demonstrate a benefit in 5-year overall survival rates (17% vs 9% for surgery and preoperative radiation, respectively; $P = .4$). Wang et al[170] randomized 206 patients to surgery alone versus 40 Gy in 2-Gy fractions delivered preoperatively. No significant survival advantage was seen for patients receiving radiation therapy (35% vs 30%; $P > .05$).

TABLE 59.7 RANDOMIZED TRIALS OF PREOPERATIVE RADIATION THERAPY FOR ESOPHAGEAL CANCER

				Local Failure		Survival (5-Y)	
Author	Patients	Dose (Gy)	Fraction (Gy)	Surgery	RT + Surgery	Surgery	RT + Surgery
Launois et al[167]	109	40	NA	NA	NA	12	10
Gignoux et al[168]	229	33	3.3	67	46	8	10
Arnott et al[169,a]	176	20	2	NA	NA	17	9

Author	Patients	Dose (Gy)	Fraction (Gy)	Local Failure		Survival (5-Y)	
				Surgery	RT + Surgery	Surgery	RT + Surgery
Wang et al[170]	160	40	2	NA	NA	30	35

NA, not applicable; RT, radiation therapy.

[a]Both squamous and adenocarcinoma.

A meta-analysis from the Oesophageal Cancer Collaborative Group updated data from five randomized trials of more than 1,100 patients comparing preoperative radiotherapy alone versus surgery alone. Most patients had squamous cell carcinoma. At a median follow-up of 9 years, the HR was 0.89, suggestive of an overall reduction in the risk of death of 11% and absolute survival benefit of 4% at 5 years with the use of preoperative radiotherapy. However, this was not statistically significant (P = .06). The authors concluded that there was no clear evidence that preoperative radiotherapy improves survival of patients with potentially resectable esophageal cancer.[4]

In general, there were no differences in resection rates or survival in almost all of the individual studies. Interpretation of these studies is complicated by differences in radiation techniques, suboptimal radiation doses, and inadequate radiation volumes. Nonetheless, although preoperative radiation therapy alone may improve local control, there are no convincing data that it results in improved survival in patients with esophageal cancer.

Postoperative Radiation Therapy

The main advantage of adjuvant versus neoadjuvant approaches is knowledge of the pathologic staging for appropriately selected patients for therapy. Postoperative therapy may allow the radiation oncologist to treat areas at risk for recurrence while sparing otherwise normal radiosensitive structures, thereby decreasing toxicity. In addition, patients with pathologic T1, N0, and M0 or metastatic disease may be spared treatment. Postoperative irradiation has historically been delivered to patients with esophageal cancer who have bulky tumors with gross residual disease or histologically proven microscopic residual disease. Potential disadvantages of postoperative radiation include limited tolerance of normal tissues after gastric pull-up or intestinal interposition and irradiation of a devascularized tumor bed, potentially larger fields compared to a preoperative approach, and potential delays in adjuvant treatment delivery.

Three randomized trials have assessed surgery alone versus surgery followed by postoperative radiation therapy.[171-173] In a French trial, 221 patients with squamous cell carcinoma of the mid-lower esophagus undergoing esophagectomy were randomized to postoperative radiation therapy or no further treatment. Patients were stratified by extent of nodal involvement. Total dose was 45 to 55 Gy at 1.8 Gy/fraction, beginning within 3 months of surgery. Five-year survival in patients with node-negative cancer was 38%

versus 7% with involved nodes. No significant survival difference was seen in patients receiving postoperative radiation versus surgery alone. Rates of locoregional recurrence were lower in patients receiving radiation therapy (85% vs 70%; P = NS). However, in patients without nodal involvement, locoregional recurrence was significantly reduced in patients receiving postoperative therapy (90% vs 65%; $P < .2$). The authors concluded that postoperative radiation therapy did not improve survival after resection for squamous cell carcinoma.[171]

Investigators from the University of Hong Kong reported the results of a randomized trial of 130 patients treated with postoperative radiation therapy versus surgery alone. Patients who underwent either curative or palliative resections were included in this trial. Radiation therapy was delivered to a total dose of 49 Gy (curative patients) or 52.5 Gy (palliative patients) using 3.5-Gy fractions. Most patients had squamous cell histology. Local recurrence was noted in 15% of patients receiving radiation and 31% of patients with surgery only (P = .06). In patients with squamous cell carcinoma, the local recurrence rate was 15% with radiation therapy versus 36% with surgery alone (P = .02). Median survival in patients was worse in patients receiving postoperative radiotherapy versus control patients (8.7 vs 15.2 months; P = .02). Ten patients undergoing surgery alone had tracheobronchial recurrence resulting in death versus three patients receiving adjuvant radiation therapy (P = .07). The authors concluded that postoperative radiation therapy was associated with increased morbidity and death caused by radiation injury, as well as with the early appearance of metastatic disease and a reduced overall survival, although patients receiving radiation therapy were less likely to have a tracheobronchial recurrence. However, it should be noted that the high rate of complications associated with radiation therapy in this study might possibly be related to the high dose per fraction and large total dose delivered.[172]

Last, a study conducted by Xiao et al[173] randomized 549 patients to radical resection versus radical resection followed by radiation therapy. All patients had squamous cell carcinoma. The radiation dose delivered was 60 Gy in 6 weeks. Patients were classified into three groups: group 1, no lymph node involvement; group 2, one to two lymph nodes involved; and group 3, three or more lymph nodes involved. Results showed T stage, stage group, and the number of lymph nodes involved by tumor were highly predictive of survival. The 5-year survival rates for groups 1, 2, and 3 were 58.1%, 30.6%, and 14.4%, respectively. Local control and survival were improved in patients receiving postoperative irradiation. For patients with involved lymph nodes, 5-year survival rates for resection-only patients versus patients receiving resection and radiation therapy were 17.6% and 34.1%, respectively (P = .04).

In summary, postoperative radiation therapy may decrease local recurrence, particularly in the setting of involved margins, although the impact of this adjuvant treatment on overall survival remains less clear.

Postoperative Combined Chemoradiation

A large randomized Intergroup trial evaluating the role of adjuvant chemoradiation after surgery versus surgery alone for patients with adenocarcinoma of the stomach and GE junction was reported. In this study, patients with resected, margin-negative gastric or GE junction adenocarcinoma were randomly assigned to surgery alone versus surgery with postoperative chemoradiotherapy. Approximately 20% of patients had lesions in the GE junction. A significant survival advantage was seen in the adjuvantly treated group (median survival 27 vs 36 months; $P = .005$). On subset analysis, this benefit was detected in patients with GE cancer.[174] Long-term results at more than 10-year median follow-up continued to show significant improvement in overall and disease-free survival in the chemoradiation group, benefiting all T- and N-stage patients included in the trial.[175] Therefore, in patients with resected-stage group IB to IV, nonmetastatic GE junctional carcinoma, it is appropriate to advise adjuvant chemoradiotherapy in efforts to potentially improve upon local control and survival. In squamous cell carcinoma, no adjuvant randomized data exist, although institutional series suggests a potential survival benefit in lymph node–positive disease with adjuvant chemoradiation.[176,177] An ongoing phase II-III randomized trial in China is comparing the role of adjuvant radiation therapy alone versus concurrent chemoradiotherapy following resection versus surgery alone in patients with advanced squamous cell carcinoma of the esophagus.

Preoperative Chemotherapy

Six randomized trials showed conflicting results with the use of neoadjuvant chemotherapy alone in the treatment of esophageal cancer, with three of these trials also including gastric cancers. Kelsen et al[115] reported the results of an Intergroup study randomizing 440 patients with squamous cell carcinoma and adenocarcinoma to receive either combined cisplatin or 5-FU chemotherapy for three cycles followed by resection, followed by a similar regimen of adjuvant chemotherapy, versus immediate resection with no chemotherapy. No apparent survival advantage (3-year survival of 23% vs 26%) was seen in patients receiving chemotherapy. In addition, rates of local failure (32% vs 31%) and distant metastasis development (41% vs 50%) were not significantly different between the two groups. The authors concluded that neoadjuvant chemotherapy with CF did not improve survival in patients with resectable esophageal cancer. Long-term results reported that only 59% and 63% of patients undergoing preoperative chemotherapy and surgery alone, respectively, underwent R0 resection, and patients undergoing less than R0 resection had an ominous prognosis, with only 5% of patients undergoing R1 resection surviving more than 5 years and no difference in median survival rates for patients with R1, R2, or no resection. Pathologic complete response rate was 2.5% in patients receiving preoperative chemotherapy. Local regional recurrence rates in patients undergoing R0 resection were 19% with surgery alone versus 25% in the chemotherapy group. In this follow-up study, patients with objective tumor regression after preoperative chemotherapy experienced improved survival. An important caveat from this study is that all long-term R1 survivors received adjuvant

radiation therapy, and the authors concluded that after R1 resection, postoperative chemoradiotherapy offers the possibility of long-term disease-free survival to a small percentage of patients.[178]

In contrast to the Intergroup study, a similar trial from the Medical Research Council (MRC) randomized 802 patients with squamous cell carcinoma or adenocarcinoma of the esophagus to either two cycles of combined CF chemotherapy or surgery alone. Patients receiving neoadjuvant chemotherapy had a statistically improved 2-year survival (43% vs 34%).[159] Follow-up analysis at a median follow-up of 6 years showed a persistent, significant survival benefit in the chemotherapy group (5-year survival 23% vs 17%), with the effect maintained for patients with both squamous cell carcinoma and adenocarcinoma.[179] The reason for outcomes differences between these trials is not clear. A follow-up trial from the MRC (OE05) randomized patients to neoadjuvant CF for two cycles versus four cycles of ECX (epirubicin, cisplatin, and capecitabine) for esophageal adenocarcinoma. R0 resection rates were similar in both groups, with median survival of 23.4 months in the CF group versus 26.1 months in the ECX group (T = 0.19). There was a trend of improved disease-free survival with the ECX regimen, although no overall survival differences were seen. The authors concluded four cycles of neoadjuvant ECX compared with two cycles of CF did not increase survival, and cannot be considered standard of care.[180]

A smaller trial of 169 patients with squamous cell carcinoma of the esophagus randomized patients to receive preoperative chemotherapy alone with two to four cycles of etoposide- and cisplatin-based chemotherapy versus surgery alone. Median and 5-year survival rates significantly favored the chemotherapy group at 16 versus 12 months and 26% versus 17%, respectively. The authors concluded that preoperative chemotherapy with a combination of etoposide and cisplatin improves survival in patients with squamous carcinoma of the esophagus.[181]

A more heterogeneous European study (the Medical Research Council Adjuvant Gastric Infusional Chemotherapy, or MAGIC, trial) randomly assigned patients with resectable adenocarcinoma of the stomach, GE junction, or lower esophagus to preoperative and postoperative chemotherapy with epirubicin, cisplatin, and 5-FU (ECF) versus surgery alone. Although originally designed to include patients with only tumors of the stomach, eligibility was later expanded to include tumors of the lower one-third of the esophagus. Approximately one-fourth of patients had adenocarcinoma involving the lower esophagus or GE junction. Pathologic complete response was noted in 5% of patients receiving perioperative chemotherapy.[182] However, patients receiving perioperative chemotherapy had a HR for death of 0.75, which was highly significant. Five-year survival in patients receiving chemotherapy was 36% versus 23% in patients undergoing surgery alone (P = .009). Subgroup analysis of patients with lower esophageal or GE junction tumors showed benefit to the delivery of perioperative chemotherapy.[182,183]

A follow-up study to the MAGIC trial investigated the role of perioperative ECX, with or without the addition of bevacizumab. One thousand sixty-three patients with esophagogastric adenocarcinoma were randomized. No survival benefit was seen in the bevacizumab arm, whereas wound healing complications were more prevalent with higher rates of postoperative anastomotic leak rates with bevacizumab, prompting discontinuation of recruitment of patients with lower esophageal or junctional tumors planned for esophagogastric resection.[184]

French investigators reported the results of a similar randomized trial of 224 patients assigned to perioperative chemotherapy (CF) versus surgery alone. Although originally designed to include only patients with tumors of the lower one-third of the esophagus or GE junction, eligibility was later expanded to include gastric cancers. Most patients (75%) had disease of the lower esophagus or GE junction. Chemotherapy consisted of planned two or three preoperative and three or four postoperative cycles. This study was prematurely terminated because of low accrual. Patients receiving chemotherapy had improved overall survival (5 years, 38% vs 24%; $P = .02$), disease-free survival (5 years, 34% vs 19%; $P = .003$), and R0 resection rates (84% vs 73%; $P = .04$). Only 50% of patients received postoperative chemotherapy. T0 disease (complete pathologic response at the primary site) was seen in 3% of patients treated neoadjuvantly. Total locoregional recurrence rates were 24% and 26%, respectively, in the chemotherapy versus surgery group, with distant recurrence rates of 42% versus 56%, respectively.[185] In addition to the foregoing studies, two meta-analyses suggested that neoadjuvant chemotherapy resulted in absolute 2- and 5-year survival benefit of 7% and 4%, respectively.[186,187]

Preoperative Chemoradiation Versus Surgery Alone

Walsh et al[158] reported a randomized study to evaluate the role of concurrent preoperative chemoradiation combined with surgery. A total of 110 patients with adenocarcinoma of the esophagus were randomized to receive cisplatin, 5-FU, and concurrent radiation therapy followed by surgery versus surgery alone. Combined-modality patients received two courses of chemotherapy at weeks 1 and 6. Patients were treated using AP-PA fields (later changed to a three-field technique) to a total dose of 4,000 cGy in 15 fractions. Surgery was performed 4 to 6 weeks later, using five separate approaches. Median survival was 16 months with preoperative chemoradiation therapy compared to 11 months for the patients treated with surgery alone ($P = .01$). The 1-, 2-, and 3-year survival rates were 52%, 37%, and 32%, respectively, for patients who received multimodality therapy and 44%, 26%, and 6%, respectively, for those patients assigned to surgery. These results were significant at 3 years ($P = .01$). The authors concluded that neoadjuvant chemoradiation was superior to surgery alone in patients with resectable esophageal adenocarcinoma. A follow-up report of this study described two simultaneously conducted randomized trials in patients with (a) adenocarcinoma and (b) squamous cell carcinoma. Combined trial results suggest that neoadjuvant

chemoradiotherapy conferred a significant survival advantage in both groups, with an associated 54% relative risk reduction in lymph node metastases (64% vs 29%; $P <$ .001). Pathologic complete response was seen in 25% and 31% of patients with adenocarcinoma and squamous cell carcinoma, respectively. Patients receiving neoadjuvant therapy, achieving pathologic complete response, and those with lymph node–negative disease demonstrated superior survival.[188] This trial has been criticized for its poor surgery-alone results, short follow-up, and lack of prerandomization CT staging.

Urba et al[57] reported the results of 100 patients with nonmetastatic esophageal carcinoma (squamous and adenocarcinoma histology) randomized to receive preoperative chemoradiation followed by surgery versus transhiatal esophagectomy alone. Chemotherapy consisted of cisplatin, 5-FU, and vinblastine. Only 69% of the patients were able to receive the intended chemotherapy dose. Radiation was delivered at 1.5 Gy twice daily for 3 weeks to a total dose of 4,500 cGy. No elective nodal irradiation was performed. Surgery was performed on day 42. Tumors more than 5 cm, patient age more than 70 years, and squamous cell histology were associated with inferior survival. At median follow-up of 8 years, no significant difference in survival was seen between treatment arms, with a median survival of 17 months. However, 3-year survival rate was 16% in the surgery-alone arm versus 30% in the combined-modality arm (P = .15). A higher incidence of locoregional failure as first site of failure was seen in patients undergoing surgery alone (42% vs 19%; P = .02). In patients experiencing pathologic complete response, a median survival of 50 months and a 3-year survival rate of 64% were seen versus patients with residual tumor in the surgical specimen, where median survival was 12 months with a 3-year survival rate of 19% (P = .01). The investigators stated that “Although this is not statistically significant, this suggests a possible trend to the benefit of multimodality therapy, but the sample size was too small to detect a more subtle survival difference,” and that surgery should be continued as a standard of care.

Bosset et al[160] reported an EORTC trial randomizing 282 patients with squamous cell carcinoma of the esophagus to either immediate surgical resection or preoperative therapy using concurrent cisplatin chemotherapy with radiation therapy. Patients were treated with split-course radiotherapy with a 2-week interval, using 3.7 Gy/fraction to a total of 37 Gy. Postoperative mortality was significantly higher in patients receiving preoperative therapy (12% vs 4%). Outcomes showed patients receiving neoadjuvant therapy experienced a significant improvement in disease-free survival, cancer-related mortality, margin-negative resection, and local control; however, no improvement in overall survival was seen versus patients undergoing surgery alone (median survival was 18.6 months for both groups). The authors concluded that neoadjuvant chemoradiation improved disease-free survival and local control in patients with squamous cell carcinoma of the esophagus but had no impact on overall survival. They judged that the increase in postoperative mortality in the combined group “could be due

to deleterious effects of the high-dose of radiation per fraction," among other factors, and believed that the dose of 3.7 Gy/fraction "probably had a detrimental effect." This trial has also been criticized for the split-course treatment approach, as well as for potential delivery of suboptimal chemotherapy.

Burmeister et al[161] reported an Australian study randomizing 257 patients with adenocarcinoma and squamous cell carcinoma of the esophagus to surgery alone versus neoadjuvant therapy using concomitant 5-FU and cisplatin. Patients received 2.33 Gy/fraction to a total dose of 35 Gy. Patients undergoing neoadjuvant therapy had a 16% pathologic complete response rate at resection. Patients receiving neoadjuvant therapy were more likely to undergo curative resection and have negative lymph nodes on histologic examination. However, no significant improvement in median survival was seen (19 vs 22 months; HR 0.89; $P = .57$). On subset analysis, there appeared to be a trend toward improved survival in patients with squamous cell carcinoma undergoing neoadjuvant therapy versus surgery alone (progression-free survival HR 0.47; $P = .01$; overall survival HR 0.69; $P = .16$). The authors concluded that neoadjuvant chemoradiation as delivered in their study provided no obvious survival benefit in patients with esophageal cancer, although further study was warranted in patients with squamous cell carcinoma. Potential criticisms of this trial include delivery of a single chemotherapy cycle, as well as delivery of lower radiation doses.

Results of a Cancer and Leukemia Group B study described 56 patients (75% with adenocarcinoma) randomized to either surgery alone or neoadjuvant chemoradiation followed by surgical resection. Patients in the neoadjuvant therapy arm received CF-based chemotherapy and 50.4 Gy of EBRT at 1.8 Gy/fraction. This trial was closed prematurely because of poor accrual. In patients undergoing neoadjuvant therapy, pathologic complete response rate was 40%. A significant improvement in local control and survival was seen in patients receiving neoadjuvant CMT (5-year survival, 39% vs 16%). The authors concluded that neoadjuvant chemoradiation in patients with esophageal cancer significantly improves progression-free and overall survival.[189]

Results of the largest randomized trial (the Chemoradiotherapy for Oesophageal Cancer followed by Surgery Study, or CROSS trial) assessing neoadjuvant chemoradiotherapy in the treatment of esophageal cancer showed a significant survival benefit in patients receiving preoperative therapy, with the majority of patients included in this trial having locally advanced adenocarcinoma.[162] Patients with resectable T1N1 or T2-3 N0-1 tumors received preoperative chemoradiotherapy consisting of weekly paclitaxel and carboplatin with concurrent radiotherapy to a dose of 41.4 Gy versus surgery alone. R0 resection rates were 92% in patients receiving neoadjuvant chemoradiotherapy versus 69% for surgery alone, with a pathologic complete response rate of 29% in patients receiving preoperative therapy. No significant differences were seen in in-hospital mortality (4% vs 4%). Median survival was 49 months in patients receiving chemoradiotherapy versus 24 months in surgery alone, with a significant improvement in 3-year survival (58% vs 44%). An updated analysis of this trial showed

that 95% of patients were able to complete the entire neoadjuvant chemoradiotherapy regimen. After a median follow-up of 84.1 months in surviving patients, median overall survival was 48.6 months in neoadjuvant arm versus 24 months with surgery alone. Most strikingly, median overall survival in patients with squamous cell carcinoma was 81.6 versus 21.1 months ($P = .008$), whereas it was 43.2 versus 27.1 months in patients with adenocarcinoma ($P = .038$). Patients receiving neoadjuvant treatment had a significant decrease in both locoregional progression (22% vs 38%) and distant progression (39% vs 48%).[59] The authors concluded that weekly administration of carboplatin and paclitaxel with concurrent radiotherapy improves overall survival compared to surgery alone and that this regimen can be considered the standard of care for patients with resectable esophageal or esophagogastric junction cancer. Ten-year outcomes from the CROSS trial demonstrated persistent overall survival benefit with use of CMT.[190] At a median follow-up of 147 months, 10-year overall survival rate was 38% in the combined-modality arm versus 25% in the surgery-alone arm ($P = .004$). Local regional recurrence was significantly reduced with CMT (HR 0.40), although the rate of distant recurrence was similar in both arms (27% vs 28%). Additionally, patients with squamous cell carcinoma histology appeared to have improved outcomes with this regimen, compared to adenocarcinoma, with 10-year overall survival rates of 46% versus 36%, respectively. In the squamous cell group, overall survival was 81.6 months for the combined-modality arm versus 21 months for surgery alone ($P = .005$), and 43.2 versus 27.1 months in the adenocarcinoma group ($P = -.059$). Ten-year overall survival results were 46% versus 23% for patients with squamous cell carcinoma and 36% versus 26% in patients with adenocarcinoma. A pattern of recurrence analysis of the CROSS study indicated that preoperative therapy reduced locoregional recurrence from 34% to 14% ($P < .001$) as well as reduction in peritoneal carcinomatosis (14% vs 4%; $P < .001$) and hematogenous spread (35% vs 29%; $P = .025$). Locoregional recurrence occurred in 5% of cases within the target volume, 2% at the field border, and 6% outside the radiation target volume, whereas only 1% had an isolated in-field recurrence.[191]

In contrast, a trial from France of 195 patients with clinically staged early-stage esophageal cancer randomized patients to receive preoperative chemoradiotherapy versus surgery alone. Study outcomes showed no significant difference in survival.[58] In this study, patients with early-stage disease (stage I-II) were randomized to receive surgery alone versus neoadjuvant chemoradiotherapy using concurrent 5-FU and cisplatin with 45 Gy. Postoperative mortality rates were 3.4% in the surgery-alone group versus 11.1% in the neoadjuvant group ($P = .049$). Three-year overall survival was 53.0% versus 47.5% ($P = .749$); however, despite the higher postoperative mortality rates, 5-year survival outcomes were 41% versus 34% in favor of the combined arm (NS). Additionally, patterns of failure analysis showed a significant improvement in local control in patients who were assigned to receive neoadjuvant therapy, nearly halving the rate of locoregional recurrence (29% vs 15%). Disease

recurrence rates were also significantly reduced in patients receiving neoadjuvant treatment. A follow-up report of surgery-alone patients in this trial reported recurrent disease in 47% of patients undergoing surgery alone versus 31% neoadjuvant therapy (P = .03); locoregional recurrence was seen in 17% versus 30% (P = .047) and distant recurrence 23% versus 31% (P = .244) in the neoadjuvant and surgery arms, respectively.[192] The authors concluded that neoadjuvant chemoradiotherapy with CF did not improve survival but increased postoperative mortality for patients with early-stage esophageal cancer. However, the lack of survival benefit with trimodality therapy in this study seems to be a result of increased postoperative mortality, which is likely multifactorial. A report from Chinese investigators of 451 patients with stage IIb-III squamous cell carcinoma of the thoracic esophagus randomized patients to receive neoadjuvant vinorelbine/cisplatin with 40 Gy followed by resection versus resection alone (the NEOCRTEC trial). Pathologic complete response was seen in 43% of patients in the radiation-containing arm. R0 resection (98% vs 91%; P = .002), and overall survival rates were significantly improved in the CMT arm (70% vs 62% 3-year survival; P = .035). The authors concluded neoadjuvant chemoradiotherapy plus surgery improved survival among patients with locally advanced esophageal squamous cell carcinoma. Updated trial results revealed a pathologic complete response rate of 43% in the combined-modality group, along with a higher R0 resection rate (98% vs 91%; P = .002), improved median survival (100 vs 67 months; P = .025), and improved disease-free survival (100 vs 42 months; P < .001). No significant difference was seen in treatment-related mortality (2.2% vs 0.4%).[193] Further analysis revealed the combined-modality group demonstrated a significantly better local regional failure-free survival as well as improved metastases-free survival.[194] At a median follow-up of 54 months, 5-year survival rate of 60% was seen in the combined-modality group (vs 49%), along with improved disease-free survival.[193] Outcomes of these trials are shown in Table 59.8.

TABLE 59.8 RESULTS OF PREOPERATIVE COMBINED CHEMORADIATION VERSUS SURGERY ALONE: PHASE III TRIALS

Study	Median Follow-Up (years)	Pathology	Regimen	No. Patients	Pathologic Complete Response (%)	3-Y Survival	Survival Difference
Urba et al[57] (Michigan)	8.2	SCC + adeno	5-FU–CDDP–vinblastine/45 Gy Surg	50 50	28 –	CMT/surg: 30% Surg alone: 16%	P = .15
Bosset et al[160] (EORTC)	4.6	SCC	CDDP/37 Gy Surg	143 138	20 –	CMT/Surg: 33%	NS

Study	Median Follow-Up (years)	Pathology	Regimen	No. Patients	Pathologic Complete Response (%)	3-Y Survival	Survival Difference
						Surg alone: 36%	
Walsh et al[158] (Ireland)	1.5	Adeno	5-FU–CDDP/40 Gy Surg	58 55	22 –	CMT/surg: 32% Surg alone: 6%	*P* = .01
Burmeister et al[161] (Australia)	5.4	SCC + adeno	5-FU–CDDP/35 Gy Surg	128 128	16 –	CMT/surg: 35% Surg alone: 31%	NS
Tepper et al[189] (United States)	6.0	SCC + adeno	5-FU–CDDP/50 Gy Surg	30 26	40 –	CMT/surg: 39% (5 y) Surg alone: 16% (5 y)	*P* = .008
van Hagen et al[59,162] (Netherlands)	7	SCC + adeno	Paclitaxel–carboplatin/41.4 Gy Surg	180 188	29 –	CMT/surg: 58% Surg alone: 44%	*P* = .003
Mariette et al[58] (France)	7.8	SCC + adeno	5-FU–CDDP/45 Gy Surg	97 98	33 –	CMT/surg: 47.5% Surg alone: 53%	NS
Yang et al[197] (China)	4.60	SCC	CDDP–vinorelbine/40 Gy Surg	224 227	43.5	CMT/surg: 65.8% Surg alone: 57.8%	

5-FU, 5-fluorouracil; adeno, adenocarcinoma; CDDP, cisplatin; CMT, combined-modality therapy; EORTC, European Organisation for Research and Treatment of Cancer; SCC, squamous cell carcinoma; Surg, surgery.

Given these conflicting results of contemporary trials, multiple meta-analyses have been performed. Two of the largest and most contemporary of these demonstrated an absolute 2- and 5-year overall survival benefit of 13% and 6.5% with the use of neoadjuvant chemoradiotherapy, respectively, when compared to surgery-alone approaches, also suggesting a larger benefit of preoperative chemoradiotherapy as

compared to chemotherapy alone.[195,196] It should be kept in mind that some of the included trials used sequential (vs concurrent) chemotherapy, delivered what would be considered suboptimal doses of radiation therapy, used antiquated radiation therapy techniques, delivered (arguably) inadequate chemotherapy, and so on, potentially underestimating the effect of neoadjuvant CMT. That being said, an updated meta-analysis including a total of 24 randomized trials evaluating the role of neoadjuvant chemoradiotherapy, neoadjuvant chemotherapy, or comparison of the two in patients with resectable esophageal cancer was reported,[195,196] evaluating the outcomes of more than 4,000 patients. All-cause mortality for neoadjuvant chemoradiotherapy trials estimated an absolute survival benefit at 2 years of 8.7%, with survival benefits similar between patients with squamous cell carcinoma and adenocarcinoma. By comparison, estimated absolute survival difference at 2 years was 5.1% in patients receiving neoadjuvant chemotherapy and was significant only for patients with adenocarcinoma. The authors concluded that neoadjuvant chemoradiotherapy improves survival compared with surgery alone in operable patients, as does neoadjuvant chemotherapy, although the benefit of neoadjuvant chemotherapy was not as great as with neoadjuvant chemoradiotherapy. They also concluded that a clear advantage of one over the other is not established, and further randomized trials comparing these two strategies are warranted.

In summary, the above data suggest that neoadjuvant concurrent chemoradiation improves local control and overall survival versus surgery alone in patients with potentially resectable esophageal cancer.

Preoperative Chemoradiation Versus Pre-/Perioperative Chemotherapy

A randomized trial comparing neoadjuvant chemotherapy alone versus neoadjuvant CMT was conducted by German investigators (Preoperative Chemotherapy, or Radiochemotherapy in Esophagogastric Adenocarcinoma, or POET, trial).[198,199] Patients with advanced esophagogastric adenocarcinoma were randomized to receive either cisplatin-/5-FU-based chemotherapy alone versus a similar induction chemotherapy, followed by concurrent cisplatin/etoposide with 30 Gy of radiation therapy. Both groups went on to receive surgery. Although this study was closed early because of poor accrual, patients receiving preoperative chemoradiotherapy had significantly higher N0 rates (37% vs 64%; $P = .04$) and pathologic complete response rates (2% vs 16%; $P = .03$), as well as significant trends toward improved local control (59% vs 76%; $P = .06$) and overall survival (3-year survival, 28% vs 47%; $P = .07$; HR 0.67). The authors concluded that preoperative combined modality improves overall survival as compared to chemotherapy alone in patients with locally advanced esophagogastric adenocarcinoma. Long-term results indicated local progression-free survival after tumor resection was significantly improved by CRT (HR 0.37; $P = .01$), with overall survival showing a trend in favor of preoperative CRT (HR 0.65; $P = .055$).[200]

A multicenter phase II Scandinavian trial randomized 181 patients with esophageal or GE cancer to neoadjuvant chemotherapy with CF or the same chemotherapy concurrent with 40 Gy of radiotherapy. Primary trial end point of histologic complete response was higher in the radiation- containing arm (28% vs 9%; P = .02), as was lymph node positivity rate (62% vs 35%; P = .001) and R0 resection rate (74% vs 87%; P = .04), although no significant survival difference was seen. The authors postulated that the lack of survival benefit may be due to increased deaths related to radiation therapy.[200] A smaller phase II study from Australian investigators randomized 75 patients to receive either preoperative chemotherapy with cisplatin and infusional 5-FU or preoperative chemoradiotherapy with the same drugs with radiation therapy commencing on day 21 of chemotherapy, delivering 35 Gy in 15 fractions.[21] Histopathologic response rate and noncurative resection rates were significantly improved in the radiation-containing arm (8% vs 31% and 11% vs 0%, respectively). However, median overall survival was not significantly different between the groups (29 vs 32 months). The authors concluded that despite there being no difference in survival, the potential advantage of achieving negative margins made preoperative chemoradiotherapy a reasonable option for bulky, locally advanced resectable adenocarcinoma of the esophagus. A meta-analysis analyzing five randomized controlled trials (709 patients) demonstrated that neoadjuvant chemoradiotherapy significantly increased rates of pathologic complete response/R0 resection rates in patients with both adenocarcinoma and squamous cell carcinoma compared to chemotherapy alone. A significant increase in 3-year survival was seen only in patients with squamous cell carcinoma (56.8% vs 42.8%; P = .003), whereas in patients with adenocarcinoma, no significant difference was seen (46.3% vs 41%; P = .34).[195] A more recent meta-analysis of randomized controlled trials evaluating surgery, chemotherapy followed by surgery, or chemoradiotherapy followed by surgery, utilizing individual patient data, reported that the approaches led to an improved overall survival when compared to surgery alone, with an overall HR of 0.9 with radiation-contained regimens (P = .27), with chemotherapy-alone appearing to have a larger effect on survival in patients with GE junction versus thoracic tumors, and CMT a more significant impact on female patients (P = .003) relative to surgery alone or chemotherapy alone. The authors concluded a strong overall survival difference was not identified between these approaches.[196]

A randomized trial from China evaluated 264 patients with locally advanced esophageal squamous cell carcinoma, randomizing patients to paclitaxel/cisplatin with or without 40 Gy with concurrent radiotherapy. Patients then went on to resection. No significant difference in post-op morbidity was seen between the groups, with similar rates of R0 resection, although pathologic complete response rate was seen in 36% receiving combined modality versus 4% with chemotherapy (P < .001). Similarly, N0 status was observed in 66% with CMT versus 46% of patients (P = .3). At short interval follow-up, 1-year survival was 87% versus 83% (P = −.3), although deaths related to tumor were significantly lower in the combined-modality arm. The authors concluded

both approaches had similar safety although better histopathologic outcome with combined-modality treatments.[201] At a median follow-up of 44 months, overall survival between the two groups was similar, with a 3-year survival rate of 64% versus 55%, without significant difference in progression-free survival or recurrence-free survival. Pathologic complete response rate was 28% in the combined modality versus 3% in the chemotherapy-alone group ($P < .001$). A trend for lower risk of recurrence was observed in the radiation-containing arm ($P = .06$).[202]

The use of perioperative FLOT (5-FU plus leucovorin, oxaliplatin, and docetaxel) in GE junction and gastric cancers was established in the FLOT 4-AIO trial. This study compared this regimen to the MAGIC trial (ECF) in 716 patients with GE junction and gastric cancer tumors. Forty-four percent of patients had gastric cancer, with the remainder GE junction cancers (24% Siewert 1; 32% Siewert 2-3). Pathologic complete response was seen in 16% of the FLOT group versus 6% in the ECF/ECX group ($P = .02$). R0 resection rate favored the FLOT group (85% vs 78%; $P = .02$). Five-year survival rate was 45% in the FLOT group versus 36% in the ECF/ECX group. This regimen demonstrated a median overall survival of 50 versus 35 months ($P = .12$) in favor of the FLOT regimen.[203] This study changed the choice of perioperative chemotherapy for locally advanced GE junction and gastric cancers to FLOT.

Multiple current trials are evaluating perioperative FLOT versus neoadjuvant chemoradiation in esophageal and GE junction adenocarcinoma, including the European Neo-AEGIS trial comparing perioperative MAGIC or FLOT versus the CROSS regimen. In a preliminary report from this trial (median follow-up of 24.5 months), 3-year survival was similar (56% vs 57%). However, R0 resection rate (95% vs 82%), N0 status, pathologic complete response rate (16% vs 5%), and grade 3 or higher neutropenia (3% vs 14%) were all in favor of the CROSS regimen. Only 15% of patients received the FLOT regimen. Unexpectedly, rates of high-grade neutropenia, diarrhea, and vomiting were significantly higher in the chemotherapy-alone arm. Although there was a decrease in postoperative pneumonia in the CROSS arm (16% vs 20%), there was a higher rate of acute respiratory distress syndrome (ARDS; 4.3% vs 0.6%), although postoperative in-hospital deaths were 3% in both arms.[204] In a follow-up of the Neo-AEGIS trial at a median follow-up of 39 months, median overall survival was 48 months in the perioperative chemotherapy group versus 49.2 months in the trimodality group. No significant difference was seen in disease-free survival or patterns of recurrence (local, regional, or systemic). Pathologic complete response, major pathologic response, and R0 resection rates favored trimodality therapy. Significantly higher rates of grade 3 to 4 neutropenia in diarrhea and pulmonary embolism were seen in the chemotherapy-alone group and no significant difference in perioperative mortality was seen. The authors concluded that although the trial was underpowered and incomplete (closed early due to second interim futility analysis), similar survival outcomes were seen with no major differences in operative and health-related quality of life outcomes.[205] A Japanese three-arm randomized trial (the NExT trial, JCOG1109) is

comparing neoadjuvant CF versus docetaxel, cisplatin, and 5-FU versus radiotherapy with concurrent CF in patients with locally advanced esophageal cancer. Preliminary results of this trial reported that when compared to the doublet regimen, CMT led to an estimated HR of 0.84 (P = .12) in terms of overall survival, with the triplet regimen performing better than the doublet regimen with a HR of 0.68 (P = .006).[206]

The Australian TOPGEAR study randomized patients with resectable gastric adenocarcinoma and GE junction to perioperative ECF versus the same plus preoperative chemo-radiotherapy. Note that patients in this trial were allowed to receive FLOT after the results of the aforementioned FLOT 4-AIO trial were published.[207] Recently published results of this study showed that a high percentage of patients in the chemo-radiotherapy group achieved higher pathologic complete response (17% vs 8%) and greater tumor downstaging; however, at a median follow-up of 67 months, no significant differences in overall or progression-free survival were seen between the groups. Median overall survival was 46 months in the chemo-radiotherapy versus 49 months in the chemotherapy-alone group (HR = 1.05, 0.83-1.31, 95% CI), with a median progression-free survival of 31 versus 32 months, with similar treatment-related toxicities between groups. The authors concluded that the addition of preoperative chemo-radiotherapy to perioperative chemotherapy did not improve survival relative to perioperative chemotherapy alone in patients with resectable gastroesophageal junction and gastric/gastroesophageal junction cancers. The ESOPEC trial from Germany randomized operable patients with esophageal adenocarcinoma to preoperative chemotherapy (FLOT) versus chemoradiation (CROSS regimen). The German RACE study is comparing perioperative FLOT versus preoperative FLOT for two cycles followed by 45 Gy concurrent with oxaliplatin and 5-FU. In this phase III study, a total of 438 patients were randomized to receive either preoperative chemoradiotherapy (41.4 Gy with concurrent carboplatin and paclitaxel) followed by surgery versus perioperative chemotherapy with FLOT followed by surgery. Eligible patients include cT1c, N+ as well as cT2-4a, CN+, or cT2-4aCN0 disease. At a median follow-up of 55 months, overall survival at 3 years was 57.5% in the FLOT group and 50.7% in the preoperative chemoradiotherapy group (HR = 0.7, 95% CI, 0.53-0.92, P = .01). Similarly, progression-free survival was 51.6% versus 35%, with an HR for disease progression or death of 0.66 (95% CI = 0.51-0.85). Grade 3+ adverse events rates were 50%, with serious adverse events 47.3% versus 41.8%, respectively. Ninety-day postoperative mortality was 3.1% versus 5.6%, respectively. The authors concluded that perioperative chemotherapy with FLOT improved survival among patients with esophageal carcinoma as opposed to preoperative chemoradiotherapy and questioned whether de-escalation to a chemotherapy doublet or utilization of preoperative chemoradiotherapy is preferred in patients in whom FLOT cannot be given. Results of this trial will likely lead to change in practice patterns among these patients.[208]

Radiation Therapy Alone Versus Chemoradiation

There are multiple randomized studies comparing radiation therapy alone with concurrent radiation and chemotherapy[65,209,210] as definitive therapy. However, small patient numbers, substandard chemotherapy delivery, and the use of suboptimal radiotherapy techniques handicap many of these studies. This makes treatment results difficult to interpret. The landmark trial establishing the superiority of concurrent chemoradiation to radiation therapy alone was RTOG 85-01. Herskovic et al[211] reported the results of this two-arm trial that treated 60 control patients with radiation alone to a total dose of 64 Gy versus 61 patients with 50 Gy of radiation therapy with concurrent 5-FU and cisplatin. The chemotherapy protocol consisted of four planned courses of infusional 5-FU and cisplatin. Although less radiation was delivered in the concurrent therapy arm, the results demonstrated a significant advantage of the combined-modality arm over the radiation-alone arm. The median survival in patients treated by radiation alone was 8.9 months compared with 12.5 months for those treated with combined therapy, with 2-year survival rate of 10% versus 38%; the incidence of local recurrence decreased from 24% to 16%, and the 2-year distant metastasis rate decreased from 26% to 12%. Because of this highly significant survival difference, the randomization was stopped, and 69 additional patients were treated on the chemoradiation arm. Updated trial results[65,212] showed that at 5 years, survival rates were 26% and 0%, respectively, for chemoradiation and radiation therapy alone. Local recurrence rates were also decreased with the use of CMT versus radiation alone (45% vs 69%), and distant metastases were more frequent in the radiation-alone arm at 40% versus 12% for the combined-modality group. The incidence of acute toxicity, however, was higher for the combined-modality arm versus the radiation-alone arm (44% vs 25%). Similarly, the incidence of life-threatening side effects, including hematologic toxicity and fistula formation, was increased from 3% to 20%. In conclusion, this study demonstrated a significant improvement in local control, median and overall survival, and distant metastasis development with the addition of chemotherapy, at the cost of increased side effects.

Comparison of outcomes data from “definitive” chemoradiation approaches suggests that survival with combined chemoradiation is similar to that achieved by surgery alone. In previously discussed studies, median survival rates of 14 to 20 months and 5-year survival rates of 20% to 30% were achieved with chemoradiation alone; in comparison, in the MRC trial and Intergroup trial evaluating surgery alone, median survival rates were 13 to 16 months, with 5-year survival rates of approximately 20%. In addition, local failure rates appear similar. For example, in the RTOG/Intergroup studies using chemoradiation therapy alone, local failure rates as a first site of failure range from 39% to 45%. In comparison, local failure rate for the Intergroup study evaluating surgery alone was 31%. However, this analysis was limited to patients undergoing R0 resection only (59% of patients).[178] This would undoubtedly be higher if all patients were considered. Therefore, local failure and survival rates appear similar between “definitive” chemoradiation and surgical approaches.

Novel Chemoradiation Approaches/Immunotherapy

In attempts to improve outcomes in patients with nonoperable esophageal cancer, the SCOPE-1 trial was initiated in the United Kingdom. Patients were randomized to receive neoadjuvant cisplatin and capecitabine for two cycles, followed by initiation of radiation therapy cycles three and four (50 Gy in 25 fractions), with or without concurrent cetuximab. Two hundred fifty-eight patients were recruited (73% squamous cell). Median overall survival was 34.5 months in the non-cetuximab arm versus 24.7 months in the cetuximab-containing arm (P = .137), and 3-year overall survival was 47% versus 38%.[68] Similarly, a trial conducted through the RTOG (0436) randomized 344 patients with nonoperable esophageal cancer to weekly cisplatin, paclitaxel, and radiation therapy (50.4 Gy), with or without the addition of weekly cetuximab. Based on interim analyses, the study stopped accrual of patients with adenocarcinoma and later patients with squamous cell carcinoma. The 12- and 24-month survival rates for the cetuximab-containing arm were 64% and 44%, respectively, versus 65% and 42%, respectively (P = .70). Additionally, no difference in outcomes was seen when stratifying by histology. The authors concluded the addition of cetuximab to concurrent chemoradiation did not improve overall survival.[213] In contrast, Xie et al randomized 352 patients with medically inoperable squamous cell carcinoma to 60 Gy plus cisplatin and paclitaxel, with and without erlotinib. Five-year survival was 40% in the erlotinib arm versus 27% in the non-erlotinib arm.[214] Similarly, in the SAKK75/08 trial, 300 patients with esophageal and GE junction adenocarcinoma were randomized to preoperative cisplatin/docetaxel for two cycles followed by 45 Gy with cisplatin-docetaxel, with versus without cetuximab, followed by surgery. Trial results showed a median survival of 5.1 versus 3 years, in favor of the cetuximab arm.[215] It is likely further study is required to better clarify which patients may benefit most from a combination of EGFR inhibitors with chemoradiation.

The French PRODIGE5/ACCORD17 phase III trial compared 5-FU/cisplatin with FOLFOX-4-based chemoradiotherapy. After a median follow-up of 25 months, progression-free survival was 9.4 and 9.7 months, respectively, with no significant differences observed in terms of high-grade toxicities between the two arms.[216]

Based on an overall survival advantage seen in patients with metastatic esophagogastric cancer with the addition of trastuzumab (a monoclonal antibody against HER-2 receptors) to fluoropyrimidine-/cisplatin-based chemotherapy,[217] the RTOG conducted a trial (RTOG 1010) randomizing 606 patients with locally advanced esophageal adenocarcinoma to receive 50.4 Gy with weekly carboplatin and paclitaxel versus the same regimen with concurrent (and maintenance) trastuzumab (patients overexpressing HER-2), with resection. At a medium follow-up of 2.8 years, no difference was seen in overall (median 38.5 vs 38.9 months; P = .85) or disease-free survival (median 19.6 vs 14.2 months; P = .97) between trastuzumab versus placebo arm.[218] These results indicate the benefit of HER-2 inhibitors in combination with chemoradiation appears limited. The PROTECT trial from France is comparing

preoperative chemoradiation with paclitaxel/carboplatin versus a FOLFOX-based regimen in resectable esophageal and GE junction tumors.

The CheckMate 577 trial randomized 1,085 patients in a 2:1 ratio to receive nivolumab for 1 year versus placebo 4 to 16 weeks following CMT followed by resection.[219] Patients with esophageal or GE junction cancer of either histology and undergoing R0 resection with incomplete response to neoadjuvant chemoradiation were eligible. Median disease-free survival favored the nivolumab arm (22.4 vs 11 months; $P < .01$), independent of histology, and seemed to favor esophageal more than GE junction cancers. Patients with a high programmed death ligand-1 (PD-L1) expression tended to have a greater degree of benefit. Overall survival data were pending on initial publication. This favored the nivolumab arm across multiple subgroups independent of PD-L1 expression, HER-2 status, histology, and radiation dose. However, grade 3 or higher toxicity rates occurred in 13% versus 6% in the placebo arm, making this a new standard of care in the adjuvant treatment of these patients. The KEYNOTE-585 trial is randomizing patients with operable esophageal cancer to receive neoadjuvant chemotherapy with/without pembrolizumab, followed by surgery, followed by additional adjuvant chemotherapy with/without ongoing pembrolizumab.

Chemoradiation Versus Chemoradiation Followed by Surgery

Two randomized trials examined whether surgery is necessary after CMT. A report from French investigators randomized 445 patients with clinically resectable squamous cell or adenocarcinoma of the esophagus.[220] All patients received concurrent 5-FU and cisplatin-based chemoradiation. Patients were treated with one of two radiation regimens: 46 Gy over 4.5 weeks (continuous) or 30 Gy at 15 Gy/week (split course). Two hundred fifty-nine patients who had at least a partial response were then randomized to either surgery or additional CMT of 5-FU and cisplatin delivered concurrent with radiation (either an additional 20 Gy at 2 Gy/day or a split course of 15 Gy). No significant difference in 2-year survival (34% vs 40%; $P = .56$) or median survival (18 vs 19 months) was seen between the groups, although 2-year local control results favored the surgical arm (66% vs 57%). The death rate at 3 months following treatment was 9% in the surgery group versus 1% in the CMT-alone group. In addition, patients undergoing surgery were found to have a worse quality of life. However, the rate of stent and dilation requirement was higher in the nonsurgical arm. Additionally, in a separate analysis, patients who were not randomized in this trial (ie, nonresponders) were found to have a survival benefit with surgical resection.[221] The results of this trial suggest that surgery after chemoradiation in responding patients does not further enhance survival.

In another study, from Germany, patients with potentially resectable squamous cell carcinoma of the esophagus received induction chemotherapy with 5-FU, leucovorin, etoposide, and cisplatin for three cycles, followed by concurrent etoposide and cisplatin with 40 Gy of EBRT.[67] Patients were then randomized to receive surgery versus

continuing with combined chemoradiation (total radiation dose increased to 60-65 Gy, with or without brachytherapy). Local control was significantly improved in patients undergoing surgery (2-year local control, 64% vs 41%; $P < .05$). Despite this, no significant difference in survival was seen (median survival, 16 vs 15 months; 3-year survival, 31% vs 24%; P = NS). The "severe" postoperative complication rate (including infection, leak) was 70%, and the hospital mortality rate was 11%. Overall, treatment-related mortality was significantly higher in patients undergoing surgery (13% vs 3.5%). In patients who did not respond to induction chemotherapy, 3-year survival was improved in patients undergoing surgery (18% vs 9%). On regression analysis, only tumor response to induction chemotherapy was found to be a significant prognostic factor. An important caveat to this trial was that only approximately two-thirds of patients in the surgery arm actually had surgery. The authors concluded that (a) surgery after CMT improves local control but had no impact on overall survival and (b) nonresponders to induction chemotherapy may benefit from surgery, and it may be appropriate to individualize therapy based on response to induction treatment. Although it has not been well studied, retrospective experience suggested that definitive chemoradiation in patients with adenocarcinoma of the esophagus results in median survival of 21 months and 2-, 3-, and 5-year survival rates of 44%, 33%, and 20%, respectively.[222]

A large, multicenter study was conducted to assess the impact of salvage esophagectomy following definitive chemoradiotherapy on clinical outcome. Comparisons were performed between patients undergoing salvage (n = 308) versus planned (n = 540) esophagectomy. Additionally, patients were analyzed in the salvage arm by persistent versus recurrent disease. In-hospital mortality was similar in both salvage and planned resections (8.4% vs 9.3%). Anastomotic leak rates (17.2% vs 10.7%) and surgical site infection were both more frequent in the salvage group. Overall and disease-free survival rates were similar between the cohorts. In the salvage group, overall survival was worse in the persistent group. Of note is that doses higher than 55 Gy were linked with increased postoperative morbidity and mortality in this analysis. The authors concluded that salvage esophagectomy can offer acceptable short- and long-term outcomes in selected patients at experienced centers and that persistent cancer following chemoradiotherapy may be more aggressive and associated with a poor survival.[223] Similarly, RTOG 0246 was a single-arm trial in which patients received induction chemotherapy with 5-FU, cisplatin, and paclitaxel followed by concurrent chemoradiation with 5-FU/cisplatin to 50.4 Gy. In follow-up evaluation, if there was clinical suspicion of residual disease, patients were taken immediately to surgery; however, clinically completely responding patients were followed with serial endoscopy and imaging. Of 41 patients entered, 21 (52%) were deemed to have persistent disease with 17 taken immediately to surgery, all with residual disease noted. Of 15 clinical complete responders, 3 (20%) developed recurrent locoregional disease without distant metastases and underwent salvage resection at 3 to 8 months following treatment

completion. Overall, 5-year survival was 37%, and 20/41 patients (49%) did not require esophagectomy. The authors concluded that selective salvage esophagectomy is a viable option in patients who are at higher risk of resection or refuse to undergo surgery.[224]

The role of salvage (vs upfront) esophagectomy following chemoradiotherapy remains a topic of investigation. The French ESOSTRATE trial is currently randomizing patients with operable esophageal cancer achieving clinical complete response following neoadjuvant chemoradiotherapy between systematic surgery and surveillance with selective salvage surgery. The nonrandomized preSANO trial from the Netherlands evaluated the feasibility of salvage surgery with endoscopic ultrasound, biopsies, and PET-CT as response assessment diagnostics, with surgical resection offered only to those patients in whom a locoregional recurrence is highly suspected or proven. This study demonstrated clinical response evaluation with EUS, bite-on-bite biopsies, and fine-needle aspiration of suspicious lymph nodes was adequate for the detection of locoregional residual disease, with PET-CT for detection of interval metastases.[225] The follow-up randomized SANO trial is evaluating patients with both squamous cell and adenocarcinoma of the esophagus or GE junction and treating with CROSS type regimen with PET and EUS-guided evaluation following completion, with consideration of nonoperative management.

In summary, although surgery after combined chemoradiation for esophageal cancer appears to improve local control, its effect on ultimate survival remains unclear.

Brachytherapy

Gaspar et al[226,227] reported the results of a prospective trial evaluating intraluminal brachytherapy in patients with nonoperable esophageal cancer. Patients initially received 50 Gy of external irradiation with concurrent chemotherapy, followed by a 2-week break and brachytherapy administration. Patients received either 15 Gy using HDR techniques over 3 consecutive weeks (5 Gy/fraction) or a single administration of 20 Gy using low-dose-rate (LDR) techniques. Dose was prescribed to 1 cm from the source axis. Treatments were accomplished by placement of a 10- to 12-French applicator inserted transnasally or transorally. The target length was defined as the pretreatment tumor length with 1-cm margin proximally and distally as determined by CT, barium swallow, and endoscopy. Both external irradiation and brachytherapy were given concurrently with 5-FU chemotherapy. After the development of fistulas in six patients, the HDR dose was reduced to 10 Gy in two fractions, and the LDR arm was ultimately closed because of poor accrual. Results showed a median survival of 11 months in all patients. Local disease persistence/recurrence was observed in 63% of 49 eligible patients receiving HDR therapy. Six patients developed esophageal fistulas, resulting in three deaths. These fistulas were deemed treatment related. The 1-year actuarial fistula development rate was 18%. The investigators concluded that esophageal brachytherapy, particularly in conjunction with chemotherapy, should be approached with caution. Chinese investigators randomized 160 patients to receive

either a stent loaded with I-125 seeds or conventional stenting. Median overall survival was 177 days in the irradiation group versus 147 days in the control group ($P = .0046$). Major complications included severe chest pain (23% vs 20%) and fistula formation (8% vs 7%).[228] Review of other combined brachytherapy/EBRT series suggests that fistula formation rates range from 0% to 12%, with a possible trend toward a higher incidence in patients receiving concurrent chemotherapy with brachytherapy. The incidence of brachytherapy-related mortality varies from 0% to 8%, with most series reporting rates of 4% or less.[229] A meta-analysis of prospective studies of brachytherapy encompassing 623 patients concluded that brachytherapy was a highly effective and relatively safe treatment option that was currently underused. However, the severe adverse event rate was 23% (stenosis 12%, fistula development 8%).[230]

Other studies have suggested that HDR brachytherapy is effective for palliation of dysphagia in up to 90% of patients.[229] Danish investigators reported the results of a randomized trial of 209 patients with dysphagia due to inoperable esophageal or GE junctional tumors.[231] Patients were randomized to either endoscopic stent placement or single-dose HDR brachytherapy. Patient exclusion criteria included tumors more than 12 cm, tumors within 3 cm of the upper esophageal sphincter, deeply ulcerated tumors, tracheoesophageal fistula/tracheal involvement, presence of a pacemaker, and previous radiation treatment or stent placement. Brachytherapy was delivered through a flexible 1-cm applicator delivering a dose of 12 Gy prescribed to 1 cm from the source axis. The treatment length was defined as gross disease plus 2 cm proximally and distally. Although trial results showed a more rapid improvement in dysphagia after stent insertion, long-term dysphagia relief was significantly improved in the group receiving brachytherapy. Patients undergoing brachytherapy experienced more days with low-grade or no dysphagia versus patients with stent placement. Complication rates were higher following stent placement (33% vs 21%), primarily because of an increased incidence of late hemorrhage in the stent group. The authors concluded that single-dose brachytherapy is preferable to stent placement as the initial treatment for patients with progressive dysphagia due to inoperable esophageal or GE junction carcinoma. A follow-up study from Dutch investigators compared outcomes from the above stent versus brachytherapy study versus a prospective cohort of patients receiving palliation with EBRT (20 Gy/5 fractions). Improvement in dysphagia was seen in 83% following external beam radiation versus 64% with brachytherapy ($P = .048$). The authors concluded that short-course EBRT appeared at least as effective as brachytherapy in the palliation of patients with esophageal cancer.[232] A trial from the International Atomic Energy Agency randomized 219 palliatively approached patients to HDR brachytherapy (8 Gy × 2), with or without the addition of 30 Gy of EBRT in 10 fractions. Dysphagia relief was significantly improved in the combined approach, with an absolute benefit of 18% at 200 days from randomization ($P = .019$).[233] In a smaller trial, 65 patients with advanced cancer of the esophagus or GE junction were randomized to either expandable stent or HDR endoluminal brachytherapy (7 Gy × 3) delivered over 2 to 4 weeks.

Although the patients receiving stent alone reported significantly better dysphagia scores at 1 month, other health-related quality-of-life scores were worse relative to brachytherapy, and at 3 months, dysphagia-related scores were improved with brachytherapy.[234]

For patients treated with curative intent (unifocal thoracic tumors <10 cm, no distant metastases, no airway involvement or cervical esophageal location), the American Brachytherapy Society recommends a brachytherapy dose of 10 Gy in two weekly fractions of 5 Gy each (HDR) or 20 Gy in a single course at 0.4 to 1 Gy/hour (LDR). The dose is prescribed to 1 cm from midsource and delivered through a 6- to 10-mm applicator. The recommended active length is the visible mucosal tumor with a 1- to 2-cm proximal and distal margin. Ideally, brachytherapy is started 2 to 3 weeks after completion of concurrent external irradiation/chemotherapy to allow mucositis resolution. Concurrent chemotherapy with brachytherapy is not recommended. In palliative cases, a similar approach is recommended, with delivery of 10 to 14 Gy in one or two fractions (HDR) or 20 to 25 Gy in a single course (LDR). In previously untreated patients with a short life expectancy (,3 months), a dose of 15 to 20 Gy in two to four fractions (HDR) or of 25 to 40 Gy (LDR) without external irradiation is recommended (Tables 59.9-59.11).[235] In summary, the use of brachytherapy in the curative approach to esophageal cancer does not appear to significantly improve results achieved with combined EBRT with chemotherapy alone. However, in the palliative setting, brachytherapy has shown good efficacy in the relief of dysphagia.

TABLE 59.9 SELECTION CRITERIA FOR BRACHYTHERAPY IN THE TREATMENT OF ESOPHAGEAL CANCER

Good candidates
Primary tumor ≤10 cm length
Tumor confined to the esophageal wall
Thoracic esophagus location
No regional lymph node or systemic metastases
Poor candidates
Extraesophageal extension
Tumor .10 cm in length
Regional lymphadenopathy
Tumor involving gastroesophageal junction or cardia
Contraindications
Esophageal fistula
Cervical esophageal location
Stenosis that cannot be bypassed

TABLE 59.10 SUGGESTED SCHEMA FOR DEFINITIVE EXTERNAL BEAM RADIATION AND ESOPHAGEAL BRACHYTHERAPY

External Beam Radiation

From 45 to 50 Gy in 1.8-2.0 Gy fractions, 5 fractions/wk, weeks 1-5

Brachytherapy

High dose rate: total dose of 10 Gy, 5 Gy/fraction, 1 fraction/wk, starting 2-3 wk after completion of external beam
Low dose rate: total dose of 20 Gy, single course, 0.4-1.0 Gy/h, starting 2-3 wk from completion of external beam

All doses are specified 1 cm from the midsource or mid-dwell position.

TABLE 59.11 SUGGESTED SCHEMA FOR EXTERNAL BEAM RADIATION AND BRACHYTHERAPY IN THE PALLIATIVE TREATMENT OF ESOPHAGEAL CANCER

Recurrent after external beam radiation and short life expectancy

Brachytherapy:
HDR: total dose of 10-14 Gy, 1 or 2 fractions
LDR: total dose of 20-40 Gy, 1 or 2 fractions, 0.4-1.0 Gy/h

No previous external beam radiation

External beam radiation:
From 30 to 40 Gy in 2-3 Gy fractions
Brachytherapy:
HDR: 10-14 Gy, one or two fractions
LDR: total dose of 20-25 Gy, single course, 0.4-1.0 Gy/h

No previous external beam radiation, life expectancy >6 mo

External beam radiation:
From 45 to 50 Gy in 1.8-2.0 Gy fractions, 5 fractions/wk, week 1 to 5
Brachytherapy
HDR: total dose of 10 Gy, 5 Gy/fraction, 1 fraction/wk, starting 2-3 wk after completion of external beam
LDR: total dose of 20 Gy, single course, 0.4-1.0 Gy/h, starting 2-3 wk after completion of external beam

All doses are specified 1 cm from the midsource or mid-dwell position.
HDR, high dose rate; LDR, low dose rate.

Palliative Treatment

Although treatment advances have occurred in esophageal cancer over the last 20 years, the majority of patients diagnosed with esophageal cancer will die of their malignancy. Therefore, palliation remains an important goal. Dysphagia is a common presenting symptom and may significantly impair patient's quality of life. Many studies report a 60% to more than 80% rate of relief from dysphagia with radiation.[236] Coia et al[236] reported that nearly half of patients with baseline dysphagia experienced an

improvement in swallowing within 2 weeks of treatment initiation. By the completion of the 6th week, more than 80% experienced improvement. A median time to maximal improvement was approximately 1 month. In another series of 148 patients receiving palliative radiation therapy (most received a dose of 20 Gy in five fractions), 75% experienced an improvement in dysphagia, with 26% of these patients requiring stent placement subsequently.[237] Given the superior outcomes of patients receiving concurrent chemotherapy with radiation therapy in nonmetastatic disease, palliative chemoradiation may be preferable to radiation alone for patients with advanced-stage esophageal carcinoma who have a good performance status. However, Trans-Tasman Radiation Oncology Group (TROG) 03.01/National Cancer Institute of Canada (NCIC) CTG (ES.2) investigators enrolled 220 patients with advanced/metastatic esophageal cancer and randomized them to receive 35 Gy in 15 fractions (or alternatively 30 Gy in 10 fractions) with or without the addition of concurrent cisplatin and 5-FU. Forty-five percent of patients in the chemoradiotherapy group and 35% in the radiotherapy group obtained dysphagia relief (P =.13). Median dysphagia progression-free survival was 4.1 versus 3.4 months in the chemoradiotherapy and radiotherapy groups, respectively (P = .58), and median overall survival was 6.9 versus 6.7 months, respectively (P = .88). Grade 3 to 4 acute toxicity occurred in 36% of patients in the chemoradiotherapy group and in 16% patients in the radiotherapy group (P = .0017). The authors concluded that a palliative chemoradiotherapy showed a modest, but not statistically significant, increase in dysphagia relief compared with radiotherapy alone, with minimal improvement in dysphagia progression-free survival and overall survival with chemoradiotherapy but at a cost of increased toxicity, and that a short course of radiotherapy alone should be considered a safe and well-tolerated treatment for malignant dysphagia in the palliative setting.[238] As described earlier, intraluminal brachytherapy has also been used for palliation of dysphagia. The previously described randomized trial from the Netherlands comparing intraluminal brachytherapy to stent placement showed that although patients undergoing stenting experienced a more rapid improvement in dysphagia, long-term palliation was significantly improved in patients treated with brachytherapy.[231]

The palliative management of patients with tracheoesophageal fistula presents a clinical dilemma. Fistulization usually precludes surgery. These patients are often treated effectively with the placement of silicone-covered, self-expanding metal stents, often obviating palliative surgery. In addition, placement of feeding gastrostomy or jejunostomy may be appropriate. Although considered a “relative” contraindication to radiation therapy, limited data from a Mayo Clinic series suggest that radiation therapy may not increase fistula severity and can be administered safely in this setting; however, the presence of fistula is a poor prognostic factor.[239]

REIRRADIATION

Although local control rates with trimodality therapy are high, the incidence of local recurrence remains common in nonoperative patients. Different investigators have

evaluated the role of reirradiation in clinical practice. In one report of 54 patients (21 previously irradiated), radiation was associated with an improvement in dysphagia in 68% and median survival of 1 year. Dose range was 30 to 68 Gy with a median of 45. No grade 5 toxicities were seen, with 1 of 21 patients previously irradiated developing a late esophageal stenosis. The authors indicated that if reirradiation of esophageal carcinoma is contemplated, 3D conformal techniques and a minimum total dose of 45 Gy are recommended.[240] In a smaller series of 10 patients who were reirradiated, the total dose of primary radiotherapy was a median of 50.4 Gy (range, 50.4-63.0 Gy). The total dose of reirradiation was a median of 46.5 Gy (range, 44.0-50.4 Gy). Three patients developed a grade 5 tracheoesophageal fistula, and five experienced progressive disease 3 months following treatment. The authors concluded that reirradiation of recurrent esophageal cancer after primary radiotherapy can cause severe toxicity.[241] A small, prospective trial of 14 patients with a history of prior thoracic radiation with newly diagnosed or locally recurrent esophageal cancer explored the use of proton beam treatment. Median reirradiation prescription dose was 54 Gy and median cumulative prescription dose was 110 Gy. Four of ten symptomatic patients had complete resolution of symptoms and four decreased or stable symptoms. One grade 5 toxicity of esophageal pleural fistula was seen, possibly related to tumor progression. Median time to local failure was 10 months and median survival 14 months. The authors conclude that reirradiation is feasible with encouraging symptom control rate and with a modest toxicity profile.[242] Another report evaluated multiple studies of patients undergoing reirradiation for local regional esophageal cancer, generally between 1 and 2 years following initial treatment of approximately 50%.[243] Reirradiation doses varied from 30 to 60 Gy, with a mean of approximately 42/46 Gy in most series, with variable chemotherapy administration. Reported median survival rates were arranged from 13.6 to 21.6 months, with acute high-grade toxicities ranging from 3% to 50% and late high-grade toxicities form 0% to 17%. Based on this and their own experience, these authors suggested that even in the setting of poor performance status, definitive reirradiation may be given safely and achieved durable response in patients with locally recurrent esophageal cancer after trimodality therapy. Finally, a meta-analysis of 573 patients with esophageal squamous cell carcinoma with locoregional recurrence undergoing reirradiation described a 2- and 5-year survival rate of 25% and 15%, respectively, with rates of complete response and local recurrence of 54% and 62%, respectively, leading to a median survival of 13.9 months. Rates of grade 3 or higher adverse events including esophageal perforation, fistula formation, and pneumonitis were more common in this group.[244]

TREATMENT SEQUELAE

Advances in surgical technique, as well as improved preoperative and postoperative management, have decreased treatment-related mortality. Contemporary operative mortality rates are generally less than 10%.[59,67,245] Complication rates can exceed 75%,

including pulmonary and cardiac complications, anastomotic leak, and recurrent laryngeal nerve paralysis. Stricture formation can occur in 14% to 27% of patients. The addition of preoperative radiation therapy and chemotherapy may enhance surgical complication rates, although this remains a subject of debate.[58,59]

More than 75% of patients receiving radiation experience transient esophagitis and dysphagia, sometimes requiring nutritional support. Chemotherapy-related leukopenia and thrombocytopenia are common, although this may be less common with contemporary chemotherapy regimens.[160] Additional acute toxicities of radiation therapy include esophagitis, dermatitis, fatigue, and weight loss in most patients. Nausea and vomiting are relatively common, particularly in patients with lower esophageal and GE junction tumors. Many symptoms resolve within 1 to 2 weeks of treatment completion. A perforated esophagus is life threatening and can be characterized by substernal chest pain, a high pulse rate, fever, and hemorrhage.[114] The addition of chemotherapy can significantly increase acute complications. Moderate-to-severe and even life-threatening toxicities have been reported in 50% to 66% of patients.[91,245,246] In the previously discussed RTOG study of chemoradiation alone, patients treated with combined therapy had a higher incidence of acute grade 3 (44% vs 25%) and grade 4 toxicity (20% vs 3%) compared to patients receiving radiation therapy alone.[65] Chemoradiation treatment–related mortality rates range from 0% to 3%.[67,91,157,162,246]

The most common late effects following radiation therapy are esophageal stenosis and stricture formation. Stenosis can occur in more than 60% of patients. Symptomatic stricture requiring dilation has been reported to occur at least 15% to 20% of the time. Dysphagia may be relieved with two to three dilations.[91] Long-term results from the RTOG study showed that late grade 3 or greater toxicity was similar in the combined versus radiation-alone arms (29% vs 23%). However, grade 4 or greater toxicity was higher in patients receiving CMT (10% vs 2%).[211] Other complications include clinically apparent damage to organs within the radiation therapy volume, although this is uncommon. Chemotherapy may further increase the risk of late treatment-related toxicities.

The effects of radiation on pulmonary and cardiac function deserve special mention. Pulmonary complications associated with either the definitive or neoadjuvant treatment of esophageal cancer patients can be broadly broken up into symptomatic pneumonitis following treatment completion and postoperative pulmonary complications in patients undergoing resection. Although they are still relatively ill-defined, various institutional series have described predictive factors for these complications (which are not mutually exclusive), which are described in the following.

Radiation pneumonitis is a relatively common complication in the treatment of thoracic (lung) malignancies, which can range from minimally symptomatic to fatal. Common symptoms include nonproductive cough, dyspnea, and, uncommonly, respiratory distress. Generally, this occurs 2 to 6 months after radiation therapy

completion. The ability to predict radiation pneumonitis has been a significant topic of investigation. However, most data come from patients with lung cancer, who may have more underlying intrinsic pulmonary/smoking-related disease. A variety of predictive parameters have been suggested, including V_{20} of more than 25% to 30%, mean lung dose of more than 15 to 20 Gy, V_5 of more than 42%, and absolute V_5 of more than 3,000 cm.[146]

In nonoperative patients, an analysis of patients with esophageal cancer from Japan treated definitively to a dose of 60 Gy with concurrent 5-FU and cisplatin showed a radiation pneumonitis incidence of 27%.[247] The authors concluded that an optimal V_{20} threshold to predict symptomatic pneumonitis was approximately 30%. In a study of 101 both operative and nonoperative patients (88% distal esophagus/GE junction) from the MD Anderson Cancer Center undergoing a mix of 3D and IMRT, 59%, 5%, and 1% of patients experienced grade 2, 3, and 5 radiation pneumonitis, respectively.[248] An analysis from Japan using fields inclusive of supraclavicular, mediastinal, and celiac regions up to a dose of 60 Gy with concurrent CF showed a 2-year cumulative incidence of late, high-grade cardiopulmonary toxicities for patients 75 years or more of 29% versus 3% in younger patients. They concluded that older patients might not tolerate extensive radiation fields.[249] Other studies have shown that significant declines in diffusion capacity and total lung capacity may occur in patients irradiated for esophageal cancer.[250] The RTOG 1010 study recommends maintaining a V_{10} of 40% or less, mean lung dose of less than 20 Gy, V_{20} of 30% or less (ideally <25%), and V_{30} of 20% or less. For IMRT, interval dose is limited to 60% of the lungs receiving 5 Gy or less.

In operative patients, a study of 110 patients treated with preoperative chemoradiotherapy followed by resection at MD Anderson Cancer Center showed that mean lung dose, effective dose, and absolute lung dose receiving 5 Gy or less were predictors of development of postoperative pulmonary complications.[251] In a report on patients from the same institution describing complications in patients receiving neoadjuvant CMT,[252] 18% experienced pulmonary complications, with higher rates when the V_{10} was 40% or more (35% vs 8%) and V_{15} was 30% or more (33% vs 10%), leading the authors to conclude that minimization of lung volume irradiation was important in the preoperative planning of these patients. This increase in postoperative pulmonary complications (pneumonia, ARDS) when the V_{10} was more than 40% suggests that the volume of remaining/undamaged functional lung may determine postoperative pulmonary function, that is, patients with a small lung volume initially may be at higher risk of experiencing pulmonary complications, even if the relative V_5 is low, and that patients with small lung volume with less functional reserve may be more susceptible to postoperative pulmonary complications. Therefore, it is important to consider not only the dose-volume histogram of the lung but also the total lung volume.

A study from China evaluating patients receiving chemoradiotherapy followed by resection showed that the volume of lung spared from doses of 5 Gy or more was the only independent dosimetric factor on multivariate analysis in predicting postoperative pulmonary complications.[253] Wang et al[254] similarly described that the relative V_5 and all spared volumes from 5 to 35 Gy significantly correlated with the incidence of postoperative pulmonary complications, although on multivariate analysis, V_5 was the only significant independent predictive factor, indicating that the volume of "unexposed" lung during induction therapy was predictive. Of note in this study was that the majority of patients were treated with induction chemotherapy alone initially (most paclitaxel), which has been shown to increase rates of pneumonitis in other disease sites. A significant association of induction chemotherapy alone prior to concurrent chemoradiotherapy was seen as a predictor of grade 2 or greater pneumonitis (49% vs 14%; $P = .003$), leading the authors to conclude that induction chemotherapy alone may sensitize lung tissue to radiation damage. In contrast to the foregoing studies, however, another analysis of 98 patients receiving preoperative chemoradiotherapy with 5-FU and cisplatin showed no difference in pulmonary complications versus patients undergoing surgery alone, with no correlation of any lung dose-volume histogram findings with the development of postoperative pulmonary complications seen, leading the authors to conclude that neoadjuvant chemoradiotherapy had no detrimental impact on postoperative course.[255] An analysis from Taiwan of patients with neoadjuvantly, IMRT-treated esophageal cancer undergoing resection suggested that preoperative (not prechemoradiation) forced expiratory volume in 1 second was an independent factor associated with postoperative pulmonary complications and that reducing the absolute volume of the right lung irradiated might decrease the risk of postoperative pulmonary complications.[256] Finally, a review from Fox Chase Cancer Center of 139 patients with esophageal cancer receiving taxane-based trimodality therapy showed that 14% of patients experienced grade 2+ radiation pneumonitis. The V_5, V_{10}, V_{20}, and V_{30} were associated with an increased risk of clinically significant grade 2 pneumonitis. Multivariable analysis showed that V_5 and V_{20} remained associated with this, with V_5 of 65% or less and V_{20} of 25% or less optimal thresholds.[259]

Radiation-induced cardiac toxicity is a broad term describing potential radiation injury to a number of cardiac structures, including the pericardium (as manifested by effusion, pericarditis), coronary arteries, the heart muscle itself/ cardiomyopathy, and cardiac valves, as well as nerve/conduction injury. Radiation injury primarily consists of fibrosis and/or small-vessel injury. "Classic" radiation tolerance (TD5/5) of the heart is about 60 Gy when 25% or less of the heart is irradiated and 45 Gy if 65% of the heart is irradiated, assuming 2 Gy/fraction. The mechanism of radiation-induced cardiac injury is relatively poorly defined, particularly in the context of esophageal cancer. Historical data from the treatment of patients with Hodgkin disease suggest that a dose of more than 40 Gy may increase the risk of cardiac death, as well as of pericarditis.[258,260]

Several studies of cardiac toxicity and patients with esophageal cancer demonstrated that a V_{30} of more than 46% predicted a significant increase in pericardial effusion, and increasing fraction size (particularly ≥3.5 Gy) also predicted the same. In addition, some authors have shown a possible trend for decrease in ejection fraction in patients with increasing V_{20} of the left ventricle.[146] In a study of 150 patients with esophageal cancer receiving chemoradiotherapy (49 neoadjuvantly), the incidence of pericardial effusion was 28%, usually developing within 15 months of radiation therapy, with median onset time of approximately 5 months. The risk of pericardial effusion was associated with mean pericardial doses over an array of dose-volume points to the pericardium from 5 to 45 Gy. A matched-pair analysis of patients in the nonradiation group receiving surgery versus those treated neoadjuvantly was performed, with 42% of patients in the radiation group demonstrating ischemia/scarring on single-photon emission CT images versus 4% in the surgical group, with a median onset to abnormality of 3 months.[256] In a Japanese study, long-term analysis of 139 patients treated with definitive chemoradiotherapy (CF with 60 Gy EBRT) for squamous cell carcinoma revealed grade 2, 3, and 4 late pericarditis occurring in 6%, 5%, and 1% of patients, respectively; grade 4 heart failure in 2 patients; grade 2, 3, and 4 pleural effusion development in 5%, 6%, and 0% of patients, respectively; and grade 2, 3, and 4 radiation pneumonitis development in 1%, 2%, and 0% of patients, respectively.[257] A more recent retrospective review of 343 patients with esophageal cancer demonstrated the rate of symptomatic cardiac disease at 5 years was 14%. Multivariable analysis revealed this increase with increasing heart dose, with the lowest significant cutoff values of V_{45}, V_{50}, and V_{55} of 15%, 10%, and 5%, respectively.[258] A more recent multi-institutional review of 465 patients with esophageal cancer receiving neoadjuvant bimodality therapy showed that heart V_{30} was associated with adverse events, with a risk of 5%, 10%, and 15% when the heart V_{30} dose was 14%, 20%, and 30%, respectively, with every 10% increase in V_{30} associated with a 24% increase in risk of cardiac toxicity.[259] As described previously, an analysis of patients with esophageal cancer showed no difference in disease-specific or pulmonary mortality in patients treated with either conformal therapy or IMRT, but did show an improvement in all-cause cardiac mortality with IMRT.[145] In a literature search concerning cardiac toxicity in patients with esophageal cancer treated with radiotherapy, with or without chemotherapy, the overall accrued incidence of symptomatic cardiac toxicity was as high as 10.8%, corresponding with several dose-volume parameters of the heart. The most frequent complications were pericardial effusion, ischemic heart disease, and heart failure. Most events occurred within 2 years following treatment. The authors concluded that normal-tissue complication probability models for esophageal cancer were not available at present.[260]

FUTURE CONSIDERATIONS

Although modest improvements in survival have been achieved by combining neoadjuvant chemoradiation and surgery, patients treated with chemoradiation alone or with surgery have unacceptably high locoregional relapse rates and mortality rates. Ultimately, approximately 75% of patients succumb to metastatic disease. As described previously, efforts at radiation dose escalation have not resulted in significant gains for this disease, although newer efforts are now underway to further define optimal dose. Current clinical trials are also evaluating new and potentially more effective chemotherapeutic agents with radiation therapy, attempting to optimize combined regimen and integrate novel systemic agent in combination with radiation, as well as to further establish the role of perioperative chemotherapy.

SUMMARY

The prognosis for patients with carcinoma of the esophagus remains poor despite recent advances in combined-modality therapies. No firm recommendation can be made for managing locally advanced disease. The data suggest that neoadjuvant chemoradiation improves outcomes in patients who are candidates for surgery. Alternatively, randomized trials have also suggested that perioperative chemotherapy improves outcomes in these patients, with a recent randomized trial showing this approach improves survival relative to an upfront combined modality therapy approach. However, many patients are not able to tolerate surgery, and combined chemoradiation may be more appropriate in selected patients because definitive chemoradiation has resulted in survival rates comparable to those from surgery alone. Locoregional failure remains a significant pattern of relapse in nonoperable patients. For patients with stage IV disease, palliation with single-modality therapy or several modalities should be used and tailored to the patient's specific symptoms. Current unresolved issues include the following:

1. Which subsets of patients are more likely to benefit from the addition of surgery than others? Is a response-based surgical approach following chemotherapy and/or chemoradiation appropriate for widespread use?
2. Which subsets of patients are more likely to benefit from the addition of neoadjuvant and/or perioperative therapies? Is there a superiority of a neoadjuvant chemoradiation versus a perioperative chemotherapy approach, and will some patients benefit from the addition of combined modality therapy to a perioperative chemotherapy approach?
3. Can introduction of newer chemotherapy/targeted agents in the neoadjuvant or concurrent setting improve the results over "standard" chemoradiation with cisplatin/5-FU or carboplatin/paclitaxel? What is the best sequencing of immunotherapy in patients receiving combined modality therapy? What is the optimal "standard" regimen in combination patients?

4. Will new technologies such as PET-based planning, IMRT, proton therapy, adaptive therapy, and image-guided radiation therapy decrease complication rates and influence cure rates? Is it appropriate to reduce radiation treatment volumes to "involved field" given the high propensity for distant metastases development?
5. Will PET scan allow early prediction of both response to treatment and ultimate outcomes and potentially allow avoidance of delivery of ineffective treatments early on during the course of therapy?
6. Will the identification of molecular prognostic markers allow "individualization" of treatments among patients? Will predicted molecular biomarkers enhance predicting response to neoadjuvant treatments?
7. Will further studies of dose escalation improve local control rates in patients treated with "definitive" chemoradiation?
8. What is the role of immunotherapy in combination with chemoradiation in esophageal cancer, including the Keynote-975 trial examining safety and efficacy of pembrolizumab combined with definitive chemoradiation in locally advanced esophageal cancer? Will the addition of additional targeted therapies (eg, Wee1, vascular endothelial growth factor [VEGF], or heat shock protein 90 [HSP90] inhibitors) in combination with chemoradiation improve outcome in these patients?

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CHAPTER 60

Tumors of the Heart, Pericardium, and Great Vessels

Aviva Berkowitz

ANATOMY

The heart is a hollow, conical organ with muscular walls. In the adult, it measures approximately 12 cm in length, 8 to 9 cm in width, and 6 cm in thickness and weighs between 200 and 425 g (7-15 oz). It is located in the inferior aspect of the middle mediastinum, with two-thirds lying to the left of midline and one-third to the right. The heart lies posterior to the sternum and rib cage, and anatomic landmarks on the chest wall may be used to approximate its position. The apex is located roughly 8 cm to the left of midline in the fifth intercostal space, and the base is at the level of the third costal cartilage. It rests on the diaphragm inferiorly. The heart receives its blood supply from the coronary arteries, which are located in the space between the myocardium and the epicardium. The pericardial fat provides a smooth contour and is also located in this space. The heart has four chambers: two ventricles with thick muscular walls and two atria with thin muscular walls. Four valves, including the mitral, tricuspid, aortic, and pulmonary valves, separate these four chambers. Pacemaker cells in the sinoatrial node create an electric current that causes the heart musculature to contract and pump blood across these valves. Although the heart is not attached to surrounding organs, it is held in position by its association with the great vessels (GVs) and the pericardium. The GVs include the aorta, superior vena cava (SVC) and inferior vena cava (IVC), pulmonary artery, and pulmonary veins, which arise from (or terminate in) the left ventricle, right atrium, right ventricle, and left atrium, respectively. The roots of the GVs, along with the heart, are encompassed by the parietal pericardium. In combination with the epicardium, this fibrous layer provides a smooth cavity in which the heart can pump freely. Externally, the pericardium is

adherent to, but separate from, the mediastinal pleura, creating a potential space through which the phrenic nerve traverses.[1]

INCIDENCE AND EPIDEMIOLOGY

Tumors of the heart, GVs, and pericardium are rare and include a range of disease presentations: primary neoplasms; secondary metastases from a known primary malignancy; or direct tumor invasion, which is seen in certain cancers such as Hodgkin or non-Hodgkin lymphoma, lung cancer, or malignant thymoma. The focus of this chapter is to review the epidemiology, diagnosis, natural history, and management of primary tumors arising from the heart, pericardium, and GVs as well as metastatic disease to these sites.

The first described case of a primary cardiac tumor was by Albers in 1835.[2] Reynen[3] performed a compilation of autopsy series consisting of over 700,000 cases and found 157 primary cardiac tumors. The overall incidence of primary tumors is approximately 0.021%, with a range from 0% to 0.3%.[3,4] Approximately 75% of primary tumors of the heart are benign, and about half of those are atrial myxomas arising from the interatrial septum.[4-7] Lipomas, papillary fibroelastomas, and rhabdomyomas each account for approximately 10% of cases. Fibromas, hemangiomas, and teratomas are less common benign cardiac tumors.[8,9] Cystic atrioventricular node tumors are extremely rare congenital tumors, which, despite their small size, may lead to sudden death through disruption of the heart's conduction system.[10,11] There is an increased incidence of cardiac myxomas among females and in patients with Carney complex, an inherited autosomal dominant disorder that also shows hyperpigmented lentigines, blue nevi, schwannomas, endocrine tumors, and endocrinopathies.[12,13] The syndrome is most commonly caused by an inactivating germline mutation of the *PRKAR1 A* tumor suppressor gene on chromosome 17q23-q24.[12,14,15] Variants include the LAMB (*l*entigines, *a*trial myxoma, *m*ucocutaneous myxoma, and *b*lue nevi) and NAME (*n*evi, *a*trial myxoma, *m*yxoid neurofibroma, and *e*phelides) syndromes.[10] Myxomas in patients with Carney complex account for 7% of all cardiac myxomas, are typically found at a younger age, and may have higher recurrence rates.[5,16] Hamartomas, rhabdomyomas, and fibromas are diagnosed almost

exclusively in children.[17] Rhabdomyomas are the most common pediatric cardiac tumor and are associated with tuberous sclerosis.

Malignant primary tumors constitute the remaining 25% of cardiac neoplasms. Primary malignancies of the myocardium constitute the bulk of the remaining cases, of which sarcomas account for the vast majority, and usually occur in the right atrium.[18] Primary cardiac sarcomas make up about 1% of all soft tissue sarcomas.[19] Malignant fibrous histiocytoma, angiosarcoma, fibrosarcoma, and rhabdomyosarcoma are among the more common histologic types.[20] Table 60.1 summarizes the relative frequency of specific subtypes of sarcoma that may be diagnosed. The median age at diagnosis is 30 to 40 years, slightly younger than that for benign tumors, and there is no sex predilection as seen in myxoma.[20,24] Lymphomas account for only about 2% of primary cardiac tumors, but the incidence appears to be increasing.[25] Melanoma and carcinoma may also occur infrequently.

TABLE 60.1 DISTRIBUTION OF HISTOLOGIC SUBTYPES OF CARDIAC SARCOMA[8,20-23]

Subtype of Sarcoma	Number of Cases	Percentage of Cases
Angiosarcoma	105	28
Rhabdomyosarcoma	43	12
Undifferentiated/NOS	43	12
Fibrosarcoma	39	10
Malignant fibrous histiocytoma	33	9
Leiomyosarcoma	26	7
Liposarcoma	20	5
Other	64	17
Total	373	100

NOS, not otherwise specified.

Primary malignant tumors of the pericardium are exceedingly rare and include mesothelioma, fibrosarcoma, angiosarcoma, and malignant teratoma.[26] An American Medical Association survey of nearly 500,000 autopsies revealed a 0.0022% incidence of primary malignant pericardial neoplasms.[27] It appears that malignant mesothelioma is the most common

primary malignancy of the pericardium, accounting for 50% of primary pericardial tumors. Histologic subtypes include epithelioid, sarcomatoid, and biphasic. Asbestos has well-established associations with pleural and peritoneal mesothelioma, and there appears to be some correlation in pericardial mesothelioma as well.[28] Unfortunately, however, because of the low incidence, this association has been inconsistent, and no other risk factors have been identified.[29-31] There were 140 cases reported in the literature in 1994, and several more cases in the following years.[26,27,29-36] A recent review by McGehee et al[36] identified 103 cases in the literature published from 2000 to 2016. Fibrosarcoma, angiosarcoma, synovial sarcoma, and teratoma of the pericardium have also been documented.[26,30,35]

With advances in echocardiography, computed tomography (CT), and magnetic resonance imaging (MRI), the postmortem diagnosis of cardiac tumors is becoming less common. Surgical series seem to demonstrate an increase in the ratio of benign to malignant tumors, with malignant tumors accounting for only 10% of cases in a narrow range of 6% to 20%.[17,21,37-41] This is likely the result of surgical management of benign myxoma, which accounts for over 80% of patients in some series, combined with changes in patient selection.[21,37,40]

The majority of primary cardiac tumors arise in adults with a median age of 45 to 55 years, but they can be seen at any age.[17,21,37-41] Among 533 cases in the database of the Armed Forces Institute of Pathology, McAllister and Fenoglio[8] noted that 83% of patients were adults. Infants (<1 year of age) constituted 9% of the patients, and in this group, 96% of tumors were benign and only 4% were malignant. In a review of the data from the National Cancer Institute Surveillance, Epidemiology, and End Results from 1973 to 1987, Mack[20] reported no sex predilection for the incidence of sarcoma of the mediastinum and heart.

Metastatic disease to the heart and pericardium can occur through several pathways, including the bloodstream, lymphatics, intracavitary diffusion through the IVC or pulmonary veins, or via direct spread.[42] Metastases occur at a frequency much greater than that of primary tumors.[43-49] In a review of more than 12,000 autopsies in Hong Kong, Lam et al[47] noted that cardiac metastases were over 20 times more common than primary tumors and may be present in up to 20% of patients dying of disease. The majority of cases involve the pericardium, whereas myocardial involvement is

uncommon. In a review of autopsy series of patients with a known malignancy, Hanfling[45] noted the rate of reported cardiac involvement increased steadily from 1.5% in the late 1800s to 18.3% in 1960. Contemporary series indicate the rate of cardiac metastases in patients dying of cancer may be as high as 20%.[8,45-48,50-52]

The sites of origin of cardiac metastases from solid tumors are summarized in Table 60.2. Lung cancer is the most common cause of cardiac metastases and accounts for nearly one-half of all cases. Upper gastrointestinal malignancies and breast cancer are also common causes of cardiac metastases, accounting for one-fourth of all cases. The remaining one-fourth of cases arise from a wide variety of other malignancies.[43-48] Melanoma is purported to have the highest propensity for metastatic spread to the heart and tends to involve the endocardium or myocardium, with some series showing its incidence of cardiac metastases rivaling or exceeding that of lung cancers.[2,51] Cardiac metastases may also originate from lymphoma or leukemia. In 1960, Hanfling[45] reported that the proportion of cardiac metastases arising from these malignancies rivals that arising from solid tumors. However, multiple medical advances in both chemotherapy and diagnosis have occurred since then, and modern series consistently report that these histologies account for approximately 17% of cardiac metastases.[43,44,46,47]

TABLE 60.2 SITE OF ORIGIN FOR CARDIAC METASTASES[43-48]

Primary Tumor	Number of Patients	Percentage of Cases
Lung	271	47
Upper gastrointestinal[a]	107	19
Breast	42	7
Genitourinary (nonprostate)	37	6
Melanoma	28	5
Other	93	16
Total	578	100

[a]Includes esophagus, stomach, small bowel, pancreas, and hepatobiliary primary tumors.

Tumors of the GVs are extremely rare, occurring about as often as primary malignant pericardial mesothelioma. The literature consists mainly of case reports, with one of the largest series reported by Burke and Virmani.[53] They evaluated 45 tumors on the files of the Armed Forces Institute of Pathology and found that all of the tumors were sarcomas, including intimal (undifferentiated) sarcoma, angiosarcoma, leiomyosarcoma, and synovial sarcoma. There appeared to be no sex predilection for tumors of the aorta or pulmonary artery, although the female-to-male ratio was 3:1 among patients with tumors of the IVC.

NATURAL HISTORY

Tumors of the Myocardium

Myxomas, as discussed previously, are the most common benign tumors of the heart, are seen in women twice as frequently as men, and are diagnosed at a mean age of 45 to 55 years but have been documented in infants and octogenarians.[21,37-41,54] Benign myxomas tend to be slow growing and are minimally invasive and as such may have a long duration of symptoms before diagnosis. Typically, these tumors arise from the interatrial septum and grow into the adjacent chamber. The left atrium is the most common site of involvement for myxoma, and this is 6 to 7 times more common than myxoma of the right atrium. The tumor may also be located in the ventricles or the valves and can be bilateral. Although they are considered benign, the tumor can elicit dramatic symptoms from valvular insufficiency, congestive heart failure, and embolic phenomena. Polypoid myxomas are more solid and compact in nature, whereas papillary myxomas are softer, less dense, and more fragile.[55] Polypoid myxomas are, therefore, more likely to present with intracardiac obstruction, while fragmentation and embolization are typical of papillary myxomas.[5,55] Surgical excision is the treatment of choice, with local recurrence rates ranging from 0% to 5.4%.[10]

Primary malignant tumors of the myocardium, most commonly sarcomas, do not show a predilection for developing in any particular part of the heart, except for angiosarcomas, which tend to occur more frequently in the right atrium, and often present late with advanced disease and lung metastases.[17,21,37,39,40] The duration of symptoms is on the order of months, and survival is poor. Even after attempts at curative resection, recurrences

are common, and the median survival ranges from 6 to 18 months.[17,21-23,37-41] The cause of death is most often complications of locally recurrent disease with invasion of adjacent chambers, valves, or pericardium. Tamponade, hemopericardium, and distant metastases are common.[23] About 30% of primary cardiac sarcomas have distant metastases at the time of diagnosis.[2] The high incidence of hematogenous dissemination of cardiac sarcoma may be explained by the high rate of blood flow through the heart.[56]

Tumors of the Pericardium

Mesothelioma is the most common pericardial neoplasm and may be either confined to the pericardial sac at diagnosis or present with locoregional spread, involving the myocardium or mediastinal structures.[29-31] In the earlier literature, only 28% of primary malignant pericardial mesothelioma cases were diagnosed antemortem.[30] In contrast, the recent review by McGehee et al[36] reported postmortem diagnosis in 16% of cases, with a median age at diagnosis of 55 years, and a male predominance (61% vs 39%). These tumors have been documented to metastasize by lymphatic and hematogenous routes to involve regional lymph nodes, lung, liver, brain, bone, and adrenal glands.[26,27,29-34] Despite the metastatic potential, pericardial tumors are more often fatal because of local complications, such as constrictive pericarditis with resultant cardiac tamponade, arrhythmia due to myocardial invasion, or vena caval obstruction. Even if the tumor can be diagnosed antemortem, survival is poor. Typically, the onset of symptoms does not occur until the tumor is well advanced, and from that time, the median survival is <6 months, with only a handful of patients surviving beyond 1 year.[32-34]

Tumors of the Great Vessels

The median age at presentation for tumors of the GVs is between 40 and 60 years.[53] The natural history and clinical presentation depend on the exact location of the primary tumor. Depending on the location, symptoms may include dyspnea, cough, hemoptysis, pain, and thromboembolic phenomena, including pulseless extremities, stroke, peripheral edema, and SVC syndrome. In the series by Burke and Virmani,[53] they found that in contrast to the tumors of the aorta and pulmonary artery that were

aggressive sarcomas arising from the vessel lumen, tumors of the IVC were mostly low-grade leiomyosarcomas originating from the medial layer of smooth muscle in the vessel wall.

CLINICAL PRESENTATION

Tumors of the heart have been referred to as the "great imitators" of the cardiovascular system, and clinical correlation is crucial to help differentiate cardiac tumors from other nonneoplastic masses, such as thrombi or vegetations. Although there are no pathognomonic signs or symptoms, cardiac tumors can be detected through careful attention to both cardiac and extracardiac manifestations of the disease.[57,58] It is not surprising that tumors of the heart are often asymptomatic until they become advanced enough to affect blood flow or cardiac function,[45] which is why delay in diagnosis is prevalent, and why cardiac tumors are often fatal. When these do present clinically, the signs and symptoms are variable and depend upon many factors, including the size, location, and invasiveness of the tumor.[59] The scope of clinical presentation is summarized in Table 60.3. Tumors involving the right heart may result in pulmonary emboli, pulmonary hypertension, tricuspid valve disease, or SVC or IVC obstruction. Left-sided tumors can cause mitral valve disease, thromboembolic phenomena, and rapidly progressive congestive heart failure, which may be refractory to treatment. A characteristic auscultation finding referred to as a tumor plop may be heard during early diastole in 30% of patients.[60] Arrhythmias are very common and are predominantly supraventricular tachycardia or nonspecific conduction anomalies.[58] Specific presenting complaints are equally varied. Dyspnea is the most common presenting complaint and is noted in 59% to 88% of patients.[22,43,61,62] Palpitations or syncope is also seen frequently and may be positional, and if the tumor obstructs a valve orifice, sudden death may result. Chest pain can be anginal, resulting from direct myocardial invasion or obstruction of the main coronary ostia. It can also be sharp, due to invasion of the pericardium, with resulting pericarditis. Constitutional symptoms also occur, with fever, malaise, anemia, and weight loss.[22,43,45,58,61,62] Tumors of the pericardium and GVs show a similarly

variable constellation of symptoms, and as such, they pose the same diagnostic difficulties as tumors of the myocardium.

TABLE 60.3 SCOPE OF CLINICAL MANIFESTATIONS OF CARDIAC TUMORS

Cardiovascular Manifestations	Extracardiac Manifestations
Electrocardiogram findings	Pulmonary
Low voltage	Rales
Atrial fibrillation or flutter	Dyspnea
Supraventricular tachycardia	Hemoptysis
Conduction anomalies	Pulmonary hypertension
Bundle branch block	Upper digestive tract
Atrioventricular block (second or third degree)	Hematemesis
Ventricular tachycardia	Dysphagia
Ventricular fibrillation	Embolic phenomena
Pericardial signs	Right-sided tumors
Friction rub	Pulmonary emboli
Pericarditis	Left-sided tumors
Effusion	Stroke
Tamponade	Splinter hemorrhages
Congestive heart failure	Peripheral arterial occlusion
Peripheral edema	Raynaud phenomenon
Jugular venous distention	Peripheral findings
Valvular insufficiency	Clubbing
Chest pain	Ascites
Palpitations	Constitutional symptoms
Syncope	Anemia
Sudden death	Fatigue
Superior or inferior vena caval obstruction	Fever
Myalgia	Weight loss
	Arthralgia

Physical examination may reveal tachycardia, murmur (which may be positional), pericardial rub, gallops, peripheral edema, jugular venous distention, rales, and stigmata of thromboembolic disease. Electrocardiography (ECG) most often reveals nonspecific ST- and T-wave changes, although low-voltage ECG, supraventricular tachycardia, bundle branch block, or second-degree (type II) or third-degree atrioventricular node block may also be noted. Laboratory studies may reveal anemia, erythrocytosis, thrombocytosis, thrombocytopenia, leukocytosis, and elevated erythroid sedimentation rate.[22,58,62,63]

DIAGNOSTIC WORKUP

Cardiac tumors may be symptomatic, as discussed above. They can also be discovered incidentally, during workup for a separate, or seemingly unrelated issue. Before the advent of echocardiography and angiography, 66% of tumors were diagnosed intraoperatively during exploration for suspected valvular disease. With current techniques, the diagnosis can be made reliably in the preoperative setting in almost 90% of cases.[21] The diagnostic evaluation of patients with suspected cardiac tumors is presented in Table 60.4.

TABLE 60.4 DIAGNOSTIC EVALUATION FOR A SUSPECTED OR KNOWN CARDIAC TUMOR

Required Studies	Optional Studies
History	Cardiac catheterization, right or left sided
Physical examination	Pressure and output measurements
Blood work	Coronary angiography
Complete blood count	Endomyocardial biopsy
Liver function tests	Transesophageal echocardiography
Renal profile	ECG-gated MRI
Electrolytes	Radionuclide scintigraphy, including PET
ECG	Pericardiocentesis
Imaging	Staging for malignant tumors
Chest radiography	CT of the abdomen, pelvis, and brain

Required Studies	Optional Studies
Transthoracic echocardiography	Bone scan
Contrast-enhanced dynamic CT	

CT, computed tomography; ECG, electrocardiography; MRI, magnetic resonance imaging; PET, positron emission tomography.

Physical examination and ECG findings have been described above. There is a wide variety of imaging techniques available in the diagnosis and evaluation of cardiac tumors, and these include chest radiography, CT, MRI, echocardiography, radionuclide scintigraphy, and cardiac catheterization. Although there is considerable overlap among these studies, each modality is unique and complements the others in evaluating the tumor. Often, a multifaceted approach, utilizing several of these imaging modalities in tandem, is necessary for diagnosis. Chest radiography shows abnormalities in over 80% of patients. Unfortunately, abnormalities are usually nonspecific and, therefore, of limited usefulness. Findings include cardiomegaly, an abnormal cardiac contour, mediastinal widening, or evidence of congestive heart failure.[58,64,65] Calcifications are present in up to 20% of cases, perhaps relating to the presence of valvular or pericardial disease.[64,66] Calcifications on imaging may also suggest the presence of a fibroma. In the setting of a malignant tumor, chest radiography may also reveal hilar nodal, pulmonary, or osseous metastatic disease.

Echocardiography, M-mode and two-dimensional, is the diagnostic procedure of choice among patients with suspected cardiac tumors. It is generally widely available and has a relatively low cost. Either transthoracic (TTE) or transesophageal (TEE) techniques can be performed, yielding valuable information regarding size, shape, location, mobility, and areas of attachment.[58] For example, a myxoma may be demonstrated as a mobile mass with finger-like projections and heterogeneous hyperechogenicity, whereas thrombi are often seen in the atrial appendage, are not very mobile, and with homogeneous echogenicity.[67] In a review of 533 primary cardiac tumors, Blondeau[21] found echocardiography provided a 98% diagnostic accuracy rate among the 437 patients for whom it was used. Bogren et al[65] found that echocardiography detected abnormalities in 63 (97%) of 65 patients with primary cardiac tumors. With this high level of diagnostic

yield, and because the use of TTE is quite safe, it should be performed for all patients. TEE is a complementary procedure to TTE. It is somewhat more invasive and not required in all patients, but it may be used for guidance during endomyocardial biopsy and may also provide better evaluation of the left atrial appendage and right-sided tumors.[68-70]

Cross-sectional imaging has also become indispensable in the evaluation of nonmyxomatous cardiac tumors. With the development of contrast-enhanced dynamic CT (Figure 60.1B) and ECG-gated MRI (Figure 60.1A, C), real-time imaging of the heart provides fine details of the tumor, including the makeup, size, and, location, with delineation of intraluminal, intramyocardial, and extracardiac extension.[58,71-74] The findings may be used to plan the surgical approach and, should adjuvant therapy be required, could also be used for radiotherapy treatment planning. Compared to chest radiographs, both CT and MRI are more sensitive in detecting metastatic disease. If these studies are positive, tissue diagnosis may be made without the need for endomyocardial biopsy or thoracotomy. If they have not been performed before surgery, CT of the brain, chest, and upper abdomen and a bone scan are recommended in the staging of malignant cardiac tumors.

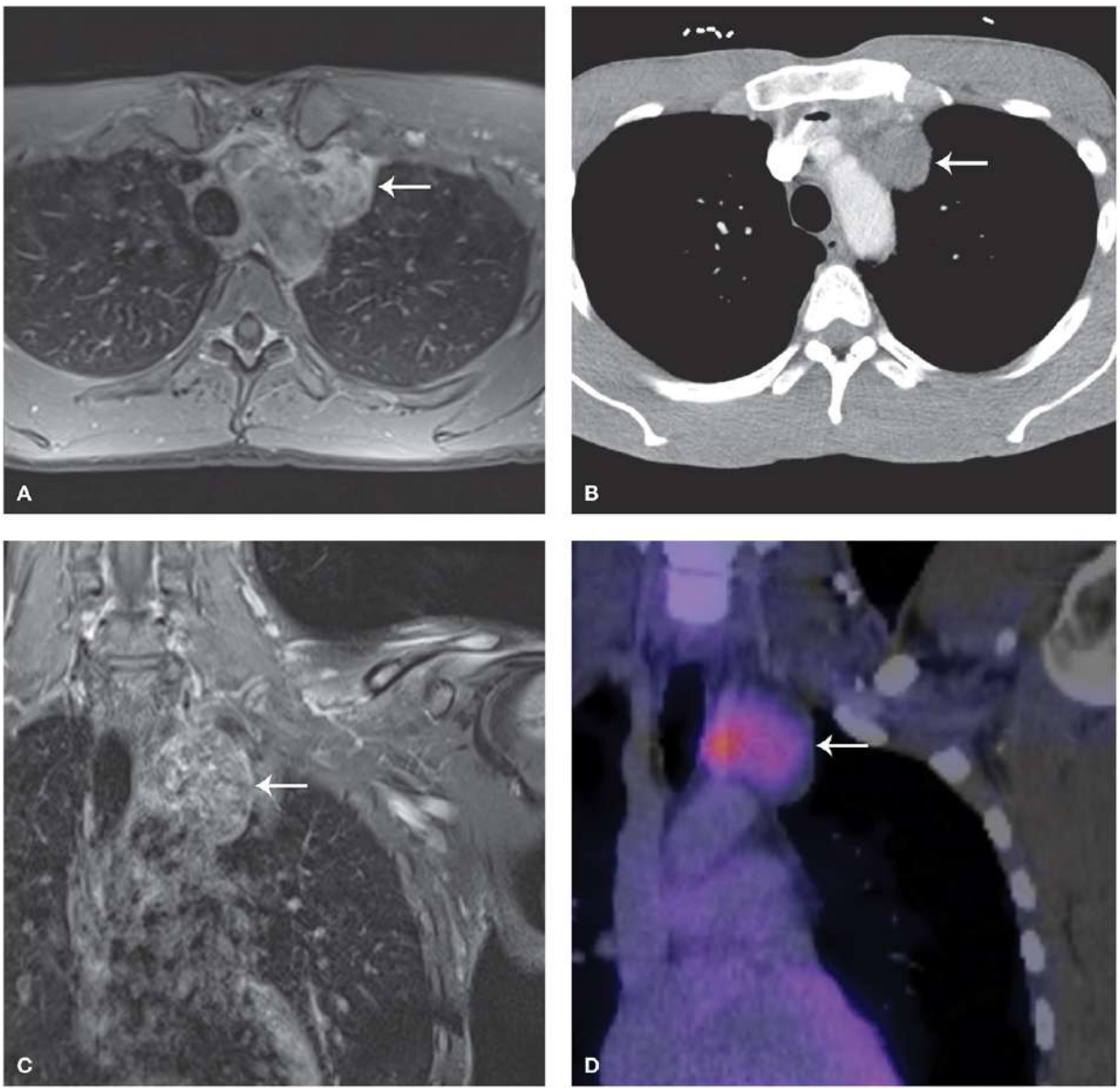

FIGURE 60.1 Axial contrast-enhanced fat-saturated T1 magnetic resonance image (MRI) of a primary cardiac neoplasm arising from the left atrium (A); corresponding axial contrast-enhanced computed tomography (CT) (B), coronal contrast-enhanced fat-saturated T1 MRI (C), and coronal fluorodeoxyglucose positron emission tomography CT (D) images. Tumor indicated by white arrows.

Radionuclide imaging has been used in the evaluation of cardiac tumors. Gated cardiac blood pool scintigraphy has limited resolution, but it may be able to detect tumors when other modalities have failed. Gallium-67 and thallium-201 scans may reveal intramyocardial invasion.[58,65] Positron emission tomography (PET), with or without CT fusion (PET-CT) (Figure

60.1D), is rapidly gaining favor in the staging of many cancers, and there are scattered case reports on its usefulness in evaluating cardiac tumors.[75,76]

Cardiac catheterization was heavily utilized in the past, but its usefulness has diminished with the emergence of the noninvasive techniques noted previously. Catheterization may reveal wall structural or motion abnormalities, intracavitary filling defects, or evidence of neovascularization of the tumor.[58,65] If a malignant tumor is suspected, endocardial biopsy may provide tissue for pathologic diagnosis. For patients who may undergo surgical resection of their tumor, catheterization is still recommended for the detection of coronary artery disease and pulmonary hypertension.

STAGING SYSTEM AND PATHOLOGIC CLASSIFICATION

There is no accepted staging system available for cardiac tumors. With respect to pathologic classification, tumors of the heart and pericardium may be classified as primary (originating from the heart) or metastatic (originating from malignancies of other organs). Primary cardiac tumors can be further subclassified by the site of origin and by malignant potential (Table 60.5).

TABLE 60.5 PATHOLOGIC CLASSIFICATION OF CARDIAC TUMORS

Pericardial Tumors	Myocardial Tumors
Benign Subtypes	*Benign Subtypes*
Teratoma	Myxoma
Pericardial cysts	Lipoma
Fibroma	Papillary fibroelastoma
Angioma	Rhabdomyoma
Lipoma	Fibroma
Malignant Subtypes	Hamartoma
Mesothelioma	Hemangioma
Angiosarcoma	Teratoma
Fibrosarcoma	*Malignant Subtypes*
Malignant teratoma	Sarcoma
	Lymphoma
	Malignant teratoma
	Melanoma
	Carcinoma

PROGNOSTIC FACTORS

In general, the prognosis for patients with either primary or secondary malignant tumors of the heart is poor. The median survival of patients with malignant primary tumors is approximately 1 year, and both local and distant relapses are common. Blondeau[21] reported that angiosarcoma had a median survival of 2.14 years, compared with only 0.75 years for fibrosarcoma. Llombart-Cussac et al,[77] on the other hand, noted a worse survival for angiosarcomas due to their propensity to present late with advanced disease. The series from Burke et al[22] and Putnam et al[23] indicate that the histologic subtype does not appear to have prognostic value, although the microscopic finding of more than 10 mitoses per high-power field does portend a worse prognosis. Tazelaar et al[78] also noted a worse outcome for tumors with high mitotic activity and necrosis. Conversely, the ability to resect all gross tumor and a left atrial site of origin predicts for longer survival.[22,23] Although the duration of symptoms is typically short, some patients have a more protracted course, and outcome may be better in those with symptoms for more than 3 months before diagnosis.[79] The use of adjuvant radiotherapy has been associated with longer median survival (22.7 vs 9.6 months), whereas adjuvant chemotherapy has provided mixed results.[22,79] Given the retrospective nature of these studies, patient selection may be a source of bias. If a controlled, prospective study could be completed, it is unclear if it would confirm an improved prognosis with either type of adjuvant therapy.

The discovery and diagnosis of metastatic disease in the myocardium is rare in the antemortem setting, and hence prognostic factors have not been well elucidated. Malignant pericardial effusion, on the other hand, is more easily diagnosed in life and can be appropriately palliated with pericardiocentesis, pericardiotomy, or pericardial sclerosis. Among patients with metastases from a solid tumor, the median survival after the procedure is approximately 3 to 4 months, and it appears to be improved with better performance status.[80,81]

MANAGEMENT

Primary Pericardial Tumors

As previously discussed, the vast majority of primary pericardial malignant tumors reported in the early literature were diagnosed postmortem,[26,27,29-34,82-85] while a more recent review reported most cases were found prior to autopsy.[36] Even among those diagnosed earlier, locally advanced or metastatic disease is common, and palliative treatment may be the most appropriate option. Relief of pericardial tamponade can be achieved rapidly through pericardiocentesis. Palliative surgical approaches include pericardiectomy or pericardial sclerosis to alleviate the symptoms of effusion and potentially prevent its recurrence. In keeping with the contemporary data supporting the use of radiotherapy in cases of primary pleural mesothelioma, it is appropriate to consider its use in the setting of primary pericardial mesothelioma, although there are few clinical data defining its use.[86] Both external-beam radiotherapy and instillation of radiopharmaceuticals (phosphorus-32, gold-198) have been reported in the palliative setting for this disease.[7,26]

Surgical resection of all gross disease is the treatment of choice in the definitive setting. As with pleural mesothelioma, a high rate of local recurrence is expected without adjuvant therapy, and postoperative chemotherapy and radiotherapy should be considered, though their benefit remains not entirely clear. McGehee et al[36] reported a survival benefit (13 vs 0.5 months) in patients who received platinum chemotherapy with or without pemetrexed. The radiation treatment volume should include the entire pericardial surface and likely should include the mediastinal lymph nodes.

Benign Cardiac Tumors

The most common benign cardiac tumors are atrial myxomas in adults and rhabdomyomas in children. These are both treated surgically with low mortality rates and local control rates in excess of 95%.[17,21,37-40,61,79] Endo et al[38] reported a 5-year overall survival rate of 86% after resection of atrial myxoma. Bogren et al[65] found the 5-year survival rate was 87% for patients with myxoma and 76% for all patients treated for a benign cardiac tumor. Blondeau[21] reported 444 patients had resection of a myxoma with a 4% 30-day surgical mortality rate, a 1% late tumor- or treatment-related mortality rate, and only a 2% risk of local relapse. Given the high rate of cure, with

an acceptable rate of morbidity, surgical resection without adjuvant chemotherapy or radiotherapy is generally appropriate for benign primary cardiac neoplasms. Some rhabdomyomas may even regress spontaneously without the need for aggressive resection.[87] Surgery also plays a role in the management of other less common benign cardiac tumors, such as papillary fibroelastomas, fibromas, and symptomatic lipomas.

Malignant Primary Cardiac Tumors

Surgical resection is the primary treatment of choice for patients with primary malignant cardiac tumors. Unfortunately, local resection is often incomplete because of the extent and invasiveness of the tumor, lack of experience with extended cardiac resection, and partly because of uncertainty of diagnosis at the time of initial surgery.[88] In experienced hands, even tumors requiring complete reconstruction of the entire right and left atria and up to 30% of the right ventricle may be resectable and still retain adequate cardiac function.[88] Even in the presence of a complete excision, local relapse is common and accounts for as much as one-third of deaths. Sarcomas account for almost all primary malignant cardiac neoplasms, and the treatment principles should be similar to those for soft tissue sarcoma arising from other areas of the body.[89] After complete or incomplete resection of the tumor, adjuvant radiotherapy and chemotherapy may be used in an attempt to gain control of local and distant disease, respectively. There are conflicting reports on the effectiveness of chemotherapy, and given the small sample sizes, it is difficult to draw conclusions, but it seems to be less beneficial if patients are not able to obtain a complete resection.[22,23,88] Combination chemotherapy appears to have greater efficacy than single-agent therapy, with different combinations of agents such as cyclophosphamide, ifosfamide, doxorubicin, and paclitaxel in use.[23,90-93]

Anecdotal cases of orthotopic heart transplantation for patients with malignant neoplasms of the heart were first described in 1981 by Jamieson et al[94] and in several reports in the literature since then, with some promising results in selected cases.[95-104] Although this technique should ideally achieve a complete tumor resection, the results have been mixed. There have been some case reports of long-term survivors, whereas many

other patients have developed distant metastases and subsequent death within months of transplant. Some have attempted cardiac explantation, tumor removal, and autotransplantation.[93] Although orthotopic heart transplantation has promise, theoretical dangers exist, including the potential protumor effect of immune suppression and a decreased ability to tolerate adjuvant radiotherapy or chemotherapy.

Primary cardiac lymphomas usually consist of aggressive B-cell lymphomas, and the treatment paradigm is generally chemotherapy and immunotherapy.

Metastatic Tumors of the Heart and Pericardium

There is no known curative therapy for patients with metastatic disease to the heart. Appropriate management of the primary metastatic tumor with systemic therapy may be indicated as a first-line approach for cardiac, pericardial, or GV metastases. Surgery may have a role in both diagnosis and palliation for patients with malignant pericardial disease.[80,81] Emergency pericardiocentesis or pericardiotomy can alleviate cardiac tamponade and yield the diagnosis, and the instillation of a sclerosing agent, such as tetracycline, can often effectively prevent the reaccumulation of the pericardial effusion. Palliative radiotherapy may be used to relieve symptoms of life-threatening outflow obstruction or pericardial disease.

Tumors of the Great Vessels

Resection of the tumor with graft reconstruction of the vessel is the treatment of choice. As with sarcomas of the heart, sarcomas of the GVs are treated based on the same philosophy as used for the treatment of soft tissue sarcoma.[89] Postoperative radiotherapy should be considered for all patients, even those with low-grade tumors, because local recurrence would likely not be amenable to salvage surgical resection.[22,40,53]

RADIOTHERAPY

In general, the most common indication for radiotherapy is in the postoperative setting, for example, as adjuvant therapy after resection of a primary malignant cardiac tumor. Less common is the use of radiotherapy

in the definitive setting for a tumor that is not technically resectable. There are rare reports of preoperative radiotherapy being used to render a technically unresectable cardiac tumor appropriate for surgery. Lastly, palliative radiotherapy may be considered when metastatic tumors to the heart cause clinically significant symptoms causing interference with cardiac function.

Decisions on radiation dose and target definitions for cardiac tumors will be determined by the tumor type and the particular clinical indication for treatment. Given that sarcomas are the most common primary malignant cardiac tumors, the radiotherapy model used in their management has been extrapolated from the approach used for soft tissue sarcomas arising at extracardiac sites. Thus, for completely resected tumors with negative margins, postoperative doses of 45 to 50 Gy at 1.8 to 2 Gy/fraction are recommended.[89] The initial target should include all areas known to harbor tumor before surgery, with a margin of about 2 cm. This target should be derived from diagnostic imaging and other investigations and also by the operative description of the surgeon. In the setting of incomplete resection (ie, involved microscopic margins or gross residual disease), an additional 10 to 20 Gy boost should be added, targeting the postoperative volume at risk. In definitive cases, the goal is to achieve a total dose of at least 70 Gy delivered to the unresected primary tumor, but normal tissues may impose limitations in achieving this. For GV tumors, the target volume will vary depending on the tumor origin but, as with cardiac primaries, should include a minimum expansion of 2 cm around the preoperative mass. Doses from 45 to 50 Gy are suggested for microscopic residual disease and 60 to 70 Gy for gross residual or unresectable disease, allowing for accepted normal tissue tolerances.[105-108] For patients with pericardial mesothelioma, the entire pericardium needs to be included in the initial target volume, but the total dose deliverable will be limited by the tolerance of the myocardium itself and may only be as high as 40 Gy if the whole heart is treated. Focal involvement of the pericardium may be treated to doses as high as 64 Gy.[109] For tumors with a high propensity for nodal involvement (ie, mesothelioma, angiosarcoma, rhabdomyosarcoma, carcinoma, or lymphoma), coverage of the mediastinal lymph nodes is also recommended. With respect to altered fractionation approaches for cardiac tumors, there are few reports on dose variations to improve the efficacy of conventional

radiotherapy. A rare example is a case report on the use of hyperfractionation for a cardiac sarcoma treated to a dose of 70.5 Gy at 1.5 Gy/fraction delivered twice daily with a radiosensitizer, iododeoxyuridine.[56] Regarding palliative radiotherapy, dose schedules should reflect the clinical urgency and the patient's performance status. The origin of the primary tumor may also have a bearing on dose schedules. A survey of palliative case reports showed wide ranges in dose/fractionation schedules with the most common ones being short-course accelerated hypofractionated approaches such as 20 to 30 Gy in 5 to 10 fractions.[110]

With respect to radiation delivery, historic practice has involved two-dimensional planning and static beam arrangements, such as anteroposterior parallel-opposed techniques to cover the desired initial target volume. Contemporary radiotherapy should now be planned using a three-dimensional (3D) conformal approach, with careful delineation of gross tumor volumes, clinical target volumes, and planning target volumes as defined by the nature of the primary tumor, its expected natural history, and the management approach (definitive or adjuvant). When planning radiotherapy, normal tissue constraints should be observed for each case, with an emphasis on cardiac, lung, spinal cord, and esophageal tolerances. If required, advanced techniques such as intensity-modulated radiotherapy (IMRT) may be of use in the delivery of desired doses to target volumes while highly limiting dose to normal structures. IMRT techniques allow for the selective intensification or reduction of dose to areas of specific concern and may allow for greater sparing of normal tissues without sacrificing tumor coverage or dosing. A recent innovation in radiotherapy highly relevant to cardiac tumors is the use of four-dimensional (4D) CT scanning at the time of patient simulation. 4DCT allows an understanding of the effect of breathing motion on the target and normal structures within the chest. For each structure, 4DCT can generate volumetric data sets representing the various phases of the respiratory cycle. By more clearly understanding tumor motion, relevant normal structures at risk can be optimally spared by restricting treatment margins.

One of the more important advances in the field of radiotherapy has been developing technology that can deliver extremely high-dose focused radiation. Stereotactic body radiotherapy (SBRT), also known as stereotactic ablative radiotherapy, involves the precise delivery of very high

(ablative) doses of radiation to discrete targets over a small number of treatment sessions (usually five or less) by treating the target with high degree of conformality and employing rigorous pretreatment setup verification. Given the complexity of heart tumors by virtue of their location and their relationships to a number of organs at risk, SBRT has proved to be of particular interest in their management. Soltys et al[111] treated a recurrent pulmonary artery sarcoma with 33 Gy in three fractions. Bonomo et al[112,113] used SBRT for recurrent and metastatic cardiac tumors, with doses ranging from 24 to 36 Gy in three to five fractions. Although the total doses used for cardiac tumors reported so far have been less than the curative doses seen in the early-stage lung cancer SBRT literature, clinicians treating heart tumors have nonetheless employed the critical organ dose constraints used in lung SBRT planning.[114-117] Mindful of the limited reported use of such high-dose, highly conformal techniques for heart tumors, it is conceivable that they may offer a means to safely escalate doses to those that would theoretically be optimal for tumor control. This is attractive, given the poor outcomes seen with current nonsurgical therapies.[111] Patients who may be the best candidates for using such novel approaches may also be those who have received prior radiotherapy and suffer an isolated in-field recurrence. Because using conventional radiotherapy techniques would likely exceed critical structure dose constraints, SBRT may make high-dose therapy feasible in the setting where otherwise anything other than palliative doses might not have been possible.

Particle-based therapies are also increasingly being investigated in the management of cancers because of their physical properties, which might provide better sparing of normal tissues. A clinical report from Japan (see further in section “Results”) is an example of this modality for a heart malignancy, describing the use of carbon ion radiotherapy for a case of cardiac sarcomas that employed 64 Gy in 16 fractions over 4 weeks.[118]

Advanced technologies must be used with caution, however, because cardiac and respiratory motions introduce considerable uncertainty in tumor localization and predictability of dose delivery. In the setting of SBRT, normal tissue and tumor motion must be, therefore, effectively evaluated using 4DCT techniques. Image guidance (image-guided radiotherapy [IGRT]) at the time of delivery to further ensure targeting accuracy is also

critical. Alternative delivery approaches such as gating procedures may be considered to decrease positioning uncertainty and thus decrease the necessary target expansions for daily setup variations.[119] An advanced method of IGRT that has emerged in recent years is MR-guided radiation therapy, enabling direct visualization of the tumor during treatment, with excellent soft tissue resolution, which is particularly helpful for cardiac tumors. In addition to real-time tumor visualization, the MR-Linac system allows for adaptive radiation therapy planning, correcting for daily changes in position of the heart and surrounding structures. These advancements enable administration of higher doses of radiation to the tumor more safely, with more effective sparing of normal tissues. Several recent reports describe their experience with MR-guided SBRT.[120-123]

As a demonstration of different planning results, representative isodose distributions, and their corresponding dose-volume histogram data, for two primary cardiac tumors are shown in Figure 60.2 for a 3D conformal radiotherapy plan and in Figure 60.3 for an SBRT plan.

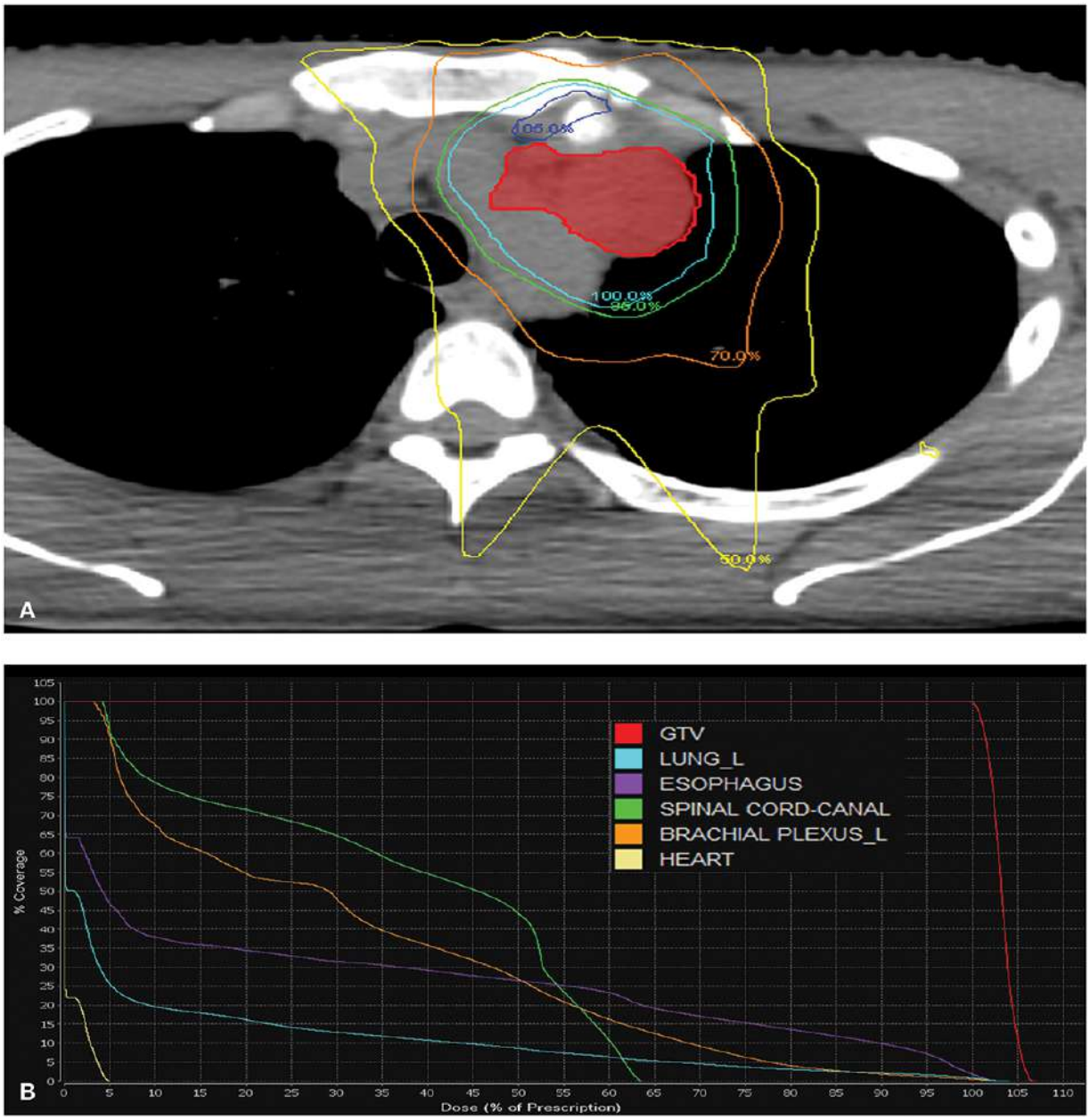

FIGURE 60.2 Sample three-dimensional conformal plan developed for a patient with an unresectable epithelioid hemangioendothelioma of the aortic arch (A) and corresponding dose-volume histogram data (B). GTV, gross tumor volume.

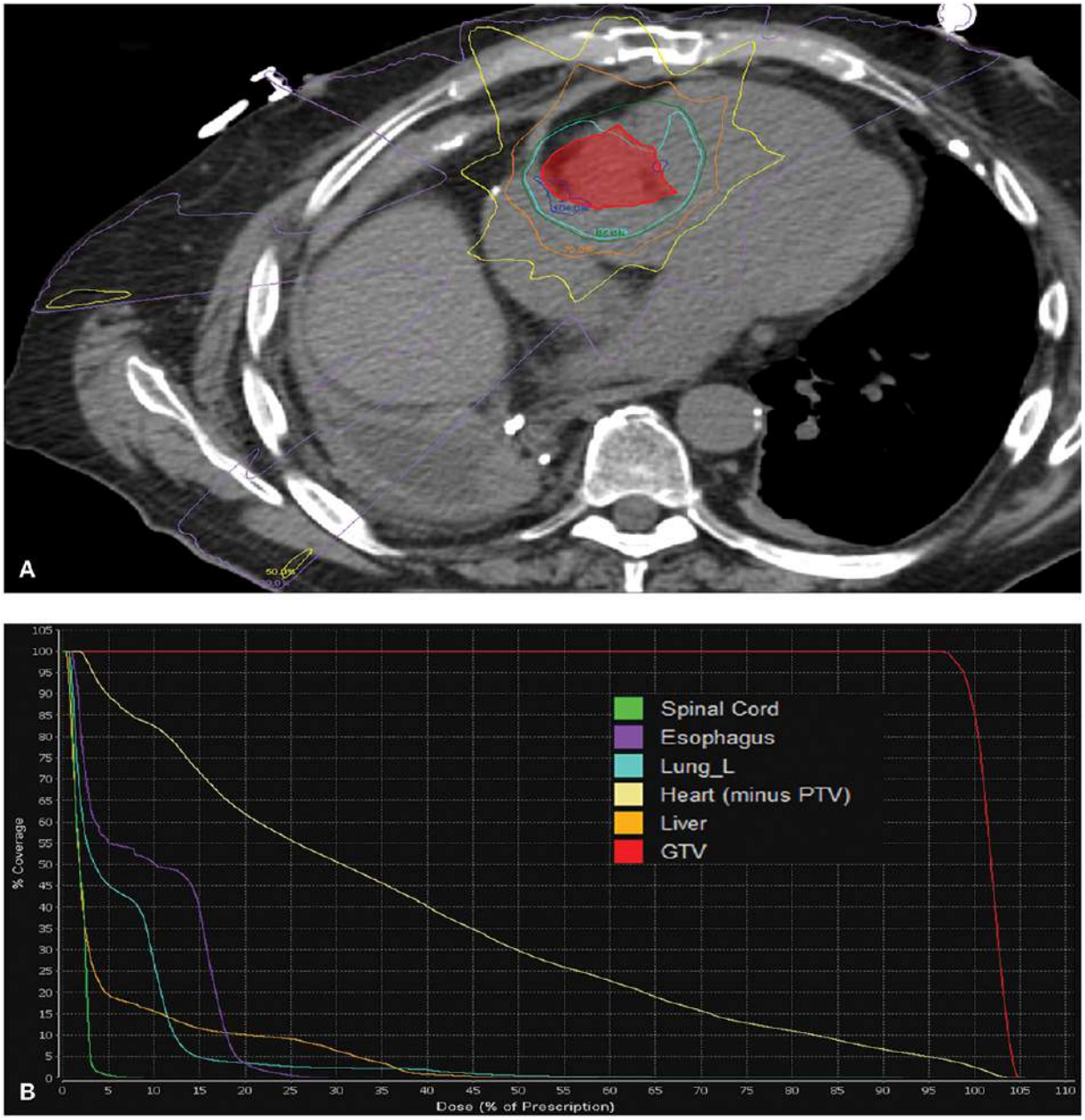

FIGURE 60.3 Sample stereotactic body radiotherapy plan developed for a patient with a local recurrence of a pleomorphic sarcoma of the pulmonary artery (A) and corresponding dose-volume histogram data (B). GTV, gross tumor volume; PTV, planning target volume.

As noted above, the total dose deliverable to any given cardiac tumor is primarily limited by heart and lung tolerance. Much of the available evidence on tolerance of the heart is based on patients previously treated for malignancies, such as Hodgkin lymphoma or breast cancer. In general, radiation-induced heart disease (RIHD) may manifest as pericarditis,

myocarditis, conduction defects, or coronary vascular disease.[124,125] Damage to the pericardium is most often observed clinically. Risk factors for developing RIHD include total dose, dose per fraction, irradiated volume, radiation technique, age at exposure, and use of concurrent or anthracycline-based chemotherapy. Emami et al[105] estimated the tolerance dose for the heart to be 40 Gy for the whole heart and 60 Gy for one-third of the heart based on a 5% complication rate of developing pericarditis within 5 years of treatment (TD5/5). However, current estimates of normal tissue tolerances tend to be more accurate, and administration of chemotherapeutic agents must also be taken into account as enhancing risk.[125] Most recently, Gagliardi et al[106] reviewed all the available data on cardiac toxicities and concluded that the whole-organ dose at which toxicity occurs in 50% of cases (TD50) is on the order of 48 to 50.6 Gy, but that side-effect profiles must be considered in relation to the probability of tumor control for the specific patient. Certainly, in aggressive tumors with poor outcomes, recurrence is equally or more morbid than the potential treatment-related toxicities, and this must be balanced and discussed with the individual patient. With respect to other normal structures relevant to 3D target planning for cardiac or GV tumors, Werner-Wasik et al[108] have reported that doses as high as 74 Gy with concurrent chemotherapy can be delivered safely to segments of the esophagus, but that no single best threshold is identifiable for limiting esophageal toxicity. In a comprehensive literature review on lung tolerances performed by Marks et al,[107] the authors recommended limiting the volume of lung receiving 20 Gy (V20) to ≤30% to 35%, and the mean lung dose to ≤20 to 23 Gy in order to minimize lung toxicity. All of these values are for patients receiving conventionally fractionated radiotherapy because as noted earlier, SBRT-based approaches employ a different set of normal tissue constraints.

RESULTS

Case reports and small retrospective series have been the primary means of understanding outcomes for this rare class of tumors. A classic example is the 1964 report by Sagerman et al,[126] which included one of the earliest descriptions of adjuvant radiotherapy for attempted cure. The patient was a 55-year-old woman with a primary cardiac fibromyxosarcoma. After

incomplete resection, she underwent external-beam radiotherapy to a dose of up to 75 Gy to the primary site, with proper shielding of the spinal cord. As a result of the use of lateral fields, the left lung received 35 Gy to a large volume. The patient was treated with prophylactic steroids to prevent radiation pneumonitis and fibrosis. She died 8 months later with brain and lung metastases. Autopsy revealed complete sterilization of the primary tumor.

Despite the use of aggressive treatment regimens including surgical resection, postoperative radiotherapy, and chemotherapy, the overall survival for patients with primary malignant cardiac tumors is poor, and this is true even in light of more recent reports that have suggested better outcomes with contemporary adjuvant radiotherapy or chemoradiotherapy.[22,90,91,93] Operative mortality is relatively common, at 8% to 9%, and is twice as high compared to that following resection of benign tumors.[88,127] The median survival in most surgical series is in the range of 9 to 12 months,[17,21,23,37,39,77,90,127,128] with outliers as low as 6 months[22,40,129] and as high as 23.5 months among patients who survived surgery in one of the most recent reports.[88] Putnam et al[23] reported a median survival of 11 months and a 2-year overall survival rate of only 14%. In this series, the authors also noted the importance of complete resection. For patients in whom complete resection was possible, the median survival was 24 months, compared with only 10 months for those with incomplete resection. Llombart-Cussac et al[77] also noted improved survival with complete resection (22 vs 7 months). Burke et al[22] reported significantly improved median survival of 12 months among patients who underwent adjuvant radiotherapy, chemotherapy, or both, compared with 3 months in those who did not have adjuvant therapy.

With respect to the use of definitive carbon ion radiotherapy in the treatment of a patient with cardiac angiosarcoma,[117] the tumor volume reduced by 86% following treatment and became negative on PET scan. After 18 months, the primary tumor remained controlled, but the patient had developed bilateral lung metastases 4 months after treatment.

Selected patients who develop recurrence after undergoing combined modality therapy may still benefit from aggressive management of their disease, with one author reporting an improvement in median survival from 25 months with no treatment to 47 months with resection, radiofrequency

ablation, or radiotherapy.[88] Others have shown similar benefits to this approach at the time of recurrences.[93]

The median survival for patients with metastatic disease to the heart is approximately 3 to 4 months, but rare cases of long-term survival, some as long as 3 years, have been documented and may be related to primary tumor histologic type and performance status.[80,81,130] Pericardiotomy or pericardial sclerosis appears to offer at least temporary control of tamponade and effusion in up to 90% of cases.[80,81] Palliative treatment with radiation is well tolerated and is effective in controlling cardiac tamponade in approximately 60% of patients. Cham et al[131] reported the results of radiotherapeutic palliation for 38 patients with secondary tumors of the heart and pericardium. Thirty-seven patients were noted to have pericardial involvement, nine also had invasion of the myocardium, and one had only endocardial involvement. The radiation dose was 25 to 30 Gy in 3 to 4 weeks for 32 patients. The dose was 15 to 20 Gy in 1.5 to 2 weeks for the remaining six patients, all of whom had lymphoreticular tumors. The overall response rate was 61%, with a median duration of response of 3 to 4 months. Lymphoreticular tumors had the best response rate (6/7 cases) followed by breast cancer (11/16 cases). Only 6 of the remaining 15 cases showed a response. Although the median survival among patients with metastases to the heart and pericardium is short, palliative efforts are not in vain because tamponade appears to be effectively controlled with these measures.

Among patients treated for GV tumors, median survival depends on the location, resectability, and grade of the primary tumor. Burke and Virmani[53] reported the median survival was 5 months for aortic sarcoma, 23 months for sarcoma of the pulmonary artery, and 37 months for sarcoma of the IVC. Two patients with sarcoma of the SVC were alive and without disease 10 and 72 months after treatment. Local relapse was documented in two patients, although metastatic disease occurred in 19 of 45 patients. The sites most commonly involved by metastases were the lung, liver, and bone. Involvement of the peritoneum, adrenals, kidneys, skin, and lymph nodes was also noted.

Treatment Sequelae

Late radiation-induced cardiac or pulmonary sequelae after the definitive treatment of cardiac tumors have not been well documented, probably as a result of the poor overall survival for these malignancies. In a recent report of 17 patients treated for different cardiac malignancies, with follow-ups ranging from 5 to 137 months, Lestuzzi et al[132] described late toxicities from cardiac radiotherapy in six of these cases. Three patients developed recurring atrial fibrillation, two segmental hypokinesis and one constrictive pericarditis. The cardiotoxic effects of doxorubicin have been well documented, and there is evidence for increased risk when it is given in conjunction with radiotherapy[125]; therefore, concurrent therapy should be avoided to the degree possible.

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PART E

Breast

CHAPTER 61

Breast Cancer: Stage Tis

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Noninvasive carcinoma of the breast (stage Tis) includes Paget disease of the nipple and two histopathologic entities that are distinct in both their clinical presentation and biologic potential: lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS). As a result of the increase in the use of mammography, these three histopathologic entities comprise a larger percentage of all breast cancer cases seen today. There remains considerable controversy regarding the optimal treatment approach, and as a consequence, treatment recommendations range from observation to breast conservation therapy to mastectomy. It is, therefore, important to understand the distinguishing pathologic appearances, biologic characteristics, and natural history of these three noninvasive breast disease entities to appropriately formulate coherent treatment recommendations.

LOBULAR CARCINOMA IN SITU

LCIS is characterized by multicentric breast involvement and consists of loose, discohesive epithelial cells that are large in size, variable in shape, and contain a normal cytoplasm-to-nucleus ratio.[1] The extent of involvement of the lobular lumen ranges from simple filling to moderate to severe distention with extension into the adjacent extralobular ducts.[2] As such, the lines of histologic delineation can become blurred between atypical ductal hyperplasia, LCIS, and, when ductal extension is seen,

DCIS. This overlap of histologic morphology may complicate the interpretation of studies from different institutions.[1-4]

LCIS has been reported to present with a multicentric distribution in up to 90% of mastectomy specimens, with bilateral involvement in 35% to 59%.[5-7] LCIS cells are commonly estrogen receptor positive, although overexpression of c-erbB-2 and p53 is uncommon.[4,8-10] The loss of E-cadherin is often observed,[8,11,12] and the absence of this adhesion molecule may explain the growth pattern seen with LCIS.

LCIS represents <15% of all noninvasive breast cancer.[13-15] Most women are premenopausal at diagnosis, with an average age of 45 years.[1,3,16] Risk factors for the development of LCIS correspond to those identified for invasive carcinoma.[17] Because the male breast lacks lobular elements, this entity has not been described in men.[3] As there are no clinical or mammographic indicators that are characteristic of LCIS, it is often detected as an incidental biopsy finding.[1,4] In a minority of cases, LCIS can be detected with mammographic calcifications; however, more commonly, calcifications are in adjacent tissue and are not histologically associated with LCIS.[18-20] In excisional biopsy specimens, DCIS or invasive carcinoma is frequently identified even when LCIS is the sole histologic entity seen on core biopsy.[21-23]

LCIS is considered a marker of increased risk for the subsequent development of invasive (usually ductal) carcinoma[3,13,14,16] that may be greatest for high-grade or more extensive lesions.[1,24] This risk appears to be nearly equal for both breasts.[25]

The question as to whether LCIS can serve as a direct precursor lesion to the subsequent development of invasive lobular carcinoma is unresolved. Some studies have suggested a clonal link of synchronously detected LCIS and invasive lobular carcinoma,[26] whereas others have not.[27] In an analysis of 182 patients with LCIS who were inadvertently enrolled on the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 trial for DCIS and treated with lumpectomy only, there was a 14.4% in-breast tumor recurrence (IBTR) rate and a 7.8% contralateral breast tumor recurrence rate after a median follow-up of 12 years.[28] Nine IBTRs (5% of the total cohort) were invasive carcinoma, and 17 (9% of the total cohort) were DCIS. Although the frequency of contralateral breast tumor recurrence rate was less than that of IBTR, the frequency of invasive contralateral breast

tumor recurrence rate (5.6% of the total cohort) was similar to invasive IBTR (5% of the total cohort). Of note, all of the IBTR were documented to be at the site of the index lesion, except for one, characterized as pure LCIS, that was found at a remote site.

The evidence associating LCIS with the subsequent development of invasive disease raises the question as to whether magnetic resonance imaging (MRI) would be a useful screening tool. Limited data exist to formulate a firm recommendation. In 2007, the American Cancer Society stated there were insufficient data; however, in 2009, a national expert consensus panel published guidelines reflecting a panel consensus opinion that annual breast MRI should be considered in patients with LCIS. Several studies have been published evaluating the role of MRI in patients with LCIS.[29-32] Each document revealed a small but defined 3.3% to 4.5% breast cancer detection rate and a positive predictive value of 31% based on biopsies performed supporting consideration for an annual MRI in this subset of patients. Management for LCIS depends on whether it is associated with another malignancy (DCIS or invasive carcinoma) or if LCIS is the sole histologic diagnosis. Approximately 10% of early-stage breast cancers have an associated component of LCIS.[33-35] The effect that LCIS has on the outcome of conservative management of early-stage breast cancer has been evaluated. Limited studies suggest that the presence of LCIS should influence treatment approach[36]; however, the most widely accepted treatment approach is to manage the breast according to the dominant malignant histology (DCIS or invasive carcinoma) and disregard the LCIS. In such circumstances, it is not necessary to pursue additional surgery to obtain clear margins for LCIS.[27,33,34,37,38]

If LCIS is the sole histologic diagnosis, treatment recommendations range from conservative to radical. When first described as an entity, the significance of LCIS was unknown and mastectomy was often performed.[39] The high frequency of contralateral breast involvement was subsequently used to justify contralateral biopsy and even bilateral mastectomy.[16,39] Observational studies after wide local excision alone have led to a better understanding of the natural history of this condition, and a more conservative approach is now commonly practiced.[3,13,14] In patients with LCIS as the sole histologic diagnosis, the most widely accepted clinical practice is close observation with regular physical examination and

mammographic surveillance.[3,13-15,28] There is no role for radiotherapy in the management of LCIS. The fact that LCIS commonly involves both breasts makes treatment with unilateral mastectomy both inadequate and illogic. Bilateral prophylactic mastectomy is likely excessive in all but those patients believed to be at highest risk: young age, diffuse high-grade lesion, and significant family history. A less radical prophylactic approach in high-risk patients is to consider the use of tamoxifen. Tamoxifen has demonstrated efficacy in the prevention of invasive carcinoma and, in the context of LCIS, has been shown to reduce risk by 56%.[40,41]

PAGET DISEASE

The clinical presentation of crusting and eczematous changes of the nipple-areola complex was first described in 1856. However, it was not until 1874 that the association with an underlying breast cancer was reported by Sir James Paget.[42] Paget disease of the nipple is characterized by the presence of Paget cells that are located throughout the epidermis.[43] Paget cells are large and have hyperchromatic, round to oval nuclei with abundant amphophilic to clear cytoplasm. Mitoses are commonly seen, and the cells can be found in clusters or individually in the basal layers. The fact that Paget disease is associated with an underlying malignancy in over 95% of cases has generated discussion regarding the origin of these malignant cells. The epidermotropic theory appears to be the prevailing opinion, with the belief that the disease originates from the underlying in situ or invasive disease. This is supported by histologic evidence of intraepithelial extension, immunohistochemical studies, and evidence suggesting that the epidermal keratinocytes release a motility factor, heregulin-*a*, that results in the chemotaxis of Paget cells that migrate to the overlying nipple epidermis.[44,45]

Paget disease is a rare entity representing less than 5% of all breast cancer cases[46,47] and is typically diagnosed in the fifth or sixth decade of life. Synchronous bilateral Paget disease and male Paget disease have been reported.[44,48,49]

Patients with Paget disease describe itching and burning of the nipple and areola. There is a slow progression toward a crusting eczematoid appearance that can extend to the periareolar skin. If neglected, bleeding,

pain, and ulceration can occur.[47,50] Alternatively, Paget disease can be asymptomatic and present as a pathologic finding after incidental surgical removal of the nipple-areolar complex.[51] The differential diagnosis includes superficial spreading melanoma, pagetoid squamous cell carcinoma in situ, and clear cells of Toker.[43,52] A palpable mass is detected in approximately 50% of patients at diagnosis; in over 90% of cases, this will be an invasive carcinoma. In contrast, if no palpable mass is detected, 66% to 86% will have an underlying DCIS. These associated malignancies are usually located centrally, although they can occur elsewhere in the breast.[44,47,53] Mammographic findings are frequent in the presence of a palpable mass; however, normal mammograms are reported in as many as 50% of cases.[47,54]

At presentation, clinical evaluation includes bilateral breast examination, mammography, and biopsy to confirm the diagnosis of Paget disease and to fully evaluate the extent of the associated malignancy. The prognosis does not depend on the diagnosis of Paget disease but rather on the associated malignancy. Therefore, local treatment, as well as systemic and regional nodal disease risk management, should be based on the associated disease.

Management of Paget disease continues to evolve. Mastectomy was employed in the past, although this has been increasingly supplanted by breast-conserving treatment.[55-58] The infrequent occurrence of this disease entity, the range of disease presentations (nipple involvement with or without an underlying mass and association with invasive vs noninvasive disease), and the variable extent of surgical resection have made the evaluation of treatment options difficult. Small series have described results with various forms of breast-conserving treatment, including wide local surgical resection alone, radiotherapy alone, and wide excision followed by whole-breast radiotherapy. Conservative surgery alone for Paget disease appears to be inadequate, with reported local recurrence rates of 25% to 40%.[5,57,59-62] The use of radiotherapy alone has been reported as achieving an 85% local control rate in a small series of patients with Paget disease of the nipple who presented without an associated palpable mass.[63] However, this approach has not been widely adopted because of the undefined histologic type and extent of the underlying disease leading to uncertainty in field design and total radiation dose.

The combination of limited surgical resection and postoperative radiotherapy appears to be the most practical breast-conserving approach.

Two studies have evaluated the combined use of surgery and radiotherapy in Paget disease of the nipple. The European Organization for Research and Treatment of Cancer (EORTC) Study 10873 was a multi- institutional registry trial that reported a 5-year local recurrence rate of 5.2%.[64] In this study, complete excision with tumor-free margins of the nipple-areolar complex and underlying breast tissue was followed by whole-breast radiotherapy. The median follow-up was 6.4 years, and most of these patients were found to have an underlying DCIS without a palpable mass. A separate study consisted of a seven-institution collaborative review of 36 patients with Paget disease without a palpable mass or mammographic density.[65,66] Patient follow-up was a median of 9.4 years. The extent of surgical resection varied as patients underwent complete (69%) or partial (25%) excision of the nipple-areolar complex and underlying breast tissue, with 6% reported as biopsy only. The final margin status was documented as negative in 56%, positive in 6%, and unknown in 39%. All received whole-breast irradiation, and most received an additional boost dose to the tumor bed. The actuarial rate of local failure as the only site of first recurrence was 9% at 5 years and 13% at both 10 and 15 years. Two additional patients recurred in the treated breast simultaneously with regional and distant metastasis at 69 and 122 months. Despite the differences in clinical, pathologic, and treatment factors, statistical evaluation did not identify any factors that significantly predicted for risk of local recurrence.

Current data suggest that a combined modality approach that conserves the breast is an appropriate alternative to mastectomy in properly selected patients with underlying noninvasive or invasive carcinoma of limited extent. As with any breast-conserving approach, patients with multicentric disease extension should be excluded. Surgical resection should include the nipple-areolar complex with microscopically clear margins surrounding both the Paget disease and the associated malignancy. Whole-breast radiotherapy is delivered with standard techniques. Management of regional nodes and the risk of systemic disease are dictated by the associated malignancy.

DUCTAL CARCINOMA IN SITU

Clinical Presentation and Epidemiology

DCIS is a neoplastic process that is confined to the ductal system of the breast and lacks histologic evidence of invasion. These cells neither disrupt the basement membrane nor involve the surrounding breast stroma. This entity lacks the ability to metastasize and is confined to the breast.[67-70] Axillary node involvement is rare (0%-5%) and most likely is associated with an undetected focus of invasive carcinoma.[71] Risk factors for the development of DCIS are the same as those identified for invasive carcinoma,[17] including family history, reproductive events such as delayed age of first live birth and nulliparity, history of benign breast biopsy, and dietary factors such as alcohol consumption. Before the use of screening mammography, DCIS typically presented as a palpable mass or nipple discharge. An invasive component commonly was found, and pure DCIS rarely was encountered. The widespread use of mammography now routinely detects DCIS smaller than 1 cm in diameter and results in breast cancer–free survival rates that approach 100%.[71]

With the increased use of mammography and as pathologists began to recognize DCIS as a pathologic entity, the incidence of DCIS has markedly increased.[72-74] The incidence of DCIS in the United States rose from 4,800 cases in 1983 to more than 50,000 cases in 2004, representing a 10-fold increase in only 20 years.[75] Of the close to 300,000 new breast cancers that occur annually, approximately 65,000 are anticipated to be noninvasive, of which 85% will be DCIS.[76] Of these, 90% are expected to be nonpalpable.[45] Studies have shown that the rate of screen-detected DCIS increases with age despite that it accounts for a progressively smaller proportion of the total breast cancers detected.[77] The rate of DCIS detection has been reported to increase from 0.56 per 1,000 mammograms among women aged 40 to 49 years to 1.07 per 1,000 mammograms among women aged 70 to 84 years.[77]

Imaging

Ninety-five percent of new cases of DCIS present with mammographic abnormalities, of which microcalcifications are most typical.[78] Noncalcified mammographic abnormalities make up the remaining findings, with asymmetric densities identified in 10%, dominant masses in 8%, and abnormal galactograms (performed for evaluation of nipple discharge) in

6%. Amorphous, coarse, fine pleomorphic, and fine linear are all forms of calcifications that can be related to DCIS. Linear and segmental calcifications are considered suspicious distribution and can be associated with DCIS in up to 80% of cases.[79] Linear and branching calcifications are frequently associated with high-grade DCIS and necrosis, whereas fine and granular calcifications are associated more commonly with low-grade DCIS[80-83] (Figure 61.1A,B).

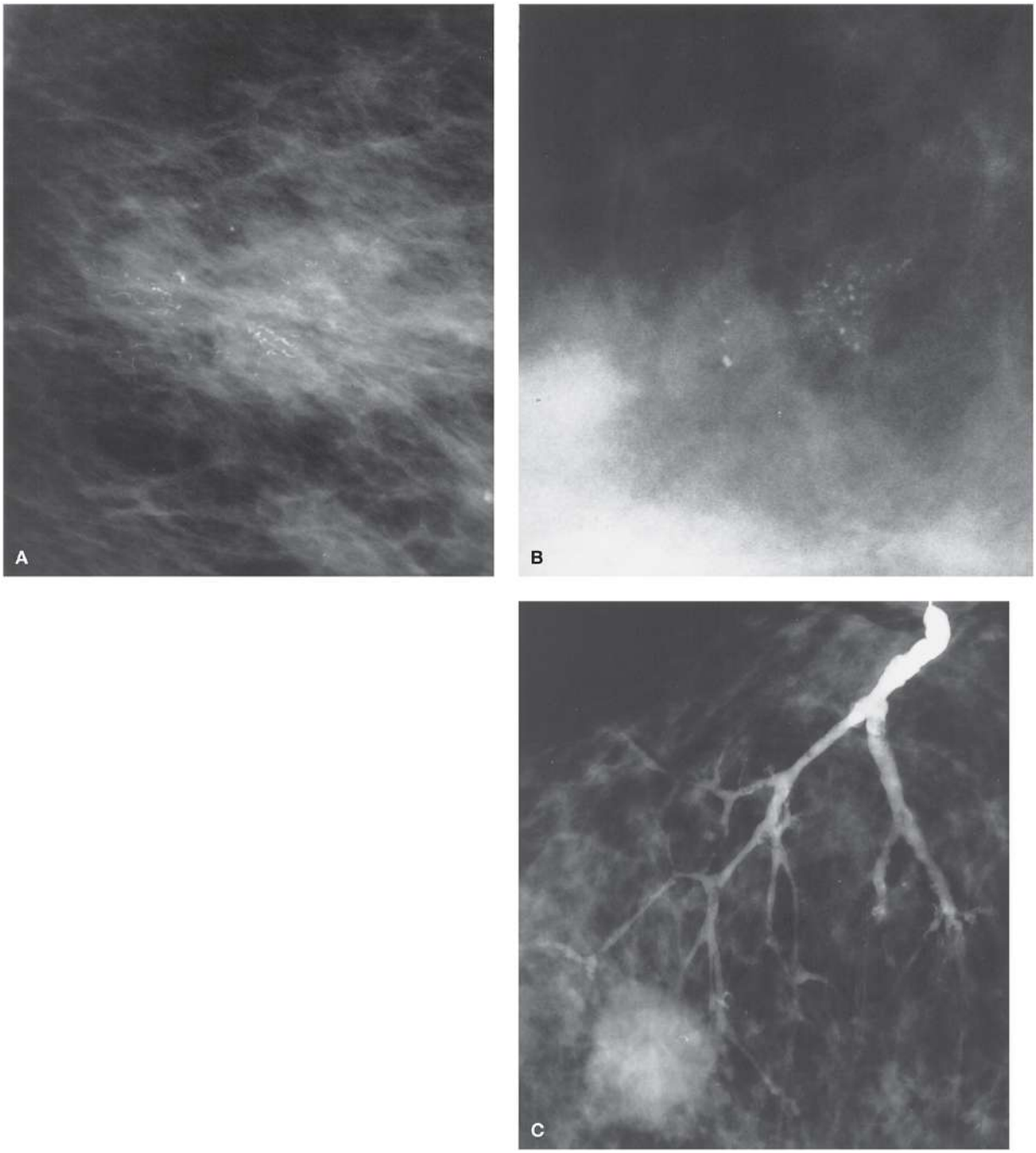

FIGURE 61.1 A. Linear and branching calcifications frequently associated with high-grade ductal carcinoma in situ (DCIS). B. Fine and granular calcifications commonly associated with low-grade DCIS. C. Galactogram with the multiple filling defects associated with DCIS.

Initial evaluation should include magnification views that allow for complete characterization of mammographic findings and determination of the need for biopsy. The extent of the lesion as determined

mammographically may be used as a guide for excision; however, the size is typically underestimated by 1 to 2 cm when compared with pathologic measurements.[81,84,85] Prior to 2000, MRI was not considered a useful imaging modality for DCIS. However, change in MRI imaging acquisition and an improved understanding of non–mass-like malignant lesion imaging characteristics now has MRI considered a valuable imaging tool for DCIS.[86] MRI now presents as the imaging modality with the highest sensitivity to detect DCIS, particularly high-grade DCIS. MRI has additionally been shown to better establish the extent of DCIS, thus aiding treatment planning.[87] In cases that present with nipple discharge and a negative mammogram, galactography may be helpful in determining the likelihood of underlying DCIS versus papilloma[88] (Figure 61.1C).

Pathology and Biology

The histologic diversity of DCIS can lead to difficulty in distinguishing it from other pathologic entities.[69,70] The spectrum of DCIS extends from noncomedo, low-grade DCIS that can be similar in appearance to atypical ductal hyperplasia to comedo, high-grade DCIS. In addition, DCIS can extend into lobules, making it difficult to distinguish from LCIS.[89] Traditionally, classification of DCIS has followed its architectural or morphologic appearance. The five subtypes of DCIS are comedo, solid, cribriform, micropapillary, and papillary,[69,70,90] and it is common to encounter a mixture of subtypes within the same specimen.[88] The characteristic features of each type are shown in Figure 61.2. Less common subtypes have been described and include apocrine, neuroendocrine, signet cell cystic hypersecretory carcinoma, and clinging DCIS.[91]

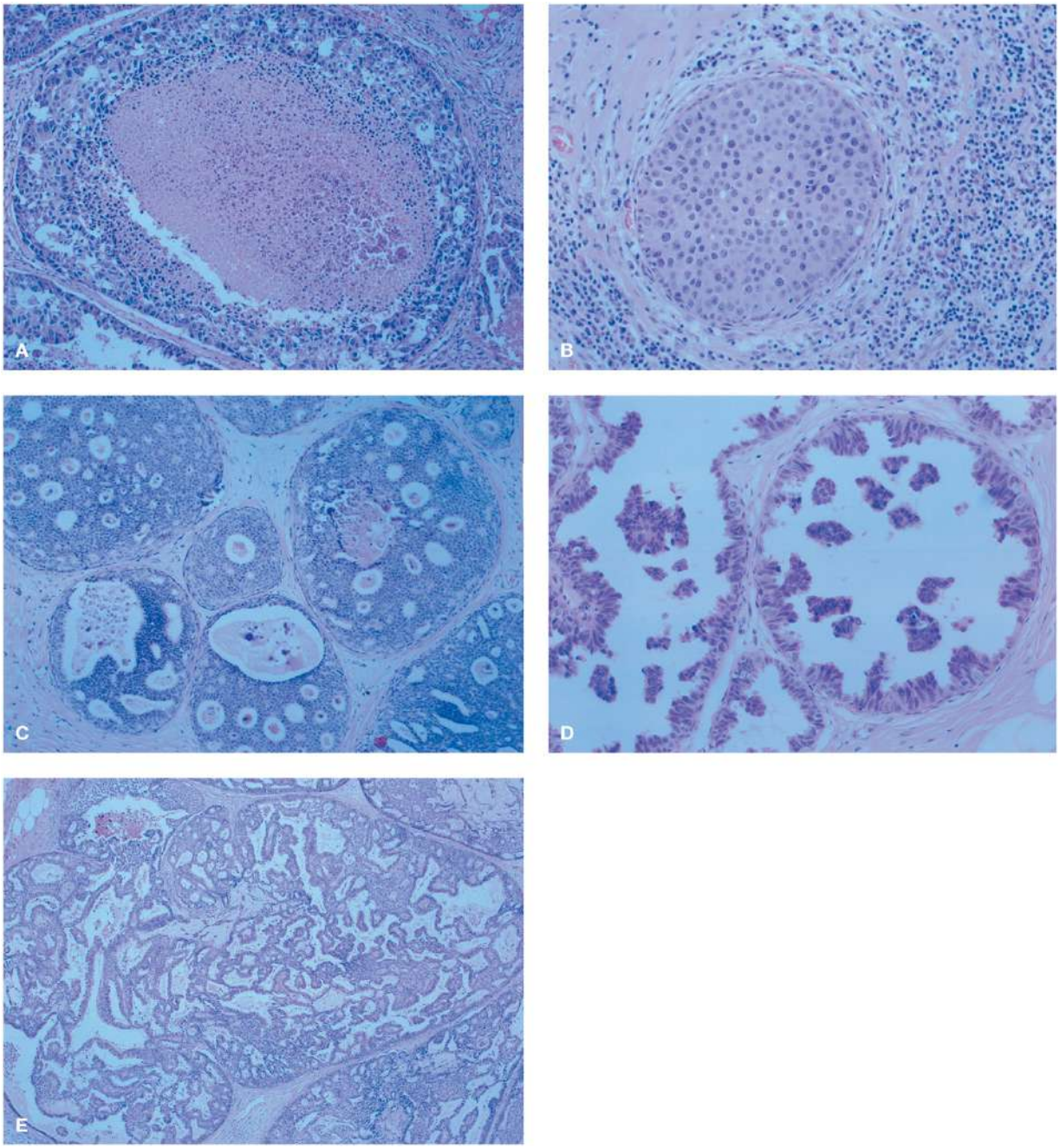

FIGURE 61.2 A. Comedo ductal carcinoma in situ (DCIS) characterized by central necrosis, large cells, and poorly differentiated nuclei. B. Solid DCIS characterized by ductal spaces filled with neoplastic cells with limited necrosis. C. Cribriform DCIS characterized by microlumens and fenestrations. D. Micropapillary DCIS characterized by intraluminal projections with no fibrovascular core. E. Papillary DCIS characterized by intraluminal projections with a fibrovascular core.

In 1997, a consensus conference committee was convened to reach an agreement on the pathologic classification of DCIS and the identification of

specific features that may convey prognostic significance.[68] Methods of processing and evaluating the pathologic specimen were also addressed. Rather than endorsing any specific classification system, the committee recommended and described features that should be documented for each case of DCIS, thus separating out important pathologic components and providing a comprehensive evaluation of the pathologic findings. These features include nuclear grade, the presence of necrosis, polarization, and architectural pattern(s). The committee extended its recommendations to include margin status, lesion size, extent of microcalcifications, and correlation between specimen x-ray and mammographic findings. The DCIS Working Party of the EORTC arrived at similar conclusions and emphasized the importance of cytonuclear and architectural differentiation.[92]

Three-dimensional examination and reconstruction techniques have resulted in a better understanding of the enormously complex structure of the mammary duct-lobular system and the patterns by which DCIS can spread within the breast[6,84,93] (Figure 61.3). Knowledge of the anatomy and distribution of DCIS within the mammary ductal tree can be useful in selecting patients for breast conservation and ensuring maximal surgical clearance of the lesion while preserving an acceptable cosmetic result. For example, Ohtake et al[6,84] studied the duct-lobular system with computer graphic reconstruction and found that the breast consists of 16 to 24 duct-lobular systems, each culminating in a corresponding collecting duct at the nipple. They also identified ductal anastomoses that established a connection between the various ductal-lobular units and provided a potential pathway for tumor extension and subsequent diffuse involvement.[6,84] Their proposed model for the development of widespread intraductal tumor extension within the breast is seen in Figure 61.4.

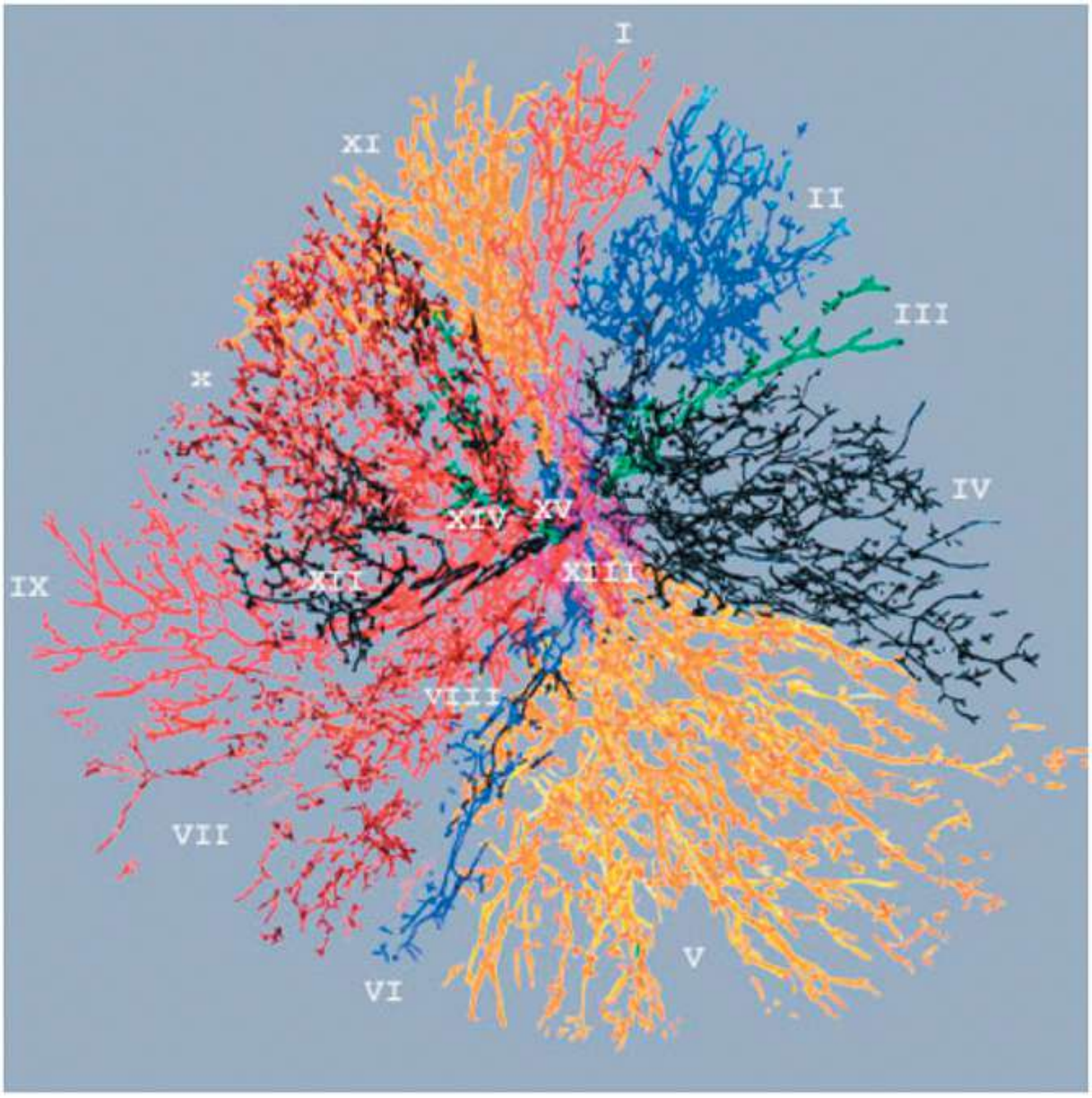

FIGURE 61.3 All ducts and their branches in an autopsy breast, viewed en face. Each Roman numeral refers to a different independent duct system. (From Going JJ, Moffat DF. Escaping from flatland: clinical and biological aspects of human mammary duct anatomy in three dimensions. *J Pathol*. 2004;203[1]:538-544. Copyright © 2004 Pathological Society of Great Britain and Ireland. Reprinted by permission of John Wiley & Sons, Inc.)

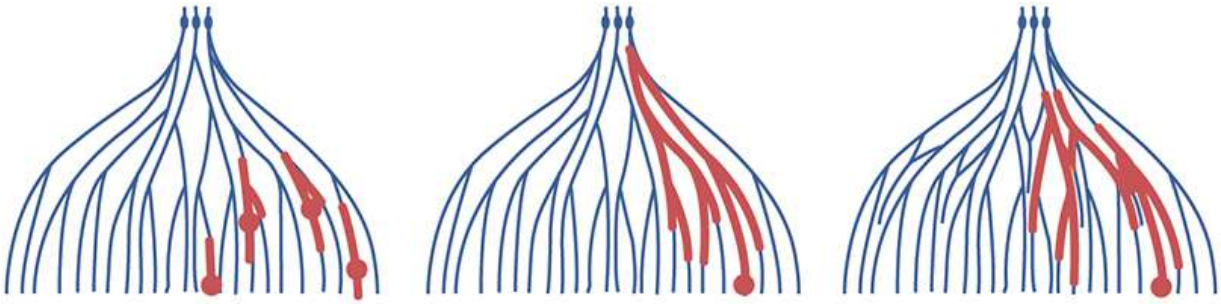

FIGURE 61.4 Models for the formation of widespread intraductal tumor extension over multiple mammary duct-lobular systems. Blue lines, normal mammary duct-lobular systems; red lines, intraductal tumor extension; closed circle, invasive tumor foci. Left: Multicentric development. Middle: Unicentric development with continuous intraductal tumor extension. Right: Unicentric development with continuous intraductal tumor extension through ductal anastomoses connecting adjacent duct-lobular systems. (From Ohtake T, Abe R, Kimijima I, et al. Intraductal extension of primary invasive breast carcinoma treated by breast-conservative surgery. Computer graphic three-dimensional reconstruction of the mammary duct-lobular systems. *Cancer*. 1995;76[1]:32-45. Copyright © 1995 American Cancer Society. Reprinted by permission of John Wiley & Sons.)

Faverly et al[94] have described the DCIS growth pattern within the ductal tree and the implications for surgical excision. The growth patterns documented include unicentric (one area only), multicentric (two distinct areas separated by >4 cm), continuous (extension along ductal system without gaps), and discontinuous or multifocal (two or more areas separated by <4 cm). They found that in mammographically detected DCIS, a multicentric growth pattern was rare (<2%), with most cases showing an even distribution between discontinuous and continuous growth patterns. Of cases with a discontinuous growth pattern, 63% had foci separated by gaps that measured under 5 mm, 83% had foci separated by less than 10 mm, and only 8% had foci separated by more than 10 mm. There was a correlation between differentiation and growth pattern such that 90% of poorly differentiated DCIS showed a continuous growth pattern, whereas 70% of well-differentiated DCIS had a discontinuous growth pattern. Based on these findings, the authors concluded that a 1-cm margin of normal tissue around the lesion would lead to complete surgical clearance of histologically evident DCIS in 90% of cases. DCIS is a precursor lesion to invasive ductal carcinoma and exists along an evolutionary continuum that starts with benign breast tissue and ends with an invasive breast carcinoma.[95] This concept has been validated in several ways. For years,

pathologists have recognized and documented confirmation of a histologic progression from benign breast cells to invasive breast cancer. The evolutionary concept is supported by the recognized association between the presence of DCIS and the subsequent increased risk of developing an invasive breast cancer.[75,96,97] In some series, a 10-fold risk of developing an invasive lesion has been reported. At the biologic and molecular levels, many studies have demonstrated that DCIS and invasive breast cancer are highly similar at the cellular and molecular levels.[95,98-102] These similarities have now been shown to extend to global gene expression profiles as DCIS has been classified under luminal, basal, and erbB2 intrinsic molecular subtypes.[98,103] In addition, these shared identical genetic abnormalities between DCIS and synchronous invasive breast cancer demonstrate a clonal relationship of biologic progression.[75,96,97,104] The biologic evolution from benign breast cells to invasive breast cancer occurs through highly diverse genetic mechanisms.

Genetic and molecular differences have been documented that differentiate DCIS from normal breast tissue. Genetic alterations have been evaluated with an analysis of loss of heterozygosity that has demonstrated gain or loss of multiple loci.[96,97,104-106] Loss of heterozygosity is not seen in normal breast tissue. The frequency of loss of heterozygosity correlates with histologic progression of breast tissue from benign to malignant. Loss of heterozygosity is seen in approximately 50% of atypical ductal hyperplasia. Among specimens harvested from cancerous breasts, 77% of noncomedo and 80% of comedo DCIS lesions share loss of heterozygosity with the synchronous invasive lesion in at least one locus.[104]

Molecular markers have been studied in DCIS and are found to have a heterogeneous distribution of expression.[75] The estrogen receptor is present in 70% of DCIS; however, the rate of expression is higher in low-grade lesions (90%) than in high-grade lesions (25%). This association with histologic grade is reversed for the rate of overexpression of HER2/neu proto-oncogene and the p53 tumor suppression gene. Approximately 50% of all DCIS lesions have overexpression of HER2/neu, and in 25%, the p53 tumor suppressor gene is also detected. Both of these molecular markers are noted in less than 20% of low-grade lesions but are present in approximately two-thirds of high-grade lesions.

Alterations in the surrounding breast parenchyma may also be seen with DCIS. High-grade DCIS, in particular, has been associated with the breakdown of the myoepithelial cell layer and basement membrane surrounding the ductal lumen,[107] proliferation of fibroblasts, lymphocyte infiltration, and angiogenesis in the surrounding stromal tissues.[108,109] Whether these stromal changes reflect important steps that facilitate primary tumor transformation or secondary alterations in response to ductal epithelium that is being transformed is unknown. Quantitative changes in the expression of genes related to cell motility, adhesion, and extracellular matrix composition—all of which may be related to the acquisition of invasiveness—occur as DCIS evolves into invasive carcinoma.[110]

Data suggest that DCIS represents a stage in the development of breast cancer in which most of the molecular changes that characterize invasive breast cancer are already present, although the lesion has not yet assumed a fully malignant phenotype. A final set of events, which probably includes gain of function by malignant cells and loss of function and integrity by surrounding normal tissues, is associated with the transition from a preinvasive DCIS lesion to invasive cancer. Most, if not all, clinically relevant features of breast cancer, such as hormone receptor status, the level of oncogene expression, and histologic grade, are probably determined by the time that DCIS has evolved.[111-114]

An occult microinvasive tumor (one that does not exceed 0.1 cm in diameter) may be seen with some cases of DCIS. Such cases are classified as *microinvasive breast cancer*[115] and are generally treated according to the guidelines for invasive disease. Occult microinvasive tumors are most common in patients with DCIS lesions that are more than 2.5 cm in diameter,[116] those presenting with palpable masses or nipple discharge, and those with high-grade DCIS or comedonecrosis.[88,117]

Natural History of Ductal Carcinoma In Situ

The overall incidence of DCIS in the general population is unclear. In an attempt to address this incidence, a small number of autopsy studies have been reported. One series examined 185 randomly selected breasts from 101 women in which a subgross sampling technique was used,[118] and one or more foci of DCIS were found in 6% of cases. A review of seven autopsy

series of women not known to have breast cancer during life showed a median prevalence of DCIS of 8.9% (range, 0%-14.7%).[119] The fact that some autopsy series document a greater incidence of DCIS in asymptomatic women than most clinical series suggests the possibility that DCIS is either underdiagnosed or that many cases are not clinically significant.

A primary consideration in the natural history of DCIS is the risk of progression to invasive carcinoma. The published evidence on the clinical course of untreated DCIS is sparse because it has been recognized as a distinct entity for only a relatively brief period, having been considered rare before the widespread use of mammography and having been treated most frequently by mastectomy. Those cases for which long-term follow-up data are available were grossly palpable DCIS—a form that may not be equivalent to the mammographic DCIS that is seen more commonly today. The few published long-term follow-up studies of DCIS after only biopsy document an overall incidence of subsequent invasive carcinoma of over 36%.[7,120-122] Most of these subsequent malignancies occur within 10 years, although as many as one-third may develop after 15 years.[7,120]

Women with DCIS in one breast are at risk for a second tumor (either invasive or in situ) in the contralateral breast[123]; the rate at which such tumors develop is similar to that among women with primary invasive breast cancer at approximately 0.5% to 1% per year.

DCIS is a part of the breast/ovarian cancer syndromes defined by BRCA1 and BRCA2, with mutation rates similar to those found for invasive breast cancer.[124] These findings suggest that patients with DCIS with an appropriate personal or family history of breast and/or ovarian cancer should be screened and followed according to the same high-risk protocols as developed for invasive breast cancer.

Treatment Options for Ductal Carcinoma In Situ

Prognostic Factors and Their Interpretation

The goal of treatment with DCIS is prevention of local recurrence, with particular emphasis on the prevention of invasive breast cancer. Treatment decisions are largely based on information provided by mammography and, most especially, pathologic evaluation of the biopsy specimen. As such, in the consideration of treatment options, it is important for the clinician to be

aware of some of the technical limitations associated with the clinical and histopathologic assessment of DCIS.

Studies performed during the past two decades clearly have suggested that DCIS is not a single disease. Rather, DCIS encompasses a diverse group of lesions that differ with regard to their clinical presentation, mammographic features, extent and distribution within the breast, histologic characteristics, and biologic markers. Moreover, clinical follow-up studies have indicated that these lesions vary in their propensity to recur or progress to invasive breast cancer. As a consequence, a significant proportion of patients diagnosed with DCIS can be treated adequately with breast-conserving therapy (ie, excision with or without radiation therapy). Which patients with DCIS can be treated safely with excision alone and which patients require radiation therapy after excision are pressing clinical questions. Attempts to resolve this issue have focused on the identification of risk factors for local recurrence after breast conservation therapy for DCIS. Through multiple retrospective studies, several factors have been identified that may be important in defining local failure risk. These include symptomatic presentation,[125,126] lesion size,[126,127] histopathologic subtype,[125] nuclear/cytologic grade,[126,128,129] central necrosis,[126,128,129] margin status,[126,130,131] and patient age.[125,131-133]

The relative importance of any histopathologic factor in predicting the probability of local recurrence and in turn selecting the appropriate therapeutic option for a given patient is unclear. This is partly the result of the inherent difficulty associated with the establishment of standardized and reproducible systems of pathologic classification, including such apparently straightforward assessments of grade, margin width, and lesion size.

Efforts to classify DCIS have been based primarily on the nuclear grade of the lesion and/or the presence or absence of necrosis. Several studies have shown that there is an association between high nuclear grade and/or necrosis and the risk of local recurrence and progression to invasion.[126,128,129] Although the criteria for histologic grading systems have been published, there are limited data regarding the ability of pathologists to apply them in a reproducible manner.

Several studies have shown that the status of the microscopic margins appears to be important in predicting the likelihood of recurrence in the breast for patients with both invasive breast cancer and DCIS treated with

breast- conserving therapy.[126,130,131] In 2016, a consensus guideline was published from the Society of Surgical Oncology, the American Society for Radiation Oncology, and the American Society of Clinical Oncology (ASCO) on appropriate margins for breast-conserving surgery with whole-breast radiation in DCIS.[134] The consensus panel recommended a 2-mm margin as the standard adequate margin and clinical judgment be used to determine the need for further surgery in patients with negative margins of less than 2 mm. However, there are numerous technical problems in the evaluation of margins of breast excision specimens. First, if a specimen is removed in more than one fragment, the margins cannot be evaluated. Second, there is no standardized method for sampling or reporting margins, and this process is subject to sampling error. Finally, it is often difficult to provide an accurate assessment of the margin width for patients who undergo a reexcision because the initial biopsy site can be eccentrically located in the surgical specimen. Furthermore, the group at MD Anderson analyzed the contemporary outcomes of women with DCIS managed with breast conservation surgery with or without adjuvant radiation therapy and the impact of margin width. Over 1,500 women were identified with a median follow-up of 8.9 years. The researchers found no difference in 10-year locoregional recurrence rates (LRRs) in patients who underwent radiation therapy with or without margins larger than 2 mm (4.8% vs 3.3%); however, in women who did not undergo adjuvant radiation therapy, there was a significant difference in 10-year LRR (5.4% vs 30.9%) in favor of wide negative margins.[135]

Most DCIS lesions present as a nonpalpable, grossly inapparent mammographic abnormality, which can make accurate determination of the size or extent of the lesion difficult (Figure 61.5). The modalities available to assess the size of the lesion are mammography, MRI, and pathologic examination. Mammography frequently will underestimate the pathologic extent of DCIS, particularly for well-differentiated lesions in which substantial areas of the tumor may not contain microcalcifications. MRI has been demonstrated to more accurately estimate the disease extent; however, it should be recognized that pathologic assessment of lesion size can be difficult. Macroscopic examination of a specimen containing DCIS rarely reveals a grossly evident tumor that can be measured. Therefore, the

assessment of the size of the lesion must be estimated from histologic sections.

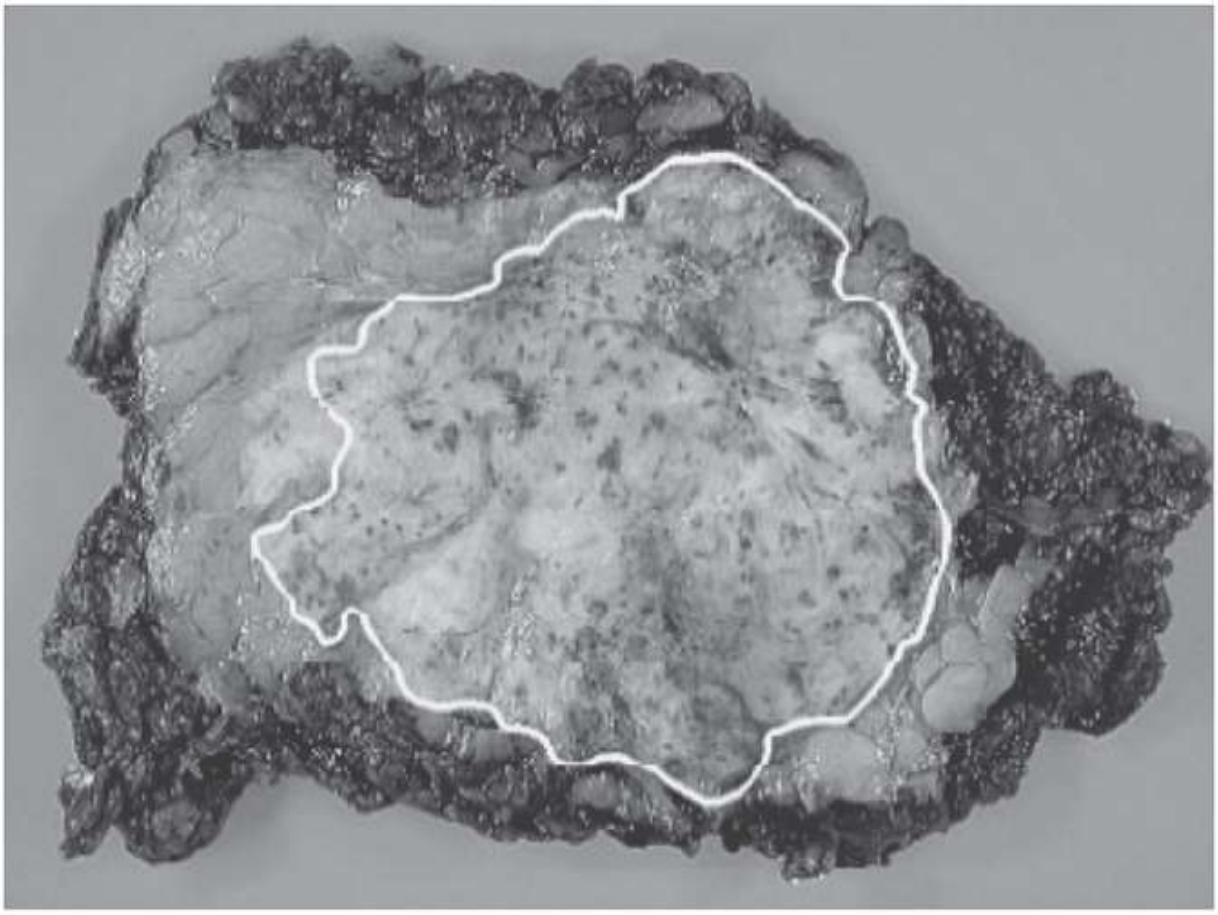

FIGURE 61.5 Extensive ductal carcinoma in situ (DCIS) in a mastectomy breast sectioned in the coronal plane. Every parenchymal structure (duct or lobule) within the marked perimeter is colonized by DCIS; outside that boundary there is none. (From Going JJ, Moffat DF. Escaping from flatland: clinical and biological aspects of human mammary duct anatomy in three dimensions. *J Pathol*. 2004;203[1]:538-544. Copyright © 2004 Pathological Society of Great Britain and Ireland. Reprinted by permission of John Wiley & Sons, Inc.)

Mastectomy for Ductal Carcinoma In Situ

Mastectomy was the standard treatment of DCIS through the first four decades of its recognition as a distinct histopathologic entity. Mastectomy is a highly effective treatment for DCIS, with a locoregional control rate of 96% to 100% and cancer-specific mortality rates of 4% or less.[37] No randomized study has compared mastectomy with breast conservation

treatment for DCIS. Therefore, the relative outcomes for mastectomy and breast conservation treatment can be estimated only by reviewing nonrandomized, retrospective studies. Local treatment failure after mastectomy[136] may occur because of unrecognized invasive carcinoma that results in local recurrence or distant metastasis, or it may be the result of incomplete removal of breast tissue with the subsequent formation of a new primary tumor.

Data from some surgical trials[137] and large treatment registries[138] suggest that the rates of local or regional recurrence are significantly lower after mastectomy than after breast-conserving surgery, although there have been no significant differences in overall survival. Metastatic breast cancer can follow the recurrence of an invasive tumor or the development of invasive cancer in the contralateral breast. However, death related to breast cancer within 10 years after the diagnosis of DCIS occurs in only 1% to 2% of all patients, irrespective of whether mastectomy or breast-conserving surgery was performed.[138]

The role of postmastectomy chest wall radiation following mastectomy or skin-sparing mastectomy and close pathologic margins has been debated in the literature but is not presently considered the standard of care. Some studies show an increased risk of chest wall failure in selected cases of high-grade DCIS undergoing mastectomy with pathologic margins smaller than 1 mm, leading to a routine recommendation of postmastectomy radiation in these cases.[139] The empiric use of a close or positive margins as a trigger for postmastectomy radiation has been challenged, providing a strong argument against postmastectomy radiation.[140] This retrospective review evaluated the risk of chest wall recurrence following mastectomy, specifically looking at skin-sparing mastectomy and high-risk features of high-grade and close margins. In this series, the overall risk of chest wall recurrence was rare at 1.7% and only 3.3% for high-grade DCIS. Margins less than 5 mm were not at increased risk. It was concluded that the chest wall failure rate was sufficiently low that a routine recommendation of postmastectomy radiation DCIS with high-risk features was not warranted. Furthermore, a population-based analysis using the Ontario Cancer Registry identified more than 1,500 women with DCIS who underwent mastectomy without radiotherapy. With a median follow-up of 10 years, the overall rate of chest wall recurrence was 2.3% with no significant difference seen

between positive, close (2 mm or less), or negative margins. Univariate and multivariate analysis failed to show a significant effect of age, nuclear grade, necrosis, or multifocality.[141]

Recent interest has surged regarding active surveillance in women with low-risk DCIS. The COMET trial is comparing guideline concordant care, which includes surgery with or without radiation therapy and choice of endocrine therapy versus active surveillance with choice of endocrine therapy in women aged 40 years or above, with a diagnosis of grade I/II DCIS with estrogen and/or progesterone receptors present and lack of comedonecrosis. Primary end point is rate of ipsilateral invasive disease development at 2 years. Three additional trials, LORIS of the United Kingdom (completed accrual in 2020), LORETTA from Japan, and LORD sponsored by the EORTC continue accrual with similar randomizations.

Breast Conservation for Ductal Carcinoma In Situ

Four prospective randomized studies of excision only versus excision plus breast irradiation for DCIS have been performed with reported results, and all have shown that the rate of local recurrence was reduced with the addition of radiation (Table 61.1). The NSABP B-17 trial[142,143] consisted of 813 patients who were stratified by age (≤49 vs >49 years), DCIS versus DCIS plus LCIS, method of detection, and whether an axillary dissection was performed. Tumor size was determined by mammogram, gross pathologic measurement, or clinical examination. Of the patients enrolled, 83% had nonpalpable tumors. The 17.5-year rate of local recurrence was 19.8% with radiation and 35.9% without radiation. The average annual incidence rates of ipsilateral noninvasive recurrences and ipsilateral invasive recurrences were reduced with breast irradiation by 47% and 52%, respectively.[144] An analysis of clinical variables showed that microcalcifications extending beyond a maximum dimension greater than 1 cm were associated with an elevated risk of breast recurrence. A central pathology review was performed, including a multivariate analysis of histopathologic variables (Table 61.2). Comedonecrosis in patients treated on NSABP B-24 did not correlate with an increased risk of IBTR; however, comedonecrosis did relate to the risk of DCIS-IBTR. The prognostic value of margin status (free vs unknown/involved) depended on the treatment

group and was greater among those treated with lumpectomy and radiotherapy alone as compared to those who also received tamoxifen.[132,143,144]

TABLE 61.1 LUMPECTOMY VERSUS LUMPECTOMY AND WHOLE-BREAST RADIOTHERAPY: RANDOMIZED CLINICAL TRIALS FOR DUCTAL CARCINOMA IN SITU

Trial Group	Number of Patients	Follow-Up	Local Recurrence (Cumulative %) DCIS + Invasive Carcinoma		
			L	L + XRT	*P* Value
NSABP B-17	818	12-y actuarial 17.25-y median	31.7 35.0	15.7 19.8	<.000005 –
EORTC 10853	1,010	15.7-y median	31.0	18.0	<.0001
UK/ANZ	1,030	12.7-y median	19.4	7.1	<.00001
SweDCIS	1,046	17-y mean	32	20	–

DCIS, ductal carcinoma in situ; EORTC, European Organization for Research and Treatment of Cancer; L, lumpectomy; L + XRT, lumpectomy and postoperative radiotherapy; NSABP, National Surgical Adjuvant Bowel and Breast Project; SweDCIS, Swedish Breast Cancer Group DCIS study; UK/ANZ, United Kingdom, Australia, and New Zealand.

TABLE 61.2 HAZARD RATIOS FOR INVASIVE IPSILATERAL BREAST TUMOR (I-IBTR) RECURRENCE OR DUCTAL CARCINOMA IN SITU (DCIS-IBTR) BASED ON COMEDONECROSIS AND MARGIN STATUS

Histopathologic Variable	I-IBTR HR (95% CI)	DCIS-IBTR HR (95% CI)
Comedonecrosis		
Absent	1.00	1.00
Present	0.87 (0.62-1.21) $P = .41$	2.21 (1.52-3.2) $P \leq .001$
Margin status		
LRT, margin free	1.00	1.00
LRT, involved/uncertain	2.61 (1.68-4.05) $P \leq .001$	1.65 (1.00-2.73) $P = .05$
LRT + TAM, margin free	1.00	1.00
LRT + TAM, involved/uncertain	1.27 (0.73-2.20) $P = .40$	1.32 (0.77-2.28) $P = .31$

CI, confidence interval; DCIS-IBTR, ductal carcinoma in situ in-breast tumor recurrence; HR, hazard ratio; I-IBTR, ipsilateral in-breast tumor recurrence; LRT, lumpectomy + radiotherapy; NSABP, National Surgical Adjuvant Breast and Bowel Project; TAM, tamoxifen.

Adapted from Wapnir IL, Dignam JJ, Fisher B, et al. Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. *J Natl Cancer Inst*. 2011;103(6):478-488. Reproduced by permission of Oxford University Press.

The EORTC 10853 trial[145,146] randomly allocated 1,010 patients with 5 cm or smaller DCIS and negative margins to excision versus excision plus breast irradiation. Lesions were nonpalpable in 79% of patients, and the mean maximal tumor diameter was approximately 2 cm. The 15-year rate of local recurrence was 18% for patients treated with radiation, as compared with 31% for patients treated without radiation ($P < .0001$). At a median follow-up of 15.7 years, radiation therapy resulted in risk reduction for both invasive and noninvasive breast relapse of 48%. As with the NSABP B-17 study, a central pathology review was performed.[125,145,146] In a multivariate analysis, factors associated with an increased risk of local recurrence were no older than 40 years of age, clinically symptomatic presentation (nipple discharge or palpable mass), intermediate or poorly differentiated DCIS, solid/comedo and cribriform histologic growth pattern, involved or uncertain margins, and treatment by local excision alone. The risk of DCIS recurrence was documented to be less following treatment of clinging/micropapillary DCIS; however, in this group, breast irradiation reduced the rate of invasive recurrence in over 50%. Although early publications suggested a relationship between histologic type and risk of distant metastasis and death, with additional follow-up, no statistically significant relationship is now appreciated.

The EORTC 10853 trial did not allow the identification of an appropriate margin width for treatment with or without radiotherapy because the eligibility criteria did not require reporting of the margin status. Nonetheless, the central review of cases did provide some information regarding the relative importance of surgical margin as related to local failure risk. A recurrence rate of 24% at 4 years was observed in cases with close/involved margins after excision alone. Radiotherapy was not adequate to compensate for involved margins because even with the application of

irradiation, the recurrence rate was 20% in this group.[147] These data and others[126,127,130,131] are strongly suggestive that obtaining a microscopic complete excision is essential for optimal local control in breast- conserving therapy for DCIS. Of further note, even in the group of DCIS cases for which margins could be considered optimal (ie, those patients who underwent a surgical reexcision in which no residual DCIS was found), a 4-year local recurrence rate of 18% was observed when these patients were treated with surgery alone.[125]

The United Kingdom, Australia, and New Zealand (UK/ANZ) DCIS trial was a randomized trial investigating the role of adjuvant radiotherapy.[148,149] With a 2 × 2 factorial protocol design, the aim of this study was to compare excision alone versus excision plus tamoxifen versus excision plus radiotherapy versus excision plus radiotherapy and tamoxifen. Tamoxifen was prescribed at 20 mg/day, and radiotherapy was delivered through whole-breast tangential fields to a total dose of 50 Gy. A boost was not recommended, and elective decision to withhold or provide one of the treatments was permitted. Data have been reported with a median follow-up of 12.7 years. The addition of radiotherapy was demonstrated to reduce the risk of IBTR. Of the 1,030 patients randomized between no radiotherapy versus radiotherapy, ipsilateral IBTR was 19.4% versus 7.1%, respectively ($P < .0001$). The addition of tamoxifen offered no benefit toward overall ipsilateral local control when administered in addition to radiotherapy; however, tamoxifen reduced the ipsilateral recurrence rate of DCIS (but not invasive carcinoma) in the absence of radiotherapy.[148,149]

The Swedish Breast Cancer Group SweDCIS study was a randomized trial that enrolled 1,067 patients from 1987 to 1999, with 1,046 of these patients followed for a median of 17 years. Patients were randomized between lumpectomy followed by radiotherapy and lumpectomy only for the treatment of DCIS.[150] Following sector resection, microscopically clear resection margins were not required, and 50 Gy in 25 fractions to the whole breast was delivered in the majority of patients. A split course, 54 Gy in 2 Gy fractions, delivered in two treatment series separated by a 2-week break was allowed. No boost dose was delivered. The in-breast failure risk reduction for the addition of radiotherapy was 12% at 20 years (95% confidence interval [CI] 6.5%-17.7%) with a relative risk reduction of 37.5% (95% CI 0.30-0.54). Detailed analysis did not identify any patient or

tumor characteristic subgroups, which did not benefit from the addition of postoperative radiotherapy. In addition, despite combining factors entailing a low risk of recurrence without radiotherapy, a low-risk group without significant benefit from the addition of radiotherapy could not be identified.

A meta-analysis was completed utilizing the individual patient data from each of the four randomized trials discussed above, and an overview of results was reported by the Early Breast Cancer Trialists' Collaborative Group.[151] With a total of 3,729 women eligible for analysis, it was demonstrated that radiotherapy reduced the absolute 10-year risk of any ipsilateral breast event (recurrent DCIS or invasive disease) by 15.2% (standard error 1.6%, 12.9% vs 28.1%, $P < .00001$). This analysis further establishes strong and consistent evidence that the addition of radiotherapy following breast- conserving surgery for DCIS approximately reduces the risk of IBTR by 50%. Subgroup analyses from these randomized trials have demonstrated that the absolute benefit of radiotherapy is greater in women at increased risk for tumor recurrence, such as women with involved surgical margins (identified on retrospective pathologic review), younger women, and those with tumors that have high-grade or comedonecrotic features.[125,142,143,145,151] However, this meta-analysis confirmed that no matter what the underlying rate of ipsilateral IBTR was within subgroups evaluated, the risk reduction of approximately 50% remained. This was demonstrated across categories defined by patient age, type of excision, use of tamoxifen, method of detection, margin status, tumor focality, and histologic or nuclear grade. There was little impact of radiotherapy on contralateral or distant events, and a difference in the risk of death from breast cancer was not appreciated.

Patient age is an important prognostic variable for local recurrence after breast conservation for DCIS.[125,131-133] In younger patients, DCIS more frequently contains adverse pathologic features and extends over a greater distance in the breast than in older patients.[133] In series with adequate follow-up, younger patients treated with lumpectomy and radiation therapy had a significantly higher rate of local recurrence than older patients, especially invasive local recurrences.[133] Some studies have suggested that careful attention to margin status and excising larger volumes of tissue can reduce this difference substantially.[131,133] No available data show that younger patients have better long-term cancer-free survival rates if treated

by mastectomy rather than lumpectomy and radiation therapy. Successful treatment of younger patients with DCIS with lumpectomy and radiation therapy requires careful attention to patient evaluation, selection, and surgical technique. When this is done, age at diagnosis should not be a contraindication to breast-conserving therapy.

The randomized trials discussed were designed and conducted over a decade ago. Since then, imaging technology, surgical techniques, and pathologic evaluation have continued to advance, suggesting that the patients encountered with DCIS presently may represent a group of patients with smaller, less extensive disease that is better surgically cleared as compared to those included in the randomized trials. As a result, the value of adjuvant radiotherapy has been hypothesized to be lower than indicated in previous trials. However, it should be noted that the tumor characteristics of those included in the randomized trials represented limited and mammographically detected disease. Despite this, several recent studies have attempted to identify and treat patients with highly selected favorable tumor characteristics with excision alone (ie, without whole-breast irradiation) and report 10-year local failure rates of 3% to 25%.[130,136] One of these studies[127] has proposed a scoring system using histopathologic features including tumor size, grade, and margin width in an attempt to stratify patients according to local failure risk after excision plus or minus whole-breast irradiation. Each variable was assigned a score of 1 to 3, and the sum total defined the Van Nuys Prognostic Index. Although appealingly simple, this schema[127] is drawn from the retrospective analysis of a patient cohort in which there existed several methodologic shortcomings, and it has not been independently validated.[152]

The Radiation Therapy Oncology Group (RTOG) published the results of a prospective randomized trial of 585 women who were defined as having good-risk DCIS (low or intermediate grade, <2.5 cm size primary, and ≥3 mm margins) treated with adjuvant whole-breast irradiation (50.4 Gy in 28 fractions and later amended to allow 42.5 Gy in 16 fractions without a boost) or observation. The use of tamoxifen was optional. The study was closed early because of low accrual (expected accrual 1,790). With a median follow-up of >7 years, the rate of local failure was 6.7% and 0.9% for the observation and radiation groups, respectively. Grade 1 to 2 acute toxicity was higher in the external beam radiotherapy (XRT) arm, 76%

versus 30%, with no difference in grade 3 to 4 toxicity in either arm. Despite the lower than expected accrual in this good-risk population, adjuvant XRT improved local failure. Additional follow-up is needed to determine long-term benefits.[153]

McCormick et al[154] performed a prospective study that attempted to identify patients with "low-risk" DCIS who can be spared whole-breast radiation therapy. This trial enrolled 158 patients with lesions that were mostly grade 1 or 2 and with a mammographic extent of no more than 2.5 cm who were treated with wide excision, with final margin 1 cm or more or a reexcision without residual DCIS. Tamoxifen was not permitted. The median age was 51 years. The most recent data, with a median follow-up of 11 years,[155] reported an estimated annual local recurrence percentage rate of 1.9%. Of those with an IBTR, 68% had a DCIS recurrence and 32% experienced recurrence with invasive carcinoma. These data provide prospective evidence that despite margin of more than 1 cm, the local recurrence rate is substantial, even in patients with small grade 1 or 2 DCIS following treatment with wide excision alone.

In an intergroup trial run by the Eastern Cooperative Oncology Group and North Central Cancer Treatment Group, wide excision only in a population of conservatively selected patients with DCIS was evaluated.[156,157] Eligibility included patients with low- or intermediate-grade DCIS measuring ≤2.5 cm (cohort 1, $n = 561$) or high-grade DCIS measuring no more than 1 cm (cohort 2, $n = 104$). Microscopic margin width was required to be at least 3 mm, with no residual calcifications on postoperative mammograms. Most of these patients had a more favorable profile than that reflected by the eligibility criteria with median lesion size of 6 and 7 mm for cohorts 1 and 2, respectively, and the majority having margins greater than 5 mm. The use of tamoxifen was optional after the year 2000, potentially impacting recurrence rates and/or time to recurrence intervals (30% and 24% for cohorts 1 and 2, respectively). With a median follow-up of 12.3 years, the 12-year rates of ipsilateral in-breast failure and invasive in-breast failure were 14.4% and 7.5%, respectively, for the low-intermediate group and 24.6% and 13.4%, respectively, for the high-grade group. Whether this identifies the low- intermediate grade group as a group that could avoid radiotherapy remains to be demonstrated, as this may represent a group with a delayed IBTR pattern, as no plateau was identified.

The NSABP and the RTOG published the results of a phase III accelerated partial-breast irradiation trial, which randomly allocated patients with early-stage breast cancer including DCIS between standard whole-breast irradiation following lumpectomy versus accelerated partial-breast irradiation. More than 4,200 women were enrolled, of which 24% had DCIS. Although the overall results did not meet the criteria for equivalence in part driven by the heterogeneous pool of patients, in a post hoc analysis, the 10-year cumulative incidence of IBTR for patient with DCIS was 6.5% versus 6.0% for whole-breast irradiation versus accelerated partial breast, with a hazard ratio of 1.01 (0.61-1.68).[158]

The value of a tumor bed boost was evaluated by the Breast International Group in association with the Trans-Tasman Radiation Oncology Group in women with non–low-risk DCIS, defined as having any of the following: age less than 50 years, symptomatic presentation, palpable tumor, microscopic tumor size 15 mm or larger, multifocal disease, grade 2 to 3, central necrosis, comedo histology, or surgical margins less than 10 mm. Patients underwent breast-conserving surgery with at least 1 mm negative radial margin followed by whole-breast radiation therapy (50 Gy in 25 fractions or 42.5 Gy in 16 fractions) with or without a tumor bed boost of 16 Gy in eight fractions. Over 1,600 patients were enrolled with a median follow-up of 6.6 years. Local recurrence was significantly lower in the boost versus no boost arm (2.9% vs 7.3%). This was at the expense of significantly higher grade 2 breast pain and induration (14% vs 10% and 14% vs 6%).[159]

Follow-Up and Management of Recurrence

Ipsilateral tumor recurrences in patients with DCIS are usually detected on surveillance mammography, although one-quarter may be detected on the basis of changes on physical examination of the breast or chest wall.[160,161] For this reason, patients should be scheduled for a baseline mammogram 6 to 12 months after initial therapy and at least annually thereafter. Distant breast cancer metastases in the absence of regional recurrence are unusual. Local recurrences after breast-conserving surgery and radiotherapy are generally treated with mastectomy. Selected patients with local recurrences who have not previously received radiotherapy may be candidates for local

excision and radiotherapy. The clinical outcome of ipsilateral tumor recurrence is governed by the nature of the recurrence. Patients with recurrent DCIS have an excellent prognosis, with less than 1% risk of further recurrence after salvage mastectomy. Patients with invasive recurrence after breast-conserving surgery for DCIS have a prognosis similar to those with early-stage breast cancer, with a 15% to 20% risk of metastatic recurrence at 8 years.[161]

The Role of Tamoxifen and Aromatase Inhibitors for Ductal Carcinoma In Situ

The use of tamoxifen in the treatment of DCIS has been studied; however, results have been conflicting. Therefore, its role is not yet clearly defined. Preliminary results on the role of Her2Neu-targeted treatment were presented in the 2020 ASCO annual meeting. In the NSABP B-43 trial, patients with Her2Neu-positive DCIS were treated with post-lumpectomy radiotherapy and randomized between trastuzumab or observation, and 2014 women were included with 6.6-year median follow-up. Of the 114 IBTR, 63 occurred in the radiation-alone arm and 51 in the radiation plus trastuzumab, which was not statistically significant.[162] The NSABP B-24 trial[132,144] compared excision plus radiotherapy to excision, radiotherapy, and tamoxifen. Patients who received tamoxifen had a decreased incidence of breast cancer events (invasive or noninvasive ipsilateral or contralateral breast cancer) compared with patients who did not receive tamoxifen. With a median follow-up of 163 months, the addition of tamoxifen translated into a significant 32% reduction in invasive IBTR (9.0% vs 6.6%, $P = .025$), a nonsignificant 16% reduction in DCIS-IBTR (7.6% vs 6.7%, $P = .33$), and a 32% reduction in contralateral breast cancer (8.1% vs 4.9%, $P = .023$); however, no survival benefit was found (Table 61.3). Positive tumor margins were significantly associated with breast recurrence. The 15-year cumulative incidence of invasive IBTR was reduced from 17.4% in patients with positive margins to 11.5% with the addition of tamoxifen. In those with tumor-free margins, tamoxifen did not improve in-breast disease control with a 7.4% and 7.5% incidence of invasive IBTR with and without tamoxifen, respectively.

TABLE 61.3 TAMOXIFEN VERSUS NO TAMOXIFEN: RANDOMIZED CLINICAL TRIALS FOR DUCTAL CARCINOMA IN SITU

Trial Group	Number of Patients	Follow-Up	Local Recurrence (Cumulative %) DCIS + Invasive Carcinoma		
			− TAM	+ TAM	*P* Value
NSABP B-24	1,798	13.6-y median	16.6	13.2	–
UK/ANZ	1,053	12.7-y median	17.0	13.2	.04
No radiotherapy	523		2.6	2.4	.8
Radiotherapy					

DCIS, ductal carcinoma in situ; NSABP, National Surgical Adjuvant Bowel and Breast Project; TAM, tamoxifen; UK/ANZ, United Kingdom, Australia, and New Zealand.

In contrast to the findings of the NSABP B-24 trial, the UK/ANZ DCIS trial found that tamoxifen had no effect in reducing local recurrence rate when combined with whole-breast radiation therapy (Table 61.3). When used as a single agent without radiation therapy after lumpectomy, tamoxifen had no effect on the incidence of invasive recurrence but did show a statistically significant reduction in the risk of DCIS recurrence (10.4% vs 7.4%, $P = .04$).[148,149] As such, the role of tamoxifen for DCIS in the absence of whole-breast radiotherapy remains to be defined.

The role of tamoxifen versus anastrozole (an aromatase inhibitor) in the management of DCIS has been evaluated in the NSABP B-35 trial.[163] Eligibility included postmenopausal women with DCIS, with or without associated LCIS with estrogen- or progesterone-positive receptors who underwent lumpectomy with clear margins and adjuvant whole-breast radiation therapy. Patients were stratified by age less than 60 years versus 60 years or above. A total of 3,104 women were enrolled, with 3,084 women having a median follow-up of 9 years. Breast cancer–free interval improved with the use of anastrozole (7.8% vs 5.7%), with no significant difference in regard to the rates of in-breast recurrence, contralateral breast cancer, or distant disease. Improvement in disease-free survival was reported in women under the age of 60 years with the use of anastrozole compared to the tamoxifen arm (89.8% vs 85.7%). Except for higher rates

of thrombosis in the tamoxifen arm, no significant difference with regard to toxicity or treatment adherence was seen.[163] Because DCIS is a precursor to invasive breast cancer and shares many biologic features of invasive carcinoma, it is increasingly recognized as a target for preventive measures. In the largest trials of the prevention of primary breast cancer among women at high risk for breast cancer by virtue of age, family history, or prior benign breast disease, tamoxifen reduced the risk of DCIS by 50% to 70%.[40,164]

A Decision Tree for Ductal Carcinoma In Situ

The management of DCIS requires the coordinated, multidisciplinary interaction of radiologists, surgeons, pathologists, and oncologists. Patients are first assessed to determine if they are candidates for breast-conserving surgery. Women with multicentric DCIS, as defined by the presence of two or more tumors in separate quadrants of the breast, and those with extensive or diffuse DCIS or suspicious-appearing microcalcifications throughout the breast are candidates for mastectomy, as are women in whom negative margins or acceptable cosmesis cannot be achieved with the use of breast-conserving surgery. Some women may prefer mastectomy to breast conservation to minimize the chance of ipsilateral recurrence or for other reasons.

Patients deemed to be appropriate candidates for breast conservation require complete surgical excision of the affected area. The extent of DCIS in the breast and the existing margin determine the likelihood of identifying residual disease on reexcision. Nearly half of patients with margin <1 mm have residual DCIS on reexcision.[38]

Neither dissection of axillary lymph nodes nor mapping of sentinel lymph nodes is routinely warranted in patients with DCIS because of the very low incidence of axillary metastases.[165] Three to 13% of patients with DCIS, and a slightly greater percentage with DCIS and microinvasion, have isolated tumor cells in sentinel axillary lymph nodes.[166] The prognostic significance of these cells is not clear. Clinical experience suggests that patients have a much better outcome than would be predicted by such rates of nodal metastases, and in most instances, these represent micrometastases of unclear metastatic potential. However, sentinel lymph node mapping may

be used in selected patients with a higher likelihood of occult invasive cancer—those with extensive, high-grade DCIS or palpable masses—and those undergoing mastectomy as sentinel node mapping cannot be performed afterward if an invasive tumor is identified.[167]

After breast-conserving surgery, radiotherapy is administered using tangential fields to the whole breast with a standard dose of 42.5 to 50 Gy delivered in 16 to 25 daily fractions. Accelerated partial-breast irradiation may also be considered in appropriately selected patients. On the basis of randomized data, a radiation boost to the tumor bed may be added to whole-breast treatment, particularly for women with non–low-risk DCIS. There is no role for postmastectomy or nodal irradiation in the treatment of DCIS.

It is not yet possible to prospectively identify women who are at sufficiently low risk that radiotherapy may not be of some clinical advantage in preventing recurrences. After discussing the various options, patients may elect not to receive radiation treatment; however, they must understand and accept the increased risk of recurrence that this choice probably entails.[168]

In summary, despite considerable advances in our clinical knowledge base, the answer to the question "When should radiotherapy be used for DCIS?" remains complex and surrounded by considerable controversy. Two fundamental considerations must be emphasized:

1. A primary goal of breast-conserving therapy for DCIS is to achieve the best possible cosmetic outcome. Attempts to obtain wide surgical margins through deforming, large-volume breast excisions represent cosmetic failures and defeat the purpose of breast conservation.
2. Breast irradiation reduces the risk of subsequent invasive or noninvasive carcinoma in the treated breast and thus reduces the risk of the ultimate cosmetic failure— mastectomy.

According to prospectively randomized trials of breast-conserving therapy for DCIS, radiotherapy reduces subsequent breast recurrence in all patient groups, irrespective of prognostic risk factors. That is not to say, however, that radiotherapy must be used for all patients with DCIS. In all cases, a realistic and balanced discussion of the relative risks and benefits of treatment options should be presented to the patient. Reasonable estimates

of breast recurrence during the ensuing decade with or without radiotherapy are available based on level I evidence from prospective clinical trials.

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CHAPTER 62

Breast Cancer: Early Stage

Nisha Ohri, Sharad Goyal, Thomas Buchholz, and Bruce G. Haffty

Radiation therapy (RT) plays an essential and critical role in the management of early-stage breast cancer. This chapter provides an overview of general concepts in breast cancer and then focuses on the management of early-stage invasive disease in the breast conservation setting. Postmastectomy radiation, as well as advanced invasive disease and locoregional recurrence (LRR), will be covered in the advanced disease chapter that follows. Management of ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS) is the focus of the previous chapter.

ANATOMY

The female breast lies on the anterior chest wall superficial to the pectoralis major muscle. The breast can extend from the midline to near the midaxillary line and cranial caudally from the second anterior rib to the sixth anterior rib. The upper outer quadrant of the breast extends into the region of the low axilla and is frequently referred to as the axillary tail of Spence. This anatomic feature results in the upper outer quadrant of the breast containing a greater percentage of total breast tissue compared with the other quadrants, and, therefore, a greater percentage of breast cancers occur in this anatomic location.

The breast is made up of the mammary gland, fat, blood vessels, nerves, and lymphatics (Figure 62.1). The surface of the breast has deep attachments of fibrous septa, called Cooper ligaments, which run between the superficial fascia (attached to the skin) and the deep fascia (covering the pectoralis major and other muscles of the chest wall). Skin dimpling may be caused by tumors affecting these supporting structures. It is important to realize, from a staging perspective, that the chest wall includes the ribs, intercostal muscles, and the serratus anterior muscle, but not the pectoral muscles.

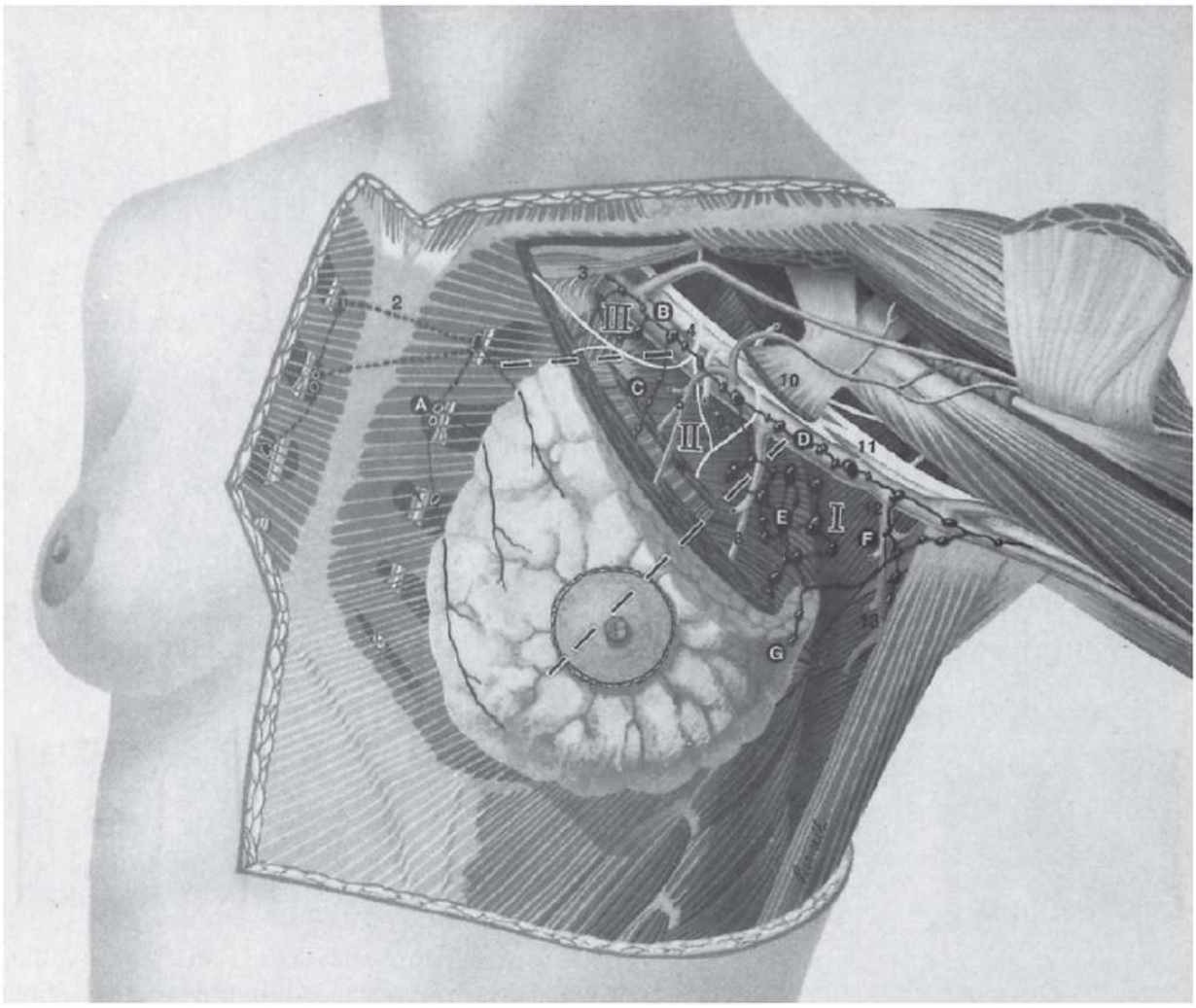

FIGURE 62.1 Anatomy of the breast and lymphatic drainage. (Reprinted with permission from Osborne MP. Breast development and anatomy. In: Harris JR, Hellman S, Henderson IC, et al, eds. *Breast diseases*. J.B. Lippincott; 1987:1-14.)

The breast parenchyma is composed of lobules and ducts. The function of the lobules is to produce milk, and the function of the ducts is to transport lactation products to the nipple. The peripheral ducts converge into major lactiferous ducts, which then communicate with the nipple-areola complex. Most breast cancers develop at the interface between the ductal system and the lobules, a region called the terminal ductal lobular unit.

The breast parenchyma is intermixed with connective tissue, which has a rich vascular and lymphatic network. Mammary gland lymphatics begin in the interlobular or prelobular spaces, follow the ducts, and end in the subareolar network of lymphatics of the skin. The predominant lymphatic drainage of the breast is to the axillary lymph nodes, which is commonly described in three levels, based on the relation of the lymph node regions to the pectoralis minor muscle (Figure 62.2). The level I axilla is caudal and lateral to the muscle, level II is beneath the muscle, and level III (also known as the infraclavicular region) is cranial and medial to the muscle. A standard axillary lymph node dissection (ALND) resects the tissue and lymph nodes within levels I and II. It is very unusual for level III of the axilla to be involved without disease in level I or II. The axillary lymph

nodes continue underneath the clavicle to become the supraclavicular lymph nodes, which can be involved in locally advanced breast cancers.

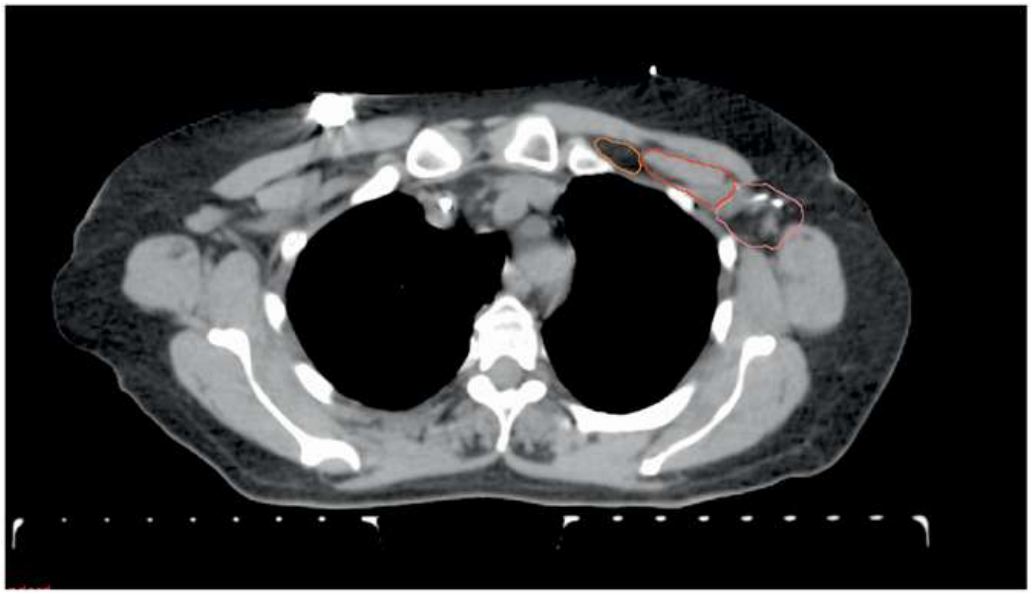

FIGURE 62.2 Location of the three levels of axillary lymph nodes (level 1—pink; level 2—red; level 3—orange).

Lymphatics can also drain directly into the internal mammary lymph node chain (IMC), which are intrathoracic structures located in the parasternal space. Although these nodes are not usually visualized on computed tomography (CT), the anatomic region of the IMC can be determined by the internal mammary artery and vein, which are easily visualized by CT (Figure 62.3) and usually lie 3 to 4 cm lateral to midline. When breast cancer involves the IMC, the majority of patients will have disease that is limited to lymph nodes in the first three interspaces. Regardless of the location in the breast, the axilla is the most common site of lymphatic involvement. However, breast cancers that develop in the medial, central, or lower breast more commonly drain to the IMC (in addition to the axilla) than do those occurring in the lateral and upper quadrants.

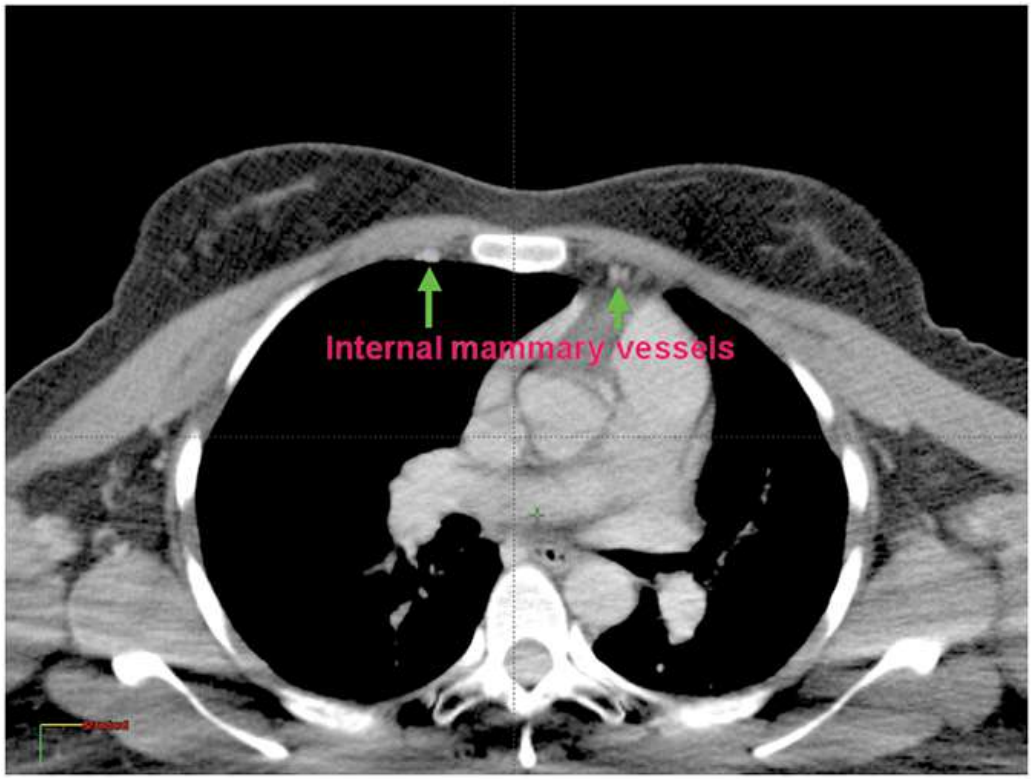

FIGURE 62.3 Treatment planning computed tomography scan of the chest demonstrating the location of the internal mammary vessels, which are typically located approximately 3 to 4 cm lateral to midline and approximately 3 cm deep to the surface. The internal mammary nodes are in close proximity to the vessels, with the most critical nodes being located in the first three intercostal spaces.

The use of lymphoscintigraphy, by injecting technetium-99 radiocolloid into the peritumoral region followed by scintillation scanning, is used for sentinel lymph node (SLN) imaging. This technique has helped to delineate primary lymphatic drainage patterns of breast cancer. Dual tracing techniques using both technetium-99 and blue dye may reduce false-negative rates. The distribution of axillary and internal mammary drainage is summarized in Figure 62.4.[1] Even in inner quadrant lesions, axillary drainage is more common than internal mammary drainage. However, internal mammary drainage was present in over 50% of lower inner quadrant lesions.

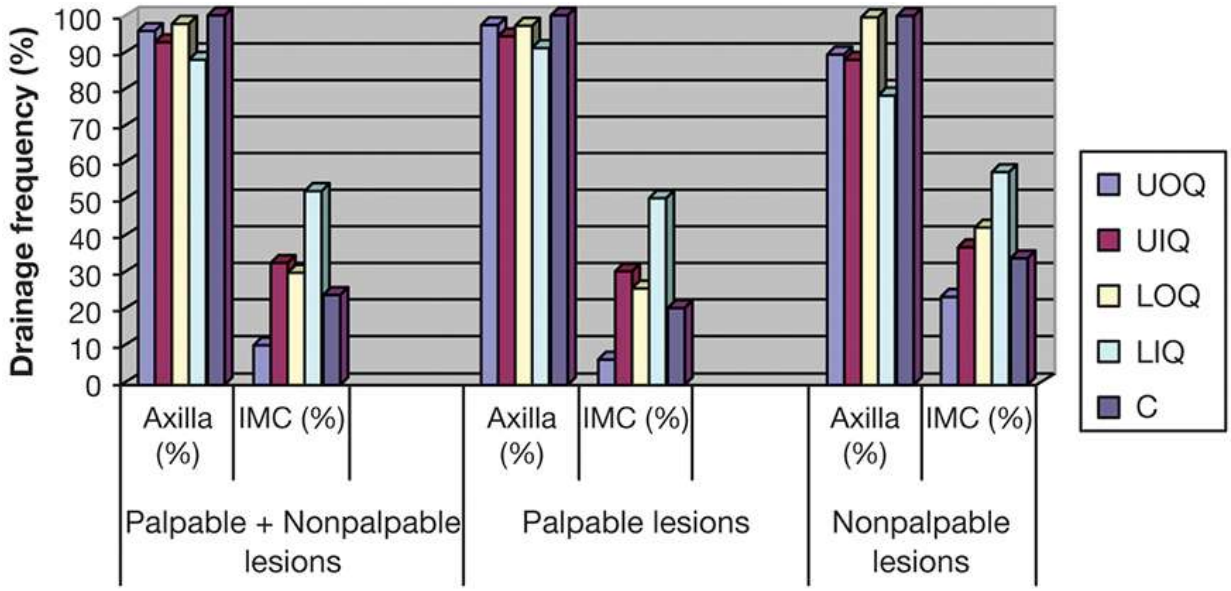

FIGURE 62.4 Distribution of lymphatic drainage of the breast to axillary and internal mammary chains (IMCs) according to the location within the breast. (Data extracted from study of 700 patients undergoing sentinel lymph node mapping by Estourgie SH, Nieweg OE, Olmos RA, et al. Lymphatic drainage patterns from the breast. *Ann Surg*. 2004;239[2]:232-237.)

EPIDEMIOLOGY

Breast cancer is the most frequently diagnosed cancer in women, and it is estimated that there will be 297,790 new cases of invasive breast cancer and 55,720 new cases of in situ breast cancers among women in the United States in 2023.[2] Primarily because of increased utilization of screening mammography, breast cancer incidence rates increased rapidly in the 1980s. Since the mid-2000s, female breast cancer incidence rates have slowly increased by about 0.5% per year, a trend that is attributed, in part, to increases in excess body weight and fertility issues. Breast cancer alone is expected to account for 31% of all new cancer diagnoses in women. It is estimated that 43,170 breast cancer deaths will occur in 2023, with breast cancer ranking second among cancer deaths in women after lung cancer. In contrast to the significant number of breast cancer cases in women, it is expected that 2,800 cases of breast cancer will be diagnosed in men in 2023, with approximately 530 breast cancer deaths in men. Because of a combination of early detection, increased awareness, and improvements in therapy, the female death rate from breast cancer has declined by 43% from 1989 to 2020.

There is considerable geographic, ethnic, and racial variability in breast cancer incidence. Ethnicity and national origin rank highly as predictors of risk for breast cancer, with up to a 10-fold variation throughout the world.[3] Compared with other well-established risk factors such as age of menarche and menopause, age at first childbirth, and family history, geographic and ethnic variability is quite significant. It is likely that a complex interaction of multiple factors, including genetic, environmental, and socioeconomic, contribute to the wide variability in age-adjusted incidence across populations.

In the United States, the incidence of breast cancer in White women is higher than in all other populations. Notably, Black women have a slightly lower incidence of breast cancer but 40% higher breast cancer mortality. This disparity has persisted over the years.[2]

Risk Factors

Table 62.1 summarizes the major risk factors associated with the development of breast cancer. With the exception of the female gender, increasing age is the most consistent and significant risk factor, with most populations demonstrating increasing incidence rates with age. Other risk factors include personal history and family history of breast cancer, nulliparity or late age at first childbirth, early menarche and late menopause, prior breast biopsy with hyperplasia or atypical hyperplasia, high breast tissue density, radiation exposure at a young age, alcohol consumption, and use of postmenopausal hormone therapy. Some of the national origin or ethnicity variability discussed earlier may be explained, in part, by differences in established risk factors, such as age of menarche, parity, and age at first childbirth. However, these factors explain only part of the variability observed in national origin, indicating underlying genetic, environmental, and dietary factors are likely to contribute to the differences in the worldwide incidence of breast cancer. Breastfeeding, physical activity, and maintaining a healthy body weight have been demonstrated in various studies to be associated with a lower risk of breast cancer.[4]

TABLE 62.1 RISK FACTORS FOR BREAST CANCER IN WOMEN

Risk Factors	Category at Risk	Comparison Category
Established Risk Factors		
Older age	Older than 50	Younger than 50
Country of residence	North America or Northern Europe	Asia or Africa
Germline mutation	With *BRCA1* or *BRCA2* mutations	Without *BRCA1* or *BRCA2* mutations
Personal history of breast cancer	With history of invasive breast carcinoma	No history of invasive breast carcinoma
High radiation exposure to chest area	With high radiation exposure to chest	Without radiation exposure
Atypical hyperplasia in breast biopsy	With atypical hyperplasia	Without hyperplasia
Cytologic findings (fine-needle aspiration; nipple aspiration fluid)	Proliferation with atypia	No abnormality detected
Family history of breast cancer	With one or more close relatives with breast cancer	No close relatives with breast cancer
Early menarche	Menarche before age 12	Menarche after age 14
Late menopause	Menopause after age 55	Menopause before age 55
Older age at first full-term birth	Older than 30 y when first child was born	Younger than 20 y when first child was born
Not having children	Without children	With one or more children
Using menopausal hormone therapy	With hormone treatment after menopause	Without hormone treatment after menopause
Obesity after menopause	Obese after menopause	Not obese after menopause
Other Reported Risk Factors		
Using birth control pills	Current use	None
Tall height	>5 ft 9 inches	<5 ft 3 inches
Regular alcohol consumption	Regularly consume alcoholic beverages	No alcoholic beverages consumption
Breastfeeding	None	>1 y

Risk Factors	Category at Risk	Comparison Category
Postmenopausal body mass index (BMI)	Higher BMI	Lower BMI
Jewish heritage	Yes	No
Possible Risk		
High-density breasts on mammograms	With high-density mammograms	With low-density mammograms
High socioeconomic position	Have high socioeconomic position	Have low socioeconomic position
Physical activity	Lower	>3 h/wk
Dietary factors	High-fat, low fiber	Low-fat, high fiber

Age

The risk of breast cancer increases exponentially up to the age of menopause, at which time the rate of increase in the risk slows significantly. After the age of 80, the incidence of breast cancer begins to show a slight decline. For women in their late 30s, the annual increase in risk of developing breast cancer is approximately 0.07% per year. This increases to 0.44% per year for women in their late 70s. Although these percentages may seem low, they represent only the risk for a given year; the lifetime risk is a summation of the annual breast cancer risks. Because younger women have a longer life expectancy than do older women, younger women have a greater lifetime risk. Only 1.9% of women develop breast cancer before the age of 50, whereas 2.3% of women develop breast cancer between the ages of 50 and 59 years, 3.5% of women develop breast cancer between the ages of 60 and 69 years, and 6.8% of women develop breast cancer over the age of 70.[5]

Childbearing/Parity/Breastfeeding

The protective effect of childbearing at younger ages on breast cancer risk is well established. In a worldwide case-control study, MacMahon et al[3,6] demonstrated a nearly linear relation between relative risk (RR) of breast cancer and age at first birth, with women aged 20 to 25 years having nearly a 50% reduction in the RR of breast cancer compared with nulliparous women. Interestingly, for women whose first childbirth occurred over age 35, the risk appears greater than that for nulliparous women. Data on the effect of breastfeeding are not as strong as the data on age at first childbirth, but they do suggest a protective effect.

Ovarian Function

The relation between ovarian function and breast cancer risk has long been recognized, with long menstrual history (early menarche and late menopause) contributing significantly to breast cancer risk. In experimental models and observational studies, removal of the ovaries reduces the risk of breast cancer. Women with surgically induced menopause have been shown to have significantly reduced risks of breast cancer compared with women whose menopause occurred naturally. In comparison with women whose menopause occurs between the ages of 45 and 54 years (RR = 1), women with early menopause before age 45 have an RR of breast cancer of 0.73, and women with late menopause at age 55 years or above have an RR of 1.48. The data on the early onset of menses and its association with breast cancer risk are also well established.[3]

Exogenous Hormone

The relationship between breast cancer risk and exogenous hormone exposure is controversial. A collaborative meta-analysis from 51 epidemiologic studies of over 150,000 women did show an increased RR of 1.35 for current or recent users of hormonal replacement therapy.[7] The authors

reported that postmenopausal hormone replacement therapy increased the annual RR of developing breast cancer by 2.3% for each year of hormonal therapy. A randomized trial of postmenopausal hormone therapy from the Women's Health Initiative Study comparing estrogen and progestin with placebo was closed prematurely, demonstrating a 24% increase in breast cancer, coronary heart disease, stroke, and pulmonary emboli.[8] This study of 46,000 women reported that the combined use of estrogen and progesterone increased the RR of breast cancer by 8% compared with the risk in nonusers, whereas the use of estrogen alone increased the RR by only 1%. After publication of this study, a dramatic decrease in almost 7% between 2002 and 2003 was primarily attributed to the reduction in the use of hormone replacement therapy.[5]

There is no clear relationship between the use of oral contraceptives and breast cancer risk, as data are conflicting.

Family History

The increased risk of breast cancer as a function of family history is well established. For women with a second-degree relative (aunt, grandmother) with breast cancer, the risk is about 1.5, and for women with a history of first-degree relatives (mother or sister), the risk is 1.7 to 2.5.[9] This may be explained, in part, by inheritance of a genetic condition that predisposes an individual to breast cancer development (eg, mutations in *BRCA1* or *BRCA2*), shared lifestyle, and inheritance of genes that affect risk factors, such as body habitus and age at menarche. Between 20% and 25% of women diagnosed with breast cancer have a positive family history of the disease, and approximately 10% of women with breast cancer are from families who display an autosomal dominant pattern of breast cancer inheritance.[10] The actual risk that family history conveys depends on the number of relatives affected and their age at diagnosis (having a first-degree relative with premenopausal breast cancer conveys a greater risk than does having a first-degree relative with postmenopausal cancer). Women with one first-degree relative affected by the disease have an increased RR of developing breast cancer 2 to 3 times that of women with no family history. Women with two or more first-degree relatives with a diagnosis of breast cancer have a still greater risk, 4 to 6 times that of women with no family history.[9]

National consensus guidelines provide an outline for testing criteria for high-penetrance breast cancer susceptibility genes (*BRCA1, BRCA2, CDH1, PALB2, PTEN*, and *TP53*). Genetic testing is recommended for patients with a personal history of breast cancer and the following features:

- Diagnosed age 50 years or below
- Diagnosed at any age with
  - Triple-negative (TN) breast cancer
  - Multiple primary breast cancers
  - Lobular breast cancer with a personal or family history of diffuse gastric cancer
  - Male breast cancer
  - Ashkenazi Jewish ancestry
  - To aid in systemic treatment decisions in the adjuvant or metastatic setting
  - One or more close blood relatives with any of the following: breast cancer age 50 or below, male breast cancer, ovarian cancer, pancreatic cancer, or prostate cancer with metastatic or high-risk group
  - Three or more diagnoses of breast cancer in the patient and/or close blood relatives
  - Two or more close blood relatives with breast or prostate cancer

Personal History of Breast Cancer and History of "Benign" Breast Biopsy

Women with a prior history of breast cancer are at an elevated risk of developing a second contralateral breast cancer. Studies with long-term follow-up have demonstrated a risk of breast cancer in the contralateral breast of approximately 10% to 15%, depending on the patient population and length of follow-up.[11] The risk of contralateral breast cancer as a function of prior radiation treatment is discussed in detail later.

Although women with a history of fibrocystic changes have been reported to have an elevated risk of breast cancer, evidence suggests that the majority of the elevated risk is due to the smaller proportion of women whose biopsy reveals atypical hyperplasia. Results from the Breast Cancer Detection Demonstration Project, which included over 280,000 women in 29 centers, demonstrated that women with atypical hyperplasia had 4.3 times the breast cancer risk of women without proliferative disease (95% confidence interval [CI], 1.7-11.0).[12] In women with proliferative disease lacking atypical hyperplasia, the RR was 1.3 (95% CI, 0.77-2.2). In that study, the joint occurrence of family history and atypical hyperplasia had a strong synergistic effect on breast cancer risk.

Radiation Exposure

Exposure to ionizing radiation during or after puberty increases the risk for the development of carcinoma of the breast. Land et al[13,14] reviewed reports on three populations of patients exposed to ionizing radiation by atomic bombings, multiple fluoroscopic examinations for tuberculosis, and multiple examinations for mastitis. They concluded that the risk of radiation-induced cancer of the breast increased approximately linearly with increasing dose and was heavily dependent on age at exposure.

In a study of 31,710 women who had tuberculosis and were examined with repeated fluoroscopic studies, a substantial proportion (26.4%) received doses to the breast of 0.1 Gy or higher; the breast cancer risk was greatest among women who had radiation exposure between the ages of 10 and 14 years (RR 4.5 per 0.01 Gy and an additive risk of 6.1 per 104 person-years per 0.01 Gy); there was substantially less excess risk with increasing age at first exposure.[15]

A high risk of solid tumors, especially breast cancer, has been described in women treated with RT at a young age for Hodgkin lymphoma. In a prior study, RRs of breast cancer were defined by radiation dose to the chest (0, 20 ≤40 Gy, or ≥40 Gy). Estimates were from a case-control study conducted within an international population-based cohort of 3,817 female survivors of Hodgkin lymphoma diagnosed at age 30 years or below.[16] For a survivor who was treated at age 25 years with a chest radiation dose of at least 40 Gy without alkylating agents, estimated cumulative absolute risks of breast cancer by age 35, 45, and 55 years were 1.4% (95% CI, 0.9%-2.1%), 11.1% (95% CI, 7.4%-16.3%), and 29.0% (95% CI, 20.2%-40.1%), respectively. The current practice of limiting radiation fields may help to further reduce the risk of radiation-related breast cancers in Hodgkin survivors.[17]

Body Mass Index, Physical Activity, and Dietary Factors

The inherent complex interaction between body mass, physical activity, and diet complicates the interpretation of epidemiologic studies correlating these factors with breast cancer risk. Body mass index (BMI) has been clearly associated with breast cancer risk in a number of studies, but it appears to influence breast cancer risk predominantly in postmenopausal women. In premenopausal women, most studies have not observed a strong relation between BMI and breast cancer risk. In postmenopausal women, a pooled analysis of prospective studies demonstrated the risk of breast cancer to be 30% higher in postmenopausal women with a BMI over 31 kg/m^2 compared with

women with a BMI of 20 kg/m^2.[18] The higher risk of breast cancer with increased BMI in postmenopausal women is likely due to higher estradiol levels associated with increased adipose tissue and increased aromatase, which is involved in the conversion of androgens to estradiol. In postmenopausal women, this is the primary source of estradiol. In premenopausal women, estradiol is predominantly from the ovaries, so there is little association with BMI and estradiol levels.

Physical activity can have a significant impact on BMI, so it is sometimes difficult to separate these two effects in interpreting breast cancer risk. A majority of studies, however, have observed a lower risk of breast cancer among women who are more physically active compared with women who are sedentary.

Although it has been suggested that obesity and high intake of meat, dairy products, and fat may increase risk and fiber, fruits and vegetables, and phytoestrogens (soy products) may reduce risk, strong links between diet and breast cancer risk have not been clearly established.

Alcohol Consumption

Chen et al[19] reported on a prospective observational study of 105,986 women enrolled in the Nurses' Health Study between 1980 and 2008. With 2.4 million person-years of follow-up, 7,690 cases of invasive breast cancer were diagnosed. They found that increasing alcohol consumption was associated with increased breast cancer risk that was statistically significant at levels as low as three to six drinks per week (RR 1.15; 95% CI, 1.06-1.24). Moreover, binge drinking, but not frequency of drinking, was associated with breast cancer risk after controlling for cumulative alcohol intake. They concluded that low levels of alcohol consumption were associated with a small increase in breast cancer risk, with the most consistent measure being cumulative alcohol intake throughout adult life.

Although the relation among physical activity, BMI, and dietary factors may be difficult to separate, it is apparent that maintaining a healthy diet and weight, limiting alcohol intake, and engaging in moderate physical activity are modifiable behaviors that can impact breast cancer risk (as well as other health-related issues) and should be encouraged.

Mammographic Density

There is a large body of evidence suggesting a correlation between mammographic breast density and breast cancer risk.[20] The risk of breast cancer associated with the highest category of density has been estimated to be 2 to 6 times greater than in the lowest category. Although the causal link between mammographic density remains poorly understood, breast density is, in part, attributable to genetic factors.

Determining an Individual's Risk

It is important to consider the combination of risk factors when a generalized risk profile is determined. Gail et al[21] have used these epidemiologic risk factors to derive a model for predicting an individual's annual and lifetime risks of breast cancer. In the Gail model, an individual's annual risk of breast cancer is based on their present age, number of first-degree relatives with breast cancer, age at first birth, age at menarche, number of breast biopsies, and history of atypical ductal hyperplasia. The use of exogenous hormones and many of the other risk factors discussed earlier are not incorporated into this specific model.

BREAST CANCER PREVENTION

Tamoxifen

Several pharmaceuticals that affect the estrogenic pathways have been studied as chemopreventive agents, but the only agent for which mature data from clinical trials are available is tamoxifen.[22-27]

Interest in tamoxifen as a chemopreventive agent arose after a number of randomized trials designed to test the efficacy of hormonal therapy for invasive breast cancer reported that tamoxifen reduced the incidence of contralateral breast cancer. On the basis of these data, in 1992, the National Surgical Adjuvant Breast and Bowel Project (NSABP) began a randomized, placebo-controlled study (the P-1 trial) to test the efficacy of 5 years of tamoxifen in the prevention of breast cancer.[27] Between 1992 and 1997, 13,388 women with a 1.67% or greater predicted risk of developing breast cancer within 5 years were enrolled in this trial. Risk was assessed using a modification of the Gail model, which permitted enrollment of any woman older than 60 years and selected women younger than 60 years with additional risk factors that increased their annual risk to at least that of a 60-year-old. In addition, women with a history of LCIS were included. Women were not allowed to use estrogen replacement therapy during their participation in the trial. The results of the NSABP P-1 trial indicated that tamoxifen reduced the rates of invasive and noninvasive breast cancer by 49% and 50%, respectively. The benefit of tamoxifen was seen in all age groups (≤49, 50-59, and ≥60 years). In addition, women with a history of atypical ductal hyperplasia had an 86% risk reduction, and women with a history of LCIS had a 56% risk reduction. Finally, the benefit was seen across all subgroups specified according to family history of breast cancer. Tamoxifen selectively reduced the incidence of estrogen receptor (ER)-positive tumors; ER-negative tumors developed at an equal rate in the tamoxifen and placebo groups. No evidence was shown of a cardioprotective effect of tamoxifen in this trial, but the number of osteoporosis-related fractures was reduced in the tamoxifen-treated cohort. Tamoxifen increased the risk of developing stage I endometrial cancer (risk ratio of 2.53).

Subsequently, a landmark study was published that compared tamoxifen to raloxifene as a preventive agent in postmenopausal women with breast cancer. Raloxifene, a drug that is primarily used in the prevention of osteoporosis, had been shown in prior studies to decrease the incidence of breast cancers. The NSABP study of tamoxifen and raloxifene was a prospective, double-blind, randomized clinical trial.[28] There were 19,747 postmenopausal women of mean age 58.5 years with increased 5-year breast cancer risk. Patients were randomized to oral tamoxifen (20 mg/day) or raloxifene (60 mg/day) for 5 years. There were 163 cases of invasive breast cancer in women assigned to tamoxifen and 168 in those assigned to raloxifene, which was not significantly different between the two arms. The main benefit of raloxifene was in toxicity. There were 36 cases of uterine cancer with tamoxifen and 23 with raloxifene. No differences were found for other invasive cancer sites, ischemic heart disease events, or stroke. Thromboembolic events also occurred less often in the raloxifene group. The number of osteoporotic fractures in the groups was similar, and there were fewer cataract surgeries with raloxifene. There was no difference in the total number of deaths (101 vs 96 for tamoxifen vs raloxifene) or in causes of death. It appeared from this study that raloxifene was as effective as tamoxifen in reducing the risk of invasive breast cancer and had a lower risk of thromboembolic events. Of note, there were slightly more noninvasive cancers in the raloxifene group, but that was not statistically significant.

A comparison of the tamoxifen prevention trials is outlined in Table 62.2.[22-26,29,30]

TABLE 62.2 RESULTS OF CHEMOPREVENTION TRIALS

	Royal Marsden (Tamoxifen vs Placebo)[29]	NSABP P-1 (Tamoxifen vs Placebo)[27]	Italian (Tamoxifen vs Placebo)[30]	IBIS-1 (Tamoxifen vs Placebo)[24]	MORE (Raloxifene vs Placebo)[23]	STARR (Tamoxifen vs Raloxifene)[28]
Entry dates	1986-1996	1992-1997	1992-1997	1992-2001	1994-1999	1999-2005
Number randomized	2,494 (1,238 vs 1,233)	6,681 vs 6,707	2,700 vs 2,708	3,573 vs 3,566	2,557 + 2,572 vs 2,576	9,726 vs 9,745
Age (y)	30-70	≥35	35-70	35-70	66.5 (median)	≥35
Agent dose	Tamoxifen 20 mg	Tamoxifen 20 mg	Tamoxifen 20 mg	Tamoxifen 20 mg	Raloxifene 60 or 120 mg	Tamoxifen 20 mg, raloxifene 60 mg
Planned length (y) of treatment	5-8	5	5	5	4	5
Breast Cancers						
Total	62 vs 75	124 vs 244	34 vs 45	69 vs 101	31/2 vs 43	220 vs 248
Invasive	54 vs 64	89 vs 175	28 vs 40	64 vs 85	22/2 vs 39	163 vs 168
Noninvasive	7 vs 7	35 vs 69	5 vs 4	5 vs 16	9/2 vs 4	57 vs 80
Unknown	1 vs 4	—	1 vs 1	—	—	—
ER Status (Invasive Only)						
Positive	31 vs 44	41 vs 130	—	44 vs 63	10/2 vs 31	115 vs 109
Negative	17 vs 10	38 vs 31	—	19 vs 19	9/2 vs 4	44 vs 51

ER, estrogen receptor.

Prophylactic Surgery

An alternative strategy used to prevent breast cancer development is prophylactic surgical intervention. Hartmann et al[31] analyzed outcomes in women with a family history of breast cancer who underwent bilateral prophylactic mastectomy at the Mayo Clinic between 1960 and 1993. With a median follow-up time of 14 years, only 4 of the 639 treated patients developed breast cancer. According to the Gail model, 37.4 cases of breast cancer would have been expected to develop in this population, so the prophylactic surgery resulted in an 89.5% risk reduction ($P < .001$).

Breast cancer prevention strategies will continue to be a dynamic area of preclinical and clinical research.

NATURAL HISTORY AND ORIGINS

All forms of breast cancer are believed to develop as a consequence of unregulated cell growth and the development of phenotypic changes, such as the ability to invade, recruit a new blood supply, and metastasize. These changes in phenotypes are secondary to the development of aberrations in genetic pathways. Some of these aberrations are inherited (germline mutations), whereas others develop during the life of a breast cell (somatic mutations). It is currently believed that most breast cancer is a consequence of a series of somatic mutations. As previously noted, only 20% to 25% of patients with breast cancer have a history of breast cancer in a first-degree relative. However, it is possible that some women without a first-degree relative with breast cancer still inherit a genetic background that predisposes to breast cancer. These mutations may be insufficient to cause breast cancer unless accompanied by other mutations and, therefore, would be predicted to have a low

penetrance. Historically, it has been much more difficult to discover low-penetrance mutations than to discover germline mutations that result in an autosomal dominant pattern of breast cancer development. However, with newer molecular techniques, such as DNA array assays, the identification of low-penetrance predisposing mutations may be more feasible.

The most common site of origin of breast cancer is the upper outer quadrant, followed by the central area, the upper inner quadrant, the lower outer quadrant, and the lower inner quadrant. These rates correlate with the amount of breast tissue in the various quadrants. As noted earlier, women with a history of breast cancer have a 10% to 15% risk of developing a new primary in the contralateral breast.

As the cancer grows, it travels along the ducts, eventually breaking through the basement membrane of the duct, invading adjacent lobules, ducts, fascial strands, and the mammary fat, spreading through the breast lymphatics and into the peripheral lymphatics. The tumor can grow through the wall of blood vessels, spread into the deep lymphatics of the dermis, and eventually produce edema of the skin (*peau d'orange*), which usually indicates that the superficial as well as deep lymphatics are involved. Skin dimpling can be caused by involvement of Cooper ligament. Ulceration and infiltration of overlying skin, which may develop late in the course of the disease, are usually preceded by fixation and localized redness of the skin over the tumor.

Axillary Spread

Breast carcinoma will typically first spread through the axillary lymph nodes, with the incidence increasing with larger and biologically more aggressive tumors. Depending on the mode of detection, tumor size, histology, and other clinical or pathologic factors, between 10% and 40% of newly diagnosed stage T1 and T2 breast cancers have pathologic evidence of axillary nodal metastases.

Up to 30% to 40% of T1 or T2 clinically node-negative breast cancers may have pathologically involved lymph nodes. However, data from NSABP-04 suggest that less than half of clinically negative but pathologically positive axilla will experience a clinical relapse in the axilla.[32] In this study, patients with operable breast cancer, who were primarily diagnosed with palpable breast tumors in the premammography era, were randomized to one of three arms: simple mastectomy without axillary dissection, simple mastectomy with axillary dissection, or simple mastectomy with comprehensive chest wall and regional nodal irradiation (RNI). In the arm undergoing axillary dissection, nodal positivity was approximately 40%. Nodal control was excellent (>97%) in this arm as well as in the arm treated with radiation. In the simple mastectomy arm, where no nodal treatment by radiation or dissection was administered, the axillary failure rate was approximately 20%. Assuming equal distribution among the arms, it is presumed the pathologic involvement was approximately 40%, indicating that half of those with pathologic involvement eventually failed clinically.

Internal Mammary Spread

Less commonly, breast carcinoma may spread to the internal mammary nodes (IMNs). Metastases to the IMNs are correlated with tumor size, are more frequent from medial half and central lesions, and occur more frequently when there is axillary node involvement. Clinical failure of the IMNs is rare (<1%).[33]

Supraclavicular Spread

Spread to supraclavicular lymph nodes usually follows involvement in the high axillary lymph nodes or IMNs depending on the location of the primary lesion and is also less common. Clinical failure in the supraclavicular fossa is relatively rare in patients with early-stage breast cancer and is dependent on the degree of axillary involvement. For patients with no or minimal nodal involvement (<3 involved axillary nodes), supraclavicular failure is extremely rare. In an analysis of 691 patients with zero to three nodes involved undergoing breast-conserving surgery and RT to tangential fields only without RNI, Galper et al[33] reported failure in the supraclavicular fossa in 1.3% of patients.

Local Control and Systemic Metastasis

Patients treated for breast cancer are at risk for locoregional failure as well as systemic metastasis. It is evident from the available literature that optimizing local control can impact systemic metastasis and survival, and similarly, systemic therapy can impact local control. Integration of systemic therapy with radiation will be discussed in detail later, but numerous studies have clearly demonstrated a significant improvement in local control with the use of RT and systemic therapy (both cytotoxic and hormonal) compared with RT alone.[34-38] Appropriate integration of both local and systemic treatments through a multidisciplinary approach is thus essential to optimize outcome. Although there is some overlap, prognostic factors for locoregional control and systemic metastasis often differ.

For patients with early-stage invasive breast cancer, even with appropriate systemic therapy, development of metastasis can vary from less than 5% in women with T1a disease and favorable histology to more than 40% for women with T2 tumors and pathologically involved lymph nodes. Similarly, locoregional failure rates can vary from less than 5% to over 40% depending on local treatment and prognostic factors for local failure.[34-37,39,40]

The impact of local control on systemic metastasis in breast cancer as well as other malignancies has been the subject of considerable debate and controversy. Although the benefits of local control with respect to cosmesis and quality of life are apparent, the independent effect of local control on systemic disease and survival has been questioned. Many studies have identified local control as an independent predictor of disease-free (DFS) or overall survival (OS).

One of the most convincing and authoritative studies related to this subject is the analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG).[41] In this analysis, over 42,000 women were enrolled in 78 randomized trials that compared 24 types of local treatment (RT vs no RT, more vs less surgery, or more surgery vs RT). The EBCTCG attempted to relate the effect of local control to breast cancer mortality by grouping studies into whether the 5-year local relapse risk difference between the two comparisons of local therapy exceeded 10%. In those comparisons in which the difference in 5-year local recurrence (LR) risk was less than 10%, there was no impact on 15-year breast cancer mortality. However, there were 25,000 women enrolled in trials in whom the comparisons involved more than 10% differences in local control. In those studies, the difference in LR risks at 5 years was 7% versus 26%, and the 15-year mortality risk was 44.6% versus 49.5% ($P < .00001$). Figure 62.5 summarizes the results of this meta-analysis with respect to the impact of radiation on breast cancer mortality both in breast conservation and following mastectomy.

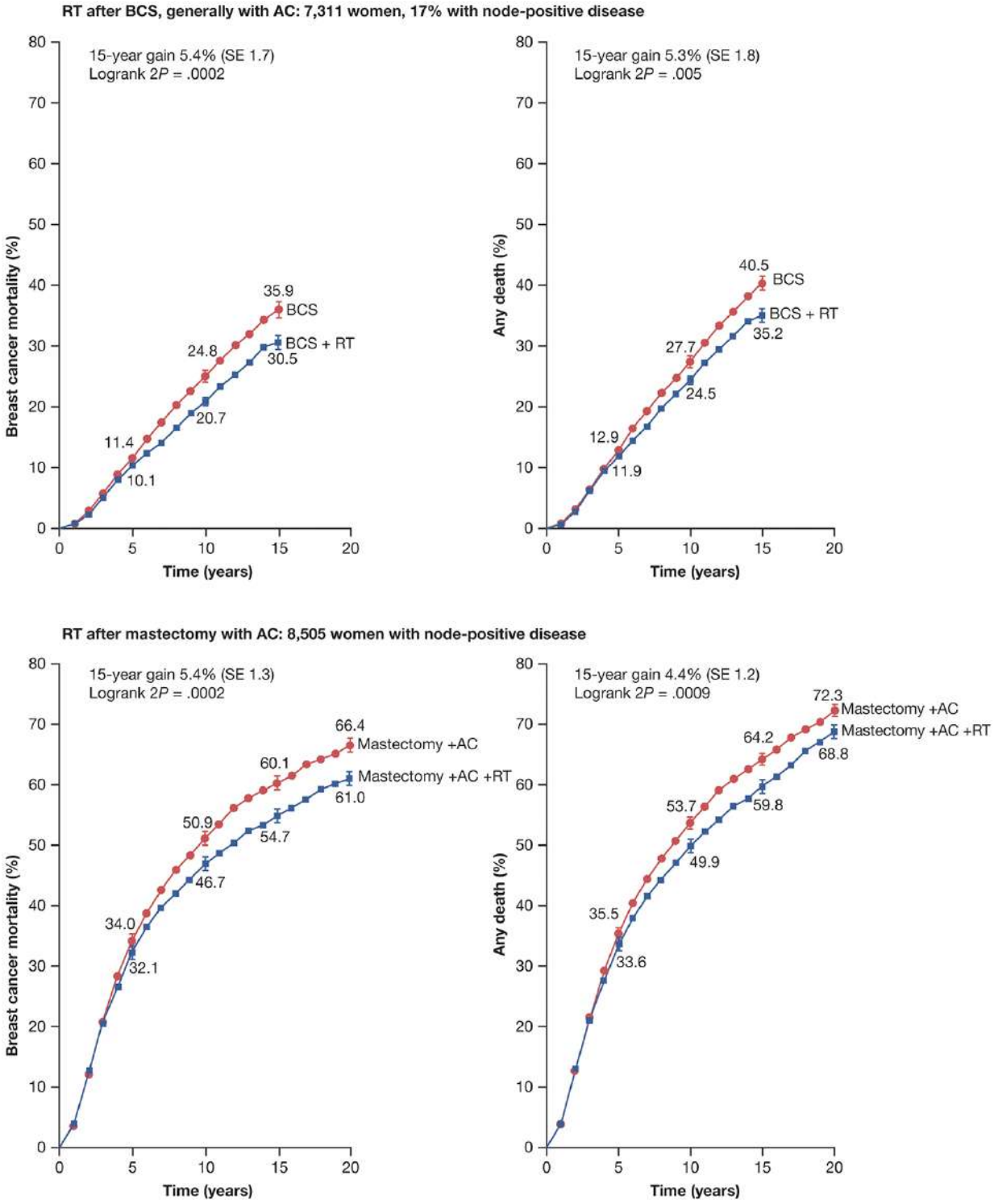

FIGURE 62.5 Effect of radiotherapy (RT) on breast cancer mortality and on all-cause mortality after breast-conserving surgery (BCS) or after mastectomy (AC) with axillary clearance: 15- or 20-year probabilities. SE, standard error. (Reprinted from Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;366[9503]:2087-2106. Copyright © 2005 Elsevier. With permission.)

An update from the EBCTCG focused on 10,801 women enrolled in 17 randomized trials of RT versus no RT after breast-conserving surgery and relates the absolute reduction in 15-year risk of breast cancer death to the absolute reduction in 10-year recurrence risk.[42] Overall, RT reduced the 10-year risk of any first recurrence from 35.0% to 19.3% (*log-rank 2p < 0.00001*) and reduced the 15-year risk of breast cancer death from 25.2% to 21.4% (*log-rank 2p = 0.00005*). In women with pN+ disease (n = 1,050), RT reduced the 10-year recurrence risk from 63.7% to 42.5% (*log-rank 2p < 0.00001*) and the 15-year risk of breast cancer death from 51.3% to 42.8% (*log-rank 2p = 0.01*). Overall, about one breast cancer death was avoided by year 15 for every four recurrences avoided by year 10.

DIAGNOSIS AND WORKUP

Most patients with T1 or T2 breast cancers present with a painless or slightly tender breast mass or have an abnormal screening mammogram. The patient should be examined both sitting up and lying down (to confirm masses felt on the sitting-up examination and to detect lesions deeper in the breast or against the chest wall). Careful inspection of both breasts should be made, including size, form, and symmetry; changes in pigmentation; scaling or discharge from the nipple; and dilated veins or edema of the skin in a patient who is nonpregnant. The location, size, consistency, tenderness, and mobility of the palpable tumor should be recorded. In addition to examination of the breast, careful evaluation of the axilla and supraclavicular node areas is mandatory. The number, consistency, tenderness, mobility or fixation, and size of lymph nodes should be noted.

The comprehensive workup of a patient with a breast mass, including complete clinical and family history, is summarized in Table 62.3.

TABLE 62.3 DIAGNOSTIC WORKUP FOR CARCINOMA OF THE BREAST, STAGES T1 AND T2

General
History with emphasis on presenting symptoms, menstrual status, parity, family history of cancer, other risk factors
Physical examination with emphasis on breast, axilla, supraclavicular area, abdomen
Special Tests
Biopsy (core biopsy directed by physical examination, ultrasound, or mammography as indicated, or needle localization)
Radiologic Studies
Before biopsy
Bilateral diagnostic mammography/ultrasonography
Chest radiographs
Magnetic resonance imaging of breast (selected cases)
After positive biopsy
Bone scan (when clinically indicated, for stage II or III disease or elevated serum alkaline phosphatase levels)
Computed tomography of the chest, abdomen, and pelvis for stage II or III disease and/or abnormal liver function tests
Laboratory Studies
Complete blood cell count
Comprehensive metabolic panel, including liver function tests and alkaline phosphatase
Other Studies
Hormone receptor status (ER, PR)

HER2/neu status
Consider genetic counseling/*BRCA* testing in high-risk patients
Counseling for fertility if premenopausal
Assess for distress

ER, estrogen receptor; PR, progesterone receptor.

Imaging in Breast Cancer Diagnosis and Workup

Mammography

Mammography remains the most critical component of diagnostic imaging in patients with breast cancer, and bilateral mammograms should be performed routinely in the workup of the patient with breast cancer. The Breast Imaging Reporting and Data System classification system, outlined in Table 62.4, has been widely adopted in classifying mammograms with respect to appropriate follow-up and intervention.[43]

TABLE 62.4 CONCORDANCE BETWEEN BI-RADS® ASSESSMENT CATEGORIES AND MANAGEMENT RECOMMENDATIONS

Assessment	Management	Likelihood of Cancer
Category 0: Incomplete – Need Additional Imaging Evaluation and/or Prior Mammograms for Comparison	Recall for additional imaging and/or comparison with prior examination(s)	N/A
Category 1: Negative	Routine mammography screening	Essentially 0% likelihood of malignancy
Category 2: Benign	Routine mammography screening	Essentially 0% likelihood of malignancy
Category 3: Probably Benign	Short-interval (6-month) follow-up or continued surveillance mammography (Figure 155, see page 152)	> 0% but ≤ 2% likelihood of malignancy
Category 4: Suspicious	Tissue diagnosis	> 2% but < 95% likelihood of malignancy
Category 4A: *Low suspicion* for malignancy		> 2% to ≤ 10% likelihood of malignancy
Category 4B: *Moderate suspicion* for malignancy		> 10% to ≤ 50% likelihood of malignancy
Category 4C: *High suspicion* for malignancy		> 50% to < 95% likelihood of malignancy
Category 5: Highly Suggestive of Malignancy	Tissue diagnosis	≥ 95% likelihood of malignancy
Category 6: Known Biopsy-Proven Malignancy	Surgical excision when clinically appropriate	N/A

Reprinted with permission from Sickles EA, D'Orsi CJ, Bassett LW, et al. ACR BI-RADS® mammography. In: *ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System*. American College of Radiology; 2013. Copyright © 2013 American College of Radiology. All rights reserved.

The radiation oncologist should be familiar with the difference between diagnostic and screening mammography, because a majority of conservatively treated patients with breast cancer will have undergone diagnostic mammography prior to treatment, as well as in follow-up. Screening mammography refers to routine mammographic images in asymptomatic women and consists of two views: craniocaudal and mediolateral oblique of each breast. Diagnostic mammography is used to characterize abnormalities detected at screening or in women with palpable masses, employs additional magnification views, and is generally done with the radiologist present to determine the need for additional views or follow-up studies. Following breast conservation, most patients will undergo diagnostic mammograms. Some mammographers recommend reverting to screening studies after several years of stable mammography in the conservatively managed patient with breast cancer.

Classically, breast carcinoma is seen as an ill-defined mass that may have spiculated margins (Figure 62.6), although rarely cancers may also be seen with a knobby, lobulated, or even a smooth contour (ultrasonography may distinguish them from cystic masses). Architectural distortion of the breast tissue may be present. The appearance of linear, radiated, or spiculated changes around a central focus should always be considered suspect for carcinoma. The tumor may be hidden by dense parenchyma; review of previous mammogram compression views, tomosynthesis views, and sometimes ultrasonograms can all be very important in detecting subtle interval changes in the appearance of the breast.

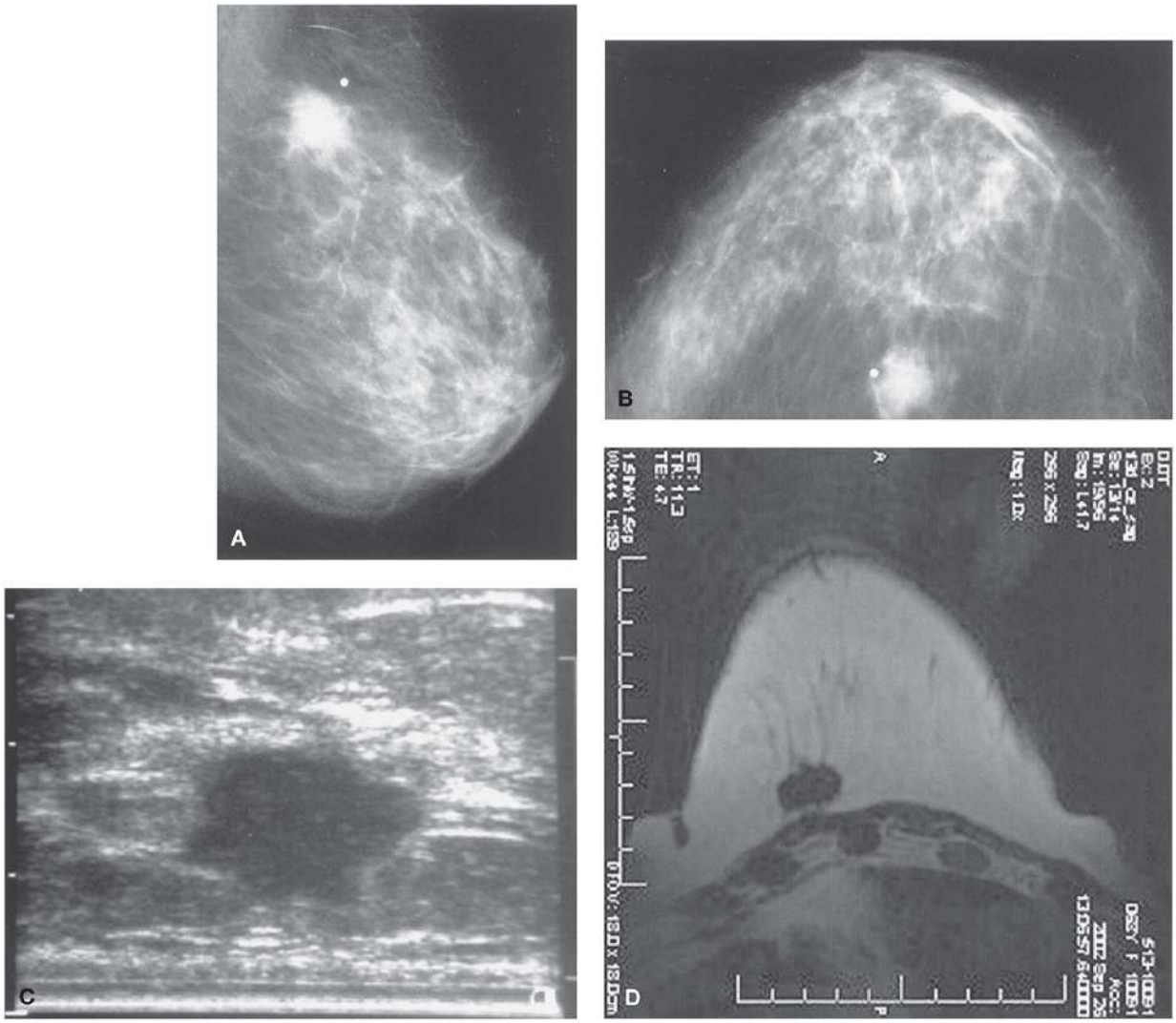

FIGURE 62.6 Mediolateral (A) and cephalocaudal (B) views of mammogram depicting a 1-cm mass with stellate margins deeply located in the upper quadrant of the left breast, histologically proven to be an invasive ductal carcinoma. Example of ultrasonogram of the breast showing a hypoechoic mass with "shadowing" deeper to the lesion, characteristic of invasive carcinoma (C). T1-weighted magnetic resonance image of the breast demonstrating a mass that proved to be an invasive carcinoma (D).

Calcifications can be associated with either benign or malignant conditions of the breast. However, calcifications associated with malignant tumors are typically 100 to 300 μm in size and are rodlike, tubular, branching, or punctate. Clusters of microcalcifications (>5) are suggestive of intraductal disease, and in nonpalpable lesions, needle localization aids in the diagnosis (Figure 62.7). For patients undergoing biopsy of a suspicious mass or calcifications, about 30% will yield a diagnosis of malignancy. The average sensitivity of mammography is approximately 90% (60%-95%), and the specificity is 94% (50%-98%). The positive predictive value is approximately 8% to 14% for screened patients but is significantly higher for patients with symptoms or palpable masses.[44] If microcalcifications were initially present, radiographs of the surgical specimen and postlumpectomy mammography are important to rule out residual disease for patients considering breast conservation therapy.

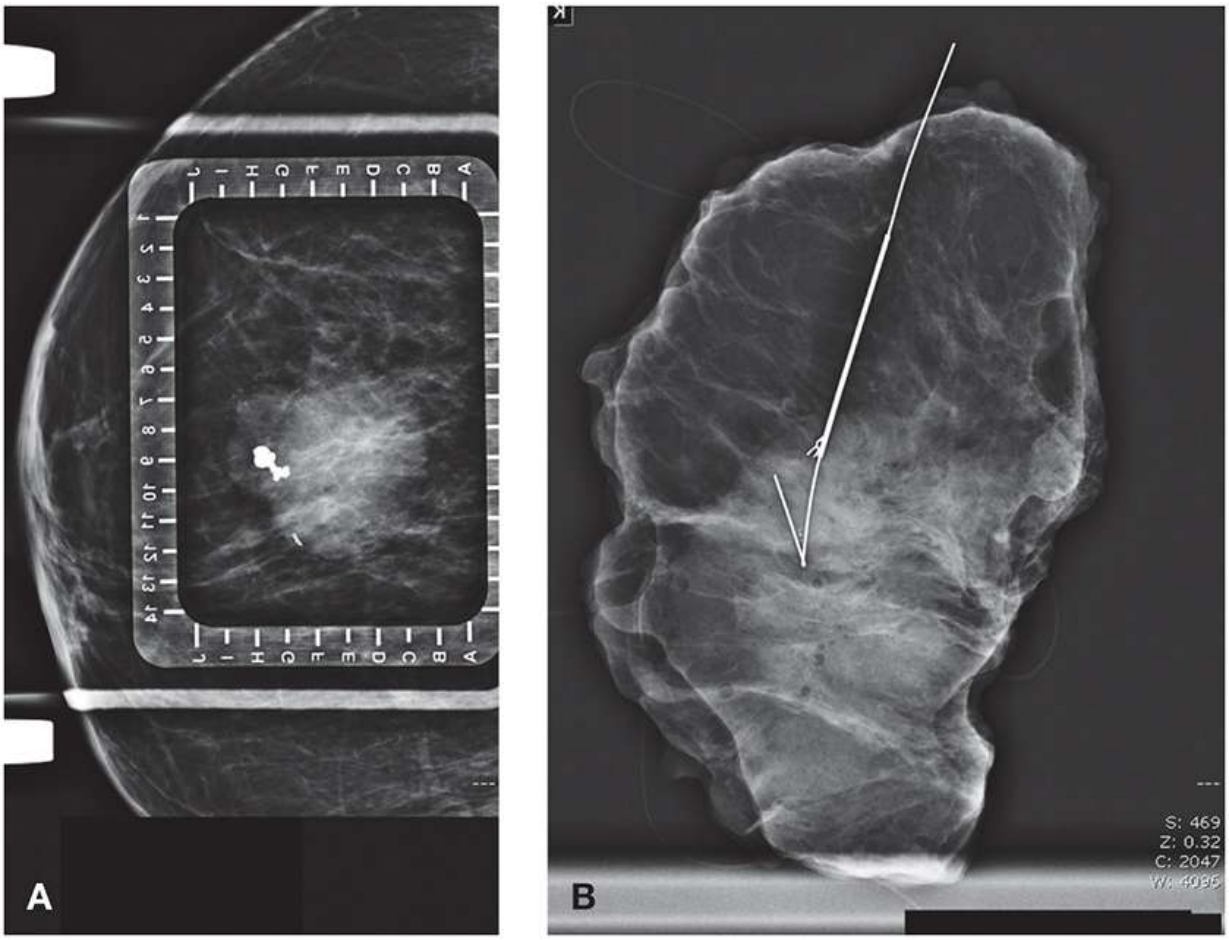

FIGURE 62.7 A. Mammogram demonstrating microcalcifications in the central portion of the breast with needle localization in place. B. Radiograph showing microcalcifications in the central portion of the wide excisional biopsy specimen. Pathologic diagnosis was intraductal carcinoma. Postlumpectomy mammogram showed no residual calcifications in the breast. The patient was treated with breast conservation surgery and irradiation years ago and remains tumor free.

Ultrasound

Ultrasound can be a useful tool to complement physical examination and mammography in the diagnosis and treatment of breast cancer. Ultrasonography has a reported sensitivity of 73% and specificity of 95%.[45] It is very helpful in differentiating cysts from solid tumors, and its primary use is the identification and characterization of palpable and nonpalpable abnormalities of the breast detected by physical examination or mammography. In the evaluation of a palpable mass in 420 patients, if both mammography and ultrasound are negative, Soo et al[46] reported the negative predictive value to be more than 99%.

In addition to complementing physical examination and mammography in diagnosis, ultrasound is often used as a guide for interventional procedures. Ultrasound-guided core biopsies are routinely performed in the diagnosis of breast cancer and have been shown to be more cost-effective than stereotactic biopsy. Ultrasound can also be used for fine-needle aspiration (FNA) biopsies, cyst aspirations, presurgical localizations, and evaluation of breast tissue surrounding implants.

Magnetic Resonance Imaging

The routine use of breast magnetic resonance imaging (MRI) as part of the breast cancer workup is controversial. National consensus guidelines recommend breast MRI for staging evaluation to define the extent of cancer or presence of multifocal or multicentric cancer in the ipsilateral breast or as screening of the contralateral breast at the time of initial diagnosis. They also indicate MRI would be useful for evaluation before and after neoadjuvant chemotherapy, to identify the primary cancer in women with axillary nodal carcinoma or occult primary cancer, or in patients with invasive lobular carcinoma (ILC) poorly defined on mammography.

Computed Tomography

There is no established role for computed tomography (CT) scans in routine staging of patients with early-stage breast cancer. The need for iodine contrast material to differentiate benign from malignant conditions, high radiation dose, cost per study, and inability to detect small lesions precludes the use of CT for initial evaluation, except under special circumstances. Most patients with node-negative breast cancer do not need to undergo routine CT scans for staging, because the yield is exceeding low. A small percentage of women with very high-risk node-negative disease or with node-positive disease may be upstaged by routine CT scans, and although the yield is low, it is common practice to CT stage patients with high-risk node-negative and node-positive breast cancer. Many women undergoing breast-conserving surgery and radiation do have CT scans as part of RT treatment planning. Without the use of contrast and specific diagnostic imaging protocols, these scans should not be considered as part of a staging procedure.

Bone Scans

Similar to CT imaging, routine bone scan at the time of initial treatment of stage I and II breast cancer is of limited value and should be reserved for patients with symptoms, such as bone pain.

Positron Emission Tomography Scanning

Positron emission tomography (PET) using ^{18}F-labeled fluorodeoxyglucose scanning is not a routine component of staging. Its application in patients on initial presentation with early-stage disease has not been established. However, per national consensus guidelines, PET staging may have a role in patients with metastatic, locally advanced, or recurrent disease.

Pathologic Studies

Histopathologic diagnosis may be obtained by FNA, core-needle biopsy (CNB), or surgical biopsy. During an FNA, a small amount of breast tissue or fluid is removed with a thin, hollow needle. If there is a palpable breast abnormality, the procedure can be done by physical examination, but it can also be done using image guidance. FNA biopsies can provide quick results; however, the sample obtained may not be sufficient for additional laboratory testing, such as receptor testing. During a CNB, a hollow needle is used to take out a higher volume of tissue from the breast. This is typically performed with image guidance, such as mammogram (stereotactic-guided CNB), ultrasound (ultrasound-guided CNB), or MRI (MRI-guided CNB). A clip is placed at the biopsy site for future localization. Compared to an FNA biopsy, a CNB can more reliably establish an accurate diagnosis and provide sufficient tissue for further testing and breast cancer subtype categorization. A surgical biopsy may be necessary after an FNA or CNB returns as nondiagnostic or benign but discordant with imaging findings.

In the United States, ER and progesterone receptor (PR) assays are routinely done for patients with breast cancer. The *HER2/neu* assay is also done routinely, either by immunohistochemical

(IHC) analysis, which tests for protein expression, or by fluorescence in situ hybridization (FISH), which tests for gene amplification. FISH testing is often employed for patients with equivocal IHC results. Patients who exhibit overexpression are candidates for *HER2/neu*-targeted therapies.

Staging

Two staging systems are widely used for breast cancer: the American Joint Committee on Cancer (AJCC) (Table 62.5) and the Union Internationale Contre le Cancer systems.[47,48] Major changes made in the eighth edition of the *AJCC Cancer Staging Manual* include the following[49]:

TABLE 62.5 AMERICAN JOINT COMMITTEE ON CANCER STAGING OF BREAST CANCER

Primary Tumor (T)	
Definitions for classifying the primary tumor (T) are the same for clinical and pathologic classification. If the measurement is made by physical examination, the examiner will use the major headings (T1, T2, or T3). If other measurements, such as mammographic or pathologic measurements, are used, the subsets of T1 can be used. Tumors should be measured to the nearest 0.1-cm increment.	
TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (Paget)	Paget disease of the nipple with no tumor
Note: Paget disease associated with a tumor is classified according to the size of the tumor.	
T1	Tumor ≤20 mm in greatest dimension
T1mic	Tumor ≤1 mm in greatest dimension
T1a	Tumor >1 mm but ≤5 mm in greatest dimension
T1b	Tumor >5 mm but ≤10 mm in greatest dimension
T1c	Tumor >10 mm but ≤20 mm in greatest dimension
T2	Tumor >20 mm but ≤50 mm in greatest dimension
T3	Tumor >50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic nodules); invasion of the dermis alone does not qualify as T4.
T4a	Extension to the chest wall; invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures does not qualify as T4.
T4b	Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria for inflammatory carcinoma
T4c	Both (T4a and T4b)
T4d	Inflammatory carcinoma
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed (eg, previously removed).
N0	No regional lymph node metastasis
N1	Metastasis to movable ipsilateral axillary lymph node(s)
N2	Metastasis to ipsilateral axillary lymph node(s) fixed or matted or in clinically apparent[a] ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastasis
N2a	Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures

N2b	Metastasis only in clinically apparent[a] ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph node metastasis
N3	Metastasis to ipsilateral mammary lymph node(s) with or without axillary lymph node involvement or in clinically apparent[a] ipsilateral internal mammary lymph node(s) and in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastasis in ipsilateral infraclavicular lymph node(s)
N3b	Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastasis in ipsilateral supraclavicular lymph node(s)
Pathologic Classification (*p*N)	
*p*NX	Regional lymph nodes cannot be assessed (eg, previously removed or not removed for pathologic study).
*P*N0	No regional lymph node metastasis histologically, no additional examination for isolated tumor cells (ITCs)
Note: ITCs are defined as single tumor cells or small cell clusters not >0.2 mm, usually detected only by immunohistochemical (IHC) or molecular methods but which may be verified on hematoxylin and eosin stains. ITCs do not usually show evidence of malignant activity (eg, proliferation or stromal reaction).	
p N0(i−)	No regional lymph node metastasis histologically, negative IHC
p N0(i+)	No regional lymph node metastasis histologically, positive IHC, IHC cluster no >0.2 mm
p N0(mol−)	No regional lymph node metastasis histologically, negative molecular findings (reverse transcriptase polymerase chain reaction [RT-PCR])
p N0(mol+)	No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)
p N1	Metastasis in 1-3 axillary lymph nodes and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection, but not clinically apparent[b]
p N1mi	Micrometastasis (approximately 200 cells, >0.2 mm, none >2.0 mm)
p N1a	Metastasis in 1-3 axillary lymph nodes, one >2.0 mm
p N1b	Metastasis in internal mammary nodes with microscopic disease detected by sentinel node dissection, but not clinically apparent[c]
p N1c	pN1a and pN1b combined
p N2	Metastasis in 4-9 axillary lymph nodes or in clinically apparent[b] internal mammary lymph nodes in the absence of axillary lymph node metastasis
p N2a	Metastasis in 4-9 axillary lymph nodes (at least one tumor deposit >2.0 mm)
p N2b	Metastasis in clinically apparent[b] internal mammary lymph nodes in the absence of axillary lymph node metastasis
p N3	Metastasis in ≥10 axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent[b] ipsilateral internal mammary lymph nodes in the presence of ≥1 positive axillary lymph nodes; or in >3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes or in ipsilateral supraclavicular lymph nodes
p N3a	Metastasis in ≥10 axillary lymph nodes (at least one tumor deposit >2.0 mm) or metastasis to the infraclavicular lymph nodes
p N3b	Metastasis in clinically apparent[b] ipsilateral internal mammary lymph nodes in the presence of ≥1 positive axillary lymph nodes or in >3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection, but not clinically apparent[c]
p N3c	Metastasis in ipsilateral supraclavicular lymph nodes
Distant Metastasis (M)	
M0	No distant metastasis

cM0(i+)	No clinical or radiographic evidence of distant metastases in the presence of tumor cells and/or no deposits no >0.2 mm detected microscopically or by using molecular techniques in circulating blood, bone marrow, or other nonregional lymph node tissue in a patient without symptoms or signs of metastases
M1	Distant metastases detected by clinical and radiographic means (cM) and/or histologically proven metastases >0.2 mm (pM)

[a]Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination or grossly visible pathologically.

[b]Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

[c]Not clinically apparent is defined as not detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

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- The inclusion of two-stage grouping systems. The *anatomic* stage group table is based solely on anatomic extent of cancer as defined by the T, N, and M categories. The *prognostic* stage group table is based on populations of persons with breast cancer who have been offered—and mostly treated with—appropriate endocrine and/or systemic chemotherapy, which includes anatomic T, N, and M plus tumor grade and the status of the biomarkers human epidermal growth factor receptor 2 (HER2), ER, and PR.
- LCIS is removed as a pathologic tumor in situ (pTis) category for T categorization. LCIS is a benign entity and is removed from TNM staging.
- The general rules for rounding to the nearest millimeter do not apply for tumors between 1.0 and 1.5 mm so that these cancers are not classified as microinvasive (T1mi) carcinomas (defined as invasive tumor foci ≤1.0 mm). Tumors greater than 1 and less than 2 mm should be reported rounding to 2 mm.

The T categorization of multiple synchronous tumors is identified clinically and/or by macroscopic pathologic examination, and their presence is documented using the (m) modifier for the T category. Figure 62.8 depicts the various clinical stages according to tumor and nodal characteristics.

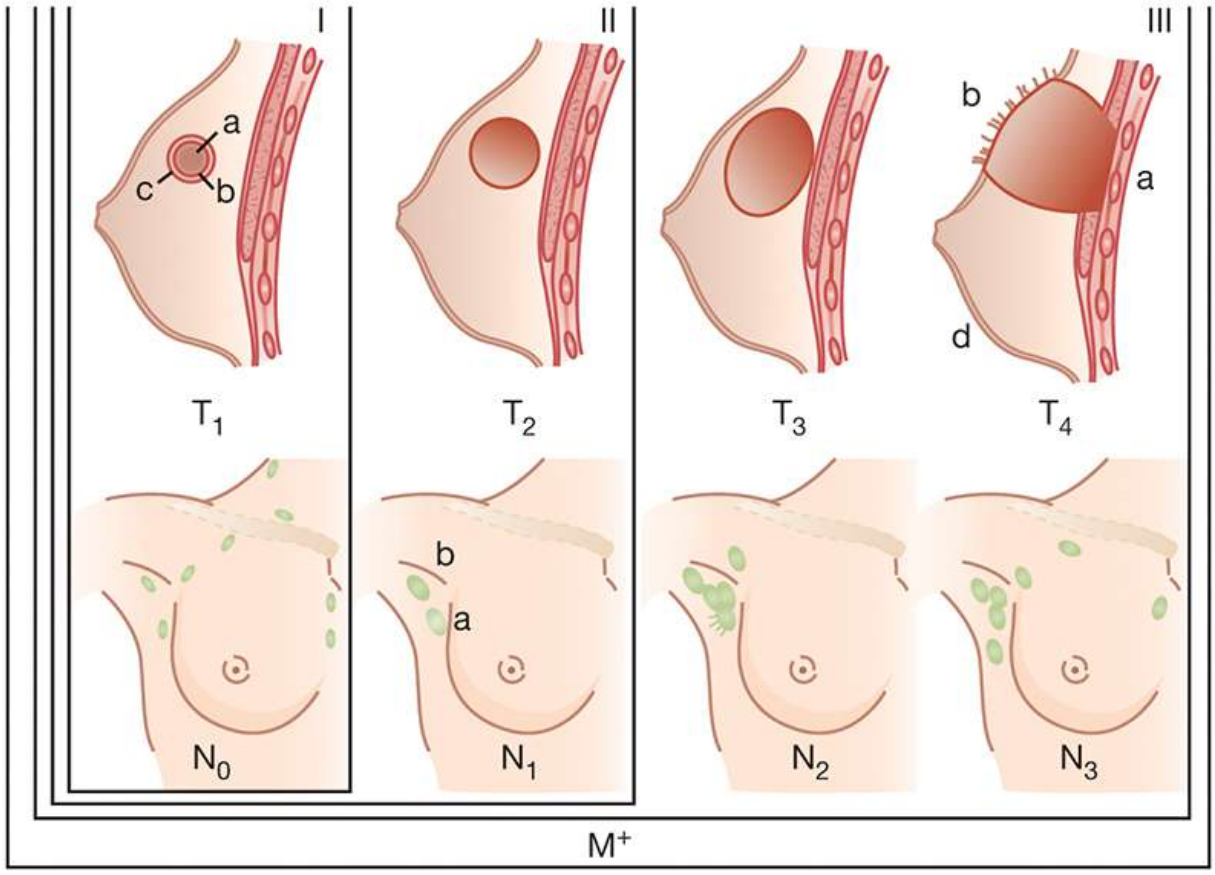


FIGURE 62.8 Clinical staging of carcinoma of the breast. Stages, in part, reflect curability by locoregional treatment modalities prognostically (surgery and radiation therapy). The equivalence of T and N categories are as follows: T2 = N1, T3 = N2, T4 = N3. The American Joint Committee on Cancer and Union Internationale Contre le Cancer classification systems use similar categories and stages. (Reprinted from Langmuir VK, Poulter CA, Qazi R, et al. Breast cancer. In: Rubin P, ed. *Clinical Oncology: A Multidisciplinary Approach for Physicians and Students*. 7th ed. W.B. Saunders; 1993. Copyright © 1993 Elsevier. With permission.)

Pathologic Classification

The World Health Organization (WHO) has classified proliferative conditions and tumors of the breast into the following categories: benign mammary dysplasias, benign or apparently benign tumors, carcinoma, sarcoma, carcinosarcoma, and unclassified tumors. The AJCC has adopted the WHO classification of tumors as shown in Table 62.6.[47]

TABLE 62.6 AMERICAN JOINT COMMITTEE ON CANCER HISTOPATHOLOGIC CLASSIFICATION OF BREAST TUMORS

Type
Precursor lesions
Ductal carcinoma in situ
Lobular neoplasia
Lobular carcinoma in situ
Classic lobular carcinoma in situ
Pleomorphic lobular carcinoma in situ
Atypical lobular hyperplasia
Intraductal proliferative lesions

- Usual ductal hyperplasia
- Columnar cell lesions including flat epithelial atypia
- Atypical ductal hyperplasia

Papillary lesions
- Intraductal papilloma
  - Intraductal papilloma with atypical hyperplasia
  - Intraductal papilloma with ductal carcinoma in situ
  - Intraductal papilloma with lobular carcinoma in situ
- Intraductal papillary carcinoma
- Encapsulated papillary carcinoma
  - Encapsulated papillary carcinoma with invasion
- Solid papillary carcinoma
  - In situ
  - Invasive

Invasive carcinoma of no special type (NST)
- Pleomorphic carcinoma
- Carcinoma with osteoclast-like stromal giant cells
- Carcinoma with choriocarcinomatous features
- Carcinoma with melanotic features

Invasive lobular carcinoma
- Classic lobular carcinoma
- Solid lobular carcinoma
- Alveolar lobular carcinoma
- Pleomorphic lobular carcinoma
- Tubulolobular carcinoma
- Mixed lobular carcinoma

Tubular carcinoma

Cribriform carcinoma

Mucinous carcinoma

Carcinoma with medullary features
- Medullary carcinoma
- Atypical medullary carcinoma
- Invasive carcinoma NST with medullary features

Carcinoma with apocrine differentiation

Carcinoma with signet-ring cell differentiation

Invasive micropapillary carcinoma

Metaplastic carcinoma of NST
- Low-grade adenosquamous carcinoma
- Fibromatosis-like metaplastic carcinoma
- Squamous cell carcinoma
- Spindle cell carcinoma
- Metaplastic carcinoma with mesenchymal
  - Differentiation
  - Chondroid differentiation
  - Osseous differentiation
  - Other types of mesenchymal differentiation
- Mixed metaplastic carcinoma
- Myoepithelial carcinoma

Epithelial-myoepithelial tumors

Adenomyoepithelioma with carcinoma

Adenoid cystic carcinoma

Rare types

Carcinoma with neuroendocrine features
Neuroendocrine tumor, well differentiated
Neuroendocrine carcinoma poorly differentiated (small cell carcinoma)
Carcinoma with neuroendocrine differentiation
Secretory carcinoma
Invasive papillary carcinoma
Acinic cell carcinoma
Mucoepidermoid carcinoma
Polymorphous carcinoma
Oncocytic carcinoma
Lipid-rich carcinoma
Glycogen-rich clear cell carcinoma
Sebaceous carcinoma

Data from Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. Springer; 2017.

The radiation oncologist should be familiar with the histologic characteristics of breast cancer because many of them affect prognosis and may have important therapeutic implications. Brief descriptions of several types of carcinoma of the breast follow.

Microinvasive carcinoma is defined as "the extension of cancer cells beyond the basement membrane into the adjacent tissues with no focus more than 0.1 cm in greatest dimension." Lesions that fulfill this definition are staged as T1mic, a subset of T1 breast cancer. The AJCC staging manual further states that "when there are multiple foci of microinvasion, the size of only the largest focus is used to classify the microinvasion" and that the sizes of the individual foci should not be added together. They also state that "the prognosis of microinvasive carcinoma is generally thought to be quite favorable, although the clinical impact of multifocal microinvasive disease is not well understood at this time." Widely varying definitions of microinvasion have been used, and some differ substantially from that offered here.[47]

Invasive (infiltrating) ductal carcinoma is the most common type of breast cancer, constituting more than 50% of all cases. It appears as solid cords or groups of ductal tumor cells varying in size and cytoplasmic content and degree of differentiation. An associated in situ component is frequently seen.

Tubular carcinoma is composed of tubular structures typically lined by a single layer of well-differentiated epithelium. The tubular cells simulate those of normal ducts or ductules, are arranged in multiglandular cribriform or adenocystic configurations, and are frequently associated with other in situ carcinomas of the breast.[50] Tubular carcinomas have a nonaggressive growth pattern with an excellent prognosis.

Medullary carcinoma is composed of cords and masses of large cells with reticular pleomorphic nuclei containing prominent nucleoli. There is a scant fibrous stroma, but lymphoid infiltrate is prominent. These tumors are microscopically and grossly well circumscribed. Prognosis, in general, is better than for other tumors. These tumors are more frequently seen in younger women and are commonly associated with patients with *BRCA1* mutations.[51]

Lobular invasive carcinoma may be interspersed; the cells appear singly or in small clusters in a targetoid or single-file pattern. Some scirrhous carcinomas probably are invasive lobular lesions; these tumors tend to be aggressive and multicentric and are prone to the development of distant metastases. Du Toit et al[52] reported five subtypes of lobular carcinomas in 171 cases and observed a 12-year actuarial survival rate of 100% for the tubulolobular subtype but only 47% for the solid variant. Two other characteristics of ILC is that it is often "mammographically silent," meaning its detection or the full appreciation of extent of disease is often not visualized mammographically.

Invasive lobular cancers are much more commonly ER positive than is invasive ductal carcinoma (IDC). Infiltrating pleomorphic lobular carcinoma is an aggressive variant of ILC.

Mucinous carcinoma, also called mucoid or colloid carcinoma, has been observed in older women with relatively long duration of symptoms. It is slow growing with a pushing border. Necrosis, lymphatic invasion, and nodal metastasis are rare. Survival is typically better than with IDC.[53]

Adenocystic carcinoma is rarely found in the breast. Histologic features and clinical behavior are similar to its counterpart in the salivary gland and the upper respiratory tract. Limited data demonstrate low LR and high DFS rates.[54]

Invasive micropapillary carcinoma of the breast is characterized by growth of tumor cell clusters in prominent clear spaces resembling dilated angiolymphatic vessels. Nassar et al[55] reported on 83 invasive micropapillary carcinomas; the mean tumor size was 4 cm, 22% invaded skin, 58% were poorly differentiated, and 71% were ER positive. Axillary node metastases were present in 77% of cases and were typically multiple (51% had three or more positive). Forty-six percent of the patients died from their disease (mean interval to death, 36 months). Skin involvement and nodal status were the only parameters predictive of poor survival ($P = .01$).

Metaplastic carcinoma is relatively rare. Beatty et al,[56] of the Swedish Cancer Institute, identified 24 cases that were compared with typical breast cancer cases matched for age; date of diagnosis; stage; and ER, PR, and *HER2* status. The mean metaplastic primary tumor diameter was 2.5 cm. The histologic or nuclear grade was high in 21 of 24 cases. ER or PR status was negative in all cases. *HER2* was negative in 10 of 11 cases tested. Epidermal growth factor receptor (EGFR; *HER1*) was positive in seven of seven cases tested. Five-year survival was 83% (95% CI, 66%-100%). Comparison with matched typical breast cancer cases revealed no significant difference in multidisciplinary treatment patterns, recurrence, or survival. The increased expression of EGFR (*HER1*) may provide an opportunity for targeted therapy in these tumors.

In an analysis of the MD Anderson Cancer Center experience and the Surveillance, Epidemiology, and End Results (SEER) database, Hennessy et al[57] identified 100 patients with metaplastic sarcomatoid carcinoma and 213 patients in the SEER database with similar histology. They concluded that these are aggressive tumors with poor response to therapy and poor outcomes, suggesting that studies evaluating novel targeted therapy are needed for these patients.

Paget disease describes involvement of the nipple by tumor. The tumor seems to travel linearly down the ducts and may appear to be multicentric. There may be an associated subareolar tumor. Breast-conserving surgery followed by radiation is effective in this disease.[58]

Cystosarcoma phyllodes is usually a benign lesion; in broad, fibrous beads that look “leaflike” are cystic clefts lined by a single layer of cells. These tumors are large; usually, they are encapsulated, without invasion of the adjacent breast. The lesions frequently develop from preexisting fibromas and have a long initial period of slow growth followed by a sudden, rapid increase in size. The grade (mitotic rate), surgical margins, and proliferative index have prognostic importance.

Primary mammary lymphomas are rare and constitute approximately 0.5% of breast malignancies and approximately 1% of all non-Hodgkin lymphomas. Diffuse large B-cell lymphoma is the most common histologic subtype of primary breast lymphoma (50%-80%). The indolent histologic subtypes of marginal zone lymphoma (10%-30%) and follicular lymphoma (10%-20%) are the next most frequent. Burkitt lymphoma (typically in pregnancy or lactation) constitutes approximately 5%, with the more recently described entity of breast implant–associated anaplastic large cell lymphoma making up an increasing proportion of the remaining cases.[59]

Sarcoma

Primary breast sarcomas are occasionally seen. McGowan et al[60] described 78 cases of primary breast sarcoma without metastatic disease (76 women, 2 men); 32 patients had malignant cystosarcoma phyllodes, and the others had stromal sarcomas (14 patients), angiosarcomas (8 patients), fibrosarcomas (7 patients), carcinosarcomas (5 patients), liposarcomas (4 patients), or other lesions (8 patients). The cause-specific survival rate was 48%, the relapse-free rate was 42%, and the local relapse–free rate was 75% at 10 years. No statistically significant difference in outcome was noted between those treated with conservation surgery and those undergoing mastectomy. Patients with negative margins had a significantly better local relapse–free rate than did those with positive margins (80% vs 33%; $P = .009$).

PROGNOSTIC FACTORS FOR SURVIVAL AND METASTASIS

Carcinoma of the breast represents a wide spectrum of tumors with a variety of clinical, biologic, and genetic characteristics resulting in a considerable variation in prognosis. It is important to understand, particularly from the radiation oncologists' perspective, that prognostic factors for systemic relapses and prognostic factors for local relapse differ significantly. Furthermore, prognostic factors for local relapse after mastectomy differ substantially from prognostic factors for local relapse after lumpectomy and radiation. For example, tumor size and nodal status are clearly among the strongest predictors of OS and metastasis and are also strong predictors of postmastectomy chest wall relapse when radiation is not used. However, these factors have not been consistently reported to be prognostic for an in-breast relapse after cancer surgery. On the other hand, margin status is a strong predictor of relapse in the conservatively treated breast but is not strongly correlated with distant metastasis. Young age is also a very strong predictor of local relapse after breast-conserving therapy (BCT), and although it has been shown to be predictive of systemic metastasis, the effect of young age on distant metastasis as an independent factor is clearly not as significant as it is for local relapse in the conservatively managed patient. Patients, as well as clinicians, often become confused regarding these issues, resulting in misconceptions regarding appropriate decision-making and treatment. Below, prognostic factors for systemic relapse (ie, distant metastasis and DFS and OS) are discussed. A more in-depth discussion of prognostic factors for local relapse following lumpectomy and radiation is included later in the section on selection factors for the conservative management of breast cancer. Prognostic factors related to postmastectomy chest wall recurrence for patients with early-stage disease are discussed in Chapters 63.

Tumor Size

The size of the primary tumor ranks among the strongest predictors of distant metastasis and DFS and OS. Although tumor size correlates strongly with the presence and number of involved axillary lymph nodes, it is clearly an independent prognostic factor. Among patients with documented node-negative disease, tumor size remains a strong and independent predictor of DFS and OS. In a classic study with over 20 years of follow-up, Rosen et al[61] reported a recurrence-free survival of 88% for tumors less than 1 cm, 72% for tumors 1.1 to 3.0 cm, and 59% for tumors 3.1 to 5.0 cm.

Axillary Nodal Status

Of all prognostic factors, nodal status continues to be the strongest predictor of DFS and OS and is the primary factor that governs breast cancer staging (Figure 62.9).[47] Although there is a direct

relation between the number of axillary nodes involved and the risk of distant metastasis, the most commonly employed schema is to group patients into four prognostic categories (node negative, 1-3 involved nodes, 4-9 involved nodes, and >10 involved nodes). These nodal prognostic categories are employed in the N staging of the current AJCC staging system. Although outcomes will continually improve as systemic therapies advance, data from previous NSABP trials treated primarily with locoregional therapy alone revealed 5-year survival rates of 82.8% for node negative, 73% for 1 to 3 positive nodes, 45.7% for 4 to 12 positive nodes, and 28.4% for more than 13 positive nodes.[32,62,63]

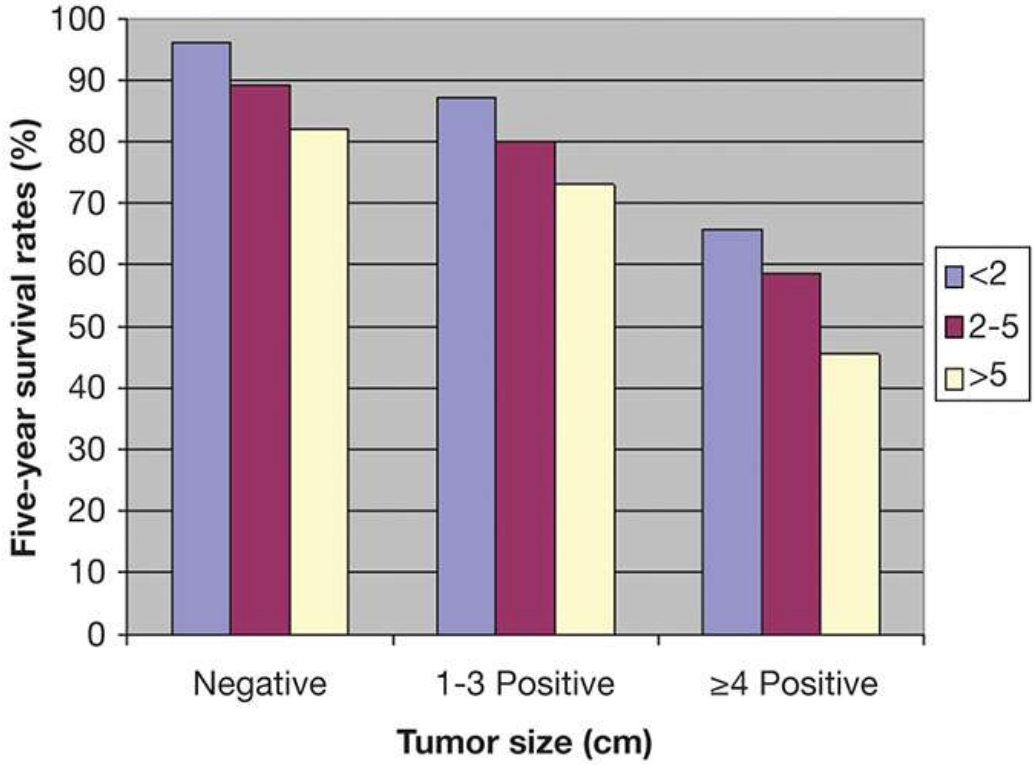


FIGURE 62.9 Five-year survival according to tumor size and nodal status. (Adapted from Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. *Cancer*. 1989;63[1]:181-187. Copyright © 1989 American Cancer Society. Reprinted by permission of John Wiley & Sons.)

Micrometastasis

The influence of microscopic disease in the lymph nodes has been the subject of several analyses because of the increased detection of micrometastasis in the era of sentinel lymph node biopsy (SLNB). Most studies have demonstrated that using a combination of blue dye and radiolabeled colloid techniques, the sentinel node can be identified in more than 95% of cases.[64-66] In experienced hands, false-negative sentinel node rates are low (<10%), and prognosis of sentinel node–negative patients is similar to that of node-negative patients who have undergone a complete axillary dissection. Although the standard of care for sentinel node–positive patients has traditionally been completion axillary dissection, results of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial have challenged the need for completion axillary dissection in selected sentinel node–positive patients.[67] The need for axillary dissection in node-positive patients will likely continue to be highly individualized and will be further evaluated in ongoing clinical trials.[68]

Hansen et al[69] evaluated the sentinel node in 696 women by hematoxylin and eosin staining and IHC. With a median follow-up of 38 months, the size of the sentinel node metastasis (<2 or >2 mm) was a significant prognostic factor. There was no difference in DFS or OS, however, between true node-negative and IHC-only–positive cases.

Tumor Type

The histologic subtype of invasive cancer has been shown to be of prognostic value in several studies. The tubular, mucinous, and medullary subtypes have been shown to have a more favorable prognosis, compared with invasive ductal.[61,70] Invasive lobular tumors appear to have a prognosis similar to invasive ductal tumors.[71] Poor prognostic categories include metaplastic, undifferentiated, and other rarer subtypes. In a classic analysis of 293 T2N0 breast cancers with over 20 years of follow-up treated by mastectomy, Rosen et al[61] reported more favorable relapse rates in medullary, mucinous, tubular, and papillary subtypes compared with invasive ductal and invasive lobular tumors.

Tumor Grade

Multiple tumor grading systems have been proposed in an effort to standardize and improve interobserver variability. The Scarff-Bloom-Richardson classification system utilizes mitotic index, differentiation, and pleomorphism, each with scores of 1 to 3. Total scores of 3 to 5 are well differentiated, 6 to 7 moderately differentiated, and 8 to 9 poorly differentiated. This system is commonly employed and has been shown to be of independent prognostic significance.[72]

Elston and Ellis of the Nottingham group refined this methodology.[73] The revised technique involves evaluation of three morphologic features—the percentage of tubule formation, the degree of nuclear pleomorphism, and an accurate mitotic count using a defined field area. A numerical scoring system is used, and the overall grade is derived from a summation of individual scores for the three variables: three grades of differentiation are used. Histologic grade, assessed in 1,831 patients, shows a very strong correlation with prognosis; patients with grade 1 tumors have a significantly better survival than do those with grade 2 and 3 tumors ($P < .0001$). If the protocol is followed, reproducible and consistent results regarding prognosis can be obtained.

Estrogen and Progesterone Hormonal Receptors in Tumor Cells

Hormone receptor–positive breast cancers have either the ER, PR, or both. The majority of breast cancers are hormone receptor positive, and they can be treated with hormone therapy drugs. Hormone receptor–positive tumors typically grow more slowly compared to hormone receptor–negative tumors, and their associated outcomes are more favorable. Recurrences of hormone receptor–positive breast cancer can, however, occur many years after treatment.

HER2/neu

The *HER2/neu* proto-oncogene (also called c-*erbB-2*) located on chromosome 17 codes for a transmembrane glycoprotein, p185, which has tyrosine kinase activity and is homologous to the EGFR.[74] It is amplified or overexpressed in up to 20% of human breast carcinomas. Overexpression of the protein is associated with tumor aggressiveness and decreased DFS in node-positive patients, with variable prognostic significance among node-negative patients. The conflicting reports regarding the prognostic significance of *HER2/neu* may be related to interobserver variability in interpretation of staining and uncertainty regarding the significance of intermediate staining.[74-76]

Staining for overexpression of *HER2/neu* is interpreted on a 0 to 3+ scale. The available data suggest that the majority of 0 to 1 staining is clearly negative and 3+ is clearly positive, while the classification of those patients with 2+ staining remains uncertain. Amplification of the oncogene identified using FISH techniques has been found to be of more prognostic value.[74-77]

Patients who are found to be positive for *HER2/neu* are candidates for targeted therapies. Romond et al[78] reported on the combined results of two trials comparing adjuvant chemotherapy with or without concurrent trastuzumab, a monoclonal antibody that binds to the *HER2/neu* protein, in patients with surgically resected *HER2/neu*-positive breast cancer. At 3 years, the DFS was 75.4% in the control group and 87.1% in the trastuzumab group (absolute difference 11.8%; 95% CI, 8.1-15.4).

Lymphatic and Vascular Invasion

Lymphatic and vascular invasion (LVI) in the peritumoral region has been clearly demonstrated to be of independent prognostic significance.[79] In the study by Rosen et al,[61] recurrence rate for patients who are LVI-positive stage I was 38% compared with 22% for patients who are LVI-negative.

Proliferative Indices, S-Phase, and Thymidine Labeling Index

Various techniques for evaluating the proliferative rate of a tumor have been shown to correlate with distant metastasis and survival. The most common are the fraction of cells in SPF, thymidine labeling index (TLI), mitotic index, or antibodies directed against proliferative markers such as Ki-67 and proliferating cell nuclear antigen.

Thymidine labeling represents the fraction of cells in S-phase of the cell cycle and is based on the active incorporation of labeled thymidine into DNA; the TLI of primary breast cancers appears closely related to steroid receptor status and generally unrelated to pathologic stage.[80] Retrospective analyses have shown that TLI is a prognostic indicator, independent of tumor size, steroid receptors, and *p53* and Bcl-2 protein expression. Together with patient age and tumor size, TLI is able to identify patients at different levels of risk for locoregional or distant metastases.

DNA Ploidy Index

Chromosomal instability (CIN), either past or present, is indicated whenever tumor cells harbor an abnormal quantity of DNA, termed "aneuploidy."[81] The most widely used approach to detecting aneuploidy is DNA cytometry—a method that involves staining of DNA in the nuclei of cells from a tissue sample, followed by analysis using quantitative flow cytometry or microscopic imaging. Most breast cancers exhibit a bimodal distribution of DNA values. DNA ploidy as measured by flow cytometry correlates with nuclear grade, with low-grade tumors being diploid and high-grade tumors being aneuploid. Ploidy was found to be associated with histologic type, tumor grade, and SPF values, but not with patient age, menopausal status, tumor size, axillary nodal status, ER status, or PR status.[82] Diploid tumors tend to be ER positive with more favorable prognosis, whereas aneuploid tumors are frequently ER negative with less favorable prognosis. Older patients are more likely to have hyperdiploid tumors.[83]

p53 Gene

The *p53* tumor suppressor gene encodes a nuclear phosphoprotein that is thought to be important to cell cycle regulation and DNA repair and may regulate induction of apoptosis by ionizing radiation.

The *p53* gene is most frequently mutated in sporadic breast cancer; alterations of this gene were identified in 43 (22%) of 192 tumors.[84] Mutations of *p53* were found more often in tumors of younger women ($P = .002$) and African American women ($P = .04$) and in tumors lacking ER ($P = .03$), PR ($P = .04$), or both ($P = .06$). In 843 cases of breast cancer, *p53* mutations were not found in low-grade carcinomas (tubular, mucinous, papillary, and invasive cribriform types) but were observed in 4.2% of ILCs (6/140 cases), 15.5% of high-grade IDCs (99/640 cases), and 50% of pure medullary carcinomas (5/10 cases).[85] The OS rates were not significantly different in patients with mutant or wild-type *p53* tumors.

Genetic Profiling

DNA microarray technologies allow for extensive profiling of tumors based on their gene expression signatures. Using this technology, investigators from the Netherlands Cancer Institute screened thousands of genes to develop a 70-gene prognostic signature that in 295 women demonstrated a 10-year DFS of 50.6% in 180 poor prognosis signature patients compared with 85.2% in 115 women with a favorable signature. In a validation study, the profiling outperformed classic prognostic criteria, but the magnitude of the prognostic value was not as strong.[86-88]

Gene expression profiling has had a marked impact on our understanding of the biology of breast cancers and is routinely used in clinical decision-making. Categorizing breast cancer into distinct clinical subtypes of luminal A, luminal B, *HER2/neu*, and basal-like has significant prognostic value and impacts on decisions regarding systemic therapy options. Although gene profiling forms the basis of this subtyping, most clinicians rely on common molecular markers of ER, PR, *HER2/neu*, Ki-67, and others as a surrogate to classify patients into these intrinsic subtypes of breast cancer for clinical decision-making.[89]

An assay using gene profiling on paraffin-embedded specimens has been developed by Genomics Health Inc.[90] The Oncotype DX Breast Recurrence Score (RS) Assay measures RNA expression levels of 21 genes (16 cancer-related and 5 reference genes) using quantitative real-time reverse transcriptase polymerase chain reaction on formalin-fixed, paraffin-embedded tissue samples to compute an RS (0-100), which is used to estimate the odds of relapse over 10 years. Specimens from patients in NSABP trials with ER-positive HER2-negative tumors treated with tamoxifen alone were used to validate this scheme in which patients were categorized as low risk (<18 score), intermediate risk, or high risk. As shown in Figure 62.10, the likelihood of distant metastasis is low in those patients with favorable scores treated with tamoxifen alone.

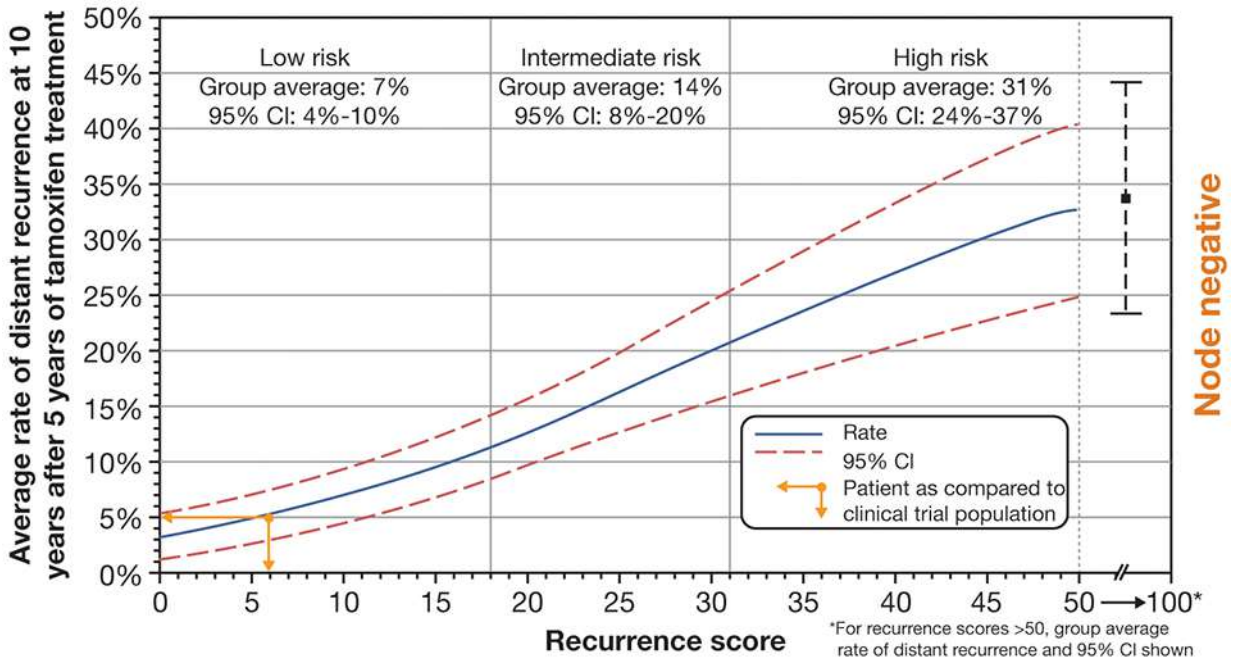


FIGURE 62.10 Risk stratification in patients with receptor-positive tumors treated with hormonal therapy broken as a function of recurrence score using the Oncotype DX gene profiling scheme. CI, confidence interval.

The Trial Assigning Individualized Options for Treatment was designed to further clarify the risk stratification groups and investigate the clinical significance of midrange scores of 11 to 25.[91] Over 10,000 women were registered and assigned to a treatment group. Women with scores of 10 or less received endocrine therapy alone, and women with scores of 26 or more received chemotherapy. Those with midrange scores of 11 to 25 were randomly assigned to receive either endocrine therapy alone or chemotherapy and endocrine therapy. Trial results demonstrated that endocrine therapy had noninferior invasive DFS compared to chemotherapy and endocrine therapy. At 9 years, invasive DFS was similar in both groups (83.3% endocrine therapy vs 84.3% chemotherapy and endocrine therapy), and OS rates were nearly identical (93.9% endocrine therapy vs 93.8% chemotherapy and endocrine therapy). It was noted that the chemotherapy benefit varied with the combination of RS and age, and there was some benefit with chemotherapy for women aged 50 years or below with an RS of 16 to 25.

Age

Although young age has consistently been shown to be a predictor of local relapse following breast-conserving surgery, there are conflicting data regarding its prognostic significance for distant metastasis and OS. The available data are confounded by the fact that younger women often present with palpable disease and have larger tumors with a higher percentage of positive nodes. Several studies, however, have shown that when corrected for stage, young age remains a significant prognostic factor for distant metastasis.[92,93]

Race

African American women are commonly diagnosed with more advanced stages of breast cancer than are White women.[5] Simon and Severson,[94] in a review of 10,502 women diagnosed with breast

cancer (82% White and 18% African American), observed that African American women were more likely to present with regional or distant disease (45%) than were White women (37%). White women had a better survival rate than did African American women during the first 4 years after diagnosis ($P < .0001$), but there were no significant differences in survival by race in women who lived longer than 4 years ($P = .64$). Other studies have also indicated that Black women more commonly develop breast cancers that are high grade and negative for ER, PR, and *HER2/neu*.[95,96]

Obesity and Body Mass Index

Obesity and elevated BMI have been associated with poor outcomes in breast cancer. Daling et al,[97] in a study of 1,177 women aged 45 years and below who had invasive ductal breast carcinoma, found that women with breast carcinoma who were in the highest quartile of BMI were 2.5 times more likely to die of their disease within 5 years of diagnosis compared with women in the lowest quartile of BMI.

Smoking

High plasma levels of estrogens are associated with increased breast cancer risk. Manjer et al,[98] in an analysis of 792 women in a mammographic screening trial with a mean follow-up of 12.1 years, observed that 145 patients died of breast cancer. The RRs for smokers and ex-smokers, compared with those who had never smoked, were 1.44 and 1.13, respectively. The association with smoking remained significant after adjustment for age and stage at diagnosis and other potential confounders.

Pregnancy

Pregnancy can transiently increase the risk of breast cancer after childbirth but has been shown to have a protective effect in later years. In women with multiple pregnancies, the short-term increase may be offset by the long-term protection from the first pregnancy.[99]

Tumor Location

There is some evidence that medially located tumors have a poorer prognosis than do laterally located tumors. An analysis of 45,880 patients from the SEER database by Gaffney et al[100] demonstrated that the hazard ratio (HR) for the inner quadrant location compared with the outer quadrant was 1.27 for breast cancer–specific survival and 1.11 for OS. Both were significant in multivariate analysis. It has been suggested that this may be due to occult spread to IMNs.

Selected Other Prognostic Factors

A wide variety of other prognostic factors have been extensively evaluated. Although some of these have been promising in initial reports, they have not been applied in routine clinical decision-making. However, these markers may help supplement information obtained with more established prognostic factors. Furthermore, with additional testing and validation, some of these markers may serve as targets for therapeutic interventions. Extensively evaluated and reported factors that may be prognostic significance include cathepsin-D, vascular endothelial growth factor, EGF, *Bcl-2*, carcinoembryonic antigen, prostate-specific antigen, E-cadherin, and others. The reader is referred elsewhere for an extensive review of molecular prognostic factors in breast cancer.[101]

SURGICAL MANAGEMENT OF BREAST CANCER

Management of invasive breast cancer should be based on the clinical extent and pathologic characteristics of the tumor, in addition to the age of the patient (menopausal status), some biologic prognostic factors, and the preference and psychological profile of the individual patient, optimally in a multidisciplinary setting. Although surgical, medical, and radiation oncology remain the primary therapeutic disciplines in the management of breast cancer, the patient's management is often dependent on input from diagnostic radiology and pathology, the primary physician involved, and support services, such as genetic counseling, social work, nursing, and others.

The surgical management of patients with early-stage operable breast cancer addresses both the primary tumor and regional lymphatics. The primary tumor may be managed by mastectomy or lumpectomy, and the nodal regions may be surgically addressed by lymph node dissection or sentinel node biopsy. The radiation oncologist should be aware of the various surgical procedures, as it may influence the radiotherapeutic management. Procedures that remove the bulk of parenchymal breast tissue include radical mastectomy, extended radical mastectomy, modified radical mastectomy, simple mastectomy (also referred to as total mastectomy), skin- sparing mastectomy, and nipple-sparing mastectomy. Partial mastectomy, lumpectomy, tylectomy, and quadrantectomy are collectively referred to as breast-conserving surgery.

Breast-conserving approaches, as well as the skin- and nipple-sparing mastectomy, used in early-stage breast cancers, are briefly discussed here as they are often used in early-stage disease. Details of the mastectomy procedures are summarized in Chapters 63.

Skin-Sparing Mastectomy

Skin-sparing mastectomy is a standard mastectomy with minimal skin sacrifice at the mastectomy site. This is often performed when immediate reconstruction is planned. This technique attempts to remove all breast tissue, but the preservation of skin provides cosmetic and reconstructive advantages. The procedure is oncologically sound, and patients undergoing skin-sparing mastectomy do not require postmastectomy radiation unless they have pathologic factors that place them at higher risk (ie, positive nodes, positive margins, large primary tumors), as discussed in Chapters 63.

Nipple-Sparing Mastectomy

The nipple-sparing mastectomy is distinct from the skin-sparing mastectomy in that the nipple and/or nipple-areola complex are conserved. This procedure may be contraindicated in patients with disease near the nipple-areola complex.

Lumpectomy

Various terms have been used to describe the breast-conserving surgical approach, including lumpectomy, wide local excision, tylectomy, tumorectomy, segmental mastectomy, partial mastectomy, and quadrantectomy. This approach is extensively discussed in this chapter. BCT includes breast-conserving surgery followed by breast irradiation. The NSABP recommends specific types of incisions depending on the location of the tumor (Figure 62.11). The radiation oncologist may play an advisory role, as in many cases the patient may be evaluated by both the surgeon and the radiation oncologist before the definitive operation.

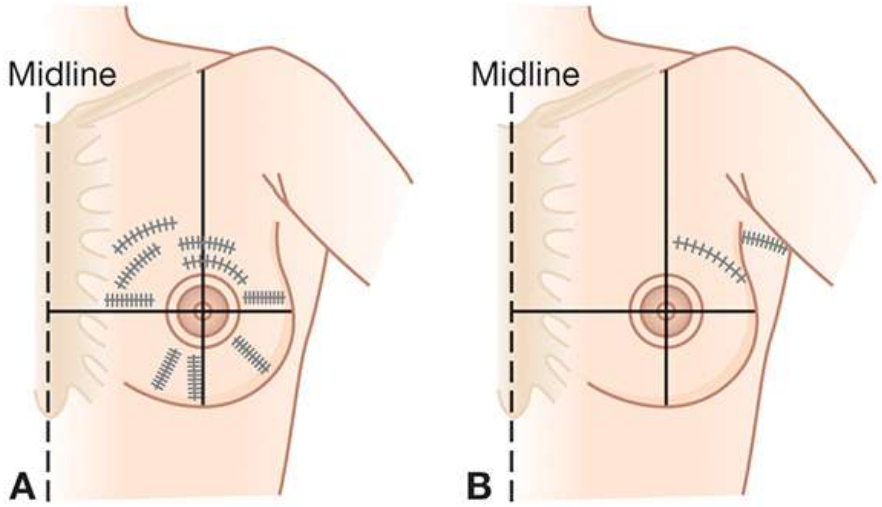


FIGURE 62.11 National Surgical Adjuvant Breast Project recommendations for the direction of incisions used for tumorectomy (A) and for axillary node dissection (B). (Courtesy of Bernard Fisher, MD, Chairman, National Surgical Adjuvant Breast Project. From Bedwinek JM. Treatment of stage I and II adenocarcinoma of the breast by tumor excision and irradiation. *Int J Radiat Oncol Biol Phys*. 1981;7[11]:1553-1559. Copyright © 1981 Elsevier. With permission.)

The optimal extent of breast resection for the treatment of T1 and T2 breast cancer has not been defined. Increasing the size of the resection may not only lower the risk of LR but also has an adverse impact on the cosmetic outcome. Because cosmesis is a critical reason for performing tumor excision and irradiation instead of mastectomy, wide local excision with microscopically negative margins is preferable to segmental mastectomy or quadrantectomy.

Surgical removal of additional breast tissue surrounding the original excision site is indicated when margins are positive and there is a substantial probability that the tumor cell burden exceeds what can be controlled by the usual doses of radiation. The percentage of patients with residual tumor at the time of reexcision varies widely depending on the criteria used for taking a patient back to the operating room for more breast surgery. Tumor size alone is not usually considered an indication for reexcision in the absence of other factors.

Other factors that may have an impact on the rate of positive reexcisions include extensive intraductal carcinoma (EIC) and residual calcifications on a postlumpectomy preirradiation mammogram. In a series from Yale by Lally et al,[102] of 34 patients with a postlumpectomy mammogram that showed suspicious residual calcification who underwent reexcision, 20 (59%) were found to have residual disease. Patients whose initial tumor was associated with calcifications with questionable, close, or positive margins should be evaluated with a postlumpectomy mammogram with guided reexcision if suspicious residual calcifications are present.

Based on these findings, the authors recommend reexcision at the primary tumor site (a) when the surgical procedure was less than a complete lumpectomy, such as an initial incisional biopsy or core biopsy; (b) when pathologic margins on the initial excisional biopsy are shown to be involved by tumor; and (c) when there are residual suspicious microcalcifications on a postlumpectomy mammogram. As discussed later, although reexcision for involved margins is indicated, selected patients with a focally involved margin may be treated with RT with acceptable local control rates.

Choices Between Mastectomy and Breast-Conserving Surgery in Early-Stage Disease

For most patients with early-stage breast cancer, breast-conserving surgery and mastectomy are both reasonable options, and patients are often conflicted regarding the choice. Patients should be reassured that provided they meet the criteria for breast-conserving surgery, all of the available medical evidence demonstrates equivalent long-term survival rates with both modalities.

A modified radical mastectomy may be preferable for some patients who wish to avoid radiation, for those in whom removal of clinical and radiographically apparent disease will result in a suboptimal cosmetic result, for those with diffusely positive margins that cannot be cleared with reexcision, and those with diffuse suspicious microcalcifications. Even patients who are ideally suited for BCT may have a personal preference for mastectomy, based on a number of factors.

Some patients with early-stage breast cancer will choose mastectomy to avoid the course of radiation. However, patients selecting mastectomy should also be made aware that this procedure does not totally eliminate the need for radiation treatment. For patients with early-stage operable breast cancer treated by a modified radical mastectomy, postoperative irradiation of the chest wall and peripheral lymphatics may be indicated in selected patients with high-risk characteristics, positive nodes, or positive resection margins. Indications for postmastectomy radiation are discussed in Chapters 63.

Surgical Management of Axillary Lymph Nodes

An axillary node dissection or sentinel node biopsy is a standard component of the staging process for a majority of women with early-stage invasive breast cancer.[47] Although the role of complete axillary dissection is evolving, there is compelling evidence that ALND is not necessary in most women with early-stage breast cancer. Two randomized trials, the ACOSOG Z0011 trial and the International Breast Cancer Study Group 23-01 (IBCSG 23-01) trial (discussed later), demonstrated that many of these patients with one or two metastatic sentinel nodes can safely avoid a completion axillary node dissection. It is not uncommon for clinicians to avoid axillary staging altogether if it is not going to influence further management. This is relevant in older women with receptor-positive tumors who will receive hormonal therapy, regardless of nodal status, and who are not thought to be candidates for cytotoxic chemotherapy. The decision to omit SLNB in older women should be discussed in a multidisciplinary setting with input from the treating oncologists to ensure all providers are in agreement as to whether axillary staging information is important for adjuvant therapy decisions. As discussed later, axillary radiation, as with axillary dissection, results in a high rate of regional control.

Axillary Node Dissection

The axillary contents are divided into three levels: Level I represents tissue between the axillary vein and the latissimus dorsi muscle and the lateral border of the pectoralis minor muscle; level II is located between the lateral and medial borders of the pectoralis minor muscle; and level III is between the medial border of the pectoralis minor and the Halsted ligament (the apex of the axilla). Thorough dissection of levels I and II has traditionally been the most common axillary surgical procedure in patients with clinically node-negative breast cancer. Complete axillary dissection, including level III, may be performed in patients with clinically positive lymph nodes. Pigott et al[103] reported on 146 patients treated with radical mastectomy (either modified or Halsted) for IDC or ILC of the breast. Eighty patients (55%) had histologically proven axillary lymph node metastases. If only the low (level I) axillary lymph nodes had been removed, 18 (25%) patients would have had metastases confined to levels II and III that would have gone undetected. However, only 1.4% of patients showed positive level III lymph nodes if levels I and II were negative.

Approximately 20% to 40% of patients with carcinoma of the breast and clinically negative lymph nodes have pathologic evidence of lymph node metastases.[63,104] Yet, in patients with stage I or II breast cancer and clinically negative axillary lymph nodes, if an axillary dissection is not performed, axillary recurrence develops in only approximately 20%. In patients with clinically positive axilla, 20% to 30% have no histologic evidence of nodal metastatic disease.[32]

In a randomized trial evaluating the necessity of axillary dissection in older women, Martelli et al[105] reported on 219 women, 65 to 80 years of age, with early breast cancer and clinically negative axillary nodes who were randomized to conservative breast surgery with or without axillary dissection. Tamoxifen was prescribed to all patients for 5 years. With a follow-up of 60 months, there were no significant differences in overall or breast cancer mortality or crude cumulative incidence of breast events between the two groups. Only two patients in the no axillary dissection arm (8 and 40 months after surgery) developed overt axillary involvement during follow-up. They concluded that older patients with T1N0 breast cancer can be treated by conservative breast surgery and no axillary dissection without adversely affecting breast cancer mortality or OS.

In light of the increased use of primary tumor-related factors, including molecular profiling, for decision-making regarding systemic therapy, combined with sentinel node procedures and low rates of regional relapse with RT or observation in selected patients, axillary dissection has been less frequently employed in the management of patients with early-stage breast cancer.

Sentinel Lymph Node Biopsies

In recent years, there has been a substantial increase in the use of SLNBs to stage patients with breast cancer. Patients are injected around the tumor with technetium-99m (^{99m}Tc) sulfur colloid and vital blue dye, and a hand-held γ-probe is used to identify areas of highest radioisotope uptake in the lymphatic system. The lymph nodes underlying this area (SLNs) are removed.[65,106-108] The sentinel node procedure has been widely embraced as an acceptable standard for women with breast cancer and has a high degree of sensitivity and specificity.[109]

The standard of care that mandated performing an ALND in patients who are node-positive was reexamined after the publication of IBCSG 23-01 and the ACOSOG Z11 studies.[110] The IBCSG 23-01 study randomized 931 patients with micrometastatic (<2 mm) deposit in the SLNB to ALND or no additional surgery.[111] The majority of the patients (97%) received adjuvant RT without RNI. In the ALND arm, additional axillary nodal involvement was detected in 13% of the patients. There was no difference in the OS or DFS between the two study arms. Although the study closed before meeting target accrual, the authors concluded that patients with breast cancer with limited SLN involvement could be spared the morbidity of an ALND.

The ACOSOG Z11 study was a prospective trial examining survival of patients with sentinel node metastases detected by standard hematoxylin and eosin staining, who were randomized to undergo ALND after sentinel lymph node dissection (SLND) versus SLND alone.[112] All patients received whole-breast irradiation. There were 446 patients randomized to SLND alone and 445 to SLND plus ALND. Those randomized to SLND plus ALND had a median of 17 axillary nodes removed compared with a median of only 2 sentinel nodes removed with SLND alone ($P < .001$). At a median follow-up time of 6.3 years, there were no statistically significant differences in LR ($P = .11$) or regional recurrence ($P = .45$) between the two groups. Interestingly, ALND also removed more positive lymph nodes ($P < .001$) in 27% of the patients in this group. The patients in this trial all had whole-breast irradiation, but RNI was not allowed. However, there was no RT quality assurance, and field design was not uniform. The reason for the low regional relapse rates is likely a combination of factors, including a favorable subset of patients with a low likelihood of a high

residual axillary burden of disease, the use of systemic therapy, and incidental radiation to the residual nodes in level I or II from the tangential breast irradiation. A subsequent review of radiation treatment records on a subset of patients from this trial noted the use of high tangent fields (cranial border within 2 cm of the humeral head) in roughly 50% of patients and directed RNI using three or more fields in roughly 20% of patients.

Several studies describe an approach to radiation field design based on probability of additional axillary nodal involvement in patients with positive sentinel nodes (Table 62.7).[68,113-116]

TABLE 62.7 SUGGESTED APPROACH FOR RADIATION FIELD DESIGN IN SENTINEL NODE–POSITIVE PATIENTS NOT UNDERGOING AXILLARY LYMPH NODE DISSECTION

Clinical Scenario	Sentinel Nodes +/Total Sentinel Nodes Sampled	Probability of Additional Nodes MSKCC[113] (%)	Probability of Additional Nodes MDACC[114] (%)	Probability of Four or More Nodes Involved[115] (%)	Field Design
IDC, 1.0 cm, ER+, LVI−	1 (IHC only)/3	3	8	<1	Tangents only
IDC, 1.8 cm, G3, ER+, LVI−, Unifocal	1 (macro)/2	27	24	2	High tangents
IDC, 2.0 cm, ER−, LVI+	2 (macro)/2	63	55	30	High tangents/consider full nodal treatment
ILC, 4.0 cm ER+, multifocal, LVI−	2 (macro)/2	77	64	40	High tangents/consider full nodal treatment
IDC, 3 cm, ER−, LVI+, multifocal	3 (macro with ENE)/3	78	95	80	Full nodal treatment

ENE, extranodal extension; ER, estrogen receptor; G, grade; IDC, infiltrating ductal carcinoma; IHC, immunohistochemistry; ILC, infiltrating lobular carcinoma; LVI, lymphovascular invasion; macro, macroscopic.

Quality-of-life measures have also been studied in the setting of SLNB and ALND, and several studies have demonstrated superior outcomes with SLNB.

The ALMANAC (Axillary Lymphatic Mapping Against Nodal Axillary Clearance) trial was a multicenter randomized trial of 1,031 patients randomly assigned to sentinel node biopsy (n = 515) or standard axillary dissection (n = 516). Mansel et al[107,108] reported the primary outcome measures, which were arm and shoulder morbidity and quality of life. Drain usage, length of hospital stay, and resumption of normal activities after surgery were all highly significantly better in the SLN group. In addition, patient recorded quality of life and arm functioning scores were also significantly better, with no increase in anxiety levels in the sentinel node group. The authors concluded that sentinel node biopsy is the treatment of choice for patients who have early-stage breast cancer and clinically negative nodes.

Veronesi et al[117] also reported on a randomized trial of 516 patients with T1 tumors, randomized to either sentinel node biopsy or total axillary dissection. Axillary dissection was performed in the sentinel node group if the sentinel node contained metastases. In the axillary dissection group, the overall accuracy of the sentinel node status was 96.9%, the sensitivity 91.2%, and the specificity 100%. There was less pain and better arm mobility in the patients who underwent sentinel node biopsy only than in those who also underwent axillary dissection. There were 15 events associated with breast cancer in the axillary dissection group and 10 such events in the sentinel node group.

Among the 167 patients who did not undergo axillary dissection, there were no cases of overt axillary metastasis during follow-up.

The role of SLN procedures in patients undergoing neoadjuvant chemotherapy is covered in Chapters 63.

SYSTEMIC MANAGEMENT OF BREAST CANCER

Systemic therapy is an essential component of both early-stage node-negative breast cancer and advanced-stage disease. Hormonal therapy, cytotoxic chemotherapy, and, the more recently introduced, biologic therapies are routinely employed in the vast majority of patients with early-stage breast cancer. For patients with all stages of breast cancer, systemic therapy has been shown to decrease the RR of relapse and mortality. However, there are subsets of patients with a very favorable prognosis and extremely low rate of relapse, in whom the risk reduction results in only a very small absolute benefit. These issues are also discussed in more detail in Chapters 63.

RADIATION THERAPY IN THE MANAGEMENT OF EARLY-STAGE INVASIVE BREAST CANCER

The radiation oncologist plays a critical role in the management of early-stage breast cancer. As noted previously, the role of RT in postmastectomy radiation and in the neoadjuvant treatment of advanced breast cancers will be discussed in Chapters 63. The remainder of this chapter is focused primarily on the role of RT in the conservative management of early-stage invasive breast cancer.

This will include an extensive discussion of the studies establishing breast-conserving surgery and radiation as the preferred standard of care for the majority of women with early-stage invasive disease and studies evaluating the avoidance of RT in selected patients. Integration of RT with systemic therapy will be discussed, as will selection of patients for BCT. Risk factors for local relapse and controversies in the management of patients with special circumstances will be discussed. Technical issues in the delivery of RT for early-stage breast cancer, including dosing and fractionation, matching techniques, and newer technical approaches, will be presented. The rapidly evolving area of partial-breast irradiation will also be discussed. Follow-up of the patient with breast cancer and sequelae of treatment will be presented. Management of local relapse in the conservatively treated breast and postmastectomy will be covered in Chapters 63. The role of RT in the management of DCIS and LCIS was discussed in Chapters 61.

Breast-Conserving Therapy and Patient Selection

Breast-conserving surgery followed by RT to the intact breast is clearly established as the most acceptable standard of care for the majority of women with early-stage invasive breast cancer. In addition to tumor control and survival, conservation of the breast with optimal cosmetic results is a crucial goal of this therapy, which is associated with improved psychoemotional adjustment of the patient to the diagnosis and treatment of carcinoma of the breast. It also enhances the acceptance by women of mammographic screening for early detection of this disease. The widespread embracement of breast-conserving surgery followed by RT is based on numerous mature and well-documented studies, both prospectively designed randomized trials and large retrospective series of appropriately selected patients treated with breast conservation followed by RT.

It is important to select appropriate patients and tumors for breast conservation therapy, with close consultation between the surgeon, medical oncologist, and the radiation oncologist and after thorough discussion of therapeutic alternatives with the patient. The risks and benefits of BCT

compared with mastectomy should be discussed. Despite the clear evidence of equivalence, some patients will still prefer mastectomy, which remains an acceptable standard of care for women with operable breast cancers. Although avoidance of radiation may be a primary rationale for some patients in choosing mastectomy, patients should realize that even with early-stage operable disease, postmastectomy radiation may be indicated based on the pathologic findings at mastectomy.

Ideally, patients electing breast-conserving surgery and radiation will have unicentric primary tumors that are less than 4 to 5 cm in diameter, as cosmesis is affected by the amount of tissue that must be removed in relation to the size of the breast. For patients in whom the size of the tumor, compared with the size of the breast, will result in an unacceptable cosmetic outcome, neoadjuvant therapy can be considered to facilitate breast conservation. This was discussed in detail in Chapters 63.

With careful attention to surgical margins, radiation technique, and the appropriate use of systemic therapy, local relapse rates in most conservatively managed patients are low, and only a minority of patients with early-stage invasive breast cancer are not suitable for BCT. There are several perceived relative "contraindications" to BCT, including patients with collagen vascular disease (CVD), patients with germline mutations that predispose to breast cancer development, those with positive margins, more advanced disease, multicentric disease, pregnancy, or patients who have had prior radiation. Although many of these factors require careful consideration and discussion between the treating physicians and the patient, as discussed in the section on special circumstances, selected patients faced with breast cancer in the setting of these controversial circumstances can be offered BCT with acceptable outcomes. Although some clinicians believe that patients at higher risk for the development of LR should not be treated with conservation surgery, there are relatively few absolute contraindications.

Perhaps with the exception of the patients with persistently positive diffuse margins or gross multicentric disease, where removal of clinically and radiographically apparent disease would result in an unacceptable cosmetic outcome, BCT followed by radiation can be offered to most women with early-stage breast cancer and may be offered to a high percentage of women with advanced cancers following neoadjuvant chemotherapy or hormonal therapy. The decision regarding BCT compared with mastectomy is often based on personal preference, as the available medical and scientific evidence suggests equivalent OS and DFS in all subsets of patients.

Randomized Studies Comparing Breast-Conserving Surgery Plus Radiation Therapy to Mastectomy

There have been numerous randomized trials that have now established breast-conserving surgery followed by RT as equivalent to mastectomy for appropriately selected patients with early-stage breast cancer. Table 62.8 summarizes these randomized trials. In all of these trials, local tumor excision (tylectomy, lumpectomy), segmental mastectomy, or quadrantectomy combined with irradiation to the breast yielded survival and tumor control rates similar to those achieved with modified or classic radical mastectomy.[34,39,40,118-122] Each of these randomized trials, as well as meta-analyses of the trials, clearly demonstrates equivalent mortality rates in conservatively treated patients compared with mastectomy.[123-125]

TABLE 62.8 PROSPECTIVE RANDOMIZED TRIALS COMPARING CONSERVATIVE SURGERY AND RADIATION WITH MASTECTOMY FOR EARLY-STAGE BREAST CANCER

	Institut Gustave-Roussy (1972-1984)[126]	Milan (1973-1980)[40]	NSABP B-06 (1976-1984)[34]	NCI (1979-1987)[127]	EORTC (1980-1986)[118]	Danish (1983-1989)[119]
Number of patients	179	701	1,219	237	874	904
Stage	1	1	1 and 2	1 and 2	1 and 2	1, 2, 3
Surgery	2-cm gross margin	Quadrantectomy	Lumpectomy	Gross excision	1-cm gross margin	Wide excision
Follow-up (y)	15	20	20	18	10	6
Overall Survival						
CS + RT (%)	73	42	46	59	65	79
Mastectomy (%)	65	41	47	58	66	82
Local Recurrence						
CS + RT (%)	9	9	14	22	20	3
Mastectomy (%)	14	2	10	6	12	4

CS + RT, conservative therapy; EORTC, European Organisation for Research and Treatment of Cancer; NCI, National Cancer Institute; NSABP, National Surgical Adjuvant Breast and Bowel Project; RT, radiation therapy.

The earliest prospective, randomized trial comparing breast conservation with radical mastectomy was conducted at Guy's Hospital in London. Three hundred and seventy women with stage I or II breast cancer were randomly assigned to receive either standard radical mastectomy or wide local excision plus irradiation.[128] Although the rates of survival and distant metastasis were not significantly different for stage I disease, in stage II, the recurrence rates in the breast and axilla were higher in the group treated with local excision and irradiation, and survival was significantly lower because of a higher rate of distant metastasis. Major weaknesses of this study were the low doses of irradiation used (35-38 Gy to the breast and 25-27 Gy to the axilla), patient selection, and surgical techniques.

Veronesi et al[122] reported on 701 patients with tumors less than 2 cm in diameter and without palpable axillary nodes of whom 352 were randomly assigned to treatment with either quadrantectomy and axillary dissection plus irradiation (50 Gy in 5 weeks to the breast and 10-Gy boost) and 349 to radical (Halsted) mastectomy. Women with positive axillary lymph nodes also received 12 cycles of adjuvant chemotherapy with cyclophosphamide, methotrexate, and fluorouracil (CMF). Actuarial 20-year OS and DFS rates were comparable in the two groups (58%). The death rates from breast cancer were 26.1% and 24.3%. The incidence of local failure was 2.3% with mastectomy and 8.8% with quadrantectomy and irradiation. There was no difference in the incidence of contralateral breast cancer (10.2% and 8.7%, respectively).[40]

Fisher et al[34,120] updated the results of the NSABP protocol B-06 in 1,843 women with clinical stage I or II carcinoma of the breast less than 4 cm in diameter. Patients were randomly assigned to be treated with total mastectomy or lumpectomy (segmental mastectomy), with or without irradiation. Patients who are irradiated received 50 Gy to the breast through tangential field irradiation, and a boost to the operative site was not given. With a 20-year follow-up, there was no significant difference in survival among patients treated with mastectomy, lumpectomy alone, or lumpectomy combined with irradiation. For the patients treated with lumpectomy alone, the ipsilateral breast relapse rates were approximately 40% if the nodes were negative and 50% if they

were positive. For patients treated with lumpectomy and irradiation, the corresponding rates were 10% for all patients and those with negative nodes and 5% for those with positive nodes, illustrating the interaction of irradiation and adjuvant chemotherapy in local tumor control.

The Institut Gustave-Roussy conducted a prospective, randomized trial comparing mastectomy with local excision plus irradiation for women with cancers measuring 2 cm or less.[126,129] The 15-year DFS rate was 55% for the tumorectomy group and 45% for the mastectomy group (P = .23). The 15-year LR rate was 9% in the conservation surgery and irradiation group and 14% in the mastectomy group.

The European Organisation for Research and Treatment of Cancer (EORTC) Breast Cancer Cooperative Group conducted a randomized trial of women with stage I or II breast cancer comparing modified radical mastectomy (420 patients) with breast conservation therapy (448 patients).[118] The actuarial 8-year local tumor control rate was similar in both arms, 91% in the mastectomy group and 87% in the breast conservation therapy group. There was one axillary recurrence in the mastectomy group and three in the conservation therapy group.

A Danish Cooperative Study carried out a similar randomized trial in 905 women (another 248 patients were treated with mastectomy or breast conservation therapy according to preference without randomization).[119] High-risk patients (tumor >5 cm, invasion to skin or deep fascia, metastatic axillary lymph nodes) who were treated with breast conservation therapy received RT to the regional lymph nodes. Those who were treated with mastectomy also received irradiation of the same target volume, and all high-risk patients received adjuvant CMF. At 6 years, the recurrence-free survival rate in 430 patients treated with breast conservation therapy was 70%, compared with 66% in 429 patients treated with mastectomy. OS rates were 79% and 82%, respectively. There were 12 (3%) breast relapses in the former group and 19 (4%) chest wall recurrences in the latter group. In the breast conservation therapy group, 31% of patients had excellent and 41% had satisfactory cosmesis.

The U.S. National Cancer Institute (NCI) reported the results of a randomized study in which 122 patients with T1-2N0M0 disease were treated with modified radical mastectomy and 125 with breast conservation therapy (45-50 Gy to breast plus 15- to 20-Gy boost). Updated by Poggi et al[127] with a median follow-up of 18.4 years, there was no detectable difference with regard to OS between patients treated with mastectomy and those treated with BCT (58% vs 54%; P = .67 overall). Twenty-seven (22%) women in the BCT arm experienced an in-breast event. After censoring in-breast events in the BCT arm that were salvaged successfully by mastectomy, DFS also was found to be statistically similar (67% in the mastectomy arm vs 63% in the BCT arm; P = .64 overall). There was no statistically significant difference in the incidence of contralateral breast carcinoma between the two treatment groups.

Van Dongen et al[39,118] reported on an EORTC trial comparing modified radical mastectomy with BCT (lumpectomy, axillary clearance, and irradiation to the breast, 50 Gy in 5 weeks and a 25-Gy boost with iridium implant) in 168 patients with stage I and 734 with stage II disease. Patients with microscopically incomplete excision of the tumor were included. Updated analysis from this trial with a median follow-up period of 13.4 years revealed that LRR rates were higher in the breast conservation therapy group (10-year rate, 19.7%) than in the mastectomy group (10-year rate, 12.2%, P = .0097). The OS rate at 10 years was 66.1% for patients undergoing mastectomies and 65.2% for patients undergoing breast conservation therapy (P = .11).

PROGNOSTIC FACTORS FOR LOCAL RELAPSE FOLLOWING BREAST-CONSERVING SURGERY PLUS RADIATION THERAPY

Local relapse in the conservatively managed breast is an active area of investigation, with numerous studies dedicated to the evaluation of factors that identify patients at increased risk for local relapse following lumpectomy and RT. Although prognostic factors for local relapse are not as well evaluated as they have been for systemic relapse, there have been numerous studies demonstrating the prognostic value of molecular and genetic markers for local relapse. Local relapse following breast-conserving surgery and radiation can be governed by a complex array of host, primary tumor, and treatment factors.

Given the complex interaction of these factors, it is sometimes difficult to separate out the independent significance of any one factor. There have, however, been several factors that have been consistently reported in influencing local relapse in the conservatively managed patient with breast cancer. Table 62.9 summarizes some of the more commonly reported prognostic factors for local relapse. The factors that most consistently have been reported to influence local relapse, namely, young age, margin status, and the use of systemic therapy, are discussed first, followed by several other commonly evaluated prognostic factors.

TABLE 62.9 SUMMARY OF RISK FACTORS FOR LOCAL RELAPSE

Prognostic Factor	Effect	Strength of Data	Comment
Age	Young age increases local relapse.	Multiple studies Upheld in multivariate analysis Few conflicting reports	Remains among the strongest factors
Margins	Positive margins increase local relapse.	Multiple studies Upheld in multivariate analysis Few conflicting reports	Remains among the strongest factors Data on “close” margins are less consistent.
Systemic therapy	Systemic therapy (chemo and hormonal) lowers risk of local relapse.	Multiple studies support Some conflicting reports	May delay rather than counteract risk
Radiation dose	Higher doses decrease local relapse.	Multiple studies support Confirmed in randomized trials (boost vs no boost) Some conflicting data regarding doses >50 Gy	Interaction with margins and age Necessity of “boost” in women over 50 and with widely negative margins unclear
Extensive intraductal component (EIC)	EIC-positive tumors have higher rates of local relapse.	Initial studies supportive Some confirmatory studies Some conflicting studies	Recent data suggest that negative margin status eliminates this as a risk factor.
LCIS as a component	LCIS as a component increases risk of local relapse.	Conflicting data with no clear consensus	Patients with LCIS are suitable candidates for BCS. Debate remains regarding need for clear LCIS margins.
Lobular histology	Lobular histology has higher local relapse rates.	Conflicting data with no clear consensus	Should be treated similar to invasive ductal cancers
BRCA1/2	Higher late local relapses in patients with *BRCA1/2*.	Several confirmatory studies Some conflicting data	Higher relapse rates related to late “new primaries.” This may be minimized by prophylactic hormonal manipulation.

Prognostic Factor	Effect	Strength of Data	Comment
Tumor size	Larger tumors result in higher local relapses.	Some confirmatory studies Several conflicting studies	Data are confounded by more frequent use of systemic therapy in larger tumors.
Nodal status	Higher local relapse rates in patients who are node-positive.	Several conflicting studies	As with tumor size, data are confounded by more frequent use of systemic therapy in node-positive patients.
Receptor status	Higher local relapse rates in patients who are triple-negative and *HER2*-positive.	Some confirmatory studies Few conflicting studies Under active investigation	Would offer these patients conventional whole-breast irradiation

BCS, breast-conserving surgery; LCIS, lobular carcinoma in situ.

Age

Young age has been shown in numerous studies to be a risk factor for breast recurrence in conservation surgery and irradiation. Different investigators have used various age cutoffs, such as 40, 35, and 30 years.

One of the most significant and powerful studies correlating young age with local relapse was the large EORTC boost versus no-boost trial.[130] Overall in this study, young patient age was a significant predictor of local relapse. As shown in Figure 62.12, the use of a boost, as discussed later, was most effective in younger women, although a later update found an advantage to the boost in all age groups.[131] In a review of 3,602 women who underwent surgery (breast conservation, 55%, or mastectomy, 45%) for early breast cancer and were rolled in EORTC studies, de Bock et al[132] clearly demonstrated the impact of young age on local relapse. The results of multivariate analysis showed that younger age and breast conservation were risk factors for isolated LRR (breast cancer under 35 years of age vs over 50 years of age: HR 2.80; 95% CI, 1.41-5.60; breast cancer age 35-50 years vs over 50 years: HR 1.72; 95% CI, 1.17-2.54; breast conservation: HR 1.82; 95% CI, 1.17-2.86). After perioperative chemotherapy, less isolated LRRs were observed (HR 0.63; 95% CI, 0.44-0.91). It was concluded that young age and BCT were both independent predictors for isolated LRR. The authors noted that as an isolated LRR is a potentially curable condition, women treated with breast conservation or diagnosed with breast cancer at a young age should be monitored closely to detect LR at an early stage.

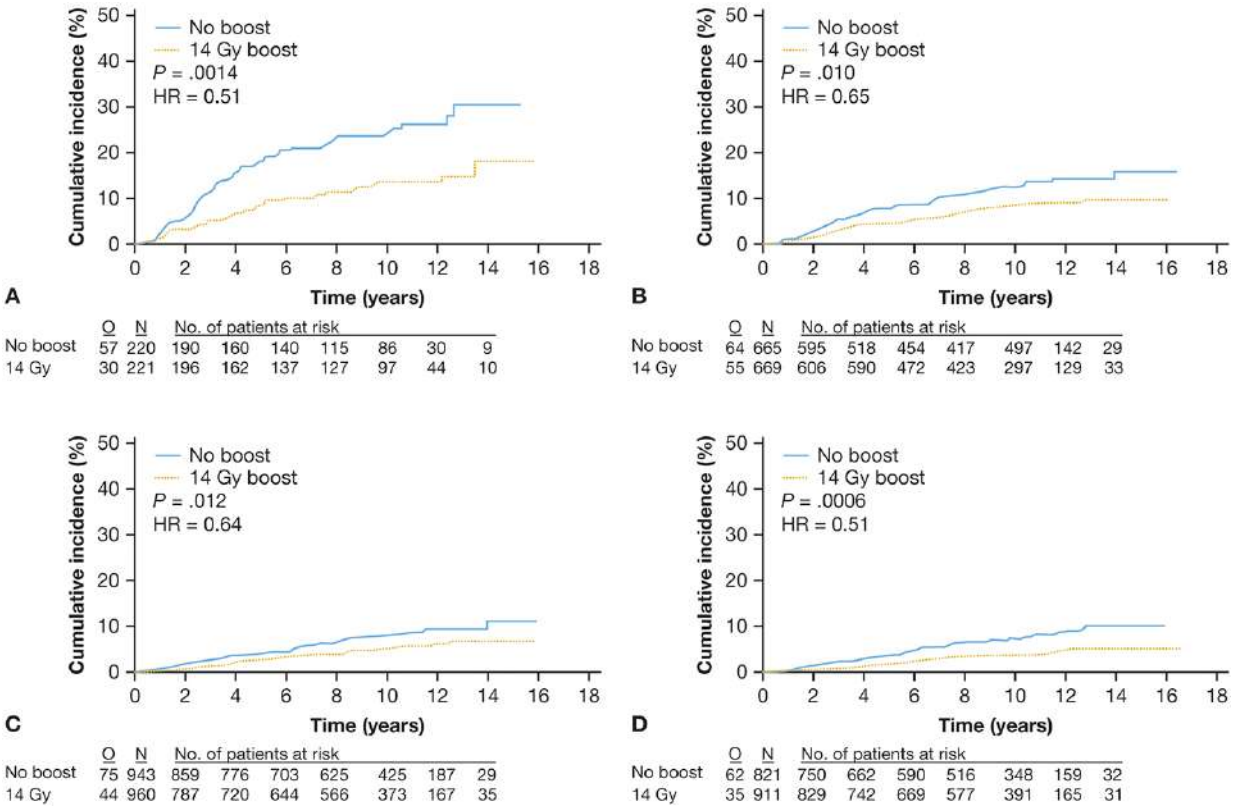


FIGURE 62.12 Cumulative incidence of recurrence of tumor in the ipsilateral breast after whole-breast irradiation at 50 Gy, with or without an additional dose to the tumor bed as a function of age group. HR, hazard ratio. (A) Age ≤ 40; (B) Age 41 to 50; (C) Age 51 to 60; (D) Age > 60 years. (Reprinted with permission from Bartelink H, Horiot JC, Poortmans PM, et al. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. *J Clin Oncol*. 2007;25[22]:3259-3265. Copyright © 2007 by American Society of Clinical Oncology.)

Margin Status

Positive margin status has been one of the most consistently reported factors associated with higher local relapse rates. Because of the varying definitions of margin status and the complex interaction between margin status and use of systemic therapy, radiation dose, and patient age, there are conflicting conclusions regarding the influence of margin status on local relapse. Definition of a negative margin is variable between institutions and in national studies. Although some consider no tumor cells seen on the inked margin definitive, as defined by the NSABP, others consider negative as margins of 1 or 2 mm beyond invasive cancer. Of note, many of the studies evaluating margin status utilized pathologic reports without a central re-review of the original pathology.

The degree of margin involvement (ie, whether it is focally involved or more diffusely involved) is also a critical issue in determining the significance of margin involvement and how it should influence management. Although there are clearly conflicting reports, it is evident that obtaining a wide negative margin is desirable. However, a focally involved margin, particularly when reexcision is not technically feasible, as may be the case with a focally involved deep margin at the pectoralis facia, is not a contraindication to BCT.

A multidisciplinary panel of breast experts from the Society of Surgical Oncology-American Society for Radiation Oncology examined the relationship between margin width and ipsilateral breast tumor recurrence (IBTR) and developed a guideline for defining adequate margins in the

setting of breast-conserving surgery and adjuvant RT.[133] The meta-analysis was based on 33 eligible studies published between 1965 and 2013 and included 28,162 patients, of whom 1,506 (5.3%) had an IBTR. The median follow-up was 79.2 months. Their conclusions and recommendations are as follows:

1. A positive margin, defined as ink on invasive cancer or DCIS, is associated with at least a 2-fold increase in IBTR. This increased risk in IBTR is not nullified by (a) delivery of a boost dose of radiation, (b) delivery of systemic therapy (endocrine therapy, chemotherapy, or biologic therapy), or (c) favorable biology.
2. Negative margins (no ink on tumor) minimize the risk of IBTR. Wider margin widths do not significantly lower this risk. The routine practice to obtain negative margin widths wider than no ink on tumor is not indicated.
3. The rates of IBTR are reduced with the use of systemic therapy. In the uncommon circumstance of a patient not receiving adjuvant systemic therapy, there is no evidence suggesting that margins wider than no ink on tumor are needed.
4. Margins wider than no ink on tumor are not indicated based on biologic subtype.
5. The choice of whole-breast RT (WBRT) delivery technique, fractionation, and boost dose should not be dependent on margin width.
6. Wider negative margins than no ink on tumor are not indicated for ILC. Classic LCIS at the margin is not an indication for reexcision. The significance of pleomorphic LCIS at the margin is uncertain.
7. Young age (≤40 years) is associated with both increased IBTR after BCT and increased local relapse on the chest wall after mastectomy and is also more frequently associated with adverse biologic and pathologic features. There is no evidence that increased margin width nullifies the increased risk of IBTR in young patients.
8. An extensive intraductal component (EIC) identifies patients who may have a large residual DCIS burden after lumpectomy. There is no evidence of an association between increased risk of IBTR and EIC when margins are negative.

Interaction Between Margin Status and Other Variables

The complex interaction between margin status and other treatment-related factors is demonstrated in a recent study by Park et al.[134] They demonstrated that local relapse was significantly higher in patients with diffuse margin involvement than in patients with negative margins. Patients with focally involved margins also had a higher risk of local relapse than did patients with negative margins. However, in those women with focally involved margins who received systemic therapy, the local relapse rate was similar to those with negative margins. Whether systemic therapy delays or negates the effect of a focally involved margin is a matter of debate, but clearly, there are confounding factors that complicate interpretation of the available data.

Freedman et al[135] studied 1,262 patients with clinical stage I or II breast cancer treated by breast-conserving surgery, axillary node dissection, and RT. The final margins were negative in 77%, positive in 12%, and close (≤2 mm) in 11%. The 5-year incidence of IBTR was not significantly different among patients with negative (4%), positive (5%), or close (7%) margins. However, by 10 years, a significant difference in IBTR became apparent (negative 7%, positive 12%, close 14%; $P = .04$). The 5-year cumulative IBTR rate in patients with close or positive margins was 1% with adjuvant systemic therapy and 13% with no adjuvant therapy. However, by 10 years, the IBTR rate

was similar (18% vs 14%), because of more late failures in the patients who received adjuvant systemic therapy.

A study by Jobsen et al[136] demonstrated some of the difficulties associated with interpretation of studies related to margin status and local relapse as it relates to other prognostic factors. In a study of 1,752 patients with known margin status and a median follow-up of 78 months, the 10-year local relapse rate was 5.6% and 12.2% for negative and positive margins, respectively. An interaction between age category and margin status was noted in relation to local relapse–free survival. The 5-year local relapse rate for women younger than 40 years of age was 8.4% for negative margins and 36.9% for positive margins ($P = .005$). On the other hand, the 5-year local relapse rate for women over 40 years old was 2.6% for negative and 2.2% for positive margins.

Although it is clear that margin status is a significant risk factor for local relapse, and negative margins are desirable, the available data suggest that patients with a focally involved margin are suitable candidates for BCT followed by RT to the intact breast.

Effect of Systemic Therapy on Local Control

The use of systemic therapy, in the form of adjuvant tamoxifen or adjuvant chemotherapy, has been clearly shown to impact local control in numerous retrospective series and prospective randomized trials. Although it has been clearly demonstrated in randomized trials that chemotherapy and tamoxifen are not appropriate substitutes for RT, in patients who are treated with RT, the use of systemic therapy improves local control.[34,35,38] As with the other critical prognostic factors, the degree to which systemic therapy influences local control is confounded by other factors.

In the NSABP B-06 trial, patients with lymph node–positive disease who were treated with RT and chemotherapy had an 8-year LR rate of 5% compared with an LR rate of 12% in patients who are lymph node–negative treated with surgery and RT alone.[120] In the NSABP B-21 trial, tamoxifen similarly improved local control rates in patients with lymph node–negative breast tumors smaller than 1 cm. The crude rate of breast tumor recurrence was only 3% in women randomly assigned to undergo lumpectomy, RT, and tamoxifen compared with 7% in women treated with lumpectomy and RT alone.[36] A retrospective analysis from the MD Anderson Cancer Center investigating the impact of systemic therapy on local control after BCT in patients with lymph node–negative breast cancer further confirmed these data.[38] In this study, 277 patients treated with systemic therapy had improved 5-year (97.5% vs 89.8%) and 10-year (95.6% vs 85.2%) local control rates compared with 207 patients who received no systemic treatment. No statistically significant difference was evident in local control between patients treated with chemotherapy and those treated with tamoxifen alone ($P = .219$). In a Cox regression analysis, the use of systemic therapy was the most powerful clinical, pathologic, or treatment predictor of local control, producing a 3.3-fold reduction in the risk of LR. Table 62.10 summarizes several of these studies that have evaluated local control as a function of systemic therapy. It is evident that both hormonal therapy and cytotoxic chemotherapy influence local relapse rates.[137-139]

TABLE 62.10 IPSILATERAL BREAST RECURRENCE RATES BY SYSTEMIC TREATMENT (SYSTX)

Study (Reference)	Number of Patients	Follow-Up (Year)	SysTx	Local Relapse		
				With SysTx (%)	Without SysTx (%)	*P*
NSABP-13[137]	760	8	CTX	2.6%	13	.001

Study (Reference)	Number of Patients	Follow-Up (Year)	SysTx	Local Relapse		
				With SysTx (%)	Without SysTx (%)	*P*
NSABP-14[138]	1,400	10	Tam	3.4	10.3	.001
Buchholz et al[38]	484	8	CTX + Tam	4.4	14.8	.004
Park et al (positive margin)[134]	45	8	CTX	7	18	.05

CTX, chemotherapy; NSABP, National Surgical Adjuvant Breast and Bowel Project; Tam, tamoxifen.

Tumor Size

Although tumor size is clearly a strong predictor of systemic relapse and OS, its prognostic value in local relapse has not been consistently reported. Differences are probably related to the treatment techniques used (eg, completeness of tumor excision, use of irradiation boost) and the complex interaction of other prognostic factors, as noted earlier.

Extensive Intraductal Carcinoma

According to the Harvard definition of EIC, 25% or more of the primary tumor is intraductal carcinoma, and intraductal carcinoma is seen outside (adjacent to) the infiltrating tumor border. Some studies reported higher incidence of breast recurrences with EIC, while others found no significant impact on local tumor control. This discrepancy may be related to the definition of EIC, adequacy of tumor excision, doses of irradiation delivered to the boost volume, and interactions with other factors.

From a group of 885 patients treated for clinical stage I or II invasive breast cancer, Schnitt et al[140] limited their study to 181 patients with IDC who received a radiation dose to the surgical site of 60 Gy or greater, whose final microscopic margins of resection were evaluable, and who had at least 5 years of follow-up. In 157 (87%) patients, the tumor was evaluable for the presence or absence of EIC. The 5-year rates of recurrence among patients with negative, close, focally positive, and more than focally positive margins were 0%, 4%, 6%, and 21%, respectively. Among the 127 patients with EIC-negative tumors, the 5-year recurrence rate was less than 10% in all margin groups. Among the 30 patients with EIC-positive tumors, the 5-year recurrence rate was 0% when margins were negative or close but 50% when margins were more than focally positive. These results provided support for the use of BCT (including an irradiation boost to the primary site) for patients with EIC-positive tumors and negative margins.

Histology

In general, studies that have evaluated local relapse in relation to histologic subtypes of breast cancer have not demonstrated higher relapse rates associated with specific histologic patterns.

Thurman et al,[70] in an analysis of the Harvard series, identified 20 clinical stage I and II patients with mucinous carcinoma, 27 with medullary carcinoma, 28 with tubular carcinoma, and 1,055 with IDC. No significant difference was seen in the site of first failure among the four histologic types within the first 10 years after treatment. Local failure was significantly associated with age less than 50 years ($P = .04$), positive surgical margins ($P = .007$), lymphovascular invasion ($P = .04$), and the presence of EIC ($P < .001$).

An analysis of medullary carcinomas treated conservatively was performed by the Yale group, who identified 46 cases of conservatively treated patients with medullary histology who were compared with 1,444 patients with infiltrating ductal carcinoma.[51] The medullary cohort presented at a younger age with a higher percentage of patients in the 35 years or below age group (26.1% vs 6.6%; $P < .00001$). Twelve patients with medullary histology underwent genetic screening, and six patients were identified with deleterious mutations. This group showed greater association with *BRCA1/2* mutations compared with screened patients in the control group (50.0% vs 15.8%; $P = .0035$). The medullary cohort was also significantly associated with greater T stage and tumor size (37.0% vs 17.2%; T2 mean size 3.2 vs 2.5 cm; $P = .00097$) as well as negative ER (84.9% vs 37.6%; $P < .00001$) and PR (87.5% vs 48.1%; $P = .00001$) status. Breast relapse-free rates were not significantly different from the invasive ductal cancers (76.7% vs 85.2%); however, 10-year distant relapse–free survival in the medullary cohort was significantly better than in the control group (94.9% vs 77.5%; $P = .028$).

Infiltrating Lobular Carcinoma

A review of the literature strongly supports local tumor resection and breast irradiation as an appropriate therapy for invasive lobular breast cancer, following the same guidelines used for invasive ductal tumors. Breast tumor control and survival after BCT are equivalent in patients with invasive ductal or lobular carcinoma. Because of the presumed multicentric nature of lobular carcinomas, several groups have attempted to assess whether these subtypes are more prone to local failure with breast-conserving approaches.[71,141-145] Table 62.11 summarizes results of several selected series of patients treated with breast-conserving surgery and radiation comparing outcomes in lobular carcinoma to IDCs. Although some of the studies show higher contralateral rates in lobular carcinomas, local relapse, DFS, and OS appear to be comparable to IDCs. The majority of studies show locoregional control, DFS, and OS rates in lobular carcinomas that are comparable to patients with IDCs.

TABLE 62.11 LOBULAR CARCINOMA TREATED WITH BREAST-CONSERVING SURGERY AND RADIATION (SELECTED SERIES WITH 10-YEAR FOLLOW-UP)

Study (Reference)	Number Lobular/Number Ductal	Local Relapse Lobular/Ductal	Contralateral Lobular/Ductal	Overall Survival Lobular/Ductal
Santiago et al[141]	55/1,093	18% vs 12% (NS)	12% vs 8% (NS)	85% vs 79% (NS)
Vo et al[142]	84/1,126	4% vs 9% (NS)	11.3% vs 11.9% (NS)	81% vs 85% (NS)
Moran et al[145]	142/1,760	20% vs 13% (NS)	26% vs 12% ($P = .006$)	68% vs 78% ($P = .08$)
Salvadori et al[144]	286/1,903	8% vs 8% (NS)	NR	NR
Peiro et al[143]	93/1,089	15% vs 13% (NS)	4% vs 6% (NS)	NR

NR, no results; NS, not significant.

Lobular Carcinoma In Situ as a Component of Invasive Cancers

Several groups have evaluated whether patients with LCIS as a component of invasive cancer or DCIS were associated with higher local relapse rates. Conflicting results from these studies preclude firm conclusions. In a series of 56 patients with an LCIS component, Jolly et al[146] reported

a higher risk of local relapse at 10 years (14%) compared with a rate of 7% in cases without an LCIS component. In multivariate analysis, a component of LCIS was associated with a higher risk of local relapse.

In contrast, Ben-David et al[147] reported on 64 cases treated at the University of Michigan and found no association between local failure and presence of LCIS. The presence of LCIS at the margins and the size and presence of multifocal LCIS did not alter the rate of local control. Ciocca et al,[148] in an analysis of 290 patients with LCIS as a component compared with 2,604 without LCIS as a component, showed no difference in local control, even if LCIS was present at the final margin.

Nodal Status

Although nodal status is the strongest predictor of distant metastasis and OS, most studies have not clearly demonstrated an effect of nodal status on local control in the conservatively managed patient with breast cancer. This may be because a majority of patients who are node-positive receive chemotherapy or hormonal therapy, which may counteract any adverse effects on local relapse. There are some data, however, that suggest an effect of nodal status on local relapse in conservatively managed patients. At the Institut Gustave-Roussy, among 356 patients, LR was noted in 26% of those with and 6.5% of those without nodal involvement; the greater the number of nodes involved, the more likely the occurrence of local failure and the lower the survival rate.[71] However, other reports noted lower survival rates but fewer breast relapses after breast conservation therapy in patients with positive nodes. Again, this is likely a result of the interaction of irradiation to the breast with adjuvant chemotherapy. Because many patients who are node-positive receive chemotherapy, which is synergistic with radiation in lowering the local relapse rate, any potential adverse effect of positive nodes on local relapse may be lost.

Molecular Factors and Local Relapse

In comparison with an explosion of data regarding molecular markers as risk factors for OS and distant metastasis in breast cancer, there are relatively few data relating molecular markers to local relapse in the conservatively managed breast. There have been several studies, however, that demonstrate the potential application of molecular markers in predicting locoregional relapse in patients with breast cancer.

Haffty et al[149] examined patients treated with BCT plus radiation and identified 482 patients with ER, PR, and *HER2* available for analysis. Patients were then stratified into TN and non-TN status. They found that at 5 years, the TN cohort had a poorer distant metastasis–free rate compared with the other subtypes (67% vs 82%; $P = .002$). TN subtype was an independent predictor of distant metastasis (HR 2.14; 95% CI, 1.31-3.53; $P = .002$) and cause-specific survival (HR 1.79; 95% CI, 1.03-3.22; $P = .047$). However, there was no significant difference in local control between the TN and other subtypes (83% vs 83%). The authors concluded that although patients classified as TN have a poor prognosis, there was no evidence that these patients are at higher risk for local relapse after conservative surgery (CS) and radiation.

In contrast, Nguyen et al[150] reported on 793 patients with invasive breast cancer who received BCT and radiation. With a median follow-up of 70 months, the 5-year rate of LR was 1.8%: 0.8% (0.3, 2.2) for luminal A, 1.5% (0.2, 10) for luminal B, 8.4% (2.2, 30) for *HER2*, and 7.1% (3.0, 16) for basal. In addition, on multivariate analysis, *HER2* and basal subtypes were associated with increased LR as compared with luminal A ($P < .01$). Luminal B and basal subtypes were associated with increased distant metastases as compared with luminal A ($P < .04$).

Voduc et al[151] investigated the rate of local and regional relapse in 2,985 patients stratified by molecular subtype. With a median follow-up of 12 years, they found that after BCT and radiation, patients with luminal A tumors had the most favorable prognosis, with local relapse and regional relapse rates of only 8% and 3% at 10 years, respectively. *HER2*-enriched and basal-like groups exhibited the highest rates of LR (21% and 14%, respectively) and regional relapse (16% and 14%, respectively). After mastectomy, patients with luminal A tumors again had the best prognosis, with rates of local relapse and regional relapse (8% and 4%, respectively, at 10 years). All non–luminal A subtypes exhibited a greater risk of local relapse and regional relapse.

An analysis of TN breast cancers from a large Canadian database revealed an interesting observation. Abdulkarim et al[152] reported a higher rate of local relapse among patients who had T1/T2 node–negative mastectomy treated without radiation and who had TN disease compared with a similar node-negative cohort treated with breast-conserving surgery and radiation. These results emphasize the point that TN breast cancers do not necessarily fare better with mastectomy, possibly because of the incidental irradiation of lymphatics in the low axilla.[153] Wang et al conducted a prospective trial where patients with stages I to II TN breast cancer were treated with mastectomy and randomized to chemotherapy with or without postmastectomy RT (PMRT). With 86.5 months of follow-up, the 5-year DFS rates were 88.3% and 74.6% for adjuvant chemotherapy plus radiation and adjuvant chemotherapy alone, respectively (P = .02). The 5-year OS was significantly improved in adjuvant chemotherapy plus radiation group compared with chemotherapy alone (90.4% and 78.7%, respectively; P = .03).[153]

Mamounas et al[154] investigated the risk of LRR in patients with early-stage, node-negative ER-positive breast cancer treated on the NSABP B14 and NSABP B20 protocols based on the Oncotype DX RS. The RS was available in 355 placebo-treated patients (B14), 424 chemotherapy plus tamoxifen patients (B20), and 895 tamoxifen patients (B14 and B20). In the tamoxifen-treated patients, the risk of LRR was 4.3% for patients with low RS (<18), 7.2% for those with intermediate RS (18-30), and 15.8% for those with high RS (>30). In placebo-treated patients, the risk of LRR was 10.8% for patients with low RS, 20.0% for those with intermediate RS, and 18.4% for those with high RS. In chemotherapy-treated patients, the risk of LRR was 1.6% for patients with low RS, 2.7% for those with intermediate RS, and 7.8% for those with high RS. The authors concluded that the Oncotype DX RS was a significant predictor of LRR.

These analyses, while showing a consistent trend, should be considered exploratory and are not significant enough to alter clinical decision-making. This is clearly an active area of investigation, ideally with molecular studies linked to large clinical trials to help identify molecular markers predictive of locoregional outcomes and potential targets for improving outcomes.

BREAST-CONSERVING SURGERY WITHOUT RADIATION

Based on the mature data from the well-conducted randomized trials outlined earlier and on long-term follow-up from several large retrospective series, it is apparent that breast-conserving surgery followed by RT is a safe and effective modality for the majority of women with early-stage invasive breast cancer. Whether subsets of patients can be treated with breast-conserving surgery alone without irradiation has been the subject of considerable debate and several randomized trials. With the possible exception of selected older women, which is discussed in a later section, subsets of patients in whom RT can be safely avoided have yet to be clearly identified. Collectively, the randomized studies to date consistently demonstrate an approximately 3-fold greater local relapse rate in the unirradiated cohorts.[155] Although the majority of these trials did not demonstrate an

impact on survival, a pooled analysis of these randomized trials demonstrates a small but statistically significant impact on mortality as a result of the omission of radiation.

Vinh-Hung and Verschraegen[155] conducted a pooled analysis of published randomized clinical trials that compared RT versus no RT after breast-conserving surgery. The outcomes studied were IBTR and patient death from any cause. A search of the literature identified 15 trials with a pooled total of 9,422 patients available for analysis. The RR of IBTR after breast-conserving surgery, comparing patients treated with no RT or RT, was 3.00 (95% CI, 2.65-3.40). Mortality data were available for 13 trials with a pooled total of 8,206 patients. The RR of mortality was 1.086 (95% CI, 1.003-1.175), corresponding to an estimated 8.6% (95% CI, 0.3%-17.5%) relative excess mortality if RT was omitted (Figure 62.13A,B).

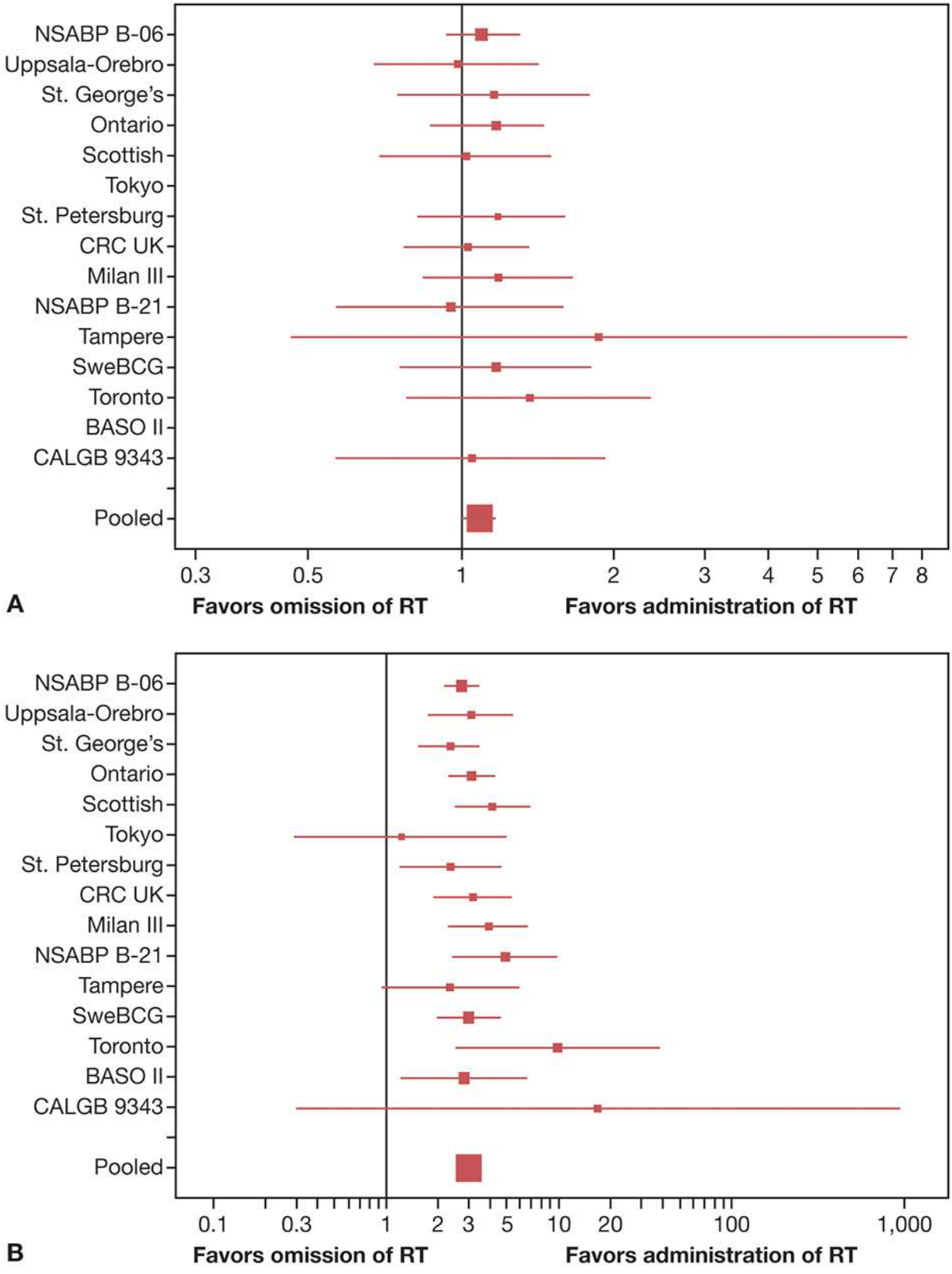


FIGURE 62.13 Meta-analysis of survival (A) and local control (B) in randomized trials comparing breast-conserving surgery with or without radiation. This meta-analysis demonstrated a 3-fold reduction in local relapse and a small but

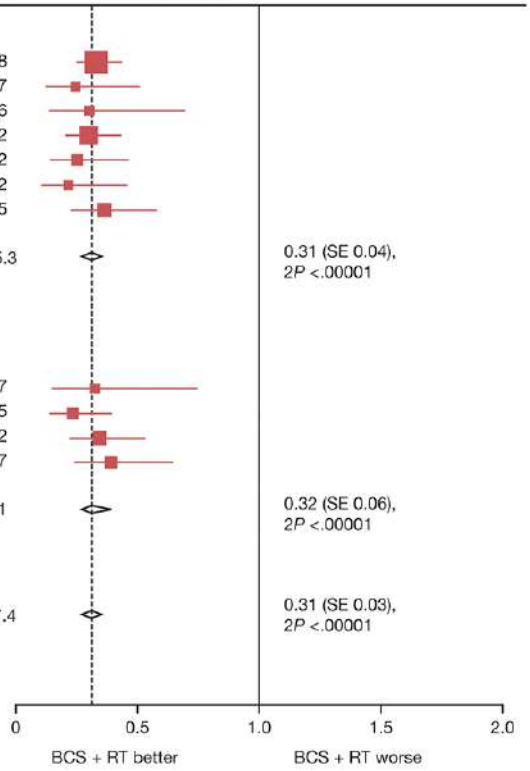
significant increase in survival with the use of radiation therapy (RT) following lumpectomy. NSABP, National Surgical Adjuvant Breast and Bowel Project. (From Vinh-Hung V, Verschraegen C. Breast-conserving surgery with or without radiotherapy: pooled-analysis for risks of ipsilateral breast tumor recurrence and mortality. *J Natl Cancer Inst*. 2004;96[2]:115-121. Reproduced by permission of Oxford University Press.)

In an analysis from the EBCTCG, similar conclusions were reached evaluating various forms of local therapy.[41,42] Within this meta-analysis were 10,801 women treated with breast-conserving surgery in trials randomizing patients to RT versus no RT. The majority included patients with axillary clearance of node-negative disease and generally were treated with radiation to the conserved breast alone. The reduction in LR (mainly in the conserved breast) in patients treated with RT was highly significant ($P < .00001$) in every separate trial. As seen in Figure 62.14, the recurrence rate ratio, comparing those allocated RT with those not, is about 0.3 in every trial, corresponding to a proportional reduction of 70%. Considering all 17 trials together, the 10-year risk of LR is 19% among those allocated RT and 35% among those not, corresponding to an absolute reduction of 16% in this 10-year risk. The proportional risk reduction for breast cancer mortality is much less than that for LR, and none of the trial-specific breast cancer mortality results are clearly significant on their own. However, collectively, there is a significant impact on breast cancer mortality (breast cancer death rate ratio 0.83, standard error [SE] 0.05; 95% CI, 0.75-0.912; $P = .0002$), indicating a reduction of about one-sixth in the annual breast cancer mortality rate. The 15-year risk of death from breast cancer (in the hypothetical absence of other causes) is 30.5% among those allocated post–breast- conserving surgery RT and 35.9% among those not (corresponding to an absolute reduction of 5.4%; SE 1.7). Figure 62.15 highlights an update of the EBCTCG, demonstrating the impact of RT on outcome in early-stage breast cancer.[42]

Isolated local recurrence (events/woman-years)

Year started and study name	RT sites	Events/woman-years: Allocated BCS + RT	Events/woman-years: Allocated BCS	BCS+RT events: Logrank O–E	BCS+RT events: Variance of O–E	Ratio of annual event rates BCS + RT: BCS
(a) Radiotherapy only to conserved breast: 14% node positive						
1976 NSABP B-06	BW*	125/6,862	285/4,991	−93.3	84.8	
1981 Uppsala-Örebro	BW	10/1,636	43/1,511	−17.7	12.7	
1982 St. George's London	BW*	12/1,202	31/1,047	−11.5	9.6	
1984 Ontario COG	BW + S	53/3,543	155/2,754	−58.2	48.2	
1987 INT Milan 3	BW + S*	19/2,478	60/2,005	−25.1	18.2	
1989 NSABP B-21	BW + S*	6/1,810	40/1,729	−17.3	11.2	
1991 Swedish BCCG	BW	33/3,718	92/3,429	−30.8	30.5	
(a) Subtotal		258/21,249	706/17.466	−254.0	215.3	0.31 (SE 0.04), 2P <.00001
5-year risk		7.2%	25.6%			
(b) Radiotherapy to conserved breast and other sites: 24% node positive						
1982 St. George's London	BW + AF*	14/620	30/380	−10.9	9.7	
1985 Scottish	BW + S + (AF) + IMC	16/2,598	83/2,260	−33.0	22.5	
1985 West Midlands, UK	BW + S + AF + IMC	42/2,398	104/1,929	−36.8	34.2	
1986 CRC, UK	Various	33/1,604	77/1,454	−24.3	25.7	
(b) Subtotal		105/7,220	294/6,023	−105.0	92.1	0.32 (SE 0.06), 2P <.00001
5-year risk		7.7%	26.7%			
Total (a + b)		363/28,469	1000/23,489	−359.0	307.4	0.31 (SE 0.03), 2P <.00001
5-year risk		7.3%	25.9%			

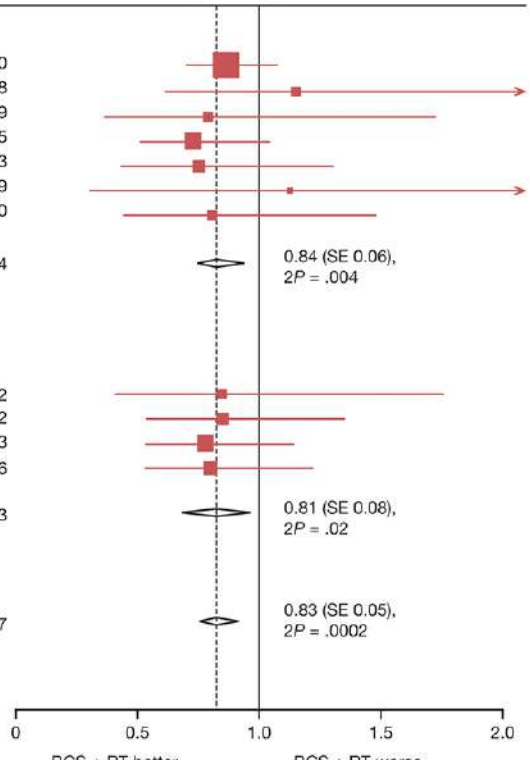
Heterogeneity between 11 strata: $\chi^2_{10} = 7.8$; $P = .6$



Isolated local recurrence (events/woman-years)

Year started and study name	RT sites	Events/woman-years: Allocated BCS + RT	Events/woman-years: Allocated BCS	BCS + RT deaths: Logrank O–E	BCS + RT deaths: Variance of O–E	Ratio of annual death rates BCS + RT: BCS
(a) Radiotherapy only to conserved breast: 14% node positive						
1976 NSABP B-06	BW*	267/731	305/719	−19.7	135.0	
1981 Uppsala Örebro	BW	37/184	34/197	2.3	16.8	
1982 St. George's London	BW*	24/128	25/122	−2.5	10.9	
1984 Ontario COG	BW + S	91/416	123/421	−16.4	51.5	
1987 INT Milan 3	BW + S*	40/294	51/273	−6.2	21.3	
1989 NSABP B-21	BW + S*	8/337	8/336	0.5	3.9	
1991 Swedish BCCG	BW	32/593	41/594	−3.9	18.0	
(a) Subtotal		499/2,683	587/2,662	−45.8	257.4	0.84 (SE 0.06), 2P = .004
15-year risk		28.0%	33.2%			
(b) Radiotherapy to conserved breast and other sites: 24% node positive						
1982 St. George's London	BW + AF*	31/80	28/70	−2.1	12.2	
1985 Scottish	BW + S + (AF) + IMC	59/293	78/296	−5.0	30.2	
1985 West Midlands, UK	BW + S + AF + IMC	88/358	107/349	−11.4	45.3	
1986 CRC, UK	Various	76/259	89/261	−8.3	37.6	
(b) Subtotal		254/990	302/976	−26.9	125.3	0.81 (SE 0.08), 2P = .02
10-year risk		28.2%	35.1%			
Total (a + b)		753/3,673	889/3,638	−72.7	382.7	0.83 (SE 0.05), 2P = .0002
15-year risk		30.5%	35.9%			

Heterogeneity between 11 strata: $\chi^2_{10} = 3.8$; $P = .96$



BCS + RT better BCS + RT worse

FIGURE 62.14 Meta-analysis of local control and survival from the Early Breast Cancer Trialists Collaborative Group demonstrating the impact of radiation therapy (RT) on both local control and survival in the management of breast cancer. BCS, breast-conserving surgery; NSABP, National Surgical Adjuvant Breast and Bowel Project; SE, standard error. * Some systemic adjuvant therapy (same polychemotherapy and/or tamoxifen) in both groups. (Reprinted from Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;366[9503]:2087-2106. Copyright © 2005 Elsevier. With permission.)

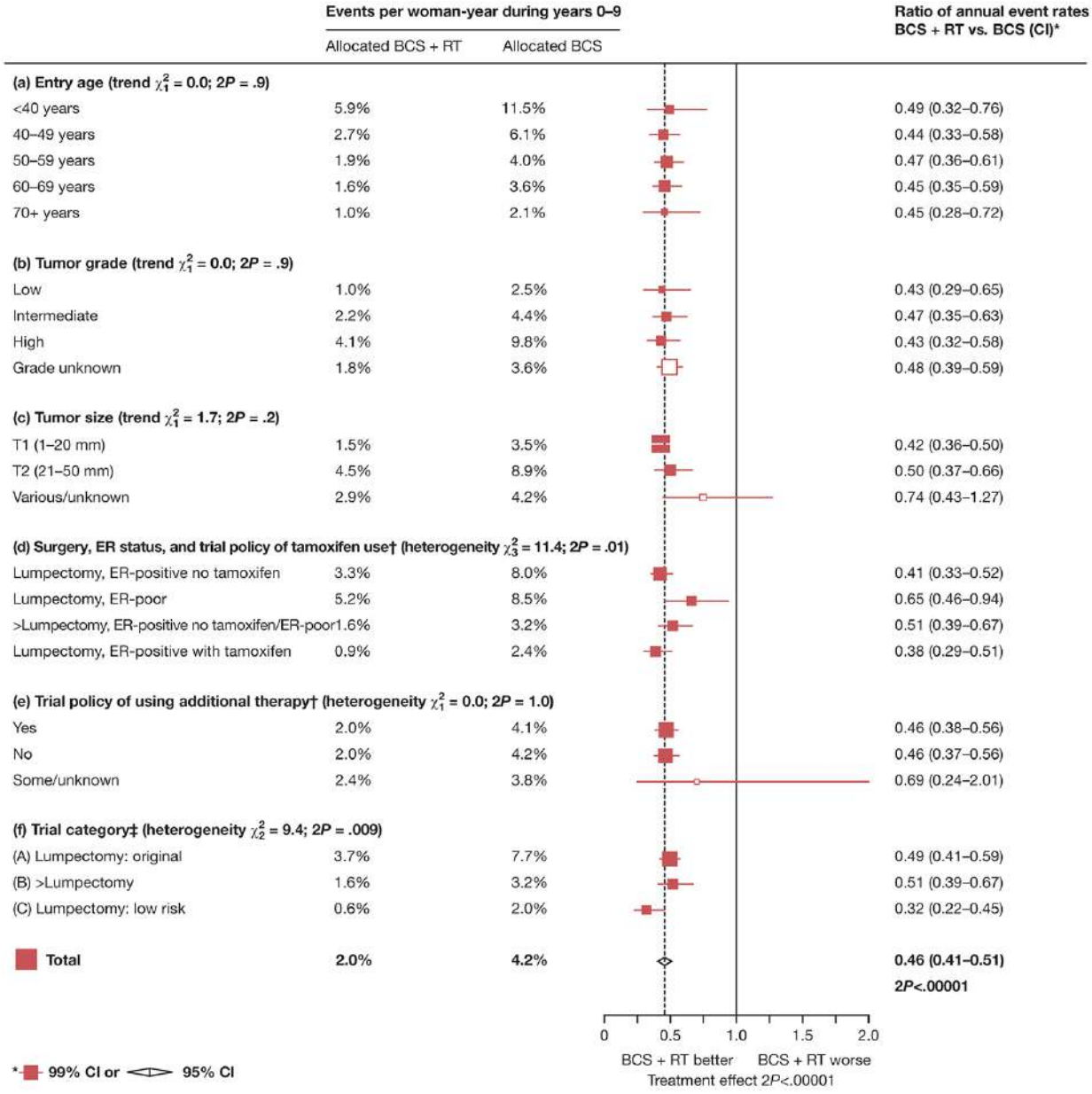


FIGURE 62.15 Updated meta-analysis from the Early Breast Cancer Trialists Collaborative Group comparing breast-conserving surgery (BCS) alone to BCS with radiation therapy (RT). CI, confidence interval; ER, estrogen receptor. (Reprinted from Darby S, McGale P, Correa C, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet*. 2011;378[9804]:1707-1716. Copyright © 2011 Elsevier. With permission.)

Randomized Trials

Selected trials comparing breast-conserving surgery alone to breast-conserving surgery with radiation are summarized in Table 62.12.[34,36,156-159]

TABLE 62.12 RESULTS OF SELECTED RANDOMIZED TRIALS OF BREAST-CONSERVING SURGERY WITH OR WITHOUT RADIATION

Study (Reference)	Criteria for Eligibility	Number of Patients	Follow-Up (Years)	Radiation Therapy		
				With (%)	Without (%)	*P*
Fisher et al B-06[34]	<4 cm node positive/negative	930	10	12.4	40.9	<.001
Liljegren et al[156]	<2 cm node negative	381	10	8.5	24.0	.0001
Veronesi et al[157]	<2.5 cm	579	10	5.8	23.5	<.001
Clark et al[158]	<2 cm node negative	837	3	5.5	25.7	<.001
Fisher et al B-21[36]	<2 cm node negative	1,009	8	2.8	16.5	<.001
Winzer et al[159]	<2 cm node negative	347	5.9	3.2	27.8	.001

The Uppsala-Orebro Breast Cancer Study group reported on a trial in which women with stage I breast carcinoma were randomly assigned to be treated with either sector resection and axillary dissection plus 54 Gy breast irradiation (184 patients) or the same surgical procedure alone (197 patients).[156] The actuarial LR rates after a median follow-up of 63 to 65 months were 2.3% in the irradiated group and 18.4% with surgery only. The 5-year DFS rates were 91% and 87%, and the 5-year OS rates were 91% and 90%, respectively.

Clark et al[158] reported on a randomized study of 421 patients with tumors 4 cm or smaller and negative nodes who were treated with wide local excision and axillary dissection alone and 416 patients who were treated with the same surgery plus breast irradiation (40 Gy in 3 weeks, 16 fractions, and 12.5-Gy boost in 5 fractions). With 7.6 years' median follow-up, breast recurrences were seen in 148 (35%) of the patients who are nonirradiated and in 147 (11%) of the patients who are irradiated ($P < .0001$); 99 (24%) patients in the former group and 87 (21%) in the latter group died during the study period.

One of the most significant trials addressing the issue of local relapse following lumpectomy alone was from the NSABP-06.[34] This trial included three arms—modified radical mastectomy, lumpectomy with radiation, and lumpectomy without radiation—and included both patients who are node-positive and those who are node-negative. In this trial, breast irradiation decreased the likelihood of a recurrence in the ipsilateral breast in the group of 1,137 lumpectomy-treated women whose surgical specimens had tumor-free margins. The cumulative incidence of a recurrence in the ipsilateral breast 20 years after surgery was 14.3% among the women who underwent irradiation after lumpectomy and 39.2% among those who underwent lumpectomy without irradiation ($P < .001$). The benefit of RT was independent of the nodal status. Among the women with negative nodes, 36.2% of those who did not receive RT and 17.0% of those who did have a recurrence in the ipsilateral breast within 20 years ($P < .001$). Among the women with positive nodes, 44.2% of those who did not undergo irradiation and 8.8% of those who did have a recurrence in the ipsilateral breast ($P < .001$). Among the lumpectomy-treated women whose surgical specimens had tumor-free margins, the HR for death among the women who underwent postoperative breast irradiation, as compared with those who did not, was 0.91 (95% CI, 0.77-1.06; $P = .23$). RT was associated with a

marginally significant decrease in deaths due to breast cancer. This decrease was partially offset by an increase in deaths from other causes.

Because of continued uncertainty regarding the need for radiation in more favorable tumors, the NSABP continued to investigate this issue of elimination of irradiation. In the B-21 trial, 1,009 women treated by lumpectomy were randomly assigned to tamoxifen (n = 336), RT and placebo (n = 336), or RT and tamoxifen (n = 337).[36] End points were divided into rates of breast relapse, distant recurrence, and contralateral breast cancer. Radiation and placebo resulted in a 49% lower hazard rate of local relapse as opposed to tamoxifen alone; radiation and tamoxifen resulted in a 63% lower rate as opposed to radiation and placebo. When compared with tamoxifen alone, radiation plus tamoxifen resulted in an 81% reduction in hazard rate of IBTR. Cumulative incidences of local relapse through 8 years were 16.5% with tamoxifen, 9.3% with radiation and placebo, and 2.8% with radiation and tamoxifen. The authors concluded that in women with tumors 1 cm or less, local relapse occurs with enough frequency after lumpectomy to justify considering RT, regardless of ER status.

In another landmark trial, Veronesi et al[157] randomly assigned 567 women with small cancers of the breast (<2.5 cm in diameter) to quadrantectomy followed by RT or to quadrantectomy alone. All patients underwent total axillary dissection. The number of IBTRs was significantly higher in patients treated with surgery alone (59 cases of 273; 10-year crude cumulative incidence of 23.5%) than in patients treated with surgery plus RT (16 cases of 294; 10-year crude cumulative incidence of 5.8%). The difference in IBTR frequency between the two treatments was high in women up to 45 years of age, tending to decrease with increasing age up to no apparent difference in women older than 65 years. OS curves for the two groups did not differ significantly (P = .326). However, a limited survival advantage was evident after RT for node-positive women.

Conservative Surgery Alone in Older Women

Given the lower reported local relapse rates in older women, the absolute benefit of RT following breast-conserving surgery may be less. The question of whether radiation can be eliminated following BCT has been addressed in retrospective studies and prospective randomized trials.

In the trial of quadrantectomy versus quadrantectomy plus radiation reported by Veronesi et al,[157] although there was a clear benefit in local control overall with radiation, the benefit was significant and apparent only in younger women; for patients over age 65, there was no significant benefit.

The Cancer and Leukemia Group B (CALGB) 9343 trial, published by Hughes et al,[160] randomly assigned 636 women with clinical stage I, ER-positive breast carcinoma treated by lumpectomy to receive tamoxifen plus RT (317 women) or tamoxifen alone (319 women). The only significant difference between the two groups was the rate of LR or regional recurrence at 5 years (1% in the group given tamoxifen plus irradiation and 4% in the group given tamoxifen alone; P < .001). There were no significant differences between the two groups with regard to the rates of mastectomy for LR, distant metastases, or 5-year rates of OS. The authors concluded that lumpectomy plus adjuvant therapy with tamoxifen alone was a reasonable choice for the treatment of women aged 70 years or above who have early, ER-positive breast cancer. An update of this trial revealed that at 10 years, 98% of patients receiving tamoxifen plus irradiation compared with 90% of those receiving tamoxifen alone were free from LR and regional recurrence. There were again no significant differences in mastectomy rates, distant metastases, or 10-year rates of OS.[161]

The PRIME II trial randomized 1,326 women aged 65 years or above with low-risk early-stage breast cancer who underwent breast-conserving surgery to receive adjuvant endocrine therapy alone or adjuvant endocrine therapy and adjuvant whole-breast radiation. Low-risk was defined as

hormone receptor-positive, node-negative, T1-T2 tumors up to 3 cm, with negative surgical margins. High-grade disease or lymphovascular space involvement (LVSI) was allowed, but not both. The primary end point was IBTR. With a median follow-up of 5 years, IBTR was 1.3% (95% CI, 0.2-2.3; $n = 5$) in the RT group and 4.1% (2.4-5.7; $n = 26$) in the no RT group ($P = .0002$). There were no differences in regional recurrence, distant metastases, or OS (93.9% in both groups; 95% CI, 91.8-96.0; $P = .34$). Trial results were overall similar to the CALGB 9343 study.[162]

Collectively, these studies indicate that the benefit of RT for older women is significant in terms of local control, but this absolute benefit is relatively small and must be weighed against comorbidities and other competing risks.

HYPOFRACTIONATED WHOLE-BREAST IRRADIATION

In breast cancer, the conventional RT schedule treatment delivers 1.8 to 2.0 Gy/day for 25 to 28 days for a total dose of 45 to 50.4 Gy. This can be followed by a five to eight fraction boost (10-16 Gy), for a total dose of 60 to 66 Gy delivered over 6 to 7.5 weeks. There has been a growing trend toward hypofractionation, which involves delivering a higher dose per fraction with fewer fractions but a biologically equivalent total dose. This has been shown to be safe and effective in multiple randomized trials and is discussed later.

The UK Standardisation of Breast Radiotherapy (START) Trial A randomized patients with early breast cancer (pT1-3a pN0-1 M0); these patients received either 50 Gy in 25 fractions of 2.0 Gy versus 41.6 Gy or 39 Gy in 13 fractions of 3.2 Gy or 3.0 Gy over 5 weeks after surgery.[163] Thus, the overall treatment time was kept constant in all three arms. The trial did allow treatment of regional lymph nodes (supraclavicular and axillary) with additional radiation fields, and these were used in 20% of the patients. With the primary end point of locoregional tumor relapse, 749 women were assigned to the 50 Gy group, 750 to the 41.6 Gy group, and 737 to the 39 Gy group. With a median follow-up of 5.1 years, the rate of locoregional tumor relapse at 5 years was 3.6% (95% CI, 2.2-5.1) after 50 Gy, 3.5% (95% CI, 2.1-4.3) after 41.6 Gy, and 5.2% (95% CI, 3.5-6.9) after 39 Gy. The authors concluded that a lower total dose in a smaller number of fractions could offer similar rates of tumor control as standard fractionation. A major limitation of the study is the use of a conventionally fractionated boost of 14 Gy in seven fractions. How this boost interacted with the altered fractionation effects is unclear.

The UK START Trial B randomized patients with early breast cancer (pT1-3a pN0-1 M0) at 23 centers in the United Kingdom who were assigned after primary surgery to receive 50 Gy in 25 fractions of 2.0 Gy over 5 weeks or 40 Gy in 15 fractions of 2.67 Gy over 3 weeks.[164] In contrast to the START Trial A, the overall treatment time was shorter in the experimental arm. With the primary end point of locoregional tumor relapse, 1,105 women were assigned to the 50 Gy group and 1,110 to the 40 Gy group. With a median follow-up of 6.0 years (interquartile range 5.0-6.2), the rate of locoregional tumor relapse at 5 years was 2.2% (95% CI, 1.3-3.1) in the 40 Gy group and 3.3% (95% CI, 2.2-4.5) in the 50 Gy group, representing an absolute difference of −0.7% (95% CI, −1.7% to 0.9%).

Whelan et al[165] reported on a study of women with invasive breast cancer who had undergone breast-conserving surgery and were randomized to whole-breast irradiation either at a standard dose of 50.0 Gy in 25 fractions over a period of 35 days (the control group) or at a dose of 42.5 Gy in 16 fractions over a period of 22 days (the hypofractionated radiation group). Notably, women with breast separations greater than 25 cm were excluded. The risk of LR at 10 years was 6.7% among the 612 women assigned to standard irradiation as compared with 6.2% among the 622 women assigned to the hypofractionated regimen (95% CI, −2.5 to 3.5). At 10 years, 71.3% of women in

the control group as compared with 69.8% of the women in the hypofractionated radiation group had a good or excellent cosmetic outcome. The authors concluded that hypofractionated whole-breast irradiation was not inferior to standard radiation treatment in women who had undergone breast-conserving surgery for invasive breast cancer with clear surgical margins and negative axillary nodes.

In 2011, a task force authorized by the American Society for Radiation Oncology (ASTRO) weighed evidence from a systematic literature review and produced recommendations regarding the use of hypofractionated RT in patients with breast cancer.[166] They stated that hypofractionated whole-breast irradiation was likely equivalent to conventional fractionation in patients who meet all of the following criteria: (a) age over 50 years, (b) pathologic state T1-2N0 treated with lumpectomy, (c) patient has not received systemic chemotherapy, and (d) the minimum and maximum dose along the central axis was not less than 93% and not more than 107% of the prescription dose, respectively. For patients not receiving a radiation boost, the task force favored a dose schedule of 42.5 Gy in 16 fractions when hypofractionated RT was planned; there was no conclusion regarding the use of a tumor bed boost in patients treated with hypofractionation. Lastly, the task force also recommended that the heart should be excluded from the primary treatment fields when hypofractionated whole-breast irradiation was used because of lingering uncertainty regarding the late effects of this treatment on cardiac function.

In 2018, an ASTRO task force provided updated guidelines, which focused on five key clinical topics, summarized in the following[167]:

1. For patients receiving whole-breast irradiation only (no additional fields to cover the regional lymphatics), the preferred dose fractionation scheme is hypofractionated whole-breast irradiation (HF-WBI) to a dose of 40 Gy in 15 fractions or 42.5 Gy in 16 fractions. The decision to offer HF-WBI should be independent of tumor grade, receptor status, margin status, laterality, receipt of systemic therapy, and age. In patients with breast augmentation or a history of CVD, HF-WBI or conventional fractionation whole-breast irradiation (CF-WBI) may be used.
2. A tumor bed boost is recommended for patients with invasive breast cancer who are 50 years or below with any grade tumor, age 51 to 70 with a high-grade tumor, or patients who have a positive margin. Tumor bed boost can be omitted for patients who are older than 70 years with low-intermediate hormone receptor–positive tumors that are resected with widely negative (≥2 mm) margins. For patients not meeting these criteria, individualized decision- making was suggested.
3. The recommended dose fractionation for tumor bed boost is 10 Gy in four to five fractions, regardless of whole-breast dose fractionation, stage, or histology. If there is a high risk of LR, such as with a positive margin, a higher boost dose of 14 to 16 Gy in 7 to 8 fractions or 12.5 Gy in 5 fractions can be used.
4. To achieve acceptable dose homogeneity, three- dimensional (3D) conformation treatment planning with a “field-in-field” technique is recommended, and the volume of breast tissue receiving greater than 105% of the prescribed dose should be minimized. The whole breast can be contoured or defined clinically, with the goal of covering at least 95% of the whole breast with 95% of the prescription dose. The tumor bed should be contoured and covered by at least 95% of the prescription dose. The heart should be contoured, and the mean heart dose should be as low as possible. Techniques to minimize cardiac exposure include deep inspiration breast-hold, prone positioning, and/or heart blocks. Dose to the contralateral breast, lung, and other normal tissues should also be minimized.

5. Tumor bed boost is recommended to be delivered sequentially after whole-breast treatment. Resimulation can be considered for repositioning or in patients with very large seromas at the time of initial planning. The tumor bed should be delineated, and conformal planning should be performed with an adequate margin. Exposure to normal tissues should be minimized.

After the publication of the updated ASTRO guidelines, HF-WBI has become the new standard of care for the majority of patients with early-stage breast cancer requiring treatment to the breast only. Newer trials are investigating even shorter courses of whole-breast irradiation with promising results thus far. The UK FAST-Forward trial, for example, was a randomized phase 3 multicenter noninferiority trial that compared a 3-week course of whole-breast or chest wall irradiation (40 Gy in 15 fractions) to two 1-week courses of whole-breast or chest wall irradiation (27 Gy in 5 fractions of 26 Gy in 5 fractions).[168] At a median follow-up of 71.5 months, the HR for IBTR compared to the 40 Gy arm was 0.86 (95% CI, 0.51-1.44) for the 27 Gy arm and 0.67 (0.38-1.16) for the 26 Gy arm. Any moderate or marked clinician-assessed normal tissue effects compared to the 40 Gy arm had odds ratios (ORs) of 1.55 (95% CI, 1.32-1.83; $P < .0001$) for the 27 Gy arm and 1.12 (0.94-1.34; $P = .20$) for the 26 Gy arm. Patient and photographic assessments of normal tissue effects were higher for the 27 Gy arm compared to the 40 Gy arm, but not for the 26 Gy arm compared to the 40 Gy arm. The authors concluded that 26 Gy in 5 fractions to the whole breast or chest wall was noninferior to the 40 Gy in 15 fractions for local tumor control and was safe for normal tissue effects up to 5 years. Longer term follow-up from this trial is awaited.

RADIATION MANAGEMENT OF THE REGIONAL LYMPHATICS

RT of the regional lymphatics remains one of the most variable aspects of BCT.[169,170] The role of RT in the management of the regional lymphatics is influenced by the risk of subclinical microscopic disease in regional nodal basins and patterns of failure. This risk is in part determined by disease characteristics and in part by the extent of surgical evaluation of the axilla, which has become increasingly relevant as a result of increased use of sentinel node biopsy, and whether completion axillary dissections are performed for those patients with sentinel node–positive disease. Furthermore, clinicians differ significantly regarding their philosophy with respect to the treatment of subclinical microscopic disease, particularly as it relates to the internal mammary chain.

The issue of whether one treats the “axilla” in conservatively managed patients is further complicated by both uncertainty and misconceptions about the degree to which the axilla receives radiation from a standard tangential (ST) field. Although this will vary considerably, as discussed in the section on radiation techniques, tangential radiation ports will likely treat most level I nodes and a portion of level II nodes.[171]

Although in the earlier years of breast conservation therapy, patients who are node-negative as well as those who are node-positive often received regional nodal treatment, most would later agree that it is not necessary to irradiate the regional lymphatics if the nodes are pathologically negative and an adequate axillary dissection has been performed.[172] This general practice has now been extended to those patients with a negative sentinel node, because available studies have demonstrated a low rate of pathologically involved nodes after a negative sentinel node procedure performed by an experienced surgeon.[64,107,173] However, several published studies have swung the pendulum toward treating the regional nodes, even in some patients who are node-negative.[174,175] As noted previously, the clinically negative axilla harbors subclinical microscopic disease in up to 40% of patients with early-stage operable breast cancer, and both axillary dissection and axillary radiation result in high rates of regional nodal control.[104,172]

Radiation Compared With Axillary Surgery

Sentinel node sampling, with or without full axillary dissection, is now the most common method of axillary management in women with early-stage breast cancer. For patients in whom full axillary staging will not affect subsequent systemic management, who have not undergone any axillary staging procedure, or who have a positive sentinel node and did not undergo further axillary staging, axillary radiation has been shown to result in high rates of regional nodal control.[172,176] Table 62.13 summarizes the results of randomized trials comparing axillary surgery to radiation or observation.[32,105,177-186]

TABLE 62.13 AXILLARY FAILURE RATES IN PATIENTS IN RANDOMIZED TRIALS COMPARING AXILLARY TREATMENTS

Trials (Reference)	Study Design	Number of Patients	Follow-Up (Month)	Positive LNs (%)	Axillary Failure Rates		
					AxD (%)	AxRT (%)	OBS (%)
NSABP B-04[104]	M (AxD vs AxRT vs OBS)	1,079	126 (ave)	40	1	3	19
Institut Curie[177]	CS (AxD vs AxRT)	658	180 (med)	18	1	3	NA
Edinburgh[178]	M (AxD vs AxRT)	275	72 (min)	30	1	14	NA
Guy's I[179]	M vs CS (AxD vs AxRT)	232	180 (min)	25	1	19	NA
Guy's II[179]	M vs CS (AxD vs AxRT)	258	120 (min)	31	1	13	NA
Manchester I[180]	M (AxRT vs OBS)	714	60 (min)	NA	NA	19	37
Manchester II[181]	CS (AxRT vs OBS)	708	65 (med)	NA	NA	10	23
International Breast Cancer Study Group[182]	M or CS (AxD vs OBS)	454	79 (med)	14	0.4	NA	1.3
Italian Oncological Senology Group[183]	CS	435	63 (med)	NA	NA	0.5	1.5
Milan[105]	CS	219	60	23	1	NA	1.8

ave, average length of follow-up; AxRT, axillary radiotherapy; CS, breast-conserving surgery; LNs, lymph nodes; M, simple or radical mastectomy; med, median length of follow-up; min, minimum length of follow-up; NA, not applicable; OBS, observation; Positive LNs, incidence of pathologically involved lymph nodes in patients undergoing axillary lymph node dissection.

Randomized Studies

One of the largest and earliest comparisons of axillary surgery to radiation was the NSABP-04 study, in which operable patients who were clinically node-negative were randomly assigned to radical mastectomy, simple mastectomy, or simple mastectomy with radiation to the chest wall and regional lymphatics.[32] The nodal relapse rate approached 20% in those assigned to simple mastectomy without radiation. The nodal control rates in the radical mastectomy arm and simple mastectomy plus radiation arm were comparable, with less than 3% relapse rate in each of these arms.

A direct comparison of axillary treatment by dissection compared with radiation was reported by Louis-Sylvestre et al,[177] in which 658 patients with a breast carcinoma less than 3 cm in diameter and clinically uninvolved lymph nodes were randomly assigned to axillary dissection or axillary RT after breast-conserving surgery with radiation to the breast. Of the group undergoing dissection, 21% of the patients in the axillary dissection group were node positive. At 10 and 15 years, survival rates were identical in both groups (73.8% vs 75.5% at 15 years). Recurrences in the axilla were less frequent in the axillary dissection group at 15 years (1% vs 3%; P = .04). There was no difference in recurrence rates in the breast or supraclavicular region or distant metastases between the two groups.

Veronesi et al[183] carried out a study in which women older than 45 years of age with breast cancer up to 1.2 cm were randomized, 214 of whom were treated with breast conservation surgery and irradiation without axillary treatment and 221 with conservation surgery plus breast and axillary RT (50 Gy in 5 weeks). After a median follow-up of 63 months, overt axillary metastases were fewer than expected: three cases in the no axillary treatment group (1.5%) and one in the RT group (0.5%). This study suggests that occult axillary metastases might never become clinically overt and axillary dissection might be avoided in patients with small carcinomas and a clinically negative axilla. Axillary RT seems to protect patients from axillary recurrence almost completely. It is possible that systemic therapy, the undamaged immunocompetent tissue in the axillary lymph nodes, and axillary irradiation may all be factors contributing to the low incidence of axillary failures in these patients. Also, in the patients receiving no axillary irradiation, it is highly likely that the level I lymph nodes were included in the ST fields.[171,186]

Irradiation of Lymphatics in Patients With Positive Axillary Lymph Nodes

Although there is general consensus that radiation to the regional lymph nodes is not necessary in patients with pathologically node-negative disease, there is variability in radiation to the regional lymphatics in patients with pathologically node-positive disease.[33,176] Based on the potential DFS and OS advantage, as well as the risk of failure in the supraclavicular region, most radiation oncologists favor at least supraclavicular nodal irradiation in patients with four or more positive lymph nodes. For patients with one to three positive lymph nodes, many radiation oncologists now favor irradiation of the regional lymphatics, given the more recent randomized data discussed later.

The Canadian MA.20 intergroup study showed the benefit for RNI in node-positive or high-risk node-negative disease.[174] The study randomized 1,832 women after lumpectomy, ALND, and adjuvant therapy (91% of patients received adjuvant chemotherapy and 71% received hormonal therapy) to either WBI with or WBI without regional nodal coverage (axillary, supraclavicular, and ipsilateral IMN in the upper three intercostal spaces). Eighty-five percent of patients had one to three positive nodes. RNI improved 10-year DFS (82% vs 77%, HR 0.76, P = .01), distant DFS (86.3% vs 82.4%, HR 0.76, P = .03), and isolated locoregional DFS (95.2% vs 92.2%, HR .59, P = .009). Certain high-risk patient populations, such as the TN subgroup, had a greater benefit with RNI. OS was not significant.

Similarly, the EORTC 22922/10925 study randomized 4,004 women with node-positive or node-negative breast cancer with central or medial tumors after lumpectomy or mastectomy and adjuvant therapy (85% of patients received either chemotherapy, hormonal therapy, or both) to either RNI or observation.[175] At a median follow-up of 11 years, RNI improved DFS (72.1% vs 69.1%, HR 0.89, P = .04), distant DFS (78% vs 75%, HR 0.86, P = .02), and breast cancer mortality (12.5% vs 14.4%, HR 0.82, P = .02).

The European After Mapping of the Axilla Radiation or Surgery Trial randomized patients after positive sentinel node biopsy to axillary dissection or axillary radiation.[187] Between 2001 and 2010, 4,806 patients were enrolled in this phase III noninferiority trial, and 1,425 had a positive sentinel node biopsy. Of these patients, ALND was performed in 744 patients and axillary RT in 681 patients. Updated 10-year results showed an axillary recurrence rate of 0.93% (95% CI, 0.18-1.68; seven events) after ALND and 1.82% (95% CI, 0.74-2.94; 11 events) after axillary RT (HR, 1.71; 95% CI, 0.67-4.39). There were no differences in OS or DFS. ALND was associated with a higher lymphedema rate at 5 years (24.5% vs 11.9%; $P < .001$). It was thus concluded that axillary RT is preferred to ALND for patients with positive sentinel nodes and cT1-2 breast cancer.

Internal Mammary Node Irradiation

The role of internal mammary nodal irradiation in patients with node-positive breast cancer remains a controversial issue. Although the MA.20 and EORTC 22922 trials provide some support for internal mammary nodal irradiation, as the IMNs were included in the RNI arms, there is no clear consensus on the role of internal mammary irradiation.

A prospective Danish study reported the results of 3,089 patients with early-stage breast cancer treated according to national guidelines that directed RNI (including IMNs) of all right-sided disease but RNI (excluding IMNs) of all left-sided disease.[188] RT was given 48 Gy in 24 fractions, regardless of cancer laterality. With a median follow-up of 8.9 years, the OS rates (75.9% vs 72.2%, HR 0.82, $P = .005$), breast cancer mortality (20.9% vs 23.4%, HR 0.85, $P = .03$), and risk of distant recurrence (27.4% vs 29.7%, HR 0.89, $P = .07$) all favored internal mammary irradiation. Subgroup analysis suggested that tumor size 51 mm or larger and four or more axillary nodes positive (especially if the primary cancer was in the lateral quadrants) predicted an OS benefit for internal mammary irradiation.

In a study by Stemmer et al[189] of 100 patients who are node-positive scheduled to receive radiation to the internal mammary chain, 67 received the radiation and 33 did not because of technical difficulties. At a median follow-up of 77 months, DFS was significantly prolonged in patients receiving internal mammary radiation compared with those without internal mammary radiation (73% vs 52%; $P = .02$). A trend was seen for OS (78% vs 64%; $P = .08$). Cox regression multivariate analysis found IMN RT to be significant for both DFS and OS. There was no treatment-related mortality.

In contrast, Fowble et al[190] compared the outcomes of 1,383 women with stage I or II breast cancer who underwent wide excision, axillary node dissection with 10 or more nodes removed, and breast irradiation. A total of 114 women had radiation to the IMNs with deep tangents and 1,269 did not. All axillary node–positive women received adjuvant chemotherapy or tamoxifen or both. There were no significant differences in IBTR, regional node recurrence, and initial or total distant metastases for the two groups. No IMN failures were observed among the 114 patients whose IMNs were treated, and only 4 IMN failures were found in the 1,269 other patients (2 of whom had distant metastases). Similarly, 5- and 10-year actuarial OS and cause-specific survival rates were not significantly different.

In a series from Yale, Obedian and Haffty[191] found no difference in the 10-year DFS rate after breast irradiation and excision, regardless of whether IMNs were irradiated. Of 984 patients with invasive breast cancer who were treated with CS and RT, patients were divided into two groups: those treated by intentionally targeting the IMNs ($n = 535$) and without intentionally targeting the IMNs ($n = 411$). The decision not to use a separate internal mammary field was a result of a change in treatment policy over time and generally not based on the number of nodes or tumor location.

There were no significant differences between the groups with respect to age, ER or PR status, or use of adjuvant chemotherapy or hormone therapy. There were more patients with T2 tumors, positive nodes, medial lesions, indeterminate margins, and slightly longer follow-up in the group treated to the internal mammary chain. There were no significant differences between the groups with respect to OS or distant metastasis–free survival.

It is evident that data are conflicting, and opinions regarding the role of internal mammary radiation remain unresolved. The presence of other high-risk features, such as extensive nodal disease, TN receptor status, or medial/central tumor location, can be used to guide decision-making on the inclusion of the internal mammary lymph nodes in the radiation fields. The radiation oncologist must be familiar with the various techniques to treat IMNs, which are summarized later in the section on techniques.

SEQUENCING CHEMOTHERAPY AND HORMONAL THERAPY

Sequencing Chemoradiation in the Conservative Management of Breast Cancer

With the increasing use of systemic therapy in patients with early-stage breast cancer, the integration of this treatment with surgery and RT has become an important clinical question. Initial retrospective series evaluating treatment sequencing suggested that a delay in the onset of RT to permit delivery of chemotherapy increased LR rates.[192-194] Most of these data were subject to criticism because of their retrospective nature, the fact that patients were treated in an earlier era with different surgical techniques and lack of attention to margins, and inclusion of heterogeneous groups of patients. However, any suggestion of a higher local relapse rate with delays in RT is an appropriate concern with respect to the integration of RT and chemotherapy in conservatively managed patients.

Initial data regarding these concerns related to the delay in radiation while chemotherapy was being delivered led the Harvard group at Joint Center for Radiation Therapy (JCRT) to investigate the sequencing of RT and chemotherapy in a randomized prospective clinical trial.[193,194] In this trial, women treated with breast-conserving surgery were randomly assigned to four cycles of doxorubicin-based combination chemotherapy followed by RT or RT followed by four cycles of the same chemotherapy. In an update of this trial, Bellon et al[195] reported no statistically significant treatment difference in the rates of freedom from any event, including breast cancer recurrence, contralateral breast cancer, second malignancy, or death (Figure 62.16). The 10-year rate of any event was 46% for patients in the chemotherapy-first arm compared with 51% in the radiation-first arm. The 10-year rates of distant metastasis were 35% and 36% in the two arms, respectively, and the 10-year rates of death were 28% and 33%, respectively. For the 123 patients with negative margins, the crude LR rates for chemotherapy- and radiation-first patients were 6% and 13%, respectively. Corresponding rates of distant and regional recurrences were 18% and 26%. Among women with close margins (n = 47), crude LR rates were 32% and 4%, respectively; distant or regional recurrences were 37% and 43%, respectively. In the group with positive margins (n = 51), LRs occurred in 23% of chemotherapy-first and 20% of radiation-first patients.

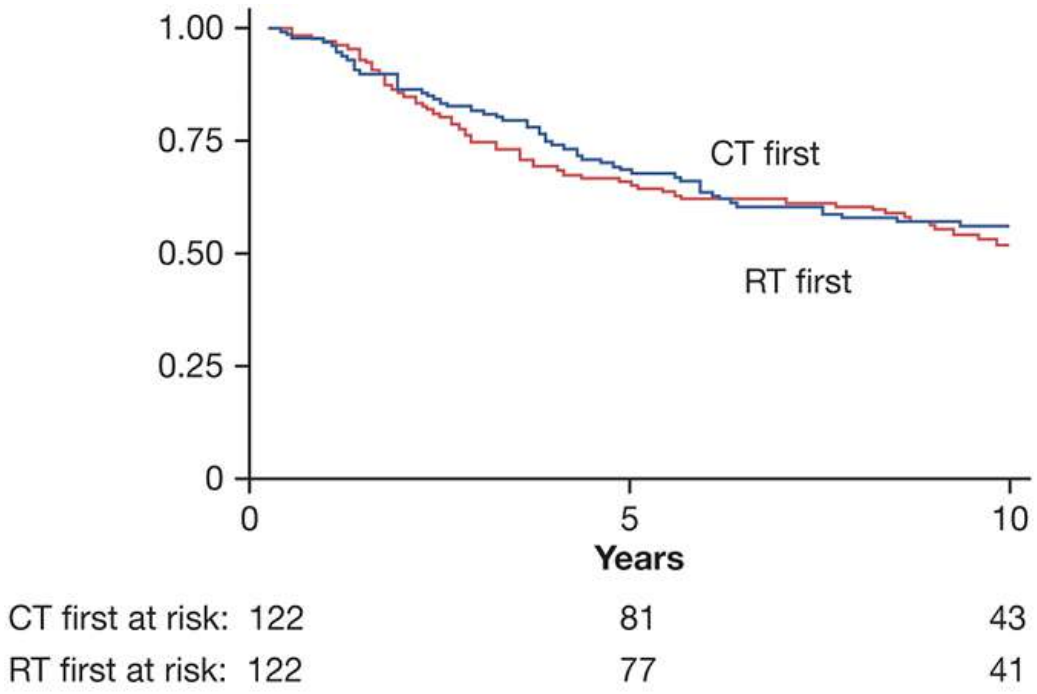


FIGURE 62.16 Event-free survival (including breast cancer recurrence, contralateral breast cancer, second malignancy, or death) by sequencing of chemotherapy (CT) and radiation therapy (RT) following breast-conserving therapy, from the Harvard randomized trial. (Reprinted with permission from Bellon JR, Come SE, Gelman RS, et al. Sequencing of chemotherapy and radiation therapy in early-stage breast cancer: updated results of a prospective randomized trial. *J Clin Oncol*. 2005;23[9]:1934-1940. Copyright © 2005 by American Society of Clinical Oncology.)

Although the JCRT study provided important data concerning treatment sequencing, this study predominantly focused on patients with lymph node–positive disease. Investigators from the MD Anderson Cancer Center performed a retrospective analysis of sequencing of chemotherapy and radiation in 124 patients with lymph node–negative disease treated with BCT.[196] In this series, 79% of the patients had negative margins. The 5-year actuarial rates of local control were 100% for the chemotherapy-first group (most commonly six cycles of doxorubicin-based chemotherapy) and 94% for the radiation- first group (P = .351). The 5-year recurrence-free survival rates for the chemotherapy- and radiation-first groups were 92% and 77% (P = .083), respectively. The median delays in radiation delivery were 6.7 months in the MD Anderson Cancer Center series and 16 weeks in the JCRT series.

With the addition of taxane-based chemotherapy to adriamycin- based regimens, concerns have arisen regarding the additional delays in initiating RT in conservatively managed patients. This was addressed in a study by Sartor et al.[197] In this randomized CALGB study evaluating adriamycin and cytoxan versus adriamycin and cytoxan followed by taxane, there were 345 conservatively managed patients. Although the sequencing of radiation was not randomized, patients in the adriamycin plus taxane arm had radiation delayed by an additional 84 days (four 21-day cycles of taxol). Despite this added delay, locoregional relapses were lower in the adriamycin plus taxane arm compared with the adriamycin arm (9.7% vs 3.7%; P = .04).

For the majority of patients undergoing breast-conserving surgery with negative margins, these data collectively indicate that administration of chemotherapy prior to RT does not result in excessive rates of local relapse, provided all modalities are given in a timely manner without

excessive delays. Whether patients with positive/close margins or other risk factors for local relapse would benefit from earlier administration of radiation remains an unresolved issue.

Concurrent Systemic Treatment in Breast-Conserving Therapy

The historical data on the use of concurrent chemoradiation for early-stage breast cancer are largely outdated, as many of the prior chemotherapy regimens are no longer utilized. More recent randomized clinical trials, however, have demonstrated improved outcomes with a variety of adjuvant systemic drugs. Some were studied in the setting of concurrent delivery with radiation, and others were given sequentially.

The CREATE-X study enrolled patients with HER2-negative breast cancer with residual disease after neoadjuvant chemotherapy and randomized patients to standard adjuvant therapy, including RT when indicated, with or without capecitabine.[198] The primary end point of DFS was longer in the capecitabine group compared with the control group at 5 years (74.1% vs 67.6%; 95% CI, 0.52-0.92; $P = .01$). The secondary end point of OS was also longer in the capecitabine group at 5 years (89.2% vs 83.6%; 95% CI, 0.39-0.90; $P = .01$). There was a greater improvement in both end points among patients with TN disease. In this study, capecitabine was initiated sequentially with RT, either after or before. Smaller, nonrandomized studies have demonstrated the feasibility of concurrent therapy with adjuvant capecitabine and RT.[199]

The KATHERINE trial enrolled patients with HER2-positive early breast cancer who had residual invasive disease in the breast or axilla after neoadjuvant chemotherapy with HER2-targeted therapy.[200] Patients were randomized to receive adjuvant trastuzumab or trastuzumab emtansine (T-DM1) for 14 cycles. On interim analysis, the 3-year invasive DFS was significantly higher in the T-DM1 group than in the trastuzumab group (88.3% vs 77.0%; 95% CI, 0.39-0.64; $P < .001$). In this study, it was recommended that RT be initiated within 60 days of surgery and be given concurrently with study treatment. Though grade 3 or higher adverse events were more common in the T-DM1 group, the most common events were decreased platelet count and hypertension. Radiation pneumonitis of any grade was slightly more common with T-DM1 (1.5% vs 0.7%).

The KEYNOTE-522 trial enrolled patients with TN breast cancer to neoadjuvant chemotherapy with or without pembrolizumab, followed by adjuvant pembrolizumab or placebo every 3 weeks for up to nine cycles.[201] At first interim analysis, the primary end point of pathologic complete response among the first 602 patients who underwent randomization was 64.8% in the pembrolizumab-chemotherapy group and 51.2% in the placebo-chemotherapy group, for an estimated treatment difference of 13.6 percentage points (95% CI, 5.4-21.8; $P < .001$). On subsequent planned interim analysis, the primary end point of event-free survival at 36 months was 84.5% in the pembrolizumab-chemotherapy group and 76.8% in the placebo-chemotherapy group (HR for event of death 0.63; 95% CI, 0.48-0.82; $P < .001$). It was noted that most treatment- related adverse events occurred during the neoadjuvant phase of therapy rather than the adjuvant phase. In patients requiring postoperative RT, adjuvant pembrolizumab or placebo could be given concurrently with radiation or begin 2 weeks after completion of radiation.

The OlympiA trial randomized patients with HER2-negative early high-risk breast cancer found to have BRCA1 or BRCA2 germline pathogenic or likely pathogenic variants to receive 1 year of oral olaparib therapy, a PARP (poly [ADP-ribose] polymerase) inhibitor, or placebo.[202] The majority (82.2%) of the study population had TN breast cancer. The primary end point was invasive DFS. At a prespecified interim analysis, the 3-year invasive DFS was higher in the olaparib group (85.9% vs 77.1%; HR for invasive disease or death 0.58, 99.5% CI, 0.41-0.82; $P < .001$). In this trial, olaparib was initiated after completion of neoadjuvant and/or adjuvant chemotherapy and local RT. To take

advantage of the potential radiosensitizing effects of PARP inhibitors in the highest risk subset of breast cancer patients, a phase II NCI trial is randomizing patients with nonmetastatic inflammatory breast cancer (IBC) to receive standard RT to the chest wall and regional lymph nodes with or without concurrent olaparib.

As data emerge on additional systemic agents, it will be important to identify the patients who might benefit most from concurrent therapy as well as the associated risks and benefits of combined modality treatment.

Sequencing Hormonal Therapy in Breast-Conserving Therapy

The question of optimal scheduling of hormonal therapy and radiation has been raised because of theoretical concerns that tamoxifen may decrease the radiation sensitivity of tumors. In cell culture studies, tamoxifen causes arrest of breast cancer cells in the relatively radioresistant G_0/G_1 phases of the cell cycle. Although there are conflicting data, clinicians and patients have been in a quandary as to whether it is reasonable to begin tamoxifen during radiation. In addition, clinical studies have suggested increased pulmonary and breast fibrosis, possibly related to increased concentrations of transforming growth factor-β with the concurrent use of tamoxifen.[203] A series of three separate retrospective series performed independently but published simultaneously reached similar conclusions that sequential and concurrent use of tamoxifen were both acceptable.

The largest study by Ahn et al[204] from the Yale group compared 254 patients treated with concurrent tamoxifen and RT to 241 treated by RT followed by tamoxifen. There were no significant differences in the risk of IBTR, DFS, or OS. The HR for IBTR comparing sequential with concurrent tamoxifen and RT was 0.93 (95% CI, 0.42-2.05; $P = .86$). In this study, morbidity outcomes were not reported.

The second study by Harris et al,[205] the group at the University of Pennsylvania, compared 174 patients treated with concurrent tamoxifen and RT with 104 patients treated with RT followed sequentially by tamoxifen. Similar to the Yale study, patients were accrued throughout a long period between 1980 and 1995, and again no significant differences in IBTR, DFS, or OS were observed between groups. The HR for IBTR (sequential vs concurrent) was 1.23 (95% CI, 0.33-4.49; $P = .78$). In this study, breast edema and arm edema as well as cosmetic outcome and pneumonitis were analyzed, and no significant differences were observed.

The third study by Pierce et al[206] evaluated results from a randomized trial in which patients were randomly assigned to cyclophosphamide, doxorubicin, and fluorouracil (CAF) followed by tamoxifen, CMF, or CMF followed by tamoxifen. Although the sequencing of tamoxifen was not randomized, 202 patients received concurrent tamoxifen and RT and 107 received RT followed sequentially by tamoxifen. In this study, no differences were noted in the risk of IBTR, DFS, or survival between RT followed sequentially by tamoxifen and concurrent tamoxifen and RT group. The HR for the risk of IBTR (RT followed sequentially by tamoxifen vs concurrent tamoxifen and RT) was 0.73 (95% CI, 0.26-2.04; $P = .54$).

Although these studies are limited by their retrospective design, they do offer some reassurance that the concurrent use of hormonal therapy with RT does not result in excessive rates of local relapse. Given the lack of more definitive data, it appears that either the concurrent or the sequential use of tamoxifen is acceptable in the patient with conservatively managed breast cancer.

The majority of available data on the use of hormonal therapy and radiation are with tamoxifen. In a prospective phase II randomized trial evaluating concurrent or sequential letrozole, Azria et al[207] reported no difference in local relapse (one in each arm) at 26 months of follow-up. In addition, only two patients in each group had grade 2 or worse late effects. An update to this trial showed no

difference between treatment arms at 74 months in grade 2 or higher radiation-induced subcutaneous fibrosis. These authors concluded that letrozole can be safely delivered concomitantly with radiation.[208]

BREAST-CONSERVING THERAPY: CONTROVERSIES AND SPECIAL CIRCUMSTANCES

The available evidence from the abovementioned trials suggests that although there are clearly cohorts of patients who are at increased risk of local relapse, there are relatively few contraindications to BCT. There is little evidence that treatment of patients at higher risk for local relapse with BCT compromises OS. Careful attention to patient selection, surgical technique, radiation technique, and the integration of systemic therapy should minimize the probability of local relapse. There are several areas of controversy and special circumstances in the selection of patients for BCT that warrant specific discussion.

Breast-Conserving Surgery and Radiation in Familial Breast Cancer and Carriers of *BRCA1/2* Mutations

BRCA1 and *BRCA2* are tumor suppressor genes located on chromosomes 17q21 and 13q12, respectively. BRCA proteins encourage genomic stability through repair of double-strand DNA breaks. Mutations in the *BRCA1/2* genes account for 5% to 10% of breast cancers. Carriers of *BRCA1* and *BRCA2* pathogenic mutations have a mean cumulative risk of breast cancer at age 70 of 57% (95% CI, 47%-66%) and 49% (95% CI, 40%-57%), respectively. Ovarian cancer risks are 40% (95% CI, 35%-46%) and 18% (95% CI, 13%-23%), respectively.[209]

Tumor characteristics of *BRCA1* carriers have been well described. Histopathologic features are often more aggressive, with high nuclear grade, aneuploidy, and high proliferation indices. Tumors with a medullary component are more common. ER and PR are more likely to be negative when compared with *BRCA2* or sporadic counterparts. Although there are some conflicting data, *BRCA1/2* carriers with breast cancer appear to have equivalent survival when compared with age- and stage-matched patients with sporadic disease.[10,210-213]

There is considerable controversy and uncertainty regarding the role of breast-conserving surgery and radiation in carriers of *BRCA1/2* mutations. The role of *BRCA1/2* in DNA repair suggests the possibility of hypersensitivity to radiation, as well as the potential for radiation-induced complications, including second cancers. The risk of local and contralateral breast cancers as a function of *BRCA1* and *BRCA2* status has been evaluated by numerous groups over the years. These are summarized in Table 62.14.[212-218]

TABLE 62.14 RATE OF IPSILATERAL BREAST TUMOR RELAPSE IN *BRCA* MUTATION CARRIERS COMPARED TO SPORADIC CONTROLS

Study (Reference)	Number of Patients Genetic	Number of Patients Sporadic	Follow-Up (Year)	IBTR Sporadic (%)	IBTR Genetic (%)	*P*	Notes
Seynaeve et al[212]	87	174	10	16	30	.05	More recurrences elsewhere? In cancers
Robson et al[213]	28	277	10	6.9	22	.25	Only tested for founder mutations in Ashkenazi women

Study (Reference)	Number of Patients Genetic	Number of Patients Sporadic	Follow-Up (Year)	IBTR Sporadic (%)	IBTR Genetic (%)	*P*	Notes
Robson et al[214]	56	440	9.6	7	13	.68	As above
Haffty et al[215]	23	135	12	21	46	.007	No oophorectomy or tamoxifen in *BRCA* group
Pierce et al[218]	160	445	7.9	17	24	.19	HR for IBTR was significant in those carriers who did not undergo prophylactic oophorectomy.
Kirova et al[217]	29	107	13	19	24	.47	
Garcia-Etienne et al[216]	54	162	5	4	15	.03	

HR, hazard ratio; IBTR, ipsilateral breast tumor recurrence.

Robson et al[213] studied breast conservation therapy in Ashkenazi women with the *BRCA* gene founder mutations (*BRCA1* 185delAG, *BRCA1* 5382insC, and *BRCA2* 617delT). Archival tissue samples were retrieved from 305 women, and 28 *BRCA* gene founder mutations were detected. *BRCA1/2* carriers had a nonsignificant trend toward increased ipsilateral breast cancer recurrence and decreased OS at 5 and 10 years. This trend may be related to the greater likelihood of young age and axillary lymph node involvement in women with *BRCA* founder mutations. On univariate analysis, age, but not *BRCA* mutation status, was associated with IBTR. The significance of age was maintained on multivariate analysis, with an RR of 2.5. The risk of contralateral breast cancer at 5 and 10 years was 14.8% and 27.0%, respectively.

This series from Memorial Hospital was later combined with data from McGill University, yielding a total of 56 women with founder mutations. Again, *BRCA1/2* carriers had an increased risk of contralateral breast cancer at a median follow-up of 9.7 years (27% vs 8%; $P < .001$). Ipsilateral breast cancer recurrence for *BRCA1/2* carriers was similar to noncarriers, and age less than 50 at diagnosis was the only significant predictor of metachronous ipsilateral disease ($P = .002$).[214] *BRCA1* mutations were an independent predictor of breast cancer mortality on multivariate analysis but only for women who did not receive chemotherapy. *BRCA2* mutations had no impact on breast cancer–specific survival.

Haffty et al[215] studied breast conservation therapy in germline carriers with early-onset breast cancer. One hundred and twenty-seven women diagnosed with breast cancer at age 42 years or below agreed to undergo genetic testing, and 22 were found to have *BRCA1/2* mutations. Adjuvant tamoxifen or oophorectomy was not used in any of the carriers of *BRCA1/2* mutations. Patients in the genetic group were younger than sporadic patients, and this difference was significant on multivariate analysis. Treatment outcomes were compared with results from patients with sporadic disease. With a median follow-up of 12.7 years, the genetic group had a higher rate of ipsilateral (49% vs 21%; $P = .007$) and contralateral breast events (42% vs 9%; $P = .001$). Nine of the 11 IBRs were classified as second primary tumors, based on a difference in tumor location ($n = 7$) or histology ($n = 8$). The rate of ipsilateral and contralateral events was much higher than those reported in earlier series and may be attributable to both the young age of the patients at diagnosis and longer duration of follow-up. The proportion of relapse-free *BRCA1/2* carriers was similar to

noncarriers at 5 years and then progressively declined with time (Figure 62.17). It is promising that all of the second events in *BRCA1/2* carriers were successfully salvaged and remained disease free.

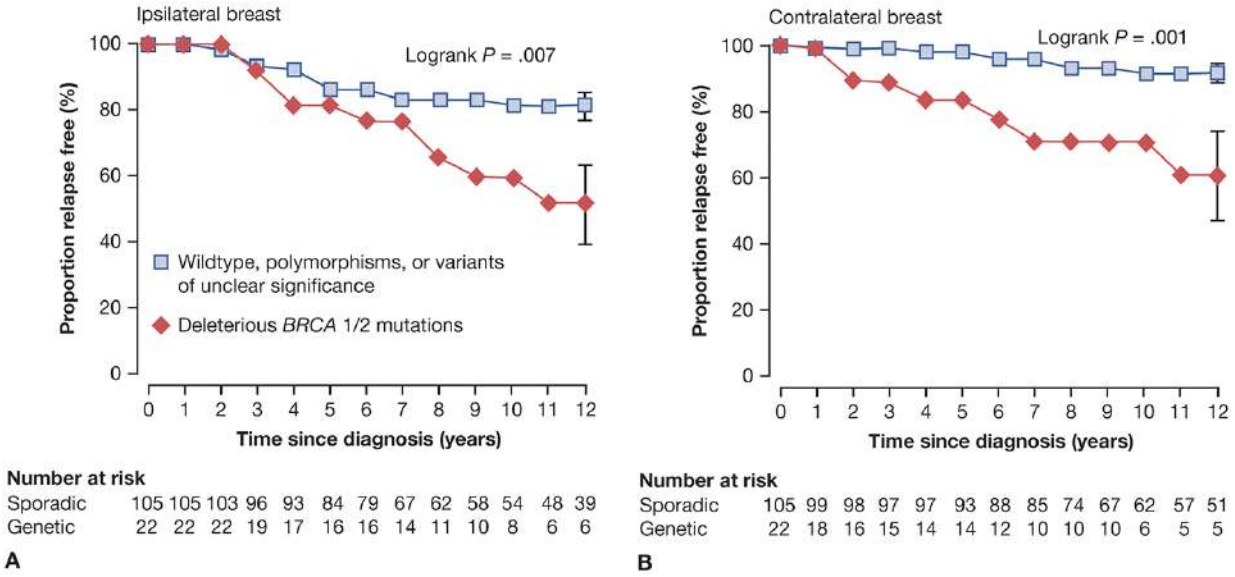


FIGURE 62.17 Risk of ipsilateral (A) and contralateral breast tumor relapse (B) as a function of *BRCA1/BRCA2* mutation status in a cohort of patients with conservatively managed breast cancer. (Reprinted from Haffty BG, Harrold E, Khan AJ, et al. Outcome of conservatively managed early-onset breast cancer by BRCA1/2 status. *Lancet*. 2002;359[9316]:1471-1477. Copyright © 2002 Elsevier. With permission.)

Case-control–type studies were undertaken by Garcia- Etienne et al[216] and Kirova et al[217] The study by Kirova et al did not show a statistically higher local relapse rate in *BRCA1/2* carriers. However, the study by Garcia-Etienne et al, comparing 54 genetic cases to 162 sporadic cases, reported a 15% local relapse rate in the genetic group compared with a 4% local relapse rate in the sporadic group ($P = .03$).

Although the above-presented data have some apparent conflicting conclusions, a study by Pierce et al[218] helped to resolve some of these issues. In a large collaborative study, these authors evaluated a total of 160 *BRCA1/2* mutation carriers with breast cancer matched to 445 controls with sporadic breast cancer (Figure 62.18). Median follow-up was 7.9 years for mutation carriers and 6.7 years for controls. Although there was no significant difference in IBTR overall between carriers and controls (15-year estimates were 24% for carriers and 17% for controls; HR 1.37; $P = .19$), a subset analysis revealed higher rates of local relapse in those carriers who had not undergone prophylactic oophorectomy. Multivariate analyses for IBTR found *BRCA1/2* mutation status to be an independent predictor of IBTR when carriers who had undergone oophorectomy were removed from analysis (HR 1.99; $P = .04$); the incidence of IBTR in carriers who had undergone oophorectomy was not significantly different from that in sporadic controls ($P = .37$). Contralateral breast cancers were significantly more frequent in carriers versus controls, with 10- and 15-year estimates of 26% and 39% for carriers and 3% and 7% for controls, respectively (HR 10.43; $P < .0001$). Tamoxifen use significantly reduced the risk of contralateral breast cancers in mutation carriers (HR 0.31; $P = .05$). Thus, it appears that this study confirms the findings of Haffty et al[215] that *BRCA1/2* carriers have a high rate of both contralateral and ipsilateral breast events if they do not undergo specific measures to reduce the risk of subsequent breast cancers by undergoing oophorectomy or tamoxifen.

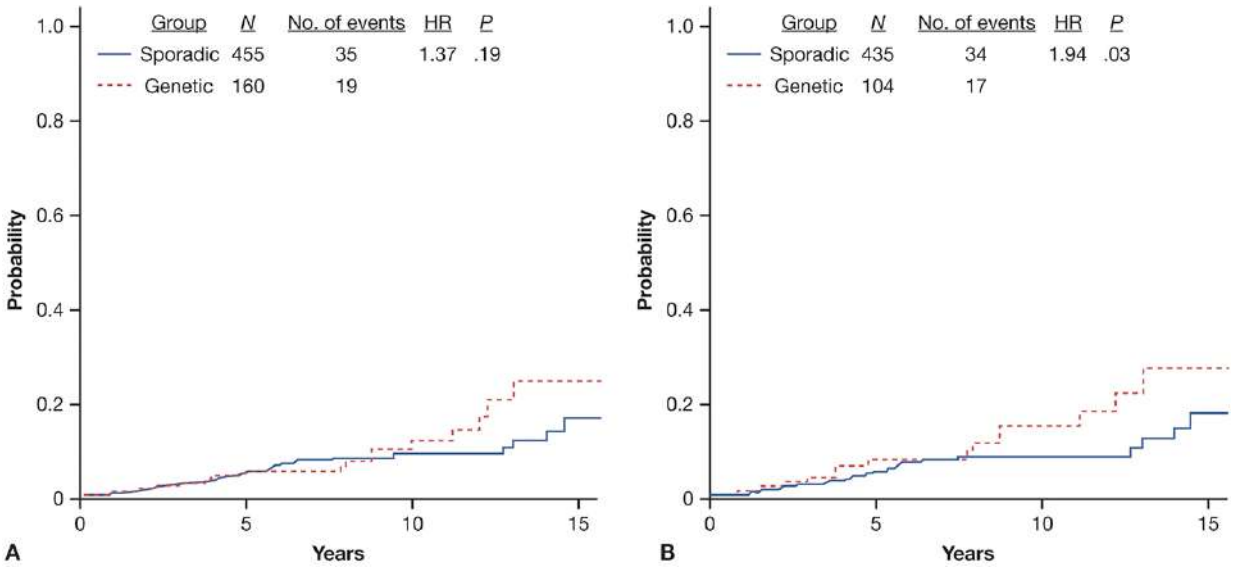


FIGURE 62.18 A.Risk of ipsilateral breast tumor relapse in *BRCA* carriers as a function of whether carriers had undergone prophylactic oophorectomy. In *BRCA* carriers who did not undergo oophorectomy (B), the risk of late local relapses was significantly greater than in sporadic controls. HR, hazard ratio. (Reprinted with permission from Pierce LJ, Levin AM, Rebbeck TR, et al. Ten-year multi-institutional results of breast-conserving surgery and radiotherapy in BRCA1/2-associated stage I/II breast cancer. *J Clin Oncol*. 2006;24[16]:2437-2443. Copyright © 2006 by American Society of Clinical Oncology.)

Prophylactic mastectomy has been shown to significantly reduce the incidence of breast cancer in women with a family history of breast cancer and specifically women with *BRCA1/2* mutations.[31] This risk reduction strategy has complex emotional and psychological implications, and there are no data to suggest an improvement in survival when compared with close surveillance. Most preventive strategies have focused on primary prevention, but prophylactic strategies should also be considered at the time of breast cancer diagnosis. Oophorectomy and tamoxifen appear to offer risk reduction for patients with breast cancer with germline mutations. These agents have not been widely used in studies of patients with conservatively managed breast cancer with *BRCA1/2* mutations. Their potential benefits must be weighed against the possible complications of premature menopause following oophorectomy and the side effects of tamoxifen.

Collagen Vascular Disease

Increased acute and late effects of irradiation have been reported in patients with preexisting CVD. Selected studies addressing this issue are summarized in Table 62.15.[219-226]

TABLE 62.15 STUDIES EVALUATING COLLAGEN VASCULAR DISEASE IN BREAST-CONSERVING THERAPY

Study (Reference)	CVD		Design	Findings
	Total Number	Number With Breast Cancer		
De Naeyer et al[219]	3	1	Case report	Necrosis and progressive fibrosis
Fleck et al[220]	9	4	Case report	Necrosis, brachial plexopathy, and severe moist desquamation

Study (Reference)	CVD		Design	Findings
	Total Number	Number With Breast Cancer		
Robertson et al[221]	2	2	Case report	Severe breast fibrosis, erythema, and pain
Chen et al[222]	36	36	Case-control	Late complication rates higher only in scleroderma
Morris and Powell[223]	209	19	Retrospective	Increased radiation late effects appear in nonrheumatoid arthritis cases.
Ross et al[224]	61	61	Case-control	No differences in acute/chronic complications
Phan et al[225]	38	38	Case-control	No difference was observed in the incidence of acute or late complications between the two groups.
Rakfal and Deutsch[226]	6	4	Case report	No severe acute or late radiation complications

CVD, collagen vascular disease.

Fleck et al[220] reported on five women in whom CVD developed 3 months to 10 years after RT and who had no complications. However, in three of four women with preexisting CVD, severe complications developed, characterized by persistent moist desquamation, paresthesias in the ipsilateral arm, chest wall necrosis requiring surgical resection, and osteonecrosis of the clavicle, sternum, and rib cage.

On the other hand, Ross et al[224] evaluated a group of 61 patients with CVD who were compared with a matched control group of 61 patients without CVD. The CVD group included 39 patients with rheumatoid arthritis, 13 with systemic lupus erythematosus, 4 with scleroderma, 4 with dermatomyositis, and 4 with polymyositis. Overall, there was no significant difference between the CVD and control groups in terms of postirradiation acute complications (11% and 7%, respectively) or late complications (10% and 7%, respectively). This was also true when only patients who were treated definitively were considered. Three patients in the CVD group had fatal complications, compared with none in the control group. Rheumatoid arthritis was associated with a slight increase in late complications in definitively treated patients, whereas systemic lupus erythematosus was associated with a slight increase in acute reactions. No significant acute or late reactions were observed in the patients with scleroderma, dermatomyositis, or polymyositis.

Morris and Powell[223] treated 96 patients with documented CVD with breast conservation therapy (127 sites irradiated). Grade 3 or higher acute complications were seen in 15 (11.8%) of the 127 sites, and the actuarial rate of significant late complications was 24% at 10 years. There was a single in-field sarcoma. Patients with rheumatoid arthritis had less severe late effects than did those with other CVD (6% vs 37% at 5 years; $P = .0001$).

In a study specifically evaluating patients with conservatively treated breast cancer, Chen et al[222] identified 36 patients with documented CVD treated for early-stage breast cancer between 1975 and 1998. All of these patients were treated with conventional RT to a median total dose of 64 Gy. Seventeen had rheumatoid arthritis; four, scleroderma; four, Raynaud phenomenon; five, lupus erythematosus; two, Sjögren disease; and four, polymyositis. Each of these patients was matched to two control patients without a history of CVD. Acute and late complications were assessed using a 6-point scale from the toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the EORTC. No significant difference was detected between the CVD and control groups with respect to acute complications (14% vs 8%). With respect to late complications, a significant difference was

observed (17% vs 3%) between the two groups. However, when patients in the CVD group were analyzed by specific disease, this significance disappeared in all but the scleroderma group.

Collectively, these data suggest that with the exception of patients with scleroderma, there does not appear to be a significantly greater late complication rate associated with CVD. Nevertheless, when patients with CVD are irradiated, it is prudent to discuss with patients the potential increased risks of radiation sequelae. There are limited data on treating breast cancer in patients with CVD with hypofractionated WBRT or partial- breast RT.

Pregnancy

Breast Cancer During Pregnancy

Breast cancer is the most common cancer diagnosed during pregnancy and represents a significant therapeutic challenge. The incidence of breast cancer associated with pregnancy is estimated to be 1.5 to 2 in 10,000 pregnancies. An expert international panel published general recommendations for breast cancer developing during pregnancy.[227] The panel noted that the goal for the pregnant women with breast cancer is the same as that of the nonpregnant women: local control of disease and prevention of systemic metastasis. However, because of adverse effects on the fetus, certain treatment modalities, including radiation, must be avoided.

The prognosis of patients developing breast cancer during pregnancy, stage for stage, appears to be similar to age-matched controls. The overall poorer prognosis in breast cancer associated with pregnancy may be related to delay in diagnosis because pregnancy impedes early detection and possibly to the more aggressive biology of the tumor.[228] Contrary to popular belief, pregnancy does not appear to stimulate the growth of breast cancer. Therefore, therapeutic abortion is not indicated in most cases, with the exception of patients with rapidly progressing disease such as IBC or metastatic disease.

As discussed later, selected chemotherapy agents can be administered during the second and third trimesters. Although therapeutic abortion is not necessary, women with high-risk disease may find this preferable. The available evidence suggests that in women with a history of breast cancer, subsequent pregnancy does not increase the risk of recurrence. In addition to requiring close coordination among multidisciplinary cancer care givers, management of breast cancer during pregnancy also benefits from having obstetricians and pediatricians closely involved in therapeutic decision-making. It is likely that as pregnancy in Western society is delayed to older ages, the incidence of breast cancer developing during pregnancy will increase.

Breast cancers during pregnancy are usually diagnosed after an abnormal physical examination finding. There may be a delay in diagnosis because the breast mass is thought to represent obstructed milk ducts, and inflammatory changes of the breast may be misdiagnosed as cellulitis. For patients who present with a breast mass, a careful history and physical examination should be performed. The overall goal of managing breast cancer during pregnancy requires attention to both the mother and the fetus. Certain diagnostic and therapeutic interventions are known to be teratogenic and, therefore, are best avoided. Although theoretically a chest radiograph may be safely performed, radiographic and scintigraphic imaging for staging should be minimized or deferred. Mammography is somewhat controversial, although the irradiation dose to the fetus is minimal. Ultrasound evaluations of the breast and lymph nodes can provide diagnostic information and serve as a method of guidance for core biopsy.[229] Pathology of breast cancer during pregnancy is most frequently invasive ductal with high nuclear grade and lower rates of ER and PR positivity.[230]

The management of the patient and the risks of certain interventions are also highly dependent on the week of gestation. In general, potentially harmful interventions carry the greatest risk during the

period of organogenesis (first trimester) and are safest during the final trimester. For patients with operable disease, data suggest that surgery can be safely performed after the 12th week of pregnancy. The type of surgical procedure is dependent on the extent of disease and the trimester of the pregnancy.[230] Few data exist concerning the safety and efficacy of SLNB. Although the blue dye used in SLN surgery is not approved for use in pregnant patients, the estimated radiation dose to the fetus from the radiocolloid tracer is low. Except for radiation, treatment should not be altered or delayed because of pregnancy. Either a modified radical mastectomy or lumpectomy with axillary dissection is acceptable local treatment. Immediate breast reconstruction should not be performed.

Systemic chemotherapy with 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) has been used in pregnancy. Investigators from MD Anderson Cancer Center reported a prospective series of 57 pregnant patients with breast cancer who were treated on a single-arm, multidisciplinary, protocol with FAC in the adjuvant (n = 32) or neoadjuvant (n = 25) setting.[231] Parents and guardians were surveyed by mail or telephone regarding outcomes of children exposed to chemotherapy in utero. All women who delivered had live births. One child had Down syndrome and two had congenital anomalies (club foot; congenital bilateral ureteral reflux). They concluded that breast cancer can be treated with FAC chemotherapy during the second and third trimesters without significant short-term complications for the majority of children exposed to chemotherapy in utero. It has been shown that administration of chemotherapy in the first trimester is associated with a high risk of birth defects (17%, 24/139), in terms of the probability of intrauterine growth retardation, prematurity, fetal malformation, or death; this risk is less in the second and third trimesters (1.3%, 2/150).[232]

As a general principle, hormonal therapy and RT should be avoided until after delivery. In one study, the estimated dose to the fetus from breast or chest wall radiation to a dose of 0.5 Gy is 0.02 Gy in the first trimester, 0.022 to 0.246 Gy during the second trimester, and 0.02 to 0.586 Gy during the third trimester. Doses to the fetus in the range of 0.1 to 0.9 Gy during the first trimester have been associated with mental retardation. Hall[233] suggested that 0.1 Gy in utero exposure be used as a dose beyond which a therapeutic abortion should be considered.

Pregnancy After Breast Cancer

Almost one-third of women of reproductive age in whom breast cancer develops later have one or more pregnancies, and 70% of these occur within 5 years of treatment.[234] No data are available to suggest that subsequent pregnancy hastens or induces breast cancer recurrence.

A population-based matched survival study assessed the risk of death for patients with breast cancer in relation to whether they delivered a live child subsequent to their cancer diagnosis.[235] Among 2,548 women younger than 40 years of age diagnosed with carcinoma of the breast, 91 experienced subsequent deliveries (10 months or longer after the diagnosis) and 471 control patients were matched for stage, age, and year of breast cancer diagnosis. The control subjects had to survive at least the interval between the cancer diagnosis and the delivery of their matched counterparts. The control subjects had a 4.8-fold greater risk of death compared with those who delivered after the diagnosis of breast cancer. These authors' interpretation of this result was that there was a "healthy mother effect" (only women who felt healthy gave birth, and those who were affected by the disease did not). Nevertheless, 6 of 8 deaths among the 91 patients who did give birth were related to breast cancer.

It may be helpful to suggest a waiting time (2-3 years) for the patient to regain health before attempting the physical stress of pregnancy and deferral of childbearing until after the period of greatest risk of recurrence of the tumor.[234] The individual woman's prognosis, well-being, desire for

children, support from spouse or significant other, and other sociodemographic factors must be carefully considered in this difficult decision-making process.

Lactation After Breast Conservation Therapy

Successful breastfeeding, from the untreated as well as the treated breast, is possible after conservation surgery and irradiation. From over 3,000 patients treated from 1965 to 2003, a cohort of 21 premenopausal women who underwent BCT and subsequently sustained full-term pregnancies were identified.[236] Lactation outcome parameters (breast swelling, ability to lactate, and volume of lactation in the treated and untreated breasts) were the main outcome measures. There were 28 pregnancies in 21 patients. One patient underwent bilateral breast treatment; therefore, a total of 22 breasts were irradiated. All patients interviewed reported little or no swelling of the treated breast during pregnancy. Of the patients studied, 4 (18.2%) elected pharmacologic suppression of lactation. Of the remaining 18 breasts, lactation occurred in 10 (55.6%), did not occur in 7 (38.9%), and was unknown for 1 (5.5%). The volume was reported as significantly diminished in 80% of breasts treated. Lactation in the contralateral breast occurred in all patients who did not undergo pharmacologic suppression. The authors confirmed that successful lactation occurs in the contralateral, untreated breast after BCT. In the treated breast, functional lactation is possible but is significantly diminished in most patients.

Breast Irradiation in Patients Previously Irradiated for Hodgkin Lymphoma

There is an increased incidence of breast cancer in female patients who have previously undergone mantle irradiation for Hodgkin lymphoma. Numerous studies have demonstrated a significantly increased RR of breast cancer in women treated for Hodgkin lymphoma, with the risk significantly increasing with decreasing age of exposure.[16,17,237-240]

Travis et al[16] estimated that for a female Hodgkin lymphoma survivor who was treated at age 25 years with a chest radiation dose of at least 40 Gy without alkylating agents, the cumulative absolute risks of breast cancer by age 35, 45, and 55 years were 1.4% (95% CI, 0.9%-2.1%), 11.1% (95% CI, 7.4%-16.3%), and 29.0% (95% CI, 20.2%-40.1%), respectively. In addition to radiation dose, treatment volumes may also play a role in determining a woman's risk of developing breast cancer after RT for Hodgkin lymphoma. A study by De Bruin et al[17] reported on a cohort of 1,122 female patients with Hodgkin lymphoma treated between 1965 and 1995. The overall cumulative incidence 30 years after treatment was 19%; for those treated before age 21 years, it was 26%. Moreover, mantle field irradiation was associated with a 2.7-fold increased risk in developing breast cancer compared with similarly dosed (36-44 Gy) mediastinal irradiation alone.

Elkin et al[241] reported on a retrospective multicenter, cohort study of 253 patients treated for Hodgkin lymphoma with RT who developed breast cancer and matched 3 to 1 with 741 patients with sporadic breast cancer. They found that patients had a median time from diagnosis of Hodgkin to breast cancer of 18 years, with a median age at breast cancer diagnosis of 42 years. Breast cancer after RT for Hodgkin lymphoma was more likely to be detected by screening, was more likely to be diagnosed at an earlier stage, and was more likely to be bilateral at diagnosis. Hodgkin lymphoma survivors had an increased risk of metachronous contralateral breast cancer (HR 4.3; 95% CI, 1.7-11.0) and death as a result of any cause (HR 1.9; 95% CI, 1.1-3.3).

Hodgkin survivors and others who receive RT to the breast at a young age are at high risk for developing breast cancers and should be carefully monitored. Women who develop breast cancer should be advised that mastectomy remains the treatment of choice. However, for patients highly

motivated for breast preservation, anecdotal experiences using a variety of approaches have revealed acceptable toxicity and cosmesis.

Patients With More Than One Invasive Carcinoma (Multicentric/Multifocal Disease)

Conservation surgery and breast RT as an alternative to mastectomy is controversial in patients with two or more lesions in the same breast. Several studies have addressed this issue, and it appears that the risk of relapse in the conservatively treated patient is slightly higher than if there is one lesion. Still, however, that risk may be acceptable in patients who achieve negative surgical margins and are highly motivated for breast conservation.

The ACOSOG Z11102 trial is a single-arm noninferiority trial of breast conservation in women with two to three sites of malignancy in the breast.[242] Of the 204 patients who underwent protocol-directed breast conservation therapy, the 5-year cumulative incidence of LR was 3.1% (95% 1.3-6.4). Age, number of biopsy-proven foci, ER/Her2 status, and pathologic T and N categories were not significantly associated with LR. However, exploratory analysis showed that the 5-year LR in patients without a preoperative MRI was 22.6% compared to 1.7% in patients with a preoperative MRI. The authors concluded that breast conservation is reasonable approach for patients with multifocal disease, particularly when evaluated with a preoperative breast MRI. Longer term follow-up is awaited to confirm the feasibility of breast conservation in patients with multiple foci of disease.

Conservation Surgery and Irradiation After Breast Augmentation

A growing number of breast cancers occur in women with prior augmentation mammoplasty. The stage of breast cancer at diagnosis in women who have undergone augmentation mammoplasty has been examined with conflicting results. In a retrospective review, Clark et al[243] reported that 24% of 33 patients with augmented breasts and 42% of 1,735 patients with nonaugmented breasts had mammographically detected cancers (P = not significant). The incidence of DCIS in the two groups was similar (18% vs 15%). Sizes of the mammographically detected tumors in the two groups were comparable. However, palpable tumors in the augmented group were significantly smaller than those in the nonaugmented group. Axillary lymph node involvement was detected in 19% of the augmented group and 41% of the nonaugmented group. Among those with mammographically detected tumors, there was no significant difference in axillary lymph node metastases between patients with augmented versus nonaugmented breasts (13% vs 15%).

Breast conservation therapy in 17 augmented patients with breast cancer was reported by Handel et al,[244] where 15 patients were available for follow-up. In 10 (67%) patients, significant capsular contracture occurred in the irradiated breast an average of 12 weeks after completion of treatment. Four patients underwent revision surgery to correct symptoms arising from contracture. These authors concluded that irradiation of the breast for cancer in augmented women results in a high incidence of scar tissue contracture and poor cosmetic results.

In contrast, Guenther et al[245] evaluated 20 women in whom breast cancer developed after augmentation mammoplasty (14 subcutaneous implants and 6 retromuscular implants). Patients were treated with wide local tumor excision and level I and II ALND. Irradiation was delivered to the breast (45-50 Gy), and a boost (14-21 Gy) was given to the tumor excision site with either photons, electrons, or iridium-192 (^{192}Ir) implant. With a median follow-up of 3.8 years (range, 6 months to 9.3 years), there were no LRs, although distant metastases developed in two patients. Seventeen patients (85%) had good or excellent cosmetic results.

Patients with breast augmentation who are diagnosed with breast cancer can be treated with conservation therapy but should be counseled on the potential cosmetic consequences of treatment.

Breast Conservation and Mammoplasty

Women with large, pendulous breasts have been documented to have poorer cosmetic outcomes when undergoing irradiation after breast conservation surgery (thought to be caused by dose inhomogeneity) compared with women who have small- or medium-sized breasts. Smith et al[246] evaluated 10 women who had undergone bilateral reduction mammoplasty for breast malignancy followed by RT. A variety of reduction techniques were used to include the malignant lesions. Patients received 50 Gy in 25 fractions in 5 weeks after surgery. RT was usually initiated within 4 weeks after surgery. With a follow-up of 37 months, no patients had complications from the surgery or RT. No locally recurrent malignancies were detected. Cosmesis was good to excellent in all patients.

TECHNICAL ISSUES IN RADIATION MANAGEMENT OF EARLY-STAGE DISEASE

Treatment Position

Most patients are treated in the supine position, with the arm abducted (≥90°). Commercially available or custom-made breast tilt boards with armrests that maintain the patient's daily position with the slope of the chest wall parallel to the table, often in combination with immobilization devices (eg, Alpha cradle, plastic molds), are typically used to reproduce daily positioning and minimize day-to-day setup errors (Figure 62.19).

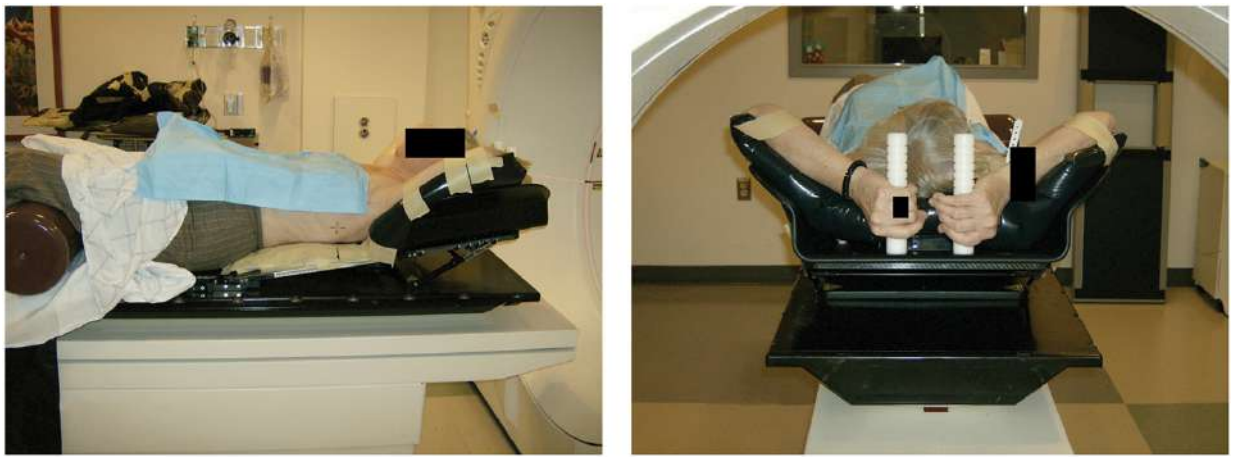


FIGURE 62.19 Patient immobilized for breast irradiation on a slant board with custom mold to minimize day-to-day positioning errors.

Irradiation in the prone position can improve dose homogeneity, particularly for patients with larger breasts. It can also reduce normal tissue exposure to the nearby heart, lungs, and contralateral breast. Patient positioning and a corresponding CT image are shown in Figures 62.20 and 62.21.

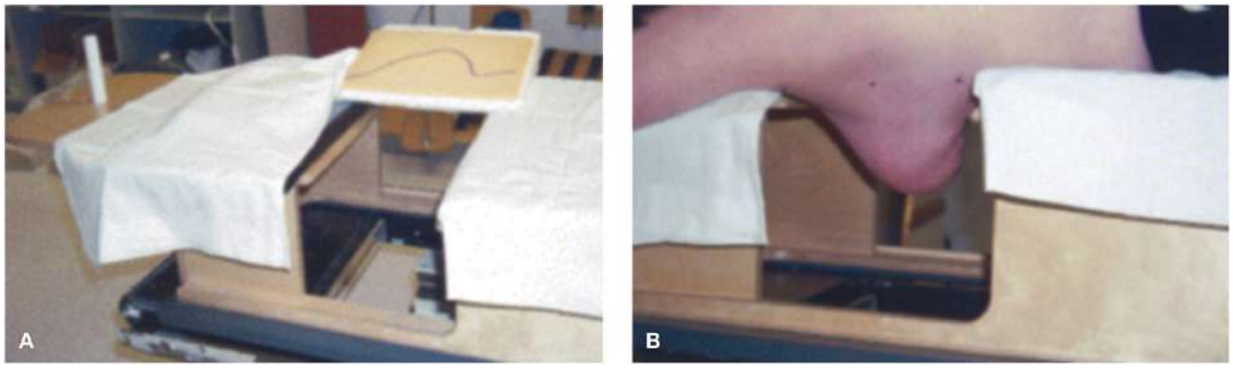


FIGURE 62.20 Prone breast board. A. Customized prone breast board with adjustable aperture and wedge for contralateral breast. B. Ipsilateral breast and anterior chest wall hang in a dependent manner away from thorax with ipsilateral arm placed above the head. (Reprinted from Goodman KA, Hong L, Wagman R, Hunt MA, McCormick B. Dosimetric analysis of a simplified intensity modulation technique for prone breast radiotherapy. *Int J Radiat Oncol Biol Phys*. 2004;60[1]:95-102. Copyright © 2004 Elsevier. With permission.)

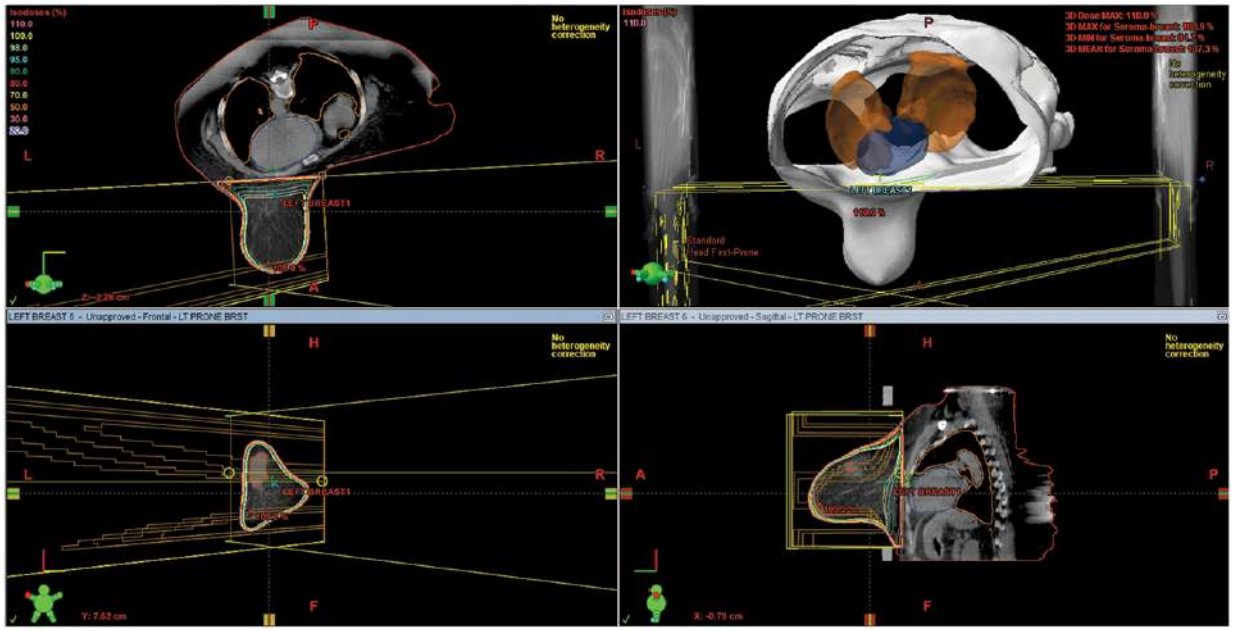


FIGURE 62.21 Computed tomography simulation images used to determine arrangement of tangent beams in prone breast irradiation. (Reprinted from Goodman KA, Hong L, Wagman R, Hunt MA, McCormick B. Dosimetric analysis of a simplified intensity modulation technique for prone breast radiotherapy. *Int J Radiat Oncol Biol Phys*. 2004;60[1]:95-102. Copyright © 2004 Elsevier. With permission.)

Treatment Volume

The entire breast and chest wall are included in the irradiated volume as shown in Figures 62.22 and 62.23. Radiopaque surgical clips placed at the margin of the tumor bed may assist in defining the target volume. The upper margin of the portals should be placed at the head of the clavicle to include the entire breast. The medial margin, if no internal mammary portal is used, should be at or 1 cm over the midline. If an internal mammary field is used, the medial tangential portal is located at the lateral margin of the internal mammary field. (See later discussion of RNI.) The lateral-posterior margin should be placed 2 cm beyond all palpable breast tissue, which is usually near the midaxillary line. The inferior margin is drawn 2 to 3 cm below the inframammary fold. The RTOG

published their consensus definitions for breast cancer RT planning, which are listed in Table 62.16. An illustration of nodal volumes drawn on an axial planning CT scan is shown in Figure 62.24.

TABLE 62.16 RADIATION THERAPY ONCOLOGY GROUP CONSENSUS DEFINITIONS FOR BREAST CANCER RADIATION THERAPY PLANNING

	Cranial	Caudal	Anterior	Posterior	Lateral	Medial
Breast	Clinical reference + second rib insertion	Clinical reference + loss of CT apparent breast	Skin	Excludes pectoralis muscles, chest wall muscles, ribs	Clinical reference/midaxillary line typically, excludes latissimus dorsi	Sternal–rib junction
Breast + chest wall	Same	Same	Same	Includes pectoralis muscles, chest wall muscles, ribs	Same	Same
Chest wall	Caudal border of the clavicle head	Clinical reference + loss of CT apparent contralateral breast	Skin	Rib–pleural interface. (includes pectoralis muscles, chest wall muscles, ribs)	Same	Same
Supraclavicular	Caudal to the cricoid cartilage	Junction of brachioceph.-axillary vns./caudal edge clavicle head	Sternocleidomastoid (SCM) muscle	Anterior aspect of the scalene m.	Cranial: lateral edge of SCM m. Caudal: junction 1st rib–clavicle	Excludes thyroid and trachea
Axilla: Level I	Axillary vessels cross lateral edge of pec. minor m.	Pec. major muscle insert into ribs	Plane defined by: anterior surface of pec. maj. m. and lat. dorsi m.	Anterior surface of subscapular is m.	Medial border of lat. dorsi m.	Lateral border of pec. minor m.
Axilla: Level II	Axillary vessels cross medial edge of pec. minor m.	Axillary vessels cross lateral edge of pec. minor m.	Anterior surface pec. minor m.	Ribs and intercostal muscles	Lateral border of pec. minor m.	Medial border of pec. minor m.
Axilla: Level III	Pec. minor m. insert on cricoid	Axillary vessels cross medial edge of pec. minor m.	Posterior surface pec. major m.	Ribs and intercostal muscles	Medial border of pec. minor m.	Thoracic inlet
Internal mammary	Superior aspect of the medial 1st rib.	Cranial aspect of the 4th rib				

Brachioceph.-axillary vns, brachiocephalic-axillary veins; CT, computed tomography; lat. dorsi m., latissimus dorsi muscle; pec. major m., pectoralis major muscle; pec. minor m., pectoralis minor muscle.

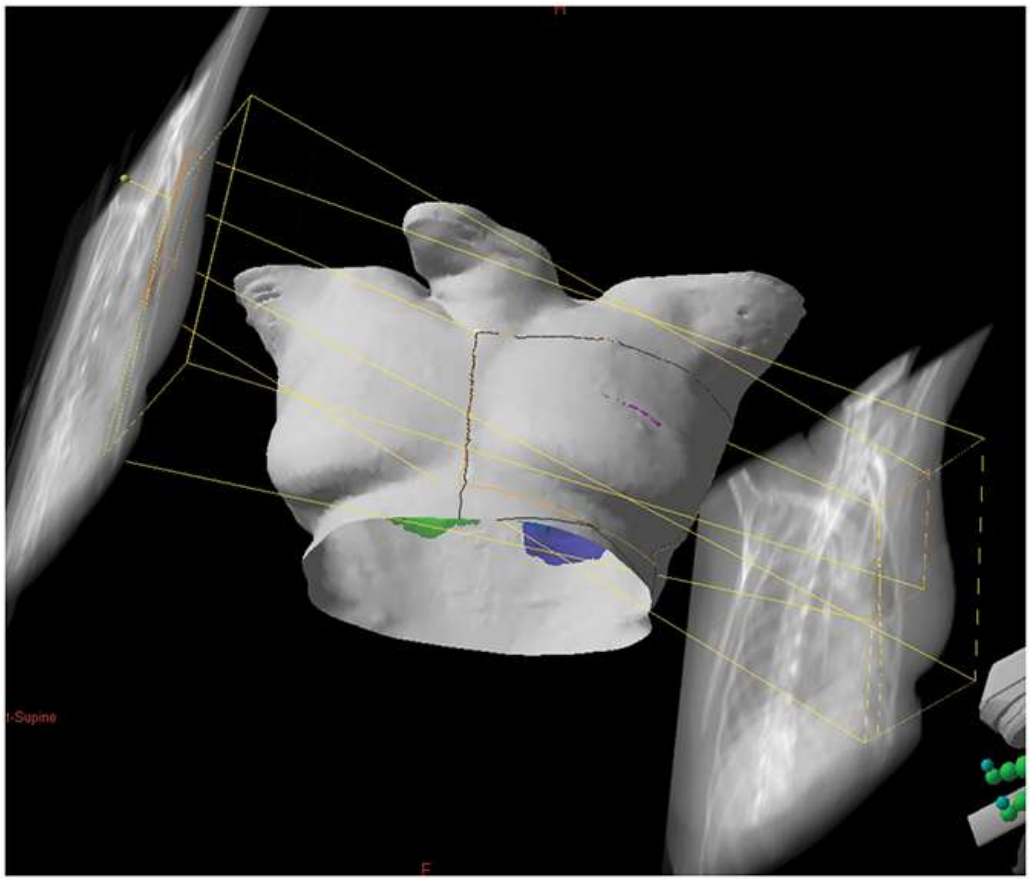


FIGURE 62.22 Axial treatment planning computed tomography cut with contours of the level I, II, and III nodes.

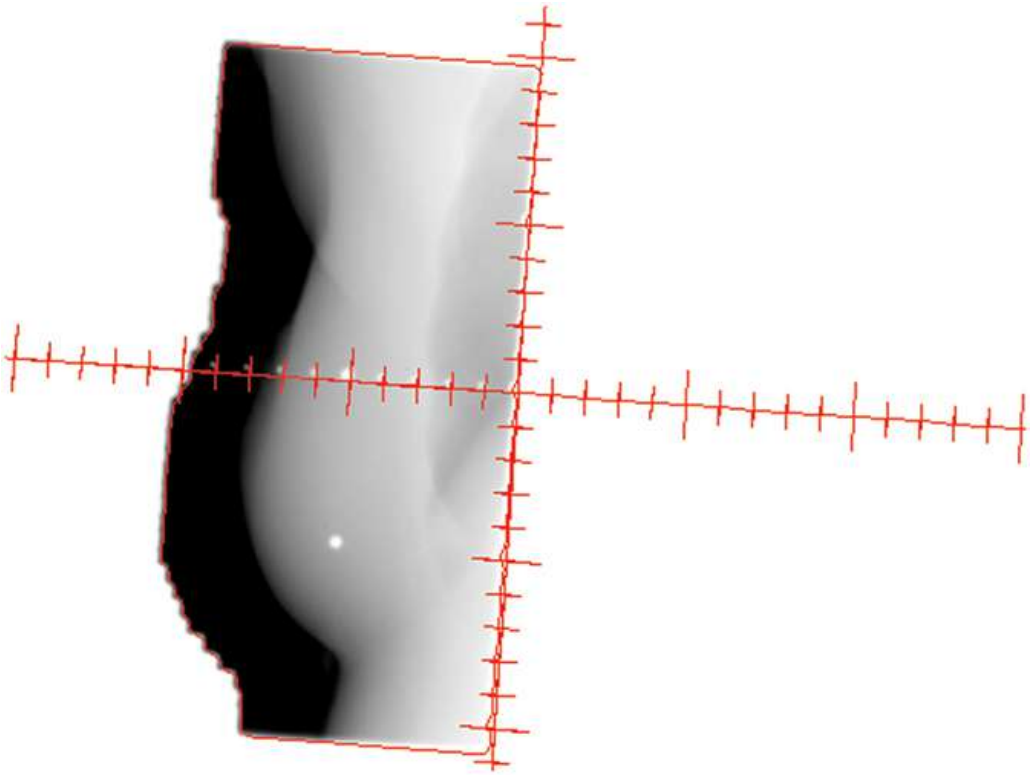


FIGURE 62.23 A tangential breast radiation field demonstrating projection of tangential field on simulation film and patient surface.

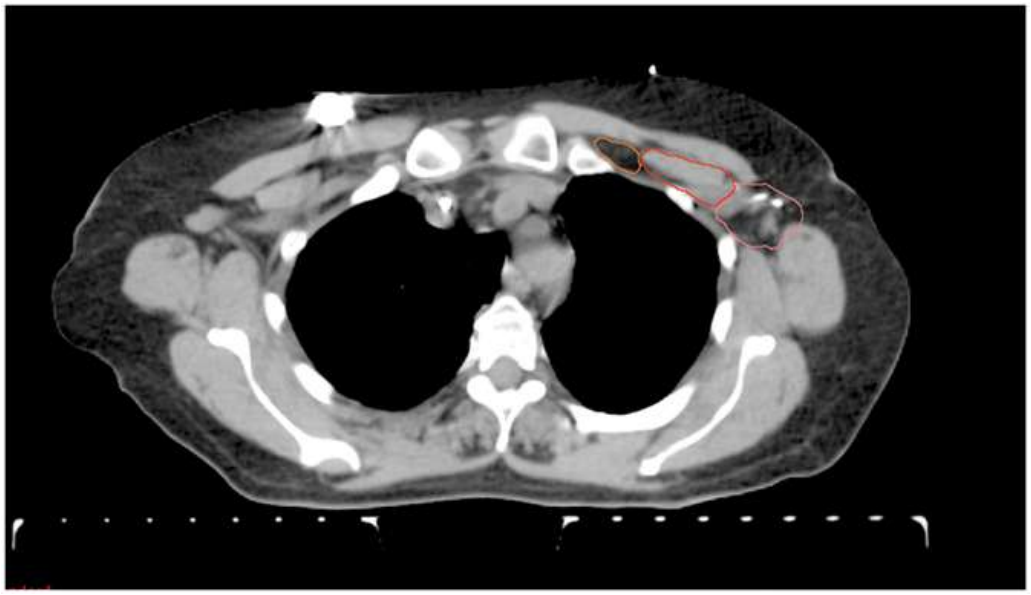


FIGURE 62.24 Nodal volumes drawn on axial planning computed tomography scan.

In patients treated with 6-MV or lower energy photons with wide tangential fields and large separation, there may be significant dose inhomogeneity in the breast, which can compromise cosmetic outcomes. This problem can be minimized by using higher energy photons (10-18 MV) to deliver a portion of the breast radiation (~50%) as determined with treatment planning to maintain

the inhomogeneity throughout the entire breast to between 93% and 105%. If desired, the buildup of the beam may be modified with a "degrader." "Simple intensity-modulated RT (IMRT)" techniques such as field-in-field or dynamic multileaf collimators (MLCs) to achieve electronic tissue compensation may be utilized to reduce dose inhomogeneity as well. Bolus should be avoided in conservatively managed patients. A variety of immobilizing devices or molds may be constructed to support the breast in the treatment position (Figure 62.25). A polyvinyl chloride, ring-shaped device, held by a strap, has been used around the breast to aid in positioning of patients with large, pendulous, or flaccid breasts.[247] Skin reactions where material is in contact with the skin should be closely monitored.

FIGURE 62.25 Immobilization material placed over breast tissue to help maintain the day-to-day positioning of the breast.

Alignment of the Tangential Beam With the Chest Wall Contour

The anterior chest wall slopes downward from the midchest to the neck. To make the posterior edge of the tangential beam follow this downward-sloping contour, the collimator of the tangential beam may be rotated, or the patient may be placed on a slant so that the slope of the chest wall is parallel to the table. An alternative is to make the deep posterior edge of the tangential beam follow the chest wall contour by means of a rotating beam splitter mounted on a tray without rotation of the collimator or using multileaf collimation. In this way, the superior edge of the tangential beam remains in the true vertical and matches perfectly the vertical inferior edge of the supraclavicular field if used.

Usually up to 2 to 3 cm of underlying lung may be included in the tangential portals. The amount of lung included in the irradiated volume is greatly influenced by the portals used. Bornstein et al[248] determined the amount of lung irradiated in 40 patients with breast cancer using CT scans for treatment planning in the treatment position. Parameters measured from simulator films included the perpendicular distance from the posterior tangential field edge to the posterior part of the anterior chest wall at the center of the field (central lung distance [CLD]), the maximum

perpendicular distance from the posterior tangential field edge to the posterior part of the anterior chest wall (maximum lung distance), and the length of lung as measured at the posterior tangential field edge on the simulator film (Figure 62.26). The best predictor of the percentage of ipsilateral lung volume treated by the tangential fields was the CLD. A CLD of 1.5 cm predicted that approximately 6% of the ipsilateral lung would be included in the tangential field; a CLD of 2.5 cm, approximately 16%; and a CLD of 3.5 cm, approximately 26% of the ipsilateral lung. A typical acceptable dose-volume histogram of a left-sided breast cancer treated with external beam radiation is given in Figure 62.27.

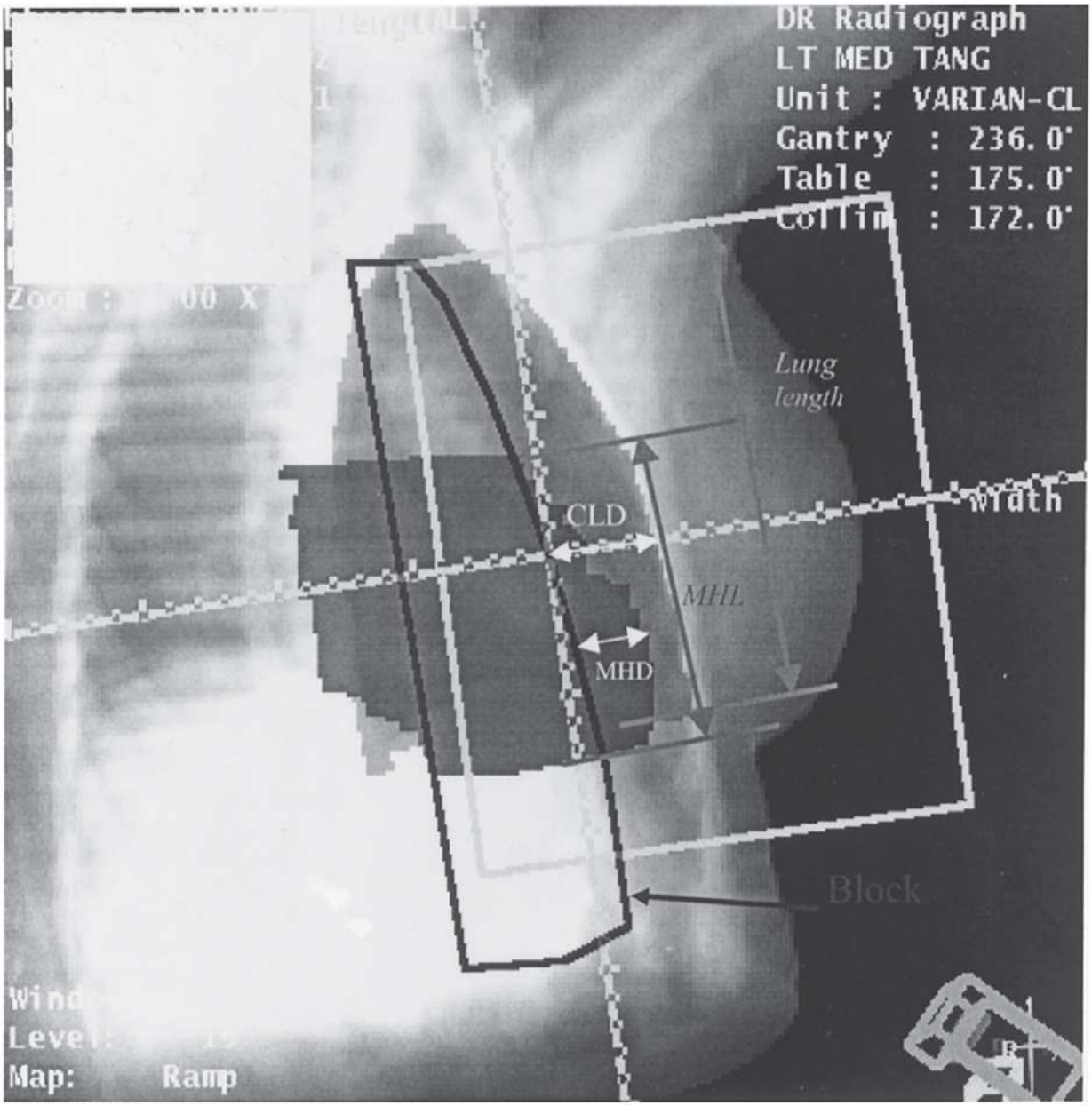


FIGURE 62.26 Measurement of the radiographic parameters using a virtual simulator. The contoured heart is shown in black and the lung in gray. The central lung distance (CLD) is the lung distance in the projection of the tangential fields at the level of the central axis. Lung length is the vertical lung distance included in the radiation port. The maximal heart distance (MHD) is the width of the heart in the tangent fields at its maximal level, whereas the maximal heart length (MHL) is the maximal length in tangential fields referring to the heart contour in a digitally reconstructed radiograph (DRR). (Reprinted from Kong F-M, Klein EE, Bradley JD, et al. The impact of central lung distance, maximal heart distance, and radiation technique on the volumetric dose of the lung and heart for intact breast radiation. *Int J Radiat Oncol Biol Phys*. 2002;54[3]:963-971. Copyright © 2002 Elsevier. With permission.)

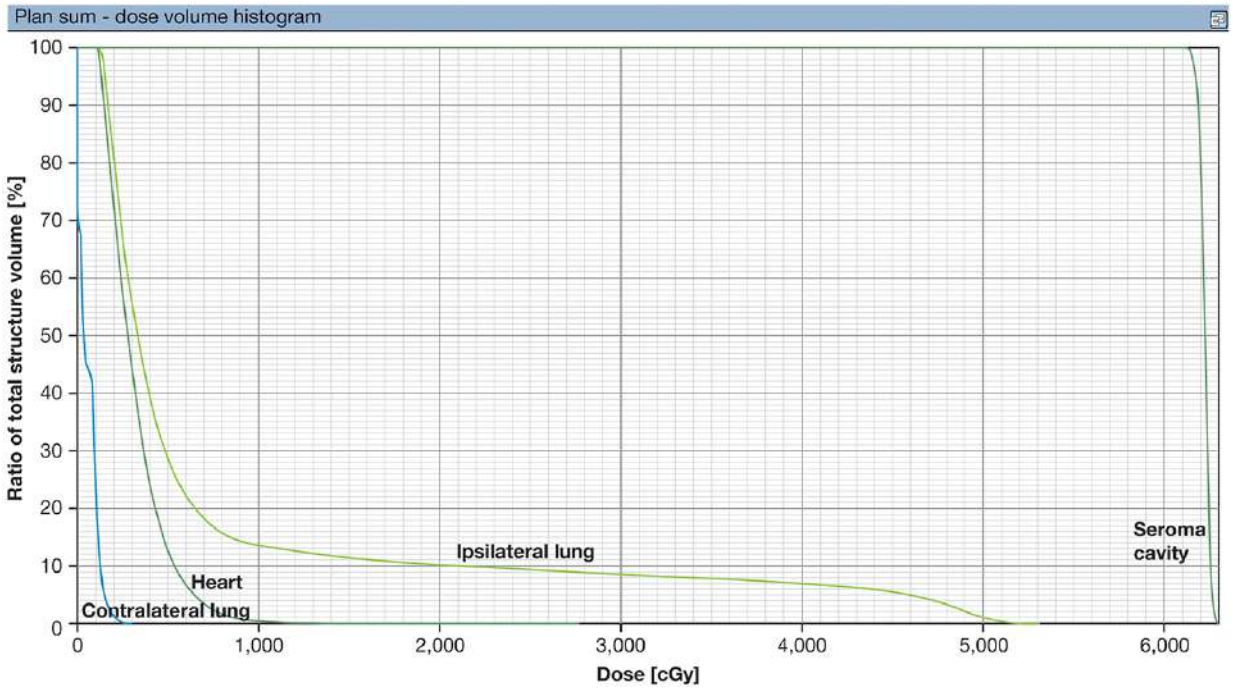


FIGURE 62.27 Dose-volume histogram of left-sided breast cancer treated with external beam radiation.

When the CLD is greater than 3 cm, in treatment of the left breast, a significant volume of heart will also be irradiated. To avoid this, a medial tangential breast port (3- to 5-cm wide), somewhat similar to an internal mammary port, may be designed. The beam is angled 10° to 15° laterally to conform to the angle of the medial breast port. The dose is prescribed to the posterior border of the chest wall as determined by CT scanning.

Special attention should be paid to minimizing the volume of heart irradiated.[249] As discussed later in the section on cardiac sequelae, even small amounts of heart in the field can affect cardiac function. Marks et al[250] have suggested the use of a cardiac block if the heart is in the tangential field, which can be supplemented by an electron field as shown in Figure 62.28. The use of short (10- to 15-second) treatments while the patient holds their breath is also feasible as a way of reducing cardiac radiation during left-sided breast cancer treatment.[251]

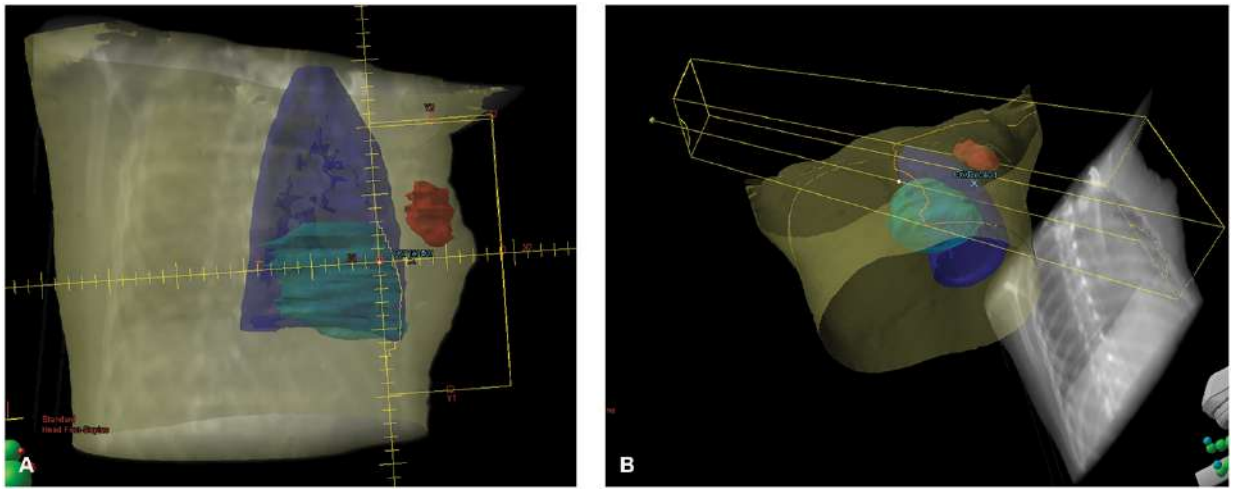


FIGURE 62.28 A and B: Left tangential breast field with heart block to shield left ventricle from radiation port. Projection of heart block on breast shields a minimal amount of breast tissue. If necessary, a shadow electron field may be added to cover the portion of breast tissue shielded by heart block.

Doses of Radiation and Fractionation

Whole-Breast Dose

Conventional fractionation delivers 45 to 50 Gy to the whole breast over 5 to 6 weeks (1.8- to 2-Gy tumor dose daily, 5 weekly fractions) and was previously the standard of care. After the publication of the updated ASTRO guidelines in 2018, HF-WBI has become the new standard of care for the majority of patients with early-stage breast cancer requiring treatment to the breast only. HF-WBI delivers 40 Gy in 15 daily fractions or 42.5 Gy in 16 daily fractions.

Alternative fractionation schemes have been investigated and have been shown to be acceptable. These are discussed in greater detail in the hypofractionation section.

Radiation Beams

X-ray energies of 4 to 6 MV are preferred to treat the breast. Photon energies greater than 6 MV underdose superficial tissues beneath the skin surface, but higher energy photons may be helpful in large breasts to decrease the integral breast dose. In these patients, the high-energy photon beam may be "degraded" to bring the maximum dose to more superficial tissues. It is not necessary to apply bolus to the breast because the skin is usually not at risk for recurrence after complete excision of a T1 or T2 lesion, as is the skin of the chest wall after a mastectomy.

Wedges or compensating filters must be used for a portion of the treatment to achieve a uniform dose distribution in the breast (5%-8% dose variance from the chest wall to the apex). Although conventional wedges improve dose homogeneity at the central axis of the breast, significant inhomogeneity can occur in the superior and inferior portions of the breast. With the use of MLCs and more sophisticated treatment planning techniques, optimization of homogeneity throughout the breast can be achieved. Dose homogeneity in a breast plan uncompensated (without wedges), with standard wedges, and with electronic dynamic wedge technique to improve homogeneity in the superior-inferior plane is outlined in Figure 62.29. These techniques are discussed in more detail later.

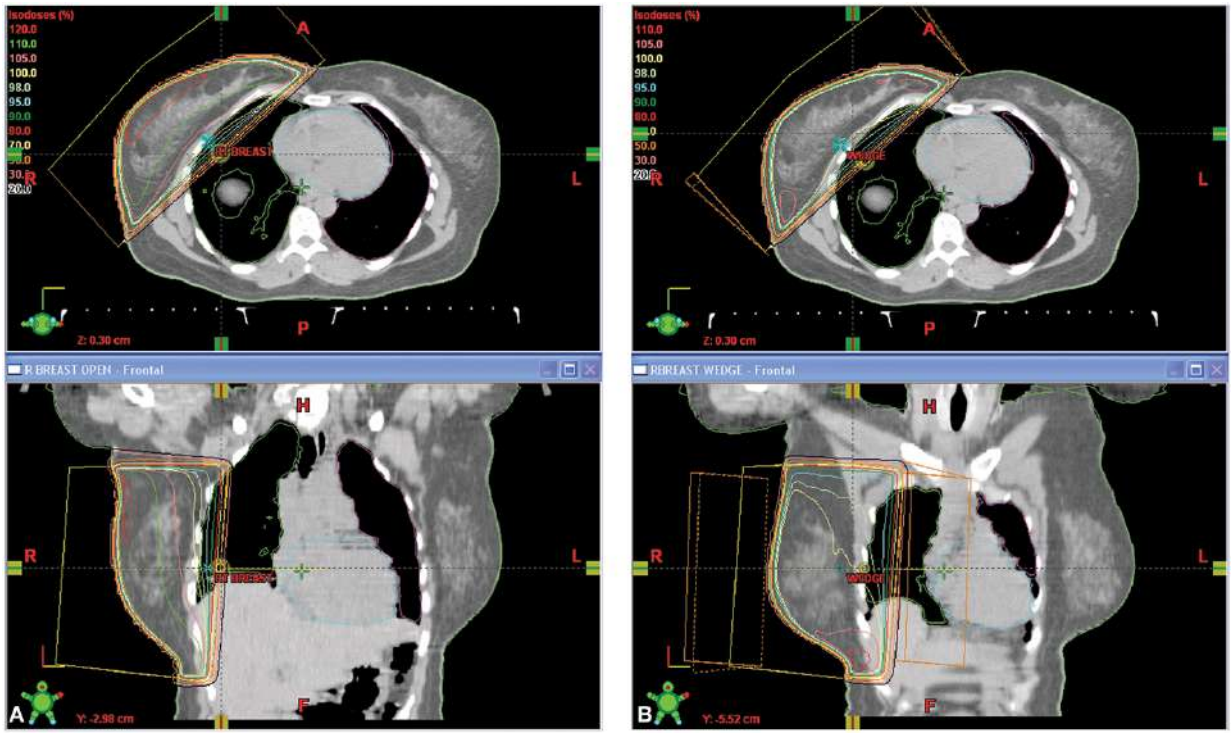

Isodoses (%)
120.0
110.0
105.0
100.0
98.0
95.0
90.0
80.0
70.0
50.0
30.0
20.0
A
R
L
P
Z: 0.30 cm
R BREAST OPEN - Frontal
H
R
L
F
A
Y: -2.98 cm
Isodoses (%)
110.0
105.0
100.0
98.0
95.0
90.0
80.0
50.0
30.0
20.0
A
R
L
P
Z: 0.30 cm
RBREAST WEDGE - Frontal
H
R
L
F
B
Y: -5.52 cm

FIGURE 62.29 Isodose distributions from three breast plans. A. Open fields demonstrating inhomogeneity. B. Standard wedges demonstrating improvement in the central axis, but with a hot spot in the superoinferior plane. C. Dynamic wedge plan showing improved homogeneity in both the central axis and the superoinferior plane.

Boost to Tumor Site

It is well known that most recurrences after breast conservation occur near the primary tumor site, which provides a strong rationale for a tumor bed boost. In low-risk patients, however, it may also be safe to omit a tumor bed boost.

Randomized Data

The Lyon Breast Cancer Trial conducted a randomized study to assess the role of the boost in BCT in patients with stage I and II breast cancer (≤3 cm) who were treated with complete local tumor

excision, axillary dissection, and 50 Gy to the breast in 20 fractions over 5 weeks.[252] Patients were randomly assigned to receive or not receive a boost of 10 Gy with electrons to the tumor bed. At 5 years, 10 (3.6%) of 521 women who received a boost and 20 (4.5%) of 503 who received no further treatment experienced a local breast relapse ($P = .044$). More patients failed after 7 years in the no-boost arm.

Bartelink et al[130] reported the results of the EORTC trial in which, after complete lumpectomy and axillary dissection, patients with stage I or II breast cancer received 50 Gy of radiation to the whole breast in 2-Gy fractions over a 5-week period and were randomly assigned to receive either no further local treatment (2,657 patients) or a boost of 16 Gy, usually given in 8 fractions by electron beam (2,661 patients). In the initial report, with a median follow-up of 5.1 years, LRs were observed in 182 of the 2,657 patients in the standard-treatment group and 109 of the 2,661 patients in the additional-radiation group. The 5-year actuarial rates of LR were 7.3% and 4.3%, respectively ($P < .001$). Patients aged 40 years or below benefited most; at 5 years, their rate of LR was 19.5% with standard treatment and 10.2% with additional radiation (RR 0.46; 99% CI, 0.23-0.89; $P = .002$). In an update of this study published in 2007, with a median follow-up of 10.8 years, a significant benefit to the boost was noted in all age groups, with an overall HR of 0.59 in favor of the boost[131] (see Figure 62.12).

If a decision is made not to use a boost, careful assessment of pathologic features, particularly lumpectomy margins, is critical.

Boost Techniques

For an electron boost, the patient is positioned with the arm toward the head to flatten the breast contour and may be rolled so the tumor bed is parallel to the table and the accelerator head can point straight down onto the target volume. An electron energy is selected that covers the target volume depth (usual range is 9-16 MeV electrons), based on review of the physical examination, mammogram, ultrasound, CT, or other imaging used to ascertain the location and depth of the tumor or metallic surgical clips. The 90% prescription isodose line is limited to the chest wall to decrease dose to the lung. The clinical setup for electron boost involves marking the projection of the postlumpectomy volume on the skin and adding 2 to 3 cm in all directions. A conformal photon boost can be utilized when the tumor bed is too deep for adequate coverage with an electron plan.

Accurate target volume definition is critical with any boost technique. Surgical clips are ideal for the localization of the tumor bed but require the cooperation of the surgical team. Despite the fact that it would theoretically take an infinite number of clips to define every extension of a typical tylectomy cavity, in practice six clips suffice (superficial, deep, medial, lateral, cephalad, and caudal). The combination of surgical clips with a treatment planning CT scan to define the lumpectomy site for boost is most ideal. In the absence of surgical clips, CT scan evaluation of the biopsy cavity or postsurgical changes, in combination with clinical information including mammography findings, scar location, operative reports, and patient input, can guide tumor bed delineation.

A multi-institutional study reported interobserver variabilities in the delineation of the seroma cavity and organs at risk in patients with breast cancer undergoing breast-conserving surgery and whole-breast irradiation.[253] Nine radiation oncologists specializing in breast RT from eight institutions independently delineated target volumes on the same three patients with breast cancer. They concluded that “variations in delineating the targets and OARs [organs at risk] for breast RT by well-experienced observers from different institutions are substantial for all relevant structures.”

To reduce these variations, guidelines for contouring the seroma cavity have been established; the Seroma Clarity Scale (SCS), developed by the British Columbia Cancer Agency and the Cavity Visualization Score (CVS), developed by a Stanford group.[254,255] Both scoring systems are remarkably similar, with the distinction being the SCS is a scale from 0 to 5, with 0 being no visible seroma cavity and 1 being a scar or shadow, and the CVS is a scale from 1 to 5, with 1 being no visible seroma cavity, and omits the presence of a scar or shadow on the scale. The score of 2 to 5 is relatively consistent between the two classification methods.

It is pertinent to note that each of these classification systems was developed without noting the presence of surgical clips or fiducial markers with respect to the seroma cavity. However, the authors, along with other investigators, have previously published that the presence of surgical clips or fiducial markers in the surgical bed improve the interphysician accuracy in the delineation of the seroma cavity in patients with early-stage breast cancer.[256,257] In a study by Shaikh et al,[258] the presence of fiducial markers improved the mean CVS score (from 2.5 to 3.5) and accuracy of physician contours compared with patients without fiducial markers. The use of titanium clips in patients treated with accelerated partial-breast irradiation (APBI) is a focus of the United Kingdom IMPORT LOW (Intensity Modulated and Partial Organ Radiotherapy) trial.[259] An audit of the trial was performed to determine inter- and intraphysician variation for tumor bed localization for RT planning. Although no control group was used, clips were essential for the localization of the surgical cavity in 22 (73%) of 30 patients and led to modifications in RT field borders in 18 (60%) of 30 patients. A study by Dzhugashvili et al[257] found that the visualization of the lumpectomy cavity was greatly improved in treatment planning CT scans when clips were present; this was found to be even more pronounced in patients with very dense mammary glands, regardless of the physician reading the CT image.

Irradiation of Regional Lymphatics

RT to the breast or chest wall and regional lymphatics can be technically challenging and, as previously discussed, remains one of the more variable and controversial aspects in management. A wide variety of available techniques, in combination with difficulties associated with matching fields, anatomic variability between patients, and lack of clear evidence regarding the superiority of any single approach, has resulted in a lack of consensus in regional nodal management.

Supraclavicular Lymph Nodes

The inferior border of the supraclavicular field is matched to the tangential field, usually just below the clavicular head. The medial border is 1 cm across the midline, extending upward, following the medial border of the sternocleidomastoid muscle to the thyrocricoid groove. The lateral border is a vertical line at the level of the coracoid process, just medial to the humeral head. This field is angled approximately 10° to 15° laterally to spare the cervical spine (Figure 62.30). The typical width of the supraclavicular field is 7 to 9 cm. The supraclavicular field is extended laterally to treat the full axilla, as clinically indicated. Figure 62.30 demonstrates a supraclavicular field with the supraclavicular and level I, II, and III nodes outlined. Level I as well as a portion of level II nodes will often be included in the tangential field; level III and supraclavicular nodes are covered in the supraclavicular field.

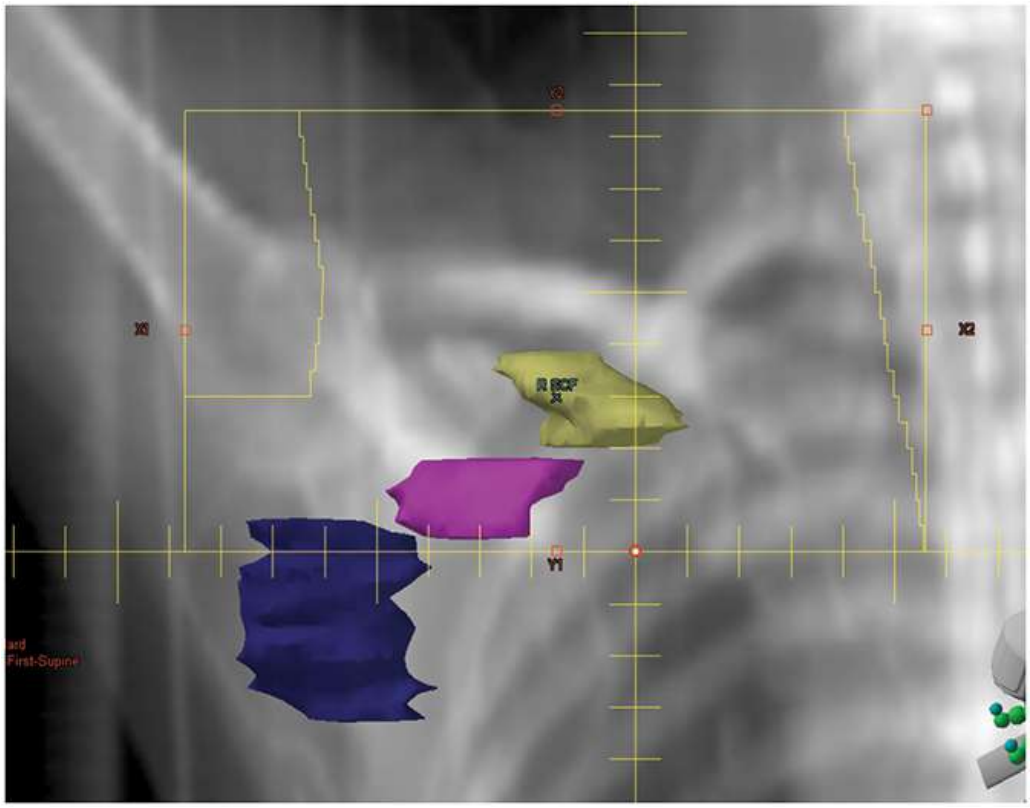


FIGURE 62.30 Supraclavicular and axillary field and field borders. Level I, II, and III nodes are demonstrated on the film. Note that level I nodes are included primarily in the tangential field in this case.

The total dose delivered to the supraclavicular field is 46 to 50.4 Gy at 1.8 to 2 Gy/day (calculated at a depth of 3 cm) in 5 fractions per week. For patients in whom the target is deeper than 3 cm, higher energy photons should be considered.

Axillary Lymph Nodes

When the axilla is treated in patients with positive nodes, or in patients with inadequate or undissected axillae, the supraclavicular field is extended laterally to cover at least two-thirds of the humeral head, as demonstrated in Figure 62.30. The dose to the midplane of the axilla from the supraclavicular field is calculated at a point approximately 2 cm inferior to the midportion of the clavicle. Depending on the dose distribution and patient's anatomy, a posterior axillary boost may be considered.

Posterior Axillary Boost

The posterior axillary boost can be employed to supplement axillary dose, as shown in Figure 62.31. The axilla should be contoured in CT treatment planning, as the depth of the axilla from the anterior-posterior skin surface varies from patient to patient, and the supplement prescription point and dose can be adjusted accordingly. When a posterior axillary boost is used, the borders are as follows: Medially, the border is drawn to allow 1.5 to 2 cm of the lung to show on the portal film; inferiorly, the border is at the same level as the inferior border of the supraclavicular field; laterally, the border just blocks fall-off across the posterior axillary fold; and lastly, the superior border splits the clavicle and the superolateral border shields or splits the humeral head.

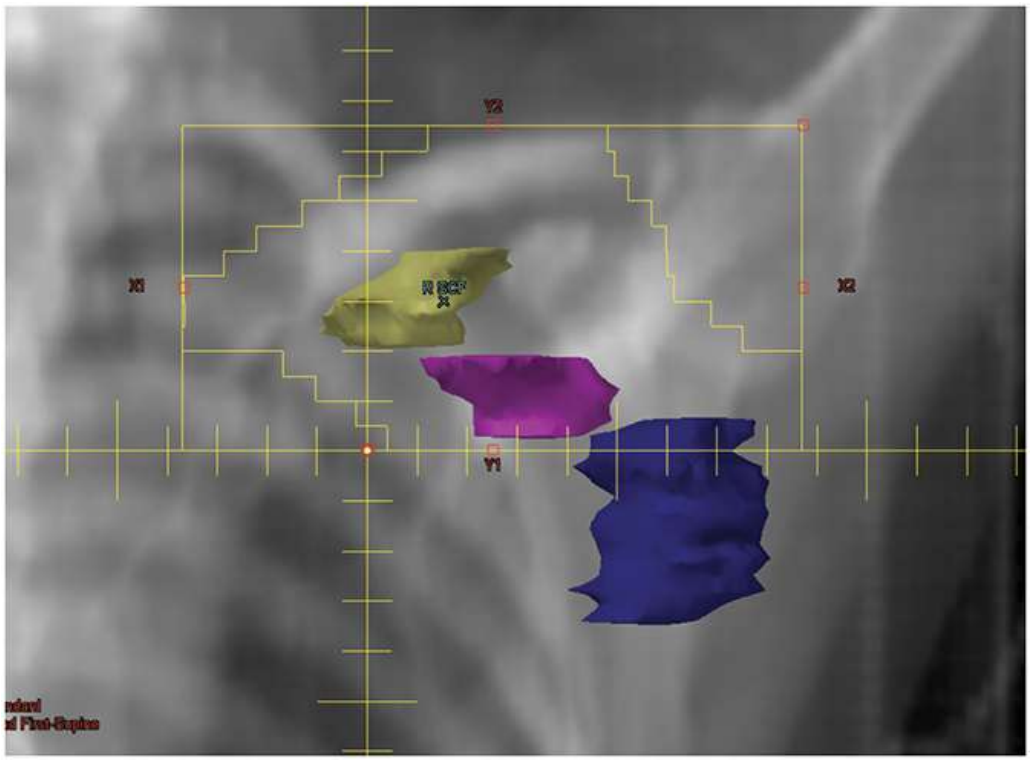


FIGURE 62.31 Posterior axillary field used to supplement the dose at the midplane of the axilla. Note the small amount of lung included and the shielding of the humeral head (whenever possible).

If the supraclavicular nodes are not felt to be at risk, a separate axillary field may not always be necessary to treat the axilla. In a study of 39 women with surgical clips in the axilla, Schlembach et al[171] demonstrated that with tangential fields, placing the caudal border of the field within 2 cm of the humeral head and 2 cm deep to the chest wall-lung interface (also called "high tangents") includes the majority of level I and level II lymph nodes (Figure 62.32).

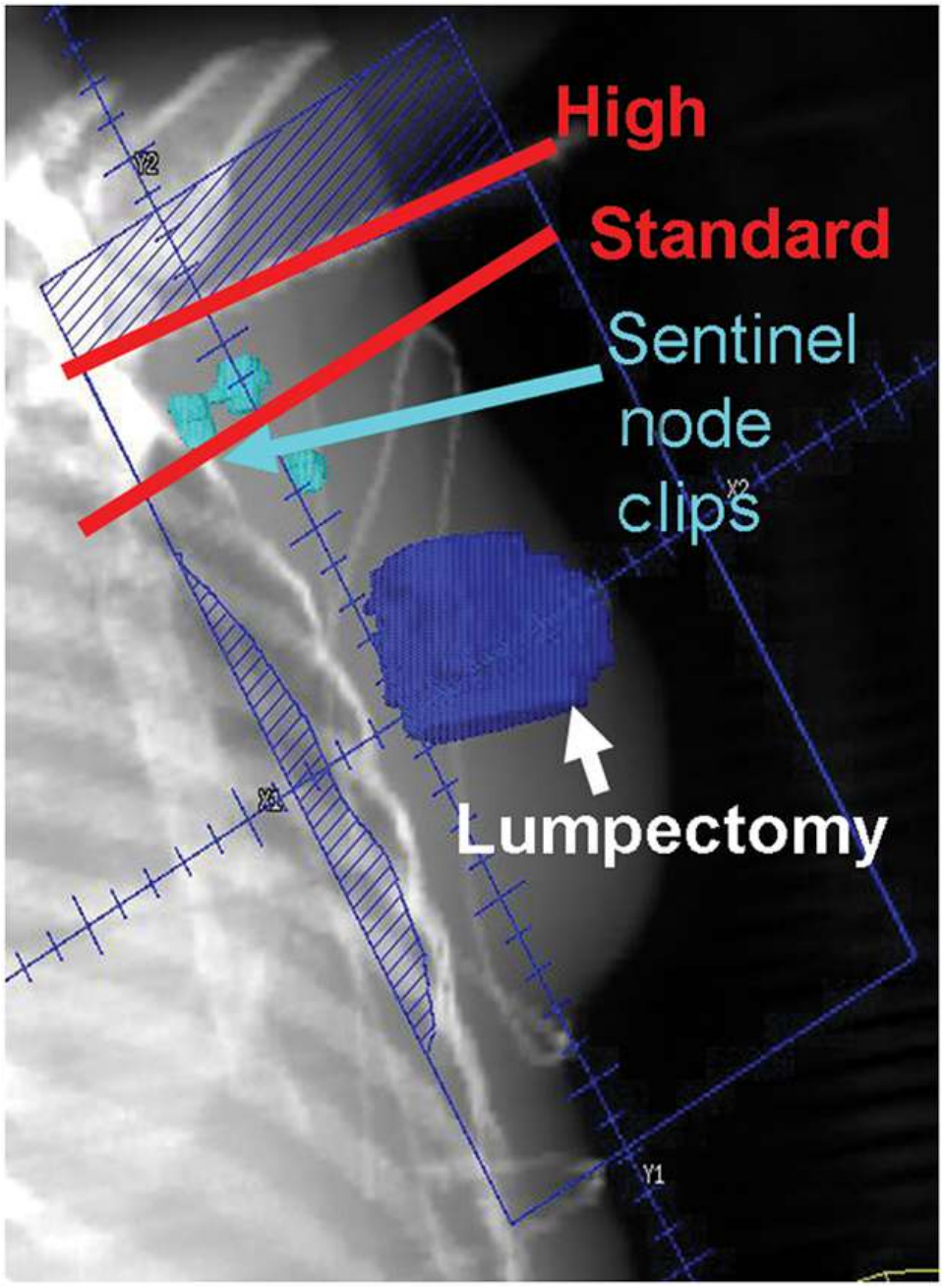


FIGURE 62.32 "High" tangential field showing coverage of level I and portion of level II nodes. With the caudal edge of the field within 2 cm of the humeral head and leading edge approximately 2 cm from lung-chest wall interface, most nodes in level I and level II will be covered by this technique.

Internal Mammary Lymph Nodes

The benefit of irradiation of the IMNs is an unresolved issue because clinical failures at this site are very rare, and most patients at risk receive adjuvant therapy.[191] However, the IMNs are difficult to treat because their exact location is often uncertain, and the radiation fields that include them irradiate more normal tissue.

One technique used to treat the IMNs is a direct anterior field matched to tangential fields, which was developed for PMRT and increases the volume of heart and lung tissue in the field. With this

technique, the rising contour of the intact breast interferes with dosimetry, which may affect the traditional dose prescription point at depths of 4 to 5 cm and may prevent an easy match to the breast tangential fields.

The medial border of the IMN field is the midline. The lateral border is usually 5 to 6 cm lateral to the midline. The superior border abuts the inferior border of the supraclavicular field, and the inferior border is at the xiphoid or higher. If only the IMNs are to be treated, the superior border of the field is at the first intercostal space (superior border of the head of the clavicle). The field is set, as described previously, with an oblique incidence to match the medial tangential portal (Figure 62.33).

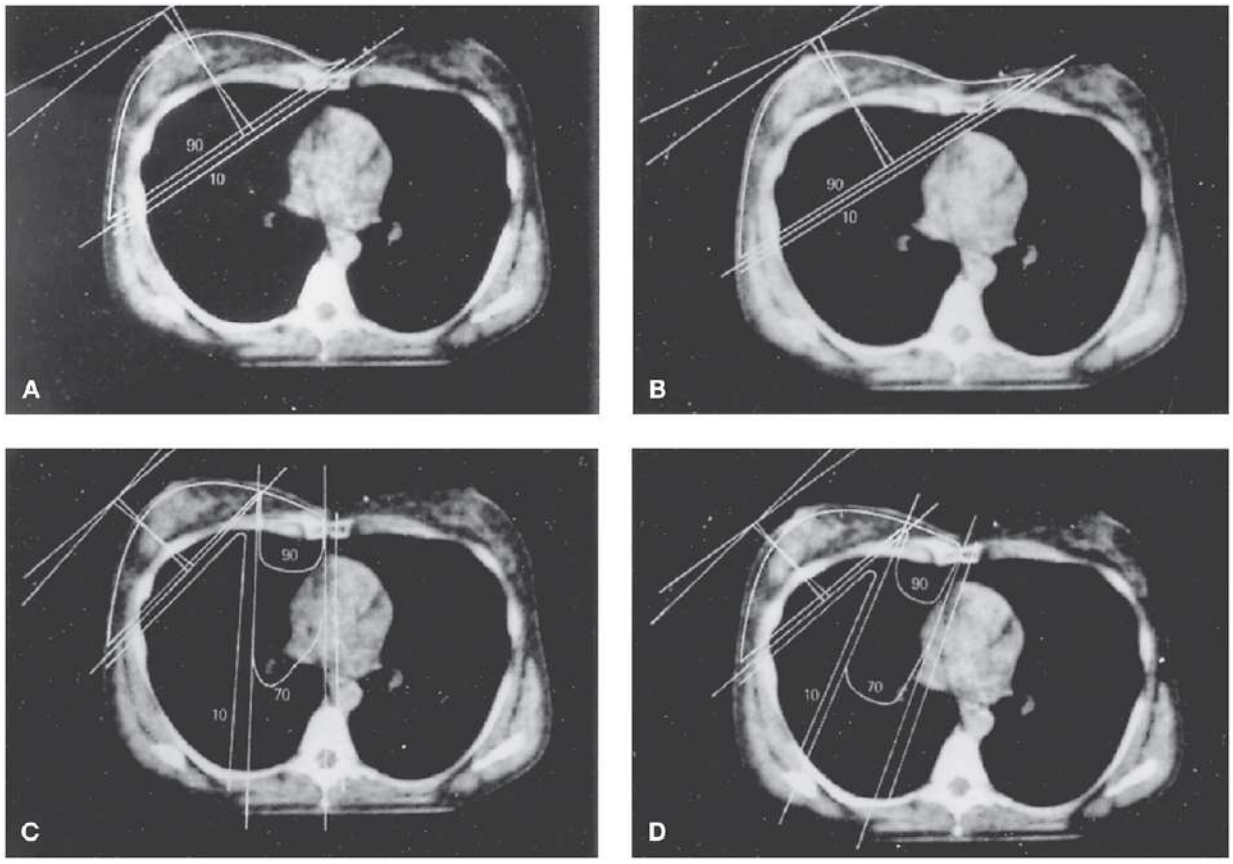


FIGURE 62.33 Irradiation of the breast: field configurations and isodose lines for 6-MV photons. A. "Standard tangents" technique. B. Deep tangents technique. C. En face internal mammary field technique. D. Twenty-degree intermaxillary fixation technique. (Reprinted from Roberson PL, Lichter AS, Bodner A, et al. Dose to lung in primary breast irradiation. *Int J Radiat Oncol Biol Phys*. 1982;9[1]:97-102. Copyright © 1982 Elsevier. With permission.)

A solution that avoids matching of fields is the use of partially wide tangential (PWT) fields to treat the internal mammary chain. However, this can result in more heart, lung, and contralateral breast exposure. Although IMNs can be imaged more clearly by radionuclide techniques, the nodes are typically located by identification of the internal mammary vessels, which can be seen on the CT simulator. The nodes in the first three intercostal spaces are thought to be most clinically significant. The medial border of the tangential field is moved 3 to 5 cm across the midline to cover the IMNs in the first three intercostal spaces. To minimize lung and cardiac exposure, a block is drawn, as demonstrated in Figure 62.34, to block the inferior mediastinal nodes. The portal films

should be inspected carefully to ensure that an excessive amount of lung or heart is not being irradiated. It is important to verify on the clinical setup that targeted breast tissue is not covered by the block.

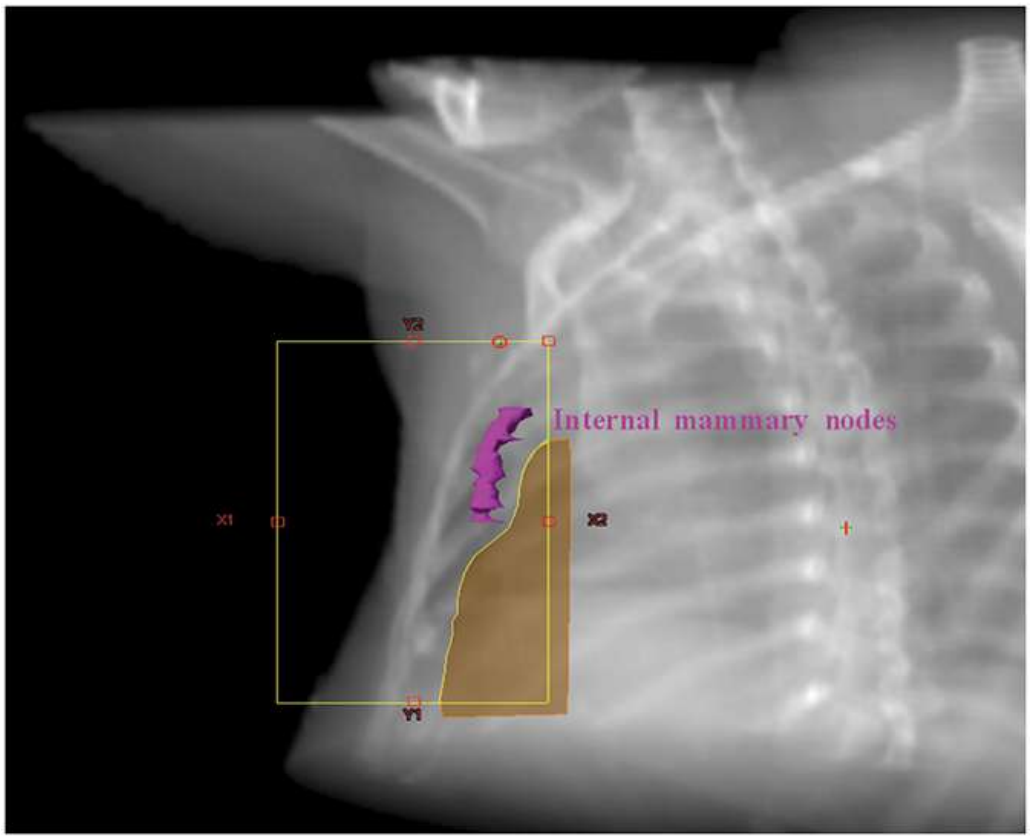


FIGURE 62.34 Partially wide tangential field covering internal mammary chain. The medial border of the tangential field is set 2 to 3 cm to the contralateral side to include the internal mammary chain. Below the fourth intercostal space, the field is blocked to minimize dose to the lungs and heart. Projection of the field on the patient's surface demonstrates adequate coverage of the involved breast-chest wall with this technique. With this technique, there may be a small amount of overlap onto the superior contralateral breast.

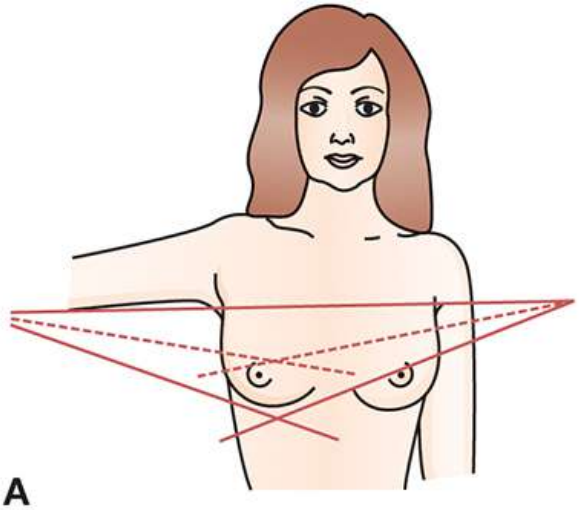
Severin et al[260] compared the PWT technique of breast and internal mammary chain irradiation with photon/electron (P/E) and ST techniques in terms of dose homogeneity within the breast and the dose to critical structures such as the heart and lung in 16 patients who underwent CT simulation for left-sided breast cancers. The mean dose to the left breast with the ST, P/E, and PWT techniques was 94.7%, 98.4%, and 96.5%, respectively ($P = .029$). The left lung received the lowest mean dose with the ST technique (13.9%) compared with PWT (22.8%) and P/E (24.3%). The internal mammary chain volume was most consistently treated with the PWT (mean dose 99%) versus P/E (86%) and ST (38.4%) techniques, although this technique was associated with the greatest amount of contralateral breast (mean dose 5.8%) versus ST (3.2%) versus P/E (2.8%). The heart received the least dose with ST (mean dose 6.7%) versus PWT (10.3%) and P/E (19%).

Matching the Tangential Fields With the Supraclavicular Field

A hot spot caused by divergence of the tangential beams into the supraclavicular field and of the supraclavicular beam into the tangential fields can exist just beneath the skin surface at the junction

of the inferior border of the supraclavicular field and the superior border of the tangential fields. The sharp beam of a linear accelerator and the “horns” at the edge of this beam produce a marked increase in dose beneath the match line if these divergences are not corrected. This increased dose may result in severe match line fibrosis or even rib fracture.

There are numerous methods to adjust for divergence of the beams and minimize match line fibrosis. The divergence of the tangential fields can be eliminated by angling the foot of the treatment couch away from the radiation source to direct the tangential beams inferiorly so that the superior edges of these beams line up perfectly with the inferior border of the supraclavicular field (Figure 62.35). In addition, the collimator may be rotated to geometrically eliminate overlap at this junction. Alternatively, the “hanging block” technique, in which a vertical block is affixed to the superior portion of the collimator to block off the nonvertical portion of the tangential beam, can be used (Figure 62.36).



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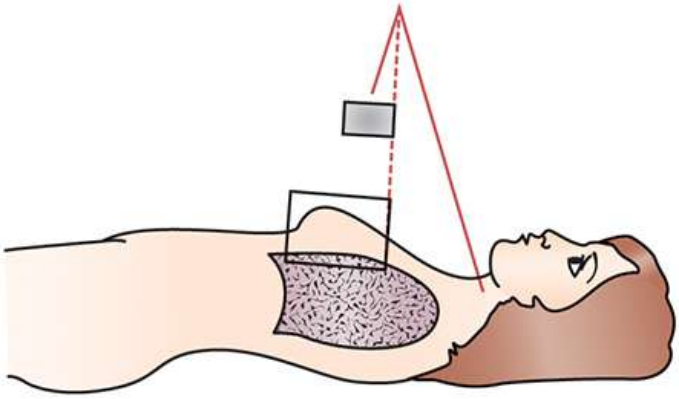

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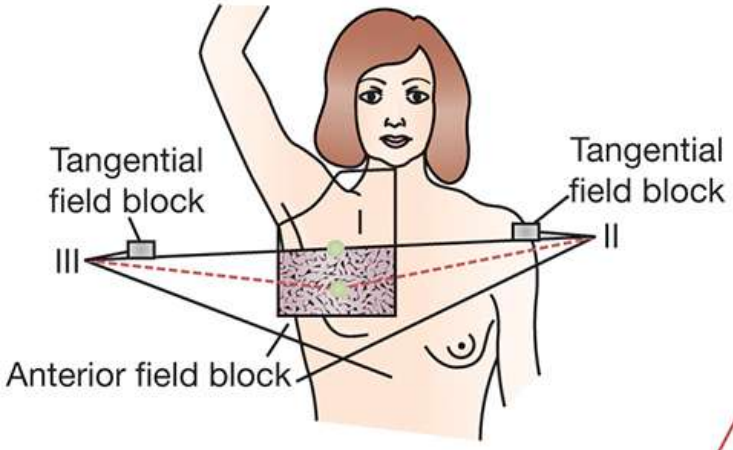
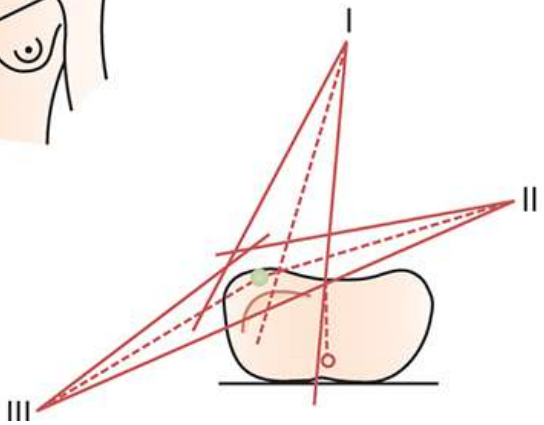

Tangential
field block
Tangential
field block
I
II
III
Anterior field block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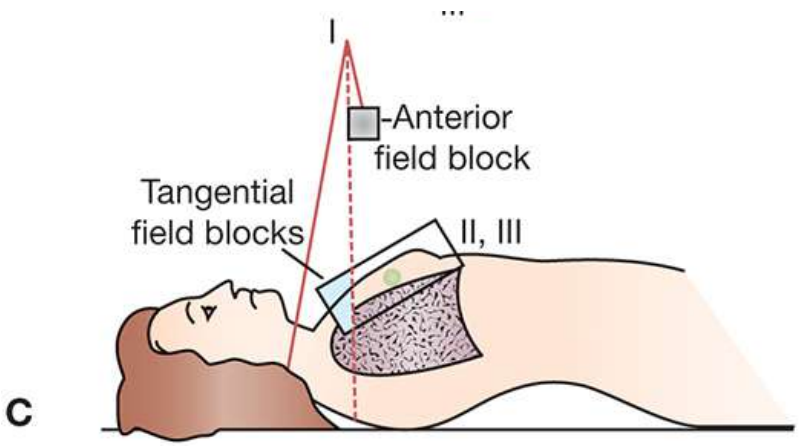


FIGURE 62.35 A. Inferior angulation of the tangential beams eliminates their divergence into the supraclavicular field. B. Splitting the supraclavicular beam eliminates its divergence down into the tangential field. (A and B reprinted from Bedwinek JM. Treatment of stage I and II adenocarcinoma of the breast by tumor excision and irradiation. *Int J Radiat Oncol Biol Phys*. 1981;7[11]:1553-1559. Copyright © 1981 Elsevier. With permission.) C. Three-field treatment beam geometry in irradiation of the intact breast and supraclavicular fields illustrated in coronal, cross-sectional, and sagittal projections. The supraclavicular and tangential field blocks are shaded. (C reprinted with permission from Svensson GK, Chin LM, Siddon RL, et al. Breast treatment techniques at the Joint Center for Radiation Therapy. In: Harris JR, Hellman S, Silen W, eds. *Conservative Management of Breast Cancer: New Surgical and Radiotherapeutic Techniques*. J.B. Lippincott; 1983.)

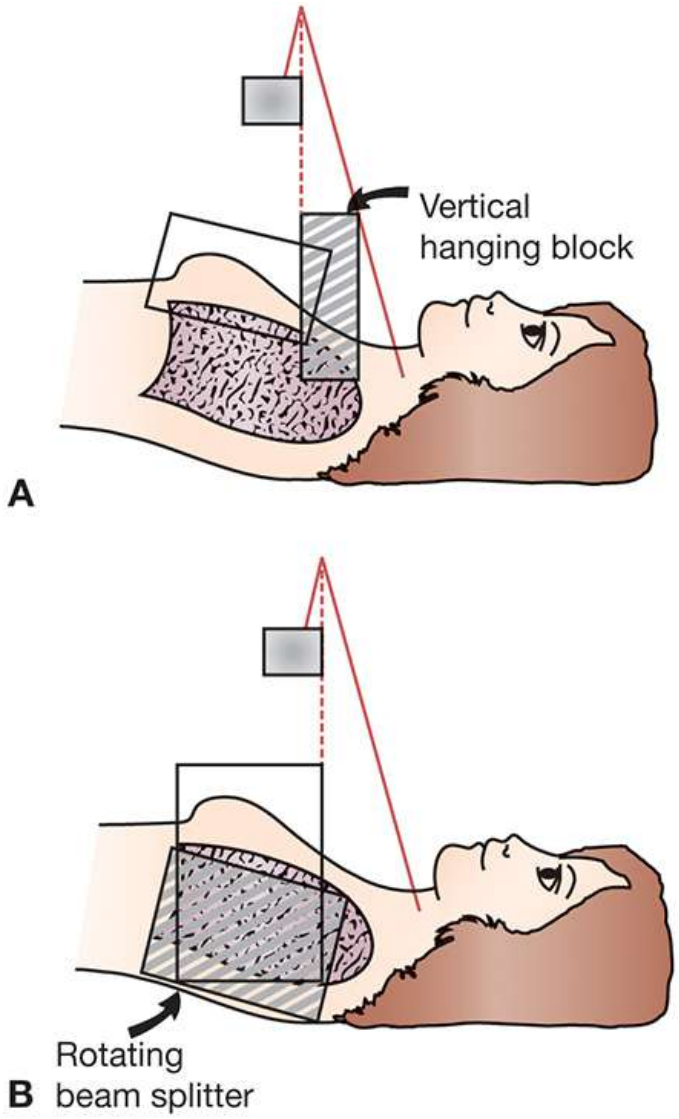


FIGURE 62.36 The superior edge of the tangential beams can be made perfectly vertical by means of the "hanging block" technique (A) or by avoiding collimator rotation with the use of a rotating beam splitter (B). (Reprinted from Bedwinek JM. Treatment of stage I and II adenocarcinoma of the breast by tumor excision and irradiation. *Int J Radiat Oncol Biol Phys*. 1981;7[11]:1553-1559. Copyright © 1981 Elsevier. With permission.)

The inferior divergence of the supraclavicular beam can be eliminated by blocking the inferior half of the beam. This can be accomplished with a beam splitter or with multileaf collimation so that the central, nondiverging portion of the beam becomes the inferior border of this field (see Figure 62.37B). The combination of the half-beam block supraclavicular field and the couch kick technique for the tangential field results in minimal overlap and has essentially eliminated the problem of match line fibrosis.

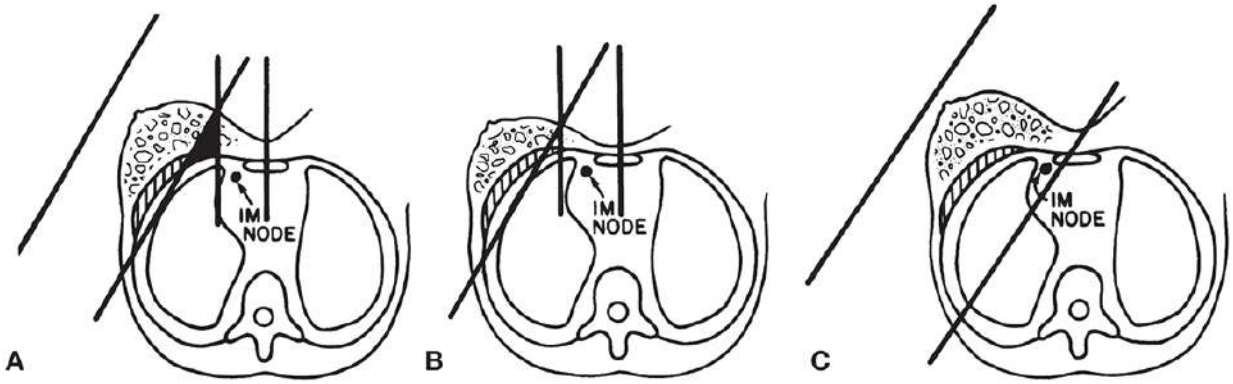


FIGURE 62.37 Diagrams showing several relationships between internal mammary (IM) and tangential fields. A. A significant cold region exists if the IM tangential match line overlies a large amount of breast tissue. B. The cold area may be negligible if the breast tissue beneath the match line is thin. C. The lack of a separate IM field can result in irradiation of an excessive volume of lung, particularly in patients with large chest. (Reprinted from Bedwinek JM. Treatment of stage I and II adenocarcinoma of the breast by tumor excision and irradiation. *Int J Radiat Oncol Biol Phys*. 1981;7[11]:1553-1559. Copyright © 1981 Elsevier. With permission.)

The Single Isocenter Technique for Matching Supraclavicular and Tangential Fields

An alternative and attractive method for minimizing field matching problems between the supraclavicular and tangential fields is to use a technique that employs a single isocenter placed at the junction of the supraclavicular and tangential fields, as demonstrated in Figure 62.38. This single isocenter serves as the isocenter for both the supraclavicular field and the tangential field, such that the nondivergent central axis single isocenter results in a perfect match of the supraclavicular and tangential fields. As demonstrated, when treating the supraclavicular field, the beam below the isocenter is completely blocked. The supraclavicular field is typically angled 5% to 10% away from the spinal cord. Without moving the isocenter or patient, the tangential field is treated by closing the field above the isocenter and angling the beam to treat the tangential fields. Using this technique, there is not an option for rotating the collimator. If the patient's anatomy and positioning are ideal, the tangential field is closed down to the central axis, an acceptable amount of lung is exposed (<3 cm), and no block may be required. In some cases, the tangential field needs to be opened up beyond the central axis and a block drawn to minimize lung exposure while maintaining coverage of the breast. Because much of the setup is performed on the CT simulator, it is critical when using this technique to clinically view the medial and lateral setups on the patient to ensure that the entire breast is covered, the medial border is not extending to the contralateral breast, and the blocks are not covering any of the targeted breast tissue.

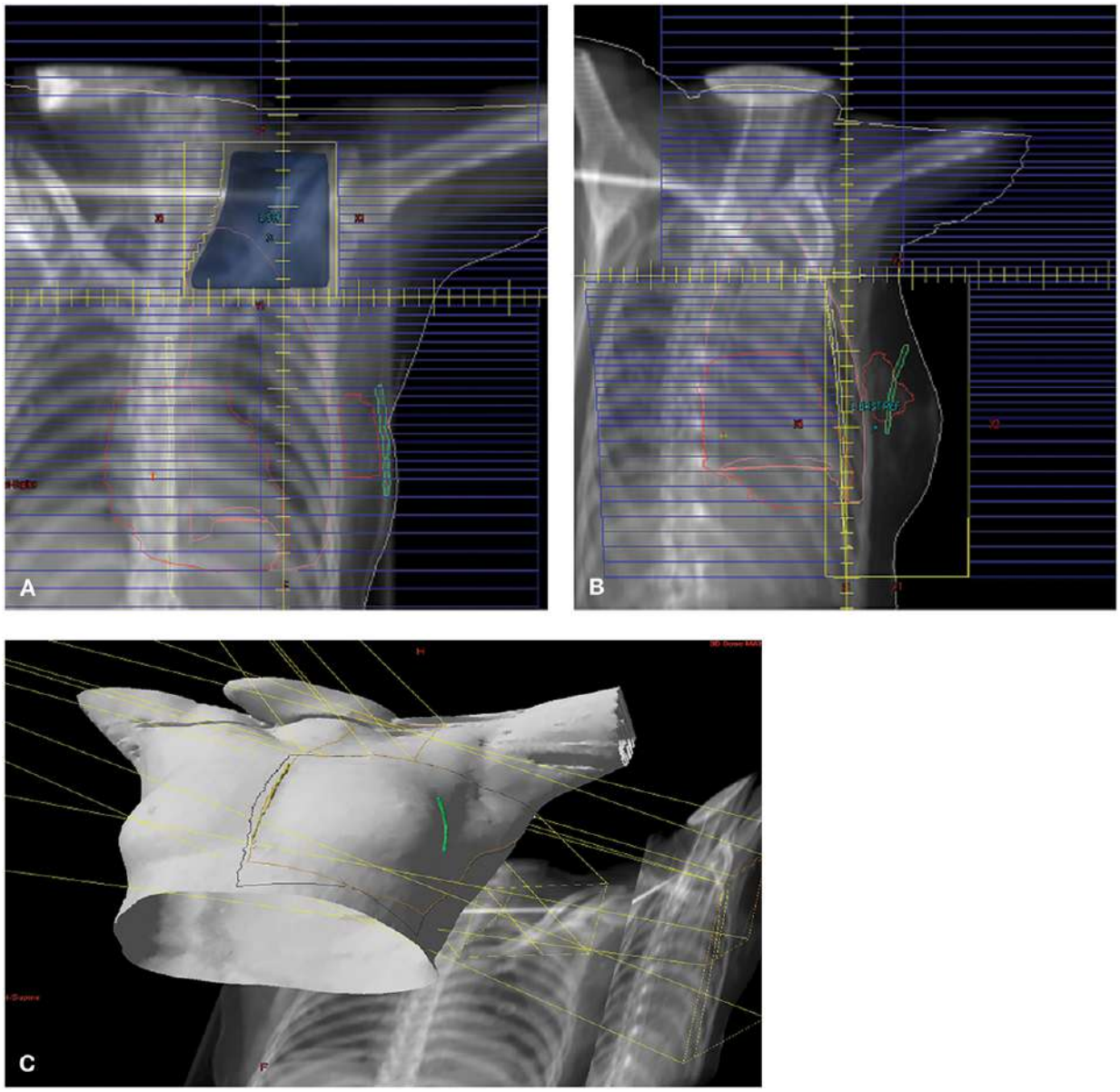
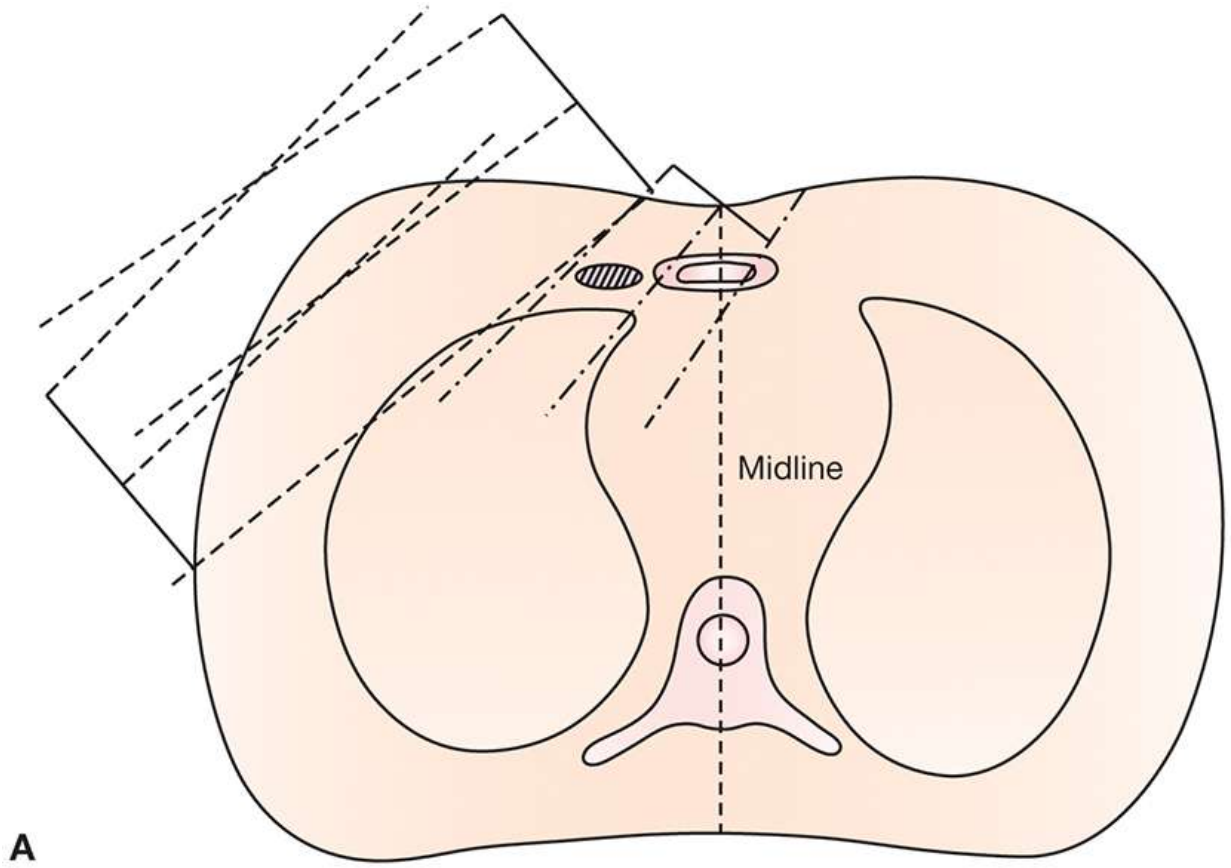


FIGURE 62.38 A-C: Monoisocentric matching technique. Single isocenter is set at the match between the supraclavicular and tangential fields. The inferior portion of the beam is blocked for the supraclavicular treatment and the superior blocked for the tangential field, with no movement of the isocenter, resulting in an ideal match. Blocks are drawn as indicated to shield lung and heart. The field should be viewed clinically to ensure that the blocks drawn to shield the heart and lungs to not block target tissue on the breast-chest wall. Projection of fields onto patient's surface demonstrates a perfect match of the supraclavicular and tangential fields.

Matching the Tangential Fields With the Internal Mammary Field

When an internal mammary field is required, the match between it and the medial tangential field can be a problem if there is a significant amount of breast tissue beneath the match line. In this situation, a cold spot can exist (Figure 62.37). The effect may be negligible if the breast tissue beneath this match line is thin (see Figure 62.37B), or it can be avoided by including the IMNs in the tangential field, as described earlier (see Figure 62.37C). Woudstra and van der Werf[261] described a technique using an oblique incidence of the internal mammary portal to match the orientation of the adjacent medial tangential portal; this results in a more homogeneous dose

distribution at the junction of the two fields (Figure 62.39). One potential advantage of the PWT field in the conservatively managed patient is that it avoids the problem of matching over breast tissue.



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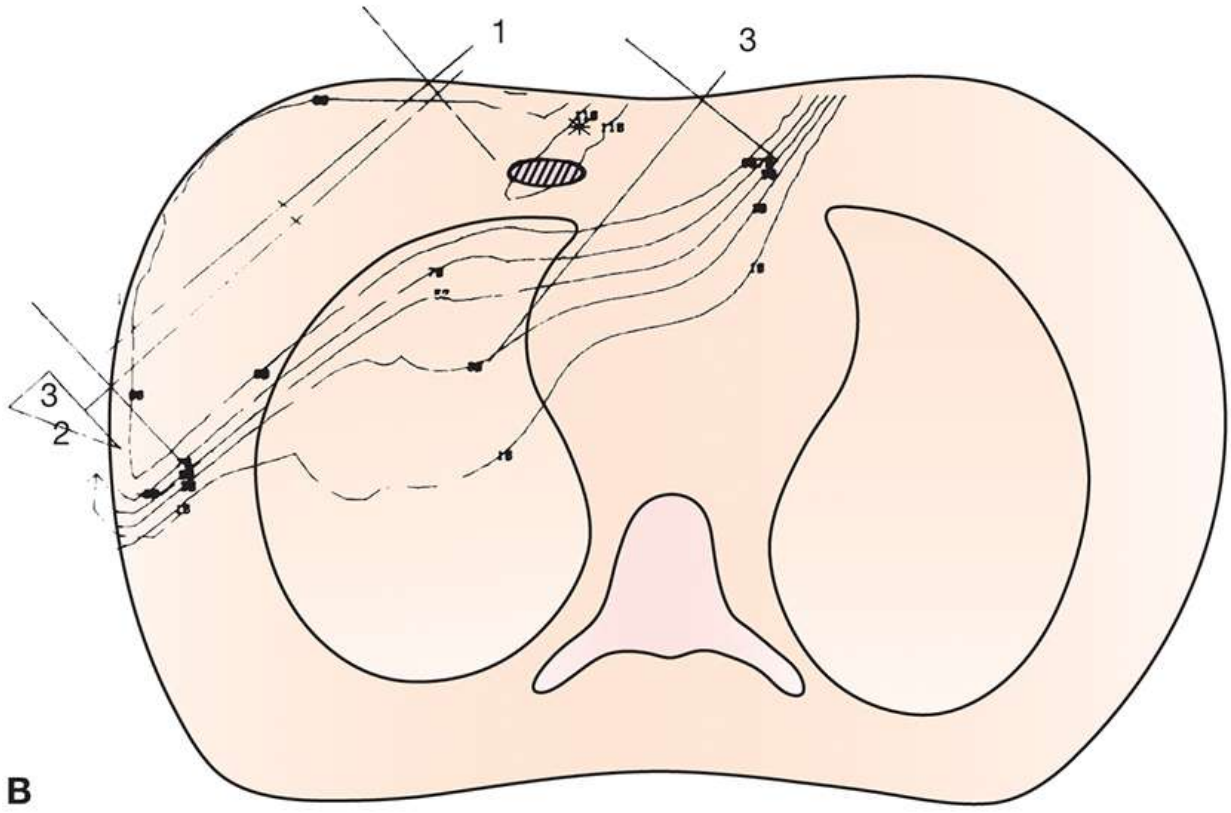


B

FIGURE 62.39 A. An obliquely incident electron beam matched to the usual tangential beams. B. Isodose presentation of optimal matching of an obliquely incident electron beam to the tangential beams. The target volume is enclosed by the 90% isodose line (= 40.5 Gy). Electron beam, 16 MeV; photon beam, 6 MV. (Reprinted from Woudstra E, van der Werf H. Obliquely incident electron beams for irradiation of the internal mammary lymph nodes. *Radiother Oncol*. 1987;10[3]:209-215. Copyright © 1987 Elsevier Ireland Ltd. With permission.)

Irradiation Dose to the Contralateral Breast

Irradiation dose to the contralateral breast is of concern because of the potential long-term carcinogenic effect of scattered radiation. The data on the risk of the contralateral breast are extensively discussed later. Although this risk appears to be minimal with modern techniques, the goal must be to expose all normal tissues not within the target volume to as low a dose as is reasonably achievable. A dosimetric study demonstrated that most of the scatter dose received by the opposite breast originates in the collimator and accessories of the accelerator, and it can be significantly decreased by increasing the distance between the source and the patient's skin. Therefore, an isocentric source-skin distance technique may be desirable. The use of half-field blocks (beam splitter) or, even better, independent jaws combined with tailored beam splitters or an MLC following the contour of the chest wall of the patient is very helpful in decreasing the dose to the contralateral breast (Figures 62.40 and 62.41).

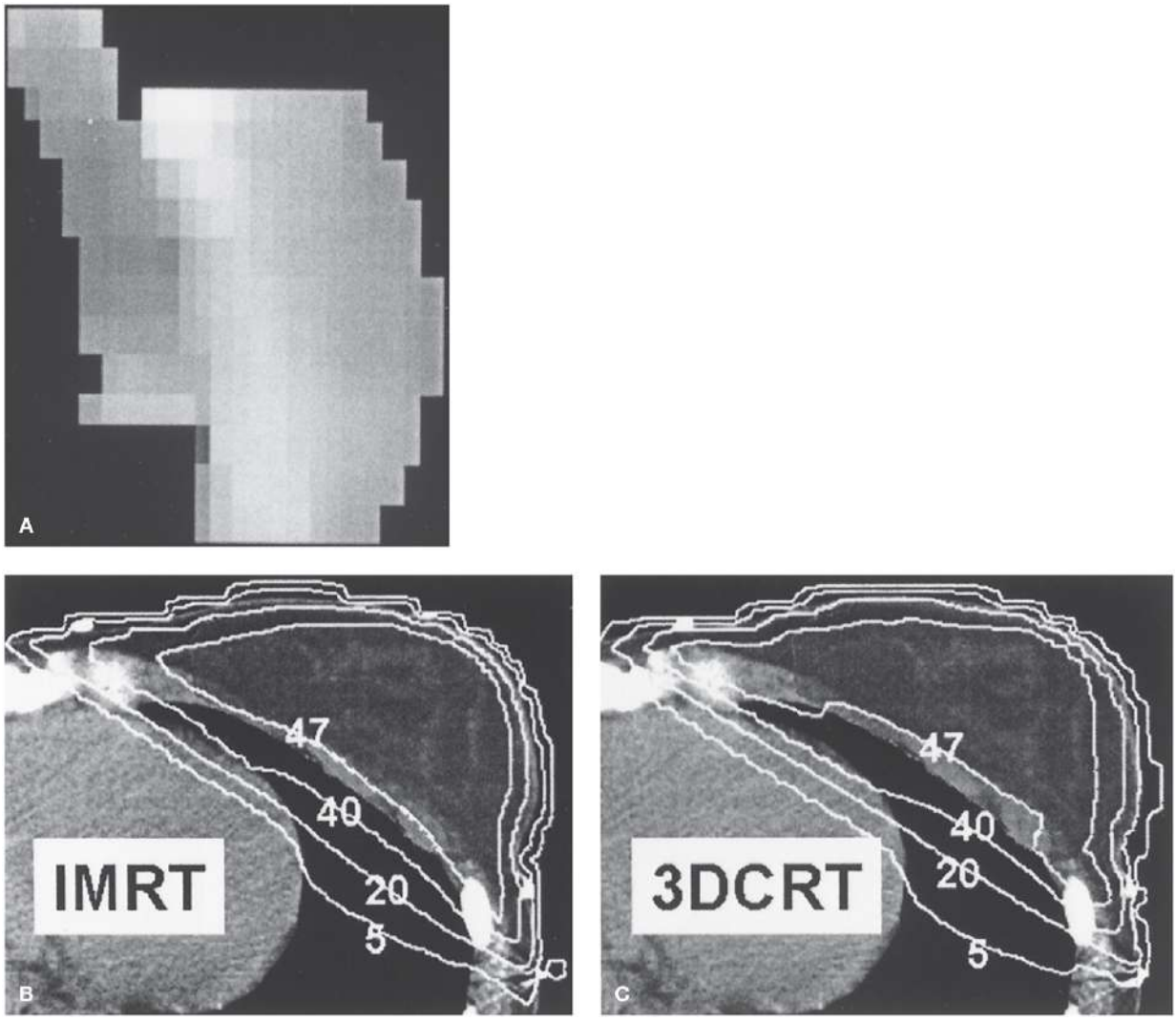


FIGURE 62.40 A. Beam intensity profile over the breast (lighter) and the internal mammary nodes (darker) to minimize dose to the heart. (A reprinted from Cho BC, Hurkmans CW, Damen EM, Zijp LJ, Mijnheer BJ. Intensity modulated versus non-intensity modulated radiotherapy in the treatment of the left breast and upper internal mammary lymph node chain: a comparative planning study. *Radiother Oncol*. 2002;62[2]:127-136. Copyright © 2002 Elsevier Science Ireland Ltd. With permission.) B. Dose distribution to the breast with intensity-modulated radiation therapy (IMRT). C. Dose distribution to the breast with three-dimensional conformal radiation therapy (3D-CRT). (B and C reprinted from Keall PJ, Arnfield MR, Arthur DW, et al. An IMRT technique to reduce the heart and lung dose for early stage breast cancer. *Int J Radiat Oncol Biol Phys*. 2001;51[3 suppl 1]:247-248. Copyright © 2001 Elsevier. With permission.)

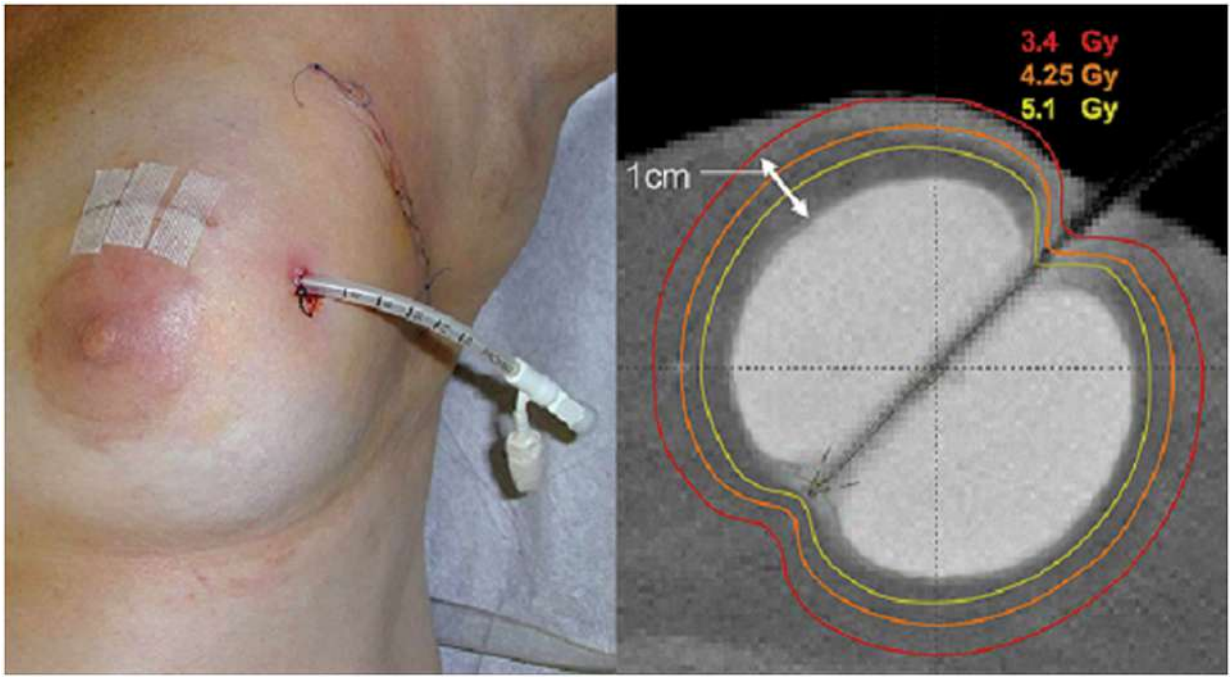


FIGURE 62.41 Partial-breast irradiation demonstrating the MammoSite breast brachytherapy device. (Reprinted with permission from Arthur DW, Vicini FA. Accelerated partial breast irradiation as a part of breast conservation therapy. *J Clin Oncol*. 2005;23[8]:1726-1735. Copyright © 2005 by American Society of Clinical Oncology.)

The clinical significance of this inadvertent radiation dose to the opposite breast is uncertain, as various investigators have shown no increased risk of contralateral breast malignancy after treatment of the original breast by RT.[11,34,262]

Three-Dimensional Conformal or Intensity-Modulated Radiation Therapy

A number of publications have explored the potential advantages of three-dimensional conformal radiation therapy (3D-CRT) or IMRT to treat patients with breast cancer. Theoretically, 3D-CRT involves a reduction in the volume of normal tissues receiving a high dose, with an increase in dose to the target volume that includes the tumor and a limited amount of normal tissue. IMRT potentially can further improve the dose distribution between the target and nontarget tissue but may also increase the volume of tissue exposed to lower doses of radiation. As suggested in a review by Hall and Wuu,[233] this may increase the risk of second malignancies; the potential gains and limitations of advanced planning techniques must be weighed carefully .

In a trial of patients undergoing BCT, 358 patients undergoing whole-breast irradiation were randomized to radiation to the breast with standard wedges or with IMRT. Those randomized to IMRT experienced significantly lower degrees of moist desquamation due to the improved homogeneity with the IMRT techniques employed.[263,264] In another randomized trial of IMRT in breast cancer, 306 women were randomized to standard treatment with tangential fields with wedge compensators compared with IMRT. The standard control patients were 1.7 times more likely to have a change in photographic appearance compared with those in the IMRT arm.[265]

It is important to recognize that the term *IMRT* has been used in various ways to describe breast cancer treatment. In some studies, IMRT is described as a method of 3D dose compensation without a change in the gantry angles of predesigned tangential fields. In such instances, dose distribution has been improved, but the fields are not more conformal. Accordingly, low dose to other organs is

not an issue. For others, IMRT attempts to improve conformality of the high-dose region by using multiple field angles that increase the volume of normal tissues that receive low radiation doses.

ACCELERATED PARTIAL-BREAST IRRADIATION

For some women, the 4- to 6-week course of daily radiation, with its associated time and travel issues, is not feasible. In response to this, a wide variety of accelerated forms of treatment have been developed and have been proven safe and effective in multiple studies. These approaches include multicatheter interstitial implants placed around the excision cavity, a single balloon catheter that can be after-loaded with a central radiation source (MammoSite) that is placed into the excision cavity, external beam conformal partial-breast irradiation, and intraoperative single-dose irradiation. Although these techniques vary considerably, they share the common strategy of delivering the radiation to a smaller volume of breast tissue around the lumpectomy site, using fewer larger fractions delivered over a shorter time. The rationale behind this approach is that the majority of breast relapses occur at or near the lumpectomy site. Randomized trials investigating partial-breast irradiation are summarized in Table 62.17.

TABLE 62.17 RANDOMIZED TRIALS OF ACCELERATED PARTIAL-BREAST IRRADIATION

Institution/Trial	Number of Cases	Control Arm	Experimental Arm
NSABP B-39 RTOG 0413	3,000	50-50.4 Gy WB+/− 10-16 Gy boost	1. Interstitial Brachytx 2. MammoSite 3. 3D conformal EBRT
National Institute of Oncology, Budapest, Hungary	570	50 Gy WB	1. Interstitial Brachytx (5.2 Gy × 7) or 2. Electrons (50 Gy)
European Brachytherapy GEC-ESTRO Working Group	1,170	50-50.4 Gy WB + 10 Gy boost	Brachytherapy only 32.0 Gy 8 fractions HDR 30.3 Gy 7 fractions HDR 50 Gy PDR
European Institute of Oncology (ELIOT)	824	50 Gy WB + 10 Gy boost	Intraoperative Single-fraction EBRT 21 Gy × 1
University College of London (TARGIT)	1,600	WBRT (per center) + boost	Intraoperative Single-fraction EBRT 5 Gy × 1
Canadian Trial (RAPID)	2,128	WBRT 42.5 in 16 or 50 in 25	3D-CRT 38.5 Gy in 10
Medical Research Council-UK IMPORT LOW	1,935	WB 2.67 Gy × 15	PBI 2.67 Gy × 15

3D-CRT, three-dimensional conformal radiation therapy; EBRT, external beam radiation therapy; HDR, high-dose rate; NSABP, National Surgical Adjuvant Breast and Bowel Project; PBI, partial-breast irradiation; PDR, pulsed-dose rate; RTOG, Radiation Therapy Oncology Group; WB, whole breast.

The NSABP-39/RTOG-0413 phase 3 equivalence trial randomized 4,216 women with early-stage breast cancer (including DCIS) to whole-breast irradiation versus APBI. This trial allowed for any one of the three techniques of partial-breast irradiation, namely, interstitial brachytherapy, MammoSite, or 3D-CRT. The techniques were selected based on physician or patient preference prior to randomization. Fraction size was slightly higher for external beam CRT (3.85 vs 3.4 Gy),

but all three techniques employed twice-daily radiation for a total of 10 treatments for a total dose of 38.5 or 34 Gy, respectively, over 5 days. Each of the various techniques of partial-breast irradiation is discussed in more detail below. At a median follow-up of 10.2 years, there were 90 (4%) patients with IBTR in the APBI group and 71 (3%) in the whole-breast group (HR 1.22, 90% CI, 0.94-1.58), for a 10-year cumulative incidence of IBTR of 4.6% for APBI (95% CI, 3.7-5.7) and 3.9% for whole breast (95% CI, 3.1-5.0). Treatment toxicities and second cancers were similar between the two groups. The authors concluded that APBI did not meet the criteria for equivalence to WBRT. However, it was noted that the study had broad eligibility criteria and thus a heterogeneous patient population and, given an absolute difference of less than 1% in 10-year cumulative IBTR rates, APBI may be an acceptable alternative for some women.[266]

Multicatheter Interstitial Techniques

Partial-breast experience is greatest with the multicatheter interstitial technique, as it was initially developed as a boost technique following whole-breast irradiation. As demonstrated in Figure 62.42, multiple catheters are generally positioned at 1.0- to 1.5-cm intervals, with the total number of catheters and planes employed dependent on the size, extent, and shape of the target. With refinements in image-guided techniques, this approach is generally quite adaptable to most cavities and locations within the breast. Because of its complexity, user dependence, and logistics, however, the use of this technique has been less widely embraced, compared with the MammoSite (described later) and external beam techniques.

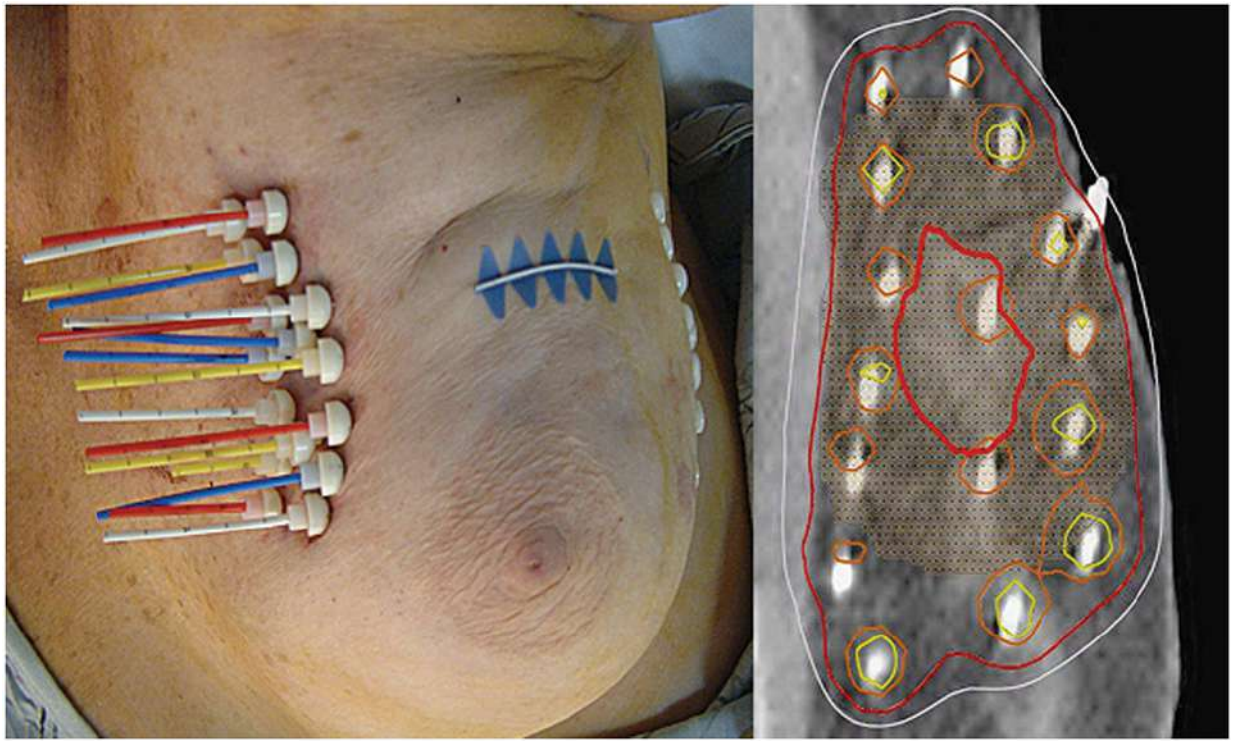


FIGURE 62.42 Partial-breast irradiation demonstrating the multiplane interstitial implant technique. (Reprinted with permission from Arthur DW, Vicini FA. Accelerated partial breast irradiation as a part of breast conservation therapy. *J Clin Oncol*. 2005;23[8]:1726-1735. Copyright © 2005 by American Society of Clinical Oncology.)

Kuske et al[267] reported the results of RTOG-95-17, a phase I and II study employing APBI using multiplane interstitial catheters in 99 women with early-stage breast cancer. The inclusion criteria for this study included invasive nonlobular tumors 3 cm or less after lumpectomy with negative surgical margins and axillary dissection with zero to three positive axillary nodes without extracapsular extension. The patients were treated with either low-dose rate (LDR) APBI (45 Gy in 3.5-5 days) or high-dose rate (HDR) APBI (34 Gy in 10 twice-daily fractions within 5 days). Chemotherapy and/or tamoxifen were administered at the discretion of the treating physicians. Of the 99 women, 33 were treated with LDR and 66 with HDR APBI. Of the 66 patients treated with HDR APBI, 2 (3%) had grade 3 or 4 toxicity. Of the 33 patients treated with LDR, 3 (9%) had grade 3 or 4 toxicity during brachytherapy. No patient experienced late grade 4 toxicity; the rate of grade 3 toxicity was 18% for the LDR and 4% for the HDR groups.

In a matched-pair analysis by Shah et al.[268], 199 patients received interstitial APBI and 199 patients received whole breast irradiation. Patients were matched by age, tumor size, nodal status, and ER status. With 12 years of follow-up, there was no difference in the rate of LR (3.8% vs 5.0%; $P = .40$), regional recurrence (0% vs 1.1%; $P = .15$), DFS (87% vs 91%; $P = .30$), cause-specific survival (93% vs 95%; $P = .28$), or OS (78% vs 71%; $P = .06$) between the WBI and APBI groups.

Wazer et al[269] reported the results of APBI using HDR interstitial brachytherapy in a phase I/II single multi-institutional study in 33 women with early-stage breast cancer. Eligible patients included those with T1, T2, N0, N1 (≤3 nodes positive), and M0 tumors of nonlobular histologic features with negative surgical margins, no extracapsular lymph node extension, and a negative postexcision mammogram. High-activity ^{192}Ir (3-10 Ci) was used to deliver 3.4 Gy per fraction, 2 fractions per day, for 5 consecutive days, to a total dose of 34 Gy to the target volume. The mean tumor size was 1.3 cm, and 55% had an EIC. Three patients had positive axillary nodes. The RTOG late radiation morbidity scoring scheme was applied. Clinically evident fat necrosis occurred in eight patients at a median of 7.5 months after HDR brachytherapy completion. The only variables significantly associated with grade 3 or 4 toxicity were the number of source dwell positions and the volume of tissue encompassed by the prescription isodose shell. The global cosmetic scores after a minimum of 18 months' follow-up were 0 cases with poor, 4 with fair, 5 with good, and 24 with excellent scores. One case of IBTR was diagnosed.

MammoSite

MammoSite as an alternative method of delivering APBI has been widely embraced because of its simplicity and less dependence on user experience.[270,271] The technique employs a single balloon catheter introduced into the lumpectomy site either at the time of lumpectomy or percutaneously after the procedure. As shown in Figure 62.42, the catheter is located centrally within a distal balloon, which is inflated once the catheter is placed in the lumpectomy cavity. Adequacy of placement requires symmetry of the balloon, conformance of the balloon surface to the lumpectomy cavity, and a minimum distance between the surface of the balloon and skin of greater than 5 mm (ideally >7 mm). Treatment is delivered via an HDR remote afterloading system to a circumferential 1-cm distance from the balloon surface.

The most extensive experience with this technique has been reported by the American Society of Breast Surgeons MammoSite Registry Trial, which included 1,419 patients treated in 87 institutions.[272,273] This was a nonrandomized single-arm registration trial in which data were collected prospectively on the clinical use of the MammoSite breast brachytherapy catheter for delivering breast irradiation. They reported on 1,237 patients (87% of enrolled patients) who received APBI (34 Gy to 1.0 cm in 10 fractions); 91% of the patients with invasive carcinoma

(977/1,068 patients) had negative lymph node status, and 99% of all patients had negative margins. The median patient age was 65 years. Five hundred fifty-four catheters (45%) were placed with an open cavity at the time of lumpectomy, and 683 (55%) catheters were placed after lumpectomy. Skin spacing ranged from 2 to 75 mm (median, 10 mm). At 5 years, 37 (2.6%) cases developed an IBTR, for a 5-year actuarial rate of 3.80% (3.86% for IBC and 3.39% for DCIS). Negative ER status (P = .0011) was the only clinical, pathologic, or treatment-related variable associated with IBTR for patients with IBC and young age (<50 years; P = .0096) and positive margin status (P = .0126) in those with DCIS. The percentage of breasts with good or excellent cosmetic results at 60 months (n = 371) was 90.6%. The authors concluded that treatment efficacy, cosmesis, and toxicity 5 years after treatment with APBI using the MammoSite device were good and similar to those reported with other forms of APBI with similar follow-up.

External Beam Conformal Radiation

3D-CRT, as shown in Figure 62.43, generally employs multiple conformal fields, although plans as simple as two opposing small conformal fields may be adequate. Challenges with this technique include daily positioning of the target, movement with breathing, and delivery of higher doses to surrounding normal breast tissue than with the brachytherapy. Nonetheless, this approach has been widely embraced and has been shown to be reproducible.

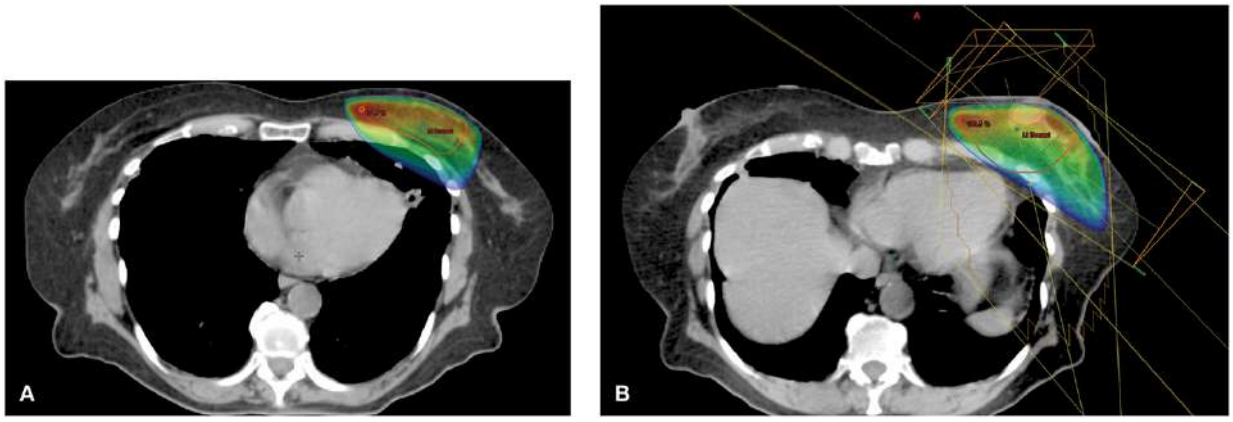


FIGURE 62.43 A and B. Partial-breast irradiation demonstrating the external beam conformal radiation technique.

In the phase I and II RTOG-0319 trial of external beam conformal radiation, Vicini et al[274] examined the use of 3D-CRT to deliver APBI. Reproducibility, as measured by technical feasibility, was the primary end point. This study was designed such that if fewer than five cases in the first 42 patients evaluable were scored as unacceptable, the treatment would be considered reproducible. Patients received 38.5 Gy in 3.85 Gy per fraction delivered twice daily. The clinical target volume (CTV) included the lumpectomy cavity plus a 10- to 15-mm margin bounded by 5 mm within the skin surface and the lung-chest wall interface. The planning target volume (PTV) included the CTV plus a 10-mm margin. A total of 58 patients were enrolled in this study over an 8-month period, 5 of whom were ineligible or did not receive protocol treatment. There were 4 cases with major variations and a total of 32 cases with minor variations in treatment plans. Based on this analysis, the authors concluded that APBI using 3D conformal EBRT was technically feasible and reproducible in a multi-institutional trial using exceptionally strict dosimetric criteria. An update of this study found that the ipsilateral breast failure rate was 6%, in-field failure rate was 2%, and

contralateral breast failure rate was 0%.[275] Only two (4%) grade 3 toxicities were observed. There have, however, been some reports of increased toxicity with external beam radiation using the fractionation schedule of 3.85 Gy per fraction, twice daily for 10 fractions.[276,277]

Whelan et al[278] published a report on the Randomized Trial of Accelerated Partial Breast Irradiation Using Three-Dimensional Conformal External Beam Radiation Therapy trial where 2,135 women older than 40 years with invasive or in situ breast cancer 3 cm or less were randomly assigned after breast-conserving surgery to 3D-CRT APBI (38.5 Gy in 10 fractions twice daily) or WBI (42.5 Gy in 16 or 50 Gy in 25 daily fractions ± boost irradiation). The 8-year cumulative incidence of IBTR was 3.0% (95% CI, 1.9-4.0) in the APBI group and 2.8% (95% CI, 1.8-3.9) in the whole-breast group. Grade 2 or higher acute toxicity occurred less frequently in the APBI group, but late toxicity (after 3 months) occurred more frequently in the APBI group. Adverse cosmesis as assessed by trial nurses was more common with APBI at 3 years (absolute difference 11.3%, 95% CI, 7.5-15.0), 5 years (16.5%, 12.5-20.4), and 7 years (17.7%, 12.9-22.3). The authors concluded that external beam APBI was noninferior to whole-breast irradiation in preventing IBTR but was associated with an increase in late toxicity and adverse cosmesis. It was suggested that this may have been a consequence of the twice-daily treatment on the APBI arm.

The University of Florence (Florence, Italy) performed a randomized phase III single-center trial of 520 patients comparing conventionally fractionated whole-breast irradiation (50 Gy in 25 fractions followed by a surgical bed boost to 10 Gy in 5 fractions) to external beam APBI (30 Gy in 5 nonconsecutive once-daily fractions) using an IMRT technique.[279] Patients aged 40 years or above with tumors 2.5 cm or less who were suitable for breast conservation were eligible. Multifocality, EIC, and surgical margins less than 5 mm were exclusion criteria. A minimum of four surgical clips were placed to mark the borders of the surgical bed. In the APBI arm, the CTV was drawn with a 1-cm margin around the surgical clips and was limited to 3 mm from the skin surface. Another 1-cm margin was added to create the PTV, which was also limited 3 mm from the skin surface but allowed to extend 4 mm inside the ipsilateral lung. Five step-and-shoot IMRT coplanar fields were used for treatment delivery. The 10-year cumulative incidence of IBTR was 2.5% in the whole-breast arm and 3.7% in the APBI group (HR, 1.56; 95% CI, 0.55-4.37; $P = .40$), with an absolute difference of 1.2%. The APBI group had lower rates of acute and late adverse effects, and a smaller proportion of APBI patients experienced adverse cosmesis (defined as fair or poor) compared to the whole-breast group when assessed by the physician (0% vs 1.9%; $P = .0001$) and patient (0.8% vs 14.6%; $P = .0001$). The authors concluded that the 10-year cumulative IBTR with external beam APBI using IMRT with five once-daily fractions was low and not significantly different from whole-breast treatment, and APBI had more favorable toxicity and cosmetic outcomes.

Intraoperative Accelerated Partial-Breast Irradiation

APBI using intraoperative therapy has been most widely employed outside the United States.[280,281] Radiation is delivered in a single intraoperative dose to the lumpectomy site at the time of surgery using electrons or photons (Figure 62.44). Vaidya et al[282] published the results of a phase III study that randomized 3,451 women to either targeted intraoperative RT (IORT) with a 50-kV spherical source delivering 20 Gy to a depth or 1 cm or whole-breast irradiation. The 5-year risks for LR in the conserved breast for IORT versus EBRT were 3.3% (95% CI, 2.1-5.1) versus 1.3% (0.7-2.5; $P = .042$). The European Institute of Oncology performed a randomized equivalence trial comparing conventionally fractionated whole-breast irradiation to a single dose of intraoperative radiation to the tumor bed during surgery.[283] The whole-breast group received 50 Gy in 25 fractions followed by a boost of 10 Gy in 5 fractions, and the intraoperative radiation group received a single dose of 21

Gy. The 5-year IBTR rate was 4.4% (95% CI, 2.7-6.1) in the intraoperative radiation group and 0.4% (95% CI, 0.0-1.0) in the whole-breast group (HR 9.3 [95% CI, 3.3-26.3]). The authors concluded that although the IBTR rate was within the prespecified equivalence margin for the intraoperative radiation group, the rate was significantly greater than with whole-breast radiation, and the IBTR with intraoperative radiation may be improved with better patient selection.

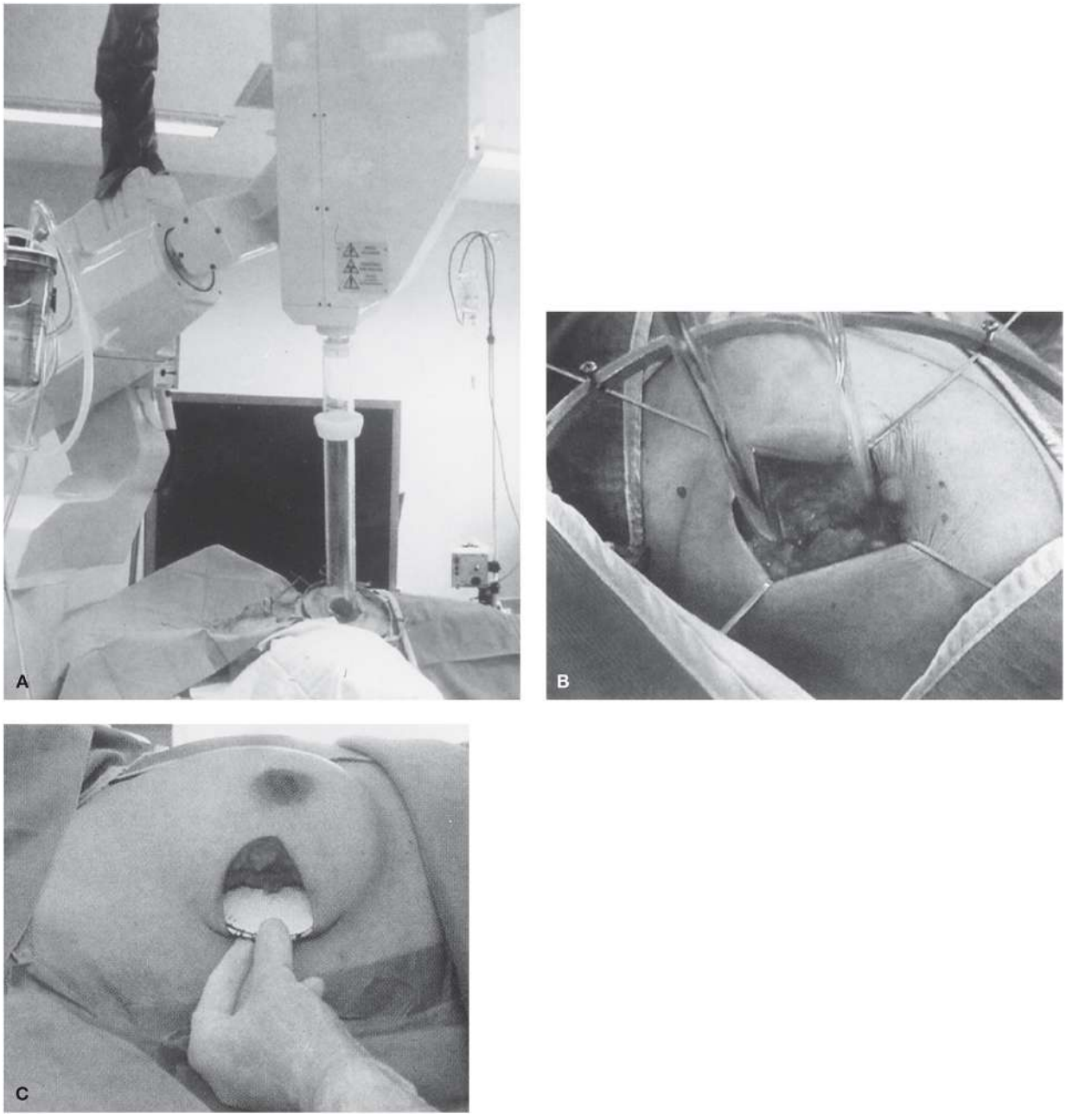


FIGURE 62.44 A. Linear electron beam accelerator in operating room during intraoperative radiation therapy. B. Proper placement of applicator in the breast. C. Before intraoperative radiation therapy delivery, an aluminum-lead disc (4-mm Al and 5-mm Pb thick) is placed between the deep face of residual breast and pectoralis muscle. (Reprinted from Veronesi U, Oreechia R, Luini A, et al. A preliminary report on intraoperative radiotherapy [IORT] in limited-stage breast cancers that are conservatively treated. *Eur J Cancer*. 2001;37[17]:2178-2183. Copyright © 2001 Elsevier. With permission.)

In 2009, a task force of experts in the field of breast cancer developed a consensus statement on behalf of ASTRO on the use of APBI. These guidelines have since been updated in 2016. They reported their recommendations on the suitability of patients receiving APBI outside the context of a clinical trial and divided patients into three categories: suitable, cautionary, and unsuitable (Table 62.18).[284,285] In general, patients aged 50 years or above, with node negative, invasive ductal or DCIS tumors 2 cm or less, with negative margins, ER positive, and no LVSI were deemed suitable for the use of APBI off-trial. The task force hoped their recommendations would provide guidance regarding the use of APBI outside a clinical trial and serve as a framework to promote additional research into the optimal role of APBI in the treatment of breast cancer (Figure 62.45).

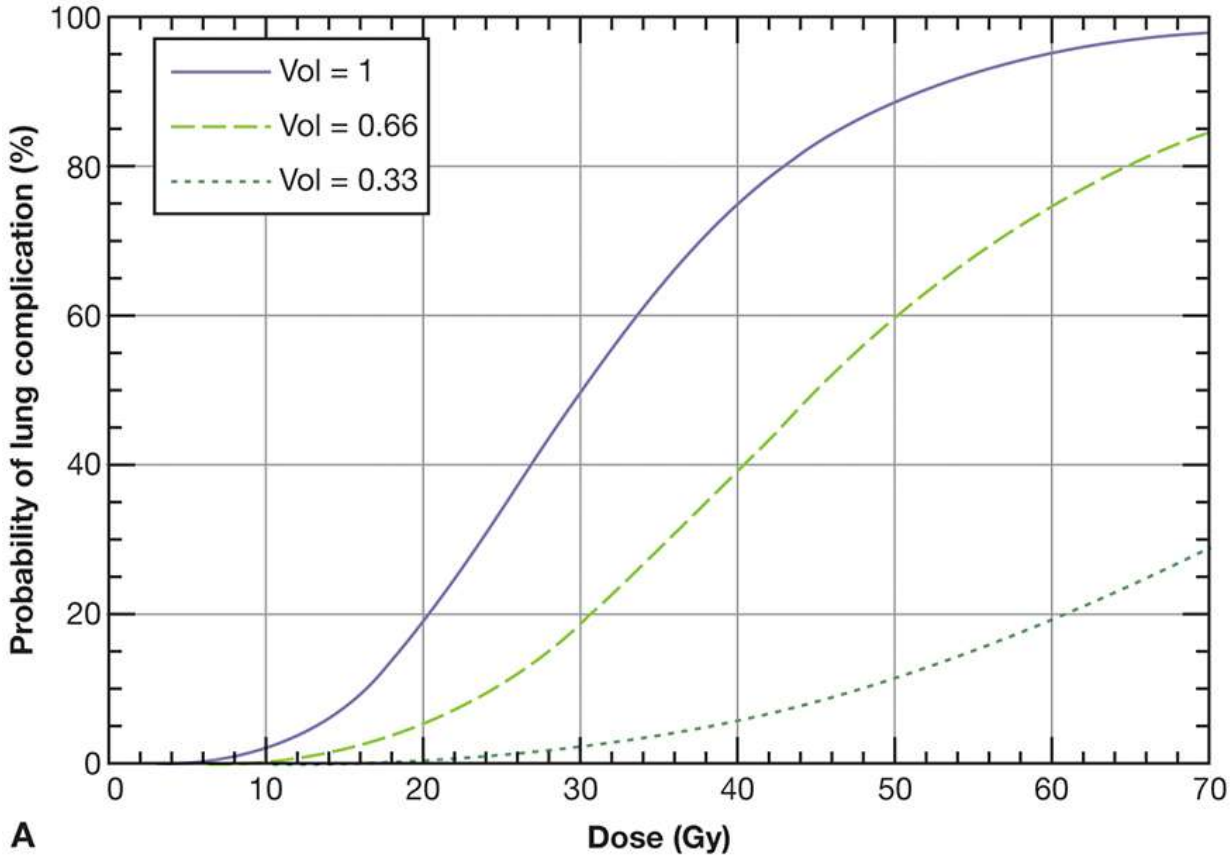
TABLE 62.18 ASTRO CONSENSUS GUIDELINES FOR SUITABILITY OF PATIENTS TO RECEIVE ACCELERATED PARTIAL-BREAST IRRADIATION (APBI) OFF-TRIAL

Patient Group	Risk Factor	Factor
Suitability	Age	≥50 y
	Margins	Negative by at least 2 mm
	T stage	Tis or T1
	DCIS	If all of the following: Screen detected • Low to intermediate nuclear grade • Size ≤2.5 cm • Resected with margins negative at ≥3 mm
Cautionary	Age	• 40-49 y if all other criteria for "suitable" are met • ≥50 y if patient has at least 1 of the following pathologic factors and does not have any "unsuitable" factors *Pathologic factors:* • Size 2.1-3.0 cm[a] • T2 • Close margins (<2 mm) • Limited/focal LVSI • ER(−) • Clinically unifocal with total size 2.1-3.0 cm[b] • Invasive lobular histology • Pure DCIS ≤3 cm if criteria for "suitable" not fully met • EIC ≤3 cm
	Margins	Close (<2 mm)
	DCIS	≤3 cm and does not meet criteria for "suitable"
Unsuitable	Age	• <40 y • 40-49 y and do not meet the criteria for cautionary
	Margins	Positive
	DCIS	>3 cm

APBI, accelerated partial-breast irradiation; DCIS, ductal carcinoma in situ; EIC, extensive intraductal carcinoma; ER, estrogen receptor; LVSI, lymphovascular space involvement; T, tumor stage.

[a] The size of the invasive tumor component;

[b] Microscopic multifocality is allowed if the lesion is clinically unifocal and the total lesion size (including foci of multifocality and intervening normal breast tissue) is between 2.1 and 3.0 cm.


Vol = 1
Vol = 0.66
Vol = 0.33
Probability of lung complication (%)
Dose (Gy)
0
20
40
60
80
100
0
10
20
30
40
50
60
70

A

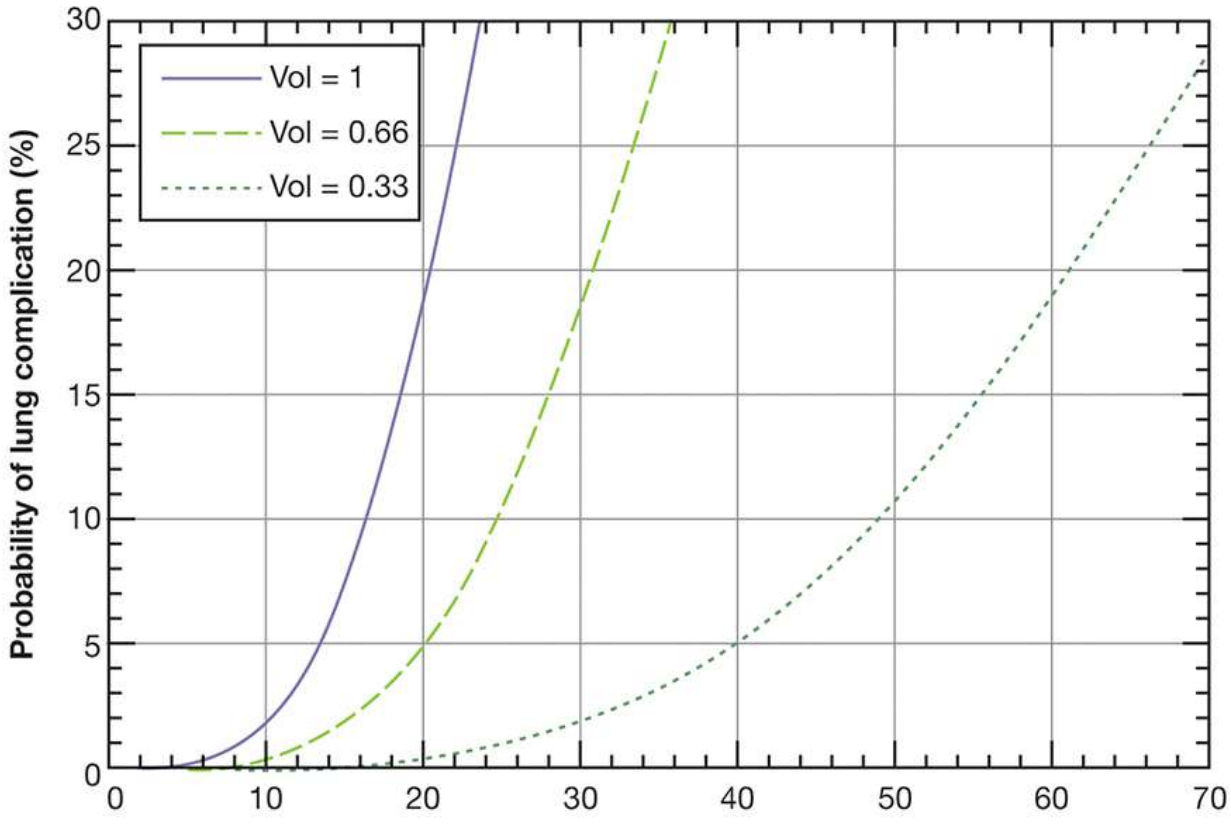

Vol = 1
Vol = 0.66
Vol = 0.33
Probability of lung complication (%)
0
5
10
15
20
25
30
0
10
20
30
40
50
60
70

FIGURE 62.45 Probability of radiation pneumonitis versus dose. The relative lung volumes are 100%, 66%, and 33%. The curve parameters are D_{50} = 30 Gy, γ = 1.01, s = 0.01. The curve covers the probability range up to 100% (A) and up to 30% (ie, within the interval of the clinical data) (B). (Reprinted from Gagliardi G, Bjöhle J, Lax I, et al. Radiation pneumonitis after breast cancer irradiation: analysis of the complication probability using the relative seriality model. *Int J Radiat Oncol Biol Phys*. 2000;46[2]:373-381. Copyright © 2000 Elsevier. With permission.)

SEQUELAE OF IRRADIATION IN BREAST CANCER

Potential complications associated with conservation surgery plus irradiation include arm or breast edema, breast fibrosis, painful mastitis or myositis, pneumonitis, and rib fracture. Apical pulmonary fibrosis can be noted when the regional lymph nodes are irradiated.

Lymphedema and Breast Edema

Complications from axillary surgery, regardless of breast surgical procedure, can occur. It should be emphasized that before the treatment of arm lymphedema after breast carcinoma, it is mandatory to differentiate between treatment-associated complications and tumor recurrence in the regional lymphatics. In general, the incidence of breast or arm edema after conservation therapy varies, and it is related to the performance and technique of axillary dissection, whether the axillary lymph nodes were irradiated, and the dose of radiation delivered.

An extensive review of the literature related to arm edema following breast surgery was conducted by Erickson et al.[286] They found that arm edema is a common complication of breast cancer therapy that can result in substantial functional impairment and psychological morbidity. The risk of arm edema increases when axillary dissection and axillary RT are used. Preventive measures have not been well studied. Nonpharmacologic treatments, such as massage and exercise, have been shown to be effective therapies for lymphedema, but the effect of pharmacologic interventions remains uncertain.

Sentinel node sampling appears to be associated with a much lower degree of lymphedema. Sener et al[287] reported that 9 (3%) of 303 patients who underwent only sentinel lymphadenectomy had lymphedema, compared with 20 (17%) of 117 patients who underwent sentinel lymphadenectomy combined with axillary dissection ($P < .0001$). Among 303 patients who underwent sentinel lymphadenectomy only, lymphedema developed in 8 (5%) of 155 patients who had tumors in the upper outer quadrant and in 1 (0.7%) of 148 patients whose tumors were in other locations. The ALMANAC randomized trial also confirmed lower morbidity and improved quality of life following sentinel node biopsy compared with axillary dissection.[107]

Various treatment regimens have been used to treat lymphedema.[288] The compression pump, along with skin care, exercise, and compression garments, is one. A second treatment is known as *complex decongestive physiotherapy* or *complex physical therapy*. Arm care, therapeutic exercises, manual lymph node drainage, and compression bandages or garments constitute this treatment regimen. Decreases in lymphedema are noted if women are compliant with the prescribed treatment program.

Skin and Breast Complications

A wide variety of local symptoms may occur following radiation treatment to the conservatively treated breast, including change in skin appearance, breast discomfort, breast edema, and rib pain. In addition to host factors such as CVS and diabetes, underlying genetic factors may play a role in radiation complications.

Rayan et al[289] reported on a randomized clinical trial of breast-conserving surgery and tamoxifen with or without RT in women aged 50 years and above treated for stage T1 or T2, node-negative breast cancer. A companion study to assess breast pain was carried out during the trial, in which 86 patients participated. Forty-one received RT and tamoxifen and 45 tamoxifen alone. The median age was 70 years. Baseline pain and quality-of-life scores were similar for the two groups. At 3 months, patients receiving RT experienced more breast pain compared with those receiving tamoxifen alone, but this did not reach statistical significance. At 3 months, the pain scores for the RT and tamoxifen and tamoxifen alone groups were 2.39 and 1.83, respectively (P = .47). At 12 months, pain scores were lower and fairly similar in both groups, with a difference of 0.20 (P = .71).

Markiewicz et al[290] analyzed complications in 1,053 women with stage I or II breast cancer treated with BCT. Of this group, 206 received chemotherapy alone, 141 had hormonal therapy alone, 94 had both, and 612 received no adjuvant therapy. The incidence of grade 4 or 5 arm edema (≥2 cm difference in arm circumference) was 2% without chemotherapy and 8% with chemotherapy (P = .00002). However, the incidence of arm edema was not affected by sequencing or type of chemotherapy; it occurred in 10% and 7% of patients with sequential or concurrent treatment, respectively, and in 8% and 18% of patients treated with CMF or CAF, respectively. The incidence of clinical pneumonitis and rib fracture was not influenced by the use of chemotherapy, sequencing of drugs, or use of hormonal therapy.

Hyperbaric oxygen therapy has been shown to be effective in the treatment of some late radiation sequelae. Carl et al[291] reported on 44 patients with persistent local symptoms after BCT. Hyperbaric oxygen therapy (100% oxygen at 240 kPa for 90-minute sessions) was administered to 32 patients for a median of 25 sessions (range, 7-60 sessions). The remaining 12 patients declined hyperbaric treatment and acted as control subjects. The patients given hyperbaric oxygen therapy demonstrated a significant reduction in pain, edema, and erythema scores compared with untreated control subjects (P < .001). Seven of the 32 women who were treated with hyperbaric oxygen therapy were free of symptoms after treatment, whereas all 12 patients in the control group had persistent complaints. However, hyperbaric oxygen therapy did not have a significant effect on fibrosis and telangiectasia in the irradiated breast.

Brachial Plexopathy

Brachial plexus dysfunction is a possible complication of regional nodal RT. In a review of 1,624 patients, Pierce et al[292] found that brachial plexus sequelae were observed in 1.8% of patients. The incidence of brachial plexopathy was significantly higher when the axillary dose was greater than 50 Gy (P = .004). However, dose alone did not determine whether radiation damage would develop in a given patient. Treatment technique (two vs three fields; P = .0009) and concomitant chemotherapy were also risk factors. Other investigators have found the incidence of this complication to be 1% or less.[293] It is very important but difficult to distinguish between metastatic and radiation-induced brachial plexopathy.

Treatment for radiation brachial plexopathy consists of transdermal electrical nerve stimulation, dorsal column stimulators, neurolysis, and neurolysis with omentoplasty. Physical therapy, tricyclics, antiarrhythmics, anticonvulsives, nonsteroidal anti-inflammatory drugs, and steroids are helpful in therapy of both radiation-induced and metastatic brachial plexopathies.[294]

Pritchard et al[295] used hyperbaric oxygen in 34 volunteers with radiation-induced brachial plexopathy who were randomized to hyperbaric oxygen or a control group. The hyperbaric oxygen group breathed 100% oxygen for 100 minutes in a hyperbaric chamber (30 sessions over 6 weeks).

The control group breathed a gas mixture equivalent to breathing 100% oxygen at surface pressure. Normalization of the warm sensory threshold was seen in two of the patients receiving hyperbaric oxygen therapy. Two cases with marked chronic arm lymphedema reported major improvement in arm volume. These authors concluded that there was no reliable evidence to support hyperbaric oxygen therapy to slow or reverse radiation-induced brachial plexopathy, although improvements in warm sensory threshold and arm lymphedema suggested a therapeutic effect and justified further investigation.

Pulmonary Sequelae

Symptomatic pneumonitis is infrequent. This clinical syndrome is noted one to several months after irradiation. Patients present with dry cough, shortness of breath, fever, and on radiographic studies, a pulmonary infiltrate is observed in the irradiated volume. The risk for the development of radiation pneumonitis may be related to the volume of lung irradiated.

The addition of regional nodal RT to breast irradiation significantly increases the incidence of symptomatic pneumonitis. In the previously discussed randomized MA.20 trial, patients who received radiation treatment to the whole breast and regional lymph nodes had a 1.3% rate of grade 2 or higher pneumonitis, which was significantly higher than the 0.2% rate seen in the whole-breast–only arm.[174] Taghian et al,[296] in 41 patients treated with RT and paclitaxel (21 concurrent, 20 sequential), described a higher incidence of pneumonitis (14.6%) compared with control patients irradiated and not receiving chemotherapy (1.1%; $P < .0001$). However, an analysis of patients treated with radiation as a component of a randomized trial, in which 50% of the patients were treated with paclitaxel and 50% were treated with a nontaxane regimen, found that the rates of pneumonitis were very low and not significantly different between the two arms.[297]

Cardiac Sequelae

The potential for excess cardiac morbidity associated with the use of RT in breast cancer has been extensively evaluated. It has been clearly demonstrated, based on data from randomized trials, overviews, and meta-analyses, that when using older techniques, excess cardiac mortality from radiation offsets some of the benefits that RT clearly produces with respect to breast cancer mortality. Although modern techniques can minimize exposure to the normal cardiac and pulmonary structures, the radiation oncologist must be cognizant of the potential for adverse cardiac effects of incidental irradiation. This is particularly relevant in the setting of left-sided breast cancers in patients receiving other cardiotoxic therapies, including adriamycin, epirubicin, and trastuzumab.

Earlier techniques of RT from large pools of randomized data have clearly been implicated in excess cardiac mortality. In an analysis of over 90,000 Swedish women, comparing left- to right-sided cancers, Darby et al[298] from the Oxford group reported excess ischemic heart disease mortality more than 10 years after initial treatment in the left-sided cancer group (HR 1.13; 95% CI, 1.03-1.25; $P = .01$). The majority of cardiovascular deaths were from earlier studies using techniques that are no longer used. However, for patients treated after 1980, although the ratio was still 1.11, the CIs were much larger (0.95-1.29), so the hazard remained uncertain for the more modern techniques.

In a separate report, Darby et al[299] conducted a population- based case-control study of major coronary events (ie, myocardial infarction, coronary revascularization, or death from ischemic heart disease) in 2,168 women who underwent RT for breast cancer between 1958 and 2001 in Sweden and Denmark. They found that rates of major coronary events increased linearly with the mean dose

to the heart by 7.4% per Gy (95% CI, 2.9-14.5; $P < .001$), with no apparent threshold. The increase started within the first 5 years after RT and continued into the third decade after RT.

Although clinical evidence of cardiac morbidity has decreased with modern techniques, care should be taken to exclude the heart from the tangential radiation field. In an analysis of 114 patients, Marks et al[250] assessed RT-induced left ventricular perfusion defects and whether these perfusion defects are related to changes in cardiac wall motion or alterations in ejection fraction. Patients were imaged 30 to 60 minutes after injection of ^{99m}Tc sestamibi or tetrofosmin. Post-RT perfusion scans were compared with the pre-RT studies to assess for RT-induced perfusion defects as well as functional changes in wall motion and ejection fraction. The incidence of new perfusion defects 6, 12, 18, and 24 months after RT was 27%, 29%, 38%, and 42%, respectively. New defects occurred in approximately 10% to 20% and 50% to 60% of patients with less than 5% and more than 5% of their left ventricle included within the RT fields, respectively. The rates of wall motion abnormalities in patients with and without perfusion defects were 12% to 40% versus 0% to 9%. These authors noted that RT causes volume-dependent perfusion defects in approximately 40% of patients within 2 years of RT and that these perfusion defects are associated with corresponding wall motion abnormalities. However, additional study is necessary to determine if these defects are associated with functional consequences.

Given these findings, the authors suggested the use of a heart block if needed to reduce or eliminate cardiac irradiation. CT-based 3D treatment planning is used to design such cardiac blocks and select the optimal gantry angle to minimize the need for a heart block. There may be a small amount of breast tissue underdosed if the block overlies the medial inferior breast, but this tissue is typically less than 5%. In situations where the heart block may underdose the high-risk volume of the breast or chest wall, an “electron patch” can be used to treat the target tissue in the shadow of the heart block. A tangential field with a heart block is demonstrated in Figure 62.27.

Patt et al[300] analyzed data from the SEER-Medicare database for women who were diagnosed with nonmetastatic breast cancer from 1986 to 1993, had known disease laterality, underwent breast surgery, and received adjuvant RT; 8,363 patients had left-sided breast cancer, and 7,907 had right-sided breast cancer. With a mean follow-up of 9.5 years (range, 0-15 years), there were no significant differences in patients with left- versus right-sided cancers for hospitalization for ischemic heart disease (9.9% vs 9.7%), valvular heart disease (2.9% vs 2.8%), conduction abnormalities (9.7% vs 9.6%), or heart failure (9.7% vs 9.7%). The adjusted HR for left- versus right-sided breast cancer was 1.05 (95% CI, 0.94-1.16) for ischemic heart disease, 1.07 (95% CI, 0.89-1.30) for valvular heart disease, 1.07 (95% CI, 0.96-1.19) for conduction abnormalities, and 1.05 (95% CI, 0.95-1.17) for heart failure.

The potential for cardiac vessel injury from radiation was explored in an elegant study by Nilsson et al[301] who analyzed radiation fields and subsequent coronary angiograms in a Swedish breast cancer cohort study. For right-sided compared with left-sided breast cancers, the OR for grade 3 to 5 stenosis in arteries likely to be within the tangential radiation port was 4.38 (95% CI, 1.64-11.7) and 7.22 (95% CI, 1.64-31.8) for grade 4 or 5 stenosis. They concluded there was an increased risk and direct link between radiation and the location of the coronary stenosis. In a related editorial, Zagar and Marks[302] emphasized the potential effects of radiation on the heart but noted that improved radiation techniques, including custom blocking of the heart and other techniques to manipulate the radiation dose, are likely to minimize these risks and improve the therapeutic ratio.

Collectively, these data suggest that although there may be excess cardiac morbidity using tangential fields to treat left-sided breast cancers, these effects can be minimized through careful treatment planning. It remains prudent to minimize cardiac exposure in all patients and particularly in those receiving left-sided radiation in combination with other potentially cardiotoxic drugs.

Risk of Stroke With Supraclavicular Radiation

For patients with node-positive disease undergoing supraclavicular radiation, there is a theoretical concern regarding the potential for the development of accelerated carotid artery stenosis. In a study by Jagsi et al,[303] rates of stroke in 820 eligible patients with early-stage breast cancer treated with RT were compared with expected rates. The relation between potential risk factors and actuarial rate of the first stroke was analyzed. On multivariate analysis, only age ($P < .001$) and hypertension ($P = .003$) remained significant predictors of cardiovascular accident or transient ischemic attack. Age was the only significant predictor of cardiovascular accident alone ($P < .001$). This study found no significant association between supraclavicular RT and stroke after controlling for other factors. Another study by Woodward et al[304] of the SEER database compared 5,281 women presumably without supraclavicular radiation with negative nodes to 482 women presumably treated to the supraclavicular region with more than four nodes and did not find any increased rate of hospitalization for stroke in the treated population. However, a nested case-control study by Nilsson et al[305] showed a significant increase in stroke (OR 1.8; 95% CI, 1.1-2.8) when comparing patients treated to the supraclavicular and internal mammary regions with those not treated to these regions.

Contralateral Breast Cancer and Irradiation

Although all patients with a diagnosis of breast cancer are at increased risk for developing a contralateral breast cancer, the additional risk contributed by radiation treatment appears to be minimal, particularly when one uses modern techniques and maintains a dose to the contralateral breast that is as low as is reasonably achievable. The available data using modern radiation techniques do not suggest a significant increase in the risk for contralateral breast cancers in patients with breast cancer who have been irradiated compared to similar cohorts of patients with breast cancer who have not undergone radiation.[11,34,262,306-308] Although there is some evidence suggesting a slight excess risk in women who are irradiated at a relatively young age (ie, <45 years at diagnosis), the risk is extremely small and may be related to the use of older techniques. Most experts would agree that the benefit of radiation far outweighs the risk. Nonetheless, it appears prudent to be aware of these potential risks and employ techniques that minimize scattered dose to the contralateral breast.

The EBCTCG overview analysis does suggest an elevated incidence of contralateral breast cancer in patients receiving radiation compared with those who did not receive radiation.[41] This overview analysis of all randomized trials comparing radiation to surgery demonstrated an increased RR of contralateral breast cancers of 1.18 ($P = .002$). Although the excess risk appears to be driven primarily by older trials using antiquated techniques, these data do demonstrate the potential long-term effects of radiation-related secondary cancers and highlight the need to minimize contralateral breast exposure.

Boice et al[306] evaluated the risk of second cancers associated with RT to the breast in 41,109 women with breast cancer who were registered in the Connecticut Tumor Registry between 1935 and 1982. They reviewed the records of 655 women in whom a second breast cancer developed 5 years or longer after initial treatment and compared the radiation exposure in these patients with the exposure in 1,189 matched control patients who did not have a second cancer. The average dose to the contralateral breast in women exposed to radiation was 2.82 Gy. The RR for the development of a second breast cancer was 1.9 in the women who received RT, and among patients who survived for 10 years or longer, the RR was 1.33. Women younger than 45 years of age had an RR of 1.59 for the development of a second breast cancer compared with 1.01 for older women. According to these authors, younger patients should be informed that, based on the results of this study, after 10 years,

the risk for the development of a second cancer increases from 14% if they do not receive irradiation to 22% if they choose treatment involving irradiation.

Obedian et al[11] compared 1,029 patients with breast cancer treated with breast-conserving surgery and radiation to a cohort of 1,387 patients with breast cancer who underwent surgical treatment by mastectomy and who did not receive postoperative radiation during the same time period. The median follow-up was 14.6 years for the conservatively treated group and 16 years for the mastectomy group. The 15-year risk of any second malignancy was nearly identical for both cohorts (17.5% vs 19%). The second breast malignancy rate at 15 years was 10% for both groups. In the subset of patients aged 45 years or below at the time of treatment, the second breast and nonbreast malignancy rates at 15 years were 10% and 5% for patients undergoing BCT versus 7% and 4% for patients undergoing mastectomy (probability not statistically significant).

To address whether radiation administered may influence the development of breast cancers on the contralateral side, Khan and Haffty[309] evaluated the location of contralateral breast cancers developing after radiation. There was not a preponderance of medial lesions developing in the contralateral group (where radiation dose would be higher), suggesting that there was no cause-effect relation with respect to the prior radiation. In a study by Hill-Kayser et al,[310] the 20-year risk of contralateral breast cancer in 1,801 patients treated with breast-conserving surgery and radiation was 15.4%. They also demonstrated that the distribution of location of the contralateral tumors did not appear to be influenced by the prior irradiation.

In an update of the Danish randomized trials of postmastectomy radiation, Nielsen et al[262] also reported no excess risk of second malignancies in the contralateral breast in patients randomized to receive radiation. In this long-term follow-up performed among 3,083 patients from the Danish Breast Cancer Cooperative Group 82B and 82C trials randomized to postmastectomy radiation or not, there was no significant difference in the risk of contralateral breast cancers (6% RT vs 5% no RT) between the two groups.

Hooning et al,[308] in a study from Amsterdam of over 7,000 predominantly young women treated with or without radiation, did note an increase in contralateral breast cancer with decreasing age with tangential breast irradiation, particularly in young women with a strong family history. Of note, patients treated with mastectomy and chest wall electrons, where scattered dose to the contralateral breast was less, did not experience an increased contralateral breast cancer risk. The joint effects of tangential breast irradiation following lumpectomy and strong family history of contralateral breast cancer resulted in an HR of 3.52 (95% CI, 2.07-6.02; $P = .043$).

With modern technology and radiation techniques, scattered dose to the contralateral breast is lower and should minimize this issue, but care should be taken, particularly in younger women, to ensure that the dose to the contralateral breast is as low as possible.

Incidence of Other Second Malignancies

The incidence of secondary malignancies, as with the issue of contralateral breast cancer, appears to be very low, and it is evident that the appropriate use of RT far outweighs the risk of radiation-induced malignancy. Nonetheless, there is some evidence, with very long-term follow-up, of higher rates of secondary cancers. Although this may be more prevalent with older techniques, it is an important component of treatment planning to minimize dose to nontarget normal tissues. In addition to the excess risk of contralateral breast cancers discussed previously, the EBCTCG overview analysis did demonstrate an excess risk of secondary cancers of the lung and esophagus as well as leukemia and sarcoma in all randomized trials of breast cancer that compared patients treated with and without radiation.[41] The increased RR for each of these secondary malignancies as

a function of radiation treatment for breast cancer was lung cancer, 1.61 (±0.18; P = .007); esophageal cancer, 2.06 (±0.53; P = .05); leukemia, 1.71 (±0.36; P = .03); and sarcoma, 2.34 (±0.62; P = .03). The total RR for all secondary nonbreast malignancies was 1.20 (±0.06; P = .001). Although the increased risk of secondary malignancies may be driven primarily by trials using older techniques, they highlight the importance of limiting dose to nontarget tissues.

Huang and Mackillop,[311] in an analysis of 194,798 women from the SEER database who were diagnosed with invasive breast carcinoma (exclusive of those with distant metastasis) between 1973 and 1995, identified 54 women in an RT cohort and 81 women in a non-RT cohort in whom soft tissue sarcoma subsequently developed. In the RT cohort, the standardized incidence ratio was 26.2 for angiosarcoma and 2.5 for other sarcomas; in the non-RT cohort, the standardized incidence ratios were 2.1 and 1.3 (95% CI, 1.0-1.7), respectively. The elevated RR was significant even within 5 years of RT, but it reached a maximum between 5 and 10 years.

More contemporary retrospective series have not reported an excess risk of secondary malignancies. However, interpretation of these series is limited by follow-up periods of less than 20 years, which may not be adequate. Obedian et al[11] reported no increased risk of second nonbreast malignancies in patients treated with conserving surgery and radiation compared with a cohort treated with mastectomy without radiation during the same time interval. The 15-year risk of a second nonbreast malignancy was 11% for the radiation group and 10% for the mastectomy group.

Deutsch et al,[312] in a long-term analysis of the NSABP-04 and NSABP-06 trials, suggested an excess risk of lung cancers associated with the extent of radiation. The records of all patients who developed a recurrence in the lung or a new primary lung tumor were reviewed to determine the incidence and laterality of confirmed and probable primary lung carcinoma. For the NSABP-04 trial, which employed more comprehensive radiation with larger lung volumes, there were a total of 23 subsequent confirmed and probable ipsilateral or contralateral primary lung carcinomas. In those patients who had received comprehensive PMRT, there was a statistically significant increase in the incidence of these new primary tumors (P = .029). With regard to the development of confirmed new primary ipsilateral lung carcinoma alone, the incidence was statistically significantly increased (P = .013) in those patients who had received RT as part of their treatment, and when confirmed and probable ipsilateral lung carcinomas were analyzed, there was a strong trend toward a statistically significant increase in those patients who had received RT (P = .066). From NSABP-06 (mean follow-up of 19.0 years), there was a total of 30 second primary lung carcinomas but no increase in either ipsilateral or contralateral primary tumors of the lung in those patients who had received RT. They concluded that extensive postmastectomy irradiation of the chest wall and regional lymphatic areas, with consequent exposure of a greater volume of lung to higher doses as administered in the NSABP-04 trial, compared with postlumpectomy breast irradiation in the NSABP-06 trial, was associated with an increased incidence of subsequent primary lung tumors. Unfortunately, data regarding smoking were not available in this analysis.

Postirradiation Angiosarcoma of the Breast

Special attention should be paid to uncommon skin changes of the treated breast because clinical suspicion is the main clue to the diagnosis of postirradiation angiosarcoma. The primary therapy is simple mastectomy if wide tumor-free margins can be achieved. There is no clear indication for standard adjuvant chemotherapy or irradiation. Angiosarcomas arising in the field of RT are rare. Unlike other radiation-induced sarcomas, cutaneous angiosarcoma often occurs within a short time after irradiation. It is important to differentiate atypical vascular lesions from angiosarcoma, but currently, there is no evidence that they represent a precursor to radiation-induced angiosarcoma.

Marchal et al[313] reported on nine breast angiosarcomas identified in a review of 18,115 patients who underwent breast-conserving treatment for carcinomas at 11 French cancer centers over a 20-year period ending in 1997. The estimated prevalence of angiosarcomas after BCT for carcinomas was 5 per 10,000, which is approximately the same as for primary angiosarcomas in healthy breasts. The patients had a mean age of 62.5 years when the primary breast cancer was treated and 69 years when the angiosarcoma was diagnosed. Most angiosarcomas were stage T1N0M0 and were treated with radical mastectomy; two patients underwent reirradiation, and two patients were given adjuvant chemotherapy. The median time to the median survival after diagnosis of an angiosarcoma was 15.5 months. One patient was alive without progression of disease 32 months after a salvage mastectomy and the rest had died.

Cost Versus Benefit in Breast Cancer Treatment

Barlow et al[314] compared the total medical care costs from a regional nonprofit health management organization of breast conservation therapy versus a mastectomy 5 years after diagnosis in 1,675 women with early-stage breast cancer who had initial diagnoses between 1990 and 1997 and were 35 years of age or older. These women were classified into four groups according to treatment: mastectomy only (group 1, $n = 183$), mastectomy plus adjuvant therapy (group 2, $n = 417$), breast conservation therapy plus RT (group 3, $n = 405$), and breast conservation therapy plus RT and adjuvant therapy (group 4, $n = 670$). At 6 months, the costs of the treatments differed significantly ($P < .001$). Breast conservation therapy was more expensive than mastectomy. At 1 year, costs still differed significantly ($P < .001$) but were influenced more by the use of adjuvant therapy. By 5 years, the overall cost for breast conservation therapy was lower than for a mastectomy, presumably because of costs of reconstruction or complications of mastectomy.

Warren et al[315] linked data of older women with breast cancer from the SEER cancer registries with their Medicare claims from 1990 through 1998. Initial care costs for the 6 months after diagnosis for women who underwent breast conservation therapy and irradiation were approximately $450 per month higher than for women with modified radical mastectomy. In the continuing-care phase, costs for women undergoing breast-conserving surgery with RT were significantly less than for modified radical mastectomy cases. The two groups had similar costs in the terminal-care phase. Long-term costs for women undergoing BCT with RT were not statistically different from those for women undergoing modified radical mastectomy.

The usage of hypofractionation, with its associated reduced number of treatments, has been evaluated with respect to its costs by Bekelman et al[316] in a retrospective, observational cohort study, using administrative claims data from 14 commercial health care plans covering 7.4% of U.S. adult women. They classified patients with early-stage breast cancer treated with lumpectomy and WBI into two cohorts: (1) the hypofractionation- endorsed cohort ($n = 8,924$) included patients aged 50 years or older without prior chemotherapy or axillary lymph node involvement and (2) the hypofractionation- permitted cohort ($n = 6,719$) included patients younger than 50 years or those with prior chemotherapy or axillary lymph node involvement. They published that hypofractionated WBI increased from 10.6% in 2008 to 34.5% in the hypofractionation-endorsed cohort and from 8.1% in 2008 to 21.2% in the hypofractionation-permitted cohort. Adjusted mean total health care expenditures in the 1 year after diagnosis were $28,747 for hypofractionated and $31,641 for conventional WBI in the hypofractionation-endorsed cohort. Hypofractionated WBI was associated with savings of 9.1% and 11.8% in the hypofractionation-endorsed cohort and hypofractionation-permitted cohort, respectively. The adjusted mean total 1-year patient out-of-pocket expenses were not significantly different between hypofractionated versus conventional WBI in either cohort.

COSMESIS AND FOLLOW-UP AFTER BREAST CONSERVATION

Cosmesis

Surgical, radiotherapeutic, chemotherapeutic, and host factors may influence long-term cosmetic outcomes. Surgical factors to be considered include the extent of surgical resection, reexcision, orientation and length of the scar, closure or not of the tylectomy cavity, separate or continuous axilla-tylectomy scars, extent of the axillary dissection, and whether an ellipse of skin over the tumor was removed. RT factors are doses to the whole breast with tangential portals, homogeneity of dose throughout the breast, use of bolus, fractionation, overall duration of therapy including breaks, type and dose of boost, beam energy, and volume treated (whole breast only vs whole breast and regional lymph nodes). Chemotherapy issues include cytotoxic agents used, timing and sequence relative to RT, and doses and combinations of drugs. Host factors include size and shape of the breast, age, race, compliance with care and hygiene, concurrent medical illnesses (eg, hypertension, diabetes, CVD), and intrinsic sensitivity to radiation.

Different methods have been used to evaluate breast cosmesis after breast conservation therapy. Some are flawed because they do not establish strict guidelines or criteria for objectively judging cosmetic outcome. A commonly employed and simple categorization, developed by the Harvard group, employs a 4-point scale: excellent, good, fair, and poor.[317] "Excellent" indicates the treated breast is nearly identical to the untreated breast. "Good" indicates the treated breast is slightly different from the untreated breast. "Fair" indicates the treated breast is clearly different from the untreated breast. "Poor" indicates that the treated breast is significantly distorted.

At Washington University, questionnaires were completed by 458 patients and their radiation oncologists at regular 6-month intervals after treatment.[318] Cosmetic outcome analysis of these patients was done for clinical and treatment-related factors. Approximately 80% of patients had excellent or good cosmesis (Figure 62.46). A variety of factors were associated with a lower proportion of excellent cosmetic scores, including patient age over 60 years ($P = .001$), larger T2 tumor ($P = .05$), volume of resection greater than 100 cm^3 ($P = .0001$), scar orientation compliance with NSABP guidelines ($P = .0034$), more than 20 cm^2 skin resection ($P = .0452$), radiation treatment volumes (tangential fields only vs three or more fields; $P = .034$), whole-breast dose greater than 50 Gy ($P = .0243$), total dose to tumor site greater than 65 Gy ($P = .06$), and use of concomitant chemotherapy with radiation ($P = .02$). Notably, Black race was also associated with lower excellent cosmetic scores ($P = .0034$). The extent of axillary surgery and sequential chemotherapy did not reduce excellent cosmetic outcomes.

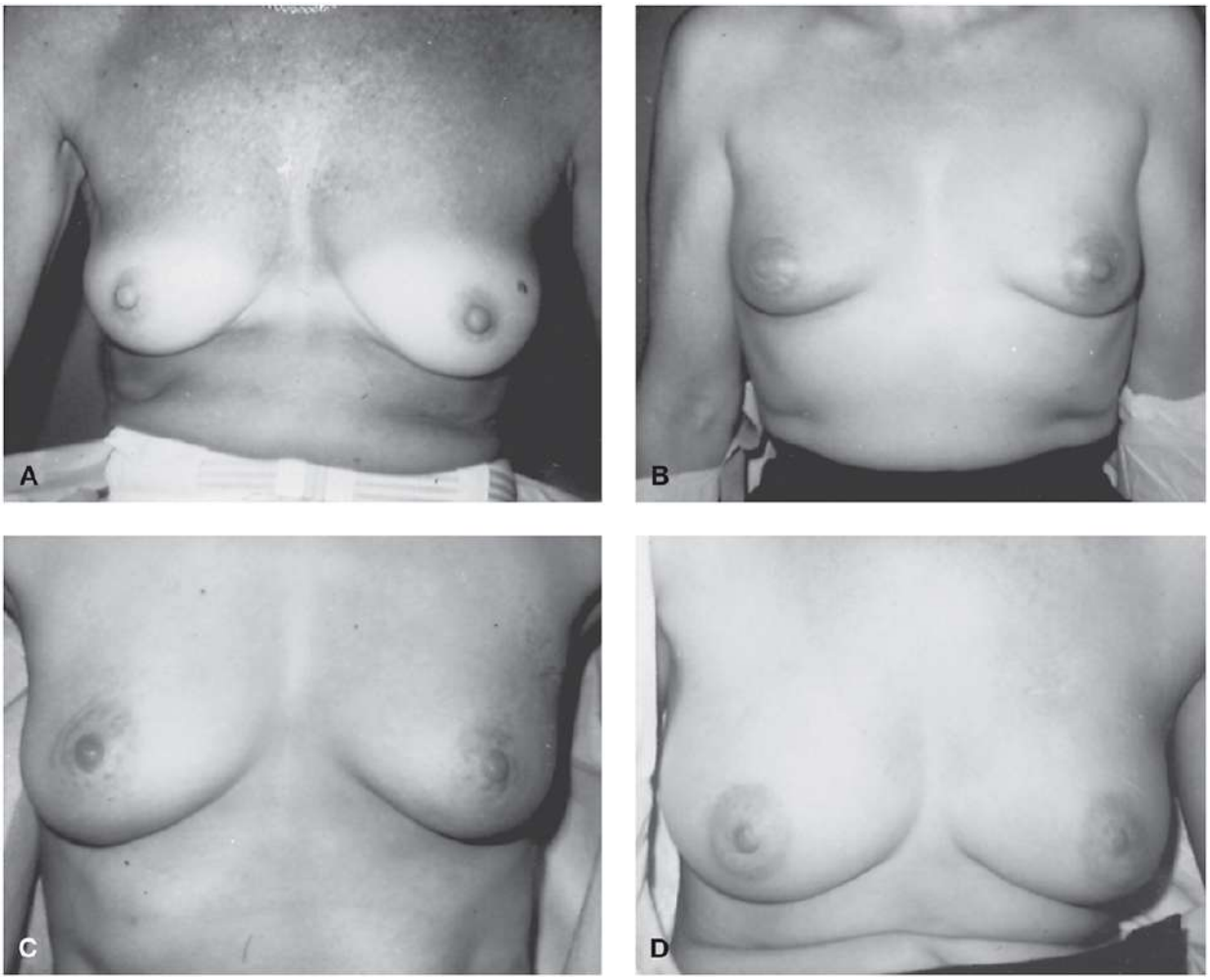


FIGURE 62.46 A-D: Photographs of patients showing excellent cosmetic results obtained with conservation surgery and irradiation for patients with T1 and T2 carcinomas of the breast. The patient in C has minimal telangiectasia in the area treated with a boost (upper region of left breast).

Poorer cosmetic outcomes in African American women have also been reported by Tuamokumo and Haffty.[96] A detailed cosmetic analysis was performed on a subset of 20 African American patients and 20 White patients. The two groups were intentionally matched by age, follow-up, adjuvant therapy, and breast size and were asked to participate in a detailed cosmetic evaluation. With respect to overall cosmetic outcome and all specific cosmetic measures (edema, fibrosis, and pigmentation), African American patients fared more poorly than did White patients. Overall cosmesis was good to excellent in 55% of African Americans, compared with 90% of Whites.

Breast Cosmetic Surgery After Irradiation

Breast deformities after conservation therapy may represent difficult reconstructive problems. When partial mastectomy is followed by RT, breast defects characterized by parenchymal loss, nipple-areola complex distortion, and cutaneous abnormalities can occur.

In a review of the MD Anderson Cancer Center experience, Kronowitz et al[319] evaluated the results of 69 patients who underwent repair of a partial mastectomy defect after radiation. They concluded that immediate repair of partial mastectomy defects with local tissues (also termed

oncoplastic rearrangement) results in a lower risk of complications and better aesthetic outcomes than does immediate repair of partial mastectomy defects with a latissimus dorsi flap.

Follow-Up of Patients Treated With Breast Conservation Surgery and Irradiation

It is important to closely monitor patients treated with conservation surgery and irradiation because early detection of an LR may allow for another wide local excision or a total mastectomy without significantly compromising the OS of the patient. According to the American Society of Clinical Oncology's follow-up guidelines, a careful history and physical examination are indicated every 3 to 6 months for 3 years, every 6 months for the following 2 years, and annually thereafter.[320] For patients who have undergone BCT, a post-treatment mammogram should be completed 1 year after the initial mammogram and at least 6 months after completion of RT. Yearly mammographic evaluation should continue unless more frequent examinations are specifically recommended. Blood and radiographic testing are not recommended for routine follow-up of an asymptomatic patient.

Radiographic Findings After Breast Conservation Therapy

Common mammographic findings after breast conservation therapy include fibrosis, fluid collection, skin thickening, and calcifications. These changes tend to peak within the first year after treatment before subsiding thereafter. Ultrasound and MRI can be used to supplement radiographic follow-up if mammographic findings are equivocal. If there is strong evidence of suspect microcalcifications, masses, or architectural distortions, a biopsy should be obtained to rule out a recurrence.

Tian et al[321] longitudinally compared the incidence of common mammographic sequelae seen after breast-conserving surgery and RT in patients treated with APBI, HF-WBI, and CF-WBI. In their cohort of 89 patients, 29 had received APBI, 30 had received HF-WBI, and 30 had received WBI. A total of 605 mammograms were evaluated, with a median follow-up of 48 months. The fractionation scheme did not affect the severity of architectural distortion when the groups were evaluated longitudinally. The likelihood of finding skin thickening decreased with increasing follow-up duration (OR 0.6; $P < .001$) adjusted for fractionation schemes. No differences were seen with respect to changes in skin thickening, fluid collections, or calcifications among the treatment groups after adjustment for the follow-up time. The clinical characteristics including age, race, T stage, and chemotherapy use were not linked to the likelihood of finding several mammographic phenomena over time. The authors concluded that fractionation did not alter the relative incidence or severity of architectural distortion, skin thickening, fluid collections, or calcifications.

CONCLUSION

RT plays an essential and critical role in the management of breast cancer, the most common cancer diagnosed in women. Early detection by mammography, followed by appropriate oncologic therapy, may be associated with reduced breast cancer mortality rates for women aged 50 years and above. After breast-conserving surgery, WBI improves local control and survival rates in appropriately selected patients and, therefore, should be considered for all patients. The development of molecular signatures predictive for LRR may revolutionize how we select patients for RT; significant progress has been made in this area with systemic therapy but, similar work is needed with regard to locoregional therapies. Accelerated forms of treatment including HF-WBI and APBI may increase

the utilization rate of RT after breast-conserving surgery. Ongoing research will help to further define the safety and acceptability of these techniques in women with early-stage breast cancer.

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CHAPTER 63

Breast Cancer: Locally Advanced and Locally Recurrent

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BACKGROUND

This chapter focuses on the management of locally advanced breast cancer (LABC) as well as locally recurrent breast cancer and selected unusual presentations of breast cancer. The emphasis is on locoregional therapy, though systemic treatments are also reviewed.

LABC is not clearly defined, though it commonly encompasses stage III disease including T3N1, any T4, and any N2/N3 disease as delineated in the *AJCC Cancer Staging Manual*, eighth edition.[1] Patients who present with LABC require care from a multidisciplinary team that includes radiologists, pathologists, surgical oncologists, medical oncologists, and radiation oncologists. Incorporating and coordinating the input of each specialty is of utmost importance in the management of patients with locally advanced disease, as these patients are at high risk of disease recurrence and require complex integrated decision-making. Breast cancer management is evolving toward an era of personalized medicine with treatment decisions increasingly made based on biologic subtypes.

Fortunately, the outcome for patients who present with LABC has improved substantially in recent decades. Prior to the routine use of chemotherapy, patients treated with mastectomy, radiation, or both had high rates of distant metastases and death.[2-4] Chemotherapy, targeted drug therapy, and endocrine therapy (ET) regimens in both the neoadjuvant and adjuvant settings have significantly improved prognosis. By decreasing the burden of distant metastases, modern chemotherapy and biologic therapies have resulted in the increased importance of local disease control. At the same time, increasingly effective systemic therapy has led to decreased rates of local recurrence and overall improved outcomes.

NATURAL HISTORY

Prior to recent decades, a diagnosis of LABC portended a poor prognosis. However, treatment advances have allowed many individuals with locally advanced disease to be cured. The clinical course of LABC may vary based on several factors, including the specific disease characteristics at presentation, the biologic features of the cancer, and the treatment given.

Infiltrating ductal and infiltrating lobular carcinomas are the two most common invasive breast cancer types. Locally, as the disease grows within the breast, the tumor

may infiltrate or invade the dermis or chest wall. Invasion of Cooper ligaments may lead to skin retraction; this can also occur in early-stage disease but is more likely as the tumor grows. When blockage or alteration of the lymphatic drainage of the breast or skin occurs, edema may develop, leading to dilated dermal hair follicles appearing like the skin of an orange; this peau d'orange appearance is often, but not exclusively, associated with inflammatory breast cancer (IBC).

Because of the propensity of more advanced tumors to invade the lymphatic system, many clinical T3 and T4 primary tumors have spread to the axillary lymph nodes (LNs) at the time of diagnosis. The axillary LN region is divided into three levels, each defined in relationship to the pectoralis minor muscle. Level I LNs are inferolateral to the muscle, level II LNs are posterior to the muscle, and level III LNs are superomedial. Level III LNs are also known as infraclavicular LNs. Other LNs that may be involved include the supraclavicular nodes, internal mammary nodes (IMNs), and Rotter nodes, located between the pectoralis minor and major muscles. Figure 63.1 shows computed tomography (CT) scans from patients with LABC presenting with involvement of the level II axilla (Figure 63.1A), an infraclavicular LN (Figure 63.1B), a Rotter LN (Figure 63.1C), and an IM LN (Figure 63.1D).

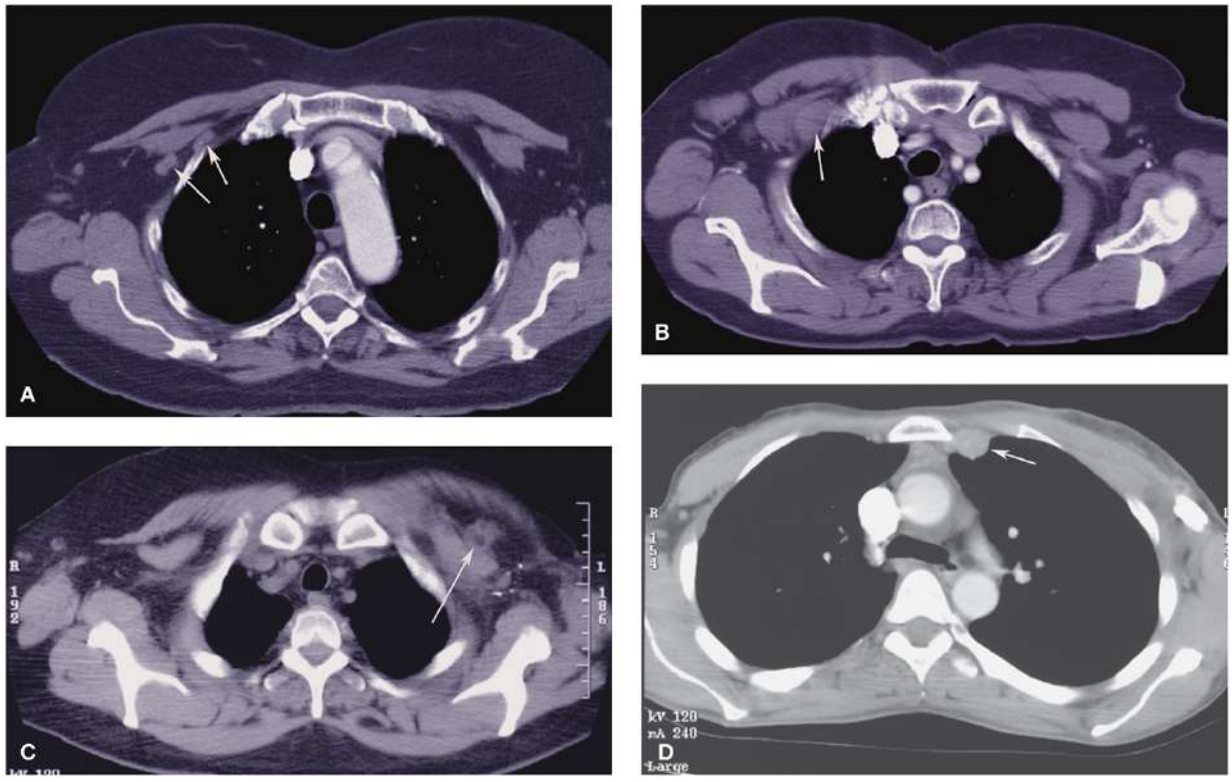

FIGURE 63.1 Computed tomography images of patients with lymph node involvement at the time of diagnosis. A. Image from a patient with involvement of axillary lymph nodes in the level II axilla. The *white arrows* show the involved lymph nodes, which are just beneath the pectoralis minor muscle. B. An involved level III axillary lymph node (*white arrow*) that extends superomedially to the pectoralis minor muscle. C. An involved Rotter lymph node (*white arrow*), which is anterior to the pectoralis minor and beneath the pectoralis major muscle. D. Image from a patient with an involved internal mammary lymph node (*white arrow*).

Local disease progression can lead to ulceration of the breast skin, pain, bleeding, and infection. In addition, arm edema, brachial plexopathy, and obstruction and thrombosis of the brachial vasculature may also occur due to the progression of regional lymphatic disease. Primary tumor growth also increases the risk of spread through the lymphatic system to regional LNs or hematogenous spread to distant sites, such as the liver, lung, bone, and brain. Without treatment, almost all LABCs will metastasize to visceral organs and eventually become life-threatening.[2,3]

Survival rates for women with LABC have improved largely due to advances in systemic therapy. Before the use of systemic treatment, individuals with advanced disease treated with mastectomy, radiation therapy (RT), or both had 5-year survival rates of only 25% to 45%.[2-4] With the development of molecular testing and the introduction of combined modality treatments including surgery, RT, chemotherapy, and targeted biologic therapy, modern 5-year survival rates range from approximately 68% to over 90% for patients with anatomic stage IIIA disease and approximately 33% to 84% for patients with anatomic stage IIIC disease depending upon the grade and molecular subtype.[1,5]

Although treatment advances may be credited for much of the improvement in prognosis for individuals with stage III disease in recent decades, it is important to recognize how stage migration has affected the statistics as well. Diagnostic imaging has improved over time, increasing the likelihood of detecting metastatic disease. As a result, some cases that would have been classified as stage III historically may now be classified as stage IV. The reclassification of patients with a relatively low burden of metastatic disease from stage III to stage IV may improve the outcome statistics for both stage III and stage IV diseases.

HISTOPATHOLOGY AND CLINICAL PRESENTATION OF LOCALLY ADVANCED BREAST CANCER

The two most common infiltrative breast cancer histologic subtypes, invasive ductal carcinoma and invasive lobular carcinoma, can present as early-stage or locally advanced disease. Less aggressive subtypes (eg, tubular carcinoma, mucinous carcinoma, and medullary carcinoma) are unlikely to present at an advanced clinical stage unless present for an extended period of time.

LABC is most commonly diagnosed after a palpable mass is detected within the breast. Locally advanced disease that has developed between annual interval screening mammograms is most often estrogen receptor (ER) negative with a high nuclear grade and a high proliferative index. These cancers may be of the luminal B, human epidermal growth factor receptor 2 (HER2)-positive, or triple-negative subtypes. In contrast, patients who present with extensive locoregional disease after years without treatment more often are found to have ER-positive disease with a low nuclear grade and a low proliferative index (luminal A subtype).[6] Advanced disease can cause symptoms such as local or regional pain, bleeding, paresthesia, and paresis. It is critically important to determine the onset of symptoms and the rate of disease progression to reach an accurate diagnosis as to

whether an advanced breast cancer should more accurately be designated IBC, which is discussed in detail in the section on IBC later in this chapter.

Diagnostic Workup

For patients with LABC, the workup should start with a careful history and physical examination. The breast examination should include a note of the breast symmetry, as well as careful inspection for involvement or edema of the skin. Peau d'orange and skin erythema can sometimes be subtle, particularly in patients of color; comparison with the contralateral side can often be helpful.

Other times, physical examination findings are more obvious. Figure 63.2 shows a photograph of a patient with a long-standing, untreated LABC presenting with peau d'orange, breast retraction and involution, and effacement of the nipple-areola complex (NAC). Medical photographs are helpful to document the extent of visible abnormalities before treatment is begun and can also be used to assess disease response.

FIGURE 63.2 Photograph of a patient with a neglected locally advanced breast cancer presenting with peau d'orange, breast retraction and involution, and effacement of the nipple-areola complex.

The extent of palpable disease should be measured and documented. Fixation of a breast mass to the pectoralis muscle or chest wall is determined by assessing the mobility of the mass with the pectoralis muscle relaxed and contracted. Regional LNs should be thoroughly evaluated by careful clinical examination with the patient in both supine and

sitting positions. Bilateral diagnostic mammography is mandatory, and supplemental breast ultrasound should be strongly considered. Biopsy of the breast tumor(s) with histologic evaluation per College of American Pathologists is standard. Ultrasonographic imaging of the axilla should be performed with fine-needle aspiration or core biopsy of suspicious LNs with clip placement.[7-9] Magnetic resonance imaging (MRI) of the bilateral breasts may be helpful to determine the extent of disease within the ipsilateral breast and regional LNs including the IM lymph chain and to gauge response to treatment in the setting of neoadjuvant systemic therapy.

All cases of locally advanced disease require complete staging before initiation of therapy. Laboratory studies should include a complete blood cell count and serum chemistry profile with liver function tests. Radiographic studies should include a CT scan of the chest, abdomen, and pelvis; a bone scan; and plain radiographs of symptomatic regions or areas of increased uptake on bone scans. If any neurologic symptoms suggestive of cerebral metastases are present, a gadolinium-enhanced MRI scan of the brain should be obtained. The use of MRI to screen asymptomatic patients has not been widely adopted. There are retrospective data suggesting that subsets of patients with breast cancer may have a higher risk of intracranial disease and may be appropriately screened with MRI. These include women with HER2-positive and triple-negative subtypes who present with extracranial metastatic disease[10] and women with IBC who present with extracranial metastases.[11]

There is increasing interest in the use of 18F- fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT for staging of patients with LABC, particularly those with IBC. Several small retrospective studies have shown that PET/CT increases detection of both previously unsuspected sites of metastatic disease and additional sites of regional nodal disease when compared to conventional imaging.[12,13] Researchers from MD Anderson showed that the addition of PET/CT in the staging of 41 women with IBC not only detected new sites of disease in 44% of patients when compared to standard imaging but also resulted in a change in radiation doses or fields in 18%.[14] FDG PET/CT can be particularly helpful when standard staging studies are equivocal. 18F-fluoroestradiol PET/CT may have clinical utility in the setting of ER-positive breast, especially invasive lobular carcinoma; however, additional studies are needed.[15]

The patient's personal and family oncologic history should be obtained and documented. The American Society of Breast Surgeons recommends that all patients with breast cancer should be offered genetic testing for deleterious mutations BRCA1/BRCA2 and PALB2 as well as other genes deemed appropriate based on the patient's personal and family history.[16] Referral to a trained genetic counselor for genetic testing recommendations is preferred.

Staging of Locally Advanced Breast Cancer

Previously, the American Joint Committee on Cancer (AJCC) staging system for breast cancer relied exclusively on the anatomic TNM staging system in which *T* refers to the size and extent of the primary tumor, *N* refers to the number and/or extent of regional

nodal involvement, and *M* refers to the presence of distant metastatic disease. As a result of a greater understanding of the importance of tumor biology in relation to prognosis and patient outcomes, the amended 2018 eighth edition of the AJCC prognostic staging system for breast cancer incorporates tumor grade, molecular markers (ER, progesterone receptor, and HER2 expression), as well as the results of the Oncotype DX (Exact Sciences) multigene panel. The AJCC breast cancer staging system continues to include clinical and anatomic staging for areas of the world where detailed molecular analysis is not widely available. Tumor registries and treating practitioners in the United States and Canada should use the AJCC eighth edition Clinical and Pathologic Prognostic Stage Groups.

A comprehensive discussion of disease staging systems for breast cancer is provided in the previous chapter. Some staging considerations are particularly relevant to patients with stage III disease. Stage III breast cancer can represent either T3 disease (tumors >5.0 cm) with involved LNs, N2 or N3 disease, or T4 disease.[1] Specific aspects of both primary tumor and nodal staging in LABC warrant additional consideration. Specifically, T4 disease may represent invasion into the chest wall (T4a), tumors associated with ulceration or satellite nodules of the skin and/or breast edema (T4b), both chest wall invasion and T4b characteristics (T4c), or IBC (T4d). Invasion of disease into the pectoralis major muscle without invasion of the chest wall structures and dimpling or fixation of the overlying skin does not qualify as T4 disease. Both clinical and pathologic staging systems have been established for N2 and N3 disease. Clinical N2 disease signifies either involved axillary LNs that are fixed to one another or to surrounding structures (N2a) or involved IM LNs without concurrent disease in the axilla (N2b), as determined by physical examination or imaging studies. Clinical N3 disease includes nodal metastases that involve the infraclavicular region (N3a), both the axilla and IM LNs (N3b), or the supraclavicular region (N3c). Pathologic N2 disease represents involvement of four to nine axillary LNs with at least one focus measuring greater than 2.0 mm (N2a) or clinical involvement of IM LNs (with or without microscopic confirmation) with pathologically negative axillary LNs (N2b). Pathologic N3 disease represents involvement of an infraclavicular LN or 10 or more involved LNs with at least one focus measuring greater than 2.0 mm (N3a), clinical involvement of IM LNs with one to nine axillary LNs involved or pathologic involvement of a sentinel IM LN with four or more axillary LNs involved (N3b), or a metastasis in the supraclavicular region (N3c).[1]

Neoadjuvant chemotherapy is recommended for most patients with LABC. The initial extent of disease is an important factor for later locoregional treatment decisions and for future research. It is, therefore, imperative that the full extent of the initial disease is assessed and documented prior to beginning any treatment.

OVERVIEW OF TREATMENT APPROACHES

Combined Modality Therapy

LABC is most appropriately treated with multimodality therapy aimed at eradicating all disease in the locoregional area and preventing distant disease recurrence. These goals are best achieved through the use of systemic therapy (generally chemotherapy and, when appropriate, endocrine, HER2-directed, or targeted therapy), surgery, and radiation.

LABC can present as either operable or inoperable disease. In general, disease is considered inoperable if an initial surgical procedure is unlikely to completely resect all gross disease with achievement of negative surgical margins. Most patients with T4 disease and/or advanced nodal disease and all patients with IBC are considered inoperable at presentation. Inoperable disease requires the administration of upfront systemic therapy to reduce tumor volume in order to facilitate definitive local therapy. Neoadjuvant therapy (also known as preoperative therapy) usually takes the form of chemotherapy with the addition of anti-HER2 therapy in the setting of HER2-positive disease, although, in certain situations as discussed later, ET may also be an option. In addition to downstaging the tumor, systemic therapy also reduces the risk of recurrence and breast cancer mortality by eradicating occult micrometastatic disease and aiding radiation in obtaining long-term local control.

For most patients with LABC, neoadjuvant systemic therapy is now the standard approach. Neoadjuvant systemic therapy is also commonly used in the setting of node-positive, HER2-positive, and triple-negative disease. Neoadjuvant systemic therapy may render some patients eligible for breast-conserving surgery (BCS) and/or sentinel lymph node biopsy (SLNB).[17-19] In addition, response to neoadjuvant systemic therapy can also help tailor adjuvant systemic therapy treatment recommendations.[20,21]

Neoadjuvant Chemotherapy

The landmark NSABP B-18 trial randomized 1,523 patients with operable breast cancer to receive neoadjuvant doxorubicin and cyclophosphamide (AC) for four cycles followed by surgery versus surgery followed by four cycles of AC.[22] Although this trial included only patients with operable breast cancer, the results demonstrated the feasibility of preoperative chemotherapy. The planned surgical approach was determined prior to randomization, with approximately two-thirds of patients in each group deemed initially eligible for lumpectomy. There was no difference in overall survival (OS) or disease-free survival (DFS) between the two groups, but a larger proportion of patients who received neoadjuvant chemotherapy were able to undergo BCS compared to those who received adjuvant chemotherapy (68% vs 60%).[22,23] This increase was largely due to a higher percentage of patients with T3 disease being offered breast conservation after responding to neoadjuvant chemotherapy. The percentage of patients with pathologically negative nodes was also higher in the neoadjuvant group compared to the adjuvant group (59% vs 43%, $P < .001$). Results from another pivotal neoadjuvant trial European Organisation for Research and Treatment of Cancer (EORTC) 10902 also demonstrated an increase in the percentage of patients eligible for BCS, with 23% of patients initially requiring mastectomy being able to undergo lumpectomy after the receipt of chemotherapy. OS and

recurrence rates were equivalent between the preoperative and postoperative chemotherapy groups.[24]

A key finding that emerged from the early neoadjuvant trials was the correlation between response to therapy and long-term outcome. In B-18, patients who achieved a pathologic complete response (pCR) in the breast after neoadjuvant chemotherapy had improved DFS (hazard ratio 0.47, $P = .0001$) and OS (hazard ratio 0.32, $P = .0001$) compared to those who did not.[17] This finding has been replicated in several other studies, though the definition of pCR varied, with some studies using the definition of absence of invasive tumor in the breast and nodes and others the absence of invasive disease in the breast. The currently accepted definition of pCR is the lack of residual invasive cancer in the breast and nodes. Patients who achieve a pCR consistently demonstrate improved long-term outcomes compared to those with significant residual disease.[25,26]

In addition to downstaging the tumor to improve surgical outcomes and providing valuable prognostic information, neoadjuvant chemotherapy also allows an *in vivo* assessment of the tumor's response to chemotherapy. Patients whose tumors demonstrate resistance to initial therapy should be offered a non–cross-resistant regimen or proceed directly to local therapy.

For patients with locally advanced but operable disease at presentation, primary surgery followed by adjuvant therapy may be a consideration. A potential advantage of this approach is a shorter time interval between diagnosis and effective treatment for patients with disease that is resistant to chemotherapy. Primary surgery also allows for more accurate pathologic staging of the tumor and axillary nodes, which is important to guide prognosis and selection of appropriate adjuvant treatment. However, the amount of residual disease after neoadjuvant chemotherapy may ultimately provide a more individualized assessment of prognosis. Furthermore, tumor biology has become a driving force in the selection of appropriate systemic therapy, and appropriate treatment decisions can often be made at the time of diagnosis based on the clinical stage and molecular subtype of the tumor. Given equivalent DFS and OS between the two approaches, there has been a paradigm shift in the treatment of LABC, with increased use of neoadjuvant chemotherapy.

As discussed earlier, pathologic evaluation of the tumor bed and LNs after neoadjuvant chemotherapy provides important prognostic information. However, the value of pCR as a prognostic tool is highly dependent on the molecular subtype of the tumor. Tumors that are highly proliferative (luminal B, nonluminal/HER2 positive, and triple negative) tend to demonstrate increased chemosensitivity and are associated with higher rates of pCR compared to low proliferative subtypes with high expression of hormone receptors (HRs) (luminal A).[27] pCR appears to be most predictive of DFS and OS in nonluminal/HER2-positive (treated with trastuzumab) and triple-negative subtypes, with those achieving a pCR having an excellent prognosis and those with significant residual disease having a high risk of recurrence and overall worse survival. pCR in patients with luminal A tumors does not appear to be a good predictor of long-term outcome, whereas the utility of pCR as a predictive tool in patients with luminal B (HER2-negative or HER2-positive) tumors

seems to be better than for luminal A tumors but worse than for nonluminal/Her2-positive or triple-negative tumors.[26,27]

HER2-Negative Disease

The optimal neoadjuvant chemotherapy regimen for patients with HER2-negative disease has not been established, but it is generally accepted that regimens with proven effectiveness in the adjuvant setting may also be used in the neoadjuvant setting. Because patients with LABC are considered to have high-risk disease, a regimen containing an anthracycline (eg, doxorubicin, epirubicin) and a taxane (eg, paclitaxel, docetaxel) is usually preferred.

These recommendations are based on results from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analyses, which demonstrated that adjuvant polychemotherapy reduced the risk of recurrence and breast cancer mortality in patients with node-positive and node-negative disease.[28] Anthracycline-based regimens were found to be superior to CMF (cyclophosphamide, methotrexate, fluorouracil) regimens, and the addition of taxanes to anthracyclines further improved outcomes.[29] Overall, taxane-plus- anthracycline–based regimens reduced 10-year breast cancer mortality by one-third.

For patients with contraindications to anthracyclines or taxanes, alternate regimens are available. A non– anthracycline- containing regimen may be preferred in patients who have cardiac disease or who have other risk factors for anthracycline-associated congestive heart failure, such as hypertension, diabetes, or advanced age. For patients with a hypersensitivity reaction to solvent-based paclitaxel, nanoparticle albumin–bound paclitaxel (nab-paclitaxel) may be used.

HER2-Positive Disease

One of the most significant advances in breast cancer treatment has been the introduction of trastuzumab, a monoclonal antibody directed against the HER2 protein, into the adjuvant treatment for patients with HER2-overexpressing cancer. Several prospective randomized trials have demonstrated that the addition of trastuzumab to chemotherapy in the adjuvant setting confers an approximate 50% improvement in DFS and 35% improvement in OS in this population.[30,31] Subsequent studies in the neoadjuvant setting have confirmed an important role for trastuzumab in the neoadjuvant setting as well, with an approximate doubling of pCR rate to around 40% with the addition of trastuzumab to chemotherapy.[26,32] pCR was also found to be a predictor of event-free survival (EFS) and OS. The subsequent development of pertuzumab, a monoclonal antibody that binds to the HER2 protein at the site of HER2/HER3 dimerization, has led to even further improvements in pCR rates when added to trastuzumab and chemotherapy.[33,34]

As there are few randomized data comparing different neoadjuvant chemotherapy regimens, a number of regimens may be considered appropriate in the locally advanced setting for HER2-positive breast cancer. The randomized phase II TRYPHAENA trial yielded a pCR rate of 56% in patients receiving neoadjuvant FEC (fluorouracil,

epirubicin, cyclophosphamide)-docetaxel, trastuzumab, pertuzumab and 64% for docetaxel, carboplatin, trastuzumab, pertuzumab.[34] The study was not powered to compare the pCR rate between the different regimens as it was primarily a cardiac safety study. Rates of cardiac toxicity were low overall, and slightly lower with the non–anthracycline-containing regimen.

The phase III TRAIN-2 trial randomized patients with stage II or III HER2-positive breast cancer to three cycles of FEC followed by three cycles of weekly paclitaxel and carboplatin or to nine cycles of weekly paclitaxel and carboplatin without an anthracycline. Trastuzumab and pertuzumab were administered with all chemotherapy cycles. pCR rates (67% vs 68%), 3-year EFS (92.7% vs 93.6%), and OS (97.7% vs 98.2%) were similar between the two arms.[35,36] There was a higher incidence of significant decline in left ventricular ejection fraction in patients who received an anthracycline (8% vs 3%), and two patients in the anthracycline group developed acute leukemia.

Given the above, a regimen containing a taxane, carboplatin, trastuzumab, and pertuzumab is preferred in the neoadjuvant setting for locally advanced HER2-positive breast cancer, although an anthracycline-containing regimen is an acceptable alternative.

Triple-Negative Disease

Chemotherapy for locally advanced triple-negative breast cancer (TNBC) should ideally incorporate an anthracycline and a taxane. In addition, randomized trials have demonstrated significantly higher pCR rates with the incorporation of a platinum, though results were conflicting with respect to the impact of carboplatin on DFS. In CALGB 40603 and GeparSixto, the addition of carboplatin resulted in an incremental increase in pCR of approximately 10% to 15% compared to standard anthracycline- and taxane-based regimens.[37-39]

These results led to the inclusion of carboplatin in the chemotherapy backbone used in the subsequent pivotal KEYNOTE-522 study.[40,41] This was a phase III trial that randomized patients with stage II or III TNBC to receive neoadjuvant paclitaxel and carboplatin followed by doxorubicin (or epirubicin) and cyclophosphamide with either the immune checkpoint inhibitor pembrolizumab or placebo. Pembrolizumab or placebo was continued in the adjuvant setting for 27 weeks, regardless of pathologic response. The co-primary end points were pCR and EFS (defined as the time from randomization to the date of disease progression that precluded definitive surgery, local or distant recurrence, occurrence of a second primary cancer, or death from any cause). The addition of pembrolizumab to chemotherapy led to a significant improvement in pCR (64.8%) compared to the placebo-chemotherapy arm (51.2%). A subsequent update demonstrated improved EFS at 36 months in the pembrolizumab-chemotherapy group compared to the placebo-chemotherapy group (84.5% vs 76.8%; hazard ratio 0.63, 95% confidence interval [CI] 0.48-0.82). Improvement in EFS was seen in both programmed death-ligand 1 (PD-L1)-positive and PD-L1–negative subsets and in patients with pCR or residual disease at surgery.[40,41]

The abovementioned data led to a paradigm shift in the treatment of locally advanced TNBC, and patients without a contraindication to an anthracycline or immunotherapy should receive pembrolizumab plus a chemotherapy backbone similar to that used in KEYNOTE-522.

Neoadjuvant Endocrine Therapy

Given the lower response rates to neoadjuvant chemotherapy in patients with tumors having high HR expression, there has been interest in evaluating the role of neoadjuvant ET in this population as an alternative method of downstaging tumors and rendering breast conservation feasible.

The IMPACT trial randomized 330 postmenopausal patients with clinical stage II or III HR-positive breast cancer to receive tamoxifen versus anastrozole versus tamoxifen plus anastrozole for 12 weeks.[42] There was no difference in clinical and radiographic response rates among the three groups, but a higher percentage of women receiving anastrozole were eligible for BCS compared with those receiving tamoxifen (44% vs 22%, $P = .022$). The authors also found that higher expression of ER was associated with increased response rates.[42] The P024 trial compared the efficacy of letrozole to tamoxifen in the neoadjuvant setting in 324 postmenopausal women with HR-positive breast cancer. After 16 weeks, treatment with letrozole resulted in improved clinical response rates compared to treatment with tamoxifen.[43]

Several efforts are underway to correlate response to neoadjuvant ET with long-term outcomes to identify patients with endocrine-sensitive disease who may be able to safely omit chemotherapy completely, including in the adjuvant setting. In patients treated with neoadjuvant ET, pathologic tumor stage, pathologic nodal stage, surgical specimen Ki67 level, and ER Allred score have been shown to be associated with relapse-free survival and breast cancer–specific survival (BCSS). The preoperative endocrine prognostic index (PEPI score) was developed based on these findings, with a PEPI score of 0 (pT1-2, pN0, Ki67 $\leq$ 2.7%) being associated with an extremely low risk of relapse (ROR).[44]

The ALTERNATE study was designed to assess a biomarker-driven treatment strategy based on Ki67 values after 4 and 12 weeks of neoadjuvant ET and employed the PEPI score to identify patients with a low risk of recurrence.[45] Approximately 1,300 patients with stage II or III HR-positive breast cancer were randomized to 6 months of neoadjuvant ET with the selective ER degrader fulvestrant or anastrozole or both. Patients with Ki67 greater than 10% at week 4 or 12 were recommended to switch to chemotherapy. Patients who remained on ET with a modified PEPI score of 0 at surgery continued their assigned ET for 1.5 years followed by anastrozole for a total of 5 years of ET (without chemotherapy). The primary end point of the neoadjuvant phase of the study was endocrine-sensitive disease rate (ESDR), defined as pCR or PEPI-0 residual disease. ESDR was similar between the treatment arms, ranging from 18.6% to 22.7%, with no difference between the fulvestrant-containing arms and the anastrozole arm.[45] However, baseline RNA-seq–based intrinsic breast cancer subtypes (by PAM50 [Veracyte] breast cancer assay) appeared to predict overall outcomes, and the combination of anastrozole

and fulvestrant was associated with enhanced antiproliferative effects compared to either agent alone in the luminal B molecular subtype.[46] Further analysis from ALTERNATE is ongoing.

The addition of CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib) to ET has led to improvements in response rates, progression-free survival, and OS in HR-positive/HER2-negative metastatic breast cancer.[47-50] As a result, there has been an interest in studying these agents in combination with neoadjuvant ET. The addition of CDK4/6 inhibitors to neoadjuvant ET consistently showed improved complete cell cycle arrest across multiple studies including PALLET, NeoPalAna, and NeoMONARCH compared to neoadjuvant ET alone.[51-53] Whether this translates into improved clinical benefit or survival remains unclear at this time.

CORALLEEN compared neoadjuvant chemotherapy to neoadjuvant ET and ribociclib in high-risk HR-positive/ HER2-negative and luminal B (by PAM50 gene signature) breast cancer.[54] The primary end point was the rate of PAM50 ROR low disease at the time of surgery. PAM50 ROR integrates gene expression data, tumor size, and nodal status to define a low-risk group in the adjuvant setting with more than 90% distant relapse-free survival at 10 years. Both arms demonstrated similar molecular downstaging to low risk by PAM50 ROR score at the time of surgery, with significantly less treatment-related toxicities in the nonchemotherapy arm.[54] However, survival data have not been reported.

Neoadjuvant ET may, therefore, be considered for select postmenopausal patients, and in particular those who may be medically unfit to receive chemotherapy. Treatment with an aromatase inhibitor appears to be superior to tamoxifen, and the recommended duration is at least 4 to 6 months. Close monitoring is advised to ensure that patients who are not responding or who lose response to neoadjuvant ET are offered alternative strategies.

The use of neoadjuvant ET in the premenopausal population has not been established. A randomized trial comparing 24 weeks of neoadjuvant chemotherapy versus 24 weeks of neoadjuvant ET in premenopausal women showed improved response rates in those receiving chemotherapy.[55] At this time, the use of neoadjuvant ET in this population is not routinely recommended.

Selection of Patients for Breast-Conserving Surgery

The decision to offer BCS is dependent on both the extent of tumor at presentation and after completion of neoadjuvant therapy and the relative breast size. Clinical and radiographic assessments are used to determine eligibility for BCS. Patients with residual tumor greater than 5 cm, residual skin edema, continued skin involvement, and/or chest wall fixation after neoadjuvant chemotherapy are not considered candidates for BCS.[19]

Surgical Management of the Axilla

Historically, axillary lymph node dissection (ALND) has been the standard surgical approach to the axilla following neoadjuvant systemic therapy in the setting of upfront axillary LN involvement. Three prospective studies, the SENTINA trial, ACOSOG Z1071, and SN FNAC, have examined the use of SLNB for patients who convert from clinically node positive (cN+) to clinically LN negative (cN−).[56-58] The false-negative rate (FNR) of SLNB for all three trials exceeded the threshold of 10%, which is the standard set by the NSABP B-32, the seminal trial that established SLNB as standard of care for patients with early-stage breast cancer.[59] Subgroup analyses have demonstrated that using dual tracers (blue dye and dual tracer), identifying and removing three or more sentinel LNs, and clip placement in the involved node(s) with removal of the clipped nodes(s) at time of surgery lead to a FNR of less than 10%.[8,56-58] Another study found that targeted axillary dissection, defined as SLNB plus localization and removal of the clipped nodes, yields an FNR of approximately 2%.[9] Based on these results, SLNB performed with the abovementioned techniques is reasonable for cN1-2 patients who become cN− after neoadjuvant systemic therapy. If any of the excised nodes are positive, ALND is indicated. Following neoadjuvant systemic therapy, ALND should be performed when the axillary disease remains palpable (cN+) as well as in the setting of infraclavicular involvement (cN3a), supraclavicular involvement (cN3c), and IBC even if the patient has been rendered cN−.

Systemic Therapy After Surgery

A full discussion of adjuvant systemic therapies is beyond the scope of this chapter. However, the following section highlights the salient points of adjuvant therapy as they pertain to patients with LABC who have completed neoadjuvant chemotherapy.

Hormone Receptor–Positive/HER2-Negative Disease

Patients with HR-positive breast cancer should receive adjuvant ET to reduce the risk of recurrence and breast cancer–specific mortality. The choice of therapy is influenced by menopausal status. Tamoxifen remains a standard for both premenopausal and postmenopausal women, whereas the use of aromatase inhibitors is limited to women who are in a low-estrogen state (ie, postmenopausal or receiving ovarian function suppression [OFS]).

The EBCTCG meta-analysis demonstrated that 5 years of adjuvant tamoxifen was associated with a one-third proportional reduction in breast cancer mortality at 15 years in patients with ER-positive disease, irrespective of age, nodal status, or receipt of chemotherapy.[60] Subsequent data from the ATLAS trial demonstrated a further reduction in recurrence risk and breast cancer mortality with 10 years of tamoxifen compared to 5 years, suggesting that compared to no ET, 10 years of tamoxifen was associated with an almost 50% reduction in disease-specific mortality.[61]

For postmenopausal women with HR-positive breast cancer, the use of an aromatase inhibitor is recommended in the adjuvant setting, either as upfront therapy or following

tamoxifen. Multiple studies have demonstrated improvement in recurrence rates and breast cancer mortality with the use of an aromatase inhibitor compared to tamoxifen. In a meta- analysis conducted by the EBCTCG, 5 years of aromatase inhibitor therapy was associated with a 15% reduction in 10-year breast cancer mortality compared with 5 years of tamoxifen.[62]

Subsequent data from the SOFT and TEXT trials established a role for OFS plus either tamoxifen or aromatase inhibition in select premenopausal women with HR-positive breast cancer. The addition of OFS resulted in a clinically meaningful improvement in recurrence rates, particularly in very young women (≤35 years) and in those whose disease was considered to be of sufficiently high risk to warrant the administration of chemotherapy. Given that women with LABC comprise a high-risk group, those who are premenopausal should be offered this strategy in the adjuvant setting.[63-65]

The landscape of adjuvant ET continues to evolve as CDK4/6 inhibitors are being evaluated in patients with high-risk disease. The monarchE study randomized 5,637 patients with HR-positive/HER2-negative high-risk disease (defined as either ≥4 involved nodes, or N1 disease with either tumor size ≥5 cm, grade 3, or Ki67 ≥20%) to receive adjuvant ET with or without 2 years of abemaciclib. At 4 years, the absolute improvement in invasive DFS (IDFS) was 6.4% (85.8% in the abemaciclib plus ET group vs 79.4% in the ET-alone group).[66,67] Based on these data, abemaciclib was approved in the adjuvant setting for patients with node-positive high-risk HR-positive/HER2-negative early-stage breast cancer.

NATALEE investigators reported at ASCO 2023 the benefit of adjuvant ribociclib in stage II and II breast cancer with high risk of recurrence including those with T2N0 disease. At a median follow-up of 34 months, adjuvant ribociclib added to ET led to a significant improvement in IDFS over ET alone, with a 3-year IDFS of 90.4% compared to 87.1%.[68] The benefit was observed across all subgroups including patients with N0 and N1 disease. In both monarchE and NATALEE, about 88% to 95% of patients also received adjuvant chemotherapy.

For patients with early-stage high-risk HER2-negative breast cancers who harbor a germline BRCA1 or BRCA2 pathogenic mutation, the addition of 1 year of the PARP inhibitor olaparib should be considered based on results from the OlympiA trial. This was a phase III study that randomized 1,836 patients to olaparib or placebo in the adjuvant setting. The 3-year IDFS was 85.9% in the olaparib group and 77.1% in the placebo group. With longer follow-up, an OS benefit was demonstrated, with a 4-year OS of 89.8% in the olaparib group compared to 86.4% in the placebo group (hazard ratio = 0.68, CI 0.47-0.97; $P = .009$).[69,70] The IDFS benefit of adjuvant olaparib was seen, regardless of HR status, carboplatin administration, or whether chemotherapy was administered in the neoadjuvant versus adjuvant setting.

HER2-Positive Disease

For patients with HER2-positive breast cancer, trastuzumab should be continued in the adjuvant setting to complete 1-year total of HER2-directed therapy. Patients who achieve

a pCR after neoadjuvant chemotherapy should continue with trastuzumab with or without pertuzumab in the adjuvant setting. Those with residual disease should be offered the option to switch to trastuzumab emtansine (T-DM1), a HER2-directed antibody-drug conjugate, based on results from the KATHERINE trial. This trial randomized patients with HER2-positive breast cancer with residual disease after neoadjuvant therapy to T-DM1 versus trastuzumab as adjuvant therapy. Patients who received adjuvant T-DM1 had improved 3-year IDFS compared to those in the trastuzumab group (88.3% vs 77.0%; hazard ratio = 0.50, $P < .001$).[21] The benefit was seen across all subgroups, regardless of HR status, pathologic nodal status, or amount of residual disease in the breast.

Neratinib is an oral pan-HER2 tyrosine kinase inhibitor. When administered for 1 year after completion of adjuvant trastuzumab in the ExteNET study, it was shown to improve IDFS, especially in patients with HR-positive/HER2-positive disease, and serves as an additional option to further reduce the risk of recurrence in the adjuvant setting.[71]

Triple-Negative Disease

Patients with TNBC who have completed neoadjuvant chemotherapy and achieve a pCR generally do not require additional chemotherapy in the adjuvant setting. If they received neoadjuvant pembrolizumab, they may continue this in the adjuvant setting to complete 1 year total of immunotherapy as was done in the KEYNOTE-522 trial.[40,41] However, as this trial did not include an arm with neoadjuvant pembrolizumab plus chemotherapy followed by no adjuvant immunotherapy, it is not clear how much incremental benefit is derived from pembrolizumab in the adjuvant setting.

In the CREATE-X study, 910 women with HER2-negative breast cancer with residual disease after neoadjuvant therapy with an anthracycline and/or taxane were randomized after surgery to either standard therapy (ET for patients with HR-positive disease or no systemic therapy for HR-negative disease) or to standard therapy plus capecitabine for eight cycles.[20] At 5 years, DFS was 74% for the capecitabine arm compared to 68% for the control arm (hazard ratio 0.70, $P = .01$). OS was also improved (89% vs 84%, hazard ratio = 0.59, $P = .01$). In the triple-negative subgroup, DFS was 70% versus 56% (hazard ratio 0.58) and OS was 79% versus 70% for the capecitabine and controls groups.[20] Patients who have residual disease after neoadjuvant chemotherapy may be offered adjuvant capecitabine based on these results. If pembrolizumab was administered in the neoadjuvant setting, it may be given concurrently with capecitabine in the adjuvant setting, although there is currently no defined standard.

Patients with locally advanced TNBC who carry a deleterious germline BRCA1/2 mutation should be offered adjuvant olaparib based on the OlympiA trial discussed earlier.[69,70] Whether to administer this in place of or in sequence with adjuvant capecitabine is not known, although given the targeted nature of PARP inhibitors for BRCA-associated cancers many favor olaparib over capecitabine in this situation.

Treatment Results for Locally Advanced Breast Cancer

As noted earlier, stage III breast cancer has historically been associated with a very poor prognosis, with high rates of locoregional recurrence (LRR), distant metastases, and death. However, advances in all disciplines, including systemic therapy with taxanes and anthracyclines as well as HER2-directed therapy and other targeted agents when appropriate, surgical interventions, and locoregional irradiation, have led to improved outcomes. Outcomes for patients with LABC vary by molecular subtype. Researchers out of MD Anderson analyzed the California Cancer Registry 2005-2008 and found 5-year rates of BCSS and OS for patients with stage III breast cancer were most favorable for patients with luminal cancers (HR positive) followed closely by HR-positive/HER2-positive cancers. Patients with triple-negative disease had the least favorable outcomes. Their analyses found that 5-year survival rates anatomic stage IIIA disease varied between approximately 68% to over 90%, while for those with anatomic stage IIIC disease, the survival rates ranged from about 33% to 84%, contingent upon grade and molecular subtype.[1,5]

Patients with supraclavicular lymph node (SCV) disease at diagnosis have a poorer prognosis than other patients with stage III disease. However, because some patients treated with chemotherapy were found to have 10-year survival rates of 30%,[72] the AJCC recategorized this stage of disease from stage IV to stage IIIC with the publication of the sixth edition of the *AJCC Staging Manual* in 2002.[73] One study investigating the outcome of 71 patients with supraclavicular disease who were treated with neoadjuvant chemotherapy, surgery, and radiation reported a 5-year locoregional control rate of 77% and a 5-year OS rate of 47%. Patients in whom the supraclavicular disease showed a clinical CR to neoadjuvant chemotherapy had better locoregional control and DFS than did those with persistent disease after chemotherapy.[74]

IMN involvement at presentation also confers a poor prognosis, although the incidence of IMN involvement is difficult to assess in modern series as extended radical mastectomies are not typically performed. Older series, prior to the use of routine screening mammography, have shown that IMN involvement is a risk factor for poor OS, independent of axillary nodal status.[75] A more modern series from the European Institute of Oncology included 107 patients with either IMN or SCV involvement between 1997 and 2009. Nodal involvement was determined by a combination of clinical examination, surgical biopsy, FDG PET/CT, and ultrasound. Five-year outcomes were better in those with IMN compared to SCV disease (DFS 84% vs 39% and OS 96.9% vs 57.1%).[76] Patients with both IMN and SCV involvement have a particularly high risk of distant disease. A study from Korea found a 33% 5-year DFS among 18 patients with disease involving both nodal sites.[77]

Patients presenting with SCV or IMN disease should receive treatment similar to other patients with stage III disease. Typically, this includes preoperative systemic therapy and breast and axillary surgery, followed by comprehensive adjuvant RT. As neither SCV nor IMN sites are readily amenable to surgery, these areas should be included in the radiation fields. There are insufficient data to guide radiation dose selection in this setting, but

consideration should be given to boost to the area of clinical involvement. Dose may be limited because of the adjacent brachial plexus (SCV) and heart and/or lung (IMN).

INFLAMMATORY BREAST CANCER

Epidemiology of Inflammatory Breast Cancer

IBC is an important subcategory of LABC that is notable for both its similarities to and differences from noninflammatory LABC. IBC is not common and accounts for 0.5% to 2% of all invasive breast cancers diagnosed in the United States but is disproportionately lethal, accounting for about 10% of breast cancer deaths.[78] In a study of nine Surveillance, Epidemiology, and End Results (SEER) registries, the incidence of IBC was found to have increased slightly during the 1990s, even while the incidence of LABC and non-T4 breast cancer decreased.[79] The rates of IBC, and mortality from IBC, were higher in Black women than in White women. IBC tends to occur in younger patients than non-IBC. Women with IBC are more likely to have positive axillary LNs, higher tumor grade, and negative HRs.[78-80] Distant metastases at diagnosis are also more common with IBC. Risk factors for IBC, including menstrual/reproductive factors, obesity, smoking, alcohol, and exposure to the mouse mammary tumor virus, have been evaluated, but results are not consistent.[80] The strongest epidemiologic associations of IBC are with Black race, young age, and high body mass index (BMI).[81]

Natural History of Inflammatory Breast Cancer

IBC, as defined by the AJCC, is a composite clinical-pathologic entity characterized by diffuse edema and erythema of the breast with acute/subacute onset and pathologic demonstration of invasive breast cancer. The erythema and skin changes must involve at least one-third of the breast, and the duration of symptoms must be less than 6 months. A critical and determinative feature of IBC is the rapid onset of clinical findings, including skin erythema, peau d'orange, brawny breast induration, warmth, and asymmetric enlargement (Figure 63.3).

FIGURE 63.3 Photograph of a patient with erythema and peau d'orange consistent with inflammatory breast cancer.

One hallmark of IBC is extensive lymphovascular invasion (LVI) of the superficial plexus of vessels in the papillary and high reticular dermis by tumor emboli. These emboli can be demonstrated with skin punch biopsies directed to areas of erythema in up to 75% of cases.[81] However, the presence of invasive cells in the dermal lymphatics alone is neither sufficient nor necessary for the diagnosis.

It is important to distinguish IBCs from LABC with secondary lymphatic congestion. Neglected primary tumors can also lead to breast erythema, edema, warmth, and asymmetric enlargement, particularly when bulky axillary adenopathy impedes the

normal lymphatic flow from the breast. However, the former has a history of rapid onset, whereas the latter tends to have a long interval between the first symptom and the presentation for medical treatment. Despite these general guidelines, the diagnosis of IBC can be uncertain. In order to establish more reproducible and objective criteria, Jagsi and colleagues proposed a scoring system based on clinical, pathologic, and imaging characteristics.[82]

Despite the natural history of IBC being one of rapid disease progression and early distant dissemination, in the United States, approximately 70% of patients with IBC have only evidence of locoregional disease at the time of diagnosis.[78] Patients with IBC typically have a worse clinical outcome than do other patients with T4 disease, suggesting that IBC is a distinct biologic entity.[83] However, the prognosis for patients with IBC has improved with combined (or tri-) modality therapy, including neoadjuvant chemotherapy, mastectomy, and postmastectomy radiation therapy (PMRT). Before the availability of combination chemotherapy, IBC was almost uniformly fatal. Fewer than 5% of patients treated with surgery, RT, or both survived the past 5 years, and the expected median survival time for such patients was less than 15 months.[84] Local recurrence rates after surgery or RT were also high at approximately 50%.[85,86] The introduction of doxorubicin-based chemotherapy was the first step toward improved outcomes.[87,88] An evaluation of the outcome of patients with IBC registered in the SEER Program found that BCSS rates for patients with IBC improved continuously throughout the 1990s.[78] Currently, local control rates for patients treated with chemotherapy, mastectomy, and postmastectomy radiation approach 80% to 95%, and 5-year survival rates are approximately 40% to 60%.[89-93] In one recent retrospective series from an institution with a dedicated IBC center, LRR rates were as low as 6.9% among patients undergoing trimodality therapy from 2007 to 2019.[94]

Diagnostic Workup

Although mammograms are considered a routine part of imaging workup for unspecified breast cancer, they are often of limited value for IBC. The diagnosis of IBC is often made without a clinically detectable mass. There are no specific IBC findings on mammography, but skin and trabecular thickening are the most frequent findings. MRI, with dynamic contrast enhancement studies, is the most accurate test for identifying primary breast lesions in IBC. MRI abnormalities on MRI can include asymmetric non–mass-like enhancement, multifocality/centricity, and postcontrast peak signal intensity higher than that for other presentations of LABC. As discussed earlier in the chapter, there is increasing interest in the use of FDG PET/CT for disease staging of patients with LABC, particularly those with IBC.[95]

General Management and Treatment Results for Inflammatory Breast Cancer

Because IBC is relatively uncommon, no data from randomized studies are available regarding the optimal therapeutic approach for this disease. From the aggregate of data reporting on IBC, it is quite clear that the best reported outcomes are with trimodality therapy, with a general sequence of neoadjuvant chemotherapy, mastectomy, and PMRT. Clearly, the management of IBC requires integrated care by a multidisciplinary team. Ideally, such patients should be evaluated in a multidisciplinary center by all specialists at the time of presentation to confirm the diagnosis of inflammatory disease, document the extent of disease (including photographs of areas of the involved skin), and agree on a treatment plan.

Chemotherapy for Inflammatory Breast Cancer

IBC is considered inoperable at presentation and should be treated initially with neoadjuvant chemotherapy (with the addition of trastuzumab and pertuzumab if the tumor is HER2 positive, and pembrolizumab if triple negative). The optimal chemotherapy regimen for patients with IBC includes both an anthracycline and a taxane. Patients should be carefully monitored for response, and after achievement of the maximal clinical response, patients should be reevaluated for mastectomy.

Surgery for Inflammatory Breast Cancer

Locoregional treatment is an essential component of therapy for IBC. Before the routine use of chemotherapy, mastectomy, with or without postmastectomy radiation, was associated with a dismal prognosis, and so many physicians abandoned mastectomy in favor of radiation-only treatments. Outcomes after RT as the sole treatment modality were equally poor. After neoadjuvant chemotherapy became routine, combinations of surgery and radiation have been reevaluated.

De Boer et al[96] reported on 54 patients with IBC treated after neoadjuvant chemotherapy with either radiation only (n = 35) or mastectomy plus radiation (n = 19). For the patients treated with radiation only, the median progression-free survival time was only 16 months, and the local recurrence rate was 34%. These results were not statistically different from the patients treated with mastectomy, and the authors concluded that surgery provided no clinical advantage over chemotherapy and radiation alone. In contrast, Perez et al[97] found that the addition of mastectomy to local treatment significantly improved the outcome of IBC treatment. Patients given neoadjuvant chemotherapy, mastectomy, and PMRT had a local control rate of 79% and a 5-year DFS of 40%. This was among the earliest demonstrations of the efficacy of trimodality therapy. These data were supported by the report from Panades et al[98] who evaluated 308 patients given chemotherapy as a component of their treatment and found that the 10-year local recurrence-free survival (LRFS) rates were significantly better for patients who underwent mastectomy than for those who did not (about 60% vs 34%; P = .0001), as were the 10-year BCSS rates (about 34% with mastectomy vs 23% without, P = .005). A multivariate analysis that considered other potential prognostic factors found that the use of mastectomy remained a significant factor for improved LRFS (P = .04). Results from

an MD Anderson study also confirmed these results, with multivariate analysis revealing that a CR or partial response to neoadjuvant chemotherapy, the use of RT, and the addition of mastectomy to the therapeutic regimen all significantly improved disease-specific survival.[99]

Radiation Therapy for Inflammatory Breast Cancer

RT also has an important role in the management of IBC. The randomized data supporting PMRT for LABC are discussed elsewhere and are not reviewed. Although IBC was not represented in those trials, the lessons are still germane to IBC. Furthermore, the best reported outcomes in IBC have all employed trimodality therapy and had aggressively designed and dosed RT. Because IBC has a rapid doubling time, investigators from MD Anderson investigated an accelerated hyperfractionated radiation delivery schedule in which 51 Gy is delivered to the chest wall and draining lymphatic fields by giving 1.5 Gy twice a day.[100] Subsequently, the chest wall was boosted to an additional 15 Gy, given in ten 1.5-Gy fractions twice daily. This approach was found to significantly improve locoregional disease control compared with a group treated with only 60 Gy, but also with a twice-daily schedule. Respective 10-year locoregional control rates were 77% versus 58% (P = .04). Statistically significant improvements were also seen in 5- and 10-year OS rates between these two groups (P = .03), and a trend toward improvement in 5- and 10-year DFS rates was noted as well (P = .06). In a more recent update from these investigators in which the outcome of 192 patients treated with neoadjuvant chemotherapy, mastectomy, and postmastectomy radiation was evaluated, the authors reported a 5-year locoregional control rate of 84%.[93] Factors associated with higher rates of locoregional control included partial response to chemotherapy, negative margins, three or fewer positive LNs, and the use of taxane chemotherapy. Similarly, good outcomes have also been reported from centers that used once-daily RT with high doses or daily use of bolus.[89]

In summary, all patients with IBC require management by a multidisciplinary team. After initial staging and careful documentation of the extent of disease, patients should receive initial chemotherapy. The chemotherapy course should include both an anthracycline and a taxane; anti-HER2 therapy with trastuzumab and pertuzumab should be given with chemotherapy for patients with HER2-positive disease, and pembrolizumab should be included for patients with triple-negative disease barring any contraindication to immunotherapy. The majority of patients who exhibit a disease response and become operable should then undergo a modified radical mastectomy. Comprehensive and aggressive postmastectomy radiation treatments to the chest wall and draining lymphatics should be given as adjuvant therapy. This approach was recently endorsed by a consensus panel of IBC experts.[93] The dose of radiation to the initial fields should be 50 Gy in 25 fractions given once a day or 51 Gy in 1.5-Gy fractions given twice a day. Subsequently, the chest wall and any areas of gross disease that have not been resected should be boosted to 60 to 66 Gy. Attention should be paid to skin dose, and many institutions use

tissue equivalent bolus material to ensure full dose to the skin of the chest wall. Patients with ER-positive disease should also receive hormonal therapy.

Clearly, great strides have been made over the past two decades in the management of IBC, and patients whose disease is managed with trimodality therapy can have locoregional control rates more than 80% and 5-year survival rates of more than 40% to 60% or more. Improvements in systemic therapy will, it is hoped, further augment these results.

LOCOREGIONAL RADIATION THERAPY AFTER MASTECTOMY OR BREAST-CONSERVING SURGERY FOR LOCALLY ADVANCED BREAST CANCER

An overview of the general management of strategies for LABC including IBC has been provided. The next section of the chapter concentrates on the role of RT as an adjunct to mastectomy or BCS in the setting of LABC. Data from meta-analyses and prospective randomized trials conducted in the past several decades that provide valuable data to define the role of locoregional RT are reviewed. RT decision-making in the context of the expanded use of neoadjuvant systemic is discussed.

In contemporary practice, the goal of safe and effective implementation of locoregional RT for patients with LABC has been advanced by technological innovations in treatment planning and delivery. The upcoming sections review locoregional RT techniques, including standardized contouring methods and dose-volume constraints. Dosimetric considerations to achieve conformal targeting and dose homogeneity to the breast/chest wall and regional nodes are discussed. The effects of RT on critical organs at risk (OAR), particularly the cardiovascular structures, along with modern techniques to minimize cardiac exposure, are examined.

Early Phase III Randomized Trials and Meta-Analyses: Postmastectomy Radiation Therapy

PMRT has been used for decades following surgery in the setting of LABC with the goal of achieving improved locoregional control and OS. Early randomized trials performed in the 1950s and 1960s demonstrated some improvement in LRR rates and no change in OS, with approximately 40% rate of distant metastases with the use of PMRT.[101-103] This lack of improvement in OS is likely due to the inferior efficacy of early systemic therapy regimens as well as the use of more rudimentary RT techniques with inadequate dose to the areas at risk and greater exposure of the heart and lungs. Nonetheless, by the mid-1970s, PMRT in the setting of LABC with involved axillary LNs was the generally accepted practice, with the goal of improved locoregional control,[103,104] although its use was controversial. For example, in 1987, Cuzick et al[105] published a meta-analysis of 7,941 patients enrolled in eight PMRT trials initiated before 1975 that reported no difference in survival in the first 10 years of follow-up; however, beyond 10 years, an excess of deaths among radiated patients was observed. RT was associated with reduced

breast cancer– specific mortality, but this was counterbalanced by an increased risk of cardiovascular death.[105,106] The work by Cuzick et al provided relevant early lessons in the association between locoregional control and improved BCSS and the importance of using heart-sparing radiation techniques to mitigate the risks of cardiac injury and death.

Three impactful randomized trials—the Danish Breast Cancer Cooperative Group (DBCG) 82b and 82c trials, and the British Columbia trial—demonstrated that PMRT was associated with not only improved locoregional control but also improved OS.[107-109] These landmark trials, which employed protocol-defined radiation techniques treating the chest wall, the IMN, supraclavicular, and axillary nodes in patients treated with adjuvant systemic therapy, contributed important prospective data that defined the role of PMRT in contemporary practice. These trials are discussed in more detail later and summarized in Table 63.1. In addition, work by the EBCTCG has provided evidence to support the use of PMRT in the setting of LABC.

TABLE 63.1 SUMMARY OF RESULTS OF THE BRITISH COLUMBIA TRIAL AND THE DBCG 82B AND DBCG 82C TRIALS EVALUATING PMRT AFTER MRM

	British Columbia[110]	DBCG 82b[107]	DBCG 82c[108]
Number of subjects	318 Premenopausal, N+	1,708 Premenopausal, high-risk pathologic stage II or III	1,460 Postmenopausal, high risk pathologic stage II or III
Accrual period	1976-1986	1982-1989	1982-1990
Breast surgery	MRM[a]	MRM[b]	MRM[b]
Randomization	PMRT vs no PMRT	9 cycles CMF vs 8 cycles CMF + PMRT	PMRT vs no PMRT
Chemotherapy	CMF	CMF	Tamoxifen[c]
Follow-up	20 y	10 y	10 y
Outcomes (PMRT vs control)	OS 47% vs 37%, $P = .03$ LRR 10% vs 26%, $P = .002$ DFS 48% vs 30%, $P = .001$	OS 54% vs 45%, $P < .001$ LRR 9% vs 32%, $P < .001$ DFS 48% vs 34%, $P < .001$	OS 45% vs 36%, $P = .03$ LRR 8% vs 35%, $P < .001$ DFS 36% vs 24%, $P < .001$

DFS, disease-free survival; LRR, locoregional recurrence rate; MRM, modified radical mastectomy; N+, node positive; OS, overall survival; PMRT, postmastectomy radiation therapy.

[a]Axillary dissection included levels I and II.

[b]Axillary dissection included level I and part of level II with median of seven nodes removed.

[c]Tamoxifen given for 1 year.

The Danish Breast Cancer Cooperative Group Trials

The DBCG 82b trial enrolled 1,708 premenopausal women with high-risk pathologic stage II or III breast cancer, accrued between 1982 and 1989.[107] High-risk status was defined as the presence of one or more of the following features: involvement of axillary

nodes, primary tumor greater than 5 cm, or invasion of the skin or pectoral fascia. After mastectomy and levels I to II axillary surgery removing a median of seven nodes, patients were randomized to systemic therapy with nine cycles of CMF chemotherapy without RT versus eight cycles of CMF plus RT of 50 Gy in 25 fractions or 48 Gy in 22 fractions to the chest wall and regional LNs, defined as the supraclavicular, infraclavicular, and axillary nodes, and IMNs in the four upper intercostal spaces. At a median follow-up of 9.5 years, women who received PMRT had significantly lower LRR (9% vs 32%, $P < .001$), improved DFS (48% vs 34%, $P < .001$), and improved OS (54% vs 45%, $P < .001$).[107]

The DBCG 82c trial evaluated 1,375 postmenopausal patients with high-risk pathologic stage II or III breast cancer, accrued between 1982 and 1990, who were randomized to mastectomy plus 1 year of tamoxifen versus mastectomy, tamoxifen, and RT.[108] Similar to the DBCG 82b results, PMRT was associated with reduced 10-year LRR (8% vs 35%, $P < .001$), improved DFS (36% vs 24%, $P < .001$), and improved OS (45% vs 36%, $P = .03$).

In the updated analysis of both DBCG 82b and DBCG 82c trials with 15-year follow-up, which also analyzed outcomes stratified by nodal subgroups (1-3 vs ≥4 positive nodes), PMRT significantly reduced LRR from 51% to 10% in patients with four or more positive nodes and from 27% to 4% in patients with one to three positive nodes.[111] OS improvement with PMRT use was demonstrated in both subgroups with one to three positive nodes (57% vs 48%, $P = .03$) and with four or more positive nodes (21% vs 12%, $P = .03$).

British Columbia Trial

The British Columbia trial was a smaller study that randomized 318 premenopausal women with node-positive disease after modified radical mastectomy and CMF chemotherapy to PMRT or no additional treatment.[109] PMRT consisted of hypofractionated prescriptions of 37.5 Gy in 16 fractions to the chest wall and 35 Gy in 16 fractions to the IMN and to the midaxilla through an anterior supraclavicular-axillary field. In the 20-year update, women treated with PMRT were confirmed to have significantly reduced rates of LRR (10% vs 26%, $P = .002$) and improved distant relapse-free survival (31% vs 48%, $P = .004$) and OS (47% vs 37%, $P = .03$).[110] The rates of cardiac death were 1.8% in the PMRT group and 0.6% in the control group ($P = .62$). Women treated with PMRT had higher rates of lymphedema (9% vs 3%, $P = .035$).

Early Breast Cancer Trialists' Collaborative Group Meta-Analyses

In 1983, the EBCTCG formed an international organization with the goal of generating and regularly updating meta- analyses using data from randomized trials of breast cancer treatment. The group defined early breast cancer as a disease "in which all clinically apparent disease can be removed surgically."[112] As such, the trials analyzed in the EBCTCG overview may include data from patients with stage III disease.

In 1995, the first published EBCTCG meta-analysis included 36 randomized trials comparing surgery alone versus surgery plus RT. Among 17,273 women enrolled in these trials, the use of RT after surgery was associated with a 3-fold reduced rate of local recurrence compared with surgery alone; however, there was no difference in the 10-year survival.[112] Similar to the work by Cuzick,[105,106] the reduced risk of death from breast cancer with RT was offset by an increased risk of death from other causes.

In 2000, the EBCTCG published findings from 40 randomized trials involving 20,000 women, half of whom had node-positive disease (EBCTCG 2000).[113] In these trials, adjuvant RT encompassed not only the breast or chest wall but also the axillary, supraclavicular, and IMN. The results showed that RT reduced local recurrence rates by about two-thirds (8.8% vs 27.2% at 10 years) and decreased breast cancer mortality ($2P$ = .0001). However, it led to an increase in cardiovascular mortality ($2P$ = .0003) while showing no significant impact on OS at 20 years (37.1% with RT vs 35.9%; $2P$ = .06).[113]

In 2005, the EBCTCG published an influential analysis reporting that, among 8,500 women with node-positive breast cancer treated with mastectomy and axillary dissection, PMRT to the chest wall and regional lymphatics reduced 5-year LRR by 17% from 22.8% to 5.8%.[114] By 15 years, breast cancer mortality was reduced by 5.4% (54.7% vs 60.1%, $2P$ = .0002) and overall mortality was reduced by 4.4% (64.2% vs 59.8%, $2P$ = .0009), suggesting the concept that for every four local recurrences prevented by RT in this group, one breast cancer death may be spared at 15 years. Although the relative risk (RR) of LRR was consistently decreased by two-thirds across trial subjects, the absolute risk reduction in individual subjects was dependent upon the baseline risk without RT. As such, PMRT was found to have the greatest impact on patients with a higher volume of nodal disease and larger primary tumors.

In the 2014 update of the EBCTCG meta-analysis, 8,135 women in 22 PMRT trials from 1964 to 1986 were analyzed.[115] The 20-year breast cancer mortality reduction associated with PMRT was statistically significant for all patients with node-positive disease, including those with one to three and four or more positive nodes. Among 3,786 subjects who underwent axillary dissection, 700 had node-negative disease, 1,214 had one to three positive nodes, and 1,772 had four or more positive nodes. Distinct from patients with node-negative disease in whom RT had no significant effect on LRR or breast cancer mortality, patients with one to three positive nodes treated with radiation experienced significantly reduced rates of LRR ($2P$ < .00001), overall recurrence (RR 0.68; 95% CI 0.57-0.82; $2P$ = .00006), and breast cancer mortality (RR 0.80; 95% CI, 0.67-0.95; $2P$ = .01). These improved outcomes were also observed among 1,133 patients with one to three positive nodes who received systemic therapy with CMF or tamoxifen. In these patients, PMRT was associated with significantly lower rates of 10-year isolated LRR (4.3% vs 21.0%, P < .00001), overall recurrence (33.8% vs 45.5%, P < .00001), and 20-year breast cancer mortality (41.5% vs 49.4%, P = .01). Among 1,677 patients with four or more positive nodes treated with systemic therapy, PMRT similarly reduced LRR (13.6% vs 31.5%, P < .00001), overall recurrence (RR 0.79; 95% CI 0.69-0.90; $2P$ = .0003), and 20-year breast cancer mortality (70.0% vs 78.0%, P = .08). Importantly, for

the 3,131 subjects with node-positive disease who underwent ALND, PMRT significantly reduced overall mortality (RR 0.89, 95% CI 0.81-0.97, 2*P* = .01). Ultimately, the 2014 meta-analysis suggested that for every 1.5 recurrences of any type avoided during the first 10 years after RT, one breast cancer death would be avoided at 20 years.[115]

The EBCTCG recently published a meta-analysis of individual patient data of 14,324 women from all randomized trials of regional nodal irradiation (RNI) versus no RNI that began before January 1, 2009, with available data.[116] In all, 2,451 patients whose data were included in the meta- analysis had four or more pathologically involved nodes. The 16 included trials were categorized as older (1961-1978) or newer (1989-2008) with the goal of assessing the effects of RNI on breast cancer recurrence and mortality for each group. In the eight older trials, RNI did not affect breast cancer mortality (RR 1.04, 95% CI 0.91-1.20; *P* = .55); however, RNI led to an increase in non-breast cancer mortality (RR 1.42, 95% CI 1.18-1.71; *P* = .00023) and all-cause mortality (RR 1.17. 1.04-1.31; *P* = .0067). In the eight newer trials, with 15 years of follow-up, there was a significant reduction in breast cancer recurrence (RR 0.88, 95% CI 0.81-0.95; *P* = .0008) and breast cancer mortality (RR 0.87, 95% CI 0.80-0.94; *P* = .0010) with the use of RNI. There was no significant difference in non-breast cancer mortality between the two groups, leading to a significant reduction in all-cause mortality with the use of RNI (RR 0.90, 95% CI 0.84-0.96; *P* = .0022). At 15 years, the absolute improvement in breast cancer mortality was 3.0% and the absolute improvement in overall mortality was 3.0% with the use of RNI. For patients with no involved axillary nodes, one to three axillary nodes, and four or more involved nodes, the absolute reduction in 15-year breast cancer mortality with RNI was 1.6%, 2.7%, and 4.5%, respectively.[116] This interesting meta-analysis indicates that with improvement in RT techniques as well as advances in systemic therapy, RNI improves breast cancer outcomes and survival for patients with high-risk disease.

In summary, the Danish and British Columbia PMRT trials reported that patients with high-risk breast cancer treated with PMRT and systemic therapy had significantly reduced risks of LRR. These improvements led to improved DFS and OS at 15- and 20-year follow-up.[111,110] These trials, taken together with the EBCTCG meta-analyses, have supported the principle that by reducing LRR in the setting of effective systemic therapies, RT contributed to improved OS. As systemic treatment lowered the competing risk of distant metastasis and RT techniques improved, the effect of optimal locoregional control on improved survival became evident.

Recent Phase III Randomized Trials: Regional Nodal Irradiation After Breast-Conserving Surgery or Mastectomy

In the setting of LABC, particularly in patients presenting with large T3 tumors or T4 disease, standard surgical treatment remains mastectomy, typically with ALND, although SLNB after neoadjuvant systemic therapy is an option for select patients (see “Surgical Management of the Axilla”). The use of BCS for patients with LABC has been increasing. BCS may be applied to patients with T2 tumors with positive nodes, selected patients with operable T3 tumors with clinically node-negative disease or limited N1

involvement, and may be considered on an individualized basis with multidisciplinary review for patients with LABC with adequate response to neoadjuvant systemic therapy. Chen et al published a retrospective study demonstrating acceptable rates of ipsilateral breast tumor recurrence (IBTR) and LRR in patients with advanced disease (cT3/T4 and cN2/N3) who underwent neoadjuvant systemic therapy with excellent response including resolution of skin findings or chest wall fixation in the setting of cT4 tumors.[19] In patients with operable stages II to III breast cancer who are candidates for BCS, prospective trial results have emerged evaluating the role of RNI as a component of adjuvant management. The characteristics and results of these trials are summarized in Table 63.2.

TABLE 63.2 SUMMARY OF RESULTS OF THE MA.20 AND EORTC 22922 TRIALS EVALUATING REGIONAL NODAL IRRADIATION IN THE SETTING OF BCS

	MA.20[117]	EORTC 22922[118] 10 y	EORTC 22922[119] 15 y
Number of subjects	1,832 N+ or high-risk N0	4,004 N+ or medial/central tumor	4,004 N+ or medial/central tumor
Accrual period	2000-2007	1996-2004	1996-2004
Breast surgery	All BCS	75% BCS	75% BCS
Randomization (radiation targets)	Breast alone vs breast + IMN/SCN/level III ± level I-II	Breast/chest wall alone vs breast/chest wall + IMN/SCV	Breast/chest wall alone vs breast/chest wall + IMN/SCV
Node positive	90% (85% 1-3N+)	56%	56%
Chemotherapy	90%	55%	55%
Outcomes (RNI vs control)	LRRFS 95.2% vs 92.2%, *P* = .009 BCM 10.3% vs 12.3&, *P* = .11 DMFS 86.3% vs 82.4%, *P* = .03 DFS 82% vs 77%, *P* = .01 OS 82.8% vs 81.8%, *P* = .38	LRRFS not reported BCM 12.5% vs 14.4%, *P* = .02 DMFS 78.0% vs 75.0%, *P* = .02 DFS 72.1% vs 69.1%, *P* = .04 OS 82.3% vs 80.7%, *P* = .06	LRRFS not reported BCM 16.0% vs 91.8%, *P* = .0055 DMFS 70.0% vs 68.2%, *P* = .18 DFS 60.8% vs 59.9%, *P* = .18 OS 73.1% vs 70.9%, *P* = .36

BCM, breast cancer mortality; BCS, breast-conserving surgery; DFS, disease-free survival; DMFS, distant metastasis-free survival; IMN, internal mammary node; LRRFS, locoregional recurrence-free survival; N+, node positive; OS, overall survival; SCV, supraclavicular lymph node; RNI, regional nodal irradiation.

National Cancer Institute of Canada Clinical Trial Group MA.20 Trial

In 2015, the National Cancer Institute of Canada Clinical Trial Group (NCIC-CTG) MA.20 trial was published after a median follow-up time of 9.5 years.[117] In this multicenter trial, 1,832 patients who underwent BCS and systemic therapy were randomized to receive RT to the whole breast (50 Gy in 25 fractions) with or without radiation to the regional nodes (45 Gy in 25 fractions). Axillary dissection was performed in 96% of subjects. Overall, 85% had one to three positive nodes, 5% had four or more positive nodes, and 10% had high-risk node- negative disease, defined as tumors >2 cm

with 10 or less nodes removed, plus one or more of the following features: grade 3 histology, LVI, or ER-negative disease. While representation of true LABC is limited in this trial, the enrolled subjects represent a higher risk cohort. RNI included the ipsilateral IMN as well as the supraclavicular and level III axillary nodes. For patients with less than 10 nodes removed or four or more positive nodes, the target volume also included level I and II axillary nodes.[117]

At 10 years, RNI was associated with improved locoregional DFS (95.2% vs 92.2%, *P* = .009), distant DFS (86.3% vs 82.4%, *P* = .03), and DFS (82.0% vs 77.0%, *P* =.01), but no difference in OS (82.8% and 81.8%, *P* = .38). In a planned subset analysis, women with ER-negative disease randomized to RNI had improved OS compared to no RNI (81.3% vs 73.9%, *P* = .05) and patients with ER-negative or PR-negative disease had a more robust improvement in DFS. The rate of lymphedema was higher in the RNI group (8.4% vs 4.5%, *P* = .001). The rates of grade 2 or higher cardiac toxicities were low (<1%) in the two study groups. The rate of acute pneumonitis was higher in the RNI group at 1.2% compared to 0.2% in the control group.[117]

European Organisation for Research and Treatment of Cancer 22922 Trial

The EORTC 22922 trial evaluated elective RNI to the IMN plus the medial supraclavicular (MS) fossa in conjunction with whole-breast radiation after BCS or chest wall radiation after mastectomy.[118] Between 1996 and 2004, 4,004 patients with stages I to III breast cancer with a central or inner quadrant tumor with node-negative or node-positive disease or an outer quadrant tumor with axillary node– positive disease were enrolled after BCS (76%) or mastectomy (24%). Initially, all patients underwent ALND; however, in the past years of the trial, SLNB with completion ALND in the setting of a positive node was allowed. The majority of patients had early-stage breast cancer; however, 13% of subjects had pN2 or pN3 disease. Systemic therapy was used in 99% of node-positive and 66% of node-negative subjects. Subjects were randomized to IM-MS RT (50 Gy in 25 fractions) or no IM-MS. IM-MS was delivered to the MS fossa and the IMN in the first three intercostal spaces and up to and including the first five intercostal spaces in patients with lower inner quadrant tumors. Dedicated full axillary irradiation was performed in 8.3% of the IM-MS group and 7.4% in the control group. Per the authors, the "operated part of the axilla was not irradiated unless adverse risk factors were present."[118] At 10 years, the IM-MS RT group had lower rate of any first recurrence (19.4% vs 22.9%, *P* = .02) and higher rates of distant DFS (78% vs 75%, *P* = .02). OS was 82.3% in the IM-MS irradiation group and 80.7% in the control groups (*P* = .06). As in the MA.20 trial, the EORTC trial demonstrated that IM-MS was beneficial for patients with node-positive disease with respect to breast cancer–specific outcomes, but the difference in OS at 10 years was small and did not reach statistical significance. The rate of lung fibrosis was higher in the IM-MS group (4.4% vs 1.7%, *P* < .001), whereas the rate of cardiac disease was comparable in the two groups (6.5% vs 5.6%, *P* = .25).[118]

After publication of the MA.20 and the EORTC 22922, Budach et al[120] performed a meta-analysis that included these two trials. RNI of the IMN and supraclavicular

nodes/upper axilla as delivered in the MA.20 and EORTC trials was associated with significant improvement in DFS (hazard ratio 0.86; 95% CI, 0.78-0.95), distant DFS (hazard ratio 0.84; 95% CI, 0.75-0.94), and OS (hazard ratio 0.88; 95% CI, 0.78-0.99).

The 15-year follow-up of EORTC 22922 was recently published in 2020.[119] While any breast cancer recurrence (24.5% vs 27.1%, *P* =.02) and breast cancer mortality (16.0% vs 19.8%, *P* =.0055) were significantly decreased in the IM-MS RT group compared to the control group, there was no significant difference in OS (73.1% vs 70.9%, *P* =.36), DFS (60.8% vs 59.9%, *P* =.18), and metastasis-free survival (70.0% vs 68.2%, *P* = .18). There was an imbalance in missing data regarding the cause of death and non-breast cancer–related deaths in the treatment arm that may play a role in the lack of OS difference. Of note, death from cardiovascular disease was the same (1.4%) in both arms.[119] As most patients in the trial had early-stage disease, it is unclear if outcomes would have been different with a higher risk cohort.

In summary, the meta-analyses and randomized PMRT trials with 15- to 20-year follow-up and the more recent trials of RNI after BCS or mastectomy with 10-year follow-up have advanced our insight into the role of RT in the management of patients with operable breast cancer with involved axillary nodes. Although LABC is a heterogeneous entity, consistent improvements in outcomes reported across these trials support the use of locoregional RT as a component of management for these patients, a population with high risks of LRR and distant recurrence. When used in conjunction with systemic therapy, RT can optimize locoregional and distant disease control, reduce the morbidity of uncontrolled cancer progression, and provide incremental improvements in survival. That said, it is not clear if these results will persist into the modern era of more effective systemic therapy.

Internal Mammary Nodal Irradiation

There has been controversy regarding indications for specifically targeting of the IMN. Historically, studies of extended radical mastectomy have identified IMN metastases in a significant proportion of patients with LABC, particularly in association with extensive nodal disease and central or medial tumor location.[121] An older, large multicenter trial that randomized patients to radical mastectomy versus extended radical mastectomy with surgical removal of the IMN was not found to improve survival or recurrence outcomes,[122] and isolated IMN recurrences are rare at approximately 0.1%.[123] While patients with clinically or pathologically involved IM LNs clearly warrant RT targeting the IMN, the role of IMN-directed therapy in patients without evident IM nodal involvement has been less clear. It is noted that in all of the randomized trials that demonstrated benefits with RNI, the IMNs were routinely included in the target volume. Although the benefits observed with RNI in these trials may be attributed to the principle of radiation eradicating subclinical disease that may be a source for distant metastasis, it is not possible to assess how much of the benefits observed may be specifically attributed to IMN treatment. Several trials have sought to address this question.

The contribution of IMN-directed RT has been examined in several trials. A French multicenter prospective trial attempted to evaluate the impact of specific IMN targeting in patients undergoing total mastectomy and axillary dissection.[124] From 1991 to 1997, 1,334 patients with stages I to III disease were enrolled, at least 30% of whom had LABC. All subjects received radiation with two-dimensional (2D) planning to the chest wall, supraclavicular, and apical axillary nodes, with randomization to radiation to the IMN in the first five intercostal spaces to 50 Gy versus no IMN inclusion. Ten-year OS rates were 62.6% in the IMN-treated group and 59.3% in the control group, but this difference was not statistically significant ($P = .8$).[124] Although the trial attempted to address an important question, its design was limited. The sample size was calculated to detect a 10% difference in 10-year OS, an expectation inconsistent with the finding from the EBCTCG meta-analysis that the survival benefit with PMRT was approximately 4% to 5%.[114] The trial was, therefore, underpowered to detect a small survival difference. Other limitations include the use of 2D planning and limited information on late-term toxicity, further limiting the trial's applicability to modern practice. That said, there was no significant difference in late-term cardiac events between groups.[124]

The DBCG-IMN study, a prospective population-based cohort study with 3,089 patients with node-positive breast cancer, provides additional insight into the effect of IMN-directed RT.[125,126] Forty percent of patients had pN2-N3 disease (ie, LABC). In this study, all subjects received whole breast or chest wall irradiation plus RT to the supraclavicular, infraclavicular, and axillary level II and III nodes to 48 Gy in 24 fractions. Patients with right-sided disease were treated with IMN irradiation, and patients with left-sided disease were not. At a median follow-up of 14.8 years, statistically significant improvements in OS (absolute difference of 4.7%), distant recurrence-free survival, and BCSS were observed with IMN irradiation.[126] While subgroup analysis found a larger benefit for patients with higher risk cancers (≥4 involved LN, medial/central tumors), all subgroups benefited from IMN irradiation and the test for heterogeneity was not significant. Cardiac-specific mortality was not elevated in the IMN-treated group, and there were no statistical differences in risk of non-breast cancer death.[126] While the study was nonrandomized, the decision to treat was made based only on laterality, which provides a reasonable randomization framework with balanced characteristics between the two study groups.[125] It is important to consider that enrollment predated the use the taxane chemotherapy as standard adjuvant therapy; however, all pN2 and N3 patients received chemotherapy.[126]

The Korean Oncology Group (KROG) 08-06 study is a multicenter randomized phase III trial investigating the role of IMN irradiation in women with node-positive breast cancer after BCS or mastectomy and ALND with the primary end point of 7-year DFS.[127] Enrollment was 2008 to 2013, and patients who received neoadjuvant systemic therapy were excluded. A total of 735 patients were enrolled. Of the subjects, 58.6% had pN2-3 disease. All patients received whole breast/chest wall and supraclavicular nodal irradiation to 45 to 50.4 at 1.8 to 2 Gy using CT-based planning. Nearly all patients were treated with taxane-based chemotherapy. The 7-year DFS did not demonstrate a

significant difference between the two groups (81.9% without IMN irradiation and 85.3% with IMN irradiation, $P = .22$). There was also no significant difference in breast cancer mortality rates and distant metastasis-free survival. Ad hoc subgroup analysis showed significantly improved DFS (hazard ratio 0.42, 5% CI 0.22-0.82, $P = .008$), lower breast cancer mortality rates (10.2% vs 4.9%, $P = .04$), and distant metastases-free survival (hazard ratio 0.44, 95% CI 0.23-0.85, $P = .01$) with IMN irradiation for patients with mediocentral tumors. There was no significant difference in cardiac morbidity and a nonsignificant difference in radiation pneumonitis between the two study groups. There were no cases or grade 3 or higher radiation pneumonitis among all patients.[127]

While KROG 08-06 suggests that IMN irradiation should be abandoned, the study was highly underpowered to detect a 10% difference in DFS. It does, however, provide reassurance that pulmonary and cardiac toxicity is low with modern CT-based treatment planning. As mentioned, an unplanned subgroup analysis did show a benefit to IMN-directed irradiation in the setting of mediocentral tumors.[127]

Based on the inclusion of IMN irradiation in all major trials in support of RNI in the setting of node-positive disease following surgery, the compelling data from the DBCG-IMN trial, and the low levels of toxicity seen with modern treatment planning techniques in the KROG 08-06 trial, the IMN should be included in the treatment fields for most patients with LABC. That said, the decision to include IMN-directed therapy should be made on a case-by-case basis. There should be strong consideration for IMN-directed RT with higher risk disease (T4/IBC, N2/N3, higher grade, medially or centrally located tumor) balanced with the risk of cardiovascular and pulmonary toxicity as seen in the dose distribution after optimal RT plan design.

Omission of Regional Nodal Irradiation

The Canadian Center Trials Group (CCTG) MA.39 trial called TAILOR RT: A Randomized Trial of Regional Radiotherapy in Biomarker Low Risk Node Positive and T3N0 Breast Cancer is an example of investigation of de-escalation of RT based on biologic subtype and cancer genomics to provide personalized medicine.[128] This trial is investigating omission of RNI in women with pT3N0 or pT1-2N1a disease with nonmetastatic invasive breast cancer, ER-positive and Her2-negative status post-BCS, or mastectomy with axillary surgery demonstrating low- volume nodal disease (1-3 positive nodes with ALND or 1-2 positive nodes with SLNB) with a low-risk Oncotype DX Recurrence score of 25 or less who have not received neoadjuvant chemotherapy, although limited neoadjuvant ET is allowed. The Oncotype DX Recurrence score is a genetic assay that measures expression of 21 genes within the tumor and provides a score from 0 to 100 that is indicative of the risk of distant metastases in patients with early-stage HR-positive breast cancer who are taking tamoxifen.[129] Although there is some nuance, an Oncotype DX Recurrence score of 25 or less is predictive of a lower risk of distant metastasis and less benefit from chemotherapy. MA.39 randomizes patients to receive whole-breast irradiation (following BCS) or no RT (following mastectomy) on arm 1 or whole-breast/chest wall irradiation plus RNI (including the supraclavicular,

nondissected axillary, and IM LNs). The primary end point is breast cancer recurrence-free interval. This trial continues to accrue. While MA.39 is not applicable for patients with LABC (defined as stage III), it is noteworthy as it represents the future direction of our field.[128]

LOCOREGIONAL RADIATION THERAPY AFTER NEOADJUVANT CHEMOTHERAPY

Treatment with neoadjuvant chemotherapy (plus anti-HER2 agents and immunotherapy when appropriate) is well established and recommended for all patients with LABC. Neoadjuvant systemic therapy provides the potential for disease downgrading, which may allow for BCS and/or less extensive axillary surgery. As discussed previously, the use of neoadjuvant systemic can provide information on tumor response to chemotherapy, which provides valuable information that can affect subsequent systemic therapy treatment recommendations. Landmark trials and choice of systemic agents are discussed in detail in the section "Overview of Treatment Approaches." Data regarding the role of RT and treatment field design in the setting of neoadjuvant systemic therapy are limited.

Retrospective Data of Local-Regional Recurrence Following Neoadjuvant Chemotherapy and Mastectomy With or Without Postmastectomy Radiation Therapy From MD Anderson

MD Anderson has published several retrospective studies regarding outcomes for patients who have undergone neoadjuvant chemotherapy. In these series, locoregional RT encompassed the chest wall, IMN, and undissected lymphatics in the supraclavicular and axillary regions.

In one series, Huang et al[130] retrospectively compared 542 patients treated with neoadjuvant chemotherapy and mastectomy with PMRT to 134 patients treated with neoadjuvant chemotherapy and mastectomy without PMRT. At 10 years, PMRT was associated with reduced LRR (11% vs 22%, $P = .0001$). Of note, the patients who received RT had statistically significant higher risk disease in regard to upfront clinical stage, response to neoadjuvant chemotherapy, number of pathologically positive nodes, and margin status. Patients with clinical stages III to IV disease and pCR who received PMRT had lower rates of LRR at 10 years compared to counterparts who did not receive PMRT (3% vs 33%, $P = .006$). (Stage IV patients had supraclavicular involvement as per AJCC staging 1988.) While there was no statistical difference in 10-year OS (54% with PMRT vs 47% without PMRT, $P = .063$) and cause-specific survival, on univariate analysis, there was a statistically significant OS benefit to PMRT for patients with clinical stage IIIB or higher (42% vs 20%), clinical T4 tumors (42% vs 20%), and more than four involved LNs at surgery (38% vs 15%, all $P < .0002$).[130]

McGuire et al[131] reported a series of 106 patients without IBC treated at MDACC who achieved pCR after NAC and mastectomy. Patients with stages I to II disease with pCR who were treated with PMRT did not experience LRR. The 10-year LRR rate among

patients with stage III disease who had pCR treated with PMRT was 7.3%, compared to 33% without PMRT (P = .04). These findings support the use of PMRT, even in the setting of a pCR. Patients with stage III disease also experienced significantly improved rates of distant metastasis-free survival, cause-specific survival, and OS (77.3% ± 6% vs 33.3% ± 14%, P = .0016).[131]

Despite selection biases inherent in retrospective studies, these contributions from MD Anderson were instructive in highlighting the finding that patients with locally advanced or T3N0 disease, despite having pCR to NAC, still have high LRR risk in the absence of PMRT. This supports the concept that PMRT decision-making must take prechemotherapy disease extent into strong consideration. In addition, PMRT was shown to have a survival benefit for patients with LABC following neoadjuvant chemotherapy and surgery. These studies indicate that PMRT has a very important role in the treatment paradigm for these patients.

NSABP B-18 and NSABP B-27 Combined Analysis of Recurrence Patterns After Neoadjuvant Chemotherapy and Mastectomy

Prospective data regarding RT for LABC in the setting of neoadjuvant chemotherapy and surgery for breast cancer are limited. As discussed previously, the NSABP B-18 and NSABP B-27 randomized trials investigated the use of neoadjuvant chemotherapy with AC alone or followed by neoadjuvant/adjuvant docetaxel.[22,132] These trials did not permit the use of chest wall/RNI after mastectomy or RNI after BCS. Trial participants had operable cT1-3N0-1 breast cancer. Patients with T4 or N2/3 disease were not included. Surgery included modified radical mastectomy or lumpectomy and ALND. In the combined analysis with 3,088 patients (1,947 mastectomy and 1,100 BCS), the 10-year cumulative incidence of LRR after mastectomy was 12.3% and 10.3% after breast-conserving therapy (8.1% local and 2.2% regional).[133] The 10-year LRR risks after neoadjuvant systemic therapy and mastectomy according to pretreatment clinical stage and postneoadjuvant chemotherapy pathologic response are summarized in Table 63.3. Among patients treated with mastectomy, independent predictors of LRR were clinical tumor size (>5 cm), clinically node-positive disease, and lack of pCR in the breast or nodes. In the setting of pathologic node-positive disease after NAC and mastectomy, LRR risks ranged between 11.2% and 22.5%, a risk magnitude at which locoregional RT should be considered. Interestingly, in patients with clinically node-positive disease before NAC but who achieved pCR at mastectomy, the LRR rate was 0% at 10 years, suggesting that this may be a favorable-risk subset in whom PMRT avoidance may be studied in a clinical trial setting. In patients with clinically node-positive disease treated with breast-conserving therapy who had pathologically involved LNs at surgery, the risk of regional nodal recurrence was approximately 7% to 9%, supporting consideration for RNI.[133] Although the NASBP combined analysis provided useful data from a large patient cohort documenting the 10-year LRR risks without adjuvant PMRT or post-BCS RNI after neoadjuvant systemic therapy, interpretation of these results in the modern context is

limited as the study was conducted before the era of more effective chemotherapy and targeted anti-HER2 therapy.

TABLE 63.3 SUMMARY OF RESULTS OF THE NSABP B-18 AND NSABP B-27 COMBINED ANALYSIS OF 10-YEAR RISK OF LOCOREGIONAL RECURRENCE AFTER NEOADJUVANT CHEMOTHERAPY IN PATIENTS TREATED WITH MASTECTOMY[133]

	ypN0; Breast pCR		ypN0; No Breast pCR		ypN+; Any Breast Response	
	N	10-y LRR (%)	*N*	10-y LRR (%)	*N*	10-y LRR (%)
≤5 cm; cN0	46	6.5	178	6.3	184	11.2
>5 cm; cN0	16	6.2	95	11.8	179	14.6
≤5 cm; cN+	21	0	37	10.8	143	17.0
>5 cm; cN+	11	0	33	9.2	128	22.5

cN0 or cN+, clinically node-negative or node-positive before neoadjuvant chemotherapy; pCR, pathologic complete response; ypN0 or ypN+, pathologically node-negative or node-positive after neoadjuvant chemotherapy.

Until additional data from more modern prospective trials become available, the outcomes derived from available institutional series and the NSABP B-18 and NSABP B-27 combined analysis[133] support the position that PMRT should be recommended after neoadjuvant chemotherapy and mastectomy and ALND for patients presenting with stage III disease. Off trial, PMRT including RNI to the undissected axilla, supraclavicular fossa, and IMNs is recommended even if the patient is rendered pathologically node negative after neoadjuvant systemic therapy.

Additional Studies Examining the Role of Radiation Therapy After Neoadjuvant Systemic Therapy

Since the publication of the combined analysis of the NSABP B-18 and NSABP B-27 trials,[133] other investigators have examined the impact of PMRT or post-BCS RNI in patients with clinically node-positive disease treated with neoadjuvant systemic therapy. In an analysis of 15,315 patients identified in the National Cancer Database with cT1-3cN1 disease, stratified into four subgroups by the type of surgery and pathologic nodal status after neoadjuvant chemotherapy (ypN0 vs ypN+), the use of PMRT was associated with improved OS for all pathologic nodal subgroups (ypN0, ypN1, and ypN2-3, all $P < .05$), whereas the addition of post-BCS RNI to breast RT was not associated with OS differences.[134]

Interesting reports have also emerged suggesting that molecular subtype correlates with recurrence rates. For example, investigators at *Memorial Sloan Kettering Cancer Center* retrospectively analyzed outcomes for 233 patients who received neoadjuvant systemic therapy, mastectomy, and PMRT between 2000 and 2009.[135] 74% of patients received trastuzumab. Following neoadjuvant systemic therapy, all patients underwent mastectomy and 99% of patients underwent ALND. The 5-year LRR rate was 0% for patients with

pCR compared to 9% without pCR (P = .05). A higher rate of LRR was associated with triple-negative disease (20%) compared to HER2-positive (6%, P = .005) and HR-positive disease (4%, P = .005). Pathologic node positivity was associated with a significant increase in LRR (hazard ratio 4.4, P = .003).[135] Investigators from MD Anderson also found that patients with triple-negative disease, clinical stage III disease, and failure to reach a pCR were associated with a higher rate of LRR. Of note, these patients received modern systemic therapy agents.[136]

Ultimately, prospective trial data are needed to address the role of locoregional RT after neoadjuvant systemic therapy and surgery. Two North American multicenter trials are underway for patients with biopsy-proven node-positive disease before neoadjuvant systemic therapy. The NRG Oncology Group 9353 (NSABP B-51/RTOG [Radiation Therapy Oncology Group] 1304) trial, initiated in 2013, randomizes patients with clinical T1-3, N1 breast cancer of all biologic subtypes (after fine-needle aspiration cytology or core biopsy confirmation of nodal involvement) who undergo neoadjuvant systemic therapy followed by mastectomy or BCS and axillary dissection or SLNB with two or more LNs removed and have pathologically negative nodes, to either no radiation or PMRT to the chest wall and regional nodes following mastectomy or radiation to the breast or breast plus RNI following BCS (ClinicalTrials.gov identifier NCT01872975).[137] This trial enrolls patients with all biologic subtypes. The Alliance for Clinical Trials in Oncology A011202 trial randomizes patients with a positive sentinel node biopsy after NAC to axillary dissection versus axillary RT without axillary surgery (ClinicalTrials.gov identifier NCT01901094). This trial is closed to accrual, and we are awaiting the results. These trials will provide valuable data to improve our understanding of the role of locoregional radiation after neoadjuvant chemotherapy for patients with limited node-positive disease. Unfortunately, randomized trials and prospective data in the setting of LABC are sparse.

Based on the abovementioned data, PMRT or whole-breast irradiation plus RNI is recommended in the setting of cT4 tumors, cN2-N3 disease, and pathologically involved LNs after neoadjuvant systemic therapy and surgery. Postsurgical RT decisions following neoadjuvant systemic therapy are generally made based on the maximum clinical stage prior to systemic therapy as well as pathologic stage at definitive surgery. Radiation field should encompass the breast or chest wall, the supraclavicular nodes, the IMNs, and the undissected axilla.[138]

RADIOTHERAPY PLANNING AND TECHNIQUES FOR LOCALLY ADVANCED BREAST CANCER

Most patients with LABC will receive RT in the postoperative setting on a linear accelerator (LINAC) with high energy photons and, at times, electrons, using 3D treatment planning with the goal of delivering the prescribed dose to the target volumes while sparing uninvolved tissues, especially the OARs including the heart, lungs, and contralateral breast. Treatment fields in the setting of LABC typically encompass the breast (after BCS) or chest wall (after mastectomy), the supraclavicular fossa, the

undissected axilla, and the IMN chain. Conformal 3D treatment planning and delivery are facilitated by tools such as CT simulators, computerized treatment planning software, and onboard imaging systems. It is now widely recognized that the techniques utilized in the early breast conservation therapy and PMRT trials using cobalt machines and older radiation delivery techniques unintentionally subjected patients to excessive doses to normal tissues with the associated risks of cardiovascular, pulmonary, and soft tissue complications including cardiac-related deaths (in left-sided treatment) and secondary malignancies. As evident in the evolution of trials in the setting of chest wall or whole-breast irradiation with RNI, the toxicity profile of RT to the breast/chest and regional nodes has markedly improved.

With improvements in treatment planning and delivery, the benefits of radiation for locoregional and disease-free outcomes for breast cancer after BCS and mastectomy have resulted in a small but significant survival benefit.[114,115,139-142] Though it is unlikely that modern radiation advances have improved the *absolute* magnitude of the benefits in locoregional control, these technological improvements have resulted in more precise and conformal treatment delivery that better spares normal tissue. In this context, improved techniques have the potential to significantly affect survival outcomes, by shifting the proportions in risks to benefits to ultimately achieve an improvement in the therapeutic ratio. This section examines the traditional tangential and more conformal radiation techniques for breast, chest wall, and RNI. We discuss considerations in target volume delineation, dose prescriptions, optimal dosimetry, and methods of delivery to maximize locoregional control and minimize toxicity.

Simulation

The first step in the treatment planning process is the virtual simulation, which is typically performed with a CT simulator. CT slice thicknesses of 2 to 3 mm should be used. It is important that the patient's treatment position is reproducible each day and that the patient remains immobile during the treatment. Immobilization devices including commonly utilized commercial supine breast boards or prone boards and/or customized molds or casts are used. The standard treatment position for a patient with LABC is supine with the ipsilateral or both arms positioned above the head but may be adjusted as needed for patient comfort, ensuring that the arm(s) do not intercept with treatment beams. It is important to have the soft tissues of the arm cranial to the junction of the tangent and supraclavicular fossa field. Raising the patient's chin and turning the head to the contralateral side can help flatten the skin folds within the supraclavicular fossa and displace the mandible and chin from the treatment fields. Patients are placed on a 10° to 15° angle board to flatten the slope of the chest wall in the region of the sternum. Radio-opaque wires are placed at the superior border (sternoclavicular junction and above palpable breast tissue), the inferior border (2 cm below the inframammary fold or best estimate using contralateral breast as guide if present), the medial border (mid-sternum), and the lateral border (midaxillary line) to use as guides when treatment planning. A radio-opaque wire is placed on the mastectomy scar to ensure that it is fully included in

the treatment fields. This will also be helpful if planning and setting up a mastectomy scar boost. Radiation oncologists at some institutions place a radio-opaque marker at any drain sites to ensure their inclusion in the treatment field, although data regarding isolated drain site recurrences in breast cancer are lacking. Figure 63.4 shows a patient undergoing CT simulation with radio-opaque wires at the superior border, lateral border, inferior border, medial border (not shown), and on the mastectomy scar, as well as two small wires placed on the drain sites.

FIGURE 63.4 Photograph of a patient undergoing computed tomography simulation. Radio-opaque wires are visible at the superior border, lateral border, inferior border, medial border (not shown), and on the mastectomy scar, as well as two small wires placed on the drain sites, to help guide treatment planning.

Target Volume Considerations

Treatment field design and target coverage are of the utmost importance in the treatment of patients with LABC. Based on the trials outlined earlier, treatment fields for these patients typically include the breast or chest wall, the SCVs, the undissected axilla, and the IMNs as these were target volumes included in the major studies in the setting of LABC/LNs-positive breast cancer outlined earlier that have found an LRR reduction and improved survival outcomes with the use of RT.

After mastectomy without RT, the most common site of locoregional relapse is the chest wall, occurring in more than 50% of patients who experienced LRR.[143-146] Another common site of LRR is the supraclavicular nodes and axillary apex, representing 20% to 40% of all LRR events.[143-146] Based on these relapse patterns, for patients with LABC who are candidates for locoregional RT, the target volume should encompass at a minimum the entire chest wall, supraclavicular nodes, and the axillary apex/level III, that is the undissected axilla. For patients who have undergone a level I and II ALND, the risk of recurrence in the inferior axilla is low. In an analysis of regional nodal failure patterns in 1,031 patients treated with mastectomy including level I to II axillary dissection and enrolled in five trials doxorubicin-based chemotherapy with no PMRT at MD Anderson,

Strom et al[146] reported that the 10-year rates of recurrence were 3% within the low-mid axilla. The risk of failure in the low-mid axilla was not significantly higher for patients with increasing numbers of involved nodes, percentage of involved nodes, nodal size, or gross extranodal extension. This was a high-risk population with more than 85% having at least one pathologically involved LN and more than 50% of patients with four than four involved nodes at surgery. These findings suggest that radiation targeting the dissected axilla may not be warranted for most patients, when balanced against increased risks of lymphedema and arm morbidity. That said, the risk versus benefit balance has shifted with the increased use of SLNB alone in the setting of LABC following neoadjuvant chemotherapy[56-58]; in this setting, the full axilla (levels I, II, and III) should be deemed target volumes. Following ALND, treatment coverage of the dissected axillary may be considered in certain higher risk situations such as IBC with pathologically involved axillary LNs after neoadjuvant systemic therapy; a large number of pathologically involved axillary LNs (often defined as ≥4 nodes), especially after neoadjuvant systemic therapy; an incomplete axillary dissection (often defined as <10 nodes dissected but varies by institution); a high nodal ratio of pathologically involved axillary nodes to dissected nodes (often defined as >20%); and extensive extranodal extension in the setting of other risk factors. As in all therapeutic decision-making for locoregional irradiation, the estimated risks of regional nodal recurrence and estimated benefits that axillary RT may provide should be carefully balanced against risks of adverse effects including lymphedema, chronic arm morbidity, and brachial plexopathy on a case-by-case basis and per institutional standards.

There are variations in physician judgment regarding which nodal basins require treatment (ie, supraclavicular, IM, axilla). Nevertheless, the vast majority of patients with LABC treated with either BCS or mastectomy have node-positive disease with high LRR risk, and therefore, the ipsilateral supraclavicular fossa and axillary apex (level III) are generally included in the treatment volume. The intentional inclusion of the dissected axilla and IMN is significantly more variable, and decisions regarding their inclusion require individualized consideration.[147,148] Typically, the volume for the IM vessels is within the first three intercostal interspaces, though the depth of the supraclavicular fossa and level III axilla varies greatly depending on individual anatomy and patient habitus. Inclusion of the intended nodal volumes in the clinical target volume (CTV) will ensure that these targets are adequately covered within the desired isodose volumes.

Target Volume Delineation

In the era of 3D treatment planning, consistent delineation of the breast, chest wall, regional LNs, and OAR is critical for accurate assessment of the dose distributions prior to approving a treatment plan. Inadequate delineation of target tissues and OAR can result in the misinterpretation of dose-volume histograms (DVHs) and ultimately influence treatment plan evaluation, which, in turn, may affect patient outcomes and toxicity.[149] The OAR include the heart, ipsilateral/contralateral lung, and contralateral breast as well as the ipsilateral brachial plexus, esophagus, thyroid, and spinal cord.

Significant variations have been reported in contoured volumes among radiation oncologists.[150,151] For example, the RTOG conducted an investigation of interobserver and inter-institutional variability in target and OAR delineation in the setting of breast cancer irradiation including the breast, boost volume, chest wall and all regional LN regions as well as the heart and lungs.[152] There was substantial variability seen with structure overlaps as low as 10% and volume variation as high as 60%. This led to meaningful differences in dosimetric planning and DVH results. To reduce these inconsistencies, several contouring guidelines have been published, with the goal of reducing variability in target delineation.[153-157] For example, the RTOG has established a breast cancer atlas based on target delineation of three illustrative patient cases performed by nine breast radiation oncologists and describes the general principles of contouring for CTVs of the breast, chest wall, axilla, supraclavicular fossa, and IMN regions (Table 63.4).[152,154] Similarly, the European Society Therapeutic Radiation Oncology (ESTRO) has developed a breast-contouring consensus for delineation of the CTV for the breast, chest wall, and regional LN basins, which additionally includes the interpectoral (Rotter) nodes and describes planning target volume (PTV).[153] In addition, the DBCG has published a national guideline and contouring atlas, which additionally provides recommended dose-volume constraints as depicted in Table 63.5.[155] More recently, the Radiotherapy Comparative Effectiveness (RADCOMP) was created for use in the RTOG 3509/3510 protocol that randomizes patients with nonmetastatic breast cancer receiving RNI to photon versus proton therapy.[157,158]

TABLE 63.4 RTOG CONSENSUS DEFINITIONS FOR BREAST CANCER TREATMENT PLANNING

	Breast/Chest Wall	Axilla			Supraclavicular Fossa	Internal Mammary Nodes
		I	II	III		
Cranial	Clinical reference + second rib insertion	Axillary vessels cross lateral edge of pectoralis minor muscle	Axillary vessels cross medial edge of pectoralis minor muscle	Pectoralis minor muscle insert on cricoid	Caudal to the cricoid cartilage	Superior aspect of the medial first rib
Caudal	Clinical reference + loss of CT apparent breast	Pectoralis major muscle insert into ribs	Axillary vessels cross lateral edge of pectoralis minor muscle	Axillary vessels cross medial edge of pectoralis minor muscle	Junction of brachiocephalic-axillary veins/caudal edge clavicle head	Cranial aspect of the fourth rib

	Breast/Chest Wall	Axilla			Supraclavicular Fossa	Internal Mammary Nodes
		I	II	III		
Lateral	Clinical reference/mid Axillary line, excludes latissimus dorsi muscle	Medial border of latissimus dorsi muscle	Lateral border of pectoralis minor muscle	Medial border of pectoralis minor muscle	Caudal: junction first rib, clavicle Cranial: lateral edge of SCM muscle	Encompass the IM/thoracic vessels
Medial	Sternal-rib junction	Lateral border of pectoralis minor muscle	Medial border of pectoralis minor muscle	Thoracic inlet	Excludes thyroid and trachea	Encompass the IM/thoracic vessels
Posterior	Br: excludes pectoralis muscles, chest wall muscles, ribs CW: includes ribs, pectoralis muscles, pleural interface. ribs, chest muscles	Anterior surface of subscapularis muscle	Ribs and intercostal muscles	Ribs and intercostal muscles	Anterior aspect of the scalene muscle	Encompass the IM/thoracic vessels
Anterior	Skin	Plane defined by anterior surface of pectoralis major muscle and lateral dorsi muscle	Anterior surface pectoralis minor muscle	Posterior surface of the pectoralis major muscle	SCM muscle	Encompass the IM/thoracic vessels

CT, computed tomography; IM, internal mammary; SCM, sternocleidomastoid.
Table adapted from online version of the 'Breast Cancer Atlas for Radiation Therapy Planning: Consensus Definitions" https://www.srobf.cz/downloads/cilove-objemy/breastcanceratlas.pdf. Reproduced with permission of RTOG (Radiation Therapy Oncology Group).

TABLE 63.5 EXAMPLE OF DOSE-VOLUME CONSTRAINTS AS RECOMMENDED BY DANISH BREAST CANCER COOPERATIVE GROUP

Organ at Risk	Danish Guideline Dosimetric Parameter
Heart	LAD $V_{20\ Gy}$ = 0% $V_{20\ Gy}$ = 10% $V_{40\ Gy}$ = 5%
Ipsilateral lung	$V_{20\ Gy}$ = 25% (no SCNI) $V_{20\ Gy}$ = 35% (with SCNI)

Organ at Risk	Danish Guideline Dosimetric Parameter
Spinal cord	Max 45 Gy
Brachial plexus	Max 54 Gy
CTV	CTV_{max}: $V_{107\%}$ = 53.5 Gy
PTV	Max dose outside PTV = 54 Gy

CTV, clinical target volume; LAD, left anterior descending artery; PTV, planning target volume; SCNI, supraclavicular nodal irradiation.

Reprinted with permission from Nielsen MH, Berg M, Pedersen AN, et al. Delineation of target volumes and organs at risk in adjuvant radiotherapy of early breast cancer: national guidelines and contouring atlas by the Danish Breast Cancer Cooperative Group. *Acta Oncol*. 2013;52(4):703-710.

Typically, in early-stage patients, the pectoralis muscle, chest wall muscles, and ribs may be excluded when contouring the breast; but for locally advanced cases, the chest wall and ribs should be included in both the breast conservation and mastectomy setting.[154] In the case of LABC, it is important to note that the abovementioned guidelines can be used as a starting point for contouring but require individual adaptation based on the extent of the primary tumor and the LN involvement. An evaluation of the RTOG Breast Cancer Atlas in the setting of LABC analyzed the validity of the atlas for patients with initial axillary nodal involvement who underwent neoadjuvant chemotherapy.[159] Of the 30 patients included in the study, 100%, 93%, and 37% had clinical involvement of axillary levels I, II, and III, respectively. In 97% of the patients, part of an involved LN was located outside the recommended anatomic borders of the axillary levels. In over 80% of patients, tumor extension was seen outside at least one of the borders of level I, ranging from 0.24 to 3.58 cm. In 80% of patients, tumor extension was seen outside the caudal border of level II (1.36 ± 1.0 cm, range, 0.27-3.86 cm), The authors state the RTOG guidelines may not sufficiently cover the axilla in patients with cN+ disease who have undergone neoadjuvant systemic therapy and incomplete axillary dissection and/or will be treated with intensity-modulated radiation therapy (IMRT). Fusion of pretreatment imaging within the treatment planning system to guide contouring and planning is recommended in these settings.[159]

The differences between the RTOG, ESTRO, and RADCOMP atlases are thoroughly described in a manuscript by Logandale et al[158] from the international TransAtlantic Radiation Oncology Network. Three main differences in regard to nodal CTVs were seen between the atlases. First, the cranial border for the supraclavicular CTV was higher for the RTOG/RADCOMP atlases, with the border at the cricoid cartilage, compared to the ESTRO atlas, with the border at the subclavian artery. Next, the posterior neck is given as an optional volume to extend supraclavicular coverage in the RADCOMP atlas. Third, to create the IMN CTV, the ESTRO and RADCOMP atlases have additional margins around the IM vessels while the RTOG CTV consists of only the IM vessels.[154,155,157,158] For patients with more advanced disease (T3-4, N2-3) or who have undergone neoadjuvant treatment, the authors recommend using the RTOG for all target volumes, except for the

IMN, which will get better coverage following the guidelines from ESTRO or RADCOMP.[158]

Ultimately, there are variations in philosophies regarding the target volumes requiring irradiation and the contouring of these volumes for LABC. Often, they are based on specific clinical/pathologic details of an individual case and patient anatomy but can be influenced also by the treating physician's opinions regarding these issues and policies of the treating institution. In the modern era, it is expected that breast/chest wall and nodal target volumes will be contoured to allow for optimal plan design and evaluation of coverage in the DVH.

Treatment Techniques

Various methods to incorporate the regional nodes in the locoregional treatment volume have been described. Older 2D tangential techniques have used bony and soft tissue landmarks to treat the entire breast or chest wall and typically only assessed the dose at the level of the isocenter. In contrast, 3D treatment planning uses CT imaging to delineate the volume and permits dosimetric and volumetric assessment at all levels above and below the central axis. Traditional 3D planning used wedges to attenuate the beam depending on the slope and thickness of the breast or chest wall to achieve a more uniform distribution and match anatomic contour using wedge-shaped pieces of metal in the head of the machine. Wedges have largely been replaced by 3D conformal radiation therapy (3DCRT) using a dynamic field-in-field technique to be discussed in detail in this chapter. When electron beams are used, such as for IMN treatment or delivery of a "boost" to the tumor bed after BCS or, in selected cases, the mastectomy scar, physical blocks made of Cerrobend or other material are placed in the path of beam in the machine head to deliver a more conformal electron beam dose.

Various forward and inverse planning solutions have been described to generate 3DCRT and IMRT plans that have been shown to significantly improve dose distribution over the standard wedge pair.[160,161] In addition, methods using a combination of both forward and inverse planning have been described and are termed *hybrid plans*.[162,163] Unlike other disease sites such as head and neck and prostate cancer where IMRT, by definition, is inverse planned, for breast treatment planning, the modulation of the tangential beams can be achieved with forward planning, inverse planning, or a combination of both. For this reason, the exact definitions of breast IMRT versus 3D treatment in breast cancer radiation treatment remain broad.[164]

Several forward-planned, "field-within-field" techniques have been described to deliver a more conformal dose by shaping the radiation beam and modulating high-dose regions.[165] Note that in some published investigations, this technique is referred to as "IMRT," although today it is considered a 3DCRT technique using subfields to obtain better dose homogeneity. Initially, the diverging posterior edges of the medial and lateral borders of the tangential beams are aligned to be nondivergent and the fields are weighted and optimized with adjustments to the beam depth, gantry angles, and collimator angles to minimize irradiation to OAR and ensure full coverage of the treatment volume, as in

traditional tangent 3D planning with wedges. Unlike a standard 3D treatment plan with wedges, forward-planned 3DCRT with the field-in-field technique has additional subfields with manually created apertures that are used to block specific hot spots in the original tangential fields. The dose distribution for these tangential fields is typically equally weighted, with open medial and lateral fields, and the normalization point is defined at approximately mid-depth and 1 to 1.5 cm superficial to the deep edge of the chest wall in the plane of the central axis of the beams. Next, the highest dose cloud of the more than 115% isodose curve volume is projected in the beam's-eye view of the treatment fields. A new segment is created using multileaf collimators (MLCs) onto the medial/lateral tangent fields to account for 15% of the dose. This process can then be repeated for the 110% dose cloud, the 107% dose cloud, and so on, typically requiring two to six additional subfields to optimize dose homogeneity, as shown in Figure 63.5.[164,166] When using forward planning techniques, modifications to the weighting of the subfields and mixing of 4 to 6 MV with higher energy photons should be manually adjusted to enhance dose homogeneity, particularly when the patient separation is large.[167] The criteria used for choosing the number of additional subfields are generally based on reducing maximum isodose volumes down to a goal of 107% of the prescription dose or until the PTV coverage starts to break up.

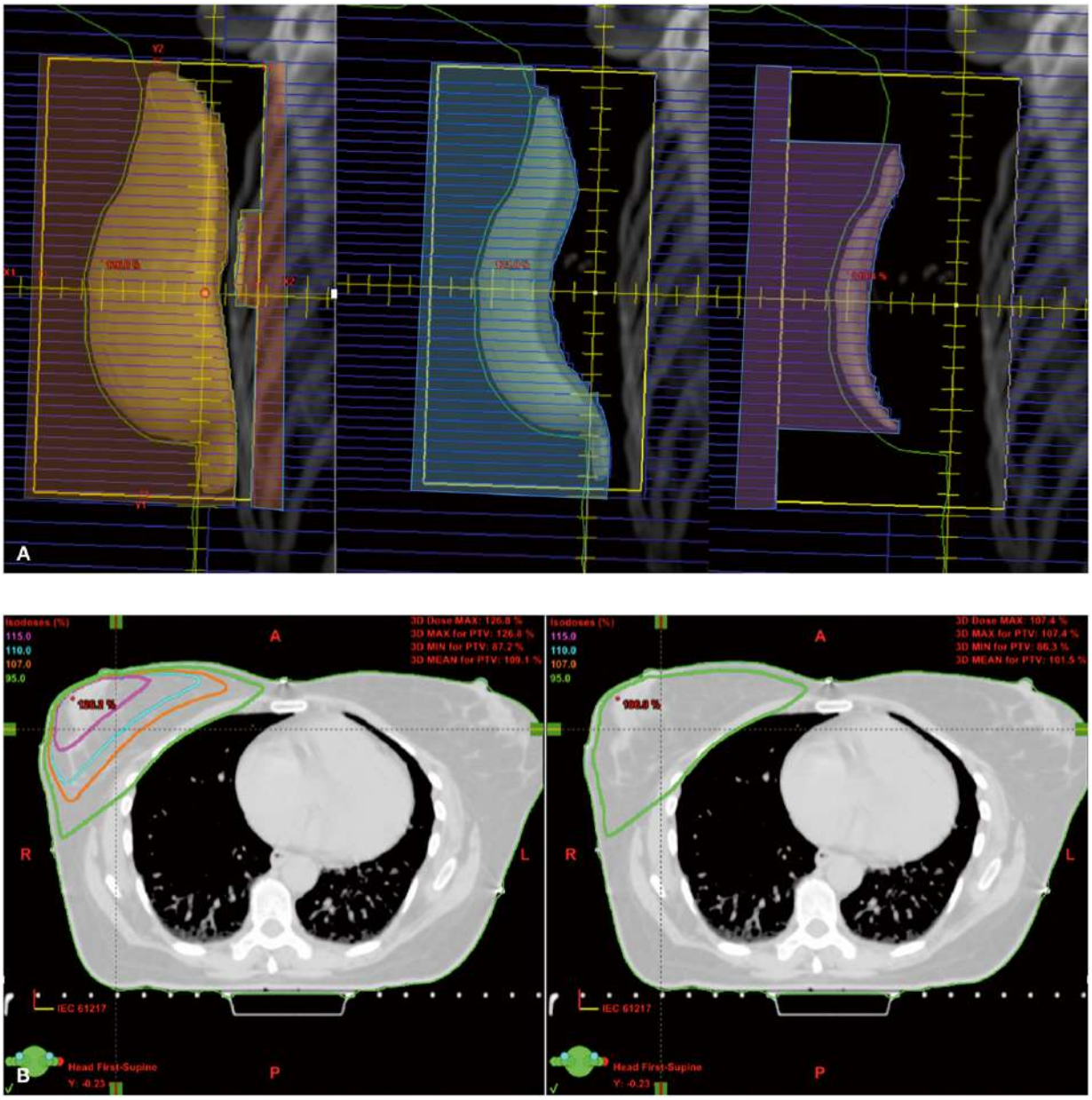

FIGURE 63.5 Field-in-field technique. A. Each segment is created as a subfield of the medial/lateral tangent fields blocking more than 115%, then more than 110%, then more than 107% dose cloud, so on. Typically, two to six additional subfields are used to optimize dose homogeneity. B. Treatment plan showing improvement in dose homogeneity with the addition of subfields. (Courtesy of Gifty Arthur, BS, CMD, Yale New Haven Hospital, New Haven, CT.)

There are now computer programs that assist with field-in-field treatment planning, such as EZFluence (RADformation). Studies have found that EZFluence creates equivalent to improved plans with greater efficiency compared to manually designed field-in-field plans.[168,169] Regardless of the field-in-field technique that is used, a careful review of the treatment plan by the dosimetrist and by the radiation oncologist with attention to the number of subfields is required. Too many subfields can lead to a longer

time on the treatment table, which can lead to increased patient movement and make deep inspiration breath-hold (DIBH) more challenging for the patient. DIBH is discussed in more detail in the section "Cardiac Avoidance Techniques."

With fully inverse treatment planning, that is, IMRT, multisegment fields are created using inverse planning software that makes use of computer-generated intensity-modulated fields by adding dose to particular areas of the breast or chest wall using individually shaped beam portals (segments) that are coplanar to the tangential fields. The inverse-planned IMRT technique uses optimization algorithms to create fluence maps to shape dose distributions[170] and can be performed using a LINAC with either dynamic or static MLCs, arc therapy, or tomotherapy.[171,172] Similar orientations and angles used for forward planning are often used with inverse planning when the intent is to deliver a more homogeneous plan with less dose to the contralateral breast, although noncoplanar beams are often necessary to generate a more conformal treatment plan. The PTV is the same used for the 3D plans plus an extension into the air anteriorly of the chest of 1.5 cm to ensure appropriate opening of the MLC. The dose is prescribed to the PTV, and initial dose-volume constraints are provided. These automated priority-based computer algorithms deliver the prescribed dose to the predefined PTV volume while taking into consideration the relative prioritized dose constraints for normal tissues. Although the use of automated inverse software provides excellent homogeneity and normal tissue sparing, particularly for anatomically challenging cases, a more conformal plan typically requires rotational IMRT techniques (ie, volumetric-modulated arc therapy [VMAT]) or fixed-gantry IMRT techniques using multiple angles and noncoplanar beams, which result in larger volumes of normal tissue structures being exposed to low-dose radiation and potential increased risk of secondary malignancy.[173,174] In addition, due to this low-dose spread, there can be difficulty in achieving heart and lung constraints, particularly with the use of VMAT, which can lead to higher mean heart dose (MHD) and increased lung V_{5Gy}, lung V_{20Gy}, and mean lung doses.[175] IMRT and VMAT expose a larger amount of cardiac and pulmonary tissue to low radiation dose. In this setting, the best metrics to follow to limit potential cardiac and pulmonary toxicity are still being explored.[176] For these reasons, full inverse planning with IMRT/VMAT is generally reserved for more challenging cases. Figure 63.6 shows an example of an inverse-planned IMRT plan treating the chest wall and regional LNs in the postmastectomy setting.

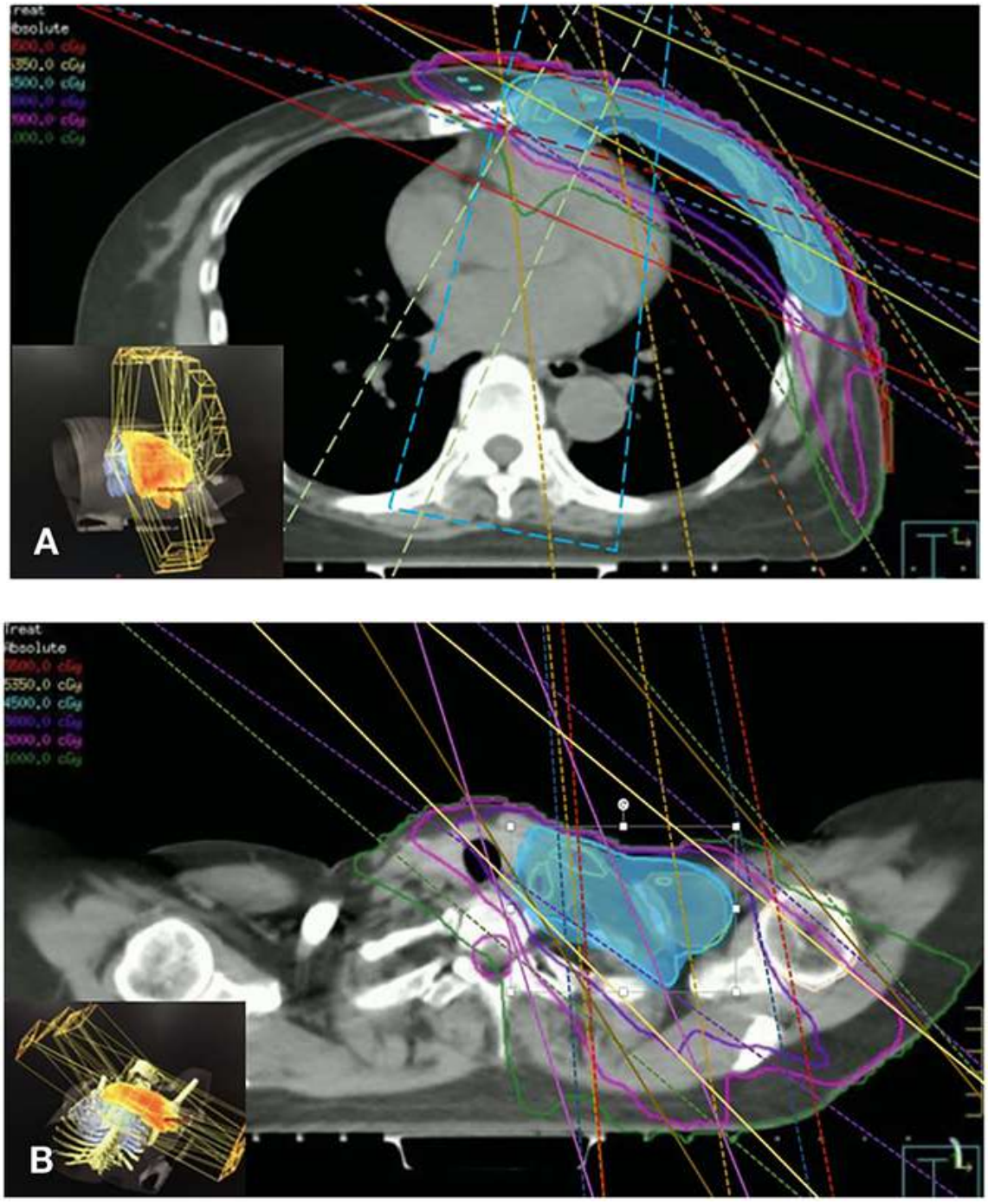

FIGURE 63.6 Inverse-planned intensity-modulated radiation therapy (IMRT) plan of postmastectomy and comprehensive regional nodal radiation. As depicted in *blue*, the prescribed dose is very conformal to the planning target volume, but multiple beams and beam angles are required, resulting in a greater volume of low-dose radiation to normal tissue structures. *Inset* depicts the multiple coplanar beams, resulting in exposure to contralateral and posterior normal tissue. A. Chest wall and internal mammary chain inverse IMRT plan. B. Supraclavicular, high axillary lymph node inverse IMRT plan.

As discussed in detail in Chapters 11 and 20, proton therapy can be more conformal than photon-based therapy techniques due to how protons deposit their dose at the Bragg

peak with a rapid dose fall off. There are limited data on the use of proton therapy in the treatment of breast cancer. Several dosimetric modeling studies have evaluated the potential benefit of decreased cardiac toxicity with proton therapy. For example, one study of 41 patients undergoing breast and RNI in Europe created optimized proton and photon plans for comparative analysis of potential cardiotoxicity using the model put forth by Darby et al.[177,178] Excess absolute risk of cardiac morbidity was small in both groups with median values of 1.0% (range 0.2%-2.9%) and 0.5% (range 0.03%-1.0%) for those with and without cardiac risk factors treated with photons compared to 0.13% (range 0.02%-0.05%) and 0.06% (range 0.004%-0.3%) with for patients with and without cardiac risk factors treatment with protons. The authors conclude that for an individual patient, proton therapy can decrease the risk of cardiac toxicity by up to 2.9%.[177] A prospective phase II study at Massachusetts General Hospital (MGH) enrolled 70 patients who were deemed suboptimal candidates for photon treatment to the breast/chest wall and regional nodes for treatment with photon therapy.[179] In all, 36% of patients had stage III disease. The 5-year LRR rate was 1.5% and OS was 91%. There were no grade 4 or 5 toxicities. In addition, 83% developed grade 2 skin toxicity, and one patient developed grade 2 radiation pneumonitis. Of note, 7% of patients developed rib fracture, which is higher than the reported risk in the modern literature with photon therapy of less than 2%.[180-182]

Although proton therapy has become more widely available in North America over the past decade, the number of centers remains limited requiring many patients to travel and to arrange accommodations to receive treatment.[183] In addition, it is more expensive than photon therapy, and due to a lack of data demonstrating a DFS and OS advantage, insurance coverage may be lacking for certain patients. That said, with its unique dose distribution, proton therapy holds promise in the treatment of LABC with potentially improved dose homogeneity and decreased dose to the cardiac structures and the ipsilateral lung. The results from MGH were used a preliminary data for the RADOMP Consortium Trial (Pragmatic Randomized Trial of Proton Versus Photon Therapy for Patients with Nonmetastatic Breast Cancer: A Radiotherapy Comparative Effectiveness; ClinicalTrials.gov identifier: NCT02603341), a phase III trial comparing photon and proton RT that is currently enrolling patients.[179] This trial will provide valuable data regarding the potential benefits as well as the cost-effectiveness of proton therapy.

Photon 3DCRT with a field-in-field technique is currently the most commonly used treatment technique for RT planning in the setting of breast cancer. For the remainder of this chapter, unless specifically stated, it is assumed that a 3DCRT technique with field-in-field as appropriate is used within the tangent fields. Field-in-field technique can also be used in the supraclavicular field, which is discussed further in the next section.

Coverage of the Supraclavicular, Axillary, and Internal Mammary Lymph Nodes

Supraclavicular and Axillary Lymph Nodes

The SCV CTV should be contoured prior to field design. Treatment of the supraclavicular and superior node basins (III and sometimes level II if targeted) typically requires the addition of a third anterior-posterior (AP) field to deliver a dose to a depth that will adequately cover the supraclavicular and axillary regions. This anterior field is typically angled 10° to 20° to avoid the spinal cord and esophagus as seen in Figure 63.7. In all cases, it is important that the inferior border of the supraclavicular (with or without axilla) field be nondivergent to avoid overlap with the tangents. This can be accomplished using either independent collimator jaws or a half-beam block. A commonly used method is the single isocenter technique, in which the isocenter is identified on the axis conjoining the tangential fields and AP supraclavicular field. The supraclavicular field can have a half-beam block at the inferior aspect of the field. The tangents can be treated with a couch kick that eliminates divergence superiorly. With this technique, the inferior border of the supraclavicular field and the superior border of the tangent fields should match with essentially no overlap. Collimator rotation of the tangents should not be performed to prevent unnecessary overlap. MLCs can be used in lieu of a collimator to create blocking to conform to the slope and shape of the chest wall for the breast/chest wall tangents. Modern treatment planning software has built in features to help facilitate the match between the supraclavicular field(s) and the breast/chest wall tangents.

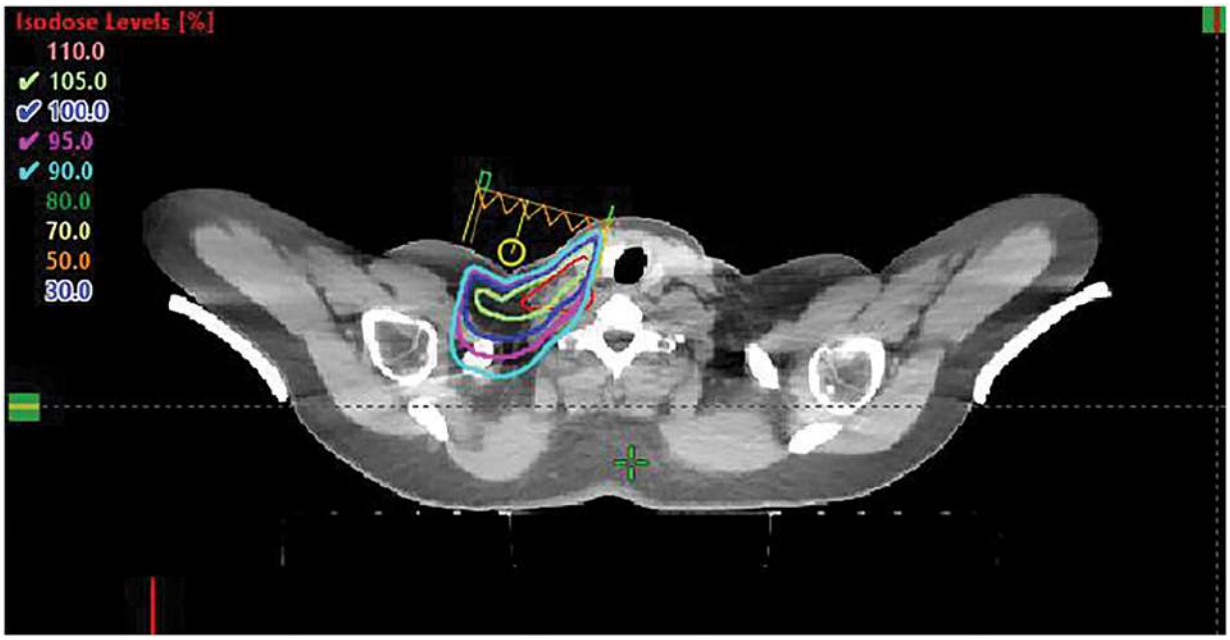

FIGURE 63.7 A left anterior oblique field designed to cover the supraclavicular and level III axillary lymph nodes. The supraclavicular lymph node region is drawn in red. Note that the beam is angled by 15° to avoid the thyroid, trachea, esophagus, and spinal cord.

When the depth of the superior axillary nodes that are included in the supraclavicular field is not adequately covered with the AP photon field, the use of higher photon energy or anterior-medial/posterior-lateral beam arrangement may be considered (ie, opposed

fields). More commonly, an additional posterior-anterior (PA) supplemental field, traditionally referred to as the posterior axillary boost, allows delivery of additional dose to the posterior aspect of the axillary target volume(s).

Axilla I is typically covered well by the tangent fields, although the most superior portion may overlap with the inferior aspect of the supraclavicular field. Axilla level II may be partially covered by the tangent fields and the matched supraclavicular field or be fully within the supraclavicular field (with the potential need of a posterior field to ensure full coverage of the most posterior aspect.) When treating the full axilla, the lateral axillary field border is opened to cover the region between the top of the tangent fields and the humeral head. The abovementioned treatment techniques to ensure coverage of the supraclavicular and designated axillary nodal targets are covered in more detail in the previous chapter.

More challenging is the coverage of the IMN, particularly in patients with left-sided disease, because the heart is located directly below the IMN and inevitably will receive more dose than when the IMNs are not covered. Several commonly described methods for IMN inclusion are described in the subsequent section.

Internal Mammary Lymph Nodes: Partially Wide Tangents

The widely used technique of partially wide tangents, that is, the use of modified tangent fields to include the IMN in the first through the third intercostal spaces while better sparing heart and lung, was described in a seminal publication by investigators from Duke in 1994.[184] This is particularly useful when DIBH techniques are available. The IMNs should be contoured to allow for proper field arrangement and to evaluate dose coverage. Three photon beams are used including the supraclavicular, wide medial and wide lateral tangential fields, with the isocenter at the inferior border of the supraclavicular photon beam. Overlapping the inferior supraclavicular field with the tangents is ensured without divergence using half-beam blocking and prohibiting collimator rotation. As earlier, in lieu of collimator rotation, MLCs can be used to allow the posterior aspect of the breast/chest wall beams to follow the chest wall at the rib cage so that the IMN, breast, and chest wall receive adequate dose while sparing normal lungs. The superior aspect of the medial border is extended onto the opposite breast/chest wall, to ensure that the ipsilateral IMNs are covered. When the wide tangents are arranged with optimized gantry angles and blocking with MLCs to minimize dose to heart and lung, this technique is termed *partially wide tangents*, as depicted in Figure 63.8. This technique avoids the issue of matching fields and, depending on the patient's anatomy, offers a preferred alternative to a separate IMN field in most patients. Care must be taken to ensure complete coverage of all target tissue and the entire chest wall and mastectomy scar in the inferior portion of the field, in the region of the block if a partially wide tangent is used.

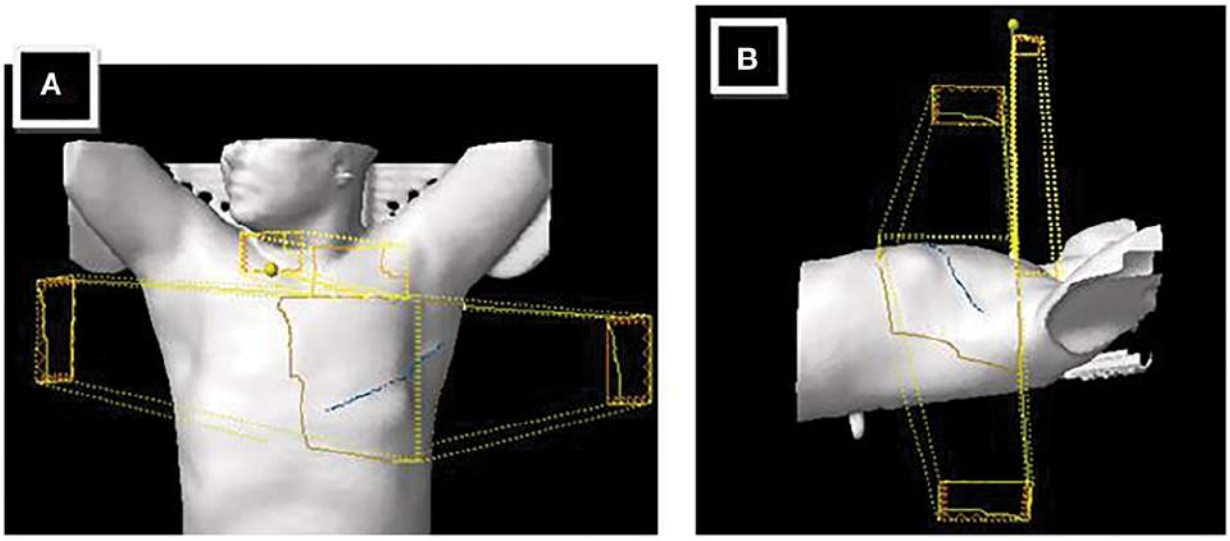

FIGURE 63.8 Skin renderings depicting the radiation therapy fields of a patient treated with postmastectomy radiation therapy using partially wide tangents. A. An anterior view that shows the widened tangents superiorly to cover the internal mammary node in the first three intercostal spaces with blocking inferiorly to better spare organ at risk. The tangent fields are nondivergent superiorly and are matched with the supraclavicular field. B. A left lateral view. The mastectomy scar is nicely included within the tangent fields.

Photon/Electron Matching Techniques

The use of an electron field to treat the IMN that is matched to the medial aspect of breast or chest wall tangents is an older technique that may be considered when attempts to encompass the IMN in partially wide tangential fields result in excessive heart and lung exposure and when DIBH techniques are not available or successful. The supraclavicular and tangential photon fields are created using the standard single isocenter, three-field technique described earlier. An IMN field using an electron beam is matched on the skin to the medial tangential field, with the medial tangential border moved laterally so that it does not include the IMN. Traditionally, IMN portals have been 5 to 6 cm in width, extending from midline medially, just below the clavicular head superiorly to include the first three intercostal spaces, with the inferior border at the fourth interspace, but should be tailored 3D based on the CT contour.[164] The electrons may be a combination of two electron beam energies, a higher energy superiorly to provide full coverage to the IM region at risk, whereas lower energy electron beams are used at the inferior portion to encompass the breast/chest wall while better sparing the underlying OAR. The electron IM field can be treated with either electrons alone or a combination of low energy photons and electrons, with a maximum of 50% of the dose being delivered by photons to minimize the dose to underlying heart and lung tissue. One technique is to tilt the gantry angle of the electron field 5° to 15° less than the medial tangent, minimizing the cold triangle just below the skin match of the two fields, and to feather this junction 1 to 3 times during the treatment course. Attempts to limit the cold triangle at the photon-electron match can lead to a hot spot at the match, as seen in Figure 63.9. This treatment technique leads to less homogeneous plans than the use of partially wide tangents and is

less commonly used in the modern era. That said, for certain patients, including patients with left-sided disease who are unable to perform DIBH, this technique may be helpful to decrease dose to the heart.

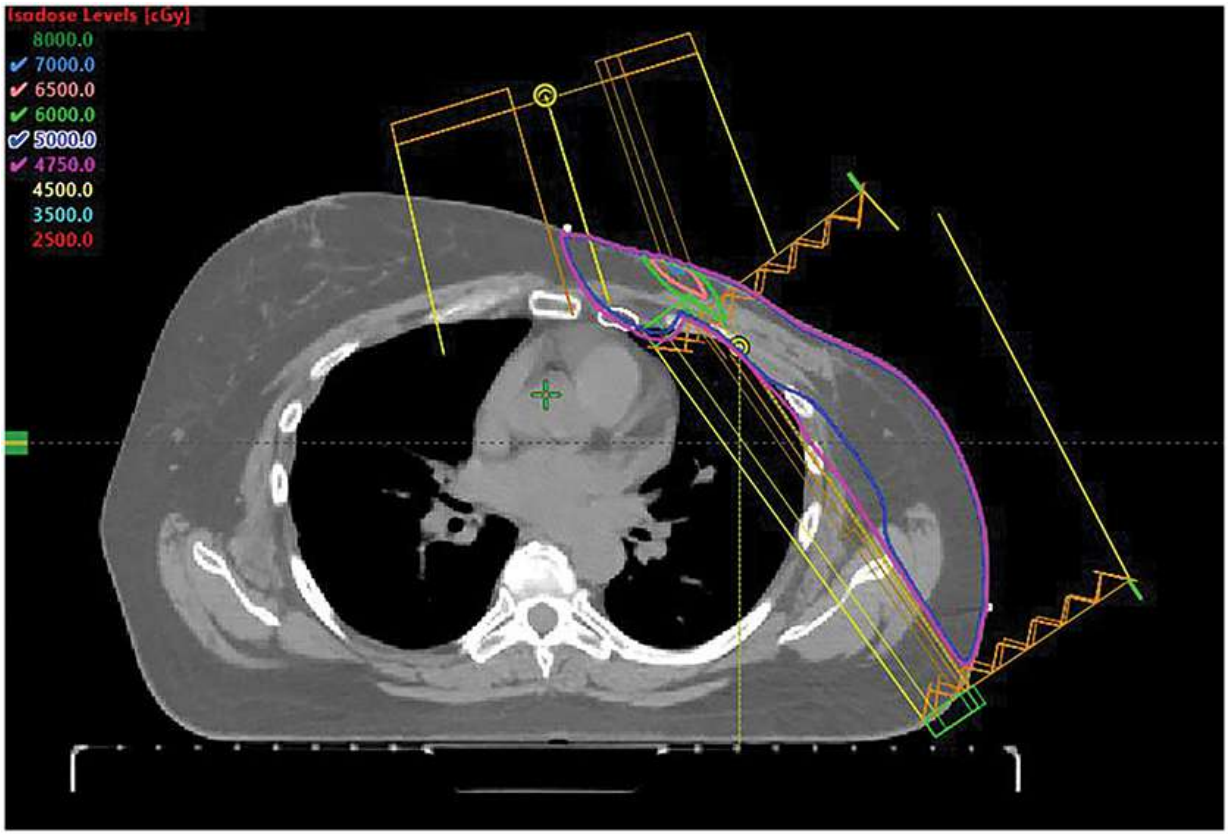

FIGURE 63.9 A radiation plan using a photon-electron matching technique to treat the internal mammary node (contoured in white, white arrow, partially obscured by isodose lines) and chest wall following mastectomy. There is a visible "hot spot" at the match line to avoid a cold triangle posteriorly. This junction was feathered twice during the treatment course.

Intensity-Modulated Radiation Therapy Inverse-Planned Internal Mammary Lymph Node Treatment

As discussed earlier, IMRT planning uses the contoured volumes to define the PTV. The treatment planning software uses a set of procedural guidelines to include specifications of the clinical planning goals to fulfill. Dose constraints for the OAR are prioritized, and the software program automatically generates an optimized treatment plan. Intended dose distributions for targets are achieved while reducing OAR doses with the use of MLCs (dynamic or static), arc therapy,[172] or tomotherapy.[171] Although the development of a plan that will meet heart and lung dose constraints is achievable with inverse-planned IMRT, this typically comes at the cost of spreading low-dose radiation to larger volumes of normal healthy tissue (see Figure 63.6).[173]

Dosimetry, Fractionation, and Dose

Fractionation Schemes

For treatment planning purposes, the breast/CTV volume is defined as clinically demarcated tissue at CT simulation, and the volume may be adjusted to include all glandular breast tissue visualized by CT. In patients with early-stage disease, the breast CTV is typically limited anteriorly to within 5 mm from the skin and excludes the chest wall. In patients with LABC, it is particularly important to contour volumes that correlate with the clinical presentation, pathology, and residual disease, if present when planning treatment. For advanced breast cancer and recurrent disease, it is important to remember that the target delineation guidelines can only be used as a starting point for contouring, but individual adaptation is essential to ensure coverage of all gross disease and tissues at risk.

The recommended dose prescription for whole-breast irradiation for most patients without RNI is 40 to 42.5 Gy in 15 to 16 fractions delivered 5 days per week, with a boost to the tumor bed of 10 to 12.5 Gy in 4 to 5 or 14 to 16 Gy in 7 to 8 fractions for higher risk patients.[185] There are additional fractionation schemes plus partial breast irradiation techniques for early-stage breast cancer that are discussed in the previous chapter. In the setting of LABC, with the addition of RNI, conventional fractionation remains the standard when treating the breast and regional nodes, that is 45 to 50.4 in 1.8 or 2 Gy fractions to all areas with tumor bed boost of 10 to 16 Gy in 5 to 8 fractions. In the postmastectomy setting, standard fractionation is also 45 to 50.5 Gy in 1.8 or 2 Gy fractions to the chest wall and regional nodal targets. A scar or chest wall boost of 10 to 16 Gy in 5 to 8 fractions may be considered. Figure 63.10 shows a postmastectomy scar boost field and dose distribution. The original ASCO postmastectomy guidelines state that there is insufficient evidence to recommend or suggest a scar boost.[186] There is a lack of prospective data regarding the use of a scar boost. One retrospective study of 140 patients who received PMRT to 50 to 50.4 Gy with or without a scar boost found that the use of a scar boost of 9 to 10 Gy was not associated with a statistically significant improvement in LRFS. Ninety four (67.1%) patients received a scar boost, and 46 (32.9%) did not.[187] Interestingly, the use of a scar boost decreased the absolute percentages of local recurrences at 5 years in the setting of high-risk features, including lymphovascular space invasion (LVSI) or positive margin (LRFS of 79.3% with scar boost and 71.1% without) and T3 or T4 tumor (LRFS of 80.9% with scar boost and 71.6% without); however, these differences were not found to be statistically significant.[187]

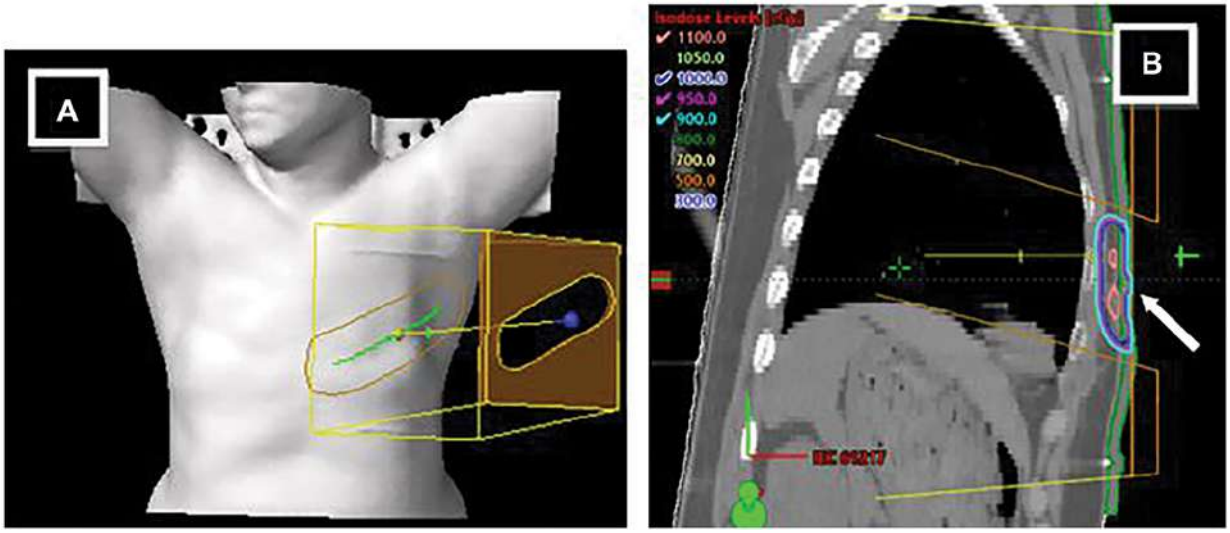

FIGURE 63.10 A. A skin rendering of a postmastectomy scar boost electron field. There is a virtual rendition of the physical electron block that shapes the beam. B. A sagittal view of the dose distribution of the scar boost electron plan. The wire over the scar is contoured in light green (white arrow). There is 0.5 cm of bolus used in this plan (dark green) to ensure adequate skin dose.

Another retrospective study of 746 patients who underwent mastectomy and breast reconstruction of various techniques (autologous reconstruction, single-stage direct-to-implant reconstruction, and two-stage expander implant) analyzed the rate of reconstruction complications including skin necrosis, fat necrosis, and infection in the patients who received a chest wall boost to those who did not.[188] At a median follow-up of 5.2 years, the patients who had chest wall boost had a significantly higher rate of skin necrosis (8% vs 3%, $P < .01$) and infection (13% vs 6%, $P < .01$). The increased risks to patients with implant-based reconstruction were striking. The rates of implant exposure (76% vs 1.76%, $P = .0025$), absolute reconstruction failure (10.18% vs 3.8%, $P < .01$), and overall implant failure with or without salvage reconstruction (34.5% vs 19.3%, $P < .0001$) were all statistically greater for the chest wall boost group. The use of chest wall boost was not found to be beneficial in regard to local recurrence, with a 10-year LRR of 5.4% in the no boost cohort and 4.3% in the boost cohort (nonsignificant). Subgroup analysis did not find an LRR benefit for patients with LVI, close or positive margins, partial response or tumor progression after neoadjuvant systemic therapy, T4 disease, or patients less than 40 years.[188]

In summary, for patients who have undergone mastectomy without reconstruction, a mastectomy scar boost encompassing 2 cm or more around the scar while remaining within the original field borders may be considered for patients with risk factors associated with an increased risk of local recurrence, such as a close or positive margin, epidermal invasion, T4 disease, extensive LVSI, and others. In the setting of IBC, which, by definition, includes the involvement of the dermal lymphatics, a generous scar/chest wall boost is typically given. A chest wall boost is often planned using electrons, although

tangent fields may also be used. In either case, bolus is usually employed. Caution is advised when considering the use of a scar boost in the setting of breast reconstruction.

While the use of hypofractionation to treat RNI is growing, it remains controversial.[189,190] There are limited phase III data regarding moderate hypofractionation treating the breast or chest wall without reconstruction plus the regional nodes. The START-A and START-B phase III randomized trials that investigated moderately hypofractionated RT to conventionally fractionated RT in the setting of BCS of mastectomy without immediate reconstruction for patients with pT1-3a, pN0-N1, M0 disease.[180] Both studies enrolled over 2,000 women. In all, 14% of patients in START-A and 7% in START-B received dedicated RT to the lymphatic regions. Also, 29% of patients in START-A and 23% of patients in START-B had positive axillary nodes. The control arm in both trials received 50 Gy in 25 fractions. The experimental arms in START-A received 41.6 or 39 Gy in 13 fractions over 5 weeks. The experimental arm in START-B received 40 Gy in 15 fractions. START-B included an optional 10-Gy boost in five fractions. AT 10 years, LRR, DFS, and OS were similar between all three arms on START-A. For START-B, the local recurrence rate was 5.2% in the conventionally fractionated arm and 3.8% in the hypofractionated arm ($P = .21$). There was a surprising increase in distant relapse (16.0% vs 12.3%, $P = .014$) and overall mortality (19.2% vs 15.9%, $P = .042$) in the 50-Gy (control) arm. An unplanned subgroup analysis supported the use of moderate hyperfractionation regardless of type of surgery and with inclusion of the regional lymphatics. In analysis of both studies, only one subject developed brachial plexopathy during the 10-year follow-up period. Ischemic heart disease was low (≤1.1%) in both trials.[180] In a detailed examination of arm and shoulder symptoms for patients on the START trials, there was no difference in physician-assessed arm shoulder symptoms between the control arm (50G) and the respective experimental arms (hypofractionated) in both the START-A and START-B trials.[191]

More recently, investigators in Beijing, China, randomized 820 patients with LABC (T3-4 or N2) who had mastectomy with ALND to receive either standard fractionation PMRT (50 Gy in 25 fractions) or hypofractionated PMRT (43.5 Gy in 16 fractions).[192] All patients received chemotherapy. Radiation treatment covered the unreconstructed chest wall, supraclavicular region, and level III axillary region; the level I to II axillary regions and the IMNs were not targeted. The chest wall was treated with 6 to 9 MeV electrons and a 5-mm tissue equivalent bolus. The supraclavicular region was predominantly treated using a 2D technique to a depth of 3 cm beneath the skin. After a median follow-up of 58.5 months, the 5-year cumulative LRR rates were 8.1% for conventional fractionation group and 8.3% for hypofractionation group, indicating the noninferiority of PMRT with hypofractionation ($P < .0001$ for noninferiority). Similarly, DFS and OS did not significantly differ between the arms, at 74% versus 70% and 84% versus 86%. There were no differences in toxicities, except that the hypofractionated patients had less grade 3 acute toxicity than the 50-Gy arm (3% vs 8%, $P < .0001$).[192] The START trials and the Beijing experience also offer data to support the use of moderate hypofractionation to the breast or nonreconstructed chest wall plus regional LNs.

The safety and efficiency of treatment to the IMNs is uncertain as the IMNs were not included in the Beijing trial, and the treatment to the regional lymphatics on the START trials is described as covering the axilla or supraclavicular fossa.[180,192] The FABREC trial, titled Study of Radiation Fractionation on Patient Outcomes After Breast REConstruction, seeks to address these questions. This multi-institutional trial randomizes mastectomy patients with immediate expander and implant placement for whom PMRT is recommended and determined to be medically necessary to the conventional RT arm (50 Gy in 25 fractions to the chest wall with or without IMN, 46-50 Gy in 2-Gy fractions to supraclavicular with or without axillary LNs) or the hypofractionation arm (2.66 Gy × 16 fractions to the chest wall with or without IMN and 2.66 Gy × 15 to the supraclavicular with or without axillary LNs). Patients with stages Tis-T3 and any *N* breast cancer were allowed. Patients with T4 cancers were excluded. Bolus was at the discretion of the treating physician. A boost was not allowed. The trial is closed to accrual. Five-year data were presented at the American Society of Radiation Oncology 2023 annual meeting.[193] At a median follow-up of 31.8 months, the number of distant (8 per arm), local (2 per arm), and regional recurrences (1 per arm) were the same in each arm. Chest wall toxicity was experienced by 19 patients in the hypofractionated arm and 16 patients in the conventionally fractionated arm ($P = .58$). Physical well-being scores were similar between arms, except that patients under 45 years of age were less bothered by side effects of treatment in the hypofractionated arm compared to the conventional fractionation arm ($P = .045$). Of note, people who took unpaid days from work reported requiring fewer hours of time off on the hypofractionated arm compared to the conventionally fractionated arm (73.7 vs 125.8 hours, $P = .046$).[193] These early results are promising; however, further follow-up is needed to more firmly establish the safety and efficacy of hypofractionated PMRT with IMN coverage and/or in the setting of implant-based reconstruction.

RT CHARM: Phase III Randomized Trial of Hypofractionated Post Mastectomy Radiation with Breast Reconstruction is an exciting trial exploring hypofractionated PMRT in the setting of all types of breast reconstruction (ClinicalTrials.gov NCT03414970). The trial closed to accrual in September 2021. The primary objective of the trial is to evaluate whether the reconstruction complication rate at 24 months is noninferior with hypofractionation compared to conventional fractionation. Secondary objectives include to evaluate acute and late-term complications, evaluate local recurrence rate and LRR, and compare complication rates based on the method (autologous with or without implant vs implant only) and timing (immediate vs intent for delayed). Mastectomy with nodal surgery of SLNB or ALND as appropriate is required. Reconstruction can include implant only before radiation, autologous reconstruction (with or without implant) prior to radiation, temporary expander with delayed implant reconstruction or autologous reconstruction, or mastectomy without tissue explained with delayed reconstruction to be performed after RT with implant or with autologous tissues with or without implants. Conventional fractionation PMRT is defined as 50 Gy in 2 Gy fractions to chest wall and/or reconstructed breast and regional nodes, to the undissected

axilla, supraclavicular fossa, and IMN. The hypofractionated PMRT arm received 42.56 Gy in 2.66 Gy fractions to the same target volumes. A boost is not allowed. Patients with T1-T3, N1-N2, M0 disease may enroll. If the patient's disease is converted to pathologically node negative by neoadjuvant chemotherapy, a pretreatment nodal biopsy confirming disease involvement is required. We are awaiting results from this very important trial.

The future direction of PMRT or intact breast irradiation with RNI is heading to even shorter fractionation schemes. The HYPORT-Adjuvant trial (ClinicalTrials.gov NCT03788213), Ontario Clinical Oncology Group Hypofractionated LocoREgional Radiotherapy in Breast Cancer (RHEAL) trial (ClinicalTrials.gov NCT04228991), and the FAST-Forward nodal study are prospective trials investigating the use of ultra hypofractionated radiation in five fractions versus moderate hypofractionation of 40 Gy in the setting of RNI. Information from these trials will provide valuable guidance for the treatment of LABC with RNI.

Radiation Treatment Plan Evaluation

Although standards for dose homogeneity vary across institutions, most 3DCRT planning techniques with inverse field-in-field or other dose modulation typically achieve a plan with a maximum dose of no more than 110% of the prescribed dose to the intact breast. Achieving this level of homogeneity in postmastectomy cases can be more challenging depending upon patient anatomy. In the supraclavicular and upper axillary targets, the "hot spot" is typically higher. With field-in-field, careful choice of beam energy and the selective use of a posterior axillary field, it is usually less than 115% unless there are anatomic challenges; for example, the SCV CTV is particularly deep (>3 cm). While target coverage goals vary by institution and per patient, a common planning criterion is to strive for at least 95% of the target volume (CTV or PTV) to be covered by at least 95% of the dose (ie, $V_{95\%} \geq 95\%$).

For all plans, DVHs of the PTV and OAR of the 3D/IMRT plans should be generated and compared. All attempts should be made to observe dose constraints for OAR, though these parameters vary depending on the volumes targeted and varying protocols. For example, the Danish Breast Cancer Guideline/Atlas suggests that the heart $V_{20\ Gy}$ should be less than 10%, heart $V_{40\ Gy}$ should be less than 5%, and the ipsilateral lung $V_{20\ Gy}$ should be less than 25% using tangents only and less than 35% when a third supraclavicular/axillary field is included[155] (Table 63.5). These dose constraints typically pertain to early-stage disease, and occasionally, despite the use of contemporary techniques in the PMRT setting, left-sided PMRT heart dose constraints may be difficult to meet. Bolus is a tissue equivalent material that increases skin and superficial dose by shifting the 95% isodose line more superficially to the skin and subcutaneous tissues.[194] In an international survey performed in 2004, the use of bolus with PMRT was found to be highly variable.[195] For example, 82% of respondents from the Americas, 31% from Europe, and 65% from Australia reported using bolus daily. There was variability in

application scheduled (33% used it daily, 46% used it alternate days) and thickness, with 35% using bolus of less than 1 cm thickness and 48% using bolus of 1 cm or higher.[195] An international consensus group of multidisciplinary experts in breast cancer initiated by ESTRO published a large systemic review regarding the use of bolus in PMRT.[194] Bolus use led to higher rates of acute grade 3 radiation dermatitis (9.6% with bolus and 1.2% without). Local recurrence rates were 3.5% with bolus and 3.6% without bolus.[194] In 2021, this expert panel published consensus recommendations in which the use of bolus was recommended only for selected cases.[196] The group recommended the use of bolus in cases of high risk of skin involvement/recurrence where the area of concern of not covered by the 95% to 100% isodose line. Indications for bolus include a positive anterior margin without removal of the overlying skin, IBC and preoperative skin involvement (T4b, T4c, and T4d tumors), chest wall recurrence, and in the setting of inoperable breast cancer or fungating mass. The thickness and shape of the bolus should be determined on a case-by-case basis. If the bolus is not found to conform adequately, a custom 3D printed bolus should be considered.[196]

While the expert panel recommended daily bolus,[196] the bolus thickness and schedule can be adjusted based on the dose distribution in the planning system and the level of risk of skin involvement or recurrence. In addition, this must be balanced against the risk of acute toxicity and the impact on the patient's reconstruction, if present. In a high-risk case, such as IBC, bolus should be used daily throughout treatment. The radiation oncologist will often remove the bolus once the skin reaction has become brisk with moist desquamation and discomfort (CTCAE grade 2 skin reaction).[197]

BREAST RADIOTHERAPY AND THE HEART

Cardiac Toxicity With Breast X-Ray Technique

It has been well documented that standard tangential RT fields used for breast cancer consequentially result in irradiation of cardiac tissues, particularly in women receiving left-sided RT, who have been demonstrated to have more cardiac exposure when comparing right-sided versus left-sided breast cancer patients receive RT.[198] It is now established that incidental dose to the heart results in coronary events, such as pericarditis, pericardial fibrosis, diffuse myocardial fibrosis, coronary artery disease, and, in more rare cases, valvular disease.[199] Although breast cancer–related cardiac toxicity typically takes a decade or more years to manifest, there is a dose gradient such that high-dose exposure above 30 Gy results in cardiac complications that become apparent within a year or 2 of exposure, with the risk of cardiac complications increasing with younger age of exposure and the presence of conventional risk factors.[199]

As a direct result of older techniques, cardiac exposure historically mitigated some of the benefits of adjuvant radiation, though more recently, with improvements in technology and treatment planning to sparing normal tissue, more recent meta-analyses in both the breast conservation and mastectomy setting demonstrate the ultimate benefits of radiation in reducing breast cancer–specific mortality.[28,139]

In 2013, Darby et al[178] published a population-based case-control study of women under 70 years of age who were treated with RT for breast cancer. The authors established a connection between the mean radiation dose to the heart (referred to as mean heart dose or MHD) and the likelihood of experiencing a cardiac event. Their findings indicated that in patients treated with pre-3D RT techniques, the RR of an acute ischemic event increased by 7.4% for each additional 1 Gy increase in MHD, without a defined safe threshold. This elevated risk emerged within the initial 5 years following RT and persisted for over 20 years post-treatment.[178] Nevertheless, the study did have certain limitations. As it was retrospective in nature, baseline cardiovascular risk was not available, real dosimetric data were lacking for all patients (MHD had to be estimated), and there were imbalances in comorbidities among the treatment groups. In 2017, van den Bogaard and colleagues validated Darby's model in a patient cohort treated with 3D RT, where actual dosimetric data were accessible. After a 9-year follow-up, they concluded that the cumulative incidence of coronary events increased by 16.5% per Gy of MHD.[200] These and other studies have demonstrated a correlation between MHD and radiation-induced cardiac toxicity and established the importance of reducing the MHD as much as possible in treatment planning. MHD is the most widely used dosimetric constraint used in radiation treatment planning for breast cancer.[176] In the modern era, a cardiac dose of an MHD less than 4 Gy has generally been considered an achievable standard to decrease the risk of radiation-induced heart disease from breast cancer RT.

Cardiac Avoidance Techniques

Efforts have been made to understand how radiation exposure to the cardiac substructures can affect the risk of ischemic and fibrotic heart disease. van den Bogaard et al found a correlation between MHD and adverse coronary events and conclude that the volume of the left ventricle receiving 5 Gy was the most predictive factor for risk.[200] Other investigators have found that strain reduction (change in myocardial fiber length over the cardiac cycle that is a measure of cardiac muscle function)[201] correlated to dose exposure of the left ventricle.[202,203] Marks et al found a greater incidence of new perfusion defects in patients with more than 5% of the left ventricle included in the radiation field.[204] Exposure of the left anterior descending artery to certain dose thresholds has been associated with increased serum levels of troponin-T during RT[205] and with coronary stenosis. There are no clearly defined dose constraints for the cardiac substructures in the treatment of breast cancer currently. While the German Society for Radiooncology has published recommended dose constraints for the left ventricle and the left anterior descending coronary artery,[206] they have not been globally adopted. That said, the importance of limiting cardiac exposure in RT planning is clear.

Heart Blocks

A heart block is one of the oldest and possibly the simplest methods for minimizing heart dose, though it is only technically possible in certain patients in whom the lumpectomy

cavity is readily identifiable to be remote from the heart block (Figure 63.11). The relationship between the tumor(s) to the chest wall is particularly important in the setting of oncoplastic reduction or any situation in which the lumpectomy cavity is ambiguous, to avoid placing the heart block in a location even remotely close to the original tumor(s). With selective and appropriate use of the heart block, the dose to the PTV has been shown to be reduced by only 2.8% and has been demonstrated to have no effect on compromising local control in appropriately selected patients.[207] A heart block is more commonly used when treating the intact breast as opposed to the chest wall.

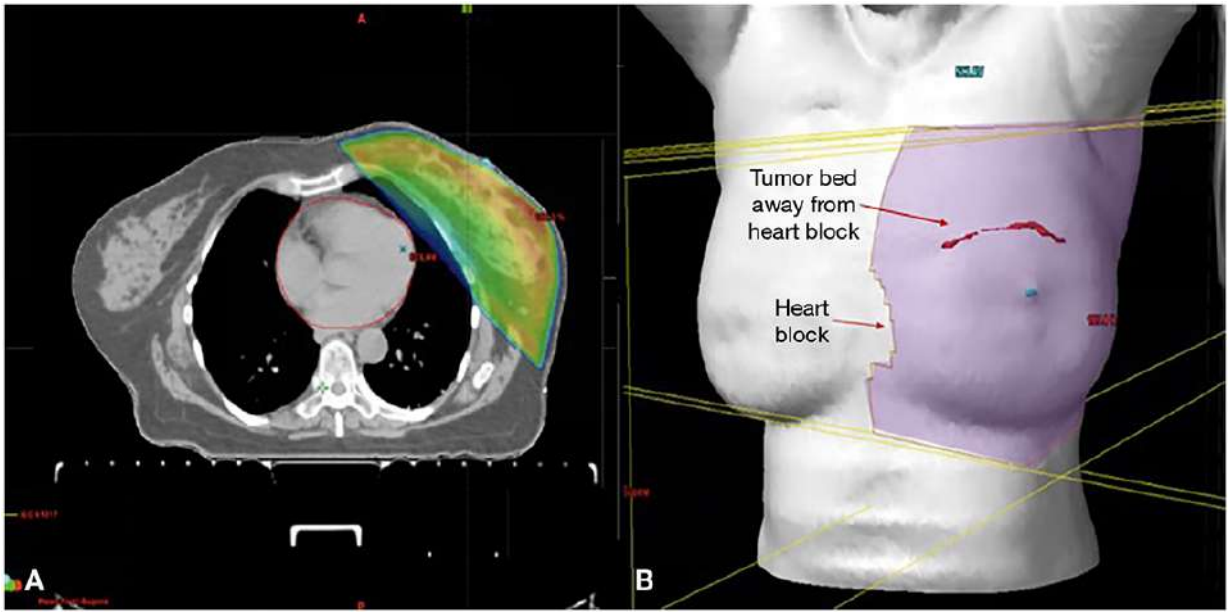

FIGURE 63.11 Multileaf collimators are used to block the heart from the direct beam in the treatment planning software and should be confirmed on the skin rendition clinically on the patient to verify that block placement is away from the tumor bed. A. Axial dose distribution at the level of the heart. B. Skin rendition showing that the heart block placement does not compromise coverage when limited to the cardiac silhouette and tumor bed is remote from the heart block.

Proton Therapy

As discussed in the section "Treatment Techniques," proton therapy is a promising technique for reduction of cardiac exposure during breast/chest wall irradiation, particularly in the setting of RNI. The RADCOMP trial, a prospective phase III randomized trial that randomizes patients to photon versus proton therapy, is currently accruing.

Deep Inspiration Breath-Hold/Respiratory Gating Method

There are several commercially available products for delivering radiation in patients with breast cancer, which synchronize the delivery of radiation with the respiratory cycle. This concept makes use of the normal physiologic inferior and posterior-medial movement of the heart relative to the chest wall when a patient takes (and holds) a deep breath and only

delivers radiation when the patient is in specified portions of the breath (or breath-hold) cycle. This, in turn, reduces the irradiated volume and the dose to the heart. Figure 63.12 shows an example of a DIBH setup that allowed for a meaningful reduction in exposure to the heart. Multiple studies have demonstrated a significant reduction in MHD with the use of DIBH for the treatment of the left-sided breast/chest wall with and without the inclusion of the regional nodes.[208,209] In one study, the percentage of patients with MHD less than 4 Gy went from 56% using the free-breathing scan to 100% using the DIBH scan for planning.[209] While the reductions in cardiac exposure are considerable in most patients with left-sided breast cancers, it is particularly notable that the benefits in decreasing cardiac dose with DIBH appear to be of greater magnitude in patients receiving PMRT, for which treatment planning to minimize cardiac dose can be more challenging because of the need to treat the much larger surgical bed including scars, compared to whole-breast irradiation following BCS.[210]

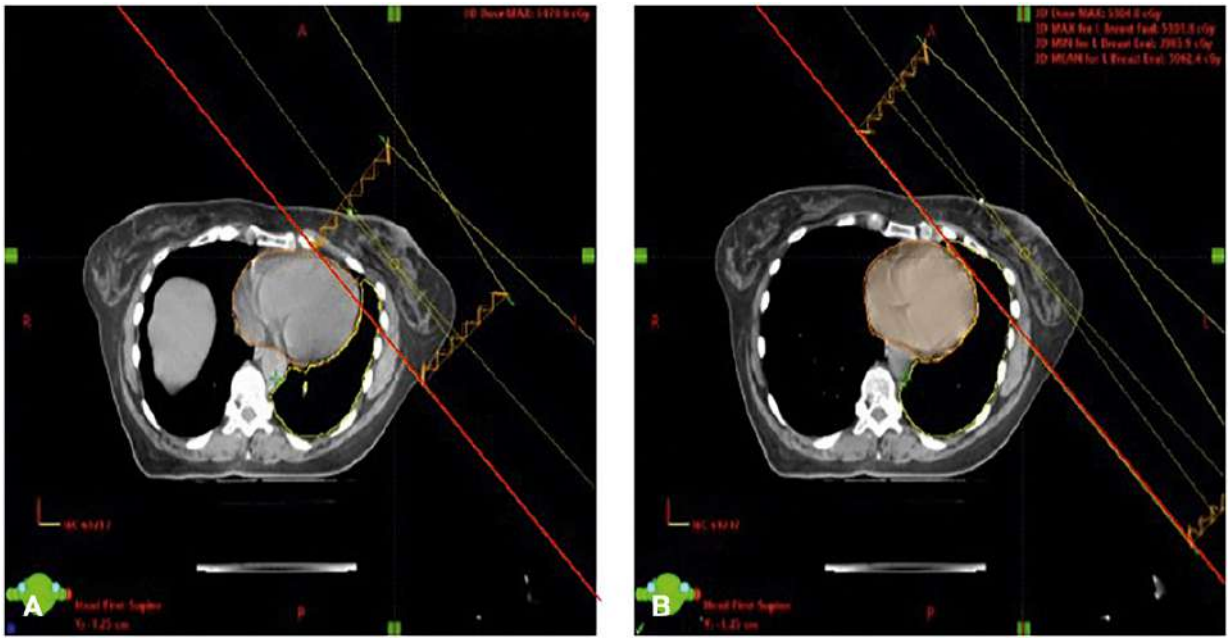

FIGURE 63.12 The use of deep inspiration breath-hold (DIBH) significantly reduces cardiac volume irradiated. A. Free-breathing scan showing tangential beams with a substantial portion of the left ventricle in the radiated field. B. DIBH scan—heart moves away from the chest wall with expansion of the diaphragm. Using the same clinical borders, the mean heart dose was reduced from 377 to 195 cGy (not shown).

The use of DIBH in right-sided breast cancer for the treatment of the breast/chest wall plus RNI has been studied. Investigators in Australia created optimized 3DCRT treatment plans using field-in-field for 10 patients with right whole-breast irradiation only and 10 patients with right whole-breast treatment plus RNI.[211] In the group receiving RNI, there was significant reduction in the right lung mean dose (18.9 ± 3.2 Gy vs 15.9 ± 2.3 Gy, P = .002) and V_{20Gy} (45.3 ± 13.3% vs 32.9 ± 9.4%, P = .03) as well as the maximum dose to the right coronary artery (11.6 ± 7.2 Gy vs 5.6 ± 2.9 Gy, P = .03).[211] A similar study for

right-sided patients at Yale University found a significant reduction in all lung and liver dose parameters with the use of DIBH.[212] The use of DIBH in the setting of RNI should be considered for better OAR sparing.

CONCLUSIONS RE: LOCALLY ADVANCED BREAST CANCER

Indications for RT have expanded with contemporary prospective trials and meta-analyses providing evidence-based data that RT reduces not only LRR but also distant recurrence and improves survival for women with breast cancer. In the setting of node-positive breast cancer, including LABC, locoregional treatment decision-making is complex and requires multidisciplinary assessment to generate individualized recommendations. With improved outcomes seen with multimodality therapy, systemic therapy, surgery, and RT will play a role in the treatment of most patients with LABC. A meticulous approach should include interdisciplinary input to coordinate systemic therapy, RT, surgery, and potentially reconstruction. Modern technological advances in radiation planning and delivery, using CT-based 3D treatment planning to minimize radiation to OAR and deliver a homogeneous treatment plan using techniques described in this chapter, will increase the potential for radiation oncologists to improve the therapeutic ratio for patients with breast cancer.

GENERAL MANAGEMENT AND TREATMENT RESULTS FOR LOCALLY OR REGIONALLY RECURRENT BREAST CANCER

Women who receive initial potentially curative therapy for invasive cancer with either breast conservation therapy or mastectomy are at risk of developing LRR. LRRs are relatively uncommon with recurrence rates at approximately 5% to 15% after mastectomy and breast conservation therapy, often in the original quadrant following BCS or at the chest wall scar following mastectomy, although the ipsilateral nodal regions are also at risk.[138,186] Patients may present clinically with a palpable mass or with findings on post-BCS surveillance imaging. Although still potentially curable, the development of an LRR after primary treatment of an invasive breast cancer portends a high risk for distant metastases and death because of breast cancer. Accordingly, patients should undergo disease restaging at the time of recurrence to rule out metastatic disease and should have a biopsy for histopathologic confirmation and reevaluation of HR and HER2 status. Given that LRRs are relatively uncommon and are heterogeneous in presentation and prior treatment, treatment strategies must be individualized.

Recurrence in the Breast After Breast Conservation Therapy

Local recurrences after breast conservation therapy can sometimes be distinguished from second primary cancers based on location, appearance on imaging, histologic subtype, and HR/HER2 status. Risk factors for local recurrence following BCS include positive margin, omission of RT, larger primary tumor size, younger age, and HR-negative disease.[213,214] Although much of the breast cancer literature does not clearly differentiate

between a new primary and recurrent cancer, it is important to try to identify true relapses from a new primary as this information has prognostic value and aides in treatment decision-making. The importance of this distinction was made evident with data from Yale University showing that compared with patients with new primaries, patients with true relapses have poorer 10-year OS (55% vs 75%; $P < .0001$) and distant DFS (41% vs 85%; $P < .0001$).[215] Subsequently, a retrospective series from MD Anderson of 126 patients suggested that patients with a new primary tumor had significantly better 10-year survival (77% vs 46%, $P = .0002$), cancer-specific survival (83% vs 49%, $P = .0001$), and distant DFS (77% vs 26%, $P < .0001$).[216] Both studies found that patients considered to have new primary tumors had significantly longer intervals between their initial primary tumor and the recurrence and had significantly lower rates of distant metastasis and death after the recurrence. These data were later validated in a study of 447 patients.[217] Patients with a triple-negative locally or regionally recurrent breast cancer have worse DFS, OS, and risk of a subsequent recurrence relative to other subtypes.[218,219]

Appropriate management for LRR after breast-conserving therapy depends on initial disease presentation and management. For an in-breast recurrence in the setting of prior BCS and RT, mastectomy is the standard salvage treatment and is associated with an approximately 80% or better local control rate depending on other prognostic factors of the disease; however, these patients are at high risk of distant metastases.[220-223] RT is usually not given following salvage mastectomy in the setting of prior RT; however, it may be considered in patients with positive nodes, tumors larger than 5 cm, or multiple adverse risk factors, particularly in patients in whom their initial radiation was many years prior to the recurrence.

As most patients treated with initial lumpectomy also receive breast irradiation, mastectomy is the generally preferred surgical approach to treat a local recurrence in the absence of metastatic disease, although repeat BCS with reirradiation can be considered. Some single-institutional studies have investigated repeat BCS with or without radiation. Salvadori et al[224] compared the outcome of 134 patients treated with mastectomy for a localized breast recurrence to 54 highly selected patients treated with a second BCS alone. They found that a second breast recurrence at 5 years was more common in the reexcision group (19% vs 4%). Interestingly, the rate of distant metastases was 47% after mastectomy compared to 20% after reexcision.[224] This may reflect the inherent biases in a nonrandomized trial. Ishitobi et al[225] also reported a relatively high rate (21.8%) of a second breast relapse at 40 months after local surgery only for recurrent disease. A disease-free interval of more than 2 years and ER-positive disease were associated with a significant reduction in the risk of a second IBTR.[225] Gentilini et al[226] examined outcomes for BCS alone after local recurrence and found that the 5 year risk of local recurrence in patients with IBTR of $\leq$2 cm and time to recurrence of $\leq$48 months was 15.2% compared to 31.2% for IBTR of less than 2 cm with time to recurrence of greater than 48 months. In addition, the rate of 5 year risk of local recurrence for IBTR of greater than 2 cm was 71.2%.[226] This suggests that the best candidates for second BCS may be those with small tumors and late recurrence.

A recent meta-analysis of 34 studies reporting on BCS with or without reirradiation in the setting of IBTR after initial lumpectomy and RT found that the 5-year OS and local control rates were 77% and 76% for repeat BCS alone and 87% and 89% for BCS plus reirradiation, respectively.[227] Among the included studies, grade 3 to 4 toxicity rates were 0% to 21% and cosmesis was unacceptable in 0% to 18% of the patients who underwent reirradiation.[227] The authors acknowledge that experience with giving a second course of RT following local resection of a breast recurrence is limited, with partial breast reirradiation preferred because of concerns for the morbidity of reirradiation to the whole breast. Updated results of RTOG 1014 at a median follow-up of 5.5 years are now available.[228] RTOG 1014 is a phase II trial of 55 patients who received external beam partial breast irradiation consisting of 1.5 Gy fractions delivered twice daily to 45Gy using a 3D conformal technique following repeat lumpectomy for in-breast recurrence. Of note, 40% of recurrent tumors were classified as noninvasive, 91% were 2 cm or smaller, 7% were HER2 positive, and 23% were triple negative. All patients had cN0 disease; 24% of patients underwent axillary surgery with pN0 disease. The range of time from initial radiation to recurrence was 1.6 to 27.7 years, with a median of 13.4 years. There were four repeat in-breast recurrences demonstrating a 5-year cumulative incidence of 5.2%. Four (7%) patients experienced grade 3 toxicity.[228] While longer follow-up and additional studies are warranted, these results indicate that for well-selected patients who are highly motived to undergo repeat BCS, this approach is reasonable.

Patients with recurrence in the breast or chest wall are also at risk for axillary metastases. No high-level evidence or consensus exists regarding the management of the axilla in this setting. Rates of positive nodes in the recurrent setting in older series where axillary dissection was standardly employed at initial diagnosis are approximately 25% but are as high as 50%.[229] In patients who have already had an axillary dissection at initial presentation, radiographic staging followed by surgical resection of gross axillary disease should be attempted if technically feasible. For patients who initially underwent sentinel LN surgery, ALND is recommended for most patients. Restaging with repeat sentinel node evaluation may be feasible, but its diagnostic accuracy and prognostic significance are unknown. A systemic review of 34 publications found that a repeat SLNB was successfully performed in 64.3% of patients (75.7% after prior SLNB and 46.1% after prior ALND).[230] Repeat SLNB can be considered in select patients with ALND performed if the SLNB is not successful.

There are no high-level data regarding radiation of the regional nodes in the setting of locally recurrent breast cancer with nodal involvement. In this setting, maximal debulking with surgical resection and/or systemic therapy is recommended to maximize local control. RT that targets the axillary and SCV nodal basins is ideally limited to patients who did not have prior RT to these areas. Reirradiation fields that include the axilla and/or the supraclavicular fossa should be approached with caution. Prior radiation records must be obtained to allow for reconstruction of the initial dose distribution. Consideration of DIBH and use of complex planning techniques such as electrons, IMRT, or protons to better spare the OAR are recommended, although often retreatment of the plexus cannot

be avoided when including SCVs. Great care must be taken to limit the cumulative maximum dose to the brachial plexus to decrease the risk of brachial plexopathy.[231]

Reconstructive surgery should be considered for patients treated with mastectomy, although previous history of breast radiation may limit the success of implant-based procedures. Historically, autologous tissue reconstruction has been favored. More recently, investigators from Memorial Sloan Kettering published a single surgeon's experience with immediate tissue expander followed by implant reconstruction in patients who underwent salvage mastectomy after prior BCS and radiation (121 patients) and patients who underwent primary mastectomy with the same reconstruction without a history of RT using a prospectively maintained database.[232] The early complication rate was higher in the irradiated group than in the nonirradiated group (29.7% vs 15.5%, $P < .001$), with the most common complication being flap necrosis. While over 95% of patients in both groups had a good or excellent aesthetic result, a proportionally greater number of patients in the nonirradiated group had excellent results ($P = .04$). In all, patient satisfaction was relatively high (84% in the previously irradiated group and 90% in the nonirradiated group), indicating that tissue expander followed by implant is reasonable in a properly consented patient undergoing salvage mastectomy after prior BCS and irradiation.[232] Researchers at the Cleveland Clinic performed a retrospective review of 103 patients with 107 reconstructions and analyzed outcomes for patients who underwent tissue expander/implant reconstruction and those who underwent autologous reconstruction following salvage mastectomy after local recurrence in the setting of prior BCS and radiation. Complications requiring reoperation and reconstruction failure were significantly greater in the tissue expander/implant-based reconstruction patients compared to the autologous reconstruction patients at 5 years (50.9% vs 25.5%; $P = .02$ and 42.1% vs 5.8%; $P < .001$).[233]

Locoregional Recurrence After Mastectomy

Recurrences after mastectomy tend to occur earlier and are more likely to be diagnosed on examination when compared to recurrences after breast-conserving therapy. The major risk factors for recurrence after mastectomy as initial therapy are the number of axillary LNs positive at surgery in addition to other poor prognostic factors, including younger age, higher grade histology, HR-negative disease, extracapsular extension, and LVI.[234-236]

Patients with recurrent disease after initial mastectomy may have a worse prognosis than those with recurrent disease after initial breast conservation therapy. In the Canadian and Danish postmastectomy radiation randomized control trials, patients who developed LRR had very high rates of subsequently developing metastatic disease.[110,143] In the Vancouver trial, of the 39 patients who developed an LRR, 37 eventually developed metastatic disease.[110] In the Danish trial, the 5-year rate of distant metastatic disease development after an isolated LRR was 73%. This rate was no different for those in whom disease recurred after mastectomy only versus those with recurrent disease after mastectomy and radiation,[143] though the ability to use radiation for combined modality

salvage therapy, especially in isolated chest wall recurrences, may lead to better outcomes.[237]

The general management strategy for an isolated LRR after mastectomy requires input from a multidisciplinary team. The initial evaluation should define the sites of disease involvement in order to determine whether the patient is able to undergo resection of all gross disease with negative surgical margins. Surgical therapy consisting of wide local excision and removal of involved axillary LNs is recommended for patients with resectable disease, provided surgery can be done with acceptable morbidity. If the patient had not previously been given RT, a standard approach would be comprehensive locoregional radiation with similar techniques used for newly diagnosed disease. An older study from Washington University found that patients with LRR who had RT to the chest wall and regional lymphatics had better outcomes than those in whom radiation fields were limited to the site of the recurrent disease, with 10-year freedom of chest wall recurrence of 63% in the patients who received larger field radiation versus 18% for patients who received small field radiation.[238]

Outcomes for patients with locally recurrent breast cancer have been found to be improved with the use of combined modality therapy. For example, a retrospective series of 115 patients with recurrence after mastectomy suggest that patients who receive combined modality therapy with wide local excision and RT plus systemic therapy have better DFS (52% vs 39%) and OS (63% vs 50%) compared to patients who get more limited treatment.[239] Patients presenting with bulky unresectable disease or who are poor surgical candidates should be considered for preoperative systemic therapy if active agents are available. If the disease responds favorably, some of these patients may become candidates for surgical resection, which then can be consolidated with comprehensive radiation. The prognosis for those with persistent gross disease is poor,[240] and radiation treatments alone are unlikely to render such patients free of disease. Nevertheless, aggressive locoregional radiation may be used to help stabilize the disease and to avoid the significant adverse consequences of uncontrolled growth of locoregional disease. For patients who have not had prior RT and do not have residual gross disease, treatment to the chest wall and draining lymphatics to a dose of 50 Gy followed by a boost to the site(s) of prior disease to 60 to 66 Gy are standardly used.[238,240] When treating unresectable gross disease with RT, concurrent systemic therapy, such as a taxane or capecitabine, can be considered.[241-243] In addition, in the setting of chest wall radiation or reirradiation for locally recurrent breast cancer, the use of hyperthermia may enhance the efficacy of RT.[244]

Few data are available to quantify the benefits of systemic therapy for patients with LRR, and decisions should be made on an individual basis according to the risk of metastatic disease, previous systemic treatments, and breast cancer subtype. The role of chemotherapy was studied in the phase III CALOR trial in which 162 patients with LRR after mastectomy or breast- conserving therapy were randomized to chemotherapy versus no chemotherapy.[245] At 9 years of follow-up, chemotherapy was associated with improved DFS in patients with ER-negative (70% vs 34%; hazard ratio = 0.29, 95% CI 0.13-0.67)

but not ER-positive disease (50% vs 59%; hazard ratio = 1.07, 95% CI 0.57-2.00). OS in the ER-negative group was 73% with chemotherapy versus 53% without (hazard ratio = 0.48, 95% CI 0.19-1.20) and in the ER-positive group 76% versus 66% (hazard ratio = 0.70, 95% CI 0.32-1.55). These data support the use of chemotherapy in the locoregionally recurrent setting for ER-negative disease. However, the trial was limited by its small size and relatively few events in the HR-positive group and thus firm conclusions regarding the role of chemotherapy in select HR-positive patients cannot be made. Patients who undergo chemotherapy in the locally recurrent setting should be given a standard adjuvant regimen, preferably with agents not previously received.

There are limited studies evaluating the use of ET in HR-positive locally recurrent disease. A randomized trial evaluated tamoxifen versus no systemic therapy after salvage local therapy for patients with recurrent disease after mastectomy found an improvement in 5-year DFS from 40% to 61% with the use of tamoxifen.[246]

Despite the lack of randomized data, given the effectiveness of ET in early- and late-stage HR-positive breast cancer and its relative lack of toxicities, all patients with a local recurrence should be treated with ET, usually with an agent different from what was previously used. Patients with HER2-positive locally recurrent disease should be offered HER2-directed therapy with a regimen different from what was previously received.

Several publications have provided insight into the factors of prognostic significance for patients with LRR after mastectomy. One of the largest series was an analysis of the 535 patients who developed a postmastectomy recurrence after treatment in the Danish 82b and 82c randomized trials.[143] In multivariable analyses, the investigators found the following factors to be associated with a poorer outcome at recurrence: large initial primary tumor, a high number of positive LNs, extracapsular extension, recurrence in the infraclavicular or supraclavicular regions, and a disease-free interval of less than 2 years.[143] Several other series have reported similar findings. Investigators from MD Anderson found that initial nodal status, time to recurrence, and ability to use radiation to treat the recurrence were all independent predictors of outcome for patients with a chest wall recurrence. The 19 patients in whom these three factors were favorable had a 5-year OS of 86%. The 5-year survival rate for the 89 patients who had one or two unfavorable features was 48%, and all 22 of the patients who had all three unfavorable factors died within 5 years of the recurrence.[237] In general, patients who present with an isolated chest wall recurrence more than 2 years out from treatment, particularly those with resectable disease and have not undergone radiation, have a greater probability of disease control and improved outcome.

UNIQUE PRESENTATIONS OF BREAST CANCER

Axillary Metastases With Unknown Primary

The presentation of metastatic disease within axillary LNs without an identifiable primary source is unusual, accounting for less than 1% of newly diagnosed breast cancer cases.[247,248] The initial workup for patients who present with axillary disease and an occult

primary is directed toward establishing if the axillary findings represent a regional metastasis from breast cancer or a distant metastasis from an unrelated site. As such, the initial evaluation should include a history and physical examination, routine serum studies, bilateral diagnostic mammography, and ipsilateral breast and axillary ultrasound. If no primary breast disease is detected with mammography and ultrasound, MRI of the bilateral breasts is indicated. Contrast-enhanced MRI can detect in-breast primary tumors in about 70% of patients with axillary metastasis and a mammographically occult breast tumor.[249,250] Cytologic confirmation of disease within axillary LNs must be obtained with ultrasound-guided core-needle biopsy or fine-needle aspiration. Core biopsy is preferred to better ensure that there is adequate tissue for full histologic evaluation. Testing for tumor markers, including ER, PR, and HER2/neu, should be performed. In the absence of evidence for a non–breast primary, and a negative mammogram/ultrasound and MRI, a patient can be assumed to have an occult or unknown breast primary and treated as such, particularly if the nodal biopsy results support a breast primary. Systemic staging studies including a CT scan of the chest, abdomen, and pelvis plus bone scan or FDG PET/CT should be performed.

Modified radical mastectomy and PMRT have been the historical locoregional treatments for patients with occult breast primary and axillary metastases. Studies vary significantly with respect to the frequency with which a primary is found within the breast during pathologic examination. Most of these studies predate the use of MRI screening or other improvements in diagnostic imaging and are less relevant in the modern era. For patients with cT0 with cN2-N3 disease, neoadjuvant systemic therapy is usually given prior to surgery and radiation. Patients with cT0N1 disease may be treated with upfront surgery or neoadjuvant systemic therapy. Pretreatment multidisciplinary evaluation is encouraged.

The safety of breast conservation therapy with ALND for patients with occult primary disease has been explored. Early attempts at breast conservation without breast irradiation resulted in high subsequent breast recurrence rates.[251] More recent studies that incorporate breast irradiation have yielded improved results. In one of the largest series, investigators from MD Anderson evaluated 45 patients with an occult breast tumor and cN1-N2 disease and compared the outcome of those treated with mastectomy (n = 13) to those treated with breast conservation (n = 32).[252] Locoregional control, DFS, and OS were equivalent between the mastectomy and breast conservation cohorts. With a median follow-up of 7 years, only 2 of the 25 breast conservation patients who received breast irradiation developed a local recurrence while 2 of the 7 who did not receive breast irradiation recurred locally.[252] Similar results have been reported from The Royal Marsden Hospital. In a series of 48 patients with axillary metastases in the setting of an occult breast primary who underwent axillary surgery with breast conservation, they found a 14% LRR rate after breast radiation and an unacceptable rate of 85% if breast radiation was omitted.[253] Several other retrospective/population-based studies and a recent meta-analysis have found equivalent outcomes with ALND with either breast conservation plus x-ray technique or mastectomy.[247,248,254,255] These data suggest that undetectable primary breast

lesions can be successfully sterilized with the combination of systemic therapy and RT. One can feel particularly reassured with this strategy for patients treated in the MRI age with lesions below the threshold for MRI detectability. Patients presenting with an occult breast primary and axillary disease should receive RNI, whether as a part of PMRT or breast conservation therapy.[117,118]

There are no studies looking at de-escalation of ALND to SLNB in the setting of occult breast cancer and axillary metastasis. That said, de-escalation of axillary surgery to SLNB to well-selected patients with cT0N1 disease who are rendered cN0 following neoadjuvant systemic therapy is not unreasonable to consider and may become the accepted treatment strategy in the future.[256] See the section "Surgical Management of the Axilla."

Male Breast Cancer

Breast cancer developing in males is uncommon and accounts for less than 1% of total new breast cancer cases in the United States.[257] The American Cancer Society estimated that in 2017, there would be approximately 2,470 new cases of male breast cancer and 460 deaths because of male breast cancer in the United States. The incidence of male breast cancer is positively correlated with age, and the highest rates occur in Black males (2.7/100,000) and White males (1.9/100,000).[257]

The presenting symptom for male patients with breast cancer is typically a breast mass or axillary adenopathy, and most male patients with breast cancer present with locally advanced disease. The ratio of the number of deaths to new cases is 19% for males, compared to a ratio of 16% for females, with a 5-year OS of 84% in men compared to 90% in women.[257] Retrospective national database evidence suggests differences in cancer-specific mortality may be attributable to stage migration, as there are no gender-specific differences when comparing outcome within stage II or stage III.[258] Leone et al compared BCSS estimates in men over three decades (1988-1997, 1998-2007, and 2008-2017) within the SEER registry. In contrast to improvements in cancer-related survival in women, there was no statistically significant changes over time among men.[259]

The known risk factors for male breast cancer, similar to those in postmenopausal female breast cancer, include family history, age, conditions that affect testosterone and estrogen levels, BRCA2 mutations, and prior history of RT.[260] Germline mutations in the *BRCA2* gene have been reported in 4% to 16% of men with breast cancer and, unlike female breast cancer, are more common than germline mutations in BRCA1.[261,262] Nevertheless, most male breast cancers present without an identifiable risk factor.

Males have a similar histopathologic spectrum of breast cancers to females with the exception of lower rates of invasive lobular carcinoma, given the lack of acini and lobules in normal breast tissue. Specifically, less than 2% of invasive male breast carcinomas are lobular, as compared to approximately 15% in female cancers.[263] In addition, male breast cancers more frequently are ER positive (estimated rate of 90%) and HER2 negative compared to female breast cancer.[258] In addition, tumor subtype in a large SEER database was shown to be associated with survival among men, as in women.[264] Diagnostic workup

and staging are similar to that for female breast cancer and should include bilateral mammography, biopsy, and staging workup. Treatment decisions are also similar to those used in women.

Mastectomy with or without postmastectomy radiation is the most common locoregional treatment approach, with increasing attention being placed on postmastectomy reconstruction and potential psychological distress related to cosmetic outcomes. Investigators at MD Anderson reviewed 142 patients treated with mastectomy without RT and found that, similar to female patients, margin status, number of positive nodes, and tumor size predicted locoregional failure.[145] Accordingly, decisions concerning postmastectomy radiation should be based on the same criteria used in the treatment of breast cancer in women.

Similarly, systemic treatments are indicated for male patients with breast cancer who have a clinically relevant risk of distant metastases, and treatment decisions should follow those for female breast cancers. Level 1 data supporting the use of particular chemotherapy regimens specifically in men are lacking, given the rarity of the disease. In addition to chemotherapy, because most male breast cancers are receptor positive, tamoxifen is indicated for the majority of cases. Retrospective series have suggested that tamoxifen can reduce the risk of recurrence and death.[265] The role of aromatase inhibitors in males is unclear, but retrospective data support the adjuvant use of tamoxifen rather than aromatase inhibitors.[266] If an aromatase inhibitor is to be used, it should be given in conjunction with a gonadotropin-releasing hormone agonist as aromatase inhibitor therapy alone does not suppress testicular production of estrogen.

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PART F

Gastrointestinal

CHAPTER 64

Stomach Cancer

Brian G. Czito and Christopher G. Willett

ANATOMY

The stomach begins at the gastroesophageal (GE) junction and ends at the pylorus. The stomach is generally divided into anatomic regions, including the gastric cardia (the region surrounding the superior opening of the stomach where it connects with the GE junction/level of the lower esophageal sphincter), the fundus (situated superiorly, a rounded portion superior to the body and to the left of the cardia), the body (a large, central portion of the stomach), and the pyloric canal (distally, connecting to the duodenum). The pylorus is composed of two parts: the pyloric antrum, which connects to the body of the stomach, and the pyloric canal, which empties into the duodenum (Figure 64.1). The pylorus communicates with the duodenum of the small intestine via the pyloric sphincter (valve). This valve regulates the passage of chyme from the stomach to the duodenum and prevents backflow from the duodenum to the stomach. A plane passing through the incisura angularis on the lesser curvature divides the stomach into the body and the pyloric portion (antrum). The anterior surface of the stomach is covered with the peritoneum of the greater sac. At the left and cranially, it abuts the diaphragm. In view of the increasing incidence of gastric cancer at the GE junction, it is important to note that there is either no or variable visceral peritoneal covering at the most proximal portion of the GE junction.[1] Positive radial margins at this site are often "true" positive margins, whereas many other positive margins in the stomach are free

serosal margins unless the tumor is adherent to an adjacent organ or structure. The right portion of the anterior gastric surface is adjacent to the left lobe of the liver and the anterior abdominal wall. Posteriorly, the stomach is covered with peritoneum of the lesser sac or omental bursa. The stomach contacts many visceral structures; from superior to inferior, it is adjacent to the spleen, left adrenal gland, superior portion of the left kidney, ventral portion of the pancreas, and transverse colon. The hepatogastric ligament or lesser omentum is attached to the lesser curvature and contains the left gastric artery and the right gastric branch of the hepatic artery. Histologically, the wall of the stomach has five layers: the mucosa, submucosa, muscularis layer, subserosa, and serosa. The muscularis layer is composed of an outer longitudinal layer, a middle circular layer, and an inner oblique layer.

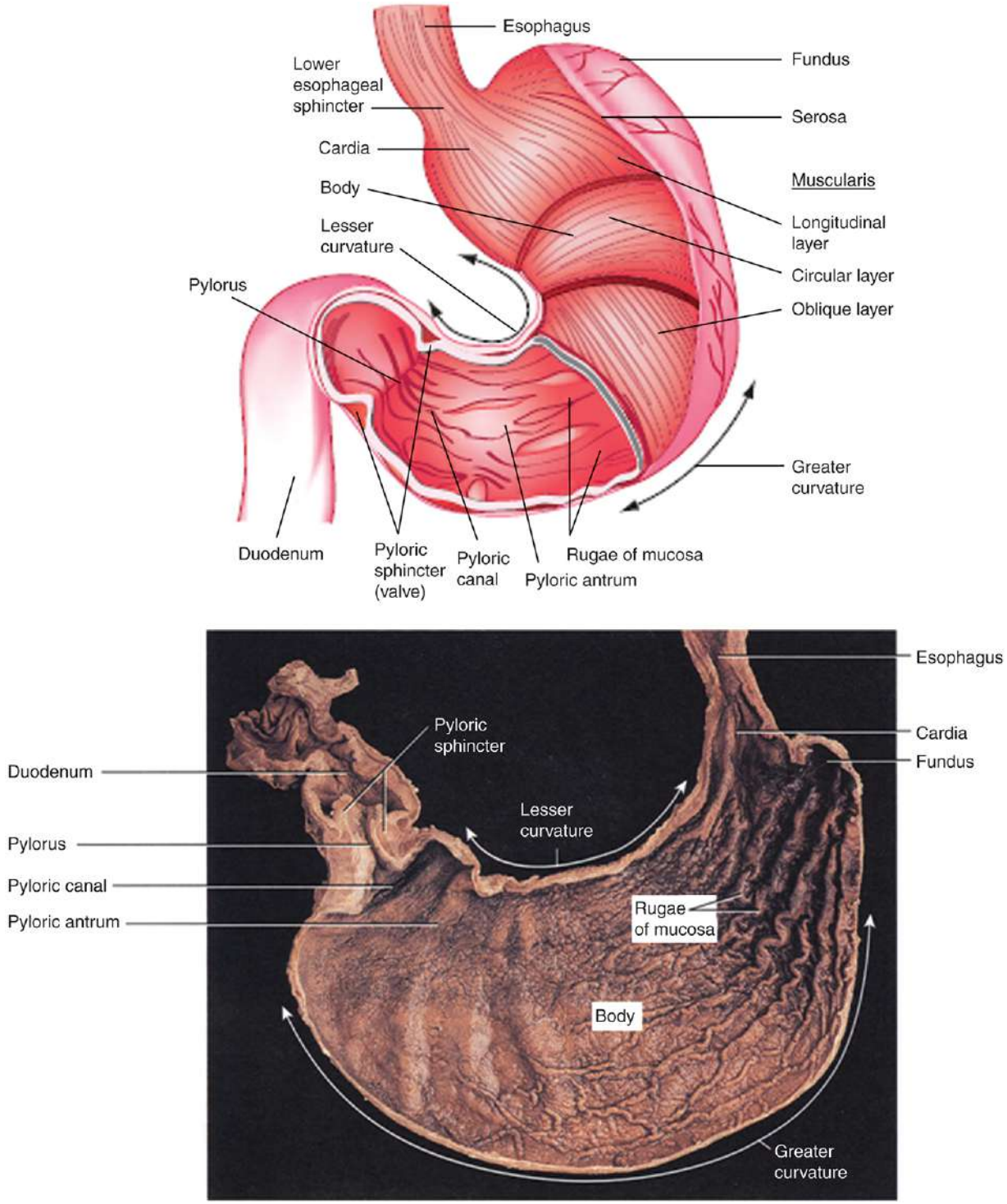


FIGURE 64.1 Gastric anatomy. (Used with permission of John Wiley & Sons—Books from Tortora GJ, Grabowski SR. *Principles of Anatomy and Physiology*. 10th ed. John Wiley & Sons; 2002. Copyright © 2003 by Biological Sciences Textbooks and Sandra Reynolds Grabowski; permission conveyed through Copyright Clearance Center.)

The stomach's vascular supply is derived from the celiac axis. The celiac artery usually has three branches: the left gastric artery, which supplies the upper right portion of the stomach; the common hepatic artery, which gives rise to the right gastric artery supplying the lower right portion of the stomach and the right gastroepiploic branch supplying the lower portion of the greater curvature; and the splenic artery, which gives rise to the left gastroepiploic supplying the upper portion of the greater curvature and the short gastric arteries supplying the fundus. Variations in this normal vascular supply are common. The celiac axis originates at or below the pedicle of T12 in approximately 75% of patients and at or above the pedicle of L1 in 25% of patients.[2] The lymphatic drainage of the stomach follows the arterial supply. Although most lymphatics ultimately drain to the celiac nodal basin, lymph drainage sites can include the splenic hilum, suprapancreatic nodal groups, porta hepatis, and gastroduodenal areas.

EPIDEMIOLOGY

Gastric cancer afflicted an estimated 26,500 people in the United States in 2023 and resulted in 11,130 deaths.[3] Worldwide, gastric cancer remains a significant cause of cancer-related mortality, with approximately 1,313,000 new cases annually and an estimated 819,000 deaths, making it the third-leading cause of cancer-related deaths.[4] During the past 70 years, there has been a significant decline in the incidence of gastric cancer in both sexes in Western countries. The causes of this decline are unknown, although it may possibly be due to decreased rates of *Helicobacter pylori* infection, improvements in socioeconomic conditions, use of antibiotics and better medical treatment, and decreasing smoking rates.[4-6] Although the overall decrease in gastric cancer incidence is encouraging, there has been a steady and dramatic increase in the incidence of proximal lesser curvature, cardia, and GE junction tumors over the past 20 years, especially in White males. In contrast to the increasing incidence of more proximal gastric cancers seen in the Western Hemisphere and parts of Europe, distal tumors continue to constitute most gastric cancers in the Far East and other parts of the world.

Risk factors for gastric cancer can be classified as modifiable or nonmodifiable (Table 64.1). Race or ethnicity, specifically being of East

Asian or Pacific Islanders descent, portends increased risk. Although potentially related to environment, this incidence persists following immigration and into offspring when migrating to the West. Age is also an important risk factor, with 90% of cases occurring in patients older than 45 years. Family history similarly contributes to risk, with studies from the East and West demonstrating that a first-degree relative likely increases an individual's risk from 2- to 4-fold. Similarly, male sex portends a 2- to 5-fold increased risk, possibly accounted for by protective effects of estrogen in females. Approximately 10% of gastric cancers are linked to genetic syndromes, with the most common being hereditary diffuse gastric cancer (HDGC), which is characterized by an autosomal dominant inheritance, portending a 60% to 80% increased risk of gastric cancer and 40% to 50% increased risk in breast cancer. Some of these cases are believed to be due to mutations in E-cadherin (*CDH1*). The presence of CDH1 mutations portends a lifetime risk of gastric cancer development of 70% to 80%.[7] Prophylactic gastrectomy is often recommended once patients are more than 20 years of age. Other syndromes associated with increased risk include Lynch syndrome (a DNA mismatch repair gene mutation), familial adenomatous polyposis (an adenomatous polyposis coli gene mutation), Peutz-Jeghers syndrome, juvenile polyposis syndrome, hereditary breast and ovarian cancer syndrome, and Li-Fraumeni syndrome.[8]

TABLE 64.1 RISK FACTORS FOR GASTRIC CANCER DEVELOPMENT

Modifiable
Helicobacter pylori infection
Tobacco smoking
Alcohol use
Obesity
High-salt diet; low-fruit or -vegetable diet
Smoked and pickled foods
Intrinsic
Ethnicity (East Asian or Pacific Islander)
Male gender
Age

Family history

In terms of modifiable risk factors, the most common is *H. pylori* infection. Although the risk of developing gastric cancer is approximately 1% once present, more than 90% of patients with gastric cancer diagnosis have been previously infected. *H. pylori* appears to contribute to gastric cancer development through development of gastritis with subsequent histopathologic changes. The increased association of *H. pylori* appears to be confined to patients with distal gastric cancer and intestinal-type histology. The Epstein-Barr virus (EBV) has been found in 5% to 16% of gastric cancer patients, supporting its possible role in the genesis of such.[7] Additionally, cigarette use appears to increase the risk of both cardia and noncardia cancers, whereas obesity (body mass index >30) appears to increase the risk of noncardia cancers. A high-salt diet seems to increase risk, whereas diets high in fruit and vegetables seem to be protective.[5,8-10]

Historically, gastric adenocarcinomas have been labeled as intestinal or diffuse types per the Lauren classification system. Intestinal types are more prevalent in high-incidence areas and responsible for much of the observed global ethnic variation of disease, although the incidence is believed to be decreasing. Intestinal-type carcinomas are primarily well to moderately differentiated. Histologically, these tumors generally show malignant epithelial cells in hyperchromatic, irregular, angulated glands with cohesiveness and glandular differentiation infiltrating the stroma. These tumors can be polypoid with a wide base, ulcerated with sharp/heaped-up margins, and ulcerated disease without obvious limits. These are generally seen more in males than in females in a 2:1 ratio. In contrast, the incidence of the less common diffuse gastric cancer appears to be increasing and is fairly uniform among geographic regions or race. More recently, there has been an emergence of another distinct subtype—proximal gastric (cardia) cancers. These are often grouped with GE junction and distal esophageal adenocarcinomas, with a rapidly rising incidence in industrialized nations. Gastric cardia cancers are associated with reflux and obesity, resembling esophageal adenocarcinomas. These malignancies are generally more aggressive and carry a worse prognosis than do noncardia tumors. These tumors are associated with White populations with a strong male predominance.

The risk factors for these individual types appear to vary significantly. Risk factors for intestinal, noncardia gastric cancers appear to center around inflammatory causes and environmental factors, primarily *H. pylori*, as well as chronic gastritis, tobacco, high salt intake, and alcohol consumption. The less common diffuse gastric cancer subtype appears to be distinct, with E-cadherin mutations/silencing thought to be a common precursor event with this histology. HDGC is a genetic syndrome in which there is loss of function/mutation in the E-cadherin gene. In proximal gastric cancer (and in contrast to intestinal types), *H. pylori* infection has been found to be potentially protective in several randomized trials, possibly through associated atrophic gastritis and reduced acid production with subsequent reduction in gastroesophageal reflux disease, although this remains controversial.[11] As opposed to intestinal types, there is often no precancerous lesion seen, and histologically, cells generally lack cohesion and invade independently or in smaller clusters. Diffuse carcinomas are poorly differentiated. These are often more diffusely infiltrating and nonulcerated and can present as a "signet ring" carcinoma, which is a variant with cytoplasmic mucin that displaces the cell nucleus peripherally. The presence of signet ring (or poorly differentiated) phenotype has been associated with therapy resistance and poor prognosis[11] (Figure 64.2). However, a large database analysis indicated patients with signet ring gastric cancer, when compared to patients with adenocarcinoma, tended to present at a younger age and less often in men. Additionally, despite more advanced stage, median survival was not different relative to patients with "traditional" adenocarcinoma.[12,13]

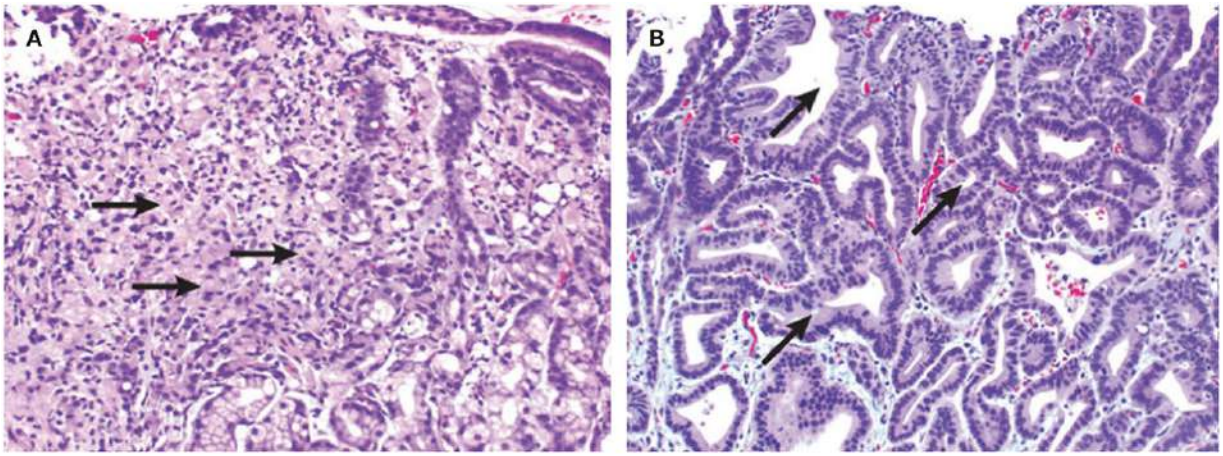


FIGURE 64.2 A. Hematoxylin and eosin–stained slide of Lauren classification diffuse-type gastric adenocarcinoma (GAC) with many cancer cells isolated from other cells. *Arrows* point to signet ring cells, in which the nucleus is pushed out to the periphery of the cytoplasm. B. Hematoxylin and eosin–stained slide of Lauren classification intestinal-type GAC. *Arrows* are pointing to gland formation by tumor cells. (Reprinted by permission from *Nature*: Ajani JA, Lee J, Sano T, Janjigian YY, Fan D, Song S. Gastric adenocarcinoma. *Nat Rev Dis Primers*. 2017;3:17036. Copyright © 2017 Springer Nature.)

An alternative gastric cancer classification from the World Health Organization is based predominantly on histologic cancer patterns (tubular, papillary, mucinous, poorly cohesive, and rare variants). The tubular and papillary subtypes roughly correspond to the Lauren intestinal type and poorly cohesive to the diffuse type. More recently, the Cancer Genome Atlas Research Network published the results of genomic profiling of 295 primary gastric adenocarcinomas. Four tumor subtypes were identified: (a) EBV (9%), (b) microsatellite-unstable tumors (22%), (c) genomically stable tumors (20%), and (d) chromosomally unstable tumors (50%). This classification has the potential to determine prognosis and help individualize treatment in the future.[12]

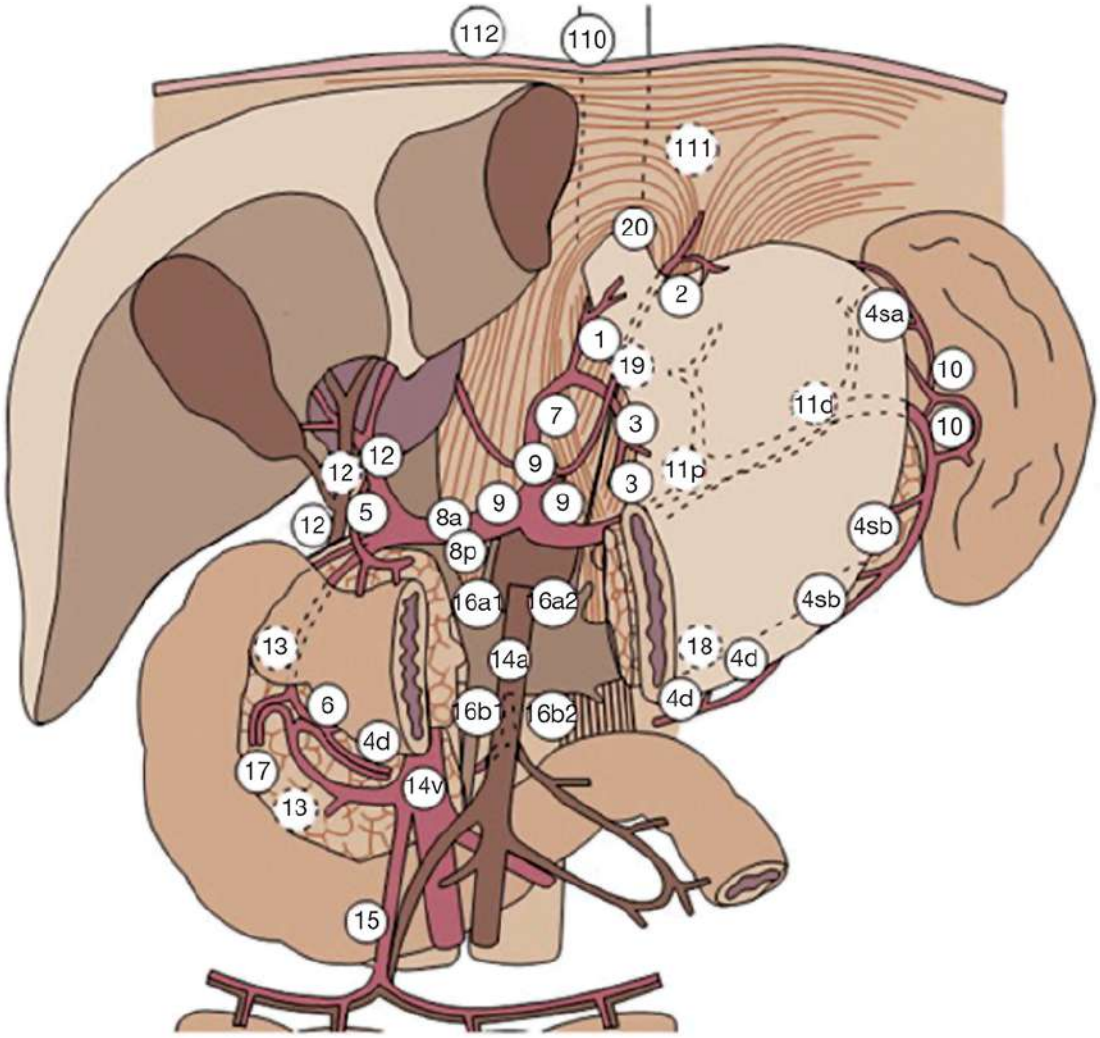
PATTERNS OF SPREAD

Cancer of the stomach may extend directly into the omentum, pancreas, diaphragm, transverse colon or mesocolon, and duodenum. Peritoneal contamination with carcinomatosis is possible after a lesion extends beyond the gastric wall to a free peritoneal (serosal) surface.[14]

Microscopic or subclinical spread beyond the visible gross lesion occurs frequently because of the abundant lymphatic channels within the

submucosal and subserosal layers of the gastric wall. The submucosal plexus in the esophagus and subserosal plexus in the duodenum allow proximal and distal spread.

It is difficult to perform a complete node dissection because of the numerous pathways of lymphatic drainage from the stomach (Figure 64.3). Initial drainage is not only to lymph nodes along the lesser and greater curvatures (ie, gastric and gastroepiploic nodes) but also includes the celiac axis, porta hepatis, splenic, suprapancreatic, pancreaticoduodenal, adjacent para-aortic, and distal paraesophageal system. The relative risks for nodal involvement in gastric cancer depend on the location of the primary tumor as well as extent of gastric wall involvement.



No. 1	Right paracardial LN
No. 2	Left paracardial LN
No. 3	LN along the lesser curvature
No. 4sa	LN along the short gastric vessels
No. 4sb	LN along the left gastroepiploic vessels
No. 4d	LN along the right gastroepiploic vessels
No. 5	Suprapyloric LN
No. 6	Infrapyloric LN
No. 7	LN along the left gastric artery
No. 8a	LN along the common hepatic artery (Anterosuperior group)
No. 8p	LN along the common hepatic artery (Posterior group)
No. 9	LN around the celiac artery
No. 10	LN at the splenic hilum
No. 11p	LN along the proximal splenic artery
No. 11d	LN along the distal splenic artery
No. 12a	LN in the hepatoduodenal ligament (along the hepatic artery)
No. 12b	LN in the hepatoduodenal ligament (along the bile duct)
No. 12p	LN in the hepatoduodenal ligament (behind the portal vein)
No. 13	LN on the posterior surface of the pancreatic head
No. 14v	LN along the superior mesenteric vein
No. 14a	LN along the superior mesenteric artery
No. 15	LN along the middle colic vessels
No. 16a1	LN in the aortic hiatus
No. 16a2	LN around the abdominal aorta (from the upper margin of the celiac trunk to the lower margin of the left renal vein)
No. 16b1	LN around the abdominal aorta (from the lower margin of the left renal vein to the upper margin of the inferior mesenteric artery)
No. 16b2	LN around the abdominal aorta (from the upper margin of the inferior mesenteric artery to the aortic bifurcation)
No. 17	LN on the anterior surface of the pancreatic head
No. 18	LN along the inferior margin of the pancreas
No. 19	Infradiaphragmatic LN
No. 20	LN in the esophageal hiatus of the diaphragm
No. 110	Paraesophageal LN in the lower thorax
No. 111	Supradiaphragmatic LN
No. 112	Posterior mediastinal LN

portal vein)

FIGURE 64.3 Locations of gastric lymph node stations. (Reprinted from Matzinger O, Gerber E, Bernstein Z, et al. EORTC-ROG expert opinion: radiotherapy volume and treatment guidelines for neoadjuvant radiation of adenocarcinomas of the gastroesophageal junction and the stomach. *Radiother Oncol*. 2009;92[2]:164-175. Copyright © 2009 Elsevier Ireland Ltd. With permission.)

Gastric venous drainage is primarily to the liver by the portal system. Liver involvement is found in as many as 30% of patients at initial exploration, and it can occur as a result of venous metastasis, peritoneal-based spread, and direct extension (Figure 64.4).

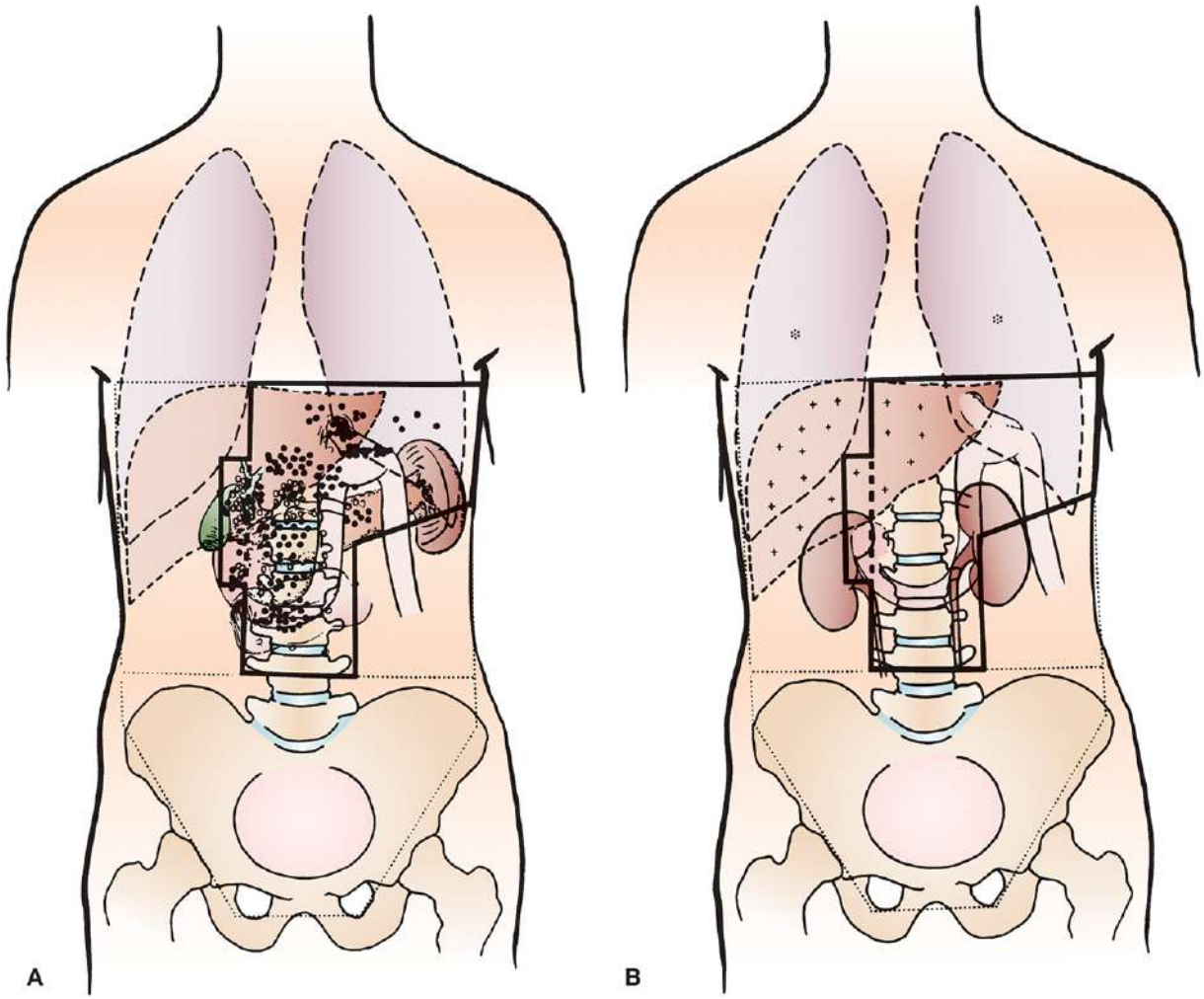


FIGURE 64.4 Patterns of failure in 82 evaluable patients in the University of Minnesota Reoperation series. A. Large bold circles indicate local failures in surrounding organs or tissues; large open circles indicate lymph node failures. B. Asterisk (*) indicates lung metastasis; *plus* (+) indicates liver metastasis. Superimposed irradiation portals encompass postsurgical gastric remnant, anastomoses, duodenal stump, gastric bed structures, and primary and secondary areas of lymph node drainage; broken lines represent upper and total abdomen fields. (Reprinted from Gunderson LL, Sosin H. Adenocarcinoma of the stomach: areas of failure in a re-operation series (second or symptomatic look) clinicopathologic correlation and implications for adjuvant therapy. *Int J Radiat Oncol Biol Phys*. 1982;8[1]:1-11. Copyright © 1982 Elsevier. With permission.)

CLINICAL PRESENTATION

The most common presenting symptoms of stomach cancer are anorexia, early satiety, abdominal discomfort, unintentional weight loss, dysphagia (notably if GE junction or proximal stomach involvement), anemia-related weakness, nausea and vomiting, and tarry stools. Duration of symptoms is

less than 3 months in almost 40% of patients and more than 1 year in 20%. Physical examination can reveal advanced disease, for which the presentation may include an abdominal mass (epigastric or liver mass as well as a periumbilical node [ie, Sister Mary Joseph node]), palpable left supraclavicular nodes (ie, Virchow node), an enlarged left axillary lymph node (Irish node), or a rectal shelf (representing peritoneal seeding [ie, Blumer shelf]).

DIAGNOSTIC WORKUP

Many patients with early-stage gastric cancer are asymptomatic, and therefore patients are often diagnosed at a more advanced stage. Diagnosis is usually confirmed by upper gastrointestinal endoscopy as well as imaging studies in some instances. Double-contrast x-ray studies may reveal small lesions limited to the inner layers of the gastric wall. Endoscopy with direct visualization, cytology, and biopsy yields the diagnosis in 90% or more of exophytic lesions; however, infiltrative (linitis plastica), small (<3 cm), or cardia lesions may be more difficult to diagnose endoscopically. Endoscopic ultrasonography is the most accurate method of determining depth of tumor invasion (intramural vs extramural extension) prior to resection but is less accurate in detecting regional nodal metastases.[15,16] In some institutions, needle biopsies of suspicious nodes are performed at the time of endoscopic ultrasound.

One principal goal of staging computed tomography (CT) is the identification of distant metastases, although it can also provide T- and N-stage data. Abdominal CT is useful in determining the abdominal extent of disease and may help to determine which lesions extend to surgically unresectable structures but are of lesser value in detecting small lymph node metastases or peritoneal spread. Distant metastases should be ruled out with contrast-enhanced CT of the chest, abdomen, and pelvis. CT may provide valuable tumor localization information if radiation is indicated. If a proximal gastric cancer extends to involve the esophagus, CT of the chest will help to rule out involvement of mediastinal nodes or the lung parenchyma. A meta-analysis suggested that CT accuracy in terms of T stage was 72% although there was an indication that multidetector (four or more) scanners demonstrated an overall accuracy of 80%.[17] However,

multidetector status did not seem to influence nodal or distant metastatic assessment. In the same study, CT accuracy, compared to histologic findings, was 66% in terms of N stage.

The value of laparoscopy in the staging of gastric cancer remains a subject of study. The primary value of laparoscopy lies in the detection of occult metastatic deposits. A large series from Memorial Sloan Kettering Cancer Center of more than 600 patients with potentially resectable gastric adenocarcinoma by conventional imaging underwent laparoscopic staging, resulting in distant metastases being detected in 31% of patients.[18] A systematic review of the role of diagnostic laparoscopy showed that change in patient management occurred in 9% to 60% of patients initially deemed resectable by preoperative imaging, with 9% to 44% avoiding laparotomy, predominantly through the identification of patients with metastatic disease who would not benefit from either laparotomy or neoadjuvant therapy, thereby avoiding unnecessary interventions. This is primarily related to patients with advanced (T3, T4) gastric cancer, with relatively minimal benefit in patients at an early stage, prompting the authors to recommend diagnostic laparoscopy for patients with locally advanced-stage disease.[19,20] In addition, peritoneal fluid can be sampled for cytology at laparoscopy by direct aspiration of ascitic fluid or peritoneal lavage. If positive, this is a poor prognostic indicator, and although the bearing on treatment approach remains somewhat controversial, the patient should be considered as having M1 disease. Some experts recommend laparoscopy with obtaining cytology in patients with T1b and higher disease who are potentially resectable, with consideration of the same in patients who are surgically unresectable.

Overall treatment planning in gastric cancer may be improved by accurate preoperative classification of key prognostic factors, namely, depth of invasion (T category) and lymph node involvement (N category). A prospective study in 108 patients evaluated endogastric ultrasonography (EUS), CT, and intraoperative surgical assessment for T and N classifications.[21] T staging was accurately characterized by CT in 43% of cases, EUS in 86% of cases, and intraoperative assessment in 56% of cases. Staging of N1 and N2 lymph nodes was correct with CT in 51% of the cases, 74% with EUS, and 54% with intraoperative assessment. EUS is particularly relevant in accuracy and sensitivity for local regional staging, including an 85% sensitivity toward distinguishing T1 from T2 disease as

well as 87% for T1a versus T1b disease, with distinguishing between early and advanced tumors with sensitivity and specificity of 86% and 90%, respectively. Advanced gastric tumors tended to be more accurately staged with CT, although CT, in general, overstages the T category and understages the N category. EUS showed a high accuracy for all the T categories, although it also tends to understage N categories. Finally, intraoperative assessment was equally accurate for all N categories but tended to overstage early T stages and to understage N categories. A meta-analysis and systematic review of the role of EUS in T and N staging in nearly 2,000 patients with gastric cancers suggested that the sensitivity for detecting T1, T2, T3, and T4 disease was 88%, 82%, 90%, and 99%, respectively. Nodal staging sensitivity for N1 and N2 disease was 58% and 65%, respectively, also suggesting that accuracy was higher with more advanced disease.[23] Another meta-analysis demonstrated the ability of endoscopic ultrasound to discriminate between T1-T2 versus T3-T4 gastric cancers, with a sensitivity of 0.86 (CI 0.81-0.90); additionally, the sensitivity for diagnosis of superficial (T1a vs T1b) and lymph node involvement was 0.87 (0.81-0.92) and 0.83 (0.79-0.87), respectively.[24] Another meta-analysis showed a pooled accuracy for T-stage diagnosis of 75%, with individual studies reporting rates from 57% to 88%. However, the diagnostic accuracy for N staging was less, with a wide range from 30% to 90%, pooled accuracy of 64%, sensitivity of 74%, and specificity of 80%.[25] EUS accuracy depends highly on the experience and expertise of the operating physician.

The role of magnetic resonance imaging (MRI) in gastric cancer remains the subject of investigation. Early reports suggest that there is good agreement with histologic T staging, with an accuracy of 83% (range 77%-87%), although experience with this technique is more limited and the subject of ongoing investigation.[20] Another systematic review concluded that EUS, multidetector CT, and MRI achieve similar results in terms of diagnostic accuracy of T staging and assessing serosal involvement.[26] Presently, MRI is primarily used in further characterization of indeterminate liver lesions seen on other staging investigations in patients with gastric cancer.

Positron emission tomography (PET) scan has a lower detection rate in some cases of gastric cancers owing to the low fluorine-18 fluorodeoxyglucose accumulation in patients with diffuse or

mucinous/signet ring tumors.[27] PET alone displays a lower sensitivity than CT in detecting nodal involvement, although specificity is improved.[28] Because of its low-resolution images, the value of PET-CT primarily lies in its ability to detect metastatic disease, with a relatively low T-stage sensitivity for T1-T2 tumors and improvement for more advanced disease. A systematic review of the role of PET in patients with gastric cancer evaluating 2,101 patients demonstrated that PET changed management between 3% and 29% of cases, with intestinal subtypes exhibiting more PET-avidity versus diffuse/signet ring subtypes. The authors concluded that the evidence for PET use is limited, but all studies reported a positive impact by preventing patients with CT-undetected metastatic disease from undergoing surgery.[29] Estimated sensitivity for N stage is 40%, although specificity has been reported as high as 98%. As mentioned earlier, the accuracy in identifying distant metastases was 88% and higher than CT alone, and PET has been reported to detect occult metastases in operable patients in 10% and to change patient management in 15%. Additionally, PET response to neoadjuvant therapy, including treatment modification in poor responders as well as a potential indicator of prognosis in these patients, remains an active area of investigation.[20] The ongoing Alliance A021302 study is comparing overall survival of patients with locally advanced gastric cancer classified as PET nonresponders following one cycle of preoperative chemotherapy, with nonresponding patients receiving either salvage chemotherapy before and after surgery or immediate surgery followed by fluorouracil (FU)-sensitized radiotherapy. Given the earlier-mentioned fact, PET alone is likely not an adequate diagnostic procedure for the evaluation of gastric cancer and generally should be used in conjunction with CT scan for correlation, allowing more accurate preoperative staging than either modality alone. A suggested diagnostic evaluation for gastric cancer is shown in Table 64.2.

TABLE 64.2 DIAGNOSTIC WORKUP FOR GASTRIC CANCER

History and Physical
Upper gastrointestinal endoscopy and biopsy
MSI/MMR testing

Chest, abdomen, pelvic CT with oral and intravenous contrast (preferably correlated with PET when PET is performed)
Complete blood count and comprehensive metabolic panel
Endoscopic ultrasound if no evidence of metastases with fine-needle aspiration as indicated
Consider laparoscopy in locoregional patients
Biopsy confirmation of suspected metastatic gastric cancer
HER2 testing if metastatic
Helicobacter pylori testing performed and treatment delivered where clinically indicated

CT, computed tomography; MMR, mismatch repair; MSI, microsatellite instability; PET, positron emission tomography.

STAGING

The current tumor-node-metastasis (TNM) system is depicted in Table 64.3.[30] In the most recent American Joint Committee on Cancer (AJCC) staging of gastric cancers, cancers whose midpoint is in the lower thoracic esophagus, GE junction, or within the proximal 2 cm of the stomach (cardia) *and* extending to the GE junction or esophagus are staged as esophageal neoplasms. All other cancers with a midpoint in the stomach lying more than 2 cm distal to and involving the GE junction or those within 2 cm of the GE junction (but not involving the GE junction or esophagus) are staged using the gastric cancer staging system.

TABLE 64.3 AMERICAN JOINT COMMITTEE ON CANCER (AJCC) EIGHTH EDITION GASTRIC CANCER STAGING

T Category	T Criteria
TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria, high-grade dysplasia
T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades the lamina propria or muscularis mucosae
T1b	Tumor invades the submucosa

T Category	T Criteria
T2	Tumor invades the muscularis propria[a]
T3	Tumor penetrates the subserosal connective tissue without invasion of the visceral peritoneum or adjacent structures[b,c]
T4	Tumor invades the serosa (visceral peritoneum) or adjacent structures[b,c]
T4a	Tumor invades the serosa (visceral peritoneum)
T4b	Tumor invades the adjacent structures/organs

Definition of Distant Lymph Node (M)

N Category	N Criteria
NX	Regional lymph node(s) cannot be assessed.
N0	No regional lymph node metastasis
N1	Metastasis in one or two regional lymph nodes
N2	Metastasis in three to six regional lymph nodes
N3	Metastasis in seven or more regional lymph nodes
N3a	Metastasis in 7-15 regional lymph nodes
N3b	Metastasis in 16 or more regional lymph nodes

Definition of Distant Metastasis (M)

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis

AJCC Prognostic Stage Groups

Clinical (cTNM)

When T is…	And N is…	And M is…	Then stage group is…
Tis	N0	M0	0
T1	N0	M0	I
T2	N0	M0	I
T1	N1, N2, or N3	M0	IIA
T2	N1, N2, or N3	M0	IIA

T Category		T Criteria	
T3	N0	M0	IIB
T4a	N0	M0	IIB
T3	N1, N2, or N3	M0	III
T4a	N1, N2, or N3	M0	III
T4b	Any N	M0	IVA
Any T	Any N	M1	IVB
Pathologic (pTNM)			
When T is…	**And N is…**	**And M is…**	**Then stage group is…**
Tis	N0	M0	0
T1	N0	M0	IA
T1	N1	M0	IB
T2	N0	M0	IB
T1	N2	M0	IIA
T2	N1	M0	IIA
T3	N0	M0	IIA
T1	N3a	M0	IIB
T2	N2	M0	IIB
T3	N1	M0	IIB
T4a	N0	M0	IIB
T2	N3a	M0	IIIA
T3	N2	M0	IIIA
T4a	N1	M0	IIIA
T4a	N2	M0	IIIA
T4b	N0	M0	IIIA
T1	N3b	M0	IIIB
T2	N3b	M0	IIIB
T3	N3a	M0	IIIB

T Category		T Criteria	
T4a	N3a	M0	IIIB
T4b	N1	M0	IIIB
T4b	N2	M0	IIIB
T3	N3b	M0	IIIC
T4a	N3b	M0	IIIC
T4b	N3a	M0	IIIC
T4b	N3b	M0	IIIC
Any T	Any N	M1	IV
Post-Neoadjuvant Therapy (ypTNM)			
When T is…	**And N is…**	**And M is…**	**Then stage group is…**
T1	N0	M0	I
T2	N0	M0	I
T1	N1	M0	I
T3	N0	M0	II
T2	N1	M0	II
T1	N2	M0	II
T4a	N0	M0	II
T3	N1	M0	II
T2	N2	M0	II
T1	N3	M0	II
T4a	N1	M0	III
T3	N2	M0	III
T2	N3	M0	III
T4b	N0	M0	III
T4b	N1	M0	III
T4a	N2	M0	III
T3	N3	M0	III
T4b	N2	M0	III
T4b	N3	M0	III

T Category		T Criteria	
T4a	N3	M0	III
Any T	Any N	M1	IV

The specific regional nodal areas are as follows:

- Perigastric along the greater curvature (including greater curvature, greater omental)
- Perigastric along the lesser curvature (including lesser curvature, lesser omental)
- Right and left paracardial (cardioesophageal)
- Suprapyloric (including gastroduodenal)
- Infrapyloric (including gastroepiploic)
- Left gastric artery
- Celiac artery
- Common hepatic artery
- Hepatoduodenal (along the proper hepatic artery, including portal)
- Splenic artery
- Splenic hilum

[a]A tumor may penetrate the muscularis propria with extension into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures. In this case, the tumor is classified as T3. If there is perforation of the visceral peritoneum covering the gastric ligaments or the omentum, the tumor should be classified as T4.

[b]The adjacent structures of the stomach include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.

[c]Intramural extension to the duodenum or esophagus is not considered invasion of an adjacent structure but is classified using the depth of the greatest invasion in any of these sites.

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PATHOLOGY

Adenocarcinomas account for 90% to 95% of all gastric malignancies. Lymphomas are the second-most common malignancies. Rarely, gastrointestinal stromal tumors, carcinoid (neuroendocrine) tumors, adenoacanthomas (1%), and squamous cell carcinomas (1%) occur.

The site of origin of gastric cancers within the stomach has changed in the United States over recent decades, and proximal lesions are being diagnosed and treated more frequently. Although the highest frequency is

still in the antrum/distal stomach (~40%), the lowest frequency is now in the body (~25%) rather than the proximal portion of the stomach, with intermediate frequency in the proximal stomach and GE junction (~35%). Several investigators have reported an increased frequency of cardia lesions. As described previously, cardia lesions appear to have different epidemiologic factors, exhibit different tumor biology, and have an inferior prognosis relative to lesions in the other sites.[31-35] Gastric cancers have historically been categorized according to Borrmann's five types. Type I tumors are polypoid or fungating; type II are ulcerating lesions surrounded by elevated borders; type III have ulceration with invasion of the gastric wall; type IV are diffusely infiltrating (linitis plastica); and type V are unclassifiable.[36]

PROGNOSTIC FACTORS

The most important prognostic indicators reflect tumor extent. If hematogenous or transperitoneal spread is present, the outcome is, essentially, uniformly fatal. Survival rates decrease with progressive tumor extension within or beyond the gastric wall.[31,37-39] The number of involved lymph nodes also has a significant impact on survival. Lymph node involvement is important, as are the number and locations of nodes affected.[31,39-41] Minimal nodal involvement adjacent to the primary lesion only moderately affects prognosis.[37,41,42] The finding of either involved lymph nodes or complete wall penetration is usually not as ominous as the presence of both.[37,39,41,43] Additional prognostic indicators include a poor performance status, elevated alkaline phosphatase levels, and ethnicity.[44] In one study, Asian Pacific Islanders born in the United States were compared to those born abroad, finding that only foreign-born Asian Pacific Islanders had a more favorable survival compared to indigenous non-Hispanic white patients.[45] The proposed hypothesis to explain disparities in survival outcomes between Western and Asian populations includes early detection in the latter, leading to stage migration, differences in treatment policy, as well as potential differences in tumor biology. In another review, gastric cancer prognostic factors included age, type, number of positive and negative lymph nodes resected, depth of invasion, microsatellite instability, AMPHIOREGULIN (AREG), epidermal growth factor receptor (EGFR),

insulin-like growth factor-1 (IGF1R), osteopontin expression, pretreatment weight, and Maruyama Index.[46]

Flow cytometry may also be prognostically valuable; aneuploidy is associated with unfavorable tumor location, lymph node metastasis, and primary tumor invasion.[47-49] Unfavorable DNA flow cytometry correlates with a poor prognosis.[47] The prognosis is worse for cardia lesions, and flow cytometry reveals a greater incidence of aneuploidy.[49] The gross pathologic appearance of the primary lesion also reveals prognostic information, although it is not known whether this factor is independent of tumor stage. Patients with Borrmann type I and II tumors have relatively favorable 5-year survival rates, although patients with type IV (linitis plastica) fare poorly.[42,50-52]

The molecular biology of gastric cancer reflects the heterogeneity of its causes and its histologic subtypes. A detailed discussion of the molecular biology of gastric cancer is beyond the scope of this chapter and is well detailed elsewhere.[11] However, identification of the genetic and phenotypic variables existing among gastric cancers may lead to more directed therapeutic approaches and a more accurate prediction of clinical outcome. Changes that may affect the behavior of gastric tumor cells involve four major types of alterations. Loss of tumor suppressor gene function, especially inactivation of the *p53* gene, appears to play a critical role. The *p53* gene is located on the short arm of chromosome 17 and plays a key role in tumor suppression and cell cycle regulation.[53] The *p53* gene halts DNA replication and triggers programmed cell death in response to DNA damage.[54] Loss of p53 function allows malignancy to develop, affects the effectiveness of chemotherapy and irradiation, and predisposes cells to genetic instability.[55,56] The latter is particularly important because p53 mutations occur early in tumorigenesis.[57]

A second major aberration affecting gastric epithelial cells is the impact of alterations in mismatch repair genes. Two such genes, *hMSH3* and *hMLH1*, on chromosomes 2 and 3, respectively, account for replication errors throughout the genome. Mutations in these genes are implicated in cancer family syndromes and hereditary nonpolyposis colorectal cancer, which is a disease associated with an increased tendency for the development of gastric tumors.[58] Mutations in these genes generate genetic instability and have the potential to lead to further alterations in oncogenes.

Two proto-oncogenes, *c-met* and *k-sam*, are associated with scirrhous carcinoma of the stomach. The former encodes hepatocyte growth factor, which is a potent endogenous promoter of gastric epithelial cell growth.[59] Its overexpression correlates with tumor progression and metastasis.[60] The latter encodes a tyrosine kinase receptor family.[60] In scirrhous carcinoma, *c-met* and *k-sam* amplification may occur independently. There is a tendency for *k-sam* to be activated in women less than 40 years of age and *c-met* to be amplified in men more than 50 years of age.[57,61]

Peptide receptors, including estrogen receptors and EGFRs, are associated with adverse prognoses.[62,63] EGF receptors and levels correlate with higher rates of primary tumor infiltration, poorer histologic differentiation, and linitis plastica.[64] The pathophysiologic relation between these peptide receptors and their association with poor prognoses is not well understood.

Modern molecular biology observations confirm the heterogeneity of human gastric cancer. Genetic alterations detected and potentially associated with a worse prognosis include CD44 expression; telomerase reactivation; *p53* gene inactivation; dysfunction of repair genes such as *hMSH3* and *hMLH1*; overexpression of proto-oncogenes such as *erb-B2*, *bcl-2*, *c-met*, and *k-sam*; estrogenic receptor expression; and presence of viral genomes.[65] Gastric cancers with class II major histocompatibility complex antigen expression have a better prognosis; however, the loss of expression is not an independent prognostic factor.[64] Illustrating the importance of understanding and potential exploitation of these genetic alterations, a randomized study was conducted in patients with human epidermal growth factor receptor 2 (HER2) overexpression. Patients with locally advanced or metastatic gastric or GE cancer (the ToGA trial) were randomized to determine whether trastuzumab (an antibody against the *HER2* gene product/receptor) enhanced treatment efficacy when added to cisplatin and 5-FU/capecitabine therapy. This study demonstrated that the addition of trastuzumab achieved a significant improvement in overall and progression-free survival.[66] These and other data led to the Radiation Therapy Oncology Group (RTOG) 1010 trial, which randomized patients with esophageal/GE junction tumors to receive preoperative radiation therapy concurrent with paclitaxel/carboplatin, with or without trastuzumab, followed by resection (discussed later).

GENERAL MANAGEMENT

Figure 64.5 is an algorithm for managing newly diagnosed gastric cancer.

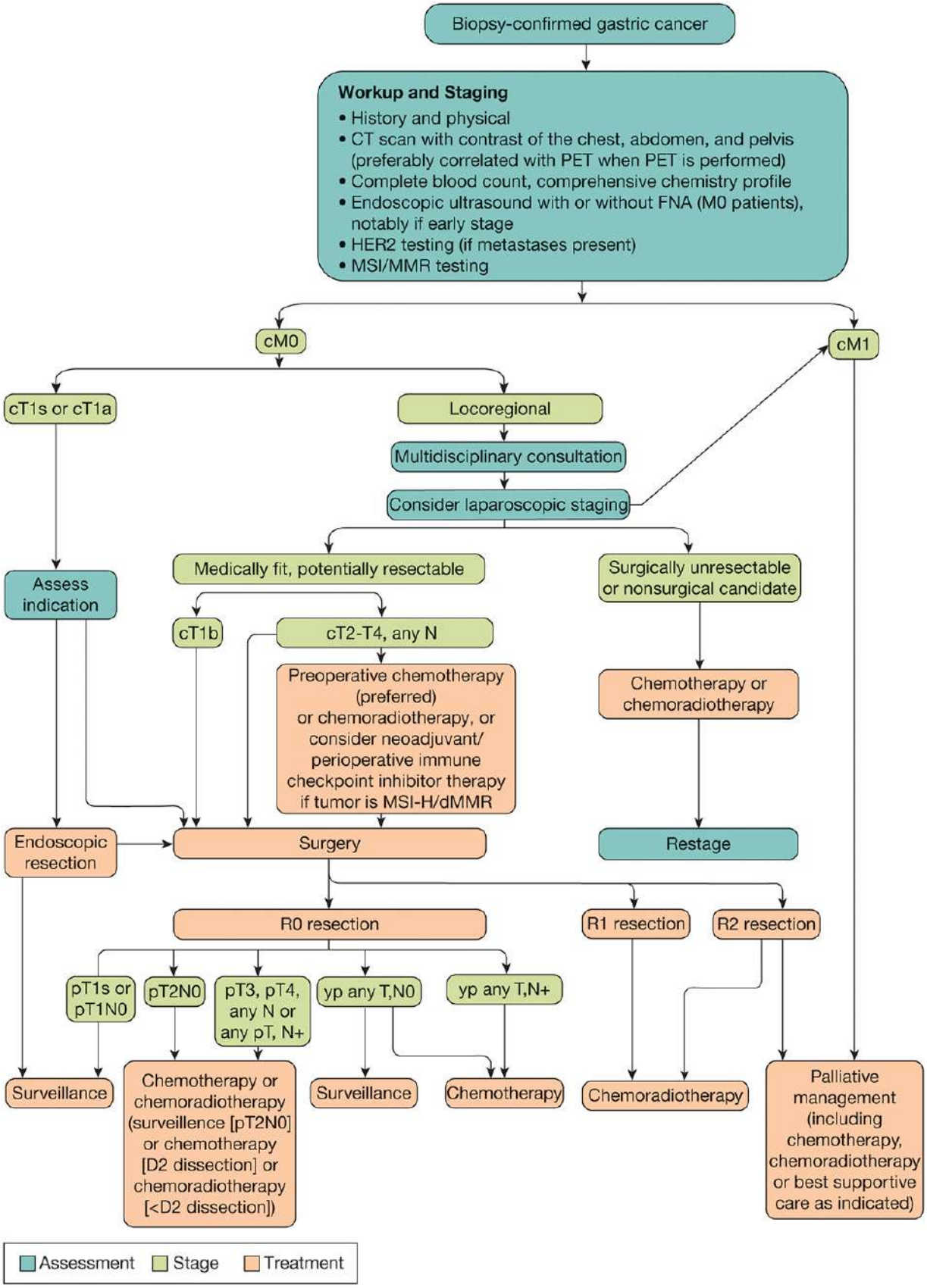

Biopsy-confirmed gastric cancer
Workup and Staging
• History and physical
• CT scan with contrast of the chest, abdomen, and pelvis (preferably correlated with PET when PET is performed)
• Complete blood count, comprehensive chemistry profile
• Endoscopic ultrasound with or without FNA (M0 patients), notably if early stage
• HER2 testing (if metastases present)
• MSI/MMR testing
cM0
cM1
cT1s or cT1a
Locoregional
Multidisciplinary consultation
Consider laparoscopic staging
Assess indication
Medically fit, potentially resectable
Surgically unresectable or nonsurgical candidate
cT1b
cT2-T4, any N
Preoperative chemotherapy (preferred) or chemoradiotherapy, or consider neoadjuvant/ perioperative immune checkpoint inhibitor therapy if tumor is MSI-H/dMMR
Chemotherapy or chemoradiotherapy
Endoscopic resection
Surgery
Restage
R0 resection
R1 resection
R2 resection
pT1s or pT1N0
pT2N0
pT3, pT4, any N or any pT, N+
yp any T,N0
yp any T,N+
Surveillance
Chemotherapy or chemoradiotherapy (surveillence [pT2N0] or chemotherapy [D2 dissection] or chemoradiotherapy [<D2 dissection])
Surveillance
Chemotherapy
Chemoradiotherapy
Palliative management (including chemotherapy, chemoradiotherapy or best supportive care as indicated)
Assessment
Stage
Treatment

FIGURE 64.5 Treatment algorithm for newly diagnosed gastric cancer. Treatment approaches are based on location and stage of the tumor, as well as surgical resectability and medical comorbidities of the patient. CT, computed tomography; EUS, endoscopic ultrasound; FNA, fine-needle aspiration; HER2, human epidermal growth factor receptor 2; MMR, mismatch repair; MSI, microsatellite instability; PET, positron emission tomography. (Adapted by permission from *Nature*: Ajani JA, Lee J, Sano T, Janjigian YY, Fan D, Song S. Gastric adenocarcinoma. *Nat Rev Dis Primers*. 2017;3:17036. Copyright © 2017 Springer Nature.)

Surgical Management

Complete tumor and regional lymph node resection remains the primary curative modality for gastric adenocarcinoma and may require total or distal gastrectomy. Operative attempts are highly successful if disease is limited to the mucosa; however, the incidence of such early lesions at diagnosis is less than 5% in most US series. In Japan, the incidence of lesions initially confined to the mucosa or submucosa was only 3.8% in 1955 and 1956, although by 1966, as a result of screening procedures, this figure had increased to 34.5%, with corresponding survival rates of 90.9%.[67] For very early gastric cancer (Tis and T1a), endoscopic mucosal dissection and endoscopic submucosal dissection have been successfully used as less radical alternatives to standard surgery. Appropriateness of endoscopic resection is based on the tumor depth, tumor diameter, histologic grade, and ulcerative component. General criteria for endoscopic resection of early gastric cancers include well or moderately differentiated disease measuring 2 cm or less, without ulceration, as well as intramucosal cancer. Some authors consider expanded criteria, including intramucosal disease more than 2 cm, ulcerated disease 3 cm or less, submucosal invasion no greater than SM1 level 3 cm or less, as well as intramucosal undifferentiated disease without ulceration 2 cm or less.[68]

As in other endoscopic procedures, outcomes are operator dependent. Endoscopic laser surgery has been applied successfully to patients with very early gastric cancer whose tumors are inoperable because of complicating medical illness. Small lesions that are pedunculated, noninvasive, and well differentiated have lymph node metastasis in less than 5% of cases and can be completely removed endoscopically in 75% of cases.[67] Radiation therapy with chemotherapy may be considered as adjuvant therapy in selected situations. These approaches in early gastric cancer (uncommonly seen in

Western society) require meticulous patient selection and remain a topic of investigation.

Curative or palliative surgical resection is possible for 50% to 60% of patients at the time of initial disease presentation. However, only approximately 25% to 40% are eligible for potentially curative resection. Generally, patients with evidence of peritoneal involvement, distant metastases, or locally advanced disease (including encasement of unresectable/major blood vessels) are considered to have unresectable disease. Palliative resection is usually reserved for rare cases, including symptomatic palliation of bleeding uncontrolled by other methods, and is generally considered a last resort in patients with locally unresectable or metastatic disease. A randomized trial from Asia (the REGATTA trial) enrolled 175 patients with gastric cancer. Patients were randomized to receive either chemotherapy (oral S1 + cisplatin) or palliative D1 gastrectomy followed by the same regimen. At interim analysis, no significant difference was seen in 2-year survival rates between the arms. The authors concluded that palliative gastrectomy could not be justified even in the setting of a solitary metastasis.[69] In some instances, unresectable tumors may be debulked successfully, with sites of minimal residual disease marked judiciously with clips. This may palliate and permit accurate delivery of postoperative radiation therapy. In patients with gastric outlet obstruction, gastrojejunostomy may be performed as an alternative to endoscopic placement of a stent in patients with expected longer survival.

No prospective randomized trials have definitively established optimal surgical therapy.[70,71] Generally, it is recommended that gastric cancer surgery be performed by experienced surgeons in high-volume centers, entailing removal of the perigastric lymph nodes (D1) as well as those along the main vessels of the celiac trunk (D2), with the goal of examining 16 or more lymph nodes (discussed later). Total gastrectomy is generally necessary in most cases of proximal and midgastric carcinomas, although proximal gastrectomy may be appropriate depending on extent of disease. However, for more distal lesions, distal gastrectomy is preferred if adequate margins can be obtained. Generally, the distal margin in subtotal gastrectomy needs to be approximately 2 cm. This operation removes approximately 80% of the stomach along with the node-bearing tissue, the gastrohepatic and gastrocolic omenta, and the first portion of the

duodenum. Larger lesions may require total gastrectomy. Total gastrectomy is not recommended where 4- to 6-cm margins can be achieved with partial gastrectomy given improved safety and long-term functional outcome improvements in the latter.[72] Patients treated with total gastrectomy characteristically have 5-year survival rates of 10% to 15%, and those undergoing radical subtotal gastrectomy have 5-year survival rates of 25% to 45%.[40,71,73] The inferior survivorship of patients undergoing total gastrectomy reflects larger tumors and unfavorable proximal lesions that prompt such a procedure. The value of splenectomy has not been addressed in prospective randomized trials; however, retrospective Japanese data do not support a survival benefit.[74] Because routine splenectomy has not shown significant improved outcomes and potentially increases complication rates, complete removal of splenic nodes is not commonly performed by Western surgeons. Roux-en-Y reconstruction may be used to avoid bile reflux gastritis/esophagitis. Vitamin B supplementation is generally required following total gastrectomy because of lack of intrinsic factor production from the stomach.

Minimally invasive gastrectomy (including laparoscopic or robot-assisted resection) is being increasingly utilized, although these approaches remain a subject of investigation. These approaches carry potential advantages, including less intraoperative blood loss, faster recovery times, reduced pain, and decreased hospital length of stay. Multiple trials have indicated that minimally invasive techniques provide equivalent surgical and oncologic outcomes to open approaches.[75] The KLASS-O2 Korean randomized trial showed a lower rate of complications with laparoscopic gastrectomy with D2 lymphadenectomy, less postoperative pain, and shorter length of hospital stay compared to open surgery.[76] However, the LOGICA trial comparing laparoscopic to open gastrectomy did not find differences in complication rates or length of stay.[77] Patient selection is important. In patients who undergo adjuvant chemoradiotherapy, it may be prudent to place a feeding jejunostomy at the time of resection.

The propensity for gastric carcinoma to spread via the submucosal lymphatics suggests that a 5-cm margin of normal tissue proximally and distally may be optimal. It may be necessary to include a portion of the esophagus or duodenum to achieve adequate margins. Frozen section pathologic evaluation of surgical margins has been advocated to confirm

their adequacy.[40] The importance of careful evaluation of longitudinal margins is emphasized in multiple series with documented positive pathologic margins in approximately one-quarter of "curatively" resected specimen.[78-85] The approximate 25% positive longitudinal margin correlates almost precisely with the incidence of locoregional recurrence in the anastomosis or stump, as discussed later.

Although R0 resection with adequate lymph node sampling is a primary goal for gastric cancer surgery, many patients end up with involved margins. Even though the longitudinal margin is routinely evaluated, equally important but frequently not assessed are the radial or circumferential margins. The incidence of radial margin positivity is not well reported in the literature. The rising incidence of T3 and T4 GE tumors may result in an increasing rate of microscopically positive radial margins. Because the perigastric tissue surrounding the GE junction and distal esophagus has no serosa, lesions that extend to the pathologic radial margin likely represent a true positive margin in a large percentage of cases.

The extent of lymph node dissection remains an ongoing area of controversy. The Japanese Research Society for gastric cancer categorizes draining stomach lymph nodes into 16 stations, 6 perigastric and 10 regional along major vessels and adjacent to the pancreas (see Figure 64.3). A D1 dissection only includes perigastric nodes (stations 1-6); a D2 dissection includes those along the common hepatic, left gastric, celiac, and splenic arteries (stations 7-11); a D3 dissection includes additional nodes with any of the porta hepatis and adjacent to the aorta (stations 12-16).[72] According to the most recent AJCC staging manual, accurate nodal staging demands evaluation of at least 16 lymph nodes. This may reduce stage migration. In a D0 dissection, there is generally incomplete removal of the lymph nodes along the greater and lesser curvature. In series with rigorous pathologic evaluation of these nodes,[86] the likelihood of discovering lymph node metastasis increases markedly in both D1 and D2 procedures. There appears to be a small subset of patients who have limited metastasis in the celiac axis, superior pancreatic, or retroduodenal chains and may be cured by a D2 lymph node resection.[87,88] Data from the Surveillance Epidemiology and End Results database show that the number of nodes examined correlated with overall survival, potentially reflecting improved staging in these patients.[89] Japanese researchers advocate complete lymph

node removal to improve the rates of local control and survival. Several nonrandomized clinical trials suggested that extended lymphadenectomy may improve survival.[90-93] Others[94] reported that increasingly radical lymphadenectomies failed to improve survival or reduce the risk of locoregional failure. Multiple prospective randomized trials of lymphadenectomies have been reported[87,95-99] and show no survival advantage with more extensive lymph node dissection. A more recent update of a Dutch randomized trial showed D2 dissections to be associated with improved disease-specific survival versus D1 at a median follow-up of 15 years.[100] An Italian gastric cancer study group report similarly evaluated D1 versus D2 dissection and found that after 15 years of follow-up, there was no significant difference in overall and disease-free survival between these groups, although disease-specific survival in gastric cancer–related mortality was improved in the D2 group.[101] However, morbidity and mortality rates have been significantly higher for patients undergoing more extensive nodal dissection. Despite the mixed evidence of randomized trials, it is generally recommended that spleen-sparing D2 lymphadenectomy be performed by experienced surgeons in high-volume centers. An even more extensive lymph node dissection may entail para-aortic nodal dissection. However, a Japanese trial comparing D2 lymphadenectomy versus the same with para-aortic (D3) nodal dissection did not show any differences in overall or relapse-free survival between the groups, indicating the latter approach should not be used in patients with curable gastric cancer.[102] However, other important principles of lymph node dissection have been elucidated through these trials. The first is that as more lymph node areas are dissected and as pathologic lymph node evaluation is more rigorous, considerable stage migration occurs. This stage migration produces an apparent improvement in stage-specific survival without improvement in survival in the group overall.

Failure Patterns After Surgical Resection

Local failures in the tumor bed and/or regional lymph nodes and distant failures by hematogenous or peritoneal routes are common mechanisms of failure after “curative” resection in clinical, reoperative, and autopsy series[43,103-106] (Tables 64.4 and 64.5). For GE junction lesions, the liver and

lungs are common sites of distant metastases. With gastric lesions that do not extend to the esophagus, the initial site of distant metastasis is usually the liver, and many failures could be prevented if an effective abdominal treatment could be combined with treatment to the primary site. In the series of Landry et al,[107] 50 of 88 (57%) failing patients had disease progression within the abdomen only. Abdominal treatment also could address peritoneal seeding, which occurs in 23% to 43% of patients postgastrectomy.[103-111]

TABLE 64.4 PATTERNS OF FAILURE AFTER "CURATIVE" RESECTION OF GASTRIC CANCER

	Incidence in Total Patient Group (%)		
Pattern of Failure	**Clinical[107]**	**University of Minnesota Reoperation[a,38]**	**Autopsy[1,104,105,108]**
Locoregional[b]	38	67	80-93
Peritoneal seeding	28	41	30-43
Localized	–	19	–
Diffuse	–	22	–
Distant metastases	52	22	49

[a]107 patients at risk.

[b]Local or regional failure based on direct extension of tumor, lymphatic spread, or operative wound implant; one or more distant metastases on hematologic basis; abdominal involvement on the basis of peritoneal seeding or peritoneal lymphatics.

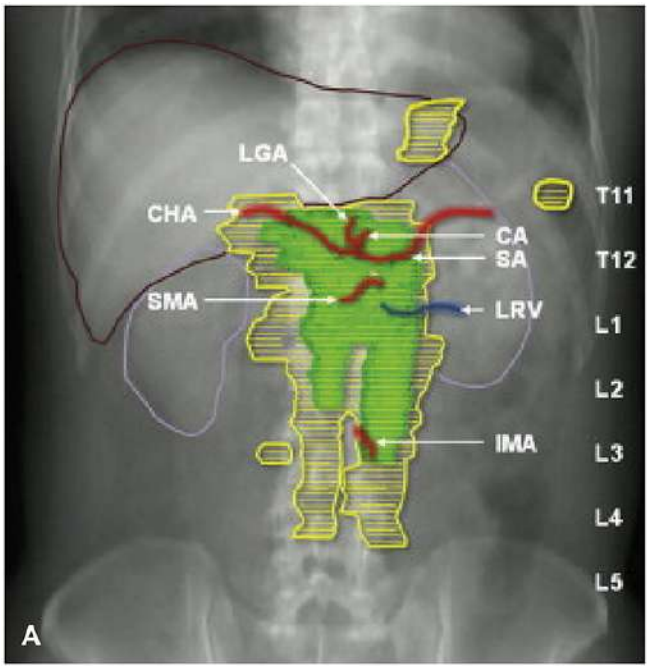
TABLE 64.5 PATTERNS OF LOCOREGIONAL FAILURE AFTER RESECTION OF GASTRIC CANCER

	Incidence (%)		
	Clinical[109]	**Reoperation[38]**	**Autopsy[110]**
Patients at risk	130	107	92 and 28
Failure area			
Gastric bed	21	54	52-68
Anastomosis or stumps	25	26	54-60

	Incidence (%)		
	Clinical[109]	Reoperation[38]	Autopsy[110]
Abdominal or stab wound	–	5	–
Lymph node(s)	8	42	52

Locoregional failures occur commonly in organs and structures of the gastric bed and in lymph nodes and is an established mode of failure (Table 64.5). Clinically detectable locoregional recurrence following surgical resection alone generally exceeds 25%. As an example, in long-term follow-up of the previously described Dutch Gastric Cancer Trial, even with D2 dissection, locoregional recurrence rates were 25% and 41% following D2 surgery.[100] However, reoperation and autopsy series have suggested that these rates are much higher.[43,103-106,109] Failures in the anastomoses, gastric remnant, or duodenal stump also are frequent, as suggested by the incidence of positive longitudinal resection margins (Table 64.5). As is true for most sites, clinical series underestimate the true incidence of locoregional failure when compared with reoperative or autopsy series (Table 64.4). Progressive extension of the operative procedure to include routine splenectomy, omentectomy, and radical lymph node dissection neither improved survival nor decreased the incidence of locoregional failures in the University of Minnesota series.[43] Subsequent failure in areas of initial node dissection occurred frequently, even with radical lymph node dissections[43] (see Figure 64.4). The high rate of regional node relapse (including para-aortic basins) provides a partial explanation for the lack of survival benefit with a D2 (extended lymphadenectomy) versus D1 (limited lymphadenectomy) node dissection in phase III surgical trials discussed previously. A more contemporary analysis of 382 patients with stage III (N3) disease undergoing D2 resection receiving adjuvant chemotherapy alone demonstrated that first site of recurrence (some patients had multiple) was local in 7% (most at anastomosis and few in gastric bed), regional failure as any component of first recurrence occurred in 24% of patients (isolated in 12.8% of patients), and peritoneal based in 33%. Most commonly involved lymph node groups were 16, 12, 14, 13, and 9 (primarily outside of the D2 nodal basin).[112] A further analysis of this trial of nodal CT recurrences suggested that vessel-based delineations of these volumes on CT may assist

in target design[113] (Figure 64.6A). A smaller study from Stanford investigators evaluated patients with locally advanced gastric cancer receiving preoperative chemotherapy followed by D2 resection. Three-year cumulative incidences of local regional failure and distant metastases were 8.4% and 41%, respectively. The authors concluded that patients with locally advanced gastric cancer with less-than-complete response to chemotherapy had poor outcomes due to high rates of distant metastases and that adjuvant regional therapy such as radiation is unlikely to affect survival.[114] A pattern of failure analysis of the Adjuvant Chemoradiation Therapy in Stomach Cancer (ARTIST) trial (discussed later) evaluating patterns of recurrence suggested a significant decrease in regional recurrence with the addition of radiation therapy in node-positive patients. Specifically, patients in the nonradiation arm had significantly higher likelihood of failure in the retroperitoneal lymph node basins, emphasizing the importance of covering this area in patients with gastric cancer, whereas true local recurrence rates did not differ significantly between the two arms (Figure 64.6B).[115]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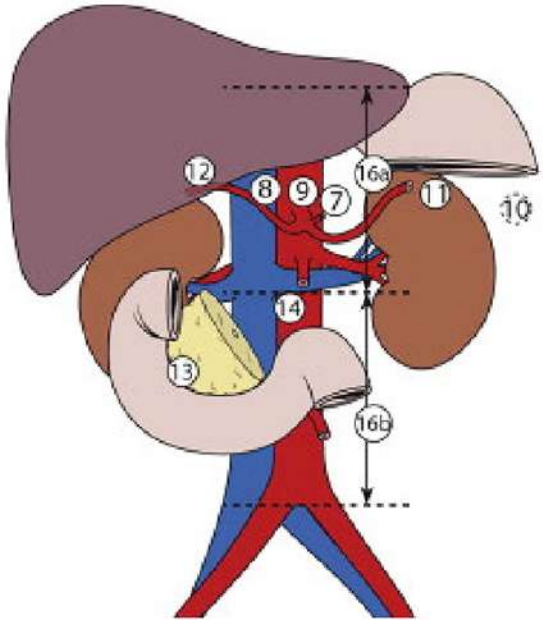
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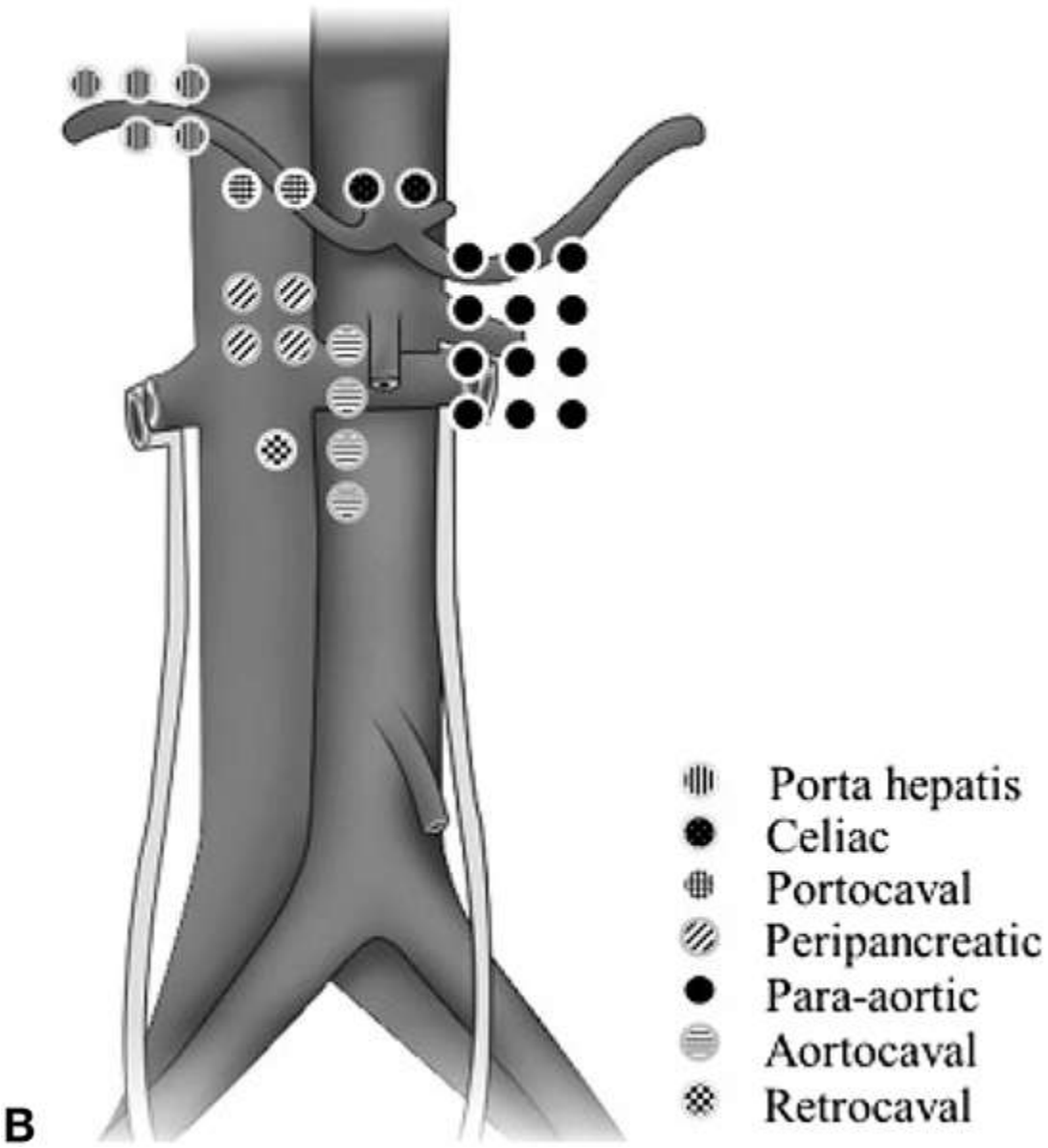


FIGURE 64.6 A. Common nodal recurrent regions (green) overlapped by more than five recurrent nodal gross tumor volumes (GTVs) depicted on a digitally reconstructed radiograph image. The volume of total GTVs (yellow), liver (cobalt purple), and both kidneys (violet) is also seen. Common hepatic artery (CHA), splenic artery (SA), left gastric artery (LGA), celiac artery (CA), superior mesenteric artery (SMA), inferior mesenteric artery (IMA), and left renal vein (LRV) are shown in solid lines. B. Retroperitoneal patterns of failure in the nonradiation arm of the ARTIST trial.

Indications for Radiation Therapy

The results of the US Gastrointestinal Intergroup Gastric Adjuvant Trial changed the standard of care in the United States to the use of both

chemotherapy and radiation therapy in the postoperative setting for patients with disease extension through the gastric wall and/or with lymph nodes positive for tumor (discussed later).[116] Postoperative irradiation plus concurrent and maintenance fluoropyrimidine-based chemotherapy is recommended for patients with stage IB-IV and M0 gastric cancer.[116] Quality control of irradiation field design was conducted during the cycle of chemotherapy given before the start of concurrent chemoradiation. The up-front quality control provided the mechanism to correct most of the major or minor deviations (35% incidence) in irradiation field design before the start of treatment and resulted in only a 6.5% final major deviation rate.

Radiation therapy, usually administered with concomitant fluoropyrimidine-based chemotherapy, is also indicated for locally confined gastric cancer that either is not technically resectable or occurs in medically inoperable patients. In this setting, therapy can be administered with curative or palliative intent, depending on the clinical situation. Those who undergo gastric resection with incomplete tumor resection or have truly positive margins of resection are also managed appropriately by combined-modality postoperative therapy. A series of 409 patients from the Netherlands Cancer Registry who underwent R1 resection were analyzed, including patients who did and did not receive adjuvant chemoradiation. Median age and percentage of patients with diffuse tumors were higher in the nonradiation group, although there is no significant difference in stage. Median overall survival was significantly improved (13 vs 24 months, P = .003) in patients receiving adjuvant radiation therapy, which was an independent prognostic factor for survival on multivariable analysis.[117]

RADIATION THERAPY TECHNIQUES

Simulation

When patients with gastric cancer are simulated, the radiation oncologist should know the extent of disease based on imaging (barium swallow, CT, PET) as well as endoscopic procedures. CT simulation is appropriate for treatment planning. Some authors have recommended fasting for more than 2 hours before simulation as well as at treatment.[118] During simulation, the patient is positioned, straightened, and immobilized on the simulation table. An immobilization device is used to minimize variation in daily setup.

Arms are generally placed upward/outside of the area being irradiated. Oral contrast is generally administered to delineate the stomach and may help define the extent of mucosal irregularity (if the patient is surgically naïve). The patient is placed on the CT simulator in the treatment position, and a scan of the entire area of interest with margin is obtained. At minimum, 3- to 5-mm slices should be used, allowing accurate tumor characterization as well as improved quality of digitally reconstructed radiographs. If patients lose more than 10% of their body weight during therapy, consideration should be given to repeat CT planning. Intravenous (IV) contrast is generally used to delineate mediastinal and abdominal vascular nodal basins, including the celiac axis, and to allow the radiation oncologist to discern normal vasculature from other adjacent normal structures and potential adenopathy. The tumor (if the patient is surgically naïve) and vital structures are then outlined on each slice on the treatment planning system, enabling a three-dimensional (3-D) treatment plan to be generated. The use of respiratory gating or breath-holding techniques may help to reduce target motion with respiration and, therefore, avoidance of normal tissue irradiation associated with larger margins used in free-breathing approaches. Four-dimensional (4-D) CT scan may be appropriate to assess respiratory/ tumoral motion, facilitating appropriate margin placement on the target volumes or implementation of respiratory motion control approaches.

Treatment Planning

Target Design

For a detailed description of target and field design in proximal gastric cancer involving the GE junction, the reader is referred to Chapters 59. In the design of radiation fields for neoadjuvantly treated or locally unresectable gastric cancer (as well as in the re-creation of tumoral volumes in adjuvantly treated patients), it is important to define varying target volumes, including gross disease as well as potential areas of subclinical involvement (ie, gross tumor volume [GTV] and clinical target volume [CTV], respectively). Defining GTV (including re-creation of volumes in the adjuvant setting) is based on multiple studies, including endoscopic descriptions (from both esophagogastroduodenoscopy [EGD] and

endoscopic ultrasound) as well as cross-sectional imaging. Gastric wall thickening correlating to the GTV can frequently be visualized on diagnostic and radiation planning CT. Similarly, EUS appears to be the most reliable test in detecting lymphadenopathy related to nodal spread. The endoscopist should be encouraged to accurately define not only the primary disease extent on EGD but also the depth of penetration and potential involvement of adjacent structures on EUS, which can also be used to help guide GTV delineation. Similarly, EUS may allow detection of lymph nodes that may not be appreciated on CT or PET imaging, and the endoscopist should be encouraged to describe the size as well as location (eg, relationship to tumor or adjacent structures). Additionally, radiographic areas of lymphadenopathy should similarly be included in the GTV. In GTV design, basing potential nodal involvement (and therefore target volumes) on nodal size is problematic given that metastatic lymph nodes may frequently be below the resolution of conventional imaging. Therefore, it is not appropriate to rely exclusively on imaging modalities to define areas of subclinical spread for gastric cancer, realizing established pathologic patterns of spread data are important in determining radiation field design.

The identification of potential direct and nodal pathways for spread of subclinical disease (ie, CTV definition) in gastric cancer is of paramount importance. These areas vary significantly depending on site of origin of disease, making gastric cancer planning somewhat complex. As described previously, the stomach is characterized by a rich network of lymphatics that facilitates early lymph node spread of disease. Some authors have recommended dividing the stomach into three equal lengths (upper/proximal, middle, and distal), with tumors classified by location of the bulk of their masses in these respective sites. Therefore, practically speaking, the stomach can be divided into proximal (remembering that in the AJCC eighth edition staging system, involvement of the GE junction by very proximal third tumors would be classified as an esophageal tumor), middle, or distal segments (Figure 64.7).

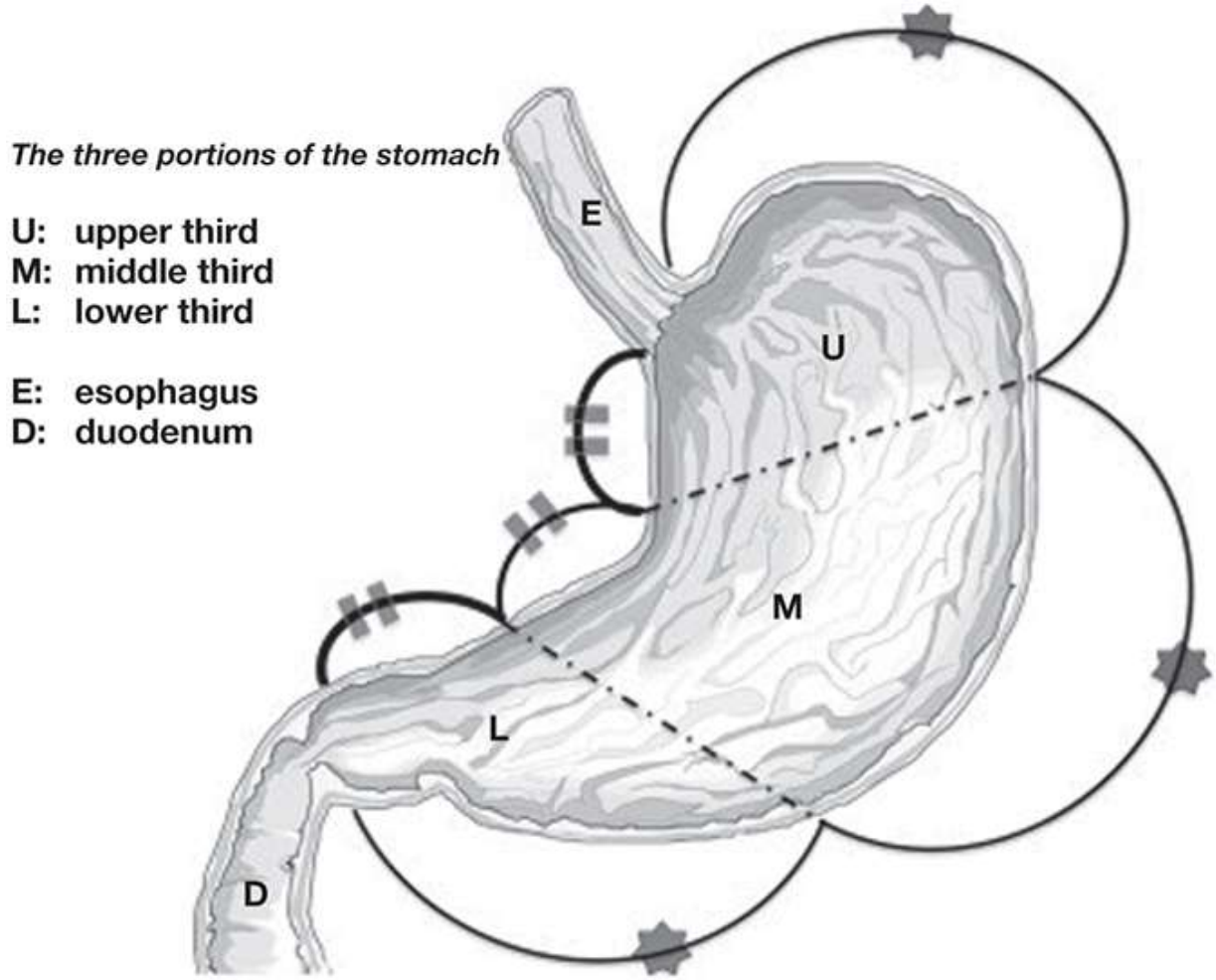


FIGURE 64.7 Subdivision of the stomach into equal lengths along greater and lesser curves. (Reprinted from Matzinger O, Gerber E, Bernstein Z, et al. EORTC-ROG expert opinion: radiotherapy volume and treatment guidelines for neoadjuvant radiation of adenocarcinomas of the gastroesophageal junction and the stomach. *Radiother Oncol*. 2009;92[2]:164-175. Copyright © 2009 Elsevier Ireland Ltd. With permission.)

Primarily based on extensive analysis of patterns of nodal spread from surgical series, Japanese investigators have developed lymph node station classifications (the Japanese classification of gastric carcinoma of the Japanese Gastric Cancer Association) that have been validated in other series (see Figure 64.3). Based on this system, general recommendations for CTV definition for tumors in varying parts of the stomach are as follows. Proximal third stomach tumors should include the contour of the stomach with exclusion of the pylorus and antrum (keeping a minimal margin of 5 cm from the GTV). Middle third tumors should include the contour of the stomach from the cardia to the pylorus. Distal third tumor CTVs should

include the stomach except for the cardia/fundus, again keeping a minimal margin of 5 cm from the GTV. However, some authors have noted that surgical series have demonstrated that less than 5% of patients have microscopic mucosal extension more than 3 cm beyond gross disease, suggesting smaller margins may be feasible.[118] If pyloric/duodenal invasion is present, the CTV would be expanded along the duodenum with a margin of 3 cm from the tumor. Nodal volumes to be included are described later, and it has been recommended that the CTV consist of a 5-mm margin around corresponding vessels. An internal target volume (ITV) may be created based on 4-D imaging, with planning target volume (PTV) expansion variable, although this typically ranges from 5 to 15 mm depending on immobilization technique and use of image guidance. If target motion is not accounted for, the minimal recommended 3-D margins to the CTV to obtain the ITV are 1.5 cm in all directions, considering physiologic organ motion, particularly respiratory motion. The PTV can then be defined as the ITV volume plus a 3-D margin of 5 mm.[119]

Field Design

Field design is based on established patterns of nodal involvement following gastrectomy and lymph node dissection as well as patterns of disease recurrence (Table 64.5). This is also dependent on tumor location within the stomach, stage of disease, as well as extent of lymph node dissection. In resected patients, the gastric/tumor bed, anastomosis and gastric remnant, and pertinent regional lymphatics should be included in most patients.[43,106,110,111,116,119] Major nodal chains at risk include the lesser and greater curvature, celiac axis, pancreaticoduodenal, splenic, suprapancreatic, porta hepatis, and, in many, para-aortic to the level of mid-L3. However, included basins are frequently modified based on margin status, type of surgery (ie, D0, D1, D2), location within the stomach, as well as stage.

The relative risk of nodal metastases at a specific nodal location depends on both the site of origin of the primary tumor[119-121] and other factors, including width and depth of invasion of the gastric wall. On the basis of previously described patterns of failure data, general guidelines in terms of field design are illustrated in Figures 64.8 to 64.10 and discussed later.

These are general guidelines, and all plans should be individualized according to available imaging and endoscopic data, and generalized portals based on patterns of failure data frequently need to be modified on the basis of the individual patient's initial extent of disease.[119-121] As seen in Figures 64.8 to 64.10, gastric tumors (ie, without GE junction involvement) that originate in the proximal portion of the stomach have a higher propensity of spread to nodes in the paracardial region but a lower likelihood of involvement of nodes in the region of the gastric antrum, periduodenal area, and porta hepatis.

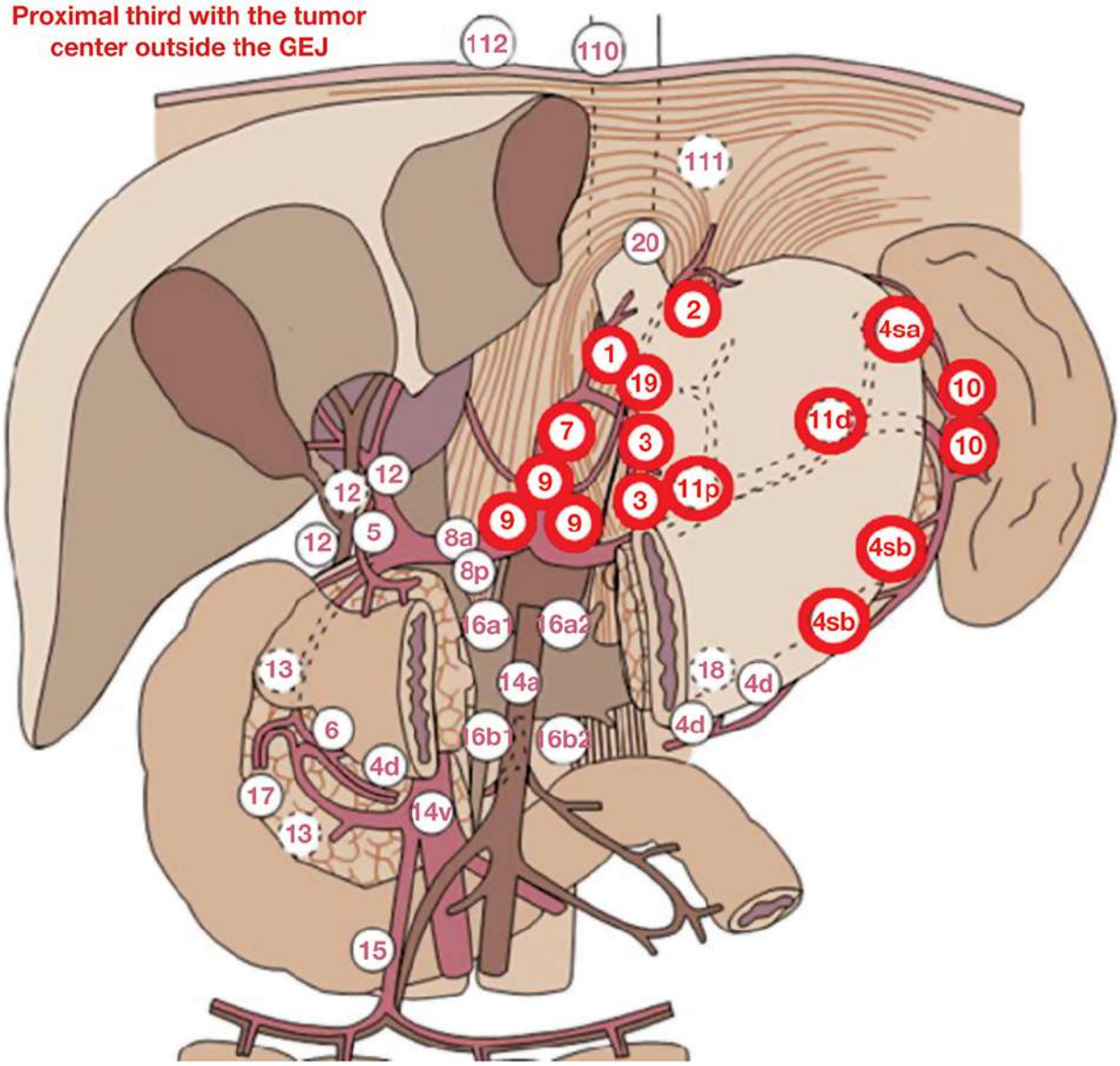


FIGURE 64.8 Suggested lymph node station coverage for tumors of the proximal third of the stomach without involvement of the GE junction (GEJ). (Reprinted from Matzinger O, Gerber E, Bernstein Z, et al. EORTC-ROG expert opinion: radiotherapy volume and treatment guidelines for neoadjuvant radiation of adenocarcinomas of the gastroesophageal junction and the stomach. *Radiother Oncol*. 2009;92[2]:164-175. Copyright © 2009 Elsevier Ireland Ltd. With permission.)

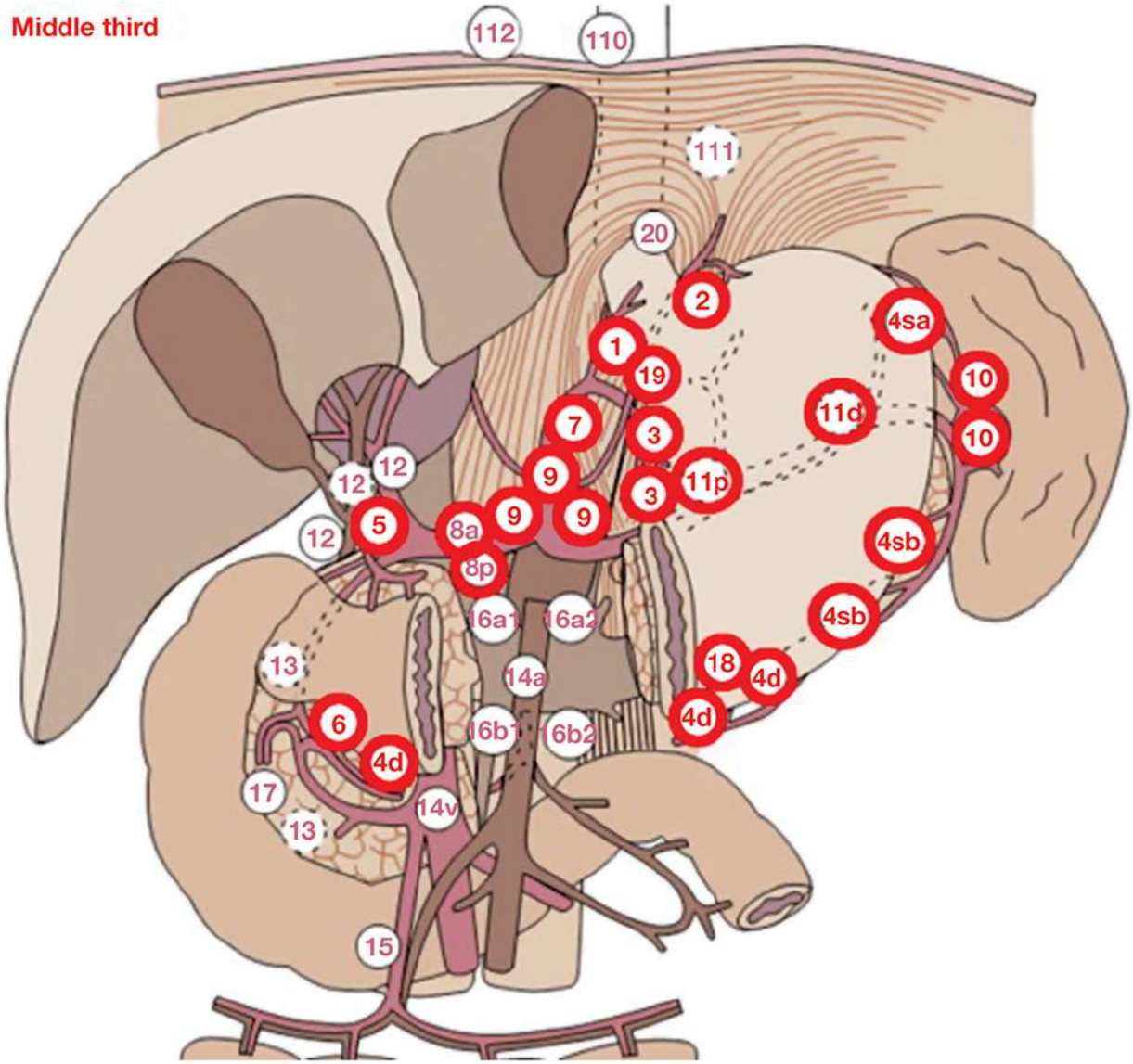


FIGURE 64.9 Suggested lymph node nodal coverage of patients with middle third gastric carcinomas. (Reprinted from Matzinger O, Gerber E, Bernstein Z, et al. EORTC-ROG expert opinion: radiotherapy volume and treatment guidelines for neoadjuvant radiation of adenocarcinomas of the gastroesophageal junction and the stomach. *Radiother Oncol*. 2009;92[2]:164-175. Copyright © 2009 Elsevier Ireland Ltd. With permission.)

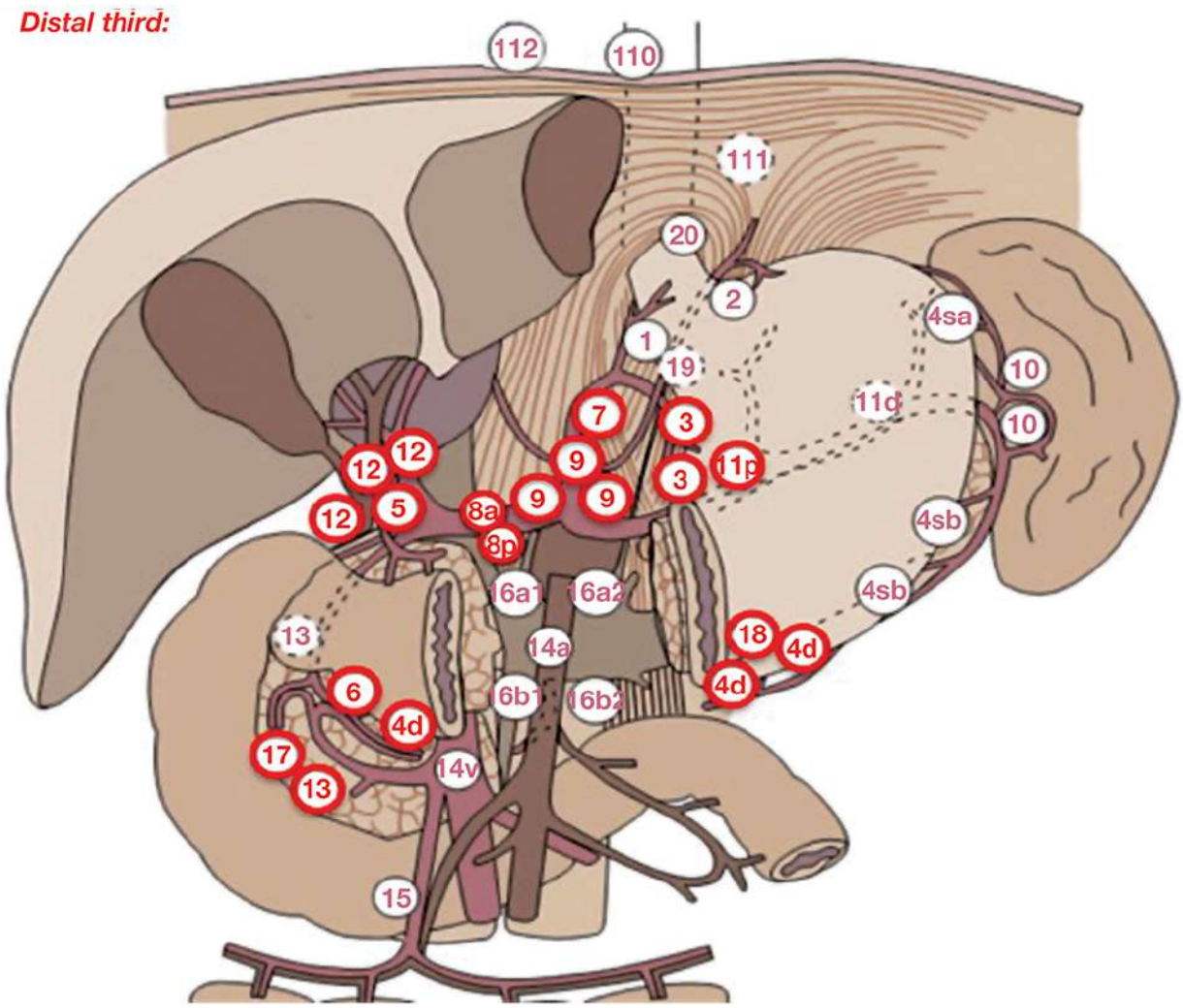


FIGURE 64.10 Suggested nodal coverage for primary gastric cancers of the distal third of the stomach. (Reprinted from Matzinger O, Gerber E, Bernstein Z, et al. EORTC-ROG expert opinion: radiotherapy volume and treatment guidelines for neoadjuvant radiation of adenocarcinomas of the gastroesophageal junction and the stomach. *Radiother Oncol*. 2009;92[2]:164-175. Copyright © 2009 Elsevier Ireland Ltd. With permission.)

In patients with proximal gastric cancers (gastric cardia and GE junction) undergoing esophagogastrectomy with intrathoracic anastomosis, the CTV typically includes 3 to 4 cm of the mucosa of the esophagus and distal stomach, tumor bed (typically determined by preoperative imaging and including the medial two-thirds of the left hemidiaphragm), as well as lymph node stations 1 to 4, 7, and 9 to 11, with some authors recommending inclusion of stations 12 to 13[118]; if the GE junction is involved, stations 20 and 110 to 111 are also included, and if the tumor extended to the middle stomach, stations 5, 6, and 8 frequently are

included.[118] Tumors that originate in the body of the stomach can spread to all nodal sites but have the highest likelihood of spreading to nodes along the greater and lesser curvature near the location of the primary tumor mass. Nodal basins are similar to upper third tumors with the exception of inclusion of nodal basins along the pyloric region, common hepatic artery, and additional coverage along the greater curvature. For middle third patients undergoing total gastrectomy with Roux-en-Y esophagojejunal anastomosis, the CTV typically includes 3 to 4 cm of mucosa of the esophagus and jejunum, tumor bed delineated as earlier, as well as lymph node stations 3 to 11, with some authors advocating inclusion of stations 12 to 13,[118] as well as consideration of 1 to 2 if there is proximal third stomach involvement. Tumors that originate in the distal stomach, in the region of the gastric antrum, have a high likelihood of spread to the periduodenal, peripancreatic, and porta hepatis nodes, whereas they have a lower likelihood of spread to the nodes near the cardia of the stomach, the periesophageal and mediastinal nodes, or to the splenic hilar nodes—that is, there is less emphasis placed on more proximal nodes (including coverage of the splenic artery course, including splenic hilum) and more comprehensive coverage of pancreaticoduodenal nodal basins. For distal third tumors undergoing distal gastrectomy with gastrojejunal anastomosis, the CTV typically includes 3 to 4 cm of the mucosa of the proximal stomach and jejunum as well as 3 to 4 cm of the duodenal stump, tumor bed delineated using preoperative imaging as given earlier, and lymph node stations 3 to 9 and 11 to 13.[118] Figure 64.11 shows an example of 3-D fields for a T3N1 antral tumor involving the gastric body. Figure 64.12 shows examples of varying nodal locations on axial CT images. Any tumor originating in the stomach has a high propensity of spread to nodes along the greater and lesser curvature, although they are most likely to spread to those sites in close anatomic proximity to the primary tumor mass.

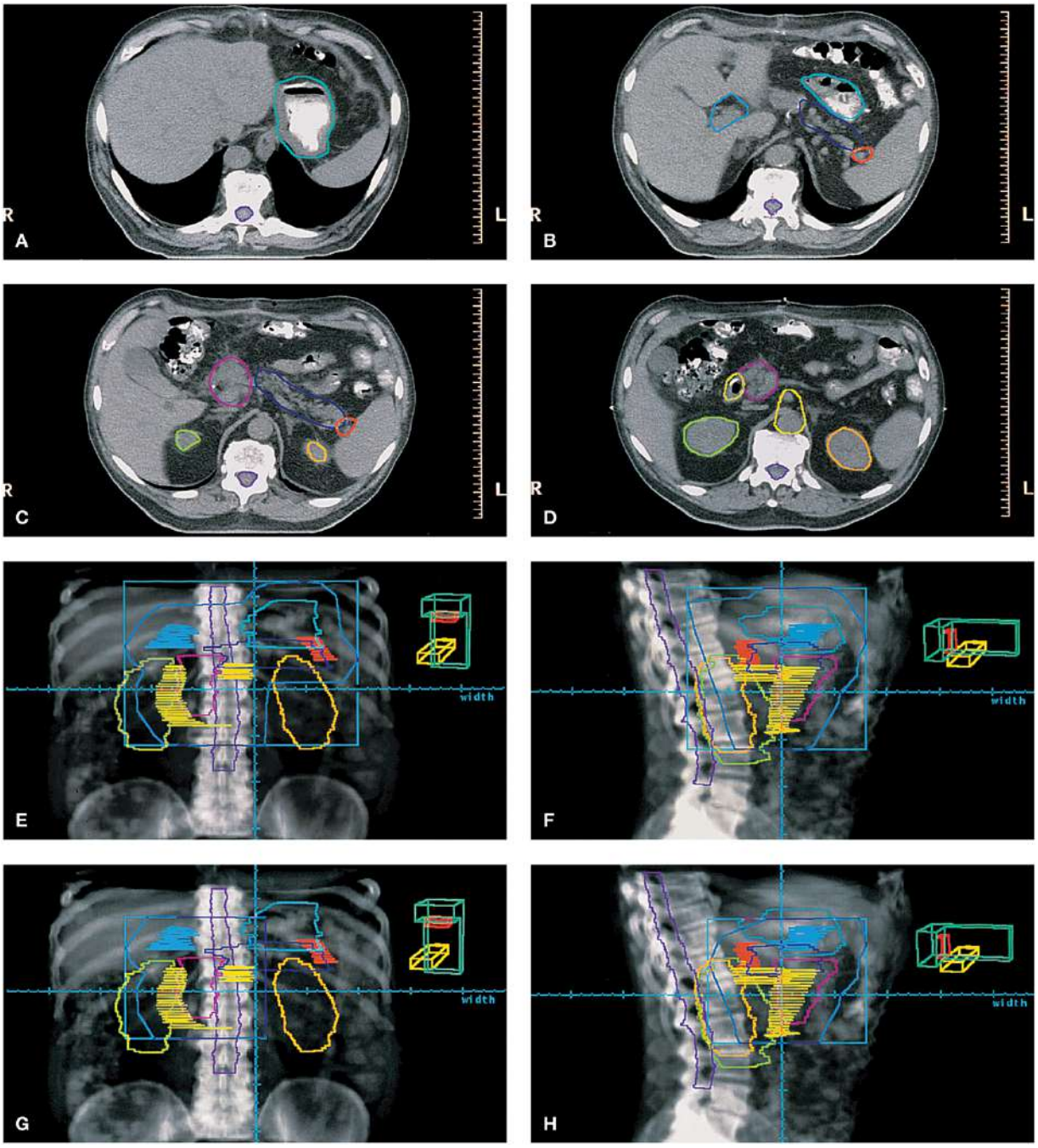
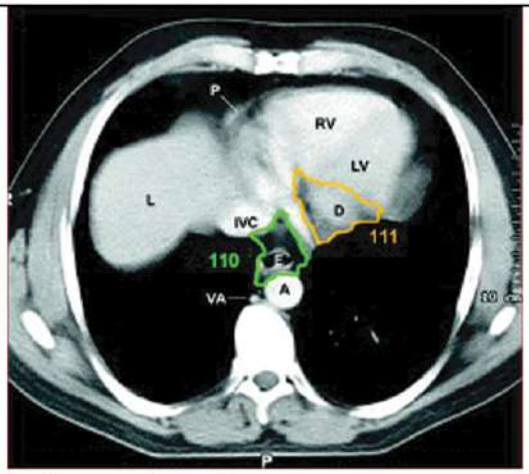
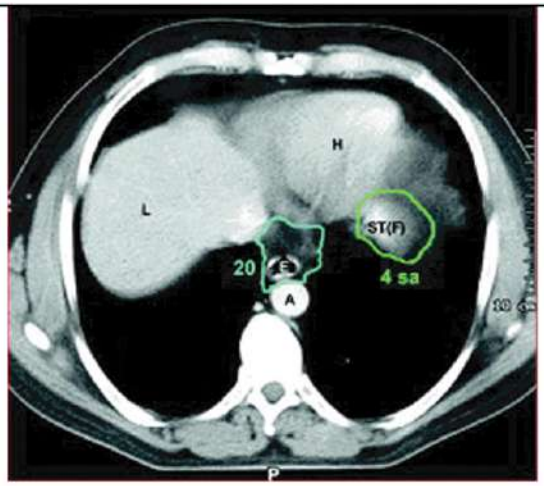


FIGURE 64.11 Optimized postoperative irradiation fields for patient with T3N1 antral primary. Structures of interest were delineated at the time of computed tomography simulation (A-D), and irradiation fields were designed with the aid of digitally reconstructed radiographs (E-H). A. Gastric remnant (teal). B. Gastric remnant plus body/tail of the pancreas (dark blue), splenic hilum (salmon), and porta hepatis (medium blue). C. Head of the pancreas (magenta) and kidneys (left, orange; right, light green) are delineated in addition to body/tail of the pancreas and splenic hilum. D. Celiac artery (yellow) and duodenum (yellow-green) are shown together with head of pancreas and kidneys. A four-field technique of AP (anteroposterior), PA (posteroanterior), and paired laterals was designed to include the gastric remnant (teal), tumor bed (head of the pancreas [magenta],

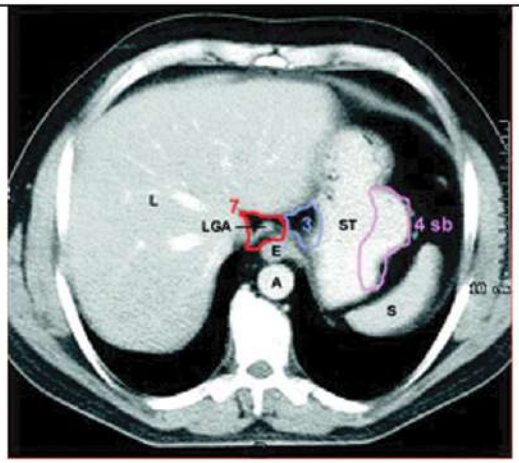
first and second part of the duodenum [yellow-green cross hatched]), pertinent nodal volumes (perigastric, pancreaticoduodenal, porta hepatic [medium blue cross hatched], celiac [yellow cross hatched], and suprapancreatic), and the optional nodal volume of splenic hilum (salmon cross hatched). E. Initial AP field (field margins as shown in medium blue exclude approximately two-thirds of the left kidney while including about 50% of the right kidney). Exclusion of the optional splenic hilar nodes would have allowed additional but minimal sparing of the left kidney in view of the adjacency of gastric antrum and splenic hilum. F. Initial right lateral field demonstrated exclusion of the spinal cord. G. Reduced AP field with exclusion of splenic hilar nodes and most of the gastric remnant. H. Reduced right lateral field.



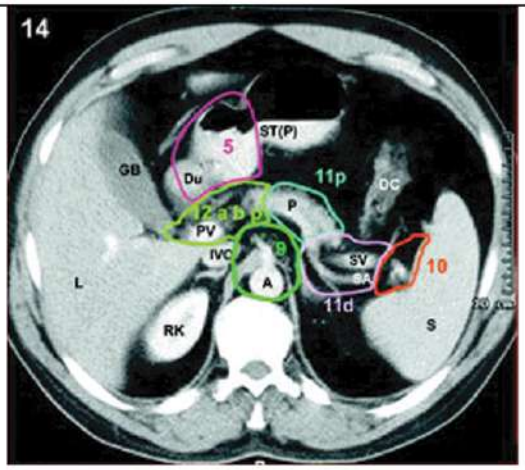
110 - Paraesophageal LN
111 - Supradiaphragmatic LN



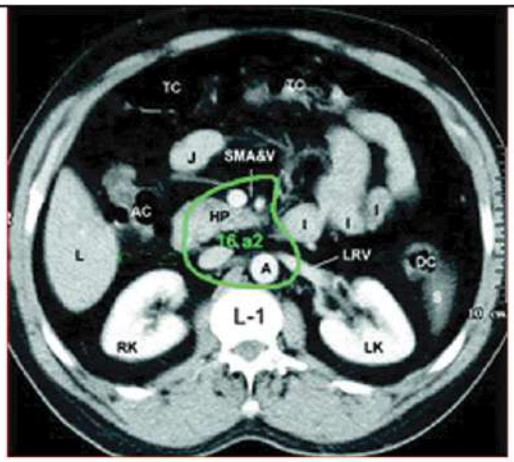
20 - LN in the esophageal hiatus of the diaphragm
4sa - LN along the short gastric vessels



3 - LN along the lesser curvature
4sb - LN along the left gastroepiploic vessels
7 - LN along the left gastric artery



5 - Suprapyloric LN
9 - LN around the celiac artery
10 - LN at the splenic hilum
11p - LN along the proximal splenic artery
11d - LN along the distal splenic artery
12a, b, p - LN in the hepatoduodenal ligament



16 a2 LN around the abdominal aorta

LEGEND:

A, Aorta; AC, Ascending colon; D, Diaphragm; DC, Descending colon; Du, Duodenum; E, Esophagus; GB, Gallbladder; I, Ilium; H, Heart; J, Jejunum; IVC, Inferior vena cava; L, Liver; L-1, First lumbar vertebra; LK, Left kidney, LN, lymph node; LRV, Left renal vein; LV, Left ventricle; P, Pancreas; PV, Portal vein; RGA, Right gastric artery; RK, Right kidney; RV, Right ventricle; S, Spleen; SA, Splenic artery; SMA&V, Superior mesenteric artery and vein; SV, Splenic vein; ST, Stomach; ST(F), Stomach fundus; ST(P), Stomach pylorus; TC, Transverse colon; VA, Azygos vein

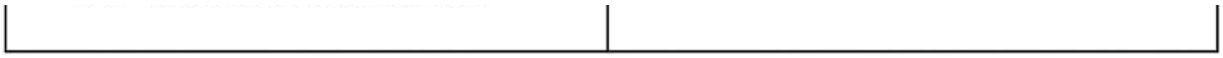


FIGURE 64.12 Examples of locations of varying nodal stations and anatomic structures on axial computed tomography slices. (Reprinted from Matzinger O, Gerber E, Bernstein Z, et al. EORTC-ROG expert opinion: radiotherapy volume and treatment guidelines for neoadjuvant radiation of adenocarcinomas of the gastroesophageal junction and the stomach. *Radiother Oncol*. 2009;92[2]:164-175. Copyright © 2009 Elsevier Ireland Ltd. With permission.)

Additional guidelines for defining the CTV for postoperative irradiation fields have been developed based on location and extent of the primary tumor (T stage) and location and extent of known nodal involvement (N stage).[120] Table 64.6 presents general guidelines on the impact of T and N stages on inclusion of the remaining stomach (gastric remnant), tumor bed, and nodal sites, whereas Tables 64.7 to 64.9 present treatment guidelines based on TN stage within each of three primary sites (proximal, mid, and distal stomach). With proximal gastric lesions or lesions at the GE junction, a 3- to 5-cm margin of distal esophagus should be included; if the lesion extends through the entire gastric wall, a major portion of the left hemidiaphragm should be included. In these circumstances, blocking can decrease the volume of irradiated heart. For unresectable lesions with moderate periesophageal extension, it may not be possible to exclude an adequate amount of the heart and adopting intensity-modulated radiation therapy (IMRT) techniques is likely indicated (Figure 64.13; discussed later). In general, for patients with node-positive disease, there should be wide coverage of tumor bed, remaining stomach, resection margins, and nodal drainage regions. For node-negative disease, if there is a good surgical resection with pathologic evaluation of at least 16 nodes, and there are wide surgical margins on the primary tumor (at least 5 cm), treatment for the nodal beds may be optional. However, it is the authors' opinion that in most cases (particularly node positive) the celiac basins/associated branches as well as periaortic nodes should be similarly covered (see earlier patterns of failure discussion). Treatment for the remaining stomach should depend on a balance of the likely normal tissue morbidity and the perceived risk of local relapse in the residual stomach.

TABLE 64.6 GENERAL GUIDELINES OF IMPACT OF T AND N STAGES ON INCLUSION OF REMAINING STOMACH, TUMOR BED, AND NODAL SITES WITHIN

IRRADIATION FIELDS

TN Stage	Remaining Stomach[a]	Tumor Bed	Nodes
T1-T2 (not into subserosa) N0	N	N	N
T2N0 (into subserosa)[b]	Variable	Y	N
T3N0	Variable	Y	N
T4N0	Variable	Y	Variable
T1-2N+	Y	N	Y
T3-4N+	Y	Y	Y

N, no; Y, yes.

[a]Inclusion of the remaining stomach is preferable in most patients if two-thirds of one kidney can be excluded. This depends on the extent of surgical resection and uninvolved margins (in centimeters).

[b]Posterior wall T2N0 lesions, or those that extend beyond the muscularis propria, especially tumors located in the proximal or distal stomach, are at risk for local relapse. In addition, patients with low-stage disease with close or positive surgical margins should be considered for treatment to the tumor bed.

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TABLE 64.7 IMPACT OF SITE OF PRIMARY GASTRIC LESION AND TN STAGE ON IRRADIATION VOLUMES: CARDIA/PROXIMAL ONE-THIRD OF THE STOMACH (GENERAL GUIDELINES)

Site of Primary and TN Stage	Remaining Stomach	Tumor Bed Volumes[a]	Nodal Volumes	Tolerance Organ Structures
Cardia/proximal one-third of the stomach	Preferred, but spare two-thirds of one kidney (usually right)	T-stage dependent	N-stage dependent	Kidneys, spinal cord, liver, heart, lung
T2N0 with invasion of subserosa	Variable, dependent on surg-path findings[b]	Medial left hemidiaphragm, adjacent body of the pancreas (± tail)	None or perigastric[c]	

Site of Primary and TN Stage	Remaining Stomach	Tumor Bed Volumes[a]	Nodal Volumes	Tolerance Organ Structures
T3N0	Variable, dependent on surg-path findings[b]	Medial left hemidiaphragm, adjacent body of the pancreas (± tail)	None or perigastric; optional: periesophageal, mediastinal, celiac[c]	
T4N0	Variable, dependent on surg-path findings[b]	As for T3N0 plus site(s) of adherence with 3-5 cm margin	Nodes related to site of adherence, ± perigastric, periesophageal, mediastinal, celiac	
T1-2N+	Preferable	Not indicated for T1, as above for T2 into subserosa	Perigastric, celiac, splenic, suprapancreatic ± periesophageal, mediastinal, pancreaticoduodenal, porta hepatis[d]	
T3-4N+	Preferable	As for T3, T4N0	As for T1-2N+ and T4N0	

Surg-path, surgical-pathologic.

[a]Use preoperative imaging (computed tomography [CT], barium swallow), surgical clips, and postoperative imaging (CT, barium swallow).

[b]For tumors with wide (>5 cm) surgical margins confirmed pathologically, treatment of residual stomach may not be necessary, especially if this would result in substantial increased normal tissue morbidity.

[c]Optional node inclusion for T2-3N0 lesions if adequate surgical node dissection (D2 dissection) and at least 10 to 15 nodes are examined pathologically.

[d]Pancreaticoduodenal and porta hepatis nodes are at low risk if nodal positivity is minimal (ie, 1-2 positive nodes with 10-15 nodes examined), and this region may not need to be irradiated. Periesophageal and mediastinal nodes are at risk if there is esophageal extension.

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TABLE 64.8 IMPACT OF SITE OF PRIMARY GASTRIC LESION AND TN STAGE ON IRRADIATION VOLUMES: BODY/MIDDLE ONE-THIRD OF THE STOMACH (GENERAL GUIDELINES)

Site of Primary and TN Stage	Remaining Stomach	Tumor Bed Volumes[a]	Nodal Volumes	Tolerance Organ Structures
Body/middle one-third of the stomach	Yes—but spare two-thirds of one kidney	T-stage dependent	N-stage dependent—spare two-thirds of one kidney	Kidneys, spinal cord, liver
T2N0 with invasion of subserosa, especially postwall	Yes	Body of the pancreas (± tail)	None or perigastric; optional: celiac, splenic, suprapancreatic, pancreaticoduodenal, porta hepatis[b]	
T3N0	Yes	Body of the pancreas (± tail)	None or perigastric; optional: celiac, splenic, suprapancreatic, pancreaticoduodenal, porta hepatis[b]	
T4N0	Yes	As for T3N0 plus site(s) of adherence with 3-5 cm margin	Nodes related to site of adherence ± perigastric, celiac, splenic, suprapancreatic, pancreaticoduodenal, porta hepatis	
T1-2N+	Yes	Not indicated for T1; as for T2N0 with invasion of subserosa	Perigastric, celiac, splenic, suprapancreatic, pancreaticoduodenal, porta hepatis	
T3-4N+	Yes	As for T3, T4N0	As for T1-2N+ and T4N0	

[a]Use preoperative imaging (computed tomography [CT], barium swallow), surgical clips, and postoperative imaging (CT, barium swallow).

[b]Optional node inclusion for T2-3N0 lesions if adequate surgical node dissection (D2 dissection) and at least 10 to 15 nodes examined pathologically.

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TABLE 64.9 IMPACT OF SITE OF PRIMARY GASTRIC LESION AND TN STAGE ON IRRADIATION VOLUMES: ANTRUM/PYLORUS/DISTAL ONE-THIRD OF THE STOMACH

(GENERAL GUIDELINES)

Site of Primary and TN Stage	Remaining Stomach	Tumor Bed Volumes[a]	Nodal Volumes	Tolerance Organ Structures
Antrum/pylorus/distal one-third of the stomach	Yes—but spare two-thirds of one kidney, usually left	T-stage dependent	N-stage dependent	Kidneys, liver, spinal cord
T2N0 with invasion of subserosa	Variable, dependent on surg-path findings[b]	Head of the pancreas (± body), first and second part of the duodenum	None or perigastric; optional: pancreaticoduodenal, porta hepatis, celiac, suprapancreatic[c]	
T3N0	Variable, dependent on surg-path findings[b]	Head of the pancreas (± body), first and second part of the duodenum	None or perigastric; optional: pancreaticoduodenal, porta hepatis, celiac, suprapancreatic[c]	
T4N0	Preferable but dependent on surg-path findings[b]	As for T3N0 plus site(s) of adherence with 3-5 cm margin	Nodes related to site(s) of adherence ± perigastric, pancreaticoduodenal, porta hepatis, celiac, suprapancreatic	
T1-2N+	Preferable	Not indicated for T1; as for T2N0 with invasion of subserosa	Perigastric, pancreaticoduodenal, porta hepatis, celiac, suprapancreatic, optional—splenic hilum	
T3-4N+	Preferable	As for T3, T4N0	As for T1-2N+ and T4N0	

Surg-path, surgical-pathologic.

[a]Use preoperative imaging (computed tomography [CT], barium swallow), surgical clips, and postoperative imaging (CT, barium swallow).

[b]For tumors with wide (>5 cm) surgical margins confirmed pathologically, treatment of residual stomach is optional if this would result in substantial increased normal tissue morbidity.

[c]Optional node inclusion for T2-3N0 lesions if adequate surgical node dissection (D2 dissection) and at least 10 to 15 nodes examined pathologically.

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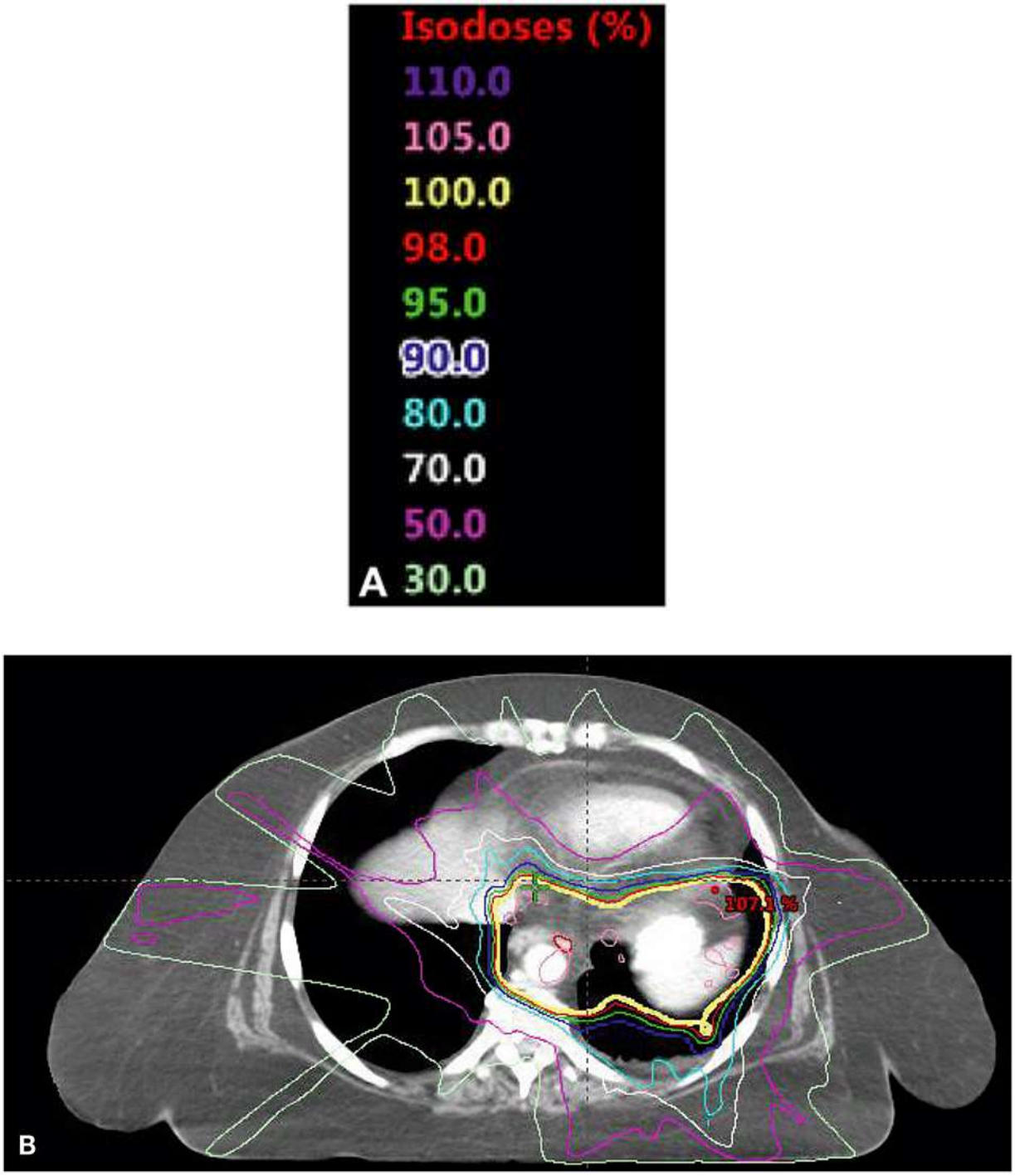
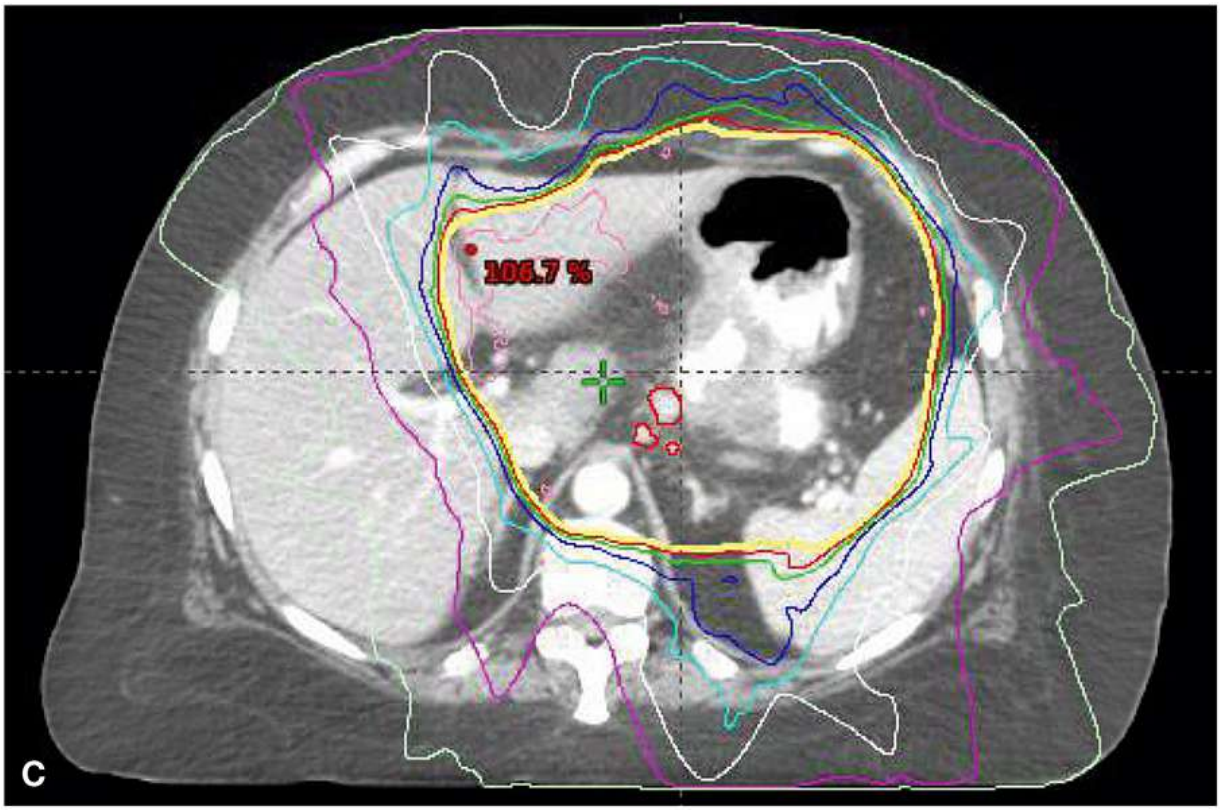

Isodoses (%)
110.0
105.0
100.0
98.0
95.0
90.0
80.0
70.0
50.0
A 30.0
B


106.7 %
C

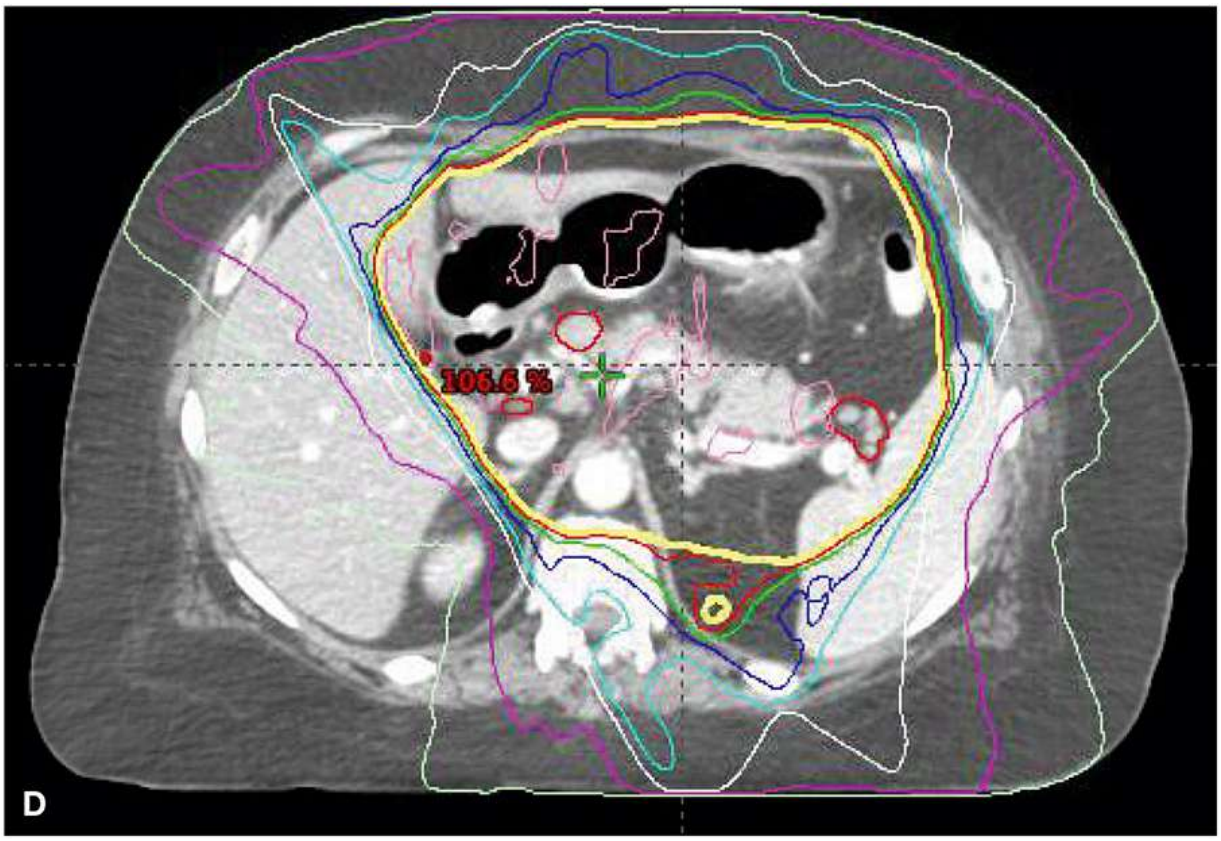

106.6 %
D

FIGURE 64.13 A 50-year-old female with a gastric body adenocarcinoma with multiple suspicious nodes noted on CT scan (delineated in red), including lower paraesophageal, perigastric, gastrohepatic, porta, and splenic hilum. IMRT was utilized to minimize adjacent normal tissue including the heart, liver, kidneys, and spinal cord. A. Relative isodose levels, percentage. B. Superior aspect of volume, including distal esophagus with associated node in red, gastric fundus as well as very proximal spleen. C. Level of splenic hilum, gastric body (with associated adenopathy in red), as well as porta region. D. Splenic hilum region with associated adenopathy, celiac, gastric body extending into pylorus. E. More distal aspect of volume including transverse duodenum/D3 along with retroperitoneal basins. CT, computed tomography; IMRT, intensity-modulated radiation therapy.

From a historical standpoint, although parallel-opposed anteroposterior (AP)/posteroanterior (PA) fields are a practical arrangement for tumor bed and nodal irradiation, multifield techniques should be used if they can improve long-term tolerance of normal tissues. Tightly contoured AP/PA fields should be designed to spare as much normal tissue as possible (Figures 64.14 and 64.15). In institutional series, the average irradiation field measured 15 cm × 15 cm.[38,121,122] More routine use of multifield techniques should be implemented when preoperative imaging exists to allow accurate reconstruction of target volumes. Single-institution data suggest that multifield arrangements may produce less toxicity. Although AP/PA fields can be weighted anteriorly to keep the spinal cord dose at

acceptable levels, a four-field technique, if feasible, can spare spinal cord with improved dose homogeneity. Depending on the posterior extent of the gastric fundus, either oblique or more routine lateral portals can be used to deliver a 10- to 20-Gy component of irradiation to spare the spinal cord or kidney. When lateral fields are used, liver and kidney tolerance limits the use of lateral fields to 20 Gy or less. Patients should be treated with high-energy photons when possible. With the wide availability of 3-D treatment planning systems, it may be possible to more accurately target the high-risk volume and to use unconventional field arrangements to produce superior dose distributions. To accomplish this without marginal misses, it will be necessary to both carefully define and encompass the various target volumes because the use of oblique or noncoplanar beams could exclude target volumes that would be included in AP/PA fields or nonoblique four-field techniques (AP/PA and laterals). Although, historically, two-dimensional (2-D)-based radiation planning has been carried out primarily using anatomic landmarks as well as fluoroscopic barium swallow to determine field borders (Figures 64.14 and 64.15), contemporary treatment planning using CT-based planning allows improved visualization of both target and nontarget structures, along with 3-D reconstruction and creation of a “beam’s eye” view of varying fields, allowing improved conformality around target structures and improvements in normal tissue sparing. Because volumetric data can be obtained by CT scans, dose-volume histogram data can also be generated. A variety of 3-D techniques are presently used and described later. Similarly, with the implementation of IMRT, utilization of this approach should be considered where meeting dose constraints with 3-D techniques proves challenging.

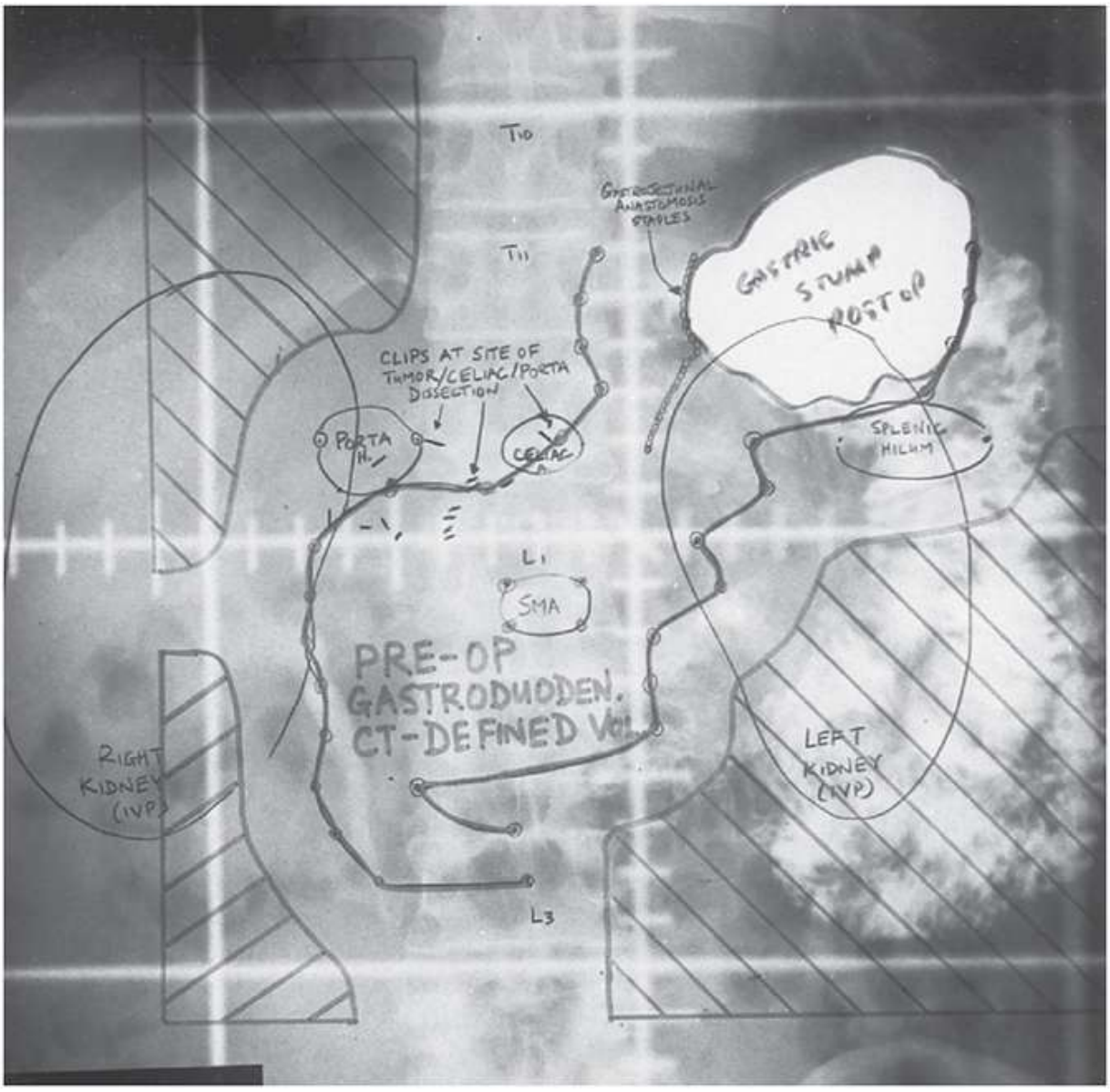


FIGURE 64.14 Simulation film for T3 antral tumor with two of five peritumoral lymph nodes metastatically involved (radical subtotal gastrectomy with D1 node dissection). Simulation film identifies areas at risk for recurrence, including preoperative gastric/tumor bed (defined by preoperative computed tomography [CT] scan), anastomotic sites and gastric stump (staple line seen on precontrast simulation films and marked on postintravenous pyelogram/postcontrast film), and regional lymphatics (celiac, porta hepatis, superior mesenteric artery, and splenic nodes identified on CT and pancreaticoduodenal nodes lying in C-loop of the duodenum identified by preoperative CT). The right kidney is spared for approximately three-fourths of its volume, whereas the left kidney has about one-third of its volume blocked. (Reprinted from Smalley SS, Gunderson L, Tepper J, et al. Gastric surgical adjuvant radiotherapy consensus report: rationale and treatment implementation. *Int J Radiat Oncol Biol Phys*. 2002;52[2]:283-293. Copyright © 2002 Elsevier. With permission.)

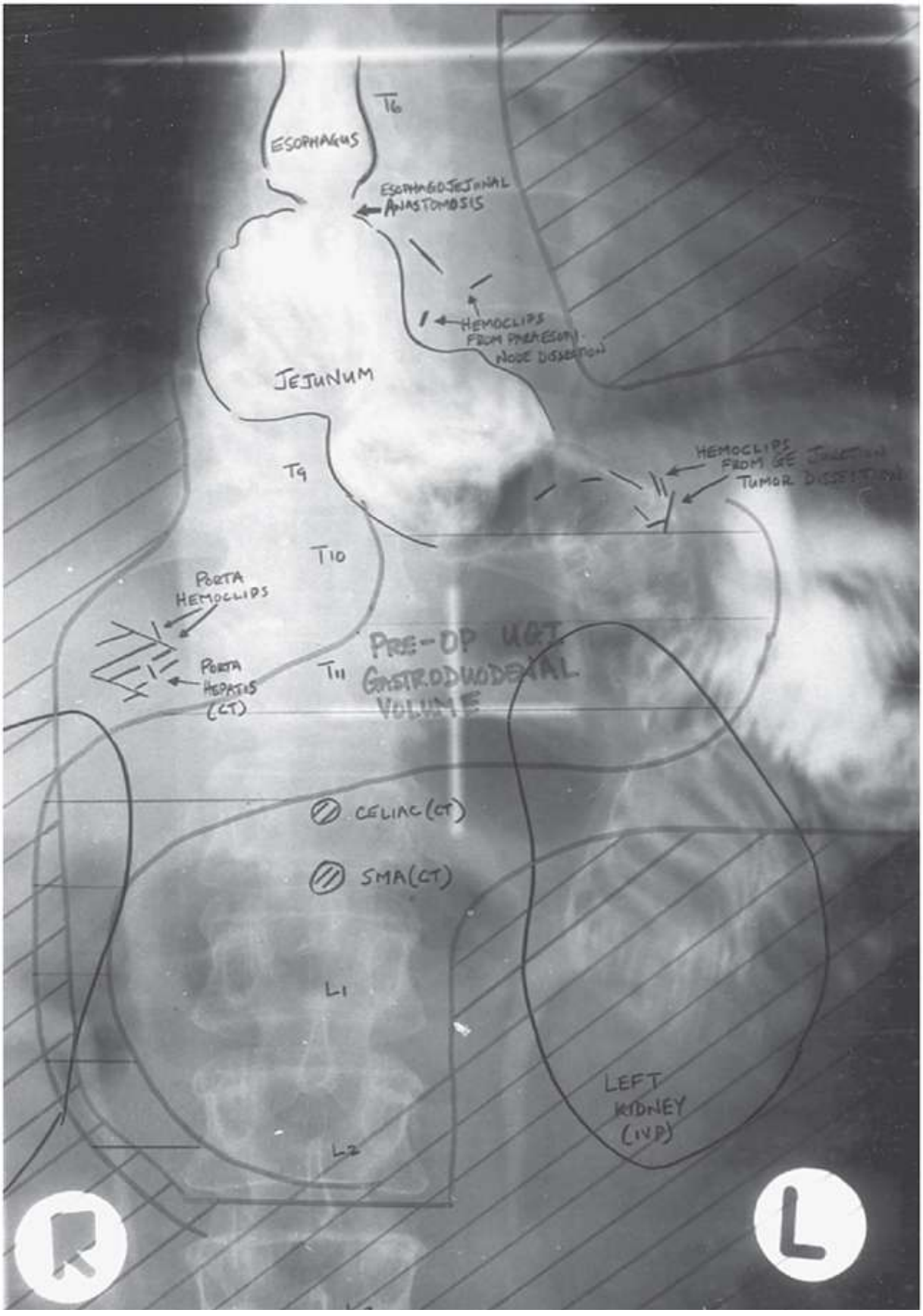

ESOPHAGUS
T6
ESOPHAGOJEJUNAL ANASTOMOSIS
HEMOCLIPS FROM PANCREATIC NODE DISSECTION
JEJUNUM
T9
HEMOCLIPS FROM GE JUNCTION TUMOR DISSECTION
T10
PORTA HEMOCLIPS
PORTA HEPATIS (CT)
T11
PRE-OP UGI GASTRODUODENAL VOLUME
CELIAC (CT)
SMA (CT)
L1
L2
LEFT KIDNEY (IVP)
R
L

FIGURE 64.15 Simulation film for a T4 (diaphragm invasion) gastroesophageal junction tumor with 4 of 15 involved lymph nodes (total gastrectomy with modified R3 node dissection). Areas at risk for recurrence include preoperative gastric/tumor bed (defined by preoperative upper gastrointestinal radiographs and hemoclips placed at the time of resection to mark tumor bed and diaphragm invasion), anastomotic sites and stump (anastomosis visualized at the juncture of residual distal esophagus and jejunum), and regional lymphatics (including the celiac, porta hepatis, and pancreaticoduodenal areas as well as the distal paraesophageal nodes). (Reprinted from Smalley SS, Gunderson L, Tepper J, et al. Gastric surgical adjuvant radiotherapy consensus report: rationale and treatment implementation. *Int J Radiat Oncol Biol Phys*. 2002;52[2]:283-293. Copyright © 2002 Elsevier. With permission.)

Because it is important to account for daily setup uncertainty as well as physiologic internal organ motion (secondary to respiration, peristalsis, cardiac motion, etc), an additional margin must be added to a CTV. Interfraction variability in stomach location occurs, often owing to variations in gastric filling. Intrafraction changes in target shape and location may be attributable to respiratory motion, which, particularly in the superior to inferior direction, may exceed 1 to 1.5 cm. In an effort to reduce this, kilovoltage radiographic matching can be used with particular emphasis on matching of surgical clips. An additional technique that may improve treatment accuracy is cone-beam CT, which allows direct target matching within a given fraction. Movement related to respiratory motion can be assessed using 4-D CT, which images the patient in all phases of respiration (similar to what is performed fluoroscopically but using CT). Similarly, respiratory gating techniques may allow reduction in the target volume/smaller margins, allowing for treatment during a more stationary phase of the respiratory cycle (example end expiration), as well as breath-holding techniques.

Another potential and likely preferred approach in the treatment for gastric cancer is the use of IMRT. IMRT also uses CT-based planning, again allowing 3-D reconstruction of varying structures. However, IMRT differs from 3-D planning through the delivery of radiation dose by partitioning a radiation field into multiple smaller fields of various shapes and sizes,

varying the dose intensity between each area. This is carried out with either dynamic IMRT (where collimating leaves move in and out of the radiation beam path during treatment) or “step-and-shoot” IMRT (where the leaves change the radiation field shape while the beam is turned off). Either method is particularly effective at conforming radiation dose to the target structures while avoiding dose to normal tissue. Radiation oncologists must determine which structures are most critical and weight their importance during the treatment planning process. Importantly, the greater the number of “avoidance” normal structures, the more difficult it is to meet all dose constraints. IMRT utilizes “inverse planning,” where an intended prescription dose is placed on target volumes and dose constraints are placed on normal tissue structures. Thereafter, computer software algorithms allow design of unconventional treatment fields that would not otherwise be possible with standard planning methods. Radiation oncologists and medical physicists critically evaluate numerous plans until dose constraints are satisfactorily met. The result should be a series of radiation doses that closely conform to the target volumes while minimizing dose to normal tissues. IMRT may be appropriate in selected cases to reduce doses to normal structures, including the heart, liver, and kidneys. A potential disadvantage of IMRT is the possibility of delivering low doses of radiation therapy to normal tissue areas that might not usually be irradiated using 2-D or 3-D techniques. Another potential disadvantage of IMRT is possible dose inhomogeneity, leading to potential “hot spots” in normal organs. Because IMRT requires precise target definition, the potential for “marginal miss” increases and careful, accurate target delineation is of paramount importance.

With setup uncertainty and physiologic organ motion, care must be taken to ensure accurate and reproducible setup, including with the use of immobilization devices as well as possible respiratory gating/breath-holding techniques. Block/volume margins may be minimized with efforts to reduce intrafractional position variability, including breath-holding techniques. Generally, high-energy photons (10-18 MV) are recommended when using 3-D conformal or IMRT therapy, potentially facilitating a reduction in the integral dose. When using more advanced radiation planning techniques, daily image guidance is generally recommended, with consideration of

frequent cone-beam CT imaging and adaptive planning pending anatomic changes.[118]

Multiple dosimetric studies comparing IMRT to two-field and 3-D conformal radiation therapy plans have shown significant reductions in kidney, liver, heart, lung, and spinal cord dose with the former. Although IMRT may result in improved normal tissue sparing, many of the acute toxicities encountered during radiation may persist given that many symptoms arise from radiation of the target, including gastric mucosa. The value of IMRT may lie primarily in normal organ sparing with potential reductions in long-term toxicity in surviving patients. A retrospective (single institution) review of 202 consecutive patients with gastric cancer analyzed patients receiving 3-D versus IMRT treatments. Grade III-IV acute toxicity was significantly lower in patients receiving IMRT (49% vs 70%, $P = .004$), along with a significant reduction in toxicity-related hospitalization, feeding tube use, hydration requirement, and breaks. The authors concluded that IMRT potentially reduced rates of high-grade acute toxicity and toxicity-related events compared to 3-D treatments.[123] There is ongoing investigation into further enhancements of this technique using volumetric modulated arc therapy, helical tomotherapy, as well as proton therapy. This may also become important with the integration of newer/novel systemic agents, in conjunction with radiation therapy, of which many act as potent tumoral (as well as normal organ) radiation sensitizers and may reduce treatment- related toxicities as well as avoidance of treatment interruptions.

Dose Constraints

In radiation therapy planning of gastric cancer, normal tissue tolerance should always be considered. The spinal cord dose is generally limited to 45 Gy using 1.8-Gy fractions (and potentially less when delivered with novel systemic agents). Accurate delineation of adjacent organs including lungs, liver, kidneys, heart, and spinal cord is important. Varying dose-volume normal organ constraints have been suggested. Historically, heart dose constraints have included maintaining one-third, two-thirds, and total heart volumes less than 45, 40, and 30 Gy, respectively. Recommended heart constraints include keeping less than 30% of the cardiac volume to a total

dose of 40 Gy and less than 50% receiving 25 Gy, minimizing dose to the left ventricle although with careful planning these constraints can be improved upon. In a secondary analysis of the NRG Oncology RTOG 0617 randomized clinical trial in which patients with lung cancer received concurrent chemotherapy of carboplatin and paclitaxel with or without cetuximab and 60- versus 74-Gy radiation doses, IMRT produced lower heart doses ($P < .05$), and the volume of heart receiving 40 Gy (V40) was significantly associated with overall survival on adjusted analysis ($P < .05$).[124] In the setting of potentially significant volumes of the heart in the radiation field, consideration of 4-D CT and/or respiratory motion management can be made. It is recommended that at least 70% of one physiologically functioning kidney receive a total dose less than 20 Gy and that collectively 50% or less of the combined functional renal volume should receive more than 20 Gy.[119] In some patients, a portion of both kidneys will fall within the treatment field; however, at least two-thirds to three-fourths of one kidney should be excluded beyond a dose of 20 Gy. For proximal gastric lesions, 50% or more of the left kidney is commonly within the irradiation portal, and the right kidney must be appropriately spared. For distal lesions with narrow or positive duodenal margins, a similar amount of right kidney often is included, and every effort must be taken to spare enough left kidney to maintain function. Late renal sequelae have not generally been encountered with these techniques.[38,82,125] One should also consider the possibility of impaired kidney function in the context of varying comorbidities, using nuclear medicine renal studies to assess individual renal function in such situations or where significant volumes of kidneys are anticipated to be within the radiation field. Generally, 70% of the liver parenchyma should be kept to a dose less than 30 Gy. Many of these constraints can be achieved through the use of 3-D planning with appropriate and careful design of shielding blocks/multileaf collimation and dose-volume histogram analysis, with the use of IMRT in appropriate cases.

Doses of Radiation

Generally, doses in the range of 45 to 50.4 Gy should be delivered at 1.8 Gy per fraction. Although primarily limited by normal tissue constraints in the

upper abdomen, several series have reported improved locoregional control with radiation dose escalation in the adjuvant setting. A report from Mayo Clinic investigators reported high locoregional control rates with radiation doses more than 54 Gy.[125] Similarly, a report from Italian investigators treating patients adjuvantly with hyperfractionated radiation therapy to a dose of 55 Gy, with concurrent 5-FU, showed an in-field recurrence rate of only 7.5% and survival rate of 52% with a median follow-up of more than 5 years.[126] With regimens using single daily fractions, the usual dose is 45 Gy delivered in 1.8- to 2-Gy fractions over 5 weeks, with a field reduction after 45 Gy in patients receiving boost-field treatments. Reduced boost fields to small areas of residual disease and a small volume of stomach or small intestine sometimes can be cautiously carried to doses of 55 to 60 Gy with multifield/IMRT techniques. In such instances, informed consent should include a discussion of an increased risk of grade 3 to 4 gastrointestinal toxicity.

RESULTS OF THERAPY

Locally Advanced Unresectable or Subtotally Resected Gastric Cancer

For patients with locally advanced unresectable or subtotally resected gastric carcinoma, radiotherapeutic approaches both with and without chemotherapy have been used because these tumors appear localized without clinically detectable metastases. Combined treatment with radiation therapy and chemotherapy appears to prolong survival but rarely results in long-term cure.[127] Although only a modest effect on survival is seen, these studies have established, importantly, the foundation of contemporary combined-modality therapy and have served as a stimulus to further clinical investigation in gastric cancer as well as other gastrointestinal disease sites. The results of these phase III studies have had a significant impact on clinical trial development in gastrointestinal malignancies (Table 64.10).

TABLE 64.10 UNRESECTABLE OR RESIDUAL GASTRIC CANCER: TREATMENT RESULTS OF RANDOMIZED TRIALS

Group or Institution	Treatment Arms	Number of Patients	EBRT Dose	Chemotherapy	Survival Results
Mayo Clinic[127]	EBRT + ChT vs EBRT	48	35-40 Gy	5-FU	Increased survival for EBRT + 5-FU with mean survival 13 vs 5.9 mo and 3/25 (12%) vs 0/23 5-y survival
GITSG[128]	EBRT + ChT vs ChT	90	50-Gy split course	5-FU + MeCCNU	Advantage in long-term survival with EBRT + ChT at 18% vs 7% ($P <$ .05)

5-FU, 5-fluorouracil; ChT, chemotherapy; EBRT, external beam radiation therapy; GITSG, Gastrointestinal Tumor Study Group; MeCCNU, 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1 nitrosourea.

In a historical trial from 1969, Moertel et al[127] reported the results of a prospective, controlled double-blind study of patients with locally advanced unresectable gastric cancer. In this study, 48 patients were randomized to 35 to 40 Gy of radiation therapy over 4 weeks with and without 5-FU. Mean survival was 13 months in patients receiving radiation therapy and 5-FU versus 5.9 months for patients receiving radiation therapy alone ($P < .01$). These results demonstrated for the first time the clinical benefit of combining concurrent 5-FU with radiation therapy and encouraged further investigation of combination therapy in gastric cancer and other gastrointestinal disease sites (esophageal, pancreatic, rectal, and anal carcinomas).

As a follow-up to this study, the Gastrointestinal Tumor Study Group (GITSG) examined the combination of 5-FU/MeCCNU, or 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1 nitrosourea, and radiotherapy (50 Gy/split course/8 weeks) versus the same chemotherapy alone in locally advanced gastric cancer.[128] Patients were eligible if the tumor involved regional lymph nodes or adjacent structures that could be completely resected en bloc. Of the 90 patients entered, 66 patients had a resection of the primary tumor. Of these, 23 patients had gross residual disease, 36 patients had microscopic residual disease, and 7 patients had no

documented residual disease. The study was closed prematurely because of an excess of early deaths in the combined chemotherapy-radiotherapy arm. The excessive early mortality of the combined-modality arm was attributed to early tumor progression and poor tolerance of the combined-modality regimen. However, further follow-up beyond 3 years indicated continuing mortality among the chemotherapy-alone arm, whereas the combined chemoradiotherapy arm exhibited a plateau with 18% of patients surviving 5 years. Thus, despite an excess of early mortality, the combined- modality arm exhibited an overall superiority in 5-year survival. It is important to note that patients who had had their primary tumor resected experienced superior survival to those without resection. All of the survival benefit in patients receiving combined modality was in patients whose primary tumor had been resected. This trial showed that combined chemoradiation therapy is capable of rendering a substantial percentage of patients with microscopic residual gastric cancer free from disease. It furthermore supported the rationale of exploring chemoradiation adjuvant trials in completely resected patients at high risk for locoregional relapse, and that chemoradiation was able to control microscopic disease and lead to long-term survival in a significant number of these patients.

A more recent multicenter phase II trial from China treated patients with medically inoperable or unresectable gastric cancer with pre- and postradiation docetaxel, cisplatin, and 5-fluorouracil, in combination with chemoradiation with concurrent cisplatin in between. Clinical complete response rate was 36%, overall response rate 83%, median survival 26 months, and 2-year survival 52%. Patients who were medically inoperable had a better prognosis than patients with frankly unresectable disease.[129]

Resectable Gastric Cancer

The recognition of the high rates of local and regional failure following surgery in patterns of failure analyses has served as the basis for clinical trials assessing the value of radiation therapy both with and without chemotherapy as an adjuvant treatment (Table 64.4). Although these studies have all addressed the important question of whether clinical outcome is enhanced by adjuvant radiation therapy, there has been marked variability in radiation dose and schedule, sequence with surgery (preoperatively,

intraoperatively, or postoperatively), and the use of concurrent and maintenance chemotherapy (Table 64.11). These differences in study design and included patients may explain in part the conflicting results observed in phase III studies.

TABLE 64.11 ADJUVANT/NEOADJUVANT IRRADIATION FOR RESECTED GASTRIC CANCER: TREATMENT RESULTS OF RANDOMIZED TRIALS

			Survival		Locoregional Relapse		
Series/Treatment Method	Patients	Median Survival (Months)	Long Term[a] (%)	*P* Value	N	%	*P* Value
Mayo Clinic[111]							
Surgery alone	23	15	4	–	–	54	–
Post-op EBRT + 5-FU	39	24	23	.05	–	39	–
British Stomach Group[130]							
Surgery alone	145	–	20	–	39	27 (3 y)	–
Post-op ChT	138	–	19	–	26	19 (3 y)	–
Post-op EBRT	153	–	12	–	15	10 (3 y)	–
China–Beijing[131]							
Surgery alone	199	–	20	–	–	52	–
Pre-op EBRT	171	–	30	.009	–	39	<.025
Intergroup 0116[116]						Disease-free survival (3 y)	
Surgery alone	275	27	41	–		31	–
Post-op EBRT + ChT	281	36	50	.005		48	<.001
ARTIST Trial[132,133]							
Post-op ChT	228	–	73	–	–	13	–
Post-op EBRT + ChT → Post-op EBRT + ChT	230	–	75	.484	–	7[b]	.0033
CRITICS Trial[141]							

Series/Treatment Method	Patients	Median Survival (Months)	Survival			Locoregional Relapse	
			Long Term[a] (%)	*P* Value	N	%	*P* Value
Pre-op ChT → Surgery → Post-op ChT	393	43	42	.90	–	–	–
Pre-op ChT → Surgery → Post-op EBRT + ChT	395	37	40				
ARTIST-II trial[134]							
Post-op ChT	182	–	65				
Post-op ChT	181	–	74	.04[c]			
Post-op EBRT plus ChT	183	–	73	.07[d]			
TOPGEAR[23]							
Preop ChT surgery	288	49	46			37[e]	
ChT surgery + pre-op EBRT plus ChT	286	46	44			33[e]	

5-FU, 5-fluorouracil; ChT, chemotherapy; EBRT, external beam radiation therapy.

[a]Long-term survival is 5-year data for Mayo Clinic, ARTIST, CRITICS, TOPGEAR, and Beijing series, and 3-year data are for British, Intergroup 0116, and ARTIST-II.

[b]In node-positive patients, 3-year disease-free survival 72% vs 76%, *P* = .04; 83% vs 94% in intestinal-type tumors.

[c]Arm 1 vs arm 2.

[d]Arm 1 vs arm 3.

[e]Local regional plus distant relapse rates 12% and 15%.

Adjuvant Radiation Therapy Alone

Two randomized phase III studies have examined the use of external beam radiation therapy (EBRT) alone with surgery.[79,130] Although both studies used similar radiation dose and schedule, sequence with surgery differed. In the British Stomach Cancer Group study, 436 patients were randomized to surgery alone, postoperative radiation therapy (45-50 Gy in 25-28

fractions), or cytotoxic chemotherapy with mitomycin, doxorubicin, and fluorouracil (FAM).[79,130] The 5-year survival for surgery alone was 20%, for surgery plus radiation therapy 12%, and for surgery plus chemotherapy 19%. In this study, no survival advantage was observed for patients who received postoperative EBRT, although there was an apparent improvement in local control, demonstrating that local disease could be affected by adjuvant radiation therapy. Locoregional failure was documented in only 15 of 153 patients (10%) in the irradiation arm versus 39 of 145 patients (27%) in the surgery-alone arm and 26 of 138 patients (19%) in the FAM group. Interpretation of the results is complicated by the inclusion of 171 patients undergoing resection with gross or microscopic residual carcinoma. These patients would not be candidates for contemporary gastric surgical adjuvant trials in the United States. In addition, approximately one-third of patients randomized to receive adjuvant treatment did not receive the assigned therapy. Of 153 patients randomized to the irradiation arm, only 104 (68%) received a dose of 40.5 Gy or more, and 36 (24%) received none.

Neoadjuvant Radiation Therapy

In contrast, the results of a phase III study from Beijing demonstrated a survival benefit for patients with gastric cardia carcinoma receiving preoperative irradiation and surgery versus surgery only.[131] In this study, 370 patients with gastric cardia carcinoma were randomized to 40 Gy in 20 fractions over 4 weeks of preoperative irradiation and surgery or surgery only. The 5-year survival rates of preoperative irradiation and surgery and the surgery-alone group were 30% and 20%, respectively (10-year rates 20% and 13%, respectively). These differences were statistically significant (P = .009). Further, local and regional nodal control was improved in patients undergoing preoperative irradiation and surgery (61% and 61%) versus surgery (48% and 45%) only. Morbidity and mortality rates were not increased in patients receiving preoperative irradiation and surgery.

Intraoperative Radiation Therapy

An alternative approach to postoperative or preoperative irradiation is intraoperative radiation therapy (IORT).[135,136] The advantage of this technique is the ability to deliver a single large fraction (10-35 Gy) of

radiation to the tumor or tumor bed while excluding or protecting surrounding normal tissue from the high-dose field. This approach permits high-dose irradiation with minimal normal tissue treatment. Two randomized trials have examined the efficacy of IORT in combination with surgery for patients with gastric carcinoma. Abe et al[135] from Kyoto University performed a randomized trial of 211 patients with gastric cancer comparing surgery alone with surgery and intraoperative radiation (28-35 Gy). Patients were randomized based on hospital day of admission for surgery. For patients with tumor confined to the gastric wall, 5-year survival rates were similar for IORT and for resection alone. However, patients with Japanese stages II to IV disease who received IORT in conjunction with resection showed improved survival over patients who underwent resection without irradiation. Among patients with stage IV disease (who usually had local residual disease after maximal resection), there were no 5-year survivors in patients who received surgery alone; however, 15% of the patients who received IORT were alive at 5 years. The experience with IORT in gastric cancer at Kyoto University suggested that IORT may be beneficial in the treatment for locally advanced malignancies of the stomach.

To further evaluate this approach, Sindelar et al[136] at the National Cancer Institute conducted a prospectively randomized controlled trial comparing surgical resection and IORT with conventional therapy in gastric carcinoma. Patients in the experimental group underwent gastrectomy, and IORT was administered to the gastric bed (20 Gy). Patients in the control group underwent resection and postoperative EBRT to the upper abdomen (50 Gy in 25 fractions) in advanced-stage lesions extending beyond the gastric wall. Of the 100 patients screened for the study, 60 patients were randomized and underwent exploratory surgery. In all, 19 patients were excluded intraoperatively because of unresectability or metastases, leaving 41 patients in the study. The median survival for patients with tumors of all stages was 25 months for the IORT group and 21 months for the control group (P = not significant [NS]). Locoregional disease relapse occurred in 7 of 16 patients with IORT (44%) and in 23 of 25 control patients (92%) ($P <$ .001). Complication rates were similar between IORT and control patients. Although IORT failed to afford a significant advantage over conventional

therapy in overall survival, it significantly improved control of locoregional disease. The use of IORT in gastric cancer remains a topic of investigation.

Adjuvant Chemoradiation Therapy

Because of the promising results in the early studies of combined-modality therapy for locally advanced unresectable or subtotally resected gastric cancer, investigators have also studied this combination in resectable gastric carcinoma. A small study from South Africa randomized 66 patients with resected gastric cancer (T1-T3, N1 or N2, M0) to low-dose postoperative irradiation (20 Gy in eight fractions over 10 days) and 5-FU or no further therapy.[99] No difference in survival was observed between the patients undergoing surgery and adjuvant therapy and those undergoing surgery alone. Given the subtherapeutic doses of radiation used in this study, it is difficult to draw any conclusions as to the efficacy of adjuvant radiation therapy and 5-FU.

In 1984, Moertel et al[111] reported the results of a prospective randomized trial conducted at the Mayo Clinic of 62 patients with poor prognosis but completely resected gastric cancers who were randomized to either surgery alone or surgery followed by irradiation (37.5 Gy in 24 fractions over 4-5 weeks) with concurrent 5-FU. A nonstratified, prerandomization scheme was used with a 2:3 ratio favoring treatment. Informed consent was requested of only the 39 patients randomized to treatment. Ten of the 39 patients refused further therapy and were observed. When analyzed by intent to treat, the adjuvant arm had statistically significant improvement in both relapse-free and overall survival (overall 5-year survival 23% vs 4%, $P < .05$). When patient outcome was compared with actual treatment received (29 adjuvant treatment, 33 surgery alone), 5-year survival still favored the adjuvant group (20% vs 12%), although the differences were not statistically significant in view of the small patient numbers. The 10 patients who refused assignment to adjuvant treatment had more favorable prognostic findings than the other two groups of patients. When the two groups with equally poor prognostic factors were compared, the 5-year overall survival was 20% versus 4%, with an advantage to those receiving adjuvant treatment. When analyzed by treatment delivered, locoregional

relapse was decreased with adjuvant treatments (54% incidence with surgery alone vs 39% with irradiation and 5-FU).

Because of these conflicting results and the fact that locoregional failure remained an established source of recurrence, an Intergroup trial (INT 0116) was initiated to evaluate postoperative combined 5-FU-based chemotherapy and irradiation to the gastric bed and regional nodes versus surgery only following resection of gastric cancer.[116] Eligibility included patients with pathologic stage group IB through IV nonmetastatic adenocarcinoma of the stomach or GE junction. After an en bloc resection (patients underwent D0-D1 dissection), 556 patients were randomized to either observation alone or postoperative 5-FU/leucovorin for one cycle followed by combined-modality therapy consisting of 45 Gy in 25 fractions plus concurrent 5-FU and leucovorin (4 days in week 1, 3 days in week 5) followed by two monthly 5-day cycles of 5-FU and leucovorin. Minor or major errors in field design were seen in 35% during preirradiation quality assurance review, allowing most deviations to be corrected prior to radiation therapy initiation, resulting in a 6.5% final major deviation rate. Nodal metastases were present in 85% of the cases. With 5 years of median follow-up, 3-year relapse-free survival was 48% for adjuvant treatment and 31% for observation (P = .001); 3-year overall survival was 50% for treatment and 41% for observation (P = .005). The median overall survival in the surgery-only group was 27 months, compared with 36 months in the chemoradiotherapy group; the hazard ratio (HR) for death was 1.35 (95% CI 1.09-1.66, P = .005). The HR for relapse in the surgery-only group as compared with the chemoradiotherapy group was 1.52 (95% CI 1.23-1.86, P < .001). The median duration of relapse-free survival was 30 months in the chemoradiotherapy group and 19 months in the surgery-only group. Patterns of failure were based on the site of first relapse only and were categorized as local, regional, or distant. Local recurrence occurred in 29% of patients who relapsed in the surgery-only group and 19% of those who relapsed in the chemoradiotherapy group. Regional relapse—typically abdominal carcinomatosis—was reported in 72% of those who relapsed in the surgery-only group and 65% of those who relapsed in the chemoradiotherapy group. Extra-abdominal distant metastases were diagnosed in 18% of those who relapsed in the surgery-only group and 33% of those who relapsed in the chemoradiotherapy group. Treatment was

tolerable, with three (1%) toxic deaths. Grades 3 and 4 toxicity occurred in 41% and 32% of cases, respectively, and 17% of patients assigned to the chemoradiotherapy group stopped treatment owing to toxicity from therapy. Long-term results at more than 10-year median follow-up continued to show significant improvement in overall and disease-free survival in the chemoradiation group, benefiting all T- and N-stage patients included in the trial.[137] The results of this large study demonstrate a clear survival advantage for the use of postoperative chemoradiation and strongly support its integration into the routine care of patients with curatively resected high-risk carcinoma of the stomach and GE junction.[137]

The follow-up Intergroup trial CALGB 80101 randomized 546 patients with resected gastric or GE junction adenocarcinoma to receive either (a) one cycle of 5-FU/leucovorin, followed by 45 Gy with concurrent continuous infusion 5-FU, followed by two additional cycles of 5-FU/leucovorin, or (b) one cycle of epirubicin, cisplatin, and 5-FU (ECF), followed by 45 Gy with concurrent, continuous infusional 5-FU, followed by two additional cycles of reduced dose ECF. With a median follow-up duration of 6.5 years, 5-year overall survival rates were 44% in the FU plus leucovorin arm and 44% in the ECF arm (P = .69, HR 0.98, 95% CI 0.78-1.24 comparing ECF with FU plus LV). Five-year disease-free survival rates were 39% in the FU plus LV arm and 37% in the ECF arm (P = .94, HR 0.96, 95% CI 0.77-1.20). The authors concluded that following curative resection of gastric or GE junction adenocarcinoma, postoperative chemoradiotherapy using ECF before and after 5-FU-based radiation does not improve survival compared to bolus 5-FU/leucovorin given in the same manner.[138]

A large retrospective study from Korea evaluated the role of adjuvant chemoradiation in patients undergoing D2 gastric cancer resection, a group that was not adequately represented in the aforementioned Intergroup trial. In the Korean study, 544 patients treated with D2 dissection and postoperative chemoradiation therapy were compared to 446 patients with similar characteristics treated with D2 dissection alone. Overall survival was significantly higher in patients treated with adjuvant chemoradiation (median survival 95 vs 63 months, P = .02) as well as significant improvement in relapse-free survival.[94] Additionally, a collective review of nine randomized trials incorporating radiation therapy approaches with

surgery alone also demonstrated a significant 5-year survival benefit with the addition of radiation therapy in patients with resectable gastric cancer.[139]

A Korean phase III trial (the ARTIST study) compared the effects of adjuvant chemoradiation (capecitabine/cisplatin [XP] + radiotherapy) to adjuvant chemotherapy alone (XP) following D2 resection of gastric cancer in 458 patients.[132] Treatment was completed as planned by 75.4% of patients (172 of 228) in the XP arm and 81.7% (188 of 230) in the XP/radiotherapy/XP arm. The addition of radiation to XP chemotherapy did not significantly prolong disease-free survival (P = .086). However, in the subgroup of patients with pathologic lymph node metastasis at the time of surgery (n = 396), patients randomly assigned to the XP/radiotherapy/XP arm experienced superior disease-free survival when compared with those who received XP alone (P = .0365), and the statistical significance was retained at multivariate analysis (estimated HR 0.69, P = .047). The authors concluded that the addition of radiotherapy to XP chemotherapy did not significantly reduce recurrence after curative resection and D2 lymph node dissection in gastric cancer. Of note is that there was a relatively high proportion of early-stage disease in both trial arms, with approximately 60% of patients exhibiting stage Ib-II gastric cancer, as well as more than 60% demonstrating diffuse-type histology (vs 39% in the Intergroup 0116 trial). A report of long-term outcomes of the ARTIST trial with 7-year follow-up showed disease-free survival remains similar between the treatment arms (HR 0.74, CI 0.52-1.05, P = .09), with similar overall survival rates. In this analysis, the effect of the addition of radiation therapy in disease-free and overall survival differed by Lauren classification and lymph node ratio. Subgroup analysis showed that chemoradiotherapy significantly improved disease-free survival in node-positive disease and intestinal-type gastric cancers with a similar trend for disease-free and overall survival by stage of disease.[133] interpretation of these trial results is challenging given the high noncompliance rates, notably in the context that only 62% of patients assigned to the radiation arm initiated radiation, with only 50% receiving the intended 5 weeks of therapy. A subsequent trial by this group (ARTIST-II) in patients with lymph node–positive/stage II-III gastric cancer undergoing D2 resection stage II-III gastric cancer randomized patients to receive (a) adjuvant S1 for 1 year versus (b) adjuvant S1/oxaliplatin for 6 months versus (c) two cycles of S1/oxaliplatin,

followed by concurrent S1/radiotherapy, followed by four additional cycles of S1/oxaliplatin with stage IB-IVA resectable gastric or gastroesophageal adenocarcinoma. A total of 546 patients were recruited. At a median follow-up of 47 months, estimated 3-year disease-free survival was 65%, 74%, and 70% in these arms, respectively, with a HR inferior in the S1 arm relative to the other two arms, which reached statistical significance with arm 2 and borderline significance with arm 3. Estimated 3-year disease-free survival rates were 64.8%, 74.3%, and 72.8%, respectively, with no significant difference between the latter two groups. The authors concluded the addition of radiation to chemotherapy did not significantly reduce the rate of recurrence after D2 gastrectomy.[134]

Chinese investigators randomized 380 patients undergoing D2 lymph node dissection to either radiation therapy using IMRT (45 Gy) with concurrent 5-FU and leucovorin or 5-FU and leucovorin alone. Five-year local recurrence rate in the radiation arm was 15.6% versus 24.2% without radiation (P = .042), although 5-year overall survival was not significantly different (48.4% vs 41.8%, P = .122). However, median relapse-free survival (50 vs 32 months, P = .029) was higher in the radiation group, and rates of all grade adverse events were similar between the two groups.[140]

Finally, a study by the Dutch Colorectal Cancer Group (the Chemoradiotherapy after Induction Chemotherapy in Cancer of the Stomach [CRITICS] trial) randomized 788 patients to receive preoperative chemotherapy (epirubicin, cisplatin, capecitabine or, alternatively, epirubicin, oxaliplatin, and capecitabine) for three cycles followed by D1+ resection, followed by a similar postoperative chemotherapy regimen, with or without radiotherapy concurrent with cisplatin/capecitabine. After preoperative chemotherapy, 372 (95%) of 393 patients in the chemotherapy group and 369 (93%) of 395 patients in the chemoradiotherapy group proceeded to surgery, with a potentially curative resection achieved in 310 (79%) of 393 patients in the chemotherapy group and 326 (83%) of 395 in the chemoradiotherapy group. Postoperatively, 233 (59%) of 393 patients started chemotherapy and 245 (62%) of 395 started chemoradiotherapy. At a median follow-up of 61.4 months, median overall survival was 43 months in the chemotherapy group and 37 months in the chemoradiotherapy group (P = .90). After preoperative chemotherapy, in the total safety population of 781 patients (assessed together), there were 368 (47%) grade 3 adverse

events, 130 (17%) grade 4 adverse events, and 13 (2%) deaths. During postoperative treatment, grade 3 and 4 adverse events occurred in 113 (48%) and 22 (9%) of 233 patients in the chemotherapy group, respectively, and in 101 (41%) and 10 (4%) of 245 patients in the chemoradiotherapy group, respectively. The authors concluded postoperative chemoradiotherapy did not improve overall survival compared with postoperative chemotherapy in patients with resectable gastric cancer treated with adequate preoperative chemotherapy and surgery, although given the poor postoperative patient compliance in both treatment groups, future studies should focus on optimizing preoperative treatment strategies.[141]

Preoperative Chemoradiation Therapy

Because preoperative radiation therapy and chemotherapy have improved the surgical and disease-related outcomes in patients with rectal, pancreatic, and esophageal cancer, this treatment is a logical approach to explore in gastric cancer as well. In the context of established limitations of perioperative and adjuvant strategies, potential advantages of preoperative therapy include improved tolerance relative to adjuvant treatments, potential downstaging with associated improvement in R0 resection rates, better target definition, better vascularization for optimal chemotherapy and radiosensitizing oxygen delivery, and allowing biologic stratification of patients for surgery, notably given that the presence of micrometastases is at initial diagnosis. Two-phase III trials for patients with esophagus cancer have included either lesions of the gastric cardia[142] or the esophagogastric junction.[143] In both trials, the trimodality arm demonstrated an improvement in survival when compared with the control arm of surgery alone. The series by Walsh et al[142] (adenocarcinoma of the esophagus or gastric cardia) demonstrated a median survival of 4.5 years versus 1.8 years (P = .002) and 5-year survival at 39% versus 16%. with the advantage to trimodality treatment. The US Gastrointestinal Intergroup phase III trial (adenocarcinoma or squamous cell of the esophagus or GE junction), which closed prematurely owing to low accrual, resulted in a median survival of 54 versus 21.6 months and 5-year survival of 39% versus 16% (P = .008), with an advantage to the trimodality arm.[143]

Preoperative chemoradiation data for patients with gastric cancer are primarily limited to phase II studies from single institutions and cooperative groups. MD Anderson Cancer Center investigators reported a study in which 33 patients completed a preoperative protocol that started with induction chemotherapy of 5-FU, leucovorin, and cisplatin, followed by 45 Gy of radiation therapy in 25 fractions over 5 weeks. Infusional 5-FU was administered concurrently with radiation therapy. In 28 patients (85%), a gastrectomy was performed and D2 lymph node dissection was attempted. Pathologic complete and partial response was found in 64% of all operated patients. These patients showed a significantly longer median survival of 64 months in comparison with 13 months in patients with tumors not pathologically responding.[144] In a study from the same institution, 41 patients with operable gastric cancer received two cycles of continuous 5-FU, paclitaxel, and cisplatin followed by 45 Gy of radiation therapy with concurrent 5-FU and paclitaxel. An R0 resection was achieved in 78% of patients, pathologic complete response in 25%, and pathologic partial response in 15%. Pathologic response, R0 resection, and postoperative T and N stages were correlated with overall and disease-free survival.[145] The RTOG reported the results of a phase II study of 49 patients undergoing induction 5-FU, leucovorin, and cisplatin followed by concurrent radiation therapy and infusional 5-FU and paclitaxel.[146] Resection was attempted 5 to 6 weeks after radiation therapy and chemotherapy. The pathologic complete response and R0 resection rates were 26% and 77%, respectively. At 1 year, more patients with tumors exhibiting a pathologic complete response (89%) were living than patients with tumors exhibiting a less favorable response (66%). Grade 4 toxicity occurred in 21% of patients. The authors indicated these data appear to support a randomized phase III study evaluating preoperative versus postoperative radiation therapy and chemotherapy.[146] Although some concerns exist regarding potential for neoadjuvant radiation to increase perioperative morbidity, a national database analysis showed no differences in overall complications or 30-day mortality relative to up-front surgery alone with this approach.[147]

Preoperative Chemoradiation Versus Preoperative Chemotherapy

A randomized trial comparing neoadjuvant chemotherapy alone versus neoadjuvant combined-modality therapy was conducted by German investigators (the Preoperative Chemotherapy or Radiochemotherapy in Esophago-gastric Adenocarcinoma Trial [POET]).[148] Patients with advanced esophagogastric adenocarcinoma were randomized to receive (a) cisplatin/5-FU-based chemotherapy alone versus (b) a similar induction chemotherapy followed by concurrent cisplatin/etoposide with 30 Gy of radiation therapy. Both groups went on to receive surgery. Although this study closed early owing to poor accrual, patients receiving preoperative chemoradiotherapy had significantly higher N0 rates (37% vs 64%, *P* = .04) and pathologic complete response rates (2% vs 16%, *P* = .03), as well as statistical trends toward improved local control (59% vs 76%, *P* = .06) and overall survival (3-year survival 28% vs 47%, *P* = .07, HR 0.67). The authors concluded that preoperative combined modality improves overall survival as compared to chemotherapy alone in patients with locally advanced esophagogastric adenocarcinoma.[148] Long-term follow-up of this study showed that local progression-free survival after tumor resection was significantly improved by chemoradiotherapy (HR 0.37, 0.16-0.85, *P* = .01, 95% CI) and 20 versus 12 patients were free of local tumor progression at 5 years (*P* = .03). Although the rate of postoperative in- hospital mortality was somewhat higher with chemoradiotherapy (10.2% vs 3.8%, *P* = .26), more patients were alive at 3 and 5 years after chemoradiotherapy (46.7% and 39.5%) compared with chemotherapy (26.1% and 24.4%). Thus, overall survival showed a trend in favor of preoperative chemoradiotherapy (HR 0.65, 95% CI 0.42-1.01, *P* = .055).[149] Along these lines, an Australian randomized phase II/III trial (the TOPGEAR study) was initiated, randomizing patients with resectable gastric and GE junction cancer to (a) preoperative chemotherapy alone (ECF) × three cycles versus (b) the same regimen (× two cycles) followed by concurrent 5-FU-based chemoradiotherapy, with both arms followed by adjuvant ECF. Interim analysis of the first 120 patients from this study demonstrated that preoperative chemoradiation could be safely delivered to the vast majority of patients without a significant increase in treatment toxicity or surgical morbidity. Specifically, 92% of patients allocated to preoperative chemoradiation received the specified treatment, which is much higher than the 50% compliance rate seen in the previously described CRITICS trial;

greater than or equal to grade III gastrointestinal toxicity occurred in 30% of combined-modality patients versus 32% in the chemotherapy-alone arm.[150] Owing to the complexity of gastric irradiation, a comprehensive radiation therapy quality assurance (RTQA) program was implemented. RTQA was undertaken in real time before treatment for the first five patients randomized to chemoradiotherapy from each center. Once acceptable quality was achieved, RTQA was completed for one-third of subsequent cases. RTQA consisted of evaluating (1) CTV and organ-at-risk contouring and (2) radiation therapy planning parameters. TOPGEAR enrolled 574 patients, of whom 286 were randomized to receive preoperative chemoradiotherapy and 203 (71%) were included for RTQA. Of these, 67 (33%) and 136 (67%) patients were from high- and low-volume centers, respectively. The initial RTQA pass rate was 72%. In total, 28% of cases required resubmission. In total, 200 of 203 cases (99%) passed RTQA before treatment. Cases from low-volume centers required resubmission more often (44/136 [33%] vs 13/67 [18%]; $P = .078$). There was no change in the proportion of cases requiring resubmission over time.[151] Recently published results showed that a higher percentage of patients in the chemoradiotherapy group achieved higher pathologic complete response rates (17% vs 8%) and greater tumor downstaging; however, at a median follow-up of 67 months, no significant differences in overall or progression-free survival were seen between the groups. Median overall survival was 46 months in the chemoradiotherapy group versus 49 months in the chemotherapy-alone group (HR 1.05, 0.83-1.31, 95% CI), with median progression-free survival of 31 versus 32 months, with similar treatment-related toxicities between groups. The authors concluded the addition of preoperative chemoradiotherapy to perioperative chemotherapy did not improve survival relative to perioperative chemotherapy alone in patients with resectable gastroesophageal junction and that at present there is little, if any, role for radiation therapy in the management of resectable gastric cancer.[152] Similarly, a follow-up Dutch phase II trial (the CRITICS-II trial) is examining the role of preoperative chemoradiotherapy using three preoperative strategies: chemotherapy (docetaxel, oxaliplatin, capecitabine) × four cycles, chemoradiotherapy (45 Gy, carboplatin, paclitaxel), and a combination of both (two cycles chemotherapy) in these patients.

Adjuvant Chemotherapy

The use of adjuvant chemotherapy has been explored in more than 30 randomized trials, many of which showed no benefit in survival compared to surgery alone. A randomized trial from Japan evaluated 579 patients undergoing resection to receive adjuvant chemotherapy alone versus observation alone. Primarily, early T-stage patients in the treatment group received a combination of mitomycin and fluorouracil twice weekly for 3 weeks following surgery, followed by delivery of uracil + tegafur (an oral 5-FU prodrug) (UFT). No survival benefit was seen with adjuvant chemotherapy.[153] However, a more recent study from Japan (the ACTS-GC trial) evaluated the efficacy of adjuvant chemotherapy in patients with stage II/III gastric cancer undergoing R0, D2 dissection (excluding T1 patients). This study randomized 1,059 patients to surgery alone versus treatment with S1, an oral fluoropyrimidine combining tegafur and oxonic acid. Three- and 5-year survival was significantly improved in patients receiving adjuvant chemotherapy (80% vs 70%; 72% vs 61%, respectively) in favor of the chemotherapy arm (HR of 0.669).[154,155] Whether the impact of S1 in the Asian population can be extrapolated to Western patients remains less clear and the subject of investigation, including potential biologic differences among populations regarding how this drug is metabolized.

A follow-up Japanese trial (the SAMIT trial) randomized patients with T4a/b gastric cancer following D2 dissection to (a) adjuvant UFT alone, (b) S1 alone, or (c) intermittent weekly paclitaxel, followed by either (a) UFT or (b) S1. The authors concluded that sequential treatment did not improve disease-free survival and UFT was not noninferior to S1 (and S1 was superior to UFT). The authors recommended S1 monotherapy should remain the standard adjuvant treatment for locally advanced gastric cancer patients in Japan.[156]

Another Asian study, the CLASSIC (capecitabine and oxaliplatin adjuvant study in stomach cancer) was conducted in South Korea, China, and Taiwan. A total of 1,035 patients with pathologic stage II-IIIB gastric cancer were randomized to a surgery-alone arm versus surgery plus adjuvant capecitabine/oxaliplatin for 6 months. Again, all patients underwent D2 gastrectomy. At a median follow-up of 62 months, the

adjuvant chemotherapy group had a significant improvement in disease-free survival compared to the surgery-alone group (68% vs 53%, $P < .0001$).[157]

Japanese investigators reported the JACCRO GC-07 trial in which 917 patients with lymph node–positive, stage IIa-IVa disease were randomized to curative gastrectomy with D2 lymphadenectomy to postoperative S-1 plus docetaxel or S-1. The docetaxel-containing group had improved 3-year relapse-free survival (66% vs 50%, $P < .001$).[158]

A meta-analysis of 17 randomized controlled trials using individual patient data comparing surgery alone to surgery with adjuvant chemotherapy in patients with resectable gastric cancer was performed. In this study, adjuvant chemotherapy was associated with a significant survival benefit in terms of overall survival (HR 0.82, CI 0.76-0.90, $P < .001$) and disease-free survival. Estimated 5-year overall survival was increased from approximately 50% to 55% with the use of chemotherapy. The authors[159] concluded that adjuvant chemotherapy with fluorouracil-containing regimens reduces the risk of death in gastric cancer compared to surgery alone. As discussed previously, how these varying studies apply to Western patients remains unclear.

Perioperative Chemotherapy

Various combinations of active drugs have been reported to improve the response rate among patients with metastatic or locally unresectable gastric carcinoma.[10] A combination of fluorouracil, doxorubicin, and methotrexate has been associated with a 30% to 40% response rate and was the most widely prescribed regimen for patients with advanced disease in the 1980s.[10] Despite an initial response rate of 64% when a combination of etoposide, doxorubicin, and cisplatin (EAP) was used by German investigators, in subsequent trials, this regimen was considerably less effective and deemed extremely toxic.[160-162] A combination of fluorouracil, doxorubicin, and high-dose methotrexate (FAMTX) was associated with a significant improvement in response rate compared with either EAP or FAM. As a result of these studies, FAMTX became standard therapy for metastatic disease.

In a British study of patients with unresectable or metastatic gastric and esophageal adenocarcinoma, 274 patients were randomized to either 5-FU,

doxorubicin, and methotrexate (FAMTX) or epirubicin, cisplatin, and continuous infusion 5-FU (ECF).[163,164] ECF was associated with a superior response rate (45% vs 21%, *P* = .0002), median survival (8.7 vs 5.7 months, *P* = .0006 vs .006), and 1-year survival (36% vs 21%). Moreover, ECF was associated with a superior quality of life and less toxicity.

The Medical Research Council (MRC) subsequently initiated a trial (the Medical Research Council Adjuvant Gastric Infusional Chemotherapy [MAGIC] trial) to address the question of perioperative chemotherapy (pre- and post-) in patients with operable gastric cancer. Patients with resectable adenocarcinoma of the stomach, GE junction, or lower esophagus were randomized to preoperative and postoperative chemotherapy with epirubicin, cisplatin, and 5-FU (ECF) versus surgery alone. Although originally designed to include patients with only tumors of the stomach, eligibility was later expanded to include tumors of the lower third of the esophagus, with approximately one-fourth of patients having adenocarcinoma involving the lower esophagus or GE junction. Of note is that there were more patients with T1/T2 disease (52% vs 37%, *P* = .002) as well as more N0/N1 patients (84% vs 71%, *P* = .01) in the chemotherapy group. Additionally, a significantly higher percentage of patients with gastric cancer receiving perioperative chemotherapy underwent surgery (79% vs 70%, *P* = .03). Nonetheless, the resected tumors were significantly smaller and less advanced in the perioperative chemotherapy group. With a median follow-up of 4 years, 149 patients in the perioperative chemotherapy group and 170 patients in the surgery group had died. As compared with the surgery group, the perioperative chemotherapy group had statistically improved progression-free and overall survival rates. No patient achieved pathologic complete response. However, patients receiving perioperative chemotherapy had an HR for death of 0.75, which was highly significant, with 5-year survival in patients receiving chemotherapy of 36% versus 23% in patients undergoing surgery alone (*P* = .009).[165] A follow-up MRC study (the ST03 trial) randomized 1,063 patients with perioperative resectable esophagogastric adenocarcinoma (36% gastric cancer, an additional 20% Siewert type III esophagogastric cancers) to epirubicin, cisplatin, and capecitabine (ECX) versus the same regimen plus bevacizumab. Three-year survival was 50.3% versus 48.1% (NS), with a higher rate of wound healing complications and anastomotic leaks in the

bevacizumab group. The authors concluded their results did not provide evidence for the use of bevacizumab in combination with ECX in patients with resectable esophagogastric cancer.[166]

French investigators reported the results of a similar randomized trial of 224 patients assigned to perioperative chemotherapy (cisplatin and 5-FU only) versus surgery alone. Although originally designed to include only patients with tumors of the lower third of the esophagus or GE junction, eligibility was later expanded to include gastric cancers, although most (75%) of the patients had disease of the lower esophagus or GE junction. Chemotherapy consisted of a planned two to three preoperative and three to four postoperative cycles. This study was prematurely terminated because of low accrual. Nonetheless, patients receiving chemotherapy had improved overall survival (5-year 38% vs 24%, $P = .02$), disease-free survival (5-year 34% vs 19%, $P = .003$), and R0 resection rates (84% vs 73%, $P = .04$). Only 50% of the patients received postoperative chemotherapy. T0 disease (complete pathologic response at the primary site) was seen in 3% of neoadjuvantly treated patients. Total locoregional recurrence rates were 24% and 26%, respectively, in the chemotherapy versus surgery group, with distant recurrence rates of 42% versus 56%, respectively.[167]

An EORTC study enrolling patients with locally advanced adenocarcinoma of the stomach or GE junction randomized patients to receive either cisplatin, leucovorin, and infusional 5-FU followed by surgery or surgery alone. Although only accruing 144 of 360 planned patients, neoadjuvantly treated patients had higher R0 resection rates (82% vs 67%, $P = .036$); however, at a median follow-up of 4.4 years, no significant difference in overall survival was seen ($P = .466$).[168]

A meta-analysis of these along with other small trials was performed, revealing that neoadjuvant chemotherapy was associated with a significant improvement in overall survival and progression-free survival and improved R0 resection rates.[169] Given these data, some authors have suggested that in terms of patient selection, a perioperative chemotherapy strategy may be most appropriate for patients with bulky primary tumors or bulky adenopathy in which there is a significant risk of micrometastatic disease as well as incomplete resection.[170]

A report from Dutch investigators described a study randomizing 716 patients with resectable gastric or GE junction cancer to 5-FU, leucovorin,

oxaliplatin, and docetaxel (FLOT) versus epirubicin, cisplatin, and 5-FU or capecitabine (ECF or ECX) given in a perioperative fashion. Disease-free and overall survival were significantly improved in patients receiving FLOT (30 vs 18 months disease-free survival, $P = .0036$; overall survival 50 vs 35 months, $P = .012$). Postoperative complications were similar in both groups. The authors concluded that in locally advanced resectable gastric or GE junction adenocarcinoma, perioperative FLOT improved overall survival compared with perioperative ECF/ECX, with these results leading to perioperative FLOT as a new standard of care in locally advanced patients with gastric cancer.[171] Ongoing[172] studies include a French study (FFCD1103) that is randomizing patients with resectable signet ring gastric cancer to receive neoadjuvant chemotherapy using perioperative ECF versus initial surgery followed by adjuvant ECF. Additionally, other ongoing randomized trials are building on a FLOT backbone, including the use of immunotherapy in patients with potentially resectable gastric cancer, the EORTC-1707 VESTIGE trial is evaluating the role of adjuvant immunotherapy with nivolumab and ipilimumab in patients with high risk for relapse following resection, and the INNOVATION study is comparing chemotherapy versus chemotherapy plus anti-HER2 therapy in operable gastric cancer. Recently results of the EORTC-1707 VESTIGE study reports reported recruitment was stopped early due to futility, with median disease-free survival for the nivolumab-ipiliumab group of 11.4 months versus 20.8 months for the chemotherapy group, with respective 12-month disease-free survival rates of 47% versus 64%, with the authors concluding that the addition of nivolumab-ipiliumab did not improve disease-free survival compared with chemotherapy in patients with ypNs+ and/or R1 gastroesophageal adenocarcinoma following neoadjuvant chemotherapy and surgery.[173]

Palliative Radiation Therapy

Radiation therapy is capable of providing substantial palliation of local gastric cancer symptoms.[174-179] It appears that 50% to 75% of patients can expect improvement of symptoms such as gastric outlet obstruction, pain from local tumor extension, bleeding, or biliary obstruction.[177] The likelihood of benefit may increase with concomitant 5-FU administration,

with less tumor bulk and if the patient's performance score is better before therapy.[125,175,180,181] The median duration of palliation varies from 4 to 18 months in reports addressing this issue.[175,180,181] A systematic review of the use of palliative radiotherapy in gastric cancer showed large variations in radiation dose and fractionation. The pooled overall response rates for bleeding, pain, and obstruction were 74%, 67%, and 68%, respectively. No difference in bleeding response rates was seen with a biologically effective dose (BED) of 39 or more versus lower doses. Grade III/IV toxicities occurred in up to 15% of patients treated with radiation alone versus up to 25% with combined-modality therapy. The authors concluded that more than two-thirds of patients receiving radiation therapy would derive clinical benefit.[182] A prospective trial from Japan evaluated the effectiveness of palliative radiation therapy. Patients requiring blood transfusion or hemoglobin <8 were entered. Response was gauged as hemoglobin more than 8, 7 consecutive days without blood transfusion between enrollment and blood sampling, and no salvage therapy or bleeding otherwise (including rebleeding). In total, 55 patients were enrolled, and per protocol response rates were 56%, 78%, and 90% at 2, 4, and 8 weeks, respectively. BED was not predictive of response.[183] Another prospective study from Singapore evaluated palliative radiotherapy in patients with symptomatic, locally advanced gastric cancer. Enrolling symptoms included bleeding, pain, or obstruction, with patients receiving a dose of 36 Gy/12 fractions. Median survival was 85 days. Eighty percent, 100%, and 100% of the patients with bleeding, obstruction, and pain responded to treatment, respectively. Improvement scores in fatigue, nausea/vomiting, and pain subscales were seen in 63%, 31%, and 50% of patients, respectively, 1 month after radiation therapy. The authors concluded that palliative gastric radiotherapy was effective and well tolerated, with significant symptomatic relief.[184]

SEQUELAE OF THERAPY

Anorexia, nausea, and fatigue are very common complaints during gastric radiation therapy; these symptoms can lead to potentially detrimental treatment breaks, with a National Cancer Database analysis evaluating overall adjuvant radiation therapy treatment time suggesting prolonged

breaks were associated with inferior survival and that efforts to minimize cumulative interruptions to less than 7 days should be considered.[185] However, the understanding of these side effects is somewhat limited.[186-189] Although visceral afferents may play some role in the acute emetogenic effects of radiation, other unknown factors, possibly chemical in nature and mediated by the chemoreceptor trigger zone, appear to be more important. Although selective serotonin (5-hydroxytryptamine 3 [5-HT_3]) antagonists effectively treat radiation-induced emesis, it is not clear whether the mechanism of action is directed at the 5-HT_3 receptor alone or has an effect on inhibition of serotonin release.[190] Additionally, the use of low-dose corticosteroids may be beneficial in patients with refractory nausea. Other compounding factors may include the altered gastric motility and prolonged gastric emptying time observed in animal experiments as a response to irradiation.[108,186,187,191] Chemotherapy-related leukopenia and thrombocytopenia may occur. If chemotherapy is used with irradiation, blood counts are generally obtained once to twice weekly. Additional acute toxicities of radiation therapy include esophagitis, epidermitis, fatigue, and weight loss in most patients. Nausea, vomiting, dehydration, and anorexia are relatively common, particularly in patients with lower esophageal and GE junction tumors. During therapy, patient tolerance, weight, and blood counts are checked at least weekly. Many symptoms resolve within 1 to 2 weeks of treatment completion. Because of potential toxicities in the treatment for patients with gastric cancer (dehydration, weight loss, anorexia, etc), aggressive supportive measurements and symptom management are indicated in efforts to avoid treatment-related interruptions, hospitalizations, or failure to complete the intended treatment course. Varying antiemetics should be used liberally, including on a prophylactic basis. Antacids including proton pump inhibitors are frequently implemented, and antidiarrheal medications may be appropriate. Additionally, nutritional supportive measurements are paramount and, when appropriate, the use of enteral methods is implemented. In selected cases, the use of feeding jejunostomy may be appropriate. Patients may require intermittent hydration both during and shortly following the treatment course. Postoperatively, vitamin B_{12}, iron, and calcium levels should be monitored and supplemented as appropriate.

Nutritional complications of treatment and myelosuppression, if concurrent chemotherapy is used during irradiation, can carry substantial morbidity and even occasional mortality from therapy. The historical GITSG reported a minimum 13% treatment-related mortality from nutritional problems or septic events on their concurrent chemoradiation arm,[127] and almost 20% of the patients of Caudry et al[192] were unable to complete therapy because of nutritional problems. However, others reported no severe or life-threatening nutritional compromise with aggressive chemoradiation.[122,125,193] Toxic gastrointestinal effects usually are managed with careful nutritional support and antiemetic therapy. It may be prudent to proactively prescribe antiemetics at the initiation of therapy in patients undergoing aggressive upper abdominal irradiation.

Myelosuppression causing serious or, rarely, lethal toxicity is also reported in many of the combined-modality trials.[122,125,193,194] If blood counts are monitored weekly during combined-modality therapy, serious problems with sepsis or bleeding should be uncommon.[193,194]

Moderate doses of 16 to 36 Gy reduce secretion of pepsin and hydrochloric acid.[1,108,195] For this reason, radiation therapy was once a common and successful therapy for peptic ulcer disease. Most of the gastric ulcers healed, although they recurred in approximately 40% of patients.[1,108,195] Gastric acid secretion decreased in almost all cases, with achlorhydria in 25% to 40%. The gastric acid decrease usually persisted from 1 to 6 months; however, 25% showed persistent decrease in acid production for 1 to 5 years or more.

Gastric late effects were categorized by the Walter Reed Group as dyspepsia, radiation gastritis, uncomplicated gastric ulcer, or gastric ulcer with perforation or obstruction.[196-198] The associations between dose and these late effects are described in Table 64.12. These data suggest a 20% to 30% incidence of ulceration with doses of 45 to 59 Gy, with complications of these ulcers in 30% to 50% of the treated patients. Some caution is necessary in interpreting this experience because the Walter Reed cohort was treated with 200 keV photons or 1 MV photons using a 70-cm target-skin distance, usually using only one field each day with daily fraction sizes of 3 Gy to midline, which sometimes produced daily given doses of 4 to 6 Gy.[197,198]

TABLE 64.12 RADIATION DOSE COMPARED WITH LATE EFFECTS IN THE WALTER REED EXPERIENCE

		Radiation Late Effects (%)[b]			
Dose (Gy)	Number of Patients[a]	Dyspepsia	Gastritis	Ulcer	Complicated Ulcer[c]
<40	111	5	2	3	0
40-44.99	23	0	22	0	0
45-49.99	27	4	19	11	11
50-54.99	34	0	24	18	12
55-59.99	14	0	50	14	7
>60	8	0	0	13	38

[a]Total number of patients treated at this dose.

[b]Results reported as number of patients with injury/total number of patients treated with this dose.

[c]Ulcers complicated by obstruction or perforation.

Most data suggest that gastric late effects are rare with doses of 40 to 52 Gy using conventional fractionation of 1.8 to 2 Gy. The relatively low risk of gastric late effects with doses less than 50 Gy is corroborated by many series using radiation therapy with or without chemotherapy for locally advanced gastric cancer.[41,48,62,74,84,142] However, doses in the range of 50 to 55 Gy may produce variable gastric late effects, which have been reported to reach 9% in some series. Doses of 60 Gy carried a 5% to 15% risk of gastric late effects.[1-3,52,62,70,93,125,142,164,175,181,188,190-193,195-200] The ability of histamine (H_2) blockers, proton pump inhibitors, and sucralfate to prevent the later development of radiation-induced gastric ulcerations is unproven. It may be reasonable to administer H_2 blockers or proton pump inhibitors prophylactically to patients receiving more than 45 Gy to any significant volume of the stomach or proximal duodenum.

Several series have described a gradual decline in renal function occurring 18 to 24 months or more following postoperative radiation therapy for gastric cancer. However, it is unclear that this is of clinical significance, and long-term renal function among gastric cancer survivors has not been reliably reported. One recent report described a dose-dependent nephrotoxicity as manifested by hypertension in patients with

gastric cancer, which may take years to manifest.[201] Similarly, another study indicated that mean creatinine clearance as well as changes in renal parenchymal volume occurred primarily within the first 4 years following radiation therapy with a clear relationship between these changes and dose volume histogram (DVH) parameters.[202] Nonetheless, advanced techniques may enhance renal sparing and also allow potential dose escalation as well as integration of novel (and potentially nephrotoxic) systemic agents.

Radiation-induced cardiac toxicity is a broad term describing potential radiation injury to a number of cardiac structures, including the pericardium (as manifested by effusion, pericarditis), coronary arteries, the heart muscle itself, and cardiac valves as well as nerve/conduction injury. Radiation injury primarily consists of fibrosis and/or small-vessel injury. The mechanism of radiation-induced cardiac injury is relatively poorly defined, particularly in the context of gastric cancer. Historical data from the treatment for patients with Hodgkin disease have suggested that dose more than 40 Gy may increase the risk of cardiac death as well as pericarditis.[203,204] Several studies of cardiac toxicity and patients with esophageal cancer have demonstrated that an increasing V_{30} predicted for a significant increase in pericardial effusion and increasing fraction size (particularly ≥3.5 Gy) also predicted for the same. Additionally, there may be a trend for decrease in ejection fraction in patients with increasing V_{20} of the left ventricle. A more detailed discussion on potential long-term cardiac sequelae of radiation therapy can be found in Chapters 59.

CONCLUSIONS AND RECOMMENDATIONS

Radiation therapy, usually administered with concomitant fluoropyrimidine-based chemotherapy, is indicated for locally confined gastric cancer that either is not technically resectable or occurs in medically inoperable patients. In this setting, therapy can be administered with curative or palliative intent, depending on the clinical situation. Those who undergo gastric resection with incomplete tumor resection or have truly positive margins of resection are also appropriately managed by combined-modality therapy. Preferably, patients that is unresectable (ie, inability to achieve R0 resection) would be identified preoperatively with endoscopic ultrasonography and CT staging. Preoperative chemoradiation then could

precede an attempt at gross total resection, alone or in combination with IORT in select situations, and maintenance chemotherapy.

With the more recent success of perioperative chemotherapy trials in gastric cancer, ongoing trials are examining the role of chemoradiation in the setting of perioperative chemotherapy and D2 lymph node dissection, including attempts to better stratify which patients might be most appropriate for (neo)adjuvant combined-modality therapy.

The irradiation field design from the phase III US Gastrointestinal Intergroup trial was based on optimized field design related to both site of the primary lesion and T and N stages of disease.[120] With the wide availability of 3-D conformal treatment planning systems, it is possible to more accurately target the high-risk volume and to use unconventional field arrangements and/or IMRT to produce superior dose distributions. To accomplish this without marginal misses, however, it will be necessary to both carefully define and encompass the various target volumes (tumor bed, nodal sites at risk), as target volumes that would be included using older approaches may be missed with more contemporary planning approaches.

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CHAPTER 65

Pancreatic Cancer

Christopher G. Willett and Brian G. Czito

ANATOMY AND PATHWAYS OF SPREAD

The pancreas lies in the retroperitoneal space of the upper abdomen at about the level of the first two lumbar vertebrae. It is divided into head (including the uncinate process), neck, body, and tail (Figure 65.1). It has intimate contact with surrounding organs, including stomach, duodenum, jejunum, kidneys, spleen, and major vessels, which can be involved by direct tumor extension. Tumors in the pancreatic head often invade or compress the common bile duct, causing jaundice and dilatation of the bile and pancreatic ducts and gallbladder.

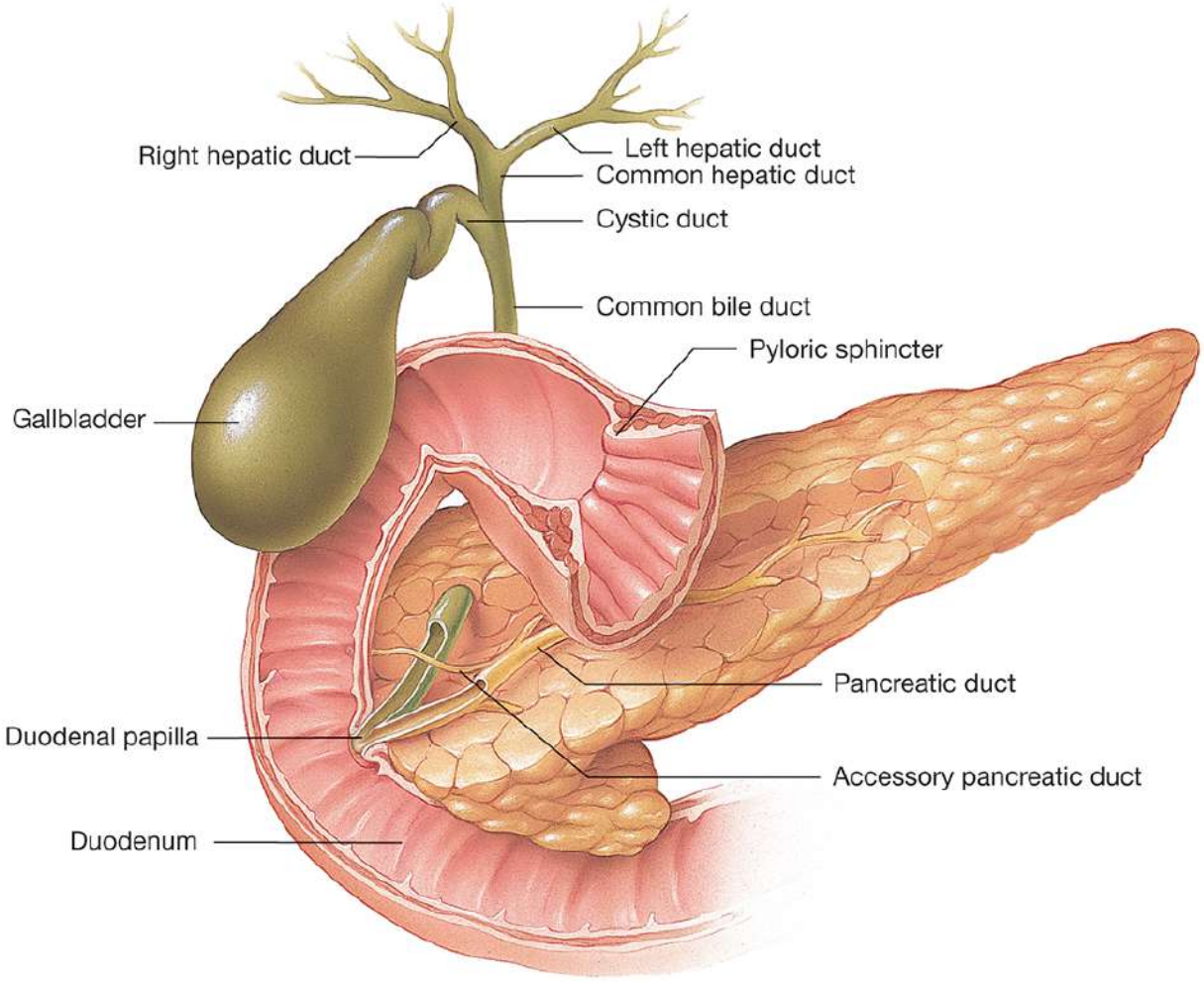

FIGURE 65.1 Pancreas and gallbladder duct anatomy. (Provided by the Anatomical Chart Company.)

The rich lymphatic drainage of the pancreas is interconnected with duodenal lymphatics. Regional drainage of the pancreatic head is to the peripancreatic, pancreaticoduodenal, porta hepatis, celiac, and superior mesenteric lymph nodes. The pancreatic body and tail drain to the splenic artery, peripancreatic, celiac, superior mesenteric, and para-aortic nodal basins.[1] With posterior, retroperitoneal tumor extension, para-aortic nodes are at risk. The main venous channels drain via the portal system to the liver. The lungs and pleura may be involved with posterior tumor extension into tissues with venous drainage by the vena cava or its tributaries. Generalized peritoneal involvement is more common with carcinoma of the body and tail than with carcinoma of the head of the pancreas.

EPIDEMIOLOGY AND RISK FACTORS

In 2023, an estimated 64,050 new cases of pancreatic cancer will be diagnosed in the United States, with 50,550 estimated deaths from the disease, making pancreatic cancer the fourth leading cause of cancer-related death in the United States.[2] At present, surgery offers the only means of cure. Unfortunately, only 10% to 20% of patients present with tumors amenable to resection. Even among patients who present with localized disease, the 5-year overall survival (OS) is approximately 20%.[3] Contemporary survival rates have reported improved results, particularly in patients with complete surgical resection (R0) and node-negative (N0) disease.[4-6] Patients who present with locally advanced, unresectable pancreatic cancer have a median survival of approximately 8 to 14 months, with rare long-term survival. Up to 60% of patients present with metastatic disease, which carries a shorter median survival of 4 to 12 months.[7]

The incidence of pancreatic cancer rises sharply after age 45, with higher rates in males than in females (1.3:1) and in Black males compared with the general population (14.8/100,000:8.8/100,000).[8] Familial aggregation of pancreatic cancer is estimated in 5% to 10% of newly diagnosed cases. It is associated with *BRCA1/2* and PALB2 mutations, familial atypical multiple mole melanoma syndrome, Peutz-Jeghers syndrome, familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, hereditary pancreatitis, ataxia telangiectasia, and Li-Fraumeni syndrome, with lifetime risk ranging from 5% to 40%.[9,10] Described risk factors for pancreatic cancer include chronic pancreatitis, smoking, alcohol consumption, *Helicobacter pylori* infection, and factors associated with metabolic syndrome, such as obesity and glucose intolerance.[11,12]

CLINICAL PRESENTATION

Most patients with pancreatic cancer experience pain, weight loss, or jaundice. Classically, pain from pancreatic cancer is characterized by radiation to the back, given the retroperitoneal location of the pancreas. Jaundice, due to biliary obstruction, is often accompanied by pruritus, acholic stools, and dark urine color. The initial presentation varies according to tumor location. Patients with tumors in the pancreatic body or tail usually present with pain and weight loss, whereas those in the head of

the gland typically present with jaundice, steatorrhea, weight loss, and pain. Recent onset of atypical or exacerbation of preexisting diabetes mellitus, unexplained thrombophlebitis, or history of pancreatitis is often noted. Patients with pancreatic cancer frequently present with unresectable or metastatic disease, in part due to these nonspecific presenting symptoms and the tendency for local and distant spread. No effective screening method to detect disease at the localized stage has been identified. Positive physical findings, if any, generally reflect incurable disease. These may include a palpable abdominal mass (ie, pancreas, liver, or gallbladder due to biliary obstruction), ascites, supraclavicular nodes, or palpable rectal shelf (ie, peritoneal seeding).

EVALUATION

Significant advances have been achieved in the imaging and staging of pancreatic cancer.[13] Currently, the principal diagnostic tools are multiphasic, helical computed tomography (CT) scan, endoscopic ultrasound (EUS), and laparoscopy. Magnetic resonance imaging (MRI) and positron emission tomography (PET) imaging techniques may be used in the initial evaluation of pancreatic malignancies. These tools have facilitated the characterization of the primary tumor (resectable or borderline resectable vs unresectable) as well as the identification of metastatic disease so patients can be appropriately and reliably triaged to operative and nonoperative therapies.

CT scan is the most commonly used staging modality. Newer generation, multidetector, high-speed helical CT coupled with a thin section imaging allows high-resolution images of the pancreas and its surrounding structures to be obtained at varying phases of enhancement. This allows for adequate imaging of the pancreas and assessment of metastatic deposits in other intra-abdominal organs, such as the liver.[14] Over 90% of patients deemed unresectable because of vascular involvement by CT are truly inoperable at the time of surgery.[15] Although CT staging is limited in detection of nodal involvement and peritoneal disease, it is useful in evaluating for metastatic disease.

Another tool for local tumor staging and diagnosis is EUS. In this procedure, an endoscope with an ultrasound transducer at its tip is passed into the stomach and duodenum, where it provides high-resolution images

of the pancreas and surrounding vessels. EUS facilitates fine-needle aspiration (FNA) without exposing the peritoneum to potential tumor seeding, as may occur with CT-guided biopsy. Sensitivity for EUS is at least comparable to CT, with tumor detection reported as high as 97%.[16] An advantage of EUS over CT is the ability to detect small or isoattenuating lesions, which might not be well visualized on cross-sectional imaging.[17] Interpretation of EUS is highly operator dependent. Frequently, EUS is performed in conjunction with endoscopic retrograde cholangiopancreatography.[18] This combined diagnostic approach allows for staging, therapeutic stenting of the common bile duct when indicated, and diagnostic FNA simultaneously.

A limitation of current imaging techniques is the inability to visualize small (1-2 mm) liver and peritoneal implants. Staging laparoscopy has been used preoperatively to assess for intraperitoneal metastases. One meta-analysis demonstrated that the adoption of staging laparoscopy and laparoscopic ultrasound will prevent up to 50% of patients from undergoing unnecessary laparotomy.[19] Patients with locally advanced disease and involved peritoneal washings or positive peritoneal biopsies have the same prognosis as do those with metastatic disease.[20]

Advances in MRI, including high-resolution imaging, faster acquisition time, three-dimensional (3D) reconstruction, functional imaging, and MR cholangiopancreatography, have led to an improved ability of MRI to diagnose and stage pancreatic cancer.[14] This modality can be used in patients with poor renal function to assess the primary tumor and determine resectability; however, studies suggest that MRI is not as sensitive as EUS or CT in tumor detection.[21] A potential advantage of MRI is identification of small foci of hepatic metastatic disease difficult to appreciate by CT or to further characterize ill-defined lesions seen on CT.[22]

Initial studies showed that PET has a higher sensitivity, specificity, and accuracy than does CT in diagnosing pancreatic carcinomas.[23-25] Integrated PET-CT had a higher sensitivity for malignancy detection than did either PET or CT alone (96% vs 84% vs 77%) but did not improve specificity (64%). PET may also be a useful adjunct in the identification of benign versus malignant lesions and the presence of metastatic disease. Although PET-CT may be useful in initial diagnosis, its role in determining resectability has been questioned as co-registration is often performed with

lesser resolution CT images and high metabolism can obscure peripancreatic planes.[26]

High-resolution pancreatic CT and EUS remain the current standard for diagnosis and staging of pancreatic malignancies. Staging laparoscopy is useful in assessing for intraperitoneal and liver disease. MRI and PET-CT are technologies that may also be useful. All imaging modalities are inadequate to stage lymph node involvement, and further advances may improve the ability to diagnose, stage, and appropriately select further therapies.

TUMOR STAGING

Staging is rarely used in published series, and tumors are instead characterized as resectable, borderline resectable, unresectable, or metastatic.

The current American Joint Committee on Cancer 2017 tumor, node, and metastasis staging system is described in Table 65.1. Common criteria of resectability are outlined in Table 65.2.

TABLE 65.1 AMERICAN JOINT COMMITTEE ON CANCER STAGING 2017 TNM CLASSIFICATION FOR PANCREATIC CANCER

Primary Tumor (T)	Regional Lymph Nodes (N)
Tis Carcinoma in situ **T1a** <2 cm, T1a ≤0.5 **T1b** >0.5 and <1 **T1c** 1-2 cm **T2** >2 and ≤4 cm **T3** >4 cm **T4** Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery.	**N0** No regional lymph node metastasis **N1** Metastasis in 1-3 regional lymph nodes **N2** Metastasis in ≥4 regional lymph nodes **Distant Metastasis (M)** **M0** No distant metastasis **M1** Distant metastasis

Stage Grouping

Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1-3	N1	M0
Stage III	T1-3N2M0; T4 any NM0	Any N	M0

Primary Tumor (T)		Regional Lymph Nodes (N)	
Stage IV	Any T	Any N	M1

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TABLE 65.2 INTERNATIONAL CONSENSUS OF CLASSIFICATION OF BORDERLINE RESECTABLE PANCREATIC DUCTAL ADENOCARCINOMA (BR PDAC) BASED ON ANATOMICAL DEFINITION USING COMPUTED TOMOGRAPHY IMAGING THAT INCLUDES CORONAL AND SAGITTAL SECTIONS

Resectable: R	• SMV/PV: No tumor contact or unilateral narrowing • SMA, CA, CHA: No tumor contact
Borderline resectable: BR	Subclassified according to SMV/PV involvement alone or arterial invasion
BR-PV (SMV/PV involvement alone)	• SMV/PV: Tumor contact ≥180° or bilateral narrowing/occlusion, not exceeding the inferior border of the duodenum • SMA, CA, CHA: No tumor contact/invasion
BR-A (arterial involvement)	• SMA, CA: Tumor contact of <180° without showing deformity/stenosis • CHA: Tumor contact without showing tumor contact of the PHA and/or CA (The involvement of the aorta is categorized as unresectable. Presence of variant arterial anatomy is not taken into consideration.)
Unresectable: UR	Subclassified according to the status of distant metastasis
Locally advanced: LA	• SMV/PV: Bilateral narrowing/occlusion, exceeding the inferior border of the duodenum. • SMA, CA: Tumor contact/invasion of ≥180°[a] • CHA: Tumor contact/invasion showing tumor contact/invasion of the PHA and/or CA • AO: Tumor contact or invasion
Metastatic: M	Distant metastasis[b]

AO, arota; CA, celiac artery; CHA, common hepatic artery; PHA, proper hepatic artery; PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein.

[a]In the cases with CA invasion of 180° or more without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a distal pancreatectomy with

en bloc celiac axis resection (DP-CAR), some members prefer these criteria to be in the BR-A category.

[b]Including macroscopic para-aortic and extra-abdominal lymph node metastasis.

Reprinted from Isaji S, Mizuno S, Windsor JA, et al. International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. *Pancreatology*. 2018;18(1):2-11. With permission.

PATHOLOGIC CLASSIFICATION

Approximately 85% to 90% of pancreatic cancers are adenocarcinomas. Other neoplasm histologic cell types include intraductal papillary mucinous neoplasm, mucinous cystic, solid pseudopapillary, acinar cell, pancreaticoblastoma, neuroendocrine, squamous cell, serous cystadenocarcinoma, and lymphoma. Management and treatment sections will focus on pancreatic adenocarcinomas, given that this is the predominate histologic subtype. The histopathology of lesions in the periampullary region of the head of the pancreas is of particular importance as different types of adenocarcinomas, originating from the pancreas, bile duct, ampullary region, or duodenum, respectively, portend different prognoses.[27]

Pancreatic adenocarcinomas evolve from noninvasive pancreatic intraepithelial neoplasias, acquiring various genetic and epigenetic mutations. Several molecular abnormalities have been implicated in contributing to the development of pancreatic cancer. The most frequent genetic alterations are activation of the oncogene *KRAS* and inactivation of tumor suppressor genes including *TP53*, p16 (*CDKN2*), *DPC4 (SMAD4*), and *BRCA2*, with reported incidences ranging from 50% to 95% in pancreatic tumors.[28] These molecular changes have the potential to identify precursor lesions with a high likelihood of progressing into carcinomas, characterizing pathologically ambiguous lesions, and are useful in the development of screening regimens.

GENERAL MANAGEMENT

Operative Considerations

Surgery, as part of a multimodality treatment approach for patients with resectable pancreatic cancer, represents the only potentially curative treatment strategy.[29] More than 80% of patients present with advanced

disease that is not amenable to curative resection, with roughly two-thirds presenting in the pancreatic head. The standard surgical treatment for pancreatic cancer of the head or uncinate is pancreaticoduodenectomy, first described by Whipple et al[30] in 1935. For pancreatic tail lesions, distal pancreatectomy is employed, frequently with splenectomy. Initially, high operative morbidity and mortality rates led to technical modifications of the operation that, combined with improvements in anesthesia and critical care, have resulted in current perioperative mortality rates of 2% or less at high-volume centers.[31-33] With reduced morbidity from the Whipple procedure, there is no age limitation, and selected patients, even at ages greater than 80 years, may undergo pancreaticoduodenectomy.[34-36]

Several studies report low postoperative mortality rates and appropriate patient selection at high-volume institutions, highlighting the importance of performing such procedures at institutions with extensive experience.[37-40] In addition, the definition of resectable lesions has broadened with the ability to perform venous reconstructions with minimal increase in morbidity or mortality.[41,42]

The prognosis, even among resectable patients, remains poor, with 5-year survival rates of 10% to 25%. The number of nodes harvested appears to impact outcomes; data suggest that 12 to 15 lymph nodes constitute an adequate assessment, although the impact on outcomes may simply reflect accurate staging.[43,44] Although appropriate lymph node dissection is desirable, trials of extended lymphadenectomy conveyed no survival benefit and compromised quality of life (QoL).[45,46] Pathologic assessment provides important prognostic information, including margin status, tumor grade, tumor size, lymphovascular invasion, and lymph node involvement. The presence of positive operative margins, poor histologic grade, larger tumor size, lymphovascular invasion, and lymph node involvement portends a poorer prognosis.[47-51] Similarly, patients with elevated preoperative and postoperative carbohydrate antigen 19-9 (CA19-9) have inferior disease-free survival (DFS) and OS rates.[51-54]

In an effort to minimize surgical morbidity, pylorus-preserving pancreaticoduodenectomy and laparoscopic resection techniques have developed. Pylorus-sparing pancreaticoduodenectomy potentially improves gastrointestinal function without compromising oncologic management.[55,56] Laparoscopic pancreatic resection was first explored in the late 1990s, and

its use has increased dramatically.[57,58] Although most experiences are small, retrospective, single-institution series, laparoscopic resection, in experienced hands, appears a reasonable option for distal pancreatic resections.[59-62] The data on laparoscopic pancreaticoduodenectomy are more limited; the difficulty with this procedure arises from more complex dissection and the need for reconstruction.[42,58] Data suggest, however, that despite prolonged operative times and potential increase in postoperative fistula formation, laparoscopic resection offers shortened hospitalization and equivalent oncologic results.[58,63-65]

Cause of Death and Patterns of Failure

For patients with locally unresectable tumors or metastatic disease, death usually results from hepatic failure secondary to biliary obstruction by local tumor extension or hepatic replacement by metastases. For the 10% to 20% of patients undergoing a potentially curative pancreaticoduodenectomy, three major sites of disease relapse dominate: locoregional, peritoneal cavity, and liver (Table 65.3). High local recurrence rates of 50% to 86% occur despite resection because of frequent lymphatic and perineural involvement and cancer invasion into the retroperitoneal soft tissues, with an inability to achieve wide retroperitoneal soft tissue margins due to anatomic constraints (superior mesenteric artery [SMA] and superior mesenteric vein [SMV], portal vein, and inferior vena cava).[50,66,67] The incidence of microscopic residual disease after careful evaluation of the posterior peripancreatic soft tissue margin is as high as 40%.[67] Therefore, tumor stage, grade, and resection margin status are the best predictors of survival after surgery.[66,67] The use of adjuvant therapy after surgery can reduce the incidence of local failure, but distant disease recurrence rates remain high.

TABLE 65.3 PATTERNS OF FAILURE AFTER RESECTION OF PANCREATIC CANCER WITHOUT ADJUVANT RADIATION THERAPY OR CHEMOTHERAPY

			Incidence of Failure (%)	
Author (Reference)	**Number of Patients**	**Local (%)**	**Peritoneal**	**Liver**
Patterns of Failure After Surgery				

Author (Reference)	Number of Patients	Incidence of Failure (%)		
		Local (%)	Peritoneal	Liver
Tepper et al[68]	26	13 (50)	NA	NA
Griffin et al[69]	36[a]	19 (53)	11 (31)	16 (44)
Whittington et al[70]	29	22 (85)	6 (23)	6 (23)
Ozaki[71]	14	12 (86)	5 (36)	11 (79)
Westerdahl et al[72]	74	64 (86)	NA	68 (92)
Patterns of Failure With Surgery and Adjuvant Therapy				
Foo et al[73]	29	3 (10)	12 (41)	12 (41)
Abrams et al[74,b]	29	10 (34)	4 (14)	9 (31)
Paulino and Latona[75]	38	- (25)	- (33)	- (80)
Hattangadi et al[76]	86	- (31)	- (55)	- (53)
Regine et al[77,b]				
Gemcitabine CRT	184	56 (30)	138 (75)[c]	
5-FU CRT	197	70 (36)	140 (71)[c]	

5-FU, 5-fluorouracil; CRT, chemoradiation; NA, not available.

[a]Ten patients received external beam irradiation.

[b]First site of failure only.

[c]Distant failure.

RADIATION THERAPY TECHNIQUES

Dose-Limiting Tissues

The dose-limiting organs for irradiation of upper abdominal malignancies include the small bowel, stomach, liver, kidneys, and spinal cord. Various techniques, such as 3D conformal radiotherapy (3DCRT) and intensity-modulated radiotherapy (IMRT), can spare these organs. Given long-term survival is low, the actual number of patients at risk for late complications is small. Late small bowel and gastric effects may also be decreased through reduction of the volume of these organs within the high-dose field.

Treatment Volumes, Fields, and Doses

In patients undergoing surgery, clips should be placed to mark the extent of the lesion for postoperative irradiation. The patient should be positioned supine during simulation and treatment. 3DCRT radiotherapy allows visualization of internal organs and target delineation. CT-based treatment planning allows the construction of normal tissue dose-volume histograms and the generation of treatment plans that optimize radiation dose delivery to tumor while sparing critical normal tissues. Multiple field, fractionated, external beam techniques use high-energy photons to deliver 45 to 50 Gy in 1.8 Gy fractions to tumor bed, unresected or residual tumor, and lymph node–bearing areas at risk. After the primary fields, a boost field can be designed to include unresected or gross residual disease, as defined by CT scans and clips, while excluding most of the stomach and small bowel. Additionally, boost can also be accomplished with a simultaneous integrated technique utilizing higher doses-per-fraction, concurrent with delivery of the larger field, using more advanced planning techniques.

With lesions in the head of the pancreas, major node groups include the pancreaticoduodenal and peripancreatic (resected at the time of Whipple) and porta hepatis and para-aortic regions. If utilizing 3D techniques, approximately two-thirds of the left kidney must be excluded from the anteroposterior/posteroanterior (AP/PA) field because the right kidney is often in the field because of duodenal (bed) inclusion. The superior field extent is often at the middle or upper portion of the T11 vertebral body for adequate margins on the celiac vessels (T12, L1) and the inferior limit at the level L2 to L3 to include the superior mesenteric lymph nodes and third portion of the duodenum. The upper field extent is sometimes more superior with body lesions to obtain adequate margin on the primary lesion. With lateral fields, the anterior field margin is 1.5 to 2.0 cm beyond the initial gross disease. The posterior margin is often 1.5 cm behind the anterior portion of the vertebral body to allow adequate margins on para-aortic nodes, which are at risk of posterior tumor extension in the head or body lesions. The lateral contribution usually is limited to 15 to 18 Gy because a moderate volume of kidney or liver may be in the irradiated volume (Figure 65.2). Similarly, more advanced radiation planning techniques (including

IMRT) can be utilized to accomplish this and further spare adjacent normal organs.

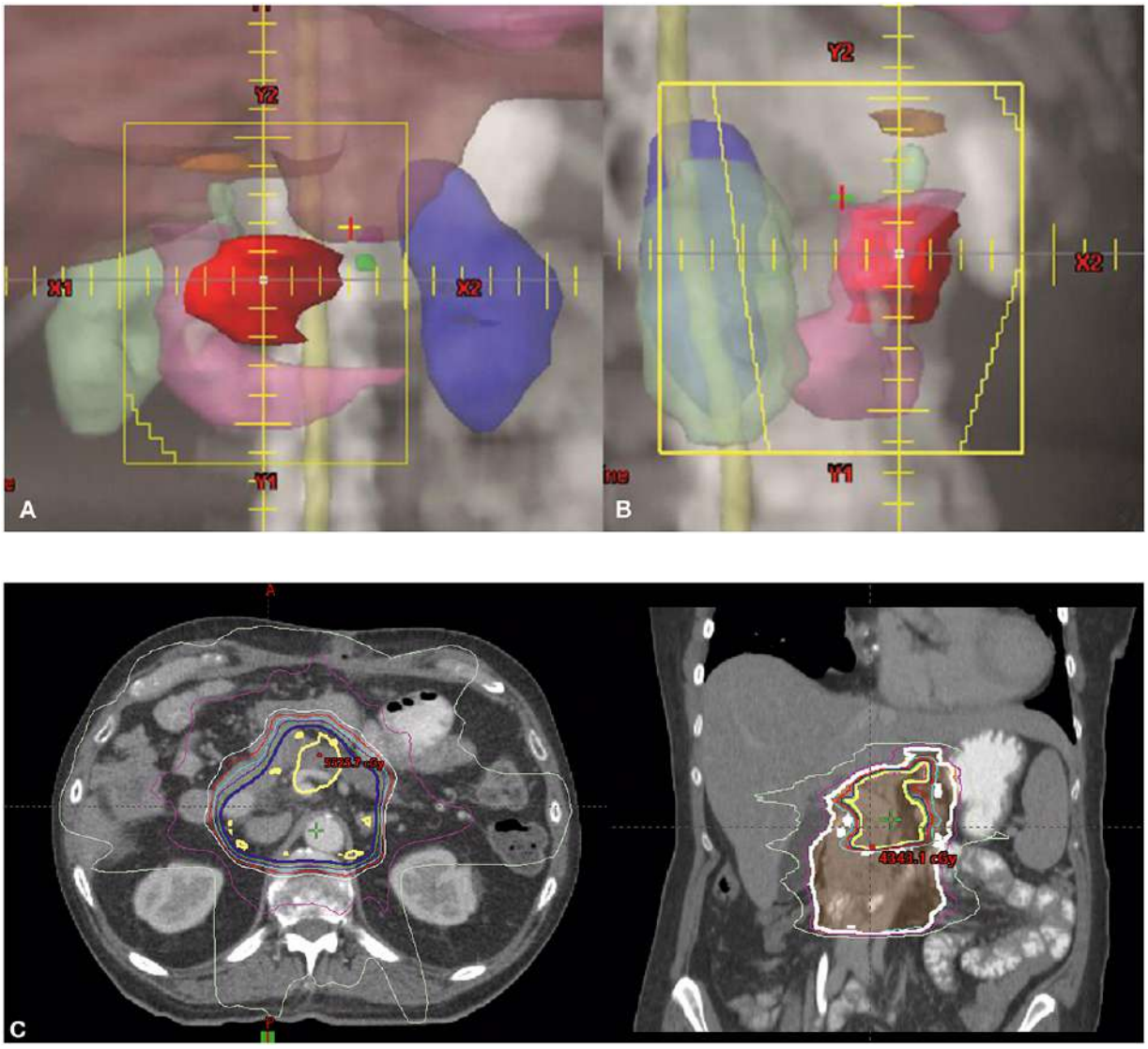


FIGURE 65.2 External beam four-field technique for pancreatic head lesion. A. The anteroposterior/posteroanterior (AP/PA) field, which includes gross tumor (red), duodenal loop (pink) (plus ~50% of the right kidney [light green]), liver (brown), and nodal areas at risk (porta hepatis: orange, superior mesenteric arteries: green, celiac: magenta). Most of the left kidney (blue) is excluded from the AP/PA field. B. The right lateral field with an anterior margin beyond gross disease and a posterior margin behind front edge of vertebral body. The liver contour (brown) has been removed from lateral field for visualization of other structures. C. IMRT-based plan for patient following R1 resection at the pancreatic neck. Note relative isodose levels, utilizing a simultaneous integrated boost technique delivered in 28 fractions.

With pancreatic body or tail lesions, at least 50% of the left kidney may be included to achieve adequate margins on node groups at risk (ie, lateral suprapancreatic, splenic artery, and splenic hilum nodes). Inclusion of the pancreaticoduodenal nodes is often not indicated with body or tail lesions, and at least two-thirds of the right kidney can be preserved (Figure 65.3).

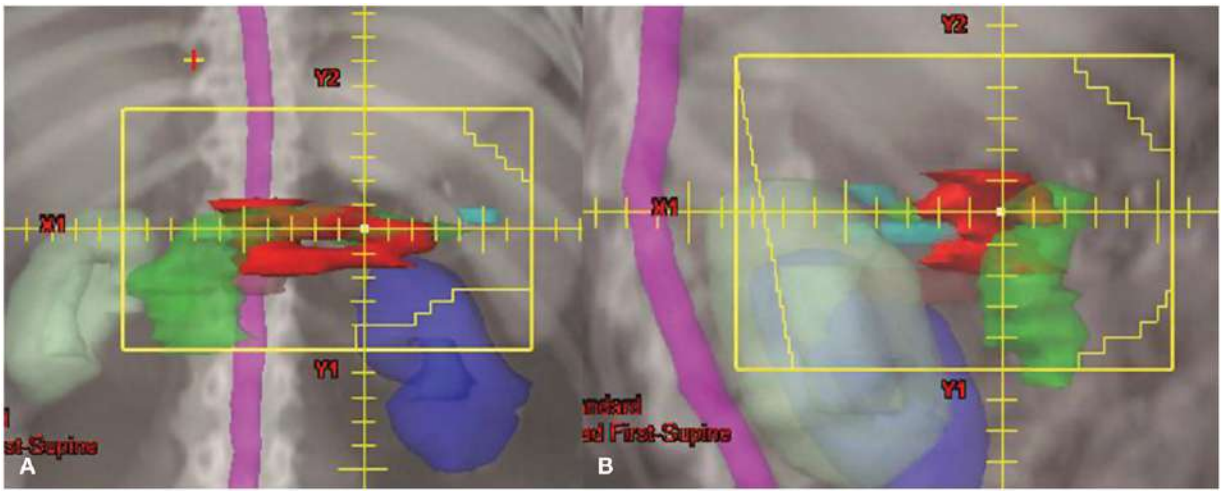


FIGURE 65.3 External beam four-field technique for unresectable tail of pancreas lesion. A. The anteroposterior/posteroanterior (AP/PA) field showing lesion (red) and head of pancreas (green). The field is extended to the patient's left to include coverage of the splenic hilum (cyan). Much of the right kidney (light green) is excluded from the field and multileaf collimators block most of the left kidney (blue). B. The right lateral field with an anterior margin beyond gross disease and a posterior margin at least 1.5 cm behind front edge of vertebral body.

After resection, AP/PA and lateral fields are often designed on the basis of preoperative CT primary tumor volumes, preoperative duodenal loop location, operative clip placement, and postoperative CT nodal volumes (Radiation Therapy Oncology Group [RTOG] contouring atlas accessible on their website). The anterior border is determined by vascular or nodal boundaries (porta hepatis, superior mesenteric, and celiac), as demonstrated on CT, as well as preoperative tumor location.[78] Again, more advanced target planning using IMRT can be utilized to further enhance normal tissue sparing.

RADIATION THERAPY RESULTS

Resectable Tumors: Adjuvant Therapy

After surgical resection of pancreatic cancer, local recurrence rates range from 50% to 86% and distant recurrence rates from 40% to 90%, most commonly to the liver or peritoneum.[50,67-69,71,72,79] This provides the rationale for adjuvant therapy, which has been employed in an effort to improve patient outcomes (Table 65.4). Despite multiple randomized trials, a definitive role for adjuvant radiotherapy for resected pancreatic cancer has not been established.

TABLE 65.4 PROSPECTIVE, RANDOMIZED TRIALS FOR ADJUVANT THERAPY FOR PANCREATIC CANCER

Series (Reference)	Number of Patients	Median Survival (Month)	2-Y Survival (%)	5-Y Survival (%)
GITSG[80]				
Chemoradiation	21	20.0	42	15
Observation	22	10.9	15	5
Chemoradiation (expanded cohort)[81]	30	18.0	46	17
EORTC[82,83]				
Chemoradiation	110	21.6	51	25
Observation	108	19.2	41	22
ESPAC-1 pooled data[84]				
Chemotherapy	238	19.7	NA	NA
No chemotherapy	235	14.0	NA	NA
Chemoradiation	175	15.5	NA	NA
No chemoradiation	178	16.1	NA	NA
ESPAC-1 2X2 analysis[85]				
Chemotherapy	147	20.1	40	21
No chemotherapy	142	15.5	30	8
Chemoradiation	145	15.9	29	10
No chemoradiation	144	17.9	41	20
CONKO[86,87]				

Series (Reference)	Number of Patients	Median Survival (Month)	2-Y Survival (%)	5-Y Survival (%)
Gemcitabine	186	23	30.5	21
Observation	182	20	14.5	9
ESPAC-3[88]				
5-FU	551	23	48	NA
Gemcitabine	537	23.6	49	NA
ESPAC-4[89]				
Gemcitabine	366	25.5	52.1	16.3
Gemcitabine and capecitabine	364	28	53.8	28.8
RTOG-9704 (pancreatic head)[77,90,91]				
Gemcitabine, then chemoradiation	187	20.5	31 (3 y)	22
5-FU, then chemoradiation[91]	201	17.2	22 (3 y)	18
PRODIGE 24/CCTG[93,94]				
m-FOLFIRINOX Gemcitabine	247 246	53.5 35.5	NA NA	43.2 31.4
APACT				
Gemcitabine/nab-paclitaxel[95,96] Gemcitabine	287 310	40.5 36.2	NA NA	38 31

5-FU, 5-fluorouracil; CONKO, Charite Onkologie; EORTC, European Organisation for Research and Treatment of Cancer; ESPAC, European Study Group for Pancreatic Cancer; GITSG, Gastrointestinal Tumor Study Group; NA, not available; RTOG, Radiation Therapy Oncology Group.

Historical Prospective Studies

The Gastrointestinal Tumor Study Group (GITSG) conducted the first multicenter prospective trial of adjuvant CRT for patients with resected pancreatic cancer and negative surgical margins, laying the foundation for the adoption of CRT in the United States. Forty-three patients were

randomized to observation or CRT to 40 Gy delivered in split-course manner with concurrent 5-fluorouracil (5-FU) (500 mg/m^2) as an intravenous bolus on the first 3 and last 3 days of radiation, followed by maintenance weekly 5-FU for 2 years or until disease progression. At interim analysis, improvements in median DFS (mDFS) and OS with CRT were observed: 11 versus 9 months and 20 versus 11 months. Two-year OS was 42% in the CRT group versus 15% in the surgery-alone arm.[80] An additional 30 patients were later enrolled to receive adjuvant CRT. These additional patients confirmed the survival outcomes seen in the original trial, with median survival of 18 months and a 2-year survival of 46%.[81]

The GITSG trial has been criticized for a number of reasons. The trial closed prematurely following enrollment of 43 of an intended 100 patients because of slow accrual over the 8-year enrollment period. The external beam radiation therapy (EBRT) approach in this trial was considered low dose and antiquated by contemporary standards because of a split-course technique and use of large treatment fields, which encompassed the entire pancreas or pancreatic bed and the celiac, pancreaticosplenic, peripancreatic, and retroperitoneal regional lymph nodes. In addition, the inclusion of both CRT and adjuvant chemotherapy after surgery evaluated two treatment variables, making it difficult to discern the true effect of either treatment alone. In the CRT arm, there were issues of compliance, with 32% of patients assigned to CRT receiving inappropriate radiation and 25% of patients failing to initiate treatment within 10 weeks postsurgery, the protocol-specified time limit. Only 9% of patients completed the planned 2-year maintenance chemotherapy course. In addition, survival in the control arm was low compared with historical studies. Despite these limitations and the failure to reach the desired patient accrual, the GITSG trial demonstrated a benefit for CRT, which became standard adjuvant therapy, particularly in the United States.

A second study sponsored by the European Organization for Research and Treatment of Cancer (EORTC) sought to confirm the findings of the original GITSG study. Two hundred eighteen patients with resected pancreas (n = 114) or periampullary cancers (n = 104) were randomly assigned to observation or CRT to 40 Gy in a split-dose manner with concurrent continuous infusional 5-FU (25 mg/kg) without further adjuvant chemotherapy. This study showed no significant improvement (P = .208) in

median survival (19 months [observation] vs 24.5 months [CRT]) or 2-year survival (41% [observation] vs 51% [CRT]).[82] Long-term follow-up of the EORTC trial demonstrated no difference in 5-year OS with CRT use: 22% (surgery alone) versus 25% (CRT). Post hoc analysis of pancreatic head lesions failed to demonstrate a benefit with CRT, with a median OS (mOS) of 1.3 years for CRT versus 1 year for surgery alone.[83]

This trial has been criticized for its heterogeneous patient population, which included patients with both pancreatic and periampullary primary tumors. Periampullary carcinomas have a significantly better prognosis compared with pancreatic cancer; the two entities thus represent truly different diseases and potentially dilute any evidence of benefit for adjuvant CRT.[97] Similar to the GITSG trial, older EBRT techniques—split course and low total dose—were used. Also, more than 20% of patients in the CRT arm did not receive the intended treatment because of postoperative complications or patient refusal. The trial did not include maintenance chemotherapy in the treatment arm. Finally, although a small subset, patients undergoing noncurative resection and patients with positive surgical margins were still eligible for enrollment. The discordant results of the EORTC and GITSG trials have led some investigators to attribute the OS benefit seen in the GITSG trial to maintenance chemotherapy administration rather than to EBRT.

An additional European trial conducted by the European Study Group for Pancreatic Cancer (ESPAC) aimed to further explore the question of appropriate adjuvant therapy for "macroscopically" resected pancreatic cancers. Treating physicians were allowed to enroll patients into one of three parallel randomized studies:

1. Chemoradiation versus no chemoradiation (n = 68), consisting of 20 Gy over 2 weeks with 5-FU (500 mg/m^2) on days 1 through 3, then repeated after a 2-week break;
2. Chemotherapy versus no chemotherapy (n = 188), consisting of bolus 5-FU (425 mg/m^2) and leucovorin (LV) (20 mg/m^2) given for 5 days every 28 days for six cycles; or
3. A 2-by-2 factorial design of 285 patients enrolled on chemoradiotherapy (n = 70), chemotherapy (n = 74), chemoradiotherapy with maintenance chemotherapy (n = 72), or observation (n = 69).

The data from the treatment groups from all three parallel trials were then pooled for analysis. There was no survival difference between the 175 patients who received adjuvant chemoradiation and the 178 patients who did not receive therapy (median survival, 15.5 vs 16.1 months; $P = .24$). In the chemotherapy arm, however, a 35% reduction in death was seen in the group who received adjuvant chemotherapy ($n = 238$) compared with those who received no chemotherapy ($n = 235$), with a difference in median survival of 19.7 versus 14 months ($P = .0005$).[84] On further follow-up of patients randomized using the 2-by-2 factorial design, the 5-year survival rate for the patients who received chemotherapy was 21% versus 8% for those who did not. In addition, adjuvant CRT was associated with a deleterious effect on survival.[85]

A number of problems are associated with the interpretation of these data. First, the complex trial design has the potential for bias, because patients or physicians could select randomization for one treatment variable. Also, as in the aforementioned trials, the EBRT technique used was, by contemporary standards, considered outdated, using split course and low total dose. No details of EBRT delivery or central quality assurance for EBRT, surgery, or pathology are available. In addition, many treatment violations occurred, as only 62% of patients received full CRT treatment and only 42% of patients in the chemotherapy arms completed the predefined regimen. Although many have attempted to draw conclusions from the updated publication, the 2-by-2 factorial cohort of the study was not powered to detect OS differences. In addition, patients receiving CRT in the ESPAC trial experienced poorer survival outcomes compared with those in other reported CRT series. Also, patients who had received prior "background" chemotherapy or radiation therapy were still eligible for enrollment. As in the EORTC trial, no maintenance chemotherapy was administered. Despite these critiques, some have speculated that the detriment seen in the CRT group may have resulted from delayed administration of systemic therapy shown to improve survival in the ESPAC trial.

A common critique of the aforementioned trials of adjuvant therapy is the lack of restaging to evaluate for the presence of persistent or metastatic disease after surgical resection and prior to the initiation of adjuvant therapy. The time between initial staging and the commencement of

adjuvant treatment can be as long as 3 to 4 months, during which a significant number of patients would be expected to develop radiographically apparent metastases. Without interval restaging, these patients may inappropriately receive CRT. Although these three trials formed the foundation for adjuvant treatment approaches to resectable pancreatic cancer, perhaps because each trial was fraught with flaws, there continues to be little consensus regarding the "most appropriate" treatment. A relative dichotomy in adjuvant treatment approaches for resectable pancreatic cancer has emerged between the United States and parts of Europe, with adjuvant CRT frequently implemented in the United States and adjuvant chemotherapy alone administered in parts of Europe.

Modern Studies

Adjuvant Systemic Therapy

Building from the data showing potential benefit to adjuvant chemotherapy, investigators in Europe conducted a randomized phase III trial of observation versus adjuvant gemcitabine in patients with resected pancreatic cancer. Three hundred sixty-eight patients were enrolled in the Charite Onkologie (CONKO) trial and randomized to observation or adjuvant gemcitabine (1,000 mg/m^2 intravenous days 1, 8, and 15 every 4 weeks for 6 months).[86] The primary end point was DFS, and patients treated with gemcitabine achieved a statistically significantly longer DFS (14.2 vs 7.5 months) than those observed after surgery. This improvement was seen in both the R0 and R1 subgroups. At initial publication, there was no difference in OS. With longer follow-up, median and 5-year OS were both improved in patients receiving gemcitabine (23 vs 20 months, and 21% vs 9%).[87] These findings were supported by a smaller randomized study from Japan, which again demonstrated a DFS benefit for gemcitabine compared with surgery alone.[98]

At the same time, the CONKO trial was enrolling patients, ESPAC-3, the largest randomized controlled trial (RCT) in pancreatic cancer to date, enrolled 1,088 patients with pancreatic adenocarcinoma who underwent R0 or R1 resection. Patients were randomly assigned to six cycles of adjuvant gemcitabine (3 weekly infusions of 1,000 mg/m^2) or six cycles of bolus 5-FU (425 mg/m^2)/LV (20 mg/m^2). Patients receiving 5-FU/LV experienced

significantly higher rates of grade 3 or 4 gastrointestinal toxicity (stomatitis and diarrhea), whereas patients receiving gemcitabine experienced significantly higher rates of grade 3 or 4 hematologic toxicity. At a median follow-up of 34.2 months, there was no difference between the two groups in the primary end point of OS.[88]

The ESPAC-4 trial randomized patients with resected pancreatic cancer to gemcitabine alone versus gemcitabine/capecitabine. Seven hundred and thirty patients with R0/R1 resection were evaluable for the primary end point of OS. The median survival for patients receiving adjuvant gemcitabine and capecitabine was 28 months compared with 25.5 months in the gemcitabine-alone arm. Estimated OS was 80.5% (95% confidence interval [CI] 76.0-84.3) at 12 months and 52.1% (46.7-57.2) at 24 months in the gemcitabine group and 84.1% (79.9-87.5) at 12 months and 53.8% (48.4-58.8) at 24 months in the gemcitabine plus capecitabine group. Although clinically significant toxicities were low in both arms, the rates of grade 3 to 4 diarrhea, infection, neutropenia, and hand-foot syndrome were statistically higher in the combined chemotherapy arm. These data suggest that adjuvant gemcitabine and capecitabine may be a reasonable alternative to single-agent gemcitabine. The focus of future European adjuvant therapies for resectable pancreatic cancer has centered on finding the ideal combination of systemic agents.[89]

Combination chemotherapy with fluorouracil, LV, irinotecan, and oxaliplatin (FOLFIRINOX) leads to longer OS than gemcitabine therapy for patients with metastatic pancreatic cancer.[92] Building on these data, the PRODIGE 24/Canadian Cancer Trials Group PA6 trial was designed to randomize 493 patients with resected pancreatic ductal adenocarcinoma to receive a modified FOLFIRINOX (m-FOLFIRINOX) regimen (oxaliplatin [85 mg/m^2 body surface area], irinotecan [180 mg/m^2, reduced to 150 mg/m^2 after a protocol-specified safety analysis], LV [400 mg/m^2], and fluorouracil [2,400 mg/m^2] every 2 weeks) or gemcitabine (1,000 mg/m^2 on days 1, 8, and 15 every 4 weeks) for 24 weeks.[93] The primary end point was DFS. At a median follow-up of 33.6 months, the mDFS was 21.6 months in the m-FOLFIRINOX group and 12.8 months in the gemcitabine group (stratified hazard ratio [HR] for cancer-related event, second cancer, or death, 0.58; 95% CI, 0.46-0.73; $P < .001$). The DFS rate at 3 years was 39.7% in the m-FOLFIRINOX group and 21.4% in the gemcitabine group.

The mOS was 54.4 months in the m-FOLFIRINOX group and 35.0 months in the gemcitabine group (stratified HR for death, 0.64; 95% CI, 0.48-0.86; $P = .003$). The OS rate at 3 years was 63.4% in the m-FOLFIRINOX group and 48.6% in the gemcitabine group. Adverse events of grade 3 or 4 occurred in 75.9% of the patients in the m-FOLFIRINOX group and 52.9% of those in the gemcitabine group. Adjuvant therapy with an m-FOLFIRINOX regimen led to significantly longer survival than gemcitabine among patients with resected pancreatic cancer, but at the expense of higher toxicity.

The long-term results of the PRODIGE 24/Canadian Cancer Trials Group PA6 confirmed the earlier results.[94] In patients receiving chemotherapy with m-FOLFIRINOX versus gemcitabine, mDFS was 21.4 months (95% CI, 17.5-26.7) vs 12.8 months (95% CI, 11.6-15.2) (HR, 0.66; 95% CI, 0.54-0.82; $P < .001$) and the 5-year DFS was 26.1% versus 19.0%. Similarly, comparison of 5-year OS was higher for patients receiving m-FOLFIRINOX (43.2%) versus gemcitabine (31.4%). As in the initial publication, the final 5-year results from the PRODIGE 24/Canadian Cancer Trials Group PA6 randomized clinical trial indicate that adjuvant treatment with m-FOLFIRINOX yields significantly longer survival than gemcitabine in patients with resected pancreatic ductal adenocarcinoma.

Other studies have explored alternative regimens to assess their efficacy and safety.[95] The APACT randomized, open-label trial compared the efficacy and safety of adjuvant *nab*-paclitaxel plus gemcitabine with those of gemcitabine for patients with resected pancreatic ductal adenocarcinoma.[96] Eight hundred and sixty-six treatment-naive patients with pancreatic ductal adenocarcinoma were randomized to *nab*-paclitaxel (125 mg/m^2) plus gemcitabine (1,000 mg/m^2) or gemcitabine alone to one 30 to 40 infusion on days 1, 8, and 15 of six 28-day cycles. The primary end point was independently assessed DFS. Additional end points included investigator- assessed DFS, OS, and safety. Two hundred eighty-seven of 432 patients and 310 of 434 patients completed *nab*-paclitaxel plus gemcitabine and gemcitabine treatment, respectively. At a median follow-up of 38.5 months, the median independently assessed DFS was 19.4 (*nab*-paclitaxel + gemcitabine) versus 18.8 months (gemcitabine; HR, 0.88; 95% CI, 0.729-1.063; $P = .18$). With a median follow-up of 63.2 months, the mOS was 41.8 versus 37.7 months (HR, 0.80; 95% CI, 0.678-0.947; $P =$

.0091). Eighty-six percent (*nab*-paclitaxel + gemcitabine) and 68% (gemcitabine) of patients experienced grade 3 or higher treatment-emergent adverse events. The primary end point (independently assessed DFS) was not met despite favorable OS seen with *nab*-paclitaxel plus gemcitabine.

Adjuvant Chemoradiation

In the United States, the GITSG trial laid the foundation for CRT as the predominant adjuvant treatment modality. The RTOG/Gastrointestinal Intergroup trial 9704 was a phase III randomized study comparing adjuvant 5-FU–based chemotherapy to gemcitabine-based chemotherapy, with both regimens followed by CRT. Four hundred fifty-one patients with resected pancreatic cancer were randomized to continuous infusion 5-FU (250 mg/m^2/day) or gemcitabine (1,000 mg/m^2 weekly) for 3 weeks prior to CRT and 12 weeks after CRT. CRT in both groups consisted of 50.4 Gy delivered with continuous infusion 5-FU (250 mg/m^2/day).[77] Prospective quality assurance of all radiation therapy plans was required. This trial was powered to demonstrate a survival benefit for the entire cohort and for the subgroup of patients with pancreatic head lesions. On initial analysis of the pancreatic head subgroup (n = 388), a nonsignificant trend toward improved median and 3-year OS was seen in the gemcitabine arm: 20.5 versus 16.9 months and 31% versus 22%. However, a higher incidence of grade 3 or higher hematologic toxicity was also seen in the gemcitabine group, with no significant differences seen in severe nonhematologic toxicities.

An update of this trial reported median and 5-year OS rates in patients with pancreatic head tumors of 20.5 months and 22% in those who received gemcitabine, compared with 17.2 months and 18% in those who received 5-FU. On multivariate analysis, in the subgroup of patients with pancreatic head lesions who received gemcitabine, there was a nonsignificant trend toward improved OS (P = .08).[90,91]

A secondary aim of RTOG-9704 was to assess the ability of postresection CA19-9 levels to predict survival. When CA19-9 levels were analyzed in a cohort of 385 patients as a dichotomized variable (<180 IU/mL vs ≥180 IU/mL, ≤90 IU/mL vs >90 IU/mL), there was a significant survival difference favoring patients with CA19-9 levels of less than 180 IU/mL. This corresponded to a 72% reduction in the risk of death.[52] Unlike

preceding randomized CRT studies, a major strength of the RTOG study was the rigorous, centralized quality control of radiation therapy techniques and delivery. A follow-up analysis demonstrated that patients treated per study guidelines had a significant survival advantage, indicating the importance of centralized review and treatment technique in this disease.[74]

The high rates of local failure and need for more efficacious systemic therapy, as well as the controversy surrounding the role of CRT in resected patients, led to the design of the current RTOG-0848/EORTC trial. Preliminary results of this trial describe 354 patients randomized, with 174 in the chemotherapy-alone arm and 180 in the chemotherapy plus combined modality therapy arm. The combined modality therapy group did not show improvement in overall survival, but did show improvement in disease-free survival. Both overall and disease-free survival were improved with combined modality therapy in patients with node-negative disease, and this treatment did not increase grade IV/V events compared to chemotherapy.[99] This trial randomly assigns patients with resected pancreatic head adenocarcinoma (stratified based on CA19-9 level, nodal involvement, and margin status) to receive treatment with gemcitabine alone for five cycles. Note initially patients were also randomized to receive erlotinib, which was ultimately discontinued due to results of the LAP07 trial discussed further, and the trial was also amended to allow oxaliplatin-based combination chemotherapy regimens. If no progression is seen on restaging following the completion of systemic therapy, patients are further randomized either to receive an additional cycle of chemotherapy (for a total of six cycles) or to receive CRT (50.4 Gy with concurrent capecitabine or 5-FU) using modern techniques and central radiation therapy quality assurance. This trial seeks to evaluate the role of CRT in the era of modern chemotherapy, particularly in patients who do not experience early disease progression (https://clinicaltrials.gov/ct2/show/NCT01013649).

Neoadjuvant Therapy

Even after undergoing curative resection for pancreatic cancer, 80% to 85% of patients will recur. In addition, positive margins or nodal disease increases this rate of recurrence to approximately 90%.[67,100] The use of

neoadjuvant therapy offers an alternative approach to improve these figures for several reasons:

1. Approximately one-third of patients experience a significant delay or do not receive adjuvant therapy following upfront resection.[49,101,102]
2. Twenty percent to 40% of patients will be spared the morbidity of resection as their metastatic disease becomes clinically apparent during the course of neoadjuvant therapy.[103-105]
3. Preoperative therapy could theoretically be less toxic and more effective as the chemotherapy and radiation would be given without the postsurgical issues of small bowel in the radiation field, decreased oxygenation, and decreased drug delivery to the remaining tumor bed.[106,107]
4. Patients with local, borderline, and unresectable lesions may be able to be downstaged to allow for surgical resection and sterilization of the operative region, which potentially facilitates R0 resection and reduces the risk of spread during surgical manipulation.

Neoadjuvant Chemoradiation

The role of neoadjuvant CRT in resectable pancreatic lesions was first explored in phase II and retrospective studies.[108] At the MD Anderson Cancer Center, multiple trials of neoadjuvant CRT with a variety of radiosensitizers have been performed.[109-113]

A review of the Surveillance, Epidemiology, and End Results (SEER) database supports the use of neoadjuvant treatment. This analysis included 3,885 patients treated for resectable pancreatic cancer: 70 (2%) patients received neoadjuvant EBRT, 1,478 (38%) received adjuvant EBRT, and 2,337 (60%) were treated with surgery alone. Given that the SEER database does not provide information on administration of chemotherapy, this variable could not be assessed. mOS was 23 months in patients receiving neoadjuvant EBRT, 17 months with adjuvant EBRT, and 12 months in the surgery-alone cohort.[114]

More recently, randomized trials comparing neoadjuvant therapy followed by surgery to initial surgery with and without adjuvant therapy have been conducted. With respect to neoadjuvant chemoradiation, the first

RCT phase II study comparing immediate surgery (arm A) with surgery after neoadjuvant chemoradiotherapy (arm B) for (potentially) resectable tumors was reported.[115] Of note, the experimental arm started with chemoradiotherapy without induction chemotherapy. Simultaneous chemotherapy was gemcitabine 300 mg/m^2 and cisplatin (CDDP) 30 mg/m^2 weekly in weeks 1, 2, 4, and 5 of radiotherapy. Conventionally fractionated, 3DCRT included a tightly restricted elective nodal volume to a dose of 50.4 and 55.8 Gy to the tumor. The trial under-recruited (73/254 planned patients) with considerable impact on statistical power. However, an important finding is that neoadjuvant therapy was well tolerated with only 7% grade 4 leukopenia and 3% grade 4 thrombocytopenia. No grade 4 gastrointestinal toxicity was observed, but grade 3 nausea and vomiting was seen in 35%, which was attributed to CDDP. Resections were R0 in 67% versus 90% in arm A versus arm B. Postoperative complications were not more frequent after chemoradiotherapy compared with immediate surgery. At intention-to-treat (ITT) analysis, OS was not different; at per-protocol analysis, mOS was 18 versus 25 months in arm A versus arm B ($P > .05$). After chemoradiotherapy, a trend for fewer local recurrences as the first site of progression was observed. Four versus eight patients (arm A vs arm B) had distant metastasis between randomization and laparotomy.[116]

The phase III PREOPANC trial randomized patients with potentially resectable or borderline resectable pancreatic cancer to neoadjuvant gemcitabine and gemcitabine-based chemoradiation followed by surgery and 4 months of adjuvant gemcitabine or to upfront surgery and adjuvant chemotherapy.[117] Two hundred and forty-six eligible patients were randomly assigned; 119 were assigned to preoperative chemoradiotherapy and 127 to immediate surgery. mOS by ITT was 16.0 months with preoperative chemoradiotherapy and 14.3 months with immediate surgery (HR, 0.78; 95% CI, 0.58-1.05; $P = .096$). The resection rate was 61% and 72% ($P = .058$). The R0 resection rate was 71% (51/72) in patients who received preoperative chemoradiotherapy and 40% (37/92) in patients assigned to immediate surgery ($P < .001$). Preoperative chemoradiotherapy was associated with significantly better DFS and locoregional failure–free interval as well as with significantly lower rates of pathologic lymph nodes, perineural invasion, and venous invasion. Survival analysis of patients who underwent tumor resection and started adjuvant chemotherapy showed

improved survival with preoperative chemoradiotherapy (35.2 vs 19.8 months; *P* = .029). Although the difference in median survival was only 1.4 months (15.7 vs 14.3 months), the 5-year OS rate was 20.5% (95% CI, 14.2-29.8) with neoadjuvant chemoradiotherapy and 6.5% (95% CI, 3.1-13.7) with upfront surgery. The proportion of patients who suffered serious adverse events was 52% versus 41% (*P* = .096). Preoperative chemoradiotherapy for resectable or borderline resectable pancreatic cancer did not show a significant OS benefit. The consistent benefits for most secondary end points and the better compliance with preoperative chemoradiotherapy compared with postoperative adjuvant chemotherapy suggest superiority of the neoadjuvant approach. Long-term results of this study, at a median follow-up of 59 months, demonstrated improved overall survival of neoadjuvant combined modality therapy versus upfront surgery groups with a median survival of 15.7 versus 14.3 months, and 5-year overall survival rates of 20.5% versus 6.5%, which was consistent across prespecified subgroups including patients with resectable and borderline resectable pancreatic cancer, with the authors concluding neoadjuvant combined modality therapy followed by surgery and adjuvant gemcitabine patients with improved overall survival compared to upfront surgery and adjuvant gemcitabine in resectable and borderline resectable pancreatic cancer.[118]

Additionally, preliminary results of the PREOPANC-2 study have been presented. In this study, 375 patients with borderline or resectable pancreatic cancer were randomized to receive neoadjuvant FOLFIRINOX for eight cycles followed by surgery versus three cycles of neoadjuvant gemcitabine with hypofractionated radiation therapy (36 Gy/15 fractions during the second cycle), followed by surgery and four cycles of adjuvant gemcitabine. At a median follow-up of 41.7 months, median overall survival was 21.9 months in the FOLFIRINOX arm and 21.3 months in the combined modality therapy arm, with resection rates of 77% and 75%, respectively, and with significant adverse effect rates of 49% and 43%, respectively. The authors concluded that neoadjuvant chemotherapy with FOLFIRINOX did not improve overall survival compared to neoadjuvant gemcitabine-based chemoradiotherapy in these patients.[119]

Additionally, preliminary results of the CONKO-007 trial reported on 525 patients randomized to receive induction chemotherapy with

gemcitabine or FOLFIRINOX, then randomized to either continue chemotherapy or receive combined chemoradiation to a dose of 50.4 Gy with concurrent gemcitabine. The majority of patients received induction FOLFIRINOX. Following subsequent exclusion of 190 patients due to progression or toxicity after initial chemotherapy, the remainder were randomized. R0 and complete pathologic response rates were significantly higher in the combined modality therapy arm, although preliminary progression-free and overall survival rates did not differ.[120]

Neoadjuvant Chemotherapy

With recent data demonstrating the efficacy of combination chemotherapy in the metastatic setting, there has been interest to assess these agents in patients with potentially resectable disease. Several randomized trials have addressed the benefit of neoadjuvant chemotherapy without CRT in potentially resectable pancreatic cancer:

A prospective, randomized phase II trial (NEONAX) was conducted with 127 patients with resectable pancreatic cancer.[121] Patients were randomized to either perioperative (two preoperative and four postoperative cycles; arm A) or adjuvant (six cycles; arm B) gemcitabine (1,000 mg/m^2) and nab-paclitaxel (125 mg/m^2) on days 1, 8, and 15 of a 28-day cycle. The primary end point was DFS at 18 months in the modified ITT population (R0/R1-resected patients who started neoadjuvant chemotherapy [A] or adjuvant chemotherapy [B]). The predefined DFS rate of 55% at 18 months was not reached in both arms (A: 33.3% [95% CI 18.5%-48.1%], B: 41.4% [95% CI 20.7%-62.0%]). Ninety percent of patients in arm A completed neoadjuvant treatment, and 42% of patients in arm B started adjuvant chemotherapy. R0 resection rate was 88% (arm A) and 67% (arm B). mOS (ITT population) as a secondary end point was 25.5 months (95% CI 19.7-29.7 months) in arm A and 16.7 months (95% CI 11.6-22.2 months) in the upfront surgery arm. This difference corresponds to an mDFS (ITT) of 11.5 months (95% CI 8.8-14.5 months) in arm A and 5.9 months (95% CI 3.6-11.5 months) in arm B. Treatment was safe and well tolerable in both arms. Patients who received perioperative therapy were also more likely to be exposed to chemotherapy; a majority of these patients completed neoadjuvant treatment (90%) and approximately 42% also completed postoperative therapy, whereas less than

half of the patients assigned to postoperative therapy alone started treatment (42%).

A randomized phase II trial assigned 93 patients (88 eligible for analysis) to receive surgery followed by 6 months of single-agent adjuvant gemcitabine (group A); surgery followed by 6 months of adjuvant cisplatin, epirubicin, gemcitabine, and capecitabine (PEGX; group B); or three cycles of PEGX before and after surgery (group C).[122] At a median follow-up of 55 months, the event-free (defined as freedom from progression, relapse, new tumor occurrence, distant metastasis, or death) survival in group A was 23% (95% CI 7%-39%); in group B, it was 50% (95% CI 32%-68%); and in group C, it was 66% (95% CI 49%-83%). The corresponding values for 3-year survival were 35%, 43%, and 55%. The R0 resection rates were 27% and 37% in both the adjuvant therapy groups, while it was 63% in group C. The trial was initially conceived as a combined phase II/III trial, but it was decided not to continue with the phase III component for two reasons: because the standard of care for adjuvant therapy had changed and because of the existence of newer chemotherapy regimens for which the evidence supporting benefit, at least in the setting of metastatic disease, was stronger than that for the PEGX regimen.

The multicenter Japanese Prep-02/JSAP-05 trial randomly assigned 364 patients with potentially resectable pancreatic cancer to two preoperative courses of gemcitabine plus S-1 versus upfront surgery; patients in both groups who were completely resected and fully recovered by 10 weeks postoperation also received 6 months of therapy with S-1 alone.[123] In a preliminary report, despite no improvement in overall and R0 resection rates, patients receiving neoadjuvant chemotherapy had significantly longer mOS (36.7 vs 26.6 months).

The Southwest Oncology Group (SWOG) phase II study compared neoadjuvant gemcitabine and nab-paclitaxel to modified 5-FU, LV, and irinotecan (m-FOLFIRNOX) for resectable pancreatic adenocarcinoma.[124] Two-year OS, the primary end point, was 47% with FOLFIRINOX and 48% with gemcitabine and nab-paclitaxel. Neither arm met the prespecified end point (58% of 2-year survival). Interpretation of these results is limited by the high rate of ineligibility after central radiologic review (44/147 enrolled patients). The ESPAC-5 trial randomized patients with borderline resectable pancreatic cancer to immediate surgery, neoadjuvant

gemcitabine/capecitabine for two cycles, neoadjuvant FOLFIRINOX for four cycles, or neoadjuvant capecitabine-based chemoradiation (50.4 Gy). Ninety patients were randomly assigned. Recruitment for this trial was described as challenging, although there was no significant difference in resection rates in patients who underwent immediate surgery versus those who underwent neoadjuvant therapy. However, there was a significant survival benefit (compared to immediate surgery) with neoadjuvant therapy, with the neoadjuvant chemotherapy-alone groups having the best survival compared to immediate surgery, supporting the use of short course neoadjuvant therapy in patients with borderline resectable pancreatic ductal adenocarcinoma.[125]

Therapy for Locally Advanced Carcinoma

Approximately 30% of patients present with locally advanced carcinoma of the pancreas, constituting a group of patients with an intermediate prognosis between resectable and metastatic disease. These patients have pancreatic tumors that are defined as surgically unresectable but have no evidence of distant metastases. A tumor is usually considered to be unresectable if it has one of the following features:

- Distant metastases
- Encasement or occlusion of the SMV or SMV/portal or vein confluence that is not amenable to reconstruction, contact with the most proximal draining jejunal branch into the SMV
- 180° or more involvement of the SMA, celiac axis, first jejunal SMA branch, or aorta or celiac axis involvement with a body or tail lesion

Recent advances in surgical technique allow for resection of selected patients with tumors involving the SMV.[41,115] Treatment with radiation and chemotherapy increases median survival for patients with locally advanced cancers to approximately 8 to 14 months but rarely results in long-term survival. The therapeutic options for patients with locally advanced pancreatic cancer include chemotherapy alone, CRT (with dose escalation), intraoperative radiotherapy (IORT), and stereotactic body radiation therapy (SBRT). In evaluating the results of these various therapies, it is useful to

remember that a median survival of 3 to 6 months has been reported for this subset of patients undergoing palliative gastric or biliary bypass only.[126]

PROSPECTIVE TRIALS

Prospective trials have evaluated the role of EBRT versus CRT, variations in CRT regimens, and CRT versus chemotherapy alone (Table 65.5). The Mayo Clinic undertook an early randomized trial in the 1960s in which 64 patients with locally unresectable, nonmetastatic stomach, large bowel, and pancreas adenocarcinoma received 35 to 40 Gy of EBRT alone or with concurrent bolus 5-FU (45 mg/kg). A significant survival advantage was seen for patients receiving EBRT with 5-FU versus EBRT only (10.4 vs 6.3 months).[127]

TABLE 65.5 PROSPECTIVE RANDOMIZED TRIALS FOR LOCALLY ADVANCED, UNRESECTABLE PANCREATIC CANCER

Series (Reference)	Number of Patients	Median Survival (Month)	Local Progression (%)	1-Y (%)	18-Mo (est %)
EBRT vs CRT					
Mayo Clinic[127]					
EBRT (35-40 Gy/3-4 wk) alone	32	6.3	NA	6	6
EBRT (35-40 Gy/3-4 wk) + 5-FU	32	10.4	NA	22	13
GITSG[128]					
EBRT (60 Gy/10 wk) alone	25	5.3	24	10	5
EBRT (40 Gy/6 wk) + 5-FU	83	9.7	26	35	20
EBRT (60 Gy/10 wk) + 5-FU	86	9.3	27	46	20
ECOG[129]					
EBRT (59.4 Gy) alone	49	7.1	NA	NA	NA
EBRT (59.5 Gy) + 5-FU/MMC	55	8.4	NA	NA	NA

Series (Reference)	Number of Patients	Median Survival (Month)	Local Progression (%)	1-Y (%)	18-Mo (est %)
Variations in CRT Regimen					
GITSG[130]					
EBRT (60 Gy/10 wk) + 5-FU	73	8.5	58 (first site)	33	15
EBRT (40 Gy/4 wk) + doxorubicin	70	7.6	51 (first site)	27	17
Taipei[131]					
EBRT (50.4-61.2 Gy) + 5-FU	16	6.7	56	31	0 (2 y)
EBRT (50.4-61.2 Gy) + gemcitabine	18	14.5	34	56	15 (2 y)
CRT vs Chemotherapy					
GITSG[132,133]					
EBRT (54 Gy/6 wk) + 5-FU and SMF	22	9.7	45 (first site)	41	18
SMF alone	21	7.4	48 (first site)	19	0
ECOG[134]					
EBRT (40 Gy/4 wk) + 5-FU	47	8.3	32	26	11
5-FU alone	44	8.2	32	32	21
FFCD/SFRO[135]					
EBRT (60 Gy) + 5-FU/CDDP	59	8.6	NA	32	NA
Gemcitabine alone	60	13	NA	53	NA
ECOG[136]					
EBRT (50.4 Gy) + gemcitabine	34	11.1	12 (first site)	50	29
Gemcitabine alone	37	9.2	30 (first site)	32	11
LAP07[137]					
Chemotherapy	136	16.5	46		

Series (Reference)	Number of Patients	Median Survival (Month)	Local Progression (%)	1-Y (%)	18-Mo (est %)
Chemotherapy, then EBRT+ capecitabine	133	15.2	32		

5-FU, 5-flurouracil; CDDP, neoadjuvant cisplatin; CRT, chemoradiation; EBRT, external beam radiation therapy; ECOG, Eastern Cooperative Oncology Group; FFCD/SFRO, Fédération Francophone de Cancérologie Digestive/Société Francophone de Radiothérapie Oncologique; GITSG, Gastrointestinal Tumor Study Group; LAP, locally advanced pancreas; MMC, mitomycin-C; NA, not available; SMF, streptozocin, mitomycin-C, and 5-flurouracil.

The GITSG followed with a similar study comparing EBRT alone to EBRT with concurrent and maintenance 5-FU. One hundred and ninety-four eligible patients with surgically confirmed unresectable and nonmetastatic pancreatic adenocarcinoma were randomized to receive 60-Gy split-course EBRT alone, 40-Gy split-course EBRT with two to three cycles of concurrent bolus 5-FU chemotherapy (500 mg/m^2), or 60-Gy split-course EBRT using a similar chemotherapy regimen. Patients in the latter groups received 2 years' maintenance 5-FU (500 mg/m^2) after EBRT completion. The EBRT-alone arm was closed early as a result of an inferior survival rate. The 1-year survival rate in the two combined modality therapy arms was roughly 40% (with no statistical difference between CRT arms) versus 11% in the EBRT-alone arm.[128]

The Eastern Oncology Group's trial ECOG-8282 randomized 114 patients to EBRT alone (59.4 Gy) with or without continuous infusion 5-FU (1,000 mg/m^2/day) on days 2 to 5 and 28 to 31 and mitomycin-C (10 mg/m^2) on day 2. There was no difference in response rates, DFS, or OS with the addition of concurrent chemotherapy. Higher rates of toxicity, primarily hematologic, were noted in the CRT group.[129]

Further studies sought to determine a more efficacious CRT regimen. A second GITSG trial randomized 157 and analyzed results for 143 eligible patients with unresectable disease to 60-Gy split-course EBRT with concurrent and maintenance 5-FU (500 mg/m^2) (as in the prior GITSG trial) or 40-Gy continuous course radiation with weekly, concurrent doxorubicin chemotherapy (10 mg/m^2), followed by maintenance doxorubicin and 5-FU. A significant increase in treatment-related toxicity was seen in the

doxorubicin arm, with no survival difference observed between the two groups (median survival 8.5 vs 7.6 months). No clinical benefit was seen in substituting doxorubicin for 5-FU.[130]

As studies emerged demonstrating significant survival advantages with gemcitabine-based chemotherapy in the metastatic setting, it was incorporated into the locally advanced setting. A trial from Taipei randomized 34 patients to EBRT with concurrent 5-FU (500 mg/m^2) or gemcitabine (600 mg/m^2). Patients received 50.4- to 61.2-Gy EBRT and maintenance gemcitabine (1,000 mg/m^2) at the completion of CRT. mOS and time to progression were prolonged in the gemcitabine arm: 14.5 and 7.1 months (gemcitabine) versus 6.7 and 2.7 months (5-FU). There were no observed differences in grade 3 or 4 toxicity or hospitalization days between the two arms. Study criticisms include the small number of patients and relatively poor outcomes in the 5-FU arm compared with historical controls.[131]

A number of trials have compared CRT with chemotherapy alone. A subsequent GITSG trial compared combination streptozocin, mitomycin-C, and 5-FU (SMF) chemotherapy to chemoradiation with 5-FU. Forty-three patients were randomized to receive SMF chemotherapy or 54 Gy of EBRT with two cycles of concurrent bolus 5-FU chemotherapy followed by adjuvant SMF chemotherapy. The chemoradiation arm demonstrated a significant survival advantage over the chemotherapy-alone arm (1-year survival 41% vs 19%).[132]

In contrast, the ECOG reported no benefit to chemoradiation versus chemotherapy only. In this study, 191 patients with unresectable, nonmetastatic pancreatic or gastric adenocarcinoma were randomized to receive either 5-FU chemotherapy (600 mg/m^2) alone or 40-Gy EBRT with concurrent bolus 5-FU during week 1 (600 mg/m^2) followed by maintenance chemotherapy. Patients with locally recurrent disease as well as patients undergoing surgery with residual disease were eligible for this trial. In the 91 patients with pancreatic cancer eligible for analysis, no survival difference was observed between the two groups (median survival 8.2 vs 8.3 months).[134]

The FFCD/SFRO trial randomized 119 patients to CRT consisting of 60 Gy EBRT with continuous infusion 5-FU (300 mg/m^2/day) on days 1 to 5 for 6 weeks and intermittent CDDP (20 mg/m^2/day) on days 1 to 5 in weeks

1 and 5 with maintenance gemcitabine (1,000 mg/m^2) versus gemcitabine alone (1,000 mg/m^2). Survival was inferior in the CRT arm at 8.6 months compared with 13 months with gemcitabine alone. Higher grade 3 or 4 toxicity rates were observed in the CRT arm during CRT (36% vs 22%) and maintenance chemotherapy phases (32% vs 18%). This trial closed early because of poor accrual. Many criticize the inferior survival in the CRT arm, which is similar to early GITSG trials, despite use of continuous infusion chemotherapy and modern EBRT techniques.[135]

The ECOG published results from a randomized trial of CRT (50.4 Gy with concurrent gemcitabine: 600 mg/m^2/week, weeks 1-5) versus gemcitabine alone (1,000 mg/m^2/week). The trial closed early because of poor accrual. Analysis of the eligible, randomized 71 patients demonstrated no difference in progression-free survival (PFS); however, a survival benefit was seen in the CRT arm: 11.1 versus 9.2 months. This benefit came at the expense of higher grade 4 or 5 toxicity rates in the CRT arm (mainly hematologic) but with no difference in QoL.[136]

A multicenter phase II study, the SCALOP trial, evaluated the role of gemcitabine-based or capecitabine-based CRT. All patients received 12 weeks of induction gemcitabine and capecitabine chemotherapy. Seventy-four patients were randomized, and mOS in the capecitabine group was 15.2 months compared with 13.4 months in the gemcitabine arm (P = .012). More patients in the gemcitabine group than in the capecitabine group had grade 3 to 4 hematologic toxicity and grade 3 to 4 nonhematologic toxicity during CRT. These data suggest that concurrent capecitabine-based CRT may be preferable to gemcitabine-based CRT.[138]

The Locally Advanced Pancreas Cancer 07 (LAP07) trial initially randomized all patients to gemcitabine or gemcitabine and erlotinib for 4 months. A second randomization was performed in patients with no evidence of progression to continuation of chemotherapy for an additional 2 months or chemoradiation. The primary study end point was OS. A total of 442 patients underwent the first randomization and 269 patients underwent the second randomization. Interim analysis was performed after 221 patients died and early stopping rules for futility were reached. The mOS was 16.5 months for patient receiving systemic therapy and 15.2 months in the cohort receiving chemoradiation. Chemoradiation was associated with decreased local progression from 46% to 32% (P = .03)[138] and median delay

to treatment reintroduction was 6.1 months (95% CI, 4.8-7.0 months) for the chemoradiotherapy group, significantly longer than the 3.7 months (95% CI, 3.0-4.6) for the chemotherapy group ($P = .02$). Some authors have critiqued the older chemotherapy regimen of gemcitabine alone, which has now largely been replaced with combination systemic therapies such as gemcitabine/nab-paclitaxel and m-FOLFIRINOX. In addition, QoL analyses were not performed, which could have demonstrated a clinically meaningful difference between the arms.

With the publication of LAP07, many consider upfront chemotherapy with subsequent response assessment and directed radiation therapy (CRT, SBRT) to facilitate selection of patients most likely to benefit from locoregional therapy as the current standard of care.

Borderline Resectable Disease

As surgery of the primary tumor remains the only potentially curative treatment for pancreatic cancer, neoadjuvant therapy has been evaluated to assess its ability to convert locally unresectable pancreatic cancer to resectable disease. Although the definition of borderline resectable disease is contentious, there are some consensus guidelines (see Table 65.2). Approximately 30% of patients with borderline resectable disease become resectable after neoadjuvant therapy.[139,140] Similarly, there appears to be higher rates of local control, R0 resection, and N0 disease in this patient subset after neoadjuvant therapy.[141-144]

A number of single-institution retrospective studies have evaluated this patient subset. An early study from the MD Anderson Cancer Center assessed 160 patients with borderline resectable disease. Patients received 50.4 Gy in 28 fractions or 30 Gy in 10 fractions with concurrent 5-FU, paclitaxel, gemcitabine, or capecitabine at radiosensitizing doses. Forty-one percent underwent pancreatectomy with margin-negative resection in 94%. Median survival in the 66 patients who completed preoperative therapy and surgery was 44 months, comparable to patients with initially resectable disease.[142]

A review from Fox Chase Cancer Center evaluated 109 patients who underwent resection of pancreatic adenocarcinoma with varying involvement of the portal vein or SMV as determined by CT. Patients

received 5-FU or gemcitabine-based CRT. Median survival in the 74 patients who received preoperative therapy was 23 months compared with 15 months in the cohort undergoing upfront surgery. Preoperative CRT was associated with a higher rate of R0 resection and N0 disease.[143]

A smaller series from the University of Virginia reviewed the outcomes of 40 patients with borderline resectable disease. Patients received 50.4 Gy in 28 fractions or 50 Gy in 20 fractions with concurrent capecitabine. Forty-six percent of patients underwent surgery, with 75% undergoing an R0 resection. Patients undergoing surgery after neoadjuvant treatment had similar median survival rates as patients undergoing upfront surgery.[144]

The ECOG initiated a randomized phase II study of two neoadjuvant gemcitabine-containing regimens in patients with potentially resectable cancer. Patients received 50.4-Gy EBRT with weekly gemcitabine (500 mg/m^2) or induction chemotherapy with gemcitabine (175 mg/m^2), CDDP (20 mg/m^2), and 5-FU (600 mg/m^2) prior to CRT with 5-FU (225 mg/m^2). All patients received adjuvant gemcitabine (1,000 mg/m^2). This trial, the only randomized trial of borderline resectable pancreatic cancer, closed early because of poor accrual with 21 patients.[145] Although the subject of ongoing study, an approach utilizing neoadjuvant chemoradiotherapy in patients with borderline resectable disease, in efforts to facilitate R0 resection, seems appropriate.

A systematic review and meta-analysis was performed of 18 studies with neoadjuvant chemotherapy or CRT with a total of 959 patients evaluating post-treatment response rates. The following response rates were achieved: complete response, partial response, stable disease, and progressive disease were observed in 2.8%, 28.7%, 45.9%, and 16.9%, respectively. The weighted frequency of resected patients was 65.3% who achieved an mOS of 25.9 months. In contrast, patients without resection had an mOS of 11.9 months and the total group of 17.9 months.[146]

DOSE ESCALATION

Given the limited tolerance of normal tissue in the upper abdomen (liver, kidney, spinal cord, and bowel) to EBRT, total doses of only 45 to 54 Gy in 25 to 30 Gy fractions have traditionally been administered. For an unresectable tumor, this dose of radiation is inadequate, as demonstrated by

the high rates of local tumor progression and poor survival seen in both prospective and retrospective studies. Local progression as the first site of failure occurred in 58% of patients treated to 60 Gy with concurrent 5-FU in the second GITSG trial.[130] Similarly, the Mayo Clinic reported a local recurrence rate of 72% for 122 patients with unresectable pancreatic cancer treated with an EBRT dose of 40 to 60 Gy.[147] Attempts have been made to evaluate whether increasing dose of radiation may improve outcomes through 3DCRT, IORT, IMRT, and SBRT.

In a report from Thomas Jefferson University Hospital, 46 evaluable patients with unresectable disease by laparotomy were treated with 63- to 70-Gy EBRT with or without chemotherapy. Despite high-dose EBRT, the local recurrence rate was 78%.[148]

IORT is an alternative method to deliver higher radiation doses. This technique allows for administration of a single high dose of radiotherapy with the advantage of enabling healthy tissues to be displaced and shielded from radiation. IORT has been utilized postoperatively and in the treatment of locally advanced disease. Institutional reports and a randomized trial have shown that surgery followed by IORT yields lower rates of locoregional recurrence; however, no significant difference in survival has been seen.[149-152] IORT has also been evaluated in patients with unresectable disease.[153,154] A study from investigators at Massachusetts General Hospital reported the results of 150 patients with unresectable pancreatic cancer treated with IORT, EBRT, and chemotherapy. Although the study spanned nearly 25 years, it demonstrated that long-term survival is possible for patients with unresectable pancreatic cancer. Furthermore, this study shows that postoperative and late treatment-related toxicity rates were acceptable.[154,155] A lower incidence of local recurrence in most series and improved median survival in some have been reported with these techniques when compared with conventional external beam irradiation, but it is uncertain whether this is due to treatment superiority or case selection.[147]

Advances in radiation technique and delivery, such as IMRT and SBRT, also enable dose escalation and potential sparing of normal tissues. IMRT is a technique that breaks up a typical radiation treatment field into smaller beamlets. It is implemented either as dynamic IMRT (collimating leaves move in and out of the radiation beam path during treatment) or as “step-

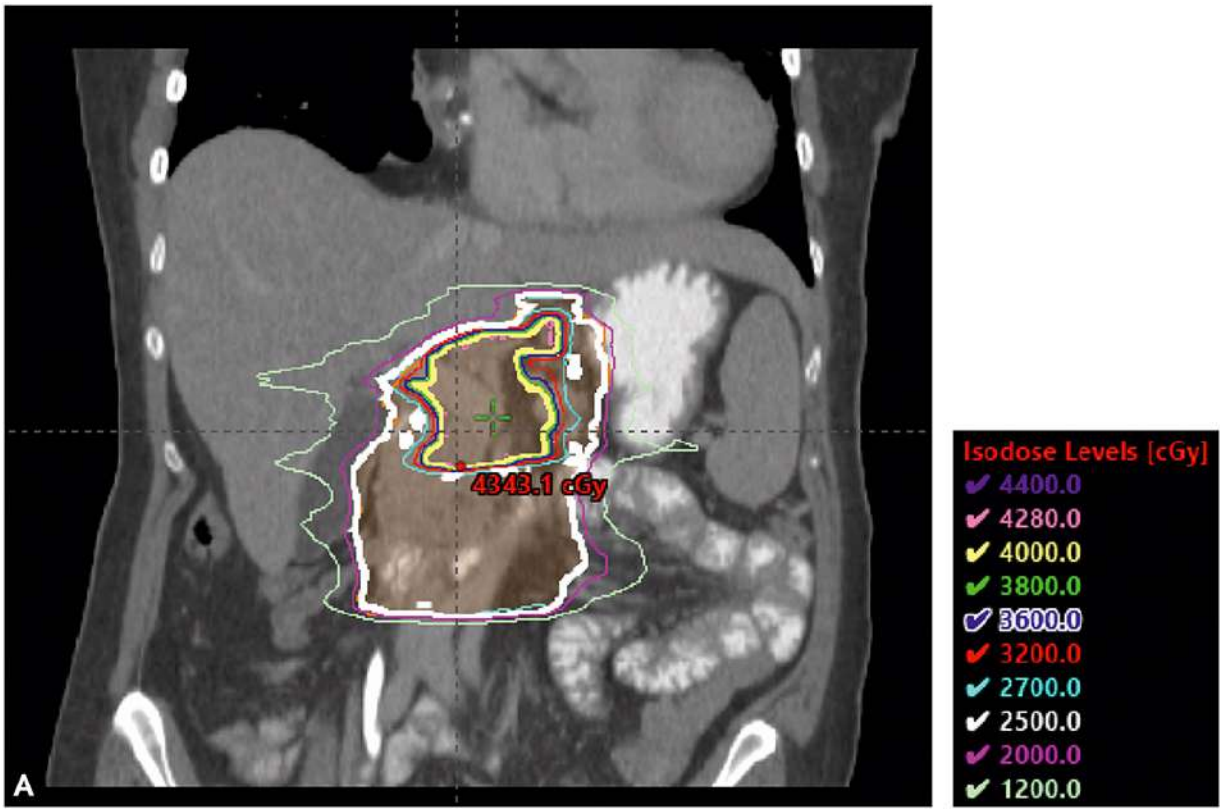
and-shoot" IMRT (leaves change field shape while the machine is off). The cumulative effect is that the prescription dose conforms around delineated target volumes, significantly reducing doses to adjacent normal tissues. This technology has increasingly been used in a number of gastrointestinal malignancies, including pancreatic cancer. Early clinical data support both the feasibility of this technique and its potential for reducing acute gastrointestinal toxicity.[156-158]

An analysis from the University of Maryland evaluated 46 patients treated with IMRT and concurrent 5-FU–based chemotherapy. Acute toxicities in these patients were compared with those in a control group enrolled in RTOG-9704 who received conventional 3D treatment. There was a statistically significant reduction in acute grade 3 or 4 gastrointestinal toxicity in the patients who received radiotherapy via IMRT compared with those who received 3DCRT.[158] IMRT can also result in a significant reduction of dose to normal structures, including the liver, kidneys, stomach, and small bowel.[157] This may allow alternate novel systemic agents to be administered with radiotherapy.[156]

Although IMRT can reduce the dose to surrounding normal tissues, it also allows the opportunity for dose escalation. A phase I/II study by Ben-Josef et al attempted to define the maximum tolerated radiation dose via IMRT in combination with gemcitabine for unresectable pancreas cancer. Fifty patients were accrued and dose-limiting toxicity was seen at 55 Gy. Median survival was 14.8 months, and 12 patients subsequently underwent resection.[159]

Another technique for dose escalation in the treatment of pancreatic cancers is SBRT, which involves the delivery of high dose per fraction radiation treatments over a small number of fractions (generally 1-5 treatments), utilizing techniques that allow very highly conformal dose delivery of EBRT. The postulated advantage of SBRT is potentially improving local control through the delivery of ablative doses of radiation while minimizing associated side effects (Figure 65.4). Early experience and data using this technique are in the setting of locally advanced disease.[160,161] Stanford University investigators initially implemented an institutional protocol for the treatment of locally advanced pancreatic cancer using a 25-Gy single fraction with systemic therapy. This single, high dose of radiation has been estimated to result in delivery of a higher

biologically equivalent dose compared with a more standard, protracted course of radiation therapy, albeit at the potential for increased risk of normal tissue injury. A report from these investigators described 77 patients who were treated with SBRT and found that freedom from local progression was 91% at 6 months and 84% at 12 months. No patients experienced grade 3 acute toxicity, and 9% had grade 3 or higher late toxicity.[161]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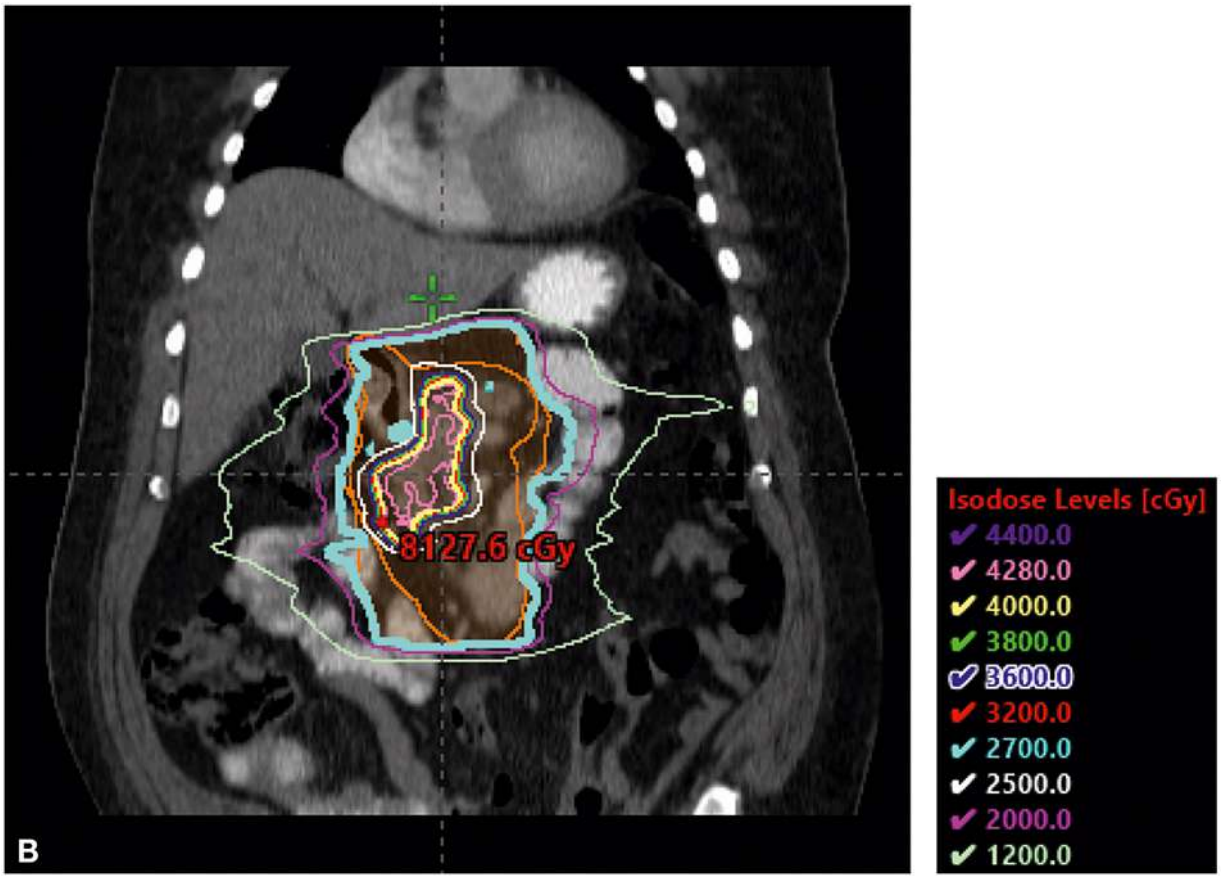

FIGURE 65.4 A. Example of SBRT in a 66-year-old female with locally advanced disease following induction chemotherapy. Note relative isodoses, utilizing a simultaneous integrated boost technique, with total prescription dose of 40 Gy in five fractions to the primary disease, delivering 25 Gy in five fractions to subclinical basins. B. Patient with medically inoperable pancreatic cancer undergoing dose escalating combined modality therapy, utilizing an SIB approach, delivering 45 Gy to subclinical volume and 75 Gy to gross disease, all in 25 fractions.

Based on these data, a prospective, multi-institutional phase II study was conducted utilizing five-fraction SBRT with primary end point to achieve a lower rate of late grade 2+ toxicity than with single-fraction SBRT. Forty-nine patients received up to three doses of gemcitabine followed by 33 Gy in five fractions. The rate of grade 2+ late toxicity was 11% and 1-year freedom from local progression was 78%. Four patients (8%) subsequently underwent a margin-negative resection.[162]

A meta-analysis of 19 studies encompassing over 1,000 patients treated with SBRT demonstrated a 1-year local control rate of 72%. The rate of acute grade 3+ toxicity ranged from 0% to 36%, and the rate of late grade

3+ toxicity did not exceed 11%.[163] Select series have demonstrated high rates of margin-negative resection in patients with borderline and unresectable pancreas cancer who ultimately underwent surgical resection.[164,165]

The ALLIANCE A021501 randomized 126 patients with borderline resectable pancreatic cancer to neoadjuvant m-FOLFIRINOX with or without hypofractionated radiation therapy with historical data and established standards for therapy.[166] Among the first 30 evaluable patients enrolled to each arm, 17 (57%) patients in arm 1 and 10 (33%) patients in arm 2 had undergone R0 resection, leading to closure of arm 2 but continuation to full enrollment in arm 1. The 18-month OS rate of evaluable patients was 66.7% (95% CI, 56.1%-79.4%) in arm 1 and 47.3% (95% CI 35.8%-62.5%) in arm 2. The mOS of evaluable patients in arm 1 and arm 2 was 29.8 (95% CI, 21.1-36.6) months and 17.1 (95% CI, 12.8-24.4) months, respectively. The authors concluded that m-FOLFIRINOX represents a reference regimen in this setting. This trial is problematic in that the study was not statistically powered to compare FOLFIRINOX with or without radiation therapy, imbalance in certain prognostic features between the two arms such as the median CA19-9 was higher in the SBRT arm versus the chemotherapy-only arm, and both arms had lower rates of pancreatectomy (35%-49%) compared with the results (84%-97%) of high-volume centers. A multicenter phase II trial evaluated SBRT in patients with borderline resectable and locally advanced cancers, utilizing an MRI-guided approach. One hundred thirty six patients were enrolled after receiving induction chemotherapy. 50 Gy was delivered in 5 fractions, with elective nodal coverage optional. At a median followup of 14 months from radiation, 2-year overall survival was 41%, with acceptable rates of toxicity. The authors concluded that trial results were encouraging with limited toxicity rates, and additional investigation warranted.[167]

Another series of 119 consecutive patients were treated with ablative radiation therapy using hypofractionated approach, using an ablative radiation dose (98 Gy biologic effective dose). Most patients were treated following induction chemotherapy for a median of 4 months. Median survival following radiation treatment was 18.4 months with 2-year survival at 38%, with 2-year local regional failure rate of 18%. The authors

concluded that this approach was associated with a durable local regional tumor control and favorable survival.[168]

Ultimately, the role of IMRT and SBRT as well as integration with systemic therapy are ongoing areas of active investigation in these patients.

CHEMORADIATION EFFECTS ON QUALITY OF LIFE

Pain, anorexia, fatigue, and cachexia are relatively common symptoms, which significantly impact a patient's QoL. When using EBRT with or without chemotherapy, approximately 35% to 65% of patients will experience pain resolution as well as some improvement in cachexia and obstructive symptoms.[130,169,170] Definite but less dramatic improvements in performance status and anorexia may be observed as well.[169,170] Patient-reported QoL with SBRT in unresectable pancreas cancer demonstrates no change in QoL at pretreatment compared with 1-month follow-up but statistical and clinical improvements in pancreatic pain and body image at 1 month.[171] Palliation from therapy can take many weeks for maximal effect, and alternative treatments, such as biliary and duodenal stents, may provide more rapid relief of obstructive symptoms. Given the high mortality rate associated with pancreatic cancer, QoL should be a study end point in trials for these patients.

TARGETED THERAPIES AND FUTURE DIRECTIONS

There is much room for improvement in the diagnosis and treatment of pancreatic cancer. Screening of high-risk individuals may allow for the detection of disease in earlier disease stages by means of novel imaging methods or assessment of serum biomarkers.[172,173] As the biologic basis of cancer is better understood, the successful use of cancer-specific targeted therapies in other cancers supports the need to identify new targets and better predictors of response to therapy in pancreatic cancer.

There is evidence of additive or synergistic effects for several targeted agents (such as antibodies against epithelial growth factor receptor [EGFR] and vascular endothelial growth factor [VEGF] receptor) with both chemotherapy and radiation therapy, making these topics of investigation. These targeted agents have been studied most extensively in the metastatic setting prior to evaluation in locally advanced and resectable disease.

Currently, the only targeted agent that has shown a modest statistically significant survival benefit in the metastatic setting compared with chemotherapy alone is erlotinib, an anti-EGFR tyrosine kinase inhibitor. However, the survival benefit with the addition of erlotinib is small, with median survival increased from 5.9 to 6.2 months and 1-year survival improvement from 17% to 24%.[174] The clinical significance of this difference has been questioned by investigators and treating physicians.

Another EGFR/*HER-1* inhibitor, cetuximab, initially showed promising phase II results in the metastatic setting. Efficacy was initially seen with the combination of cetuximab and EBRT in the treatment of locally advanced squamous cell carcinoma of the head and neck and subsequently tested in a phase III trial.[175] However, in pancreatic cancer, a phase III randomized study of gemcitabine plus cetuximab versus gemcitabine plus placebo (SWOG S0205) as first-line therapy in locally advanced, unresectable, or metastatic disease enrolled over 700 patients from the United States and Canada. No survival improvement was seen with the addition of cetuximab to gemcitabine (6.3 months gemcitabine plus cetuximab vs 5.9 months gemcitabine alone). Even among patients tested for EGFR expression (90% of specimens positive for expression), no benefit to cetuximab was seen in this patient subgroup.[176] An additional phase II study evaluated the efficacy and safety of multiagent chemotherapy in combination with cetuximab. Sixty-nine patients with locally advanced pancreatic cancer received cetuximab, gemcitabine, and oxaliplatin followed by cetuximab, capecitabine, and radiotherapy. Diagnostic cytology specimens were stained for Smad4 (Dpc4) expression. mOS was 19.2 months, and the pattern of failure for patients with Smad4 (Dpc4) expression was primarily local, rather than distant, disease failure.[177] The addition of EGFR inhibitors in localized disease is currently being evaluated in phase I and phase II trials.

VEGF inhibitors bind to receptors involved in tumor growth via vasculogenesis and angiogenesis pathways. Preclinical data have shown that inhibition of VEGF has radiosensitizing effects. Initially, promising results in the metastatic setting, however, have ultimately not shown a benefit from the addition of an anti-VEGF antibody to chemotherapy. A phase II trial of the combination of gemcitabine and bevacizumab in 52 treated patients with advanced pancreatic cancer showed a response rate of 21%, a median PFS of 5.4 months, and mOS of 8.8 months.[178] In response

to these positive results, a phase III randomized study of gemcitabine plus bevacizumab versus placebo (Cancer and Leukemia Group B CALGB-80303) was initiated. No significant difference was observed in OS or PFS.[179] Bevacizumab has also been evaluated in combination with radiotherapy. An initial phase I study of radiotherapy, capecitabine, and bevacizumab led to incorporation in the phase II setting in patients with locally advanced pancreatic cancer (RTOG-0411).[180] Eighty-two patients were treated with radiotherapy to the gross tumor, capecitabine (825 mg/m^2), and bevacizumab (5 mg/kg on days 1, 15, 29), followed by adjuvant gemcitabine (1,000 mg/m^2). The median and 1-year survival rates were 11.9 months and 47%, respectively. These results were similar to prior RTOG trials of locally advanced pancreatic cancer.[181] An additional phase II trial assessed the efficacy of full-dose gemcitabine (1,000 mg/m^2), bevacizumab (10 mg/kg), and radiotherapy to 36 Gy (in 2.4 Gy fractions) with maintenance gemcitabine and bevacizumab in patients with unresected tumors with no evidence of disease progression. Median PFS and OS were 9.9 and 11.8 months, respectively.[182] The incorporation of bevacizumab with radiotherapy has not led to profound improvements in treatment outcomes compared with 5-FU–based CRT.

Although improvements with targeted agents have been modest, other pathways are being evaluated. Pancreatic cells deficient in *BRCA* repair pathways are sensitive to poly-adenosine diphosphate-ribose polymerase (PARP) inhibitors. PARP inhibitors have been evaluated in ovarian and breast cancer, with response rates of 40%. Clinical trials of PARP inhibitors in the treatment of patients with pancreatic cancer are underway.[7,183] Other therapeutic agents under evaluation include hedgehog pathway inhibitors, multikinase inhibitors (sorafenib), and agents targeting v-src sarcoma, γ-secretase, stem cell factor receptor (c-kit), secreted protein acidic and rich in cysteine, mitogen-activated protein kinase, mesothelin, *RAS*, prostate stem cell antigen, tumor necrosis factor-α, mucin-1, mammalian target of rapamycin, tumor necrosis factor superfamily member 10, and type 1 insulin-like growth factor receptor.[7,184]

There is growing interest in immunotherapies to target the heterogeneous pancreas tumor and immunosuppressive microenvironment. A number of clinical trials in pancreas cancer alone or advanced solid tumors have been completed or ongoing evaluating the role of immune checkpoint

monotherapy, dual checkpoint blockade, immune checkpoint in combination with vaccine therapy, and in combination with cytotoxic and other systemic therapies.[185,186]

SUMMARY

Treatment of pancreatic cancer remains a challenge in oncology. Despite advances in many aspects of oncologic evaluation and management, including preoperative evaluation, surgical techniques, perioperative care, systemic therapy, and radiotherapy, the 5-year OS rate for patients with resectable pancreatic cancer remains around 20%. Local tumor control has been improved by the use of specialized radiation techniques, allowing safe dose escalation. Even with these techniques, it is not clear that a survival benefit is achieved given the proclivity of metastases in this malignancy. Similarly, even in patients with metastatic disease, morbidity and mortality associated with locoregional progression remain a major cause of morbidity and mortality. Further advances in systemic therapies, study of the optimal sequencing of therapies, earlier detection of disease, and development of new and novel therapeutic options are urgently needed in the treatment of this formidable disease. QoL should be considered a paramount end point in the care and protocol design of clinical trials for these patients. Significant improvements in long-term survival will likely be achieved through ongoing attempts at the exploitation of the malignancy's basic biologic anomalies.

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CHAPTER 66

Cancer of the Liver and Hepatobiliary Tract

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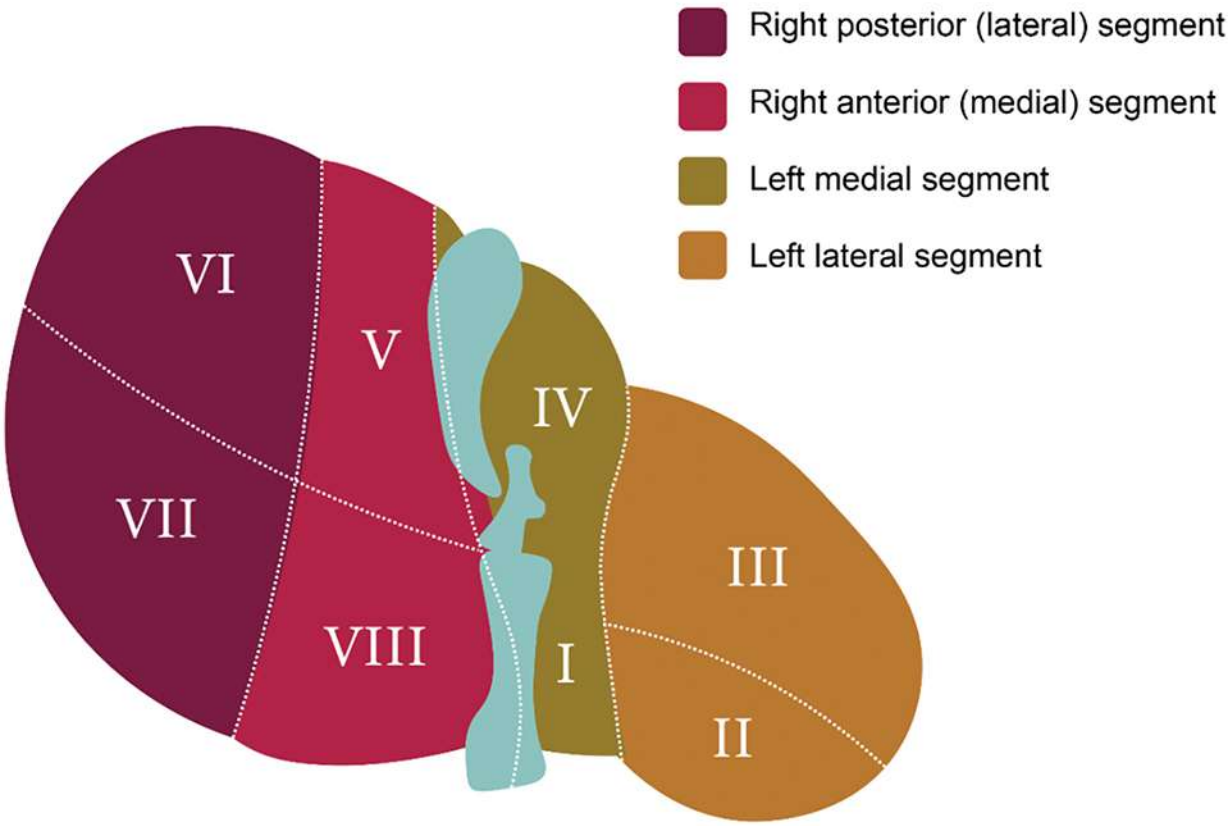
Liver and hepatobiliary malignancies are cancers that arise from the liver or extrahepatic biliary tract. Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) are the most common primary liver cancers. Other primary liver cancers include combined hepatocellular carcinoma-cholangiocarcinoma (cHCC-ICC), along with rarer neoplasms such as sarcoma, neuroendocrine tumor, and hepatoblastoma. Gallbladder cancer and extrahepatic cholangiocarcinoma arise from outside the liver. The 2019 fifth edition of the World Health Organization (WHO) classification of digestive system tumors divides tumors of the liver and intrahepatic bile ducts into benign hepatocellular tumors (focal nodular hyperplasia and hepatocellular adenoma), malignant hepatocellular tumors and precursors (including HCC and hepatoblastoma), benign biliary tumors and precursors (bile duct adenoma, biliary adenofibroma, mucinous cystic neoplasm of the liver and biliary system, and intraductal papillary neoplasm of the bile ducts), malignant biliary tumors (ICC), combined hepatocellular-cholangiocarcinoma and undifferentiated primary liver carcinoma, and hepatic neuroendocrine neoplasms.[1] This chapter focuses on malignant tumors of the liver and hepatobiliary tract, particularly HCC and cholangiocarcinoma.

PRIMARY LIVER CANCER

Topographic Anatomy

The liver is the largest solid organ in humans. Traditionally, it is divided into left and right lobes. Surgeons need to understand the spatial relationship of a tumor to the hepatic vascular system preoperatively to determine resectability. Fortunately, progress in imaging modalities has made feasible the segmental division of the liver based on the anatomy of the portal and hepatic veins. The most used segmentation scheme, which was proposed by Couinaud, divides the liver parenchyma into right and left livers with four segments each (Figure 66.1). The anatomic landmark that separates the left and right liver is drawn between the gallbladder fossa and the inferior vena cava, to the right of the falciform ligament. The left liver consists of the caudate lobe (segment I), lateral segment (segments II and III), and medial segment (segment IV). The anatomic landmark that separates the left medial and lateral segments is the left hepatic vein. The right liver consists of the anterior segments (segments V and VIII) and posterior segments (segments VI and VII). The anatomic landmark that separates the anterior segment from the posterior segment is the right hepatic vein, while the one separating the anterior segment from the left medial segment is the middle hepatic vein. Dynamic computed tomography (CT) and magnetic resonance imaging (MRI) are useful for distinctly defining segmental anatomy as the portal vein, hepatic vein, and inferior vena cava can be demonstrated well within the same study.[2]

Liver segments



Inferior view

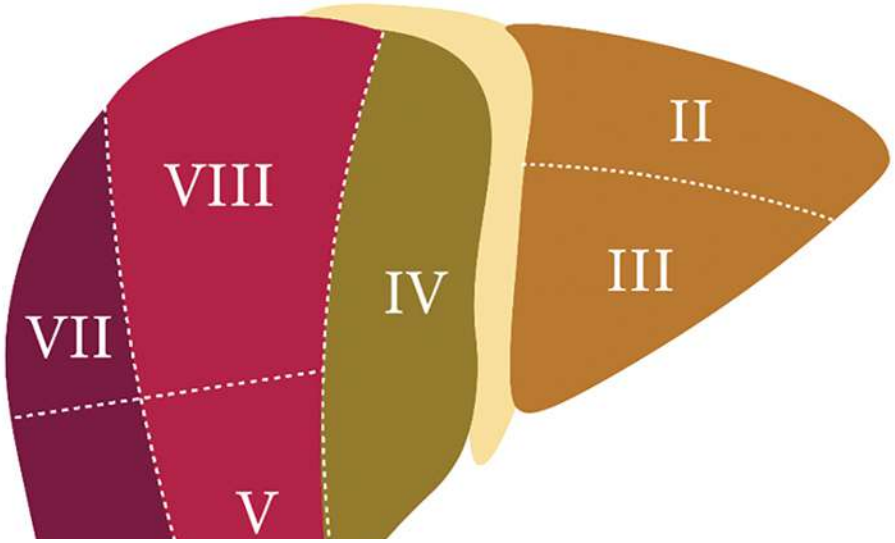


FIGURE 66.1 Segmentation scheme of the liver proposed by Couinaud.

Epidemiology

Primary liver tumor is the fifth most commonly diagnosed cancer and the second most common cause of cancer death globally.[3] It is reported to be the most frequently diagnosed cancer in six countries (Cambodia, Egypt, Laos, Mongolia, Thailand, and Vietnam) and the most common cause of cancer death in 15 countries (Burkina Faso, Cambodia, Egypt, Gabon, Gambia, Ghana, Guatemala, Laos, Mongolia, Nicaragua, Republic of Congo, the Solomon Islands, Thailand, Vanuatu, and Vietnam).[4] It is also among the top three causes of cancer death in 46 countries and among the top five causes of cancer death in 90 countries.[4]

Worldwide, there were 905,700 patients with liver cancer and 830,200 patients who died of liver cancer in 2020, according to the GLOBOCAN database.[4,5] The age-standardized incidence and mortality rates (ASRs) were 9.5 and 8.7 for new cases and deaths per 100,000 people, respectively.[4] These rates were highest in East Asia (17.8 new cases, 16.1 deaths), Northern Africa (15.2 new cases, 14.5 deaths), and Southeast Asia (13.7 new cases, 13.2 deaths)[4,5] (Figure 66.2). The male-to-female incidence ratio was about 2.5, with male-to-female ASR ratio ranging between 1.2 and 3.6.[4] Liver cancer rates are predicted to rise 55% in the next two decades, with a possible 1.4 million people diagnosed with and 1.3 million people dying from liver cancer in 2040.[4,5] A US national report showed that, although the incidence and mortality rates of cancer decreased from 2000 to 2014, the incidence and mortality rates of liver and intrahepatic bile duct cancers increased in both male and female patients.[6] However, a more recent report showed a decreasing incidence rate in the following years.[7]

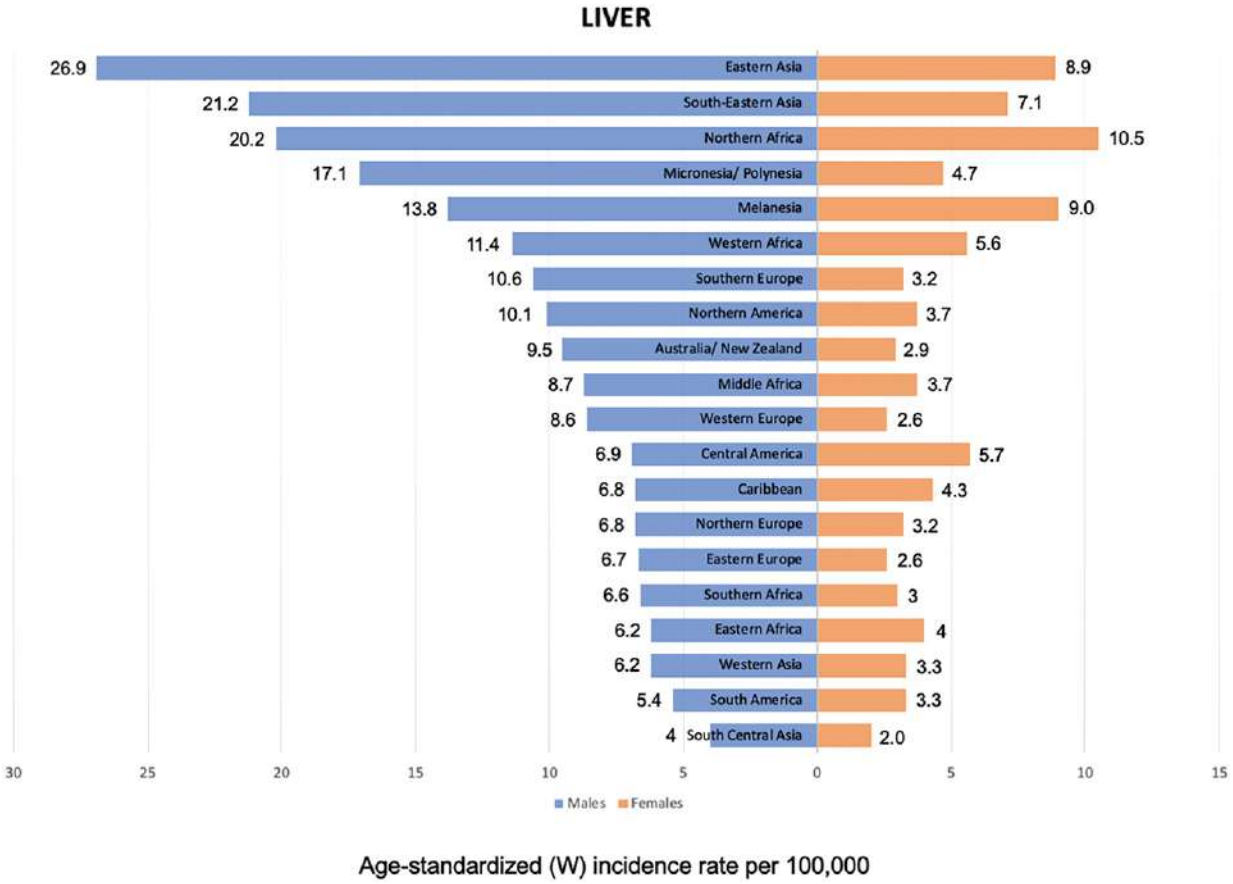


FIGURE 66.2 Incidence rates of primary liver cancer.[4,5]

Incidence rates of liver cancer are higher in East Asia, Southeast Asia, Central Africa, and West Africa compared to other parts of the world.[4] Age-standardized incidence rates per 100,000 people for liver cancer were higher in developing versus developed countries (16:7) for both genders in 2013.[8] HCC accounted for the majority of all primary liver cancers at 70% to 90%,[9] followed by intrahepatic cholangiocarcinoma at around 20%.[10] The reported incidence rate of cHCC-ICC varied from 0.4% to 14.2% between studies,[11] which may be related to changes in diagnostic criteria within the past two decades and possible misclassification as HCC or ICC if a tissue diagnosis was not obtained. According to a report from the U.S. Surveillance, Epidemiology, and End Results (SEER) database, cHCC-ICC accounted for 0.77% of primary liver cancers among over 60,000 patients.[11]

Clinical Presentation and Management of Primary Liver Cancer

Patients with liver cancer are usually asymptomatic in the early stage aside from symptoms related to chronic liver disease. However, symptoms are typically associated with advanced disease. Overall prognosis is dismal, with 5-year survival rates ranging from 0% to 10%. Only about one in five affected patients were amenable to curative resection before the implementation of screening programs for HCC, the main type of primary liver cancer, using α-fetoprotein (AFP) and ultrasonography.[12,13] Improvements in surgical techniques have raised resection rates to 30% to 50%.[14,15] The advent of liver transplantation in recent decades has further contributed to the curability of liver cancer. Surgical resection remains the primary curative treatment for hepatobiliary malignancies as many patients have inoperable or unresectable disease at diagnosis. For patients

with unresectable intrahepatic disease, treatment modalities such as transplantation, transarterial chemoembolization (TACE), local radiofrequency ablation (RFA), systemic chemotherapy, radiotherapy (RT), molecular targeted therapy, and immunotherapy are treatment options. Treatment options for different types of primary liver cancer are discussed later in this chapter (Figure 66.3).

Regional
Locally advanced or multi-focal

Systemic
Liver and distant disease

Local
Solitary tumor, technically resectable

Treatments

- Embolization
- HAI
- Transplant
- Radiation

- Cytotoxic chemotherapy
- Cytotoxic chemotherapy + Immunotherapy
- Targeted therapy
- Targeted therapy + Immunotherapy
- Clinical Trial

- Local surgery
- Local therapy
  - Ablation
  - Cryotherapy, etc.
- Radiation
- Clinical trial

FIGURE 66.3 Treatments for primary liver cancer. HAI, hepatic arterial infusion.

HEPATOCELLULAR CARCINOMA

HCC is the most common primary cancer of the liver, the fifth most common cancer worldwide, and the second highest cause of cancer mortality.[16] The male-to-female ratio ranges from 2:1 to 4:1 in most studies.[17]

High-risk regions are East Asia and Africa.[17,18] The highest incidence rates are seen among the male population of South Korea, North Korea, Thailand, China, Gambia, and Senegal (28.5-48.8/100,000 populations).[16] In low-risk areas, such as Canada, Columbia, and the United Kingdom, HCC occurs in only 1 to 3 per 100,000 people.[16] However, while the incidence rates of primary liver cancer have recently declined among the Chinese population in Hong Kong, Shanghai, Taiwan, and Singapore, the incidence rates have risen in some low-rate areas, such as the United States, the United Kingdom, and Australia.[17] This rise is most likely related to the increased prevalence of viral hepatitis infection.[19,20]

Clinical Presentation

Early-stage HCC is asymptomatic; it is generally detected by abnormalities on either or both AFP or ultrasonography screening or as an incidental finding in the evaluation of other conditions, such as chronic liver disease.[21] Some patients remain asymptomatic even in advanced stages. Symptoms experienced by patients with HCC are usually related to their chronic hepatitis and liver cirrhosis. Clinical symptoms include generalized fatigue, poor appetite, ascites, jaundice, upper gastrointestinal bleeding, splenomegaly, dilated abdominal veins, palmar erythema, gynecomastia, testicular atrophy, leg edema, and weight loss. Tumor-related symptoms include palpable masses in the upper abdomen (hepatomegaly), abdominal fullness, dull pain in the right upper quadrant of the abdomen, acute-onset abdominal pain (because of hemorrhage from a ruptured tumor), low-grade fever, obstructive jaundice, and splenomegaly.[22] Very few individuals with HCC present initially with metastatic disease affecting extrahepatic organs, such as the lungs, bones, adrenal glands, pancreas, intra-abdominal lymph nodes, and neck lymph nodes.[23] These occur mainly in patients with T4, multicentric disease, or with earlier stage disease following treatment. The most common sites of metastasis are the lungs, abdominal lymph nodes, and bones.[24]

Risk Factors

Ninety percent of patients with HCCs have at least one known underlying risk factor.[3,25] HCC is strongly associated with hepatitis B (HBV) and hepatitis C (HCV) viral infections, cirrhosis of any etiology, and other chronic liver cell injury. Chemical injury induced by ethanol, nitrites, hydrocarbons, solvents, organochlorine pesticides, primary metals, and polychlorinated biphenyls has also been implicated.[26,27] Environmental toxins, including aflatoxin, contaminated drinking water, smoking, and betel nut chewing, may also be associated with the pathogenesis of HCC.

Chronic Hepatitis B

Hepatitis B is the most important risk factor for HCC, contributing to about 50% of HCC cases globally.[3] This proportion is higher in Asia and Africa, where hepatitis B accounts for approximately 60% of HCC cases, compared to 20% in the West.[3,28] HBV is a DNA virus that can integrate into the host's genome, inducing insertional mutagenesis and leading to oncogene activation.[3] Patients with HBV can develop HCC even without cirrhosis, but the majority of patients with HBV-induced HCC cases occur in patients with cirrhosis at presentation. Those with chronic HBV infection and

cirrhosis are at the highest risk of developing HCC.[28] The relative risk (RR) of individuals with HCC with persistent HBV infection is 223 times that of uninfected individuals.[29] The presence of hepatitis B e antigen (HBeAg) suggests active HBV replication, and HBeAg-positive patients face an even higher risk of HCC than HBeAg-negative patients.[30] A synergistic effect further increases the risk of HCC in patients coinfected with both HBV and HCV.[31]

Chronic Hepatitis C

The HCV is a hepatotropic RNA virus and a major cause of chronic liver disease. Past studies showed the risk of HCC in patients with a positive HCV antibody was 17 times the risk in those with a negative result. The risk of developing HCC is about 1% to 8% per year[32] and is usually associated with cirrhosis. The RR of HCC among individuals with chronic HCV infection and cirrhosis is also approximately 100 times that of uninfected persons.[33]

Cirrhosis of Any Etiology

Cirrhosis, which is noted in about 80% of adult patients with HCC, is a strong risk factor for HCC. However, the risk varies for cirrhosis from other etiologies.[9] In general, in patients with cirrhosis, the risk of developing HCC is about 1% to 4% per year.[3,23,32]

Alcohol

Ethanol is the most common culpable chemical agent and is thought to lead to HCC through the development of liver cirrhosis or by playing the role of a co-carcinogen. Chronic alcohol use of >80 g/day for more than 10 years is associated with approximately a 5-fold risk for HCC. Alcohol use doubles the risk of HCC in patients with HCV.[34] Several pathogenic pathways for liver damage from alcohol have been proposed, including increased oxidative stress from reactive oxygen species during alcohol metabolism.

Aflatoxin

Aflatoxins, a well-known group of hepatotoxic agents produced by the fungi *Aspergillus flavus* and *Aspergillus parasiticus*, are associated with HCC. Aflatoxins can contaminate corn, soybeans, and peanuts. High dietary aflatoxin intake is known to be related to the development of HCC.[35] Its combination with other risk factors may synergistically increase the risk of HCC. In Africa, the diagnosis of HCC among patients in their early 30s or 40s is likely related to aflatoxin B1 exposure acting synergistically with HBV to increase the risk of HCC.[31,36] Rates of HCC are reported to be 4-fold among persons with elevated levels of aflatoxin B1, 7-fold among chronic HBV carriers, and 60-fold among persons with both risk factors.[37]

Aflatoxin B1 is metabolized by CYP2E1, which is induced by alcohol.[37] One case-control study suggests that combining aflatoxin B1 load and alcohol intake has a synergistic and statistically significant effect on RR (= 35). The pathogenesis of aflatoxin B1 in patients with HCC may be due to a mutational hotspot of the p53 tumor suppressor gene at codon 249.[32]

Hereditary Disease

Patients with hereditary liver diseases, such as hemochromatosis, Wilson disease, hereditary tyrosinemia, and glycogen storage disease (GSD) type I, are also at risk of developing HCC.[31,38] The common mechanism in these incidences of HCC may be related to chronic injury and inflammation of the liver. Past studies have reported hereditary tyrosinemia, α-1 antitrypsin deficiency (AATD), and GSD type I to be associated with early-onset cirrhosis and HCC in childhood.

Hereditary hemochromatosis (HH), an autosomal recessive inherited disorder,[38,39] occurs in approximately 1 in 200 to 300 individuals.[39] It is caused by mutations in the *HFE* gene and leads to excess iron absorption and damage to cardiomyocytes, pancreatic islet cells, and hepatocytes.

HCC has been reported to develop in 19% to 27% of patients with HH, representing a 200-fold risk of HCC. When early dysplasia and HCC are combined, the rate is even higher, up to 43% in prior studies.[38] Patients with HCC are usually men with cirrhosis over the age of 50. A study of 18,031 hospitalizations from the National Inpatient Sample database in the United States during 2011 to 2019 revealed an HCC incidence rate of 1.2% (95% confidence interval [CI]: 0.78%-1.53%) in patients with HH and an approximately 29-fold risk of developing HCC if without cirrhosis.[39]

Hereditary tyrosinemia type 1 (HT1) is an autosomal recessive inborn disease of tyrosine metabolism that usually leads to liver failure in infancy but can also present as later onset cirrhosis, renal tubulopathy, or intermittent porphyria in childhood. Patients can currently be treated with 2-(2 nitro-4-3 trifluoro-methylbenzoyl)-1,3-cyclohexanedione, which blocks the tyrosine degradation pathway and prevents toxic product accumulation. However, the risk of primary liver cancer remains, especially when treatment is initiated after symptom onset.[41] HT1 has been reported to be associated with both HCC and hepatoblastoma.[40]

GSD is a group of inherited metabolic diseases related to glycogenolysis and gluconeogenesis. The most common type is GSD type Ia, an autosomal recessive disease where glycogen accumulates via a defect in glucose-6-phosphatase. GSD has been reported to be associated with HCC and hepatic adenoma. A case series from Korea described 32 patients who developed hepatic adenoma at a young age (7.9-26.3 years, median 14.3 years) and an additional 4 patients who later developed HCC (average interval 6.7 years between diagnosis of hepatic adenoma and development of HCC).[41]

AATD is a potentially lethal inborn disease that increases the risk of liver fibrosis or cirrhosis (odds ratio [OR] = 21.7; 8.8-53.7) and primary liver cancer (OR = 44.5; 10.8-183.6).[42] It often causes lung and liver injury as well as morbidity and mortality. Mutation of the *SERPINA1* gene, which encodes for AAT, leads to proteotoxic liver injury. In patients with AATD, inborn genotype is not the only factor associated with liver disease. Obesity, diabetes, and older age are also associated with the development of liver fibrosis or cirrhosis and primary liver cancer. Male sex is an additional factor associated with liver disease in individuals with AATD.[42-44]

Although Wilson disease is reported to be associated with primary hepatobiliary cancer, the actual incidence rate is very low. A case series of 1,186 individuals confirmed to have Wilson disease reported only 14 patients with primary liver cancer, including 8 with HCC and 6 with ICC. The prevalence of primary liver cancer in the cohort was 1.2%, and the incidence rate was 0.28 per 1,000 person-years. In addition, pathologic analysis demonstrated no abnormal concentrations of copper within the tumors.[45]

Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

Nonalcoholic fatty liver disease and nonalcoholic steato hepatitis (NAFLD/NASH) are increasingly significant causes of cirrhosis. Due to the increasing prevalence of obesity, NASH has become the most common cause of cirrhosis in most regions of the world. NAFLD currently affects one-fourth of the global population.[46] Since 2010, the proportion of HCC attributed to NASH has rapidly increased, representing 15% to 20% of cases in Western countries.[9] Furthermore, the affected population may be greater than estimated due to its coexistence in patients with other liver diseases.[9] A recent study used Bayesian models to estimate that the age-standardized incidence rate of NAFLD-related liver cancer will increase from 0.92 per 100,000 inhabitants in 2018 to 1.18 per 100,000 inhabitants in 2030.[47] Other related metabolic diseases are also associated with an increased RR of HCC, including diabetes mellitus, with an estimated RR of about 2% to 2.5%, and metabolic

syndrome, with an estimated RR of about 1.81%.[32] In 2023, new nomenclature was announced that renamed NAFLD as metabolic dysfunction-associated steatotic liver disease (MASLD) and NASH as metabolic dysfunction-associated steatohepatitis (MASH), with a separate category termed *metabolic and alcohol-related/associated liver disease* for those with MASLD who consume increased weekly amounts of alcohol (140-350 and 210-420 g/week for females and males, respectively).[44]

Other Rare Causes

According to limited data, the prevalence of HCC is 17.6% in patients with Budd-Chiari syndrome and 26.5% in patients with inferior vena cava obstruction.[32] There are no statistically significant differences in sex, age, or site of obstruction between HCC and non-HCC groups.

Risk Factors and Genetic Correlation

Approximately one-quarter of HCC tumors present with actionable mutations; however, the prevalence of most mutations is <10%, thus complicating proof-of-concept studies.[9] *TP53*, *TERT* promoter, and *CTNNB21* are the most frequently found mutated genes, except in patients with HBV-related HCC. Related gene mutations are shown in Table 66.1.

TABLE 66.1 GENE-RELATED PATHOGENESIS OF HEPATOCELLULAR CARCINOMA[1,9]

Driver Gene	Pathway Involved	Related Etiologies
TP53	DNA repair and surveillance	HBV (10%-65%), HCV (24%), nonviral (16%), highest risk in areas of chronic aflatoxin B1 exposure
CTNNB1	Wnt/β-catenin signaling pathway	HBV (15%), HCV (30%), nonviral (39%)
AXIN1		HBV (12%), HCV (13%), nonviral (6%)
ARID1A	Chromatin remodeling	HBV (12%), HCV (2%), nonviral (16%)
ARID1B		HCV (4%), nonviral (2%)
ARID2		HBV (4%), HCV (4%), nonviral (7%)
ARID5A		Reported in NAFLD-related HCC
NFE2L2	Oxidative stress	HCV (9%), nonviral (6%)
KEAP1		HBV (4%), HCV (7%), nonviral (6%)
TERT promoter[a]		HBV (50%), HCV (61%), nonviral (65%)
HBV integration		HBV (65%-100%)
RPS6KA3	Oncogenic MAPK signaling	HBV (4%), HCV (9%), nonviral (6%)
CDKN2A	DNA repair and surveillance	HCV (4%), nonviral (2%)
RB1		HBV (8%), HCV (4%), nonviral (2%)
KMT2A(MLL)	Histone modification	HCV (4%), nonviral (2%)
KMT2C(MLL3)		HBV (8%), nonviral (3%)
KMT2D(MLL4)		HBV (4%), HCV (4%), nonviral (2%)
FGF19 amplification	Regulation of bile acid synthesis and hepatocyte proliferation via activation of its receptor FGFR4	HCV (5%-10%)
GSTT1		Related to toxic effect of aflatoxin B1 potentiated by HBV infection

Driver Gene	Pathway Involved	Related Etiologies
PNPLA3		NAFLD/NASH
TM6SF2		NAFLD/NASH
HSD17B13		NAFLD
MBOAT7	Regulation of hepatic lipid metabolism	NAFLD
APOB		NAFLD
TSC		
Cel	Cholesterol and lipid ester hydrolysis and absorption	NAFLD

ACVR2A, activin receptor type 2A; ARID, AT-rich interaction domain; CDKN2A, cyclin-dependent kinase inhibitor 2A; Cel, carboxyl ester lipase; CTNNB1, β-catenin; FGF19, fibroblast growth factor 19; MBOAT7, membrane-bound O-acetyltransferase domain containing 7; mTOR, mechanistic target of rapamycin; PNPLA3, patatin-like phospholipase domain containing protein 3; SNP, single-nucleotide polymorphism; TERT, telomerase reverse transcriptase; TM6SF2, transmembrane 6 superfamily member 2; TP53, tumor antigen p53; TSC, tuberous sclerosis complex.

[a]Most common mutation in HCC.

Prevention and Surveillance of At-Risk Groups

As most cases of HCC are related to viral hepatitis and chemical injuries, public health measures for the prevention of viral infection and avoidance of chemical exposure are essential for preventing HCC (Table 66.2). The HBV vaccine has been available for decades. Universal HBV vaccination in many countries, such as Taiwan, has led to a significant decrease in the incidence of HCC, from 0.70 to 0.36 per 100,000 children aged 6 to 14 years,[48] and subsequently a decrease in young adults with HCC.[49] In patients with evidence of HBV or HCV infection, oral antiviral agents should be used to effectively control the progression of infection. Antiviral therapy has also been shown to reduce recurrence and improve survival in patients with HBV-related HCC.[50]

TABLE 66.2 COMPARISON OF CURRENT GUIDELINES FOR PRIMARY PREVENTION OF HCC

	APASL 2017[32]	EASA 2018[3]	AASLD 2023[10]	Notes
HBV vaccination	Recommended	Recommended	Recommended	All newborns and high-risk adults
Antiviral therapy • HBV	Recommended	Recommended	Recommended	
Antiviral therapy • HCV	Recommended	Recommended	Recommended	HCC risk may remain higher in patients right after DAA therapy.
Lifestyle modification/bariatric surgery	Consider bariatric surgery for patients who are morbidly obese but lack data.	Not mentioned	Recommended	Healthy weight, balanced diet, avoidance of tobacco and alcohol, adequate control of comorbid conditions, including components of metabolic syndrome
Coffee consumption	Recommended	Recommended in patients with chronic liver disease	May be recommended	Suggested in patients with chronic liver disease, but unclear what preparation and quantity of coffee is most beneficial

	APASL 2017[32]	EASA 2018[3]	AASLD 2023[10]	Notes
Statins	Unclear	—	Not recommended for prevention of HCC	Can be used in other settings of chronic liver disease
Metformin	Unclear	—	Unclear; not recommended for prevention of HCC	An emerging strategy but has conflicting data

AASLD, American Association for the Study of Liver Disease; APASL, Asian Pacific Association for the Study of the Liver; DAA, direct antiviral agent; EASL, European Association for the Study of the Liver; HCC, hepatocellular carcinoma; HCV, hepatitis C virus.

Vaccination against HCV is currently not available. Strategies to prevent HCV infection include blood screening, the use of disposable needles and syringes, adoption of universal precaution for health care workers, and timely treatment of chronic HCV infection. Recent advances in interferon (IFN)-free direct antiviral agents have achieved highly effective control of HCV in infected individuals. Given good responses to antiviral therapy, major guidelines advise the use of antiviral therapy in patients with viral hepatitis B or C.[3,10,32] More recently, emerging cases of cirrhosis and HCC related to NASH/NAFLD have raised the importance of lifestyle modification to prevent HCC. Existing data suggest coffee is beneficial for preventing HCC, leading to its recommendation by current major guidelines.[3,10]

The goal of surveillance is to detect HCC in high-risk groups via serial screening tests at an early stage when curative treatment can be applied. However, cost-effectiveness of surveillance is also an important issue. A recent study has suggested a threshold of approximately 1.0% annual HCC incidence for initiating surveillance in patients with cirrhosis—lower than the traditional threshold of 1.5% per year.[51]

Patients with cirrhosis develop HCC at an approximate rate of up to 4% per year.[23] A randomized study demonstrated a 37% reduction in mortality in patients with hepatitis B undergoing surveillance.[52] A systematic review of surveillance also showed a relationship between increased detection of early-stage HCC and improved survival.[53] Abdominal sonography of the liver combined with serum AFP measurement is still the major method of HCC surveillance. Patients infected with HBV and HCV and those with autoimmune hepatitis are candidates for surveillance. Several professional organizations have proposed different surveillance guidelines. Readers may follow the updated guidelines for HCC management based on their geographic area of clinical practice. The most commonly used guidelines are the Asian Pacific Association for the Study of the Liver from 2017,[32] the European Association for the Study of the Liver from 2018,[3] and the American Association for the Study of Liver Disease (AASLD) from 2023.[7] Guidelines have evolved over time due to new evidence and treatments available, as shown in the comparison of HCC surveillance recommendations in (Table 66.3).

TABLE 66.3 COMPARISON OF HCC SURVEILLANCE SUGGESTIONS BETWEEN GUIDELINES

Population Group (Risk Factor and With/Without Cirrhosis)	Risk of HCC	Surveillance Suggestion		
		APASL 2017[32]	EASL 2018[3]	AASLD 2023[10]
Cirrhosis of any etiology; Child A-B	≥1.0% per year	≥1.0% per year	Recommended	Recommended (insufficient data for cirrhosis from NASH or etiologies that have already been treated)	Recommended

Population Group (Risk Factor and With/Without Cirrhosis)		Risk of HCC	Surveillance Suggestion		
			APASL 2017[32]	EASL 2018[3]	AASLD 2023[10]
HBV	No cirrhosis	≥0.2% per year	Recommended	Recommended for intermediate-/high-risk groups (PAGE-B ≥10)	Recommended for intermediate-/high-risk groups (PAGE-B ≥10)
HCV	No cirrhosis but severe fibrosis (METAVIR F3)		Recommended	Recommended	Not recommended routinely
	No cirrhosis		Consider	Consider	Not recommended
	No cirrhosis, post-treatment with SVR	~0.33%	Consider	Unclear	Not recommended
Alcohol	No cirrhosis	—	—		Not recommended
NASH/NAFLD	No cirrhosis	—	No conclusive recommendations	Unclear	Not recommended
Liver transplantation candidate on waiting list			—	Recommended	Recommended
Child-Pugh C cirrhosis and not candidate for transplantation)			—	Not recommended	Not recommended
Life-limiting comorbid conditions			—	Not recommended	Not recommended
Post–curative treatment of previous HCC			Recommended	Recommended	Recommended

AASLD, American Association for the Study of Liver Disease; APASL, Asian Pacific Association for the Study of the Liver; DAA, direct antiviral agent; EASL, European Association for the Study of the Liver; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; SVR, sustained virologic response.

History-Taking and Diagnosis of Hepatocellular Carcinoma

In a patient in whom HCC is suspected, a history of hepatitis, jaundice, blood transfusion, use of intravenous drugs, or exposure to aflatoxins should be noted. Asking about a family history of hepatitis and possible risk factors, such as alcohol abuse and industrial exposure to potential carcinogens, is also helpful. The physical examination should include a search for signs of underlying liver disease, such as jaundice, ascites, ankle edema, spider angiomata on the anterior chest wall, palmar erythema, splenomegaly, increasing abdominal girth, and weight loss. Evaluation of the abdomen for liver size, existence of tumor masses, tenderness, and abdominal bruits should also be included.

Laboratory testing should include liver function tests, serologies for HBV and HCV, and AFP. If HBV or HCV serologies are positive, quantitative HBV DNA or HCV RNA should be obtained.[54] Evaluation of hepatic functional reserve should include prothrombin time, activated partial thromboplastin time, and serum albumin. Platelet, red cell, and white blood cell counts should also be obtained to look for the simultaneous existence of portal hypertension and hypersplenism from liver cirrhosis. The diagnosis of HCC should be considered in the differential diagnosis for any patient with an underlying liver disease, such as cirrhosis or chronic viral hepatitis. Any dominant solid nodule that is not clearly a hemangioma should be considered HCC unless proven otherwise.[55]

Unlike other cancers that require a traditional pathologic diagnosis, HCC can also be diagnosed noninvasively via laboratory tests and clinical imaging, in accordance with current clinical guidelines worldwide. Noninvasive imaging diagnosis is an important part of the management of HCC, as HCC frequently coexists with liver cirrhosis, increasing the risk of bleeding during biopsy procedure. The identification of patterns typical of HCC on dynamic imaging has also changed diagnostic guidelines. The use of biomarkers alone as a diagnostic tool is not recommended.

Ultrasonography, CT, and MRI are the most commonly used diagnostic imaging modalities for evaluating tumors in the liver. Ultrasound examination of the liver is commonly used for screening rather than for diagnosis. Small tumors are often hypoechoic. As tumors grow, the echo pattern tends to become isoechoic or hyperechoic, and HCC can be difficult to distinguish from the surrounding liver.[56] At the author's institution, nodules <1 cm are followed with ultrasonography at intervals of 3 months. Nodules >1 cm in a cirrhotic liver should be investigated further with a four-phase dynamic CT scan. If a four-phase dynamic CT scan is not suitable for the patient or cannot confirm the diagnosis of HCC, contrast-enhanced MRI or biopsy is the next step. Contrast-enhanced sonography, which uses an intra-arterially administered microbubble agent as ultrasound contrast, can overcome the limitations of conventional B-mode and Doppler ultrasound techniques when evaluating focal lesions in the cirrhotic liver.[57] However, the technique needs to be performed by an experienced operator, and current major guidelines still focus on the use of CT or MRI dynamic studies for imaging diagnosis.

Nonpathologic diagnostic criteria for HCC have been proposed since the 2005 AASLD guidelines and consist of serum AFP level >200 ng/mL or a typical enhancement pattern (arterial enhancement and delayed portal vein washout) on dynamic imaging of hepatic masses >2 cm in a cirrhotic liver.[58] The AASLD further validated the diagnostic accuracy of a single dynamic technique in patients with chronic hepatitis B or cirrhosis of any etiology if intense arterial uptake followed by washout of contrast in the portal venous or delayed venous phases can be demonstrated.[57] A prospective validation study of 206 consecutive patients from Korea showed that the positive predictive value of typical CT findings or a serum AFP >200 ng/mL was 97.8% in patients with cirrhosis, 89.6% in high-risk patients without cirrhosis, and 82.4% in low-risk patients.[59] However, even when imaging diagnostic criteria are fulfilled, histopathologic confirmation is worthwhile in certain ambiguous situations. In the absence of cirrhosis or hepatitis B infection, histologic diagnosis is usually recommended.

For patients with risk factors for HCC, most recent clinical guidelines have established diagnostic criteria based on dynamic imaging alone that uses the Liver Reporting and Data System (LI-RADS) classification (Figure 66.4). A meta-analysis suggested a sensitivity of 82% using MRI and 66% using CT with similar specificity (MRI: 92%; CT: 91%). LI-RADS classification for CT and MRI has been widely accepted for clinical use in patients warranting HCC surveillance, including individuals with cirrhosis, noncirrhosis HBV infection with an intermediate or high risk of HCC, or a history of prior HCC.[59]

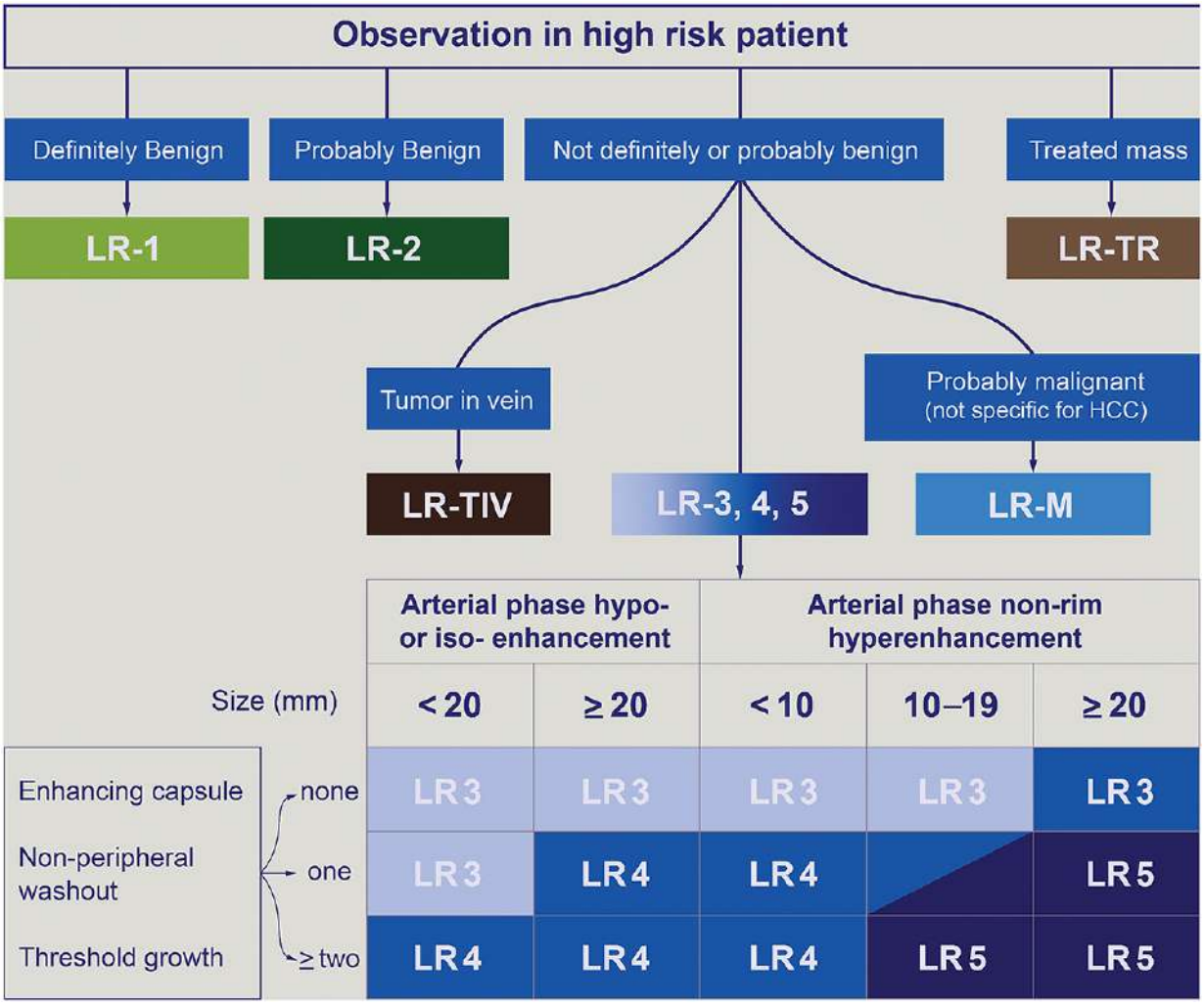


FIGURE 66.4 Liver Reporting and Data System classification.

Histologic diagnosis of HCC is also recommended for patients whose treatment plan is nonsurgical.[60] For patients for whom surgery is considered, a concern exists over the possibility of tumor seeding from biopsy or fine-needle aspiration.[60] The reported risk ranges from 1.6% to 5%.[61-63] In patients who demonstrate coagulopathy or significant ascites, biopsy or fine-needle aspiration may be contraindicated. At the author's institution, fine-needle aspiration under ultrasound guidance is frequently performed for tissue confirmation by cytology and cell block.[62] Core biopsy of the mass is generally reserved for patients in whom a definitive diagnosis by fine-needle aspiration and cell block cannot be made. A coaxial cannula is used to reduce the chance of needle-track seeding.[64] In patients with small hepatic nodules for whom diagnostic possibilities range from well-differentiated malignancy to benign disease such as nodular hyperplasia, ultrasound-guided needle, or core biopsy should be considered.[65]

Pathologic diagnosis is usually based on the International Consensus Group for Hepatocellular Neoplasia definition.[7,66] Major histologic features of HCC include stromal invasion, increased cell density, intratumoral portal tracts, unpaired arteries, pseudoglandular pattern, and diffuse fatty changes. According to the most recent fifth edition of the WHO classification of digestive system tumors, HCC can be classified into eight subtypes: fibrolamellar, scirrhous, clear cell type,

steatohepatic, macrotrabecular massive, chromophobe, neutrophil rich, and lymphocyte rich (Table 66.4).[1] Diagnosis by imaging may not be possible for these eight subtypes as they may not demonstrate typical patterns in dynamic studies. Major guidelines do not currently differentiate treatment plans by pathologic subtype.

TABLE 66.4 WHO CLASSIFICATION OF DIGESTIVE TUMORS, FIFTH EDITION: SUBTYPES OF HCC

Subtype	Relative Frequency (%)	Prognosis	Histologic Features	Molecular Features	Clinical Correlates
Steatohepatic	5-20	Similar	Cell ballooning, inflammation, pericellular fibrosis, and Mallory-Denk bodies	IL-6/JAK/STAT activation; lower frequency of CTNNB1, TERT, and TP53 mutation	Steatohepatitis background
Clear cell	3-7	Better	Cytoplasmic accumulation of glycogen with clear cell morphology (>80% of tumor)	—	—
Macrotrabecular massive	5	Poor	Macrotrabecular (>6 cells thick) architecture in >50% of tumor, with satellite nodules and macrovascular and/or microvascular invasion	TP53 mutations and FGF-19 amplifications	High serum AFP
Scirrhous	4	Variable	Dense intratumoral fibrosis in >50% of tumor	TSC1/2 mutations; TGF-β signaling activation	Mimics cholangiocarcinoma on imaging
Chromophobe	3	Similar	Light, clear cytoplasm, bland tumor nuclei, but focal areas of more striking nuclear atypia	Alternative lengthening of telomeres	—
Fibrolamellar carcinoma	1	Similar to HCC without cirrhosis	Large eosinophilic tumor cell with prominent nucleoli, dense intratumoral fibrosis	Activation of PKA via DNAJB1-PRKACA fusion gene	Young (median age 25 y/o)
Neutrophil rich	<1	Poor	Diffuse neutrophils within tumor, can have sarcomatoid loci	Tumor produces G-CSF.	Elevated white blood cell count, CRP, and IL-6
Lymphocyte rich	<1	Better	On H&E staining, lymphocytes outnumber tumor cells in most fields	Not related to EBV	—

AFP, α-fetoprotein; CRP, C-reactive protein; CTNNB1, β-catenin; EBV, Epstein-Barr virus; FGF-19, fibroblast growth factor-19; G-CSF, granulocyte colony-stimulating factor; HCC, hepatocellular carcinoma; H&E, hematoxylin and eosin; IL-6, interleukin-6; PKA, protein kinase A; TGF-β, tumor growth factor β; TERT, telomerase reverse transcriptase; TP53, tumor antigen p53; TSC, tuberous sclerosis complex; WHO, World Health Organization.

WHO Classification of Tumours Editorial Board. Digestive system tumours [Internet]. Lyon (France): International Agency for Research on Cancer; 2019 [cited YYYY Mmm D]. (WHO classification of tumours series, 5th ed.; vol. 1). Available from: https://tumourclassification.iarc.who.int/chapters/31.

Staging

HCC generally carries a poorer prognosis compared to other cancers due to negative effects from underlying liver disease. Several factors have been identified as important determinants of survival: the severity of underlying liver disease, the size and number of tumors, vascular invasion, regional lymph node metastasis, and the presence of distant disease. Routine metastatic survey in patients with HCC is not recommended unless transplantation is being considered. There is no worldwide consensus on the use of any given HCC staging system. However, most major trials of HCC therapy have chosen the Barcelona Clinic Liver Cancer (BCLC) staging system (Table 66.5), making it the de facto reference staging system.[67,68] Other systems, such as the American Joint Committee on Cancer (AJCC) TNM staging system,[69] the Okuda staging system,[70] and the Cancer of the Liver Italian Program scoring system,[65] are also in common use.

TABLE 66.5 BCLC STAGING SYSTEM FOR HEPATOCELLULAR CARCINOMA

BCLC Stage	ECOG Performance Status	Tumor Features	Liver Function
0	ƒ0	Single nodule <2 cm	Child-Pugh A
A	0	Single or three nodules < 3 cm	Child-Pugh A-B
B	0	Multinodular	Child-Pugh A-B
C	1-2	Portal invasion, N1, M1	Child-Pugh A-B
D	3-4		Child-Pugh C

BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; M, metastasis classification; N, node classification.

General Management

Surgical resection remains the primary treatment approach. However, a significant number of patients are ineligible for surgery due to either the extent of their tumor or underlying liver dysfunction. HCC is frequently multicentric, particularly when associated with HCV infection. The rate of multicentric disease in HCV-related HCC (53.3%) is significantly higher than in non–HCV-related HCC (7.7%).[71] The likelihood of multicentric occurrences also increases as chronic liver disease and cirrhosis progress.[72,73] While multiple tumors are less common in HBV-associated HCC, patients with persistent HBeAg positivity and high HBV DNA serum levels have a notably higher risk of intrahepatic HCC recurrence. For patients who are not eligible for surgical resection, several other treatment modalities can be considered, including liver transplantation, percutaneous ablation, TACE, RT, molecular targeted therapy, and immunotherapy. Most treatment guidelines have recommended treatments based on the BCLC staging system. In general, potentially curative treatments such as surgical resection, transplantation, and local ablation are recommended for patients with early-stage HCC. First-line treatments for intermediate- and advanced-stage HCC are TACE and systemic therapy, respectively.[9]

Surgical Resection

Surgical resection is a reliable method to achieve long-term disease control. The main limiting factors for performing resection include poor liver function, the presence of portal hypertension or vascular invasion, and the size, location, and number of tumors. The extent of hepatic tumor resection depends on the functional reserve of the residual liver after surgery. Historically, patient selection for resection was based on the Child-Pugh functional classification (Table 66.6), but this method has been found to be inconsistent in predicting outcomes. Many Japanese and other Asian physicians prefer using the 15-minute retention rate of indocyanine green (ICG) before treatment for

patient selection.[74] In Europe and the United States, the selection of optimal candidates for resection usually involves assessing portal hypertension, either clinically or via hepatic vein catheterization.[75] Clinically significant portal hypertension is suspected if the platelet count is below 100,000/μL and associated with significant splenomegaly. Other parameters proposed for liver function assessment before surgery include the model for end-stage liver stage score and the albumin-bilirubin score.[76] The goal of surgery is to remove the gross tumor with a margin of 1 to 2 cm of normal liver. Five-year survival after resection has improved through careful preoperative assessment as stated above and can reach 50% to 70%. However, the recurrence rate can still be as high as 70% within 5 years.[9]

TABLE 66.6 GRADING SYSTEM FOR CIRRHOSIS: THE CHILD-PUGH SCORE

Score	Bilirubin (mg/dL)	Albumin (g/dL)	Prothrombin Time (s)	Hepatic Encephalopathy (Grade)	Ascites
1	<2	>3.5	<4	None	None
2	2-3	2.8-3.5	4-6	1-2	Mild (detectable)
3	>3	<2.8	>6	3-4	Severe (tense)

Child class: A, 5 to 6; B, 7 to 9; C, >9.

From Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1973;60(8):646-649. Reproduced by permission of BJS Foundation Ltd.

Liver Transplantation

Many patients are not candidates for tumor resection because of underlying liver dysfunction. The increasing availability of liver transplantation has made this procedure a viable alternative to tumor resection for selected patients. Based on the Milan study and others, liver transplantation is an effective option for patients with HCC,[77,78] and the Milan criteria are still today's benchmark for patient selection. The major selection criteria are a solitary tumor less than 5 cm in size or up to three tumors less than 3 cm in size.[77] Elevated AFP concentration adds prognostic information and may be used for decision-making in combination with imaging criteria.[79] Outcomes after transplantation have been excellent, with 5- and 10-year survival rates of 70% and 50%, and recurrence rates of 10% to 15% at 5 years, respectively.[9] Risk factors for recurrence after transplantation include tumor size, number of tumors, vascular invasion, and persistence of HBV infection.[80-82] A major disadvantage of orthotopic liver transplantation is the unpredictable and potentially long waiting time for donor organs.[82] Living donor transplantation can be offered for HCC if the waiting time will likely be long.[79] The concept of downstaging with local treatment such as TACE or RFA to make more patients fit within the Milan criteria, which was first introduced by the University of California San Francisco group in 2008.[83] Downstaging could increase the opportunity for transplantation and improve survival. A US multicenter study reported excellent outcomes after liver transplantation, with a 10-year survival rate of 61.5% and recurrence rate of 13.3% for those always within the Milan criteria and a comparable 10-year post-transplant survival rate of 52.1% and recurrence rate of 20.6% for those who were downstaged.[84] In addition, local treatment could also serve as bridging therapy for patients on the transplant waiting list to prevent disease progression, thereby increasing the chance of transplantation.

Percutaneous Ablation

For patients with early-stage HCC who are not candidates for resection or transplantation, percutaneous ablation, by injecting chemical substances (ethanol or acetic acid) or modifying the

temperature (with radiofrequency, microwave, laser, or cryotherapy), could be a potentially curative option. Percutaneous ethanol injection is highly effective for small HCC. It achieves a necrosis rate of 90% to 100% for HCC <2 cm in size, but the necrosis rate is reduced to 50% if tumor size is >3 cm.[85-87]

RFA involves the local application of radiofrequency thermal energy to the lesion. RFA is a reasonable option for patients who do not meet resectability criteria for HCC due to location or patient condition and yet are still candidates for a liver-directed procedure. The best outcomes are in patients with a single tumor >2 and <4 cm in diameter. Randomized controlled trials comparing RFA and ethanol injection have shown that RFA provides superior local disease control that could result in an improved survival.[86-89] Two of three randomized controlled prospective trials comparing RFA with surgical resection for small HCCs concluded that both have similar efficacy.[90] Several guidelines have thus recommended RFA as the first-line treatment for single tumors <2 cm. For patients with early-stage single tumors 3 to 4 cm or two to three tumors <3 cm not suitable for surgical resection, RFA is an acceptable alternative.[3,91]

Intra-arterial Therapies (Transcatheter Arterial Chemoembolization and Others)

HCC is a highly vascular tumor that mainly receives its blood supply from the hepatic artery or other nearby arteries. This tumor shows significant neoangiogenic activity as it progresses, which not only forms the theoretical basis for its radiologic diagnosis but also provides the rationale for using arterial embolization as a treatment option. In contrast, normal liver parenchyma receives dual blood supply from both the portal venous and hepatic arterial system and thus is relatively protected when the hepatic arterial supply is disrupted. TACE involves selective injection of chemotherapeutic agents through arteries feeding the tumor followed by intra-arterial embolization of tumor-feeding arteries with lipiodol, an iodized oily contrast agent, Gelfoam, or plastic particles such as Ivalon. In the early 2000s, two prospective randomized controlled trials and a meta-analysis demonstrated survival benefit with TACE compared with conservative management in intermediate-stage HCC.[92-94] TACE has since been accepted as the standard treatment for unresectable disease or inoperable patients, such as those with multicentric disease or repeated relapses. It can be used selectively for tumors in different organ locations and can be repeated if necessary.[95,96] The recently reported median survival after TACE ranges from 25 to 30 months.[9] In an attempt to better standardize drug delivery and decrease postembolization syndrome, drug-eluting beads (DEB)-TACE was developed to ensure more constant and tumor-specific drug delivery. However, a phase 2 randomized study comparing DEB-TACE with TACE did not meet its primary end point of improving the objective response rate, although DEB-TACE was associated with fewer side effects.[97,98]

Transarterial radioembolization (TARE) is a procedure involving the intra-arterial delivery of glass or resin microspheres embedded with the radioactive isotope yttrium-90. Although smaller uncontrolled trials have reported encouraging outcomes in patients with portal hypertension, randomized trials have failed to confirm survival benefit compared with sorafenib in advanced disease. TARE does not cause ischemia or alteration in hepatic arterial flow; hence, postembolization syndrome may be avoided.[97]

Conventional Radiotherapy

HCC is known to be sensitive to radiation.[99] However, the radiation tolerance of surrounding normal liver tissue is poor, and precisely locating the tumor for RT can be challenging.[100,101] Advances in RT technology, such as intensity-modulated radiation therapy (IMRT), image-guided radiation therapy, respiratory gating, and stereotactic body radiation therapy (SBRT), have improved the potential and feasibility of using radiation to treat HCC. These advancements allow for more accurate targeting of

the tumor, enabling more conformal radiation dose distribution, thus sparing more normal liver tissue from high-dose radiation.[100,101] For patients with liver-confined disease treated with conformal radiotherapy (CRT) with or without TACE, local control response rates ranged from 40% to 90%, and the median survival ranged from 10 to 25 months.[102] Indications for CRT are as follows:

Early stage

1. For those unsuitable for resection or RFA
2. As a bridging therapy to transplantation

Intermediate stage

1. For patients who fail to respond or have an incomplete response to TACE
2. In combination with other local treatments to treat multiple tumors
3. To potentially downstage the disease

Advanced stage

1. For tumor-induced portal vein thrombosis
2. For palliation of symptoms
3. For a potentially additive or synergistic effect with other systemic treatments

Radiation Tolerance of the Liver

Radiation-induced liver disease (RILD) is a critical complication that can arise following liver RT and serves as an important measure of outcome in various studies. RILD is categorized into two distinct types: "classic" and "nonclassic."[103]

1. Classic RILD: This type is characterized by symptoms of anicteric hepatomegaly and ascites. It typically occurs between 2 weeks and 3 months following the completion of RT. The key laboratory finding is a significant elevation in alkaline phosphatase levels, often greater than twice the upper limit of normal or baseline level. Classic RILD can occur in patients who had relatively good liver function before undergoing RT.
2. Nonclassic RILD: This variant usually develops between 1 week and 3 months post-therapy. The liver transaminases are greater than 5 times the upper limit of normal within 3 months of completing RT. The Child-Pugh score worsens by two points or more in the absence of symptoms typical of classic RILD.

Classic estimation of whole-liver tolerance is 30 Gy in 2-Gy fractions.[104] Data from the Radiation Therapy Oncology Group (RTOG) 84-05 showed that RILD developed in 0 of 122 patients receiving 27 to 30 Gy in twice daily 1.5 Gy fractions of whole-liver RT compared to 5 (9.8%) of 51 patients receiving 33 Gy in 1.5-Gy fractions. More recently, the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) initiative recommended limiting palliative whole-liver doses to ≤30 Gy (2 Gy/fr) or 21 Gy in seven fractions for liver metastases and to ≤28 Gy (2 Gy/fr) or 21 Gy in seven fractions for primary liver cancers.[103] Preexisting liver dysfunction may render patients more susceptible to RT-induced liver injury.

Radiation Doses

Before the era of CRT, the radiation dose for liver cancer was limited to <30 to 40 Gy due to the risk of hepatotoxicity, leading to <30% of patients showing a partial response. Seong et al[105] reported a response rate of 67% in patients who did not respond to TACE and were treated with CRT with a mean dose of 51.8 ± 7.9 Gy. Dawson et al[106] found that patients with unresectable hepatobiliary cancer who received escalated radiation doses >70 Gy had better median survival (>16.4 months). This suggests that higher radiation doses can lead to better tumor responses (Table 66.7). However, caution is advised in cases of HBV-related HCC, as RT may worsen liver function due to RILD, portal hypertension, and HBV reactivation. Prophylactic treatment of HBV is recommended to prevent its reactivation during treatment.[107]

TABLE 66.7 RADIOTHERAPY WITH AND WITHOUT CHEMOTHERAPY FOR UNRESECTABLE HEPATOCELLULAR CARCINOMA

Series	Patient Number	Radiation Dose (Gy)	Chemotherapy	Response Rate (%)
Stillwagon et al[109] (RTOG)	135	21, 3 daily	Concurrent ADR, 5-FU	22
Order et al[110] (RTOG)	105	21, 3 daily + I^{131} 10-12 × 2 courses	Concurrent ADR and 5-FU	48
Seong et al[105]	27	51.8 (mean), 1.8 daily	None	67
Dawson et al[106]	25	58.5 (median), 1.5 bid	Concurrent HAI fluorodeoxyuridine	68

5-FU, 5-fluorouracil; ADR, doxorubicin; bid, twice daily; HAI, hepatic arterial infusion; RTOG, Radiation Therapy Oncology Group.

Treatment Volumes

While higher radiation doses can lead to better treatment responses, patients with HCC often have liver cirrhosis and dysfunction, which unfortunately limits the use of higher radiation doses. Studies of 3DCRT using photon beams indicate that tumor-affected liver areas can tolerate higher doses with acceptable side effects. Lawrence et al[108] developed a model to predict normal tissue complication probability (NTCP) from RT for intrahepatic malignancy. Based on this model, the authors designed a protocol in which each patient can receive maximum tolerated doses of radiation with no more than a 10% risk of RILD. The mean doses that can be delivered according to this protocol are 56.6 ± 2.31 Gy (range, 40.5-81 Gy). Using this dosing range, they observed a reduction of radiation complication rate to 4.8% (95% CI, 0%-23.8%). This model, however, was derived using patients with relatively normal liver function, and only 4 of 21 in their study population had HCC.[108]

The QUANTEC study analyzed the effect of fractionated partial liver irradiation using a 3D conformal technique in patients with HCC. The patient population had baseline Child-Pugh A or B liver function and was from the US and Asia- Pacific regions. This study, also using the NTCP model, found that RILD rates varied from 9.5% to 17%. The mean normal liver dose in patients with RILD ranged from 23 to 37 Gy and was lower in those without RILD, ranging from 19 to 31.3 Gy.[102] Hence, the authors suggested keeping the mean normal liver dose to <28 Gy in 2 Gy fractions for primary liver cancer and <32 Gy in 2 Gy fractions for liver metastases.[103]

Patients with hepatitis B infection and liver cirrhosis have an increased risk of developing RILD.[111] In patients with cirrhosis but classified as Child-Pugh grade A only, the liver can typically tolerate a mean dose of 23 Gy.[112] The authors suggested a dose-volume histogram for irradiation to normal liver in which volumes receiving over 10, 20, 30, and 40 Gy should be less than 68%, 49%,

28%, and 20%, respectively. Furthermore, multivariate analyses identified the severity of hepatic cirrhosis as the sole independent predictor for RILD.

The ICG retention test is useful for determining the appropriate treatment volume for HCC.[113] Based on this test, we proposed a treatment guideline for CRT in patients with impaired liver function (Table 66.8). Our guideline recommends against radiation treatment for patients with Child-Pugh class C liver cirrhosis or prolonged ICG retention, except in cases where only a very small portion of the liver is within the radiation treatment field.[99]

TABLE 66.8 RADIATION TREATMENT GUIDELINES FOR HEPATOCELLULAR CARCINOMA

	ICG (Gy)		
Nontumor Part of Liver	**≤10%**	**10.1%-20%**	**20.1%-30%**
<1/3	40 (Gy)	No RT	No RT
1/3-1/2	50 (Gy)	40 (Gy)	No RT
>1/2	60 (Gy)	50 (Gy)	40 (Gy)

ICG, indocyanine green; RT, radiation therapy.

From Cheng SH, Lin YM, Chuang VP, et al. A pilot study of three-dimensional conformal radiotherapy in unresectable hepatocellular carcinoma. *J Gastroenterol Hepatol*. 1999;14(10):1025-1033. Copyright © 1999 Blackwell Science Asia Pty Ltd. Reprinted by permission of John Wiley & Sons, Inc.

Stereotactic Body Radiotherapy

SBRT has recently become a promising treatment option for intrahepatic tumors, thanks to advancements in planning systems and modern linear accelerators. This technique, leveraging advances in respiratory motion management and image guidance, allows for the delivery of higher biologic equivalent dose (BED) to liver tumors with similar or even reduced damage to normal tissue. A key benefit of SBRT is its rapid dose fall-off, which helps preserve more of the nontumor liver tissue.

There is a wide variety of dosing and fractionation schedules using SBRT to treat HCC, ranging from 24 to 60 Gy in three to six fractions. Over 400 patients have been treated in nine prospective clinical trials utilizing SBRT for HCC[114] (Table 66.9). The 1-year local control rates in these trials ranged from 65% to 100%. According to a recent meta- analysis including 1,889 patients from 17 retrospective studies reported between 2013 and 2022, the 3- and 5-year overall survival rates after SBRT were 57% and 40% and the 3- and 5-year local control rates were 84% and 82%, respectively. The analysis identified tumor size as the only prognostic factor for local control and found that tumor size and region were significantly associated with overall survival.[115]

TABLE 66.9 PROSPECTIVE STUDIES OF SBRT FOR HCC

Study	*N*	Lesions	CP B/C (%)	PVTT (%)	Prior Liver Therapy (%)	Tumor Size	Dose Scheme	1-Year LC (%)	I-Year OS (%)	Toxicity
Mendez-Romero et al[125]	25 (8)[a]	45 (11)[a]	25	25		3.5 cm	<4 cm and no cirrhosis: 37.5/3 ≥4 cm, cirrhosis: 25/5 or 30/3	94	82	20% grade 3+

Study	*N*	Lesions	CP B/C (%)	PVTT (%)	Prior Liver Therapy (%)	Tumor Size	Dose Scheme	1-Year LC (%)	I-Year OS (%)	Toxicity
Tse et al[126]	41 (31)[a]		0	42	17	173 cc	24-54/6	65	51	26% grade 3 enzymes 23% had decline in CP score.
Andolino et al[127]	60	71	41	—	—	29 cc	44/3 for CPA, 40/5 for CPB	2-year 90%	2-year 67%	20% had decline in CP score within 3 mo.
Kang et al[128]	47	56	13	11	57	2.9 cm	57/3	2-year 94.6%	2-year 68.7%	11% grade 3+ GI ulcer 4% grade 3+ ascites 11% grade 3+ thrombocytopenia
Bujold et al[129]	102	60.8% multiple lesions	0	55	52	7.2 cm	36 (range 24-54)/6	87	55	30% grade 3+
Culleton et al[130]	29	Median 2 lesions	100	76	14	8.6 cm	30/6	100	32	63% had decline in CP score.
Lasley et al[131]	59	65	36	20	15	33.6 cc	CPA 48/3 CPB 40/5	CPA 91 CPB 82	CPA 94 CPB 57	CPA: 11% grade 3+
Scorsetti et al[132]	43	63	47	20	44	4.8 cm	<3 cm: 48-75/3, 3-6 cm: 36-60/6	86	78	16% grade 3+
Feng et al[133]	90 (69)[a]	116	23	18	Median 2 treatments	3 cm	49 Gy	99	67%	14% had 1-point increase in CP score. 7% had 2-point increase in CP score.

CP, Child-Pugh; HCC, hepatocellular carcinoma; LC, local control; OS, overall survival; PVTT, portal vein tumor thrombosis.

[a]Total patient numbers included those treated for histologies other than HCC. The number of patients with HCC is reported in parentheses.

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Evaluating tumor response after SBRT can be challenging. A radiology-pathology response correlation study from the University of Michigan concluded that persistent central arterial hyperenhancement and washout within the first 12 months after SBRT may not represent residual viable tumor if there is no increase in size. There were findings of early inflammation followed by late fibrosis in liver parenchyma adjacent to the treated lesion. However, no patients in the study had significant liver function impairment.[116,117]

Simulation

It is advisable to assess the motion of the liver tumor, which is best achieved with a 4D CT. The 4D CT can generate images in 10 respiratory phases, capturing tumor motion throughout the respiratory cycle.[118] In addition, small bowel and intravenous contrast should be used to clearly demarcate the

tumor and nearby organs at risk (OARs), such as the stomach and intestines. Techniques such as abdominal compression, breath-holding, and respiratory gating can be employed during radiation treatment to reduce uncertainties caused by both inter- and intrafraction motion. This helps in minimizing the volume of tissue treated and in reducing damage to normal tissues.[119]

Tumor Contouring

Delineating the tumor target using 4D images can be challenging. For patients who have undergone TACE, the lipiodol may provide useful landmarks during the contouring process. Other helpful landmarks for contouring include fiducial markers, calcifications, and any surgical clips or stents. A contrast-enhanced MRI can provide complementary information that aids in defining the target area. Some researchers have also employed deformable image registration techniques to enhance this process.[120]

Motion Management

CRT aims to accurately target tumors while minimizing injury to surrounding normal tissue. Managing respiratory organ motion, which is the largest source of "intrafraction" movement during treatment, is especially crucial in SBRT for liver tumors. Respiratory motion management is recommended if target motion is greater than 5 mm, or when the procedure will enhance normal tissue sparing.[121] Effective motion management may allow the use of smaller margins during radiation delivery, which is important, since liver tumors may move several centimeters during respiration, and substantial rotations and deformations have also been reported.[122] Aruga et al[123] studied organ motion using CT images captured during both static exhalation and inhalation phases for upper abdomen irradiation. They observed tumor shifts between the two respiratory phases, with variation ranging from 0.4 to 5.9 mm laterally, 2.2 to 24.5 mm longitudinally, and 0.2 to 11.7 mm vertically with the patient in the supine position. Park et al[124] studied the motion of liver tumors in 20 patients using fiducial markers and reported motion ranges of 3.0 ± 2.0, 5.1 ± 3.1, and 17.9 ± 5.1 mm in the left-right, anterior-posterior, and craniocaudal directions, respectively, during planning 4D CT and similar ranges during treatment cone-beam CT.

Respiratory motion management techniques include passive approaches, such as motion-encompassing techniques (internal target volume [ITV]) and forced shallow breathing (or abdominal compression), and active approaches, such as respiratory gating in free-breathing or in breath-hold and respiratory synchronization (tracking).[121,122] These techniques may help mitigate respiratory movement during RT. In general, radiation field margins to the target can be about 6 to 9 mm laterally, 9 to 12 mm vertically, 10 mm superiorly (subphrenic), and 19 to 21 mm inferiorly.[134,135] To further preserve liver function, radiation field margins can be reduced to 5 mm if the patient receives gated radiation treatment in the expiratory or inspiratory phase. The beam-on time would be about 30% to 40% of the whole respiratory cycle, determined based on tumor motion observed on 4D CT images.

Planning and Prescription

The gross tumor volume (GTV) includes the liver tumor and any tumor thrombi. Prophylactic nodal irradiation is not necessary. The clinical target volume (CTV) is usually defined as the GTV with no expansion.[136] However, sometimes regions at high risk for harboring microscopic disease, including nontumor vascular thrombi and adjacent TACE or RFA sites, are included in the CTV. An ITV is generated from 4D CT based on the respiratory phases to be used during radiation delivery. The planning target volume (PTV) is generated by adding a margin around the CTV or ITV to

compensate for setup and internal organ motion. Depending on the methods of respiratory motion control used, the PTV margins usually range from 5 to 20 mm. Use multiple coplanar and noncoplanar beams to generate a plan with conformal dose distribution and rapid dose fall-off outside the PTV. Quality assurance is mandatory for patients at our institution treated with a daily fraction dose ≥6 Gy.

Dose and Organs at Risk

When determining doses of SBRT, it is crucial to consider the radiation tolerance of the liver and nearby organs, such as the stomach, duodenum, large bowel, kidney, and spinal cord. To ensure liver function remains adequate, a minimum volume of normal liver must be spared from receiving a critical dose of radiation. Drawing from the concept of surgical partial hepatectomy and the idea of "critical volume," the QUANTEC paper recommends that at least 700 mL of normal liver should receive ≤15 Gy in three to five fractions. Incorporating data from published prospective studies, QUANTEC, and American Association of Physicists in Medicine recommendations, the American Society for Radiation Oncology (ASTRO) published a practice guideline. The guideline provides recommended dose constraints for uninvolved liver and bowel structures across different fractionation schedules[137] (Table 66.10).

TABLE 66.10 RECOMMENDED DOSE CONSTRAINTS FOR UNINVOLVED LIVER AND BOWEL STRUCTURES

OARs	Ultrahypofx (3 fx)	Ultrahypofx (5 fx)	Moderate Hypofx (15 fx)	Standard fx (≥20 fx)	Toxicity End Point
Uninvolved liver, noncirrhotic (MLD)	Mean <1,200-1,500 cGy ≥700 cc <1,900 cGy	Mean <1,500-1,800 cGy >700 cc <2,100 cGy	Mean <2,400 cGy	Mean <3,200 cGy	RILD
Uninvolved liver, CP class A (MLD)	Mean <1,000-1,200 cGy	Mean <1,300-1,500 cGy ≥700 cc <1,500 cGy	Mean <2,000 cGy	Mean <3,000 cGy	CP increase ≥2 at 3 mo RILD
Uninvolved liver (MLD) CP class B7	Not recommended	Mean <800-1,000 cGy ≥500 cc <1,000 cGy	Mean <1,600 cGy	Mean <2,400 cGy	CP increase ≥2 at 3 mo RILD
Central bile ducts	D0.03 cc <3,570 cGy	D0.03 cc <4,050 cGy			Stenosis
Stomach	D0.03 cc <2,200 cGy D10 cc <1,650 cGy	D0.03 CC <3,200 cGy D10 cc <1,800 cGy	D0.03 cc <4,200 cGy	D0.03 cc <5,400 cGy V45 Gy <33.3% V40 Gy <66.7%	Ulcer
Duodenum	D0.03 cc <2,200 cGy D5 cc <1,650 cGy	D0.03 cc <3,200 cGy D5 cc <1,800 cGy	D0.03 cc <4,500 cGy	D0.03 cc <5,400 cGy	Ulcer
Small bowel	D0.03 cc <2,500 cGy D5 cc <1,800 cGy	D0.03 cc <3,200 cGy D5 cc <1,950 cGy	D0.03 cc <4,500 cGy	D0.03 cc <5,400 cGy V45 Gy <195 cc	Ulcer
Large bowel	D0.03 cc <2,800 cGy D20 cc <2,400 cGy	D0.03 cc <3,400 cGy	D0.03 cc <4,500 cGy	D0.03 cc <6,000 cGy V55 Gy <5 cc	Ulcer

OARs	Ultrahypofx (3 fx)	Ultrahypofx (5 fx)	Moderate Hypofx (15 fx)	Standard fx (≥20 fx)	Toxicity End Point
		D20 cc <2,500 cGy		V45 Gy <60 cc V35 Gy <150 cc V30 Gy <200 cc	

CP, Child-Pugh; MLD, mean liver dose; OAR, organ at risk; RILD, radiation-induced liver disease; x, fractions.
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Acute and Late Complications

After undergoing radiation treatment for HCC, patients may experience acute complications, such as generalized fatigue, temporary elevation of liver enzymes, nausea and vomiting (especially for tumors in the left lobe of the liver), fever, and pancytopenia.[99,105] Subacute and late complications include hepatic failure, radiation pneumonitis, and gastrointestinal bleeding. Extra caution is necessary for tumors located in the inferior portion of the right lobe of the liver where the duodenum and jejunum are in close proximity, particularly if radiation doses exceed 50 Gy.[111,138] Life-threatening complications such as hepatic failure can be avoided by adhering to the recommended radiation dose limits for the aforementioned OARs.

Stereotactic Body Radiation Therapy and Other Local Treatment Modality

Stereotactic Body Radiation Therapy and Radiofrequency Ablation

RFA is the recommended alternative curative approach for patients who are not candidates for surgical resection or transplantation. However, RFA use may be limited by tumor size or location, such as tumors that are more than 4 to 5 cm in size and those adjacent to the gallbladder, liver hilum, major vessels, bowel, stomach, or the diaphragm. SBRT may be a good alternative in such situations.[139] No randomized trials directly comparing SBRT with RFA have been published. According to three meta-analyses comparing SBRT with RFA, while the local control rate achieved by SBRT was equivalent to or higher than by RFA, the survival rate after SBRT was lower in two of those three studies. This may be explained by differences in tumor burden or baseline liver function.[140] Nevertheless, SBRT has been recommended in cooperative group guidelines from many countries as an alternative to RFA.[141]

Combined Transarterial Chemoembolization and Radiation Therapy

TACE alone rarely results in complete pathologic remission, especially for larger tumors (>3 cm).[142,143] Additional therapy is required to eradicate residual disease to achieve longer term control of HCC. The combination of TACE and CRT shows promising results in treating large HCC (Table 66.11). Guo and Yu[144] reported 107 patients with large unresectable HCC who underwent TACE followed by external beam irradiation. The tumors ranged from 5 to 18 cm in size. After a median follow-up of 24 months, the cumulative survival rates at 3 and 5 years were 28.4% and 15.8%, respectively, with a median survival time of 18 months. Cheng et al[99] treated 17 patients with unresectable HCC using TACE and CRT. The mean tumor size was 8.6 cm (range, 3.7-18 cm). The 2-year overall survival rate was 58%, with 83% local progression-free tumor control. After 24 months of follow-up, median survival had not been reached, and 4 of 17 patients remained progression free (Figure 66.2). Another study that combined TACE and local RT in 50 patients with

unresectable HCC reported a partial response rate of 66% and a 3-year survival rate of 43%.[138] Wu et al[145] treated 94 patients with HCC with 3DCRT combined with TACE. The response rate was 90.5%. The overall survival rates at 1, 2, and 3 years were 93.6%, 53.8%, and 26.0%, respectively, with a median survival of 25 months. Patients with portal vein branch thrombosis may benefit from combined treatments. Tazawa et al[146] reported 19 patients with a tumor thrombus in the first branch of the portal vein who received 3DCRT with TACE. Eleven (58%) patients had an objective response, and the 1-year survival rate was 41%. A systematic review and meta-analysis of 25 clinical trials comparing TACE plus RT with TACE alone concluded that the combination was beneficial in terms of significantly improved 1- and 5-year survival rates (OR = 1.36 and 3.98) and complete response rates (OR = 2.73). However, patients receiving TACE plus RT had a higher incidence of complications such as gastroduodenal ulcers and impaired liver function (elevated alanine transaminase [ALT] and total bilirubin levels) than patients receiving TACE alone (OR = 12.8).[147]

TABLE 66.11 INCIDENCE OF ERECTILE DYSFUNCTION AFTER RADIATION THERAPY FOR PROSTATE CANCER

Study	Treatment	Follow-Up (Months)	Pre-RT Potency (No ED)	Post-RT Potency (No ED)
Chen et al[148]	IMRT	24	100%	73%
Hoffman et al[149]	IMRT	60	78%	50%
Friedland et al[150]	SBRT	24	100%	82%
Chen et al[151]	SBRT	28	100%	79%
Obayomi-Davies et al[152]	SBRT	24	100%	54%
Nobes[153]	LDR	24	100%	62%
Solan[154]	LDR	26	100%	77%
Taira[155]	LDR	84	100%	56%

ED, erectile dysfunction; IMRT, intensity-modulated radiotherapy; SBRT, stereotactic body radiotherapy; LDR, low dose rate brachytherapy.

Adapted from Hunt AA, Choudhury KR, Nukala V, et al. Risk of erectile dysfunction after modern radiotherapy for intact prostate cancer. *Prostate Cancer Prostatic Dis*. 2021;24(1):128-134.

For patients with HCC with macrovascular invasion, systemic treatments like sorafenib had been the only option. A randomized trial by Yoon et al[156] compared sorafenib with TACE plus external beam RT (45 Gy, with 2.5-3 Gy per fraction). The combination significantly improved the 12-week progression-free survival (86.7% vs 34.3%), objective response rate (33.3% vs 2.2%), time to progression (31.0 vs 11.7 weeks), and overall survival (55 vs 43 weeks) compared to sorafenib alone. The rates of serious adverse events were similar in both arms. In addition, five (11.1%) patients in the TACE-RT group were able to undergo curative surgical resection due to downstaging. No patients in the TACE-RT group developed hepatic decompensation, leading to treatment withdrawal.

Particle Therapy

Charged particle therapy, which includes proton beam therapy (PBT) and carbon ion radiotherapy (CIRT), is increasingly used to treat HCC. By leveraging the physical advantage of Bragg peak, particle therapy may allow the preservation of more surrounding healthy liver tissue based on

dosimetric studies. CIRT also has higher relative biologic effectiveness, allowing for increased hypofractionation regimens. Some institutions have reported promising results, with high rates of local control of cancer and overall survival as well as low incidences of hepatotoxicity.[157] A small, randomized trial of 69 patients compared PBT (70.2 Gy equivalent in 15 fractions) with TACE and showed a trend toward improved local control and progression-free survival and fewer hospitalization days. Among 22 patients who underwent liver transplantation (12 PBTs and 10 TACEs), the pathologic complete response rate was 25% for PBT and 10% for TACE. However, overall survival rates were similar.[158] More comparative studies and randomized clinical trials are needed to confirm the clinical benefit of particle therapy compared to photon-based RT or other liver-directed therapies.

Systemic Treatment

For patients with advanced HCC not suitable for any locoregional treatment or with distant metastases, systemic therapy is recommended for palliation. There have been drastic changes in the medical treatment for HCC over the past decade. Thanks to a series of successful clinical trials, molecular targeted therapy and immunotherapy are now recommended over cytotoxic chemotherapy, and the survival rate of patients with advanced disease has gradually increased.

Chemotherapy

HCC shows only modest responses to most conventional cytotoxic chemotherapy agents, and there is no clear evidence of a survival benefit for any regimen. Hence, chemotherapy is less frequently used in clinical practice today. Some historically active drugs include gemcitabine, cisplatin, doxorubicin, oxaliplatin, and 5-fluorouracil (5-FU).

Molecular Targeted Therapy

In 2000, Hanahan and Weinberg[159] summarized the six hallmarks of cancer: self-sufficiency in growth signals, insensitivity to antigrowth signals, evasion of apoptosis, sustained angiogenesis, limitless replicative potential, and tissue invasion and metastasis. Advances in molecular biology have uncovered the structures and functions of molecules in signaling pathways associated with cancer cell growth. These have led to the development of molecular agents targeting specific molecules or pathways that drive tumor growth and survival. Molecular targeted therapy seeks to disrupt the cancer's ability to proliferate while sparing healthy cells. Molecular targeted therapy targeting the epidermal growth factor receptor and vascular endothelial growth factor (VEGF) signaling pathways has exhibited potential in inhibiting HCC tumor growth.[160] Thalidomide, a sedative with antiangiogenic activity previously associated with severe fetal malformations but highly effective for myeloma, has limited value in the treatment of HCC.[161,162] Sorafenib was the first active multitarget tyrosine kinase inhibitor for advanced HCC targeting VEGF, the platelet-derived growth factor receptor, and Raf and was approved by the U.S. Food and Drug Administration (FDA) in 2007. The SHARP phase 3 randomized trial showed that, compared with placebo, sorafenib significantly extended overall survival (10.7 vs 7.9 months) and median time to radiologic progression (5.5 vs 2.8 months).[163] The result was confirmed by a similar trial conducted in the Asia-Pacific region.[164] Sorafenib remained the only approved targeted agent for a decade, until another multi-kinase inhibitor, lenvatinib, was proven noninferior to sorafenib in the first-line setting. In the REFLECT phase 3 randomized noninferiority trial,[165] median survival times were 13.6 months for patients who received lenvatinib and 12.3 months for patients who received sorafenib (hazard ratio 0.92, 95% CI 0.79-1.06). Other approved second-line targeted agents for

patients whose disease progressed after or were intolerant to sorafenib include regorafenib,[166] cabozantinib,[167] and ramucirumab.[168] Common side effects of multi-kinase inhibitors include hypertension, hand-foot skin reaction, anorexia, and fatigue.

Some clinical studies showed benefits in local control by combining sorafenib with conventional irradiation.[169,170] However, the combination of sorafenib with radiation should be given cautiously. A single 8-Gy irradiation to the lumbar spine has been reported to be associated with the complication of bowel perforation.[171] We recommend stopping antiangiogenic agents during RT.

The NRG/RTOG 1112 trial was a randomized phase 3 trial comparing SBRT followed by sorafenib with sorafenib alone. The trial ended early. However, with 177 randomized patients, adding SBRT improved overall survival (15.8 vs 12.3 months, $P = .042$ after adjustments) and progression-free survival (9.2 vs 5.5 months, $P = .0001$), with no observed increase in adverse reactions and a strong suggestion for quality of life benefit at 6 months.[136] Therefore, adding SBRT may have the potential to further improve the treatment outcomes of targeted therapy.

Immunotherapy

Most patients with HCC have underlying cirrhosis and viral hepatitis, which cause chronic inflammatory conditions in the liver. The liver is a central immunomodulator that ensures organ and systemic protection while maintaining immune tolerance. Deregulation of this tightly controlled liver immunologic network is a hallmark of chronic liver disease and HCC, providing a rationale for the exploration of immunotherapy.[172] Inhibitors of immune checkpoints such as cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), programmed cell death protein-1 (PD-1), and programmed cell death ligand 1 (PD-L1) were developed and tested. A phase I/II study including 262 patients demonstrated that the PD-1 inhibitor, nivolumab, was safe and effective in advanced HCC. The overall response rate was 20%, and the responses were more durable than with targeted agents (median 17 months). Common adverse effects included skin rash, pruritus, and elevation of aspartate transaminase, ALT, lipase, and amylase.[173] The trial did not observe excessive toxicity among patients with HBV or HCV infection. Another anti–PD-1 agent, pembrolizumab, also showed a response rate of 17% in the KEYNOTE-224 trial.[174]

VEGF can have immunosuppressive effects, and VEGF expression in HCC cells has been associated with expression of immune-modulating molecules on endothelial cells, including PD-L1.[175] Therefore, VEGF inhibitors may potentiate the effect of immune checkpoint inhibitors. The IMBrave150 trial was a phase 3 randomized trial comparing atezolizumab, an anti–PD-L1 inhibitor, plus bevacizumab with sorafenib for patients with advanced HCC (mostly BCLC stage C) with Child-Pugh A classification.[176] The combination significantly improved 12-month overall survival (67.2% vs 54.6%, $P < .001$) and median progression-free survival (6.8 vs 4.3 months, $P < .001$). Atezolizumab plus bevacizumab is recommended as a first-line regimen, and several other checkpoint inhibitor and VEGF inhibitor combinations are also being tested in clinical trials.

Combinations of immune checkpoint inhibitors have also been investigated. The combination of CTLA-4 and PD-L1 inhibitors has shown additive antitumor activity associated with complementary immunostimulatory effects. In the randomized 3-arm phase 3 HIMALAYA trial, the STRIDE regimen, tremelimumab (anti–CTLA-4) plus durvalumab (anti–PD-L1), was compared to durvalumab alone and sorafenib. STRIDE significantly improved median overall survival versus sorafenib (16.43 vs 13.77 months). Durvalumab monotherapy was noninferior to sorafenib (16.56 vs 13.77 months).[177]

Areas of Failure and Cause of Death

Survival with various treatments depends largely on HCC clinical stage and liver function. The 5-year survival in resectable HCC after partial hepatectomy is 50% to 73% in stage I patients, 30% to 56% in stage II patients, 10% to 29% in stage III patients, and approximately 10% in stage IV patients.[178,179] The 5-year survival rate for patients with unresectable HCC is usually <10%.[180] The major cause of failure after resection is tumor recurrence within the liver. Extrahepatic metastasis in advanced HCC has become more frequently encountered in recent years, probably due to improvements in survival from intrahepatic disease.[181,182] Patients with HCC mostly die of liver tumor progression, treatment-related complications (eg, infection), or underlying disease such as complications of chronic hepatitis with cirrhosis (eg, hepatic failure, variceal bleeding, hepatorenal syndrome).

Future Study

Currently, the prognosis for patients with HCC following various treatments remains unsatisfactory, primarily due to the high rates of intrahepatic recurrence. Future efforts should focus on preventing HBV infection by increasing vaccination and curbing HCV infection through rigorous blood product screening and adherence to universal needle precautions, particularly in endemic regions. New antiviral agents targeting HCV have been successful in managing infected individuals.

Recently, MR-guided linear accelerators (MR-Linac) combine an MRI scanner with a linear accelerator and can track and visualize tumors in real time. Compared with cone-beam CT, MR-Linac can provide better soft tissue contrast, especially in the abdominal-pelvic region. This, along with real-time tracking, improves localization of the tumor before and during the radiation treatment, allowing for minimization of treatment margins.[183] MR-Linac also provides the opportunity for daily adaptive planning and dose escalation. Treatment results from Washington University are encouraging. With a dose of 50 Gy in five fractions, the 2-year local progression rate was only 9.8%.[184]

OTHER PRIMARY LIVER TUMORS

Primary sarcomas of the liver are extremely rare in adults and represent only 1% of primary liver cancers.[185] Leiomyosarcoma is the most common histologic type, followed by malignant fibrous histiocytoma, epithelioid hemangioendothelioma, and angiosarcoma.[186] Some patients with angiosarcoma have a history of occupational exposure to vinyl chloride monomer.[187] The severity of the histologic grade determines overall patient survival. Complete resection offers a chance of long-term survival.[185]

A hemangioma is a benign lesion and is generally asymptomatic. For symptomatic hemangiomas, treatments include steroids, IFN-α, arterial embolization, and surgery.[188] If patients fail the above treatments, RT may play a role. Long symptom-free duration has been obtained with doses to the involved area as low as 13 to 30 Gy in 2.5 to 4 weeks.[188]

HEPATOBLASTOMA

Hepatoblastoma is the most common malignant liver tumor of childhood. Hepatoblastoma occurs most commonly (~48%) in young children (median age, 13-16 months) and usually presents in adults at an advanced stage with grave prognosis.[189,190] Children with familial adenomatous polyposis of the colon and rectum are at high risk for hepatoblastoma. The risk of hepatoblastoma in these children is 700 to 7,500 times that of the general population.[191,192] Chemotherapy combined with surgery has resulted in dramatic improvements in prognosis.[193] With the combination of

chemotherapy and surgery, 75% to 80% of patients may be cured.[189] Preoperative chemotherapy often converts tumors from unresectable to resectable and may reduce blood loss and technical complications.[194]

BILIARY TRACT CANCER

Biliary tract cancers consist of cancer of the gallbladder, the bile ducts, and the ampulla of Vater. They are clinically highly aggressive tumors and are usually discovered at a locally advanced stage of disease. The current edition of the WHO classification of digestive system tumors classifies these cancers into primary liver tumors and extrahepatic biliary tract tumors.[1] Biliary tract cancer can appear in small intrahepatic bile ducts as well as large intrahepatic and extrahepatic bile ducts. The term *cholangiocarcinoma* is used to describe cancers arising from the epithelial cells of the bile ducts. At present, biliary tract cancers that can be completely removed with surgical excision are associated with good long-term survival. For unresectable tumors, the treatment goal is relief of obstructive jaundice via biliary drainage and management of biliary tract infection, pain, and ascites.

CHOLANGIOCARCINOMA

Topographic Anatomy

The bile ducts originate within the liver, with the left and right hepatic ducts joining to form the common hepatic duct. At the origin of the cystic duct, it becomes the common bile duct. The cystic duct drains bile from the gallbladder into the common bile duct. The gallbladder is adjacent to the undersurface of the liver.

There is a rich lymphatic network along the submucosa of bile ducts. The primary lymphatic drainage of the biliary tract is to the pericholedochal, periportal, hepatoduodenal ligament, common hepatic artery, and pancreaticoduodenal lymph nodes.[195,196]

Epidemiology and Risk Factors

Cholangiocarcinoma is a rare tumor in developed countries; there are approximately 2,000 to 3,000 cases per year in the United States. However, it is one of the most common cancers in endemic areas of developing countries, with incidence rates as high as 87 per 100,000 people in northeast Thailand.[197] Cholangiocarcinoma accounts for about 15% of primary liver cancer worldwide. However, the proportion varies regionally: 20% in Western countries, <10% in Asian nations, and as high as 90% in northern Thailand.[197,198]

A number of risk factors have been identified as important in the development of cholangiocarcinoma; most share a history of long-standing inflammation and chronic injury of the biliary epithelium.[199] The major risk factor in Western countries is primary sclerosing cholangitis, which is closely associated with chronic inflammatory bowel disease, particularly ulcerative colitis.[200] The risk of developing cholangiocarcinoma is higher in patients with primary sclerosing cholangitis and ulcerative colitis with colonic neoplasms than in patients with primary sclerosing cholangitis and ulcerative colitis without colonic neoplasms.[200] Studies in Japan and the United States have shown that chronic hepatitis C infection elevates the incidence of ICC with an OR between 4 and 17.[201,202] In Asia, chronic infections of the biliary tract related to infestation by certain liver flukes, such as *Clonorchis sinensis* and *Opisthorchis viverrini*, are associated with cholangiocarcinoma and hepatolithiasis.[196] Hepatolithiasis itself is also a risk factor for cholangiocarcinoma. Five to 10% of patients with intrahepatic stones develop this

complication.[203,204] Moreover, the combination of liver fluke infestation and nitrosamine exposure may explain the very high incidence of cholangiocarcinoma in northeast Thailand.[205]

Other risk factors, although rare, include congenital fibropolycystic disease of the biliary system, such as choledochal cysts and Caroli disease (cystic dilatation of intrahepatic bile ducts).[206] The observed incidence and mortality of ICC have increased in the past three decades in Japan, the United States, and the United Kingdom.[21,207,208] However, the incidence of extrahepatic cholangiocarcinoma remains almost the same.[209] In the United States, the age-adjusted mortality rate has increased from 0.07 per 100,000 in 1973 to 0.69 per 100,000 in 1997. The estimated annual percent increase in mortality rate was 9.44% during this period. Between 1973 and 2012, the incidence of ICC increased from 0.44 to 1.18 cases per 100,000, representing an annual percentage increase of 2.3%; this trend has accelerated during the past decades to an annual percentage increase of 4.36%.[209] Better case ascertainment and diagnosis from improved imaging, use of image-guided biopsies, or increased use of endoscopic retrograde cholangiopancreatography (ERCP) cannot fully explain this observation.[208,210]

Diagnosis

The most common presenting symptoms of biliary tract cancer are caused by obstruction of the bile duct. These include painless jaundice, clay-colored stools, tea-colored urine, and pruritus. Other signs and symptoms include abdominal pain, fever, generalized malaise, abdominal distention, abdominal fullness, anorexia, and weight loss. The spectrum of cholangiocarcinoma can be classified into three broad groups: (a) intrahepatic, (b) perihilar, and (c) distal tumors. The age of onset is similar among these three groups and ranges from 60 to 65 years.[211] Patients with extrahepatic tumors usually present with jaundice, alcoholic stools, and tea-colored urine. Patients with intrahepatic tumors are less likely to be jaundiced and more likely to present with abdominal symptoms and more advanced disease.

There are no reliable screening methods, and early diagnosis is almost impossible even in patients with high-risk conditions, such as primary sclerosing cholangitis, parasitic infestation, and hepatolithiasis.[212] Some patients are diagnosed when blood work demonstrates elevation of alkaline phosphatase and γ-glutamyl transferase. Ultrasonography and CT are the primary tools used initially to evaluate biliary tract tumors (Table 66.12). Further tests include percutaneous transhepatic cholangiography; ERCP with brush cytology; serum carbohydrate antigen 19-9 (CA 19-9) levels; radiologic imaging with dynamic CT scan, MRI, or both; and angiography.

TABLE 66.12 DIAGNOSTIC WORKUP FOR CARCINOMA OF THE BILE DUCT

General
History
Physical examination
Laboratory studies
Complete blood cell counts
Blood chemistry profile including liver function studies
Tumor markers: CA 19-9, CEA
Radiographic studies
Standard
Computed tomography scan
Ultrasonography
Transhepatic cholangiography
Endoscopic retrograde cholangiopancreatography

Optional
Endoscopic ultrasound
Magnetic resonance cholangiopancreatography
Dynamic computed tomography scan
Arteriography

CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen.
Modified from Gunderson LL, Willett CG. Pancreas and hepatobiliary tract. In: Perez CA, Brady LW, eds. *Principles and Practice of Radiation Oncology*. 3rd ed. Lippincott-Raven; 1997.

A serum CA 19-9 value >100 U/mL has a sensitivity of approximately 75% and a specificity of approximately 80%.[213] The optimal cutoff value for serum CA 19-9 that best discriminates between benign and malignant biliary tract diseases is influenced by the presence of cholangitis. Thus, in patients with symptoms of acute cholangitis, serum CA 19-9 concentrations should ideally be reevaluated after recovery. The sensitivity of serum carcinoembryonic antigen (CEA) is low, helpful only in one-third of patients.[214] Biliary CEA levels increase significantly in patients with cholangiocarcinoma and also in patients with intrahepatic cholelithiasis (average 50.2-57.4 ng/mL) compared to patients with benign strictures (average 10.1 ng/mL) and patients with sclerosing cholangitis and choledochal cysts (average 20.0-21.6 ng/mL).[214] Serum AFP may increase in some cases of cholangiocarcinoma, and this would suggest a diagnosis of mixed HCC and cholangiocarcinoma.[215]

Pathology

Cholangiocarcinomas arise from the epithelium of the biliary tract. There are two main histologic subtypes: bile ductular type (mixed), arising from small intrahepatic bile ducts, and bile duct type (mucinous), arising from large intrahepatic and extrahepatic bile ducts.[216] Histologic diversity in cholangiocellular carcinoma reflects the different cholangiocyte phenotypes.[217] The majority of these cancers are adenocarcinomas (>90%). Squamous cell carcinoma is the second most common histologic type. Rare histologies include mucoepidermoid carcinoma, cystadenocarcinoma, and carcinoid tumor.

Adenocarcinomas are divided into three types: sclerosing, nodular, and papillary. Sclerosing tumors are characterized by an intense desmoplastic reaction. This type of tumor tends to invade the bile duct wall early and, as a result, is associated with low resectability and cure rates. Most cholangiocarcinomas are of this type.[211] Nodular cholangiocarcinomas are also highly invasive tumors. Most patients have advanced disease at diagnosis. Resection and cure rates are both very low. In contrast, papillary-type tumors usually present as masses in the lumen of bile ducts, causing biliary obstruction early in the disease course. Therefore, these tumors have a more favorable prognosis.[218] Microscopically, cholangiocarcinoma ranges from well differentiated to undifferentiated. Cells tend to be cuboidal or low columnar and resemble biliary epithelium; mucin is always demonstrable in the cytoplasm. Readers should be aware that bile duct obstruction can be associated with reactive hyperplasia of subepithelial mucous glands in the presence or absence of cholangiocarcinoma.[219] Cholangiocarcinomas frequently invade lymphatic, perineural, and periductal spaces and portal tracts. Spread along the lumen of large bile ducts can also be seen, especially in perihilar cholangiocarcinoma.[220]

The positive association of cholangiocarcinoma with CEA, CA 19-9, and immunohistochemical staining with cytokeratin-19 can help with its differentiation from HCC.[221] Mutations in the p53 tumor suppressor gene and K-RAS proto-oncogene have been identified in cholangiocarcinoma.[222-224] p53 overexpression and K-RAS mutations are associated with a shortened survival.[222] Recent

marker analysis of cholangiocarcinoma from The Cancer Genome Atlas revealed a distinct subtype enriched for isocitrate dehydrogenase (IDH) mutants.[225] IDH mutations block normal cellular differentiation and promote tumorigenesis via the abnormal production of the oncometabolite D-2-hydroxyglutarate. Mutant IDH is a therapeutic target of tumor growth inhibitors under development.[226]

Pathways of Tumor Spread

Bile duct cancers commonly spread by direct extension through the biliary tract and the abundant lymphatic network in the submucosa. These tumors also commonly involve the surrounding structures by direct invasion. Lymph node metastases in the porta hepatis and celiac axis are common. The lymph nodes in the porta hepatis are more frequently involved with tumors in the intrahepatic duct and proximal extrahepatic bile duct, while the pancreaticoduodenal nodes are more often involved with tumors in the distal bile duct.[220,227]

The incidence of lymph node metastasis in ICC ranges from 50% to 60%.[228,229] ICCs, irrespective of their intrahepatic location, mainly spread to nodes in the hepatoduodenal ligament, then to the para-aortic, retropancreatic, or common hepatic artery nodes. In addition, the left peripheral type or hilar type of cholangiocarcinoma tends to spread along the left gastric nodes through the lesser curvature.[229] Lymph node metastasis in perihilar cholangiocarcinoma is common, occurring in about half of all patients, with a frequency of 43% in pericholedochal nodes, 31% in periportal nodes, 27% in common hepatic nodes, and 15% in posterior pancreaticoduodenal nodes. The celiac and superior mesenteric nodes are rarely involved.[220]

Lymph node metastasis in distal duct cancer is commonly observed near the pancreaticoduodenal region. Yoshida et al[227] examined 20 consecutive patients with distal bile duct cancer who underwent pancreaticoduodenectomy with extended lymph node dissection. Histologic evidence of lymph node metastasis was seen in 55% of the patients. The areas with frequent metastases were the posterior pancreaticoduodenal lymph nodes (35%), the nodes around the hepatoduodenal ligament (35%), and those around the common hepatic artery (30%). Para-aortic lymph node involvement occurred in 25% of patients and was significantly associated with pancreatic parenchymal invasion.

Staging for Cholangiocarcinoma

The AJCC TNM classifications (eighth edition) for ICC are shown as follows:

T category:

T1: solitary tumor without vascular invasion

T1a: solitary tumor ≤5 cm

T1b: solitary tumor >5 cm

T2: solitary tumor with intrahepatic vascular invasion or multiple tumors, with or without vascular invasion

T3: tumor perforating the visceral peritoneum

T4: tumor involving local extrahepatic structures by direct invasion

N category:

N0: no regional lymph node metastasis

N1: regional lymph node metastasis present

M category:

M0: no distant metastasis

M1: distant metastasis present

The complete staging groups are listed in Table 66.13. The AJCC TNM staging for both perihilar and distal cholangiocarcinoma was revised in 2017 (Table 66.13). The N category is classified based on the number of positive nodes (N1: one to three positive nodes; N2: four or more positive nodes). The T category of perihilar cholangiocarcinoma is as follows: T1 is a tumor confined to the bile duct, T2 is a tumor invading beyond the bile duct wall, T3 is a tumor invading unilateral branches of the portal vein or hepatic artery, and T4 is a tumor invading the main portal vein or its branches bilaterally. The T category in distal bile duct cancer is classified based on the depth of invasion (T1: <5 mm; T2: 5-12 mm; T3: >12 mm).

TABLE 66.13 AJCC STAGE GROUPS BY TNM CLASSIFICATION (EIGHTH EDITION)

Intrahepatic Cholangiocarcinoma
Stage IA: T1aN0M0
Stage IB: T1bN0M0
Stage II: T2N0M0
Stage IIIA: T3N0M0
Stage IIIB: T4N0M0, or any T, N1M0
Stage IV: any T, any N, M1
Perihilar Cholangiocarcinoma
Stage I: T1N0M0
Stage II: T2a-bN0M0
Stage IIIA: T3N0M0
Stage IIIB: T4N0M0
Stage IIIC: any T, N1M0
Stage IVA: any T, N2M0
Stage IVB: any T, any N, M1
Distal Cholangiocarcinoma
Stage I: T1N0M0
Stage IIA: T2N0M0, T1N1M0
Stage IIB: T2-T3N1M0
Stage IIIA: T1-T3N2M0
Stage IIIB: T4, N1-N2, M0
Stage IV: any T, any N, M1

AJCC, American Joint Committee on Cancer.

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The primary prognostic factors for cholangiocarcinoma include resectability, regional lymph node metastasis, and distant metastasis. Multivariate analysis using a Cox proportional hazards model demonstrated that multifocality, extrahepatic extension, grade, node positivity, and age >60 years (MEGNA) are independently associated with decreased overall survival. The MEGNA prognostic score was developed to improve prognostication over the AJCC seventh staging system.[230] However, one report showed that it did not perform better than the AJCC eighth staging system.[231]

General Management

Surgical resection currently is the only potentially curative treatment for cholangiocarcinoma. According to data from a large series, the resection rates for intrahepatic, perihilar, and distal lesions are 50%, 56%, and 91%, respectively.[211] The 5-year survival rates after resection range from 10% to

40%, depending on the location of the primary tumor.[211] Patients with unresectable cholangiocarcinoma generally have a very poor prognosis. Chemotherapy and RT have been the mainstay treatments, but the results are disappointing.[232]

Intrahepatic Cholangiocarcinoma

ICC accounts for 5% to 10% of all biliary tract cancers and 10% to 20% of primary liver malignancies. Only 30% to 50% of patients are eligible for surgical resection.[233,234] Postsurgical prognosis is notably poorer in patients with lymph node metastasis, regardless of the site of nodal metastasis. The 5-year survival rate for patients with lymph node metastasis is significantly lower than for those without (0% vs 51%; $P < .0001$).[229] Key factors influencing tumor recurrence include lymph node metastasis, the presence of satellite nodules, positive resection margin, tumor size, and bilobar distribution.[229,235,236] Following surgical resection of ICC, the most common sites for disease recurrence are the liver (56%), regional lymph nodes (20%), and peritoneal seeding (24%).[237]

The role of postoperative adjuvant RT, with or without chemotherapy, in the management of ICC is controversial. Limited low- to moderate-quality retrospective data suggest that adjuvant external beam RT, primarily in combination with concurrent chemotherapy, may improve locoregional control and relapse-free survival with a trend toward overall survival improvement.[137] Future phase II studies would benefit from a rational delineation of radiation fields based on patterns of failure analysis and lymph node spread.

For unresectable ICC, systemic therapy is the mainstay of treatment. However, historical median overall survival and intrahepatic progression-free survival rates after chemotherapy alone are less than 1 year. Studies suggest that consolidative RT after chemotherapy, or as salvage therapy after disease progression, may prevent liver failure caused by vascular obstruction and improve local control and overall survival.[137] The 1-year survival for patients treated with external beam radiation ranged from 39% to 70%.

Additional treatments for select patients with unresectable ICC include ablation, TACE, TARE, and RT. The efficacy of intra-arterial therapy (TACE, DEB-TACE, or TAE) was assessed in a multicenter retrospective analysis (median tumor size 8.1 cm; 47.5% of patients with a solitary lesion), which reported a median overall survival of 13.2 months with no significant difference in patient responses to different intra-arterial therapies.[238]

Emerging data suggest that liver transplantation may be an option in patients with ICC.[239] In a multinational cohort of patients with cirrhosis who underwent transplantation for presumed small HCC, incidental ICC was found on explant pathology. The 1-, 3-, and 5-year actuarial survival rates in patients with very early ICC (≤2 cm) were 93%, 84%, and 65%, respectively.[240] Lunsford et al[241] reported a 5-year survival rate of 83.3% in patients with locally advanced, unresectable ICC who underwent transplantation after neoadjuvant chemotherapy and were stable for at least 6 months, although the recurrence-free survival was only 50%.

Perihilar Cholangiocarcinoma

Perihilar cholangiocarcinoma, also known as Klatskin tumors[242] when involving the bifurcation of the hepatic duct, is the most common biliary tract carcinoma, comprising 65% to 70% of all cases (Figure 66.5).[211] These tumors are classified by Bismuth et al[243] into several types based on their location: Type I tumors are below the confluence of the left and right hepatic ducts; type II tumors reach this confluence; type IIIa and IIIb tumors obstruct the common hepatic duct and either the right or left hepatic duct; and type IV tumors are multicentric or involve the confluence as well as both the right and left hepatic ducts.

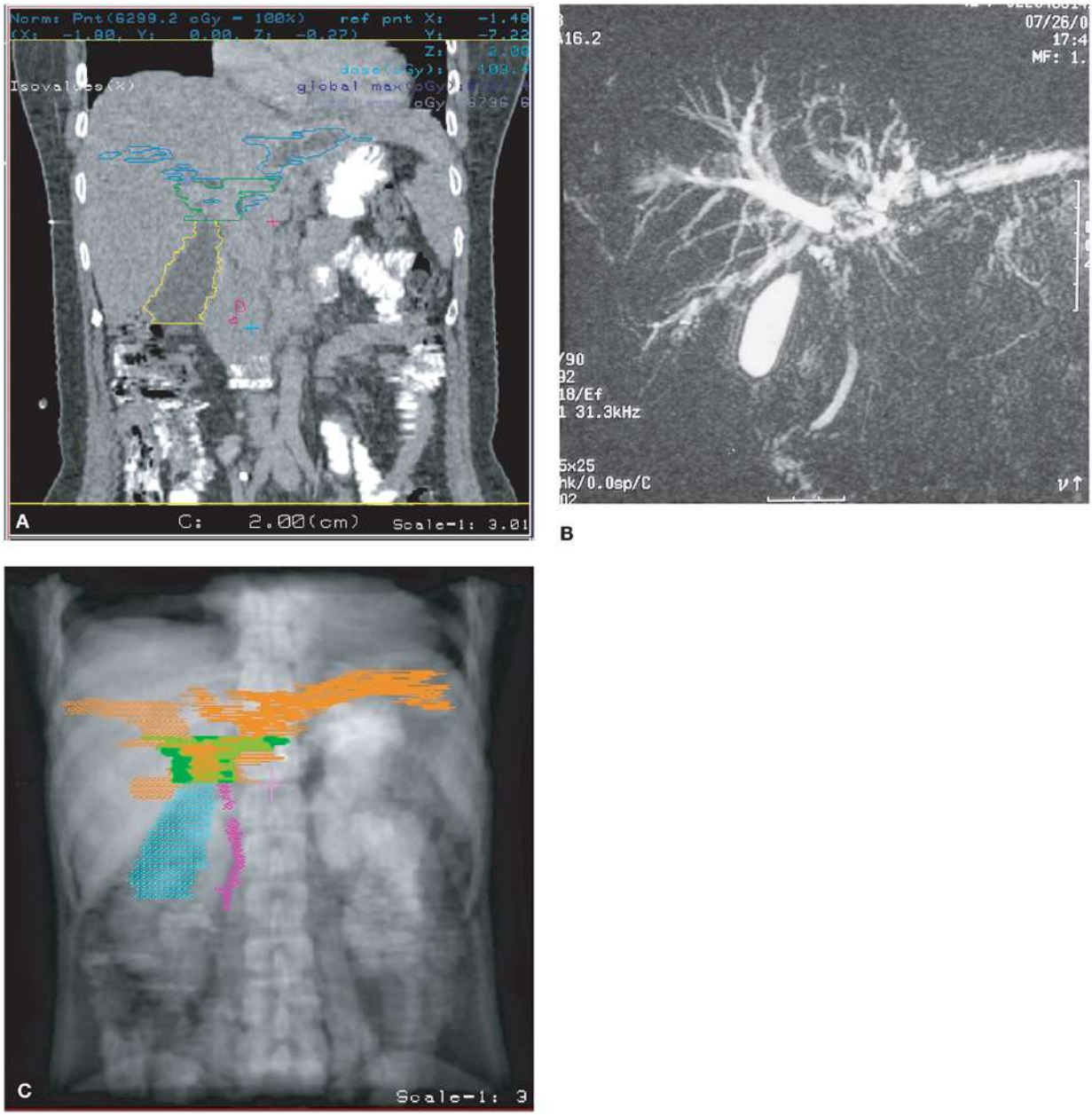

FIGURE 66.5 A. Computed tomography (CT) was performed in a 39-year-old woman who had cholangiocarcinoma of perihilar area. This image was reconstructed from a CT at 2-mm slice intervals. The tumor involved the right and left hepatic ducts (green line). B. Magnetic resonance cholangiopancreatography confirmed the extent of tumor involvement. C. Digital reconstruction radiography revealed the gross tumor volume (green) and clinical target volume (purple).

Surgical resection is only possible in 25% to 79% of patients. Definitive surgery often requires a combination of bile duct and liver resection, including caudate lobectomy.[244] The surgical approach to perihilar cholangiocarcinoma has become more aggressive over time. While more patients with locally advanced disease undergo surgery, the long-term survival rate has also increased.[239] In a series of 574 patients with perihilar cholangiocarcinoma undergoing surgical resection, the 5-year disease-specific survival rate was 32.5%. Between 2001 and 2010, 243 patients with R0 disease and no lymph node metastasis after resection had a 5-year survival rate of 67.1%, but 142 patients with

nodal metastasis had a 5-year survival rate of 22.1%.[245] Multivariate analysis revealed that lymph node metastasis was the strongest prognostic indicator.

The role of postoperative RT with or without chemotherapy in patients with completely resected cholangiocarcinoma remains unclear. A meta-analysis by Horgan et al[246] including 20 studies of adjuvant therapy for biliary tract cancers from 1960 to 2010 found a nonsignificant improvement in overall survival with adjuvant treatment compared to surgery alone (P = .06). However, patients treated with chemoradiotherapy (OR = 0.61) or chemotherapy (OR = 0.39) derived greater benefit than patients treated with RT alone (OR = 0.98, P = .02), particularly those with positive lymph nodes (OR = 0.49, P = .004) and R1 disease (OR = 0.36, P = .002). A meta-analysis of 21 clinical trials involving 1,465 patients with extrahepatic cholangiocarcinoma and gallbladder cancer showed significantly higher 5-year overall survival rates with adjuvant RT for patients with lymph node–positive disease (OR = 0.15) and margin-positive disease (OR = 0.40) and nonsignificantly higher 5-year overall survival rates for margin-negative disease (OR = 0.54).[247]

For unresectable perihilar cholangiocarcinoma, neoadjuvant chemoradiotherapy followed by liver transplantation is a viable treatment option. Data from the Mayo Clinic revealed that the 5-year survival in transplant patients of unresectable hilar cholangiocarcinoma after induction chemoradiotherapy was 80%; in resection-only patients, it was 21%.[248] Others also have reported similar promising results by treating these unresectable cholangiocarcinomas with induction chemoradiotherapy followed by liver transplant.[249,250] Data from 12 large-volume centers in the United States showed that patients with early-stage, unresectable perihilar cholangiocarcinoma who underwent neoadjuvant chemoradiation followed by liver transplantation had a 5-year post-transplant recurrence-free survival of 65% and an intent-to-treat survival of 53%.[239,251]

Patients with inoperable perihilar cholangiocarcinoma typically experience obstructive jaundice and initially require either endoscopic or percutaneous drainage or stent placement, or both. Although external beam RT alone is often insufficient for controlling advanced disease, a combination of external beam RT, chemotherapy, and intraluminal brachytherapy can be effective in alleviating pain and aiding in biliary decompression, occasionally leading to long-term survival. The most active chemotherapy agents include 5-FU, gemcitabine, docetaxel, and oxaliplatin,[252,253] with a median survival time ranging from 17 to 21 months.[254,255]

Distal Bile Duct Carcinoma

Primary distal bile duct adenocarcinoma, which includes carcinoma of the ampulla of Vater, accounts for 25% to 30% of all biliary tract carcinomas.[211] Surgical resection, the primary treatment modality for distal duct carcinoma, typically involves a pancreaticoduodenectomy (Whipple procedure). This procedure includes the removal of the gallbladder and bile duct, the head of the pancreas, and the first part of the duodenum.[239]

Patients with distal duct carcinoma have a higher likelihood of undergoing a curative resection compared to those with proximal duct carcinomas. A study of 680 patients from Korea compared surgical treatment outcomes of patients with perihilar and distal cholangiocarcinoma. The study reported a higher R0 resection rate (77.3% vs 89.9%, P = .001) and an improved 5-year survival rate (30.8% vs 47.8%, P = .001) in patients with distal cholangiocarcinoma. Patients with distal duct carcinoma confined to the bile duct without lymph node metastasis had the highest 5-year survival rate (64.3%).[256]

The role of postoperative RT is uncertain. A propensity-matched analysis of patients from the National Cancer Database undergoing pancreatoduodenectomy for nonmetastatic distal cholangiocarcinoma concluded that adjuvant RT was associated with a survival benefit. The median

survival was 29.3 months with adjuvant RT and 26.8 months without RT ($P < .001$). Multivariable interaction analysis showed this benefit, irrespective of nodal or margin status.[257]

Systemic Chemotherapy

Because of the high recurrence rate and suboptimal overall survival following surgery with curative intent in patients with cholangiocarcinoma, adjuvant chemotherapy has been explored in multiple nonrandomized and randomized clinical trials. The phase 2 Southwest Oncology Group (SWOG) S0809 trial evaluated adjuvant capecitabine plus gemcitabine followed by chemoradiotherapy with capecitabine for the treatment of resected extrahepatic cholangiocarcinoma and gallbladder carcinoma with pT2-4, N+, or positive resection margins. This trial reported a median overall survival of 35 months, with 2-year survival rates of 67% for R0 resections and 60% for R1 resections, surpassing historical rates of 55% and 38%, respectively. These results suggest a potential benefit with adjuvant therapy.[258] In addition, adjuvant chemotherapy alone has been shown to be a viable strategy. In the BILCAP trial, adjuvant capecitabine for 6 months following curative surgery demonstrated a significant survival benefit (median overall survival in the capecitabine arm was 53 vs 36 months in the observation group, $P = .028$) in a protocol-specified sensitivity analysis.[259]

For the treatment of advanced and metastatic cholangiocarcinoma, the most frequently used agents include 5-FU, gemcitabine, cisplatin, and oxaliplatin.[252,253] The phase 3 ABC-02 study enrolled 410 patients with locally advanced or metastatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer. As compared with gemcitabine alone, cisplatin plus gemcitabine was associated with a significant survival advantage (11.7 vs 8.1 months) without substantially increased toxicity. Cisplatin plus gemcitabine is considered the standard first-line option for the treatment of patients with advanced biliary tract cancer.[260] Gemcitabine plus S1 is noninferior to gemcitabine plus cisplatin according to a Japanese phase 3 trial.[261] In patients whose disease has progressed on gemcitabine and cisplatin, the ABC-06 study demonstrated the benefit of folinic acid, 5-FU, and oxaliplatin in the second-line setting.[262]

Targeted Therapy

Advancements in targeted therapy for cholangiocarcinoma are increasingly driven by an in-depth understanding of its molecular biology. The advent of next-generation sequencing has identified novel molecular alterations, presenting opportunities for targeted therapy.[263] Promising therapeutic molecular targets for cholangiocarcinoma include *IDH1* and *IDH2* and fibroblast growth factor receptor 2 (*FGFR2*) gene products. The genomic landscape of ICC and extrahepatic cholangiocarcinoma notably differs. FGFR2 and IDH mutations, primarily IDH1 versus IDH2, are more prevalent in ICC. In contrast, BRCA, HER2, and BRAF mutations are more common in extrahepatic cholangiocarcinoma.[264] FGFR2 alterations, including rearrangements, amplifications, and mutations, occur in 10% to 16% of patients with ICC. In 2019, the FDA granted accelerated approval for pemigatinib, an FGFR2 inhibitor, as the first targeted therapy for locally advanced or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements. The approval was based on the phase 2 FIGHT-202 trial, which showed an objective response rate of 35.5% and median progression-free survival and overall survival of 6.9 and 21.1 months, respectively.[265] Several other FGFR inhibitors, such as infigratinib, futibatinib, and derazantinib, are currently being developed.

IDH1 gene mutations, found in approximately 13% of ICC cases, are targeted by ivosidenib, a small molecule inhibitor. The phase 3 ClarIDHy trial, a randomized, double-blind, placebo-controlled study, demonstrated that ivosidenib significantly improved progression-free survival

compared to placebo (2.7 vs 1.4 months) in patients with advanced cholangiocarcinoma and IDH1 mutations who had progressed on prior therapy.[266]

Immunotherapy

PD-L1 expression has been detected in 10% to 70% of biliary tract cancer cases. However, monotherapy with PD-1/PD-L1 checkpoint inhibitors did not achieve satisfactory results in unselected patients with cholangiocarcinoma.[267] This led to an investigation of the combination of a PD-1/PD-L1 inhibitor with chemotherapy, based on evidence of the immunomodulatory effect of chemotherapy.

Both durvalumab (anti–PD-L1) and pembrolizumab (anti–PD-1) improved overall survival when combined with the standard first-line chemotherapy: gemcitabine plus cisplatin. The phase 3 TOPAZ-1 trial showed that the 24-month overall survival rate was 24.9% for durvalumab plus chemotherapy and 10.4% for placebo plus chemotherapy (hazard ratio 0.8, $P = .021$). Objective response rates were 26.7% with durvalumab and 18.7% with placebo.[268] In the KEYNOTE-966 trial, the median overall survival was 12.7 months in the pembrolizumab plus chemotherapy group versus 10.9 months in the placebo plus chemotherapy group (hazard ratio 0.83, $P = .02$).[269] Therefore, an immune checkpoint inhibitor plus gemcitabine and cisplatin is also increasingly accepted as a first-line treatment for patients with metastatic or unresectable biliary tract cancer.

Radiation Therapy

Despite advancements in systemic therapy for unresectable or advanced biliary tract cancers, the prognosis remains poor, with a median overall survival of only 11 to 12 months using systemic therapy.[260,268] Many patients with biliary tract cancer die of hepatic failure caused by local tumor progression. Palliative RT may relieve pain and biliary obstruction, but conventional RT often results in high rates of locoregional failure (60%-75%) at 1-year post-treatment, with median survival ranging from 7 to 12 months.[270,271] Local failure remains the first site of disease progression.[271] Combining RT with 5-FU–based chemotherapy is generally recommended to enhance treatment efficacy.[272,273]

SBRT, known for its ability to deliver highly conformal ablative doses of radiation, has been studied for its potential to improve RT outcomes in cholangiocarcinoma. Many prospective and retrospective series have reported encouraging local control rates. A systematic review by Frakulli et al[274] of 10 studies involving 231 patients showed that the pooled overall survival rate was 58.3% at 1 year and 35.5% at 2 years. The pooled 1-year local control rate was 83.4%. The median prescribed dose ranged between 30 and 60 Gy in three to five fractions. The reported rate of severe toxicities, including biliary stenosis, cholangitis, gastroduodenal ulcer and perforation, and liver failure, was about 10%.

RT techniques for cholangiocarcinoma closely mirror those for HCC. A notable consideration during radiation treatment is tumor movement due to respiration. To mitigate this movement and minimize the exposure of normal adjacent organs to radiation, several techniques are recommended. During simulation, oral contrast is used to clearly define the boundaries of the duodenum, and 4D CT captures the tumor's movement over the respiratory cycle, aiding in precise treatment planning. In addition, breath-holding technique and abdominal compression may be utilized to limit organ and tumor movement during radiation delivery. The critical organs that require protection include the liver, duodenum, stomach, and spinal cord. These organs are carefully considered in the planning process to ensure they receive as little radiation as possible while still effectively targeting the tumor.

Treatment Volumes

The extent of a tumor within the bile duct can be defined by percutaneous cholangiography, ERCP, and MR cholangiopancreatography. However, identifying extraductal disease noninvasively remains challenging. Surgical clip placement is useful in delineating the extrahepatic portion of ductal lesions and helps define the primary tumor bed.

To minimize errors in radiation treatment planning, it is advisable to position patients for pretreatment CT scans as they would be during treatment. Scans should be performed with 1 to 3 mm slices and use a contrast medium to reconstruct the anatomy of bile ducts and GTV (Figure 66.3). GTV is defined as any visible tumor presence on either CT or MRI. The CTV is defined as a 1- to 1.5-cm margin beyond the GTV, especially along the bile duct and potential lymphatic drainage areas, including pericholedochal, porta hepatis, hepatic artery, pancreaticoduodenal, celiac, and superior mesenteric artery nodes.[227-229,275,276]

The PTV is defined by adding a margin of 0.5 to 2 cm to the CTV, depending on the respiratory motion control method used. For SBRT, it is recommended to irradiate only the primary tumor and metastatic lymph nodes, excluding high-risk lymph node drainage areas.[277]

In 2017, Socha et al[278] refined the delineation of lymph node regions for CTV in RT planning by analyzing the postoperative nodal involvement and recurrence data from existing research. Their findings suggested that previous RT plans might have missed some lymph nodes, such as the para-aortic and superior mesenteric lymph nodes. Conversely, certain lymph nodes, such as celiac lymph nodes in the middle or distal extrahepatic cholangiocarcinoma, were sometimes unnecessarily included in the target area. They proposed specific lymph node areas be included in the CTV depending on the primary tumor locations (right ICC; left or hilar ICC; proximal, middle, or distal extrahepatic cholangiocarcinoma; and gallbladder cancer). Marinelli et al[279] also conducted a similar analysis.

Radiation Doses

For conventional external beam 3DCRT or IMRT, ASTRO recommends conventional fractionation based on the SWOG S0809 trial.[258] This involves administering 45 Gy to nodal basins and 52.5 to 59.4 Gy to the tumor bed delivered in 25 to 33 fractions.[264] The recommended final dose is 54 Gy in 30 fractions for R0 resection and 59.4 Gy in 33 fractions for R1 resection. If using the simultaneous integrated boost technique, recommended dosages are 52.5 Gy in 25 fractions for R0 resection and 55 Gy in 25 fractions for R1 resection.

If boost-dose irradiation is feasible with brachytherapy techniques, the GTV should receive 45 to 50 Gy via external beam techniques, plus an additional 20 to 30 Gy delivered via intraluminal catheter.[280] The most common brachytherapy technique for the biliary tract involves placement of a percutaneous drainage catheter through the tumor area by an interventional diagnostic radiologist. The radiation oncologist then threads a catheter inside the drainage system catheter. When a low-dose rate system is employed, a wire with Ir-192 is positioned at the desired location inside the catheter.[280] In contrast, a high-dose rate remote afterloading system requires selection and programming of dwell time and position. It is a matter of some debate as to where the brachytherapy prescription point should be placed. Some physicians select the tumor's peripheral edge, away from the catheter, as determined by CT or MRI. Other practitioners prefer a point 0.5 or 1 cm away from the catheter. It is important to be familiar with the valves used to direct bile flow in the drainage system to prevent bile leakage onto the patient's skin and dressings during the administration of brachytherapy. Prolonged drainage system placement (ie, a month) can lead to enteric bacterial colonization and biliary tract infection. The combination of external beam irradiation and brachytherapy employed at Thomas Jefferson University resulted in 2-fold improved 2-year and

median survival rates when doses were brought up to >55 Gy.[280] However, investigators at the University of Amsterdam reported no improved survival at doses >55 Gy.[281] The role of RT and its optimal dosage remains to be determined.

More recent studies, particularly in ICC, have employed a hypofractionated regimen or SBRT. Analysis by Tao et al[282] of a hypofractionated, simultaneous integrated boost approach (ranging from 35 to 100 Gy in 3 to 30 fractions, with a median of 58.05 Gy in 15 fractions) found that the 3-year local control and overall survival rates were higher for patients treated with BED10 >80.5 Gy (78% and 73%) than those treated with BED10 ≤80.5 Gy (45% and 38%). In another retrospective cohort study of patients who received photon or proton therapy of 3,750 to 6,750 cGy (median 5,805 cGy) in 15 fractions for unresectable or locally recurrent ICC, 84% 2-year local control and 58% 2-year overall survival rates were achieved.[283] One multi-institutional retrospective series reported results using SBRT, in which 42% of patients were treated with three- and five-fraction approaches. The median prescribed BED (α/β = 10) was 67.2 Gy (range 36-115 Gy) in a median of 8 fractions (range 3-17); a median BEDmax was 91 Gy. BED >91 Gy was associated with improved local control and overall survival.[284] High-grade toxicities were uncommon in all of these series. The choice of hypofractionated external beam RT regimen should be based on tumor location, underlying liver function, the ability to meet normal tissue constraints, and the available technology, aiming to safely deliver an escalated prescription dose while meeting OAR constraints.[137]

Acute and Late Complications

The acute complications of external beam RT and brachytherapy are usually mild, including nausea, vomiting, and transient elevation of transaminases.[285]

The late and potentially dangerous complications are gastrointestinal bleeding, biliary bleeding, and duodenal stenosis.[280,286,287] The risk of gastrointestinal complications is dose dependent. It is about 5% to 10% if the dose to the duodenum or stomach is less than 55 Gy but rises to about 33% if the dose is greater than 55 Gy.[285]

Future Directions

Despite recent progress, the prognosis of most patients with cholangiocarcinoma remains poor. Due to the poor response rate or high recurrence rate of either surgery, RT, or systemic therapy alone, we should continue to explore the benefit of combined modality treatment. For example, novel combinations of SBRT and immune checkpoint inhibitors are being tested in clinical trials based on preclinical data suggesting a potential synergistic effect.[288]

ADENOCARCINOMA OF GALLBLADDER

Gallbladder carcinoma is a relatively rare malignancy of the biliary tract system with a high mortality rate. It constituted 0.9% of all cancer deaths in 2020.[6] Its incidence indicates large geographic variation.[289] In 2023, the American Cancer Society estimated approximately 12,220 new cases in the United States—5,750 in men and 6,470 in women.[290] Predisposing factors for gallbladder cancer include cholelithiasis, anomalous junction of pancreaticobiliary ducts, and porcelain gallbladder.[291] Cigarette smoking, alcohol consumption, and obesity may also contribute to cancer risk. Notably, patients with gallbladder polyps exceeding 10 mm in diameter may be at increased risk for gallbladder cancer.[292,293] Chronic infection with *Salmonella typhi* and *Helicobacter bilis* is also associated with increased risk.[289,294,295]

The most common clinical presentation is pain, followed by anorexia, nausea, and vomiting. Patients with early invasive gallbladder carcinoma are most often asymptomatic or have nonspecific

symptoms that mimic or are due to cholelithiasis or cholecystitis. Patients with gallbladder carcinoma who present with symptoms such as jaundice, anorexia, and weight loss generally have more advanced disease, which accounts for their poor prognosis.[206] A French study of 724 patients indicated that only 4% of the patients had Tis lesions, while 11% had T1 to T2 lesions and 85% had T3 to T4 lesions.[296] The 5-year survival rates reported in the SEER database were 69% for localized stage, 28% for regional stage, and 3% for distant stage.[297] However, improved outcomes have been noted since the 1990s and have continued through the past decade, likely attributable to more aggressive surgery and the use of postoperative adjuvant therapy.[298,299] Studies from Japan report 5-year survival rates of 100% for stage I, 50% to 78% for stage II, 0% to 69% for stage III, and 0% to 11% for stage IV.[300,301]

Lymphatic metastasis initially involves cystic and pericholedochal nodes, progressing to the pancreaticoduodenal system and potentially to the rest of the celiac axis or the superior mesenteric or aortic nodes.[300,301] The lymph node metastasis rate is associated with primary tumor stage: 0% to 2.5% in pT1a disease (involvement limited to the mucosa), 15% in T1b disease, 62% in pT2 disease, and 81% in pT3 or pT4 disease.[300,302,303]

Surgery remains the only curative option, but only one-quarter of patients are eligible for resection.[304] Standard surgical procedures include removal of the gallbladder, resection of various amounts of liver surrounding the gallbladder bed, resection of the extrahepatic bile duct, and dissection of the regional lymph nodes. Patients with jaundice should be considered for preoperative percutaneous transhepatic biliary drainage for relief of biliary obstruction. Overall curative resection rates for gallbladder carcinoma range from 10% to 30% in Western countries.[305] Prognosis is related to the possibility of curative resection, primary tumor extension, and regional lymph node metastasis.

GALLBLADDER CANCER TREATMENT

Patients with T1a disease are often cured after simple cholecystectomy and require no further adjuvant treatment.[303] In contrast, radical resection is recommended for more advanced stages (≥T2 disease).[298,302,306] The benefit of adjuvant RT is uncertain. After “curative” resection, locoregional relapse in the tumor bed or regional nodes is common. Patients who received radiation postoperatively had a median survival of >16 months. This was compared to <6 months for patients treated with surgery alone. Factors predicting recurrence are positive surgical margins, lymph node metastasis, and perineural invasion.[307] Several retrospective analyses demonstrated that postoperative RT improves local control and survival.[308-310] Benefits are also seen in patients who have microscopic residual tumors.[310] Combination RT and chemotherapy with 5-FU also show similar benefits.[311-313] However, there is a lack of phase 3 studies. Whether combination treatment is better than the single modality remains unknown.

Patients with stage III and IV disease are at high risk for distant metastasis. The most frequent sites of involvement are the liver, peritoneum, and lung, with less frequent spread to the ovaries, spleen, bones, and other organs.[312] In general, patients who are locally unresectable should be referred for chemoradiotherapy. Median survival is improved in several retrospective studies.[314] Systemic chemotherapy has limited success in the treatment of advanced gallbladder carcinoma. Objective response rates range from 25% to 50%. Active agents include infusion of 5-FU in combination with agents such as leucovorin modulation, capecitabine, cisplatin, oxaliplatin, gemcitabine, docetaxel, and 5-FU combined with recombinant IFN-α-2b.[315-320] Currently, the standard of care for systemic chemotherapy is cisplatin and gemcitabine, as mentioned in the section on cholangiocarcinoma.[260]

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CHAPTER 67

Cancer of the Colon and Rectum

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ANATOMY

The colorectum consists of the cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, and rectum. Variability in the peritoneal investment, bowel mobility, and lymph node drainage of the colon and rectum presents unique therapeutic issues.[1]

The posterior and lateral surfaces of the ascending and descending colon directly contact the retroperitoneum, whereas peritoneum drapes the anterior colonic surface.[1] These posterior attachments limit colonic mobility, increasing the difficulty of surgical resection. In contrast, peritoneum surrounds the more mobile transverse colon, which is supported on a long mesentery. As the sigmoid colon evolves distally into the rectum, the peritoneal coverage recedes. The rectum, approximately 12 to 15 cm in length, extends from the rectosigmoid junction to the puborectalis ring. The upper one-third of the rectum is draped with peritoneum anteriorly and laterally on both sides. Deeper in the pelvis, the middle one-third of the rectum is only covered by peritoneum anteriorly where the posterior border of the rectouterine pouch or rectovesical space dips between the anterior rectum and posterior bladder/uterus. The lowest one-third of the rectum is devoid of peritoneal covering and in proximity to adjacent structures, including the bony pelvis (Figure 67.1). Distal rectal tumors have no serosal barrier to invasion of adjacent structures and are more difficult to resect, given the close confines of the deep pelvis.

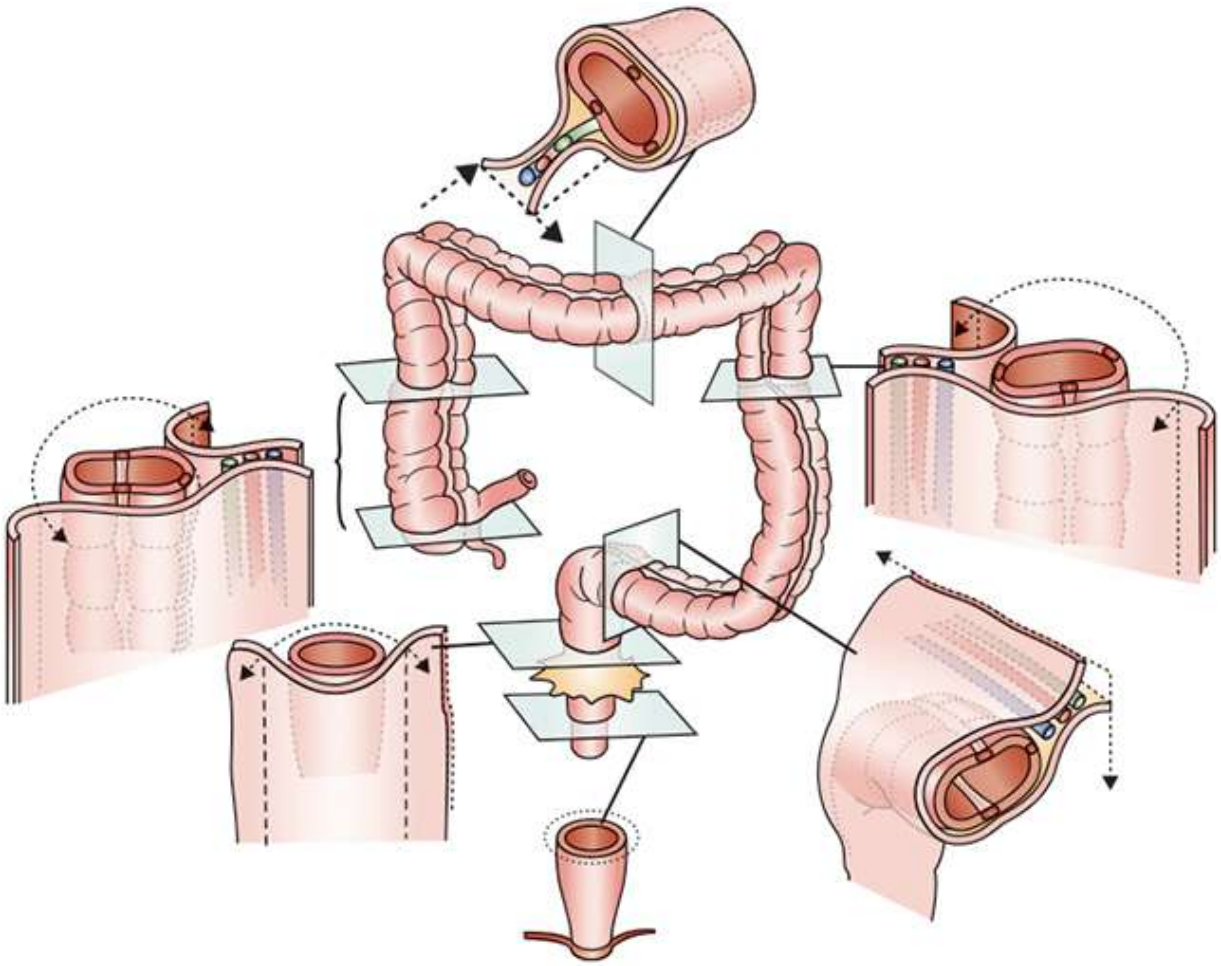

FIGURE 67.1 Idealized depiction of peritoneal relationships in the colon and rectum. The transverse and sigmoid colon are intraperitoneal, with a complete peritoneal covering (serosa) and mesentery. The ascending and descending colon are retroperitoneal, lack a true mesentery, and usually do not have a peritoneal covering posteriorly or laterally. The upper rectum begins above the peritoneal reflection and has peritoneum anteriorly and laterally. The lower one-half to two-thirds of the rectum is below the peritoneal reflection (infraperitoneal). (Used with permission of McGraw-Hill LLC from Gunderson LL, O'Connell MJ. The postoperative chemotherapy/irradiation adjuvant strategy. In: Cohen AF, Winawer SJ, eds. *Cancer of the Colon, Rectum, and Anus*. McGraw-Hill; 1995:635, Figure 67-1; permission conveyed through Copyright Clearance Center.)

Colonic nodal drainage consists of pericolic nodes and mesenteric nodes associated with the colonic vascular supply. The mobility and extent of the colonic mesentery limit the ability to strategically cover colonic regional lymph nodes using external beam radiotherapy (EBRT), but these nodal basins are usually well-treated surgically. In contrast, the major regional

groups for rectal nodal drainage can be covered within a reasonable EBRT field and include the perirectal, presacral, and internal iliac nodes.

Developmentally, the proximal or right-sided colon (cecum, appendix, ascending colon, hepatic flexure, and proximal two-thirds of the transverse colon) originates from the midgut, whereas the more distal or left-sided colon (distal one-third of transverse colon, descending colon, sigmoid, rectum) derives from the hindgut.[2] The gross appearance of colorectal tumors deriving from each location varies; right-sided colorectal cancers (CRCs) tend to have polypoid morphology, whereas left-sided CRCs classically have "apple core" annular lesions.[3] The embryologic etiology of specific CRCs has implications for underlying molecular alterations as well as potential therapeutic options, as discussed later in this chapter.

GENETICS AND CANCER BIOLOGY

A detailed discussion of the biologic and genetic pathways of development of CRC and their relevance to CRC treatment efficacy is beyond the scope of this chapter. In brief, multiple factors influence the development of colon cancer, including genomic instability, mutational inactivation of tumor suppressor genes, and activation of oncogene pathways.[3] CRC appears to arise through inactivation of the tumor suppressor genes adenomatous polyposis coli (APC), P53, and transforming growth factor beta (TGF-β), as well as activation of the RAS, BRAF, and phosphatidylinositol 3-kinase (PI3K) proto-oncogenes.[4] Though canonically presented as a stepwise accumulation of sequential mutations, modern sequencing analyses suggest CRC oncogenesis may also involve early "big bang"-like mutational expansion and subsequent neutral evolution and/or more complex concurrent subclonal evolutionary processes that contribute to pronounced intratumoral genetic mutational heterogeneity.[5-8]

Reflecting the unique developmental biology of the colon, left- and right-sided colon cancers possess some shared features (eg, APC mutation in the majority of cases) while also exhibiting differential molecular features. Microsatellite instability (MSI) and/or CpG Island Methylator Phenotype occurs more often in right-sided/proximal CRC, along with associated molecular/mutational features like mutations or hypermethylation of mismatch repair (MMR) genes and activating *BRAF* mutations.

Chromosomal instability occurs more often in left-sided/distal CRC, along with mutations in genes like *TP53*, *KRAS*, *PIK3CA*, *FBXW7*, *SMAD4*, and others.[3]

Genetic features may influence prognosis and predict treatment responsiveness. The majority of CRC occurring in patients with hereditary nonpolyposis colorectal cancer (HNPCC) syndrome, as well as a minority of sporadic CRCs, demonstrate MSI deriving from mutations or dysregulation of genes encoding enzymes that repair DNA replication errors. These defects in MMR lead to high-frequency MSI.[9] Studies suggest that patients with tumors possessing MSI have more favorable outcomes and lower likelihood of developing metastatic disease.[10-12] Current guidelines incorporate this into treatment recommendations; for example, deintensified regimens exist for mismatch repair-deficient (dMMR)/microsatellite instable (dMMR/MSI) CRC relative to recommendations for the same stage for MMR-preserved/microsatellite stable (pMMR/MSS) CRC.[13] Promising initial data in rectal cancer, where a tiny minority of tumors exhibit MSI, hint at the potential for immunotherapy alone or in combination with surgery as a management for microsatellite unstable rectal cancer (though larger studies are needed for confirmation).[14] Some initial studies indicate other mutational characteristics that might influence treatment responsiveness but further investigations are needed to confirm.[15,16] Specific features predicting radio-responsiveness have been elusive; mutations in key tumor suppressors or oncogenes (eg, *TP53* or *KRAS*, respectively) may be associated with radiation resistance in preclinical settings, but clinical manifestations might require co-mutational combinations of multiple specific mutational alterations.[17,18] Associations between genetic features and resistance to standard chemotherapies or radiotherapy (RT) warrant further investigation.

Other recurrent CRC molecular alterations present targeted therapy options, which are increasingly incorporated into treatment algorithms for CRC. Molecules that specifically target tumors bearing *BRAF* V600E mutation, *HER2* amplification, *KRAS* G12C mutation, *NTRK* gene fusion, *POLE/POLD1* mutation, and *RET* fusion have been incorporated into first- and second-line therapies.[19-30] Even if targeted options are available, appropriate integration of molecularly targeted agents will likely require a comprehensive understanding of the active mutational profile of a given

tumor. Further elucidation of the genetic pathways in the development of CRC and their impact on treatment responsiveness remains an active area of investigation.

EPIDEMIOLOGY AND RISK FACTORS

CRC remains a major worldwide health problem. In the United States alone, in 2024 it was estimated that there would be 152,810 patients diagnosed with CRC and 53,010 deaths, with a 3.9% to 4.3% lifetime probability of developing CRC.[31] Worldwide in 2022, approximately 1.9 million new cases per year were diagnosed, with 900,000 deaths, according to the World Health Organization (WHO) International Agency for Research on Cancer.[32]

In the United States, the incidence of CRC over the last several decades declined by 2% to 3% annually, though recently the rate has diminished to a decline of 1.2% annually between 2012 and 2018.[33] Though CRC remains the second most common cause of cancer death in men and women combined, death rates from CRC have also decreased over time, declining 1.8% annually between 2012 and 2021.[31] Factors like risk factor modifications, screening implementation, and improved treatment may contribute to this trend. Age-adjusted relative CRC survival rates continue to differ by race and ethnicity in the United States, with 5-year survival rates of 64% and 59% in White and Black patients, respectively.[31] Encouragingly, recent studies have shown improvements in diminishing race-associated disparities in CRC mortality after targeted interventions to improve screening compliance, follow-up of abnormal findings, and initiation/completion of therapy.[34,35] Nevertheless, further research is needed regarding the etiologies of disparities in CRC incidence and survival by race and ethnicity, and interventions to diminish such disparities are needed.

Contrary to the trends suggesting decreased overall CRC incidence and mortality, there has been a worldwide increase in incidence of early-onset CRC in adults younger than 50 years. Since 2012, early-onset CRC has increased by approximately 1.8% annually, but this upward trend in incidence of early-onset CRC likely dates at least to the 1980s in many Western countries.[36] Associated mortality trends reflect this increased incidence of early-onset CRC; in 2021, CRC was the leading cause of

cancer-related death in US males in the age groups 20 to 39 and 40 to 49 (being the third and second most common, respectively, in females of these age groups).[31] By 2030, an estimated 1 in 10 colon cancers and 1 in 4 rectal cancers will occur in patients under the age of 50.[37] Epidemiologic data indicate this trend extends to other regions of the world, including Australia, Europe, Canada, and Asia.[38-41] Younger patients appear more likely to present with regional or distant disease than older patients, and histologically tend to display more adverse features potentially reflecting differential detection/screening or altered tumor-specific biologic factors, respectively.[42] Genetic factors may account for upward of one-third of these early-onset CRC diagnoses. Many of the epidemiologic studies have suggested birth cohort association with early-onset CRC risk, supporting hypotheses that altered environmental factors and exposures might account for the remaining increase in incidence. Factors like metabolic dysregulation/obesity, diet, alcohol consumption, vitamin D intake, microbiome features, or nonsteroidal anti-inflammatory drug (NSAID) consumption have been proposed.[36] Nevertheless, no consensus exists regarding the etiology of increasing CRC incidence in younger populations so it remains a subject of intense research interest.

Genetic and environmental factors influence CRC incidence. A number of hereditary CRC syndromes exist, including familial adenomatous polyposis (FAP), MUTYH-associated polyposis, and Lynch/HNPCC syndrome. Factors proposed as associated with elevated CRC risk include the following: increasing age; male sex; family history of CRC; inflammatory bowel disease diagnosis; increasing height; prior abdominopelvic radiation; cystic fibrosis diagnosis; metabolic dysregulation (obesity, diabetes mellitus); high consumption of processed meat, refined grains, starches, and sugars; low consumption of fiber, folic acid, vitamin B6 or vitamin D; and excessive alcohol intake and smoking. Of the non-genetic risk factors, only family history of CRC, personal history of inflammatory bowel disease, increasing age, male sex, obesity, smoking and excessive alcohol use have been associated with rectal cancer.[43-45] Discordant data exist for many of the consumption-associated risk factors, however, possibly relating to confounding factors in the studies. Other studies suggested that NSAIDs, folate, statins, or vitamin D may serve in reducing recurrent adenomas and CRC, but long-term therapy

must be weighed against potential side effects. The role of chemopreventative agents in CRC remains an area of active investigation.[43]

PATHOLOGY AND PATHWAYS OF SPREAD

Tumors of the colorectum arise in the mucosa and virtually all (>90%) are adenocarcinomas.[46] Other histologic types include squamous cell carcinoma, melanoma, small cell carcinoma, carcinoid, sarcoma, and lymphoma. Most grading systems classify adenocarcinoma as well, moderately, or poorly differentiated. Large bowel tumors invade from mucosa through the bowel wall and beyond, with involvement of lymphatic channels and lymph nodes. Hematogenous spread can occur, primarily to the lung and liver. There is little propensity for colon cancer to spread longitudinally within the bowel wall, in contrast to esophageal or gastric cancers.

SCREENING

Neoplastic polyps, including tubular adenomas, villous adenomas, tubulovillous adenomas, and serrated polyps are precursors of colon cancers.[43] Most CRCs arise from preexisting polyps during a slow transformation process occurring over an average of 10 years.[47] Though it has decreased over time, the cumulative lifetime risk of CRC in the United States remains about 4%, so screening programs for the general population continue to be implemented. Screening aims to detect preinvasive polyps or early invasive cancer. Numerous randomized studies now document that screening asymptomatic, average-risk individuals detects CRC at early, curable stages, reducing CRC mortality.[48-58]

Given the data in favor of screening, many published screening guidelines recommend screening in average-risk individuals starting at age 50 (American College of Radiology, American College of Physicians, American Association of Family Physicians), with a recent move from multiple organizations to change the age of screening to 45 (the US Multi-Society Task Force on Colorectal Cancer, the US Preventive Services Task Force, and the American Cancer Society).[52,59-61] Most of these groups recommend individualizing decisions about screening or terminating them altogether in adults aged 76 and above. Recommended screening options

and recommended intervals vary according to the guideline used, but broadly fall under headings of visual colorectal examination (colonoscopy, sigmoidoscopy, computed tomography [CT] colonography), stool-based tests (fecal occult blood test, immunochemical or DNA detection), or specific combinations of the above for detection of adenomatous polyps and cancer. As a representative set of options, the American Cancer Society recommendations are as follows:

- Flexible sigmoidoscopy every 5 years
- CT colonography every 5 years
- Colonoscopy every 10 years
- Yearly guaiac-based fecal occult blood test, fecal immunohistochemical test, and stool DNA test may be performed for CRC, but likely not polyp, detection.[62]

In high-risk patients (patients with adenomatous polyps, history of CRC, first-degree relative diagnosed with CRC or advanced adenomas below age 60, two first-degree relatives with CRC or advanced adenomas at any age, a personal history of inflammatory bowel disease, or high risk due to family history or genetic testing), more intensive surveillance is recommended. Patients with inflammatory bowel disease should initiate screening with colonoscopy 8 to 10 years after initial diagnosis. The U.S. Multi-Society Task Force on Colorectal Cancer (representing the American College of Gastroenterology, American Gastroenterological Association, and the American Society for Gastrointestinal Endoscopy) recommends the following for high-risk individuals without known genetic CRC risk syndromes based on family history:[63]

- Colonoscopy screening (vs other screening methods) is indicated for all of the indicated high-risk groups.
- If a person has a single, first-degree relative diagnosed with CRC, or advanced adenoma at age less than 60 years or two or more first-degree relatives with CRC or advanced adenoma at any age, colonoscopy screening begins at age 40 years, or 10 years before the youngest relative’s diagnosis. Screening should be performed every 5 years.

- In patients with a prior personal history of CRC or advanced adenomas, colonoscopy surveillance begins 1 year after surgical or endoscopic removal with subsequent surveillance determined by findings on that first colonoscopy (yearly if advanced adenomas found on surveillance exams, or after 3 years and then 5 years if no advanced adenomas found).[64]

Hereditary syndromes with increased CRC risk necessitate intensified screening schedules. A detailed discussion of recommendations for each genetic variant/syndrome is beyond the scope of this review but some considerations and recommendations are discussed later for context. Individuals with classical FAP have a lifetime risk of close to 100% for developing CRC without treatment. Annual sigmoidoscopy or colonoscopy beginning at age 10 to 12 years is recommended until standard (procto)colectomy treatment occurs, usually after age 18. Patients with HNPCC have a lifetime risk for CRC of 8% to 52% depending on the genetic Lynch variant, so screening recommendations vary depending on the specific molecular alteration.[65] National guidelines suggest screening every 1 to 2 years at age 20 to 25 years or 2 to 5 years prior to the earliest familial CRC diagnosis if it is diagnosed before age 25. This interval is individualized based on other risk factors; for example, some of the less pathogenic variants (eg, MSH6- or PMS2-associated Lynch syndrome) may require less stringent ages for initiation and screening intervals. Other hereditary syndromes (eg, PTEN hamartoma syndrome, juvenile polyposis syndrome, Peutz-Jeghers syndrome, MUTYH-associated polyposis) also necessitate increased screening intensity, and the timeline of initiation and testing frequency varies depending on syndrome and associated features.

Despite the successes of the screening procedures discussed earlier and the increased adoption of screening among the population, advanced CRC diagnoses still occur in many patients and may reflect persistently low rates of disease awareness, as well as the infrequency of screening in eligible candidates, as well as the perplexing increase in early-onset CRC in patients less than 50 years old. Approximately 60% to 80% of eligible adults aged 50 to 75 years underwent CRC screening in 2022.[66] Lower rates of screening are seen in younger patients, Hispanic patients, Black patients, Asian patients, individuals of lower socioeconomic status, and individuals

without health insurance.[66,67] Although all screening tests have potential drawbacks, patients should be educated regarding relative risks and benefits of screening modalities, including potential benefits in reducing the risk of CRC.

CLINICAL PRESENTATION

CRC often produces minimal or no symptoms, emphasizing the need for screening programs in the general population. Patients with symptomatic CRC most commonly experience abdominal pain, change in bowel habits, hematochezia/melena, weakness, iron deficiency anemia, and weight loss.[47,68] Less commonly, patients present with nausea, vomiting, or abdominal distention, which may be signs of tumor-related obstruction.

The clinical presentation of CRC is determined largely by site of the tumor. Cancers of the right colon are often exophytic and commonly associated with few symptoms aside from iron deficiency anemia due to occult blood loss, resulting in delayed diagnosis. Cancers of the left colon and sigmoid colon are often deeply invasive and annular ("apple core lesions") and accompanied by obstruction, rectal bleeding, and alteration in bowel habits.

PATIENT EVALUATION/STAGING

CRC workup should include a complete history and physical exam, including digital rectal examination (DRE). Careful attention to family history of CRCs, colonic adenomas, and other cancers may reveal patients suspected of bearing hereditary or familial cancer syndromes, who should be referred for genetic counseling. On DRE, rectal mass size, location, distance from the verge, mobile versus fixed, and sphincter function should be noted. Pelvic exam should be performed in women diagnosed with rectal cancer to assess for vaginal involvement where appropriate. Pretreatment evaluation should include pathologic confirmation of adenocarcinoma, colonoscopy to evaluate extent of tumor and rule out synchronous primaries (occurring in 1%-5%), and baseline lab tests, including blood counts, liver function tests, and carcinoembryonic antigen (CEA) levels. Tattooing may be used at the time of colonoscopy to mark the proximal and distal disease extent; such markings take special importance in localizing the initial tumor

where patients embark upon nonoperative management (NOM) protocols with repeat posttreatment endoscopy. Biopsies should be evaluated for primary histology as well as the presence or absence of lymphovascular invasion (LVI), perineural invasion (PNI), and other pathologic features. All tumors, including rectal tumors, should be evaluated for MMR protein status and MSI on initial biopsy and potentially other actionable mutations/alterations (eg, *BRAF* V600E, *HER2* amplification), as this impacts prognosis and treatment options.

For rectal cancer, decisions regarding the utility of neoadjuvant chemotherapy and/or RT are often based largely on physical exam and the radiographic characteristics of the primary tumor. Pelvic magnetic resonance imaging (MRI) assesses T and N stage and now is recommended as the primary T and N clinical staging assessment tool.[69,70] Lymph node assessments by MRI leverage numerous features besides size alone, adding to the utility of this imaging modality in addition to CT imaging alone. MRI also evaluates features like sphincter involvement, distance of tumor from the circumferential resection margin (CRM), extranodal tumor deposits and extramural venous invasion, which are features indicative of more aggressive disease and may influence neoadjuvant treatment decisions and/or surgical planning.[71,72] Generally speaking, pelvic MRI staging is now preferred to endoscopic ultrasound (EUS) techniques in the workup of rectal cancer.[69,70] However, due to its ability to visualize the layers of the rectal wall, EUS also has quite high sensitivity and specificity for T staging when performed by experienced endoscopists and can still play an important role in staging tumors for patients in whom MRI is contraindicated or when MRI findings are equivocal.[73] In staging early depth of invasion (Tis, T1, T2) to determine suitability for transanal approaches or in posttreatment response assessment, EUS can provide helpful complementary information to MRI, where invasion depth may be difficult to assess.[74]

Contrasted abdominopelvic and chest CT scans assess for the presence or absence of distant metastases (DMs). Standard CT does not permit the visualization of the layers of the rectal wall, and therefore its utility in the assessment of primary cancer extent is limited, especially with the implementation of high-quality reproducible MRI techniques. The ability of CT scans for detecting DM, including pelvic and para-aortic lymph nodes,

is higher than for detecting perirectal nodal involvement.[75] Suspected liver metastases on initial staging CT exams could be evaluated with follow-up MRI abdomen with contrast. 18F-Fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT is not routinely recommended, although it may be useful in addition to contrasted CT staging in circumstances of oligometastatic disease for which surgical and/or local metastasis-directed therapies might be available.[76,77]

All rectal cancer imaging techniques have advantages and limitations and should be considered complementary to physical examination. Radiographic assessment of response after neoadjuvant therapy has high rates of false positivity.[71,72,78]

Prognostic factors influencing survival in patients with CRC include the depth of tumor invasion into and beyond the bowel wall, the number of involved regional lymph nodes, and the presence or absence of DMs. Additional prognostic factors recommended for clinical care and staging include the presence of tumor deposits in the pericolic/perirectal fat and/or adjacent mesentery; when present, these are staged as N1c and likely have a prognostic impact similar to having positive nodes. The tumor, node, metastasis (TNM) system of the American Joint Committee on Cancer can be used as a clinical (preoperative) staging system (Tables 67.1 and 67.2).[79]

TABLE 67.1 AMERICAN JOINT COMMITTEE ON CANCER 2017, 8TH EDITION, TNM STAGING OF COLORECTAL CANCER

Primary Tumor (T)	
TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intramucosal (invasion of lamina propria with no extension through muscularis mucosae)
T1	Tumor invades submucosa.
T2	Tumor invades muscularis propria.
T3	Tumor invades through the muscularis propria into the subserosa or into pericolorectal tissues.
T4	Tumor invades visceral peritoneum or invades/adheres to adjacent organs or structures.
T4a	Tumor penetrates the surface of the visceral peritoneum.[a]

T4b	Tumor directly invades or is adherent to other organs or structures.

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis
N1	Metastasis in one to three regional lymph nodes (0.2 mm size or greater), or any number of tumor deposits
N1a	Metastasis in one regional lymph node
N1b	Metastasis in two or three lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolorectal tissues without regional nodal metastasis
N2	Metastasis in four or more regional lymph nodes
N2a	Metastasis in four to six regional lymph nodes
N2b	Metastasis in seven or more regional lymph nodes

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed.
M0	No distant metastasis by imaging
M1	Distant metastasis to one or more distant sites or organs or peritoneal metastasis
M1a	Metastasis confined to one organ or site without peritoneal metastasis
M1b	Metastasis in more than one organ/site without peritoneal metastasis
M1c	Metastasis to the peritoneal surface with or without metastasis to other sites or organs

[a]T4a tumors are characterized by involvement of the serosal surface (visceral peritoneum). Perforated tumors with tumor cells continuous with serosal surface through inflammation are also T4a. Inflammation within 1 mm of the serosa is not T4a unless careful microscopic analysis indicates serosal surface involvement. T4a designation is not applicable to those portions of the colorectum that are not peritonealized (such as the posterior aspects of ascending/descending colon and distal rectum).

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

TABLE 67.2 STAGING OF COLON AND RECTAL CANCER

Stage	American Joint Committee on Cancer			Dukes[a]	MAC
	T	N	M		

Stage	American Joint Committee on Cancer			Dukes[a]	MAC
0	Tis	N0	M0	—	—
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1-T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3-T4a	N1/N1c	M0	C	C2
	T2-T3	N2a	M0	C	C1/C2
	T1-T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3-T4a	N2b	M0	C	C2
	T4b	N1-N2	M0	C	C3
IVA	Any T	Any N	M1a	—	D
IVB	Any T	Any N	M1b		
IVC	Any T	Any N	M1c		

M, metastasis; MAC, modified Astler-Coller classification; N, node; T, tumor.

[a]Dukes B is a composite of better (T3 N0 M0) and worse (T4 N0 M0) prognostic groups, as is Dukes C (any TN1 M0 and any T N2 M0).

Data from Edge SB, Greene FL, Schilsky RL, et al, eds. Colon and rectum. In: *American Joint Committee on Cancer Staging Manual*. 8th ed. Springer; 2017.

COLON CANCER

Treatment of Colon Cancer

Surgery

Surgery is the primary treatment modality for patients with invasive nonrectal colonic cancers. Resection with curative intent is possible in approximately 75% of patients. Surgical approaches for primary colon cancer reflect the anatomy and mechanisms by which this disease spreads. Adenocarcinomas of the colon may grow by direct extension into the lymphatics of the submucosa and bowel wall. Resection of sufficient lengths of bowel proximal and distal to the primary cancer helps avoid transecting intramural lymphatics with microscopic tumor involvement.

Colon cancer often extends through the serosa into mesenteric lymphatics that run along the blood vessels draining into the portal watershed at the root of the mesentery. Resection involves removal of the major lymphatic drainage system in the mesentery including those lymph nodes at the origin of the feeding vessels. Consensus guidelines recommend that a minimum of 12 lymph nodes should be excised for appropriate staging.[76,79] Anatomic resections intentionally include named blood vessels and draining lymphatics; thus, the boundaries for resecting large bowel cancer are relatively uniform. Right hemicolectomy, transverse colectomy, left hemicolectomy, and sigmoid resection following surgical oncologic principles largely preserve large bowel function. Some more advanced tumors may necessitate more extensive surgical procedures; for example, curative resection for colon cancers that adhere to or invade neighboring organs requires complete en bloc resection with negative margins, and obstructive or perforated tumors may require specialized procedures or two-stage colostomy/resection procedures.[76]

Multiple large multi-institutional randomized trials established that laparoscopic resection has equivalent oncologic outcomes versus open resection for non-rectal colon cancers, with the benefits of decreased length of hospital stay and improved short-term outcomes associated with laparoscopic approaches.[80-84] Surgical guidelines now reflect a strong preference for implementing laparoscopic approaches for suitable tumors.[76] Surgeons should have experience performing laparoscopic operations and using laparoscopic methods does not remove the necessity for a thorough abdominal exploration.[85-88] Laparoscopic techniques are not appropriate for patients with perforation, complete obstruction, or particularly invasive disease (eg, extremely large size or adjacent organ invasion).

Resection results in excellent cure rates for lesions limited to the bowel wall with negative nodes (5-year overall survival [OS] 97% for T1-T2N0). Survival drops somewhat for tumors with a single high-risk feature of extension beyond the colonic wall (5-year OS 87.5% for T3N0 and 71.5% for T4N0) or involved nodes (5-year OS 67%-88% for T0-2 N+), warranting adjuvant therapy in many cases. When both high-risk features are present (T3-4 N+), 5-year survival drops to approximately 47% to 67% (T3 N+) and 27% to 50% (T4 N+), even when considering that most of these patients receive adjuvant therapy.[89] If higher T or N stage–related risk

factors are suspected on presurgical imaging, consideration for neoadjuvant treatment may be indicated to facilitate margin-negative resection (see "Neoadjuvant Treatment" section below).[76]

Surgical pathology reports should include all information to designate the T and N stage of the tumor, as well as highlight all potential pathologically prognostic information. Features to be reported include: specimen morphology and tumor site, presence or absence of macroscopic tumor perforation, tumor extension into bowel wall and adjacent organs (T stage), number of regional lymph nodes retrieved and quantification of number involved with cancer (N stage), margin status and distance (proximal, distal, radial), presence or absence of tumor deposits and tumor budding, presence or absence of LVI or PNI, and MMR protein and MSI/MSS status.[90]

Adjuvant Chemotherapy

The benefit of adjuvant chemotherapy has been clearly demonstrated in patients with stage III disease. Prospective randomized trials initially showed that adjuvant combination treatment with 5-fluorouracil (5-FU) and leucovorin (LV) improves survival for resected patients in stage III disease, and capecitabine (an oral 5-FU prodrug) in place of 5-FU/LV confers similar clinical benefit.[91-94] Subsequent trials adding oxaliplatin to 5-FU/LV (FOLFOX) demonstrated improved disease-free survival (DFS) in patients in stage III disease treated with oxaliplatin-containing regimens, with some of these studies identifying a potential OS benefit.[95-98] Addition of irinotecan to 5-FU/LV appears not to improve DFS or OS for patients with stage III colon cancer and increases toxicity.[99-103] These data helped to establish FOLFOX or capecitabine and oxaliplatin (CAPOX/XELOX) as standard chemotherapeutic regimens in the adjuvant treatment of completely resected, high-risk colon cancer. The use of monoclonal antibodies, such as bevacizumab and cetuximab, although potentially efficacious in the metastatic setting, has not yielded similar results in the setting of adjuvant treatment of non-metastatic disease.[104-109]

The utility of adjuvant treatment for patients in stage II disease varies and thus requires individualization. For the most part, these decisions are made based on pathologic risk factors (T4 disease, poorly differentiated pathology, LVI, PNI, tumor budding, bowel obstruction or perforation,

close/positive margins, inadequate nodal sampling).[110] Multigene assays and immunophenotyping analyses, while not currently incorporated into treatment decision-making algorithms, may supplement other pathologic features to help with making decisions regarding chemotherapy in difficult cases. Promising new data indicate that circulating tumor cell DNA (ctDNA) measurements may aid in determining the utility of adjuvant chemotherapy.[111] However, due to questions about the value added beyond normal risk factors and potential drawbacks, national guidelines do not currently include ctDNA in the algorithms for management but have indicated it might help with decision-making in difficult cases.

The molecular features of colon tumors contribute to whether adjuvant therapy might augment clinical outcomes. For patients with dMMR or MSI tumors, standard adjuvant treatment recommendations differ from their pMMR/MSS counterparts. Chemotherapy is not recommended for stage II high-microsatellite instability (MSI-H) or dMMR tumors. This is partially related to the improved overall prognosis of these tumors[11,112,113] and studies suggesting that these tumors may be less intrinsically prone to metastasize.[15,114] Some retrospective evidence suggests that chemotherapy for patients with stage II dMMR/MSI tumors may not improve clinical outcomes relative to surgery, or may even be detrimental, although other retrospective analyses of large trials have shown discrepant results.[10,113,115] In the setting of stage III tumors, typical chemotherapy regimens remain standard-of-care adjuvant management for dMMR/MSI-H tumors. Other molecular markers (eg, *BRAF* or *KRAS* status) do not currently factor into adjuvant therapy decision-making.

Adjuvant Irradiation With or Without Concurrent Chemotherapy

Given the documented efficacy of adjuvant chemotherapy, as well as the perception by many oncologists that colonic (as opposed to rectal) cancer is much more likely to relapse distantly than locally, there has been little evaluation of the efficacy of postoperative irradiation with chemotherapy. The potential indications for adjuvant RT in colon cancer are based on analyses of patterns of failure following resection.[66] Advanced stage predicts for local failure (LF) in both colon and rectal cancers; however, LF in colon cancer also depends on anatomic origin. The ascending and

descending colon are considered “anatomically immobile,” and their close proximity to the retroperitoneal tissues often limits wide surgical resection (Figure 67.1). Limitations in achieving satisfactory circumferential margins increase the risk of residual disease and consequently LF. In contrast, the midsigmoid and midtransverse colon are relatively “mobile,” with a wide mesentery, permitting the surgeon to obtain wide margins regardless of extent of disease invasion into the mesentery. Unless there is adjacent organ adherence/invasion by tumor, LF at these sites is uncommon. LF rates for cecal, hepatic/splenic flexure, and proximal/distal sigmoid tumors are variable, depending on the amount of mesentery present, tumor extension, and the adequacy of radial margins. When colon cancers adhere to or invade adjacent structures, LF rates exceed 30% following surgery alone. In summary, LF occurs in patients with colonic tumors where there are anatomic constraints on radial resection margins, including tumors adherent to or invading adjacent structures.

A retrospective report from the Massachusetts General Hospital (MGH) compared high-risk (T4, T3N+, and T3N0 with close margins) patients with colon cancer receiving resection and adjuvant RT (n = 171; 63 treated with concurrent 5-FU chemoradiotherapy [CRT]) with a similar cohort of patients (n = 395) treated with surgery only over the same period.[116] The tumor bed plus a 3 to 5 cm margin received 45 Gy via parallel-opposed or other 3D conformal multi-field radiotherapy techniques, followed by reduced fields to a total dose of 50.4 to 54 Gy. Draining nodes were included if they were believed to be at high risk for involvement. For patients with T4N0 and T4N+ lesions, adjuvant radiation was associated with improved local control (LC) and relapse-free survival (RFS). No significant outcome differences were observed in patients with T3 N0 and T3 N+ lesions. A trend toward improved LC in patients receiving 5-FU CRT was seen. This study concluded that postoperative radiation may benefit patients with T4 tumors, abscess/fistula formation, or margin-positive resection. In a subsequent analysis from MGH, 152 patients with T4 tumors received adjuvant irradiation and were compared to historical controls.[117] For patients with negative margins (N = 110), the 10-year actuarial LC in patients with T4 N0 and T4 N+ lesions was 78% and 48%, respectively. In patients with node-negative tumors, the 10-year actuarial LC and RFS rates were 87% and 58%, respectively, compared to 65% and

33%, respectively, in patients with node-positive tumors. In comparison with historical controls, these patients who underwent irradiation had comparably favorable LC.

Consistent institutional data in support of adjuvant RT for high-risk colon cancers were published out of the Mayo Clinic and the University of Florida. The Mayo Clinic experience described 103 patients receiving a median of 50.4 Gy RT (most with concurrent 5-FU-based chemotherapy) following surgery for locally advanced colon cancer. Most patients (>90%) had T4 disease, and many had residual disease (n = 18 with microscopic, n = 35 with gross residual).[118] Eleven patients received an intraoperative radiotherapy (IORT) boost of 10 to 20 Gy. Five-year actuarial LC was 40%; for R0 patients, LC was 90%, while it was 46% and 21% for R1 and R2 resections, respectively. Five-year OS tracked with margin status as well (66% in R0, 47% in R1, and 23% in R2 resections). In patients with residual disease, LC rates in those undergoing IORT boost were 89%, compared to 18% in those undergoing external irradiation alone, and IORT administration was associated with improved survival (76% vs 26%). The University of Florida experience described outcomes for patients with locally advanced but completely resected colon cancers receiving adjuvant radiation.[119] Their reported LC rate of 88% was similar to the 90% reported from the Mayo Clinic series for R0 patients. In addition, there appeared to be a dose-response relationship to LC. The 5-year rate of LC was 96% for patients receiving 50 to 55 Gy versus 76% for patients receiving less than 50 Gy (P = .0095).

Based on these institutional experiences, in 1992 the U.S. Intergroup designed a randomized, prospective phase III trial to assess whether the addition of RT to adjuvant chemotherapy would result in superior OS and LC rates in patients with resected, high-risk colon cancer.[120] Eligible patients had resected, high-risk colon cancer (defined as margin-negative T4 tumors, excluding peritoneal invasion; or node-positive tumors arising from the ascending or descending colon). Patients were randomized to receive (a) weekly 5-FU combined with levamisole for 12 months or (b) 5-FU and levamisole for 12 months with combined RT and chemotherapy beginning 1 month after the first 5-FU administration. The recommended total radiation dose was 45 Gy in 25 fractions over 5 weeks to the tumor with an elective nodal volume, with an optional 5.4-Gy boost. The initial

trial accrual goal was 700 patients; however, the study was closed in 1996 because of poor accrual (222 patients; 189 evaluable). Total accrual was less than one-third of the initial goal, and there was reduced statistical power to detect differences between the groups. No difference in OS or DFS was seen between the two groups. Five-year OS of patients receiving chemotherapy only was 62% versus 58% for patients randomized to chemoradiation ($P > .50$). Local recurrence rates were identical in both arms (18 patients each). Grade 3 or 4 hematologic toxicity was higher in patients receiving RT. Interpretation of study results was handicapped by decreased statistical power, high ineligibility rates, and lack of surgical clips or preoperative imaging to assist in the definition of appropriate RT fields in a high percentage of patients. Therefore, no definitive conclusions can be made regarding the efficacy of postoperative irradiation with 5-FU and levamisole based on this study.

A potential benefit for EBRT in highly selected cases might still exist, especially considering technical improvements with RT delivery and image guidance, as well as the improved systemic disease control associated with modern chemotherapy regimens. A recent study examined the role of adjuvant RT in locally advanced colon cancer in the era of modern chemotherapy.[121] The investigators reported the outcome of 62 patients with T4 colonic cancer treated with surgery only, surgery followed by adjuvant chemotherapy only, or 13 patients with adjuvant chemoradiation. A multivariate analysis demonstrated that treatment with adjuvant chemoradiation (vs adjuvant chemotherapy alone) enhanced locoregional control and DFS. The investigators concluded that adjuvant RT may be appropriate in select patients, specifically those with T4b lesions and/or residual disease following resection. Database analyses from the Surveillance, Epidemiology and End Results Program (SEER) and National Cancer DataBase (NCDB) suggest ongoing, yet very infrequent, administration of adjuvant RT for colonic tumors with very high-risk factors for local recurrence (eg, T4b tumors and/or positive margins). These studies hint at a potential association between adjuvant RT use and improved clinical outcomes, although the inherent limitations of database studies would require further data to confirm.[122-124]

As seen in some of the early institutional experiences, IORT remains an alternative means by which to administer RT to regions at high risk for

recurrence after surgery, often due to close or positive margins. Reported data on IORT for non-rectal colon cancer are rare, but extrapolation from the rectal and rectosigmoid literature supports it as a reasonable option to consider in select circumstances.[125,126]

To summarize, early institutional and some database analyses support some role for adjuvant CRT or RT (EBRT or IORT) in treating advanced non-rectal colon cancer. This approach could be considered for highly select cases with close or positive margins or T4b disease and ideally in situations where the tumor bed and/or region at risk is easily identified by surgical clips or other nonvariable anatomic markers to permit accurate localization. However, since there are no randomized data supporting this approach, decisions should be individualized and implementation of this strategy taken with care.

Neoadjuvant Treatment

Neoadjuvant therapy can be considered for locally advanced or unresectable colon cancer. The most frequently employed neoadjuvant modalities include chemotherapy or immunotherapy. Building on promising pilot results, the international FOxTROT randomized controlled study assessed the role of neoadjuvant systemic therapy administration for locally advanced colon cancer staged as T3-4, N0-2, M0.[127] A total of 1,053 patients were randomized 2:1 to a neoadjuvant/adjuvant FOLFOX group (6 weeks neoadjuvant, 18 adjuvant) versus an adjuvant-only group (24 weeks adjuvant); RAS-wildtype tumors were randomized 1:1 to additionally receive panitumumab during neoadjuvant chemotherapy. Neoadjuvant chemotherapy administration was associated with a 28% improvement in the primary outcome, 2-year residual or recurrent disease, with 16.9% in the neoadjuvant chemotherapy arm and 21.5% in the control arm ($P = .037$). Additionally, neoadjuvant chemotherapy improved R0 resection rates, augmented T and N downstaging, and was associated with fewer serious postoperative complications. This benefit was largely limited to patients with pMMR/MSS tumors. Panitumumab did not enhance the effect of neoadjuvant chemotherapy.

Neoadjuvant immunotherapy treatment regimens exist for dMMR or MSI-H colon tumors. Though very promising and likely to have very high

utilization and impact, at this point these regimens are based on nonrandomized studies with little longer-term clinical follow-up. The NICHE study demonstrated 100% pathologic response (including 57% pathologic complete response [pCR]) in 21 patients with stage I to III dMMR treated with nivolumab and ipilimumab.[128] Patients with pMMR/MSS evaluated had minimal response to this regimen. The follow-up, larger NICHE-2 study including 112 patients with stage I to III dMMR treated with nivolumab and ipilimumab remains unpublished, but meeting abstracts and presentations indicate a 99% pathologic response rate with 67% pCRs, with no recurrences after a median follow-up of 13 months.[129] Notably, the majority of enrolled patients had stage III disease. Long-term clinical outcomes for this regimen remain unreported, but clinical guidelines have now included immunotherapy as a preferred option when neoadjuvant treatment of dMMR/MSI-H tumors is planned (eg, for cT4b disease or locally unresectable). Standard neoadjuvant chemotherapy technically remains an option for dMMR/MSI-H tumors, but guidelines favor neoadjuvant immunotherapy for these patients since the FOxTROT neoadjuvant chemotherapy trial showed little benefit for dMMR/MSI-H tumors.[127]

Neoadjuvant RT (with or without concurrent chemotherapy) remains very infrequently used, for many of the same reasons as described in the previous section. Although neoadjuvant chemoradiation has been shown in randomized trials to improve LC/DFS in patients with rectal cancer, there is no high-level evidence demonstrating its effectiveness in patients with colon cancer although high rates of R0 resection and LC with low toxicity rates have been reported in retrospective studies.[130] Though its utility broadly may be limited, especially in light of improved neoadjuvant systemic options (discussed later), neoadjuvant RT may be an appropriate option for highly selected T4b tumors needing downstaging for surgical removal in fixed, reproducible anatomic locations. Addition of IORT at the time of surgery could also be considered, as described earlier.

Locally Advanced Disease and Palliation

Patients with unresectable tumors or metastatic disease at presentation often receive systemic therapy, but a complete review of systemic treatment

options for unresectable metastatic disease is outside the scope of this chapter. In many cases of metastatic colon cancer, systemic therapy can extend progression-free survival and OS. Frequently used treatments include irinotecan-based (eg, FOLFIRI: irinotecan-FU-LV) or oxaliplatin-based (eg, FOLFOX: oxaliplatin-FU-–LV or CAPEOX: oxaliplatin-capecitabine). In contrast to localized disease, the addition of bevacizumab[131] or an epidermal growth factor receptor (EGFR) inhibitor (eg, panitumumab or cetuximab)[132] prolongs progression-free survival and potentially OS. Molecular tumor features and tumor sidedness (left or right) contribute to decisions on which of these agents to include. For example, EGFR inhibition with panitumumab or cetuximab may be appropriate for patients with left-sided tumors with wild-type *KRAS/NRAS/BRAF*, and HER2-directed inhibition may be appropriate for some patients with *HER2* amplification and wild-type *RAS/BRAF*. Patients with dMMR/MSI-H or *POLE/POLD1* mutations and metastatic disease preferentially receive checkpoint inhibition immunotherapy. Patients with refractory disease may be treated with alternate regimens, depending on the initially used regimens. Treatment of refractory disease may additionally include multikinase inhibitors like regorafenib, fruquintinib or tipiracil/trifluridine, or biomarker-directed therapy for tumors bearing specific molecular alterations (eg, *BRAF* V600E, *HER2* amplification, *KRAS* G12C, *NTRK* gene fusion, or *RET* gene fusion).

Patients with near colonic obstruction may benefit from a diverting ostomy or stenting. Nonsurgical candidates may benefit from palliative radiation to shrink a painful, near- obstructing or bleeding mass.

Techniques of Irradiation

Patterns-of-failure data and the indication for treatment inform treatment field design in colon cancer. Historically, adjuvant treatment was utilized for locally advanced and/or node- positive tumors, and the larger field designs utilized reflect the goals of improving both local and regional nodal recurrence rates. However, current indications for adjuvant treatment are largely limited to treating T4 tumors, often in settings of perforation or positive margin, to prevent LF. Treatment objectives generally do not include attempts to limit regional nodal recurrences, especially considering

improved systemic therapy options. Thus, applying historical field design and doses to modern patient care should be interpreted through this refined lens. The discussion further will attempt to reconcile historical field design with modern three-dimensional (3D) CT-based planning and image-guided radiotherapy (IGRT) technologies in light of goals to reduce local recurrence.

Postoperative radiation field delineation requires great care to ensure accurate target coverage while minimizing normal tissue (especially bowel) exposure (Figures 67.2 and 67.3). If adjuvant therapy is planned, surgical clip placement in high-risk volumes (eg, positive margins) can assist with accurate field delineation as well as daily setup and alignment and should be discussed with the surgeon prior to the operation. Field arrangement will vary, depending on the site of the primary disease, as well as on areas judged to be at high risk for local recurrence. Optimal patient positioning (supine, prone, decubitus) displaces uninvolved bowel from the target volume while causing minimal target volume variability. It may be useful to compare simulation imaging in both the decubitus and supine positions to determine the actual amount of small bowel displacement. Immobilization aids and devices can be individualized to facilitate reproducibility and patient comfort. CT-based planning should be implemented to appropriately delineate target and organs at risk (OARs), and cone-beam CT image guidance utilized during treatment to ensure adequate target volume localization.

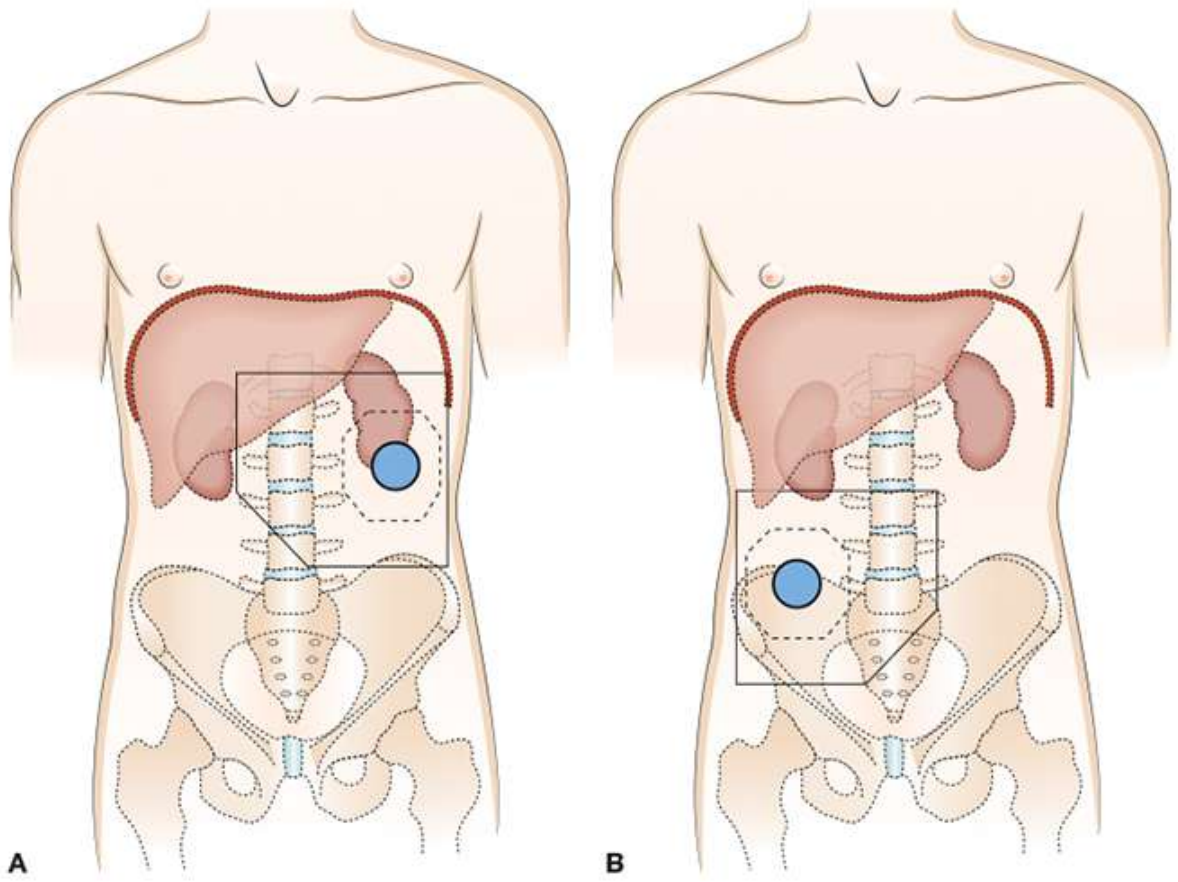

FIGURE 67.2 Historical postoperative anteroposterior/posteroanterior irradiation fields of extrapelvic colon cancer (tumor bed and nodal regions). If treated preoperatively, lateral fields could be added based on imaging with computed tomography of the abdomen and colon radiograph. A. Para-aortic nodes may be at risk, in addition to tumor bed, because of tumor adherence to posterior abdominal wall with descending colon cancer. B. External and common iliac nodes may be at risk, in addition to tumor bed, from a proximal cecal/ascending colon cancer. Note that these historical fields may be adjusted in contemporary treatments, as improved IGRT and conformal planning in light of improved systemic and surgical approaches may facilitate decreased field sizes. (From Gunderson LL, Martenson JA, Smalley SR, Garton GR. Lower gastrointestinal cancer: rationale, results, and techniques of treatment. In: Meyer JL, ed. *The Lymphatic System and Cancer: Mechanisms and Clinical Management: 28th Annual San Francisco Cancer Symposium, San Francisco, Calif., March 1993*. S. Karger AG; 1994:140-154. Copyright © 1994 S. Karger AG, Basel, Switzerland. Reprinted by permission.)

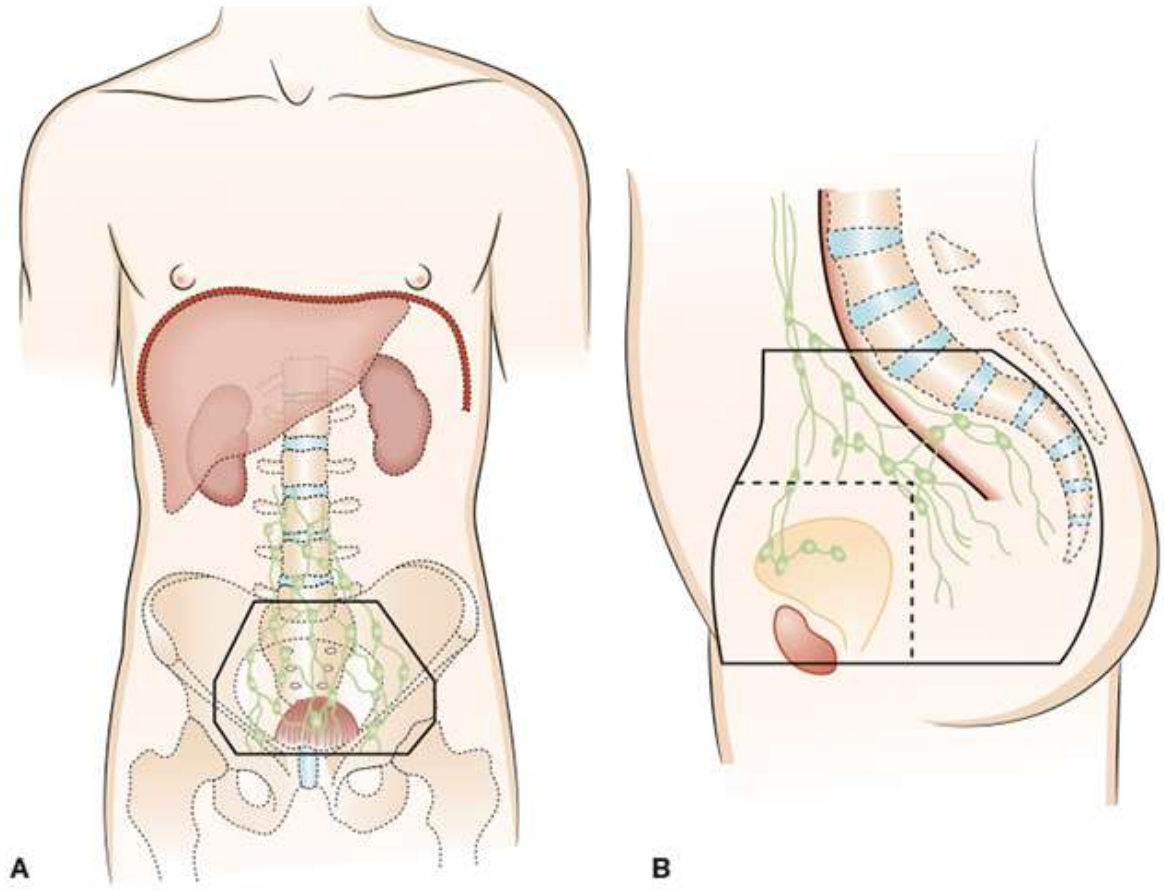

FIGURE 67.3 Historical multiple-field preoperative or postoperative irradiation technique for a sigmoid colon cancer adherent to the bladder. Solid lines, large field; interrupted lines, boost field. A. Anteroposterior/posteroanterior. B. Paired laterals. (From Gunderson LL, Martenson JA, Smalley SR, Garton GR. Lower gastrointestinal cancer: rationale, results, and techniques of treatment. In: Meyer JL, ed. *The Lymphatic System and Cancer: Mechanisms and Clinical Management: 28th Annual San Francisco Cancer Symposium, San Francisco, Calif., March 1993*. S. Karger AG; 1994:140-154. Copyright © 1994 S. Karger AG, Basel, Switzerland. Reprinted by permission.)

The total radiation dose used in the adjuvant treatment of colon carcinoma depends on the amount of suspected residual disease and tolerance constraints of surrounding normal tissue, and fields/treatment volumes depend on accurate target delineation and maintenance of safe doses to OARs like the small bowel. Much of the data regarding treatment of non-rectal colon cancers derives from studies predating the implementation of 3D conformal CT-based planning. Historically an initial dose of 45 Gy in 25 fractions at 1.8 Gy/fraction would be administered by

two-dimensional or 3D conformal multi-field radiotherapy plans to a larger at-risk region sometimes including elective nodal volumes, followed by a reduced-volume boost field to at least 50 Gy (and sometimes 54-60 Gy if a T4 tumor). Surgical clips were not always obtained and thus very large volumes were required to ensure target coverage. Historical fields covered the primary tumor site with a 4- to 5-cm margin proximally and distally and with a 3- to 4-cm margin medially and laterally. Elective nodal coverage beyond the primary volume was sometimes intentionally included in the early studies of adjuvant RT for colon cancers (as in the randomized Intergroup trial). However, the nodal basins in the mesentery beyond surgical margins rarely need treatment due to satisfactory margin clearance in these sites, and elective nodal coverage increases risk of toxicity from unnecessarily large treatment fields. For most tumors, treatment can be restricted to the tumor bed only, depending on the risk factors for recurrence and whether intensive chemotherapy is planned. Right colon tumors may represent an exception to this, depending on the circumstance, since the dual supply of the ileocolic vessels limits extent of mesenteric resection. Treatment of proximal mesenteric nodes may be appropriate if nodes adjacent to the surgical or resection margin are involved. In some instances, treatment of the para-aortic nodes may be indicated, particularly with extensive retroperitoneal involvement by tumor, but generally omission of para-aortic nodes is appropriate.

Implementing the general guidance that routine cases need not include elective nodal coverage, with modern CT-based planning and IGRT margins, can often be reduced considerably from those historically used. However, for the volume receiving 45 Gy, one should often retain a generous margin on the target of at least 1 to 2 cm (or even more if clips are not available or the site is particularly mobile) to account for target motion during either 3D conformal or IMRT planning. Ideally this at-risk volume is determined by concurrent consideration of both pre- and postoperative scans. Sequential boosting or simultaneous integrated boost IMRT strategies may permit dose escalation to 54 Gy or more to the site of highest risk while retaining appropriate OAR doses. Dosing to target is often determined by proximity to OARs and plans might require selective undercoverage in regions to maintain safety to nearby organs. Ideally, no more than 1 mL of small bowel should receive over 50 Gy and point

maximum should be limited to 54 to 55 Gy, with minimization of the volume of small bowel receiving 45 to 50 Gy. As in other abdominal malignancies, irradiation of a portion of one kidney is acceptable and results in minimal long-term clinical sequelae, assuming that baseline function in the contralateral kidney is normal.[133] At least two-thirds of one functional kidney should receive no more than 18 to 20 Gy, and at least two-thirds of the total liver volume should not receive more than 30 Gy.

Colon Cancer Summary

Advanced colon tumors may recur locally, regionally, or distantly after curative surgery, and numerous techniques have been implemented in attempts to reduce recurrence in each location. Studies investigating chemotherapy, immunotherapy, or RT as adjuncts to surgery have shown variable success rates. Depending on the tumor type and molecular features, neoadjuvant or adjuvant treatment with systemic chemotherapy or immunotherapy is often indicated for advanced colon cancers. Despite promising early data suggestive of a role for adjuvant RT in preventing local recurrences for advanced non-rectal colon cancers, the randomized Intergroup trial failed to recapitulate these findings. Although a failure to meet accrual goals, and the resultant limited statistical power, as well as several other flaws limit interpretation of that study, practice patterns have evolved since this time to reserve adjuvant RT or CRT for only very select cases where a risk of local recurrence is felt to be particularly high. Nevertheless, adjuvant (or potentially neoadjuvant) tumor bed irradiation with concurrent 5-FU-based chemotherapy should be considered for patients (a) with tumors invading adjoining structures, (b) with tumors complicated by perforation or fistula, and (c) with tumors where incomplete resection is performed. IORT with or without EBRT could also be considered for select cases, though much of the supportive literature derives from rectal cancer experiences and/or recurrent cancers.

RECTAL CANCER

Rectal cancer management paradigms differ from those for non-rectal colon cancers and generally reflect the unique features in anatomy, molecular biology, and patterns of recurrence for rectal cancers versus other CRCs.

Management of cancer of the rectum has undergone dramatic changes in the last several decades, including a rapid expansion of appropriate treatment paradigms for various clinical scenarios within the last several years. Historically, surgical resection represented the primary treatment modality. However, it became clear that in spite of radical resections, without additional treatment a significant proportion of patients developed local recurrence of disease (20%-50%), in contrast to colon cancer, which has less propensity for local recurrence (Table 67.3).[134,135] Local tumor recurrence of rectal cancer highly correlates with both the depth of penetration of the tumor and the number of regional nodes, and also likely reflects the limited space afforded for surgical interventions in the pelvis.[136] Over time, numerous cooperative group and randomized trials indicated that multimodality treatment approaches, particularly neoadjuvant treatment, result in a significantly better outcome than does surgery alone. Simultaneously, improvements in the efficacy of each treatment modality over time have revealed new opportunities to now consider de-escalation strategies that may omit one or more treatments previously considered essential for optimal management. Now, a patient with locally advanced rectal cancer may have the ability to choose between numerous excellent options for management, depending on the tumor features and anatomy, clinical comorbidities, and patient preferences.

TABLE 67.3 LOCAL AND DISTANT FAILURES: COLON AND RECTAL CANCERS TREATED WITH SURGERY ALONE

Stage	Locoregional Recurrence Rate
Colon cancer	
T1-T2 N0	3%-7%
T3/T4	13%-24%
N+	2%-19%
Rectal cancer	
T1-T2 N0	3%-14%
T3/T4	11%-31%
N+	14%-50%

Defining the True Rectum and Impact of Tumor Location

Rectal cancer comprises a spectrum of disease stages that needs careful definition to optimize multimodality treatment strategies. Moreover, as management of non-rectal colon cancers differs considerably from rectal cancer treatment paradigms, defining the true rectum remains crucial. Traditionally, the rectum extends for 12 to 15 cm from the anal verge, but this can vary considerably by sex, body habitus, and measurement technique. The inferior border of the true surgical rectum exists at the anorectal ring, just proximal to the dentate line. This represents the internal anal sphincteric muscle and is necessary for anal continence. It also represents the practical inferior limit for functional sphincter preservation surgery and defines the lymphatic watershed for rectal cancer spread. Tumors arising above the anorectal ring tend to metastasize along the distribution of the middle rectal vessels to the internal iliac lymph nodes, as compared to tumors that may extend into the anal canal, which may spread via nodes along the inferior rectal and external iliac pathways (Figure 67.4).[137] Cancers that arise in the anal canal may metastasize to the lungs (caval drainage) rather than the liver (portal drainage), as is common with most true rectal cancers. The prognosis of patients including the likelihood for LF worsens with more distal location of cancer, and these differences persist even with the addition of adjunctive therapy.[138]

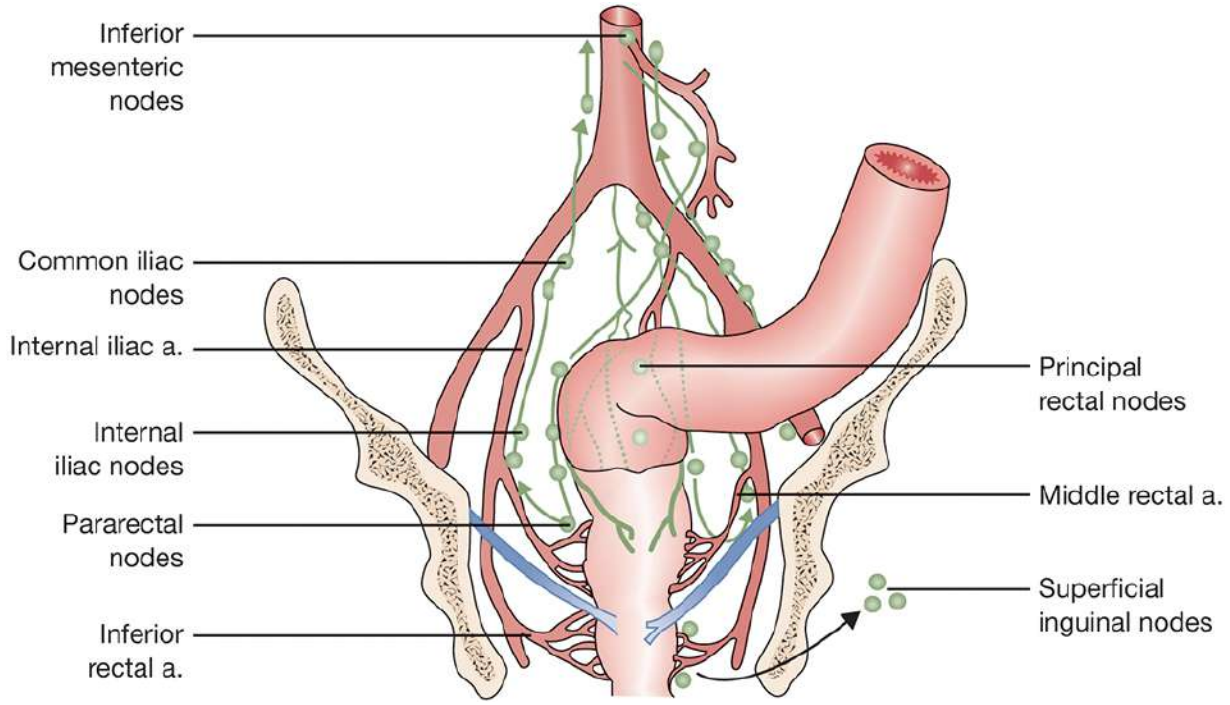

FIGURE 67.4 Lymphatics of the rectum.

During the workup of a patient with a suspected rectal cancer, information available through physical examination, radiologic studies, and endoscopy/proctoscopy examinations helps discriminate rectal cancers from more proximal sigmoid (ie, non-rectal colon) cancers or from more distal anal carcinomas.[139] Discrimination of the rectosigmoid junction can be particularly problematic.[74] A quick radiographic method to estimate the superior rectal extent from CT imaging alone involves drawing a straight line from the sacral promontory to the pubic symphysis, with the rectum generally falling below this (Figure 67.5). While a helpful tool for estimation, this technique is not foolproof in discriminating the rectosigmoid junction and may vary with patient anatomy so other tools must be utilized to determine the primary tumor site. Anatomically, the proximal rectum begins at the level at which the peritoneum is reflected along the anterior surface of the rectum (usually at the level of S3); additionally, proximally in the non-rectum colon, the teniae coli will be observed.[140] These are surgical observations and may be difficult to define in an intact patient, although MRI assists in identifying the anterior peritoneal reflection.[141] Endoscopically, the transverse folds of the rectum (also known as the valves of Houston) serve as helpful landmarks both for

rectal localization as well as distance markers from the anorectal ring. The upper valve of Houston demarcates the rectosigmoid junction endoscopically and the middle valve of Houston is a useful landmark that can often be identified endoscopically (usually about 6 cm from the anorectal ring) and can be used to differentiate proximal tumors from more distal lesions.[142] However, locations of these valves can vary from patient to patient.

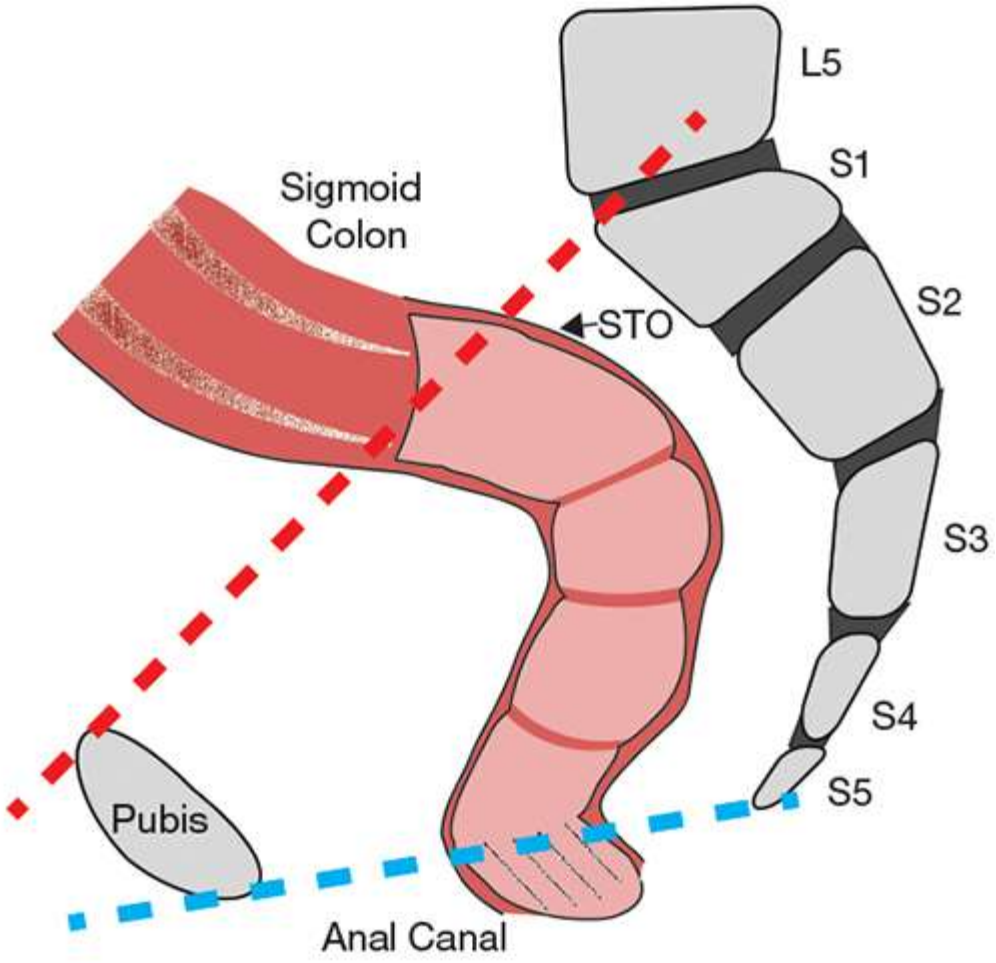

FIGURE 67.5 Schematic of rectal boundary landmarks. Sagittal view of schematized relationship between lumbar-sacral spine, rectosigmoid, anal canal, and pubis. Recent radiographic consensus indicates that the sigmoid takeoff (STO, black arrow) is the most reliable radiographic indicator of the upper rectal boundary and is the location where the rectum flexes anteriorly from the sacrum. This can vary considerably from patient to patient, so as a quick reference, the rectosigmoid boundary can be estimated as the place where a line drawn between sacral promontory and pubis intersects with the rectum (red dotted line). Though the anorectal junction is generally fairly easily distinguished at the level of the upper puborectalis sling on coronal magnetic resonance imaging, its location can be estimated on sagittal imaging as the location where a line drawn from the lower sacrum to the inferior pubis intersects with the anorectal region (blue dotted line).

Distally, the dentate line represents the transition point from columnar rectal epithelium to squamous anal epithelium, which can be observed endoscopically but is not recognizable on imaging. Radiographically, MRI can readily discriminate the anorectal junction, and this location is often

used as the landmark for rectal measurements. On CT or MRI, an estimate of the location of the anorectal junction can be made by drawing a line between the lower margin of the sacrum and the lower boundary of the pubic symphysis on sagittal sections. More accurately, on MRI the anorectal junction occurs at the level of the upper boundary of the puborectalis sling.[139] Most tumors that can be digitally palpated are generally considered distal cancers, and one can palpate the anorectal junction (the surgically defined anal/rectal boundary) at the level of the muscular anorectal ring, usually about 1 to 2 cm above the dentate line. While anal cancers tend to more often be characterized by squamous cell histology (and rectal cancers by adenocarcinoma), histology alone does not discriminate the origin of a tumor since anal adenocarcinomas and rectal squamous cell carcinomas do exist.

Prognostic Factors

Several prognostic factors, in addition to tumor location, have been shown to have a significant impact on tumor behavior. Tumor stage, as defined by the American Joint Committee on Cancer staging, clearly remains the dominant determinant of survival. Pathologic factors like LVI, PNI, mesorectal integrity on total mesorectal excision (TME), and CRM status have clinical significance and should be incorporated into treatment decision-making.[143,144] Circumferential tumors or those with total or near-total obstruction (lumen <1 cm) may respond very poorly, and tumors with deep central ulceration are associated with a high incidence of lymph node involvement.[145] Tumor mobility can be a key factor in both choice and outcome of treatment.[146,147] Mobile cancers have a much more favorable outcome as compared to tethered or fixed cancers. Surgery for fixed cancers can be ineffective, and these tumors are often classified as unresectable. Tumor fixation, although harder to assess in the proximal rectum, is less often encountered without other adverse factors such as circumferential disease with obstruction or perforation.[148] Tumor fixation is much more problematic in the distal rectum because the confines of the bony pelvis inhibit the surgeon’s ability to achieve adequate lateral/circumferential margins. Other patient factors, such as age, gender, and ethnicity, appear to have little association with outcome but may affect choice of therapy. As

neoadjuvant therapy has emerged as the standard of care, degree of tumor regression has become an important prognostic factor.[149,150] Pathologic assessment of tumors after neoadjuvant therapy receives a special designation of ypTNM in annotating pathologic staging.

Treatment

Surgical Considerations and Total Mesorectal Excision

Historically, curative treatment for rectal carcinoma required surgery. Even with the more recent proliferation of non- operative strategies for rectal cancer (discussed later), they are only possible due to the availability of high-quality oncologic surgical procedures should other modalities fail or tumors recur.

Surgical management depends on the stage and location of a tumor within the rectum. Early cancers can be managed with limited surgery (ie, local excision) in selected situations; however, the majority of tumors tend to present as more advanced disease and require either a low anterior resection (LAR) or abdominoperineal resection (APR). The general principles of a surgical approach involve the removal of all gross and microscopic disease with negative proximal, distal, and circumferential margins. In the case of radical resection, this means removal of the adjacent mesorectal tissue (TME), containing the regional lymphatics and potential tumor deposits. Several studies have shown that the surgeon's experience with resection of CRC is an independent variable in the outcome of treatment.[151] The Intergroup 0114 trial found that for stage II and III rectal cancers, not only were APR rates higher in hospitals with low procedural volume (46% vs 32%), but more patients had positive resection margins.[152]

Despite historical practices suggesting 5-cm distal margins of normal rectum were required for adequate surgical resection, distal intramural spread of tumor is rare beyond 1.5 cm, and therefore, a 2-cm distal margin is generally considered acceptable except in lesions that are poorly differentiated.[153-156] The American Society of Colon and Rectal Surgeons (ASCRS) additionally specify that for very distal tumors a margin of 1 cm or even less may be acceptable for highly selected patients who are highly motivated for sphincter preservation and demonstrate good response to neoadjuvant treatment modalities.[141] The reduced distal margin extent

requirement has led to a significant increase in the likelihood of sphincter preservation procedures in this disease.

Transanal Local Excision

Early rectal cancer (Tis or T1 disease) may be resected with local excision techniques, avoiding major surgery and a colostomy. However, patients should be carefully selected for these procedures and warned that the rate of local recurrence exceeds that seen with radical resection and that if pathologic findings indicate more advanced disease, they may still require radical resection as well as potentially treatment with other modalities. Local recurrence after local excision of T1 tumors may be as high as 7% to 21%, and historical data indicate that even T1 tumors may have occult nodal disease in 5% to 10% of patients, most often with more advanced pathologic features.[157-162] However, with proper selection T1 lesions have very good results with local excision alone, with 5-year LC ranging from 82% to 97% and OS rates of 90% or better.[163] Local excision is not oncologically appropriate for T2 lesions due to excessively high local recurrence rates (26%-47%) and the elevated risk of occult nodal disease (verging on 20%-35% for T2 disease). Given these results, efforts have been made to provide sphincter-sparing opportunities for >T1 disease by combining local excision with other modalities, like CRT, as discussed in later sections.

Transanal approaches currently dominate local excision techniques, though historical options for local excision included transsphincteric excision (York-Mason) and a posterior parasacral approach (Kraske). Transanal excision approaches are suitable for small (<3-4 cm), accessible (<8 cm from the anal verge), Tis or T1 cancers involving less than 30% of the rectal circumference that are mobile, polypoid, and not ulcerated and bear favorable histologic features like well/moderate differentiation and no tumor budding, no LVI, and no PNI.[74,164,165] An adequate resection requires full thickness resection (into the fat), with the tumor being removed in one uninterrupted specimen with at least a 1-cm radial margin and 2-mm deep margin, with orientation of the specimen so that careful pathologic assessment can be performed.[74] Multiple platforms support transanal

excisions, including transanal endoscopic microsurgery and transanal minimally invasive surgery.

Radical Surgical Approaches: Abdominoperineal Resection and Low Anterior Resection

APR has a long history of use for surgical resection of distal rectal cancer and requires removal of the primary tumor along with a complete proctectomy, leading to a permanent colostomy. As sphincter-sparing options have proliferated, the rate of APR has declined, dating back to the 1980s.[166] APR may be associated with a slightly higher morbidity and mortality than LAR and a worse quality of life (QOL) related to changes in body image and depression due to the presence of a colostomy.[166-168] There is also a higher risk of positive margins with APR because the mesorectum is thin in the distal segment of the rectum and margins are often restricted by the proximity of the prostate or vagina. The confines of the bony pelvis, particularly in males, can also restrict surgical access.[169] Perineal wound complications occur relatively commonly after APR, and neoadjuvant RT increases the risk of such complications. One meta-analysis of 7,247 patients reported a perineal wound complication rate of 15.3% without radiation, and 30.2% when APR followed neoadjuvant RT.[170] Many of the studies evaluating neoadjuvant therapy for rectal cancer have derived from a desire to avert the need for APR and its attendant side effects.

The advent of circular stapling devices expanded the role of sphincter-preserving surgical options in rectal cancers, and LAR transitioned from utilization only for upper rectal tumors to implementation for tumors in middle and even distal rectal tumors using “ultralow” anterior resections.[171] Choice of coloanal or colorectal anastomosis depends on the site of tumor and margins required. Preserving adequate anorectal function becomes increasingly difficult the more distal the level of anastomosis.[172] Patients should have good anal sphincter continence prior to considering sphincter-preserving options. Patient age, pelvic anatomy, gender, and body habitus can affect suitability for sphincter preservation. For upper tumors, routine excision of at least 5 cm of distal margin is recommended. For mid or distal tumors, guidelines recommend an ideal 2-cm distal margin, but note that 1 cm margins may be acceptable in well-selected patients and even shorter

distal margins may be acceptable in patients motivated for sphincter preservation with tumors exhibiting favorable responses to neoadjuvant therapy.[74] Creating a tension-free anastomosis may aid in preventing postoperative anastomotic leaks, so many surgeons employ splenic flexure mobilization to facilitate this reconstruction. In the irradiated pelvis, this can also ensure the availability of an unirradiated bowel segment for use in the anastomosis. Generally, contraindications for LAR include tumors involving the anal sphincter or levators, where there is loss of the intersphincteric plane, or where margin-negative resections would result in unacceptable sphincter function. For these cases, APR likely represents the best radical surgical option. Several studies comparing the results of LAR to APR generally reported similar outcomes for local and distant recurrence rates and survival as long as surgical margins are negative.[167,173] The absence of a colostomy may augment some aspects of QOL after LAR, but other toxicities including LAR syndrome (bowel urgency, frequency, or poor sphincter control) occur with some frequency and can negatively impact QOL.[74,174,175]

Total Mesorectal Excision

Historically, high rectal cancer local recurrence following standard APR or LAR (15%-30% or more) was attributed to blunt surgical dissection techniques violating the mesorectal fascia.[176] Moreover, despite limited distal intramural tumor spread beyond rectal cancers, the mesorectum facilitates more distal spread of tumors. Whereas intramural tumor is rarely found more than 1 cm beyond the edge of the tumor, deposits of mesorectal tumor or nodal spread can occur up to 4 cm distal from the tumor. Heald et al recommended en bloc removal of the tumor within the envelope of the endopelvic fascia as necessary to obtain adequate lateral clearance of disease and reduced likelihood of local recurrence.[177,178] TME, as they described, has become the established standard for all radical rectal cancer resections and requires sharp dissection along the plane that separates the visceral from the parietal pelvic fascia with complete en bloc removal of the rectum so that all of the rectal mesentery remains within the envelope of the specimen.[145] Indeed, pathologic assessment in a large randomized trial found that the plane of surgery—mesorectal, intramesorectal, or muscularis

propria plane—predicted for local recurrence. Three-year local recurrence was 4% in patients undergoing complete mesorectal excision, compared with 7% and 13% in the intramesorectal and muscularis propria groups, respectively.[100]

On gross pathology, an adequate TME specimen will have a bilobed, encapsulated appearance, with the surface looking smooth and unbroken, like a lipoma (Figure 67.6). On pathologic review, an appropriate dissection should include a minimum of 12 to 15 perirectal and pelvic lymph nodes.[74] TME, although more difficult with APR than LAR, may be associated with a somewhat higher anastomotic leak rate, especially for low rectal lesions (15%-17%).[104,145,151] Multiple series using TME surgery have reported low rates of local recurrence (ranging from 5% to 10%) and an improvement in OS approaching 80% to 85% for stage II and 65% to 70% for stage III disease.[100,139,152-154] The implementation of TME into clinical treatment paradigms drove the local recurrence rates of rectal cancer downward, and it remains an important reason for the extremely low local recurrence rates seen using modern multimodal treatments for locally advanced rectal cancer.

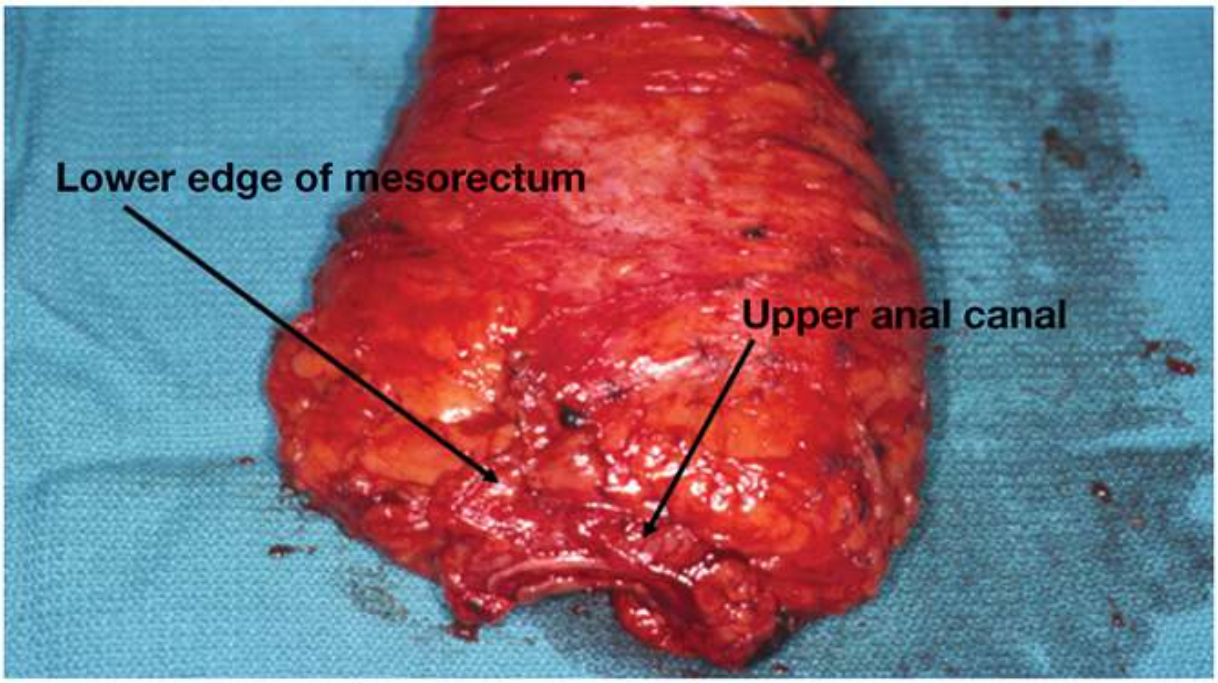

FIGURE 67.6 Total mesorectal excision specimen with designation of the lower mesorectum and upper anal canal.

Transanal TME approaches have begun to find traction in the surgical repertoire, though recommendations for routine use remain guarded. Early concerns regarding intraoperative complications and multifocal local recurrences during use of these operations led to temporary moratoria on the use of this technique in several countries.[179-181] However, two randomized trials have subsequently lent support to the safety and utility of this technique in comparison to laparoscopic TME approaches, when performed by experienced surgeons.[182,183] This has led to a conditional recommendation by the ASCRS that transanal TME may yield similar complication rates and functional outcomes, with a meta-analysis identifying no statistically significant differences in oncologic outcomes relative to open TME or laparoscopic TME.[184] More data will be required to fully characterize the efficacy of this technique in terms of oncologic outcomes, and concerns regarding the possibility for higher rates of LAR syndrome with transanal TME will be addressed in ongoing studies.[185]

Laparoscopic Approaches

As for colon cancer surgery, laparoscopic surgery for rectal cancer offers potential advantages of reduced blood loss/perioperative morbidity and shorter hospitalizations. Initial randomized studies suggested that in the hands of an experienced surgeon, outcomes from laparoscopic surgery appear no different than those from open resection in a number of randomized trials.[186-188] However, subsequent randomized controlled phase III trials prompted a reevaluation of this initial impression, as they failed to demonstrate noninferiority of laparoscopic methods versus open methods for composite pathologic outcomes or successful resection.[189,190] Meta-analyses similarly raise concerns about incomplete resection in patients treated with laparoscopic approaches.[191,192] Corroboration within survival data has lagged, as long-term results remain pending for most of these studies. Short-term oncologic outcomes did not significantly differ for local recurrence or DFS in these studies, but events were limited and thus longer term follow-up is needed.[174,193] The current ASCRS guidelines recommend laparoscopic and/or robotic TME in the hands of experienced surgeons.[74]

Radial Margin

It has long been recognized that a principal reason for local recurrence in resected rectal cancer appears to be related to the anatomic constraints in obtaining wide radial margins, despite adequate proximal and distal margins. As early as the 1980s, using whole-mount specimens, Quirke et al found that 27% (14 of 52) of patients showed spread to the lateral radial margin, even though the margins appeared negative with standard pathologic assessment. Eighty-six percent of those with positive radial margins developed local recurrence of disease, as compared to only 3% without lateral resection margin involvement.[194] A positive radial margin is a predictor not only of local recurrence but also of inferior survival.[145] In the era of widespread use of TME, a positive CRM continues to associate with increased local recurrence and decreased survival.[195,196] Fortunately, with the implementation of routine MRI local tumor staging, prediction of close or involved CRMs can yield information about recurrence risk and help guide multimodal treatment decisions.[196,197]

Adjuvant Therapy

Early Postoperative Treatment

The problem of unacceptably high local recurrence after surgery for rectal cancer prompted initial interest in selective use of adjuvant therapy. Though selective administration of adjuvant therapy based on pathologic factors (eg, T3/T4 or N+ disease) has the capacity to minimize the number of patients receiving adjunctive treatments, disadvantages exist. A potentially hypoxic postsurgical bed impacts the efficacy of radiation and chemotherapy. Postsurgical anatomy often increases the small bowel in the radiation field, increasing complications especially considering the larger treatment volumes required, particularly in patients undergoing an APR where the perineal scar may need to be covered. Though adjuvant treatment played an important role in the evolution of treatment patterns for rectal cancer and is still occasionally utilized, current paradigms strongly favor neoadjuvant treatment for locally advanced disease (see section “Neoadjuvant”).

Several early trials assessed the role of adjuvant RT compared to surgery alone. These trials showed reduced LFs with RT; however, no improvement in DFS, DM, or OS was seen. Thus, in an effort to improve outcomes, the

role of adjuvant CRT was evaluated. Summarizing the results, surgery alone resulted in a 25% LF rate and 40% to 50% OS for T3 or T4 or node-positive patients, whereas adjuvant CRT yielded a lower LF rate of 10% to 15% and higher OS of 45% to 60%. Notably, during this same era, improved surgical techniques like TME either had not been employed or were just beginning implementation. Thus, review of the results and specific outcomes numbers for each trial should consider this context.

Two early randomized studies demonstrated an OS benefit to adjuvant CRT. The Gastrointestinal Tumor Study Group (GITSG) study (1975-1980) was a four-arm trial of 227 patients with R0 resections of stage B2 and C (corresponding to T3 or N+) rectal cancer.[198] The four randomization arms were: surgery alone, postoperative bolus 5-FU/semustine, postoperative split-course radiation (40-48 Gy), and postoperative bolus 5-FU-based CRT (40-44 Gy). Early review indicated substantial benefits for CRT and the trial was terminated early, and a subsequent update reported that postoperative CRT improved 10-year OS, 45% versus 27%, compared with observation after surgery. Covariate-adjusted comparisons of survival relative to the other arms trended toward improvement with CRT, but were not statistically significant. LF rate was decreased to 10% with CRT versus 25% with surgery alone. Therefore, this trial concluded that there was a significant OS advantage (near doubling of survival) for patients who had CRT after surgical resection. The Mayo–North Central Cancer Treatment Group (NCCTG) study (1980-1986) compared postoperative RT against postoperative CRT.[199] Two hundred and four patients with T3/T4 or node-positive tumors received chemotherapy (1 cycle 5-FU/semustine) before randomization. The radiation dose was 45 to 50.4 Gy to tumor bed and adjacent lymph node regions and CRT utilized a bolus 5-FU regimen. All 5-year outcomes favored the CRT group, including locoregional failure (25% RT only vs 13% CRT) and OS (40% RT only vs 55% CRT).

In contrast to the GITSG and NCCTG trials, the NSABP R-02 study did not identify a survival benefit to CRT treatment. This study enrolled 694 patients with Dukes stage B and C (corresponding to patients with T3/T4 or N+). One of the study questions assessed the utility of 5-FU-based CRT (50.4 Gy) versus 5-FU/LV without radiation. The 5-year locoregional failure rate was 13% for the chemotherapy-only arm as compared to 8% with CRT, but survival was not impacted.[200]

Given the potential benefits seen with CRT, additional trials attempted to refine the type and delivery of chemotherapy to maximize benefit with lower toxicity. The NCCTG 86-47-51 study compared chemotherapy regimens (5-FU vs 5-FU/semustine) and methods of chemotherapy delivery (bolus or continuous infusion [CI]) when added to postoperative RT (50.4-54 Gy).[201] Semustine had no additional benefit beyond 5-FU chemotherapy, but CI 5-FU showed benefits with respect to relapse-free survival (63% CI vs 53% bolus 5-FU), DM (31% vs 40%), and 4-year OS (70% vs 60%). Toxicity type varied, but overall were temporary and manageable. Considering the absence of an LC difference, the disease outcome improvements associated with CI 5-FU likely reflected systemic rather than local disease control. The Intergroup 0114 study compared different chemotherapy in CRT regimens in 1,695 patients and found no clinical benefit, and increased toxicity, to the addition of levamisole or LV to bolus 5-FU.[164]

Adjuvant Treatment for Favorable T3 N0

Tumors that have a cT3N0 stage and other favorable features (upper rectum location, no LVI, shallow perirectal depth of invasion, and well- or moderately differentiated histology) may not warrant adjuvant treatment (chemotherapy or RT) after up-front TME. Several studies demonstrate a subset of tumors that might not need adjuvant therapy (chemotherapy or CRT or both), given the low risk of recurrence with surgery alone. Memorial Sloan Kettering Cancer Center evaluated 95 patients with T3 N0 rectal cancer treated by surgery alone.[202] Seventy-nine patients underwent LAR and 16 patients underwent APR, both with sharp mesorectal excision. With 53.3-month follow-up, 6% had local recurrence, 13% had DM, and 3% had both local recurrence and DM. LVI was the only histologic factor that was important for local recurrence. This study suggests that sharp mesorectal excision with LAR or APR for T3 N0 rectal cancers results in low local recurrences of less than 10% without the use of adjuvant therapy.

In a retrospective review of 117 patients with T3 N0 rectal cancer treated at the MGH, perirectal tumor invasion of 2 mm or more, LVI, and poorly differentiated histology were independent factors for increased risk of DM and worse RFS.[203] Only depth of invasion was significant for LC. Of the 25

patients with favorable histologic features (well differentiated/moderately differentiated, invading less than 2 mm into the perirectal fat, no LVI), the 10-year actuarial LC and RFS were 95% and 87%, respectively, as compared to 71% and 55% in the unfavorable group.

A pooled analysis of five randomized, controlled trials assessed survival and relapse rates by T and N stage in patients receiving or not receiving additional therapy after resection.[204] In patients with T3 N0 disease, 5-year survival of patients undergoing surgery and adjuvant chemotherapy alone was 84% and compared favorably to the 74% to 80% survival in patients undergoing surgery and adjuvant CRT. DFS in the T3 N0 subgroup was 69%. Notably most of these studies did not stage using EUS or MRI.

Now that neoadjuvant administration of nonsurgical treatment dominates treatment timelines, discrepancies between clinical staging and pathologic stage persist as an issue impacting treatment decision-making for the cT3N0 subset, despite the routine use of EUS- and now MRI staging. As discussed earlier, cT3N0 rectal cancers, especially those with favorable risk factors, may often be treated effectively with surgery alone or surgery plus adjuvant chemotherapy. Moreover, the German Rectal Cancer Study indicated approximately 18% of cT3/T4 or cN+ tumors were overstaged and were actually stage II disease.[205] However, a report from Memorial Sloan Kettering of 188 patients with cT3N0 rectal cancer (staged by EUS or MRI) treated with neoadjuvant CRT and radical resection indicated that 22% of patients had mesorectal nodal disease at surgery after CRT.[206] In other words, at least as many, if not more, patients are understaged than overstaged. This general perception, as well as the additional toxicity and local recurrence risk associated with adjuvant RT sequencing, had driven most oncology teams to favor neoadjuvant treatment for cT3N0 patients, even considering the likelihood that a minority are likely overstaged and thus overtreated. As discussed in section “Attempts to De-Escalate Multimodal Therapy For Rectal Cancer,” the PROSPECT trial supports providing patients an option for de-escalation of neoadjuvant multimodal therapy by omitting radiation for a subset of favorable tumors. Notably these patients still received neoadjuvant chemotherapy. Regardless, this approach lends credence to notions that some favorable T3N0 tumors may permit some de-escalation of therapy intensity, though omission of both chemotherapy and RT has not been evaluated in a randomized context.

Neoadjuvant Therapy

Neoadjuvant Radiotherapy

Though both preoperative and postoperative treatment regimens can be effective, neoadjuvant treatment has emerged as the standard of care. Neoadjuvant therapy provides tumor downstaging, improved resectability and tolerance (both acute and chronic), and potential for expanded sphincter preservation options in the distal rectum. Studies from Europe have demonstrated that appropriate neoadjuvant preoperative radiation results in improvement of LC (and OS in some studies, though this was restricted to the era predating modern surgical and chemotherapy approaches), and these results have had a significant impact on the current management of this disease.

The Swedish Rectal Cancer Trial included 1,168 patients accrued from 1987 to 1990 with resectable, Dukes A to C rectal cancer.[207] Patients were randomized to 25 Gy in five fractions in 1 week followed by surgery 1 week later versus surgery alone. At a median of 13 years, local recurrence was 9% versus 26% and OS was 38% versus 30%, both in favor of preoperative RT, with all stages benefiting.[208] One major caveat of this study is that the surgery-alone arm did not use TME, which likely contributed to the unacceptably high 13-year LF rate of 26%. Preoperative RT administration was associated with elevated rates of late effects, including increased bowel movement frequency, incontinence, urgency, and soiling in the preoperative radiation treatment arm, although overall QOL was rated good.[209] A higher rate of small bowel obstruction was also seen in the preoperative RT arm.[210] This trial set the standard of care in many European centers, but the dose of 5 Gy times five fractions may potentially contribute to late toxicity, and the short interval between radiation and surgery likely did not allow sufficient time for tumor regression (downstaging) for improved sphincter preservation. The contemporaneous Stockholm-I and -II studies had made similar comparisons, randomizing between short-course 25 Gy in five-fraction neoadjuvant RT followed by surgery versus surgery alone.[211,212] These studies corroborated the benefit of preoperative RT on LC and (for Stockholm-II) OS in the pre-TME era.

The TME experience by Heald et al[177] suggested that TME alone may be sufficient for achieving low local recurrence rates, so it was unclear what

additional benefit neoadjuvant radiation provided in the TME era. A Dutch (CKVO 95-04) multicenter, phase III study of 1,861 patients was undertaken to evaluate the role of short-course preoperative radiation with TME. Patients were randomized to TME alone versus 25 Gy in five fractions followed by TME surgery after 1 week.[213] The included patients had relatively favorable tumors—no fixed tumors were included in the study, and approximately half of the patients had T1 or T2 disease. The 2-year OS was 82% in both arms of the study; however, the 2-year local recurrence was 8.2% in the TME-only arm as compared to 2.4% in the preoperative arm. Ten-year follow-up indicates persistent benefit in local recurrence of 5% (RT) versus 11% (TME alone) ($P < .0001$) without difference in DMs or OS.[214] This highlighted the value of radiation treatment for LC, despite the use of TME and the inclusion of less advanced disease. Notably, this study also used a short interval (1 week) between RT and surgery, so the sphincter preservation rate was the same in both arms, and there was no clear evidence of any downstaging effect. The perineal complication rate was slightly higher in the preoperative radiation arm of 26% versus 18% in the TME arm.[215,216] Updated toxicity analysis indicates a higher incidence of sexual dysfunction and slower recovery of bowel function, more fecal incontinence, and generally poorer QOL with short-course preoperative radiation.[217,218] Since this trial enrolled earlier stage disease (no fixed tumors, half with T1-T2 disease), these data indicated a role for RT alongside TME, even in less advanced rectal tumors.

The UK Medical Research Council CR07 supported the Dutch TME experience, demonstrating that neoadjuvant RT administration was associated with lower locoregional recurrence rates (LRRs) in patients who largely received TME radical surgeries. This multinational study of 1,350 patients with operable non-metastatic rectal carcinoma was randomized to preoperative RT (25 Gy in five fractions) or initial surgery with selective adjuvant CRT based on CRM involvement.[219] TME was not mandated, but surgeons assessed it had been performed in 93% of operations, and pathologic specimen analysis indicated 86% were TME specimens, and those patients with appropriate TME resection planes demonstrated improved LC.[143] Neoadjuvant RT decreased local recurrence by an absolute difference of 6.8% at 5 years (4.7% in RT arm, 11.5% in up-front surgery arm; $P < .0001$), with no difference in OS.

Multiple large meta-analyses corroborate a role for preoperative radiation treatment in preventing local recurrence.[220-222] One early analysis included 14 randomized, controlled trials, albeit with wide-ranging RT and surgical techniques employed, and reported that neoadjuvant radiation treatment was associated with significantly fewer LRs, improved cancer-specific survival, and an OS benefit.[222] The Cochrane meta-analysis included four trials comparing neoadjuvant RT and surgery to surgery alone, with a total of 4,663 patients analyzed, limiting the study to trials utilizing 3D conformal multi-field RT techniques.[221] The analysis again indicated improved LC after neoadjuvant RT, regardless of whether TME was performed. OS was higher in the RT group, though this was not evident in a subgroup analysis including only those patients who received TME. In sum, these meta-analyses substantiate a role for neoadjuvant RT in decreasing local recurrence rates; any OS or cancer-specific survival benefit was quite small and likely related to premodern surgical and chemotherapy regimens.

Neoadjuvant Chemoradiation Therapy

The improvement in outcomes with CRT in the postoperative/adjuvant setting led to implementation of this approach in neoadjuvant treatment of this disease. While readily implemented in the United States, the standard European treatment paradigm remained neoadjuvant RT alone, including numerous regimens with standard fractionation (rather than the short-course RT utilized in many of the trials discussed earlier). Several studies were undertaken to compare neoadjuvant RT alone versus neoadjuvant CRT approaches using standard fractionation.

Preoperative RT was compared with combined preoperative CRT in a French study (Fédération Francophone de la Canérologie Digestive 9203; 1993-2003).[223] Seven hundred and thirty-three patients with resectable T3 and T4 tumors accessible by DRE were randomized to 45 Gy (in 1.8 Gy fractions) of radiation alone versus the same dose and radiation fractionation with concurrent bolus 5-FU plus LV and four adjuvant chemotherapy cycles. Although there was no difference in 5-year OS (primary endpoint) between the two arms, pCR rates (11.4% vs 3.6%) were higher and local recurrence rates (8.1% vs 16.5%) were lower with CRT.

Grade 3/4 acute toxicity was more frequent in patients receiving CRT, at 14.6% versus 2.7%.

A similar study undertaken by the European Organization for Research and Treatment of Cancer (EORTC 22921) randomized more than 1,000 patients to four arms (2 × 2 design): 45 Gy alone versus 45 Gy plus bolus 5-FU and LV followed by surgery, with patients further randomized to adjuvant therapy with 5-FU/LV or no adjuvant therapy.[224] Results of the study were similar to those of the French study, with increased tumor downstaging (14% vs 5.3%; $P = .0001$) and lower rates of local recurrence (9% vs 17%) but no difference in 5-year OS (65% in both arms). This information suggests that although there are lower rates of recurrence, there is no conclusive evidence that combined treatment offers a survival benefit compared to radiation alone in the neoadjuvant setting. There is, however, a higher incidence of acute toxicity associated with combined CRT.

A subsequent meta-analysis pooled four trials and compared results of preoperative RT with preoperative CRT in patients with resectable stage II or III rectal cancer.[225] The addition of chemotherapy significantly increased rates of grade 3/4 acute toxicity (odds ratio [OR], 1.68-10) and higher rates of pCR (OR, 2.52-5.27) and lowered the incidence of local recurrence (OR, 0.39-0.72). No difference was seen in 5-year DFS or OS. Although the aforementioned studies and meta-analysis do not show a DFS or OS benefit with the addition of chemotherapy to neoadjuvant RT, given higher pCR as well as improved LC, neoadjuvant CRT supplanted standardly fractionated neoadjuvant RT as a reasonable standard of care.

Long-Course Neoadjuvant Chemoradiotherapy Versus Short-Course Neoadjuvant Radiotherapy

In parts of Europe where a hypofractionated preoperative RT regimen became preferred, the Polish rectal cancer group initiated a study to determine whether outcomes of a short-course approach (5 Gy for five fractions and surgery within 1 week) surpassed a protracted approach (50.4 Gy using 1.8- to 2-Gy fractions with concomitant bolus 5-FU/LV in weeks 1 and 5).[226] TME was specified as the surgical approach. Although a higher pCR rate was seen with CRT (16% vs 1%) along with fewer positive radial margins (4% vs 13%) and considerable size reduction of the tumor (by ~1.9

cm), no difference in the rate of sphincter preservation (the primary outcome), LC, or OS was seen.

In the Australian Intergroup Trial, 326 patients with cT3NxM0 rectal cancer within 12 cm of the anal verge were randomized to short-course RT (25 Gy in five fractions) with surgery within 1 week or long-course CRT (50.4 Gy in 28 fractions with the more standardly used CI 5-FU) with surgery 4 to 6 weeks following completion of CRT.[227] Both regimens were followed by adjuvant 5-FU-based chemotherapy. Over 90% of patients were clinically staged with pelvic MRI or EUS. With a median follow-up of 5.9 years, there was no difference in 3-year local recurrence (7.5% short course vs 4.4% CRT; primary endpoint), 5-year OS (74% short course vs 70% CRT), or late toxicity. Despite tumor downstaging, there was no difference in rates of sphincter-sparing surgery. An examination of acute adverse events (AEs) and postoperative complications demonstrated more AEs in the long-course arm, and no statistically significant differences in surgical complication rates, though the authors note trends favoring long course for permanent stoma and anastomotic breakdown and favoring perineal wound complications with short course.[228]

The optimal neoadjuvant approach for resectable rectal cancer remains far from clear and approaches vary by site of treatment, with CRT more common in the United States and short course more common in Europe. Regardless, both short-course RT (25 Gy in five fractions) and long-course CRT (50.4 Gy in 28 fractions) with concurrent 5-FU-based chemotherapy represent reasonable therapeutic options. As discussed in section "Total Neoadjuvant Therapy," neoadjuvant intensification by combining preoperative local and systemic therapy has also become a frequently employed treatment option.

Preoperative Versus Postoperative Therapy

Numerous phase III trials have compared preoperative versus postoperative CRT treatment strategies. Initial smaller phase III studies provided support for the neoadjuvant administration of CRT. The NSABP R-03 study was scheduled to accrue 900 patients but closed after accruing 267 patients.[229] This study randomized individuals with operable rectal adenocarcinoma to surgery followed by one cycle of 5-FU/LV and then concurrent bolus 5-

FU/LV with radiation treatment versus 5-FU/LV for one cycle and then concurrent CRT treatment followed by surgery. Although the study was underpowered and TME was not mandated, 5-year DFS was superior in the preoperative therapy group: 64.7% versus 53.4% (P = .011), with a trend toward improved OS and a 15% pCR rate. A Korean trial randomized 240 patients with locally advanced (cT3/T4 or N+) rectal cancer to preoperative or postoperative CRT (50 Gy in 25 fractions, plus concurrent capecitabine), with TME resection and four cycles of adjuvant 5-FU- or capecitabine-based chemotherapy. The 5-year DFS, OS, and local recurrence rates were no different between the two arms. Patients with low-lying rectal tumors (<5 cm from the anal verge) had higher rates of sphincter preservation in the preoperative arm (68% vs 42%; P = .008).

The definitive phase III study in favor of preoperative RT was the CAO/ARO/AIO-94 study performed by the German Rectal Cancer Group.[205,230] Eight hundred twenty-three cT3/T4 or node-positive rectal cancers (not MRI staged) were randomized to preoperative CRT followed by TME 6 weeks later or TME followed by postoperative CRT. The radiation dose was 50.4 Gy in 28 fractions in all patients, with a 5.4-Gy small-volume boost in the postoperative arm. 5-FU (1 g/m^2/day) was administered during weeks 1 and 5 of RT as a 120-hour CI. Both arms received four additional cycles of adjuvant 5-FU (500 mg/m^2/day for 5 days every 4 weeks). All surgeons were trained in the use of TME and were asked, prior to treatment, to evaluate the possibility of sphincter preservation. There was significant tumor downstaging after preoperative CRT, with an 8% pCR. Nodal positivity was 25% in the preoperative versus 40% in the postoperative arm. The sphincter preservation rate in 188 patients with low-lying tumors (declared by the surgeon prior to randomization to require an APR) revealed that 39% versus 19% had a sphincter-preserving LAR (P = .004) in the preoperative versus the postoperative arm. Perioperative complications did not differ between the groups, but overall rates of both acute- and long-term toxicities (especially acute and chronic diarrhea, and anastomotic strictures) were lower in the pretreatment group. Consistent with the 5-year results, the 10-year LC favored neoadjuvant treatment (7.1% in pre- and 10.1% in postoperative arms, P = .048), with no difference in DFS, OS, or DMs. Thus, preoperative CRT resulted in improved LC and doubled the sphincter preservation rate

compared to postoperative therapy, while also demonstrating an improved toxicity profile.

Along with the MRC CR07 trial,[219] which demonstrated LC improvement to neoadjuvant short course RT versus selective postoperative CRT (see section "Neoadjuvant Radiotherapy"), the German rectal trial provides the basis for preoperative therapy as the current standard of care for locally advanced rectal cancers.

Surgical Timing After Neoadjuvant Radiotherapy and Chemoradiotherapy

Despite promising LC results from neoadjuvant short course and CRT regimens, in many cases the pathologic findings and improvement of sphincter sparing rates were underwhelming. The initial implementation of short-course RT included immediate (within 1 week) surgery, and even CRT was often followed by surgery in a relatively quick timeframe. Questions arose around whether increasing this interval between neoadjuvant treatment and surgery might permit improvements in downstaging, pCR, and potentially sphincter-sparing capabilities.

Justification for a longer interval after preoperative radiation treatment before surgery was demonstrated in a French trial, Lyon 90-01, which delivered 39 Gy as 3 Gy/fraction (no preoperative chemotherapy).[231,232] Two hundred and one patients were randomized to surgery within 2 weeks versus 6 to 8 weeks of RT. The LC and OS after a median follow-up of 6.3 years were the same in both arms of the study, and there was no difference in sphincter-sparing intervention or long-term anal function. However, the pCR was 7% versus 14% (P = NSS [not statistically significant]), and the pathologic downstaging was 10% versus 26% (P = .007) in favor of the longer interval before surgery.

The more recently published Stockholm III trial evaluated both fractionation and timing after RT to surgery.[233] Patients with resectable rectal cancer were randomized to: (1) 5 Gy × 5 followed by surgery within 1 week, (2) 5 Gy × 5 followed by surgery after 4 to 8 weeks, and (3) 50 Gy in 25 fractions followed by surgery after 4 to 8 weeks. The primary endpoint was time to local recurrence. Pathologic response appeared improved in the short course with delay arm, relative to the long course or

short course without delay arm. Other outcomes were similar between all three treatment arms. Although there was noted to be an increase in radiation-related acute toxicities in the short-course RT arm with delay to surgery, there was a significant decrease in postoperative complications in these patients. The authors suggest that short-course RT with delay may be an alternative to conventional short-course RT followed by immediate surgery.

Systematic comparison of longer intervals has not been attempted for neoadjuvant long-course CRT, but extrapolation from the short-course experience, and incorporation of data from studies that alter the sequencing of CRT and chemotherapy in total neoadjuvant regimens (see section "Total Neoadjuvant Therapy") support approaches that permit relatively longer intervals between short-course or CRT regimens, without being so long as to impede the surgical procedure itself.

Alternative Chemotherapy Regimens With Neoadjuvant Radiotherapy

There is considerable variability in the administration of chemotherapy in many of the trials undertaken and those that are ongoing. 5-FU has been used concurrent with radiation because of its well-established potentiating effect with radiation. However, several studies have used bolus 5-FU, whereas others have administered LV-modulated 5-FU during the first and last weeks of radiation. The results of the Intergroup study demonstrating a superiority of low-dose CI-FU were extrapolated to the neoadjuvant setting, and it appears to be a preferred approach to treatment.[201] Subsequently, newer drugs such as oral fluoropyrimidines (capecitabine), oxaliplatin, and irinotecan were shown to be effective in the treatment of metastatic CRC. Oral fluoropyrimidines, as part of a CRT regimen, now commonly replace infusional 5-FU. The incorporation of oxaliplatin and irinotecan into the neoadjuvant CRT regimen has been less promising, though in the era of watch-and-wait therapeutic options they may have a role in total neoadjuvant approaches in the chemotherapy-only component of treatment.

Capecitabine is an oral fluoropyrimidine prodrug that is readily absorbed in the gastrointestinal tract and mimics the efficacy of CI 5-FU while avoiding the risk of side effects and complications due to a central line for

CI 5-FU.[234] Capecitabine requires the presence of thymidine phosphorylase (TP) for conversion to the active form of 5-FU within the cells. TP is present in higher concentration in tumor cells, particularly CRC, than in normal tissues, and this potentially creates a therapeutic advantage for capecitabine as compared to intravenous 5-FU.[235] Capecitabine is generally given in two divided doses twice a day during the course of radiation treatment. Toxicities differ between CI 5-FU and capecitabine and may determine the best agent for an individual patient; leukopenia may occur more frequently in CI 5-FU while diarrhea, proctitis, and hand-foot syndrome may occur more often for capecitabine.

Two randomized reports supported the use of capecitabine in both neoadjuvant and adjuvant chemoradiation regimens. A German trial documented noninferiority for capecitabine versus CI 5-FU with respect to OS, with similar DFS and local recurrence noted and fewer metastases in the capecitabine group.[236] Diarrhea was the most common AE in both groups (any grade, 53% patients in the capecitabine group vs 44% in the FU group; grade 3-4, 9% vs 2%). Patients in the capecitabine group had more hand-foot skin reaction, fatigue, and proctitis than did those in the FU group, whereas leukopenia was more frequent with the FU arm. A second study, the NSABP R-04, compared the efficacy of four chemotherapy regimens. More than 1,600 patients were randomized to 5-FU (225 mg/m^2, 5 days/week) or capecitabine (825 mg/m^2, twice a day, 5 days/week) with RT with subsequent randomization to ±oxaliplatin (50 mg/m^2/week ×5).[237] For patients who received 5-FU versus capecitabine, there were comparable rates of tumor downstaging, pCR, and sphincter preservation.

The NSABP R-04 study also documented that addition of oxaliplatin failed to improve surgical outcomes, but did add significant toxicity (grade 3-4 diarrhea, $P < .001$).[237] Other randomized studies (STAR-01, ACCORD 12) also demonstrated that oxaliplatin added to standard CI 5-FU increases toxicity without improving outcomes.[238,239] In contrast, the German CAO/ARO/AIO-04 trial demonstrated a potential DFS benefit for oxaliplatin (50 mg/m^2 on days 1, 8, 22, and 29), when paired with a modified infusional 5-FU regimen (infusional FU 250 mg/m^2 on days 1-14 and 22-35) without undue toxicity.[240] Overall, the results of these randomized studies have resulted in oxaliplatin omission from most CRT regimens.

The addition of irinotecan to 5-FU-based chemotherapy has also been investigated. The Radiation Therapy Oncology Group (RTOG) conducted a randomized, phase II study of neoadjuvant CRT for distal rectal cancer. One hundred and three patients with T3 or T4 distal rectal cancer were randomized to CI 5-FU plus hyperfractionated radiation treatment of 55.2 to 60 Gy (1.2 Gy twice a day) versus CI 5-FU and irinotecan with conventional fractionation radiation of 50 to 54 Gy (1.8 Gy/fraction).[241] The response rate between the two arms was similar, with an impressive pCR of 28%, and no difference in toxicity. Other groups attempted to incorporate biologic agents into the neoadjuvant regimen. Although reports of the addition of bevacizumab and cetuximab to conventional preoperative regimens appear tolerable, the benefit remains unclear, and no phase III evaluation of these agents has been performed.[242-248] In the absence of convincing phase III data for these alternative concurrent chemotherapies, infusional 5-FU or capecitabine remains the standard choices for concurrent CRT.

Total Neoadjuvant Therapy

Total Neoadjuvant Therapy With Long-Course Chemoradiation

The role of total neoadjuvant therapy (TNT) in patients with rectal cancer was examined in the GCR-3 phase II trial from Spain. Patients with clinical stage T3/T4 tumors or node-positive disease with lesions in the distal or middle third of the rectum were randomized to neoadjuvant CRT followed by surgery and adjuvant CAPOX or a TNT regimen comprised of four cycles of induction CAPOX followed by chemoradiation and then surgery. Clinical endpoints (local recurrence, DM, DFS, and OS) were similar between the two groups at 5 years. There was improvement in compliance and lower rates of acute toxicity in patients undergoing TNT treatment.[249] A subsequent prospective multi-institutional phase II trial reported high pCR rates following a TNT regimen consisting of CRT and two to six additional cycles of mFOLFOX6 prior to surgery.[250] Increasing cycles of mFOLFOX6 improved the rate of pCR (18% in CRT alone, 25% in CRT+2 cycles, 30% in CRT+4 cycles, 38% in CRT+6 cycles).[214] It is unclear whether this improved pCR reflected increased local tumor response due to additional

chemotherapy, or simply reflected a longer interval between CRT and surgery leading to a more apparent improvement in pCR.

The PRODIGE-23 study assessed the efficacy of an intensified TNT regimen of mFOLFIRINOX followed by long-course CRT prior to TME versus CRT followed by TME.[251] Both arms received mandatory adjuvant mFOLFOX6. Improved pCR rates were seen in the TNT regimen (28% vs 12%, $P < .0001$). DFS (primary endpoint) at 3 years was improved in the TNT arm. Updated results indicate persistent 7-year DFS benefit (62.5% vs 67.6% for standard vs TNT; $P = .048$ by restricted mean survival time [RMST] test) as well as a 7-year metastasis-free survival benefit (72.3% vs 79.2%, $P = 0.021$ by RMST) and a 7-year OS benefit (76.1% vs 81.9%, $P = .033$ by RMST).[252] Locoregional failures were not significantly different, suggesting that much of this effect related to intensified chemotherapy and systemic benefits. This study confirms a utility for a TNT approach, but how and when to intensify chemotherapy to mFOLFIRINOX versus a more standard FOLFOX or CAPOX approach is unclear.

Total Neoadjuvant Therapy With Short-Course Chemoradiation

The Polish-II trial evaluated short-course RT as a component of a total neoadjuvant regimen in comparison to standard long-course CRT.[253] Patients with fixed cT3 or cT4 cancer (not staged by MRI) were randomized either to 5 × 5 Gy and three cycles of FOLFOX4 (group A) or to 50.4 Gy in 28 fractions combined with bolus and LV 20 mg/m^2/day with five weekly infusions of oxaliplatin 50 mg/m^2 (group B). The protocol was amended in 2012 to allow oxaliplatin to be then foregone in both groups; roughly two-thirds of enrolled patients received oxaliplatin-containing regimens. In the 515 patients eligible for analysis (of 547 enrolled), preoperative treatment acute toxicity was lower in group A than in group B ($P = .006$). Margin negative resection rates (primary endpoint; 77% group A vs 71% group B [$P = .07$]) and pCR rates (16% vs 12%; $P = .17$) were not significantly different. Over long-term follow-up, OS, DFS, DM, and LF showed no difference at 8 years despite an early 3-year OS benefit favoring the short-course arm.[254] The rate of late complications was similar (11% vs 9% in groups A and B, respectively; $P = .66$). There was no superiority to

the preoperative short-course TNT arm in this study, but the study was not powered for clinical endpoints.

The RAPIDO study evaluated high-risk rectal cancer (defined as T4 tumors, N2 or enlarged lateral LN, extramural venous invasion, or threatened CRM) and randomized 912 participants to receive TNT with short-course RT and CAPOX/FOLFOX versus standard neoadjuvant CRT, both followed by TME.[255] The CRT arm suggested optional chemotherapy after TME, but only 47% of these received six cycles of chemotherapy. On initial report, the short-course TNT arm had improved pCR rates (28% vs 14%), no difference in locoregional recurrence, and fewer disease-related treatment failures at 3 years (23.7% vs 30.4%, respectively), likely relating to better chemotherapy compliance in the TNT arm, with fewer chemoradiation-arm patients receiving systemic-dose chemotherapy.[256] The follow- up report indicated persistent disease-related treatment failure and DM benefit to the TNT arm, potentially related to the additional chemotherapy received by the TNT group.[257] Though overall the LRR was favorable for such a high-risk patient group, longer term follow-up revealed a significant LRR recurrence difference, with the TNT arm demonstrating more frequent LRR (10.2% in TNT arm vs 6.1% in CRT arm, $P = .027$), including more frequent LRR after R0 resection. The reason for the LRR decrement is unclear; pathologic features were similar between the two populations, R0 rates were not different, and the TNT arm had an improved pCR rate. The authors make note of a more frequent rate of mesorectal breach in the TNT arm that could have contributed to additional risk of LRR. The TNT arm more frequently received 3D CRT, which in theory should not differ in target coverage from IMRT/volumetric modulated arc therapy (VMAT), especially considering the sites of failure that were largely central in the treatment volume (anastomotic and presacral). Though this study did not compare TNT with short course versus TNT with long course, it is reasonable to extrapolate that tumors with high risk of local recurrence may benefit from the long-course TNT option (eg, ultralow tumors, threatened CRM with other concurrent risk factors, T4b). Considering the overall low rate of LRR in this study for even high-risk tumors, other lower risk tumors (eg, mid- or high rectal tumors without additional risk factors) may be suitable for a short course–based TNT regimen, albeit without this having been explicitly studied in a randomized

fashion. Ongoing studies like the ACO/ARO/AIO-18.1 trial will evaluate the efficacy of short-course TNT versus long-course TNT regimens.

Sequencing of Total Neoadjuvant Therapy

Initially, the optimal sequencing for TNT was unclear. Some rationalized that providing chemotherapy first, followed by (C)RT would provide early systemic control and would permit earlier (and thus potentially easier) operation after the RT component. Others reasoned that extension of the interval between RT and surgery may only help tumor response and pCR rates, and many patients with near-obstructive or highly symptomatic tumors may benefit from up-front RT. Several trials systematically compared these different sequencing approaches in the context of long-course CRT TNT regimens.

The CAO/ARO/AIO-12 randomized phase II study[258] from Germany allocated 300 patients to two different TNT regimens: chemo-first TNT (FOLFOX × three cycles, then CRT with the German infusional 5-FU/oxaliplatin regimen[240]) versus CRT-first TNT. Powered for a pCR comparison to historical controls, the CRT-first arm demonstrated improved pCR (25% vs 17% in the chemo-first), as well as improved overall complete response (pCR + clinical complete response [cCR] in patients who declined surgery; 21% and 28% for chemo-first vs CRT-first, respectively). Both treatments were overall well tolerated though with the CRT-first arm demonstrating lower CRT and post-op toxicities, margin-negative surgical results were not different. Importantly longer-term results documented no difference in DMs, with similar DFS, arguing that the theoretical benefits of treating micrometastatic disease with a chemo-first regimen may not drive outcomes.[259]

The Organ Preservation in Patients with Rectal Adenocarcinoma (OPRA) trial (discussed in more detail in section "Nonoperative Management" under "Attempts to De-Escalate Multimodal Therapy for Rectal Cancer") incorporated a randomization between two different TNT sequences—CRT-first versus chemo-first. Chemotherapy was FOLFOX or CAPOX for 16 to 18 weeks, and CRT included 50 to 56 Gy of standard fractionated radiation with either CI 5-FU or capecitabine.[250] Either TME radical resection or an option for NOM (for near-complete and complete clinical responders) was

employed after TNT. The study was powered to detect a difference in DFS between each arm and historical controls. The study was expanded due to favorable pCR in both arms, and ultimately accrued 324 patients. The primary outcome of DFS difference from historical controls was not significant, and DFS and OS were similar between the two arms. More importantly, the sequencing of TNT appeared to have a substantial impact on organ sparing, with a substantial difference in TME-free survival seen between the arms (at 5 years, 39% in chemo-first arm vs 54% in the CRT-first arm).[78]

In sum, these studies overall support sequencing TNT regimens with the radiation-containing component first, followed by chemotherapy. Though sequencing has not been directly compared in short course–containing regimens, it seems reasonable to cautiously extrapolate these findings to adopt an RT-first approach for those regimens when they are selected (similar to what was used in the RAPIDO trial), albeit with the caveats mentioned in the section "Total Neoadjuvant Therapy With Short-Course Chemoradiation."

Attempts to De-Escalate Multimodal Therapy for Rectal Cancer

Nonoperative Management

Despite the oncologic benefits of TME in patients with rectal cancer, there are potentially serious complications associated with this procedure including vascular injury, infection, wound complications, ureteral injury, and sexual dysfunction.[216-221] Long-term complications include chronic bowel dysfunction, urinary incontinence, and small bowel obstruction.[4,5] Despite these risks, most patients with rectal cancer undergo surgery. However, there has been increasing interest in NOM, especially in patients with distal rectal cancers requiring APR, in older patients, or those with significant medical comorbidities. Additionally, many patients experience significant impact on their QOL following either LAR or APR procedures. Another potential rationale for NOM management comes from the rate of pCR observed in patients undergoing neoadjuvant therapy, particularly those who undergo long-course CRT.

Investigators from the University of São Paulo School of Medicine evaluated NOM for patients with potentially resectable rectal cancer. The

study included patients with T2-T4 and N0-N1 disease who received neoadjuvant CRT to 50.4 Gy with concurrent 5-FU. Patients were reevaluated 8 weeks post-CRT. Response was assessed radiographically and pathologically via endoscopic biopsies. Patients with an incomplete response were sent immediately for resection. Those with cCR were followed closely with monthly physical exams, frequent proctoscopy with biopsies of any suspicious areas, serial CEA monitoring, and abdominopelvic CT scans every 6 months for the first year. Patients without evidence of disease for 1 year were considered to have a cCR.[253] Updated results have also been published with a larger cohort of patients.[260] This indicates that 31% of patients with an initial cCR went on to develop a local recurrence, the majority of which occurred in the first 12 months. Only 7% of these patients were not amenable to salvage surgery. Five-year cause-specific OS and DFS were 91% and 68%, respectively, with 14% of patients failing distantly.[261]

Maas and colleagues attempted to build upon the results of the São Paulo group by employing modern MRI staging techniques. In this study, there was a noticeably lower rate of cCR, likely the result of the strict imaging criteria that was used.[262] Memorial Sloan Kettering investigators compared the outcomes of 32 patients who had a cCR with NOM to a comparable group who had achieved a pCR with surgical resection.[263] The local recurrence rate for patients undergoing NOM was 21% versus 0% in the pCR group after 28 months; however, all patients that failed locally were successfully salvaged with surgery. The clinical outcomes were otherwise similar between the groups. This series has since been updated, with OS and DFS remaining similar between the NOM and pCR groups.

Taking a different approach, a prospective trial from Denmark evaluated patients with resectable T2-T3 primaries and N0-N1 disease who were treated with high-dose radiation to 60 Gy in 30 fractions with a 5-Gy endorectal brachytherapy boost and oral tegafur-uracil.[264] Response was assessed via endoscopy and MRI/CT. If patients achieved a cCR, they were followed closely with exams, endoscopy, and PET scans. Only 26% of patients had local recurrence failure by 2 years and all patients were surgically salvaged.[229] A subsequent randomized controlled trial allocated 148 patients with small (<5 cm) T2-T3b, N0 or N1 (<8 mm), low/mid-rectal adenocarcinoma to neoadjuvant CRT (45 Gy in 25 fractions with concurrent

capecitabine) followed by either an external beam boost of 9 Gy in five fractions or a contact x-ray brachytherapy boost (90 Gy in three fractions over 4 weeks). In the initial report, the 3-year organ preservation rate (primary outcome) was 59% in the external beam boost group versus 81% in the contact brachytherapy group (P = .0026).[265] These results are promising, and the acute and late toxicities were limited. However, the limited availability of contact x-ray endocavity brachytherapy equipment and experience, particularly for rectal treatment, may limit applicability of this approach.

As discussed earlier, the OPRA trial implemented a watch-and-wait nonoperative option into the randomized study allocating 306 patients with stage II/III distal rectal cancer to two different TNT sequencing options (chemo-first or CRT-first).[250] Though the primary outcome was DFS of each arm relative to historical controls (no difference seen), the major impact for this study has been documenting the efficacy of total "neoadjuvant" therapy in facilitating NOM. Roughly three-fourths of the enrolled patients were offered NOM after demonstrating either a near-complete or complete response (71% in the chemo-first group, and 76% in the CRT-first group). Of these, 36% developed a regrowth that prompted TME, and the vast majority of regrowths on NOM occurred within 2 years (94%). In the CRT-first arm, a 53% TME-free survival was documented at 3 years (41% in the chemo-first arm), substantiating NOM as an option for a large number of patients with locally advanced rectal cancer. Importantly, the 5-year DFS for patients receiving TME up-front and those "salvaged" after regrowth on NOM surveillance did not differ (61% vs 62%, respectively; P = .86).[78] It is worth emphasizing that the NOM surveillance on this protocol mandated very close follow-up to detect and intervene on persistent or recurrent disease early. Flexible sigmoidoscopy, and DRE and CEA measurements were taken every 4 months for 2 years, then every 6 months for 3 years; rectal MRI was performed every 6 months for 2 years, then every year for 3 years; CT chest/abdomen/pelvis performed yearly for 5 years; and colonoscopy 1 year after diagnosis and per guidelines thereafter.

The OPRA study, while not randomizing between NOM and surgical intervention, documents the feasibility, efficacy, and safety of a NOM approach with aggressive surveillance. In combination with the historical data and a systematic review[266] supporting the safety and efficacy of this

approach, these data support the judicious implementation of NOM approaches in various guidelines and widespread practice patterns.[184]

Neoadjuvant Chemotherapy with Surgery (No Radiation)

The FORWARC trial out of China investigated numerous neoadjuvant regimens, randomizing relatively advanced rectal adenocarcinomas to neoadjuvant treatment with (a) CRT with 5-FU/LV and standardly fractionated RT to 45 to 50.4 Gy, (b) CRT with mFOLFOX6 × five cycles and the same RT regimen, and (c) mFOLFOX6 × four to six cycles without CRT.[267] All groups received TME and additional matched chemotherapy after TME. TME was reported as "good" in 80%, "moderate" in 10%, and "poor" in 5%. In the initial reports and the updated data recently presented, there were no significant differences in clinical outcomes like DFS (primary outcome; 10-year DFS 55.5% in 5-FU/LV CRT arm, 63% in FOLFOX CRT arm, and 62.8% in FOLFOX-only arm) or OS.[268] Though the final treatment groups' pathologic characteristics appeared somewhat unbalanced (eg, chemo-only arm with 69.7% T2/T3 tumors vs 65.4% in the 5-FU/LV CRT and 58.3% in the FOLFOX CRT arm), and the aforementioned variable TME quality, this study suggested a potential for omitting RT for a subset of patients.

The PROSPECT trial evaluated the efficacy of neoadjuvant chemotherapy (without RT), utilizing contemporary chemotherapy regimens in hopes of permitting more selective use of RT.[269] Patients with overall lower-risk disease, with cT2N1, T3N0, or T3N1 disease located in the upper or middle thirds of the rectum, who are without evidence of mesorectal fascial involvement, were eligible. A total of 1,194 patients were enrolled. In the experimental arm, patients received six cycles of FOLFOX with subsequent assessment of treatment response. If the tumor has decreased in size by at least 20%, patients proceeded directly to TME followed by six cycles of adjuvant FOLFOX. If the tumor did not decrease by at least 20%, patients received neoadjuvant long-course CRT (with 5-FU or capecitabine), TME, and then two cycles of adjuvant FOLFOX. In the control arm, standard long-course CRT (with 5-FU or capecitabine) was followed by TME and eight cycles of adjuvant FOLFOX. Primary endpoint was changed from DFS and local recurrence to DFS alone due to overall

low rate of recurrence. The FOLFOX-alone arm was noninferior for DFS (P = .005), with a 5-year DFS of 80.8% in the chemotherapy-alone group versus 78.6% in the CRT group. There was no difference in OS or local recurrence. The local recurrence was exceedingly low in both groups for this trial of well-selected, relatively low-risk patients (1.8% in FOLFOX alone vs 1.6% in CRT group). Patient-reported outcomes (PROs) indicated more acute side effects in the FOLFOX-alone arm during neoadjuvant treatment, with 16 worse in FOLFOX-alone (anxiety, appetite loss, constipation, depression, dysphagia, dyspnea, edema, fatigue, mucositis, nausea, neuropathy, and vomiting) and one worse in CRT arm (diarrhea).[270] Late PROs indicated higher fatigue and neuropathy in the CRT arm, possibly related to closer proximity to adjuvant chemotherapy at time of survey. Sexual side effects were worse up to 24 months posttreatment, but overall health-related quality-of-life (QOL) was not significantly different.

Ultimately, the improvements in chemotherapy regimens and surgical technique have permitted consideration of omission of RT in a subset of well-selected patients, as substantiated by the PROSPECT trial. For now, omission of RT requires selection of relatively low-risk tumors for this treatment until findings are extended to more advanced disease. Moreover, a systematic method to assess neoadjuvant treatment response must be developed within institutions to permit rigorous assessment of whether or not 20% treatment response is achieved. Finally, patient guidance in decision-making is critical, as there were an assortment of toxicities that varied by treatment. Engaging in a paradigm that omits RT may eliminate options for NOM, so patient priorities should be considered in deciding upon which regimen (if either) is warranted.

Local Excision Paired With Neoadjuvant or Adjuvant Chemoradiotherapy

As mentioned previously, local excision provides a sphincter-sparing alternative to radical surgery for distal cT1 tumors. However, if pathologic findings after excision indicate T2 disease or high-risk T1 lesions, standard treatment includes radical oncologic resection, which may involve temporary or permanent colostomy depending on the tumor location. Moreover, for T2 lesions the standard treatment is radical surgery. Many

patients refuse such intervention, or may not be surgical candidates, prompting interest in administration of adjuvant or neoadjuvant treatments like radiation paired with local excision.

The RTOG 89-02 examined the efficacy of CRT after local excision in a study of 65 patients with T1-T3 distal rectal cancers not amenable to sphincter-sparing radical surgery that were node-negative by CT, with favorable pathologic features (well or moderately differentiated, negative margins, no LVI).[271] There were 13 patients with T1 tumors, 25 patients with T2 tumors, and 13 patients with T3 tumors who received postoperative CRT of 50 to 65 Gy with 5-FU (1,000 mg/m^2 on days 1-3 and 29-31); 14 patients with T1 tumors were observed without CRT. Local recurrence rates were 0% for CRT-treated T1 (vs 7% for untreated), 20% for CRT-treated T2, and 23% for CRT-treated T3 tumors. These local recurrence rates for T2 and T3 tumors exceed those seen even for more advanced tumors treated with radical surgery alone or multimodal therapy (in the case of T3), suggesting that local excision plus CRT is a potentially inferior approach for patients with T2 or more advanced tumors.

Similarly, in the CALGB 8984 study, 59 patients with T1 disease were treated with local excision alone, and 51 patients with T2 disease received adjuvant therapy with 54 Gy and 5-FU (500 mg/m^2 on days 1-3 and 29-31).[272] Outcomes were acceptable for the T1 patients (who did not receive CRT), with 10-year local recurrence, DFS, and OS rates of 8%, 75%, and 84%, respectively. However, for T2 patients (who did receive CRT), 10-year local recurrence, DFS, and OS were 18%, 64%, and 66%, respectively. Though detailed information about salvage techniques was not published in the final report, an 18% LF rate and 64% DFS for T2 cancers are both considerably inferior to the results of radical surgery with TME alone or neoadjuvant therapy followed by surgery. Like the RTOG8902 study, the CALGB8984 study supports the possibility of conservative local excision surgery for well-selected T1 lesions, but for T2 tumors, the high rate of local recurrence despite CRT warrants caution.

Interest shifted to assess whether neoadjuvant CRT combined with local excision might provide acceptable oncologic outcomes for high-risk T1 or T2 tumors. The American College of Surgeons Oncology Group (ACOSOG) conducted a multi- institutional, single-arm, open-label, nonrandomized, phase II trial of 79 patients with T2N0 distal rectal cancer

staged with EUS or MRI, treated with neoadjuvant CRT.[273] Tumors were less than 4 cm in greatest diameter, involving less than 40% of the circumference of the rectum, located within 8 cm of the anal verge, were treated with neoadjuvant CRT consisting of capecitabine, oxaliplatin, and 54 Gy radiation (primary course to 45 Gy, followed by a boost of 9 Gy) followed by local excision. AEs during CRT prompted dose reduction of capecitabine (from 825 mg/m^2 twice daily to 725 mg/m^2 twice daily) and RT (boost reduced to 5.4 Gy for a total dose of 50.4 Gy). After a median follow-up of 56 months, the estimated 3-year DFS for the intention- to-treat group was 88.2% and for the per-protocol group (n = 72 patients) was 86.9%, which was lower than anticipated for similarly staged patients treated with radical surgery. Additionally, the regimen was not without toxicity—29% had grade 3 gastrointestinal AEs, 15% grade 3 to 4 pain, and 15% grade 3 to 4 hematologic AEs during chemoradiation.

The GRECCAR2 multicenter randomized trial assessed local excision or TME for CRT-treated early-stage T2 to T3 low rectal cancers.[274,275] Eligible patients were those who responded well to CRT (50 Gy in 2 Gy fractions with concurrent 5-FU chemotherapy), as measured by a tumor size of 2 cm or less and no evidence of deep infiltration on post-CRT MRI at 6 to 8 weeks. This study did not quantify how many patients were “good responders” since that was a criterion for enrollment, and notably nodal status was not used to define eligibility. Patients were randomized to local excision or TME. In the local excision group 27/74 patients underwent TME (1 up-front, 26 as completion TME due to pathologic features), while 8 additional patients declined TME despite it being recommended per protocol. In the TME group, the majority received TME as planned (60/74; 3 excluded for various reasons, 8 underwent local excision instead as protocol deviations, and 3 elected for watch-and-wait as a protocol deviation). Five-year local recurrence, metastatic disease, OS, and DFS metrics were not statistically different between the groups, though the study was underpowered to assess for these outcomes individually (study power was calculated for a composite outcome endpoint). The earlier report identified no significant differences in acute side effects between the groups, largely due to the relatively high rate of completion TMEs required; those patients who only required local excision had less acute toxicity than the TME group, but those patients who required local excision then

completion TME appeared to have more toxicity at 2 years in many categories than the up-front TME group. In looking at the cT2 patients in particular (who are typically managed by TME without CRT, using typical management paradigms), 31% of patients in the local excision group required completion TME, suggesting that almost a third of these already-selected cT2 patients with "good" response to CRT ultimately received this additional CRT therapy without any clinical benefit and with additional toxicity beyond what would be expected with TME alone. However, this trial also demonstrated that 51% of locally excised T3 tumors were ypT0-1 after neoadjuvant CRT and did not require TME. Although they did not specifically quantify the outcomes for this T3 population, it suggests a subset of T3 patients might tolerate surgical de-escalation after neoadjuvant CRT, which many of them would receive as a typical component of management even if proceeding to TME.

The phase II CARTS study[276] out of the Netherlands assessed the feasibility of utilizing local excision by transanal endoscopic microsurgery for good responders to neoadjuvant CRT with cT1-3N0 tumors. This study documented 63.6% of patients were treated with CRT followed by local excision alone, while TME was performed in 29% of patients (half with completion after TEM, a quarter with inadequate responses necessitating TME up-front, and a quarter with salvage TME for recurrence); these numbers were consistent with the GRECCAR2 study, as were the clinical outcomes (5-year local recurrence of only 7.7% with DFS of 81.6% and OS of 82.8%). Importantly, this study quantified health care–related QOL metrics, which indicated improved emotional functioning in the local excision group. Although these metrics were quantified in the group of patients requiring TME after local excision, they were not compared to local excision-alone or TME-alone patients, which would be expected to have higher toxicity.

Short-course RT (5 Gy per fraction for five daily fractions) represents an additional potential neoadjuvant approach for downstaging tumors to permit local excision, as preliminarily examined in the TREC feasibility study for cT1-T2 tumors out of the United Kingdom.[185] Though this study had relatively few patients treated with short-course RT followed by local excision (n = 27), and the study had a fair bit of crossing over between arms, ultimately 70% of patients randomized to the local excision arm

achieved organ preservation. Patients in the organ preservation arm reported improved patient-reported bowel toxicities and QOL scores relative to the radical surgery arm. Further evaluation of this approach alongside neoadjuvant CRT as per the CARTS study in organ-sparing local excision paradigms is underway in the STAR-TREC study.[277]

In summary, local excision is a potential option for surgical de-escalation and sphincter preservation for T1 tumors. This approach can also be considered after CRT downstaging of cT1-T3N0 tumors, avoiding TME if pathologic analysis confirms sufficient treatment response (ie, ypT0-T1). However, a substantial percentage of cT2 tumors may not sufficiently respond to CRT and may require TME regardless, so this approach will likely lead to overtreatment of a proportion of patients. Moreover, toxicities in patients with local excision and then TME may be higher than with up-front TME alone, though in general the QOL assessments showed benefits for the patients who were treated with local excision alone. Many of the above trials did not implement routine posttreatment endoscopy/proctoscopy in assessing response prior to excision, and MRI can be difficult to interpret in the posttreatment setting. Real-world implementation of comprehensive response assessment including direct visualization might further refine how to identify patients appropriate for local excision after treatment. Moreover, an intensified follow-up regimen may permit some of these patients to be followed with watch-and-wait protocols similar to the locally advanced setting, although data for this in the cT1-T2 setting are limited.

Unresectable, Locally Advanced Rectal Cancer

Tumors that are fixed or adhere to adjacent structures often have a particularly high likelihood of residual gross or microscopic disease that may be unresectable. A preoperative therapy approach is recommended to potentially facilitate curative resections.

Similar to the superiority of CRT versus fractionated RT alone for locally advanced resectable rectal cancers, the superiority of preoperative CRT over RT alone was shown in a phase III, randomized controlled trial of 207 patients with unresectable T4 or locally recurrent rectal cancer. Margin-negative resections, LC, and cancer-specific survival all favored the CRT

arm, with a nonsignificant trend to improved OS with CRT. Patients receiving concurrent chemotherapy experienced higher grade 3/4 acute toxicity with no difference in late toxicity.

Despite preoperative CRT and complete surgical resection, local recurrence rates in this subgroup remain high; the LC in the randomized study mentioned earlier was only 82% even with CRT. In situations in which the margin of resection is compromised, IORT offers the possibility of improved LC. The IORT experience at MGH was reviewed by Nakfoor et al.[278] Preoperative CI 5-FU plus 50.4 to 54 Gy of radiation was given, followed by a 4- to 6-week break and surgery. No IORT was given if metastases were present at surgical exploration, if there were adequate margins more than 1 cm, or if there was less than T4 disease. Dose of IORT varied by pathologic characteristics (10-12.5 Gy for complete resection, 12.5-15 Gy for microscopic residual disease, and 17.5-20 Gy for gross residual disease). The 5-year LC was 90%, 65%, and 55%, and the disease-specific survival at 5 years was 65%, 45%, and 15%, for these three dose levels, respectively. However, the 5-year actuarial risk of complications was 15%. The risk of peripheral neuropathy was 20% for doses more than 15 Gy. IORT appeared to improve LC, especially with a gross total resection, but not OS for locally advanced rectal cancers.

A series from the Mayo Clinic evaluated outcomes in 146 patients with primary locally advanced CRC.[126] Patients received conventionally fractionated EBRT (45-50 Gy) with chemotherapy, surgery, and IORT (10-20 Gy). The rates of 5-year freedom from local recurrence and DFS were 86% and 43%, respectively. Late complications occurred in 77 patients (53%) and included peripheral neuropathy (19%), bowel obstruction (14%), and ureteral obstruction (12%). In summary, IORT is a valuable tool in an effort to improve LC in situations in which the risk of microscopic residual disease following resection remains high, albeit with potential risks for late toxicity.

Recurrent Rectal Cancer

Recurrent rectal cancer is often approached in the same way as T4 disease, often with an aggressive treatment plan of CRT, surgery (with or without IORT), and adjuvant chemotherapy. Recurrences may occur along the

pelvic sidewall or in nonpelvic sidewall areas such as the uterus, prostate, or vagina. Given the difficulty of surgical resection of pelvic sidewall recurrences, these tend to fare worse. Surgical removal often requires exenterative surgeries.

Patients with recurrent rectal cancer and no prior history of EBRT are generally treated with a course of concurrent, preoperative CRT (50-54 Gy with 5-FU-based chemotherapy) followed by surgical resection (and consideration of IORT). Patients with prior history of RT may receive reirradiation to doses of 30 to 39 Gy with or without IORT, but have the potential to experience significant late toxicity; therefore, efforts should be made to avoid small bowel within treatment fields. Hyperfractionated approaches help limit normal tissue toxicity while maintaining antitumor effect. Ultimately, the goal is to maximize the likelihood of complete surgical excision, which is a primary determinant of outcomes after treatment for locally recurrent rectal cancer.

In patients with no prior history of radiation, neoadjuvant CRT (45-60 Gy) followed by surgical resection is a reasonable treatment approach. In several series reporting outcomes for locally recurrent rectal cancer, combinations of aggressive neoadjuvant CRT, resection, IORT, and additional chemotherapy achieve 5-year LC ranging from 24% to 54%, with OS ranging from 18% to 42%.[279-281] Patients able to undergo complete resection with negative surgical margins fare better.[282] One randomized controlled trial compared outcomes of preoperative CRT or RT alone prior to surgical resection in patients with unresectable or recurrent rectal cancer without prior RT treatment; 25 of the patients included had recurrent disease.[209] Higher rates of R0 resection, LC, time to treatment failure, and cancer-specific survival were seen in the chemoradiation arm (see section “Locally Advanced Rectal Cancer”). Five-year OS rate in patients with recurrent rectal cancer was still poor, at 37%.[283]

Reirradiation for patients previously treated with radiation to the pelvis may be considered in selected situations where additional therapy might help facilitate a margin-negative operation. Modern conformal and IMRT treatment techniques provide more opportunities for these treatments, but reirradiation likely still carries additional toxicity risks. Retrospective studies examining reirradiation with 23.4 to 30.6 Gy of EBRT suggest higher disease control for patients receiving additional CRT and radical

resection, particularly R0 resected tumors; many of these patients received some combination of neoadjuvant CRT, IORT at the time of surgery, and additional adjuvant chemotherapy. Toxicities were not reported in all experiences, but one long-term study of 103 patients reported relatively tolerable acute and late toxicity though numerous patients were noted to experience severe, persistent diarrhea (18 patients), small bowel obstruction (15 patients), fistula formation (4 patients), and stricture (2 patients).[284]

Hyperfractionated RT may reduce late toxicity in reirradiated patients. A multicentric Italian phase II study of 59 patients implemented a hyperfractionated CRT regimen of CI 5-FU paired with 30 Gy given in 1.2 Gy fractions twice daily, with a reduced-field boost of 10.8 Gy (also in hyperfractionated fashion). Tumor resection was achieved in 50.8% of patients, with a total of 35% of patients having R0 resections. Five-year OS was higher in R0 resected patients (66.8%) than in patients not undergoing surgery or with subtotal tumor removal (22.3%). Toxicity during treatment was low, with 5.1% grade 3 GI toxicity and no grade 4 toxicity. Late toxicities occurred in seven patients (fibrosis, impotence, urinary complications requiring diversion, and small bowel fistula requiring diversion). A retrospective series from the MD Anderson Cancer Center evaluated reirradiation outcomes in 102 patients with prior history of pelvic RT.[285] Patients were treated in 1.5 Gy fractions twice daily to a total dose of 30 to 45 Gy (depending on the time interval between RT treatment courses). Concurrent chemotherapy was administered to the majority of patients. The 3-year freedom rate from local progression and OS rate in the entire cohort were 40% and 39%, respectively. Three-year OS rate was 62% in patients undergoing surgery (vs 20% in those without surgery), and the 3-year rate of grade 3/4 late toxicity was 34%, which was higher (54%) in those who did undergo surgery.

Radiotherapy Technique

External beam treatment fields for rectal carcinoma should encompass potential sites at greatest risk for harboring disease, including the presacral space, primary tumor site, and (for post-APR cases) the perineum. Other areas at risk include the internal iliac and distal common iliac nodes. Generally, the risk of disease involvement of the para-aortic region is

sufficiently low, and the morbidity from treatment is sufficiently high, to exclude this region from radiation fields. The external iliac nodes may be covered for lesions involving the anterior structures, including the bladder, prostate, and vagina. Notably, T4a lesions involving anterior peritoneum only do not require coverage of external iliac nodes. Inguinal node coverage may be considered for tumors invading the anal canal distal to the dentate line.

Prone positioning may help reduce the volume of small bowel within the pelvis. Maneuvers to reduce the volume of small bowel include treatment with a full bladder and the use of bowel displacement techniques such as a bellyboard (a device with a false tabletop to allow the upper abdominal contents to fall anteriorly).[286] In 3D conformal plans, the use of shaped lateral fields reduces the dose to small bowel located in the anterior and superior aspects of the pelvis. For IMRT and VMAT planning, the small bowel should be included as an avoidance structure, though it is worth mentioning that even for these plans, simulation maneuvers can greatly assist with minimizing small bowel exposure. A marker is generally placed at the anal verge. Intravenous, rectal, and small bowel contrast can be administered at the time of simulation for accurate target and normal tissue delineation if MRI fusions or other mechanisms for tumor delineation are anticipated to be difficult.

Traditional four- or three-field techniques can be used to treat rectal cancer in many cases, though depending on the patient's anatomy it may be difficult to achieve optimal OAR doses. For 3D conformal anteroposterior and posteroanterior fields, traditional borders are as follows: the superior field edge is placed at the L5/S1 interspace, the inferior field edge should be at least 4 to 5 cm below gross disease while covering the entire mesorectum, and lateral border should be shaped with multileaf collimators to cover a 1.5 cm margin around the pelvic brim. For postoperative cases, the distal field edge is about 5 cm below the best estimate of the preoperative tumor bed and (if an APR has been performed) below the perineum. Lateral fields have the same superior and inferior borders. The posterior border should encompass the entire sacrum with a 1-cm margin to ensure presacral cover, and the anterior border should extend approximately 4 cm anterior to the rectum (ensuring adequate coverage of the mesorectum) while blocking as much of the anterior abdominal contents

and bladder as possible without compromising nodal coverage. If the tumor has considerable extrarectal extension, these guidelines should be modified to make certain that all disease is encompassed with appropriate margin.

Since CT-based planning dominates modern treatment, contour delineation of elective and high-risk clinical target volumes (CTVs) helps ensure that the above blocks cover the entire treatment volume for a given patient. The elective CTV includes the entire mesorectum, and perirectal/presacral/internal iliac LN with a superior border at the bifurcation of the common iliacs and an inferior border at the pelvic floor or 2 cm beyond gross disease.[287] External iliac lymph nodal regions should be included if there is anterior pelvic organ involvement. The high-risk CTV extends for 1.5 to 2.5 cm superior/inferior beyond the primary GTV and/or 1 cm beyond involved lymph nodes and should include the elective CTV volume (including mesorectum and nodal regions) within that extent.

Modern IMRT or VMAT planning may assist in facilitating target coverage while minimizing OAR exposure, particularly for difficult patient anatomy or patients with large amount of small bowel falling into the pelvis.

The usual dose given to initial pelvic fields is 45 Gy in 25 fractions of 1.8 Gy each. An additional tumor boost may be administered, usually through opposed lateral fields, to an additional 5.4 to 9 Gy. Historically, small bowel was excluded from the boost volume after about 50 Gy in an effort to minimize acute and late toxicity, but this can largely be achieved with IMRT or subfielding of the 3D conformal plan (Figures 67.7 and 67.8).

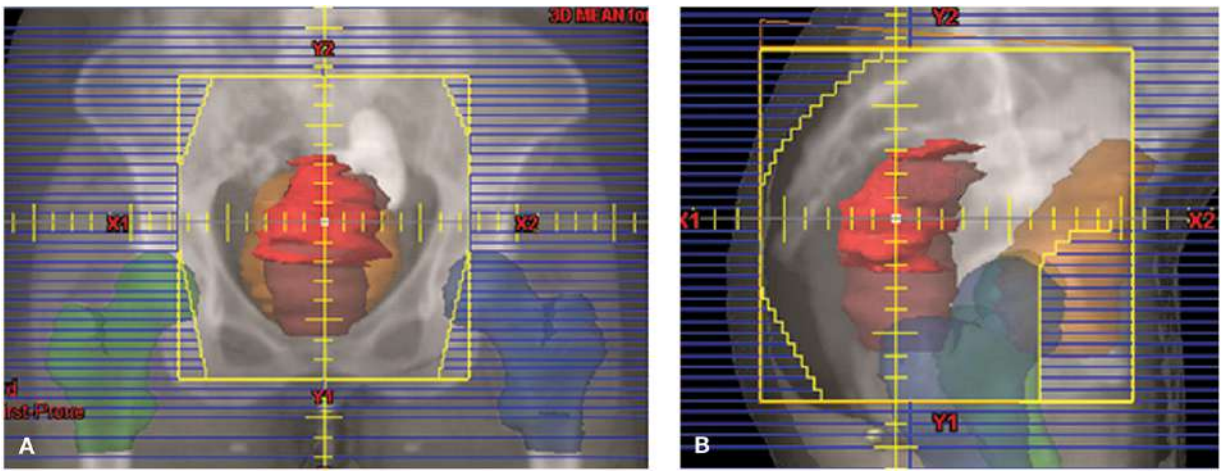

FIGURE 67.7 A. Posteroanterior treatment field of patient with T3 N1 rectal cancer. B. Lateral treatment field of a patient with T3 N1 rectal cancer. Red, gross tumor volume; brown, rectum; orange, bladder; green/blue, femoral heads.

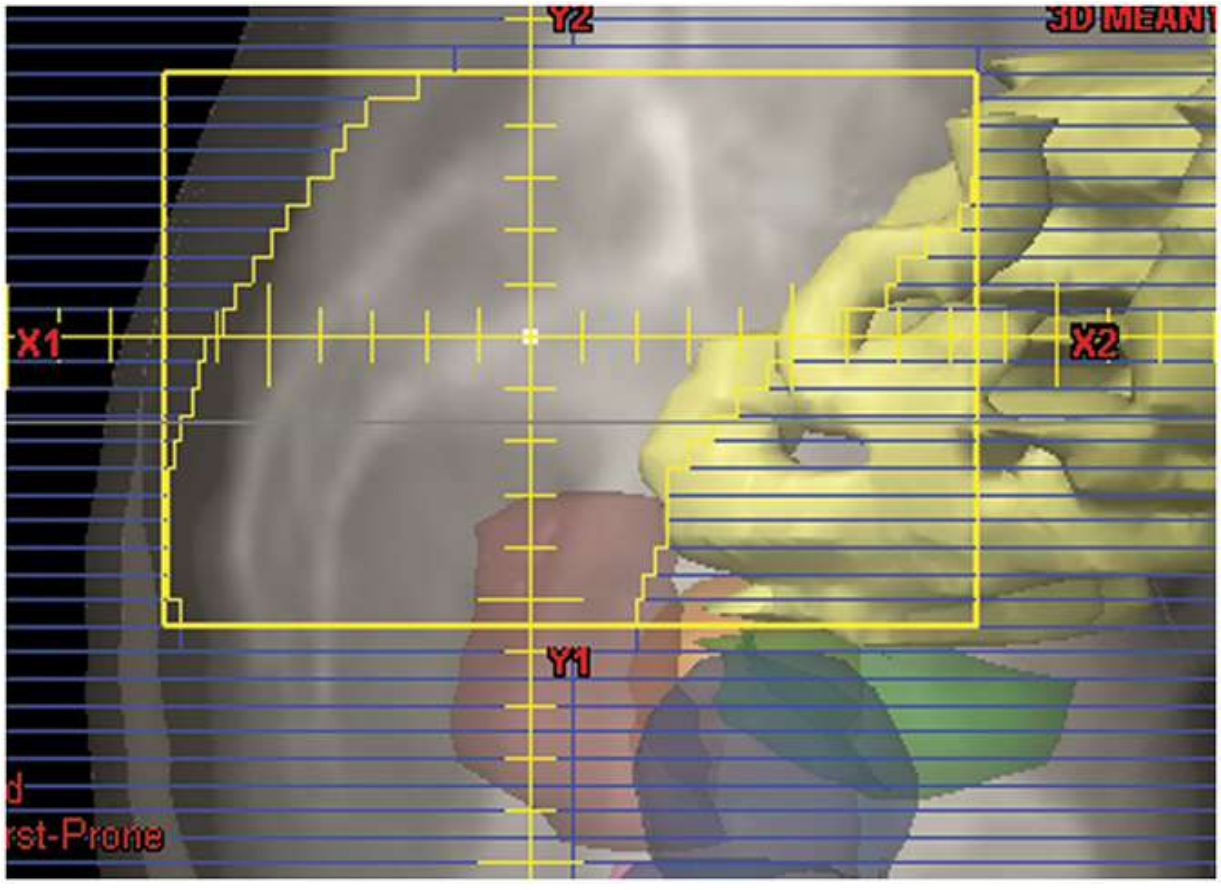

FIGURE 67.8 Lateral treatment field of patient with recurrent rectal cancer (with prior history of radiation) along presacral space. Brown, rectum; yellow, small bowel; green, bladder; orange/blue, femoral heads.

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CHAPTER 68

Anal Cancer

Paul Riviere and James D. Murphy

The standard treatment for primary squamous cell cancers of the anal canal is chemoradiation, using concurrent radiation therapy (RT), 5-fluorouracil (5-FU), and mitomycin C (MMC), with surgery typically reserved for the salvage setting. This chemoradiotherapy (CRT) approach was originally developed empirically as preoperative neoadjuvant therapy in the 1970s[1] and has evolved to become on its own the standard of care without preplanned surgical resection. Trials of other chemotherapy or systemic agents in combination with radiation have thus far not improved results. About 65% of those with cancer confined to the pelvis will survive 5 years or more, and about 75% will retain anorectal function.[2]

In this chapter, the emphasis is on the management of squamous cell cancer of the anal canal. Note is also made of the role of RT in the treatment of squamous cell cancers of the perianal skin and of adenocarcinomas of the anal region.

ANATOMY

The anal canal is 3 to 4 cm in length, with the posterior wall being longer than the anterior. The canal ends superiorly at the palpable upper border of the anal sphincter and puborectalis muscle of the anorectal ring. The distal end at the anal verge is the level at which the walls of the anal canal come in contact in their normal resting state; it approximates the palpable groove between the lower edge of the internal sphincter and the subcutaneous part of the external sphincter and the junction with true skin. The American Joint Committee on Cancer (AJCC) clinical staging[2] and the International Union Against Cancer (UICC)[3] recommend this definition rather than a convention used by some centers under which carcinomas that are above or exactly astride the dentate line are classified as anal canal tumors and those lying

mainly or entirely below that line are called anal margin tumors (Figure 68.1). The terms *anal margin* and *perianal skin* are now generally used interchangeably. Perianal carcinomas are arbitrarily considered to be cancers arising from the skin within a 5-cm radius of the anal verge. Tumors arising from the anus into the perineum are treated as anal canal tumors, whereas tumors arising from the vulva into the perineal body are treated as primary vulvar cancer. For tumors of the perineum in female patients, clinical judgment may be needed to determine where the tumor likely arose from and which treatment paradigm is to be applied.[2]

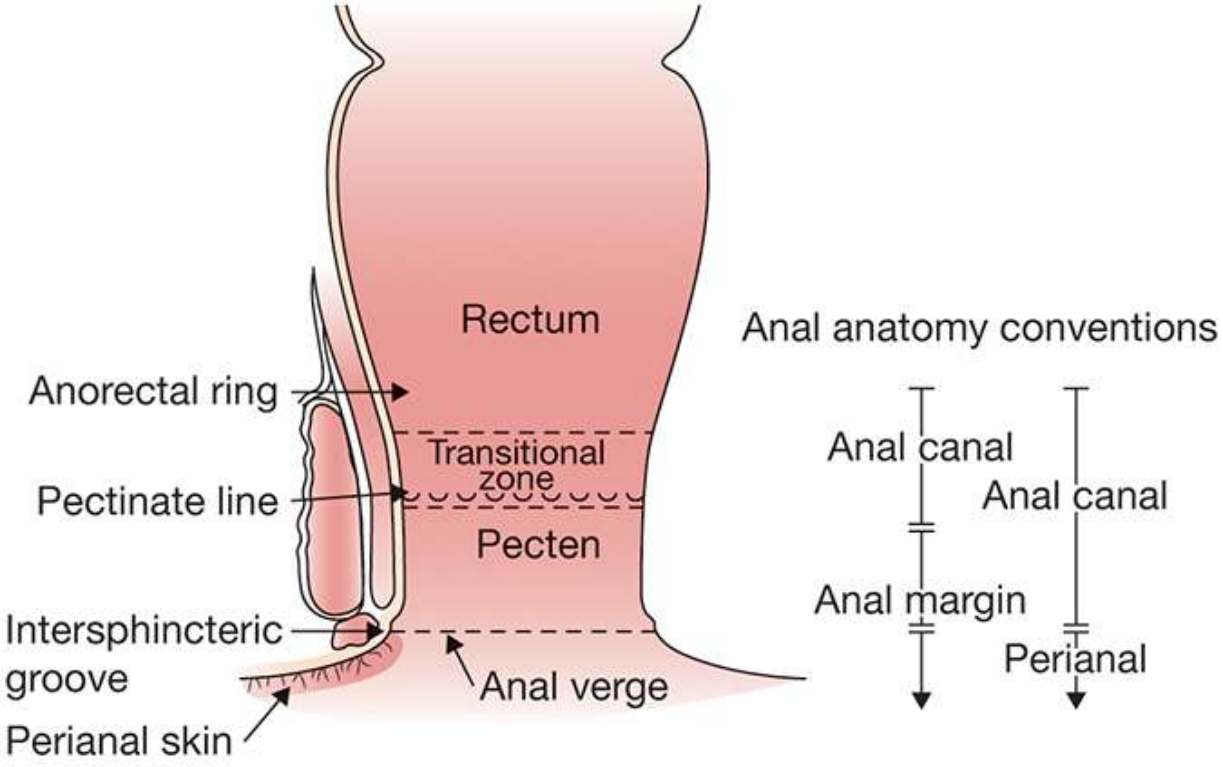

FIGURE 68.1 Anatomy of the anal region.

The anal region is composed of four different types of epithelium corresponding to its anatomic subdivisions.[4] From distal (caudal) to proximal (cranial), first, the perianal skin is similar to hair-bearing skin elsewhere. At the anal verge, the skin blends with a pale-colored zone, sometimes called the pecten, lined by modified squamous epithelium that lacks hair or glandular structures. At the level of the dentate or pectinate line (marked by the mucosal folds of the anal valves), this modified squamous

zone merges with a transitional epithelium that incorporates features of rectal, urothelial, and squamous epithelium. Most proximally, the purplish red–colored transitional zone extends proximally for about 2 cm until the pinker glandular mucosa of the rectum becomes dominant.

The major lymphatic pathways flow to three lymph node systems. The perianal skin, the anal verge, and the canal distal to the dentate line drain predominantly to the superficial inguinal nodes, with some communication to the femoral nodes and to the external iliac systems. Lymphatics from around and above the dentate line flow with those from the distal rectum to the internal pudendal, hypogastric, and obturator nodes of the internal iliac systems. The proximal canal drains to the perirectal and superior hemorrhoidal nodes of the inferior mesenteric system. There are numerous lymphatic connections between the various levels of the anal canal, and an intramural system links the lymphatics of the canal with those of the rectum.[5]

The veins of the anal canal connect with both the systemic and the portal venous systems. Venous plexuses, which lie in and surround the mucosal and muscular structures of the anal wall, anastomose around the junction of the anal verge and distal canal. The veins draining the inferior parts of these plexuses communicate with the systemic venous system via the internal pudendal and internal iliac veins, and those from the superior canal flow predominately to the inferior mesenteric vein and then to the portal system.[5]

Anorectal continence is mediated by both cerebrospinal nerves and the autonomic system. The smooth muscle of the internal sphincter is supplied by parasympathetic fibers from the second, third, and fourth sacral segments as well as sympathetic fibers from the hypogastric plexus. The upper canal has selective sensitivity for intraluminal differences in pressure, and the autonomic nerves mediate both the inhibitor and facilitator reflexes of the internal sphincter. The striated muscle of the external sphincter is under voluntary control and innervated by the internal rectal nerve, a branch of the pudendal nerve arising from the second, third, and fourth sacral nerves. The internal rectal nerve also transmits pain, touch, and other sensations from the anal lining below the dentate line and from the perianal skin.[5]

PATHOLOGIC CLASSIFICATION

The most recent revision of the World Health Organization (WHO) classification of anal tumors, published in 2010, describes intraepithelial and invasive neoplasms.[6] The term *anal intraepithelial neoplasia* (AIN) is applied to precancerous changes in the epithelium of the anal canal and perianal skin.[7]

For invasive cancers, the term *squamous cell carcinoma* is applied to all the various subtypes: squamous, large cell keratinizing and nonkeratinizing, and basaloid, cloacogenic, and transitional, all of which were considered separate entities in the previous classification.[6] Squamous cell carcinomas account for about 85% to 90% of primary anal canal cancers; the remaining 10% to 15% are predominantly adenocarcinomas, most of which arise from anal glands or within anal fistulae. Adenocarcinomas from the rectal-type mucosa in the upper canal are classified as primary rectal cancers. The WHO system retains as separate entities rare variants, such as squamous cell carcinoma with mucous microcysts, small cell, and undifferentiated cancers.

Primary cancers of the perianal skin are similar to cancers of the skin in other sites. Most are squamous cell cancers, with occasional basal cell cancers and skin adnexal adenocarcinomas.

EPIDEMIOLOGY

Anal cancers are about one-fifth as common as cancers of the rectum. Cancers arise in the canal with 3 to 4 times the frequency of perianal cancers. In North America and Europe, anal canal cancers are more common in women than in men, although this difference is decreasing[8]; perianal cancers occur with about equal frequency in both sexes. The annual age-adjusted rates per 100,000 for squamous cell cancers of the anus, anal canal, and anorectum in the U.S. Surveillance, Epidemiology, and End Results (SEER) registry for 2010 to 2014 were 1.5 for males and 2.1 for females.[8] The incidence varies widely in different parts of the world but has been increasing in North America and Europe over the past 40 years.[8] The annual incidence of invasive and intraepithelial neoplasia almost doubled in men and rose by about half in women between the periods 1973 to 1979 and 1994 to 2000.[9] The risk of anal cancer increases with age; the median age at diagnosis is 61 years.

RISK FACTORS

The most significant risk factors so far identified are sexually transmissible viruses, immunosuppression, and tobacco smoking. The role of sexual practices and sexually transmissible agents has been investigated intensively. Several mucosotropic types of human papillomavirus (HPV) are linked to cancer and precancerous lesions in the anogenital epithelium.[10-12] Subtypes of HPV with a high risk of association with cancer are type 16 in particular and, to a lesser extent, types 18, 31, 33, 35, and others.[10-12] These high-risk HPV types have been found in about 85% of anal squamous cancers in many series,[10,12] more commonly in cancer of the canal than of the perianal skin.[12,13] Some geographic variation was noted in the types of high-risk HPV identified.[12,14] Case-control studies suggest that a history of multiple sexual partners in homosexual or heterosexual relationships or of unprotected anal intercourse in males and in females is predictive of an increased risk of AIN and invasive anal cancer.[15] For instance, one study found that compared to the overall annual incidence of anal cancer in White males in the United States of approximately 0.7 per 100,000 in the early 1980s, the estimated incidence in the male homosexual population, prior to the human immunodeficiency virus (HIV) epidemic, ranged from about 12 to 37 per 100,000.[16] This rate increased to about 70 per 100,000 among HIV-positive homosexual men.[17]

Compromise of cell-mediated immunity reduces the body's ability to prevent or eliminate infection by viruses, such as HPV. An increased risk of anal cancer is associated with at least two situations in which cell-mediated immunity is significantly altered: infection with HIV and iatrogenic suppression of immunity in patients with organ transplant. Interactions between HPV and HIV are complex. Although anal cancer has not been designated an acquired immunodeficiency syndrome (AIDS)-defining condition, data from the U.S. AIDS Cancer Registry linkage study showed that the rate of HPV-associated cancers and precursors was increased in HIV-infected persons for all anogenital sites compared with the general population. The relative risk for anal cancers was 6.8 in women and 37.9 in men.[18] A national cohort study in Sweden of 5,931 patients who had undergone organ transplantation showed a 10-fold excess risk of developing anal cancer.[19] Whatever the cause of suppression of cell-mediated immunity,

those affected have increased rates of HPV infection, higher progression rates from normal epithelium to AIN and from lower to higher grade AIN, and lower rates of clearance of HPV and regression from abnormal to normal epithelium.[20,21]

The increasing effectiveness of antiretroviral therapy has led to longer survival of patients who are HIV infected and an increased number with anal cancer.[22,23] There was a 3-fold increase in incidence in the HIV-positive population from the period prior to the introduction of highly active antiretroviral therapy (HAART) in about 1996 and the later HAART era.[23] Although there was a decrease in the incidence of Kaposi sarcoma and lymphoma by a few years after HAART became available, at the time of the review, there had been no significant reduction in the incidence of less common malignancies, such as anogenital cancers.[24] Early success of prophylactic vaccines against HPV in both men and women suggests that the incidence of anal cancer can be reduced in the future.[25,26]

In addition, tobacco smoking is also associated with up to a 4-fold increase in risk of developing anal cancer in several case-control studies. Current smokers are at greater risk than are past smokers.[15,27] Benign conditions such as fistulae, fissures, and hemorrhoids do not appear to predispose to cancer.[28] Chronic anal inflammation due to inflammatory bowel disease has also been discounted as a risk factor.[29]

NATURAL HISTORY

Most squamous cell cancers of the anal region, especially the canal, are believed to be preceded by high-grade AIN.[7] However, it has been estimated that no more than 1% of cases with AIN develop invasive cancer per year,[30] a rate lower than that described for cervical intraepithelial neoplasia. Anal dysplasia recurs frequently despite excision, laser ablation, or topical therapies, presumably because of incomplete treatment or persistence of the HPV infection with which dysplasia is associated.[22] The natural history of AIN coexisting with anal cancers exposed to radiation, with or without chemotherapy, is unknown.

Squamous cancers of the anal canal spread most commonly by direct extension and lymphatic pathways. Hematogenous metastases are less common. Direct invasion from the anal mucosa into the sphincter muscles

and perianal connective tissue spaces occurs early; in a series of 137 cases, cancers were confined to the mucosa and submucosa at diagnosis in only 12%, and to the sphincter muscles, without regional lymph node involvement, in only 34%.[31] In about half the cases, anal cancers extend into the rectum or perianal skin. Invasion of the vaginal septum and vaginal mucosa is more common than invasion of the prostate gland, but anovaginal fistulas occur in fewer than 5% of women. Extensive tumors may infiltrate the pelvic walls.

Lymphatic invasion occurs relatively early. The overall risk of regional nodal involvement at diagnosis is about 25%.[32,33] Pelvic lymph node metastases were found in as many as 30% of patients treated by abdominoperineal resection.[31,34,35] In an illustrative series, metastases were present in the superior hemorrhoidal nodes in 25% (15/61); in the external iliac, obturator, or hypogastric nodes in 30% (8/27); and in the inguinal nodes in 16% (12/74) of patients.[35] Inguinal metastases were detected clinically in up to approximately 20% of patients at initial diagnosis and were present subclinically in a further 10% to 20%.[31,35-37] Nodal metastases were associated with 30% of cancers confined to the sphincter muscles, and 60% of those that had extended through the sphincters or were more poorly differentiated.[34] Lymphatic metastases increase in frequency with progressive enlargement of the primary cancer.[34,38]

Extrapelvic metastases are identified at the time of first presentation in less than 10% of patients. They are found most frequently in the liver, lungs, and para-aortic nodes. Local or regional nodal relapse is more common than in extrapelvic organs. In chemoradiation series, locoregional relapse rates as high as 30% and extrapelvic failure as high as 20% have been reported, depending on stage and chemoradiation regimen (though improvements in imaging likely have affected these rates).[31,39-41]

Perianal cancers tend to grow locally and may extend into the anal canal. When the site of origin is in doubt, it is conventional to classify the cancer as arising in the anal canal (given that involvement of the anal canal would often make a patient with perianal cancer a poor surgical candidate). The ipsilateral inguinal nodes are the most common site of metastasis and are involved in from 5% to 20% of cases (discussed later). Extrapelvic metastases are uncommon, except in locally advanced cancer or those with nodal metastases.

CLINICAL PRESENTATION

The symptoms of anal cancer are often nonspecific, contributing to delay in presentation by the patient and in diagnosis by the physician of more than 6 months in one-third of patients.[42,43] Bleeding and anal discomfort are the most common symptoms and are reported by about half of patients.[44] Less common complaints include awareness of an anal mass, pruritus, and anal discharge. Pain is uncommon but may be severe. In patients with tumors in the proximal canal, there may be an alteration in bowel habits, but this is uncommon with distal cancers.[44] Occasionally, asymptomatic tumors are found during physical examination or in the course of investigation of an enlarged inguinal node. Unsuspected microinvasive carcinoma is sometimes found in mucosa removed at hemorrhoidectomy.[45]

Small carcinomas are often nodular or plaque like, but larger tumors are more typically ulcerated and infiltrative. Coexisting benign conditions such as anogenital warts, hemorrhoids, and anal fissures may be present. Anal sphincter tone is usually preserved and may be increased by painful spasm. Gross fecal incontinence is rare but tends to be more common with more advanced T-stage as a result of sphincter destruction.[46] Similarly, vaginal fistulas are uncommon. Rarely, extrapelvic metastases may be the only symptomatic feature or finding.

DIAGNOSTIC WORKUP

The history and physical examination should stress features that delineate the extent of the primary tumor, including anal sphincter competence and possible invasion of adjacent organs including a pelvic examination and cervical cancer screening in female patients (given risk of HPV field cancerization). A biopsy of the primary tumor is necessary to establish the diagnosis and the histologic type. General anesthesia may be needed to permit detailed pelvic and anorectal examination, which should include proctoscopy. Sigmoidoscopy and colonoscopy, although often performed, infrequently disclose colonic pathology.[47] Physical examination should include detailed examination of the genital region, especially in patients who give a history of previous anogenital area dysplasia or cancer, genital warts, or anal-receptive intercourse or are HIV positive.

Only the inguinal lymph nodes are accessible to clinical examination. Because lymph node enlargement may be caused by reactive hyperplasia in as many as half of those with palpable inguinal nodes, clinically suspicious nodes should be assessed histologically by needle biopsy.[44] Metastases in the internal iliac and superior hemorrhoidal node chains, about half of which are less than 0.5 cm in diameter,[48] cannot be identified reliably by current techniques of computed tomography (CT), magnetic resonance imaging (MRI), or transanorectal ultrasonography. MRI is considered the most accurate method for assessing the primary cancer and pelvic nodes and is guideline recommended as a part of workup.[49] Both fluorodeoxyglucose (FDG) positron emission tomography (PET) with CT and inguinal sentinel lymph node (ISLN) biopsy have been used to identify inguinal node metastases and to refine RT plans.[50-52] However, a comparison of FDG-PET-CT and ISLN biopsy in 27 patients found several false-positive PET studies (4/7).[53] A meta-analysis of 12 studies found that FDG-PET resulted in a change in nodal staging in 28% of patients with anal cancer. Subsequent sections further discuss the risk of isolated inguinal recurrence in patients who are clinically/radiographically inguinal node negative.[54] Finally, in addition to MRI of the pelvis and considering a PET-CT (if available), some guidelines recommend CT of the chest and pelvis to finalize staging.[55]

Laboratory workup should include full blood count, renal and liver function tests, and, if not previously tested, assessment of HIV antibody status (see section on HIV coinfection with anal cancer).

STAGING

The staging systems for anal canal and perianal cancers most commonly used are those proposed by the UICC[3] and the AJCC[2] (Tables 68.1 and 68.2). Most authors continue to report results by T (tumor) category or N (node) category rather than by composite tumor, node, metastasis stages. Under the UICC and AJCC systems, the regional lymph nodes for anal canal cancer are the perirectal, internal iliac, and inguinal nodes. Spread to all other pelvic node groups, including the external iliac, common iliac, and sigmoid nodes, is classified as metastasis (M1). For perianal cancers, the only regional nodes are the ipsilateral inguinal nodes. The eighth edition of

the AJCC staging manual for anal cancer includes changes to nodal classification and stage groupings.

TABLE 68.1 ANAL CANAL TNM CLASSIFICATION—EIGHTH EDITION

Primary Tumor (T)			
Tis	High-grade squamous intraepithelial lesion		
T1	Tumor ≤2 cm in greatest dimension		
T2	Tumor >2 cm but not >5 cm in greatest dimension		
T3	Tumor >5 cm in greatest dimension		
T4	Tumor of any size invades adjacent organ(s) (eg, vagina, urethra, bladder) (invasion of the rectal wall, perirectal skin, subcutaneous tissue, or sphincter muscle is not included as T4).		
Regional Lymph Nodes (N)			
N0	No regional lymph node metastases		
N1a	Inguinal, mesorectal, or internal iliac lymph nodes		
N1b	External iliac nodes		
N1c	External iliac nodes *plus* any node in the N1a group		
Distant Metastases (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Stage Grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
	T3	N0	M0
Stage IIIA	T1	N1	M0
	T2	N1	M0
Stage IIIB	T4	N0	M0

Stage IIIC	T3	N1	M0
	T4	N1	M0
Stage IV	Any T	Any N	M1

TNM, tumor, node, metastasis.

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TABLE 68.2 PERIANAL SKIN TNM CLASSIFICATION

Primary Tumor (T)	
TX	Primary tumor (T)
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor >2 cm but not >5 cm in greatest dimension
T3	Tumor >5 cm in greatest dimension
T4	Tumor invades deep extradermal structures (ie, cartilage, skeletal muscle, or bone)
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant Metastasis (M)	
MX	Distant metastasis cannot be assessed.
M0	No distant metastasis
M1	Distant metastasis

Stage Grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2, T3	N0	M0
Stage III	T4	N0	M0

	Any T	N1	M0
Stage IV	Any T	Any N	M1

TNM, tumor, node, metastasis.

From Sobin LH, Gospodarowicz M, Wittekind C. *TNM Classification of Malignant Tumours*. 7th ed. Wiley-Blackwell; 2009. Copyright © 2010 Blackwell Publishing Ltd. Reproduced with permission of John Wiley & Sons Limited through PLSclear.

In a review of 19,199 patients with squamous cell carcinoma of the anal canal, diagnosed between 1985 and 2000 and recorded in the U.S. National Cancer Database (NCDB), the stage distribution per AJCC seventh edition was stage I, 25.3%; II, 51.8%; III, 17.1%; and IV, 5.7%. Tumors were greater than 5 cm in size (T3) in at least 20.6% (tumor size in T4 category not available). Nodal involvement was present in 21.8% of those for whom information on nodal status was recorded.[32]

PROGNOSTIC FACTORS

Tumor Factors

Features related to the anatomic extent of disease generally provide the most prognostic value.[56] The most adverse factor for survival is the presence of extrapelvic metastasis.[57-59] When anal cancer is confined to the pelvis, the size of the primary tumor is the most useful predictor for local control and preservation of anorectal function and survival.[40,60,61] Involvement of regional lymph nodes is an adverse factor for survival, but, in most series, not for control, of the primary tumor.[40,60]

Among the 19,199 patients recorded in the NCDB between 1985 and 2000, the overall 5-year survival was 58%.[33] Patients with distant metastases had a 5-year survival of 18.7% versus 59.4% for those without metastases. Patients with regional node metastases had a 5-year survival of 37.4% versus 62.9% in patients who were node negative. Five-year survival rates by T category were T1, 68.5%; T2, 58.9%; T3, 43.1%; and T4, 34.3%. The survival rates by AJCC stage are shown in Figure 68.2. More recent data from SEER find that in the United States from 2000 to 2019, the incidence of anal cancer has increased by 1.8% annually, possibly accompanied by an

increased mortality rate, though survival has modestly improved in that time by an annualized average absolute change in survival of 0.3%.[62]

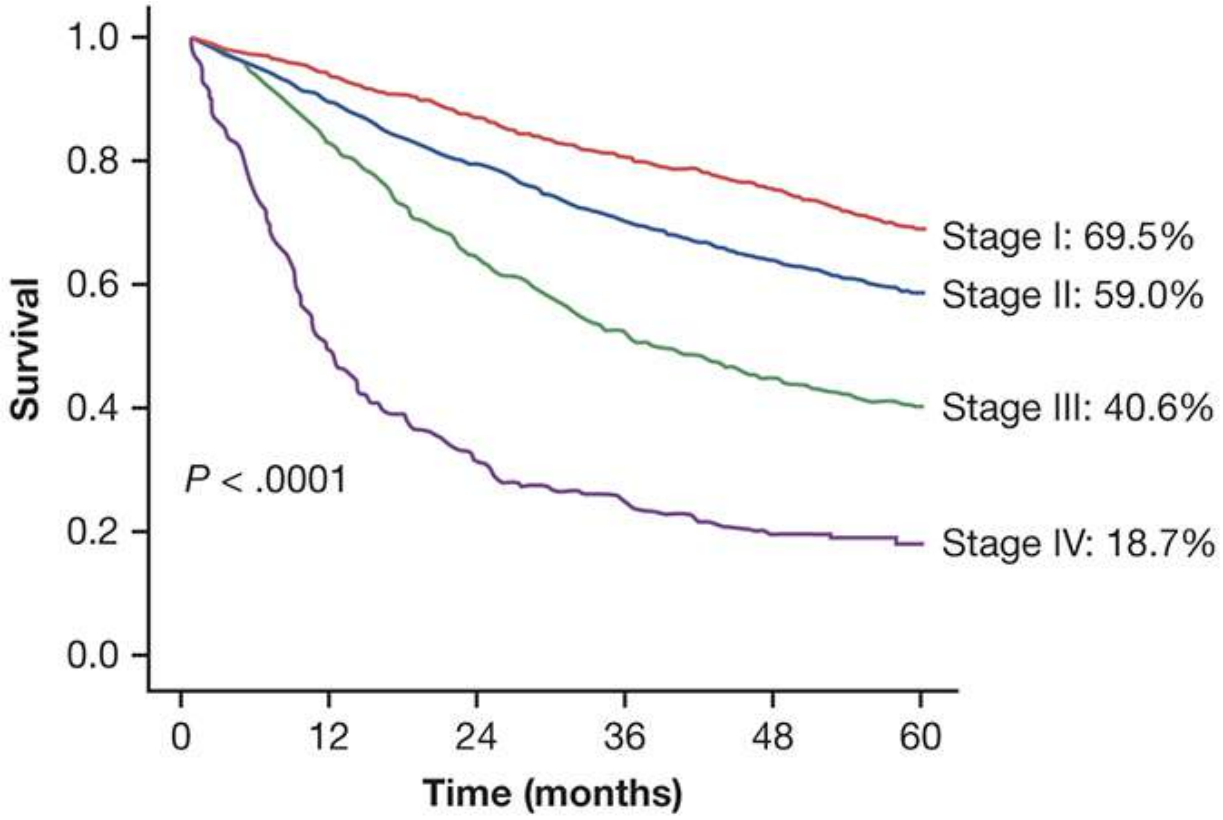

FIGURE 68.2 Five-year survival rates by American Joint Committee on Cancer clinical staging and the International Union Against Cancer stages, for 19,199 patients recorded in the U.S. National Cancer Database between 1985 and 2000. (Reprinted with permission from Bilimoria KY, Bentrem DJ, Rock CE, Stewart AK, Ko CY, Halverson A. Outcomes and prognostic factors for squamous-cell carcinoma of the anal canal: analysis of patients from the National Cancer Data Base. *Dis Colon Rectum*. 2009;52[4]:624-631. Copyright © The ASCRS 2009.)

In detailed analyses of data collected prospectively for Radiation Therapy Oncology Group trial RTOG-9811,[60,63] tumor diameter greater than 5 cm correlated with an increased likelihood of colostomy (hazard ratio [HR] 1.8; $P = .008$)[60] (Table 68.3). A tumor size greater than 5 cm and clinically positive nodes were each associated with significantly poorer 5-year disease-free and overall survival (OS).[63] These findings were combined into prognostic groups.[63] These groups are shown in Table 68.3, with additional

data drawn from the analyses by Ajani et al.[60,63] These groupings have not been verified prospectively.

TABLE 68.3 PROGNOSTIC GROUPS BASED ON DATA FROM RTOG TRIAL 9811[60,63]

End Points (3 Y)	Group 1	Group 2	Group 3	Group 4
	T ≤5 cm, N− (*n* = 365)	T >5 cm, N− (*n* = 112)	T ≤5 cm, N+ (*n* = 107)	T >5 cm, N+ (*n* = 60)
Disease-free survival (actuarial) (%)	74	65	48	30
Colostomy rate (crude) (%)	11	17	9	24
Overall survival (actuarial) (%)	86	75	75	63

N, any regional node; RTOG, Radiation Therapy Oncology Group; T, primary tumor.
Data from pooled trial groups treated by radiation therapy (RT), 5-fluorouracil, and mitomycin C or RT, 5-FU, and cisplatin (CDDP). Median follow-up 2.2 years. Most events occurred by 2 years.

Patient Factors

Patient-related factors are not consistent between series. Age, performance status, gender, baseline hemoglobin level, and race have all been considered prognostic in one or more series. Patients who continue to smoke tobacco may be at greater risk of local relapse.[64] In some series of patients who are HIV positive, high viral load, low lymphocyte CD4-positive counts, and AIDS have been prognostic of poor local tumor control and survival and, in some series, of impaired tolerance of RT and chemotherapy.[65-67]

Biochemical and Molecular Factors

A survey of nearly 50 reports on cytogenetic, flow cytometric, immunohistochemical, and other factors considered that these studies offered some insights on pathogenesis but did not help with selection of treatment or provide guidance on prognosis.[68] Studies suggest that biomarkers such as p53, Ki 67, nuclear factor κ B, 5HH, and Gli-1[69] may be associated with locoregional control or disease-free survival. High levels of MCM7 protein detected in gene expression analysis were associated with

improved cancer survival in one series.[70] None of these suggested markers has yet been validated in prospective studies.

Treatment Factors

Early response and the extent of response to chemoradiation were correlated with survival in several multivariate analyses.[56,71,72] An association with total radiation dose or with treatment duration has not been demonstrated consistently for locoregional control nor survival. A daily fraction size of 2.5 Gy appeared to be associated with increased acute and late toxicity, compared with 2-Gy fractions.[40]

TREATMENT OF ANAL CANCER

Although squamous cell cancer of the anal canal is a relatively uncommon malignancy, several practice-defining multicenter randomized trials have been completed successfully. These have established RT with concurrent 5-FU and MMC, with surgery reserved for failure, as the standard against which other treatments should be compared. These trials are outlined here and in Table 68.4.[39,73-79] The original references should be consulted for full details of patient eligibility, treatment regimens, outcomes, and statistical analyses. There have also been over 100 nonrandomized studies, many of which provided hypotheses subsequently tested in the randomized studies, or information that guided the development of technical aspects of radiation treatment.[80]

TABLE 68.4 SELECTED RESULTS OF PHASE III TRIALS

Reference	*N*	Treatment	Local (LF) or Locoregional (LRF) Failure (%)	Colostomy Rate (CR) or Colostomy-Free Survival (CFS) (%)	Disease-Free Survival (%)	Overall Survival (%)
			3-y LRF	**3-y CR**	**3 y**	**3 y**
UKCCCR (ACT I)[39]	292	RT, 5-FU, MMC	39	24	np	65

Reference	*N*	Treatment	Local (LF) or Locoregional (LRF) Failure (%)	Colostomy Rate (CR) or Colostomy-Free Survival (CFS) (%)	Disease-Free Survival (%)	Overall Survival (%)
	285	RT	61	40	np	58
	RR		0.54	np	np	0.86
	P		<.0001	np	np	.25
			10-y LRF	**10-y CFS**	**10 y**	**10 y**
Update[77]	292	RT, 5-FU, MMC	34	36	36	42
	285	RT	59	26	24	36
	HR		0.46	np	0.70	0.86
	P		<.001	sig	<.001	.12
			5-y LRF	**5-y CFS**	**5 y**	**5 y**
EORTC[74]	51	RT, 5-FU, MMC	32[a]	72[a]	np	58[a]
	52	RT	48[a]	40[a]	np	53[a]
	P		.02	.002	np	.17
			4-y LF	**4-y CR**	**4 y**	**4 y**
RTOG 8704/ECOG 1289[75]	146	RT, 5-FU, MMC	16	9	73	76
	145	RT, 5-FU	34	22	51	67
	P		.0008	.002	.0003	.31
			5-y LRF	**3-y CR**	**3 y**	**3 y**
RTOG 9811[73]	324	RT, 5-FU, MMC	25	10	60	75
	320	RT, 5-FU, CDDP	33	19	54	70
	HR		1.32	1.68	1.20	1.28
	P		.07	.02	.17	.10
			5-y LRF	**5-y CR**	**5 y**	**5 y**

Reference	*N*	Treatment	Local (LF) or Locoregional (LRF) Failure (%)	Colostomy Rate (CR) or Colostomy-Free Survival (CFS) (%)	Disease-Free Survival (%)	Overall Survival (%)
Update[76]	325	RT, 5-FU, MMC	20	12	68	78
	324	RT, 5-FU, CDDP	27	17	58	71
	P		.089	.075	.004	.021
			3 y	**3-y CR**	**3 y**[b]	**3 y**[b]
UKCR (ACT II)[78]	471	RT, 5-FU, MMC	np	14	np	np
	469	RT, 5-FU, CDDP	np	11	np	np
	446	No maintenance chemo	np	np	75	85
	448	Maintenance chemo	np	np	75	84
	HR		np	11	0.89	0.79
	P			.26	.42	.19
			3-y LF	**3-y CFS**	**3-y Event-Free Survival**	**3 y**
ACCORD-03[79]	307 total	Std RT, 5-FU, CDDP	10	86	67	np
		HD RT, 5-FU, CDDP	13	80	68	np
		Ind CT + Std RTCT	20	83	70	np
		Ind CT + HD RTCT	4	85	78	np
		Ind CT arms	np	84 vs 83		

Reference	*N*	Treatment	Local (LF) or Locoregional (LRF) Failure (%)	Colostomy Rate (CR) or Colostomy-Free Survival (CFS) (%)	Disease-Free Survival (%)	Overall Survival (%)
		HD RTCT arms	np	84 vs 83		
	P		not sig	not sig	not sig	not sig

5-FU, 5-fluorouracil; CDDP, cisplatin; CFS, colostomy-free survival; CR, colostomy rate; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research on Treatment of Cancer; HD RT, high-dose radiation; Ind CT, induction chemotherapy; LF, local failure; LRF, locoregional failure; MMC, mitomycin C; not sig, not significant; NP, not published; RT, radiation therapy; RTCT, chemoradiation; RTOG, Radiation Therapy Oncology Group; sig, significant; Std, standard; UKCCCR, UK Coordination Committee for Cancer Research; Y, year.

[a]Numbers derived from curves.

[b]In patients who received maintenance chemotherapy.

It is of note that the combination of RT and chemotherapy has long supplanted surgery as the preferred treatment for anal canal squamous cell cancer without formal comparison in a randomized trial. Nonrandomized comparisons of radical resection with this combination of RT, 5-FU, and MMC[33] or with RT alone[81] have shown the ability of radiation-based regimens to produce survival rates at least equal to those of surgical series while allowing preservation of anorectal function in the majority of patients.

Combined Radiation and Chemotherapy

Radiation, 5-Fluorouracil, and Mitomycin C Versus Radiation Alone

In both the United Kingdom and Europe in the 1970s, more so than in North America, there was already some acceptance of RT as the primary treatment for anal cancer[82]; this facilitated the development of the first multi-institutional randomized trials in which RT alone was compared with RT plus chemotherapy. The randomized trials conducted by the UK Coordination Committee for Cancer Research (UKCCCR)[39] and the European Organization for Research and Treatment of Cancer (EORTC)[74]

both demonstrated significant improvement in control of the primary cancer and regional nodes and in colostomy rate or colostomy-free survival in patients who received RT, 5-FU, and MMC. OS rates were not improved significantly in the initial reports. However, in a later report of the UKCCCR trial after a median of 13-year follow-up, locoregional control, colostomy-free survival, disease-free survival, and deaths due to anal cancer all significantly favored chemoradiation.[74] The absolute difference in risk of dying from all causes was 5.1% lower in the chemoradiation group at 5 years and 5.6% lower at 12 years from randomization. This difference approached statistical significance (HR 0.86; 95% confidence interval [CI], 0.70-1.04; $P = .12$).[74]

The UKCCCR trial included 577 patients with all stages (UICC staging system, 1987 edition) of squamous cell cancer of the anal canal (75% of patients) or anal margin (23%).[39] The radiation dose was 45 Gy in 20 to 25 fractions in 4 to 5 weeks. Those randomized to chemotherapy received 5-FU (1,000 mg/m^2/day for 4 days or 750 mg/m^2/day for 5 days) by continuous peripheral intravenous (IV) infusion in the first and final weeks of radiation treatment, plus MMC (12 mg/m^2) by bolus IV injection on day 1 of the first course of chemotherapy. If the primary tumor had not regressed by at least 50% by 6 weeks after treatment (as occurred in 10% in each group), surgery was recommended; otherwise, the patients received an additional 15 Gy in 6 fractions by a perineal field or 25 Gy over 2 to 3 days by iridium-192 implant. The locoregional recurrence rates at 3 years were 61% after RT and 39% after RT, 5-FU, and MMC ($P < .0001$). The OS rates at 3 years were 58% and 65% ($P = .25$), respectively. There were six (2%) deaths due to treatment in the combined modality arm and two (0.7%) in the irradiation-alone arm. Acute toxicity, other than hematologic, was considered comparable in each group. In the first few years after treatment, surgery that included colostomy was necessary for the management of toxicity in 10 patients (3.5%) in each group.[39] Late toxicity events (severity was not graded) after a median of 13-year follow-up were similar in each treatment group.[77]

In the EORTC study, 103 patients with advanced cancers of the anal canal were randomized in a trial of similar design.[74] The radiation dose was 45 Gy in 25 fractions over 5 weeks. Chemotherapy included 5-FU (750 mg/m^2/day for 5 days) in weeks 1 and 5 of radiation and a single dose of MMC (15

mg/m^2) by bolus IV injection on day 1 of the first course of 5-FU only. After 6 weeks, boost irradiation of 15 Gy (if complete clinical response to previous treatment had occurred) or 20 Gy (after partial response) was given by external beam or interstitial irradiation. The 5-year locoregional recurrence rate was 48% after RT and 32% after RT, 5-FU, and MMC (P = .02). The difference between OS rates (53% and 58%, respectively) was not significant. One of 51 patients who received combined modality treatment died of toxicity. Otherwise, acute and late toxicity rates did not differ markedly. These two trials established RT, 5-FU, and MMC as the standard first-line treatment.

Radiation, 5-Fluorouracil, and Mitomycin C Versus Radiation and 5-Fluorouracil

The RTOG and Eastern Cooperative Oncology Group (ECOG) established in the randomized trial RTOG 8704 that the combination of MMC with 5-FU and RT is more effective than is 5-FU alone with RT.[75] Given the hematologic toxicity of MMC, there was interest in determining if it was a necessary component of a concurrent chemotherapy regimen. Two hundred and ninety-one patients with cancers of the anal canal of any T and N category (RTOG staging system) who did not have evidence of extrapelvic metastases received 45 to 50.4 Gy in 25 to 28 fractions over 5 weeks, plus 2 courses of 5-FU (1,000 mg/m^2/day by continuous peripheral IV infusion) over 4 days, with or without MMC (10 mg/m^2 by bolus IV injection) on the first day of each course of chemotherapy. Chemotherapy was administered in weeks 1 and 5 of RT. All patients underwent biopsy of the primary tumor site 6 weeks after treatment. Biopsies were positive in 15% of those who received 5-FU only and in 8% of those who received both MMC and 5-FU (P = .14). Patients with positive biopsies had the option of receiving an additional 9 Gy in five treatments concurrently with a 4-day infusion of 5-FU (1,000 mg/m^2/day) and a single injection of cisplatin (CDDP) (100 mg/m^2) if it was thought that anal function might still be salvaged. At 4 years, the rates of local failure (16% vs 34%; P = .0008) and colostomy (9% vs 22%; P = .002) significantly favored the MMC arm. There was no significant difference in OS rates (76% with RT, 5-FU, and MMC vs 67%); however, the disease-free survival rate (73% vs 51%; P = .0003) favored the

addition of MMC. Acute hematologic toxicity was more common in the patients who received MMC, but the rates of other acute and late toxic effects were similar in each treatment group. Four of 146 (2.7%) patients who received both 5-FU and MMC suffered fatal toxicity as did 1 of 145 treated with RT and 5-FU alone. On the evidence from this trial, MMC was retained in combination with RT and 5-FU.

Radiation, 5-Fluorouracil, and Mitomycin C Versus Radiation, 5-Fluorouracil, and Cisplatin

Several pilot studies suggested high tumor response rates to concurrent, induction, or induction plus concurrent 5-FU and CDDP with RT.[83-87] CDDP was known to be effective against squamous cell cancers in several other sites and to be associated with stronger laboratory evidence as a radiosensitizer than MMC. Two large, randomized studies detailed later explored this question, ultimately resulting in MMC remaining the standard of care delivered concurrently with 5-FU and radiation. It should be noted that though MMC has unique hematologic toxicities, it does not carry the same ototoxicity nor renal toxicity risks of CDDP and is more convenient to administer (brief injection with some protocols even using a single bolus dose).

The RTOG elected to evaluate a strategy of CDDP-based induction chemotherapy intended to downsize the primary tumor and nodal metastases prior to concurrent chemoradiation. This trial included a higher total radiation dose than the earlier RTOG 87-04 randomized trial,[75] based on the analysis of nonrandomized studies that suggested a radiation dose-control relationship[80,81] and on pilot studies, which had demonstrated that a proportion of patients could tolerate uninterrupted radiation schedules of up to 59.4 Gy over 6.5 weeks with either concurrent MMC with 5-FU[88] or CDDP with 5-FU.[86]

In RTOG-9811,[73] patients received up to 59 Gy in 6.5 weeks (45 Gy in 1.8-Gy fractions, followed without interruption by 14 Gy in 2-Gy fractions boost for T3-4N+ or T2 with residual disease) with concurrent 5-FU (1,000 mg/m^2/day) by continuous infusion on days 1 to 4 and 29 to 32, and were randomized to either combination concurrent MMC (10 mg/m^2 IV bolus on days 1 and 29) versus two cycles of induction chemotherapy with 5-FU plus

CDDP (75 mg/m^2 bolus injection) and then chemoradiation with the same radiation approach substituting CDDP (75 mg/m^2 days 1 and 28) for MMC. Acute grade 3 or 4 nonhematologic toxicity rates were 75% in each arm, but hematologic toxicity was higher in the MMC group (67% vs 47%). No treatment-related deaths were reported. The rate of severe long-term toxicity was similar in each group (11% MMC vs 10% CDDP). The final report of this trial favored the MMC arm with 5-year disease-free survival of 68% versus 58% (P = .004) and OS of 78% versus 71%; (P = .021).[76] The 5-year colostomy rates and locoregional failure rates showed trends in favor of the standard of care of 5-FU/MMC chemoradiation, which did not meet significance threshold. The investigators concluded that RT, 5-FU, and MMC should remain the standard approach. It should be noted that in addition to replacing MMC with CDDP, the experimental arm of this study included two cycles of induction 5-FU/CDDP, which may have delayed time to initiation of definitive chemoradiation.

Also informing the decision of MMC versus CDDP in the concurrent setting is the second UK Anal Cancer Trial (ACT II).[78] The trial used a 2 × 2 randomization, either to 5-FU and MMC or to 5-FU and CDDP concurrently with RT and then to either no additional therapy or two cycles of adjuvant 5-FU and CDDP. Complete tumor response rates at 6 months were similar: 94% (MMC arm) and 95% (CDDP arm), and there was no significant difference in progression-free survival (PFS) between these arms at a median of 5.1 years of follow-up (HR 0.95 95% CI 0.75-1.19; P = .63). The 3-year PFS with or without maintenance chemotherapy was 74% versus 73% (P = .70). Patients who were MMC-treated had more severe hematologic toxicity (G3-4 26% vs 16%), but rates of neutropenic sepsis were similar (about 3%).

Another study exploring the use of CDDP (without comparing it to MMC) was the French study ACCORD 03, which used a four-armed factorial design to study (1) two cycles of induction 5-FU and CDDP to definitive chemoradiation with these agents (vs chemoradiation without induction) and (2) whether a higher dose of boost RT (20-25 Gy vs standard 15 Gy) would impact colostomy-free survival as the primary end point.[79] The baseline standard RT schedule was 45 Gy in 25 fractions in 5 weeks. Regarding the induction therapy question specifically, 5-year colostomy-free survival was 76.5 versus 75.0 (P = .37).[79] Local control, event-free

survival, and OS rates were similar in each arm. Taken together, both the ACCORD 03 (finding no benefit to induction chemotherapy) and the ACT II adjuvant chemotherapy arms (which did not improve PFS) suggest that the curative modality in locally advanced anal cancer is chemoradiation. Whether inferior outcomes in the CDDP arm of RTOG 9811 are due to delayed time to chemoradiation (knowing that induction outcomes in ACCORD 03 were not worse than omitting induction) or inferiority of CDDP compared to MMC remains an unanswered question, but MMC with 5-FU remains the standard chemotherapeutic regimen in combined chemoradiation. In specific circumstances such as patients with poor hematopoietic function for whom the toxicity of MMC would be a specific concern, CDDP can be considered a reasonably well-studied option.

Other Drug-Radiation Combinations

In an effort to develop a simplified schedule, the UK National Cancer Research Institute Anal Subgroup conducted a phase II trial of RT (50.4 Gy in 28 fractions in 5.5 weeks), a single IV injection of MMC (12 mg/m^2 on day 1), and oral capecitabine (825 mg/m^2 twice daily on each RT treatment day).[89] The schedule was described as well tolerated with acceptable compliance (although only 58% received the full planned doses). The overall tumor response rate after treatment was 90% (complete in 24/31 and partial in 4/31). Several guidelines list oral capecitabine as an option in lieu of IV infusions of 5-FU, though the latter remains standard.

Because epidermal growth factor receptor (EGFR) is known to be overexpressed in many epithelial cancers, including squamous cell cancer of the anal canal,[90] there was initially interest in exploring the addition of EGFR blockers to chemoradiation. This approach was found to be highly toxic, with a G3-4 acute toxicity of 88% in the UNICANCER ACCORD 16 trial resulting in early termination of that study.[91] Similarly, ECOG 3205 was a phase II study of RT, 5-FU, CDDP, and cetuximab in patients who were HIV negative, which found a 93% G3-4 toxicity rate when combined with induction chemotherapy and 82% when omitting induction therapy and a 5% treatment-associated death rate while still reporting a 23% locoregional failure rate at 3 years.[92] A similar phase II study conducted by the AIDS Malignancy Clinical Trials Consortium in patient with both anal

cancer and HIV infection reported a 72% G3-4 toxicity rate and 4% treatment-associated deaths despite a 42% locoregional recurrence rate at 3 years.[93] In light of these findings, excitement for this approach has diminished, and there are no ongoing phase III studies to explore this further.[94]

Summary

Concurrent chemoradiation is the cornerstone of curative- intent therapy for locally advanced anal cancer; the addition of neoadjuvant or adjuvant systemic therapy does not appear to offer an oncologic benefit in these patients. The standard of care for systemic agents in this setting remains 5-FU with MMC; data for replacing MMC with CDDP are mixed but do not demonstrate a conclusive equivalence to change the standard of care. Attempts at treatment intensification with adding EGFR-targeting drugs have in early studies added unacceptable toxicity without appearing to improve outcomes. There remain knowledge gaps in the optimal drug dosing (radiation dose escalation/de-escalation is discussed separately) such as more prolonged (but less daily dose-intense) infusions of 5-FU with the 96- to 120-hour infusions generally favored, nor of bolus injections with continuous infusions of 5-FU or CDDP. In addition, there is study variability in one versus two bolus injections of MMC at various doses. Finally, in most series, the timing of delivery of chemotherapy each day relative to irradiation was not tightly controlled, and the importance of this scheduling is not known.

Radiation Monotherapy

The use of RT alone, either brachytherapy or external beam, has been greatly reduced since the confirmation of improved outcome of combined modality therapy. Radiation alone is now recommended mainly to patients who are unable to undergo RT plus chemotherapy or for the treatment of smaller cancers up to about 3 to 4 cm in size where the physician does not wish to add chemotherapy. As with combined RT and chemotherapy, primary tumor control is better with small tumors. Selected results, mainly from the period prior to the adoption of chemoradiation, are shown in Tables 68.5 and 68.6.

TABLE 68.5 SELECTED STUDIES OF THREE-DIMENSIONAL CONFORMAL RADIATION AND INTENSITY-MODULATED RADIATION THERAPY

	Reference			
	RTOG 9811 MMC arm[73]	Boston[95]	RTOG 0529[96,97]	Toronto[98]
Number of patients	324	43	52	58
Radiation technique	3D conformal	IMRT	IMRT	IMRT
Acute grade 3 or 4 toxicity				
Hematologic (%)	61	49	NP	29
Skin (%)	48	7	20	46
GI (%)	36	7	22 (GI/GU)	9
GU (%)	4	5	22 (GI/GU)	0
Treatment breaks	61	40	49	26 (45%)
2-y results				
Locoregional control (%)	77	95 (local)	80	84
Colostomy-free survival (%)	84	94	86	84
Disease-free survival (%)	71	NP	77	77

3D, three-dimensional; GI, gastrointestinal; GU, genitourinary; IMRT, intensity-modulated radiation therapy; MMC, mitomycin C; NP, not published; RTOG, Radiation Therapy Oncology Group.

TABLE 68.6 SELECTED RESULTS OF RADIATION THERAPY ALONE

Author (Reference)	Radiation	Primary Tumor Control			Serious Complications—Colostomy	5-Y Survival
		T1	T2	T3-T4		
Newman et al[99]	50 Gy/20/4 wk	8/9 (≤2 cm)	42/52 (81%) (≤5 cm)	13/20 (65%) (>5 cm or T4)	2	66%
Cummings et al[40]	50 Gy/20/4 wk (some EB-I/I)	6/6 (≤2 cm)	19/29 (66%) (≤5 cm)	13/28 (46%) (>5 cm or T4)	6	61%

Author (Reference)	Radiation	Primary Tumor Control			Serious Complications —Colostomy	5-Y Survival
		T1	T2	T3-T4		
Martenson and Gunderson[100]	45-50 Gy/25-28/5-6 wk Plus boost to 55-67 Gy	9/9 (≤2 cm)	17/17 (100%) (≤5 cm)	—	2 temp	94%, actuarial
Otim-Oyet et al[101]	60-65 Gy/30-33/6-7 wk	2/2	16/22 (73%)	8/17 (47%)	1	56%
	(Some with boost)	(≤2 cm)	(≤4 cm)	(>4 cm)		Cause specific
Papillon and Montbarbon[81]	42 Gy/10/2.5 wk Plus I 20 Gy at 8 wk	NS	29/39 (74%) (≤4 cm)	27/64 (42%) (>4 cm)	6	60%

EB, external beam; I, interstitial brachytherapy; NS, not stated; temp, temporary.

Surgery

Surgery for Residual and Recurrent Cancer

Random biopsies from the site of the primary tumor, or abnormal nodes, shortly after chemoradiation are generally discouraged in the absence of clinical progression on serial exams. Elective biopsies at predetermined times do not lead to better results than biopsies guided by clinical evidence of residual or recurrent cancer. A negative biopsy does not exclude the possibility of cancer regrowth.[102,103] Importantly, residual masses at the site of the original anal cancer are common at the time of treatment completion and may take several months to resolve fully after chemoradiation or RT alone.[40,103] A post hoc analysis of the ACT II chemoradiation study evaluated the optimal timepoint to assess clinical complete response with assessments at 11, 18, and 26 weeks after treatment completion. The investigators found that among patients who did not have a clinical complete response by 11 weeks, 151 (72%) of 209 would ultimately achieve a clinical complete response by 26 weeks.[104] Together, these findings highlight the potentially slow primary anal tumor response to CRT and support the practice of serial

clinical examination reserving biopsy only for when persistent cancer is suspected clinically.

Suspected residual or recurrent cancer at the primary site or in regional nodes should be confirmed histologically if possible. Full restaging imaging is recommended, including with FDG-PET specifically.[105] In cases of local recurrence, abdominoperineal resection or multivisceral pelvic resection is usually required. Unfortunately, survival rates are poor when R0 resection cannot be achieved,[106,107] and even with apparent R0 resection, locoregional recurrence is common.[106,108] Five-year survival rates following salvage surgery range from 30% to 50%, reflecting the varying criteria applied when selecting patients for surgery.[106-109]

Salvage for inguinal node metastases is usually treated with radical or selective inguinofemoral lymphadenectomy. Pelvic sidewall node metastases may not be resectable because of invasion of muscle or bone or neurovascular structures.

Surgery for Primary Cancer

Surgery is the principal treatment for AIN[110] but is not a preferred option for the management of anal canal cancer. Primary definitive local excision preserving anorectal function for perianal primary lesions is discussed separately later. In the setting of a lesion of the anal canal with intact sphincter function, surgery is not the preferred intervention. There is no evidence that elective management by limited tumor excision and postoperative radiation-based protocols improves local control.[111]

In the setting of recurrent disease in the inguinal nodes, salvage groin dissection is standard, with or without adjuvant radiation, depending on prior treatment. In the upfront node-positive setting, there is no consensus on whether control of the nodal region involved is improved by limited node dissection prior to chemoradiation nor how such an approach affects morbidity, such as late limb edema.[36,38,40,41]

Extrapelvic Metastases

Deaths from extrapelvic metastases alone are relatively infrequent. Extrapelvic metastases are identified in about 10% to 20% of patients. For instance, among 585 patients randomized in the UKCCCR ACT I study, 77

patients died of anal cancer after chemoradiation, among whom 38 (49%) of 77 had cancer in the pelvis only and 21 (27%) had extrapelvic metastases only. The overall crude rate of metastasis in those who received RT and chemotherapy was 10% and in those treated by RT alone was 17%.[39] Similarly, in the EORTC trial, 17% of those treated by RT and chemotherapy developed metastases, as did 21% of those treated by RT only.[74] In RTOG-9811, the rates of distant metastases at 5 years were 13% in those who received RT, 5-FU, and MMC and 18% after RT, 5-FU, and CDDP.[76]

There is still considerable uncertainty regarding the effects on subclinical metastases outside the pelvis from the chemotherapy given concurrently with RT or as short-term induction or adjuvant treatment. Of note, in the UK ACT II trial (which omitted patients with metastatic disease at presentation), the addition of two cycles of 5-FU and CDDP did not improve 3-year disease-free survival nor OS.[78]

The median survival time after diagnosis of extrapelvic metastases ranges from 8 to about 24 months.[57,58,112] These metastases have been relatively resistant so far to all chemotherapy, RT, or combined modality protocols.[113] More recently, the preferred frontline systemic therapy regimen has become carboplatin and paclitaxel, which, in the randomized phase II InterAACT study, achieved similar efficacy as CDDP and 5-FU (the prior standard) but with a significantly lower G3-4 toxicity rate (36% vs 62%; $P = .016$). However, even in this modern series with relatively fit patients who were chemotherapy naïve, OS in the carboplatin/paclitaxel arm was only 20 months with a PFS of 5.7 months.[114] Given this, the ongoing POD1UM-303/InterAACT 2 phase III study will seek to improve these outcomes with the addition of the anti-programmed cell death protein 1 (PD-1) monoclonal antibody retifanlimab in patients with metastatic or inoperable locally recurrent anal cancer.[115] There are some preliminary clinical data supporting the use of checkpoint immune therapy in anal cancer. In the refractory metastatic setting, single-agent anti–PD-1 antibody nivolumab in a phase II study found an overall response rate of 24%.[116] Another small phase II study in patients with refractory metastatic anal cancer found that the combination of cetuximab and avelumab (a PD-L1 monoclonal antibody) results in an overall response rate of 17%.[117]

TREATMENT OF PERIANAL CANCER

The most common histologic type of invasive cancer of the perianal skin is squamous cell carcinoma, usually keratinizing. Basal cell cancers and adenocarcinomas can also occur. The principle difference between perianal cancer and anal canal cancer is the potential for definitive surgical excision in well-selected patients with T1-2N0 tumors that are well/moderately differentiated and are in an anatomic position such that wide local excision would not compromise sphincter function.[118-120] This approach is based on surgical series finding that less than 5% of well-differentiated squamous cell cancers less than 2 cm in size have nodal metastases to the pararectal or superior hemorrhoidal system.[31,34] Local excision of small cancers of the distal canal or perianal skin is generally more expedient and associated with less morbidity than radiation-based treatments. However, if resection margins are positive or considered inadequate (1 cm in perianal cancer),[113] and further local excision is not possible, the patient should receive chemoradiation or RT alone.

Either radiation alone or in combination with chemotherapy is also effective against perianal squamous cell cancers.[41,72,121-125] In patients not meeting the abovementioned surgical criteria, or who are otherwise not receiving surgery, radiation treatment protocols remain the same as for anal canal cancer. In the UKCCCR ACT I trial, one of four patients had a cancer that arose in the perianal skin (anal margin). Results by site of cancer origin were not reported, but local control and cause-specific survival rates favored combined modality therapy.[41,71] The UK investigators also included perianal cancers in their subsequent trial.[76] In institution-based series, locoregional control rates ranged from 60% to 90%, sphincter preservation rates from 65% to 85%, and 5-year OS from 55% to 80%.[41,72,121-125] Local necrosis was seen as a complication more frequently when brachytherapy was used, although, in general, the rates of serious complications were less than 5%.

The regional nodes for the perianal skin are the ipsilateral inguinal nodes. Perirectal and pelvic node metastases are uncommon unless the cancer involves the anal canal. The risk of inguinal node metastases is about 10%, principally with T3 or T4 tumors or poorly differentiated cancers. Elective bilateral inguinal nodal irradiation may be considered when these larger tumors are treated, although some advocate elective inguinal RT for all

perianal cancers.[123] The lower pelvic nodes should be included if the anal canal is invaded. The management of abnormal inguinal nodes is similar to that for anal canal cancer.

The principles of management for the uncommon basal cell and adenocarcinomas of the perianal skin are similar to those for these histologic types elsewhere on the skin.

PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS/ACQUIRED IMMUNODEFICIENCY SYNDROME

Anal cancer is a common malignancy in HIV-infected adults, but is not an AIDS-defining cancer. With the improvement in HIV-specific survival in the era of modern antiretroviral therapy, numbers of patients who are HIV infected and with anal squamous cell cancer are increasing,[126] including those previously diagnosed with AIDS.[23] Among patients with AIDS in particular, the median age at diagnosis is in the fourth decade, about 20 years earlier than in patients who are non–HIV infected.[23] Importantly, patients who were HIV infected were excluded from many of the randomized trials described earlier. The chemoradiation approach for anal cancers in patients who are HIV infected is the same as in noninfected individuals, but patients who are HIV infected are at increased risk of toxicity, particularly in the perineal skin, anorectal mucosa, and hematologic system.[127-131] The mechanisms for this increased toxicity are not known.[132] Two factors may predict for heightened acute normal tissue toxicity or poor cancer control: a CD4 count less than 200/μL at the start of treatment or the presence of AIDS.[67,133] Concurrent antiretroviral therapy does not reliably reduce the severity or incidence of toxicity of RT and chemotherapy.[30]

Locoregional control rates of about 65% or better were described in some series, similar to those in patients who were HIV negative. However, lower pretreatment CD4 count is associated with higher risk of recurrence and may increase the risk of cancer-specific mortality, suggesting a dose-response relationship between immune surveillance post-treatment.[134] Further supporting this are series reporting lower rates of local control and sphincter preservation in patients who are HIV positive, despite earlier stage disease and good initial tumor response.[66,127] A study of 40 patients who were HIV positive found that the 5-year OS rate was similar to that in 81

patients who were HIV negative, but that the major cause of death in patients who were HIV positive was anal cancer, in contrast to the patients who were HIV negative in whom causes other than cancer predominated.[66]

ADENOCARCINOMAS

Most adenocarcinomas involving the anal canal arise from rectal-type mucosa that extends below the upper muscular boundary of the canal. They are generally treated similarly to those that arise in the rectum.[50] The uncommon adenocarcinomas that develop from anal glands or in fistulae are more aggressive than squamous cancers and often metastasize early.[135] They have historically been managed with therapeutic approaches that parallel rectal cancer treatment, including neoadjuvant chemoradiation followed by abdominoperineal resection. Five-year survival rates following surgery alone are commonly below 50%, with local recurrence rates of about 25%.[33,120,135-138] Any advantage from adjuvant radiation and chemotherapy is unknown. Some small case series are reported in patients whose anal adenocarcinomas were treated with chemoradiation; in general, recurrence rates are higher than with comparable squamous tumors, though a minority of patients can achieve a cure while retaining anorectal function.[136,139,140]

RADIATION THERAPY: TECHNIQUES AND DOSES

Current radiation treatment strategies have been informed by the natural history of anal cancer, drawing from experience with sites of treatment failure after local therapy.[98,141,142] Most failures occur at the site of the primary tumor, followed by the regional and other pelvic node groups. Contemporary chemoradiation is standardly given with intensity-modulated radiation therapy (IMRT) with 1.8-Gy fractions, treating the primary tumor to 50.4 Gy (T1-2) to 54 Gy (T3-4) using simultaneous integrated boost (SIB) techniques to treat involved or elective nodal volumes. Risk-adapted radiation dose escalation and de-intensification are both areas of ongoing clinical trials.

Radiation Dose to the Primary Tumor

Older radiation trials typically treated the primary tumor in a split course, with tumor boost delivered after about a 6-week delay.[39,74,75] This practice has fallen out of favor (modern trials treat through the entire radiation schedule without interruption) but did provide information on tumor control probability and dose; RTOG 8704 was a study demonstrating superiority of concurrent chemoradiation with 5-FU and MMC over chemoradiation with 5-FU alone. The radiation schedule was 45 Gy in 1.8-Gy daily fractions to the whole pelvis (and inguinal nodes for patients with N1) with a 5.4 Gy sequential anteroposterior/posteroanterior or perineal boost for residual palpable tumor. The patients then underwent a 6-week break at which point a biopsy determined whether to treat with an additional 9 Gy to the primary tumor. In the MMC arm, 101 (69.2%) of 146 patients received between 41.76 and 47.25 Gy (ie, neither boost dose), and negative biopsy rate in this arm at 6 weeks postcompletion of induction chemoradiation was 92.2%. Importantly, this study found a 10% difference in negative biopsy rate between patients whose primary tumor was less than 5 versus 5 cm or larger. While this end point has been called into question since (see discussion earlier), the 4-year local control rate in the MMC arm was 84%, suggesting that chemoradiation with a relatively intermediate dose achieves durable local control for many patients, particularly those with smaller primary tumors.[75] In contrast, the EORTC studied chemoradiation with 5-FU and MMC in a population with much higher rates of T3-4 disease (84% of patients compared to 43% in the RTOG 8704 study) with a radiation prescription of 45 Gy in 1.8-Gy daily fractions followed by a 6-week delayed boost of 15 or 20 Gy if patients had residual disease, resulting in a 5-year local control rate of only 68% in the MMC/5-FU arm.[74] Similarly, in the 5-FU/MMC arm of ACT I (with 56% of patients having T3-4 disease), patients received 45 Gy of radiation (anus, inguinal nodes, and partial pelvis) followed by a 6-week delayed boost to either 25 Gy with iridium brachytherapy implant over 2.5 days or 15-Gy external beam boost. Of 48 patients with a more than 50% clinical response who did not complete this boost, 17% failed within 3 months; when looking at the chemoradiation arm overall, at 5 years, the local failure rate was 32.3%.[77]

This persistent issue of local failure (despite the refinement of chemoradiation), particularly in patients with bulkier primary tumors, led to the design of ACCORD 03,[79] a 2 × 2 factorial study of the addition of

induction chemotherapy (which failed as discussed in detail earlier) and boost dose escalation. Patients with primary tumors 4 cm or greater or N1-3 disease (median tumor size was 44.4 mm) received chemoradiation with CDDP 80 mg/m^2 on days 1 and 29 and infusional 5-FU 800/m^2/day on days 1 to 4 and 29 to 32 with 45 Gy in 25 fractions to the gross tumor, pelvis, and inguinal nodes (if positive or anal margin involved, or if pelvic nodes were positive); from there, randomization was between 15-Gy standard boost or high-dose boost to 20 Gy for a 80% or more response or 25 Gy otherwise. Boost could be delivered with either external beam or low-dose brachytherapy. In the radiation dose intensification arms, only 23% received a 25-Gy boost, and the median boost dose was 20 Gy compared to 15 Gy in the radiation standard-of-care arms. At 5 years, colostomy-free survival with intensified boost was 77.8 compared to 73.7 (P = .067), with an effect that was only apparent after about 2 years (albeit statistically insignificant). Given that the median dose in the standard radiation arm was already relatively high compared to other studies and that the median escalation was only 5-Gy difference, the optimal dose of radiation for bulky primary tumors remains an open question.[79] The ongoing ACT V dose escalation study may help better refine this in the future, though the highest dose arm of that study will be 61.6 Gy in 28 fractions.[143]

In contrast to bulkier, higher stage disease, patients with earlier stage disease, particularly with primary tumors less than 5 cm in size, tend to have better local control (see Table 62.3) often achieved with lower radiation doses in prior trials.[144] Two ongoing phase II studies will explore radiation de-intensification: the ACT IV study[143] will compare 41.4 Gy to the standard 50.4 in patients who were node negative with T1-2 primary tumors measuring 4 cm or less,[143] and the ECOG-ACRIN DECREASE study in similar patients will de-escalate the dose even further to 36 Gy.[94]

Management of Lymph Nodes

Similarly, older surgical data initially guided the design of clinical trials on the use of elective lymph node irradiation (ENI). One case series of 132 patients treated with surgical resection at a single institution found that almost 30% of patients without clinical inguinal node involvement subsequently had inguinal node failure and that node dissection and

radiation were effective at preventing nodal failure in patients with clinically node-positive disease.[34] In contrast, another study performed a subanalysis of 12 patients diagnosed with superficial, 2 cm or less, distal canal tumors treated with local excision resulting in only one local failure and no nodal recurrences.[31] With regard to the management of these patients with clinically negative inguinal nodes, this question of ENI was studied in a 2010 publication by a French group in a multicenter retrospective series of 181 patients.[38] Among patients receiving 40 to 50 Gy inguinal ENI, the rate of inguinal recurrence was 2% ($N = 75$) versus 16% in those who did not ($N = 106$). Specifically, among patients with T1-2 tumors who did not receive ENI, inguinal recurrence rates were 12%. Further supporting inguinal ENI in T1-2 anal cancer was the TROG 99.02 published a year later and demonstrating a 22.5% total failure rate in untreated inguinal nodes (12.5% isolated inguinal recurrence rate).[145] With regard to pelvic ENI, there is less direct evidence, but its efficacy can be inferred from the low failure rates reported radiation/chemoradiation series.[141,142] The minimum effective dose for ENI is not known. Doses as low as 24 Gy in 12 fractions in 2.5 weeks appeared effective in one series,[40] but most centers prescribe between 30.6 Gy in 17 fractions in 3.5 weeks to 50 Gy in 25 fractions in 5 weeks.[38,73,75]

Radiation Technique

Older randomized trials used radiation plans generated by two- or three-dimensional (2D or 3D) planning techniques with 1.8-Gy fractionation and sequential cone-down or boost. This has largely been supplanted by dose-painted (ie. SIB) IMRT, which is now the recommended standard of care in most consensus guidelines.[55] While IMRT has not been compared to older techniques in a randomized trial, it is hypothesized to reduce cutaneous, hematologic, and gastrointestinal (GI) toxicity without compromising oncologic outcomes and avoid many of the technical challenges of field matching for inguinal nodal coverage and oftentimes obviate the need for bolus.

The practice changing phase II nonrandomized study RTOG 0529 sought to reduce the rate of grade 2 or higher combined GI/genitourinary (GU) toxicity by 15% in patients with nonmetastatic anal canal cancer staged T2-4/N0-3 treated with concurrent 5-FU (1,000 mg/m^2/day on days 1-5 and 29-

33) and MMC (10 mg/m^2 bolus, days 1 and 29) as compared to RTOG 9811.[96] The authors initially published guidelines[146] for elective nodal coverage due to observed contouring variability, and subsequently, the Australasian Gastrointestinal Trials Group (AGITG) elaborated on these with their guidelines refining gross tumor and organ-at-risk delineation.[147] They found that among 51 analyzed patients, there were no major deviations for the primary tumor nor nodal coverage, with 14% and 6% rates of minor deviation for these, respectively. On initial reports, the combined end point of acute grade 2 or higher GI/GU toxicity overall was 77%, which was equivalent to the RTOG 9811 results, but when studying secondary end points of acute grade 3 or higher GI/GU toxicity, IMRT showed significant improvement from a historic 85% to 73% (P = .032), mostly driven by a reduction in GI toxicity. IMRT also demonstrated reduced acute grade 3 or higher dermatitis from 49% to 23% and reduced acute grade 2 or higher hematologic toxicity from 85% to 73%.[96] Importantly, at a median of 7.9 years of follow-up, oncologic outcomes were almost identical to RTOG 9811: 5-year local-regional failure 16% (95% CI, 7%-27%), OS 76% (95% CI 61%-86%), and disease-free survival 70% (95% CI 56%-81%).[97] In addition, secondary analysis of RTOG 0529 helped define small-bowel dose constraints for reducing acute grade 2 or higher GI toxicity: V25 less than 186 mL, V30 less than 155 mL, V35 less than 41 mL, and V40 less than 30.4 mL.[148] Taken together, IMRT is feasible, reproducible, and likely reduces toxicity as compared to older techniques.

With respect to patient setup during radiation, patients undergoing treatment can be treated in supine frogleg or prone position. Prone positioning may offer some bowel displacement and may help with dose to skin folds in patients with a large pannus when treating inguinal nodes. Conversely, supine positioning treatment is more easily reproducible. Both positions were permitted on RTOG 0529 and are accepted on the AGITG guidelines.[96,146,147] The intergluteal cleft does create an auto-bolusing effect for most patients, but bolus may be necessary in specific clinical circumstances, such as larger perianal tumors or fungating/superficial inguinal nodes. In patients with adequate renal function, IV contrast should be used to help with nodal delineation (in patients with a recent contrast-enhanced diagnostic CT scan that can be fused to the simulation scan it is reasonable to omit contrast); oral contrast was used on RTOG 0529 but adds

to patient appointment duration for simulation and may not reliably improve small-bowel visualization. Prior MRI and PET-CT scans should be fused to help with primary and gross nodal target delineation; given variability in pelvic tilt between imaging studies, it may be necessary to use deformable registration or separate fusions for the nodes and primary tumor. In male patients, the external genitalia is generally moved inferiorly for setup reproducibility. In female patients, some centers place a vaginal obturator at Sims and for treatment that may reduce vaginal/vulvar dose by creating additional separation; the ongoing DECREASE study has a secondary end point of female sexual function with obturator use.[94]

Regarding the volumes themselves, the gross tumor volume (GTV) and grossly involved nodes should be contoured with the assistance of fused imaging. The primary tumor clinical target volume (CTV1) should include the GTV with an isotropic margin (2 cm superior/inferior expansion, 1-2 cm radial expansion) and the entire anal canal; it is important with this to cover the perianal skin in the expansion (RTOG 0529 required a 2.5-cm expansion of perianal skin from the anal verge or gross tumor; and the RTOG atlas recommends a minimum of 2 cm). CTV may crop out of uninvolved structures such as bone or musculature. The CTV2 should include the involved nodes with a 1- to 2-cm isotropic expansion (again respecting anatomic boundaries with uninvolved structures). Finally, CTV3 is the elective nodal volume that should also include CTV1 and CTV2 as well as the following structures: (1) mesorectum (perirectal nodes), which is bound by the anorectal junction, the presacral space, the rectosigmoid junction, and anteriorly by the penile bulb/prostate in males and by the vagina, bladder, cervix, and uterus in female patients (the mesorectum is best seen on fat-saturated T2 MRI if available); (2) the presacral space, bound by the inferior edge of the coccyx, the sacral promontory, and a 1-cm volume anterior to the sacrum, including sacral hollows; (3) the internal/external iliac nodes, using a 7-mm anatomic expansion beginning at the bifurcation of the common iliac arteries and connecting to the mesorectal volume or inguinal volume; and (4) the inguinal nodes, with an anatomic volume covering at least a 7-mm expansion from the vessels and bound by the muscular structures (iliopsoas, pectineus, and adductor longus posteriorly and sartorius or iliopsoas medially) extending to about 2 cm inferiorly from the junction of the saphenous/femoral vein (guidelines differ on this inferior

extent of coverage). The RTOG and Australasian guidelines differ on whether to systematically cover the ischioanal fossa in the absence of radiographic invasion into this structure.[146,147] If image-guided RT is being used with frequent setup imaging, PTV expansions of 5 to 7 mm are reasonable, but otherwise 1 cm is standard.

Radiation Alone

If external beam irradiation is given without concurrent chemotherapy, it is usual, as in other cancers, to prescribe doses close to the tolerance of the normal tissues. There have been no studies to establish the optimum dose-time factors. A dose to the primary tumor of up to 60 to 65 Gy over 6 to 7 weeks, in 1.8- to 2-Gy fractions, is commonly prescribed, with doses to lymph nodes to be treated electively in the range of 36 Gy in 4 weeks to 50.4 Gy in 5.5 weeks. Brachytherapy may be used for part of the treatment. As with chemoradiation, interruptions in treatment should be minimized.

Perianal Cancer Considerations

If small (<4 cm) perianal cancers with low risk of regional node metastases are treated by radiation, a dose of 60 to 66 Gy in 2-Gy fractions over 6 weeks may be used. A direct perineal field is an option as this minimizes the area of skin irradiated. Orthovoltage equipment may suffice, and electrons or low-energy megavoltage photons (with bolus) are options as well. Care should be taken to flatten the perineum as much as possible to avoid areas of over- or underdosage. Larger perianal cancers, or cancers invading the anal canal, are usually treated by the techniques and schedules of radiation and chemotherapy used for anal canal cancers, based on the results of the UKCCCR ACT I trial.[39] ENI is given to the inguinal and lower external iliac nodes and to the lower perirectal and internal iliac nodes if the tumor extends into the anal canal as described earlier. If treating sequentially rather than with an SIB, the final phase of radiation may be given by direct perineal photon or electron therapy. Although brachytherapy may be used as a boost in patients undergoing sequential treatments (discussed later), full treatment of perianal cancers by brachytherapy is associated with high rates of necrosis in some series. The question of adjuvant radiation for patients undergoing resection for low-risk perianal cancers with close margins is an

ongoing study in the phase II ACT III study.[143] Data and guideline recommendations are mixed on whether resection with inadequate margins should be followed by reexcision or, possibly, radiation/chemoradiation.[149]

Other Considerations

In the era of 2D treatment planning, and later with 3D conformal planning, interruptions in external beam treatment, generally of no more than 2 weeks but of up to 4 weeks in some series, were introduced into many combined modality protocols, either as elective breaks after about 3 weeks of treatment or as required by individual patients, to reduce the severity of acute anoproctitis and perineal dermatitis. Longer intervals of 6 to 8 weeks were part of some schedules to allow time for tumor regression, particularly where further RT was to be prescribed based on the extent of the clinical or histopathologic response to the first phase of treatment.[39,74,75] The possible adverse effects of split-course irradiation on the control of anal cancer have not been studied formally, but the limited data available on the potential tumor doubling time of anal cancer suggest that it is relatively rapid and of the order of 4 days (range 1-30 days; $n = 26$).[150] Post hoc analyses suggest that the overall treatment time (OTT), including time for induction chemotherapy if given and for prolonged intervals prior to boost RT, may have more influence on outcome than the duration of radiation. Review of the UKCCCR ACT I trial did not identify an association between OTT and locoregional failure.[144] In contrast, analysis of two RTOG trials[73,75] showed a significant association with local failure. These studies are retrospective and nonrandomized with many potentially confounding factors, but the general principle recommended is to avoid or minimize the length of interruptions in the delivery of radiation.

The use of proton radiation for the treatment of anal cancer is currently under investigation in Sweden with the Proton Versus Photon Therapy in Anal Squamous Cell Carcinoma phase 2 study, with a primary end point of reduction in higher grade 2 hematologic toxicity and several other secondary toxicity and quality-of-life end points.[94] A prior pilot study of pencil beam scanning proton therapy in 25 patients found that this approach is feasible, the authors of this study noted that the reported rates of grade 2+ toxicities with proton therapy were similar to RTOG 05-29 rates of grade 2+

toxicities, and if anything, grade 3+ GI toxicity was slightly higher (36% with protons compared to 21% in RTOG 05-29). In addition, although two patients did die while on treatment, one felt to be potentially related to therapy.[151]

Brachytherapy is used more commonly in Europe than in North America, where external beam treatment is favored. Brachytherapy may have a limited role with the advent of dose painting and the equivocal data on dose escalation for local tumor control. Historically, there are a number of reports of effective brachytherapy, including low-dose rate,[72,152] pulsed-dose rate,[153-155] and high-dose rate (HDR) techniques.[156] Brachytherapy has usually been given 2 to 8 weeks after external beam therapy, although one schedule introduced HDR in the interval during split-course external beam therapy.[156] There is no agreement on whether the treatment volume should include the full extent of the initial primary cancer[72,155,156] or only the tumor remaining at the time of implant.[157] The brachytherapy dose depends on the composite dose of the total radiation prescription. Occasionally, significant toxicity has been encountered.

SEQUELAE OF THERAPY

Surveys of published studies suggest that the delivery of chemotherapy concurrently with RT is associated more with increases in acute rather than late normal tissue toxicity, beyond that expected with RT alone. Some nonrandomized series have described higher acute and late toxicity rates from combined modality therapy than those reported in the multicenter randomized trials. This probably results from the use of different criteria for recording and reporting toxicity.

In programs that combined RT, 96- to 120-hour infusions of 5-FU (750-1,000 mg/m^2/24 hour) and bolus injections of MMC (10-15 mg/m^2), moderate leukopenia, thrombocytopenia, anoproctitis, and perineal dermatitis were recorded in about 30% of patients after doses of 25 to 30 Gy in 2.5 to 3 weeks.[40,158] More profound proctitis and dermatitis occurred in up to 55% of those who received from 50 Gy in 4 to 5 weeks to 59.4 Gy in 6.5 weeks.[40,103] When CDDP has been substituted for MMC, marrow toxicity is less, but at radiation doses of 59.4 Gy in 6.5 weeks, acute soft tissue toxicity rates are similar.[73,86] Most large studies of RT, 5-FU, and MMC or CDDP

reported some mortality (<2% overall) associated with acute toxicity, usually as a result of neutropenia with sepsis. This risk can potentially be reduced with prophylactic antibiotics[39] and aggressive supportive care.

Serious late toxicity has not been reported after doses of 30 Gy in 3 weeks with 5-FU and MMC, but significant complications, often requiring surgery, were recorded in about 5% to 10% of those receiving higher radiation doses (see Table 62.5). A review of anal cancer management in Denmark from 1995 to 2003 found 5-year cumulative incidences of tumor- and treatment-related colostomy of 26% (95% CI, 21%-32%) and 8% (95% CI, 5%-12%), respectively.[159] In the randomized RTOG-9811 trial, in those who received RT, 5-FU, and MMC, only 10 of the 30 colostomy procedures performed by about 3 years were for treatment-related problems, a crude rate of about 3%.[60] It is probable that some reports, many of which were retrospective, also overlooked some treatment-related toxicity. For example, a large cohort study of 556 women aged 65 years or above who developed anal cancer showed a higher risk of pelvic fracture, principally of the hip, in those who received radiation (n = 399) compared to those not irradiated (n = 157). The cumulative 5-year fracture rate was 14% versus 7.5% ($P < .01$).[160] One of the objectives of current 3D conformal and IMRT techniques is to reduce RT dose to the proximal femurs.

There are two additional areas of possible toxicity that need further study. Pelvic RT increases the risk of secondary malignancies,[161] and some of the chemotherapy agents used to treat anal cancer also are associated with a raised risk; these risks have not been quantified in detail for patients treated for anal cancer. Second, in the only report so far of long-term follow-up of patients in a randomized trial, it was found that there were more deaths due to causes other than cancer, particularly cardiovascular related, in the first 10 years following treatment with RT, 5-FU, and MMC.[77] This difference reached +9% at 5 years, but the effect almost disappeared by 10 years. The magnitude of this difference was less than the reduction in deaths from anal cancer. Information from other randomized trials is needed to determine whether this observation was a chance phenomenon or a risk that should be addressed by further research.

Although preservation of anorectal anatomy is an advantage of treatment by chemoradiation, late anorectal function is often abnormal. Side effects of treatment are very common and may cause patients considerable discomfort

and social disability, although they are often graded as only level 1 or 2 toxicity.[162-165] These effects include changes in anorectal function, such as urgency and frequency of defecation, bleeding from anorectal telangiectasia, perineal dermatitis, pelvic fibrosis, dyspareunia, and impotence. They are usually managed medically with varying success. Systematic and prospective evaluations of the function of the anorectum and other organs potentially affected by treatment are now being reported, as are formal quality-of-life studies.[98,166] There is often dissociation between a patient's and their physician's assessment of anal and rectal function and continence and physiologic measurements of anorectal function. The few studies in this area have been inconclusive.[165,167] Prospective studies of pelvic organ function can be expected to assist the development of radiation treatment protocols by facilitating correlation of function with radiation-chemotherapy interactions, radiation techniques and dose distributions, and time-dose factors.

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PART G

Urinary Tract

CHAPTER 69

Cancer of the Kidney, Renal Pelvis, and Ureter

Hiram A. Gay and Jeff M. Michalski

ANATOMY

The kidneys are retroperitoneal structures located at the level between the 11th rib and the transverse process of the 3rd lumbar vertebral body. Usually, the right kidney is inferior to the right hepatic lobe and slightly inferior to the left kidney. The renal axis runs parallel to the lateral margin of the psoas muscle. Each kidney is approximately 11 to 12 cm in length. The kidney is encased by a fibrous capsule and surrounded by perinephric fat enveloped by Gerota fascia. At the renal hilus are the pelvis, ureter, renal artery, and vein. The organs adjacent to the right kidney include the liver superiorly, the duodenum and the vertebral bodies medially, and the transverse colon and small bowel anteriorly. On the left, the kidney abuts the spleen laterally; the stomach, pancreas, and vertebral bodies medially; and the small bowel and colon anteriorly.

The kidney consists of the cortex (glomeruli, convoluted tubules) and the medulla (Henle loops, collecting ducts, and pyramids of converging tubules). Each papilla opens in the minor calyces, which unite in the major calyces and drain into the renal pelvis. The calyceal collecting systems lie on the anteromedial surface of each kidney. The ureteropelvic junction is variable in position but is the landmark to separate the renal pelvis and the ureter. The ureters course posteriorly and inferiorly, paralleling the lateral border of the psoas muscle until they curve anteriorly to join the bladder at the trigone. The mucosal surfaces of the renal collecting tubules, calyces, renal pelvis, ureter, bladder, and urethra all have the same embryologic origin. The renal pelvis and ureter have the following layers: epithelium, subepithelial connective tissue, and muscularis, which is continuous with a connective tissue adventitial layer.

The lymphatics of the kidney and renal pelvis drain along the renal vessels. The right kidney drains predominantly into the paracaval and interaortocaval lymph nodes, and the left kidney drains exclusively to the para-aortic lymph nodes.[1] The lymphatic drainage of the ureter is segmented and diffuse. It may involve any of the renal hilar, abdominal para-aortic, paracaval, common iliac, internal iliac, or external iliac lymph nodes.

EPIDEMIOLOGY AND RISK FACTORS

The lesions discussed in this chapter are limited to adult renal cell carcinoma (RCC) and urothelial carcinoma of the renal pelvis and ureter. Lymphomas, primary retroperitoneal sarcomas, and Wilms tumors are discussed in Chapters 85, 76, and 91, respectively. Approximately 88% of solid renal masses are malignant, and the probability of malignancy is proportional to the size of the lesion.[2] RCCs constitute 80% to 85% of primary kidney tumors, whereas urothelial (transitional cell) carcinomas of the renal pelvis account for 7% of kidney tumors.

Renal Cell Carcinoma

Globally in 2020, the estimated new female and male kidney cancer cases in 2020 were 431,288 (2.2%), with 179,368 (1.8%) deaths. The male kidney cancer incidence and mortality age-standardized rate per 100,000 was 7.8 and 3.0 in more developed areas and 1.8 and 1.1 in less developed areas.[3]

In the United States in 2023, the estimated number of new cases of kidney and renal pelvis cancer was 81,800, with 14,890 deaths. Men are 1.7 times as likely as women to be diagnosed with kidney cancer. Kidney cancer incidence continued to increase by about 1% annually in both men and women. Kidney cancer survival is lower in Black patients for every histologic subtype of the disease. It is only similar overall because of a higher proportion than Whites of papillary and chromophobe RCC, which have a better prognosis than other types.[4]

The median age of RCC diagnosis is 65 years. Few large epidemiologic studies have demonstrated a significant link between occupational exposure and RCC. Danish workers exposed to trichloroethylene, an industrial solvent used as a metal degreaser, had an 8-fold higher incidence of kidney cancer.[5] Occupations associated with a higher risk of RCC are employment in the blast furnace, coke oven, or the iron and steel industry and exposure to asbestos, cadmium, dry-cleaning solvents, gasoline, and other petroleum products.[6] Several other environmental (eg, exposure to thorium dioxide), hormonal (eg, diethylstilbestrol), dietary (eg, high total energy intake and fried meats increase the risk, while vegetables, fruits, and alcohol are protective), cellular, and genetic factors have been associated with the development of RCC.[7-9]

Long-term cigarette smoking is associated with an increased risk of developing RCC. Obesity, diabetes, hepatitis C, and hypertension are also associated with a higher relative risk for the development of these tumors.[10-12] Cytotoxic chemotherapy may predispose childhood cancer survivors to translocation RCC bearing *TFE3* or *TFEB* gene fusions.[13]

Acquired cystic kidney disease (ACKD), which occurs in up to 50% of patients on dialysis for more than 3 years, increases 50-fold the risk of developing RCC.[14,15] The ACKD-associated RCC is seen mainly in males, occurs approximately 20 years earlier than in the general population, and is frequently bilateral (9%) and multicentric (50%).[15]

Several inherited cancer syndromes affect the kidney: von Hippel-Lindau (VHL) disease, hereditary papillary renal cancer (HPRC), hereditary leiomyomatosis RCC

(HLRCC), Birt-Hogg-Dubé (BHD), BAP1 tumor predisposition syndrome, hereditary succinate dehydrogenase (SDH)-deficient RCC, and constitutional chromosome 3 translocation. VHL is autosomal dominant caused by germline mutations of the VHL tumor suppressor gene, located on chromosome 3p25-26. The VHL protein is involved in cell cycle regulation and angiogenesis. In patients with VHL disease, loss of the sole functioning VHL allele in somatic tissues causes a situation similar to hypoxia, with elevated levels of HIF-1α despite normal oxygen tension.[16] The renal manifestations of VHL are kidney cysts and clear cell RCC. The mean age onset for VHL-associated clear cell RCC is 37 years, and periodic screening with magnetic resonance imaging (MRI) should start after the age of 10 years.[17]

Renal cancer has low penetrance in HLRCC syndrome, with an estimated incidence from 2% to 6% to 15%, and possibly as high as 32% of germline mutation–affected families, depending upon selection bias and imaging utilized. Individuals affected with HLRCC are at risk for renal carcinoma as well as cutaneous and uterine leiomyomas. Unlike other hereditary renal carcinoma syndromes, HLRCC renal cancer usually presents as a solitary lesion, can be highly aggressive, and can metastasize early, often initially to regional and distant lymph nodes. HLRCC renal malignancies may have an early onset. The gene responsible for HLRCC was found to encode fumarate hydratase (FH), a Krebs cycle enzyme. Loss of FH shunts the cycle to overaccumulate intracellular fumarate, leading to a state of pseudohypoxia through overexpression of HIF. Overexpression of HIF and upregulation of HIF-regulated genes are postulated to be the mechanism by which a mutation in FH leads to renal malignancy.[18]

HPRC is autosomal dominant with high penetrance and is characterized by multiple, bilateral, late-onset papillary RCCs. HLRCC is autosomal dominant with a predisposition to papillary type 2 RCC. Due to the multifocal bilateral nature of these lesions, patients with HPRC are often managed by surveillance and close observation with nephron-sparing surgery when the largest tumor reaches 3 cm. The proto-oncogene mesenchymal epithelial transition (MET) factor, located on the long arm of chromosome 7, is the gene responsible for HPRC. MET encodes for a tyrosine kinase membrane receptor. The constitutively active tyrosine kinase allows for unregulated proliferation, transformation, and invasive potential.[18]

BHD is autosomal dominant with incomplete penetrance and is associated with multiple chromophobe and clear cell RCCs, papillary RCCs, and oncocytomas. Constitutional chromosome 3 translocation is associated with multiple, bilateral clear cell RCCs.[19]

SDH, formed by four subunits SDHA, SDHB, SDHC, SDHD, and an assembly factor SDHAF2, functions as a critical respiratory enzyme. Biallelic inactivation of genes encoding any of the components, mainly in the presence of a germline mutation, causes loss of function of the entire enzyme complex. Subsequent development of SDH-deficient neoplasms includes pheochromocytoma/paraganglioma, gastrointestinal stromal tumor, and RCC. SDH-deficient RCC accounts for 0.05% to 0.2% of RCCs,

frequently occurs in young adults (median age: 35 years; range: 14-80 years) and a slight male predominance (M:F ratio: 1.8:1). Up to 30% of cases present as bilateral or multifocal tumors.[20]

Autosomal dominant polycystic kidney disease does not appear to increase the incidence of RCC. However, the tumors are more often multicentric (28% vs 6%), bilateral (12% vs 1%-5%), and sarcomatoid in type (33% vs 1%-5%) than in the general population.[21]

Renal Pelvis and Ureter Carcinoma

Urothelial carcinoma of the upper urinary tract accounts for 7% of all kidney tumors and 5% of all urothelial malignancies.[22] The incidence of bilateral upper urinary tract tumors is 1.5% to 2% for synchronous and 6% to 8% for asynchronous presentations.[23] Renal pelvis tumors are found 2 to 3 times more commonly in men than in women, and the peak incidence is in the fifth and sixth decades of life. Because the mucosal surfaces of the renal pelvis, ureter, and bladder have the same embryologic origin, many of the etiologic factors in the renal pelvis and ureter tumors also apply to urinary bladder tumors. Urothelial carcinomas of the upper urinary tract tend to be multifocal due to "field cancerization," which may be caused by exposure of the urothelium to potential carcinogens. Urothelial tumors can also spread to urothelial structures that are either distal or proximal to the primary tumor and are referred to as "drop metastases." About 40% to 50% of patients with upper urinary tract tumors will have synchronous or metachronous bladder cancer.[24,25]

Cigarette smoking is the most important factor contributing to the overall incidence of urothelial cancer in Western countries. Patients with Lynch syndrome, an autosomal dominant genetic condition due to inherited mutations that impair DNA mismatch repair, have an increased risk of developing urinary tract cancer.[26]

Exposure to aristolochic acid has been associated with acute, near end-stage renal disease. Aristolochic acid is commonly found in the Aristolochiaceae family of plants, which is commonly used in Chinese herbal medicine. A high incidence of cellular atypia and urothelial carcinoma of the renal pelvis, ureter, and bladder has been associated with aristolochic acid nephropathy.[27] Arsenic-contaminated water has been associated with a high incidence of upper urinary tract urothelial carcinoma in Taiwan.[28] Prolonged heavy phenacetin-containing analgesic use can lead to urothelial carcinomas of the renal pelvis, ureter, and bladder (which may be multiple and bilateral).[29]

Balkan endemic nephropathy (BEN) is a chronic tubulointerstitial disease of unknown etiology most commonly reported in southeastern Europe. A high frequency of urothelial atypia, occasionally progressing to tumors of the renal pelvis and urethra but also involving the bladder, is associated with BEN.[29]

NATURAL HISTORY

Renal Cell Carcinoma

Primary renal cell tumors may spread by local infiltration through the renal capsule to involve the perinephric fat and Gerota fascia. The tumor may grow directly along the venous channels to the renal vein or vena cava. Lymph node metastases occur with an incidence of 9% to 27% and most often involve the renal hilar, para-aortic, and paracaval lymph nodes.[30,31] The renal vein is invaded by tumor in 21% of cases, and the inferior vena cava is invaded in as many as 4% of cases.[32]

Approximately 45% of patients with RCC have localized disease, 25% have regional disease, and about 30% have evidence of distant metastases at the time of diagnosis.[31,33] About 1% to 3% of patients with metastases have solitary lesions.[34] About half of the patients with RCC eventually develop metastatic disease.[35]

Among patients presenting with metastatic RCC, metastatic sites include lung, bone, brain, liver, adrenal gland, and distant lymph nodes. RCC can metastasize to unusual sites like nasal sinuses, skin, penis, and others. Patients with metastatic disease at diagnosis have a poor prognosis, with an expected survival of less than 5 years, regardless of the site of metastasis.[31,33]

Renal Pelvis and Ureter Carcinoma

Upper urinary tract carcinoma is frequently a multifocal process. Patients with cancer at one site in the upper urinary tract are at significant risk for the development of tumors elsewhere along the urothelium. The probability of multifocal occurrence is greatest in patients with large tumors and those with carcinoma in situ. Ureteral tumors tend to occur in the distal third of the ureter.

Urothelial carcinoma of the upper urothelial tract may spread by direct extension and hematogenous and lymphatic metastases. Implantation of tumor cells in the bladder has been demonstrated, especially in previously traumatized areas. The incidence of lymph node metastasis is highly dependent on the grade of the primary tumor. Low-grade tumors have a very low metastatic propensity. In a series of 94 patients, none of the 43 low-grade tumors had lymph node metastasis, compared with 3 of 22 grade 3 or 4 tumors.[36] Lymph node metastases were reported in 9 of 26 patients selected to receive adjuvant radiotherapy (RT).[37]

CLINICAL PRESENTATION

Renal Cell Carcinoma

Patients with RCC may present with an occult primary tumor or with signs and symptoms attributable to a local mass or systemic paraneoplastic syndromes. Gross hematuria, palpable flank mass, and pain describe a classic triad that occurs only in 5% to 10% of patients.[38,39] Indeed, a finding of the classic triad often suggests advanced disease with a poor prognosis. The most frequent symptom associated with RCC is gross or microscopic hematuria, when there is invasion of the collecting system.[40] Scrotal

varicoceles, mostly left sided, are observed in 11% of men with RCC.[41] Other symptoms include anemia, hepatic dysfunction in the absence of liver metastases (called Stauffer syndrome and due to a paraneoplastic elevation in alkaline phosphatase), secondary amyloidosis, fever, hypercalcemia, cachexia, erythrocytosis, thrombocytosis, and a syndrome resembling polymyalgia rheumatic.[41-47] RCC presenting as an incidental mass on a diagnostic imaging study ordered for other purposes accounts for 61% of all diagnoses.[48]

A wide range of paraneoplastic syndromes has been associated with RCC. Parathyroid-like hormones, erythropoietin, renin, gonadotropins, placental lactogen, prolactin, enteroglucagon, insulin-like hormones, adrenocorticotropic hormone, and prostaglandins have been identified in patients with RCC.[43,49]

Renal Pelvis and Ureter Carcinoma

Gross or microscopic hematuria occurs in 70% to 95% of patients with renal pelvis or ureter tumors.[22] The other less common symptoms include pain (8%-40%), bladder irritation (5%-10%), or other constitutional symptoms (5%). About 10% to 20% of patients may present with a flank mass secondary to tumor or hydronephrosis.

DIAGNOSTIC WORKUP

Renal Cell Carcinoma

Renal masses are not uncommon, and most of them are benign. A central renal mass may suggest the presence of urothelial carcinoma; if so, urine cytology, ureteroscopy, and biopsy should be considered. Renal masses are frequently diagnosed as incidental findings during abdominal imaging for metastatic evaluation for an unrelated malignancy or other disease. An algorithm for the workup of renal masses has been proposed.[50] Most contrast-enhancing masses tend to be malignant, and the odds ratio of malignancy increases with increasing size.[51] No further workup is necessary if computed tomography (CT) or ultrasound clearly identify the mass as a cyst. If a solid lesion is identified, then tumor removal by nephrectomy should be considered. In the case of small lesions, a follow-up CT scan to evaluate the potential growth of the mass may raise the suspicion of malignancy. The diagnostic and staging workup for RCC is given in Table 69.1. The diagnosis of RCC is established clinically and radiographically in most cases. Pathologic confirmation is often made at the time of nephrectomy.

TABLE 69.1 DIAGNOSTIC WORKUP FOR RENAL CELL CARCINOMA

General
History and physical examination
If multiple renal masses, ≤46 years,[52] or family history, consider genetic evaluation.
Avoid biopsy if resection is being considered. Consider core-needle biopsy (FNA not adequate), if clinically indicated, for small lesions to confirm the diagnosis or guide surveillance, cryosurgery, or

radiofrequency ablation strategies.
Radiographic studies
Abdominal ± pelvic CT (preferred because it shows calcification and better visualization of other body parts) or abdominal MRI with or without contrast, depending on renal function. MRI is superior to CT when evaluating the inferior vena cava and right atrium for tumor involvement.
Consider CT urography, which allows imaging of both the renal parenchyma and the collecting system.
As clinically indicated to rule out metastases:
Chest CT (preferred) or chest x-ray
Bone scan if the patient has bone pain or has an elevated alkaline phosphatase
Brain MRI with or without contrast depending on renal function, if clinical signs, presentation, and symptoms are suggestive of brain metastases
Laboratory studies
Urinalysis
Complete blood cell count (CBC)
Comprehensive metabolic panel (including LDH, serum corrected calcium, liver function tests, blood urea nitrogen, and serum creatinine)

CT, computed tomography; FNA, fine-needle aspiration; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging.

Once a radiographic diagnosis is made, a staging evaluation should be undertaken, including a complete history and physical examination, complete blood count, and liver and kidney function tests. A metastatic workup should include a chest CT and an abdominal/pelvic CT or abdominal MRI scan of the abdomen. Patients with symptoms suggestive of bone metastases and those with an elevated alkaline phosphatase level should undergo a bone scan. If metastatic lesions are detected, histologic confirmation should be made by biopsy of either the metastatic focus or the primary tumor. MRI can be valuable when evaluating the extent of involvement of the collecting system or inferior vena cava, or radiographic contrast cannot be administered. Renal arteriography is sometimes helpful in planning surgery.

Renal Pelvis and Ureter Carcinoma

The diagnostic workup for renal pelvis and ureter carcinoma is listed in Table 69.2. Staging includes a complete history and physical examination, complete blood count, and liver and kidney function tests. CT urography is now used to evaluate patients with renal pelvis carcinoma. CT or MRI of the abdomen and pelvis before and after contrast administration gives useful information regarding the possible extension of the tumor outside the collecting system. Ureteroscopic visualization of the tumor is desirable, and tissue biopsy through a ureteroscope should be performed if feasible. Cystoscopy is very important due to the high incidence of multiple tumors. Urine cytology may help determine tumor grade if tissue is not available, but false-negative rates can be high for upper tract and low-grade tumors.

TABLE 69.2 DIAGNOSTIC WORKUP FOR RENAL PELVIS AND URETER CARCINOMA

General
History and physical examination
Radiographic studies
CT of the abdomen and pelvis or MRI urogram
Multidetector CT urography (CTU)
Chest CT or chest radiograph
Bone scan if the patient has bone pain or has an elevated alkaline phosphatase
Brain MRI, if suspecting brain metastases
Special tests
Cystoscopy, the entire urinary tract has to be evaluated due to the high incidence of multiple tumors
Ureteroscopic visualization of the tumor is desirable, and tissue biopsy through a ureteroscope may be performed if feasible.
Urine cytology may help determine tumor grade if tissue is not available. The false-negative rate can be high in upper tract and low-grade tumors.
Percutaneous biopsy, if indicated
Laboratory studies
Complete blood cell count
Comprehensive metabolic panel (including liver function tests, blood urea nitrogen, and serum creatinine)
Urinalysis

CT, computed tomography; MRI, magnetic resonance imaging.

STAGING

Renal Cell Carcinoma

The American Joint Committee on Cancer (AJCC) system is currently being utilized to stage patients with RCC (Table 69.3).[51] T1 and T2 cancers are limited to the kidney. T3 tumors extend into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota fascia. T4 tumors invade beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland). Regional lymph node metastases may involve spread to the renal hilar, caval, and aortic drainage sites. Metastasis in regional lymph node(s) is classified as N1.[51]

TABLE 69.3 2017 KIDNEY CANCER TNM STAGING AJCC UICC

T Category	T Criteria
TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor
T1	Tumor ≤7 cm in greatest dimension, limited to the kidney
T1a	Tumor ≤4 cm in greatest dimension, limited to the kidney
T1b	Tumor >4 cm but ≤7 cm in greatest dimension limited to the kidney
T2	Tumor >7 cm in greatest dimension, limited to the kidney

T Category	T Criteria
T2a	Tumor .7 cm but ≤10 cm in greatest dimension, limited to the kidney
T2b	Tumor .10 cm, limited to the kidney
T3	Tumor extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota fascia.
T3a	Tumor extends into the renal vein or its segmental branches, or tumor invades the **pelvicalyceal system**, or invades perirenal and/or renal sinus fat but not beyond Gerota fascia.
T3b	Tumor extends into the vena cava below the diaphragm.
T3c	Tumor extends into the vena cava above the diaphragm or invades the wall of the vena cava.
T4	Tumor invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland).

N Category[a]	N Criteria
NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis

AJCC Prognostic Stage Groups			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1 or T2	N1	M0
	T3	N0, N1	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

Histologic grade (G)	
GX	Grade cannot be assessed.
G1	Nucleoli absent or inconspicuous and basophilic at 400× magnification
G2	Nucleoli conspicuous and eosinophilic at 400× magnification, visible but not prominent at 100× magnification
G3	Nucleoli conspicuous and eosinophilic at 100× magnification
G4	Marked nuclear pleomorphism and/or multinucleate giant cells and/or rhabdoid and/or sarcomatoid differentiation

TNM, tumor-node-metastasis.

[a]The regional lymph nodes are as follows: renal hilar, caval (precaval, interaortocaval, paracaval, and retrocaval), and aortic (preaortic, para-aortic, and retroaortic).

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Renal Pelvis and Ureter Carcinoma

Tumors of the renal pelvis and ureter have a natural history that is not too dissimilar from other urothelial malignancies originating in the bladder. Their prognoses are dependent on tumor invasiveness and pathologic grade. The 2017 AJCC eighth edition staging classification for renal pelvis and ureter carcinoma is shown in Table 69.4.[51]

TABLE 69.4 2017 TUMORS OF THE RENAL PELVIS AND URETER TNM STAGING AJCC UICC

T Category	T Criteria		
TX	Primary tumor cannot be assessed.		
T0	No evidence of primary tumor		
Ta	Papillary noninvasive carcinoma		
Tis	Carcinoma in situ		
T1	Tumor invades subepithelial connective tissue.		
T2	Tumor invades muscularis.		
T3	For renal pelvis only: Tumor invades beyond the muscularis into peripelvic fat or into the renal parenchyma. For ureter only: Tumor invades beyond the muscularis into the periureteric fat.		
T4	Tumor invades adjacent organs, or through the kidney into the perinephric fat.		
N Category[a]	**N Criteria**		
NX	Regional lymph nodes cannot be assessed.		
N0	No regional lymph node metastasis		
N1	Metastasis in a single lymph node, ≤2 cm in greatest dimension		
N2	Metastasis in a single lymph node, >2 cm; or multiple lymph nodes		
M Category	M Criteria		
M0	**No distant metastasis**		
M1	Distant metastasis		
AJCC Prognostic Stage Groups			
Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0

T Category	T Criteria		
Stage III	T3	N0	M0
Stage IV	T4	N0	M0
	Any T	N1 or N2	M0
	Any T	Any N	M1

Histologic grade (G)	
WHO/ISUP recommended grading for urothelial histologies:	
G	G Definition (Urothelial Carcinoma)
LG	Low grade
HG	High grade
For squamous cell carcinoma and adenocarcinoma:	
G	G Definition
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

ISUP, International Society of Urologic Pathology; NOS, not otherwise specified; TNM, tumor-node-metastasis; WHO, World Health Organization.

[a]The regional lymph nodes for the renal pelvis are renal, hilar, paracaval, aortic, and retroperitoneal, NOS. The regional lymph nodes for the ureter are as follows: renal hilar, iliac (common, internal [hypogastric], external), paracaval, periureteral, and pelvic, NOS.

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PATHOLOGIC CLASSIFICATION

Renal Cell Carcinoma

RCC is a group of malignancies arising from the epithelium of the renal tubules and comprises 90% of all malignancies in the kidney. The World Health Organization (WHO) classifies renal cell tumors into six main categories: clear cell renal tumors (clear cell RCC and multilocular cystic renal neoplasm of low malignant potential), papillary renal tumors (papillary adenoma and papillary RCC), oncocytic and chromophobe renal tumors (oncocytoma, chromophobe cell renal carcinoma, and other oncocytic tumors of the kidney), collecting duct tumors (collecting duct carcinoma), other renal tumors (clear cell papillary renal cell tumor, mucinous tubular and spindle cell carcinoma, tubulocystic RCC, acquired cystic disease–associated RCC, eosinophilic solid and cystic RCC, and RCC not otherwise specified [NOS]), and molecularly defined renal carcinomas (TFE3-rearranged RCCs, TFEB-altered RCCs, ELOC [formerly TCEB1]-mutated RCC, FH–deficient RCC, HLRCC syndrome–associated

RCC, SDH-deficient RCC, anaplastic lymphoma kinase–rearranged RCCs, medullary carcinoma NOS, SMARCB1-deficient medullary-like RCC, SMARCB1-deficient undifferentiated RCC NOS, and SMARCB1-deficient dedifferentiated RCCs of other specific subtypes).[19]

Clear cell RCC is the most common (80%-90% of tumors), followed by papillary RCC (10%-15%) and chromophobe RCC (4%-5%). Renal medullary carcinoma is a very aggressive malignancy mostly associated with young Black patients with sickle cell trait, and less commonly, sickle cell disease.[53]

Renal Pelvis and Ureter Carcinoma

More than 90% of malignant tumors arising from the renal pelvis and ureter are urothelial (also called transitional cell) carcinomas. The WHO classifies urothelial tumors as invasive urothelial carcinoma, or urothelial carcinoma with the following variants: with squamous differentiation, with glandular differentiation, with trophoblastic differentiation, nested, large nested, tubular and microcystic, micropapillary, lymphoepithelioma-like, plasmacytoid, giant cell, lipid-rich, clear cell (glycogen-rich), sarcomatoid, and poorly differentiated.[19]

PROGNOSTIC FACTORS

Renal Cell Carcinoma

The 5-year relative survival rate of patients with kidney cancer has increased from 65.9% in 2000 to 78% in 2015.[54] The stage at initial presentation remains the most important prognostic factor for RCC survival. Prognostic features for RCC are tumor, patient, and laboratory related. Tumor-related prognostic factors include stage, tumor size, tumor grade, histologic type, tumor necrosis, sarcomatoid transformation, and two or more sites of organ metastases. Patient-related factors include asymptomatic versus local symptoms versus systemic symptoms, weight loss, paraneoplastic syndromes, and an interval of less than a year from original diagnosis to the start of systemic therapy. Laboratory prognostic factors include thrombocytosis and elevated erythrocyte sedimentation rate or C-reactive protein.[51,55]

For patients with metastatic RCC, the following factors were predictive of survival in a retrospective study of 670 patients: low Karnofsky performance status (KPS) (<80), high lactate dehydrogenase (>1.5 times upper limit of normal), low hemoglobin (<lower limit of normal), high “corrected” serum calcium (>10 mg/dL or 2.5 mmol/L), and absence of prior nephrectomy.[56]

Lymph node metastases are associated with increased local recurrence and distant metastasis rates.[38,57-59] Nuclear grade, sarcomatoid component, tumor size, stage, and tumor necrosis increase the likelihood of lymph node involvement.[60] The risk of lymph node metastases is 20%.[61,62] Patients with lymph node metastases in radical nephrectomy specimens have a local failure rate of 21%, compared with only 4% in patients without

lymph node metastases ($P = .0002$).[59] A select group of patients with solitary metastases may have a 5-year survival rate of 25% to 35%.[63,64]

Nuclear grade, after stage, is the most important prognostic feature of clear cell carcinoma. Fuhrman developed a four-tier grading system that is based on nuclear and nucleolar size, shape, and content.[65] Fuhrman grade is the most widely used grading system. Grade is also an independent prognostic factor for papillary RCC and chromophobe RCC, especially when using standardized criteria.[66] Worsening pathologic grade is associated with poor 5-year disease-free survival.[33,38]

Papillary RCC has a 5-year survival rate of 90% and metastasizes less frequently than clear cell RCC. The RCC's spindle cell or sarcomatoid variants are associated with statistically significant inferior 5-year survival rates, compared with pure clear, or clear and granular histologic variants.[33,38]

Nuclear morphology strongly predicts tumor stage and prognosis.[65] High nuclear grade is associated with an increased incidence of advanced tumor stage, lymph node involvement, distant metastases, renal vein involvement, tumor size, and perirenal fat involvement. In a series of 190 patients reported by Bretheau and colleagues,[67] the 5-year actuarial survival rates of patients with grade I, II, III, and IV tumors were 76%, 72%, 51%, and 35%, respectively. Sarcomatoid differentiation has a significantly poorer prognosis than the clear cell or granular cell subtypes. Almost half of patients with sarcomatoid RCC have bone metastases at presentation. The median survival time of patients with sarcomatoid renal cell cancer is only 6.6 months, compared with 19 months for other histologic types.[68]

Nomograms and algorithms have been described to facilitate the determination of cancer-free survival in patients with RCC. Based on 601 patients treated at Memorial Sloan Kettering Cancer Center with radical nephrectomy, Kattan used variables including patient symptoms (incidental, local, or systemic), histology (chromophobe, papillary, or conventional), tumor size, and pathologic stage to predict the risk of recurrence after surgery (this uses older 1997 staging and is available at the Memorial Sloan Kettering Cancer Center website https://www.mskcc.org/nomograms/renal/post-op).[69] Frank et al from the Mayo Clinic developed a predictive algorithm based on 1801 patients treated with radical nephrectomy.[70] This system combines stage, size, grade, and necrosis to predict patient survival. Finally, Zisman et al from the University of California, Los Angeles (UCLA) have developed an algorithm that utilizes AJCC tumor-node-metastasis stage, Fuhrman grade, and Eastern Cooperative Oncology Group (ECOG) performance status to divide patients into low-risk, intermediate-risk, and high-risk groups.[71] This model is also known as the UCLA-integrated staging system.

Renal Pelvis and Ureter Carcinoma

The major prognostic factors in patients with renal pelvis or ureter carcinoma are the initial stage and grade of the tumor. There is no significant difference in prognosis

between urothelial carcinomas originating in the ureter compared to those in the renal pelvis.[72]

High-grade tumors are associated with a higher incidence of metastases and worse survival. Corrado and associates[73] reported 5-year survival rates of 83%, 75%, 52%, and 0% for grades 1 through 4, respectively. These results are comparable to those described by Heney and colleagues,[74] who reported 100% survival for grade 1, 81% for grade 2, and 0% for grade 3. Local recurrence was identified in three of 24 patients with grade 3 tumors. No survival differences were seen for patients with papillary versus solid tumors. In the series of Charbit and coworkers,[25] lymph node metastases were seen exclusively in patients with high-grade tumors. Of tumor-related deaths, 90% were in patients with high-grade tumors. Hall reported a retrospective series of 252 patients treated surgically for upper urinary tract urothelial cancers.[75] Significant factors for recurrence included high tumor grade and advanced clinical stage. Older patients and patients treated with parenchymal-sparing surgical procedures had higher recurrence rates. In their series of 77 patients, Akdogan reported from a multivariate analysis that higher recurrence rates were associated with tumor location, higher grade, and advanced T-stage.[76] Tumors in the ureters were more likely to recur than tumors involving the renal pelvis. In a series of 86 patients, Park also reported a higher rate of recurrence in ureteral tumors compared to those arising in the renal pelvis.[77]

A prior history of bladder cancer has been reported to worsen the prognosis of patients with second urothelial cancers involving the upper tracts.[76,78] From the Memorial Sloan Kettering Cancer Center series of 129 patients, multivariate analysis demonstrated that patients with advanced primary tumors and a prior history of bladder cancer were associated with worse disease-free survival.[78]

Flow cytometry may aid in estimating long-term prognosis. In a multivariate analysis, Corrado and colleagues[73] demonstrated that, although stage and grade were the most important prognostic indices, DNA pattern (diploid vs nondiploid) and the number of lesions (unifocal vs multifocal) identified at initial diagnosis also determined prognosis. Patients with diploid tumors had a 79% survival rate, compared with only 46% in patients with nondiploid tumors ($P = .0003$). Recent data suggest that hypermethylation of the promoter region of patients with urothelial cancers of the urothelium is associated with a worse prognosis. Tumors of the renal pelvis and ureters demonstrate hypermethylation in 94% of cases compared to 76% of similar-appearing tumors in the bladder ($P < .0001$). Hypermethylation was also associated with higher tumor stage, tumor progression, and mortality.[79]

GENERAL MANAGEMENT

Renal Cell Carcinoma

Surgery is the therapeutic foundation for the management of kidney cancer. RT has an important and growing role in the palliative management of RCC. Although RCC is traditionally considered to be radioresistant, it has a clear dose-response to radiation.[80,81]

As long as sufficient radiation dose is delivered to the tumor while respecting normal tissue dose constraints, RCC "radioresistance" can be overcome with modern techniques. National consensus guidelines recommend the following surgical options depending on the stage:

- pT1a: partial or radical nephrectomy, active surveillance, or ablative techniques
- pT1b: partial or radical nephrectomy, active surveillance, or ablative techniques in selected patients
- Stage II: partial or radical nephrectomy
- Stage III: radical or partial nephrectomy if clinically indicated
- Stage IV: if potentially surgically resectable primary, cytoreductive nephrectomy in select patients or systemic therapy especially in clear cell histology with poor-risk features

Surgery

A radical nephrectomy includes a perifascial resection of the kidney, perirenal fat, regional lymph nodes, and ipsilateral adrenal gland. It is the preferred treatment if the tumor extends into the inferior vena cava and usually requires the assistance of a cardiovascular surgeon if there is a caval or atrial thrombus. Adrenalectomy is not indicated when imaging shows a normal adrenal gland or if the tumor is not high risk.[82] An experienced team should be involved in the context of thrombus, as treatment-related mortality can reach 10%. Open, robotic, and laparoscopic techniques may be used to perform a radical nephrectomy. Improved preoperative assessment with CT can identify patients who have no significant risk of adrenal gland involvement.[83] In 76% of cases, the adrenal gland can be spared during surgery. The European Organisation for Research and Treatment of Cancer conducted a randomized trial of radical nephrectomy with or without an elective lymph node dissection, and there was no survival advantage between the two study groups. The incidence of unsuspected lymph node metastases was low (4%).[84] Nevertheless, the lymph node dissection does provide valuable prognostic information.

Radical nephrectomies should be avoided if nephron-sparing surgery is feasible for T1a and T1b renal tumors. In this setting, nephron-sparing surgery has shown equivalent outcomes to radical nephrectomy.[85,86] Radical nephrectomy–induced chronic renal insufficiency is associated with an increased risk of cardiovascular death and death from any cause.[87] For this reason, nephron-sparing surgery is preferred in T1a and T1b tumors. Nephron-sparing surgery is also preferred in patients with hereditary RCC to preserve renal function and decrease the risk of cardiovascular events.[88] In a matched pair analysis of 164 patients undergoing nephron-sparing surgery at the Mayo Clinic, the disease-free survival was 79%, which compared favorably to 77% in patients undergoing radical nephrectomy.[89] In 117 patients with renal tumors 4 cm or less undergoing partial nephrectomy at the Memorial Sloan Kettering Cancer Center, the 5-

year freedom from recurrence was 98.6% compared to 96.4% in a similar group of 173 patients undergoing radical nephrectomy. Compared with patients undergoing partial nephrectomy, those undergoing radical nephrectomy were at a higher risk of chronic renal insufficiency.[90] There is some risk that sparing of the renal parenchyma may leave microscopic residual tumor or inadequately treat multifocal cancers.[91-93] Bilateral RCC occurs in 2% to 3% of patients. In these patients, nephron-sparing surgery is an attractive option because bilateral radical nephrectomy sentences the patient to a lifetime of renal dialysis or the need for a renal transplant.

Following surgery, 20% to 30% of patients with localized tumors relapse, with a median time to relapse of 1 to 2 years and most occurring within 3 years. Although there is no role for adjuvant therapy after surgery, a number of recent trials are exploring the role of targeted therapy.

Patients who have local symptoms, such as hematuria, pain, hypertension, or other paraneoplastic syndromes, may benefit from a palliative nephrectomy. Spontaneous regression of metastatic renal cell cancer after nephrectomy has been reported. In an extensive literature review, the incidence of regression of metastatic foci induced by nephrectomy was 0.8% (4/474 patients).[35] Cytoreductive surgery performed to prolong or increase the response of metastatic disease in response to systemic therapy may be beneficial.[94-96]

Thermal Ablation

The minimally invasive ablative technologies of cryoablation and radiofrequency ablation (RFA) have emerged as potential treatment options for clinically localized RCC, especially in the older patients or patients with a solitary kidney or comorbidities impeding surgery. Long-term oncologic efficacy for these modalities remains to be established. The most favorable lesions for this approach are less than 4 cm and in the periphery of the kidney. Relative contraindications for RFA and cryoablation include distant metastases, tumors greater than 5 cm, tumors in the hilum or central collecting system, and life expectancy less than a year. A meta-analysis comparing cryoablation and RFA suggested that cryoablation results in fewer retreatments and improved local tumor control and that cryoablation may be associated with a lower risk of metastatic progression than RFA.[97]

Systemic Therapy in the Treatment for Relapsed, Metastatic, or Unresectable Renal Cell Carcinoma

National consensus guidelines recommend the following preferred first-line systemic therapies for favorable-risk clear cell histology: axitinib plus pembrolizumab, cabozantinib plus nivolumab, lenvatinib plus pembrolizumab. First-line systemic therapies for poor-/intermediate-risk clear cell histology include axitinib plus pembrolizumab, cabozantinib plus nivolumab, lenvatinib plus pembrolizumab,

ipilimumab plus nivolumab, and cabozantinib. For non–clear cell histology, first-line systemic therapies include cabozantinib.

Axitinib is a small-molecule tyrosine kinase inhibitor targeting vascular endothelial growth factor (VEGF), c-KIT, and platelet-derived growth factor receptor (PDGFR). Pembrolizumab binds to the programmed cell death protein 1 (PD-1) receptor, blocking both immune-suppressing ligands, programmed death ligand-1 (PD-L1) and PD-L2, from interacting with PD-1 to help restore T-cell response and immune response. Cabozantinib is a small-molecule inhibitor of the tyrosine kinases c-Met and VEGFR2. Nivolumab is an antibody that selectively blocks the interaction between PD-1 and its ligands. Lenvatinib exerts its mechanism of action via inhibition of multiple receptors of tyrosine kinases: VEGFR1 (FLT1), VEGFR2 (KDR), VEGFR3 (FLT4), FGFR-1, FGFR-2, FGFR-3, FGFR-4, PDGFRa, RET, and c-KIT.

Metastasectomy

Patients with a solitary metastatic lesion have a 5-year survival rate of 24% (compared with 4% for those with more than one metastatic focus), and they may benefit from aggressive therapy.[98] The resection of one or a limited number of metastases in combination with nephrectomy or at relapse has been associated with a 13% to 50% 5-year survival in a small series of selected patients.[99-101] Selected lung, bone, brain, liver, and even pancreatic metastases, among other sites, have been treated using this approach.

Neoadjuvant (Preoperative) Radiotherapy

Neoadjuvant RT is not recommended in patients with resectable RCC. Two European studies were undertaken to test the efficacy of neoadjuvant/preoperative RT in RCC (Table 69.5). A prospective randomized study of neoadjuvant RT and nephrectomy versus nephrectomy alone was conducted in Rotterdam. No advantage was demonstrated in patients receiving 30-Gy RT in 2-Gy fractions concerning overall survival (OS) or survival free of distant metastasis. Neoadjuvant RT did appear to increase the rate of complete resectability in patients with locally advanced tumors.[102] Subsequent patients received 40 Gy in 2-Gy fractions. No benefit was demonstrated at the higher radiation dose.[103] In Sweden, a second prospective randomized clinical trial could also not demonstrate an advantage for neoadjuvant RT. In this trial, patients were randomly assigned to receive neoadjuvant RT to 33 Gy in 15 fractions administered to the flank with a betatron unit followed by nephrectomy or nephrectomy alone. Patients receiving neoadjuvant RT had a 5-year survival rate of 47%, compared with 63% for patients undergoing surgery alone.[104]

TABLE 69.5 SURVIVAL AFTER NEPHRECTOMY OR NEOADJUVANT RADIOTHERAPY AND NEPHRECTOMY FOR RENAL CELL CARCINOMA, PROSPECTIVE RANDOMIZED TRIALS

Study	Number of Patients	Radiation Dose/ Fraction Size (Gy)	Treatment	5-Y Survival Rate (%)	Comments
van der Werf-Messing et al[102,103]	85	—	N	50	No significant survival difference
	89	30-40/2	N + NART		
Juusela et al[104]	50	—	N	63	No significant survival difference
	38	33/2.2	N + NART	47	

N, nephrectomy; NART, neoadjuvant radiotherapy.

Adjuvant (Postoperative) Radiotherapy

Adjuvant RT is not recommended in RCC after complete resection. Two prospective randomized studies testing the value of adjuvant RT did not demonstrate an advantage to patients receiving RT after surgery (Table 69.6). The first study from New Castle, UK, showed an inferior survival for patients receiving adjuvant RT compared with those treated by surgery alone.[105] Local recurrence rates were not affected by adjuvant RT. Four patients died of fatal hepatotoxicity after RT to a right-sided nephrectomy bed. Patients in this study received 55 Gy in 2.04-Gy daily fractions.[7] A second randomized study conducted by the Copenhagen Renal Cancer Study Group compared patients with stage II or III renal cell cancer treated with nephrectomy alone with patients who received nephrectomy and adjuvant RT to 50 Gy in 20 fractions to the kidney bed and regional ipsilateral and contralateral lymph nodes. No difference in the relapse rate was found between the two study groups. There were significant complications involving the stomach, duodenum, and liver in 44% of patients receiving adjuvant RT. Specifically, 19% of deaths in the RT group were attributed to RT-induced complications.[106]

TABLE 69.6 SURVIVAL AFTER NEPHRECTOMY OR NEPHRECTOMY AND ADJUVANT RADIOTHERAPY FOR RENAL CELL CARCINOMA, PROSPECTIVE RANDOMIZED TRIALS

Study	Stage	Number of Patients	Radiation Dose/Fraction Size (Gy)	Treatment	5-Y Survival Rate (%)	Local Recurrence (%)	RT-Related Mortality (%)	RT Complications (%)
Fugitt et al[105]	NS	48	—	N	47 (17/35)	7	18	.20
		52	55/2.04	N + ART	36 (14/39)	7		
Kjaer[63]	II, III	33	—	N	63[a]	1	19	44
		32	55/2.5	N + ART	38[a]	0		

ART, adjuvant radiotherapy; N, nephrectomy; NS, not stated.

[a]Interpolated from graph; number at risk not known.

Aref et al analyzed the patterns of failure in 116 patients undergoing nephrectomy for RCC. They observed that local regional failure is rare following nephrectomy and that

distant metastases are the main pattern of failure. Consequently, their data did not support the role of adjuvant radiation in RCC.[107] Moreover, a retrospective study of 1,344 patients who underwent 1,390 partial nephrectomies for kidney cancer found that positive surgical margins were not associated with an increased risk of local recurrence or metastatic disease.[108] A Surveillance, Epidemiology, and End Results–based study of adjuvant RT in sarcomatoid RCC did not show an OS benefit.[109]

In contrast, a meta-analysis including the two prospective randomized trials previously mentioned and five retrospective trials with 735 patients observed a significant reduction in locoregional failure with adjuvant RT ($P < .0001$). The patient accrual for all the studies combined spanned from 1968 to 1999. There was no difference in OS or disease-free survival. The authors proposed a prospective randomized trial using modern RT techniques for high-risk patients with tumor size greater than 5 cm, positive margins or gross residual disease, perinephric fat invasion, capsule invasion, renal vein/inferior vena cava invasion, positive lymph nodes, or high-grade histology.[110]

Stereotactic Ablative Radiation Therapy for Primary Treatment

The terms *stereotactic ablative radiation therapy* (SABR/SAbR) and *stereotactic body radiation therapy* (SBRT) are often used interchangeably. Some have suggested that the term *stereotactic ablative radiation therapy* (SABR/SAbR) should be used in reference to stereotactic therapies delivered with curative intent for patients with oligometastatic disease. In contrast, the term *stereotactic body radiation therapy* (SBRT) should be used to describe RT delivered with palliative intent to sites of metastases regardless of OS burden.[111]

SABR may be considered for medically inoperable patients with stage I kidney cancer or with stage II/III kidney cancer. Figure 69.1 shows SABR to a left renal mass 14 Gy × 3.

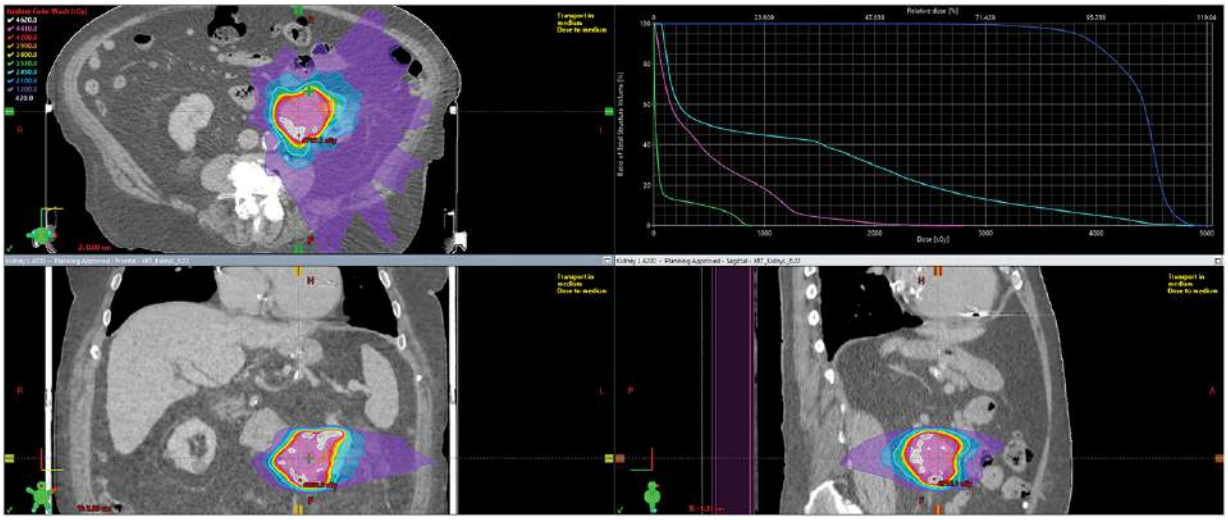

FIGURE 69.1 A 77-year-old man with a history of right renal mass status post radiofrequency ablation who now presents with a growing left renal mass. Definitive stereotactic ablative body radiation prescribed to 4,200 cGy in three fractions showing axial (left top), coronal (left bottom), dose-volume histogram (DVH) (right top), and sagittal (right bottom). Dose color wash values are 4,620 cGy (white), 4,410 Gy (magenta), 4,200 Gy (red), 3,990 (orange), 3,800 Gy (yellow), 3,570 Gy (green), 2,850 Gy (cyan), 2,100 Gy (blue), 2,000 Gy (pink), 1,260 Gy (purple), and 420 cGy (lavender). DVH structures from top to bottom (blue, planning target volume; light blue, internal target volume; purple, bowel; green, spinal cord). (Courtesy of Young Suk Kwon and Raquibul Hannan, UT Southwestern.)

Hannan et al reported the first phase 2 trial of SABR for patients with primary renal cancer. Patients with biopsy-confirmed radiographically enlarging primary RCC (≤5 cm) were enrolled. SABR was delivered in three (12 Gy) or five (8 Gy) fractions. Radiographic local control (LC) at 1 year was observed in 94% of patients, and this was accompanied by pathologic evidence of tumor response (hyalinization, necrosis, and reduced tumor cellularity) in all patients. By RECIST, 100% of the sites remained without progression at 1 year. SABR was well tolerated with no grade 2 or higher (acute or late) toxicities. The average glomerular filtration rate (GFR) declined from a baseline of 65.6 to 55.4 mL/min at 1 year ($P = .003$).[112]

An individual patient data meta-analysis from the International Radiosurgery Consortium of the Kidney included 190 patients treated with SABR for primary RCC across 12 institutions in five countries (Australia, Canada, Germany, Japan, and the United States). Single-fraction SABR was delivered in 43% of patients and multifraction SABR in 57% of patients. The median follow-up was 5 years. Median tumor diameter was 4 cm. Median baseline estimated glomerular filtration rate (eGFR) was 60 mL/min/1.73 m^2 and decreased by 14.2 mL/min/1.73 m^2 by 5 years post-SABR. Seven (4%) patients required dialysis post-SABR. The cumulative incidence of local failure at 5 years was 5.5% overall, with single-fraction SABR yielding fewer local failures than multifraction. Single fractions were as follows: 25 Gy ($n = 52$), 26 Gy ($n = 18$), and 22 Gy ($n = 6$). There were no grade 3 toxicities or treatment-related deaths. One patient developed an acute grade 4 duodenal ulcer and late grade 4 gastritis.[113]

A systematic review and meta-analysis of ablative RT for primary RCC included 383 tumors in 372 patients, most of whom were deemed inoperable. Weighted averages (ranges) of median follow-up, median age, and mean tumor size were 28.0 (5.8-79.2) months, 70.4 (62-83) years, and 4.6 (2.3-9.5) cm, respectively. RCC histology was confirmed in 78.9% of patients who underwent pretreatment biopsy. Dose fractionation varied, but 26 Gy in one fraction and 40 Gy in five fractions were the most common. The random-effect estimates for LC, grade 3 to 4 toxicity, and post-SABR eGFR change were 97.2%, 1.5%, and −7.7 mL/min, respectively. Six patients with preexisting renal dysfunction (2.9%) required dialysis. The authors concluded that renal SABR is locally effective and associated with low toxicity rates for primary RCC despite treatment of larger tumors in older, mostly medically inoperable patients.[114]

A phase II trial by the NRG (NRG-GU012), a randomized phase II SABR for metastatic unresected RCC receiving immunotherapy, will randomize patients between standard immunotherapy and SABR to the primary (42 Gy in three fractions) with standard immunotherapy.

Stereotactic Ablative Radiation Therapy for Oligometastatic Disease

A retrospective study of 47 patients with oligometastatic RCC treated with SABR to 88 metastases observed an LC rate of 91.5% at 2 years with no reported grade 3 or higher toxicity. The most common systemic therapies initiated after SABR were pazopanib (60.7%) and sunitinib (14.3%). The duration of first-line systemic therapy appeared unaffected by SABR. Improved freedom from systemic therapy was observed in patients with metachronous disease, solitary metastasis, and non–bone metastasis. One- and 2-year OS after SABR were 93.1% and 84.8%, respectively.[115]

A prospective phase II single-arm trial enrolled 23 patients who received SABR to 33 initial and 57 total sites. The median follow-up was 21.7 months. One-year progression-free survival (PFS) was 82.6%, and LC was 100%. There were no grade 3/4 toxicities, but there was one death due to immune-related colitis 3 months after SABR while on subsequent checkpoint inhibitor therapy, where an SABR contribution could not be excluded. One-year OS was 95.7%, and 1-year cancer-specific survival was 100%.[116]

A phase III trial by ECOG-ACRIN (EA8211), “Focused Radiation versus Systemic Therapy for Kidney Cancer Patients with Limited Metastasis, SOAR Trial,” will randomize patients to SABR followed by standard-of-care systemic therapy, to standard-of-care systemic therapy alone, in patients with RCC. Figure 69.2 shows SABR to a right adrenal oligometastasis 13 Gy × 3.

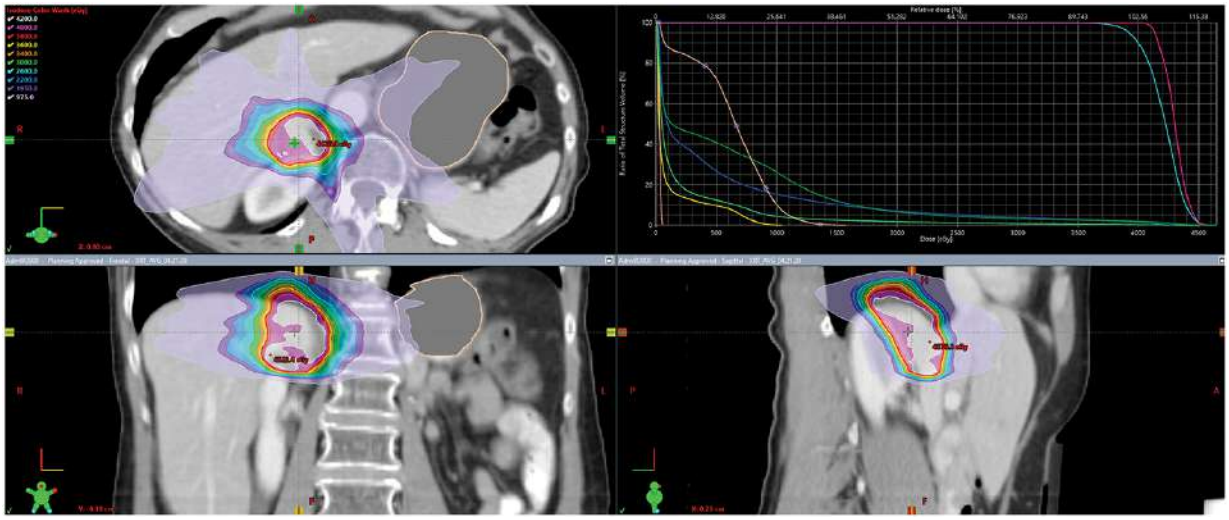

FIGURE 69.2 A 66-year-old woman with a history of left renal cell carcinoma with inferior vena cava tumor thrombus status post left radical nephrectomy with pathology revealing pT3b disease who has subsequently developed an oligometastatic lesion in the right adrenal gland. Definitive stereotactic ablative body radiation prescribed to 3,900 cGy in three fractions showing axial (top left), coronal (bottom left), dose-volume histogram (DVH) (top right), and sagittal (bottom right). Dose color wash values are 4,200 cGy (white), 4,000 Gy (magenta), 3,800 Gy (red), 3,600 Gy (yellow), 3,400 Gy (orange), 3,000 Gy (green), 2,600 Gy (cyan), 2,200 Gy (blue), 1,950 Gy (purple), and 975 cGy (lavender). DVH structures from top to bottom (magenta, internal target volume; cyan, planning target volume; orange, liver; green, R kidney; blue, R lung; yellow, esophagus). (Courtesy of Young Suk Kwon and Raquibul Hannan, UT Southwestern.)

Stereotactic Body Radiation Therapy for Oligoprogressive Disease

A retrospective study included 36 patients with extracranial metastatic RCC treated with SABR to 43 sites with a median dose of 36 Gy (range, 18-50) in three fractions (range, 1-5). The median time to SABR from the start of systemic therapy was 11.4 months. Median modified progression-free survival (mPFS) was 9.2 months. Patients receiving SABR while on immunotherapy exhibited a longer median mPFS (>28.4 months) than patients not on immunotherapy (9.2 months). The median OS from SABR administration was 43.4 months. The 1-year LC rate was 93%. Most SABR-related toxicities were grade 1 to 2 (33% of patients), with one grade 5 hemoptysis event possibly related to SABR or disease progression.[116]

A phase II trial of stereotactic ablative radiation for oligoprogressive metastatic kidney cancer enrolled 20 patients who received upfront and sequential SABR to a total of 37 sites. The LC rate was 100%. At a median follow-up of 10.4 months, SABR extended the duration of the ongoing systemic therapy by greater than 6 months in 14 patients. The median time from SABR to the onset of new systemic therapy or death was 11.1 months. One patient developed grade 3 gastrointestinal toxicity, possibly related to treatment. There was no significant decline in quality of life.[117]

Stereotactic Body Radiation Therapy for Inferior Vena Cava Thrombus

A phase 2 trial enrolled six patients who received neoadjuvant SABR for RCC inferior vena cava tumor thrombus (IVC-TT). Patients underwent neoadjuvant SABR (40 Gy in five fractions) to the IVC-TT followed by open radical nephrectomy and thrombectomy. No grade 4 to 5 adverse events (AEs) were observed.[117] Figure 69.3 shows SABR to an IVC-TT 8 Gy × 5.

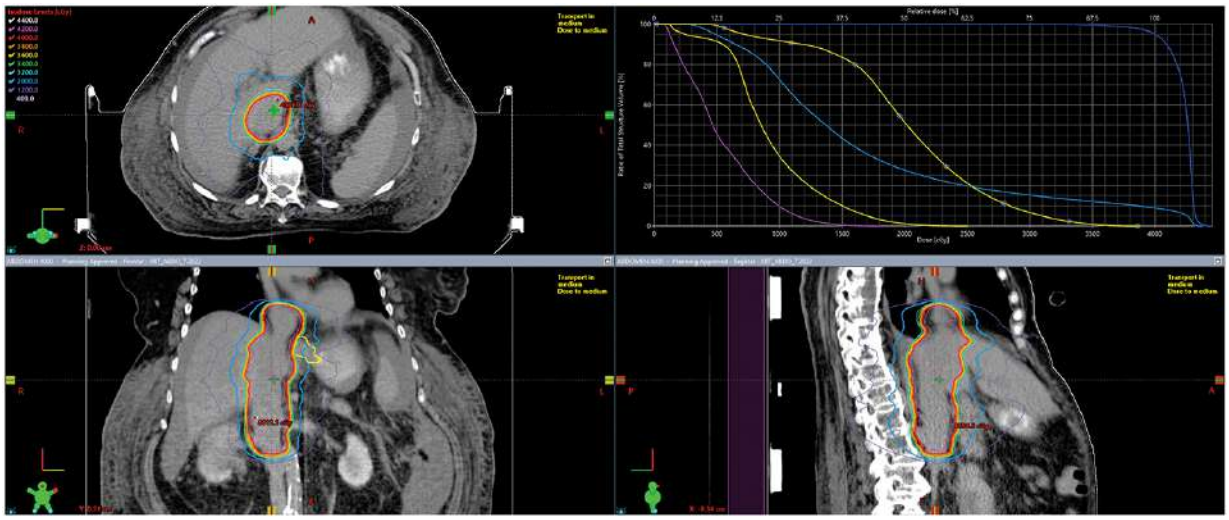

FIGURE 69.3 A 70-year-old woman with right renal mass with inferior vena cava tumor thrombus causing venous congestion. Palliative stereotactic ablative body radiation prescribed to 4,000 cGy in five fractions showing axial (top left), sagittal (bottom left), dose-volume histogram (DVH) (top right), and coronal (bottom right). Dose color wash values are 4,400 cGy (white), 4,200 Gy (magenta), 4,000 Gy (red), 3,800 Gy (orange), 3,600 Gy (yellow), 3,400 Gy (green), 3,200 Gy (cyan), 2,000 Gy (blue), 1,200 Gy (purple), and 400 cGy (lavender). DVH structures from top to bottom (blue, planning target volume; yellow [lateral], esophagus; light blue, heart; yellow [medial], duodenum; bowel, purple). (Courtesy of Young Suk Kwon and Raquibul Hannan, UT Southwestern.)

A retrospective study of IVC-TT included 15 patients. All patients received SABR to the IVC-TT. Most did not receive surgery due to high surgical risk (7/15) or recurrent thrombus (3/15). Radiographic response was observed in 58% of patients. Symptom palliation was recorded in all patients receiving SABR for this indication. Only grade 1 to 2 AEs were noted.[118]

Stereotactic Body Radiation Therapy for Oligometastatic Disease

SBRT may be considered for oligometastatic kidney cancer.

Stereotactic Body Radiation Therapy for Extracranial Metastases

A systematic review including 10 publications of extracranial RCC showed that the weighted LC was 89%, OS ranged from 11.7 to 22 months, grade 3 to 4 toxicity ranged from 0% to 4%, and the weighted rate of treatment-related mortality was 0.5%.[119]

Zelefsky et al reported 105 RCC lesions treated with either single-dose, image-guided, intensity-modulated radiotherapy (IMRT) to a prescription dose of 18 to 24 Gy

(median, 24) or hypofractionation (3 or 5 fractions) with a prescription dose of 20 to 30 Gy. The 3-year local PFS for those who received a high single-dose (24 Gy; $n = 45$), a low single-dose (<24 Gy; $n = 14$), or hypofractionation regimens ($n = 46$) was 88%, 21%, and 17%, respectively. Multivariate analysis showed significant predictors of improved local PFS: 24 Gy versus a lower dose ($P = .009$) and a single dose versus hypofractionation ($P = .008$).[81]

In a series of 50 patients with metastatic RCC, Wersall et al reported that stereotactically delivered radiation to sites including the lung, liver, and adrenal resulted in complete regression in 30% of cases and either partial regression or stabilization of the lesions in 60%.[120] Of the 162 treated tumors, only 3 recurred. Dose and fractionation ranged from 8 Gy × 4, 10 Gy × 4, and 15 Gy × 3, all delivered in 1 week.

Stereotactic Body Radiation Therapy for Spine Metastases

In a study of 48 patients (55 lesions) with metastatic RCC to the spine, patients received 24 Gy × 1, 9 Gy × 3, or 6 Gy × 5 fractions. The actuarial 1-year spine tumor PFS was 82.1%. At the pretreatment baseline, 23% of patients were pain free; at 1 and 12 months post-SBRT, 44% and 52% of patients were pain free, respectively. No grade 3 to 4 neurologic toxicity was observed.[121] A prospective study of 71 spinal segments treated with SBRT showed that the 1-year OS and LC rates were 64% and 83%, respectively. The 1-year vertebral compression fracture (VCF)-free probability rate was 82%. Multivariate analysis identified single-fraction SBRT (18-24 Gy) and baseline VCF as significant predictors of SBRT-induced VCF ($P = .028$ and $P = .012$, respectively).[122] A retrospective study of 57 patients with RCC metastases to the spine who received single-fraction SBRT to 88 treatment sites showed that the median time to radiographic failure and unadjusted pain progression were 26.5 and 26.0 months, respectively. The median time to pain relief from simulation and duration of pain relief from treatment were 0.9 months (range 0.1-4.4 months) and 5.4 months (range 0.1-37.4 months), respectively. Multivariate analyses demonstrated that multilevel disease and neural foramen involvement were correlated with radiographic failure; multilevel disease and vertebral fracture were correlated with unadjusted pain progression. Twelve treatment sites (14%) were complicated by subsequent vertebral fractures.[123]

Stereotactic Body Radiation Therapy for Bone Metastases

A study of 46 consecutive patients with RCC with 95 lesions was treated as follows: 50 SBRT and 45 conventional fractionation RT (CFRT). A biologically effective dose (BED) of 80 Gy or greater ($\alpha/\beta = 7$) predicted clinical LC. Median time to symptom control between SBRT and CFRT were 2 (range, 0-6 weeks) and 4 weeks (range, 0-7 weeks), respectively. Toxicity rates were low and equivalent in both groups, with no grade 4 or 5 toxicity reported.[124]

A potential added benefit of extracranial stereotactic RT is the abscopal effect, in which there is tumor response at a distance from the irradiated volume. Wersall and

colleagues observed an abscopal effect in 4 out of 28 patients with RCC with treated and untreated metastatic lesions. In these four patients, nonirradiated metastases regressed temporarily or seemingly permanently after treatment with SBRT of the primary tumor or other metastatic lesions. The authors' findings argued for a more active and liberal use of SBRT in metastatic RCC. They suggested that further studies were necessary to define the underlying mechanisms behind such responses or to combine SBRT with immunomodulating agents.[125]

Whole-Brain Radiotherapy for Brain Metastases

A retrospective study of 60 patients receiving whole-brain radiotherapy (WBRT) for RCC brain metastases showed that LC at 6 months was 21% after 3 Gy × 10 and 57% after higher doses of 2 Gy × 20 or 3 Gy × 15 (P = .013). The LC at 12 months was 7% and 35%, respectively. The OS at 6 months was 29% after 3 Gy × 10 and 52% after higher doses (P = .003). The OS at 12 months was 13% and 47%, respectively. The authors concluded that escalating the WBRT dose beyond 3 Gy × 10 could improve the outcomes in patients with RCC with brain metastases.[126]

Stereotactic Radiosurgery for Brain Metastases

A retrospective study of 280 consecutive patients with metastatic brain tumors (of which 80 were RCC) treated with gamma knife radiosurgery (GKS) observed that to control symptomatic peritumoral edema, a higher marginal dose of 25 Gy or more was necessary. The authors developed an algorithm for the management of RCC metastases where lesions 3 cm or greater undergo resection, lesions greater than 2 cm with symptomatic peritumoral edema undergo resection (since a 25 Gy was not considered safe for tumors >2 cm) and those without it GKS, and lesions 2 cm or less receive GKS.[127] Another retrospective study of 46 patients and 99 RCC brain lesions treated with radiosurgery observed that the good response group (as assessed by MRI) survived significantly longer than the poor response group (median survival times of 18.0 and 9.0 months, respectively; P = .025).[128]

Kano et al reported 158 consecutive patients with RCC (531 lesions) who underwent stereotactic radiosurgery (SRS). The OS after SRS was 60%, 38%, and 19% at 6, 12, and 24 months, respectively, with a median survival of 8.2 months. Median survival for patients with less than 2 brain metastases, higher KPS (>90), and no prior WBRT was 12 months after SRS. Sustained local tumor control was achieved in 92% of patients. Symptomatic adverse radiation effects occurred in 7%. Overall, 70% of patients improved or remained neurologically stable.[129]

A retrospective study of 61 patients with RCC treated with GKS, median dose 20 Gy, showed that the use of targeted agents (tyrosine kinase inhibitors, mammalian target rapamycin inhibitors, and bevacizumab) was the only factor that predicted improved survival. The median survival for patients receiving targeted agents (n = 24) was 16.6

months compared with 7.2 months (n = 37) for those not receiving targeted therapy (P = .04).[130]

A systematic review including 16 publications of cranial RCC showed that the weighted LC was 92%, OS ranged from 6.7 to 25.6 months, grade 3 to 4 toxicity ranged from 0% to 6%, and the weighted rate of treatment-related mortality was 0.6% secondary to intratumoral hemorrhage.[119]

Conventional Radiotherapy for Extracranial Metastases

Palliative RT is effective at relieving symptoms of metastatic renal cell cancer.[131-134] A patient with a solitary bone metastasis may have a long survival time, and a sufficient radiation dose should be administered to allow durable pain relief. If surgery is used to remove a metastatic lesion, postoperative RT is indicated to prevent its recurrence. In a prospective phase II study using validated quality-of-life questionnaires, Lee and colleagues from the Princess Margaret Hospital demonstrated that 83% of patients treated for pain had experienced significant pain relief with 30-Gy radiation delivered in 10 fractions.[133] DiBiase et al observed a dose-response in the palliative treatment of 107 patients with RCC. A BED greater than 50 Gy_{10} (α/β ratio of 10) was associated with a statistically significant increased rate of response: 59% versus 39% (P = .001).[80]

Figure 69.4 illustrates a painful RCC cutaneous metastasis that had a complete response after 375 cGy × 13 fractions (BED = 67 Gy_{10}) over 5 weeks. The lesion was treated with electrons, a custom bolus, and a 2-cm peripheral margin.[135]

FIGURE 69.4 This painful renal cell carcinoma cutaneous metastasis (A) had a complete response (B) after 375 cGy × 13 fractions (biologically effective dose = 67 Gy_{10}) over 5 weeks. The lesion was treated with electrons, a custom bolus, and a 2-cm peripheral margin. (From Gay HA, Cavalieri R, Allison RR, Finley J, Quan WD Jr. Complete response in a cutaneous facial metastatic nodule from renal cell carcinoma after hypofractionated radiotherapy. *Dermatol Online J*. 2007;13[4]:6. Reprinted with permission of Dr. Hiram A. Gay.)

Intraoperative Radiation Therapy for Advanced or Recurrent Renal Cell Carcinoma

A retrospective study of 98 patients who received intraoperative radiation therapy (IORT) for advanced or locally recurrent RCC at 9 institutions showed a 5-year OS of 37% for advanced disease and 55% for locally recurrent disease. The respective 5-year disease-free survival was 39% and 52%. IORT was delivered during nephrectomy for advanced disease (28%) or resection of locally recurrent RCC in the renal fossa (72%). Preoperative or postoperative external beam radiation therapy was administered to 27% and 35% of patients, respectively. Initial nodal involvement, sarcomatoid features, and higher IORT dose were statistically significantly associated with decreased survival. The outcomes for patients receiving IORT in the setting of local recurrence compared favorably to similar cohorts treated by local resection alone.[136]

Renal Pelvis and Ureter Carcinoma

Surgery is the therapeutic foundation for the management of renal pelvis and ureter carcinoma. National consensus guidelines recommend the following treatment options for renal pelvis low-grade tumors: endoscopic resection with or without postsurgical intrapelvic chemotherapy or Bacillus Calmette-Guerin, or nephroureterectomy with cuff of bladder with or without perioperative intravesical chemotherapy. High-grade renal pelvis tumors, large tumors, or tumors that invade the renal parenchyma have the following recommended treatment: nephroureterectomy with cuff of bladder plus regional lymphadenectomy with or without perioperative intravesical chemotherapy, with consideration of neoadjuvant chemotherapy in selected patients. The management of ureter tumors depends on the tumor location: upper, mid, or distal location, and disease extent.

For both the renal pelvis and ureter tumors, patients with pathologic stage pT3, pT4, or pN_+ should be considered for adjuvant platinum-based chemotherapy or adjuvant nivolumab if no platinum neoadjuvant treatment was given. Consider adjuvant nivolumab if platinum neoadjuvant chemotherapy was given and ypT2-ypT4 or ypN_+. The “y” classification is used after neoadjuvant therapy.

Surgery

Radical nephroureterectomy is the only potentially curative treatment for most patients with urothelial carcinoma of the renal pelvis or ureter. This operation includes the removal of the contents of Gerota fascia, including the ipsilateral ureter with a cuff of the bladder at its distal extent. High local or regional recurrence rates have plagued less radical surgeries, sometimes approaching 30%.[137] Hall reported an increased rate of recurrence when parenchymal-sparing procedures were performed.[75] Conservative surgical excision should be considered only in patients with low-grade, low-stage, solitary tumors in whom radical nephrectomy is not indicated because of poor kidney

function or an absent contralateral kidney. Conservative surgical options in selected cases include laparoscopic nephroureterectomy, nephrectomy and partial ureterectomy, endoscopic resection, and fulguration. The role of lymph node dissection in this disease is unclear. Patients who have the highest risk of lymph node metastases also have a high risk of systemic disease.

Adjuvant Radiotherapy

There are no randomized trials on the role of postoperative RT in patients who have had a complete resection of upper urinary tract cancer. Tumors of the renal pelvis and ureter have a significantly high local recurrence rate after nephroureterectomy, particularly in patients with high-grade tumors or deep invasion.[138] Retrospective studies suggest that adjuvant RT may diminish the likelihood of local recurrence, but it does not appear to impact OS or reduce future distant metastases.[36,139]

Cozad et al reported a retrospective study of 94 patients with urothelial carcinoma of the renal pelvis, of which 77 had resections without residual. On multivariate analysis, adjuvant RT had a significant effect on LC (P = .02). Regarding survival, the use of adjuvant RT was of borderline significance (P = .07). Of the 27 patients who were excluded from local failure and survival analysis, 19 had unresectable local disease, and of these, 11 received RT. Two long-term disease-free survivors in this group received 45 and 50.4 Gy, respectively. The authors recommended consideration of adjuvant RT in patients with high grade or stage, close surgical margins, or positive lymph nodes to improve LC.[36]

In another retrospective study of 133 patients with urothelial carcinoma of the renal pelvis, 67 patients received external beam RT following surgery (RT group), and 66 patients received intravesical chemotherapy (non-RT group). The clinical target volume included the renal fossa, the course of the ureter to the entire bladder, and the paracaval and para-aortic lymph nodes (Figure 69.5). The tumor bed or residual tumor was targeted in 14 patients. The median radiation dose administered was 50 Gy. There was a significant difference between the survival rates for these groups based on patients with T3/T4 stage cancer. A significant difference between the irradiated and nonirradiated bladder groups was observed in the bladder tumor relapse rate (P = .004). The authors concluded that RT may improve the OS of patients with T3/T4 cancer of the renal pelvis or ureter and delay bladder tumor recurrences.[140]

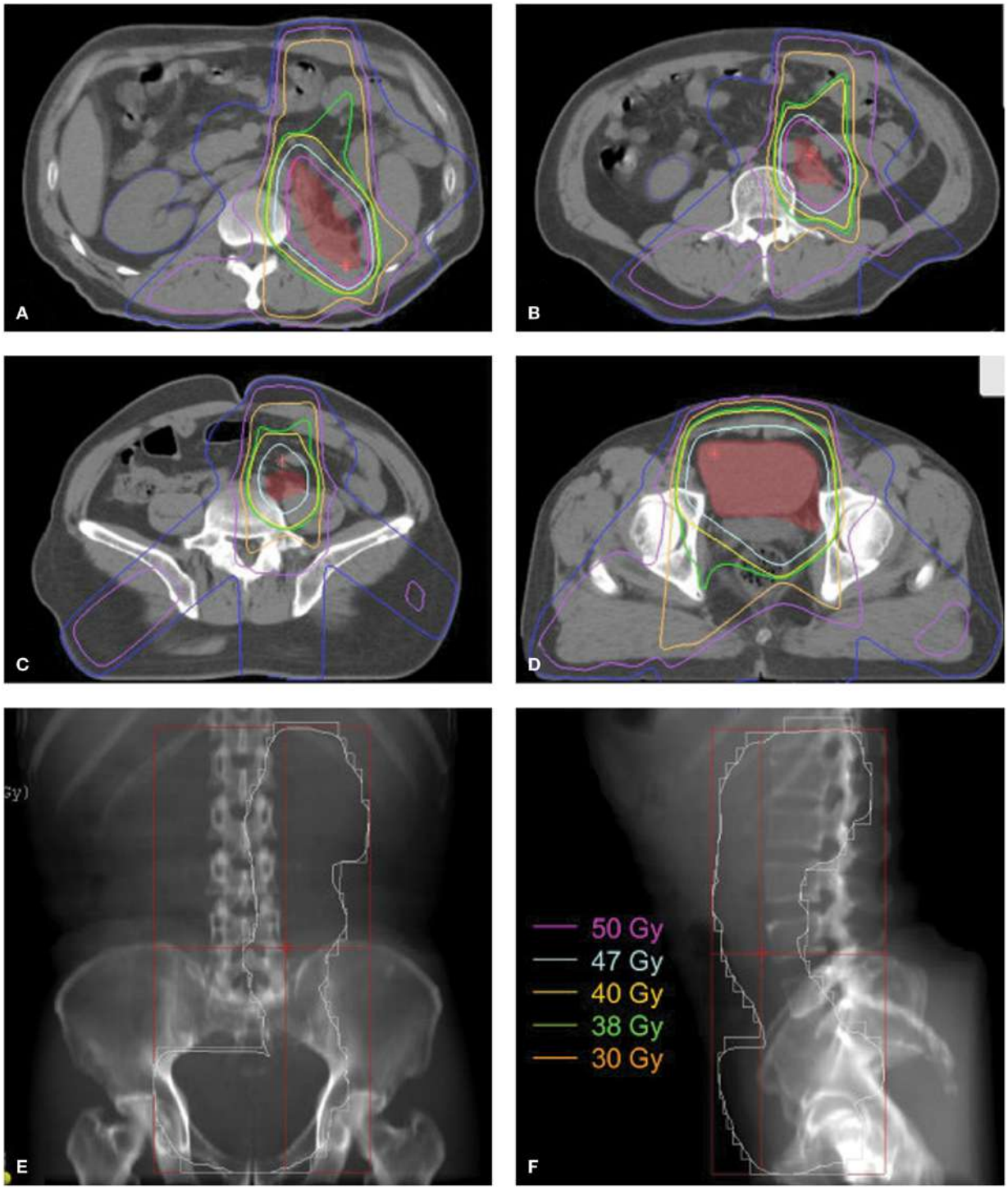

FIGURE 69.5 Dose distribution of a patient with renal pelvis cancer and beam arrangements of 0°, 129°, and 229° gantry: renal fossa (A), course of ureter (B, C), and bladder (D). Digitally reconstructed radiograph for views of 0° gantry (E) and 90° gantry (F). Internal pink and yellow lines represent the CTV50 and CTV40, respectively. CTV, clinical target volume. (Reprinted from Chen B, Zeng ZC, Wang GM, et al. Radiotherapy may improve overall survival of patients with T3/T4 transitional cell carcinoma of the renal pelvis or ureter and delay bladder tumour relapse. *BMC Cancer*. 2011;11:297. http://creativecommons.org/licenses/by/2.0.)

The patterns of failure were described in 252 patients undergoing surgery at the University of Texas Southwest Medical Center for urothelial carcinoma of the upper urinary tract.[75] Local recurrence occurred only 9% of the time, whereas new invasive urothelial tumors or distant metastases occurred in 69% and 22% of cases, respectively. Isolated local recurrences were rare. Another series from the Princess Margaret Hospital confirms the high rate of distant metastases. Although local failure occurred in 35% of patients with locally advanced disease, most patients also experienced distant metastases as well.[141]

Systemic Chemotherapy

The pathologic similarity of urothelial carcinoma of the renal pelvis and ureter to bladder cancer has encouraged medical oncologists to use similar chemotherapeutic regimens in the management of upper tract urothelial carcinomas. Dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin for three to six cycles and gemcitabine and cisplatin for four cycles are considered standard neoadjuvant or adjuvant regimens. Radiosensitizing chemotherapeutic agents include cisplatin, low-dose gemcitabine, and 5-fluorouracil (5-FU) and mitomycin. Other recommended regimens include cisplatin and 5-FU, as well as cisplatin and paclitaxel.

RADIOTHERAPY TECHNIQUES

Normal Tissue Dose Constraints

Several organs at risk have to be taken into consideration when palliating an unresected kidney tumor or a kidney tumor bed recurrence. These organs include the spinal cord, liver, spleen, stomach, duodenum, small bowel, normal contralateral or ipsilateral kidney, and normal adrenal gland(s).

There are no established dose constraints for sparing the remaining kidney after nephrectomy or in the palliative setting when both kidneys are present. In the context of two normal kidneys, the QUANTEC kidney panel recommended a mean bilateral kidney dose of less than 15 to 18 Gy and a bilateral kidney dose-volume histogram with a V12 less than 55%, V20 less than 32%, V23 less than 30%, and V28 less than 20%.[142] The dose to the stomach should be kept below 45 Gy, and the small bowel V45 less than 195 mL when it is contoured as a bowel bag (Figure 69.6).[143] The male and female Radiation Therapy Oncology Group normal pelvis atlases illustrate how to contour the bowel bag and are accessible at https://www.nrgoncology.org/About-Us/Center-for-Innovation-in-Radiation-Oncology. The mean liver dose should be kept below 30 to 32 Gy, excluding patients with preexisting liver disease or hepatocellular carcinoma who have a lower tolerance. Sparing at least 700 mL of liver from radiation is another potential strategy to avoid complications.[144] There are no recognized splenic or adrenal dose constraints. Nevertheless, based on the spleen's exquisite radiosensitivity and experience with palliative RT for myeloproliferative disorders,[145] it seems prudent to

limit the spleen to 5 to 10 Gy. The spinal dose should be limited to an absolute maximum of 45 Gy.

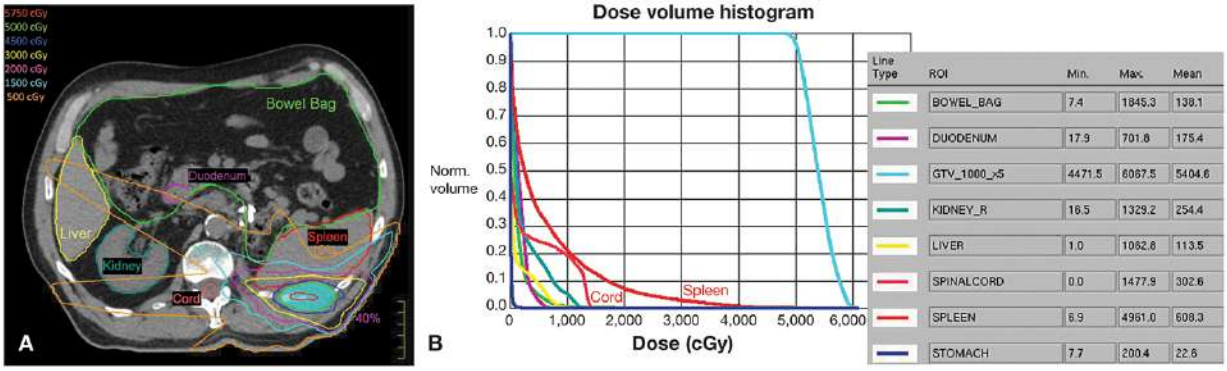

FIGURE 69.6 Treatment plan (A) and dose-volume histogram (B) showing the normalized volume versus dose (cGy) for a patient with metastatic clear cell renal cell carcinoma, with sarcomatoid and rhabdoid differentiation, after left radical nephrectomy, pT3aN1M1. The kidney tumor was Fuhrman nuclear grade IV and 15.5 cm in diameter. The patient was treated with temsirolimus, pazopanib, bevacizumab, and, finally, adriamycin plus gemcitabine with some objective response. The patient developed a painful, destructive 55-mL metastasis in the left 12th rib. The metastasis was treated with 10 Gy × 5 using a six-field (RPO 210, LAO 60, LT LAT 90, LPO 120, LPO 150, PA) 6-MV intensity-modulated radiotherapy (IMRT) technique. RPO, right posterior oblique; LAO, left anterior oblique; LT LAT, left lateral; LPO, left posterior oblique; PA, posterior-anterior. The isodose-based methodology used to evaluate the plan is explained in detail in Gay et al.[146] The skin was limited to the 40% isodose (400 cGy × 5), the spinal cord to the 30% isodose (300 cGy × 5), and the spleen to the 10% isodose (100 cGy × 5) or less as feasible. Doses to the bowel, liver, remaining kidney, and duodenum were well below tolerance. Daily imaging with 2D:2D match and cone-beam computed tomography (CT) were used prior to the delivery of the five fractions over 3 weeks.

Renal Cell Carcinoma

Neoadjuvant or adjuvant RT is not routinely recommended for patients with RCC. However, there may be special cases where the clinician may consider neoadjuvant RT to improve respectability or adjuvant RT if there are clinical tumor features suggestive of a high risk of local recurrence. Careful planning is paramount because ignoring any of the critical structures surrounding the kidney or nephrectomy bed could result in serious, even fatal, patient toxicity.

Patients receiving RT to the kidney may be simulated supine, arms up, using a wing board or alpha cradle, a wire on the surgical scar, and a planning CT scan. The kidneys are mobile organs and move vertically within the retroperitoneum an average of 0.9 to 1.3 cm and as much as 4 cm during normal respiration.[147-149] In going from the supine to upright position, the kidneys can shift inferiorly between 0.5 and 7.5 cm with an average of 3.6 cm.[150] This finding, although critical for total body irradiation treatments, further highlights the mobility of the kidneys.

The high complication rates reported in the prospective trials of postoperative RT have taught radiation oncologists an important lesson regarding RT planning, patient selection, and the tolerance of the upper abdominal viscera. IMRT may be a reasonable

consideration due to the sensitivity of adjacent surrounding structures. If IMRT is considered, a plan to manage the uncertainties in target localization, such as four-dimensional (4D) CT treatment planning, IGRT, abdominal immobilization devices, gating, or breathing control, needs to be considered. Renal function scans may assist in the treatment planning or patient selection process, but this has not been formally studied.

In unresectable lesions, 40 to 50 Gy neoadjuvant RT (1.8- 2 Gy/fraction) directed to the kidney tumor and regional lymphatics may improve resectability.[103] Multiple-field techniques, similar to those described for adjuvant RT, should be considered in patients receiving preoperative treatment.

CT-based treatment planning contributes to good LC with minimal morbidity. Careful definition of the target volume to encompass the nephrectomy bed, lymph node drainage sites, and surgical clips on the planning CT scan is important. Exclusive use of anterior- and posterior-field arrangements, particularly on the right side, is likely to result in irradiation of large volumes of bowel and liver beyond tolerance. The use of multiple beams is paramount for protecting the surrounding normal structures. Total radiation doses of 45 to 50 Gy (1.8-2 Gy/fraction) to the nephrectomy bed and regional lymph nodes with a boost to small volumes of microscopic or gross residual disease of 10 to 15 Gy (total dose 50-60 Gy) are appropriate. Stein and coworkers[151] reported two scar recurrences and recommended that the incision site be included in the target volume. If the scar cannot be covered without increasing the amount of normal tissue irradiated, an additional electron beam field to treat the scar may be considered.

Figure 69.6 illustrates a patient with metastatic clear cell RCC, with sarcomatoid and rhabdoid differentiation, status post left radical nephrectomy, pT3aN1M1. The kidney tumor was Fuhrman nuclear grade IV and 15.5 cm in diameter. The patient was treated with temsirolimus, pazopanib, bevacizumab, and, finally, adriamycin plus gemcitabine with some objective response. The patient developed a painful, destructive 55-mL metastasis in the left 12th rib. The metastasis was treated with 10 Gy × 5 using a six-field (right posterior oblique 210, left anterior oblique 60, left lateral 90, left posterior oblique [LPO] 120, LPO 150, posteroanterior) 6-MV IMRT technique. The isodose-based methodology was used to evaluate the plan and is explained in detail in the reference.[146] The skin was limited to the 40% isodose (400 cGy × 5), the spinal cord to the 30% isodose (300 cGy × 5), and the spleen to the 10% isodose (100 cGy × 5) or less as feasible. Doses to the bowel, liver, remaining kidney, and duodenum were well below tolerance (Figure 69.6A). Daily imaging with 2D:2D match and cone-beam CT was used prior to the delivery of the five fractions over 3 weeks.

Stereotactic Ablative Radiation Therapy

At UT Southwestern, for kidney SABR, 36 to 42 Gy in three fractions is preferred with 40 Gy in five fractions as an alternative.

Simulation Imaging

Contiguous CT slices of no greater than 3-mm slice thickness should be obtained starting from the level of the diaphragm and extending inferiorly through the pelvis. Contrast-enhanced diagnostic CTs and positron emission tomography/CTs should be registered and used to guide tumor and normal organ volume definition. Oral contrast to assist in visualization of the small bowel is recommended and should be given approximately 15 to 20 minutes before simulation. It is recommended that patients do not eat or drink for at least 2 hours before simulation or treatment to ensure consistent gastric filling. The reconstructed slice thickness in the target region should be 2 mm or less for SABR.[152]

Motion Management Technique

Motion management techniques include monitored voluntary or involuntary breath-hold, and gating or tracking based on implanted fiducial markers within or in the immediate vicinity of the tumor.[152]

Organs at Risk

Organs at risk may include small bowel, large bowel, duodenum, heart, kidneys, liver, skin, spinal cord, stomach, and ribs.

Renal Pelvis and Ureter Carcinoma

Adjuvant RT has been used in the management of renal pelvis and ureter cancers. For elective RT, the clinical target volume should include the renal fossa, the course of the ureter to the bladder, the entire bladder, and the paracaval and para-aortic lymph nodes (Figure 69.6).[140] As in RCC, CT-based planning may facilitate dosimetric coverage of the regions at risk while minimizing dose to normal tissues. Radiation doses of 45 to 50 Gy at 1.8 to 2 Gy per day are appropriate to treat subclinical and microscopic disease. For more extensive disease (eg, multiple positive nodes), R1 (microscopic positive margins) or R2 (macroscopic residual margins) resections, a boost of 5 to 10 Gy should be considered. For unresectable or gross residual disease, higher doses may be necessary. In this event, multiple-field arrangements, including oblique and lateral fields with field reductions, are important to minimize toxicity to surrounding normal structures (see Figure 69.5). CT-based simulation, 3D treatment planning, and contrast-enhanced radiographs are helpful in defining the RT target volume. IMRT can be considered if organ motion is managed to avoid underdosing the planning target volume. Chemotherapy may allow a lower radiation dose for gross disease.

FOLLOW-UP

Renal Cell Carcinoma

Follow-up after ablative techniques includes the following:

- History & Physical Exam annually
- Laboratory tests as indicated annually
- Abdominal CT, MRI with and without intravenous contrast at 1 to 3, 6, and 12 months after ablation, then annually after that
- Chest imaging: chest x-ray or CT annually for 5 years for patients with biopsy-proven low-risk pathologic features

The greatest risk of recurrence following surgery for RCC is in the first 1 to 2 years, with most relapses occurring within 3 years, but recurrences can occur more than a decade later.

Renal Pelvis and Ureter Carcinoma

Since patients with urothelial carcinoma of the upper urinary tract are at a high risk of urothelial tumors of the bladder, monitoring with cystoscopy at periodic intervals is necessary. For patients who have undergone a renal-sparing procedure, imaging with CT or MRI and/or ureteroscopy may be necessary. Follow-up includes the following:

- Cystoscopy every 3 months for 1 year, then at longer intervals. Consider cytology for high grade.
- Nephron-sparing surgery: imaging of upper tract collecting system or ureteroscopy at 3- to 12-month intervals ± abdominal/pelvic CT or MRI with and without contrast

SEQUELAE OF RADIOTHERAPY

The side effects and complications from RT for cancer of the kidney, renal pelvis, and ureters are similar to those expected from irradiation of the upper abdomen and pelvis. These side effects include nausea, vomiting, diarrhea, and abdominal cramping. Patients with right-sided tumors may have significant portions of the liver irradiated, and radiation-induced liver damage is possible. The Copenhagen Renal Cancer Study Group reported that 12 (44%) of 27 patients developed significant complications: 3 had biochemical changes indicating radiation hepatitis, 3 had duodenum and small-bowel stenosis, and 6 had duodenum and small-bowel bleeding.[106] Surgery was performed on four of nine patients with bowel-related RT complications, and five patients died of treatment-related complications. The total radiation dose in this study was 50 Gy given in 2.5-Gy fractions per day. Fugitt also reported four cases of "liver" failure among 52 patients who received postoperative RT.[105]

The complication rate after RT for tumors of the kidney and upper urinary tract is related to the total dose, fraction size, and technique of irradiation. CT-based simulation and 3D treatment planning may decrease the risk of complications after elective RT in patients with upper urinary tract malignancies. In a prospective clinical trial, patients received single-fraction renal SABR (26 Gy) for tumors less than 5 cm or fractionated SABR (3 × 14 Gy) for tumors 5 cm or larger. For every 10 Gy of physical dose

delivered, an exponential decline in affected kidney GFR was observed at 39% for 26 Gy in 1 fraction and 25% for 42 Gy in three fractions. When normalized to BED_{3Gy}, the dose-response relationship for each treatment prescription was similar, with a plateau beyond 100 Gy. The authors concluded that sparing the functional kidney from high-dose regions (>50% isodoses) may help reduce the risk of functional loss.[153]

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CHAPTER 70

Adjuvant and Neoadjuvant Radiation Therapy for Locally Advanced Bladder Cancer

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Patients with locally advanced bladder cancer who undergo radical cystectomy have an estimated 5-year overall survival (OS) of 10% to 40%.[1] While the problem of distant relapse is well recognized, locoregional recurrences are common, with approximately one-third developing a locoregional recurrence as the initial site of failure after surgery.[1-4] Adjuvant chemotherapy is frequently employed for patients with locally advanced bladder cancer who did not receive neoadjuvant chemotherapy to address the risk of distant disease. Many patients are not candidates for postoperative chemotherapy because of the morbidity of surgery, coupled with preexisting medical illnesses.

Adjuvant radiotherapy (RT) is an alternative, and potentially complementary, adjuvant treatment that has been assessed in clinical trials to reduce the risk of locoregional recurrence in patients with ≥pT3 or node-positive disease.[5] Prospective data demonstrate that the addition of adjuvant RT decreases the risk of locoregional recurrences and improves disease-free survival (DFS).[5-7] There is growing evidence to suggest that improvements in these intermediate end points translate into improvements in OS for patients with locally advanced disease. In this chapter, we review the problem of locoregional failure (LRF) after cystectomy, identify patients most likely to benefit from adjuvant RT, review the patterns of pelvic failure after cystectomy, discuss technical details of radiation treatment, and review the modern literature on this topic. We also discuss preoperative RT. We also discuss the potential role of adjuvant RT now that adjuvant immunotherapy has emerged as a new standard of care for patients treated with radical cystectomy with or without neoadjuvant chemotherapy.

EARLY CLINICAL STUDIES OF POSTOPERATIVE RADIOTHERAPY

Adjuvant RT was first studied in the 1970s and 1980s in Europe and the United States but largely fell out of favor due to the toxicity using large nonconformal radiation fields.[7,8] Zaghloul et al reported results from a clinical trial of

postoperative RT conducted at the Egyptian National Cancer Institute (NCI) in Cairo that randomized 236 cystectomy patients with pT3a-pT4a disease to receive either observation or postoperative RT given either as 37.5 Gy in 1.25 Gy fractions given 3 times per day separated by at least 3 hours over 12 days or 50 Gy in 2 Gy daily fractions over 5 weeks.[9] The study reported a 5-year DFS of 44% with conventional fractionation, 49% with hyperfractionation, and 25% with observation ($P < .01$). Local-regional control at 5 years also significantly favored the RT arms, with pelvic control rates of 93%, 87%, and 50%, respectively ($P < .01$). While 80% had squamous and 20% urothelial histology, the results were not different based on histology.[9] This trial helped to establish adjuvant RT as a standard therapy for locally advanced bladder cancer in Egypt, but the results were interpreted with some caution outside of Egypt and the Middle East, where urothelial carcinoma is the predominant histology.

INCIDENCE OF LOCOREGIONAL FAILURES

Interest in adjuvant RT was revived several years ago outside the Middle East as modern prospective cystectomy series reported that locoregional recurrences were more common for patients with locally advanced disease than was previously thought. In the SWOG 8710 trial of radical cystectomy with or without neoadjuvant methotrexate, vinblastine, Adriamycin, and cisplatin (MVAC), the 5-year cumulative incidence of LRF for patients with ≥pT3 urothelial carcinoma was 32%.[1] The 2011 update of the Medical Research Council (MRC) trial of neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy followed by cystectomy or definitive RT reported a 5-year locoregional recurrence rate of ~46% to 58% for cystectomy patients.[10] The University of Pennsylvania experience of 442 cystectomy patients who were followed with routine surveillance computed tomography (CT) or magnetic resonance imaging (MRI) every 6 months also demonstrated a high risk of locoregional recurrence for ≥pT3 patients with a 5-year cumulative incidence of 28%.[2] In PROMETRICS 2011, a cohort of prospectively followed European patients who underwent cystectomy in 2011, LRF was 15% to 39% for ≥pT3 patients.[11] Data from Korea[12] and Tata Memorial Hospital in India[4] also demonstrated high rates of local recurrence. A review of the literature demonstrates that local recurrence after radical cystectomy for locally advanced disease is relatively common, even in the modern era with chemotherapy.

RATIONALE FOR ADJUVANT RADIOTHERAPY

Adjuvant RT is a potentially attractive treatment option for patients with locally advanced disease because it can potentially prevent locoregional relapses, which can cause considerable mortality and morbidity.[13] Multiple cooperative group trials and large retrospective studies demonstrate that perioperative chemotherapy does not improve locoregional control in patients with locally advanced disease, including the SWOG 8710 study,[1,14,15] the MRC trial,[10] and the Penn experience.[1,2] Unfortunately, salvage therapy for locoregional recurrences after radical cystectomy is usually unsuccessful, with a median survival of 9 months after development of pelvic recurrence. Only 1 out of 80 patients with pelvic relapse survived at 5 years in the Penn series.[16] Salvage surgery is often precluded in these patients. Curative-intent salvage radiation is also difficult because of the radiosensitivity of the adjacent small bowel or neobladder, the absence of the native bladder to displace the bowel away from the radiation target(s), and the need for a dose >60 Gy (using standard fractionation), beyond the maximum tolerance of the small bowel (~54 Gy). A dose that would be effective and safe to eradicate microscopic residual disease in the adjuvant setting (~50 Gy in standard fractionation) is unlikely to eradicate gross disease in the salvage setting. We would argue that even if there were no measurable improvement in survival, adjuvant local therapy can potentially prevent the often substantial morbidity of pelvic recurrences,[17] which can cause obstruction of the ureters or bowel, pain, venous obstruction, and lower extremity edema. Improvements in radiation technique with the use of intensity-modulated radiation therapy (IMRT) and proton therapy offer the potential to reduce toxicity and limit radiation dose to the urinary diversion and bowel.[18,19]

There is some evidence that improving locoregional control may reduce distant disease spread and thereby improve survival.[20,21] Although there appears to be a clear rationale for adjuvant RT for locally advanced disease in combination with perioperative chemotherapy, clinical data on the utility of adjuvant RT in a majority patient population with urothelial carcinoma have been lacking, until recently.

STUDIES UTILIZING ADJUVANT RADIOTHERAPY FOR BLADDER CANCER

Several retrospective and prospective studies have been published in the past few years that demonstrate an oncologic benefit for adjuvant RT in a majority of patients with urothelial carcinoma. A 2019 study using the National Cancer Database found that adjuvant RT (n = 512) was associated with a statistically significant improvement in OS compared with no adjuvant RT in U.S. patients

with locally advanced disease, regardless of histology or receipt of chemotherapy. The results showed an improvement in OS in favor of adjuvant RT using both standard Cox multivariable analyses and propensity matching techniques.[22]

The Egyptian NCI undertook a series of randomized trials in patients with locally advanced disease who underwent radical cystectomy plus pelvic lymph node dissection with negative margins who had any of the following: pT3b/T4, pathologically node-positive, or grade 3 disease. The majority of patients had urothelial carcinoma. The initial trial was a phase III randomized trial of adjuvant RT versus sequential adjuvant chemotherapy plus RT,[6] with chemo + RT consisting of four cycles of "sandwich" chemotherapy with gemcitabine/cisplatin with adjuvant RT given after the second cycle to 45 Gy in 1.5 Gy twice-daily fractions to the cystectomy bed and pelvic nodes. Because of changes in the standard of care, a third arm of adjuvant chemotherapy alone (gemcitabine/cisplatin × 4 cycles) was added later as part of a randomized phase II clinical trial comparing adjuvant chemotherapy with or without RT.[6]

In the randomized phase II trial of 120 patients, adjuvant chemo + RT significantly improved locoregional control (the primary end point) versus adjuvant chemotherapy alone, regardless of histology, with a 2-year locoregional control of 96% versus 69% ($P < .01$).[6] OS and DFS were improved with the addition of RT, but the study was not powered for those end points, and the differences were not statistically significant (2-year DFS: 68% chemotherapy plus RT vs 56% chemotherapy alone; $P = .07$; 2-year OS: 71% chemotherapy plus RT vs 60% chemotherapy alone; $P = .11$). Adjuvant chemo + RT was reasonably well tolerated using three-dimensional (3D) conformal radiation techniques. The rate of late grade 3+ gastrointestinal (GI) toxicity was 6.7% for chemo + RT versus 2.2% for chemo alone.[6]

The results of the randomized phase II trial demonstrating a benefit for combined modality adjuvant therapy were also seen in a subgroup analysis of the original phase III trial of RT with or without chemotherapy ($N = 153$). Although there was no difference in the primary end point of DFS for the entire cohort for the RT versus chemo + RT arms, there was a statistically significant improvement in DFS and OS for chemo + RT versus RT alone in the urothelial carcinoma subgroup on the post hoc analysis (81 patients).[23] These findings showing an improvement with adjuvant chemotherapy for patients with urothelial carcinoma are notable because an improvement in OS has not been reported in the published clinical trials of adjuvant chemotherapy and suggests that there may be a role for adjuvant therapies to address the risk of both local and distant failure.[5] Several have theorized that previous trials of adjuvant chemotherapy may not have shown

a benefit in DFS or OS because those trials did not include adjuvant local therapy to address the high competing risk of locoregional relapse.

While the results of the randomized phase II trial and the post hoc analysis of the patients with urothelial carcinoma from the phase III trial both demonstrate that the combined modality adjuvant therapy appears to be the most effective approach, prospective data from the Egyptian NCI studies also support the use of adjuvant RT alone as an alternative to observation in patients with good performance status when adjuvant chemotherapy may not be appropriate or desired by either the patient or the clinical provider. In a post hoc analysis of 123 patients with locally advanced bladder cancer treated with adjuvant RT compared with adjuvant chemotherapy presented during the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting, Zaghloul et al found that there was no statistically significant difference in the 2-year DFS (54% for RT vs 47% for chemotherapy).[24] Local-regional control was significantly improved with RT, while distant disease was not significantly different. OS was comparable between the two cohorts. Subgroup analysis of the urothelial cohort (n = 63) reported similar findings. Based on these data, there was a greater than 90% probability that the true difference in 2-year DFS for RT versus chemo alone was less than 10%—the prespecified noninferiority margin.[24] The study was not designed as a noninferiority trial, so we cannot confirm the noninferiority of adjuvant RT versus adjuvant chemotherapy. However, results of the post hoc noninferiority assessment suggest a role for adjuvant RT in lieu of observation for patients with good performance status who decline systemic therapy or are medically unfit for systemic therapy.

In a post hoc subset analysis of the 77 patients with squamous cell carcinoma from the Egyptian NCI trial, adjuvant RT with or without chemotherapy was associated with significantly improved OS versus chemotherapy alone (71% vs 43%, $P < .05$).[25] These results suggest that adjuvant RT should be strongly considered for patients with locally advanced squamous cell carcinoma treated with radical cystectomy, especially as systemic therapy options have proven less effective for this patient population.[25,26]

These studies set the groundwork for later studies to identify the patients most likely to benefit from radiation, the patterns of recurrence in the pelvis to design radiation targets, and radiation treatment techniques.

IDENTIFYING PATIENTS MOST LIKELY TO BENEFIT FROM ADJUVANT RADIOTHERAPY

Several investigators have examined key questions that would be needed to design modern clinical trials of adjuvant RT for urothelial carcinoma. These include (1) identifying the patients at highest risk for locoregional recurrence who may benefit from radiation, (2) identifying the patterns of pelvic failure to inform design of radiation clinical target volumes (CTVs), and (3) assessing the optimal radiation technique for adjuvant RT.

Several researchers have developed risk stratification tools to identify patients at the highest risk for LRF.[7,27,28] Baumann et al developed a risk stratification model combining data from a cohort of 442 cystectomy patients who were followed with routine pelvic CT/MRI.[2] They combined this cohort with the SWOG 8710 prospective cohort of 317 patients with cT2-T4a disease randomized to receive cystectomy with or without neoadjuvant MVAC chemotherapy.[1,14,29] LRF was defined as any failure below the aortic bifurcation detected before or within 3 months of distant metastases. From the combined cohorts, a risk stratification model was developed using pathologic T-stage, number of nodes excised (<10 vs ≥10), and margin status using cumulative incidence and competing risk analysis.[1] Three patient subgroups were identified with significantly different LRF risk: low risk (≤pT2), intermediate risk (≥pT3 with negative margins and ≥10 nodes identified), and high risk (≥pT3 with positive margins OR ≥pT3 with <10 nodes identified) with the 5-year cumulative incidence of LRF of 8%, 20%, and 41% in the SWOG cohort and 8%, 19%, and 41% in the Penn cohort, respectively.[1,30] Froehner et al validated the model using a multinational, European prospective cohort of 565 patients (PROMETRICS 2011),[11,31] and Ku et al also validated the model in a retrospective cohort of 398 Korean patients.[12] These results suggest that the risk stratification is valid in U.S., European, and Korean patients. Baumann et al performed internal validation of the model, demonstrating that trial accrual bias or changes in surgical technique over time would not affect the overall model findings.[30] The Penn/SWOG risk stratification was revisited to see if a combination of clinical/pathologic and transcriptomic data could improve the risk stratification model using The Cancer Genome Atlas. Carmona et al reported that the addition of smoking status was found to improve the model but there were no transcriptomic genetic factors that improved the risk stratification.[32]

Reddy et al proposed an alternative to the Penn/SWOG risk stratification.[3] In their single-institution series, only the pT and pN stages were significant independent predictors of pelvic failure. The Reddy study did not use competing risk analytic techniques. In the Penn/SWOG analysis, pN status was significant when doing a standard Cox regression but was no longer significant when a

competing risk model was used. More recently, Murthy et al proposed an alternative risk stratification in patients treated with cystectomy with or without adjuvant chemotherapy based on the pT stage, pN stage, and lymphovascular invasion that stratifies patients into low-, intermediate-, and high-risk groups with a cumulative incidence of LRF of 7%, 22%, and 35%, respectively.[4]

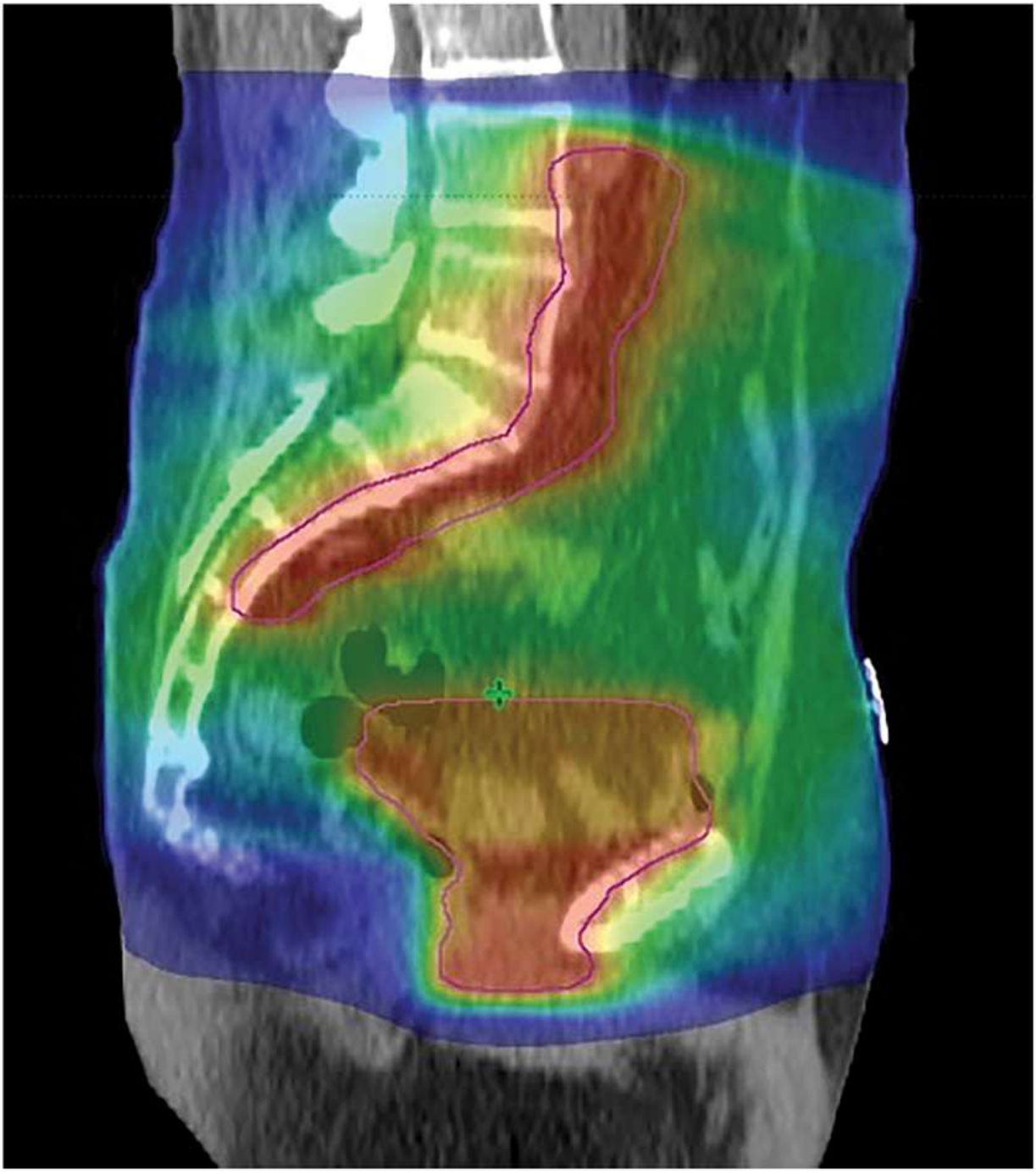
PATTERN OF RECURRENCE IN THE PELVIS

Mapping the patterns of failure in the pelvis to define appropriate RT targets is as important as identifying patients at increased risk for LRF. Baumann et al reviewed 5-year LRF rates after cystectomy for eight pelvic sites among 442 patients with urothelial carcinoma.[16] Patients with ≥pT3 disease had significantly higher LRF rates at nearly all pelvic sites compared to early-stage patients. Among stage ≥pT3 patients, margin status was the only factor that significantly altered the pattern of failure. In stage pT3 patients with negative margins, failures occurred primarily in the common iliac, obturator, and internal/external iliac nodes, with 5-year LRF rates of 9.7%, 8.8%, and 7.0%, respectively, while failure in the cystectomy bed and/or presacral nodes was uncommon (5-year LRF rates of 2% and 0.7%, respectively). For margin-negative patients, 76% of their sites of failure would have been encompassed within CTVs covering only the iliac/obturator nodes. For stage pT3 patients with positive margins, failures were most common in the pelvic sidewall nodal region, with 5-year LRF rates of 18.5%, 16.5%, and 9% for the external/internal iliac, obturator, and common iliac nodes, respectively, but the incidence of cystectomy bed and presacral nodal failures increased significantly (13.1% and 5.5%, respectively). Expanding the CTV to include the presacral and cystectomy bed regions increased the percentage of local failures encompassed to 91%. These data suggested that adjuvant RT protocols should target at least the obturator and iliac regions in stage pT3 patients with negative margins. Coverage of the presacral region and cystectomy bed was felt to be warranted for stage pT3 patients with positive surgical margins.[16] Reddy et al also showed that most failures occurred in the pelvic sidewall nodal regions with an increase in failures noted in the cystectomy bed and presacral region when the surgical margins were positive.[3]

The recent study by Murthy et al reported that the majority of failures occur in the pelvic lymph node regions, though they did report that 29% (9/31) had recurrence in the cystectomy bed despite negative surgical margins.[4] This study is important for raising awareness that cystectomy bed failures may be more common than previously reported, especially for those with particularly advanced local disease.

ADJUVANT RADIATION PLANNING AND DELIVERY TECHNIQUES

Early studies of adjuvant RT using 2D radiation treatment techniques were associated with relatively high rates of late GI toxicity.[8] A more precise identification of the organs at risk (OARs), combined with advances in radiation delivery modalities, such as 3D conformal RT, IMRT, and proton therapy, could potentially reduce GI toxicity and improve the therapeutic ratio of adjuvant RT. To date, one study has compared different radiation treatment modalities to assess the effect of each modality on bowel and rectal dose-treating CTVs that include the pelvic sidewall regions alone (for margin-negative patients) and the pelvic sidewall, presacral, and cystectomy bed regions (for margin-positive patients).[18] The study reported a dosimetric advantage for IMRT and pencil-beam scanned proton RT over 3D conformal radiation to improve rectal and bowel dose, with no significant difference between the proton and IMRT plans. Based on this dosimetric analysis, the ongoing trials at the GETUG-AFU and Tata Memorial Hospital and the prior NRG trial (NRG GU-001) require an IMRT approach.[7] A representative IMRT treatment plan is shown in Figure 70.1.



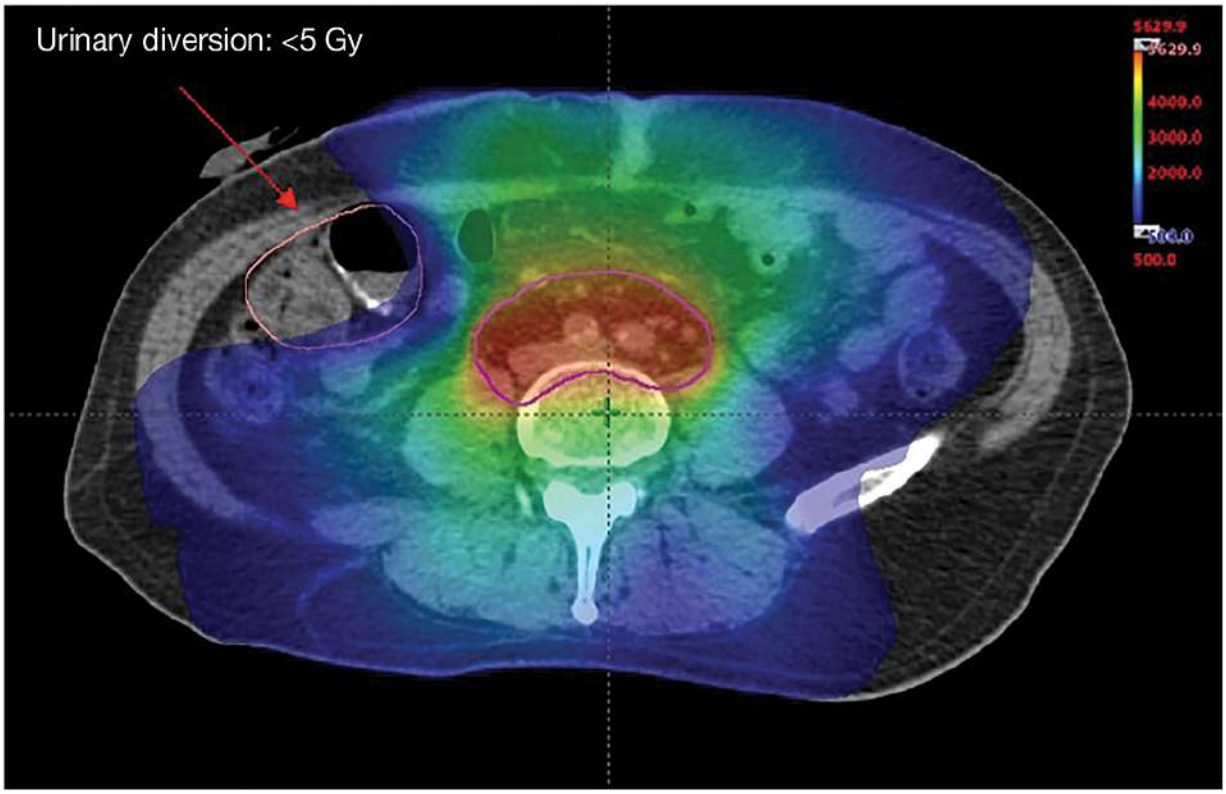


FIGURE 70.1 Pelvic nodes and cystectomy bed treated with intensity-modulated radiation therapy (IMRT). IMRT allows sparing of bowel and the urinary diversion (mean dose ≤5 Gy to the urinary diversion).

International consensus guidelines were developed for the CTVs and OARs for adjuvant RT, as these structures were not well defined in the literature.[33] Twenty-four radiation oncologists and urologists from 15 institutions and 5 countries participated in the study. The group proposed that patients at higher risk for LRF with negative margins should be treated to the pelvic nodes alone (internal/external iliac, distal common iliac, and presacral) whereas patients with positive margins should be treated to the pelvic nodes and cystectomy bed.[16,33] Proposed OARs included the rectum, bowel space, bone marrow, and urinary diversion. The area of greatest discussion in the development of the consensus contours was the cystectomy bed CTV (Table 70.1). Consensus language describing the CTVs and OARs was developed and externally validated, and the revised instructions were found to produce consistent contours.[33] The consensus contouring guidelines have been adopted for the NRG, GETUG-AFU, Tata Memorial Hospital, and the University of Ghent trials. External validation of this consensus contouring guidelines was published by researchers from the University of Chicago who recommended a slight increase in the superior border of the common iliac to cover the aortic bifurcation and a slight increase in the

medial coverage of the obturator nodal regions, based on their patterns of failure analysis.[34] Table 70.2 provides additional expert guidance on adjuvant RT treatment and planning.

TABLE 70.1 SUMMARY OF ANATOMIC BORDERS OF THE CYSTECTOMY BED CLINICAL TARGET VOLUME FROM NRG CONSENSUS CONTOURING GUIDELINES (AND CONFIRMED IN THE CONSENSUS CONTOURING GUIDELINES FROM THE IBIS GROUP)

Superior	The contour will extend 2 cm superior to the superior aspect of the pubic symphysis.
Anterior	The contour will extend to the posterior aspect of the pubic rami/symphysis. Above and below the pubic symphysis, the contour will stop anteriorly at the planes defined by extending lines superiorly and inferiorly from the posterior aspect of the symphysis.
Posterior	The contours will abut the anterior one-third of the external anorectal circumference without extending into the anorectum. Above the level of the rectum, the contour will stop posteriorly at the plane defined by extending a line superior from the anterior border of the rectum.
Lateral	The contour will extend to the medial border of the obturator internus muscles bilaterally. Inferior to the obturator internus muscles, the lateral border of the contour will extend to the vaginal wall or the prostate bed.
Inferior	The contour will stop 2-3 mm (1 axial CT slice) above the penile bulb for males and 1 cm below the lower pole of the obturator foramen for females.

CT, computed tomography.

TABLE 70.2 TIPS FOR RT PLANNING OF POSTOPERATIVE BLADDER CANCER

Topic	Commentary
Patient Selection	• Offer adjuvant RT for any of the following: pT3-4, positive margins, or pN+ disease, with strong consideration of adjuvant RT for positive margins and locally advanced squamous cell carcinoma • Presence of neobladder is not an absolute contraindication to adjuvant RT delivered with bowel-sparing IMRT technique.[35] • Postcystectomy cross-sectional imaging is recommended to rule out distant metastatic disease and to assess for gross nodal disease prior to initiation of adjuvant RT. • Gross nodes may be amenable to a boost dose depending on proximity of adjacent small bowel.
Simulation	• Intravenous contrast may be considered for ease of delineation but often not feasible due to renal insufficiency. • Oral contrast is preferable if individual bowel loops are to be delineated. • Stoma bag should be emptied prior to simulation. • Anticipate rectal distension postcystectomy and avoid aggressive use of laxatives, as distension is likely to persist through the duration of RT.

Topic	Commentary
	• Patients are typically treated 1.5-3 mo after cystectomy but can be treated up to 4 mo after cystectomy for patients treated with adjuvant chemotherapy.
Contouring	• Cystectomy bed should generally be included in target volume irrespective of margin status, especially for more advanced disease (decide on a case-by-case basis). • Cystectomy bed can be omitted for patients with neobladder who have negative surgical margins, though inclusion of the cystectomy bed in select cases is reasonable. • Cystectomy bed and nodal contour should not be carved out of the bowel loops, as variability in bowel position could lead to underdosing in this region. • While small-volume lymphoceles may be included within the pelvic nodal contour, larger ones may be partially excluded in node-negative patients. • Upper limit of nodal contour can extend to the aortic bifurcation to ensure coverage of the common iliac lymph nodes. • If the common iliac nodes are pathologically involved, upper limit of nodal contour may be extended 1-2 cm above the aortic bifurcation. • Entire bowel should be contoured as a single structure superiorly at least 3 cm above the target volume contour and inferiorly till the last visible bowel. • To identify and delineate ileal conduit, trace the ureter down from the renal pelvis. Discussion with a radiologist and intravenous contrast may help. • Delineate the stoma region as an avoidance structure to minimize RT dose.
Planning	• IMRT or proton therapy is strongly recommended. • Sparing of the stoma, ileal conduit, and neobladder should be prioritized during RT planning.
Treatment	• Stoma bag should be emptied before delivering each fraction. • Image guidance with daily CBCT is recommended for setup verification.

CBCT, cone-beam computed tomography; IMRT, intensity-modulated radiation therapy; RT, radiation therapy.

Adapted from Baumann BC, Zaghloul MS, Sargos P, Murthy V. Adjuvant and neoadjuvant radiation therapy for locally advanced bladder cancer. *Clin Oncol (R Coll Radiol)*. 2021;33(6):391-399. With permission.

While the NRG consensus contouring atlas favored omission of the cystectomy bed for patients with negative margins, it is reasonable to include the cystectomy bed for patients with margin-negative resections who are felt to be at higher risk for cystectomy bed failure (eg, pT3b-T4 or close margin). This line of thinking is based on the subsequent publication of the randomized Egyptian NCI trials, which included the cystectomy bed in the target volume for all patients and achieved excellent local control (2-year local control 92%-96%) with acceptable toxicity.[36] In addition, there are recent data from Tata Memorial Hospital showing

relatively high rates of local recurrence in the cystectomy bed despite negative margins, suggesting inclusion of the cystectomy bed.[4]

Updated international consensus contouring guidelines were recently published by the International Bladder Investigator Society (IBIS) group, an organization of radiation oncologists from the United States, Europe, Asia, and the Middle East with a focus on adjuvant radiation for bladder cancer. In these guidelines, the committee recommended adopting the NRG pelvic nodal contouring guidelines to determine the nodal contouring, which recommends inclusion of the full common iliac region (extending superiorly to the aortic bifurcation) with the modification that the standard 7-mm expansion of the vessels should not be cropped out of the bowel, as NRG had recommended for pelvic nodal radiation for prostate patients. Guidance on how to contour the cystectomy bed remained unchanged, but guidelines recommend including the cystectomy bed for all pT3-T4 or pN+ patients, regardless of margin status. Inclusion of the cystectomy bed can be omitted for patients with negative margins who have a neobladder.

The modern adjuvant trials have treated patients to 50 or 50.4 Gy in standard fractionation, with the Tata Memorial Hospital trial allowing a boost to 54 Gy. 50 Gy in standard fractionation has a similar biologically effective dose (BED) to the twice-daily dose/fractionation scheme used on the Egyptian NCI trials. National guidelines currently recommend 45 to 50.4 Gy in standard fractionation.

Modern series have reported favorable toxicity results using IMRT for adjuvant RT.[37] A retrospective study of 25 patients who underwent adjuvant RT to the pelvic nodes following radical cystectomy with neobladder diversion found that no patients had acute grade ≥3 GI toxicity, with one patient having grade 3 GU toxicity. There were no grade 2 or higher late GI and genitourinary side effects.[38]

LATEST STUDIES UTILIZING ADJUVANT RADIATION

There have been several recently reported trials using adjuvant RT (Table 70.3). A single-arm trial performed at Ghent University Hospital in Belgium was reported in 2022, in which 72 patients with high-risk disease after cystectomy were treated with adjuvant RT with IMRT to a dose of 50 Gy in 25 fractions.[39] Patients had to have pT3 disease with either fewer than 10 lymph nodes removed, pathologically involved nodes, or positive surgical margins. Patients were treated to the pelvic nodes with inclusion of the cystectomy bed for patients with positive margins. Five patients had acute grade ≥3 GI toxicity (7%). With a median follow-up of 18 months, the 2-year local relapse-free rate was 83% ± 5%. This trial showed several relapses in the cystectomy bed in patients where the

cystectomy bed was omitted from the CTV. Overall, local control was very good, and the treatments were well tolerated.

TABLE 70.3 SUMMARY OF KEY PUBLISHED STUDIES EVALUATING ADJUVANT RADIATION FOR BLADDER CANCER

Study Type	Selection Criteria	# of Patients	Adjuvant Tx Arms	Local-Regional Control (2-y)	Disease-Free Survival (2-y)	Overall Survival (2 y)	Comments
Randomized phase II[6]	pT3b/T4a or pN + w/neg margins	120	Chemo + RT vs chemo (gem/cis × 4)	96% vs 69% (*P* < .01)	68% vs 56% (*P* = .07)	71% vs 60% (*P* = .11)	Positive trial: Adding RT improved local control vs chemo alone
Prospective randomized[24]	Same as above	123	RT vs chemo (gem/cis × 4)	92% vs 69% (*P* < .01)	54% vs 47% (*P* = .63)	61% vs 60% (*P* = .83)	Adj RT comparable to adj chemo for DFS
NCDB[22]	pT3-4N0-N+	512 got RT	RT vs no RT	NA	NA	HR 0.87 *P* < .01	RT associated with improved OS
Prospective single arm[39]	pT3-4N0-N+	72	RT	83%	NA	52%	6% acute grade 3 GI toxicity
Prospective randomized arm[35]	pT3-4N0-N+	122	RT vs no RT	81% vs 71% (3-y), *P* < .01	59% vs 50% (3-y), NS	47% vs 44% (3-y), NS	Adj RT improved local control in urothelial patients

DFS, disease-free survival; GI, gastrointestinal; NA, not applicable; NCDB, National Cancer Database; NS, nonsignificant; OS, overall survival; RT, radiation therapy.

A recent randomized trial from Egypt was published in 2024 in which 122 patients with locally advanced urothelial bladder cancer after radical cystectomy with or without neoadjuvant chemotherapy were randomized to receive adjuvant RT to 50 Gy in 25 fractions to the pelvic nodes and cystectomy bed versus observation. Twenty-four patients in the adjuvant RT cohort and 30 patients in the

observation cohort received neoadjuvant chemo. The 3-year adjusted locoregional recurrence-free survival rate was improved in the adjuvant RT arm, measuring 81% (95% confidence interval [CI], 69%-94%) compared with 71% (95% CI, 60%-80%; P = .0457). Adjuvant RT significantly improved the locoregional relapse-free rate in the cystectomy bed and the pelvic sidewall (P = .016 and P = .001, respectively). The trial was not powered to show a benefit in DFS or OS, but results favored the adjuvant RT cohort.

The NRG Oncology opened a trial assessing adjuvant RT versus observation (NRG GU-001), but the trial closed due to poor accrual. Large trials are ongoing assessing observation versus adjuvant radiation, including the BART trial at Tata Memorial Hospital (NCT02951325) and the GETUG-AFU-30 cooperative group trial in France. The recently published data on adverse events from the BART trial from Tata Memorial Hospital adds important data on the safety and tolerability of adjuvant radiation (REF). This trial represents the largest randomized trial comparing adjuvant RT versus observation in urothelial carcinoma patients. The preliminary toxicity results from this trial add to the existing clinical trial data from Ghent University and the Egyptian NCI and provide additional reassurance that adjuvant RT with IMRT to the pelvic nodes and cystectomy bed can be achieved with relatively low marginal risk of acute or late grade ≥3 adverse events, even in a cohort where 90% received peri-operative chemotherapy. The study reported more acute grade 2 adverse events in the radiotherapy arm; however, there was no difference in acute grade 3 adverse events (1.6% for RT vs. 4.2% for observation). Late grade 3-4 adverse events were also comparable, 10.5 % for observation vs. 8.4% for radiation.[45]

PREOPERATIVE RADIATION THERAPY

Preoperative RT for bladder cancer was explored in the 1970s and 1980s, with six clinical trials assessing preoperative RT versus cystectomy alone. Five of six trials were negative,[40-44] but the trial by Awwad et al reported improved 2-year DFS and, unlike the other trials, was limited to patients with locally advanced disease (cT3-T4 disease).[46] A meta-analysis of the preoperative RT studies showed no benefit.[47] These early studies of preoperative RT were limited by poor patient selection, with inclusion of early-stage patients unlikely to benefit from preoperative RT, and the higher toxicity of radiation in the 2D treatment era. As postoperative RT has gained traction, preoperative RT is being reconsidered by some, as improvements in preoperative imaging, radiomics, and the emergence of genomic biomarker testing allow us to better select patients who might benefit from preoperative RT.[48] Preoperative RT has several theoretical advantages over

postoperative RT, including the ability to improve the likelihood of an R0 resection, smaller radiation target volumes and less irradiated normal bowel, and enhanced tumor oxygenation in the preoperative setting that improves the effectiveness of RT. Preoperative RT is the preferred approach for other pelvic malignancies (eg, rectal cancer) where pre-op and post-op RT have been compared in a randomized trial.[49] The currently accruing RACE IT trial is a single-arm study exploring preoperative RT with immunotherapy (NCT03529890).

ADJUVANT IMMUNOTHERAPY

The role of adjuvant RT has come into question based on the results of the CHECKMATE 274 randomized trial that found a statistically significant improvement in DFS with the use of adjuvant nivolumab versus observation for patients with locally advanced disease.[50] A clinical trial of adjuvant atezolizumab was negative, though in the subgroup with detectable circulating tumor DNA levels prior to adjuvant therapy, adjuvant immunotherapy did improve DFS and OS.[51,52]

To the best of our knowledge, studies of immunotherapy have not separately reported rates of LRF, so it is unclear to what extent immunotherapy impacts on rates of LRF versus distant failure.

In small case series, adjuvant RT can be safely combined with immunotherapy, though phase I trial data are currently lacking. There is ample data on the safety of immunotherapy in combination with higher dose definitive radiation for bladder cancer. The initial toxicity results of the SWOG/NRG 1806 trial demonstrated favorable acute toxicity for patients treated with concurrent chemo + RT plus atezolizumab with intact bladders to a dose of ~64 Gy in standard fractionation.[53] Most of these patients were treated to the elective nodes. While the nodal targets are larger for adjuvant radiation than the more limited small pelvic nodal fields that many use for definitive bladder chemo + RT, the absence of concurrent chemotherapy and the overall lower radiation dose points to treatment that is likely to be reasonably well tolerated in appropriately selected patients.

In our opinion, adjuvant RT can be considered in patients who are also being treated with adjuvant immunotherapy. In the AMBASSADOR trial randomizing patients to observation vs. adjuvant pembrolizumab, adjuvant radiation therapy was allowed but had to be performed prior to initiation of pembrolizumab. In general, we would recommend treating with adjuvant radiation before initiation of immunotherapy as per the AMBASSADOR trial, since immunotherapy

continues for approximately 1 year.[54] For patients who start immunotherapy first, it may be prudent to hold immunotherapy while adjuvant RT is being delivered due to the absence of phase I trial data confirming the safety of combined modality treatment in the adjuvant setting. If the two treatments are given concurrently, tolerance to immunotherapy with respect to GI side effects should be confirmed prior to initiation of adjuvant RT, which has the potential to exacerbate immunotherapy-related side effects.

An upcoming American Society for Radiation Oncology (ASTRO) consensus project will address many of these questions.

CONCLUSIONS AND ONGOING STUDIES OF ADJUVANT RADIATION

The Egyptian NCI trials demonstrate that adjuvant RT significantly improves locoregional control and suggest that this improvement in locoregional control may translate to a benefit in survival, a benefit in OS that was seen in a larger retrospective cohort using the National Cancer Database.[22] Given the considerable morbidity and mortality of LRFs, which are rarely salvageable, reducing the risk of local recurrences is an important goal even if such a reduction does not translate to an improvement in survival outcomes, provided the treatment is well tolerated.[7] Adjuvant RT using older 3D conformal RT techniques was well tolerated in the clinical trial, with low rates of late GI complications.[6] Toxicity is expected to be even lower with the use of modern IMRT or proton therapy.[18,19,38]

Based on the existing literature, national cancer guidelines now include adjuvant RT as an option to consider along with adjuvant chemotherapy in patients with ≥pT3 disease or pN+. Adjuvant RT should strongly be considered for patients with positive surgical margins given the very high risk of LRFs[22] and those with locally advanced squamous cell carcinoma, as adjuvant RT with or without chemotherapy was associated with significantly improved OS compared with chemotherapy alone in a post hoc analysis from the Egyptian NCI trial.[25] Patients with locally advanced disease who are not eligible or refused systemic chemotherapy also warrant special consideration for adjuvant RT.[24]

Additional prospective trial data are needed to better define the role of adjuvant RT in the treatment of urothelial carcinoma. Clinical trials are ongoing, and accrual to these trials is very important. The GETUG-AFU 30 (Bladder-ART) cooperative group trial in France is actively accruing, randomizing patients to adjuvant RT versus observation. A similar randomized trial completed accrual recently but oncologic outcomes have not been published yet. at Tata Memorial Hospital (BART) (Table 70.4). These studies will contribute important data that

will help us better understand the role of RT in locally advanced bladder cancer. The IBIS group is planning a meta-analysis to pool the data from the GETUG, Egyptian, and Tata Memorial Hospital trials.

TABLE 70.4 ADJUVANT RADIOTHERAPY FOR BLADDER CANCER IN CONTEMPORARY TRIALS

Trial	Design	Patients	RT Technique and Dose	RT Volume	Status
Nonrandomized Trials					
Bladder-Aid Istituto Clinico Humanitas Rozzano, Milan, Italy NCT03718741	Phase II *n* = 80	Any of: ≥pT3/≥pN/≥R1	IMRT 50 Gy/25 fx SIB 55 Gy/25 fx to bed if R+	Cystectomy bed (+residual tumor if any) + pelvic nodes	Closed early due to poor accrual
Adjuvant Radiotherapy After Cystectomy for Muscle Invasive Bladder Cancer Ghent University, Belgium NCT02397434	Phase II *n* = 76	Any of: ≥pT3 + LVI/pT4/pN+/R+/<10 LN removed	IMRT 50 Gy/25 fx SIB 64 Gy to positive nodes	Pelvic nodes Cystectomy bed only if R+	Completed accrual and reported
Adjuvant Radiation for High-Risk Bladder Cancer Emory University, Atlanta, Georgia NCT01954173	Phase II *n* = 41	Any of: ≥cT3a/cN+/≥pT3a/pN+	3DCRT or IMRT 50.4 Gy/28 fx Sequential boost to 55.8 Gy if R+	Cystectomy bed + pelvic nodes	Recently closed (20 enrolled)
Randomized Trials					
El-Monim et al., NCI-Cairo, Egypt	Phase II *n* = 100	T3-T4 90% N+: 20%	2DRT, 3-4 fields 50 Gy/25 fx	Pelvic nodes to L5-S1 junction	Results published
Zaghloul et al, NCI-Cairo, Egypt NCT01734798	Phase II-III *n* = 198	R0 resection with ≥pT3b/grade 3/pN+ Neobladder excluded	3-Field 3DCRT 45 Gy/30 fx twice daily	Cystectomy bed + pelvic nodes (to upper	Results published

Trial	Design	Patients	RT Technique and Dose	RT Volume	Status
				border of S1 or S2)	
NRG-GU001 NRG Oncology NCT02316548	Phase III *n* = 185	Any of: ≥pT3/pN+/R+/<10 LN removed	IMRT 50.4 Gy/28 fx	Pelvic nodes to L5-S1 junction Cystectomy bed only if R+	Closed due to slow accrual
BART Tata Memorial Centre, Mumbai, India NCT02951325 PI: Vedang Murthy Multicentric	Phase III *n* = 153	Any of: ≥pT3/pN+/R+/<10 LN removed/Neoadj chemo for cT3-T4, cN1-3	IMRT 50.4 Gy/28 fx SIB 54-56 Gy to bed if R+	Cystectomy bed + pelvic nodes (till aortic bifurcation)	Completed accrual with initial toxicity results reported
Egyptian NCI, Cairo NCT04740866	Phase III *n* = 100	R0 resection Any of: ≥pT3/pN+/G3 ± Neoadj chemo	IMRT 50 Gy/25 fx	Cystectomy bed + pelvic nodes (till common iliac bifurcation)	Results published
GETUG-AFU 30 (Bladder-ART) UNICANCER (27 locations in France) NCT03333356	Phase II *n* = 109	Any of: ≥pT3/pN1-2/R+ Neobladder excluded when positive margins	IMRT 50.4 Gy/28 fx	Pelvic nodes to L5-S1 junction Cystectomy bed only if R+	Recruiting

IMRT, intensity-modulated radiation therapy; LN, lymph node; RT, radiation therapy; SIB, simultaneous integrated boost; 3DCRT, three-dimensional conformal radiation therapy.

Adapted from Baumann BC, Zaghloul MS, Sargos P, Murthy V. Adjuvant and neoadjuvant radiation therapy for locally advanced bladder cancer. *Clin Oncol (R Coll Radiol)*. 2021;33(6):391-399. With permission.

Future efforts should examine the role of adjuvant RT in combination with immunotherapy and chemotherapy, as there may be a synergistic effect with radiation and certain immune therapies. These combinations are currently being investigated for patients undergoing definitive chemoradiation for bladder cancer (SWOG 1806 and KEYNOTE-992). While the IMvigor010 phase III trial (NCT02450331) of adjuvant atezolizumab versus observation after radical cystectomy was negative for the primary end point of DFS,[55] the phase III

Checkmate-274 trial randomizing patients to nivolumab versus observation met its primary end point of DFS in an interim analysis.[56] Evaluating the role of adjuvant RT in the setting of immunotherapy offers an exciting opportunity to improve outcomes.

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CHAPTER 71

Bladder Cancer

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Since the publication of the seventh edition of this textbook, there have been many exciting developments in the field of bladder cancer (BC) management. The treatment landscape for non–muscle-invasive bladder cancer (NMIBC), previously referred to as "superficial" BC (an imprecise term to be avoided), is rapidly changing. Although the mainstay of treatment is typically transurethral resection followed by intravesical therapy, depending on the grade of disease, novel treatment approaches are being explored, particularly for patients with bacillus Calmette-Guérin (BCG) unresponsive or refractory disease.[1,2] In addition, a randomized phase II trial (NRG/RTOG 0926) evaluating the utility of radiation therapy (RT) in this space demonstrated encouraging outcomes in patients unwilling or unfit for cystectomy (NCT00981656).[3] Targeted therapies will continue to evolve in this space as more molecular-level information is understood about NMIBC.

For muscle-invasive bladder cancer (MIBC), the traditional view of cystectomy as the only gold standard treatment option is evolving. Recent studies demonstrate comparable long-term survival rates and cancer outcomes between surgery and radiation-based approaches.[4-8] Functionally, patients do well after radiation-based therapy for MIBC[9] with low rates of significant long-term toxicity.[10,11] These, and other data, have led to the incorporation of RT for MIBC as a category 1 recommendation per national cancer guidelines. The generally widespread acceptance of RT as a reasonable treatment option for MIBC is evidenced by the recently completed accrual of the SWOG/NRG 1806 (NCT03775265) trial, the largest completed randomized, phase III trial to date of bladder-sparing chemoradiotherapy (chemoRT). With 485 patients accrued, this trial evaluates the addition of atezolizumab, an immune checkpoint inhibitor, to the standard-of-care chemoradiation treatment. Other advances in the field of radiation include the incorporation of hypofractionated regimens to shorten treatment courses[12] and adaptive RT to decrease toxicity,[13] as well as further understanding of biomarkers for improved patient selection.[14-17]

This chapter outlines the evidence base for the current therapeutic approaches to BC and highlights many exciting advances in the treatment of both NMIBC and MIBC, specifically the improved personalization of therapy as more trials are performed in this disease space.

ANATOMY

The bladder is a hollow, muscular organ situated in the pelvis when empty but able to extend up into the abdomen when full, particularly in situations where bladder emptying is impeded.

The bladder is described as having an apex, a superior surface, two inferolateral surfaces, a base or posterior surface, a trigone, and a neck. The apex reaches a short distance cephalad above the pubic bone and ends as a fibrous cord, the remnant of the fetal urachus, which connects the bladder to the allantois. The urachus lies anterior to the peritoneal cavity and is important as tumors can arise in the urachal remnant. The superior surface is covered by the peritoneum, again an important anatomic feature, as it means that there is a bowel lying superiorly to the bladder. This is a critical site to consider when planning RT. In women, it is associated with the uterus and ileum. The base of the bladder is posterior and is separated from the rectum by the vas deferens, seminal vesicles,

and ureters in the male and by the uterus and vagina in the female. The ureters typically enter into the bladder slightly superior and lateral to the seminal vesicles in men; therefore, enlarging tumors either at the base or in the prostate can involve the ureters with consequent hydronephrosis. Inferiorly and laterally to the bladder lie the various pelvic bones and muscles: pubis, the levator ani, and obturator internus muscles. Within the pelvis, the lateral parts of the bladder are surrounded by loose connective tissue. Anteriorly, the bladder is separated from the pubic bone by the retropubic space. The inferior part of the bladder is described as the neck and is in continuity with the urethra and the prostate gland in males. The superior portions distend and expand upward as the bladder fills, while the neck of the bladder is typically more closely anchored to the pelvis.

The mucosal lining of the bladder comprises a transitional epithelium that extends from the renal pelvis to the urethra. The most common tumors arising in the urinary system are urothelial carcinomas (UCs), historically known as transition cell carcinomas.[18] These tumors can arise from anywhere within the urothelium, so diagnosis, treatment, and surveillance protocols must take into account of this important biologic feature. As a distendable organ, the macroscopic appearance of the urothelium varies with distension from smooth and flat to folded when empty. A ridge called the interureteral fold lies between the ureteric orifices.

EPIDEMIOLOGY

The incidence of BC is increasing worldwide, with 613,791 cases diagnosed in 2022 based on data from GLOBOCAN.[19] BC is a major cause of cancer morbidity and leads to 220,349 deaths worldwide. The median age at diagnosis is above 70 years, and as the tumor is often smoking-related, many patients have significant comorbidity, posing risks for radical surgical approaches. Survival rates are poor, with around 45% of patients with muscle-invasive cancer surviving 5 years irrespective of treatment modality.[6,7,20] Overall, around 75% to 80% of patients with BC are male, mostly reflecting historic trends in cigarette smoking.

There are well-known associations of squamous cell carcinomas (SCC) of the bladder with bilharzia caused by *Schistosoma haematobium* infection in Africa, particularly in Egypt.[21] Aromatic amines, polycyclic aromatic and chlorinated hydrocarbons, arsenic-laced drinking water, aristolochic acid, cyclophosphamide exposure, and a range of industrial chemicals have been implicated in urothelial carcinogenesis. Importantly, as with most carcinogens, there are variations in individual susceptibility, and the basis of some of these polymorphisms regulating varied detoxification mechanisms has been identified.[22] With increasing awareness of these industrial associations, regulation of these processes means that these cases are becoming increasingly rare in the developed world. In Egypt, there have been successful public health approaches to the control of *S. haematobium* infections, leading to a substantial decline in incidence and mortality from squamous carcinomas of the bladder.[23]

Within the developed world, most bladder tumors are now UCs, and the main known causative factor is tobacco (particularly cigarette) smoking,[24-29] explaining approximately half of the cases in men and one-third of the cases in women in Europe.

NATURAL HISTORY

Non–Muscle-Invasive Bladder Cancer

Most cases (70%-80%) present with NMIBC (stage Ta, T1, and carcinoma in situ [CIS; Tis]), which is rarely lethal, but shows a high recurrence rate of 50% to 70% after treatment by transurethral resection of bladder tumor (TURBT).[30] In about 10% to 20% of patients with NMIBC,

the disease progresses to muscle invasion (≥T2 lesions), which can lead to metastasis and death.[30] However, the majority of patients with NMIBC will die of other causes, given the typically advanced age at presentation and the strong association with cigarette smoking,[24-29] although it is worth noting that up to 21% of patients with Ta tumors and 49% of patients with T1 tumors will die from BC.[31] For patients with NMIBC, it has been observed that tumor grade and stage, and also tumor number, size, presence of CIS, recurrence rate, and age at diagnosis are risk factors of progression.[32-34] The risk of both recurrence and progression necessitates lifelong follow-up for patients with bladder tumors with cystoscopies.

Muscle-Invasive Disease

MIBC has a poorer prognosis because of a very high rate of occult metastatic disease at the time of diagnosis. Evidence for this comes from the high rate of death from metastasis after apparently successful surgery.[35] Furthermore, reported 5-year cancer-specific survival (CSS) rates with RT or surgery are remarkably similar at around 80% to 85% in modern series for well-selected candidates (tumors <7 cm, no or unilateral hydronephrosis, and no extensive multifocal CIS),[8] suggesting that prognosis is driven by the presence, or otherwise, of metastases at the time of diagnosis, driven by tumor-related factors such as stage and grade.

Metastatic Disease

A minority of patients (<10%)[36] present with metastatic disease, carrying a poor prognosis. Treatment intent for patients is generally palliative, but the goal of therapy is to control tumor burden, treat cancer-related symptoms, and improve survival. Historically, for patients fit for chemotherapy, extensive randomized studies carried out in the 1980s and 1990s demonstrated the superiority of cisplatin-based combination chemotherapy over those containing other drugs or cisplatin alone. Of the platinum-based combinations, methotrexate/ vinblastine/doxorubicin (adriamycin)/cisplatin (MVAC)[37] and gemcitabine/cisplatin (GC)[38] have proven to be superior to other combinations and broadly similar in efficacy to each other[39,40] (as reviewed by Hussain and James).[41] Median survival is 12 to 18 months, depending on the extent of disease and fitness of the patient. Intriguingly, however, a small minority of patients do appear to survive long term after chemotherapy for metastatic disease, but this percentage has sadly proved very hard to increase from that originally observed in the MVAC trials.

However, newer systemic agents have proved superior to some of the traditional combination platinum-based chemotherapy. Enfortumab vedotin (EV) is an antibody targeting the cell adhesion molecule nectin-4 linked to a microtubule inhibitor conjugate. In combination with immune checkpoint inhibitor pembrolizumab, data demonstrate superiority of this regimen over standard platinum-based combination chemotherapy.[42] Thus, initial therapy is now recommended to be EV plus pembrolizumab for patients with untreated metastatic UC. This is based on the recent phase III trial, which found that overall survival (OS) was improved (median 32 vs 16 months, hazard ratio [HR] 0.47, 95% confidence interval [CI] 0.38-0.58) as well as progression-free survival (PFS) (median 13 vs 6 months, HR 0.45, 95% CI 0.38-0.54) with EV/pembrolizumab compared to standard chemotherapy. Further details on optimal systemic therapy approaches are evolving rapidly and outside the scope of this chapter.

ETIOLOGY

The link between occupational exposure and an increased risk of UC of the bladder was established more than a century ago when Rehn[43] reported on three cases of BC in a German chemical dye works in 1895. During the following 40 years, similar reports appeared from around the world. In 1938, Hueper et al[44] demonstrated that when naphthylamine, an industrial arylamine used in the synthetic dye industry, was fed to dogs, it caused BCs identical to the human disease. The link between industrial arylamines and BC was thus established and later confirmed by Case et al[45] in 1954. These authors also identified an excess of BC in the tire industry, attributable to the use of 2-naphthylamine in the manufacture of rubber.[45] Around this time, the "o-aminophenol hypothesis" of arylamine-induced human BC was proposed, suggesting that conjugation of aromatic amines by the liver and excretion in the urine with subsequent urinary reactions would liberate the carcinogen o-aminophenol.[46] Other workers later added to this hypothesis: Arylamines are hydroxylated in the liver and conjugated with glucuronic acid, followed by excretion into urine and reliberalization of the active carcinogenic metabolite into the bladder lumen by urinary glucuronidases.[44,47,48] Slow acetylation by *N*-acetyltransferase, an enzyme involved in the metabolism of arylamines, has been shown to be a contributory risk factor for bladder carcinogenesis.[25,49,50]

Because of the widespread use of arylamines in textile dyes, hair dyes, and paint pigments, a number of high-risk occupations have been identified, including chemical, dye, textile, and rubber workers and painters and hairstylists.[29,51-53] In addition, the presence of various arylamines in tobacco smoke means that a significant proportion of BC cases can be attributed to cigarette smoking.[25,26,28,29] In fact, abandonment of the manufacture of many of these arylamines in the latter half of the 20th century means that smoking is currently the single most important cause of UC.[24,54-56] Tobacco (particularly cigarette) smoking explained approximately half of BC cases in men and two-fifths of cases in women in the United States in 2014.[19,57] It has been demonstrated that an increased smoking frequency and duration and a lower age at initiation are associated with an increased risk of BC, whereas cessation seems to reduce the risk.[54] The relation between smoking and other prognostic factors is interesting, as it could give insight into biologic mechanisms of disease and, perhaps more importantly, have clinical implications by increasing the ability to identify patients at risk of more malignant disease. Cigarette smoking also appears to be a risk factor for disease recurrence following a diagnosis of bladder UC.[54,58]

Studies also demonstrate a relation between *N*-acetyltransferase-2 slow acetylators and cigarette smoking, resulting in a further increase in the risk of BC, especially in those individuals with a high smoking intensity.[59-61] A similar relation has also been demonstrated with arylamine exposure.[62,63] A number of other susceptibility loci have also been identified, although such markers do not yet have sufficient discriminatory ability to be utilized for risk prediction in the general population or for prediction or prognostication in patients diagnosed with BC.[61,64]

CHRONIC INFLAMMATION AND BLADDER CANCER

Squamous metaplasia is considered a precursor of SCC of the bladder and is a relatively common occurrence, especially on the trigone of the female bladder where a prevalence of up to 50% is reported.[65] Experimental evidence suggests that this does not occur by direct transformation of the superficial apical umbrella cells of the urothelium or by their dedifferentiation and redifferentiation; it is postulated that basal cells (probable stem cells) are selectively activated.[65] The normal urothelium is slowly proliferating, but urothelium undergoing squamous metaplasia becomes hyperplastic, and it may be that the hyperplasia component of urothelial squamous metaplasia is a major contributor to an enhanced risk of cancer formation.

SCC and adenocarcinoma of the bladder often occur in the presence of chronic inflammation. In Africa and the Middle East, where these tumors are much more prevalent, the chronic inflammation occurs as a result of infestation with the parasite *S. haematobium* (bilharziasis), with a BC incidence of 2 to 4 per 100,000 in *S. haematobium* endemic areas.[66-69] This infestation can lead to malignancy through local tissue damage, mechanical irritation, bilharzial toxins, secondary bacterial infection, and the production of nitrosamines.[70,71] With liver involvement and subsequent liver dysfunction, tryptophan metabolism may be disturbed, resulting in excretion of carcinogenic metabolites.[70] In *S. haematobium*–infected individuals, the prevalence of squamous metaplasia rises significantly during the first 10 to 15 years of life, with a plateau at roughly constant levels thereafter (30%-40% in males and 40%-50% in females) when the active infection may have subsided.[68] It is suggested that proliferative changes in the bladder urothelium may become independent of ongoing infection after long periods of chronic *S. haematobium*–induced inflammation.[70,72] Severe metaplasia of the bladder may represent a precancerous transformation in some individuals, but in others, it may only represent a marker for the prolonged inflammation that is associated with a high cancer risk.[70] This sort of proliferative growth combined with the increased excretion or local formation of mutagens in the *S. haematobium*–inflamed bladder may significantly contribute to the onset of cancer formation, possibly involving mutations of the *p53* and *CDKN2* tumor suppressor genes.[70]

In Europe and North America, the stimulus of chronic bladder inflammation is usually chronic bacterial infection, bladder calculi, or long-term indwelling catheters.[73-76] A number of metaplastic conditions (squamous metaplasia, von Brunn nests, cystitis cystica, and cystitis glandularis) may occur prior to frank malignant change, although the premalignant nature of some of these lesions is still unclear.[73-82]

Molecular Basis of Multifocality of Urothelial Carcinoma

UC is a multifocal disease, characterized by the high frequency of synchronous and metachronous primary cancers. These tumors can occur anywhere in the urinary tract, from the renal pelvis to the urethra. The multifocality can be explained by two potential theories. The first is the "field characterization effect," suggesting that the whole urothelium is exposed to the same urinary carcinogens, leading to the transformation of many independent separate urothelial cells and resulting in multiple tumors developing independently in multiple sites. These multiple tumors are thus genetically unrelated.[83] A separate theory postulates that the multifocality of UC arises because of a single carcinogenic insult to a single cell or group of cells. The progeny or clones of these cells spread throughout the urinary tract, either through intraepithelial migration or through cell shedding and reimplantation, leading to multiple synchronous and metachronous tumors.[84] These tumors are thus topographically distinct but are genetically related. Molecular studies now demonstrate that UCs present as a heterogeneous group of tumors, and these may evolve along two different pathways with distinct biologic behavior. Papillary, low-grade, noninvasive tumors are thought to arise from urothelial hyperplasia/papillomas and are often multifocal with high recurrence rate. MIBC arise through sequences of events starting from normal to dysplasia, CIS and then invasion. T1 high-grade tumors are more complex, with overlapping molecular features between the abovementioned two groups.[85] Further work into the molecular basis of UC is ongoing, particularly with the discovery of cancer stem cells (discussed in further detail later), which add a new dimension for occurrence of multifocality and recurrence of UCs.

Molecular Classification of Urothelial Carcinoma

In 2014, the Cancer Genome Atlas Research Network reported an integrated analysis of 131 UCs to provide a comprehensive landscape of UC alterations.[86] This was updated in 2017, with 412 tumors.[87] These and other studies have allowed us to further classify bladder tumor–based molecular alterations. For example, low-grade pTa tumors frequently demonstrate FGFR3 mutation and infrequent p53 mutation.[88] However, muscle-invasive tumors demonstrate complex chromosomal changes with frequent TP53 mutation and rare FGFR3 mutation. In addition, the overall mutational load observed with MIBC associates with APOBEC signature mutagenesis. Knowles et al[89] demonstrated that deletions of chromosome 9 occur in over half of bladder tumors of all grades and stages (9p, 51%; 9q, 57%). Loss of heterozygosity also occurs on 17p (32%), 11p (32%), 8p (23%), 4p (22%), and 13q (15%), and loss of heterozygosity of 5p, 8p, and 21q is significantly associated with worse grade and stage.[89] Genomic copy number alterations are also frequent in bladder UC, with the most frequent changes involving complete or partial loss of 4q (83%) and gain of 20q (78%).[88] Other frequent losses are of 18q (65%), 8p (65%), 2q (61%), 6q (61%), 3p (56%), 13q (56%), 4p (52%), 6p (52%), 10p (52%), 10q (52%), and 5p (43%).[88]

Gene expression profiling has been found to play a large role to further subclassify BC into clinically relevant subtypes. The Bladder Cancer Molecular Taxonomy Group has identified a set of six molecular classes of MIBC: luminal papillary, luminal- nonspecified, luminal-unstable, stroma-rich, basal/squamous, and neuroendocrine-like.[90] Additional work is ongoing to classify subtypes with reduced gene sets, which can potentially further inform future trials and personalized therapies.

Pathways to Muscle-Invasive and Non–Muscle-Invasive Bladder Cancer

Several different approaches can be taken to describe the molecular alterations involved in bladder urothelial tumorigenesis. Prior descriptions[91,92] exist in detail based on the six original "hallmarks of cancer" described by Hanahan and Weinberg[93] in 2000. In 2011, Hanahan and Weinberg[94] updated their original landmark review, describing genome instability and inflammation as underlying these hallmark changes and proposed "reprogramming of energy metabolism" and "evading immune destruction" as two emerging hallmarks with potential for generality. In addition, they reported that tumors exhibit another dimension of complexity by containing a repertoire of recruited, ostensibly normal cells that contribute to the acquisition of hallmark traits by creating the "tumor microenvironment." The timing and sequence of hallmark events can vary widely between tumors of the same type and within the same tumor, but ultimately, these hallmark capabilities of cancer will be reached. In their 2011 update, Hanahan and Weinberg[94] also introduce the concept of "cancer stem cells," a concept that has existed for quite some time for hematopoietic malignancies.[95] Cancer stem cells are a subset of tumor cells that have the ability to self-renew and to generate all of the heterogeneous cells that comprise a tumor (properties that are analogous to a stem cell, the original cell of an organ, and responsible for organogenesis and organ maintenance).[96] It is proposed that these cells are responsible for tumorigenesis, tumor differentiation, tumor maintenance, tumor spread, and tumor relapse.[97] In the setting of BC, cancer stem cells appear to play a role in a subset of tumors, but their true significance has yet to be clarified.[98,99]

Several other authors have also reviewed this field in detail,[100-107] and there is general consensus on a divergent pathway for the development of Ta/T1 disease and Tcis/T2+ disease (Figure 71.1)[107-112] (Leeds, UK). In their 2010 review, Goebell and Knowles[100] propose a third hypothetical pathway for the development of high-grade papillary tumors. Significant contributions to work in this field have been made by Knowles and colleagues.[101-107]

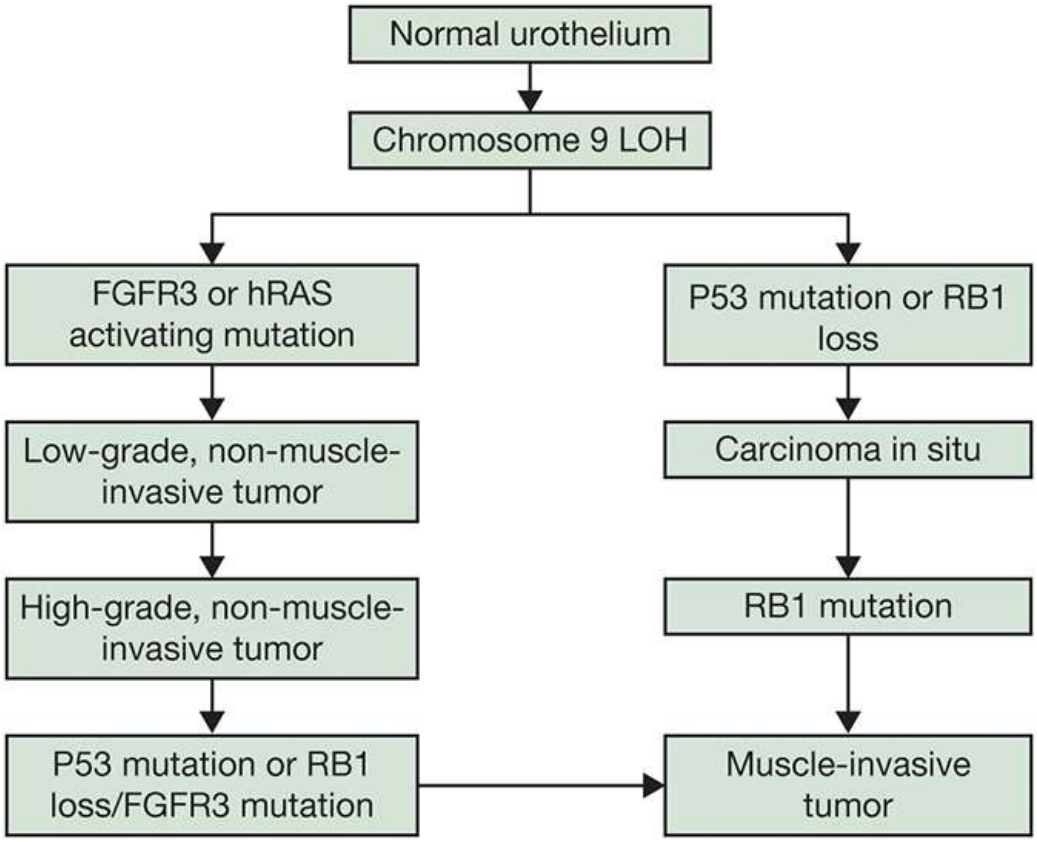

FIGURE 71.1 Pathways to the development of bladder cancer. LOH, loss of heterozygosity. (Adapted from Pollard C, Smith SC, Theodorescu D. Molecular genesis of non-muscle-invasive urothelial carcinoma (NMIUC). *Expert Rev Mol Med*. 2010;12:e10. Copyright © 2010 Cambridge University Press. Reproduced with permission.)

A detailed examination of these pathways and related biomarkers is beyond the scope of this chapter. In addition, this is a rapidly changing field, and new developments appear frequently with the advent of high-throughput experimental platforms, including "deep sequencing,"[87,113,114] proteomics,[115] and metabolomics,[116] so readers are directed to the reviews cited earlier or to the latest work in this field.

SIGNS AND SYMPTOMS

The classic presentation for BC includes painless, visible hematuria; however, irritative voiding symptoms (dysuria, lower urinary tract symptoms) can also be the presenting symptom. As hematuria is typically transient and urinary tract symptoms can often be attributed to the prostate (in men), or urinary tract infections (in women), patients often go undiagnosed for considerable periods, and it is known that delays in diagnosis lead to worsened prognosis.[117] Evidence suggests that poorer survival in women with BC is associated with delayed diagnosis compared to men.[118] Hematuria from BC is more likely to be misinterpreted in women of child-bearing age, given the association of blood in urine when women are menstruating. However, given the intermittent nature of the hematuria associated with BC, patients presenting with a convincing episode of hematuria require urgent assessment.

DIAGNOSIS

In developed countries, most patients will be referred for evaluation because of hematuria or suspected BC. A minority may present via other routes (eg, with metastatic symptoms). Workup for suspicion of BC generally includes a clinical assessment, urinalysis, complete blood count and metabolic profile, prostate-specific antigen (if indicated), urine cytologic examination, flexible cystoscopy, and imaging of the urothelial tract (eg, computed tomography [CT] urogram or magnetic resonance [MR] urogram). Patients identified as having a bladder tumor on flexible cystoscopy will then require further investigations to stage the disease.

STAGING

As part of the workup for suspected BC, an examination under anesthesia coupled with TURBT is needed. The presence or absence of a residual mass after TURBT is an important prognostic factor, as it potentially indicates either unsuccessful clearance of tumor, extravesical extension, or both. This serves as both definitive staging of the bladder lesion and a substantial proportion of the initial treatment. Pathologic review of the resected specimen will ascertain whether muscle invasion is present and whether there is CIS. These are the key determinants of further investigation and treatment. Patients with NMIBC, including CIS, do not usually require detailed further imaging, and treatment and surveillance are primarily by intravesical means. The main exception to this is patients with either extensive CIS or grade 3 lesions for whom additional cross-sectional imaging may be warranted. Patients with MIBC will require detailed cross-sectional staging with CT or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis. If there are any features suggestive of bone metastasis (eg, raised alkaline phosphatase, bone pain), a bone scan is additionally indicated.

A major confounding factor with imaging in BC is the effect of TURBT on the interpretation of the extent of the primary bladder tumor. Recent TURBT will cause perivesical changes that may be interpreted as extravesical spread. For similar reasons, enlarged pelvic nodes may be related to reactive rather than metastatic effects. On the other hand, changes such as infiltration of adjacent organs or hydronephrosis are likely to be reliable indicators of tumor stage and poor prognosis. However, MRI is a promising modality to better assess the extent of disease and improve local staging, particularly prior to TURBT.[119] Due to the improved resolution with MRI, a standardized approach to imaging and reporting for bladder MRI was developed, called the Vesical Imaging-Reporting And Data System.[120] This system is useful given the increasing use of pelvic MRI for BC staging and can allow for improved communication between physicians and better staging accuracy for patient care.

STAGING SYSTEMS

The American Joint Committee on Cancer (AJCC) TNM staging system (eighth edition, 2017) and the Union for International Cancer Control (UICC) TNM staging system (eighth edition, 2016) are the currently used staging systems.[121] Both use the same TNM definitions, albeit with minor terminology variations. Staging is based on the size and extent of the primary tumor (T), presence or absence of nodal (N), and metastatic spread (M) (Table 71.1). The TNM stage must be used in conjunction with the pathologic assessment of tumor removed at TURBT to decide on optimal therapy.

TABLE 71.1 AJCC TNM STAGING SYSTEM FOR BLADDER CANCER, EIGHTH EDITION

T	*Primary Tumor*

Tx	Primary tumor cannot be assessed.		
T0	No evidence of primary tumor		
Ta	No invasive papillary carcinoma		
Tis	Carcinoma in situ: “flat tumor”		
T1	Tumor invades lamina propria (subepithelial connective tissue).		
T2	Tumor invades muscularis propria. T2a invades superficial muscularis propria (inner half). T2b invades deep muscularis propria (outer half).		
T3	Tumor invades perivesical tissue: T3a microscopically T3b macroscopically (extravesical mass)		
T4	Tumor invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall. T4a tumor invades prostate, stroma, seminal vesicles, uterus, or vagina. T4b tumor invades pelvis or abdominal wall.		
N	*Regional Lymph Nodes*		
Nx	Nodes cannot be assessed.		
N0	No lymph node metastasis		
N1	Metastasis in a single lymph node in the true pelvis (perivesical, obturator, internal and external iliac, or sacral)		
N2	Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)		
N3	Metastasis in a common iliac lymph node(s)		
M	*Distant Metastasis*		
M0	No distant metastasis		
M1	Distant metastasis M1a distant metastasis limited to lymph nodes beyond the common iliacs M1b non–lymph node distant metastases		
Stage grouping			
Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a,b	N0	M0
Stage IIIA	T3a,b	N0	M0
	T4a	N0	M0
	T1-T4a	N1	M0
Stage IIIB	T1-T4a	N2, N3	M0
Stage IVA	T4b	Any N	M0
	Any T	Any N	M1a
Stage IVA	Any T	Any N	M1b

AJCC, American Joint Committee on Cancer.

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PATHOLOGY

Over 90% of BCs are UCs. Nonurothelial BC accounts for less than 5% of all bladder tumors. Approximately 90% of nonurothelial BCs are epithelial in origin, including SCC (associated with infestation with *S. haematobium)*, adenocarcinoma (which are associated with urachal remnants), and small cell carcinoma. Small cell carcinoma is generally very chemosensitive, and treatment tends to follow paradigms of small cell lung cancer. Nonepithelial tumors include sarcoma, melanoma, lymphoma, paraganglioma, and carcinosarcoma. These are extremely rare.

Bladder UCs are typically graded using Gx (cannot be assessed) and then G1 through to G3 (well differentiated through poorly differentiated).[122] CIS will frequently be found in addition to a tumor mass and can affect treatment choices.

MANAGEMENT OF BLADDER CANCER

Non–Muscle-Invasive Bladder Cancer

Around 70% to 75% of patients with BC present with NMIBC.[123] These are classified as Tis, Ta, and T1 by the TNM classification system, and histology for NMIBC should be classified using the 2004 World Health Organization/International Society of Urological Pathology grading system.[124] The gold standard for diagnosis is the resection of the lesion with adequate sampling of the detrusor muscle deep to the lesion (TURBT). This will give tissue for accurate staging of the bladder lesion as well as definitive treatment for the lesion.

Prognostication and management strategies are based on accurate initial staging and grading of the disease. If the initial TURBT results in a macroscopically incomplete resection, there is a high volume of tumor, there is not muscle available in the specimen, or there is high-grade T1 disease, repeat TURBT should be performed approximately 4 to 6 weeks after initial resection. At the time of diagnosis, the upper urinary tract also needs assessment. This is typically done with CT urography.

Between 40% and 80% of NMIBC recurs within 6 to 12 months after complete TURBT without any additional therapy, and approximately 10% to 25% will progress to muscle-invasive, regional, or metastatic disease.[125] Therefore, the recommendation for additional therapy to reduce the risk of recurrence is based on multiple tools to risk stratify and prognosticate BC recurrence.

Multiple prognostication tools are available to guide potential adjuvant therapies and surveillance, including the European Organisation for Research and Treatment of Cancer (EORTC) BC recurrence risk calculator,[34] the Club Urologico Espanol de Tratamiento Oncologico risk stratification system,[126] and the American Urological Association/Society of Urological Oncology (AUA/SUO) risk stratification system.[127,128] All of these generally incorporate the following clinical and pathologic factors: number of tumors, tumor size, prior recurrence rate, T category, presence of concurrent CIS, and tumor grade. In the United States, the AUA/SUO system is primarily used and described as follows:

- *Low-risk* tumors include following: (1) solitary, low grade, 3 cm or less, and Ta; and (2) papillary urothelial neoplasms of low malignant potential.
- *Intermediate-risk* tumors include the following: (1) recurrent tumors within 1 year that are low-grade Ta; (2) solitary low-grade Ta, greater than 3 cm; (3) multifocal low-grade Ta; (4) high-grade Ta, 3 cm or less; and (5) low-grade T1.
- *High-risk* tumors include the following: (1) high-grade T1; (2) any recurrent high-grade Ta; (3) high-grade Ta, greater than 3 cm or multifocal; (4) any CIS; (5) any patient with high-grade

NMIBC and BCG failure; (6) any variant histology; (7) any lymphovascular invasion; and (8) any high-grade prostatic urethral involvement.

A comprehensive discussion regarding risk-adapted adjuvant therapy in NMIBC is outside the scope of this chapter. In general, low-risk tumors have a 15% probability of recurrence and a 0.2% risk of progression at 1 year.[34] These patients should undergo cystoscopic surveillance, but immediate intravesical chemotherapy can be considered. For surveillance, the use of flexible cystoscopy with urine cytology is the standard. Based on a systematic review and individual patient data meta-analysis of randomized trials, immediate intravesical instillation of chemotherapy reduced the 5-year recurrence rate from 59% to 45%.[129] Gemcitabine and mitomycin-C (MMC) are the two chemotherapy agents used most frequently and with the strongest data supporting their use.[130,131] Gemcitabine is typically preferred to MMC due to lower toxicity and cost.

Intermediate- and high-risk tumors have up to a 38% to 61% probability of recurrence and a 5% to 17% risk of progression at 1 year, respectively.[32] The mere presence of CIS in the bladder carries a 50% risk of disease progression to muscle-invasive disease within 5 years without any treatment post-TURBT, and a 30% to 40% risk of progression within 10 years despite treatment.[132] Therefore, adjuvant treatments are more strongly recommended for these tumors. In patients with intermediate-risk tumors, either intravesical chemotherapy or intravesical immunotherapy using BCG can be offered.[127,128] Patients with high-risk tumors should be offered BCG therapy (European Association of Urology [EAU] and AUA guidelines).[127,128,133] Patients with high-risk tumors with aggressive features (CIS, lymphovascular invasion, or variant histologies) should be recommended for radical cystectomy (RC).[128]

For BCG therapy, there are a variety of treatment schedules in the literature, but per AUA/SUO guidelines, generally an intravesical treatment once a week for 6 weeks for induction followed by a rest period of 4 to 6 weeks, with a full cystoscopic evaluation 12 weeks after initial BCG therapy.[134] If there is no cystoscopic evidence of recurrence, the patient should then be offered ongoing maintenance BCG with a 3-week BCG regimen. In a meta-analysis of trials with BCG maintenance, a 32% reduction in the risk of recurrence was seen for BCG compared with MMC ($P < .0001$), whereas there was a 28% increase in the risk of recurrence ($P = .006$) for patients treated with BCG in the trials without BCG maintenance.[135] There are multiple schedules that have been evaluated; however the strongest data support a 3-week regimen used in the SWOG trial, demonstrating reduced disease progression and metastasis.[136] Patients can receive maintenance BCG for 1 to 3 years. A randomized study of 1,355 patients with a median follow-up of 7.1 years found that there was no benefit to continuing maintenance BCG for 3 years compared to 1 year for intermediate-risk patients. However, 3-year maintenance BCG reduced recurrence but did not impact progression or survival in high-risk patients.[137] Thus, 1 year of maintenance BCG is offered for patients with intermediate-risk disease, while 3 years is offered for patients with high-risk disease.

In treatment-refractory disease within 12 months of completion of adequate BCG therapy (defined as persistent or recurrent high-grade NMIBC after two courses of BCG [eg, two induction 6-week courses or a 6-week induction course and maintenance 3-week course]), the patient should be offered RC treatment for the bladder.[127] Yet many patients decline to undergo RC, given the associated negative impact on quality of life (QoL),[138,139] or they may not be eligible due to age or comorbidities. Management for such situations has yet to be fully defined. Pembrolizumab is a programmed cell death protein-1 immune checkpoint inhibitor that was approved in patients with BCG-unresponsive NMIBC with CIS based on the single-arm KEYNOTE-057 trial.[1] Of 96 patients enrolled, 39 (41%) achieved a complete response (CR) at 3-months. The CR rate was 31% at 6

months and 19% at 12 months. A similar trial with atezolizumab reported a CR rate of 27% at 6 months and 25% at 12 months.[2,140] A recent single-arm, prospective phase II cooperative group clinical trial, NRG/RTOG 0926, evaluated patients with high-grade recurrent T1 BC using bladder-sparing chemoradiation. Patients received 61.2 Gy concurrently with either cisplatin or MMC/5-fluorouracil (5-FU) after maximal TURBT. This trial was recently presented in 2021,[3] and of 34 evaluable patients with a median follow-up of 4.2 years (>5 years in surviving patients), the 3-year freedom from cystectomy rate was 88%. The 3- and 5-year OS rates were 69% and 53%, respectively. The cumulative incidence of distant metastasis at 3 and 5 years was 12% and 20%, respectively. Twenty patients had grade 3 adverse events, including anemia, gastrointestinal events, urinary tract infections, lymphopenia, metabolism and nutrition disorders, as well as hematuria. These results need further validation; however, they may represent a well-tolerated option for select patients with high-grade T1 disease who have recurred despite intravesical therapy. A follow-up trial, NRG-014, will begin enrollment soon and will randomize 160 patients with cystectomy-eligible high-risk T1 BC to chemoradiation to the bladder only (BO) versus radiation to the BO plus 1 year of pembrolizumab (PIs: Baumann & Delacroix). Patients will be stratified based on recurrent versus de novo disease and on the basis of urothelial/mixed histology versus nonurothelial histology. Focal CIS is allowed. The trial hypothesizes that RT plus pembrolizumab will result in an improvement in 3-year bladder-intact event-free survival versus chemoRT.

Muscle-Invasive, Nonmetastatic Disease

For a review of recent guidelines and recommendations for broad therapeutic options in the multidisciplinary integrated management of invasive non–metastatic MIBC by the AUA, American Society of Clinical Oncology, the American Society for Radiation Oncology, SUO, and the EAU, the reader is referred to the original publications in the *Journal of Clinical Oncology* and the *Journal of Oncology Practice*.[141,142]

Radical Cystectomy Versus Bladder Preservation Therapy

RT has been offered as a primary treatment for MIBC for many years, but utilization rates vary around the world from around 12% to 18% in the United States[143,144] to over 50% in the United Kingdom.[145] In addition, there is significant underutilization of bladder preservation therapy in noncystectomy candidates, particularly the older and racial minorities.[146,147] Bladder-sparing approaches are reasonable (and preferred) in patients who are medically unfit for surgery. However, between 23% to 50% of patients aged 65 years and above receive no treatment or nonaggressive therapy, despite prospective, phase II data demonstrating good outcomes and acceptable toxicity in this cohort of patients, with 2-year OS of 94.4% and 2-year disease-free survival (DFS) of 72.6%.[148]

For patients who are surgical candidates, RC was traditionally the gold standard treatment for MIBC. Bladder preservation trials, particularly in the United States, are largely phase II studies because of historical lack of acceptance of bladder preservation.[149] The two largest phase III, randomized controlled trials published to date of bladder preservation for MIBC were both performed in the United Kingdom. These demonstrated benefit for locoregional DFS (BC2001)[150] and OS (BCON),[151] using either chemotherapy (BC2001) or hypoxia-modifying therapy (BCON)[151] along with RT, compared to RT alone. The BC2001 trial[150] allowed either 55 Gy in 20 fractions or 64 Gy in 32 fractions for RT. Patients were then randomly assigned to receive synchronous chemotherapy (5-FUl and MMC) or no chemotherapy. The BCON trial[151] allowed for the same RT fractionations, and patients were randomly assigned to receive synchronous treatment with

carbogen and nicotinamide or no synchronous treatment. Despite these data demonstrating good efficacy with the use of bladder preservation for MIBC, there are no completed direct head-to-head randomized comparisons comparing surgery with RT, so the data on comparative efficacy can only be inferred indirectly. The only randomized controlled trial evaluating RC versus bladder-sparing RT (+/− concurrent chemotherapy) that was performed is the UK SPARE trial (randomized trial of Selective Bladder Preservation against Radical Excision [cystectomy] in muscle-invasive T2/T3 transitional cell carcinoma of the bladder), which was closed due to poor accrual.[152] Yet, data from RTOG/NRG prospective protocols as well as other modern series comparisons demonstrate similar long-term clinical outcomes between RC and bladder-sparing therapy, helping to solidify bladder preservation with RT as an appropriate, alternative option for well-selected patients.[4,5,8] It is listed as a category 1 recommendation in national consensus guidelines, as well as multiple international organizations and evidence-based consensus guidelines.[141,153] Several highlights of the data demonstrating comparable outcomes between surgery and radiation for MIBC are discussed later.

Large population-based studies suggest that the main determinants of survival after diagnosis of BC are stage, grade, age, and, to some extent, social class. For example, Hayter et al[154] studied patterns of care and outcomes in over 20,000 patients with BC in Ontario. There were significant variations in the use of cystectomy and RT between different districts, but there was no evidence that these variations led to any differences in long-term outcomes. It was thus concluded that bladder-sparing approaches were equivalent to surgery for invasive BC.[155]

In the United Kingdom, both surgery and RT approaches are routinely employed for MIBC; therefore, it is possible to compare their outcomes in Cancer Registry data. A paper from Munro et al[145] examined outcomes in 458 patients with invasive BC treated in Yorkshire between 1993 and 1996. The ratio of cystectomy to RT was 1 to 3, reflecting UK practice at the time. Overall 10-year survival was similar between those who underwent RT (22%) and RC (24%). Prognostic factors for inferior outcome at 10 years included female versus male, poor performance status, hydronephrosis, and increasing T-stage; treatment modality was not a factor in the prognosis.

Giacalone et al[4] conducted a contemporary analysis of 465 patients with cT2-T4a BC treated at a single institution with maximal TURBT followed by concurrent cisplatin-based chemotherapy and RT. A subset of patients also received neoadjuvant chemotherapy. Repeat cystoscopy with biopsies was performed after 40 Gy. Patients with a CR received consolidation chemoradiation to 64 to 65 Gy, and those with less than a CR or invasive recurrence were recommended to undergo salvage RC. Median follow-up was 4.5 years for all patients and 7.2 years for surviving patients. Seventy-five percent of patients had a CR to induction chemoradiation, 84% after a visibly complete TURBT achieved a CR versus 58% with an incomplete TURBT ($P < .001$). When divided into three treatment eras, the CR rate has improved from 66% in years 1986 to 1995 to 88% in years 2005 to 2013. One hundred twenty-nine patients (28%) underwent salvage RC, 65 for less than CR and 64 for superficial or invasive recurrences. The 10-year actuarial rates for noninvasive, invasive, regional nodal, and distant failures were 26%, 18%, 14%, and 35%, respectively. The 5-, 10-, and 15-year disease-specific survival (DSS) rates were 66%, 59%, and 56% (cT2 74%, 66%, 60%; cT3-T4a 50%, 45%, 45%), respectively. The 5-, 10-, and 15-year OS rates were 57%, 39%, and 25% (cT2 65%, 46%, 29%; cT3-T4a 42%, 26%, 17%), respectively. Neither neoadjuvant nor adjuvant chemotherapy improved DSS or OS. The authors noted this series represented one of the largest cohorts of MIBC treated with combined modality treatment (CMT) and the data supported the high rates of CR and bladder preservation in patients receiving CMT and demonstrated long-term DSS similar to modern cystectomy series.

Using the National Cancer Database (NCDB), patients with AJCC clinical T2-T3, N0, and M0 UC (MIBC) diagnosed between 2004 and 2013, Zhong et al[156] carried out an analysis of patients treated with definitive intent with either RC (with or without chemotherapy) or concurrent chemotherapy and radiation (bladder preservation) (BPCRT). Only patients documented to undergo a transurethral tumor resection followed by a definitive course of radiation with chemotherapy were included in this BPCRT cohort. Among 8,454 patients with MIBC, 7,276 (86%) underwent RC with or without chemotherapy, and 1,178 (14%) underwent BPCRT. Patients undergoing BPCRT were significantly older (median age 77 vs 68 years, $P < .001$) and had higher comorbidity scores ($P = .002$). The median follow-up time was 4.5 years. Using matched propensity score analysis, there were 1,002 patients remaining in each cohort, and there was no significant difference in 4-year OS between the two groups (39.1% surgery vs 42.6% BPCRT, $P = .15$). BPCRT demonstrated similar survival outcomes compared to those treated with RC with or without chemotherapy. In the absence of prospective randomized studies, these results may help guide decision-making for patients with MIBC considering nonsurgical management options.

Vashistha et al[157] searched seven databases (PubMed, Scopus, EMBASE, Proquest, CINAHL, and ClinicalTrials.gov) for randomized controlled trials and prospective and retrospective studies directly comparing RC with CMT from database inception to March 2016. They conducted a meta-analysis evaluating OS, DSS, and PFS with HRs. Nineteen studies evaluating 12,380 subjects were selected. For the eight studies encompassing 9,554 subjects eligible for meta-analyses, there was no difference in OS at 5 years (HR 0.96, favoring CMT) or 10 years (HR 1.02, favoring cystectomy). No difference was observed in DSS at 5 years (HR 0.83, favoring radiation) or 10 years (HR 1.17, favoring cystectomy), or PFS at 10 years (HR 0.85, favoring CMT). The cystectomy arms had higher rates of early major complications, whereas rates of minor complications were similar between the two treatments. In summary, this meta-analysis showed no differences in OS, DSS, or PFS between RC and CMT.

The Surveillance, Epidemiology, and End Results (SEER) program was used by Wilhite et al[158] to identify patients diagnosed from 1992 to 2013 with localized, muscle-invasive bladder (stages II-III) UC, SCC, or adenocarcinoma histology. Cystectomy was defined as partial or radical. Those who did not receive either cystectomy or RT were excluded. Treatment utilization patterns over time were assessed using Cochran-Armitage tests. Among 16,175 patients eligible for analysis, 11,917 (74%) and 4,258 (26%) received cystectomy and RT, respectively. Patients who received RT were older (median age 79 vs 68, $P < .01$), Over time, there was a statistically significant increase in the proportion of patients receiving RT relative to cystectomy (24% 1992-2002 vs 28% 2003-2013, $P < .01$), despite median patient age throughout the study period remaining unchanged (71 for both 1992-2002 and 2003-2013). For RT, compared with patients diagnosed from 1992 to 2009, those diagnosed from 2010 to 2013 showed improved CSS (71% vs 67% at 1 year, $P = .01$; 51% vs 40% at 3 years, $P < .01$) and OS (64% vs 60% at 1 year, $P < .01$; 38% vs 29% at 3 years, $P < .01$). The significant improvement in CSS and OS for patients receiving RT who were diagnosed in more recent years compared with earlier years support continued use of bladder preservation strategies utilizing RT.

A multi-institutional study using propensity score matching (PSM) and inverse probability treatment weighting (IPTW) along with 3:1 matching with replacement provides the best evidence to date demonstrating similar oncologic outcomes between RC and bladder preservation with TURBT followed by chemoradiation (trimodality therapy, TMT). Zlotta et al[8] included 722 patients with clinical stage T2-T4N0M0 MIBC (440 underwent RC, 282 received TMT) who would have been eligible for both approaches (eligibility criteria: solitary tumors <7 cm, unilateral

hydronephrosis allowed, no extensive or multifocal CIS, adequate bladder function). In the PSM analysis, the 3:1 matched cohort comprised 1,119 patients (837 RC, 282 TMT). Median follow-up was 4.38 years versus 4.88 years for surgery versus TMT. The 5-year metastasis-free survival was 74% (95% CI 70-78) for RC and 75% (95% CI 70-80) for TMT with IPTW and 74% (95% CI 70-77) and 75% (95% CI 68-79) with PSM. There were no differences in metastasis-free survival with either IPTW or PSM between the two groups (P = .40 and P = .64, respectively). Adjusted 5-year regional failure-free survival was 95% (95% CI 93-97) for RC and 91% (95% CI 89-93) for TMT using IPTW, and 95% (95% CI 93-96) and 92% (95% CI 87-95) using PSM. There were no differences between the two groups with respect to CSS using IPTW or PSM (P = .071 and P = .057, respectively) and DFS (P = .35 and P = .37, respectively). OS favored TMT (IPTW HR, 0.70, 95% CI 0.53-0.90, P = .010; PSM HR 0.75, 95% CI 0.58-0.97, P = .0078, Figure 71.2). These data further emphasize that TMT should be offered to eligible patients in the setting of multidisciplinary shared decision-making.

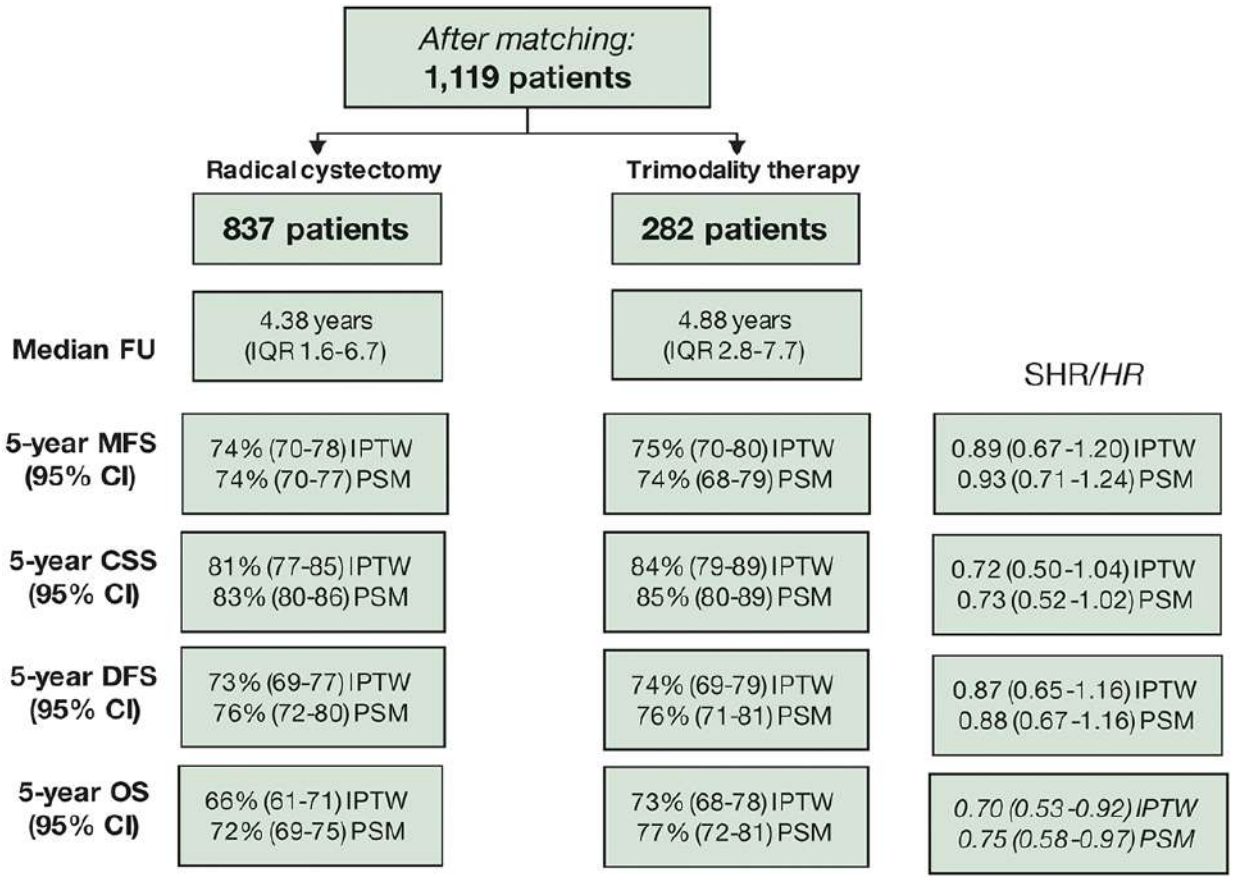

FIGURE 71.2 Outcomes in the matched analysis between radical cystectomy and trimodality therapy.[8] CSS, Cancer-specific survival; CI, confidence interval; DFS, disease-free survival; FU, follow-up; HR, hazard ratio; IPTW, inverse probability treatment weighting; MFS, Metastasis-free survival; OS, overall survival; PSM, propensity score matching; SHR, subdistribution hazard ratio.

A proportion of patients, approximately 10% to 15% in contemporary series, undergoing RT will relapse within the bladder and go on to salvage cystectomy. An important consideration, therefore, is whether cystectomy after RT can be carried out safely and whether the delay compromises survival. However, modern series generally do not suggest significant differences in terms of DSS

and OS or acute toxicities between those who undergo primary cystectomy versus salvage cystectomy.[159] An analysis by Pieretti et al[160] evaluated 265 patients who underwent RC at Massachusetts General Hospital between 2003 and 2013. Patients were grouped by primary cystectomy (n = 216), primary cystectomy in patients with a history of any abdominal/pelvic RT (n = 28), versus salvage cystectomy (after chemoradiation for bladder preservation, n = 23). Early (≤90 days) and late (>90 days) complications were compared, as well as DSS and OS. With a median follow-up time of 65.5 months, there was no difference in intraoperative and early complications between the groups. Late complications were higher in the salvage cystectomy group compared to both the primary cystectomy and the primary cystectomy in patients with a history of RT groups (P = .03). This was also found on multivariable Cox regression analysis that salvage cystectomy was associated with a higher incidence of any late (HR 2.3, P = .02) and major late complications (HR 2.1, P < .05). However, there was no difference in DSS (P = .8) or OS (P = .9). These data suggest that salvage cystectomy following chemoradiation for bladder preservation is feasible with acceptable complication rates and good clinical outcomes and can be offered at an experienced institution.

In summary, surgery and RT should not compete and should be complementary approaches of treatment of invasive BC. There are particular groups of patients who appear to do poorly with primary RT, for example, those with poorly functioning bladders or extensive CIS in addition to their invasive disease. In the former case, RT is unlikely to improve bladder function; in the latter, the lack of effect of RT on CIS means that the patient remains at risk of further bladder intervention and ultimately cystectomy.[161] Older studies also cited features such as hydronephrosis as a contraindication to RT.[162] However, hydronephrosis is also a poor prognostic factor for surgery and does not help in selecting patients one way or another.[163] On the other hand, there are many patients who may benefit from radical therapy but are poor surgical candidates, such as older patients, those who are obese, patients with diabetes, poor anesthetic-risk patients, or those who may struggle with their urinary diversion; thus, a radiation-based approach would be beneficial. In general, although there are no absolute criteria for selecting patients for one treatment option versus another (Table 71.2), the following factors are important considerations when considering a radiation-based versus surgical approach:

TABLE 71.2 FACTORS INFLUENCING SURGERY VERSUS BLADDER PRESERVATION THERAPY

Favor radical cystectomy
Poor bladder function
Inflammatory bowel disease
Prior abdominal or pelvic radiation
Diffuse CIS
Tumor-associated hydronephrosis
Favor bladder preservation therapy
High surgical risk
Strong desire to preserve bladder
Favor both
Good performance status
T2 disease
Unifocal tumor
Unfavorable for either treatment[a]
Poor performance status
Poor renal function (cisplatin ineligible)

T3-4 disease Multifocal tumor

CIS, carcinoma in situ; TURBT, transurethral resection of bladder tumor.

[a]In patients with poor performance status, a nonsurgical approach would favor.

- Maximal TURBT achieved
- Clinical T2-T4a disease
- Absence of tumor-associated hydronephrosis or only unilateral hydronephrosis
- Kidney function (for receipt of concurrent chemotherapy, namely, if cisplatin)
- Absence of extensive CIS
- Unifocal tumors less than 6 cm
- Good bladder function/capacity
- No history of prior abdominal/pelvic RT

Clinicopathologic factors as earlier may be insufficient to fully provide guidance in selection of one treatment over another, particularly if patients are good candidates for either approach. Advances in the molecular understanding of UC have identified new predictive biomarkers that may guide the tailored selection of therapy as discussed later.

Predictive and Prognostic Molecular Biomarkers

Extensive work has been performed to understand the molecular and genomic characteristics of BC. This work has led to the identification of potential molecular biomarkers that can be either prognostic or predictive factors, with the latter that may help with selection of appropriate therapy for a patient presenting with MIBC (Table 71.3).[164-166] BCs frequently display mutations in DNA repair pathways. MRE11 demonstrates promise as a biomarker of radiation response. In a study using immunohistochemical (IHC) staining of MRE11 in a cohort of patients treated with RT alone found that patients with the lowest amounts of MRE11 staining had worse 3-year CSS.[167] A validation study using tissues from patients enrolled in six NRG/RTOG bladder-sparing radiation trials found that low levels of MRE11 nuclear/cytoplasmic expression scores were associated with significantly higher disease-specific mortality.[168] Laurberg et al[169] similarly found that low MRE11 staining was associated with worse DSS in a cohort of 148 patients treated with bladder preservation and did not find any association with MRE11 staining and outcomes among patients who received cystectomy.

TABLE 71.3 PROMISING MOLECULAR BIOMARKERS FOR IMPROVED TREATMENT SELECTION FOR MIBC

Biomarker	Evidence
MRE11	• MRE11 measured by immunohistochemistry in a radiation-alone cohort found low MRE11 levels were associated with worse 3-y cancer-specific survival.[166] • Separate study confirmed low levels of MRE11 nuclear/cytoplasmic expression scores were associated with higher disease-specific mortality in tissues from six NRG/RTOG bladder-sparing trials.[167]
ERCC2	• In a homogenously treated TMT cohort of 76 patients with MIBC, those with *ERCC2* mutations had significantly improved bladder-intact event-free survival as well as improved bladder-intact event-free survival.[15] • Having any DNA repair pathway alteration was associated with improved locoregional control and modified bladder-intact event-free survival.

Biomarker	Evidence
EGFR	• EGFR expression assessed by immunohistochemistry was associated with improved outcomes in a study using tissue from patients enrolled on RTOG 8802, RTOG 8903, RTOG 9506, and RTOG 9706.[173]
HER2	• HER2 expression via immunohistochemistry was associated with poorer outcomes using tissue from patients enrolled on RTOG 8802, RTOG 8903, RTOG 9506, and RTOG 9706.[173] • HER2 overexpression was associated with pathologic incomplete response and worse cancer-specific survival in a cohort of 119 patients treated with bladder preservation therapy.[174] • RTOG 0524 evaluated the use of trastuzumab in patients with HER2/neu overexpression with concurrent chemoradiation, demonstrating that the addition of trastuzumab mitigated previously known worse prognosis in patients with HER2 overexpression.[175]
T-cell activation and interferon-γ signaling signatures	• In a large bladder preservation cohort, immune signature evaluation found that signatures associated with T-cell activation and interferon-γ signaling were associated with improved disease-specific survival.[14] • In a validation study using tissues from patients on prospective trials of MIBC, gene expression profiles with clusters of high immune cell content were associated with longer DFS and OS compared to the cluster with low immune cell content.[16] • In addition, higher expression of T-cell infiltration genes was also associated with longer DFS and OS.[16]
24-Gene hypoxia signature	• In the BCON trial, patients with “high hypoxia” signatures had better overall outcomes compared to those with “low hypoxia” signatures.[179]
Circulating tumor DNA (ctDNA)	• In a study of 68 patients undergoing neoadjuvant chemotherapy followed by radical cystectomy, the presence of ctDNA at various time points throughout the care pathway was prognostic for worse outcomes.[182]

DFS, disease-free survival; MIBC, muscle-invasive bladder cancer; OS, overall survival; TMT, trimodality therapy.

Additional investigations into DNA repair pathway alterations have been performed. A small study of 48 patients treated with bladder preservation found that deleterious mutations in DNA repair pathways, specifically ERCC2, were associated with improved outcomes after chemoradiation. In a homogenously treated TMT cohort of 76 patients with MIBC with a median follow-up of 74.6 months,[15] patients with ERCC2 mutations had significantly improved modified bladder-intact event-free survival (a composite end point that reflects long-term cancer control with bladder preservation, HR 0.15, 95% CI 0.06-0.37, P = .030) as well as improved bladder-intact event-free survival (an end point that includes all-cause mortality, HR 0.33, 95% CI 0.15-0.68, P = .044). In addition, having any DNA repair pathway alteration was associated with both improved locoregional control (HR 0.31, 95% CI 0.12-0.80, P = .0088) and modified bladder-intact event-free survival (HR 0.51, 95% CI 0.27-0.97, P = .004). A separate study evaluated ataxia telangiectasia mutated (ATM) deficiency in the same aforementioned cohort of 76 patients, finding that, among 11 patients with ATM alterations and tumor tissue available for study, among those with loss of ATM expression by IHC, clinical outcomes were improved, with significantly longer modified bladder-intact event-free survival among those with ATM expression loss (P = .015).[170]

Alterations in signal transduction pathways have been implicated in bladder preservation. A study of patients enrolled in four prospective bladder preservation studies (RTOG 8802,[171] RTOG 8903,[162] RTOG 9506,[172] and RTOG 9706[173]) found that EGFR expression assessed by IHC was associated with improved outcomes; however, HER2 expression was associated with poorer

outcomes.[174] This finding was confirmed by work by Ionue et al in a cohort of 119 patients treated with bladder preservation therapy. HER2 overexpression was associated with pathologic incomplete response and worse CSS.[175] The RTOG 0524 phase I/II trial evaluated the use of trastuzumab along concurrent chemoradiation (paclitaxel for chemotherapy) among patients who were HER2/neu 2+ or 3+.[176] Patients who were HER2/neu negative or 1+ by IHC were treated with chemoradiation alone. Both groups had similar CR rates, suggesting that in patients with HER2/neu 2+ or 3+ expressing tumors, the addition of trastuzumab mitigated the associated worse prognosis, demonstrating the ability of biomarker-driven trials to improve outcomes in challenging diseases.

Gene expression profile work has led to definitions of various molecular subtypes within UC.[86,87,177-179] These subtypes have been broadly characterized based on luminal and basal gene expression patterns and correlated with response to cystectomy and neoadjuvant chemotherapy. Using patients from the BCON trial[151] to evaluate outcome by molecular subtype, it was found that the basal subtype patients had a greater benefit with hypoxia modification than those with a luminal subtype.[180] A 24-gene hypoxia signature was developed and validated in the BCON cohort of patients. Patients with a "high hypoxia" signature had improved outcomes than those with a "low hypoxia" signature.[181] In one of the largest studies of molecular subtypes within a cohort of patients receiving TMT, four subtypes were described: luminal, luminal-infiltrated, basal, and claudin-low.[14] There was no association between subtype and CR, DSS, or OS. However, upon further defining immune signatures based on gene expression, signatures associated with T-cell activation and interferon-γ signaling were associated with improved DSS in the TMT cohort. In a comparison cohort of patients treated with neoadjuvant chemotherapy and RC, this association did not hold. In a separate analysis validating prognostic immune biomarkers from prospective trials of MIBC (RTOG 0524[176] and 0712[182]), genes correlating with immune cell activation and gene expression profiles with clusters with high immune cell content associated with longer DFS and OS compared to the cluster with low immune cell content. Higher expression of T-cell infiltration genes was also associated with longer DFS and OS.[16] These findings will need to be further examined in the ongoing trials evaluating TMT plus immune checkpoint inhibitors, including the INTACT: SWOG/NRG 1806 study, evaluating chemoRT with or without atezolizumab in MIBC (NCT03775265); the KEYNOTE-992 study, evaluating chemoRT with or without pembrolizumab in MIBC (NCT04241185); and the CCTG BL13 trial, evaluating chemoRT followed by with or without adjuvant durvalumab.

Finally, there is a growing interest in the use of liquid biopsy tools including circulating tumor cells and circulating tumor DNA (ctDNA) to help personalize treatment recommendations for patients with MIBC. However, at this time, completed studies of ctDNA to predict responses after chemoradiation are lacking. In a study of 68 patients undergoing neoadjuvant chemotherapy followed by cystectomy, the presence of ctDNA was prognostic for worse outcomes. This was found to be highly specific and significant at diagnosis before chemotherapy, after chemotherapy and before cystectomy, and during disease surveillance after cystectomy. It will be important to assess the utility of ctDNA presence and the association with outcomes at various time points throughout the care of patients with MIBC undergoing TMT.[183]

As ongoing trials with correlative translational studies close, findings will help inform improved treatment selection for patients with MIBC.

TREATMENT OPTIONS

Surgery

Management of Invasive Bladder Cancer

Although the majority of patients present with NMIBC, 20% to 40% will either present with or ultimately develop muscle-invasive disease.[123] Invasive BC is potentially lethal; if untreated, over 85% of patients will die of the disease within 2 years of diagnosis.[184] Furthermore, a certain percentage of patients with high-grade bladder tumors without involvement of the lamina propria will recur or progress or fail intravesical management, and they may be best treated with an earlier cystectomy when survival outcomes are optimal.[127]

The rationale for an aggressive treatment approach employing RC for high-grade, invasive BC is based on several important observations. First, the good long-term survival rates, coupled with the lowest local recurrences, are seen following a definitive surgical approach to removing the primary bladder tumor and regional lymph nodes.[7,185] Second, the morbidity and mortality of RC have substantially improved over the past several decades.[185,186] Third, advocates say that RC provides accurate pathologic staging of the primary bladder tumor and regional lymph nodes, thus selectively determining the need for adjuvant therapy based on precise pathologic evaluation. However, it should be noted that the evidence base for adjuvant (as opposed to neoadjuvant) therapy is rather weak. For the abovementioned reasons, RC has become a standard form of therapy for high-grade, invasive BC.

The evolution and improvements in lower urinary tract reconstruction, particularly orthotopic diversion, have been major components in enhancing the QoL for patients requiring cystectomy. Currently, most men and women can safely undergo orthotopic lower urinary tract reconstruction to the native, intact urethra following cystectomy,[187,188] although availability varies worldwide. Orthotopic reconstruction aims to mimic the native bladder in location and function, provides a continent means to store urine, and allows volitional voiding per urethra, although patients need to do this by coordinating opening the sphincter with a Valsalva maneuver, which does require training. The orthotopic neobladder eliminates the need for a cutaneous stoma, urostomy appliance, and the need for intermittent catheterization in most cases. These efforts have improved the QoL of patients who require removal of their bladders and have also stimulated patients and physicians to consider RC at an earlier more curable stage for high-grade, invasive BC.[189,190] A dedicated effort has been made to improve the surgical technique of RC and to provide an acceptable form of urinary diversion, without compromising a sound cancer operation.

Timing of cystectomy after the TURBT is important, and it has been demonstrated that a delay of more than 3 months undermines patient survival. This evidence forms the basis to negotiating resource needs with health care providers.[191] Certain technical issues regarding RC and an appropriate lymph node dissection are critical to minimize local recurrence and positive surgical margins and to maximize CSS.[192] Attention to surgical detail is important in optimizing the successful functional outcomes of orthotopic diversion by preserving the urinary sphincter mechanism and, therefore, continence. Finally, the observed associations between hospital volume and operative mortality are largely mediated by surgeon volume. Patients can often improve their chances of survival substantially, even at high-volume hospitals, by selecting surgeons who perform the operations frequently, as those centers that have adopted this strategy have demonstrated declining mortality in the past decade.[193,194]

RC by definition implies the en bloc removal of the pelvic-iliac lymph nodes along with the pelvic organs anterior to the rectum: the bladder, urachus, prostate, seminal vesicles, and visceral peritoneum in men and the bladder, urachus, ovaries, fallopian tubes, uterus, cervix, vaginal cuff, and the anterior pelvic peritoneum in women. An appropriate lymphadenectomy is an important component of RC and is related to the clinical outcomes of patients with high-grade, invasive BC. Evidence suggests that a more extended lymphadenectomy is beneficial in both lymph node–

positive and lymph node–negative patients with BC,[195-197] although this could be a surrogate for either case selection or surgical skill. Although the exact limits of the lymphadenectomy for patients with BC undergoing cystectomy are currently debated, the boundaries include initiation at the level of the inferior mesenteric artery (superior limits of dissection), extending laterally over the inferior vena cava or aorta to the genitofemoral nerve (lateral limits of dissection), and distally to the lymph node of Cloquet medially (on Cooper ligament) and the circumflex iliac vein laterally. This dissection includes bilaterally all obturator, hypogastric, presciatic, and presacral lymph nodes.[198,199] Removal of more than 15 lymph nodes has been postulated to be both sufficient for the evaluation of the lymph node status and beneficial for OS in retrospective studies.[199,200] However, potential interindividual differences in the number of pelvic and retroperitoneal lymph nodes and difficulties in processing the removed tissue by pathologists are issues. Furthermore, the reality is that even in today's practice, the number of lymph nodes retrieved is low (<10) in a majority of patients (75%) and the chances are even lower if the patients are older, Hispanic (in the United States), and managed at low-volume, nonurban centers.[199] The true curative value of lymph node dissection and the optimal extent of dissection are both still unknown.

Technical variations from the standard cystectomy have been performed to improve patients' QoL, including prostate-sparing cystectomy, to preserve continence and potency. However, this carries a higher risk of missing unsuspected adenocarcinoma of the prostate. Coexistent prostate cancer and prostatic UC are reported in 23% to 54% of cases, respectively, of which 29% were clinically significant, leading to local recurrence and even metastasis.[201]

Both laparoscopic and robot-assisted cystectomy have been shown to be feasible and safe, but with a relatively shorter follow-up.[202,203] Despite an increased materials cost for a robotic-assisted cystectomy, it has been demonstrated to be cost-effective in a subgroup of patients undergoing ileal conduit when the impact of complications is considered in a single-institution series.[202,203]

Morbidity and Mortality of Radical Cystectomy and Lymphadenectomy

The early clinical results and outcomes regarding the morbidity and mortality of RC were disappointing. The lack of universal acceptance of this procedure was attributed to the considerable complication rate and the need for improvements in urinary diversion. Prior to 1970, perioperative complication rates of RC were approximately 35%, with a mortality rate of nearly 20%.[204] However, with contemporary medical, surgical, and anesthetic techniques, along with better patient selection, the mortality and morbidity from RC have dramatically decreased. Frequency of complications and mortality appears to be related to surgeon experience and hospital volume,[193,194] as well as age/comorbidities of the patient.[205] The issue of the need to select patients for surgery complicates the comparison of bladder-sparing techniques, because frequently those not suitable for surgery will be the ones who appear in the RT-based series.

The early complication rate following RC should not be underestimated. Of the 1,054 patients undergoing cystectomy in a University of Southern California series,[7] 28% developed an early complication within the first 3 months of surgery. Early complications included all events related to the cystectomy, perioperative care, and urinary diversion. The administration of preoperative therapy (radiation or chemotherapy) and the form of urinary diversion did not significantly increase the early complication rate in these cystectomy patients. Most early complications following RC are unrelated to the urinary diversion (85% diversion unrelated) and can be managed conservatively without the need for reoperation in approximately 90% of cases.[206] The most common early diversion-unrelated complication is dehydration, whereas the most common early diversion-related complication following RC is prolonged urinary leakage. Overall, most surgical

complications after cystectomy are associated with urinary diversion in relation to the intestinal segments.[185,207]

RC may appropriately be performed in carefully selected older patients; however, this emphasis in the surgical literature on "careful selection" highlights as much the deficiencies as the efficacy of cystectomy as it emphasizes that the published results are not applicable to the entire population. It is emphasized that physiologic age may be more important than chronologic age when determining appropriate candidacy for RC. Proper patient selection, strict attention to perioperative details, as well as a dedicated and meticulous team-oriented surgical approach are critical components to minimize the morbidity and mortality of surgery and to ensure the best clinical outcomes in all patients following RC.[206,208] A recommended approach is the adoption of an enhanced recovery pathway protocol (Figure 71.3).[209]

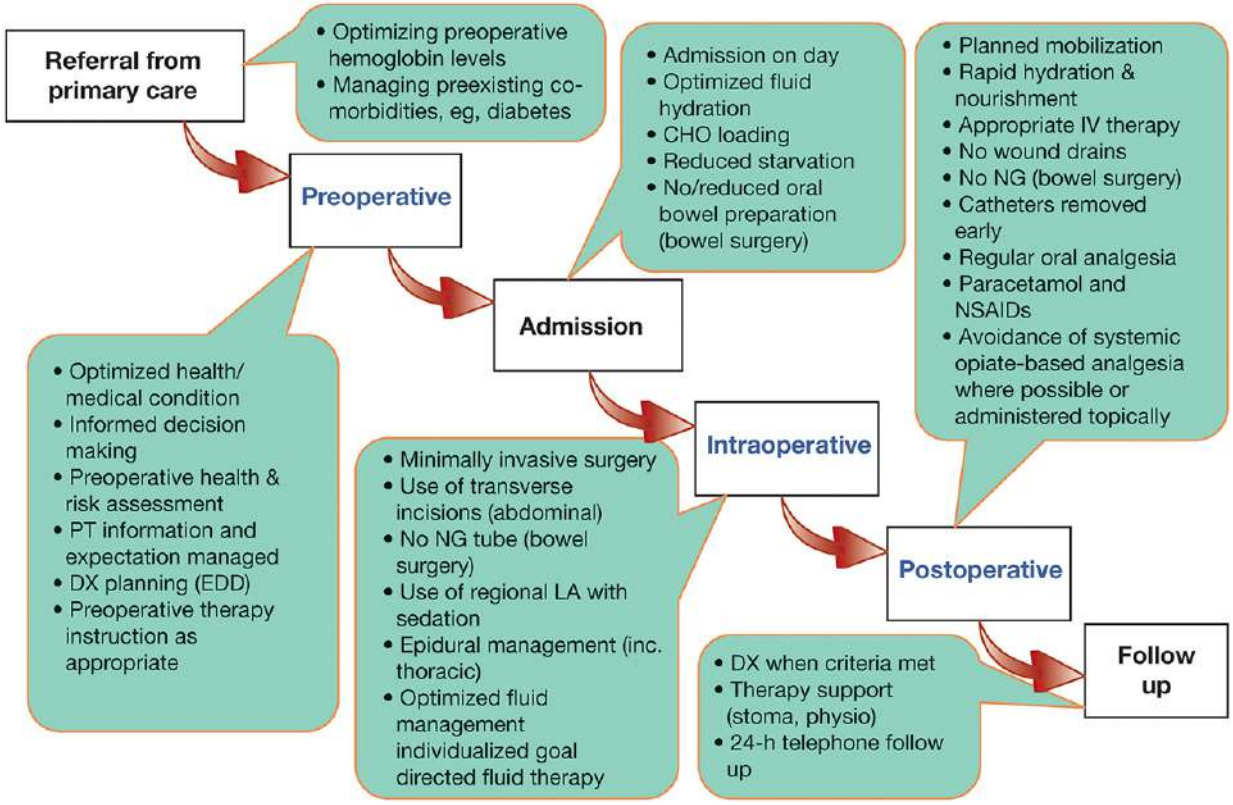

FIGURE 71.3 Schematic representation of the enhanced recovery program in patients undergoing a radical cystectomy. CHO, carbohydrate; IV, intravenous; LA, local anesthesia; NG, nasogastric; NSAIDs, nonsteroidal anti-inflammatory drugs; PT, physical therapy.

Prognostic Factors for Survival Outcomes

The 5-year recurrence-free survival and OS rates for the entire group of 1,054 patients in the University of Southern California series were 68% and 66%, respectively, and it was 60% and 43%, respectively, at 10 years. Most deaths occurred within the first 3 years following RC and were attributed to cancer recurrence. However, with longer follow-up (>3 years), most deaths in this older group of patients were primarily related to comorbid diseases unrelated to BC. This underscores the effective and durable outcomes of RC.

Tumor stage is among the most important factors to predict both relapse and survival following RC.[7,185,210,211] In patients with organ-confined disease without lymph node involvement, long-term survival is reported to be about 75% to 85%. In patients with extension to the perivesical fat and/or adjacent pelvic viscera, long-term survival is reported to be around 45% to 55%. In patients with regional nodal metastasis, patients generally have a poorer prognosis.

The receipt of neoadjuvant chemotherapy is also associated with lower risk of recurrence and improvement in OS (see "Role of Neoadjuvant/Adjuvant Systemic Therapy").

Negative surgical margins and removing sufficient lymph nodes have been associated with improved survival and local recurrence. A 2017 meta-analysis of 36 studies associated a positive surgical margin with poorer survival after RC for BC.[212] Removal of >10 lymph nodes has also been found to be associated with increased OS (HR 0.52, 95% CI 0.43-0.64).[213] Surgeon experience and institutional volume strongly predict favorable outcomes as well.[193,194] Lymphovascular invasion is an independent predictor of progression in T1 and MIBC in several cohorts.[214-216] Finally, molecular markers, including p53, p21, p27kip1, pRB, and p16, have been found to be independent predictors of postcystectomy survival in several series,[217-220] but these are not routinely evaluated and require further validation before widespread adoption into clinical practice.

Organ-Confined, Lymph Node–Negative Tumors

In the University of Southern California series, 56% of patients demonstrated pathologically organ-confined, lymph node–negative tumor.[7] The outcomes in this pathologic subgroup were excellent, with a 5- and 10-year recurrence-free survival of 85% and 82%, respectively, while 5- and 10-year OS was 78% and 56%, respectively. No significant survival differences were observed when comparing superficially noninvasive (Tis, Ta), lamina propria invasive (T1), and muscle-invasive (T2a, T2b) tumors as long as the tumor was confined to the bladder without evidence of lymph node involvement. Similar outcomes for patients with pathologic non–muscle-invasive bladder tumors following cystectomy have been previously reported.[221] Collectively, these data support the treatment of patients with surgery when a tumor is confined to the bladder, without evidence of extravesical extension or lymph node metastasis. Treatment delays in patients with invasive BC should be avoided. Evidence suggests that prolonged delays may lead to more advanced pathologic stage and decreased survival in patients with MIBC.[191] Furthermore, caution should be taken in delaying definitive therapy in patients with high-risk, non–muscle-invasive bladder tumors or those with non–muscle-invasive tumors that have not appropriately responded to conservative forms of therapy.

Extravesical, Lymph Node–Negative Tumors

Non–organ-confined (extravesical), lymph node–negative tumors were found in 20% of the University of Southern California series patients undergoing cystectomy. No obvious survival differences between extravesical T3 and T4 (node-negative) tumors were observed. The 5- and 10-year recurrence-free survival and OS rates for this pathologic subgroup were 58% and 55%, and 47% and 27%, respectively.[7] Similar outcomes were reported by Madersbacher et al,[185] demonstrating a 56% 5-year recurrence-free survival for the same pathologic subgroup. A more contemporary analysis of 2,287 patients treated with RC[221] demonstrated a 5-year OS and DSS for non–organ-confined node-negative disease (>pT2N0) of 53% and 62%, respectively.

Lymph Node–Positive Disease

Approximately one-fourth of patients in a large cystectomy series were found to have positive lymph nodes at the time of surgery. Although patients with lymph node tumor involvement are a high-risk group of patients, the AJCC eighth edition[121] was modified and reclassified node-positive disease (defined as N1-N3 disease) as stage III (previously identified as stage IV disease). This is because node-positive disease behaves differently than patients with metastatic (M1) disease. One prospective observational study of patients treated with RC found that 5-year CSS was 81% for patients with node-negative versus 40% for patients with node-positive BC.[222] The 5-year CSS is reported as 20% for M1 disease, which is lower than node-positive disease.[223]

The prognosis in patients with lymph node–positive disease can be stratified by the number of lymph nodes involved (tumor burden), the stage of the primary tumor, and the presence of extracapsular extension[224] of lymph node metastases. Patients with fewer than five positive lymph nodes among those with lymph node–positive organ-confined bladder tumors had a significantly improved recurrence-free survival rate.[197]

The number of lymph nodes involved with tumor and the extent of the lymph node dissection are both important variables for patients undergoing cystectomy for BC. Stein et al[197] examined 244 patients with lymph node tumor involvement following RC to evaluate other prognostic factors in this high-risk group. They used lymph node density to account for the extent of the lymph node dissection (number of lymph nodes removed) and the tumor burden (number of positive lymph nodes) following cystectomy for patients with lymph node–positive disease. Lymph node density as defined in this study was a significant and independent prognostic variable in patients with lymph node metastases.

Future staging systems and the application of adjuvant therapy in clinical trials may consider applying these concepts to better stratify pathologic node-positive patients.

Role of Neoadjuvant/Adjuvant Systemic Therapy

The addition of neoadjuvant therapy to RC is a widely accepted standard of care based on several trials demonstrating an OS and DFS benefit.[20,32,225] The meta-analysis (Advanced Bladder Cancer Collaboration) of 11 randomized trials,[32,225] which included 3,005 patients with localized MIBC, evaluated neoadjuvant platinum-based combination chemotherapy to local therapy. Compared with local therapy alone, neoadjuvant platinum-based chemotherapy improved 5-year OS (HR 0.86, 95% CI 0.77-0.95) and DFS (HR 0.78, 95% CI 0.71-0.86). There are multiple systemic regimens that can be used; however, for cisplatin-eligible patients, dose-dense MVAC (ddMVAC) and GC are good options. There are ongoing investigations into neoadjuvant immunotherapy as part of therapy; however, these are not recommended as part of routine clinical practice as of yet.

Conversely, the role of adjuvant therapy for patients found to be at high risk for recurrence based on findings at the time of surgery is more complex. Given the morbidity associated with cystectomy, it may be difficult to get patients to adjuvant therapy and to receive all intended cycles of therapy. Nevertheless, for patients with high-risk characteristics (which include pathologic T3 or T4 disease and/or pathologic node involvement), adjuvant therapy is recommended. Most studies suggest that adjuvant cisplatin-based chemotherapy delays recurrences and improves OS.[226-229] A meta-analysis included 10 randomized trials with 1,183 patients who did not receive neoadjuvant chemotherapy.[230] At a median follow-up of 6 years, the addition of adjuvant cisplatin-based chemotherapy postcystectomy improved OS (HR 0.82, 95% CI 0.70-0.96). Adjuvant cisplatin-based chemotherapy also improved recurrence-free survival (HR 0.71, 95% CI 0.60-0.83).

In patients who previously received neoadjuvant cisplatin-based chemotherapy and have high-risk features at the time of surgery (namely, persistent muscle-invasive [ypT2-T4a] or node-positive

disease), 1 year of immunotherapy with either nivolumab or pembrolizumab is recommended. Separate randomized trials found that adjuvant nivolumab confers both a DFS and OS advantage,[231] while adjuvant pembrolizumab confers a DFS advantage.[232]

In patients who are ineligible for adjuvant cisplatin-based chemotherapy, 1 year of adjuvant immunotherapy using either nivolumab or pembrolizumab. The aforementioned immunotherapy randomized phase III trials[231],[232] included this cohort of patients as part of their patient population and found that both of these therapies improved DFS. However, these studies were not powered to evaluate this specific subgroup of patients separately.

Summary of Surgical Therapy

Surgery is an important mode of therapy for invasive BC and undoubtedly can provide durable disease control for many patients with the disease. In addition, an integrated approach with other treatment modalities such as neoadjuvant chemotherapy is essential if the best results are to be achieved in the entire patient population. RC provides an accurate evaluation of the primary bladder tumor along with the regional lymph nodes, yielding important prognostic information. This, coupled with the evolution and successful application of orthotopic lower urinary tract reconstruction in both men and women, has provided patients with a more physiologic and acceptable means to store and eliminate urine. However, most deaths from BC still occur due to distant metastases, presumably present at the time of original surgery, so further improvements in outcome will depend on the development of both better systemic therapies and predictive (as opposed to prognostic) markers that will allow better selection of therapies.

Radiation Therapy

External Beam Radiation Therapy

Although RC is the most common treatment used for MIBC, RT use is increasing, in part due to the recently accrued SWOG/NRG 1,806 study (NCT03775265) trial, the largest randomized, phase III trial to date of bladder-sparing chemoRT. However, treatment patterns vary worldwide. In the United States, RT is administered as part of a package of multidisciplinary care comprising maximal TURBT, chemotherapy, and RT, also known as trimodality therapy (TMT) (Figure 71.4).[149] There are options in the treatment schedules used, in terms of dose and treatment frequency. In addition, treatment volumes are varied, with multiple acceptable choices.

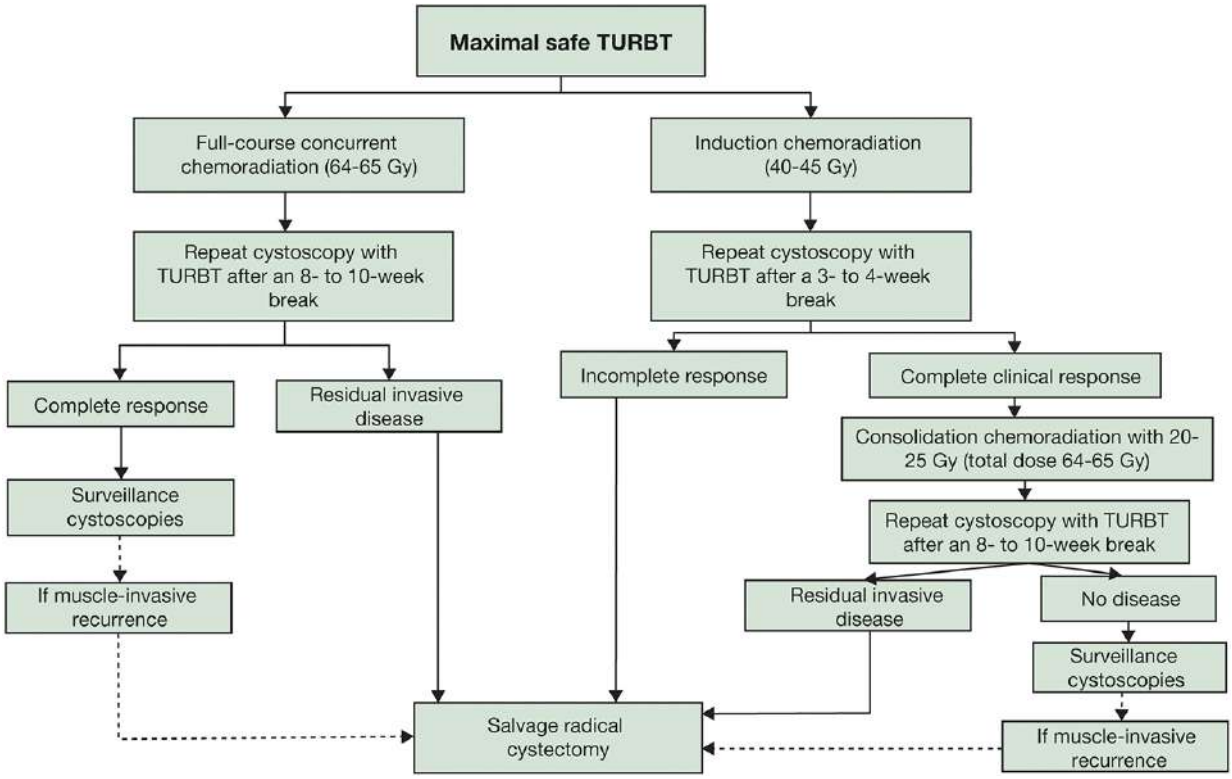

FIGURE 71.4 Trimodality therapy schema in the United States. TURBT, transurethral resection of bladder tumor.

Dose and Fractionation

Radiation dose has been fairly standardized through multiple trials, typically in the 60 to 66 Gy range using a standard fractionation of 1.8 to 2 Gy/fraction. However, moderate hypofractionation, in the form of 2.75 Gy/fraction to a total dose of 55 Gy, like what was used in the BC2001 trial,[150] is also an acceptable standard of care.

Korpics et al[233] conducted a retrospective cohort study of 843 patients with cT2-4 N0-3 M0 transitional cell MIBC treated with RT using the NCDB. Patients were divided into dose groups: less than 50, 50 to 59, 60 to 66, and greater than 66 Gy, using conventional fractionation. A subgroup analysis was performed for patients treated with 60 to 66 Gy by dividing them into three groups (60-62, 63-64, and 65-66 Gy). Median follow-up was 16.3 months; 267 (32%) patients received less than 50 Gy, 169 (20%) received 50 to 59 Gy, 376 (45%) patients received 60 to 66 Gy, and 31 (4%) patients received greater than 66 Gy. Patients receiving concurrent chemoRT were more likely to receive an RT dose of 60 Gy ($P < .001$), and patients with higher T-stage were more likely to receive a lower RT dose ($P = .003$). Two-year OS rates, when divided by RT dose, were 26%, 31%, 56%, and 55%, respectively, for less than 50, 50 to 59, 60 to 66, and greater than 66 Gy. Univariate analysis demonstrating increasing RT dose ($P < .001$) was associated with improved OS. On multivariate analysis (MVA), when compared to a dose of 60 to 66 Gy, less than 50 Gy (HR 2.36, $P < .001$) and 50 to 59 Gy (HR 1.72, $P < .001$) were associated with worse OS. Escalation of dose to higher than 66 Gy was not associated with OS (HR 1.01, $P = .977$). In the subgroup of patients treated with 60 to 66 Gy, MVA revealed that compared to 65 to 66 Gy, there was worse OS with a dose of 60 to 62 Gy (HR 1.66, $P = .020$), but no difference in OS with a dose of 63 to 64 Gy (HR 1.12, $P = .549$). The authors concluded that RT doses of less than 60 Gy are

associated with worse OS in patients undergoing bladder RT and thus should be avoided in definitive treatment. In addition, there is no survival advantage to increasing dose beyond 66 Gy.

Separately, Huddart et al[234] evaluated whether reducing radiation dose to the uninvolved bladder while maintaining dose to the tumor would reduce side effects without impairing local control (LC) in the treatment of MIBC. In the phase III multicenter trial BC2001, there was a component of comparing radiation treatment volumes in its 2 × 2 design. Two hundred nineteen patients were randomized to standard whole-bladder radiation therapy (WBRT) (sRT) or reduced high-dose volume radiation therapy (RHDVRT) that aimed to deliver a full radiation dose to the tumor and 80% of the maximum dose to the uninvolved bladder. Overall incidence of late toxicity was less than predicted, with a cumulative 2-year RTOG grade 3/4 toxicity rate of 13% and no statistically significant differences between groups. The difference in 2-year locoregional recurrence-free rate (RHDVRT vs sRT) was 6.4% under an intention-to-treat analysis and 2.6% in the "per protocol." The authors concluded that RHDVRT did not result in a statistically significant reduction in late side effects compared with sRT and that noninferiority of locoregional control could not be concluded formally.

A meta-analysis of BC2001 and BCON trials[12] to evaluate the hypofractionated treatment schedule compared to the conventional fractionation schedule found that a hypofractionated schedule of 55 Gy in 20 fractions is noninferior to 64 Gy in 32 fractions with respect to toxicity and is superior with regard to invasive locoregional control. Specifically, 782 patients with known fractionation schedules were evaluated and included in the meta-analysis. With a median follow-up of 120 months, patients who received hypofractionation had a lower risk of invasive locoregional recurrence (adjusted HR 0.71, 95% CI 0.52-0.96) compared to conventional fractionation.

A small phase II trial of 65 patients with MIBC deemed unfit for radical therapy (surgery or standard chemoradiation) was planned to receive 36 Gy in 6 weekly fractions, randomized to either adaptive plan of the day (POD) or standard planning.[235] It was found that toxicity rates were low overall (6%, 2/33, 95% CI 0.7%-20.2% for the POD group and 13%, 4/30, 95% CI 3.8%-30.7% for the standard group). In 48 patients assessed at 3 months post-treatment, disease was present in nine, giving an LC rate of 81.3% (95% CI, 67.4%-91.1%). Thus, it was concluded that this treatment schedule is safe and provides good LC for older patients unfit for radical therapy.

Radiation Treatment Frequency

Radiation can be delivered either daily or twice daily (BID). Some earlier studies had a built-in treatment break after approximately 40 to 45 Gy (induction) for restaging cystoscopy (also known as split-course therapy). If a patient had a CR or Ta/Tis residual disease on restaging cystoscopy, the patient could proceed with consolidation chemoradiation (to a total dose of 64-68 Gy). If not, prompt salvage cystectomy was recommended.[149] However, an interim check cystoscopy is no longer necessary, and many centers/institutions are now simply continuing treatment to completion (single definitive course RT).

To understand how the split-course approach arose, it must be understood that TMT was offered as an alternative to cystectomy in countries where the prevailing opinion is that surgery is the treatment of choice. Patients undergoing this treatment are offered what is termed *selective bladder preservation*, with the multiple checkpoints allowing early exit to surgery aimed at providing reassurance to surgeons in particular that the opportunity for cure is not being lost. The median ages (mid-60s) reported in studies using this approach reflect this patient selection and are similar to large surgical series.[7,156] Yet, this approach was not used in the United Kingdom, as there is a long tradition of using radical RT after TURBT, and the much older patient groups compared with

surgical series reflect a different decision-making process in which younger, more fit patients are more likely to get surgery and older or less fit patients RT.[145,151,157,158] Overall, the treatment break in the split-course schedule is debated. It allows for early identification of patients who are responding poorly so that early salvage cystectomy can be performed and allows surgery to occur after only approximately 40 to 45 Gy of dose rather than the full-dose RT. However, radiobiologic concerns exist with such a treatment break,[236,237] and there are a subset of patients who may not have yet responded to just 40 to 45 Gy of dose and need a higher dose before seeing response; thus, these patients may be recommended for surgery prematurely and potentially unnecessarily. Overall, given the complexity of coordinating a treatment break with a cystoscopy followed by consolidative chemoradiation, most centers have moved away from this split-course treatment toward a daily radiation regimen, as what was allowed on the SWOG/NRG 1806 trial.

Historically, RTOG trials[162,171-173,176,182,238-240] have evaluated radiation regimens that are either delivered once daily or BID (Table 71.4). Most RTOG protocols utilized BID treatment,[149] but, as mentioned previously, this presents a logistical burden to patients and treating centers. NRG/RTOG 0712[182] compared once-a-day radiation with gemcitabine to BID radiation using a cisplatin-based chemotherapy regimen, finding a rate of freedom from distant metastasis of more than 75% with either treatment schema, suggesting that the two are comparable.

TABLE 71.4 RADIATION THERAPY ONCOLOGY GROUP/NRG ONCOLOGY BLADDER PRESERVATION TRIALS

Study	Phase	N	Neoadjuvant Chemotherapy	RT	Arms	Adjuvant Chemotherapy	OS
RTOG 8512[237]	II	42	None	40 Gy + 24 Gy	Cisplatin + RT	None	3 y: 64%
RTOG 8802[170]	II	91	MCV	39.6 Gy + 25.2 Gy	Cisplatin + RT	None	4 y: 62%
RTOG 8903[161]	III	Arm 1: 61	MCV	39.6 Gy + 25.2 Gy	Cisplatin + RT	None	5 y: 48%
		Arm 2: 62	None	39.6 Gy + 25.2 Gy	Cisplatin + RT	None	5 y: 49%
RTOG 9506[171]	I/II	34	None	24 Gy BID + 20 Gy BID	Cisplatin/5FU + BID RT	None	3 y: 83%
RTOG 9706[172]	I/II	47	None	40.8 Gy BID + 24 Gy BID	Cisplatin + BID RT	MCV	3 y: 61%

Study	Phase	N	Neoadjuvant Chemotherapy	RT	Arms	Adjuvant Chemotherapy	OS
RTOG 9906[238]	I/II	80	None	64.3 Gy BID	Cisplatin/paclitaxel + BID RT	Cisplatin/gemcitabine	5 y: 56%
RTOG 0233[239]	II	Arm 1: 46	None	64.3 Gy BID	Cisplatin/paclitaxel + BID RT	Cisplatin/paclitaxel/gemcitabine	5 y: 71%
		Arm 2: 47	None		Cisplatin/5FU + BID RT		5 y: 75%
RTOG 0524[175]	I/II	Arm 1: 20	None	64.8 Gy daily RT	Paclitaxel/trastuzumab + RT	None	NR
		Arm 2: 46	None		Paclitaxel + RT	None	NR
NRG/RTOG 0712[181]	II	Arm 1: 33	None	64.3 Gy daily RT	Cisplatin/5FU + BID RT	Cisplatin/gemcitabine	BI-DMFS 3 y: 67%
		Arm 2: 33	None	64 Gy BID	Low-dose gemcitabine + daily RT		BI-DMFS 3 y: 72%
RTOG/NRG 0926[3]	II	37	None	61.2 Gy daily RT	Cisplatin + RT or MMC/5-FU + RT	None	3 y: 69% 5 y: 53%

BI-DMFS, bladder-intact, distant metastasis-free survival; BID, twice daily; CR, complete response; FU, fluorouracil; fx, fractions; MCV, methotrexate, cisplatin, vinblastine; MMC, mitomycin-C; NR, not reported; OS, overall survival; RT, radiotherapy.

Treatment Volumes

There are few data on the optimal RT volume. There are multiple reasonable options based on trials/experiences to use certain doses and fields for radiation.[241] The SWOG/NRG 1806 trial (ClinicalTrials.gov NCT03775265) is very inclusive, and radiation fields are as per physician discretion. Patients can be treated with a small pelvic radiation field, followed by (1) whole-bladder boost followed by bladder tumor boost, (2) whole-bladder boost alone, or (3) bladder tumor boost alone. Alternatively, patients can be treated without a small pelvic field and receive only (1) whole-bladder radiation followed by a bladder tumor boost, (2) whole-bladder radiation alone, or (3) bladder tumor radiation alone.

Inclusion of the pelvic lymph nodes in the initial course of RT is an area of debate. The rationale for treatment of the lymph nodes is due to the potential for occult lymph node metastases in these regions.[242] Extensive lymphadenectomy at the time of surgery was also shown to improve survival in an NCDB analysis.[243] This is being formally evaluated in a randomized trial (SWOG S1011, ClinicalTrials.gov NCT01224665). However, the nodal relapse rate in the BC2001 trial[150] was only 4.9% in the chemoRT arm and 6.7% with RT only. A single-institution study of patients treated with chemoradiation with weekly cisplatin randomized patients to either whole-pelvic RT (WP-RT)

versus BO-RT. There was no difference in 5-year DFS, bladder preservation rates, nodal failures, nor OS observed.[244] This study had an editorial comment of concern,[245] due to questions about the validity of the data, the analyses, and other irregularities noted; therefore, there is a low likelihood of full confidence in the data as presented. Patel et al investigated the impact of treatment volumes using the NCDB.[246] Among 2104 patients with BC treated with chemoradiation with a median follow-up of 6.2 years, there was no difference in survival between the two groups of BO versus bladder plus pelvic lymph node (BPN) irradiation (5- and 10-year OS 27.4% [95% CI 23.4%-31.4%] in the BO group vs 31.9% [95% CI 29.3%-34.6%] in the BPN group, and 13.1% [95% CI 9.7%-17.1%] in the BO group vs 13.2% [95% CI 10.6%-16.0%] in the BPN group [log-rank $P = .10$]). A recently presented study of 599 patients with MIBC[247] who underwent curative RT at 10 academic centers across Canada evaluated the utility of RT volume on outcomes: WP-RT versus BO-RT. IPTW was used to evaluate the two groups. In MVA, WP-RT did not impact CR post-RT (OR 1.13, $P = .526$), but was associated with improved CSS (HR 0.66, $P = .016$) and OS (HR 0.68, $P = .002$). We must await the final publication of these data, but it may suggest that there could be a benefit to pelvic nodal treatment.

Follow-Up Post-Radiation Therapy

After completion of treatment, patients remain on long-term cystoscopic surveillance, along with imaging to assess for distant disease. Noninvasive recurrence can be managed by further TURBT and intravesical therapy. Those with isolated muscle-invasive recurrence or failure to respond (but with no systemic relapse) can undergo salvage cystectomy with or without further chemotherapy.

Radiation Therapy Practice Patterns

At this time, practice patterns to implement TMT, particularly in the United States, vary widely among radiation oncologists. Solanki et al[248] conducted an electronic survey of U.S. radiation oncologists regarding the management of patients with cT2-3N0M0 transitional cell MIBC; 277 physicians completed the survey. Most respondents (58%) stated that they only treated one to three patients with BC in the prior year. Seventy- four percent of respondents primarily treated patients deemed unfit for cystectomy, whereas only 28% saw patients prior to cystectomy for consultation to discuss bladder preservation therapy. Most radiation oncologists (91%) used conventional fractionation instead of hypofractionation (7.6%), but more variability existed for RT targets. Sixty percent used a small pelvic field, 29% used a whole-pelvic field, and 12% treated the BO. There was increased use of hypofractionation (29%) and BO-RT (34%) in patients who were not candidates for cystectomy or chemotherapy ($P < .001$). Cisplatin-based concurrent chemotherapy was most preferred (89%). In noncisplatin candidates, most respondents preferred 5-FU plus MMC (32%) or carboplatin (32%), although the latter is a nonpreferred option. IMRT use and midtreatment cystoscopic reevaluation were variable, whereas hyperfractionation use was low. Although there are areas of consistency, variability exists in many technical and practical aspects of treatment delivery. It is important to note, however, that this study was published in 2017, and since then, BO-RT has increased, along with hypofractionation, and noncisplatin regimens such as gemcitabine are in greater use and preferred to carboplatin. Further research and education are needed to determine the optimal RT target, dose/fractionation, and concurrent chemotherapy regimen.

Practical *External Beam Radiation Therapy* Planning/Treatment Techniques

Patient Position and Immobilization

- The patient should be planned and treated in the same position; supine with arms on their chest.[241] Knee and ankle immobilization should be used to ensure patient positioning is reproducible.
- Patients may be simulated prone using a belly board to minimize small bowel in the field; however, this is not standard and is dependent on institutional experience.
- The rectum should be empty of flatus and feces. The use of daily microenemas may be considered.
- Patients should be asked to empty the bladder 10 to 15 minutes prior to scanning. This allows for more reproducibility and helps to minimize field size.
- All planning and treatment should be carried out with the bladder empty to minimize the risk of geographic miss and to keep the treated volumes as small as possible. Patients with significant residual volumes postvoiding should be considered for planning and treatment with a catheter in situ, although this is likely to increase urinary toxicity.
- However, it is reasonable to simulate the patient with a fuller bladder for tumor boost planning.
- While breathing normally, the patient should have a CT scan performed with 3- to 5-mm slices. Patients are scanned from the bottom of ischial tuberosities to 3 cm above the dome of the bladder or bottom of L5 (whichever is higher). If including a small pelvic field, the scan should go higher, to at least the top of L1.
- Intravenous contrast may be used to further delineate the pelvic vessels.
- Reference tattoos should be made at the base of the abdomen and over each hip. The location of the tattoos should be marked on the planning scan by the use of radio-opaque markers to allow cross-referencing of the planning scan and setup instructions.

Delineating Target Volumes

- The gross tumor volume can be difficult to define and should integrate information from the staging CT or MRI as well as the cystoscopy report and TURBT. MRI-CT fusion may be helpful, where available.
- If treating a small pelvic field, this typically includes the entire bladder, the prostatic urethra (in males) or proximal urethra (in females), as well as the lymph node basins in the pelvis (external iliac, internal iliac, and obturator lymph nodes). The top border is around the midsacroiliac joint (~S1/S2 or S2/S3). The inferior border is typically at the bottom of the obturator foramen. The lateral field extends 1.5 cm laterally from the pelvic brim. When using CT simulation, these borders are determined by contouring the target organs and vessels.
- The whole-bladder target volume contains the entire bladder, including the outer wall. For three-dimensional conformal RT, an expansion of 1.0 to 1.5 cm is needed. A 0.5 to 1.0 cm expansion for intensity-modulated RT constitutes the planning target volume (PTV) for this structure.
- The bladder tumor target volume is defined as including any original bladder tumor per imaging, cystoscopy, and TURBT. This volume can be difficult to define, especially if the tumor has been fully resected. The use of fiducial markers at the time of TURBT is being explored and may help identify the tumor target for image-guided adaptive RT (ClinicalTrials.gov NCT04442724).

Novel Techniques

Inter- and intrafraction anatomy changes in patients undergoing RT for BC are common and have been studied with implanted fiducial markers, CT, MRI, as well as online adaptive RT.

Fischer-Valuck et al[249] assessed the soft tissue imaging capabilities of an integrated magnetic resonance image-guided RT (MR-IGRT) system to analyze daily positioning in a preliminary study of 14 patients with BC treated on an MR-IGRT system (ViewRay Corp). Patient setup was performed via volumetric MRI with a resolution of 0.15 × 0.15 cm^2. Alignment was performed according to skin marks and shifts assessed by comparing the treatment volume from the planning CT to the daily MRI. Two hundred forty pretreatment MRIs were analyzed, and three shifts were recorded for each image. The daily volumetric MRI allowed for accurate alignment and daily monitoring of bladder volume and normal tissue anatomy. Recorded shifts of the treated volume were 0.9 × 0.5 cm^2 in the right/left direction, 0.7 × 0.3 cm^2 in the anterior/posterior direction, and 0.7 × 0.4 cm^2 in the craniocaudal direction. In 66 (28%) cases, the vector shift was initially greater than the PTV margin. For two patients, pretreatment MRI showed the tumor reduced in size and dose to the bowel would have exceeded constraints, and treatment adaptation was performed to reduce the normal tissue toxicity. Using CTCAE criteria, no grade 3 or higher toxicities were reported.

Daily image guidance, particularly with cone-beam CT, can improve the accuracy of radiation targets, particularly when boosting small volumes to a higher dose. Identifying where the pre-TURBT tumor was located within the bladder can be tricky. Some institutions implant fiducial markers into the area where bladder tumor was resected. This is being formally studied in a trial (ClinicalTrials.gov NCT04442724) to determine whether implanted fiducials help reduce collateral dose to uninvolved areas.

Online adaptive RT is being explored for its utility for MIBC treatment, given its increasing adoption in RT centers. Foroudi et al[250] described a multicenter feasibility study at 12 departments of online adaptive RT, using a choice of three “POF” for patients with MIBC (which used a uniform 7-mm margin to create PTVs from each of the three adaptive clinical target volumes [CTVs]). Departments were activated if they were part of the pilot study or after a site-credentialing visit and real-time review of the first two cases from each department. Fifty-four patients (mean age 78 years, 43 males and 7 females) were recruited, with 50 proceeding to RT. The tumor stages included T1 (one patient), T2 (35 patients), T3 (10 patients), and T4 (four patients). One patient died of an unrelated cause during RT. The three adaptive plans were created before the 10th fraction in all cases. In eight (16%) of the patients, a conventional plan using a “standard” CTV-to-PTV margin of 1.5 cm was used for one or more fractions where the pretreatment bladder CTV was larger than any of the three adaptive plans. The bladder CTV extended beyond the PTV on post-treatment imaging in 9 (18%) of the 49 patients. In general, it was concluded that an online adaptive RT technique is feasible and can be instituted in a multicenter setting. Without further bladder filling control or imaging, a CTV-to-PTV margin of 7 mm was determined to be insufficient.

Ongoing trials are evaluating the utility of adaptive planning for the treatment of advanced BC. One such trial is the RAIDER study (ClinicalTrials.gov NCT02447549), which is a randomized phase II trial of either standard planning and radiation delivery, adaptive image-guided tumor-focused radiation, or adaptive image-guided dose-escalated tumor boost radiation. The primary end point is the proportion of patients meeting radiation dose constraints to the bladder, bowel, and rectum in the dose-escalated group, as well as the proportion of patients experiencing severe late side effects following treatment. Late toxicity outcomes of 345 randomized patients from the study were recently presented.[13] Patients were randomized to standard WBRT, standard dose adaptive

tumor-focused RT (SART), or dose-escalated adaptive tumor boost RT (DART). Two fractionation schemes were utilized, either 64 Gy in 32 fractions or 55 Gy in 20 fractions for WBRT and SART or 70 Gy in 32 fractions or 60 Gy in 20 fractions for DART. In terms of RT-related grade 3 or higher toxicities, in 20-fraction DART, it was 1 of 58 (90% CI 0.1-7.9) and in 32-fraction DART, it was 0 of 57. It was concluded that 20- and 32-fraction DART was safe and feasible to deliver with toxicity rates below predefined thresholds.

Synchronous Chemotherapy and Other Systemic Therapies

There are several data sources that support the use of concurrent chemotherapy with radiation as part of TMT for MIBC. A pooled analysis of six NRG/RTOG trials studied the efficacy of chemoRT and included 468 patients with a median follow-up of over 4.3 years.[5] The CR to chemoRT was 69%. The 5- and 10-year DSS rates were 71% and 65%, respectively. The 5- and 10-year rates of muscle-invasive local failure were 13% and 14%, respectively, while the 5- and 10-year rates of non–muscle-invasive recurrence were 31% and 36%, respectively, and the 5- and 10-year rates of distant metastases were 31% and 35%, respectively. Of the 205 patients alive at 5 years, 80% had an intact bladder.

Single-institution retrospective series also support the use of concurrent chemotherapy with radiation for bladder preservation. The aforementioned study by Giacalone et al[4] found that, in a cohort of 475 patients with cT2-T4a MIBC treated at the Massachusetts General Hospital between 1986 and 2013, with a median follow-up of 7.2 years in surviving patients, 75% of patients had a CR to induction chemoradiation. The 5- and 10-year OS were 57% and 39%, respectively. The risk of salvage cystectomy was 29% at 5 years and was performed in 129 patients. In the more contemporary era (2005-2013), the rate of salvage cystectomy decreased to 16%.

A separate observational study of 415 patients with high-risk cT1 or cT2 to T4 BC were treated at the University of Erlangen between 1982 and 2000 with radiation (n = 126) or chemoradiation (n = 302).[6] Patients received either cisplatin or carboplatin-based chemotherapy. With a median follow-up of 5 years, the CR rate following RT or chemoRT was 72% for all patients. For patients receiving RT alone, the CR rate was 61%, and for those receiving chemotherapy, the rates were 66% (carboplatin), 82% (cisplatin), and 81% (5-FU/cisplatin). The 5- and 10-year OS rates were 51 and 31%, respectively, while the 5- and 10-year DSS rates were 56 and 42%, respectively. In MVA, chemoRT was associated with improved OS and CR rates compared with RT alone.

The aforementioned randomized trials of radiosensitization, the BC2001[150] and BCON[151] studies, used UK treatment schedules. These trials used radiosensitization with either concurrent chemotherapy (BC2001) or carbogen and nicotinamide (BCON). BC2001 has shown a significant improvement in locoregional DFS with concurrent 5-FU and MMC (HR 0.68; 95% CI, 0.48-0.96, P = .03).[150] Figure 71.5 shows the Kaplan-Meier curves for invasive locoregional DFS. Survival data show a trend toward an improvement in OS (HR 0.82; P = .16), although not statistically significant. The BCON trial[12] with synchronous carbogen and nicotinamide found that 3-year OS improved with carbogen and nicotinamide (59% vs 46%, P = .04), with a trend toward improvement for local relapse-free survival (54% vs 43%, P = .06). In multivariate comparison, RT plus carbogen and nicotinamide reduced the risk of relapse (P = .05) and death (P = .03).

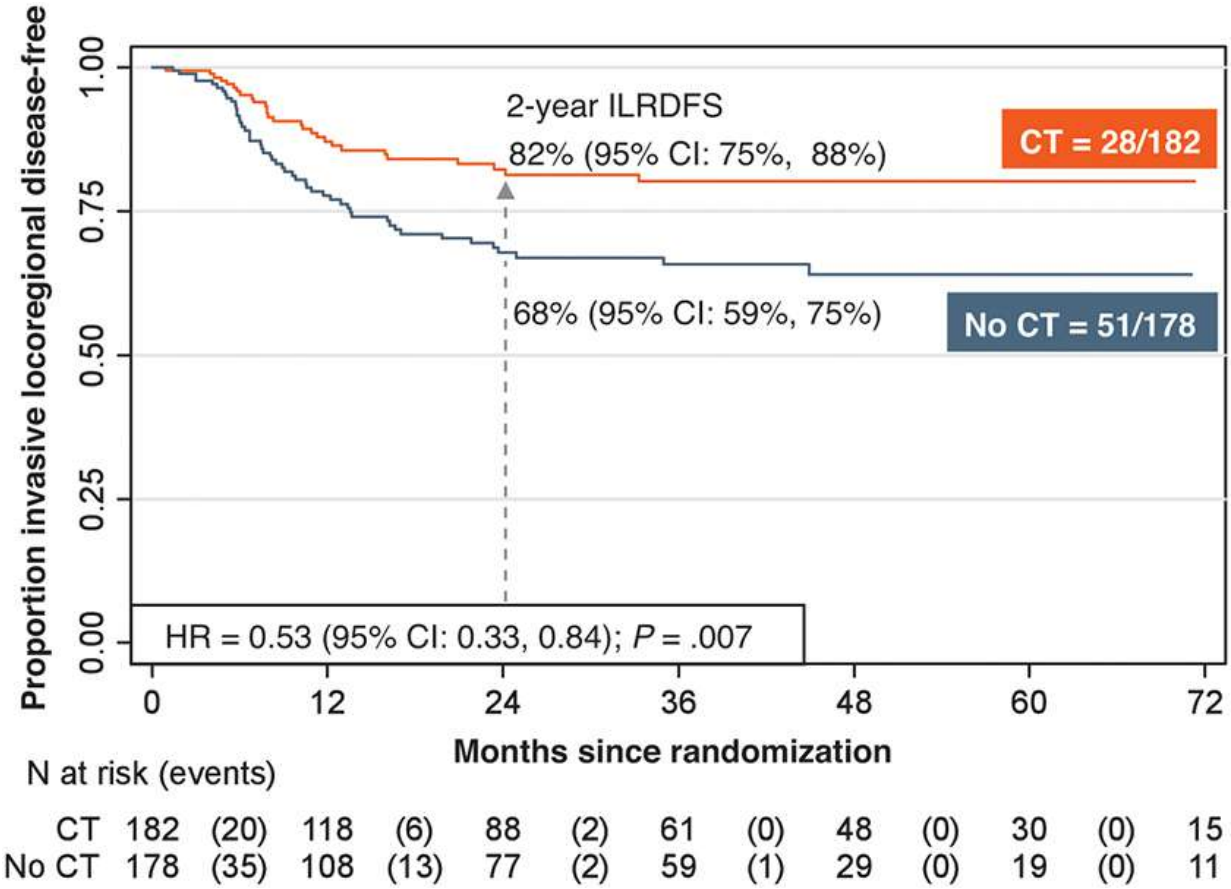

FIGURE 71.5 Invasive locoregional disease-free survival with or without chemotherapy. CI, confidence interval.

A small trial conducted by the NCIC randomly assigned patients to concurrent cisplatin with RT or RT alone.[251] There was a significant decrease in the incidence of first recurrence in the pelvis (15/51 vs 25/48) with the addition of cisplatin; however, the study failed to demonstrate an improvement in OS (although it was not powered for this end point).

Taken together, the trial data with chemoRT suggest good tolerability even in relatively older patients with excellent late toxicity profiles in the majority of patients whether treated with the North American TMT approach or the UK approach. Benefit observed in multiple studies suggests that range of chemotherapy approaches can probably be used with the selection based on toxicity. This is also evidenced by the multiple chemotherapy schedules evaluated in the NRG/RTOG studies in North America. The ongoing SWOG/NRG 1806 trial allows for one of three concurrent chemotherapy options (cisplatin, 5-FU/MMC, gemcitabine).

Immunotherapy has been shown to have efficacy in metastatic BC (see section on role of systemic therapy). Other data suggest that the combination of immunotherapy and radiation may improve outcomes in localized MIBC.[252,253] This is actively being studied in ongoing INTACT: SWOG/NRG 1806 trial, which evaluates chemoRT with or without atezolizumab in the localized MIBC disease space. The 1806 trial recently completed accrual and is the largest U.S.-based trial of bladder preservation to date (accrued 485 patients). The permissive radiation design was highly pragmatic to aid in accrual, allowing a range of radiation fields to be treated. This contemporary design will allow the results to be interpreted within the context of modern use of RT for MIBC.

Toxicity

The toxicity of definitive RT varies with the dose and schedule used. Within BC2001 and BCON, there were two schedules: 55 Gy in 20 fractions and 64 Gy in 32 fractions. Acute and late toxicities are shown in Figures 71.6 and 71.7, respectively, for both schedules, with and without chemotherapy with 5-FU/MMC. In BC2001, synchronous chemotherapy increased toxicity but was predominantly grade 1 or 2, with a nonstatistically significant effect on grade 3 or 4 events (27.5% vs 36%; $P = .07$; boundary for significance set at 0.01 to reflect multiplicity of testing).[150] As discussed earlier, the component of comparing radiation treatment volumes in its 2 × 2 design, evaluating WBRT compared to RHDVRT (or partial bladder) did not find that the RHDVRT resulted in lower rates of toxicity compared to standard WBRT.[234] Treatment completion rates in both trials were very high, with an excess of 95% of patients receiving the prescribed dose. The majority of patients failing to complete did so for tumor-related reasons rather than toxicity. Late toxicity was of great interest in both trials and was analyzed somewhat differently. In BCON, the cumulative rates of grade 3 or 4 events were reported, which gives the worst-case scenario but does not reflect the overall toxicity at any given time point post-treatment. BC2001 reports the toxicity rates at prespecified times.

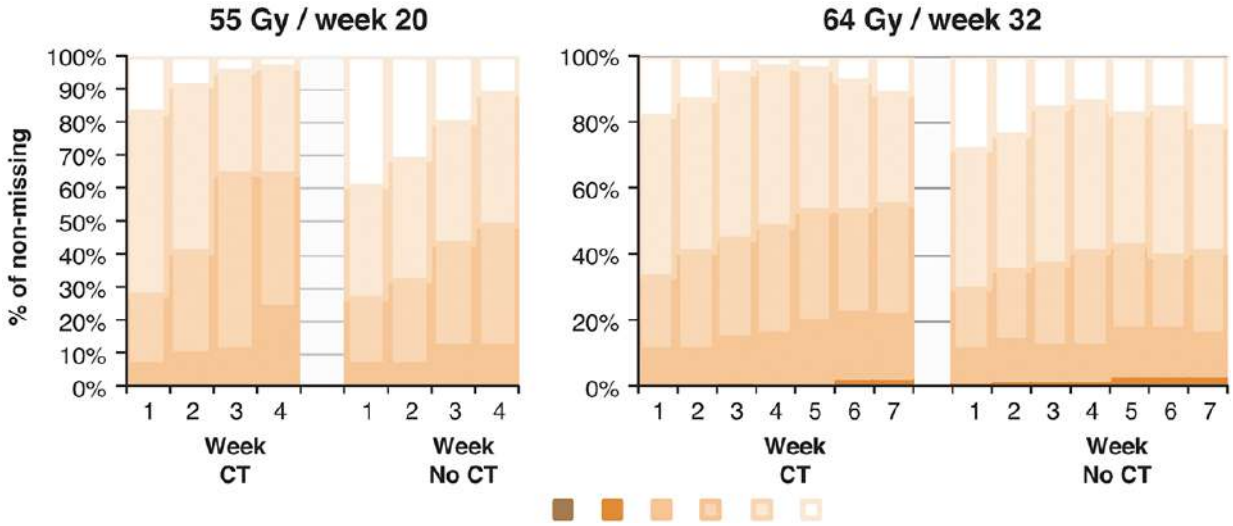

FIGURE 71.6 Acute toxicity of radiotherapy with and without synchronous chemotherapy. Graphs show a worst grade of on-treatment toxicity by radiotherapy dose and week. Darkest bars indicate National Cancer Institute common terminology class grade 4; white indicates grade 0. Proportions with a grade 3 or 4 at any time on treatment: 64/178 (36.0%) chemotherapy (CT) versus 50/182 (27.5%). No CT-stratified chi-square test ($P = .07$).

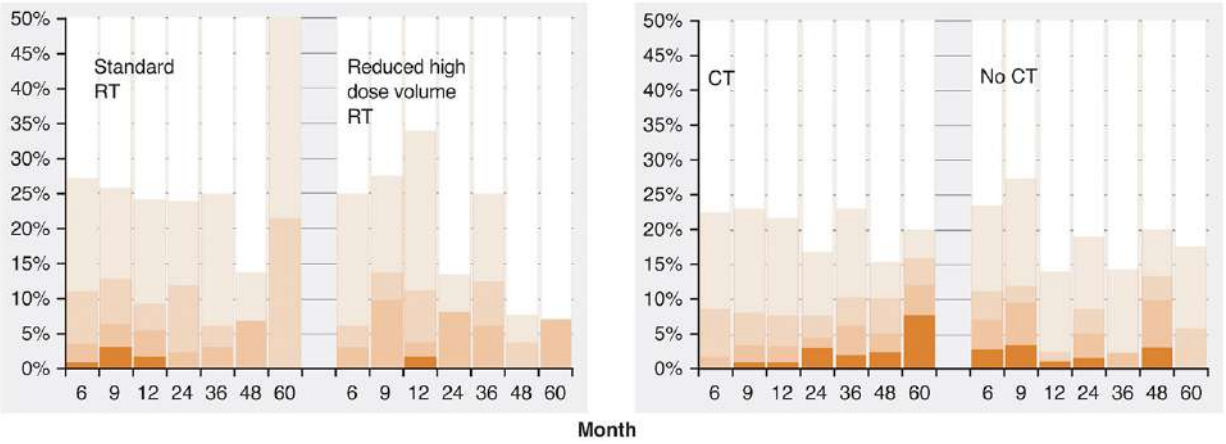

FIGURE 71.7 Late toxicity in the BC2001 trial. Darkest bars indicate Radiation Therapy Oncology Group (RTOG) grade 4; white indicates grade 0. Proportion of patients with grade 3 or 4 RTOG toxicity at any month during follow-up (6 months onward), up to 3 months before a recurrence: RT, 12.9% sRT versus 17.9% RHDV; odds ratio (95% confidence interval) 1.34 (0.55, 3.24); *P* = .52; CT, 8.3% CT versus 15.7% no CT; odds ratio 0.48 (0.21, 1.10); *P* = .07. Patients with no available assessment were excluded from analysis. CT, chemotherapy with radiotherapy; RHDV, reduced high-dose volume radiotherapy; RT, radiotherapy; sRT, standard volume radiotherapy.

There are a number of points of note here. First, late toxicity was the same with both randomizations in BC2001 (ie, reduced-volume RT did not impact late toxicity). More significantly, the addition of synchronous chemotherapy also had no effect on reported late side effects. In addition, at any given point, 75% to 80% of patients report no late toxicity at all. This is supported by bladder capacity measurements in BC2001, which show a mean change in bladder volume at 1 year of less than 5 mL. Of those reported grade 3 or 4 RTOG adverse events, fewer than 10% reported events in the chemoRT group and fewer than 20% reported events in the RT group at some point during follow-up. Very similar findings pertain to the BCON trial.[151]

Other data support the good acute tolerance of bladder RT. A large, retrospective study of 487 patients treated with radiation to a mean total dose of radiation dose of 65.5 Gy, the incidence of RTOG grade 3 or higher acute bladder and bowel toxicity was 5% and 3%, respectively.[254]

In terms of late toxicity, in the same retrospective analysis of 487 patients, the incidence of RTOG grade 3 or higher late bowel/bladder toxicities, defined as toxicities that occurred or persisted after the third month from the end of RT, was 12% and 3%, respectively.[254] In 2009, Efstathiou et al[10] reported late toxicity results in 285 patients who had participated in four RTOG TMT trials. Median follow-up was 5.4 years. Overall 5.7% reported persistent late genitourinary and 1.9% gastrointestinal toxicity of grade 3 or higher, consistent with the BCON and BC2001 results.

The good toxicity and functional results associated with RT are borne out by surveys of QoL and symptoms in cystectomy and RT patients carried out by multiple groups.[9,255-257] Furthermore, RT and cystectomy patients report different patterns of symptoms, with sexual dysfunction being more prominent in surgical patients and bowel symptoms more prominent in RT patients.

In a study evaluating long-term health-related QoL in MIBC survivors who either received TMT or RC[9] found that, after a median follow-up of 5.6 years, patients who received TMT had improved general QoL compared to those who received surgery (9.7 points, *P* = .001) and higher physical, social, emotional, role, and cognitive function by 6.6 to 9.9 points, *P* = .04. Bowel function was improved, as well as sexual function and body image.

One study compared effectiveness of TMT and RC using decision-analytic modeling with the end point of quality- adjusted life years (QALYs).[257] It was found that TMT resulted in an incremental gain of 0.59 QALYs over surgery. When limiting the model to favorable, contemporary cohorts, TMT remained more effective with an incremental gain of 1.61 QALYs. These data support the need for prospective validation of QoL end points in future studies evaluating surgery as well as bladder preservation for patients with MIBC. This is particularly important as less is known about toxicity/QoL in female patients treated with TMT. In a small study of TMT patients completing health-related QoL questionnaires (64/74 TMT patients with completed questionnaires, 86%), 14 (22%) were women.[258] Fewer women reported no diarrhea compared to men (50% vs 86%, $P = .02$), and a greater percentage of women reported some degree of sexual activity in the 4 weeks prior to questionnaire completion ($P = .04$) as well as less decline in sexual interest with age compared to men. However, given the small numbers in the study, it is important to gather further information surrounding QoL by age and gender for patients undergoing surgery and TMT.

When using immunotherapy in conjunction with RT for localized MIBC, the safety and tolerability must be adequately assessed. Two early phase I studies evaluated immunotherapy in combination with hypofractionated RT to the bladder.[259,260] The PLUMMB trial (ClinicalTrials.gov NCT02560636) was a phase I study of five patients with locally advanced/metastatic BC, treated with 36 Gy in 6 weekly fractions along with pembrolizumab starting 2 weeks prior to radiation and concurrently with radiation.[260] This trial was stopped early as two patients experienced severe bladder irritation (cystitis or pain). These were determined to be protocol-defined dose-limiting toxicities judged to be related to treatment. A separate phase I trial evaluated atezolizumab along with weekly gemcitabine for 4 weeks concurrent with hypofractionated radiation (50 Gy in 20 fractions) for localized MIBC.[259] The protocol included radiation to the pelvic lymph nodes. There were a total of eight patients enrolled. The first give patients received atezolizumab at 1,200 mg intravenously every 3 weeks for 16 cycles. Three patients developed grade 3 side effects (gastrointestinal), two of which qualified as dose-limiting toxicity. Thus, the dose of atezolizumab was decreased to 840 mg for the remaining three patients. However, the study was ultimately terminated due to the development of additional grade 3 toxicity in two patients treated with the reduced dose. The toxicities were mostly gastrointestinal. Four patients developed grade 3 colitis. Due to these findings, the SWOG/NRG 1806 trial did not allow for hypofractionation. An early analysis of safety data of 73 patients enrolled onto the trial (36 receiving standard TMT, 37 receiving TMT + atezolizumab) found reasonable toxicity rates, with 11 grade 3 or higher toxicities on the standard arm versus 23 on the experimental arm.[261] An updated analysis presented in 2022 of 213 patients (100 receiving standard TMT, 113 receiving TMT + atezolizumab) found 44 patients with grade 3 or higher toxicity events on the standard arm versus 65 on the experimental arm.[262] The most common toxicity was hematologic and considered nonimmune related, with overall reasonable rates of toxicity in these early safety analyses. Thus, the combination of conventionally fractionated radiation and immunotherapy appears to be safe with acceptable early toxicity. The combination of hypofractionated RT and immunotherapy may be a good use case for online adaptive RT—the ability to adapt the treatment daily to avoid high-dose RT near-critical organs at risk, such as the small bladder, may circumvent the observed toxicities observed in the aforementioned phase I trials.

Pattern of Failure

The BC2001 study gives a good indication of patterns of failure in response to bladder preservation therapy.[150] A summary of relapse patterns in the chemoRT arm of the trial is shown in Figure 71.8.

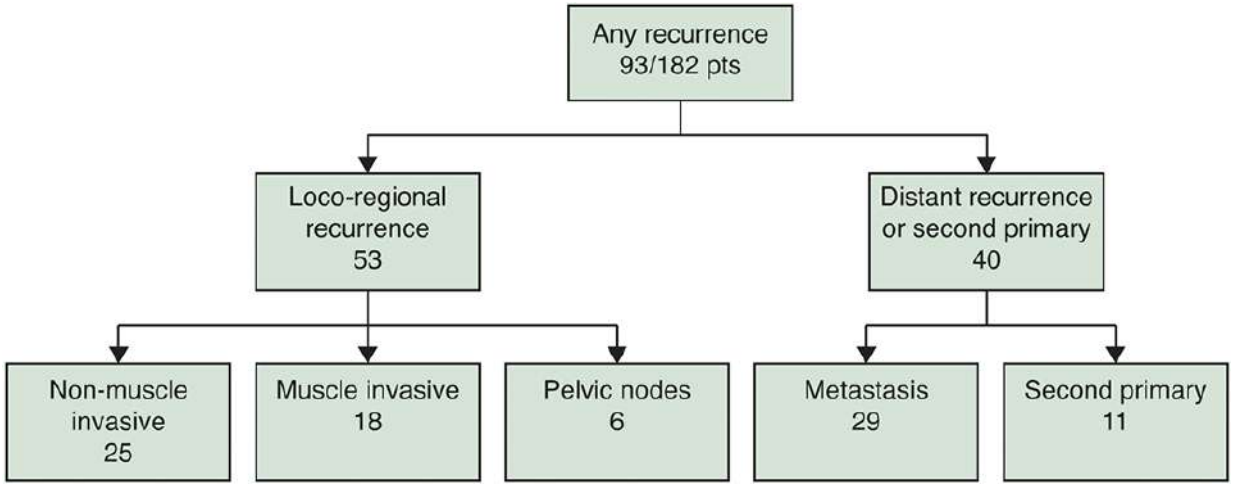

FIGURE 71.8 Patterns of failure after chemoradiotherapy in BC2001.

There are a number of features of note here. First, the majority of locoregional failures are in the bladder, and there are more noninvasive than invasive recurrences. This underlines the need for regular surveillance post-RT and the requirement for multidisciplinary care if patients are to be managed by bladder conservation. Many noninvasive recurrences can be successfully managed conservatively without the need for cystectomy. For those with invasive recurrence, cystectomy remains an option if the patients are sufficiently fit. The low rate of nodal relapse in BC2001 is also of interest, as no attempt was made to include pelvic nodes in the field, although lower pelvic nodes would have been included in the treated volume. For improvement in the metastatic relapse rate, better systemic therapies must be found.

Role of Systemic Neoadjuvant/Adjuvant Therapy

Contrary to management with RC, the role of neoadjuvant or adjuvant chemotherapy in conjunction with concurrent chemoradiation is not firmly established, given the limited high-quality data for either approach, as reviewed later.

The RTOG 89-03 trial[162] assigned 123 patients to two cycles of neoadjuvant cisplatin/methotrexate/vinblastine (MCV) chemotherapy prior to concurrent chemoradiation or to concurrent chemoradiation without neoadjuvant chemotherapy. The addition of neoadjuvant chemotherapy did not improve OS or decrease the rate of distant metastases. There were four treatment-related deaths in the arm that received neoadjuvant chemotherapy versus one in the control arm. Three of the four deaths in the neoadjuvant chemotherapy arm were due to neutropenic sepsis. Given the risks observed with no improvement in oncologic outcomes, it was concluded that neoadjuvant MCV chemotherapy was not beneficial when combined with TMT. However, there are some limitations worth mentioning, including that the study did not fully accrue (planned accrual $n = 174$) as it was closed early due to the unexpectedly high rate of severe neutropenia and sepsis, patients were planned for two cycles of MCV instead of three, and there was not good supportive care in that era for chemotherapy treatments, likely contributing to high rates of complications and deaths in the neoadjuvant chemotherapy arm.

The BA06 30894 trial[35] randomized 976 patients (treated with either cystectomy or curative-intent RT) to either three cycles of MCV neoadjuvant chemotherapy or no neoadjuvant chemotherapy. There was a 16% reduction in the risk of death with neoadjuvant chemotherapy compared to no neoadjuvant chemotherapy (HR 0.84, 95% CI 0.72-0.99). Five-year OS rate in the

no neoadjuvant chemotherapy group was 43% versus 49% in the neoadjuvant chemotherapy group, while 10-year OS rate in the no neoadjuvant chemotherapy group was 30% versus 36% in the neoadjuvant chemotherapy group. The patients in the RT group did not receive concurrent chemotherapy along with the RT; thus, it is unclear whether this benefit would be maintained in a cohort of patients treatment with modern techniques and concurrent chemoRT.

A retrospective analysis of 2,566 patients in the NCDB with cT2-4N0M0 urothelial cell carcinoma of the bladder treated with definitive concurrent chemoradiation between 2004 and 2015 evaluated the receipt of neoadjuvant chemotherapy versus those without neoadjuvant chemotherapy.[263] With a median follow-up of 6.2 ears, there was no difference in survival between groups (neoadjuvant chemotherapy, 462 patients vs chemoradiation alone, 2,104 patients): 5-year OS 30.6% (95% CI 28.4%-32.9%) in neoadjuvant group versus 31.8% (95% CI 27.0%-36.8%) in the standard chemoradiation group; 10-year OS 13.3% (95% CI 11.2%-15.5%) in the neoadjuvant group versus 13.0% (95% CI 8.4%-18.7%) in the standard chemoradiation group (log-rank P = .19). There was no association between receipt of neoadjuvant chemotherapy and OS on MVA (P = .921). These results suggest that that there is no benefit to the routine addition of neoadjuvant chemotherapy to standard chemoradiation for BC.

Finally, the BC2001 study[150] allowed neoadjuvant chemotherapy prior to RT or chemoRT. Thirty-three percent of patients received neoadjuvant chemotherapy. The benefit observed from concurrent chemoRT compared to RT alone was similar in those who received neoadjuvant chemotherapy (HR 0.62, 95% CI 0.35-1.13) and in those who did not receive neoadjuvant chemotherapy (HR 0.71, 95% CI 0.46-1.10). The effectiveness of neoadjuvant chemotherapy was unable to be fully assessed, given the small numbers of patients who received it.

Given the limited data available, we certainly feel that neoadjuvant chemotherapy is an option with TMT depending on the clinical situation. Importantly, we do not feel that the receipt of neoadjuvant chemotherapy should preclude the option of proceeding with a bladder-sparing approach.

Role of External Beam Radiation Therapy for Node-Positive Disease

As reviewed in the Surgical section, the AJCC eighth edition[121] was modified and reclassified node-positive disease (defined as N1-N3 disease) as stage III (previously identified as stage IV disease), because node-positive disease has more favorable outcomes compared to M1 disease.

However, there is a paucity of data on optimal treatment approach for patients with clinically node-positive disease, particularly with respect to bladder preservation strategies. The phase II ECOG-ACRIN/NRG EA8185 trial (INSPIRE) evaluated the role of chemoRT with or without durvalumab in node-positive BC to identify an appropriate treatment approach for these patients (ClinicalTrials.gov NCT04216290). This trial was also novel given the nodal treatment design, which could help answer the question of whether regional nodal involvement may be considered curable with the use of chemoRT. Unfortunately, this study was recently closed due to poor accrual; hence, we must await additional studies/data to further understand the optimal treatment approach for these patients.

Palliative Radiation Therapy

In patients in whom palliative radiation is warranted, the Medical Research Council prospective randomized trial BA09 established that 21 Gy in 3 fractions on alternate weekdays is as effective as 35 Gy in 10 fractions.[264] Five hundred patients were recruited, but data on symptomatic improvement at 3 months were only available on 272 patients. Of these, 68% achieved

symptomatic improvement (71% for 35 Gy, 64% for 21 Gy), with no evidence of a difference in efficacy or toxicity between the two arms. On the basis of these results, 21 Gy in three fractions is widely used in the United Kingdom as a palliative schedule. The data are congruent with other data on hypofractionation for palliation as well as the growing trend for hypofractionation in other pelvic sites, in particular the prostate.

Electron and Proton Beam Therapy

Electron beams are only of interest in the context of intraoperative RT. The role of this modality for carcinoma of the bladder needs to be assessed in a prospective trial and cannot at present be recommended outside a suitable study.

There is scanty published information on the use of protons in the treatment of patients with MIBC. Takaoka et al[265] retrospectively reviewed patients with MIBC who received TMT using proton beam therapy at a single institution. Between 1990 and 2015, 70 patients with cT2-3N0M0 MIBC were treated. Median follow-up was 3.4 years. The 5-year cumulative OS rate, PFS rate, and time to progression rate were 82%, 77%, and 82%, respectively. Twenty-six (18%) patients had grade 3 to 4 acute hematologic toxicities, and two (3%) patients had late grade 3 genitourinary toxicity. Overall, treatment was well tolerated, and patients had favorable clinical outcomes. A separate study by Araya et al[266] reviewed the outcomes of 36 patients with MIBC enrolled in the Proton-Net prospective registry study and received proton beam therapy with concurrent chemotherapy between May 2016 and June 2018. OS, PFS, and LC rates were 90.8%, 71.4% and 84.6%, respectively, after 3 years. Only one case (2.8%) experienced a treatment-related late adverse event of grade 3 urinary tract obstruction, and no severe gastrointestinal adverse events occurred. More data from long-term follow-up are needed to further guide the use of proton beam therapy for MIBC.

Brachytherapy

There is considerable historic literature on the use of brachytherapy (BT), particularly from the Netherlands. The main advantage for this technique is the conservation of bladder function. Reported results seem to be very good; for example, van der Werf-Messing et al[267] report the outcomes in 328 patients treated with 3 × 3.5 Gy external irradiation followed by a radium implant. Overall 5- and 10-year survival rates were 56% for T2 tumors and 39% and 13%, respectively, for T3 disease. Similar results have been obtained in more recent series with iridium-192 implants and manual afterloading.[268,269] There are also descriptions in the literature of the use of high-dose rate (HDR) afterloading, although one paper suggests that this may be less effective and more toxic than low-dose rate treatment.[270] The striking feature of most of these series is the very low patient numbers and long time spans reported, suggesting that these techniques are only rarely used, even in centers with relevant expertise.

van der Steen-Banasik[271] reported on 57 patients with a T2 solitary bladder tumor treated with transurethral bladder resection followed by external beam irradiation to the bladder and regional iliac lymph nodes (40 Gy in 20 fractions, 5 fractions per week), and within 1 week interstitial HDR BT, in selected cases combined with partial cystectomy and lymph node dissection. The BT catheters were placed via a transabdominal approach with robotic assistance from a Da Vinci robot. The fraction schedule for HDR was 10 fractions of 2.5 Gy, 3 fractions per day, which was calculated to be equivalent to a reference low-dose rate schedule of 30 Gy in 60 hours. Average postoperative hospitalization was 6 days, with minimal blood loss and no wound healing problems. Two patients had severe acute toxicity: one pulmonary embolism grade 4 and one cardiac death.

Late toxicity was mild (two urogenital grade 3 toxicity). The median follow-up was 2 years; the 2-year OS, DFS, DSS, and local tumor control rates were 59%, 71%, 87%, and 82%, respectively.

The GEC-ESTRO/ACROP (Groupe Européen de Curiethérapie- European Society for Radiotherapy and Oncology/Advisory Committee on Radiation Oncology Practice) published recommendations to perform bladder implants and BT as a treatment option for MIBC and techniques were described.[272]

Summary of Radiation Therapy

RT for BC has evolved tremendously with many exciting technological advances and opportunities for further enhancement. Radiation treatment has emerged as a viable alternative to RC for selected patients with MIBC. The largest trial to date of bladder preservation therapy in North America recently completed accrual (n = 485 patients, SWOG/NRG 1806), and it is a highly pragmatic and contemporary trial with or without the inclusion of immunotherapy to potentially improve upon clinical outcomes. We eagerly await the results of this and other studies, as well as await corresponding correlative analyses, which may identify biomarkers of response and treatment selection.

ROLE OF SYSTEMIC THERAPY

Up to 50% of patients will develop metastatic disease. BC is a chemosensitive disease, with responses reported to a range of agents. Systemic combination chemotherapy can be effective and result in tumor responses and symptom control. Overall response rates may be as high as 70%, with a median survival of approximately 12 to 14 months.[41,204]

Separately, the development of immune checkpoint inhibitors as well as antibody-drug conjugates has changed the treatment landscape for metastatic UC.[273] These agents have been evaluated as first-line therapy for metastatic UC, with improvement in median OS to as high as 30 months, such as in the case of combination EV plus pembrolizumab,[42] redefining the treatment paradigm for this disease. Their role in localized disease is not fully established, although there are ongoing studies evaluating safety and efficacy in this clinical space.

Systemic Regimens in Metastatic Disease

Initial therapy for patients with metastatic UC is actively evolving. Based on recent data, patients with advanced or metastatic UC should undergo initial therapy with EV plus pembrolizumab rather than platinum-based chemotherapy with maintenance immunotherapy (Figure 71.9). This is pasted on a phase III study (EV-302)[42] where EV conferred a large OS benefit with an acceptable toxicity profile. Patients who were eligible for platinum-based chemotherapy were randomized to EV plus pembrolizumab versus chemotherapy (gemcitabine plus either cisplatin or carboplatin). EV plus pembrolizumab improved OS (median 32 vs 16 months, HR 0.47, 95% CI 0.38-0.58) and PFS (median 13 vs 6 months, HR 0.45, 95% CI 0.38-0.54) in the entire study population. Among cisplatin-eligible patients, both OS (median 32 vs 18 months, HR 0.53, 95% CI 0.39-0.72) and PFS (median 15 vs 7 months, HR 0.48, 95% CI 0.38-0.62) were improved. Among cisplatin-ineligible patients, EV plus pembrolizumab improved both OS (median not reached vs 13 months, HR 0.43, 95% CI 0.31-0.59) and PFS (median 11 vs 7 months, HR 0.43, 95% CI 0.33-0.55) compared to chemotherapy.

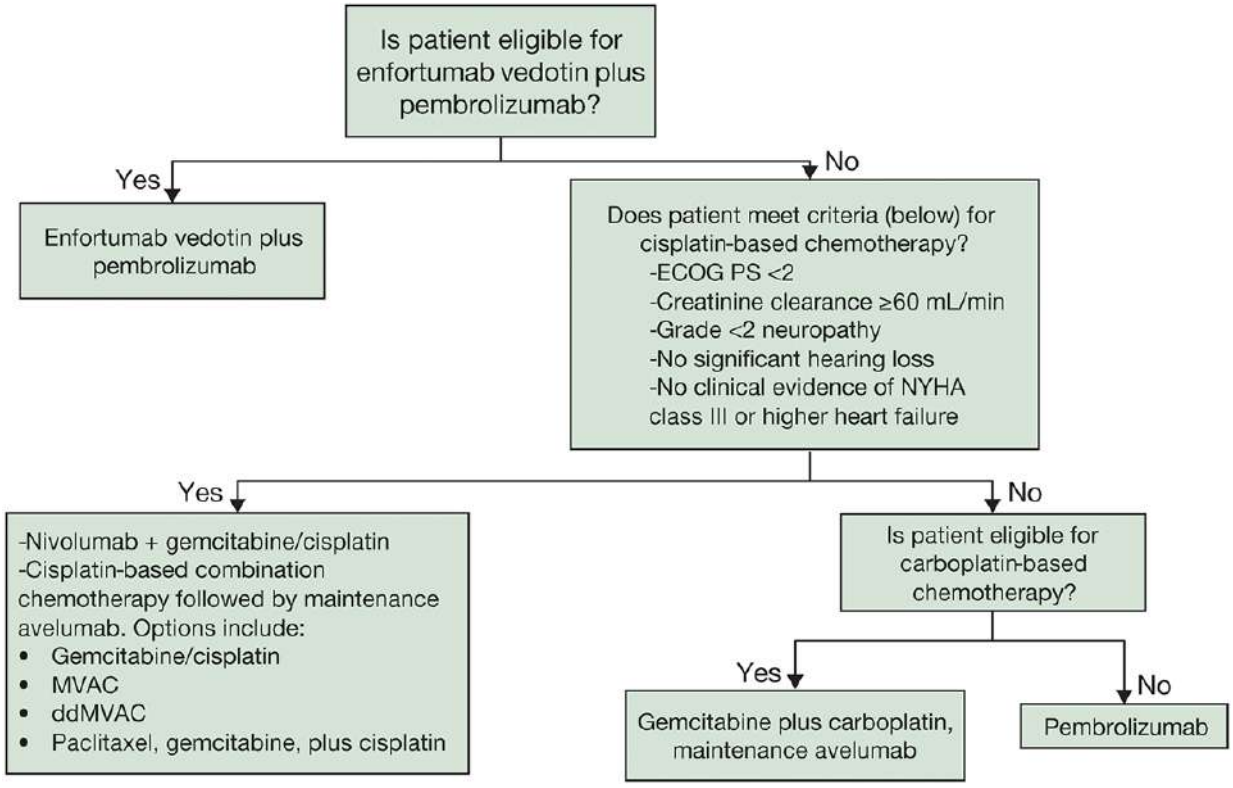

FIGURE 71.9 First-line systemic therapy for metastatic urothelial carcinoma. MVAC, methotrexate/vinblastine/doxorubicin (adriamycin)/cisplatin; NYHA, New York Heart Association.

For those who are not eligible for EV plus pembrolizumab (eg, patients with preexisting or poorly controlled neuropathy or have preexisting cutaneous disorders), first-line therapy depends on cisplatin eligibility.

Cisplatin Eligible

There are several cisplatin-based regimens available to patients, and the choice is based on provider and patient preferences.

Nivolumab plus GC is an option for cisplatin-eligible patients. An open-label phase III trial (CheckMate-901)[274] with 608 cisplatin-eligible patients were randomly assigned to either nivolumab plus GC followed by maintenance nivolumab, or GC. At a median follow-up of 33.6 months, the addition of nivolumab to GC improved OS (median 21.7 vs 18.9 months, HR for death 0.78, 95% CI 0.63-0.96, $P = .02$). PFS was also longer (HR for progression or death, 0.72, 95% CI 0.59-0.88, $P = .001$). Median duration of CR was 37.1 months with the nivolumab/gemcitabine/cisplatin regimen compared to 13.2 months with GC alone. Grade 3 or higher toxicity rates were higher with the combination therapy; however, health-related QoL after 4 months of treatment was similar between the two groups.

The four-drug combination MVAC is one such treatment option for the initial therapy of patients with locally advanced or metastatic UC. A multicenter trial of 269 patients were randomly assigned to treatment with either MVAC or single-agent cisplatin.[275] The use of MVAC significantly improved the response rate (39% vs 12%, $P < .0001$), a significant increase in median PFS (10 vs 4 months) and a significant improvement in median OS (13 vs 8 months). However, it is associated with more toxicity compared to single-agent cisplatin.

ddMVAC, which increases the dose intensity of MVAC by administering treatment every 2 weeks with granulocyte colony-stimulating factor support, has been evaluated with the hope of improving long-term survival. A phase III study (EORTC 30924)[276] randomized 263 patients to either classic MVAC or ddMVAC found that ddMVAC improved median PFS (9.1 vs 8.2 months) as well as 2-year PFS (25% vs 12%, HR 0.75, 95% CI 0.58-0.98) and was associated with higher CR rates (21% vs 9%). However, ddMVAC failed to improve OS over classic MVAC (median 15.5 vs 14.1 months, 2-year OS 35% vs 25%, HR 0.80, 95% CI 0.60-1.06). The 7-year update of the trial demonstrated improved 5-year survival with ddMVAC (21.8%) over classic MVAC (13.5%), but this difference was not statistically significant.[277] ddMVAC was also associated with an improved toxicity profile over classic MVAC.

GC is another option for initial therapy. It has been found to have similar efficacy and less toxicity compared with MVAC. A phase III trial of 405 patients randomized to either GC or MVAC[39],[278] found that, after a median follow-up of 19 months, OS was similar between both arms (HR 1.04, 95% CI 0.82-1.32, $P = .75$) as was time to progression (HR 1.05, 95% CI 0.85-1.30), time to treatment failure (HR 0.89, 95% CI 0.72-1.10), and response rate (GC 49%, MVAC 46%). There was less grade 3 or higher toxicity with GC.

The addition of paclitaxel to gemcitabine and cisplatin (PCG) was evaluated in a phase III clinical trial by EORTC (study 30987), which enrolled 627 patients with advanced UC. The regimens were well tolerated. Results showed that the PCG arm resulted in a higher rate of overall response rate (55.5% vs 43.6%, $P = .0031$) and median OS (15.8 vs 12.7 months, HR 0.85, $P = .075$) compared with GC arm. Both treatments were well tolerated.

Cisplatin Ineligible

In patients who are not eligible for either EV plus pembrolizumab or cisplatin, gemcitabine plus carboplatin is a reasonable alternative for these patients. In a randomized phase II/III trial (EORTC 30986),[279] 238 patients were randomized to either gemcitabine plus carboplatin versus a more complex carboplatin regimen (methotrexate, carboplatin, and vinblastine—M-CAVI). With a median follow-up of 4.5 years, gemcitabine plus carboplatin resulted in similar OS (median 9.3 vs 8.1 months, $P = .64$) compared to the M-CAVI regimen. There was no difference in PFS between the two arms ($P = .78$). There were lower grade 3-4 toxicity rates in the gemcitabine and carboplatin arm (9% vs 21%).

Maintenance Therapy

In patients who have not progressed on platinum-based chemotherapy alone and are eligible to receive immune checkpoint inhibitors, it is recommended to proceed with maintenance avelumab based on results from the randomized phase III JAVELIN Bladder 100 trial.[280,281] In this study, 700 patients who experienced either an objective response or stable disease after four to six cycles of gemcitabine plus platinum-based chemotherapy were randomly assigned to maintenance avelumab or best support care. After a median follow-up of 39 months, in the entire study population, the addition of avelumab improved OS and PFS (3-year OS 36% vs 30%, median 24 vs 15 months, HR 0.76, 95% CI 0.63-0.91; 3-year PFS 16% vs 5%, median 6 vs 2 months, HR 0.54, 95% CI 0.46-0.64). This was demonstrated regardless of type of platinum-based chemotherapy regimen received. Although this study evaluated maintenance avelumab in patients who received gemcitabine plus platinum-based chemotherapy, it is suggested to offer this approach who have not progressed on other platinum-based chemotherapy regimens, extrapolating from this study.

Second-Line Therapy and Beyond

For patients who progress post-initial therapy, the choice of second-line therapy is largely dependent on what the patient received as part of initial therapy and is beyond the scope of this chapter. Similarly, later-line therapies are dependent on multiple clinical factors, including prior therapies received, molecular alterations present, and patient comorbidities, as well as treatment goals. We encourage clinical trial enrollment where possible.

TREATMENT OF PATIENTS WITH UNCOMMON BLADDER TUMORS

Squamous Cell Carcinoma

SCC is uncommon in the developed world, and many reported cases may in fact reflect sampling of squamous elements within UC. As these tumors are often excluded from systemic therapy trials, there are few data on outcomes with treatment as most papers are retrospective collections of unconnected observations.[282,283] It appears that local failure may be more prevalent than distant relapse, but even that observation is based on very few cases.

Although SCC is represented in many of the studies on bladder preservation, some physicians may be reluctant to offer this approach to patients with MIBC with this rare histology because of its perceived poor response to therapy and adverse outcomes in comparison to more common histologies of MIBC. Stokes et al[284] queried the NCDB for patients with T2-T4 or TX, N0M0 SCC of the urinary bladder diagnosed from 2004 to 2012 receiving both chemotherapy and high-dose RT (>55 Gy) without upfront cystectomy. Patients with UC were queried separately to serve as a comparison group. Fifty-four patients with SCC and 2,054 those with UC were identified. Patients with SCC were more likely to be younger, female, or non-White and were more likely to have more advanced disease at presentation. Age greater than 70, comorbidity score greater than 0, and stage T3 or higher were associated with worse OS, whereas gender, race, insurance status, household income, facility type, chemotherapy (single vs multiagent), and histology showed no association with OS. OS estimates were not significantly worse for SCC compared to UC (5-year OS 25.4% vs 33.3%; adjusted HR, 1.34, $P = .12$). Overall, it was concluded that OS did not significantly differ between patients with SCC and those with UC undergoing organ preservation for MIBC, whereas other prognostic factors were relevant in both groups.

Using the SEER database queried from 1998 to 2007, Li et al[285] evaluated patients with muscle-invasive (stage II-IV) SCC of the urinary bladder who underwent complete cystectomy. A total of 331 patients were included in the analysis. The majority had cystectomy alone ($n = 297$), whereas 10% ($n = 34$) received postoperative RT. Factors associated with postoperative RT were younger age ($P = .03$) and more advanced stage at diagnosis ($P < .001$). The addition of RT was not associated with an OS benefit ($P = .55$). Median survival was 21 months for patients treated with cystectomy alone and 18 months for postoperative RT. Cox regression analysis confirmed the lack of improvement in OS among patients who received postoperative RT ($P = .47$).

A prospective randomized trial conducted in patients with locally advanced BC after RC sought to evaluate whether adjuvant sequential RT plus chemotherapy could improve locoregional recurrence-free survival compared with adjuvant chemotherapy alone.[286] As this study was conducted in Egypt, of the 120 patients enrolled, almost 47% had SCC or other histology. The chemotherapy plus RT arm had 75 patients, while the chemotherapy alone arm had 45 patients. Adjuvant chemotherapy plus RT was significantly associated with improved locoregional recurrence-free survival (2-year outcome of 96% vs 69%, adjusted HR 0.08, 95% CI 0.02-0.39, $P < .001$) and marginal improvements in DFS (2-year outcome of 68% vs 56%, adjusted HR 0.53, 95%

CI 0.27-1.06, P = .07) and OS (2-year outcome of 71% vs 60%, adjusted HR 0.61, 95% CI 0.33-1.11, P = .11). In addition, adjuvant RT was reasonably well tolerated.

Urachal Adenocarcinomas

Urachal adenocarcinomas are extremely rare. Surgical resection with a partial cystectomy and en bloc resection of the urachal ligament with umbilicus are the treatment choices in the setting of localized disease. A retrospective analysis of 66 cases at a single institution between 1951 and 2004 evaluated the efficacy of different treatments.[287] Most patients received partial cystectomy (70%), followed by complete cystectomy in 21% and RT in 9%. Five-year OS was 49%. MVA found that low tumor grade and negative surgical margins were associated with better survival, while higher pathologic stage and surgical margin involvement were associated with a poor prognosis. There is currently no definitive role for neoadjuvant or adjuvant chemotherapy in this tumor. Unfortunately, there are many patients who present with metastatic disease, which currently is not likely to be curable. There is no standard chemotherapy regimen for these patients.

Small Cell Carcinoma

Small cell carcinoma of the bladder is rare; however, it is associated with aggressive clinical behavior and has high metastatic potential.[288] These patients generally get treated along the same lines as small cell lung carcinoma, but the benefit of prophylactic cranial irradiation is unclear.[289-292]

Pasquier et al[293] reported on a retrospective study at 15 Rare Cancer Network medical centers that contributed 107 cases of pure or mixed small cell carcinoma of the bladder. Patients could have local, locoregional, or metastatic disease. Mean follow-up time was 4.4 years, with 66% of these patients having pure small cell carcinoma of the bladder. Seventy-two percent and 12% of the patients presented with T2-4N0M0 and T2-4N1-3M0 stages, respectively, and 16% presented with synchronous metastases. When employed, the most frequent curative treatments were radical surgery and chemotherapy, sequential chemotherapy and RT, and radical surgery alone. The median (interquartile range, IQR) OS and DFS times were 12.9 months (IQR, 7-32 months) and 9 months (IQR, 5-23 months), respectively, for the entire cohort. The metastatic, T2-4N0M0, and T2-4N1-3M0 groups differed significantly (P = .001) in terms of median OS and DFS. In the patients with nonmetastatic disease, the type of treatment (ie, radical surgery with or without adjuvant chemotherapy vs a bladder-sparing approach) did not significantly influence OS or DFS (P = .7), suggesting that a bladder-sparing treatment is appropriate in these patients.

A retrospective analysis of patients presenting with pure or predominant histology small cell carcinoma of the bladder in the United Kingdom between 2006 and 2016 was conducted.[288] A total of 409 patients were included, and 189 (46.2%) patients had pure histology small cell carcinoma of the bladder. The median OS of the entire cohort was 15.9 months (95% CI 13.2-18.7 months). A total of 247 patients received primary chemotherapy, with a median OS of 21.6 months (95% CI 15.5-27.6 months) versus a median OS of 9.1 months (95% CI 5.4-12.8 months) among those who did not receive primary chemotherapy (HR 0.46, 95% CI 0.37-0.59, P < .001). Chemotherapy choice did not impact outcomes. Among those with bladder-confined disease, 61 underwent cystectomy and 104 underwent RT. Survival outcomes were similar between both treatments. Only six patients (1.5%) were identified as having brain metastases at any time during their clinical course, confirming their relative rarity. Survival is improved in those who are able to receive chemotherapy.

Histologic Variants of Urothelial Carcinoma Treated With Trimodality Therapy

Outcomes of patients with histologic variants of UC, specifically with respect to treatment with TMT, are emerging. Given that TMT is associated with excellent and comparable outcomes to RC for those with pure UC histology, Krasnow and authors sought to evaluate the outcomes of patients with histologic variants following TMT.[294] Of 303 patients treated with TMT, 66 (22%) were found to have variant urothelial carcinoma (VUC). These patients were compared to 237 with pure urothelial carcinoma (PUC). CR rate after induction TMT was not different between the two groups (83% in PUC vs 82% in VUC, $P = .9$). The 5- and 10-year DSS was 75% and 67% in PUC versus 64% and 64% in VUC. The 5- and 10-year OS was 61% and 42% in PUC versus 52% and 42% in VUC. Salvage cystectomy rates were similar in the two groups ($P = .3$). This analysis suggests that the presence of VUC should not necessarily exclude the option of TMT for the treatment of MIBC.

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PART H

Male Genitourinary

CHAPTER 72

Low-Risk Prostate Cancer

Hiram A. Gay and Bridget F. Koontz

ANATOMY

Gross Anatomy and External Architecture

The prostate gland is an ovoid-shaped structure that is part of the male reproductive system. The prostate is made up of several types of tissue, including glandular and stromal tissue. Glandular tissue is responsible for producing prostate fluid, one of the components of semen. This fluid is rich in enzymes, proteins, and minerals that are vital for the viability and motility of sperm cells. The stromal tissue, which includes muscle and elastic fibers, helps in the expulsion of semen during ejaculation.

The prostate is located in the pelvis, adjacent to dorsal and periprostatic venous complexes, pelvic sidewall musculature, the pelvic plexus, and cavernous nerves, inferior to the bladder, anteroinferior to the seminal vesicles (SVs), and anterior to the rectum. The prostate surrounds segments of the urethra before it passes through the genitourinary diaphragm (GUD; Figure 72.1). Two of the five segments of the male urethra are the preprostatic urethra adjacent to the preprostatic sphincter and the prostatic urethra, which is placed from the verumontanum to the GUD. The paired SVs are situated posterosuperiorly to the prostate gland and secrete seminal fluid into the bilateral ductus deferens as they become the ejaculatory ducts. These ducts transverse the prostate to join the urethra at the verumontanum (Figure 72.1, right). At this point, the urethra changes its angulation by bending 30° to 40° anteriorly.

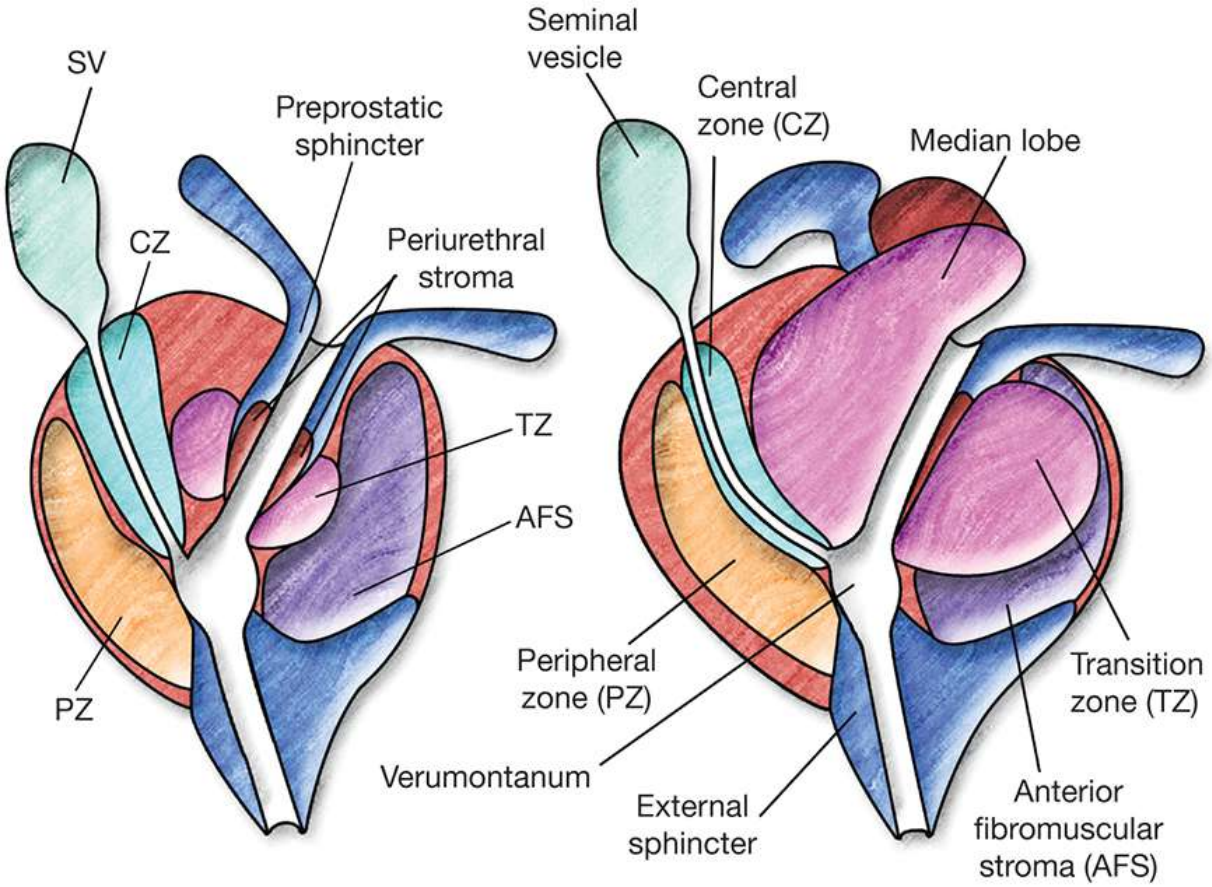

FIGURE 72.1 Zonal anatomy of the prostate. On the left, a young man with minimal transition zone (TZ) hypertrophy. Note that the preprostatic sphincter and periejaculatory duct zone (central zone of McLean) are clearly defined. On the right is an older man with TZ hypertrophy, which effaces the preprostatic sphincter and compresses the periejaculatory duct zone. AFS, anterior fibromuscular stroma; CZ, central zone; PZ, peripheral zone; SV, seminal vesicle. (Reprinted from McLaughlin PW, Troyer S, Berri S, et al. Functional anatomy of the prostate: implications for treatment planning. *Int J Radiat Oncol Biol Phys.* 2005;63[2]:479-491. Copyright © 2005 Elsevier. With permission.)

The prostate is contained within a thin, fibrous, adherent capsule that is structurally continuous with the stroma of the gland. The apex of the gland rests above the GUD. The GUD surrounds the membranous sphincter and may vary in length and thickness. The puboprostatic ligaments extend anteriorly from the gland's surface to the pubic symphysis. The prostate is separated from the rectum posteriorly by Denonvillier fascia (rectovesical septum), which attaches above to the peritoneum and below to the GUD. This portion of the prostatic fascia restricts posterior extension of prostatic carcinoma into the rectum. The lateral margins of the prostate are usually delineated against the levator ani muscles, forming the lateral prostatic sulci.

The anterior aspect of the prostate and the lateral pelvic floor are covered with the periprostatic fascia (Figure 72.2). The endopelvic fascia lateral to the prostate gland contains neurovascular structures, including the venous plexus of Santorini, which is the primary drainage for the prostate and penis. This venous network, also called the *dorsal vein complex*, covers the anterolateral surfaces of the prostate. The primary arterial blood supply to the prostate is via branches of the internal pudendal, inferior vesical, and middle rectal arteries. The internal pudendal arteries also provide the blood flow to the penis. The nerves originate from the pelvic plexus, containing both sympathetic and parasympathetic fibers, and are distributed to the prostate, SVs, and the corpora cavernosa of the penis and urethra.

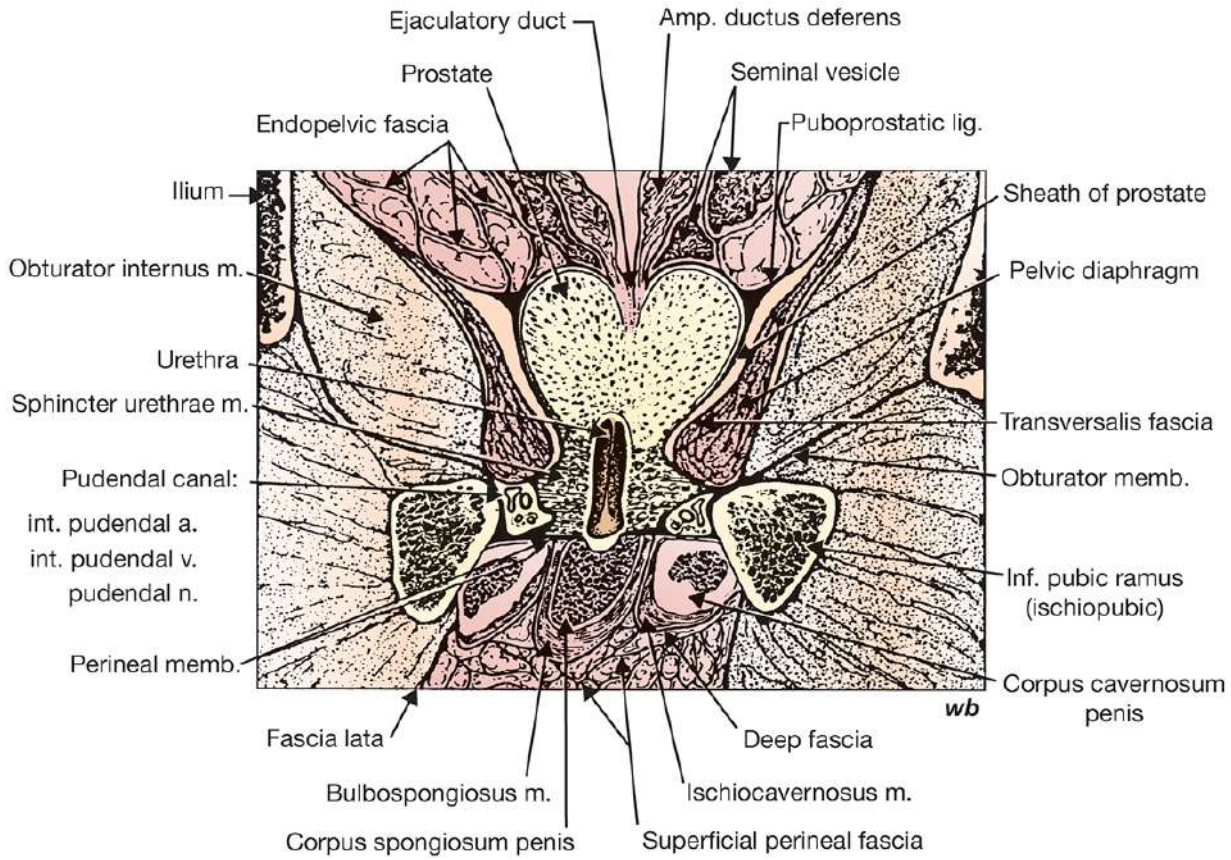

FIGURE 72.2 Frontal section of the male pelvis at right angles to perineal membrane. (From Oelrich TM. The urethral sphincter muscle in the male. *Am J Anat*. 1980;158[2]:229-246. Copyright © 1980 Wiley-Liss, Inc. Reprinted by permission of John Wiley & Sons, Inc.)

The prostatic apex is definable on diagnostic imaging and is very important anatomically for radiation therapy (RT) treatment planning.

Although the apex and the GUD, which surrounds the membranous sphincter, are easily visualized on coronal magnetic resonance imaging (MRI), it is important to recognize that the level of the GUD from the apex to the penile bulb may vary because the absence of an apical capsule contributes to the difficulty in discrimination of the gland from the GUD during computed tomography (CT)-based treatment planning. Delineation of the neurovascular bundle is also limited on CT imaging.

Prostatic Zonal Anatomy

There are four zones of the prostate (Figure 72.1): the peripheral zone (PZ), transition zone (TZ), central zone (AZ), and anterior fibromuscular stroma (AFS) zone. The PZ is the posterior region of the prostate and constitutes the largest portion of the gland, comprising about 70% of the gland's volume in a young man. It is the most common site for prostate cancer (PCa), accounting for approximately 70% to 80% of cases, and is the region palpated during rectal examination. The CZ accounts for approximately 25% of the prostate's volume and surrounds the ejaculatory ducts. The TZ surrounds the urethra and constitutes about 5% to 10% of the prostate's total volume in a young man but becomes with age due to benign prostate hypertrophy (BPH). The TZ is the primary area where BPH occurs. The AFS is a nonglandular area that constitutes about 5% of the prostate's total volume. It consists of muscle and fibrous tissue and is located anterior to the prostate and contiguous with the bladder muscle and external sphincter.

It is important to note that there is no "median lobe" zone in this nomenclature, although such a "lobe" may be present in some patients with PCa and may have important implications for treatment planning and treatment selection. Histologically, the median lobe arises from the TZ or periurethral stroma, with varying proportions of fibrous, glandular, and muscle tissue.

Prostate Physiology

Histologically, the prostate consists of compound tubuloalveolar glands lined by two layers of cells. The glands are embedded in connective tissue comprising collagen and abundant smooth muscle that make up the prostatic stroma. This fibromuscular stroma functions both to control micturition by

acting as a sphincter of the urethra and to express acidic prostatic secretions into the urethra by contracting during ejaculation.

The primary function of the prostate is the production of seminal fluid that protects and nourishes the sperm after ejaculation. The prostate contributes approximately 30% to the seminal fluid, and the SVs, testicles, and bulbourethral glands provide the remaining 70%. Enzymes, including acid phosphatase and prostate-specific antigen (PSA), are secreted into the seminal fluid. PSA is a serine protease involved in the liquefaction of the seminal coagulum. Because PSA is produced primarily by benign and malignant prostatic epithelial cells and normally found at low concentrations in the serum, it is useful for PCa screening and post-treatment monitoring of disease status.

Androgens regulate the synthetic activity and growth of the prostate gland. The primary circulating androgen is testosterone. In the prostatic stroma, testosterone is converted to its active and more potent form, α-dihydrotestosterone, by 5-α-reductase. Secretory epithelial cells and stromal cells have intracellular androgen receptors (ARs). Dihydrotestosterone forms a complex with the dihydrotestosterone-binding domain of the AR, altering the structure of the DNA-binding domain such that it can reversibly bind DNA sequences known as *androgen response elements* in promoter or enhancer regions of androgen-regulated genes. The response includes cell division stimulation, apoptosis inhibition (programmed cell death), or cellular differentiation. In secretory epithelial cells, testosterone stimulation may result in the production and secretion of prostatic fluid. These mechanisms are tightly regulated at many levels, from the hypothalamus secreting luteinizing hormone–releasing hormone (LHRH) to maintain testosterone levels in the blood, to the local regulation of 5-α-reductase in the prostate stroma.

EPIDEMIOLOGY AND RISK FACTORS

Clinical Incidence

Adenocarcinoma of the prostate is the most frequently diagnosed visceral cancer of men in the United States, accounting for 29% of non–skin cancers in 2023.[1] The lifetime risk for American men is one in eight. It was estimated

that 288,300 new cases of PCa would be diagnosed in 2023, but only 34,700 patients would die of the disease.

The incidence rate for PCa dropped approximately 40% from 2007 to 2014 because of declines in the diagnosis of localized tumors through PSA testing, the prevalence of which decreased after the United States Preventive Services Task Force (USPSTF) recommended against screening for men aged 75 years and above in 2008[2] and for all men in 2012.[3] However, the PCa incidence rate has risen by 3% per year from 2014 through 2019, and about half of these cases were advanced. This is driven by increases of about 4.5% annually for regional- and distant-stage diagnoses that began as early as 2011.[1] These patterns are consistent with continued reports of a shift toward higher grade and stage at diagnosis since 2010.[4] Efforts to regain the benefit of early PCa detection while lessening overdiagnosis and overtreatment include a USPSTF upgrade to informed decision-making in men aged 55 to 69 years in 2018.[5]

Black men benefit more from screening in general[6,7] and from the integration of personalized biomarkers because they are more likely to harbor genomically aggressive cancer, even with clinically low-risk disease.[8] High overall cancer incidence in Black men is mainly because of PCa, which is 70% higher than in White men, 2 times higher than in American Indian/Alaska Native (AIAN) and Hispanic men, and 3 times higher than in Asian American/Pacific Islander (AAPI) men.

PCa mortality has declined by 53% since the peak in 1993 because of earlier detection through widespread screening with the PSA test and advances in treatment.[9] PCa remains the second greatest cause of male cancer mortality, behind cancer of the lung and bronchus. PCa mortality rates in Black men are approximately 2 times higher than White men, AIAN, and Hispanic men, and 4 times higher than AAPI men.[1]

Of the known or suspected risk factors for PCa, the most important is age (Table 72.1). The Göteborg-1 Prostate Cancer Screening Trial showed that for men with screen-detected PCa, age was associated with the risk of clinically significant PCa above and beyond the screening round and year of testing ($P < .001$). For each 1-year increase in age, the risk of being diagnosed with a Gleason score (GS) 3 + 4 cancer or higher (vs <7) increased by 11%, whereas the risk of being diagnosed with a GS 4 + 3 cancer or higher (vs <7) increased by 8.5%.[10]

TABLE 72.1 KNOWN OR SUSPECTED RISK FACTORS FOR PROSTATE CANCER

Factor	Effect on Prostate Cancer Risk
Age	Increase
African American race	Increase
Geography	**High**: Guadeloupe, Martinique, Ireland, Barbados, Saint Lucia, Estonia, Puerto Rico, Sweden, France, Bahamas, Norway, New Caledonia; **Low:** India, China
Family history	Increase
Agent Orange	Increase
Tobacco	Decrease in incidence, but current smokers have an increased prostate cancer mortality risk
Chlordecone	Increase
NSAID	Decrease

NSAID, nonsteroidal anti-inflammatory drug.

The median age at diagnosis is 66 years, and the disease incidence escalates sharply with increasing age. The incidence among men aged 50 to 59 years is 1 in 55, increasing to 1 in 19 among men aged 60 to 69 years, and 1 in 11 among those aged 70 years and above.[1] According to autopsy data, 70% of men older than 80 years and 40% of men older than 50 years have pathologic evidence of cancer in the prostate.[11]

Risk Factors

Hormonal Influences

Khera et al reviewed the relationship between serum testosterone and PCa.[12] The authors concluded that high endogenous serum testosterone does not increase the risk of developing PCa and that low serum testosterone does not protect against PCa. Although limited in size and duration, current studies similarly fail to indicate any increased risk of PCa in men receiving testosterone therapy. These results indicate a finite ability of androgens to stimulate PCa growth (the saturation model). The saturation model explains the paradoxical observations that prostate tissue is exquisitely sensitive to changes in serum testosterone at low concentrations but becomes indifferent

at higher testosterone concentrations. A threshold effect occurs in which increasing androgen concentrations reach a limit (the saturation point) beyond which there is no further ability to induce androgen-driven changes in prostate tissue growth. Most studies demonstrate an association between low serum testosterone and poor prognostic features of PCa, including high-grade disease, advanced pathologic stage, and increased risk of biochemical recurrence (BCR) following radical prostatectomy (RP). Current evidence indicates that maximal androgen-stimulated PCa growth is achieved at relatively low serum testosterone concentrations.

Muller et al reported on 3,255 men in the placebo arm of the reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial who underwent planned prostate biopsies at 2 and 4 years and found no association between PCa risk and baseline serum testosterone or dihydrotestosterone.[12,13]

Dietary Influences

A systematic review and meta-analysis of the associations between body mass index (BMI), PCa, advanced PCa, and PSA noted that there is little or no evidence of an association between BMI and the risk of PCa or advanced PCa. However, there was strong evidence of an inverse and nonlinear association between BMI and PSA. In the meta-analyses with continuous BMI, a 5 kg/m^2 increase in BMI was associated with a percentage change in PSA of −5.88%. Using BMI categories, compared to normal weight men, the PSA levels of men who are overweight were 3.43% lower, and men who are obese were 12.9% lower. The association between BMI and PCa is likely biased if missed diagnoses are not considered.[14]

The results of a long, prospective, cohort study (The National Institutes of Health [NIH]-AARP Diet and Health Study) in a cohort of 175,343 U.S. men aged 50 to 71 years, red meat (hazard ratio [HR] = 1.31), processed meat (HR = 1.32), heme iron (HR = 1.28), nitrite (HR = 1.24)/nitrate (HR = 1.31) from meat, grilled/barbecued meat (HR = 1.36), and benzo[a]pyrene (HR = 1.28) were associated with elevated risks of advanced PCa.[15]

In the Danish “Diet, Cancer and Health” cohort of 27,178 men aged 50 to 65 years, neither toenail selenium nor plasma selenoprotein P (SELENOP) was associated with advanced, high-grade, or advanced-stage PCa.[16] The Selenium and Vitamin E Cancer Prevention Trial (SELECT) with a total of 35,533 men showed that dietary supplementation with vitamin E (400 IU/d)

significantly increased the risk of PCa among healthy men. This study also observed an increased PCa risk among men with high blood concentrations of long-chain Ω-3 polyunsaturated fatty acids (LCΩ-3PUFA). Compared with men in the lowest quartiles of LCΩ-3PUFA, men in the highest quartile had increased risks for low-grade (HR = 1.44), high-grade (HR = 1.71), and total PCa (HR = 1.43).[17]

The screening arm of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial evaluated the association between PCa risk and intake of fruits and vegetables in 1,338 patients with PCa among 29,361 men. Although vegetable and fruit consumption was not related to PCa risk overall, the risk of stage III or IV PCa decreased with increasing vegetable intake (relative risk [RR] = 0.41).[18]

Lycopene is abundant in tomatoes and a potent antioxidant. A systematic review and meta-analysis of 26 studies with 17,517 cases of PCa reported from 563,299 participants showed that higher lycopene consumption/circulating concentration is associated with a lower risk of PCa.[19] A study among 49,898 male health professionals observed that dietary intake of lycopene was associated with a reduced risk of lethal PCa and a lesser degree of tumor angiogenesis.[20]

A systematic review and meta-analysis of 266,699 study participants with 21,612 PCas reported observed that total soy food ($P < .001$), unfermented soy food ($P < .001$), and soy isoflavones genistein ($P = .008$) and daidzein ($P = .018$) intakes were significantly associated with a reduced risk of PCa.[21]

A 30-year prospective cohort study of 11,372 Finnish twins observed that compared to light drinkers (≤3 drinks/week; nonabstainers), heavy drinkers (.14 drinks/week) were at a 1.46-fold higher risk (HR = 1.46) of PCa, adjusting for important confounders.[22] Among current drinkers, binge drinkers were at a significantly increased risk of PCa (HR = 1.28) compared to nonbinge drinkers. Abstainers were at a higher risk (HR = 1.90) of PCa-specific mortality compared to light drinkers, but no other significant associations for mortality were found. Co-twin analyses suggested that alcohol consumption may be associated with PCa risk, independent of early environmental and genetic factors.[22]

A systematic review and meta-analysis with 57,732 cases of PCa and 1,081,586 total cohort members showed that higher coffee consumption was significantly associated with a lower risk of PCa. Compared with the lowest

category of coffee consumption, the pooled RR was 0.91 for the highest category of coffee consumption. There was a significant linear trend for the association (P = .006 for linear trend), with a pooled RR of 0.988 for each increment of one cup of coffee per day. For localized, advanced, and fatal PCa, the pooled RRs were 0.93, 0.88, and 0.84, respectively.[23]

A meta-analysis of dairy product and calcium intakes and PCa risk observed that men with the highest intake of dairy products (RR = 1.11) and calcium (RR = 1) were more likely to develop PCa than men with the lowest intake. The authors concluded that a high intake of dairy products and calcium may be associated with an increased risk of PCa, although the increase appears to be small.[24]

A summary of associations of various dietary factors with PCa development is shown in Table 72.2.

TABLE 72.2 NUTRITIONAL RISK FACTORS FOR PROSTATE CANCER

Food or Nutrient	Direction of Association With Prostate Cancer Risk
Selenium	Null
Tomato and lycopenes	Inverse
Vitamin E	Positive
Vegetable and fruits	Null
Calcium and dairy	Positive
Red meat, processed meat	Positive
Soy/isoflavones	Inverse
Alcohol	Positive
Coffee	Inverse
LCΩ-3PUFA	Positive

LCΩ-3PUFA, long-chain Ω-3 polyunsaturated fatty acids.

Familial Associations

Men with a family history of PCa are at a significantly greater risk of developing the disease compared to those with no such history. The risk is even higher for individuals with relatives diagnosed at a young age (before age 60) or with more than one relative affected. RRs to sons of cases appeared to be lower than in brothers.[25] The Swedish Family-Cancer

Database supports family history as an important factor in PCa, especially in cases of fatal PCa. Familial risks were somewhat higher for fatal than for incident PCa, suggesting that fatal PCas may be a genetic subgroup. If the father had PCa, the HR for sons was 2, and it increased to 17.7 when three brothers were affected. The highest HR (23) was observed for men before age 60 years with three affected brothers.[26]

Genetic and Molecular Influences

The proportion of PCa attributable to hereditary factors has been estimated in the range of 5% to 15%. The genes more consistently associated to hereditary PCa susceptibility include mismatch repair (MMR) genes 0.7% to 1.74% (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) and homologous recombination genes *BRCA1* (0.9%-1.25%), BRCA 2 (1.2%-5.3%), *ATM* (1.6%-2.7%), *PALB2* (0.4%-0.5%), and *CHEK2* (1.8%-2.8%). Additional genes are also recommended to be integrated into specific research, including *HOXB13* (0.6%-6.5%), *BRIP1* (0.1%-0.2%), and *NBS1* (0.1%-0.2%).[27] The previous PCa susceptibility genes are summarized in Table 72.3.[27,28]

TABLE 72.3 PARTIAL LIST OF PROSTATE CANCER SUSCEPTIBILITY GENES[26]

Gene	Location	Molecular Mechanism	Prostate Cancer Risk Increase
MLH1	3p22.2	DNA mismatch repair	2.0-3.7 fold RR
MSH2	2p21-p16.3	DNA mismatch repair	2.0-3.7 fold RR
MSH6	2p16.3	DNA mismatch repair	2.0-3.7 fold RR
PMS2	7p22.1	DNA mismatch repair	2.0-3.7 fold RR
BRCA1	17q21.31	DNA damage repair	1.8-3.8 fold RR
BRCA2	13q13.1	DNA damage repair	2.5-4.6 fold RR. In < 55 y old, 8-23 fold RR
ATM	11q22.3	DNA damage response	6.3-fold RR
PALB2	16p12.2	DNA damage repair, essential component of the BRCA complex formation	8.05 odds ratio for developing high-risk prostate cancer
CHEK2	22q12.1	DNA repair through phosphorylation of BRCA2	1.9-3.3 fold overall risk. In Sweden, CHEK2 was the

Gene	Location	Molecular Mechanism	Prostate Cancer Risk Increase
			most frequently mutated DNA repair gene (3.8%).
HOXB13	17q21.32	Androgen receptor repressor	3.4-8.6 fold RR
BRIP1	17q23.2	DNA damage repair, binds directly to the BRCA1 C-terminal repeats	2.4 odds ratio
NBN	8q21.3	Nibrin carries the MRE11A and RAD50 proteins into the cell's nucleus and guides them to sites of DNA damage.	4.6 odds ratio

RR, relative risk.

Adapted from Heidegger I, Tsaur I, Borgmann H, et al. Hereditary prostate cancer—primetime for genetic testing? *Cancer Treat Rev*. 2019;81:101927. Copyright © 2019 Elsevier. With permission.

HOXB13 is a homeobox transcription factor localized on chromosome 17. HOXB13 remains the most widely replicated and specific PCa susceptibility gene. BRIP1 is localized on chromosome 17 and encodes a DNA helicase that binds directly to the BRCT repeats of BRCA1 and that is involved in double-strand break (DSB) repair. Another gene of interest is *NBN*, located on chromosome 8 and encodes another protein involved in DSB repair since it is responsible for the localization of the complex and for the interactions with other proteins belonging to repair signaling complexes.[27]

Research delving into the molecular physiology of the prostate gland has also uncovered specific DNA sequences that may be related to the occurrence and progression of PCa. It is well known that PCa cells, like their normal counterparts, are usually sensitive to androgens, and their growth depends on androgen-stimulated cell division. Two main polymorphisms include CAG and GGN repeats in the AR gene. Moreover, CAG is associated with the transcriptional activity of the AR in response to ligand binding. A meta-analysis of AR gene polymorphisms and the risk of PCa showed that short CAG repeats (,22 repeats) carriers presented an elevated risk of PCa than long CAG repeats (≥22) carriers (odds ratio [OR] = 1.31). Short GGN repeats (≤16) carriers presented an increased risk of PCa than long GGN repeats (.16) carriers (OR = 1.38). In subgroup analyses, the abovementioned

significant association was predominantly observed in Caucasian populations.[29]

In addition to these genetic alterations identified in PCa, epigenetic changes such as abnormal DNA methylation have also been observed. They may play a role in upregulation or loss of expression of genes. Peripheral blood DNA methylation was measured for 133 of the 469 members of 25 multiple-case PCa families. After correcting for multiple testing, 41 heritable methylation marks were associated with PCa risk. Separate analyses, based on 869 incident cases and 869 controls from a prospective cohort study, showed that nine of these marks near the metastable epiallele VTRNA2-1 were also nominally associated with aggressive PCa risk in the population.[30]

Other Risk Factors

A cigarette smoking and PCa systematic review and meta-analysis of 17 prospective cohort studies included a total of 2,537,664 participants and 47,536 incident cases. Fifteen studies showed that cigarette smoking has an inverse association with PCa incidence, with an RR of 0.84. However, the five studies that examined the association between current smokers and the risk of death from PCa showed that current smokers had a 42% higher risk of death from PCa when compared to nonsmokers with an RR of 1.42.[31]

A cohort of all Vietnam-era veterans registered within the Northern California VA Health System was stratified as either exposed (56,214) or unexposed (56,930) to Agent Orange. Agent Orange–exposed men were diagnosed at a younger age (59.7 years) compared with unexposed men (62.2 years), had a 2-fold increase in the proportion of GSs 8 through 10 (21.8%) compared with unexposed men (10.5%), and were more likely to have metastatic disease at presentation than men who were not exposed (13.4%) than unexposed men (4%).[32]

Chlordecone, an organochlorine insecticide with well-defined estrogenic properties, was extensively used from 1973 to 1993 in the French West Indies to control the banana root borer. A study with 623 men with PCa and 671 controls found a significant increase in the risk of PCa with increasing plasma chlordecone concentration (OR = 1.77) and cumulative exposure index (OR = 1.73).[33]

The American Cancer Society's Cancer Prevention Study II Nutrition Cohort examined the association between nonsteroidal anti-inflammatory

drug (NSAID) and aspirin use and PCa incidence among 70,144 men. Long-duration regular use (≥30 pills per month for ≥5 years) of NSAIDs was associated with reduced risk of PCa (RR = 0.82). Long-duration regular use of aspirin was also associated with a reduced risk of PCa (RR = 0.85).[34]

NATURAL HISTORY

Local Growth Patterns

The studies of prostate morphology conducted by McNeal[35] showed that almost all prostatic carcinomas (.70%) develop in the PZ of the prostate, whereas benign prostatic hyperplasia (.90%) arises from the TZ. In addition, examination of prostatectomy specimens revealed that small tumors tend to occur in the anteromedial gland, adjacent to the fibromuscular stroma, whereas larger, more advanced T-stage tumors are often located in the posterior gland near the prostatic capsule.[36,37]

Multifocality is characteristic of PCa. On digital rectal examination (DRE), the disease may be nonpalpable or there may be one or many nodules, located unilaterally or bilaterally. Histologic and molecular studies of prostatectomy specimens of patients with PCa have revealed that most contain a dominant or index tumor and one or more spatially separate, often heterogeneous, tumors.[38-41] Jewett[42] reported that multiple foci of disease were found throughout the prostate in 77% of prostatectomy specimens. Wise et al[43] noted that only 17% of 486 patients treated by radical retropubic prostatectomy had one carcinoma detected by 3-mm step-section histologic examination. Of the 83% with multifocal disease, secondary cancers were mostly small; 58% were less than 0.5 cm^3 in volume. Qian et al,[44] using fluorescence in situ hybridization to detect chromosomal abnormalities, found that an increasing incidence of chromosomal anomalies among specimens was positively correlated with progression from high-grade prostatic intraepithelial neoplasia to prostatic carcinoma. When lymph node (LN) involvement was present, there was usually evidence of one or more foci of the primary tumor sharing chromosomal anomalies with associated LN metastases, suggesting that just a single focus of carcinoma may give rise to metastases. This heterogeneity and multicentricity may account for the discrepancy between needle biopsy GS and the grade determined from the dominant tumor in the prostatectomy specimen.

Tumors arising from the TZ tend to demonstrate a lower frequency of extracapsular extension (ECE) and may harbor large volumes of disease with relatively high PSA levels but remain confined to the prostate. Despite a high PSA value (≥10 ng/mL), these tumors should be considered to have a favorable prognosis and be managed accordingly. Noguchi et al[45] described the histologic characteristics of 148 cases of TZ PCa from RP specimens. Seventy percent were clinical stage T1c, with a preoperative serum PSA of 10 ng/mL or greater in almost two-thirds of cases. Only 63% had a positive initial prostatic biopsy. On pathologic review, 80% had organ-confined disease, and more than one-third of cases had a cancer volume greater than 6 mL. When compared with 79 PZ cancers matched by volume, there were no differences in percentage Gleason grade 4/5, serum PSA, or prostate weight, although differences in clinical stage T1c to T2c and organ-confined cancer were highly significant. The actuarial 5-year PSA relapse-free survival (RFS) rate was 71.5% among men with TZ cancer, compared with 49.2% for those with PZ cancer.

PZ cancers tend to spread along the capsular surface of the gland and may extend through the capsule of the gland, invade SVs and periprostatic tissues, and involve the bladder neck or the rectum. Clinical stage closely correlated with risk of ECE and disease progression.[46-48] The incidence of microscopic tumor extension beyond the capsule of the gland (at the time of RP) in patients with clinically organ-confined disease ranges from 8% to 57%.[48,49] Catalona et al,[50] in an analysis of patients with stage T1c disease treated with RP, noted that 53% had pathologically organ-confined tumors, 35% had ECE, and 9% had SV invasion. Of the last group, 66% had positive surgical margins, an incidence comparable with that for clinical stage T2 tumors. In a similar group of patients with T1c tumors, Epstein et al[51] found that 34% had established ECE, 6% had SV invasion, and 17% had positive surgical margins.

Pretreatment serum PSA is also predictive of extraprostatic extension and SV invasion. The rate of organ-confined PCa ranges from 53% to 67% for men with a PSA level between 4 and 10 ng/mL and from 31% to 56% for men with a PSA level between 10 and 20 ng/mL.[52-54] D'Amico et al,[55] in a pathologic evaluation of 347 RP specimens, reported that none of 38 patients with PSA of 4 ng/mL or less had SV involvement, in contrast to 6% of 144 patients with PSA of 4 to 10 ng/mL, 11% of 101 with PSA of 10 to 20

ng/mL, 36% of 45 with PSA of 20 to 40 ng/mL, and 42% of 19 with PSA of greater than 40 ng/mL. The incidence of positive surgical margins for these PSA subgroups was 11%, 20%, 33%, 56%, and 63%, respectively. The incidence of SV involvement also is associated with the level of PSA, the GS, and the clinical stage.[56,57] SV involvement has been observed in from 10% of patients with A2 tumors to 30% of the patients with B2 lesions.[58,59]

Roach[60] proposed formulas based on analysis of RP specimens to estimate the probability of ECE+ and SV+ involvement here provided in Table 72.4.

TABLE 72.4 ROACH FORMULAE CALCULATING THE LIKELIHOOD OF PATHOLOGIC STAGE BASED ON CLINICAL FACTORS

Predicted Stage	Formula
Extraprostatic extension	(PSA × 3/2) + ([Gleason score − 3] × 10)
Seminal vesicle involvement	PSA + ([Gleason score − 6] × 10)
Lymph node involvement	(PSA × 2/3) + ([Gleason score − 6] × 10)

PSA, prostate-specific antigen.

Reprinted with permission from Roach M III. Re: the use of prostate specific antigen, clinical stage and Gleason score to predict pathological stage in men with localized prostate cancer. *J Urol*. 1993;150(6):1923-1924. Copyright © 1993 by The American Urological Association Education and Research.

Regional Lymph Node Involvement

Tumor size and degree of differentiation affect the tendency of prostatic carcinoma to metastasize to regional lymphatics. With an increasing number of patients being diagnosed in earlier stages (as a result of screening PSA), there has been a decreased incidence of LN metastases in patients with clinical stage T1c and T2 tumors.[61] In the patients with low-risk PCa, the risk of LN involvement is generally considered less than 10%.

Several groups[52,62-67] have developed models based on clinical or pathologic data that predict the risk of LN metastases. This information is important to decide whether a patient with PCa should be subjected to a staging lymphadenectomy (including laparoscopic technique) or considered for irradiation of the pelvic LNs. Partin et al[68] analyzed data from 703 patients and generated a nomogram for predicting nodal metastases based on three factors: clinical stage, preoperative PSA, and tumor biopsy grade. This model was validated in a larger multicenter study of 7,014 men and

accurately predicted nodal metastases in 78% of patients.[69] The negative predictive value (NPV) was 99%. Bluestein et al[64] tested a model based on multivariate logistic regression analysis on 1,632 patients who underwent pelvic lymphadenectomy at the Mayo Clinic for staging of PCa. Using this method, they determined that 29% of the patients with clinical stage T1a to T2c disease would have been spared pelvic lymphadenectomy, with only a 3% rate of missed nodal metastases. Bishoff et al[63] reported similar results demonstrating that 20% to 63% of patients with PCa could be spared pelvic lymphadenectomy when accepting a 2% to 10% risk for missed nodal metastasis. Machine-learning algorithms can outperform traditional tools in the ability to predict LN metastases.[70] These results suggest that many patients can be spared pelvic lymphadenectomy solely by analyzing preoperative PSA, Gleason grade, and clinical stage, without incurring an unacceptable risk for failing to identify regional metastasis.[71]

Stock et al,[57] in a study of 99 patients who underwent laparoscopic LN dissection, correlated incidence of positive nodes with PSA, GS, stage, and involvement of SVs. None of the patients with a GS of 4 or lower, even those with PSA of greater than 20 ng/mL, had positive pelvic LNs, and 8% in the group with GSs of 5 or 6 and PSA levels of 4 to 10 ng/mL had positive nodes. However, the incidence of positive LNs increased significantly (to 24%) in patients with PSA greater than 20 ng/mL. These results are similar to those reported in patients treated with RP.[64,68]

In an analysis of 2,144 patients treated at two institutions, Rees et al[72] noted that only 30 (2.2%) of 1,390 patients with a negative DRE and either PSA of 5 ng/mL or less, GS of 5 or less, or a combination of PSA of less than 25 ng/mL and GS of 7 or less had pelvic LN metastases.

It has been suggested that the Roach formula cutoff of 15% does not identify up to one-third of patients with LN involvement. A study of 3,115 patients treated by RP and extended pelvic lymph node dissection (PLND) validated the Roach formula and found that Roach accuracy was 80%. With a cutoff of 33% of the patients with nodal involvement would not have been recommended for nodal irradiation. Using the 15% benchmark, 33% of patients with nodal involvement would not have been recommended for nodal irradiation.[73]

Prognosis is closely related to the presence of regional LN metastases; patients with positive pelvic LNs have a significantly greater probability

(.85% at 10 years) for the development of distant metastasis (DM) than those with negative nodes (,20%).[74] However, a single nodal metastasis is not an unfavorable prognostic sign. In a study by Cheng et al,[75] 322 patients with positive LNs after RP and bilateral pelvic lymphadenectomy were followed up for a median of 6 years. Patients with prostate carcinoma who had multiple regional LN metastases had an increased risk of death from disease, whereas patients with a single positive LN appeared to have a more favorable prognosis after RP and immediate adjuvant hormonal therapy. Prout et al,[76] in 92 patients with various stages of prostatic carcinoma, noted solitary LN metastasis in 11 (34%) of 32 patients with positive nodes. Bilateral pelvic LN involvement was present in 14 (58%) of 24 patients who had more than one metastatic LN. Only 2 (18%) of 11 patients with a single metastasis showed tumor progression, compared with 15 (76%) of 21 with multiple LN involvement. Golimbu et al[77] reported a 10-year survival rate of 50% in patients with a single positive LN, compared with 20% for those with multiple LN involvement.

The prognostic significance of multiple involved LNs should be considered with the extent of lymphadenectomy. Several studies have evaluated the anatomic extent of PLND on outcome.[78,79] At Johns Hopkins University Hospital, two surgeons performed 4,000 RP with or without an extended LN dissection. The extended dissection removed more LNs (mean 12 vs 9; $P < .0001$) and detected more LN-positive PCa (3.2% vs 1.1%; $P < .0001$) than more limited procedure. If disease was found involving less than 15% of the extracted LNs, extended LN dissection resulted in a more favorable 5-year PSA progression-free survival (PFS). Thus, in certain subgroups, an extended dissection may be beneficial. In another study, the number and percentage of involved LNs correlated with recurrence-free and overall survival (OS).[79] These results need additional validation in prospectively controlled studies.

CLINICAL PRESENTATION AND DIAGNOSTIC WORKUP

Screening Methods and Markers

Although DRE is still an essential element in screening and assigning clinical stage, only 25% to 50% of men with an abnormal DRE have PCa on biopsy. Moreover, because carcinoma of the prostate can be asymptomatic until

attaining a significant size, if a patient presents with a palpable tumor, there is a significant risk that there already may be locally advanced or metastatic disease. With the advent of PSA screening, the diagnosis of PCa may precede palpable disease on DRE and the symptoms of urinary obstruction or metastatic disease by many years. DRE is associated with 70% sensitivity and 50% specificity.[80] In fact, 70% of cancers detected by PSA screening are confined to the prostate, and 40% of cancers detected by PSA are not palpable.[50]

The first widely available clinical biomarker was prostatic acid phosphatase (PAP), used to diagnose and monitor treatment response for PCa in the 1940s and 1950s. However, PAP has a sensitivity of approximately 10% and a specificity of about 90% for malignant tumors[80] and, to a large extent, has been superseded by PSA testing. Stamey et al[81] reported PSA and PAP measurements by radioimmunoassay in 2,200 serum samples from 699 patients, 378 of whom were known to have prostatic carcinoma. PSA was elevated in 122 of 127 patients with newly diagnosed prostatic carcinoma, whereas PAP was elevated in only 57 patients with cancer and correlated less closely with tumor volume than did PSA.

Initially identified and purified from prostatic tissue by Wang et al[82] in 1979, PSA is a protein with a molecular weight of 33,000. It is localized in the cytoplasm of ductal epithelial cells and in secretory materials in ductal lamina.[83] PSA is detected not only in prostatic tissue (normal tissue, benign hyperplasia, and malignant tumors) and seminal fluid but also in the sera of patients with prostatic cancer. PSA has been detected with immunohistochemical techniques in pancreas and salivary glands and in women; therefore, it is not absolutely specific for prostatic epithelium.[84] After RP for cancer, PSA routinely declines to undetectable levels, with an associated half-life of 2.2 days.

The incidence of PCa rose dramatically with the onset of PSA screening in the early 1990s.[85] However, concern of possible overscreening and two landmark screening trials led to the USPSTF recommending in 2008 against PSA screening in men aged 75 years or above and concluding that current evidence was inadequate to make a PSA screening recommendation for men younger than the age of 75 years.[86] These decisions were partly based on two large screening trials. The European Randomized Study of Screening for Prostate Cancer (ERSPC) randomized 162,387 men aged 50 to 74 years to

PSA screening an average of once every 4 years or to no such screening.[87] At a median follow-up of 9 years, PSA screening showed a modest reduction in death from PCa that would require screening of 1,410 men and treatment of 48 men to prevent one death from PCa. The reduction in death from PCa was apparent only in men aged 55 to 69 years. The contemporaneous US-based Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer screening trial randomized 76,693 men aged 55 to 74 years to annual PSA testing for 6 years and annual DRE for 4 years versus no such screening.[88] At a median follow-up of 7 years, no difference in mortality was noted between the arms.

As a result of the USPSTF 2008 recommendation, PCa incidence decreased from 534.9 men per 100,000 in 2005 to 416.2 men per 100,000 in 2012.[89] The incidence of metastatic PCa began to rise by 0.58% per year after 2008, for the first time since 2004, and continued to increase to a rate of 2.74% per year in 2012.[90] In 2017, the USPSTF updated their recommendation to support PSA screening in men aged 55 to 69 years (grade C) but continues to recommend against PSA screening in men aged 70 years or higher.[5] This partial reversal in approach toward PSA screening was in part due to longer follow-up of the ERSPC trial, which at 13 years of follow-up found significantly reduced PCa mortality in the screening cohort, with one cancer death averted for every 781 men screened.[91]

Several investigators[92-94] reported no significant impact of DRE on the plasma levels of PSA in patients with various prostatic abnormalities in whom blood samples were collected before, immediately after, and 30 minutes after rectal examination of the prostate. Others[95-97] detected a significant increase in PSA after DRE. Ornstein et al[97] noted an increase in both total and free PSA in 31% and 48% of men, respectively, at 1 hour after DRE. Matzkin et al[98] found no significant change in PSA levels after inserting a urethral catheter and maintaining it for several days. Yet, significant PSA elevation has been demonstrated after prostatic massage, transrectal ultrasonography (TRUS), prostate biopsy, and transurethral resection of prostate (TURP).[94,95,99,100] The kinetics of serum PSA elevation after DRE and needle biopsy were investigated in a Dutch study with few participants.[101] Blood samples were taken at 1 and 30 minutes and 1, 3, 6, and 12 hours and then every 24 hours until 5 days had elapsed. The peak levels were between 30 and 60 minutes after DRE and returned to baseline 24 to 72 hours after the examination. There was a 3-fold increase in PSA after needle

biopsy, and only two of seven patients had returned to their baseline PSA at 5 days. Studies reporting the effect of ejaculation on PSA also have contradictory results. Some authors found no effect at all,[102,103] whereas others demonstrated that ejaculation increased PSA levels in 87% of 64 men evaluated with serial determinations (at 1, 6, 24, and 48 hours).[104] A return to baseline was observed in 92% of subjects by 24 hours and in 97% by 48 hours.

Nadler et al[105] quantified the causes of elevated PSA in 148 men with PSA of greater than 4 ng/mL (a finding suspect for cancer) and multiple negative biopsies. They were compared with 64 men who had a suspect DRE, multiple negative biopsies, and PSA of 4 ng/mL or less. Acute or chronic inflammation of the prostate was more prevalent in the high PSA group (63% vs 27%; $P = .0001$). Patients with elevated PSA had significantly larger prostate volumes (median, 68 cm^3) than those without PSA elevation (median, 32.5 cm^3). Simultaneous regression analysis demonstrated that prostatic size accounted for 23%, inflammation for 7%, prostatic calculi for 3%, and nonisoechoic ultrasonographic lesions for 1% of the PSA serum variances.

The positive predictive value for PSA of greater than 4 ng/mL ranges from 31% to 54%. A greater yield is observed when elevated PSA is coupled with positive ultrasonographic and rectal examinations[106] (Tables 72.5 and 72.6). The estimated rate of cancer detection by PSA screening ranges from 1.8% to 3.3%. The percentage of clinically localized tumors detected by PSA ranges from 81% to 97%. The percentage of pathologically localized tumors ranges from 36% to 91% and is significantly higher when serial PSA screening is done.

TABLE 72.5 LIKELIHOOD OF DETECTING PROSTATE CANCER ON TRANSRECTAL BIOPSY FOR 2,054 MEN AGED 40 TO 80 YEARS AS A FUNCTION OF SERUM PSA LEVEL, INDEPENDENT OF DRE RESULT

	Likelihood at Given Age[a]			
PSA (ng/mL)	<50 Y	51-60 Y	61-70 Y	>71 Y
<2.5	10	14	17	23
2.6-4.0	11	15	19	24
4.1-6.0	12	16	21	26

	Likelihood at Given Age[a]			
PSA (ng/mL)	<50 Y	51-60 Y	61-70 Y	>71 Y
6.1-10.0	14	18	23	29
10.1-20.0	17	23	31	37
>20.0	40	49	60	69

Ninety-five percent confidence intervals are within 2% to 12% for all probabilities.
DRE, digital rectal examination; PSA, prostate-specific antigen.

[a]Recorded at the time of PSA collection.

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TABLE 72.6 LIKELIHOOD OF DETECTING PROSTATE CANCER ON TRANSRECTAL BIOPSY FOR 2,054 MEN AGED 40 TO 80 YEARS AS A FUNCTION OF PATIENT AGE, SERUM PSA LEVEL, AND DRE FINDINGS

	Likelihood at Given Age[a]							
	<50 Y		51-60 Y		61-70 Y		71-80 Y	
PSA (ng/mL)	DRE−	DRE+	DRE−	DRE+	DRE−	DRE+	DRE−	DRE+
<2.5	9	37	12	39	15	42	20	44
2.6-4.0	9	41	12	42	16	44	20	47
4.1-6.0	10	41	14	44	17	47	22	48
6.1-10.0	11	–	15	48	19	50	25	42
10.1-20.0	13	55	19	54	25	58	31	60
>20.0	22	82	45	74	43	81	59	84

Ninety-five percent confidence intervals are within 2% to 12% for all probabilities.
DRE, digital rectal examination; PSA, prostate-specific antigen.

[a]Recorded at the time of PSA collection.

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An important issue is the clinical significance of small tumors detected by PSA testing. Epstein et al[51,107] identified a subset of patients with potentially biologically insignificant tumors among men with clinical stage T1c disease who underwent RP. On multivariate analysis, the best model predicting

insignificant tumor was a PSA density of less than 0.1 ng/mL/g and no adverse pathologic findings on needle biopsy, or a PSA density of 0.1 to 0.15 ng/mL/g, with a low- to intermediate-grade cancer less than 3 mm found in only one needle biopsy core specimen. The positive predictive value of the model was 95%, with a NPV of 66%.[51] Dugan et al[108] offered a definition of clinically insignificant cancer as a tumor that gives rise to no more than 20 cm^3 of cancerous tissue in the prostate by the time of expected death and a GS of less than 4 in 40-year-old patients, 5 in 50- to 59-year-old patients, 6 in 60- to 69-year-old patients, and 7 in 70- to 79-year-old patients. Using these definitions, a review of 337 prostatectomy specimens showed that, for cancer volume doubling times of 2, 3, 4, and 6 years, clinically insignificant cancer was identified in 1 (0.3%), 13 (3.9%), 25 (7.4%), and 49 (14.5%) of specimens, respectively. Humphrey et al[109] determined that in 11% to 30% of PSA-detected PCas, the tumor volumes were less than 0.5 mL. Therefore, by these definitions, most men treated with RP or RT have clinically significant cancer.

The incidence of clinically unimportant cancers has been reported to be between 4% and 16%.[51,61,110,111] Researchers at the Fred Hutchinson Cancer Research Center developed a computer model to estimate the rates of PCa overdiagnosis because of PSA testing. Using the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) registry data as a comparison for their computer-generated incidence rates, they calculated overdiagnosis rates of 15% in Whites and 37% in Blacks. These men were predicted to have PCa that would be detected only at autopsy.[112] Conversely, an epidemiologic study randomizing men from Göteborg, Sweden, to PSA screening or a control group demonstrated that screening did not lead to overdiagnosis of PCa; rather, most cancers detected at PSA-guided screening would eventually develop into clinical, frequently fatal, disease.[113]

Although PSA screening–detected cancers may be smaller, they may harbor aggressive disease. Investigators from the Netherlands studied 121 RP specimens from screened patients and found that screening-detected specimens were more likely to be pathologically organ-confined tumors and to have GSs of less than 8.[114] However, 60% of screening-detected tumors contained areas with high-grade cancer (Gleason pattern 4 or 5) and 50% had a GS of 7, suggesting that most of these tumors are clinically important. Updated results from a study of expectant management of patients with

nonpalpable PCa believed to have small-volume disease showed a 6.5-year median survival free of intervention and a 33% intervention rate at a median of 2.2 years, with a median follow-up among the entire cohort of 2.7 years.[115] Increased PSA density and decreased percentage free PSA correlated with progression of disease. Ninety-two percent of patients had curable disease at the time of their diagnosis of progression. These investigators concluded that observation with close follow-up may be a reasonable alternative for older men with a high likelihood of harboring small-volume PCa.

Refinements of the PSA screening test have been introduced to increase the sensitivity and specificity of the test. It was anticipated that such approaches would be able to more readily find curable cancers in younger men and to avoid unnecessary biopsies of benign hypertrophic disease in older men. Unfortunately, none of these modifications listed in the following sections has proven reliable enough alone on which to base a treatment decision for the individual patient.

Prostate-Specific Antigen Density

PSA density relies on the fact that cancers produce less PSA per cell than nonmalignant prostatic tissues. It is calculated by dividing the serum PSA concentration by the volume of the prostate gland measured by TRUS. A higher PSA density is associated with malignancy.

Prostate-Specific Antigen Velocity

Another method is to obtain serial PSA measurements and calculate the rate of rise in PSA, or PSA velocity. A rate of rise of greater than 0.75 ng/mL/year has been associated with a higher frequency of cancer. Two large retrospective analyses suggested that an increase greater than 2.0 ng/mL in PSA in the year prior to diagnosis is correlated with greater PCa-specific mortality following RT[116] and RP[117] for localized PCa, respectively.

Free Prostate-Specific Antigen

Serum tests for the molecular forms of PSA (free vs complexed vs total) have been developed to discriminate between elevated PSA levels from benign prostatic hyperplasia versus cancer. This is based on the concept that PSA exists in serum in a complex form bound to either α_1-antichymotrypsin or α_2-

macroglobulin, two extracellular protease inhibitors. Bound to α_1-antichymotrypsin or α_2-macroglobulin, the enzyme is inactive but still detectable using conventional immunoassays. In a study of free PSA, complexed PSA, and total PSA (free + complexed), the complexed-to-total ratio was higher and free PSA lower in patients with PCa relative to those with benign prostatic hyperplasia.[118] Catalona et al[119] reported on 113 patients with PSA levels between 4.1 and 10 ng/mL (63 with histologically confirmed benign prostatic hyperplasia, 30 with PCa and enlarged gland, and 20 with cancer and a normal-sized gland). The median percentage of free PSA was 9.2% for men with cancer and a normal-sized gland, 15.9% for those with cancer and an enlarged gland, and 18.8% for those with benign prostatic hyperplasia ($P < .001$). Men with PCa and either a normal or an enlarged gland had a significantly lower percentage of free PSA than men with benign prostatic hyperplasia only. At Washington University, a ratio of free to total PSA of 0.2 or less was most likely associated with PCa and with higher percentages with BPH. A ratio of 0.15 or less was associated with a higher GS and poorer prognosis.[120]

Oesterling et al[121] analyzed free, complexed, and total PSA in 422 healthy men aged 40 to 79 years. The respective recommended age-specific reference ranges (95th percentile) for the three forms were 0.5, 1, and 1 ng/mL for men aged 40 to 49 years; 0.7, 1.5, and 3 ng/mL for men aged 50 to 59 years; 1, 2, and 4 ng/mL for men aged 60 to 69 years; and 1.2, 3, and 5.5 ng/mL for men aged 70 to 79 years. Similar observations were made by investigators at Johns Hopkins.[122]

Reverse Transcriptase Polymerase Chain Reaction Assay

Molecular biologic methods, particularly reverse transcriptase polymerase chain reaction (RT-PCR), can be used to measure markers by detecting low levels of messenger RNA (mRNA) for PSA and prostate-specific membrane antigen (PSMA) expressed by circulating metastatic PCa cells. The assay is highly specific because the only cells expressing PSA in the peripheral blood are circulating PCa cells. However, there is a wide range of sensitivities of detection of PSA-expressing cells in the peripheral blood reported in the literature.[122]

Katz et al,[123] in 94 patients on whom RT-PCR assay for PSA mRNA was performed, reported an enhanced reaction in 26 (72%) of 36 patients who had extraprostatic tumors at the time of surgery. The test was negative in 51 (88%) of 58 patients with organ-confined disease. Six months after surgery, an increased PSA level was noted in 19% and 2% of the two groups, respectively. This bioassay may have significant staging value in patients who are candidates for RP. Cama et al[124] noted that, in contrast to the RT-PCR assay for PSA, the assay for PSMA did not correlate with pathologic stage of PCa.

Oefelein et al,[125] using RT-PCR for PSA, identified positive cells in 20 (91%) of 22 operative field samples, and 4 (25%) of 16 had evidence of intraoperative hematogenous dissemination ($P = .046$). Their results suggest that tumor cell spillage and, less frequently, hematogenous dissemination may be associated with operative manipulation of the prostate during RP and may potentially represent the mechanism of failure after this treatment.

Israeli et al,[126] using the PCR assay, also reported circulating prostatic tumor cells in 2 (6.7%) of 30 men. However, prostate-specific membrane primer assay demonstrated tumor cells in 19 (63%) of 30 patients. All 16 negative control subjects had negative PSA and PSMA PCR results. Using PSA mRNA as a marker for prostatic epithelial cells, Seiden et al[127] noted that 5 of 65 patients with clinically localized carcinoma of the prostate had PSA mRNA-detectable cells by transcription and PCR. On the other hand, 10 of 20 patients with hormone-refractory and progressive PCa also demonstrated the same increased frequency of PSA mRNA-detectable cells.

Overall, most studies report a 0% PSA rate by RT-PCR in negative control cases, whereas the positive rate in the metastatic group ranges between 31% and 88%.[125] However, 25% of men with localized PCa who underwent RP and had specimen-confined disease had a positive PCR PSA assay.[123] These men would be denied surgery if it was concluded that circulating PCa cells are synonymous with incurable disease. A new approach is to use a combination of primers to improve the overall staging accuracy of RT-PCR. Preliminary work from the Cleveland Clinic suggests that combining RT-PCR for PSA and PSMA may improve the staging accuracy.[128] Until the significance of a positive PCR assay is determined with long-term follow-up, RT-PCR remains experimental and should not change treatment recommendations.

Evaluation and Diagnosis

Patients with localized prostatic carcinoma are frequently asymptomatic; the diagnosis is often made with a screening PSA test. In the pre-PSA era, asymptomatic patients were diagnosed on the basis of palpating a firm prostate nodule on DRE. Patients with locally advanced tumors have presented with bladder outlet obstructive symptoms such as urinary hesitancy, decreased force of the urinary stream, and postvoid dribbling as the tumor impinges on the membranous urethra. Chronic obstruction and bladder distension can lead to decreased compliance of the detrusor muscle that is manifested by symptoms of urinary frequency, urgency, and nocturia. Very early-stage disease (T1a or T1b) may occasionally be diagnosed at TURP for symptoms of bladder outlet obstruction caused by benign prostatic hyperplasia. With local invasion into the urethra or ejaculatory ducts, patients may experience hematuria or hematospermia. As the disease penetrates the capsule of the prostate, there may be invasion into the neurovascular bundles that course along the lateral aspects of the prostate, leading to erectile dysfunction. Disseminated disease frequently manifests as bone pain from distant osseous metastases.

A complete clinical history and a general physical examination including DRE are mandatory. The DRE is best performed with a well-lubricated glove; the patient may be standing and bent over at the waist with their elbows resting comfortably on a firm surface or in the lateral decubitus position on the examining table. The examiner should note the size of the prostate gland, its overall consistency, the presence of any firm areas, and, currently, rarely, extraprostatic tumor extension. A typical neoplastic nodule of prostatic carcinoma is extremely firm, often not elevated above the surface of the gland, but surrounded by compressible prostatic tissue. The examiner should determine whether the lateral sulci are involved by tumor and also the degree of spread superiorly. In most patients, the SVs cannot be palpated as discrete structures, and the finding of a firm area extending above the prostate suggests that the SVs are involved by malignancy. Only approximately 50% of prostatic nodules found on DRE are confirmed to be malignant on biopsy.[42]

An abnormal DRE result, a consistently elevated PSA, or a combination of the two warrants a biopsy to establish a pathologic diagnosis. A TRUS-guided needle biopsy is the most common method for obtaining

representative samples of the prostatic tissue. Ten to 18 cores are taken, including cores from the base, mid, and apex bilaterally and additional cores from the midline and lateral PZ. If clinically indicated by obstructive symptoms, a separate biopsy of the TZ is taken. The pathology report frequently includes the length of each core and the length of each core that contains tumor.

Once the tissue diagnosis of PCa is ascertained, the patient should undergo a staging workup including laboratory data such as a baseline PSA, complete blood count, and testosterone level. The standard tests required in the evaluation of patients with prostatic carcinoma (Table 72.7) have significantly changed with the advent of molecular imaging.

TABLE 72.7 DIAGNOSTIC WORKUP FOR CARCINOMA OF THE PROSTATE

Clinical
Perform physical examination.
Perform digital rectal examination (DRE) to confirm clinical stage.
Estimate life expectancy.
Inquire about known high-risk germline mutations.
Obtain family history.
Assess quality-of-life measures.
Laboratory
Perform and/or collect prostate-specific antigen (PSA) and calculate PSA density.
Total serum testosterone if ADT indicated
Pathology
Obtain and review diagnostic prostate biopsies (transrectal, transperineal, and/or MRI guided).
Radiographic imaging
Multiparametric magnetic resonance imaging of the abdomen and pelvis
Transrectal ultrasonography (for biopsy guidance)
PSMA PET (for intermediate and high risk)

ADT, androgen deprivation therapy; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.

Imaging Studies

Some diagnostic imaging studies have become an essential aspect of pretreatment evaluation and treatment selection. New techniques have allowed for more precise assessments of tumor location, volume, and extent, as well as biologic activity. As a result, clinical staging can be used more accurately as a prognostic factor for defining treatment options.

Transrectal Ultrasonography

The normal adult prostate imaged by TRUS appears as a symmetric, triangular, relatively homogeneous structure with an echogenic capsule. TRUS is used routinely for guidance during the transrectal biopsy and during prostate brachytherapy (BT). However, only PCas located in the PZ can be reliably detected by ultrasonography. Attempts to characterize adenocarcinoma by pattern on TRUS have indicated that PCas can have variable echogenicities. Rifkin et al,[129] in 443 men undergoing TRUS of the prostate, found 130 pathologically proven cancers and 313 cases of benign prostatic disease. Cancers were hyperechoic in 69% of the cases and had poorly defined margins, whereas benign lesions were hyperechoic in only 46% of the cases.

Chodak et al,[130] in a prospective, randomized study of TRUS in 216 men, reported a sensitivity of 86% but a specificity of only 41%; tumors less than 1 cm were the most difficult to detect. For staging purposes, Rifkin et al[129] found a sensitivity of only 60% using TRUS to distinguish between T2 and T3 lesions.

Positron Emission Tomography

Molecular imaging has transformed PCa staging. Staging at diagnosis has relied on PSMA, a transmembrane protein that is overexpressed in PCa, particularly high-grade PCa.[131,132] In one study of PSMA positron emission imaging (PET) in high-risk PCa, PSMA PET detected nodal disease in 32% of men.[133] Most nodal metastases were pelvic versus extrapelvic (64% vs 36%).

Multiple diagnostic tracers targeting PSMA have been U.S. Food and Drug Administration (FDA) approved. The first was Ga-68-PSMA-11, based on the proPSMA trial performed in Australia. This study compared Ga-68-PSMA-11 to conventional bone scan and CT and found that Ga-68-PSMA-11 had greater accuracy (92% vs 65%), sensitivity (85% vs 38%), and specificity (98% vs 91%).[134]

F-18-DCFPyl is also FDA approved, based on the OSPREY[135] and CONDOR[136] studies. These studies evaluated F-18-DCFPyl in newly diagnosed and biochemically recurrent PCa, respectively. In newly diagnosed high-risk PCa, the OSPREY found a sensitivity of 38% for any positive LN, which increased to 60% for diagnosing nodes larger than 5 mm.

F-18-rhPSMA-7.3 is a third FDA-approved molecular tracer that was engineered to have strong diagnostic characteristics with a specificity of 94% to 97% and somewhat delayed renal excretion, which may improve the detection of recurrence within the prostate bed.[137] PET imaging is essential for higher risk disease but is not indicated in low-risk disease.

Computed Tomography

The primary role of CT in PCa is for size determination of the prostate gland, RT treatment planning, and assessment of pelvic nodal metastases. CT lacks the soft tissue resolution needed to detect intraprostatic disease, capsular extension, or SV involvement. Moreover, for most patients with newly diagnosed PCa, the incidence of positive LNs is less than 5%; thus, there is little role for CT as a routine staging procedure.[138] CT identification of pelvic adenopathy depends on LN enlargement, and the correlation between nodal size and metastatic involvement is poor.[138-140]

Albertsen et al[141] performed a population-based analysis to determine the positive yield of imaging studies performed on men with newly diagnosed PCa. The positive yield of a CT scan was less than 12% for men with PSA of 4 to 20 ng/mL. More than 10% of men with PSA of greater than 20 ng/mL and GS of 6 or greater were likely to have CT scans positive for extracapsular or metastatic disease. For combinations of high GS and PSA of greater than 50 ng/mL, the positive yield on CT scan was as high as 62%. Flanigan et al[138] retrospectively studied 173 men who underwent preoperative CT scanning and found that none of the patients with a PSA of less than 25 ng/mL had an abnormality by CT scan. Of 33 patients with PSA levels of greater than 25 ng/mL, 9 had nodal metastases, but only 3 (9%) of these 33 patients were correctly diagnosed by CT scanning. These authors concluded that routine preoperative CT scanning could not be justified in patients with a PSA of less than 25 ng/mL. Although the histologic incidence of positive pelvic LNs is substantial when PSA levels exceed 25 ng/mL, the sensitivity of CT for detecting positive nodes is only approximately 30% to 35% even at these levels.[142]

Bone Scan

A close correlation exists between pretreatment PSA level and incidence of abnormal bone scan results.[143,144] Given the low risk of osseous metastasis in

patients with early-stage PCa, the yield of a bone scan is low unless the PSA is greater than 20 ng/mL or the patient complains of bone pain. In a retrospective analysis of 589 patients with untreated carcinoma of the prostate and PSA levels of 20 ng/mL or less, Rees et al[142] reported that only 3 (1%) of 274 patients evaluated by bone scan and 3 (1%) of 262 patients evaluated by CT scan had evidence of metastatic disease. Only 1 of 108 patients with a PSA of 10 ng/mL or less had metastatic disease, and no patient with a GS of 5 or less had an abnormal bone scan or CT scan result or positive LNs.

Huncharek and Muscat,[145] in an analysis of 265 patients with localized carcinoma of the prostate, noted that no patients with PSA of less than 4 ng/mL had a positive bone scan. In patients with PSA of 4.1 to 10 ng/mL and PSA of 10.1 to 20 ng/mL, 2.2% and 3.6%, respectively, had positive bone scans. In patients with PSA of greater than 20 ng/mL, 6.7% had a positive bone scan. The guidelines established by the American College of Radiology appropriateness criteria for pretreatment staging of clinically localized PCa recommend that a radionuclide bone scan be considered only for patients with PSA of 20 ng/mL or more, T3-T4 disease, or GS of 8 or higher or for patients with skeletal symptoms.[146]

From a clinical standpoint, a baseline bone scan may be helpful before treatment with RT, especially in older patients or those with a history of arthritis, to document degenerative changes that may later be interpreted as metastatic osseous disease. Bone scintigraphy in routine follow-up has no value because PSA is more sensitive in detecting recurrence, and treatment of asymptomatic bone metastases (except in cases of impending pathologic fracture) cannot be justified. Periodic PSA assessment is adequate for follow-up of these patients, and bone scan should be limited to patients with rising PSA levels when clinically warranted.[147]

Magnetic Resonance Imaging

MRI can be very useful in delineating intraprostatic tumor and local extension beyond the capsule. Kagawa et al,[148] using CT-MRI fusion software for planning three-dimensional conformal radiation therapy (3DCRT), demonstrated that MRI was clearly superior to CT in defining the prostate apex, neurovascular bundles, and anterior rectal wall. The

discrepancy in prostate location between the two imaging studies was also greatest at the apex and base of the gland.

There have been significant improvements in MR technique and performance for imaging the prostate, such as the use of multiparametric MRI (MP-MRI) that improves spatial resolution, analytic image correction software to eliminate artifacts, fast spin-echo imaging to reduce image acquisition time and provide higher signal-to-noise ratio, and magnetic resonance spectroscopy imaging (MRSI) to detect metabolic activity in the prostate.[149] Moreover, increasing reader experience has greatly improved the accuracy of MRI staging for PCa. Strict MRI criteria for the diagnosis of ECE have been elucidated. Nevertheless, there is still interobserver variability, depending on the experience of the radiologist. One study demonstrated that the specificity for diagnosis of ECE was 93% for senior readers and 94% for junior readers, whereas sensitivity was 50% for senior readers and only 14% for junior readers.[150]

The appearance of the prostate and the information that can be gleaned for staging purposes depend on the MR technique used. On axial T1-weighted images, the prostate gland appears homogeneous and the zonal anatomy is not well appreciated.[151] However, there is a larger field of view, allowing for the detection of locoregional adenopathy and suspected bony lesions (Figure 72.3A). Postbiopsy hemorrhage is evident on T1-weighted images as high T1 signal intensity (Figure 72.3B), which may be in the prostate, SVs, or both. This is an important observation because hemorrhage may mimic tumor on T2-weighted images and because hemorrhage greatly limits the accuracy in the assessment of ECE.[152]

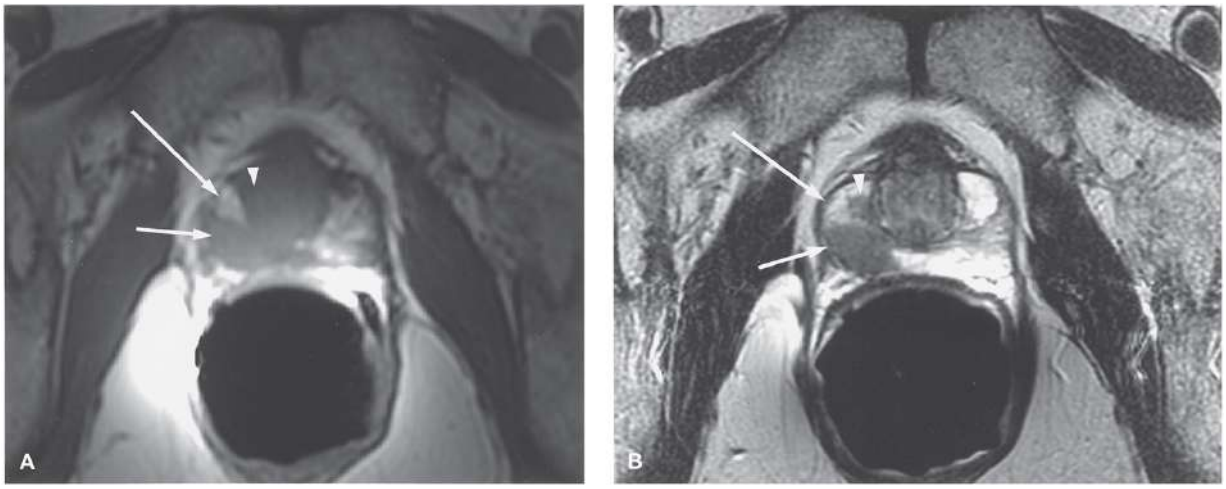


FIGURE 72.3 A. Normal T1-weighted axial magnetic resonance image. Age-related benign prostatic hyperplasia in the transition zone is evident (long arrow). The neurovascular bundles lie adjacent to the peripheral zone (short arrow). B. The T2-weighted axial image of the same level of the gland demonstrates areas of low signal intensity adjacent to the postbiopsy hemorrhage that are suspect for tumor (short arrow and arrowhead). This is an example of the hemorrhagic exclusion sign. (Courtesy of Steven Eberhardt, MD.)

The zonal anatomy of the prostate is clearly depicted on axial and coronal T2-weighted images. The vas deferens and SVs are also discernible on T2-weighted axial and coronal images, whereas the neurovascular bundles can be seen best on axial images[151] (Figure 72.4). The penile bulb is better imaged on T2-weighted coronal sections and is seen much more accurately than with CT. The PZ is normally of high signal intensity, whereas tumor appears as low signal intensity. There are many other causes of low T2 signal intensity, including hemorrhage, prostatitis, hormone treatment, and RT. An area of low signal intensity can be attributed to hemorrhage if it causes high T1 signal intensity in the corresponding region. Low T2 signal intensity due to treatment (RT or hormonal therapy) may be suspected when the signal change is diffuse and associated with a small, featureless prostate gland. Signs of ECE are a focal, irregular capsular bulge, asymmetry or invasion of the neurovascular bundles, and obliteration of the rectoprostatic angle.[150]

FIGURE 72.4 Normal T1-weighted axial magnetic resonance image. Age-related benign prostatic hyperplasia in the transition zone is evident (long arrow). The neurovascular bundles lie adjacent to the peripheral zone (short arrow). (Courtesy of Steven Eberhardt, MD.)

MP-MRI can visualize prostate tumor characteristics (extraprostatic extension [ECE], tumor volume, etc) that can be predictive of final pathologic findings such as LN involvement, pathologic ECE (pECE), and BCR, all pivotal factors in the decision-making process regarding treatment. Tumor contact length (TCL) is defined as the length of cancer in contact with the prostatic capsule. Kongnuyun et al[153] evaluated the ability of 3T MP-

MRI–determined TCL in predicting pECE, BCR, and LN in patients undergoing RP. All 1,260 patients who underwent a 3T MP-MRI at the NCI from 2007 to 2015 were retrospectively classed into no ECE, suspicious ECE (sECE), and frank ECE (fECE) based on MP-MRI findings. sECE was defined as tumor with capsular bulge on MRI, whereas fECE was clear capsular obliteration and tumor extension beyond the prostatic capsule. Demographic data were obtained on patients with fECE and sECE on MP-MRI with the presence of pECE, LN, and BCR status following RP from a single surgeon (PP) experience. The authors focused on 146 patients who had sECE[68] or fECE[78] on MP-MRI. Median PSA was 11.7 ng/mL. Logistic regression analysis showed that MP-MRI–determined TCL was predictive of ECE (P = .01), LN status (P = .0001) on final pathology, and BCR (P = .05) during follow-up. Patients with pECE had a longer median MP-MRI TCL (2.8 cm) compared to those without pECE (2.4 cm), P = .04. When analyzed individually, fECE correlated with pECE (P = .05), whereas s ECE did not correlate with pECE (P = .11). Although not statistically significant, the median MP-MRI TCL for sECE with pECE was still longer than in sECE with no pECE in the subgroup analysis.

Magnetic Resonance Spectroscopy Imaging

Spectroscopy is based on the principle that the electron cloud surrounding different chemical compounds shields the resonant atoms of interest to varying degrees, depending on the specific atomic structure of the compound.[154] Because MRSI uses the same clinical MRI scanner, gradients, and radiofrequency coils as MRI, it can be added to an MRI examination, and the metabolic data can be overlaid directly on the corresponding anatomic images.[149] This modality is particularly useful in the prostate because there are metabolic compounds that localize to regions of the prostate and can be used to distinguish between normal prostate cells and malignant cells. Human prostatic glandular cells produce large amounts of citrate during cellular metabolism that are secreted into the prostatic fluid, yielding concentrations 240 to 1,300 times greater than blood plasma concentrations. High levels of citrate are found in the glandular regions of the prostate such as the PZ and lower levels in the TZ and CZ. Choline is another metabolite found at intermediate levels in the normal prostate and SVs. On MRSI, regions of PCa can be identified by differences in these two

metabolite levels. A significant reduction in prostate citrate and a significant increase in prostate choline levels relative to the normal PZ have been observed.[149] The elevated levels of choline in PCa may be attributed to the increased rate of cell proliferation, an increase in cell density in regions of cancer, and a change in the composition of the cell membrane leading to higher concentrations of choline-containing phospholipids.[149] The result of MRSI is a metabolic map of the prostate corresponding to normal and abnormal metabolic activity that can be used to pinpoint the location of prostatic tumors. This is exceptionally useful for accurate localization of prostate tumors and, in particular, when distinguishing between tumor and postbiopsy hemorrhage, which obscures MRI interpretations of PCa. Moreover, there is great potential for the use of this technique for follow-up after treatment and in the development of more focused therapy.

The contribution of metabolic information gleaned from MRSI to MR anatomic imaging has improved the diagnostic accuracy of MRI both in localizing and staging PCa.[154] Investigators at the University of California, San Francisco,[155] assessed the accuracy of combined MRSI and MRI for tumor detection and localization in 62 patients by comparing preoperative imaging results with histopathologic step-section examination after prostatectomy. MRI tended to have a higher sensitivity and MRSI a higher specificity for detecting definite sites of cancer. The addition of MRSI significantly improved specificity over MRI alone. Compared with step-section pathology results, the specificity for tumor location with combined MRI and MRSI reached 91%. Combined MRI/MRSI allowed localization of cancer to a sextant of the prostate with a sensitivity of up to 95% compared with MRI alone when either MRI or MRSI was positive. Moreover, a study from the University of California, San Francisco,[156] found MRI and MRSI are comparable with biopsy in accurately localizing intraprostatic cancer and are more accurate than biopsy in the prostate apex.

In addition to improving PCa localization, MRSI is complementary to MRI in staging and risk-stratifying patients with PCa. Combined MRI/MRSI enhances the assessment of both ECE and SV invasion.[150] Furthermore, the addition of MRSI to MRI improves the accuracy of less experienced MRI readers and reduces interobserver variability in the diagnosis of ECE.[154] Metabolic information from MRSI may also be predictive of tumor aggressiveness. Preliminary MRI/MRSI studies have shown that citrate

levels are lower in poorly differentiated PCas and that choline levels may be elevated in more aggressive tumors with greater membrane phospholipid synthesis.[157]

RISK STRATIFICATION SYSTEMS AND STAGING CLASSIFICATION

Based on tumor stage, pretreatment PSA, and biopsy GS, PCa is generally grouped according to one of several risk stratification models. These systems are useful to stratify disease-free survival (DFS), compare treatment results, and provide a means to recommend treatment options appropriately. A nomogram developed by Partin et al[53] first combined PSA at diagnosis, clinical stage, and biopsy pathology to predict pathologic stage, which assisted in guiding treatment decision-making. The original "D'Amico stratification" criteria were published in 1998, finding that these three tumor characteristics determined at diagnosis were predictors of response after surgery or RT.[56] Over time, multiple iterations have updated a widely used stratification model predicting low, intermediate, or high risk of PSA failure and risk of metastasis after primary treatment.

The 2017 American Joint Committee on Cancer/Union for International Cancer Control staging system is less used for treatment decision-making, but its TNM components are used in summarizing disease extent. All information that is available before first definitive treatment (DT) may be used for clinical staging, including imaging studies. For example, pelvic MRI findings of ECE are frequently used to determine cT3a status.

Genomic Testing and Molecular Biomarkers

Molecular biomarkers have extended the potential for risk stratification beyond traditional TNM, PSA, and GS. Three tissue-based tests for PCa risk stratification/prognosis for very low- and low-risk PCa: Decipher, Oncotype DX prostate, and Prolaris. These are further described in Table 72.8.

TABLE 72.8 TISSUE-BASED TESTS FOR LOW- AND VERY LOW-RISK PROSTATE CANCER RISK STRATIFICATION/PROGNOSIS

Test	Platform	Populations Studied	Outcome(s) Reported (Test Independently Predicts)	Molecular Diagnostic Services Program (MolDX) Recommendations
Decipher	Whole-transcriptome 1.4M RNA expression (46,050 genes and noncoding RNA) oligonucleotide microarray optimized for FFPE tissue	Biopsy, localized prostate cancer post-RP or EBRT	• Non–organ confined (pT3) or grade group 3 disease at RP • Lymph node metastasis • Biochemical failure/recurrence • Metastasis • Prostate cancer–specific mortality • Grade group ≥4 disease at RP	Cover postbiopsy for very low-, low-, favorable intermediate-, and unfavorable intermediate-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy
Oncotype DX Prostate	Quantitative RT-PCR for 12 prostate cancer–related genes and 5 housekeeping controls	Biopsy, very low- to high-risk treated with RP	• Non–organ-confined pT3 or grade group 4 disease on RP • Biochemical recurrence • Metastases • Prostate cancer–specific mortality	Cover postbiopsy for very low-, low-, and favorable intermediate-risk prostate cancer in patients with at least 10 y life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy
Prolaris	Quantitative RT-PCR for 31 cell cycle–related genes and 15	• Biopsy, conservatively managed (active surveillance)	• Prostate cancer–specific mortality	

Test	Platform	Populations Studied	Outcome(s) Reported (Test Independently Predicts)	Molecular Diagnostic Services Program (MolDX) Recommendations
	housekeeping controls			
		• Biopsy, localized prostate cancer	• Biochemical recurrence • Metastasis	
		• Biopsy, intermediate-risk treated with EBRT	• Biochemical recurrence	
		• Biopsy, Gleason grade 3 + 3 or 3 + 4	• Non–organ-confined pT3 or grade group ≥3 on RP	

EBRT, external beam radiation therapy; FFPE, fresh frozen paraffin embedded; RP, radical prostatectomy; RT-PCR, reverse transcriptase polymerase chain reaction.

The Genomic Prostate Score (GPS), based on the Oncotype DX Prostate Cancer assay, ranges from 0 to 100, with increasing scores indicating more biologically aggressive disease. Previous studies have validated it as a predictor of adverse pathology and BCR after RP. Van Den Eeden and colleagues[158] retrospectively assessed how the GPS predicted DMs and PCa-specific death in 259 men with localized PCa treated with RP between 1995 and 2010. During a median follow-up of 9.8 years, 64 PCa-specific deaths, 79 metastatic events, and 117 BCRs occurred, according to a 2017 European Urology online report. Each 20-point increase in GPS was associated with a 2.34-fold increased risk of DMs, a 2.69-fold increased risk of PCa-specific death, and a 2.11-fold increased risk of BCR, after adjustment for other variables. Among the four biologic pathways represented in the GPS, downregulation of androgen signaling and upregulation of stromal response gene groups were most strongly associated with each outcome, although all four gene groups contributed to the prediction. The score predicted all three outcomes within clinically relevant subsets of patients by, age, race, and

central biopsy GS. One of the authors noted that “it was unclear which subset of patients might benefit most from this test, because men with low-risk PCa have very high 10-year survival, and those with high-risk cancer are usually recommended for treatment. Furthermore, our study was limited to patients who had undergone RP, and it is unknown how the test may perform for those treated with radiation therapy or who undergo active surveillance.” The authors commented that “several other genomic assays exist and have been validated to predict the risk of death from PCa. In addition, other refined risk prediction tools include advanced imaging, such as MP-MRI, that allows for more accurate clinical staging. Comparative studies are currently lacking, and may be increasingly important as we seek to understand how best to evaluate patients with newly diagnosed prostate cancer.”

Prolaris is a panel of RNA cell cycle progression (CCP) genes measuring cancer proliferation. The primary end point of this test is the 10-year risk of PCa death with conservative management. Cuzick et al[159] examined the biopsy specimens from 761 men diagnosed with PCa who were managed conservatively. After adjusting with PSA and GS, CCP score was a significant predictor of PCa death (HR = 1.65).

The Prolaris test measured on biopsy has also been shown to predict outcomes after radical treatment. Freedland et al[160] reported on 141 men diagnosed with PCa who received external beam radiation. CCP score was a significant predictor of BCR (HR = 2.11, P = .034) after adjusting for PSA, GS, positive cores, and use of hormonal therapy. There was also a statistically significant relationship with PCa death on univariate analysis, but the number of events was small. Similarly, Bishoff et al[161] showed that biopsy CCP scores were a significant predictor of BCR after RP (HR = 1.47) in a multi-institutional cohort. It was also a significant predictor of metastatic disease on univariate analysis. Another recent study by Oderda et al[162] in 52 Italian men treated by RP showed that mean Prolaris scores were −1.2, −0.444, and 0.208 in low-, intermediate-, and high-risk patients, respectively. Prolaris was a significant predictor of high-risk disease (OR, = 5.73). Prolaris was also significantly associated with BCR on univariate, but not multivariate, analysis, although there were only 15 events.

Clinical utility studies have been performed using surveys, such as shown by Shore et al[163] who surveyed 15 urologists about the influence of Prolaris results in 294 different cases, and they reported that approximately one-third

of the results would potentially lead to changes in practice. Another study by Crawford et al[164] reported changes from interventional to noninterventional management, and vice versa due to Prolaris results. Less is known about the long-term impact of changing initial management decisions on the basis of genomic test results or how these tests fit in a context with widespread MP-MRI use.

The Ontario (Canada) Technology Assessment[165] conducted a systematic review of the clinical and economic evidence of the CCP test in low- and intermediate-risk, localized PCa in a medical and health economic databases search from 2010 to June or July 2016. For the review of clinical effectiveness, 3,021 citations were screened, and two before-after studies met their inclusion criteria. In one study, the results of the CCP test appeared to change the treatment plan (from initial to final plan) in 64.9% of cases overall (GRADE rating of the quality of evidence: very low). In the other study, the CCP test changed the treatment received in nearly half of cases overall, compared with the initial plan (GRADE: very low). No evidence was available on clinical outcomes of patients whose treatment was informed by CCP results. For the review of cost-effectiveness, 100 citations were identified and screened, and no studies met the inclusion criteria. Patients viewed the test as potentially helpful but, because of the complexity of treatment decision-making, were unsure the test would ultimately change their treatment choices. The study found no evidence to demonstrate the impact of the Prolaris CCP test on patient-important clinical outcomes. The limited evidence available showed that the test appeared to provide information that, when considered in addition to clinical risk stratification, may change the treatment plan or actual treatment for some patients with low- and intermediate-risk PCa, but there are insufficient data to assess the cost-effectiveness of the CCP test.

The Oncotype Dx prostate biopsy test calculates a GPS based on genes from four different pathways involved in PCa: stromal response, androgen signaling, proliferation, and cellular organization. The primary end point of this test is to predict the risk of adverse disease at RP. Unlike Prolaris and Decipher (in postprostatectomy patients), Oncotype Dx was designed for use with biopsy tissue and does not have a commercially available test for postprostatectomy risk stratification.

Klein et al[166] defined the 17-gene panel for use in the Oncotype Dx GPS and tested it in the biopsies of 395 men with low- to intermediate-risk PCa. A 20-unit increase in GPS was associated with a significantly increased risk of high-grade and/or high-stage disease (OR = 2.1; 95% confidence interval [CI] = 1.4-3.2), after adjusting for the CAPRA score. Adding in a GPS measurement improved the discrimination of adverse disease compared with that of the CAPRA risk classification alone (area under the receiver operating characteristic curve [AUC] 0.67 vs 0.63). Cullen et al[167] subsequently validated the Oncotype Dx biopsy test in independent populations of men from military hospitals. On multivariable analysis, a 20-unit increase in Oncotype DX GPS associated with 3.3 times increased risk of adverse disease at RP and 2.7 times increased risk of BCR. Badani et al[168] reported that the GPS was discordant to the risk category, as defined by national consensus guidelines, in 39% of patients and that 18% of recommendations between active surveillance (AS) and treatment changed as a result of Oncotype Dx. Clinicians also reported that the results increased their confidence in decisions.

Ehro et al[169] using a transcriptome-wide assay developed a biomarker signature for patients assessed as low risk at diagnosis who are upgraded or upstaged following RP. Gene expression data of 56 RP samples from the Memorial Sloan Kettering Oncogenome Project (GSE21034) that met the low-risk criteria (ie, biopsy GS $\leq$ 6, clinical stage T1 or T2A, and pre-op PSA $\leq$10 ng/mL) were used. Of these tumors, 31 underwent upgrading or upstaging (defined by pathologic GS $\geq$7 or a pathologic tumor stage > T3A). In the training set (n = 29), a median fold difference filter (MFD > 1.4) was applied to select features. The top 16 t-test ranked features were modeled with a K-nearest neighbor (KNN) classifier (k = 3), which predicted upgrading/upstaging events. The KNN was applied to the test set (n = 27) and achieved an AUC of 0.93, significantly better discrimination than pre-op PSA (AUC = 0.52) or tumor stage (AUC = 0.63). Compared to the null model's accuracy of 56%, the KNN correctly predicted 81% (P < .005) of the upgrading/upstaging events. In multivariable analysis with pre-op PSA, tumor stage, and age at diagnosis, the KNN remained the only significant (P < .05) factor with an OR of 2.7. Validation studies of this signature in prospectively designed cohorts of AS candidates have been underway to

determine if the molecular signature can improve treatment and management decisions for patients with low-risk PCa.

PATHOLOGY

Adenocarcinoma, arising from peripheral acinar glands, is the most common tumor in the prostate. It is graded as well, moderately, or poorly differentiated according to cellular characteristics, such as nuclear content, number of nuclei, pleomorphism, gland formation, and invasion of the stroma.[56]

In the 1960s, Gleason[170,171] and Gleason and Mellinger[172] initially proposed a prognostic classification system based on the clinical stage and the degree of differentiation of primary and secondary morphologic patterns of the tumor, each graded from 1 to 5. Subsequently, only pathologic features were scored, resulting in a GS that sums grades to yield nine discrete scores ranging from 2 to 10. The GS is one of the strongest predictors of biologic behavior in PCa, including invasiveness and metastatic potential; however, it is limited by its subjectivity. There is significant interobserver and intraobserver variability reported using the Gleason grading system.[173] In addition, the treatment with hormonal therapy agents can affect the pathologist's ability to accurately identify a GS.[173]

In 2016, a new grading system was accepted by the World Health Organization simplified the groups based on pathologic features and clinical outcomes. This system was validated in a landmark paper by Epstein et al, evaluating 20,000 men with long-term outcomes after prostatectomy.[174] Grade groups 1, 2, 3, 4, and 5 correlated with 5-year biochemical PFS of 98%, 93%, 78%, 64%, and 49%, respectively. The grade groups combine previous GSs (Table 72.9).

TABLE 72.9 DEFINITION OF HISTOLOGIC GRADE GROUP (G)

Grade Group	Gleason Score	Gleason Pattern
1	≤6	≤3 + 3
2	7	3 + 4
3	7	4 + 3
4	8	4 + 4

Grade Group	Gleason Score	Gleason Pattern
5	9 or 10	4 + 5, 5 + 4, or 5 + 5

Recently, the Gleason system has been compressed into the so-called grade groups.
Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

Grading errors may reflect sampling error because the needle biopsy samples a small fraction of the prostate gland, and the grade of cancer obtained on needle biopsy may not always be representative of the actual histologic subtype or degree of differentiation of the tumor. Most studies demonstrate a tendency of pathologists to undergrade biopsy specimens. Johnstone et al[175] noted that, compared with subsequent RP specimens, the incidence of correct grading of prostatic carcinoma from needle biopsies was 71%, with 23% undergrading and 6% overgrading. In a study from Memorial Sloan Kettering Cancer Center (MSKCC), GSs from 18-gauge needle biopsies were compared with radical retropubic prostatectomy specimens in 226 consecutive patients. The biopsy score was identical to the specimen score in 31% of cases, whereas 26% were discrepant by 2 or higher GSs. Overall, 54% of biopsies were undergraded and 15% were overgraded.[176] A large, retrospective analysis[177] of the correlation between GSs from biopsy and prostatectomy specimens and prediction of DFS was carried out among 1,031 patients. Overall accuracy was 58.3%. When categorized by GSs of less than 7, 7, and greater than 7, patients with tumors of GSs of less than 7 on prostatectomy specimens had a significant survival advantage over those with GSs of less than 7 by biopsy, whereas DFS was superior for patients with GSs of greater than 7 by biopsy than those with GSs of greater than 7 on prostatectomy specimens. The overall DFS was similar among all patients with GS of 7. These data should be kept in mind when the results of RP and irradiation are compared.

Predicting tumor extent and location using biopsy results was investigated by Humphrey et al[109] in a correlative study of multiple parameters with pathologic features in 50 RP specimens. They noted that it was very difficult to predict tumor extent in the gland quadrants based on the extent of tumor in the needle biopsy. There were 53 negative quadrant biopsies with carcinoma present in that quadrant in the RP specimen. Gregori et al[178] evaluated the

accuracy of sextant biopsies in predicting tumor location among 289 patients with clinically localized PCa who underwent radical perineal prostatectomy. These investigators found that 33% of patients with a unilateral positive biopsy had cancer confined to one side of the gland, whereas 66% showed bilateral disease in the prostatectomy specimen.

Stamey et al[179],[180] emphasized that, with regard to the natural history of PCa and prognosis, it is not just the GS that is important but also how much of the tumor is present. In a study of histologic prognostic variables for PSA relapse among 372 men with PCa followed for 3 years after retropubic prostatectomy, the most important variables predicting biochemical disease-free status for PZ cancers were percentage Gleason grade 4/5, cancer volume, serum PSA, and prostate weight.[180] Percentage Gleason grade 4/5, cancer location in the PZ, cancer volume, and LN involvement had prognostic value in large-volume PCa. These investigators also noted that TZ cancers have a better prognosis than PZ tumors because they are separated from the neurovascular bundles and the ejaculatory ducts by the compressed surgical capsule caused by expanding benign hyperplastic nodules.[36] From the Stanford experience,[181] cancer location in the PZ and percentage Gleason grade 4/5 were the most powerful predictors of biochemical failure in men whose cancer was 6 cm^3 or higher and contained in the prostatic capsule. Preoperative serum PSA was not helpful in distinguishing biochemical failure rates in large-volume cancers, regardless of whether they were organ confined.

D'Amico et al[182],[183] showed that the percentage of positive prostate biopsies added clinically significant information regarding time to PSA failure among 960 men with PSA-detected or clinically palpable PCa treated with RP. Investigators at the University of Michigan,[184] in an analysis of preoperative factors, including clinical stage, PSA, biopsy GS, greatest percentage of a biopsy core involved by cancer, number of biopsy cores containing cancer, and perineural invasion, found that only PSA, GS, and greatest percentage of a biopsy core involved by cancer were highly predictive of PSA RFS on multivariate analysis. This additional prognostic information may identify patients who are candidates for adjuvant therapy after RP. In addition, with the use of RT, histologic features from prostatectomy specimens are not available to incorporate into prognostic

models, and pretreatment risk stratification is important owing to the increasing use of nonsurgical treatment options.

Prostate core biopsy histologic features have been investigated for predicting extraprostatic extension and LN involvement. Researchers at the Mayo Clinic[185] compared biopsy specimen GSs, percentage positive cores, and percentage surface area involved in all cores with pathologic stage determined from RP specimens. Multivariate analysis using these pathologic variables, in addition to patient age, clinical disease stage, and PSA, showed that the percentage of positive cores, initial serum PSA, and GS of cancer in the needle biopsy were the only parameters that jointly predicted pathologic stage (T2 vs T3 disease). Narayan et al[66] used the combination of preoperative PSA plus biopsy GS in 932 patients who had undergone pelvic lymphadenectomy to predict the risk of positive pelvic LNs. Patients with biopsy GSs of 6 or less and preoperative PSA concentrations of 10 ng/mL or less had a less than 1% false-negative rate for pelvic LN metastases, suggesting that a staging pelvic lymphadenectomy is unnecessary.

Finally, the tumor histologic characteristics change with time and progression of disease. Cheng et al[186] reported a trend toward histologic dedifferentiation when prostate carcinoma metastasized to regional LNs. Among 242 patients treated with RP and pelvic lymphadenectomy at the Mayo Clinic, GS in the LN metastases was higher than in the primary tumor in 45% of patients, lower in 12% of patients, and matched exactly in 43% of patients. The 5-year PFS rate was significantly different between patients with histologic dedifferentiation and those without dedifferentiation.

Other Histologic Subtypes

Periurethral duct carcinoma is a separate clinicopathologic entity, usually consisting of a transitional cell type of carcinoma, although a mixture of glandular and transitional cells is also observed. Large anaplastic tumor cells cluster in the periurethral ducts and spread into the stroma. Mitoses are frequently seen. This tumor does not invade the perineural spaces as commonly as does adenocarcinoma of the prostate.

Reese et al[187] reviewed 49 patients with *transitional cell carcinoma* of the prostate; 29 patients had stromal invasion and 20 had transitional cell carcinoma in the prostatic ducts only. LN metastases were found in 14 (54%) of 26 patients with stromal invasion, compared with 4 (24%) of 17 with

duct/acinar involvement. The 5-year survival rates were 80% for stromal node–negative, 45% for ductal node–negative, 55% for ductal node–positive, and 30% for stromal node–positive patients.

Ductal adenocarcinoma arises rarely from the major ducts. These tumors are usually papillary and on microscopic sections are composed of tall columnar cells with eosinophilic cytoplasm that may resemble endometrial carcinoma.[188] Originally, this lesion was believed to originate in the prostatic utricle, a Müllerian remnant; however, most ductal adenocarcinomas are not derived from Müllerian remnants and behave as acinar adenocarcinomas.[40]

Most reports point to aggressive behavior, with invasion of the prostatic stroma and the bladder neck and metastases to the LNs, bone, and lung. In most series, the majority of patients die of the tumors within 4 years.[189,190] This tumor is moderately hormonally responsive and is sensitive to RT.[189] The treatment of choice is RP.[189,191] Kopelson et al[192] reported a good prognosis in early stages; however, in stage C, the 5-year survival rate was only 34.5%. They noted a 76% local tumor control rate and a 58% 5-year survival rate in patients treated with irradiation, in contrast to 14% local tumor control and 24% 5-year survival rates in patients not receiving this treatment. Brinker et al[193] also observed a shortened average time to progression relative to a previous study group of men with acinar carcinoma among 58 patients treated with RP at Johns Hopkins.

Neuroendocrine tumors are a rare variant of a malignant tumor composed of small or carcinoid-like cells. Neuroendocrine cell substances found in these tumors include serotonin, neuron-specific enolase, chromogranin, calcitonin, and others. PAP and PSA are valuable to determine the prostatic origin of the tumor. Of 22 patients with stage T2 lesions, 4 died of the disease and 3 of them had positive neuroendocrine cell findings.[194] Of the 20 patients with stage T3, 5 died of the disease and all 5 had positive neuroendocrine cell features.

Mucinous carcinoma, not arising in major ducts or the urethra, with positive histochemical stains for PAP, has been reported.[195]

Sarcomatoid carcinoma is a rare tumor and is difficult to distinguish from a true sarcoma. There is coexistence of prostatic adenocarcinoma with sarcomatoid components that have spindle cells with large pleomorphic hyperchromatic nuclei. The pattern is that of a high-grade sarcoma in most patients, similar to the malignant fibrous histiocytoma of soft tissues. Mitotic

figures range from 6 to 36 per 10 high-power fields. In 12 patients reported by Shannon et al,[196] tumor presentation was stage A or B in 4, C or D in 5, and unknown in 3 patients. Metastases data were available for 10 patients; the most common metastatic sites were the bone (seven patients), LNs (two patients), lung (two patients), liver (one patient), and skin (one patient). Immunostaining or electron microscopy demonstrated epithelial differentiation in the sarcomatoid areas in 6 of 11 patients on whom these studies were performed. All nine patients for whom follow-up data were available died of disease within 3 to 48 months after diagnosis. In three patients, sarcomatoid elements were part of the tumor at initial diagnosis; in the other nine, the sarcomatoid component was confirmed in subsequent evaluations after initial diagnosis (2-89 months). Four patients were treated with RT without beneficial result. These tumors are considered a very aggressive variant of prostatic adenocarcinoma.

Endometrioid tumors occasionally arise from the verumontanum. Endometrial glands and cells with numerous mitotic figures may be seen. These tumors may have an exophytic configuration in the prostatic urethra or infiltrate the adjacent tissues.

Adenoid cystic carcinoma is a rare tumor in the prostate (representing <0.1% of all tumors of this gland). The histologic appearance is similar to that of its salivary gland counterpart.

Other epithelial tumors, such as carcinoid or small cell carcinoma, have been reported in the prostate.[197,198] The experience with these lesions is very limited and, in most patients' behavior, is highly aggressive and fatal.[199] A review of the literature showed that in 130 patients reported with small cell carcinoma of the prostate, the 2-year survival rate was 3.6%, the 3-year rate was 1.8%, and the 5-year rate was less than 1%.[200] A subsequent SEER database analysis of 241 cases of small cell carcinoma of the prostate identified 1- and 5-year OS of 47.9% and 14.3%, respectively.[201] Squamous cell carcinoma originating primarily in the prostate is rare.[202] Metastatic malignant tumors from other locations to the prostate are occasionally reported.[202,203]

Sarcomas (leiomyosarcoma, rhabdomyosarcoma, or fibrosarcoma) constitute approximately 0.1% of all primary neoplasms of the prostate. Leiomyosarcoma is more common in middle-aged or older men, whereas rhabdomyosarcoma is found more frequently in younger patients. These

tumors tend to invade lymphatics and blood vessels, causing widespread regional lymphatic and DMs.

Carcinosarcoma of the prostate constitutes 0.1% of prostatic neoplasms. A mixture of adenocarcinoma invading the stroma and sarcomatous elements is seen histologically; smooth or striated muscle, fibroblasts, or other mesenchymal malignant cells may be identified.

Primary lymphoma of the prostate is rare, with less than 100 cases having been reported. It accounted for only 0.1% of newly diagnosed lymphomas and only 0.09% of all prostatic neoplasias at MD Anderson Cancer Center.[204]

GENERAL MANAGEMENT IN THE UNITED STATES

The optimal management of clinically localized PCa remains controversial and is often a source of confusion, frustration, and anxiety for many patients who are compelled to make a decision regarding a treatment intervention for their disease. The practitioner must be aware that the natural history of this tumor is variable and influenced by multiple prognostic factors. All of the various forms of therapy for PCa can affect quality of life (QoL) and sexual function in varying degrees. In the process of counseling and discussing therapeutic options, it is important for the radiation oncologist to present all available data regarding the natural history of this disease, prognostic significance of the diagnosis, potential therapeutic benefit of the various modalities, and immediate as well as late treatment-related sequelae. Life expectancy and QoL considerations should be carefully discussed with the patient and spouse or significant other.

Based on the available data, when comparing patients with similar prognostic features, there are no significant differences in the biochemical and DFS outcomes for patients with early-stage PCa treated with AS, RP, high-dose external beam or stereotactic body radiation therapy (EBRT or SBRT), or interstitial BT.[205-209] The United Kingdom landmark Prostate Testing for Cancer and Treatment (ProtecT) trial provides randomized evidence in support of similar cancer control outcomes between RP and EBRT. ProtecT was a British trial randomizing 1,643 men to AS, RP, or EBRT. Most men had low-risk disease (66%), although a significant minority were intermediate risk (24%). With 15-year follow-up, death from PCa was similar for all three groups (3.1%, 2.2%, and 2.9%, respectively). However,

clinical progression was significantly greater in men treated with AS compared to either treatment group (25.9%, 10.5%, and 11.0%).[210]

However, there has been long-standing wide geographic variation in the preferred therapeutic intervention for early-stage PCa practiced by urologists and radiation oncologists prior to the publication of the ProtecT trial. Observations from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database—a registry of 11,000 men accrued from 36 community-based urologic practices across the United States—shed light on practice patterns. Cooperberg et al[211] reported that, in this cohort of patients, 50% elected to be treated with RP, 12% were treated with EBRT, 13% received BT, 4% received cryotherapy, and 14% were treated with primary androgen deprivation therapy (ADT). In these patients, it was noted that among those with higher prognostic risk features, there was an increased use of primary ADT. Younger patients and especially those with low-risk disease were more often selected for prostatectomy. In addition to age playing a role in treatment selection, the presence of medical comorbidities, the socioeconomic status of the patient, and the personal practice trends of individual clinic treatment sites (irrespective of the patient's stage of disease) played important roles in treatment selection as well.

A report based on the SEER-Medicare linked database included 85,088 men with the diagnosis of PCa at age 65 years and above.[212] In this cohort of patients, 42% were treated with RT, 21% were treated with RP, 17% were treated with primary ADT, and 20% were followed expectantly. The authors also noted a strong association between the type of specialist seen (urologist vs radiation oncologist vs medical oncologist) and the primary therapy the patient had received. For patients who were 65 to 69 years old and evaluated by a urologist, 70% underwent a prostatectomy, whereas among patients who were 70 to 74 years old, surgery was selected in 45% of patients. In addition, among men who were seen by both a urologist and a radiation oncologist, RT was the most commonly used treatment modality (83% of this cohort). These data are consistent with prior studies showing that specialists more often made treatment recommendations favoring their particular specialty.

Within the practice of radiation oncology, there have been trends in management and treatment delivery. Higher radiation doses, shorter courses, and the use of adjunctive ADT with RT for various prognostic risk groups are more common than in the past. Intensity-modulated radiation therapy

(IMRT) and image-guided radiation therapy (IGRT) have become standard with a shift toward moderate and ultra-hypofractionation (also known as stereotactic body radiotherapy, or SBRT). Daily target localization (cone-beam imaging) has progressed to application of adaptive treatment technology.

In 2013, Zelefsky et al[213] reported the results of the Quality of Research Radiation Oncology group, which surveyed 414 patients with clinically localized PCa treated with EBRT or BT that were selected from 45 institutions in the United States. Among favorable-risk patients, 72% were treated to 75 Gy or higher. For high-risk EBRT patients, 60 (87%) were treated with ADT in conjunction with EBRT and 13% (n = 9) with RT alone. Among low- and intermediate-risk patients, 10% and 42%, respectively, were treated with ADT plus EBRT. For patients treated with EBRT, weekly electronic portal imaging was obtained as verification films without daily target localization in 35%, and the remaining 64% were treated with daily localization of the target, such as fiducial markers, cone-beam imaging, TomoTherapy, or intrafraction localization with a ferromagnetic marker device. In 2023, Qureshy et al reported on the increasing use of moderate hypofractionation and SBRT for PCa, reaching 31% and 12.2% of EBRT courses in 2020, respectively, compared to only 10% and 0.2% in 2004.[214]

Active Surveillance

For selected patients with low-risk PCa, expectant management (AS) is an increasingly acceptable approach to avoid overtreatment and the potential morbidity associated with any therapy. Candidates for expectant management include those patients with low PSA values with relatively slow doubling times who have low-volume disease (5% core involvement) and GS 6 disease based on biopsy findings.

Three large trials compared AS with treatment in the low-risk population: the Scandinavian Prostate Cancer Group Trial Number 4 (SPCG-4),[215] the Prostate Cancer Intervention versus Observation Trial (PIVOT) trial,[216] and the ProtecT study.[210] All three studies suggest that AS and active treatment both have roles in the management of low-risk PCa.

The long-term results of a phase III, randomized trial from SPCG-4 demonstrated a reduction in the cause-specific mortality with local therapy compared to an expectant management approach.[215] In this study, 695 men

were included with early-stage T1 or T2 PCa. The median follow-up was 12.8 years, the primary end point was death attributed to PCa, and the secondary end point was OS. In the watchful-waiting group, 58% died, compared with 48% in the RP group ($P = .007$). The cumulative incidence of death directly related to PCa was 14.6% in the surgery group versus 20.7% for the expectant management cohort. The survival benefit was noted among low-risk patients, and this benefit was limited to patients who were younger than 65 years of age.

The PIVOT[216] enrolled 761 U.S. patients diagnosed by PSA screening. At 12-year follow-up, prostatectomy did not significantly reduce all-cause or PCa-specific mortality compared with observation for localized PCa in selected patients (T1-T2NxM0 with PSA <50 ng/mL, life expectancy of at least 10 years, negative bone scan for metastatic disease, and age no .75 years). Unlike the SPCG study, the PIVOT study stratified OS and PCa-specific survival by patient race; nearly one-third of study patients (233/761) were African American. The generalizability of PIVOT conclusions to the contemporary U.S. population has been questioned by a recent National Cancer Database (NCDB) analysis of PIVOT-eligible patients, which found that U.S. men were younger, healthier, and more likely to have RP for higher risk disease than men in the PIVOT study.

The ProtecT study[210] provides insight into the expectant management of PCa. The median age was 62 years (range, 50-69 years), the median PSA level was 4.6 mg/L (range, 3-19.9 mg/L), 77% of patients had a GS of 6, and 76% of patients had T1c disease. The AS protocol was based on PSA levels alone with no routine imaging or repeat biopsies. A more than 50% increase in PSA level triggered review. EBRT was delivered as 74 Gy in 37 fractions using 3DCRT with ADT for 3 to 6 months. Failure was defined according to nadir plus 2 mg/L.

As noted earlier, the trial showed no difference in PCa mortality or all-cause mortality among all three groups. However, disease progression as defined by metastatic disease, clinical T3 or T4 disease, or initiation of lifelong ADT was higher in the AS group ($P < .001$).

While ProtecT is often used to support patient choice between RP and EBRT techniques, it also highlights the natural history of low- and intermediate-risk men initially managed with AS. While noting that these patients form a younger age group than those men often seen in the clinic,

not only are the death rates from PCa very low at 10 years, with only 17 deaths overall (~1%), but all-cause mortality is also very low across all three groups (~10%).

In addition, more than half of the men assigned to AS have undergone active treatment by 10 years, but 44% of men had undergone no treatment (NT) at all and had thus been spared any overtreatment.[217] This is despite the fact that AS protocols have evolved since the conception of this trial with the regular use of MP-MRI and repeat, often targeted biopsies.

A companion article to the original ProtecT publication after 10-year follow-up describing patient-reported outcomes is of particular interest as a comparison of toxicity across the three groups.[218] Sexual and urinary outcomes are significantly worse with surgery, whereas the rate of bowel side effects is higher with EBRT. However, the long-term side effects after surgery are far from inconsequential, with approximately one in five men using urinary incontinence pads and a similar number unable to maintain an erection at 6 years. This does beg the question: If men are to be treated for their low-risk PCa, is EBRT the treatment of choice? Surgeons will say that there has been an evolution in prostatectomy with robotic laparoscopic surgery and nerve-sparing techniques; however, there is little evidence that in the multicenter setting, late effects are significantly different in the modern era.[219]

Conversely, there is significant evidence that with the advent of image-guided IMRT and BT, RT toxicity has decreased further since the conception of ProtecT. The results of two moderate hypofractionation studies—the Conventional or Hypofractionated High-Dose IMRT for Prostate cancer trial[220] and RTOG 0415[221]—have confirmed that hypofractionated RT is as effective as conventional RT, leading to a change of practice, with EBRT being delivered in 4 to 5 weeks with minimal side effects and favorable long-term QoL compared with prostatectomy; advocates of surgery for low-risk PCa should be wary.

Unfortunately, subsequent SEER-based work has indicated that the encouragement of deferring definitive intervention (RP or definitive RT) in favor of AS may be deleterious for African American patients with low-risk PCa. One study involving more than 51,000 men with low-risk PCa (T1-T2a, GS = 6, and PSA = 10 ng/mL) found African American race to be an independently predictive risk factor for PCa-specific mortality (43,792

Caucasian vs 7,523 African American patients). Another analysis found that definitive intervention for screening-detected, low-risk PCa (T1c, GS = 6, PSA = 10 ng/mL) was more likely to occur in men who were Caucasian, married, and/or with high socioeconomic status.

As noted by McClelland et al,[222] the absence of race-based results from two of these randomized controlled trials (RCTs) and questions about generalizability of PIVOT results to the general population (even more so to African American men), combined with findings from SEER, which examined more than 7,500 African Americans with low-risk PCa, indicate that the results of AS versus definitive intervention for clinically localized PCa may not be as robust for African Americans as the RCTs indicate.

This situation sheds light on the dangers of interpreting RCT results independent of patient race or sociodemographic factors such as insurance status, when these factors have clearly influenced access to optimal care for cancers of the prostate and other organ systems. Work using genomic sequencing samples from within The Cancer Genome Atlas has found Caucasians overrepresented in comparison with the U.S. population, with samples from racial minorities being comparatively insufficient to detect moderately common mutational frequencies. The relatively low enrollment of racial minorities in cancer sequencing studies hinders the ability to detect race-specific targetable mutations, which could prove particularly pertinent for African Americans with PCa.

The authors concluded that the findings from a low-risk PCa population more than 30 times larger than the ProtecT study and 75 times larger than the SPCG and PIVOT studies should at minimum raise questions toward endorsing a blanket recommendation of delaying intervention for the sake of AS for African Americans or other underrepresented ethnic groups (Hispanics, Native Americans) with low-risk PCa.

Musunuru et al[223] reported on 522 patients with low-risk PCa (T1-T2a, GS = 6, and PSA = 10 ng/mL) between 2006 and 2008 who were recruited to AS, low-dose rate brachytherapy (LDR-BT), stereotactic ablative radiotherapy (SABR), or standard EBRT. Out of the 522 patients, 178 opted for AS program, 76 for standard EBRT (76 Gy/38 fractions), and 83 for SABR (35 Gy/5 fractions) as part of a phase 2 trial, and 185 patients had LDR-BT (I-125 implant-median dose of 145 Gy). Median follow-up was 51 months for the entire cohort; 10.1%, 16.85%, 6.02%, and 21.05% of the

patients in AS, LDR, SABR, and EBRT groups had clinical T2 disease, respectively; median pretreatment PSAs for the four groups were 4.65, 5.66, 5.90, and 6.57 ng/mL, respectively ($P < .0001$). In the AS cohort, 38 (21.3%) patients underwent active treatment. Median time to treatment was 18.25 months (8-72 months). Among the 522 patients, 17 had biochemical failure. The 6-year biochemical DFS (bDFS) was 96.1%. There was no difference in bDFS when stratified by clinical stage or pretreatment PSA. The results for 6-year bDFS were 97.7%, 93.2%, 97.4%, and 96.8% for the AS, LDR, SABR, and EBRT groups, respectively ($P = .28$). Hematochezia was observed in 2.24%, 3.13%, 7.14%, and 9.88% of the AS, LDR, SABR, and EBRT groups, respectively. Higher incidence of hematuria was noticed in the LDR-BT cohort (11.98%), when compared to the other groups. Thus, AS, LDR, EBRT, and SABR were effective management options for patients with low-risk PCa.

Lester-Coll et al[224] investigated trends and predictors of AS in a large national cohort of men with low-risk PCa (nonmetastatic cT1eT2a, GS 6, and PSA < 10), in the NCDB from 2010 to 2012. Management strategy and facility type (academic vs nonacademic) were compared using univariable logistic regression. Additional covariates tested against management strategy included T-stage (T1c vs T2a), age (age <65 vs 65 or older) Charlson/Deyo comorbidity score, location, insurance, rurality, race, education, and income.

Eighty-one thousand six hundred ninety men were identified, among whom 34,612 (42%) were evaluated at an academic center and 47,078 (58%) at a nonacademic center. Median age was 63. Initial management was AS in 8,228 (10%), DT in 70,064 (86%), and NT in 3,398 (4%). Patients evaluated at academic centers were significantly more likely than those at nonacademic centers to receive AS than DT or NT (15% vs 7% AS, 81% vs 89% DT, 4% vs 4% NT, $P < .001$). After adjusting for age, T-stage, insurance, and location, evaluation at an academic versus nonacademic facility was independently associated with increased odds of AS utilization (adjusted OR = 1.91; 95% CI = 1.83-1.99, $P < .001$).

Even now, there is still controversy as to AS protocols. Both ASCO[225] and a European coalition[226] have published guidelines as to surveillance testing and frequency. DT is recommended for men with localized PCa at high risk of tumor progression. RP, EBRT with hormone therapy in selected patients,

and BT are all acceptable options. High-intensity ultrasound or cryotherapy was not recommended unless the patient is part of a clinical trial.

Thankapannair et al evaluated the UK National Institute for Health and Care Excellence tiered prognostic groupings for men undergoing AS.[227] All patients were initially screened by MP-MRI for low-risk status. Based on PSA density and initial Likert lesions from the MRI at diagnosis, men underwent follow-up MRIs either every 12, 18, or 36 months. PSAs were monitored every 3 months for all participants. Biopsy was only performed for a change in PSA or MRI for the lowest risk group and mandated only for higher risk groups at 36 months. Overall, only 8.9% of the 156 men enrolled in the prospective study had pathologic progression, although median follow-up was short at 1.5 years. There was excellent compliance for the protocol, with 86.5% of men remaining on AS.

National consensus guidelines recommend AS for men with low-risk PCa and life expectancy of 10 years. Keeping men well informed of their options and considering individual preferences are key tenets of these guidelines. It is clear that patient information and careful selection are key. There are a number of studies seeking to address the role of genomic markers of both RT responses to tumor and normal tissues. Recent suggestions that molecular subgroups outside the traditional prognostic factors can stratify patients more accurately need to be explored further. No definitive data on genetic or molecular markers in primary PCa are available.[228]

Treatment Techniques

Radical Prostatectomy

RP is a treatment option for patients with very low-risk PCa with a life expectancy of longer than 20 years or low-risk PCa with a life expectancy of at least 10 years.

RP has had a limited role in the management of gross extracapsular disease or SV involvement or the presence of LN metastases; however, more recently, there has been an increased use of surgery for locally advanced disease. Two approaches for the classic RP are used: retropubic and perineal. The procedure consists of the complete removal of the prostate and its surrounding capsule, together with the SVs, the ampulla, and the vas deferens. The prostate is entirely removed by excision of the urethra at the prostatomembranous junction, leaving no residual prostatic tissue at the

apex. Many urologic surgeons prefer the retropubic approach as this procedure also facilitates access for performing a bilateral PLND.

There has been an increasing interest and practice of laparoscopic and robotic RP approaches in the United States and Europe. Advantages cited for using the laparoscopic procedure versus the open approach include improved visualization of the anatomy optical magnification, less blood loss, less postoperative pain, and more rapid resumption of everyday activities. Preliminary functional and oncologic outcomes with this approach compare favorably to those achieved with open RP approaches. The da Vinci robotic surgical system (Intuitive Surgical) uses three multijoint robotic arms, with one arm controlling the binocular endoscope and the other arms controlling small-wristed instruments. This system is controlled by the surgeon, who can be in a remote location from the patient, seated at an operative console. The stereoscopic view of the operative field provides the surgeon with 3D visualization with a 10-fold magnification.

A prospective randomized single-center study of 145 consecutive men referred to RP in a tertiary referral center in Finland randomized 1:1 to robot-assisted laparoscopic prostatectomy (RALP) (n = 75) and 3D laparoscopic radical prostatectomy (3D-LRP) (n = 70). Postoperative continence at 12 months after surgery, according to the EPIC-26 incontinence domain, was 79.25 in both groups (P = .4). At 12 months, there was no statistically significant difference in the rates of positive surgical margin or BCR between the two surgical modality groups.[229]

An evidence-based meta-analysis of comparative outcomes between robot-assisted radical prostatectomy (RARP) versus standard LRP included 16 “high-quality” (RCTs and Newcastle-Ottawa scale 8-9) studies were included. Among the 13,752 patients included, 6,135 (44.6%) and 7,617 (55.4%) were RARP and LRP, respectively. Overall and major complication (Clavien-Dindo ≥ III) rates were similar in the LRP than in the RARP group. The BCR rate at 12 months was significantly lower for RARP (OR 0.52; P < .00001). RARP reported a lower urinary incontinence rate at 12 months (OR 0.38; P = .01). The erectile function recovery rate at 12 months was higher for RARP (OR 2.16; P = .007). Current evidence shows that RARP offers favorable outcomes compared with LRP, including higher potency and continence rates and less likelihood of BCR. An assessment of longer term

outcomes is lacking, and higher cost remains a concern of robotic versus laparoscopic PCa surgery.[230]

Radiation Therapy Techniques

In the late 1980s, 3D (also known as conformal) treatment techniques became increasingly available. CT-based images referenced to a reproducible patient position are used to localize the prostate and normal organs and to generate high-resolution 3D reconstructions of the patient anatomy. Treatment field directions are selected using beam's-eye view techniques, and the fields are shaped to conform to the patient's CT-defined target volume, thereby minimizing the volume of normal tissue irradiated. CRT simulation, treatment planning, and delivery incorporate various additional maneuvers to reduce treatment uncertainties and enhance setup reproducibility required during a protracted course of therapy.

IMRT is a refinement of 3D conformal techniques that uses treatment fields with highly irregular radiation intensity patterns to deliver exquisitely conformal radiation dose distributions.[231] IMRT delivery is significantly more complex than 3D conformal delivery, requiring a computer-controlled beam-shaping multileaf collimator.

There has been increasing use of SBRT for the treatment of low- and intermediate-risk PCa. The main advantage is that the highly conformal treatment, based on image-guided approaches with narrow margins, is delivered in five fractions (750-800 cGy per fraction), with lower doses to adjacent organs at risk, more convenient for the patient. Biochemical control has been comparable to standard IMRT, and treatment morbidity has been low.

Katz and Kang[232] reported on 515 patients with organ-confined PCa (471 T1c and 44 T2a, all N0M0) who received robotic radiosurgery SBRT. The mean PSA was 6.48 ng/mL; 343 were low risk, 134 intermediate risk, and 38 high risk. ADT was administered to 70 patients. One hundred fifty-eight patients received 3,500 cGy delivered in five daily fractions. The remaining patients, from all risk groups, received a total dose of 3,625 cGy in five daily fractions. At a median follow-up of 54 months (range, 9-79 months), 40 patients died of other unrelated causes and 33 were lost to follow-up. The median PSA at 60 months was 0.11 ng/mL. Biochemical failures occurred for eight low-risk patients (none locally), nine intermediate-risk patients (one

locally), and nine high-risk patients (two proven local failures). The actuarial 6-year freedom from biochemical failure was 97.4%, 92%, and 70.4%, for the low-, intermediate-, and high-risk groups, respectively ($P < .001$). Late RTOG toxicity was mild with 4% grade 2 rectal, 7.8% grade 2 urinary, and 1.4% grade 3 urinary (all with 36.25 Gy). Late grade 2 urinary toxicity for 35 Gy was 5.1% versus 9.9% for 36.25 Gy. Sexual QoL declined by 23% at 6 to 12 months where it remains. Seventy-four percent and, at 8 years, 62% of the patients potent at baseline remain potent.

Meier et al[233] described results in 309 patients with biopsy-proven adenocarcinoma of the prostate 172 low-risk (CS T1-T2a, GS 6, PSA < 10 ng/mL) and 137 intermediate-risk (CS T1c-T2b with either GS 7 and PSA < 10 ng/mL or GS 6 and PSA between 10 and 20 ng/mL) treated with a nonisocentric robotic SBRT using real-time tracking of implanted fiducials, at 21 community, regional, and academic hospitals. The prostate dose was 40 Gy in five fractions of 8 Gy and SVs received 36.25 Gy. Normal tissues were rigidly constrained (rectal V_{36Gy} <1 mL; bladder V_{37Gy} <5 to 10 mL). No patient had concomitant or adjuvant androgen ablation therapy. The median follow-up was 61 months. Five grade 3+ toxicities (1.6%) were reported, far below the 10% rate deemed excessive. There were no grade 4 or 5 toxicities. All reported grade 3 genitourinary (GU) toxicities occurred between 11 and 51 months after treatment. Five patients (1.6%) developed urinary retention, which required a temporary catheter placement. Seven patients were diagnosed with bladder cancers between 21 and 50 months after treatment. For the entire population, actuarial 5-year OS was 95.6%. Actuarial 5-year nadir +2 RFS was 97.1% for all patients and was 97.3% and 97.1% for the low- and intermediate-risk groups, respectively. Actuarial 5-year ASTRO RFS was 92.3% and 91.3% for these respective risk groups.

Blacksburg et al[234] reported on 773 patients with PCa treated with robotic SBRT (35 Gy in five daily fractions) without the use of ADT. Mean age was 67 years; 43.2%, 47.7%, and 9.1% of patients had low-, intermediate-, and high-risk disease, respectively. The GS was 6 in 50.5%, 7 in 42.0%, and 8 to 10 in 7.5%. The median pretreatment PSA was 5.73 ng/mL (range 1.2-68.18): At 30 months, the median PSA was 0.36, 0.41, and 0.40 ng/mL in low-, intermediate-, and high-risk patients, respectively. Despite a convergence in absolute PSA values at this time point, the shape of post-treatment PSA curves prior differs considerably based on GS and initial PSA.

At 12 months, 42.2%, 50.0%, and 70.8% of patients with low-, intermediate-, and high-risk disease, respectively, have a PSA that has declined by at least 80% ($P < .0001$). 44.3%, 50.3%, and 66.7% of patients with GS 6, 7, and 8 to 10, respectively, experience this decline at the same time point ($P = .007$). 44.5% of patients with an initial PSA less than 10 ng/mL experience this decline as compared to 70.9% of those with an initial PSA greater than 10 ng/mL ($P < .0001$).

More recently, a multiarm randomized trial comparing SBRT with other treatment modalities, including RP and conventional IMRT, is maturing. The Prostate Advances in Comparative Evidence (PACE) trials performed by the UK Institute of Cancer Research include three foci: PACE-A enrolled low- or intermediate-risk patients into a randomized trial comparing RP or SBRT. PACE-B enrolled the same population to a noninferiority trial randomizing to either SBRT or conventional fractionation (62 Gy or 78 Gy). PACE-B reported 5-year outcomes at ASTRO 2023 noting that SBRT was noninferior to conventional EBRT with an unadjusted HR of 0.73 (90% CI, 0.47-1.12).[235] There was a slight but not statistically significant increase in 2+ GU toxicity in the SBRT arm (8.5% vs 5.9%, $P = .19$).

Another important trial evaluated an emerging technology in RT delivery —MRI guidance. The MRI-Guided Stereotactic Body Radiotherapy for Prostate Cancer trial enrolled 178 patients and randomized them to 40 Gy in five fractions delivered by traditional CT-guided therapy versus MRI guidance. The study was written with different expansion margins for CT (4 mm) versus MRI (2 mm) because of the ability for MRI-LINAC (linear accelerator) to provide intrafractional real-time imaging. Similar numbers of patients had perirectal spacers. The study found that MRI guidance significantly reduced the incidence of acute (up to 90 days) grade 2+ GU toxicity by CTCAE (24.4% vs 43.4%, $P = .01$). Grade 2+ gastrointestinal (GI) toxicity was also reduced with MRI guidance (29.5% vs 44.7%, $P = .001$). While most patients were intermediate or high risk, the results have been extrapolated to low-risk PCa.[236]

Simulation, Treatment Planning, Target, and Normal Tissue Contouring

The techniques for simulation and treatment planning have been described in detail in earlier chapters. Anatomic details and target volumes are defined in

CT scan sections of 1 to 3 mm thickness. Although in the past patients with PCa were treated in the prone position at MSKCC based on comparative studies[237] that demonstrated improved geometry of the normal anatomy juxtaposed to the prostate target, currently patients are routinely treated in the supine position. These changes were made based on the observation of less prostate motion observed in the supine compared to the prone position.[238]

Image guidance is the standard of care to allow for small setup uncertainty margins and reduced normal tissue radiation. Fiducial marker placement via transrectal ultrasound guidance is widely utilized, but other methods exist. Fiducials are implanted prior to simulation. With the advent of image guidance, immobilization technique varies, from the use of a thermoplastic mold to just a toe-ring. At simulation, the patient is scanned through an approximately 20- to 30-cm region around the prostate with a slice spacing and thickness of 3 mm (thinner slices can be used for SBRT). Before the start of the CT planning study, several transverse images through the prostate and bladder are obtained to ensure that the rectal lumen is clearly visible, the bladder and rectum are not excessively filled, and the patient is properly positioned within the scan circle. With the use of the CT data set, a "virtual simulation" is performed, using digitally reconstructed radiographs to localize the treatment area rather than conventional simulation films. The treatment isocenter is placed according to anatomic landmarks near the center of the prostate gland: midline, at the caudad aspect, and approximately 5 cm posterior to the symphysis pubis. The triangulation points for the isocenter are then tattooed or temporarily marked, along with an additional alignment tattoo, along the sagittal line, approximately 10 cm superior to the isocenter.

Perirectal hydrogel spacers within Denonvillier fascia have been used as a method of increasing the distance between the posterior prostate and the anterior rectum. Several prospective studies have shown that the use of hydrogel spacers decreases rectal dose. In the first large trial, Mariados et al[239] noted a significant reduction in mean rectal V_{70} (12% in control vs 3% in spacer, $P < .0001$) and a reduction in rectal toxicity at 15 months (7% vs 2%, $P = .04$). Later follow-up at 3 years noted grade 2 or higher rectal toxicity (5.7% vs 0%; $P = .012$), with no difference in grade 2 or higher urinary toxicity.[240] A separate report noted that men with good sexual function at baseline had maintained sexual QoL better when treated with a spacer versus

the control. A more recent study using a different spacer also noted similar reduction in rectal toxicity associated with the use of a hydrogel spacer: 14% versus 3% (P = .01).[241] Main risk of the spacer is rectal infiltration, which may delay treatment but at least in one retrospective series was not associated with late rectal toxicity.[242]

MRI-supported planning is key to accurate delineation of the prostate, prostatic apex, and adjacent organs at risk. T2-weighted MRIs are merged with the planning CT to aid in delineation of these structures. Roach et al[243] evaluated 10 patients with both MRI and CT images of the prostate and noted that the prostate volume was 32% larger when defined by noncontrast CT than when determined by MRI. Areas of disagreement tended to occur in the posterior and posteroinferior-apical portions of the prostate, the apex (because of disagreement between urethrography and MRI), and the regions corresponding to the neurovascular bundle. Rasch et al[244] also observed differences in CT- and MR-defined volumes. On average, the prostate and SV volume defined on CT was 40% larger than that defined on MR. The CT-defined prostate was 8 mm larger at the base of the SVs and 6 mm larger at the prostatic apex. This difference was found to be significantly larger than interobserver variation.

For low-risk PCa, the clinical target volume (CTV) is defined as the prostate and proximal 1.5 cm of SVs. The planning target volume (PTV) is defined as the CTV with a margin to account for physical uncertainties, including setup reproducibility and interfractional and intrafractional organ motion.

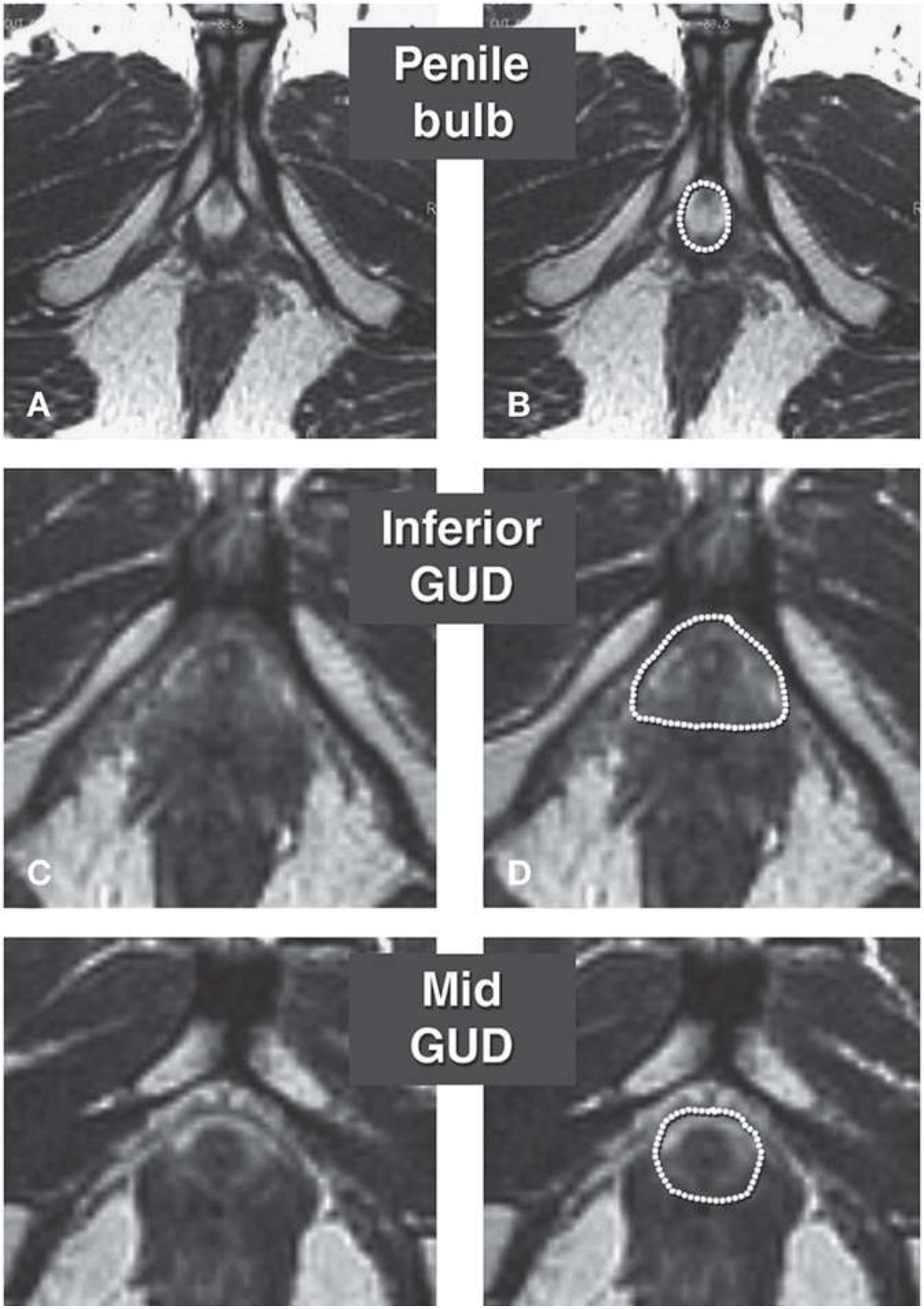
Without image guidance, a 0.8- to 1-cm margin is added to the CTV to form the PTV in all directions, except posteriorly at the interface with the rectum, where the margin is reduced to 0.5 cm. Clinically, these margins were found to provide adequate target coverage based on a serial CT scan study evaluating organ motion during a course of 3DCRT.[237] When using image-guided approaches with daily target localization, margins are reduced to 5 to 6 mm circumferentially around the CTV. For SBRT, when increased imaging is used to ensure more precise targeting, these PTV expansions can be reduced to 0.3 to 0.5 cm. Normal tissues identified on each CT slice include the inner and outer walls of the rectum and bladder, the femoral heads, and the outer skin surface. Portions of the small bowel or sigmoid colon within 1 cm of the PTV are also contoured and taken into

consideration, if necessary, during planning. In addition, the central 1-cm-diameter portion of the prostate encompassing the prostatic urethra is defined for dosimetric consideration and evaluation during IMRT planning.

Accurate anatomic delineation of the prostate and, in particular, the prostatic apex has been a topic of some controversy. Prior to routine use of MRI, some used urethrography at the time of simulation as a method to accurately localize the apex.[238] Mah et al[245] performed sagittal MR scans immediately before and after urethrogram in 13 patients. No significant systematic motion of the prostate itself or the apex was observed, leading the authors to conclude that urethrography during simulation does not introduce localization error.

Contouring Techniques

There have been several reports documenting the variability of prostate-contouring techniques among practitioners. McLaughlin et al[246] provided an excellent demonstration of common contouring errors, such as overestimation of the prostatic apex and underestimation of the prostatic base. The apex and the base in particular represent regions of the target volume that can be challenging to identify on CT images and better defined with MRI. Two methods recommended include the inspection of lateral view projections of the contours to detect regions of the irregularities of the target geometry and improved recognition of the GUD elements. These elements are shown in the MRI representation of the GUD in Figure 72.5 and in the CT representation in Figure 72.6.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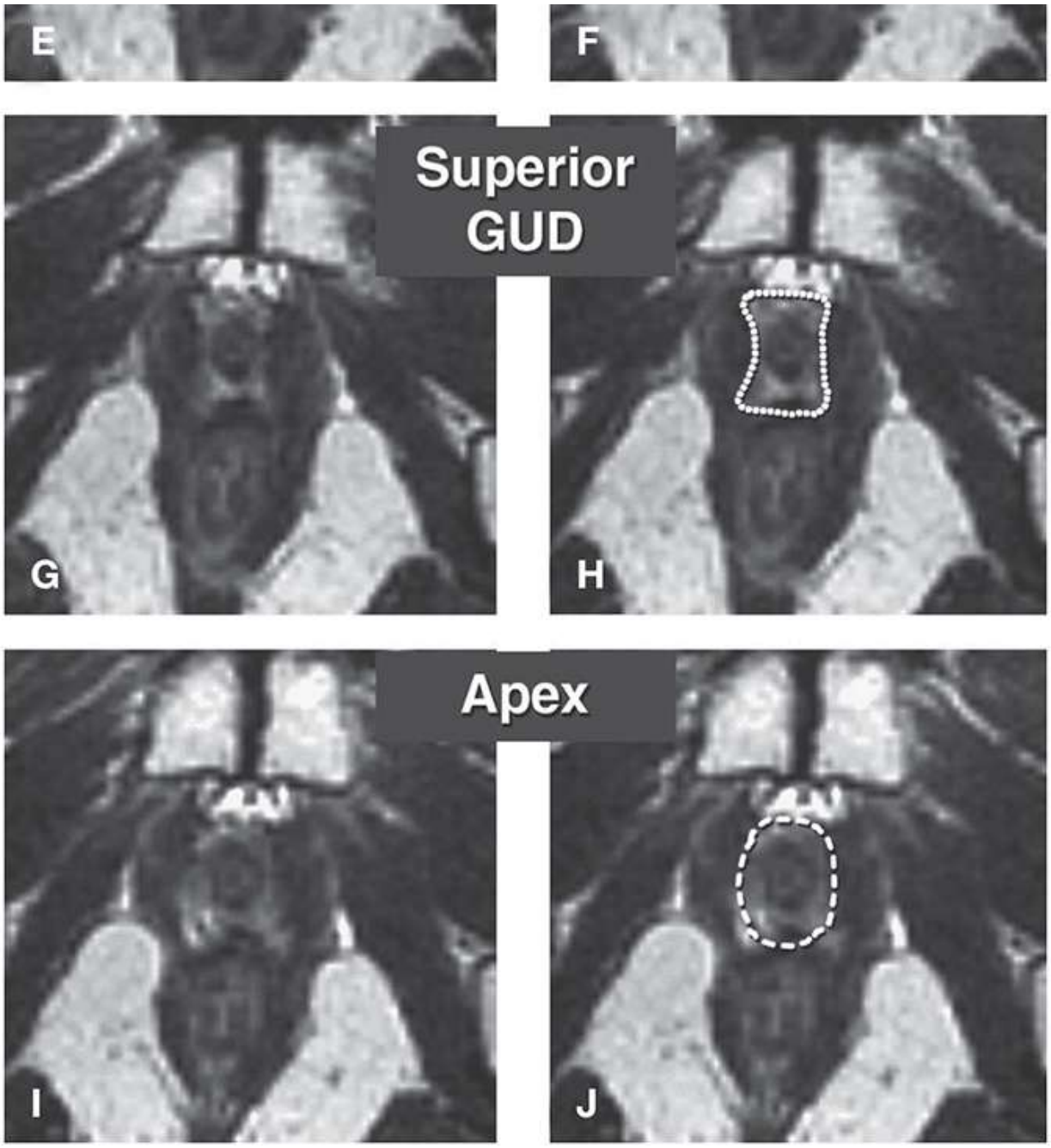
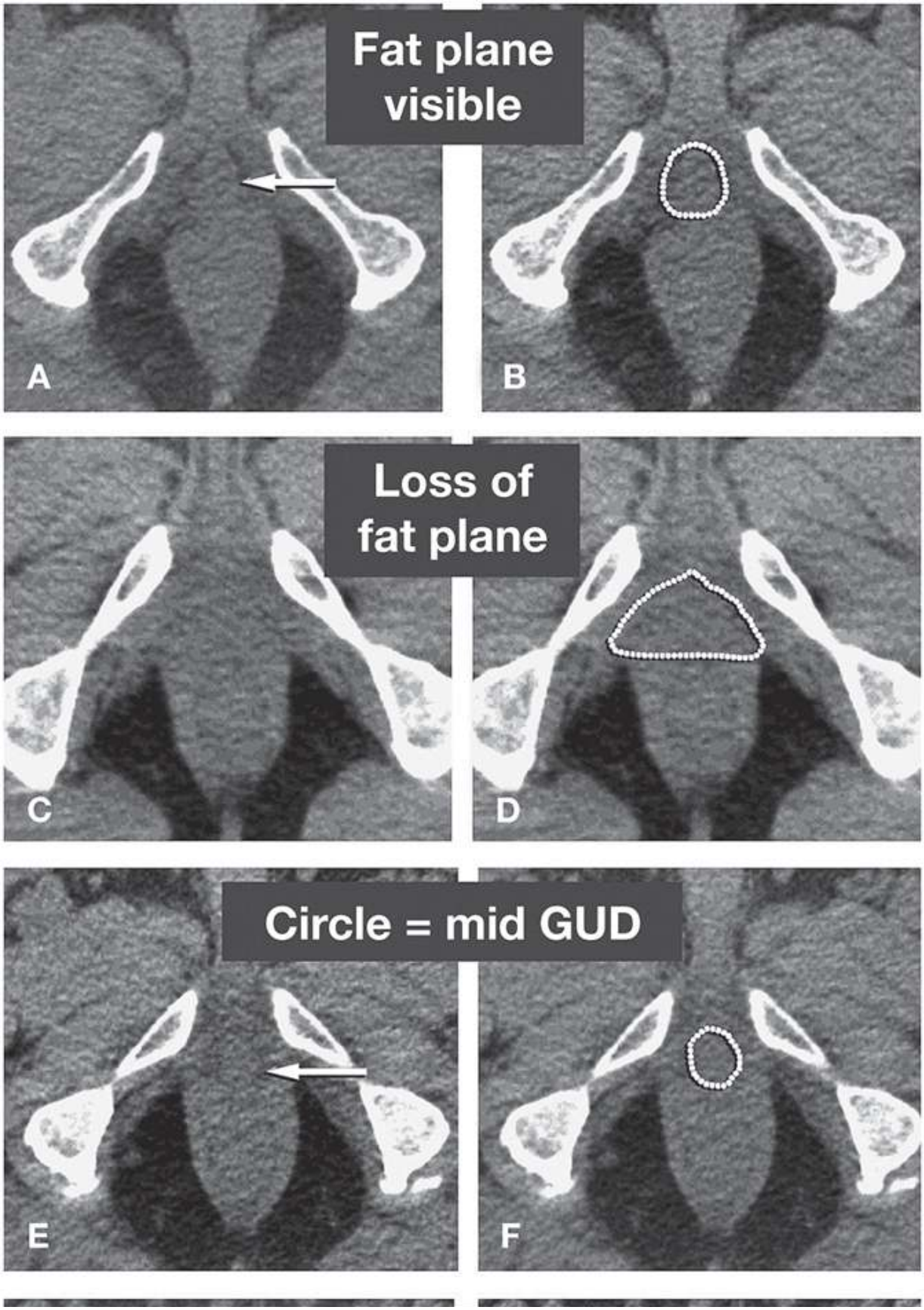


FIGURE 72.5 A-J. Representation of the genitourinary diaphragm (GUD) on axial magnetic resonance imaging slices, demonstrating the anatomic configuration that can be used as a guide for contouring of the clinical prostate target volume. (Reprinted from McLaughlin PW, Evans C, Feng M, Narayana V. Radiographic and anatomic basis for prostate contouring errors and methods to improve prostate contouring accuracy. *Int J Radiat Oncol Biol Phys*. 2010;76[2]:369-378. Copyright © 2010 Elsevier. With permission.)


Fat plane visible
A
B
Loss of fat plane
C
D
Circle = mid GUD
E
F

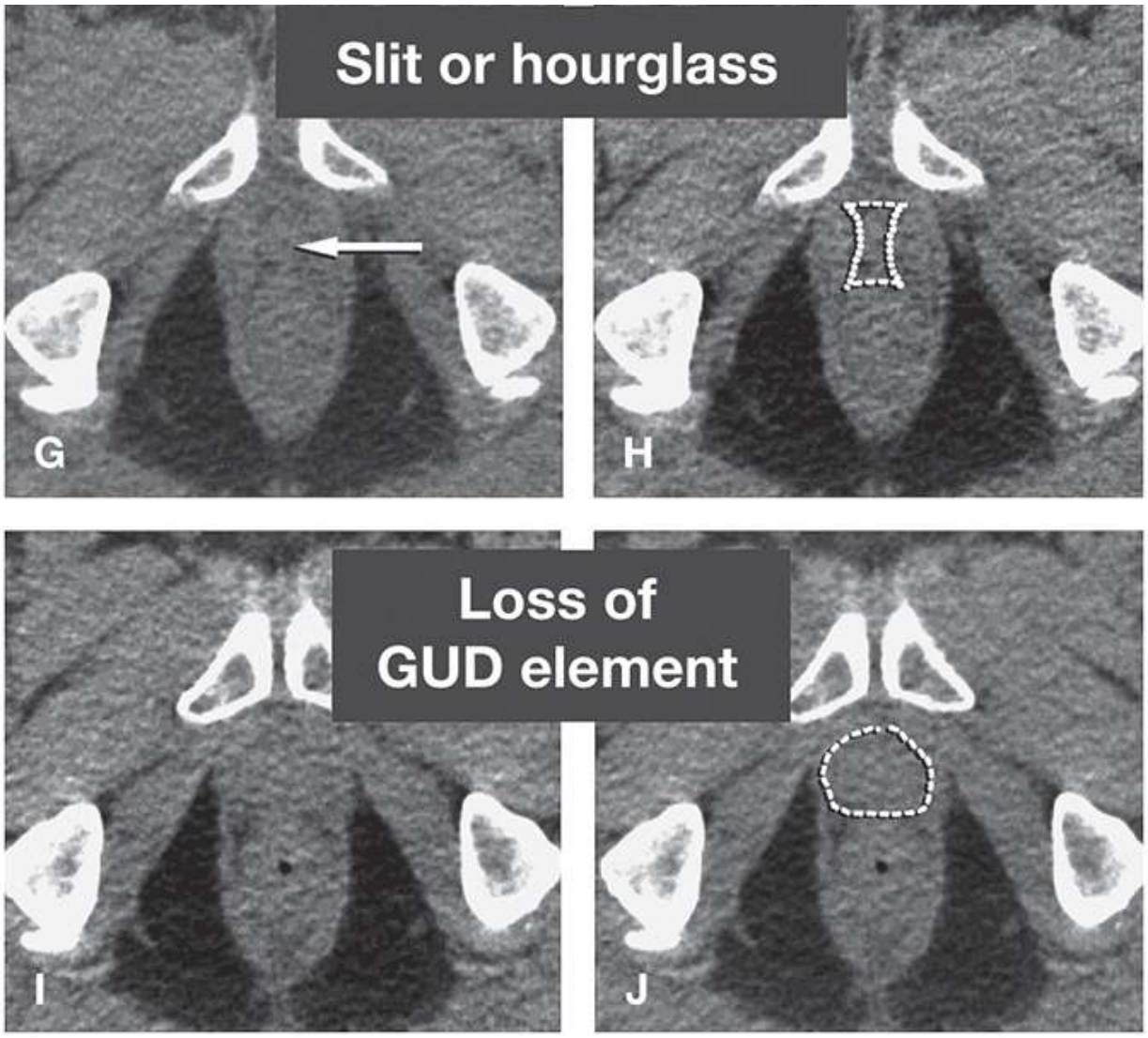


FIGURE 72.6 A-J. Representation of the genitourinary diaphragm (GUD) on axial computed tomography slices, demonstrating the anatomic configuration that can be used as a guide for contouring of the clinical prostate target volume. Arrow indicates fat plane at edge of urogenital diaphragm. (Reprinted from McLaughlin PW, Evans C, Feng M, Narayana V. Radiographic and anatomic basis for prostate contouring errors and methods to improve prostate contouring accuracy. *Int J Radiat Oncol Biol Phys*. 2010;76[2]:369-378. Copyright © 2010 Elsevier. With permission.)

The beam weights are adjusted to obtain a uniform dose within the PTV and to place the hot spots away from the rectum. The plan was normalized so that the prescription isodose (95%-100%) covers the PTV with a hot spot of 6% to 9% within the PTV. Although a small volume of the rectal wall close to the PTV is expected to receive the prescription dose, the rectal wall volume receiving greater than prescription should be minimal. For 60 Gy in

20 fractions, for example, the volume of rectum receiving more than 60 Gy should be less than 10 mL. Other normal tissue dose limits for these 3DCRT plans included limiting the maximum dose to the femurs to 48 Gy or less in 2 Gy equivalent (90%), the maximum dose to large bowel to 60 Gy or less in 2 Gy equivalent, and the maximum dose to small bowel to 50 Gy or less in 2 Gy equivalent.

A variety of beam arrangements have been proposed for prostate IMRT treatment, including multifield axial or noncoplanar arrangements, in addition to intensity-modulated arc therapy. Primarily because of concern about an increased risk of secondary cancers from higher neutron doses associated with IMRT treatment at high energies,[247,248] 6-MV IMRT techniques are preferred for the treatment of PCa. As shown by Pirzkall et al,[249] however, a larger number of treatment fields may be necessary to achieve a dose distribution similar to that observed with 15-MV x-rays.

Dosimetric guidelines defining acceptable target coverage, dose uniformity, and normal tissue doses have grown out of the 3DCRT and IMRT planning experience during the past 20 years and include several refinements resulting from the retrospective outcome and toxicity analyses. Most notably, studies by Skwarchuk et al[250] and Jackson et al[251] retrospectively evaluating the rectal wall dose-volume histograms (DVHs) for patients treated to 70.2 and 75.6 Gy, respectively, using 3DCRT techniques found that, on average, patients with late rectal bleeding had significantly higher rectal DVHs than patients who did not bleed. Both high- and intermediate-dose levels were found to be independently correlated with rectal bleeding.

The physician should carefully review the treatment plan and DVHs of the target and normal tissue structures to select the optimal treatment plan for the patient. Target coverage should be carefully assessed, as well as the dose inhomogeneity and location of hot spots. In addition, careful attention should be given to determining whether the treatment plan adequately meets acceptable dose constraints for the rectum, bladder, and bowel.

Prescription Doses for Intensity-Modulated Radiation Therapy and Stereotactic Body Radiation Therapy

Historically since the understanding of the benefit of fractionation on normal tissue dose recovery, with conventional fractionation, that is, daily fractions of 1.8 to 2 Gy, five fractions per week, was the standard for PCa. The current

standard dose for conventional fractionation based on clinical trials has been 78 Gy, although dose escalation up to 86 Gy has been delivered to favorable-risk patients using IMRT. At doses above 80 Gy, PTV coverage may be sacrificed as needed to respect the target and normal tissue goals. Typically, at least 90% to 95% of the PTV receives the prescription dose. However, with the publication of multiple moderate hypofractionation trials, doses of 60 Gy in 20 fractions or 70 Gy in 28 fractions have become routine.[252,253] In addition, ultra-hypofractionation with SBRT (36.25 Gy in five fractions) has become more common, providing excellent control with acceptable toxicity burden.

Treatment Delivery and Organ Motion Control

Movement of the prostate during treatment or between treatment fractions has long been a concern for prostate RT. Many studies investigating interfractional and intrafractional motion of the prostate and SVs have been reported.[254-257] Most groups have measured prostate motion relative to bony landmarks through repeated imaging of implanted radiopaque markers or serial CT studies. Although the reported magnitude of motion has varied, relatively little motion in the lateral direction and potentially significant movement in the anterior-posterior and superior-inferior directions has been consistently reported. Many studies have also observed a correlation between prostate and SV motion and rectal or bladder filling.

Interfractional prostate motion was studied in approximately 50 patients by Crook et al.[256] Gold seeds implanted in the prostate were visualized on kilovolt radiographs taken at the simulation and approximately midway through treatment. Minimal prostate motion was observed in the lateral directions (0.1-0.5 cm), but inferior displacements of 0.5 and 1.0 cm or more were observed in 43% and 11% of their patients, respectively. Average displacement in the posterior direction was 0.72, 0.62, and 0.46 cm for seeds placed at the SVs, posterior aspect of the prostate, or apex of the gland, respectively; 60% of patients showed greater than 0.5 cm posterior displacement of the prostate base, and 30% showed greater than 1 cm.

Zelefsky et al[257] obtained four serial CT studies for 50 patients (planning scan and three additional scans during the course of therapy). Prostate displacements in the anteroposterior and superior-inferior directions were most frequently observed. The mean prostate motion in the anteroposterior,

superoinferior, and left-right directions was 1.2, 0.5, and 0.6 mm, respectively. Anterior-posterior movements were correlated with changes in rectal volume. Patients with large rectal volumes (.60 cm^3) and large bladder volumes (.40 cm^3) on the planning scan experienced a higher likelihood of having greater than 3-mm systematic displacement of the prostate and SVs, leading the authors to conclude that these patients may require more generous PTV margins to ensure adequate CTV coverage. However, among patients without larger bladder and rectal volumes, a 1-cm margin around the CTV with a 6-mm margin at the prostate-rectal interface enclosed the posterior, anterior, superoinferior, and left-right aspects of the CTV within the prescription dose level with a probability of 90%, 100%, 99%, and 100%, respectively, indicating that the MSKCC margins provided adequate CTV coverage for most patients.

Intrafractional prostate motion was studied in 20 patients by Huang et al[258] using pretreatment and post-treatment B-mode rectal ultrasound evaluations. Although the intrafractional motion was relatively insignificant in all directions, the predominant directions of motion were in the anterior and superior directions. Standard deviations of 0.4, 1.3, and 1.0 mm were observed in the lateral, anterior, and superior directions, respectively. Several methods have been developed to reduce uncertainty because of interfractional organ motion and thereby improve treatment delivery using computer-assisted transabdominal ultrasonography, radiopaque marker tracking, or CT/cone-beam image guidance. Recent technological advances have opened up the possibility of acquiring pretreatment or post-treatment megavoltage or kilovoltage CT images directly on the LINAC with the patient in the treatment position, such as TomoTherapy. Langen et al[259] compared three methods of registering megavoltage CT images from a TomoTherapy unit with the kilovoltage planning CT images and found that manual registration performed using implanted fiducial markers exhibited the least interobserver variability and agreed best with automatic registration computed from the center of mass of the three implanted fiducial markers. LINAC-based kilovoltage image guidance systems are routinely used now for image-guided therapy approaches. They possess capabilities for kilovoltage 2D projection imaging (radiographs), fluoroscopy, and 3D cone-beam CT and are ideally suited for monitoring of interfractional and intrafractional motion.

Using IMRT (volumetric modulated arc therapy), 10-year biochemical control has been in the range of 85% to 88%, and 15-year biochemical control 76% with acceptable morbidity.[260] These recent technological advances have allowed dose escalation, with improvement in the results of treatment. A study from MD Anderson Cancer Center[261] showed that patients with favorable (low-risk) PCa treated with 78 Gy had a 10-year biochemical control of 88% compared to 63% in patients treated with 70 Gy. Grade 3 toxicity was 7% versus 1%. A French multicenter trial compared 8,000 to 7,000 cGy in patients with various risk prognostic groupings.[262] The 5-year biochemical freedom-from-failure rate (BCFFR) was 76.5% versus 67.9%. There was a trend toward more toxicity in the 8,000-cGy group (grade 3 rectal toxicity 6.5% and 1.5%, respectively).

In a study comparing 8-year outcomes of RP or EBRT, Kupelian et al[263] (Cleveland Clinic) reported on 1,054 patients who were treated with surgery and 628 with EBRT. With a median follow-up of 51 months, the PSA RFS was 72% and 70%, respectively.

Brachytherapy for Early-Stage Disease: Treatment Techniques

Low-Dose Rate Brachytherapy

Preplanned Transperineal Implantation Techniques. The preplanning technique essentially attempts to map the seed-loading patterns before the implantation procedure. During the procedure, the brachytherapist will simulate the preplanned needle positions with the operative conditions and settings. The technique can be summarized as follows: TRUS imaging is obtained before the planned procedure to assess the prostate volume. A computerized plan is generated from the transverse ultrasound images, producing isodose distributions and the ideal location of seeds within the gland to deliver the prescription dose to the prostate. Several days to weeks later, the implantation procedure is performed. Needles are then placed under ultrasonographic guidance through a perineal template according to the coordinates determined by the preplan. Radioactive seeds are individually deposited in the needle with an applicator's aid or preloaded seeds on a semirigid strand containing the preplanned number of seeds. In the latter case, this is accomplished by stabilizing the needle obturator that holds the seed column in a fixed position while the needle is withdrawn slowly, depositing a row or series of seeds within the gland. One of the inherent

advantages of a stranded seed approach is the reduction of seed migration and lung embolization compared with the use of free seeds. Among patients implanted with loose seeds, usually less than 2% of the implanted seeds are likely to migrate. There is no evidence of any adverse effect caused by seed embolization.[264]

Careful evaluation of the preplan with attention to DVH analyses of both the target and normal tissues is essential to ensure that the dose to the urethra and rectum is within tolerance ranges and the prescription dose is being delivered to the prostate target. In a multi-institutional analysis, there remains a great deal of variability within preplans regarding acceptable target volume, seed strength, dose homogeneity, treatment margins, and extracapsular seed placement, although prostate BT prescription doses are uniform.[265]

Intraoperative Planning Techniques for Prostate Brachytherapy. With the current availability of sophisticated treatment planning programs that can rapidly generate highly conformal dose distributions in the operating room, intraoperative planning for prostate BT is an attractive method. Intraoperative planning takes advantage of the opportunity of using real-time measurements of the prostate during the procedure. In contrast, preplanning is often performed several weeks before implantation, frequently under different conditions than the actual operative procedure. Subtle changes in the position of the ultrasound probe, as well as the distortion of the prostate associated with needle placement and subsequent edema, may result in profound changes in the shape of the gland compared with the preplanned prostatic contour. Consequently, intraoperative adjustments of seed and needle placements are frequently required using a preplanned technique, and the postplan CT-based dosimetry only sometimes corresponds to the idealized preplan.

At MSKCC, intraoperative conformal optimization and planning for ultrasound-based transperineal implantation have been routinely used for over the two decades.[266] This technique involves a sophisticated optimization system that incorporates acceptable dose ranges allowed within the target, and dose constraints for the rectal wall and urethra. An ultrasound probe is positioned in the rectum, and the prostate and normal anatomies are identified. Needles are inserted through the perineal template at the periphery

of the prostate. The prostate is subsequently scanned from apex to base, and these 0.5-cm images are transferred to the treatment planning system using a computer-based video capture system. On the computer monitor, the prostate contours and the urethra are digitized on each axial image. Needle positions are identified on each image, and their coordinates are incorporated into a genetic algorithm optimization program. After the optimization program identifies the optimal seed-loading pattern and the dose calculations are completed, isodose displays are superimposed on each transverse ultrasound image and carefully evaluated. DVHs for the target volume, rectum, and urethra are also carefully assessed. For the intraoperative plan, the V_{100} for the prostate is set at 95% or higher, and the maximum urethral and rectal dose thresholds are set at less than 130% and 1 cm^3 less than 100% of the prescription doses, respectively. The entire planning process, from the contouring of images to the generation of the seed-loading pattern, requires approximately 10 minutes. Seeds are then loaded with a standard applicator. A cone-beam CT scan from a mobile unit is routinely used to obtain postimplantation dosimetric analysis while the patient is under anesthesia before the conclusion of the procedure to ensure optimal coverage of the target volume with the prescription dose. Figure 72.7 shows a postimplantation CT image used for dosimetric evaluation.

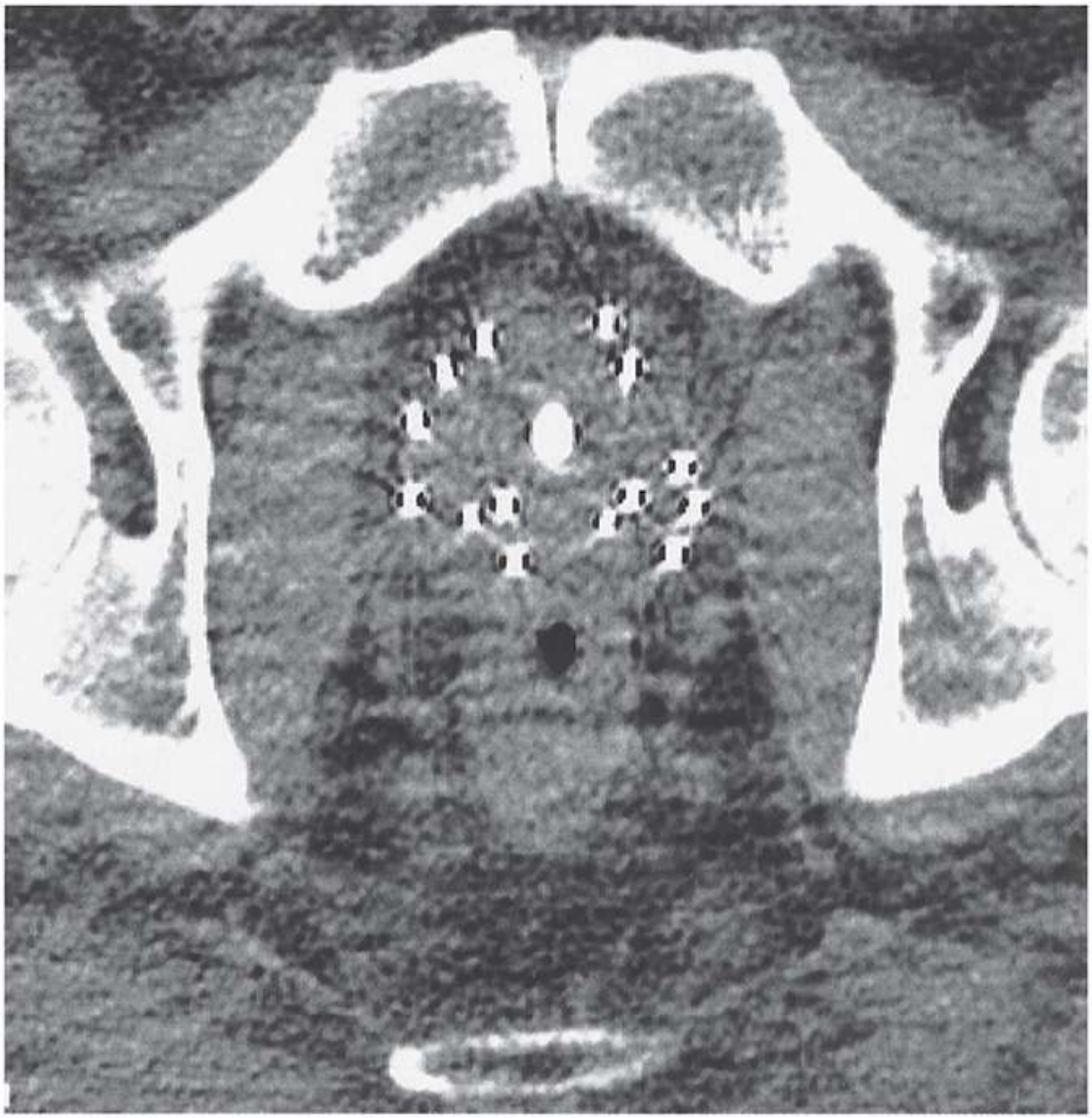


FIGURE 72.7 Postimplantation computed tomography scan after permanent transperineal ultrasound-guided seed implantation with urethral sparing.

Dose, Isotope, and Activity Considerations for Prostate Low-Dose Rate Brachytherapy. At present, the commonly used dose for LDR interstitial implantation when using ^{125}I is 144 to 145 Gy, prescribed to the isodose surface that completely encompasses the prostate as contoured from imaging studies. For ^{103}Pd, 125 Gy is the recommended prescription dose when the isotope is used as monotherapy.[267] There are clear physical

differences between these two isotopes. The half-life of ^{125}I is 59.4 days, with a mean photon energy of 28.4 keV and an initial dose rate of 7 cGy/hour. In contrast, the half-life of ^{103}Pd is 17 days, with a mean photon energy of 20.7 keV and an initial dose rate of 19 cGy/hour. Dosimetric analyses of treatment plans performed with either isotope have not revealed significant differences.[268]

A prospective trial randomized 125 patients between ^{125}I (144 Gy) and ^{103}Pd (125 Gy) for low-risk disease. The actuarial BCFFR at 3 years was 89% for ^{125}I patients versus 91% for Pd-103 patients (P = .76). The 3-year BCFFR for patients with a D_{90} less than 100% of the prescription dose was 82% versus 97% for patients with a D_{90} 100% or more of the prescription dose (P = .01). Similarly, the 3-year BCFFR for patients with a V_{100} less than 90% of the prescription dose was 87% versus 97% for patients with a V_{100} 90% or more of the prescription dose (P = .01). The effect of the dosimetric parameters on biochemical control was most pronounced for ^{125}I but also apparent for ^{103}Pd.[269] Patients treated with ^{103}Pd had more intense radiation prostatitis in the first month after implantation, but they recovered from their radiation-related symptoms sooner than ^{125}I patients, consistent with palladium's shorter half-life.[270]

A prospective randomized trial randomized patients between ^{125}I and ^{131}Cs. The prescription dose was 144 Gy for ^{125}I and 115 Gy for ^{131}Cs. ADT or supplemental EBRT was not allowed. One hundred forty men were enrolled; 81.4% were low risk, and 18.6% were intermediate risk. The median follow-up was 97 months. The 9-year biochemical RFS was 87.2% and 84.0% for the ^{125}I and ^{131}Cs group, respectively (P = .897). Short- and long-term urinary, sexual and bowel QoL, and long-term biochemical control were comparable between ^{125}I and ^{131}Cs.[271]

Postimplantation Dosimetric Evaluation. Postimplantation dosimetric evaluation after prostate BT is recommended as the standard assessment of the quality of permanent interstitial implantation used for the treatment of PCa. Recommended preimplant dosimetry PTV parameters are as follows for ^{125}I: V_{100} 95% or more, V_{150} 65% or less, and V_{200} 30% or less; for ^{103}Pd: V_{100} 95% or more, V_{150} 75% or less, and V_{200} 45% or less; and for ^{131}Cs V_{100} 95% or more, V_{150} 55% or less, and V_{200} 20% or less.[267]

Commercial software is routinely available to determine prostate coverage and dose to critical normal tissue structures. Isodose curves and DVHs produce a detailed analysis of the radiation dose distribution relative to the prostate and surrounding normal tissues. Postimplantation evaluation is performed on the day of the procedure or 30 days after. Although the latter time point takes advantage of assessments when prostate edema is less significant after the implant, with a potential decreased underestimate of the prostate coverage with the prescription dose, assessments made on the day of the procedure provide more rapid feedback regarding the adequacy of the dose delivered to the prostate.

Postimplantation evaluation is a critical quality assurance procedure for prostate BT. It provides important feedback to the brachytherapist concerning the quality of the implant, the dose delivered to the prostate, and what corrections need to be made to optimize target coverage to reduce normal tissue dosing. Postimplant dosimetry parameters include D_{90}, V_{100}, and V_{150}. Acceptable postimplant dosimetry parameters are D_{90} 80% or more and V_{100} 85% or more.[267]

A study analyzed patients with N0, M0, and nonsurgical PCa diagnosed between 2004 and 2015 from the NCDB. Patients were grouped into six categories based on RT modality: IMRT with BT boost, IMRT with/without IMRT boost, proton therapy, SBRT, LDR-BT, and high-dose rate (HDR)-BT. For low-risk patients, both LDR-BT and HDR-BT have been declining. During 2004-2007, 2008-2011, and 2012-2015, the LDR-BT monotherapy utilization percentages were 40.5%, 34.6%, and 33.5%, respectively. During 2004-2007, 2008-2011, and 2012-2015, the HDR-BT monotherapy utilization percentages were 22.4%, 17.3%, and 13%, respectively.[272]

High-Dose Rate Brachytherapy

HDR-BT (iridium-192 sources) is used for prostate HDR monotherapy of 13.5 Gy × two implants and 9.5 Gy BID × two implants. Recommended PTV planning goals are V_{100} 95% or more and D_{90} greater than 100%.[273]

The reader is referred to Chapters 23 and 24 for techniques' description and dose schedules.

Results of Standard Treatment Interventions for Clinically Localized Prostate Cancer

Outcome With Radical Prostatectomy

The National Institute for Health Research-supported ProtecT trial recruited men aged 50 to 69 years in the United Kingdom. Approximately 66% of patients were low risk.[274] A total of 1,643 agreed to undergo randomization to active monitoring (545 men), surgery (553), or RT (545). There were 17 prostate cancer–specific deaths overall: 8 in the active-monitoring group, 5 in the surgery group, and 4 in the RT; the difference among the groups was not significant. In addition, no significant difference was seen among the groups in the number of deaths from any cause. Metastases developed in more men in the active-monitoring group (33) than in the surgery group (13) or the RT group (16) (P = .004 for the overall comparison). Higher rates of disease progression were seen in the active-monitoring group (112 men) than in the surgery group (46) or the RT group (46). At a median of 10 years, prostate cancer–specific mortality was low irrespective of the treatment assigned, with no significant difference among treatments.[274]

Of the three treatments, prostatectomy had the greatest negative effect on sexual function and urinary continence, and these outcomes remained worse in the prostatectomy group than in the other groups throughout the trial. The negative effect of RT on sexual function was greatest at 6 months, but sexual function then recovered somewhat and was stable thereafter. RT had little effect on urinary continence. Sexual and urinary function declined gradually in the active-monitoring group. Bowel function was worse in the RT group at 6 months than in the other groups but then recovered somewhat, except for the increasing frequency of bloody stools. Bowel function was unchanged in the other groups. Urinary voiding and nocturia were worse in the RT group at 6 months but then mostly recovered and were similar to the other groups after 12 months.[218]

Outcome With External Beam Radiation Therapy for Low-Risk Disease

Kuban et al[275] reported the results of a large multi-institutional analysis of 4,839 patients with T1-T2 PCa treated with EBRT between 1986 and 1995; no patient received neoadjuvant hormone therapy. The median follow-up was 6.3 years. Most of the patients included (70%) were treated with

conventional EBRT, and 30% were treated with 3DCRT planning techniques. Prescription doses ranged from 60 to 78 Gy. For the cohort of patients treated to dose levels of less than 70 Gy, the median dose was 67 Gy; among those patients who received 70 Gy or more, the median dose in this cohort was 72 Gy. PSA failure as defined according to ASTRO definition was three consecutive rising PSA values above the nadir value. The overall 8-year PSA control rates for patients with pretreatment PSA values of 0 to 4, 4 to 9.9, 10 to 20, and greater than 20 to 30 ng/mL were 80%, 60%, 46%, and 34%, respectively. The overall 8-year PSA control rates for patients with post-treatment nadir PSA values of 0 to 0.49, 0.5 to 0.99, 1 to 1.99, and 2.0 ng/mL or more were 93%, 88%, 86%, and 72%, respectively. Higher prescription dose levels of 72 Gy or more were associated with a significant decrease in PSA relapse rates, and these differences were most noted among patients with intermediate- and higher risk disease. Although there was no apparent dose response for low-risk patients, the number of patients who received higher doses in this study was small.

The randomized phase III PACE-B compared prostate SBRT to conventional or moderate hypofractionation.[235] The study randomized 884 low- or favorable intermediate-risk patients to 36.25 Gy in 5 fractions versus either 78 Gy in 29 fractions or 60 Gy in 20 fractions. Five-year follow-up reported BCR-free survival (BRFS) at 95.8% for the SBRT arm and 94.6% with conventional/moderate hypofractionation.

Reported separately, urinary and bowel toxicity were not statistically different between SBRT and conventional/moderate hypofractionated regimens.[276] RTOG 2+ urinary toxicity at 2 years was 3% versus 2% (P = .39). Bowel toxicity was 2% versus 3% (P = .32).

Dess et al[277] evaluated sexual potency preservation in 830 men treated with SBRT in a prospective trial at a single institution. Prospective health-related QoL data were collected via the EPIC-26, including five major domains of urinary irritative, urinary incontinence, bowel, sexual, and hormonal. The median age was 69 years old, 25% were low risk, 57% were intermediate risk, and 18% were high risk. Twenty percent received ADT and 16% received supplemental standard fractionation radiation in addition to SBRT for higher risk features. With a best possible score of 100, the mean baseline urinary irritative, urinary incontinence, bowel, sexual, and hormonal scores were 91, 87, 95, 53, and 92, respectively. Depending on the time point post-

SBRT, between 10% and 15% of patients had 1× MID multidomain decline, and 1% to 5% of patients had 2× MID multidomain declines. On multivariable analysis, early toxicity in urinary incontinence, bowel, and hormonal domains predicted 3- and 12-month multidomain declines, with no consistent predictors at 2-, 3-, and 5-year time points.

Johnson et al[278] evaluated bowel, urinary, and sexual patient-reported QoL following treatment for PCa with either moderately hypofractionated RT (,5 Gy/fraction) or SBRT (5-10 Gy/fraction). Three hundred seventy-eight men who underwent moderate hypofractionation were compared to 534 men treated with SBRT. After 1 year, patients receiving moderate hypofractionation were more likely to experience worsening in bowel symptoms (39.5%) when compared to SBRT (32.5%; $P = .06$), with a more substantive difference at 2 years (37.4% vs 25.3%, $P = .002$).

Similarly, patients receiving moderate fractionation had worsening urinary symptom score compared to patients who underwent SBRT at 1 and 2 years (34.7% vs 23.1%, $P < .001$; and 32.8% vs 14.0%, $P < .001$). Patients receiving moderate hypofractionation had more frequent worsening in sexual symptom score, although the difference was nonsignificant at either 1 or 2 years (32.7% vs 29.1%, $P = .30$; and 38.5% vs 33%, $P = .18$). After adjusting for age and cancer characteristics, patients receiving moderate hypofractionation were more likely to experience worse urinary symptoms scores than patients receiving SBRT at 2 years (OR = 0.24; 95% CI = 0.07-0.79); there was no difference in likelihood of worsening bowel or sexual symptoms scores between groups at 1 or 2 years in the adjusted analysis.

Dose Escalation for Low-Risk Prostate Cancer

Five randomized clinical trials in men with nonmetastatic PCa showed that dose-escalated EBRT resulted in lower rates of biochemical failure and local progression but did not affect OS.[261,279-283] Two of these trials yield further insights into the impact of dose escalation in low-risk PCa.[261,282]

The phase III trial from MD Anderson Hospital[261] accrued 301 patients with T1b-T3 PCa, of whom 150 were treated to 70 Gy (conventional EBRT) and 151 were treated to 78 Gy (conventional EBRT followed by a 3D boost). A significant improvement in 8-year biochemical control was noted among low-risk patients who received 78 Gy compared to 70 Gy (88% vs 63%; $P = .042$; Figure 72.8). GI toxicity of grade 2 or greater occurred twice as often

in the high-dose patients (26% vs 13%), although GU toxicity of grade 2 or greater was less (13% vs 8%) and not statistically significantly different.

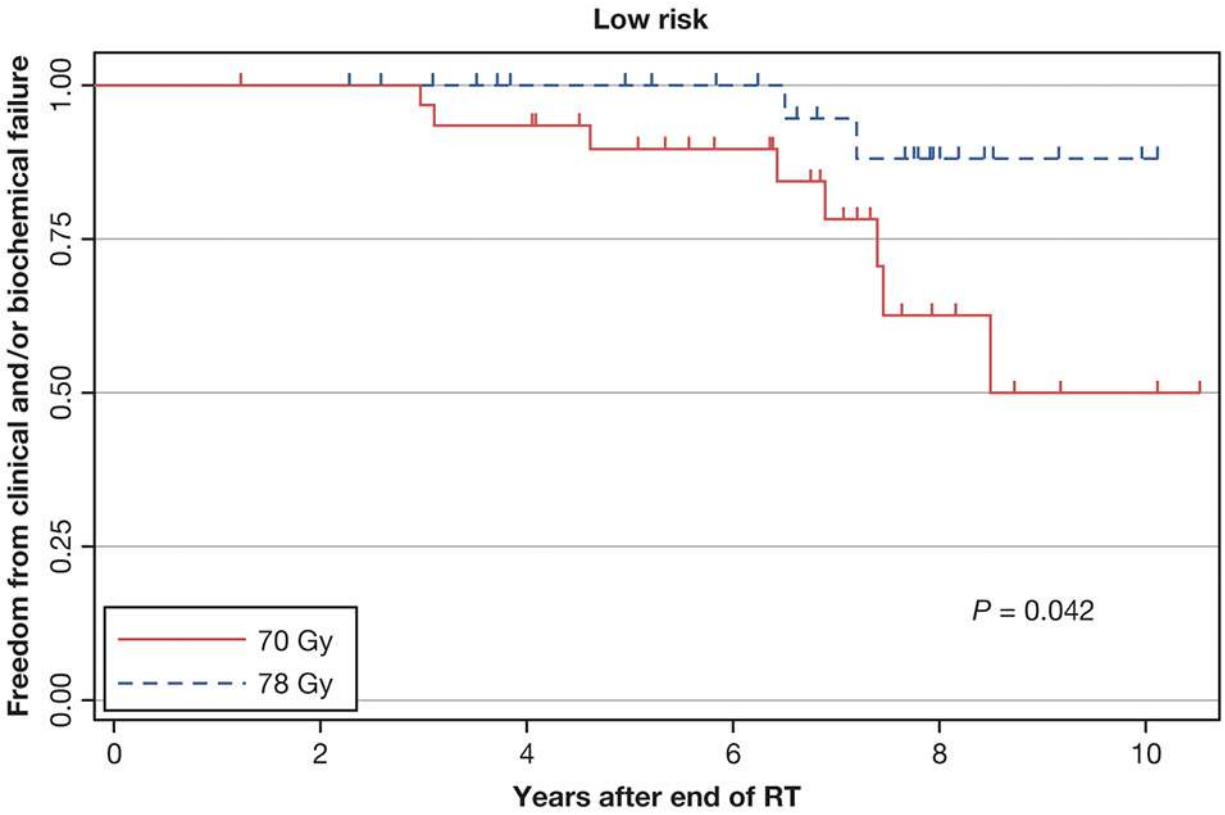


FIGURE 72.8 Freedom from biochemical failure for the subset of low-risk patients treated in the MD Anderson randomized trial with 78 versus 70 Gy. RT, radiation therapy. (Reprinted from Kuban DA, Tucker SL, Dong L, et al. Long-term results of the M.D. Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys.* 2008;70[1]:67-74. Copyright © 2008 Elsevier. With permission.)

Zietman et al[282] reported the result of a randomized trial of 393 patients with T1b-T2b PCa with pretreatment PSA levels of 15 ng/mL or less. Patients were randomized to receive conventional EBRT to a dose level of 70.2 or 79.2 Gy equivalents. In both treatment arms, RT was delivered using a combination of photon and proton beams. The median follow-up in this study was 8.9 years. The 10-year ASTRO biochemical failure rates were 32.4% for conventional dose and 16.7% for high-dose RT ($P < .0001$). This difference was held when only those with low-risk disease ($n = 227$; 58% of total) were examined: 28.2% for conventional and 7.1% for high dose ($P < .0001$).

The experience from MSKCC was reported by Zelefsky et al in 2,551 patients with T1-T3 PCa treated with follow-up that extended beyond 20 years. The radiation dose was systematically increased from 64.8 to 86.4 Gy by increments of 5.4 Gy in consecutive groups of patients. This study also demonstrated an advantage for dose escalation in low-risk patients. The 10-year PSA RFS among patients with low-risk disease who received dose levels of 75.6 Gy and higher was 84%, compared to 70% for patients who received lower dose levels (P = .04; Figure 72.9). This report showed no apparent differences in long-term outcomes among patients who received 81 versus 75.5 Gy for low-risk disease.[279-283]

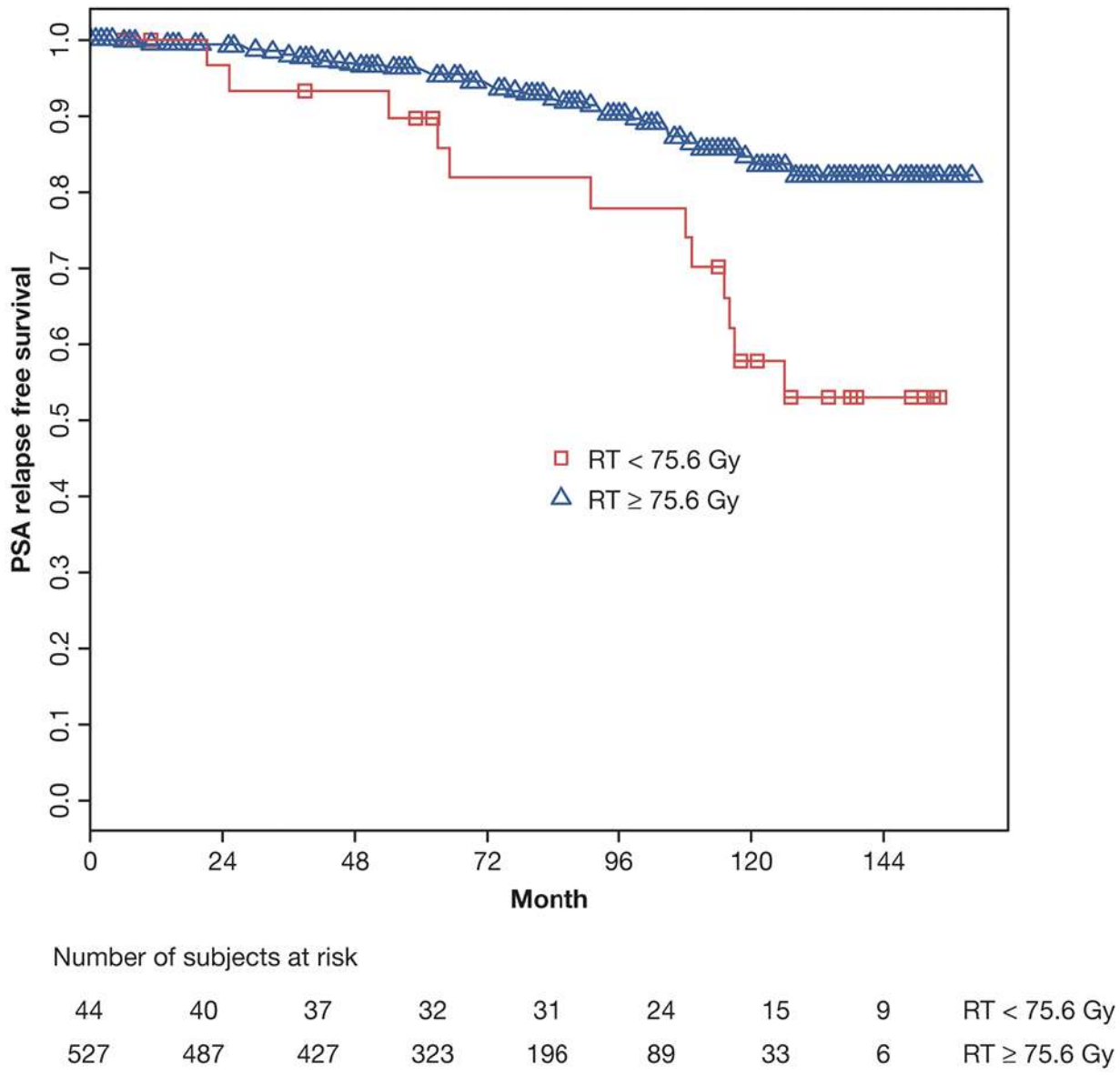


FIGURE 72.9 Memorial Sloan Kettering Cancer Center experience for prostate-specific antigen (PSA) relapse-free survival outcomes for low-risk patients treated with 75.6 Gy and higher versus lower doses. RT, radiation therapy. (Reprinted with permission from Zelefsky MJ, Chan H, Hunt M, Yamada Y, Shippy AM, Amols H. Long-term outcome of high dose intensity modulated radiation therapy for patients with clinically localized prostate cancer. *J Urol*. 2006;176[4 Pt 1]:1415-1419. Copyright © 2006 by American Urological Association.)

Michalski et al reported the outcome of RTOG 94-06, which evaluated dose escalation using 3DCRT for patients with localized PCa. Patients were accrued on five sequential dose levels: 68.4, 73.8, 79.2, 74, and 78 Gy. For patients with low-risk disease (n = 403), the 5-year PSA RFS outcomes for these respective dose levels were 68%, 73%, 67%, 84%, and 80%.[284]

A retrospective, nonrandomized comparative effectiveness study of dose-escalated versus standard-dose EBRT for PCa diagnosed from 2004 to 2006 using the NCDB evaluated three cohorts: men with low-risk (n = 1,229), intermediate-risk (n = 16,714), or high-risk (n = 13,538) PCa. Patients were categorized patients in each risk cohort into two treatment groups: standard-dose (from 68.4 to <75.6 Gy) or dose-escalated (≥75.6-90 Gy) EBRT. Dose-escalated EBRT is associated with improved OS in men with intermediate- and high-risk PCa, but not with low-risk PCa.[285]

Comparison of External Beam Radiation Therapy Outcomes With Surgery for Early-Stage Prostate Cancer

Kupelian et al[263] compared the 8-year outcomes of surgery and EBRT from the Cleveland Clinic. In this report, 1,054 patients were treated with surgery and 628 were treated with EBRT. Treatments (surgery or RT) were given between 1990 and 1998, and the median follow-up was 51 months. There were significant differences in the patient groups because, in general, those treated with surgery were younger and had lower clinical stages, pretreatment PSA levels, and GSs. The 8-year PSA RFS outcome for patients who underwent RP and EBRT was 72% and 70%, respectively (P = .01). Multivariate analysis demonstrated that the clinical stage, pretreatment PSA, biopsy GS, use of neoadjuvant therapy, and year of treatment were all independent predictors of disease relapse, whereas the treatment modality (RT vs surgery) did not influence likelihood of failure. These authors also noted a benefit for higher radiation doses in the favorable-risk subset of patients. Among favorable-risk patients who received 72 Gy or more, the 8-year PSA RFS outcome was similar (P = .08) to that of patients treated with RP and significantly better, in turn, than that of patients treated with RT to dose levels of less than 72 Gy (P < .001). Similarly, Zelefsky et al[208] found similar DM-free survival outcomes between high-dose IMRT and surgery for low-risk patients.

The PACE-A study compared SBRT for low- and intermediate- risk PCa to RP.[286] The trial halted accrual early secondary to the COVID-19 pandemic but enrolled 123 patients. Cancer outcomes have not yet been reported, but early- to intermediate-term toxicity results show excellent outcomes for SBRT. Most of the patients assigned to RP underwent RARP (84%), and 76% of SBRT patients used Cyberknife technology. The primary end point of

urinary incontinence, defined as any use of pads, was reported at 2 years: 47% for RP and 4.5% for SBRT ($P < .001$). However, SBRT did result in worse patient-reported bowel symptoms per the EPIC bowel subdomain: 88.7 for SBRT versus 97.3 for RP ($P < .001$), although patient reports of bowel symptoms being a significant detractor on QoL was very low (2.2%). Sexual outcomes favored SBRT: The EPIC sexual bother subdomain mean scores were 57.7 for SBRT versus 29.3 for RP ($P < .001$).

Proponents of RP have argued that, whereas the results of radiation and radical surgery are comparable up to 10 years, there is a rapid decrement in the probabilities of both DFS and OS after that time point among irradiated patients. However, such conclusions are likely erroneous owing to selection bias factors favoring a younger cohort with more favorable prognostic features who are more often chosen for surgery compared with RT. In addition, because of the lack of information in most RT series of the pathologic status of the LNs, patients with microscopic nodal disease will likely be included in RT reports yet routinely excluded from surgical series. An additional argument posed for surgery is that if such an approach fails, salvage RT remains a viable option, whereas for those who fail RT, salvage surgery can be associated with an increased risk of postoperative complications. Nevertheless, patients need to be informed that there are risks associated with salvage RT after a failed prostatectomy and that the likelihood of a successful outcome after well-delivered primary RT is high and comparable to surgery outcomes.

Outcome With Brachytherapy

Low-Dose Rate Brachytherapy

The single-arm phase II prospective RTOG 9805 study enrolled 101 patients with low-risk disease treated with I-125 monotherapy (145 Gy). No patients received ADT. At a median follow-up of 8.1 years among 94 eligible patients, the 8-year cumulative incidences of biochemical failure and metastasis were 8% and 1.1%, respectively.[287]

Appropriate candidates for BT monotherapy include low-risk disease for patients declining AS and favorable intermediate-risk disease. Recommended radionuclides for permanent prostate BT include iodine-125, palladium-103, and cesium-131. The suggested monotherapy doses are 144 to 145 Gy for iodine-125, 125 Gy for palladium-103, and 115 Gy for cesium-131.[267]

Crook et al analyzed data from seven institutions for 14,220 patients with localized PCa treated with LDR-BT, either alone (8,552) or with EBRT (n = 1,175), ADT (n = 3,165), or both (n = 1,328). Since 98.7% of patients with PSA 0.2 ng/mL or less at 4 years after LDR prostate BT were disease free beyond 10 years, the authors suggested adopting this biochemical definition of cure for patients with 4 years or more follow-up after LDR-BT.[288]

Similar to the predictors of biochemical outcome after EBRT for PCa, PSA RFS after permanent seed implantation depends on several prognostic variables, including the pretreatment PSA, biopsy GS, clinical stage, and the implant dose delivered to the target volume. In general, among patients with pretreatment PSA of 10 ng/mL or less, permanent seed implantation alone is associated with excellent biochemical outcomes and appears comparable with other local interventions.[289] Fifteen-year outcomes were reported by Sylvester et al from 215 patients treated between 1988 and 1992. The PSA RFS outcomes were 86%, 80%, and 62% for favorable-, intermediate-, and high-risk patients, respectively. Similarly, Taira et al reported on 1,656 patients.[290] For low-risk patients, the 7-year biochemical tumor control, cause-specific survival, and OS outcomes were noted to be 98.6%, 99.8%, and 77.5%, respectively.

Eleven institutions combined data on 2,693 patients treated with permanent interstitial BT monotherapy for T1-T2 PCa.[291] Of these patients, 1,831 (68%) were treated with ^{125}I (median dose, 144 Gy) and 862 (32%) were treated with ^{103}Pd (median dose, 108 Gy). The median follow-up was 63 months. The 8-year PSA RFS outcomes for low-, intermediate-, and high-risk patients were 82%, 70%, and 48%, respectively ($P < .001$) according to the ASTRO consensus definition.

Stone et al reported on 2,111 patients who underwent BT followed for a median of 6 years. In this group, 55.5% of the patients were treated with ^{125}I, 10.4% were treated with ^{103}Pd, and 34.1% were treated with combined EBRT and ^{103}Pd implant.[292] Among low-risk patients, the PSA RFS outcome at 12 years was 88.1%.

Table 72.10 summarizes the published biochemical outcomes after LDR interstitial seed implantation according to prognostic risk groups.

TABLE 72.10 BIOCHEMICAL CONTROL AFTER BRACHYTHERAPY ALONE FOR CLINICALLY LOCALIZED PROSTATE CANCER ACCORDING TO PROGNOSTIC RISK GROUP CLASSIFICATIONS

Study	Patients	Years	Low Risk (%)
Taira et al[290]	1,656	12	98.6
Sylvester et al[289]	215	15	86
Multi-institutional[291]	2,693	8	82
Stone et al[292]	2,111	12	88
Potters et al[352]	1,449	12	89
Zelefsky et al[353]	1,466	5	98

High-Dose Rate Brachytherapy

Morton et al reported the efficacy results from a randomized phase II clinical trial of one fraction of 19 Gy or two fractions of 13.5 Gy. The median follow-up was 60 months. The 5-year bDFS and cumulative incidence of local failure were 73.5% and 29% in the single fraction arm and 95% (P = .001) and 3% (P < .001) in the 2-fraction arm. The authors concluded HDR monotherapy delivered as two fractions of 13.5 Gy is well tolerated with a high cancer control rate at 5 years, and 19-Gy single fraction monotherapy is inferior and should not be used.[293]

A systematic review of HDR-fractionated BT monotherapy for localized PCa identified 7 studies and 2,123 patients. Low-, intermediate-, and high-risk patients comprised 40%, 40%, and 20% of patients, respectively. The 5-year BRFS rate was 95%.[294]

ACUTE AND LATE TREATMENT-RELATED SEQUELAE OF STANDARD TREATMENT INTERVENTIONS

Sequelae of Radical Prostatectomy

Complication rates after prostatectomy vary in the literature and recently have been shown to depend on the experience of the surgeon. Begg et al[295] used the Medicare claim records from 11,522 patients who underwent prostatectomy between 1992 and 1996. Postoperative morbidity was found to be significantly reduced in hospitals that were considered to have high volume compared with lower volume ones (27% vs 32%; P = .03) and among surgeons with a high-volume practice compared to those with lower volumes (26% vs 32%; P < .001).

Immediate intraoperative/postoperative complications include pelvic pain and transient incontinence. Although intraoperative blood loss can range from 300 to 4,000 mL, meticulous surgical technique should reduce blood loss. The operative mortality rate has been reported to be 1% to 2%, but in experienced hands, the incidence is a fraction of 1%. The incidence of postoperative stress incontinence ranges from 5% to 57%.

Catalona et al[296] reported on the complication rates in 1,870 patients who underwent RP. They reported a 2% incidence of a thromboembolic event and a 4% incidence of an anastomotic stricture. Recovery of urinary continence depended on the age of the patient. Among patients in their 50s, 60s, and 70s, the likelihood of persistent urinary incontinence was 3%, 8%, and 13%, respectively. The incidence of impotence after bilateral and unilateral nerve-sparing surgery procedures was 53% and 32%, respectively. Bilateral nerve-sparing procedure was associated with improved potency preservation among patients who were younger than 70 years of age (71% vs 48%; $P <$ .001), whereas these differences were not significant in the older age group.

Bianco et al[297] reported continence and potency outcomes in 1,472 patients who underwent surgery since 1991 and were operated on by a single surgeon. Among 1,288 patients who were continent prior to surgery, the actuarial likelihood of maintained continence was 91% at 12 months and 95% at 24 months. Of 785 patients with potency information available, the median time to erectile function recovery was 12 months, and the 2-year likelihood of potency preservation was 70%.

A large review from the Nationwide Inpatient Sample extracted from this data set 11,889 patients who underwent RARP and compared the perioperative complication rates to 7,389 patients who underwent an open RP.[298] This analysis found that, among patients undergoing an RARP, significantly lower likelihoods for blood transfusions and intraoperative and postoperative complications were observed compared to the open prostatectomy procedure. In addition, a shorter duration of hospital stay was noted for the patients who underwent an RARP. However, one of the limitations of this retrospective study was the fact that these findings were not adjusted by the clinical stage of the patients and the surgeon's experience or volume, which play important roles in the frequency of surgical-related complications.

A large meta-analysis of 910 studies reporting outcomes for either open or RARP found that the annual volume of surgeries performed correlated with complication rate.[299] For open RP, the expected annual volume to achieve a complication rate of 12% or less was 95.3 surgeries per year. For RARP, the annual volume to achieve the same complication rate was at least 30.2 surgeries per year.

Sequelae of Conventional External Beam Radiation Therapy

EBRT delivered with conventional techniques is fairly well tolerated, although grade 2 or higher acute rectal morbidity (discomfort, tenesmus, diarrhea) or urinary symptoms (frequency, nocturia, urgency, dysuria) requiring medication occur in approximately 60% of patients. Symptoms usually appear during the third week of treatment and resolve within days to weeks after treatment is completed. The incidence of late complications that develop 6 months or more after completion of treatment is significantly lower, whereas serious complications that require corrective surgical intervention are rare. In general, the incidence of chronic urinary sequelae (ie, cystitis, hematuria, urethral stricture, or bladder contracture) using conformal treatment delivery techniques is less than 5%, and the incidence of grade 3 and 4 urinary-related complications requiring major surgical interventions or hospitalization is less than 1%. The incidence of chronic intestinal or rectal sequelae (chronic diarrhea, proctitis, or rectal bleeding) that requires medical management ranges from 3% to 10%, and less than 1% of grade 3 to 4 complications are observed after more targeted treatment delivery techniques, such as IMRT and IGRT. Fecal urgency and incontinence are documented side effects after treatment and have been reported to occur in less than 2% of patients, occur less than once per week, and are often associated with incontinence for flatulence.[300] Most complications attributed to RT are observed within the first 3 to 4 years after treatment, and the likelihood of complications developing after 5 years is low. Even patients with a prior history of inflammatory bowel disease currently in remission may have significant increases in rectal toxicity, and alternative treatments should be considered for these patients. Among patients who undergo RT and experience acute rectal side effects, a higher incidence of late rectal toxicity has been observed.[301,302]

The NRG Oncology/RTOG 0126 randomized clinical trial randomized 1,532 patients from 104 North American RTOG institutions. Men with stage cT1b to T2b, GS 2 to 6, and PSA level of 10 or greater and less than 20 or GS of 7 and PSA less than 15 received 3DCRT or IMRT to 79.2 Gy in 44 fractions or 70.2 Gy in 39 fractions. The 5-year rates of late grade 2 or greater GI and/or GU toxic effects were 21% and 12% with 79.2 Gy and 15% and 7% with 70.2 Gy (P = .006 and P = .003, respectively).[303] Erectile dysfunction at 12 months based on the single question was not significantly different between the 70.2 Gy arm (38.1%) versus the 79.2 Gy arm (49.7%). The treatment arm (70.2 vs 79.2) had no significant impact on any patient-reported outcome metrics measured across all collected domains.[304]

Michalski et al published a report on the toxicity outcomes of various risk groups enrolled in RTOG 9406, a phase I/II dose escalation study. The dose for level I was 68.4 Gy, 73.8 Gy for level II, 79.2 Gy for level III, 74 Gy for level IV, and 78 Gy for level V. Disease group I patients were treated to the prostate only; group 2 patients were treated to the prostate and the SVs with a prostate boost, and group 3 patients were treated to the prostate and SVs. The median follow-up period for surviving patients was 6.1 years for 68.4 Gy to 12.1 years for 78 Gy. The incidence rates of RTOG grade 3 or less GI or GU toxicity were 3%, 4%, 6%, 7%, and 9% in group 1 and 6%, 2%, 6%, 9%, and 12% in group 2 at dose levels of I, II, III, IV, and V, respectively. There was significantly more grade 2 or greater toxicity with a dose of 78 Gy at 2 Gy/fraction than with 68.4 to 79.2 Gy at 1.8 Gy/fraction and 74 Gy at 2 Gy/fraction.[305]

Storey et al reported late rectal toxicity among patients treated in the phase III trial from the MD Anderson Hospital. The 5-year Kaplan-Meier risks of late grade 2 or higher rectal and bladder toxicity for the 70- and 78-Gy dose level arms were 14% and 21%, and 20% and 9%, respectively. The 5-year risks of grade 2 or higher late bladder toxicity were 20% and 9% for the 70 and 78-Gy groups, respectively.[306]

Zelefsky et al[307] reported the long-term tolerance of high-dose CRT at MSKCC. The 10-year actuarial rate of grade 2 or higher rectal toxicity was 9%. The use of IMRT significantly lowered the risk of grade 2 and higher toxicities from 13% to 5% (P < .001). This decline in rectal toxicity was observed despite the application of higher doses of 81 Gy with IMRT compared to generally lower doses used with 3DCRT of 75.6 Gy (Figure

72.10). In addition, patients who experienced acute GI (AGI) side effects during treatment were 6 times more likely to experience late GI (LGI) toxicities than patients who did not experience such acute side effects (42% vs 9%; $P < .001$). The 10-year incidence of grade 2 or higher late urinary toxicities was 15%, and the predictors for late toxicity included higher radiation doses and the presence of acute urinary symptoms during EBRT. The 10-year actuarial incidence of grade 2 and 3 GI toxicities was 2% and 1%, respectively. The 10-year actuarial incidence of grade 2 and higher urinary-related toxicities was 17%.[308]

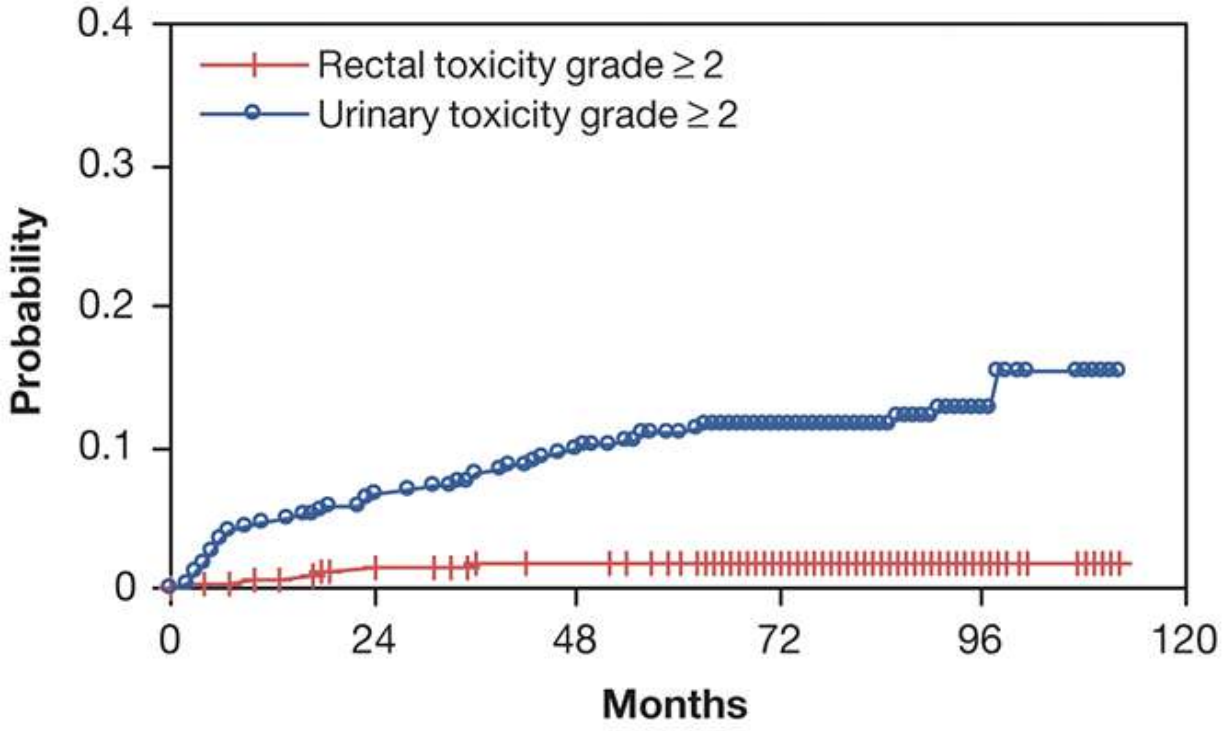


FIGURE 72.10 Actuarial likelihood of late grade 2 or greater rectal toxicities or late grade 2 or greater rectal toxicities. (Reprinted with permission from Zelefsky MJ, Chan H, Hunt M, Yamada Y, Shippy AM, Amols H. Long-term outcome of high dose intensity modulated radiation therapy for patients with clinically localized prostate cancer. *J Urol*. 2006;176[4 Pt 1]:1415-1419. Copyright © 2006 by American Urological Association.)

Peeters et al described the incidence of acute and late complications in a multicenter randomized trial comparing 68- to 78-Gy 3DCRT.[309] The median follow-up was 31 months. The 3-year incidence of grade 2 and higher GI and GU toxicities for the 68-Gy dose arm was 23.2% and 28.5%, respectively. The 3-year incidence of grade 2 and higher GI and GU toxicities for the 78-

Gy dose arm was 26.5% and 30.2%, respectively. The differences were not statistically significant. However, the authors did note a significant increase in grade 3 rectal toxicity requiring laser treatment or transfusion for the higher dose arm.

Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) recommended the following rectal dose-volume constraints as a conservative starting point for 3D treatment planning: V_{50} less than 50%, V_{60} less than 35%, V_{65} less than 25%, V_{70} less than 20%, and V_{75} less than 15%. Contemporary protocols like NRG GU010 have stricter dose constraints for V_{75} less than 10% and add V_{80} less than 5%.[310] For typical DVHs, the normal tissue complication probability models predict that following these constraints should limit grade 2 or higher late rectal toxicity to less than 15% and the probability of grade 3 or higher late rectal toxicity to less than 10% for prescriptions up to 79.2 Gy in standard 1.8 to 2 Gy fractions.[311] The QUANTEC recommended bladder dose constraints are V_{65} less than 50%, V_{70} less than 35%, V_{75} less than 25%, and V_{80} less than 5%.[312] Contemporary protocols like NRG GU010 have stricter bladder dose constraints: V_{50} less than 0%, V_{65} less than 40%, V_{70} less than 35%, V_{75} less than 20%, and V_{80} less than 10%.[310]

Potency Preservation With External Beam Radiation Therapy

The rates of erectile dysfunction after EBRT ranged from 6% to 84%.[313] The wide range of outcomes reflects the varying assessment tools used and disparity in the patient population, with heterogeneity of comorbidities, ages, and baseline functional status. Most studies show a progressive decline in erectile function with longer follow-ups, consistent with what is observed in an aging population with coexisting comorbidities such as hypertension, atherosclerotic heart disease, and diabetes. In one report comparing erectile function between patients who received 68 versus 78 Gy,[314] no differences were observed between the different dose levels. Overall, in the studied cohort, the incidence of erectile dysfunction at 1 and 2 years after therapy was 27% and 36%, respectively. Aside from erectile dysfunction, other aspects of sexual dysfunction after RT include decreased volume of ejaculate, absence of ejaculate, decreased intensity of orgasm, and decreased

libido. A summary of reported potency rates after treatment is shown in Table 72.11.

TABLE 72.11 INCIDENCE OF ERECTILE DYSFUNCTION AFTER RADIATION THERAPY FOR PROSTATE CANCER

Study	Treatment	Follow-Up (Months)	Pre-RT Potency (No ED)	Post-RT Potency (No ED)
Chen et al[315]	IMRT	24	100%	73%
Hoffman et al[316]	IMRT	60	78%	50%
Friedland et al[317]	SBRT	24	100%	82%
Chen et al[318]	SBRT	28	100%	79%
Obayomi-Davies et al[319]	SBRT	24	100%	54%
Nobes et al[320]	LDR	24	100%	62%
Solan et al[321]	LDR	26	100%	77%
Taira et al[322]	LDR	84	100%	56%

ED, erectile dysfunction; IMRT, intensity-modulated radiotherapy; LDR, low dose rate brachytherapy; SBRT, stereotactic body radiotherapy.

Adapted by permission from *Nature*: Hunt AA, Choudhury KR, Nukala V, et al. Risk of erectile dysfunction after modern radiotherapy for intact prostate cancer. *Prostate Cancer Prostatic Dis*. 2021;24(1):128-134.

Significant limitations exist with the aforementioned reported potency preservation rates because the data are derived from retrospective analyses and information was often obtained without the use of validated questionnaires. Prospective studies suggest that when patients are assessed with validated tools, erectile dysfunction—defined as the inability to achieve adequate erection sufficient for sexual intercourse—reaches 60% to 70%. What also complicates the interpretation of published incidence rates is the multifactorial nature of erectile dysfunction. The factors that impact erectile function include age, presence of medical comorbidities such as cardiac disease and diabetes, antihypertensive medications, baseline erectile function, and the use of neoadjuvant and concurrent hormonal therapy. Pinkawa et al observed that the presence of spontaneous erection in the

evening or morning before treatment was a strong predictor for maintaining erectile function after RT.[323] The QUANTEC recommended penile bulb dose constraints are a mean dose to 95% of the penile bulb volume to less than 50 Gy, D_{70} less than 70 Gy, and D_{90} less than 50 Gy. It is acknowledged that the penile bulb may not be the critical component of the erectile apparatus, but it seems to be a surrogate for yet to be determined structure(s) essential for erectile function for at least some techniques.[324]

Brachytherapy: Acute and Late Toxicity

Urinary Toxicity

Low-Dose Rate Brachytherapy

The most common urinary toxicities after LDR-BT within the first 3 years include the following grade 1 to 2 toxicities: dysuria (7%-13%), weak stream (8%-49%), frequency (7%-62%), urgency (7%-20%), hematuria (0%-14%), incontinence (,0.5%-8.9%), and acute urinary retention (2%-34%). Rare urinary complications following LDR-BT include urinary infection 3%, late urinary retention (0.6%-6%), urethral stricture grade 3+ (1%-9%), and vesicourethral fistula less than 0.2%.[325] BT monotherapy is associated with transient urinary irritative symptoms that peak within the first 3 months of treatment and tend to resolve toward baseline at 1 year for I-125 and 6 months for Pd-103.[267]

Management of irritative/obstructive symptoms may consist of α-1 adrenoceptor antagonists and anticholinergics, NSAIDs, and dietary modification to reduce the consumption of bladder irritants such as caffeine and alcohol. The best evidence is for α-adrenergic medications. Two RCTs compared an α-adrenergic blocker to no further therapy. In one trial of 118 patients, 2 months of tamsulosin 0.8 mg daily resulted in a significant improvement in the American Urological Association score at 5 weeks compared to placebo.[326] Another randomized trial involving 105 patients showed that adding silodosin 8 mg daily for 6 months improved International Prostate Symptom Score at 1, 3, and 6, but not at 12 months.[327] Acute urinary retention may require a temporary Foley catheter. Urethral strictures may require endoscopic urethral dilation. A fistula could be managed with conservative treatment with urinary diversion or surgical treatment.

Recommended metrics for preimplant and postimplant I-125 dosimetry (day 0-60) for the urethra are D_5 less than 150%.[267]

High-Dose Rate Brachytherapy

A systematic review of HDR-fractionated BT monotherapy for localized PCa identified 7 studies and 2,123 patients. Low-, intermediate-, and high-risk patients constituted 40%, 40%, and 20% of patients, respectively. The estimated adjusted late grade 3 or higher GU was 2%.[294] Grade 2 or higher CTCAE GU toxicity ranges from 0 to 25%.[328]

For a 13.5 Gy × 2 monotherapy HDR implant, Washington University in Saint Louis uses the following dose constraints: urethra: V_{125} less than 1 mL, D_{max} less than 150%; and bladder: V_{75} less than 1 mL, D_{max} less than 150%. The American Brachytherapy Society consensus guidelines for HDR-BT list additional dose constraints used at other institutions.[329]

Rectal Tolerance

Low-Dose Rate Brachytherapy

Acute LDR-BT bowel toxicity includes urgency/frequency (3%-11%), incontinence (1%-4%), grade 1 rectal bleeding (1%-30%), radiation proctitis grade 2+ (0.5%-6%), and rectal pain (1%-5%). Late rectal toxicity grade 3+ includes rectal ulcer (0.1%-0.3%) and rectal fistula, with rectourethral the most reported (,0.5%).[325]

Rectal ulcers may require conservative medical management, colostomy, and/or hyperbaric oxygen. Biopsies should be avoided to prevent progression into a fistula. Rectal fistulas may require conservative treatment with urine diversion, colostomy, hyperbaric oxygen, and/or surgical management.

Recommended metrics for preimplant I-125, Pd-103, and Cs-131 dosimetry (days 0-60) for the rectum are RV_{100} less than 1 mL, RV_{100} less than 1 mL, and RV_{100} less than 0.5 mL. Acceptable postimplant dosimetry is as follows: RV_{100} less than 1 mL for I-125/Pd-103, and RV_{100} less than 0.5 mL for Cs-131.[267]

High-Dose Rate Brachytherapy

The same systematic review of 2,123 patients treated with HDR-fractionated BT monotherapy for localized PCa and estimated adjusted late grade 3 or higher GI toxicity rate at 0.3%.[294] Grade 2 or higher CTCAE GI toxicity ranges from 0% to 6%.[328]

For a 13.5 Gy × 2 monotherapy HDR implant, Washington University in Saint Louis uses the following rectal dose constraints: V_{75} less than 1 mL, D_{max} less than 150%. The American Brachytherapy Society consensus guidelines for HDR-BT list additional dose constraints used at other institutions.[321]

Erectile Function

Low-Dose Rate Brachytherapy

Erectile dysfunction after LDR-BT can range between 19% and 50%.[325] Erectile dysfunction is often managed with phosphodiesterase type 5 inhibitors. Dutasteride and bicalutamide, when used for cytoreduction, allow for improved sexual function preservation compared with LHRH agonists.[267] Even though no prospective randomized trials compare LDR and HDR monotherapy, nonrandomized evaluations have suggested that potency impairment is less frequent after HDR than LDR treatment. Martinez et al carried out a comprehensive toxicity comparison between 248 HDR and 206 LDR monotherapy patients, documenting a 5-year potency preservation rate of 80% for HDR and 70% for LDR.[330]

High-Dose Rate Brachytherapy

Potency preservation rates of 60% to 90% have been documented.[328] Although no prospective randomized trials compare LDR and HDR monotherapy, nonrandomized evaluations have suggested that potency impairment is less frequent after HDR than LDR treatment. Martinez et al carried out a comprehensive toxicity comparison between 248 HDR and 206 LDR monotherapy patients, documenting a 5-year potency preservation rate of 80% for HDR and 70% for LDR.[330]

POSTIRRADIATION PROSTATE-SPECIFIC ANTIGEN

A transient increase in PSA during RT, even as soon as the first fraction, has been reported in some patients.[331,332] Because there is no prognostic

significance to the PSA response during a course of RT, obtaining PSA levels during treatment is not necessary or recommended. PSA fluctuations are common in the follow-up period and have been termed *PSA bounce*. In one report,[333] 35% of patients after combined permanent interstitial implantation and EBRT experienced a transient rise in their PSA value after treatment. The median time from treatment to this bounce effect was 18 months, and 92% of the fluctuating levels were observed during the first 26 months after RT. These investigators reported fluctuations ranging from 0.11 to 15.8 ng/mL. Similar results have been reported by Cavanagh et al[334] for patients treated with implantation alone or when combined with EBRT. Hanlon et al[335] observed a PSA bounce effect in approximately one-third of patients treated with EBRT alone. In that series, the 5-year biochemical control rate for patients who experienced a PSA fluctuation was inferior to that in those patients who did not have a PSA bounce in their follow-up period (69% vs 52%; $P = .02$). On the other hand, investigators from the MD Anderson Hospital[336] noted that, of 964 patients treated with EBRT, only 12% experienced a PSA bounce, and the 5-year PSA outcome was superior for those patients who experienced this PSA fluctuation compared with those who did not (82% vs 58%; $P = .0001$).

Ciezki et al[337] defined PSA bounce as an increased PSA level of at least 0.2 ng/mL greater than the nadir PSA with a subsequent PSA value declining back to the nadir level or lower. One hundred sixty-two patients were treated with a permanent ^{125}I implantation and followed for a minimum of 5 years. With this as the definition of a PSA bounce, almost half of the patients (46%) experienced this phenomenon. The authors observed that the patients who experienced this fluctuation were more likely to be younger and less likely to develop a biochemical relapse. The authors also noted that PSA bounces generally occurred much sooner after treatment than did a true PSA relapse. The median time to the first rise in PSA from the nadir was 15 months, compared with 30 months for an ASTRO-defined biochemical relapse or 22 months for a nadir +2-defined relapse. Other reports define PSA bounce in various ways, and for this reason, the literature needs to be interpreted with caution.[338]

Although a low absolute PSA level or nadir value after RT has prognostic significance for improved DFS, it is difficult to assign a specific PSA cut-point or nadir level as a definition of biochemical relapse. Currently, the

nadir +2 definition (a rise by ≥2 ng/mL above the nadir PSA) is considered the standard definition for biochemical failure after EBRT with or without hormonal therapy. A consensus panel[339] also recommended that the date of failure be determined "at call" (not backdated). Several studies examined the significance of post-treatment PSA doubling time (PSADT). Following prostatectomy, in a single-institution experience, Pound et al[340] noted that, for patients treated with RP, PSADT of less than 10 months predicted the development of metastatic disease. Zelefsky et al[341] reported on the impact of PSADT in a cohort of patients who developed biochemical relapse after EBRT. The PSADT for favorable-, intermediate-, and unfavorable-risk patients who developed a biochemical failure was 20.0, 13.2, and 8.2 months, respectively ($P < .001$). The 3-year incidence of DM for patients with PSADT of 0 to 3, 3 to 6, 6 to 12, and greater than 12 months was 49%, 41%, 20%, and 7%, respectively ($P < .001$). Patients with PSADT of 0 to 3 and 3 to 6 months demonstrated a 7.0 and 6.6 increased hazard of developing DMs or death, respectively, compared with patients with a doubling time of greater than 12 months. Freedland et al[342] noted that PSADT of less than 9 months correlated with PCa-specific mortality but did not evaluate postprostatectomy PSADT as a surrogate for cause-specific survival. Using larger, multi-institutional databases, Albertsen et al[141] and D'Amico et al[343] noted that short PSADT correlated with an adverse effect on survival in patients treated with either prostatectomy or RT for PCa.

To date, data strongly correlate a rising PSA level with positive postirradiation prostate biopsies. Crook et al[344] reported on 226 patients treated with conventional EBRT who underwent serial biopsies after treatment. At 13 months after RT, the incidence of a positive biopsy was 51%, but it decreased to 30% for biopsies obtained at 30 months. Post-treatment biopsies require an experienced pathologist to interpret because of the significant radiation effect that takes place in the prostate, which can easily be mistaken at times for residual disease. Immunohistochemical staining for high-molecular-weight keratin can often distinguish radiation atypia in benign glands from residual tumor.

Proton/Heavy Ion Particle Therapy

Proton beam therapy (PBT) and carbon ion radiotherapy (CIRT) offer unique biologic and physical advantages over conventional RT with x-rays. Carbon

ion beams have an estimated 3-fold higher relative biologic effectiveness (RBE) than x-rays.[345] CIRT and PBT can create a better dose distribution based on the ability of accelerated ions to release a maximum amount of energy at the end of their track, resulting in a Bragg peak.[346] These features permit dose escalation for tumors with less toxicity in normal tissues. In the absence of randomized trials comparing efficacy and toxicity to high-dose photon therapy, no cogent evidence supports its superiority over other forms of EBRT.

Five-year outcomes from three prospective trials of image- guided proton therapy for PCa included a total of 211 patients with PCa (89 low risk, 82 intermediate risk, and 40 high risk). Treatment consisted of 88 cobalt gray equivalent (CGE) in 39 fractions for low-risk disease, 78 to 82 CGE for intermediate- risk disease, and 78 CGE with concomitant docetaxel therapy, followed by ADT for high-risk disease. Five-year rates of biochemical and clinical freedom from disease progression were 99%, 99%, and 76% in low-, intermediate-, and high-risk patients, respectively. Actuarial 5-year rates of late CTCAE, version 3.0 (or version 4.0) grade 3 GI and urologic toxicity were 1.0% (0.5%) and 5.4% (1.0%), respectively.[347]

Five-year outcomes from a prospective trial of image-guided accelerated hypofractionated proton therapy for PCa included 215 patients with PCa receiving 70 Gy (RBE) in 28 fractions for low-risk disease (n = 120) and 72.5 Gy (RBE) in 29 fractions for intermediate-risk disease (n = 95). Five-year rates of freedom from biochemical and clinical disease progression were 95.9%, 98.3%, and 92.7% in the overall group and the low- and intermediate-risk subsets, respectively. Actuarial 5-year rates of late radiation-related CTCAE v3.0 grade 3 or higher GI and urologic toxicities were 0.5% and 1.7%, respectively.[348]

Five-year outcomes from 284 patients treated with an ultrahypofractionated intensity-modulated proton therapy (IMPT) schedule (36.25 GyE in five fractions) included 121 low-risk, 125 favorable, and 33 unfavorable intermediate-risk patients with PCa. The 5-year bDFS was 96.9%, 91.7%, and 83.5% for the low-, favorable, and unfavorable intermediate-risk groups, respectively. Late toxicity CTCAE v.4 was as follows: GI: grade 1, 62 (22%) patients, grade 2, 20 (7.2%) patients, and grade 3, 1 (0.36%) patient; GU: grade 1, 80 (28.7%) patients, grade 2, 14 (5%) patients, and grade 3, 0 patients.[349]

The Prostate Advanced Radiation Technologies Investigating Quality of Life study is a multi-institutional phase III randomized clinical trial of proton therapy versus IMRT for low- or intermediate-risk PCa. The hypothesis is that proton therapy will improve patient-reported outcomes for a given radiation dose. The trial has enrolled 454 patients. Results are pending.

A Prospective Comparative Study of Outcomes with Proton and Photon Radiation in Prostate Cancer is a large, prospective, pragmatic, controlled comparison of patient-centric outcomes (QoL, toxicity, and disease control) between parallel cohorts of men with PCa treated simultaneously at proton therapy facilities and at geographically similar conventional (photon-based) radiation facilities using IMRT techniques. The study completed enrollment on October 31, 2022, after enrolling 2,524 patients over 4 years. Results are pending.

The evidence suggests that proton therapy is a safe and effective treatment option for low-risk PCa, offering comparable efficacy to traditional therapies with potentially fewer side effects. However, cost-effectiveness remains a consideration. The ongoing clinical trials and future research are expected to provide more definitive data on the role of proton therapy in PCa treatment.

Carbon ion therapy is currently offered in five countries: Japan, Germany, China, Italy, and Austria. A systematic review and meta-analysis comparing the clinical efficacy and safety of PBT and CIRT for PCa included 13 CIRT- and 20 PBT-related publications involving 54,101 participants. The quality of the studies was either low or moderate. Random model single-arm meta-analysis showed that both the CIRT and PBT have favorable efficacy and safety, with similar 5-year OS (94% vs 92%), the incidence of grade 2 or greater acute genitourinary (AGU) toxicity (5% vs 13%), late genitourinary (LGU) toxicity (4% vs 5%), AGI toxicity (1% vs 1%), and LGI toxicity (2% vs 4%). However, compared with CIRT and PBT, photon RT was associated with lower 5-year OS (72%-73%) and a higher incidence of grade 2 or greater AGU (28%-29%), LGU (13%-14%), AGI (14%-19%), and LGI toxicity (8%-10%). The meta-analysis showed the 3-, 4-, and 5-year local control rate of CIRT for PCa was 98%, 97%, and 99%, respectively; the 3-, 4-, 5-, and 8-year biochemical relapse-free rate was 92%, 91%, 89%, and 79%, respectively. Given that the quantity and quality of the available evidence are insufficient, more high-quality controlled studies are needed in

the future. The need for more CIRT high-quality controlled studies is evident to strengthen the evidence base, especially in the context of low-risk PCa.

Focal Ablative Therapies

As the trend for low-risk PCa has been to minimize the toxicity of treatment through AS, there has also been an increased interest in focal therapies, those which are targeted to PCa but do not treat the whole prostate gland. The rationale for such focal therapies is to provide therapeutic effect on the known cancer while limiting injury to normal tissues, such as bladder, rectum, and peripheral nerves.

The two approaches to focal therapy are cryoablation and high-intensity focal ultrasound (HIFU). Cryotherapy was initially developed in the 1960s and for many years has been used as a salvage treatment for post-RT local recurrence.

HIFU was developed in the 1990s first as a partial gland tumor–targeted therapy, and more recently as a "whole gland" therapy, although care is taken to avoid the urethra, bladder neck, and neurovascular bundles.

A systematic review and meta-analysis was performed in 2023, including both retrospective and prospective studies of at least 50 patients and follow-up of at least 5 years.[350] The meta-analysis pooled 29 studies, with 52% of patients having a GS of 6 or less and 32% with a GS of 7. Pooled BRFS rate (most using the Phoenix definition of BCR) for both cryoablation and HIFU was 69% at 5 years and 58% at 10 years. HIFU had somewhat better oncologic outcomes, with a 5-year BRFS of 73% compared to 64% for cryotherapy. When the cohort was evaluated by risk classification, 5-year BRFS ranged from 66% to 89%.

The review noted that complications were not always reported. However, in studies that reported urinary toxicity, rates of stricture, urinary retention, and rectourethral fistulae were 11%, 10%, and 0.7%, respectively. Erectile function was preserved in 37% of patients potent prior to ablation. HIFU studies overall reported better erectile preservation (46% vs 23% with cryoablation).

MRI guidance has also been applied to focal therapy. Ghai et al[351] reported the 6-month follow-up of a phase 1 trial of four patients treated with focal transrectal MRI-guided focused ultrasound in North America. The patients had PSA level of 10 ng/mL or less, tumor stage cT2a or less, and a GS of 6

(3 + 3). Under MRI guidance and real-time monitoring with MR thermography, focused high-frequency ultrasound energy was delivered to ablate the target tissue. MRI and repeat transrectal ultrasound-guided biopsy were performed 6 months after treatment. All four patients had normal MRI findings in the treated regions (100%); biopsy showed that three patients (75%) were clear of disease in the treated regions, representing complete ablation of five target lesions (83%). It was concluded that MRI-guided focused ultrasound is a feasible method of noninvasively ablating low-risk PCas with low morbidity.

Overall, focal therapy data have not yet matured, and there are minimal randomized comparisons to definitive curative intent options such as RP, EBRT, or BT. While these therapies continue to improve with better targeting technology, the excellent treatment options that already exist for low-risk PCa and which provide very high recurrence-free survival rates with low toxicity burden create a high bar for focal therapy to achieve.

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CHAPTER 73

Management of Intermediate- and High-Risk Prostate Cancer

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The management of clinically localized prostate cancer has changed considerably over the past 10 years. Fewer men are being treated for low-risk disease (eg, prostate-specific antigen [PSA] ,10 ng/mL, Gleason score [GS] ,7, and T-stage ,T2b), as more frequently, such men are being managed by active surveillance (AS).[1] Consequently, a higher percentage of men diagnosed with prostate cancer are now being treated with what is categorized as "intermediate-" (IR) to "high"-risk (HR) disease.[2] Concurrent with these developments, there has been a resurgence in enthusiasm among urologists for recommending radical prostatectomy (RP) as the treatment of choice for men with HR and locally advanced disease.[3,4] This trend appears to be in part fueled by the plethora of post hoc retrospective studies.[5-7] This practice is not supported, however, by other recent studies that attempt to account for the "quality of care delivered," defined as treatment delivered in compliance with national consensus guidelines nor is it supported by the findings from contemporary phase III randomized trials.[2,8-13] This chapter was written in an attempt to bring clarity to the controversies surrounding the management of patients currently considered to have IR and HR disease. We focus on the radiation-based therapeutic options and the evidence behind our recommendations. Since the last edition, a number of advances have been made in the technical delivery of radiation for prostate cancer, and some have now been established as "standard of care." Details on the management of low-risk prostate cancer can be found elsewhere in the textbook.

CLINICAL PRESENTATION

Patients with IR or HR prostate cancer *may* present with locoregional symptoms, but this is not common (although it appears to have increased after PSA screening declined). Lower urinary tract symptoms, when seen, may include nocturia, urinary frequency, urgency, decreased flow, incomplete voiding, intermittent flow, hesitancy, and, occasionally, erectile dysfunction (ED) and/or bloody ejaculations. Rarely, patients with bulky primary disease may present with urinary tract obstruction or difficulty in passing stool or even bloody stool. When patients do present with obstruction, aggressive local regional radiation including stereotactic body radiotherapy (SBRT) may be very effective at relieving this obstruction.[14] With increasing PSA and GS, the risk of metastases increases. Metastatic spread is generally sequential, proceeding from the prostate to the periprostatic pelvic lymph nodes, but some metastases appear to spread directly to the common iliac nodes and then to bone. Rarely, patients may present with renal failure, lymphedema of the lower extremities, and bone pain.

DEFINITIONS OF INTERMEDIATE- AND HIGH-RISK DISEASE

Risk Stratification Groups

Three prognostic factors have traditionally been used to define IR and HR patients: (a) clinical T-stage (generally based on palpation [although imaging when compelling is frequently included]), (b) the pretreatment PSA, and (c) the biopsy GS. To simplify treatment recommendations and prognostication, several risk classification schemes have been proposed by grouping patients who are thought to have similar biochemical and/or clinical outcomes.[15-18] Low risk is defined as meeting all the criteria: T1c to T2a, PSA less than 10 ng/mL, and GS 6 or less. Intermediate risk (IR) is defined as T2b to T2c, PSA 10 to 20 ng/mL, or GS = 7. HR prostate cancer is any of the following: T3a or higher, PSA greater than 20 ng/mL, or GS 8 to 10.[19] This system represents a modification of the system proposed by D'Amico et al,[20] and given the widespread acceptance of this system, for practical purposes, the readers should assume that we are referring to this classification system throughout this chapter.

Limitations of Risk Group Classifications, Age, and Biomarkers

Perhaps the greatest misunderstanding in using the risk groups based on PSA, GS, and T-stage is the implied assumption that each of these factors is roughly equally important. For example, a patient can be considered IR if either the clinical stage is T2b, PSA 10 to 20, *or* GS of 7. However, the clinical T-stage is relatively subjective with a high degree of interobserver variability. Pretreatment PSA appears to be a strong predictor of biochemical (PSA) recurrence, but a relatively weak predictor of cause-specific survival (CSS) and GS is the most powerful predictor of CSS, followed in importance by T-stage.[21] This has major implications for post hoc comparisons of the results of treatment wherein the distribution of these factors cannot be adequately controlled for. Of note, somewhat paradoxically, very high PSAs are not as important as most people think and very low PSAs can be associated with a worse prognosis.[22,23] Despite the clear importance of GS, it is important to understand the exceptions to the rule. At one extreme, patients whose GS = 3 + 4 but only 5% grade 4 behave more like a 3 + 3.[24] At the other end of the spectrum are patients with focal high grade (eg, GS = 4 + 4) who behave more like a GS = 7.[25-27]

Another major limitation of the risk groups most used is their dependence on biochemical failure (BF) or PSA relapse after radiation therapy (RT). In 2005, the Radiation Therapy Oncology Group (RTOG) and American Society for Radiation Oncology (ASTRO) co-sponsored a conference in 2005 in Phoenix, Arizona, and developed a revised definition for BF, now known as the "Phoenix definition" (to distinguish it from an earlier definition).[28] PSA relapse was defined as a rise of 2 ng/mL or more above the absolute PSA nadir. This definition was considered applicable only to patients treated with external beam radiation therapy (EBRT) with or without short-term androgen deprivation therapy (ADT). The date of failure is taken at the time of meeting the definition (ie, not backdated). Any salvage therapy initiated prior to meeting the criteria should also be declared as a failure. With the Phoenix definition, sensitivity and specificity are 64% and 78%, respectively. This definition to date continues to be considered the standard definition for BF but should *not* be used to determine cure rates (eg, compared to RP) nor should PSAs that are consistently rising be ignored in men who could potentially benefit from salvage therapies.[28-30]

In addition to the T-stage, GS, and PSA, other factors are known to impact outcomes. More than 20 years ago, a number of studies showed that the number and/or percentage of biopsy cores positive for prostate cancer (PPC) impacted the outcomes of patients treated definitively by RP or EBRT.[31,32] For example, status post-RP, those patients with less than 34% PPC had similar outcomes as low-risk patients (5-year PSA control 85% vs 91%), whereas patients with more than 50% PPC had similar outcomes as HR patients (5-year PSA control 30% vs 43%). The prognostic significance of PPC has also been reported to extend to prostate cancer–specific mortality (PCSM) in IR patients such that when stratified by 50% or less and more than 50% PPC, 7-year prostate cancer–specific survival was 100% versus 57% ($P = .004$).

In addition to the percentage of positive biopsies, an analysis of RTOG data demonstrated that older age (.70) was associated with a reduced risk of PCSM and metastases, after adjusting for the expected increased risk of non-PCSM in this subgroup.[33] This observation was recently extended and supported by a systematic review.[34] In this systematic review, Shaheen et al showed that for men older than 70 ± 5 years treated for prostate cancer with RT with or without ADT, age is a favorable prognostic factor, but for patients treated with RP, age is an adverse factor. For example, in patients undergoing RP when adjusted for other factors, older age is associated with a more advanced pathologic stage. Thus, older men treated with RT should also be expected to do worse, due to the more advanced stage. The more favorable outcome seen in association with RT suggests that the radiobiology of prostate cancer may be different in older men.

In this era of personalized medicine, biomarkers have become increasingly important. However, confusion exists surrounding the distinction between predictive and prognostic biomarkers. A predictive biomarker offers insights into improving outcomes, by enabling the determination of treatment responses between biomarker-positive and biomarker-negative patients.[35] Whereas a prognostic biomarker provides information about disease outcomes in patients, irrespective of any therapeutic interventions.[35] There have been a number of unsuccessful attempts to incorporate biomarkers as prognostic and/or predictors of response to RT with or without ADT-based treatments.[36-42] More recently,

however, a number of studies have demonstrated that some biomarkers can offer prognostic insight.

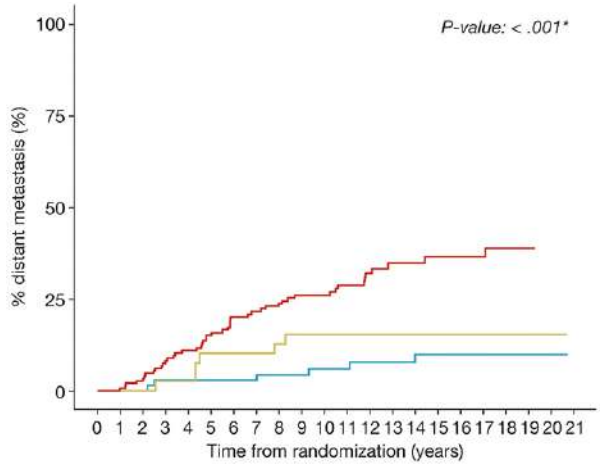
Tissue-Based Molecular Biomarkers

Among the rigorously validated risk stratification assays, at least three rely on multigene analysis (Decipher, Oncotype Dx Prostate, and Prolaris), whereas ProMark is founded on protein analysis.[43]

Prolaris uses reverse transcriptase polymerase chain reaction (RT-PCR) to determine the expression of 31 genes associated with cell cycle progression (CCP) and 15 housekeeping genes in tumor samples obtained from RP, biopsy, and transurethral resection of the prostate (TURP). The ensuing analysis generates the CCP score aimed at evaluating disease aggressiveness, which has the potential to predict clinical outcomes. Retrospective analyses have demonstrated that the CCP score can predict biochemical recurrence (BCR) following RP, and with patients whose disease was diagnosed after a TURP, it was useful in predicting the time to death from prostate cancer.[44] In a cohort with localized prostate cancer managed conservatively, the CCP score obtained on biopsy specimens was predictive of the 10-year risk of prostate cancer death.[45] Furthermore, in a pooled analysis of 1,062 patients with localized prostate cancer treated with either RP or RT, the CCP score showed a correlation with the 10-year risk of metastasis, indicating its utility as a risk stratification tool.[46]

Decipher generates a score ranging from 0 to 1.0 by analyzing the expression of 22 genes in samples collected from either a prostate biopsy or RP. These 22 genes are involved in diverse cellular processes, including cell proliferation, differentiation, adhesion, motility, CCP, and immune response.[47] When analyzing a biopsy specimen, the Decipher score can classify a patient into either HR, IR, or low-risk group, informing decisions about treatment or surveillance.[48] In the postprostatectomy setting, this score, which correlates with adverse pathology, has been proposed as a guide to the selection of therapeutic interventions, including adjuvant versus salvage therapy or no treatment.[48] Genomic classifier groups were initially selected and validated using retrospective cohorts composed of RP specimens and pretreatment biopsy samples, and further validated using prospective patient cohorts.[48] Analysis of a retrospective cohort of patients

who underwent RP revealed relatively small differences in the cumulative incidence of metastasis and PCSM between the low-risk group and the favorable IR group, or between the unfavorable IR and HR/very HR groups. However, using the clinical genomic risk system, statistically significant differences in outcomes, including the cumulative incidence of metastasis and PCSM, were observed between the low, intermediate, and high tiers.[48] The use of the Decipher-based clinical genomic classification appears to improve our ability to accurately identify prognostic subgroups and potentially improve our ability to make more logical therapeutic recommendations for patients. For instance, data by Spratt et al demonstrated that 15% of patients initially said to have a low-risk disease, for whom AS could have been considered, would be reclassified as IR based on the clinical genomic risk system and, as such, may not have been suitable for AS. Conversely, up to 56% of those patients classified as favorable IR group could be reclassified into the low-risk group based on the clinical genomic risk grouping system, potentially qualifying them for AS.[48] While early efforts to validate biomarkers were relatively unfruitful, genomic classifiers have been shown to be highly prognostic in patients treated with definitive EBRT, based on patients treated on multiple phase III randomized trials conducted by the NRG (Figure 73.1).[37,49] Even more recently, this genomic classifier has been shown to be predictive of the benefits of dose escalation in patients with IR prostate cancer (Figure 73.2).[50]

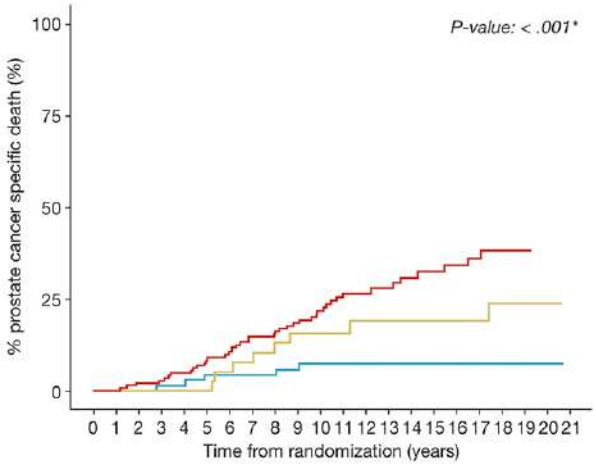


High	150	103	47	13	
Intermediate	41	33	19	6	2
Low	74	65	41	20	4

Number of patients at risk

High	15% (9%-21%)	26% (19%-33%)	36% (27%-46%)
Intermediate	10% (1%-19%)	15% (4%-27%)	15% (4%-27%)
Low	3% (0%-7%)	6% (0%-11%)	10% (2%-18%)

Event rate (95% CI)



High	150	114	55	13	
Intermediate	41	37	20	6	2
Low	74	65	41	21	4

Number of patients at risk

High	8% (4%-13%)	22% (15%-29%)	32% (23%-41%)
Intermediate	0% (0%-0%)	16% (4%-27%)	19% (6%-32%)
Low	4% (0%-9%)	7% (1%-13%)	7% (1%-13%)

Event rate (95% CI)

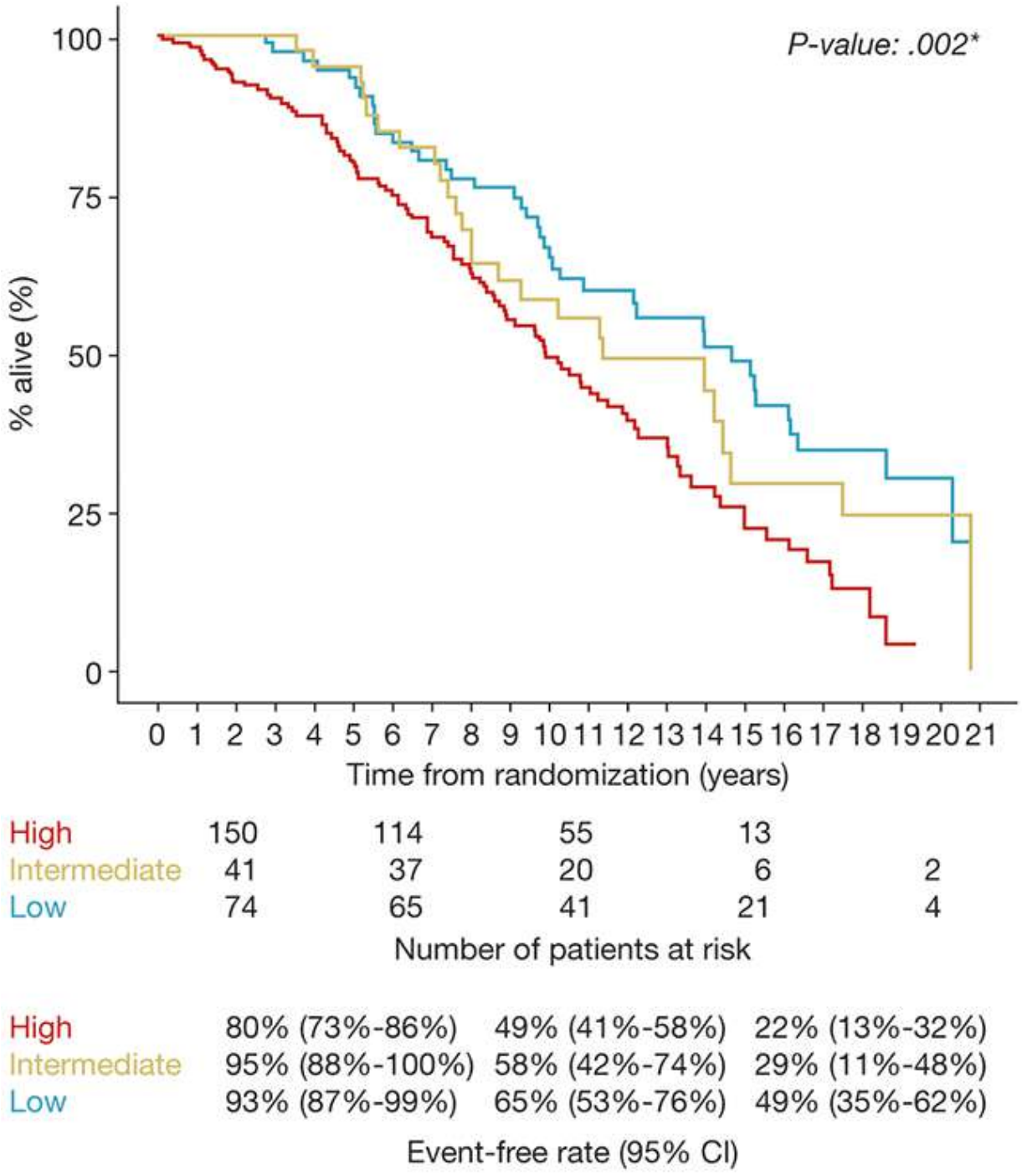


FIGURE 73.1 Cumulative incidence estimates of distant metastasis, prostate cancer–specific mortality, and Kaplan-Meier estimates of overall survival by genomic classifier low-(,0.23), intermediate- (0.23-0.32), and high-risk (.0.32) groups. CI, confidence interval. *Comparative analyses between groups were performed using Kruskal-Wallis test for continuous variables (Adapted from Nguyen PL, Huang HR, Spratt DE, et al. Analysis of a biopsy-based genomic classifier in high-risk prostate cancer: meta-analysis of the NRG Oncology/Radiation Therapy Oncology Group 9202, 9413, and 9902 phase 3 randomized

trials. *Int J Radiat Oncol Biol Phys*. 2023;116[3]:521-529. http://creativecommons.org/licenses/by/4.0/.)

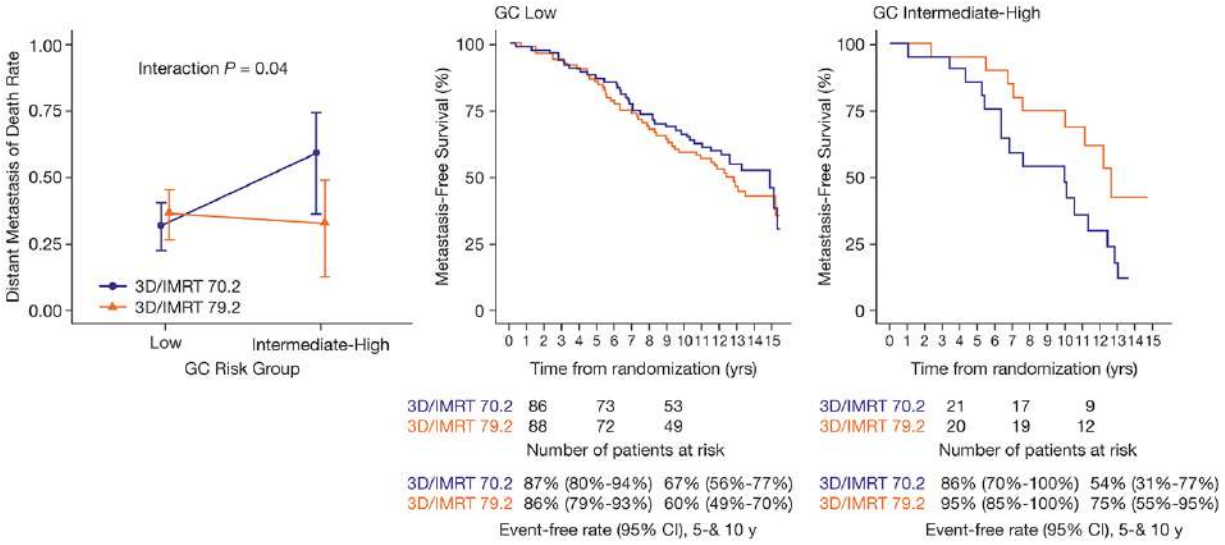


FIGURE 73.2 Interaction plot for GC risk group and randomization arm for the metastasis-free survival end point. CI, confidence interval; GC, genomic classifier; 3D/IMRT, three-dimensional intensity-modulated radiation therapy. (Reprinted from Spratt DE, Liu VYT, Michalski J, et al. Genomic classifier performance in intermediate-risk prostate cancer: results from NRG Oncology/RTOG 0126 randomized phase 3 trial. *Int J Radiat Oncol Biol Phys*. 2023;117[2]:370-377. Copyright © 2023 Elsevier. With permission.)

The Oncotype Dx Prostate Cancer Assay employs RT-PCR to assess the expression of 5 reference genes and 12 cancer-related genes on biopsy samples. These cancer-related genes are implicated in various pathways, such as androgen pathway, stroma response, cell proliferation, and organization. From these gene analyses, the Genomic Prostate Score (GPS), ranging from 0 to 100, is derived.[51] The Oncotype Dx Prostate Cancer Assay has been validated in biopsy specimens and demonstrated its ability to predict the likelihood of high-grade disease and adverse pathologic features, including extracapsular extension (ECE) and seminal vesicle invasion (SVI) after RP.[51,52] A primary objective of the GPS is to aid therapeutic decisions in patients diagnosed with low-risk or low-IR prostate cancer.[53] Indeed, analysis of oncologic practices has shown that the use of the GPS led to an increase in recommendation for AS in cohorts with very low- and low-risk prostate cancer.[54] While the GPS has been validated for predicting adverse pathologic features after RP, emerging evidence suggests

that it may also independently prognosticate clinical outcomes, including time to BF, distant metastasis (DM), and prostate cancer–related mortality after EBRT.[55] However, further validation through prospective studies is still warranted.

ProMark is a proteomic assay based on the expression of eight proteins detected using immunofluorescence in tumor specimens. These proteins are involved in various cellular processes, including proliferation, differentiation, survival, and metabolism.[56,57] Through the analysis of these proteins, a risk score from 0 to 1 is generated, aiming to categorize patients into favorable or nonfavorable disease pathology groups. Validation studies have shown that for a risk score of 0.33 or less, the ProMark assay can identify individuals with favorable pathology among a cohort of very low-risk, low-risk, and favorable IR disease, with positive predictive values (PPV) of 95% and 81.2%, respectively, who may be suitable for AS. Conversely, a risk score greater than 0.8 has a PPV of 76.9% for nonfavorable pathology, and such PPV is nearly 100% for a score greater than 0.9.[57]

Although initial validation studies mainly involved American men of European ancestry, comprising 94%, 76%, and 86% of patients for Prolaris, Oncotype Dx Prostate, and Decipher, respectively, it is important to extend their application to African American (AA) men as well.[58] Howard et al evaluated the performance of the Decipher genomic classifier in the post-RP setting to predict outcome (5-year metastasis and PCSM) in a cohort of 548 patients, 55% of whom were AA men. It followed that Decipher was a strong predictor of these outcomes and race was not found to impact the performance of Decipher.[59]

Artificial Intelligence–Based Biomarker

Tissue-based biomarkers have the potential to transform the risk stratification of patients with prostate cancer. Among the limitations that have hindered the widespread use of tissue-based biomarkers have been the absence of validation through prospective randomized trials, the financial burden incurred due to limited insurance coverage, and the lack of direct comparison among these tissue-based biomarkers.[60] The Multimodal Artificial intelligence (MMAI) has emerged as a promising solution to

address some of these challenges, given its capacity to analyze large data sets, including digitized images, at a lower cost than other tissue-based biomarkers. Esteva et al utilized digital histopathology and clinical data, including age, PSA, and GSs (combined, primary, and secondary), from five NRG Oncology phase III randomized clinical trials (RTOG-9202, RTOG-9408, RTOG-9413, RTOG-9910, RTOG-9910, and RTOG-0126), to develop an MMAI as a digital biomarker (Figure 73.3). The resulting prognostic model performed better than currently used risk stratification tool across all selected end points, including 5- and 10-year BF, 5- and 10-year DM, 10-year prostate cancer–specific survival, and 10-year overall survival (OS).[61] More recently, this MMAI approach has been shown to also be predictive of the need for ADT in patients with IR disease (Figure 73.4).[62]

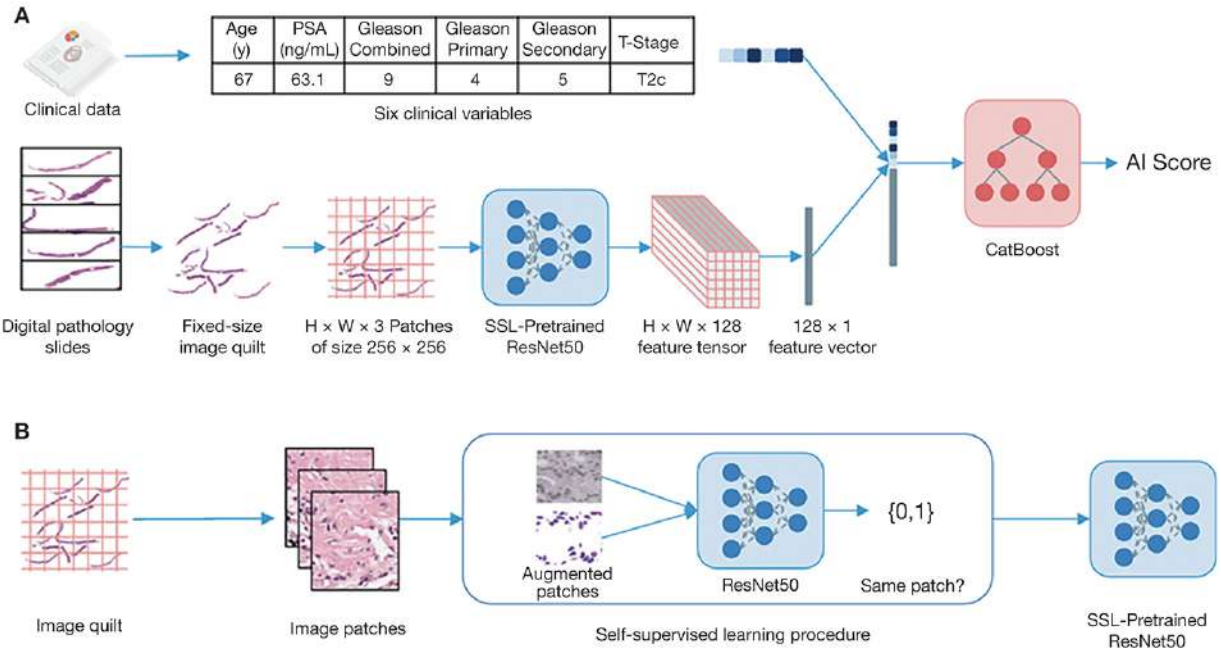


FIGURE 73.3 Multimodal deep learning system and data set. A. The multimodal architecture is composed of two parts: a tower stack to spare a variable number of digital histopathology slides and another tower stack to merge the resultant features and predict binary outcomes. B. The training of the self-supervised model of the image tower stack. AI, artificial learning; PSA, prostate-specific antigen. (Reprinted from Esteva A, Feng J, van der Wal D, et al. Prostate cancer therapy personalization via multi-modal deep learning on randomized phase III clinical trials. *NPJ Digit Med*. 2022;5[1]:71. http://creativecommons.org/licenses/by/4.0/.)

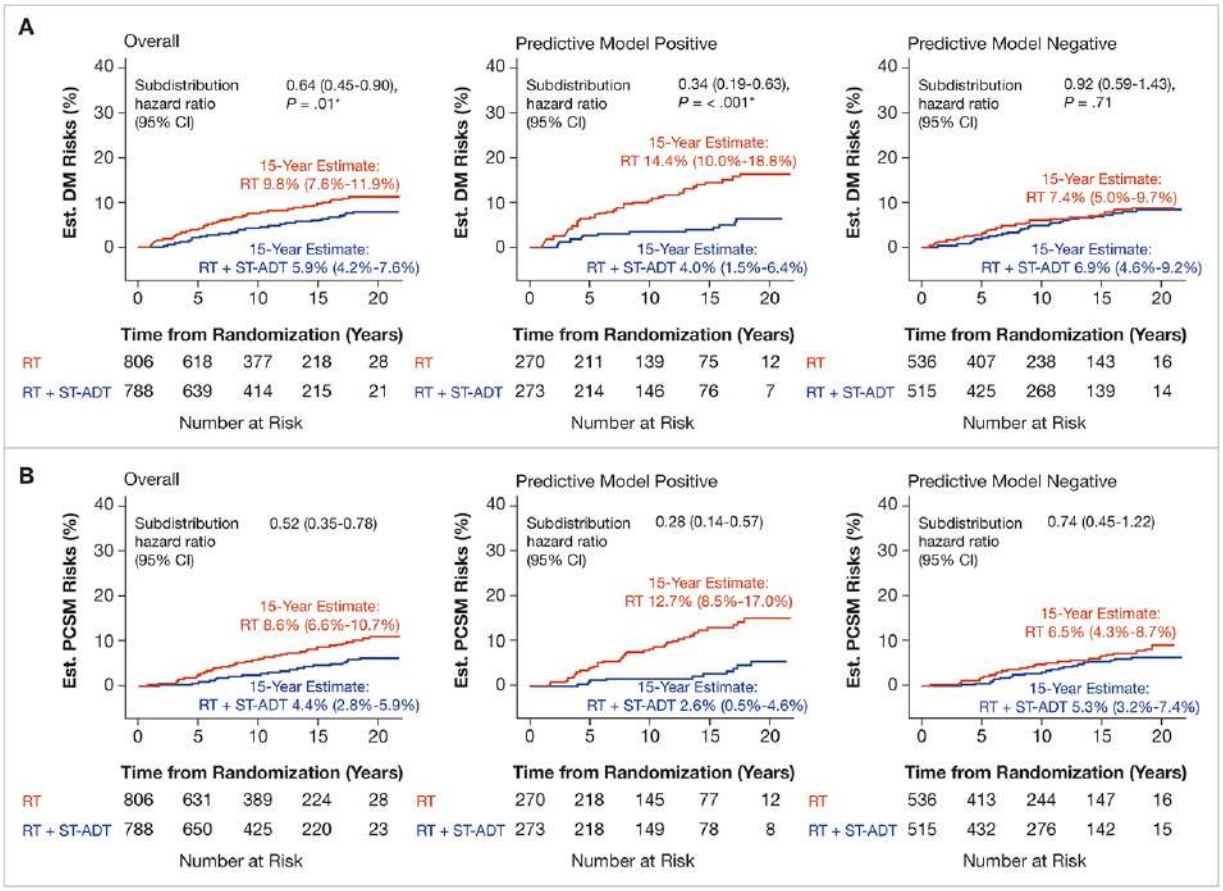


FIGURE 73.4 Cumulative incidence in the validation cohort (NRG/RTOG-9408) of histopathology-imaged patients by artificial intelligence predictive model subgroups for distant metastasis (A) and prostate cancer–specific mortality (B). ADT, androgen-deprivation therapy; CI, confidence interval; DM, distant metastasis; PCSM, prostate cancer–specific mortality; RT, radiation therapy; RTOG, Radiation Therapy Oncology Group. (From Spratt DE, Tang S, Sun Y, et al. Artificial intelligence predictive model for hormone therapy use in prostate cancer. *NEJM Evid*. 2023;2[8]:EVIDoa2300023. Copyright © 2023 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

#1 Beware of Randomized Trials that Are Too Small and Heterogeneous Patient Selection!

Roach et al assessed the performance of a novel MMAI tool across racial groups (AA and non-AA men) treated for localized prostate cancer during phase III randomized clinical trials (NRG/RTOG-9202, RTOG-9408, RTOG-9910, RTOG-0126) using an "algorithmic fairness" framework. The MMAI algorithms demonstrated strong prognostic signals for DM and PCSM in both AA and non-AA patient subgroups. Despite biases associated with general artificial intelligence (AI) use, no issues related to "algorithm

fairness" were observed with these cohorts of patients using MMAI models.[63] These findings suggest that AI biomarkers may be used across racial groups (AA and non-AA) for treatment selection.

Altogether, molecular- and AI-based biomarkers have substantially changed our understanding of how to select patients who need dose escalation and ADT.[50,62]

Cautionary Notes on Selected Phase III Randomized Prostate Cancer Trials

Much of the confusion concerning the optimum management of men with IR to HR prostate cancer comes from the misinterpretation of high-profile phase III randomized controlled trials (RCTs). There are what can be called the "three classic sins" in trial design that are common to a number of these trials: (1) selection criteria, "you can't prove something does not work by treating people who don't need it"; (2) statistical power, "you can't prove something does not work with an underpowered study"; and (3) nonoptimized interventions, "you can't prove something does not work if it is not done properly."

The first "sin" arises in part because when eligibility criteria for a trial are defined, they are usually heterogeneous in terms of their impact on prognosis, and prior to enrollment, there is no simple way to guarantee what the distribution of prognostic factors will be. The design of underpowered studies tends to arise in part because for most studies, the data necessary to accurately estimate the required sample size do not exist; thus, assumptions and guesses must be made. In addition, investigators tend to be overly optimistic about their ability to accrue patients, do not adequately account for stage migration, changes in practice patterns, and relevant new information about treatment. Another sin arises from the use of nonoptimized interventions, it tends to arise from the fact that it can take several years to design and launch a trial. Unfortunately, prior to completion of the trial, the standard of care could change, making the intervention being studied no longer relevant.

An example of a high-profile trial committing these "three sins" is the GETUG-01 (Groupe d'Etude des Tumeurs Uro-Génitales) trial. This French multicenter phase III reported by Pommier et al concluded that there was no

value to the use of prophylactic lymph nodal irradiation.[64] The majority of the patients did not have HR disease (ie, risk of positive nodes ,15%) (sin #1), not only was this trial grossly underpowered with only 203 men with a risk of lymph node involvement (LNI) more than 15% (sin #2), but *none* of the patients actually received "whole-pelvic" EBRT but instead were treated using a "mini-pelvic" technique (sin #3).[65] The limitations of trials are discussed in more detail elsewhere.[66]

Another example of a trial committing these three sins is the trial reported by Nabid et al[67] This RCT has been purported to support the notion that 18 months of long-term ADT is as effective as 36 months in 630 men with HR prostate cancer receiving EBRT.[67] Based on these data, some physicians have concluded that it has established a "new standard of care" for HR patients.[68] However, there were several methodological issues that we and others have pointed out.[66] First, the patients in general were probably not as HR as the earlier study conducted by the European Organization for Research and Treatment of Cancer (EORTC) that required clinical evidence of locally advanced disease (ie, "palpable T3-4") and allowed some node-positive patients (~9%).[69] Furthermore, pretreatment PSA greater than 20 ng/mL (a less powerful predictor of survival) alone was not included for the eligibility criteria for the earlier HR study (PSAs up to 160 ng/mL were allowed). The earlier EORTC trial verified that 6 months of ADT was *inferior* to 36 months, based on an assessment of 970 patients (~50% more patients than the Nabid trial). To prove that lengthening ADT by 12 months (ie, 18 months) was *noninferior* should be expected to require at least as many patients, particularly if they were lower risk (eg, fewer T3 patients). However, they chose to perform a *superiority* trial, which could be done with fewer patients. At 5 years, they noted a trend for a better OS favoring 36 months over 18 months (91% vs 86%; *P*-value of .07). Also of note, the 10-year BF at 10 years (25% vs 31%) and disease-free survival (DFS) (45% vs 39%; $P = .08$), favoring 36 months over 18 months. Had the trial been much larger it is likely that these differences in outcome would have been clearer. Further evidence that this study Nabid et al[67] was underpowered is supported by the observation that known prognostic factors such as GS and T-stage were also not significant predictors of outcome. The desire to shorten the duration of ADT is admirable, and many

patients would love to be spared the unnecessary use of ADT, but for most, a loss of life may be deemed an excessive price.

The three trials evaluating the role of salvage radiotherapy (SRT) versus adjuvant radiotherapy (ART) in the postoperative setting are perhaps the best examples of the concept of violating the "three sins" and discussed in detail in the section on postoperative RT. In addition to the "three sins" of clinical trial design and implementation (described earlier), there is a hazard of biased large post hoc retrospective studies comparing surgery versus RT and/or assessing post-treatment toxicity.

#2 Beware of Large Post Hoc Population-Based and Biased Retrospective Studies!

Unfortunately, urologists have continued to publish a plethora of fundamentally flawed large and small retrospective studies attempting to prove that RP is more effective than RT at curing prostate cancer.[5,6] The systematic review and meta-analysis published by Wallis et al garnered the most attention when first published. A review of some of the biases and some of the numerous methodological flaws have been touched on previously.[9,10,70] Most noteworthy was the decision to use an unreliable method to assess bias, the incorporation of studies with biases previously shown to have incorporated unreliable data, and the failure to include RT series with contemporary management techniques.[10,71,72] Also of concern is the dependence on data extracted from national registries and databases such as the Surveillance, Epidemiology, and End Results (SEER), the National Cancer Database (NCDB), or the Cancer of the Prostate Strategic Urologic Research Endeavor.[10,73-75] There are numerous limitations using these population-based registries and databases that require comment.[6,76] First, after adjusting for all available factors (many excluding PSA data), SEER data continue to show evidence of a selection bias, in favor of the results of patients treated by RP, even when compared to patients who do not have prostate cancer.[77] This observation is strongly supported by a study from Johns Hopkins demonstrating that men undergoing RP had an all-cause mortality standardized mortality ratio (SMR) less than half of men in the general population (SMR = 0.47, 95% confidence interval [CI] 0.44-0.49).[76] Of note, their risk of death from second cancers was also less than

half of men in the general population (SMR = 0.45, 95% CI 0.40-0.49), highlighting the fact that post-RP patients *should not* be considered an appropriate control group for estimating the risk of second cancer in patients treated with RT.

Additional limitation arises from attribution bias. For instance, in a study examining the survival of men with high-grade prostate cancer, death was attributed to prostate cancer if it was listed as the primary or contributing cause of death, meaning that prostate cancer appeared on the first three lines of the death certificate.[78] Thus, potentially leading to a misattribution in the cause of death, in part because men undergoing RT tend to older, have more comorbidity. If a man is more likely to die from these things, even a small absolute error rate can result in highly statistically significant differences being asserted when large data sets such as SEER are used. Hoffman et al evaluated the concordance between prostate cancer–related deaths recorded on death certificates by the New Mexico Bureau of Vital Statistics and evaluations by board-certified physicians, experts in cancer epidemiology, who independently reviewed the clinical data, in 1985 and 1995. This assessment revealed a net misattribution rate of 16.8% in 1995 compared to 1.9% in 1985. Over this period, crude prostate cancer mortality increased by 33.5%; however, after adjusting for misattribution, the increase in prostate cancer mortality was only 15.9%, indicating that approximately half of the observed rise in prostate cancer deaths could be attributed to misattribution.[79]

Most studies indicating a potential benefit of RP over RT in localized prostate cancer have relied on data from registries, thus subjected to the biases and limitations mentioned earlier.[5,73-75] However, a Swedish RCT that compared RP to high-dose rate (HDR brachytherapy plus EBRT) in localized/locally advanced prostate cancer found no significant difference in treatment outcome and health-related quality of life (QoL) and complications, including urinary incontinence, bowel, and sexual functions after a 10-year follow-up between the two groups.[11] It is worth noting that this study was underpowered. The ProtecT trial is a randomized study that accrued over 1,500 men that evaluated the efficacy of three interventions: RT, RP, and active monitoring in patients with localized prostate cancer.[80] Subsequent stratification of study patients revealed that 34% had IR or HR prostate cancer.[81] After a median follow-up of 15 years, death from any

causes was similar across all three interventions groups. Specifically, prostate cancer survival rates were 96.6%, 97.2%, and 97.7% for active monitoring, RP, and RT, respectively; more importantly for freedom from progressive disease was similar with RP and RT.[82] Furthermore, no new treatment-induced side effects were observed beyond those reported during the 10-year analysis.[12] This suggests that based on randomized studies available thus far, there seems to be no difference in outcomes between RP and RT.

While we await the results from SPCG-15, a prospective phase III trial that randomized patients with locally advanced prostate cancer to RT with ADT or RP, a reliability score (RS) has been proposed to assist in assessing the trustworthiness of conclusions drawn from studies comparing the effectiveness of RP to RT with or without ADT.[83,84] This scoring system evaluated various aspects of a study, including the data source, the appropriate use and duration of ADT, the provision of the Charlson comorbidity index, additional comorbidity adjustments, sample size, adjustment of survival curves for prognostic factors, and the provision of cancer-related prognostic factors, such as GS, T-stage, and PSA levels. Using this framework, studies with high RS, indicating greater reliability, typically demonstrate minimal differences, often less than 1%, in 10-year CSS between men treated with RP and those undergoing RT.[84] Table 73.1 summarizes the key points highlighted earlier regarding the misconception that RP is more effective than RT.

TABLE 73.1 SELECTED MYTHS REGARDING INTERMEDIATE- AND HIGH-RISK PROSTATE CANCER

Myth and Example of Arguments	Arguments Against the Myth	Comments
"RP is associated with better OS than RT ± ADT." *Sources of data: Observational databases and registries (SEER, NCDB, CaPSURE, etc)*[73-75]	Existing RCTs: No difference in OS	Swedish randomized trial[a]: No difference in OS, HRQoL, and complications at 10 y[11] ProtecT trial[b]: Similar PCS with RP, RT, and AM at 15 y[82]
	Biases with observational databases and registries:	Selection bias: Lower all-cause mortality in RP pts

Myth and Example of Arguments	Arguments Against the Myth	Comments
	• Selection bias • Attribution bias	compared to noncancer control group[77] Attribution bias: Misattribution in the cause of death[78,79]
	Older age (.70 ± 5 y): Risk factor for RP but not for RT	30-d mortality after RP: 3-fold increase with each decade increase in age[104] Outcome of RT and RP in older patients (70 ± 5 y)[34]: • 74% of RT studies: Age associated with better outcome or trend toward better outcome; age not linked to worse outcome • 50% of RP studies: Age associated with worse outcome; older age not linked to favorable outcome
"Sexual function not worse after RP compared to RT± ADT with long-term follow-up" *Based on similar sexual function scores*[73,91,92]	Sexual function of RP patients better at baseline RT patients older with more comorbidities	Larger decrease in sexual functions in RP pts than RT patients in long term Older age and comorbidities associated with sexual dysfunctions[93,94]
"RT is available as a 'salvage' option for recurrences after RP, but there are no good 'salvage' options (such as RP) for recurrences after RT." *Challenges with salvage RP after RT: Poor wound healing, RT-induced fibrosis, intra-op injuries, stricture,*	There are multiple published surgical and nonsurgical series documenting "salvage" options for patients recurring after RT with .160 studies including .10,000 patients documenting the effectiveness of "salvage" results.	Meta-analysis data-modality 5-y RFS[97]: RP 54%, SBRT 60%, HDR 60%, LDR 56%, cryotherapy 50%, HIFU 53% Phase II trial salvage LDR after EBRT 10-y outcomes[98]: OS 70%; DSS 70%; LF 5%; DF 19%

Myth and Example of Arguments	Arguments Against the Myth	Comments
and anastomotic leaks[95,96]		
"Prostate cancer is inherently more aggressive in AA men than other races." *Genetic mutations favoring aggressive disease*[99]	AA have lower survival in multiple other cancer types.	Lower survival for AA in breast, colorectal, esophageal, lung, cervix, bladder, and uterine cancers[100] Prostate cancer biology in AA men likely not the culprit[99]
	Racial disparities in screening, early detection, quality care, and urology practice	2012-2018→ higher decline in PSA testing in AA men than other groups[101] AA men less likely to undergo MRI after elevated PSA compared to White men[102] Medicare recipients AA men less likely to receive definitive treatment[103]
	Biomarkers performance not affected by race	Cohort of 548 men (55% AA), Decipher predictive, and race did not impact the performance.[59] MMAI algorithms applied to phase III RCTs[c]: Strong and equally prognostic for DM and PCSM in AA and non-AA men[63,d]
	Same QoC: Black race not an adverse prognostic factor	Most phase III RCTs suggest race is not an independent prognostic factor[105] (see Table 73.2).

AA, African American; ADT, androgen-deprivation therapy; AI, artificial intelligence; AM, active monitoring; CaPSURE, Cancer of the Prostate Strategic Urologic Research Endeavor; DF, distant failure; DM, distant metastasis; DSS, disease-specific survival; HDR, high-dose rate; HIFU, high-intensity focused ultrasound; HRQoL, health-related quality of life; LDR, low-dose rate; LF, local failure; MMAI, multimodal AI; NCDB, National Cancer Database; OS, overall survival; PCS, prostate cancer survival; PCSM, prostate cancer–

specific mortality; QoC, quality of care; RCT, randomized clinical trial; RFS, relapse-free survival; SEER, Surveillance, Epidemiology, and End Results.

[a]Underpowered study.

[b]One-third of all patients had intermediate- or high-risk prostate cancer.

[c]NRG/RTOG-9202, RTOG-9408, RTOG-9910, RTOG-0126.

[d]Abstract.

TABLE 73.2 IMPACT OF RACE ON CLINICAL TRIAL THERAPEUTIC INTERVENTIONS

Reference	Therapy	Stage	Patients	Conclusions and Comments
Crawford et al[106]	Leuprolide ± flutamide	D2	603	Black race not associated with worse outcome
Vogelzang et al[107]	Goserelin vs orchidectomy	D2	283	Race not significant
McLeod et al[108]	LHRH drugs + bicalutamide or flutamide	D2	813	No significant effect of race on outcome (similar benefits expected in either race)
Thompson et al[109,a]	Orchiectomy ± flutamide	mCPC	1,263	AA men with metastatic disease had worse prognosis not explained by explored variables.
Roach et al[110]	RT ± LHRH or flutamide	T1-T4 Nx-1	2,048	Race was not significant.
Halabi et al[111]	CALGB randomized trials	CRPC	1,183	No difference in OS between Blacks and Whites with metastatic hormone–refractory prostate cancer
Roach et al[112]	RTOG 9202	Locally advanced	1,514	Race not associated with poorer outcome
Spratt et al[113]	Pooled analysis on data from five modern trials	mCRPC	1,613	No significant difference in survival between Black and White races
Sartor et al[114]	Sipuleucel-T (PROCEED trial: phase III)	mCRPC	657	Sipuleucel-T–treated AAs, improved OS compared to Caucasians. The largest difference at lower PSA (implications for immunotherapy)
Halabi et	Docetaxel	mCRPC	8,820	Increased OS in Black vs White men

Reference	Therapy	Stage	Patients	Conclusions and Comments
al[115]				
Dess et al[116]	Therapeutic interventions from 3 cohorts[b]	Localized to metastatic	.300,000	Black race not associated with inferior stage-for-stage PCSM
Ma et al[117]	RTOG trials[c]	Clinically localized	5054	Better biochemical control in AA vs non-AA men

AA, African American; CALGB, Cancer and Leukemia Group B; LHRH, luteinizing hormone–releasing hormone; mCPC, metastatic prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PCSM, prostate cancer–specific mortality; ROTG, Radiation Therapy Oncology Group; RT, radiation therapy; SEER, Surveillance Epidemiology and End Results; VA, Veterans Administration.

[a]Only RCT suggesting a worse outcome for AA men.

[b]Mixed cohorts SEER (*n* = 296,273); five centers within the VA (*n* = 3,972), and four RTOG phase III trials (*n* = 5,854).

[c]RTOG-9202, RTOG-9408, RTOG-9413, RTOG-9902, RTOG-9910, RTOG-0126, and RTOG-0415.

Adapted with permission from Roach M III, Coleman PW, Kittles R. Prostate cancer, race, and health disparity: what we know. *Cancer J*. 2023;29(6):328-337.

Androgen Deprivation Therapy and/or Other Drugs and Survival From Prostate Cancer

Short-term ADT for unfavorable IR and long-term ADT for HR prostate cancer has become the mantra for managing these subsets of patients.[8] In addition, there is a growing body of data that suggest that for men with locally advanced disease being managed with definitive RT, there may be benefits associated with adding chemotherapy and/or "next-generation" drugs as well.[85-87] While the addition of chemotherapy yielded negative (RTOG 9902) or relatively unconvincing results (RTOG 0521), the addition of "next—generation" agents seems more promising. For example, STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) was a large, RCT (*n* = 1,917), complicated by its very heterogeneous design. STAMPEDE included patients with metastatic and nonmetastatic disease (the latter including node-positive patients with HR localized prostate cancer), making it difficult to parse out who benefited the most. Per protocol, EBRT was mandated for patients with node-negative, nonmetastatic disease and

"encouraged" for those with positive nodes. The primary outcome measure was OS, with failure-free survival (treatment failure was defined as radiologic, clinical, or PSA progression or death from prostate cancer) as an "intermediate primary outcome." The authors concluded that "among men with locally advanced … prostate cancer, ADT *plus* abiraterone … was associated with significantly higher rates of overall and failure-free survival than ADT alone …." However, they reported no OS advantage for "nonmetastatic" patients and no trend for benefits for men older than 70 years of age (the median age for men treated on previous phase III RTOG trials involving RT and ADT). Thus, although encouraging, it remains unclear of the role of abiraterone in the setting of typical HR prostate cancer managed with ADT and EBRT, particularly in those older than 70 years of age (who may have more favorable biology as mentioned earlier).

#3 Beware of Confusion Concerning the Importance of Radiation Dose and Volume!

We (radiation oncologist) have been a bit illogical, concerning our interpretation of the data from trials involving the three most commonly "tweakable" interventions—radiation dose, radiation volume, and the use of ADT. Despite a plethora of trials involving dose-escalated radiation, all failing to prove that higher doses improve OS, high doses have become standard of care (see JNCI and other consensus guidelines). These studies have generally demonstrated improved biochemical control based on PSA but at increased cost and in some cases with increased toxicity. Despite the improvements in PSA control associated with whole-pelvic radiation therapy (WPRT) in at least three well-powered phase III trials, nearly half of radiation oncologists have not adopted WPRT as standard for HR patients (personal communication, based on an informal audience surveys).[88-90] Also of concern is the willingness of radiation oncologists to completely abandon ADT or shorten or lengthen the duration or based on post hoc retrospective data, despite their lack of reliability. Omitting ADT because "maybe, it would not be needed if higher doses of radiation were used" is potentially dangerous and should require a randomized trial to justify.

Selected Myths Regarding Intermediate- and High-Risk Prostate Cancer

In addition to the misconception that RP is associated with a better OS than RT, we highlight existing myths associated with IR and HR prostate cancer (Table 73.1). Another common myth is that after a long-term follow-up, RP does not lead to a worse sexual function compared to RT with or without ADT. A commonly used argument to support this myth is that the sexual function scores are similar after long-term follow-up.[73,91,92] While sexual function at long follow-up may be similar as reported, it is important to remember that in these studies, patients undergoing RP had significantly better sexual functions before treatment initiation than those treated with RT, highlighting the fact that RP patients experience a larger decline in sexual functions than RT patients. Furthermore, RT patients tend to be much older with more comorbidities than patients undergoing RP, two factors (older ager and comorbidities) that are known to be associated with sexual dysfunctions.[93,94]

Another myth that is commonly mentioned by urologists is that RT is available as a salvage option for recurrences after RP, but there are no good "salvage" options for recurrences after RT. While it is true that there are reports of poor wound healing, intraoperative injuries, strictures, and anastomotic leaks after salvage RP, not all series report such negative results.[95,96] Furthermore, in addition to surgical salvage, there are numerous nonsurgical salvage options after RT including SBRT, brachytherapy (HDR and low-dose rate [LDR]), cryotherapy, and high-intensity focused ultrasound with documented effectiveness.[97,98]

There is also a myth that prostate cancer is more aggressive in AA men than other races. An argument used in support of this myth includes genetic mutations in AA men favoring aggressive disease.[99] However, numerous other cancers including breast, colorectal, esophageal, lung, and cervix are associated with lower survival in AA, suggesting the existence of other etiologies.[100] It is highly likely that such etiologies comprise racial disparities, including in screening, early detection, and quality of care.[101-103] Moreover, when such quality of care is the same across all treated patients, Black race is not an adverse prognostic factor and, in some instances, AA men tend to have better outcomes (Table 73.2).

Novel Imaging Techniques: Implications of Nodal Imaging for Radiation Therapy

Until very recently, imaging contributed relatively little to the management of patients with clinically localized prostate cancer, such that the patient eligibility for early RTOG trials has initially been based primarily on palpation T-stage.[118] This philosophy was by necessity largely based on the fact that neither CT nor magnetic resonance imaging (MRI) has been shown to be sensitive or specific enough to be routinely used to rule out LNI.[119] In the absence of definitive evidence of the presence and location of LNI, a class solution is used to design radiation fields when WPRT is intended.[120,121] However, there are at least three imaging approaches that may compliment the use of class solutions—positron emission tomography (PET) imaging, the use of lymphotropic nanoparticles, and sentinel lymph node imaging, with the first of these options becoming the standard of care.

The use of prostate—specific membrane antigen (PSMA)-based PET imaging for staging and managing unfavorable IR and HR prostate cancer has been rapidly adopted in the United States over the past 5 years. This practice evolved after a compelling body of evidence primarily from Europe and Australia demonstrated the utility of PSMA-PET imaging. Subsequently, the hard work of investigators in the United States resulted in U.S. Food and Drug Administration (FDA) approval.[122-128] The underlying principle for approval was based on studies showing superiority to conventional imaging such as CT scans and better than other available imaging agents.[129-131] For example, higher detection rates have been observed with ^{68}Ga-PSMA-PET/CT compared to ^{11}C-choline PET/CT, and fewer false positives have been noted.[132]

Currently, there are multiple compounds available for targeting PSMA in prostate cancer. However, clinically, two of the most commonly used radioactive isotopes utilized for PSMA imaging are fluorine-18 (^{18}F) and gallium-68 (^{68}Ga).[133] The FDA-approved PSMA imaging agents include ^{68}Ga-gozetotide (^{68}Ga-PSMA-11), ^{18}F-piflufolastat (^{18}F-DCFPyL), and ^{18}F-flotufolastat (^{18}F-rhPSMA-7.3).[134] The choice of PSMA imaging agent can be guided by factors such as regulatory institutions' approvals, the capacity to produce the needed radioisotope (^{18}F vs ^{68}Ga), and their physical properties, including half-life.[135] A comprehensive meta-analysis conducted

by Jeet et al assessed the accuracy of PSMA-PET/CT across various settings in prostate cancer, including localized disease, lymph node metastasis (LMN) in IR and HR prostate cancer, and BCR.[136] The sensitivity and specificity of PSMA-PET/CT varied across these settings, with primary staging demonstrating a sensitivity of up to 71.0% and a specificity of 92.0%. In patients with LMN, sensitivity and specificity were 57% and 96%, respectively, while in patients with BCR, sensitivity was 84% and specificity was 97%.[136]

While the use of PSMA-PET/CT in the staging in prostate cancer has resulted in change in the clinical management in upward of 28% of patients with primary prostate cancer and 54% of patients with BCR, there are some pitfalls associated with PSMA-PET/CT.[136] In addition to known physiologic uptake of these PSMA tracers in the lacrimal and salivary glands, there are various PSMA—avid benign lesions that can confound the interpretation of PSMA-PET/CT.[134,137] Thus, it is crucial for the PSMA-PET/CT scan interpreter to understand and be aware of the appearance of cancerous lesions and the metastasis pattern of prostate cancer.[134] These benign lesions have been observed in multiple anatomic locations, including the lung (eg, sarcoidosis, infectious diseases: histoplasmosis and SARS-CoV-2), adrenal gland (eg, adenoma), soft tissues (eg, desmoid tumors, nodular fasciitis), and bone (eg, trauma, Paget disease, hemangioma).[138-146] The presence of these PSMA—avid osseous benign lesions can complicate clinical management decisions, as highlighted by findings indicating that PSMA-avid solitary rib lesion on pretreatment 68Ga-PSMA-PET/CT may be benign, suggesting caution in interpreting PSMA-PET/CT results.[147] For example, in a study involving patients with prostate cancer presenting with solitary rib lesions, 98.4% met their criteria for having benign lesions. Also, of particular concern when using RT for the treatment of patients with more advanced disease is the recognition that ureters, neural ganglia, and, rarely, schwannomas can be easily misinterpreted as nodes and irradiated in error.[148-151]

Sentinel lymph node dissections are standard in a variety of cancer sites (eg, breast cancer), but its application in prostate cancer has been very limited. Intraoperative gamma probe and dynamic lymphoscintigraphy appear to be a very sensitive approach for defining disease intraoperatively. For example, Wawroschek et al reported that about one-third of sentinel

lymph nodes were in areas outside of a limited node dissection, such as the presacral, hypogastric, and pararectal regions.[152] Holl et al also demonstrated that sentinel lymph node dissections guided by using radiolabeled nanocolloid were reliable in detecting positive nodes in over 2,000 patients.[153] Using a 2-day protocol, involving injection of a radioisotope injected into the prostate, combined with intraoperative scanning, they concluded that the detection rate was 97.6% and false-negative rate only 6%. Krengli et al reported on the application of sentinel lymph node imaging (single-photon emission computed tomography [SPECT]-CT) to pelvic RT for prostate cancer and reported that at least 25% of patients had nodes outside the standard nodal pelvic clinical target volume (CTV).[154]

Chen et al reported on a feasibility study performed at University of California San Francisco (UCSF) using sentinel lymph node image–guided intensity-modulated radiation therapy (IMRT) for prostate cancer and compared it to RTOG-based IMRT plans.[155] Patients were injected with 99^{m}Tc-sulfur colloid into six prostate locations and then imaged with SPECT-CT to generate a lymphatic drainage map. Although all patients had sentinel nodes identified in the internal or external iliac nodal basins, 50% had sentinel nodes in the para-aortic area. We concluded that RTOG consensus guidelines on pelvic lymph coverage would have included all relevant lymph nodes in only 30% of cases. Guided by this sentinel nodal study, we reported that in comparative RT plans, there would have been no significant increase in the doses received by organs at risk, in part because volume reductions in areas not including a sentinel node.

Perhaps the most sensitive (but least available) diagnostic imaging test involves the use of lymphotropic superparamagnetic nanoparticles, which, combined with MRI, has been reported to be a very sensitive and specific test for detecting LNI.[156,157] It not only appears to be more specific than the “Roach equation” in assessing nodal involvement, but it can also identify the location of disease. These nanoparticles are transported by lymphatic vessels and filtered by lymph nodes. Lymph nodes that have been infiltrated by metastases will have distorted lymphatic flow and accumulate the nanoparticles. Of particular note, documented by histologic confirmation, 71% would not have met the MRI size criteria for malignancy. This imaging approach was associated with sensitivity in excess of 90% versus

35% with MRI alone (*P* , .001). When only nodes that were between 5 and 10 mm in diameter on the short axis were considered, the sensitivity increased from 28.5% to 96.4% (*P* , .001). Shih et al proposed margins around major vessels as an alternative based on their studies because of the lack of availability of this imaging agent.[158] Dinniwell et al proposed a pelvic nodal model based on nanoparticles and recommended CTV margins to the distal para-aortic (12 mm), common iliac (10 mm), external iliac (9 mm), and internal iliac (10 mm), drawn in continuity with a 12-mm expansion anterior to the sacrum and 22-mm expansion medial to the pelvic sidewall.[159] Unfortunately, despite great promise, at last, we checked this agent is currently only available in the Netherlands.[160]

MANAGEMENT OF PELVIC LYMPH NODES: THE RATIONALE AND EVIDENCE

The Rationale

Despite the improvements in the detection rate of LNI provided by PET imaging agents, the ability of current imaging techniques to detect involved nodes is hampered by their sole reliance on size criteria.[161] The true incidence of clinically occult disease is generally much higher when sophisticated assays, imaging agents that have increased affinity to lymph nodes, and more extensive node dissections are performed. For example, Shariat et al used RT-PCR assay to detect human glandular kallikrein 2 (hK2) messenger RNA expression in *histopathologically* normal pelvic nodes in patients with pT3N0 prostate cancer.[162] Of the 199 evaluable men, 20% and 40% had positive and equivocal results, respectively. In multivariate analysis, a positive RT-PCR/hK2 result was associated with PSA progression, development of DMs, and PCSM.

When an extended pelvic lymph node dissection (including the nodes surrounding obturator vessels and internal iliac veins) is performed rather than the traditional limited dissection (or sampling), wherein the posterior extent is carried to the obturator nerve, more disease is found. For example, Bader et al conducted a prospective study of the anatomic extent of pelvic nodal involvement in a cohort of 365 men who underwent an extended lymph node dissection and RP.[163] The median number of nodes retrieved was 21. They used hematoxylin and eosin (H&E) stains to evaluate the

extracted nodes, 24% of patients had node-positive disease. The internal iliac nodes (which are not usually dissected in a limited dissection) were involved in 58% of men with node-positive disease. Of note, 19% of node-positive men had involved nodes that were exclusively found in the internal iliac region, suggesting that the lymphatic drainage of prostate cancer is variable. The rate of problematic lymphocele was 2%.

Another important consideration, when reviewing surgical studies, is whether H&E staining was performed or whether more sensitive analyses were included, such as immunohistochemistry (IHC) or RT-PCR. Heidenreich et al reported on the incidence of LNI between standard and extended pelvic lymphadenectomies in 203 patients.[164] IHC staining was performed if the H&E findings were negative. There were more dissected nodes in the extended dissection group (28 vs 11; *P* , .01), at the expense of longer operative time (179 vs 125 minutes; *P* , .03). There were more than twice the number of patients with positive nodes (26% and 12%; *P* , .03) in the extended dissection group, with 42% of all metastases lying outside the planes of a limited dissection. In patients deemed as HR (GS 7-10 and PSA ≥10.6 ng/mL) for LMN, 60.9% of patients had histologically positive nodes. There was no difference in pelvic lymphocele or postoperative complications between the two groups. Data reported by Briganti et al also attempted to address the question concerning the optimal number of lymph nodes to be removed during a nodal dissection.[165] In a cohort of 858 men who were treated predominantly with an extended lymph node dissection and who had a median PSA of 5.8 ng/mL, 62% with GS 6 or less and approximately 25% had GS of 7, based on a receiver operator curve analysis, they concluded that the removal of 28 nodes yielded a 90% ability to detect LNI, while the assessment of 10 or fewer nodes was associated with a very high false-negative rate. These data highlight the shortcomings of studies postulating much lower rates of LNI involvement than suggested by the so-called Roach equation.[166-169]

Relevant to the rationale of recognizing the true incidence of LNI are circumstantial data to suggest that there may be a benefit of removing more involved lymph nodes even if they are occult. For example, in a retrospective study from Johns Hopkins, the pathologic findings and biochemical outcomes were compared between two high-volume surgeons, each of whom exclusively performed either limited (*n* = 1,865) or extended

(*n* = 2,135) node dissections during RP.[170] As expected, the extended dissection group had more lymph nodes retrieved than the limited group (11.6 vs 8.9 nodes; *P* , .0001). Yet, the proportion of patients with involved nodes was also significantly higher in the extended dissection group (3.3% vs 1.2%; *P* , .0001). When only patients with GS of 7 or 8 to 10 were considered, the difference was even more striking (8.2% vs 2.4% and 23.2% vs 8.9%). The relative risks of detecting a patient with involved nodes were remarkably similar, varying between 2.5 and 3 when adjusted by GS, organ-confined status, SVI, and surgical margin status. There was a trend in favor of the extended dissection group for 5-year BCR-free survival (34.4% vs 16.5%; *P* = .07). Among patients with less than 15% positive lymph nodes, the difference was more remarkable (42.9% vs 10%; *P* = .01), suggesting a therapeutic benefit of an extended dissection in low-volume disease. Clinically significant lymphoceles occurred in only 0.3% in the extended dissection group. However, more recent studies have questioned the therapeutic value of more extensive dissection.[171]

On the basis of these studies, national consensus guidelines recommend an extended lymph node dissection for all patients who have a predicted probability of lymph node metastases of more than 2% for both diagnostic and potentially therapeutic reasons. Although there have been numerous nomograms to predict nodal involvement, most are derived from surgical data where only limited node dissections were performed.[172,173] Nomograms also have been developed using surgical data from patients who had an extended lymph node dissection to predict pelvic nodal involvement.[174] Despite these advances from a practical standpoint, because of its simplicity, it appears that the so-called Roach equation is still held relevant and has been validated with a cohort of over 3,000 patients treated with RP and *extended* lymph node dissections.[169,175] Overall, the accuracy of this equation was found to be 80% in this cohort; however, Abdollah et al found that applying the recommended cutoff of 15% or more (to decide on whether to treat the pelvic nodes) might lead to missing about one-third of patients with LNI, and thus, they recommended that the threshold be lowered to 6%.[169]

Collectively, these studies argue that an extended node dissection may or may not yield a therapeutic benefit in the subgroup of patients with minimal nodal disease.[171] In the application of radiation with curative intent, this

issue may have great relevance to prophylactic WPRT. Unfortunately, only one relevant large phase III trial has been completed to date, and although most retrospective studies have been supportive, some post hoc population-based studies have yielded conflicting results.[176-178] Much of this confusion concerning this issue stems from a misunderstanding of the data available from RTOG-9413.[179] Table 73.3 summarizes a body of selected literature addressing WPRT in patients with IR to HR disease managed in the definitive and postoperative setting.

TABLE 73.3 MAJOR TRIALS ASSESSING WPRT IN DEFINITIVE AND POSTOPERATIVE SETTINGS

Reference	Source	Patients	Study Design	Key Findings
Roach et al[176,180]	RTOG 9413	1,323	RCT compared sequence of ADT, and WPRT vs PORT Primary end point: PFS	WPRT improved PFS when preceded by ADT but not when administered before ADT.
Pommier et al[64,181]	GETUG-01	444	RCT PORT vs partial pelvic RT (superior border at S1-S2); 55% had risk + nodes ,15%	Patients did not receive WPRT (defined as top L5-S1); most were low risk for lymph nodes.
Mason et al,[182] Warde et al[183]	UK, Canada, USA	1,205	Prespecified final analysis of an RCT ADT vs ADT + RT	Patients planned for WPRT showed a trend for improved OS vs PORT (HR = 0.70; *P* = .12); DSS (HR = 0.53; *P* = .098).
James et al[184]	STAMPEDE trial	721	Exploratory analysis using data to assess the impact of RT on FFS by nodal status	FFS outcomes favored planned use of RT for HR pts with N0M0 *and* N+M0 disease.
Murthy et al[89]	POP-RT	224	Phase III RCT WPRT vs PORT in high-risk patients (*n* = 224)	WPRT improved PSA control, DFS.
Pollack et al[90]	RTOG/NRG 0534	1,792	Phase III three-arm RCT in the salvage	Improve PFS with neoadjuvant ADT with

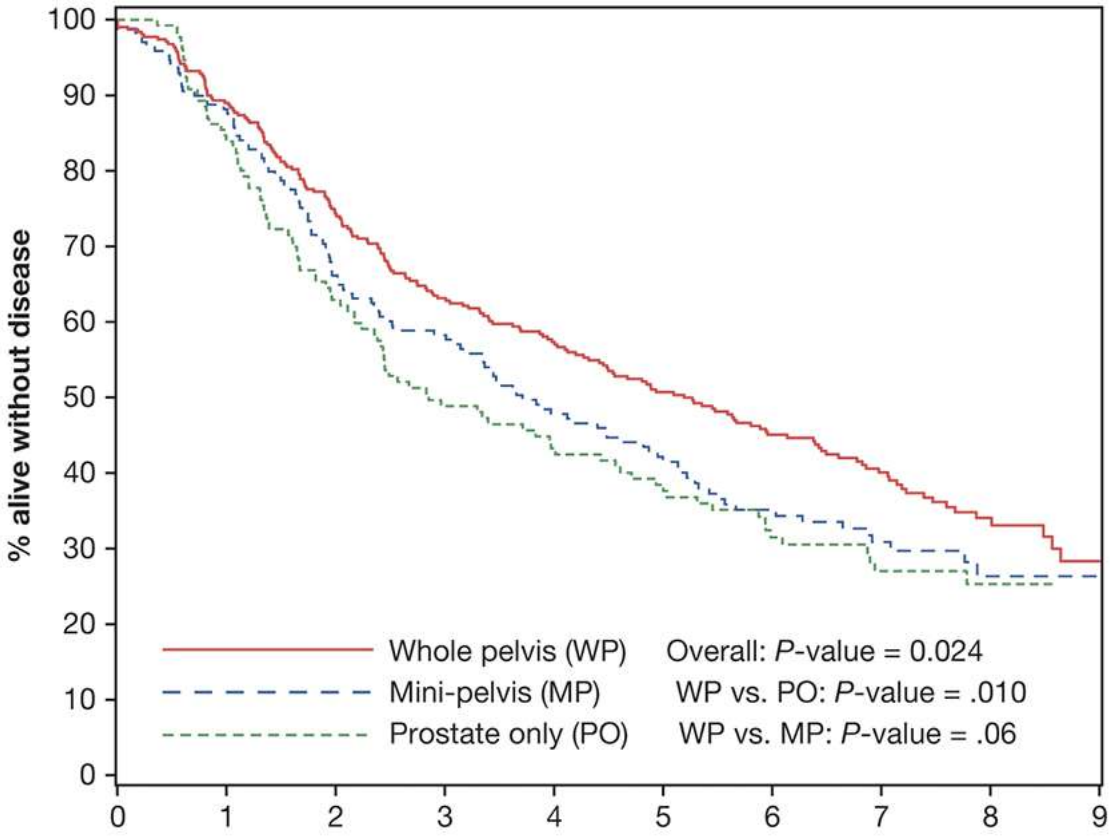
Reference	Source	Patients	Study Design	Key Findings
			setting post-RP	WPRT vs PBRT

ADT, androgen-deprivation therapy; FFS, failure-free survival; HR, high risk; OS, overall survival; PBRT, prostate bed radiation therapy; PFS, progression-free survival; PORT, prostate-only radiotherapy; pts, patients; RCT, randomized controlled trial; RP, radical prostatectomy; RT, radiation therapy; WPRT, whole-pelvic radiation therapy.

RTOG-9413 was a landmark trial that featured a two-by-two factorial randomization scheme to either prostate-only radiation therapy (PORT) or WPRT followed by a prostate boost and either 4 months of neoadjuvant and concurrent hormones or 4 months of adjuvant ADT (AHT) at the completion of EBRT.[176] Patients with an estimated nodal risk of more than 15% or T2c to T4 with a GS of 6 or higher were eligible for the study. The 4-year progression-free survival (PFS) was 54.2% and 47% in the combined WPRT arms and PORT arms (P = .02), respectively. When the four arms were analyzed separately, the neoadjuvant hormone and WPRT arm (59.6%) had a significantly better 4-year PFS than the other three arms (44.3%-49.8%; P = .008). Although there was no difference in acute (3% vs 4%; P = .39) and late (2% vs 2%; P = .85) grade 3 to 5 genitourinary (GU) morbidities, a trend toward increased acute (2% vs 1%; P = .06) and late (1.7% vs 0.6%; P = .09) grade 3 to 5 gastrointestinal (GI) morbidities was seen in the combined WPRT and prostate-only arms, respectively.

Although RTOG-9413 affirmed the role of WPRT and neoadjuvant hormonal therapy (NHT) in HR prostate cancer, there has been some lingering reluctance among some radiation oncologists, with many instead opting for “mini-pelvic” fields or omitting the pelvic field entirely.[185] To reinforce this notion of the volume dependence on control of microscopic nodal disease, we conducted a secondary post hoc secondary subset analysis of patients treated on RTOG-9413.[65] Because of the disparity in the time point at which the neoadjuvant and AHT arms became susceptible to relapse (ie, end of both RT and ADT), only patients (n = 649) who received NHT were included in this analysis. After stratifying by volume irradiated, the 7-year PFS was 40%, 31%, and 27% in the groups that received WPRT, mini-pelvic RT, and PORT, respectively (P = .02; Figure 73.5). There was no difference in acute grade 3 or higher GU or GI toxicities among the three volumes. No difference was seen in the incidence of late grade 3 or higher

GU toxicities between the WPRT, mini-pelvic RT, and PORT groups at 48 months (3.0%, 2.4%, and 0%, respectively; $P = .24$). There was a small but significant increase in the incidence of late grade 3 or higher GI toxicities with larger fields at 48 months (4.3%, 1.2%, and 0%, respectively; $P = .006$). Of note, three-dimensional conformal radiation therapy (3DCRT), let alone IMRT, was not routinely performed in this study. It is conceivable that with either modality, late toxicities may be further decreased (Figure 73.6).



At risk:										
WP	309	274	227	189	167	142	109	78	35	10
MP	170	149	109	96	77	61	44	29	10	2
PO	131	109	81	61	54	47	34	22	10	0

FIGURE 73.5 Progression-free survival of subgroup analysis of the Radiation Therapy Oncology Group (RTOG-9413) comparing WP, MP, and PO radiotherapy. (Reprinted from Roach M III, DeSilvio M, Valicenti R, et al. Whole pelvic, "mini-pelvic" or prostate-only external beam radiotherapy after neoadjuvant and concurrent hormonal therapy in patients treated in the Radiation Therapy Oncology Group 9413 Trial. *Int J Radiat Oncol Biol Phys.* 2006;66[3]:647-653. Copyright © 2006 Elsevier. With permission.)

FIGURE 73.6 Isodose lines and dose-volume histogram from a representative patient treated with single-fraction 15-Gy high-dose rate prostate brachytherapy with ultrasound-based planning. Twelve catheters were implanted. On dose-volume histogram, the prostate (red line), urethra (blue line), and rectum (brown line) are represented. (Courtesy of Gerard Morton, MD, Sunnybrook Odette Cancer Centre, University of Toronto, Toronto, Canada.)

Although the results of GETUG-01 seem to contradict that of RTOG-9413, there are significant differences in the methodology of the two studies that warrant mention. First, more than half of the patients (~54%) had an estimated nodal risk of less than 15% ("Roach formula"), meaning that these patients had more favorable disease than those in RTOG-9413 and, therefore, would likely not benefit from WPRT. Thus, this study was vastly underpowered, as is made a bit clearer, by considering this example. Suppose you designed a trial wherein the minimum eligibility was a risk of LNI more than 15%, such that the average risk for this cohort was one-third. If you enrolled 1,200 patients, then 400 would really be the basis for the study outcome because only this number could potentially benefit. If the

local recurrence rate was 50% (eg, as might be expected after 66 Gy), then only 200 patients would be left to assess the merits of WPRT. This means that only 100 patients would remain on the WPRT arm that could potentially benefit. If competing causes of death eliminated 50% of the patients, the remaining assessable patients would then be down to 50 per arm. Thus, even starting off with 1,200 patients, it would be challenging to assess the potential impact of WPRT. Clearly, GETUG-01, which only started out with 200 patients with a risk of more than 15%, was not adequately powered to either disprove or prove the value of WPRT.

Equally important, the protocol-defined pelvic fields on GETUG-01were much smaller than those used in RTOG-9413. Specifically, the superior border was taken at the level of S1-S2 interspace, rather than L5-S1 interspace, which meant that a significant portion of the presacral and common iliac nodes were not treated. Thus, *none* of the patients included in this trial received WPRT in accordance with RTOG-9413, and *all* of the patients assigned to the "pelvic nodal" radiation arm would have been included in the PORT arm of RTOG-9413.

NRG/RTOG-0924, opened in 2011 and completed accrual in June 2019, was designed using a subset of patients from RTOG-9413 that appeared to have benefited the most from WPRT.[176,177] In addition, it incorporated the percentage of positive biopsy cores into the eligibility criteria. For NRG/RTOG-0924, the WPRT superior border was placed slightly higher and the PORT fields slightly smaller, with the phase I dose of 45 Gy in both arms and can be delivered with 3DCRT or IMRT. The phase II prostate boost (a stratification variable) could be delivered by IMRT (34.2 Gy; total dose 79.2 Gy), LDR brachytherapy (110 Gy for iodine-125 [^{125}I] and 100 Gy for palladium-103 [^{103}Pd]), or HDR brachytherapy (15 Gy in one fraction with iridium-192 [^{192}Ir]). Patients were also stratified by duration of ADT into 4 to 6 or 32 months.

The bottom line concerning WPRT as summarized in Table 73.3 is as follows:

1. Most retrospective studies involving EBRT support the value of WPRT. Thus, there is no strong evidence to withhold WPRT based on retrospective data.

2. Every major RTOG and EORTC trial including HR patients with ADT included WPRT. In fact, even the largest trials populated by IR patients were treated with WPRT. For example, nearly 75% of the patients treated on RTOG-9408 received WPRT.[186,187] Thus, there is no evidence that the results of these trials would be the same if WPRT was withheld.
3. The three largest contemporary phase III randomized trials completed to date (RTOG-9413, RTOG-0534, and POP-RT) support an improved PSA control when NHT is added to WPRT compared to PORT.[88-90]
4. A larger confirmatory study with a survival end point is pending with greater than 2,500 patients already enrolled (RTOG/NRG-0924) and is expected to be reported out by early 2025.

RADIATION THERAPY TECHNIQUES: REGIONAL AND LOCAL

Boost Techniques: Options and Considerations

Over the past two decades, the therapeutic options for definitive radiation in men with clinically localized disease have evolved immensely. At UCSF, favorable IR patients are usually managed with monotherapy, a permanent prostate implant (PPI), an HDR implant, or SBRT directed only at the prostate and/or the proximal seminal vesicles (SVs) with or without ADT. For patients with more unfavorable IR disease, image-guided EBRT (IGRT) directed at periprostatic tissues (± the pelvic lymph nodes) is generally combined with a PPI, HDR, or an SBRT boost and/or short-term ADT (eg, 4 months), whereas for HR patients, long-term ADT (eg, 2-3 years) with WPRT is usually recommended.

Off study, the authors continue to recommend prophylactic WPRT using IMRT to patients with an estimated risk of nodal involvement of more than 15% for unfavorable IR and HR prostate cancer. The authors recommend either adherence to the RTOG Genitourinary Radiation Oncology consensus statement on pelvic nodal volumes or use of a higher superior border.[120,188,189] If positive pelvic nodes are suggested by imaging (eg, CT or PET), prophylactic para-aortic nodal treatment is usually added to WPRT. The prostate boost is delivered with either an IMRT, a PPI, HDR brachytherapy, or an SBRT boost. Brachytherapy or SBRT is generally preferred by the authors because of their ability to deliver a higher biologic

dose to the prostate. Brachytherapy or SBRT can be performed either before or 1 to 3 weeks following pelvic RT. For T3 disease, the authors use an SBRT, HDR, or IMRT boost, which allows better coverage of extracapsular disease than PPI boost. Table 73.4 summarizes some of the consideration when selecting the type of boost preferred for a given patient. Figures 73.7 and 73.8 provide a summary of some of the data supporting SBRT with or without ADT.[2] Based on the results of patients treated on RTOG-0232 comparing PPI to PPI plus EBRT, the former is preferred in favorable IR patients.[190]

TABLE 73.4 RADIATION THERAPY "PREFERRED" OPTIONS AND RELATIVE CONTRAINDICATIONS FOR PROSTATE CANCER AT UCSF (CIRCA 2024)

Type of Radiation Therapy	Primary Indications	Relative Contraindications
IGRT (intensity-modulated image-guided external beam radiation)[a]	1. Combination therapy pre-/postboost treatment 2. Post-op adjuvant treatment 3. Post-op salvage treatment 4. Large transurethral resection of the prostate (TURP) defects 5. Other options not covered by insurance 6. Patient preference	1. Previous full-dose radiation 2. Patient preference (eg, logistically problematic) 3. Focal recurrence (favor focal treatments) 4. Technical issues (eg, too large for CT scan but BT suitable) 5. Inflammatory bowel disease or connective tissue disorder 6. Noncompliant for many visits
PPI (permanent prostate implant) BT (brachytherapy)	1. Monotherapy for low- or favorable intermediate-risk pts 2. Boost in clinically T1-T2 with IMRT 3. Focal salvage postrecurrence after IMRT 4. Focal salvage postrecurrence after PPI 5. Patient preference	1. Not a candidate for anesthesia 2. Discontinuation of anticoagulation is unadvisable 3. Excessive pubic arch interference (PAI) 4. Excessively large TURP defect 5. Severe baseline urinary symptoms (eg, urinary retention)

Type of Radiation Therapy	Primary Indications	Relative Contraindications
HDR (high-dose rate) BT	1. Monotherapy for low- or favorable intermediate-risk pts 2. Boost in clinically T1-T3 with IMRT 3. Focal salvage postrecurrence after IMRT 4. Pubic arch interference prohibiting PPI 5. Median lobe too large for SBRT 6. Insurance prohibits SBRT 7. Patient preference	1. Not a candidate for anesthesia 2. Discontinuation of anticoagulation is unadvisable 3. Excessive pubic arch interference 4. Excessively large TURP defect 5. Severe baseline urinary symptoms (eg, urinary retention)
SBRT (stereotactic body radiation therapy)	1. Monotherapy for low- or favorable-risk pts 2. Boost for clinically T1-T4 with IMRT 3. Focal salvage in selected pts postrecurrence after IMRT when not a candidate for BT salvage 4. Patients presenting with obstruction because of locally advanced disease (eg, “reverse” boost) 5. Patient preference (eg, convenience)	1. Very large median lobe 2. Unable to lie still and flat for 45 min (eg, tremor) 3. Poor localization because of metal artifacts (eg, hip replacement, presence of PPI seeds) 4. Poor seed positioning (“too close”) 5. Not covered by insurance 6. Protocol requires other treatments

IMRT, intensity-modulated radiation therapy; pts, patients; UCSF, University of California San Francisco.

[a]Delivered with either conventional fractionation or hypofractionation. “Primary”: This term reflects the clinical nuances that go into the decisions concerning the use of various radiation options considered while practicing the “Art” of radiation therapy. There may be exceptions to what physicians decide to recommend to specific patients, but these “Primary” options as listed in this table reflect our typical considerations and our practice habits. It is recognized that for purposes of continuity of care and presumed clinical equivalence, patients who could be managed appropriately by more than one boost modality are more likely to be managed via the modality favored by the “clinical lead” radiation oncologist as listed earlier.

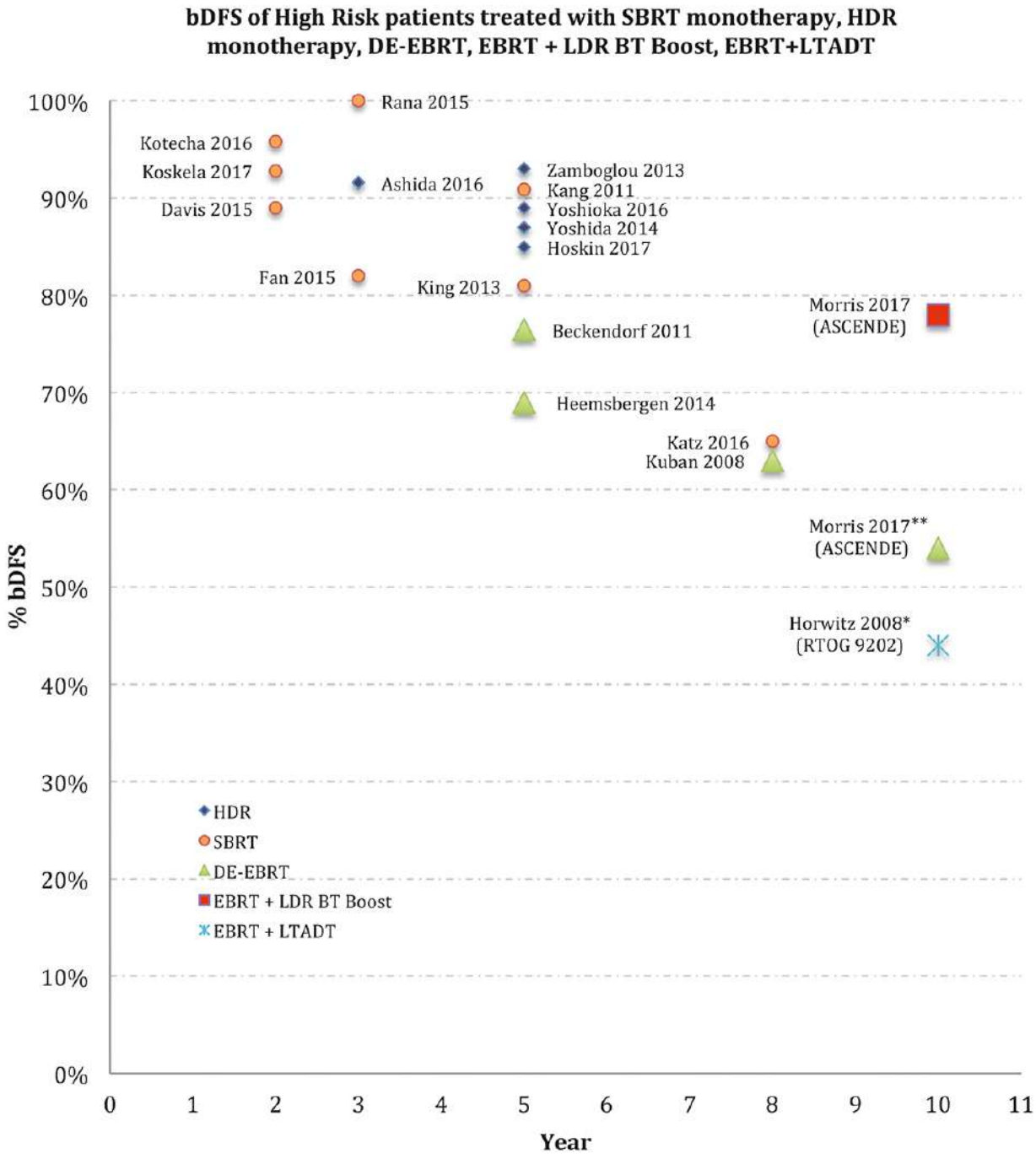


FIGURE 73.7 Biochemical disease-free survival (bDFS) (Phoenix) of high-risk (HR) patients treated with stereotactic body radiation therapy (SBRT) boost, high-dose rate (HDR) boost, external beam radiation therapy plus long-term androgen deprivation therapy (EBRT + LTADT), dose-escalated external beam radiation therapy (DE-EBRT), and low-dose rate brachytherapy (LDR-BT) arm of the ASCENDE-RT trial. Data from the ASCENDE-RT trial were estimated from the Kaplan-Meier curve of bDFS for HR patients. Data for RTOG-9202 (EBRT + LTADT) were estimated from biochemical rate reported. *RTOG-9202 used the ASTRO definition for biochemical failure. **DE-EBRT arm of the ASCENDE-RT trial received 8 months of neoadjuvant androgen deprivation therapy. (Reprinted from

Gonzalez-Motta A, Roach M III. Stereotactic body radiotherapy (SBRT) for high-risk prostate cancer: where are we now? *Pract Radiat Oncol*. 2018;8[3]:185-202. Copyright © 2017 American Society for Radiation Oncology. With permission.)

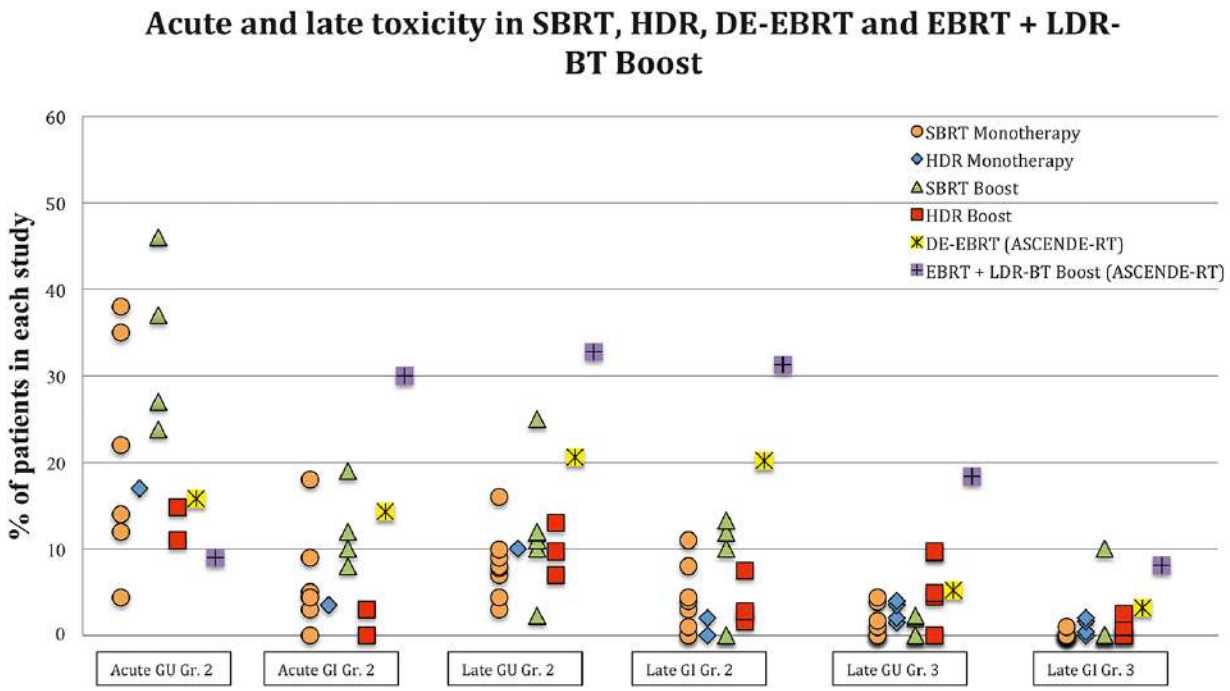


FIGURE 73.8 Acute and late toxicity reported in stereotactic body radiation therapy (SBRT), high-dose rate (HDR) monotherapy, dose-escalated external beam radiation therapy (DE-EBRT), and low-dose rate brachytherapy (LDR-BT) studies. Not all SBRT and HDR studies reported toxicity data. Three scales were used in the studies: the common terminology criteria for adverse events, the Radiation Therapy Oncology Group scale, and the late effects normal tissue task force/subjective, objective, management, and analytic scale. However, they were plotted together in the figure. GI, gastrointestinal; GU, genitourinary. (Reprinted from Gonzalez-Motta A, Roach M III. Stereotactic body radiotherapy (SBRT) for high-risk prostate cancer: where are we now? *Pract Radiat Oncol*. 2018;8[3]:185-202. Copyright © 2017 American Society for Radiation Oncology. With permission.)

Brachytherapy and Stereotactic Body Radiation Therapy Boost

Brachytherapy Boost

Notwithstanding the downsides that brachytherapy is an invasive procedure that requires anesthesia, additional resources, and clinical expertise, the advantages of incorporating prostate brachytherapy to boost the dose to the prostate are compelling. First, the achievable biologically effective dose to the prostate exceeds what can be achieved by IMRT, which appears to translate into a higher rate of local control and possibly cure. In addition to

the ASCENDE-RT trial involving PPI boost, there are several other comparative studies supportive of HDR brachytherapy boost as well.[191] For example, Hoskin et al reported the results of their phase III trial comparing EBRT alone (55 Gy in 20 fractions) with combined EBRT (35.75 Gy in 13 fractions) followed by HDR prostate brachytherapy (17 Gy in two fractions over 24 hours) among 218 patients with clinically localized prostate cancer.[192] Biochemical control was significantly higher in patients treated with EBRT plus HDR ($P = .04$). In multivariate analysis, risk category and ADT were significant covariates for risk of relapse. The improvement noted in the biochemical control still held after 12-year follow-up.[193] Of note perhaps because of the study size, there were no differences in OS. Fortunately, the incidence of severe late urinary and bowel morbidity was similar. In addition to apparently rendering improved PSA results, with a brachytherapy boost, the overall treatment time is usually less than the usual 8 weeks of conventionally fractionated x-ray therapy and, therefore, more convenient for patients.

As compared to LDR brachytherapy, HDR brachytherapy yields the following advantages: greater flexibility in source positioning, adaption of dose to target and healthy organs, target volume-dose optimization, high-quality planning and dose distribution, lower risk of radiation exposition to health care personnel or public, and reduced cost. The potential disadvantage of HDR is that it is often fractionated and takes more time and, therefore, may require more workload and careful coordination from the health care personnel. The indications of combined EBRT and brachytherapy boost include those with IR or HR prostate cancer, particularly in patients who are relatively young and have high-volume disease. Relative contraindications to the use of a brachytherapy boost include those with a large prostate (.60 mL), prior TURP with a large residual urethral defect, anticoagulation use, and significant urinary symptoms (ie, International Prostate Symptom Score >20).

As noted previously, HDR brachytherapy may be performed before, during, or after the EBRT. The optimal HDR dose fractionation is currently unknown, and there is significant variability across centers. Nonetheless, there is a shift toward fewer implants, fewer fractions, and higher dose per fraction because of the radiobiologic advantage of high dose per fraction in prostate cancer. Reflecting this lack of consensus, RTOG-0815 and RTOG-

0924 stipulate different HDR prescription doses. In RTOG-0815, the HDR brachytherapy boost may be performed during EBRT or within 1 week prior to its initiation or following its completion. The prescription is 21 Gy delivered in two equal fractions of 10.5 Gy, separated by at least 6 hours, and given within 24 hours. In RTOG-0924, the implant may be done during EBRT or within 2 weeks prior to its initiation or following its completion. The prescription is 15 Gy in a single fraction. In both protocols, the dose constraints to the bladder are V_{75} less than 1 mL, rectum is V_{75} less than 1 mL, and urethra is V_{125} less than 1 mL and V_{150} is 0%. An example of HDR brachytherapy with ultrasound planning and dose-volume histogram for various organs at risk is shown in Figure 73.6.

Stereotactic Body Radiotherapy Boost

Over the past 10 years, there has been an increased interest in the use of SBRT as an alternative to brachytherapy.[2] The review by Gonzalez-Motta and Roach, the systematic review and meta-analysis including more than 6,000 patients by Jackson et al, and the propensity matched retrospective study by investigators at UCSF provide a supportive body of work for using SBRT as a boost following EBRT or as monotherapy for selected patients with HR disease.[2,194,195] These systematic literature reviews and matched comparisons cited document high rates of biochemical disease-free survival (bDFS) and reasonable toxicity associated with the use of SBRT in HR prostate cancer either as monotherapy or as a boost. In addition, they compared their outcomes to selected series including patients treated with HDR, PPI, and EBRT (Figure 73.7). Cited 5-year bDFS were 81% to 91% or higher with monotherapy and 90% to 98% in boost studies comparable to studies reporting bDFS of 85% to 93% and 72% to 93%, respectively, with HDR monotherapy or boost in selected HR patients. They also reported that the incidence of late grade 3 GU toxicity was 0% to 4.4% and 0% to 2.3% in SBRT monotherapy and SBRT boost studies, respectively, not dissimilar to those seen with other forms of radiation (Figure 73.8). Table 73.4 summarizes the generally preferred options and the associated indications for how various types of boost techniques are chosen in patients undergoing definitive RT for clinically localized prostate cancer at UCSF.

TECHNICAL CONSIDERATIONS FOR EXTERNAL BEAM RADIATION

External Beam Radiation Therapy

IMRT (as opposed to 3DCRT) is recommended for optimal target coverage and avoidance of rectum and bladder.[196] At a minimum, the prostate, proximal SVs, and periprostatic tissue should be irradiated. Inclusion of the first echelon lymph nodes (ie, mini-pelvis) or the entire pelvic nodal contents (ie, whole pelvis) may be considered, based on the estimated risk of involvement. The recommended EBRT dose is 45 to 50.4 Gy in 1.8 to 2.0 Gy per fraction. Several investigators have conducted relatively small studies evaluating the merits of ultra-hypofractionated pelvic nodal RT.[197] In a systematic review and meta-analysis reported by Mohamad et al,[197] they identified 16 studies, with 7 meeting their criteria for a meta-analysis (n = 417, patients). The median dose to the pelvic nodes was 25 Gy (range, 25-28.5 Gy), with a median of five fractions. All patients received ADT, for a median of 18 months. They reported that the rates of acute grade 2 or higher GI and GU toxicity were 8% and 29%, respectively. For late grade 2 or higher GI and GU toxicity, the rates were 13% and 29%, respectively. They concluded that "ultra-hypofractionated pelvic nodal irradiation appears to be a safe approach in terms of acute and late genitourinary and gastrointestinal toxicity." We believe these rates are a bit high, considering that patients tend to report higher rates than physicians, and we suspect that the fields used are likely to be substantially smaller than the superior border used on RTOG-0924 (L4-L5). Thus, although promising, generally speaking, the role of hypofractionated regimens has not been well defined in patients with unfavorable to higher risk disease.[198-200]

Prostate Motion and the Use of Image-Guided Intensity-Modulated Radiation Therapy

While the use of fiducial gold seed markers and daily electronic portal imaging (EPI) with online correction and/or the use of cone-beam computed tomography (CBCT) are favored at UCSF, the use endorectal balloons or rectal spacers may be considered standard elsewhere.[201,202] Well-placed marker migration was found to be minimal, with 79% within 1 mm and 96% within 1.5 mm. The latter results have been corroborated by

Kupelian et al, who demonstrated that the average absolute variation in intermarker distance was 1.01 ± 1.03 mm.[203-205] Only 1% of the markers exhibited frequent movement, and it was found to be due to prostate deformation secondary to rectal filling. CBCT for online correction is gaining popularity as it allows for soft tissue matching and does not require an invasive procedure to implant fiducial markers. Moseley et al compared kilovoltage CBCT with fiducial markers and EPI and found no significant difference as a means for image guidance.[202] Langen et al described broadly two different types of intrafraction motions.[206,207] One type of motion is a slow, small drift, usually posteriorly and inferiorly, that is thought to be associated with pelvic muscle relaxation or the gradual movement of rectal contents away from the prostate. Second is a sudden and transient motion, usually anteriorly and superiorly, that can be significant in extent and is thought to be due to peristalsis. In the cohort of 17 patients (550 fractions), the average proportion of the total treatment time that the prostate was displaced by greater than 3 and greater than 5 mm was 13.6% and 3.3%, respectively. However, when analyzed by patient-to-patient basis, the prostate was displaced by 36.2% and 10.9%, respectively.

In an analysis of patients treated at UCSF, Chen et al demonstrated that an isocenter shift of 5 or 10 mm in the superior direction could reduce nodal target coverage by 11% and 26%, respectively, with whole-pelvic IMRT. Xia et al compared multiple adaptive plans, iso-shifting, and multileaf collimator (MLC) shifting and concluded that MLC shifting was the most effective in addressing the independent movement of the prostate and pelvic nodes during RT.[208-210] In a study by Chung et al, patients treated with image-guided IMRT to pelvic nodes had significantly lower dose to the rectum and bladder and fewer toxicities than those who received IMRT only.[211]

Rectal spacers are not generally recommended for unfavorable IR and HR patients because of the potential concern for areas of ECE and the observed marginal impact on grade 1 toxicity.[212,213] Serious concerns have been raised by several investigators about the use of this technology.[214] These concerns are supported by a recent review of “Real-World” complications following the placement of rectal spacers, suggesting there should great caution for all patients receiving definitive RT.[215]

Volumes and Setup Variation

We routinely have three fiducial gold seed markers placed into the prostate under transrectal ultrasound guidance—one in the base, one in the mid-gland, and one in the apex. Each marker is approximately 1.1 mm in diameter and 3 mm in length. We use an amorphous silicon flat panel detector to make any necessary adjustments prior to each treatment. As such, the authors typically apply a 3-mm margin around the prostate gland and SVs in defining the planning target volume (PTV). For patients with hip replacements, the authors use CBCT for image guidance. At institutions without daily EPI to control for intra- and interfraction prostate motion, larger margins such as 0.5 to 1 cm should be considered. Patients are instructed to empty their rectum with an enema prior to simulation. Patients are told to maintain a full bladder during simulation and treatment. A retrograde urethrogram is no longer performed at UCSF to assist in identifying the apex of the gland, except in patients undergoing SBRT for whom an MRI is not possible or contraindicated. Three-millimeter slice thickness is used for the CT simulation. The critical organs that are contoured include the penile bulb, small bowel, rectum, bladder, and femoral heads. The entire rectum is contoured from the anus to the rectosigmoid junction. Rectal spacers are not recommended for patients with IR and/or HR disease.

Intensity-Modulated Radiation Therapy Treatment Planning

For patients opting for definitive IMRT to the pelvis and prostate, the authors use a two- or three-phase plan. The first phase delivers 25 to 30 fractions of 1.8 Gy (total 45-60 Gy [the latter PET-positive sites], superior border L4-L5 with node negative by imaging). Concurrently, 2 Gy per fraction (total 54-56 Gy) to the SVs and prostate PTV. PET-positive nodes are boosted to 60 Gy and para-aortic nodes added if pelvic nodes are positive. The second phase is a cone-down boost to the prostate PTV alone with 12 fractions of 2.0 Gy per fraction. Therefore, the minimum total dose to the prostate (prescribed to the PTV) is 78 Gy. In postoperative patients opting for pelvic RT, the authors prescribe 25 fractions of 1.8 Gy to the nodes (total dose 45 Gy) and 2 Gy per fraction to the tumor bed PTV (total

dose 50 Gy) and then 9 or 10 fractions of 2.0 Gy per fraction to the prostate bed (total minimal PTV dose 68-70 Gy).

Bounders and Considerations for Pelvic Intensity-Modulated Radiation Therapy

Over the past 15 years, IMRT has been adopted as standard of care for pelvic nodal irradiation. For historical purposes, with conventional technique, pelvic irradiation is usually treated with a four-field box. The target volume usually includes the prostate, SVs, obturator, and proximal internal and external iliac nodal regions. Occasionally, common iliac, para-aortic, and even perirectal nodes are included in the initial target. The traditional field borders of the anteroposterior portals previously were as follows: superior at the L5-S1 interspace, inferior at 2 cm distal to the membranous urethra (defined by the apex of the urethrogram peak), and 1.5 to 2 cm lateral of the pelvic brim. Based on work involving sentinel lymph nodal imaging, we now recommend extending the superior border to L3-L4 or L4-L5 instead of L5-S1.[155] In the lateral portals, the superior and inferior borders are placed at the same point as the anteroposterior portals; the anterior border is placed at the anterior most aspect of the pubic symphysis, and the posterior border is placed at the S2-S3 interspace. With CT planning, the prostate, SVs, rectum, small bowel, bladder, pelvic vessels, and penile bulb may be contoured to facilitate shielding of the rectum and small bowel.

Compared to conventional technique, IMRT allows unprecedented sparing of nearby critical structures like the rectum, small bowel, bladder, and femoral heads. In a study from UCSF, Wang-Chesebro et al compared the nodal target coverage by conventional field borders with IMRT (Figure 73.9).[216] The nodes that were contoured included the obturator, internal or external iliac, common iliac, and presacral regions. In the conventional four-field plan, only 70.3% of the nodal target volume received the prescription dose of 45 Gy, whereas 96.2% was covered in the IMRT plan (P = .002). Even worse, conventional field placement led to 20.2% of the nodal target volume to receive less than 80% of the prescription dose. The rectal and bladder volume receiving 95% of the prescribed dose was

significantly reduced with IMRT, with an absolute reduction of 23% and 80%, respectively.

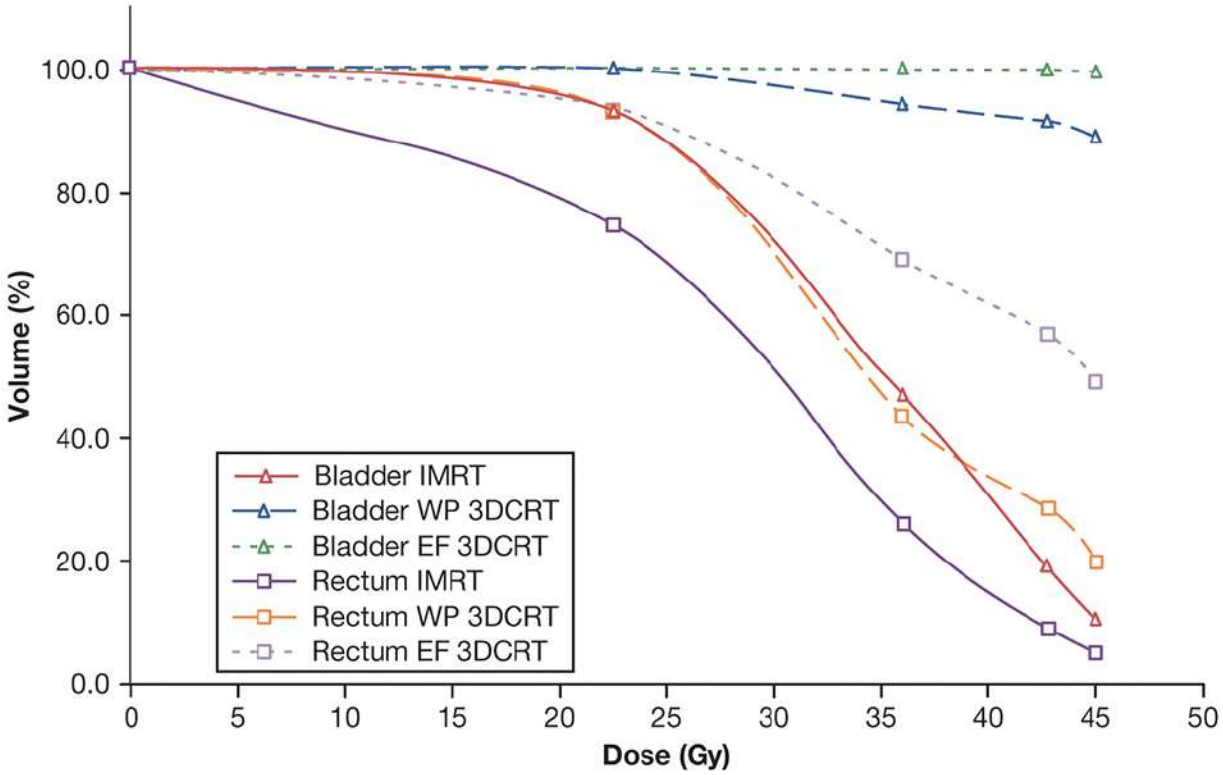


FIGURE 73.9 Comparison of dose-volume histograms for the rectum and bladder for whole-pelvic only phase using intensity-modulated radiotherapy (IMRT), whole-pelvic (WP) three-dimensional conformal radiotherapy (3DCRT), and extended-field (EF) 3DCRT plans. For both the bladder and rectum, IMRT significantly reduced V_{45}, $V_{42.75}$, V_{36}, and $V_{22.5}$ (P , .01 for all comparisons) compared to both WP and EF 3DCRT plans. (Reprinted from Wang-Chesebro A, Xia P, Coleman J, Akazawa C, Roach M III. Intensity-modulated radiotherapy improves lymph node coverage and dose to critical structures compared with three-dimensional conformal radiation therapy in clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2006;66[3]:654-662. Copyright © 2006 Elsevier. With permission.)

Whereas conventional technique involved simply placing field borders based on bony anatomy, IMRT requires the delineation of a nodal target volume based on vasculature. Investigators have used lymphotropic nanoparticle-enhanced MRI and ultra-small superparamagnetic iron oxide lymph node contrast agent, ferumoxtran-10, to develop nodal CTV models.[119] These MRI studies have formed the foundation for the RTOG Genitourinary Radiation Oncology consensus on pelvic nodal CTV delineation, as shown in Figure 73.10.[120,189] However, the RTOG guidelines

did not use sentinel lymph node imaging, which in a study by Chen et al demonstrated that the RTOG pelvic nodal CTV included all identified sentinel lymph nodes in only 30% of patients.[155] In the same consensus, Lawton et al recommended dose constraints to the rectum (V_{50} Gy ≤50%, V_{70} Gy ≤20%), bladder (V_{55} Gy ≤50%, V_{70} Gy ≤30%), femoral heads (V_{50} Gy ,5%), and small bowel (maximum dose ,52 Gy). Based on an extensive literature search, Chan et al proposed guidelines on rectal dose constraints for patients receiving pelvic RT.[196]

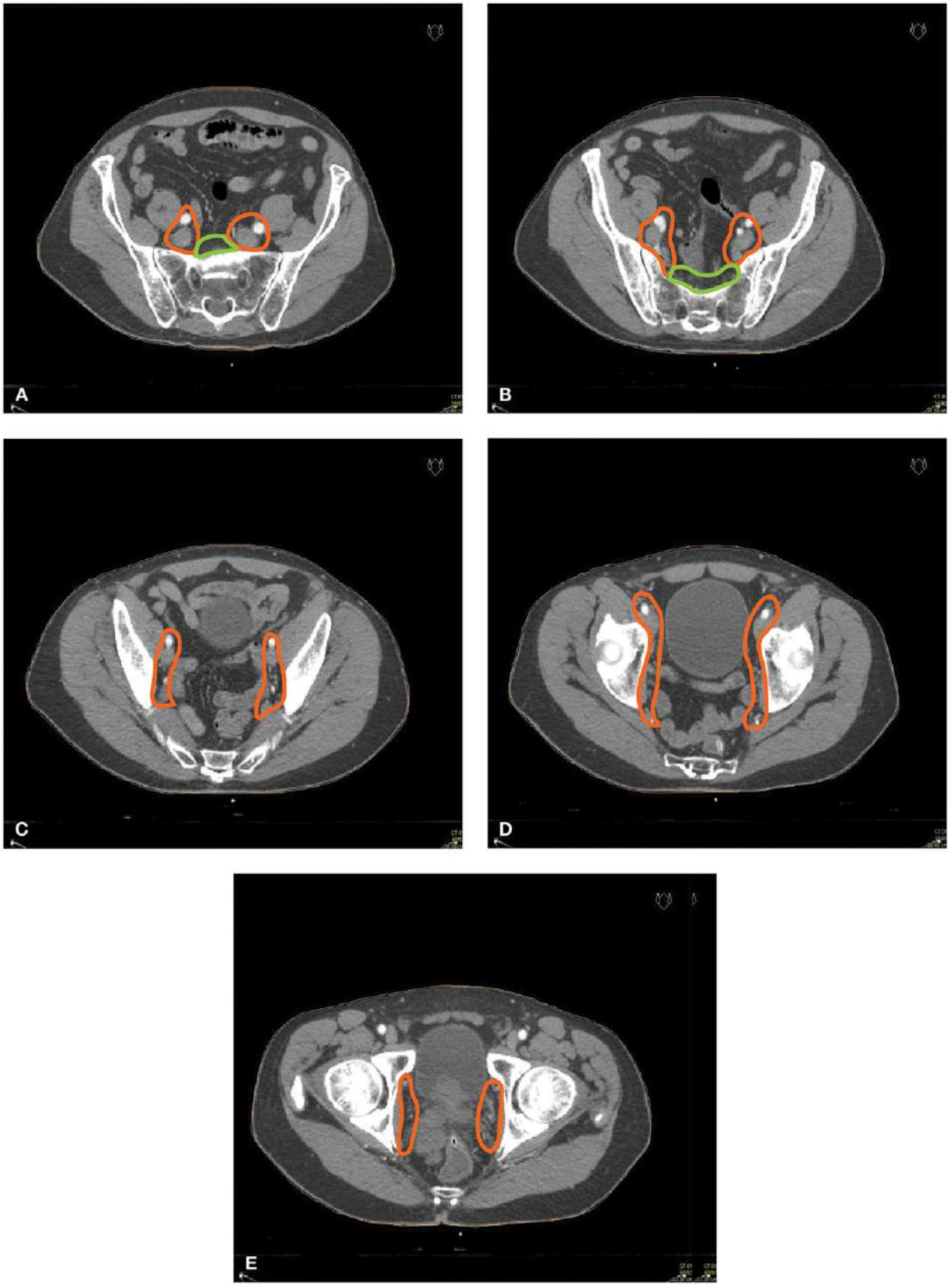

A
B
C
D
E

FIGURE 73.10 Representative pelvic lymph node clinical target volume contours of (A) common iliac and presacral at L5-S1; (B) external, internal, and presacral at S1-S3; (C) external and internal iliac below S3; (D) end of external iliac at top of femoral heads (bony landmark for the inguinal ligament); and (E) obturator at the top of the pubic symphysis. (Adapted from Lawton CA, Michalski J, El-Naqa I, et al. RTOG GU radiation oncology specialists reach consensus on pelvic lymph node volumes for high-risk prostate cancer. *Int J Radiat Oncol Biol Phys*. 2009;74[2]:383-387. Copyright © 2009 Elsevier. With permission.)

DOSE ESCALATION AND ANDROGEN DEPRIVATION THERAPY: EVIDENCE AND INDICATIONS

EBRT Alone Versus EBRT Plus ADT and ADT Alone Versus ADT Plus EBRT

The optimal dose of radiation required to obtain a high level of local control while maintaining an acceptably low level of complications is not known. Several phase III randomized trials have compared conventional dose with high-dose (76-82 Gy) EBRT, and although essentially all have demonstrated an improvement in PSA control, no survival advantage attributable to radiation dose were observed.[8,217,218] The largest and most recent of dose escalation trials is RTOG-0126, which compared 70.2 Gy in 39 fractions versus 79.2 Gy in 44 fractions.[219,220] In the initial report, at 8 years while there was no improvement in OS, the rate of DM was 4% for the 79.2 Gy arm versus to 6% on the 70.2 Gy arm (P = .05), and BF was 20% versus 35% (P , .001). Although the 5-year rates of late grade 2 or higher GI and GU toxicities were 21 and 12% for 79.2 Gy versus 15 and 7% for 70.2 Gy (P = .006 and P = .003), the overall impact on QoL was modest at best, with no significant impact on any patient-reported outcome (PRO) metrics measured across all collected domains. Of note, however, at 12 months, 49.7% versus 38.1% developed ED on the 79.2 versus 70.2 Gy arms (P = .051) a finding not inconsistent with earlier work.[221]

Recently, the RTOG (now NRG [NSAB, RTOG, and GoG]) reported the first analysis of RTOG-0815.[222,223] This phase III multicenter trial compared dose-escalated RT alone (arm 1), achieved by either 3DCRT or IMRT (79.2 Gy), combined LDR (110 Gy with ^{125}I or 100 Gy with ^{103}Pd) brachytherapy boost with 3DCRT or IMRT (45 Gy to the prostate and SVs), or combined HDR (two fractions of 10.5 Gy per fractions) to dose-escalated RT with the addition of 6 months ADT (arm 2).[222,223] This trial was specifically designed to address the question of the need for ADT when dose-escalated radiation

is used. Eligible patients had either clinical stage T2b-T2c, or a GS of 7, or pretreatment PSA greater than 10 and 20 ng/mL or less. Patients harboring all three or more than 50% of cores positive were ineligible (but eligible for RTOG-0924). While this trial with a median follow-up of 6.3 years failed to demonstrate an OS advantage (the primary end point), there was an improvement in the risk of metastasis (*P* , .001), prostate cancer–specific survival (*P* = .007), and PSA failure (*P* , .001). Only 219 deaths occurred triggering the interim analysis, with only 10 in arm 1 (RT alone) and 1 in arm 2 (RT + ADT) attributed to prostate cancer. Thus, we believe that with longer follow-up, an OS end point may be met.

At UCSF, we have long favored brachytherapy boost (or SBRT) for suitable patients treated with curative intent, based on the lower PSA nadir, degree of metabolic atrophy noted, and PSA control rates compared to any form of dose-escalated EBRT (including proton beam RT).[224-226] This philosophy seems to have been vindicated by the findings from the ASCENDE-RT trial, which confirmed a substantially higher PSA control rate with an LDR brachytherapy boost after ADT and EBRT compared to ADT and dose-escalated EBRT alone (see the discussion of brachytherapy).[191,227]

Multiple phase III RCTs and several meta-analyses have been published in the peer-review literature that compared RT alone with RT and ADT.[8] At UCSF, the authors' practices regarding integrating pelvic RT and hormonal therapy are summarized in Table 73.5. Previously, RTOG-9408 was designed to evaluate whether similar duration and timing of ADT (2 months neoadjuvant [NHT] and 2 months concurrent) could improve outcomes in patients with primarily IR disease.[186] Among the 1,979 eligible patients, 54% had IR disease and 11% had HR disease. With a median follow-up of 9.1 years, 10-year OS (57% vs 62%; *P* = .03), PCSM (8% vs 4%; *P* = .001), PSA failure (41% vs 26%; *P* , .001), and DMs (8% vs 6%; *P* = .04) were significantly in favor of the ADT arm. In a post hoc analysis, the benefit in OS and PCSM appeared to be primarily among IR patients. Two-year positive prostate biopsy rates (39% vs 20%; *P* , .001) were significantly improved with ADT. The authors give 2 months of NHT using a luteinizing hormone–releasing hormone (LHRH) agonist and an antiandrogen. An updated post hoc subset analysis of RTOG-9408 concluded that ADT was only beneficial in patients with unfavorable IR prostate cancer.[228] An even

more recent analysis using an MMAI system demonstrated that this same study could be used identify patients who are most likely benefit from the addition of ADT.[229]

TABLE 73.5 GENERAL RECOMMENDATIONS FOR RADIATION THERAPY AND ADT

Therapy	Low Risk	Favorable Intermediate Risk	Unfavorable Intermediate Risk	High/Very High Risk
Active surveillance	Preferred	In highly selected patients	Only appropriate in those with a short life expectancy	Only appropriate in those with a very short life expectancy
Radiation therapy	PORT	PORT ± ADT (4 mo)[a]	WPRT + NHT (4 mo)	WPRT
ADT	Not indicated	None or neoadjuvant and concurrent with (4 mo) or adjuvant ADT if prostate-only EBRT (4 mo)	Neoadjuvant and concurrent with (4 mo) ADT with	Neoadjuvant, concurrent and adjuvant (18-36 mo)
Other				± Second-generation ADT or chemotherapy in selected patients[b]

ADT, androgen deprivation therapy; EBRT, external beam radiation therapy; NHT, neoadjuvant hormonal therapy; PORT, prostate-only radiation therapy; WPRT: whole-pelvic radiation therapy.

[a]Omit ADT if low risk by Artera assay.

[b]STAMPEDE trial.

In addition to NHT, 2 to 3 years of AHT (eg, LHRH agonist) is recommended for HR disease, but on occasion, lifelong androgen deprivation is used in patients with very HR disease (Table 73.5). Early trials demonstrated that for men with locally advanced disease, initial management with hormonal therapy resulted in a survival advantage when compared to deferred ADT.[8,230] Subsequently, numerous trials showed that the addition of ADT to EBRT improved survival for men with IR and HR

disease.[8] There is also clear level I evidence that EBRT plus ADT renders a better survival than ADT alone for men with locally advanced disease.[183,231,232]

SEQUENCING, TIMING, AND DURATION OF ANDROGEN DEPRIVATION THERAPY AND RADIOTHERAPY

Sequence-Dependent Interactions Between Androgen Deprivation Therapy and External Beam Radiation Therapy

NHT implies delivery of the hormone prior to definitive radiation, whereas AHT implies the initiation of hormonal therapy after the completion of radiation. Few studies have assessed the optimal sequence or precise duration of ADT. RTOG-9413 randomized 1,323 men to either receive 4 months of NHT (commenced 2 months prior to starting EBRT) compared to 4 months of AHT.[176] The authors noted sequence-dependent beneficial interactions, such that when NHT is used, PSA control favored the use of WPRT over PORT. However, NHT plus WPRT was also associated with higher rates of late grade 3 GI toxicity at 10 years occurring in 5.1%, compared to 1.6% and 0.6% in both AHT groups and patients treated with NHT plus PORT (P = .0009). Of note, when PORT is used, AHT appears to be at least as effective as NHT. The mechanism by which these sequence-dependent interactions occur is unknown.

Optimal Duration of Short-Term Androgen Deprivation Therapy (Indicated for Intermediate-Risk Patients)

To date, there are at least eight randomized trials (two Canadian, one Irish, one Australian, two conducted in the United States [RTOG-9202, RTOG-9910], and two conducted by the EORTC) evaluating the optimal duration of ADT with a survival end point and an additional three randomized trials (two Canadian and one EORTC) with a PSA control end point.[8] The Canadian Urologic Oncology Group study randomized 378 patients to either 3 or 8 months of NHT plus EBRT, whereas the Irish Clinical Oncology Research Group designed a randomized study comparing 4 and 8 months of NHT with EBRT.[233,234] TROG compared 0 versus 3 versus 6 months ADT with EBRT, whereas RTOG-9910 compared 8 versus 28

weeks of NHT (total 4 vs 9 months).[235,236] Taken together, these studies suggest that for patients with IR disease, there is no reason to extend short-term ADT beyond 4 months when combined with EBRT.[8,118]

Optimal Duration of Long-Term Androgen Deprivation Therapy (High-Risk Patients)

A meta-analysis of RTOG trials conducted more than 20 years ago suggested that long-term ADT was superior to short-term ADT for patients with HR disease.[118] This assertion was subsequently confirmed by EORTC-22961 that compared 6 months with 36 months of AHT in 1,113 patients with locally advanced prostate cancer and demonstrated the superiority of the latter.[69] RTOG-9202, another phase III trial, also demonstrated that the addition of 24 months of AHT could improve the outcome in HR patients, compared to short term (4 months).[237] Aside from OS, all other end points were significantly in favor of the long-term ADT arm: PCSM (83.9% vs 88.7%; $P < .0001$), DFS (13.2% vs 22.5%; $P < .0001$), and biochemical control (31.9% vs 48.1%; $P < .0001$). In subgroup analysis, again, patients with a GS of 8 to 10 had a significant improvement in OS with long-term ADT, but not with a GS of 2 to 7. The authors speculate that the absence of OS difference may be due to insufficient follow-up among patients with a GS of 2 to 7. These data, as previously noted, are completely consistent with the meta-analysis of five consecutive RTOG randomized controlled prostate cancer trials (including RTOG-8531 and RTOG-8610), where 2,742 men were stratified into four previously identified risk groups based on GS, clinical T-stage, and pelvic nodal involvement.[118] More recently, Nabid et al compared 18 versus 36 months of ADT in patients with HR disease (discussed earlier).[67] This was a *superiority* trial (should have been a noninferiority trial) that was 35% smaller ($n = 630$) than the earlier EORTC trial that showed that 6 months was inferior to 36 months.[69] The EORTC trial also included more patients with T3-4 disease and node-positive patients.[67] Despite this suboptimal study size, at 5 years, the trial led by Nabid et al[67] demonstrated a trend in favor of 36 months in terms of OS (91% vs 86% [$P = .07$]), as well as biochemical control ($P = .02$) and DFS (45% vs 39%; $P = .08$) at 10 years. Thus, for patients who are primarily at HR because of a PSA greater than 20 ng/mL and node-negative disease, 18

months may be adequate, but for patients with bulkier or node-positive disease, we favor longer term ADT.

Toxicities Associated With Androgen Deprivation Therapy

Having established that ADT improves survival when combined with RT, enthusiasm has been somewhat tempered by the increasing recognition of the potentially serious complications of ADT.[238] Some of these complications have been exaggerated.[239] What is clear is that the risks of fractures, fatigue, weight gain, osteoporosis, depression, decreased cognitive function, ED, loss of libido, gynecomastia, anemia, decreased high-density lipoprotein, insulin resistance, and hot flashes are increased with ADT. For example, in a study of 50,613 men with prostate cancer compiled from a linked database of SEER and Medicare, the addition of ADT significantly increased the risk of any fracture from 12.6% to 19.4%; fractures requiring hospitalization similarly increased from 2.37% to 5.19%.[240]

More controversial is the issue of the impact of ADT on cardiovascular disease.[241-245] Some studies have raised the question of whether ADT, by way of increasing body fat and cholesterol levels, increases the risk of cardiovascular disease.[239] In an observational study of a population-based cohort of 73,196 patients with clinically localized prostate cancer, ADT was associated with an increased risk of incident diabetes (hazard ratio 1.44; P , .001), cardiovascular disease (hazard ratio 1.16; P , .001), myocardial infarction (hazard ratio 1.11; P = .03), and sudden cardiac death (hazard ratio 1.16; P = .004). However, data from RCTs of RT with or without ADT have generally not shown any increased cardiovascular disease, although these studies were not powered adequately.[246] The bottom line is that *if* ADT increases the risk of cardiovascular disease, the risk is quite low and the subset of patients who are at risk are those with severe underlying cardiovascular disease.[242]

Many investigators adopted the belief that LHRH agonist might be more cardiotoxic than the gonadotropin-releasing hormone (GnRH) antagonist. Despite encouraging findings from the HERO trial involving the oral antagonist relugolix, the subsequent randomized trial evaluating major adverse cardiovascular events in patients with prostate cancer with

concurrent cardiovascular disease treated with the GnRH antagonist degarelix or antagonist leuprolide was closed early due to a small number of events and no difference in major cardiovascular side effects at 1 year between the treatment groups.[247,248] Thus, this question remains unanswered.

In addition to cardiovascular risk, another area to which much attention has been paid is the risk of the potential impact of ADT on the brain. For example, Nead et al published a series of methodologically flawed studies that essentially ignore the tendency for men with declining mental status to be at greater risk for receiving ADT.[249,250] The best data suggest that the risk of damage to both the central nervous system and cardiovascular systems is low, such that with rare exceptions the benefits justify the risk.[246,251]

POSTOPERATIVE (POSTPROSTATECTOMY) RADIATION THERAPY

Local Versus Distant Recurrence

A significant number of men undergoing an RP for IR and HR prostate cancer will experience a recurrence, with the only curative treatment afterward being postoperative radiation.[252] Such patients tend to have adverse characteristics, such as a high percentage of positive biopsies (eg, ≥50%), higher GSs (eg, ≥7), SVI, positive surgical margins (PSMs).[31,253] For example, D'Amico et al reported 5-year recurrence rates exceeding 75% in IR patients with more than 50% of their biopsies positive who underwent RP at the University of Penn or Harvard University.[31] Another frequently overlooked fact is that patients with high-grade tumors tend to recur after RP, even if they have *pathologically* confined disease. For example, from a series of 904 patients undergoing post-RP at the Mayo Clinic in the subset of patients with high-grade tumors (eg, ≥8-10), the recurrence rates at 5 years exceeded 50%, even if they have pathologically confined disease (most do not have organ-confined disease).[254] In an analysis of patterns of treatment failure in the study by the South West Oncology Group, SWOG-8794, the first randomized trial evaluating ART in patients with adverse pathologic features (pT3a-b or PSM), the predominant site of failure was believed at that time to be local rather than metastatic.[255] However, these historical data must now be considered unreliable, given the fact that PSMA-PET imaging was not available and that conventional imaging (eg,

CT, MRI, and bone scans) has a very poor sensitivity in this setting. More recent data incorporating PSMA imaging tends to support the notion that regional recurrences may be as common or more common than local recurrences.[256]

Based on three early trials, the American Urological Association (AUA) and ASTRO produced guidelines in 2013, which encouraged the consideration of ART in patients with adverse pathologic feature following RP.[257-260] However, subsequently, three more contemporary trials, and an associated meta-analysis, specifically comparing adjuvant versus early salvage, provided support for a contrary opinion.

The largest of three earlier studies was EORTC-22911 (n = 1,005) in men with pT2-3N0 and at least one of the following risk factors: ECE, PSM, or SVI.[261] In the ART arm, radiation was commenced at a median of 90 days postoperative. ART consisted of 50 Gy in 25 fractions to a large volume that encompassed the surgical limits and subclinical disease, followed by 10-Gy boost given over five fractions to a reduced margin around the prostatic bed. The protocol SRT was a bit more aggressive delivering 70 Gy in 35 fractions. Five-year biochemical PFS was significantly improved from 52.6% to 74.0% (P , .0001) with ART, representing a 52% reduction in PSA relapse. The treatment benefit was significant for all postoperative prognostic factors, including negative surgical margins or absence of SVI and ECE. Long-term results, with a median follow-up of 10.6 years, were recently published and continued to support the use of ART.[258] The ART arm continued to have significantly improved biochemical PFS (60.6% vs 41.1%; hazard ratio 0.49, $P < .0001$). Similarly, 10-year cumulative rate of locoregional relapse was lower in the ART arm (7.3% vs 16.6%; hazard ratio 0.45, $P < .001$). No difference in metastases-free survival or OS was observed, though it was not powered to detect a difference. However, the 10-year cumulative incidence of severe (grade 3) late toxicities (5.3% vs 2.5%, $P = .052$) and late grade 2 or higher GU toxicities (21.3% vs 13.5%; $P = .003$) were higher in the ART arm. There was no significant difference in cumulative incidence of DMs ($P = .94$), prostate cancer mortality ($P = .34$), or OS ($P = .20$). In the wait-and-see arm, 275 patients had clinical or biochemical progression, of which 231 (84%) went on to receive active treatment and 155 (56%) received SRT at a median PSA of 1.7 ng/mL.

The first of the early trials, SWOG-8794, randomly assigned 425 node-negative patients initially treated with RP but found to have either PSM or pT3 (ECE and/or SVI) disease to ART or observation.[262] Central pathology review was performed in 73% of patients, and there was a 95% concordance with the community pathologist. Ninety percent of patients had ECE or PSM. Two-thirds of patients had a postoperative PSA less than 0.2 ng/mL. ART consisted of 60 to 64 Gy. Median PSA relapse-free survival was significantly longer with ART (10.3 vs 3.1 years; hazard ratio 0.43; *P* , .001). Updated results have been published with a median follow-up of 12.6 years.[257] The 10-year DM-free survival (71% vs 61%; hazard ratio 0.71; *P* = .016) and OS (74% vs 66%; hazard ratio 0.72; *P* , .023) were significantly improved with ART. The median DM-free survival was prolonged from 12.9 to 14.7 years with ART, and OS from 13.3 to 15.2 years. On subgroup analyses, there was no interaction between the adverse pathologic features and treatment effect, and therefore, the benefit in DM-free survival was seen in all subsets. Among patients in the ART arm, those with an undetectable postoperative PSA had a significantly better 10-year DM-free survival (73% vs 65%; *P* = .03) than those with a PSA greater than 0.2 ng/mL. In the observation arm, only one-third of patients eventually received SRT, of which the median pre-RT PSA was 1.0 ng/mL. Hormonal therapy was initiated later (median 12.4 vs 9.9 years) and less frequently (39% vs 50%) in the ART arm. Complications observed in the ART arm included proctitis (3.3% vs 0%), urethral stricture (17.8% vs 9.5%), and total urinary incontinence (6.5% vs 2.8%).

From the German Cancer Society, ARO-96-02/AUO-09/95 accrued 388 patients from 22 centers with pT3 or PSM to either ART (60 Gy in 2 Gy fractions) or observation.[263] In contrast to SWOG-8794 and EORTC-22911, only patients who achieved an undetectable post-op PSA were included, 3DCRT planning was mandated, and central pathology review was required. In the initial report with a median follow-up of 54 months, using intention-to-treat analysis of only patients who achieved an undetectable postoperative PSA, ART significantly improved PFS (*P* , .0001). When analyzed according to the received treatment, 5-year PFS was 72% versus 54% in favor of ART (*P* = .0015; hazard ratio 0.53). ART was very well tolerated, with only 3% reporting acute grade 3 bladder toxicity and none with grade 3 rectal toxicity (12% had grade 2 rectal toxicity). Of note, the

compliance in the ART arm was surprisingly poor—19% did not proceed with RT. Updated results with 10-year follow-up have since been published.[259] The 10-year PFS was significantly better in the ART arm (56% vs 35%; hazard ratio 0.51, *P* , .0001). However, despite longer follow-up, no difference in the development of DMs (*P* = .53) or OS (*P* = .59) was seen. The cumulative incidence of late grade 3 toxicities was 5.3% with ART and 2.5% with observation (*P* = .052). There was only one event of late grade 3 toxicity, which involved the bladder, and no late grade 4 GI or GU toxicities were observed.

A significant limitation of these three clinical early trials was that they were conducted prior to the current era of ultrasensitive PSA assays, which can detect PSA levels as low as 0.01 ng/mL. For instance, the ARO trial defined undetectable PSA as those less than 0.1 ng/mL, of which 59% had a PSA of greater than 0.03 to 0.1 ng/mL. In the EORTC-22911 and SWOG-8794 studies, 11% and 34% of patients, respectively, had a postoperative PSA greater than 0.2 ng/mL. In effect, a significant proportion of patients enrolled in these trials had "measurable disease" and thus received SRT.[264] Although there was an initial surge in enthusiasm in embracing ART, it has given way to increasing skepticism. In an observational study of post-op patients identified by the NCDB, which tracks outcomes on 71% of newly diagnosed cancer cases in the United State, 130,681 patients with at least one HR pathologic factor and diagnosed between 2004 and 2011 were analyzed.[265] The overall rate of ART was surprisingly low (9.9%) and did not change during the study period despite three RCTs demonstrating improved outcomes with ART. Similarly, SEER data of 35,361 post-op patients diagnosed between 2004 and 2011 revealed that ART utilization remained low, 15.8% after March 2009 versus 13.5% before.[266]

Given the prevalence of ultrasensitive PSA assays, it is unclear whether a strategy of AS with PSA tests and the early initiation of RT only when PSA has shown an upward trend can yield equivalent or better results. The advantage of such an approach is that perhaps the 50% of patients who do not relapse after surgery will be spared from RT. The disadvantage is that biochemical control and DM-free survival (SWOG-8794) may be compromised by waiting too long to intervene with definitive treatment, which could serve as a nidus for metastatic spread. In an editorial, King showed that for every 0.1 ng/mL increment in postoperative PSA, there is

an estimated 4% reduction in biochemical control.[264] Nonetheless, the EORTC-22911, SWOG-8794, and ARO-96-02 provide consistent level I evidence that ART is better than expectant management in terms of biochemical control, at an acceptable toxicity. It remains to be seen whether with longer follow-up this translates into an improvement in survival. Accordingly, in 2013, the ASTRO/AUA published guidelines based on a systematic review on ART and SRT.[260] The panel recommended that those with adverse pathologic features (SVI, EPE, and PSM) should be counseled and that there is level I evidence that ART reduces the risk of BCR, local recurrence, and clinical cancer progression.

Three Newer Trials and the ARTISTIC Meta-analysis

The three key more recent randomized phase III trials, RADICALS, RAVES, GETUG-17, and their associated meta-analysis also investigated ART versus early SRT.[267-270] As a group, these trials tended to suggest that SRT should be preferred to ART, primarily due to reduced toxicity (because of sparing RT is a significant subset of patients). RADICALS was a MRC-led phase III trial that randomized postoperative patients to immediate postoperative RT or early SRT. RADICALS also has a hormone duration randomization substudy in which patients were randomized to RT alone or 6 months or 2 years of adjuvant hormones. RAVES was a phase III multicenter study ran in Australia and New Zealand, while GETUG-17 was a French study that randomized patients to ART and ADT versus early SRT with ADT. The major shortcoming of these three trials is that the committed the "three sins" of trial design described earlier. First, the patient eligibility included patients for whom we would never recommend ART, including those with GS of 7 or pre-op PSA greater than 10 ng/mL (sin #1). As a result, only 15% to 20% of the recruited patients had HR disease. Second, the studies were grossly underpowered due to discontinuation by the monitoring committees because of their low event rates (sin #2). In addition, ADT was not used nor was elective nodal irradiation (ENI) applied (sin #3). Thus, although it is likely to be safe to defer RT pending a detectable PSA for many patients, for those with truly HR disease, ART should still be considered.

Salvage Radiation Therapy

An update of the often-cited Stephenson predictive nomogram to estimate BCR following SRT was published.[3,271] This was based on multi-institutional data of 2,460 patients. Unlike the initial nomogram, patients with pre-SRT PSA less than 0.2 ng/mL were included in the updated nomogram. The median pre-SRT PSA was 0.5 ng/mL, with 18% of patients having less than 0.2 ng/mL. Higher pre-SRT PSA was associated with worse outcomes. The 5-year freedom from BF was 71%, 63%, 54%, 43%, and 37% for those with a pre-SRT PSA of 0.01 to 0.2, 0.21 to 0.50, 0.51 to 1.0, 1.01 to 2.0, and greater than 2.0 ng/mL, respectively (P , .001). Similarly, the 10-year cumulative incidence of DM was 9%, 15%, 19%, 20%, and 37%, respectively (P , .001). Independent predictors of BCR included higher pre-SRT PSA, higher GS, presence of ECE, SVI, negative surgical margins, lack of ADT, and SRT dose less than 66 Gy.

Genomic classifiers are being used to identify post-op patients with adverse pathologic features who would benefit from ART. In a study by Dalela et al, they evaluated a risk stratification tool that included the Decipher multigene expression array score (GenomeDx Biosciences, Vancouver, British Columbia, Canada) with routine clinicopathologic features.[272] Their cohort included 512 post-op patients with at least one pathologic adverse feature (≥pT3a disease, PSM, or pathologic LNI) and received either ART or initial observation (with 42% subsequently receiving SRT). In multivariate analysis, in addition to GS, pathologic pT3b-4 disease, and LNI, a high Decipher score was an independent predictor of higher risk of clinical recurrence. Based on these factors, a novel nomogram was created to identify those at higher risk of clinical recurrence and thus would benefit from ART, with a predictive accuracy of 85%. In another study of Decipher, Freedland et al investigated whether it could predict for the subsequent development of metastatic disease in 170 post-op patients treated with SRT for recurrence.[273] On multivariate analysis, the Decipher score was significantly predictive of metastases (hazard ratio 1.56, P = .003). By identifying patients at HR of developing metastases, treatment intensification with hormonal therapy and/or systemic therapy can be explored. Likewise, patients with low risk of developing clinical recurrence

or metastases could be observed. While encouraging, external validation in larger prospective cohorts is needed.

As it stands, we have only retrospective data, though very large patient cohorts, that suggest that early SRT is more effective than later SRT, and this is likely due to reduced tumor burden.[3,271] Whether *early* SRT is as good as ART is unknown. Although RADICALS, RAVES, and GETUG-17 tend to suggest that SRT should be preferred to ART, there are some major limitations with these studies, as discussed earlier.

Androgen Suppression Therapy and Postoperative Radiation Therapy

Extrapolating from the benefits of shown in multiple phase III trials in the definitive setting, it is not surprising that ADT would be investigated in the postoperative setting. Recently, the results of RTOG-9601, a placebo-controlled phase III study to evaluate the addition of 2 years of antiandrogen therapy with SRT, were published.[274] Eligible patients included those with pathologic stage T2 with a PSM or T3 without nodal involvement. Patients were also required to have a detectable PSA of 0.2 to 4.0 ng/mL and were considered eligible. Bicalutamide 150 mg daily for 24 months was used in the antiandrogen arm. The median follow-up among surviving patients was 13 years. The addition of antiandrogen significantly improved 12-year OS (76.3% vs 71.3%; hazard ratio 0.77, P = .04), incidence of death from prostate cancer (5.8% vs 13.4%, P , .001), cumulative incidence of metastatic prostate cancer (14.5% vs 23.0%, P = .005), and BCR (44.0% vs 67.9%, P , .001). Post hoc subgroup analyses suggested that those with a PSA greater than 1.5 ng/mL or a GS of 7 had the greatest OS benefit. There was no difference in radiation-related acute or late toxicities. As expected, gynecomastia was more common in the antiandrogen arm and occurred in 69.7% of patients. Of note, antiandrogens alone are rarely used currently, replaced by gonadotropin-releasing hormone agonist and antagonist, and are no longer approved by the FDA.

GETUG-AFU16 was a phase III trial that randomized 743 postoperative patients undergoing SRT for BCR with or without 6 months of goserelin.[275] All patients had to have an undetectable post-op PSA before BCR. The PSA at the time of randomization was less than 0.5 ng/mL in 80% of patients,

with the upper limit of acceptance being 2 ng/mL. After a median follow-up of 63 months, the 5-year PFS was significantly better in the hormone arm (80% vs 62%, *P* , .0001). Independent predictors of disease progression were pre-SRT PSA greater than 0.5 ng/mL, SVI, negative surgical margins, and pre-SRT PSA doubling time less than 6 months. There was no significant difference in acute or late GU and GI adverse events between the two arms.

In post-op patients with *very HR* clinicopathologic features, investigators are evaluating the addition of docetaxel to RT and ADT based on docetaxel and found improved survival in men with metastatic prostate cancer.[276] RTOG-0621 is a phase II study of 74 patients who had either a post-op PSA nadir greater than 0.2 ng/mL and a GS 7 or higher or a PSA nadir 0.2 ng/mL or less, GS 8 or higher, and pT3 or higher. Patients received 6 months of ADT, RT, and six cycles of docetaxel after RT. The 3-year freedom from progression was 73%. Although grade 3 to 4 hematologic toxicities were common, only 4.1% of patients developed febrile neutropenia. Currently accruing, the follow-up phase II/III trial is NRG-GU002, which is randomizing patients with a GS 7 or higher and post-op PSA nadir 0.2 ng/mL or greater to ART and ADT with or without adjuvant docetaxel.

Postoperative Radiation Therapy Dose

Currently, ART doses of 60 to 64 Gy and SRT doses of 66 to 70 Gy appear to be the most used. The ASTRO/AUA guidelines recommend at least 64 to 65 Gy in the post-op setting, with no distinction between adjuvant and salvage doses.[277] In a retrospective study by Cozzarini et al, 334 patients with adverse pathologic features and an undetectable postoperative PSA who received ART were analyzed for a dose response.[278] From 1993 to 2003, the RT dose gradually increased from 55.8 to 72 Gy. When stratified by dose (,70.2 Gy [median 66.6 Gy] vs ≥ 70.2 Gy [median 70.2 Gy]), the high-dose group had significantly better 5-year biochemical relapse-free survival (83% vs 71%; *P* = .001) and DFS (94% vs 88%; *P* = .005). In a systematic review, 71 studies (10,034 patients) of patients treated with SRT were identified.[189] The median radiation dose prescribed was 65.8 (range 60-76 Gy). A sigmoidal dose-response relationship was identified between SRT dose and relapse-free survival, with a TCD_{50} of 65.8 Gy and a 2.0%

improvement with each additional Gy within a dose range of 60 to 70 Gy. Based on the sigmoidal dose-response curve, the relapse-free survival was 58.4% and 38.5% for 70 and 60 Gy, respectively. The clinical outcomes of the SAKK-09/10 trial, which randomized patients to conventional dose (64 Gy) or dose-intensified SRT of 70 Gy to the prostate bed without ADT, showed no differences in outcomes, including PFS, time to ADT, or radiation dose OS, but a significant increase in late grade 2 or higher GI toxicity.[279]

NRG-GU003 is a randomized phase III trial of hypofractionated (62.5 Gy in 25 fractions) versus conventionally fractionated (66.6 Gy in 37 fractions) RT in postprostatectomy patients. After a median follow-up of 2 years, no difference in the BF rate was noted between the two arms. Although patient-reported GI toxicity was higher with the hypofractionated RT regimen when the radiation was completed, after 2 years, the hypofractionated regimen was noninferior to the conventionally fractionated regimen with respect to patient-reported GI or GU toxicities.[280]

Postoperative Radiation Therapy Volume

Several consensus guidelines on delineation of the CTV in post-op patients have been published.[281-285] We refer to readers to these details but acknowledge that PSMA-PET imaging and clinical features in individual patients should result in personalized refinement of these fields. Another area of controversy has involved the utility of prophylactic ENI in the post-op setting, especially for those with higher risk disease.[286-289] As a historical note, retrospective data assessing ENI with SRT have been supportive, with a significantly better 5-year freedom from BF of 62% versus 49% (*P* , .001), but more importantly, RTOG-0534 confirmed the value of evaluated ENI and ADT.[1,90]

Postoperative Radiation Therapy: Conclusions

We continue to endorse the original ASTRO/AUA guidelines whereby patients with adverse pathologic features should be jointly counseled by their urologist and radiation oncologist on the pros and cons of ART.[66,277] In those devoid of very unfavorable features (eg, SVI, nodes positive) and undetectable post-op PSA of less than 0.02 ng/mL, we recommend

observation with a PSA every 3 to 6 months. We recommend offering early SRT in those with a consisting rising PSA, even if below 0.2 ng/mL. The authors recommend adherence to the 2021 NRG updated consensus guidelines on the definitions of CTV in the postoperative setting.[285] For adjuvant patients, the authors usually prescribe 66 Gy, whereas for salvage patients, the authors use 70 Gy, both of which are in 1.8 Gy per fraction to the pelvis and 2.0 Gy to the bed. WPRT, as defined by the RTOG contouring guidelines, to a dose of 45 Gy, is considered depending on the extent of pelvic lymph node dissection, presence of SVI, and the estimated nodal involvement.[285] For both the prostate bed and ENI, we recommend IMRT technique with image guidance.

There are now at least three phase III trials that support the addition of ADT with post-op RT.[91,274,275] We recommend that those at higher risk of developing metastatic disease, including a detectable post-op PSA, pre-SRT PSA greater than 0.5 ng/mL, SVI, PSA doubling time less than 6 months, or node-positive disease, be considered for 4 to 6 months of LHRH, or longer for those at particularly HR (eg, GS = 9-10). In addition, we favor IGRT in the postoperative setting guided by the place of gold marker seeds at the anastomosis.[290]

CONCLUSIONS AND RECOMMENDATIONS

In summary, compared to patient convenience, cost, and PSA control, we favor PPI, HDR, or SBRT monotherapy for patients with favorable IR disease. For unfavorable IR disease, we favor short-term ADT (4 months) combined with IMRT and a boost with either PPI, HDR, or SBRT, with WPRT. In selected patients with biomarkers indicative of nonbenefit from ADT, low-volume disease omitting ADT seems appropriate. For truly HR patients, we favor long-term ADT (eg, ≥28 months) combined with WPRT and an HDR, an SBRT, or a PPI boost. For patients who are HR by PSA (eg, PSA . 20 ng/mL) but no other factors, 18 months of ADT may be adequate. Image-guided techniques *without* rectal spacer are preferred at UCSF. In selected patients (especially those age ,70 years with node positive), additional systemic agents (eg, abiraterone) are strongly considered. Based on recent data, leveraging novel biomarkers and/or molecular assays as well as advances in imaging will help us refine what we

mean by the categories that range from favorable IR to very HR disease. In the postoperative setting, we favor adjuvant over early salvage IMRT guided by ultrasensitive PSA monitoring combined with ADT, in the very highest risk patients but salvage in the more favorable patients.

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CHAPTER 74

Testicular Cancer

Gerard C. Morton

EPIDEMIOLOGY

Testicular cancer is the most common malignancy among young men in North America and most Western European countries, although it accounts for only 1% of all male tumors.[1] More than 95% of testicular cancers are germ cell tumors, with almost equal division between seminomas and nonseminomas. Seminomas are most commonly diagnosed between the ages of 30 and 34 years, whereas nonseminomas are usually diagnosed 5 to 10 years earlier. Other histologies such as sex cord-stromal tumors and lymphomas are less frequent, although the latter is the most common testicular malignancy in men older than 60 years.[2] It is estimated that just over 9,000 new cases of testicular cancer are diagnosed annually in the United States, with approximately 470 deaths.[1]

There is a marked variation in incidence worldwide. The highest incidence occurs in Northern and Western European countries (up to 9 per 100,000) and the lowest in Asian and African populations (<1 per 100,000).[3] In North America, the incidence of testicular cancer in White males is around 4 to 5 times that in African American or Asian American males, with an overall increase in age-adjusted incidence rate in the United States of 72% between 1975 and 2004.[4,5] A continued increasing incidence is seen worldwide, with a particularly rapid increase in the past decade in Asian countries, which previously had a low incidence. Despite the increased incidence of both seminoma and nonseminoma, there has been a significant reduction of mortality and improvement in survival. The most dramatic reduction in mortality occurred in the 1970s with the introduction of cisplatin-based chemotherapy.[6,7] The 10-year survival for seminoma increased from 81% in the 1970s to 95% in 2000 to 2002 and that for nonseminoma increased from 54% to 92%.[8] Survival continues to improve in most countries.[9]

A history of undescended testicle has long been recognized as a risk factor for the development of testicular cancer. There is also an increased risk of malignancy in the normally descended contralateral testicle. The relative risk (RR) is estimated to be 6 in the undescended testicle and 2 in the contralateral testicle.[10] The mechanism of the increased risk is unclear. It is hypothesized that a common etiologic agent predisposes to both testicular maldescent and subsequent malignancy (uterine theory). Nevertheless, it is also possible that the maldescended testicle is subject to a hostile and malignancy-inducing environment (position theory). If that were the case, orchidopexy during the prepubertal phase would be expected to reduce the risk of testicular cancer. However, the RR of developing testicular cancer remains higher than in the general population, even after early orchidopexy.

The temporal and geographic variation in incidence rates strongly suggests environmental etiologic factors. Global epidemiologic studies demonstrate an association between gross domestic product, alcohol consumption, inactivity, obesity and high cholesterol, and testicular cancer incidence.[3] Male infertility is associated with an increased risk of testicular cancer, and infertile men with abnormal semen analyses have a 20-fold greater risk of testicular cancer than the general population.[11,12] The increasing incidence has paralleled a decline in semen quality over the past several decades.[13] This has led to the hypothesis that poor semen quality, testicular cancer, cryptorchidism, and hypospadias represent a testicular dysgenesis syndrome as a result of disruption of gonadal development during embryonal development.[14] Various exogenous hormonal disruptors (eg, exogenous estrogens, herbicides) have been proposed, although with no conclusive evidence implicating one particular agent.[15]

A few modifiable environmental exposures have been identified as possible risk factors for testicular cancer. Men who have used muscle-building supplements were found to have an increased incidence of testicular cancer. The association was greatest in men who started supplement use at a younger age and were exposed to different supplement types or used supplements for a longer duration.[16] Likewise, cannabis exposure was found to be associated with the risk of testicular germ cell tumors in some, but not all, reports.[17,18] These associations need further validation, but the magnitude of the association and the positive correlation between dose and incidence support a causal relationship.

Approximately 2% of patients report a positive family history. Sons of cases have a 4- to 6-fold increase in risk and brothers a 6- to 10-fold increase.[19,20] Migration studies in the Nordic countries have strengthened the hypothesis of shared genes rather than shared environmental exposure, and several candidate genes have been proposed to explain familial testicular cancer; however, it is likely that no single genetic change explains most familial cases.

In summary, germ cell tumors are thought to arise in testes predisposed to the development of malignancy owing to a combination of familial predisposition and intrauterine hormonal imbalance, later compounded by environmental factors and manifested by impaired spermatogenesis.

PATHOLOGY

More than 95% of testicular neoplasms are germ cell tumors. The most recent World Health Organization (WHO) classification of testicular tumors[21] divides germ cell tumors into two groups: those derived from germ cell neoplasia in situ (GCNIS) and those unrelated to GCNIS. The former group includes seminomas and nonseminomas that share recognizable morphologic and genetic similarities, such as impaired spermatogenesis, microlithiasis, and amplification of chromosome 12. Nonseminomas include embryonal carcinoma, yolk sac (postpubertal type), choriocarcinoma, trophoblastic tumors, and postpubertal teratomas. The group not derived from GCNIS is heterogeneous and includes spermatocytic tumors, prepubertal teratoma, dermoid cysts, and prepubertal yolk sac tumors. Sex cord-stromal

tumors make up the remaining 3% to 4% of testicular neoplasms, and most are benign (Table 74.1).

TABLE 74.1 CLASSIFICATION OF TUMORS OF THE TESTIS

Germ Cell Tumors Derived From Germ Cell Neoplasia In Situ
Noninvasive Germ Cell Neoplasia
Germ cell neoplasia in situ
Germinoma Family of Tumors
Seminoma
Seminoma with syncytiotrophoblastic cells
Nonseminomatous Germ Cell Tumors
Embryonal carcinoma
Yolk sac tumor, postpubertal type
Choriocarcinoma
Trophoblastic tumors, epithelioid and cystic
Teratoma, postpubertal type
Teratoma with somatic-type malignancy
Mixed Germ Cell Tumors
Germ Cell Tumors Unrelated to Germ Cell Neoplasia In Situ
Spermatocytic tumor
Spermatocytic tumor with sarcomatous differentiation
Yolk sac tumor, prepubertal type
Teratoma, prepubertal type
Mixed teratoma and yolk sac tumor, prepubertal type
Sex Cord-Stromal Tumors
Leydig cell tumor
Sertoli cell tumor
Granulosa cell tumor
Tumors in the fibroma-thecoma group
Mixed sex cord-stromal tumor

Adapted from Moch H, Amin MB, Berney DM et al. The 2022 World Health Organization classification of tumours of the urinary system and male genital organs—part A: renal, penile, and testicular tumours. *Eur Urol*. 2022;82(5):458-468. https://creativecommons.org/licenses/by/4.0/.

CLASSIFICATION OF TESTICULAR TUMORS

Germ Cell Tumors

Tumors Derived From Germ Cell Neoplasia In Situ

Germ Cell Neoplasia In Situ

GCNIS, previously called intratubular germ cell neoplasia or testicular carcinoma in situ, is currently the WHO recommended term for this precursor lesion.[22] This entity is found

adjacent to invasive germ cell tumors in >95% of cases and also in all clinical groups known to be at high risk for testicular cancer development: cryptorchidism (2%-4%), infertility (1%), ambiguous genitalia (25%), and contralateral testes of patients with testicular cancer (5%).[23] GCNIS is characterized by seminiferous tubules showing decreased spermatogenesis in which the normal constituents of the tubules are replaced by abnormal germ cells with the appearance of seminoma cells. These cells stain strongly for placental-like alkaline phosphatase (PLAP), whereas normal germ cells are negative. GCNIS is a precursor to testicular germ cell cancer and has a 50% risk of developing into an invasive tumor within 5 years. It is hypothesized that the cells originate from primordial germ cells early during embryogenesis, possibly owing to an excess of estrogens. They likely remain within the seminiferous tubules in a dormant stage until puberty when replication begins, possibly as a consequence of raised sex hormone levels. Transition to an invasive germ cell tumor then occurs.

SEMINOMA

Seminoma accounts for >50% of all germ cell neoplasms. Serum level of human chorionic gonadotropin (hCG) is elevated in 15% to 30% of men at presentation, related to the presence of syncytiotrophoblastic cells. These may be identified in 7% of tumors on routine hematoxylin and eosin sections or by immunoperoxidase stains in 24%. The presence of syncytiotrophoblastic cells does not alter prognosis. Serum α-fetoprotein (AFP) is not elevated in pure seminoma. Grossly, seminoma is a soft tan-colored diffuse multinodular mass. Focal necrosis is sometimes present. A prominent lymphocytic infiltrate is commonly seen within the fibrous stroma. More than 90% of seminomas will stain positive for PLAP.

NONSEMINOMATOUS GERM CELL TUMORS

Nonseminomatous germ cell tumors (NSGCTs) usually contain a mixture of germ cell types (embryonal, yolk sac, teratoma, and choriocarcinoma), although tumors composed of just one component may also be found. Commonly, NSGCTs are heterogeneous and present with a considerable amount of necrosis and hemorrhage on gross examination.

Embryonal carcinoma is the most common component in mixed tumors, and AFP- and hCG-positive cells are present in 33% and 20%, respectively. Postpubertal yolk sac tumors rarely occur in a pure form and have a complex histology. High levels of AFP are usually present. Postpubertal teratoma has marked morphologic differences from the prepubertal type with a predominantly solid appearance, disordered tissue arrangement, and frequent mitotic figures.[24] This tumor is not associated with elevated AFP or hCG and presents with distant metastasis in approximately 20% of the cases. Trophoblastic tumors have choriocarcinoma as the main component. This is the least common type of pure NSGCT and is present in about 4% of mixed tumors. It is particularly aggressive, almost always metastatic at diagnosis, often to brain, and is associated with high levels of hCG. Seminomatous components are also common in mixed tumors, and serum markers (AFP and hCG) are elevated depending on the relative germ cell elements present.

Tumors Unrelated to Germ Cell Neoplasia In Situ

This heterogeneous group of tumors lacks association with GCNIS and abnormalities on chromosome 12. These include spermatocytic tumor, prepubertal-type yolk sac tumor, and prepubertal-type teratoma.

Spermatocytic Tumor

Previously known as spermatocytic seminoma, the spermatocytic tumor accounts for 2% of testicular tumors. It tends to occur in an older age group at a mean age of 57 years and is more common in African Americans.[25] The new nomenclature better differentiates this from seminoma, which reflects its different origin and natural history. Spermatocytic tumor is confined to the testes, is not associated with elevated hCG levels, and is almost always cured by orchiectomy alone.[26] Bilaterality occurs in 10%, and metastasis is rare. Metastases are more common in those with aggressive histology (sarcomatous differentiation) and respond poorly to chemotherapy.[27] The cell of origin of the spermatocytic tumor is probably the postpubertal mature spermatogonia that acquire abnormal proliferative capacity. Spermatocytic tumor does not contain glycogen, stains negative for PLAP, and is not associated with GCNIS. It has a unique amplification on chromosome 9 and is not associated with other germ cell tumors.[28,29]

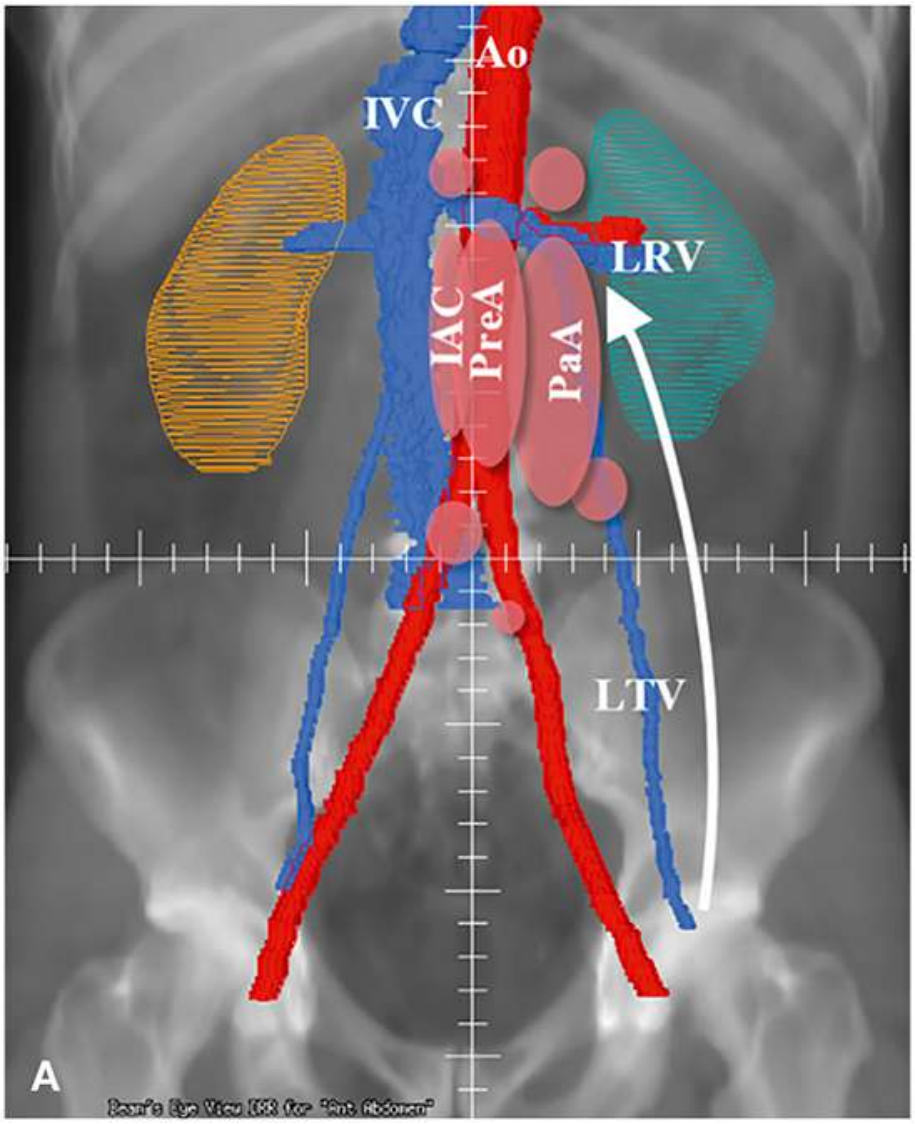
Yolk Sac Tumor and Teratoma, Prepubertal Type

Prepubertal-type yolk sac tumor is the commonest type of germ cell testicular cancer in infants and children and is associated with high levels of AFP. This malignancy arises from a distinct pathway to the postpubertal-type yolk sac tumors, although it has no significant morphologic difference. The prepubertal teratoma is composed of somatic elements from ectoderm, mesoderm, and endoderm. These tumors lack cytologic atypia and arise from a germ cell line that has not undergone malignant transformation. Both prepubertal yolk sac tumor and teratoma are less aggressive and have a better prognosis than the postpubertal versions.

ANATOMY AND NATURAL HISTORY

In the developing embryo, the testes originate from the genital ridge located near the second lumbar vertebra. Accompanied by their blood supply and lymphatics, they descend into the scrotum via the inguinal canal. As a result, the primary lymphatic drainage from the testis is to the retroperitoneal lymph nodes. The lymphatic vessels first drain into the collecting trunks at the hilum of the testicle. These lymphatic trunks accompany the testicular artery, vein, and spermatic cord through the internal inguinal ring and then continue proximally to the retroperitoneal lymph nodes. The retroperitoneal lymph nodes are situated anterior to the T11 to L4 vertebral bodies, concentrated at the L1-3 level. On the left, the lymphatics drain primarily into the preaortic and para-aortic lymph nodes around the left renal hilum and from there to the interaortocaval nodes (Figure 74.1A). On the right, the first nodes involved are usually in the precaval or interaortocaval region,

followed by the preaortic lymph nodes (Figure 74.1B). Contralateral spread is mainly seen with right-sided tumors and rarely with left-sided tumors. Exclusive metastasis in the contralateral nodes (without ipsilateral involvement) is rare.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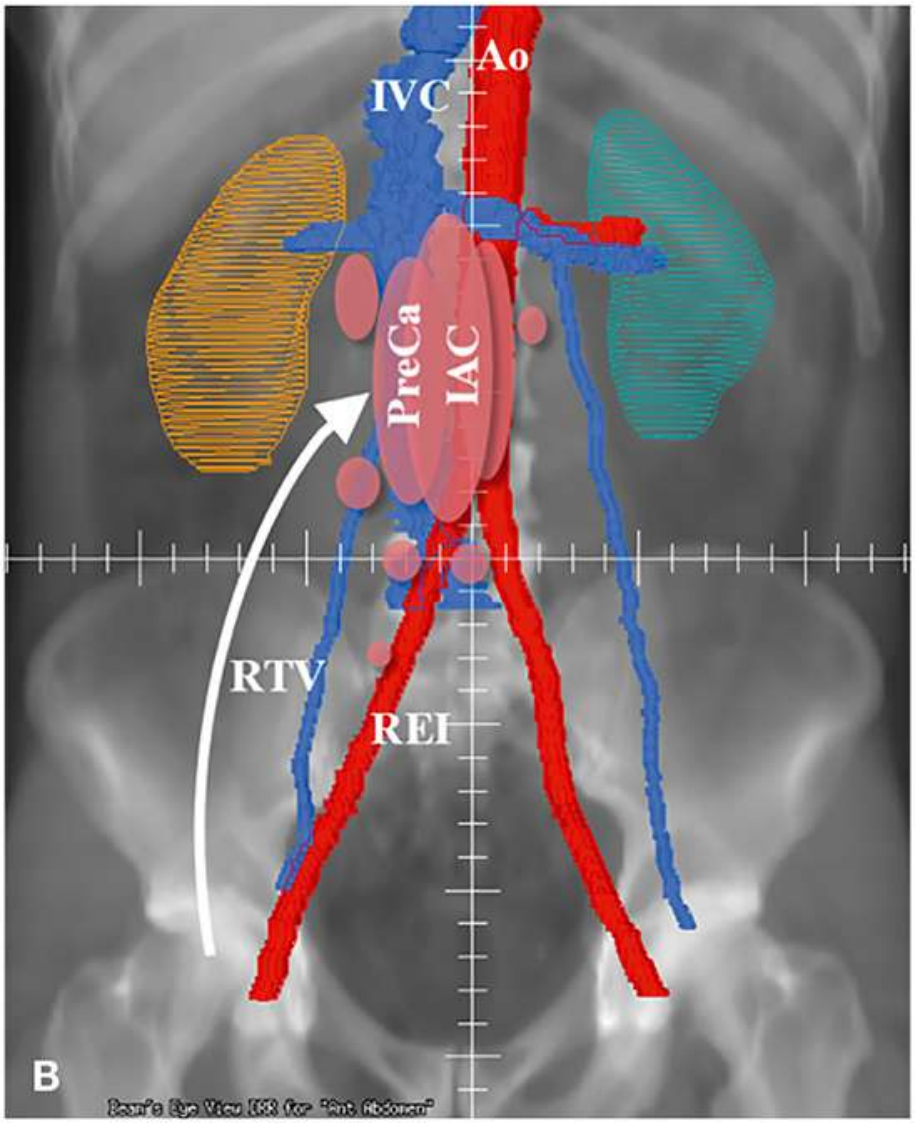

FIGURE 74.1 A. The left testis drains primarily by lymphatics along the left testicular vein (LTV) to lymph nodes inferior to the left renal vessels (LRV). Left para-aortic (PaA), preaortic (PreA), and interaortocaval (IAC) nodes are most commonly involved. Less commonly, nodal involvement may be found inferior to bifurcation of the aorta (Ao) or inferior vena cava (IVC), or superior to the renal vessels. B. Primary lymphatic drainage from the right testis (arrow) is along the right testicular vein (RTV) to precaval (PreCa) and then to IAC and PreA nodes. Less commonly, PreA, right common iliac, or right external iliac (REI) nodes are involved.

From the retroperitoneal nodes, the lymph drains into the cisterna chyli, thoracic duct, posterior mediastinum, and left supraclavicular fossa. The thoracic duct drains into the left subclavian vein in the left supraclavicular region. In 5% to 10% of patients, drainage into the right supraclavicular area can occur.

Aberrant lymphatic drainage may occur in the event of previous scrotal or inguinal surgery. Hernia repair alters the drainage of the testicle. The testicular lymphatic vessels anastomose with the regional lymph vessels, resulting in drainage into the ipsilateral inguinal and iliac lymph nodes. In addition, the testicular trunks may abandon the spermatic vessels at the internal inguinal ring and pass posteriorly and superiorly into the

external iliac lymph nodes. The scrotum drains directly into the inguinal and external iliac lymph nodes. Therefore, direct invasion of the tunica vaginalis or scrotum could result in spread to pelvic and inguinal nodes.

Seminoma has an orderly and predictable pattern of spread. Locoregional lymphatics are the first site of metastatic disease. From the retroperitoneal lymph nodes, seminoma spreads proximally to involve the next echelon—the mediastinal lymph nodes—and then the supraclavicular lymph nodes. Very occasionally, metastases from retroperitoneal lymph nodes can drain directly via the thoracic duct to the supraclavicular fossa, resulting in supraclavicular metastases in the absence of mediastinal disease. Hematogenous metastases are rare in pure seminoma, being much more common with NSGCT. Lung is the most common site of distant disease, although bone, liver, and brain may also be involved.

CLINICAL PRESENTATION

A testicular tumor usually presents as a painless swelling in the scrotum; however, pain, heaviness, and tenderness at presentation are not uncommon. Disease in the lymph nodes of the retroperitoneum may produce back pain or abdominal swelling. Widely disseminated parenchymal disease in the lungs, liver, bone, or brain is rare but, if present, may produce systemic symptoms. Gynecomastia is a rare presentation of embryonal carcinoma that may be seen in association with the very uncommon sex cord-stromal tumors. Gynecomastia and hyperthyroidism may rarely result from high levels of hCG produced by the tumor. Occasionally, patients present with metastatic germ cell malignancies diagnosed by biopsy or elevated levels of serum tumor markers without evidence of a palpable mass in the testis. Occult primary disease in the testis is often detected by testicular ultrasound. If there is no evidence of a primary tumor in the testis, a diagnosis of an extratesticular germ cell tumor —usually mediastinal, retroperitoneal, or pineal—may be made.

DIAGNOSTIC WORKUP (TABLE 74.2)

TABLE 74.2 DIAGNOSTIC WORKUP FOR TUMORS OF THE TESTIS

General
History (document cryptorchidism and previous inguinal or scrotal surgery)
Physical examination
Laboratory Studies
Complete blood count
Chemistry profile
α-Fetoprotein (AFP)
β-Human chorionic gonadotropin (β-hCG)
Lactate dehydrogenase (LDH)
Surgery
Radical inguinal orchiectomy

Diagnostic Radiology
Chest x-ray films, posterior/anterior and lateral views
Computed tomography (CT) scan of the abdomen and pelvis
CT scan of the chest for nonseminomas and stage II seminomas
Bilateral testicular ultrasound
Special Study
Semen analysis

A complete history should be taken, including information about previous inguinal or scrotal surgery, cryptorchidism, retractile testes, and orchidopexy. The physical examination should pay special attention to possible sites of lymph node metastases. The presence or absence of gynecomastia is an important observation. If testicular tumor is suspected, testicular ultrasound should be performed. This helps define the origin of the scrotal mass as the vast majority of extratesticular lesions are benign.[30] Testicular tumor usually appears as a solid mass within the testis, often with associated testicular microlithiasis. The contralateral testis should be examined clinically and by ultrasound. Inguinal biopsy of the contralateral testis may sometimes be considered during surgery if atrophy, cryptorchidism, or suspicious abnormalities on ultrasound are found. Radical orchiectomy through an inguinal incision is diagnostic and removes the primary tumor.

Laboratory Studies

A routine complete blood count and chemistry screen, including renal function tests, should be performed. Pulmonary or renal function tests should be performed for patients who may receive bleomycin or combination chemotherapy. NSGCTs of the testes are uniquely associated with reliable serum tumor markers: the β-subunit of human chorionic gonadotropin (β-hCG) and AFP. One or both of these serum markers are elevated in 80% to 85% of patients with disseminated nonseminomatous disease. These markers are important prognostic factors and contribute to cancer staging.

The metabolic half-life of AFP is approximately 5 days and for β-hCG is approximately 18 to 24 hours. Although β-hCG may be modestly elevated in 15% to 30% of patients with pure seminomas, usually, any elevation of AFP connotes nonseminomatous disease. In the setting of elevated AFP with pure seminoma seen in the pathology specimen, an undetected nonseminomatous focus may be assumed, and the clinical management should follow accordingly. Serum tumor markers may be elevated in other circumstances or conditions, such as laboratory error, cross-reactivity with luteinizing hormone, marijuana use, hepatitis, or the development of antibodies to the glycoproteins. Serum lactate dehydrogenase (LDH), although nonspecific, is elevated in 80% of patients with advanced testicular cancer and has prognostic value.

If a testicular cancer is suspected, serum tumor markers should be assayed before and after orchiectomy, and interpretation of the levels of markers should take into account their metabolic half-lives. Serum tumor markers can document persistent or recurrent cancer after surgery or chemotherapy and may predict the responsiveness of nonseminomas to

treatment. The level of β-hCG should decrease by ≥90% every 21 days with each successful treatment cycle of chemotherapy. A slow decline in β-hCG after treatment may imply suboptimal response to chemotherapy, permitting early implementation of salvage therapy before the development of overt resistance to chemotherapy. The decline in AFP is less predictable.

Semen analysis and banking of sperm should be considered for patients in whom treatment is likely to compromise fertility. With newer technologies, it is possible to retrieve and bank sperm even with poorer quality sperm.

Radiographic Studies

Investigations should routinely include chest x-ray films for all patients and computed tomography (CT) of the thorax for any patient with NSGCTs of the testis. CT scans of the abdomen and pelvis should be performed to evaluate the retroperitoneal nodal areas and assess the liver. A thoracic CT scan should also be performed in patients with seminoma with an abnormal abdominal CT scan or chest x-ray. Magnetic resonance imaging (MRI) of the brain and bone scan are indicated if symptoms are present. Brain MRI is also indicated for choriocarcinoma.

CT of the abdomen and pelvis relies on nodal size to assess the retroperitoneal nodes, with lymph nodes >1 cm in the short axis highly suspicious for metastatic disease. Reported overall sensitivity ranges from 65% to 96% and specificity from 81% to 100%, depending on the threshold size used[31] CT, therefore, has limited ability to exclude the presence of disease, although enlarged lymph nodes in the appropriate clinical context (location, laterality, disease parameters) are very likely to be truly positive. Likewise, lymph nodes with certain morphologic features, such as central necrosis and rounded shape, are considered more suspicious.[32] MRI appears equivalent to CT in determining the size and location of retroperitoneal adenopathy and is considered an equally appropriate staging investigation.[31,33] Fluorodeoxyglucose-positron emission tomography (FDG-PET) scan is not recommended for initial staging.[34,35] While it has a high negative predictive value, its positive predictive value varies across studies. It is unable to detect lesions <5 mm in size or teratomas of any size owing to their very low metabolic activity. It has an important role in evaluating residual retroperitoneal disease following chemotherapy.

In ultrasound imaging, a solid intratesticular mass associated with internal vasculature suggests tumor. Testicular Doppler ultrasonography has a high accuracy in detecting malignancy, with both sensitivity and specificity over 90%.[36] Ultrasonography is not reliable in predicting tumor histology, but in general, seminomas are commonly hypoechoic and homogeneous, whereas calcifications and heterogeneity in echotexture are more often seen in NSGCTs. Baseline ultrasonography of the remaining testis should also be performed. If the contralateral testis is atrophic and the patient is <30 years of age, then there is a 30% risk of GCNIS. Biopsy of the contralateral testis is suggested by some authorities in this setting.

STAGING AND PROGNOSTIC FACTORS

Patients are staged according to the American Joint Committee on Cancer (AJCC) criteria as indicated in Table 74.3, which incorporates features of the primary tumor (T), node (N), metastasis (M), and level of serum tumor markers (S).[37] Approximately 80% of patients with seminoma and 50% to 60% of patients with nonseminoma have stage I disease at presentation. For stage I seminoma, tumor size (>4 cm) and rete testis invasion (RTI) are the most commonly reported predictors of recurrence. For nonseminomas, T stage, extensive embryonal component, and lymphovascular invasion (LVI) are prognostic. Increased age has also been identified as an adverse risk factor and is associated with lower cause-specific survival.[38]

TABLE 74.3 AMERICAN JOINT COMMITTEE ON CANCER 2017 STAGING FOR TESTICULAR CANCER

Primary Tumor (T) (Pathologic Classification)	
*p*Tx	Primary tumor cannot be assessed.
*p*T0	No evidence of primary tumor (scar, etc)
*p*Tis	Intratubular, noninvasive
*p*T1	Tumor limited to testis and rete testis, no vascular/lymphatic invasion pT1a <3 cm pT1b ≥3 cm
*p*T2	Tumor limited to testis with vascular/lymphatic invasion *or* tumor invading hilar soft tissues or epididymis *or* tumor penetrating through tunica albuginea
*p*T3	Tumor invades spermatic cord.
*p*T4	Tumor invades scrotum.
Lymph Node (N)	
N0	No regional node metastasis
N1	Metastasis in single or multiple nodes ≤2 cm in greatest dimension
N2	Metastasis in single or multiple nodes 2-5 cm greatest dimension
N3	Metastasis in lymph nodes >5 cm in maximum diameter
Distant Metastasis (M)	
M0	No distant metastasis
M1a	Nonregional lymph node or pulmonary metastasis
M1b	Nonpulmonary visceral metastasis
Serum Tumor Markers (S)	
Sx	Serum tumor markers not performed
S0	Serum tumor markers within normal limits
S1	LDH <1.5 × N and hCG <5,000 and AFP <1,000
S2	LDH 1.5-10 × N or hCG 5,000-50,000 or AFP 1,000-10,000
S3	LDH >10 × N or hCG >50,000 or AFP >10,000

AFP, α-fetoprotein; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; N, node.

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

The International Germ Cell Cancer Collaborative Group (IGCCCG) developed a widely accepted classification system for patients with metastatic germ cell malignancies,[39] which has been incorporated into the TNM system (Table 74.4). The prognostic classification is based on data collected on approximately 6,000 patients with metastatic germ cell tumor from 10 countries during the platinum era. The classification was internally and prospectively validated on subsequent cohorts of patients. The factors most strongly associated with a poor prognosis were mediastinal primary, nonpulmonary visceral metastases, or grossly elevated tumor markers (AFP >10,000 ng/mL, hCG >50,000 IU/L, or LDH >10 times normal). Patients with NSGCT were divided into three prognostic groups (good, intermediate, and poor prognosis) and seminomas into either good or intermediate prognostic groups (Table 74.4). The good prognosis group comprised >50% of all patients with metastatic NSGCTs and 90% of seminomas and was associated with a 5-year survival of >90%. The intermediate prognosis group comprised 25% to 30% of patients and had a 5-year survival of 80%. The poor prognosis group comprised 15% to 20% of patients with NSGCT and had a 5-year survival of approximately 50%. Contemporary series continue to validate the prognostic value of this classification system, now with reported 5-year overall survivals as high as 98%, 96%, and 66% for those in the good, intermediate, and poor prognostic groups, respectively.[40]

TABLE 74.4 INTERNATIONAL GERM CELL CANCER COLLABORATIVE GROUP CONSENSUS CLASSIFICATION OF METASTATIC GERM CELL CANCER[A]

Nonseminoma	Seminoma
Good Prognosis Group With All of the Following:	
Testis/retroperitoneal primary	Any primary site
No nonpulmonary visceral metastases	No nonpulmonary visceral metastases
AFP <1,000 ng/mL	Normal AFP
hCG <5,000 IU/L	Any hCG
LDH <1.5 × normal	Any LDH
Intermediate Prognosis Group With All of the Following:	
Testis/retroperitoneal primary	Any primary site
No nonpulmonary visceral metastases	Nonpulmonary visceral metastases
Intermediate markers:	
AFP > 1,000 and <10,000 ng/mL *or*	Normal AFP
hCG > 5,000 and <50,000 IU/L *or*	Any hCG
LDH > 1.5× and <10× normal	Any LDH
Poor Prognosis Group With Any of the Following:	
Mediastinal primary *or*	

Nonseminoma	Seminoma
Nonpulmonary visceral metastases *or*	
AFP > 10,000 ng/mL	
hCG > 50,000 IU/L *or*	
LDH > 10× normal	

AFP, α-fetoprotein; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase.

[a]Survival at 5 years is approximately 91%, 80%, and 50% for good, intermediate, and poor prognostic groups, respectively.

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GENERAL MANAGEMENT (FIGURE 74.2)

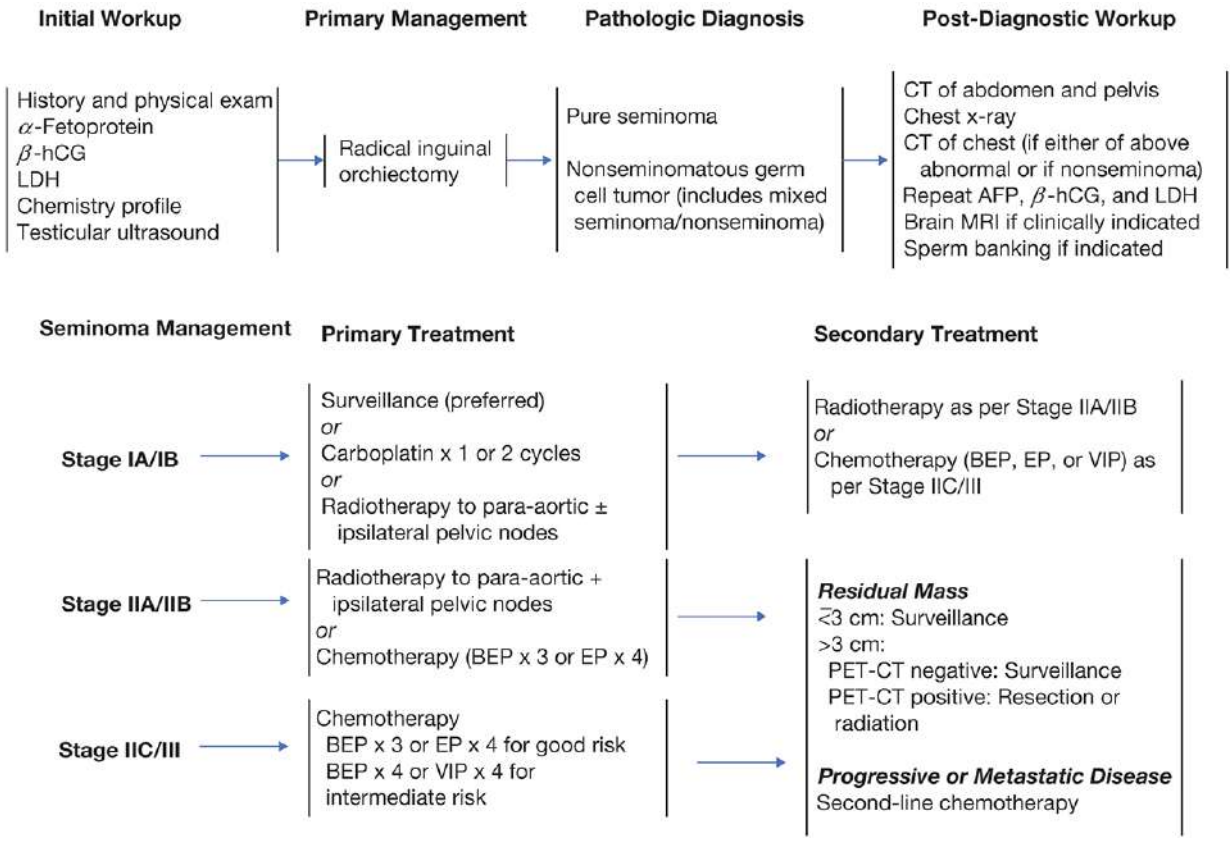


FIGURE 74.2 Diagnosis and management of testicular cancer. BEP, bleomycin, etoposide, and cisplatin; CT, computed tomography; EP, etoposide and cisplatin; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PET, positron emission tomography; VIP, cisplatin, etoposide, and ifosfamide.

The initial management of a suspected malignant germ cell tumor of the testis consists of obtaining serum AFP, β-hCG, and LDH measurements and then performing a radical (inguinal) orchiectomy with division of the spermatic cord at the internal inguinal ring. In

this procedure, the involved testis is removed en bloc with the spermatic cord, enclosed by the tunica layers through an inguinal incision, minimizing the chance of tumor spillage. Historically, it had been thought that scrotal violation (transscrotal orchiectomy, open testicular biopsy, or fine-needle aspiration) compromised prognosis. Scrotal violation is associated with a slight increase in local recurrence rate compared with inguinal orchiectomy (2.9% vs 0.4%) but is not associated with any difference in distant recurrence rates or overall survival.[41] Orchiectomy is both diagnostic and therapeutic. Further management depends on pathologic diagnosis and the stage and extent of disease. Radiation treatment plays a significant role in the management of seminomas. Nonseminomatous tumors are generally managed by cisplatin-based combination chemotherapy and/or surgical resection.[42] A detailed discussion of the management of nonseminomatous tumors is beyond the scope of this chapter.

Seminoma

Stage I

Most patients with stage I seminoma are cured by orchiectomy alone, and 15% to 20% will relapse if no adjuvant therapy is offered. Either adjuvant radiation therapy or adjuvant chemotherapy with single-agent carboplatin is associated with a disease-free survival of >95% and disease-specific survival approaching 100%.[43] Surveillance, with treatment at the time of relapse, is associated with a similar survival outcome and allows over 80% of patients to avoid the morbidity of treatment.

Surveillance

There has been a major change in the standard management of stage I seminoma over the past several decades, as adjuvant radiotherapy has been replaced with surveillance. Kollmannsberger et al document the increasing use of surveillance for managing patients with stage I seminoma in a population-based cohort from British Columbia, Canada, and Oregon.[44] Between 1999 and 2008, the proportion of patients receiving adjuvant radiation therapy decreased from 50% to 9%, and the proportion being managed by surveillance increased from 47% to 87%. A similar trend was seen in the United States by Matulewicz et al through analysis of the National Cancer Database.[45] The authors reported that the use of surveillance for stage I seminoma increased from 25% in patients diagnosed between 1998 and 2000 to 61% in those diagnosed between 2010 and 2012. Jia et al reported similar trends using the Surveillance, Epidemiology, and End Results (SEER) database.[46] Over a 40-year period, the rate of adjuvant radiotherapy use decreased from 100% in 1975 to 47% in 2008 and 5% in 2015. Over that same time period, the use of surveillance increased from about 20% before 2000 to 77% in 2015, with the steepest increase noted around the turn of the century. Of 411 patients with stage I seminoma diagnosed between 2000 and 2022 in the Australian and New Zealand iTestis database, only a single patient received adjuvant radiotherapy.[47] Adjuvant carboplatin (almost always single dose) was administered to 26%, and 74% were managed by surveillance.

The early surveillance series (Table 74.5) all reported similar rates, timing, and patterns of recurrence.[44,48-56] When managed by surveillance, up to 20% of patients were found to relapse at a median time of around 14 months. Over 90% of relapses occur in the first 3 years. An early pooled analysis of 638 patients with stage I seminoma from four series (Princes Margaret, Royal Marsden Hospital, Royal London Hospital, and the Danish Testicular Cancer Study Group) reported 5- and 10-year relapse-free rates of 82.3% and 78.7%, respectively.[57] Most relapses (69%) occurred within the first 2 years of surgery, whereas 7% relapsed beyond 6 years. The 5-year cause-specific survival was 99.3%. A further pooled analysis of databases from Sweden and Norway, the Princess Margaret Cancer Centre, British Columbia and Oregon, Bart's Cancer Institute, and the University of Oxford reported similar findings.[58] With a median follow-up time of 52 months, relapse occurred in 13% of 1,344 patients with stage 1 seminoma at a median of 14 months. No patient died from seminoma, although one patient died from complications of treatment.

TABLE 74.5 PATTERNS OF RECURRENCE FOR STAGE I SEMINOMA MANAGED BY SURVEILLANCE IN SELECTED SERIES

Author (Reference)	Number	Median Follow-Up (Months)	Relapse-Free Survival (%)	Proportion Relapsing in Retroperitoneum (%)	Disease-Specific Survival (%)	Median Time to Relapse (Months)
Kollmannsberger et al[44]	313	34	81	—	100	14
von der Maase et al[48]	261	48	80	94	99	14
Chung et al[49]	203	110	82	91	99.5	17
Francis et al[50]	120	55	82	94	100	4
Daugaard et al[51]	394	60	83	87	100	13
Choo et al[52]	88	145	80	76	100	14
Cummins et al[53]	164	160	87	82	98.7	16
Aparicio et al[59]	396	80	88	86	100	14
Kamba et al[55]	186	45	79	79	100	21
Tandstad et al[56]	512	60	86	94	99.8	17

Almost all patients (99%) who relapse after surveillance are classified by IGCCCG in the good risk category, and the predominant site of relapse is in the retroperitoneum (76%-94%). Approximately 5% to 15% of patients relapse in the mediastinum or lungs, with inguinal relapse described in 3% to 11%, usually only after previous scrotal interference. Some variability is reported in management at the time of relapse. Traditionally, most (74%-82% of patients in the older series) were initially managed by radiation therapy, with a second relapse occurring in about 10% (6%-16%). Second relapse almost always occurred at distant sites, with a 90% to 95% rate of successfull salvage with chemotherapy. More recent series describe a greater use of chemotherapy as initial salvage

treatment. In the population-based study from the Swedish Norwegian Testicular Cancer Study Group (SWENOTECA), cisplatin-based combination chemotherapy as salvage treatment was given to 89% of relapsing patients, with further relapse in only 1 of 58 patients.[56] Kollmannsberger et al report the use of salvage chemotherapy in 68% of relapsing patients in the British Columbia and Oregon Testis Cancer Program database.[44] No further relapse occurred in the 32 patients managed by chemotherapy, whereas relapse occurred in 3 of 15 patients who received salvage radiotherapy. Although salvage chemotherapy is effective, it is associated with greater toxicity than salvage radiotherapy.

The outcome of patients relapsing on surveillance is likely no worse and possibly better than that of those presenting with de novo metastatic seminoma. In a retrospective bi-institutional review of 73 patients treated with radiation therapy, Rosen et al reported higher progression-free survival in relapsed (92%) compared with de novo metastatic (73%) patients, although with 100% cause-specific survival in both groups.[60] Lauritsen et al reported outcome data of 1,014 patients with metastatic seminoma from the ICGCCG database—298 who had relapsed on surveillance for stage I disease and 716 with de novo metastatic disease.[61] There was no significant difference in 5-year progression-free survival (84.6% vs 80.0%) or overall survival (93.3% vs 88.7%) between the two groups.

Risk factors for relapse on surveillance were identified early on. In the pooled analysis, tumor size, RTI, and LVI were predictive of relapse on univariate analysis.[57] On multivariate analysis, tumor size (hazard ratio [HR] 2.0) and RTI (HR 1.7) remained significant. The relapse-free rate decreased from 87.8% for tumors <4 cm without RTI to 68.5% for tumors >4 cm with RTI. Tyldesley et al also noted the importance of size >4 cm and RTI, reporting a 5-year relapse-free rate of 86%, 71%, and 50% in patients with no risk factor, one risk factor, or both risk factors, respectively.[62] These risk factors were validated by the SWENOTECAVII study.[63] In this prospective and population-based protocol, a significant difference in relapse was seen between patients with no risk factor (4%) and patients with these one to two factors (15.5%) managed by surveillance. Wagner et al investigated risk factors for recurrence in 924 patients on surveillance for stage I seminoma diagnosed between 2013 and 2018 from the prospective Danish Testicular Cancer database.[64] Relapse occurred in 16% at a median follow-up of 6.3 years. Invasion of the testicular hilum, LVI, and elevated preorchiectomy levels of β-hCG and LDH were independent predictors of recurrence and could be used to define groups with risk of relapse ranging from 6% (no risk factors) to 62% (all risk factors).

The European Association of Urology Testicular Guidelines Panel performed an individual patient data analysis of 1,016 patients with stage I seminoma managed by surveillance from nine institutions.[65] After a median follow-up of 7.7 years, 14.7% had relapsed. Ninety-seven percent of relapses were in the retroperitoneal lymph nodes, and 54% were then treated with radiotherapy and 46% with chemotherapy. Tumor size, presence of RTI, and LVI were independently associated with the risk of recurrence and were used to define risk groups with a low, intermediate, and high risk of recurrence. Low-risk patients comprised 56% of the cohort and were defined as having tumor size ≤5 cm without RTI or LVI, *or* ≤2 cm with either RTI or LVI. Their risk of recurrence at 5 year was 8%. Intermediate-risk patients comprised 41% of the cohort and had tumor size ≤2 cm with

both RTI and LVI, *or* >2 to 5 cm with either RTI or LVI, *or* >5 cm, but not with both RTI and LVI. Relapse risk was 20%. Less than 3% of patients belonged to a high-risk group having tumor size >5 cm with both RTI and LVI and having a risk of relapse of 44%. Results were validated in a further cohort of 285 patients.

Surveillance involves regular axial imaging of the abdomen and pelvis, with the frequency based on the risk and time course of recurrence. Although chest x-ray was routinely used in most surveillance series, no relapse was detected on chest x-ray alone and can be omitted.[66] Similarly, there is no role for routine measurement of serum tumor markers.[67] The use of low-dose CT, less intensive imaging protocol, and MRI have been investigated to further reduce long-term radiation exposure.

Based on the pattern and timing of relapse, surveillance policies have been proposed by various organizations, including the European Association of Urology, the European Society of Medical Oncology, the American Urologic Association, and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group. Either CT or MRI can be used for cross-sectional imaging of the retroperitoneum, the primary site of recurrence. MRI has the advantage of avoiding ionizing radiation but does take longer and has been shown to be noninferior to CT in the Trial of Imaging and Surveillance in Seminoma Testis study.[68] This phase III noninferiority trial randomized 669 patients with stage I seminoma to a surveillance policy of either seven or three CTs or MRIs. The primary outcome was bulky relapse (>5 cm) at 6 years. Although more events occurred with three scans (2.8% vs 0.3%), this was statistically noninferior and MRI was found to be noninferior to CT. Five-year survival was 99% with no tumor-related deaths. Chavarriaga and colleagues comprehensively reviewed these clinical practice guidelines to propose a unifying schedule based on current best evidence.[69] They suggest CT or MRI scans of the abdomen and pelvis every 6 months for the first 2 years, then annually until year 5. Consideration could also be given to further imaging at year 7 and year 9. They do not recommend routine chest x-ray or serum tumor markers.

Surveillance has become the preferred approach for most men with clinical stage I seminoma, particularly those at low or intermediate risk of recurrence. Although more costly than upfront adjuvant treatment due to the increased number of radiologic investigations, it leads to less overall treatment burden to patients.[70,71] Given the high efficacy of salvage treatment, cause-specific survival approaches 100%, and population-based data from Denmark show no excess of deaths or second malignancy compared to a population-based control group out to 20 years.[72] Surveillance is an option even for patients at higher risk of relapse. Mortensen et al identified 473 patients with stage I seminoma and tumor size ≥6 cm from the Danish Testicular Cancer database, managed with adjuvant radiotherapy (n = 254) or surveillance (n = 219).[73] The 10-year estimate of disease recurrence was 3% with radiotherapy and 32% with surveillance, but with no difference in overall survival.

Adjuvant Radiation Therapy

In the past, the standard postoperative management of patients with stage I seminoma had been adjuvant radiation therapy to the para-aortic and ipsilateral pelvic lymph nodes (the

"dog-leg" or "hockey stick" radiation field). This is a highly effective treatment, with a reported relapse rate between 1% and 5% and a disease-specific survival of 100% in many mature series[56,74-84] (Table 74.6) without the need for ongoing abdominal imaging.[85] Adjuvant treatment evolved to commonly only include the para-aortic region. Series that treat just the para-aortic report a higher rate of failure in the pelvic nodes; however, the disease-free survival is minimally compromised. A multicenter single-arm trial of para-aortic radiotherapy was reported by the German Testicular Cancer Study Group, which included 721 patients with stage I seminoma.[80] Disease-free survival at 8 years was 95%. Of 26 recurrences, 21 were within infradiaphragmatic lymph nodes beyond the treatment volume (mostly ipsilateral pelvic), with no in-field recurrences. The Medical Research Council (MRC) performed a randomized controlled trial comparing classic dog-leg irradiation to para-aortic irradiation in stage I seminoma.[84] Those with previous ipsilateral inguinal or scrotal surgery were excluded. Radiation therapy was better tolerated in the para-aortic alone arm with a reduction in the severity and frequency of acute gastrointestinal and hematologic toxicity. At a median follow-up of 4.5 years, there was no difference in the 3-year relapse-free survival or overall survival. For those in the para-aortic radiation therapy arm, the pelvis was the most frequent site of recurrence, whereas the pelvis was a rare site of recurrence in those in the para-aortic and ipsilateral pelvic radiotherapy arm. A retrospective review showed that the median size of pelvic nodal recurrence was 7.3 cm (range, 2.8-13 cm) if CT scans were not included in the follow-up schedule of patients treated with para-aortic radiation therapy.[86]

TABLE 74.6 RATE OF RELAPSE AND LOCATION FOR STAGE I SEMINOMA MANAGED BY ADJUVANT RADIOTHERAPY IN SELECTED SERIES

Author (Reference)	Number	Median Follow-Up (Years)	Radiation Dose (Gy)	Fields	Number Relapsing	Para-aortic	Pelvic/Inguinal	Distant	Cause-Specific Survival (%)
Tandstad et al[56]	481	6.1	25.2	DL	4 (0.8%)	2	0	2	100
Fosså et al[74]	365	9.1	36-40	DL	13 (4%)	1	7	6	99
Bauman et al[75]	169	7.5	30	DL	5 (3%)	1	0	4	100
Logue et al[76]	431	5.2	20	PA	15 (3%)	1	9	5	99
Santoni et al[77]	487	10	30	DL, PA	21 (4%)	4	8	9	—
Niazi et al[78]	71	6.25	25	PA	1 (1%)	0	1	0	100%
Melchior et al[79]	87	7.7	36	DL	3 (3%)	0	0	3	100%
Classen et al[80]	721	5.1	26	PA	26 (4%)	6	21	5	99.6

Author (Reference)	Number	Median Follow-Up (Years)	Radiation Dose (Gy)	Fields	Number Relapsing	Para-aortic	Pelvic/Inguinal	Distant	Cause-Specific Survival (%)
Bruns et al[81]	80	7.1	20	Mini PA	4 (5%)	1	3	0	100
Jones et al[82]	313 312	5.1	30 20	PA (88%) PA (89%)	10 (3%) 11 (3%)	2 1	6 3	2 7	100 99.7
Oliver et al[83]	904	6.5	20-30	PA (86%)	33 (4%)	3	11	19	99.9
Fosså et al[84]	236 242	4.5	30	DL PA	9 (4%) 9 (4%)	0 2	0 4	9 6	100 99.3

DL, dog leg; PA, para-aortic.

Given that nearly all recurrences following para-aortic radiation therapy are in the lower common iliac or upper external iliac nodes, another approach was to use a modified dog leg wherein the inferior border is placed at the midpelvic level. This encompasses the nodal areas at risk while further reducing the volume of normal tissue irradiated.[87]

Adjuvant Chemotherapy

Adjuvant chemotherapy using single-agent carboplatin has emerged as an alternative to radiotherapy for stage I seminoma. For men with advanced seminoma, carboplatin has long been known to have significant efficacy with relatively low toxicity.[88] It was logical to investigate the use of one or two cycles of carboplatin as adjuvant treatment following orchiectomy.[89-91] With a median follow-up of 75 months, Steiner et al reported a 5-year relapse-free survival of 98% in a population of 276 men with stage I seminoma treated with two cycles of carboplatin.[92] Aparicio et al described a risk-adaptive strategy wherein patients with stage I seminoma deemed at low risk of recurrence were managed with surveillance, and those considered at higher risk based on RTI or tumor size >4 cm received two cycles of carboplatin.[93] With a median follow-up of 67 months, relapse occurred in 56 (12%) of 467 on surveillance and in 13 (3%) of 412 following carboplatin.[94] The predominant site of recurrence was in the retroperitoneum (88% vs 85%), and 90% were subsequently treated with cisplatin-based chemotherapy. No seminoma-related deaths occurred.

Recurrence following adjuvant carboplatin tends to be in the retroperitoneum and can be salvaged with cisplatin-based chemotherapy, in approximately 85% of the cases resulting in an overall disease-specific survival approaching 100%.[95] Between 2001 and 2006, the use of single-course carboplatin following orchiectomy for stage I seminoma increased from 0% to 70% in Sweden and Norway.[56] Over the same time period, the use of adjuvant radiotherapy decreased from 40% to 5%. The relapse risk with chemotherapy was higher than that following radiotherapy (3.9% vs 0.8%); however, overall survival was the same.

In the British Columbia/Oregon database, 73 of 545 patients received either one or two cycles of carboplatin, with only one relapse, yielding a relapse-free survival probability of 98% and a cause-specific survival of 100%.[44]

The MRC performed a randomized comparison of single-agent carboplatin and nodal irradiation in stage I seminoma.[83] Almost 1,500 patients from 14 European countries were randomized to receive either adjuvant radiation therapy or one injection of carboplatin. Radiation was limited to para-aortic fields in 87%, and the remainder also had inclusion of the ipsilateral pelvic nodes. Information on tumor size and RTI was not detailed. With a median follow-up time of 6.5 years, the 5-year relapse-free survival rates were similar at 96.0% and 94.7% in the radiation therapy and carboplatin arms, respectively. In the adjuvant radiation therapy arm, the most common site of recurrence was either distant (57%) or in the pelvic nodes (31%). In the carboplatin arm, most of the relapses (74%) were in para-aortic nodes. Only one death from testicular cancer occurred in the radiation therapy group, with no cancer-related deaths in the chemotherapy group. An 80% reduction in the rate of contralateral testicular cancer was seen in the carboplatin arm (2 vs 15 cases). Long-term toxicity (eg, risk of leukemia) is unknown; however, the regimen is well tolerated acutely with only mild myelotoxicity. Powles et al found no increased risk of death from circulatory disease or risk of second malignancy in a cohort of 199 patients who received adjuvant carboplatin and were followed for a median of 9 years.[96] Ruf et al reported a higher than expected rate of second malignancy (2.4-fold) in a cohort of 451 patients with stage I seminoma who had received carboplatin rather than surveillance, but the number of events was small and the results need further validation.[97]

Mead et al[98] analyzed mature results of three randomized noninferiority MRC clinical trials for stage I seminoma, which included nearly 2,500 patients. They concluded that either radiation therapy or carboplatin was a reasonable adjuvant therapy. It is clear that the survival of patients with stage I seminoma approaches 100%, no matter what treatment strategy is employed.[99] The goal of management is to limit treatment morbidity without compromising the chance of cure. For the compliant patient, surveillance is the option of choice. For patients not suitable for surveillance, adjuvant radiation therapy or adjuvant chemotherapy significantly reduces the risk of relapse.

Stage II

For patients with stage II seminoma, the recommended treatment depends on the bulk of retroperitoneal nodal disease. Radiotherapy and chemotherapy are standard options, with retroperitoneal lymph node dissection (RPLND) being offered on some protocols.[42],[100] Radiation therapy (25-35 Gy) remains the treatment of choice for patients with nonbulky stage II seminoma, generally considered to be <3 cm. Irradiation of the para-aortic and ipsilateral pelvic nodes is a highly effective treatment strategy with a recurrence rate of <10% (Table 74.7) and a disease-specific survival rate of 97% to 100%.[75,101-109] The most common site of relapse following infradiaphragmatic radiation therapy is in the supraclavicular fossa or mediastinum. In the past, some authors recommended prophylactic supraclavicular irradiation.[103] However, the proportion of patients destined to relapse

exclusively in the supraclavicular fossa is <5%, and the results with infradiaphragmatic irradiation alone with chemotherapy as salvage are excellent.[110]

TABLE 74.7 RELAPSE RATE FOLLOWING INFRADIAPHRAGMATIC +/− MEDIASTINAL RADIOTHERAPY BY NODAL STAGE FOR STAGE II SEMINOMA IN SELECTED SERIES

	Stage IIA (≤2 cm)		Stage IIB (2-5 cm)		Stage IIC (>5 cm)	
Author (Reference)	***N***	**Relapses**	***N***	**Relapses**	***N***	**Relapses**
Bauman et al[75]	29	2	10	1	4	2
Chung et al[101]	49	4	30	4	16	10
Classen et al[102]	66	2	21	2	—	—
Zagars and Pollack[103]	6	0	38	5	25	3
Patterson et al[104]	46	6	34	9	—	—
Whipple et al[105]	31	2	14	3	—	—
Vallis et al[106]	26	1	22	2	5	2
Dosmann and Zagars[107]	55	7	13	4	—	—
Mason and Kearsley[108]	—	—	25	1	24	6
Evensen et al[109]	6	0	18	1	49	11
Total	**314**	**24 (8%)**	**225**	**32 (14%)**	**123**	**34 (28%)**

Chemotherapy with bleomycin, etoposide, and cisplatin (BEP) for three cycles, or etoposide and cisplatin (EP) for four cycles, is an alternative to radiotherapy for patients with stage II disease. It is often recommended as the treatment of choice for disease >3 cm.[100] Although it is clear that most patients with stage IIA/B seminoma can be cured with cisplatin-based chemotherapy, greater levels of toxicity are expected with this treatment than that associated with radiotherapy alone.[111] Chemotherapy toxicity includes pulmonary toxicity (including death), ototoxicity, peripheral neuropathy, and nephrotoxicity. Given the high cancer control and disease-specific survival associated with radiotherapy, it is considered preferable to BEP for nonbulky stage II seminoma.

Less toxic alternatives to standard cisplatin-based chemotherapy have been investigated. Single-agent carboplatin has less toxicity than BEP or EP, but early clinical trials suggested inferior cancer control and survival.[112] A phase II study by the German Testicular Cancer Study Group delivered three or four cycles of carboplatin to patients with stage IIA or stage IIB seminoma, respectively.[113] The overall failure rate was 18%, with all relapses occurring in the retroperitoneum, which seemed higher than that expected with cisplatin combinations or radiotherapy. The problem, however, may have been dose. A multicenter UK study treated 216 men with good prognosis metastatic seminoma with three or four cycles of carboplatin AUC10 every 21 days.[114] Two-thirds had stage IIA or IIB disease. The progression-free survival was 96.5%, with a 5-year disease-specific survival of 98.3%. The main toxicity was hematologic with grade III neutropenia in 37% and neutropenic sepsis in

5%. Results were an improvement on historical experience with single-agent carboplatin and similar to what might be reported with BEP with the potential less late toxicity.

Another way to de-intensify treatment with carboplatin was explored in the GETUG SEMITEP trial.[115] The trial enrolled 102 patients with metastatic seminoma, mostly stage IIB, and all were treated with two cycles of EP chemotherapy. Those with a negative FDG-PET at that point (73%) received one further cycle of carboplatin, while those with a positive FDG-PET went on to receive a further two cycles of EP. One patient died from chemotoxicity after the second cycle of EP. The cumulative incidence of peripheral neuropathy and ototoxicity was less in the carboplatin arm. Over 90% of patients in both arms were free of recurrence at 3 years.

A few authors have retrospectively assessed the benefit of a combined approach using neoadjuvant carboplatin followed by radiation therapy in patients with stage IIA/B seminomas.[104,116] SAKK 01/10 was a single-arm, multicenter trial of carboplatin followed by involved field radiotherapy, which enrolled 120 patients with stage IIA and IIB seminoma.[117] Patients received a single dose of carboplatin 7AUC, followed by involved field radiotherapy to a dose of 30 Gy in 15 fractions for stage IIA or 36 Gy in 18 fractions for stage IIB. Grade 3 hematologic toxicity occurred in 7%. The 3-year progression-free survival was 95.2% in those with stage IIA disease and 92.6% in those with stage IIB disease. Disease-specific survival was 100%. Although these results are not definitive, this strategy appears to reduce the rate of relapse compared to carboplatin alone and may be a promising approach, especially for patients with bulkier disease.

Several authors have investigated RPLND as a treatment option for patients with stage IIA and IIB seminoma in order to avoid potential toxicities of radiation or chemotherapy. The PRIMETEST trial enrolled patients with retroperitoneal metastases <5 cm, either de novo or on relapse after surveillance or carboplatin for stage I disease.[118] Patients underwent either an open or robot-assisted unilateral RPLND. After a median follow-up of 32 months, progression-free survival was 64%, with almost all of the recurrences in the retroperitoneum. These were further successfully treated with cisplatin-based chemotherapy. The SEMS trial was a single-arm prospective trial of RPLND in men with one or two ipsilateral retroperitoneal nodal metastases <3 cm in maximal size.[119] With a median follow-up of 33 months, recurrence occurred in 12 of 55 patients, with a 2-year recurrence-free survival of 81%. Again, most of the recurrences were in the retroperitoneum. While enabling a significant proportion of men to avoid chemotherapy or radiotherapy, RPLND is not considered the standard of care and is being investigated in ongoing clinical trials.

Factors other than stage may be considered in the selection of treatment strategy after orchiectomy in stage II seminoma. A greater number of retroperitoneal nodal metastases may suggest an overall greater bulk of disease, indicating a higher likelihood for distant metastasis. Furthermore, Domont et al[120] have reported that nodal diameter ≥3 cm on CT is associated with a higher risk of distant failure following local therapy and suggested that these patients would be better managed with systemic treatment. The risk of distant metastasis is likely proportional to the extent of disease seen in the retroperitoneal nodes, and this should be taken into account when deciding which strategy to follow.

Patients with stage IIC retroperitoneal disease (nodes >5 cm) are usually managed with systemic chemotherapy. Radiation therapy remains a treatment option; however, the relapse rate of >30% is considered by many to be excessive. Chung et al[101] reported recurrence in 10 of 16 patients with stage IIC disease managed with radiation therapy compared to only one relapse in a similar group of 23 patients managed by chemotherapy. The choice of modality is also influenced by the size and location of the retroperitoneal nodal mass. If the mass is centrally located and does not overlie most of one kidney or significantly overlap the liver, primary radiation therapy remains an option. If the location of the mass is such that the irradiation volume covers most of one kidney or significant volumes of the liver, then the potential morbidity of radiation therapy can be avoided by the use of primary cisplatin- containing combination chemotherapy (usually EP or BEP). For nodal disease >10 cm in diameter, the relapse rate is >40% with radiotherapy, and such patients should be managed with systemic chemotherapy.

For the rare patient with stage III disease (ie, supradiaphragmatic nodal disease or dissemination to parenchymal organs), or those with relapse following radiation therapy, the current standard therapy is three courses of BEP or four courses of EP chemotherapy. These patients are classified into either a good prognosis or intermediate prognosis group by the International Germ Cell Cancer Collaborative Group Consensus Classification, depending on the absence or presence of nonpulmonary visceral metastases, respectively. The 5-year survival is expected to be over 95%.[40]

Residual Mass

For patients with stage II or III disease treated with primary chemotherapy, residual masses are present at 1 month in up to 80% of patients. Most of these then gradually regress over a period of several months. Fléchon et al[121] reported that 50% of residual masses disappeared on follow-up and that viable cancer cells were found only in masses >3 cm in size. Management strategies involve the use of consolidative radiotherapy, surgical resection, or observation. In an effort to define the role of postchemotherapy radiation therapy, the MRC Testicular Tumour Working Party conducted a retrospective review of patients with advanced seminoma managed by chemotherapy from 10 European centers.[122] Of 302 patients identified, 174 (58%) had residual masses on completion of chemotherapy, with a subsequent 3-year progression-free survival of 85%. Approximately half of these patients underwent postchemotherapy radiation therapy, with selection based predominantly on institutional preference. Radiation therapy did not significantly influence the risk of progression, contributing to an absolute increase in progression-free survival of only 2.3%. Instead, the most important prognostic factors for progression were the presence of prechemotherapy visceral metastases or raised LDH, or persistent visceral metastases postchemotherapy. At St Bartholomew's Hospital, 43 (40%) of 107 patients with advanced seminoma had a residual mass postchemotherapy.[123] Positive histology was found in 3 (15%) of 19 patients who underwent surgical exploration, whereas relapse at the site of the mass occurred in 3 other patients observed. Residual disease was only found in masses >3 cm in size. Of the 107 patients, 98 (92%) patients remained alive and free from recurrence. The largest report of surgical resection following chemotherapy comes from the Memorial

Sloan- Kettering Cancer Center.[124] A total of 55 patients with advanced seminoma underwent resection or biopsy of residual mass within 4 weeks of chemotherapy. Of 27 patients with a mass >3 cm, eight (30%) patients had residual tumor. No viable tumor was found in any of the 28 patients with a residual mass <3 cm in maximal diameter.

From the reports discussed, it is clear that observation alone is adequate for a residual mass <3 cm in size. Two patterns of response to chemotherapy are evident on CT: The residual mass may be well defined with discrete borders or the mass may have indistinct borders merging into surrounding structures and resembling a fibrous plaque. The former is more amenable to surgical resection. Furthermore, if the tumor is well defined on CT and measures >3 cm in greatest dimension, positive histology can be found in 50%. It is reasonable to resect these masses. If the mass is poorly defined, even if >3 cm, the chance of finding positive histology is <10%. Resecting such a mass is hazardous, with the risk of great vessel, ureteric, and small bowel injury. These should be observed.

FDG-PET scans have been shown to reliably predict the presence of viable disease in retroperitoneal masses postchemotherapy in seminomas. This diagnostic examination has a higher accuracy in identifying persistent disease than CT.[125] De Santis et al[126] evaluated the efficacy of FDG-PET by analyzing 51 patients with 56 postchemotherapy lesions. The FDG-PET correctly identified 54 lesions with two false-negative results, both in nodes <3 cm. For the whole cohort, this test sensitivity was 80%, but FDG-PET accuracy for residual masses >3 cm was 100%. Based on this result, authors estimated that 45% to 73% of patients with >3 cm residual mass would be overtreated with surgery if FDG-PET information is not taken into account, as a negative scan may be reliably used as a tool for avoiding surgical resection. Radiotherapy may also be considered for FDG-positive residual masses following chemotherapy. Murthy and colleagues reported a nonrandomized trial of radiotherapy and observation in patients with FDG-PET–positive residual masses postchemotherapy.[127] Patients treated with radiotherapy, to a median dose of 36 Gy in 18 fractions, had a lower rate of local failure (1/27) compared to those observed (8/27). This improvement in locoregional control did not translate into an improvement in overall survival. FDG-PET should be performed 6 weeks after day 21 of the last chemotherapy cycle, as earlier imaging has a higher risk of false-positive results.

Bilateral Testicular Cancer

Testicular cancer is bilateral in up to 5% of cases, with one-third being synchronous and two-thirds being metachronous.[128] Although bilateral orchiectomy is an effective management strategy in synchronous disease, the option of testis-sparing surgery and postoperative radiation therapy has emerged as an alternative.[129] Partial orchiectomy may be considered for selected patients with bilateral disease or a solitary testicle. Ideally, tumors should be <2 cm in size and have negative surgical margins for invasive disease. Postoperative radiotherapy to a dose of 18 to 20 Gy is usually administered to the residual testicle to eradicate GCNIS, which is found in >80% of cases.[130,131] Observation alone has also been reported.[132] In either case, some degree of hormonal dysfunction is common, and many patients may still require lifelong testosterone replacement. Patients with testicular cancer are at a higher risk of developing contralateral malignant disease. In consequence,

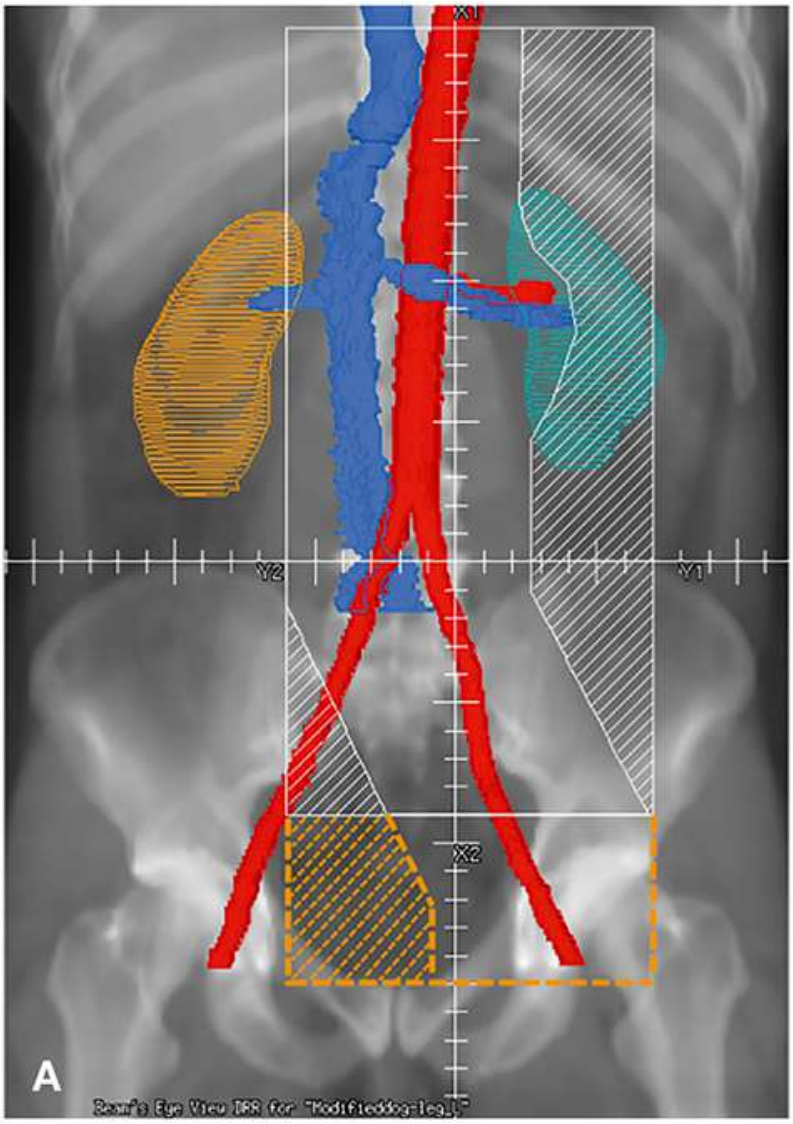
some authors advocate performing a biopsy of the contralateral testis during the radical orchiectomy procedure for early diagnosis of GCNIS or invasive disease. However, routine biopsy of the contralateral testicle has not been shown to significantly reduce the incidence of metachronous germ cell malignancy.[133] In the setting of GCNIS identified by the biopsy, a course of radiation therapy may be considered to the contralateral testis for the treatment of the in situ component of the neoplasia, as patients with GCNIS almost invariably progress to invasive cancer. In this setting, a low dose of radiation is able to preserve some function of the Leydig cells and avoid progression of disease.

RADIATION THERAPY TECHNIQUE

Target Volume and Field Borders

For stage I disease, the clinical target volume (CTV) encompasses the interaortocaval, preaortic, and para-aortic nodes (see Figure 74.1). The left renal hilar nodes are included for left-sided tumors. The ipsilateral external iliac and common iliac nodes may also be included, particularly if there is concern about aberrant drainage. Inclusion of the inguinal scar, inguinal lymph nodes, or hemiscrotum is not routinely warranted. For stage II disease, a gross tumor volume is identified from diagnostic imaging, and the CTV also usually includes the ipsilateral pelvic nodes.

The planning target volume (PTV) includes the CTV plus a margin to account for positional and setup uncertainties. To cover the known location of the retroperitoneal and iliac lymph nodes with an appropriate margin, standard anatomic field borders have been used. This is commonly referred to as the dog-leg or hockey stick field. Classically, the superior border is placed between the T9 and T10 vertebral bodies, with the inferior border at the top of the obturator foramen. A modified approach is now commonly used wherein the superior border is placed between T10 and T11 and the inferior border is placed at the superior aspect of the acetabulum (Figure 74.3). The field is approximately 9 cm wide in the para-aortic region and usually covers the transverse processes. On the left, the lateral border is extended to include the left renal hilum, and customized shielding is positioned to reduce the amount of kidney irradiated. Field width here is typically 11 to 12 cm. At the mid-L4 level, the field is extended laterally to cover the ipsilateral external iliac nodes. Multileaf collimators are used to define the field shape. If retroperitoneal nodes alone are to be treated, the superior and lateral borders are as described previously, and the inferior border is placed at the L5/S1 disc space. Some report using a lower superior border, T11-12, and a higher inferior border, the bottom of L4.[81]


X1
Y2
Y1
X2
A
Beam's Eye View DRR for "Modifieddog-leg_1"

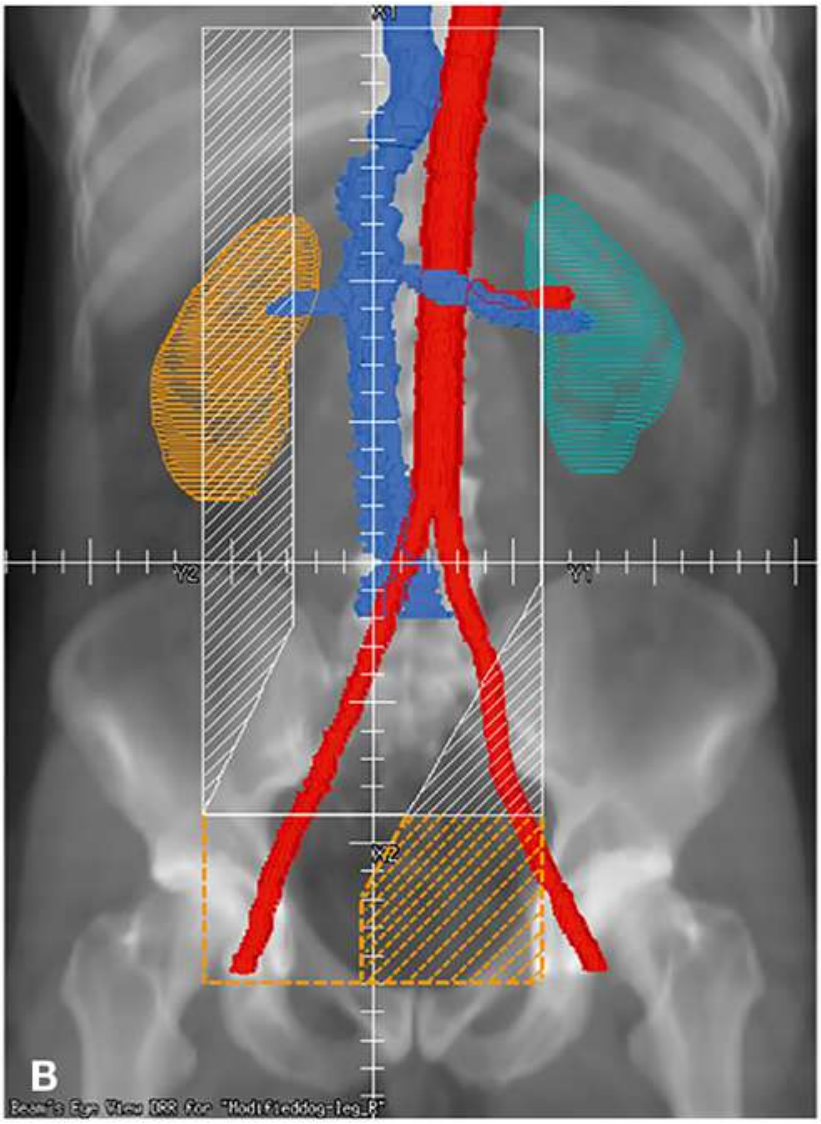


FIGURE 74.3 For stage I seminoma, a modified "dog-leg" field is used to encompass nodal regions at risk. The superior border is placed at the upper border of T10 or T11 and the inferior border at the superior aspect of the acetabulum. Traditionally, the inferior border was placed at the superior obturator foramen (indicated in orange) to include all external iliac nodes. These nodes are rarely involved, and using a higher border as indicated will reduce toxicity. If para-aortic fields are to be used, the inferior border is placed at the bottom of L5. The left renal hilum is included for left-sided tumors (A), but not for tumors on the right (B).

Once these borders are placed, the planning CT can be used to ensure adequate coverage of the target volume. Distance from the PTV to the field border is 8 to 15 mm depending on field size, energy, separation, and shielding. It should be noted that there is often a distance of several centimeters between the cranial and caudal field edges and the 95% isodose, which is related to the large field size and variability in separation.

In stage II disease, the PTV includes the same CTV as for stage I disease with an appropriate margin. Care must be taken to include the gross nodal disease in the CTV (Figure 74.4). If the lymphadenopathy is >2 cm in size, a boost to gross disease is commonly used. This may be delivered either concurrently or sequentially. The advantage

of a sequential approach is that it allows for reduction in disease volume and less irradiation of normal tissues. This is particularly appropriate where the initial disease is large and overlies the kidney.

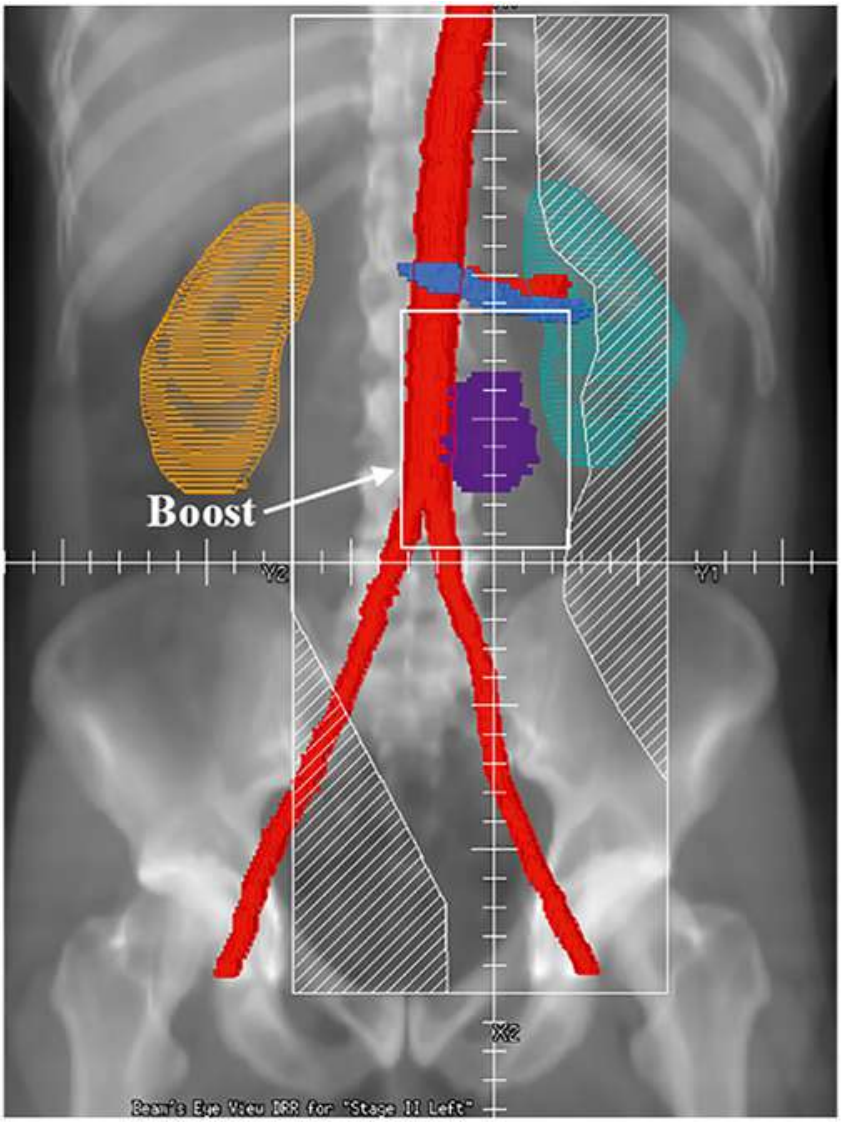


FIGURE 74.4 Stage IIA and stage IIB seminomas may be treated with a traditional or modified dog leg to a dose of 25 Gy in 20 fractions, with a boost of 10 Gy in 5 fractions to nodes >3 cm in diameter.

Paly et al analyzed the location of metastatic lymph nodes relative to vascular structures in stage II or stage I patients presenting with nodal relapse after surveillance.[87] They found, after analyzing 90 patients, that almost all detected nodes were contained within a 2.5-cm posterior and lateral margin and a 2.1-cm anterior margin from the arterial vasculature. No positive nodes were identified above the L1 level. Although requiring further validation, this suggests that the classic field borders based on bony anatomy treat a larger volume than

required, and modification, for example, by lowering the superior border, may be considered.

Simulation and Treatment Planning

A volumetric planning CT scan is acquired with the patient supine and arms at the sides. Testicular shielding (often in the form of a clamshell device) is used. Utilization of a CT-based planning technique enables visualization of the location of the lymph node regions, adjacent tissues, and critical normal structures, including the kidneys and liver. In addition, the beam's-eye view allows evaluation of the coverage of the PTV, and shielding can be appropriately placed. Treatment is delivered with a linear accelerator using anterior and posterior parallel- opposed fields. Depending on the separation, 6- to 18-MV photons are utilized. More elegant treatment techniques using intensity-modulated radiotherapy (IMRT) to cover the target volume with greater sparing of organs at risk are described.[134] Although IMRT enables reduction of dose to organs at risk (stomach, bowel, bone marrow), it increases integral doses to surrounding normal tissues, and it is not clear how this is reflected in the reduction of early or late side effects of treatment, including the risk of second malignancy. Proton radiation therapy has also been described. It allows conformality of dose to the CTV similar to that with IMRT but with less integral dose and potential risk of second malignancy.[135-137]

Dose and Fractionation

Stage I Seminoma

Radiation doses between 20 and 40 Gy at 1.25 to 2 Gy per fraction have been reported. A dose of 25 Gy in 20 fractions has been the most commonly used dose/fractionation at North American institutions,[138] with close to 100% control of retroperitoneal disease. The UK MRC (MRC TE18) completed a randomized controlled trial of 30 Gy in 15 fractions over 3 weeks or 20 Gy in 10 fractions over 2 weeks.[82] Relapse-free survival was similar in both groups. Acutely, there was significantly more moderate or severe lethargy and inability to carry out normal work in the group that received 30 Gy. However, by 12 weeks, there were no differences between the two groups.

Stage II Seminoma

In general, patients with stage II seminoma should have the ipsilateral pelvic nodes treated. The optimal radiation dose is yet to be determined, and several regimens are used. One regimen of 25 Gy in 20 fractions is frequently used with a boost (10 Gy in 5 fractions) to the residual mass for lymphadenopathy >2 to 3 cm.[101] Alternatively, 30 Gy in 15 fractions for stage IIA and 36 Gy in 18 fractions for stage IIB seminoma have been shown to provide excellent local control.[139]

Testicular Shielding

During a fractionated course of radiotherapy to the retroperitoneal and ipsilateral iliac lymph nodes, the dose to the remaining testis ranges between 0.3 and 1.5 Gy. Dose received strongly depends on the distance from the testicle to field edge. Several effective shielding devices have been described to reduce dose received by the testicle to <1% of the midplane dose.[140-142] Most departments use simple forms of gonadal shielding, such as the clamshell device, which consists of a cup that is 1 cm thick. This shields the testicle from low-energy scattered photons and effectively reduces the testicular dose by a factor of 4.

RESULTS OF THERAPY

Seminoma

The outcome of treatment depends on the stage and extent of disease at presentation. Age >40 years at diagnosis is also an adverse prognostic factor in most series.[38,143,144] For stage I disease, routine irradiation of the para-aortic and ipsilateral pelvic nodes results in 10-year relapse-free survival rates of 96% to 98%. Approximately 1% to 4% of patients relapse after infradiaphragmatic irradiation, usually within the first 3 years. The sites of relapse are usually evenly distributed between the mediastinum and distant sites. Occasional relapses occur as nonseminomatous germ cell malignancies, even after careful review of the initial tumor has shown a pure seminoma. Deaths from stage I seminoma are extremely rare. Most relapsing patients are salvaged with subsequent treatment, usually chemotherapy. Cause-specific survival rates in the large series are 99% to 100%.

The outcome for patients with stage II disease treated with infradiaphragmatic irradiation is shown in Table 74.7. Disease- free survival is approximately 92% and 86% for patients with stage IIA and IIB disease, respectively. Relapse most commonly occurs in the mediastinum, supraclavicular nodes, and lungs. Cisplatin-based chemotherapy is able to salvage in excess of 80% of the relapses, leading to a 5-year cause-specific survival of 96% to 100%. The relapse rate for patients with stage IIC disease managed by primary radiotherapy is >30%, and these patients are best managed with initial chemotherapy. Because of the ability to salvage patients who relapse following radiotherapy with cisplatin-based combination chemotherapy, the survival results following primary radiotherapy or chemotherapy as initial therapy even in patients with bulkier nodal disease are comparable. The potential toxicities of each approach must be evaluated for each patient, along with other factors influencing the choice of therapy.

Cisplatin-based chemotherapy (BEP × 3 fractions or EP × 4 fractions) is the standard treatment for patients with stage III seminoma, as well as for those with retroperitoneal masses >3 to 5 cm. Even those with advanced metastatic seminoma can expect a favorable response rate of over 95%, with a 5-year survival of over 90%.[40]

SEQUELAE OF TREATMENT

Radiation Therapy

The long-term sequelae of standard infradiaphragmatic irradiation for stages I and IIA disease are related to the dose of radiation used. There appears to be no curative advantage

for doses >25 Gy; however, there is an increase in toxicity. In the MRC randomized trial comparing 30 Gy in 15 fractions delivered to either dog-leg or para-aortic fields, 33 (7%) of 478 patients were diagnosed with a peptic ulcer during follow-up. The occurrence rate was similar in both treatment arms. Very few patients report diarrhea as a long-term consequence, and most patients report a satisfactory quality of life, with a maintained body image and few side effects.[82]

Approximately 50% of patients with testicular seminoma have some degree of impairment in spermatogenesis at the time of diagnosis, with rates of reported abnormal sperm morphology as high as 90%.[145] Exposure of the remaining testis to therapeutic irradiation may further impair fertility, and the degree of impairment is dose dependent. Available data suggest that hormonal function and spermatogenesis may be compromised at dose levels as low as 0.5 Gy and those cumulative doses >2 Gy probably lead to permanent injury.[146] Hahn et al[147] reported the induction of aspermia in 10 of 14 patients who received >65 cGy to the remaining testis. Aspermia was not detected at doses <50 cGy. Recovery of sperm in the semen occurred in most within 30 to 80 weeks of radiation therapy. A detailed assessment of fertility and sexual function was performed in the Southwest Oncology Group Study 8711 in a series of men following orchidectomy and radiation therapy for seminoma.[148] Fourteen of 26 (54%) patients were subfertile at baseline, with a sperm count <20,000/mL. The average prescribed dose was 26 Gy in 1.6-Gy fractions, delivering a median dose of 79 cGy to the remaining testis. With a testicular dose below the median, the sperm count tended to drop to a nadir value around 6 months, with recovery of fertility by 12 months. With a higher testicular dose, recovery of sperm count was further delayed. Jacobsen et al[149] reported a 50% reduction in sperm count at 1 year in 21 men following dog-leg radiation therapy (median testis dose, 32 cGy). No change in sperm count was noted in 24 men treated with para-aortic fields (median testis dose 9 cGy). Baliga et al[150] reported similar findings from the PENTEC task force—a testicular dose <1 Gy results in a 50% to 80% risk of oligospermia, but this recovers by 12 months in 75% to 100% of men. A dose of >1 Gy is associated with oligospermia in 90% of men at 12 months. There also is a dose-related effect on hormone production. Doses of 0.2 to 12 Gy result in low testosterone in 25% of men, with a steep dose-response above 20 Gy where 68% of men can be hypogonadal. Subclinical hypogonadism, with elevation of follicle-stimulating hormone and luteinizing hormone, is noted with doses over 0.5 Gy. So most men treated with radiotherapy can expect at most a temporary effect on sperm count, and rarely any long-term effect on hormonal function.

Patients are at an increased risk of developing a second primary malignancy following treatment for testicular cancer.[151-153] Travis et al[154] investigated the occurrence of second malignancies among >40,000 men who had undergone treatment for a testicular cancer between 1943 and 2001 from 14 population-based cancer registries in North America and Europe. The risk of developing a second solid tumor among 10-year survivors was almost twice that of the general population, with an RR of 1.9. The risk remained elevated for 35 years, with the highest risk for cancers of the stomach (RR 4.0), pancreas (RR 3.6), and bladder (RR 2.7). There was also an increased risk of developing cancers of the lung, esophagus, colon, and pleura. An increased risk was found for both seminomas and

nonseminomas and in patients treated with radiation therapy alone (RR 2.0), chemotherapy alone (RR 1.8), and both modalities (RR 2.9). Milano et al[155] investigated the incidence of second malignancy in a U.S. SEER population diagnosed with testicular cancer between 1973 and 2014. The 30-year cumulative incidence of second solid malignancy was 8.8%, 10.1%, and 16.9% in men treated with surgery alone, chemotherapy, and radiotherapy, respectively. Radiotherapy was associated with a significantly increased risk of pancreatic cancer in every decade beyond 10 years, with standardized incidence ratios increasing to 4.8 beyond 30 years. A significant increased risk of late hematologic malignancy was seen with chemotherapy, with a 7-fold increased risk of acute myeloid leukemia, but not with radiotherapy. A case-control study of leukemia risk in a cohort of 18,567 patients treated for testicular cancer between 1970 and 1993 has also been reported.[156] Radiation therapy (mean dose 12.6 Gy to bone marrow) without chemotherapy was associated with a 3-fold elevated risk of leukemia. Risk increased with increasing dose of radiation to the bone marrow largely associated with the use of mediastinal irradiation. The cumulative dose of cisplatin was also predictive of excess leukemia risk, being 3.2 with the commonly administered dose. In absolute terms, it is estimated that 25 Gy to the retroperitoneum would result in nine excess cases of leukemia in 10,000 patients followed for 15 years. Commonly used doses of cisplatin might result in 16 excess cases. Although treatment factors are strongly implicated in the development of second primary malignancies following treatment, an excess risk of second cancers is seen even among patients with testicular cancer who have just been observed. An increased rate of spontaneous chromosomal translocations is seen in lymphocytes of patients with early-stage seminoma compared to healthy controls.[157] Following radiation therapy, the translocation rate increases before returning to preradiotherapy levels at around 30 months.[158] It is hypothesized that this genomic instability may be a predisposing factor toward malignancy development.

Long-term survivors following radiation therapy for seminoma are also at increased risk of death related to cardiac disease, even without mediastinal irradiation,[159] with a cardiac standardized mortality ratio of 1.85 in patients followed out beyond 15 years. Survivors are also at an increased risk of hypertension, diabetes, and atherosclerosis,[160] with an increased standardized mortality ratio even beyond 25 years.[161]

Chemotherapy

Cisplatin-based chemotherapy is associated with alopecia and the potential for substantial nausea and vomiting. Modern antiemetics have improved gastrointestinal reactions. Serious short-term problems are myelosuppression, bleomycin- induced pulmonary fibrosis, and nephrotoxicity. Myelosuppression and pulmonary fibrosis are fatal in 0.5% to 4% of treated patients. There is also an increased risk of secondary malignancy. As discussed previously, the cumulative dose of cisplatin strongly correlates with the risk of subsequent malignancy.[156] Etoposide exposure also increases the risk of leukemia. Morphologically, these leukemias are usually monocytic or myelomonocytic. Characteristic chromosomal translocations are frequently, but not invariably, present. The onset of leukemia is ordinarily closer to chemotherapy exposure than is the typical leukemia induced by alkylating agents.

Other late toxicities reported include high-tone hearing loss, neurotoxicity, Raynaud phenomenon, ischemic heart disease, hypertension, renal dysfunction, and pulmonary toxicity.[162] In an observational study of 1,800 men treated with cisplatin-based chemotherapy for testicular cancer, Brydøy et al[163] noted long-term Raynaud-like phenomena in 39%, paresthesia in 29%, hearing impairment in 22%, and troubling tinnitus in 22%. Long-term fertility seems a little impaired following chemotherapy.[164] BEP causes immediate azoospermia; however, with time, more than half of patients may recover normal or near-normal spermatogenesis. The paternity rate following two to four cycles of BEP is 70% to 85%.[165] Symptomatic hormone dysfunction only occurs with high cumulative doses of cisplatin,[166] although subclinical endocrine abnormalities are more common.[167]

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CHAPTER 75

Cancer of the Penis and Male Urethra

Vivek Verma and Hiram A. Gay

ANATOMY

The basic structural components of the penis include two corpora cavernosa and the corpus spongiosum. These are encased in a dense fascia (Buck fascia), separated from the skin by a layer of loose connective tissue. Distally, the corpus spongiosum expands into the glans penis, which is covered by a skin fold known as the prepuce. The skin extends over and is firmly attached to the glans.

The male urethra is composed of a mucous membrane and the submucosa. It extends from the bladder neck to the external urethral meatus. The posterior urethra is subdivided into the membranous urethra (the portion passing through the urogenital diaphragm) and the prostatic urethra, which passes through the prostate. The anterior urethra passes through the corpus spongiosum. It is subdivided into fossa navicularis (a widening within the glans); the penile urethra, which passes through the pendulous part of the penis; and the bulbous urethra, the dilated proximal portion of the anterior urethra. The prostatic urethra is covered by transitional epithelium only. The distal portion of the anterior urethra is covered by stratified squamous epithelium, which changes proximally to pseudostratified columnar epithelium. The columnar epithelium gradually changes into transitional epithelium in the membranous urethra.

The lymphatic channels of the prepuce and the skin of the shaft drain into the superficial inguinal nodes located above the fascia lata. The rich anastomotic network of the lymphatics within the penis and at the base of the penis means that, for practical purposes, lymphatic drainage may be considered bilateral. There is some disagreement about whether the glans and the deep penile structures drain into the superficial or deep inguinal lymph nodes (those under the fascia lata). The so-called sentinel nodes located above and medial to the junction of the epigastric and saphenous

veins have been identified as the primary drainage sites in carcinoma of the penis.[1] Selective biopsy of this group of nodes is of obvious importance in the assessment of tumor extent because, if they are not involved by tumor, a complete nodal dissection may not be necessary. Some have not supported the reliability of this procedure.[2,3] Catalona[4] found that biopsy of the sentinel nodes showed false-negative results in 10% of Cabanas's[5] cases who died of carcinoma.

The lymphatics of the fossa navicularis and the penile urethra follow the lymphatics of the penis to the superficial and deep inguinal lymph nodes. The lymphatics of the bulbomembranous and prostatic urethra may follow three routes. Some pass under the pubic symphysis to the external iliac nodes, some go to the obturator and internal iliac nodes, and others end in the presacral lymph nodes. The pelvic (iliac) lymph nodes are rarely involved without inguinal lymph node involvement.[6]

EPIDEMIOLOGY AND RISK FACTORS

Penile Cancer

In the United States in 2023, the estimated number of new cases of penis and other genital cancers cancer was 2,050, with 470 deaths. This accounts for less than 1% of cancer in males in the United States.[7] In the European Union, the annual number of males who develop penile cancer is estimated at 3,100, which is equivalent to an age-standardized rate (ASR) of 12 per million males. Squamous cell carcinoma is the predominant morphologic entity.[8]

A systematic review and meta-analysis showed that men circumcised in childhood/adolescence are at substantially reduced risk of invasive penile cancer, and this effect could be mediated partly through an effect on phimosis. In contrast, there was some evidence that circumcision in adulthood was associated with an increased risk of invasive penile cancer.[9] A trade-off analysis of routine newborn circumcision was performed on the Comprehensive Hospital Abstract Reporting System for Washington State. Routine newborn circumcisions performed over 9 years (1987-1996) were retrospectively examined. Of 354,297 male infants born during the study period, 37% were circumcised during their newborn stay. Overall, 0.2% of circumcised children and 0.01% of uncircumcised children had

complications potentially associated with circumcision. The authors estimated that almost two complications can be expected for every case of penile cancer prevented.[10]

A study of 1,010 penile invasive cancers diagnosed between 1983 and 2011 from 25 countries showed that between one-quarter to one-third of penile cancers were related to human papillomavirus (HPV), with HPV-16 being the most frequent HPV subtype in HPV-positive cancers.[11] A more recent meta-analysis of 1,836 patients showed that the rate of HPV positivity was considerably higher (51%).[12] A Brazilian study of 110 asymptomatic men and 30 patients who underwent circumcision due to phimosis showed that HPV was present in 46% of patients with phimosis, of whom 50% were high-risk phenotypes. They detected a significantly high rate of HPV genital infection in patients presenting with phimosis compared with asymptomatic men. The prevalence of high-risk HPV genotypes in patients with phimosis was also statistically significant.[13]

The quadrivalent vaccine against HPV serotypes 6, 11, 16, and 18 has been approved for females aged 9 to 26 years to prevent cervical cancer. Based on the demonstrated ability to significantly decrease the incidence of penile lesions (primarily HPV-6 and HPV-11 associated genital warts) in young men, the U.S. Food and Drug Administration also approved the use of the vaccine in males aged 9 to 26 years. Because the incidence of penile cancer in the United States is much lower than that of genital warts, the reduction in penile cancer incidence is expected to be low cancer rates. Perhaps the greatest benefit of vaccination of young men in the United States would be the reduced HPV infection rate in the overall population and subsequent reduced transmission to females at risk for cervical cancer.[14] Other potential strategies for the prevention of penile cancer could include smoking cessation and hygienic measures.[15]

Urethral Cancer

Carcinoma of the male urethra is also rare. Each year, around 650 individuals in the European Union develop cancer of the urethra. The ASR for cancer of the urethra is 1.1 (males 1.6; females 0.6) per million inhabitants. The 5-year relative survival rate for cancer of the urethra is

54%. Transitional cell carcinoma (TCC) is the predominant morphologic entity of cancer of the urethra.[8]

There are no recognized racial or geographic predisposing factors. Although the etiology remains unknown, there seems to be some correlation between the incidence of carcinoma of the urethra and chronic irritation (infection, venereal diseases, strictures). Some evidence suggests that some cases of female urethral carcinoma may originate from Skene glands.[16] Significant past medical history of patients with male urethra cancer includes venereal disease (24%-37%), urethral stricture (35%-54%), urethral trauma (7%), and urethral polyps (2%).[17,18] The part of the urethra covered by the transitional epithelium (prostatic and membranous urethra) may be susceptible to the same carcinogenic factors that affect the bladder and the upper urinary tract. The average age at presentation of these tumors is 58 to 60 years, although 10% occur in men younger than 40 years.[5,18]

NATURAL HISTORY

Penile Cancer

Most carcinomas of the penis start within the preputial area, arising in the glans, coronal sulcus, or the prepuce itself. Lesions arising in the skin of the shaft are rare. In most patients, carcinoma of the penis is characterized by slow locoregional progression. The penis is handled and observed daily, yet there is often significant debate as to when patient recognition and medical diagnosis should have occurred. The patient often experiences fear and embarrassment, leading to delayed diagnosis. Therefore, expeditious diagnosis of all penile lesions should be the rule. Extensive primary lesions may involve the corpora cavernosa or even the abdominal wall. The inguinal lymph nodes are the most common site of metastatic spread. Pathologic evidence of nodal metastases is reported in about 35% of all patients and approximately 50% of those with palpable lymph nodes.[5,19-21]

Distant metastases are uncommon (about 10%), even in patients with advanced locoregional disease, and usually occur in patients with inguinal lymph node involvement. These patients often die of septic complications, erosion of large vessels in the groin, or a combination thereof.

Tumors can also metastasize to the penis. The most common primary sites are the genitourinary tract (mostly bladder urothelial carcinoma and

prostatic adenocarcinoma) and the lower gastrointestinal tract (rectal and sigmoid colon adenocarcinomas). Secondary tumors tend to be localized in the penile shaft and invade the vascular spaces of erectile tissues, with corpora cavernosa involved in most cases. For patients with penile metastasis, the cancer-related death rate is high, and the prognosis is dismal.[22]

Urethral Cancer

The natural history of carcinoma of the anterior urethra in the male is similar to that of penile carcinoma. Approximately 40% of tumors originate in the anterior urethra.[17] Many tumors are low grade and progress slowly at primary and regional sites rather than spread to distal areas. Tumors of the penile urethra spread to the inguinal lymph nodes first, whereas those of the bulbomembranous and prostatic urethra metastasize first to the pelvic lymph nodes. Approximately one-third of men will present with either clinically or pathologically involved lymph nodes.[17]

Urethral cancers tend to spread by direct extension to adjacent structures. Invasion into the vascular space of the corpus spongiosum in the periurethral tissues is common. Malignancies beginning in the bulbomembranous urethra often invade the deep structures of the perineum, including the urogenital diaphragm, prostate, and adjacent skin. In the majority of prostatic urethral tumors, the bulk of the prostate gland is invaded at the time of diagnosis. Hematogenous spread is uncommon, except in advanced regional disease. Kaplan et al[18] reported distant metastases in about 15% of patients, and most had corpora cavernosa invasion at diagnosis.

CLINICAL PRESENTATION

Penile Cancer

Carcinoma of the penis may present as either an infiltrative ulcerative or an exophytic papillary lesion. Figure 75.1 demonstrates the localization of penile tumors in 259 patients from 14 cancer institutes in France. The glans and the prepuce were the predominant sites of the primary lesion, whereas tumors of the shaft were rare.[23] The presence of phimosis may obscure the assessment of the primary lesion. Secondary infection and associated foul

smell are quite common. Urethral obstruction is an unusual symptom of carcinoma of the penis. The most common presenting symptom is a mass, which occurs in over two-thirds of patients. Ulceration is also common, occurring in approximately half of patients.[21,24] In a collective series of 552 patients with penile carcinoma, the presenting symptoms were mass lesions (78%), pain or itching (12%), bleeding (7%), groin mass (7%), and urinary symptoms (4%).[25-27] Inguinal lymph nodes are palpable on presentation in 30% to 45% of patients[5,19,20,26,28,29]; however, only half contain tumor.[20,21] Enlargement of the lymph nodes is often related to inflammatory (infectious) processes. Administration of antibiotics over several weeks results in regression of inguinal lymph nodes in a substantial proportion of cases, and many have advocated this practice before the status of the regional lymph nodes is definitively assessed. Conversely, between 20% and 40% of patients with clinically negative inguinal lymph nodes have occult metastases.[3,30-33]

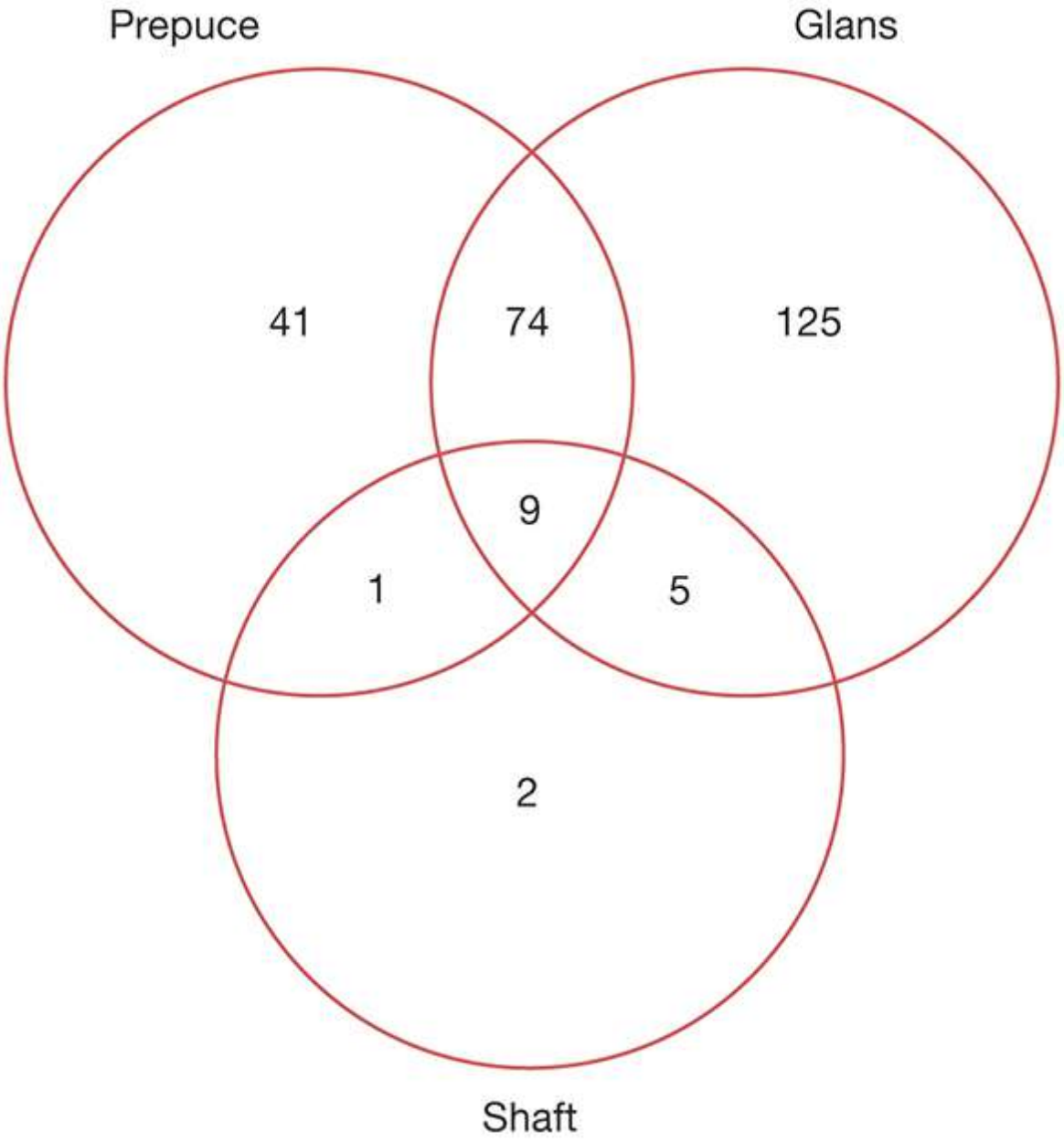

FIGURE 75.1 Localization of the primary tumor in 259 patients; each circle represents one anatomic compartment. Intersections indicate the involvement of two or three compartments. Unknown: two. (Reprinted from Rozan R, Albuisson E, Giraud B, et al. Interstitial brachytherapy for penile carcinoma: a multicentric survey (259 patients). *Radiother Oncol*. 1995;36[2]:83-93. Copyright © 1995 Elsevier Ireland Ltd. With permission.)

Urethral Cancer

Patients with urethral carcinoma most commonly present with obstructive symptoms (43%). Other presenting signs and symptoms include mass (28%), bleeding (20%), abscess (20%), and irritative symptoms (20%).[17]

These symptoms are often attributed to urethritis or urethral stricture, which may precede the development of urethral carcinoma and may also result in a delay in diagnosis. The majority of urethral carcinomas occur in the bulbomembranous (posterior) region (61%), and tumors in this location have a worse prognosis compared with those arising in the anterior urethra.[17]

DIAGNOSTIC WORKUP

In penile and urethral cancers, imaging plays a crucial role in enhancing the precision of clinical staging and facilitating optimal surgical planning. High-resolution magnetic resonance imaging (MRI) now represents the gold standard for evaluating the primary tumor and its local extension. Lymphotropic nanoparticle-enhanced MRI and dynamic sentinel lymph node biopsy combined with fine-needle aspiration seem to be superior for imaging regional lymph nodes. Positron emission tomography/computed tomography (PET/CT) has shown great promise for the detection of distant metastases.[34]

Penile Cancer

See Table 75.1 for the diagnostic workup of penile cancer.

TABLE 75.1 DIAGNOSTIC WORKUP FOR PENILE CANCER

History and physical examination

- Risk factors: Balanitis, chronic inflammation, penile trauma, lack of neonatal circumcision, tobacco use, lichen sclerosus, poor hygiene, sexually transmitted
- Lesion characteristics: Diameter, location, number of lesions, morphology (papillary, nodular, ulcerous, or flat), relationship to other structures (submucosal, corpora spongiosa, cavernosa, and/or urethra)
- Lymph node characteristics: Diameter, unilateral or bilateral, number, relationship to other structures, mobility or fixation, skin involvement

Histologic diagnosis

- Punch, excisional or incisional biopsy
- Assess human papillomavirus (HPV) status

Cross-sectional imaging of chest/abdomen/pelvis may include:

- Abdomen/pelvis CT or MRI with contrast
- Chest x-ray or CT with contrast
- PET/CT
- CT/MRI of the pelvis with contrast for nodal evaluation if difficult to clinically assess

CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

On MRI, penile tumors are best evaluated on T2-weighted images owing to the superior contrast resolution between the hypointense fascial layers and the adjacent hyperintense corporal bodies. Squamous cell carcinomas typically appear as hypointense lesions when compared to the adjacent corpora. On MRI, nonsquamous variants of penile cancer can appear different from squamous carcinomas. Although penile cancers enhance with gadolinium, the normal corporal bodies enhance even more, which makes contrast enhancement less useful.[34]

The presence of central nodal necrosis and/or an irregular nodal border of the regional lymph nodes on preoperative CT images are accurate and reproducible (sensitivity of 95% and a specificity of 82%) criteria to identify high-risk pathologic node-positive penile cancer.[35]

Sentinel lymph node biopsy with a radiotracer (Tc-99m nanocolloid) is a reliable method with low morbidity associated with a low radiation burden for clinical staff. The false-negative rate and morbidity are less than 5%.[36]

Limited prospective data regarding the use of PET with CT are available, but preliminary results show encouraging sensitivity (88%) and specificity (98%) in evaluating inguinal lymph nodes[37] and diagnostic accuracy of 96% in evaluating pelvic lymph nodes in patients with known inguinal metastases.[38]

Urethral Cancer

See Table 75.2 for the diagnostic workup of urethral cancer.

TABLE 75.2 DIAGNOSTIC WORKUP FOR URETHRAL CANCER

General

- History and physical examination
- Cystourethroscopy, examination under anesthesia, transurethral resection, or transvaginal biopsy

Radiographic studies

- MRI of the pelvis with and without contrast
- Chest x-ray or CT

- Palpable lymph nodes: chest, abdominal, and pelvic CT with contrast. Lymph node biopsy

CT, computed tomography; MRI, magnetic resonance imaging.

A cystourethroscopy is essential for urethral primaries. Inguinal lymph nodes should be thoroughly evaluated. CT is useful in identifying enlarged pelvic and periaortic lymph nodes in patients with involved inguinal lymph nodes.[34]

On MRI, urethral tumors tend to show a decreased signal intensity relative to the surrounding normal corporal tissue on T1- and T2-weighted images. Malignant lesions usually enhance with gadolinium.[34]

STAGING

Penile Cancer

Urethral Cancer

The American Joint Committee on Cancer (AJCC) staging systems for carcinoma of the penis and urethra are shown in Tables 75.3 and 75.4, respectively.[39]

TABLE 75.3 2017 PENIS CANCER TNM STAGING AJCC UICC

T Category	T Criteria
TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor
Tis	Carcinoma in situ (penile intraepithelial neoplasia [PeIN])
Ta	Noninvasive localized squamous cell carcinoma
T1	Glans: Tumor invades the lamina propria. Foreskin: Tumor invades dermis, lamina propria, or dartos fascia. Shaft: Tumor invades connective tissue between epidermis and corpora regardless of location. All sites with or without lymphovascular invasion or perineural invasion and is or is not high grade
T1a	Tumor is without lymphovascular invasion or perineural invasion and is not high grade (ie, grade 3 or sarcomatoid).
T1b	Tumor exhibits lymphovascular invasion and/or perineural invasion or is high grade (ie, grade 3 or sarcomatoid).

T Category	T Criteria		
T2	Tumor invades into corpus spongiosum (either glans or ventral shaft) with or without urethral invasion.		
T3	Tumor invades into corpus cavernosum (including tunica albuginea) with or without urethral invasion.		
T4	Tumor invades other adjacent structures (ie, scrotum, prostate, pubic bone).		
Regional Lymph Nodes (N)[a]			
Clinical N (cN)			
cN Category	**cN Criteria**		
cNX	Regional lymph nodes cannot be assessed.		
cN0	No palpable or visibly enlarged inguinal lymph nodes		
cN1	Palpable mobile unilateral inguinal lymph node		
cN2	Palpable mobile ≥2 unilateral inguinal nodes or bilateral inguinal lymph nodes		
cN3	Palpable fixed inguinal nodal mass or pelvic lymphadenopathy unilateral or bilateral		
Clinical N (pN)			
pN Category	**pN Criteria**		
pNX	Lymph node metastases cannot be established.		
pN0	No lymph node metastasis		
pN1	≤2 unilateral inguinal metastases, no ENE		
pN2	≥3 unilateral inguinal metastases or bilateral inguinal metastases		
pN3	ENE of lymph node metastases or pelvic lymph node metastases		
M Category	**M Criteria**		
M0	No distant metastasis		
M1	Distant metastasis present		
AJCC Prognostic Stage Groups			
0is	Tis	N0	M0
0a	Ta	N0	M0
I	T1a	N0	M0
IIA	T1b or T2	N0	M0

T Category	T Criteria		
IIB	T3	N0	M0
IIIA	T1-3	N1	M0
IIIB	T1-3	N2	M0
IV	T4	Any N	M0
	Any T	N3	M0
	Any T	Any N	M1
Histologic Grade (G)			
GX	Grade cannot be assessed.		
G1	Well differentiated		
G2	Moderately differentiated		
G3	Poorly differentiated/high grade		

AJCC, American Joint Committee on Cancer; ENE, extranodal extension; NOS, not otherwise specified; UICC, International Union Against Cancer.

[a]The regional lymph nodes are as follows: superficial and deep inguinal lymph nodes, pelvic nodes (NOS), and pelvic nodes (specified): external iliac, internal iliac (also called hypogastric), and obturator.

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

TABLE 75.4 2017 URETHRA CANCER TNM STAGING AJCC UICC

Male Penile Urethra and Female Urethra	
T Category	**T Criteria**
TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ
T1	Tumor invades subepithelial connective tissue.
T2	Tumor invades any of the following: corpus spongiosum, periurethral muscle.
T3	Tumor invades any of the following: corpus cavernosum, anterior vagina.
T4	Tumor invades other adjacent organs (eg, invasion of the bladder wall).
Prostatic Urethra	

T Category	T Criteria
Tis	Carcinoma in situ involving the prostatic urethra or periurethral or prostatic ducts without stromal invasion
T1	Tumor invades urethral subepithelial connective tissue immediately underlying the urothelium.
T2	Tumor invades the prostatic stroma surrounding ducts either by direct extension from the urothelial surface or by invasion from prostatic ducts.
T3	Tumor invades the periprostatic fat.
T4	Tumor invades other adjacent organs (eg, extraprostatic invasion of the bladder wall, rectal wall).
N Category	**N Criteria**
NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis
N1	Single regional node metastasis in the inguinal region or true pelvis (perivesical, obturator, internal [hypogastric] and external iliac), or presacral lymph node
N2	Multiple regional lymph node metastases in the inguinal region or true pelvis (perivesical, obturator, internal [hypogastric] and external iliac), or presacral lymph node
M Category	**M Criteria**
M0	No distant metastasis
M1	Distant metastasis

AJCC Prognostic Stage Groups			
0is	Tis	N0	M0
0a	Ta	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T1 or T2	N1	M0
	T3	N0 or N1	M0
IV	T4	N0 or N1	M0
	Any T	N2	M0
	Any T	Any N	M1

Histologic Grade (G) Urothelial Carcinoma	
LG	Low grade
HG	High grade
Squamous Cell Carcinoma and Adenocarcinoma	
GX	Grade cannot be assessed.
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

AJCC, American Joint Committee on Cancer; NOS, not otherwise specified; UICC, International Union Against Cancer.

[a]The regional lymph nodes are as follows: superficial and deep inguinal lymph nodes, pelvic nodes (NOS), and pelvic nodes (specified): external iliac, internal iliac (also called hypogastric), and obturator.

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PATHOLOGIC CLASSIFICATION

Penile Cancer

The World Health Organization (WHO) classifies malignant epithelial tumors of the penis as squamous cell carcinoma (Basaloid, warty [condylomatous], verrucous, papillary not otherwise specified, sarcomatous, mixed, and adenosquamous carcinoma), Merkel cell carcinoma, small cell carcinoma of neuroendocrine type, sebaceous carcinoma, clear cell carcinoma, and basal cell carcinoma.[40] Basaloid carcinoma has a poor prognosis and frequently early inguinal nodal metastases. Warty carcinoma has a good prognosis with rare metastases. Verrucous carcinoma has a good prognosis with no metastases. Papillary carcinoma has a good prognosis with rare metastases. Sarcomatous carcinoma has a very poor prognosis with early vascular metastases. Mixed carcinoma has a heterogeneous prognosis. Adenosquamous carcinoma occurs in the central and perimeatal glans and is high grade with high metastatic potential but low mortality.[41]

Most malignant penile tumors are well-differentiated squamous cell carcinomas.[42] Although an apparent adverse prognostic effect of anaplasia

has been reported in some series,[19] others found no significant correlation between histologic grade and survival.[26,43]

Bowen disease is squamous cell carcinoma in situ that may involve the shaft of the penis as well as the hairy skin of the inguinal and suprapubic area. Clinically, the lesion is a solitary, dull red plaque with areas of crusting and oozing. Approximately 25% to 50% of patients with this disease have a concomitant visceral malignancy.[6]

Erythroplasia of Queyrat is an epidermoid carcinoma in situ involving the prepuce or glans' mucosal or mucocutaneous areas.[42] It appears as a reddened, elevated, or ulcerated lesion. Graham and Helwig[44] reported that 10 of 100 patients presenting with erythroplasia of Queyrat had invasive squamous cell carcinoma at diagnosis. Mikhail[45] reported on 5 of 15 patients with the same presentation.

Basal cell carcinoma of the penis is an extremely rare entity, accounting for less than 0.03% of all basal cell carcinomas.[46]

Extramammary Paget disease is a rare intraepithelial apocrine carcinoma. The most common sites are the scrotum, inguinal folds, and perineal region.[45] The lesion tends to metastasize, necessitating frequent assessment of regional nodes. Radiation therapy (RT) can be recommended as palliative treatment.[45]

Soft tissue tumors are uncommon. Approximately half of the tumors are benign and may include angiomatous, neurogenous, myogenous, fibrous, and lymphoreticular tumors.[47,48] Most soft tissue tumors occur on the shaft and are malignant.

Primary lymphoma of the penis was reported in one patient with Peyronie disease without other evidence of lymphomatous involvement. Five cases of secondary involvement of the penis by lymphoma were reported in the literature.[49]

Cancers metastatic to the penis are rare and usually represent late, advanced carcinomatosis. The most common neoplasms metastasizing to the penis are from the genitourinary organs, followed by the gastrointestinal and respiratory systems (Table 75.5). The predominant cell type is carcinoma, occurring in 202 of 219 cases.[50] Sarcomas and tumors of unknown histologic type are rare. A palpable mass, swelling, nodule, or skin change frequently occurs. Priapism as an initial presenting feature or subsequent development occurs in 40% of patients.[50]

TABLE 75.5 PRIMARY MALIGNANCIES ASSOCIATED WITH SECONDARY CANCERS OF THE PENIS IN 219 PATIENTS

Site of Primary Malignancy	Number of Patients
Genitourinary Tract	
Bladder	65
Prostate	65
Kidney	23
Testis	10
Ureter	1
Gastrointestinal Tract	
Rectum/sigmoid	34
Colon	1
Anus	1
Liver	1
Pancreas	1
Respiratory Tract	
Lungs	8
Nasopharynx	1
Other	
Lymphosarcoma/reticulum cell sarcoma	4
Bone	2
Burkitt lymphoma	1
Skin (malignant melanoma)	1

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Urethral Cancer

The histologic subtypes in the Memorial Sloan-Kettering Cancer Center series of urethral cancers included squamous cell carcinoma (52%), TCC (33%), epidermoid carcinoma (11%), adenocarcinoma (2%), and anaplastic carcinoma (2%).[17] Primary malignant melanoma arising from the urethra has

been reported.[51,52] The frequency of histologic type varies with site. Over 90% of carcinomas of the prostatic urethra are of transitional cell type. Adenocarcinomas occur only in the bulbomembranous urethra.

PROGNOSTIC FACTORS

Penile Cancer

The principal prognostic factors in carcinoma of the penis are the extent of the primary lesion and the status of the lymph nodes.[24,53] The incidence of nodal involvement is related to the size, location, and grade of the primary lesion. Invasion of deep-seated structures (corpora cavernosa) carries a high risk of deep inguinal node involvement.

Several studies have corroborated that HPV-associated cases have improved prognosis as compared to HPV-negative disease.[54,55] In addition, p16 positivity, a surrogate for HPV infection, confers an improved prognosis and has excellent interobserver reproducibility.[56]

Tumor-free regional nodes imply an excellent (80%-90%) long-term survival or cure.[20,29,53] Patients with involvement of the inguinal nodes fare considerably worse, and only 40% to 50% survive long term.[20,29,53,57] Pelvic lymph node involvement implies a worse prognosis; less than 20% of these patients survive.[5,20,26] Gerbaulet and Lambin[58] reported the results of 109 patients with penile carcinoma at the Institut Gustave-Roussy. The actuarial survival rates of patients with negative nodes were 82% at 5 years and 59% at 10 years. The survival rates for patients with positive nodes survival rates were 36% and 18%, respectively. The number of positive lymph nodes has also been reported to have prognostic significance. Brkovic et al[59] reported a 5-year survival rate of 71% in patients with solitary inguinal lymph node metastasis compared with 33% in patients with multiple positive inguinal nodes. Extranodal extension in dissected nodes is another poor prognostic factor, with median survival around 10 to 12 months.[60]

Fraley et al showed tumor differentiation as an important prognostic factor.[61] None of nine patients with carcinoma in situ, 1 of 20 with well-differentiated, 5 of 13 with moderately differentiated, and 3 of 4 with poorly differentiated lesions died of their tumors. Other investigators have confirmed the prognostic significance of tumor grade.[24,53,62,63]

Carcinoma of the penis has been reported to have a greater propensity to metastasize and poorer prognosis in patients younger than 50 years[61] and patients older than 65 years.[62] Soria et al[24] and O'Kelly et al[64] reported younger age at presentation adversely affected disease-free survival and cancer-specific survival (CSS), respectively, but neither discerned differences in overall survival. Marcial et al[65] observed no difference in survival in relation to age.

An epithelial-mesenchymal transition (EMT) phenotype at the invasion front of squamous cell carcinoma of the penis confers a worse prognosis. EMT is a process that allows polarized epithelial cells to undergo biochemical, molecular, and morphologic changes that affect the acquisition of a mesenchymal cell phenotype with increased migration, tissue invasion, and resistance to apoptosis. A retrospective study of 149 penile cancers showed that the 10-year overall survival and CSS rates in patients with the presence or absence of complete EMT status were 38.0% and 55.6% and 48.0% and 91.9%, respectively.[66] Activation of mTOR signaling may contribute to penile squamous cell carcinoma progression and aggressive behavior.[67] CD44 levels and expression patterns can be considered markers for penile squamous cell carcinoma aggressiveness and may serve as predictive markers for lymph node metastases.[68]

Predictors of cancer-specific mortality after disease recurrence in patients with squamous cell carcinoma of the penis include shorter time to disease recurrence, lymph node metastasis at the time of initial treatment, and regional recurrence.[69] Nomograms have been developed to predict outcomes based on several of the aforementioned prognostic factors.[70]

Urethral Cancer

A Surveillance, Epidemiology, and End Results (SEER) database study of 2,065 men from 1988 to 2006 showed that predictors of death and death from disease included advanced age, higher grade, higher T stage, systemic metastases, other histology versus TCC, and no surgery versus radical resection. Adenocarcinoma was associated with a lower likelihood of death and death from disease as compared with TCC. Nodal metastasis was a predictor of death. Surgery had a better outcome than radiation for stage T2-T4 nonmetastatic disease.[71]

Another SEER database study of 722 women from 1983 to 2008 showed that advanced age, T stage, node-positive disease, nonsquamous histologic features, and Black race were associated with reduced CSS. Surgical resection was associated with a longer CSS.[72]

Overall prognosis in males with carcinoma of the urethra varies considerably with the location of the primary lesion.[17,73-78] Distal lesions generally have a prognosis similar to that of carcinoma of the penis. Lesions of the bulbomembranous urethra are usually quite extensive and are associated with a dismal prognosis. Dalbagni et al[17] reported a 5-year overall survival of 69% in patients with anterior tumors compared with 26% in patients with posterior tumors. Other prognostic factors included lymph node status and histology (superficial vs invasive). A study of an international cohort of 154 patients with primary urethral cancer showed that clinical nodal stage is a critical parameter impacting outcomes.[79] Tumors of the prostatic urethra show prognostic features similar to those in bladder carcinoma. Superficial lesions have a good prognosis and may be managed with transurethral resection.[76] Deeply invasive tumors have a greater tendency to develop inguinal or pelvic lymph node and distant metastases.

GENERAL MANAGEMENT

Penile Cancer

General Treatment Approach

According to U.S. cancer guidelines for penile cancer, as well as guidelines from the European Association of Urology and American Society of Clinical Oncology,[80] clinical Tis, Ta, and T1 penile cancer lesions may be amenable to organ-sparing approaches, such as topical therapy (5-fluorouracil [5-FU] or imiquimod), laser therapy, glansectomy, wide local excision, and Mohs micrographic surgery. For T1 G1-2 tumors, interstitial brachytherapy (preferred) or external beam radiation therapy (EBRT) can be considered (category 2B). Circumcision should always precede RT to prevent radiation-related complications. For T1 G3-4 or T2 tumors smaller than 4 cm with negative nodes, interstitial brachytherapy or EBRT with or without inguinal lymph node RT are options after circumcision. Tumors 4 cm or larger, or unresectable node-positive disease, circumcision followed by

chemoradiotherapy, and carefully selected patients may be amenable to brachytherapy. Postsurgical RT to the primary tumor site may be considered for positive margins.

If the patient is unable or unwilling to undergo surgical management, prophylactic EBRT to the lymph nodes should be considered. For patients with pN2-N3 disease, a pelvic lymph node dissection with or without adjuvant chemotherapy or chemoradiotherapy should be considered. Definitive chemoradiotherapy is also an option. Postoperative RT or chemoradiotherapy may be considered after pelvic lymph node dissection, particularly in the setting of a positive surgical margin, viable cancer in multiple inguinal or pelvic lymph nodes, and/or extranodal extension on pathology.

The InPACT, International Penile Advanced Trial (NCT02305654), sponsored by the Institute of Cancer Research (United Kingdom), will consist of two randomizations. The first randomization relates to inguinal management and has three arms: therapeutic inguinal node dissection (arm A), neoadjuvant chemotherapy followed by therapeutic inguinal node dissection (arm B), and neoadjuvant chemoradiotherapy followed by therapeutic inguinal node dissection (arm C). Pathologically high-risk patients (defined as ≥3 nodes or extranodal spread) undergo a second randomization: Arm A and arm B are randomized between adjuvant chemoradiotherapy or prophylactic pelvic lymph node dissection followed by adjuvant chemoradiotherapy, and arm C is randomized between surveillance or prophylactic pelvic lymph node dissection. Neoadjuvant chemotherapy consists of up to four cycles of paclitaxel, ifosfamide, and cisplatin (TIP), and concurrent chemoradiotherapy uses cisplatin.[81]

Conservative Therapies

Treatment for carcinoma in situ and very small penile carcinomas includes topical imiquimod and 5-FU.[82] Conservative laser surgery[83] or Mohs micrographic surgery is used for larger lesions.[84]

Surgery

Treatment of patients with carcinoma of the penis is generally performed at two separate levels: (1) management of the primary tumor and (2) treatment

of the regional lymphatics. According to national cancer guidelines, organ-sparing surgical interventions at the primary site include laser therapy, wide local excision, glansectomy, and Mohs micrographic surgery. Partial or total penectomy should be considered for high-grade primary penile tumors or tumors invading the corpus cavernosum.

In very advanced proximal tumors, more aggressive resections such as total emasculation (penectomy, scrotectomy, orchiectomy) or cystoprostatectomy may be indicated. Although surgical resection is a highly effective and expedient treatment modality in most cases, it may not be acceptable to sexually active patients. Radical surgery, especially total penectomy, may be psychologically devastating to the patient. The ideal surgical procedure removes the disease with adequate margins while preserving sexual and urinary function, although this is not always possible because of the extent of the disease. The high local recurrence rates described in some reports with limited surgery[85,86] illustrate the need for careful patient selection in choosing a surgical approach.

Lesions confined to the prepuce may be treated with wide circumcision. Microsurgical techniques have shown local excision to be an acceptable and desirable option with small superficial lesions. A local control rate of 92% was achieved in 29 patients, with a 5-year survival rate of 81% for stage I and 57% for stage II lesions.[87] A study of 129 patients at MD Anderson Cancer Center undergoing various organ-sparing surgical procedures demonstrated a local control of 84% at a median follow-up of 28 months, with local failures salvageable with further penile-sparing procedures.[88] A large multicenter study of 1,188 patients undergoing organ-preserving surgery demonstrated a 5-year local recurrence-free survival of 74%, which was roughly comparable between Ta/Tis, T1, and T2 cases; the secondary penectomy rate was 19%.[89]

Some patients can remain sexually active after partial penectomy. Jensen[90] reported that 45% of patients with 4 to 6 cm and 25% of patients with 2 to 4 cm of penile stump could perform sexual intercourse. D'Ancona et al[91] evaluated the quality of life in 14 patients treated with partial penectomy. Sexual function was reported to be normal or only slightly decreased in 64% of patients. Complete loss of sexual function was reported in 14% of patients.

Surgical Treatment of Inguinal Lymph Nodes

According to national cancer guidelines, standard or modified inguinal lymph node dissection (ILND) or dynamic sentinel lymph node biopsy (DSNB) is indicated in patients with high-risk features for nodal metastases: lymphovascular invasion, pT1G3 or higher or T2 or higher, or more than 50% poorly differentiated. The sensitivity of DSNB is roughly 87% for clinically N0 disease (95% confidence interval, 82%-91%).[92]

For clinically node-positive disease, ILND is the standard of care. For clinically node-negative disease, either DSNB or ILND can be performed per physician judgment. The goal of DSNB is to potentially avoid ILND and its associated sequelae; however, if DSNB turns out positive, then ILND remains the standard approach because the degree/extent of nodal involvement is the most powerful predictor of additional inguinal lymph node metastases.[93-95]

ILND can occur either at the same time as penile resection or separately in a staged manner.[96] Open surgical approaches have been traditionally utilized, but endoscopic approaches offer fewer complications and side effects.[97] Although bilateral ILND remains the standard of care, emerging data have suggested that unilateral ILND with contralateral DSNB may not compromise outcomes.[98] There is no optimal cutoff regarding how many nodes should be removed, but some data have suggested a threshold of 15.[99]

Pelvic lymph node dissection (PLND) should be considered at the time or following ILND in patients with two or more positive inguinal nodes on the ipsilateral ILND site or any evidence of extranodal extension on pathology. A bilateral PLND should be considered at the time or following ILND in patients with four or more total positive inguinal nodes. It has been suggested that an adequate PLND comprises removing at least nine nodes, but there remains no consensus to date.[99]

The clinical evaluation of inguinal lymph nodes in men with penile cancer is unreliable. Several series have shown the sensitivity of clinical staging of the nodes to be 40% to 60% and false-negative rates of 10% to 20%.[3,4] McDougal et al[100] reported the correlation between clinical findings and pathologic positivity of inguinal nodes in patients with penile carcinoma. For tumors with no invasion or superficial invasion, moderately or well differentiated, only 12% of clinically enlarged inguinal nodes were pathologically positive. However, 78% to 88% of invasive or poorly

differentiated tumors metastasized to inguinal nodes, regardless of clinical findings. In a prospective study involving 37 patients with clinically negative groins, Solsona et al[33] have demonstrated the predictive value of histologic grade and T stage in predicting the likelihood of occult positive lymph nodes. Three groups were identified: low, intermediate, and high risk, with an incidence of occult positive nodes of 0%, 33%, and 83%, respectively (Table 75.6).

TABLE 75.6 T STAGE AND GRADE PREDICT THE RISK OF OCCULT POSITIVE LYMPH NODES

Risk Group		Occult Positive Lymph Nodes (%)
Low	Tis, T1 grade 1	0/13 (0)
Intermediate	T1 grade 2-3 T2 grade 1	4/12 (33.3)
High	T2 grade 2 T2-3 grade 3	10/12 (83.3)

Data from Solsona E, Iborra I, Rubio J, Casanova JL, Ricós JV, Calabuig C. Prospective validation of the association of local tumor stage and grade as a predictive factor for occult lymph node micrometastasis in patients with penile carcinoma and clinically negative inguinal lymph nodes. *J Urol*. 2001;165(5):1506-1509.

Radiation Therapy

The primary advantage of RT is organ preservation. According to national cancer guidelines for penile cancer, T1-T2 tumors less than 4 cm can be managed with circumcision followed by brachytherapy alone (category 2B), EBRT (category 2B), or EBRT with concurrent chemotherapy (category 3) to a total dose of 65 to 70 Gy with conventional fractionation. Prophylactic EBRT to the inguinal lymph nodes may be considered for nonsurgical candidates or those who decline surgery.

T1-T2 tumors 4 cm or larger can be managed with circumcision followed by EBRT with concurrent chemotherapy (category 3) to 45 to 50.4 Gy to a portion of or the whole penile shaft depending on the extent of the lesion plus pelvic lymph nodes, followed by a boost to the primary lesion to 60 to 70 Gy with conventional fractionation. Brachytherapy alone may be considered in select cases.

T3-T4 or N positive tumors (surgically unresectable) can be managed with circumcision followed by 45 to 50.4 Gy to the whole penile shaft, pelvic lymph nodes, and bilateral inguinal lymph nodes followed by a boost to the primary lesion to 60 to 70 Gy with conventional fractionation.

If the margins are positive following penectomy, postsurgical EBRT to 60 to 70 Gy to the primary tumor site and surgical scar is recommended. Brachytherapy may be considered in select cases. Bilateral inguinal lymph nodes and pelvic lymph nodes may be irradiated for inadequate (or lack of) lymph node dissection, but adjuvant RT to the dissected inguinal basin(s) is currently not routinely performed.[101]

Palliative courses of 20 to 25 Gy in 5 fractions or 30 to 35 Gy in 10 fractions are acceptable for painful metastases. These regimens are unlikely to palliate advanced locoregional disease effectively. If the patient's general condition permits, a more prolonged fractionation, especially with the addition of chemotherapy, such as low-dose weekly cisplatin, may produce longer lasting benefits.[102]

Chemotherapy

The use of systemic chemotherapy, either adjuvant to or concomitantly with RT, has not been fully investigated in patients with penile cancer. Modern multiagent chemotherapy regimens have overall response rates ranging from 15% to 55% in patients with advanced disease (Table 75.7). Additional clinical trials are needed to adequately define the role of chemotherapy in the management of cancer of the penis.

TABLE 75.7 MULTIAGENT CHEMOTHERAPY IN ADVANCED PENILE CARCINOMA

Reference	Agents	*n*	PR (%)	CR (%)	Median Survival (Month)	Fatal Toxicity (%)
Corral et al[103]	Bleomycin Cisplatin Methotrexate	29	41	14	11.5	3.4
Di Lorenzo et al[104]	Cisplatin 5-FU	78	32	0	8	0
Di Lorenzo et al[105]	Paclitaxel	25	20	0	5.25	0

Reference	Agents	*n*	PR (%)	CR (%)	Median Survival (Month)	Fatal Toxicity (%)
Hass et al[106]	Bleomycin Cisplatin Methotrexate	40	20	12.5	7	12.5
Kattan et al[107]	Varied (platinum based)	13	8	8	7.6	—
Pagliaro et al[108]	Paclitaxel Ifosfamide Cisplatin	30	40	10	17.1	0

CR, complete response; PR, partial response; 5-FU, 5-fluorouracil.

Preoperative TIP can yield clinically significant responses among patients with regionally advanced penile cancer. About 50% of such patients with an objective response to chemotherapy who undergo consolidative lymphadenectomy will remain alive at 5 years.[109] Cetuximab has antitumor activity in metastatic penile cancer and may enhance the effect of cisplatin-based chemotherapy.[110]

According to national cancer guidelines, the preferred chemotherapy regimens are TIP and 5-FU plus cisplatin (not recommended neoadjuvantly).[111] Cisplatin with or without 5-FU is preferred for chemoradiotherapy with mitomycin-C plus 5-FU or capecitabine (palliation) as alternatives.[112]

Targeted Therapy

Presently, there are limited data regarding the efficacy of targeted therapies for penile carcinoma. A retrospective study of 17 metastatic cases that underwent chemotherapy and dual pharmacologic inhibition of the epidermal growth factor receptor, as well as programmed cell death-1, revealed that 13 patients had partial responses; of the 12 who subsequently received resection, half achieved a pathologic complete response. The 2-year progression-free and overall survival were 68% and 63%, respectively.[113]

In contrast to the above, the prospective data have not been as encouraging. A single-arm phase II trial examined the pan-HER tyrosine kinase inhibitor dacomitinib for advanced or nonmetastatic disease, noting a

response rate of 32% and 1-year progression-free and overall survival of 26% and 55%, respectively.[114] In addition, the nonrandomized phase II PERICLES trial of atezolizumab for 32 patients with advanced disease showed a response rate of 17%, along with a 1-year progression-free survival of 12.5%, which did not meet the primary end point.[115]

Urethral Cancer

The primary mode of therapy for carcinoma of the male urethra is surgical excision. According to U.S. national cancer guidelines and European Association of Urology guidelines, patients with clinical Tis, Ta, or T1 tumors should be managed with a transurethral resection followed by intraurethral chemotherapy or Bacillus Calmette-Guérin in selected cases.[116]

Clinical T2 tumors of the male pendulous urethra can be managed with a distal urethrectomy or partial penectomy. Positive margins are managed with further surgery, RT, or chemoradiotherapy (preferred). Clinical T2 tumors of the male bulbar urethra are managed with urethrectomy with or without cystoprostatectomy. Subsequently, pathologic T3-T4 or N1-N2 tumors can be considered for adjuvant chemoradiotherapy or chemotherapy.

Clinical T3 and T4 tumors that are cN0 can receive neoadjuvant chemotherapy and consolidation with surgery or RT, chemoradiotherapy, or RT. (Of note, the European Association of Urology guidelines also extend this recommendation to clinical T2 disease.)[116] Clinical T3 and T4 tumors that are cN1 or cN2 can be treated with RT, preferably with chemotherapy (especially for squamous cell carcinoma), chemotherapy, or chemoradiotherapy, followed by consideration of consolidative surgery. Combined modality therapy has become more common in recent years and may offer improved outcomes in select patients.[117]

Owing to the rarity of this disease, comparison of the cure rates with RT or surgery is difficult. The principal advantage of RT is organ preservation. Noninvasive carcinoma of the proximal urethra can be treated with transurethral resection. In lesions of the distal urethra, results with either penectomy or RT are similar to those for carcinoma of the penis, and the 5-year survival rates are comparable (50%-60%).[118] Involved regional lymph nodes are treated with lymphadenectomy. A study of 2,614 patients from a large national database showed similar survival with surgery or RT, but

information on other end points was not available; however, for locally advanced disease, adding adjuvant radiation improved survival over surgery alone, particularly for nonsquamous histologies.[119]

Most patients, however, present with advanced invasive lesions, which are difficult to manage with either radical surgery or RT. The major problem remains the high rate of local recurrence. In an attempt to improve the locoregional control rate, extended resections encompassing the inferior pubic rami, prostate, bladder, and perineum have been performed after preoperative RT.

Chemotherapy

Gheiler et al[51] reported their experience with multimodality treatment of 21 patients (10 women, 11 men) with urethral carcinoma. Treatment consisted of cisplatin- and 5-FU–based chemotherapy for squamous cell carcinoma and concurrent external beam irradiation. Patients with TCC were treated with concomitant methotrexate, vinblastine, Adriamycin (doxorubicin), and cisplatin. Some patients underwent surgical resection following chemoradiation. With a median follow-up of 42 months, the overall disease-free survival rate was 62%. Of significance is the pathologic complete response rate of 87.5% in eight women undergoing resection following chemoradiation.

Another retrospective study of 29 males with urethral cancer treated with two cycles of 5-FU and mitomycin-C with concurrent EBRT to the genitalia, perineum, and inguinal and external iliac lymph nodes showed that 79% had a complete response to treatment, while the rest did not respond and died of their disease. Of the complete responders, 42% had disease recurrence at a median of 12.5 months. The 5-year overall, disease-specific, and disease-free survival rates were 52%, 68%, and 43%, respectively.[120]

A series of 124 patients with primary urethral cancer treated between 1993 and 2012 from 10 referral centers showed that those who received neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy with adjuvant chemotherapy for cT3 and/or cN+ tumors appeared to demonstrate improved survival compared with those who underwent upfront surgery

with or without adjuvant chemotherapy. Proximal tumor location correlated with an inferior 3-year relapse-free survival and overall survival.[121]

Another large study of a national database of 191 patients (2004-2016) demonstrated that chemotherapy reduced the rate of all-cause mortality. Although the database did not capture response rates or disease recurrence rates, overall survival was higher with neoadjuvant chemotherapy than adjuvant chemotherapy. The median survival figures were 66 versus 33 months (5-year values not reported).[122]

RADIATION THERAPY TECHNIQUES

Penile Cancer

If indicated, circumcision must be performed before RT is initiated. The purpose of this procedure is to minimize RT-associated morbidity: swelling, irritation of the skin, moist desquamation, and secondary infection.

Although external beam therapy has become prevalent in the treatment of the primary lesion in carcinoma of the penis, plastic molds or interstitial implants are still used.

External Beam Radiation Therapy

External beam therapy requires specially designed accessories (including bolus) necessary to achieve homogeneous dose distribution to the entire penis. Frequently, a plastic box with a central circular opening that can be fitted over the penis is used. The space between the skin and the box must be filled with tissue-equivalent material (Figure 75.2). This box can then be treated with parallel-opposed megavoltage beams. An alternative to the box technique is the use of a water-filled container to envelop the penis while the patient is in a prone position.[123]

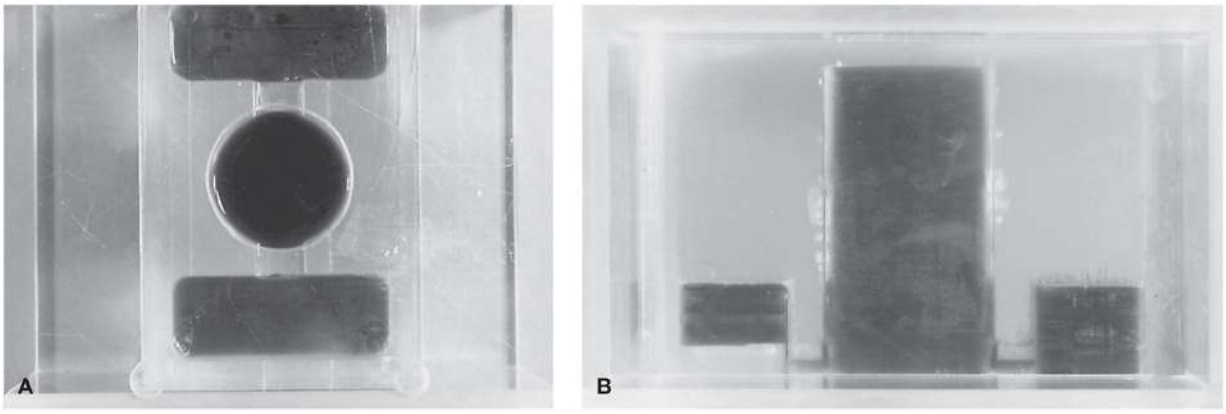


FIGURE 75.2 A. View from above of plastic box with a central cylinder for external irradiation of the penis. Patient is treated in the prone position. The penis is placed in the central cylinder, and water is used to fill the surrounding volume in the box. The depth dose is calculated at the central point of the box. B. Lateral view.

Another more complex device is a Perspex tube attached to a baseplate resting on the skin.[124] This is placed as close as possible to the base of the penis, and a flexible tube is connected to a vacuum pump. The suction effect keeps the penis in a fixed position during treatment. Appropriate bolus is placed outside the tube. The patient can also be treated in the prone position, with the penis hanging through a small hole placed in the Perspex cylinder.

Regional lymphatics may be treated with EBRT, with bilateral groins irradiated most frequently. The fields should include inguinal *and* pelvic (external iliac and hypogastric) lymph nodes (Figure 75.3). The posterior pelvis may be partially spared by anterior loading of the beams. Depending on the extent of the nodal disease and the proximity of the detectable tumor to the skin surface or the presence of skin invasion, the application of a bolus to the inguinal area should be considered. Techniques such as intensity-modulated RT are preferred, as they better allow for the treatment of the inguinal lymph nodes and/or pelvic lymph nodes while sparing the bladder, small and large bowel, and rectum. Primary lesions should be boosted with 2 cm margins. Treatment doses are discussed in the previous section “Radiation Therapy.”

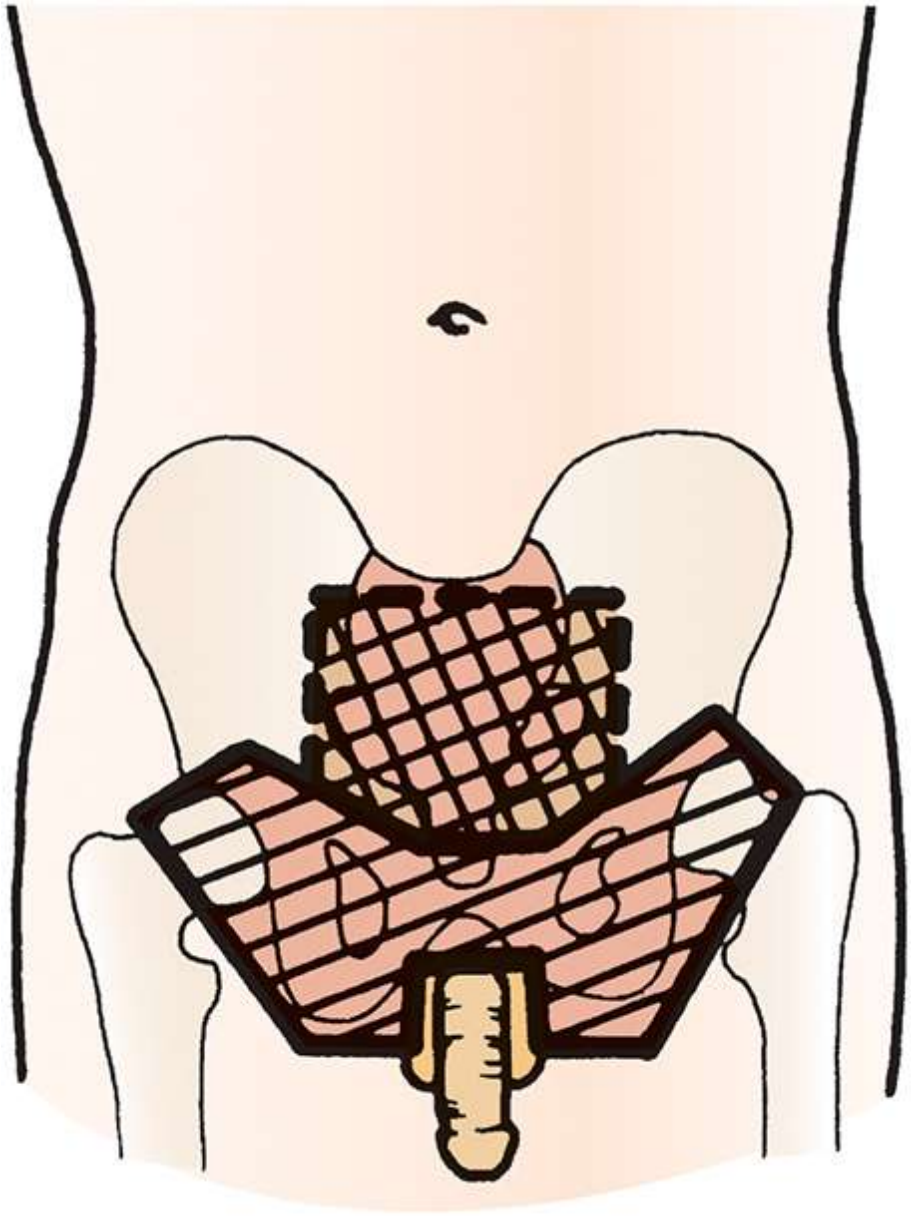


FIGURE 75.3 Portals encompassing inguinal and pelvic lymph nodes.

Brachytherapy

For detailed coverage of this topic, we refer the reader to the American Brachytherapy Society–Groupe Européen de Curiethérapie–European Society of Therapeutic Radiation Oncology (ABS-GEC-ESTRO) consensus statement for penile brachytherapy. Tumors of clinical stage T1b or T2 and less than 4 cm in maximum diameter are most suitable for primary brachytherapy. Lesions confined to the glans are ideal, but those with minor

extension across the coronal sulcus are also suitable, provided the extension can be covered with no more than one additional plane of needles.[125]

The low-dose rate (LDR) prescribed dose is generally 60 Gy at 0.5 to 0.6 Gy/hour, with the treatment completed in about 5 days. For pulsed-dose rate (PDR) treatments, pulses equivalent to the hourly dose rate of an LDR implant are delivered every hour. According to the Paris system, the prescription for LDR and PDR is to 85% of the dose rate minima between the planes (Figure 75.4).[125]

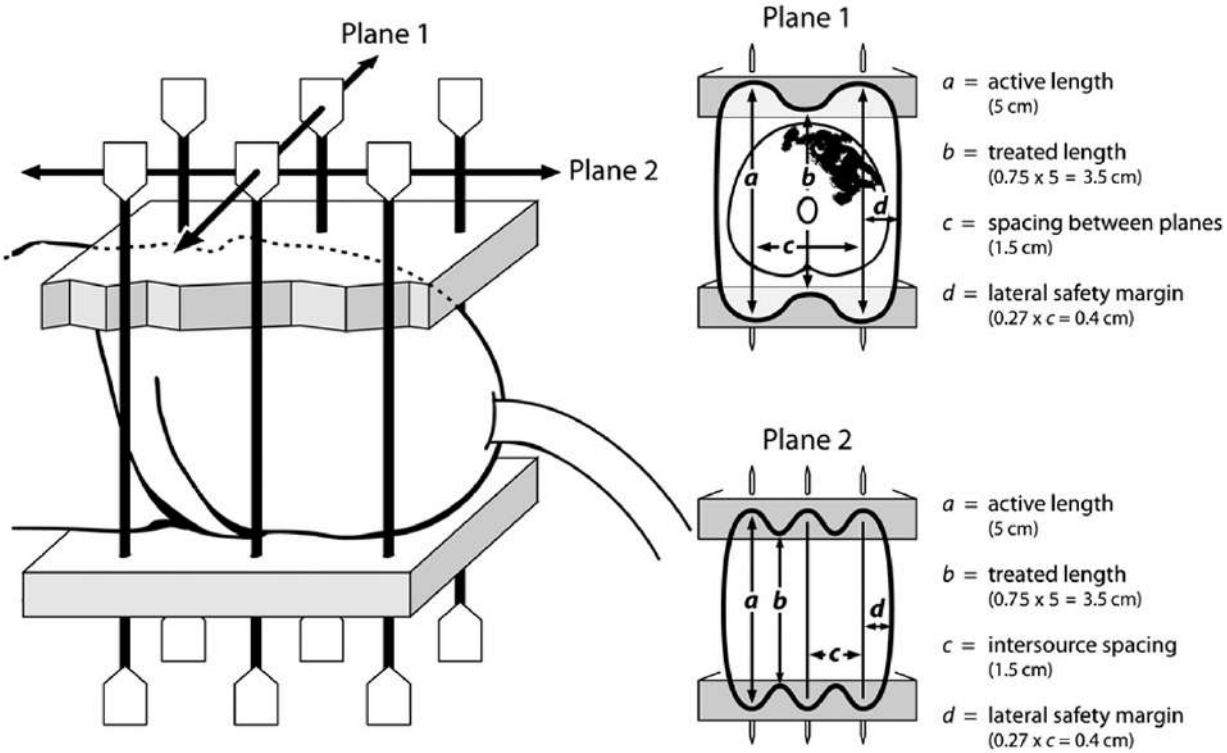


FIGURE 75.4 Schematic of a two-plane, six-needle implant showing the prescription isodose coverage according to the Paris System rules. (Reprinted from Crook JM, Haie-Meder C, Demanes DJ, Mazeron JJ, Martinez AA, Rivard MJ. American Brachytherapy Society-Groupe Européen de Curiethérapie-European Society of Therapeutic Radiation Oncology (ABS-GEC-ESTRO) consensus statement for penile brachytherapy. *Brachytherapy*. 2013;12[3]:191-198. Copyright © 2013 American Brachytherapy Society. With permission.)

ABS-GEC-ESTRO experts concluded that high-dose rate (HDR) fractionation volume implants of 3.2 Gy twice daily for 38.4 Gy in 6 days is well tolerated (Figures 75.5 and 75.6). The interval between fractions should be at least 6 hours. Penile necrosis has been observed after doses of 3.5 to

3.75 Gy × 12 Gy in 6 days, but this risk may be reduced if attention is paid to dose homogeneity and the V125 (percentage of the planning target volume receiving 125% of the prescribed dose) is less than 40% and the V150 is less than 20%. To decrease the incidence of urethral strictures, the urethra V115 should be less than 10% and the V90 less than 95% of the volume. Confluent areas of the skin receiving more than 125% of the prescription will reduce the risk of skin necrosis. CT-based planning is mandatory for HDR ^{192}Ir penile brachytherapy, with three-dimensional delineation of the gross tumor volume, clinical target volume, skin, and urethra.[125]

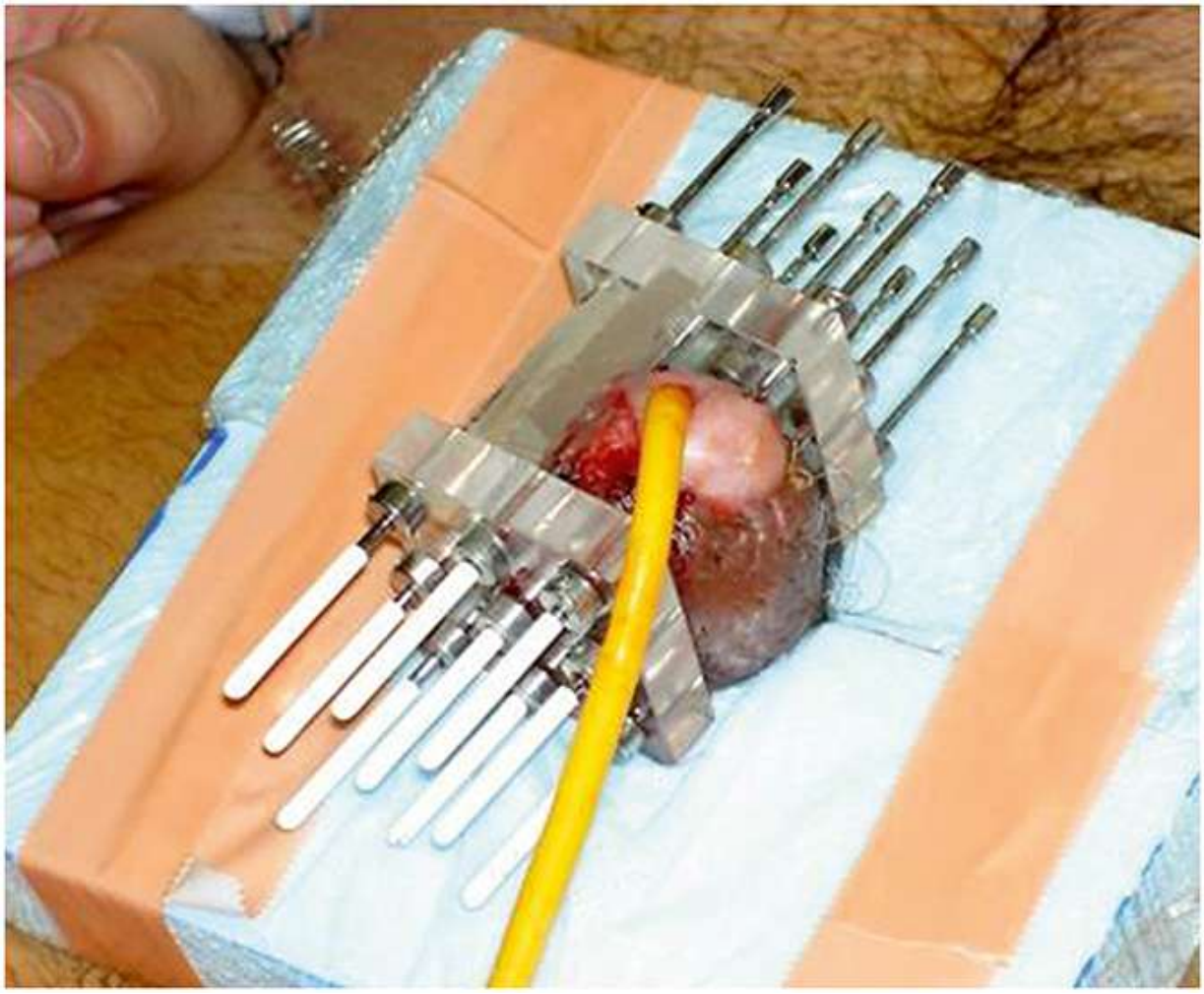


FIGURE 75.5 Interstitial implant showing the templates and needles in place. A layer of tissue-equivalent bolus material is seen on the left side of the photograph (patient's right) with an overlying plane of needles to ensure that full dose is delivered to the skin surface. (Reprinted from Crook J. The role of radiotherapy in the management of penile cancer. *Curr Probl Cancer*. 2015;39[3]:158-165. Copyright © 2015 Elsevier. With permission.)

FIGURE 75.6 Three-dimensional printing can be used to make a custom mold fitted with catheters to deliver the high-dose rate (HDR) source. This device would be applied twice daily for 5 days and is used to treat superficial cancers where no more than 5-mm depth of treatment is required. (Courtesy of Dr. Gerard Morton, Department of Radiation Oncology, Odette Cancer Center, University of Toronto. Reprinted from Crook J. The role of radiotherapy in the management of penile cancer. *Curr Probl Cancer*. 2015;39[3]:158-165.)

Urethral Cancer

RT for carcinoma of the anterior (distal) urethra is quite similar to that for carcinoma of the penis; lesions of the bulbomembranous urethra can be treated with a set of parallel-opposed fields covering the groins and the pelvis, followed by perineal and inguinal boost. Lesions of the prostatic urethra can be treated with techniques and doses similar to those used for carcinoma of the prostate.

RESULTS

Penile Cancer

At many institutions, patients with carcinoma of the penis are treated surgically. A summary of selected modern surgical series is presented in Table 75.8. Ornellas et al[32] reported the results of 350 patients treated with surgery alone. Five-year disease-free survival was 62% for patients treated with immediate lymphadenectomy versus 8% for those treated with delayed lymphadenectomy. For all patients who are node-negative, 5-year disease-free survival was 87% compared with 29% for patients who are node-positive. Boon et al[126] reported tumor control in 13 (81%) of 16 patients with carcinoma in situ or T1 and T2 tumors treated with wide local excision and lasers.

TABLE 75.8 SURGICAL RESULTS IN PATIENTS WITH CARCINOMA OF THE PENIS

			Local Failure (%)		
T Stage	Reference	*n*	Conserving Surgery[a]	Partial/Total Penile Amputation	5-Year Overall Survival (%)
T1	Brkovic et al[59]	22	56	0	77
	Feldman and McDougal[127]	28	21		—
	Horenblas et al[86]	—	10	—	—
	Lindegaard et al[62]	41	—	—	72
T2	Brkovic et al[59]	23	100	18	70
	Horenblas et al[86]	—	32	—	—
	Lindegaard et al[62]	26	—	—	55
T3/T4	Brkovic et al[59]	6	—	—	0
	Horenblas et al[86]	—	100	—	—
	Lindegaard et al[62]	6	—	—	10
T1-T3	Philippou et al[128]	179	T1: 6.8 T2: 10.3 T3: 13.0	—	—
T1-T4	Lindegaard et al[62]	63	35	5	—
	Derakhshani et al[21]	42	—	—	78
	Zouhair et al[129b]	16	—	25	—

T Stage	Reference	*n*	Local Failure (%)		5-Year Overall Survival (%)
			Conserving Surgery[a]	Partial/Total Penile Amputation	
	Lopes et al[57]	145	—	—	54

[a]Includes wide excision, Mohs micrographic surgery, laser ablation, radical circumcision, partial glansectomy, and local excision.

[b]All patients treated with postoperative radiation therapy.

Tables 75.9, 75.10, and 75.11 summarize tumor control rates achieved with external beam irradiation alone, LDR and PDR brachytherapy, and HDR brachytherapy, respectively.

TABLE 75.9 SELECTED RESULTS OF EXTERNAL BEAM RADIOTHERAPY FOR PENILE CANCER

Reference	*n*	Follow-Up (Month) Med (Range)	Dose (Gy)	Local Control	5-Y CSS	Penile Preservation	Comments
Sarin et al[131]	59	62 (2-269)	60 Gy in 30 fx	55%	66%	50%	
Zouhair et al[129]	23	12 (5-139)	45-74 Gy in 25-37 fx	41%	—	36%	
Ager et al[132]	146	Not listed	45 Gy in 20 fx (most common)	56%	51%	N/A (all adjuvant)	All pN3 cases

CSS, cause-specific survival; fx, fractions.

From © 2015 Juanita Crook; licensee X.[102]

TABLE 75.10 RESULTS OF LDR AND PDR BRACHYTHERAPY FOR PENILE CANCER

Reference	Number of Patients	Dose (Gy)	Mean Follow-Up in Month (Range)	% 5-Y Local Control (Year)	% 5-Y + Cancer-Specific Survival (Year)[a]	Complications	% Penile Preservation (Year)
Chaudhary et al[133]	23	50	21 (4–117)	70 (8)		0% necrosis and 9% stenosis	70 (8)

Reference	Number of Patients	Dose (Gy)	Mean Follow-Up in Month (Range)	% 5-Y Local Control (Year)	% 5-Y + Cancer-Specific Survival (Year)[a]	Complications	% Penile Preservation (Year)
de Crevoisier et al[134]	144	65	68 (6–348)	80 (10)	92 (10)	26% necrosis and 29% stenosis	72 (10)
Crook et al[135]	67	60	48 (6–194)	87 (5) 72 (10)	83.6 (10)	12% necrosis and 9% stenosis	67 (10)
Delannes et al[136]	51	50–65	65 (12–144)	86 crude	85	23% necrosis and 45% stenosis	75
Kiltie et al[137]	31	63.5	61.5	81	85.4	8% necrosis and 44% stenosis	75
Mazeron et al[130]	50	60–70	36–96+	78 crude		6% necrosis and 19% stenosis	74
Rozan et al[23]	184	63	139	86	88	21% necrosis and 45% stenosis	78
Soria et al[24]	102	61-70	111	77	72	Not stated	72 (6)

LDR, low-dose rate; PDR, pulsed-dose rate.

[a]Corrected for intercurrent death.

Reprinted from Crook JM, Haie-Meder C, Demanes DJ, Mazeron JJ, Martinez AA, Rivard MJ. American Brachytherapy Society-Groupe Européen de Curiethérapie-European Society of Therapeutic Radiation Oncology (ABS-GEC-ESTRO) consensus statement for penile brachytherapy. *Brachytherapy*. 2013;12(3):191-198. Copyright © 2013 American Brachytherapy Society. With permission.

TABLE 75.11 RESULTS OF HDR BRACHYTHERAPY FOR PENILE CANCER

Reference	*n*	Follow-Up (Month) Med (Range)	Dose (Gy)	Local Control	CSS (Year)	Penile Preservation
Petera et al[138]	10	20	51 Gy, 3 Gy twice daily	100%	100% (5 y)	100%

Reference	*n*	Follow-Up (Month) Med (Range)	Dose (Gy)	Local Control	CSS (Year)	Penile Preservation
Sharma et al[139]	14	22 (6-40)	42-45 Gy, 3 Gy twice daily	86%	83% (3 y)	93%
Kellas-Sleczka et al[140]	76	76 (7-204)	25-43 Gy (previous resection) or 47-49 Gy (definitive), 3-3.5 Gy twice daily	71%	85% (5 y)	87%

CSS, cause-specific survival; HDR, high-dose rate.

Reprinted from Crook J. The role of radiotherapy in the management of penile cancer. *Curr Probl Cancer*. 2015;39(3):158-165. Copyright © 2015 Elsevier. With permission.

The 20-year experience of the Institut Gustave-Roussy was reported by Soria et al.[24] In all, 102 patients with tumors less than 4 cm in diameter with less than 1 cm corpora cavernosa invasion were treated with a conservative approach consisting of limited surgery (biopsy, local excision, or therapeutic circumcision) and interstitial brachytherapy (65-70 Gy delivered over 5-7 days). Regional lymph nodes were not treated electively but were dissected in patients with clinically enlarged nodes. With a median follow-up of 111 months, the local tumor recurrence rate was 25%. A regional nodal recurrence developed in 21% of patients. Disease-free survival at 5 and 10 years was 56% and 42%, respectively. Overall survival at 5 and 10 years was 63% and 50%, respectively.

Irradiation of the involved regional lymph nodes in patients with carcinoma of the penis results in durable control for a substantial proportion of patients. In the classic series of Staubitz et al,[43] 13 patients with proven involvement of regional lymph nodes received RT to these nodes. Five of 13 (38%) survived 5 years. Mazeron et al[130] observed tumor control in 8 of 9 patients with stage T1, 21 of 27 with T2, and 10 of 14 with T3 tumors treated with ^{192}Ir, using the Paris dosimetry system, to deliver doses of 60 to 70 Gy to the 85% minimal tumor isodose. The tumor-free 5-year actuarial survival rate was 63%. The penis was preserved in 75% of patients with a follow-up of 8 years. Thirty-seven patients received no prophylactic treatment to the inguinal nodes, and only two (one with a T2 and another with a T3 lesion) later developed inguinal lymph node metastases treated by

inguinal node dissection and postoperative irradiation. One patient was alive with no evidence of disease at 10 years. Five patients with metastases to the lymph nodes at the time of diagnosis were treated with therapeutic nodal dissection and postoperative irradiation. Four patients had uncontrolled lymph node metastases, and all five died with distant disease.

Urethral Cancer

Historically, men with urethral carcinoma have been treated surgically. Dalbagni et al[17] have reported the outcome of 46 patients with carcinoma of the anterior and bulbar urethra treated at the Memorial Sloan-Kettering Cancer Center. The majority of patients were treated with definitive surgery. With a median follow-up of 125 months, the local control rate was 51%. The 5-year overall survival was 42%. Improved survival was seen in patients with anterior lesions (69%) compared with those with posterior lesions (26%).

Bracken et al[141] described results in 11 patients with tumors at or anterior to the penoscrotal junction, 8 of which were epidermoid carcinoma, 2 TCC, and 1 melanoma. Three of four patients treated with total penectomy and perineal urethrostomy had tumor control. Partial penectomy controlled the local tumor in two patients. The patient with melanoma had a local recurrence after the operation. Two patients were treated with RT, and one-third with a combination of preoperative irradiation (45 Gy) and total penectomy. In all of these patients, the tumor recurred locally. In four patients with inguinal lymph node metastases, the regional disease was controlled by bilateral lymphadenectomy. All six patients in whom local and regional tumor was controlled remained alive and disease free at 1 to 20 years. In 16 patients, the urethral tumors arose posterior to the penoscrotal junction: 13 lesions were squamous cell carcinoma, 2 TCC, and 1 adenocarcinoma. Penectomy was performed in five patients, all of whom had tumor control and no evidence of recurrence 5 to 29 months after therapy. Two patients treated with local excision died of disease 14 and 18 months after surgery. Irradiation was used in three patients unsuccessfully, and all died of cancer 13 to 31 months after therapy.

Kaplan et al[18] reported on 29 patients treated at Northwestern University and reviewed the literature. In their analysis, lesions of the distal urethra

carried the best prognosis and those in the bulbomembranous urethra the worst. Five-year survival rates were 22% (16/71 patients) with tumors in the distal urethra, 10% (10/99 patients) with bulbomembranous urethra lesions, and 25% (4/16 patients) with prostatic urethra tumors. RT was infrequently used for these patients. Table 75.12 demonstrates equivalent local tumor control with either definitive RT or en bloc resection.

TABLE 75.12 LOCAL TUMOR CONTROL OF MALE URETHRAL CARCINOMA WITH RADIATION THERAPY OR EN BLOC RESECTION

Author (Reference)	Number of Patients	Number Controlled
Radiation Therapy		
Hopkins et al[142]	1	1
Kaplan et al[18]	11	9
Raghavaiah[118]	2	2
En Bloc Resection		
Anderson and McAninch[143]	2	1
Klein et al[75]	7	5
Kaplan et al[18]	28	25

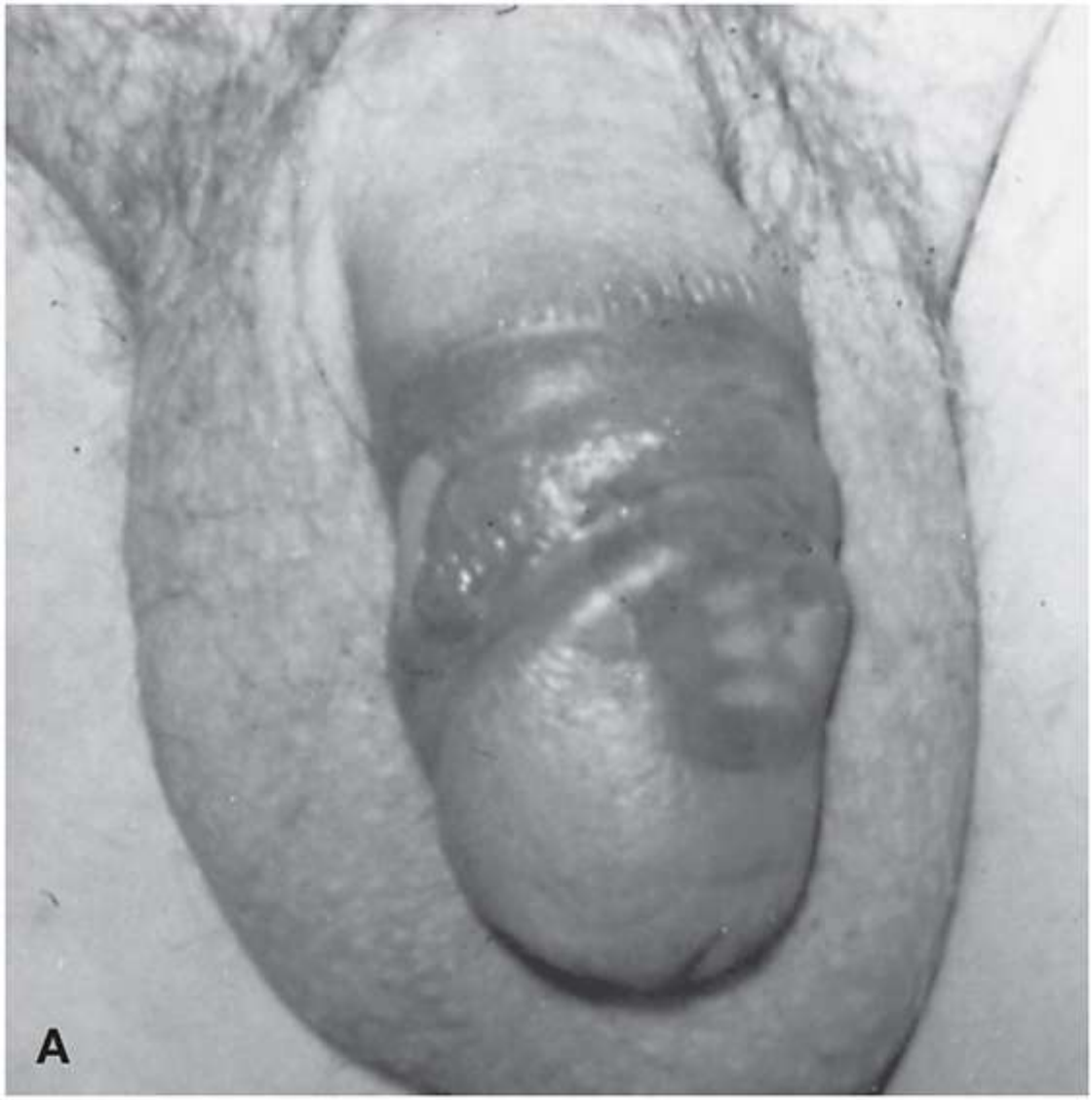
The combination of RT and chemotherapy using 5-FU and mitomycin-C has been reported for urethral carcinoma for organ preservation in locally advanced tumors. Reports by Baskin and Turzan,[144] Johnson et al,[145] Licht et al,[146] and Shah et al[147] support the efficacy of this combination for squamous cell carcinoma of the male and female urethra. The Cleveland Clinic[146] reported results of patients with locally advanced squamous cell carcinoma of the urethra treated with concomitant chemoirradiation, including 5-FU (1 g/m^2 intravenous infusion on days 1-4 and days 29-32) and mitomycin-C (50 mg/m^2 bolus intravenous injection on day 1). External beam irradiation (30 Gy in 15 fractions) to the pelvis and inguinal lymph nodes began on day 1. An additional 20 Gy tumor boost was given. Complete response was obtained in three patients, who remained disease free after 43 months of follow-up. One grade 3 acute toxicity (skin reaction) occurred that did not compromise the therapeutic plan, and one patient developed urethral stricture that was managed successfully with urethral dilatation.

The Wayne State experience[51] involved concomitant 5-FU and cisplatin for squamous cell carcinoma and concomitant methotrexate, vinblastine, doxorubicin, and cisplatin for TCC. A pathologic complete response was reported in 87.5% of women undergoing resection following chemoradiation. With a median follow-up of 42 months, the overall disease-free survival rate was 62%.

SEQUELAE OF TREATMENT

Irradiation of the penis produces brisk erythema, dry or moist desquamation, and swelling of the subcutaneous tissue of the shaft in virtually all patients. Although quite uncomfortable, these reversible reactions subside with conservative treatment within a few weeks. Telangiectasia is a common late consequence of RT and is usually asymptomatic (Figures 75.7 and 75.8).

FIGURE 75.7 Telangiectasia and area of hypopigmentation 6 years after pulsed-dose rate brachytherapy. (Reprinted from Crook JM, Haie-Meder C, Demanes DJ, Mazeron JJ, Martinez AA, Rivard MJ. American Brachytherapy Society-Groupe Européen de Curiethérapie-European Society of Therapeutic Radiation Oncology (ABS-GEC- ESTRO) consensus statement for penile brachytherapy. *Brachytherapy*. 2013;12(3):191-198. Copyright © 2013 American Brachytherapy Society. With permission.)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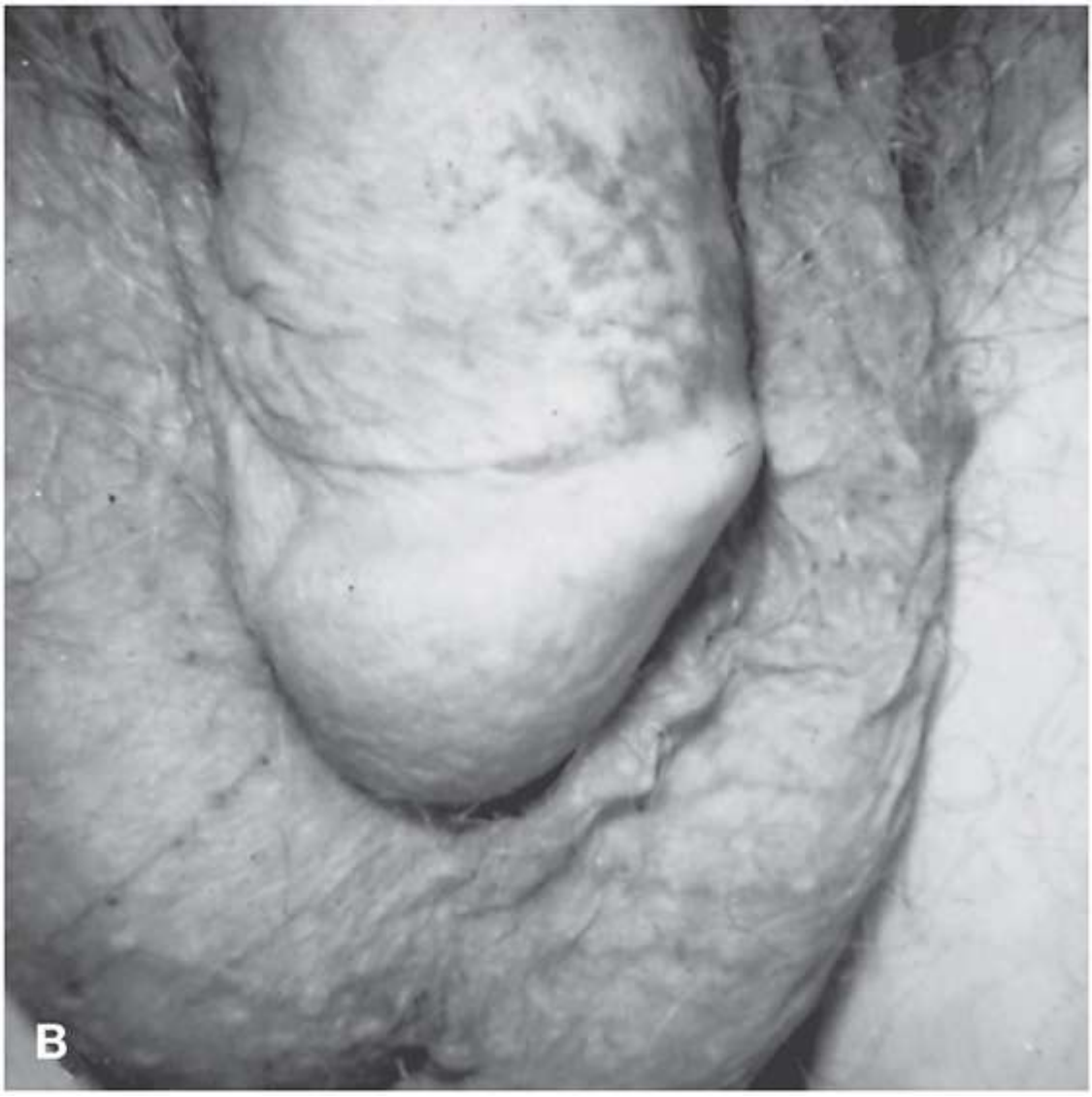

FIGURE 75.8 A. Squamous cell carcinoma of the balanopreputial region with extension into the glands (stage I). The patient was treated with 120-kVp x-rays, 0.3-mm Cu half-value layer, receiving a 60-Gy skin dose in 5 weeks. B. Same patient 4 years later with no evidence of disease. Telangiectasia is present.

In the reported LDR and PDR brachytherapy series, stenosis occurs in 9% to 45% of patients and necrosis in 0% to 26% (see Table 75.10).[23,24,130,133-137] This incidence compares favorably with the incidence of urethral stricture following penectomy.[21] Most strictures following RT are at the meatus.

Lymphedema of the legs has been reported following inguinal and pelvic RT, but the role of irradiation in the development of this complication

remains controversial. Many patients with this symptom have active lymphatic disease that may be responsible for lymphatic blockage.

Routine use of a meatal dilator in the healing phase and for a few months beyond can decrease the rate of meatal stenosis. Soft tissue ulceration is more frequent in larger and more deeply invasive cancers but will usually heal with conservative measures, such as attention to hygiene, topical antibiotics, or steroid creams.[102] More severe cases may respond to a course of hyperbaric oxygen.[148]

Of all male genitourinary cancers, penile cancer poses the greatest threat to sexual function and carries the most devastating psychological impact of penectomy. Despite recent advances in treatment, sexual function is not likely to be adequately preserved in some patients. These patients and their partners need information about the physical impairments after surgical intervention and should be taught adjustment skills before undertaking treatment. Referral to a trained sexual consultant or therapist for help is indicated.

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PART I

Gynecologic

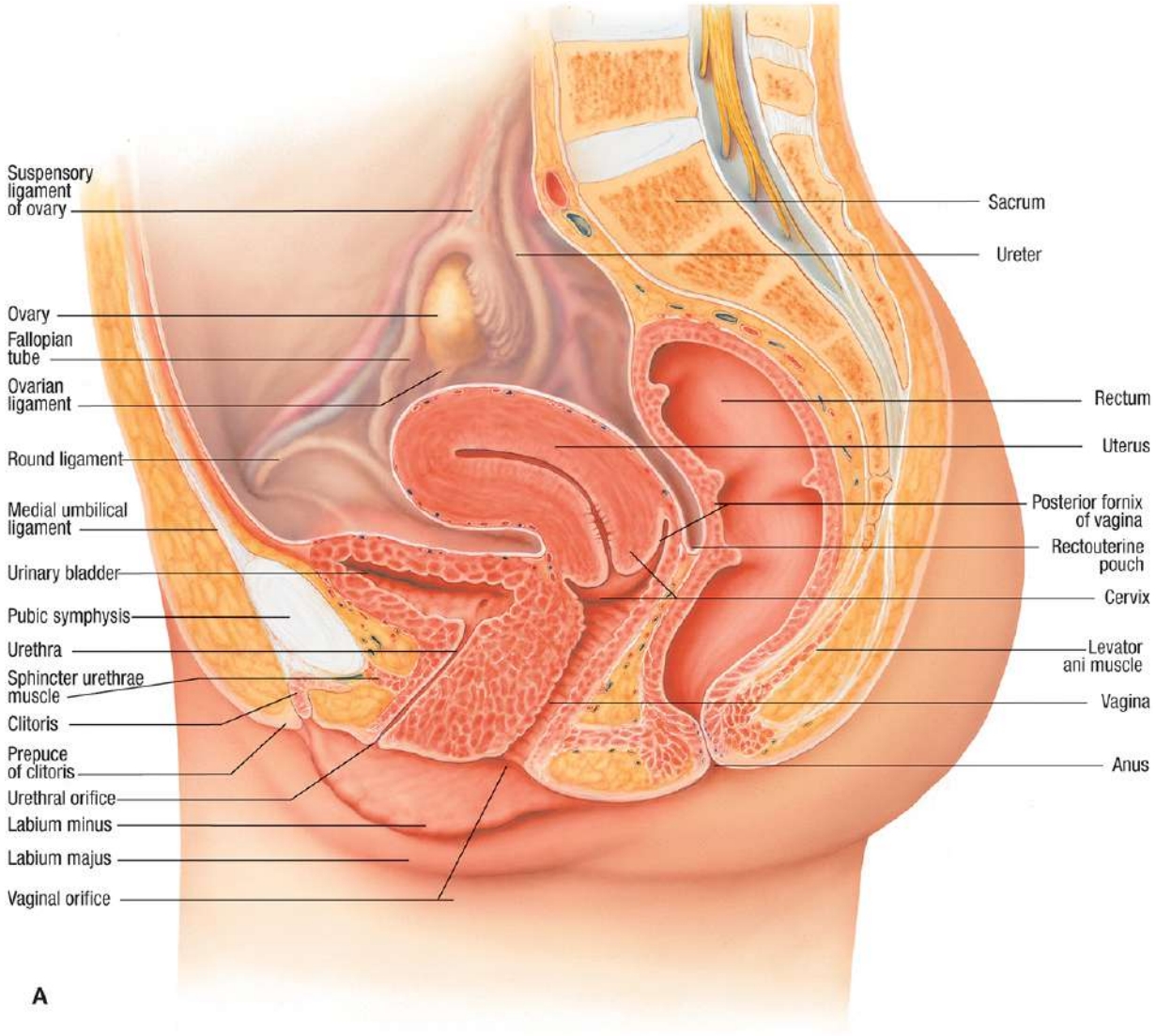
CHAPTER 76

Cancer of the Uterine Cervix

Yosef Landman-Gigi, Darien Colson-Fearon, Akila N. Viswanathan

ANATOMY

The uterus is a hollow, thick-walled, pear-shaped, muscular organ located in the pelvis above the vagina, behind the bladder, and in front of the rectum (Figure 76.1A). On average, it is approximately 7 to 8 cm long, 5 to 7 cm wide, and 2 to 3 cm thick. The uterus is divided into the uterine corpus superiorly and the uterine cervix inferiorly, with the most superior part of the corpus also known as the fundus and the middle portion of the corpus known as the body. The fundus is located superiorly to the line joining the entrance of the fallopian tubes. The body of the uterus is enclosed between layers of the broad ligament and is freely mobile. The regions of the body where the fallopian tubes enter are called the cornua. The most inferior, slightly constricted, portion of the uterus is called the isthmus or lower uterine segment (LUS). The cervix rests inferior to the LUS.


Suspensory ligament of ovary
Ovary
Fallopian tube
Ovarian ligament
Round ligament
Medial umbilical ligament
Urinary bladder
Pubic symphysis
Urethra
Sphincter urethrae muscle
Clitoris
Prepuce of clitoris
Urethral orifice
Labium minus
Labium majus
Vaginal orifice
Sacrum
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Rectum
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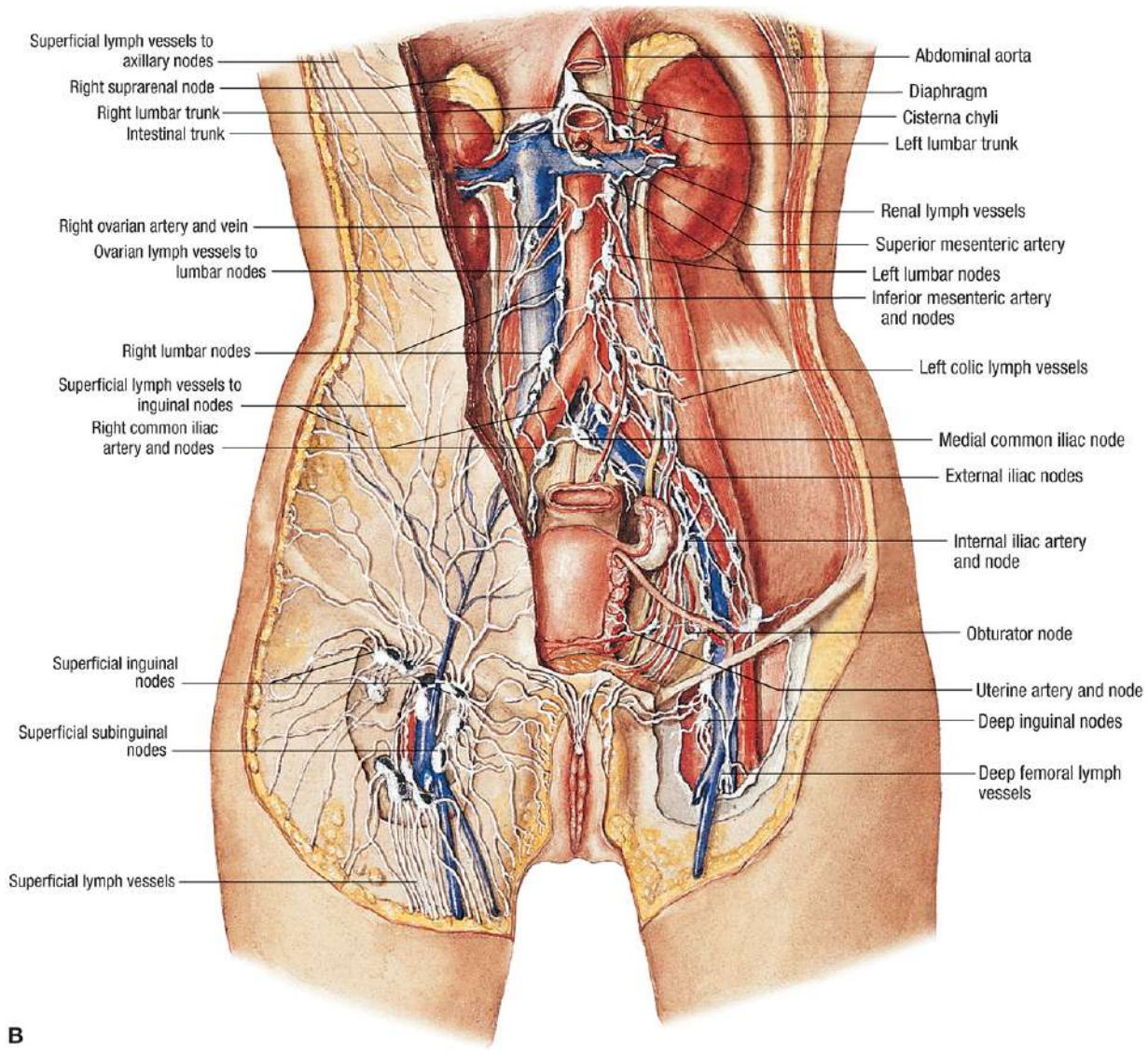


FIGURE 76.1 A. Anatomy of the pelvis. B. Lymph vessels and lymph nodes of the cervix and the body of the uterus. (Anatomical Chart Company, Lexington, SC.)

The uterus is usually bent anteriorly (anteflexed) between the cervix and the uterine body. The entire uterine cervix structure is normally bent anteriorly (anteverted) in the pelvis. The uterus may be posteriorly retroverted, especially in older women who have a small uterus. The wall of the uterus has three layers: the outer serosal layer; the middle myometrium, which is approximately 12 to 15 mm of muscle through which the main blood vessels and nerves flow; and the inner coat called the endometrium.

The cervix measures approximately 3 by 3 cm and is predominantly a fibrous organ. The cervix is divided into an upper or supravaginal portion,

above the ring containing the endocervical canal, and the vaginal portion, projecting in the vaginal vault. Central in the rounded vaginal region is the external os, bounded by the anterior and posterior lips of the cervix, extending inward to the internal os, the endocervical canal, and endometrial canal.

The uterus is partially covered by peritoneum in its fundal and posterior portions; its anterior and lateral surfaces are related to the bladder and the broad ligaments, respectively. It is attached to the surrounding structures in the pelvis by two pairs of ligaments—the broad and round ligaments. The broad ligament is a double layer of peritoneum extending from the lateral margin of the uterus to the lateral wall of the pelvis. It contains the fallopian tubes. The two layers of peritoneum forming the broad ligament enclose the parametrium as it reaches the uterus. Inferiorly, the broad ligament follows the plane of the pelvic floor and ends medially in the upper portion of the vagina.[1]

The round ligament, a band of smooth muscle and connective tissue that contains small vessels and nerves, extends forward horizontally from its attachment in the anterolateral portion of the uterus to the lateral pelvic wall. The cord ascending from the lateral wall of the true pelvis crosses the pelvic brim and extends laterally to reach the abdomino-inguinal ring, through which it leaves the abdomen to traverse the inguinal canal and terminates in the superficial fascia.

The uterosacral ligaments are paired supports for the lower uterus, extending from the uterus to the sacrum and running along the rectouterine peritoneal fields. The cardinal ligaments, also called transverse cervical ligaments (Mackenrodt), are thickened connective tissue and fascia arising at the upper lateral margins of the cervix and inserting into the fascial covering of the pelvic diaphragm.

The uterus, including the uterine cervix, has a rich lymphatic network (Figure 76.1B) that drains principally into the paracervical lymph nodes; from there, it goes to the external iliac (of which the obturator nodes are the innermost component) and the hypogastric lymph nodes. The major lymphatic drainage of the cervix runs in the cardinal ligament superior to the ureter and in the uterosacral ligaments to the rectal area. No lymphatic vessels run in the vesicouterine space, rather those from the upper vagina fuse with those from the bladder and extend laterally into the parametrium. The pelvic lymphatics drain into the common iliac and the para-aortic lymph nodes (PANs).

Lymphatics from the fundus pass laterally across the broad ligament and are continuous with those of the ovary, ascending along the ovarian vessels into the PANs. Some of the fundal lymphatics also drain into the common iliac lymph nodes. The main artery supplying the uterus is the uterine artery, which originates from the anterior division of the hypogastric artery.

EPIDEMIOLOGY

Over the past century, the relative morbidity and mortality of locally advanced invasive cervical cancer has declined in the United States and Europe because of effective screening and treatment of preinvasive lesions. In the United States, 50% of women who develop cervical cancer have never been screened.[1] However, in the past decade, incidence rates of invasive carcinoma have remained relatively constant due to population growth and aging. The American Cancer Society estimates in 2023 that approximately 13,960 new cases of invasive carcinoma of the cervix arise in the United States and about 4,310 deaths will occur per year (Figure 76.2).[2] Worldwide, cervical cancer remains the eighth most common cancer by incidence and the ninth most common cause of cancer mortality, with over 662,301 women globally developing this tumor as reported in 2022 and 348,874 dying of the disease every year.[3] Adjusting for population growth and aging, the global incidence rate for cervical cancer declined by 1.2% from 2005 to 2015.[4] The majority of cases are in Africa, because of the paucity of screening measures and the prevalence of immunodeficiency because of human immunodeficiency virus (HIV). Unfortunately, it often affects young women, with therapies that commonly result in loss of the ability to bear future children and other chronic toxicities.

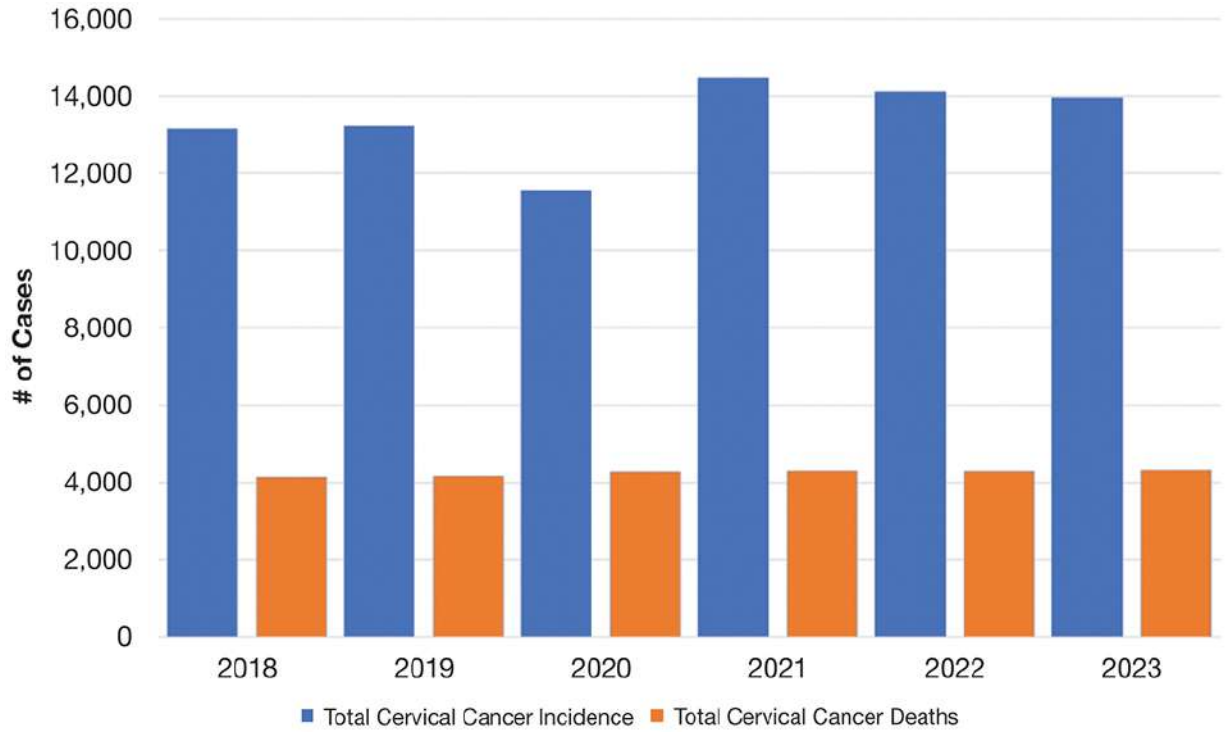


FIGURE 76.2 The incidence of cervical cancer increased slightly in the United States from 2018 to 2023.

Cervical cancer is more common in areas where women have less access to screening, including parts of Asia, Africa, and Central and South America. Whether regional differences in predisposition to developing cervical cancer exist is debated because it is impossible to adequately correct for unknown and known confounders, such as socioeconomic status, access to health care, parity, smoking, presence of other infections, immune status, and other factors affecting host immunity such as nutritional status.

Human Papillomavirus

Estimates indicate that more than 90% of cervical cancers are related to the presence of human papillomavirus (HPV) and are contracted via sexual intercourse.[5] HPV is a small, double-stranded deoxyribonucleic acid (DNA) virus; HPV-16 and HPV-18, as well as a long list of other, less frequent subtypes, including, but not limited to, HPV types 31, 33, 35, 39, 45, 51, 52, 56, and 58, have been well characterized as causative agents for cervical cancer, with some geographic variation. The HPV genome integrates into the host cell chromosomes in cervical epithelial cells and codes for six early and

two late open reading frame proteins, of which three (E5, E6, and E7) alter cellular proliferation. Two viral genes, E6 and E7, are typically expressed in HPV-positive cervical cancer cells. The E6 protein inactivates the major tumor suppressor p53; this causes chromosomal instability, inhibits apoptosis, and activates telomerase. The E7 protein affects the retinoblastoma protein, resulting in a loss of regulation of the cell's proliferation and immortalization. The Cancer Genome Atlas identified three main subtypes: keratin-low, keratin-high, and adenoma-rich. HPV integration was observed in all HPV-18 and 76% of HPV-16–related cases. Endometrial-like cervical cancer was HPV negative, occurred in 5% of cases, and had high frequencies of *KRAS*, *ARID1A*, and *PTEN* mutations.[6]

Although a high prevalence of HPV exists worldwide, peaking at ages 25 to 35 years, less than 15% of exposed women develop persistent infection that results in dysplasia, whereas the majority of women clear the infection within 2 years.[7] Cervical cancer may develop 10 to 20 years after initial exposure to HPV. Social factors related to cervical cancer include those associated with HPV transmission, such as early age of first intercourse, a history of multiple sexual partners, a male partner with a history of multiple sexual partners, a large number of pregnancies, and a history of sexually transmitted disease, including gonorrhea, chlamydia, herpes simplex virus II, and/or HIV. A higher incidence of cervical cancer exists among women whose spouses are known or suspected to have had higher exposure to HPV or whose partners have a history of penile carcinoma. Whether circumcision may be protective to women is controversial because circumcision may be a surrogate for unknown factors related to HPV transmission. The integration pattern of HPV as episomal (best), single-copy or multiple-copy tandem repetition, or undetectable (worst) is a strong prognostic factor for disease-free survival (DFS) after radiation therapy (RT) in cervical cancer.[8]

Chemical, hormonal, or other carcinogens may be implicated in cervical cancer. An association between cervical carcinoma and oral contraceptive use has been reported but is considered controversial. Prenatal exposure to diethylstilbestrol (DES) is linked to the development of clear cell adenocarcinoma (AC), although the overall incidence is small (0.14-1.4 per 1,000 DES-exposed women). Cigarette smoking may increase the risk of cervical cancer, HPV infection, and carcinogenesis.[9] However, passive smoking may not be an independent factor in the absence of active smoking.[10]

Current smoking (relative risk [RR] = 1.55) and younger age at HPV exposure (RR = 1.75) are considered risk factors among HIV-positive women.[11] Intrauterine device use may decrease cervical cancer risk, potentially through an increase in cellular immunity triggered by the device.[12] Immunocompromised individuals, including those with HIV or autoimmune conditions on immunosuppressants, have also been observed to higher risk of persistent HPV infection and cervical cancer.[13] Specifically, for HIV, an up to 22-fold increased risk for the development of cervical cancer has been observed.

Human Papillomavirus Vaccination

The nine-valent HPV recombinant vaccine for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, more commonly known as Gardasil-9, was first approved in the United States in 2014 for all individuals aged 9 to 26 years. This was done after a randomized study involving over 14,000 girls and women showed noninferiority to the previous quadrivalent HPV vaccine in reducing any high-grade cervical disease and increased efficacy in reducing disease related to the five additional HPV types.[14] In 2018, approval was expanded to include those aged 27 to 45 years. There are two previous vaccines that have been approved, including the quadrivalent covering HPV types 6, 11, 16, and 18 and bivalent covering types 16 and 18.[15,16]

Equitable distribution of the vaccine around the world has historically been hindered due to cost and access; however, efforts continue to be made to mitigate these disparities.[17] To date, 117 nations have added the HPV vaccine to their routine national immunization schedules.[18] Globally, an estimated 15% of girls and 4% of boys within the target age have been fully vaccinated, as of 2019.[19] With an increase in understanding and availability, the hope is that all children will be given a vaccine covering all subtypes in the future.

NATURAL HISTORY AND PATTERNS OF SPREAD

Squamous cell carcinoma (SCC) of the uterine cervix usually originates at the squamous columnar junction (transformation zone) of the endocervical canal and portion of the cervix.

Cellular transformation follows a stepwise progression from normal to higher levels of dysplasia. Of patients diagnosed with cervical intraepithelial neoplasia (CIN) type 1, 60% have regression of the lesion, and of those with

CIN2, 40% regress. Higher levels of dysplasia are more likely to progress to cancer, particularly in the presence of cofactors such as smoking or impaired immunity. Although progression typically takes 10 to 20 years, in some instances, a rapid development of carcinoma may be associated with aggressive disease.

The development of a malignant phenotype results from cells that break through the basement membrane of the epithelium and invade the cervical stroma. Invasion may result in spread to pelvic lymph nodes or other, more distant sites. If the cells are detected at this stage by a Papanicolaou (Pap) or thin preparation test, appropriate minimally invasive therapy may suffice. However, if the lesion progresses, it may present as a superficial ulceration or exophytic tumor in the ectocervix or with extensive infiltration of the endocervix. If untreated, the tumor may spread to the adjacent vaginal fornixes, paracervical or parametrial tissues, or adjacent organs, including the bladder, the rectum, or both. Paracervical extension was related to the depth of stromal invasion, tumor size, lymphatic invasion, and presence of lymph node metastasis.

Approximately 10% to 30% of patients with carcinoma of the uterine cervix have extension into the LUS and the endometrial cavity. Decreased survival rates and a greater incidence of distant metastases were reported in patients with stromal endometrial invasion (EI) or replacement of normal endometrium by cervical carcinoma. Regional lymphatic or hematogenous spread may occur and increases with stage, although dissemination does not always follow an orderly sequence, and occasionally, a small primary tumor may spread to the pelvic lymph nodes, invading the bladder or rectum, or metastasizing distantly.

Both adjacent parametrial and pelvic lymph nodes may be involved. Girardi et al[20] analyzed 359 radical hysterectomy (RH) specimens and found positive parametrial nodes in 280 (78%) patients; the incidence of positive nodes was 11.4% in stage IB and 21.5% in stage IIB disease. With negative parametrial nodes, only 26% of patients had positive iliac lymph nodes, whereas 81% of patients with positive parametrial lymph nodes also had pelvic node metastases. These data underscore the need to irradiate the parametrial tissues or carry out a complete bilateral pelvic lymphadenectomy with an RH in patients with invasive cervical carcinoma.

Spread of carcinoma of the cervix may progress to the obturator lymph nodes, considered a medial group of the external iliac chain, to other external iliac nodes, and to the hypogastric lymph nodes. From these, there may be tumor metastases to the common iliac or PANs. In one study, pelvic lymph nodes were dissected in 225 patients with cervical carcinoma treated with RH[21]; positive pelvic nodes were identified in 13 (14.2%) of 91 women with stage IB and IIA, 16 (19.8%) of 81 with stage IIB, and 11 (28%) of 40 with stage IIIB diseases. The most commonly involved groups were the parametrial, obturator, external iliac, and common iliac nodes (Figure 76.3). PANs were involved in 3 (3.3%) of 91 patients with stage IB or IIA tumors 4 cm or less and in 5 (13.1%) of 38 patients with stage IIB or III disease.

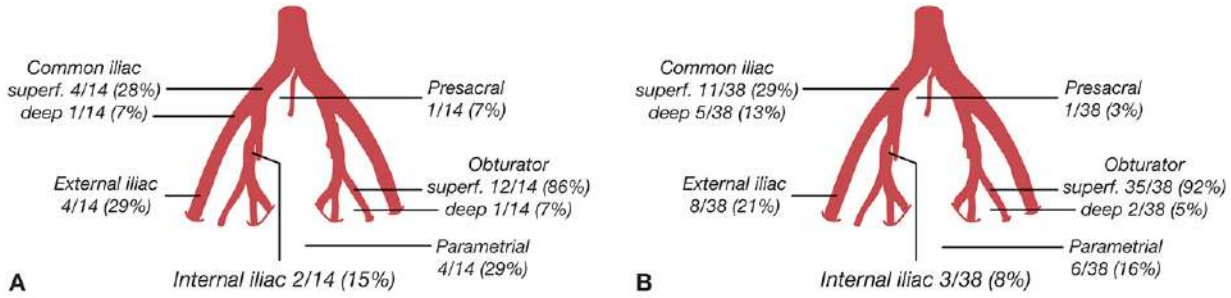


FIGURE 76.3 Distribution of pelvic node metastases in 14 patients with stage IB to IIA cervical cancers, tumor size <4 cm (A), and 38 patients with locally advanced cervical cancer treated with neoadjuvant chemotherapy (B). (Reprinted from Benedetti-Panici P, Maneschi F, Scambia G, et al. Lymphatic spread of cervical cancer: an anatomical and pathological study based on 225 radical hysterectomies with systematic pelvic and aortic lymphadenectomy. *Gynecol Oncol*. 1996;62[1]:19-24. Copyright © 1996 Elsevier. With permission.)

Spread through the venous plexus and the paracervical veins resulting in hematogenous dissemination, though infrequent, is relatively common with more advanced stages. In an analysis of 322 patients in whom distant metastases developed, the most frequently observed metastatic sites were the lung (21%), PANs (11%), abdominal cavity (8%), and supraclavicular lymph nodes (7%). Bone metastases occurred in 16% of patients, most commonly to the lumbar and thoracic spine.[22] Spinal epidural compression from metastatic tumor, often involving lumbar segments, can occur rarely, and metastases to the brain and the heart have been reported, although it is unusual to have spread to the brain without evidence of pulmonary metastases already present, even for small cell carcinoma of the cervix.

PAPANICOLAOU SMEAR SCREENING

The U.S. Preventive Services Task Force and the American College of Obstetrics and Gynecology published updated guidelines in 2021, which have been reaffirmed in 2023, recommending that cervical cytology screening should begin at age 21 years regardless of sexual activity status and continue every 3 years until age 29 years. Starting at age 30 to 65, screening can include cytology alone every 3 years, Food and Drug Administration-approved primary high-risk human papillomavirus (hrHPV) testing alone every 5 years, or co-testing with cytology and hrHPV every 5 years.[23,24] HPV testing is not recommended for women younger than age 30. After age 30, women have the option of having Pap smears every 3 years or having Pap with HPV testing every 5 years. At age 65, women can stop having Pap smears as long as their routine screening was within the past 10 years, with normal results. Women who have had a hysterectomy for benign reasons and have no history of high-grade squamous intraepithelial lesion (SIL) may discontinue testing. Women who have been treated for CIN2 or CIN3 need annual screening for at least 20 years. Those who have had a hysterectomy and a history of CIN2/CIN3 should continue to undergo screening with annual pelvic examinations.

When obtaining the Pap smear, special attention should be directed to not using a lubricating agent (warm water on the speculum will suffice), to obtaining good "scrapings" from the cervix and vaginal posterior fornix (without blood), and to using a small brush to obtain an endocervical sample. The patient should be instructed not to cleanse with a douche before the examination, and if indicated, specimens should be obtained to check for trichomonas. If the cytologic smear shows atypia or mild dysplasia (class II), it should be repeated no sooner than 2 weeks after the initial test to allow representative cellular exfoliation to occur. Guidelines for reporting results of cervical and vaginal cytology were promulgated in 1988. The Bethesda system eliminated the classes of Pap cytology. The correlation between the cytologic diagnosis and subsequent histologic examination is more than 90%. This system was updated in 2014.[25]

CLINICAL PRESENTATION

Cervical cancer in the United States is most frequently identified during routine gynecologic examination. Intraepithelial or early invasive carcinoma

of the cervix may be detected by cytologic smears before symptoms appear; Pap smear, colposcopy and biopsies, and HPV testing have high specificity and sensitivity. Visible lesions present with an exophytic mass or a barrel-shaped cervix because of an endocervical lesion. Patients may present complaining of metrorrhagia (intermenstrual bleeding), menorrhagia (heavier menstrual flow), or postcoital bleeding. If chronic bleeding occurs, the patient may complain of fatigue or other symptoms related to anemia.

In cases with more advanced disease, bowel obstruction, renal failure, foul-smelling serosanguinous or yellowish vaginal discharge, pelvic pain, flank and/or leg pain, rectal bleeding, obstipation, dysuria, hematuria, or persistent edema of lower extremities because of lymphatic/venous blockade by pelvic sidewall disease may occur. Pain in the pelvis or hypogastrium may be caused by tumor necrosis or associated pelvic inflammatory disease. In patients with pain in the lumbosacral area, the possibility of PAN involvement with extension into the lumbosacral roots or hydronephrosis should be considered.

DIAGNOSTIC WORKUP

Diagnostic workup for abnormal smear results is based on a patient risk, factoring in smear results, current HPV status, and prior findings.[26,27] When a patient presents with abnormal squamous cells of undetermined significance (ASCUS) but HPV status is negative and prior results are unknown or negative, follow-up testing in 3 years is recommended. When both ASCUS and HPV are present or AC in situ or an SIL is identified, directed biopsies at the time of colposcopy should be carried out. Endocervical curettage may be performed, except in pregnant women. If the biopsy results are negative, the procedure should be repeated in 6 months, and if they are positive, a conization should be performed.

Patients presenting with low-grade squamous intraepithelial lesions (LSILs) on cytology are further triaged based on age and HPV status. Women aged 25 years and above with LSIL and positive HPV are evaluated with colposcopy. For women aged 21 to 24 years, ASCUS or LSIL on cervical cytology is managed with repeat cytology at 12 months.

Results from a large-scale cervical cancer screening trial, conducted over a span of 15 years from Mumbai, India, were reported. Over 75,000 women were screened every 2 years using visual inspection and acetic acid vinegar. There was a significant 31% reduction in cervical cancer mortality in the

screening group, compared with the control group. The 7% reduction in all-cause mortality in the screening group did not reach significance. These results suggest acetic acid screening can be utilized in places that lack standard Pap smear screening and treatment resources.[28]

Patients who present with a clinically visible lesion should be jointly evaluated by the radiation and gynecologic oncologists. After obtaining a careful clinical history and performing a general physical examination, with attention to the inguinal and supraclavicular (nodal) areas, abdomen, and liver, a careful pelvic examination should be carried out with as little discomfort to the patient as possible without compromising the thoroughness of the evaluation. Pelvic examination should include inspection of the external genitalia, vagina, and uterine cervix; a rectal examination; and bimanual palpation of the pelvis. Pelvic examination under anesthesia (EUA) is a universally accepted component in the evaluation and clinical staging of patients in order to provide a pain-free examination that allows a clearer estimation of parametrial or sidewall tumor extension. In countries in which magnetic resonance imaging (MRI) is available, this may be used to assist with assessing tumor extension beyond the lower cervix, and in many institutions, it has replaced the EUA. Cystoscopy or rectosigmoidoscopy should be performed in all patients with symptoms consistent with the presence of a fistula of the urinary or lower gastrointestinal (GI) tract, patients with clinical stage IIB, III, or IVA disease who cannot undergo an MRI, or patients with an MRI suspicious for bladder or bowel invasion. The diagnostic procedures for carcinoma of the cervix are presented in Table 76.1.

TABLE 76.1 DIAGNOSTIC WORKUP FOR CARCINOMA OF THE UTERINE CERVIX

General
History, with special emphasis on possible interventions:
Fertility preservation
Comorbidity management
Smoking cessation
Nutritional and mental support
Physical examination, including bimanual pelvic and rectal examinations
Diagnostic Procedures
Cytologic smears (Papanicolaou) if not bleeding
Colposcopy
Conization (subclinical tumor)
Punch biopsies (edge of gross tumor, four quadrants)
Endocervical curettage

Cystoscopy, rectosigmoidoscopy (stages IIB, III, and IVA)

Radiographic Studies
Computed tomography
Magnetic resonance imaging
Positron emission tomography scan

Laboratory Studies
Complete blood count
Blood chemistry
Urinalysis
Squamous cell antigen levels
HPV circulating tumor DNA
Immunohistochemistry for programmed death ligand 1 (PD-L1) expression

Conization/Loop Excision

Conization involves a conical removal of a large portion of the ectocervix and endocervix. Cold knife cone biopsy specimens should always be obtained with a scalpel or other appropriate instrument. At least 50% of the endocervical canal should be removed without compromising the internal sphincter. Curettage of the remaining endocervical canal should be carried out.

Conization must be performed in the following situations: No gross lesion of the cervix is noted and an endocervical tumor is suspected; the entire lesion cannot be seen with the colposcope; diagnosis of microinvasive carcinoma is made on biopsy; discrepancies are found between the cytologic and histologic appearances of the lesion; or the patient is not reliable for all necessary follow-up. With careful selection of patients who have a negative positron emission tomography (PET) scan and an MRI with a central lesion less than 2 cm in width, knife conization with lymphadenectomy may be considered for fertility preservation. Laser conization and loop diathermy excision are frequently done in an office setting as an alternative to conization; loop excision is less expensive and more reliable than laser conization.

Biopsy

Multiple punch biopsies of a grossly visible lesion should be adequate to confirm the diagnosis of invasive carcinoma. Specimens should be obtained from any suspect area and from all four quadrants of the cervix and any suspect areas in the vagina. It is important to obtain tissue from the periphery of the lesion with some adjoining normal tissue; biopsy specimens from

central ulcerated or necrotic areas may not be adequate for diagnosis. Dilation and curettage are not required if other biopsies confirm the diagnosis of invasive disease.

Laboratory Studies

For invasive carcinoma, patients should have the following laboratory studies: complete peripheral blood evaluation, including hemogram, white blood cell count, and differential and platelet count; blood chemistry profile, with particular attention to blood urea nitrogen and creatinine; liver function values; and urinalysis.

Imaging Studies

In countries where three-dimensional (3D) imaging is not routinely available, International Federation of Gynecology and Obstetrics (FIGO) recommended evaluation for patients with cervical cancer includes a chest radiograph to assess for lung metastases and an intravenous pyelogram (IVP) to determine whether hydronephrosis is present. The IVP in many countries has been replaced by computed tomography (CT) scan of the pelvis and abdomen with intravenous (IV) contrast material or by PET-CT scan. In places where CT is not available, patients with stage IIB, III, and IVA diseases who have symptoms in the colon and rectum may benefit from a barium enema. A skeletal survey may be performed to determine whether bone metastases are present. Historically, pedal lymphangiography was used to assess lymph node involvement in the pelvic or PAN with mixed results. The number of physicians trained to perform lymphangiography has declined in the United States, and instead, PET scan is preferred.

Since the 1990s, the use of CT scanning has rapidly increased worldwide. A CT provides diagnostic information about the presence of metastases, enlarged lymph nodes, and the primary tumor. On a CT scan, the cervical tumor may be seen as an enlarged, irregular, hypoechoic cervix or as a mass with ill-defined margins. Parametrial regions appear dense when involved, and uterosacral involvement may be seen. Lymph nodes appear enlarged, with most greater than 1 cm on axial dimension considered pathologic. The overall accuracy of CT scanning in staging cervical cancer ranges from 63% to 88%.[29,30] In the detection of lymph node abnormalities, the overall accuracy of

conventional CT scanning is 77% to 85%, with sensitivity of 44% and specificity of 93%.[31]

In order to correlate radiographic and surgical findings, Camilien et al[32] reported on 61 patients with carcinoma of the cervix who had both preoperative CT scans and exploratory laparotomy; results showed that 75% of the enlarged pelvic lymph nodes on CT contained metastases, and 97% of patients with negative nodes on CT scan had pathologically negative findings (specificity of 97%). However, histologically positive pelvic nodes were often missed on CT scan (sensitivity of 25%). The CT scan is more valuable in the evaluation of the PANs (specificity of 100% and sensitivity of 67%).

Several studies explored the role of CT or PET-CT with regard to PAN evaluation (Table 76.2). The ACRIN6671/GOG0233 trial enrolled 109 patients with PET and pathology available; sensitivity of PET was 0.5 and for diagnostic CT was 0.42 (P = .052).[33] Heller et al[34] conducted a prospective evaluation of 320 patients with stage IIB to IVA carcinomas of the cervix entered into a Gynecologic Oncology Group (GOG) protocol in which preoperative CT scan, lymphangiography, and ultrasonography of the aortic area were performed. PAN dissection was done in patients with negative staging studies. Lymphangiography, CT scan, and ultrasonography had false-negative frequencies for pelvic lymph node evaluation of 14.2%, 25%, and 30%, respectively. The sensitivity was 79% for lymphangiography, 34% for CT scan, and 19% for ultrasonography, and the specificity ratings were 73%, 96%, and 99%, respectively. Ultrasonography, therefore, is not reliable in preoperative detection of lymph node metastases, but it has limited value in evaluating extrauterine tumor involvement. Ultrasound (US) has a primary role in assisting with intracavitary brachytherapy (BT) applicator insertion and may detect uterine perforation, allowing for proper positioning, which is critical for adequate dosing and affects survival.[35] PET has a higher sensitivity than CT and higher specificity than MR in detecting bone metastases.[36]

TABLE 76.2 COMPUTED TOMOGRAPHY AND POSITRON EMISSION TOMOGRAPHY IN THE EVALUATION OF PARA-AORTIC LYMPH NODES

Author	Number of Cases	FIGO Stage	Sensitivity (%)	Specificity (%)	Accuracy (%)
Kilcheski et al[30]	36	I-IV	–	80	–

Author	Number of Cases	FIGO Stage	Sensitivity (%)	Specificity (%)	Accuracy (%)
Camilien et al[32]	51	IB-IIA	67	100	100
Camilien et al[32]	10	IIB-IV	67	100	90
PET-CT					
Leblanc et al[131]	125	IB2-IIA	33.3	94.2	–
Yildirim et al[442]	16	IIB-IVA	50	83.3	–

FIGO, International Federation of Gynecology and Obstetrics.
Modified from Camilien L, Gordon D, Fruchter RG, Maiman M, Boyce JG. Predictive value of computerized tomography in the presurgical evaluation of primary carcinoma of the cervix. *Gynecol Oncol*. 1988;30(2):209-215. Copyright © 1988 Elsevier. With permission.

Magnetic Resonance Imaging

MRI is frequently used for the initial assessment of the cervical tumor and of extracervical tumor extension, often in lieu of a EUA. MRI is contraindicated in patients with pacemakers/implantable cardioverter-defibrillators, cochlear implants, metallic prostheses, metallic fragments from prior accidents, or large vascular clips. On T2-weighted images, a cervical cancer may be seen as a mass of intermediate to high signal intensity, usually of greater intensity than the fibrocervical stroma. On T1-weighted images, tumors are usually isointense with the normal cervix and may not be seen but can increase in intensity with the administration of IV contrast. Abnormal, irregular cervical margins; prominent parametrial strands; exocentric parametrial enlargement; and loss of parametrial fat planes on T1-weighted images or high signal in the parametria or cardinal/uterosacral ligaments on T2-weighted images are indicative of more extensive tumors. Parametrial tumor may be identified as brighter regions on T2-weighted images when compared to the low signal intensity of the cervix and uterine ligaments.

Pretreatment tumor staging and volume were assessed by EUA, transrectal ultrasonography (TRUS), and MRI in 60 patients with invasive carcinoma of the cervix.[37] TRUS and MRI assigned the same tumor stage in only 30% of patients, and EUA and MRI agreed on tumor stage in an additional 27%. In

cases of disagreement, the MRI staging correlated better with outcome than TRUS or EUA. Sixty-two percent of patients with enlarged lymph nodes on pretreatment MRI either died or had tumor recurrence or metastases. MRI was superior to both TRUS and EUA in assessing the full extent of bulky tumors and lymph node enlargement.

Postema et al[38] compared MRI with pelvic examination (including under general anesthesia in selected patients) and surgico-pathologic findings in 103 patients with invasive cervical carcinoma. MRI was better at identifying extracervical tumor spread, but it had more false-positive results. The pelvic examination led to correct treatment decisions in 89% of patients. In a study by Hansen et al,[39] clinical assessment (done according to FIGO recommendations) was superior to low-field MRI with contrast enhancement in staging cervical cancer in 95 women who had both within 2 weeks after clinical diagnosis; the clinical staging correctly classified 57 patients (accuracy, 92%) compared with 52 for MRI (accuracy, 84%).

A prospective study by the American College of Radiology Imaging Network compared clinical examination, CT, and MRI.[40] MRI was significantly better than clinical examination or CT for detecting uterine body involvement or measuring tumor size, but no method was accurate at evaluating the cervical stroma. MRI was significantly better at detecting the tumor and parametrial involvement. MRI also somewhat increased detection of involved lymph nodes.[31]

The tumor is less likely to be as visible on MRI for AC cases, compared to squamous cell cancer. Haider et al[41] evaluated 56 patients with AC involving the cervix using MRI and noted that only 42 (75%) had a visible mass.

Radiation-induced changes detected over the course of radiation may predict local recurrence (LR) and survival. Mayr et al[42] studied 34 patients with cervical cancer of various FIGO stages who underwent 1.5-T MRI before and after RT. Tumor volumetry (3D measurements) based on T2-weighted images quantified the tumor regression rate. Sequential tumor volumetry using MRI may be a very effective measure of the responsiveness of cervical cancer to irradiation. MRI dynamic contrast enhancement during the first 2 weeks of RT may provide early prediction of tumor regression rate. In seven patients, tumor regression rates ranged from 2% to 15.2% per day and correlated positively with changes in both peak and mean tumor enhancement ($P < .01$). Hatano et al[43] evaluated MRI in 42 patients with

advanced cervical cancer treated with external beam irradiation and high-dose rate (HDR) BT. In biopsies performed immediately after RT, no residual cancer was found in 36 (86%) patients. The simultaneous MRI study demonstrated no high signal intensity on T2-weighted images in 28 (75%) patients. A high signal intensity area was observed in 14 patients, and this disappeared 3 months after RT in 8 patients with a negative biopsy. The sensitivity, specificity, and accuracy of MRI tumor response studies at 3 months after RT were 100%. MRI studies performed after 30 Gy of external beam irradiation and 3 months after all RT predicted local tumor control. Furthermore, MRI is useful in providing accurate target volume definition in BT treatment planning (Figure 76.4).[44]

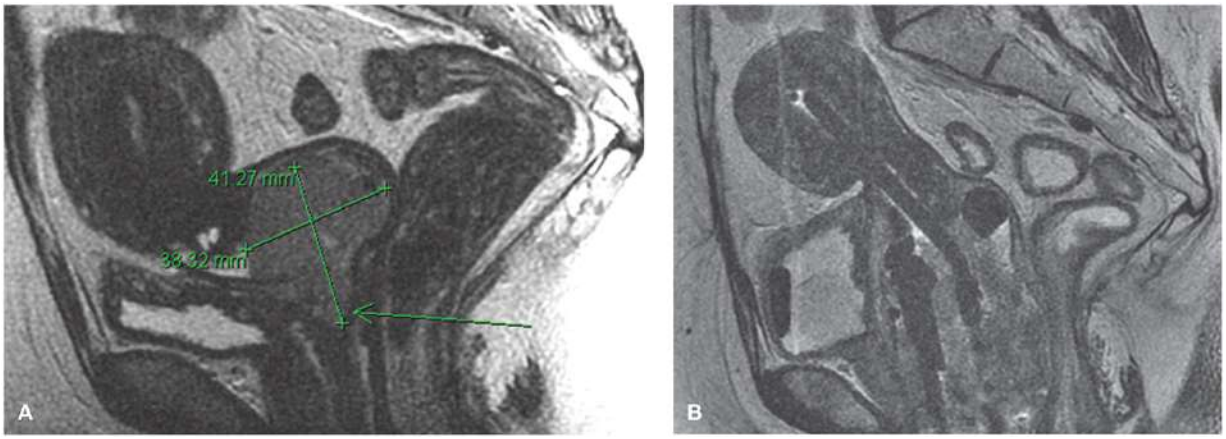
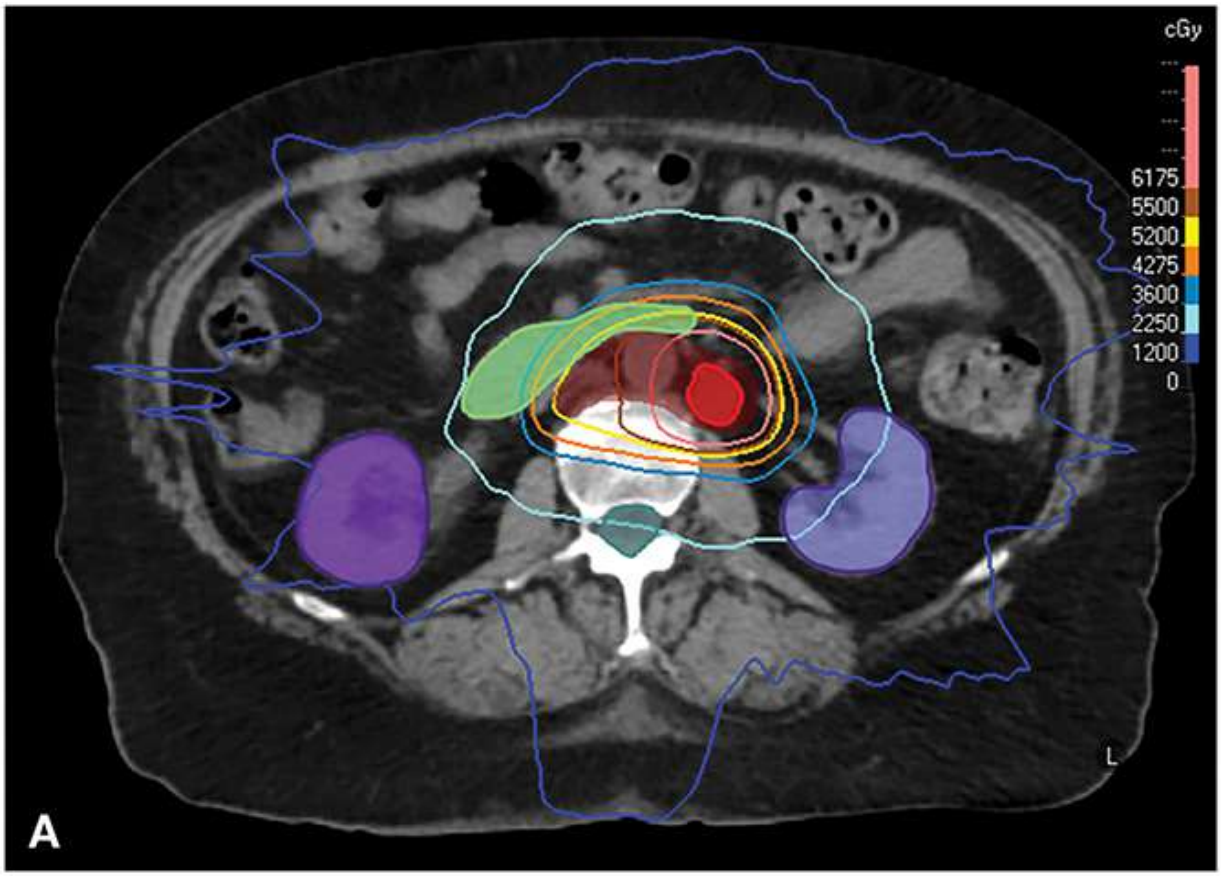


FIGURE 76.4 A. Magnetic resonance imaging (MRI) at diagnosis showing an enlarged cervical tumor. B. MRI with tandem and ring brachytherapy applicator in place showing dramatic shrinkage of the tumor after concurrent chemotherapy with external beam radiation.

Positron Emission Tomography

PET scanning is increasingly used in the evaluation of patients with malignant neoplasia, including invasive cervical cancer, using 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG). Rose et al[45] observed uptake in 91% of the primary tumors in 32 patients with locally advanced carcinoma of the cervix. SCC is more often FDG avid than is AC. Compared with surgical staging, PET scanning had a sensitivity of 75% and a specificity of 92% in detecting para-aortic metastasis.[46] PET-CT provides highly accurate localization of focal radiotracer uptake, which significantly improves the diagnostic accuracy compared with PET or CT alone. Diagnostic PET images may be fused with simulation CT images to ensure accurate radiation dose coverage of the target and any PET-

avid lymph nodes. Proton therapy may provide a favorable distribution of dose allowing dose escalation while maximally sparing normal tissues (Figure 76.5). Care must be taken in interpretation because physiologic FDG excretion into the urinary bladder may result in false-positive assessment of the primary tumor, and ureters may be contoured as lymph nodes; therefore, tracing the ureters and complete bladder voiding prior to imaging are recommended.


cGy
6175
5500
5200
4275
3600
2250
1200
0
L
A

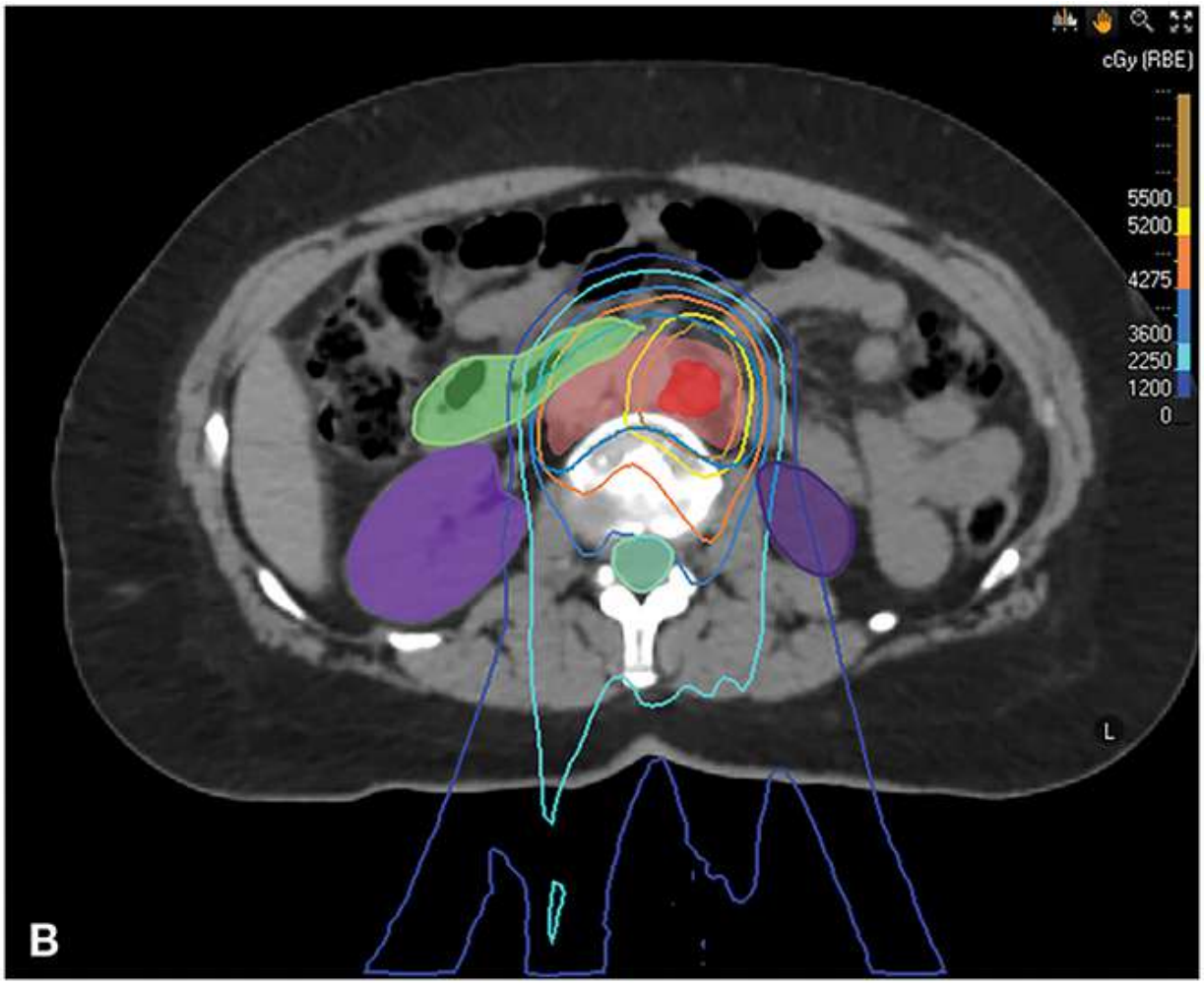


FIGURE 76.5 Target coverage of positron emission tomography–positive para-aortic lymph nodes on a computed tomography. Comparison between a photon intensity-modulated radiation therapy plan (A) and a proton plan (B) for the treatment of the para-aortic lymph node region, with a required boost to a gross pathologic node in two different patients. The duodenum (green) and the kidneys (purple) may cause a challenge to safely escalate dose to the involved node(s). Proton therapy has less scatter allowing a better dose distribution that in some cases is crucial to meet normal tissue constraints and may be especially beneficial in patients requiring reirradiation.

Grigsby et al[46] compared CT and FDG-PET scanning for lymph node staging in 101 patients with carcinoma of the cervix. CT demonstrated abnormally enlarged pelvic lymph nodes in 20 patients and PANs in 7, whereas PET demonstrated abnormal FDG uptake in pelvic lymph nodes in 67, in PANs in 21, and in supraclavicular lymph nodes in 8. The 2-year progression-free survival (PFS) rate, based solely on PAN status, was 64% in CT-negative and PET-negative patients, 18% in CT-negative and PET-positive

patients, and 14% in CT-positive and PET-positive patients ($P < .0001$). The most significant prognostic factor for PFS was the presence of positive PANs on PET imaging ($P = .025$). Among 76 patients with no abnormal FDG uptake, the 2-year survival rate was 86%, with persistent abnormal uptake in 40%; there were no survivors among patients who developed new sites of abnormal uptake.[47] In a follow-up study of 152 patients, the authors reported a 5-year cause-specific survival (CSS) rate of 80% in 114 patients without abnormalities on post-therapy FDG-PET versus 32% in 20 patients with persistent uptake and no survivors among 18 patients with new sites of abnormal uptake.[48] In another study, Grigsby et al[49] noted in 208 patients a close correlation between radiation doses, the number and size of positive lymph nodes, and outcome (treatment failures and survival; Figure 76.6). Hope et al[50] performed FDG-PET scans in 58 patients with cervical carcinoma who had an endometrial biopsy or dilation and curettage; 36 (64%) had pathologic EI. Pelvic lymph node metastasis was more commonly detected in this group than in patients without EI (70% vs 23%; $P < .001$), as were para-aortic and supraclavicular nodal metastasis (30% vs 0%; $P = .006$). Furthermore, 2-year survival rates were 78% versus 58%, and overall survival (OS) rates were 92% versus 65% ($P = .047$).

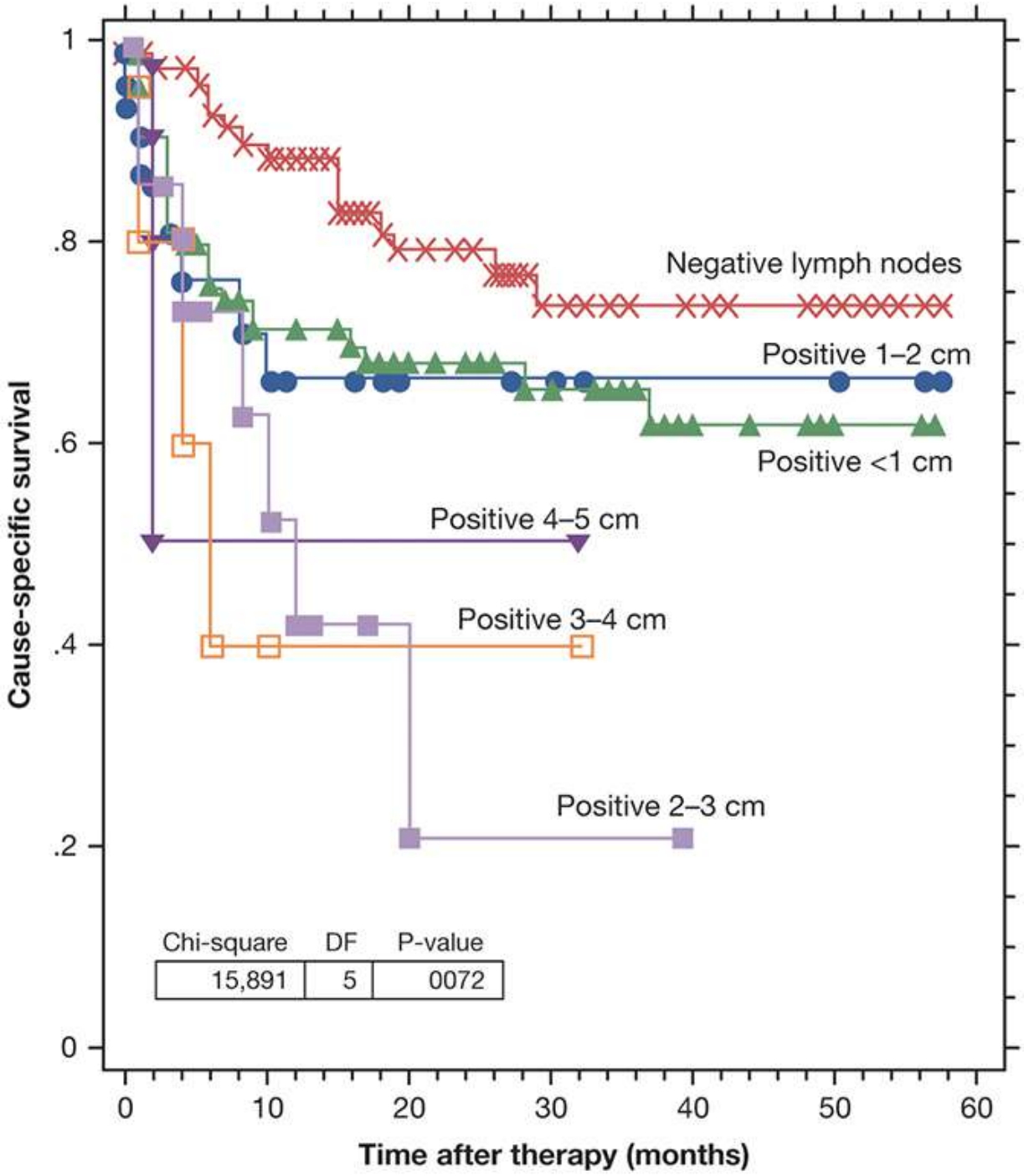


FIGURE 76.6 Cause-specific survival in patients with carcinoma of the cervix correlated with pelvic lymph node status on post-treatment 2-[^{924}F]fluoro-2-deoxy-D-glucose/positron emission tomography. (Reprinted from Grigsby PW, Singh AK, Siegel BA, Dehdashti F, Rader J, Zoberi I. Lymph node control in cervical cancer. *Int J Radiat Oncol Biol Phys*. 2004;59[3]:706-712. Copyright © 2004 Elsevier. With permission.)

Kidd et al[51-53] demonstrated that maximum standardized uptake value (SUVmax) is an independent predictor of death from cervical cancer and is associated with persistent disease. Similarly, the SUV of the pelvic node predicts pelvic disease recurrence. Survival rates are worse with supraclavicular nodal PET positivity; PAN metastases portend a survival rate between those of pelvic node and supraclavicular positivity. The detection of supraclavicular metastases on FDG-PET at diagnosis and its relationship to clinical outcome for 186 patients with cervical cancer was reported by Tran et al.[54] Fourteen patients (8%) had abnormal FDG uptake in the left supraclavicular lymph nodes without palpable disease, confirmed on biopsy; six were treated with palliative intent, and seven received definitive irradiation and concurrent chemotherapy. The median OS was 7.5 months; all patients developed distant metastases. After external beam radiation is finished, an FDG-PET scan provides important information about post-treatment uptake and is prognostic with regard to outcome.[55]

STAGING

The FIGO staging system was historically based on clinical evaluation (inspection, palpation, colposcopy); roentgenographic examination of the chest, kidneys, and skeleton; and endocervical curettage and biopsies. The updated 2018 FIGO staging system allows for the use of imaging to determine the size of cervical tumor in stage I and stage II disease and for the identification of retroperitoneal lymph nodes in stage I to III. In addition, the 2018 FIGO staging system for cervical cancer has several other modifications from the previous version: Stage IA1 is characterized by stromal invasion of less than or equal to 3 mm with IA2 correlating to stromal invasion of greater than 3 mm but less than 5 mm. Stage IB disease has now been divided into IB1, IB2, and IB3 based on the depth of stromal of greater than 5 mm to 2 cm or less, greater than 2 cm to 4 cm or less, and greater than 4 cm, respectively. The updated staging system also introduces the category stage IIIC. This has been further subdivided into stage IIIC1 to include all tumors with pelvic lymph node metastases only and stage IIIC2 to include tumors with PAN metastases. Both of these subcategories exist, irrespective of the tumor size and extent.

Patients with hydronephrosis or a nonfunctioning kidney ascribed to extension of the tumor are classified as stage IIIB, regardless of the pelvic

findings. Other prognostic factors, such as endometrial extension of cervical carcinoma, stromal invasion, lymphatic/vascular permeation, and involvement of the lateral parametrium (as opposed to the medial parametrium) in stage IIB, are not included in the staging system. Suspected invasion of the bladder or rectum should be confirmed by biopsy. Bullous edema of the bladder and swelling of the mucosa of the rectum are not accepted as definitive criteria for staging. For a lesion to be classified as stage IIIB based on tumor extension without hydronephrosis, the tumor should extend to the lateral pelvic wall, although fixation is not required.

A parallel tumor-node-metastasis staging system is published by the American Joint Committee on Cancer; however, this system requires nodal staging, which is not feasible in many settings, and radiologic nodal information is not available to most patients with cervical cancer worldwide. The FIGO system remains the standard staging system, given the lack of 3D imaging to determine nodal status in countries with the highest incidence of cervical cancer. All histologic types should be included. When there is a disagreement regarding the staging, the earlier stage should be recorded (Table 76.3; Figure 76.7).

TABLE 76.3 FIGO STAGING OF CARCINOMA OF THE UTERINE CERVIX

I	Cervical carcinoma confined to the cervix (extension to the corpus should be disregarded)
IA	Invasive carcinoma, diagnosed by microscopy only, maximum depth of invasion ≤5 mm
IA1	Stromal invasion ≤3 mm
IA2	Stromal invasion .3 mm and ≤5 mm
IB	Invasive carcinoma, .5 mm depth, confined to the cervix
1B1	>5 mm depth of stromal invasion and ≤2 cm
IB2	>2 cm and ≤4 cm in greatest dimension
IB3	>4 cm in greatest dimension
II	Invasion beyond uterus, limited to upper two-thirds of vagina, no pelvic wall invasion
IIA	Limited to upper two-thirds of vagina, no parametrial involvement
IIA1	≤4 cm in greatest dimension
IIA2	>4 cm in greatest dimension
IIB	Parametrial involvement, but not pelvic wall

III	Cervical carcinoma extends to the pelvic wall and/or involves lower one-third of the vagina and/or causes hydronephrosis or nonfunctioning kidney.
IIIA	Involves lower one-third, no pelvic wall extension
IIIB	Tumor extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney.
IIIC	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
IVA	Tumor invades mucosa of the bladder or rectum and/or extends beyond the true pelvis.[a]
IVB	Distant metastasis

FIGO, International Federation of Gynecology and Obstetrics.

[a]Presence of bullous edema is not sufficient evidence to classify a tumor as T4.

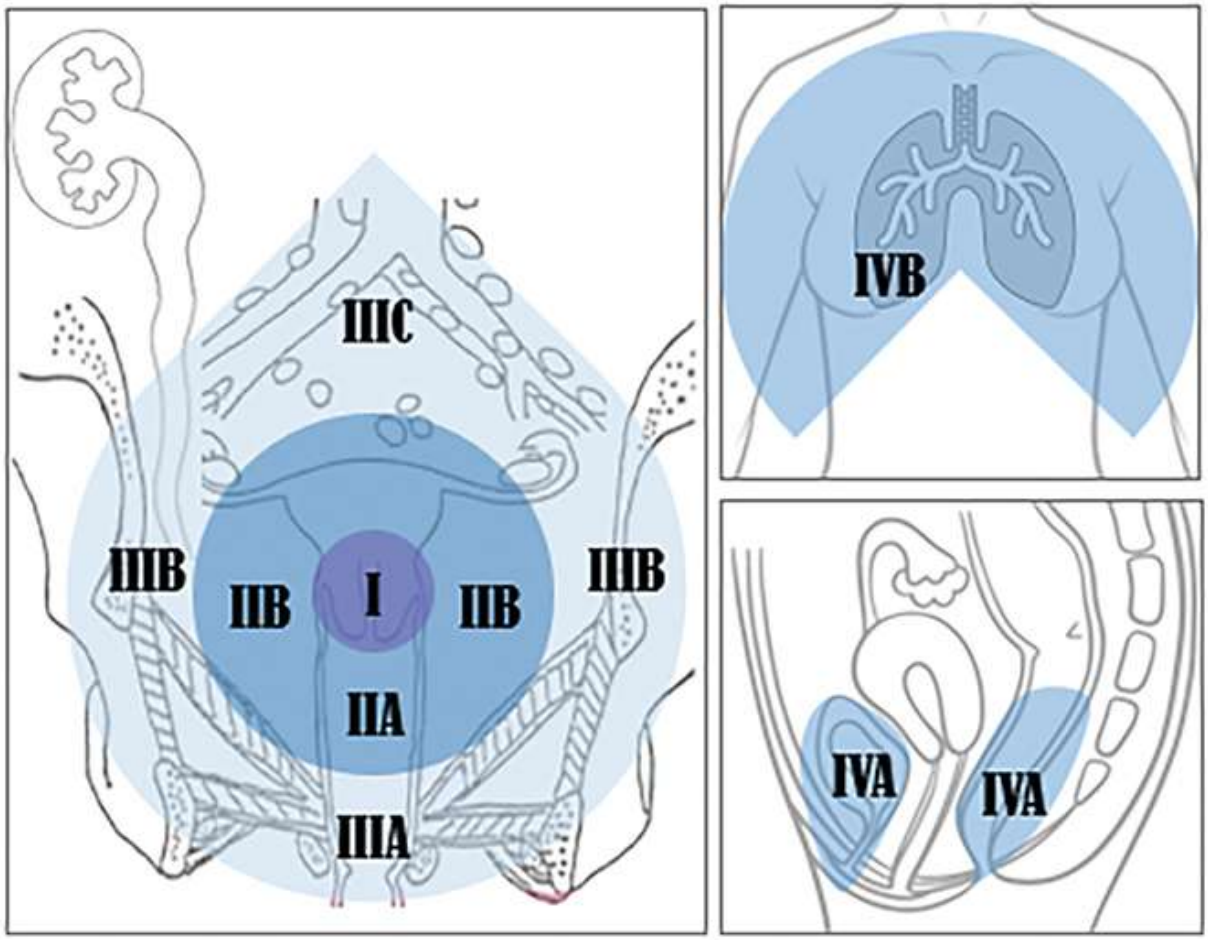


FIGURE 76.7 Diagrammatic representation the anatomic stages of carcinoma of the uterine cervix, according to the 2018 International Federation of Gynecology and Obstetrics classification. Stage I is further divided by depth of invasion and size. Stage IIA has been divided by size up to and over 4 cm to stage IIA1 and IIA2, respectively. Stage III is divided by area of invasion—IIIA in lower vagina, IIIB in pelvic sidewall or obstruction of ureter, and IIIC to lymph nodes (IIIC1 pelvic and IIIC2 in para-aortic nodes). Stage IVA invades pelvic organs and IVB is distant metastases.

PATHOLOGIC CLASSIFICATION

More than 90% of tumors are SCC. Approximately 7% to 10% are classified as AC, and 1% to 2% are the clear cell mesonephric type. Squamous cell (or epidermoid) carcinoma is composed of cores and nests of epithelial cells arranged randomly; cells show central keratinization with pearls and sometimes necrosis. Nonkeratinizing tumors may be seen. Electron microscopy may show desmosomes and tonofilaments. SCCs are divided into three types: large cell keratinizing, nonkeratinizing, and small cell

carcinomas. They are subdivided according to the degree of differentiation into well, moderately, or poorly differentiated.

Verrucous carcinoma is a variant of a very well- differentiated SCC that characteristically has a tendency to recur locally, but not to metastasize. Mitotic activity is very low. It may be difficult to discriminate verrucous carcinoma from a giant condyloma with cytologic atypia or from a well-differentiated invasive squamous carcinoma. Microscopically, verrucous carcinoma is exophytic, with an undulating, hyperkeratotic surface; the deep margin is composed of large, bulbous masses that invade along a wide front in a “pushing” manner.

AC arises from the cylindrical mucosa of the endocervix or the mucus-secreting endocervical glands. Mucinous is the most common subtype of AC. This endocervical AC may form mucosal glands lined by high columnar cells and produce tubular folds oriented in many directions. In another subtype, cells resemble those of the intestines; the epithelium tends to be pseudostratified and may contain goblet cells. The third variant is the signet-ring cell AC, which is rare and usually mixed with the endocervical or intestinal patterns.

Endometrioid carcinoma is the most common cell type of endocervical AC; the cells resemble those of the endometrium, and the presence of intracytoplasmic mucin in some cells may be seen in a substantial proportion of tumors. The World Health Organization recommends that endometrioid or endocervical types of ACs be graded according to their architecture, based on the degree of gland formation. Sometimes, it is difficult to differentiate a primary endocervical AC from an endometrial tumor. HPV is greatly associated with cervical ACs, with an overall prevalence of 90%, and has been identified in most subtypes with varying rates.[56]

Adenoma malignum is a rare form of cervical cancer that is difficult to diagnose and often highly malignant and refractory to treatment. Adenoma malignum is associated with Peutz-Jeghers syndrome and has an ominous natural history, with few reported cures. Adenosquamous carcinoma is also relatively rare (2%-5%) and consists of intermingled epithelial cell cores with squamous features and glandular structures. The squamous component is frequently nonkeratinizing. If the squamous component is benign metaplasia, the tumor is called adenoacanthoma.

Glassy cell carcinoma (1%-2%) is considered a poorly differentiated adenosquamous tumor; it is rare and highly malignant. Survival is poor after surgery or irradiation. Light and electron microscopy demonstrate both glandular and squamous differentiation.

Adenoid cystic carcinoma is a rare variant of AC of the cervix (<1%), with an appearance similar to its counterparts in the salivary gland or the bronchial tree. The tumor is composed of nests and nodules of small carcinoma cells with a few characteristic cribriform patterns. Immunohistochemical findings for type IV collagen and laminin reveal intercellular cylinders composed of basement membrane material in the solid area without a cribriform pattern. They are locally aggressive and prone to metastasize.[57]

Clear cell carcinoma (mesonephric), not related to DES exposure, comprises approximately 2% primary cervical ACs and is believed to arise in mesonephric remnants. These tumors are submucosal, composed of clear and "hobnail" cells, and may grow in a tubular, glandular, papillary, or solid pattern. They appear at any age, with one-third occurring in women younger than 30 years of age. The clear cell is characterized by a voluminous cytoplasm filled with glycogen and the hobnail cell by single-cell apical projections into the neoplastic lumina. These tumors tend to be deeply positioned, with the bulk of the lesion on the stroma forming tubular structures, diffusely infiltrating the cervical stroma.

Cervical malignant mixed Müllerian tumors, compared with their counterparts in the corpus, are more commonly confined at presentation and may have a better prognosis. Clement et al[58] described the clinicopathologic features with mixed Müllerian tumors of the cervix in nine patients. Gross examination revealed polypoid or pedunculated masses that invaded the cervical wall in 50% of the hysterectomy specimens. On microscopic examination, five tumors contained basaloid carcinoma or SCC and four contained AC. In seven tumors, the sarcomatous component was homologous, usually resembling fibrosarcoma or endometrial stromal sarcoma, and two tumors contained heterologous sarcomatous elements.

Small cell carcinoma of the cervix, according to some authors, arises from endocervical argyrophilic cells or their precursors, multipotential neuroendocrine cells; however, some small cell tumors do not contain morphologic evidence of neuroendocrine origin. Nuclear molding, absence of nucleoli, cell necrosis, and high mitotic activity are common. One-third to

one-half stain positively for neuroendocrine markers, such as chromogranin, serotonin, synaptophysin, or somatostatin. In the majority of patients, the cervical stroma is extensively infiltrated by single small, round cells. Lymphatic and vascular invasion are significantly more common in small cell carcinomas (noted in 58% of patients with stage IB disease; 40% of these patients had lymph node metastases at the time of radical surgery). HPV-18 has been detected in the majority of these tumors.[59,60] Survival rate is considered poorer to matched large cell SCCs. Viswanathan et al[61] studied 21 patients. All were confirmed after central pathology review to stain positively for chromogranin, synaptophysin, or CD56. The median time to first relapse from the initiation of treatment was 8.4 months. No patient had brain metastases as the sole site of first recurrence. However, two patients developed brain metastases concurrently with lung metastases. The OS rate was 29% at 5 years; none of the patients who had disease more extensive than stage IB1 or clinical evidence of lymph node metastases survived their disease. A 5-year OS of 29% was also reported in 487 patients in the Surveillance, Epidemiology, and End Results (SEER) registry.[62]

Basaloid carcinoma or adenoid basal carcinoma, an extremely uncommon tumor, is characterized by nests or cords of small basaloid cells, prominent peripheral palisading of cells in the tumor nests, no significant stromal reaction or capillary space invasion, and an infiltrating growth pattern. Some authors have suggested a slow growth pattern with limited local invasiveness and low probability of lymph node metastases. Prognosis is excellent.

Primary sarcomas of the cervix have been occasionally described (eg, leiomyosarcoma, rhabdomyosarcoma, stromal sarcoma, carcinosarcoma). Malignant lymphomas, primary or secondary in the cervix, have been sporadically reported. They should be treated like other lymphomas. Melanoma of the cervix is similarly extremely rare and difficult to cure despite attempts at radical surgery and immunotherapy. Metastasis of distant tumors to the uterine cervix is rare (about 4% of all tumors) and should be considered in the differential diagnosis. Metastases to the cervix from the breast, ovary, and kidney have been reported.

PROGNOSTIC AND PREDICTIVE FACTORS

The NRG/GOG combined data from randomized trials of chemoradiotherapy (CRT) and created nomograms predicting PFS, OS, and pelvic recurrence in

locally advanced cervical cancer. Multivariable analysis of 2,042 patients identified histology, race/ethnicity, performance status, tumor size, stage, grade, pelvic node status, and treatment with cisplatin-based chemotherapy concurrently as significant measures for outcomes.[63]

Patient-Related Factors

Age

According to some reports, age is not a prognostic factor in carcinoma of the cervix. Other authors noted decreased survival in women younger than 35 or 40 years, who have a greater frequency of poorly differentiated tumors. In contrast, two European studies showed improved outcome for younger patients. This apparent contradiction may be explained by an analysis by Rutledge et al,[64] who showed an interaction between age and stage in the relative hazard plots for 250 patients younger than 35 years of age and matched control subjects, with a detriment to the younger group. Mitchell et al[65] evaluated 398 patients with stage I to III cervical carcinomas treated with RT. Patients were divided into non-older (35-69 years of age; n = 338) and older (≥70 years of age; n = 60) groups. Comorbid conditions in the older patients resulted in diminished ability to undergo intracavitary BT. Although the 5-year actuarial DFS and CSS rates were comparable in the two groups, tumor recurrence and death from cervical cancer were more common beyond 5 years in the older group.

Race/Ethnicity

Several authors noted a correlation between racial characteristics of patients and outcome of therapy. Mundt et al[66] examined factors affecting outcome in 316 African American and 94 White patients undergoing RT for cervical cancer. With a median follow-up of 72.4 months, African Americans had a trend toward poorer 8-year CSS rates (47.9% vs 60.6%; P = .10) compared with White patients. Factors correlating with poor outcome, including lower hemoglobin (Hb) levels during RT (P = .001), lower median income (P = .001), and less frequent intracavitary BT (P = .09), were more likely to be present in the African American group. Multivariate analysis demonstrated that race was not an independent prognostic factor after controlling for differences in patient, tumor, and treatment factors. In a report on 452 White and 124 African American women with stage II or III cancer of the cervix

treated with RT alone, Grigsby et al[67] observed 5-year CSS rates of 66% and 61% (P = .56) for those with stage II and of 38% and 47% (P = 0.34) for those with stage III disease. OS rates for stage II for the two racial groups were different (60% and 51%, respectively; P = .02) and may be related to non–cancer-related comorbidity factors.

More recently, differential rates of BT underutilization across racial and ethnic strata have been redemonstrated. Colson-Fearon et al utilized the National Cancer Database (NCDB) to evaluate factors related to BT use and survival differences between patients receiving and those not receiving BT for the treatment of cervical cancer.[68] African Americans (P < .001) and Hispanic (P < .001) patients were observed to have significantly lower rates of BT receipt. In addition, patients not receiving BT were noted to have significantly worse OS (P < .01).

Social Determinants of Health

A number of social determinants of health have been studied for their impact on outcomes among patients with cervical cancer. Tjioe et al performed a meta-analysis utilizing 24 studies performed from 2001 to 2022 to identify potential social determinants as predictors of differential prognosis. It was observed that not being married at the time of diagnosis, lack of insurance, being insured under Medicaid/Medicare, and receiving treatment in a low-volume facility may be associated with worse OS.[69]

Moreover, in an analysis of the 1994 Patterns of Care study of 471 cases of SCC treated in the United States and a randomly selected 215 additional cases from 17 institutions that admitted more than 40% minority patients, women who lived in low-income neighborhoods, who had only Medicaid coverage, or who were treated at large academic or minority-rich institutions tended to have a poorer initial performance status, higher stage or bulky central tumor, and a lower pretreatment Hb level.[70]

Social factors may also play a role in a patient's decision to pursue treatment. Samuel et al evaluated the impact of social determinants on rates of refusal of surgery for the treatment of gynecologic malignancies, including cervical cancer.[71] Utilizing the NCDB, 788,164 patients were identified of which 5,875 refused surgical treatment. Factors significantly associated with refusal included lack of insurance, coverage under Medicaid, and lower regional rates of high school completion. Similarly, Colson-Fearon et al[72]

analyzed rates of refusal of radiation treatment among patients with gynecologic cancer in the NCDB. Of 12,081 of 209,976 patients who refused radiation, predictive factors included lower annual income and lack of insurance.

General Medical Factors

Anemia

Although stage, tumor volume, histologic type of the lesion, and vascular or lymphatic invasion are known to affect the prognosis of patients with cervical carcinoma, whether Hb levels contribute to patient prognosis is controversial. Many radiation oncologists routinely administer red blood cell transfusions to correct anemia before treatment with RT. This may have a generally favorable effect on the patient's sense of well-being and energy level and an impact on tumor radiosensitivity. Typically, patients receive transfusion to maintain Hb levels greater than 10 to 12.5 g/dL. However, in practice, the effect on outcome is less evident.

A randomized trial reported by Bush[73] on 132 patients with stage IIB to III cervical cancers required the control arm to receive transfusions only if the Hb level dropped to less than 10 g/dL, whereas the experimental arm had to maintain the Hb level 12.5 g/dL or more. The results suggested an improved outcome for patients in the experimental arm who received transfusion; however, there was not a statistically significant difference in outcome between treatment arms when compared using an intent-to-treat analysis.[74] Second, the randomization was not stratified according to the potentially confounding influence of tumor size. Finally, the thresholds for transfusion were based on anemia during therapy, not the initial Hb.

Retrospective reports, mainly prior to the CRT era, on targeting anemia with transfusion have failed to show clear benefit that was not related to other patient and tumor factors. The largest one was a large retrospective review of 2,454 patients with cervical cancer showed on multivariate analysis, an Hb level of less than 10 g/dL during RT was found to be significant for lower disease-specific survival (DSS) (hazard ratio [HR] 1.28) and freedom from distant metastases (HR 1.33), but not freedom from central recurrence. In a subset analysis of patients receiving CRT, transfusion did not provide a benefit.[75]

Koulis et al[76] conducted a retrospective single-institutional study, identified 257 patients with cervical cancer, and observed that anemia identified prior to the start of primary CRT and on-treatment anemia were associated with significantly worse 5-year PFS and OS. Those who underwent correction of anemia diagnosed prior to treatment had improved survival when compared to those who did not.

Recombinant human erythropoietin is not routinely recommended as an alternative means of sustaining or raising Hb levels during RT. Thrombotic complications[77] and the lack of any survival benefit[78] mitigate the utility of this as a therapeutic intervention.

Thus, a prudent recommendation is to treat anemia prior to and during therapy in any symptomatic patient and to maintain Hb levels above 9 to 10 g/dL.

Other Medical Factors

Older reports observed a higher incidence of pelvic recurrences and complications in patients with arterial hypertension (diastolic pressure of .110 mm Hg) and a higher incidence of distant metastases and a lower survival rate in patients with temperatures of greater than 101 °F during BT procedures. In patients with cervical cancer screened for HIV and treated with RT, Campbell et al[79] observed a 4.2% positive HIV rate. These patients had more advanced tumors. The duration of remission was shorter than in the HIV-negative group. RT had no effect on the HIV titers. Women who are HIV positive or have acquired immunodeficiency syndrome associated with in situ or invasive carcinoma of the cervix are at a higher risk for tumor recurrence after treatment and death as a consequence of the malignant process.

Evidence suggests that increasing levels of plasma micronutrients are associated with a decreasing risk of cervical cancer. Increasing serum lycopene and α- and γ-tocopherol levels and higher intake of dark green and deep yellow vegetables and fruit were significantly inversely associated with cancer.[80] Women should be counseled to eat a well-balanced diet, particularly those at high risk for developing cervical cancer.

The neutrophil-to-lymphocyte ratio (NLR) has been shown to be prognostic, with an NLR greater than 2.95 associated with a worse OS (HR 1.65, $P < .001$) and event-free survival (HR 1.57, $P < .001$).[81]

Tumor Factors

Human Papillomavirus Subtype

HPV-16 and HPV-18 are the most frequent HPV subtypes worldwide. Studies have reported a higher risk of lymph node and other distant metastases with HPV-18 compared to HPV-16.[82] Wang et al[83] studied 1,010 patients with cervical cancer after RT between 1993 and 2000. The HPV genotypes were determined by a gene chip that can detect 38 types of HPV. A total of 25 genotypes of HPV were detected in 992 specimens, of which 8 types that predominated were HPV types 16, 58, 18, 33, 52, 39, 31, and 45. Two high-risk HPV species were identified: α-7 (HPV types 18, 39, and 45) and α-9 (HPV types 16, 31, 33, 52, and 58). Risk groups determined included the high-risk group, which consisted of patients without HPV infection or those infected with the α-7 species only. The medium-risk group included patients coinfected with the α-7 and α-9 species. Demarco et al[84] evaluated rates of clearance, persistence without progression, and progression to CIN3+ among 11,573 HPV-positive patients. They observed that the viral subtype with the highest risk of progression to CIN3+ within 7 years was HPV-16 (22%). Given the significant differences of disease progression observed in their study, the categorized subtypes into four groups. Rates of infection clearance in the absence of progression and persistence with progression were similar across subtypes.

Tumor Volume

There is a close correlation between depth of stromal invasion, tumor size and local extent, and incidence of parametrial and pelvic node metastases and survival in patients with cervical cancer. This is true, regardless of treatment modality. In a study of women treated with RH, the 5-year DFS rate was 90% in 181 patients with stage IB1 ($\leq$4 cm) and 72.8% in 48 patients with stage IB2 disease (P = .02).[85] Perez et al[86] reviewed 1,499 patients (stages IA-IVA) treated with definitive irradiation (combination of external beam irradiation plus two intracavitary insertions to deliver doses of 70-90 Gy to point A). There was a close negative correlation between increasing tumor size and extent and pelvic tumor control, freedom from distant metastasis, and DFS in all stages. Local extent of the tumor into the uterine corpus, parametria, and other pelvic organs is also well known to impact prognosis, and thus, it is incorporated in the staging system. In a SEER database validation study for

the 2018 FIGO staging system, it was shown that increasing tumor size negatively affects survival also in node-positive patients (stage IIIC).[87]

Impact of Histology on Outcomes

Several series have questioned whether AC has a worse prognosis than SCC. A SEER analysis of women with stage IB to IVB cervical cancers treated between 1988 and 2005 stratified 24,562 women by SCC (77%), AC, or adenosquamous histology. Patients with AC were younger and presented with early-stage disease ($P < .0001$). For both early- and advanced-stage diseases, women with AC had an increased likelihood of dying from disease compared to those with squamous neoplasms (HR 1.39 and HR 1.21, respectively).[88]

In a retrospective analysis of 1,671 patients accrued on prior prospective GOG trials with locally advanced cervical carcinoma treated with either radiation alone or CRT, a total of 70 patients with AC treated with radiation alone had a borderline poorer survival difference ($P = .0499$) compared to 647 patients with SCC. In patients treated with concurrent CRT, 112 patients with AC had no difference in OS ($P = .47$) compared to 842 patients with SCC. The authors conclude that in the era of CRT, no difference in outcome exists between squamous cell and AC in this large retrospective analysis.[89]

Alvarado et al[90] retrospectively evaluated survival differences between those with SCC against those with AC among patients with locally advance cervical cancer receiving concurrent CRT. Of 1,291 patients, 134 patients with AC had significantly worse DFS ($P = .043$) and OS ($P = .002$) when compared to 1,154 patients with SCC.

Histologic Grade

Most reports have shown no significant correlation of survival or tumor behavior with the degree of differentiation of SCC or AC of the cervix. Alfsen et al[91] analyzed 417 ACs and 88 other non-SCC of the cervix; on multivariate analysis, small cell histology, corpus infiltration, vascular invasion, and positive lymph nodes were significant prognostic variables. In the era of CRT, Monk et al[92] showed no significant impact of histology or grade on survival in postoperative patients with cervical cancer with other high-risk features.

Margin Status After Radical Hysterectomy

In addition to the known high-risk factors of positive margins, positive parametrial spread, and/or positive lymph nodes and the intermediate-risk factors of depth of stromal invasion, lymphovascular invasion, and tumor size, a small series have indicated the significance of close margin status. Viswanathan et al[93] studied 284 patients after RH and central pathology review. The crude rates for any recurrence were 11%, 20%, and 38% for patients with negative (≥1 cm), close (.0 and <1 cm), and positive margins, respectively. Postoperative RT decreased the rate of LR from 10% to 0% for negative, 17% to 0% for close, and 50% to 25% for positive margins. The significant predictors of decreased relapse-free survival on univariate analysis were the depth of tumor invasion (HR = 2.14/cm increase, $P = .007$), positive margins (HR = 3.92, $P = .02$), tumor size (HR = 1.3/cm increase, $P = .02$), lymphovascular invasion (HR = 2.19, $P = .03$), and margin status (HR = 0.002/increasing millimeter from cancer for those with close margins, $P = .03$).

Treatment Duration

In patients treated with RT, overall treatment time (OTT) should be as short as possible, and any planned or unplanned interruptions or delays should be avoided. Attempts to mitigate their harmful effect should be made by adding an additional fraction per week. Timely integration of external beam and BT in patients with carcinoma of the uterine cervix is an important factor in improving pelvic tumor control (Figure 76.8). Perez et al[94] in 1,330 patients treated with definitive irradiation noted a strong correlation between OTT and CSS. Regression analysis confirmed previous reports that prolongation of OTT resulted in an increased failure rate of 0.59% per day in stage IB and IIA and 0.86% per day in stage IIB disease. Performance of all intracavitary insertions within 4.5 weeks from initiation of irradiation yielded lower pelvic failure rates (8.8% vs 18% in stage IIB tumors; $P \leq .01$)

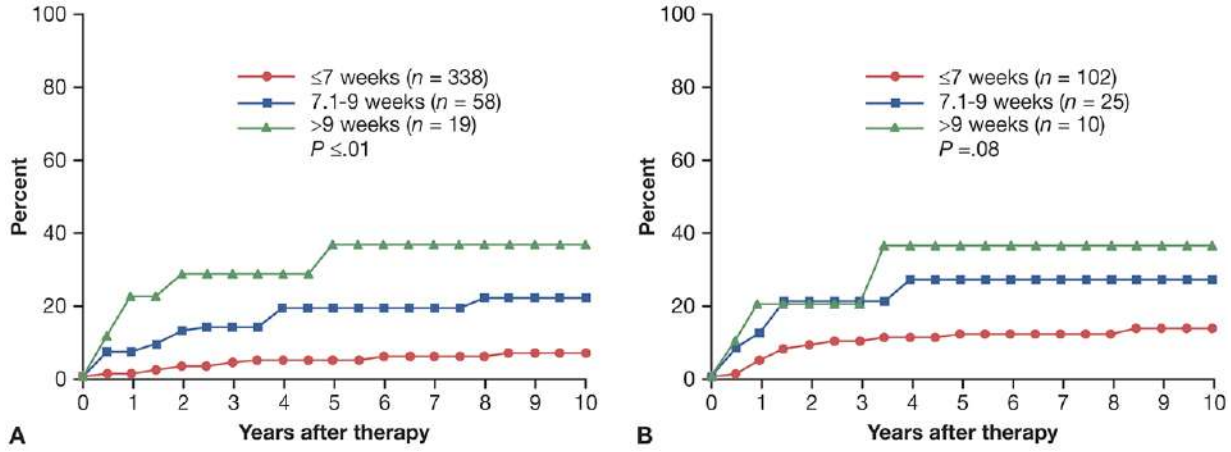


FIGURE 76.8 Pelvic failure rate correlated with length of treatment in stage IB (A) and IIA (B) carcinomas of the uterine cervix. (Reprinted from Perez CA, Grigsby PW, Castro-Vita H, Lockett MA. Carcinoma of the uterine cervix. I. Impact of prolongation of overall treatment time and timing of brachytherapy on outcome of radiation therapy. *Int J Radiat Oncol Biol Phys*. 1995;32[5]:1275-1288. Copyright © 1995 Elsevier. With permission.)

Whether treatment duration has an impact in the era of CRT has also been demonstrated. In a retrospective review of 488 patients all treated with CT or MRI-based BT in the retroEmbrace study, the high-risk clinical target volume (HR-CTV) volume, D90 dose, and longer OTT were associated with local control (LC).[95] The authors calculated that 1 week of delay was equivalent to 5 Gy decrease in the HR-CTV D90, which caused a 1% reduction in the rate of 3-year LC. This was further validated in the prospective EMBRACE cohort, which included 1,318 patients with a median of 46-month follow-up, and the OTT was significantly associated with LC in a multivariate analysis. Each additional day of OTT above the median 46 days had an HR for local failure of 1.03 (95% confidence interval [CI] 1.01-1.06, $P = .024$).

Clinical Biomarkers

Cytokeratin Markers and the Epidermal Growth Factor Receptor Pathway

Altered expression of c-ercB-2 (HER2) protein was shown to have prognostic significance in AC, but not in SCC, of the cervix. HER1, as well as coexpression of epidermal growth factor receptor and HER2, has been associated with poor DFS.[249] PTEN mutations have also been associated with poor prognosis.[96] A meta-analysis of studies examining the prevalence of HER2 overexpression in cervical cancer reported a pooled rate of 5.7%

(1.5%-11.7%).[97] Trastuzumab deruxtecan is an HER2-directed antibody-drug conjugate that after showing activity in breast and gastric cancers was also examined in other HER2-expressing solid tumors (determined with immunohistochemistry as either +3 or +2) in the DestinyPanTumor02 phase 2 trial.[98] It was found that in 40 patients with metastatic cervical cancer previously treated with at least one standard-of-care systemic treatment, the response rate was 50%, with a median PFS of 7 months, and better results with increased Her2 expression. In 80 patients with carcinoma of the cervix, expression of cytokeratin 10, cytokeratin 13, and involucrin was found in 24%, 64%, and 53%, respectively.[251] There was no difference in the expression of cytokeratin or involucrin between patients with positive or negative lymph nodes, although, in the lymph node–positive group, survival was higher in patients lacking cytokeratin 13 expression ($P = .02$).

Squamous Cell Carcinoma Antigen and Carcinoembryonic Antigen

Tsai et al,[99] in 117 patients with AC of the cervix, 28 of whom had preoperative carcinoembryonic antigen (CEA) levels of greater than 5 ng/mL, noted a correlation with larger tumor size, deeper cervical invasion, and lymphovascular invasion ($P < .001$). A Spanish study of 96 patients with invasive carcinoma of the cervix and 7 with intraepithelial neoplasia showed elevated CEA levels in 33%, carbohydrate antigen 19-9 (CA 19.9) in 32%, and CA 125 in 21.5% of patients.[100] Specificity for each tumor marker was 98%. Increased CEA and CA 19.9 levels were found with more advanced stages of the disease and in patients with AC compared with SCC. At follow-up, all cases of progressive tumor or recurrence were detected by elevation of one of the three antigens. Specificity during follow-up was 92% for CEA and CA 125 and 92.6% for CA 19.9.

In a study of 272 patients with invasive carcinoma of the cervix with 1,053 samples, Bolli et al[101] noted an elevation of squamous cell carcinoma antigen (SCC-Ag) before treatment in 53% of 103 patients, increasing with advancing tumor stage at diagnosis. In 70 patients with recurrent tumor, 81% had elevated SCC-Ag.

Hong et al,[102] in 401 patients with stage I to IV SCC of the cervix treated with RT, noted that the preirradiation SCC-Ag level strongly correlated with disease stage. A persistently elevated SCC-Ag level 3 months after RT was a

stronger predictor for treatment failure than residual induration by pelvic examination, and it was associated with a higher incidence of distant metastasis. A later report including 1,031 patients with SCC cancer treated with RT with or without chemotherapy noted that independent risk factors for local relapse were advanced stage, age less than 45 years, and lower SCC-Ag levels; 5-year local relapse–free survival was higher (90%) if SCC-Ag was less than 2.[103] Markovina et al have shown that SCC-Ag is a significant independent predictor of positive post-therapy FDG-PET/CT, recurrence, and death.[104]

A meta-analysis by Charakorn et al,[105] which included 61 different trials assessing either pretreatment or post-treatment SCC-Ag levels in relation the disease outcomes, found that both were associated with poorer outcomes, but the persistently elevated levels conveyed higher risk for recurrence—HR 3.14: 95% CI 1.29, 7.65 from post-treatment SCC-Ag versus HR 2.23: 95% CI 2.03, 2.45 from pretreatment SCC-Ag. The cutoff variability between high and low SCC-Ag levels was also lower for the post-treatment levels, residing between 0.9 and 3.5 and 1.5 and 2.0 ng/mL for predicting recurrence and survival, respectively, making it a useful tool to predict prognosis in clinical practice and research.

Human Papillomavirus Circulating Tumor DNA

Tumors release fragments of DNA into circulation, allowing accessible testing. It was shown that circulating HPV DNA is associated with increased FIGO stage while not being useful for detecting premalignant lesions and primary diagnosis of cervical cancer.[106,107]

However, its use in monitoring disease response and identification of patients most at risk for recurrence was shown by Han et al.[108] A prospective validation study in 70 patients with HPV+ cervical cancer showed that detectable HPV circulating tumor DNA at the end of CRT, 4 to 6 weeks post-CRT, and 3 months was associated with worse 2-year PFS (77% vs 51%, $P = .03$; 82% vs 15%, $P < .001$; and 82% vs 24%, $P < .001$). This could allow better selection of patients for treatment escalation trials.

Programmed Death Ligand 1 Expression

Immune checkpoint inhibitors such as anti-programmed cell death protein 1 antibodies have shown clinical benefit in patients with metastatic cervical

cancer, both in the first-line setting and in subsequent lines.[109-111] The combined positive score (CPS) of programmed death ligand 1 (PD-L1) is determined with immunohistochemistry as the number of positively stained cells (either tumor cells, lymphocytes, or macrophages) divided by the number of viable tumor cells multiplied by 100. It has emerged as a useful and reproducible method to predict response to checkpoint inhibition.[112] In the KEYNOTE-826 trial, a CPS 1 or greater conveyed a significant reduction in the risk of progression or death with the addition of pembrolizumab to chemotherapy with or without bevacizumab (HR 0.62 and HR 0.64, respectively, in both $P < .001$), while no benefit was seen in the CPS less than 1 group.[110]

TECHNIQUES USED FOR TREATMENT

Preinvasive Disease

Patients with CIN may be candidates for observation or treatment. CIN1-2 has a spontaneous regression rate in 1 to 3 years of more than 50%; therefore, observation may be an appropriate course. For patients with persistent dysplasia, cryotherapy has a very low complication rate and is highly successful but may be less effective than laser ablation for high-grade dysplasia. Patients with no visible lesion undergo frequent serial examinations. Cold knife conization (CKC) may be used for diagnostic and therapeutic intent, with side effects of bleeding, cellulitis, cervical stenosis, or loss of cervical competence. Loop electrosurgical excision procedure (LEEP) has become popular, although bleeding and stenosis may occur; pregnancy outcomes may be better with LEEP than with CKC.[113]

Invasive Disease

Surgical Techniques

Simple Conization

In patients with minimal invasion, no parametrial involvement, and small tumor size, simple conization with lymphadenectomy has been reported.[114] Although only 36 patients were studied, after a median follow-up of 66 months, only one pelvic nodal relapse was observed.

In more advanced disease with patients pursuing fertility preservation, neoadjuvant chemotherapy (NACT) followed by CKC can be attempted. A

prospective study by De Vincenzo et al[115] showed that of the 13 patients with initially stage IB2 to IIA1 larger than 2 cm, 11 (85%) were able to undergo CKC, 1 had stable disease and underwent radical surgery, and 1 had progressive disease and eventually died of disease. Of those undergoing CKC, four needed LEEP and one had an RH due to involved margins with SIL and invasive disease, whereas one developed distant recurrence on follow-up. Only three patients eventually tried to conceive with two succeeding spontaneously.

Radical Trachelectomy

Described in the 1960s, trachelectomy entails removal of the cervix entirely. Radical trachelectomy also removes the parametrial tissue. As a means of fertility preservation in patients with early-stage cervical cancer, trachelectomy should be combined with preoperative PET imaging to confirm no nodal involvement and with MRI to confirm no endocervical canal extension of tumor into the uterus. A laparoscopic lymphadenectomy should accompany the trachelectomy to confirm no nodal involvement. A nonabsorbable cerclage is placed around the uterine isthmus. Radical abdominal trachelectomy also may result in successful fertility preservation. Selection criteria for a trachelectomy include those patients requesting fertility-sparing surgery; age less than 40 years; stage IA1, IA2, or IB1 with no nodal involvement detected on MRI or PET scan; squamous cell or AC with a lesion less than 2 cm; no lymphovascular invasion on initial biopsy; and no upper endocervical involvement. The main site for recurrence is the central pelvis (average 5% risk), at the cervicouterine junction, or in the adjacent parametrial tissue. In a retrospective review of 29 patients with stage IB1 disease with tumor size 2 cm or greater treated with radical trachelectomy, patients with high-risk features were taken to immediate hysterectomy, and 21% required CRT. A total of nine patients (31%) were able to undergo a fertility-sparing procedure, with one recurrence at a median follow-up of 44 months.[116] If high- or intermediate-risk features are present (ie, presence of positive lymph nodes or positive margins) after a trachelectomy, radiation should be performed without requiring a completion hysterectomy. Leaving the uterus intact results in less small-bowel dose; radiation or CRT followed by image-based BT with an attenuated dose based

on the amount of residual disease in the uterus is feasible in order to minimize bladder and rectal dose.[117]

Types of Hysterectomy

Several types of hysterectomy are used in the management of carcinoma of the uterine cervix (Table 76.4).

TABLE 76.4 TYPES OF ABDOMINAL HYSTERECTOMY

	Intrafascial	Extrafascial Type I	Modified Radical Type II	Radical Type III-IV[a]
Cervical fascia	Partially removed	Completely removed	_____	_____
Vaginal cuff removal	None	Small rim removed	Proximal 1-2 cm removed	Upper one-third to one-half removed
Bladder	Partially mobilized	_____	_____	Mobilized
Rectum	Not mobilized	Rectovaginal septum partially mobilized	_____	Mobilized
Ureters	Not mobilized	_____	Unroofed in the ureteral tunnel	Completely dissected to the bladder entry
Cardinal ligaments	Resected medial to the ureters	_____	Resected at level of the ureter	Resected at the pelvic sidewall
Uterosacral ligaments	Resected at level of the cervix	_____	Partially resected	Resected at postpelvic insertion
Uterus	Removed	_____	_____	_____
Cervix	Partially removed	Completely removed	_____	_____

[a]Type IV, extended radical hysterectomy (partial removal of the bladder and/or ureter), in addition to type III.

Note: Line indicates that the procedure from the prior column moves forward into the next column(s) to the right.

Total (extrafascial) abdominal hysterectomy (class I) consists of removal of the cervix and adjacent tissues, as well as a small cuff of the upper vagina in a plane outside the pubocervical fascia. There is minimal disturbance of the

ureters and the trigone of the bladder. This may be the surgical treatment of choice for stage IA1 cervical cancer.

The use of an RH for cervical cancer was first described by Wertheim in 1912. In a modified radical extended hysterectomy (class II), the cervix and upper vagina are removed, including paracervical tissues, and the ureters are dissected in the paracervical tunnel to their point of entry into the bladder. Because the ureters are unsheathed and retracted laterally, parametrial and paracervical tissue can be safely removed medial to the ureter. This operation is performed with a lymphadenectomy. This is the most common surgical approach selected for stage IA2 cervical cancer.

Radical abdominal hysterectomy (class III) with bilateral pelvic lymphadenectomy consists of a wider resection of the parametrial tissues to the pelvic wall, with dissection of the ureters and mobilization of the bladder, as well as of the rectum to allow for more extensive removal of tissues. This approach was described by Meigs in 1944. In addition, a vaginal cuff of at least 2 to 3 cm is always included in the procedure, as well as the uterosacral ligaments. A bilateral pelvic lymphadenectomy is usually carried out. This operation is often referred to as the Wertheim or Meigs procedure. The extended RH (class IV) includes complete dissection of the ureter from the vesicouterine ligament, sacrifice of the superior vesicle artery, and removal of the upper three-fourths of the vagina. Because of the high rate of fistula and significant morbidity, it is rarely used. In 2007, after a consensus conference in Japan, a new classification system was released based only on the lateral extent of the resection.[118] Four levels of hysterectomy are described (A-D) and four levels of lymphadenectomy (1-4). The levels of lymph node dissection include the internal and external iliac (level 1), common iliac and presacral (level 2), aortic intramesenteric (level 3), and aortic infrarenal (level 4). The levels of primary tumor resection include the following:

Type A: Extrafascial hysterectomy, with minimum resection of the paracervix medial to the ureter and minimal vaginal resection less than 1 cm, without removal of the paracolpos

Type B: Modified RH with partial resection of the vesicouterine and uterosacral ligaments, unroofing of the ureter, transection of the parametrial tissue at the ureter, and removal of at least 1 cm of the vagina. This type is divided into B1, without removal of paracervical lymph nodes, and B2, with removal of lateral paracervical nodes.

Type C: Classic RH, variant in which the entire uterosacral and vesicouterine ligaments are removed, 1.5 to 2 cm of the vagina with paracolpos is excised, and neuronal preservation is critical

Type D: Includes the complete RH and resects tissues to the pelvis sidewall, including the hypogastric (internal iliac) vessels, and exposes the sciatic nerve (type D1). Type D2 also removes the fascial and lateral muscles, called the laterally extended endopelvic resection.

Open Abdominal Versus Minimally Invasive Approach

Historically, the standard approach for hysterectomy was open abdominal for cervical cancer. As pelvic laparoscopic surgery, with or without robotic techniques, became more prevalent, retrospective reports, prospective observational, and multicentered matched cohort studies reported comparable outcomes with the open approach.[119-121] However, the LACC trial, published by Ramirez et al,[122] which was a phase III noninferiority trial between open and minimally invasive approaches in 631 patients with early cervical cancer, showed significantly lower rates of 3-year DFS and OS (91.2% vs 97.1% and 93.8% vs 99.0%). Additional epidemiologic studies support this finding of better survival with the open approach.[123] Thus, even though minimally invasive approaches have known surgical morbidity benefits, such as reduced blood loss, shorter hospital stay, and less febrile morbidity,[119] the open abdominal approach remained the standard of care.

Pelvic Exenteration

Pelvic exenteration has been used for en masse removal of the pelvic viscera for recurrent carcinoma of the cervix. Modern RT with concurrent chemotherapy results in high complete response (CR) rates and has made residual extensive disease a rare indication for exenteration. Patients with adjacent organ invasion are given a course of primary concurrent CRT, followed by interstitial BT, with exenteration reserved for salvage.

This operation, which is not done as a palliative procedure, consists of an RH, pelvic lymph node dissection (PLND), and removal of the bladder (anterior exenteration), removal of the rectosigmoid colon (posterior exenteration), or both (total exenteration). The ileum or sigmoid has been the usual means of achieving urinary diversion. Because some patients have a pelvic recurrence after RT, the bowel is used for the urinary conduit. Proof

that there is no fixation to the pelvic wall and no extension of disease beyond the pelvis is mandatory. Metastases outside the pelvis, including those in PANs or any viscera, are absolute contraindications to the procedure. Bilateral ureteral obstruction secondary to tumor is also a relative contraindication. Patients with sacroiliac or hip pain or leg edema rarely benefit from this procedure and should be excluded on a clinical basis.

Chiantera et al[124] published a European multicenter series of 167 patients who underwent pelvic exenteration for cervical cancer from 1998 to 2011, 93 (56%) of 167 after primary or adjuvant pelvic RT, with or without chemotherapy. With a median follow-up of 68 months, the entire group's 5-year OS was 38%. Positive margins, positive lymph nodes, sidewall involvement, persistent and recurrent disease, and shorter interval from primary treatment were associated with poorer survival. Surgical complications resulted in death in 10 (6%) of 167 patients. As significant mortality and morbidity are associated with this procedure, it precludes its use as palliative therapy. Urinary diversion, either by nephrostomy or by ileal bladder, may be of palliative value in patients with either recurrent carcinoma in the pelvis or complications.

Pretreatment Surgical Nodal Assessment

Exploratory laparotomy and nodal staging to evaluate the presence of metastases to the pelvic or PAN may provide diagnostic information but have not had a demonstrated impact on survival.[125] A number of studies compared the significance of PAN metastases with other clinical and surgical findings with regard to PFS and OS. In 626 patients treated on GOG randomized studies, the RR associated with positive PAN was 11.0 for time to recurrence and 6.2 for survival time.[126] In addition to the significant increase in risk of regional relapses, patients with PAN metastasis are more likely to have extrapelvic failure.

Cosin et al[127] reviewed 266 patients with locally advanced cervical carcinoma who underwent extraperitoneal pelvic and para-aortic lymphadenectomy before RT. Patients were divided into four groups: Group A had negative lymph nodes; group B had resected, microscopic lymph node metastases; group C had macroscopically positive lymph nodes that were resectable at the time of surgery; and group D had unresectable lymph nodes. Lymph node metastases were detected in 50% of patients. All patients

received pelvic external beam radiation therapy (EBRT) (pre–intensity-modulated radiation therapy [IMRT] era) and BT; patients with lymph node metastases received extended-field irradiation. Five- and 10-year DFS rates were similar for all patients in groups B and C. All patients in group D recurred. There was a 10.5% incidence of severe radiation-related morbidity and a 1.1% incidence of treatment-related deaths.

The potential benefit of surgical nodal debulking followed by irradiation has been studied. Potish et al[128] noted that more than half of the patients with advanced cervical cancer with grossly positive pelvic nodes were debulked survived, compared with none with unresectable lymph nodes; however, this predated the ability to implement dose escalation with IMRT to the involved nodes. Nonetheless, surgical debulking of nodes decreases the dose of radiation required to these regions. The use of high-energy photon beams and limitation of the tumor dose to extended volumes in the para-aortic region for those with completely resected but positive nodes to 45 to 50 Gy decrease the probability of complications. IMRT also enhances the sparing of adjacent abdominal normal tissues. However, if node dissection is not feasible or would result in a treatment delay, patients may successfully be managed with IMRT with dose escalation to approximately 60 to 65 Gy to the grossly enlarged lymph nodes.[129,130]

Complication risk for surgical para-aortic assessment is high, particularly when patients are treated with postresection RT. Transperitoneal lymphadenectomy should be avoided.

Because of a high rate of complications, preirradiation laparotomy was discontinued in most cases. The status of the lymph nodes can be investigated with lymphangiography or PET-CT and verified when needed with percutaneous transabdominal needle biopsy. It is important though to remember that the false-negative rate of PET-CT can still be substantial. In one study, 125 patients had a PET-CT followed by para-aortic lymphadenectomy.[131] Seventeen percent had positive PAN metastases, 66% of whom had a negative PET-CT. The sensitivity and specificity of PET-CT were 33% and 94%, respectively. Morbidity of the surgery was 7%, and there was no delay in initiating CRT. Alternatively, PAN sampling may be performed through a laparoscopic approach; the procedure is well tolerated, recovery is prompt, and yield is adequate.[132]

Aside from PAN, supraclavicular metastases may rarely be involved. However, there is no indication for routine removal of the clinically negative supraclavicular nodes.

Sentinel Lymph Node Biopsy

Sentinel lymph node (SLN) studies show mixed results, with a 20% false-negative rate and a 50% incidence of other pelvic metastases.[133] However, the method allows for aborting surgery and pursuing RT instead. A seven-center prospective study analyzed 139 patients and detected 454 SLNs. Intraoperative examination did not detect micrometastasis or isolated tumor cells. Other techniques, such as molecular assays, may improve SLN assessment in the future.[134] The SENTICOL study[135] injected 145 patients with stage IA1 to IB1 cervical cancer with combined technetium-99 and patent blue. The sensitivity (92%) and lack of false-negative results were favorable, but SLN biopsy was reliable only when SLNs were detected bilaterally.

In the SENTICOL-2 trial,[136] 206 patients with early cervical cancer were randomized to SLN resection only versus SLN and PLND. Lymphatic morbidity and neurologic symptoms were significantly lower in the SLN-only arm (31.4% vs 51.5% and 7.8 vs 20.6%), but that difference became less evident after 6-month follow-up and was not significant regarding severe lymphedema. There were no false negatives found in the SLN+PLND group, and 3-year DFS was not statistically significant (92% in SLN-only vs 94.4% in the SLN+PLND group). The SENTICOL-3 trial is currently underway to further validate no difference in survival outcomes.

Ovarian Transposition

In premenopausal women, surgery and radiation may directly impact gonadal function. For women with early-stage cervical cancer who undergo an RH, ovarian function may be preserved. In patients who require postoperative radiation, transposition of ovarian tissue outside the radiation field may help preserve ovarian function, although even low doses to the ovaries may cause acute ovarian failure (Figure 76.9). In women who require radical radiation to the uterus and ovarian tissue, counseling before treatment begins with a fertility expert in reproductive endocrinology may be of benefit if an intervention such as egg retrieval is desired. Care must be taken to ensure that any potential intervention does not delay the initiation of curative treatment.

In addition, women with early-stage cervical cancer have an approximately 1% risk of ovarian metastasis. A retrospective report of 3,165 women under 50 who underwent hysterectomy with oophorectomy for early cervical cancer identified several independent risk factors for ovarian metastases—AC histology, lymphovascular space invasion (LVSI), and involvement of either the parametria, uterine corpus, or regional lymph nodes. Without any or just with AC, the risk for ovarian metastasis is 0.14% or 0.17%, respectively.[137] A combination of these risk factors can increase the risk up to 16.7%. Therefore, women should be carefully considered for ovarian preservation and counseled on its potential risks.

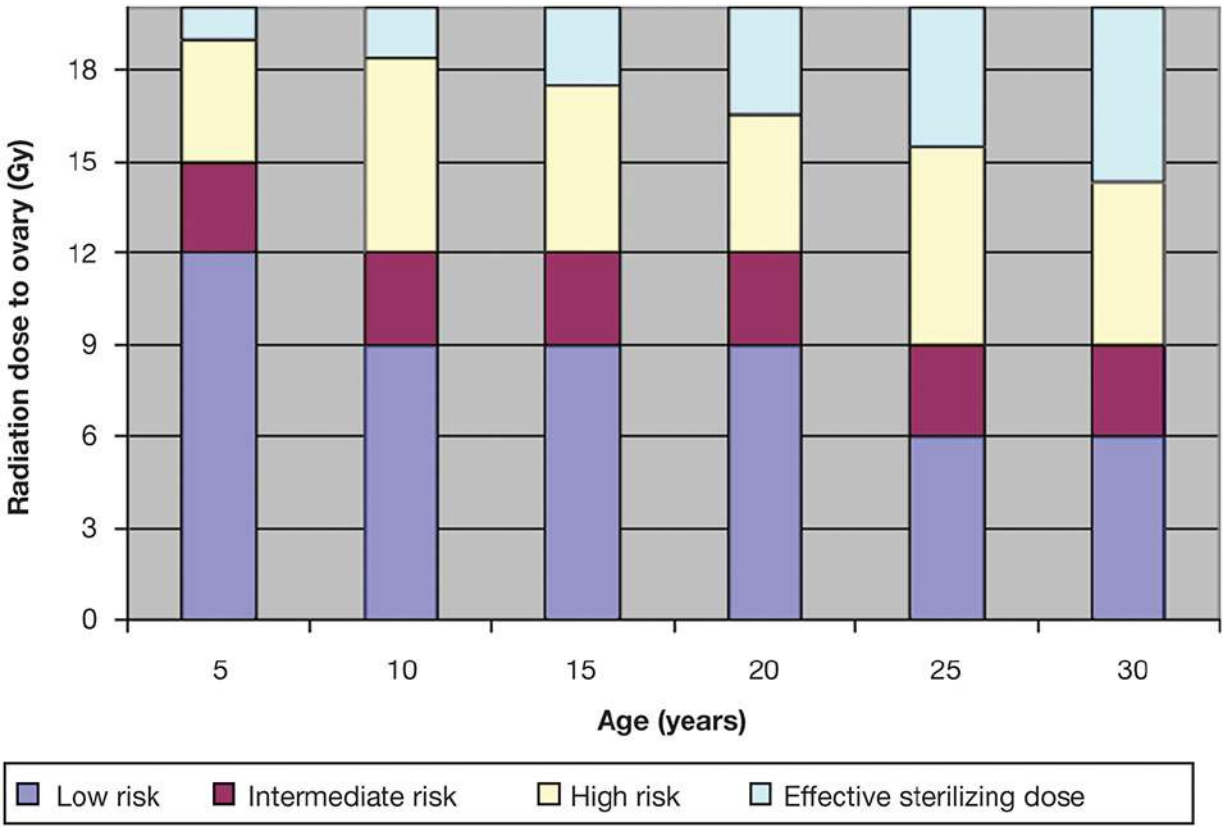


FIGURE 76.9 Risk of developing acute ovarian failure, defined as ovarian failure within 5 years, stratified by age and radiation dose to the ovary. (Reprinted from Wo JY, Viswanathan AN. Impact of radiotherapy on fertility, pregnancy, and neonatal outcomes in female cancer patients. *Int J Radiat Oncol Biol Phys.* 2009;73[5]:1304-1312. Copyright © 2009 Elsevier. With permission.)

The success rate of ovarian function preservation with ovarian transposition is affected by the treatment modalities used. A meta-analysis of 29 different

reports including 1,160 patients showed that for patients undergoing surgery alone or surgery with BT, the ovarian function was preserved in 91% and 93%, respectively. For patients treated with EBRT with or without BT and/or surgery, it was preserved in only 61%.[138] It is important to mention that the success rate was shown to diminish with follow-up period and that younger age was the most predictive factor for ovarian function preservation.

Newer techniques of radiation, such as IMRT or proton therapy, offer better ways to preserve ovarian function by lowering the dose to the transposed ovaries. Yin et al[139] reported a retrospective study of 105 patients with early cervical cancer who underwent RH and ovarian transposition before pelvic irradiation with IMRT and dose constraints on the ovary as low as possible. Ovarian function was determined 1 year after radiation with sex hormonal levels and menopausal symptoms. Ovarian function was preserved in 41 (39%) patients. The optimal cutoff for dose constraints was $V_{5.5}$ less than 29.65%.

Radiation Therapy Techniques

Since the early 1900s, radiation has been used in the curative management of cervical cancer, with a combination of external beam and BT resulting in the highest survival rates. Over the ensuing 100 years, treatment planning techniques have evolved, as has the equipment used for treatment. Several methods have been developed to aid with conformality and normal tissue sparing. External irradiation is used to treat the whole pelvis. Structures treated include the uterus and cervix or, in the postoperative cases, the tumor bed, the vagina, the parametrial tissue, and the pelvic lymph nodes, including the internal, external, and common iliac nodes. In selected cases, the PANs may be treated. In patients with locally advanced disease, in addition to external beam radiation, treatment of central disease (cervix, vagina, and medial parametria) relies heavily on dose given with intracavitary sources through BT. The techniques described apply, with some individualization, to most patients with locally advanced cervical carcinoma.

External Beam Irradiation

External beam treatments may be routinely administered to patients with cervical cancer with stages IB2 to IVA in a curative manner. Patients with stages IA to IB1 may be considered for external beam treatment if they are

deemed inoperable or prefer to avoid surgery. Patients with stage IVB disease may receive palliative radiation to the pelvis for selected indications, such as to stop vaginal bleeding, relieve pain, or alleviate urethral obstruction from extrinsic compression. External beam radiation covers the primary cervical tumor; treats any adjacent parametrial or uterosacral, uterine, or vaginal extension; and, most important, addresses microscopic disease present in pelvic lymph nodes. In treatment of invasive carcinoma of the uterine cervix, it is important to deliver adequate doses of irradiation not only to the primary tumor but also to the pelvic lymph nodes to maximize tumor control.

The initiation of external beam radiation typically precedes BT. Although BT may be interdigitated with external beam treatment, based on the desire to minimize the duration of treatment, the BT dose to the normal tissues may be better optimized after maximal tumor shrinkage; therefore, many institutions prefer to wait until the completion of 45-Gy treatment before initiating BT, particularly for patients with large tumors.

Patient Positioning

Patients may be positioned in either the supine position for stability or the prone position on a belly board. The prone position aids in shifting the small bowel out of the pelvis. In patients who have had a hysterectomy, the small bowel may drop into the pelvic area. For those patients treated for cervical cancer with an intact cervix, the small bowel often lies superior to the uterus and above the pelvic brim, creating less need to shift the bowel out of the pelvis. For patients receiving IMRT, because of stability of the pelvis, the supine position is typically preferred with immobilization devices surrounding the pelvis to ensure minimal motion during treatment. IV contrast may be helpful to localize the pelvic vessels for contouring but is not routinely used in most centers. Oral contrast delineates the small bowel. Rectal contrast and placement of a Foley catheter for bladder contrast are not considered necessary in with CT simulation because the outer wall of these normal tissue structures can be contoured without contrast on CT.

Plain X-Ray Simulation

If CT is not available, simple plain film simulation may be performed. The standard plain radiographic simulation to the pelvis with x-rays, typically using opposed anterior-posterior/ posterior-anterior (AP-PA) fields, results in

comprehensive coverage of all pelvic regions. Because of the lack of visible soft tissue detail, contrast may be placed using barium in the rectum, a vaginal tube in the vagina, and/or a wire marker over surgical scars. The superior border is set at the L4 to L5 interspace in order to cover the common iliac lymph nodes and the lateral borders 1.5 to 2 cm from the pelvic brim, and the inferior border covers at least the obturator foramen (Figure 76.10). More commonly in patients with large tumors, the inferior border extends to the ischial tuberosities. When there is vaginal involvement, the entire length of this organ should be treated down to the introitus. It is very important to identify the distal extension of the tumor at the time of simulation by placing a radiopaque clip or bead on the vaginal wall or inserting a small fiducial marker into the vagina. When the tumor involves the distal half of the vagina, the portals should be modified to cover the inguinal lymph nodes because of the increased probability of metastases (Figure 76.11).

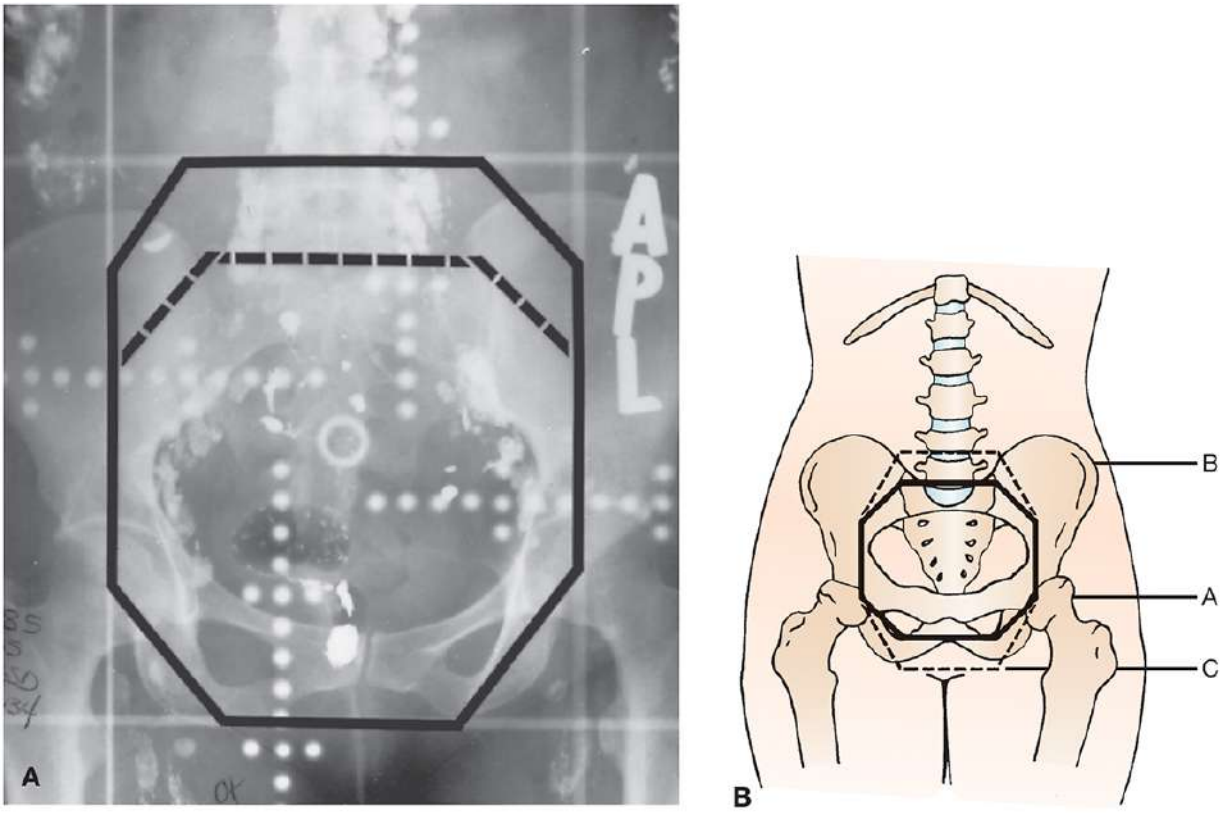


FIGURE 76.10 A. Anteroposterior simulation film of the pelvis illustrating portals used for external irradiation. The 15 by 15 cm portals at source-to-skin distance are used for stage IB (broken line), and 18 by 15 cm portals are used for more advanced disease (solid line). This allows better coverage of the common iliac lymph nodes. The distal margin is usually placed at the bottom of the obturator foramina. B. Diagram of pelvic portals used in external irradiation of carcinoma of uterine cervix. Standard portal for stage IB tumors is outlined (solid line indicated as A). When the common iliac nodes are to be covered, the upper margin is extended to the L4 to L5 space (indicated in section B). If there is vaginal tumor extension, the lower margin of the field is drawn at the introitus (indicated in section C).

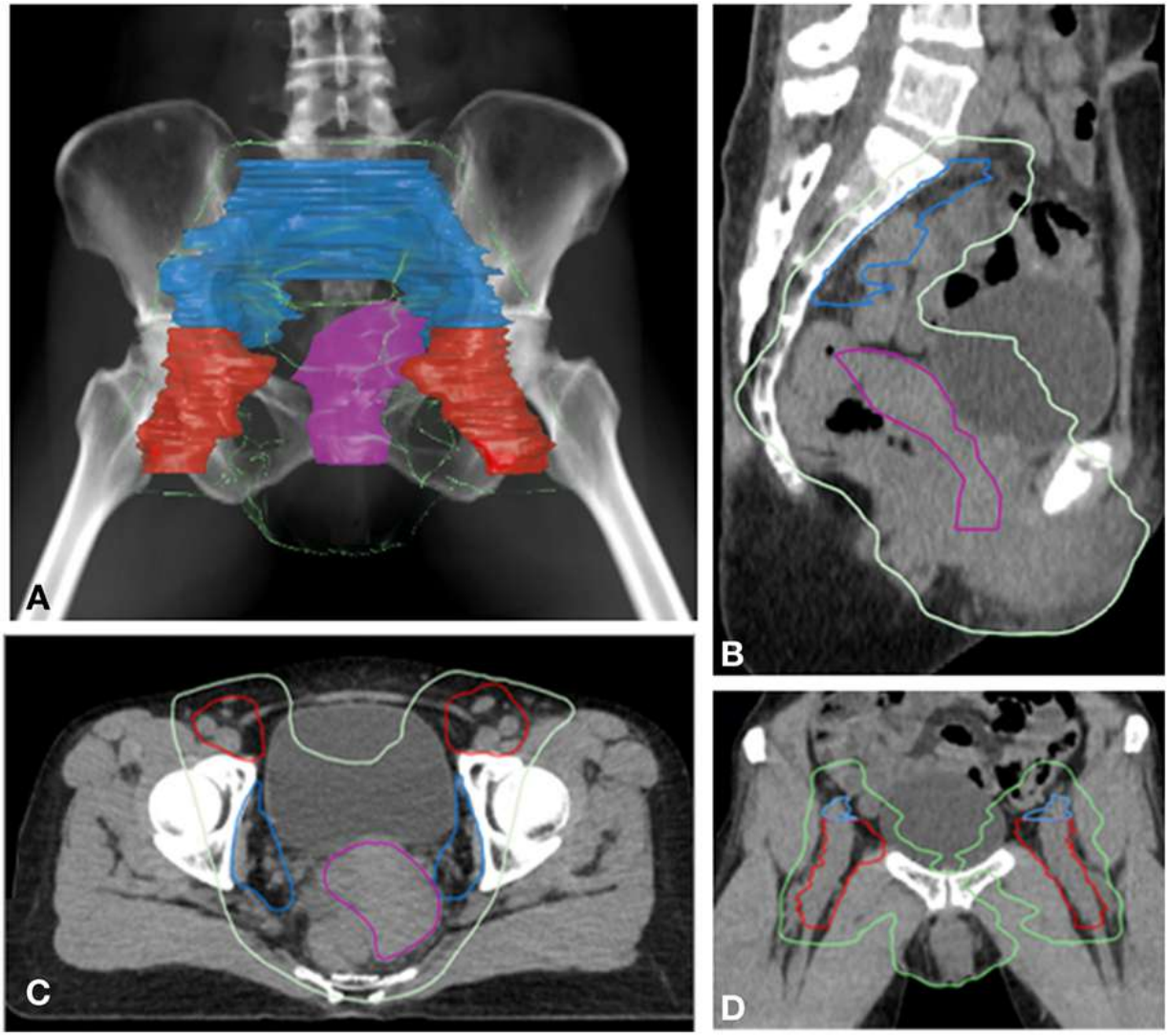


FIGURE 76.11 Pelvic (blue) and inguinal (red) lymph nodes contoured on a computed tomography scan in a patient with cervical carcinoma involving the distal vagina (purple), requiring inguinal node coverage with the 42.75 Gy (95% of elective dose). Isodose line (green). Displayed are a three-dimensional reconstruction (A), a mid-pelvic sagittal (B), axial (C), and mid-inguinal coronal (D) sections.

For the lateral field borders, in both postoperative and intact cervix settings, the posterior border must be set in such a way that the entire sacrum is covered because the uterosacral ligaments are at high risk for harboring microscopic extension. The uterosacral ligaments insert onto the sacrum, and therefore, the posterior block should ensure coverage of the entire sacrum. The anterior border on the lateral field should be set at a vertical line anterior to the pubic symphysis, because the external iliac lymph nodes must be covered.

For patients with PAN involvement, simple plain film simulation followed by AP-PA treatments to the PAN chain may overdose the kidneys, spinal cord, and small bowel. Dose escalation to para-aortic region to greater than 45 Gy is not feasible with AP-PA fields, given potential bowel complications. The use of four fields, including AP-PA and two lateral fields, is implemented as an alternative to AP-PA alone as a way to reduce some of the dose to the anterior small bowel. Patients receive oral barium approximately 30 minutes before the simulation to ensure blockage of as much small bowel as feasible superiorly. The superior border covers the renal hilum, often at the T12-L1 interspace, and the inferior borders cover the obturator foramen, unless there is distal vaginal or inguinal node involvement. For the para-aortic portion of the field, the anterior border rests 2 cm in front of the vertebral body or enlarged nodes as contoured, and posteriorly, the border bisects the mid-vertebral body. The pelvic portion mimics that described for the four-field pelvic setup. The use of lateral fields allows a decrease in dose to the small bowel, but care must be taken to include all structures of interest.

Three-Dimensional Conformal Treatment Planning

CT simulation allows direct assessment of the pelvic vessels and by adjacent location the para-aortic nodes (PANs) and pelvic nodes. Oral contrast is beneficial to identify the small bowel. Cerrobend customized blocks or multileaf collimator blocking is used on each field to block the radiation to selected areas, including the skin, muscle, soft tissue, anterior small bowel, and portions of the anus and lower rectum (Figure 76.12).

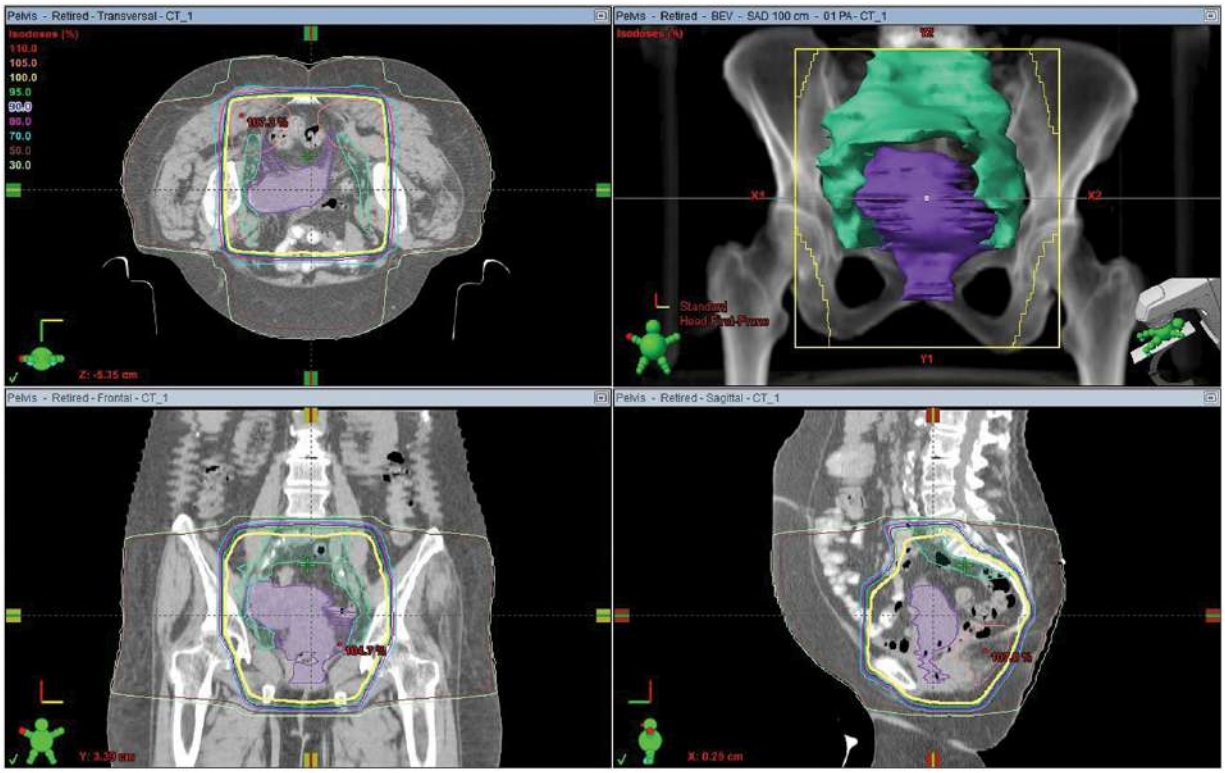


FIGURE 76.12 Anterior-posterior and lateral (4-Field) digitally reconstructed radiograph simulation film of the pelvis illustrating portals used for external irradiation with the patient in the prone position on a belly board to minimize small-bowel dose. Pelvic lymph nodes are indicated in their approximate position. The uterus, cervix, and vagina are contoured to ensure adequate coverage.

The superior border is set based on the CT-visualized bifurcation of the common iliac nodes into the external and internal iliac nodes, which may lie as high as the L3-L4 interspace. If patients have positive pelvic nodes based on PET imaging, the superior border may be shifted to either the superior border of the common iliac nodes or the superior aspect of the renal hilum to treat the PAN. In postoperative cases in which the patient has had an extensive surgical staging, the superior border may be reduced to the L5-S1 interspace. Similar to plain x-ray simulation, in patients with vaginal involvement, the inferior border is extended to cover 2 cm below the lowest extent of disease, which may lie in the vulvar tissue, and in such cases, the inguinal lymph nodes are treated, resulting in a wider AP field.

On the lateral fields, the anterior border covers the front of the pubic symphysis. Bonin et al,[140] in a review of 22 patients on whom detailed anatomic mapping of the anatomy of the pelvic lymph nodes was carried out by lymphangiography, concluded that if the criteria for adequacy of standard

pelvic fields as defined in prior clinical trials were applied (AP: 1.5-cm margin on the pelvic rim; lateral field anterior edge is a vertical line anterior to the pubic symphysis and posterior border), 10 (45%) patients would have had inadequate nodal coverage in the irradiation fields. The incompletely irradiated lymph nodes were in the lowest lateral external iliac group. However, CT simulation with contouring may prevent omission of these nodes.

For the lateral borders in postoperative and intact cervix cases, posterior coverage of the entire sacral hollow is imperative. Zunino et al[141] reviewed the appropriateness of RT box technique for cancer of the cervix in 35 sagittal MRIs and 10 lymphangiograms. If the posterior border were to be placed at the S2-S3 interspace, for 50% of the patients with FIGO IB and in 67% with stage IIA disease, the posterior border of the lateral field would not adequately encompass the planning target volume (PTV). In stage IIB, the posterior border was inadequate in eight patients (42%). In patients with stage IIB and IVA diseases, the PTV was not encompassed. Furthermore, Knocke et al[142] used standard simulator planning guided by bony landmarks for pelvic irradiation in 20 patients with primary cervical carcinoma, stages I to III, using a four-field box technique. After defining the PTV with a 3D planning system, they compared the field configuration of the simulator planning with a second one based on the defined PTV. They evaluated the ability of the PTV to encompass the treatment volume (International Commission on Radiation Units and Measurements [ICRU]). Planning by simulation resulted in 1 geographic miss, and in 10 more cases, the coverage of the PTV by the treatment volume was inadequate.

Finlay et al[143] contoured pelvic blood vessels on CT scans as surrogates for lymph nodes in 43 patients and found this to be more accurate than bony landmarks for field delineation. In total, 95% of patients planned with conventional fields had inadequate coverage of some portion of lymph node coverage, whereas 56% additional normal tissue was treated that did not require radiation. Therefore, most centers implement 3D simulation when feasible. Taylor et al[331] used MRI to outline the pelvic lymph nodes in 20 patients and noted that with margins of 10 mm, nodal coverage was 94% and with 15 mm, 99%; with a modified 7-mm margin, they ensured 99% nodal coverage with less volume of small bowel at risk.

In the postoperative setting, van den Berg et al,[144] using 47 lymphangiograms and 15 CT scans, asked radiation oncologists (n = 17) to define the CTV and PTV and to delineate on simulation films the RT treatment portals to be used after an RH with lymph node dissection for stage IB or IIA cervical carcinoma with positive iliac lymph nodes. Large variations were observed in the portals used and in treatment techniques. From the digitized films, it appeared that in 50% of the cases, the defined PTV was not covered adequately. Furthermore, 71% of the treatment plans would not cover the lateral borders of the reference PTV sufficiently. Thus, there is a need for careful adherence to standardized guidelines.

Treatment techniques may have an effect on outcome. Yamazaki et al[145] compared 34 patients with cervical cancer treated with irregularly shaped four-field whole-pelvis RT using CT simulation and 40 patients receiving whole-pelvis EBRT with parallel-opposed fields in a nonrandomized study of postoperative RT consisting of 50 Gy in 25 fractions in 6 weeks. With a mean follow-up of 60 months, the actuarial 5-year pelvic tumor control was 94% with the two-field technique and 100% for the irregularly shaped four-field technique. The incidence of grade 2 or 3 bowel complications in the irregularly shaped technique group (2.9%, 1/34) was significantly lower than that in the two-field technique group (17.5%, 7/40; $P < .05$).

Intensity-Modulated Radiation

IMRT was developed using the techniques required for inverse planning. That is, one starts with the necessary dose around the target and then works backward to develop the requisite beam intensities. IMRT spatially modulates the intensity of the beam using the motion of multileaf collimators. This allows high conformality with the target volume, while reducing the volume of normal tissue exposed to the full dose of radiation. However, it mandates a growing emphasis on imaging the pelvic anatomic structures, for both treatment planning and delivery, what is generally termed *image-guided radiation therapy* (IGRT). It is increasingly challenging to employ different imaging modalities for target volume selection as uncertainties in the definition of target volumes arise using conformal techniques. In addition, what constitutes adequate margins in different settings continues to be a matter of concern, given significant pelvic organ motion during treatment. Nevertheless, the use of IMRT has been standardized in the postoperative

setting and is more frequently used for intact cervix cases. The PARCER trial was a randomized controlled trial of IMRT versus 3D conformal adjuvant pelvic radiation in 300 patients with cervical cancer posthysterectomy.[146] It showed reduced late GI toxicity with IMRT while 3-year DFS was not significantly different (76.9% vs 81.1%, $P = .89$). In the intact cervix setting, no large-scale randomized trial comparing IMRT to 3D conformal RT was performed. A meta-analysis of six reports of a total of 1,008 patients undergoing primary CRT (only 88 of them prospectively randomized) showed no difference in OS and PFS but significantly reduced acute and chronic toxicities with IMRT.[147] In the EMBRACE registry, which accrued a cohort of 1,416 patients with locally advanced cervical cancer treated with primary CRT in multiple international centers, 40% were treated with IMRT for the EBRT part of treatment, determined by local availability. They published that IMRT use reduced the median V_{43} Gy by around 500 mL.[148] Thus, the ASTRO guidelines for the treatment of cervical cancer also strongly recommend the use of IMRT in the postoperative setting, and in the definitive setting, it recommends on the condition that IGRT is available to ensure adequate coverage of the target volumes throughout treatment.[149]

Bladder filling and rectal filling changes require accurate definition of margins for the PTV. Several reports have shown cervix motion can be up to 18 to 21 mm in all directions and that even a uniform CTV planning treatment volume margin of 15 mm would not encompass the cervical CTV in 32% of fractions.[150,151] With IMRT, there might be a need for adaptive replanning given rapid tumor regression that makes the pelvis less fixed, thus increasing internal organ motion, though the frequency for such imaging has not been clearly defined, and wide margins (≥2 cm) are indicated on the cervix in order to adequately account for organ motion. Larger margins of up to 2 to 3 cm in the AP direction and bladder volumes at 150 to 300 mL are recommended.[152]

After a CT and/or MRI scan for simulation, the images are brought into a treatment planning workstation. Contouring the gross tumor volume (GTV) on MRI may include the uterus, cervix, and/or vagina. Lim et al had 19 experts in gynecologic radiation oncology contour for a case of locally advanced cervical cancer on axial MRI of the pelvis. The sensitivity and specificity values as per Substantial Simultaneous Truth and Performance Level Estimation (STAPLE) agreement were seen for GTV delineation (0.84 and 0.96, respectively), with a kappa statistic of 0.68 ($P < .0001$). Agreement

for delineation of the cervix, uterus, vagina, and parametria was moderate. The greatest variability in physician contouring was in the parametrial tissue.[153]

The CTV for the pelvic lymph nodes was based on the Radiation Therapy Oncology Group (RTOG) atlas for the female postoperative pelvis.[154] Fiducial markers may be placed in the apex of the vagina for identification on CT scan and show up to 3.5 cm of vaginal cuff motion during treatment.[155] Therefore, for postoperative patients, the vagina is contoured using a full bladder CT scan fused to an empty bladder CT scan to account for vaginal mobility because of differences in bladder filling. This vaginal target volume has been referred to as an integrated target volume (ITV). The expansion of the CTV and/or ITV to the PTV is necessary, although, given the movement of the pelvic organ, the exact amount of margin is a matter of debate. When targeting an intact cervix, generous margins of approximately 2 to 3 cm are considered, particularly in the regions of the uterus and cervix. An example of dose distribution achieved with IMRT pelvic irradiation is illustrated in Figure 76.13. In order to cover the uterosacral ligaments, the rectum cannot be spared. Rectal filling with gas may change the position of the anterior rectal wall over 5 cm during treatment. Dose constraints required for an optimal IMRT plan have not been standardized. In the RTOG postoperative clinical trial 0921 using IMRT,[156] a PTV of 7 mm around the nodal contours is recommended, and the dose is prescribed to cover 97% of the vaginal PTV and nodal PTV. A volume of 0.03 mL within any PTV should not receive more than 110% of the prescribed dose. No more than 0.03 mL of any PTV will receive less than 93% of its prescribed dose. Any contiguous volume of 0.03 mL or larger of the tissue outside the vaginal/nodal PTVs must not receive more than 110% of the dose prescribed to the vaginal/nodal PTV; for normal tissues, the small/large bowel (30% of the entire bowel volume must not receive .40 Gy), rectum/sigmoid (60% of the rectosigmoid volume must receive ≤40 Gy), bladder (35% of the bladder volume must receive ≤45 Gy), and femoral head (15% of the femoral head volume must receive <35 Gy) constraints are being tested in RTOG 0921. Careful attention must be paid to all normal tissue organ motion because the bladder and rectum may have 3- to 5-cm shifts because of filling changes in a short time frame.

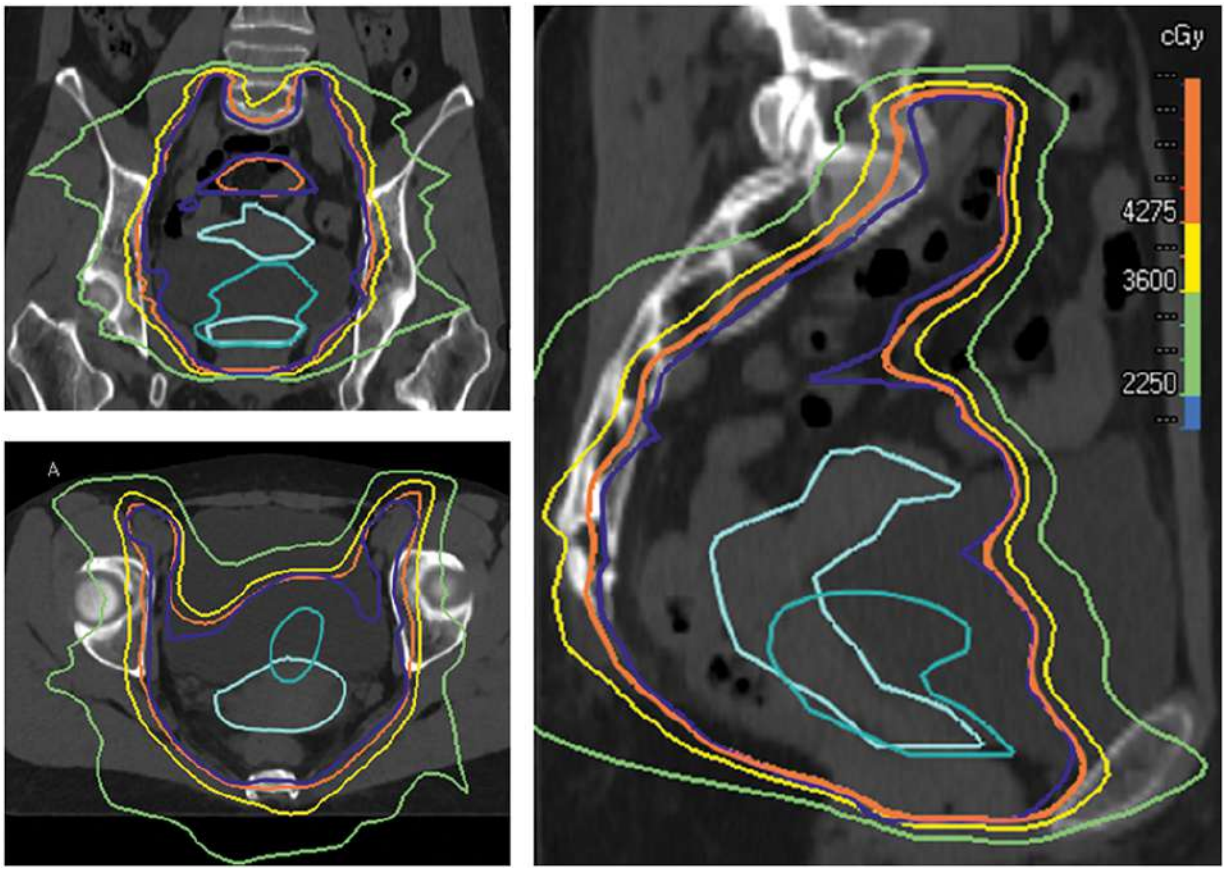
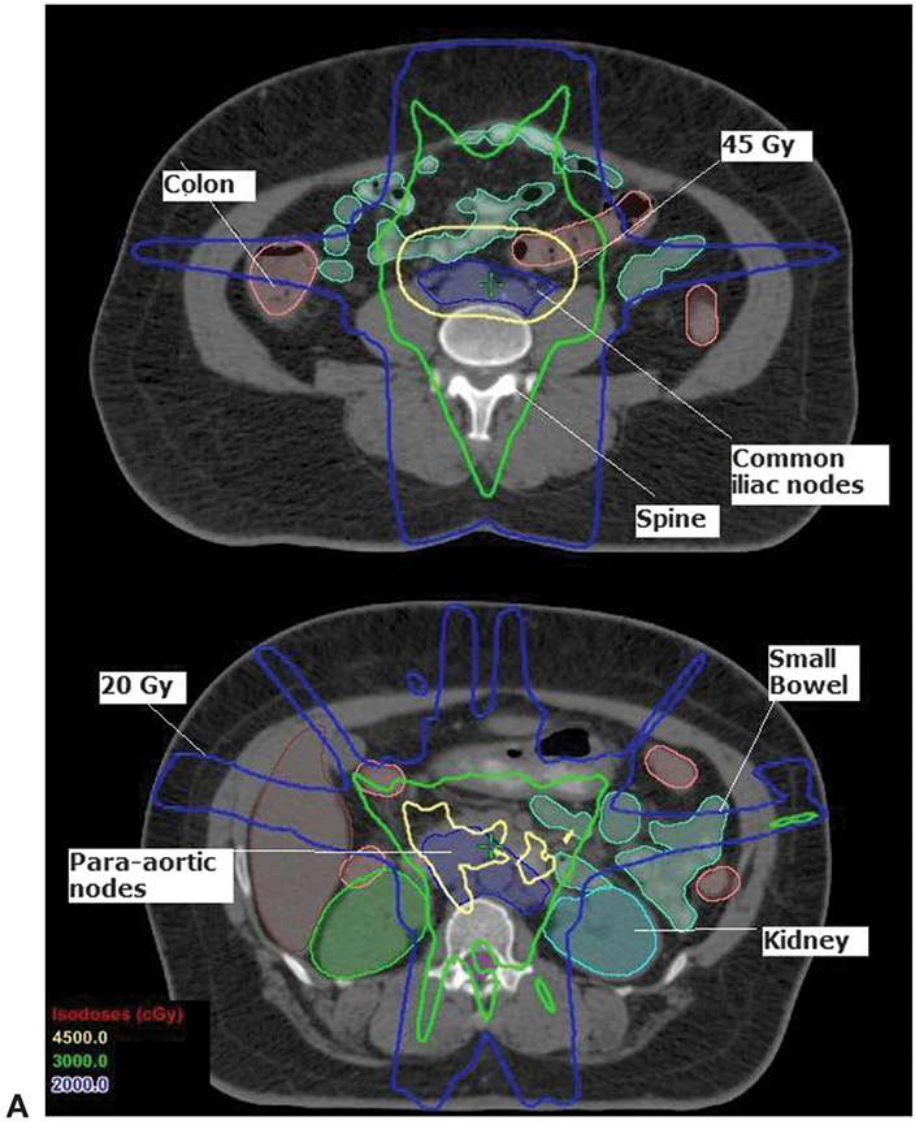


FIGURE 76.13 Intensity-modulated radiation therapy treatment plan for external irradiation of an intact cervix. The uterine motion is taken into account by contouring it with a full and empty bladder (light and dark teal) and using image guidance when delivering the dose.

For patients who have had a diagnostic PET or MRI before the simulation, these images may be registered to create a fused data set for contouring, particularly when a nodal boost is required. This allows the physician to visualize areas of PET enhancement or tumor volume, as seen on the MRI, onto the simulation films. Some recommend to use a PET-defined target volume contoured with a metabolically active tumor specified at the 40% threshold. Normal tissue structures, including the rectum, sigmoid, bladder, and small bowel, are routinely contoured for patients treated with IMRT who will be undergoing a nodal boost in order to limit the dose received primarily to the small bowel. Based on an overview of published data, the absolute volume of small bowel receiving 15 Gy or greater should be held to less than 120 mL, when possible, to minimize severe acute toxicity if delineating the contours of bowel loops themselves. Alternatively, if the entire volume of peritoneal space in which the small bowel can move is delineated, the volume

receiving greater than 45 Gy should be less than 195 mL as a starting point, though this is often not possible.[157] For the rectum, dose-volume constraints selected as a conservative starting point that have not yet been validated for 3D treatment planning include V_{50} less than 50%, V_{60} less than 35%, V_{65} less than 25%, V_{70} less than 20%, and V_{75} less than 15%.[158] No dose constraint for external beam planning for the bladder could be identified, although the limits for prostate cancer may be adopted for gynecologic IMRT, including a dose constraint of no more than 15% of the volume to receive a dose greater than 80 Gy, no more than 25% of the volume to receive a dose greater than 75 Gy, no more than 35% of the volume to receive a dose greater than 70 Gy, or no more than 50% of the volume to receive a dose greater than 65 Gy.[159]

Imaging may guide more accurate definition of lymph nodes. Portelance et al[160] carried out IMRT as well as conventional planning with two- and four-field techniques in 10 patients. Prescription was 45 Gy in 25 fractions to the uterus and the pelvic and PANs. All IMRT plans were normalized to obtain a full coverage of the cervix with the 95% isodose curve (Figure 76.14A). The volumes of the small bowel receiving the prescribed dose (45 Gy) with IMRT para-aortic–only technique were 11% with four fields, 15% with seven fields, and 13.5% with nine fields (Figure 76.14B). These dose distributions were all significantly better than with two-field or four-field conventional techniques ($P < .05$). Other works have similarly demonstrated the feasibility of escalating the dose to 60 Gy while reducing dose to the kidneys, spinal cord, small bowel, rectum, bladder, and bone marrow. However, small volume of bowel received 55 to 60 Gy with the IMRT plans.[161] Positioning the patient prone on a belly board was shown to reduce the volume of small-bowel irradiated. However, patients on a belly board may have large daily anatomic shifts that make prone IMRT unreproducible.


Colon
45 Gy
Common iliac nodes
Spine
20 Gy
Small Bowel
Para-aortic nodes
Kidney
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3000.0
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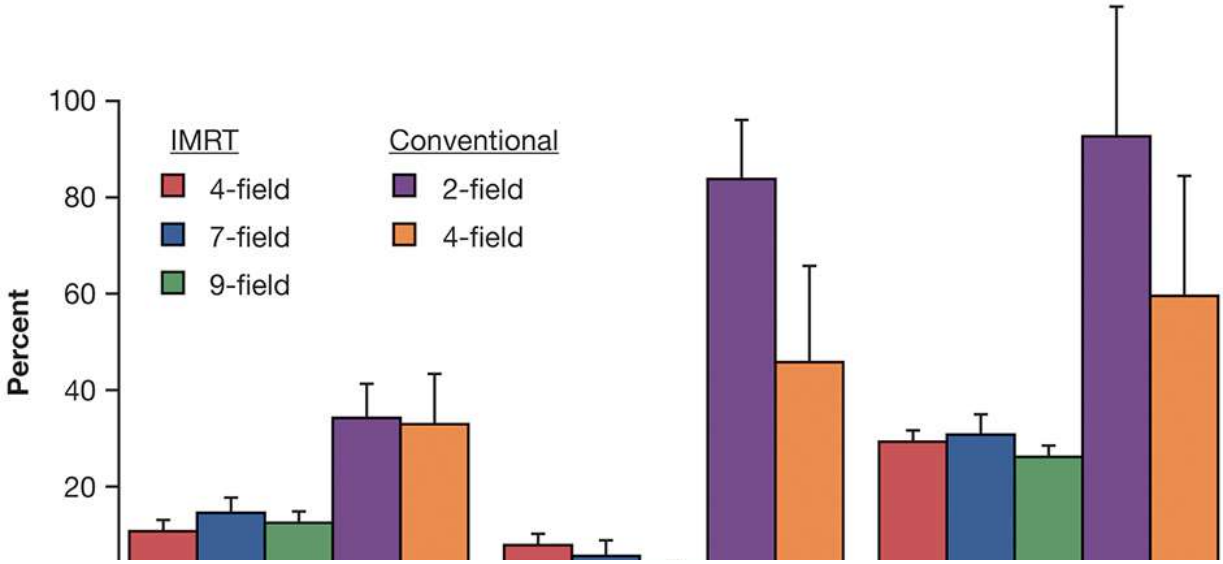
100
80
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IMRT
4-field
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9-field
Conventional
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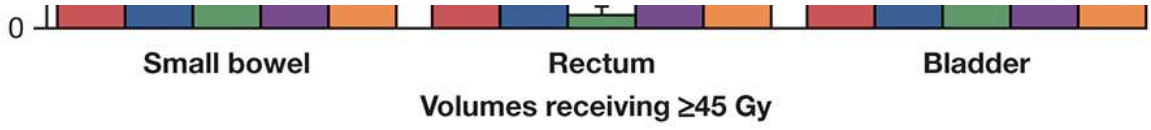


FIGURE 76.14 A. Axial views of intensity-modulated radiation therapy (IMRT) dose distribution. B. The functional volume of the small bowel, rectum, and bladder receiving ≥45 Gy with IMRT or conventional techniques when 100% of the target volume (uterus) receives ≥95% of the prescription dose (45 Gy). (Reprinted from Portelance L, Chao KS, Grigsby PW, Bennet H, Low D. Intensity-modulated radiation therapy (IMRT) reduces small bowel, rectum, and bladder doses in patients with cervical cancer receiving pelvic and para-aortic irradiation. *Int J Radiat Oncol Biol Phys*. 2001;51[1]:261-266. Copyright © 2001 Elsevier. With permission.)

IMRT can be used to spare the bone marrow of patients with gynecologic tumors. If receiving concurrent chemotherapy, less grade 2 white blood cell toxicity was observed (31.2% vs 60%).[162] PET-detected bone marrow was spared using an atlas in a single-arm phase II study of 83 patients, with a median follow-up of 26.0 months; the incidence of grade 3 or higher neutropenia and clinically significant GI toxicity was 19.3% (95% CI, 12.2%-29.0%) and 12.0% (95% CI, 6.7%-20.8%), respectively. Compared with patients treated without image-guided IMRT (IG-IMRT) (n = 48), those treated with IG-IMRT (n = 35) had a significantly lower incidence of grade 3 or higher neutropenia (8.6% vs 27.1%; two-sided χ^2 P = .035), nonsignificantly lower incidence of grade 3 or higher leukopenia (25.7% vs 41.7%; P = .13), and any grade 3 or higher hematologic toxicity (31.4% vs 43.8%; P = .25).[163]

Hasselle et al[164] report on 111 patients treated with multiple different approaches, including 22 treated with postoperative IMRT, 8 with IMRT followed by intracavitary BT and adjuvant hysterectomy, and 81 with IMRT followed by planned intracavitary BT. Median follow-up time was 27 months. Acute and late grade 3 toxicity or higher was 2% (95% CI, 0%-7%) and 7% (95% CI, 2%-13%), respectively. Attempts using an IMRT simultaneous integrated boost (SIB) as an alternative to conventional whole-pelvis irradiation found that accelerated fractionation caused an unacceptably high rate of complications. A combination of an SIB to approximately 50 Gy followed by a sequential boost to 60 to 65 Gy has been shown to be feasible to both pelvic nodes and PANs. Caution in the pelvis when also administering BT is required to ensure bowel dose is limited, and in the para-aortic region, rapid shrinkage of the tumor may result in movement of bowel into the boost

field, and replanning immediately prior to beginning the sequential portion of the boost is recommended.[165]

Although IMRT has dosimetric advantages over conventional RT, IMRT exposes a greater amount of normal tissue to lower irradiation levels, which has the potential to increase the incidence of radiation-induced second cancers,[166] a phenomenon already described with conventional RT techniques.

Image-Guided Radiation Therapy

Daily cone-beam CT (CBCT) imaging for in-room IGRT permits visualization of the bladder and rectum. Particularly in cases with a large, mobile uterus, such as is seen in young women, if an extended field is used and there is concern that the uterus may be out of the field, this may be helpful to confirm full coverage of the CTV daily. Criteria for replanning were reported by Jensen et al[167] on 23 patients treated with IMRT for 45 Gy in 25 fractions and followed with daily CBCT. The CBCTs were online checked by radiation therapists and offline checked by treating MD. The report showed that in only 9.6% of CBCT, the therapists were unable to assess the coverage due to inadequate quality, and there was 99% concordance with the treating MD. Consideration of replanning was made if either the cervix went out of the PTV at least once or if the fundus went out 3 times or more. In seven patients, replanning was done, with only four gaining over 1 Gy in the underdosed area; three were in the fundus (1.2-1.8 Gy) and one in the vaginal area, with 12.7 Gy added. This highlighted the fact that a downward motion out of the field harbors more underdosing risk than an upward one, where dose to the nodal volume mitigates the lost coverage.

Another way to use IGRT to reduce coverage of normal tissue is “plan of the day” approach, where a set of plans is prepared in advance and chosen daily according to the CBCT. A study by Ghosh et al,[168] in which for each patient four plans were made (CTV-to-PTV margins of 7, 10, or 15 mm, and a robust 3D conformal plan), showed that the two larger plans were needed in only 21% of fractions and higher acute toxicity was associated with the larger plans use.

As technological advancement in auto-segmentation and auto-planning evolve, daily adaptive replanning of each pelvic fraction could potentially allow for even greater sparing of normal tissue. Some reports have already shown that with a 3-mm margin, CTVs can still be adequately covered with

improved organ at risk (OAR) dosimetry and with less than 20 minutes of extra planning time per fraction.[169]

Stereotactic Body Radiotherapy

Stereotactic body radiotherapy (SBRT) uses highly conformal treatments with large fraction sizes and, in selected cases, has been considered for a nodal boost of an isolated PAN, although care must be taken to treat the entire para-aortic chain to 45 Gy with IMRT or 4 Field prior to considering an SBRT boost in order to ensure eradication of adjacent micrometastatic disease. SBRT should not be used instead of BT, given the significant increase in normal tissue doses with SBRT compared to BT and lack of equivalent efficacy.[170] SBRT techniques should be employed for recurrences and various oligometastatic disease settings in which a focused localized approach is deemed of benefit, mainly for distant metastases in lymph nodes or solid organs or reirradiation.[171]

Midline Shielding in Anteroposterior-Posteroanterior Portals and Use of a Parametrial Boost

Depending on the institution and BT dose administered, midline shielding with rectangular or specially designed blocks has been traditionally used for a portion of the external beam dose delivered with the AP-PA ports. Midline blocks may be individualized, based on the point A isodose line or a rectangular block of approximately 4-cm width. In one series, OS and incidence of chronic complications were not related to the type of shielding. However, in the era of 3D BT planning, the use of a midline block has been questioned because it may result in tumor underdosing while still contributing significant dose to the bladder, sigmoid, and rectum.[172]

Several institutions reported placing a midline block after a full course of external beam treatment to the pelvis in order to boost the parametria or nodes for patients with persistent disease after approximately 45 to 50 Gy. When parametrial tumor persists, 50 to 60 Gy may be delivered to the parametria, with reduced AP/PA portals (8 by 12 cm for unilateral and 12 by 12 cm for bilateral parametrial coverage). However, careful estimation of dose to the small bowel, sigmoid, and rectum is needed. In the modern era, the use of highly conformal boosts with 3D planning allows an increase in normal tissue sparing. Contours on CT of the parametrial and nodal region allow more

precise tailoring of dose. For patients with enlarged nodes, when available, IMRT techniques may be best at providing conformal dose escalation to 54 to 65 Gy.

Similarly, with 3D BT and computerized optimization as available with high HDR or pulsed-dose rate (PDR) BT, the physician may cover the adjacent parametria using large enough fraction sizes that an additional external beam boost is not needed. When one prescribes HDR BT, the per fraction nodal dose is approximately 25% of prescription. In one study, the per fraction dose to the pelvic lymph nodes by HDR BT, when the HR-CTV received 5.5 Gy per fraction, was 1.4 Gy per fraction. Therefore, HDR BT may obviate the need for a parametrial boost, given the high per fraction dose to the parametria and pelvic sidewall.[172]

In a comparison of three different approaches, Fenkell et al[173] reported on parametrial boost with midline shielding in six patients with locally advanced cervical cancer (IIB-IIIB) treated with definitive CRT and MRI-guided BT. A three-phase plan was modeled: 45-Gy (1.8 Gy per fraction) four-field box, 9-Gy (1.8 Gy per fraction) midline-shielded AP/PA fields (midline-blocked boost [MBB]), and intracavitary MRI-guided BT boost of 28 Gy (7 Gy per fraction). Midline shields 3, 4, and 5 cm wide were simulated for each patient. BT and MBB plans were volumetrically summed. After a 4-cm MBB, HR-CTV D_{90} remained less than 85 Gy in all cases (mean, 74 Gy; range, 64-82 Gy). Bladder, rectum, or sigmoid D_{2cc} increased by more than 50% of the boost dose in four of six patients. The authors concluded that a midline block may not be beneficial in patients receiving 3D image-planned BT with adequate optimization of dose to the tumor and away from the normal tissues.

Para-Aortic Lymph Node Irradiation

If PAN metastases are enlarged or suspected to harbor disease, patients are treated with 45 to 50 Gy to the PAN area plus a sequential 5- to 10-Gy boost to enlarged lymph nodes through reduced lateral or rotational portals. If feasible, 3D planning with IMRT treatment is preferred to spare normal tissues, superiorly covering above the level of the renal hilum or the highest extent of disease and inferiorly covering 2 to 4 cm below the lowest extent of disease (Figure 76.15).

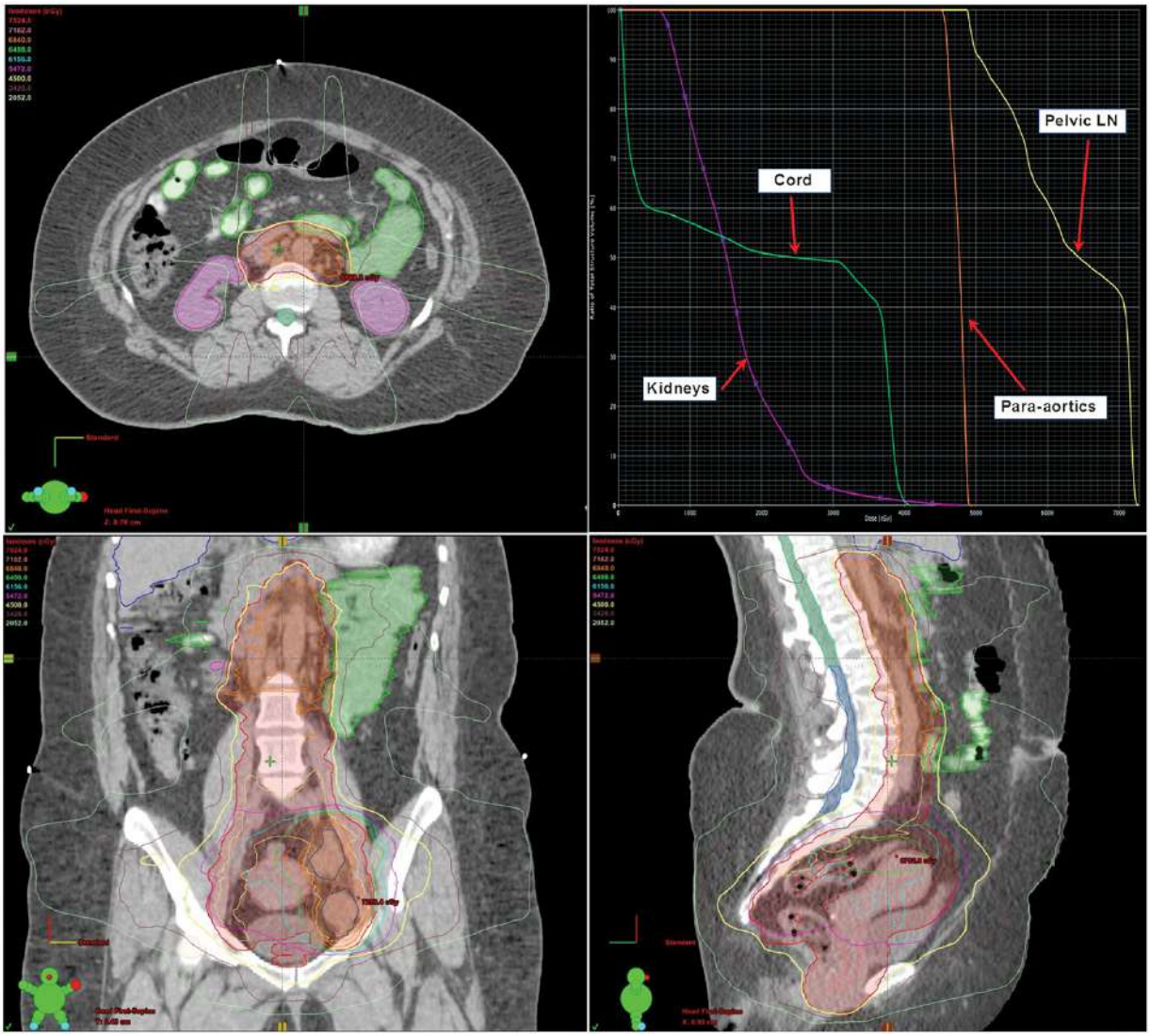


FIGURE 76.15 Extended-field intensity-modulated radiation therapy for external irradiation of the uterine cervix and pelvic and para-aortic lymph nodes (LNs). Dose-volume histogram values for the spinal cord, kidneys, para-aortic nodes, and pelvic node boost are shown for a patient who had an unresectable 4-cm pelvic LN.

The use of IMRT has allowed dose escalation to PAN, particularly unresectable nodes. Clinical reports show excellent control of disease with dose escalation, with one report demonstrating an 85% 2-year nodal control rate after IMRT with a median dose of 63 Gy.[174] Esthappan et al[129] described a technique using CT and FDG-PET to treat the PANs (50.4 and 59.4 Gy) with IMRT while treating the pelvis with 3/4 field RT, and it can be utilized if image guidance is less available. With IMRT, acceptable dose distribution of the target volumes and sparing of the spine, stomach, liver, and colon are

achievable. Sparing of small bowel can also be accomplished, but it may be limited because of overlap with the target volume. An example of IMRT use for dosing the para-aortic region up to 65 Gy while still maintaining constraints for the adjacent OARs can be seen in Figure 76.16.

FIGURE 76.16 Example of treatment plan with intensity-modulated radiation therapy for irradiation of para-aortic and pelvic lymph nodes to 65 Gy. Dose-volume histogram illustrating sparing of kidneys, spinal canal, bladder, and small intestines while achieving dose escalation to the nodal area.

IMRT also allows an integrated boost approach with doses up to 55 Gy in 25 fractions were reported with reasonable toxicity rates,[175] but controversy still remains about the increased per fraction dose and the potential for added toxicity it brings, particularly in the regions adjacent to the duodenum. A report from MD Anderson reported grade 5 toxicity with an SIB approach and therefore recommends limiting the SIB dose to 2 Gy rather than the larger 2.15 Gy or higher.[176] A combined approach of an integrated boost with an additional sequential dose up to 65 Gy was also reported, to avoid a larger per fraction dose[167] to the small bowel. Attention must be made to both the high and medium doses and the volume of bowels and kidney exposed.

When only conventional techniques are available, the PANs are irradiated either with an extended field, often using a four-field approach, that includes both the para-aortic region and the pelvis or through a separate portal (Figure 76.17). This may be done as one long field, or in cases requiring extended distance, one may instead choose to separate the pelvic and para-aortic fields.

This requires a “gap calculation” between the pelvic and para-aortic portals to avoid overlap and excessive dose to the small intestines. The upper margin of the field is at the T12-L1 interspace to reach the infrarenal hilum and the lower margin at L5-S1. The width of the para-aortic portals (in general, 8-10 cm) can be determined by CT scans, MRI, lymphangiography, FDG-PET scans, or IV pyelography outlining the ureters, with the goal to treat all tissue between the right and left psoas muscle. The spinal cord dose (T12 to L2-L3) should be kept to less than 45 Gy by interposing a 2-cm-wide five-half-value-layer shield on the posterior portal (usually after 40-Gy tumor dose) or using lateral ports and limiting the kidney dose to less than 18 Gy. A technique using four isocentric fields weighted 2:1 AP/PA over lateral portals and 1.8-Gy fractions was described to deliver high-dose therapy (56-61 Gy). Kodaira et al[177] evaluated a four-field para-aortic irradiation technique with 10-MV photons (mean, 50.4 Gy) in 97 patients with cervical cancer. The 5-year CSS rate was 32.2%. Grade 1 or 2 stomach and duodenum sequelae developed in 26.8%, grade 2 sequelae of small bowel in 3.1%, and grade 2 sequelae of bone in 3.1%. Rates of toxicity with IMRT are lower, though dose escalation with a SIB to large nodes next to the duodenum must be done with caution, given the risk of duodenal perforation.[130]

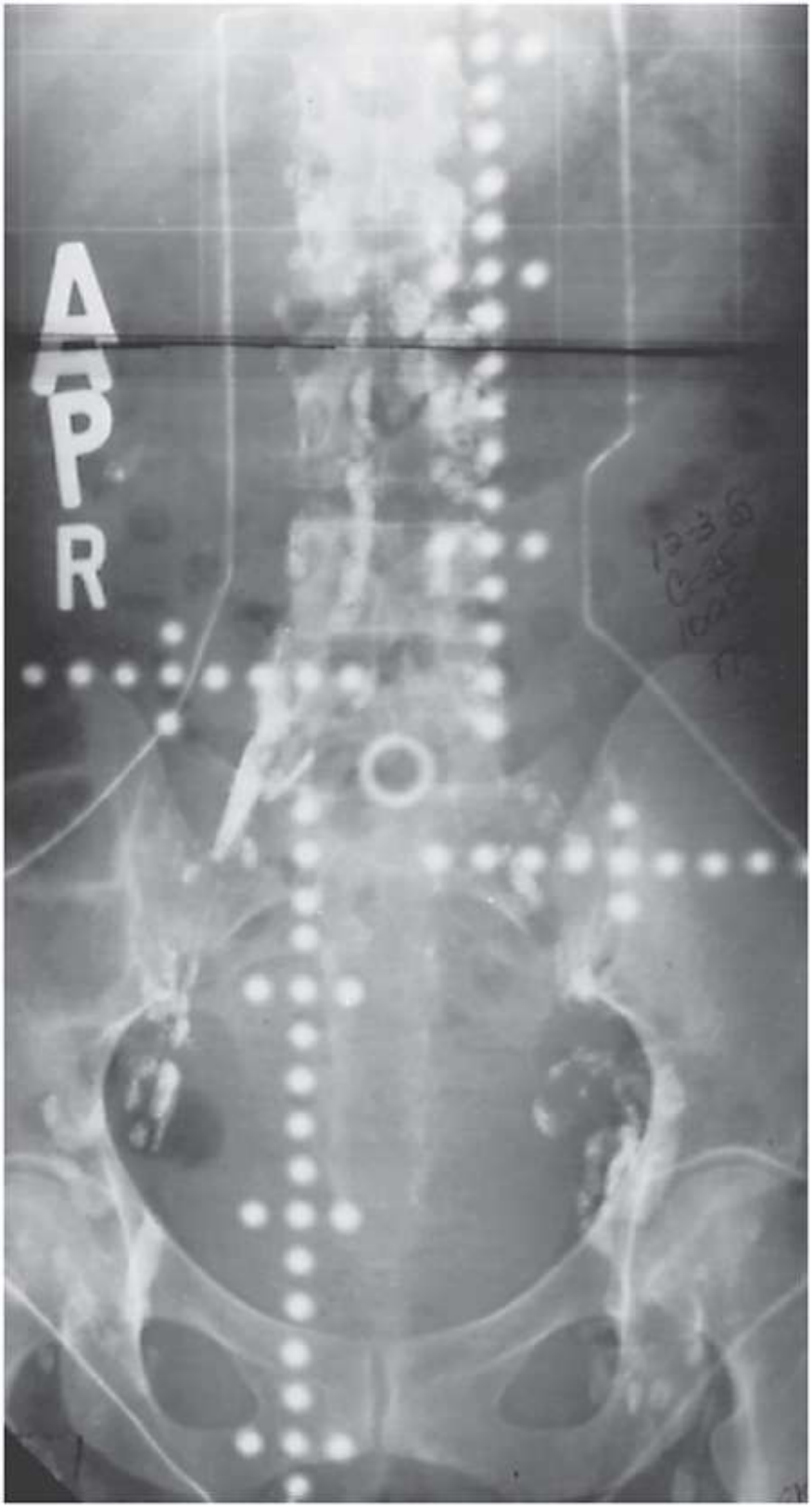


FIGURE 76.17 Extended field simulated with conventional plain films for external irradiation of pelvic and para-aortic lymph nodes.

Beam Energies

For IMRT, 6-MV energy is used to provide the most homogeneous dose. However, in conventional irradiation, because of the thickness of the pelvis, high-energy photon beams (≥10 MV) are especially suited for this treatment. They decrease the dose of radiation delivered to the peripheral normal tissues (particularly bladder and rectum) and provide a more homogeneous dose distribution in the central pelvis, which would allow more accurate combination with the BT dose (Figure 76.18). With lower energy photons (^{65}Co or 4-6 MV x-rays), higher maximum doses must be given, and more complicated field arrangements should be used to achieve the same midplane tumor dose (three-field or four-field pelvic box or rotational techniques) while minimizing the dose to the bladder and rectum and to avoid subcutaneous fibrosis. The presence of a metallic prosthesis when using lateral fields or a box pelvic irradiation technique may result in a dose decrease of approximately 2% for 25-MV x-rays and average increases of 2% for 10-MV x-rays and 5% for ^{65}Co. Better pelvic tumor control and survival and fewer complications were seen in 65 patients with stage IIB and III cervical carcinomas treated with 23-MV photons compared with 61 treated with external irradiation with ^{65}Co in addition to BT in both groups.[178] In contrast, Holcomb et al[179] compared outcome of 195 patients with stage IIB and IVA cervical carcinomas treated with ^{65}Co RT (group 1) and 53 treated with linear accelerators (group 2). There was no significant difference in OS, although there was a trend toward increasing pelvic recurrence in the ^{65}Co group (50.8%) compared with group 2 (35.8%; P = .08). Mixed beam external radiation with neutrons and photons resulted in unacceptably high toxicity rates and is not recommended. Similarly, carbon ion therapy was reported but resulted in major intestinal complications.[180]

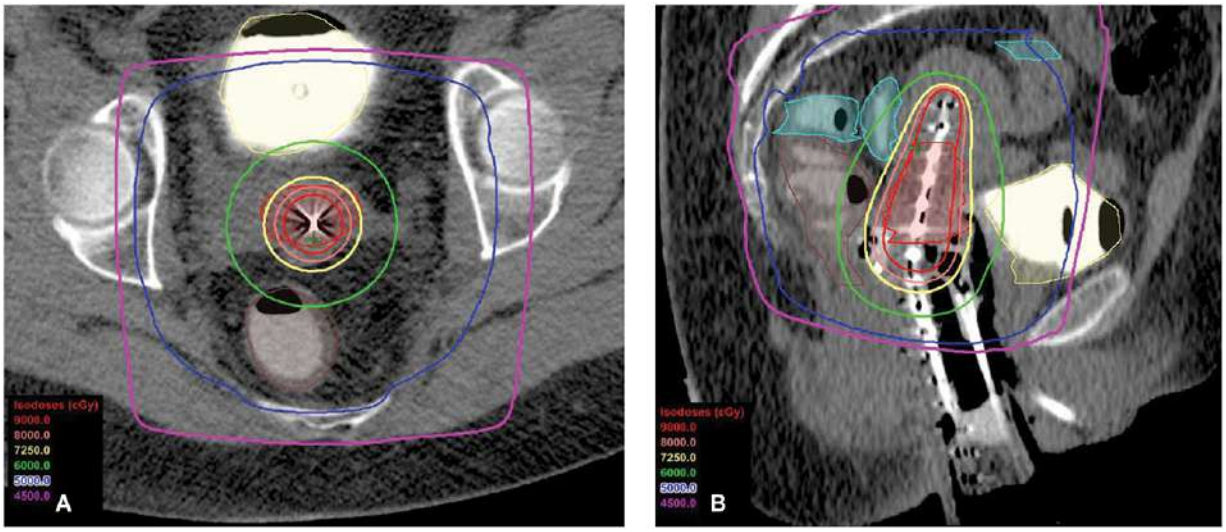


FIGURE 76.18 Example of isodose curves of 4-Field box irradiation of the pelvis with high-energy photons and computed tomography–based high-dose rate brachytherapy optimized to cover the tumor and minimize dose to the bladder and rectum. A. Axial. B. Coronal view.

Hyperfractionated or Accelerated Hyperfractionated Radiation Therapy

Studies on hyperfractionation with or without chemotherapy report comparable outcomes but higher toxicities. MacLeod et al[181] reported on a phase II trial of 61 patients with locally advanced cervical cancer treated with accelerated hyperfractionated RT (1.25 Gy administered twice daily at least 6 hours apart to a total pelvic dose of 57.5 Gy). A boost dose was administered with either low-dose rate (LDR) BT or EBRT to a smaller volume. Thirty patients had acute toxicity that required regular medication. One patient died of acute treatment-related toxicity. The overall 5-year survival was 27%, relapse-free survival was 36%, and actuarial local tumor control was 66%. There were eight severe late complications observed in seven patients, who required surgical intervention (actuarial rate of 27%). Five patients also required total hip replacement.

Another study reported on 30 patients with stage II or III cervical cancer randomized to receive either hyperfractionation (15 patients) or conventional fractionation (15 patients).[182] At 5 years, two patients in the hyperfractionation group and eight patients in the conventional treatment group had recurrent tumor (P = .04). Delayed bowel complications (grades 2 and 3) occurred in nine women in the hyperfractionation group and two patients in the conventional group (P = 0.0006).

RTOG 88-05 conducted a phase II trial of hyperfractionation (1.2 Gy to the whole pelvis twice daily at 4- to 6-hour intervals, 5 days/week) with BT in 81 patients with locally advanced carcinoma of the cervix. Comparison with historical control patients treated on other RTOG studies showed equivalent rates of pelvic tumor control, survival, and grade 3 and 4 toxicities at 3, 5, and 8 years, respectively.

Calkins et al[183] assessed the toxicities of multiple daily fractionated (twice daily, 1.2-Gy fractions) whole-pelvis radiation plus concurrent chemotherapy for locally advanced carcinoma of the cervix. In the first study (GOG 8801), for 38 patients, hydroxyurea was given orally (80 mg/kg to a maximum of 6 g) at least 2 hours before irradiation, twice every week. In the second study (GOG 8901), for 30 patients, cisplatin and 5-fluorouracil (5-FU) were used concomitantly with RT. Acute toxicity was primarily enteric and appeared to be dose related. The maximum tolerated dose of whole-pelvis radiation that could be delivered in a hyperfractionated setting with concomitant chemotherapy was 57.6 Gy in 48 fractions, followed by BT.

GENERAL MANAGEMENT

Carcinoma In Situ

Patients with persistent high-grade carcinoma in situ are usually treated with a total abdominal hysterectomy with or without a small portion of the upper vagina removed. The decision to remove the ovaries depends on the age of the patient and status of the ovaries. Occasionally, when the patient wishes to have more children, carcinoma in situ may be treated conservatively with a therapeutic conization, laser therapy, or cryotherapy. This approach should be judiciously selected when the extent of tumor allows it and the patient is reliable for continued follow-up. Conization microscopic margins are critical in decision-making regarding a conservative approach or proceeding with a hysterectomy. A therapeutic hysterectomy can be performed 6 weeks after the conization.

Irradiation may be useful for the treatment of carcinoma in situ, particularly in patients with strong medical contraindications to surgery or when there is extension of the lesion to the vaginal wall or multifocal carcinoma in situ in both the cervix and the vagina. In a group of 26 patients with carcinoma in situ treated at Washington University with intracavitary BT alone (~5,000 mgh, 45 Gy to point A with LDR) with tandem and ovoids, no recurrences

were recorded. Ogino et al[184] used HDR BT in 14 patients with grade 3 cervical, 6 with grade 3 vaginal intraepithelial neoplasia (3 with microinvasion), and 6 with recurrent CIN after hysterectomy. Seventeen patients were treated with HDR BT alone, and three in combination with EBRT without surgery. The mean dose of HDR BT was 26.1 Gy (range, 20-30 Gy) prescribed at point A for intact uterus, at 1 cm superior to the vaginal apex, or 1 cm beyond the vaginal mucosa for lesions of the vaginal stump. At a mean follow-up of 90 months, 14 patients were alive and 6 had died from intercurrent disease; none had recurrent disease. Rectal bleeding occurred in three patients and subsided spontaneously. Moderate and severe vaginal reactions were noted in two patients in whom the treatment included the entire vagina.

Invasive Disease

Based on available resources globally and the stage of disease, a debate continues among those who advocate radical surgery, those who favor radiation, and those who favor CRT for the treatment of carcinoma of the uterine cervix. Patients should be treated with close collaboration between the gynecologic oncologist and the radiation oncologist, and an integrated team approach should be vigorously pursued. In countries with access to RT facilities and financial resources to supply chemotherapy, the use of concurrent CRT represents the accepted standard for patients with stages IB3, IIA2, and IIB to IVA cervical cancer. For earlier stage patients, the use of either surgery or CRT is recommended.

A survey of patterns of RT practice documented a rise in the use of cisplatin-based concurrent CRT in patients with advanced stages, from 63% in 1999 to 74% in 2007.[185] Moreover, Barbera et al also reported a significant increase in the use of CRT in Canada after the *U.S. National Cancer Institute Bulletin* on the subject.[186] Whenever determining treatment strategy, it is important to keep in mind that almost all the trials discussed in this chapter were conducted prior to the FIGO 2018 staging system, which shifted all the node positive, less locally invasive tumors, from stages I and II to become stage IIIc. Thus, extrapolating from these data on newly diagnosed and staged patients should be done with due consideration

Carcinoma of the Cervix Inadvertently Treated With a Simple Hysterectomy

Occasionally, a simple or total abdominal hysterectomy is performed, and invasive carcinoma of the cervix is incidentally found in the surgical specimen. In general, extrafascial abdominal hysterectomy is not curative because the paravaginal or paracervical soft tissues and vaginal cuff are not removed. Furthermore, it may be technically difficult to perform an adequate radical operation after previous simple hysterectomy. If only microinvasive carcinoma is found when a total or extrafascial hysterectomy with a wide cuff is performed, no additional therapy is necessary for lesions with deeper stromal invasion; at most, one or two vaginal intracavitary insertions to deliver a 65-Gy LDR mucosal dose (or 7 Gy × six fractions prescribed at the vaginal surface or 5 Gy at 0.5 cm × six fractions with HDR BT) to the vault are sufficient. If a less comprehensive resection was carried out, it is critical that these patients receive RT immediately with or without concurrent chemotherapy, depending on the risk factors present pathologically when their postoperative status allows it because the prognosis is worse if postoperative irradiation is not administered.

In patients with fully invasive tumor, therapy consists of approximately 45 Gy to the whole pelvis with cylinder BT to the vaginal vault for an approximately 60-Gy mucosal dose. If there is gross tumor present in the vaginal vault or parametrium, the dose to the whole pelvis should be 45 Gy with concurrent weekly cisplatin chemotherapy, followed by an additional parametrial dose of 10 to 20 Gy. An intracavitary insertion should be performed. If there is gross residual tumor, an interstitial implant should be carried out to selectively increase the dose to this volume.

Several studies have reported results of postoperative external beam irradiation after conservative surgery. Münstedt et al[187] reported on 119 patients who received postoperative RT after RH and 80 who received it after simple hysterectomy. There was a trend toward better survival in the RH group, but the authors concluded that postoperative RT is a good treatment in patients with invasive cervical cancer who undergo a simple hysterectomy. In another report of 105 patients with invasive cervical carcinoma found in inadequate surgery specimens treated with postoperative RT, 5-year pelvic tumor control was 72% and the survival rate was 55%. Late rectal toxicity was 19%, bladder toxicity was 4.8%, and small-bowel toxicity was 14.3%.[188]

In a series of 147 patients treated at Asan Medical Center in Korea, 48 patients with stage IA1 lesions did not receive further treatment. Another 99 patients had stage IA2 to IIA lesions incidentally identified. Of these, 26 received no further therapy, 44 had either radiation or CRT, and 29 had a radical parametrectomy. For patients with stage IA1 disease who were observed, 0% relapsed, whereas 35% of patients with stage IA2 to IIA diseases who were observed suffered from a recurrence.[189] Either radical parametrectomy or radiation is required for patients with stage IA2 or higher cancer after a simple hysterectomy. However, these treatments increase the risk of side effects[190] including for those patients receiving robotic parametrectomy.[191]

Microinvasive Disease

The definition of microinvasive carcinoma of the cervix includes invasive carcinoma diagnosed only by microscopy, staged by the FIGO 2018 system as IA1 and IA2, according to the depth of invasion (DOI). Conization is mandatory for a more accurate diagnosis. Lesions less than 1 mm in depth can be treated with conization, provided all margins are tumor free and continued careful follow-up is instituted. Margins of 8 to 10 mm are used as guidelines for clearance in conization. Smaller margins and lymphovascular invasion in addition to DOI were prognostic factors for recurrence.

Tumor volume in the stroma may be a more reliable criterion than DOI to arrive at a definition of stage IA. Vascular space involvement does not impact stage. DOI and tumor confluence have been identified as prognostic factors that should be taken into consideration in the planning of therapy.

Early invasive carcinoma of the cervix (stage IA2) is usually treated with a total abdominal or modified RH or, in some cases, with simple conization or radical trachelectomy. When the depth of penetration of the stroma by tumor is less than 3 mm, the incidence of lymph node metastasis is 1% or less, and a lymph node dissection or pelvic external irradiation is not warranted. With more extensive lesions, an RH with bilateral pelvic lymphadenectomy (with or without sentinel mapping) is the preferred treatment. Tumor control with all treatment methods is more than 95%, with patients eventually dying of intercurrent disease. Gadducci et al[192] treated 30 patients with conization and 82 with total and 54 with RH; the recurrence rates were 10%, 4.9%, and 9.3%, respectively. None of 67 patients subjected to lymphadenectomy had

positive pelvic nodes. In 98 patients with AC of the cervix, none of 48 with DOI of ≤5 mm had involved parametria or positive nodes, in contrast to 6 (16%) of 36 with DOI of greater than 5 mm.[193]

Vaginal trachelectomy (removal of the cervix) and laparoscopic lymphadenectomy have been used to treat young patients with microinvasive carcinoma to preserve fertility. The overall incidence of central recurrence is approximately 5%. Webb et al[194] analyzed lymph node status and survival rates of women with microinvasive cervical AC (FIGO stages IA1 and IA2) from the SEER database between 1988 and 1997. Among reported cases, 131 had stage IA1 and 170 had stage IA2 disease. Simple hysterectomy was done in 54 women with IA1 and 64 women with IA2 disease and RH in 50 and 83 women. Only 1 of 140 women who had lymphadenectomy had a single positive lymph node. There were four tumor-related deaths (one with IA1 and three with IA2 disease). The survival rate was 98.7%.

Inoperable patients may be treated with intracavitary radioactive sources alone with 6,500 to 8,000 mgh, 60 to 75 Gy to point A, in two LDR insertions, respectively, or with the equivalent dose using HDR BT, approximately 10 fractions of 5 Gy per fraction. In 47 patients with microinvasive carcinoma treated at Washington University—20 with intracavitary therapy only and 27 patients with combined external irradiation and intracavitary BT—only 1 patient had a pelvic recurrence and distant metastases 10 years later; the 5-year DFS rate was 96%. Hamberger et al,[195] in patients with stage IA or IB lesions less than 1 cm in diameter treated with intracavitary therapy alone to high doses (8,640, 9,340, and 13,680 mgh), noted no failures in 41 patients with stage IA disease and only 4 (4%) of 93 patients with stage IB, small-volume disease. Only 3 (0.2%) of 151 patients in the report, which also included some larger stage IB tumors, had grade 3 complications.

Early Local Disease

This category includes nonbulky (<4 cm) tumors, confined to the uterus (stages IB1 and IB2) or limited to the upper two-thirds of the vagina (stage IIA1). The choice of definitive chemoirradiation with BT or radical surgery remains controversial, and the preference for one procedure over another depends the patient's fertility, the available resources of the treating institution, the gynecologic oncologist or radiation oncologist involved, the

general condition of the patient, and characteristics of the lesion, such as histology and size. An operation has been preferred by some in young women to preserve the ovaries, attempting to prevent premature menopause, but that should be considered against the low risk of ovarian metastases (~1%).[137] Postmenopausal or comorbid patients may benefit with CRT as they avoid operative risks. When therapeutic results in invasive carcinoma of the cervix are evaluated, a direct comparison of surgically treated or irradiated patients is fraught with many uncertainties, including patient selection, reporting of surgical cases using staging determined by laparotomy findings, and different treatment techniques. As mentioned, the introduction of the 2018 FIGO staging system, which drew out the node-positive cases from this stage group, can also complicate interpretation of older data. In particular, in the modern era when concurrent CRT is known to increase survival, and both surgical and radiation techniques have improved to cause less toxicity, a direct comparison of CRT versus surgery in early-stage cervical cancer is needed. Surgery provides an opportunity for a thorough pelvic and abdominal evaluation. However, surgical staging has not been shown to improve overall patient survival. Kupets et al[196] assessed the value of debulking large nodes and concluded that the incremental overall benefit by stage was small. In the era of MRI and PET, surgeons may rely on imaging findings to screen for operability. The impact of patient selection in results of surgical series was illustrated by Whitney and Stehman who evaluated the frequency with which intended RH for cervical cancer is abandoned and the outcomes for those selected patients.[197] In 1,127 patients with stage IB carcinoma of the cervix entered on GOG Protocol 49, 98 (8.7%) women were found at surgery to have extrauterine disease, and the proposed radical operation was abandoned. Patients had both pelvic and extrapelvic diseases, including grossly positive pelvic nodes, other pelvic implants, and gross serosal extension. Sixty-three (65%) patients subsequently underwent pelvic RT and BT. Para-aortic fields were added for eight patients who were found to have positive PANs. The DFS was longer for patients with direct pelvic extension than for those with extrapelvic disease.

However, with proper preoperative evaluation, patients with early-stage cervical cancer undergoing hysterectomy enjoy particularly good results. In the previously mentioned LACC trial,[122] which compared minimally invasive to open surgery, 92% of the 631 randomized patients had macroscopic less

than 4 cm, node-negative cancers (or FIGO 2018 stage IB1-2). The 3-year OS rates were 93.8% and 99%, respectively. Totally, only 4.3% had aborted surgery, and any adjuvant therapy was required in 28.2%.

Primary RT, using EBRT and BT without chemotherapy, is also an option for early cervical disease, if patients are deemed unsuitable for surgery or if a higher likelihood of adjuvant therapy is suspected. Randomized trials have shown similar survival outcomes to surgery and are discussed further in the next section. The importance of combining EBRT and BT to improve pelvic tumor control when treating larger localized lesions has been documented. The previously mentioned report by Hamberger et al,[195] which used intracavitary therapy alone, noted that 3 (18%) of 17 patients with over 1 cm IB lesions had regional failures. In addition, Volterrani and Lombardi[198] reported 5-year survival of 82.6% in 23 patients with occult stage IB carcinoma of the cervix treated with intracavitary ^{251}Ra only (7,500 mgh), in contrast to only 64.8% with larger stage IB tumors and 50% with stage II. Unfortunately, the authors did not report the exact location of the failures.

Concurrent chemotherapy significantly improves survival, including in stage IB to IIA diseases. In RTOG 90-01, for the subset of 272 stage IB to IIA patients, the 8-year OS was 55% with RT alone versus 78% with concurrent CRT ($P < .001$).[199] In the EMBRACE study, a total of 98 node negative, with less than 4 cm tumors, FIGO 2009 stage IB and IIA patients were included, and their 5-year OS was 88% and 85%, respectively.[200]

Randomized Studies: Surgery Versus Radiation

Few randomized trials have compared the results of RH with definitive RT, and none have compared surgery to CRT. Outcome between radiation alone versus surgery is comparable. Prospectively randomized studies reported in the 1970s on equivalent survival and pelvic recurrence rates in patients with stage IB and IIA carcinomas of the uterine cervix treated with an RH or irradiation alone.[201] Landoni et al[202] published results of a prospective, randomized trial of RT versus surgery; 469 women with stage IB and IIA cervical carcinomas were referred for treatment, and 343 were randomized (172 to surgery and 171 to RT). Postoperative irradiation was delivered after surgery for women with surgical stage pT2b or greater, less than 3 mm of cervical stromal invasion and cut-through margins, or positive pelvic nodes. Scheduled treatment was delivered to 169 and 158 women, respectively. In

the surgery group, 62 of 114 women with cervical diameters of less than 4 cm and 46 of 55 women with greater than 4 cm received adjuvant RT. After a median follow-up of 87 months (range, 57-120 months), 5-year OS and DFS rates were nearly identical in the surgery and RT groups (83% and 74%, respectively); recurrent disease developed in 86 women: 42 (25%) in the surgery group and 44 (26%) in the RT group (Figure 76.19). Forty-eight patients (28%) in the surgery group had severe morbidity, compared with 19 (12%) in the RT group (P = .0004; Table 76.5). The combination of surgery and RT had the worst morbidity, especially urologic complications.

TABLE 76.5 RANDOMIZED TRIAL OF RADICAL SURGERY OR IRRADIATION IN STAGE I TO II CERVICAL CANCERS: RELAPSES AND MORBIDITY

	Surgery							
	Surgery Only		Surgery Plus Radiation Therapy		Total		Radiation Therapy Alone	
	≤4 cm	>4 cm	≤4 cm	>4 cm	≤4 cm	>4 cm	≤4 cm	>4 cm
Number of patients[a]	53 (52)	9 (9)	62 (62)	46	115 (114)	55 (55)	114 (105)	54(53)
Relapses	7 (13%)	2 (22%)	15 (26%)	17 (37%)	23 (20%)	19 (34%)	21 (18%)	23 (42%)
Pelvic	4	2	7	9	11	11	12	16
Distant morbidity	3	–	9	8	12	8	9	7
Grade 2-3[b]	16 (31%)	3 (33%)	18 (29%)	11 (24%)	34 (30%)	14 (25%)	13 (12%)	6 (11%)
Short term	10 (16%)	–	22 (20%)	–	32 (19%)	–	11 (7%)	–
Long term	15 (24%)	–	31 (29%)	–	46 (27%)	–	25 (16%)	–

[a]Parentheses show the number of patients who actually received this treatment instead of intention to treat.

[b]Percentage calculated for the number of patients who actually received treatment.

Reprinted from Landoni F, Maneo A, Colombo A, et al. Randomized study of radical surgery versus radiotherapy for stage IB-IIA cervical cancer. *Lancet*1997;350(9077):535-540. Copyright © 1997 Elsevier. With permission.

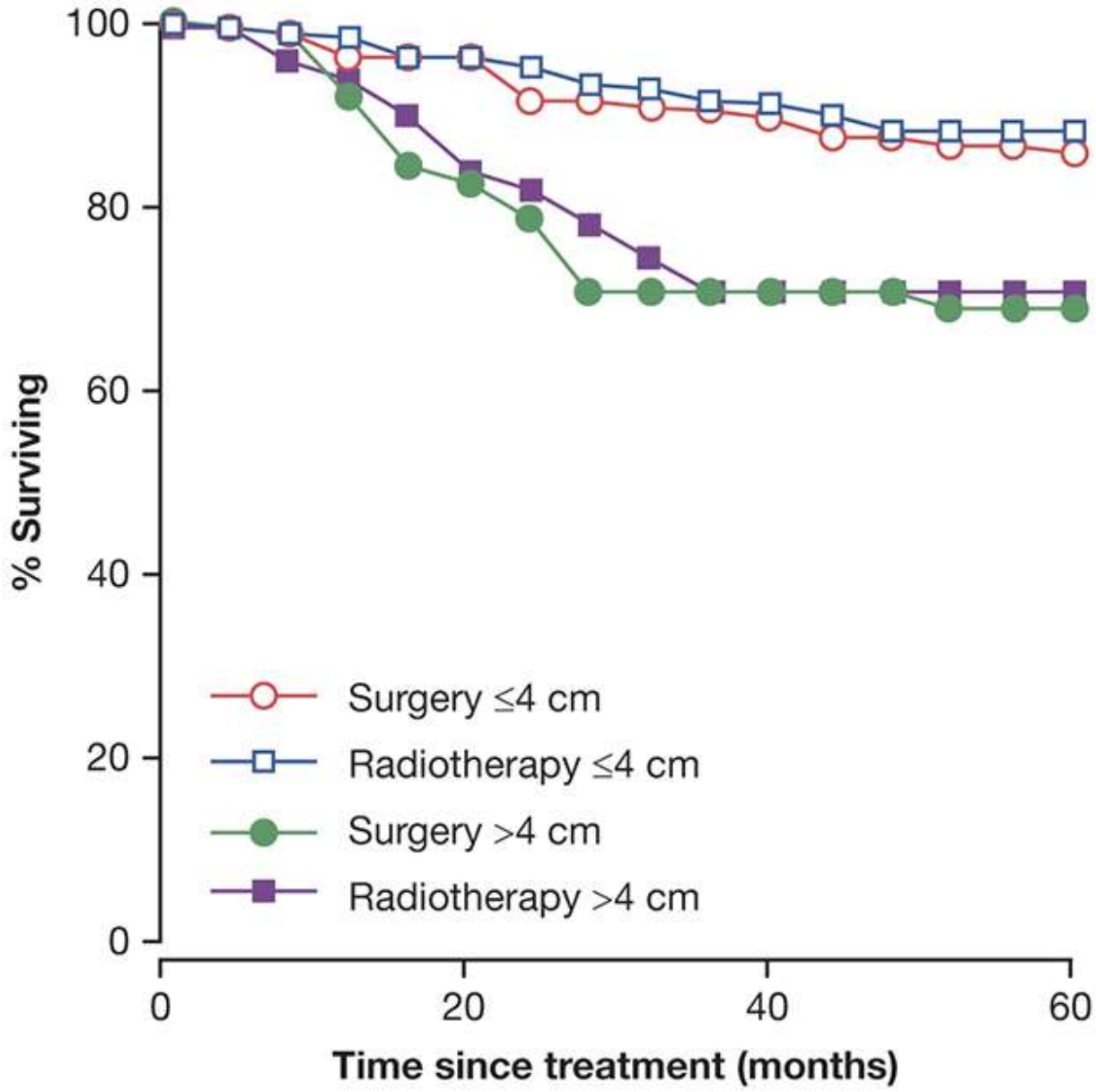


FIGURE 76.19 Overall actuarial survival of patients with carcinoma of the cervix randomized to treatment with radical surgery or radiation therapy according to treatment group and cervical diameter. (Reprinted from Landoni F, Maneo A, Colombo A, et al. Randomized study of radical surgery versus radiotherapy for stage IB-IIA cervical cancer. *Lancet.* 1997;350[9077]:535-540. Copyright © 1997 Elsevier. With permission.)

Of note, no randomized study has compared primary CRT to RH, although CRT has a significant survival advantage over RT alone for patients with stage IB to IIA cervical cancer. In a meta-analysis looking at the value of adjuvant cisplatin-based chemotherapy after RH, RT, or both for patients with stage IA2, IB1, or IIA cervical cancer, three randomized clinical trials were

evaluated.[203] Two of the three trials showed a significant benefit compared to adjuvant chemotherapy concurrent with radiation, with a reduced risk of death (HR = 0.56, 95% CI = 0.36-0.87). No benefit was seen when chemotherapy was given prior to RT.

NACT plus surgery does not improve survival over surgery alone.[204] In a meta-analysis of six trials, although there was an improvement in PFS with NACT (HR = 0.76, 95% CI = 0.62-0.94, *P* = .01), this did not translate into an OS benefit.

Randomized Trials of Radiation or Chemoradiotherapy After Radical Hysterectomy

Patients who have undergone RH with no preoperative RT are considered for postoperative CRT therapy if they have high-risk prognostic factors, which include positive pelvic lymph nodes, as are patients with negative nodes who have microscopic positive margins of resection or parametrial involvement.[205]

Patients with any two of deep stromal invasion, vascular/lymphatic permeation, and large tumor size are candidates for postoperative radiation.[206] These patients have an intermediate risk of failure. Whether to add concurrent chemotherapy to postoperative radiation in the intermediate-risk group is being tested in an accruing randomized trial (GOG0263).

One randomized study showed improved recurrence-free survival with postoperative pelvic irradiation (46-50.4 Gy in 23-28 fractions) after radical surgery in the presence of positive pelvic nodes or node-negative high-risk factors in women with stage IB cervical cancer treated by RH and pelvic lymphadenectomy. There were 277 eligible patients with at least two of the following risk factors: greater than one-third stromal invasion, capillary lymphatic space involvement, and large clinical tumor diameter; 137 patients were randomized to pelvic RT and 140 to no further treatment.[206] The results were updated by Rotman et al[207]; 24 (17%) patients in the irradiation group and 43 (30.7%) in the no-further-treatment group had cancer recurrences. In the RT group, 27 patients died of cancer, and in the no-further-treatment group, 40 died from cancer. There was a statistically significant reduction in risk of recurrence in the irradiation group, with recurrence-free rates at 2 years of 88% versus 79% for the irradiation and no-further-treatment groups. OS difference did not reach statistical difference (*P* = .074; Figure 76.20). Severe or life-threatening (GOG grade 3 or 4) adverse effects occurred in nine

patients (6.6%) in the RT group and three (2.1%) in the observation group. A meta-analysis of trials including stages IB1 to IIA cervical cancer found that women who received postoperative radiation had a significantly lower risk of disease progression at 5 years (RR = 0.6, 95% CI =0.4-0.9). The risk of serious adverse events was not significantly higher if women received RT rather than no further treatment, possibly because the rate of adverse events was low.[208]

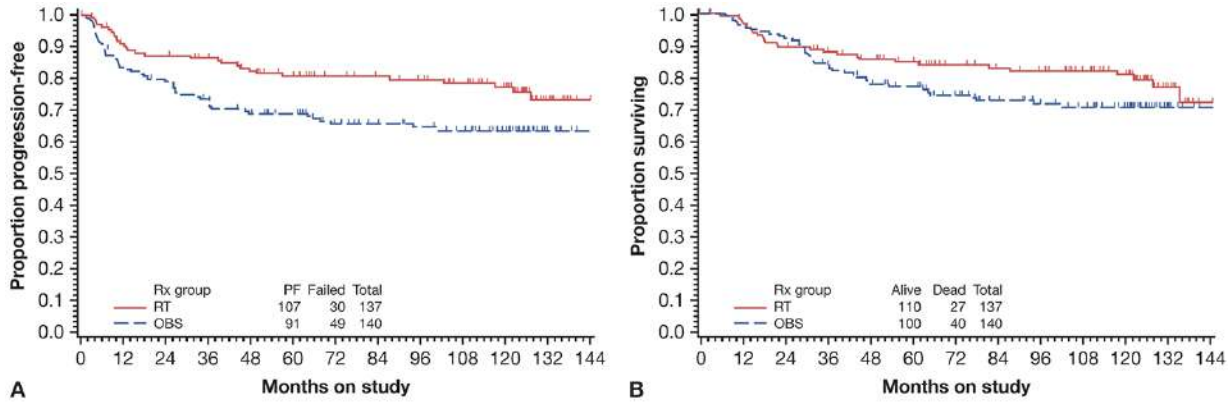


FIGURE 76.20 Recurrence-free survival (A) and overall survival (B) of patients with stage IB carcinoma of the cervix, correlated with treatment method. RT, radiation therapy. (Reprinted from Rotman M, Sedlis A, Piedmonte MR. A phase III randomized trial of postoperative pelvic irradiation in patients with stage IB cervical carcinoma with poor prognostic features: follow up of a Gynecologic Oncology Group study. *Int J Radiat Oncol Biol Phys.* 2006;65[1]:169-176. Copyright © 2006 Elsevier. With permission.)

Southwest Oncology Group 8797 was a study for women with FIGO stage IA2, IB, or IIA carcinoma of the cervix with metastatic disease in the pelvic lymph nodes, positive parametrial involvement, or positive surgical margins at the time of primary RH with total pelvic lymphadenectomy. Patients had confirmed negative PANs; if the PANs were not sampled, the patients had confirmed negative common iliac lymph nodes. One hundred twenty-seven patients were randomized to treatment with pelvic EBRT with 5-FU infusion and cisplatin, and 116 were treated with irradiation alone. The 4-year PFS and OS for women on the adjuvant cisplatin/5-FU and RT arm were 80% and 81%, compared with 63% and 71% for women on the pelvic irradiation arm.[205] The difference was statistically significant.

Postoperative External Beam Radiation Dose

When metastatic pelvic lymph nodes are present, treatment has consisted of 45 Gy to the whole pelvis delivered with a four-field technique with concurrent weekly cisplatin. If gross residual disease is present, dose escalation to 54 to 65 Gy, depending on small-bowel dose limits (eg, $D_{5cc} < 55$ Gy), may be considered with a sequential IMRT nodal boost.[49] Patients with positive common iliac or PAN metastases should receive 45 Gy to the entire para-aortic region with the superior border covering the renal hilum, with consideration of a boost to the tumor bed. If gross residual nodal disease is left, a nodal boost up to 65 Gy with IMRT is particularly suited to treat these patients.[130]

In patients for whom postoperative irradiation is indicated for deep stromal invasion in the cervix or close or positive surgical margins, an alternative is to deliver 45-Gy pelvic external irradiation in combination with an intracavitary insertion (LDR, PDR, or HDR) and LDR equivalent dose of 65 Gy to the vaginal mucosa, using colpostats or a cylinder.[209] At some institutions, external irradiation alone (50 Gy to the midplane of the pelvis) with a four-field box technique has been used. Hong et al[210] recommended, for node-negative patients with high-risk factors, to irradiate only the low pelvis (median dose, 50 Gy), which resulted in a reduction of grade 3 small-bowel morbidity (3/149 = 2%) in comparison with patients treated to the whole pelvis (6/79 = 8%). Five-year DSS was 84% and 86%, respectively.

Postoperative Brachytherapy

Depending on the extent of surgical resection of the vagina, the vaginal cuff may be at risk for recurrence. There is no clear agreement on the indications for vaginal BT after RH, although adjuvant vaginal BT for cervical cancer is most commonly used as a boost after EBRT, particularly in patients with positive margins.[211] Based on the American Brachytherapy Society guidelines, vaginal cuff boost should be considered in patients with a less than RH, close or positive margins, large or deeply invasive tumors, parametrial or vaginal involvement, or extensive lymphovascular invasion.[209] Consideration of postoperative vaginal intracavitary BT after external beam therapy is recommended for patients with carcinoma at the vaginal margin of resection. If parametrial margins were close or positive, defined by either surgical clips or in the region of the surgical tumor bed, an external beam dose of at least 54 Gy for close margins and higher for positive margins is recommended.

In patients receiving postoperative irradiation, extreme care should be exercised in designing treatment techniques, including intracavitary insertions; because of the surgical extirpation of the uterus, the bladder and rectosigmoid may be closer to the radioactive sources than in the patient with an intact uterus. Furthermore, vascular supply may be affected by the surgical procedure, and adhesions can prevent mobilization of the small-bowel loops that may be fixed in the pelvis. HDR BT after surgery is particularly suited for patients with cervical cancer because it prevents the prolonged immobilization required for LDR BT. In some patients at higher risk for parametrial tumor or lymph node metastases, HDR BT is combined with external beam pelvic irradiation.

Locally Advanced Disease

Patients with stage IB3, IIA2, and IIB to IVA tumors are best treated with irradiation, including external beam and BT combined with concurrent chemotherapy. Larger tumors and tumors extending beyond the uterus are not suitable for primary surgical treatment as the need to add adjuvant RT results in higher toxicity without additional efficacy compared to primary RT.[202] In addition, NACT followed by surgery approach trials showed inferior results compared to primary cisplatin-based CRT.[212,213]

Numerous reports have been published on the concomitant use of irradiation and cytotoxic agents (hydroxyurea, cisplatin, and 5-FU, in some trials combined with mitomycin C) administered to obtain a radiosensitizing effect.[199,205,214] Cisplatin is one of the most active cytotoxic agents in SCC of the uterine cervix. When cisplatin and irradiation are used concomitantly, substantial enhancement of cell killing is observed. Suggested mechanisms for radiation enhancement by cisplatin (a) in hypoxic or oxygenated cells, free radicals with altered binding of cisplatin to DNA are formed at the time of irradiation, and (b) interaction inhibits repair of sublethal damage.

A 2005 updated meta-analysis of concomitant chemotherapy and RT by Green et al found 24 trials including 4,921 patients and concluded that CRT improves OS and PFS, whether cisplatin was used, with absolute benefits of 10% and 13%, respectively.[215] Similarly, a 2008 meta-analysis of the 13 trials that compared CRT to radiation found that there was an absolute 6% improvement in 5-year survival with concurrent CRT (HR 0.81, $P < .001$). The effect was attributed to a reduction in both local and distant recurrence.

CRT increased acute hematologic and GI toxicity, but no confirmation was made about a difference in late toxicity.[216]

Patients with stage IVA disease (bladder and/or rectal invasion) can be treated with either higher doses of external radiation to the whole pelvis with concurrent chemotherapy followed by intracavitary or interstitial insertions (total dose to point A with LDR BT about 90 Gy) and additional parametrial irradiation or with pelvic exenteration. Niibe et al,[217] in an analysis of 179 patients with stage IIIB AC, suggested that an optimal dose for large tumors was a total biologically effective dose (BED) of greater than 100 Gy.

A prospective single-arm trial, RTOG 0116, treated patients with positive para-aortic or high common iliac lymph nodes with extended-field radiation combined with cisplatin chemotherapy followed by BT.[218] IMRT was not allowed. The trial showed that this regimen is feasible, but the late grade 3 and 4 toxicity rate was 40%. There was no reduction in acute toxicity with the addition of amifostine. The use of extended-field IMRT has been shown to reduce the risk of GI toxicity in two retrospective series reports[130] and has become standard where available to patients with positive common or PANs requiring extended-field radiation with concurrent chemotherapy.

Randomized Trials of Chemoradiotherapy

Results from several randomized controlled trials demonstrated that cisplatin-based chemotherapy, when given concurrently with primary RT, prolongs survival in women with locally advanced cervical cancers, as well as in women posthysterectomy receiving adjuvant RT who have metastatic disease in the pelvic lymph nodes, positive parametrial disease, or positive surgical margins at the time of primary surgery.

The GOG conducted randomized Protocol 85, in which patients with carcinoma of the cervix, a clinical stage of IIB to IVA, and negative PAN were treated with external pelvic irradiation (51 Gy) combined with 30 Gy to point A with LDR BT.[219] One hundred twenty-seven patients received 5-FU (IV infusion, 1 g/m^2 for 4 days) and cisplatin (50 mg/m^2 IV) on days 1, 29, and 30 to 33, and 191 patients received hydroxyurea (80 mg/kg orally twice weekly). With a median follow-up for survivors of 8.7 years, the 5-year survival rate in the cisplatin/5-FU arm was 60%, compared with 47% for women in the hydroxyurea arm.

After completion of GOG 85, the group opened GOG 120[220,221] for the same patient population, which was a three-arm randomized trial comparing irradiation plus hydroxyurea versus irradiation plus weekly cisplatin versus irradiation plus hydroxyurea, cisplatin, and 5-FU. In 526 evaluable patients with a median follow-up for survivors of 106 months, the 5- and 10-year survival rates for women in both the weekly cisplatin and irradiation arm and the irradiation, 5-FU, and cisplatin arm were 60% and 53%, respectively, compared with 40% and 34% in the hydroxyurea and irradiation arm ($P \leq .01$). OS was also significantly better in the two patient groups receiving cisplatin. Hematologic toxicity was greater in the group treated with the three drugs compared with cisplatin or hydroxyurea alone.

The RTOG conducted a randomized study of 389 patients with stage IB to IIA of greater than 5 cm, proven positive pelvic lymph nodes, or stage IIB to IVA carcinoma of the cervix in which patients were treated with either pelvic and para-aortic irradiation (best arm of RTOG Protocol 79-20) or pelvic irradiation and three cycles of concomitant chemotherapy with cisplatin (75 mg/m^2) and 4-day infusion of 5-FU (1,000 mg/m^2/day). Updated results were reported by Eifel et al[199] with a median follow-up of 6.6 years for 228 survivors, the 8-year OS rate for women on the irradiation and cisplatin/5-FU arm was 67% versus 41% in the irradiation-only arm ($P < .0001$). DFS rates were 66% and 36%, respectively. There were no significant differences in late complications in the treatment groups.

In GOG 123, 369 women were enrolled. One hundred eighty-three women with bulky (≥4 cm) stage IB carcinoma of the cervix with negative pelvic nodes and PANs radiographically or surgically determined were randomized to be treated with pelvic EBRT and BT, followed by extrafascial hysterectomy, and 186 received EBRT and BT with weekly cisplatin (40 mg/m^2; total dose not to exceed 70 mg/week) followed by extrafascial hysterectomy. In an updated analysis with a median follow-up of 101 months,[222] the 6-year PFS rate for women treated with irradiation and cisplatin was 71%, compared with 60% for those treated with RT alone, after adjusting for age and tumor size ($P < .004$). The unadjusted 6-year OS rates were 78% and 64%, respectively ($P < .015$).

The results of randomized trials using concurrent CRT are summarized in Table 76.6. Curtin et al[223] completed a small phase III trial in which 89 patients with high-risk stage IB or IIA undergoing RH and pelvic node

dissection were randomized to be treated with postoperative cisplatin/bleomycin alone (44 patients) or combined with pelvic RT (45 patients). There were 9 and 10 recurrences, respectively, and survival was equivalent.

TABLE 76.6 RANDOMIZED STUDIES OF CONCURRENT CHEMOIRRADIATION IN CERVICAL CARCINOMA

Author (Reference)	Drugs	Number of Patients	Median Follow-Up Time (Year)	Survival		
				Chemoradiation Therapy (%)	Radiation Therapy (%)	*P*
Chemoradiation vs Radiation Alone						
Eifel et al[199] (RTOG 9001)[a]	CF	389	6.6	67	41	<.0001
Keys et al[251]; Stehman et al[222] (GOG 123)	C	369	8.4	78	64	<.015
Peters et al[205] (SWOG 8797)	CF	243	5.2	80	66	NR
Pearcey et al[224] (NCIC)	C	253	6.9	62	58	.53
Shrivastava et al[226]	C	850	7.3	54	46	.04
Comparative Trials of Chemoradiation Regimens						
Whitney et al[219] (GOG 85)	CF vs H	368	8.7	55 CF	43 H	.018
Rose et al[220] (GOG 120)	C vs H	526	8.8	5 yr, 60; 10 yr, 53	5 yr, 40; 10 yr, 34	.002
	CHF vs H			5 yr, 61; 10 yr, 53	5 yr, 40; 10 yr, 34	.002
Lanciano et al[233] (GOG 165)[b]	F vs C	316	3.4	64	55	NR

C, cisplatin; CI, confidence interval; F, 5-fluorouracil; GOG, Gynecologic Oncology Group; H, hydroxyurea; HR, hazard ratio; RTOG, Radiation Therapy Oncology Group; SWOG, Southwest Oncology Group.

[a]Eight-year results.

[b]Trial terminated early because of higher risk of treatment failure and higher mortality with 5-fluorouracil (HR = 1.37, 95% CI = 0.96-1.97).

Modified from Viswanathan AN. Advances in the use of radiation for gynecologic cancers. *Hematol Oncol Clin North Am.* 2012;26(1):157-168. Copyright © 2012 Elsevier. With permission.

On the other hand, Pearcey et al[224] reported on a Canadian randomized study in which 127 patients with stage IB to IIA of greater than 5 cm or IIB carcinoma of the cervix were randomized to be treated with cisplatin (40 mg/m^2 weekly) and RT, and 126 patients were treated with RT alone (50.4 Gy to the pelvis combined with BT). With a median follow-up of 65 months, the 5-year survival rates were 59% and 56%, respectively (P = .43). There was a somewhat greater incidence of significant late morbidity in the RT-alone group (12% vs 6%; P = .08). Possible explanations for the discrepancy in results between the five U.S. and the Canadian study were that a higher percentage of early-stage patients were accrued, who, therefore, had less of a difference in survival, given that the baseline survival rate for both arms was quite high and that treatment time was short for both arms, again minimizing the difference in improving survival in the chemotherapy arm. This was the smallest of the randomized CRT trials, and although the HR was reduced, given the factors equalizing the two arms, a larger number of patients would have possibly shown a significant difference.

In a randomized trial comparing monthly 5-FU and cisplatin versus weekly cisplatin concurrent with pelvic radiation, Kim et al[225] enrolled 158 stage IIB and IVA patients. With a median follow-up of 39 months, the acute grade 3 and 4 hematologic toxicities were significantly worse in the fluorouracil/cisplatin arm (43% vs 26%; P − .04). The trial was not powered to detect a survival difference, and no difference in the OS or PFS was noted.

As the data about the benefit of cisplatin-based CRT in patients with an advanced primary tumor were less robust, a later Indian trial randomized 850 patients with 2009 FIGO stage IIIB cervical cancer to pelvic RT and BT with or without weekly cisplatin. The results showed a significant 8% to 8.5% increase in the 5-year DFS and OS with addition of weekly cisplatin.[226]

In the United States, weekly cisplatin has become the preferred approach, with less toxicity than an every 3-week regimen and increased likelihood of completing the treatment on schedule. It is important that patients complete the full course of 45 Gy with, ideally, five to six weekly doses of cisplatin or a cumulative dose of over 180 to 200 mg/m^2. The number of completed cycles of weekly treatment was shown by Nugent et al[227] to be predictive of survival. One hundred eighteen patients with locally advanced cervical cancer (stages IB2-IVA) were treated with combination weekly cisplatin (40 mg/m^2) and radiation between 2003 and 2007. Thirty percent of patients completed fewer than six cycles of chemotherapy. In multivariate analyses, the number of chemotherapy cycles was independently predictive of PFS and OS. Patients who received fewer than six cycles of cisplatin had a worse PFS (HR = 2.65; 95% CI = 1.35-5.17; P = .0045) and OS (HR = 4.47; 95% CI = 1.83-10.9; P = .001). Advanced stage, longer time to RT completion, and absence of BT were also associated with decreased OS and PFS (P < .05). Similar results were found when analysis was conducted using a breakpoint of at least but not less than five chemotherapy cycles. The authors concluded that aggressive supportive care to minimize missed chemotherapy treatments may improve survival after CRT. A retrospective review[228] questioned whether patients with cervical cancer should receive cisplatin 20 mg/m^2 × 5 days every 21 days concomitant with RT or weekly 40 mg/m^2 weekly concomitant with RT, given that an advantage with regard to both acute toxicity and PFS was seen in the 5-day regimen.

Alternatives to Concurrent Cisplatin-Based Chemoradiotherapy

No randomized trials compared carboplatin and cisplatin as concurrent chemotherapy with RT in cervical cancer. Carboplatin is a known radiosensitizer and sometimes used as replacement for cisplatin in ineligible patients, but it should be carefully considered as the evidence for equivalence is lacking. Nam et al reported on a prospective cohort of 51 patients who were compared to historical controls treated with cisplatin and RT. No significant differences were reported in response rate, OS, PFS, or toxicity.[229] A randomized trial has shown no difference in OS and PFS with carboplatin alone or in combination with oral tegafur-uracil.[230] Katanyoo et al[231] reported 148 patients with stage IIB to IVA cervical cancers treated with concurrent weekly carboplatin (100 mg/m^2 or area under the curve 2) for a median of six

cycles and radiation. Among the 142 responders, 36 experienced recurrences: pelvic recurrences in 7 (4.7%), distant failure in 25 (16.9%), and both pelvic and distant in 4 (2.7%). The 2- and 5-year PFS rates were 75.1% and 63.0%, respectively, with the corresponding 2- and 5-year OS rates of 81.9% and 63.5%. No grade 3 or 4 hematologic and nonhematologic toxicities were observed during treatment in any patients. Late grade 3 to 4 GI or genitourinary (GU) toxicities were 10.1% and 0.7%, respectively.

A Chinese trial randomized cisplatin and nedaplatin given concurrently with RT in 160 patients. No significant differences were found in PFS and OS, with less GI and renal toxicity but higher liver toxicity in the nedaplatin group.[232]

In GOG Protocol 165, patients with stage IIB to IVA cervical cancers received either RT and concurrent weekly cisplatin (40 mg/m^2) or RT and a protracted venous infusion (PVI) of 5-FU. Lanciano et al[233] reported that the study was prematurely closed after an interim analysis showed a failure rate 35% higher and would not result in improved DFS with PVI 5-FU/RT compared with weekly cisplatin.

Mitomycin C acts as an alkylating agent and inhibits DNA and RNA synthesis. Activation of mitomycin C is increased in hypoxic conditions, and thus, it acts as a hypoxic radiosensitizer. Interstitial pneumonitis and pulmonary fibrosis are usually related to the dose of drug. The use of IV dexamethasone before administration of the drug may prevent pulmonary toxicity.

Christie et al[234] described results in three groups of patients with stage IIB and III carcinomas of the cervix treated with pelvic irradiation and an intracavitary insertion combined with chemotherapy. Group A (64 patients) received 5-FU infusion during the first and last weeks of irradiation combined with mitomycin C (10 mg/m^2 IV). Group B (29 patients) received 5-FU without mitomycin C, and group C (84 patients) received irradiation alone. With a median follow-up of 7.2 years, the 5-year survival rates were 56%, 32%, and 36%, and the local tumor control was 73%, 53%, and 50%, respectively. Toxicity was greater in group A (36% grades 3 and 4) compared with the 5-FU and irradiation group (14%) and the irradiation-alone group (20%).

Roberts et al[235] reported on a trial in which 160 patients with locally advanced cervical cancer were randomized to receive RT alone (82 patients)

or RT with concomitant mitomycin C (78 patients). The 4-year actuarial survival was 72% and 56%, respectively (P = .13), and the LR-free survival rate was 78% and 63%, respectively (P = .11). There were no treatment-related deaths. No excess in nonhematologic toxicity has been observed with combined mitomycin C and irradiation.

Several small phase II studies have been performed, showing no advantage to weekly taxanes over weekly cisplatin[236] and too high toxicity with concomitant cisplatin-paclitaxel.[237]

Older randomized trials of irradiation with concomitant hydroxyurea (HOU) in patients with cervix cancer suggested that survival was higher in the HOU group. Symonds et al,[238] in a review of seven randomized trials, found no evidence to support the use of hydroxyurea with RT in cervix cancer.

Singh et al[239] published a randomized comparison of cisplatin and gemcitabine as concurrent CRT in 60 patients with cervical cancer, showing higher hematologic toxicities with gemcitabine and higher GI toxicities with cisplatin. There was also a nonsignificant higher CR rate with cisplatin (87% vs 73.3, P = .20).

Adjuvant Chemotherapy After Chemoradiotherapy

Whether there is benefit from adjuvant chemotherapy after CRT in some patients is controversial. A randomized trial of 515 cases of stage IIB to IVA cervical carcinomas treated with concurrent gemcitabine plus cisplatin followed by adjuvant gemcitabine and cisplatin compared to standard concurrent cisplatin with radiation showed a significant 3-year PFS benefit of 74% versus 65% (P = .03) and a significant reduction of risk of death. (HR = 0.68, 95% CI = 0.49-0.65).[240] Grade 3 and 4 toxicities were higher in the extended chemotherapy arm, including two deaths. In contrast, two other randomized trials failed to show added benefit with adjuvant chemotherapy after CRT. Tangjitgamol et al[241] reported on the ACTLACC trial that randomized 259 patients after CRT to continue observation or receive three cycles of carboplatin and paclitaxel. No significant differences were found in PFS or OS, just reduced systemic recurrences in the adjuvant chemotherapy group (5.4% vs 10.1%, P = .029). The larger multinational OUTBACK trial randomized 926 patients after CRT to observation or adjuvant four cycles of carboplatin and paclitaxel and found higher toxicity but no benefit in OS after median 5 years of follow-up (72% vs 71%, P = .81).[242] About 22% of patients

in the adjuvant group did not start the adjuvant chemotherapy, which was similar to other adjuvant chemotherapy trials.

Trials of Additional Systemic Agents Concurrently With Chemoradiotherapy

Bevacizumab With Chemoradiotherapy

RTOG 0417 treated patients with once-weekly cisplatin (40 mg/m^2) chemotherapy and standard pelvic RT and BT. Bevacizumab was administered at 10 mg/kg IV every 2 weeks for three cycles. A total of 49 patients were evaluable. The median follow-up was 12.4 months (range, 4.6-31.4 months). There were 15 (31%) protocol-specified, treatment-related adverse events within 90 days of treatment start; the most common were hematologic (12/15; 80%). Eighteen (37%) occurred during treatment or follow-up at any time. An update with 3.8-year follow-up (range 0.8-6 years) showed a 3-year OS 81.3%, DFS 68.7%, and locoregional failure 23.2%, with 26.5% grade 3 adverse events (mainly hematologic) and 10.2% grade 4 events.[243]

Epidermal Growth Factor Receptor Inhibition With Chemoradiotherapy

Nogueira-Rodrigues et al[244] reported a phase I study administering escalating doses of erlotinib (50/100/150 mg) combined with cisplatin (40 mg/m^2, weekly, five cycles) and RT (external beam, 4,500 cGy in 25 fractions, followed by four fractions/600 cGy weekly of BT) in patients with SCC of the cervix, stages IIB to IIIB. Fifteen patients were enrolled, 3 at dose level (DL) 50 mg, 4 at DL 100 mg, and 8 at DL 150 mg. Three patients did not complete the planned schedule. One patient at DL 100 mg withdrew informed consent because of grade 2 rash; at DL 150 mg, one patient presented with Raynaud syndrome and had cisplatin interrupted, and another patient presented with grade 4 hepatotoxicity. The latter was interpreted as dose-limiting toxicity, and a new cohort of 150 mg was started. No further grade 4 toxicity occurred. Grade 3 toxicity occurred in six cases: diarrhea in three patients, rash in two patients, and leukopenia in one patient. Treatment did not lead to limiting in-field toxicity.

Checkpoint Inhibition and Chemoradiotherapy

As checkpoint inhibitors have shown survival benefit in patients with metastatic cervical cancer, their use in earlier stages is under active research. The CALLA trial,[245] which included 770 patients with stage IB2 to IIB, node-positive, or stage III to IVa cervical cancer, added durvalumab or placebo to CRT for up to 2 years. With a median follow-up of 18.4 months, it showed no significantly added benefit with durvalumab to 12-month PFS (76% vs 73%, HR 0.84, *P* = .17). A post hoc analysis found that in patients with high PD-L1 expression, determined as 20% and higher tumor area positivity, durvalumab slowed progression with HR 0.62 (95% CI, 0.4-0.91). The KEYNOTE-A18 trial, a similarly designed trial, randomized 1,060 patients to receive either pembrolizumab or placebo concurrently to CRT and then up to two and half years. Results have shown significant improvement in 2-year PFS with pembrolizumab (67.8% vs 57.3%, HR 0.7 [95% CI, 0.55-0.89], *P* = .002) for all comers. OS data showed a favorable trend, and grade 3 and higher adverse events incidence was reported higher with pembrolizumab (67% vs 60%).[246]

Neoadjuvant Chemotherapy

Although response rates to the chemotherapy are between 30% and 85%, none of the studies in the preconcurrent cisplatin era, comparing NACT followed by surgery or RT to primary RT alone, showed an advantage for pelvic tumor control or survival. It was hypothesized to be related to accelerated repopulation and that receiving upfront chemotherapy may compromise immune status and the patient's ability to receive definitive treatment with radiation or surgery.

As concurrent cisplatin with RT became standard, trials comparing NACT followed by CRT or surgery to CRT alone also failed to show benefit to this approach and some even showed harm. Da costa et al[247] randomized 107 patients with stage IIB to IVa cervical cancers to NACT with cisplatin and gemcitabine for three cycles followed by CRT. CR was seen in 56% of the NACT arm versus 80% in the CRT arm (*P* = .008), which translated to reduced 3-year OS (60.7% vs 86.7%, *P* = .006).

Gupta et al[212] randomized 635 patients with FIGO 2009 stage IB2, IIA, and IIB cervical cancers to receive three cycles of carboplatin and paclitaxel followed by surgery or primary CRT alone. The 5-year DFS rates were significantly higher in the CRT group (76.7% vs 69.3%, *P* = .038), and no OS difference was observed.

Kenter et al[213] randomized 626 patients with bulky stage IB and stage II cervical cancers to platinum-based NACT followed by surgery to CRT alone. Only 71% of patients in the NACT arm were able to complete therapy, versus 82% in the CRT arm. Adjuvant RT was needed in 47% of patients who underwent hysterectomy. No significant 5-year OS rate difference was seen (72% vs 76%).

The INTERLACE trial[248] randomized 500 patients with locally advanced tumors to receive either NACT of 6 weekly cycles of carboplatin and paclitaxel followed by CRT or CRT alone. We await full publication of this trial as its applicability is important for countries where a wait time for RT exists, and patients cannot immediately start concurrent CRT.

Radiation Alone With or Without Surgery

For patients unable to tolerate concurrent chemotherapy or in countries where chemotherapy is not readily available, radiation alone may be used as an alternative to CRT. Outcomes were reported in a previously mentioned meta-analysis as 60% 5-year OS, compared to 66% with CRT.[216]

Bulkier tumors can be more challenging to fully eradicate with BT; thus, they have a higher incidence of central recurrence, and regional and distant dissemination. When using plain x-ray point-based planning for BT, because of the inability of intracavitary sources to encompass the entire tumor in a high-dose volume, larger doses of external radiation to the whole pelvis, extrafascial hysterectomy, or both have been advocated to improve therapeutic results. Alternatively, the use of 3D planning for the BT component significantly improves survival, and the ability to dose escalate because of a more precise dose delivery improves LC.[249] Prior to 3D BT planning becoming widely available, primary RT with adjuvant hysterectomy was investigated as another approach to improve LC.

Eifel et al[250] evaluated 1,526 patients, of whom 371 had tumors 6 cm or greater. There were biases in treatment selection, but a statistically significantly higher 10-year survival rate was noted in patients treated with irradiation and surgery (64% vs 45%). Tumor diameter was highly significant as a prognostic factor, and the authors concluded that only patients with lesions greater than 8 cm in diameter benefited from adjuvant hysterectomy. In the same study, 98 patients with stage IB and IIB bulky endocervical carcinomas (≥6 cm in diameter) were treated with RT alone. Twenty-four

patients received less than 6,000 mgh of intracavitary treatment, and 73 received higher doses. Despite having somewhat more favorably treated tumors, patients who received less than 6,000 mgh had a higher rate of pelvic recurrence at 5 years (33%) than those who received higher doses (16%; P = .03). Actuarial 5-year survival rates were 44% and 60% for low- and high-dose groups, respectively (P = .14).

The GOG and RTOG conducted a randomized phase III clinical trial in which 282 patients with carcinoma of the cervix measuring 4 cm or greater (exophytic or barrel shaped) were treated with either external beam and intracavitary irradiation or a slightly lower dose of intracavitary irradiation and the same pelvic EBRT followed by an extrafascial hysterectomy.[251] The survival rates were 61.4% for irradiation alone and 64.4% for the combined irradiation and surgery group. The incidence of recurrences was 43.3% in the irradiation group compared to 34.5% with combined therapy (P = .081). The incidence of LRs was 25.8% and 14.4%, respectively. The incidence of grade 3 and 4 sequelae of therapy was 10.5% and 9.8%, respectively. Thus, the addition of hysterectomy to standard irradiation did not significantly affect survival, although there was a small reduction in the LR rate. When combined therapy is used, the dose of irradiation delivered to the lymph nodes, the time of the operation, and the pathologic examination of the specimens are critical in determining the presence of postirradiation residual tumor.

Chemoradiotherapy With Adjuvant Hysterectomy

Keys et al[251] reported on 183 women with bulky (≥4 cm) stage IB carcinoma of the cervix with negative pelvic nodes and PANs radiographically treated with pelvic EBRT and BT, with or without weekly cisplatin, followed by extrafascial hysterectomy. A significant survival advantage was seen with the combination of concurrent CRT. However, in comparison to other trials, the survival was not significantly improved with the addition of a hysterectomy. A subsequent reanalysis including GOG 123 and GOG 71 analyzed 464 patients allocated to pelvic radiation (75 Gy, n = 291) plus hysterectomy or to pelvic radiation (75 Gy) and cisplatin (40 mg/m^2, n = 176) plus hysterectomy. A benefit to adding cisplatin was seen only for patients who had a poor response, defined as over 10% viable tumor.[252] This suggested that whatever benefit was seen for adjuvant hysterectomy became obsolete with concurrent cisplatin in most cases, while its risks remained. Touboul et al[253] reported on

toxicities for 150 patients with stage IB2 to IVA cervical cancers treated at Institut Gustave Roussy (IGR) with extrafascial versus modified RH after CRT. After a median follow-up of 3.6 years, 15% had grade 2 or greater side effects, including lymphedema, ureteral fistula, bowel fistula, and iliac and vessel rupture. There were two postoperative deaths. Modified radical versus extrafascial hysterectomy had a higher odds ratio for complications of 2.4 (P = .04), as did the presence of residual disease.

Morice et al[254] reported a randomized trial of 61 patients treated with adjuvant hysterectomy versus none after EBRT with concurrent weekly cisplatin and vaginal BT (15 Gy to intermediate-risk CTV) for stage IB2 or II cervical cancer. Hysterectomy increased the number of deaths, with an 11% nonsignificant survival advantage in the no-hysterectomy arm (86% vs 97%). As a result of this trial, routine adjuvant hysterectomy is no longer practiced for patients who have no residual disease at 6 weeks after CRT. Therefore, patients should receive definitive doses of CRT, with hysterectomy reserved for salvage in patients with either gross residual disease or PET-positive disease that is biopsy proven at 3 months after completion of radiation.

Elective Para-Aortic Lymph Node Irradiation

Prior to the cisplatin CRT era, randomized trials have shown that in some high-risk patients with no clinical or radiographic evidence of pathologic PAN, improved local-regional control and even survival is gained with the addition of elective para-aortic irradiation to pelvic irradiation, at the cost of increased bowel toxicity.

No randomized trials of extended fields to the PAN were performed in the cisplatin CRT era.

Huang et al[255] assessed 758 patients initially treated with pelvic RT, with only 23% of them receiving two or more cycles of concurrent chemotherapy. The study reported that 38 (5%) and 42 (6%) had isolated and nonisolated PAN recurrences after a median follow-up of 50 months (range, 2-159 months), respectively. The 3- and 5-year OS rate after PAN recurrence was 35% and 28%, respectively, with those with isolated recurrences faring better than those with a nonisolated recurrence (P < .001). An SCC-Ag level of greater than 40 ng/mL (P < .001), advanced parametrial involvement (score 4-6; P = .002), and the presence of pelvic lymphadenopathy (P = .007) were independent factors associated with PAN relapse on multivariate analysis.

Subsequently, focusing specifically into the subgroup that received concurrent CRT therapy, this group identified pretreatment CEA of 10 ng/mL or higher as an additional risk factor of PAN relapse in patients with pretreatment SCC-Ag levels of less than 10 ng/mL.[256]

The multicenter EMBRACE cohort, which had varying upper field limits, showed that in the 1,338 patients included, a total of 104 any PAN recurrences were seen, 55 of which were isolated. Risk factors identified were any nodal disease and tumor width.[257]

PAN irradiation was shown to be protective from these recurrences. A risk-based algorithm was suggested and implemented in the ongoing EMBRACE II study, mandating elective para-aortic lymph nodes (PAN) irradiation in any patients with three or more positive pelvic nodes or any positive common iliac nodes, to potentially reduce these isolated recurrences.[258] Until further results are reported, the role of prophylactic para-aortic radiation, particularly in patients with large tumor size, parametrial involvement, or heavily involved pelvic lymph nodes, must be carefully weighed against the potential toxicities of para-aortic radiation.

METASTASES TO PARA-AORTIC LYMPH NODES

In the FIGO 2018 staging system, this was defined as stage IIIC2 and could be determined by either imaging or surgical assessment. This state harbors worse prognosis than patients with pelvic nodal disease, but it is still curable, especially with concurrent chemotherapy and IMRT. One retrospective report of 102 patients treated with up to 59.4 Gy to the PAN with a 3-year PFS and OS of 57% and 69%, respectively. Acute major toxicity (grade 3 and higher) was mostly hematologic (61%), with even two deaths, and to 3% GI. Late grade 3 to 4 toxicities were reported as 14% hematologic, 8% GI, and 3% GU.[259]

Toxicity to the small bowel and duodenum is important to consider when treating PANs. In 105 patients with enlarged PANs, 36% had cervical cancer; the 3-year rate of duodenal toxicity was 11.7%, with fatal events in two patients because of perforation. The recommended V_{55} less than 15 mL resulted in 7% toxicity, whereas V_{55} greater than 15 mL resulted in 48% toxicity.[260] A retrospective analysis of 103 patients with cervical cancer and PAN metastases demonstrated factors associated with improved DSS included concurrent CRT ($P = .001$), baseline PET imaging ($P = .01$), and treatment of

PANs with IMRT (P = .02). The crude rate of grade 3 or higher late treatment-related adverse effects was 17%.[176] SIB to 50 to 54 Gy followed by a sequential boost to 60 to 65 Gy has been demonstrated, with adherence to small-bowel dose constraints.[165,175]

METASTATIC, PERSISTENT, OR RECURRENT DISEASE

This category includes patients diagnosed with stage IVB at presentation, patients who recurred after local therapy, or patients whose disease did not fully respond to definitive RT. The main modality of treatment is systemic therapy, which may be combined with RT as needed.

Several chemotherapy agents were tested as monotherapies and combinations. Responses were observed for platinum agents, taxanes, camptothecin derivatives, and nucleoside, with a better response in dual platinum combination and no added benefit but higher toxicity with triple combinations. A four-arm comparison of cisplatin/paclitaxel versus cisplatin/vinorelbine, cisplatin/gemcitabine, or cisplatin/topotecan in 513 patients found that the use of cisplatin/paclitaxel remained the best option for patients with stage IVB, recurrent or persistent cervical carcinoma, with a median OS of 12.9 months.[261]

In a phase II GOG study of cetuximab 400 mg/m^2 initial dose followed by 250 mg/m^2 weekly until disease progression or prohibitive toxicity, 38 (15%) patients had no progression for at least 6 months. The median OS was 7 months. When cetuximab was combined with cisplatin, no additional benefit beyond cisplatin was identified.[262]

Antiangiogenic tyrosine kinase inhibitors pazopanib and lapatinib were tested in 230 patients with stage IVB persistent/ recurrent cervical carcinoma. An improvement in PFS and OS was seen with pazopanib.[263] Bevacizumab, a recombinant humanized anti-vascular endothelial growth factor monoclonal antibody, has shown efficacy in later lines.[264] The addition of bevacizumab to first-line chemotherapy in a median OS of 17 months compared to 13.3 months in the chemotherapy-only arm (HR 0.71, P = .004).[265] The added toxicity included hypertension (25% vs 2%) and thromboembolic events (8% vs 1%).

Immune checkpoint inhibitors have proven to be beneficial in the metastatic setting. After showing OS benefit,[109,111] the KEYNOTE-826 trial randomized 617 patients to receive either pembrolizumab or placebo to first-

line chemotherapy with or without bevacizumab. Patients were stratified according to CPS. Colombo et al[110] published the results, showing that in the CPS greater than 1 group that included 548 patients, median PFS and 2-year OS was 10.4 months and 53% in the pembrolizumab group versus 8.2 months and 41.7% in the placebo group. The main added toxicity with pembrolizumab was higher rates of hypothyroidism (18.2% vs 9.1%). The BEATcc trial, published by Oaknin et al,[266] also showed increased PFS and OS with the addition of atezolizumab, an anti–PD-L1 antibody to the first line of carboplatin, paclitaxel, and bevacizumab. The trial randomized 410 patients with metastatic, persistent, or recurrent cervical cancer, regardless of PD-L1 expression. The median OS was significantly higher with atezolizumab, 32.1 versus 22.8 months in the standard therapy group (P = .0046). Grade 3 and higher toxicity rates were similar between the groups, and grade 1 to 2 diarrhea, arthralgia pyrexia, and rash were higher in the atezolizumab groups.

Radiotherapy in Metastatic Disease

The administration of RT to the pelvis or other involved sites in patients that previously were not irradiated should be considered. Before systemic treatment was available, the RTOG 8502 trial has shown that in good performance status metastatic patients, radiation, even at palliative doses, can allow for prolonged remission with some surviving over 2 years.[267] An NCDB analysis in 2,838 patients found that the addition of definitive local treatment (either surgery and/or RT in doses over 45 Gy, with RT being given in 90% of the cases) to systemic chemotherapy was associated with better OS (HR 0.57, $P < .001$), with a median OS of 19.2 months compared to 10.1 months.[268] Perkins et al[269] reported on a multi-institutional series of 95 patients, all were treated systemically, 34 treated also with pelvic RT. The median OS was significantly longer with pelvic RT (41.6 vs 17.6 months, $P < .01$). Notably, 20 patients were also treated with bevacizumab, with higher proportion in the systemic therapy–only group (26% vs 12%). The combination of bevacizumab might increase the risk of GI bleeding and fistula formation, but pelvic toxicity rates were not significantly different between the groups. Wiley et al[270] reported on 29 patients who were all treated with a platinum doublet and at least three cycles of bevacizumab. Definitive radiation was given to 11 of them, and 9 received palliative doses. Definitive RT was

associated with longer OS, and no significant toxicity differences were seen. As systemic therapy continues to improve OS and distant metastases control, the importance of LC may become even greater.

Aggressive combined modality treatment might even be curative in some patients with limited metastatic disease. Kim et al[259] reported on 25 patients with supraclavicular metastases at diagnosis who were treated with curative intent with concurrent CRT and BT. Mean dose to the supraclavicular area was to 59.4 Gy, and 3-year PFS and OS were reported as 33% and 49%, respectively. A series of 60 patients in China with oligometastatic (up to five metastases) stage IVB disease at diagnosis were treated initially with definitive CRT to both primary and metastatic lesions using IMRT, volumetric modulated arc therapy, and BT. Ablative doses were safely achieved, and the reported outcomes were 5-year PFS and OS rates of 25.9% and 51.4%, respectively.[271] Lymphatic spread compared with hematogenous spread, lower number of metastases, and smaller primary tumor were shown to be positive prognostic factors. In a SEER database analysis looking into patients with cervical cancer with distant lymph node metastases, the utilization of BT with EBRT was associated with better CSS compared with EBRT alone.[272]

Almost all of the data described earlier are retrospective, and so it is prone to selection bias. Thus, the decision to irradiate must be carefully considered in each patient according to their specific presentation, comorbidities, availability of other therapies, and toxicity risk.

CARCINOMA OF THE CERVICAL STUMP

A supracervical hysterectomy, which removes the uterus and leaves the cervix behind, may be performed for benign conditions of the uterus. The use of subtotal hysterectomy has declined, given the persistent risk of cervical cancer arising in the remnant tissue and the difficulty of managing cancer of the cervical stump.

It is important to divide carcinoma of the cervical stump into true, when the first symptom occurs 3 years or more after subtotal hysterectomy, or coincidental, when the symptoms are noticed before the third postoperative year. This separation is important because the prognosis for true carcinoma of the stump is significantly better than for coincidental lesions, in which carcinoma was probably present when the hysterectomy was performed.

The natural history and patterns of spread of carcinoma of the cervical stump are similar to those of the cervix in the intact uterus. The diagnostic workup, clinical staging, and basic principles of therapy are the same. Treatment also follows similar paradigms. When surgery is indicated for early-stage I tumors, it may be more difficult because of the previous surgical procedures and the presence of adhesions in the pelvis. With RT, external beam treatments are identical, although small bowel may be adherent to the superior portion of the cervix because of scar tissue, and using the prone position, as well as having the patient maintain a full bladder for treatment, may aid in attempting to move the small bowel out of the radiated field. Whole-pelvic radiation is recommended, with the superior border set at the level of the bifurcation of the common iliac vessels as determined by a CT simulation, or at the L4-L5 interspace for those planned with plain film radiographs. A dose of 45 Gy in 1.8-Gy fractions over 5 weeks is the most commonly recommended dose, with concurrent weekly cisplatin at 40 mg/m^2 given for five doses. For BT, if greater than 2 cm of the endocervical canal remain, it is best to insert a short tandem surrounded by ovoids, a ring, or, if indicated because of vaginal extension or lateral extension, interstitial catheters. For LDR insertions, as many sources as technically feasible should be inserted into the remaining cervical canal. For HDR BT, the tandem should extend from the cervical os superiorly to the full extent of the canal. When there is no opportunity to insert any sources into the cervical canal, an interstitial implant to bring the tumor dose to approximately 80 to 90 Gy for BT after completing a standard dose of 45 Gy to the whole pelvis is recommended while monitoring the radiation dose to the OARs. The use of external beam radiation alone is not recommended due to the significant mobility of the cervix because of bladder motion, the low-dose tolerance of the surrounding small bowel, and the high dose of radiation necessary for cure in patients with bulky disease. Total dose (external and LDR intracavitary BT) to the upper vaginal mucosa should not exceed 150 Gy, and tolerance doses to small volumes (D_{2cc}) of the bladder (90-100 Gy) or rectum and sigmoid (70-75 Gy) should be carefully monitored.

The 5-year survival rate for carcinoma of the cervical stump treated with irradiation is similar to that reported for patients with carcinoma of the intact uterus. The anatomic sites of failure and the incidence of recurrences are

similar to those of patients in whom the uterus is intact. Distant metastases also follow the same distribution.

Hellstrom et al[273] published a retrospective study of 145 patients treated for carcinoma of the cervical stump from 1959 up to 1987, representing 2.2% of all cervical cancers. Three control cases to each case were matched from the cohort of cases with cervical carcinoma with intact uterus. The dose of irradiation from the intracavitary application given to the stump cancers was lower than for comparable cases with intact uterus. Long-term prognosis for SCC of the uterine stump was comparable to that of the ordinary cervical carcinomas. Stump ACs had a worse prognosis compared with AC of the intact uterus ($P < .07$) and with SCC stump ($P = .05$). The complication rate was higher for stump cancer cases compared with that for cervical cancers with an intact uterus. The same group published an update of this series with patients up to 2004, with similar findings.[274] Only 16 more patients were added, perhaps due to the declining prevalence of women who are postsupracervical hysterectomy. Because of the close proximity of the bladder, rectum, and small intestine to the intracavitary sources and to the often higher doses of external beam irradiation given to the whole pelvis, complications are somewhat more frequent than in carcinoma of the cervix with an intact uterus. Care in BT treatment planning, including the use of 3D-based treatment planning to minimize dose to the normal tissues, should be considered.

Wang et al[275] reported on a retrospective series of 31 patients, all treated with concurrent chemotherapy, EBRT, and BT. The 5-year PFS, OS, and LC were 69.6%, 84.9%, and 77.1%, respectively. The BT method was changed from 2D (plain radiography) to 3D (CT based) in the study period, with 14 treated with 2D BT, 5 transferred from 2D to 3D due to poor coverage, and 12 were completely 3D. LC was 100%, 91%, and 25% in the 3D, 2D, and combined groups, respectively. Toxicity was shown to be significantly lower and dosimetric parameters better in the 3D arm compared to the 2D arm.

NEUROENDOCRINE CARCINOMA OF THE CERVIX

Neuroendocrine carcinoma (NEC) of the cervix is a highly aggressive form of cervical cancer. It accounts for 1.4% of cases, with the small cell subtype being the most common, roughly 80%.[276] Like its counterparts in the lung and other anatomic locations, it has a high proliferation rate and marked

propensity for regional lymph node and distant metastases. All small cell carcinomas of the cervix are aneuploid, compared with only 30% of large cell nonkeratinizing squamous carcinomas. The incidence of lymphatic vascular space invasion is 80% to 90% and that of lymph node metastases has been reported to be 40% to 67%. Patients have extremely poor outcomes, with a Cochrane review by Tempfer et al[276] reporting that in 3,538 patients from 112 reports, the pooled median PFS and OS was 16 and 40 months, respectively. As it is a rare disease, data are mostly retrospective and consist of small series and cancer registries studies, and treatment paradigm is extrapolated from other types of cervical cancer and NEC from other locations. While it is very chemoresponsive, chemotherapy alone is rarely curative. Immune checkpoint inhibitors can be considered as they have shown benefit in NEC of the lung when combined with chemotherapy. However, their benefit alone in later stages of metastatic NEC of the cervix was minimal.[277]

These patients must be evaluated in conjunction with a medical oncologist; the workup should include a PET-CT and brain MRI if available and consider bone marrow aspiration biopsy of the iliac crest. Therapy should include radical surgery and platinum-based regimens with consideration of adjuvant RT in earlier stages, and in locally advanced disease pelvic EBRT and intracavitary BT, combined with similar systemic regimens. Chu et al[278] published a study of two cancer registries, from the United States and China, including 1,288 patients. They have shown an association of longer OS with radical surgery in FIGO 2018 stage IB3 to IIA2 disease. This may support the use of NACT and radical surgery in places with long wait times for definitive RT. If bleeding is present, prompt institution of RT with concurrent chemotherapy is necessary. Prophylactic cranial irradiation is not indicated because cervix cancer will most commonly spread first to lung and then to brain.

Patients with NEC of the cervix are treated with the same irradiation techniques and doses as outlined for other histologic varieties of cervical carcinoma in combination with multiagent chemotherapy, including external beam radiation to 45 to 50 Gy, followed by nodal boost if PET-positive nodes are identified, followed by BT. The most frequently prescribed drugs are cisplatin and etoposide (VP-16) every 3 weeks.

Hoskins et al[279] reported the outcomes of 31 patients with a multimodality regimen of combination chemotherapy (either cisplatin and etoposide or

carboplatin and paclitaxel) with concurrent involved-field RT. The 3-year OS and failure-free survival (FFS) rates were 60% and 57%, respectively. Outcome did not differ between regimens, but toxicity was lower with carboplatin and paclitaxel. Stage was the only prognostic factor with 3-year FFS of 80% and 38% for stages I to II and III to IV, respectively. Distant failure occurred in 28% and local failure in 13% of patients. Wang et al[280] published a retrospective study on adjuvant therapy after hysterectomy of 110 patients with stages I to III. Median follow-up was 39.6 months. The 5-year OS rates were 84.9%, 85.7%, and 60.9% for each stage, respectively. Longer OS was associated with patients receiving over three cycles of chemotherapy, but no significant difference was found between different platinum-based regimens or with the addition of RT.

Combined modality therapy may also have benefit in the metastatic setting. A series of 71 patients with stage IVB was reported by Salvo et al.[281] Survival outcomes were significantly superior in the 15 patients who were treated in addition to chemotherapy with pelvic RT in doses greater than 45 Gy, with 2-year PFS and OS rates of 24% and 49.2% versus 7.8% and 21.5%. In addition, a SEER database analysis by Dong et al[282] showed that adjuvant RT after radical surgery in 130 metastatic patients was also associated with a survival benefit compared to no RT (1-year OS rate of 79.3% vs 52.2%, P = .004).

ADENOCARCINOMA OF THE CERVIX

SCC accounts for 80% of cervical cancers, AC for 15%, and adenosquamous carcinoma for 3% to 5%. SEER data from 1972 to 2002 suggest that the incidence of cervical AC is rising, but based on SEER data, cause-specific mortality is not significantly different than that for SCC.[283] A separate SEER analysis of patients from 1988 to 2005 showed that patients with AC had an increased risk of dying compared to patients with SCC.[88] AC has been linked to HPV-18, which has a higher rate of nodal and distant metastases than HPV-16.[82] Despite a slower regression after irradiation, reflecting cellular kinetics and slow growth, no difference in tumor control or survival has been observed in ACs compared with SCCs, although prognosis is related to clinical stage, volume of disease, and dose of irradiation. Because of the predilection for endocervical involvement in AC, a combination of irradiation and conservative hysterectomy has been advocated by some authors, although

results are comparable with those obtained with irradiation alone. Given a lower toxicity profile with CRT, this is preferable to a planned course of RT alone followed by hysterectomy upfront. Patients who are younger had larger tumors or most importantly have residual disease after CRT may be candidates for adjuvant hysterectomy.[284]

An updated Cochrane database review[285] found only one randomized trial, the Landoni study,[202] in which a small subgroup analysis that was not powered to detect a difference showed an apparent improvement with surgery, although the majority of patients required adjuvant RT, which increases the rates of toxicity. In addition, the RT in this study was not optimal, and surgery was not compared to CRT, which is the current standard. A review of GOG prospective trial patients showed that there was no difference between AC and SCC if patients received CRT.[89]

Thus, surgery to early AC of the cervix should be pursued only after adequate staging to avoid the added toxicity of trimodal therapy. Primary CRT is considered the standard for patients with locally advanced cervical AC.

A renewed analysis of several GOG trials published by Levinson et al showed that intermediate-risk factors for recurrence for early cervical cancer after hysterectomy differed in their impact between AC and SCC, with LVSI and invasion being more pronounced in SCC compared to tumor size, which was more pronounced in AC, and histology-specific nomograms were created.[286]

Genomic profiling has also been shown to differ between AC and SCC, with the first more inclined to microsatellite instability; immunotherapy resistance–related STK11 alterations; actionable mutations, such as HER2 enrichment; and lower immune infiltration, while the latter was more inclined to high tumor mutational burden, PD-L1 expression, and higher immune infiltration.[287] As systemic therapy becomes more relevant in earlier stages of this disease, histology might play a greater role in treatment selection.

TREATMENT OF OLDER PATIENTS

Advanced age in patients with cervical cancer can impact their diagnosis and treatment. Registry studies from the United States showed that patients older than 65 had a higher stage at diagnosis and lower OS.[288] As most guidelines for cervical cancer screening recommend stopping after 65, opportunistic screening of older patients is relevant, especially in populations with lesser

access to regular screening. A SEER analysis has shown that older patients are less likely to undergo surgery, lymph node sampling, adjuvant RT, and BT and that cancer-related mortality was higher even after adjusting for treatment disparities.[289] As patients are older, rates of comorbidities, such as diabetes, hypertension, and nutritional deficits, become higher and increase the risks for complication of care.

Treatment decisions have less robust data as patients over 65 years are underrepresented in randomized data. However, retrospective data still support the use of more aggressive therapies in selected fit patients. Mitchel et al[65] reported that in a cohort of 398 patients treated with RT, 60 of them over 70 years, those receiving BT and not needing treatment breaks had similar survival to younger patients. In a Chinese report of 73 patients over 70 years, concurrent chemotherapy was a significant predictor of OS.[290] Nomograms designed for patients over 65 years from retrospective databases also showed the prognostic benefit of chemotherapy and RT. A systematic review of 24 reports on outcomes and toxicity in older patients found that when treated with adequate doses of RT with concurrent chemotherapy, equivalent or near-equivalent survival results can be achieved. Hematologic, vaginal, bone, and neurologic toxicities from CRT were reported as higher with age.[291]

As RT techniques become less toxic with IMRT and image guidance, and better support and symptoms management for older patients is available, more patients should be considered candidates for lifesaving therapy.

CARCINOMA OF THE CERVIX AND PREGNANCY

The concurrent presence of carcinoma in situ or invasive carcinoma of the uterine cervix and pregnancy, although rare, poses a therapeutic dilemma to gynecologic and radiation oncologists. Reported incidence is approximately 1 to 10 per 10,000 pregnancies.[292] In the United States, the incidence has decreased. Norstrom et al,[293] in Sweden, found that cervical cancer was diagnosed in 33 women in association with pregnancy (incidence, 11.1 cases per 100,000 deliveries and 7.5 per 100,000 pregnancies). Abnormal bleeding was the symptom that led to diagnosis in 54.5% of the women; 45.5% were asymptomatic but had an abnormal cervicovaginal cytologic test result (39.4%) or abnormal vaginal examination (6.1%) in association with pregnancy. During the follow-up, 1 of 12 women with cervix cancer in the

first trimester, 4 of 12 in the third trimester, and 2 of 9 postpartum died of the disease. Primary surgery was used more frequently than RT.

For carcinoma in situ, if the pregnancy is allowed to reach full term, confirmation of the diagnosis by colposcopy and conservative management with monthly Pap smears constitutes the best approach. Conization has frequently been performed. Punch biopsies can be obtained, but the diagnostic accuracy is less reliable. As many as 50% of the patients have residual carcinoma in situ after delivery.

In patients with invasive carcinoma, the lesion is usually clinically apparent. Multiple punch biopsies are adequate to confirm the diagnosis. Management is individualized based on tumor size and stage, patient age, and desires of the patient (or couple) regarding the pregnancy. The majority of patients with cervical cancer diagnosed during pregnancy (~75%) have stage I tumors, and prognosis is the same as in nonpregnant patients.[292] Cancer incidence is similar between the trimesters, and survival is the same, regardless of the trimester of the pregnancy in which definitive treatment is instituted.

Women with tumors diagnosed early in pregnancy are often recommended to abort the fetus. Because there is a greater need to institute therapy as soon as possible, the accepted method of treatment in patients in the first 6 months of pregnancy is to carry out definitive surgery or RT, as indicated by the stage of the disease, with resultant loss of the fetus. An abortifacient may be administered before initiating radiation to ensure fetal demise and delivery of the placenta prior to initiation of treatment. The whole pelvis is irradiated (40-45 Gy in 4-5 weeks). However, some patients will not abort spontaneously, and surgical evacuation will be required; misoprostol may be administered as an alternative to surgical evacuation after failed spontaneous abortion. After this dose of radiation, careful evacuation of the uterus and LDR (or equivalent-dose HDR) BT may be performed under general anesthesia. If an RH is performed and positive pelvic lymph nodes are found, the usual postoperative irradiation, including external beam with or without intracavitary insertion, should be carried out.

If the woman refuses abortion, serial clinical examinations and MRI scans at 2- to 3-month intervals to ensure no rapid growth or spread to lymph nodes are recommended. Small series show that delaying definitive treatment under follow-up is relatively safe, especially in early disease. Bigelow et al[294]

reported a case-control study of 28 pregnant patients diagnosed with cervical cancer, 82% were stage I. Only 7 decided to terminate, and compared to 52 matched controls, the median time from diagnosis to surgery was delayed from 7 to 20 weeks, perioperative hemorrhage was greater in the pregnant group, with no significant difference in survival. Recurrences and cancer death were only in the group that decided to terminate.

When patients are diagnosed in midpregnancy (second trimester), attempting neoadjuvant approach while carrying the pregnancy to term could be considered, especially in more advanced disease or in a rapidly growing tumor. A pooled analysis of 48 patients reported disease control rates of 96.6% with mostly cisplatin-based regimen and a median PFS of 48 months.[295] Another pooled analysis of the results of 39 reports of 84 patients treated with platinum-based regimens until delivery showed that all but 2 who miscarried were delivered at median week of 33 (range 27-38), all but 1 with cesarean surgery with a median birth weight of 2,162 g (range 1,330-2,990 g). Of the 88 neonates delivered, 80.6% had uncomplicated follow-up. The rest had transient respiratory, hematologic, and metabolic complications, and one severe bilateral hearing loss and one intraventricular hemorrhage. In a median follow-up of 17 months (range 0-150), two pediatric malignancies were noted.[296] The desire to preserve the pregnancy must be weighed by possible detriment to maternal survival and complications to the child.

Occasionally in late pregnancy (final trimester), if tumors are small and an MRI or laparoscopic sampling confirms no lymph node involvement, definitive therapy is postponed until after imminent delivery. While intentional treatment delay over 6 weeks was associated with a potential risk recurrence or death, (~5%), no recurrence occurred in proven node-negative disease.[292] In the third trimester of pregnancy, some gynecologic oncologists prefer a cesarean delivery, combined with an RH and lymphadenectomy followed by radiation for high-risk features when present. However, some authors report that vaginal delivery has no detrimental effect on the prognosis.

Patients who require high doses of pelvic irradiation should be counseled regarding the permanent loss of reproductive capability, not only because of ovarian ablation (which happens with doses of ≥8 Gy) but also as a consequence of radiation effects in the uterus.

Sood et al[297] performed a retrospective analysis of 26 women with cervical carcinoma diagnosed during pregnancy and treated primarily with RT (mean

dose, 46.7 Gy) and LDR intracavitary radiation (mean dose, 56.5 Gy to point A). These cases were matched with 26 nonpregnant control patients based on age, histology, stage, treatment, and year of treatment. There were no statistically significant differences in recurrence rates or survival between the pregnant group and the control patients. Short-term toxicity was comparable in pregnant and nonpregnant patients. Long-term complication rates were 12% in pregnant patients and 27% in control patients, but this difference was not statistically significant. Most complications were likely related to radiation techniques (particularly the predominance of ^{65}Co).

Sood et al[298] compared the prognosis of 56 women who had cervical cancer diagnosed during pregnancy and 27 who were diagnosed within 6 months after delivery. Control patients (cervical cancer diagnosed at least 5 years since last delivery) were matched one to one with cases based on age, histology, stage, treatment, and time of treatment. Among the postpartum women, 11 were treated with radical hysterectomies and 14 with RT, and 2 with stage IA1 disease were treated with vaginal hysterectomies. One of seven patients who had cesarean sections had a local and distant recurrence. In contrast, 10 (59%) of 17 patients who delivered vaginally had recurrences (P = .04). In multivariate analysis, vaginal delivery was the most significant predictor of recurrence, followed by high tumor stage. Survival for patients diagnosed in the postpartum period was significantly worse than for control patients and for those diagnosed during pregnancy. The authors concluded that pregnant women with cervical cancer should be delivered by cesarean section.

The practice popularized in the early 20th century of administering a "restraining dose of radium" and deferring definitive RT until delivery is carried out should be strongly rejected. Complications reported include infants being born with microcephaly, alopecia, facial deformity, eye damage, and chromosomal abnormalities.

BRACHYTHERAPY

After the discovery of radium in 1898 by the Curies, publications followed describing the use of the first glass radium capsule in 1904 and a metal BT applicator for cervical cancer in 1905. The incorporation of BT after external beam treatment arose from the recognition that tumor control probability correlated with radiation dose and cancer volume. Evidence confirms that BT

as used for dose escalation after external beam treatment for cervical cancer significantly improves survival. Therefore, BT is a standard part of the treatment of locally advanced (stages IB2-IVA) cervical cancer after external beam radiation; BT alone may be used as primary treatment for selected cases with early-stage (stages IA-IB1) cervical cancer. The increasing complexity of BT administration, including the use of complex imaging, mandates implementation of careful quality assurance measures and a culture of open communication to ensure safe practices in the clinic.[299]

Dose Rate

The ICRU in its Report 38 defines BT dose rate as follows: LDR, 0.4 to 2 Gy/hour; medium-dose rate (MDR) or PDR, 2 to 12 Gy/hour; and HDR, greater than 12 Gy/hour. For LDR, the most commonly used isotope is ^{144}Cs, and for PDR and HDR, it is ^{206}Ir. The use of HDR has significantly increased in the United States, from 13% in the 1996 to 1999 Quality Research in Radiation Oncology (formerly known as the Patterns of Care) survey to 62% in the 2007-2009 survey.[185] In other U.S., European, and Japanese surveys of gynecologic BT practitioners, approximately 85% state that they use HDR BT,[300] whereas in Canada, the reported use is 68% HDR, 10% PDR, and 23% LDR.[301] The dose delivered per fraction for HDR and proportion of dose delivered with external beam versus BT vary substantially in different centers around the world.[301]

Most institutions in the United States have either LDR or HDR BT available. Larger centers may have LDR, PDR, and/or HDR. Overall, outcomes are similar regardless of dose rate, with the caveat that for HDR, 3D imaging should be incorporated to ensure coverage of the tumor, particularly for large-volume disease.[302]

Biology of High-Dose Rate Brachytherapy for Cervical Carcinoma: Equivalent Dose in 2 Gy and Biologically Effective Dose

To achieve tumor control using HDR equivalent to that with LDR BT, attention to the dose/fractionation schedule and to normal tissue doses is mandatory. The linear-quadratic (LQ) model provides calculation estimates of biologically equivalent dose taking into account dose rate, dose per fraction, and OTT. For comparison of LDR to HDR, the LQ model doses are

normalized to an equivalent dose in 2 Gy (EQD2). The α/β ratio is a critical component of the LQ model. For cervix cancer, an α/β ratio of 10 Gy is used for tumor and an α/β of 3 Gy is used for normal tissues, which may have inherent inaccuracies in generalizability, although an α/β ratio of 3 Gy for the rectum has been correlated with late rectal complications.[303,304]

Spreadsheets to assist with HDR EQD2 dose conversions are available from the American Brachytherapy Society (https://www.americanbrachytherapy.org/resources/for-professionals/physics-corner/). The values derived are not actual doses but biologically effective ones that take into consideration dose rate and effect of fraction size.

Although the use of a detailed EQD2 conversion is preferred, an approximation of these values was proposed by Orton et al[305] with an LDR-to-HDR reduction factor of 0.54 to 0.6. These conversion factors are valid when three to five HDR fractions are used, but with a higher number of fractions (six to eight), the conversion factor is closer to 0.75. Therefore, the use of the EQD2 worksheet is recommended.

Figure 76.21 illustrates the late normal tissue effect, which is proportional to log cell kill, and the relationship to the number of HDR treatment fractions.[306] Each solid curve is calculated assuming the same log cell kill. Late damage rises sharply as the number of HDR fractions is decreased. When these curves are above the dashed lines that represent the maximum late effect of 70 Gy of LDR BT given at 0.5 Gy/hour, the risk of late complications increases. Displacing the bladder and rectum away from the HDR sources for the short duration of therapy may offset the radiobiologic disadvantage of using a few BT fractions.

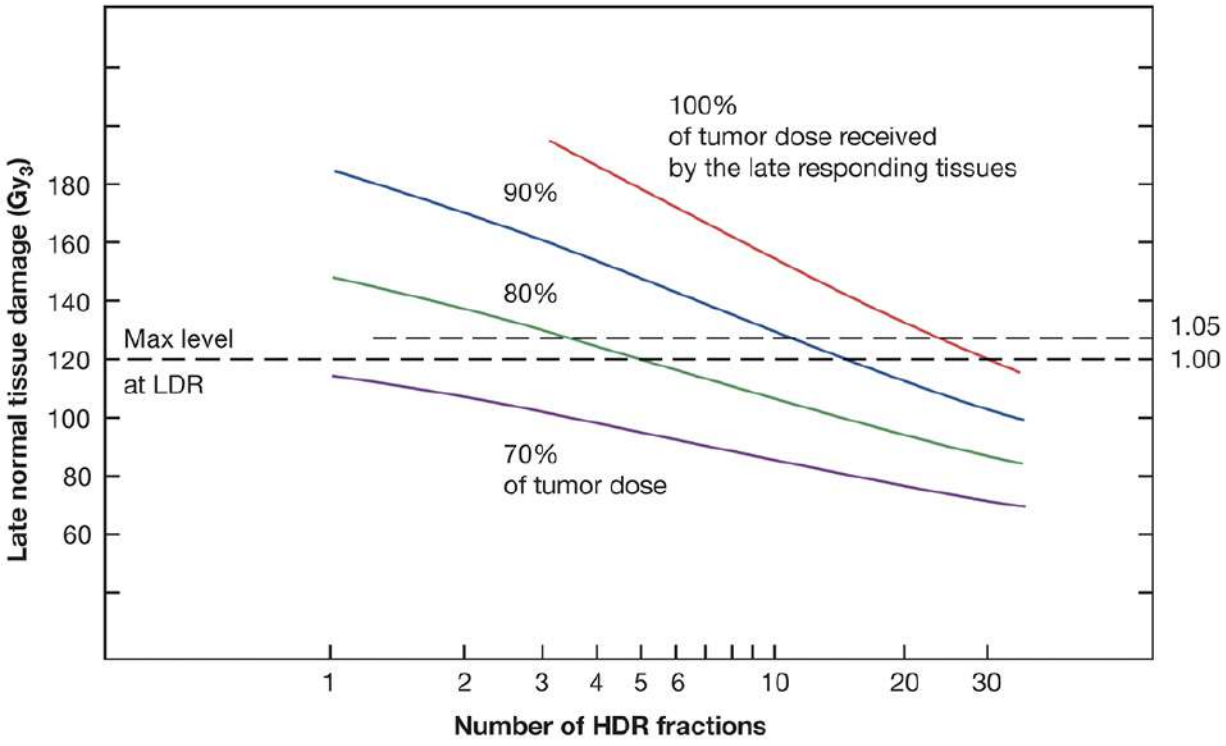


FIGURE 76.21 Relationship between number of high-dose rate (HDR) fractions and late normal tissue effects. Solid lines show the increase in normal tissue late effects as the number of HDR fractions used to treat cervical cancer decreases. Dotted lines indicate the maximum level of late damage calculated for conventional low-dose rate (LDR) brachytherapy of 70 Gy at 0.5 Gy/hour for 140 hours and an arbitrary level 5% above this. The intersection of the solid lines with the dotted lines indicates the number of HDR fractions needed to give equal late normal tissue effects. In this model, the dose to late-responding tissues should be kept at 83% of the tumor dose when treating with four to six HDR fractions. (Modified with permission from Fowler JF. The radiobiology of brachytherapy. In: Martinez AA, Orton CG, Mould RF, eds. *Brachytherapy HDR and LDR*. Nucletron International BV; 1990:121-137.)

Brachytherapy Process: Preparation and Timing

Standard procedures for pretreatment evaluation, imaging, anesthesia use, and treatment duration should follow accepted general principles in the guidelines published by the American Brachytherapy Society in 2012.[299,307,308] Planning the course of BT should begin at the time of initial presentation. An examination at diagnosis assessing disease extension and tumor size should be recorded. Periodic examinations during external beam treatment should be performed to monitor response. For patients receiving concurrent CRT, rapid shrinkage should be expected because treatment may regress the tumor to 70% to 80% of the pretherapeutic volume. Therefore, a clinical gynecologic examination at the time of BT is also important. Inserting radiopaque marker

seeds (“fiducials”) at the time of diagnosis that mark the inferior, lateral, and superior extension of a vaginal tumor may aid in identifying regions requiring dose escalation with BT, even after complete regression during external beam treatment.

Treatment schedules integrating external beam irradiation and BT were initially designed with regard to the disease stage and volume. For LDR, insertion of the applicator may be done after all external beam finishes, with the caveat that one or two insertions may be required, approximately 1 week apart. All treatments, including external beam treatment and BT, should finish 8 weeks from the initiation of radiation.

The optimal time-dose-fractionation scheme and the technique for remote control afterloading intracavitary BT for cervical cancer have yet to be established through systematic clinical trials. For HDR or PDR BT, the applicator insertion and treatment may commence after external beam treatment finishes, to ensure optimal geometry with normal tissues far from the applicator. Alternatively, the physician may choose to insert the applicator for treatment as early as during the second week of external radiation if the tumor is small enough, to minimize total treatment time. Preferably, BT and external beam treatments should not be given on the same day, and if they must, a 6 hours difference should be maintained.

Applicator Selection

The tandem and ovoid applicator provides radiation dose covering the cervix, uterus, inner parametria, and approximately 1 to 2 cm of the upper vagina. The tandem and ring applicator has a slightly narrower dose distribution, but with HDR, the dose distribution may be optimized and mimics that obtained with the tandem and ovoid applicator. For patients with a very narrow vagina because of stricturing, a tandem and cylinder applicator may be the only option available. However, this applicator provides insufficient dosing to the parametrial tissue and should be used with caution. For patients with large tumors with residual bulky disease after external beam radiation or those with vaginal extension, fistulae, or pelvic sidewall invasion, a combination of tandem/ring or ovoid with interstitial applicator or tandem/interstitial applicator alone may be inserted.

Applicator Insertion and Imaging During Insertion

General guidelines from the American Brachytherapy Society should be followed.[299] The patient receives appropriate anesthesia for pain management. In the lithotomy position, the perineum is sterilely prepped and draped. The Foley catheter is inserted into the bladder. The catheter is clamped and the bladder filled with 150 to 200 mL of saline if US is used. US with a transabdominal probe can significantly speed up the insertion process and assist with accurate placement because the uterine canal is often clearly visible after instilling fluid in the bladder (Figure 76.22). Transabdominal US can measure uterine width and height in patients who do not have large fibroids or tumor volumes that greatly distort uterine configuration. US does not define the target volume as clearly as MRI but may be used to assist with 3D-based planning when CT or MRI is unavailable.[309] Transrectal US may assist with interstitial BT when other imaging modalities are not available. For interstitial insertions, CT or MRI may be used during the insertion process either iteratively or as real-time guidance to ensure proper tumor coverage and no inadvertent insertions into the rectum or bladder. After tandem and ovoid or tandem and ring applicator placement, vaginal packing covered with lubricant gel is placed in the vagina to separate the bladder and rectum, which also helps to maintain applicator position.

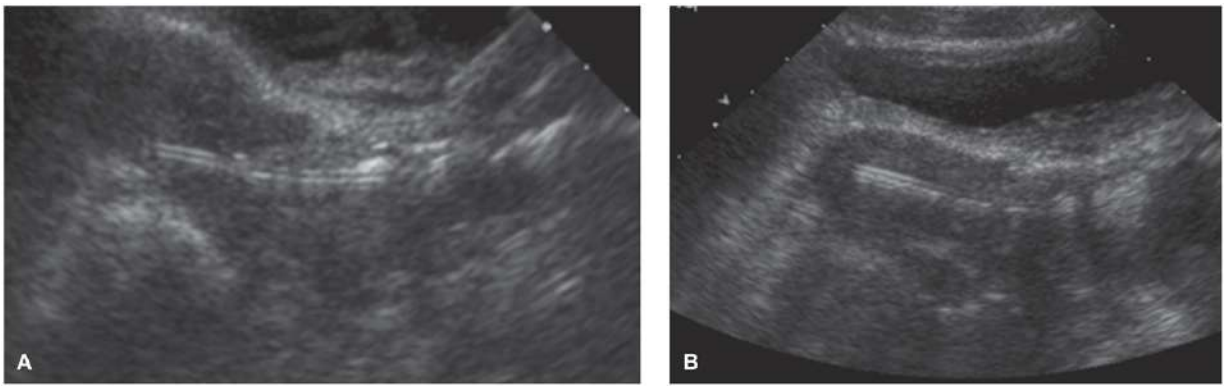


FIGURE 76.22 Ultrasound used during intrauterine tandem insertion can ensure proper placement into the intrauterine canal and shorten overall procedure time. A. Ultrasound depicts that the tandem is placed in the posterior myometrium. B. Ultrasound directs the tandem into the intrauterine canal.

Applicator Position

An experienced brachytherapist has greater familiarity with applicator insertion and evaluation. Applicator position is a critical determinant of dose

specification and pelvic control. As Fletcher emphasized, conditions for an adequate intracavitary insertion include the following:

1. The geometry of the insertion must prevent underdosing around the cervix.
2. Sufficient dose must be delivered to the paracervical areas.
3. Vaginal mucosal, bladder, and rectal tolerance doses must be respected.

For LDR Fletcher-Suit applicators, Potish et al[310] used linear least squares regression to show that although there was a moderately good correlation between the milligram-hours and dose to point A, it was markedly affected by the position of the colpostats and the tandem. A review of plain films of 808 LDR intracavitary applications in 396 patients with cervical cancer treated at MD Anderson[311] quantified acceptable implant geometry. The median distance from the tandem to the sacrum was 4 cm, or one-third the distance from the pubis to the sacrum. The distance between the vaginal ovoids and the cervical marker seeds was 7 mm, and the median distance between the tandem and the posterior edge of the ovoids was 50% of the ovoid length. In 92% of insertions, vaginal packing was posterior to or within 5 mm of a line that passed through the posterior edge of the ovoids, parallel to the tandem. The median doses to point A and rectal, bladder, and vaginal surface reference points were 87, 68, 70, and 125 Gy, respectively. Analysis of the LDR and HDR BT positions for 103 patients enrolled on RTOG trials 0116 and 0128 found that patients with unacceptable symmetry of ovoids to the tandem had a significantly higher risk of LR than patients in the acceptable group (HR = 2.67; 95% CI = 1.11-6.45; P = .03).[35] Patients with displacement of ovoids in relation to the cervical os had a significantly increased risk of LR (HR = 2.50; 95% CI = 1.05-5.93; P = .04) and a lower DFS rate (HR = 2.28; 95% CI = 1.18-4.41; P = .01). Inappropriate placement of packing resulted in a lower DFS rate (HR = 2.06; 95% CI = 1.08-3.92; P = .03).

Imaging After Insertion

For LDR BT, active sources may be inserted after the films have been reviewed and the position of the applicators judged to be satisfactory. Placing a small amount of contrast into the bladder and rectum before CT or plain film may clarify the location of these structures.

When a CT scan is obtained after applicator insertion, it also verifies proper placement (no perforation) and analyzes cervix and normal tissue location in relationship to BT dose distribution. CT provides a reasonable estimate of the location of the uterus and cervix. The CT contours of the cervix overestimate the tumor contours compared to an MRI, although the additional width contoured on a CT may not be of detriment to the patient because cervical cancer tends to spread laterally along the parametrial tissues.[312] CT depicts changes in the OAR related to tumor shrinkage, organ motion, and the location of the BT applicator in relation to the uterus. However, separating the OAR, such as the sigmoid or the small bowel from portions of the uterus or cervix, may be difficult on CT, given the lack of contrast. OAR dosimetry based on CT is similar to that based on MRI when optimized similarly. CT may not provide sufficient detail of the tumor if selected dose escalation is required, such as in cases with large residual tumors. In the vast majority of cases, however, it should suffice. The uterus and cervix cannot be distinguished as separate structures on a CT, whereas they can be on an MRI. Therefore, some CT-based contouring guidelines recommend delineating the entire cervix and uterus.[312] Other guidelines recommend using preinsertion MRI or any other clinical assessment if available, to better define the targets.[313] In a multicenter study, MRI was significantly better than CT for tumor visualization and detection of parametrial involvement.[40] Other advantages of MR include multiplanar capability and excellent soft tissue contrast resolution. The strength of a magnet in an MR scanner is expressed by a unit of measurement referred to as a tesla (T). Higher field strength produces a better overall signal-to-noise ratio and more accurate imaging.

Regardless of whether a plain film radiograph, CT, or MR is obtained after insertion to aid treatment planning, in order to properly visualize the apparatus, radiopaque markers should be inserted to identify source position to aid with dosimetric planning. Identifying the applicator using either a radiopaque marker inserted into it or for interstitial cases undergoing MR, a special 3-T MR sequence may be used to create artifact that allows the tip of the needle to appear as a balloon on the sagittal image and as a cross on the axial images.[314]

Dose Specification

Point A

Several methods for specifying dose in BT evolved over the 20th century.

Because of the limited availability of 3D imaging worldwide and a 100-year history of plain film radiography, in a survey from 2012, the majority of institutions internationally reported using point-based dosimetry based on the ICRU 38 nomenclature defining point A rather than prescribing dose to a tumor volume.[300] Other institutions use a system of milligram-hours, whereas others consider the volume of the region of interest. Based on the general principles guidelines for cervical cancer BT published by the American Brachytherapy Society and the ICRU report, the point A definition was updated in 2012.[299] To determine point A, connect a line through the center of each ovoid or the lateral most dwell position in the ring; extend this line superiorly along the radius of the ovoids (or ring), and then move an additional 2 cm superior along the tandem. From this point, extend out 2 cm on each side laterally on a line perpendicular to the tandem (Figure 76.23). For tandem and cylinders, begin at the flange or cervical marking seed and move 2 cm superiorly along the tandem and then 2 cm laterally.

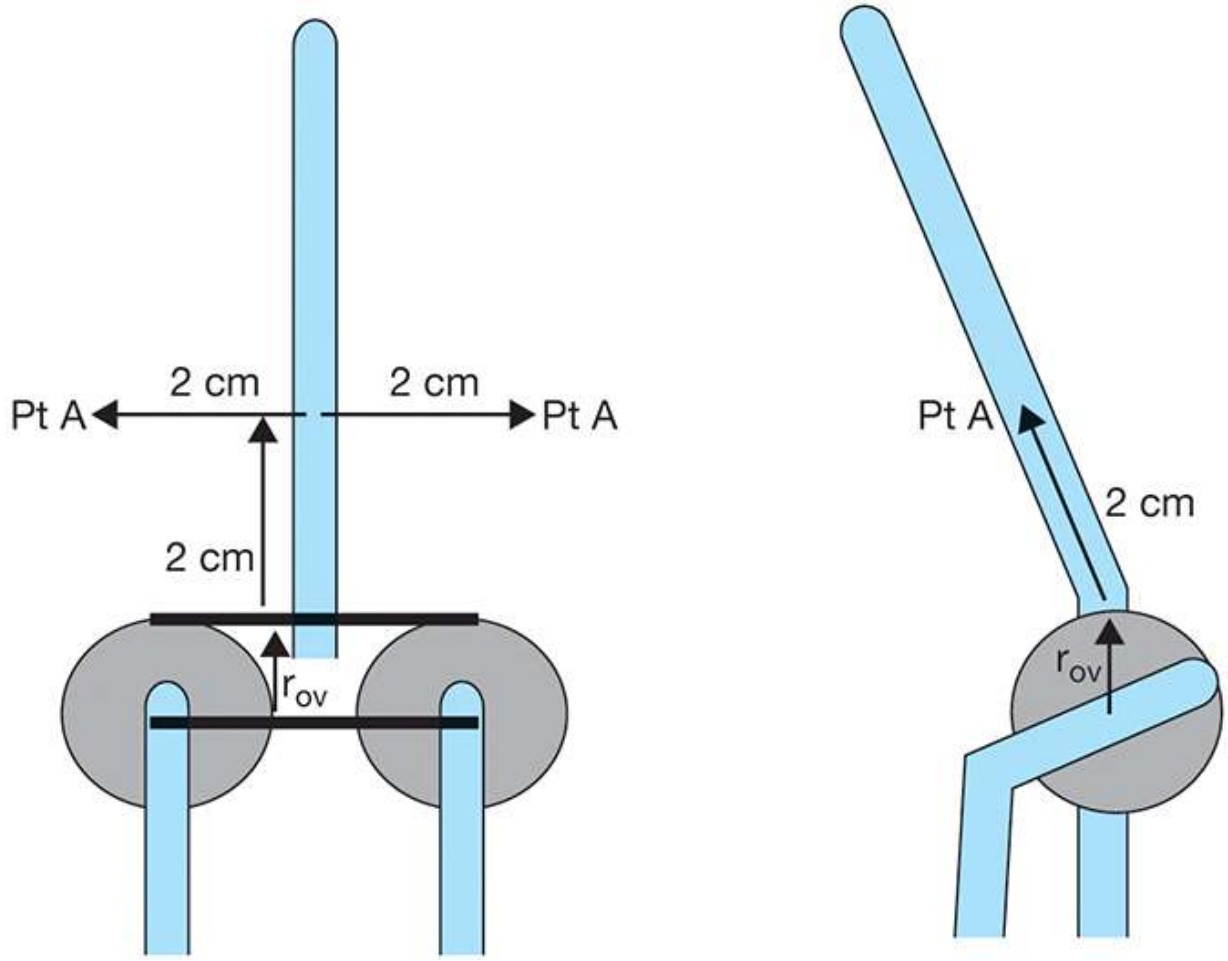
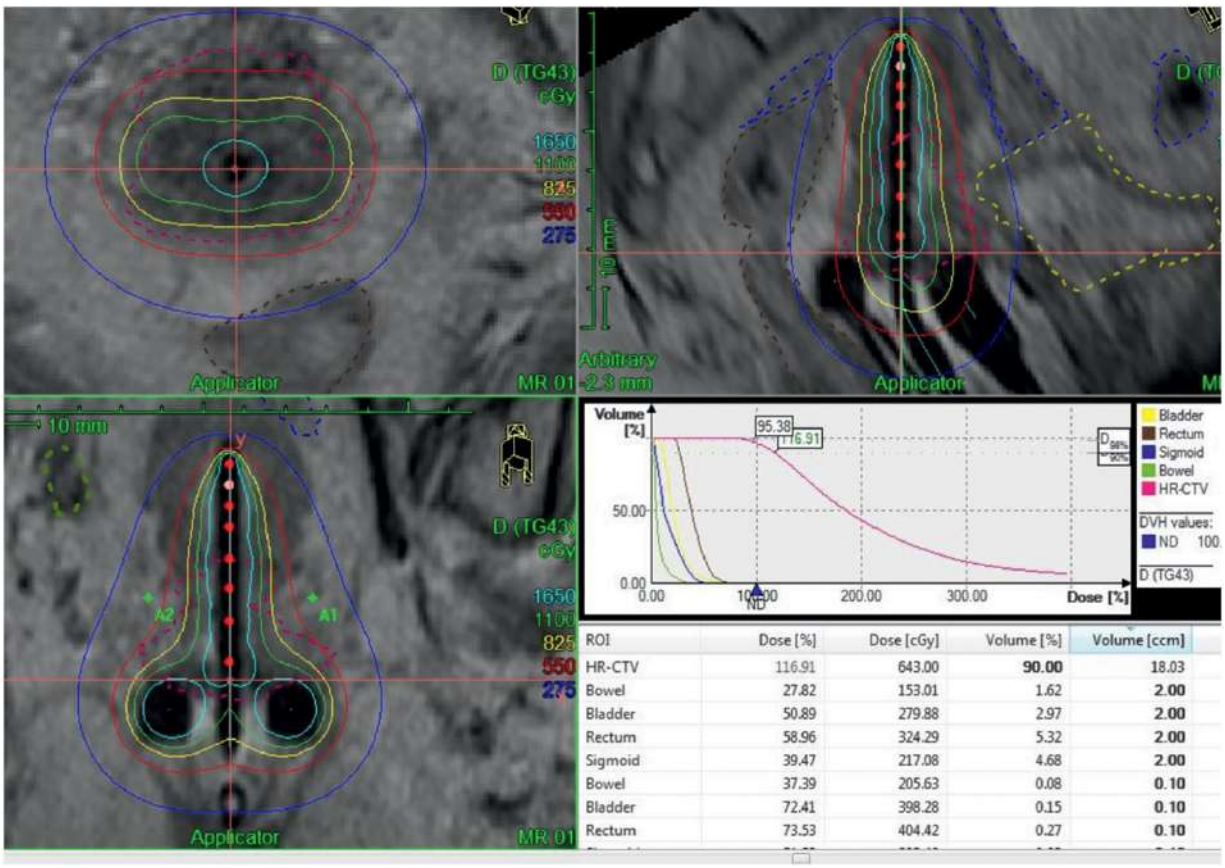


FIGURE 76.23 Definition of point A shown on a tandem and ovoid applicator based on the American Brachytherapy Society 2012 Guidelines for Cervical Cancer.

3D image-based BT treatment planning better defines the tumor and aids with the precision of radiation dose delivery, which may increase efficacy and may reduce the dose to the normal tissues and reduce toxicity.[249] In the era of increasing use of HDR BT, proper applicator placement and precise estimation of the location of the normal tissue are critical. When 3D imaging is available, point-based radiographic dosimetry has limited utility for the dose adaptation required for HDR BT because point A may overestimate or underestimate the tumor dose based on 3D imaging. Kim et al[315] found that dose to point A was significantly lower than the D_{90} for HR-CTV calculated using 3D image-based optimization. With imaging, one may visualize the tumor volume and conform dose to the volume, which may result in the dose to point A being lower than the prescription 100% isodose line (covering a smaller tumor volume) or a higher than prescription dose to point A because

of a large tumor volume extending beyond the boundaries of point A. The tumor coverage relies on tumor volume at the time of BT, with larger tumors requiring greater optimization to be adequately covered by the prescribed isodose line.

Accurate delineation of the tumor and OAR is critical for precise treatment planning (Figure 76.24). Because of the rapid falloff of dose, imprecise contouring can dramatically change dosing to normal tissue structures. Formal contouring education programs reduce the variability of interobserver contours.[316] The dose to point A should still be reported to ensure consistency in terminology between centers with different capabilities. In addition, as point A reporting is not dependent on contouring, it is still a useful safety measure, and the EMBRACE II prospective trial still aims for a dose of over 65 Gy to the A point across participating centers.[258]



ROI	Dose [%]	Dose [cGy]	Volume [%]	Volume [ccm]
HR-CTV	116.91	643.00	**90.00**	18.03
Bowel	27.82	153.01	1.62	**2.00**
Bladder	50.89	279.88	2.97	**2.00**
Rectum	58.96	324.29	5.32	**2.00**
Sigmoid	39.47	217.08	4.68	**2.00**
Bowel	37.39	205.63	0.08	**0.10**
Bladder	72.41	398.28	0.15	**0.10**
Rectum	73.53	404.42	0.27	**0.10**

FIGURE 76.24 Tandem and ring implant showing the use of three-dimensional (magnetic resonance [MR] or computed tomography) imaging to adequately cover the high-risk clinical target volume (HR-CTV) while minimizing dose to the organs at risk (OARs)—the rectum, sigmoid, and bladder. Dose-volume histograms (DVHs) record the D_{2cc} limits to the OAR. The dose at point A is recorded but varies between patients based on optimization of the HR-CTV and OAR. ROI, region of interest.

Computed Tomography Imaging for Brachytherapy Contouring

A CT scan can define a CTV with the lateral borders of the cervix and any parametrial extension defined based on suspicious regions seen on the scan. CT contouring guidelines should be followed.[312,313] Uterosacral ligaments may be visualized on CT, and if detected, they should be included in the CTV contours. No GTV may be identified on CT. The superior border of the cervix is not defined; instead, the entire tandem length is planned and the top dwell is optimized off the sigmoid to reduce bowel dose.

Magnetic Resonance Imaging for Brachytherapy Contouring

For MR-based contouring, the Groupe European Curietherapy-European Society for Therapeutic Radiation Oncology (GEC-ESTRO) guidelines can be used.[303] The recommended volumes include the GTV, including all T2 bright areas of enhancement; the HR-CTV, which is the entire cervix, any regions of high to intermediate signal intensity in the parametria, uterus, or vagina, and any residual disease detected on clinical examination at the time of BT; and the intermediate-risk clinical target volume (IR-CTV), which subtracts out the OARs but includes the tumor extension at the time of diagnosis, adding 1 cm to the HR-CTV volume. The IR-CTV defines regions with potential microscopic seeding of tumor cells (Figure 76.25).[303] Lang et al,[317] in a multicenter study, confirmed the feasibility of these recommendations, with total doses to point A from both BT and EBRT ranging from 85 to 91 Gy and to CTV from 69 to 73 cGy. Doses to OARs were comparable to those obtained with standard dosimetric methods, although they were more accurately determined with dose-volume histograms (DVHs).

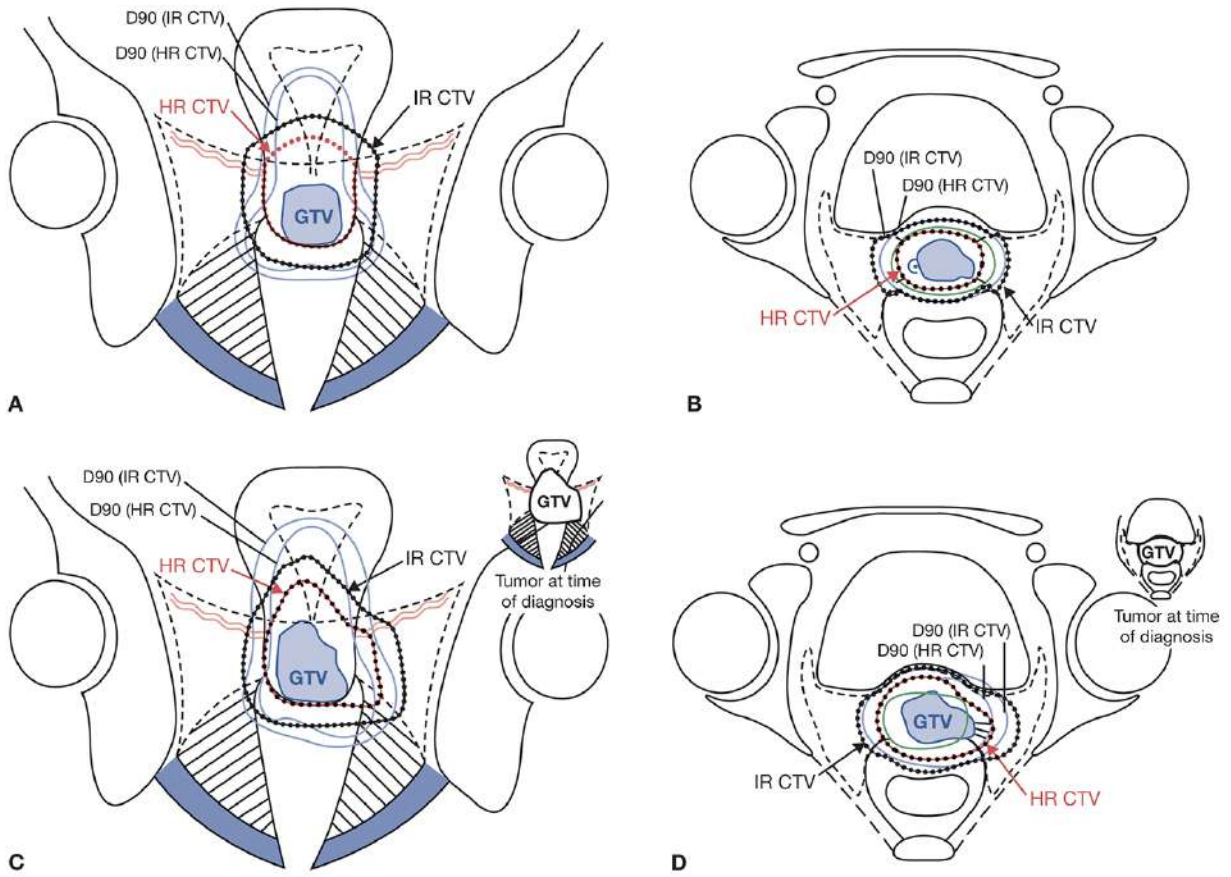


FIGURE 76.25 Diagrammatic representation of gross tumor volume (GTV) and clinical target volume (CTV) for three-dimensional treatment planning in carcinoma of the uterine cervix. Coronal (A and C) and transverse (B and D) sections for limited (A and B) and advanced (C and D) disease (gray zones in left parametrium). HR, high-risk; IR, intermediate-risk. (Reprinted from Pötter R, Haie-Meder C, Limbergen EV, et al. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. *Radiother Oncol.* 2006;78[1]:67-77. Copyright © 2005 Elsevier Ireland Ltd. With permission.)

The American Brachytherapy Society conducted a survey on the use of image-based BT in 2007 and updated this in 2014. Of 219 respondents in 2014, 13% obtain an MRI with the first fraction of BT and 7% with subsequent fractions, whereas 6% use MR for every fraction. The majority (52%) specify dose to a contoured volume rather than to point A.[318]

A panel of gynecologic radiation oncologists generated a 95% consensus volume contouring atlas to delineate the CTV in locally advanced cervical cancer. Patients with parametrial extension benefited most from MR at the time of BT, particularly those with an apparent CR.[319] The atlas is available

online at https://www.nrgoncology.org/Scientific-Program/Center-for-Innovation-in-Radiation-Oncology/GYN-Cervical-Brachytherapy.

Dose-Volume Histogram Reporting

With MR-planned BT, the most common dose-volume parameters reported for target structures of the entire cervix and any residual disease at the time of BT, the HR-CTV, are D_{90}, defined as the dose received by at least 90% of the target volume, D_{100}, and V_{100}, based on the GEC-ESTRO recommendations. The cumulative D_{90} equals the sum of D_{90} values from the individual fractions plus the dose from a homogeneous 3D conformal external beam treatment. D_{100}, the minimum target dose, may be more sensitive to inaccuracies in contouring and dose calculation. V_{100} assesses dose coverage of the whole target volume and is 100% when the entire target is covered by the prescribed dose. V_{150} and V_{200} are often reported in interstitial BT. One may report these for CT, although the dimensions of the target will differ significantly from the absolute dimensions on MR, and the CT contour of the HR-CTV will include the cervix, residual areas in the parametria or uterosacral ligaments, and part of the uterus because the superior border of the cervix is not visible. CT contours are more accurate if an MRI can be performed immediately before or with the first fraction of BT.[320] In both CT and MRI, prescribed dose is based on the physician's directive of the dose intended for the target volume, that is, the volume covered by the 100% isodose line, and point A should be recorded. Several reports have validated the use of these guidelines with HDR, LDR, or PDR BT.[200,320]

With 3D imaging, one may define the surrounding normal tissue structures as the OARs, including the rectum, sigmoid, and bladder. With 2D imaging, the ICRU 38 report requires only reporting point estimates for the rectum and bladder because the sigmoid cannot easily be visualized. However, the ICRU bladder point may underestimate maximum doses to the OAR, in particular for the bladder; it is less likely that rectal doses will be incorrectly estimated. Numerous publications correlate the ICRU point dose and the probability of late complications for bladder and rectum.[321] Nevertheless, DVH metrics may provide a more reliable predictor of long-term complications.[322]

Pelloski et al[323] compared CT-based volumetric calculations and ICRU reference point radiation doses in 60 patients with cervix cancer treated with

LDR BT. Of 118 insertions performed, 93 were evaluated, and the minimal doses delivered to 2 or 3 cm of bladder or rectum (DBV2 and DRV2, respectively) were determined on a DVH. They concluded that the ICRU dose was a reasonable surrogate for the DRV2, but not for the DBV2. Furthermore, these calculations may not be applicable to other treatment guidelines or intracavitary applicators.

Both CT- and MR-based OAR dosimetry report similar cumulative DVH parameters, including D_{2cc} and $D_{0.1cc}$. The D_{2cc} is the minimum dose received by the most exposed 2-cm^3 volume of the analyzed organ. For CT-based BT, contrast placed in the OAR may cause some artifact, resulting in some variation in contouring the wall of the organ. MR-based BT relies less on contrast because the organ wall may be more clearly visualized. Wachter-Gerstner et al[324] analyzed the correlation between DVHs for the bladder and rectum and found that D_{2cc} served as a good estimate for doses to the organ wall, whereas D_{5cc} was less reliable as it changes more based on filling status. Rectal wall thickness did not significantly affect D_{2cc}.

Based on CT dosimetry, Koom et al[325] showed that more severe rectal side effects (endoscopy score .2) occurred in patients with a higher D_{2cc}. Seventy-one patients with FIGO stage IB to IIIB uterine cervical cancers had CT-based HDR intracavitary BT. The mean values of the DVH parameters and ICRU rectal point (α/β = 3) were significantly greater in patients with a score of greater than 2 than in those with a score of less than 2 at 12 months after BT (ICRU, 71 vs 66 Gy [P = .02]; $D_{0.1cc}$, 93 vs 85 Gy [P = .04]; D_{1cc}, 80 vs 73 Gy [P = .02]; D_{2cc}, 75 vs 69 Gy [P = .02]). The probability of a score of greater than 2 was significantly correlated with the DVH parameters and ICRU rectal point (ICRU, P = .03; $D_{0.1cc}$, P = .05; D_{1cc}, P = .02; D_{2cc}, P = .02).

For MR-based dosimetry, Georg et al[322] tested the predictive value of dose-volume parameters for late effects of the rectum, sigmoid colon, and bladder using the D_{2cc}, D_{1cc}, and $D_{0.1cc}$ of these three OARs for 141 patients with cervical cancer treated with tandem and ring HDR BT after EBRT. The mean D_{2cc} values for bladder, rectum, and sigmoid were 95 ± 22, 65 ± 12, and 62 ± 12 Gy, respectively. This study confirmed that D_{2cc} was a predictor of late toxicity for the rectum and bladder. A rectoscopy study[326] was done in 35 patients in which EQD2 (α/β = 3 Gy) of the $D_{0.1cc}$, D_{1cc}, and D_{2cc} of the rectum

was recorded. After a mean follow-up time of 18 months, telangiectasia was found in 26 (74%) patients, and 5 had ulceration that corresponded to the $D_{0.1cc}$ of the anterior rectal wall. The D_{2cc} was higher in patients with rectoscopy score of greater than 3 compared to less than 3 (72 ± 6 vs 62 ± 7 Gy; $P < .001$) and in symptomatic versus asymptomatic patients (72 ± 6 vs 63 ± 8 Gy; $P < .001$).

Mazeron et al[327] described late rectal morbidity in 960 patients treated with MR-based BT in the EMBRACE study. With a median follow-up of 2 years, rectal events peaked at 2 years post-treatment. The total crude rate of events was 28%, including 18% proctitis, 16% bleeding, 1% stenosis, and 1% fistula. Rectal dose morbidity was 6% 60 Gy, 8% 65 Gy, 10% 70 Gy, and 13% 75 Gy. The authors conclude that a D_{2cc} less than 65 Gy results in a less than 10% risk of rectal toxicity.

For interstitial BT, in which a much longer portion of the anterior rectal wall is treated as part of the target volume, D_{2cc} greater than 62 Gy predicted for late toxicity.[328] The development of mucosal and clinical changes in the rectum seems to follow a clear dose effect and volume effect. For patients receiving interstitial BT who require treatment to the entire vaginal length, the dose to the rectum should be reduced as much as possible without compromising target coverage.

The dose given to the vagina is also associated with vaginal toxicity,[329] with a threshold of 108 Gy analyzed in one study.[330]

Three-Dimensional Treatment Planning for Pulsed- and High-Dose Rate Brachytherapy

Treatment planning for PDR and HDR BT can be accomplished by a variety of techniques. Treatment planning for LDR is covered in a separate chapter. For cervical cancer, customized optimization of source loading for each HDR insertion is recommended (Figure 76.26), given significant changes in tumor and OAR dosimetry between fractions. Individualized computer treatment optimization of source position and the dwell time for each position are needed. Customized planning does increase the time needed for planning and requires experience on the part of the physics and dosimetry staff.

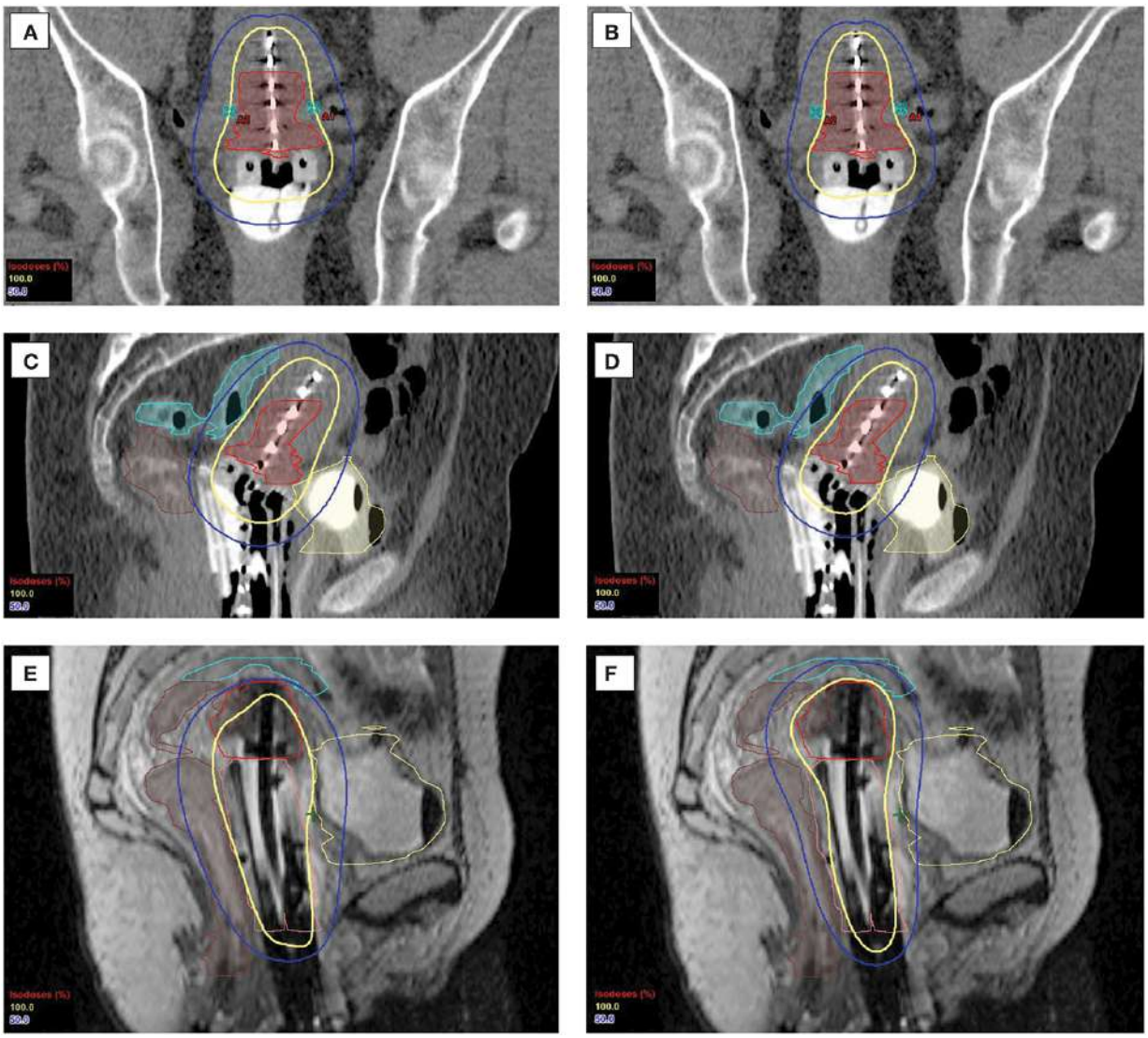


FIGURE 76.26 A. Coronal view of a computed tomography (CT)-planned tandem and ring applicator with standard high-dose rate (HDR) loading (to point A). B. Tandem and ring treatment plan optimized to maximize tumor coverage and minimize the dose to the organs at risk (OARs), including the rectum (brown), sigmoid (blue), and bladder (yellow). C. Sagittal CT of the standard plan at point A. D. Sagittal CT image of the optimized plan showing the reduction in OAR dose. E. Cervical stump cancer showing a magnetic resonance–planned tandem and interstitial brachytherapy implant without HDR optimization. F. Optimized tandem and interstitial plan cover the posterior border of the cervical stump while minimizing dose to the bladder and rectum..

Computed Tomography–Based Treatment Planning

Dewitt et al,[331] in 15 patients with cervical cancer, defined target and OAR for planning of HDR BT and established guidelines for volume and dose constraint parameters using image-guided inverse treatment planning.

Careful assessment of the quality of BT and dose distributions is critical. Suyama et al[332] analyzed the minimal radiation dose to the peripheral area of the cervix in relation to local tumor failure using CT images taken at the time of intracavitary BT in 80 patients with carcinoma of the cervix. After CT scanning, isodose curves were superimposed on the CT images. Histograms of both the minimum percentage peripheral dose and the dose to the cervical area showed significant correlation in the local tumor control and local failure groups ($P < .001$).

With HDR intracavitary applicators, the use of a rectal retractor has been shown to substantially reduce the rectal dose. Lee et al,[333] in a study of 15 patients, found that this reduction was significant only in the subgroup who received more than 70% of the prescription dose ($P < .05$).

Wanderas et al[334] reviewed data from 19 patients (72 fractions) retrospectively. Standard library plans were compared to individually optimized plans using a Fletcher HDR applicator. For standard treatment planning, the tolerance dose limits were exceeded in the bladder, rectum, and sigmoid in 26%, 4%, and 15% of the plans, respectively. This was observed most often for the smallest target volumes. The individualized planning of the delivered treatment gave the possibility of controlling the dose to critical organs to below certain limits. The dose was still prescribed to point A. An increase in target dose coverage was achieved when additional individual optimization was performed while keeping the dose to the OARs below predefined limits. Relatively low average target coverage was seen, however, especially for the largest volumes.

Magnetic Resonance–Based Treatment Planning

Basic principles of MRI during BT have been described.[335] Several institutions have reported the dosimetric advantages of MR-based BT, with reduction in OAR doses with optimization. Tanderup et al[336] showed that point A dose was a poor surrogate of HR-CTV dose, and MR-based planning improved target coverage and reduced OAR dose. Starting with a standard plan is important for consistency because relative uniformity of the dose distribution should be maintained.

A comparison of MR to US was reported by Van Dyk et al[309] for 71 patients, showing comparability between the two modalities in terms of target volume and rectal point dose. Mahantshetty et al[313] similarly confirmed the

feasibility of US for institutions that do not have easy access to MR or CT. One study hypothesizes that US may be more similar to MR than CT.[337]

Recommended Doses

Stage IA (microinvasive) tumors are treated with intracavitary therapy only. LDR dose is approximately 60 Gy in one insertion or 75 to 80 Gy in two insertions to point A, or with HDR an equivalent dose, with one or two fractions per week. This may be given in approximately 5 Gy per fraction for 10 fractions or other regimens based on normal tissue exposure.

For stage IB to IVA cervical cancers in the United States, the most common EBRT dose treats the elective pelvic nodes to 45 to 50 Gy given in 1.8 Gy per fraction.[299] Some institutions instead use lower doses of whole-pelvis external irradiation (20-40 Gy) in addition to parametrial doses to complete 50 to 60 Gy to the involved parametrial tissues or nodal regions for more advanced stages. BT follows, with a goal EQD2 dose of 80 to 90 Gy to point A or to the HR-CTV. For LDR, intracavitary treatment for approximately 4,000 to 5,000 mgh (36-50 Gy to point A at 60 cGy/hour) is given, depending on the tumor volume and stage and age of the patient. Fyles et al[338] identified FIGO stage as the most significant prognostic factor in 965 patients with invasive carcinoma of the cervix, followed by dose of irradiation to point A and overall time of RT. The 10-year survival rate was 62% in 743 patients receiving doses to point A of 85 Gy or higher, in contrast to 53% for 222 patients receiving lower doses.

For HDR, one study found that a dose to the HR-CTV of greater than 87 Gy resulted in an LR rate of 4% compared to 20% for D_{90} less than 87 Gy when the tumor was greater than 5 cm and using an HDR tandem/ring or tandem/ring/ interstitial approach. They concluded that LC rates of greater than 95% can be achieved for patients with a poor response after EBRT if D_{90} for the HR-CTV is 87 Gy or higher.[339] The IR-CTV intended dose should be approximately 60 Gy EQD2. In the United States, the most common regimen uses five fractions (5-6 Gy per fraction), with two fractions per week, 24 to 48 hours between fractions.

DVH constraints for both PDR and HDR are 90 Gy (EQD2) for bladder and 70 to 75 Gy (EQD2) for both rectum and sigmoid as minimal doses to the most exposed D_{2cc} of the OAR. There are no generally accepted constraints for the 0.1-cm^3 level. Given the rapid regression of the tumor and the dramatic

change in the location and size of the normal tissues, it is recommended to replan and determine the doses to the OAR with each fraction if the patient is treated on an outpatient basis.[340]

Dose Fractionation in High-Dose Rate Brachytherapy

Based on the LQ model, isoeffect tables were developed to convert traditional LDR doses and number of fractions to point A to HDR BT; depending on dose rate, different dose values can be calculated for various fractionation schedules. It was calculated using therapeutic gain ratio[341] that similar results would be obtained with BT modality with either two to four fractions of LDR or four to seven fractions of HDR. Petereit and Pearcey,[342] based on their preliminary results and published reports in the literature, recommend doses of 45 to 50.5 Gy in a 1.8-Gy per fraction external beam followed by HDR with either 5.5 or 6 Gy per fraction in the era before the standardization of CRT. Since the implementation of concurrent CRT, several institutions in the United States have standardized the use of 5.5 Gy for five fractions, given some concerns about rectal toxicity with 6 Gy per fraction.[343]

Hama et al[344] compared the effectiveness and safety of once-weekly versus twice-weekly HDR BT for cervical cancer in 124 patients treated with EBRT (50 Gy); 74 patients (group A) were treated with one HDR BT insertion weekly (three fractions of 7 Gy each to point A), and 50 patients (group B) were treated twice weekly (six fractions of 4.5 Gy each to point A). OS rates were 65.2% and 65.3%, respectively ($P = .96$). LR-free survival rates were 69% for group A and 90% for group B ($P < .001$). The rate of grade 2 (moderate) and grade 3 (severe) complications was significantly lower for group B (6%) versus 32% in group A ($P < .001$).

Mayer et al[345] compared HDR BT in two schedules used to treat 210 patients with cervix cancer—one sequential (SRT), consisting of four fractions of 8 Gy followed by EBRT, and the other continuous (CRT), consisting of five fractions of 6 Gy one session per week integrated with EBRT (four fractions per week). Total dose to point A was 68 to 70 Gy. PFS was 71% with CRT versus 56% with SRT ($P > 0.05$). Late bladder and rectal morbidity were 13% in the CRT group and 25% in the SRT group ($P = .037$), related to the higher dose per fraction (8 Gy).

The optimal time-dose-fractionation scheme for HDR BT for cervical cancer has yet to be established. In an international survey from the

Gynecologic Cancer Intergroup, 28 different fractionation regimens were used by international cooperative group members (Table 76.7); the most common was 6 Gy for five fractions after 45 Gy.[300] The American Brachytherapy Society published recommendations for HDR BT for carcinoma of the cervix.[307] Each institution should follow a consistent treatment policy, including complete documentation of treatment parameters and correlation with clinical outcome (pelvic tumor control, survival, and complications). The goals are to treat point A to at least a total LDR equivalent of 80 to 85 Gy for early-stage disease and 85 to 90 Gy for advanced-stage disease. The pelvic sidewall dose recommendations are 50 to 55 Gy for early lesions and 55 to 65 Gy for advanced ones. As with LDR BT, every attempt should be made to keep the bladder and rectal doses to less than 100 Gy and 75 Gy LDR equivalent doses, respectively. Interstitial BT should be considered when the tumor cannot be optimally encompassed by intracavitary BT. Some suggested dose and fractionation schemes for combining the EBRT with HDR BT for each stage of disease have been presented by the American Brachytherapy Society, although they have not been thoroughly tested. The responsibility for the medical decisions ultimately rests with the treating radiation oncologist. Petereit and Pearcey,[342] in a review of 24 HDR dose fractionation schedules published in the past three decades, found no dose relationship for either tumor control or late morbidity. Viswanathan et al,[300] for the Gynecologic Cancer Intergroup, found significant international variation in the HDR dose/fractionation regimens reported, but aside from Japan, where the ratio of HDR BT dose to external beam is higher, there was consistency in converted EQD2 doses administered.

TABLE 76.7 HIGH-DOSE RATE BRACHYTHERAPY DOSE AND FRACTIONATION REGIMENS WORLDWIDE

Percentage Respondents (Number)	Dose/Fraction	Number of Fractions	EQD2
Standard Fractionation for Stage IB to IIA Cervical Cancers			
18% (12)	6	5	40
15% (9)	6	4	32
12% (7)	7	3	29.75
8% (5)	5	6	37.5
8% (5)	7	4	39.7

Percentage Respondents (Number)	Dose/Fraction	Number of Fractions	EQD2
5% (3)	5	5	31.25
5% (3)	5.5	5	35.52
Standard Fractionation for Stage IIB to IVA Cervical Cancers			
23% (14)	6	5	40
10% (7)	7	4	40
10% (7)	7	3	30
8% (5)	6	4	32
7% (4)	5.5	5	35.5
5% (3)	5	6	37.5
5% (3)	7	6	59.5
5% (3)	6	3	24
5% (3)	8	3	36

Gynecologic Cancer Intergroup physicians worldwide who use high-dose rate (HDR) brachytherapy for cervical cancer were queried regarding the specific fractionation regimen that they routinely implement for patients with stage IB to IIA and stage IIB to IVA cervical cancers. Results are shown for regimens reported by three or more respondents. The most common external beam dose was 45 Gy in 1.8 Gy per fraction, followed by five fractions of 5 to 6 Gy per fraction. The EQD2 formula was used to convert the HDR dose and number of fractionations and does not include the external beam dose contribution.

Modified from Viswanathan AN, Creutzberg CL, Craighead P, et al. International brachytherapy practice patterns: a survey of the Gynecologic Cancer Intergroup (GCIG). *Int J Radiat Oncol Biol Phys*. 2012;82(1):250-255. Copyright © 2012 Elsevier. With permission.

Clinical Outcomes of Brachytherapy

Comparing High-Dose Rate to Low-Dose Rate Using Plain X-Ray Dosimetry

A meta-analysis[346] including four trials and 1,265 patients reported a pooled RR for HDR versus LDR of 0.95 (95% CI = 0.79-1.15), 0.93 (95% CI = 0.84-1.04), and 0.79 (95% CI = 0.52-1.20) for 3-, 5-, and 10-year OS rates and 0.95 (95% CI = 0.84-1.07) and 1.02 (95% CI = 0.88-1.19) for 5- and 10-year DSS rates, respectively. For LC rates, the RR was 0.95 (95% CI = 0.86-1.05) and 0.95 (95% CI = 0.87-1.05) at 3 and 5 years, respectively. For bladder, rectosigmoid, and small-bowel complications, the RR was 1.33 (95% CI = 0.53-3.34), 1.00 (95% CI = 0.52-1.91), and 3.37 (95% CI = 1.06-10.72), respectively, indicating no significant differences, except for increased small-

bowel complications with HDR (P = .04). Of note, none of the randomized studies used 3D imaging to optimize away from normal tissues.

The use of 3D imaging to guide BT treatment planning has allowed optimization of HDR and PDR BT, thereby reducing the high per fraction doses to the normal tissues that might potentially cause significant side effects. A retrospective comparison of LDR and HDR with pretreatment MRI used for tumor volume determination showed a significant reduction in complications with HDR when image-based planning was implemented. Similarly, the use of 3D imaging optimizes tumor coverage, which is critical with fractionated HDR therapy.

Prospective Data Using Point A Dosimetry

A prospective study in Japan of stage I and II cervical cancer with tumors less than 4 cm (by T2 MRI) and no lymphadenopathy treated 60 patients with whole-pelvis EBRT 20 Gy per 10 fractions with midline block followed by 30 Gy per 15 fractions and HDR 24 Gy per 4 fractions (at point A).[347] The cumulative BED was 62 Gy (α/β = 10) at point A, which is lower than that reported by any other institution worldwide. Median tumor diameter was 28 mm (range, 6-39 mm). Median OTT was 43 days. Median follow-up was 49 months (range, 7-72 months). Seven patients developed recurrences: Three patients had pelvic recurrences (two central, one nodal), and four patients had distant metastases. The 2-year DFS and OS rates were 90% (95% CI = 82%-98%) and 95% (95% CI = 89%-100%), respectively. The 2-year late complication rates (according to RTOG/EORTC grade ≥ 1) were 18% (95% CI = 8%-28%) for large intestine/rectum, 4% (95% CI = 0%-8%) for small intestine, and 0% for bladder. No cases of grade 3 or higher were observed for GU/GI late complications.

Retrospective Results Using Point A With Pulsed-Dose Rate Brachytherapy[348]

Kaneyasu et al[349] treated 419 patients with SCC of the cervix from 1969 to 1999 with LDR or MDR. LDR required overnight admission, whereas MDR was given over approximately 5 hours on an outpatient basis. The 5-year OS rates for stages I, II, III, and IVA in the LDR group were 78%, 72%, 55%, and 34% versus 100%, 68%, 52%, and 42% in the MDR group (not statistically different). The actuarial rates of late complications of grade 2 or greater at 5

years for the rectum, bladder, and small intestine in the LDR group were 11.1%, 5.8%, and 2.0%, respectively, whereas for the MDR group, they were 11.7%, 4.2%, and 2.6%, respectively (not significantly different).

Bachtiary et al[350] reported on 109 patients treated with LDR BT and 57 who received PDR BT. The 3-year OS and DFS rates were 70% and 57% for the LDR group and 82% and 70% for the PDR group, respectively (P = .25 and .19). The 3-year probability rate for late grade 3 or worse toxicity was 7.4% for patients who had LDR BT and 7.6% for those who had PDR BT (P = .69) and was 6.9% and 7.6% for concurrent chemotherapy versus none (P = .69).

Rath et al[351] reported on 48 patients treated with PDR BT (intracavitary radiation therapy) and pelvic irradiation. A single session delivered a dose of 27 Gy to point A by PDR (hourly pulse, 70 cGy). Ten patients had disease recurrence (five each in stage IIB and stage IIIB). Eight patients had pelvic failure, one had bone metastases, and one had supraclavicular node metastases. Overall, the grade III to IV late toxicity rate at 50 months was 6%. For the median follow-up period of 15 months, the actuarial recurrence-free survival in stages I to II was 82% and in stages III to IV was 78%.

Prospective Trials With Computed Tomography or Magnetic Resonance Planning

The French STIC trial[348] collected data from 20 centers prospectively and stratified to 2D versus 3D (mainly with CT) BT. Its clinical outcomes are listed in Table 76.8. A total of 705 patients with stage IB to IIIB cervical cancers were treated with one of three arms: (a) BT followed by surgery (stage IB1, 165 patients); (b) EBRT plus chemotherapy, BT, then surgery (305 patients); or (c) EBRT plus chemotherapy and then BT (235 patients). The median follow-up was 2 years. Toxicity and survival were significantly improved with 3D-based treatment planning. Detailed results are shown in Table 76.8. For the 235 patients treated with concurrent CRT and then BT, 2-year OS was 74% for 3D versus 65% for 2D (P = .27); DFS was 60% versus 55% (P = .09); local-regional relapse–free survival was 70% versus 61% (P = .001), and local-only relapse-free survival was 79% versus 74% (P = .003). Toxicity was reduced overall from 23% with 2D to 2.6% with 3D (P = .002); urinary from 9% in 2D to 1% with 3D (P = .02), GI from 9% to 0% (P = 0.17), and gynecologic from 15% to 1% (P = .01).

TABLE 76.8 TWO-DIMENSIONAL VERSUS THREE-DIMENSIONAL IMAGE-GUIDED BRACHYTHERAPY IN THE PROSPECTIVE STIC STUDY

Mode of Treatment	Number of Patients (*N* = 705)	Imaging During BT	Local Control (%)	Disease-Specific Survival (%)	Overall Survival (%)	Late Grade 3-4 Toxicity (%)
Pre-op LDR or PDR	76	X-ray	92	87	95	14.6
Pre-op PDR	89	CT	100	90	96	8.9
Pre-op CRT/LDR or PDR	142	X-ray	85	73	85	12.5
Pre-op CRT/PDR	163	CT	93	77	86	8.8
CRT/LDR or PDR	118	X-ray	74	55	65	22.7
CRT/PDR	117	CT	78.5	60	74	2.6

All survival outcomes refer to 2-year rates.

CRT, chemoradiotherapy; CT, computed tomography; LDR, low-dose rate brachytherapy; PDR, pulsed-dose rate brachytherapy; Pre-op, preoperative therapy; STIC, Soutien aux Thérapeutiques Innovantes et Couteuses.

Data from Charra-Brunaud C, Harter V, Delannes M, et al. Impact of 3D image-based PDR brachytherapy on outcome of patients treated for cervix carcinoma in France: results of the French STIC prospective study. *Radiother Oncol*. 2012;103(3):305-313.

A meta-analysis of 24 studies, both retrospective and prospective, assessed outcomes of point A (1,538 patients) and volume-based (3,995 patients) approaches, using both CT and MRI. The 3-year DFS for point A and volume-based studies were 67% (95% CI = 60%-73%) and 79% (95% CI = 76%-82%), respectively ($P = 0.001$). Three-year LC for point A and volume-based studies were 86% (95% CI = 81%-90%) and 92% (95% CI = 91%-94%), respectively ($P = 0.01$). The difference in 3-year OS (72% vs 79%, $P = .12$) was not statistically significant. The proportion of prospectively enrolled patients was 23% for point A studies and 33% for volume-based studies. There was no difference in late grade 3 or higher GI (3% vs 4%, $P = 0.76$) and GU toxicities (3% vs 3% $P = 0.45$) between the two groups.[249]

The EMBRACE study was an international collaboration of 24 centers that set out to prospectively investigate a cohort of patients with locally advanced

cervical cancer treated with cisplatin-based CRT followed by MRI-guided adaptive BT. The focus was the standardized application of the GEC-ESTRO MRI contouring and reporting guidelines, with the aim to report outcome and toxicity in a large-scale setting. They accrued a total of 1,341 patients with data available for disease outcomes and 1,251 with sufficient data for toxicity analysis. The median HR-CTV was 28 mL (interquartile range [IQR] 20-40), and the median D90% was 90 Gy (IQR 85-94). After a median follow-up of 51 months, the 5-year LC, pelvic control, DFS, and OS rates were 92%, 87%, 68%, and 74%, respectively.[200]

Retrospective Comparison of Computed Tomography to Magnetic Resonance–Planned Brachytherapy

Three studies compared CT to MRI contouring for HDR tandem and ring BT. Wachter-Gerstner et al[324] compared MR-based plans in 15 patients to those derived with either CT or orthogonal films. CT and MR enabled higher dose to the target volume with similar OAR dosing. Viswanathan et al[312] compared CT contours to MR contours based on a standard set of guidelines; the CT contours were larger in width, but no other significant differences in DVHs were identified. Using an MR for the first fraction and CT for subsequent fractions, Beriwal et al[320] treated 44 patients with 5- to 6-Gy per fraction HDR after EBRT. Ninety-three percent had a CR by PET at 3 months. Of those with a CR, two had an LR at 6 and 8 months. With a median follow-up of 8 months (range, 2.5-38 months), 2-year LC, DSS, and OS rates were 88%, 85%, and 86%, respectively.

One study compared CT to MR interstitial-based BT for cervical cancer and showed 2-year LC rates for MR- and CT-based treatments as 96% and 87%, respectively (log-rank $P = .65$). At 2 years, OS was significantly better in the MR-guided cohort (84% vs 56%, $P = .036$). On multivariate analysis, squamous histology was associated with longer OS (HR 0.23, 95% CI, 0.07-0.72) in a model with MR BT (HR 0.35, 95% CI, 0.08-1.18). There was no difference in toxicities between CT and MR BT.[352]

Toxicities

In the Medical University of Vienna series reporting patients treated from 2001 to 2008, 73% received concurrent cisplatin chemotherapy.[353] A total of 11 grade 3 and 4 late events were recorded in 143 patients. With a median

follow-up of 3.5 years, the actuarial grade 3 and 4 late morbidity at 3 and 5 years was, respectively, as follows: GI, 4% and 4%; urinary, 2% and 3%; and vaginal, 1% and 3%. Two patients developed massive rectal bleeding requiring transfusions. Three patients required stoma (grade 4) for rectal wall ulceration, resulting in a fistula, a rectal perforation, and a rectovaginal fistula. Three patients developed grade 3 urinary frequency or urgency. Three patients experienced grade 3 or 4 coaptation of the vagina.

At IGR, of the 45 patients studied,[354] 23 and 2 developed acute grade 1 or 2 and grade 3 complications, respectively; 21 patients presented with delayed grade 1 or 2 complications. One other patient presented with a grade 3 vesicovaginal fistula. No grade 4 or greater complications, whether acute or delayed, were observed. In the IGR experience with LDR BT from 2000 to 2004, 39 late complications were reported: 13 bladder, 7 rectal, 5 small bowel, 4 urethral, 3 colic, 2 vaginal, 1 pelvic fibrosis, and 4 others. Grade 3 complications were one rectal, two bladder, and one urethral. Tan et al[355] reported on 28 patients treated with CT-guided BT for stage IB to IIIB cervix cancer. Their overall actuarial 3-year grade 3 and 4 morbidity rate was 14%. Two patients had grade 3 abdominal pain and one had a colovaginal fistula. Overall, the data indicate that a potential reduction in morbidity appears to be a benefit of image-guided BT. Advocating for contouring bowel as a separate OAR during image-based BT, a report of 32 patients showed that when bowel was present around the BT applicator, contouring the bowel reduced the D_{2cc} optimized dose.

In the EMBRACE study, of the 1,251 patients with available toxicity data from a median follow-up of 48 months (IQR, 20-62), 270 patients had 534 severe adverse events (grade ≥3). The 5-year actuarial estimate of all severe events was 26.6%. When restricted only to organ-related events (GI, GU, vaginal, or fistula), it goes down to 18.4%, broken down to 6.8%, 8.5%, 5.7%, and 3.2%, respectively. The risk for fistula was increased with stage. The most common non–organ-related events were fatigue and insomnia. Further toxicity information is displayed in Table 76.9. The 5-year cumulative actuarial risk of treatment-related death was 1.2%, mostly due to GI complications, sepsis, and GU complication.[356]

TABLE 76.9 MAIN GRADE ≥3 TOXICITY EVENTS IN PATIENTS TREATED WITH CRT AND MR-GUIDED BRACHYTHERAPY IN THE EMBRACE COHORT WITH AT LEAST 1 FOLLOW-UP (*N* = 1,251)

Event	Number (%) of Grade ≥3 events		
	At Baseline	At Follow-Up	5-Y Actuarial Estimates Grade ≥3 (95% CI)
GI category			
Diarrhea	1 (0.1%)	20 (1.6%)	1.9% (1.2%-3.0%)
Incontinence	0 (0.0%)	5 (0.4%)	0.5% (0.2%-1.3%)
Proctitis	0 (0.0%)	6 (0.5%)	0.6% (0.3%-1.4%)
Bleeding	0 (0.0%)	22[a] (1.8%)	2.2% (1.4%-3.4%)
Stenosis	0 (0.0%)	26 (2.1%)	2.8% (1.9%-4.2%)
Ileus	0 (0.0%)	10 (0.8%)	1.2% (0.6%-2.2%)
Bowel perforation	0 (0.0%)	10 (0.8%)	1.1% (0.6%-2.1%)
Total GI events	1	117	
Total patients w/ GI events	1 (0.1%)	81 (6.5%)	8.5% (6.9%-10.6%)
GU category			
Frequency	8 (0.6%)	19 (1.5%)	1.8% (1.1%-2.8%)
Incontinence	3 (0.2%)	24 (1.9%)	2.2% (1.4%-3.3%)
Cystitis	2 (0.2%)	14 (1.1%)	1.3% (0.8%-2.3%)
Bleeding	0 (0.0%)	6 (0.5%)	0.8% (0.3%-1.8%)
Ureteral stricture	24 (1.9%)	36[b] (2.9%)	2.9% (2.1%-4.2%)
Renal failure	1 (0.1%)	9 (0.7%)	0.7% (0.3%-1.5%)
Total GU events	40	112	
Total patients w/ GU events	32 (2.6%)	75 (6.0%)	6.8% (5.4%-8.6%)
Vaginal category			
Stenosis	0 (0.0%)	36 (2.9%)	4.0% (2.8%-5.7%)
Mucositis	0 (0.0%)	14 (1.1%)	1.4% (0.8%-2.3%)
Bleeding	37 (3.0%)	5 (0.4%)	0.5% (0.2%-1.2%)
Total vaginal events	37	59	
Total patients w/ vaginal events	37 (3.0%)	55 (4.4%)	5.7% (4.3%-7.6%)
Fistula category			
Total fistula events	1	42	
Total patients w/ Fistulas	1 (0.1%)	34 (2.7%)	3.2% (2.2%-4.5%)

Event	Number (%) of Grade ≥3 events		
	At Baseline	At Follow-Up	5-Y Actuarial Estimates Grade ≥3 (95% CI)
Pelvic organs category			
Total GI, GU, vaginal, or fistula events	79	330	
Total patients w/ GI, GU, vaginal, or fistulas events	72	183 (14.6%)	18.4% (16.0%-21.2%)
Non-pelvic organs category			
Lower limb lymphedema	0 (0.0%)	5 (0.4%)	0.4% (0.1%-1.0%)
Hot flashes	0 (0.0%)	23 (1.8%)	2.1% (1.4%-3.2%)
Fatigue	10 (0.6%)	63 (5.1%)	6.5% (5.1%-8.4%)
Insomnia	8 (0.6%)	47 (3.8%)	4.8% (3.6%-6.5%)
Neuropathy	0 (0.0%)	6 (0.5%)	0.6% (0.3%-1.3%)
Total non-GI/GU/vaginal events	27	204	
Total patients w/non-GI/GU/vaginal events	24 (1.9%)	149 (11.9%)	14.5% (12.4%-17.0%)
Overall			
Total events overall	106	534	
Total patients w/events overall	90 (7.2%)	270 (21.6%)	26.6% (23.8%-29.6%)

CI, confidence interval; CRT, chemoradiotherapy, G, grade; GI, gastrointestinal; GU, genitourinary; MR, magnetic resonance; w/, with.

[a]In 15 patients, the bleeding originated from the rectum.

[b]Twelve out of 36 patients had G ≥3 ureteral stricture at baseline. Among these, five patients had persistent ureteral stricture until the end of follow-up or resolution without subsequent reoccurrence, whereas in seven patients, the ureteral stricture resolved to reoccur at a later time point.

Modified from Vittrup AS, Kirchheiner K, Pötter R, et al; EMBRACE Collaborative Group. Overall severe morbidity after chemo-radiation therapy and magnetic resonance imaging-guided adaptive brachytherapy in locally advanced cervical cancer: results from the EMBRACE-I study. *Int J Radiat Oncol Biol Phys*. 2023;116(4):807-824. http://creativecommons.org/licenses/by/4.0/.

Template-Based Interstitial Brachytherapy

Interstitial implants with ^{240}Ra, ^{144}Cs needles, or ^{206}Ir afterloading plastic catheters to limited tumor volumes are helpful in specific clinical situations.

Indications include large residual bulky cervical tumors after external beam treatment, residual tumor with sidewall invasion, vaginal extension, presence of a fistula and/or adjacent organ invasion, or a prior supracervical hysterectomy (Figure 76.27). The Syed-Neblett and the Martinez Universal Perineal Interstitial applicators are the most commonly selected. Methods for insertion have been described.[299] A tandem should be inserted when a uterus is present. If the os is not visible, US guidance to determine the proper placement of the tandem is advised. Both ring- and ovoid-based applicators modified to allow simultaneous insertion of interstitial needles are available.

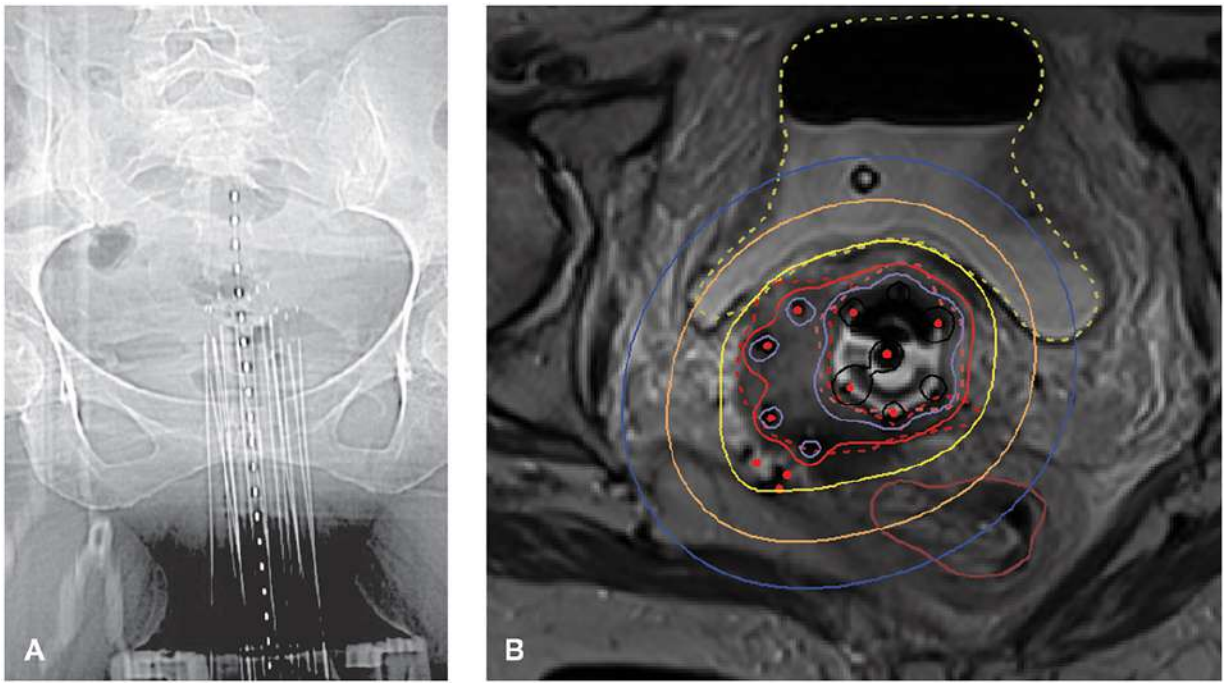


FIGURE 76.27 A. Picture of anterior scout computed tomography showing a template-based interstitial brachytherapy application. B. Magnetic resonance imaging during interstitial needle insertion in a patient with stage IIIB cervical cancer ensures proper placement of the catheters adjacent to the tandem. The 100% isodose line is in yellow.

Traditionally, plain x-ray films are used for BT treatment planning. Determination of normal tissue doses and optimization is not feasible, and the risk of complications is high. In these cases, consideration of laparoscopic approaches is recommended. Syed et al[357] reported on 185 patients with locally advanced cervical cancer treated with LDR interstitial BT from 1977 to 1997. Patients received external beam treatment to 50.4 Gy, followed by interstitial BT to 40 to 50 Gy. LC was 82%; 5-year DFS rates were 65%, 67%,

49%, and 17% for patients with stage IB, II, III, and IV diseases, respectively. Eighteen (10%) of the 185 patients developed RTOG grade 3 or 4 late complications.

Clinical outcomes using traditional techniques have been reported by several institutions.

Fallon et al[358] reported on 315 patients treated from 1992 to 2009 with interstitial BT. The 10-year LC was 87%, and late grade GU and GI toxicities were 4.8% G3 and 5.4% G4, respectively.

Recio et al[359] used laparoscopy at the time of interstitial BT in six patients with FIGO stage IIB to IVA cervical carcinomas after completion of whole-pelvis radiation; a total of 98 needles were inserted to deliver a median interstitial BT dose of 20 Gy. Eleven perforations in the pelvic peritoneum or bladder were identified during surgery in five of the six patients, leading to immediate repositioning of needles. No acute or short-term morbidity related to the procedure was noted.

Sharma et al[360] presented results on 42 patients treated from 2005 to 2007 in a prospective study of two weekly sessions of 10 Gy, 1 week after finishing external beam radiation. Median follow-up was 23 months. Delayed toxicity was 9%. The 3-year OS for all stages was 47%, and the 3-year recurrence-free survival for stages IIB, IIIB, and IVA was 67%, 34%, and 20%, respectively. Sharma et al[361] also reported on the use of transrectal US to assist with insertion of the interstitial needles.

With image-based planning including either a CT or an MRI, the physician evaluates the placement of the needles and may choose either to not treat specific catheters or to lower the dose given through catheters close to normal tissue structures. An approximate 11% rate of bowel insertion and a long-term fistula rate of 4% to 10% have been reported in studies using CT for planning after insertion. When a physician has the facility to insert the applicator in a CT or MR suite while the patient is under anesthesia, an iterative process of image-guided needle insertion ensures proper placement of the catheters and prevents an inadvertent insertion into a surrounding normal tissue structure, such as the rectum, sigmoid, or bladder.[314]

Dose optimization with either PDR or HDR may improve the normal tissue doses for interstitial therapy for some patients. The University of Pittsburgh reported on 11 patients with cervical cancer treated with CT-guided HDR interstitial BT (five fractions of 3.5 Gy per fraction).[362] From 1998 to 2004,

interstitial BT was chosen for cases with distorted anatomy or extensive vaginal disease. The 5-year actuarial LC rate was 63%. No patient had acute grade 3 or 4 toxicity. Grade 3 or 4 late toxicity occurred in one patient, with a 5-year actuarial rate of 7%. Three patients had late grade 2 rectal toxicity, and one patient had grade 2 small-bowel toxicity.

Dimopoulos et al[363] reported on the use of tandem/ring with short interstitial needles and MR-planned HDR BT for 22 patients with cervical cancer followed for a median of 20 months; no grade 3 or 4 toxicities were noted, and one patient had an LR. Nomden et al[364] described the use of tandem/ovoid application with short interstitial needles for the second insertion with MR-planned PDR BT for 20 patients with cervical cancer. They compared the first insertion with just a tandem and ovoid applicator to the second insertion, which included the addition of interstitial needles. There was an average increase in dose of 4.4 Gy (standard deviation 2.3), with better coverage of the HR-CTV with the second insertion.

A prospective cohort of MR-guided interstitial BT showed an LC rate of 96%. In a comparison of CT- to MR-based BT, no difference in toxicities was noted, whereas MR had superior outcomes.[352] A systematic review of 672 patients described an LC rate of 79% with image-based planning.[365]

As interstitial insertions are challenging to both perform and plan, keeping the applicator in place over the course of a few days and performing multiple fractions per insertion become more prevalent. Mikami et al[366] analyzed needle applicator displacement in 10 patients treated with 30 Gy HDR in five fractions and found on daily CT scans an average of 1 to 2 mm of caudal displacement. Shifts of greater than 3 mm were replanned. Shukla et al[367] presented data on 20 patients with cervical cancer treated with interstitial BT who underwent every-other-fraction CT imaging. The mean needle displacement was 2.5 (range, 0-7.4), 17.4 (range, 0-27.9), 1.7 (range, 0-6.7), 2.1 (range, 0-9.5), 1.7 (range, 0-9.3), and 0.6 mm (range, 0-7.8 mm) in cranial, caudal, anterior, posterior, right, and left directions, respectively. The mean displacement in the caudal direction was higher between days 1 and 2 than that between days 2 and 3 (13.4 vs 3.8 mm; $P = .01$). Damato et al,[368] in a study of 10 patients treated with interstitial BT, found on average that less than 1-cm displacements and deformations of the implant occurred over the course of treatment. The most significant dosimetric consequences were due to changes in organ filling rather than catheter shifts. Proper quality assurance

methodologies should be in place to detect shifts that can potentially result in inadvertent insertion into normal tissue.

Brachytherapy in the Older Patients

Magné et al[369] reported on 113 patients with a median age of 76 years (range, 70.7-94.4 years) treated by conventional LDR BT as a part of their treatment. For rectal complications, grade 1/2, 3/4, and 5 (fatal) crude incidences were 19.4% (22/113), 1.8% (2/113), and 0.9% (1/113), respectively. Acute toxicity death occurred in one patient with major diarrhea associated with a hemodynamic shock. For small-bowel complications, grade 1/2 and 3/4 crude incidences were 3.5% (4/113) and 0.9% (1/113), respectively. For urinary tract complications, grade 1/2 and 3/4 crude incidences were 11.5% (13/113) and 2.7% (3/113), respectively. With a median follow-up of 3.1 years, 10 patients developed distant metastases, and 10 others had local relapses. The 3-year specific OS rate was 88.6% (95% CI = 77-92), and the corresponding DFS rate was 81% (95% CI = 72-88). Age did not influence the effectiveness of BT in older patients, and BT should be considered whenever possible, even in older patients presenting with a cervix cancer.

Image-Guided Brachytherapy Versus Intensity-Modulated Radiation Therapy or Stereotactic Body Radiotherapy Boost

Studies of external beam treatment as an alternative boost instead of BT demonstrate significantly inferior survival rates compared to those that use BT. In a SEER analysis, 63% of 7,359 women received BT in combination with EBRT, and 37% received EBRT alone. The BT utilization rate decreased from 83% in 1988 to 58% in 2009 ($P < .001$). In a propensity score-matched cohort, BT treatment was associated with higher 4-year CSS (64.3% vs 51.5%, $P < .001$) and OS (58.2% vs 46.2%, $P < .001$). BT treatment was independently associated with better CSS (HR, 0.64; 95% CI, 0.57-0.71) and OS (HR 0.66; 95% CI, 0.60-0.74).[370] In an updated analysis, the rate of BT utilization improved further to 76% in 2018 to 2020 with still a significant effect on survival.[371] In a study of the NCDB, only 44% of patients received standard-of-care therapy; Black patients were less likely to receive any boost or BT.[372]

A phase 2 single-arm trial of SBRT as a boost after CRT in 15 patients unfit or who refused BT was reported by Albuquerque et al.[170] The trial closed early

due to poor outcomes and high toxicity. The 2-year LC, PFS, and OS were 70.1%, 46.7%, and 53.3%, respectively. Grade 3 and higher 2-year cumulative toxicity rate was 26.7%, mainly rectal bleeding/fistula.

The dosimetry of BT cannot be adequately mimicked by external beam techniques. A treatment planning report compared inversely planned EBRT with photons (IMRT/SBRT) and proton (intensity-modulated proton therapy) to 3D MRI-guided BT.[373] EBRT was planned to deliver the highest possible doses to the PTV while respecting D_{2cc} limits from BT, assuming the same fractionation. Volumes receiving 60 Gy (in equivalent dose in 2-Gy fractions) were approximately twice as large for IMRT compared with BT, and the high central tumor dose was lower than that seen with BT. Both IMRT and proton were inferior to 3D image-based BT. With IMRT, there is a need for replanning because of rapid tumor regression and an increase in integral dose, with normal tissues throughout the pelvis receiving more radiation than with BT. Given the large movement and the increased dose to the normal tissues resulting in an increase in normal tissue toxicity, highly conformal (IMRT, IGRT, SBRT) methods for boosting the cervix are not routinely recommended. Every effort should be made to use image guidance to insert a tandem into the uterus in order to provide adequate BT doses for all cervical cancer cases receiving radiation.

Occasionally, BT procedures cannot be performed because of medical reasons or unusual anatomic configuration of the pelvis or the tumor (ie, extensive lesion, inability to identify the cervical canal). These patients may be treated with higher doses of external beam irradiation alone, although survival is significantly worse than when BT is implemented and normal tissue toxicity is higher due to the excessive dose to the rectum and bowel. Therefore, every attempt to treat with BT should be made because BT moves with the patient and provides high regions of dose in the central regions of the tumor. With IMRT, a significantly higher normal tissue dose is administered, and the desired high central regions of radiation cannot safely be administered.

FOLLOW-UP

After treatment, patients should be regularly followed by both the radiation and the gynecologic oncologist. Careful history-taking and a complete physical and pelvic/rectal examination are usually performed as clinically

needed in the first 3 months after completion of irradiation, especially for toxicity management or for concerning residual disease.

A PET-CT scan performed 3 months after definitive CRT is useful in assessing response and determining prognosis. A meta-analysis including 1,104 patients in 12 cohorts was reported by Kim et al.[374] The pooled HRs for OS and PFS of patients with complete metabolic response versus partial response or progressive disease were 0.20 (95% CI, 0.12-0.34) and 0.12 (95% CI, 0.07-0.19).

Dependent on specific risk assessment, clinical evaluation should continue every 3 to 6 months for the remainder of the first year, every 4 to 8 months the second year, every 6 to 12 months during the third through the fifth year, and yearly thereafter.[375]

The use of Pap smears for cervical and vaginal cytology as a follow-up study is controversial because of postirradiation cellular morphology that renders it difficult to distinguish postirradiation changes from residual or recurrent malignant cells. DNA analysis of postirradiation cytologic smears demonstrating atypia or dysplasia may provide ancillary information.

Rintala et al[376] evaluated the reliability of cytologic analysis and atypia after RT in 89 patients treated for cervical carcinoma. A total of 697 Pap smears were taken; during the follow-up, 44 patients had recurrent disease, which was local in 17 (39%) cases. The rate of false-positive samples was only 3%. Radiation-induced atypia was detected in 28% of the Pap smears taken during the first 4 months after RT, and its incidence decreased thereafter. In 1,000 patients treated with either surgery or RT at the MD Anderson Cancer Center for stage IB cervical cancer post-treatment, Pap smears did not detect a single asymptomatic recurrence among 133 patients with recurrent disease.[377]

The presence of apparently viable tumor cells in the cytologic smear 3 months after irradiation should be evaluated with cervical biopsies, dilation and curettage, and careful EUA, as indicated.

Complete blood counts and chemistry profile tests are obtained as clinically indicated. If a known tumor marker such as SCC-AG was elevated prior to therapy, then its level afterward can be useful to detect asymptomatic recurrences. Chest radiography is commonly obtained on a yearly basis, usually for the first 5 years post-treatment, although its value to detect curable

lung metastasis is not proven. If radiographs are consistently negative, obtaining them every other year thereafter may be sufficient.

Other imaging studies, such as CT, MRI, PET scanning, or bone scans, are usually performed when clinically warranted but can be considered for routine follow-up in high-risk patients when available. PET-CT imaging in asymptomatic patients has been shown to detect recurrences amenable to curative salvage therapy.[378]

When persistent or recurrent tumor is suspected, biopsies should be obtained for histologic confirmation. If a biopsy is positive, immediate treatment should be instituted, as is discussed later.

Usually, hematometra after RT for cervical carcinoma is related to recurrent disease but occasionally may be related to estrogen replacement therapy, endometrial activity, or fibrosis and obliteration of the endocervix.

It is important to keep in mind that cervical cancer survivors are at increased risk for second malignancies from their exposure to HPV infection and/or high doses of radiation, especially as some may have decades of life ahead of them. Thus, relevant screening measures and patient education are appropriate.[379]

TREATMENT OF RECURRENT CARCINOMA OF THE CERVIX

After Previous Surgery

Radiation may salvage approximately 50% of patients with localized pelvic recurrences after surgery alone. A combination of whole-pelvis external irradiation (45-50 Gy) with concurrent chemotherapy followed by interstitial BT is recommended. If the tumor lies outside an accessible region for BT, dose escalation with conformal or IMRT techniques may be attempted, depending on the location of the tumor and the need to protect the bowel, with at least 65 to 70 Gy necessary for adequate control. In the setting of recurrent disease, the total mucosal dose from the external and BT can approach 140 Gy to the upper vagina and 95 Gy to the distal vagina without a high risk. With interstitial BT, doses of 20 to 35 Gy are administered with single, double-plane, or volume implants, for a total tumor dose of approximately 80 Gy, depending on the extent of the tumor.

Shan et al[380] retrospectively reported on 72 patients with locoregional recurrences after surgery without adjuvant RT, who underwent salvage platinum-based CRT. The 5-year PFS and OS were 57.6% and 65.9%,

respectively. Regional nodes were irradiated to 45 to 50 Gy and a boost of 18 to 30 Gy was given with BT in central recurrences or with EBRT in other locations up to 60 to 66 Gy. Better prognosis was associated with a central recurrence, fewer lesions, and regional irradiation rather than targeting only gross disease.

After Definitive Irradiation

Therapy for previously irradiated patients must be considered with caution and tailored for each specific case. It is important to analyze the techniques used in the initial treatment (beam energy, volume, doses delivered with external or intracavitary irradiation), the period of time to recurrence, its location and extent, and the general condition of the patient. Patients with longer interval and location above the field that conforms to lymphatic spread (para-aortic, left supraclavicular) can be candidates for aggressive LC with CRT. A shorter interval and larger volume might benefit more from standard first-line systemic therapy and later adding RT to involved fields in patients that achieved disease control, similar to some newly diagnosed stage IVB patients. Different uses of RT in disease recurrences are demonstrated in Figure 76.28.

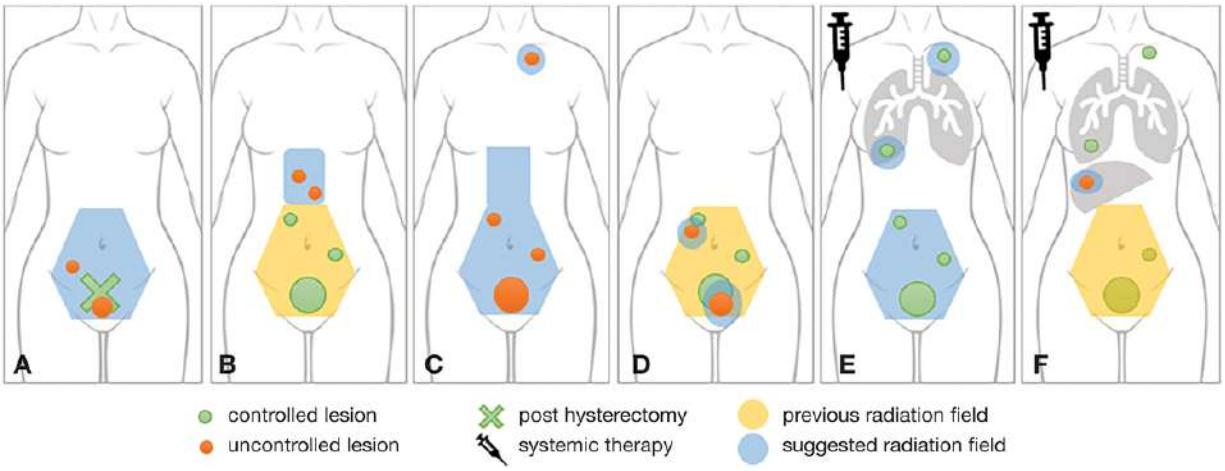


FIGURE 76.28 Recurrences and oligometastatic states. Posthysterectomy central recurrence and pelvic lymph node recurrence (A), above-the-field-recurrence with metachronous para-aortic metastases (B) and synchronous oligometastatic disease (C) are all candidates for concurrent chemoradiotherapy with curative intent. In-field recurrences (D) could also be salvaged with recurrence-directed therapy (surgery or reirradiation with external beam radiation therapy and/or brachytherapy) with or without systemic therapy. Involved-field consolidation radiotherapy (E) should also be considered in responding oligometastatic patients to prolong survival. Limited progression, or oligo-progression, under systemic therapy (F) could also benefit from local therapy such as stereotactic body radiotherapy to the progressing lesions.

Recurrences in Previously Nonirradiated Locations

"Above-the-filed" locations usually refer to upper pelvic echelons and the para-aortic regions. PAN metastases are frequently combined with distant dissemination but are clinically apparent in only 10% to 20% of patients who have recurrences. Isolated recurrences in the PANs after pelvic irradiation, now considered to be stage IIIC2, have been described in about 3% to 8% of patients and may be cured with CRT. The advent of IMRT makes treatment easier, with less morbidity. Singh et al[381] detected 14 isolated PAN metastases in 816 patients previously treated with RT; these women were subsequently treated with RT to the PANs combined with concurrent chemotherapy. Seven patients survived for 5 years.

In a review of 1,955 patients treated with RT for cervix cancer, Jhingran et al[382] identified 120 patients with recurrent tumor above the pelvic fields. Initially, 10 had common iliac and 5 had PAN involvement. In 104 patients, recurrences were immediately adjacent to the upper borders of the RT fields. In 15 patients treated with curative intent for the PAN recurrence, 5-year survival was 25%.

Niibe et al reported that from a multihospital registry of over 5,000 patients, 84 isolated PAN recurrences were identified (82% occurring after primary or adjuvant RT). Definitive treatment with RT with or without chemotherapy resulted in 31.3% 5-year OS. Shorter OS was associated with less than 50 Gy dose and with symptoms.[383]

Distant recurrences, in organs such as the liver or lung, or in distant lymph nodes, could also benefit from metastases-directed therapy, with most achieving a delay in the need for systemic therapy and some even long-term remission.[171]

Ning et al[384] reported on 38 patients with metastases to the supraclavicular or mediastinal nodes, and the lung, of whom 9 were synchronous and the rest were recurrences after CRT with BT. For nodal disease, conventional fractionation with integrated boost was given to the gross disease to a median dose of 60 Gy and the lymph node basin up to 45 to 50 Gy with the para-aortics included in supraclavicular disease. SBRT was given when feasible in pulmonary disease usually with 50 Gy in four fractions. Chemotherapy was given to 34 (89%) patients as induction concurrently or adjuvantly. Rates of 2-year PFS and OS were 48.4% and 73.5%, respectively. LC was good with only one in-field recurrence. The toxicity profile was tolerable and reflected the area treated; 13 (34%) patients experienced grade 2 esophagitis, and 5 (13%) had grade 2 dermatitis. Only one grade 3 esophagitis was reported, with a short-term feeding tube needed.

Macchia et al[385] reported a multicenter Italian cohort of 83 patients with oligometastatic, persistent, or recurrent cervical cancer treated for 125 lesions with SBRT. All patients had primary disease controlled, unfit for systemic therapy and had up to five lesions. The median dose was 35 Gy (10-60) in a median of 5 (1-10) fractions. Lesions were either nodal 54.2% or parenchymal 44.8%. Complete, partial, and stable response were achieved in 73 (58.4%), 29 (23.2%), and 16 (12.8%) lesions, respectively, and 46 (55.4%) patients gained CR. Rates of 2-year LC, PFS, and OS in patients with or without CR were 89%, 43%, and 69% versus 22%, 8%, and 43%. Toxicity was mild, with 15 (18%) and 4 (5%) patients reported as having acute and late events, respectively, and only one grade 3 pain.

Recurrence in Previously Irradiated Locations

Reirradiation is feasible, with some patients achieving long-term remission. The time between the two treatments must be taken into consideration because it is postulated that some repair of the initial damage may take place in the interval. In general, external irradiation for recurrent in-field tumor is given to limited volumes. Conventionally fractionated doses were reported, preferentially using lateral portals, but IMRT is better preferred where available. Occasionally, intracavitary or interstitial irradiation can be used to treat relatively circumscribed recurrences. Surgery could also be appropriate in select cases. Whatever the local treatment selected, systemic therapy, as discussed previously in metastatic disease, should be considered to potentially reduce the volume of the recurrence, allowing for less exposure of normal tissue to higher ablative doses of radiation or to surgical complications.

Chopra et al[386] reported on outcomes of oligorecurrences treated with varied RT techniques in 58 patients, with 30 (52%) of them as reirradiation. Median dose of reirradiation in was 44 Gy [IQR 33-68 Gy], with a cumulative dose of 116 Gy [IQR 95-148], conferring 2-year LC and OS as 74% and 61%, respectively. Crude grade 3 and higher toxicity incidence at 2 years was overall 19%, nonsignificantly higher in the reirradiation group (26% vs 11%, $P = .49$).

Kim et al[387] reported on outcomes of salvage RT in 125 patients with recurrent cervical cancer. The report included 45 patients who recurred “in field” as central lesions in 62%, pelvic and para-aortic nodes lesion in 29%, and both in 9%. Only gross disease was targeted when re-irradiating, with mostly IMRT to median 54 Gy dose or intracavitary BT to median 25 Gy. Rates of 5-year local FFS, PFS, and OS were 47.1%, 33.2%, and 66.5%, respectively. On multivariate analysis, shorter PFS was significantly associated with higher stage at initial diagnosis, non-SCC histology, and higher SCC-Ag levels at recurrence.

Ling et al[388] reported on 20 patients with 21 isolated pelvic and para-aortic recurrences, either in-field or marginal, with mixed gynecologic cancers (six with cervical cancer). All were reirradiated with SBRT to a dose of 40 to 45 Gy in five fractions, with a median BED of 82.7 Gy. Rates of 3-year LC, distant PFS, OS, and grade 2 and 3 toxicity were 61%, 44%, 51%, 38%, and 14%, respectively. This emphasizes that while some patients may gain prolonged remission with SBRT reirradiation of isolated lesions, toxicity risk must be considered.

Selected patients with limited pelvic recurrences not fixed to the pelvic wall and without evidence of extrapelvic metastases can be potentially salvaged by RH or pelvic exenteration. Selection should be based on interval from primary treatment and the ability of the patient to withstand the morbidity involved with this procedure.[124]

Intraoperative Irradiation

Intraoperative radiation therapy (IORT) has been used for the treatment of locally advanced and recurrent carcinoma of the cervix, with 3-year survival rates of 8% to 21%, respectively. Central recurrences, particularly in patients who were nonirradiated, and resection of the gross recurrent tumor in those who were irradiated improve the benefit from IORT. Significant toxicity includes peripheral nerve injury and ureteral stenosis (with doses .15-20 Gy).

IORT was used in 70 patients with pelvic recurrences in a European cooperative study.[389] Complete tumor resection was carried out in 30 patients, partial in 37, and unspecified in 3. Sixty-five patients had electron beam therapy (12-25 MeV), with mean doses of 18 Gy (10-25 Gy) after gross complete resection and 19 Gy (10-30 Gy) after partial resection. The 3-year OS rate was 8%. Grade 2 or 3 toxicity was observed in 19 (27%) of 70 patients, with 10 complications being related to IORT.

URGENT BLEEDING AND PALLIATIVE IRRADIATION

Frequently, the radiation oncologist is faced with the challenge of treating a patient with stage IVB or recurrent carcinoma requiring palliation of pelvic pain or bleeding. Tumors respond rapidly to radiation, and bleeding usually resolves within a few days of treatment. If vaginal bleeding is the main concern, several possibilities may be effective. In a descriptive review of eight papers that presented palliative treatment data,[390] five papers were found to report using 10 Gy per fraction, with the best resolution of bleeding and/or pain when each 10-Gy fraction was given at 3- to 4-week intervals for a total of three fractions. Alternatively, common palliative regimens used in other sites of the body, such as 4 Gy for 5 or 6 fractions or 3 Gy for 10 fractions, or a Quad shot regimen may be implemented. Patients who present with a new diagnosis may be treated with 3 to 4 Gy for two or three fractions, followed by standard 1.8 Gy to approximately 39.6 Gy and then BT. Alternatively, patients may receive 1 to 2 days of 1.8 Gy twice a day, switching to once-a-

day treatment with 1.8 Gy per fraction after bleeding has stopped on day 2 or 3, completing treatment after 45 Gy and then commencing routine BT.

If the situation calls for it, a single LDR intracavitary insertion with tandem and colpostats for approximately 6,000 mgh (55 Gy to point A) or the HDR equivalent may be used for palliation. If irradiation was delivered previously, lower intracavitary doses should be prescribed (4,000-5,000 mgh).

Several high-dose fractionation schedules with external beam radiation have been used. Spanos et al[391] reported on a phase II study of daily multifractionated split-course irradiation in 142 patients with recurrent or metastatic disease in the pelvis. Irradiation consisted of 3.7 Gy per fraction given twice daily for 2 consecutive days, repeated at 3- to 6-week intervals for a total of three courses, aiming at a total tumor dose of 44.4 Gy. Occasionally, this regimen was combined with an LDR intracavitary insertion (4,500 mgh), blocking the midline for the last 14.4-Gy external dose. Twenty-seven patients survived greater than 1 year. There were only two recorded cases of grade 3 toxicity (lower GI tract). This study was expanded to a phase III protocol randomizing 136 patients between a short (2 weeks) or a longer (4 weeks) rest period between the split courses of irradiation.[267] There was a trend toward increased acute toxicity in patients with shorter rest periods (5/58 vs 0/68; P = .07). Late toxicity was not significantly different in the two groups. Pelvic tumor response was comparable in both groups (34% vs 26%). The study team reported a 6% complication rate in the total 290 patients treated in RTOG Protocol 85-02. No patient receiving less than 30 Gy experienced late toxicity. There was no significant difference in the incidence of complications for patients with a 2- or 4-week rest (P = .47).

IRRADIATION AND HYPERTHERMIA

Regional hyperthermia is a treatment that applies moderate heat to tumors in an attempt to potentiate the effects of oncologic treatments and improve responses. A Cochrane database review identified six randomized controlled trials published between 1987 and 2009 comparing RT versus combined hyperthermia and RT.[392] A significantly higher CR rate (RR = 0.56, 95% CI = 0.39-0.79) and lower LR rate (HR = 0.48, 95% CI = 0.37 to 0.63) and improved OS (HR = 0.67, 95% CI = 0.45-0.99) with no difference in acute or late grade 3 to 4 toxicity were seen for patients treated with combined therapy. In the concurrent chemotherapy era, the benefit of additional hyperthermia is

less clear. A polish randomized trial in 205 patient undergoing BT with or without hyperthermia did not show improvements in outcomes.[393] In contrast, a meta-analysis of two randomized trials of the addition of hyperthermia to chemoradiation, comprising 536 patients, did show significantly higher 5-year OS with hyperthermia with an HR of 0.67 (95% CI = 0.47-0.96, P = .03).[394] The local relapse–free survival was nonsignificantly higher, and no differences were observed in toxicities. Another randomized trial in 210 patients reported by Minnaar et al[395] has shown a benefit to OS in patients with stage III disease only. Thus, along with the technical limitations in the delivery of adequate heat to large parts of the body such as the pelvis, the use of hyperthermia in the treatment of carcinoma of the uterine cervix has not been widely adopted.

SIDE EFFECTS: SURGERY AND RADIATION

Descriptions of sequelae vary among institutions because toxicity grading scales are not uniform and the scoring system for complications is not clearly stated in all reports. Surgical side effects alone depend on the extent of surgery and the amount of disease. RH alone may cause long-term side effects, such as urinary retention requiring chronic suprapubic catheter placement, sciatic nerve injury, postoperative seroma or hematoma formation, pelvic pain, or, when lymphadenectomy is performed, lifelong edema. Oophorectomy also may induce menopause; hysterectomy removes the ability to carry a pregnancy, and removal of a portion of the vagina may significantly change sexual function if vaginal shortening is severe.

With improved anesthesia, surgical techniques, and antibiotic therapy, the mortality rate for RH with pelvic lymphadenectomy has decreased to 1% or less. Open surgery is the standard due to better survival outcomes,[122] even though it is associated with more blood loss and longer hospital stay.[121] Nam et al[120] reported intraoperative complications to be comparable between approaches (6.8% and 5.7%, P = .71), but postoperative complications were significantly higher in the open surgery group (9.2% vs 21%, P < .001). The most frequent sequela after RH is urinary dysfunction as a result of partial denervation of the detrusor muscle. Patients may have various degrees of loss of bladder sensation, inability to initiate voiding, residual urine retention, and incontinence.

Patients who had a pelvic lymphadenectomy experienced a greater incidence of lower extremity lymphedema than those who did not undergo this procedure. Some loss of defecatory urge associated with chronic rectal dysfunction may occur after RH. Manometric studies suggest a disruption of the spinal arcs controlling defecation.

Other complications include ureterovaginal fistula (the incidence of which has decreased to <3%), hemorrhage, infection, bowel obstruction, stricture and fibrosis of the intestine or rectosigmoid colon, and bladder and rectovaginal fistulas. Postsurgical complications are usually more amenable to correction than late complications after irradiation.

When postoperative RT is given to selected patients, further complications of the additional therapy are expected. The main areas of side effects because of radiation are bowel, bladder, skin, and sexual function.[396] Because of intestinal adhesions to denuded surfaces in the pelvis, enteric complications, such as obstruction, fistula, or dysfunction, were observed in up to 24% of patients in the pre-IMRT era. Findings at surgery consisted of minimal incisional adhesions, but extensive matted small-bowel loops adherent to the pelvic operative sites.

Lower body mass index (BMI) is correlated with an increase in toxicity. A total of 404 patients with stage IB1 cervical cancer with positive lymph nodes or stage IB2 or higher were treated from 1998 to 2008. A BMI of less than 18.5 was associated with a decreased OS (HR = 2.37, $P < .01$). Grade 3 and 4 complications appeared to trend higher; overall, 17% versus 14%; specifically, for fistula, 11% versus 9% ($P = .05$), for bowel obstruction, 33% versus 4% ($P < .01$), and for lymphedema, 5.6% versus 1.2% ($P = .02$).[397]

The dose of irradiation, technique, and type of surgical procedure performed are important in determining the morbidity of combined therapy. A significant number of complications are associated with pretherapy staging laparotomy, particularly if irradiation (>55 Gy) is given to metastatic PANs. The incidence of complications is between 5% and 20%, depending on the extent of the PAN dissection, use of transperitoneal or retroperitoneal approach for the operation, and dose of irradiation given.

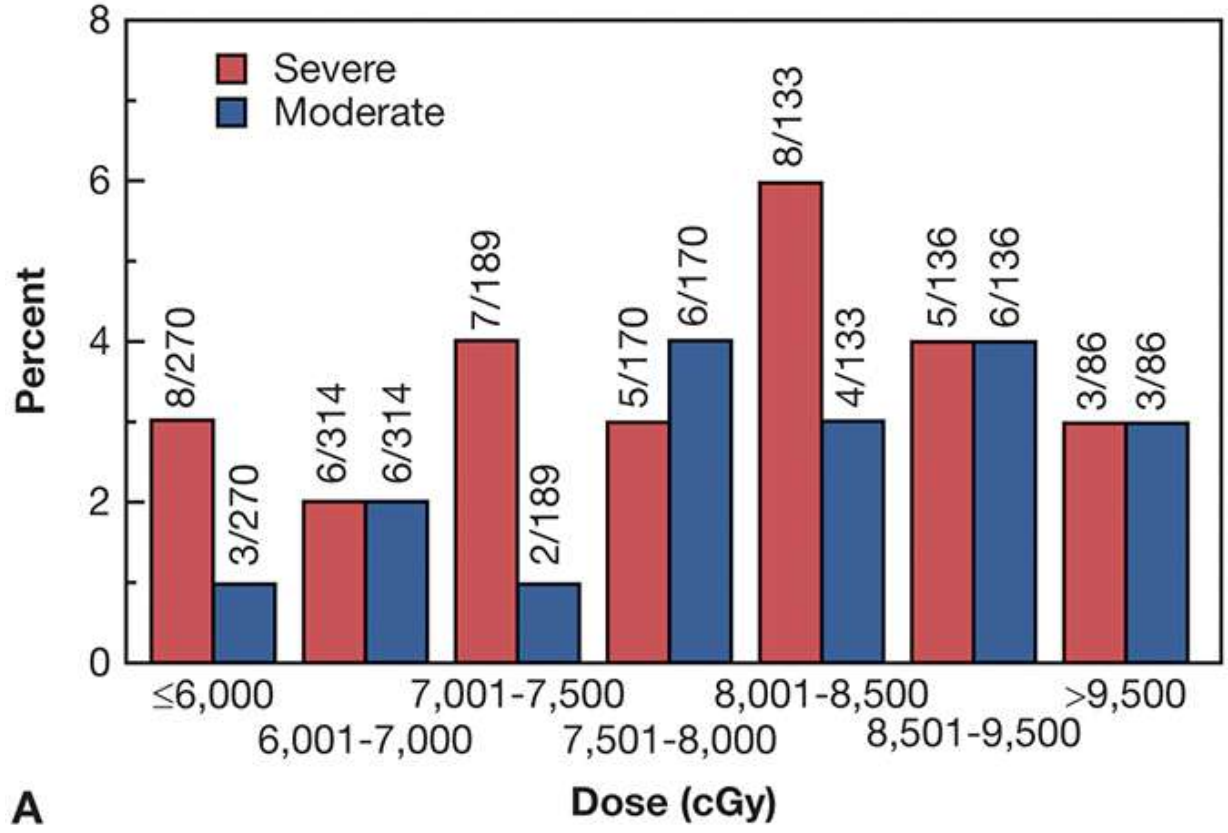
Newer techniques of RT were shown to decrease postoperative irradiation toxicity. In the phase III PARCER trial,[146] which randomized patients with posthysterectomy cervical cancer to pelvic RT with IMRT versus 3D conformal RT, toxicity was shown to be significantly lower with IMRT. The

3-year cumulative risk of grade 2 and 3 late GI toxicity was 21.1% and 2.9% versus 42.4% and 15.5% ($P < .003$). Quality-of-life questionnaires have shown that the IMRT group reported better functional scores and lower symptoms scores. Differences were not significant for late GU or acute GI toxicities.

Late Sequelae: Overall

The incidence of major late sequelae of RT for stage I and IIA carcinomas of the cervix ranges from 3% to 5% and for stages IIB and III between 10% and 15%. Injury to the GI tract usually appears within the first 2 years after RT, whereas complications of the urinary tract are seen more frequently. Actuarial estimates rather than frequency of sequelae should be reported to avoid underestimation of the risks of late morbidity after RT in long-term survivors. In fact, Eifel et al,[398] in 1,784 patients with stage IB carcinoma of the cervix, noted that the greatest risk of sequelae is in the first 3 years after therapy. The risk of rectal complications declined after the first 2 years of follow-up to 0.6% per year, whereas the risk of major urinary tract complications for survivors continued at 0.3% per year, with a 20-year actuarial risk of major complications of 14.4%.

A greater incidence of complications is associated with higher doses of irradiation. Perez et al[399] and Pourquier et al reported that with doses less than 75 to 80 Gy delivered to limited volumes, grade 2 and 3 complications in the urinary tract and rectosigmoid were approximately 5%. However, the incidence increased to more than 10% with higher doses of irradiation to these organs (Figure 76.29). Doses greater than 60 Gy were also correlated with a greater incidence of small-bowel injury (Figure 76.30). The same analysis showed that patients who experienced sequelae of therapy had slightly better survival rates than patients without any complications. This was related to improved tumor control with higher doses of irradiation.


Severe
Moderate
Percent
0
2
4
6
8
8/270
3/270
6/314
6/314
7/189
2/189
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8/133
4/133
5/136
6/136
3/86
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≤6,000
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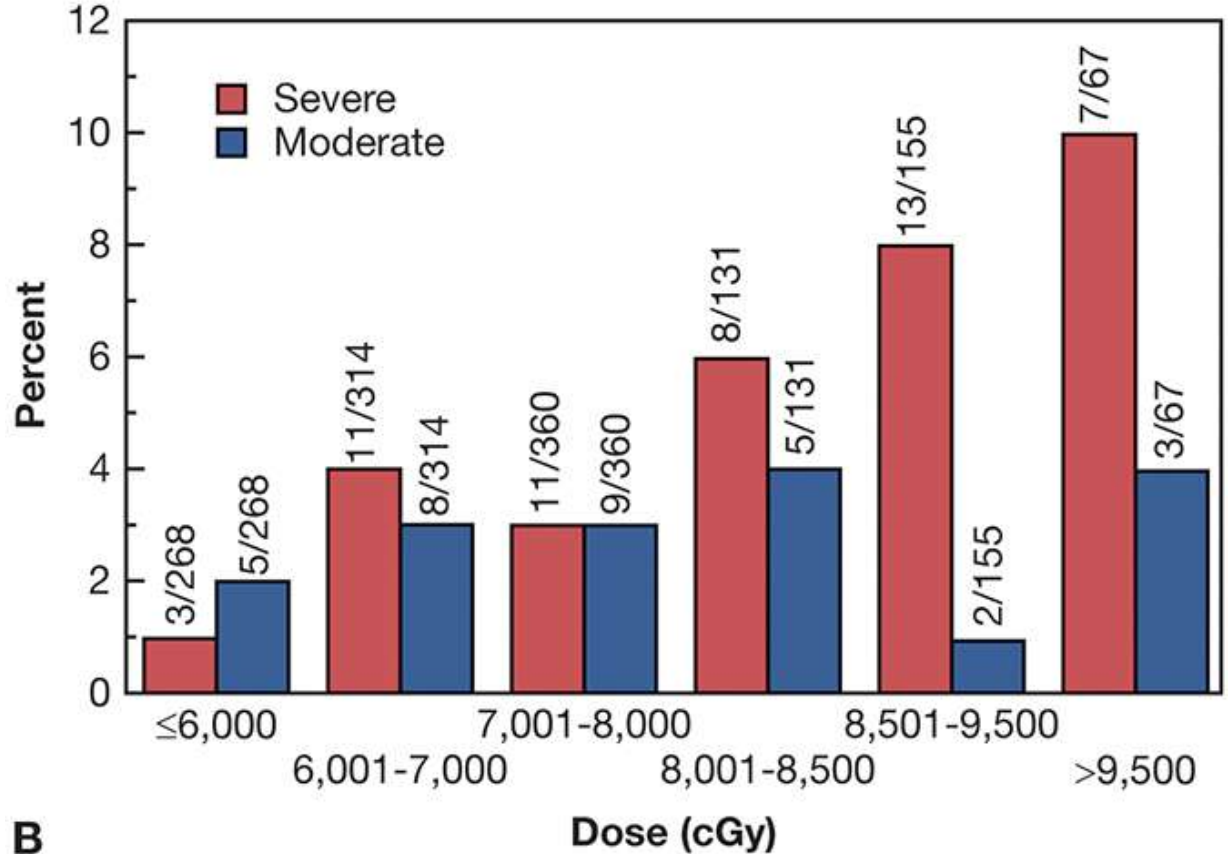
Dose (cGy)

A


Severe
Moderate
Percent
0
2
4
6
8
10
12
3/268
5/268
11/314
8/314
11/360
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8/131
5/131
13/155
2/155
7/67
3/67
≤6,000
6,001-7,000
7,001-8,000
8,001-8,500
8,501-9,500
>9,500
Dose (cGy)

B

FIGURE 76.29 Incidence of moderate or severe genitourinary (A) or rectosigmoid (B) complications in patients with carcinoma of the uterine cervix (all stages) treated with irradiation alone (external and brachytherapy). A greater frequency of complications is noted with maximum doses of .75 to 80 Gy to the bladder or rectum.

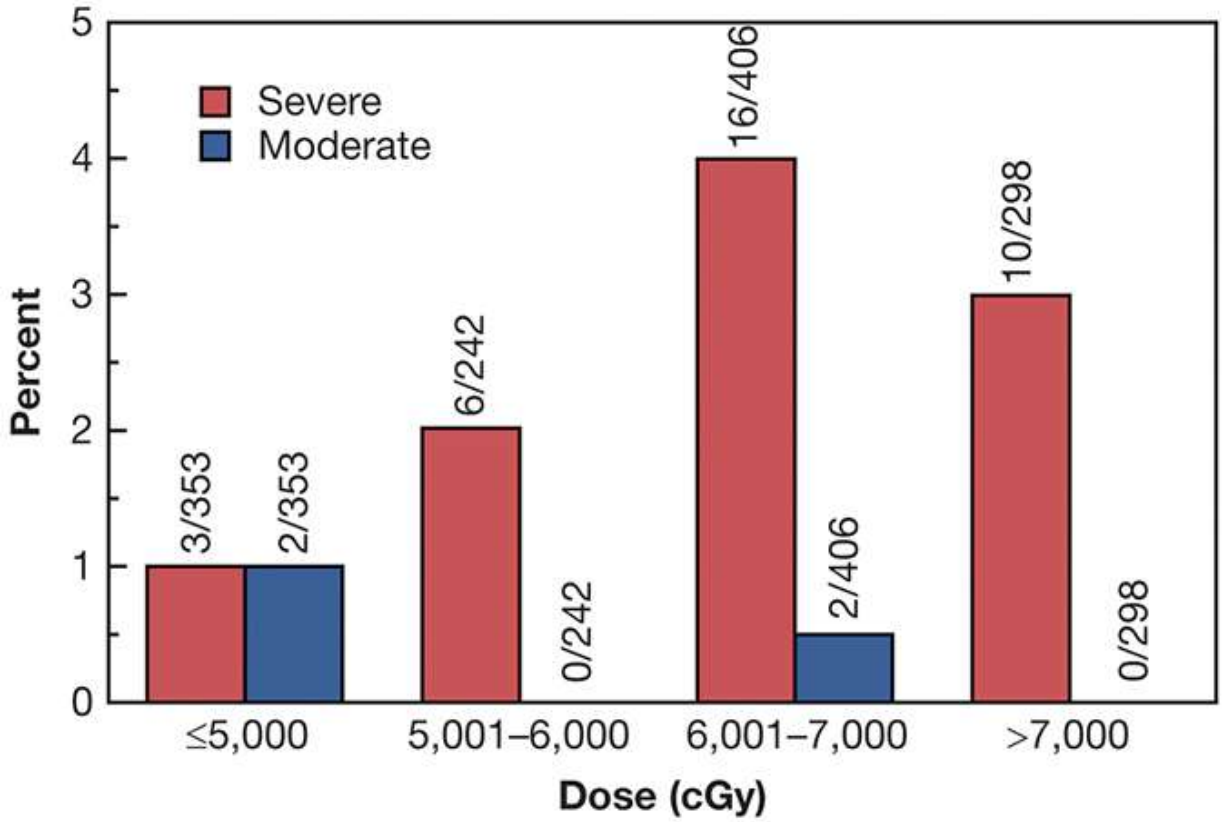

FIGURE 76.30 Incidence of moderate or severe complications in small intestine correlated with doses of irradiation.

Perez et al[399] quantitated the effect of total doses of irradiation, dose rate, and ratio of doses to bladder or rectum and point A on sequelae in 1,456 patients treated for cervical cancer with external beam irradiation plus two LDR intracavitary insertions to deliver 70 to 90 Gy to point A. Median follow-up was 11 years. In stage IB, the frequency of grade 2 morbidity was 9%, and in grade 3, it was 5%; in stages IIA, IIB, III, and IVA, the frequency of grade 2 morbidity was 10% to 12% and that of grade 3 was 10%. The most frequent grade 2 urinary/rectal sequelae were cystitis and proctitis (0.7%-3%). The most common grade 3 sequelae were vesicovaginal fistula (0.6%-2% in patients with stage I-III tumors), rectovaginal fistula (0.8%-3%), and intestinal obstruction (0.8%-4%). In the bladder, doses less than 80 Gy

correlated with a less than 3% incidence of morbidity, which was 5% with higher doses (P = .31). In the rectosigmoid, the incidence of significant morbidity was less than 4% with doses less than 75 Gy and increased to 9% with higher doses. For the small intestine, the incidence of morbidity was less than 1% with 50 Gy or less, 2% with 50 to 60 Gy, and 5% with higher doses to the lateral pelvic wall (P = .04). Multivariate analysis showed that dose to the rectal point was the only factor influencing rectosigmoid sequelae and dose to the bladder point affected bladder morbidity.

Mitchell et al[65] evaluated 398 patients with stage I to III cervical carcinomas treated with RT. Patients were divided into non-older (35-69 years of age; n = 338) and older (≥70 years of age; n = 60) groups. The frequency and severity of acute and chronic sequelae were equivalent in both groups.

The persistence of late substantial patient-reported symptoms was reported for the EMBRACE cohort.[400] Substantial symptoms were defined as whether the patient reported them as quite a bit or very much. Sufficient follow-up, meaning at least three late follow-up assessments, was available in 741 patients. This was evaluated in nine different symptoms, and across all symptoms, median persistence was 4.6%. Urinary frequency, neuropathy fatigue, insomnia, and menopausal symptoms persisted in more than 10%. Vomiting, rectal or vaginal bleeding, and urinary pain/burning were persistent in less than 1%. The occurrence of corresponding physician-assessed severe grade toxicity was apparent in only 12% of patients reporting persistent symptoms, highlighting that the sequelae of care in cervical cancer survivors can be underappreciated. Persistent symptoms were also shown to be associated with quality-of-life scores reductions, especially fatigue and pain with around 20% reductions.[401]

Gastrointestinal Toxicity

When late radiation proctitis occurs, initial treatment is the same as for acute proctitis. If the symptoms and rectal bleeding persist, laser treatment of rectal telangiectasia or ulcers is frequently beneficial. Argon plasma coagulation (APC) is the most common endoscopic method. It is a noncontact thermal method of hemostasis and thus considered to add increased safety.[402] Outpatient intrarectal application of formaldehyde 4% can also be used. If patients continue to bleed, another application 3 weeks later can be attempted. Patients are sedated, a local anesthetic block is administered, and a sponge

moistened with 4% formalin is applied for 4 minutes to each bleeding area of the rectum. Care is taken to protect the perianal skin from any caustic effects of the formalin. Complications such as burns or late stenosis of the deep layers of the rectum are extremely rare, and this technique is well tolerated. A randomized trial of APC and formalin in 30 patients did not show a significant advantage to either.[403]

Occasionally, a colostomy is necessary if conservative management fails. The importance of performing colonoscopy in patients with rectal bleeding to exclude other lesions in the colon, including polyps or cancer, is emphasized. If routine screening colonoscopy is not urgent, unless there is a medical reason, the colonoscopy may be postponed until 1 year after pelvic radiation to ensure no issues with poor wound healing, bleeding, or ulceration secondary to biopsy performed at the time of colonoscopy.

Anal incontinence is occasionally observed. This sequela must be assessed in light of a report by Nelson et al,[404] who, in a survey of 6,959 patients who were nonirradiated, identified 153 (2.2%) who reported anal incontinence, without specific etiology. Thirty percent of incontinent subjects were greater than 65 years of age, and 63% were women. Of those with anal incontinence, 36% were incontinent to solid feces, 54% to liquid feces, and 60% to gas.

Kim et al[405] investigated the effects of radiation on anorectal function using manometry in 24 patients with carcinoma of the uterine cervix who had late radiation proctitis. These data were compared with those from 24 age-matched nonirradiated female volunteers. Regardless of the severity of proctitis symptoms, 75% of patients who were irradiated exhibited abnormal manometric parameters for sensory or motor functions. Radiation damage to nerves and the external sphincter muscle was considered to be an important cause of motor dysfunction.

Perez et al[399] reported that the incidence and type of complications with interstitial therapy were approximately the same as in patients treated with intracavitary technique only. In contrast, Kasibhatla et al[406] noted 6% small-bowel obstruction in 36 women with gynecologic cancer treated with EBRT and interstitial BT, which was aggravated by previous abdominopelvic surgery. The 3-year risk of rectovaginal fistula was 18%, and it was significantly higher in patients who received total doses of greater than 76 Gy (100% vs 7%; $P = .009$).

An analysis of late GI toxicity in the EMBRACE cohort showed that in general, EBRT parameters are associated with late diarrhea and BT parameters affect rectal toxicity. Late diarrhea G1, 2, and 3 crude rates were 16%, 8.3%, and 1.5%, respectively. Patient-related risk factors were baseline diarrhea, smoking, and diabetes. Treatment-related risk factors were the prescribed elective dose (45 Gy vs 50 Gy), V_{43}, V_{57} (the nodal boost volume), and extended-field use.[401] These were also associated with other grade 3 and higher bowel toxicity.[407] Rectal toxicity was shown to be correlated to BT doses.[327] The equieffective D_{2cc} dose for a 10% probability of G2 and higher rectal toxicity was 69.5 Gy. Higher doses were associated with bleeding, proctitis, and fistula. A D_{2cc} over 75 Gy was associated with a 12.5% risk of fistula compared to 0% to 2.7% lower doses, and a D_{2cc} of less than 65 Gy is protective from proctitis. This corresponds with the soft (65 Gy) and hard (75 Gy) rectal constraints of BT planning. The 5-year actuarial incidence of severe bowel morbidity including 3 to 4 grade diarrhea, flatulence, and incontinence was 5.9% and any grade stenosis, stricture, and fistula was 2.6%.[408] Out of the 13 treatment-related deaths in the EMBRACE cohort, 8 were associated with GI morbidity.[356]

Willett et al[409] reported on 28 patients with inflammatory bowel disease (10 with Crohn disease, 18 with ulcerative colitis) who underwent external beam abdominal or pelvic irradiation. Patients were treated either by specialized techniques (16 patients) to minimize small- and large-bowel irradiation or by conventional approaches (12 patients). The overall incidence of severe toxicity was 46% (13/28 patients), and six patients (21%) experienced severe acute toxicity, necessitating cessation of RT. Late toxicity requiring hospitalization or surgical intervention was observed in 8 (29%) of 28 patients. For patients treated with conventional approaches, the 5-year actuarial rate of late toxicity was 73% versus 23% for patients treated by specialized techniques ($P = .02$). In patients with inflammatory bowel disease, abdominal or pelvic irradiation must be used judiciously.

In contrast, Song et al,[410] in a review of 24 patients with a history of inflammatory bowel disease who received RT (median dose of 45 Gy in 1.8-3 Gy fractions) to fields encompassing some portion of the GI tract, noted that 5 (21%) patients experienced acute intestinal toxicity of grade 3 or greater and 2 (8%) had grade 3 or higher late intestinal toxicity. Fifteen patients also

received concurrent chemotherapy. The authors believed that the GI toxicity in these patients was more modest than generally perceived.

Genitourinary Toxicity

Levenback et al[411] identified 116 (6.5%) of 1,784 patients with stage IB carcinoma of the cervix treated with irradiation in whom hemorrhagic cystitis developed, 23% grade 2 (repeated minor bleeding), and 18% grade 3 (hospitalization required for medical management). The median interval to onset of hematuria was 35.5 months. The risk of severe hematuria requiring surgical intervention was 1.4% at 10 years and 2.3% at 20 years. Minor episodes of hematuria are managed by antibiotic therapy. Cystoscopic, laser, or cautery treatment of bleeding points is indicated. Clot evacuation and continuous bladder irrigation are important elements in the acute management of patients with heavy bleeding. Occasionally, a urinary diversion is required for intractable severe hematuria.

Ureteral stricture at 20 years was observed in 2.5% of 1,784 patients with stage IB carcinoma of the cervix treated with irradiation (274 followed for up to ≥20 years).[412] The most common presenting symptoms were flank pain and urinary tract infection. In five patients, ureteral stricture was complicated by a vesicovaginal fistula. Seven of 43 patients who had no evidence of cancer and had hydroureter or hydronephrosis died of radiation complications. Treatment of ureteral stenosis may consist of stenting or resection of the fibrotic segment and reimplantation of the ureter with either ureteroneocystostomy or ureteroileocystostomy. In approximately half of the patients, diversion of urinary stream and ileal conduits is necessary. Occasionally, a nephrectomy is performed for removal of a nonfunctional kidney.

A pooled analysis from the EMBRACE studies, combining 1,860 patients, with a median follow-up of 34 [2-163] months, reported that 31 patients developed grade 3 to 4 ureteral stricture, amounting to a 5-year actuarial risk of 2.1%. Larger T3 to T4 tumors and hydronephrosis at diagnosis were risk factors.[413] Patients with gynecologic malignancies, including those receiving RT, are prone to the development of urinary tract infections. The most common organism isolated was *Escherichia coli*, followed by *Enterococcus* species. Appropriate urine bacterial studies and cultures are indicated in patients suspected of having superimposed urinary tract infection during the course of RT.

Parkin et al[414] reported a 26% incidence of severe urinary symptoms (urgency, incontinence, and frequency) in patients treated with irradiation alone for cervical carcinoma. They carried out urodynamic studies in 42 women and compared them with 28 women having urodynamic evaluations before and after treatment. There was no difference in the mean maximum flow rate or mean *residual* volume in the two groups. However, mean volume of full bladder sensation was significantly lower in the postirradiation group than in the pretreatment group, as was the mean maximum cystometric capacity. This same dysfunction may be noted in approximately 10% of the general female population, and the incidence increases in older women.

An analysis from the EMBRACE prospective cohort, which included 1,153 patients with median 48 [3-120] months of follow-up, reported a crude incidence of G2 and higher frequency of 13% and incontinence of 11%. Overweight and comorbidity were associated with both, older age with incontinence and IMRT use was protective for frequency. The ICRU bladder point was a stronger predictor of incontinence, with rates increasing from 11% in lower than 65 Gy to 20% in higher than 75 Gy.[415] Ureteroarterial fistula is a rare occurrence, and it is associated with a high mortality rate. When profuse urinary tract bleeding occurs in patients previously diagnosed with a gynecologic malignancy and treated with RT and extensive surgery, ureteroarterial fistula should be considered in the differential diagnoses.

Neurologic Toxicity

In the EMBRACE cohort, grade 3 to 4 neuropathy was rare, with six events amounting to a 5-year actuarial incidence of 0.6%.[356] This can be a result of both cisplatin exposure and direct pelvic radiation damage. Although extremely rare, lumbosacral plexopathy has been occasionally reported in patients treated for pelvic tumors with doses of 60 to 67.5 Gy. This syndrome was observed in 4 of 2,410 patients with cervical or endometrial carcinoma receiving 45 Gy to the PANs (without spinal cord shielding) or external pelvic irradiation (60 Gy to the parametria) and BT, with the lumbosacral plexus receiving total doses of 70 to 79 Gy.[416] Lower extremity paralysis secondary to lumbosacral plexopathy was also reported in standard doses.

Patients previously reported as having radiation myelopathy to the lumbar spine may have suffered a lumbar and sacral nerve plexopathy instead of or in addition to the spinal cord injury. The differential diagnosis of plexopathy

with recurrent tumors is sometimes difficult. Indolent leg weakness usually occurred early in radiation-induced plexopathy, whereas pain is most frequently associated with tumor plexopathy. Muscular weakness, numbness, and paresthesia are common in both situations. Electromyography may show abnormal myokymic discharges in radiation-induced plexopathy, whereas this finding was very unusual in tumor-induced plexopathy. CT is extremely helpful in the detection of pelvic masses or bone destruction caused by tumor. Although cystometrograms have demonstrated bladder atonicity in some cases, several authors have failed to observe bladder or rectal sphincter disturbances. Unfortunately, as in radiation myelopathy, the neurologic deficit is irreversible, and no effective therapy other than supportive care has been found.

Fatigue and insomnia are quite common as well in patients with cervical cancer. An analysis of the embrace cohort showed a grade 1/2 prevalence of fatigue, insomnia, and hot flushes at baseline (pretreatment) and at 3-year prevalence of 29%/6.2%, 18%/3.1%, and 7.9%/1.6% versus 29%/6.8%, 17%/4.4%, and 19%/5.9%. Rates of fatigue and insomnia were relatively stable in treatment and follow-up, and hot flushes increased after treatment. These symptoms were all observed more in younger, premenopausal patients, suggesting an association with ovarian failure.[417] Late persistent fatigue was also associated with the larger sizes volumes irradiated to intermediate and high EBRT and BT doses and other organ-related morbidity.[418]

Vaginal Toxicity and Sexual Function

Vaginal stenosis is a common toxicity of pelvic irradiation. An analysis from the EMBRACE cohort including 630 patients reported a 21% 2-year actuarial incidence for grade 2 and higher vaginal stenosis. Higher dose to the rectovaginal point with BT, higher than 45 Gy prescription dose, and tumor extension to the vagina were identified as risk factors. The risk for stenosis rose from 20% for 65 Gy to 34% at 85 Gy to the rectovaginal point.[329] Other reports found similar dose effects in other vaginal reference points and also identified age and tandem and ovoids applicator use as additional risk factors.[419]

Other clinically significant sequelae have been described. Vaginal length decreased in most patients at 24 months. This was correlated with increased

dyspareunia and with decreased frequency of sexual intercourse, desire, orgasm, and enjoyment of intercourse in 16% to 47% of patients.

Lammerink et al[420] published a systemic review of 20 studies on sexual functioning of cervical cancer survivors. Survivors had a higher rate of dyspareunia compared to controls, with pain during intercourse reported more frequently and for a longer duration of time in patients treated with RT.

An analysis of 1,045 patients with a median follow-up of 50 months from the EMBRACE cohort reported a sexual activity prevalence of 22% compared to 40% to 47% prior to treatment and on later follow-up. Vaginal issues reported were dryness, shortening, tightening, and painful intercourse in about one-fifth of patients and compromised enjoyment in 37% to 47%. Pain during intercourse was associated with tightening, shortening, dryness, and less sexual enjoyment. Regular hormonal replacement therapy (HRT) was significantly associated with less vaginal symptoms and trended to be associated to higher sexual enjoyment ($P = .062$).[421]

Regular vaginal dilation is widely recommended to maintain vaginal health and sexual functioning; however, the compliance rate with this recommendation is not consistent. In a study to test the effectiveness of an "information-motivation-behavior skills" model, the intervention improved the use of vaginal dilation after RT and decreased fear about sex after treatment.[422] There was no evidence that the experimental intervention improved global sexual health. Jensen et al[423] described persistent sexual dysfunction throughout 2 years after RT in 118 women; 85% had low or no sexual interest, 35% had lack of vaginal lubrication, and 55% had mild-to-severe dyspareunia. However, 63% of the sexually active patients before RT remained active, although with decreased frequency.

Radiation causes ovarian failure with a cessation of menses over a 6-month to 1-year period after treatment. Radiation also causes uterine fibrosis in a dose-dependent manner. The dose required for radical cervical cancer treatment causes sufficient uterine fibrosis that even if a woman were to become pregnant through embryo donation, the pregnancy terminates as a stillbirth because of insufficient uterine distensibility.

Bone Toxicity

Grigsby et al,[424] in 1,313 patients with gynecologic tumors treated with RT, identified 207 who received pelvic irradiation to the inguinal areas, including

the hips. Femoral neck fractures developed in 10 (4.8%) patients; 4 were bilateral. The cumulative actuarial incidence of fracture was 11% at 5 years and 15% at 10 years. Most of the fractures occurred in patients receiving 45 to 63 Gy, and although radiation dose could not be correlated with the occurrence of fracture, no fractures were noted in patients receiving less than 42 Gy. Cigarette smoking and osteoporosis were significant prognostic factors for increased risk of fracture.

A retrospective cohort study using SEER cancer registry data linked to Medicare claims data analyzed 6,428 women aged 65 years and above diagnosed with pelvic malignancies from 1986 through 1999 and compared the results for women who did (n = 2,855) with those who did not (n = 3,573) undergo RT.[425] Results demonstrated that women who underwent RT were more likely to have a pelvic fracture than women who did not undergo RT. The cumulative 5-year fracture rate was 8.2% versus 5.9% in women with cervical cancer; the difference was statistically significant, and most fractures (90%) were hip fractures. Concurrent chemoradiation may result in a higher risk than for patients treated with RT alone because the highest fracture rates were seen in patients with anal carcinoma treated with concurrent chemoradiation. A meta-analysis of 15 cohort studies including 3,633 patients reported a pooled estimate of pelvic insufficiency fractures of 14% [95% CI, 10-19], with higher incidence when using more advanced imaging, and with increasing age.[426]

Radiation-induced insufficiency fractures of the pelvis on MRI are characterized by edema on T1-weighted images. They may also be falsely diagnosed as metastases on PET-CT. In patients over 50 years old, a sacrum D50% reduced from 40 Gy to 35 Gy EQD2 reduced fracture risk from 45% to 22%.[427]

The most common complaint is persistent low back pain. The most common form of treatment is conservative management, followed by sacroplasty with polymethylmethacrylate. The vast majority have resolution of symptoms within less than 1 year with conservative therapy, including nonsteroidal anti-inflammatory medication and rest. However, they are associated with reduced life quality. Bye et al[428] assessed health-related quality of life (HRQoL) at 3 to 4 years after pelvic RT for carcinoma of the endometrium and cervix in 94 survivors, 79 (84%) of whom answered a survey. The treated women scored lower than the general population on role

functioning (81.5 vs 90.6; $P < .01$) and higher on diarrhea (23.8 vs 9.5; $P < .01$). Compared with pretreatment conditions, an increase in cases with pain in the lower back, hips, and thighs was seen and was associated with deterioration in HRQoL.

Toxicities Related to Brachytherapy

Descriptions of sequelae vary among institutions because toxicity grading scales are not uniform and the scoring system for complications is not clearly stated in all reports. Jhingran and Eifel,[429] in 4,043 patients with carcinoma of the cervix who had undergone 7,662 intracavitary procedures, observed 11 (0.3%) documented or suspected thromboembolisms, resulting in four deaths; the incidence of postimplant thromboembolism did not decrease significantly with the routine use of low-dose heparin prophylaxis. Other life-threatening perioperative complications included myocardial infarction (one death in five patients), cerebrovascular accident (two patients), congestive heart failure (three patients), and halothane liver toxicity (two deaths). Intraoperative complications included uterine perforation (2.8%) and vaginal laceration (0.3%), which occurred more frequently in patients aged 60 years or above ($P < .01$).

Acute GI side effects of pelvic irradiation include diarrhea, abdominal cramping, rectal discomfort, and, occasionally, rectal bleeding, which may be caused by transient enteroproctitis. Patients with hemorrhoids may experience discomfort earlier than other patients. Diarrhea and abdominal cramping can be controlled with the oral administration of diphenoxylate hydrochloride, with loperamide, atropine sulfate, or opium preparations or emollients such as kaolin and pectin. Proctitis and rectal discomfort can be alleviated by small enemas with hydrocortisone and anti-inflammatory suppositories containing bismuth, benzyl benzoate, zinc oxide, or Peruvian balsam. Some suppositories contain cortisone. Small enemas with cod liver oil are also effective. A low-residue diet with no grease or spices and increased fiber in the stool (psyllium, polycarbophil) usually help to decrease GI symptoms.

GU symptoms secondary to cystourethritis are dysuria, frequency, and nocturia. The urine is usually clear, although there may be microscopic or even gross hematuria. Methenamine mandelate and antispasmodics such as phenazopyridine hydrochloride or a smooth muscle antispasmodic such as flavoxate hydrochloride, hyoscyamine sulfate, oxybutynin chloride, or

tolterodine tartrate can relieve symptoms. Fluid intake should be at least 2,000 to 2,500 mL daily. Urinary tract infections may occur; diagnosis should be established with appropriate urine culture studies, including sensitivity to sulfonamides and antibiotics. Therapy should be promptly instituted.

Erythema and dry or moist desquamation may develop in the perineum or intergluteal fold. Proper skin hygiene and topical application of petroleum jelly, petrolatum, or lanolin should relieve these symptoms. U.S.P. zinc oxide ointment and intensive skin care may be needed for severe cases.

Management of acute radiation vaginitis includes douching every day or at least three times weekly with a 1:5 mixture of hydrogen peroxide and water. Douching should be continued on a weekly basis until the mucositis has resolved or for 2 or 3 months as necessary. Superficial ulceration of the vagina responds to topical (intravaginal) estrogen creams, which stimulate epithelial regeneration within 3 months after irradiation. The use of vaginal dilators several times daily, started during the course of treatment, prevents vaginal stenosis. Psychoeducational intervention and motivation improve the compliance in use of dilators. More severe necrosis may require debridement on a weekly basis until healing takes place. Judicious use of biopsies is recommended to rule out persistent or recurrent cancer.

Petereit et al[430] reported 16 acute events (9.5%) in 169 patients treated with HDR BT (128 with cervical cancer also receiving external irradiation and 41 medically inoperable endometrial carcinomas). The overall 30-day morbidity rate for the patients with cervical cancer was 5.5%, and the 30-day mortality rate was 1.6% (two patients; one died of pulmonary edema 12 days after first HDR insertion, and the other had enteritis and died in a nursing home).

Spontaneous intraperitoneal rupture of the urinary bladder, an extremely rare event, was reported by Fujikawa et al[431] after RT for cervical cancer in 6 of 148 patients treated with HDR intracavitary BT combined with EBRT. All six patients underwent laparotomy and repair of the perforation; however, re-rupture of the bladder occurred in three of these patients.

Hyperbaric Oxygen

Exposure of tissues harmed by radiation to hyperbaric oxygen therapy (HBOT) was shown to decrease symptoms, including in the settings of cystitis, proctitis, and soft tissue necrosis and osteonecrosis, and also reduce complication of surgical debridement.[432] HBOT entails exposure to oxygen at

2 to 2.5 atm in daily sessions of 45 to 120 minutes for 2 to 6 weeks for a total of 10 to 40 sessions. HBOT is thought to promote wound healing by temporary increasing oxygenation of tissues that had their vascular beds damaged as a result of radiation exposure. It is better to use it early when a toxicity occurs but preferably after disease remission is verified, though it is important to note that a comprehensive review of clinical and animal studies found no evidence to support HBOT has cancer growth-promoting effects.[433] The HORTIS study was a multicenter, double-blind, crossover study in 120 patients with chronic radiation proctitis. A subjective symptoms score and clinical response assessment were shown to be significantly improved in the HBOT group after 30 sessions compared to the sham group, and after crossover symptoms were reduced also in the control group, and the differences became nonsignificant.[434]

Hormonal Replacement After Treatment of Cervical Cancer

After pelvic irradiation or bilateral salpingo-oophorectomy, usually carried out with an RH in patients treated for carcinoma of the uterine cervix, symptoms of menopause may occur. They can be treated with replacement hormones, although some gynecologists have expressed reservations. HRT has been shown to reduce the risk of cardiovascular diseases, osteoporotic fractures, and colon carcinoma. In addition, better vaginal health and sexual function are associated with their use.[421] On the other hand, there is a significant increase in the risk in breast cancer with prolonged use of estrogen plus progesterone for greater than 5 years. Consideration may be given to progesterone alone, which does not increase the risk of endometrial cancer but has potential thromboembolic risks.[435]

Patients with SCCs of the cervix, vulva, and vagina are unlikely to be influenced by HRT. In a study of women aged 50 years or below with ovarian cancer, estrogen replacement therapy did not have a negative influence on DFS. Long-term HRT in women treated for a gynecologic cancer must be based on the medical history of and discussion of risk with the individual patient.[436]

Second Malignancy

The risk for induction of secondary primary cancers by pelvic irradiation is low, and many potential confounders either are unknown or may not be fully

accounted for, given the available information. Using the population-based cancer registries of Denmark, Finland, Norway, Sweden, and the United States, Chaturvedi et al[437] found a significantly increased cancer risk in both SCC and AC survivors, with standardized incidence ratio of 1.31 (95% CI = 1.29-1.34) and 1.29 (95% CI = 1.22-1.38), respectively. The risk of smoking-related lung cancer was higher in the SCC than in the AC population, whereas second malignancies of the colon, soft tissue, melanoma, and non-Hodgkin lymphoma were higher in the AC population. Similarly, 1-year survivors of cervical cancer had an increased risk of HPV-related cancers, including pharynx, genital, and anal cancers. Higher HRs for second cancer of the rectum, anus, bladder, and genital sites was seen for younger patients, with a 40-year cumulative risk of any second cancer of 22% for women diagnosed with cervical cancer before age 50 years versus 16% for those diagnosed at age greater than 50 years.

Wu et al[379] performed a SEER database study finding 23,112 patients with cervical cancer, 64% of whom were treated with RT. Second malignancies were diagnosed in 2,545 (11%) patients. After adjusting for age and using propensity score matching, RT was associated with significantly increased risk for cancer of the colon, rectum and anus (HR 1.43), lung and bronchus (HR 1.41), urinary bladder (HR 2.18), ovary (HR 2.79), and corpus uteri (HR 3.71). The risk of breast cancer was significantly decreased (HR 0.67).

In an analysis of 199,268 individuals by Wright et al,[438] the risk of secondary leukemia increased 72% in patients who received pelvic RT, with a peak at 5 to 10 years after treatment; there was no increased risk of multiple myeloma.

Second uterine corpus cancers are more likely to be with more aggressive histology.[439] Mark et al[440] identified 13 of 114 patients diagnosed with uterine sarcoma who had a prior history of pelvic irradiation (doses of 40-80 Gy). Criteria for radiation-induced sarcomas included a prior history of pelvic irradiation, a latent period of several years, development of sarcoma within previously irradiated field, and histologic confirmation of malignancy. Histologic types of tumors were mixed Müllerian in six, leiomyosarcoma in four patients, endometrial stroma sarcoma in one, fibrosarcoma in one, and angiosarcoma in one. Sarcoma developed in the uterus in 12 patients and at the vaginal cuff in one patient. Ten patients were treated with surgery and two with RT. The 5-year DFS rate after salvage therapy was 17%.

In a theoretical analysis of IMRT risk in postoperative cases relative to 3D conformal RT, the estimated increase in second cancer risk was 6% for 6-MV IMRT and 26% for 18-MV IMRT, with large increases in organs away from the primary beam and skin because with IMRT a much larger volume of skin was exposed.[441]

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CHAPTER 77

Endometrial Cancer

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ANATOMY

The uterus is a hollow, muscular organ located in the true pelvis positioned dorsocranially between the bladder and the rectum. The average adult uterus is about 8 cm long, 5 cm wide, and 2.5 cm thick. It is divided into the fundus, body (corpus), and cervix. The junction between the body and the cervix is called the isthmus. The fundus is pierced at each cornu by the fallopian tubes. The uterine surface is partially covered by the peritoneum. The uterine cavity is lined by endometrium, made up of columnar cells forming many tubular glands. The thickness of the endometrium varies during the menstrual cycle, but by the end of menstruation, it should be 2 to 3 mm in thickness. The wall of the uterus is composed of myometrium, consisting of smooth muscle fibers. The major supports of the uterus are the broad, round, uterosacral, and cardinal ligaments. The major blood supply to the uterus is the uterine artery, which enters the uterus at the isthmus after it crosses over the ureter. The lymphatic drainage for the body of the uterus is mainly to the obturator and internal and external iliac lymph nodes. The lymphatics from the fundus accompany the ovarian artery and drain into the para-aortic lymph nodes.

EPIDEMIOLOGY AND RISK FACTORS

Endometrial cancer is the most common gynecologic cancer and the fourth most frequently diagnosed cancer in women in the United States. According to 2024 cancer statistics, the estimated number of newly diagnosed cases is 67,880,[1] with a probability of 1 in every 35 women (2.8%) developing it during her lifetime.[2] Although it is a cancer that affects predominantly postmenopausal women, 14% are diagnosed in premenopausal women, with 5% being younger than 40 years.[3] The expected number of deaths from

endometrial cancer in 2024 is 13,250, making it the fifth leading cause of death from cancer in women.[1] Recent estimates on the death rate from endometrial cancer seemed to indicate that the rate is on the rise, by about 2% per year.[2] In fact, uterine cancer is the only cancer for which survival has decreased over the past four decades in the United States.[1]

The incidence of endometrial cancer is higher in more developed areas of the world (5.5%) compared to less developed countries (4.2%), indicating a possible influence of environmental factors on the incidence of this disease.[4] The exact etiology of endometrial cancer remains unknown, but several risk factors have been associated with it, chiefly unopposed estrogen. It is well established that endometrial cancer risk is increased among women who have high circulating levels of bioavailable estrogens and low levels of progesterone so that the mitogenic effect of estrogens is insufficiently counterbalanced by the opposing effect of progesterone.[5] The source of unopposed estrogen could be endogenous or exogenous. Regarding endogenous estrogen,[6] in a nested case-control study of 93,676 postmenopausal women, parent estrogens (estrone and estradiol) were positively related to endometrial cancer risk, with the highest risk observed for unconjugated estradiol (odds ratio [OR] fifth vs first quintile = 6.19; 95% confidence interval [CI], 2.95-13.03, *P* trend = .0001). The association with unconjugated estradiol was stronger for type I than type II tumors (Phet = 0.01). Lifetime cumulative number of menstrual cycles, that is, menstruation span, is associated with an increased risk of developing endometrial cancer. This is due to the fact that endometrial cell proliferation increases during the follicular phase, which is the longest in the menstrual cycle. Thus, *early age at menarche* (estimated relative risk [RR], 1.5-2) and *late age at menopause* (RR, 2-3), examples of increased menstruation span, are risk factors for endometrial cancer.[7] *Nulliparity* (RR, 3) is also associated with an increased risk of endometrial cancer[7] due, in part, to anovulatory menstrual cycles. *Obesity* is a significant risk factor for endometrial cancer, with an estimation that 38.4% of endometrial cancer worldwide could be attributed to high body mass index (BMI).[8] The increase in endometrial cancer risk is mainly through changes in endogenous hormone metabolism. After menopause, when ovarian production of both estrogen and progesterone ceases, the major source of estrogen is via peripheral conversion, mostly within adipose tissue, of

androgens that continue being produced by the adrenal glands and ovaries. Thus, with obesity, there is an increase in the amount of bioavailable estrogens in the circulation and the endometrial tissue.[5] Obesity may also influence endometrial cancer risk via chronic hyperinsulinemia, which appears to be a key factor for the development of ovarian hyperandrogenism, associated with anovulation and progesterone deficiency, especially for premenopausal women.[9] *Non–insulin-dependent diabetes mellitus* and *hypertension* (RR, 1-3) also increase the risk of endometrial cancer. This is often believed to be secondary to obesity, but there are data showing that these risk factors could be independent of obesity.[10] With regard to exogenous estrogen, it is well established that the use of *estrogen-only hormone replacement therapy* and *sequential oral contraceptives* greatly increases endometrial cancer risk, whereas combined preparations, that is, those that contain a progestogen as well as estrogen throughout the treatment period, have a protective effect (RR, 0.3-0.5).[11,12] The use of *tamoxifen* in patients with breast cancer has been associated with an increased risk of endometrial cancer. The mechanism of action of tamoxifen is in competition with that of endogenous estrogen for estrogen receptors. In premenopausal women, tamoxifen has an antiestrogenic effect, but in postmenopausal women, it has a weak estrogenic effect because of the upregulation of estrogen receptors. In a meta-analysis on adjuvant tamoxifen and endometrial cancer, for patients who were younger than 55 years of age, there was little absolute risk compared to patients aged 55 to 69 years, for whom the 15-year incidence was 3.8% in the tamoxifen group versus 1.1% in the control group (absolute increase 2.6% [standard error 0.6], 95% CI = 1.4-3.8), highlighting the influence of age and the length of its use on the risk of endometrial cancer from tamoxifen use.[13,14] Initial data seemed to indicate that the majority of endometrial cancers associated with tamoxifen use were of early stage with favorable features.[15] More recent data, however, show a change in the profile of these endometrial cancers, with a rise in the rate of serous, clear cell, carcinosarcoma, and sarcoma types.[16] It appears that most endometrial carcinomas arise as a result of a sequence of somatic DNA mutations, possibly including PTEN, mismatch repair (MMR) genes, and TP53 mutations.[17] A large proportion of cases also may progress through a premalignant phase of intraepithelial endometrial neoplasia, such as hyperplasia with atypia.[18] TP53 mutation appears to be

particularly important in serous endometrial cancer and is a marker of poor prognosis.[19] Approximately 30% of uterine serous carcinomas also overexpress HER2.[20] Inherited genetic predisposition, especially in the setting of hereditary nonpolyposis colorectal cancer (HNPCC), probably accounts for less than 5% of all endometrial cancer cases. Mutations in one of the four MMR genes *hMLH1, hMSH2, hMSH6*, and *hPMS2* have been identified in patients with Lynch syndrome. Lynch syndrome is found in approximately 3% of women with endometrial cancers and in 10% of those with tumors found to have mismatch repair deficiency (MMRd).[21] Although HNPCC is thought of primarily in terms of the risk of developing colorectal cancer, it is important to note that lifetime cumulative risk of endometrial cancer for women with HNPCC is 40% to 60%, which equals or exceeds their risk of colorectal cancer.[22] There seems to be a high rate of lower uterine segment involvement (LUSI) in patients with HNPCC-associated endometrial cancer.[23]

CLINICAL PRESENTATION AND NATURAL HISTORY

The most common presentation for endometrial cancer is postmenopausal vaginal bleeding, which is reported by 80% to 90% of patients. The incidence of endometrial cancer in women presenting with postmenopausal bleeding is only 10% to 15%. This incidence, however, could range from 1% up to 25%, depending on patient age and the presence of other risk factors. In a report of a total of 3,548 women presenting with postmenopausal vaginal bleeding, 201 (6%) had a diagnosis of endometrial carcinoma. The use of a multiple logistic regression model showed that recurrent episodes of bleeding (OR, 3.64), a history of diabetes (OR, 1.48), older age (1.06), and high BMI (OR, 1.07) increased the risk of endometrial malignancy when corrected for other characteristics.[24] Other patterns of presentations include vaginal discharge, abnormal Papanicolaou test, or thickened endometrium on routine transvaginal ultrasound. For patients with advanced disease, they may present with urinary or rectal bleeding, constipation, pain, lower extremity lymphedema, abdominal distension due to ascites, and cough and/or hemoptysis.

The International Federation of Gynecology and Obstetrics (FIGO) annual report[25] showed that the 5-year survival rate for 8,110 patients with

endometrial cancer treated between 1999 and 2001 was 80%. Such an excellent outcome is a reflection of the fact that the majority of patients are diagnosed with early-stage disease. The tumor was limited to the corpus uteri in 71% of cases, involved the cervix in 12%, and extended beyond the uterus, but short of distant spread in 13%. For patients with disease limited to the endometrium or with less than 50% myometrial invasion, the 5-year survival rate was 91%. However, the rate dropped to 66% when the disease extended to adnexa/serosa/positive peritoneal cytology, to 57% with regional lymph node involvement, to 25.5% with bladder or rectal involvement, and to 20% with distant spread. For clinically staged patients, the 5-year survival rate ranged from 67% for early-stage disease down to 15% for advanced disease. Mass screening for endometrial cancer in women at average risk or increased risk due to a history of unopposed estrogen therapy, tamoxifen therapy, late menopause, nulliparity, infertility or failure to ovulate, obesity, diabetes, or hypertension is not recommended. The American Cancer Society (ACS) recommends that women at average and increased risk should be informed about risks and symptoms (in particular, unexpected bleeding and spotting) of endometrial cancer at the onset of menopause and should be strongly encouraged to immediately report these symptoms to their physician. However, screening has been recommended by the ACS for women who carry, or are related to carriers of, the HNPCC mutation, starting at age 35 years, including annual transvaginal ultrasound and endometrial biopsy.[26] Prophylactic hysterectomy and bilateral salpingo-oophorectomy (BSO) once childbearing is completed have been shown to effectively reduce the risk of endometrial cancer in patients with HNPCC and should be strongly considered.[27]

DIAGNOSTIC WORKUP

Endometrial tissue sampling remains the gold standard by which the diagnosis of endometrial cancer is established. This is achieved via biopsy or dilation and curettage (D&C). *Endometrial biopsy*, which can be easily performed in the office with a Pipelle or similar device, is the preferred approach. Its sensitivity in detecting endometrial cancer in postmenopausal women is 99.6% compared to 91% in premenopausal women. Its specificity

is more than 98% for both groups.[28] If the patient is undergoing hysterectomy, routine D&C is not necessary after an office Pipelle sampling has documented malignancy. However, if symptoms persist, the office sampling is inadequate, or the patient is being considered for conservative fertility-sparing approaches, a D&C should be performed. In addition, D&C provides more reliable assessments of final pathologic findings in hysterectomy specimens, mainly with regard to tumor grade.[29] Given that the incidence of endometrial cancer in women with postmenopausal bleeding is only 10% to 15%, it is unclear how feasible it is to perform endometrial sampling on every patient. *Transvaginal ultrasonography* (TVU) may be considered a useful tool to assess patient's vaginal bleeding. Normal endometrium looks thin and homogeneously hyperechoic, but it is thickened and heterogeneous, with hyperplasia, polyps, and cancer[30] as shown in Figure 77.1. The consensus statement from the Society of Radiologists in Ultrasound defines an endometrial thickness of 5 mm or greater as being abnormal.[31] If the thickness of the endometrium is less than 5 mm, the risk of endometrial cancer is minimal; the false-negative rate is about 4%. If the TVU is abnormal but the biopsy is negative/nondiagnostic or the uterine cavity is inaccessible, then *saline infusion sonography* or *hysteroscopy*[32,33] should be considered to help exclude intracavitary lesions, especially polyps that might contain cancer. In addition, these methods are also helpful in premenopausal women, for whom the accuracy of TVU is limited because the endometrial thickness fluctuates, depending on the level of female hormones. The potential downside to saline infusion or hysteroscopy is that there have been reports that the insufflation of the distending medium into the canal has been associated with an increase in positive peritoneal cytology, although the prognostic implications are unclear of such positive cytology "induced" by sampling.[34] Several imaging studies are available to define the extent of disease preoperatively.[35] Good-quality pelvic *computed tomography* (CT) scans obtained with oral and intravenous contrast can demonstrate the extent of the endometrial tumor. The endometrial carcinoma is a hypodense mass relative to the normal myometrium and may be seen as a diffuse, circumscribed vegetative or polypoidal mass within the uterine cavity. CT is helpful in assessing regional and distant metastasis. *Magnetic resonance imaging* (MRI) is considered the most accurate imaging study to assess tumor extension in

endometrial cancer, especially myometrial invasion.[36,37] Dynamic contrast-enhanced and diffusion-weighted MRI are equivalent in detecting deep myometrial invasion.[38] A clear junctional zone or preservation of a sharp delineation between the tumor and the myometrium implies disease limited to the endometrium. Disease characterized by disruption of the junctional zone, increased signal intensity tumor in the inner half of the myometrium with preservation of the outer myometrium, or both correlates with superficial myometrial invasion. If there is extension of the high-signal intensity tumor into the outer myometrium with preservation of a peripheral rim of normal, intact myometrium, then that is considered deep myometrial invasion (Figure 77.2). MRI also helps to delineate tumor extension into the cervix. The normal cervical stroma is hypointense on T2-weighted images and is replaced by intermediate-signal intensity tumor in cases of invasion.[39] The reported sensitivity of MRI in detecting lymph node metastasis is on average 43.5% and the specificity is 95.9%.[37] *Positron emission tomography (PET)/CT* is also being used in endometrial cancer.[40] There seems to be little benefit in assessing the primary tumor extension. With regard to regional lymph node metastasis, the reported sensitivity is 72% and the specificity is 94%. The main advantage of PET-CT over other imaging modalities is its accuracy in detecting distant metastasis.[39] The FIGO staging for endometrial cancer is a surgical staging, and thus, preoperative imaging studies (except chest x-rays) are not part of the staging but are often acquired to assist in treatment planning; especially when nodal or distant metastatic disease is suspected. *Cancer antigen 125* (CA-125) serum levels could be elevated in patients with endometrial cancer. Kim et al[41] in a review of 413 patients found that 23.9% of patients had greater than 35 U/mL serum CA-125 levels. Hsieh et al[42] found that preoperative levels of greater than 40 U/mL correlated significantly with regional lymph node metastasis and suggested that such levels could be used as an indication for full-pelvic and para-aortic lymphadenectomy at the time of surgical staging in the absence of metastatic disease.

A

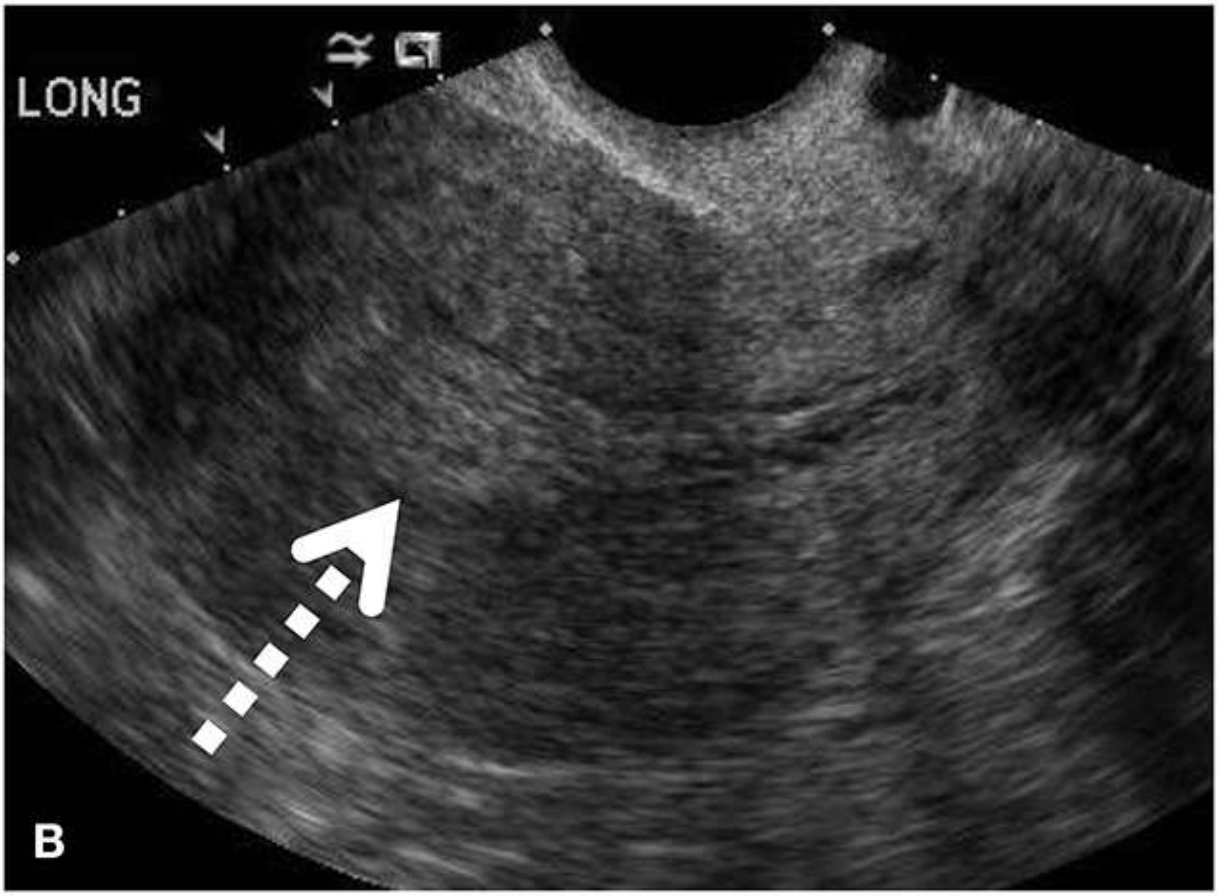


FIGURE 77.1 Sagittal view of the uterus on transvaginal ultrasound. **A.** Normal thin endometrium (arrow). **B.** Thickened endometrium (arrow).

A

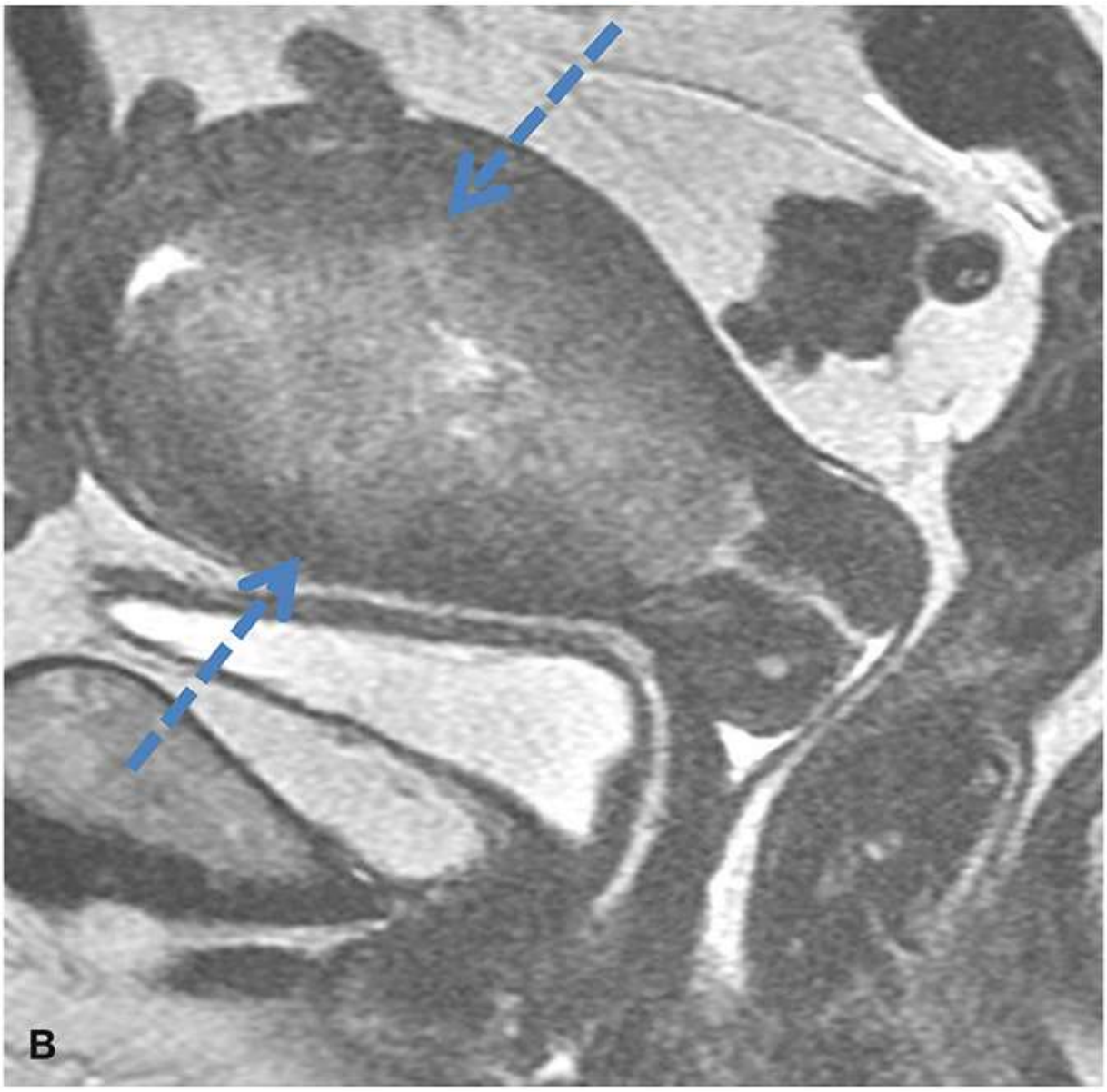


FIGURE 77.2 Sagittal magnetic resonance imaging view of the uterus. **A.** Normal uterus. **B.** Deep myometrial invasion (arrows).

Pathologic Classification

Endometrial Hyperplasia

The diagnostic criterion for hyperplasia is an increase in the number and size of proliferating glands. The International Society of Gynecologic Pathologists standardized the subclassification of endometrial hyperplasia. In simple hyperplasia, there is only glandular proliferation and enlargement with increased stromal cellularity. This rarely progresses to carcinoma

(<1%). Complex hyperplasia is characterized by back-to-back proliferation of glands with intraluminal papillae, epithelial pseudostratification, and few mitotic figures. If there is no cytologic atypia, the risk of malignant degeneration is again quite low, on the order of 3%. Any proliferation demonstrating cytologic abnormalities (in cellular or nuclear morphology) is classified as atypical hyperplasia. Atypical hyperplasia has a much higher risk of progression to an invasive carcinoma—8% for simple atypical hyperplasia, increasing to 29% for complex hyperplasia associated with atypia.[18] The Gynecologic Oncology Group (GOG) conducted a prospective trial in which all patients with atypical hyperplasia of the uterus underwent an immediate hysterectomy. The rate of underlying concurrent carcinoma in the uterus was 42.6% in these patients.[43] The standard recommended treatment for atypical hyperplasia of the uterus is hysterectomy if childbearing is complete and the patient has no other contraindications to surgery. In patients who desire future fertility or have an absolute contraindication to surgery, progestational therapies may be used with caution.[44]

Carcinoma of the Endometrium

Endometrioid Carcinoma

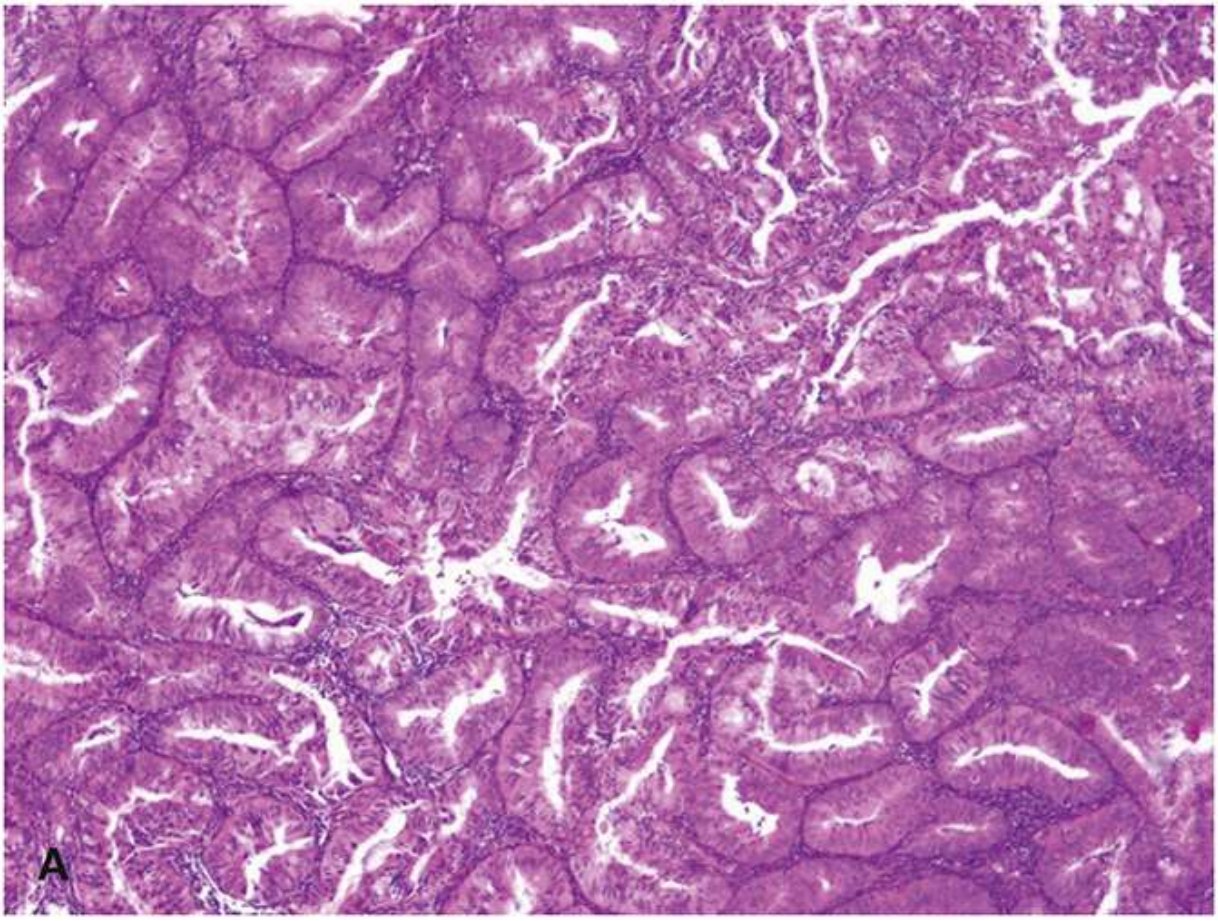
Endometrioid adenocarcinoma is the most common endometrial carcinoma, constituting 75% to 80% of all cases (Table 77.1). The classic histologic appearance is that of marked glandular proliferation with back-to-back proliferation of glands and little intervening stroma (Figure 77.3A). The name endometrioid is derived from resemblance to proliferative-phase endometrium. Architectural grading is determined by the amount of solid mass of tumor cells compared to well-defined glands. Grade 1 is an endometrioid cancer in which less than 5% of the tumor growth is in solid sheets. Grade 2 is an adenocarcinoma in which 6% to 50% of the tumor is composed of solid sheets of cells. Grade 3 occurs when more than 50% of the tumor is made up of solid sheets. Nuclear grading is determined by the nuclear shape, size, chromatin distribution, and size of the nucleoli. The grading is primarily driven by the architectural grading, but if there is marked nuclear atypia in an otherwise grade 2 architectural grading, it should be increased to grade 3. Within endometrioid adenocarcinoma, the

subtypes are endometrioid carcinoma not otherwise specified (NOS), endometrioid carcinoma with squamous differentiation, villoglandular endometrioid carcinoma, secretory carcinoma, and a ciliated cell variant.[45] Most of the endometrioid adenocarcinomas are designated NOS. Foci of squamous differentiation are often found with endometrioid adenocarcinoma. The squamous component could be benign, with the designation of adenoacanthoma, or malignant, in which case it is called adenosquamous carcinoma. Such designations have not been very useful, however, because the degree of differentiation of the squamous component parallels that of the glandular architectural grading. Therefore, most gynecologic pathologists use the term *adenocarcinoma with squamous differentiation*. Other subtypes of endometrioid adenocarcinoma include the relatively common *villoglandular carcinoma*, which grows in a papillary manner. The prognosis of this subtype is similar to that of low-grade endometrioid cancer, and it must not be confused with serous carcinoma because of its papillary features. *Secretory carcinoma*, which represents less than 2% of all endometrial carcinomas, is characterized by a very well-differentiated glandular pattern with much intracellular glycogen, thus resembling early secretory endometrium. Although the cells have clear cytoplasm, their histologic and cytologic features are different from those of clear cell carcinoma. *Ciliated carcinoma* is a very rare subtype, characterized by the presence of ciliated cells comprising more than 75% of the tumor specimen. It is usually associated with a history of prior estrogen use, and the prognosis is quite good, because most are well differentiated.

TABLE 77.1 PATHOLOGIC CLASSIFICATION OF ENDOMETRIAL CANCERS

Endometrioid adenocarcinoma
Not otherwise specified
Villoglandular
Secretory adenocarcinoma
Ciliated carcinoma
Adenocarcinoma with squamous differentiation
Uterine papillary serous
Clear cell carcinoma
Mucinous carcinoma
Squamous cell carcinoma
Transitional cell carcinoma
Mixed cell type

Undifferentiated carcinoma
Metastatic carcinoma to the endometrium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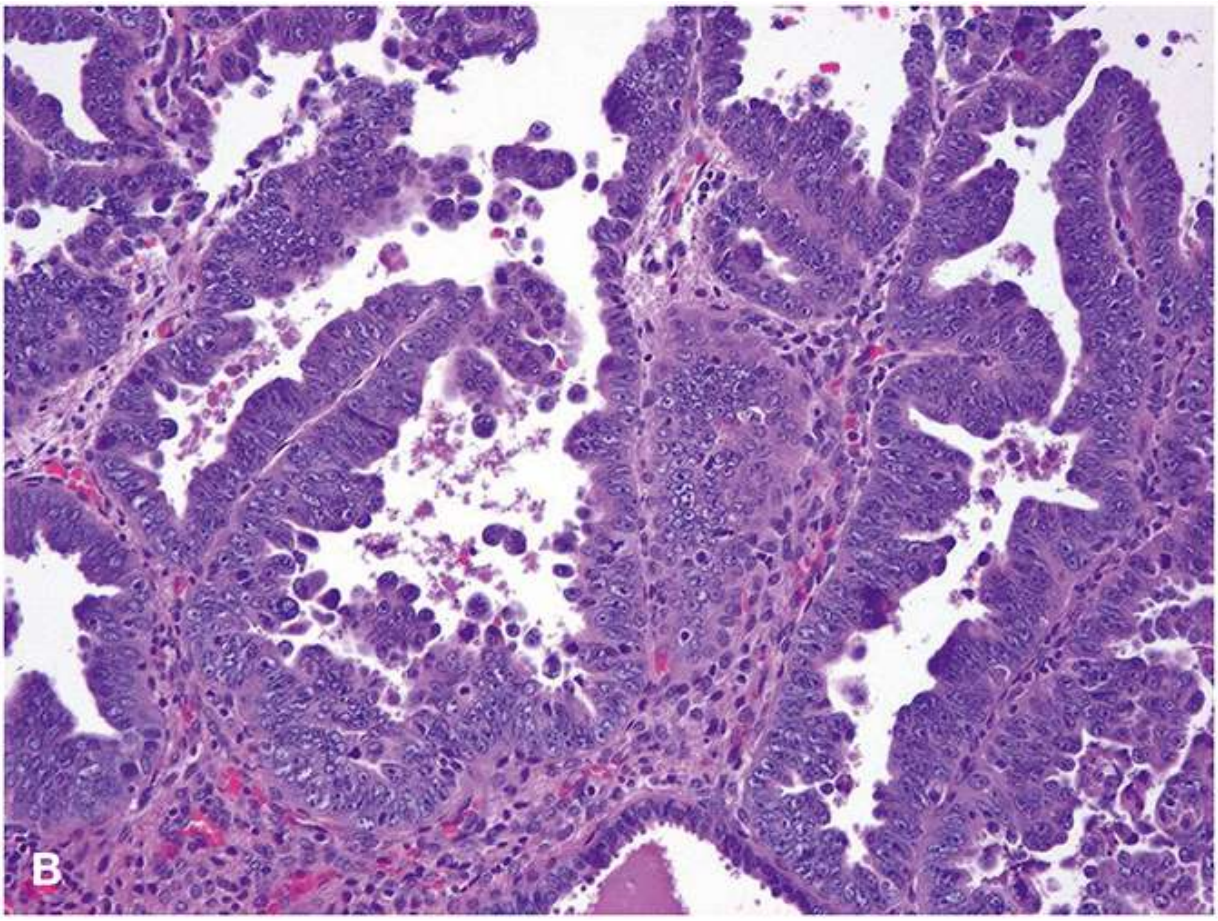
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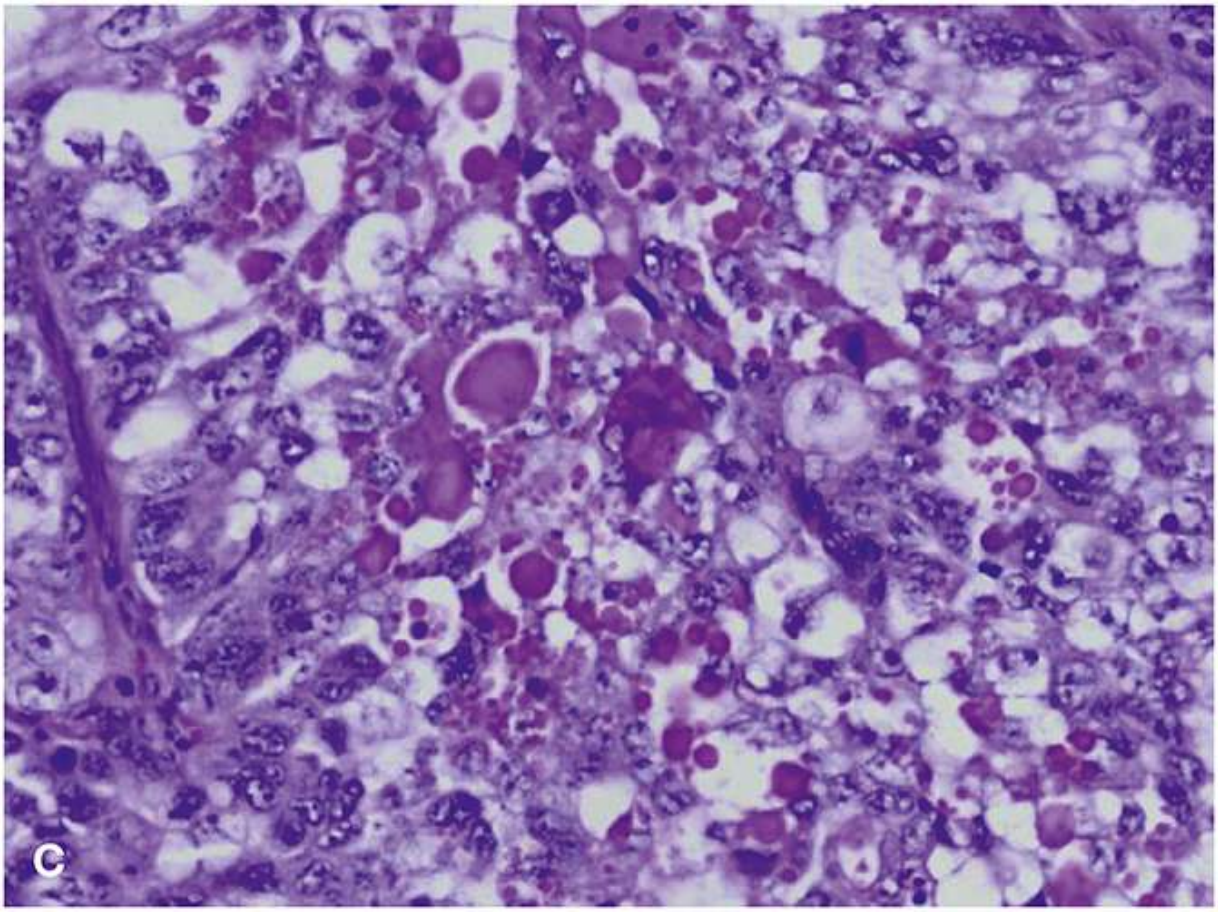
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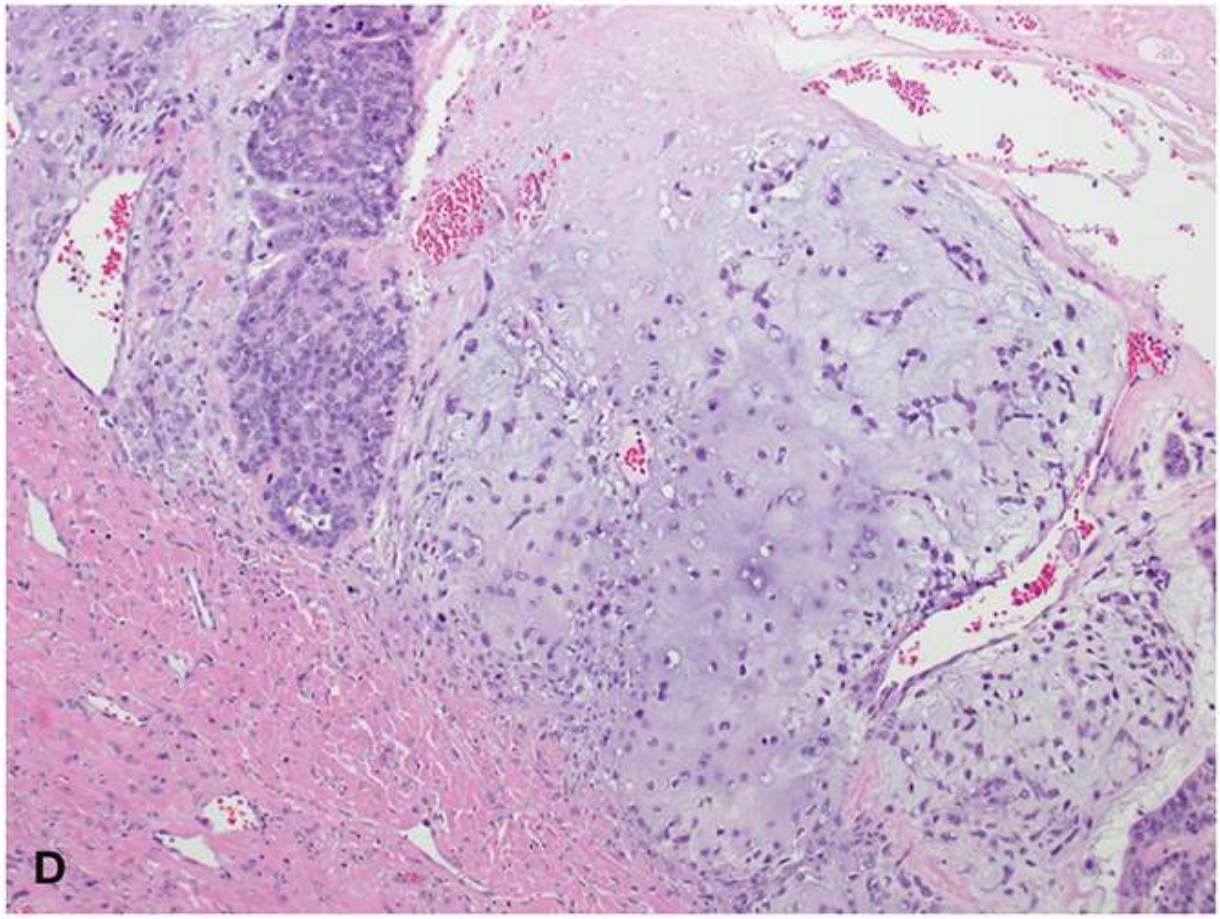


FIGURE 77.3 Different histologic types of endometrial cancer. **A.** Endometrioid. **B.** Papillary serous. **C.** Clear cell. **D.** Carcinosarcoma (heterologous; chondrosarcoma).

Mucinous Carcinoma

This designation requires more than 50% of the tumor cells to be mucinous. These cells are carcinoembryonic antigen positive and are laden with mucin, which stains positively with mucicarmine and periodic acid–Schiff stains but is diastase resistant. Because of the resemblance to endocervical adenocarcinoma, it is essential to exclude it by endocervical curettage. Mucinous carcinomas are usually well differentiated and have the same prognosis as ordinary endometrioid carcinomas.

Serous Carcinoma

Serous carcinomas, also known as papillary serous cancers, resemble ovary cancer in terms of histology and to some extent in terms of behavior. The mere presence of papillary structure is not diagnostic because other

histologic types may have papilla as well. However, the presence of marked cellular atypia in addition to papilla distinguishes serous carcinoma from others (Figure 77.3B). Psammoma bodies are found in up to 33% of cases. The incidence of serous endometrial cancer is about 11.4% that of endometrial carcinomas.[46] This is an aggressive subtype, with a high propensity for early lymphatic and intraperitoneal dissemination, often despite little myometrial penetration. In the FIGO annual report, the 5-year survival rate was 52.6% compared to 83.2% for endometrioid carcinoma.[25]

Clear Cell Carcinoma

Clear cell carcinoma of the endometrium resembles renal carcinoma, but its origin from Müllerian structures is now well established. Unlike vaginal and cervical clear cell carcinoma, it is not related to intrauterine diethylstilbestrol exposure. The microscopic structure may vary from solid patterns to glandular differentiation (Figure 77.3C). In the latter pattern, small cells resembling "hobnail" cells line spaces and glands. These are cells that extruded their cytoplasm, leaving bare nuclei that protrude into the glandular lumens. The rate of clear cell carcinoma is about 3.5% of endometrial carcinomas.[46] The prognosis of this cancer is in between that of endometrioid and serous cancer.[47] In the FIGO annual report, the 5-year survival rate was 62.5% compared to 83.2% for endometrioid carcinoma and 52.6% for serous carcinoma.[25]

Squamous Carcinoma

This type of cancer is extremely rare, and the diagnosis has to be made after the exclusion of cervical origin. The 5-year survival rate based on the FIGO report is 68.9% overall, but the prognosis is poor for patients with extrauterine disease or distant spread.[25]

Undifferentiated Carcinoma

The World Health Organization (WHO) classification system for endometrial cancer describes undifferentiated carcinomas as a rare subtype with distinct histologic features. Undifferentiated carcinomas are characterized by the absence of histologic differentiation into specific cell types, such as glandular or squamous differentiation, seen in other subtypes

of endometrial cancer. These tumors typically exhibit sheets or nests of highly pleomorphic cells with marked nuclear atypia and frequent mitotic activity.[48]

Undifferentiated carcinomas of the endometrium are considered aggressive tumors associated with a poorer prognosis compared to well-differentiated subtypes. They may be further classified based on their immunophenotypic characteristics, such as expression of certain markers like p16, p53, and MMR proteins.[48]

It is important to note that undifferentiated carcinomas are rare among endometrial cancers, comprising a small proportion of cases. Their diagnosis and management require careful histopathologic evaluation and consideration of immunohistochemical markers to distinguish them from other high-grade tumors. Some of these tumors may belong to the spectrum of gynecologic neoplasms seen in the setting of microsatellite instability and possibly Lynch syndrome.[48]

Mixed Histology

Mixed cell–type endometrial cancer composed of two or more pure types was observed in 4.5% of patients in the GOG 210 study.[46] By convention, in order to be designated as mixed, the other cell-type component has to comprise at least 10% of the tumor. Except for mixed endometrioid and serous or clear cell carcinoma, the clinical significance of mixed cell type is questionable.

Simultaneous Tumors

Occasionally identical tumor type, mainly endometrioid histology, can be discovered in the ovary and endometrium. Usually, the site of the largest tumor is assigned the primary origin, but at times, true primary endometrial and ovarian malignancies may coexist.[49] If the endometrial tumor is less than 5 cm in diameter, well differentiated, with no vascular invasion, limited to less than the middle one-third of the myometrium, and the ovarian lesions are bilateral, it is more likely that there are two concomitant primary tumors. Genetic profiling may represent a powerful tool in clinical practice for distinguishing between metastatic and dual primaries in patients

with simultaneous ovarian/endometrial cancer and for predicting disease outcome.[50]

Molecular Biology

Classically, there have been considered to be two distinct types of endometrial cancer.[51,52] In type I endometrial cancer typically considered to include tumors with endometrioid histology and grade 1 or 2, which accounts for approximately 90% of endometrial cancers, there is strong correlation with prior estrogen stimulation. The cancers in this category are often indolent in nature, with minimal myometrial invasion and low-grade histology. They affect premenopausal and perimenopausal women. Type II endometrial cancer, in contrast, is considered to include grade 3 endometrioid carcinoma or other aggressive histologies, such as serous or clear cell. It often affects postmenopausal women with no prior history of estrogen stimulation. These tumors often have deep invasion, and at a more advanced stage at the time of presentation.[3] What is intriguing is the fact that at the molecular level, the existence of two distinct types of endometrial cancer seems to be validated.[53] The most frequently altered molecular pathway in type I endometrial carcinomas is the PI3 K/PTEN/AKT pathway, which is dysregulated by oncogenic mutations, PTEN loss of function, and/or overexpression of upstream tyrosine kinase growth factor receptors, leading to uncontrolled cell proliferation and survival. On the other hand, the main pathway alterations in type II endometrial cancers involve the tumor suppressors p53.

The findings from The Cancer Genome Atlas (TCGA) have revolutionized our understanding of endometrial cancer.[54] In that study, the genomic landscape of endometrioid and serous carcinoma histologies was evaluated (Figure 77.4). Most endometrioid tumors had frequent mutations in PTEN, CTNNB1, PIK3CA, ARID1A, and KRAS; novel mutations in the SWI/SNF chromatin remodeling complex gene *ARID5B*; and few copy number alterations or TP53 mutations. Uterine serous tumors and about 25% of high-grade endometrioid tumors (serous-like) had frequent TP53 mutations and extensive copy number alterations, but few DNA methylation changes, and low estrogen receptor/progesterone receptor levels. A subset of endometrioid tumors (about 10%) that was identified had a markedly

increased mutation frequency and newly identified hot spot mutations in the exonuclease domain of DNA polymerase epsilon (*POLE*). Based on these results, endometrial cancers can be classified into four categories: POLE ultramutated, microsatellite instability hypermutated, copy number low, and copy number high. The somatic copy number alteration (SCNA) analysis showed that most endometrioid tumors have few SCNAs, whereas most serous and serous-like tumors (endometrioid) exhibit extensive SCNAs. In addition, copy number high tumors also highly correlated with TP53 mutations. Genomic analysis of clear cell carcinoma of the uterus demonstrated that, akin to endometrioid carcinomas, there are four gnomically distinct groups: POLE, MMRd tumors, copy number low, and copy number high.[55]

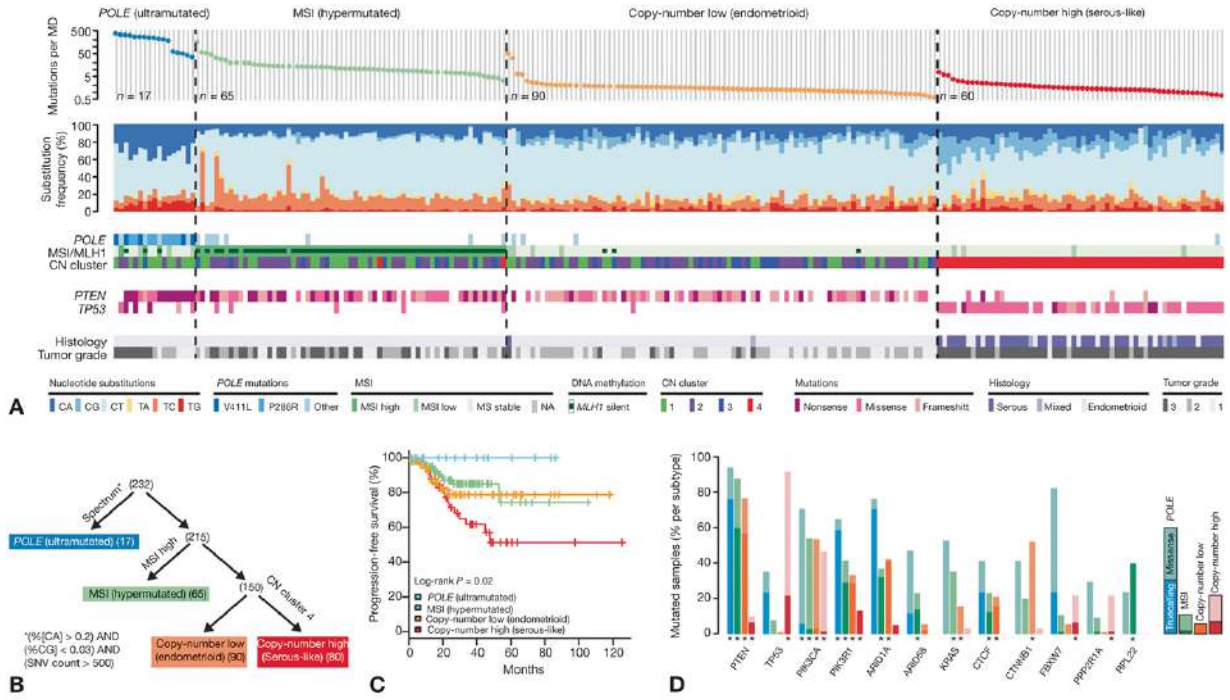


FIGURE 77.4 Genomic landscape of endometrial cancer. a, Mutation frequencies (vertical axis, top panel) plotted for each tumour (horizontal axis). Nucleotide substitutions are shown in the middle panel, with a high frequency of C-to-A transversions in the samples with *POLE* exonuclease mutations. CN, copy number. b, Tumours were stratified into the four groups by (1) nucleotide substitution frequencies and patterns, (2) MSI status, and (3) copy-number cluster. SNV, single nucleotide variant. c, *POLE*-mutant tumours have significantly better progression-free survival, whereas copy-number high tumours have the poorest outcome. d, Recurrently mutated genes are different between the four subgroups. Shown are the mutation frequencies of all genes that were significantly mutated in at least one of the four subgroups (MUSiC, asterisk denotes FDR < 0.05).

A validation study (n = 982) of these molecular subgroups of endometrial cancer was conducted in GOG 210.[56] Forty-nine percent of tumors were classified as copy number stable, 39% MMRD, 8% copy number altered, and 4% POLE mutant. Cancer-specific mortality occurred in 19% of patients with copy number–altered tumors, 7.6% with MMRD tumors, 5% with copy number–stable tumors, and 2.6% with POLE-mutant tumors.

Over time, surrogate markers that are easier to apply on formalin-fixed, paraffin-embedded tissue were developed, allowing identification of subgroups analogous to the ones described in the TCGA analysis[57] (Figure 77.5).

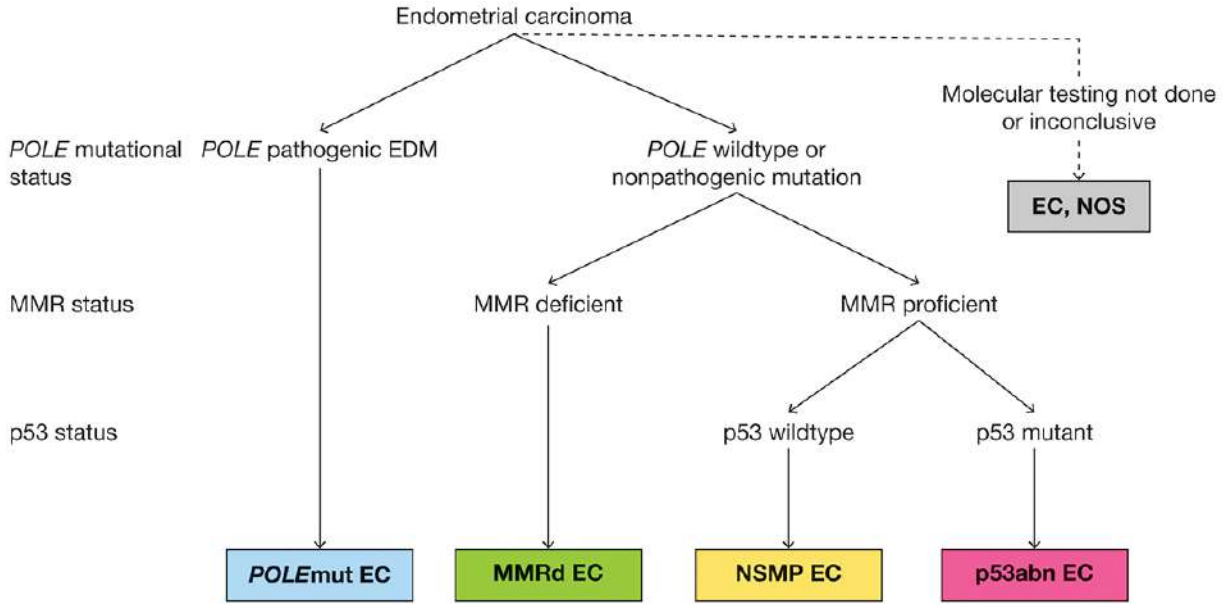


FIGURE 77.5 Diagnostic algorithm for the integrated molecular endometrial carcinoma (EC) classification. EDM, exonuclease domain mutation; MMR, mismatch repair; MMRd, mismatch repair deficient; NOS, not otherwise specified; NSMP, nonspecific molecular profile; p53abn, p53 abnormal. (Adapted from Léon-Castillo A. Update in the molecular classification of endometrial carcinoma. *Int J Gynecol Cancer*. 2023;33[3]:333-342. Copyright © 2023 IGCS and ESGO 2023. With permission.)

Specifically, sequencing may identify *POLE*-ultramutated (*POLE*mut) tumors. Loss of one or more MMR proteins defines MMRD tumors. p53 immunohistochemistry is an acceptable surrogate marker test for TP53 abnormal (p53abn) mutations. Tumors not falling within these categories are classified as having nonspecific molecular profile (NSMP). It is notable

that the p53abn and NSMP categories closely correspond to the copy number high/abnormal and copy number low/stable groups in the previous TCGA analysis.

STAGING

Radiation oncologists should be familiar with several FIGO staging systems due to the need to reference historical systems for interpreting clinical trials and for treatment planning since the newest 2023 system has not yet been fully implemented at many institutions. Although a staging system from the American Joint Committee on Cancer (AJCC) exists for uterine cancer, most clinicians around the world use the FIGO stage.

Before 1988, the staging system for endometrial cancer was clinical. The last clinical staging system was the FIGO 1971 system: Stage I was tumor limited to the uterus, with IA designation if the length was 8 cm or less and IB if it was greater than 8 cm. Stage II was for when the cervix was involved, stage III when disease extension beyond the uterus/cervix was limited to the true pelvis, and stage IV when it extended beyond the true pelvis or involved bladder or rectum (IVA) or distant spread (IVB). This system is applicable today to the few patients who cannot have surgery and are treated with definitive radiation.

In 1988, FIGO switched to a surgical staging system based on pathology findings reported after hysterectomy. Stage I was tumor limited to the uterus, with IA to the endometrium only, IB to 50% or less of the myometrium, and IC to more than 50% of the myometrium. Stage II was for cervix involvement, with IIA limited to endocervical glands, and IIB to include stromal invasion. Stage III was for extension beyond the cervix/uterus, with IIIA involving the serosa, adnexa, or having positive cytology, IIIB for the lower vagina, and IIIC for the pelvic or para-aortic nodes. Stage IV was for distant spread, with IVA for bladder or rectal invasion and IVB for distant metastatic disease.

Using the FIGO 1988 staging system, Creasman et al reported a GOG 210 study on 5,855 patients with endometrial cancer who underwent hysterectomy/BSO and peritoneal cytology.[46] During the initial phase of the study of 3,715 patients, enrollment was unrestricted, but in the later phase, enrollment was restricted to patients (n = 2,151) with adverse features, such

as nonendometrioid histologies, non-Caucasian race, and preoperative imaging suggestive of deep myometrial invasion, and such histologies were as follows: endometrioid (grade 1 was 37.8%, grade 2 was 26.3%, and grade 3 was 9.7%), serous 11.4%, clear cell 3.5%, and mixed 4.5%. The rate of positive peritoneal cytology was 8.9% and that of adnexal involvement was 8.6%. The breakdown by stage (FIGO 1988) was as follows: IA 24.8%, IB 38.4%, IC 11.2%, IIA 2.3%, IIB 4.4%, IIIA 4.6%, IIIB 0.2%, IIIC 9.8%, and IV 4.4% (Table 77.2).

TABLE 77.2 SURGICOPATHOLOGIC FINDINGS FROM GOG-210 STUDY

Characteristics	*n*	%
Age (years)		
<40	92	2.5
40-49	293	7.9
50-59	1,165	31.4
60-69	1,212	32.6
70-79	698	18.8
>80	255	6.9
Race		
Asian	50	1.3
Black/African American	294	7.9
White	3,307	89.0
Other	25	0.7
Unknown	39	1.0
BMI (kg/m^2)		
<18.5	20	0.5
18.5-24.9	609	16.4
25.0-29.9	833	22.4
30.0-34.9	786	21.2
>35	1,449	39.0
Prior cancers	305	8.2
Stage (FIGO 1988)		

Characteristics	*n*	%
IA	922	24.8
IB	1,426	38.4
IC	416	11.2
IIA	85	2.3
IIB	162	4.4
IIIA	169	4.6
IIIB	9	0.2
IIIC	364	9.8
IV	162	4.4
Histology, grade		
Endometrioid, grade 1	1,403	37.8
Endometrioid, grade 2	978	26.3
Endometrioid, grade 3	360	9.7
Serous	423	11.4
Clear cell	129	3.5
Carcinosarcoma	153	4.1
Mixed	168	4.5
Other	101	2.7
Myometrial invasion		
Endometrium only	899	24.2
Inner half	1,823	49.1
Outer half	863	23.2
Serosa	114	3.1
Other characteristics		
Positive peritoneal cytology	330	8.9
Adnexa involvement	318	8.6
Pelvic node metastasis	363	9.8
Aortic node metastasis	188	5.1
Other extrauterine metastasis	396	10.7

Characteristics	*n*	%
Lymphovascular involvement	842	22.7

BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics.
Adapted from Creasman WT, Ali S, Mutch DG, et al. Surgical-pathological findings in type 1 and 2 endometrial cancer: an NRG Oncology/Gynecologic Oncology Group study on GOG-210 protocol. *Gynecol Oncol*. 2017;145(3):519-525. Copyright © 2017 Elsevier. With permission.

In 2009, 2018, and, most recently, in 2023, the FIGO staging system was modified.[58-60] Patients who formerly were staged as IB, that is, less than 50% of myometrial invasion, were now considered IA. Patients with more than 50% of myometrial invasion are designated as stage IB. Endocervical glandular involvement no longer affects staging; only patients with cervical stromal invasion are considered stage II. Having positive peritoneal cytology no longer affects staging. Parametrial extension is now considered IIIB. Patients with stage IIIC are now subdivided into IIIC1 if pelvic nodes are involved and IIIC2 if para-aortic nodes are involved. Notably, until the update of the FIGO system in 2009, uterine sarcomas and carcinomas were staged using the same system. Thereafter, uterine sarcomas are staged using the AJCC sarcoma staging system. Carcinosarcomas remain staged with the carcinomas in the FIGO systems. Thus, stage I was tumor limited to the uterus, with IA to the endometrium only or to 50% or less of the myometrium and IB to more than 50% of the myometrium. Stage II was for cervix stromal invasion. Stage III was for extension beyond the cervix/uterus, with IIIA involving the serosa or adnexa, IIIB for the lower vagina, IIIC1 for pelvic nodes, and IIIC2 for para-aortic nodes. Stage IV was for distant spread, with IVA for bladder or rectal invasion and IVB for distant metastatic disease. Because this system has been used for the past decade, it is still the staging most familiar to currently practicing gynecologic oncologists and radiation oncologists, reported in much of the recent published literature, and is still used for treatment planning in institutions that have not yet transitioned to the FIGO 2023 system.

In addition, in the FIGO 2023 staging, the updates include the various histologic types, tumor patterns, and molecular classification to better reflect the improved understanding of the complex nature of the several types of endometrial carcinoma and their underlying biologic behavior

(Table 77.3). The reader is instructed to reference the table for detailed information. However, for clarity, major changes are described henceforth.

TABLE 77.3 2023 FIGO STAGING OF CANCER OF THE ENDOMETRIUM

Stage	Description
I	Confined to the uterine corpus and ovary[a]
IA	Disease limited to the endometrium OR nonaggressive histologic type, ie, low-grade endometrioid, with invasion of less than half of myometrium with no or focal LVSI OR good prognosis disease
IA1	Nonaggressive histologic type limited to an endometrial polyp OR confined to the endometrium
IA2	Nonaggressive histologic types involving less than half of the myometrium with no or focal LVSI
IA3	Low-grade endometrioid carcinomas limited to the uterus and ovary[a]
IB	Nonaggressive histologic types with invasion of half or more of the myometrium, and with no or focal LVSI[b]
IC	Aggressive histologic types[c] limited to a polyp or confined to the endometrium
II	Invasion of cervical stroma without extrauterine extension OR with substantial LVSI OR aggressive histologic types with myometrial invasion
IIA	Invasion of the cervical stroma of nonaggressive histologic types
IIB	Substantial LVSI[b] of nonaggressive histologic types
IIC	Aggressive histologic types[c] with any myometrial involvement
III	Local and/or regional spread of the tumor of any histologic subtype
IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis
IIIA1	Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)[a]
IIIA2	Involvement of uterine subserosa or spread through the uterine serosa
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum
IIIB1	Metastasis or direct spread to the vagina and/or the parametria
IIIB2	Metastasis to the pelvic peritoneum
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both[d]
IIIC1	Metastasis to the pelvic lymph nodes

Stage	Description
IIIC1i	Micrometastasis
IIIC1ii	Macrometastasis
IIIC2	Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes
IIIC2i	Micrometastasis
IIIC2ii	Macrometastasis
IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa
IVB	Abdominal peritoneal metastasis beyond the pelvis
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone

EEC, endometrioid carcinoma; ESGO, European Society of Gynecological Oncology; ESP, European Society of Pathology; ESTRO, European Society for Therapeutic Radiology and Oncology; FIGO, International Federation of Gynecology and Obstetrics; ITC, isolated tumor cell; LVSI, lymphovascular space involvement; MMRd, mismatch repair deficient; NSMP, nonspecific molecular profile; p53abn, p53 abnormal; SLN, sentinel lymph node; WHO, World Health Organization.

Endometrial cancer is surgically staged and pathologically examined. In all stages, the grade of the lesion, the histologic type, and LVSI must be recorded. If available and feasible, molecular classification testing (POLEmut, MMRd, NSMP, p53abn) is encouraged in all patients with endometrial cancer for prognostic risk group stratification and as factors that might influence adjuvant and systemic treatment decisions.

[a]Low-grade EECs involving both the endometrium and the ovary are considered to have a good prognosis, and no adjuvant treatment is recommended if all the below criteria are met. Disease limited to low-grade endometrioid carcinomas involving the endometrium and ovaries (Stage IA3) must be distinguished from extensive spread of the endometrial carcinoma to the ovary (stage IIIA1), by the following criteria: (1) no more than superficial myometrial invasion is present (<50%); (2) absence of extensive/substantial LVSI; (3) absence of additional metastases; and (4) the ovarian tumor is unilateral, limited to the ovary, without capsule invasion/rupture (equivalent to pT1a).

[b]LVSI as defined in WHO 2021: extensive/substantial, 5 or more vessels involved.

[c]Grade and histologic type:

- Serous adenocarcinomas, clear cell adenocarcinomas, mesonephric-like carcinomas, gastrointestinal- type mucinous endometrial carcinoma, undifferentiated carcinomas, and carcinosarcomas are considered high grade by definition.

• Nonaggressive histologic types are composed of low-grade (grades 1 and 2) EECs. Aggressive histologic types are composed of high-grade EECs (grade 3), serous, clear cell, undifferentiated, mixed, mesonephric-like, gastrointestinal mucinous type carcinomas, and carcinosarcomas.

• It should be noted that high-grade EECs (grade 3) are a prognostically, clinically, and molecularly heterogeneous disease, and the tumor type that benefits most from applying molecular classification for improved prognostication and for treatment decision-making. Without molecular classification, high-grade EECs cannot appropriately be allocated to a risk group and thus molecular profiling is particularly recommended in these patients. For practical purposes and to avoid undertreatment of patients, if the molecular classification is unknown, high-grade EECs were grouped together with the aggressive histologic types in the actual FIGO classification.

[d]Micrometastases are considered to be metastatic involvement (pN1[mi]). The prognostic significance of ITCs is unclear. The presence of ITCs should be documented and is regarded as pN0(i+). According to TNM8, macrometastases are greater than 2 mm in size, micrometastases are 0.2-2 mm and/or greater than 200 cells, and isolated tumor cells are 0.2 mm or larger and 200 or fewer cells. *Based on staging established by FIGO and the American Joint Committee on Cancer (AJCC)*. AJCC Cancer Staging Manual. 8th ed. Springer; 2017.

From Berek JS, Matias-Guiu X, Creutzberg C, et al. FIGO staging of endometrial cancer: 2023. *J Gynecol Oncol*. 2023;34(5):e85. Copyright © 2023 Asian Society of Gynecologic Oncology, Korean Society of Gynecologic Oncology, and Japan Society of Gynecologic Oncology. Reproduced by permission of the *Journal of Gynecologic Oncology*.

For uterine/cervix-confined disease (FIGO 2023 stages I-II), it is now necessary to incorporate lymphovascular space invasion (LVSI) and histiotype with anatomic information. LVSI is subclassified according to the rules of the WHO into the following three categories: “LVSI negative” (0 vessels), “LVSI focal” (<5 vessels), or “LVSI substantial/extensive” (≥5 vessels). As for histology, nonaggressive and aggressive histiotypes are defined: Nonaggressive histologies are defined as endometrioid adenocarcinoma grades 1 to 2, while aggressive histologies are grade 3 endometrioid, clear cell, undifferentiated, mixed, mesonephric-like, gastrointestinal (GI) mucinous type, and carcinosarcomas. Stage I defines tumor confined to the uterine corpus and good prognosis, meaning limited to the endometrium or polyp (IA1), nonaggressive histiotype involving less than 50% of myometrium with no or focal LVSI (IA2), or nonaggressive

histiotype involving 50% or more of the myometrium with no or focal LVSI (IB). A unique substage is created for low-grade endometrioid carcinomas limited to the uterus and ovary (IA3). Stage II disease includes involvement of the cervical stroma (IIA), substantial LVSI (IIB), or aggressive histiotypes with myometrial involvement (IIC).

For locoregional spread of tumor (FIGO 2023 stage III), the stages are subdivided into invasion of the uterine serosa, adnexa (IIIA); spread to the vagina, parametria, or pelvic peritoneum (IIIB); or to pelvic and/or para-aortic lymph nodes (IIIC); with substages for each, which are listed in the table. Of interest for stage IIIA, spread to the ovary or fallopian tube is classified as IIIA1, except for when meeting stage IA3 criteria. In addition, metastasis to the pelvic peritoneum is now classified as stage IIIB2. For stage IIIC disease, the presence of cancer in the lymph nodes is now subclassified in the following method: Macrometastases are greater than 2 mm in size, micrometastases are 0.2 to 2 mm and/or more than 200 cells, and isolated tumor cells (ITCs) are 0.2 mm or less and 200 cells or less. Pelvic (IIIC1) and para-aortic (IIIC2) nodal involvement are subclassified by the presence of micrometastatic (1) or macrometastatic (2) disease. ITCs are not considered positive lymph nodes for FIGO staging but can be designated pN0(i+) if detected. Stage IV has been subclassified into invasion of the bladder or intestinal mucosa (IVA), abdominal peritoneal metastasis (IVB), or distant metastatic disease (IVC).

In the FIGO 2023 staging system, when molecular classification is known, the stage may be modified in certain situations. For stages I to II, POLEmut is considered a good prognostic class and the stage is modified to $IAm_{POLEmut}$, while p53abn is a poor prognostic class and the stage is modified to $IICm_{p53abn}$. MMRd and NSMP are considered intermediate prognostic classes and do not modify the FIGO stage. Molecular classification does not modify FIGO stage III or IV.

A study of three European institutions investigated changes in staging and prognosis in the FIGO 2023 versus 2009 system.[61] Stage shifts occurred in 27% of patients, with 23% increasing in stage or substage. The 5-year progression-free survival (PFS) in the 2023 versus 2009 FIGO systems were 93% versus 87% in stage I, 70% versus 71% in stage II, and 44% versus 54% in stage III.

Prognostic Factors

Several clinicopathologic factors have been identified in patients with endometrial carcinoma to help predict the prognosis and individualize the treatment plan. At Memorial Sloan Kettering Cancer Center (MSKCC), a nomogram was developed for predicting overall survival (OS) of women with endometrial cancer (n = 1,735) after primary therapy.[62] The use of five prognostic factors—age, grade, histologic type, number of lymph nodes removed, and FIGO 1988 surgical stage—predicted OS with high concordance probability. Postoperative Radiation Therapy in Endometrial Cancer (PORTEC) group also developed nomogram for predicting recurrence in FIGO stage I disease.[63]

Age

The influence of older age on worse outcome has been well established. The adverse impact of older age is often explained by pointing out that older patients tend to present with aggressive histology and more advanced disease and are generally treated less aggressively. What is intriguing, however, is that the strongest correlation between older age and poor outcome is seen in patients with otherwise favorable characteristics. Furthermore, the adverse impact of advanced age on outcome persists even when older patients are treated as aggressively as their younger counterparts.[64,65]

Race

The incidence of endometrial cancer is lower in African American than White women, yet the rate of high-risk features in this group is higher. In a GOG study, 24.3% of African Americans presented with stage III as opposed to 17.6% for White and the histology was serous in 24.4% as opposed to 11.2%. The higher recurrence rate could not be accounted for based on treatment received, indicating the need for better understanding of the biology of this disease.[66]

Histologic Subtype

According to the FIGO annual report, the 5-year survival rate was 83.2% for endometrioid adenocarcinoma, compared to 52.6% for serous cancer

and 62.5% for clear cell cancer in 8,033 surgically staged patients. Patients with endometrioid histology have surgical stage III to IV diseases only in 13.8% of patients, compared to 41.7% with serous and 33% with clear cell carcinoma, which could explain the worse outcome. However, the influence of histology was seen even in patients with surgical stage I disease (n = 5,285), for whom 5-year survival dropped from 90% for endometrioid histology to 79.9% with serous and 85.1% with clear cell carcinoma.[25]

Grade

Tumor grade is one of the most sensitive indicators of prognosis. Grade directly affects the depth of myometrial penetration and the frequency of lymph node involvement. In GOG 210 report by Creasman et al,[46] the rate of deep myometrial invasion was 15% for grade 1, 25% for grade 2, and 38% for grade 3. The rate of positive pelvic and para-aortic nodes based on the depth of invasion and histology is shown in Table 77.4. In the FIGO annual report,[25] grade 3 was an independent predictor of poor survival on multivariate analysis within each stage—stages I (hazard ratio [HR], 2.45), II (HR, 2.14), III (HR, 2.44), and IV (HR, 2.55). The recognition that about 25% of grade 3 endometrioid histology has copy number high mutations, that is, serous-like, further highlighting the impact of genomic stratification on prognosis.[54]

TABLE 77.4 RATE OF PELVIC AND PARA-AORTIC METASTASIS BASED ON HISTOLOGY AND DEPTH OF INVASION

	EG1	EG2	EG3	Serous	Clear Cell
Depth of Invasion	**Pel/PA%**	**Pel/PA%**	**Pel/PA%**	**Pel/PA%**	**Pel/PA%**
Endometrium only	0.8/0	1.6/1.1	1.7/0	7.9/4.2	1.3/0
Inner half	2.0/1.3	3.9/1.7	3.9/0.8	18.3/11.3	15.5/6.4
Outer half	15.4/6.9	16.8/8.4	29.1/14.5	44.3/32.4	40.5/28.4
Serosa	42.9/28.6	50/33.3	67.6/43.2	66.7/61.5	70/60

E, endometrioid; G, grade; PA, para-aortic; Pel, pelvic.

Myometrial Invasion

Regardless of grade, only 1.7% of tumors limited to the endometrium had lymph nodal involvement, as compared with 29% pelvic and 14.5% para-aortic involvement with deep penetration.[46] Before the 1988 FIGO staging system, the depth of invasion had been reported as none or inner, middle, or outer one-third of the myometrium. The 1988 FIGO staging system subdivided myometrial invasion into none or inner or outer half. Under that staging system, for patients with less than 50% myometrial invasion, it seems that invasion to less than versus greater than one-third is not a significant predictor of outcome.[67] In the current 2023 FIGO staging system, the depth of invasion for nonaggressive histologic types in stage I is divided into two categories: A (no or <50% myometrial invasion) and B (>50% invasion); aggressive histologic types confined to the endometrium are a third category, C 61.

Lymphovascular Invasion

In the GOG 210 study,[46] the rate of lymphovascular invasion (LVI) was 22.7%. The presence of LVI increased the rate of positive pelvic node from 4.1% to 37.5%, and para-aortic node from 2.3% to 23.8%. LVI is also associated with higher rate of relapse in the vagina[68] and a poorer outcome, especially if it was substantial.[69] The presence of LVI needs to be viewed in the context of other risk factors so that its mere presence does not trigger excessive therapy.[70]

Lower Uterine Segment Involvement

The presence of LUSI is associated with worse outcome. In a study of 481 surgically staged endometrioid endometrial cancers (FIGO stage I-II), LUSI was present in 223 (46.4%) cases and was associated with both decreased disease-free survival (P = .02) and OS (P = .01) in univariate analysis.[71] There seems to be a high rate of LUSI in patients with HNPCC-associated endometrial cancer.[72]

Cervical Involvement

In the 1988 FIGO staging system, cervical involvement was divided into IIA when limited to endocervical glandular involvement and IIB when it involves the cervical stroma. According to the FIGO report, the 5-year

survival for stage IIA was very good (89.9% for grade 1 and 83.7% for grade 2). In contrast, the corresponding figures for stage IIB were 81.2% and 76.9%.[25] This led to a change in the 2009 FIGO staging system, in which only cervical stromal invasion is considered stage II. Although the prognosis of the old stage IIA grades 1 and 2 approximated stage I rather than stage IIB, it is important to note that in the same FIGO annual report, patients with stage IIA grade 3 did not fare as well; their 5-year survival was 68.3%, which was worse than that for IC grade 3 (74.9%) and similar to that for IIB grade 3 (64.9%).

Peritoneal Cytology

In the 2009 FIGO staging, having positive peritoneal cytology is no longer considered stage IIIA. The reason for the change is due to the lack of clear correlation between positive cytology and outcome for early-stage endometrial cancer. However, the true prognostic significance of positive peritoneal cytology on outcome cannot be devoid of the influence of surgical techniques or other prognostic factors. There is some suggestion of a higher rate of positive cytology for patients undergoing laparoscopic hysterectomy, because of manipulation of the uterine cavity. In a randomized trial[73] trying to address this issue, the rate of positive cytology was 7.2% when manipulator was used compared to 1.8% when it was not, but that difference was not statistically significant (P = .147). In the GOG 210 study, positive peritoneal cytology was found in 11.3% of patients undergoing surgical staging. This was associated with 31.8% pelvic lymph node involvement and 22.7% para-aortic node involvement.[46] Histology also impacts the rate of positive cytology: 7.7% for endometrioid histology compared to 20.2% for nonendometrioid histologies.[47] In patients with early-stage disease (low-grade endometrioid histology, minimal invasion), the influence of positive peritoneal cytology on outcome is not evident.[74] In contrast, for patients with stage III disease, having positive cytology affects prognosis significantly and needs to be taken into account.[75]

Adnexal/Serosal Involvement

In the GOG 210 study,[46] the rate of positive adnexal involvement was 8.6%. The rate of positive pelvic node with such involvement is 41% and that for

para-aortic is 31.4%. Jobsen et al[76] reported on 46 patients with isolated adnexal involvement and 21 with isolated serosal involvement. There was no statistically significant difference in outcome between adnexal and serosal involvement. The 5-year disease-free survival was 76.4% versus 59.6% (P = ns), and the disease-specific survival (DSS) was 76.3% and 75.4%, respectively.

Pelvic and Para-Aortic Lymph Node Involvement

The pattern of lymphatic spread in endometrial cancer is different than that in cervical cancer. In endometrial cancer, a simultaneous spread to both pelvic and para-aortic nodes could occur, whereas in cervical cancer, the spread to para-aortic nodes is almost always secondary to pelvic lymph node involvement. Overall, about 12.6% of patients with stage I and occult stage II endometrial cancer have pelvic nodal involvement. This increases to 27.7%, 41%, and 45.7% with deep myometrial invasion, adnexal involvement, and extrauterine spread, respectively.[46] Lymph node involvement is a major predictor of outcome; the 5-year disease-free survival rates drop to 65% to 70% in patients with pelvic lymph node involvement as their only risk factor.[77] In the GOG 210 study, the rate of para-aortic nodal metastases is about 7.2%.[46] The biggest risk factor for para-aortic node involvement is the presence of pelvic nodal metastases. The 5-year disease-free survival rates drop to about 30% in this subpopulation.[77]

Molecular Prognostic Factors

In the TCGA report on endometrial cancer,[54] there was a correlation between prognosis and genomic group (Figure 77.4). In the PORTEC trials, patients with *POLE* mutations had excellent prognosis, with very low risk of recurrence, which could be attributed to its high mutational burden.[78] On the other end of the spectrum, patients with copy number high had the worst prognosis in the TCGA report.[54] The recognition that about 25% of grade 3 endometrioid adenocarcinoma (serous-like) do belong to the copy number high group (mainly serous), further highlighting the prognostic importance of genomic classifications of endometrial cancer.[56] Patients with CTNNB1 (β-catenin) mutations do significantly worse even in patients with early-

stage endometrioid histology.[79] Analysis of GOG 210 showed that in endometrioid adenocarcinoma of the uterus, the presence of MMR defects was associated with higher rate of LVI and higher grade cancers. But interestingly, MMR defects were not associated with significantly worse prognosis.[80] Based on currently available evidence, FIGO has further updated the 2023 staging guidelines to include a molecular classification. When feasible, the addition of molecular subtype evaluation to the staging criteria should be performed as it allows a better prediction of prognosis in a staging/prognosis scheme (Table 77.3).[60] The performance of complete molecular classification (*POLEmut*, MMRd, NSMP, p53abn) is encouraged in all cases of endometrial carcinoma for prognostic risk group stratification and as potential influencing factors for adjuvant or systemic treatment decisions.

SURGICAL MANAGEMENT

Surgery is the main treatment for endometrial cancer. It consists of simple hysterectomy, BSO, and inspection of the pelvic and abdominal cavities, with biopsy of any suspicious extrauterine lesions, accompanied by peritoneal washings. The FIGO staging system did not say that obtaining peritoneal washings is no longer required but only that the finding does not alter the stage. Surgical assessment of lymph nodes ranges from palpation, biopsy of suspicious nodes, to pelvic and para-aortic lymphadenectomy.

Hysterectomy

There are several approaches to simple hysterectomy, also known as extrafascial hysterectomy, but in the main, it consists of removal of the entire uterine corpus and cervix without contiguous parametrial tissue. The pubocervical fascia is entered, and the ureters are not unroofed. *Total abdominal hysterectomy/BSO* (TAH/BSO) is the most prevalent and time-tested form of simple hysterectomy in endometrial cancer. It is an abdominal approach, usually via a vertical midline incision that allows thorough exploration of intra-abdominal and pelvic cavities. The main drawback of TAH/BSO is that it is a laparotomy-based approach, in a group of patients with preexisting comorbidities such as obesity, hypertension, and diabetes. Therefore, it is not surprising that minimally invasive surgery,

whether laparoscopically or robotically, has gained a great deal of acceptance in the surgical management of endometrial cancer. In *laparoscopic vaginal hysterectomy/BSO* (LAVH/BSO), the uterus is removed vaginally rather than abdominally. The benefit of using the laparoscope is to enable the surgeon to have a thorough intra-abdominal exploration and to perform BSO, which is difficult to accomplish with just a vaginal hysterectomy. The GOG completed a trial in which patients with clinical stage I to occult IIA uterine cancer were randomly assigned to laparoscopy (n = 1,696) or open laparotomy (n = 920), including hysterectomy, salpingo-oophorectomy, pelvic cytology, and pelvic and para-aortic lymphadenectomy. The main study end points were 6-week morbidity and mortality, hospital length of stay, conversion from laparoscopy to laparotomy, recurrence-free survival, site of recurrence, and patient-reported quality of life outcomes.[81] Laparoscopy had fewer moderate to severe postoperative adverse events than laparotomy (14% vs 21%; $P <$ .0001). Hospitalization of greater than 2 days was significantly lower in laparoscopy than in laparotomy patients (52% vs 94%; $P <$ .0001). The conversion rate to laparotomy was 25.8%. With a median follow-up time of 59 months for 2,181 patients still alive, there were 309 recurrences (laparoscopy 210, laparotomy 99) and 350 deaths (laparoscopy 229, laparotomy 121). The estimated 5-year recurrence rate was 11.61% in the laparotomy arm and 13.68% for laparoscopy. The estimated 5-year OS rate was 89.8% for laparoscopy and 89.8% for laparotomy. The study demonstrated that surgical treatment of endometrial cancer can be performed laparoscopically with relatively small differences in recurrence rates (estimated difference at 3 years, 1.14%). These results, combined with improved quality of life and decreased complications associated with laparoscopy, are reassuring to patients and allow surgeons to reasonably suggest this method as a means to surgically treat and stage patients with presumed early-stage uterine cancers.[82] In recent years, *robotic-assisted hysterectomy*/BSO has emerged as an alternative minimally invasive surgery in endometrial cancer. It affords many advantages, including three-dimensional (3D) visualization, increased freedom of instrument movement, and enhanced ergonomics and surgeon comfort. The question of difference in cost is under debate debatable.[83] *Radical hysterectomy* is not routinely performed in endometrial cancer because of low incidence of

parametrial involvement. There is no evidence to show that the cure rates are any better with such radical operations. The possible exception to this might be in patients with gross cervical involvement.[84]

Surgical Assessment of Lymph Nodes

The question of which patients need routine surgical lymph nodal staging and, if so, to what extent is a matter of great debate. The uncertainty about lymphadenectomy relates to whether the benefit from it is prognostic rather than therapeutic. Those who advocate for *no lymphadenectomy* and limit nodal assessment to inspection and removal of any enlarged/suspicious pelvic or para-aortic nodes cite the lack of documented survival advantages to lymphadenectomy. Furthermore, patients who have adverse pathologic features that increase the risk of microscopic lymph node metastasis are generally offered adjuvant pelvic radiation. Advocates for *full-pelvic and para-aortic lymph node sampling* on the other end of the spectrum reason that surgical staging is the most accurate method to assess the extent of disease and that the sensitivity and specificity of palpation of lymph nodes are only 72% and 81%, respectively.[85] Lymphadenectomy in endometrial cancer includes removal of the fat pads surrounding the major vessels in the abdomen and pelvis without skeletonizing them. According to the GOG surgical guidelines, pelvic lymph nodes are to be removed from the distal one-half of the common iliac artery down to the circumflex iliac vein, and nodal tissue is to be removed anterior to the obturator nerve and surrounding the iliac arteries and vein. The para-aortic nodes include those overlying the vena cava, between the vena cava and the aorta, and to the left of the aorta. The cephalad boundary of the para-aortic specimen is generally, but not limited to, the inferior mesenteric artery, and the distal boundary is the midpoint of the common iliac artery. For the sampling to be adequate, five lymphatic stations from each side need to be removed—para-aortic, common iliac, internal iliac, external iliac, and obturator—or a total of 10 nodes.[46]

Two trials addressed the role of lymphadenectomy. The first was an Italian study[86] in which 514 eligible patients with preoperative FIGO stage I endometrial carcinoma were randomly assigned to undergo pelvic lymphadenectomy (n = 264) or no lymphadenectomy (n = 250). The

median number of lymph nodes removed was 30 in the pelvic lymphadenectomy arm. Both early and late postoperative complications occurred more frequently in patients who had received pelvic systematic lymphadenectomy (81 patients in the lymphadenectomy arm and 34 patients in the no-lymphadenectomy arm; $P = .001$). Lymphadenectomy improved surgical staging, as statistically significantly more patients with lymph node metastases were found in the lymphadenectomy arm than in the no-lymphadenectomy arm (13.3% vs 3.2%; $P < .001$). At a median follow-up of 49 months, the 5-year disease-free survival and OS rates in an intention-to-treat analysis were similar between arms (81.0% and 85.9% in the lymphadenectomy arm and 81.7% and 90.0% in the no-lymphadenectomy arm). In the second trial (Medical Research Council [MRC]/A Study in the Treatment of Endometrial Cancer [ASTEC]), patients with endometrial cancer believed preoperatively to be confined to the uterine corpus were first randomized to standard surgery consisting of hysterectomy/BSO, pelvic washing, and palpation of para-aortic nodes ($n = 704$) or to lymphadenectomy ($n = 704$). In the lymphadenectomy group, patients underwent standard surgery plus systematic dissection of the iliac and obturator nodes.[87] If the nodes could not be dissected, sampling of suspect nodes was recommended. Whether to dissect the para-aortic nodes was left to the discretion of the surgeon. After a median follow-up of 37 months, 191 women (88 standard surgery group, 103 lymphadenectomy group) had died, with an absolute difference in 5-year OS of 1% (95% CI = 4-6) and an absolute difference in 5-year recurrence-free survival of 6%. The conclusion from both trials was that pelvic lymphadenectomy significantly improved surgical staging, that is, it is a good prognosticator, but it did not improve disease-free survival or OS. *Optional lymphadenectomy* is another approach, in which preoperative tumor grading with intraoperative assessment of depth of myometrial invasion, as well as histologic subtype, is frequently used to decide whether lymph node dissection is necessary at the time of hysterectomy. With such a policy, patients with grade 3 disease or serous or clear cell histology and those with deep myometrial invasion on frozen section will undergo lymphadenectomy. Opponents of this selective lymphadenectomy approach point out that the depth of invasion on frozen section correlated with final pathology in only 67% of cases.[88] With regard to grade, preoperative FIGO

grade 1 diagnosis correlates with final grade diagnosis in only 85% of cases of endometrial cancer.[29]

As a trade-off between lymphadenectomy and no surgical assessment at all in patients with endometrial cancer, there has a growing interest in adopting a *sentinel lymph node (SLN) mapping* approach similar to that in breast cancer (Figure 77.6). In a report from MSKCC, 266 patients with endometrial cancer underwent SLN mapping. At least one sentinel node was identified in 84% of cases. Location of SLN was in the pelvis in 94% of cases, in the pelvis and para-aortic in 5%, and in the para-aortic in 1%. Positive nodes were diagnosed in 12% of patients.[89] In a recent report of a prospective study[90] of 385 patients, 86% had successful mapping of at least one SLN. Positive node rate was 12%, with nodal metastases being identified in the SLNs in 97% of these 36 patients, yielding a sensitivity to detect node- positive disease of 97.2% (95% CI = ·0-100) and a negative predictive value of 99.6% (97.9-100). It is important to note that if a patient did not have bilateral mapping, a side-specific lymphadenectomy needs to be performed on the site that failed to map, because one reason for failed mapping might be due to the presence of nodal metastasis. In addition, any suspicious node on inspection needs to be removed even if it did not map. With such encouraging results, SLN mapping is gaining more acceptance in the staging of endometrioid adenocarcinoma for sure. This approach is gaining acceptance not only in the gynecologic oncology community[91,92] but also in other histologies. In a prospective study of 123 patients with grade 3 endometrioid histology, serous, clear cell, and carcinosarcoma, all underwent sentinel node mapping followed by lymphadenectomy. Overall, sentinel node detection rate was 89%, with an overall sensitivity of 95% and false-negative rate of 5% (1/20). The rate of positive node was 23%, with only one patient having negative sentinel nodes but positive nonsentinel node.[93]

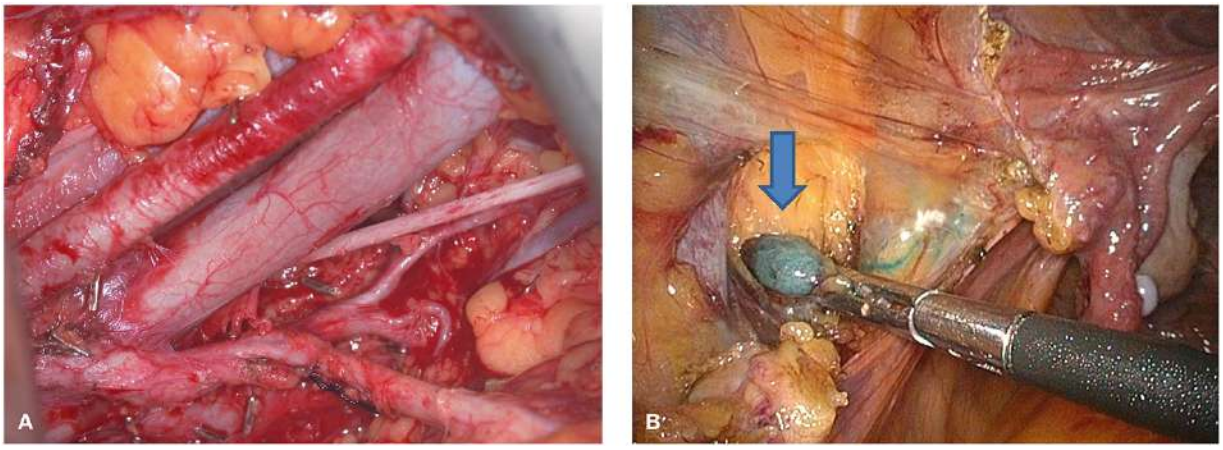


FIGURE 77.6 Comparison of nodal dissection **(A)** to sentinel node biopsy **(B)**. Solid arrow points to the blue dye in the sentinel node.

ROLE OF RADIATION

Radiation therapy (RT) plays a significant role in the management of endometrial cancer. It is often used as an adjuvant treatment after surgery (which is discussed here) or as definitive treatment for patients who are medically inoperable or with local recurrence (which is discussed later). In the past, most patients were treated with preoperative intracavitary brachytherapy (BT) with or without external beam radiotherapy (EBRT), followed by hysterectomy. This approach is not without its merit, especially in patients with gross cervical involvement. However, most patients nowadays undergo surgery first; then, depending on the prognostic features obtained from the pathology review, the need for RT is determined. In recent years, there has been a plethora of data from prospective, randomized trials addressing several aspects of the management of endometrial cancer. However, unlike in cervical cancer, for which the data from the majority of the randomized trials pointed in the same direction, that is, chemoradiation is better than RT alone, the data in endometrial cancer are less conclusive. Therefore, it is important for radiation oncologists to be familiar with the methodology of these studies so that objections to the use of any form of adjuvant RT can be addressed with facts.

Role of Radiotherapy in Stages I and II

Treatment options for patients with early-stage endometrial cancer after hysterectomy include observation, vaginal cuff brachytherapy (VCBT), or pelvic RT. At many institutions, VCBT is the preferred approach for most patients because it provides the best therapeutic ratio. As the discussion demonstrates, observation may have the best morbidity profile, but it does not provide the best therapeutic ratio because of the increased risk of local recurrence. Pelvic RT, on the other hand, although very effective in reducing recurrence, has a higher morbidity profile than VCBT. The results of prospective, randomized trials are discussed first and then treatment recommendations based on risk factors follow.

Results of Radiotherapy Randomized Trials

There are six randomized trials regarding the role of adjuvant RT in early-stage endometrial cancer, mainly pertaining to endometrioid histology and conducted in the "modern" era.

Observation Versus Pelvic Radiotherapy

Three randomized trials compared pelvic RT to observation in early-stage endometrial cancer. The first trial was the PORTEC trial, which randomized 715 patients after TAH and BSO to observation or pelvic RT.[94] Patients included were those with stage (FIGO 1988) IB grades 2 and 3 and those with IC grades 1 and 2. Those with IB grade 1 and those with IC grade 3 were excluded because it was felt that adjuvant RT was not indicated for the former and that most physicians would not omit it for the latter. No lymph node sampling was done, and the dose of pelvic RT was 46 Gy at 2 Gy per fraction. At 5 years, there was a statistically significant difference in the rates of vaginal/pelvic recurrence in favor of adjuvant pelvic RT (14% vs 4%; $P < .001$). OS, however, was not different between the two groups (81% RT vs 85% surgery; $P = .31$), and the complications with pelvic RT were significantly higher (25% vs 6%; $P < .0001$). In addition, many of the patients who relapsed locally after surgery alone were successfully salvaged with subsequent definitive RT. The second randomized trial was GOG 9996. There were 190 patients with stages (FIGO 1988) IB to IIB (grades 1-3), who all underwent TAH/BSO, pelvic washing, and pelvic/para-aortic lymph node sampling and then were randomized to observation versus

pelvic RT to a dose of 50.4 Gy at 1.8 Gy per fraction.[95] At 2 years, there was a statistically significant difference in the rates of relapse in favor of the adjuvant pelvic RT arm (3% vs 12%; $P = .007$). The 2-year estimated incidence of isolated vaginal/pelvic recurrence was 1.6% in the RT group and 7.4% in the surgery-alone group. There was, however, no significant difference in 4-year OS (92% RT vs 86% with surgery alone; $P = .557$), but there were more complications with pelvic RT. The third trial consisted of two trials with separate randomizations consolidated into one intergroup trial. One trial was conducted by the MRC and the other by the National Cancer Institute of Canada (NCIC). Furthermore, the MRC ASTEC trial in itself consisted of two trials with separate randomizations designed to answer a surgical as well as a radiation question.[96] The surgical question was discussed earlier and regarded the need for lymphadenectomy in clinical localized endometrial cancer. The radiation question was whether pelvic RT is needed. Intermediate- or high-risk early-stage patients were then randomized to observation or pelvic RT. Intermediate risk included stage (FIGO 1988) IA grade 3, IB grade 3, IC grades 1 and 2, and IIA grades 1 and 2. High risk included IC grade 3, IIA grade 3, and IA to IIA serous and clear cell tumors. Patients who had positive pelvic nodes (stage IIIC) were allowed, but not those with cervical stromal invasion (IIB). The pelvic RT was given to a total dose of 40 to 46 Gy in 20 to 25 fractions over 4 to 5 weeks. VCBT was permitted regardless of the pelvic RT randomization as long as it was the stated policy for the treating center to do so. The recommended dose was 4 Gy in two fractions prescribed to a depth of 0.5 cm treating the upper one-third of the vagina when using high-dose rate (HDR) and 15 Gy when using low-dose rate. The NCIC had a similar design but with a few exceptions. Patients with stage IIA serous or clear cell carcinoma were excluded, as were those with positive nodes. The dose of pelvic RT was 45 Gy in 25 fractions, and VCBT was permitted in accordance with local practice.

Of the 905 patients (789 MRC and 116 NCIC) in the trial, 453 were randomized to observation and 452 to pelvic RT. The two arms were balanced, except for more high-risk patients (113; 25%) in the observation arm than in the pelvic RT arm (89; 20%). There were 137 (32%) patients in the observation arm in whom nodes were removed, and 5 (4%) had positive nodes. In the pelvic RT arm, 159 (38%) had nodes removed, and 6 (4%)

were positive. In the observation arm, 228 (51%) patients received intravaginal RT (IVRT), 7 (2%) received pelvic and IVRT, 3 (1%) received pelvic RT, and 3 (1%) were unknown. Only 212 (47%) received no form of adjuvant RT. Conversely, in the pelvic RT arm, 24 (5%) did not receive any adjuvant RT, 10 (2%) received VCBT, and 2 (0.4%) were unknown. Combined VCBT and pelvic RT were given to 232 (52%) patients, and only 184 (41%) received pelvic RT alone. The primary end point of this study was OS. With a median follow-up of 58 months, the 5-year OS was 84% in both arms ($P = .77$). The 5-year cumulative incidence for isolated vaginal or pelvic recurrence was 6.1% in the observation group and 3.2% in the pelvic RT group. This difference was statistically significant ($P = .2$) with an HR of 0.46 (95% CI = 0.24-0.89). The rate of any acute toxicity was 27% in the observation arm compared to 57% for pelvic RT. Similarly, late toxicity was more prevalent in the pelvic RT compared to observation (61% vs 45%).

The triad of lack of OS advantage, increased toxicity, and high salvage rate of local recurrence for patients who are observed has led some to conclude that all forms of adjuvant RT, not simply pelvic RT, should be abandoned. The morbidity of pelvic RT and the validity of omitting adjuvant RT in favor of RT for salvage policy are discussed later in the chapter. With regard to OS, it is considered the gold standard for primary end point in many randomized trials in oncology, but for early-stage endometrial cancer, it is perhaps unattainable with adjuvant RT for two reasons. First, many of the patients have other, competing causes of death such as hypertension, diabetes, and obesity. In the PORTEC trial, the 8-year actuarial rates of intercurrent death were 19.7% in the RT arm and 15.6% in the surgery-alone arm.[97] Endometrial cancer–related deaths in comparison were only 9.6% and 7.5%, respectively. Similarly, in the GOG 99 trial,[95] approximately half of the deaths were due to causes other than endometrial cancer or treatment (surgery alone, 19/36; RT, 15/30). This led the authors of GOG 99 to write, “With this number of intercurrent deaths in both arms, even if RT reduces the risk of endometrial cancer-related deaths, the size of this trial is not adequate to reliably detect an overall survival difference.” That is why OS was not the primary end point in GOG[98] but rather the disease-free interval, which was significantly different in favor of adjuvant pelvic RT over surgery alone.[95] Therefore, it is not unreasonable to conclude that neither PORTEC nor GOG 99 was large enough to conclusively show

whether adjuvant pelvic RT affected OS. The second difficult hurdle for adjuvant RT to overcome when discussing OS has to do with its localized nature. In the MRC/NCIC trial, the rate of first vaginal/pelvic recurrence was reduced from 11.4% (n = 37/453) in the observation arm to 2.8% (n = 13/452) with pelvic RT. Adjuvant pelvic RT, however, did not affect distant spread; the rate of first distant spread was 8.1% (n = 37/453) in the observation compared to 9% (n = 41/452) in the pelvic RT arm.[96] One would expect adjuvant RT to make a difference in OS only when systemic therapy has an effect on the rate of distant spread. This is exactly the story learned from postoperative chest wall irradiation in breast cancer. Because pelvic RT significantly improved local control, albeit with increased toxicity, why not replace it with VCBT rather than advocating observation for all early-stage endometrial cancer?

Observation Versus Vaginal Cuff Brachytherapy

In a trial reported by Sorbe et al,[98] 645 patients with stage (FIGO 1988) IA to IB grades 1 and 2 endometrioid adenocarcinoma were randomized after surgery to observation (n = 326) or VCBT (n = 319). Surgery consisted of TAH/BSO (laparoscopic surgery was allowed), pelvic washing, and removal of enlarged nodes. The dose and type of VCBT varied among the six centers participating in this trial, but 347 of 645 patients were treated with HDR to 18 Gy in six fractions. The proximal upper two-thirds of the vagina was treated with the dose prescribed to 0.5 cm from the surface of the cylinder. The rate of vaginal recurrence was 3.1% in the observation arm compared to 1.2% for the VCBT arm (P = .114). The rate of pelvic recurrence was 0.9% in the observation arm and 0.3% in the treatment arm (P = .326). No significance difference was seen between the two arms in terms of OS. There was significantly more grade 1 vaginal toxicity with VCBT (8.8% vs 1.5%; P = .00004). There was no significant difference in GI or genitourinary (GU) toxicity.

Pelvic Radiotherapy Versus Vaginal Cuff Brachytherapy

In the PORTEC-2 trial, 427 patients were randomized to pelvic RT (n = 214) or VCBT (n = 213).[99] Patients enrolled were those with stage (FIGO 1988) IB grade 3 and older than 60 years, IC grades 1 and 2 and older than

60 years old, and IIA grades 1 and 2 of all ages but with less than 50% myometrial invasion. During surgery, patients underwent TAH/BSO, pelvic washing, and removal of suspicious pelvic or para-aortic lymph nodes. Routine lymphadenectomy was not performed. The dose of pelvic RT was 46 Gy given in 23 fractions. VCBT was delivered using a cylinder to treat the upper half of the vagina. The dose was prescribed to 0.5 cm from the surface of the cylinder. Three types of BT were used: HDR to 21 Gy in three fractions, low-dose rate to 30 Gy at 0.5 to 0.7 Gy/hour, and medium-dose rate to 28 Gy at 1 Gy/hour. With a median follow-up of 36 months, the 3-year vaginal recurrence rates were 0.9% in the VCBT arm and 1.9% in the pelvic RT arm (P = .97). The pelvic recurrence was significantly different; the 3-year rate was 3.5% in the VCBT arm compared to 0.6% in the pelvic RT arm (P = .03). The corresponding rates of isolated pelvic recurrence, however, were not significant (0.6% vs 1.2%, P = .54). There was no significant difference in disease-free survival or OS between the two arms. The rate of grades 1 and 2 acute GI toxicity was 53% versus 12% in favor of VCBT (P < .001). This trial showed that VCBT alone is sufficient to control vaginal recurrence even in patients with intermediate- to high-risk features.[99]

In the Swedish trial reported by Sorbe et al,[100] patients with stage (FIGO 1988) I endometrioid adenocarcinoma with at least one of the risk factors grade 3, 50% or more myometrial invasion, or DNA aneuploidy were randomized to adjuvant VCBT (n = 263) or pelvic and VCBT (n = 264). Lymphadenectomy was required. There was no difference in vaginal recurrence, which was 2.7% (7/263) in the VCBT-alone arm compared to 1.9% (5/264) in the combined arm (P = .555). Pelvic recurrence rate, however, was different: 5.3% in the VCBT arm compared to 0.4% in the pelvic plus VCBT arm (P = .0006). There was no significant difference in OS between the two arms (90% vs 89%). The toxicity was significantly higher in the combined arm compared to VCBT alone.

Radiation Treatment Recommendations for Early-Stage Disease Based on Risk Factors

Based on the results of these trials in early-stage endometrial cancer, it is clear that pelvic RT is an excessive treatment for most of those patients.

Therefore, the treatment recommendations should be individualized based on risk factors. When deciding on whether to recommend observation, VCBT, or pelvic RT, the risk of vaginal recurrence and pelvic recurrence should be assessed separately. With respect to vaginal recurrence, the data from randomized trials indicate that adjuvant VCBT alone is sufficient to control potential microscopic disease in the vagina. The PORTEC-2 trial showed that VCBT is as good as pelvic RT in controlling vaginal recurrence (0.9% vs 1.9%; $P = .97$) despite the fact that patients included in this trial were at high risk for vaginal recurrence based on age 60 years or above, deep myometrial invasion, or endocervical gland involvement.[99] The data from the Swedish randomized trial further confirmed that when it comes to vaginal control, VCBT alone is sufficient.[100] The vaginal recurrence was 2.9% in the VCBT arm compared to 1.9% ($P = .555$) in the pelvic plus VCBT arm. How best to reduce pelvic recurrence is more controversial. For patients at low risk of having pelvic lymph node involvement, that is, endometrioid grade 1 or 2 with no or minimal myometrial invasion, neither lymphadenectomy nor pelvic RT is likely to be of significant benefit because of low rate of pelvic node involvement.[46] Those who are at higher risk of having lymph node involvement may need to have their lymph nodes surgically assessed to ensure that they are pathologically negative or receive pelvic RT to control potential microscopic disease. However, the two PORTEC trials, as well as the Swedish trial, showed that the risk of pelvic recurrence was only 2% to 6%, even in the absence of lymphadenectomy.[94,99,100] This low rate of pelvic recurrence, coupled with the lack of survival advantage to lymphadenectomy and pelvic RT, raises the question of whether either approach is needed for the majority of patients with early-stage endometrial cancer. In the eyes of many, having LVI is almost indicative of nodal involvement. Cohn et al[101] correlated LVI and the risk of positive pelvic nodes in 366 surgically staged patients. The rate of LVI was 25%, and the rate of positive pelvic nodes was 13%. Patients with LVI were significantly more likely to have nodal metastasis (35/92 vs 11/274; $P < .001$). However, the influence of LVI on pelvic nodal metastasis was the strongest in patients with deep myometrial invasion and high grade. Data from MSKCC on 126 patients with endometrioid FIGO (1988) stages IB to IIB and LVI also showed that the mere presence of LVI should not be a trigger for giving pelvic RT, especially when patients had

lymphadenectomy. Patients were divided into two groups: those from the old era, when treatment was often pelvic RT, and those from the modern era, when patients were more often treated with lymphadenectomy and VCBT 70. The rate of pelvic relapse for patients with LVI was 7% in the old era compared to 3% ($P = .3$) in the modern era.

No Myometrial Invasion, Grades 1 and 2

The risk of vaginal recurrence is almost negligible. Straughn et al[102] reported no vaginal recurrence in 103 such patients treated with surgery alone. Pelvic lymph nodal positivity was less than 3%. The 5-year PFS rate in this group was on the order of 95% to 98%. It is unlikely that postoperative pelvic or VCBT would add anything to the final outcome, and therefore, radiation is not routinely recommended to this group.

No Myometrial Invasion, Grade 3

In the GOG 210 study, there were only 69 patients out of 5,866 (1.1%) with disease limited to endometrium and had grade endometrioid histology, making it difficult to draw any meaningful conclusion.[46] Straughn et al[102] reported on eight patients with stage IA grade 3 disease treated with surgery alone, with two of patients developing isolated vaginal recurrence. The risk of lymph node metastasis in this group of patients is about (1.7%) in the GOG 210 study.[46] These patients are commonly offered either VCBT alone or observation.

Less Than 50% Myometrial Invasion, Grades 1 and 2

This group of patients constitutes the most common stage subgroup of all endometrial cancers. Straughn et al[102] reported a 3% (9/296) risk of vaginal recurrence when surgery alone was done. In the surgery-alone arm of the PORTEC-1 trial,[94] the 5-year vaginal recurrence rate for patients with less than 50% myometrial invasion grade 2 was 5%. In a randomized trial reported by Sorbe et al,[98] the vaginal recurrence rate was 3.1% for those in the observation arm compared to 1.2% for those in the VCBT arm ($P = .114$). The trial was designed to detect a difference of 1% versus 5% in the vaginal recurrence rate in the two groups. The data were not reported separately based on whether myometrial invasion was present, making it

difficult to determine the true impact of VCBT on the rate of vaginal recurrence in patients with myometrial invasion. Data from MSKCC on 233 patients with less than 50% myometrial invasion grade 1 or 2 showed a vaginal recurrence rate of only 1% using VCBT alone.[103,104] In addition, Sorbe et al[105] reported on 110 patients with IB grade 1 or 2 who were part of a prospective, randomized trial evaluating two different IVRT doses; the rate of vaginal recurrence was 0.9%. The risk of pelvic recurrence was only 1.8%, even though lymphadenectomy was not required. This low rate of pelvic recurrence is similar to those reported by Straughn et al[102] of 0.3% (1/296) and by Horowitz[106] of 0% (0/62) in the setting of lymphadenectomy. This indicates that pelvic RT is of limited use, and therefore, it seems reasonable to suggest that either observation or VCBT is a reasonable option for patients with grade 1 or 2 and less than 50% myometrial invasion.

However, when deciding on whether adjuvant RT is needed, it is important to address two issues. First, older patients tend to have higher rates of relapse. In the study by Straughn et al,[102] 8 of the 10 vaginal/pelvic recurrences were in patients aged 60 years or above. In the randomized trial by Sorbe et al[98] comparing adjuvant IVRT to observation, patients with vaginal recurrences were significantly (P = .018) older (mean age, 68.6 years) than patients without vaginal recurrences (mean, 62.6 years). Second, patients with LVI have a higher chance of vaginal recurrence, as demonstrated by Mariani et al[68] who reported on 508 patients with endometrial cancer limited to the corpus treated with surgery alone. The presence of LVI significantly increased the vaginal relapse rate from 3% to 7% (P = .02). The rate of vaginal relapse would have been even higher if patients without myometrial invasion (152/508) had been excluded because LVI is exceedingly rare in patients without myometrial invasion. At many institutions, patients who are older than 60 years and/or have LVI are recommended to have VCBT.

Less Than 50% Myometrial Invasion, Grade 3

Some advocate observation for patients with less than 50% myometrial invasion grade 3, yet the 5-year vaginal recurrence rate in PORTEC-1 was 14% for such patients treated with surgery alone compared to none for those

treated with pelvic RT.[94] Perhaps a better choice for those patients is VCBT. The incidence of positive pelvic lymph nodes at the time of surgery in this subset of patients is about 3.9%. In the PORTEC-1 trial, none of the 37 patients with grade 3 disease and less than 50% myometrial invasion who were treated with TAH/BSO alone relapsed in the pelvis.[94] At many institutions, VCBT is recommended for this subset of patients, irrespective of whether lymphadenectomy was performed.

Fifty Percent or Greater Myometrial Invasion, Grades 1 and 2

The risk of vaginal recurrence with surgery alone in this group of patients is not minimal. In the PORTEC-1 trial,[94] the 5-year vaginal recurrence for patients with 50% or more of myometrial invasion treated with surgery alone was 10% for those with grade 1 and 13% for grade 2. The corresponding 5-year vaginal recurrence rates for patients treated with pelvic RT were 1% and 2%. With regard to pelvic control, the 5-year pelvic recurrence for patients with more than 50% myometrial invasion treated with surgery alone was 2% for grade 1 and 6% for grade 2. The data from the PORTEC-2 trial[99] and the Swedish trial[100] in which patients with more than 50% myometrial invasion grade 1 or 2 were included indicate that the omission of pelvic RT increased the risk of pelvic recurrence. In PORTEC-2 trial,[99] the 3-year rate was 3.5% in the IVRT arm compared to 0.6% in the pelvic RT arm (P = .03). In the Swedish trial,[100] the pelvic recurrence rate was 5.3% in the VCBT arm compared to 0.4% in the pelvic plus VCBT arm (P = .0006). At many institutions, most of these patients undergo SLN mapping, and if the nodes are pathologically negative, they undergo VCBT. Pelvic RT can also be considered if age 60 years or above, grade 2, and surgical pathology has LVI.

Fifty Percent or Greater Myometrial Invasion and Grade 3

In GOG 210, the risk of finding positive lymph nodes in this group of patients was 29.147. Such patients were not enrolled in the PORTEC trials because it was felt that omitting pelvic RT when lymphadenectomy was not performed could not be justified. In the registry study reported by Creutzberg et al,[107] 99 patients with 50% or more myometrial invasion grade 3 were treated with postoperative pelvic RT. The 5-year rate of

vaginal recurrence was 5%, that of pelvic recurrence was 8%, and that of distant relapse was 31%. Very few investigators would recommend surgery alone for these patients. In fact, an argument could be made that pelvic RT might be needed even after a negative lymphadenectomy, especially for older patients and those with LVI. In the GOG 99 trial, factors associated with an increased recurrence rate (25% at 5 years) were identified using proportional hazards regression modeling of historical data from GOG 3396. These factors were increasing age, moderate to poorly differentiated tumor grade, the presence of LVI, and outer one-third myometrial invasion. From the results of that analysis, a subgroup of patients with high-intermediate risk (HIR) was defined as follows: at least 70 years of age with only one of the other risk factors, at least 50 years of age with any two of the other risk factors, or any age with all three of the other risk factors. Those on the RT arm demonstrated a somewhat lower overall death rate when compared to those on the observation arm (relative hazard [RH] = 0.73, 90% CI = 0.43-1.26) in the HIR subgroup. At many institutions, patients with deep myometrial invasion grade 3 who are HIR per GOG 99 are offered postoperative pelvic RT. If they are not HIR, which is not that common in this subset of patients, they could be considered for VCBT, but only in the setting of adequate surgical lymph node assessment.

Cervical Involvement

Gross cervical involvement increases the risk of parametrial extension as well as spread to pelvic lymph nodes in a way similar to primary cervical cancer. Such patients could undergo radical hysterectomy and pelvic lymph node dissection or preoperative radiation including pelvic radiation and intracavitary BT followed by simple hysterectomy. The FIGO 2009 staging system only recognizes cervical stromal invasion, and not endocervical gland involvement, as being stage II. However, it is important to note that patients with endocervical gland involvement were included in the POTEC-2 trial comparing pelvic RT to IVRT.

There are also emerging data on the role of IVRT alone in highly selected patients with cervical stromal invasion. Elshaikh et al reported on 27 patients treated with IVRT. There were no vaginal recurrence, and only one pelvic recurrence.[108,109] At MSKCC, patients with endocervical glandular

involvement are often treated with IVRT. For patients with cervical stromal invasion grades 1 and 2 and the depth of cervical stromal invasion less than50%, IVRT could be offered if they underwent adequate surgical lymph node assessment. For those with grade 3 or deep cervical stromal invasion, pelvic RT is recommended, irrespective of lymphadenectomy. Table 77.5 shows overall treatment recommendations for early-stage endometrioid adenocarcinoma.

TABLE 77.5 TREATMENT RECOMMENDATIONS FOR STAGE I AND II PATIENTS WITH ENDOMETRIOID ADENOCARCINOMA

FIGO Stage	Histologic Grade	Adjuvant Treatment
IA	G1, G2	Observation preferred or consider VBT if LVSI and/or age ≥60 y
	G3	VBT preferred or consider observation if no myoinvasion or consider EBRT if either age ≥70 y or LVSI
IB	G1	VBT preferred or consider observation if age <60 y and no LVSI
	G2	VBT preferred or consider EBRT if ≥60 y and/or LVSI or consider observation if age <60 y and no LVSI
	G3	RT (VBT and/or EBRT) +/− systemic therapy
II	G1-2	EBRT (preferred) and/or VBT or VBT alone if G1 or G2, <50% MMI, no LVSI, and microscopic cervical invasion
	G3	EBRT +/− VBT +/− systemic therapy

EBRT, external beam radiation therapy; LVSI, lymphovascular space invasion; RT, radiation therapy; VBT, vaginal cuff brachytherapy.

ROLE OF SYSTEMIC THERAPY IN COMBINATION WITH RADIOTHERAPY

Hormonal therapy has been used in the treatment of recurrent/advanced endometrial cancer for many years. Agents used include megestrol acetate (Megace), medroxyprogesterone acetate (Provera), and, to a lesser extent, tamoxifen.[109-111] The response rate ranges from 9% to 33%, with an OS of 6

to 14 months. In GOG 107, doxorubicin was compared to doxorubicin and cisplatin.[112] The response rate was 42% versus 25% (P = .004), and the progression-free interval was 5.7 versus 3.8 months (P = .014) in favor of combination chemotherapy. However, this did not translate into OS advantage (9 vs 9.2 months). In the GOG 177 trial,[113] doxorubicin/cisplatin was compared to doxorubicin/cisplatin/paclitaxel. The three-drug regimen was superior in terms of response rate (57% vs 34%, P < .01), progression-free interval (8.3 vs 5.3 months, P < .01), and survival (15.3 vs 12.3 months, P = .037).

However, limitations of the three-drug paclitaxel-doxorubicin- cisplatin (TAP) regimen included tolerability and cumbersome scheduling. The GOG 209 trial evaluated carboplatin plus paclitaxel as a noninferior alternative to TAP in stage III, stage IV, and recurrent endometrial cancers, who were determined to have poor potential for cure by surgery and/or RT.[114] From 2003 to 2009, 1,381 women were enrolled, of which 41% were stage III and 23% received pelvic RT. In this study, carboplatin/paclitaxel was determined to be noninferior for OS (median, 37 vs 41 months) and PFS (median, 13 vs 14 months). In addition, carboplatin/paclitaxel had a favorable toxicity profile and better quality of life. This study conclusively established carboplatin/paclitaxel as the preferred systemic therapy regimen over the past decade (prior to studies establishing the use of immunotherapy in combination with chemotherapy for advanced-stage disease).

It is important to emphasize that historically, pelvic, whole-abdomen, or volume-directed RT has been commonly recommended in the adjuvant treatment of locally advanced endometrial cancer (stages III, IVA).[115] However, with the widespread use of chemotherapy in the recurrent/advanced setting, its use in the adjuvant setting has also started to increase and challenge the role of adjuvant RT. There are several randomized trials addressing the role of adjuvant chemotherapy in combination with or as an alternative to RT in advanced endometrial cancer.

Chemotherapy Versus Radiotherapy Trials

There are three randomized trials comparing adjuvant chemotherapy to radiation. The Japanese Gynecology Oncology Group (JGOG) trial randomized 385 patients with stages (FIGO 1988) IC to III (25% with stage

III) endometrial cancer to pelvic radiation (193 patients) or to chemotherapy (192 patients).[116] The surgery was hysterectomy with optional lymphadenectomy. The dose of pelvic RT was 45 to 50 Gy using open anteroposterior/posteroanterior (AP/PA) fields. Chemotherapy consisted of cyclophosphamide (333 mg/m^2), cisplatin (50 mg/m^2), and doxorubicin (40 mg/m^2) every 4 weeks for three cycles or more. There was no significant difference in PFS (P = .726) or OS rate (P = .462) between the two groups. A trial from Italy had a similar design, in which 340 patients with stage (FIGO 1988) IC grade 3, stage II grade 3, and stage III (two-thirds of patients) were randomized to radiation consisting of 45 to 50 Gy to the pelvis or pelvis plus para-aortic fields, or to chemotherapy.[117] With a median follow-up of 95.5 months, the 5-year disease-free survival rate was 63% in both arms (P = .44) and the 5-year OS rate was 69% in the radiation arm and 66% in the chemotherapy arm (P = .77). Again, there was no significant difference in outcome despite using five cycles of Cytoxan, cisplatin, and doxorubicin. It is important to emphasize that these first two trials used pelvic or pelvic plus para-aortic RT depending on the extent of nodal involvement rather than whole-abdomen radiation.

In GOG 122, 396 patients with stages (FIGO 1988) III to IV disease were randomized to whole-abdomen radiation (n = 202) versus doxorubicin/cisplatin (n = 194) for eight cycles. PFS was the primary end point of this study. With a median follow-up of 74 months, there was significant improvement in both PFS (50% vs 38%; P = .007) and OS rate (55% vs 42%; P = .004), in favor of chemotherapy.[118] However, before concluding that chemotherapy alone is the answer, a closer examination of the data is warranted. The overall absolute rate of relapse was 54% in the radiation arm compared to 50% in the chemotherapy arm, a small difference, if any, and yet the corresponding 5-year PFS rates were 38% and 50% (P = .007). The reason for the discrepancy is that in this study, there was stage imbalance, in which there were more stage IIIA patients in the RT arm (28.2%) than in the chemotherapy arm (18%). Conversely, there were more patients with stage IIIC disease in the chemotherapy arm (51.5%) than in the RT arm (44.6%). Therefore, the 5-year disease-free survival rate for the chemotherapy arm was increased from 42% to 50%, which became significantly different than the RT arm (50% vs 38%, P = .007) rather than 42% versus 38%, which is not likely to be significant. The 5-year OS rate in

the chemotherapy arm was 55% compared to 42% for the RT arm (P = .004). What are we to make of the significant difference in OS? There were 15 deaths unrelated to endometrial cancer or protocol treatment in the radiation arm compared to only six in the chemotherapy arm, raising a question about whether the two arms of the study were truly balanced, especially because no stratification was performed in that trial.[118] The results of GOG 122 have led to the adoption of adjuvant chemotherapy as the preferred treatment for stage III endometrial cancer. It is important to note, however, that GOG 122, JGOG, and the Italian study all showed no significant difference in the patterns of relapse between RT and chemotherapy. If one were to use the unadjusted PFS from GOG 122, then all three randomized trials failed to show that adjuvant chemotherapy is superior to adjuvant RT.

Chemoradiation Versus Radiotherapy Trials

There are four randomized trials comparing adjuvant chemoradiation to radiation (Table 77.6). In the first trial from Finland,[119] 156 patients with stage (FIGO 1988) IA or IB grade 3 (n = 28) or stage IC to IIIA grades 1 to 3 (n = 128) were postoperatively randomized to receive RT (56 Gy) only (n = 72) or RT combined with three cycles of cisplatin (50 mg/m^2), epirubicin (60 mg/m^2), and cyclophosphamide (500 mg/m^2) chemotherapy (n = 84). The disease-specific overall 5-year survival was 84.7% in the RT arm versus 82.1% in the chemoradiation arm (P = .148). The second trial reported by Hogberg et al[120] is two trials (Mario Negri Gynecologic Oncology Group [MaNGO] and Nordic Society of Gynecological Oncology [NSGO]/European Organisation for Research and Treatment of Cancer [EORTC]) combined in one report. In the MaNGO trial, there were 157 patients (two-thirds were stage III); 76 were randomized to postoperative pelvic RT (45 Gy) and 80 to chemotherapy followed by pelvic RT. The chemotherapy consisted of three cycles of doxorubicin (60 mg/m^2) and cisplatin (50 mg/m^2). The 5-year PFS was 61% in the RT group compared to 74% for the chemoradiation group, but that difference was not significant (P = .1). The 5-year OS was also not significant (73% vs 78%; P = .41). In the NSGO/EORTC trial, 383 patients were randomized to RT (n = 191) versus RT and chemotherapy (n = 187). The type of chemotherapy varied,

and only a handful of patients were stage III. The 5-year PFS was better for the chemoradiation arm (79% vs 72% for RT; $P = .04$), but OS was not significantly better (83% vs 76%; $P = .1$).

TABLE 77.6 EFFECT OF CHEMORADIATION COMPARED TO RADIATION ON OUTCOME IN HIGH-RISK ENDOMETRIAL CANCER

	Finland	NSGO	MaNGO	GOG 249	PORTEC-3
PFS	↔	↑	↔	↔	↔ stage I-II ↑ stage III
OS	↔	↔	↔	↔	↔

Gynecologic Oncology Group (GOG) 249 compared chemotherapy plus intravaginal RT to pelvic RT, whereas the Finland trial, Nordic Society of Gynecological Oncology (NSGO), Mario Negri Gynecologic Oncology Group (MaNGO), and PORTEC-3 compared chemotherapy plus pelvic RT to pelvic RT.

↔, chemoradiation equivalent to pelvic RT; ↑, chemoradiation better than pelvic RT; OS, overall survival; PFS, progression-free survival.

The third trial is GOG 249, where 601 patients with stages I to II high- to intermediate-risk endometrioid adenocarcinoma and all stages I to II serous or clear cell carcinoma were randomized to either pelvic RT (45 Gy) or IVRT plus three cycles of carboplatin/paclitaxel. With a median follow-up of 53 months, the 3-year recurrence-free survival was 82% in both arms. The OS rate was 91% in the pelvic RT arm compared to 88% for the chemotherapy and IVRT arm. There was no significant difference in the rate of vaginal relapse or distant metastasis. There was a higher rate of pelvic recurrence in the chemotherapy arm compared to pelvic RT (25 vs 6 patients). Toxicity was also higher in the chemotherapy arm.[118] The fourth trial is PORTEC-3, which included stage III patients as well as high-risk early-stage disease. There were 660 patients who were randomized to either pelvic RT (46.8 Gy) or pelvic RT with concurrent cisplatin (50 mg/m^2) on weeks 1 and 4 followed by four cycles of carboplatin/paclitaxel.[121] With a median follow-up time of 60.2 months, the 5-year OS was 81.8% for chemoradiation arm versus 76.7% for RT arm (HR 0.79, 95% CI = 0.57-1.12, $P = .183$). The corresponding 5-year failure-free survival rates were 75.5% versus 68.9%, with an HR of 0.77 (0.58-1.03, $P = .078$).

Chemoradiation Versus Chemotherapy Trial

In the GOG 258 trial, 736 patients with stage III or IVA endometrial carcinoma according to FIGO 2009 staging criteria of any histologic subtype or had FIGO 2009 surgical stage I or II clear cell or serous endometrial carcinoma and positive peritoneal washings were randomized to six cycles of carboplatin/paclitaxel versus postoperative EBRT with concurrent cisplatin (50 mg/m^2) on weeks 1 and 4 followed by four cycles of carboplatin/paclitaxel.[122,123] Residual gross disease after surgery up to 2 cm was allowed. Pelvic and para-aortic lymph node biopsy or dissection was optional, but surgery to remove lymph nodes was reported in more than 94% of patients, with a median number of 13 pelvic nodes and 3 para-aortic nodes removed. The EBRT regimen was 45 Gy in 25 fractions to the pelvis, with extended fields allowed if there was evidence of para-aortic involvement. Intensity-modulated RT (IMRT) was used in 30% of cases. Vaginal BT boost was allowed for vaginal, cervix, or LUSI, or for LVSI and was administered in 201 patients. With a median follow-up of 47 months, the 5-year recurrence-free survival was about 58% in both arms. The 5-year OS was 73% in the chemotherapy-alone arm compared to 70% in the chemoradiation arm. When comparing the chemoradiation arm to chemotherapy-alone arm, there were some differences in the rates of relapse: vaginal recurrence (3% vs 7%), pelvic/para-aortic (10% vs 19%), and distant (27% vs 21%). The long-term OS outcome for this study (median follow-up of 112 months) was presented in 2023.[124] The stratified HR for death comparing chemoradiation therapy (CRT) versus CT was 1.05 (95% CI: 0.82-1.34, P = .72), demonstrating similar long-term OS. The overall conclusion from GOG 258 is that adjuvant chemotherapy should be routinely recommended in patients with stages III and IVA endometrial cancer. RT clearly decreases the incidence of locoregional recurrence but may not affect OS.

There are several important points to consider in interpreting GOG 258 as a radiation oncologist and to advocate for the benefit of RT in a multidisciplinary environment.[125] First, *RT accomplished what it set out to do*, which was to dramatically reduce locoregional recurrence. It has long been known that RT in HIR endometrial cancer improves local control, with similar OS, and an analogous outcome was demonstrated for stage III/IVA

disease in GOG 258. Second, *chemotherapy alone was insufficient to sterilize high-risk nodal basins*. The median number of dissected pelvic nodes was 13 in GOG 258, and with the increasing use of SLN mapping, future patients may have fewer dissected nodes and thus a greater burden of unresected disease, increasing the risk of locoregional recurrence even further. For instance, in the SENTOR study, a prospective study of SLN biopsy followed by lymphadenectomy, only 52% of patients with node-positive disease had metastases in the SLN specimen only, while the other patients had additional disease identified in the lymphadenectomy specimens.[126] Unresected gross disease less than 2 cm was allowed on GOG 258 (but not on PORTEC-3), and 11 of 17 of these patients later developed recurrence. While local recurrence in the vagina or nodes might be curable with salvage RT, the treatment is often more difficult and associated with greater toxicity than adjuvant RT. Third, *the increase in distant recurrence in the CRT arm was not due to RT, but possibly due to insufficient and possibly inadequately sequenced chemotherapy*. The CRT arm had four cycles of carboplatin/paclitaxel after cisplatin-based chemoradiation, while the CT arm had six cycles. The cisplatin used concurrently with radiation is not expected to be as effective as carboplatin/paclitaxel at treating occult distant disease, and therefore patients randomized to CRT may have received less treatment than necessary to reduce distant metastasis. In addition, only 75% of patients in the CRT arm received all four cycles of carboplatin/paclitaxel versus 85% of patients in the CT arm received all six cycles of carboplatin/paclitaxel. Furthermore, carboplatin/paclitaxel was delayed until after the completion of cisplatin radiation in the CRT group and recovery (5 weeks of RT plus up to 8 weeks after the end of RT), which possibly postponed the start of effective systemic therapy. In retrospective data, multiagent CT followed by RT is associated with improved outcomes compared with treatment with RT followed by CT or either treatment alone, further supporting the importance of early chemotherapy.[127] It is interesting to note that when GOG 258 was designed, there was vigorous debate about the combined modality treatment regimen, and some investigators favored a "sandwich regimen" consisting of three cycles of dual-agent chemotherapy followed by RT and then additional chemotherapy.[128] The specific CRT regimen ultimately selected (that used in Radiation Oncology Cooperative Group [RTOG] 9708) was chosen because these data were prospectively

obtained while there were less prospective data supporting sandwich therapy at the time. However, since that era, multiple studies have supported the safety and efficacy of the sandwich approach.[129,130] A randomized trial of sandwich therapy versus cisplatin chemoradiation followed by carboplatin/paclitaxel (identical to GOG 258) unfortunately failed to accrue.[131] The overall proposal from these sequence considerations is that chemotherapy should be started first and that RT may be incorporated later as a sandwich method or possibly after the conclusion of all six cycles of carboplatin/paclitaxel. Fourth, if *RT is recommended, then external radiation is an important component of treatment for locally advanced disease*. It is attractive to consider chemotherapy plus vaginal BT alone due to convenience and low toxicity, and indeed, this is likely superior to omission of RT entirely. However, the recurrence patterns from GOG 258 showed that vaginal recurrences are a minority of all recurrences and also a minority of locoregional recurrences (about one-third) and that nodal recurrence risk is an important consideration. Therefore, if the goal of RT in stage III/IVA disease is to improve local control as much as possible, then this goal would be best accomplished with external radiation, possibly with a vaginal BT boost. This argument also avoids the "cognitive dissonance" that might arise from an overall treatment strategy that involves recommending external radiation and/or vaginal BT for patients with certain early-stage endometrial cancer while omitting RT for patients with stage III/IVA, who have even higher risks of local recurrence.[126] Fifth, *external RT is likely to be better tolerated now than in GOG 258*, in which only 30% of patients received IMRT. IMRT is now a standard treatment option and has been shown in a randomized trial to decrease acute toxicity, especially diarrhea.[132] Bone marrow–sparing IMRT approaches are under active investigation to reduce hematologic toxicity and limit the impact of RT on tolerance of additional cycles of chemotherapy.[133]

After the publication of GOG 258, the radiation oncologist will be faced with the argument in multidisciplinary discussions that the role of RT in the adjuvant treatment of locally advanced endometrial cancer is settled and is now very limited. It is the authors' belief that RT still has an essential role in this setting in decreasing local recurrence, based on the abovementioned arguments, and that it is important for radiation oncologists to engage with gynecologic oncologists to optimize outcomes for patients.

Chemotherapy and Immunotherapy Trials for Advanced Disease

In 2023, two trials established the role of immunotherapy in combination with carboplatin/paclitaxel for advanced or recurrent endometrial cancer. NRG-GY018 enrolled 816 patients and evaluated standard chemotherapy with paclitaxel plus carboplatin plus either pembrolizumab or placebo in patients with advanced or recurrent endometrial cancer. Eligible patients had stage III or IVA with measurable disease or stage IVB or recurrent endometrial cancer with or without measurable disease.[134] The two treatment strategies were analyzed in two independent cohorts—patients with MMRD disease and those with MMR-proficient (MMRp) disease. The published report did not include the patient breakdown by stage. Previous RT was administered in 43% of patients in the MMRD cohort and 40% in the MMRp cohort. In the 12-month analysis, median PFS in the MMRD cohort was 74% in the pembrolizumab group and 38% in the placebo group ($P < .001$). In the MMRp cohort, median PFS was 13.1 months with pembrolizumab and 8.7 months with placebo ($P < .001$).

The RUBY trial enrolled 494 patients with FIGO stage III, IV, or recurrent endometrial cancer that was generally not amenable to curative therapy.[135] The specific eligibility criteria were complex and included stage IIIA, IIIB, or IIIC1 with measurable disease, stage IIIC1 with carcinosarcoma, clear cell, serous, or mixed histologies regardless of the presence of measurable disease, stage IIIC2 or stage IV regardless of the presence of measurable disease, and recurrent disease. Patients were randomized to dostarlimab, a programmed cell death protein 1 inhibitor, or placebo in combination with carboplatin and paclitaxel. In the trial population, 18.6% of the patients had primary stage III, 33.6% had primary stage IV, and 47.8% had recurrent disease. Previous RT was administered in 17% of patients. In the overall population, PFS at 24 months was 36.1% in the dostarlimab group and 18.1% in the placebo group ($P < .001$), while OS at 24 months was 71.3% with the dostarlimab regimen and 56.0% with the placebo regimen ($P = .0021$).

It is important to note that RT was not excluded in NRG-GY018 and RUBY and that most patients in these studies had recurrent, metastatic, or locally advanced stage with measurable disease. The addition of immunotherapy to chemotherapy is now recommended for patients who

meet entry criteria for either study. However, the implications of these studies for patients considered for adjuvant RT with locally advanced disease without measurable residual disease are debatable. It is suggested that RT, by improving local control, may complement immunotherapy, which improves distant recurrence rates and that RT can be safely delivered during immunotherapy maintenance either concurrently or between cycles.[136]

Systemic Therapy Recommendations Based on Risk Factors

When considering the use of adjuvant chemotherapy in endometrial cancer based on risk factors, one needs to pay attention to whether we are dealing with an isolated as opposed to multiple risk factors. This is particularly important when dealing with FIGO 2009 stage III disease.

Early-Stage High-Risk Endometrioid Adenocarcinoma

In the GOG 249 randomized trial[118] limited to high-risk stage I to II disease, 71% of patients had endometrioid histology. In PORTEC-3, patients with stage I (grade 3 with deep myometrial invasion and/or LVI) as well as stage II were included (55%); endometrioid histology was seen in 71% of patients.[121] In both trials, the addition of chemotherapy did not impact outcome of particularly distant metastasis, which was equivalent in GOG 249 and only slightly less in PORTEC-3 (23.1% for chemoradiation vs 29.7% for pelvic RT; $P = .077$). Therefore, routine use of adjuvant chemotherapy in addition to radiation could not be recommended for all high-risk early-stage endometrioid adenocarcinoma.

Early-Stage Serous and Clear Cell Cancer

Serous cancer and, to a lesser extent, clear cell cancer tend to spread in a way similar to ovarian cancer, with a high propensity for upper abdominal relapse. Therefore, it is important to perform comprehensive surgical staging because of the high rate of surgical upstaging. For serous endometrial cancer, the preferred approach is IVRT plus carboplatin/paclitaxel.[104,137,138] In a report from MSKCC on 41 patients with stages I to II (all had negative peritoneal cytology) treated as such, with a median follow-up time of 58 months, the 5-year disease-free survival and

OS rates were 85% and 90%, respectively.[138] The 5-year actuarial recurrence rates were 9% in the pelvis, 5% in the para-aortic nodes, and 10% at distant sites. None of the patients developed vaginal recurrence. In a subsequent report, the presence of deep myometrial invasion and/or cervical stromal invasion was associated with a higher rate of pelvic recurrence.[104] This issue raises the question of whether pelvic RT alone or in combination with chemotherapy should be considered for such a subset of early-stage serous cancers. More mature data from PORTEC-3 and GOG 249 may shed more light on the role of pelvic RT in this histology. At MSKCC, most patients with early-stage serous endometrial cancer disease who are surgically staged are treated with IVRT interdigitated with six cycles of concurrent carboplatin/paclitaxel. Treatment recommendations for clear cell carcinoma often mirror those for serous, but it is debatable if that is always warranted. At MSKCC, patients with early-stage clear cell carcinoma are treated with IVRT, with concurrent carboplatin/paclitaxel being reserved for those with deep invasion or cervical involvement.

Stage IIIA

The results of postoperative EBRT in patients with *isolated* adnexal or serosal involvement are generally good. However, the rate of distant relapse is still 26% to 33%, indicating the need for adjuvant systemic therapy.[76] Furthermore, patients with more than one site of involvement, that is, *multiple risk factors*, do worse. Jobsen et al[139] reported on 141 patients with IIIA endometrioid adenocarcinoma (patients with isolated positive peritoneal cytology were excluded) treated with postoperative RT. The risk of abdominal relapse was 12.4% (11/89) for patients with one site of involvement compared to 36.5% (19/52) for more than one site ($P < .001$). Distant metastasis rate was 23.9% (21/89) compared to 34.6% (18/52). The 5-year DSS was 70.4% for one involved site compared to 43.3% for more than one ($P = .001$). On multivariate analysis, grade 3 (HR, 2.5; $P = .045$) and more than one site involvement (HR, 2.2; $P = .012$) were independent predictors of poor DSS. In the ongoing debate on whether chemotherapy alone is better than chemoradiation in patients with stage III, it is in this group of patients with multiple sites of involvement especially with positive peritoneal cytology and/or aggressive histologies[75,140] in which

chemotherapy plus IVRT might be a better choice than combining with pelvic RT.

Stage IIIC

The outcome of patients with *isolated* lymph node involvement (especially pelvic nodes) treated with postoperative pelvic RT is relatively good.[77] Some institutions recommend external beam radiation with concurrent cisplatin followed by carboplatin/paclitaxel to try to reduce the risk of recurrence even further. Milgrom et al[141] reported on 40 patients with stage III (82% were IIIC) treated with such an approach. With a median follow-up time of 49 months, the 5-year freedom from relapse was 79% and OS was 85%. The rate of vaginal recurrence was 3%, pelvic recurrence 3%, para-aortic 11%, peritoneal 5%, and other distant 11%.

Because stage IIIC is the most common subset in stage III disease (73% of patients in GOG 258), a discussion here about how to reconcile the data from GOG 258 and those from PORTEC-3 (stage III subset 45%) is in order. In PORTEC-3, the 5-year failure-free survival was 58% for RT alone compared to 69% for chemoradiation (P = .032) in stage III patients. The corresponding rates for OS were 70% and 79%.[121] In GOG 258, the 5-year relapse-free survival was about 58% in both arms, and OS was 70% in the chemoradiation arm and 73% in the chemotherapy-alone arm.[122] The question then becomes: Why was the rate of OS and relapse-free survival of the radiation-alone arm in PORTEC-3 for patients with stage III similar to both arms of in GOG 258? The answer might be found in the different inclusion criteria: GOG 258 allowed for patients with less than 2 cm gross residual disease (17 patients with 11/17 developing recurrence), whereas POTEC-3 excluded patients with gross residual disease.

As mentioned earlier in stage IIIA, the presence of *multiple risk factors* in stage IIIC has been shown to be a predictor of poor outcome.[142] In a recent Surveillance, Epidemiology, and End Results review, Garg et al[143] showed that for patients with stage IIIC disease (n = 2,559), the 5-year DSS was 67%, which dropped to 43% when extranodal involvement (ie, positive washing, adnexa/serosal, and vaginal/parametrial involvement) was present (P < .001). At MSKCC, such patients are treated with full systemic

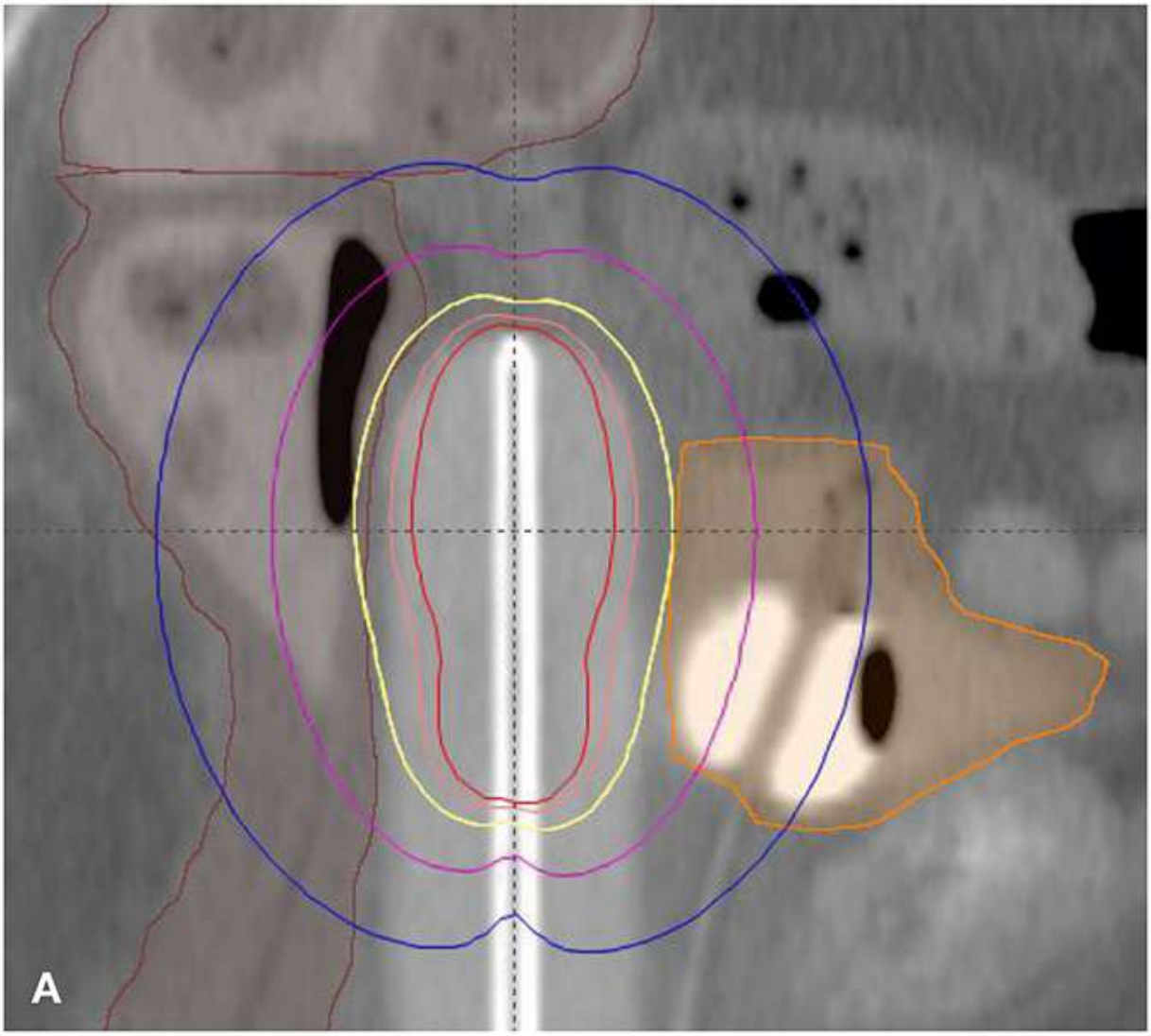
chemotherapy plus IVRT rather than external beam and concurrent chemotherapy.

RADIATION THERAPY TECHNIQUES

Vaginal Cuff Brachytherapy

The purpose of this treatment modality is to deliver the highest dose of radiation to the vaginal mucosa while limiting the dose to the surrounding normal structures, such as the bladder, rectum, sigmoid, and small intestines. HDR BT using ^{192}Ir sources is the preferred method of delivering VCBT. The type of applicator used is generally a cylinder. The treatment is given on an outpatient basis without the need for anesthesia and without the radiation exposure to medical personnel. Patients typically start their treatment 4 to 6 weeks postoperatively, depending on the vaginal cuff healing, and treatment should ideally be delivered no later than 12 weeks after surgery. It should be noted that it takes longer for the vaginal cuff to heal after LAVH/BSO and robotic hysterectomy than after TAH/BSO.[144] HDR BT is often delivered in multiple fractions over a short treatment period. Common fractionation schemes include 6 Gy × 4 fractions (total dose of 24 Gy) delivered twice weekly over 2 weeks, 5 Gy × 5 fractions (total dose of 25 Gy) delivered twice weekly over 2 weeks, and 7 Gy × 3 fractions (total dose of 21 Gy) delivered weekly over 3 weeks.[145] These fractionation schemes are commonly used and have been reported in various clinical studies and treatment guidelines. The American Brachytherapy Society (ABS) has made specific recommendations for applicator selection, insertion techniques, target volume definition, dose fractionation, and specifications for postoperative adjuvant VCBT.[145] The ABS recommends that applicator selection should be based on patient anatomy, target volume geometry, and physician judgment. The dose prescription point should be clearly specified. When VCBT is given with chemotherapy, it is given concurrently, but not during the week when the patient is receiving chemotherapy. When the 7 Gy × 3 fractions (total dose of 21 Gy) fractionation scheme is utilized, the dose is prescribed to a 0.5-cm depth from the mucosal surface (Figure 77.7). The treatment is usually delivered using a 3-cm diameter cylinder to treat a 3.5- to 7-cm length of the vagina, depending on the depth of invasion and tumor grade. For

patients with grade 3, serous, or clear cell carcinoma, the length of vagina treated is generally 7 cm (assuming an average length of vagina after a simple hysterectomy of about 10 cm). This is done to account for the potential submucosal extension that may lead to relapse in the distal periurethral region with these aggressive histologies. For patients with grade 1 or 2 endometrioid adenocarcinoma, the treated vaginal length increases from 3.5 cm if the myometrial invasion is less than 50%, to 5 cm for more than 50% myometrial invasion, and to 6 cm for cervical involvement. If the diameter of the cylinder is less than 3 cm, it is recommended to use a greater than three fractionation scheme (4-6 fractions). This is usually done to avoid a very high dose of radiation to the vaginal mucosa. The dose per fraction is also lowered to 4 to 5 Gy when pelvic radiation is added.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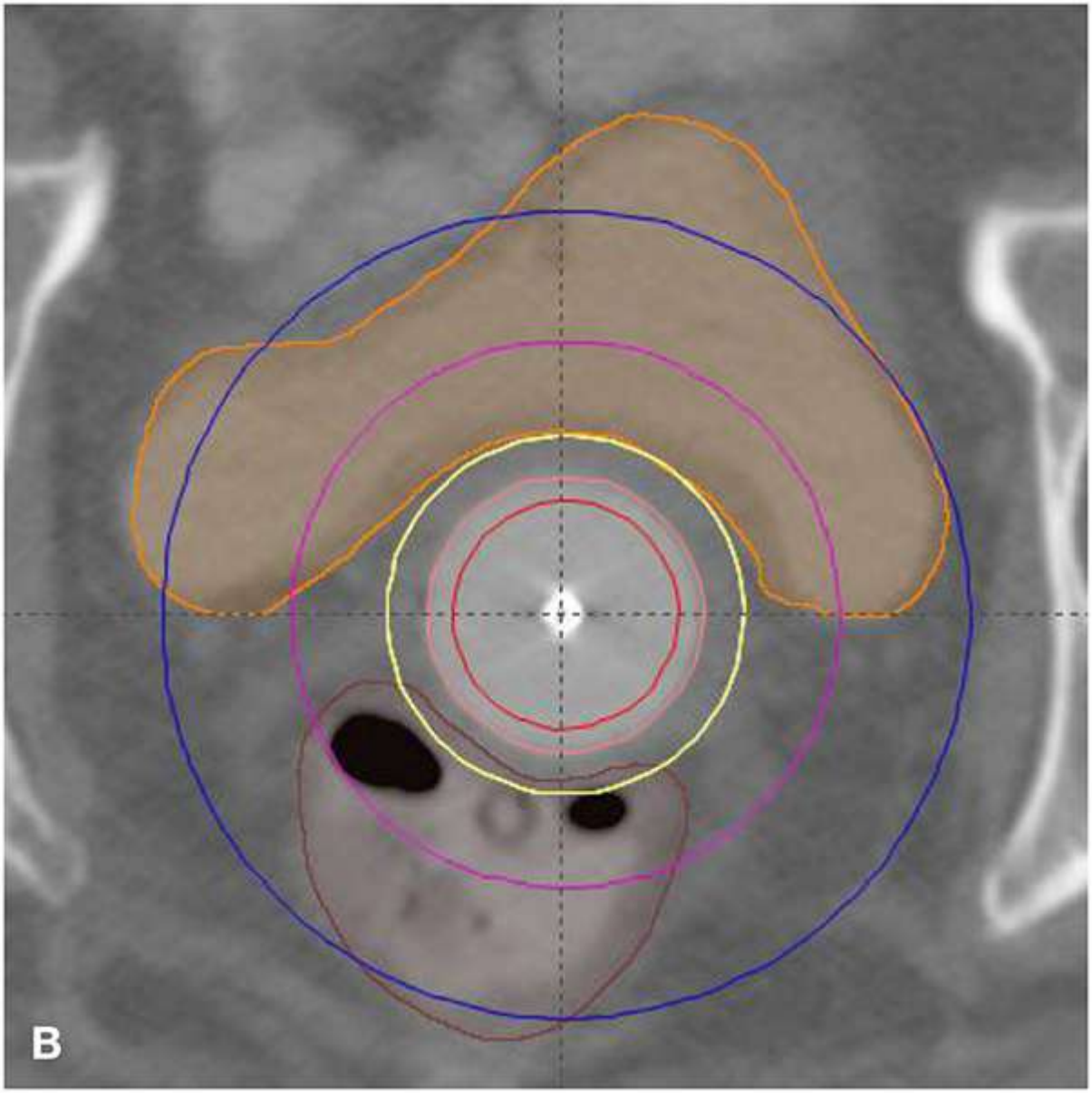

FIGURE 77.7 Dose distribution with intravaginal radiation therapy (prescription dose 7 Gy in solid yellow). **A.** Sagittal view. **B.** Axial view.

External Beam Radiation

Conventional Radiotherapy

At the time of simulation for *pelvic* RT, the small bowel is often opacified using oral contrast, a vaginal marker can be used to define the vaginal cuff, and the rectum can opacified with barium or CT-compatible contrasts. Patients are sometimes placed in the prone position to displace the small intestines from the radiation field, but supine is also acceptable. The target

volume consists of the pelvic lymph nodes, including obturator, external, internal, and lower common iliac groups and the proximal two-thirds of the vagina. The presacral nodes are not included unless patients have gross cervical involvement. High-energy linear accelerators (15 MV) are preferred because of their sparing of the skin and subcutaneous tissue. The ideal beam arrangement with conventional radiation is the four-field pelvic box technique to reduce the dose to the small intestines and, to some extent, the bladder and rectum. For AP/PA fields, the superior border is L5-S1, the inferior border is the bottom of the obturator foramina, and the lateral border is 2 cm beyond the widest point of the inlet of the true bony pelvis. For lateral fields, the anterior border is in front of the pubis symphysis and the posterior border at least at S2-S3. The superior and inferior borders are the same for the AP/PA fields. All fields are treated daily to a dose of 1.8 Gy. A total dose of 50.4 Gy is generally given when pelvic radiation is used alone, or 45 Gy when combined with VCBT.

When para-aortic nodes are involved, *extended field* RT is used, and CT simulation is crucial for accurate delineation of the kidneys, small bowel, and liver in addition to nodal target. The latter should include, in addition to the pelvic nodes, the pericaval, interaortocaval, and para-aortic areas, defined by contrast-enhanced blood vessels. The preferred approach is the four-field box technique rather than AP/PA in order to lower the dose to the small intestines. However, attention should be paid to the dose that the kidneys might receive with the four-field arrangement. The lower border is the same as in pelvic radiation, but the upper border is extended usually to the T12-L1 interspace. The typical dose is 45.0 Gy at 1.8 or 1.5 Gy if patients develop acute GI toxicity.

Intensity-Modulated Radiotherapy

At most institutions, postoperative IMRT is used for most patients with endometrial cancer who need pelvic or extended field radiation (Figure 77.8). At the time of simulation, patients are placed in the prone (pelvic) or supine (extended) position and immobilized using Aquaplast. Oral and rectal contrasts can be used to better visualize the small and large intestines. In addition, contrast is inserted into the vaginal cuff to better visualize the upper vagina. Because pelvic lymph nodes are poorly visualized by CT

when normal, they should be defined by encompassing the contrast-enhanced blood vessels. Taylor et al[146] found that a modified 7-mm margin around contrast-enhanced vessels offers a good surrogate target for pelvic lymph nodes. Small et al[147] reported on consensus guidelines for delineation of clinical target volume (CTV) for intensity-modulated pelvic RT in postoperative treatment of endometrial and cervical cancer. A modified 7-mm margin (excluding bowel and muscles) is recommended around the iliac vessels to create nodal CTV. To create nodal planning target volume (PTV), an additional expansion of 7 mm all around nodal CTV is generally recommended. At many institutions, a vaginal PTV is created by outlining the contrast-enhanced vaginal cuff and adding a 3-cm margin axially and 2 cm superior and inferior to account for the impact of bladder and rectal filling, as well as of vaginal motion.[148] An alternative approach would be to simulate patient with bladder full and bladder empty and create an internal target volume. The RTOG established dose constrains for using postoperative IMRT in endometrial cancer.[149] For bladder, less than 35% receives 45 Gy or more; rectum, less than 60% receives 45 Gy or more; small bowel, less than 30% receives 40 Gy or more; femoral heads, less than 15% receives 30 Gy or more; and any 1% or less or 1 mL or less receives more than 110% prescribed dose normal tissue.

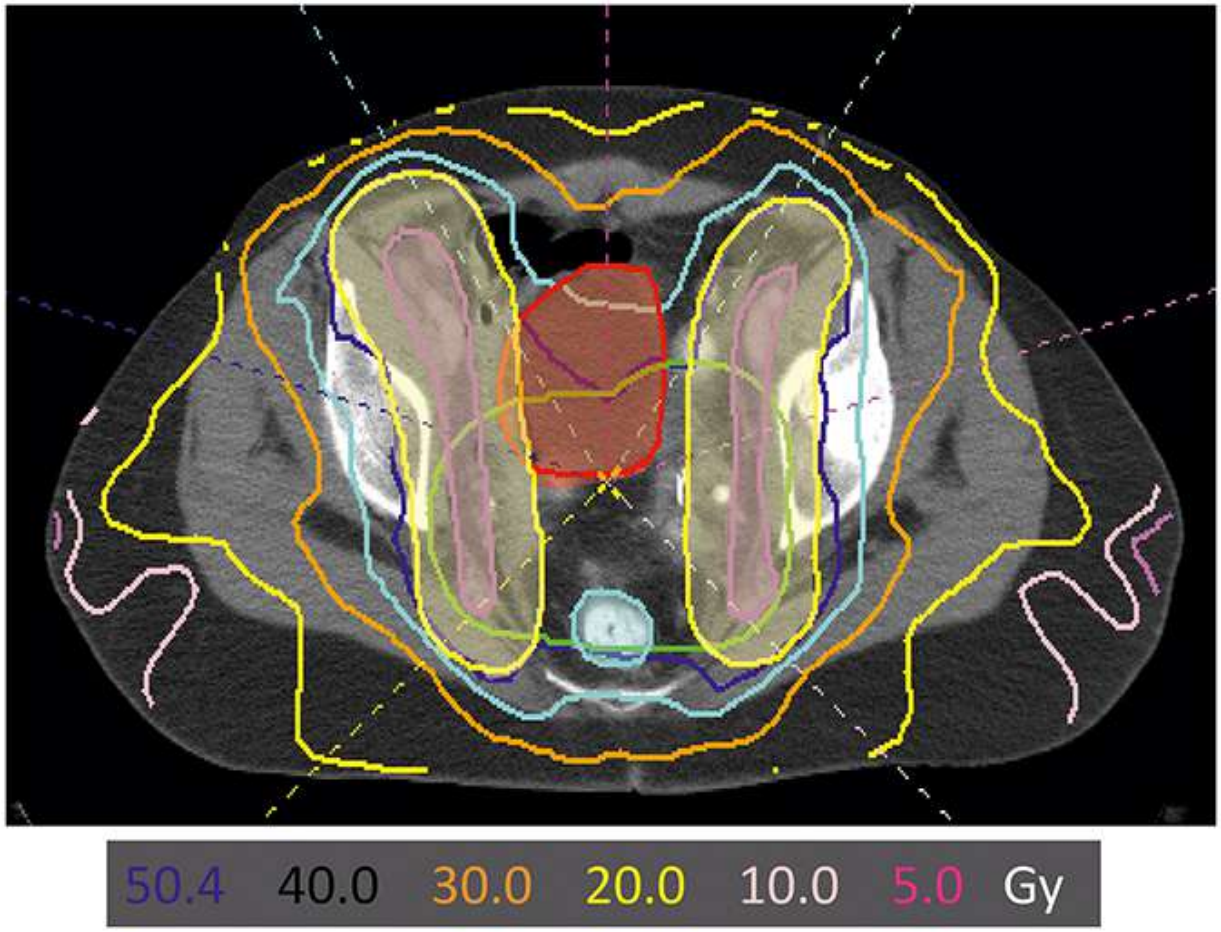

FIGURE 77.8 Pelvic intensity-modulated radiation therapy dose distribution. Outlined iliac vessels are shown in pink and nodal planning target volume in yellow.

Data on outcome with postoperative IMRT in endometrial cancer are encouraging. He et al reported on 129 patients (77% stages I to II). With a median follow-up of 57 months, the 5-year DFS in the subset of patients with stages I to II (n = 98) was 85.7% for those with low-intermediate risk and 71.6 for HIR. The corresponding rates for OS were 91.7% and 76.2%.[150] Shih et al reported on 46 patients with high-risk endometrial cancer treated with postoperative IMRT. With a median follow-up of 52 months, the 5-year disease-free survival and OS rate in stage III (n = 36) were 84% and 95%, respectively.[151]

COMPLICATIONS OF TREATMENT

Surgery

In the PORTEC-1 trial,[94] the rate of complications in the surgery-alone arm was very low (6%). Surgical toxicity data are generally collected within 30 days of surgery, that is, before patients were enrolled in the trial. Therefore, it is important to assess surgical toxicity from trials addressing a surgical question. In the GOG LAP2 trial comparing laparotomy to laproscopy,[81] the rate of intraoperative complications was 8% versus 10% ($P = .106$). More importantly, the rate of postoperative (within 6 weeks of surgery) grade 2 or greater complications was 21% for laparotomy versus 14% for laparoscopy ($P < .001$). In the Italian randomized trial comparing hysterectomy to hysterectomy and lymphadenectomy, both early and late postoperative complications occurred significantly more frequently in patients with lymphadenectomy (81/264; 30.6%) than for hysterectomy alone (34/250, 13.6%; $P = .001$). Most of the difference in morbidity was due to lymphoceles and lymphedema, which occurred in 35 patients in the lymphadenectomy arm and 4 patients in the no-lymphadenectomy arm.[85]

Radiation

Vaginal Cuff Brachytherapy

The main advantage of intravaginal BT is its ability to deliver a relatively high dose of radiation to the vagina while limiting the dose to the surrounding normal structures, such as the bowels, rectum, and bladder. In the PORTEC-2 trial, the long-term health-related quality of life analysis showed at 7 years, clinically relevant fecal leakage was reported by 10.6% in the pelvic RT group versus 1.8% for VCBT ($P = .03$), diarrhea by 8.4% versus 0.9% ($P = .04$), limitations due to bowel symptoms by 10.5% versus 1.8% ($P = .001$), and bowel urgency by 23.3% versus 6.6% ($P < .001$). Urinary urgency was reported by 39.3% of pelvic RT patients, compared to 25.5% for VCBT ($P = .05$). No difference in sexual activity was seen between treatment arms.[152] However, such a low rate of severe complications cannot be taken for granted because special attention needs to be paid to the depth of prescription, the dose per fraction, the length of vagina treated, and the diameter of the cylinder used. Sorbe and Smeds[153] reported a 15% late complication rate and a very high incidence of vaginal stenosis after postoperative HDR intravaginal irradiation. This was attributed to the high dose per fraction of 6 to 9 Gy; moreover, this dose

was prescribed at a depth of 10 mm from the surface of the cylinder, resulting in very high vaginal mucosal, bladder, and rectal doses. Adherence to vaginal dilator use[154] after VCBT as well as routine use of vaginal lubricants and moisturizers may further reduce the rate of vaginal stenosis.

In a cohort of 104 patients with early-stage endometrial cancer treated with surgery and VCBT, Female Sexual Function Index (FSFI) questionnaires were used to quantify levels of sexual functioning.[112] Sexual dysfunction defined as an FSFI score of less than 26 was reported by 81% of respondents. Multivariate analysis isolated factors associated with lower FSFI scores, including having laparotomy as opposed to minimally invasive surgery (effect size, −7.1 points; $P < .001$), lack of vaginal lubricant use (effect size, −4.4 points; $P = .040$), and short time interval (<6 months) from hysterectomy to questionnaire completion (effect size, −4.6 points; $P = .059$).

In a subsequent report[155] from MSKCC, 205 early-stage endometrial cancer survivors (>1 year from surgery) completed questionnaires containing the EuroQol (EQ5D) and the FSFI. A total of 136 (66.3%) underwent surgery alone, and 69 (33.7%) received additional VCBT. A majority of patients (80%) met criteria for sexual dysfunction by FSFI less than 26.5. The two groups were well balanced with respect to demographics, comorbidities, and baseline sexual activity. Controlling for age and surgery type (open vs minimally invasive), VCBT was not associated with poorer health state or sexual function. Receipt of laparotomy was associated with both poorer health state and sexual function ($P = .0156$ and $P = .0247$, respectively). These studies highlight the fact patients with endometrial cancer whether treated with surgery alone or with additional VCBT, when compared to the index population (healthy women ages 18-74), all scores were low.

Pelvic Radiation

In the PORTEC-1 randomized trial,[156] the overall (grades 1-4) rate of late complications was 26% in the RT group compared to 4% in the observation group ($P < .0001$). Most of the late complications in the RT group, however, were grades 1 and 2 (22%), and only 3% were grades 3 and 4. It is also important to note that many patients in this trial were treated with AP/PA

fields, for which the overall rate of complications was 30%, compared to 21% for those treated with the four-field box (P = .06). In GOG 99 when lymphadenectomy was performed, chronic lymphedema was seen in 2.5% of the patients randomized to surgery alone compared to 5% with postoperative pelvic RT.[95] There is an increased awareness of sacral insufficiency fractures (SIFs) as a potential complication of pelvic RT in gynecologic cancers. In a report from MSKCC, 222 patients were treated with postoperative pelvic RT.[157] In the subset of endometrial cancer (n = 144), the 5-year rate of SIF was 5.7%. Risk of secondary malignancies is often cited as one of the main reasons to avoid pelvic RT in patients with endometrial cancer; however, when the PORTEC-1 and PORTEC-2 trials were combined, there was no clear evidence of increased risk.[158]

The use of IMRT seems to be associated with less risk of obstruction (bowel obstruction or BO). In a report from MSKCC on 224 patients (152 with endometrial cancer) treated with postoperative radiation,[159] the 5-year rate of BO in the IMRT group was 0.9% compared to 9.3% for 3D RT (P = .006). Patients with BMI 30 kg/m^2 or higher were less likely to develop BO (2.6% vs 8.3%; P = .03). On multivariate analysis, only IMRT retained its significance as an independent predictor of less BO (P = .022).

In the PORTEC-3 trial, the addition of chemotherapy to radiation showed increased physician and patient-reported toxicities. However, by 24 months, results equalized, with the exception of persistence of patient-reported sensory neurologic symptoms in 25% of patients in the chemoradiation arm.[160]

DEFINITIVE RADIATION FOR INOPERABLE DISEASE

In medically inoperable patients with endometrial cancer, radiation is an effective alternative to surgery. These patients are usually treated in a way similar to those with cervical cancer by using intracavitary applicators with or without pelvic radiation. In a systematic review of 25 reports of patients treated with RT as single treatment, the 5-year DSS was 78.5%. EBRT combined with BT was used in 1,278 (47.4%) patients, BT alone in 1,383 (51.3%) patients, and EBRT alone in 33 (1.2%) patients. The average rate of grade 3 or worse late toxicity was 3.7% for EBRT + BT, 2.8% for BT alone, and 1.2% for EBRT alone.[161] The ABS established general guideline

recommendations regarding HDR either alone or in combination with EBRT in terms of prescription point (2 cm from the central axis at the midpoint along the intrauterine sources), number of fractions, dose per fraction, combination with EBRT, and optimization. Patients with stage IIIB disease (vaginal involvement), an uncommon presentation, are usually not surgical candidates and are also treated with definitive radiation, including a combination of EBRT and intracavitary/interstitial RT tailored to the extent of their disease.[162]

For patients with clinical stage I grade 1 or 2 and no evidence of myometrial invasion or lymph node metastasis on MRI, intracavitary BT alone is sufficient. Gebhardt et al reported on 45 patients with grades 1 to 2, clinical stage I endometrial adenocarcinoma, less than 50% myometrial invasion, and tumor 2 cm or less treated with five to six fractions HDR intracavitary BT to a median total dose of 37.5 Gy. Median follow-up among living patients was 18.6 months. The 2-year local control, cancer-specific survival, and OS rates were 90%, 86%, and 97%, respectively. No grade 3+ acute or late toxicity was observed.[163] In another report, 43 consecutive patients with endometrial cancer FIGO stages I to III were treated definitively with HDR BT with or without EBRT.[164] Mean follow-up was 29.7 months. Median BMI was 50.2 kg/m^2. The 2-year OS was 65.2%. The 2-year cumulative incidence of pelvic and distant failures was 8.3% and 13.5%, respectively. Grade 3 disease was associated with a higher risk of all failures (HR, 4.67; P = .044). The incidence of acute grade 3 GI/GU toxicities was 4.6%.

RADIATION THERAPY FOR LOCAL RECURRENCE

RT can be curative in a select group of patients with small vaginal recurrences who have not received prior radiation. Creutzberg et al reported on survival after relapse based on the PORTEC-1 randomized trial.[97] In patients who were initially randomized to surgery alone (n = 46/360), the 5-year survival after vaginal relapse was 65%. However, before adopting salvage radiation as a treatment policy for all early-stage endometrial cancer, a few aspects of this trial need to be addressed. First, the 5-year survival rate from the PORTEC trial is much higher than what is reported in the literature.[165-168] Most likely, the vaginal recurrences in this trial were

detected very early, unlike the situation for patients in the community. The extent and size of local recurrence in endometrial cancer are very significant predictors of outcome.[168] Second, this high rate of salvage pertains only to isolated vaginal recurrence. The rate of survival at 3 years for pelvic recurrence in the PORTEC-1 trial[97] was 0%. Third, although the trial does not mention any data on complications, it is not unrealistic to expect a higher complication rate than what is normally seen with adjuvant radiation. With salvage radiation, EBRT and BT are often combined, and the doses of radiation required are much higher than those used with adjuvant radiation. The study from MD Anderson Cancer Center by Jhingran et al[165] clearly highlights these issues. They reported on 91 patients who were treated with definitive radiation for isolated vaginal recurrence. The 5-year local control and OS rates were 75% and 43%, respectively. The median dose of radiation was 75 Gy, which often included external radiation and BT. The rate of grade 4 complications (requiring surgery) was 9%. Thus, when talking with a patient about adjuvant radiation versus radiation reserved for salvage, these issues need to be addressed and compared to the excellent local control and low morbidity obtained with adjuvant intravaginal BT. In a report from the University of Pittsburgh,[169] 41 patients were treated with HDR BT using image-based planning with contouring/optimization with each fraction to a median dose of 23.75 Gy in five fractions. BT was combined with pelvic IMRT in 90% of patients to a dose of 45 Gy. At a median follow-up of 18 months, the 3-year local control, distant control, recurrence-free survival, and OS were 95%, 61%, 68%, and 67%, respectively. The 3-year rate of grade 3 or higher late toxicity was 8%. This indicates that even with more modern techniques, the morbidity of salvage RT cannot be ignored.

With the increased use of IMRT, salvage rate of nodal recurrence in endometrial cancer is better. In a report by Ho et al, 38 patients with endometrial cancer who had no prior external beam radiation were treated definitively using IMRT for regionally confined pelvic or para-aortic nodal recurrences. Chemotherapy was given to 33 out of 38. The total dose of IMRT was 64.7 Gy (range 59-73 Gy). The 2-year survival was 71%. Three patients (8%) experienced grades 3 to 4 late GI toxicity.[170]

UTERINE CARCINOSARCOMA

Uterine carcinosarcoma (UCS) is no longer considered a uterine sarcoma. In GOG 210, UCS represented about 4.1 of endometrial cancinomas.[46] Molecular evaluation of UCS revealed that frequent mutations were found in TP53, PTEN, PIK3CA, PPP2R1A, FBXW7, and KRAS, similar to endometrioid and serous uterine carcinomas. The range of epithelial-to-mesenchymal transition (EMT) scores in UCS was the largest among all tumor types studied via TCGA. UCSs shared proteomic features with gynecologic carcinomas and sarcomas with intermediate EMT features.[171]

The etiology of UCS is not well established but seems to share some similarity with endometrial adenocarcinoma. History of prior pelvic radiation has been reported in some patients with carcinosarcoma.[172] These neoplasms are often bulky, necrotic, and deeply invasive. The epithelial component is generally serous carcinoma. Homologous tumors have stroma that contains cell types normally seen in the uterus, in contrast to heterologous tumors, which may contain striated muscle cells (rhabdomyosarcoma), cartilage (chondrosarcoma), and bone (osteogenic sarcoma) (Figure 77.3D).

The main treatment is surgery, and these patients should undergo comprehensive surgical staging similar to that with serous cancer. Pelvic nodal metastasis is seen in 21.1%, and in para-aortic node in 15.2% of patients.[46] For carcinosarcomas, the 2009 staging system for carcinomas of the endometrium is used, recognizing the similarity in patterns of spread.

With regard to the role of *adjuvant radiation*, the EORTC performed a prospective, randomized trial addressing the role of postoperative pelvic RT in stages I to II uterine sarcomas. There were a total of 224 patients in the trial who underwent TAH/BSO, and 166 who had peritoneal washings. Lymphadenectomy was optional. There were 91 carcinosarcomas included in that study; the rate of pelvic recurrence only was 4% in the pelvic RT arm compared to 24% for the surgery-alone arm. The corresponding rates for any local recurrence were 24% and 47%, for this subset of patients.[173]

Adjuvant chemotherapy has been evaluated mainly in carcinosarcoma. Sutton et al[174] reported on 65 patients with completely resected stage I or II carcinosarcoma of the uterus treated with adjuvant ifosfamide and cisplatin. None of the patients received adjuvant RT. Overall 5-year survival was

62%. The initial site of relapse was vaginal apex in 6 of 65 and pelvis in 4 of 64, suggesting that a combined chemoradiation approach might be ideal. GOG-150 is a phase III randomized study of whole abdominal RT versus three cycles of cisplatin, ifosfamide, and mesna. Eligible patients (n = 206) included those with stages I to IV UCS, no greater than 1-cm postsurgical residuum, and/or no extra-abdominal spread. Stage distribution was as follows: I, 64 (31%); II, 26 (13%); III, 92 (45%); and IV, 24 (12%). The estimated crude probability of recurring within 5 years was 58% for chemotherapy and 52% for RT. Adjusting for stage and age, the recurrence rate was 21% lower for chemotherapy patients than for RT patients (RH, 0.789; 95% CI = 0.530-1.176; P = .245, two-tailed test). The estimated death rate was 29% lower in the chemotherapy group (RH, 0.712; 95% CI = 0.484-1.048; P = .085, two-tailed test). The conclusion was that there was not a statistically significant advantage in recurrence rate or survival for adjuvant chemotherapy over RT in patients with UCS. However, the observed differences favor the use of combination chemotherapy in future trials. The rate of vaginal recurrence was 4 (3.8%) of 105 in the whole abdominal irradiation compared to 10 (9.9%) of 101. The corresponding abdominal relapse rates were 27.6% (29/105) and 18.8% (19/101). There was no difference in pelvic recurrence between the two arms. The rates of lung metastasis (14/105 vs 14/101) or other distant sites (13/101 vs 10/101) were similar. Analysis of the patterns of relapse from this trial also indicates the need for chemoradiation in patients with stages I to III carcinosarcoma.[175]

The use of IVRT and chemotherapy is appealing in stages I to II carcinosarcoma. Desai et al reported on 60 patients with stages I to II UCS and compared them to 112 stage I to II serous endometrial cancers.[176] Adjuvant therapy was to 90% of patients. With a median follow-up of 48 months, outcomes were better for serous versus UCS: 5-year actuarial rates of recurrence (17% vs 45%; P < .001), disease-specific mortality (11% vs 30%; P = .016), and all-cause mortality (12% vs 34%; P = .007). However, in a subgroup analysis of 111 patients (77 serous, 34 UCS) who receive IVRT and chemotherapy, UCS no longer was associated significantly with increased recurrence (29% vs 15%, P = .18), disease-specific mortality (22% vs 10%, P = .39), or all-cause mortality (22% vs 10%, P = .45). This

indicates that when early-stage UCS were treated aggressively, their outcome were not significantly different than serous endometrial cancer.

Commonly, patients with surgical stage I or II carcinosarcoma are treated with intravaginal BT and chemotherapy. Most patients with stage III are treated in a similar manner, with few exceptions when extrauterine disease is limited to nodal disease. Then, consideration is given to concurrent pelvic RT/cisplatin followed by carboplatin/paclitaxel.

UTERINE SARCOMA

Uterine sarcomas are uncommon, representing about 3% to 7% of all uterine cancers.[177] The most common histology is leiomyosarcoma (LMS), followed by endometrial stromal sarcoma (resemble proliferative-phase endometrial stroma), undifferentiated uterine sarcoma, and adenosarcoma (benign epithelial component and low-grade sarcoma). Age-related incidences vary among the histologic types. The mean age at diagnosis for endometrial stromal sarcoma is 41 years, for LMS 53.5 years, and for adenosarcoma 57.4 years. Little is known about the risk factors for uterine sarcomas. Most uterine sarcomas present with vaginal bleeding, but LMSs are more commonly discovered incidentally after simple hysterectomy for presumed uterine leiomyomata.

Pathology and Staging

Endometrial stromal sarcomas are generally divided into endometrial stromal sarcomas, which are low grade by definition, and undifferentiated endometrial sarcoma, which are high grade. Tumor cells in endometrial stromal sarcoma resemble those found in the stroma of proliferative endometrial lining. In contrast, tumor cells in undifferentiated endometrial stromal sarcoma do not resemble endometrial stroma. LMSs of the uterus have a fleshy appearance, often with areas of necrosis. They display nuclear atypia, high mitotic rates, and areas of coagulative tumor necrosis. *Adenosarcomas* have two components—a benign epithelial tumor and a malignant mesenchymal component (generally low-grade sarcoma that resembles endometrial stroma). Sarcomatous overgrowth, defined as the presence of pure sarcoma, usually of high grade and without a glandular component, occupying at least 25% of the tumor, has been reported in 33%

of uterine adenosarcomas.[177] The 2009 FIGO staging recognizes the uniqueness of each uterine sarcoma. For LMSs and endometrial stromal sarcomas, the staging system recognizes the importance of tumor size on outcome. For adenosarcomas, the new staging system recognizes the importance of depth of myometrial invasion.

Management

The main treatment for uterine sarcoma is *surgery* in a similar manner to endometrial adenocarcinoma. The extent of surgical staging varies, depending on the risk of lymph node involvement. Nodal metastases are seen in less than 5% of LMS unless there is obvious extrauterine disease.[178] For stromal sarcomas, dos Santos et al[179] reported a 19% (7/36) rate of nodal metastasis. The rate of occult metastasis was only 10%. The corresponding rates from the literature review were 10.1% and 8.1%. Thus, patients with endometrial stromal sarcomas and adenosarcomas might benefit from lymph node sampling. On the other hand, for patients with LMSs, the rate of nodal involvement is too low to justify routine lymphadenectomy.

With regard to the role of *adjuvant radiation*, the EORTC performed a prospective, randomized trial addressing the role of postoperative pelvic RT in stage I to II uterine sarcomas.[173] A total of 224 patients in the trial underwent TAH/BSO, 166 of whom had peritoneal washings. Lymphadenectomy was optional. There were 103 LMSs and 28 endometrial stromal sarcomas. The 5-year cumulative incidence of locoregional recurrence was 18.8% in the pelvic RT arm compared to 35.9% in the surgery-alone arm. That difference was statistically significant ($P = .0013$). The 5-year cumulative incidence of distant relapse was 45.3% for the pelvic RT and 33.6% for surgery alone, but the difference was not statistically significant ($P = .2569$). There was no significant difference in PFS ($P = .3254$) or OS ($P = .923$) between the two arms. For patients with LMS, the rate of pelvic recurrence only was 2% in the pelvic RT compared to 14% in patients treated with surgery alone, and for any local recurrence, it was 20% versus 24%. It is important to note that the primary end point of this trial was pelvic control, which it met ($P = .0013$). The study was not powered to detect a significant difference in PFS or OS. Sampath et al[180] performed a

retrospective review of patients with uterine sarcoma using the National Oncology Database. The impact of adjuvant radiation was assessed in patients who presented with nonmetastatic disease and underwent definitive surgery (n = 2,206). For endometrial stromal sarcoma, the rate was 97% with RT versus 93% for surgery alone (n = 252; P < .05). For LMS, it was 98% for RT (n = 131) compared to 84% with surgery alone (n = 398; P < .01).

For patients with LMSs, the main treatment is surgery, and the role of adjuvant treatment, either RT or chemotherapy, is not well defined. The high rate of distant relapse in these patients overshadows any local control benefit attained with adjuvant RT. These patients should be encouraged to participate in trials assessing the role of chemotherapy and/or targeted therapy. For patients with low-grade endometrial stromal sarcomas, observation is feasible, because most are hormonally sensitive and generally behave in an indolent manner, with long disease-free intervals. For those with undifferentiated endometrial sarcomas, adjuvant pelvic RT is reasonable. For patients with adenosarcomas, especially with sarcomatous overgrowth, adjuvant pelvic RT is also reasonable.

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CHAPTER 78

Ovarian and Fallopian Tube Cancer

Christopher Weil

Ovarian neoplasms encompass a wide array of benign and malignant tumors with diverse histologic cell types, clinical features, and survival outcomes. Primary malignant tumors of the ovary include the epithelial ovarian cancers, germ cell tumors, and sex cord tumors. Low malignant potential (LMP) tumors of the ovary are noninvasive epithelial tumors often confined to the ovary, although extraovarian tumor implants may be detected. Metastases to the ovary occur from other primary malignancies, including uterine, gastrointestinal (Krukenberg tumors), and breast cancers. Primary lymphoma, sarcoma, and melanoma of the ovary are rare. Relative to its incidence, epithelial ovarian cancers have substantially high mortality because effective screening tools are lacking; only 25% are detected as stage I at diagnosis, and current therapies for advanced cancer, although improving, have approached a therapeutic plateau. Surgery is the mainstay for diagnosis, staging, and the initial treatment for ovarian cancer. Platinum-based chemotherapy, with or without anti-angiogenic therapies, are indicated for patients with high-risk or advanced disease. Poly (ADP-ribose) polymerase (PARP) inhibitors, immunotherapies, and other targeted therapies are utilized in the maintenance, recurrent, or metastatic setting. The use of whole-abdomen irradiation (WAI) or intraperitoneal (IP) radioisotopes is primarily historical, and radiation therapy now has a limited role in the management of ovarian cancer. Nonetheless, palliative radiotherapy may be of significant benefit for symptomatic disease relapse or select patients with localized recurrence.

ANATOMY

In premenopausal women, the ovaries are almond-shaped, gray-pink solid organs that measure approximately 4 × 2.5 × 1 cm^2, with an average weight of 4 to 5 g. After menopause, the ovaries atrophy and become nonfunctional

and smaller in size. When normally positioned, the ovary is attached by the mesovarium to the broad ligament that covers the uterus and fallopian tubes. The infundibular pelvic, or suspensory, ligament extends from the surface of the ovary to the lateral pelvic wall, forming the superior and lateral aspects of the broad ligament (Figure 78.1). The blood supply of the ovary is derived from the ovarian arteries, which arise from the aorta immediately below the level of the renal arteries and course through the retroperitoneum and infundibular pelvic ligaments. The venous return of the ovary empties to the renal vein on the left and directly to the venae cavae on the right. The primary lymphatic drainage of the ovary parallels the course of the ovarian veins, with secondary lymphatic flow passing through the inguinal canal and to the iliac nodal system.[1] Histologically, the outer cortex of the ovary is covered by a layer of pseudocolumnar or cuboidal epithelium, termed the *germinal epithelium of Waldeyer* or *ovarian surface epithelium* (OSE). The inner medulla consists of a superficial tunica albuginea and dense stromal tissue filled with blood vessels and spindled, “muscle-like” connective tissue. Within the medulla, maturing follicles are present throughout the various layers.

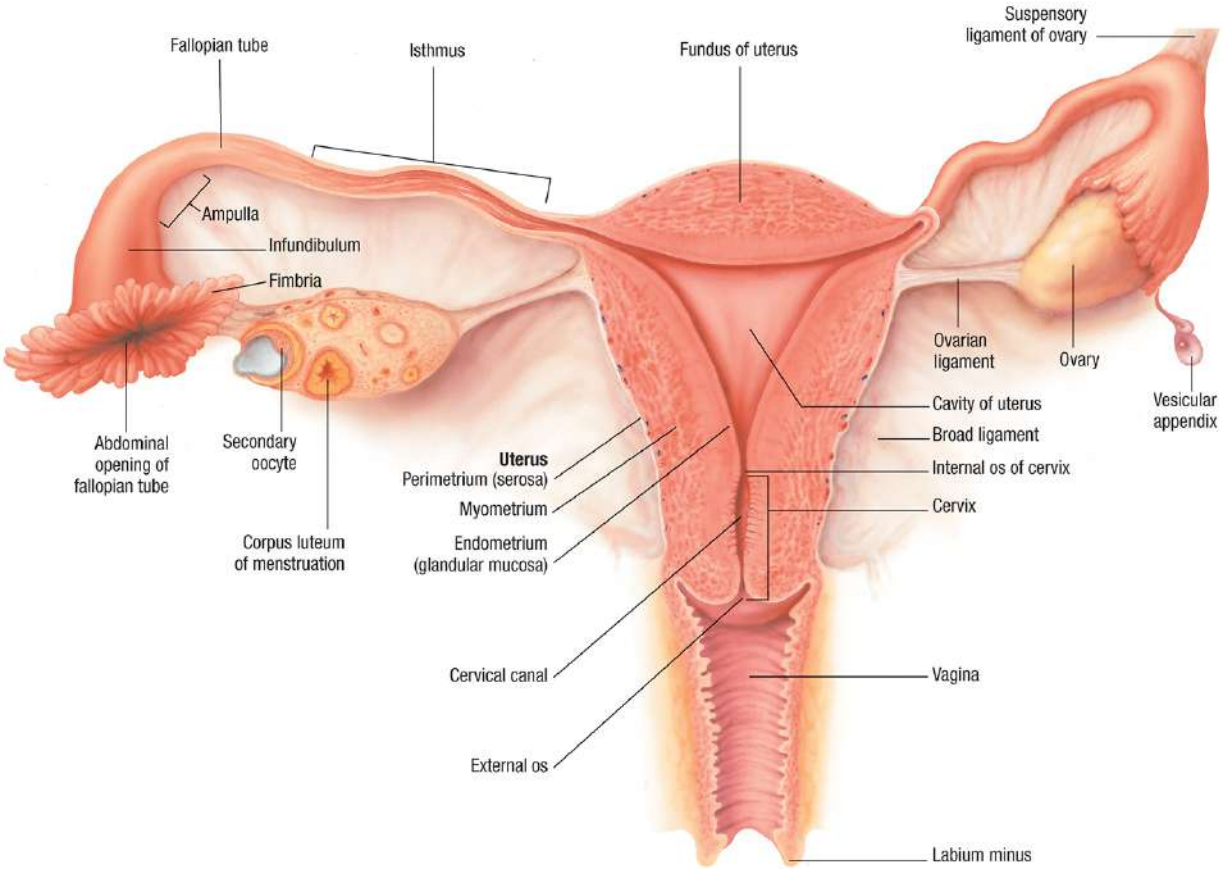

FIGURE 78.1 Anatomy of the ovary and female reproductive tract. (Asset provided by the Anatomical Chart Company.)

The fallopian tubes are positioned horizontally within the superior part of the broad ligament and extend from the superior-posterior portion of the uterine fundus to the ovaries. The fallopian tubes are hollow, muscular viscera that are in direct communication with the peritoneal cavity. The ovarian artery anastomoses with the uterine artery to supply the fallopian tube, and venous drainage is through the pampiniform plexus to the ovarian vein and uterine plexus. The mucosa of the fallopian tube contains a rich network of intercommunicating lymphatic sinusoids that anastomose with adjacent organs and drain into the ovarian lymphatics and para-aortic and iliac lymph nodes.[2] The fallopian tubes consist of four separate histologic layers: the mucosa, submucosa, muscularis (external longitudinal and inner circular layers), and outer serosal layer, which is continuous with the visceral peritoneum of the uterus. The mucosa is intricately folded, with the number of folds increasing from the interstitial portion to the ampulla. The epithelium is composed mainly of ciliated cells and secretory cells. Cyclic changes are

evident in the tubal epithelium, similar to those of the endometrium, in response to estrogen and progesterone.

EPIDEMIOLOGY

Ovarian cancer is the second most common gynecologic malignancy in the United States after endometrial cancer. An estimated 19,680 women in the United States will receive a diagnosis of epithelial ovarian cancer in 2024, and 12,740 will die of the disease[3,4] (Figure 78.2). Ovarian cancer represents the fifth leading cause of cancer-related death in U.S. women, following lung, breast, colorectal, and pancreatic cancers. The lifetime risk of ovarian cancer is approximately 1 in 77 women with a median age at diagnosis of 63 years; more than 80% of women are diagnosed after the age of 40 years.[5] The incidence of ovarian cancer rises with increasing age and peaks in the eighth decade of life. Differences in race and ethnicity are apparent in the age-adjusted annual incidence per 100,000 women, which in 2010 to 2014 was highest for White women (12.2), followed by Hispanic (10.6), American Indian/Alaska Native (9.5), Black (9.4), and Asian/Pacific Islanders (9.5).[5] The incidence of ovarian cancer also varies significantly by geography, with the highest rates in North America and northern Europe, which are 3 to 7 times higher than that observed in Japan.[6] Survival rates for ovarian cancer have been increasing in the United States since 1975, when the 5-year survival rate reported by the Surveillance, Epidemiology, and End Results program was 34%, which has increased to 47% in 2009.[5]

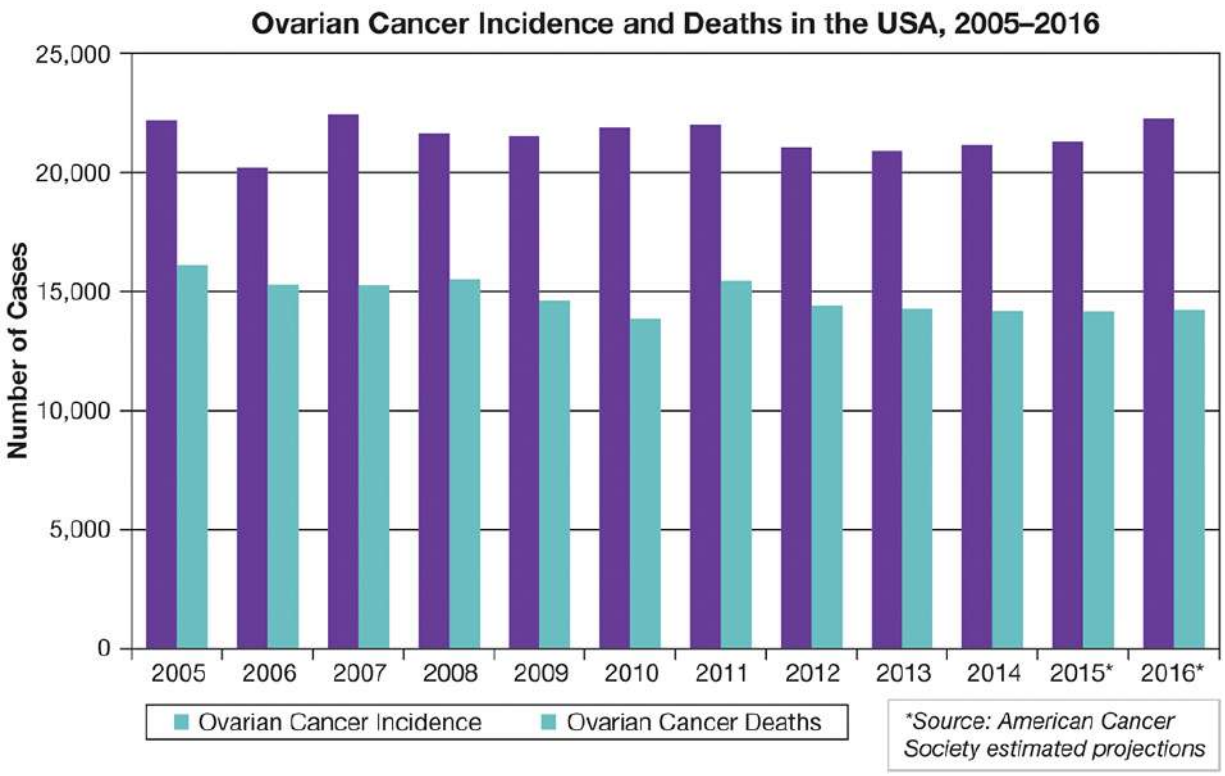

FIGURE 78.2 Ovarian cancer incidence and deaths in the United States from 2005 to 2016. (Courtesy of the American Cancer Society.)

Primary cancer of the fallopian tube was once considered a rare disease, accounting for 0.2% to 0.5% of female gynecologic malignancies. However, the true incidence has likely been underestimated considering a large proportion of extrauterine high-grade serous carcinomas may actually originate in the fimbriated end of the fallopian tube.[7,8] Precursor lesions, known as *serous tubal intraepithelial carcinoma*s (STICs), have been detected in the fallopian tubes of prophylactic salpingo-oophorectomy specimens from high-risk patients. The model of the fallopian tube as the primary site of origin for extrauterine high-grade serous carcinoma is supported by epidemiologic, morphologic, and genetic data, as discussed later.

PATHOGENESIS

The female reproductive tract originates from the Müllerian ducts, which are paired embryologic structures of mesodermal origin that give rise to the fallopian tubes, uterus, cervix, and upper vagina. Ovarian tissue is composed

of embryonic yolk sac cells that give rise to the ova or germ cells, stromal cells that produce the steroid hormones, and mesothelium that provides the epithelial covering for the follicle cysts. These cell types give rise to germ cell tumors, sex cord-stromal tumors, and epithelial tumors of the ovary, respectively. The traditional view of ovarian cancer pathogenesis is that all tumor subtypes arise from the OSE. In the "incessant ovulation hypothesis," ovarian cancer develops from an aberrant repair process as a result of repeated rupture of the surface epithelium during each ovulatory cycle, thought to produce inflammation and scarring that serves as a nidus for carcinogenesis.[9-11] A second proposed mechanism is related to hormonal and reproductive factors such as persistent exposure to gonadotropins and elevated estradiol levels that stimulate malignant transformation.[12,13] Strong evidence exists that many borderline tumors and low-grade carcinomas of the ovary arise from cortical inclusion cysts (CICs) within the ovarian parenchyma. These benign cysts are composed of Müllerian epithelium that closely resembles the fallopian tube. CICs are thought to result from invaginations of the OSE into the ovarian stroma through repeated ovulation and aging, acquiring a Müllerian phenotype through metaplasia.[8] An alternate explanation is that remnants of Müllerian-derived epithelia from the fallopian tube may adhere to the ovarian surface and become incorporated into CICs in a process known as endosalpingiosis. Nonetheless, as a result of hormone exposure, damage repair processes, and inflammation within the ovary, neoplastic transformation gives rise to a variety of Müllerian cell type differentiations, including serous carcinomas that resemble the fallopian tube, mucinous tumors as seen in the endocervix, endometrioid tumors from the endometrium, and glycogen-rich clear cell cancers similar to secretory-phase endometrial glands.

High-grade serous ovarian carcinomas are infrequently associated with benign or borderline precursor lesions within the ovary, a contradiction of the OSE-CIC model. Furthermore, high-grade serous carcinomas of the ovary share distinct morphologic and genetic characteristics with high-grade serous carcinomas of other extrauterine sites, including serous fallopian tube carcinoma and primary peritoneal serous carcinoma. In this context, a second model of ovarian carcinogenesis has emerged with the recognition of the distal fallopian tube as the primary site of origin for many high-grade serous carcinomas. With rigorous pathologic processing, occult fallopian tube

cancer has been detected in the fimbria of prophylactic salpingo-oophorectomy specimens from high-risk patients.[14,15] Furthermore, STICs have been found in a large proportion of high-grade serous carcinomas initially designated as primary ovarian cancers.[16] An adenoma-carcinoma sequence has since been described that involves a dysplastic tubal precursor lesion with loss of p53 detectable by immunohistochemical staining ("p53 signature") with progression to a STIC characterized by increased proliferation, followed by the development of frank invasive serous carcinoma.[7,17] The concept of the fallopian tube as the primary site of high-grade serous carcinoma suggests that previously undetected serous STICs may spread to the adjacent ovary or peritoneal cavity early in the disease process of serous carcinogenesis.

In the two-pathway model of ovarian carcinogenesis, type I tumors include all major histologic subtypes (serous, endometrioid, mucinous, clear cell, and transitional) with low nuclear and architectural grade that may be linked to well-defined benign precursor lesions, and type II tumors account for the bulk of high-grade serous carcinomas (Table 78.1). The type I tumors are associated with distinct molecular alterations, such as mutations in *KRAS*, *BRAF*, and *PTEN*, which are rarely found in type II serous tumors.[18] Mutually exclusive *KRAS* and *BRAF* mutations, both of which activate the oncogenic *MAPK* signaling pathway, are observed in 65% of serous borderline tumors but are rarely seen in high-grade serous carcinomas.[19] *KRAS* mutations also occur in Müllerian histologic subtypes, including 60% of mucinous, 5% to 16% of clear cell, and 4% to 5% of endometrioid carcinomas.[18] Mutations in *PTEN*, which lead to constitutive activation of the related PI3 kinase signaling pathway, have been detected in 20% of endometrioid carcinomas,[20] whereas activating mutations in *PIK3CA* have been identified in 30% of clear cell cancers.[21] Somatic mutations in *ARID1A*, a novel tumor suppressor gene, have been identified in 46% of ovarian clear cell cancers and 30% of endometrioid cancers. *ARID1A* mutation and corresponding loss of BAF250a expression, a key component in chromatin remodeling, were also seen in preneoplastic lesions and may represent an early event in the transformation of endometriosis.[22] In contrast, type II tumors exhibit a high frequency of p53 mutation and widespread DNA copy number change. Inactivation of the BRCA pathway, a critical component of DNA repair by homologous recombination, is also a hallmark of high-grade

serous carcinomas.[23] Disruption of the BRCA pathway by germline or somatic mutation, epigenetic silencing, or microRNA regulation has been observed in more than 50% of serous cancers,[24] and functional assays show defective formation of homologous recombination repair foci following DNA damage.[25]

TABLE 78.1 TWO-PATHWAY MODEL OF EPITHELIAL OVARIAN CARCINOGENESIS

Type 1	Type 2
All Müllerian subtypes (serous, endometrioid, mucinous, clear cell, transitional)	High-grade serous carcinoma
Usually low grade	High grade
Linked to benign or borderline precursor lesions	Associated with serous tubal intraepithelial carcinomas (STICs)
KRAS or *BRAF* mutation (MAPK pathway) *PTEN* or *PIK3CA* mutation (PI3K pathway) *ARID1A* mutation, loss of BAF250a expression	Inactivation of *BRCA* pathway
Wild-type p53 status	High frequency of p53 mutation
Chromosomally stable	Widespread DNA copy number change
Frequently platinum insensitive	Usually platinum sensitive

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Angiogenesis plays an important role in normal ovarian function, as heavy vascularization occurs at the beginning of each ovulatory cycle with predictable variation in the serum levels of vascular endothelial growth factor (VEGF). Epithelial ovarian cancers frequently overexpress VEGF, fibroblast growth factor, platelet-derived growth factor (PDGF), and angiopoietin.[26] In preclinical models, expression of VEGF provides a survival advantage to transformed cells of the ovary. Other studies have found an association between preoperative serum VEGF level and clinical outcome.[27] Targeting the tumor microenvironment in ovarian cancer is an attractive treatment strategy, given the inherent genomic instability of high-grade serous cancers.

RISK FACTORS

Epidemiologic studies have identified hormonal, genetic, and environmental factors that may play an important role in ovarian carcinogenesis (Table 78.2). The OSE-CIC model is consistent with well-established epidemiologic data indicating that suppression of ovulation results in a substantial reduction of ovarian cancer risk. New insights into the pathogenesis of high-grade serous carcinomas have emerged through the study of high-risk populations with a genetic predisposition for the development of ovarian cancer. Nevertheless, the pathogenic mechanisms are not well understood and likely multifactorial, associated with both patient-related and environmental factors.

TABLE 78.2 FACTORS INFLUENCING THE RISK OF OVARIAN CANCER

Factor	Estimated Risk (%)	Estimated Relative Risk
Baseline lifetime risk	1.4	1
Race		
White	12.2/100,000	—
Hispanic or American Indian	10.6/100,000	—
African American	9.4/100,000	—
Risk factors		
Family history	9.4	5-7
BRCA1 mutation	35-46	18-29
BRCA2 mutation	13-23	16-19
Lynch II/HPNCC	3-14	6-7
Infertility	–	2-5
Obesity	–	1.1-4
Nulliparity	–	2-3
Late menopause	–	1.5-2
Early menarche	–	1-1.5
Unopposed estrogen use	–	1.2-2
Protective factors		
Multiparity	–	0.4-0.6
Oral contraceptive use	–	0.7
Hysterectomy or tubal ligation	–	0.6-0.7

HPNCC, hereditary nonpolyposis colorectal cancer.

Adapted from Holschneider CH, Berek JS. Ovarian cancer: epidemiology, biology, and prognostic factors. *Semin Surg Oncol* 2000;19(1):3-10. Copyright © 2000 Wiley-Liss, Inc. Reprinted by permission of John Wiley & Sons, Inc.

Patient-Related Factors

Risk factors associated with a higher frequency of ovulatory events, such as advancing age, low parity, infertility, early menarche, and late menopause, support the proposed mechanism of incessant ovulation.[28-31] Although infertility is associated with ovarian cancer, the use of fertility drugs has not been conclusively linked.[32-34] Suppression of ovulatory events from pregnancy, breast feeding, and oral contraceptive use may explain the observed protective benefit.[30,31,35] With oral contraceptive use for 4, 8, or 12 years, the risk of ovarian cancer is reduced by 40%, 53%, and 60%, respectively.[36] In a collaborative meta-analysis of 45 epidemiologic studies from 21 countries, the use of oral contraceptives was significantly associated with a decreased risk of ovarian cancer in every user (hazard ratio [HR] 0.73, $P < .0001$), with larger reductions observed for a longer duration of use.[37] The authors conclude that 200,000 ovarian cancers and 100,000 deaths have been prevented since the introduction of oral contraceptives 50 years ago.

Other patient-related risk factors such as polycystic ovarian disease and endometriosis may act through hormonal mechanisms attributable to elevated gonadotropins or by chronic inflammation. In a meta-analysis of eight case-control studies, women with polycystic ovarian disease had a 2.5-fold increase in ovarian cancer risk.[38] Endometriosis has been shown to be an independent risk factor for ovarian cancer with an estimated rate of malignant transformation of 2.5%.[39] Ovarian cancers that arise from endometriosis are most often low-grade tumors with endometrioid or clear cell histology and are associated with a better prognosis.[40] Altered hormonal levels such as elevated androgens may also increase risk, whereas progestins have been shown to be protective.[41] Large prospective cohort studies have demonstrated an increase in ovarian cancer risk and mortality with the use of exogenous estrogen and hormone replacement therapy.[42-44] Surgical procedures, including hysterectomy and tubal ligation, are independently associated with a 34% reduction each in ovarian cancer risk, although the protective mechanism is unknown.[29,45-47] Chronic inflammatory conditions such as pelvic inflammatory disease and tuberculous salpingitis were once believed

to be causative factors in the development of fallopian tube malignancies, although this theory remains unproven.

Genetic Factors

Heredity tumors account for 10% to 15% of all ovarian cancers, and family history is the strongest risk factor after increasing age.[48,49] The risk of developing ovarian cancer in the general population is approximately 1.4%, whereas the lifetime risk for a woman with one first-degree family member with ovarian cancer is 5% and climbs to 7% with two first-degree relatives. If a hereditary syndrome is present, the lifetime risk is on the order of 25% to 50%, with an age of diagnosis approximately 10 years younger than women with sporadic disease.[50]

Three distinct familial ovarian cancer syndromes have been identified by pedigree analysis with autosomal dominant patterns of inheritance.[51,52] *BRCA1* and *BRCA2* mutations are the most common genetic alterations, with up to 90% of all hereditary cases associated with a deleterious mutation of the *BRCA1* gene, located on chromosome 17q21, or the *BRCA2* gene, located on chromosome 13q22. The lifetime risk of ovarian cancer is approximately 40% in *BRCA1* mutation carriers and 18% in *BRCA2* mutation carriers.[53] BRCA-associated ovarian cancers are the most frequently invasive serous adenocarcinomas and less likely borderline or mucinous tumors.[54] Mutation carriers are also more likely to present with advanced-stage disease and have poorly differentiated tumors.[55] Nonetheless, *BRCA1* or *BRCA2* mutation carriers have a more favorable clinical course with a significantly longer recurrence-free and overall survival compared to noncarriers. The improved outcome appears related to a higher sensitivity to platinum chemotherapy across the first and subsequent lines of treatment.[56-60]

The importance of the fallopian tube in the pathogenesis of extrauterine serous carcinoma was initially recognized in *BRCA1* and *BRCA2* mutation carriers. In a prospective study of 483 *BRCA1* mutation carriers, the incidence of fallopian tube cancer was reported as 120 times that of the general population.[61] High-grade serous primary peritoneal carcinomas are also frequently observed in mutation carriers.[62] Further attention was focused on the fallopian tube as the primary site of origin following reports of epithelial dysplasia and occult serous carcinomas in prophylactic salpingo-oophorectomy specimens from mutation carriers.[63-66] In contrast to the

standard pathologic sampling of the ampullary region of the fallopian tube in ovarian cancer cases, more extensive complete sectioning of the tube revealed an abundance of lesions in the fimbria of the distal tube.[14-16] The detection of early serous carcinomas, or STICs, lent further support to the emerging concept of the fallopian tube as the primary site for extrauterine serous carcinoma. In this context, the national cancer guidelines recommend that any woman with a diagnosis of ovarian, fallopian tube, or primary peritoneal carcinoma be referred to a cancer genetics professional for consideration of BRCA mutation testing. BRCA screening in a population of women with nonmucinous ovarian cancer detected germline mutations in 14% of women, including 22% with high-grade serous cancer, reinforcing the importance of offering testing to all patients.[67]

Hereditary nonpolyposis colorectal syndrome, or Lynch type II cancer syndrome, is responsible for the remaining 10% of hereditary ovarian cancers.[68] In this syndrome, germline mutations of DNA mismatch repair genes lead to an increased risk of colorectal, stomach, endometrial, and ovarian cancer owing to underlying microsatellite instability. A total of seven mismatch repair genes have been identified, with mutations in *MLH1* and *MSH2* accounting for 90% of the observed mutations in Lynch syndrome families.[69,70] Mutations in *MSH6* and *PMS2* have been reported in the remaining 10% of families, whereas alterations in the remaining three identified genes are uncommonly observed. Inactivating mutations in specific genes may modify the underlying cancer predisposition. Women with *MSH6* mutations are twice as likely to develop endometrial cancer compared to carriers of *MSH2* or *MLH1* gene mutations, which are the most common alterations underlying colorectal cancer risk.[71] Women with *MSH2* gene mutations have been shown to have a risk of epithelial ovarian cancer twice that of *MLH1* carriers. In contrast to *BRCA1* and *BRCA2* mutation carriers, women with Lynch syndrome may present with a variety of nonserous epithelial tumor types, including endometrioid and clear cell histologies. Ovarian cancer associated with Lynch syndrome is more often diagnosed at an earlier stage with well- to moderately differentiated tumor grade. The lifetime risk of ovarian cancer in women with Lynch syndrome is estimated at 3% to 14% and is most commonly diagnosed in the fifth decade of life.[72] In women with a family or personal history suggestive of Lynch syndrome, tumor testing may be performed by microsatellite instability analysis or

immunohistochemical staining for mismatch repair genes. Direct sequencing of the mismatch repair genes is used for the detection of germline mutations. Other less common germline mutations have been identified by genomic sequencing and involve the following genes: *PALB2, BARD1, BRIP1, RAD51C, RAD51D, MSH2, MLH1, PMS2*, and *MSH6*.[73]

Other genetic disorders linked with nonepithelial ovarian cancers include Peutz-Jeghers syndrome, which is associated with an increased risk of sex cord-stromal tumors, and gonadal dysgenesis, associated with dysgerminomas and gonadoblastomas.

Environmental Factors

Environmental or physical causes of ovarian cancer have been investigated through numerous case-control studies. Women in developing countries have a lower incidence of ovarian cancer than those living in industrialized nations,[74] although, to date, no specific chemical carcinogens have been identified. Chronic exposure to asbestos-related products, including talc products, has long been implicated in the development of ovarian cancer.[75] The Nurses' Health Study reported a modestly elevated risk of invasive serous cancers with talc use (relative risk [RR] 1.4), although no association was detected with overall ovarian cancer risk.[76] The development of mucinous ovarian cancer has been found to be associated with cigarette smoking (RR 2-2.2), but not with other epithelial subtypes.[77,78]

Dietary and metabolic factors have also been explored in large population-based studies as possible contributors to ovarian cancer risk. To date, there have been no consistent associations of coffee or alcohol consumption with increased risk. Large epidemiologic studies also showed no relationship between consumption of animal fat and the development of ovarian cancer.[79,80] In a Swedish population–based cohort study of the effect of body mass index on cancer risk in greater than 35,000 women, a 36% higher risk of cancer was observed in obese women (body mass index $\geq$ 30) relative to women with body mass index in the normal range (18.5-25); cancer sites most strongly related to obesity were endometrium, ovary (risk for top quartile 2.09; 95% confidence interval [CI], 1.13-4.13), and colon.[81] Obesity has also been associated with increased ovarian cancer mortality in a large prospective study of adults in the United States.[82] There is no clear relationship between exercise and ovarian cancer risk.

SCREENING

In the absence of a reliable screening test, most women with ovarian cancer are diagnosed with advanced-stage disease. In contrast to women with localized disease (stage I/II) who have estimated 5-year survival rates of 70% to 90%, overall survival for women with advanced disease (stage III/IV) is poor, ranging from 20% to 45% (Table 78.3). The low sensitivity and specificity of the available screening modalities and the low prevalence of the disease in the general population have hindered the development of a robust screening test. Recent screening approaches have been associated with a low positive predictive value and unacceptable false-positive rates without impacting disease mortality in the general population or high-risk groups.

TABLE 78.3 EPITHELIAL OVARIAN CANCER STAGE DISTRIBUTION AND SURVIVAL BY STAGE

FIGO Stage	Patients (*n* = 4,825) (%)	5-Yr Overall Survival (%)
IA	13	90
IB	1	86
IC	14	83
IIA	2	71
IIB	2	66
IIC	5	71
IIIA	3	47
IIIB	6	42
IIIC	42	33
IV	13	19

FIGO, International Federation of Gynecology and Obstetrics.

Adapted from Heintz APM, Odicino F, Maisonneuve P, et al. Carcinoma of the ovary. FIGO 26th annual report on the results of treatment in gynecological cancer. *Int J Gynaecol Obstet.* 2006;95(suppl 1):S161-S192. Copyright © 2006 International Federation of Gynecology and Obstetrics. Reprinted by permission of John Wiley & Sons, Inc.

Several screening strategies have been investigated, including pelvic examination, the serum tumor marker cancer antigen 125 (CA-125), and transvaginal ultrasound (TVUS), either alone or in combination.[83] CA-125 values greater than 35 U/mL are observed in 80% of patients with epithelial

ovarian cancer, including 90% of women with advanced-stage disease, but only in 50% of early-stage patients.[84] CA-125 is nonspecific for ovarian cancer, as it can be elevated in benign gynecologic and nongynecologic conditions, including endometriosis, uterine leiomyoma, cirrhosis, pelvic inflammatory disease, the presence of pleural or peritoneal fluid, as well as endometrial carcinoma and nongynecologic cancers of the breast, lung, and pancreas. Screening with CA-125 alone has been found to lack specificity in an average-risk population of postmenopausal women. Ultrasound alone is able to detect early-stage disease in an average-risk population,[85-87] although the significant false-positive rate remains a concern. In a United Kingdom multimodality screening study, diagnostic surgeries were performed 9 times more frequently to detect one cancer in the group screened by TVUS alone compared to multimodality screening (CA-125 and TVUS).[88]

Several large screening trials currently in progress in the United States, the United Kingdom, and Japan have been designed to assess reduction in mortality with early detection of ovarian cancer. The Prostate, Lung, Colorectal, and Ovarian Cancer screening trial in the United States randomized 78,216 women aged 55 to 74 years to annual screening with CA-125 and TVUS versus usual medical care. Following baseline screening, 570 surgical procedures, including 325 laparotomies, were performed; 29 tumors were detected, 9 of which were of LMP.[89] The positive predictive value for the detection of invasive ovarian cancer was 3.7% for an abnormal CA-125, 1.0% for an abnormal TVUS, and 23.5% for both. Publication of the mortality data with 12-year follow-up showed no difference in the stage of cancer detected by screening (90% stage III or IV) and no reduction in cause-specific or overall mortality for women who underwent screening.[90] Furthermore, diagnostic evaluation for women with false-positive screening resulted in a serious complication rate of 15%.

A second trial, the United Kingdom Collaborative Trial of Ovarian Cancer Screening, has accrued greater than 200,000 postmenopausal women to evaluate multimodality screening with TVUS and serum CA-125. In the prevalence screen, the sensitivity, specificity, and positive predictive values of multimodality screening for invasive epithelial ovarian and tubal cancers were 89.5%, 99.8%, and 35.1%, respectively.[88] The initial results of baseline screening were more promising than the U.S. study, with 43% of invasive cancers detected as stage I or II, which may reflect differences in study

design and the diagnostic algorithm. However, after a median follow-up of 11 years, a significant mortality reduction with multimodality screening was not observed.[91] The multicenter, randomized Japanese study utilizes a similar screening strategy with TVUS and CA-125 and has accrued greater than 80,000 women. Unlike the U.S. and UK trials, there was a nonsignificant trend for the detection of more stage I cancers in the screened population (63% vs 38%), although mortality rates have not yet been reported.[92]

The present data do not support routine screening for ovarian cancer in the general population. All of the North American expert groups, including the U.S. Preventive Services Task Force, the American College of Obstetricians and Gynecologists, the Society of Gynecologic Oncologists (SGO), and the Canadian Task Force on the Periodic Health Examination, recommend against routine screening in asymptomatic women. The incidence of ovarian cancer is relatively low in the general population; thus, the concerns for false-positive screening and the associated risks of exploratory surgery are significant.[93] However, women at high risk for ovarian cancer with *BRCA1* or *BRCA2* mutations or hereditary nonpolyposis colorectal syndrome could potentially benefit from chemoprevention; screening with pelvic examinations, TVUS, and CA-125 on a biannual or annual basis; or prophylactic surgery.[94] Although the efficacy of screening has been disappointing in the high-risk population,[95] some physicians will follow women with high-risk factors, such as *BRCA* mutation or family history, with pelvic examination, CA-125, and TVUS. The U.S. National Institutes of Health Consensus Development Panel recommends that prophylactic salpingo-oophorectomy be considered in women with ovarian cancer syndromes at age 35 years or after childbearing is complete, as the risk reduction with salpingo-oophorectomy is 80%.[96,97] Removal of the ovaries also reduces the risk of breast cancer in BRCA mutation carriers.[98]

HISTOLOGIC CLASSIFICATION

The World Health Organization and International Federation of Gynecology and Obstetrics (FIGO) have adopted a unified classification of the common epithelial, germ cell, sex cord, and stromal tumors[99,100] (Table 78.4). Most ovarian malignancies (60%-65%) are epithelial, with germ cell tumors (20%), sex cord-stromal tumors (5%), and metastases to the ovary (5%-10%) accounting for the remainder.[101] Serous tumors are most common, comprising

50% to 60% of epithelial tumors. Other subtypes include mucinous carcinoma in 10%; endometrioid carcinoma, 8%; clear cell carcinoma, 3% to 5%; transitional, 3% to 5%; and undifferentiated carcinoma, 1%. Bilateral presentation occurs frequently in epithelial tumors, most commonly in serous tumors followed by endometrioid (15%) and mucinous tumors (5%-10%).

TABLE 78.4 WORLD HEALTH ORGANIZATION CLASSIFICATION OF OVARIAN TUMORS

Serous low-grade carcinoma
Serous high-grade carcinoma
Mucinous carcinoma
Endometrioid carcinoma
Clear cell carcinoma
Malignant Brenner tumor
Seromucinous carcinoma
Undifferentiated carcinoma
Germ cell tumors
Dysgerminoma
Yolk sac tumor
Embryonal carcinoma
Nongestational choriocarcinoma
Mature teratoma
Immature teratoma
Mixed germ cell tumor
Germ cell and sex cord-stromal tumors
Mixed germ cell-sex cord-stromal tumor, unclassified
Gonadoblastoma
Sex cord-stromal tumors
Pure sex cord tumors
Adult granulosa cell tumor
Juvenile granulosa cell tumor
Sertoli cell tumor
Sex cord tumor with annular tubules
Pure stromal tumors
Fibroma
Cellular fibroma
Thecoma
Luteinized thecoma associated with sclerosing peritonitis
Fibrosarcoma
Sclerosing stromal tumor
Signet-ring stromal tumor
Microcystic stromal tumor
Leydig cell tumor
Steroid cell tumor

Mixed sex cord-stromal tumors
Sertoli-Leydig cell tumors
Sex cord-stromal tumors, NOS
Monodermal teratoma and somatic-type tumors arising from a dermoid cyst
Struma ovarii
Carcinoid
Neuroectodermal-type tumors
Sebaceous tumors
Carcinomas
Mixed epithelial and mesenchymal tumors
Carcinosarcoma
Adenosarcoma

NOS, not otherwise specified.

High-grade serous carcinomas are often widely disseminated at diagnosis and account for most deaths from ovarian, tubal, and peritoneal cancers. In contrast, 5-year survival for low-grade serous carcinoma is 85%. Most serous tumors present as large ovarian masses and grossly appear nodular with multiple papillary projections and cysts filled with clear serous fluid. A two-tier grading system separates high-grade serous carcinomas from low-grade tumors,[102,103] which have a similar prolonged natural history to noninvasive borderline tumors, or tumors of LMP.[104] As discussed previously, there is increasing evidence that high-grade serous carcinomas originate in the fimbria of the fallopian tube and may spread rapidly to the adjacent ovary and peritoneal sites. Low-grade tumors appear to follow a stepwise progression from borderline tumor to invasive carcinoma and involve molecular pathways distinct from their high-grade counterparts.[105-107] Although treatment is similar for all serous tumors, low-grade tumors have been shown to be less responsive to chemotherapy.[104,108,109]

LMP or borderline tumors have nuclear abnormalities and mitotic activity intermediate between benign and malignant tumors of similar cell type but lack stromal invasion (Figure 78.3). Borderline tumors are a subcategory of ovarian malignancies that account for 10% to 20% of all epithelial neoplasms.[110,111] The prognosis, surgical approach, and postoperative treatment recommendations are vastly different as compared with those of their invasive counterparts. The majority of LMPs (75%) present with stage I disease, which directly contrasts with the 75% advanced stages in the invasive epithelial tumors. The 5- and 10-year survival rates for women with

LMP tumors are more than 95%. Significant heterogeneity exists in the biologic behavior of borderline tumors. Women with nonlocalized LMP tumors of the ovary have decreased survival compared to those with localized LMP tumors, but this is similar to that of women with localized, well-differentiated epithelial ovarian carcinoma.[112] Other pathologic features that affect prognosis include the cell type, tumor stage, implant type (invasive vs noninvasive), the presence of micropapillary architecture, and microinvasion. Extensive sampling of all pathologic specimens is required to firmly establish the diagnosis.

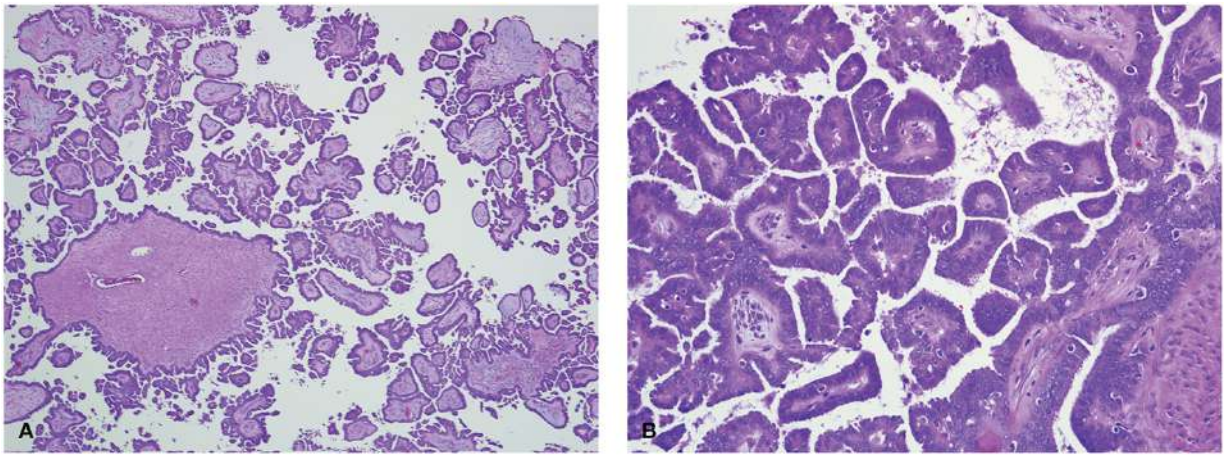

FIGURE 78.3 Serous tumor of low malignant potential of the ovary at low power (A) and high power (B). At low power, note the progressively branching papillary fronds with fibrovascular support and detached papillary clusters; at high power, note the serous epithelium with nuclear hyperchromasia and cytologic atypia. By definition, there is no destructive stromal invasion.

Most endometrioid and clear cell carcinomas arise in foci of endometriosis and follow an adenoma to borderline tumor to carcinoma sequence. Endometrioid carcinoma of the ovary resembles its endometrial counterpart (Figure 78.4), and synchronous primary cancers are detected in 10% of women with ovarian cancer and 5% of women with endometrial cancer.[113] Bilateral ovarian involvement, small multinodular ovaries, and surface and hilar spread suggest metastatic involvement from an endometrial primary, particularly if the endometrial tumor is high grade, deeply invasive, and associated with lymphovascular invasion. A large, cystic, unilateral tumor of low grade arising in a focus of endometriosis likely represents a primary ovarian tumor. Endometrioid tumors appear to have a better prognosis than

serous cancers, regardless of tumor stage.[114] Multiple synchronous primary tumors may represent a field defect related to endometriosis, which is associated with improved survival.[115]

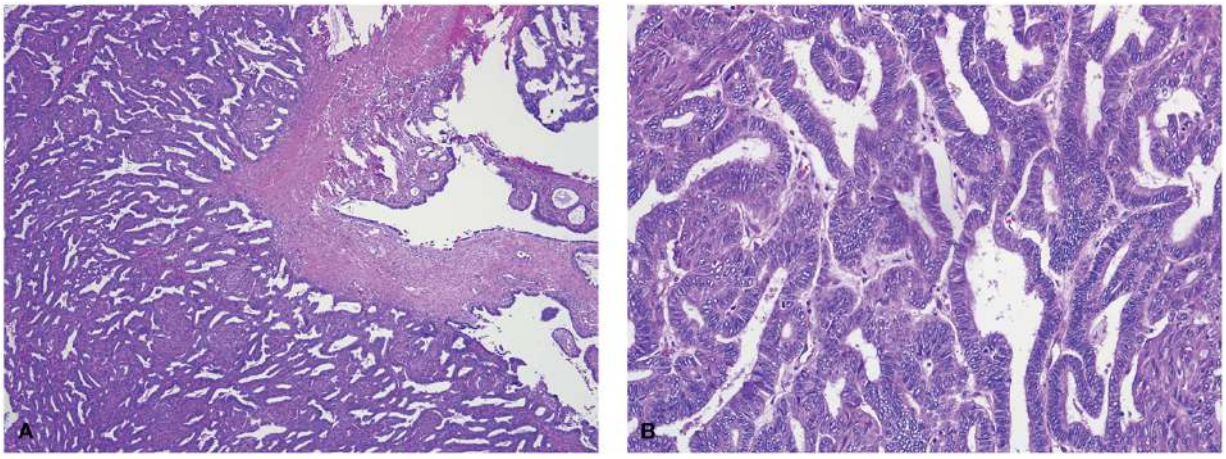

FIGURE 78.4 Endometrioid adenocarcinoma of the ovary. A. At low power, note the tumor composed of back-to-back endometrioid glands. B. At high power, note the squamous metaplasia, commonly seen in this epithelial variant. Assignment of tumor grade is based on similar criteria as for carcinomas arising in the endometrium. This tumor would qualify as well differentiated or grade 1.

Mucinous tumors follow a similar progression from cystadenoma to borderline tumor prior to invasion. All subtypes are more likely to be diagnosed when confined to the ovary. Mucinous cancers may grow to a very large size, often measuring up to 20 cm in diameter and filled with large pockets of thick, necrotic, mucinous debris.[116,117] Ovarian mucinous tumors closely resemble mucin-secreting tumors originating from other sites—most commonly the gastrointestinal tract. The pathologic distinction between primary and metastatic mucinous carcinoma may be challenging, despite the use of immunohistochemical analysis. Further clinical evaluation is often required to exclude a clinically occult nonovarian primary source. Secondary involvement of the ovary may also occur in association with pseudomyxoma peritonei arising from a low-grade tumor often of appendiceal origin.[118]

Clear cell carcinoma is characterized by clear and hobnail cells with a similar histologic appearance to clear cell carcinoma of the kidney, endometrium, and vagina. Ovarian clear cell carcinoma is often seen in association with venous thromboembolism and hypercalcemia. Although more likely to be stage I than serous carcinoma, clear cell histology is

associated with a lower response rate to platinum-based chemotherapy, higher recurrence rate, and worse survival.[119] The transitional cell tumors, including Brenner tumors, are benign in most cases (98%) and carry a favorable prognosis.

Ovarian germ cell tumors comprise less than 5% of ovarian malignancies and are classified by the World Health Organization (Table 78.4). Dysgerminomas are the most common of the germ cell tumors and occur bilaterally in 10% to 20% of cases. The other germ cell tumor types are typically unilateral. Endodermal sinus tumors, also known as yolk sac tumors, are characterized by Schiller-Duval bodies. Embryonal carcinomas are rare and tend to occur in younger populations; they may be seen with nongestational choriocarcinomas as part of mixed germ cell tumors (10% of all germ cell tumors). Immature teratomas are characterized by immature elements from the germ layers. The grade, treatment recommendations, and outcome are directed by the amount of immature neural elements.

Sex cord-stromal tumors are also classified by the World Health Organization (Table 78.4), with granulosa cell tumors being the most common (70%). Histologically, the granulosa cell tumors are composed of granulosa cells that have a pale, grooved, "coffee bean" nucleus or a rosette of cells surrounding eosinophilic material, a Call-Exner body. Thecomas (hormonally active) and fibromas (hormonally inactive) are both clinically benign tumors and are most common in middle-aged women.

The most common histopathology of primary fallopian tube malignancies is papillary serous adenocarcinoma. Other less common Müllerian subtypes include endometrioid, clear cell, and malignant mixed Müllerian tumors.[120,121] Rare reports of squamous cell carcinoma, immature teratoma, glassy cell tumor, and sarcoma have also been described. Benign tumors are found even less frequently than malignant neoplasms. Metastatic involvement of the fallopian tube is reported in up to 12% of women with uterine cancer and 4% with cervical cancer.[122,123]

PATTERNS OF SPREAD

The primary mode of spread for epithelial ovarian and fallopian tube cancers is transperitoneal, as malignant cells exfoliate into the peritoneal cavity. IP spread is favored by intestinal peristalsis and negative hydrostatic pressure below the diaphragm. The exfoliated tumor cells follow the intra-abdominal

fluid stream passing along the paracolic gutters toward the diaphragm, predominately on the right side, before implantation on any peritoneal surface.[124,125] Metastatic deposits are frequently seen in the posterior cul-de-sac, paracolic gutters, diaphragmatic surfaces, liver capsule, intestinal surfaces, and omentum. Metastases may also be found in the uterus or contralateral ovary from peritoneal spread or flow through the fallopian tubes. Dense tumor "caking" can cause infiltration into the abdominal organs creating a mass effect on the omentum, ureter, bowel, liver, pancreas, spleen, or adrenals, resulting in advanced disease stage at presentation with associated ascites.

Lymphatic drainage constitutes the second most common pattern of spread. The lymphatic capillaries of the ovary converge on the hilus and follow the ovarian blood vessels in the infundibular ligament to drain to the para-aortic nodes at the level of the renal hilum. Lymphatics also drain along the broad ligament to the hypogastric and external iliac nodes in the pelvis. Less frequently, spread can occur to the inguinal nodes via the round ligament.[126] Approximately 10% to 15% of women with disease that appears confined to the ovary have para-aortic lymph node involvement,[127] which becomes increasingly common in advanced-stage disease. Because of the rich lymphatic supply of the fallopian tubes, lymph node involvement is common, even in the absence of tubal musculature involvement.[128] Pelvic and para-aortic lymph node involvement has been reported in 10% to 30% of women with fallopian tube cancer at diagnosis.[129]

Transdiaphragmatic spread occurs in the pleural cavity and is the most common finding in stage IV disease. Hematogenous spread is infrequent at the time of presentation, with only 2% to 3% of patients with parenchymal liver or lung disease. Brain metastasis is also rare. However, more than 50% of recurrences occur both within and outside the peritoneal cavity at the time of treatment failure.

CLINICAL PRESENTATION

As ovarian cancer has insidious growth and is asymptomatic in early-stage disease, most women do not present until symptoms arise from advanced disease progression. Vague gastrointestinal complaints of dyspepsia, nausea, early satiety, bloating, constipation, or obstipation are common presenting symptoms, as are genitourinary symptoms including frequency, urgency, or

incontinence. Other ill-defined symptoms include fatigue, back pain, pain with intercourse, and menstrual irregularities. These nonspecific symptoms can be present for several months but may not trigger diagnostic evaluation until after the symptoms fail to clear with other medical therapy.[130] Detection of early-stage disease may occur by palpation of an asymptomatic adnexal mass on routine examination, although most adnexal masses require moderate size for palpation. In premenopausal women, most of these masses are benign, as ovarian cancer represents less than 5% of adnexal neoplasms. An adnexal mass in a postmenopausal woman has a higher likelihood of malignancy, and surgical exploration is often indicated. Physical examination findings such as a fixed pelvic mass, palpable upper abdominal mass, and ascites are highly suggestive of an ovarian malignancy. According to a consensus statement on the symptoms of ovarian cancer published by the Gynecologic Cancer Foundation, SGO, and American Cancer Society, new and persistent symptoms of bloating, pelvic or abdominal pain, difficulty eating, early satiety, or urinary urgency or frequency should prompt women to seek medical evaluation.

A portion of women with fallopian tube carcinoma may present with early clinical signs and symptoms. Two triads have been described as pathognomonic for fallopian tube malignancy: (a) pelvic pain, pelvic mass, and leukorrhea and (b) vaginal bleeding, vaginal discharge, and lower abdominal pain. However, the percentage of patients presenting with either triad of symptoms has been reported as low as 11%.[131] Another classic sign—hydrops tubae profluens—is a sudden emptying of accumulated fluid in the distended fallopian tube that causes profuse, watery, serosanguinous vaginal discharge. The discharge is often accompanied by a decrease in pelvic mass size on physical examination. In a meta-analysis of 122 patients with primary fallopian tube cancer, hydrops tubae profluens was a presenting sign in only 9%.[122] In other series,[125,128] it has been specifically reported that neither a triad nor hydrops tubae profluens was present in any of the patients reviewed. When clinically apparent, the fallopian tube may be dilated and mimic more benign pathologic processes such as hydrosalpinx, pyosalpinx, or hematosalpinx.[132] In more advanced disease with tubal wall invasion, extension of a necrotic mass to involve the ovary may give the initial impression of a tubo-ovarian abscess.

Germ cell and stromal cell malignancies present at an earlier stage than epithelial ovarian or fallopian tube cancers, often related to abdominal discomfort or symptoms of excessive estrogen or androgen production. Granulosa cell tumors may lead to precocious puberty in young girls, and Sertoli-Leydig cell tumors may cause virilization.

DIAGNOSTIC WORKUP

Evaluation of a pelvic mass will be influenced by the patient's age, clinical presentation, and imaging features. An ovarian mass is more likely to be a malignant neoplasm in the pediatric, perimenopausal, and postmenopausal age groups and benign during the reproductive years. Ultrasound is often the first, noninvasive step for the evaluation of a pelvic mass. Sonographic characteristics suggestive of malignancy include irregular borders, a solid component that is not hyperechoic and often nodular or papillary, Doppler demonstration of flow in the solid component, dense multiple irregular septa (>2-3 mm), and the presence of ascites, peritoneal masses, enlarged nodes, or matted bowel. Computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and pelvis (performed with contrast) may be useful preoperatively to assess disease extent for surgical planning.[133-135] Fluorodeoxyglucose positron emission tomography CT may also be used to characterize indeterminate lesions and has increased sensitivity for the detection of occult metastatic disease when compared with CT alone or MRI, although further study is warranted.[136-138] Although limited as a screening tool, an elevated CA-125 level may suggest a more advanced or greater bulk of disease and high-grade serous histology but in general is a weak predictor of surgical resection.[139,140] Human chorionic gonadotropin (β-hCG), α-fetoprotein (AFP), total inhibin, and lactate dehydrogenase levels may aid in the diagnosis of and treatment for nonepithelial germ cell ovarian tumors, particularly in women younger than age 35 years with a pelvic mass.[141,142]

Other conditions may mimic ovarian cancer in their presentation, including colon, gastric, and appendiceal carcinomas as well as metastatic breast cancer and primary lymphoma.[143] Although ideally the primary site of disease is determined in the preoperative setting, the diagnosis often cannot be made accurately until the time of surgery, and frozen section pathologic evaluation may guide the surgical approach. Among gynecologic malignancies, primary endometrial and cervical cancer may also present with an adnexal mass, and

synchronous tumors of the ovary and endometrium have been reported in up to 10% of women, often in the setting of Lynch syndrome or an estrogen-secreting tumor.[113,115] Primary malignancies of the fallopian tube have been difficult to diagnose prior to surgical exploration, as the clinical presentation may be similar to that of salpingitis, ovarian abscess, pelvic inflammatory disease, or even ectopic pregnancy. Occult tubal primaries may be detected only by careful pathologic processing of the fimbriated tubal end.[144]

Referral to a gynecologic oncologist should be considered for any woman with a suspicious pelvic mass, family history of ovarian or fallopian tube cancer, or elevated CA-125.[145] Initial evaluation should include a thorough history and full physical and pelvic examination, laboratory studies (complete blood count, chemistries), and imaging (abdominal and pelvic CT/MRI, directed ultrasound, chest x-ray, or CT). National cancer guidelines do not recommend the use of biomarkers such as CA-125 or HE4 for determining the status of an undiagnosed pelvic mass. However, a baseline CA-125 drawn prior to surgery may be useful in follow-up to evaluate treatment response and monitor for recurrence. Further evaluation with mammography, upper gastrointestinal endoscopy, or colonoscopy may be indicated in some scenarios to exclude an extraovarian primary cancer.[146] If possible, fine-needle aspirate (FNA) for diagnostic purposes should be avoided in patients with presumed early-stage disease to prevent cyst rupture and tumor spillage, although it is often necessary in patients with bulky, nonoperable disease. Comorbid conditions may prompt additional evaluations, including cardiac risk assessment, pulmonary function testing, and nutritional evaluation.

SURGICAL STAGING

Surgical advances in staging and the therapeutic benefit of a maximal safe tumor resection have improved the progression-free and overall survival of women with ovarian cancer over the past two decades. Surgical staging for ovarian cancer is based on the FIGO staging system as shown in Table 78.5,[147] which was updated in 2024 and approved by the American Joint Committee on Cancer. The 2021 staging system combines the ovary, fallopian tubes, and primary peritoneal cancers.

TABLE 78.5 FIGO STAGING FOR OVARIAN, FALLOPIAN TUBAL, AND PERITONEAL CARCINOMA

Stage I Tumor limited to the ovaries or fallopian tube(s)
IA Tumor limited to 1 ovary; ascites and peritoneal washings negative for malignant cells. No tumor on the external surface of ovary or fallopian tube; ovarian capsule intact
IB Tumor limited to both ovaries or fallopian tubes; ascites and peritoneal washings negative for malignant cells. No tumor on the external surfaces of ovaries or fallopian tubes; ovarian capsules intact
IC Tumor stage IA or IB, and including any of the following:
IC1: Surgical spill of ovarian or fallopian tube contents
IC2: Ovarian capsule ruptured before surgery, or tumor on surface of the ovaries or fallopian tube(s)
IC3: Ascites or peritoneal washings positive for malignant cells

Stage II Tumor involving 1 or both ovaries with pelvic extension or primary peritoneal cancer
IIA Extension and/or implants on the uterus and/or fallopian tubes and/or ovaries
IIB Extension to other intraperitoneal pelvic tissues (below pelvic brim)

Stage III Tumor involving 1 or both ovaries or fallopian tubes, or primary peritoneal cancer, with pathologically confirmed peritoneal implants outside the pelvis and/or positive retroperitoneal lymph nodes
IIIA1 Tumor grossly limited to the true pelvis, but with pathologically confirmed retroperitoneal lymph nodes or microscopic seeding of extrapelvic peritoneal surfaces (above the pelvic brim)
IIIA1(i): Metastasis up to 10 mm in greatest dimension
IIIA1(ii): Metastasis >10 mm in greatest dimension
IIIA2: Microscopic extrapelvic (above the pelvic brim) peritoneal sites, with or without retroperitoneal nodal involvement
IIIB Macroscopic peritoneal metastases involving extrapelvic peritoneal surfaces up to 2 cm in greatest dimension, with or without retroperitoneal nodal involvement
IIIC Macroscopic peritoneal metastases involving extrapelvic surfaces >2 cm in greatest dimension, with or without retroperitoneal nodal involvement. Tumor may extend to the capsule of the liver or spleen without parenchymal involvement.

Stage IV Presence of distant metastasis outside the peritoneal cavity
IVA: Pleural effusion with positive cytology
IVB: Parenchymal metastasis (including the liver and spleen) and metastases to extra-abdominal organs, including the inguinal lymph nodes and nodal basins outside the abdomen and pelvis

FIGO, International Federation of Gynecology and Obstetrics.
Adapted from Berek JS, Renz M, Kehoe S, Kumar L, Friedlander M. Cancer of the ovary, fallopian tube, and peritoneum: 2021 update. *Int J Gynaecol Obstet*. 2021;155 suppl 1(suppl 1):61-85. http://creativecommons.org/licenses/by/4.0/.

Comprehensive surgical staging is the mainstay of diagnosis and initial treatment for ovarian, fallopian tube, and peritoneal cancers. Based on

improved outcomes, surgical staging and cytoreduction should be performed by a gynecologic oncologist.[148,149] In apparent early-stage cancers, surgical evaluation is required for accurate pathologic staging to guide adjuvant treatment recommendations. In patients with advanced disease, surgery represents the initial treatment by providing optimal cytoreduction. Comprehensive surgical staging begins with an exploratory laparotomy via a vertical midline incision followed by a collection of peritoneal washings or any ascitic fluid for cytology. Select patients with early-stage disease may be candidates for minimally invasive procedures if performed by an experienced gynecologic oncologist.[150-152] The surgeon performs a thorough inspection of all visceral and peritoneal surfaces within the abdomen and pelvis, with particular attention to the intestinal serosal surfaces, mesentery, paracolic gutters, hemidiaphragms, gallbladder, and liver. Any peritoneal surface or adhesion that is suspicious for metastasis should be excised or biopsied. In the absence of suspicious areas, random peritoneal biopsies should be taken from the pelvis, paracolic gutters, and/or undersurfaces of the hemidiaphragms. Total hysterectomy, bilateral salpingo-oophorectomy, and omentectomy should be performed with intact removal of the adnexal mass when possible. National cancer guidelines state that pelvic and para-aortic nodal dissection should be performed in patients with pelvic-confined disease or extrapelvic implants measuring 2 cm or less (presumed stage IIIB disease), although recent level 1 data suggest that there is not a therapeutic benefit for lymphadenectomy in clinically node-negative patients with advanced disease.[153] Every effort should be made to achieve maximal cytoreduction of all gross disease in the pelvis, abdomen, and retroperitoneum.[154] In patients with advanced disease, bowel resection and/or appendectomy, diaphragm stripping, splenectomy, partial cystectomy and/or ureteroneocystostomy, partial hepatectomy, partial gastrectomy, cholecystectomy, and/or distal pancreatectomy may be considered. In the operative report, the surgeon should describe the following: (1) the extent of initial disease prior to cytoreduction, (2) the amount of residual disease following cytoreduction, and (3) whether a complete or incomplete resection was performed (including a description of the size and number of residual lesions).[155] In select cases, preservation of the contralateral unaffected ovary and the uterus can be achieved in young women wishing to retain fertility who have stage I (stage 1A or 1C, but not 1B) and/or low-risk tumors (early-stage, low-grade

invasive tumors, LMP/borderline lesions, or malignant stromal or germ cell tumors).[156,157] In the setting of unilateral salpingo-oophorectomy, comprehensive surgical staging should be performed to exclude occult disease. Exceptions to upfront surgical management include patients with significant medical comorbidities who are poor operative candidates and patients with a complex ovarian cyst where extraovarian disease has not been excluded. Neoadjuvant chemotherapy followed by interval cytoreduction may be considered in patients with bulky stage III or IV disease. Before initiation of neoadjuvant chemotherapy, the pathologic diagnosis should be confirmed by biopsy, FNA, or paracentesis. National cancer guidelines recommend that patients who are evaluated for neoadjuvant chemotherapy be seen by a fellowship-trained gynecologic oncologist before being deemed a nonsurgical candidate.

PROGNOSTIC FACTORS

Tumor stage, grade, histology, and optimal cytoreduction by a trained gynecologic oncologist are the most important determinants of survival for ovarian and fallopian tube cancer. Patients with FIGO stage 1A disease who have negative staging laparotomy have 5-year survival rates of 80% to 90%. If extrapelvic disease is detected at the time of surgical staging, the patient is upstaged to stage III disease with corresponding 5-year survival rates of 30% to 50%. Primary or interval cytoreductive surgery should be performed by a gynecologic oncologist based on published evidence of a 6- to 9-month median survival benefit.[148,149,158]

The volume of residual disease after primary surgery is also an important determinant of outcome.[159-164] The extent of cytoreduction may be defined as complete, no gross visible disease; optimal, residual disease that is 1 cm or less in maximal tumor diameter (Gynecologic Oncology Group [GOG] definition); or suboptimal, residual tumor nodules greater than 1 cm. Patients who have optimal cytoreduction of tumor have a 22-month improvement in median survival compared to those with suboptimal resection. In a meta-analysis of 18 studies, which included over 13,000 women with stage IIB or higher ovarian, tubal, or peritoneal carcinoma, each 10% increase in the proportion of patients undergoing complete cytoreduction showed a 2.3-month increase in median survival when compared to a 1.8-month increase for those with optimal cytoreduction.[164] Complete cytoreduction has also

been associated with improved response to chemotherapy and less platinum resistance.[163,165] Preoperative CA-125 measurement is not independently prognostic, as it likely reflects disease burden. In contrast, the half-life and nadir of CA-125 during induction chemotherapy are associated with improved outcome in ovarian and fallopian tube cancers.[121,166-170]

Although a strong correlation exists between histologic grade and stage, grade has independent prognostic significance, particularly in early-stage disease. Survival rates for stage I disease with grade 1, 2, or 3 tumors are 96%, 78%, and 62%, respectively.[171] The impact of histologic subtype on survival is less robust owing to other more important clinical variables, including stage, grade, and volume of disease. Patients with mucinous and endometrioid subtypes have improved survival rates compared to serous adenocarcinoma, predominately related to the earlier stage at presentation. Clear cell carcinomas appear to be more aggressive than other epithelial malignancies. The 5-year survival rate for stage I clear cell carcinoma is 60% and for other stages is less than 15%.[119] Younger patients also have a more favorable prognosis, as they are more likely to have tumors of lower grade and less aggressive histology, as well as better baseline performance status.[172]

MANAGEMENT OF EPITHELIAL TUMORS

Treatment for ovarian and fallopian tube cancer depends largely on the stage and grade of disease at presentation. Table 78.6 presents a general schematic for treatment recommendations for women with epithelial ovarian, fallopian tube, and primary peritoneal cancer.

TABLE 78.6 SCHEMATIC OF THE PRIMARY TREATMENT FOR EPITHELIAL OVARIAN CANCER

Low risk, early stage	
Stage IA/B, grade 1	Observation
Stage IA/B, grade 2	Observation or IV taxane/carboplatin for 3-6 cycles
High risk, early stage	
Stage IC, all grades Stage IA/B, grade 3	IV taxane/carboplatin for 3-6 cycles IV taxane/carboplatin for 3-6 cycles
Stage II	IV taxane/carboplatin for 6 cycles IP chemotherapy in optimally cytoreduced patients
Advanced stage	

Low risk, early stage	
Optimal cytoreduced stage III	IP chemotherapy IV taxane/carboplatin for 6 cycles Clinical trial
Suboptimal cytoreduced stage III/IV	IV taxane/carboplatin for 6 cycles Clinical trial Interval cytoreduction if indicated by tumor response and resectability

IP, intraperitoneal; IV, intravenous.

Early-Stage Disease

Surgical Therapy

Comprehensive surgical staging should be performed in all women with apparent early-stage disease to confirm that the cancer is confined to the adnexa. Fertility-sparing surgery with unilateral salpingo-oophorectomy may be considered in a small subset of women with stage IA disease if the contralateral ovary is normal in appearance.[173] In addition to abdominal exploration and full surgical staging, endometrial biopsy should be considered to sample the endometrium.

Postoperative Management

Early studies by the GOG and others have identified a small subgroup of patients with well- to moderately differentiated (grade 1 or 2) stage IA and IB tumors who have a low risk of relapse and may not require adjuvant therapy.[174,175] National cancer guidelines recommend that women with early-stage (FIGO IA or IB) grade 1 endometrioid carcinoma of the ovary may be treated with surgical resection and observation with expected 5-year survival rates on the order of 90%.[176] If observation is considered for women with early-stage grade 2 disease, full surgical staging should be performed.

Adjuvant Chemotherapy

Women with early-stage disease and a less favorable prognosis include patients with grade 3 tumors, clear cell histology, or disease extension beyond the ovarian capsule, positive peritoneal cytology, or pelvic extension or implants (stage IC or II). Various adjuvant treatment approaches have been investigated to improve clinical outcomes, although the optimal management

remains controversial. Few randomized trials have been conducted in this population, and they have been limited by small sample size and lack of power to demonstrate a survival advantage.

Nonetheless, two large multi-institutional trials conducted in Europe randomized women with early-stage ovarian cancer to platinum-based chemotherapy or observation following surgery (Table 78.7). The International Collaborative Ovarian Neoplasm 1 (ICON1) trial enrolled 477 women with FIGO IA-C ovarian cancer inclusive of all tumor grades and histologic subtypes.[177] Adjuvant chemotherapy consisted of six cycles of a platinum-based regimen per institutional preference. With a median follow-up of 9.2 years, 10-year recurrence-free survival was 67% for the chemotherapy arm and 57% for observation (HR 0.7, $P = .02$).[178] Overall survival also favored the chemotherapy group (72% vs 64%, $P = .06$). When stratified by histology and grade, the largest benefit for adjuvant chemotherapy was seen in patients with high-risk disease, defined as FIGO stage IA grade 3, stage IB or IC grades 2 and 3, or any clear cell histology. HRs for recurrence and death for the high-risk subset were 0.52 and 0.48, respectively (both $P < .01$). The second trial, Adjuvant Chemotherapy in Ovarian Neoplasm (ACTION), assigned 448 women with early-stage ovarian cancer to four to six cycles of platinum-based adjuvant chemotherapy or observation following surgery. Women with FIGO IA grade 2 and 3 diseases, all stages IC-IIA, or any clear cell histology were eligible for the trial. Recurrence-free survival, but not overall survival, was significantly improved in the chemotherapy group (70% vs 62% at 10 years).[179,180] The greatest benefit was seen in the subset of women with nonoptimal surgical staging. In a combined analysis of the ICON1 and ACTION trials, adjuvant chemotherapy was associated with significantly improved overall survival at 5 years (82% vs 74%) compared to observation.[181]

TABLE 78.7 RANDOMIZED STUDIES OF ADJUVANT CHEMOTHERAPY IN EARLY-STAGE OVARIAN CANCER

Trial	Stage	Study Design	Number of Patients	5-Y DFS%	5-Y OS%	Notes
Observation vs chemotherapy						
GOG (1990)	IA, IB grades	Observation	44	91	94	No survival difference; optimal staging

Trial	Stage	Study Design	Number of Patients	5-Y DFS%	5-Y OS%	Notes
	1-2					
		Melphalan	48	98	98	
ICON1 (2003, 2007)	I/II	Observation	236	62	70	Largest benefit for high-risk group; no surgical staging
		Platinum based	241	73[a]	79[a]	
ACTION (2003, 2010)	IA, IB grades 2-3	Observation	224	68	78	Optimal staging in 1/3
	IC-IIA all grades	Platinum based	224	76[a]	85	
	Clear cell					
Duration of chemotherapy						
GOG (2006, 2010)	IA, IB grade 3	3 cycles CT	232	75	81	No survival difference; greatest benefit for serous tumors
	IC-II all grades	6 cycles CT	225	80	83	
	Clear cell					

ACTION, Adjuvant Chemotherapy in Ovarian Neoplasm; CT, carboplatin and paclitaxel; DFS, disease-free survival; GOG, Gynecologic Oncology Group; ICON1, International Collaborative Ovarian Neoplasm 1; OS, overall survival.

[a]Statistically significant.

The GOG conducted a randomized trial to determine the optimal duration of adjuvant chemotherapy in women with high-risk, surgical stage I disease by comparing three versus six cycles of carboplatin and Taxol chemotherapy.[182] Rates of recurrence (25% vs 20%) and overall survival (81% vs 83%) were similar at 5 years for three and six cycles of chemotherapy, although six cycles were associated with significantly more toxicity, including neuropathy, granulocytopenia, and anemia. However, subset analysis revealed a significantly lower risk of recurrence for women with serous tumors.[183] At 5 years, recurrence-free survival for women with serous tumors was 83% for six cycles of chemotherapy versus 60% for three

cycles (HR 0.33, P = .04). Overall survival was also improved at 5 years (86% vs 73%), although not statistically significant.

Adjuvant Whole-Abdomen Irradiation

WAI was an accepted standard modality in the adjuvant postoperative treatment for completely resected ovarian cancer; however, its use declined significantly after 1975. The practical advantage of WAI was the ability to treat all of the peritoneal surfaces within the abdomen and pelvis, although the delivered dose was limited by the relatively low tolerance of the liver and kidneys. Interest in WAI was established following the publication from Princess Margaret Hospital of a randomized comparison of 147 patients with FIGO IB, FIGO II, or FIGO III debulked ovarian cancer who received WAI with a pelvic boost or pelvic radiotherapy followed by chlorambucil.[184] WAI significantly improved 10-year survival rates over limited pelvic radiotherapy and chemotherapy (64% vs 40%). The greatest magnitude of the survival benefit was observed in patients with less than 2 cm of residual disease (10-year survival 78% vs 51%). No significant benefit was observed in patients with extensive residual tumor.

Subsequent randomized studies did not find a benefit for WAI compared to combined adjuvant treatment modalities. A multi-institutional trial by the National Cancer Institute of Canada (NCIC) randomized 257 high-risk patients with stage I or optimally debulked stage II or III disease to receive melphalan, WAI, or IP phosphorus-32 (^{32}P).[185] All patients had previously received 22.5 Gy to the pelvis prior to study entry. The WAI arm delivered 22.5 Gy to the abdomen in 2.25-Gy fractions. Actuarial 10-year survival rates failed to demonstrate a statistically significant difference among all groups.[186] A second study from the Danish Ovarian Cancer Group reported similar outcomes for women who received adjuvant WAI versus pelvic radiotherapy with cyclophosphamide or melphalan (4-year survival, 63% vs 55%).[187]

WAI has also been shown to be comparable to single-agent or combination chemotherapy in the adjuvant setting. A prospective study from the MD Anderson Cancer Center randomized 149 women with stages I through III ovarian cancer and less than 2 cm of residual disease to WAI or melphalan.[188] WAI was delivered by a moving strip technique with a pelvic boost. Overall survival at 5 years was 71% for WAI and 72% for the melphalan arm. Severe late gastrointestinal toxicity requiring surgical intervention was reported in

14% of patients who received WAI, attributed to the moving strip technique that delivered excessive pelvic dose. A second prospective trial from the Northwest Oncologic Cooperative Group of Italy randomized 70 women with early-stage high-risk disease to adjuvant WAI or six cycles of cisplatin plus cyclophosphamide. Despite protocol violations in the assigned treatment groups, there was no difference in relapse-free or overall survival when analyzed by treatment received.[189] From these studies, WAI appears equivalent to chemotherapy when delivered in patients with optimally debulked disease but is no longer used. Further escalation of WAI to 27.5 Gy does not appear to provide additional survival benefit.[190]

The role of consolidative radiotherapy in patients with stage I or II disease and clear cell, endometrioid, or mucinous histology has recently been raised by population-based studies. In a multicenter retrospective study of 241 patients with stages I and II ovarian clear cell carcinoma, consolidative radiation was associated with a 20% benefit in disease-free survival at 5 years for patients with stage IC or II disease.[191] Following surgical staging, patients were treated with either three cycles of carboplatin and paclitaxel followed by WAI (45 Gy to pelvis and 22.5 Gy to whole abdomen) or six cycles of chemotherapy alone. The survival benefit was most pronounced among patients with negative or unknown peritoneal cytology. Similar results were also seen for patients with stage I or II ovarian cancer of endometrioid, clear cell, and mucinous subtypes in a larger analysis of this population-based study, which reported a 40% reduction in disease-specific mortality and 43% reduction in overall mortality with the addition of consolidative radiotherapy. A survival benefit with the addition of consolidative radiotherapy was not observed in patients with stage II disease or serous tumors.[192] However, at this time, there is no level 1 evidence to support the role of adjuvant or consolidative radiation for patients with early-stage disease and nonserous histology.

Adjuvant Intraperitoneal Phosphorus-32

IP instillation of ^{32}P was extensively studied as an alternative to external beam radiotherapy but is no longer in clinical use. In patients with high-risk, early-stage ovarian cancer, randomized trials of adjuvant IP ^{32}P versus chemotherapy from the GOG and Norwegian Radium Hospital found no significant differences in disease-free or overall survival in a population with

high-risk early-stage disease.[175,193,194] Given a higher incidence of bowel toxicity and limitations of delivery, ^{32}P has largely been replaced by platinum and taxane combination chemotherapy as the adjuvant treatment for early-stage and advanced disease.

Advanced-Stage Disease

Surgical Considerations

Optimal or complete cytoreduction is one of the most important prognostic factors for survival in patients with advanced-stage ovarian cancer. Cytoreductive surgery in advanced-stage disease may improve the patient's disease-related symptoms such as abdominal pain and early satiety and allow for the ability to maintain nutritional status. Optimal cytoreduction may also enhance chemotherapy delivery and response by the removal of large hypoxic tumor masses. Bowel resection may be required to remove metastatic implants involving the bowel mesentery or serosa. Extensive upper abdominal surgery, including splenectomy, partial hepatectomy, partial gastrectomy, partial cystectomy and/or ureteroneocystostomy, cholecystectomy, distal pancreatectomy, and/or diaphragmatic resection, also results in prolonged palliation and improved survival.[154,195,196] Select patients may be potential candidates for IP chemotherapy, as discussed later, and consideration should be given to the placement of an IP catheter at the time of surgery. Laparoscopy may be utilized to identify which patients with advanced ovarian cancer have the greatest likelihood of attaining complete cytoreduction with primary surgery.[197,198] However, based upon the evaluation of 2,655 patients in GOG 182, patients with larger tumor burden still have worse survival despite aggressive surgery attaining no residual disease.[199]

Second-look laparotomy (SLL) was introduced to assess the extent of residual disease following cytoreductive surgery and adjuvant chemotherapy. Up to 20% to 50% of patients may have residual disease after adjuvant therapy that was not detected on physical examination or by CA-125 levels or imaging. Although SLL demonstrated the prognostic importance of a pathologic remission, it was not found to have a therapeutic benefit in a GOG trial of 800 patients.[200] Therefore, second-look evaluations for the purposes of determining therapy, and not for interval cytoreduction, should be reserved for women enrolled in clinical trials.

Several studies have evaluated the importance of interval cytoreduction following an initial attempt at surgical debulking. In a randomized trial by the European Organisation for Research and Treatment of Cancer (EORTC), 319 women with suboptimally debulked disease (.1 cm residual) were assigned to six cycles of cisplatin/cyclophosphamide chemotherapy or interval cytoreduction after three cycles of chemotherapy, followed by additional three cycles.[201] Progression-free and overall survival were significantly improved with interval cytoreduction (median overall survival 26 vs 20 months, $P = .04$) without increased surgical morbidity. However, a subsequent GOG trial of 550 women failed to reproduce these results.[202] Following a suboptimal resection in the GOG trial, patients were randomized to three cycles of cisplatin and paclitaxel followed by interval debulking or chemotherapy alone for a maximum of six cycles in both arms. The absence of a survival benefit may be attributable to differences in the chemotherapy used or more aggressive initial surgical management by gynecologic oncologists in the GOG trial. National cancer guidelines state that patients should be evaluated for potential interval cytoreduction before the fourth cycle of neoadjuvant chemotherapy.

The role of neoadjuvant chemotherapy has been explored in a randomized EORTC/NCIC trial of 670 women with stages IIIC and IV ovarian, fallopian tube, or primary peritoneal cancer randomized to initial surgical debulking followed by six cycles of cisplatin-based chemotherapy or interval debulking after three cycles, followed by three additional cycles.[203] The cohort had extensive bulky disease, with more than 60% of patients with metastases greater than 10 cm. Although progression-free and overall survival were similar between the two groups, interval surgery achieved optimal cytoreduction more often (81% vs 42%) and with fewer surgical complications. A major criticism of the trial is that the median survival was significantly lower than that of recently reported U.S. trials (~30 months compared to overall survival averages of 50 months),[204,205] which may be related to selection of higher risk patients. In a retrospective analysis of the EORTC/NCIC trial, patients with stage IVB disease and bulky tumors had better 5-year survival rates with neoadjuvant therapy, whereas those with stage IIIC and less bulky tumors had a greater survival benefit with upfront surgery.[206] National cancer guidelines indicate that neoadjuvant chemotherapy may be considered for patients with bulky stage III to IV

diseases who are not surgical candidates following assessment by a gynecologic oncologist. However, more data will be necessary prior to recommending neoadjuvant chemotherapy in patients with potentially resectable ovarian cancer, as upfront debulking surgery remains the treatment of choice in the United States. In a single U.S. institutional series of 586 patients with advanced ovarian cancer, upfront debulking surgery was associated with an improved median overall survival of 72 months compared to 43 months for those selected for the treatment with neoadjuvant chemotherapy.[207]

Chemotherapy for Advanced-Stage Disease

Platinum agents are the most active class of compounds in the adjuvant treatment for ovarian cancer. Before 1980, alkylating-based regimens such as cyclophosphamide and doxorubicin were used with clinical response rates of 15% to 20%. GOG 47 demonstrated an improvement in clinical complete response rates (51% vs 26%) and progression-free survival (13 vs 8 months) with the addition of cisplatin to cyclophosphamide and doxorubicin. Cisplatin has since been used extensively in both single-agent and multidrug studies. A meta-analysis of 49 trials from the Advanced Ovarian Cancer Trialists' Group found that platinum combination chemotherapy improved survival rates over the same nonplatinum regimen (HR 0.88, 95% CI 0.79-0.98) and nonplatinum monotherapy (HR 0.93, 95% CI 0.83-1.05).[208] The women in the nonplatinum groups routinely received platinum chemotherapy at the time of relapse, likely obscuring the magnitude of the benefit. This meta-analysis also incorporated data from 11 trials that directly compared carboplatin and cisplatin, either as single agents or in combination with other drugs, which suggested no difference in efficacy between the two agents. Carboplatin clearly has fewer treatment-related side effects, including less nephrotoxicity, neurotoxicity, and emetogenic potential, and is considered standard of care. However, carboplatin does have more associated myelosuppression, primarily thrombocytopenia, which is cumulative and may be dose limiting.

In addition to platinum compounds, taxanes have become a cornerstone of the treatment schemas for women with epithelial ovarian cancer. GOG 111 was a randomized study comparing cisplatin and paclitaxel with cisplatin and cyclophosphamide in women with suboptimally debulked, large-volume

ovarian cancer. The paclitaxel-containing arm demonstrated improved clinical response rates (73% vs 60%), progression-free survival (18 vs 13 months), and overall survival (38 vs 24 months).[209] A second GOG study of 614 women with advanced disease and suboptimal resection compared single-agent cisplatin to 24-hour infusion of paclitaxel and to the combination of paclitaxel and cisplatin.[210] Either cisplatin alone or in combination with paclitaxel resulted in improved clinical response rates and progression-free survival, although overall survival was similar in the three arms. Combination chemotherapy also had lower cumulative toxicity. As several trials have demonstrated the comparable efficacy of cisplatin and carboplatin, the combination of carboplatin and paclitaxel has become the preferred first-line chemotherapy regimen. Although the standard dosing of intravenous (IV) carboplatin and paclitaxel is every 21 days, a phase III trial from Japan demonstrated significant gains in progression-free and overall survival with a dose-dense regimen of weekly paclitaxel in combination with carboplatin given every 3 weeks[211,212] (Table 78.8). Grade 3 or 4 anemia was more common in the dose-dense arm, although other toxicities were similar. In the GOG-262 trial, weekly paclitaxel was associated with an increase in progression-free survival that was 3.9 months longer than that observed with paclitaxel administered every 3 weeks among patients who did not receive bevacizumab.[213] Carboplatin and docetaxel are also an acceptable first-line alternative and may be considered for patients at high risk for neuropathy.[214] In older patients or those with poor performance status, weekly paclitaxel and carboplatin may be considered.[215] Phase III trials have failed to show a benefit for the addition of a third cytotoxic agent to the carboplatin and paclitaxel regimen. GOG 182-ICON5 was a five-arm randomized trial of 4,312 women that compared the addition of gemcitabine, liposomal doxorubicin, or topotecan to carboplatin and paclitaxel. There were no improvements in progression-free or overall survival with any experimental regimen.[216] The recommended IV regimens include (1) paclitaxel and carboplatin given every 3 weeks for six cycles, (2) dose-dense weekly paclitaxel plus carboplatin every 3 weeks for six cycles, (3) weekly paclitaxel and carboplatin for 18 weeks, and (4) docetaxel and carboplatin every 3 weeks for six cycles.

TABLE 78.8 RANDOMIZED STUDIES OF ADJUVANT CHEMOTHERAPY IN ADVANCED-

STAGE OVARIAN CANCER						
Trial	**Stage**	**Study Design**	**Number of Patients**	**Median PFS (Months)**	**Median OS (Months)**	**Notes**
GOG 172 (2006)	III	IP/IV cisplatin/paclitaxel	415	23.6	65.6	Greater toxicity in IP/IV arm
	#1 cm residual	IV cisplatin/paclitaxel		18.3[a]	49.7[a]	
Japanese GOG (2009, update 2013)	II-IV	Dose-dense CT	631	28.2	100.5	More anemia with dose-dense schedule
		CT (every 21 d)		17.5[a]	62.2[a]	
GOG 218 (2010)	III-IV	CT	1,873	10.3	39.3	Higher rates of hypertension, GI perforation, and fistula
		+ c. bevacizumab		11.2	38.7	
		+ c./m. bevacizumab		14.1[a]	39.7	
ICON7 (2010)	High risk I-II	CT	1,528	17.4	–	Greatest benefit in high-risk subset
	III-IV	+ c./m. bevacizumab		19.8[a]		

c., concurrent; CT, carboplatin and paclitaxel; GI, gastrointestinal; GOG, Gynecologic Oncology Group; ICON7, International Collaborative Ovarian Neoplasm 7; IP, intraperitoneal; IV, intravenous; m., maintenance; OS, overall survival; PFS, progression-free survival.

[a]Statistically significant.

The role of novel biologics in the first-line treatment for ovarian, fallopian tube, and primary peritoneal cancers is under active investigation. Antiangiogenics have demonstrated activity in the recurrent treatment setting, and the addition of bevacizumab to conventional first-line chemotherapy has been tested in two randomized trials. Bevacizumab is a humanized monoclonal antibody directed against the VEGF receptor that may inhibit

tumor angiogenesis and improve chemotherapy delivery. GOG 218 reported that the addition of concurrent and maintenance bevacizumab for 15 months significantly improved progression-free survival compared to six cycles of carboplatin and paclitaxel alone (14.1 vs 10.3 months).[217] The benefit was not seen in the group who received concurrent bevacizumab without maintenance therapy. Rates of hypertension, gastrointestinal perforation, and fistula formation were higher with the use of bevacizumab. With a median follow-up of 17.4 months, overall survival was similar between the treatment arms, as was quality of life. In a subsequent analysis, women with ascites who received bevacizumab maintenance regimen had significantly improved progression-free and overall survival.[218] Long-term results with a median follow-up of 102.9 months demonstrated no disease-specific survival and no survival advantage with the addition of bevacizumab.[219] The ICON7 trial also reported a progression-free, but not overall, survival benefit with concurrent bevacizumab and carboplatin/paclitaxel chemotherapy when compared to chemotherapy alone, although the absolute benefit was modest (2.4 months).[220] The greatest benefit was observed in patients at high risk for progression, defined as FIGO stage IV or greater than 1 cm of residual disease and FIGO stage III (median progression-free survival of 16 vs 10.5 months). In an updated analysis, the addition of bevacizumab did not increase overall survival in the whole study population, although patients with a poor prognosis had a significantly longer survival time with bevacizumab (39.3 months) compared to those who received chemotherapy alone (34.5 months).[221] Concerns about cost and lack of an overall survival and/or quality of life benefit have tempered the widespread adoption of bevacizumab to the first-line chemotherapy backbone. National cancer guidelines include the addition of bevacizumab to upfront therapy with carboplatin/paclitaxel and maintenance therapy with a Category 2B recommendation.

Several VEGFR tyrosine kinase inhibitors (TKIs) have been evaluated in the concurrent and/or maintenance setting in the upfront treatment of ovarian cancer. A phase III trial of the oral antiangiogenic nintedanib (BIBF 1120) in combination with carboplatin and paclitaxel reported a significant benefit in progression-free survival (17.2 vs 16.6 months), although a higher rate of serious adverse gastrointestinal events was observed when compared to chemotherapy alone.[222] Pazopanib, a potent multitargeted TKI against VEGF receptor, PDGF receptor, and c-Kit, was evaluated as maintenance therapy

following surgical debulking and first-line chemotherapy in a randomized phase III trial of 940 patients (AGOOVAR 16 trial).[223] The addition of maintenance pazopanib resulted in a median progression-free survival benefit of 5.6 months at the expense of increased toxicity, and no overall survival difference was observed.

Intraperitoneal Chemotherapy

Because of the unique peritoneal dissemination of epithelial ovarian and fallopian tube cancer, there has been a significant interest in evaluating IP administration of chemotherapy, which allows for a several-fold increase in drug concentration compared to systemic delivery. However, penetration into tumor tissue may be limited such that therapy is best suited for patients with minimal residual disease after surgical cytoreduction. The National Cancer Institute published a consensus statement in 2006 stating that IP chemotherapy should be offered to every woman with optimally debulked advanced-stage ovarian cancer based on the findings of GOG 172 (Table 78.8), which showed a progression-free and overall survival benefit to IP chemotherapy when compared with IV therapy alone (23.6 vs 18.3 months and 65.6 vs 49.7 months).[204] In women with stage III disease, survival was significantly increased by 16 months after IP therapy using cisplatin/paclitaxel when compared to standard IV therapy (65.6 vs 49.7 months). Only 42% of patients completed all six cycles of IP chemotherapy owing to treatment-related toxicity and catheter-related complications, which included gastrointestinal events, abdominal pain, metabolic abnormalities, neuropathy, catheter infection, and blockage. Despite the higher incidence of toxicity, additional support for IP chemotherapy is derived from a meta-analysis of eight trials comparing IP to IV administration of platinum-based chemotherapy. IP delivery resulted in a 22% decrease in the risk of death, which translated into a 12-month median survival benefit.[224] With advances in IV chemotherapy and targeted therapies, IP chemotherapy is no longer part of cancer guidelines, with all IV starting with platinum-based therapy.

CONSOLIDATIVE THERAPY FOR EPITHELIAL OVARIAN CANCER

Consolidative radiotherapy was introduced in hopes of eradicating subclinical residual disease in women who remain at high risk for relapse following surgical cytoreduction and adjuvant chemotherapy. Despite a

negative SLL, 30% to 50% of women with confirmed clinical remission ultimately relapse, most commonly in the pelvis or upper abdomen. Consolidative WAI as well as IP radiocolloid have been evaluated in several studies, although randomized data are currently lacking. Radiotherapy is not currently used as a consolidative treatment for ovarian or fallopian tube carcinomas, although it may have a role in the salvage or palliative treatment of select cases.

Consolidative Whole-Abdomen Irradiation

The efficacy of WAI has been demonstrated in early-stage patients with minimal residual disease (,2 cm) after cytoreductive surgery. A few early, prospective randomized trials have evaluated the role of consolidative WAI compared to extended chemotherapy in patients with advanced-stage disease (stage III/IV) after initial surgical cytoreduction, adjuvant chemotherapy, and SLL. In all of these trials, disease-free and overall survival rates were not found to be significantly different between WAI and chemotherapy.[225-227] A possible limitation of these trials was that women with macroscopic residual disease after SLL were eligible for enrollment.

Two trials have evaluated consolidative WAI in patients with complete clinical or pathologic remission following cytoreductive surgery and adjuvant chemotherapy. A randomized study from Austria demonstrated improved disease-free and overall survival for consolidative WAI, with the greatest benefit seen in patients with stage III disease.[228] The Swedish-Norwegian Ovarian Cancer Study Group recently reported their long-term results from a randomized trial of patients with stage III disease.[229] Following primary cytoreductive surgery and four cycles of cisplatin-based chemotherapy, women with complete remission at second-look surgery were randomized to WAI, six additional cycles of chemotherapy, or observation (if pathologic remission confirmed). In the subgroup with pathologic remission, WAI improved progression-free survival compared to chemotherapy or no further therapy (56%, 36%, and 35%, respectively). Overall survival was not statistically different, although statistical power was limited because only 172 (23%) of 742 enrolled patients were randomized to consolidative treatment.

WAI does not appear to compromise the ability of patients to receive and tolerate salvage chemotherapy following relapse, as recently reported in a phase II study from Princess Margaret Hospital.[230] However, the long-term

complication rate using conventional radiotherapy techniques is significant. In a multicenter retrospective study from France with a median follow-up of 14 years, late symptomatic enteritis occurred in 20% of patients, of which 8% required surgical intervention for bowel obstruction, and death related to bowel complications occurred in 4%.[231] At this time, WAI is not included in national cancer guidelines as a treatment recommendation for initial or consolidative treatment in ovarian cancer.

Consolidative Intraperitoneal Phosphorus-32

Randomized data evaluating IP ^{32}P as consolidative treatment following SLL are limited. The Norwegian Radium Hospital randomized 50 patients with stage IA high grade and IB through III disease and negative SLL to ^{32}P versus observation and found no significant difference between the arms.[193] The GOG also conducted a prospective randomized trial of 202 patients with stage III disease with complete clinical remission and microscopically negative disease at SLL.[232] Compared with patients who received no further therapy, those who received ^{32}P (15 mCi) within 10 days of SLL did not have improved 5-year disease-free survival (36% vs 42%) or overall survival (63% vs 67%).

Recurrent Ovarian Cancer

Women in clinical remission following initial adjuvant treatment for ovarian cancer may be followed with a combination of physical examination, serial CA-125 levels, and/or abdominal and pelvic CT. Detection of early relapse by a rising CA-125 is fairly specific, although the lead time between biochemical and clinical progression may be up to 6 months. Patients should also be educated about the signs and symptoms of recurrence, such as pelvic pain, bloating, early satiety, obstruction, weight loss, and fatigue. Second-line chemotherapy is not curative; thus, the timing of salvage therapy is controversial. The EORTC conducted a randomized trial of early versus delayed treatment for relapsed ovarian cancer that showed no difference in overall survival between the arms and a decrement in quality of life.[233] These findings have not been widely adopted in the United States owing to criticisms regarding the study design, including lack of stratification by known prognostic factors and nonstandard second-line therapies. Cancer

guidelines encourage physicians to discuss the pros and cons of CA-125 monitoring with their patients and the implications regarding early treatment and quality of life.

Chemotherapy

The selection of second-line chemotherapy for recurrent ovarian cancer is based on the interval to disease relapse and the determination of platinum sensitivity or resistance. The intent of recurrence therapy is to decrease tumor burden, control symptoms, improve progression-free survival, and/or increase length or quality of life. Patients who experience an early recurrence within 6 months of the completion of initial chemotherapy, have stable disease, or progress during initial induction chemotherapy are considered platinum resistant with low likelihood of cure. Women who suffer an early recurrence do have treatment options, including second-line chemotherapy agents (topotecan, weekly paclitaxel, pegylated liposomal doxorubicin, gemcitabine, oral etoposide, docetaxel), hormonal therapies, targeted therapeutics, and the opportunity to participate in clinical trials. For women with a late recurrence, retreatment with a platinum-based combination is a reasonable option, and the longer the disease-free interval, the higher the response rate to the agents. Preferred platinum-based combinations include carboplatin/paclitaxel, cyclophosphamide/bevacizumab, carboplatin/liposomal doxorubicin, carboplatin/weekly paclitaxel, carboplatin/docetaxel, carboplatin/gemcitabine, cisplatin/ gemcitabine, or topotecan/bevacizumab, among multiple other options. With the exception of those women who have a prolonged disease-free interval, the opportunity for a meaningful second remission is low, and one needs to carefully balance quality of life, chemotherapy-related toxicity, cost, and the patient's goals of care. Several randomized phase III studies are testing the role of antiangiogenics in the recurrent setting with combination chemotherapy. The AURELIA trial evaluated bevacizumab in combination with liposomal doxorubicin, weekly paclitaxel, or topotecan compared to chemotherapy alone in patients with platinum-resistant ovarian cancer. The addition of bevacizumab resulted in a statistically significant progression-free survival benefit (6.7 vs 3.4 months) and nonsignificant overall survival benefit (16.6 vs 13.3 months) when compared to chemotherapy alone.[234] As the gastrointestinal perforation rate in the bevacizumab arm was 2.2%, these

combination regimens are contraindicated in patients at increased risk. In the OCEANS trial, the addition of bevacizumab to carboplatin/gemcitabine chemotherapy resulted in improved response rates (79% vs 57%) and progression-free survival (median 12.4 vs 8.4 months) in women with platinum-sensitive recurrent disease.[235] In the final survival analysis, there was not a significant increase in overall survival with the addition of bevacizumab when compared to chemotherapy alone (33.6 vs 32.9 months).[236] A third large multi-institutional trial of 674 women evaluated the role of secondary surgical cytoreduction and bevacizumab in women with recurrent platinum-sensitive ovarian cancer and found that the addition of bevacizumab followed by maintenance therapy until progression improved median overall survival by sensitivity analysis.[237] Phase II studies of bevacizumab have demonstrated single-agent activity in patients with platinum-resistant recurrent ovarian cancer with response rates of 15% to 20%.[238,239] However, one of these studies reported a gastrointestinal perforation rate of 11% in a heavily pretreated population. Based on the phase III trials discussed earlier, national guidelines recommend combination regimens with bevacizumab for patients with platinum-resistant recurrent ovarian cancer, although there is less consensus for those with platinum-sensitive disease.

Emerging data are confirming the activity of PARP inhibitors in select patients with recurrent ovarian cancer. This new class of targeted therapy inhibits key enzymes involved in DNA repair and has been shown to be particularly active in treating cancers in BRCA mutation carriers. In the setting of BRCA deficiency, PARP inhibition results in the accumulation of double-strand DNA breaks that are lethal to tumor cells through a mechanism known as synthetic lethality. A substantial number of patients with ovarian cancer have been found to have BRCA-deficient tumors related to germline or somatic mutation, epigenetic silencing, or alteration in microRNA levels. Olaparib has shown single-agent response rates ranging from 28% to 41% depending on dose and BRCA mutation status. In phase II of 298 patients with germline BRCA1/2 mutation and advanced cancer, olaparib resulted in an overall response rate of 31% for those with platinum-resistant ovarian cancer.[240] In the platinum-sensitive setting, olaparib maintenance therapy resulted in a progression-free survival benefit of 8.4 months compared to 4.8 months with placebo for women with relapsed ovarian cancer, although an

overall survival benefit was not observed.[241] Single-agent olaparib is now recommended as recurrence therapy for patients with advanced ovarian cancer who have a germline BRCA mutation and received three or more lines of chemotherapy. Olaparib maintenance therapy was recently granted the Food and Drug Administration (FDA) approval based on the results of the SOLO-2 trial, which showed a significant improvement in progression-free survival in patients with germline BRCA-mutated, platinum-sensitive recurrent ovarian cancer when compared to placebo.[242] Two other PARP inhibitors have also been recently granted FDA approval. In the NOVA trial, patients with recurrent epithelial, fallopian tube, or primary peritoneal cancer were stratified by germline BRCA mutation status and randomized to either niraparib or placebo following complete or partial response to platinum-based chemotherapy. Maintenance niraparib resulted in a significant improvement in progression-free survival, with the greatest benefit among patients with germline BRCA mutations.[243] Rucaparib was granted accelerated approval for patients with germline or somatic BRCA mutation who have been treated with two or more chemotherapy regimens. BRCA mutation status was determined by a next-generation sequencing diagnostic test. The overall response rate in a single-arm open-label clinical trial was 54% and ranged from 66% for patients with platinum-sensitive disease to 25% for those with platinum-resistant disease.[244]

In summary, there are four PARP inhibitors that are FDA approved for recurrent ovarian cancer that clinicians may select from[245]:

- Olaparib for patients with recurrent germline BRCA-mutated ovarian cancer who have received three or more prior lines of chemotherapy or as maintenance therapy following response to platinum therapy for those with platinum-sensitive recurrence
- Rucaparib for patients with BRCA-mutated ovarian cancer (either deleterious tumor or germline mutation) who have received at least two prior lines of chemotherapy
- Niraparib for patients with platinum-sensitive recurrent ovarian cancer as maintenance therapy following response to platinum-based chemotherapy, regardless of BRCA or tumor homologous recombination status

- Pazopanib, which showed negative results relative to paclitaxel as maintenance therapy in persistent or recurrent ovarian cancer, but is still included as an option in some cancer guidelines[245]

Further studies of PARP inhibitor agents as single agents and in combination therapy are underway in patients with platinum-sensitive and platinum-resistant disease.

A number of TKIs have been tested in the recurrent setting as single agents, with demonstrated response rates of 3% to 29%.[27,246] These agents include cediranib (targets VEGF receptor and c-Kit), sunitinib (targets VEGF receptor, c-Kit, PDGF receptor, RET, and FLT-3), sorafenib (targets VEGF receptor, c-Kit, RAF, and PDGF receptor-b), ENMD2076 (targets VEGF receptor and aurora A), pazopanib (targets VEGF receptor, PDGF receptor, and c-Kit), trebananib (inhibits binding of angiopoietins 1 and 2 to the Tie2 receptor), and cabozantinib (targets VEGF receptor and c-MET). In the phase III ICON6 trial, patients with platinum-sensitive recurrent ovarian cancer were randomized to platinum-based chemotherapy with or without cediranib as concurrent and/or maintenance therapy. The addition of maintenance cediranib showed a significant progression-free survival benefit, although at the expense of increased toxicity.[247] Trebananib has also been tested in the phase 3 setting with weekly single-agent paclitaxel and, similar to other agents in its class, resulted in prolonged progression-free survival, but with higher rates of serious adverse events, treatment discontinuation, and chronic edema.[248] Combinatorial therapy with PARP and VEGF inhibition has also been explored with promising results in a phase II study,[249] and large phase III evaluations are underway.

Palliative Surgery

Secondary cytoreductive surgery with the intent of prolonging survival may benefit a select subset of patients with a long disease-free interval, good performance status, and single or few sites of recurrence.[250,251] A recently reported phase III trial randomized 407 women with platinum-sensitive disease at the time of first relapse to cytoreduction followed by second-line chemotherapy versus chemotherapy alone. Eligible patients had an excellent performance status, volume of ascites of 500 mL or less, and complete cytoreduction at diagnosis. The median progression-free survival was 21

versus 13.9 months in favor of surgery. The primary end point of overall survival will be reported in subsequent analysis.[252] Palliative surgery may also be considered in women who present with symptomatic tumor masses or intestinal obstruction. However, the risk of perioperative mortality and reobstruction is significant, and the patient's medical condition, performance status, and anticipated life expectancy should be carefully considered before operative intervention. For patients who are not surgical candidates, percutaneous decompression and IV hydration with consideration of palliative chemotherapy and/or hospice referral may be appropriate.

Palliative Radiation Treatment

Radiation therapy may be an effective palliative treatment modality in settings where localized recurrences are causing significant symptoms that are unresponsive to systemic therapy. Symptoms such as bleeding, pain, or obstruction in the pelvis, groin, abdomen, or chest may be palliated with an abbreviated course of radiation treatment. Clinical response rates have been reported in the range of 70% to 100%, with complete clinical response rates of 30% to 70% and a median duration of 5 to 11 months.[253-257] Palliative radiotherapy is effective even in patients heavily pretreated with systemic or IP chemotherapy. Pain relief and cessation of bleeding are achieved in more than 80% of patients and symptoms from bowel or ureteral obstruction in 60% to 75%.[258] A recent report found that response rates to palliative radiation did not vary among patients with platinum-resistant versus platinum-sensitive disease either at the time of diagnosis or at the time of radiation treatment. However, patients with clear cell ovarian cancer had lower clinical response rates when compared to those with serous or endometrioid cell types, although these patients may still experience symptomatic relief with radiation.[259] When delivered locally to symptomatic sites, radiation therapy appears to be of significant and durable benefit and should be considered for palliative purposes in select patients with symptomatic relapses, particularly in those who are refractory to chemotherapy.

The role of salvage radiotherapy in select patients with isolated pelvic recurrences has been suggested by several reports. In a series by Firat and Erickson,[260] 28 patients with recurrent or persistent disease involving the vagina and/or rectum received palliative radiotherapy delivered by external

beam radiotherapy, brachytherapy, or a combination of both. Bleeding was controlled in all cases, and 79% achieved a complete symptomatic response. Of the 21 patients with no evidence of liver or extra-abdominal disease, 2-year survival was 57% compared to 0% for the seven patients with liver and extra-abdominal metastases at the time of radiotherapy. In the group of 14 patients with pelvic-confined disease, 5 patients had recurrences in the upper abdomen and 4 patients were long-term survivors greater than 5 years after radiotherapy administration. A second study by Albuquerque et al[261] evaluated the outcomes of 20 women treated with salvage radiotherapy for isolated extraperitoneal recurrence. Most recurrences were in the pelvis, although three patients had regional nodal recurrences and one patient had an abdominal wall recurrence. The median delivered dose to a tumor-directed volume was 50.4 Gy, and a brachytherapy boost was delivered in select cases. Local recurrence–free survival at 2 years was 89% for patients with optimal debulking prior to radiotherapy compared to 42% for patients with suboptimal debulking or gross residual disease. The corresponding disease-free survival rates at 3 years were 72% and 22%, and overall survival rates at 5 years were 50% and 19%, respectively. In a large single-institutional series of 102 patients with epithelial ovarian cancer who received salvage involved-field radiotherapy, 5-year rates of progression-free and overall survival were 40% and 24%, respectively, with an infield control rate of 71%. Of note, the time interval to relapse and subsequent chemotherapy was prolonged following radiation treatment compared to the time interval to relapse before radiation. Furthermore, 25 patients did not experience relapse for a median of 61 months, and patients with clear cell histology had the highest rates of progression-free and overall survival after salvage radiation therapy.[262] Another study by Corrigan, et al retrospectively evaluated the outcomes of patients who received definitive radiation therapy doses to 48 patients with oligometastatic gynecologic malignancies, of which 20 were ovarian cancer. Patients had higher rates of median disease-free survival with treatment compared with surveillance (93 vs 34 months, $p = 0.05$).[263] Given the exceptional local control rates, minimal toxicity, and long-term survival, select patients with isolated extraperitoneal recurrences may be appropriate candidates for salvage involved-field radiation treatment.

Ovarian cancer metastatic to the brain is a rare occurrence reported in less than 1% of patients in autopsy cases and in 2% of clinical series.[264,265] More

recent series have suggested an increased incidence as chemotherapy regimens have become more effective.[265] Nonetheless, long-term prognosis is poor, as brain metastases are often a late manifestation of advanced disease, with a median survival time less than 12 months. In a series of 24 patients with metastatic brain disease treated with whole-brain radiotherapy, stereotactic radiosurgery (SRS), or a combination of whole-brain radiotherapy and SRS, median survival was 8.5 months. Patients with solitary metastatic lesions had significantly improved survival compared to those with multiple metastases (17 vs 6 months).[266] Platinum sensitivity was also recently identified as an important prognostic factor in women with metastatic brain involvement from ovarian cancer. In an analysis of 4,277 women treated at six German hospitals, 74 (1.7%) patients had clinical documentation of brain metastases, of which 61 patients received either radiotherapy alone or in combination with surgical resection and chemotherapy.[267] On multivariate analysis, platinum sensitivity (HR 0.23) and good performance status (HR 0.45) were associated with improved survival, whereas multiple lesions (HR 4.4) and low tumor grade (HR 3.1) were associated with adverse outcome. Although the extent of extracranial disease was not associated with outcome in this study, it is unclear whether the prognostic importance of platinum sensitivity was related to control of intracranial or systemic disease. In a retrospective analysis from the Multicenter Italian Trials in Ovarian cancer group that included 174 women with epithelial ovarian cancer, most of which had platinum-sensitive disease, the presence of extracranial disease (HR 1.8), older age (1.7), monotherapy (HR 2.6), and multiple brain metastasis (HR 1.9) were associated with worse overall survival following a diagnosis of brain metastases.[268]

SPECIALIZED RADIATION THERAPY TECHNIQUES

Whole-Abdominal Radiation Therapy

The clinical target volume for WAI includes the entire peritoneum from the diaphragm to the pelvic floor, encompassing both the visceral and parietal surfaces and the pelvic and para-aortic nodes. Conventionally, large anterior and posterior fields have been used. The simulation technique requires attention to the excursion of the diaphragm at the superior margin during respiration to ensure appropriate coverage. The field should encompass the pouch of Douglas inferiorly as well as the lateral extent of the peritoneal

margins, which may be located outside the pelvic brim in patients who are obese. Fluoroscopy may be used to assess the range of quiet respiratory motion. Alternatively, image fusion of CT scans obtained at inspiration and expiration or throughout the respiratory cycle (four-dimensional CT) may be used to design the treatment fields. Extended source to skin distance may be required in some patients to ensure adequate coverage. Organs at risk that are dose limiting include the kidneys, liver, small and large bowel, and bone marrow. Kidney doses are limited to 15 Gy with customized blocking, and whole-liver tolerance is 30 Gy. The standard whole-abdomen dose is 30 Gy delivered in 1.2- to 1.5-Gy fractions. An additional boost may be delivered to the pelvis and para-aortic lymph nodes to 45 to 50 Gy, depending on the clinical requirements. Patients will need to be monitored for acute gastrointestinal and hematologic toxicity as well as nutritional support.

The use of intensity-modulated radiation therapy (IMRT) to deliver WAI has been proposed as a means to reduce the radiation dose to the bone marrow and kidneys to decrease the incidence of myelotoxicity and renal damage. Dosimetric analysis has demonstrated improved planning target volume (PTV) coverage and significant dose reductions to bones with equivalent kidney sparing using dynamic multileaf collimator IMRT when compared with conventional fields.[269] The PTV receiving 95% of the prescribed dose improved from 72% to 84%, and the volume of pelvic bones receiving greater than 21 Gy was reduced by a relative 60% from 86% to 35%. Dose inhomogeneity, however, increased slightly, with small regions of underdosing near the kidneys. Similar improvements in PTV dose coverage were reported in a study using IMRT arc therapy.[270] It remains to be seen whether the dosimetric advantages gained from WAI-IMRT will translate to a significant and clinically relevant benefit. Furthermore, technical considerations must be considered with great care, given the complex anatomy and delineation of the peritoneal cavity boundaries. Patient breathing motion and setup uncertainties will also need to be addressed. Early-phase clinical trials assessing the feasibility and toxicity of WAI-IMRT as consolidation following optimal cytoreduction and platinum-based chemotherapy are ongoing.[271]

Intraoperative Radiation for Ovarian Cancer

Several studies have suggested that intraoperative radiation therapy (IORT) as part of salvage surgery for locally recurrent gynecologic cancers, including ovarian cancer, may improve local-regional control and overall survival.[272-276] The largest IORT retrospective study to date that reported results of 22 patients with ovarian cancer treated with IORT (median dose, 12 Gy; range, 9-14 Gy) suggests that the addition of IORT to cytoreductive surgery may potentially improve local-regional control and achieve palliation in highly selected patients with locally recurrent ovarian cancer.[272] Various sites were treated, most commonly the pelvic sidewall. Most patients received additional treatment after IORT, including WAI, pelvic and/or inguinal radiation, and chemotherapy. Local-regional control was achieved in 68% of patients, with a median time to recurrence of 14 months and 5-year disease-free survival of 18% and overall survival of 22%. Overall treatment-related grade 3 toxicities occurred in 41%. Bowel obstruction occurred in seven patients, all of whom received postoperative WAI and two of whom also had a component of local-regional relapse. No long-term neurologic sequelae were reported.

SEQUELAE OF TREATMENT

Acute Toxicity

Acute toxicity from WAI is common but rarely severe. The use of large radiation fields that encompass multiple abdominal organs, including the liver, kidneys, gastrointestinal tract, bladder, spleen, lungs, and pancreas, contributes to the development of predictable side effects. Gastrointestinal side effects are the most common acute and subacute toxicities encountered with WAI, given the large volume of bowel within the treatment field. Up to 75% of patients treated with WAI experience mild-to-moderate diarrhea; severe diarrhea requiring hospitalization and IV hydration is seen in 10% of patients. Limiting bowel exposure through the use of shielding or appropriately timed field reductions can minimize or prevent this toxicity. Approximately 60% to 70% may also experience nausea, particularly early during treatment, although emesis occurs infrequently. Premedication with antiemetic therapy 30 to 60 minutes prior to treatment may help mitigate this side effect. Routine IV hydration to prevent dehydration is also recommended. Appetite loss accompanied by weight loss is a frequent concern. It is thus essential to closely monitor and ensure proper nutrition to

avoid malnourishment and dehydration that may result in hospitalization and treatment interruption.

Clinically significant liver damage is extremely rare with appropriate shielding.[277] Approximately 50% of patients will develop transiently elevated alkaline phosphatase levels; however, symptomatic hepatitis occurs in less than 1%.[278] Hematologic toxicity including leukopenia and thrombocytopenia occurs in 10% to 20% of patients, although significant drops in blood counts causing treatment interruption are rare. Splenic damage may occur even at low radiation doses because of the exquisite radiosensitivity of the spleen, resulting in transient reduction in platelet counts.

Urethritis and bladder spasm from pelvic irradiation may occur and should be treated symptomatically. Adequate and careful shielding of the kidneys to limit the delivered dose to less than 15 Gy is critical to minimize renal damage and failure. Stricture of the ureters or urethra is rare, occurring in less than 1% of cases and is usually not seen until 3 to 6 months postradiation. Because treatment to the entire peritoneal cavity with adequate margins requires extension of fields above the diaphragm, inclusion of the lung bases bilaterally is required. Chest radiographs may show fibrosis or bibasilar pneumonitis in 5% to 20% of patients but is generally self-limited and rarely symptomatic.

Late Toxicity

Late toxicities following WAI were more common with the moving strip technique than with the open-field technique, primarily because of the higher doses and hot spots that were generated. High radiation doses can exceed normal organ tolerances, leading to permanent organ damage and failure. Chronic gastrointestinal damage (ie, bloating, intermittent diarrhea) occurs in less than 5% of treated patients. The overall incidence of bowel obstruction has been reported to be 5% to 10% at 5 years in cases in which IP ^{32}P or WAI is used independently. Approximately 50% of these patients who develop bowel obstructions will require surgical intervention (incidence, 3%-5%); however, recent data suggest that this incidence may be higher and closer to 10% in long-term survivors at 10 years.[231] Bowel obstructions occur more frequently with doses greater than 45 Gy and in patients with gapped or abutted split fields. In addition, adhesions in the peritoneal cavity and the combination of additional pelvic radiation to ^{32}P or WAI may double the risk

of significant bowel complications up to 20% to 25%.[185,193] As with most anatomic sites, escalating doses of radiation come with an increase in rate and degree of toxicity. Major bowel complications from 10 pooled series of 1,098 patients reported an incidence of 1.4% with abdominal dose of 22.5 Gy compared with 14% with 30 Gy.[278]

MANAGEMENT OF GERM CELL TUMORS

In general, the presentation and management of nonepithelial tumors are similar to those of their epithelial counterparts, as patients usually experience vaginal bleeding, abdominal bloating, or pain and typically require surgical intervention and chemotherapy. On presentation, routine workup is identical to that for other ovarian cancers as outlined previously. Pretreatment AFP and β-hCG levels are of particular importance in diagnosis and treatment. An elevated β-hCG with a normal AFP is strongly suggestive of dysgerminoma. Lactate dehydrogenase and CA-125 levels should also be drawn, as the germ cell tumors may have several tumor markers that can be followed (Table 78.9). Variations in surgical management and adjuvant chemotherapy and radiation do exist among the nonepithelial tumors, and treatments should consider the patient's desire to maintain fertility while offering the greatest chance for cure.

TABLE 78.9 SERUM MARKERS FOR OVARIAN GERM CELL TUMORS

Tumor Type	AFP	hCG	LDH
Dysgerminoma	−	+/−	+
Choriocarcinoma	−	+	−
Endodermal sinus tumor	+	−	−
Immature teratoma	+/−	−	−
Mixed germ cell tumor	+/−	+/−	+/−
Embryonal carcinoma	+/−	+	−
Polyembryoma	+/−	+	−

AFP, α-fetoprotein; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase.

Most ovarian neoplasms diagnosed in children and adolescents are germ cell tumors, with approximately two-thirds of these tumors being malignant

at the time of diagnosis. Germ cell tumors comprise 20% of all ovarian neoplasms and 2% to 5% of all ovarian malignancies. The most common germ cell tumor is the mature cystic teratoma (also the most common ovarian neoplasm); however, fortunately, only the minority contain a malignancy or immature elements.

Dysgerminoma

Dysgerminoma is the most common of the malignant germ cell tumors and also has the highest bilaterality rate (20%), with 10% of the ovaries being grossly involved and 10% being microscopically involved. As shown in Table 78.9, dysgerminomas may secrete lactate dehydrogenase and have elevated β-hCG levels. Most women with dysgerminomas receive a diagnosis of early-stage disease, and 80% are present before the age of 30 years. In many instances, young women affected by this disease wish to maintain fertility after therapy. The high rate of contralateral disease confers a greater risk with conservative surgical therapy. Comprehensive staging is recommended as initial surgery for patients who do not desire fertility preservation, although may be omitted in children or adolescents.

Postoperative therapy for patients with dysgerminoma can be separated into those women with stage I disease and those with disease of a more advanced stage. Women with stage I dysgerminoma may be monitored closely without compromising the cure. Approximately 15% to 25% of these women will experience a recurrence, although successful salvage treatment with chemotherapy results in survival rates close to 100%. For women with more advanced-stage disease, chemotherapy with three to four cycles of BEP (bleomycin, etoposide, and cisplatin) is recommended.[279] In a report from MD Anderson Cancer Center, more than 95% of the patients with ovarian dysgerminoma were free from relapse at a median of 7 years of follow-up.[280] Of the 16 women treated with fertility-sparing surgery, 10 patients maintained menstrual function during chemotherapy and 13 patients returned to their prechemotherapy baseline. Five pregnancies were reported, and two of the women had difficulty conceiving.

Dysgerminomas are unique in that they are exquisitely radiosensitive tumors. Radiotherapy may be considered for patients who are not candidates for platinum-based chemotherapy. The appropriate radiation dose for dysgerminoma is 25 Gy in 12 to 14 fractions with a boost of 10 Gy for gross

residual disease. However, radiotherapy will affect ovarian function and fertility, which must be taken into consideration when recommending adjuvant radiation therapy in a young patient.

Other Germ Cell Tumors

Nondysgerminomas are almost always unilateral. For apparent early-stage disease, unilateral salpingo-oophorectomy appears to be as effective as more extensive surgery. Patients with stage I grade 1 immature teratomas usually require no further therapy after unilateral salpingo-oophorectomy. All others, including stage I grade 2 and 3 immature teratoma, should be treated with three or four cycles of BEP chemotherapy. Because of the low number of diagnosed cases, large-scale studies comparing adjuvant therapy are uncommon.

Extrapolation of data regarding the efficacy of chemotherapeutic regimens in the treatment of nonseminomatous testicular germ cell tumors has had a great impact on treatment in patients with nondysgerminoma ovarian germ cell tumors. Patients with less well-differentiated tumors and all those with endodermal sinus tumor, embryonal carcinoma, choriocarcinoma, or mixed germ cell tumors should receive adjuvant postoperative chemotherapy. Various regimens have been used, including vincristine, dactinomycin, and cyclophosphamide; cisplatin, vincristine, and cyclophosphamide; and cyclophosphamide, vincristine, and bleomycin. The BEP regimen was prospectively evaluated by the GOG in patients with completely resected, surgically staged I, II, and III diseases and resulted in a 96% disease-free survival rate.[281] Cancer guidelines recommend three to four courses of BEP as the standard treatment for well-staged patients with resected ovarian germ cell tumors. Six cycles of chemotherapy may be considered for patients with gross residual or stage IV disease.

Management of Sex Cord-Stromal Tumors

Sex cord-stromal tumors derive from the intraovarian matrix of mesenchymal and connective tissue elements that supports the germ cells. The most common sex cord-stromal tumors are the granulosa cell tumors, derived from the sex cord cells along with Sertoli cell tumors. The mesenchymal derivatives include fibromas, thecal cell tumors, and Leydig cell tumors.

These tumors are responsible for less than 5% of all ovarian malignancies but account for 90% of all functioning ovarian neoplasms. One-third of the tumors will produce estrogen, progesterone, testosterone, or other androgens. This hormonal expression may lead to presenting signs and symptoms such as precocious puberty, postmenopausal bleeding, hirsutism, or virilization. Sex cord-stromal tumors can develop in women of any age (with the granulosa cell tumors having a bimodal age distribution), with a peak incidence in postmenopausal women around 50 years of age. These tumors typically behave in a benign manner with LMP. Surgery remains the mainstay of treatment; however, occasionally, postoperative therapy is required, although these tumors are considered relatively insensitive.

Adult granulosa cell tumors account for 95% of all granulosa cell tumors. Most women are diagnosed after 30 years of age, with a median age of 52 years. Abdominal pain, distension, and vaginal bleeding are the most common signs and symptoms. Because of the relative state of estrogen excess produced by these tumors, 25% of women will also have concomitant endometrial pathology, such as hyperplasia or adenocarcinoma.[282] These tumors tend to be large with an average diameter of 12 cm. If a granulosa cell tumor is suspected preoperatively, inhibin A and B levels may be elevated and useful in narrowing the differential diagnosis. Ninety percent of patients present with stage I disease, and the tumors are typically unilateral in 90% of cases. Stage is the most important prognostic factor for granulosa cell tumors; other factors include tumor rupture, stage IC disease, poorly differentiated tumor, and tumor size greater than 10 to 15 cm. The 10-year survival for women with stage I disease is approximately 90%, with 15% to 25% of patients with stage I disease ultimately suffering a disease recurrence. The 10-year survival for women with advanced-stage disease is 26% to 49%.

Juvenile granulosa cell tumors are rare, although they account for 90% of the granulosa cell tumors that occur in prepubertal girls and women less than 30 years of age.[283] Similar to the adult form, the juvenile tumors may also secrete estrogen; therefore, prepubertal girls may present with isosexual precocious puberty. This may be the most dramatic presentation; however, the most common presentation is that of an abdominal mass. As with the adult variant, the juvenile variant is rarely bilateral, with bilaterality occurring in only 5% of cases. More than 90% of cases will be stage I at the time of diagnosis, and other prognostic factors apply as with the adult

variant. The 5-year survival rate is 95%, and the prognosis remains poor with advanced-stage or recurrent disease.

Most granulosa cell tumors are unilateral and can be treated with fertility-preserving therapy consisting of unilateral salpingo-oophorectomy and appropriate surgical staging. Given the rarity of pelvic and para-aortic nodal involvement, lymphadenectomy may be omitted for patients with stage IA or IC disease. Endometrial sampling should be performed in all women retaining their uterus, as these tumors may be associated with concomitant hyperplasia or adenocarcinoma. In women not wishing to preserve fertility or those who are postmenopausal, complete hysterectomy with bilateral salpingo-oophorectomy is the procedure of choice. Surgery alone is typically curative. However, risk factors for relapse that should be considered in adjuvant treatment for stage I disease include tumor rupture, stage IC disease, poorly differentiated tumor, and tumor size greater than 10 to 15 cm. Adjuvant treatment options for high-risk stage I and advanced-stage disease include observation or consideration of platinum-based chemotherapy. Radiation therapy may also be considered for patients with stage II to IV tumors and localized disease. Inhibin levels, if initially elevated, may be a useful tumor marker for the surveillance of patients under observation.[284]

FUTURE DIRECTIONS

Ovarian cancer represents a spectrum of distinct disease processes, ranging from noninvasive borderline tumors to disseminated high-grade serous carcinomas. The cell of origin may be extraovarian in a large proportion of cases, as many high-grade serous carcinomas appear to originate in the distal fallopian tube. Clear cell, endometrioid, and mucinous cancers may arise from metaplastic transformation of the OSE, although an extraovarian origin has been proposed. Recent insights from molecular and genomic studies also support the concept of distinct biologic subtypes of ovarian cancer. Gene expression profiling has revealed greater similarity between ovarian clear cell carcinoma and renal clear cell carcinoma than other ovarian subtypes.[285] High-grade serous carcinoma shares genomic and transcriptional features with the basal subtype of breast cancer, characterized by a BRCA-deficient phenotype.[23] Driver mutations that activate the PI3 kinase signaling pathway and mutations in the tumor suppressor *ARID1A* have been identified in

endometrioid and clear cell ovarian cancers, which share a strong epidemiologic link with endometriosis.

The recognition of distinct ovarian cancer subtypes has implications for prevention, early detection, clinical trial design, and the identification of new therapeutic targets, particularly for advanced-stage and recurrent disease. Results from the large screening trials of postmenopausal women in the United States, the United Kingdom, and Japan using CA-125 and TVUS do not at present support routine screening for ovarian and fallopian tube cancer in the general population. Future screening strategies may focus on women at greatest genetic risk by high-throughput sequencing and mutation testing. Genome-wide association studies have recently identified new ovarian cancer risk loci.[286,287] Novel screening strategies will also be needed to detect precursor lesions within the fallopian tube, particularly for high-grade serous carcinomas. It is not yet known whether prophylactic salpingectomy without removal of the ovaries is an acceptable prevention strategy for premenopausal women with familial ovarian cancer syndromes. Clinical trials will soon incorporate targeted therapies with blood and imaging biomarkers to assess pathway inhibition and accurately measure disease response. Trial end points should also include robust quality-of-life tools to assess the effect of palliative chemotherapy on symptom control as well as evaluation of its toxicity.

Although no longer used in the initial management of ovarian cancer, the role of radiation therapy in definitive management of isolated oligometastatic recurrences and in palliation of symptomatic recurrences remains significant, particularly for women with chemotherapy-refractory disease. To date there have been no published prospective studies on the role of radiation in these settings. Nevertheless, this remains an area of active study.

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CHAPTER 79

Vaginal Cancer

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ANATOMY

The vagina is a fibromuscular tube that extends from the cervix down to the vestibule, or cleft, between the labia minora. The average length of the vagina is 3 to 4 inches or 7.5 cm. It lies dorsal to the urethra and bladder base and ventral to the rectum. Embryologically, the vagina is believed to be of dual origin, with the upper third derived from the uterine canal, whereas the lower two-thirds are derived from the urogenital sinus.[1]

Proximally, the vagina joins the uterine cervix at an angle, and, as a result, the posterior vaginal wall is longer than the anterior wall (Figure 79.1). The proximal posterior vaginal wall is separated from the rectum by the rectovaginal septum or fascia. The overlying peritoneal reflection forms the posterior cul de sac, also known as the pouch of Douglas. Invaginations between the vaginal mucosa and the cervix form the anterior, posterior, and lateral fornices. Laterally, the vagina is adjacent to the pelvic fascia and levator ani muscles. Inferiorly, the vagina extends through the urogenital diaphragm to lie dorsal to the urethra and ventral to the rectum. The fibromuscular perineal body separates the vagina from the anal canal. At the introitus, the vagina has a perforated fold of thin connective tissue and mucous membrane known as the hymen.

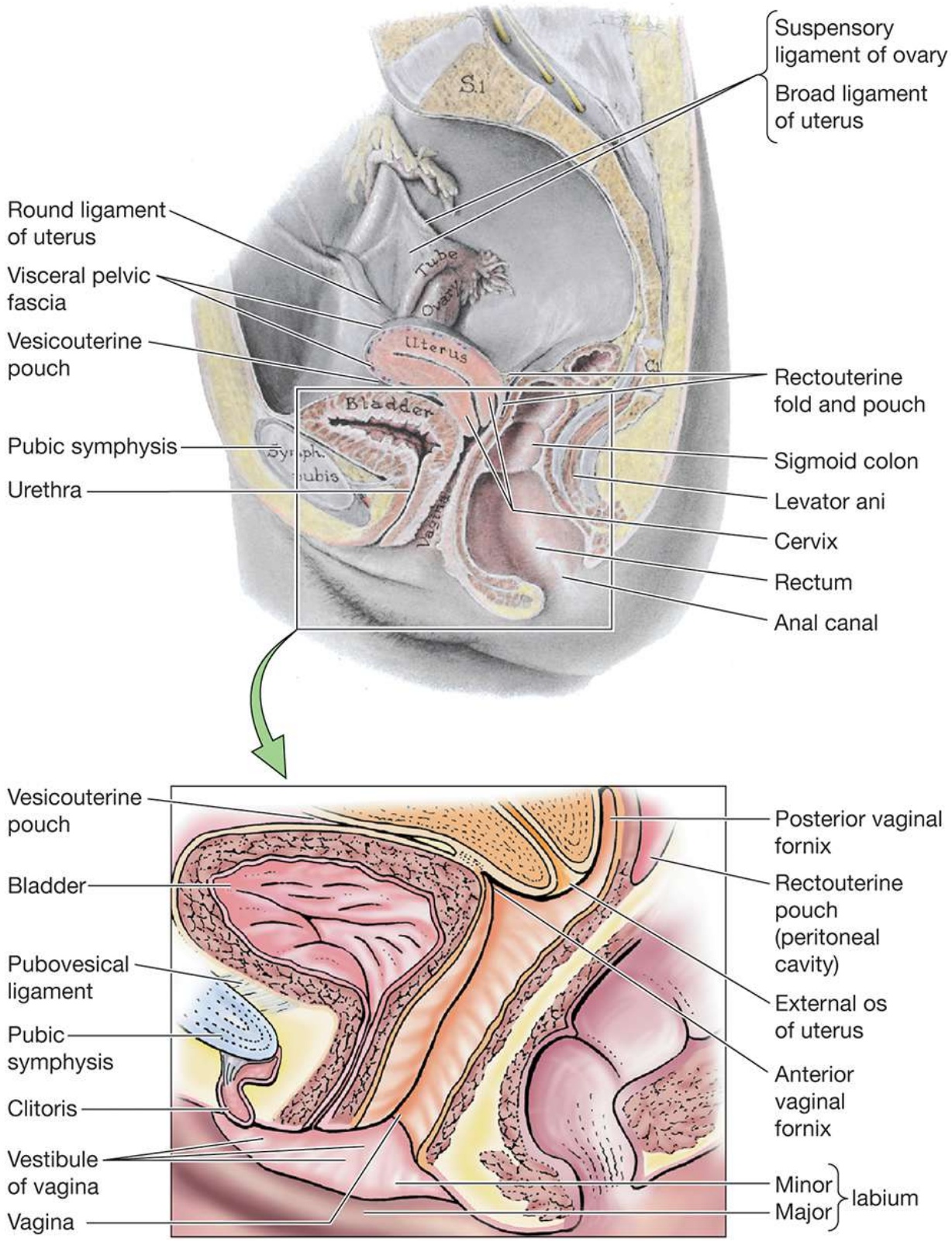


FIGURE 79.1 Anatomy of female pelvis.

The vaginal wall is composed of the mucosa, muscularis, and adventitia. The innermost lining of the vagina is formed by a nonkeratinizing, stratified squamous epithelium overlying a basement membrane. This epithelial mucosa lacks significant glandular structures and instead receives most lubrication from mucous secretions originating in the cervix. Underneath the mucosa is the connective tissue composed of elastin and a thick muscularis layer composed of two layers of smooth muscle. The inner layer is arranged circularly, whereas the outer layer is arranged longitudinally. This muscular layer is covered by the third layer, a thin adventitia that merges with neighboring organs.

The vagina has a complex, extensive network of lymphatic drainage, with vessels that course through the submucosal and muscularis layer (Figure 79.2). The proximal portion drains primarily via cervical lymphatics. The proximal anterior vagina drains along cervical channels to the internal iliac, and parametrial nodes and the proximal posterior vagina drains into the inferior gluteal, presacral, and anorectal nodes. The distal aspect of the vagina drains into the superficial inguinal nodes, and ultimately to the pelvic nodes, following drainage patterns of the vulva. Lesions in the midvagina have been shown to drain either way.[2] Lesions infiltrating the rectovaginal septum may spread to the pararectal and presacral nodes because there are multiple interconnections between the lymphatic channels, and the pattern of drainage cannot be reliably predicted based on the location of the primary tumor.

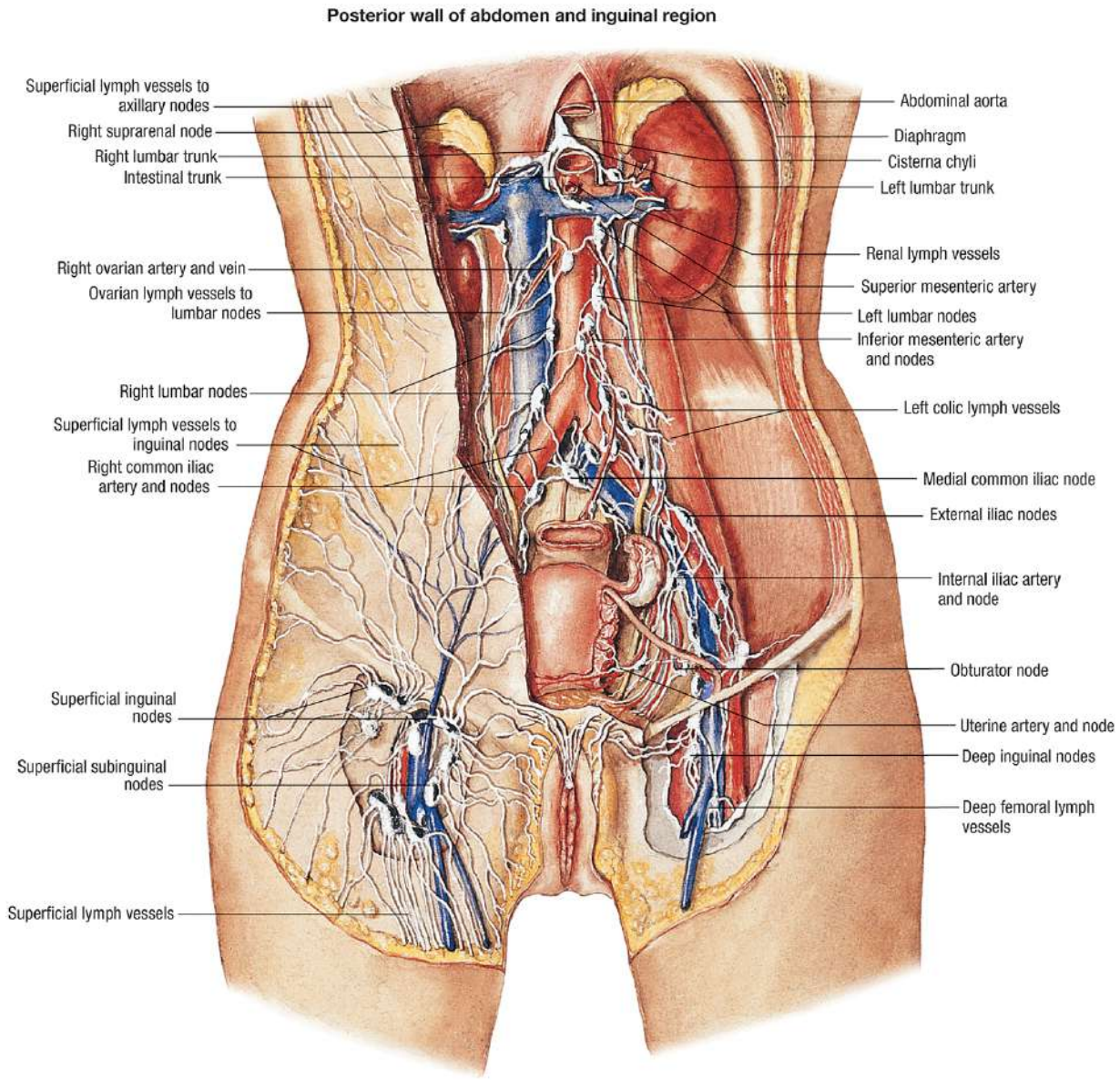


FIGURE 79.2 Lymphatic drainage of the vagina.

The vagina is supplied by the vaginal artery, which arises from the cervical branch of the uterine artery and runs lateral to the vagina until it anastomoses distally with the inferior vesical and middle rectal arteries. The venous plexus runs parallel to the arteries, draining into the internal iliac vein. The vaginal vault is innervated by the lumbar plexus and pudendal nerve, with branches from sacral roots 2 to 4.[3]

EPIDEMIOLOGY, PRESENTATION, AND MANAGEMENT

Primary vaginal cancer is a rare malignancy, constituting 1% to 2% of all gynecologic malignancies. There were approximately 8,470 new cases and 1,740 deaths from primary vaginal cancer in the United States in 2023.[4]

The majority of malignant lesions in the vagina are attributable to direct spread or metastases from other gynecologic malignancies. According to the staging system set by the International Federation of Obstetrics and Gynecology (FIGO), any tumor involving both the vagina and cervix should be classified as a cervical carcinoma. Similarly, any tumor involving both the vagina and vulva is to be classified as a vulvar carcinoma.[5] A malignant vaginal lesion in a patient with prior history of invasive cervical carcinoma within the past 5 years also excludes diagnosis as a primary vaginal cancer.[6] As a result, only a minority of vaginal carcinoma cases meet the criteria of being a primary vaginal cancer. Approximately 70% of vaginal cancers are human papillomavirus (HPV) positive.[7]

The peak incidence of primary vaginal cancer is in the sixth and seventh decades of life. According to data from the Surveillance, Epidemiology, and End Results (SEER) program,[8] 2,149 women in the United States were diagnosed with primary vaginal cancer from 1990 to 2004. The mean age at diagnosis was 65 ± 14 years, and incidence rates increased with age. There has been an overall decrease in the incidence of primary vaginal tumors, possibly secondary to earlier detection and implementation of strict exclusion criteria in the FIGO staging system.

According to the SEER study by Shah et al,[8] most women diagnosed with primary vaginal cancer are non-Hispanic Whites (66%), followed by African Americans (14%), Hispanic Whites (12%), Asian/Pacific Islanders (7%), and others (1%). Incidence rates were highest for African American women (1.24/100,000 person-years) and lowest for Asian/Pacific Islanders (0.64/100,000 person-years).

A review of five series, encompassing a total of 1,375 cases of vaginal cancer, reported a FIGO stage distribution as follows: 26% stage I, 37% stage II, 24% stage III, and 13% stage IV.[9] Consistent with this, the National Cancer Database (NCDB) review by Creasman et al, for the period of 1985 to 1994, revealed 3,244 cases of invasive primary vaginal carcinoma, with 24% of patients presenting with American Joint Committee on Cancer (AJCC) stage I disease, 20% AJCC stage II, 24% AJCC stages III to IV, and

32% unknown.[10] Most tumors were moderately (28%) or poorly (28%) differentiated at presentation.

Because of the low incidence, treatment recommendations are based on results from relatively small retrospective series comprised of heterogeneous patient populations and treatments, or extrapolated from treatment recommendations for cervical or vulvar cancer, and it remains unlikely that randomized clinical trials will be feasible.

Vaginal Intraepithelial Neoplasia

It is hypothesized that vaginal intraepithelial neoplasia (VAIN) is a precursor lesion to squamous cell carcinoma (SCC) of the vagina.[11] There has been a steady increase in the diagnosis of VAIN over the past several decades, perhaps because of a combination of increased cytologic screening, awareness, and incidence of HPV. VAIN is defined as atypia of squamous cells without evidence of stromal invasion and was first reported by Hummer and colleagues in 1933.[11]

VAIN is further classified into low grade (VAIN 1) and high grade (VAIN 2 and VAIN 3). VAIN 1 is characterized by cytomorphologic changes limited to the upper one-third of the epithelium. Such changes include nuclear enlargement, nuclear hyperchromasia, cytoplasmic halos, and occasional binucleation. VAIN 2 and VAIN 3 are characterized by cytomorphologic changes in the basal keratinocytes, including nuclear pleomorphism, nuclear hyperchromasia and crowding, and mitotic figures (including atypical forms). VAIN 2 and VAIN 3 are distinguished by the depth of cytologic change. Cytologic changes confined to the lower two-thirds of the epithelium are designated VAIN 2, whereas changes involving the full thickness of the epithelium are VAIN 3. Carcinoma in situ encompasses the full epithelial thickness and is included under VAIN 3.

The overall incidence of VAIN is estimated to be 0.2 to 0.3 cases per 100,000, with peak incidence found in women who are 40 and 60 years of age.[11] The incidence of VAIN 3, or in situ vaginal cancer, is estimated to be 0.1 per 100,000 women with peak incidence between ages 70 and 79 years, according to data from the U.S. Centers for Disease Control and Prevention's National Program of Cancer Registries and the National Cancer Institute's SEER Program.[12]

VAIN is typically asymptomatic.[13] As a result, many cases are detected after cytologic evaluation as part of surveillance in patients with a history of cervical intraepithelial neoplasia or invasive cervical carcinoma. Although the likelihood of VAIN progressing to invasive disease is difficult to predict for individual cases, multiple clinical series have demonstrated a significant overall increase in the risk of invasive vaginal cancer after a diagnosis of VAIN. Several retrospective studies have demonstrated a range of 2% to 20% of patients with VAIN progressing to invasive vaginal cancer.[13,14] The rate of occult invasive disease in patients with VAIN 3 has been reported to be as high as 28%.[15] The risk of malignant transformation in VAIN 1 and VAIN 2 is less clearly elucidated.

Risk Factors

HPV is implicated in the development of VAIN, though the relationship between HPV and the development of intraepithelial neoplasia has been best demonstrated for cervical lesions. HPV 16 and HPV 18 are the most prevalent subtypes associated with VAIN. It is estimated that HPV 16/18 is identified in 40% of VAIN 1 and 60% of high-grade VAIN 2/3 cases.[16] With the widespread implementation of HPV vaccination, it is anticipated that the incidence of VAIN will start to decline. It is predicted that HPV vaccination will ultimately prevent up to 70% of VAIN cases.[17]

The diagnosis of VAIN is often associated with prior or concurrent neoplasia elsewhere in the lower genital tract. Multiple series suggest approximately 50% to 90% of patients with VAIN have concurrent or prior history of intraepithelial neoplasia or carcinoma of the cervix or vulva.[14,18,19]

Treatment Options

In general, women with low-grade VAIN can be offered close surveillance, as lesions often regress spontaneously (Algorithm 79.1). In a study by Aho et al, 78% of patients with VAIN 1 or VAIN 2 had spontaneous regression of disease without treatment.[14] Over time, however, VAIN 1 can recur; in one series, up to 54% of patients with VAIN 1 who were observed ultimately developed recurrent, persistent, or progressive disease,[11] at a median time of 17 months. High-grade VAIN has a higher likelihood of occult invasive disease and progression to invasive disease[15,20] and is

typically treated aggressively. There is currently no consensus on optimal treatment modality for patients with high-grade VAIN. Treatment approaches include local excision, partial or total vaginectomy, laser vaporization, electrocoagulation, topical 5% fluorouracil administration, topical 5% imiquimod, and radiation.[19-27] Reported success rates for different approaches range from 48% to 100% for laser vaporization,[28,29] 52% to 100% for colpectomy,[15,20,30] 75% to 100% for topical 5-fluorouracil (5-FU),[21,31-35] 57% to 86% for topical 5% imiquimod,[27] and 83% to 100% for radiation[23,36-39] (Table 79.1). Given the breadth of available therapies, an individualized approach to patient management is advised, with consideration given to the patient's overall health, desire to preserve sexual function, candidacy for surgery, disease multifocality, and prior treatment failures.

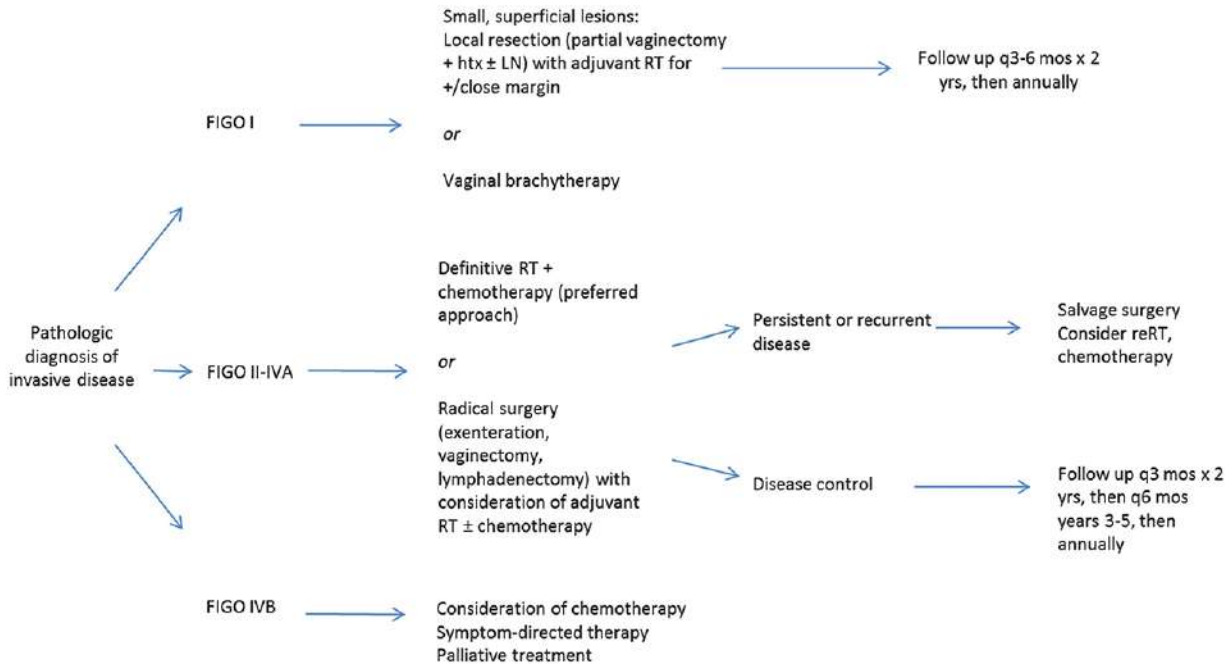
TABLE 79.1 VAGINAL INTRAEPITHELIAL NEOPLASIA OUTCOMES BY TREATMENT MODALITY

Series	Follow-Up	# of Pts	% Recurrence	Comments
Radiation				
Prempree et al[76]		7	0	ICB 70-80 Gy
Chyle et al[59]		37	17	ICB or orthovoltage radiation
MacLeod et al[39]	46 mo (mean)	14	14	HDR-ICB, 34-45 Gy to vaginal surface, 4-10 fx
Ogino et al[38]	13-153 mo	6	0	HDR-ICB, mean dose 23.3 Gy
Perez et al[58]		20	6	ICB 60-70 Gy
Graham et al[25]	77 mo	22	14	MDR-ICB, 48 Gy to point Z
Blanchard et al[36]	79 mo	28	7	LDR, 60 Gy to 5 mm below mucosa
Song et al[40]	48 mo	34	6	HDR-ICB, 40 Gy in 8 fx
Zolciak-Siwinska et al[60]	39 mo	20	10	HDR-ICB, 6-7.5 Gy × 3-5 fx
Surgery				
Benedet et al[53]	>5 y	136	25	WLE, PV, TV
Lenehan et al[13]	5-112 mo	19	16	PV, TV

Series	Follow-Up	# of Pts	% Recurrence	Comments
Ireland and Monaghan[41]	3 mo-11 y	25	4	PV, TV
Hoffman et al[15]	6-73 mo	32	17	PV; 28% invasive cancer
Fanning et al[42]	1.8 y	15	0	PV; 6.6% invasive cancer
Cheng et al[18]	1-124 mo	35	34	WLE
Dodge et al[43]	>7 mo	13	0	PV
Indermaur et al[20]	2-9 mo	105	12	PV, 12% invasive cancer
Terzakis et al[44]	24 mo	23	25	
Gunderson et al[11]	1-194 mo	44	27	PV, LE
Laser Therapy				
Jobson and Homesley[45]	6-27 mo	24	17	
Audet-LaPointe et al[46]	7-85 mo	32	28	3.8% invasive cancer at excision 3/11 w/invasive cancer at recurrence
Hoffman et al[28]	2.2 y (mean)	26	42	
Diakomanolis et al[47]	35-82 mo	25	32	
Campagnutta et al[48]	13-90 mo	39	23	
Dodge et al[43]	>7 mo	42	38	
Perrotta et al[49]	12-78 mo	21	14	
Gunderson et al[11]	1-194 mo	34	47	
Topical 5-FU				
Woodruff et al[32]	3-7 y	9	11	1%-2% 5-FU q mo
Petrilli et al[21]	2-60 mo	15	20	BID × 5 d

Series	Follow-Up	# of Pts	% Recurrence	Comments
Kirwan and Naftalin[35]	4-42 mo	14	7	q wk × 10 wk
Krebs[31]	12-84 mo	37	19	q wk × 10 wk
Audet-Lapointe et al[46]	9-42 mo	12	17	q d × 5 d
Dodge et al[43]	>7 mo	22	59	
Topical Imiquimod				
Diakomanolis et al[55]		3	See note	3 × weekly × 8 wk 3 pts with high-grade disease, therapy revealed regression to VAIN1 (*n* = 2) or cure (*n* = 1).
Buck and Guth[54]		56	14	0.25 g q wk × 3 wk

HDR, high-dose rate; ICB, intracavitary brachytherapy; LDR, low-dose rate; MDR, medium-dose rate; PV, partial vaginectomy; TV, total vaginectomy; WLE, wide local excision.



ALGORITHM 79.1 Treatment schematic for vaginal cancer based on International Federation of Obstetrics and Gynecology classification.

Surgical and Ablative Therapies

Surgical excision for VAIN is an option in select cases, particularly for vaginal vault lesions or lesions close to the introitus. Approaches include wide local excision, partial vaginectomy, and, in rare cases, total vaginectomy for highly extensive disease, which provides the advantage of obtaining a complete pathologic diagnosis. Most resections can be performed through a transvaginal approach. Smaller lesions can be excised or ablated using a cold-knife approach, electrosurgical loop excision, laser, or via ultrasonic surgical aspiration.[50-52]

Location of VAIN in the vaginal vault or posthysterectomy suture recesses may require partial vaginectomy for complete resection, as redundancy of the vaginal mucosa makes it difficult to rule out occult disease with biopsy alone. Multifocal or extensive lesions may require a more extensive approach, such as total vaginectomy with or without skin grafting.[20]

Overall, a series looking specifically at upper vaginectomy report control rates of 68% to 88%.[15,20,30,53] Potential complications depend on the location of the lesion and the extent and method of surgical resection and range from vaginal shortening and stenosis to standard postoperative morbidity associated with abdominal procedures, such as injury to bowel or bladder. Complication rates of upper vaginectomy have been variably reported; in the series by Indermaur, there was a 9% complication rate. It should be noted that patients with a history of radiation treatment are at higher risk of postoperative complications, with a higher rate of fistula formation reported in one study.[18]

Topical Treatments

Topical treatments include topical 5-FU and 5% imiquimod cream, with response rates of 41% to 88% for 5-FU and 50% to 86% for imiquimod.[23,31-33,35,54-56] Imiquimod increases the levels of interferon-α (IFN-α), interleukin-12, and tumor necrosis factor[55] and is thought to result in immunomodulation of the vaginal mucosa. Long-term efficacy is unknown as well as response rates in immunocompromised patients.

Topical therapies have been utilized in patients with early-stage lesions, multifocal disease, or multiple comorbidities, rendering them nonideal

surgical candidates. Topical creams are favored in the management of young, HPV-positive women presenting with multifocal lesions. Topical applications have also been utilized prior to surgery to reduce lesion size and improve the stripping of neoplastic epithelial cells from the underlying stroma.[19] Side effects of topical treatments include local irritation, burning, and ulceration.[32,33]

Radiation Therapy

In general, radiation is reserved for patients who relapse after more conservative treatments, are poor surgical candidates, have extensive multifocal disease, and/or have VAIN 3, particularly if there is an in situ disease component. Numerous small series over the past 20 to 30 years have reported control rates ranging from 80% to 100%.[13,23-25,36-38,57] Drawbacks to radiation include potential undertreatment of occult invasive disease, the risk of secondary malignancy, and long-term morbidity, although there are no prospective data available regarding the impact of treatment on sexual function and quality of life. High-dose rate (HDR), medium-dose rate (MDR), and low-dose rate (LDR) techniques have been reported with acceptable results, although it is difficult to compare regimens because of small patient numbers, generally short follow-up times, and overall nonuniformity among series.

Overall, excellent local control and low toxicity have been reported for LDR brachytherapy (BT). LDR treatment is delivered with an intracavitary vaginal cylinder using cesium-137. Typically, a dose of 60 Gy is prescribed to the vaginal mucosa, but a wide range of doses, depending on the depth of dose prescription, as well as a variety of techniques, have been reported.[23,36,37,58] Chyle et al[59] prescribed 70 to 80 Gy to the vaginal surface and reported a 17% recurrence rate at 10 years in their series of 37 patients. Perez et al[58] treated patients to the vaginal surface with a dose of 60 to 70 Gy and reported one recurrence out of 20 patients. The recurrence occurred in the distal vagina and was noted to be a marginal recurrence. Blanchard et al[36] published a series on 28 patients with VAIN 3 treated at Institut Gustave Roussy from 1985 to 2008. Patients were treated with LDR BT, using a vaginal mold technique, to a dose of 60 Gy prescribed 5 mm below the vaginal surface; 18 patients received treatment to the upper half of the

vagina, 6 were treated to the upper two-thirds, and 4 were treated to the whole-vaginal length. With a median follow-up time of 41 months, the authors report only one in-field recurrence, with a 10-year local control rate of 93%. Treatment with LDR BT is overall well tolerated; in the Perez series, there was only one grade 3 urinary complication among 40 patients with VAIN 3 or stage 1 vaginal cancer treated with LDR.[58]

There are limited data on the use of MDR BT treatment for VAIN. Graham et al[25] reviewed their experience using MDR intracavitary brachytherapy (ICB) for VAIN 3 at the Beatson Oncology Centre in Glasgow, UK. Using an MDR Selectron, 48 Gy was prescribed 0.5 cm lateral to the ovoid surface (point Z) over two insertions, spaced 1 week apart. Ovoids were chosen over vaginal cylinder placement in order to adequately cover epithelium sutured into the superolateral vagina at hysterectomy. With a median follow-up duration of 77 months, recurrent/residual VAIN 3 was documented in three patients, and two of these patients subsequently developed invasive or microinvasive vaginal carcinoma. One other patient developed late progression 14 years after treatment.

Several series have reported promising results for HDR BT, with disease-free survival (DFS) rates of 90% or greater. Ogino et al[38] reported their experience treating six patients with VAIN 3 at Kanagawa Cancer Center from 1983 to 1993, with a mean dose of 23.3 Gy (range, 15-30 Gy); most treatments were delivered in five fractions using two ovoids, with dose calculated to a point 1 cm superior to the vaginal apex. Lesions distal to the vaginal vault had doses calculated 1 cm beyond the plane of the vaginal cylinder in order to deliver adequate dose to the entire vagina. The median follow-up was 90.5 months, with no evidence of disease recurrence in the treated patients. MacLeod et al[39] reviewed their experience treating 14 patients with VAIN 3 from 1985 to 1995. Total dose was 34 to 45 Gy to the vaginal surface, in 8.5-Gy fractions delivered twice a week, or 4.5-Gy fractions delivered 4 times a week. One patient developed invasive cancer, and one patient had persistent VAIN 3. There were no major acute toxicities, and two patients developed late grade 3 vaginal atrophy and stenosis. According to one study that evaluated toxicity after the use of HDR BT for VAIN in 20 patients, with utilization of the CTCAE scale, a biologically equivalent dose of 70 Gy or greater results in significantly

greater toxicity. The most commonly seen toxicities were decreased libido, vaginal discharge, dryness, mucositis, stenosis, and vaginitis.[60]

Squamous Cell Carcinoma

Clinical Presentation

Symptoms

Up to 20% of women are asymptomatic at the time of diagnosis,[61] with lesions detected via cytologic screening or by speculum examination. SCC accounts for 65% to 85% of vaginal cancer cases,[8] and the greatest proportion of women present with stage I disease (36%). Up to 65% of patients with vaginal cancer present with irregular vaginal bleeding as their primary symptom.[61,62] Vaginal discharge is the second most common symptom, occurring in 10% to 15% of patients. Less frequent symptoms, associated with locally advanced disease, include the presence of a mass; pain; urinary symptoms including frequency, dysuria, or hematuria; or gastrointestinal complaints, such as tenesmus, constipation, or melena. Because of the proximity of anterior wall lesions to the urethra and bladder, urinary symptoms can be seen more commonly in vaginal cancer than in cervical cancer.

Location

Vaginal cancer most frequently involves the superior one-third of the vaginal canal, with series reporting 50% to 83% of cases occurring in this region.[53,63-66] There is approximately equal involvement of the middle and inferior thirds,[53] although some studies suggest that involvement of the lower third is more common than involvement of the middle third.[61,63] The lateral walls are less frequently involved. Tumors may exhibit an exophytic or ulcerative, infiltrating growth pattern.

A high proportion of patients have a history of prior hysterectomy. Involvement of the cervix (if present) or vulva at the time of diagnosis excludes classification as a primary vaginal cancer. Lesions can extend radially, either into the lumen to form exophytic masses or through the vaginal wall to invade surrounding musculature and organs. Anterior wall lesions can infiltrate the vesicovaginal septum, urethra, and/or bladder. Posterior wall lesions can infiltrate the rectovaginal septum and involve the

rectal mucosa. Advanced disease can extend laterally toward the parametrium and paracolpal tissues or into the urogenital diaphragm, levator ani muscles, or pelvic fascia and eventually to the pelvic side wall.

Advanced or recurrent disease can present with distant metastases. The most frequent site of hematogenous metastasis is the lung, with less commonly noted sites being liver and bone.[59] In a series by Perez et al,[67] the incidence of distant metastasis was 16% for stage I, 31% for stage II, 46% for stage IIB, 62% for stage III, and 50% for stage IV. Some histologies may have a higher likelihood of distant metastases than others. Chyle et al[59] noted a higher incidence of distant metastases in patients with adenocarcinoma (48%) than in those with SCC (10%), with correspondingly lower 10-year survival rates (20% vs 50%).

Histopathology

Grossly, SCC of the vagina can present as nodular, ulcerated, indurated, exophytic, or endophytic lesions. Histologically, tumors are graded as well, moderate, or poorly differentiated and have been described as keratinizing, nonkeratinizing, basaloid, warty, or verrucous. The majority of these lesions are nonkeratinizing and moderately differentiated.[68] It is not possible to histologically distinguish a primary vaginal SCC from recurrent cervical or vulvar carcinoma.

Verrucous carcinoma is a distinct histologic variant of vaginal SCC[69] that typically presents as a well-circumscribed, soft, cauliflower-like mass that is microscopically well differentiated, with a papillary growth pattern and acanthotic epithelium. There is surface maturation with parakeratosis or hyperkeratosis without koilocytosis. This variant of SCC exhibits less aggressive behavior and rarely metastasizes.[69] Given the extremely low incidence of these cancers, it has been difficult to evaluate therapeutic efficacy; while case reports from other sites question the utility of radiation, there is no clear evidence of resistance of transformation to a more aggressive histology in the more modern literature.

Sarcomatoid SCC is a rare subset of vaginal SCC, comprising 2% of all cases. It is characterized by spindle-shaped neoplastic cells that can initially be mistaken for sarcoma. However, positive stains for cytokeratin help

distinguish sarcomatoid SCC as a poorly differentiated variant of vaginal SCC.[70]

Patterns of Lymphatic Drainage

The vagina has a complex pattern of lymphatic drainage, with multiple interconnections. The upper vagina drains to the obturator and hypogastric nodes, similar to the cervix. The lower vagina drains to the inguinal, femoral, and external iliac nodes, and posteriorly situated lesions can drain to the inferior gluteal, presacral, or perirectal nodes. Lymphatic channels in the mucosa run parallel to networks of channels in the submucosa and muscular layer, ultimately converging to form trunks at the vaginal wall periphery, which subsequently drain into major pelvic nodal groups.

Because of considerable crossover drainage, the location of the primary tumor is not a reliable indicator of drainage site. Frumovitz et al utilized lymphoscintigraphy to determine patterns of lymphatic drainage in 14 women diagnosed with primary vaginal cancers[71] and found a substantial degree of anomalous drainage, resulting in a change in radiation treatment for 33% of patients. For example, among four women with lesions located in the upper third of the vagina, which is predicted to drain along the cervical lymphatic chains to the pelvis, two (50%) were found to have a sentinel node in the inguinal region. Among five women with lesions located at the vaginal introitus, a location predicted to drain along the vulvar lymphatic chains to the inguinal triangle, three (60%) were found to have a sentinel node in the pelvis.

The risk of nodal involvement increases significantly with stage. At diagnosis, up to 20% of patients have clinically positive inguinal nodes, with reported ranges of 5.3% to 20%.[58,67] Sparse data on nodal metastases are derived from a series in which exploratory laparotomies and lymphadenectomies were performed.[72] However, the true incidence of positive lymph nodes is difficult to determine because most patients receive treatment with radiation therapy (RT) and do not undergo surgical lymphadenectomy. The incidence of lymph node involvement has been reported to be 0% to 14% in stage I and 21% to 32% in stage II disease.[72-74] The incidence of nodal involvement in stages III and IV has been reported to be as high as 78% and 83%, respectively.[63]

The risk of nodal failure increases significantly if there is local recurrence. Chyle et al[59] reported 10-year inguinal and pelvic failure rates of 16% and 28%, respectively, in patients with local recurrence, in contrast to 2% and 4%, respectively, in patients without local recurrence.

Staging

The AJCC[75] and FIGO[5] systems are used to stage vaginal cancer (Tables 79.2 and 79.3). Neither system incorporates computed tomography (CT), positron emission tomography (PET), or magnetic resonance imaging (MRI) findings, though these are recommended where available to provide enhanced information about sites of disease spread. Primary vaginal melanomas and lymphomas are staged according to the AJCC staging systems for melanomas and lymphomas, respectively.[75]

TABLE 79.2 INTERNATIONAL FEDERATION OF GYNECOLOGY AND OBSTETRICS STAGING SYSTEM FOR CARCINOMA OF THE VAGINA

Stage	Description
Stage I	Carcinoma is limited to vaginal wall.
Stage II	Carcinoma has involved the subvaginal tissue but has not extended to the pelvic wall.
Stage III	Carcinoma has extended to the pelvic wall.[a]
Stage IV	Carcinoma has extended beyond the true pelvic or has involved the mucosa of the bladder or rectum; bullous edema as such does not permit a case to be allotted to stage IV.
Stage IVA	Tumor invades bladder and/or rectal mucosa and/or direct extension beyond the true pelvis.

[a]Pelvic wall is defined as muscle, fascia, neurovascular structures, or skeletal portions of the bony pelvis.

From FIGO Committee on Gynecologic Oncology. Current FIGO staging for cancer of the vagina, fallopian tube, ovary, and gestational trophoblastic neoplasia. *Int J Gynaecol Obstet*. 2009;105(1):3-4. Copyright © 2009 International Federation of Gynecology and Obstetrics. Reprinted by permission of John Wiley & Sons.

TABLE 79.3 AMERICAN JOINT COMMISSION ON CANCER STAGING OF VAGINAL CANCER, SEVENTH EDITION

Primary Tumor (T)

Tx	Primary tumor cannot be assessed.
T0	No evidence of primary tumor
Tis/0	Carcinoma in situ
T1/I	Tumor confined to the vagina.
T2/II	Tumor invades paravaginal tissues but not to the pelvic wall.
T3/III	Tumor extends to the pelvic wall.[a]
T4/IVA	Tumor invades the mucosa of the bladder or rectum and/or extends beyond the pelvis (bullous edema is not sufficient to classify a tumor as T4).
Regional Lymph Nodes (N)	
Nx	Regional lymph nodes cannot be assessed.
N0	No regional lymph nodes
N1/IVB	Pelvic or inguinal lymph node metastasis
Distant Metastasis (M)	
Mx	Distant metastasis cannot be assessed.
M0	No distant metastasis
M1/IVB	Distant metastasis
Stage Groupings	
Stage 0	Tis N0 M0
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T1–3 N1 M0, T3 N0 M0
Stage IVA	T4, any N, M0
Stage IVB	Any T, any N, M1

[a]Pelvic wall is defined as muscle, fascia, neurovascular structures, or skeletal portions of the bony pelvis.

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For patients with a prior gynecologic malignancy, a 5-year period free of disease is generally considered adequate to allow for distinction between

recurrent disease and a new primary vaginal cancer. FIGO no longer recognizes carcinoma in situ as stage 0.

Stage I disease is defined as limited to the vaginal wall, and stage II disease involves subvaginal tissue without extension to the pelvic wall. Discriminating between stages I and II can be subjective; thin tumors less than 0.5 cm are generally classified as stage I, with thicker infiltrating tumors or those with paravaginal nodularity classified as stage II. Perez et al proposed a modification to the FIGO system in 1973, distinguishing tumors with paravaginal submucosal extension only (stage IIA) from tumors with parametrial infiltration (stage IIB).[58] The study reported a 20% 5-year survival difference (55% vs 35%) between stages IIA and IIB. This modification has not been adopted into FIGO staging. However, some investigators consider the distinction to be prognostically relevant.[67,76] Stage III disease extends to the pelvic sidewall, has caused hydronephrosis, extends to the lower third of the vagina, or involves lymph nodes. Stage IVA disease reflects spread to the bladder or bowel, while stage IVB disease indicates spread to distant sites.

Diagnostic Workup

The diagnostic workup should start with a thorough history and physical examination. During speculum examination, the speculum blades can obscure the anterior and posterior walls, so it is essential to rotate the speculum for visualization of all four walls from the introitus to the apex. Bimanual and rectovaginal examinations, with careful digital palpation, should be performed, assessing for parametrial and pelvic sidewall involvement and invasion of tumor to the rectal mucosa. Complete assessment of tumor extent and assessment of vaginal walls are facilitated by examination under anesthesia.

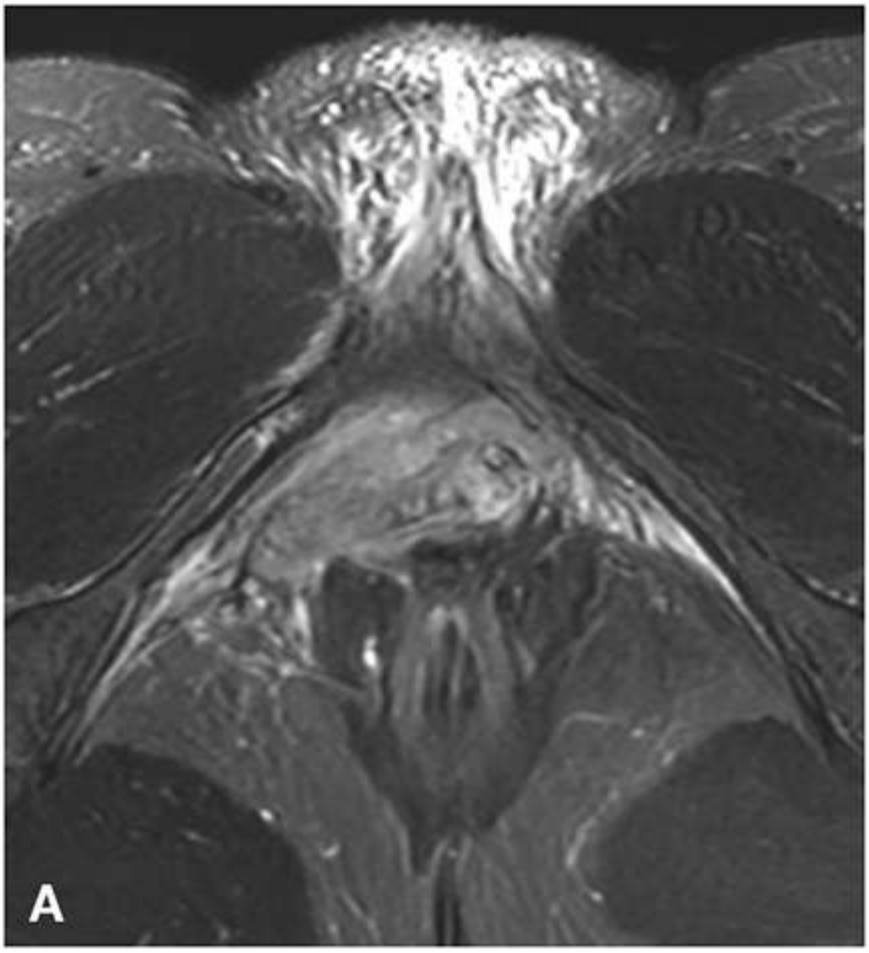
Inguinal nodes should be palpated for disease involvement, particularly if the primary lesion is situated in the lower portion of the vagina, as 5% to 20% of patients have been reported to have involved inguinal nodes at presentation.[58,67] Suspicious nodes usually warrant a biopsy. Laboratory tests include a complete blood count with differential and assessment of renal and hepatic function.

A definitive diagnosis is achieved with biopsy of suspected lesions, which can present as an exophytic mass, plaque, or ulcer. If a lesion is not visible in the setting of abnormal cytology, colposcopy with acetic acid, followed by Lugol iodine stain, can be conducted, along with biopsies of any white epithelium or atypical vascularity. Iodine will identify Schiller-positive regions, which are nonstaining and should correspond with areas identified following application of acetic acid. Adequate biopsies should include the cervix, if present, to rule out a cervical primary. Patients can present with multiple regions of abnormality.

FIGO staging of vaginal cancer is clinical and allows chest x-ray, intravenous pyelography (IVP), barium enema, cystoscopy, and proctosigmoidoscopy. FIGO encourages the utilization of more advanced imaging modalities, such as CT imaging, MRI, and PET, as guidance for treatment, though imaging findings cannot be used to reassign stage.[77] Cystoscopy or proctosigmoidoscopy may be necessary in patients with symptoms suggestive of bladder or rectal infiltration. CT of the pelvis can be obtained in place of IVP to assess the renal parenchyma and also to obtain information on the extent of local disease and lymph node status. MRI can provide salient treatment planning information by characterizing the extent of invasion and differentiating malignant tumor, which is isointense to muscle on T1, and hyperintense on T2, from normal structures and/or fibrosis.[78] Advantages of MRI over other imaging modalities include superior soft tissue contrast resolution, allowing accurate assessment of tumor volume and extent of local invasion and accurate assessment of pelvic nodal involvement. In general, MRI is regarded as superior to CT for staging of gynecologic malignancies and should be obtained when available.

PET has shown efficacy in detecting the extent of primary tumor and abnormal lymph nodes in vaginal cancer with higher sensitivity than CT (Figure 79.3), as is the case with cervical carcinoma.[79,80] Primary vaginal carcinoma and metastatic lesions demonstrate avid uptake of 2-[fluorine 18] fluoro-2-deoxy-D-glucose (FDG). In one study, 23 patients with primary vaginal carcinoma received both PET and CT during staging. CT identified the primary tumor in only 43% of patients, whereas PET identified the tumor in 100%. PET identified suspicious uptake in groin and pelvic nodes

in 8 of 23 patients, compared to 4 of 23 with CT. Treatment planning was modified in 14% of patients because of findings from PET, and the authors concluded that PET detects primary tumor and abnormal lymph nodes more often than CT.[79] Another series compared detection of suspicious lymph nodes using PET/CT versus MRI and CT; PET/CT outperformed both MRI and CT, resulting in a change in management in 36% of cases.[80] It is important that the patient have an empty bladder prior to imaging, as physiologic FDG activity in a filled bladder can potentially interfere with accurate estimation of vaginal involvement. In practice, most patients undergo planning for radiation treatment with multiple imaging modalities.[81]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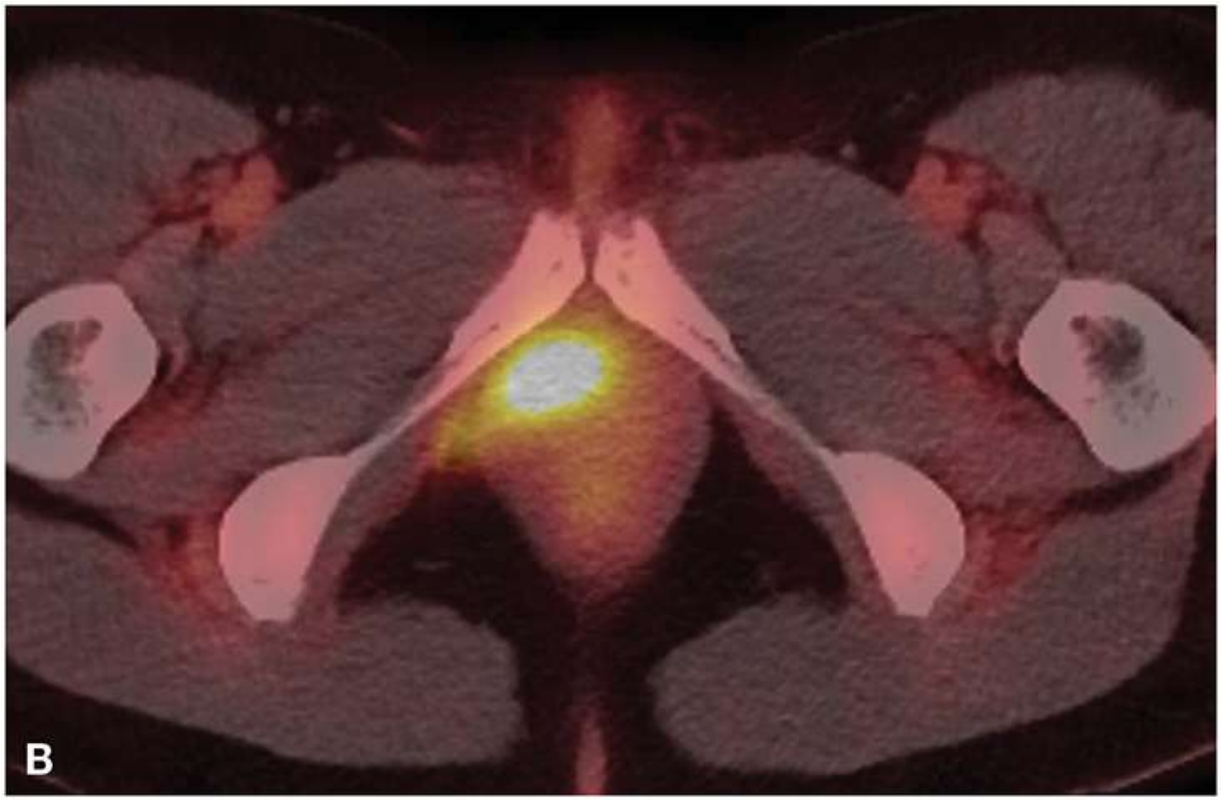
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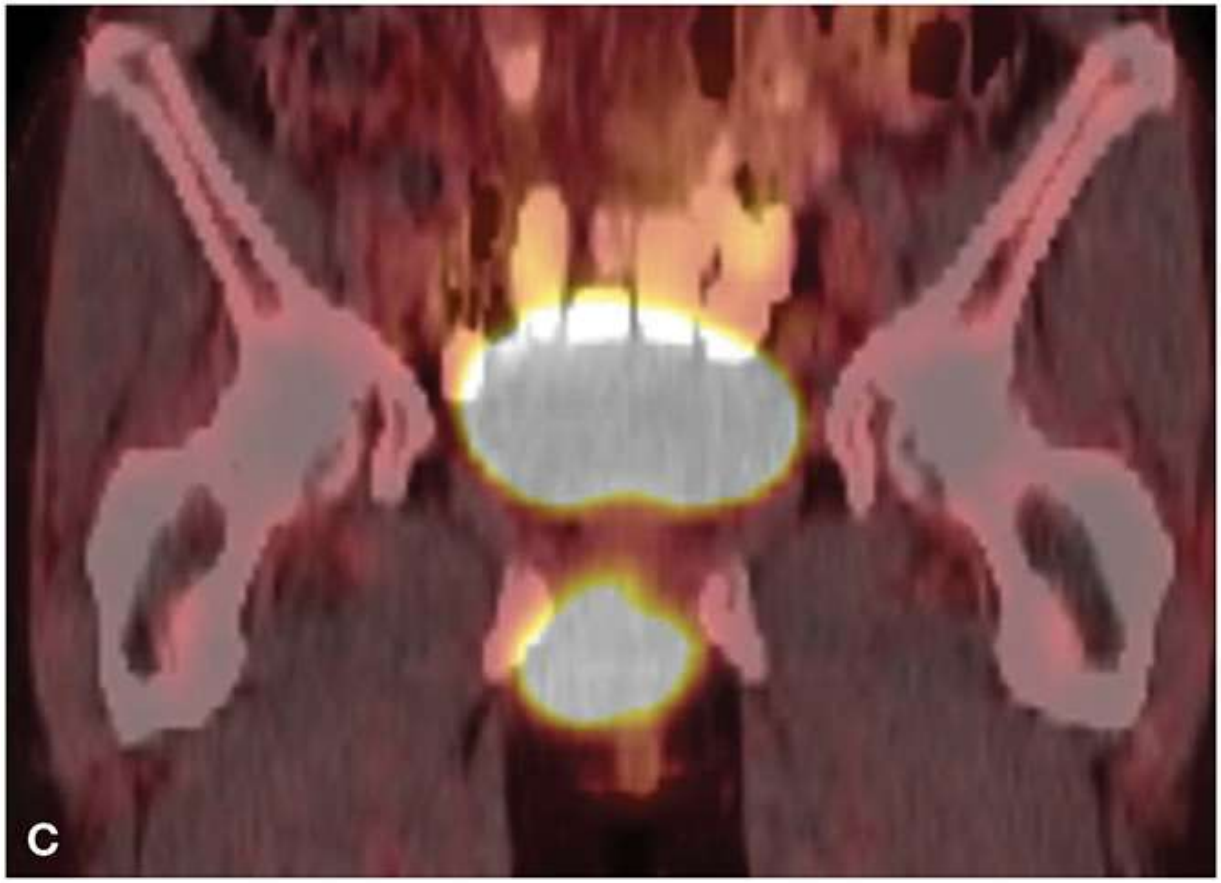


FIGURE 79.3 A. T2-weighted axial magnetic resonance imaging (MRI) of the pelvis showing a low pelvic mass arising in the vagina and spreading to the urethra and abutting the vulva. MRI is able to delineate individual anatomic structure and can assist in tumor segmentation for treatment planning. B. Fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) axial image showing hypermetabolic activity to identify the region but with less precision than MRI. C. Coronal FDG-PET showing a distinct region separating the vagina from the bladder.

The European Society for Radiotherapy and Oncology (ESTRO), European Society of Gynaecological Oncology (ESGO), and European Society for Paediatric Oncology (SIOPe) have developed joint evidence-based guidelines that include the workup of vaginal cancers, which concur with these recommendations.[81]

Risk Factors

Risk factors for primary vaginal SCC are similar to VAIN and cervical neoplasia. Commonly cited factors include HPV infection and/or history of

cervical or vulvar intraepithelial neoplasia, immunosuppression, multiple sexual partners, smoking, and early age at first intercourse.

It is believed that majority of cases of vaginal cancer can be attributed to HPV infection. According to a meta-analysis composed of 14 studies, the overall HPV prevalence was 70% for vaginal carcinomas, with the most common subtypes as follows: HPV 16 (53.7%), HPV 18 (7.6%), and HPV 31 (5.6%). Multiple subtypes of HPV were identified in 3.4% of vaginal carcinoma cases.[82] In a population-based case-control study of 156 women with VAIN or invasive cancer, HPV DNA was detectable in 80% of patients with in situ disease and 60% of those with invasive disease, and 30% of patients reported a history of treatment for invasive malignancy, most commonly cervix, or in situ anogenital neoplasia.[83]

Patients with a history of cervical cancer have a significantly higher risk of developing in situ as well as invasive carcinoma of the vagina. Studies suggest that 10% to 50% of patients with a history of VAIN or invasive carcinoma of the vagina have undergone treatment for in situ or invasive cervical carcinoma,[13,59,61,67,84-88] with the interval from the treatment of cervical disease to the development of vaginal carcinoma averaging approximately 14 years.[61,72] Early hysterectomy appears to be a risk factor in some studies, if performed for malignant or premalignant disease.[83,89]

The role of ionizing radiation to the pelvis in the development of vaginal carcinoma is unclear, with conflicting reports. According to one study that analyzed 1,200 patients treated over a 20-year period for carcinoma of the cervix, prior RT was not shown to result in increased secondary pelvic neoplasms.[90] A second study by Boice et al,[91] however, reported a 14-fold increased risk of vaginal cancer in women with a history of pelvic irradiation before the age of 45, with a significant dose-response relationship.

Another potential risk factor is chronic irritation of the vaginal mucosa, resulting in chronic inflammation, hyperkeratosis, thickening, and acanthosis,[92] with subsequent metaplastic and dysplastic changes; however, this is not proven. Although older studies showed that more vaginal cancers arise from the posterior vaginal wall, other studies report approximately equal distribution of invasive carcinomas on the anterior and posterior walls,[53,61,63,64,93] arguing against the theory that pooling of irritating substances in the posterior fornix contributes to the development of vaginal

cancers, particularly on the posterior wall. Chronic irritation from the use of vaginal pessaries has also been implicated as a contributor in vaginal cancer development.[94]

Other, lesser reported risk factors include low socioeconomic status, history of genital warts, and vaginal trauma.[95] A larger case-control study of 36,856 women found an increased risk of vaginal cancer in alcoholic women, likely associated with a higher incidence of lifestyle factors, such as promiscuity and smoking, which are also associated with a higher incidence of HPV infection. HIV-infected and other immunocompromised women are at higher risk of developing vaginal carcinoma, which tends to behave more aggressively than in the immunocompetent patients.[92]

Prognostic Factors

Stage at the time of presentation is the most significant prognostic factor.[8,58,86,96] According to an NCDB study by Creasman et al, 5-year survival rates are as follows: 96% for stage 0, 73% for stage I, 58% for stage II, and 36% for stage III/IV disease.[10]

The series by Shah et al,[8] based on SEER data for women diagnosed between 1990 and 2004, also reveals the correlation between stage and outcome, with 5-year disease-specific survival rates of 84% for stage I, 75% for stage II, and 57% for stage III/IV; the adjusted hazard ratio (HR) for mortality, on multivariate analysis, was 4.67. In the Perez et al series,[67] 165 patients with primary vaginal cancer were treated with definitive RT and had 10-year actuarial DFS rates of 94% for stage 0, 75% for stage I, 55% for stage IIA, 43% for stage IIB, 32% for stage III, and 0% for stage IV.[97]

The size of the initial lesion is a prognostic factor that has shown significance in several series. The SEER database study,[8] which included 2,149 women with primary vaginal cancer, noted a significantly lower 5-year survival rate in women with tumors 4 cm or larger than in women with tumors smaller than 4 cm (65% vs 84%); however, size information was missing for 52% of women. After multivariate analysis, the women with the larger tumors had an adjusted HR of 1.71 for mortality. Chyle et al,[59] in their review of 301 patients treated at MD Anderson Cancer Center (MDACC) from 1953 to 1991, found that women with lesions larger than 5 cm in maximum diameter had a significantly higher 10-year local

recurrence rate than those with smaller lesions (40% vs 20%). The series by Hellman et al,[96] with 314 patients treated at the Karolinska University Hospital from 1956 to 1996, found only three factors to independently predict for poor survival on multivariate analysis: advanced age, tumor size 4 cm or larger, and advanced stage. Tumors comprising two-thirds or more of the vagina and tumors growing circumferentially were associated with an extremely poor prognosis. The series by Tran et al,[98] which reviewed records of 78 patients with SCC treated at Stanford University Medical Center from 1959 to 2005, also found size to be a prognostic factor for DFS on multivariate analysis, along with stage, prior hysterectomy, and pretreatment hemoglobin level. Smaller series by Tjalma et al[99] and Kirkbride et al[86] also describe adverse outcomes with larger tumor size. Other series have failed to show significance, but likely are hindered by small numbers, difficulties in accurate assessment of size, and treatment heterogeneity.

Extent of vaginal canal involvement has also been examined and found to be significant, perhaps because it is a surrogate for tumor size. In a series by Stock et al,[64] which examined 100 cases of primary vaginal carcinoma treated at Magee-Women's Hospital from 1962 to 1992, patients with involvement of one-third of the vaginal canal or less had a significantly higher 5-year DFS rate (61%) than patients with more extensive involvement (25%).

Several studies suggest HPV status is an indicator of a favorable prognosis. Fuste et al found a trend toward longer survival in women with HPV-positive tumors in their series of 32 patients, with median survival times of 113.9 versus 19.7 months for women with HPV-positive and HPV-negative tumors ($P = .15$).[100] Alonso et al evaluated 57 total patients, of whom 70.2% had evidence of high-risk HPV.[101] On multivariate analysis, HPV-positive status was a favorable prognostic variable for overall survival (OS) (HR 0.35, $P = .038$). Brunner et al,[102] evaluated 35 patients with primary invasive SCC of the vagina. Using in situ hybridization, HPV was detected in 51.4% of cases. There was no significant influence on clinical stage, grade, or tumor size, nor did prognosis differ between HPV-positive and HPV-negative tumors. However, in a subset of patients with FIGO stage III or higher disease, HPV positivity was found to correlate with improved DFS and OS, with *P* values of .004 and .023, respectively.

There is conflicting evidence on the impact of lesion location on prognosis; it has been noted in some,[59,65,103] but not all,[66,67] reports. In an analysis of 110 patients by Kucera et al,[104] 5-year survival rates were 60% for lesions of the upper third of the vagina, 37.5% for lesions of the middle third, and 37% for the lower third. Chyle et al[59] noted a 17% rate of pelvic relapse in patients with tumors in the upper third of the vagina, 36% for patients with tumors in the middle or lower third, and 42% for patients with whole-vaginal involvement. Lesions in the posterior wall were also noted to be associated with a worse prognosis than lesions involving the anterior vaginal wall,[59] with 10-year recurrence rates of 32% versus 19% on univariate analysis ($P < .007$). The Hellman series,[96] however, found no difference in prognosis between the anterior and posterior tumors. Similarly, histologic grade has been found to be an independent significant predictor of survival in several series,[65,86,103] but not others.[96] Hellman et al[96] evaluated the impact of tumor grade and other histopathologic variables (mitotic activity, koilocytosis, growth in vessels, lymphocytic reactions) and found no correlation with survival.

Several series suggest there is a correlation between older age and decreased survival.[11,96,103] For example, age was also noted to be a significant prognostic factor in the Urbanski et al series,[103] with 5-year survival rates of 83% for patients younger than 60 years compared to 25% for those aged 60 years or above ($P < .0001$). Age greater than 60 years was negatively associated with survival in the series by Gunderson et al, which examined a total of 110 patients (HR 2.16; $P = .0339$). Other series have failed to demonstrate the statistical significance of age.[58,105]

For patients treated with radiation, treatment time may be a significant factor impacting tumor control.[106,107] Overall treatment time of 9 weeks or less was associated with a pelvic tumor control rate of 97% as compared to 57% for treatment time greater than 9 weeks ($P < .01$).[121] Pingley et al also noted a correlation between treatment time and outcome; patients receiving BT within 4 weeks of external beam radiation therapy (EBRT) had a 5-year DFS rate of 60%, compared to a 30% rate in patients who had an interval greater than 4 weeks.[106]

Other possible prognostic factors include hemoglobin levels, prior hysterectomy, and smoking status. A hemoglobin level less than 12.5 g/dL prior to definitive treatment was prognostic for worse pelvic control and

disease-specific survival on multivariate analysis, along with prior hysterectomy, stage, and tumor size. Prior hysterectomy was a favorable prognostic factor on multivariate analysis.[98] This may reflect more rigorous surveillance in posthysterectomy patients, resulting in tumors discovered at an earlier stage, or may be a reflection of less overall vaginal tissue as a substrate for tumorigenesis. Two subsequent studies have identified hysterectomy as a significant prognostic factor, but only in univariate analysis.[59,96]

Treatment Options

Surgery

For most patients with invasive vaginal cancer, surgery has a limited role and radiation is the treatment of choice (see Algorithm 79.1). Because of the rarity of these lesions and the required individualization of treatment, it is recommended that patients are referred to a tertiary center with experienced practitioners. In general, surgery is considered beneficial only in carefully selected patients. Typically, amenable lesions are small, superficially invasive and well demarcated, and localized to the upper vagina. For patients who have previously undergone hysterectomy, a radical upper vaginectomy and pelvic lymphadenectomy can be considered. If the uterus is present, a radical hysterectomy (which include upper vaginectomy and radical parametrectomy) with lymph node assessment could be considered, particularly for patients with a lesion in the posterior proximal vagina.[6] Regardless of surgical procedure, wide negative margins are necessary.

Older surgical series often required pelvic exenteration in 40% to 50% of cases to obtain negative margins.[63,72] Invasive anterior wall lesions may require anterior exenteration, which removes the vagina, urethra, and bladder. Posterior exenteration for posterior vaginal wall lesions requires resection of the vagina and rectum. Deeply invasive, circumferential lesions may require a total exenteration in order to achieve clear margins. If there are positive margins, adjuvant radiation should be offered. Lesions that extend to the inferior vagina require a total vaginectomy with radical hysterectomy, pelvic lymphadenectomy, and, possibly, vulvovaginectomy and inguinofemoral lymphadenectomy.[61,63,64,85] It is not uncommon for

relatively small lesions to invade the rectum or urethra early in the disease course, given the close proximity of the vagina to these structures. Many of these exenterative surgeries also require plastic surgery reconstruction.

Extrapolating from the more robust evidence for cervical cancer, combining both surgery and radiation would likely increase toxicities. Given the similar survival outcomes with surgery alone and radiation alone for vaginal cancers, as well as the potentially devastating functional results associated with radical surgery, definitive radiation is the treatment of choice for most patients with invasive vaginal cancer and has largely replaced surgery as the primary therapeutic modality.

Exenterative surgical procedures can be considered for previously irradiated patients with a pelvic confined tumor who cannot receive further radiation.

Patients with advanced disease are typically not candidates for curative-intent surgery because of difficulty achieving negative margins, morbidity of resection, and metastatic disease.

Reported 5-year OS rates for stage I vaginal cancer treated with surgery range from 75% to 100% (Table 79.4).[10,64,72,85,99,108] The distinction between stages I and II disease is made clinically, based on physical examination, and can be subject to variability. The NCDB review for cancers of the vagina noted superior survival rates in patients treated with surgery,[10] though this likely reflects selection of healthier patients with good performance status for radical surgery. A more recent analysis utilizing the SEER database[8] found women with stage I disease treated with surgery only to have a lower risk of mortality than those treated with radiation only, combined modalities, or no treatment; however, this difference did not reach statistical significance. For patients with stage II vaginal cancer, there was a similar trend toward increased mortality in women who did not have surgery alone as their primary treatment modality, but values once again did not reach statistical significance in their multivariate-adjusted model.

TABLE 79.4 OUTCOMES AFTER PRIMARY SURGERY IN EARLY-STAGE VAGINAL CANCER

Series	Stage	# of Pts	Outcomes	Comments
Jain et al (2010-2015)[109]	I	10	1 y DFS 89%	6 pts received adjuvant treatment for + margins/nodes.
	II	1	1 y OS 100%	2 RV; 5 TV; 4 PV
Tjalma et al (1974-1999)[99]	I	26	5 y OS 91%	4 pts received adjuvant RT. 5 LE, 19 HTX, 2 EXT
Creasman et al (1985-1994)[10]	I	76	5 y OS 90%	
	II	34	5 y OS 70%	
Otton et al (1982-1998)[108]	I	8	5 y OS 100%	6 PV; 2 HTX + removal of vaginal cuff
Stock et al (1962-1992)[64]	I	17	5 y DFS 56%	6 LE, 7 PV, 4 RV
	II	33	5 y DFS 68%	6 EXT, 17 RV, 8 PV, 2 LE
Davis et al (1960-1987)[72]	I/II	52	5 y OS 85%	21 EXT
Rubin et al (1957-1980)[63]	I/II	9	5 y OS 75%	
Ball and Berman (1947-1978)[85]	I	19	5 y OS 84%	4 EXT
	II	8	5 y OS 63%	1 EXT

DFS, disease-free survival; EXT, exenteration; HTX, hysterectomy; LE, local excision; OS, overall survival; pts, patients; PV, partial vaginectomy; RV, radical vaginectomy; TV, total vaginectomy.

Ling et al, in a small series consisting of four patients with stage I disease, report their experience using laparoscopic radical hysterectomy with vaginectomy and reconstruction of the vagina.[110] With follow-up times ranging from 40 to 54 months, they report all patients to be free of disease, with satisfactory sexual function. The authors suggest that laparoscopic surgery can be an option for select patients with early-stage disease, with good outcomes.

Other series also report excellent results with primary surgical therapy, though authors acknowledge bias resulting from the selection of healthier patients with less extensive disease for primary surgery over radiation. In a review of 100 cases by Stock et al,[64] with 85 SCC cases, surgical treatment was noted to be a significantly favorable prognostic factor for DFS (63%), compared to treatment with radiation alone (26%). This benefit appears to skew from the advanced-stage patients and potentially, therefore, with a selection bias. For stage I patients, DFS rates were 56% and 80% for patients treated with surgery versus radiation. For stage II patients, survival rates were 68% and 31% after surgery and radiation, respectively, though this likely reflects selection bias, with patients with more extensive involvement offered radiation. Overall 5-year survival was 47%. Stock et al concluded that surgery consisting of radical hysterectomy, pelvic lymphadenectomy, and upper vaginectomy could be reasonable for stage I lesions and select stage II lesions, with radiation being the preferred primary modality for patients with stage IIB disease. It should be noted, however, that 23 (70%) of 33 stage II patients treated with surgery required a total vaginectomy or exenterative procedure, which carries significant morbidity and functional impairment.

Smaller series also support the use of surgery in select patients with early-stage disease. Tjalma et al[99] reported on 55 cases of primary vaginal SCC. Of 27 patients with stage I disease, 26 received surgery, with 4 subsequently receiving some form of adjuvant radiation. With a median follow-up time of 45 months, 5-year survival was reported to be 91%. Otton et al,[108] in their retrospective review of 70 patients with stages I to II vaginal carcinoma, treated at Queensland Centre for Gynaecological Cancer between 1982 and 1998, report that patients treated with surgery alone or a combination of surgery and radiation had significantly longer survival times than patients treated with radiation alone. The authors suggest that surgery may be effective in a select subset of patients with small, localized tumors that permit clear surgical margins. Peters et al[66] reviewed records of 86 patients with vaginal carcinoma, including 68 SCC cases, treated at University of Michigan Medical Center. Twelve selected patients had surgery as primary therapy, with a 75% survival rate. Similarly, Rubin et al[63] reported on eight patients with stage I or II disease who received surgery as primary treatment; 5-year survival was 75% and the overall local

control rate for the stage I patients was 80%, suggesting that highly selected patients can achieve excellent outcomes with surgery. Davis et al[72] reported on 89 patients with vaginal carcinoma, treated primarily at the Mayo Clinic from 1960 to 1987. A total of 52 patients were treated with surgery as primary therapy, with 5-year survival of 85%, compared to 65% for patients who received radiation alone. In the stage II patients, the 5-year survival rates were 49%, 50%, and 69% for surgery, radiation, and combined treatment with surgery and radiation, respectively. However, treatment modalities cannot be effectively compared using retrospective series, given selection biases.

Neoadjuvant chemotherapy is not recommended, given limited data and risk of progression during chemotherapy. A case report documented the use of neoadjuvant chemotherapy consisting of bleomycin and cisplatin, followed by radical surgery, for one patient with stage II SCC of the vagina. The patient was free of disease, with satisfactory sexual function, at 30 months.[111] Results on 11 patients with stage II SCC of the vagina,[112] treated with three cycles of neoadjuvant paclitaxel and cisplatin followed by surgical resection, showed that 27% achieved a complete response. All patients had disease-free resection margins after surgery, and only one patient had positive lymph nodes. At a median follow-up time of 75 months, 10 (91%) of 11 patients were alive, and of those, 8 (73%) were free of disease. Postoperative complications were mild. However, more series and larger numbers of patients treated with this approach, with longer follow-up, are necessary to further evaluate the feasibility of this treatment.

Advanced vaginal cancers are generally treated with definitive radiation in combination with chemotherapy. The use of combined modality treatment is imputed from the cervical cancer literature. Several series report their experience using surgery for advanced stages III or IV patients, with most cases requiring radical excision, typically pelvic exenteration.[61,63,64,85] Control rates, at best, are around 50%, even with highly selected patients.

Radiation

For most patients, radiation is the treatment of choice given the desire for organ preservation and the significant morbidity that may be incurred by

exenterative surgery. It is important to individualize RT techniques based on the size, depth, and location of the lesion. The outcomes of the retrospective series on the use of radiation for vaginal cancer are summarized in Table 79.5 and in detail later.

TABLE 79.5 OUTCOMES BY STAGE FOR VAGINAL CANCER TREATED WITH PRIMARY RADIATION WITH OR WITHOUT CHEMOTHERAPY

Series	Outcome	Stage I (%)	Stage II (%)	Stage III (%)	Stage IV (%)	Treatment	Notes
Kanayama et al (1993-2012)[118]	3 y OS	81	86	83 (St III = IV combined)		EBRT + BT (*n* = 9), EBRT (*n* = 8), BT (*n* = 7); 12% CRT	
Chang et al (1976-2011)[113]	5 y OS	75	69	68	69	EBRT + BT (*n* = 112), EBRT (*n* = 22) BT (*n* = 4)	CRT 41%
Miyamoto and Viswanathan (1972-2009)[135]	3 y OS	56 (combined I-IV)				RT ± S	CRT 31%
Damast et al (1998-2008)[124]	5 y OS	67 (St I-II combined)				EBRT + MRI-based BT; 40% CRT	
Beriwal et al (2000-2006)[315]	2 y crude LC		100	100	100	EBRT + HDR BT	
Lian (1986-2006)[114]	5 y DSS	90	87	32	26	EBRT + BT (*n* = 28), EBRT (*n* = 17), BT (*n* = 4), S + RT (*n* = 6)	
Tran et al (1959-2005)[98]	5 y PC	83	76	62	26	EBRT + BT (*n* = 43), EBRT (*n* = 22), BT (*n* = 10)	
	5 y DSS	92	68	44	30		
Shah et al (1990-2004)[8]	5 y DSS	84	75	57		RT and/or S	
de Crevoisier et al	5 y PC	79		62		EBRT and/or BT	

Series	Outcome	Stage I (%)	Stage II (%)	Stage III (%)	Stage IV (%)	Treatment	Notes
(1970-2001) [115]							
Frank et al (1970-2000)[62]	5 y PC	86	84	71		EBRT + BT (*n* = 119), EBRT (*n* = 63)	
Mock et al (1986-1999)[57]	5 y DSS	92	57	59	0	EBRT + BT (*n* = 55), EBRT (*n* = 5), BT (*n* = 26)	
Hellman (1956-1996)[96]	5 y DSS	75	36	36	20, 0[a]	RT and/or S	
Creasman et al (1985-1994)[10]	5 y OS	73	58	36		RT and/or S	
Stryker (1976-1994)[116]	5 y DSS	78	63	33	50	EBRT + BT (*n* = 25), EBRT (*n* = 7), BT (*n* = 2)	
Stock et al (1962-1992)[64]	5 y LC	72	62	0	21	RT and/or S	
	5 y DFS	67	53	0	15		
	5 y OS	42	68	58	0	EBRT and/or BT	
Perez et al (1953-1991)[58]	PC	85	66, 56[b]	65	27	EBRT and/or BT	
	10 y DFS	80	55, 35[b]	38	0		
Chyle et al (1953-1991)[59]	10 y PC	84	75	60	40	EBRT + BT (*n* = 121), EBRT (*n* = 95), BT (*n* = 26)	
	10 y OS	55	51	37	40	transvaginal cone (*n* = 2)	
Lee et al (1964-1990) [107]	5 y PC	87	88, 68[b]	80	67	EBRT and/or BT	
	5 y CSS	94	80, 39[b]	79	62		

Series	Outcome	Stage I (%)	Stage II (%)	Stage III (%)	Stage IV (%)	Treatment	Notes
Kirkbride et al (1974-1989)[86]	5 y DSS	72	70	53	42	RT and/or S	
Dixit et al (1985-1989)[105]	2 y DSS	100	70	19	0	EBRT and/or BT	
Urbanski et al (1965-1988)[103]	5 y DFS	73	54	23	0	EBRT + BT (*n* = 77), EBRT (*n* = 15), BT (*n* = 11)	
Kucera et al (1975-1984)[104]	5 y OS	81	44	35	32, 0[a]	EBRT and/or BT	
Rubin et al (1958-1980)[63]	5 y OS	75	48	54	15	RT and/or S	

BT, brachytherapy; CRT, conformal radiation therapy; CSS, cause-specific survival; DFS, disease-free survival; DSS, disease-specific survival; EBRT, external beam radiation therapy; HDR, high-dose rate; LC, local control; OS, overall survival; PC, pelvic control; RT, radiotherapy; S, surgery.

[a]Outcomes for stages IVA, IVB, respectively.

[b]Outcomes for stages IIA, IIB, respectively.

Stage I. For very small, superficial tumors, BT alone can be considered, but appropriate patient selection is critical. Reported local control rates range from 62% to 100.[62,65,67,87,93,93,117,118] Perez et al[58] reported pelvic tumor control of 88% in patients with stage I disease who received BT alone, using a dose of 60 to 70 Gy, prescribed 5 mm beyond the plane of the implant or vaginal mucosa, with a vaginal surface dose of 80 to 120 Gy. Notably, tumor control in stage I vaginal carcinoma was similar to BT alone, versus BT plus EBRT. This observation is consistent with reports from some groups,[58,104,119] but not others.[62,118] Other series suggest high locoregional failure rates with BT alone. Kanayama et al report three out of eight (38%) patients with stage I vaginal cancer, treated with BT alone, developed lymph node recurrence.[118] Frank et al[62] reported on 21 patients with stage I disease who were treated with local radiation only, without regional node coverage. Nine received BT alone, 11 received EBRT with or without BT, and 1 received local EBRT using a transvaginal orthovoltage cone. Three of nine patients treated with BT alone developed recurrent

disease in the pelvis, resulting in a 10-year pelvic disease control rate of 67%. Patients who received EBRT with or without BT did not have pelvic recurrences. A pelvic relapse rate of 18% at 10 years was noted by Frank et al,[62] with all pelvic failures occurring in patients treated with BT alone. Overall, results suggest caution should be taken when BT alone is used without prophylactic lymph node irradiation, given fairly high rates of lymph node recurrence. Appropriate patient selection is critical when utilizing BT alone as primary treatment, particularly since the distinction between stages I and II is based on clinical examination and can vary between providers.

With LDR, treatment can be delivered in two applications, with the first designed to treat the entire vaginal wall and a second application to cover the tumor volume. When HDR BT is the primary treatment, the entire length of the vagina is typically treated to a mucosal dose of 60 to 65 Gy, with an additional mucosal dose of 20 to 30 Gy delivered to the area of tumor involvement.[120] Treatment can be delivered with a shielded vaginal cylinder or with a multichannel HDR cylinder to treat the tumor with a 2-cm margin and block uninvolved mucosal surfaces.[121] HDR can also be used to treat superficial lesions.

The use of a multichannel HDR cylinder is an alternative technique with favorable local control and low toxicity. The standard multichannel HDR cylinder is composed of a central channel with 6 to 12 peripheral channels, allowing preferential dosing to the target while decreasing dose to normal structures. Vargo et al reported their outcomes for 41 patients with vaginal cancer treated with this technique to median EQD2 (equivalent dose in 2-Gy fractions) of 77.1 Gy.[122] Definitive treatment consisted of EBRT followed by BT. The majority (71%) of patients had FIGO 1 disease. At 2 years, there was 93% local control and 4% overall late grade 3 or higher toxicity, demonstrating comparable results to historical treatments. A tumor thickness cutoff of 5 mm for the apex and posterior vagina and 7 mm for other locations was utilized.

Guidelines from the American Brachytherapy Society, as well as the ESTRO/ESGO/SIOPe guidelines, recommend a cumulative D_{90} (dose to 90% of volume) EQD2 of 70 to 85 Gy prescribed to the vaginal tumor.[81,123] Various regimens can be utilized to achieve this dose, with commonly

utilized schedules of 45 Gy in 25 fractions EBRT followed by HDR BT in 5 fractions of 4.5 to 5.5 Gy (EQD2 = 71.4-79.8 Gy) or 9 to 10 fractions of 3 Gy (EQD2 = 73.5-76.8 Gy).

Poorly differentiated or extensively infiltrating stage I lesions should be treated with a combination of EBRT and BT. Given a possible underestimation of submucosal disease and/or nodal disease, resulting in a potentially high likelihood of recurrence with BT alone, some groups recommend incorporating EBRT into the treatment of all stage I patients, except for those with very small, superficial lesions.[62,118] Damast et al reported outcomes for early-stage vaginal cancer treated with a combination of EBRT and MRI-based ICB between 1998 and 2008.[124] With mean EBRT dose of 45, followed by HDR-ICB, 5-year OS, disease-specific survival, and local failure-free survival were 67%, 80%, and 90%, respectively. Notably, 60% of patients had a complete response after EBRT; of this group, there were no recurrences. Concurrent cisplatin was used as a radiosensitizer in 40% of patients.

Actuarial 5-year survival rates for stage I disease range from 60% to 85%.[8,62,67,98] Disease-specific survival rates for stage I disease, treated with definitive radiation, range from 75% to 95%.[58,59,88] The 10-year pelvic relapse rate, composed of local, pelvic nodal, and inguinal nodal failures, was noted to be 16% by Frank et al for stage I patients.[62] Most failures are locoregional. Distant metastases are uncommon and occur in about 5% of patients.[58,72,117]

Stage II. Stage II vaginal carcinoma involves the subvaginal tissue but does not extend to the pelvic side wall. The primary treatment for stage II disease is radiation, most commonly as a combination of EBRT followed by vaginal BT; chemo therapy is typically considered. Outcomes with BT alone have been poor; thus, this approach is not recommended. With BT alone, Perez et al[58] noted a 36% pelvic tumor control rate in stage II patients, compared to 67% in patients treated with a combination of EBRT and BT. The benefit of combining EBRT and BT, as opposed to using either alone, has been shown in other series as well.[59,64]

During EBRT, the pelvis generally receives 45 to 50.4 Gy in 1.8-Gy fractions, with consideration of a parametrial boost if there is extensive primary infiltration or high suspicion of nodal disease. Inguinal lymph

nodes are included in a modified whole-pelvic field for lesions involving the distal one-third of the vaginal canal.

Subsequent BT should be carefully delivered to ensure adequate coverage of tumor volume. An interstitial technique, ideally with three-dimensional (3D) imaging for treatment planning, is required for tumors greater than5 mm in depth.[87] Image-guided adaptive brachytherapy (IGABT) is highly recommended, preferably with the use of MRI.[81] Using IGABT, local control rates are high with acceptable morbidity. In a series of patients treated only using IGABT, Westerveld et al report 5-year local control rates of 85% for stage I to II tumors.[125]

Extensive tumors, or deeply infiltrating tumors with non distinct margins, may be poor candidates for BT.[81] In such cases, boosting tumors with conformal techniques or intensity- modulated radiation therapy (IMRT) can be considered and may yield better outcomes than suboptimal BT. The tumor volume should receive a minimum of 75 to 80 Gy using combined EBRT and BT. Fleming et al[126] and Puthawala et al[127] both report improved outcomes with higher doses of 80 to 100 Gy. The 5-year survival rate for patients with stage II disease treated with RT alone ranges from 35% to 70% for stage IIA and 35% to 60% for stage IIB.[30,128,129] Pelvic relapse at 10 years has been reported to be 25% by Frank et al, consistent with recent series reporting 5-year pelvic control rates ranging from 76% to 84%.[62,98] The likelihood of distant metastasis is higher for stage IIB lesions compared to stage IIA,[67,119] with overall reported rates ranging from 22% to 46%.[67,72]

Stages III and IVA. Locally advanced vaginal cancer is treated with a combined modality approach of radiation and chemotherapy, extrapolating from favorable outcomes with use of conformal radiation therapy (CRT) in patients with cervical cancer, and endorsed by the ESTRO/ESGO/SIOPe vaginal cancer guidelines.[81,130,131] Radiation is delivered as pelvic EBRT, followed by an additional parametrial boost when warranted. If adequate tumor coverage can be achieved without undue toxicity, interstitial BT is employed to deliver a minimum tumor dose of 75 to 80 Gy. If BT is not feasible because of extensive tumor infiltration of the rectovaginal septum or bladder, a shrinking field technique or IMRT has been used to deliver additional dose to the primary lesion.[132,133] The overall cure rate for patients with stage III disease ranges from 30% to 50%. Stage IVA carries a worse

prognosis. In highly selected patients with small-volume stage IV disease, pelvic exenteration can yield good long-term control; however, in practice, EBRT remains the primary treatment.[8,10,58,62-64,103]

Five-year actuarial survival rates for women with stage III disease range from 25% to 58%,[8,10] with local failure rates of 30% to 75%.[62,67,98] Outcomes for stage IV disease are worse, with survival rates of 0% to 40%.[59,64,134] Despite treatment with EBRT and BT, only 20% to 30% of patients with stages III to IV disease achieve local control. Pelvic recurrences occur more often than distant recurrences.[62]

However, with the use of IGABT, 5-year local control rates approach 75%, and there is some suggestion that there is improved local control in advanced stage II to IV tumors if the primary tumor receives more than 80 Gy.[125] In these patients, pelvic recurrences are roughly equal to distant recurrences, given the improved rates of local control. In general, lymph node involvement is a poor prognostic factor for DFS.[125]

Role of Combined Chemotherapy and Radiation

Chemotherapy has been incorporated with radiation for the treatment of vaginal cancer, extrapolating from studies in cervical cancer showing improved progression-free survival and OS when cisplatin is added to RT.[58,130,131,135,136] Given rarity of vaginal cancer, there are no randomized trials comparing radiation alone to radiation plus chemotherapy.

Retrospective series are limited by small numbers or inclusion of other cancers, such as cervical and vulvar carcinomas. Nonetheless, the majority of retrospective studies suggest that a combined modality approach is feasible and may yield improved outcomes. These studies are summarized in Table 79.6.

TABLE 79.6 OUTCOMES AFTER COMBINED CHEMORADIATION IN VAGINAL CANCER

Series	Stage	Outcomes	Notes
Miyamoto and Viswanathan (1972-2009)[136]	St I, *n* = 18; St II, *n* = 19, St III, *n* = 8, St IVA, *n* = 6	3 y OS 79%	RT + cis, 5-FU, or carboplatin

Series	Stage	Outcomes	Notes
Dalrymple et al (1986-1996)[142]	St I, *n* = 1; St II, *n* = 10, St III, *n* = 1	NED *n* = 9(FU 74-168 mo) DOD *n* = 1 (12 mo) DID *n* = 4 (46-109 mo)	RT + 5-FU, cis/5FU, or MMC
Gunderson et al (1990-2004)[137]	St I, *n* = 31; St II, *n* = 30; St III/IV, *n* = 69	4 y OS 64% (stage I), 40% (stage II), 12% (stage III/IV)	CRT, *n* = 87; S + CRT, *n* = 43
Samant et al (1999-2004)[143]	St II, *n* = 6; St III, *n* = 4; St IVA, *n* = 2	5 y OS 66%	RT + cis
Nashiro et al (2002-2005)[144]	St II, *n* = 2; St III, *n* = 1; St IVA, *n* = 3	DOD *n* = 1 (25 mo) NED *n* = 4 (FU 19-54 mo) AWD *n* = 1 (FU 19 mo)	RT + cis or cis/5-FU
Gardener et al. (2016-2022)[145]	St I, *n* = 10; St II, *n* = 12, St III, *n* = 10; St IVA, *n* = 6	2y OS 67% DFS 57% LC 93%	RT + weekly cis MR-BT

AC, adenocarcinoma; AWD, alive with disease; B, brachytherapy; cis, cisplatin; CRT, conformal radiation therapy; DID, died of intercurrent disease; DOD, died of disease; EBRT, external beam radiation therapy; FU, fluorouracil; 5-FU, 5-fluorouracil; LC, local control; PFS, locoregional progression-free survival; MMC, mitomycin-C; NED, no evidence of disease; OS, overall survival; SCC, squamous cell carcinoma; MR-BT, MR-guided brachytherapy.

An NCDB study identified 13,689 women with primary vaginal cancer treated between 1998 and 2011 and explored the impact of concurrent chemoradiation on survival.[138] Median survival with chemotherapy and radiation was significantly longer, compared to radiation alone (56.2 vs 41.2 months, $P < .0005$). It was noted that only 48.6% of all patients received chemotherapy, but there was a consistent trend toward increased use of concurrent chemoradiation from 20% to 59.1% between 1998 and 2011.

Ghia et al[139] published a retrospective patterns-of-care analysis using the SEER database, analyzing data from women with primary vaginal cancer treated with EBRT and/or BT between 1991 and 2005. Of the 326 women in the study cohort, 80.4% had SCC. It was noted that CRT was used in 7.5% of patients treated before 1999 compared to 36.1% of those treated afterward ($P < .001$). Cisplatin was the most frequently utilized agent, accounting for 59% of CRT treatments. Chemotherapy was significantly less likely to be used in conjunction with radiation for women older than 80 years; otherwise, there was no difference for race, stage, grade, histologic diagnosis, comorbidities, or BT use. On multivariate analysis, CRT was not found to correlate with improved cause-specific survival or OS.

In a retrospective analysis of 71 patients with primary vaginal cancer treated from 1972 to 2009, 51 patients were treated with radiation alone and 20 were treated with CRT and RT.[136] Of the patients treated with chemosensitization during radiation, 85% of patients received weekly cisplatin chemotherapy, whereas the remainder received either carboplatin or 5-FU. Three-year actuarial OS and DFS was 56% for the RT-alone group, compared to 79% for the CRT group ($P = .01$). Three-year DFS was 43% for the RT-alone group, compared to 73% for the CRT group ($P = .01$). At a median follow-up of 3 years, tumor relapse was seen in 15% of patients treated with CRT compared to 45% of patients treated with radiation alone ($P = .03$). On multivariate analysis, the addition of chemotherapy was a significant predictor of DFS (HR 0.31).

Evans et al[140] reported the use of radiation with 5-FU and mitomycin-C (MMC) in seven patients with vaginal cancer. Four out of seven patients were free of disease with follow-up times ranging from 19 to 39 months. Roberts et al[141] reported results for seven patients with vaginal cancer treated with concurrent 5-FU, cisplatin, and radiation. Three patients received interstitial BT after EBRT, and two patients received ICB after EBRT. Eighty-five percent of patients achieved a complete response initially. Ultimately, 61% recurred, with a median time to recurrence of 6 months. There were three local recurrences and one distant metastasis, and the 5-year OS rate was 22%. Kirkbride et al[86] reported on the use of concurrent 5-FU, with or without MMC, in 26 of 153 patients with vaginal carcinoma treated at Princess Margaret Hospital. Seventy-seven percent of the patients had stage III/IV disease. Radiation was EBRT followed by

interstitial BT or ICB to a total dose of 62 to 74 Gy. The 5-year survival rate was 50%. Dalrymple et al[142] reported results using 5-FU–based chemotherapy in combination with radiation for the treatment of primary SCC of the vagina. Thirteen of 14 patients (93%) had stage I or II disease. The median dose of radiation was 63 Gy, achieved using EBRT alone or EBRT with ICB. The 5-year survival rate was 86% for all patients, and nine patients were free of disease with a median follow-up time of 100 months, suggesting that good local control can be achieved despite the use of lower radiation doses. There was a 31% rate of severe bowel complications reported, with two deaths as a result of bowel obstruction.

A retrospective series from MDACC by Frank et al[62] included nine patients with stages II to IVA SCC of the vagina treated with RT and concurrent cisplatin-based CRT. With a mean follow-up time of 129 months, improved local control with the use of chemotherapy was noted, with 44% of patients treated with concurrent CRT remaining free of disease. Samant et al published a review of 12 patients with stages II to IVA vaginal cancer treated with concurrent weekly cisplatin at a dose of 40 mg/m^2 for 5 weeks.[143] Patients received concurrent EBRT to a median dose of 45 Gy, with LDR interstitial BT or an HDR-ICB boost of median dose 30 Gy. Six patients had stage II disease, four had stage III disease, and two had stage IVA. Ten of 12 patients (83%) had SCC; the other two had adenocarcinoma. Overall, treatment was well tolerated, with 92% of patients completing therapy as prescribed. Two of 10 patients who received interstitial BT required surgery for fistula repair. The 5-year OS, progression-free survival, and locoregional progression-free survival rates were 66%, 75%, and 92%, respectively, supporting the use of concurrent weekly cisplatin therapy. A small series of six patients treated with CRT at the University of the Ryukyus was reported by Nashiro et al[144] All patients received EBRT to 50 Gy, followed by either a boost with shrinking fields (n = 4) or ICB (n = 2). Radiation was delivered with two to three cycles of cisplatin. Two patients had stage II, one had stage III, and three had stage IVA disease. All six achieved a complete response, and four of six patients remained free of disease at follow-up times of 18 to 55 months.

Outcomes

In general, the rate of locoregional recurrence ranges from 10% to 20% for stage I and 30% to 40% for stage II. Patients with advanced disease often have persistent disease despite treatment. In a series by Dixit et al,[105] 68% of failures in stage III patients were due to persistent disease. Most treatment failures occur within 5 years, with a median time to recurrence of 6 to 12 months,[62,146] and local recurrence is the most common pattern of treatment failure in the majority of published series. Extravaginal recurrences in the pelvic lymph nodes are less common. The reported rates of distant metastasis vary, ranging from 7% to 33% and usually occur later in the course of disease, with approximately half of all distant metastases presenting at the time of local recurrence.[67,87,105,147]

According to SEER-based data, outcomes for vaginal cancer may be improving. A recent study by Shah et al[8] analyzed records from the SEER database of 2,149 women diagnosed with primary vaginal cancer between 1990 and 2004. The risk of mortality is noted to have decreased over time, with a 17% decrease in the risk of death for women diagnosed after 2,000 relative to those diagnosed between 1990 and 1994. The authors reported 5-year disease-specific survival rates of 84% for stage I, 75% for stage II, and 57% for stages III to IV. An older study by Creasman et al[10] focused on 4,885 women diagnosed with vaginal cancer between 1985 and 1994 and reported 5-year survival rates of 96% for stage 0, 73% for stage I, 58% for stage II, and 36% for stages III to IV, with 85% of invasive cases being SCC, MR-guided brachytherapy resulted in 2y LC 93% after RT and weekly cisplatin.[145]

Melanoma

Vaginal melanomas constitute approximately 4% of all primary vaginal cancers,[9] with just over 100 new cases of vaginal melanoma reported each year in the United States. Melanomas arising from the vaginal mucosa are thought to originate from mucosal melanocytes in regions of melanosis or from atypical melanocytic hyperplasia.

The incidence of vaginal melanoma has remained stable and is reported to be approximately 0.26 per million.[148] The majority of reported cases are in Caucasian women; one study of 37 women with primary melanoma of the vagina reported 84% of patients to be Caucasian, and only 3% African

American.[149] According to a report by Hu et al[150] analyzing SEER data from 1992 to 2005 on 125 cases of vaginal melanoma with known race/ethnicity, there is no significant difference in incidence rate of vaginal melanoma between Caucasian and African American women, with a White/Black ratio of 1.02 after age adjustment. In the report by Creasman et al,[10] most patients were of advanced age at presentation, with only 23% of patients diagnosed before the age of 60; 28% were diagnosed between the ages of 60 and 69 years, 28% were diagnosed between the ages of 70 and 79 years, and 22% were diagnosed at age 80 years or above.

Grossly, melanoma of the vagina tends to be pigmented and may present as a dark mass, plaque, or ulceration; multifocal presentation is also common. In a case series of 37 women with primary vaginal melanoma reported by Frumovitz et al,[149] median tumor size at presentation was 3 cm (range, 0.4-5 cm), with median depth of invasion of 7 mm (range, 1-21 mm). Twenty-one percent of patients presented with multifocal disease. Twenty-four patients (65%) presented with lesions in the distal third of the vagina or introitus. The most common appearance is polypoid-nodular.[151] The most common location at presentation is the anterior vaginal wall and lower one-third of the vagina.[149]

Microscopically, tumors may be composed of epithelioid, spindle, or nevus-like cells, with variable morphology, and stain frequently positive for S-100 protein, HMB-45, and Melan A. When S-100 is negative or only focally positive, tyrosinase and MART-1 are useful markers. Poorly differentiated tumors may be difficult to distinguish from carcinomas or sarcomas. Tumor thickness correlates with prognosis and is measured by the methods of Breslow.[152]

Vaginal melanoma is a high malignant disease with a propensity for early hematogenous spread. The most common presenting symptoms reported have been slight vaginal bleeding and vaginal discharge, which is usually blood tinged, foul smelling, or purulent.[153] Reid et al reviewed 115 patients with primary melanoma of the vagina and found depth of invasion and lesion size greater than 3 cm to be negative prognostic factors.[154] Stage was not found to be prognostic for outcome, but only 42 of the 115 patients had this information available. Compared to women with SCC, patients with vaginal melanoma have a significant 1.5-fold increased risk of mortality.[8]

Treatment Options

Primary vaginal melanoma is uncommon, and treatment outcomes for only a small number of patients have been reported.[149,153,155-158] As a result, it is difficult to make definitive treatment recommendations. Treatments used in published series include wide local excision, radical surgery, radiation, chemotherapy, immunotherapy following principles from skin melanoma, or a combination of modalities.

Some authors advocate incorporation of radical surgical resection into the treatment paradigm, when feasible.[159,160] The rationale for favoring surgery over radiation is based upon the observation that melanoma tends to be radioresistant. Geisler et al[159] recommend primary pelvic exenteration for vaginal melanomas with greater than 3 mm invasion, reporting a 5-year survival rate of 50% if pelvic nodes are free of disease. Morrow and DiSaia,[161] in their review of gynecologic melanoma, recommend radical surgery based on a review of the literature revealing 3 out of 19 long-term survivors after exenteration with wide local excision. Chung et al[155] reviewed 19 cases of primary vaginal melanoma treated between 1934 and 1976. All patients who received wide local excision developed recurrence. Five-year survival was only 21%. Miner et al[162] reported on 35 patients treated at Memorial Sloan-Kettering Cancer Center from 1977 to 2001. Sixty-nine percent underwent surgery, which was either en bloc removal of the involved pelvic organs, wide excision, or total vaginectomy, with elective pelvic lymph node dissection in 74% of cases. Thirty-one percent of patients received definitive radiation. Primary surgical therapy was significantly associated with a longer OS time (25 vs 13 months). Recurrence-free survival was not found to correlate with surgical extent. A study by Huang et al found 5-year OS to be 32% but as high as 47% in patients who underwent surgical treatment.[163]

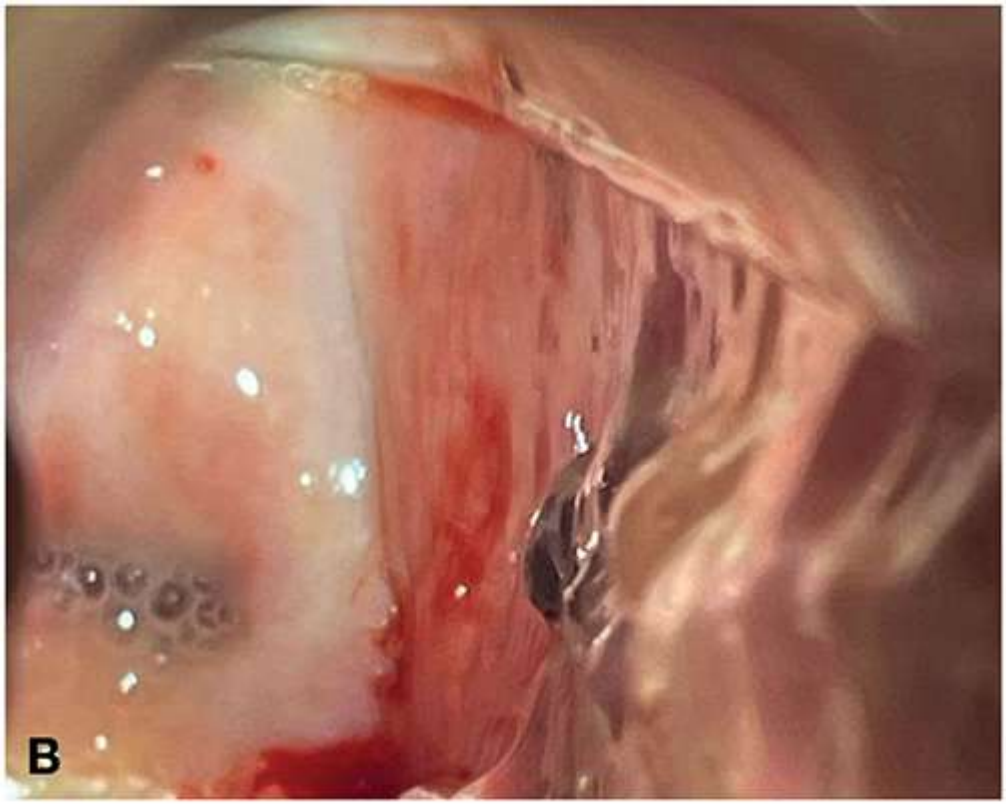
The goal of surgical excision should be complete resection with a negative margin. Drawing on the general melanoma guidelines this would be between 0.5 and 2 cm depending on the Breslow thickness of the primary tumor. Given the close proximity of the bladder and rectum, a wide local excision can rarely achieve this. Due to the risk of metastatic disease and the aggressive nature of the tumor, however, several series comparing radical surgery and local excision find equivalent outcomes.[153,156,164,165]

The role of surgical lymphadenectomy, lymph node sampling, or sentinel lymph node mapping is not established in vaginal cancer, given the vast variability in lymphatic drainage and substantial morbidity in the form of lymphedema that could result from sampling of both the inguinal and pelvic nodal basins. Lymphadenectomy could be considered in patients with nodal disease with the goal of locoregional control.

The use of wide local excision followed by postoperative EBRT and BT has been proposed. Bonner et al[166] reported on nine cases of vaginal melanoma. Three patients were treated with wide local excision, and six underwent radical surgery. All nine patients developed locoregional recurrence. As a result, the authors suggest adding pelvic RT to improve local control. A more recent review by Frumovitz et al[149] reported that radiation after wide local excision can reduce local recurrences. However, most patients develop distant metastases, most commonly in the lungs and liver. New advances in immunotherapy hold promise for changing the outcomes of patients and evolving the management of patients with melanoma. There is no general recommendation for the treatment of primary vaginal melanoma. When radiation is administered, vaginal melanoma is treated similarly to vaginal carcinoma, with volumes and doses ranging from 50 Gy for subclinical disease to 75 Gy for gross tumor.

Retrospective data suggest that radiation may improve local control for vaginal melanoma.[153,167] Among the few long-term survivors reported in the literature are a handful of patients who were treated with radiation. Harwood and Cummings[168] described a complete response in four patients with vaginal melanoma treated with radiation, although two subsequently relapsed. Rogo et al,[169] in their series of 22 cases of vulvovaginal melanoma, reported comparable results for surgery and radiation, with eight patients (36%) alive 5 years after treatment. Petru et al,[167] in their series documenting 14 patients treated for primary malignant melanoma of the vagina, noted that three of nine patients treated with radiation, either as primary treatment (n = 2) or in the postoperative setting (n = 1), survived longer than 5 years. The median OS for all patients was 10 months, with a 5-year DFS rate of 14% and an OS rate of 21%. Figure 79.4 shows a vaginal melanoma lesion treated with five-fraction stereotactic body radiation therapy (SBRT) that had a rapid regression of disease.

A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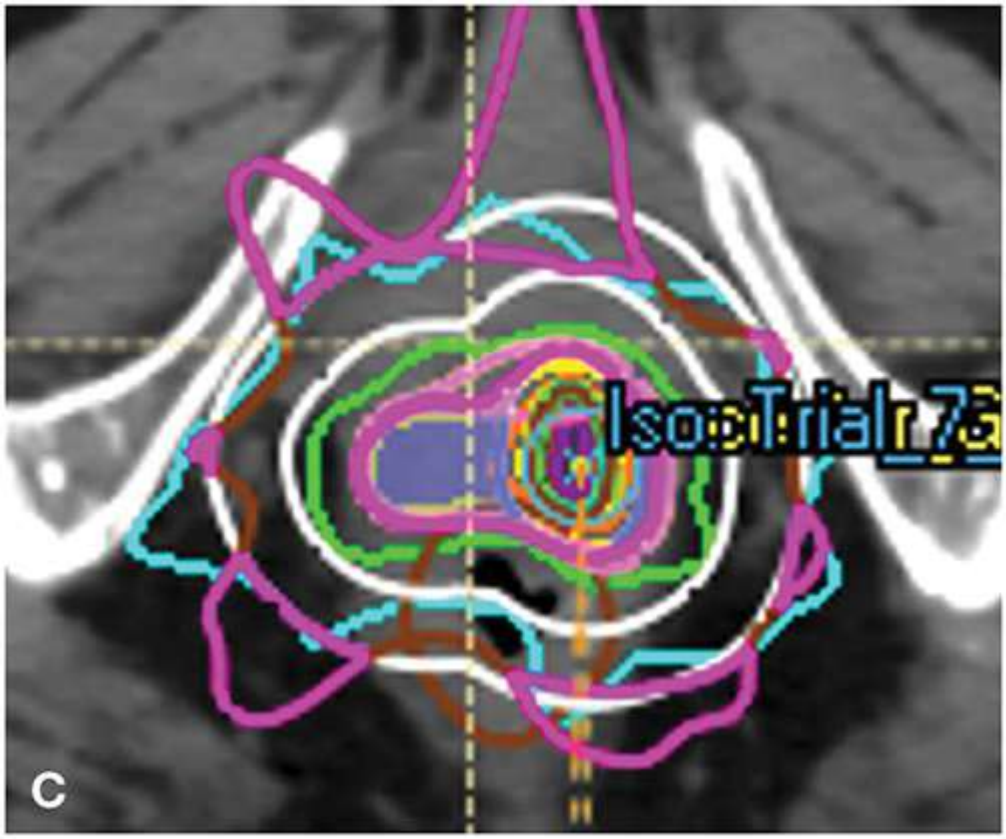


FIGURE 79.4 Vaginal melanoma treated with stereotactic body radiation therapy (SBRT) using 8 Gy for five fractions to the mass defined on a magnetic resonance (MR) simulation and 6 Gy for five fractions to the rest of the vaginal mucosa. Fiducial markers were placed surrounding the mass before the magnetic resonance imaging (MRI) and used for set up daily. A. Mass at diagnosis presenting as a pedunculated 2-cm mass. B. Flattened mass 3 months after SBRT. C. SBRT simultaneous integrated boost of the gross tumor volume (GTV) and the vaginal clinical target volume (CTV).

Frumovitz et al,[149] in their review of 37 women with stage I melanoma of the vagina treated at MDACC between 1980 and 2009, report very poor prognosis even in this group of patients with localized disease, with a 5-year OS rate of 20%. In that study, 10% of patients received nonsurgical treatment with radiation, chemotherapy, or both. Patients treated surgically had significantly longer survival times compared to those treated nonsurgically. Radiation delivered after wide local excision reduced local recurrence and demonstrated a trend toward longer survival times, from 16.1 to 29.4 months.[170] A study by Xia et al evaluated 44 women, diagnosed and treated for vaginal melanoma between 2002 and 2011.[158] There was no difference in OS between local excision and radical surgery. However, the

authors note increased progression-free survival with the addition of adjuvant chemotherapy and radiation (8.6 vs 16.0 months, $P = .038$). Given the high rates of distant metastases, chemotherapy has been used, either alone or in conjunction with radiation.[149,171] Other reports have described the use of immunotherapy after surgery.[163]

Recommendations for the use of adjuvant chemotherapy for vaginal melanoma derive from the general melanoma literature where multiple agents have been the focus of investigation. One of the first drugs used was IFN-α, which was been found to bring an improvement in recurrence-free survival with no OS benefit. More recently in a phase II study, patients treated with surgery followed by adjuvant temozolomide in combination with cisplatin were noted to have a 48.7-month OS, superior to IFN-α (40.4 months) or observation (21.2 months) ($P < .01$). Further studies are ongoing.[172]

The effectiveness of targeted molecular therapies and immunotherapy in cutaneous melanoma has significantly expanded the options for patients with advanced melanoma. Approved therapies for advanced, unresectable melanomas include ipilimumab (antibody against cytotoxic T-lymphocyte–associated protein 4), nivolumab (inhibitor of programmed cell death 1 [PD-1] protein), pembrolizumab (PD-1 inhibitor), vemurafenib (B-raf proto-oncogene serine/threonine kinase [BRAF] inhibitor), dabrafenib (BRAF inhibitor), and trametinib (mitogen-activated protein kinase inhibitor). However, it is difficult to extrapolate the effectiveness of these therapies for cutaneous melanoma to vaginal melanoma, and there are no specific trials that have validated the efficacy of these regimens in vaginal melanoma. Testing of tumors for BRAF, NRAS, and c-KIT can be used to guide therapy. There appear to be high levels of PD-1 and PDL-1 expression in both vaginal and vulvar melanomas, suggesting utilization of immunotherapy may have efficacy for this disease.[128]

Regardless of primary treatment, outcomes have been disappointing. Overall prognosis is poor, with historic 5-year survival rates ranging from 5% to 30% regardless of treatment modality or extent of surgical resection.[154,155,157] There is a high rate of distant metastases, ranging from 66% to 100%.[155,173]

Sarcoma

Sarcomas represent 3% of all primary vaginal cancers.[10] In a report based on data from the NCDB between 1985 and 1994,[10] there were 135 cases of primary vaginal sarcoma of heterogeneous histologies and varying age. Twenty-two percent of patients were under 14 years of age, with a median age at presentation of approximately 50 years. Consistent with this, a recent analysis of the SEER database identified 221 patients with primary vaginal sarcoma, diagnosed between 1988 and 2010, with mean age of 54.9.[174] Compared to other vaginal cancers, sarcomas tended to be larger, with decreased likelihood of lymph node involvement, and more likely to be treated with primary surgery without radiation. It was estimated that, after adjusting for other variables, vaginal sarcomas had a 69% greater risk of cancer-related mortality when compared to SCC.

Vaginal sarcoma most frequently presents as an asymptomatic vaginal mass.[175] In one series, this was the most frequent symptom, found in 35% of patients, followed by vaginal, rectal or bladder pain (26%), bleeding or serosanguinous discharge from the vagina or rectum (18%), leucorrhea (9%), dyspareunia (7%), or difficulty in micturition (7%).

Leiomyosarcoma is the most common histology in adults, representing up to 65% of all vaginal sarcoma cases; however, overall numbers are very small, with less than 150 published reports in the literature.[175] Vaginal leiomyosarcomas not only originate from the smooth muscle of the vaginal wall but may also develop from smooth muscle cells in tissues adjacent to the vagina. Leiomyosarcomas have a predilection for the posterior vaginal wall, with published reports suggesting approximately 43% to 45% in the posterior vagina, 17% to 21% anteriorly, and 34% to 39% laterally.[175,176]

Grossly, patients present with a palpable submucosal nodule, although advanced tumors may demonstrate palpable necrosis or exophytic polypoid tissue.[177] Criteria to distinguish between benign leiomyoma and leiomyosarcoma include the mitotic index, cytologic atypia, and coagulative tumor necrosis.[178] Because of considerable variation in smooth muscle tumors from area to area, adequate sampling is recommended to achieve an accurate diagnosis. Microscopically, leiomyosarcomas demonstrate interlacing bundles of spindle-shaped cells, with blunt-ended nuclei and fibrillar cytoplasm.[153,179] Leiomyosarcomas are also aggressive;

they undergo early hematogenous dissemination, recur locally,[10,175] and demonstrate pulmonary metastases.[180]

Other less common histologies include endometrial stromal sarcoma and angiosarcoma.[181,182] Fewer than 10 cases of angiosarcoma of the vagina have been reported in the literature.[183,184] A history of pelvic radiation is a risk factor for pelvic sarcomas, particularly angiosarcoma.[185] In the pediatric population, embryonal rhabdomyosarcoma/sarcoma botryoides is the most common histology,[185] with 90% of cases occurring in children younger than 5 years.[186]

Prognostic Factors

Review of the literature indicates that vaginal sarcomas undergo early hematogenous dissemination as well as frequent local recurrence. Pulmonary metastases are common.[175,176] Adverse prognostic factors for vaginal sarcoma include high histologic grade, stage, size greater than 3 cm, infiltrative borders, and cytologic atypia.[180]

Treatment Options

Despite surgery and the use of adjuvant RT in select cases, patients with sarcoma sustain poor outcomes because of a high incidence of local recurrence and distant metastasis. Locoregional control is especially important for vaginal leiomyosarcoma. The addition of systemic treatment, typically with doxorubicin, is standard for leiomyosarcoma.[187] Postoperative RT has been used to manage soft tissue sarcomas in other sites, to reduce locoregional recurrence rates.[188] Results from adjuvant radiation for high-grade sarcoma in other regions of the body have been extrapolated to vaginal cancer. In patients with involved margins, high doses above 62.5 Gy are generally required to achieve local control.[189]

A series by Peters et al[190] reported on 17 cases, composed of 10 patients with leiomyosarcoma, 4 with MMT, and 3 with other types of sarcomas. There were only three patients alive and free of disease with follow-up times of 84 to 161 months. All three patients had undergone pelvic exenteration. Patients who received other forms of primary therapy all died of recurrence, with the pelvis as the first site of recurrence in all cases. In 50% of cases, the pelvis was the only site of failure, stressing the

importance of local treatment. OS of 8 and 10 years following wide local excision have been reported.[176]

Outcomes

In the SEER analysis, 5-year survival was 89% for stage I and under 50% for stage II vaginal sarcomas of all types.[174] Other series describe similarly poor outcomes. A 5-year survival was 36% for patients with leiomyosarcoma in the Peters et al's series.[190]

Malignant Mixed Müllerian Tumors

Mixed Müllerian tumors (MMT), also called carcinosarcomas, are highly aggressive, biphasic neoplasms composed of an epithelial component as well as a sarcomatous component. The epithelial component in vaginal MMT is most often SCC.[181] The sarcomatous component can be composed of fibroblasts and smooth muscle, or include cartilage, striated muscle, bone, and other heterologous tissues. The metaplastic carcinoma theory suggests that there is a common cell of origin for MMT, with carcinoma giving rise to the sarcomatous component via metaplasia.[191] The most common differential diagnosis is sarcomatoid carcinoma. The spindle and carcinomatous components are positive for cytokeratin in sarcomatous carcinoma, whereas MMT demonstrates a sarcomatous component that is positive for vimentin, with the carcinomatous component positive for cytokeratin.[181] The first case of vaginal MMT was described in 1975 by Davis et al,[192] since then, only 11 cases have been reported in the literature, with age ranging from 57 to 74 years.[181,193,196] At least one case report of MMT of the vagina detected high-risk HPV in both the carcinomatous and sarcomatous components, suggesting that some vaginal MMTs may be related to HPV.[193]

The survival rate for patients with MMT was even lower, at 17%. There are only a few case reports and small series detailing treatment of primary vaginal MMT. Neesham et al[195] published a case report of a 74-year-old patient treated with wide local excision and radiation for a 5.5-cm stage I MMT. The patient developed distant metastases within 6 months of local therapy. Analysis of patterns of failure suggests that local therapy does not have a significant impact on survival because of early distant spread. For

that reason, chemotherapy is typically administered after surgery for MMT in other sites and should be considered for primary vaginal lesions, along with adjuvant radiation as warranted. Platinum-based chemotherapy has been used for MMT occurring elsewhere in the pelvis. It has not yet been determined whether platinum agents are best administered either alone or in combination with other agents. Combination regimens include a paclitaxel with either ifosfamide or a platinum agent.[197-199]

Clear Cell Adenocarcinoma

Epidemiology

Clear cell adenocarcinoma of the vagina was first reported in 1971 by Herbst and Scully,[200] who documented six cases of primary vaginal clear cell carcinoma in patients aged 15 to 22 years: five of the six had been exposed to the synthetic estrogen diethylstilbestrol (DES) in utero during the first trimester. This was the first report suggesting that in utero exposure to DES, prescribed during the mid-1940s to 1960s for high-risk pregnancies, could result in an increased risk of clear cell adenocarcinoma. DES-related clear cell adenocarcinoma presents at a young age, with studies documenting median age at presentation to be within the second or third decade of life.[200]

Studies suggest that there is a bimodal distribution for clear cell adenocarcinoma of the vagina, with the first peak containing young women with a mean age of 26, most of whom were exposed to DES in utero, and a second peak containing women with a mean age of 71 years, not exposed to DES.[200] The majority of patients present with stages I to II disease.[200,201] DES-related clear cell adenocarcinoma is rarely seen today, as DES is no longer administered to pregnant women.

Risk Factors

In 45% to 95% of cases, clear cell adenocarcinoma of the vagina is associated with vaginal adenosis, defined as the abnormal presence of glandular epithelium in the vagina.[170,202] Vaginal adenosis has three patterns: endocervical, tuboendometrial, and embryonic.[170,203,204] Grossly, vaginal adenosis appears as red, velvety, grapelike clusters in the vagina. Glandular columnar epithelium of Müllerian type either appears beneath the squamous

epithelium or replaces it, undergoing progressive squamous metaplasia.[205] Vaginal adenosis is believed to be a precursor lesion to clear cell adenocarcinoma of the vagina. It is a common histologic abnormality in women who have been exposed to DES in utero, presenting in up to 95% of such women.[170,202]

The risk of developing clear cell adenocarcinoma in DES-exposed women is estimated to be 1 in 1,000,[201] suggesting that there are multiple factors contributing to pathogenesis. However, it is not strictly confined to this population; there are rare, sporadic cases of primary adenocarcinoma of the vagina that is not associated with DES exposure.[206]

Histopathology

Clear cell adenocarcinoma of the vagina is most often located in the upper third of the anterior vagina and can vary greatly in size. Grossly, they exhibit exophytic growth and are superficially invasive.[207] Microscopically, they are composed of vacuolated, glycogen-rich cells, hence the term *clear cell carcinoma*. The most common histologic pattern is tubulocystic, although solid, papillary, and mixed cell patterns have also been described.[74,208] Cells are cuboidal or columnar in shape, with large, atypical protruding nuclei, rimmed by a small amount of vacuolated cytoplasm.

Clinical Presentation

Patients with clear cell adenocarcinoma most often present with abnormal vaginal bleeding,[200] which is found in 50% to 75% of cases. Cytology is not reliable, revealing abnormalities in only 33% of cases; therefore, careful assessment of the entire vaginal vault to assess for submucosal irregularity is recommended, in addition to four-quadrant cytologic assessment.[209] The cervix should be carefully inspected, as clear cell adenocarcinoma can arise from this region as well. Abnormal discharge, urinary symptoms, and lower gastrointestinal complaints can also be noted, particularly in advanced cases. The differential diagnosis of vaginal adenocarcinoma is often challenging, because it must be distinguished from metastases from distant sites.

Prognostic Factors

Prognostic variables associated with worse survival include advanced stage, nontubulocystic pattern of histology, size greater than 3 cm, and depth of invasion greater than 3 mm.[207] A study of 21 women with clear cell carcinoma of the vagina and cervix reported overexpression of wild-type p53 to be associated with a more favorable prognosis.[210] Primary adenocarcinoma of the vagina not associated with DES exposure is extremely rare, with poor outcomes. In a review of 26 such cases by Frank et al, 5-year OS was 34%, worse than in patients with SCC.[211] A recent series described five cases of clear cell adenocarcinoma in patients without prior DES exposure, treated between 1990 and 2013.[212] Patients were all older than 40 years. There was high incidence of distant spread, especially to the lungs. OS at 5 years was 55%.

Treatment Options

The optimal management of clear cell adenocarcinoma is unclear. There are several published series on DES-related clear cell adenocarcinomas[74,129,207,213,214] using conventional treatments similar to those used for SCC of the vagina for stages I and II disease, including surgery with radical hysterectomy, vaginectomy, and lymphadenectomy with construction of a neovagina or definitive radiation with consideration of radiosensitizing concurrent chemotherapy.[215,216] In these series, there has been an emphasis on preservation of ovarian and vaginal function, because of the earlier age at diagnosis in DES-exposed patients. According to data from the United States Registry for Research on Hormonal Transplacental Carcinogenesis, approximately one half of all vaginal clear cell adenocarcinoma cases were treated with radical surgery alone as primary therapy.[217]

Wharton et al report the use of intracavitary or transvaginal irradiation for early-stage disease, with excellent tumor control and preservation of ovarian function.[218] Herbst et al[219] reported on 142 cases of stage I clear cell adenocarcinoma. For the 117 patients treated with radical surgery, there was an 8% risk of recurrence and 87% OS. For patients treated with radiation, there was a 36% risk of recurrence. The authors acknowledge that it is difficult to compare surgery to radiation, as radiation was most likely used in patients with larger lesions less amenable to resection.

A series by Senekjian et al[214] reported on 219 cases of stage I clear cell vaginal adenocarcinoma. Forty-three patients received local therapy alone, consisting of vaginectomy, local excision, or local irradiation with or without excision, and the rest had conventional radical surgery. At 10 years, the actuarial survival rates were equivalent (88% vs 90%) for patients who received local therapy only and those treated conventionally. However, the actuarial recurrence rate was significantly higher (40% vs 13%) with local excision alone. Patients who received local irradiation, with or without local excision, had decreased local recurrence compared to those treated with excision alone ($P < .03$).

A subsequent series by Senekjian et al reviewed 76 cases of stage II clear cell adenocarcinoma.[74] The 10-year OS rate was 65%. The 5-year survival rates were 80% for patients treated with surgery, 87% for patients treated with radiation, and 85% for patients treated with both. The authors advocate treatment with a combination of EBRT and BT for stage II disease, with surgery reserved for smaller, more easily resectable lesions in the upper vagina. The use of pelvic exenteration for primary and recurrent lesions has been reported by Senekjian et al.[129] Survival outcomes were comparable to those of patients treated with other modalities. Thus, to minimize morbidity and preserve quality of life, exenterative approaches are advocated only for patients with disease recurrence after radiation. The 5-year survival rate after pelvic relapse is reported to be 40% by Herbst et al.[213]

Most recurrences occur within 3 years of therapy, although recurrences occurring 10 to 20 years after treatment have been reported.[220] Most recurrences are local or locoregional, with approximately one-third detected at distant sites, most commonly in the lungs or extrapelvic lymph nodes, although there have been rare cases of central nervous system metastases manifesting years after treatment.[221] The 10-year actuarial survival rate for clear cell adenocarcinoma of the vagina is 79%. For stages I and II disease, survival rates are 90% and 80%, respectively.

Other Adenocarcinomas

The majority of adenocarcinomas that present in the vagina are attributed to metastatic spread from other sites. Vaginal metastases from adenocarcinoma of the breast, kidneys, or other gynecologic primary sites have been

described.[222-224] Primary non–clear cell adenocarcinoma of the vagina is extremely rare and occurs predominantly in postmenopausal women. Histologic variants include endometrioid, mucinous, mesonephric, and papillary serous adenocarcinoma. Vaginal endometrioid adenocarcinoma is the most common non–clear cell subtype and presents most often in women with a history of endometriosis. Only a handful of case reports or series have been published in detail about endometrioid adenocarcinoma of the vagina.[225-229] In one series of 18 cases of primary vaginal endometrioid adenocarcinoma,[225] 10 cases arose from the apex. Fourteen out of 18 cases had vaginal endometriosis, important in indicating a primary vaginal tumor rather than secondary spread from the endothelium. The median age at presentation was 57, with a range from 45 to 81 years. There have been case reports of mucinous adenocarcinoma of the vagina,[230-232] with at least one arising from a focus on endocervicosis.[233]

On gross examination, endometrioid adenocarcinomas can be polypoid, papillary, rough, granular, fungating, exophytic, or flat, and most arise from the superior aspect of the vagina. Microscopically, tumors display a predominant component of typical endometrioid carcinoma, with tubular glands lined by columnar cells with moderate amounts of eosinophilic cytoplasm and large elongated nuclei. Only a handful of cases of mucinous adenocarcinoma have been described,[223,230-232] including rare cases arising in neovaginas[234] or arising from endocervicosis.[233] Mesonephric adenocarcinoma arises from mesonephric duct remnants situated in the lateral vaginal wall.[235,236] Primary papillary serous adenocarcinoma of the vagina has rarely been reported.[237]

Lymphoma

Lymphomas of the female genital tract are rare, accounting for only 1% of all primary extranodal lymphomas.[238] Lymphomas of the vagina are exceedingly uncommon, with fewer than 30 cases reported in the literature thus far.[239-252] In one review from the Armed Forces Institute of Pathology, only 4 of 9,500 cases of lymphoma were determined to originate from the vagina.[253] Diffuse large B-cell lymphoma is the most common histology, though there have also been reports of lymphoplasmacytic, Burkitt, and mucosa-associated lymphoid tissue lymphomas.[244]

On examination, tumor is typically palpable, with infiltrative thickening and/or ulceration of the vaginal wall.[251] Immunohistochemical analyses are valuable techniques for confirming the diagnosis, with tumors typically expressing CD20.[245,252] The most common symptom at presentation is vaginal bleeding. Leukemic infiltrates may be difficult to distinguish from lymphoma; therefore, chloroacetate esterase or myeloperoxidase staining may be useful. Though there is no established treatment protocol for primary lymphoma of the vagina, it seems reasonable to extrapolate from results for extranodal lymphomas elsewhere in the body and to use similar chemotherapeutic and response-based radiation regimens. For patients wishing to retain fertility, chemotherapy alone may be an option in select cases.

If diagnosed at an early stage, the prognosis for vaginal lymphoma is excellent, with 5-year survival rates ranging up to 90%. Of 10 cases reported in the literature between 1994 and 2007, all patients, except one, were cured of disease after treatment with chemotherapy or a combination of radiation and chemotherapy.[243,245,249,250,254-257] Follow-up periods for these 10 case reports ranged from 6 to 120 months, and one patient died from other causes. Eight patients had Ann Arbor stage IEA disease, one had IIEA, and one did not have stage reported. The most common chemotherapy regimen was cyclophosphamide, doxorubicin, vincristine, and prednisone. Complete remission was also achieved using methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin in one patient. Half of the patients did not receive radiation because of an excellent response with chemotherapy alone.

Small Cell Carcinoma of the Vagina and Other Rare Histologies

Primary small cell carcinoma of the vagina is an exceedingly rare entity, with fewer than 25 cases reported in the literature.[258] The mean age at diagnosis is 59 years, with poor outcome due to early widespread dissemination. Eighty-five percent of patients die within 1 year of diagnosis.[259,260] Neuroendocrine differentiation is often manifested by secretory granules, argyrophilia, and expression of neuroendocrine markers,[261,262] staining positive for cytokeratin, neuron-specific enolase, chromogranin A, and serotonin. Thyroid transcription factor-1 can also be

positive and should not be used to differentiate primary from metastatic disease.[263] Microscopically, it is indistinguishable from that of the lung. These tumors can occur in pure form or be associated with squamous or glandular elements.[259,261] Ectopic Cushing syndrome has been documented to occur in primary small cell carcinoma of the vagina.[262] Treatment typically follows general principles for small cell carcinomas of the cervix, with aggressive therapy, including combination cisplatin-based chemotherapy, RT, BT, and surgery if feasible indicated.

Vaginal paraganglioma is a rare neuroendocrine tumor, with less than 10 cases reported in the literature in younger women, with median age at presentation of 31 years.[264-266] It is thought to be an indolent tumor, managed surgically. The tumor can manifest with catecholamine secretion, similar to paragangliomas elsewhere in the body.[264]

Adenosquamous carcinoma of the vagina is also uncommon. Microscopically, tumor cells are composed of glandular and squamous elements. One case report described adenosquamous carcinoma associated with small cell carcinoma of the endometrium in a 64-year-old female.[267] Treatment similarly follows general approaches for SCC of the vagina, including consideration of combination chemoradiation for patients with gross disease.

RADIOTHERAPY TECHNIQUES

Definitive treatment of primary vaginal cancer with radiation typically involves a combination of EBRT and BT. The use of 3D-based imaging to guide BT treatment planning is evolving, and recent results for vaginal cancer show excellent outcomes.[81,268,269] Because of advances in CRT, tumor dose can be escalated, whereas the dose to surrounding normal structures, such as small bowel, rectum, bladder, urethra, and the femoral heads, can be minimized. BT can be delivered via intracavitary or interstitial approaches, using LDR or HDR techniques.

External Beam Radiotherapy

In general, when radiation is delivered as primary therapy, EBRT is prescribed prior to or, in rare select cases, without BT for a subset of patients with stage I and all patients with stages II to IVA disease. The

treatment technique, dose prescription, and selection of the appropriate energy level must be individualized for each patient.

At the time of simulation, it may be helpful to identify the distal tumor margin with a radiopaque marker. Unless contraindicated, the use of oral and intravenous contrast can be helpful, allowing delineation of vascular structures and facilitating the contouring of the bladder, small bowel, and rectum. CT simulation allows the contouring of vessels as a surrogate for lymph node localization, allowing more precise and individualized field delineation relative to pelvic bony anatomy.[270] When available, the fusion of diagnostic pelvic MRI or PET-CT to the treatment planning CT can assist in defining the tumor (Figure 79.3). If inguinal nodes are to be treated, a "frog-leg" position to expose the groin region can be considered.

Three-Dimensional Conformal Treatment

The use of 3D imaging for treatment planning has increased dramatically over the past two decades and is currently used at almost all centers for simulation and treatment planning. This allows treatment fields to be tailored to a patient's specific anatomy.

The target volume for EBRT is influenced by diagnostic imaging results and the stage of disease. Treatment fields are designed to ensure coverage of the vagina and internal iliac, external iliac, and obturator lymph nodes. Coverage of the common iliac, para-aortic, and inguinal lymph nodes can be considered depending on the extent of disease and the location of the tumor. A standard field has the L5 to S1 interspace as the superior border, which ensures coverage of retroperitoneal nodes that lie caudal to the common iliac bifurcation.[271] However, because many initial failures occur predominantly in the vagina, paracolpos, and parametria, some authors suggest setting the superior border 1 to 2 cm superior to the inferior margin of the sacroiliac joints in patients with negative imaging of regional nodes, in order to minimize treatment toxicity.[272] If there are positive pelvic lymph nodes, the superior border should be raised to the L4 to L5 interspace or higher in order to cover the common iliac nodes. The inferior border lies at the introitus to ensure coverage of the entire vagina or 4 cm distal to the most caudal aspect of the vaginal tumor. Lateral borders are 1.5 to 2.0 cm lateral to the pelvic brim. Lateral fields, when utilized, should extend

anteriorly to the pubic symphysis and posteriorly to the junction of the S2 to S3 interspace. The border should be extended accordingly to include the inguinal nodes, if warranted. The dose to the inguinal nodes should be calculated during treatment planning, to ensure appropriate coverage. When designing treatment fields, the interconnectivity of vaginal lymph node drainage should be kept in mind. Unexpected nodal drainage is possible and should be considered. In a study of 14 women with vaginal cancer who received pretreatment lymphatic mapping with sentinel lymph node identification, two out of four women with a lesion in the upper one-third of the vagina were found to have a sentinel lymph node in the inguinal region.[71]

Several techniques can be considered when treating the inguinal region, to minimize dose to the femoral heads. An electron boost can be used to raise the inguinal dose to appropriate levels. Alternately, unequally weighted beams (2:1, anteroposterior:posteroanterior [AP:PA]) or a combination of low- and high-energy photons (4-6 MV AP; 15-18 MV PA) can be used. Another method uses a wide AP and a narrow PA field, with a daily photon boost to the inguinal nodes delivered with asymmetric collimator jaws.[273]

The gross tumor volume (GTV) is defined as the extent of gross disease found on clinical examination, as well as palpable lymph nodes and suspicious lymph nodes and regions seen on CT, MRI, and/or PET. The GTV is expanded by 1 to 2 cm to form the clinical target volume (CTV), which also includes the entire length of the vagina, paravaginal tissue up to the pelvic sidewall, and bilateral pelvic lymph nodes. Visualization of vessels allows approximation of lymph node locations. The pelvic nodal CTV can be defined as a 1- to 2-cm margin around blood vessels and should include the common iliac, external iliac, internal iliac, obturator, perirectal, and presacral lymph node regions. For distal vaginal involvement, inguinal lymph nodes are commonly included, with the inferior border set at the lowest aspect of the ischial tuberosity or lesser trochanter. The CTV is expanded by 1 cm to form the planning target volume (PTV). The small bowel, bladder, and rectum are contoured and doses to normal structures calculated.

Standard dose to the pelvis is 45 to 50.4 Gy in 1.8-Gy fractions, followed in select cases by a parametrial boost ranging from 50 to 65 Gy. Elective

nodal irradiation of the inguinal nodes may be delivered to 45 to 50 Gy. Gross nodal disease should receive 60 to 65 Gy, if feasible, using conformal therapy. For clinically palpable inguinal nodes, this can be achieved with reduced portals, using low-energy photons or electrons.

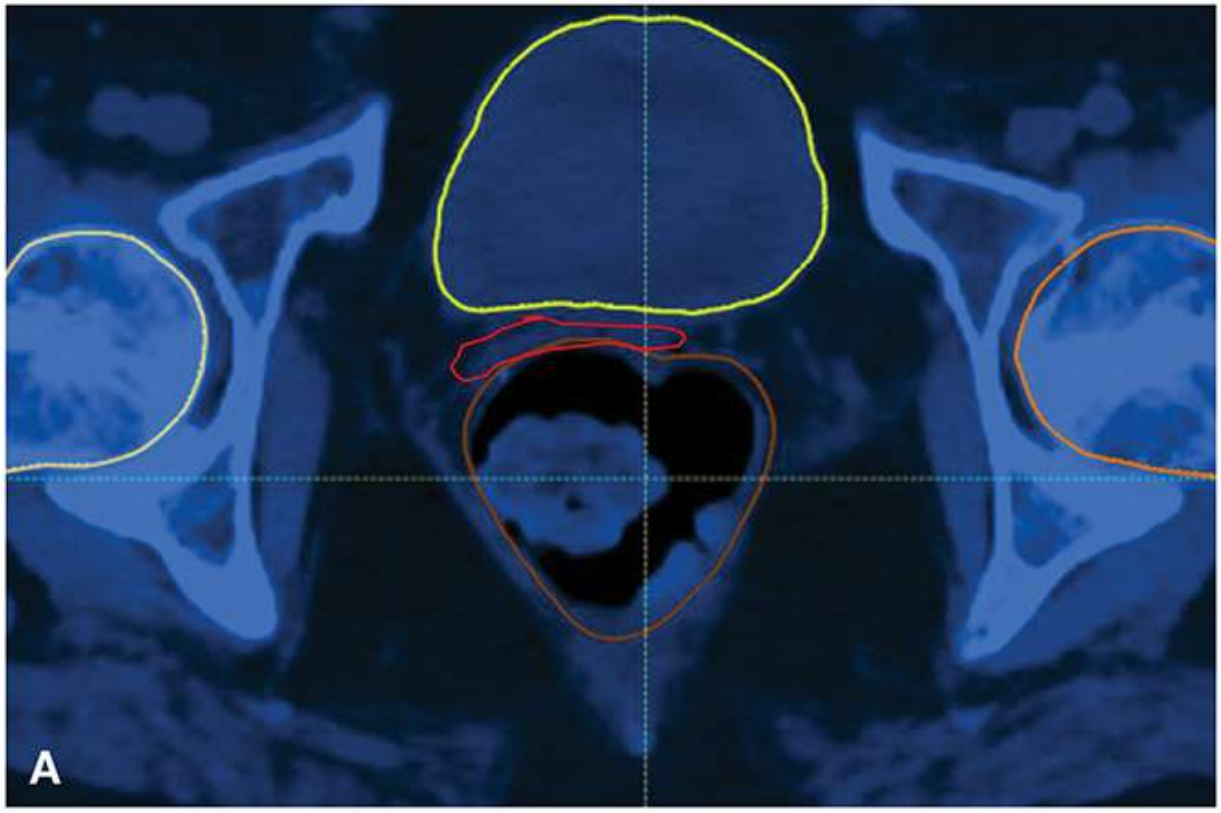
The location of the tumor, size, and extent of disease and treatment response are factors to be taken into consideration when individualizing treatment for each patient. After EBRT to the pelvis, tumors of the vaginal apex greater than 0.5 cm in depth should be considered for interstitial BT or external beam boost; tumors less than 0.5 cm should be treated with ICB. Depending on location, tumors of the midvagina can be treated with external beam boost or considered for freehand interstitial BT, particularly if they are located anteriorly or laterally. Tumors of the distal vagina are also amenable to treatment with interstitial BT, especially if the tumor is relatively confined. In general, BT is delivered upon completion of EBRT and allows dose escalation to the vaginal tumor to 70 to 80 Gy.

Intensity-Modulated Radiation Therapy

IMRT, which includes volumetric arc therapy, may allow dose escalation to gross disease in areas such as inguinal or pelvic lymph nodes, diffusely infiltrative disease, or sidewall tumors inaccessible to BT. Shrinking field techniques, or IMRT, can be used for dose escalation if BT is not feasible.[274,275] In such circumstances, a total dose of 70 to 75 Gy minimum should be delivered to gross disease. Higher doses are difficult to achieve without substantially increasing the risk of toxicity to adjacent normal tissues, such as the urethra, bladder, and rectum. IMRT input parameters include 30% or less of the bowel to receive 40 Gy or less; 35% or less of the bladder to receive 40 Gy or less; 60% or less of the rectum and sigmoid to receive 40 Gy or less; and the femoral heads 15% to receive 35 Gy or less. The IMRT plans are optimized to minimize the volume of PTV that receives more than 110% of the prescribed dose.[276]

When utilizing IMRT technique, it is important to take into account the possibility of significant shifts in tumor position because of constant normal tissue changes and rapid tumor regression. As a result, we recommend contouring an integrated vaginal volume, which reflects the CTV volume, paying close attention to rectal and bladder filling, and contouring the

position of the vagina with both bladder full and bladder empty (Figure 79.5).[277] A PTV margin of 1 to 2 cm is recommended, given the degree of motion and uncertainties in target definition.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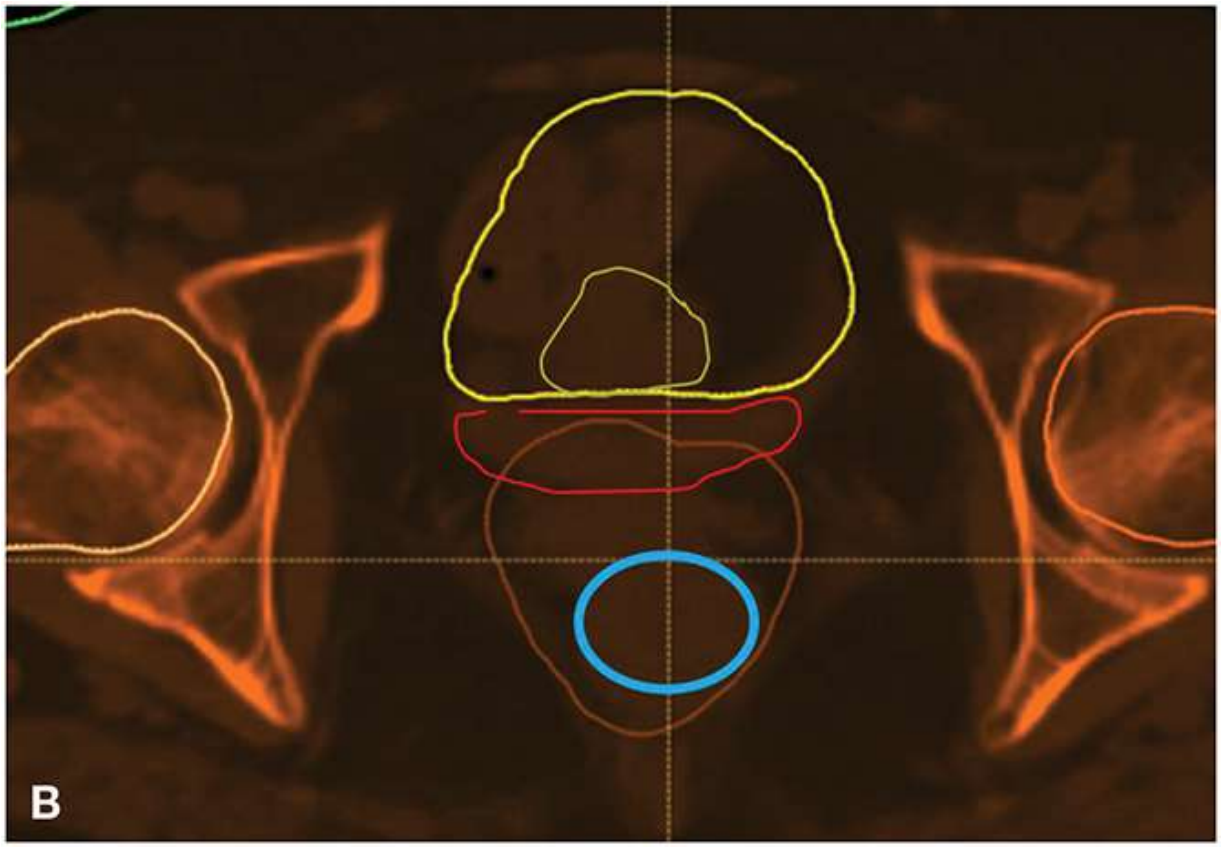

B

FIGURE 79.5 A. Bladder and rectum full scan. B. Depiction of the original full contours on the bladder and rectum empty scans showing the movement of the vagina into the rectal volume. Margins of more than 2 cm are required on the vagina to cover the organ when bladder and rectal filling change.

Image-guided RT is also widely used to ensure proper patient and organ positioning, which is particularly useful when treating with IMRT. X-rays prior to each radiation fraction can assist with lining up the patients according to bony anatomy, allowing patients to be shifted in the right-to-left (X), anterior-to-posterior (Y), and superior-to-inferior (Z) dimensions, minimizing the impact of daily patient setup differences. Low-dose cone-beam CTs prior to each radiation fraction can take full advantage of the six degrees of freedom on modern radiation tables, which include yaw, pitch, and roll shifts, in addition to the traditional X-Y-Z shifts. In addition, the use of cone-beam CT during treatment can validate that organ motion has not inadvertently shifted the target outside the treatment volume.

Brachytherapy

The utilization of BT should be considered for all patients with vaginal cancer who are undergoing radiation, unless they are unable to tolerate the procedure. According to a SEER database analysis spanning the years 1974 to 2011, the use of BT as a boost or definitive treatment provided a disease-specific survival and OS benefit across all FIGO stages of primary vaginal cancer.[278] An NCDB study spanning 2004 to 2011 found the use of BT as a boost in vaginal cancer has been declining, however, from 87.7% in 2004 to 68.4% in 2011 ($P < .001$), with an increase in the use of IMRT boost from 4.5% to 23.5%.[279] Treatment at a high-volume facility predicted for greater likelihood of BT as a boost. Given the mobility of the organ during treatment, SBRT is recommended only in the most rare of circumstances, requiring careful placement of fiducials and daily imaging with adaptive planning.

ICB as monotherapy can be considered for patients with VAIN and highly selected patients with minimally invasive stage I disease. In most cases, BT is offered after EBRT to boost the cumulative dose to a minimum of 70 to 80 Gy. Tumor response to EBRT is used to assess suitability for ICB or interstitial BT. In general, patients with superficial disease that is 5

mm in thickness or less can receive intracavitary treatment, whereas thicker lesions require interstitial BT in order to achieve adequate dose coverage. Image-based interstitial BT technique should be utilized to optimize target dose delivery and minimize dose to organs at risk; this has been shown to maximize disease control compared to non–image-based techniques.[280]

Intracavitary Brachytherapy: Low-Dose Rate

ICB can be delivered with LDR or HDR technique. LDR-ICB is most commonly performed using a vaginal cylinder loaded with cesium-137 radioactive sources. LDR remote control afterloading can be utilized to minimize radiation exposure to hospital personnel.

A variety of vaginal applicators are available, such as Burnett, Bloedorn, Delclos,[281] or MIRALVA.[282,283] Some cylinders have lead shielding to protect regions of the vagina, bladder, and rectum. Most applicators come in different diameters, and the largest diameter cylinder that can be comfortably accommodated by the patient should be used to improve the ratio of mucosa to tumor dose.

Typically, two to three cesium sources are placed along the central tandem of the cylinder, and labia are sutured closed to secure the implant during the treatment. To minimize skin toxicity, it is important to avoid placing a source over the vulva. With appropriate selection of dose specification points, a uniform dose distribution can be achieved over the entire length of the vagina. In cases where disease is localized to the upper vagina or vaginal fornices, an intrauterine tandem can be used to anchor the vaginal cylinder or be used with vaginal colpostats. Vaginal colpostats alone can be used to treat the upper vagina. Some institutions report good results using custom vaginal molds.[284]

A retrospective series by Pingley et al[106] reported their experience treating 134 women with primary vaginal cancer ranging from stage I to IV; ICB was delivered using the LDR technique. Only the 75 patients who completed treatment were analyzed. Most patients received EBRT to 50 Gy, and 59 of 75 patients received subsequent BT (30 with LDR-ICB, 29 interstitial). The 5-year DFS rate was 53% for patients treated with LDR-ICB and 30% for patients who did not receive BT. Patients who received BT within 4 weeks of EBRT had a DFS rate of 60%, compared to 30% in

those who did not, suggesting that a shorter interval between EBRT and BT is preferable.

Intracavitary Brachytherapy: High-Dose Rate

HDR-ICB is typically performed using iridium-192, with applicators that are similar to those described for LDR. HDR-ICB delivers treatment over a span of several minutes and has the potential advantages of limiting exposure to caregivers, as well as the ability to optimize dose distribution through varying dwell times.[285,286] The largest cylinder that a patient can comfortably tolerate should be selected.

Compared to LDR radiation, there is theoretically less potential sublethal damage repair and thus an increased likelihood of normal tissue toxicity. However, this has not been demonstrated in vaginal cancer, nor in cervical cancer, where multiple prospective and retrospective studies have failed to note any significant difference in local control, survival, or toxicity outcomes between HDR BT and LDR BT.[287]

Several single-institution studies have reported their outcomes for HDR BT. The largest series of HDR BT for vaginal cancer is from Vienna by Mock et al[57] and reported on 86 patients. Patients with stage 0 to stage II disease received treatment with HDR-ICB alone (n = 26). Prescribed dose per fraction ranged from 5 to 8 Gy, with a mean dose of 7 Gy, and the number of insertions ranged from 2 to 6, with a median of 5. In that series, the 5-year recurrence-free survival rates were 100%, 77%, and 50% for stages 0, I, and II, respectively. The authors noted similar local failure rates for HDR BT administered with or without EBRT, for both stage I and II diseases. Treatment was well tolerated.

Kucera et al[288] described their experience with 80 patients who received treatment with HDR-ICB, with or without EBRT. Compared to a historical group of patients treated with LDR-ICB, with or without EBRT, no significant differences were noted for local and distant recurrences or rate of complications. Three-year actuarial OS and disease-specific survival rates were 51% and 61%, respectively. Three-year disease-specific survival rates for stage I and stage II patients were 83% and 66%, respectively.

Stock et al[93] reported results for 49 patients treated with primary carcinoma of the vagina. Of this group, 15 patients were treated with EBRT

and HDR BT for vaginal carcinoma, with dose per treatment ranging from 3 to 8 Gy. The total median dose delivered via HDR was 21 Gy, and the total median tumor dose overall was 63 Gy. No significant difference in outcome was noted between patients treated with LDR versus HDR. Five-year actuarial survival was reported to be 50% in the HDR BT group. In comparison, the 5-year survival rate for patients who received EBRT alone ($n - 11$) was 9% ($P < .001$), with a higher rate of stage IV disease in the EBRT-alone group (36%) compared to the BT group (5%).

The use of image-based HDR-ICB was reported by Vargo et al,[122] in a series of 41 patients with vaginal cancer treated with chemotherapy and definitive radiation with image-based multichannel vaginal cylinder HDR BT. CT (41%) or MRI (59%) was used for each fraction, and high-risk CTV (HRCTV) drawn. The median dose to 90% of the HRCTV was 77.1 Gy (equivalent dose of 2 Gy per fraction), and outcomes were favorable, with 2-year local, regional, and distant control of 93%, 100%, and 81%, respectively. There was 4% grade 3 or higher toxicity at 2 years.

Among 148 patients with vaginal cancer from five separate institutions reported by Westerveld et al, 67 of these patients had ICB using image guidance with MRI or CT, with the remainder receiving interstitial BT.[125] For the entire cohort, the median dose to 90% of the CTV was 80 Gy (equivalent dose of 2 Gy per fractions), with 5-year local and pelvic control of 83% and 79%, respectively, and 5-year DFS and OS of 66% and 68%, respectively.

Interstitial Brachytherapy

According to the American Brachytherapy Society Consensus Guidelines for interstitial BT for vaginal cancer, any lesions greater than 5 mm in thickness after EBRT should be considered for interstitial BT, and image guidance is recommended to minimize dose to normal organs and optimize dose to the target volume.[123] Any paravaginal extension at the time of diagnosis, regardless of treatment response, merits consideration of interstitial BT, as a vaginal cylinder is unable to deliver sufficient coverage to this region. Other candidates for interstitial BT include patients with lesions thicker than 5 mm, distal vaginal extension, or those with a vagina that is unable to accommodate standard intracavitary applicators. When

possible, image-based interstitial BT should be utilized, as outcomes are superior to non–image-based techniques.[280] Further details of the procedure and planning are detailed later.

Preoperative Assessment

When determining tumor thickness, MRI is superior to other imaging modalities. T1 with gadolinium and T2-weighted MRI should be obtained if possible after EBRT to assess residual disease.[121] Contrast, such as ultrasound gel placed to distend the vagina, may also aid in visualization of the tumor. Clinical examination provides an imprecise estimate of tumor thickness. An examination under anesthesia can be performed after EBRT; placement of gold fiducial markers can be considered to mark the proximal and distal end of residual disease. The use of a radiopaque marker in the vagina placed at the time of diagnosis and after external beam will facilitate assessment of the lesion on CT imaging.

The patient should be assessed for general, epidural, or spinal anesthesia. When feasible, a combination of general anesthesia during the insertion followed by an epidural patient-controlled anesthesia approach that continues during the entire inpatient hospitalization maximizes pain relief. Epidural anesthesia allows the patient to control the degree of pelvic anesthesia while avoiding the systemic effects, somnolence, and potential mental status changes that may occur with a peripheral patient-controlled anesthesia device. Patients with a history of laminectomy, significant degenerative disease, or labile blood pressure are suboptimal candidates for epidural anesthesia.

Patients on anticoagulation with medications such as warfarin should switch to low-molecular-weight (LMR) heparin approximately 1 week prior to the procedure, and LMR heparin may be discontinued 24 to 48 hours prior to insertion time and be withheld during the duration of the implant, though subcutaneous heparin for thrombosis prophylaxis may be initiated after the procedure is completed. The need for therapeutic levels of anticoagulation may also play a role in deciding if patients can receive epidural or spinal anesthesia.

Particularly if patients receive concurrent chemotherapy prior to their implant, it is important to monitor their blood counts, particularly their

absolute neutrophil count and platelets. As with other procedures and surgeries, it is preferable to have an absolutely neutrophil count greater than 500/μL and platelets greater than 40,000/μL in order to minimize the risk of infection or bleeding. Patients may have a gentle bowel preparation orally or an enema before the procedure.

Applicator Selection

Template systems are available to secure the position of the needles in the target volumes and include the Syed-Neblett template, the modified Syed-Neblett, and the Martinez Universal Perineal Interstitial Template.[289] These systems consist of a perineal template, a vaginal cylindrical obturator, and hollow guides for loading radionuclide sources. The perineal template requires suturing to the perineal skin. The vaginal obturator allows for the placement of a tandem, making it possible to combine interstitial with intracavitary treatment if desired. Lower vaginal tumors may be suitable for freehand technique, if the mass can be readily visualized and palpated.

Procedure

The insertion procedure is performed with the patient in a dorsal lithotomy position. A sterile setup is used at the time of insertion. A Foley catheter is placed for bladder drainage. A digital and speculum examination allows assessment of vaginal width, tumor size and location, amount and thickness of residual parametrial or paravaginal disease, and presence of any fistulas. For patients with an intact uterus, a central tandem may be inserted to anchor the applicator. A vaginal central plastic cylinder is placed over the tandem and secured. The template, which contains multiple openings through which needles can be inserted, is placed onto the perineum. The tumor volume is implanted by inserting the needles through the holes of the template, with the goal of covering the GTV with a 1- to 2-cm margin, utilizing 3D imaging afterward to confirm proper needle location and uniform dose distribution around the tumor volume. Generally speaking, needles should extend approximately 5 to 10 mm past the disease, with 5 to 10 mm between each needle.[121] The physician should be mindful that slight needle displacement can occur when legs are lowered back to the supine position.

When possible, utilizing image guidance to perform implants is ideal in order to improve target localization and guide needle placement. Available modalities include laparoscopic guidance, ultrasound, CT, and MRI. The results with these various techniques are summarized below.

Several investigators have used laparoscopic guidance or laparotomy[290-292] to improve the accuracy and safety of interstitial implant placement. With open laparotomy, the bladder and urethra can be visualized during needle placement. The bladder and rectum can be protected either by using slings or tissue expanders or by lysis of adhesions. Disaia and Creasman[293] described the creation of an "omental carpet," where a section of omentum is placed along the descending colon into the pelvis in order to separate the bladder and rectum from the implant and prevent small-bowel adhesions. If laparotomy is performed in a two-application course of treatment, it is typically done for the first application only. As expected, there is higher associated morbidity with the use of laparotomy compared to other techniques, as a result of increased operative time, longer postoperative recovery, risk of bleeding, and ileus.

Laparoscopic visualization is an alternative to open laparotomy that has also been reported. Though laparoscopy is less invasive, both laparoscopic approaches and open laparotomy are limited by an inability to visualize extraperitoneal structures, such as parts of the bladder, uterus, and cervix, as well as the vagina and paravaginal tissues. However, these techniques can be considered when CT or MRI is not available during BT, to avoid needle insertion through the small bowel and sigmoid.

Stock et al reported results using real-time transrectal ultrasound as visualization.[290] The ultrasound probe was brought into close proximity to the vagina, parametria, and cervix, and the longitudinal mode of the ultrasound probe was useful in determining the optimum depth of needle insertion. Transverse imaging was utilized during the procedure to ensure coverage of the target area and avoid entry into the bladder, rectum, or small bowel. Using this technique, invasive laparotomy or laparoscopy was able to be avoided.

In general, temporary implants are preferred to permanent implants because of their relative safety/simplicity, cost-effectiveness, easy applicability, readily controlled distribution of sources, and easier modification of dose distribution. HDR interstitial BT has the advantage of

limiting exposure to caregivers and visitors and offers the ability to optimize dose distribution using 3D image-based treatment planning.[268,286] The use of permanent radioactive implants using gold-198 or iodine-125 has also been reported for smaller volume disease[294] and can be considered for select patients; reports suggest long-lasting control can be achieved with appropriate selection of patients.

Image-Guided Brachytherapy

The use of 3D imaging during HDR BT has increased with the rise of CT and MR availability and has been a favored approach when available because of lower morbidity and invasiveness compared to historical approaches.[295] Only a few institutions have access to real-time image guidance during BT[145,296]; most scan patients after insertion is complete, with subsequent readjustment as needed. It is not feasible at many institutions to obtain an MRI at the time of BT. A diagnostic MRI obtained after EBRT prior to BT can be used instead to assist with treatment planning. MRI provides superior tumor delineation, whereas CT images can cause overestimation of tumor extension.[297]

The integration of 3D imaging during the BT procedure allows determination of depth and location of insertion and enables repositioning if perforation into the bladder or rectum is detected. Treatment planning based on 3D imaging allows high dose to be delivered to the tumor volume while sparing critical adjacent organs. The use of 3D image–based HDR BT has been shown to improve local control and decrease treatment-related toxicities.[125,280,298] There are fewer published reports on 3D HDR BT for primary vaginal cancer, but results suggest similar outcomes.[269,280]

Dosimetry

Given the close proximity of the rectum and bladder, it is important to minimize treatment toxicity by avoiding overdose of critical normal structures. However, underdosing the target volume is also a serious risk; thus, it is critical to optimize target localization and needle placement.[299]

Vaginal cancer with gross residual disease at the time of BT is prescribed a cumulative EQD2 dose of 70 to 90 Gy, with 60 Gy prescribed to the entire vaginal surface. Special care should be taken to minimize the dose to the

bowel, which often lies in close proximity to gross disease. Image-based planning software, when available, allows the dose to conform to the target areas while avoiding organs at risk. As a result, optimal dose distribution can be achieved. Image-guided technique should be utilized when possible to reduce toxicity and improve local control.

Proposed dose schedules for HDR interstitial BT, depending on dose of initial EBRT, have been released by the American Brachytherapy Society[123] (Table 79.7). The number of fractions ranges from 3 to 10, with the goal of delivering a total EQD2 of over 70 Gy to the CTV. Given the difficulty of insertion, physicians may insert the applicator once and treat patients over a several-day inpatient hospitalization. Twice-a-day (BID) regimens range from 9 to 10 fractions of 200 to 300 cGy per fraction, BID, or 3 to 6 fractions, ranging from 450 to 650 cGy, BID, with at least 6 hours between fractions. It is also feasible to perform two separate insertions with two hospitalizations required.

TABLE 79.7 DOSE SCHEDULES FOR HDR INTERSTITIAL BRACHYTHERAPY IN COMBINATION WITH EBRT, AS PROPOSED BY THE AMERICAN BRACHYTHERAPY SOCIETY CONSENSUS GUIDELINES FOR INTERSTITIAL BRACHYTHERAPY FOR VAGINAL CANCER

EBRT		HDR		EQD2
Total Dose (Gy)	**# Fx**	**Dose per Fx (Gy)**	**# Fx**	**CTV**
36[a]	18	5.0	6	72.9
		5.5	6	87
39.6[a]	22	5.0	6	76.4
		5.5	6	81.5
45	25	3.0	9	73.6
		3.0	10	76.8
		4.5	5	71.5
		5.0	5	75.5
		5.5	5	79.8
		7.0	3	74.1
50.4	28	4.0	5	72.9

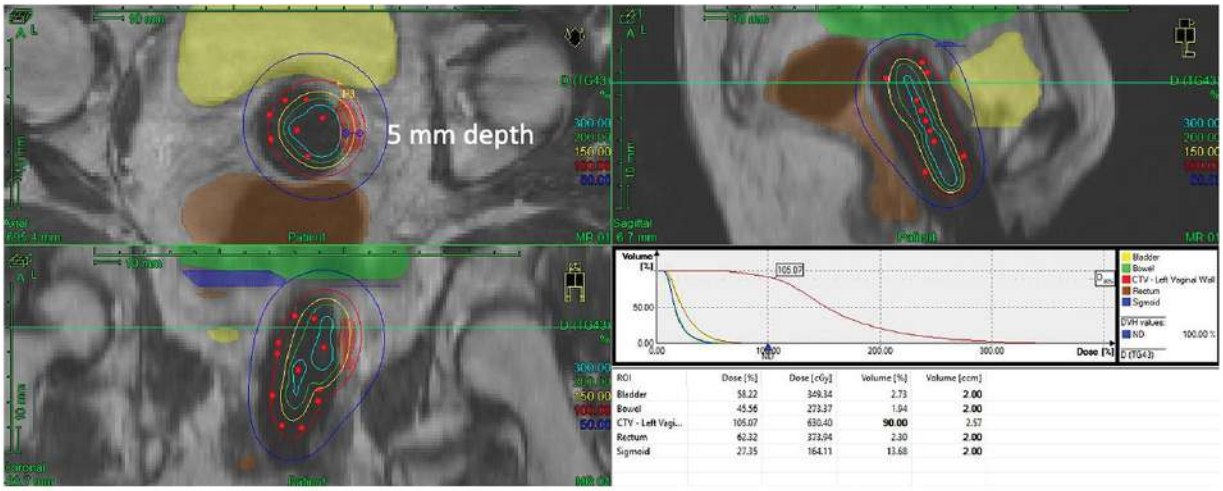
EBRT		HDR		EQD2
Total Dose (Gy)	# Fx	Dose per Fx (Gy)	# Fx	CTV
		4.5	5	76.8
		5.0	5	80.9
		7.0	3	79.4

CTV, clinical target volume; EBRT, external beam radiation therapy; EQD2, equivalent dose in 2-Gy fractions; fx, fractions; HDR, high-dose rate.

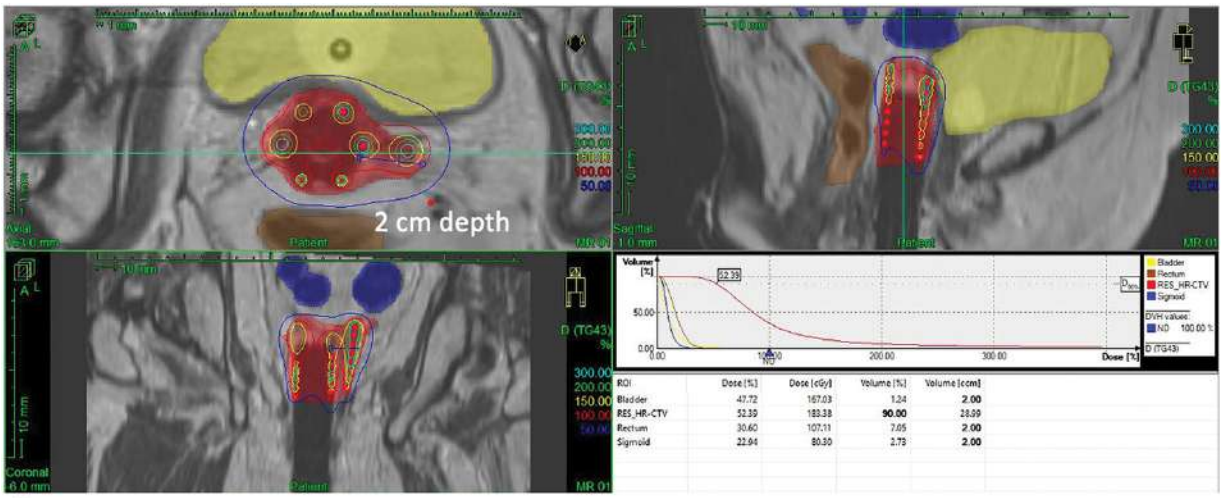
[a]Assumes midline block after 36 to 39.6 Gy, with total pelvic dose to 50.4 Gy.

Modified from Beriwal S, Demanes DJ, Erickson B, et al. American Brachytherapy Society consensus guidelines for interstitial brachytherapy for vaginal cancer. *Brachytherapy*. 2012;11(1):68-75. Copyright © 2012 American Brachytherapy Society. With permission.

For CT- or MRI-based 3D treatment planning, the D_{90}, D_{100}, V_{100}, V_{150}, and V_{200} are parameters used to describe tumor volumes and the doses to those volumes. D_{90} and D_{100} are defined as the minimum dose delivered to 90% and 100% of the volume, respectively. V_{100}, V_{150}, and V_{200} are defined as the volumes receiving 100%, 150%, and 200% of the prescribed physical dose, respectively.[300] Figure 79.6 depicts a representative isodose distribution comparing multichannel vaginal cylinder for a lesion less than 5 mm in depth versus interstitial BT for a mass greater than 5 mm in depth.



A



B

FIGURE 79.6 Comparison of a multichannel vaginal cylinder versus interstitial implant for vaginal cancer in the upper one-third of the vagina. A. Gross tumor volume (GTV) in red at less than 5-mm depth covered with 100% isodose whereas the entire vagina receives 50% of prescription. B. GTV in red with disease in the left fornix extending over 2 cm and inferiorly to the upper one-third of the vagina. The entire vagina is covered with 50% of the prescribed dose.

When MRI-guided adaptive BT is utilized, the HRCTV is defined as a clinically palpable disease, plus any residual disease seen on MRI, and the entire circumference of the adjacent vagina at the level of the residual tumor. The intermediate-risk CTV (IRCTV) includes the region of initial tumor extension and the remaining vagina, in order to encompass potential submucosal tumor spread. The low-risk CTV (LRCTV) is the remaining vagina.

The bladder, rectum, sigmoid, urethra, and small bowel are contoured as volumes at risk, and the D_{2cc} and $D_{0.1cc}$ are calculated.[317] The recommended maximum EQD2 D_{2cc} to the rectum and sigmoid is 65 to 75 Gy and should be less than 65 Gy when feasible.[143] Maximum EQD2 D_{2cc} for the bladder should be 80 to 90 Gy based on cervical cancer dose limits. There are no dose-volume histogram parameters specific to the female urethra, but in general, the D_{2cc} should be comparable to the parameters for the bladder and rectum. The small-bowel dose can be limited with the use of a full bladder; some institutions limit the EQD2 maximum point dose to 60 to 65 Gy.[141] The actuarial rates of grade 3 to 4 complications at 2 years were 20% gastrointestinal, 9% vaginal, 6% skin, 3% musculoskeletal, and 2% lymphatic in 51 women undergoing HDR 3D-planned interstitial BT,[136] with median D_{2cc} for the bladder, rectum, and sigmoid were 64.6, 61.0, and 51.9 Gy, respectively. The D_{2cc} for the rectum was significantly higher in patients with grade 2 or more gastrointestinal toxicity.

Precautions for Interstitial Patients

Appropriate measures should be taken to reduce the likelihood of needle displacement during hospitalization. Patients should be instructed to remain in bed, with head of the bed raised no more than 15 degrees. To ensure there has been no needle displacement between fractions, the needle length protruding the template can be measured and validated prior to every treatment.

Skin care is also critical. Given the risk of decubitus ulcer, it is advisable to utilize an air mattress, when available. Careful rolling of the patient and placement of foam or pillows to change contact points with the mattress can be used to decrease the risk of pressure ulcers. To minimize skin abrasion, gauze or Duoderm can be placed between the template and perineal skin.

To prevent the development of a deep vein thrombosis, patients should receive subcutaneous heparin and pneumoboots.

Patients should be seen in follow-up 2 to 4 weeks after implant removal for a skin check, then at 3-month intervals up to a year, and then every 6 months. Dilute hydrogen peroxide douching is advised for patients with tissue necrosis development. Antibiotics with anaerobic coverage are

recommended if a malodorous discharge accompanies the necrosis. Hyperbaric oxygen should be considered for those that have been proven on biopsy not to have recurrent disease.

Outcomes With Interstitial Technique

There are only a handful of series describing outcomes for vaginal cancer treated with interstitial BT. They are summarized later.

The use of MRI-guided adaptive BT in locally advanced vaginal cancer was reported by Dimopoulos et al[301] with excellent outcomes, supporting the use of the following parameters for IGABT: for HRCTV, D_{90} of 85 Gy or more; for IRCTV, D_{90} approximately 60 Gy; and for LRCTV, D_{90} of approximately 50 Gy. Thirteen patients with stages II to IV disease were treated. Mean D_{2cc} doses to the bladder, urethra, rectum, and sigmoid colon were 80, 76, 70, and 60 Gy, respectively. Toxicity was acceptable, with two fistulas reported and one case of periurethral necrosis. The 3-year local control and OS rates were 92% and 85%, respectively, with a mean D_{90} to the HRCTV of 86 (±13) Gy. Consistent with these promising outcomes, image-guided interstitial BT results were reported by Manuel et al,[280] with 2-year local control, DFS, and OS of 93%, 86%, and 82%, respectively, in their cohort of 72 patients. Patients were treated with image-guided (n = 50) or non–image-guided (n = 25) technique treated during the time period of 1973 to 2014.[269] With the use of image-guided technique, there was a trend toward improved DFS (2-year DFS 77% vs 42%; P = .072), improved OS (84% vs 47%; P = .26), and decreased gastrointestinal and genitourinary toxicity, supporting the incorporation of CT and/or MRI as image guidance when available.

Kushner et al[302] reported outcomes of HDR BT in 19 patients with primary vaginal cancer. 2D treatment planning was performed, with interstitial BT delivered to eight patients at a median dose of 23 Gy in four fractions. The 2-year OS rate for patients for all patients was 66.1%. Three patients (15.8%) had serious late effects, including ureteral stenosis, vaginal necrosis, and small-bowel obstruction; two of these patients were treated with interstitial BT.

A series by Tewari et al[303] reviewed long-term results using interstitial BT, with or without EBRT, in 71 patients with primary vaginal cancer. A

Syed-Neblett template was used with an interstitial iridium-192 after loading technique. Patients received a minimum of 20 Gy via implant, with a total tumor dose of approximately 80 Gy. With a median follow-up time of 66 months, 5-year DFS rates were reported to be 100%, 60%, 61%, 30%, and 0% for stages I, IIA, IIB, III, and IV patients, respectively. Significant complications were noted in 13% of patients and included necrosis, fistula, and small-bowel obstruction. Overall, 75% of patients achieved local control.

Beriwal et al describe results using 3D image–based HDR interstitial BT[268] at the University of Pittsburgh Cancer Institute. A total of 30 patients with primary vaginal cancer (n = 17) or recurrent gynecologic cancer to the vagina (n = 13) were treated using the Syed-Neblett template, with a CT scan done after the placement of needles for confirmation and treatment planning. Of the subset of 17 patients with primary vaginal cancer, the number of patients with stage I, II, III, and IVA disease were 2, 9, 5, and 1, respectively. Fifty-three percent of patients received concurrent chemotherapy with weekly cisplatin at 40 mg/m^2, and apical lesions had laparoscopic guidance during needle placement. The CTV and organs at risk were contoured on a CT scan for treatment planning after the placement of needles. Most patients (93.3%) received EBRT to a median dose of 45 Gy, followed by HDR interstitial BT at 3.75 to 5 Gy per fraction in five fractions to a median dose of 21.3 Gy. Overall median D90 to the HRCTV was 74.3 Gy, and median D_{2cc} to the bladder, rectum, and sigmoid were 58.5, 57.2, and 50 Gy, respectively, showing excellent sparing of critical organs. At a median follow-up time of 16.7 months, the 2-year locoregional control and OS rates were 78.8% and 70.2%, respectively, suggesting good local control. Overall, the treatment was fairly well tolerated. There were no grade 3 or higher gastrointestinal complications. One patient developed late grade 3 vaginal ulceration, and another had grade 4 vaginal necrosis.

Westerveld et al reported 148 patients with vaginal cancer of all stages from five institutions, of which 81 received interstitial BT as part of their treatment.[125] The vast majority (145 patients) had EBRT prior to BT, and 64% had concurrent cisplatin. For the entire cohort, the median dose to 90% of the CTV was 80 Gy (equivalent dose of 2 Gy per fractions), with 5-year local and pelvic control of 83% and 79%, respectively, and 5-year DFS and

OS of 66% and 68%, respectively. Morbidity was acceptable, with 25 patients developing grade 3 or higher toxicity, including one grade 4 event, which was a life-threatening vesicovaginal fistula in the setting of reirradiation. There were no grade 5 toxicities.

Brachytherapy Versus External Beam Boost

In select circumstances when patients are not appropriate candidates for BT, IMRT can be considered an alternative for boost to residual gross disease. A retrospective dosimetric analysis from Princess Margaret Hospital[304] reported data comparing IMRT boost treatment plans with conventional and four-field radiation boost plans for 12 patients with cervical (n = 8), endometrial (n = 2), or vaginal (n = 2) cancer. IMRT conferred a significant improvement in dose conformity, with an overall improvement in rectal and bladder dose-volume distributions, relative to conformal radiation, though inferior to BT. However, when comparing an ideal photon or proton external beam boost to BT, BT provided the best coverage and normal tissue sparing.[305]

Barraclough, et al[306] used an EBRT boost in 21 patients with cervical cancer who could not undergo ICB. A 3D conformal boost was used to deliver a total dose of 54 to 70 Gy. With a median follow-up time of 2.3 years, 48% of patients had recurrent disease, with central recurrence in 16 of 21 patients, significantly higher than 3% to 4% local recurrence rates reported with MR-planned BT. These results are dramatically inferior to those reported with BT, suggesting that external beam boosts should only be considered an alternative when BT is not feasible.

SBRT is a relatively newer treatment modality with very little data to support its use. A review by Higginson et al[307] reported on two patients with vaginal cancer treated with an SBRT boost instead of BT. Fiducials were placed into the paravaginal, parametrial, or cervical tissues during outpatient clinical examination. The two patients with vaginal cancer received 40 to 45 Gy EBRT followed by 25 Gy in five fractions of SBRT; one patient had a local recurrence at 5 months, and another developed distant disease 17 months post-treatment. Toxicity included one acute grade 2 cystitis and one late grade 3 rectal bleeding.

Treatment Toxicity and Management

Acute Toxicity

The bladder and rectum are located in close proximity to the vagina, and it is common for patients to develop acute bowel and urinary toxicity during treatment.[308] Increased urinary frequency, urgency, and dysuria can be managed with phenazopyridine, a urinary tract analgesic, as well as oral anticholinergic and antispasmodic medications. Antidiarrheal medications such as loperamide, or in more severe cases, tincture of opium, should be prescribed for symptom management early in the development of symptoms. Irritation of the anal mucosa can cause exacerbation of hemorrhoids and occasional hemorrhagic spotting and discomfort with defecation; topical hemorrhoidal ointments or suppositories can be used.

Acute irritation of the vaginal mucosa can be managed symptomatically through hygiene, recognition and treatment of infection, and pain control. Sitz baths and topical ointments may be useful for radiation dermatitis, and both topical and oral analgesics can be prescribed for mucositis and general discomfort during radiation and immediately thereafter. As *Candida* can exacerbate vaginitis, there should be a low threshold for starting antifungal medications.

Late Toxicity

Late toxicity after radiation can manifest as rectovaginal or vesicovaginal fistulas, strictures in the rectum or vagina, premature menopause from radiation exposure to the ovaries, or cystitis, proctitis, or necrosis of the soft tissue or bone.

Clinically, vaginal stenosis and shortening can manifest several months after radiation, although presentation as late as 15 years post-treatment has been documented.[309] Pathologic changes in the vaginal mucosa after radiation treatment include marked mucosal atrophy with epithelial thinning and loss of the overlying stratified squamous layer. There can be hyalinization and collagenization of submucosal connective tissues, with fibrosis of the muscular layer and vasculature. Such changes result in compromised oxygenation of injured tissues, promoting ulceration and fistula formation. It is common to find cytologic abnormalities within the first 6 months after radiation, and it is important to distinguish postradiation

atypia from new or recurrent malignancy during post-treatment follow-up.[310]

Regular use of a vaginal dilator to decrease stenosis and shortening should be recommended shortly after completion of radiation treatment, as it is difficult to reverse stenosis and shortening once fibrosis has ensued. Without the use of a vaginal dilator, complete agglutination or vaginal obliteration can occur. Topical estrogen, applied 3 times a week for 6 to 9 months after radiation, was shown in a randomized controlled trial published in 1975 to reduce the incidence of stenosis, dyspareunia, and cytologic changes in vaginal epithelium.[311] However, due to a small potential for systemic absorption with untoward effects on endometrial proliferation, the use of topical estrogens is not favored for patients.

Radiation necrosis can be conservatively managed with local debridement, peroxide douches, antimicrobials, and estrogen. There is some evidence that hyperbaric oxygen can facilitate healing, with a more than 50% reduction in vaginal ulceration noted in one series.[312] Fistulas present more of a treatment challenge. Despite the use of interventions such as urinary or fecal diversions, additional surgical correction is often required for effective management, particularly in the case of rectovaginal fistulas.[313]

PATTERNS OF FAILURE

Most treatment failures occur within 5 years, with a median time to recurrence of 6 to 12 months,[62,146] and local recurrence is the most common pattern of treatment failure in the majority of published series. Extravaginal recurrences in the pelvic lymph nodes are less common.

Overall outcomes, by stage, are shown in Table 79.5. In general, the rate of locoregional recurrence ranges from 10% to 20% for stage I and 30% to 40% for stage II. Patients with advanced disease often have persistent disease despite treatment, up to 68% according to one series.[105] The reported rates of distant metastasis vary, ranging from 7% to 33%, and usually occur later in the course of disease, with approximately half of all distant metastases presenting at the time of local recurrence.[67,87,105,147]

GENERAL MANAGEMENT, TREATMENT OPTIONS, AND OUTCOMES: SPECIAL SCENARIOS

The Posthysterectomy Patient

Approximately 60% of patients with primary vaginal cancer have had a prior hysterectomy. This likely reflects patients with a history of cervical neoplasia and carcinoma requiring surgical management.[314,315] Finding methods to improve target positioning during EBRT becomes especially important as treatment delivery becomes increasingly more conformal.

After hysterectomy, the small bowel tends to fall lower into the pelvis, increasing the likelihood of it being irradiated during treatment. There is also daily variation in vaginal vault position. A study by Jhingran et al[277] evaluated the variations in vaginal vault position and bladder and rectal volumes in posthysterectomy patients undergoing IMRT and found significant variations in the position of the vaginal vault depending on bladder and rectal filling. Patients were instructed to have a full bladder prior to radiation treatment; however, the study showed a median difference of 247 mL despite this. It is likely that bladder movement impacts vaginal position. For patients with fiducial markers placed in the vagina, the median movement during treatment was 0.59 cm in the right-left direction, 1.46 cm in the AP direction, and 1.2 cm in the superior-inferior direction. Thus, it is important to be mindful of target movement when delineating the treatment volume.

To minimize uncertainly, the treating physician can fuse planning CT scans taken with full and empty bladder in order to estimate the potential range of target volume positions during treatment. Another approach, though less practical, is to fill the bladder with a fixed volume of saline using a Foley catheter immediately prior to treatment or to utilize fiducial markers for daily localization.

History of Prior Pelvic Radiation

Up to 10% to 50% of patients with VAIN or invasive carcinoma of the vagina have a previous diagnosis of cervical carcinoma,[13,59,61,67,84-88] with average time interval of 14 years between diagnosis of cervical disease to the development of vaginal carcinoma.[61,72] As a result, a proportion of patients with vaginal cancer have a history of prior pelvic radiation. Reirradiation can be considered in this setting, but there is an increased risk of toxicity, particularly radionecrosis and fistula formation. Xiang et al[316]

published a series on 73 patients with a history of radiation treatment for cervical carcinoma who received a second diagnosis of vaginal malignancy 5 to 30 years later. All patients received EBRT and BT for the treatment of their initial cancer. Reirradiation for the vaginal malignancy was planned according to the site and volume of the vaginal tumor and the location and dose of the prior radiation. Patients received BT, using either radium delivered to the tumor base (30-40 Gy in three to five fractions) or HDR with cobalt-60 to the tumor base (20-35 Gy in three to five fractions), followed by a dose to 0.5 cm below the vaginal mucosa at 20 to 30 Gy in four to six fractions delivered using a vaginal mold. For involvement of the vulva or groin, patients additionally received EBRT to a dose of 30 to 40 Gy. Most patients received radiation alone; 11 also received chemotherapy, most typically cisplatin based. The 5-year survival rate was 40.3%, and three patients survived more than 15 years. There were significant side effects with reirradiation: 18 of 73 patients developed radionecrosis. Other side effects included one (1.4%) vesicovaginal fistula and eight (11%) rectovaginal fistulas, hematuria (12.3%), and moderate-to-severe rectal sequelae (13.6%).

Beriwal et al reported on the use of HDR interstitial and ICB for five patients with recurrent vaginal cancer with a history of prior pelvic radiation.[317] Significant grade 3 or higher toxicities were noted in patients who received a total EQD2 dose above 140 Gy. The median time from prior radiation to recurrence was 4 years (range, 6 months to 18 years). The recurrence was within 2 cm of the prior field in two patients and within the previous field in four patients. All patients received EBRT to a median dose of 45 Gy, followed by BT. For the four patients with prior overlapping fields, the cumulative EQD2 to the vaginal mucosa ranged from 120.7 to 154.54 Gy. Of these patients, one developed a rectovaginal fistula 2 years after treatment, and another developed chronic vaginal ulceration with vaginal shortening to 2 cm; the EQD2 values were 142.98 and 154 Gy, respectively.

Carcinoma of the Neovagina

The neovagina is a surgically constructed vaginal canal, typically described in patients with congenitally deformed or absent genitalia or patients

desiring reconstruction of a functional vaginal after surgery for gynecologic malignancy. Various methods have been utilized for neovaginal construction, including split-skin grafts, myocutaneous flaps, and the formation of an artificial canal between the rectum and the vagina.[318] Given its overall rarity, there are very few reports of in situ or invasive carcinoma arising in the neovagina.

A review of published literature reveals six published reports of carcinoma in situ.[319-324] The period of development of carcinoma in situ ranged from 6 months to 20 years after constructive surgery. Invasive carcinoma of the neovagina tends to be poorly differentiated, and the majority of reported cases have been SCC. All reported patients have presented with large tumor masses and evidence of rapid progression, with poor overall outcomes.[234,325,326]

Treatment options include radiation, with or without an attempt at radical resection, and, in select cases, lymph node dissection. Of 16 reported cases from a review by Steiner et al,[318] nine received primary radiation alone, one received radiation followed by exenteration and intraoperative radiation, and four underwent exenteration. Recurrence status was not documented for all patients. Three were found to have rapid disease recurrence within several months. Two patients were free of disease at 10 and 18 months, respectively. One patient had a recurrence-free interval of 3 years but died a year later from disease.

Though there is no optimal treatment, resection followed by consideration of adjuvant radiation is preferable to definitive radiation alone, as surgery can offer a full pathologic diagnosis. The extent of disease, patient characteristics, and treatment goals should be used to guide the choice of treatment.

Salvage Therapy for Recurrent or Persistent Disease

For patients with recurrent or persistent disease, it is important to determine whether there is a reasonable chance of cure with salvage treatment or whether the primary goal is palliation. Thus, multiple factors, including histology, sites and extent of recurrence, disease-free interval, patient age, comorbidities, and overall performance status, must be considered.

Early-stage lesions that recur after RT can be surgically salvaged. A retrospective review of pelvic exenteration for recurrent gynecologic malignancies at University of California Los Angeles Medical Center from 1956 to 2001 reported survival rates for patients with recurrent cervical and vaginal cancer to be 73% at 1 year and 54% at 5 years.[327]

Patients with tumor persistence or recurrence after limited surgical procedures can be considered for more extensive surgery. If not, systemic chemotherapy and/or radiation can be administered.

Recurrent disease in advanced-stage patients is more challenging to treat. Most patients have received prior EBRT and thus have options limited to radical surgery or, in patients with localized disease, reirradiation. For patients with small pelvic recurrences, reirradiation with ICB or interstitial BT has been reported, with control rates between 50% and 75% and grade 3 or higher complication rates between 7% and 15%.[316,317,328-331] Beriwal et al[317] evaluated HDR BT for primary and recurrent vaginal malignancy. In the subset of patients with a previous malignancy, crude local control rates were 100% for patients without prior radiation and 67% for patients with a history of radiation.

Palliative Therapy

Local treatment can provide symptomatic benefit for patients with advanced disease, who have no curative options. Advanced disease can result in vaginal bleeding, pelvic pain, lymphedema, and visceral obstruction. Vaginal bleeding is a common symptom, which can become brisk if tumor erodes into a larger vessel. Large fractions of radiation delivered initially during the treatment course may be useful in achieving hemostasis for such cases. Other options include embolization, infusion of vasopressin, and balloon catheterization for severe hemodynamic losses.

FOLLOW-UP

Recommendations for post-treatment surveillance are based on Society of Gynecologic Oncologist (SGO) guidelines for gynecologic malignancies.[332] Patients with early-stage lesions, treated with surgery alone, can be followed every 6 months for 2 years, then annually thereafter. Patients with more advanced lesions are at higher risk of recurrence and are

recommended follow-up every 3 months for the first 2 years, then 6 months for the next 3 years, and annually thereafter.

There is insufficient evidence to support the use of regular cervical or vaginal cytology to detect cancer recurrence. However, the SGO recommends annual cytology as surveillance to detect lower genital tract dysplasia. The routine use of CT or PET as surveillance is not recommended.

SUMMARY

Vaginal cancer is a rare disease, accounting for 1% to 2% of all gynecologic malignancies. Treatment options depend on stage. For early-stage disease, definitive surgery and radiation are efficacious; more advanced disease is generally managed with a combination of chemotherapy and radiation.

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CHAPTER 80

Female Urethral

Benjamin D. Hopkins and Tony Y. Eng

Primary urethral carcinoma is an infrequent neoplastic entity, accounting for less than 1% of all malignancies. While data derived from the Surveillance, Epidemiology, and End Results (SEER) study suggest a predominance of primary urethral cancer in males as compared to females,[1,2] the management of female urethral cancer presents heightened complexity due to the peculiarities of its anatomic location and its rarity within the clinical landscape. Given the absence of prospective studies, the optimal approach to addressing female urethral cancer is predicated upon retrospective data analysis, with key determinants encompassing the clinical staging tumor localization, extent of nodal involvement, the patient's overall health status, and individualized treatment preferences.

ANATOMY

The female urethra is approximately 3 to 4 cm long and 0.6 cm in resting diameter. It is located in the anterior vaginal wall behind the pubis symphysis, extending inferiorly and anteriorly from the urinary bladder through the urogenital diaphragm to the vestibule, where it forms the urethral meatus. Because of the proximity of the pubic symphysis, a small curve is formed with an anterior concavity. The lower distal half of the urethra is considered the anterior urethra, and the upper proximal half is considered the posterior urethra. Figure 80.1 illustrates the urethra and adjacent organs in the female pelvis.

FIGURE 80.1 Magnetic resonance T1-weighted sagittal image of the female pelvis.

The wall of the urethra consists of three layers. The muscular layer is continuous with that of the bladder. At the vesicular end of the urethra, this muscular wall forms the internal sphincter. The voluntary urethral sphincter is located at the plane of the urogenital diaphragm. A thin layer of erectile tissue consisting of a plexus of veins and muscle fibers, forms the middle layer of the wall. The inner layer is the mucous membrane, which is continuous with the bladder proximally and with the vulva distally. This membrane consists of transitional epithelium near the bladder but distally changes to nonkeratinizing stratified squamous epithelium and pseudostratified columnar epithelium. The distal urethra also contains small mucous recesses and periurethral or Skene glands, most of which are located in the region of the meatus.

The lymphatic drainage of the distal urethra and urethral meatus parallels that of the vulva to the superficial and deep inguinal and external iliac lymph nodes. The primary

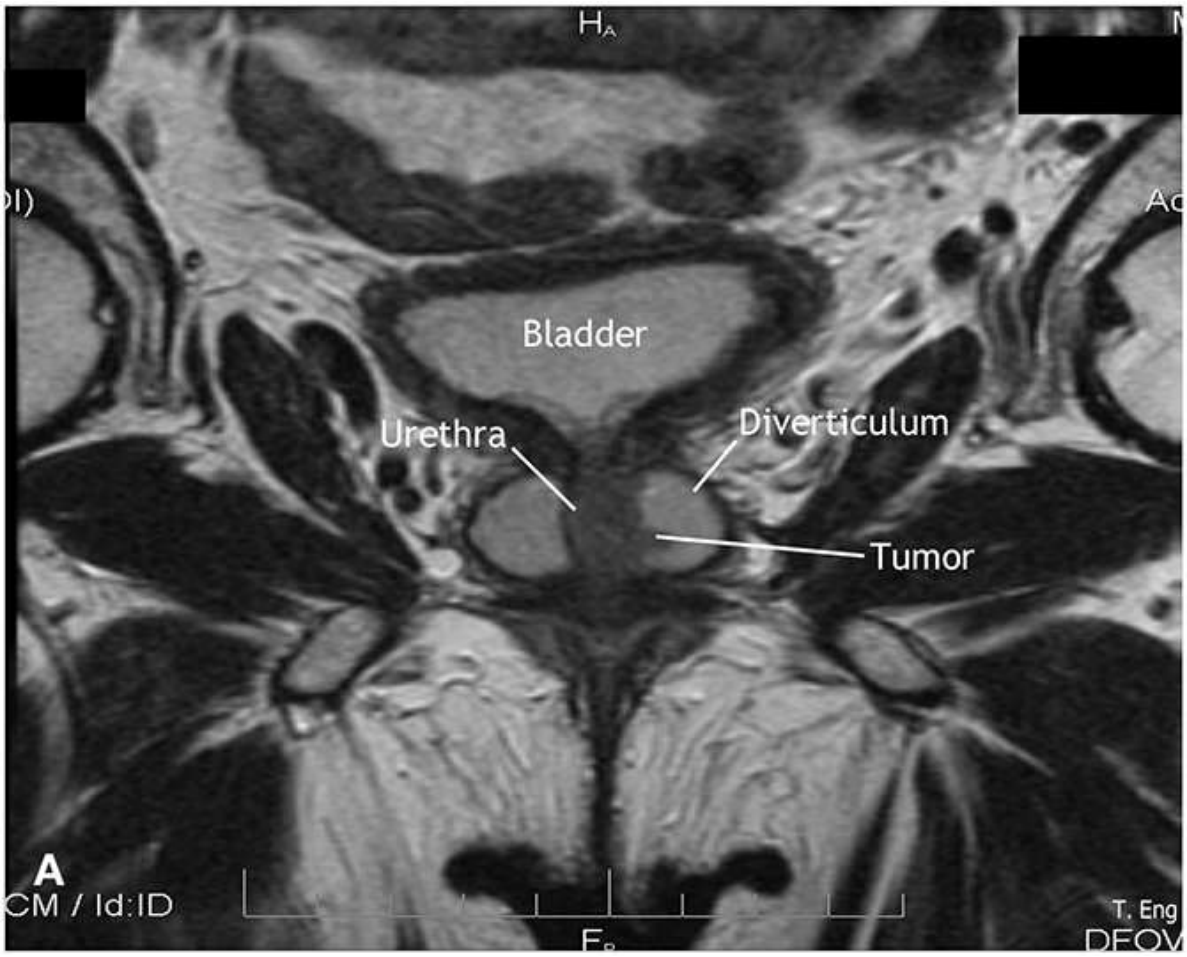
drainage of the posterior or entire urethra is mainly to the obturator and internal and external iliac nodes.

EPIDEMIOLOGY AND ETIOLOGY

From 2004 to 2016, the SEER database identified a total of 1,907 individuals afflicted with primary urethral cancer. Notably, age-standardized incidence rates per 1,000,000 were found to be notably higher in males (2.70) as opposed to females (0.55).[2]

The overall annual incidence for women stood at 1.5 per million, whereas for men, it was 4.3 per million. Although prior observations had indicated a higher prevalence of this malignancy among White women compared to Black women,[3,4] SEER data reveal an increased incidence among Black women, which exhibits a progressive rise with advancing age. Given the rarity of carcinoma of the urethra in women, major cancer centers only encounter a limited number of cases annually.[5-7] Carcinoma of the female urethra constitutes a mere 0.02% of all malignancies in women and contributes to approximately 0.1% of the broader spectrum of gynecologic cancers.[8,9] The average patient age at the time of diagnosis is 60 years, with most patients between 50 and 80 years of age.[1-12]

While various hypotheses have been put forth, the precise etiology of female urethral cancer remains enigmatic. Unlike other forms of transitional cell carcinoma within the urinary tract, there is no documented correlation between cigarette smoking and the incidence of urethral carcinoma. A study by Weiner and Walther[13] delved into the analysis of archival surgical specimens obtained from women diagnosed with urethral carcinoma. This examination unveiled the presence of human papillomavirus (HPV) in 10 out of 17 patients afflicted with invasive disease, with HPV type 16 identified in eight of these cases. Eight women presenting with squamous cell carcinoma and two with transitional cell carcinoma were also found to harbor HPV infections. Furthermore, there exists a potential association between female urethral cancer and the presence of urethral diverticula,[14-16] as depicted in Figure 80.2, which illustrates carcinoma originating within a urethral diverticulum.


Bladder
Urethra
Diverticulum
Tumor
A
CM / Id:ID
T, Eng

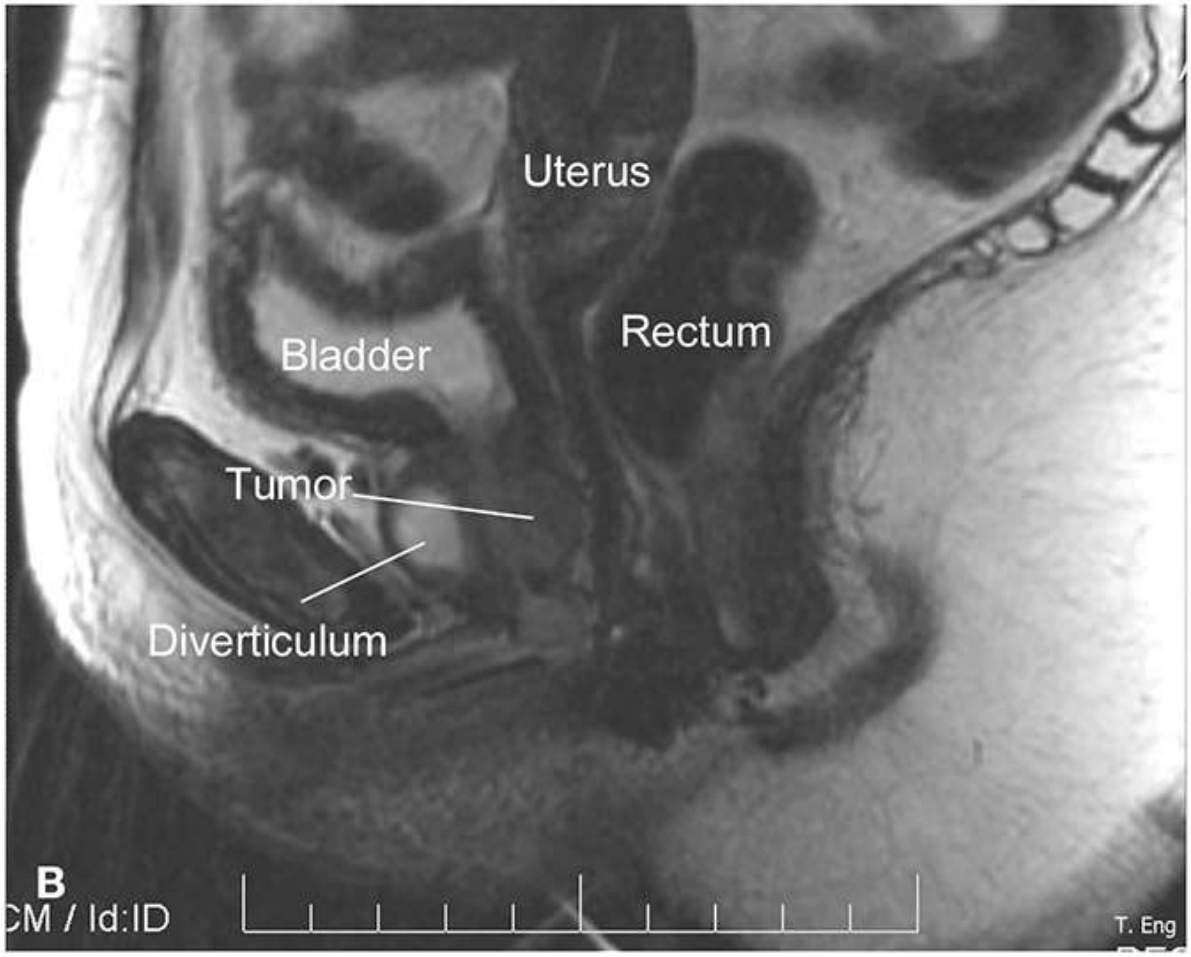


FIGURE 80.2 Coronal (A) and sagittal (B) T2-weighted magnetic resonance images demonstrate a large diverticulum surrounding the urethra with a tumor mass arising within the confines of the diverticulum posteriorly that results in an impression at the vagina.

Notably, patients diagnosed with transitional cell carcinoma of the bladder, particularly those involving the bladder neck, may carry an elevated risk of developing urethral cancer either synchronously or metachronously.[17,18]

NATURAL HISTORY

Most urethral cancers are clinically aggressive and historically carry a poor prognosis. During the later stages, cancers of the middle or posterior urethra tend to extend proximally into the urinary bladder, distally to invade the remainder of the urethra, and posteriorly into the vaginal mucosa. Lesions involving the anterior urethra account for approximately 30% of all cases.[10,19]

Regional lymph node involvement is uncommon in early tumors (stage 0) of the urethral meatus. Advanced tumors (stages II and III) of the urethra have been associated with a 35% to 50% incidence of inguinal or pelvic lymph node

involvement.[7,11,20-22] Bilateral nodal involvement occurs in approximately one-third of patients with positive nodes. Grabstald[10] confirmed nodal involvement in 24 of 25 patients with clinically palpable nodes. In his series of patients with advanced disease, 26 underwent pelvic lymph node sampling and 13 (50%) had nodal involvement.

Distant metastases are found in approximately 10% of patients at presentation, and approximately 30% to 50% ultimately die of distant disease. The most common sites of metastasis are the lung, liver, bone, and brain.[10,23]

CLINICAL PRESENTATION

A majority of patients with urethral cancer present with some degree of irritative or obstructive urethral symptoms.[24] Bleeding (hematuria) or spotting is the prevailing presenting sign in 50% to 60% of patients.[3,25,26] Approximately 30% to 50% of patients experience pain or irritative symptoms, difficulty urinating, and frequent micturition. Urinary retention and overflow incontinence may occur in advanced cases. Less frequently cited signs and symptoms are a mass in the introitus (10%-20% of patients), dyspareunia, perineal pain, and inguinal lymphadenopathy.[21,23] Urethrovaginal and vesicovaginal fistulas may develop in advanced, neglected cases.

Small tumors involving the urethral meatus are often mistakenly diagnosed as urethral caruncle, a benign, inflammatory lesion, or a prolapse of the mucosa through the urethral orifice. As the lesion progresses, it enlarges and eventually ulcerates.[23] Tumors may arise in a urethral diverticulum.[16,27,28] Larger lesions of the distal urethra are readily identified on inspection (Figure 80.3). Tumors occupying the proximal urethra may produce a fusiform enlargement that can be palpated during pelvic examination.

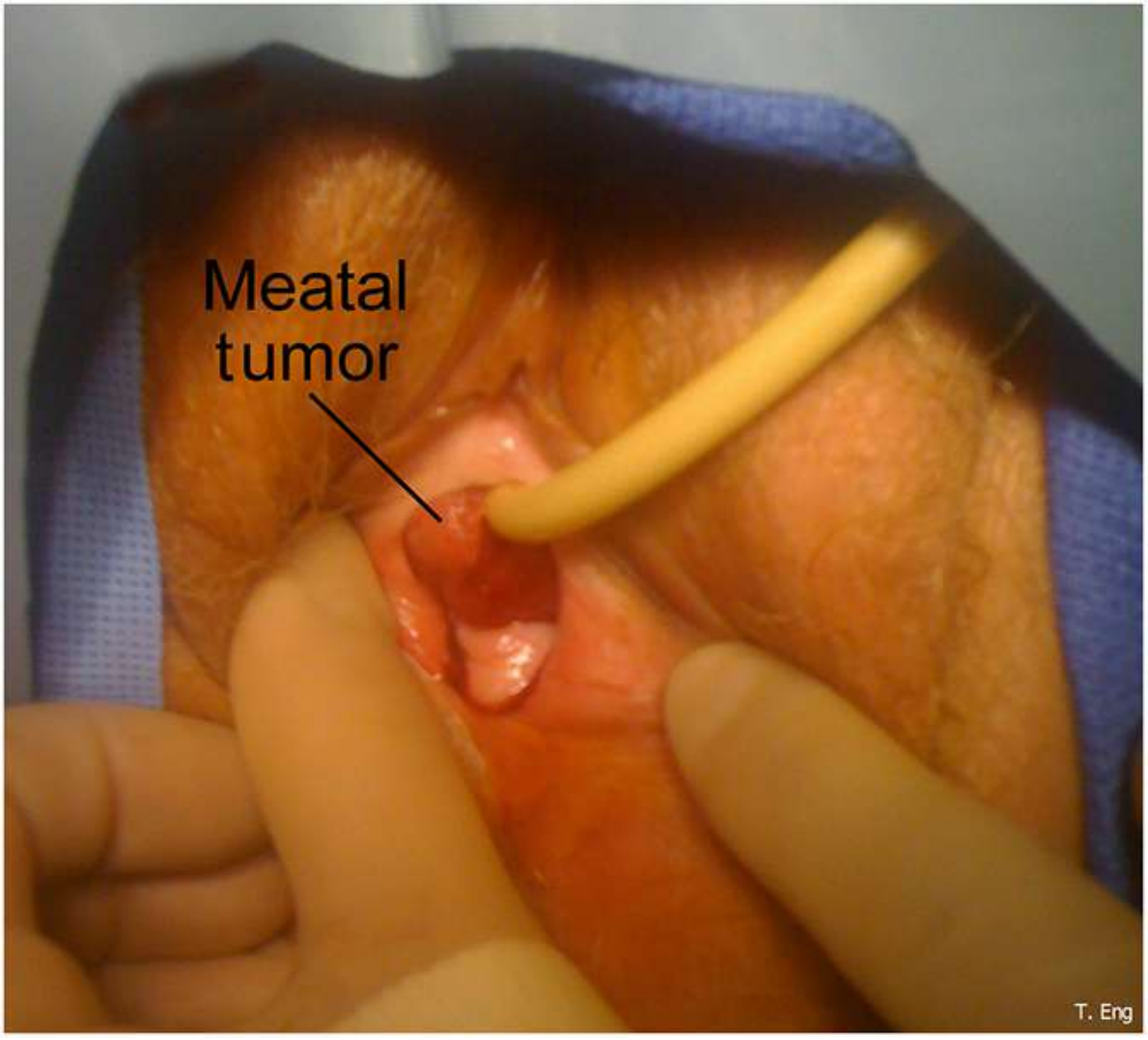


FIGURE 80.3 A meatal carcinoma of the urethra in a 68-year-old White woman presenting with hematuria.

DIAGNOSTIC WORKUP

An outline for the diagnostic workup for carcinoma of the female urethra is presented in Table 80.1. A routine history and general physical examination should be performed for all patients. A detailed pelvic examination under anesthesia is necessary to fully evaluate the clinical extent of the disease. This examination can be performed at the time of urethroscopy and cystoscopy. Urine cytologic analyses have a high false-negative rate.[29] The definitive diagnosis is made by punch or incisional biopsy.

TABLE 80.1 DIAGNOSTIC WORKUP FOR CARCINOMA OF THE FEMALE URETHRA

General
History

Physical examination, including detailed pelvic examination under anesthesia
Special procedures
Punch biopsy
Urethroscopy
Cystoscopy
Rectosigmoidoscopy (advanced stages or if symptomatic)
Radiographic evaluation
Standard:
Computed tomography scan (chest, abdomen, and pelvis)
Magnetic resonance imaging Intravenous urography
Complementary:
Bone scan (if symptomatic or elevated alkaline phosphatase)
Barium enema (if symptomatic or advanced stages)
Ultrasound
Urethrography
Laboratory evaluation
Complete blood count
Chemistry profile
Urinalysis

Routine radiographic evaluation should include an intravenous urogram and a computed tomography (CT) scan of the chest, abdomen, and pelvis[30,31] (Figure 80.4A). Sometimes, a positron emission tomography (PET)-CT may be helpful (Figure 80.4B). Barium enema can be cost-effective for patients with symptoms of advanced disease. Magnetic resonance imaging of the pelvis helps delineate the tumor extent, especially when an endourethral coil is used (see Figure 80.2). It provides a discrete view of the muscular layers of the urethra.[32,33] Additional complementary studies include interactive virtual urethrography and ultrasonography that can help detect a urethral diverticulum without contrast agent filling.[34] Multidetector CT voiding urethrography yields real-time urethral images during micturition.

FIGURE 80.4 Transaxial computed tomography (A) and positron emission tomography/computed tomography (B) images of a patient with urethral cancer illustrating the periurethral and anterior vaginal

wall expansion and deviation of the urethra (arrow).

There are no studies addressing the role of PET-FDG (fluorodeoxyglucose) scan in urethral cancer. Perhaps, some genitourinary tumors do not accumulate sufficient FDG, which may not be a useful tracer for the detection of primary genitourinary tumors because of its physiologic excretion in the urine.[35] However, PET scans may potentially be useful for identifying nodal and distant sites of disease, especially in patients with equivocal findings on conventional imaging.[36-38]

STAGING SYSTEMS

Clinical staging is based on findings on physical examination, chest X-ray, and CT scan of the abdomen and pelvis. Many attempts have been made to formulate a staging system for carcinoma of the urethra. Urethral tumors can be classified into two groups: those involving the distal half of the urethra and those located in the proximal or entire urethra. Most authors have found that this classification correctly depicts the feasibility of treatment and the prognosis. A staging system based on location has been proposed by Prempree et al[39] (Table 80.2). The current TNM staging system of the American Joint Committee on Cancer[40] is shown in Table 80.3.

TABLE 80.2 PROPOSED CLINICAL STAGING SYSTEM FOR CARCINOMA OF THE FEMALE URETHRA

Tumor Stage	Characteristics
I	Disease limited to distal one-half of urethra
II	Disease involving entire urethra, with extension to periurethral tissues, but not involving vulva or bladder neck
III	
A	Disease involving urethra and vulva
B	Disease invading vaginal mucosa
C	Disease involving urethra and bladder neck
IV	
A	Disease invading parametrium or paracolpium
B	Metastasis
B1	Inguinal lymph nodes
B2	Pelvic lymph nodes
B3	Para-aortic nodes
B4	Distant metastasis

From Prempree T, Amornmarn R, Patanaphan V. Radiation therapy in primary carcinoma of the female urethra. II. An update on results. *Cancer*. 1984;54(4):729-733. Copyright © 1984 American Cancer Society. Reprinted by permission of John Wiley & Sons.

TABLE 80.3 TNM CLASSIFICATION OF CARCINOMA OF THE URETHRA (MALE OR FEMALE)

Primary Tumor (T)	
TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ
T1	Tumor invades subepithelial connective tissue.
T2	Tumor invades any of the following: corpus spongiosum, periurethral muscle.
T3	Tumor invades any of the following: corpus cavernosum, anterior vagina.
T4	Tumor invades other adjacent organs (eg, invasion of the bladder wall).
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis
N1	Single lymph node metastasis in the inguinal region or true pelvis [perivesical, obturator, internal (hypogastric), and external iliac] or presacral lymph node
N2	Multiple regional lymph node metastasis in the inguinal region or true pelvis [perivesical, obturator, internal (hypogastric), and external iliac] or presacral lymph node
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

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PATHOLOGIC CLASSIFICATION

As the urethra is lined by transitional cells proximally and stratified squamous cells distally, transitional cell carcinoma occurs typically in the proximal urethra, whereas squamous cell carcinoma occurs frequently in the distal urethra. The SEER data report the most common histologic type is transitional cell carcinoma, followed by squamous cell and adenocarcinoma.[1,2] However, most published series suggest that squamous cell carcinoma is the most common histologic type in cancer of the female urethra, representing more than 50% of all cases, whereas transitional cell carcinoma and adenocarcinoma represent approximately 15% to 20% and 10% to 15%, respectively.[15,41,42] The remainder of the histologic types includes adenoid cystic

carcinoma, melanoma, clear cell adenocarcinoma, anaplastic tumors, Kaposi sarcoma, lymphomas, and metastatic lesions.[6,36,43-46]

PROGNOSTIC FACTORS

Conventional prognostic factors such as grade and histology have not been consistently predictive for recurrence or survival of female urethral cancer. In the literature, some of the most important factors in determining prognosis and survival are stage, depth of invasion, tumor size, and anatomic location.[3,15,21,29,47,48] The 1983-2008 SEER database shows that advanced age, T stage, node positivity, nonsquamous histology, and Black race were associated with reduced cause-specific survival.[49] Dalbagni et al[3] showed that the primary stage was one of the major independent predictors of survival in 72 female patients with a 5-year survival of 83% for low-stage tumors and 33% for high-stage tumors.

Lesions located in the meatus or distal urethra tend to be superficial, with a better prognosis. Lesions in the posterior urethra are often deeply invasive and tend to have a worse prognosis.[9] Most investigators found that patients with advanced-stage disease do poorly, often irrespective of their treatment.[3,24,48,50]

Grigsby and associates[25,51] demonstrated a worsening prognosis with increased tumor size. The 5-year progression-free survival was 81% for patients with lesions <2 cm, compared with 37% for those with lesions 2 to 4 cm and 7% for patients with lesions >4 cm ($P = .0001$). For lesions confined to the proximal urethra, local control was observed in all four patients. However, patients with tumors involving the distal urethra had a 5-year progression free survival rate of 69%, and there was a 12% survival rate for those with involvement of the entire free urethra ($P = .0001$). Patients with meatal tumors, if diagnosed early and treated appropriately, can achieve an 80% to 90% survival rate (Figures 80.5 and 80.6).[25] Bladder neck involvement, parametrial extension, and inguinal lymph node involvement have been identified as poor prognostic factors.

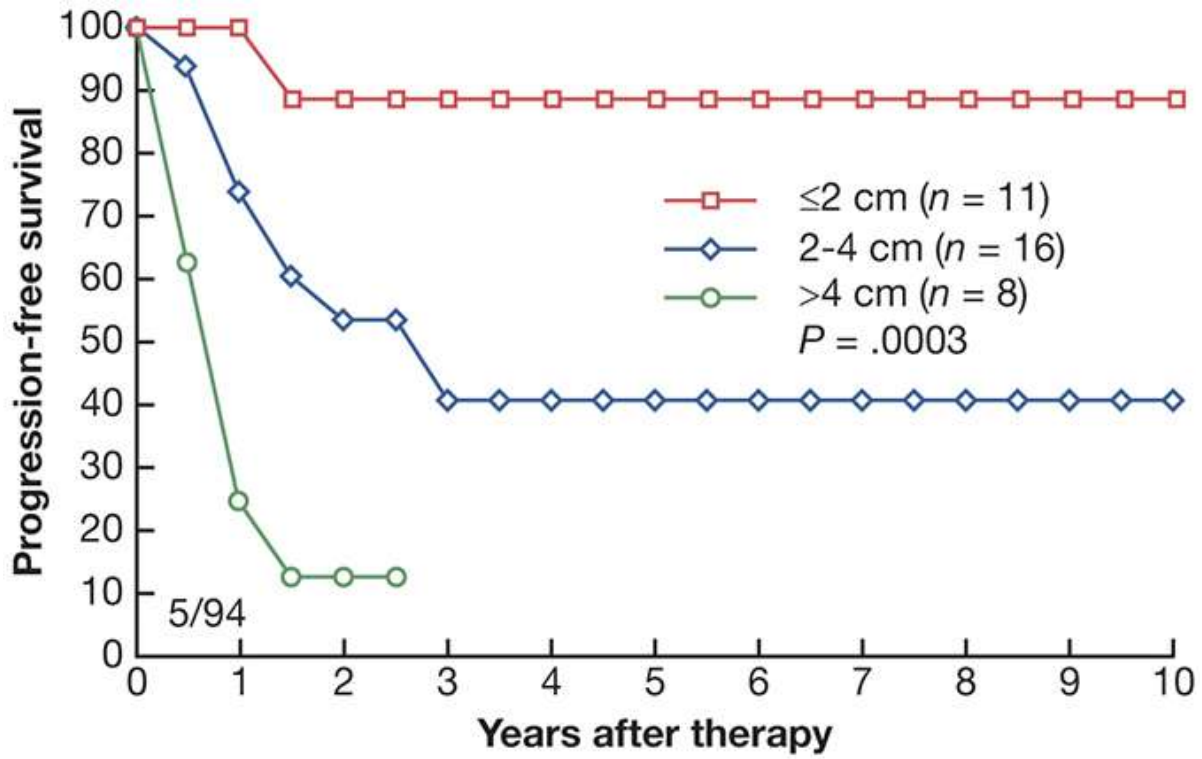


FIGURE 80.5 Progression-free survival correlated with tumor size. (Reprinted with permission from Grigsby PW, Herr HW. Urethral tumors. In: Vogelzang NJ, Scardino PT, Shipley WU, Coffey DS, eds. *Comprehensive Textbook of Genitourinary Oncology*. Williams & Wilkins; 1996:1117-1123.)

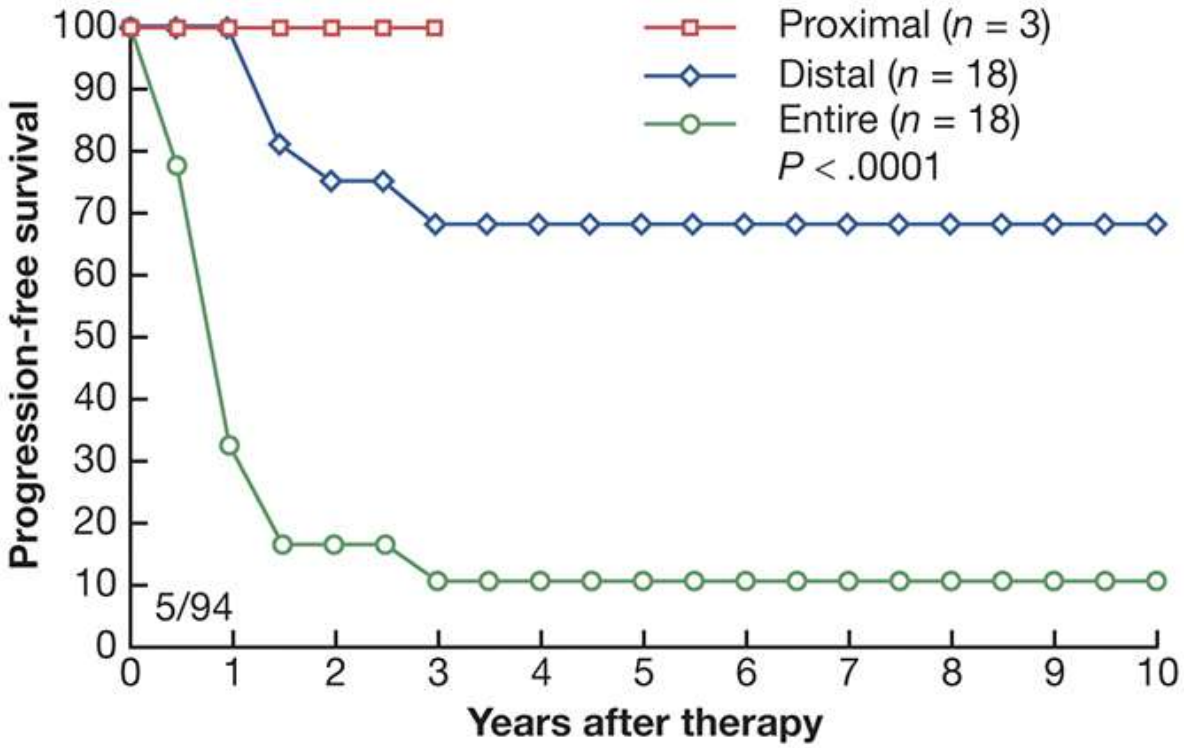


FIGURE 80.6 Progression-free survival correlated with tumor location. (Reprinted with permission from Grigsby PW, Herr HW. Urethral tumors. In: Vogelzang NJ, Scardino PT, Shipley WU, Coffey DS, eds. *Comprehensive Textbook of Genitourinary Oncology*. Williams & Wilkins; 1996:1117-1123.)

The histology of the primary lesion appears to be less important as a prognostic factor in determining response to therapy and survival. Most studies have shown no difference in survival among patients with adenocarcinoma, squamous cell carcinoma, and transitional cell carcinoma.[10,14,39,47] Grigsby[25] found a worse prognosis in patients with adenocarcinoma, with 0 of 13 treated patients with this histology alive at 5 years, although this trend has not been maintained in more recent registry trials.[52,53] It has been described that adenocarcinoma has a proclivity to present as more advanced disease, which may explain observed survival differences in prior small series.[54] Primary melanoma of the urethra, although rare, has a very poor prognosis.[55-57]

GENERAL MANAGEMENT

Although various therapeutic approaches have been advocated for the management of carcinoma of the female urethra, there are no established therapeutic guidelines. The variety of treatments reflects the dimensions and locations of the disease and the approaches of the treating physicians.[4] In general, surgical resection is the primary mode of treatment.[58] Radical urethral resection with urinary diversion and pelvic lymphadenectomy are commonly performed for lesions not involving the bladder neck. However, early-stage lesions of limited extent may be amenable to organ-

sparing radiation therapy or conservative surgical management, with or without adjuvant radiation therapy to minimize the morbidity associated with surgical intervention. Surgical approaches include neodymium:yttrium-aluminum-garnet (Nd:YAG) laser coagulation,[59] Mohs micrographic surgery, and partial or total urethrectomy.[42] Radiation therapy may include external beam radiation, interstitial brachytherapy, or a combination of these treatments.[60] For patients who are medically nonsurgical candidates because of potential risks of anesthesia, outpatient high-dose rate (HDR) intracavitary and intraluminal brachytherapy may be an option.[61,62]

Multimodality Therapy

For patients with locally invasive urethral carcinoma, anterior exenteration may be required. Although most available data are insufficient, in patients with more advanced disease, some authors have advocated adjuvant radiation therapy and/or combined irradiation and chemotherapy including 5-fluorouracil, cisplatin, vinblastine, epirubicin, carboplatin, bleomycin, methotrexate, or mitomycin C after surgical extirpation.[58,63-66] A subgroup of patients with positive nodes may also benefit from preoperative cisplatin-based chemotherapy.[67]

Multimodality therapy is associated with better overall results, even though patients who receive combined modality tend to have more advanced disease. Although most studies included a small number of patients, those patients who received combined therapy seem to have better disease-free survival.[15,48,50] Unfortunately, National Cancer Database (NCDB) studies suggest that the majority of patients with locally advanced disease do not receive multimodality care.[52] Combination therapy often consists of either chemotherapy with radiotherapy or radiotherapy with surgery. Combined chemotherapy and radiation therapy for locally advanced urethral cancer has shown a reasonable response in several reports.[48,50,63,65,68]

Anterior (Distal) Urethral Cancer

For stage 0 and I (Ta, Tis, or small T1) lesions, open excision, electroexcision, fulguration, and laser (Nd-YAG or CO_2) coagulation are possible for tumors at the meatus or with in situ involvement of the distal urethra (stage 0). For larger and more invasive lesions (stages T1 and T2), surgical resection of the distal third of the urethra is often adequate. Alternatively, interstitial irradiation or a combination of interstitial and external beam irradiation can be considered. For T3 to T4 or recurrent anterior urethral lesions previously treated by local excision or radiation therapy, anterior exenteration and urinary diversion may be curative. Adjuvant radiation therapy may be required, depending on surgical findings.

If a limited number of inguinal nodes are involved, ipsilateral node dissection or irradiation is indicated because cure is still achievable. If no inguinal adenopathy

exists, node dissection is not recommended, but prophylactic groin irradiation is recommended for patients with invasive lesions.[6,47]

Posterior (Proximal) Urethral Cancer

Cancers of the posterior or entire urethra are usually associated with invasion of the bladder, a high incidence of inguinal and pelvic lymph node metastases, and a worse prognosis. For lesions <2 cm, radical resection, definitive radiation therapy, or combined treatment may provide adequate control.[51] However, for larger lesions or locally advanced disease, the best results have been achieved with preoperative irradiation, exenterative surgery, and urinary diversion. Pelvic lymphadenectomy is performed and inguinal node dissection may be indicated if the inguinal nodes are involved. In selected patients, it is possible to remove part of the pubis symphysis and the inferior pubic rami to maximize the surgical margin. A transpubic approach has been advocated by Golimbu et al[69] Perineal closure and vaginal reconstruction can be accomplished with the use of myocutaneous flaps. Hedden et al[70] have advocated the use of bladder-sparing surgery with or without irradiation.

Recurrent Urethral Cancer

In most cases, locally recurrent urethral cancer after surgery alone should be considered for combination radiation therapy and wider surgical resection. Locally recurrent urethral cancer after radiation therapy should be treated by surgical excision. For those who are not surgical candidates, local reirradiation (i.e., hyperfractionated intensity-modulated radiation therapy [IMRT] or brachytherapy) may be considered if radiation tolerance has not been exceeded. Patients with metastatic urethral cancer should be considered for investigational chemotherapy protocols. Palliative radiation therapy may provide good symptomatic relief.

RADIATION THERAPY TECHNIQUES

Small meatal and distal urethral lesions are curable with limited therapy. Interstitial implants have been the usual method for treating meatal carcinomas. Radioactive needles, forming a double-plane or a volume implant, have been used (Figure 80.7). Both low-dose rate (LDR) and HDR afterloading implants using ^{192}Ir have replaced radium.[8,61,62] For early localized disease without involvement of adjacent organs, a volume implant composed of 8 to 12 needles arranged in an arc around the urethral orifice is used (Figure 80.8). Radiographs may be used to verify needle placement (Figure 80.9). Computer planning with CT-based simulation and three-dimensional (3D) treatment planning should be the standard of care to spare the adjacent normal organs. A dose of 60 to 70 Gy (LDR) should be given in 6 to 7 days (0.4-0.5 Gy/hour to the target volume) when an implant alone is used.

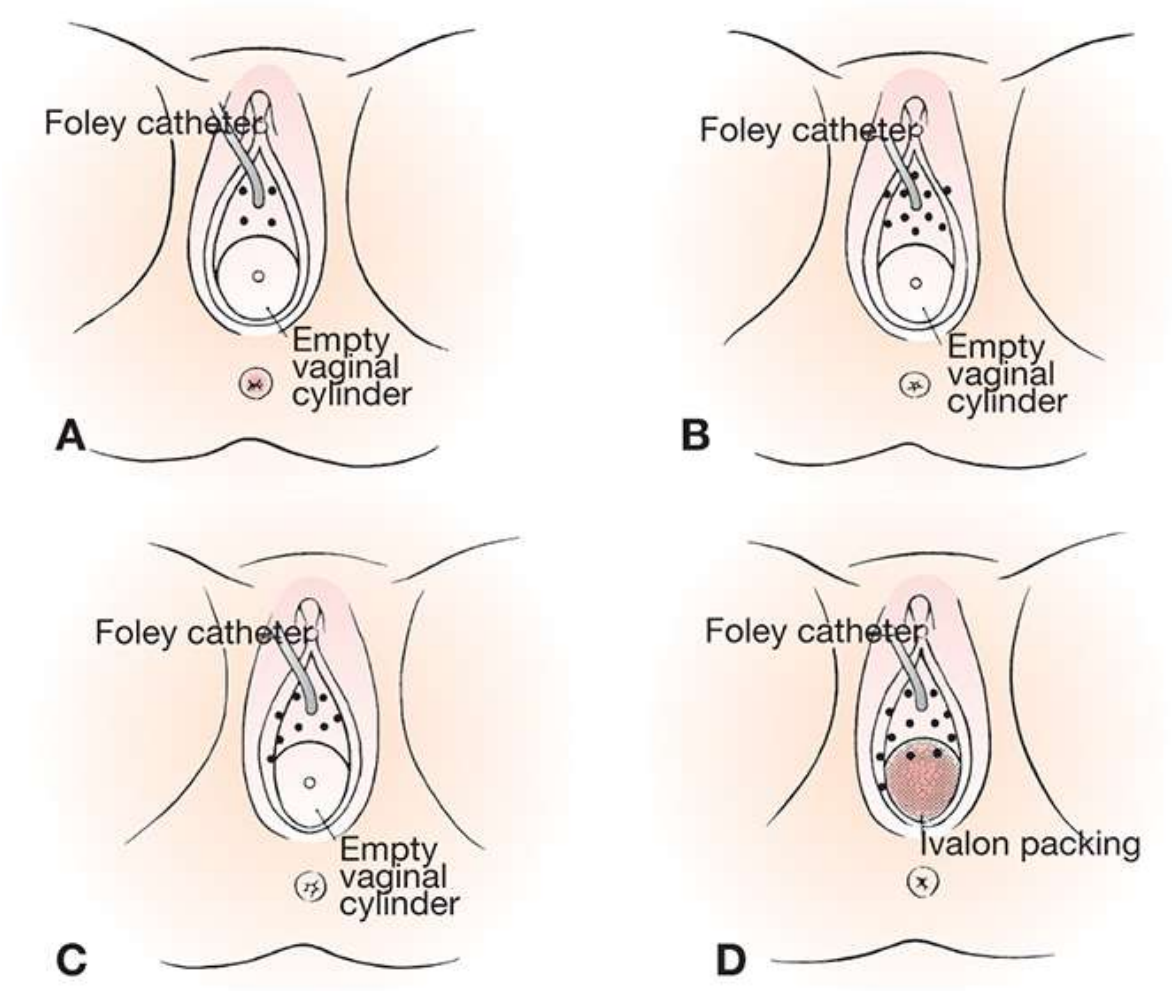


FIGURE 80.7 Diagrams of implants. A. Tumor limited to the urethra. B. Tumor extending to the periurethral tissues or originating in the periurethral glands. C. Tumor extending into the vagina or labia minora. D. Tumor involving the suburethral area. (Reprinted from Delclos L. Carcinoma of the female urethra. In: Johnson DE, Boileau MA, eds. *Genitourinary Tumors: Fundamental Principles and Surgical Techniques*. Grune & Stratton; 1982:275-286. Copyright © 1982 Elsevier. With permission.).

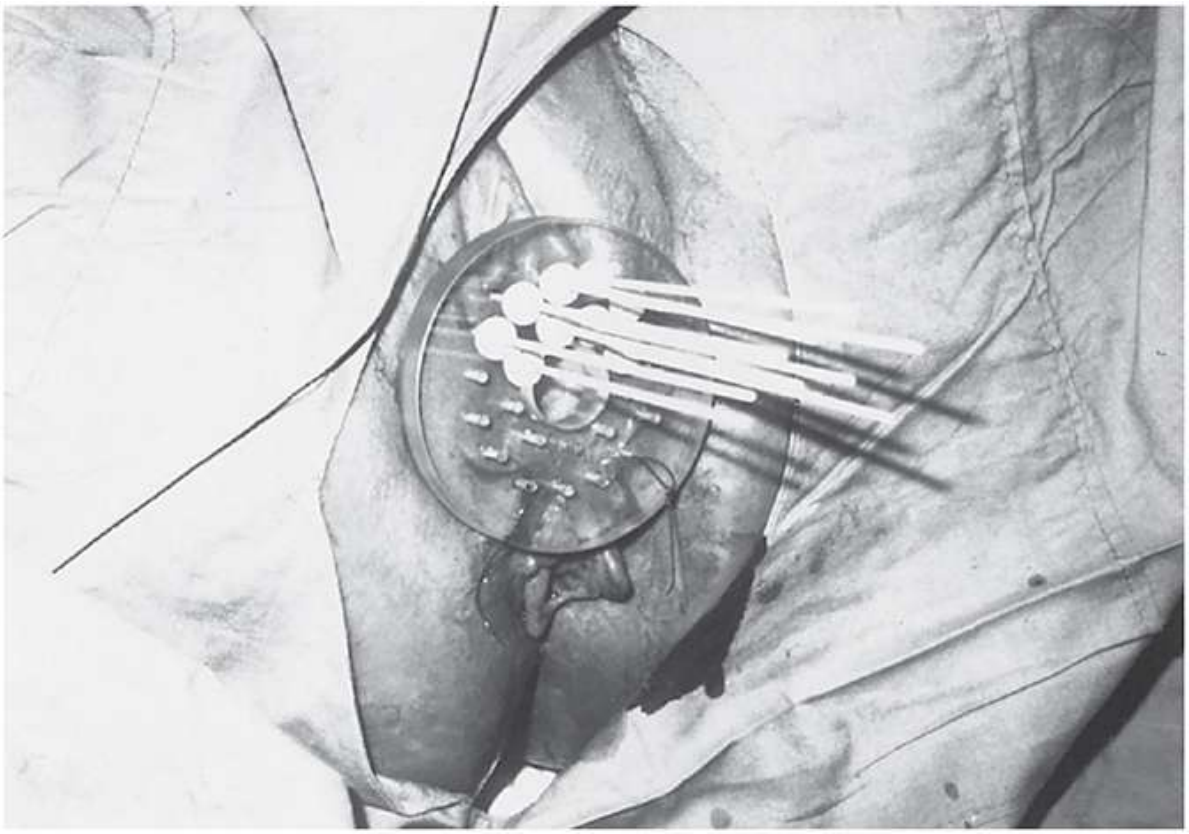


FIGURE 80.8 A template used for a curved, double-plane implant that surrounds the urethra. The closed-end flexible catheters inserted in the periurethral or vaginal tissues are glued to the template, which is sutured to the skin. The catheters are afterloaded with ^{192}Ir.

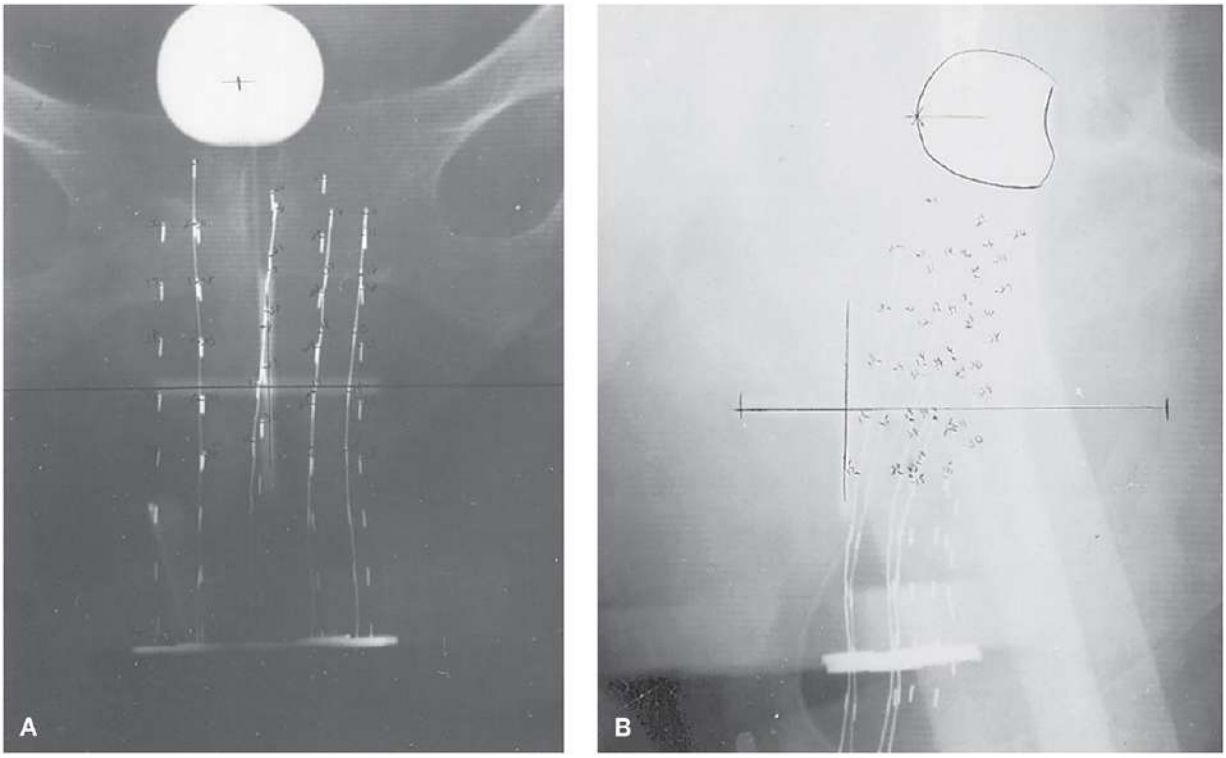


FIGURE 80.9 Anteroposterior (A) and lateral (B) simulation radiographs with dummy seeds in place. Contrast material is used to inflate the balloon of the urinary catheter, which is used to localize the bladder.

Alternatively, in patients with small localized disease receiving radiation therapy alone, noninvasive intracavitary or intraluminal HDR brachytherapy without sedation or anesthesia after pelvic external beam radiation has been used.[48,62] Figure 80.10 illustrates an intraluminal HDR brachytherapy using a Foley catheter. The resultant conformal radiation dose covers the periurethral tissue well while sparing the surrounding normal structures. At the Emory University Winship Cancer Institute in Atlanta, we deliver 5 to 6 Gy twice a week, 3 days apart, to a total dose of 24 to 25 Gy with a good response.

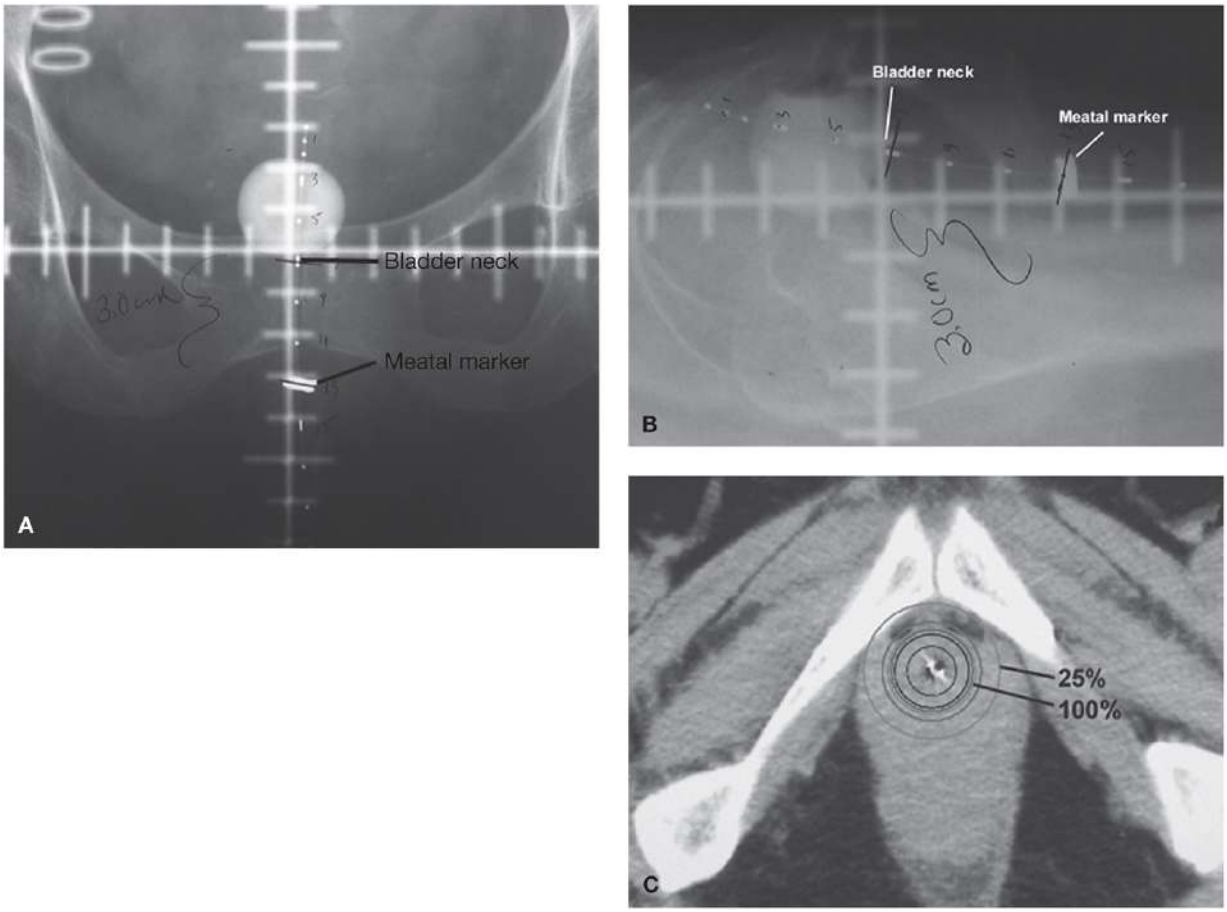


FIGURE 80.10 High-dose rate brachytherapy with a Foley catheter. Anteroposterior (A) and lateral simulation films (B) and transaxial computed tomography image with isodose plan (C). The resultant uniformed, steep isodose lines cover the periurethral tissue well.

Large tumors or advanced disease extending into the labia, vagina, entire urethra, or base of the bladder should not be treated with an implant alone. For these patients, a combination of external beam irradiation and implant is recommended.[62,71,72] The external beam portal should flash the perineum to cover the entire urethra. The conventional portal should be wide enough to cover the inguinal nodes and should extend cephalad to the L5-S1 interspace to include the pelvic nodes (Figure 80.11).[73] A bolus, appropriate for the photon energy used, should be added to the groin when inguinal nodes are positive. This technique minimizes the hazard of groin failure due to underdosing of gross tumor. Hahn et al[74] have demonstrated the importance of treating the inguinal lymph nodes in all patients. The whole pelvis is treated to a dose of 45 to 50 Gy. A boost of 10 to 15 Gy is delivered to positive groin nodes through reduced anteroposterior fields.

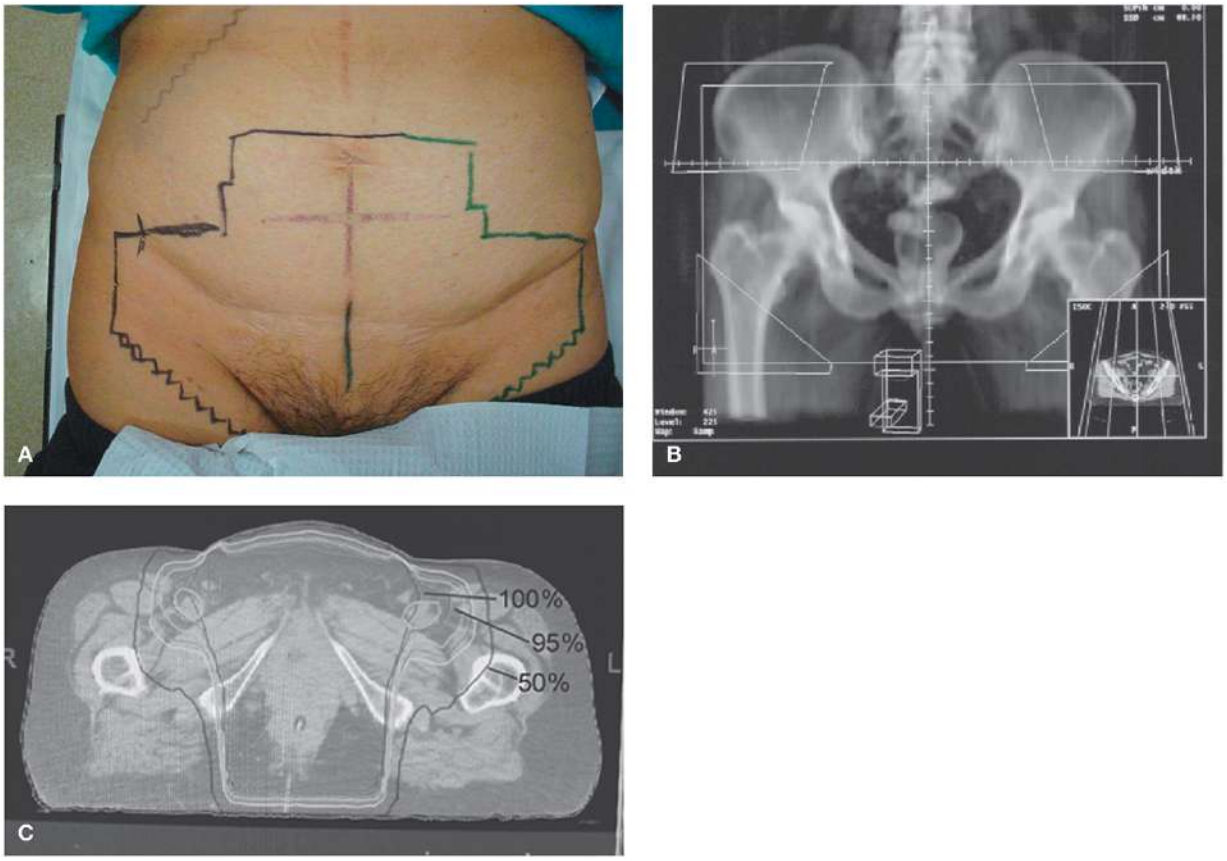
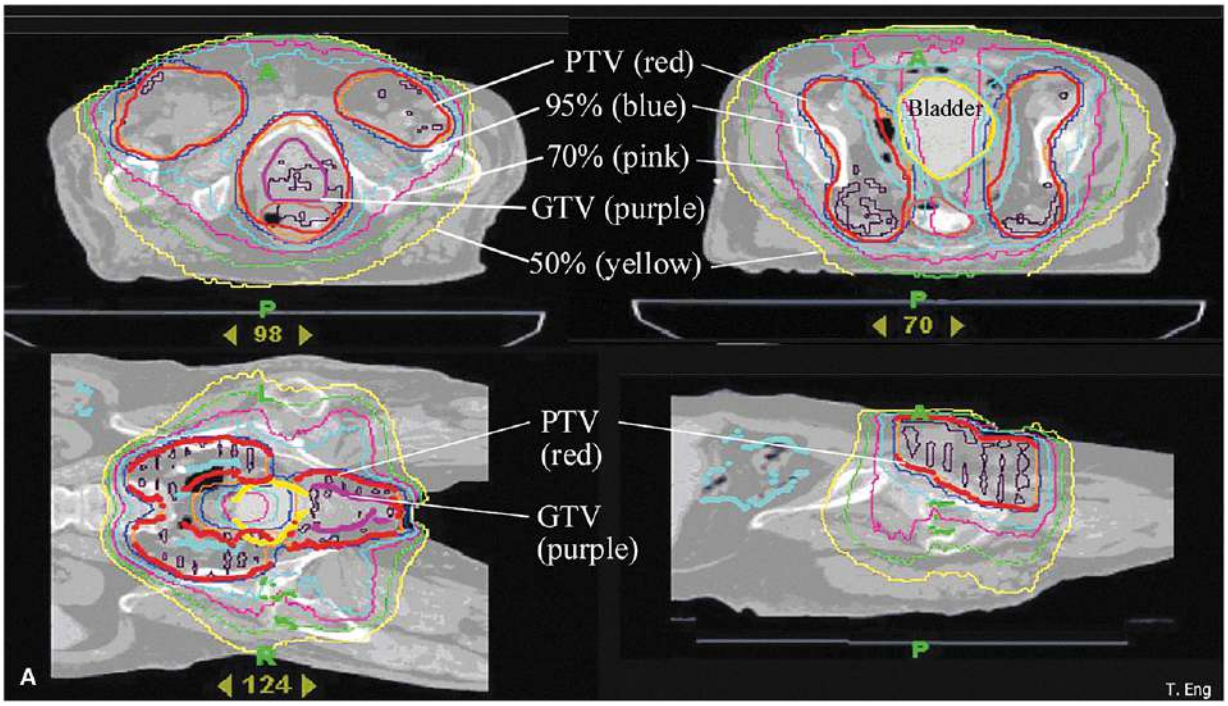


FIGURE 80.11 Whole pelvis and inguinal field. External skin marking (A) and anteroposterior simulation film (B) of a pelvic portal showing the lateral extension to cover the inguinal lymph nodes and the isodose plan (C).

After pelvic radiation therapy, the primary tumor can be treated with a vaginal cylinder to bring the dose to the entire urethra to approximately 60 Gy. An interstitial implant is administered to raise the total tumor dose to 70 to 80 Gy. For patients undergoing postoperative therapy, the tumor bed is treated after pelvic radiation therapy with an additional 10 to 15 Gy using interstitial brachytherapy.[61] Intracavitary irradiation with the vaginal cylinder and an interstitial implant are almost never used simultaneously because of the resultant HDR at the vaginal mucosa interface of the intracavitary and interstitial implant fields. A vaginal cylinder with partial shielding posteriorly can be used in select patients. Gerbaulet et al[75] have demonstrated the use of a catheter or a vaginal mold applicator for intraluminal/intracavitary brachytherapy and needles or guide gutters for interstitial brachytherapy.

At the Emory University Winship Cancer Institute in Atlanta, we commonly deliver external beam therapy, 45 to 50.4 Gy, to the primary tumor and pelvic lymphatics using IMRT technique with CT image guidance (Figure 80.12). This is followed by interstitial HDR brachytherapy, 5 to 6 Gy twice a week, 2 days apart. A vaginal cylinder is always employed to provide spatial protection of the posterior vagina and

rectum. The HDR brachytherapy is repeated in 1 week to achieve a total dose of 20 to 24 Gy (Figure 80.13). The major advantage of interstitial HDR brachytherapy is geometric or volume optimization by changing the dwell time and dwell position of the radioactive source along the afterloading catheter so that the target volume is well covered with good conformity while the doses to the vaginal mucosa and surrounding structures are kept below their tolerances. Modification of dose and fractionation may be made depending on the tumor size and response to external beam therapy. The HDR brachytherapy is performed as an outpatient treatment.


PTV (red)
95% (blue)
70% (pink)
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50% (yellow)
Bladder
98
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PTV
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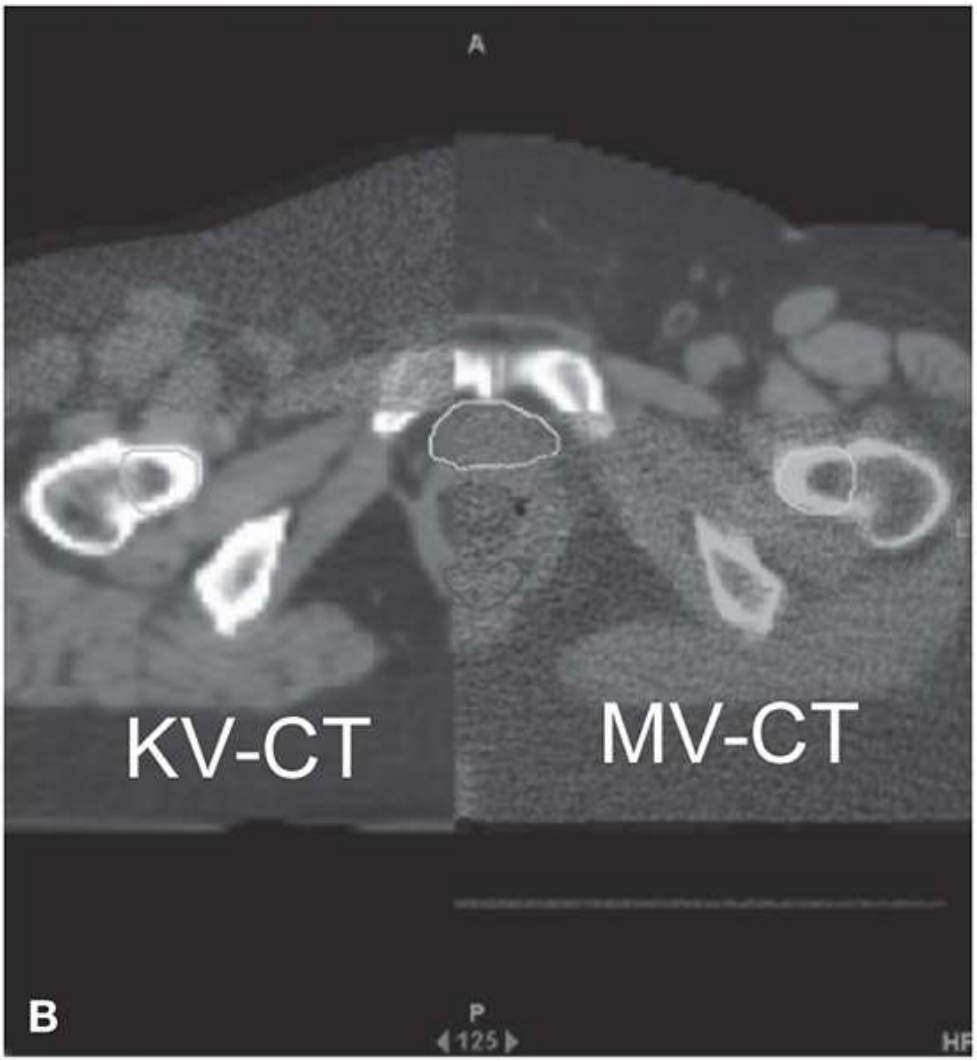
A
T. Eng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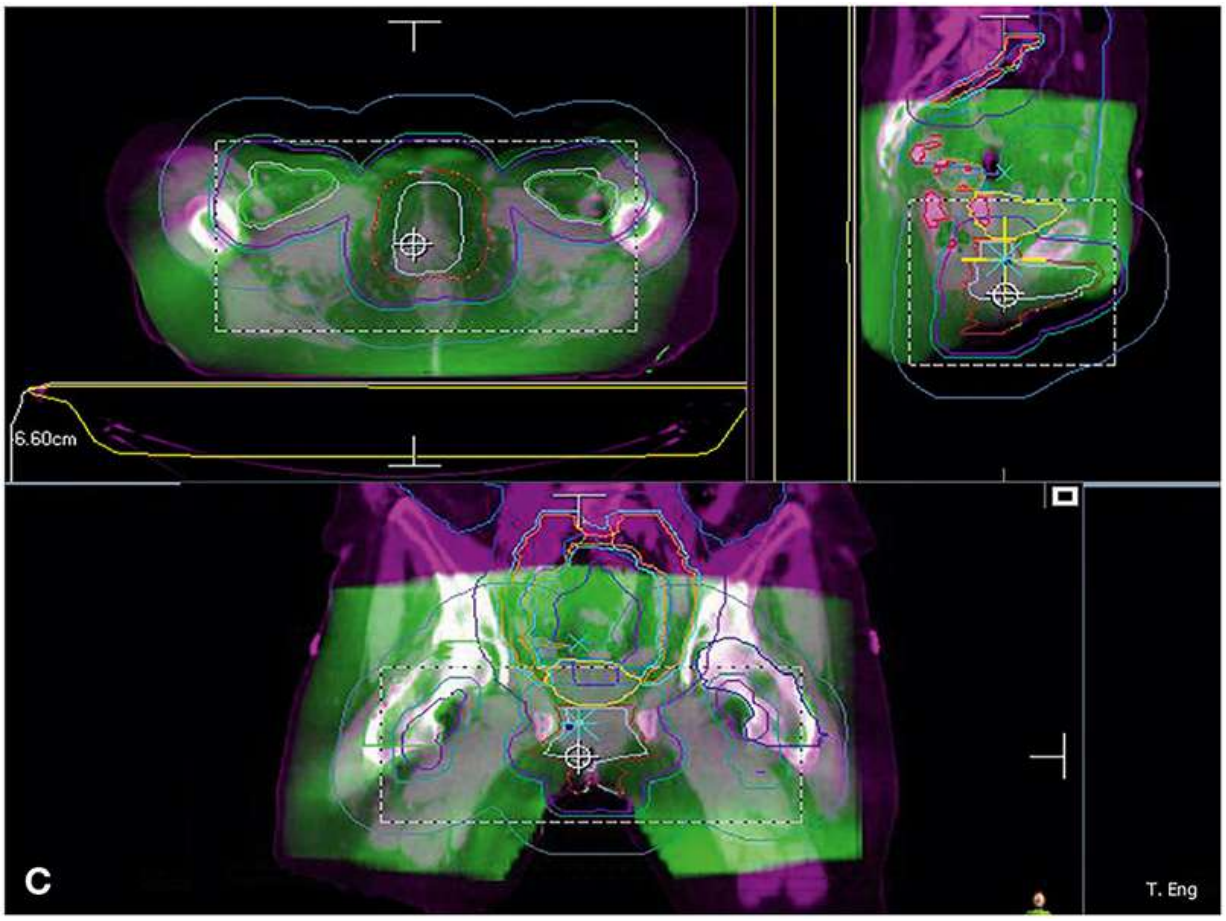
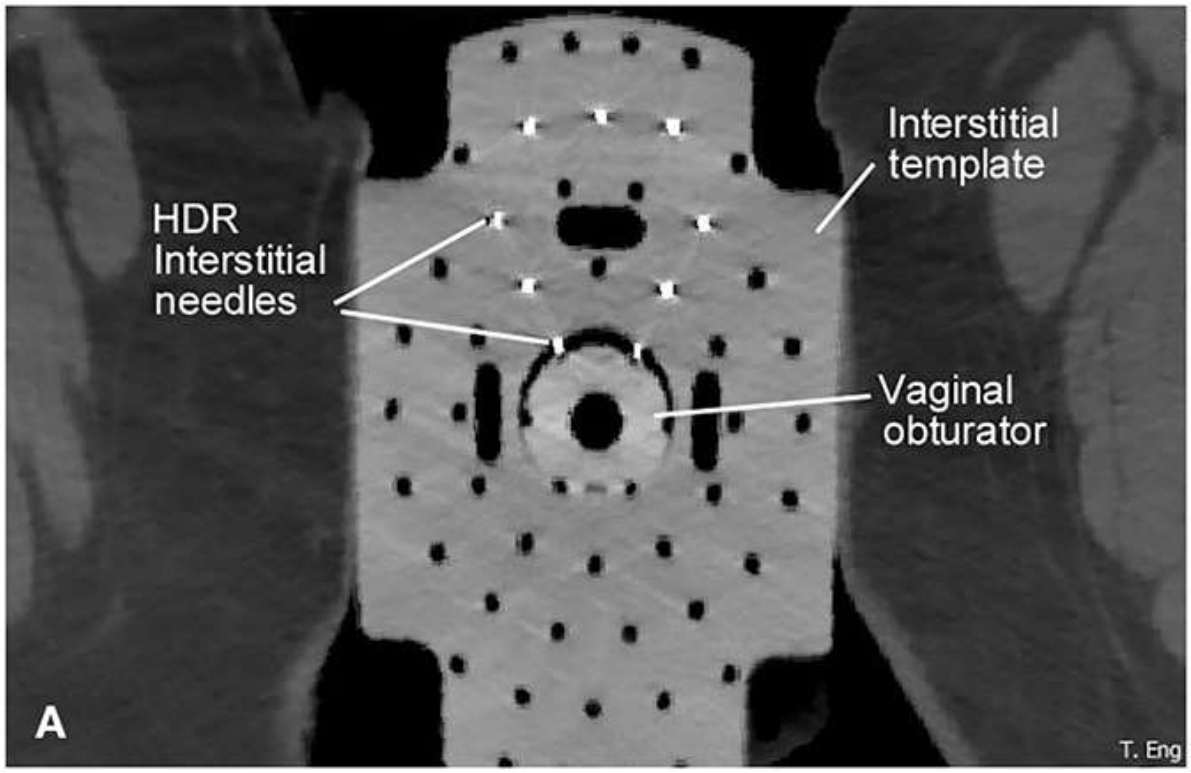


FIGURE 80.12 A. Pelvic intensity-modulated radiation therapy plan showing a conformal dose distribution covering the lymphatics and primary target volume or the planning target volume (PTV). Daily matching of MV-CT with the reference planning CT (KV-CT) (B) or cone beam computed tomography (C) images are done prior to each treatment. GTV, gross tumor volume; KV-CT, kilovoltage computed tomography; MV-CT, megavoltage computed tomography.


Interstitial
template
HDR
Interstitial
needles
Vaginal
obturator
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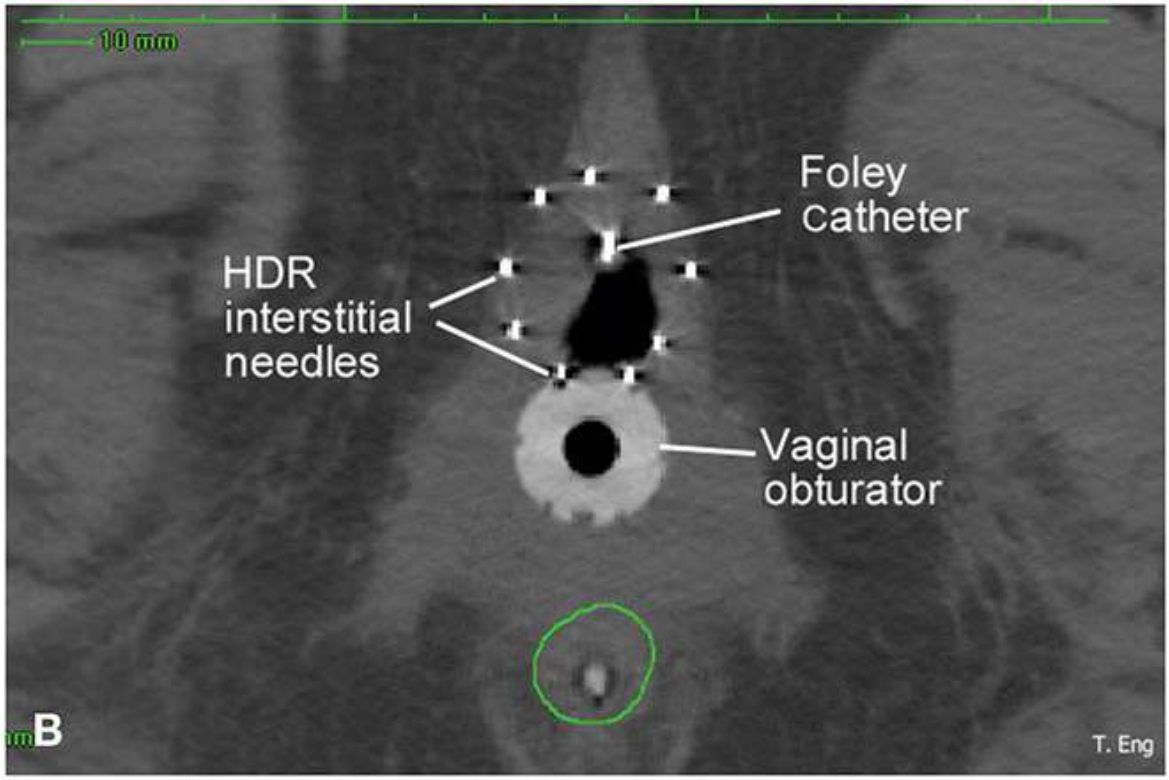
10 mm
Foley
catheter
HDR
interstitial
needles
Vaginal
obturator
B
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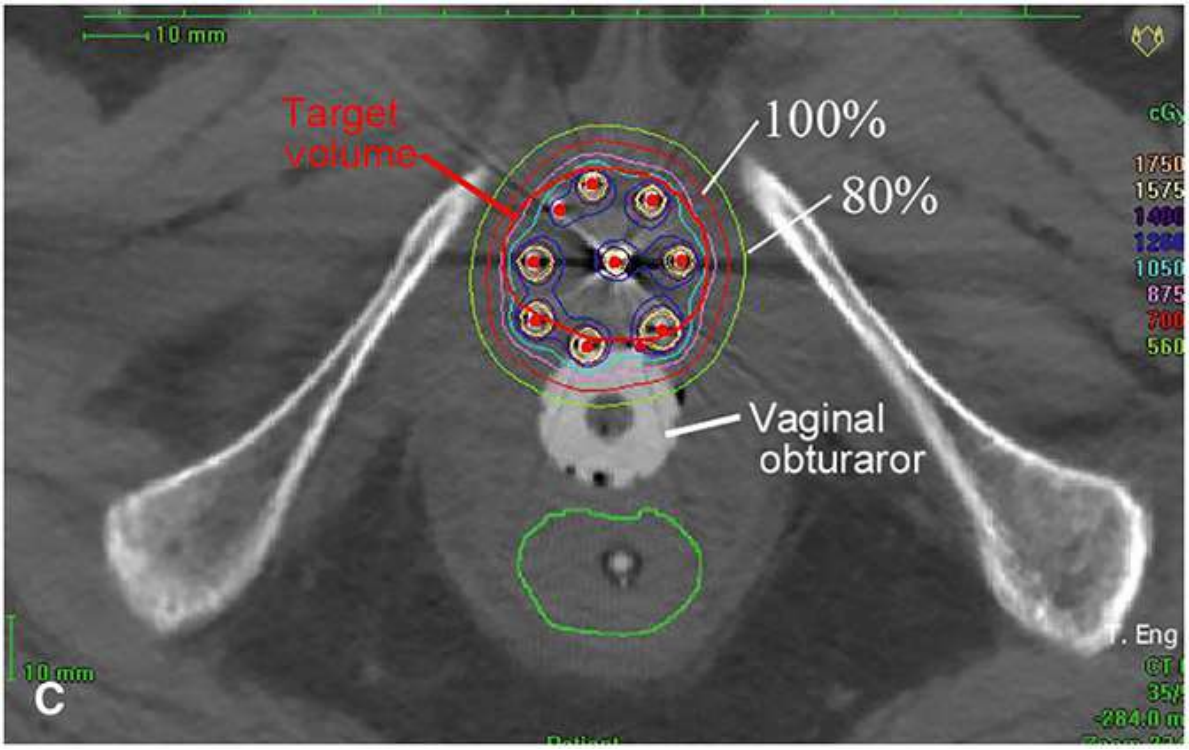
10 mm
Target volume
100%
80%
Vaginal obturaror
10 mm
C

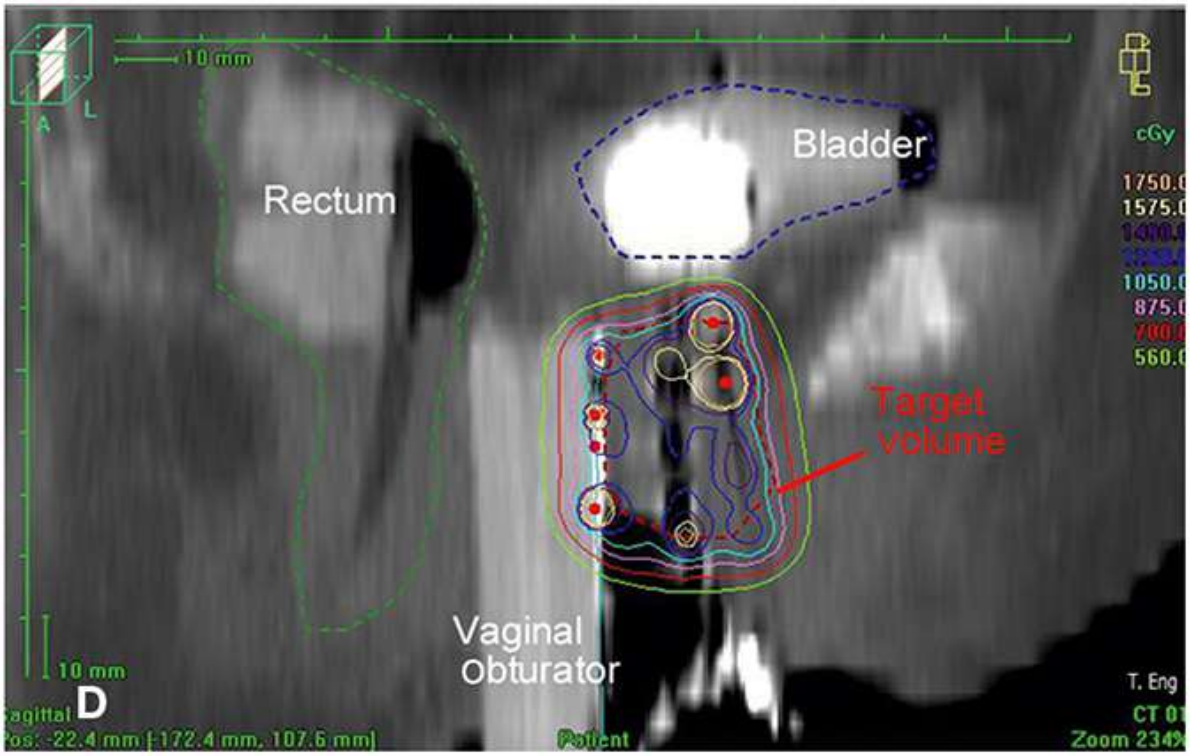
10 mm
Bladder
Rectum
Target volume
Vaginal obturator
10 mm
D

FIGURE 80.13 High-dose rate (HDR) interstitial brachytherapy: A. An interstitial template with a vaginal obturator is used to guide the needle placement. B. The needles surround the urethra at approximately a 1 cm distance. C and D. With proper optimization, the resultant dose distribution conforms to the target volume while sparing all the surrounding organs. E. Dose-volume histogram shows a large dose separation of the target from the bladder and rectum.

One of the limiting factors in the use of external beam irradiation is the tolerance of the perineal and vulva skin (i.e., confluent moist desquamation). Extensive disease combined with advanced age can be a formidable obstacle to completing the irradiation course. Proper radiation therapy techniques and diligent personal hygiene and individualized skin care during and after treatment are necessary if patients are to complete the course of treatment.

RESULTS OF THERAPY

The 1983-2008 SEER database identified 722 women with urethral cancer.[49] The median overall survival was 42 months, and the 5- and 10-year overall survival was 43% and 32%, respectively. The median cause-specific survival was 78 months, and the 5- and 10-year cause-specific survival was 53% and 46%, respectively. A subsequent NCDB analysis published by Son et al in 2018 identified 2,614 patients treated for primary urethral cancer.[53] Three-year overall survival was found to be 54%. Furthermore, a benefit was found with the addition of radiation to surgery compared to surgery alone (hazard ratio 0.77, $P \leq .01$). Table 80.4 summarizes the recent treatment results from various institutions. Depending on the various prognostic and

treatment factors, the 5-year overall survival and cause-specific survival rates range from 32% to 59% and 40% to 61%, respectively. The recurrence rates range from 58% to 64%.

TABLE 80.4 FEMALE URETHRA TREATMENT SUMMARY

Study	Patients	Stage	Treatment	Radiation Dose (Gy)	Follow-Up (y)	Results	Prognostic Factors
Qian et al Emory 2022[76]	37	T1-4, N0-2, M0-1	27 EBRT ± surg ± chemo Brachy: 6 surg + RT + brachy ± chemo 4 RT + brachy ± chemo	45-64.8 primary 55-59 nodes 15-33 HDR brachy	2.9 (median)	Median RFS 43 mo (brachy) vs 22 mo (patients who did not receive brachy)	Stage, brachytherapy utilization
Eng et al UTHSCSA 2018[77]	18	Tis-3, N0-2, M0-1	5 Part urethrectomy 3 surg ± RT ± chemo 5 RT ± brachy 5 RT/chemo ± brachy	30-68 primary 50 nodes 25 HDR brachy	7.1 (mean)	5-y OS 56% 5-y CSS 61%	Stage
Kang et al Seoul National University 2015[78]	19	T1-4, N0-N+, M0-1	7 surg 7 surg ± RT ± chemo 3 RT ± chemo 2 biopsy only	No details	7.2 (median)	5-y RFS 34.8% 5-y CSS 58.9% 5-y OS 58.9% Recurrence rate 57.9%	Stage, nodal status
Thyavihally et al Tata Memorial 2005[29]	18	T1-4, N0-N+, M0	2 LE/RT 4 exent 4 exent/RT 4 RT 4 palliative RT/chemo	45-50 pelvis 20-25 boost	1.5-5.8	5-y OS 33% (45%, distal vs 16%, proximal lesions; 50%, low vs 0% high stage)	Stage, disease site
DiMarco et al Mayo Clinic 2004[24]	53	pT1-3, N0-N+	26 part urethrectomy 27 exent (20 adj RT/3 brachy/3	20-60 (50, median)	12.8 (mean)	10-y CSS 60% 10-y CS 42%	Path stage, nodal status, partial urethrectomy

Study	Patients	Stage	Treatment	Radiation Dose (Gy)	Follow-Up (y)	Results	Prognostic Factors
			chemo)			LR 15 pts, DM 2 pts, LR+DM 10 pts	
Milosevic et al PMH 2000[72]	34	T1-4, N0-N+, M0	5 brachy 14 RT 15 RT + brachy	35 brachy (median) 50 RT (median)		LR 62% 7 y AS 41% 7 y CSS 45%	Brachytherapy, tumor size
Dalbagni et al MSKCC 1998[3]	72	Tx-4, Nx-N+	42 exent/part urethrectomy 25 RT/brachy 10 pre-op RT	No details	7.1 (median)	5-y OS 32% (78%, low vs 22%, high stage) 5-y DSS 46% (89%, low vs 33%, high stage)	Stage, nodal status, surgery type, disease site
Grigsby MIR 1998[25]	44	T1-4, N0-2	7 surg 25 RT 12 surg + RT	30-73.68 adj RT (50.4 median) 12-70 RT (42.59 median) 20-95 brachy (42.72 median)	8.25 (mean)	5-y OS 42% 5-y DSS 40% (89%, 36%, 19% for <2, 2-4, >4 cm) LR 8 pts, LR + DM 15 pts, DM 4 pts	Tumor size and histology
Garden et al MDA 1993[4]	97	T1-4, N0-N+	86 LE + RT: (35 RT + brachy, 21 RT, 30 brachy) 11 pre-op RT	40-106 RT (65 median) 45-75 brachy (60 median)	8.75 (median)	5-y AS 41% 10-y AS 31% 15-y AS 22% LC 64% (RT only)	Local extension, fixation, involvement of entire urethra

adj, adjuvant; AS, actuarial survival; brachy, brachytherapy; chemo, chemotherapy; CS, crude survival; CSS, cancer-specific survival; DM, distant metastasis; DSS, disease-specific survival; exent, exenteration; HDR, high-dose rate; LC, local control; LE, local excision; LR, local recurrence; MDA, MD Anderson Cancer Center; MIR, Mallinckrodt Institution of Radiology; MSKCC, Memorial Sloan-Kettering Cancer Center; OS, overall survival; part, partial; PMH, Princess Margaret Hospital; pts, patients; RFS,

recurrence-free survival; RT, radiation therapy; surg, surgery; UTHSCSA, University of Texas Health Science Center at San Antonio.

Surgery

There is a paucity of long-term outcome data. In general, female urethral cancers are clinically aggressive with high recurrence and poor survival rates.[3,10,15,22,50] DiMarco et al[24] reviewed 53 female patients with primary urethral carcinoma undergoing partial urethrectomy or radical extirpation. The estimated 10-year cancer-specific survival was 60%. In a study of 72 patients treated at Memorial Sloan-Kettering Cancer Center between 1925 and 1994, the 5-year disease-specific survival was 89% for low-stage tumors and 33% for high-stage tumors.[3] The overall survival was 78% and 22%, respectively, as shown in Table 80.4.

Five of seven patients with early meatal tumors were cured of disease in the series reported by Grabstald[10] after partial urethrectomy. In the remaining two patients, both local recurrences and distant metastases developed. Bracken et al[47] reported local control in just one of four patients treated with local excision only for distal urethral lesions. Peterson et al[23] reported on two patients in whom squamous cell carcinomas were excised successfully. In the same series, a patient with adenocarcinoma treated with local excision had a local recurrence and left inguinal adenopathy developed 4 years later.

Grabstald et al[21] performed radical surgery on 15 patients with advanced disease; there were only three survivors at 5 years. Peterson et al[23] performed radical surgery on seven patients, three of whom were alive at 5 years. Primary radical cystectomy with anterior vaginectomy and total urethrectomy was performed on eight patients by Mayer et al.[79] Three of these patients were free of disease at 1, 4, and 11 years.

Radiation Therapy

A study published by DiMarco et al[24] in 2004 found that adjuvant radiation did not improve local control or survival in the study of 53 female patients with urethral carcinoma, although treatment selection bias may have played a role as the higher stage tumors tended to receive adjuvant radiation therapy. Eng et al[48] reported only one of six patients with low-stage disease was referred for adjuvant radiation therapy, whereas four of five patients with advanced disease received radiation therapy. The one who did not receive radiation died 10 months after surgery. A case review of early-stage urethral cancer treated with external beam radiotherapy, brachytherapy, or a combination of both seems to have equivalent results as surgery alone.[60,61,68,73] More recently, multiple series have now found that multimodality therapy with the addition of adjuvant radiation confers a survival benefit.[52,53]

Control of tumors of the urethral meatus or the distal urethra with irradiation alone is often satisfactory. Early meatal tumors have cure rates of 70% to 90%.[39] Chu[20]

reported a 5-year progression-free survival rate of 64% for 11 patients with tumor involvement of the anterior urethra treated with irradiation alone. Prempree et al[39] treated three patients with stage I disease with interstitial irradiation alone (50-65 Gy) and achieved local control in all three. In the same series, two of four patients with stage II disease achieved local control and were alive 5 years after treatment. Weghaupt et al[9] reported a 5-year survival rate of 71% for 42 patients with cancer of the anterior urethra. Their doses ranged from 55 to 70 Gy from intracavitary and external irradiation. Princess Margaret Hospital reported an 87% relapse-free survival rate in patients with stage I or II disease.[72] The majority of patients with small primary tumors received brachytherapy as a component of their treatment. Patients receiving brachytherapy and external beam radiation therapy had a median total dose of 65 Gy.

Tumors of the proximal urethra or the entire urethra are more difficult to treat. The overall local control rate is 20% to 30%. Bracken et al[47] treated 81 patients, and the 5-year survival rate was approximately 25% for patients with stage III and 20% for those with stage IV disease. Princess Margaret Hospital reported stage III and IV tumors to have cause- specific survival rates of 26% and 16%, respectively.[41] Weghaupt et al[9] reported a 5-year survival rate of 50% among 20 patients with tumor involvement of the posterior urethra who received irradiation alone or preoperative irradiation and surgery. Garden et al[4] treated 86 patients with irradiation only after excision or biopsy of the primary lesion. Radiation doses ranged from 40 to 106 Gy (median, 65 Gy). The 5-year disease-specific survival rate was 49%, and the 5-year local control rate was 64%. Preoperative irradiation combined with radical surgery is an approach used by Klein et al[22] They treated five women in this manner and achieved a 5-year survival rate of 40%. Dalbagni et al[61] used anterior pelvic exenteration with intraoperative tumor bed interstitial brachytherapy using ^{192}Ir, followed several weeks later by pelvic external beam radiation therapy. A variety of chemosensitizing agents were used. The median brachytherapy dose was 15 Gy, and pelvic radiation therapy dose given was 45 Gy. Local control was achieved in four of six women with T2 and T4 disease.

Several investigators have found that the use of brachytherapy improves local control and further enables organ preservation.[61,72,80] Milosevic et al[72] reported that patients who were treated with external beam therapy only were 4.2 times more likely to recur locally independent of other prognostic factors, compared with those who received brachytherapy as a component of management. Similarly, in a study of six patients with locally advanced urethral carcinoma, Dalbagni et al[61] noted that high-dose intraoperative brachytherapy followed by external beam radiation appeared to improve local control.

Chemotherapy and Multimodality

Dayyani et al[67] reported a response rate of 72% in 36 patients with locally advanced urethral cancer who had received definitive or preoperative platinum-based chemotherapy. The median overall survival was 25.6 months. Gheiler et al,[50] reported a disease-free survival rate of 60% in selected patients with advanced T3 or higher disease treated with a multimodality regimen consisting of neoadjuvant chemotherapy and radiation therapy. A phase 2 study has shown the combination of ifosfamide, paclitaxel, and cisplatin used in 45 patients with advanced transitional carcinoma of the urothelial tract is well tolerated and results in a median survival of 20 months.[81] Similar encouraging results have been reported in patients with advanced urethral cancer receiving concomitant fluorouracil, mitomycin C, and radiation therapy.[63,64,82] While immunotherapies have begun to be used in bladder cancer and other cancers of urothelial origin, there have not been data reported on their use in urethral cancers, which warrants future investigation.

SEQUELAE OF THERAPY

Complications as a result of surgery, irradiation, or combined-modality therapy vary greatly, from 0% to 42%, because of different tumor stages, the extent of surgery, and various irradiation doses.[11,20,25,70,83] In general, more aggressive treatment is expected to result in a higher complication rate. Garden et al[4] reported that 27 (49%) of 55 patients achieving local control had complications, including urethral stenosis, fistula, necrosis, cystitis, and hemorrhage. Urethral strictures develop in some patients, necessitating dilation or urinary diversion. Others may experience incontinence, cystitis, and vaginal stenosis. Severe complications include fistula formation, bowel obstruction, and, occasionally, operative death. In the case of advanced neoplasms, fistula formation may be unavoidable because of tumor erosion of adjacent organs and subsequent tumor necrosis. Unlike the male counterpart, the physical loss of the female urethra is not uniformly associated with sexual impotence; nevertheless, the associated treatment side effects and negative self-image may affect sexual function and quality of life.

FUTURE DIRECTION

Early detection and intervention provide the best chance of organ preservation and cure. Although most clinical information comes from retrospective case series accumulated over a long span of time using various treatment modalities, multimodality shows encouraging results and should always be considered, especially in patients with locally advanced or metastatic disease. Clinical trials are clearly needed to obtain prospective data. Improved knowledge of tumor and normal tissue radiobiology, along with continued technological advances in external beam radiation

therapy and brachytherapy delivery will maximize organ preservation and minimize some of the treatment-related complications.

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CHAPTER 81

Carcinoma of the Vulva

Diandra N. Ayala-Peacock, Mary Katherine Anastasio, and Junzo P. Chino

ANATOMY

Vulva

The vulva is composed of the mons pubis, clitoris, labia majora and minora, vaginal vestibule, and their supporting subcutaneous tissues. The vulva blends with the urinary meatus anteriorly and with the perineum and anus posteriorly. The mons pubis consists of prominent tissue located anteriorly to the pubic symphysis. The labia majora are two elongated skin folds that course posteriorly from the mons pubis and blend into the perineal body. The skin of the labia majora is pigmented and contains hair follicles and sebaceous glands. The labia minora are a smaller pair of skin folds located medial to the labia majora. Anteriorly the labia minora separates into two components that course above and below the clitoris, fusing with those of the opposite side to form the prepuce and frenulum, respectively. The skin of the labia minora contains numerous sebaceous glands but no hair follicles and has no underlying adipose tissue. The clitoris is 2 to 3 cm anterior to the urethral meatus and is supported externally by the fusion of the labia minora.

The vaginal introitus is demarcated laterally by the labia minora and posteriorly by the perineal body. Anteriorly numerous small vestibular glands are located beneath the mucosa and open onto its surface adjacent to the urethral meatus. The Bartholin glands (or greater vestibular glands) are two small mucous-secreting glands situated within the subcutaneous tissue in the posterior aspect of the labia majora. The ducts of the Bartholin glands open onto the posterolateral portion of the introitus. The Skene glands (or paraurethral glands) open in the anterior aspect of the introitus but can be variable in location. The perineal body is a 3- to 4-cm band of skin that separates the vaginal introitus from the anus and forms the posterior margin of the vulva with the fusion of the labia minora, the fourchette.

Lymphatic Drainage

The inguinofemoral nodes are located within the triangle formed by the inguinal ligament superiorly, the border of the sartorius muscle laterally, and the border of the adductor longus muscle medially. There are superficial inguinal lymph nodes (LNs)

that lie along the saphenous vein and its branches between Camper fascia and the cribriform fascia overlying the femoral vessels. There are usually three to five deep nodes, the most superior of which (Cloquet node) is located under the inguinal ligament. Lymph drains from these nodes into the external and common iliac pelvic LNs.

Lymphatic drainage is specific to the location of a vulvar lesion. Labial lesions drain into the superficial inguinal and femoral LNs, then penetrate the cribriform fascia and reach the deep femoral nodes. Lesions of the fourchette and perineum follow the lymphatics of the labia. Lymphatic drainage from the glans clitoris or perineal body enters either unilateral or bilateral superficial femoral nodes or the deep femoral and pelvic LNs. Some lymphatics originating in the clitoris enter the pelvis directly, bypassing the femoral nodes to connect with the obturator and external iliac LNs, though, in practice, the pelvic LNs are rarely involved without synchronous involvement of the inguinal nodes (Figure 81.1).

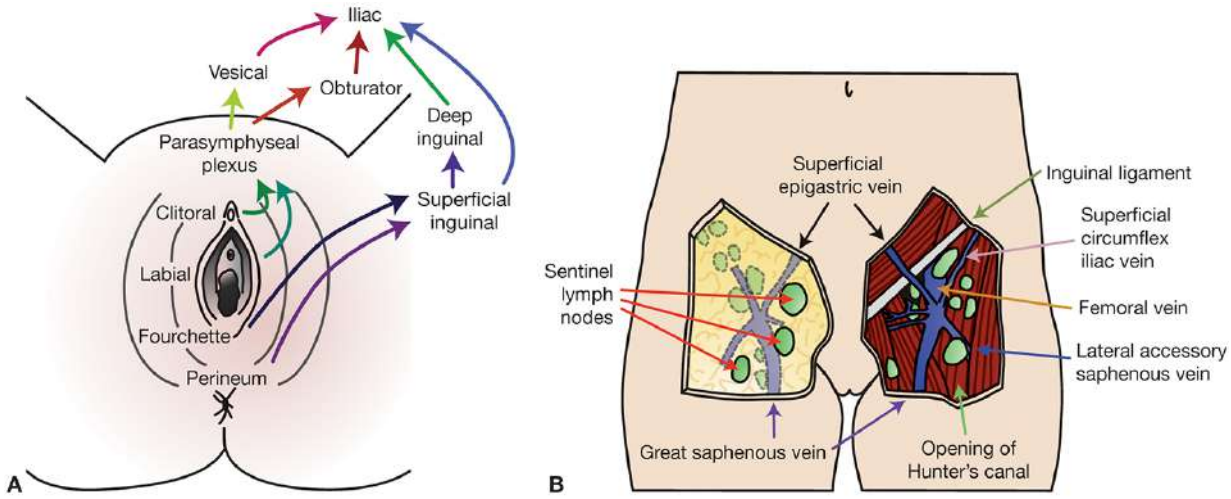

FIGURE 81.1 A. The lymphatic drainage of the vulva initially flows to the superficial inguinal nodes and then to the deep femoral and iliac group. Drainage from midline structures may flow directly beneath the symphysis to the pelvic nodes. B. Anatomic relation of inguinal lymphatics. (A: Modified from Plentl AA, Friedman EA, eds. *Lymphatic System of the Female Genitalia*. WB Saunders; 1971. Copyright © 1971 Elsevier. With permission. B: Modified from DiSaia PJ, Creasman WT, Rich WM. An alternative approach to early cancer of the vulva. *Am J Obstet Gynecol*. 1979;133[7]:825-832. Copyright © 1979 Elsevier. With permission.)

EPIDEMIOLOGY

Vulvar cancer is a rare malignancy representing less than 1% of all cancers diagnosed in women and less than 4% of all gynecologic neoplasms.[1] In the United States, there were an estimated 6,470 new cases in 2023 with an estimated 1,670 deaths—both representing approximately 0.3% of all new cancer cases and cancer deaths, respectively. There are two primary mechanisms believed to be involved in

carcinogenesis: human papillomavirus (HPV) or vulvar dystrophy, including lichen sclerosus (LS) and squamous hyperplasia. HPV DNA can be identified in approximately 30% to 40% of invasive vulvar cancers, with serotypes 16, 18, and 33 being the predominant subtypes.[2] As HPV infection is related to numerous other cancers of the anogenital region (eg, cervical cancer and anal canal cancer), the risk factors for HPV-related vulvar cancers are similar: previous diagnosis of genital warts, multiple sexual partners, smoking history, previous abnormal Papanicolaou test, and immune suppression.[3] However, vulvar dysplasia such as LS is often associated with HPV-negative cancers, although there is no histopathologic evidence of direct transformation.[4] Women with existing LS have a 5% to 7% risk of developing invasive disease, with risk increasing with older age and concurrent differentiated vulvar intraepithelial neoplasia (dVIN), up to a 19% risk of invasive cancer at 10 years.[5,6] In 2019, the incidence for women of age greater than 75 in the United States was 15.0 per 100,000 women in contrast to the incidence of 2.6 per 100,000 women for all ages.

The evidence for VIN as an obligate precursor to invasive vulvar disease is less compelling than that established between cervical intraepithelial neoplasia and cervical cancer. Only one-third of vulvar cancers have an associated VIN-3 lesion, and only 5% to 7% of women with an existing VIN lesion will subsequently be diagnosed with invasive disease.[7]

VIN may be divisible into two general types, depending on the lesion association with HPV (Table 81.1).[8] Usual type vulvar intraepithelial neoplasia (uVIN) is associated with HPV in 70% to 90% of cases and occurs in younger women with HPV risk factors. The aforementioned dVIN arises in the setting of LS and other chronic inflammatory processes and is associated with older age. These differing precursor lesions may then transform into two distinct classifications of squamous carcinoma: keratinizing squamous carcinomas (KSCs) arising from HPV-independent dVIN and basaloid squamous carcinomas (BSCs) arising from HPV-associated uVIN,[9] with KSC as the more common of the two (representing 60%-80% of cases). p53 mutations may also play a role in pathogenesis in a subset of these neoplasms, with some KSCs staining positive for p53. In contrast, p16 is rarely positive in KSCs, indicating a lack of association with HPV.[10,11] The less common BSCs (20%-40% of cases) often stain negative for p53 but are often p16 positive due to their association with HPV. Similar to findings related to HPV-related cancers in other sites, HPV-driven lesions (uVIN and BSC) portend a better prognosis.[12] Overexpression of p16 may also be associated with an improved prognosis, even when high-risk HPV DNA is not detected.[13]

TABLE 81.1 HISTOPATHOLOGIC PATTERNS OF SQUAMOUS CELL CARCINOMAS OF THE VULVA

	Keratinizing Squamous Carcinoma	Basaloid Squamous Carcinoma
Prevalence	More common (60%-80%)	Less common (20%-40%)
Age	Older age	Younger age
Distribution	Usually unifocal	Can be multifocal
Morphology	Keratinizing	Warty
Association with VIN	Uncommon: Differentiated type (dVIN)	Common: Usual type (uVIN)
Association with HPV	No	Yes (serotypes 16, 18, 31, 33)
Association with vulvar dystrophy	Common	Rare
Immunohistochemistry	p53: May be positive or negative p16: Negative or focally positive at stromal interface	p53: negative p16: positive

HPV, human papillomavirus; VIN, vulvar intraepithelial neoplasia.

PATHOLOGY

Squamous Carcinoma

Eighty to 90% of invasive disease of the vulva is squamous cell carcinoma (Figure 81.2), arising within the squamous epithelium, within or adjacent to areas of epithelial abnormalities or of premalignant conditions such as LS, erythroplasia of Queyrat, and Bowen disease.[14] The depth of invasion (DOI), critical for appropriate staging and management, previously defined as the distance from the epithelial-stromal junction of the most *superficial* adjacent dermal papillae to the deepest point of invasion has undergone revision since 2015. Current recommendations are to measure from the basement membrane of the *deepest* adjacent, dysplastic, tumor-free rete ridge or peg to the deepest point of invasion, resulting in a lesser depth in many cases.[15] Tumor thickness is measured from the overlying surface epithelium, or the bottom of the granular layer if the surface is keratinized, to the deepest point of invasion.

FIGURE 81.2 Squamous cell carcinoma of the vulva. A. Squamous cell carcinoma with ulceration, arising from the right labia minora. This older woman had no apparent predisposing disease. B. Photomicrograph of invasive keratinizing squamous cell carcinoma of the vulva. Note the keratin pearls. (Courtesy of Dr. Stanley Robboy, Duke University Medical Center, Durham, NC.)

There are three recognizable types of growth pattern of squamous carcinoma: confluent, compact, and spray or finger-like growth. Confluent growth is defined as a tumor mass composed of interconnected tumor greater than 1 mm in dimension. This type of growth is characteristic for being deeply invasive with associated stromal desmoplasia. Compact growth is associated with well-differentiated tumors, which maintain continuity with the overlying epithelium, infiltrating as a well-defined and circumscribed tumor mass, which rarely invades the vascular space. Histologically, the tumor cells resemble squamous cells of adjacent and overlaying epithelium. The spray or finger-like growth pattern is characterized by a trabecular appearance with small islands of poorly differentiated tumor cells found within the dermis or submucosa, deeper than the main tumor mass. This growth pattern is often associated with desmoplastic stromal response and a lymphocytic inflammatory infiltrate. Vascular space involvement is seen more commonly with this growth pattern than with tumors with a compact pattern.[16]

Uncommon Histologic Types and Management

Melanoma

Malignant melanoma of the vulva accounts for approximately 10% of all primary tumors of the vulva. It occurs more commonly in White women (incidence ratio 3:1 White/Black), with a peak incidence in the sixth and seventh decades (Figure 81.3).[17,18] Melanomas may arise in preexisting pigmented lesions; the differential diagnosis includes benign vulvar melanosis and pigmented VIN. Vulvar melanomas can be subclassified into three specific categories: superficial spreading malignant melanoma, nodular melanoma, and acral lentiginous melanoma. As is the case for

melanomas arising in other mucosal sites, the level of invasion, tumor thickness, and nodal evaluations dictate the therapy and determine the prognosis.[19] Compared to nongynecologic melanomas, BRAF and KIT mutations are more frequently detected in vulvar and vaginal melanomas, and programmed death-ligand 1 (PD-L1) and programmed cell death protein 1 (PD-1) may be more frequently expressed, having implications for targeted therapies and immunmodulation.[20]

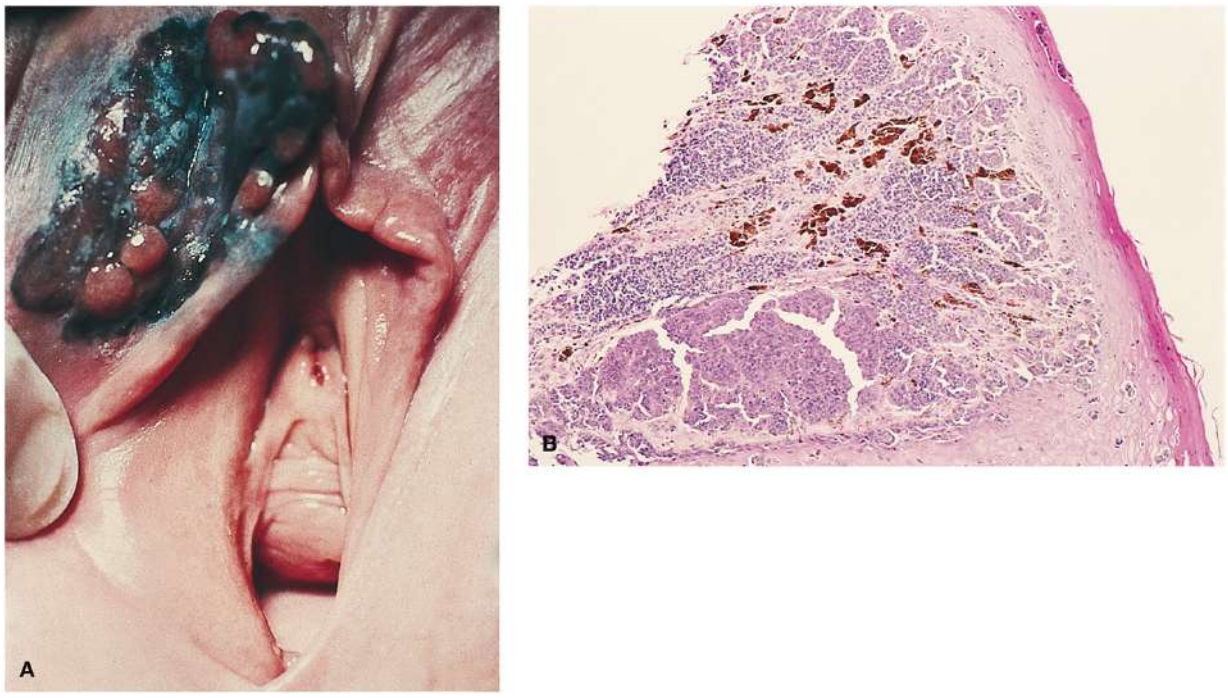

FIGURE 81.3 Melanoma of the vulva. A. A nodular, elevated, and darkly pigmented lesion arising from the right labia majora. B. Photomicrograph of invasive melanoma, with melanin apparent in portions of the tumor. (Courtesy of Dr. Stanley Robboy, Duke University Medical Center, Durham, NC.)

The prognosis is worse than with squamous cell carcinoma, with a 5-year overall survival (OS) of approximately 35%, particularly in those with deep invasion, ulceration, nodular growth pattern, epithelioid cell type, and high mitotic rate.[21,22] The prognosis is also worse in older patients. Primary surgical excision with nodal evaluation is preferred if possible, with adjuvant radiotherapy (RT) for nodal disease or close margins at the primary site. In a study of 32 patients treated at the Royal Marsden Hospital in London, there was no difference in the outcome between patients treated with wide local excision and those treated with more radical surgical procedures.[23] Radiation may be considered for patients with positive margins, positive LNs, or for palliation of symptoms. As with other mucosal melanomas, there is a high incidence of distant metastasis.

Adenocarcinoma

Adenocarcinomas of the vulva arise predominantly in the Bartholin glands, although apocrine, eccrine, and Skene glands can also be the site of origin. In the rare instances when adenocarcinomas arise in the absence of glandular tissue, they may be of cloacogenic origin. Carcinoma of Bartholin gland is seen more frequently in older women and is often solid and deeply infiltrative. The overlying epidermis or mucosa may remain intact, leading to misinterpretation as a benign process. Other histopathologic types are mucinous, papillary, mucoepidermoid, adenosquamous, and transitional. Adenocarcinomas often present with more locally advanced disease and metastases to the inguinal-femoral LNs.

The general approach to treatment, however, follows squamous cell carcinomas, with initial surgery followed by tailored adjuvant RT for resectable disease, and multimodality therapies for advanced stages. Survival after treatment is comparable to stage-matched squamous cell cancers.[24] The role of radiation for Bartholin gland carcinoma has been studied by Copeland et al and Leuchter et al.[25,26] These two studies suggest that adjuvant radiation to the vulva and regional nodes after conservative surgery may decrease local recurrence, with 7% recurrence with radiation and 27% recurrence without it in the Copeland et al's study. Five-year survival of 67% was reported by Cardosi et al in patients who were found to have close margins and were treated with primary surgery and adjuvant radiation.[27]

Paget Disease of the Vulva

Paget disease of the vulva (intraepithelial adenocarcinoma) is seen most often in postmenopausal, older White women. The disease varies in appearance, but most often, it presents as an eczematoid, red, and/or weeping lesion, and it can be mistakenly diagnosed as eczema or contact dermatitis (Figure 81.4). The lesion may be flat, raised, or ulcerated and may appear whitish (leukoplakia), red (erythroplastic), or hyperpigmented. This condition has a typical histologic pattern and often immunohistochemically positive for carcinoembryonic antigen. Vulvar Paget disease is associated with invasive carcinoma in 10% to 20% of the cases.[28,29] The associated invasive disease may be an underlying adenocarcinoma of the apocrine or Bartholin glands, or it may be an adenocarcinoma arising elsewhere in the anogenital region. Management is generally focused on maximal safe resection, though RT is an effective therapy for recurrent or unresectable disease.[30] Topical imiquimod also shows promise as an effective nonoperative therapy.[31] HER2 may be overexpressed in 15% of extramammary Paget disease, and anti–HER2-directed therapy may have clinical activity in these cases.[32,33]

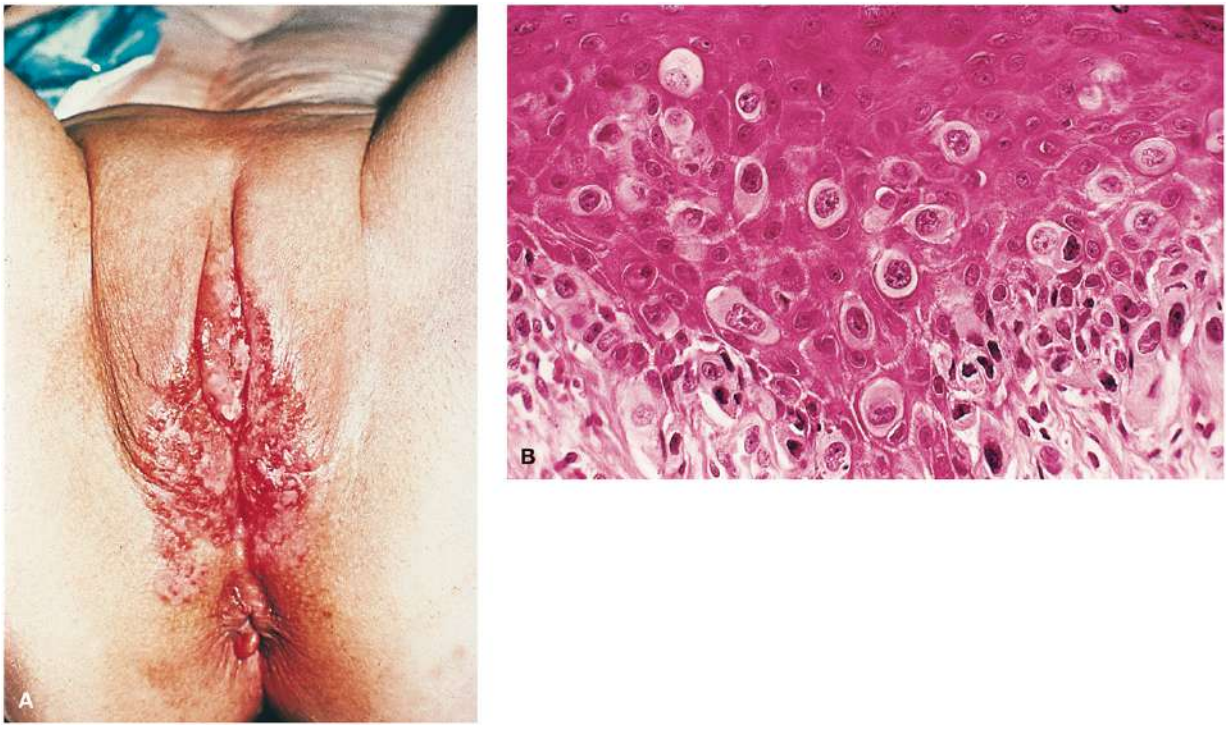

FIGURE 81.4 Paget disease of the vulva. A. Photo of extensive perineal disease, extending to the perianal skin. B. Photomicrograph of intraepithelial Paget cells, with copious pale cytoplasm, occurring singly or in small clusters, and appearing slightly larger than neighboring squamous cells. (Courtesy of Dr. Stanley Robboy, Duke University Medical Center, Durham, NC.)

Verrucous Carcinoma

Verrucous carcinomas of the vulva are uncommon, usually diagnosed in the fifth or sixth decade of life. They are locally invasive tumors that present as fungating, ulcerative masses. Histologically, these tumors are often well differentiated and have a low incidence of metastasis to LNs. In the early stages, excellent results are obtained with radical wide excision.[34] Inguinofemoral dissections are not recommended routinely due to the rarity of nodal metastases.

The literature regarding vulvar verrucous carcinomas consists largely of case reports, with the exception of the series by Japaze et al.[35] This study was based on 24 patients, 17 of whom were treated with surgery only and 7 of whom were treated with surgery and radiation. In the surgery group, only one patient developed recurrence and died as a result of it. In the radiation group, four patients developed recurrence, and all died from the disease. Although it is difficult to draw conclusions from this small series, there are no convincing data to recommend the routine use of RT for this disease. However, there is also no sufficient evidence to support the notion that radiation induces anaplastic transformation.[36]

Other Histologies

Other vulvar malignancies arising from epidermal cell types are rare. Merkel cell tumors (neuroendocrine carcinomas) are aggressive locally, have a high incidence of distant metastasis, and carry a poor prognosis. Basal cell carcinomas, on the other hand, seldom spread to LNs and are appropriately treated with wide excision alone.[37] Transitional cell carcinomas may arise from the Bartholin glands or may represent metastasis from the bladder and/or lower urinary tract.

Leiomyosarcomas are the most common subtypes of vulvar sarcoma, followed by undifferentiated pleomorphic sarcomas, epithelioid sarcomas, and rhabdomyosarcomas. Rhabdomyosarcomas of the vulva require combination therapy, chemotherapy, and radiation, as per rhabdomyosarcoma protocols of other sites. Results of treatment with other sarcomas of the vulva are variable; wide resection and/or radical RT should be considered, given the relative inactivity of chemotherapy.

CLINICAL PRESENTATION

Vulvar pruritus is the most common presenting symptom, often associated with bleeding, pain, or discharge. If there is a visible lesion on physical examination, a biopsy is required to distinguish it from other vulvar lesions, such as dystrophia, benign condylomata, and VIN. Presenting symptoms may also be related to the invasion of regional structures, including difficulty with urination or defecation. Metastatic disease is an uncommon presenting symptom because the primary lesion is usually much more problematic, although consequences of groin and distant disease may also be seen at presentation.

PATTERNS OF DISEASE AND SPREAD

Primary Site

Approximately 70% of vulvar malignancies arise in the labia majora and minora, 15% in the clitoris, 5% in the perineum and fourchette, 5% in the prepuce Bartholin glands and urethra, and 5% are too extensive at presentation to classify.[38]

Lymphatic Spread

High-grade tumors with “spray” growth pattern and lymphatic space invasion have a proclivity to spread to the regional lymphatic nodes. The superficial inguinofemoral LNs are the first echelon, followed by the deep inguinofemoral nodes. For well-lateralized lesions, metastasis to the contralateral inguinal or pelvic LNs is unusual in the absence of ipsilateral inguinofemoral node involvement. Lesions of the clitoris or urethra are occasionally noted to directly metastasize to pelvic LNs, although this is rare without inguinal node involvement.[39,40]

The frequency of inguinal LN metastasis in surgically staged patients ranges from 6% to 50%, depending on tumor invasion and extent of disease (Table 81.2).[41-45] Physical examination alone is inaccurate to assess LN involvement: Plentl and Friedman reported a 62% incidence of LN metastases in patients with clinically palpable adenopathy and 35% involvement in patients without clinically palpable adenopathy.[38] In the Gynecologic Oncology Group (GOG) protocol 36, 24% of the patients with clinically negative inguinal nodes were found to have nodal metastasis on final pathology. When the LNs were clinically suspicious, 76% had histologically positive nodes.

TABLE 81.2 INCIDENCE OF LYMPH NODE INVOLVEMENT CORRELATED WITH PRIMARY TUMOR SIZE AND EXTENT

Primary Tumor Size and Depth of Invasion	Number of Patients	Number of Patients With Positive Lymph Nodes (%)
Depth		
<1 mm	120	0 (0)
1.1-2 mm	121	8 (6.6)
2.1-3 mm	97	8 (8.2)
3.1-4 mm	50	11 (22)
4.1-5 mm	40	10 (25)
Size		
>5 mm	32	12 (37.5)
>2 cm	168	77 (45.8)
Any size of primary tumor extending beyond the vulva	70	38 (54.2)

Adapted from Perez CA, Grigsby PW, Chao C. Vulva. In: Perez CA, Brady LW, eds. *Principles and Practice of Radiation Oncology*. 3rd ed. Lippincott-Raven; 1997.

Multiple clinical and histologic features of the primary tumor are associated with nodal metastasis, including tumor thickness, histologic grade, capillary-like space involvement, DOI, location of the tumor, and tumor size.[46,47] Rutledge et al. also described the adverse effect on local control and survival based on tumor size, clinical stage, positive inguinal or pelvic nodes, and positive margins at the primary site.[47] When the tumor thickness is 1 mm or less, the probability of nodal metastasis is 3% or less, but with tumor a tumor thickness 5 mm or larger, the probability increases to 33.3%. DOI of 1, 2, and 3 mm corresponds to a 4.3%, 7.8%, and 17% incidence of nodal involvement. It should be noted that the thickness of the epithelium in the vulva varies significantly from one area to another, in some areas being greater than 0.8 mm thick, which can influence the relative value given to

tumor thickness and DOI. Measuring tumor thickness in superficially ulcerated tumors can be misleading and may lead to underestimating the DOI. Perineural invasion correlates strongly with LN metastasis.[48]

In an analysis of the GOG database on carcinoma of the vulva, several clinical and histologic tumor characteristics were identified as predictors of nodal involvement. In order of importance, these are clinical node status (palpable vs nonpalpable), grade, capillary-lymphatic space involvement, tumor thickness, and patient's age.[46,49,50] There is also a correlation between the size of the primary tumor and the involvement of the LNs. In Donaldson et al.'s series of 66 patients, the probability of having positive inguinal nodes rose from 18.9% for patients with lesions less than 3 cm to 72.4% for patients with primary tumors 3 cm or more.[42] In a GOG study of 267 patients with superficial vulvar cancer reported by Sedlis et al, the frequency of positive inguinal nodes was 18.1% for patients with lesions up to 3 cm in size and 29.3% for patients with lesions 3 cm or more.[46] Extension of the primary tumor to the urethra, vagina, and anal area is associated with an increased incidence of nodal involvement and worse prognosis.

Inguinal nodal involvement is a strong predictor for pelvic nodal disease. In a GOG study of patients with positive inguinal nodes, the incidence of pelvic node involvement was 28%.[51] Due to the rarity of isolated pelvic nodal metastasis, the status of the inguinal nodes often determines the management of the pelvic nodes. Although pelvic node involvement is currently staged as IVB disease, many are still potentially curable, and definitive local therapy remains indicated. In a series from MD Anderson, 5-year OS for women with involved pelvic nodes was 43% when treated with aggressive local therapy.[52]

Distant Metastases

Hematogenous dissemination generally occurs late in the natural history of the disease, with the most common sites being the lungs, liver, and bones. The OS is limited in these cases to a median of approximately 6 months.[53]

PROGNOSTIC FACTORS

LN metastasis is the most important prognostic factor in patients with vulvar cancer. The presence of inguinal node metastases is accompanied by a 50% reduction in long-term survival.[54] LN extracapsular tumor extension has been noted in several series to impact disease recurrence and all-cause mortality.[55] Origoni et al evaluated the significance of the size of the metastases in the LNs, the number of positive LNs, and extracapsular extension (ECE) of the disease and found that the presence of any one of these factors worsened the prognosis.[56] Extracapsular tumor extension as an independent adverse prognostic factor on survival was also described by van der

Velden et al.[57] Pelvic nodal metastasis has an even more profound negative effect on survival, though as noted earlier, definitive local therapy can still result in long-term survival.[58]

In an analysis of formalin-fixed tissue specimens, a UCLA series reported a sharp rise in the incidence of local recurrence for tumors with close microscopic surgical margins (48% if <8 mm, with no local recurrences if >8 mm).[59] This corresponds to a margin of 1 cm in fresh, unfixed tissue. In addition to margin status, DOI was reported as an important prognostic factor, with 30% of patients with 10 mm or more DOI experiencing recurrence, in contrast to 0 of the 52 patients with less than 2.5 mm. Although the frequency of local recurrences correlated with the adequacy of the margins of the surgical resection, larger or thicker tumors, or when those that involve midline structures, adequate surgical margins may be difficult to obtain.

Faul et al published a retrospective series evaluating the role of adjuvant radiation for close and positive surgical margins in which a 5-mm margin of excision was a predictor for local recurrence (58% if observed).[60] More modern series, however, have put into question the relationship between surgical margins and recurrence, with a 2019 series from the Netherlands suggesting that locoregional recurrence did not correlate with pathologic tumor-free margins, but rather the presence of precursor lesions at the surgical margin, such as LS, dVIN or both.[61]

Kurzl and Masserer analyzed 124 patients with various stages of vulvar carcinoma treated with simple vulvectomy alone and local/inguinal irradiation.[62] They found that age, disassociated growth, lymphatic spread, thickness, and ulceration of the primary tumor were important prognostic factors. In a detailed analysis of a GOG clinicopathologic study of 558 women with vulvar cancer, two significant risk factors were identified that predispose for recurrence in the vulva: tumor size greater than 4 cm and capillary-lymphatic space involvement.[49] If either of these factors was present, the risk of local recurrence after radical vulvectomy was 21% versus 9% without. In this study, the DOI did not predict for vulvar failure.

INITIAL EVALUATION

A thorough examination of the genitourinary system is warranted in all those with vulvar cancer to evaluate for multifocal disease. Examination of the vagina, cervix, perianal skin, and anal canal is of particular importance in order to delineate the extent of disease and to identify synchronous lesions, particularly in the setting of HPV-mediated disease. Special attention as well is paid to the inguinofemoral basins for clinical detection of lymphatic spread, though clinical negative groin examinations have a 25% to 30% false-negative rate, as noted earlier.

Imaging studies may not be necessary in early lesions that may be approached with surgery as the first treatment modality. However, imaging in women with

locally advanced disease or with clinically suspicious LNs help the clinician select the most appropriate treatment. Computed tomography (CT) scans can identify suspicious lymphadenopathy in the inguinofemoral chains, pelvis, or para-aortic regions.[63] Contrast-enhanced magnetic resonance imaging (MRI) is also helpful to delineate the primary lesion and contributes to the evaluation of inguinal LNs, with a sensitivity of 80% and a specificity of 88%.[64] Clinically or radiographically detected inguinal nodes may be evaluated with ultrasound-guided fine-needle aspiration, though a negative result does not rule out involvement.[65] Fluorodeoxyglucose (FDG) positron emission tomography (PET) has been used to evaluate the groin prior to surgical evaluation, with a sensitivity of 67% and a specificity of 95%.[66] FDG-PET at diagnosis may change the prior clinical impression in up to 50% of cases.[67] However, the sensitivity of all imaging modalities available remain insufficient to omit surgical evaluation in women with a high risk of nodal involvement.

STAGING

The most recent Federation of Gynecology and Obstetrics staging revision was performed in 2021 (Table 81.3).[68] The definition of DOI is now defined as the measurement from the basement membrane of the deepest, adjacent, dysplastic, tumor-free ridge to the deepest point of invasion. Stage III is divided into three substages with changes based on nodal involvement. Stage IIIA involves tumor extension to the upper urethra, upper vagina, bladder or rectal mucosa, or regional (inguinal and femoral) nodal metastases 5 mm or less, whereas nonosseous organ extension was previously stage IVA. Stage IIIB includes regional nodal metastases greater than 5 mm, and stage IIIC involves nodal metastases with extracapsular spread. Stage IVA includes disease fixed to the pelvic bone or fixed regional LN metastases, and stage IVB is defined by distant metastases. The presence of pelvic nodal metastases remains stage IVB disease.

TABLE 81.3 VULVAR CANCER: 2009 AJCC STAGING AND CORRESPONDING 2021 FIGO STAGING

2009 AJCC			2021 FIGO
Tis	Carcinoma in situ		–
T1a	Confined to vulva/perineum, size ≤2 cm, stromal invasion ≤1 mm	N0	IA
T1b	Confined to vulva/perineum, size >2 cm, or stromal invasion >1 mm	N0	IB
T2	Adjacent spread to distal 1/3 urethra and/or vagina or anus	N0	II
T3	Extension to proximal 2/3 urethra and/or vagina, bladder/rectal mucosa		IIIA
N1a, N2a	Regional (inguinal and femoral) nodal metastases ≤5 mm		IIIA
N1b, N2b	Regional lymph node metastases >5 mm		IIIB

2009 AJCC		2021 FIGO
N2c	Any lymph nodes involved with extracapsular extension	IIIC
N3	Fixed or ulcerated lymph nodes	IVA
	Disease fixed to the pelvic bone	IVA
M1	Distant metastasis (including pelvic lymph node metastasis)	IVB

AJCC, American Joint Committee on Cancer; FIGO, International Federation of Gynecology and Obstetrics.

According to the AJCC, femoral and inguinal nodes are considered regional spread, whereas iliac nodes are considered distant metastasis.

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MANAGEMENT OVERVIEW

Many factors make the treatment of carcinoma of the vulva challenging. Many women with this disease are older and have comorbidities. The tumor, by virtue of its location, can easily involve adjacent organs such as the urethral meatus and anal canal, and the frequency of nodal involvement is high. Because of the relatively low incidence, most published reports consist of small and heterogeneous groups of patients. Management of carcinoma of the vulva is further complicated by the major impact on genitourinary function that the disease itself and its treatment can have on patients.

The management of vulvar carcinoma has evolved significantly in the past decades. En bloc resection of the primary tumor and a full inguinal node dissection are no longer routinely utilized, replaced by multimodality therapy, with surgery being more tailored to the extent of the disease. This change is in large measure due to the recognition of the morbidity associated with radical surgery and improving results achieved with multimodality therapy.[69-71] The likelihood of controlling the primary tumor with surgery largely depends on the adequacy of the margins of resection, and it is not necessary to remove the entire vulva. A clear margin of greater than 8 mm in all directions is sufficient to achieve a high rate of local control of the primary tumor.[59]

There have been refinements in the surgical technique that have made the procedures more tolerable. Examples of such improvements include primary closure of the perineal wound, the use of myocutaneous flaps to close the surgical defect in the inguinal area, and the use of separate incisions for the resection of the primary tumor and the inguinal nodes. These developments have resulted in a decrease in operative mortality and morbidity.

There have been also significant advances in all aspects of RT that apply to the treatment of carcinoma of the vulva. The technical resources available now make it

possible to deliver effective doses of radiation to the vulvovaginal and inguinal regions with less acute and late morbidity. With high photon energy units, well-collimated fields, multileaf collimators, electron beams of different energies, and intensity- modulated radiation therapy (IMRT), radiation is now delivered to the primary disease and LNs with precise account of the differences in contour, tissue thickness, and extent of the disease. It is possible to tailor the treatment to the specified treatment volume while keeping the dose to the normal tissues within acceptable limits of tolerance. In particular, IMRT has allowed for dose escalation to involved sites of disease for locally advanced vulvar cancers. This has resulted in higher response rates in more modern series such as GOG 279 (71% clinical complete response [CCR]) when compared to the response rates observed in GOG 101 (48% CCR) and GOG 205 (48% CCR).[72] In very select cases, brachytherapy (BT) may also be used as either primary treatment or in combination with external beam to bring the dose higher to limited volumes. Chemotherapy, radiation, and surgery in sequence and/or in combination lessen the impact of any one modality and can lead to functional organ preservation with comparable or improved local tumor control and survival (Figure 81.5).

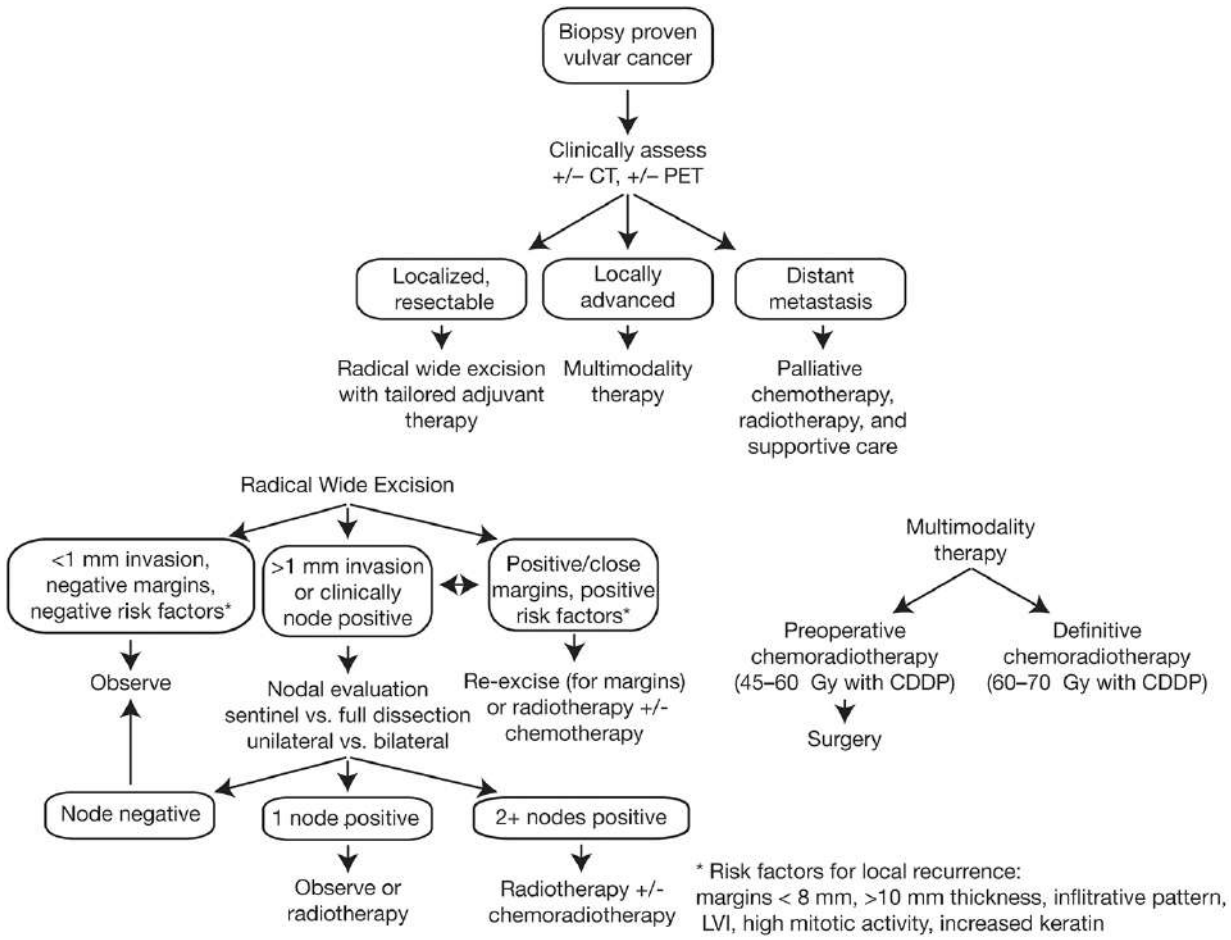


FIGURE 81.5 Cancer of the vulva treatment algorithm. CDDP, cisplatin; CT, computed tomography; LVI, lymphatic-vascular invasion; PET, positron emission tomography.

SURGERY

Wide Local Excision, Radical Vulvectomy, Exenteration

In the past, even patients with early-stage IB disease were considered to have diffuse disease, and a radical vulvectomy was considered the standard of care, yielding 90% survival rates but with considerable long-term sequelae. While there is a lack of prospective data comparing radical local excisions versus more extensive radical vulvectomies, several retrospective studies reveal no difference in recurrence or survival outcomes.[73] For T1 and smaller T2 lesions (<4 cm) with 1 mm or less invasion, a wide local excision is recommended without inguinofemoral node evaluation, given the risk of nodal involvement in these cases is less than 1%.[74] For tumors with greater than 1 mm invasion, an inguinofemoral groin node evaluation is recommended. If these tumors are well lateralized (>2 cm from the midline), only an ipsilateral groin evaluation is necessary; however, for midline lesions, bilateral groin node evaluation is recommended.

At surgical resection, the depth of the excision should be to the deep perineal fascia or periosteum of the pubis for more anterior lesions. Excision of 2-cm margins of grossly normal-appearing tissue is recommended when possible, with a goal of obtaining at least 1-cm microscopic margins in fresh tissue, and greater than 8 mm following tissue processing. If the tumor involves or abuts the clitoris, preservation of this structure may not be possible. Positive margins can also be considered for reresection, if there are no other indications for postoperative therapy, and critical structures can be preserved.

Radical vulvectomy is reserved for patients with large or multifocal lesions in whom preservation of normal vulvar tissue is not possible or would not serve a functional or reconstructive benefit. When the anus, vagina, or urethra is involved by malignancy, extended radical vulvectomy or pelvic exenteration is required to clear the disease surgically.[75,76] However, surgery alone for patients with advanced disease yields disappointing long-term results, stimulating interest in multimodality treatment in the mid- to late 1980s.[77,78]

Surgical Evaluation of Inguinofemoral Lymph Nodes

Attention to risk factors for nodal involvement is critical as inguinal recurrences are very difficult to treat and a full inguinofemoral node dissection can be morbid. The main complications of groin surgery are wound breakdown, infection, and lower extremity lymphedema. Although wound breakdown will often heal successfully by secondary intention, chronic lower extremity edema is very difficult to deal with and can lead to significant disability. To reduce the frequency and severity of these complications, efforts have been made to identify patients in whom the extent of the node dissection can be decreased or eliminated altogether without compromising the likelihood of control of the disease.

As mentioned previously, patients with small (<2 cm diameter) superficial squamous cell carcinomas with a DOI 1 mm or less and no lymph vascular invasion have a very low risk of nodal involvement, and the groin dissection may be omitted.[79] For lesions with greater than 1-mm invasion, groin node assessment should be performed in the form of superficial inguinal lymphadenectomy or sentinel node procedure. Small (<4 cm), lateralized lesions (>2 cm from the midline) may be treated by unilateral groin evaluation, whereas for midline and clitoral lesions, both groins should be assessed. For patients undergoing primary surgery, palpable inguinal nodes should be removed if present.

The need to perform bilateral inguinal node dissection in patients with unilateral vulvar lesions, as well as the need to dissect the deep nodes whenever a superficial node dissection is carried out, has been reexamined in light of the additive morbidity of each procedure. When bilateral superficial and deep inguinal node dissections are

performed, the potential for wound breakdown and lower extremity lymphedema increases. When a unilateral dissection is indicated and nodes are found to be negative, a contralateral node dissection is not required due to the low likelihood of contralateral metastasis.[80,81] The deep inguinal node dissection is usually omitted, based on the fact that if the superficial nodes are free of tumor, the deep nodes are rarely involved.[82] However, control of the disease in the LNs is of utmost importance as groin recurrences can be difficult to treat.[83]

Women with fixed or ulcerated inguinal nodes are rarely curable with surgery alone. These patients should have a biopsy to document the nodal involvement and should be treated with combined radiation and chemotherapy, either primarily or in a preoperative manner as discussed later.

Sentinel Lymph Node Dissection

Sentinel nodal procedures have become a standard of care for the assessment of inguinal disease. In the multicenter Groningen International Study on Sentinel Nodes in Vulvar Cancer (GROINSS-V), a sentinel node procedure using radioactive tracer and blue dye was performed in 623 groins and resulted in a 2.3% groin recurrence rate following a negative sentinel node.[84] This compares favorably to the 5% ipsilateral groin recurrence rate following negative full superficial inguinal dissection in a prospective GOG study of low-risk vulvar cancer.[83] Patients who underwent a sentinel node dissection had significantly lower groin wound breakdown when compared to full dissections (12% vs 34%). Long-term follow-up of the GROINSS-V trial demonstrated 5- and 10-year overall recurrence rates of 24.6% and 36.4% for sentinel node–negative patients versus 33.2% and 46.4% in patients who had positive sentinel nodes with subsequent completion inguinofemoral node dissection.[85] Optimal lesions for sentinel node procedures are those with small (<4 cm) unifocal lesions. If a sentinel node approach is undertaken, it is recommended that the sentinel nodes be evaluated prior to vulvar resection to avoid disruption of lymphatic channels emanating from the tumor. If no sentinel node is found, a full inguinofemoral lymphadenectomy is still recommended.

The GOG 88 protocol tested whether RT alone could supplant nodal dissections after vulvectomy.[86] Women with clinically negative nodes after radical vulvectomy were randomized between 50 Gy to the bilateral inguinal regions or an LN dissection with selective radiation delivered to those with positive nodes. The radiation-alone arm had increased recurrences within the inguinal regions (at 2 years: 32% RT alone vs 6% nodal dissection, $P = .033$), with an associated decrement in OS (59% RT alone vs 90% nodal dissection, $P = .035$). A critique of this trial is whether the prescribed radiation treatment depth to the inguinal nodes provided adequate coverage, which may have accounted for the difference in local control and

survival.[87] Ultimately, the study does suggest that 50 Gy alone is not sufficient for elective control of subclinical nodal disease.

Intraoperative diagnosis of inguinal node metastasis necessitates further diagnostic or therapeutic procedures. The GROINSS-V II/GOG 270 study evaluated inguinofemoral RT versus inguinofemoral lymphadenectomy in patients with vulvar cancer and a metastatic sentinel LN.[88] Among patients with sentinel node micrometastases (≤2 mm) who received inguinofemoral RT, the ipsilateral isolated groin recurrent rate was 1.6% at 2 years. Among those with sentinel node macrometastases (>2 mm) or ECE, isolated groin recurrences remained unacceptably high, with a rate of 22% with RT versus 6.9% with completion inguinofemoral lymphadenopathy. Thus, similar to GOG 88, 50 Gy alone is not a safe alternative to inguinofemoral lymphadenectomy in patients with sentinel node macrometastases. Drawing on the response rates seen in locally advanced vulvar cancers with combination chemoradiation, the ongoing GROINSS-V III study is evaluating the safety of replacing inguinofemoral lymphadenectomy with a higher dose of 56 Gy and concurrent weekly cisplatin for early-stage vulvar cancer with sentinel node macrometastasis (>2 mm) and/or ECE.

Pelvic Lymph Nodes

Patients with clinically or pathologically positive groin nodes are at risk for having contralateral groin and pelvic nodal involvement. Thus, the status of the groin nodes is to be taken into consideration when determining the management of the pelvic nodes. Radiation to the pelvic nodes is generally preferred to surgery as women in need of treatment to the pelvis often also require radiation to the primary and/or inguinal nodes.

ADJUVANT RADIATION THERAPY

In the setting of early invasive disease treated with wide local excision, radiation to the tumor bed may be advised to prevent local recurrence. More modern series have highlighted the importance of local control at the primary site, including the long-term follow-up GROINSS-V I data that demonstrated a significant detriment to disease-specific survival at 10 years in the case of vulvar local recurrence (90.4% vs 68.7%).[85] As noted previously, pathologic features associated with higher risk of local recurrence at the primary site include lymphatic-vascular invasion (LVI), DOI greater than 5 mm, margins less than 8 mm, and microscopically positive margins.[59] Faul et al reported a retrospective study of 62 patients with close (≤8 mm) or positive surgical margins and found that local recurrence was significantly reduced from 58% with observation to 16% with postoperative radiation.[60] Although postoperative radiation reduces the incidence of local recurrence, some may be successfully treated

with repeat surgery or chemoradiation. In the absence of randomized trials, women with positive margins, margins less than 8 mm, deep invasion, and/or LVI should be considered for adjuvant radiation in a multidisciplinary discussion.

The role of radiation in the management of inguinal and pelvic nodes was evaluated in the GOG 37 trial reported in 1986.[51] In this trial, women underwent bilateral inguinal lymphadenectomy, and those with positive groin nodes were randomized to either pelvic lymphadenectomy or radiation to the pelvis and bilateral groins. The radiation group had significantly lower groin recurrence rate of 5%, compared to 24% for the group that did not receive radiation. This translated into a 2-year significant survival benefit of 68% versus 54% ($P = .03$) in favor of the group that received postoperative radiation. Subgroup analysis of this study identified that the benefit was seen primarily in patients with more than one pathologically positive node. An update of this trial suggested that if the ratio of involved nodes to submitted nodes was more than 20%, there were increased rates of contralateral LN metastases, relapse, and cancer-related death. This suggests that more than 20% positive inguinal nodes may be an alternative definition of a cohort that may benefit from radiation.[89] An analysis of the Surveillance, Epidemiology, and End Results databases in patients with one node positive revealed a significant survival difference in patients with less than 12 nodes submitted, supporting the hypothesis that the benefit of radiation may be greater in patients with an insufficient nodal dissection.[90] However, based on the entry criteria for the GOG 37 study, adjuvant radiation to the pelvis and both groins can be considered for all patients with nodal involvement.

All women with ECE of tumor in the nodes or with residual disease in the inguinal areas should receive postoperative radiation to the pelvis and inguinal areas, due to the increased risk of recurrence at the primary site and the LNs.[57] When the surgical margins are clear and there is no pathologic indication to treat the vulva, vulvar sparing to avoid acute and late effects is controversial. A series from Dusenberry et al found the probability of vulvar recurrence to be 48% when the vulva was excluded. In contrast, the vulvar recurrence rates in GOG 37 and GOG 88, where the vulva was similarly excluded from the treatment field, were only 4% to 9%.[51,86,91] Given these conflicting data, vulvar sparing should be carefully considered, balancing the risks of recurrence versus acute and late effects.

Historically, adjuvant radiation to the primary site was delivered with either photons or en face electrons with bolus. When treating a large area of the vulva and groins, anteroposterior/ posteroanterior (AP/PA) photon fields were previously used. However, in modern practice, IMRT has become the preferred method of delivery. There is now sufficient data suggesting the use of IMRT may be equally effective with much less morbidity. This delivery approach has also allowed for further dose escalation, associated with increased response rates while mitigating toxicity.[72,92]

Further details in regard to treatment planning may be found later in the chapter. The elective volume (grossly uninvolved nodal basins) can be treated to 45 to 50.4 Gy. When microscopic disease in the primary tumor area is suspected, a dose of greater than 56 Gy is recommended.[93] When there is ECE of tumor in the LNs, the dose to the groins can be carried up to 60 Gy. If there is gross residual disease postsurgery, the dose to the area should be brought to a minimum of 65 to 70 Gy, as for definitive therapy.

The GOG 37 study required treatment to both groins; however, in the dissection arm of GOG 88, only the ipsilateral groin and hemipelvis were treated, suggesting that with well-lateralized lesions, ipsilateral-only treatment may be effective. In a small series of 20 women undergoing ipsilateral radiation alone (44 Gy in 2 Gy fractions), no contralateral recurrences were observed.[94] In fact, although there were no contralateral recurrences, the *ipsilateral* recurrence rate was quite high (45% crude rate), suggesting that 44 Gy is an insufficient dose. The decision to treat unilateral or bilateral groin/pelvis remains an active clinical question with the current GROINSS-VIII study, which offers ipsilateral groin and pelvic RT. For well-lateralized, low-risk lesions unilateral radiation may be appropriate in the postoperative setting.

The use of adjuvant chemotherapy with RT, either sequentially or concurrent, has not been tested prospectively. A National Cancer Database (NCDB) study found that adjuvant chemotherapy has been used more frequently since 1999 (11% in 1998 to 41% in 2006) and that the use of chemotherapy was associated with improved OS (hazard ratio [HR] 0.62, 95% confidence interval 0.48-0.79).[95] In extrapolation from cervix cancer, the most common concurrent regimen is cisplatin at 40 mg/m^2 weekly for women with higher risk of recurrence (≥2 nodes positive). However, in lack of higher quality evidence, the use of chemotherapy in this setting remains controversial.

PREOPERATIVE RADIATION THERAPY WITH CONCURRENT CHEMOTHERAPY

For locally advanced vulvar cancer, multimodality therapies have become the standard of care.[96] When a preoperative approach is used, after concurrent chemoradiation is complete, the response to the therapy at the primary site and the LN is assessed. If there is complete clinical regression of the disease at the site of the primary, one option is to perform biopsies of the primary site, foregoing resection if there is a pathologic complete response (pCR).[97] In the case of persistent clinical or pathologic disease, vulvectomy with or without nodal dissection is considered if possible.

Preoperative chemoradiation was tested in the phase II GOG 101 trial for patients with advanced primary and/or nodal disease.[96,97] Radiation treatment consisted of 170 cGy twice daily on days 1 to 4 and 170 cGy once a day on day 5 and days 8 to 12, for a dose of 2,380 cGy. Cisplatin, 50 mg/m^2, was given on day 1, and 5-fluorouracil (5-FU), 1,000 mg/m^2 by a 24-hour infusion, daily on days 1 to 4. The combined cycle of chemotherapy and radiation was repeated after a 2-week break, thus delivering a total radiation dose of 4,760 cGy. In the locally advanced cohort, the pCR rate was 34% and R0 resections were possible in 77% of subjects. In all, 55% were alive and without disease at the last follow-up. In the group of women with advanced nodal disease, the nodes became resectable in 83%, with a pCR rate of 40% in those who underwent surgery, with 43% of the patients being alive and disease free at the last follow-up.

The follow-up phase II GOG 205 study enrolled women with T3 or T4 tumors, treated with a total dose of 5,760 cGy (180 cGy/fraction) and weekly cisplatin (40 mg/m^2), with no planned treatment breaks.[98] In all, 69% of women were able to complete the protocol per plan, 64% achieved a complete response, and 50% had a pCR. OS at 2 years (estimated from curves provided in the manuscript) was 40% for those with no or partial clinical response, 62% for those with a complete clinical response, and 81% for those with a pCR.

GOG 279 was recently reported, utilizing a combination of gemcitabine at 50 mg/m^2 and cisplatin at 40 mg/m^2 weekly with IMRT.[72] The vulva was treated to 64 Gy, with varying groin doses according to LN status. The reported pCR rate of 73.1% and CCR rate of 71.2% was superior to prior GOG studies. The progression-free survival (PFS) rate at 12 months was 74%. It is uncertain if these encouraging results were a result of a higher radiation dose (64 Gy), better radiation delivery (via IMRT), the addition of gemcitabine, or a combination of these factors. Final publication of this trial is pending as of this writing, but this treatment protocol is likely to become part of the standard of care.

DEFINITIVE RADIATION THERAPY

The standard of care for early lesions is surgical resection; however, selected patients with small central lesions may be considered for definitive radiation, particularly when the lesions are in close proximity to the urethra, clitoris, or anus. There are few published series of radiation alone used as definitive therapy for vulvar cancer.[99-101] The reported series include patients with recurrent disease postsurgery and patients who are not medically suitable for surgery or have declined it. In Ellis's series of 65 patients treated with BT and or external beam, the crude 5-year survival rate was 23%, with crude local control in 40%.[99] Slevin and Pointon reported on the results of 58 patients treated also with BT and/or external beam, depending on the extent of the

disease.[101] The crude 5-year survival rate was 26% with a similar local control rate of 40%. These series reflect the difficulty of achieving appropriate curative doses for gross disease with radiation alone in the pre-IMRT era.

BT has been used for inoperable vulvar cancer and as a boost to the primary tumor and/or to the LNs. The efficacy of this treatment is difficult to evaluate due to small numbers and heterogeneity in the reported populations. A series from the Centre Alexis Vautrin Institute in France describes 34 patients, 21 with primary and 13 with recurrent disease, treated with BT only.[100] The median dose was 60 Gy, with a range of 53 to 88 Gy. In the group of 21 patients who underwent BT as primary treatment, 3 patients developed locoregional recurrence, for a 5-year local control rate of 80% and a disease-specific survival of 70%. In the group of 13 patients who were treated for recurrence, 8 developed local recurrence, with or without disease at other sites, for a local control rate of 19%. Of the entire group of 34 patients, 5 developed vulvar necrosis. This relatively low complication rate most likely reflects that extensive experience and high quality of the BT carried out in this institution. Similarly, Tata Memorial published on their institutional outcomes with high-dose rate BT for vulvar cancer. Treatment was delivered at 3.4 to 4 Gy per fraction at 2 fractions per day at least 6 hours apart to a total of 4 to 5 fractions as boost or 10 to 13 fractions if BT monotherapy alone. Five-year local control rate for the entire cohort was 77%: 100% for patients treated with radical BT and 68% for those treated with the combination of external beam radiation therapy (EBRT) and interstitial BT boost. The 5-year disease-free survival (DFS) and OS for the entire group were 51% and 82%, respectively, with the data favoring better DFS and OS outcomes for those treated with radical BT as compared to combination EBRT and BT boost. Nonetheless, due to the risk of necrosis, the use of BT should be limited to selected cases and performed by experienced practitioners.

DEFINITIVE CHEMORADIATION THERAPY

Definitive chemoradiation is used for patients with advanced tumors considered unresectable at presentation or for patients who are medically inoperable (Table 81.4). This may be used when the tumor does not become resectable in the midst of preoperative-intent chemoradiation or as an upfront alternative to surgically based treatment. Elective pelvic and inguinal volumes are treated to 45 to 50.4 Gy, while the primary and involved nodes are boosted to 60 to 70 Gy. The total dose to certain areas is dependent upon the location and extent or bulk of the disease, the response to the therapy, and the estimated tolerance of the area requiring the high radiation dose. Often, it is the tolerance of normal tissue that limits the dose to 65 or less to 70 Gy. The use of simultaneous integrated boosts to the primary should be used with caution due to the risk of vulvar necrosis. Selected patients at low risk of having nodal

involvement (<1 mm invasion, or negative LN dissection or sentinel node biopsy) may be treated to the vulvar area alone. Bolus material should be used also to avoid underdosing the surface of the tumor.

TABLE 81.4 STUDIES OF CONCURRENT RADIATION AND COMBINATION CHEMOTHERAPY AS PRIMARY TREATMENT FOR ADVANCED VULVAR CANCER

Authors	Number of Patients	Chemotherapy	Radiation Therapy Dose (Gy)	Number of Posttreatment Surgeries	Median and Range of Follow-Up (month)	Clinical Complete Response (%)	Clinical Outcome (%)
Moore et al[98]	58	P	57.6	34	NS	64	NS
Mak et al[102]	16	P	50	4	32	60	62 (2 y DFS)
Mak et al[102]	28	F + P/M	55	6	32	58	56 (2 y DFS)
Tans et al[140]	28[a]	F + M	60	NS	42	72[a]	71[a] (4 y PFS)
Beriwal et al[109]	42	P ± F	46.4	33	29	51	66 (3 y LC)
Montana et al[96]	46	F + P	47.6	38	78 (56-89)	NS	54 (crude NED)
Moore et al[97]	71	F + P	47.6	64	45	48	63 (crude NED)
Landoni et al[141]	58[a]	F + M	54	42	(4-48)	27[a]	49[a] (crude NED)
Lupi et al[142]	24	F + M	54	22	34 (22-73)	42	55 (5 y OS)
Wahlen et al[143]	19	F ± M	45-50	6	(3-67)	53	89 (5 y DSS)
Sebag-Montefiore et al[144]	37	F + M	45	14	NS	47	37 (2 y OS)
Koh et al[145]	17	F ± P/M	54	10	(1-75)	53	49 (5 y DSS)
Russell et al[132]	18	F + P	46.8-72	1	24 (2-52)	89	75 (crude NED)

Authors	Number of Patients	Chemotherapy	Radiation Therapy Dose (Gy)	Number of Posttreatment Surgeries	Median and Range of Follow-Up (month)	Clinical Complete Response (%)	Clinical Outcome (%)
Natesan et al[146]	25	P ± F/M	64	3 (recurrence only)	26	NS	71 (3 y OS) 65 (3 y LC)

DFS, disease-free survival; DSS, disease-specific survival; F, 5-fluorouracil; M, mitomycin-C; NS, not stated; NED, no evidence of disease; OS, overall survival; P, cisplatin; PFS, progression-free survival.
[a]Includes patients treated for recurrent disease.

There are no prospective comparative trials for chemotherapy selection with concurrent treatment; however, a retrospective series from Dana-Farber/Brigham and Women's Cancer Center and Massachusetts General Hospital does shed some light.[102] In this series of 44 women, 24 of whom were treated definitively without surgery, 16 received weekly platinum-based regimens and 28 received a 5-FU–based regimen every 3 to 4 weeks. The 2-year OS (74% platinum, 70% 5-FU), DFS (62% platinum, 56% 5-FU), and locoregional recurrence (31% platinum, 33% 5-FU) were not significantly different. The grade 3 or higher skin toxicity was higher with weekly platinum (62% platinum, 32% 5-FU), but the nonskin toxicity was higher with 5-FU (13% platinum, 46% 5-FU). Given these data and the positive results of GOG 205 (discussed earlier), weekly cisplatin at 40 mg/m^2 is a reasonable option for concurrent treatment.[98] Pending the publication of GOG 279, it remains uncertain if a new standard will be established with combination of cisplatin and gemcitabine.

There are no prospective data comparing chemoradiotherapy alone and combined with surgery; however, an NCDB study has examined survival after both strategies have been reported.[103] In the overall cohort, women undergoing primary radiation had OS at 3 years of 42% compared to 57% with radiation plus surgery. However, when limiting the definitive cohort to those who received concurrent chemotherapy and radiation to doses greater than 55 Gy, the survival was 57%, comparable to preoperative approaches. While there are multiple possible confounders that affect NCDB analyses, this suggests that initial radiation and concurrent chemotherapy may be considered, with surgery reserved for persistent or recurrent disease.

TREATMENT VOLUME AND TECHNIQUE

Simulation and Target Delineation

Appropriate identification of the targets of treatment is a challenging but critical process in vulvar cancer. CT- or MR-based three-dimensional planning is essential to establish the location, extent, and depth of the inguinal and pelvic nodal basins, as well as the primary site.

At the time of simulation, markers should be placed on the primary site, the LNs, and scars from previous surgery to document the extent of the disease. “Frog-leg” positioning may be used to reduce skin folds in the inguinal regions, though this may be less important if IMRT is used. Radio-opaque markers at natural anatomic landmarks such as the introitus and anus may also be useful in outlining treatment fields. Advanced immobilization devices such as a cradle can be considered, though, for some, the cradle itself may become uncomfortable during treatment due to the expected skin reaction. Bubble wrap or bariatric slings may also be used to reduce skin folds, particularly in patients with a pronounced panniculus. Bolus is often critical over the vulva and groins, which may be applied at the time of simulation, or applied “virtually” at the time of treatment planning. Obtaining good contact against the skin at all points to eliminate significant air gap is challenging but critical. The use of wet gauze, towels, or impregnated gauze may be necessary. Placement of bolus should be confirmed at the time of treatment, either through direct inspection of setup or through the use of onboard imaging such as a cone-beam CT. Verification of dose at the surface is also an important evaluation and can be achieved with dosimeters such as OSLDs (optically stimulated luminescent dosimiters) or TLDs (thermoluminescent dosimeters) at the start of treatment.

The primary vulvar lesion (primary gross tumor volume) may be hard to identify on CT imaging alone, making the use of radio-opaque markers critical. MRI and PET imaging, if available, may also aid in the identification of the primary lesion. When defining a primary planning target volume (PTV), ample margins (1.5-2 cm) should be placed to account for microscopic spread of disease and the potential variations in daily setup. Additional clinical tumor volume (CTV) coverage of the vagina should be added for lesions that involve the introitus or distal vagina. The uterus, if present, is not usually targeted.

The nodal targets include the inguinal basins, which should be defined based on anatomic compartment; symmetric margins around the vessels are inadequate, leading to undertreatment medially and overtreatment to deep structures (Figure 81.6).[104] This compartment is defined by:

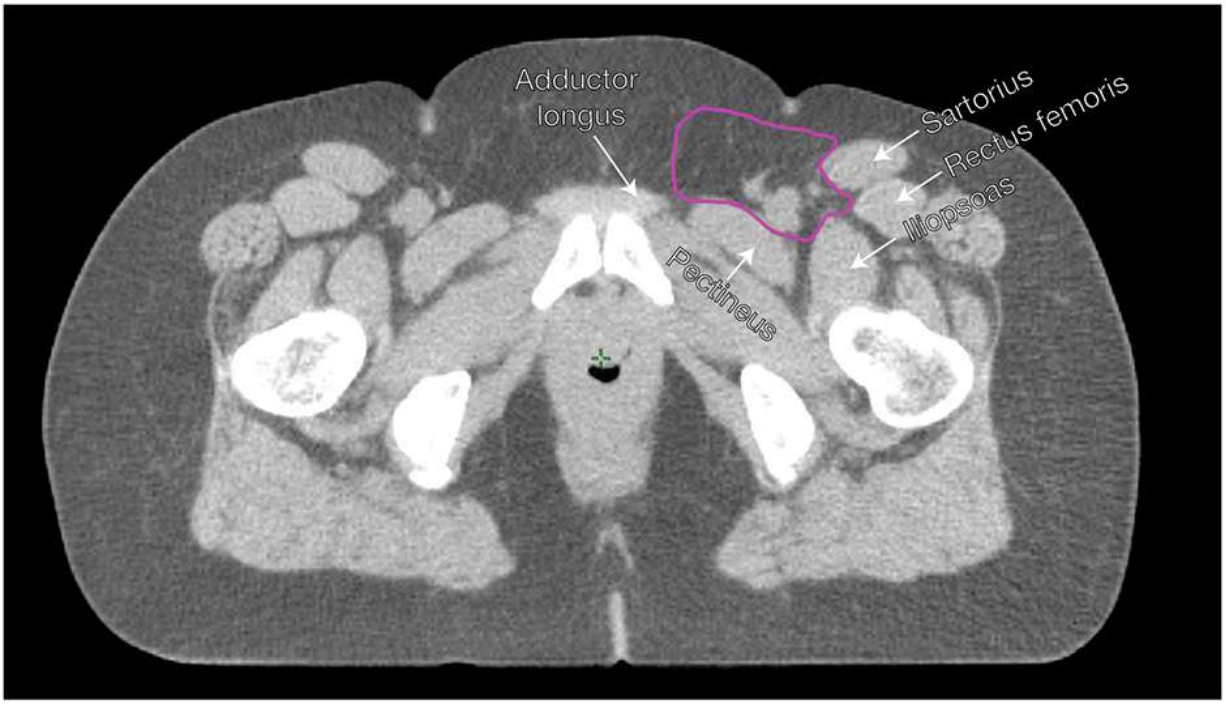


FIGURE 81.6 Example of a clinical tumor volume (CTV) for inguinal treatment (purple contour). The lateral border is the medial edge of the iliopsoas. The medial border is the lateral extent of the adductor longus or medial end of pectineus. The posterior border is bounded by the iliopsoas muscle laterally and anterior aspect of the pectineus muscle medially. The Anterior border is carried over from the anterior edge of sartorius muscle. All benign-appearing nodes also should be included, and the inferior extent should extend 1 to 2 cm below the vulva and perineum.

Lateral: The medial border of the iliopsoas

Medial: The lateral border of adductor longus or medial end of pectineus

Posterior: The iliopsoas muscle laterally and anterior aspect of the pectineus muscle medially

Anterior: The anterior edge of sartorius muscle

The pelvic nodes are often also targets of treatment and include the obturator, external, and internal iliac chains, defined in a manner similar to uterine or cervical disease. Common iliac nodes or para-aortic basins may be added if there are nodes positive in the more distal pelvic echelons. Presacral basins are usually not target, unless there is involvement of the anal canal or rectum. Consensus contours are now available to guide treatment and may be very helpful, particularly when more conformal techniques such as IMRT are used.[105]

Historical Two- and Three-Dimensional Conformal Treatments and the Transition to Intensity-Modulated Radiation Therapy

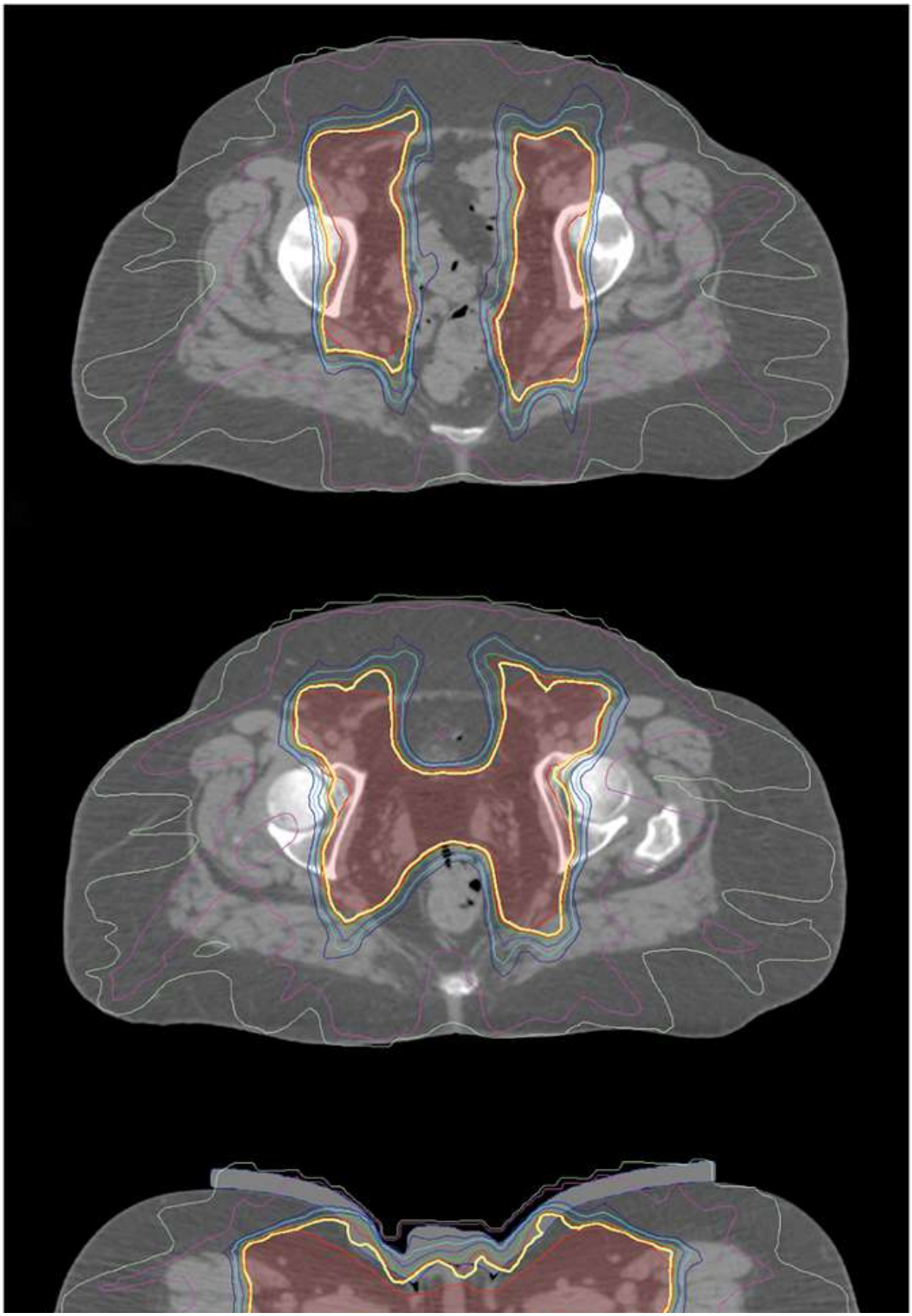
IMRT has replaced 2D/3D delivery techniques in this disease site due to improved conformality and capacity for dose escalation. Historically, 2D/3D techniques employed an AP/PA beam arrangement in which a wider AP field was paired with a narrower PA field in order to encompass the inguinal LNs in the anterior approach, while allowing for traditional midline prescription of the pelvic nodal coverage using AP/PA beams. This technique would spare additional posterior dose to the femoral heads. The photon fields were weighted equally, and the inguinal dose was then supplemented by separate anterior electron patch fields, matched to the pelvic field.

A derivation of this method consisted of using an AP/PA approach to the primary and pelvis while utilizing anterior electron fields alone for the inguinal nodes. Although this approach had the advantage of a simpler treatment setup, ensuring adequate dose at the inguinal electron-photon match line could be challenging in the setting of gross nodal disease, and significant late skin changes were associated with electron fields carrying the entire dose.

Alternatively, a wide AP field was again paired with a narrow PA field, with a partial transmission block placed in the central portion of the AP field. The desired dose at a specified depth was delivered to the inguinal nodes through the AP field.[106] The degree of central anterior beam attenuation was calculated so that the midpoint of the pelvis received equal doses from the AP and PA beams. This technique eliminated the dosimetric problems of photon/electron field matching, as well as the potential for daily setup variation, but the design of a precise partial transmission block remained difficult.

A growing body of literature has supported the substitution of these techniques with IMRT.[107-109] Early in its adoption, Beriwal et al reported 15 patients treated with IMRT using a median of seven fields.[107] The CTV was defined as a 1- to 2-cm margin around bilateral external iliac, internal iliac, and inguinofemoral nodes, as well as a 1-cm margin around the entire vulvar region. Gross tumor was also expanded by 1 cm for the CTV. The planning treatment volume was defined as 1-cm margin beyond the CTV, and the prescription dose was 43 to 48 Gy for preoperative treatment and 50 Gy for postoperative treatment, delivered partly on a twice-daily schedule. This early experience yielded excellent clinical response, with 13 of 15 patients having no evidence of disease at the last follow-up. This technique also resulted in improved dose conformality and lower doses to normal structures, including rectum, bladder, small bowel, and femoral heads. The most recent update of this series found a pCR rate of 48%, 3-year OS of 61%, and 3-year local recurrence-free survival of 66%.[109] These results were comparable to the GOG 101 results and resulted in less acute skin toxicity than 2D or 3D techniques. IMRT was prospectively allowed on the GOG 279 trial, allowing dose escalation to 64 Gy with cisplatin and gemcitabine, resulting in a pCR of 73.1%, confirming the benefits of this approach.[72]

Careful quality assurance is required when using IMRT. In particular, care should be placed to ensure that the surface of the vulvar tumor receives adequate dose. This may be accomplished by creating a “virtual flash” during treatment planning, where the PTV is expanded out of the skin by 1 to 2 cm, with additional placement of virtual tissue equivalent to allow for dose buildup. This protects against underdosing the tumor surface if there is superior displacement of the patient during treatment. Again, placement of thermoluminescent dosimetry chips or similar in the inguinal and perineal regions is recommended to confirm adequate dose to the skin and target areas (Figure 81.7).



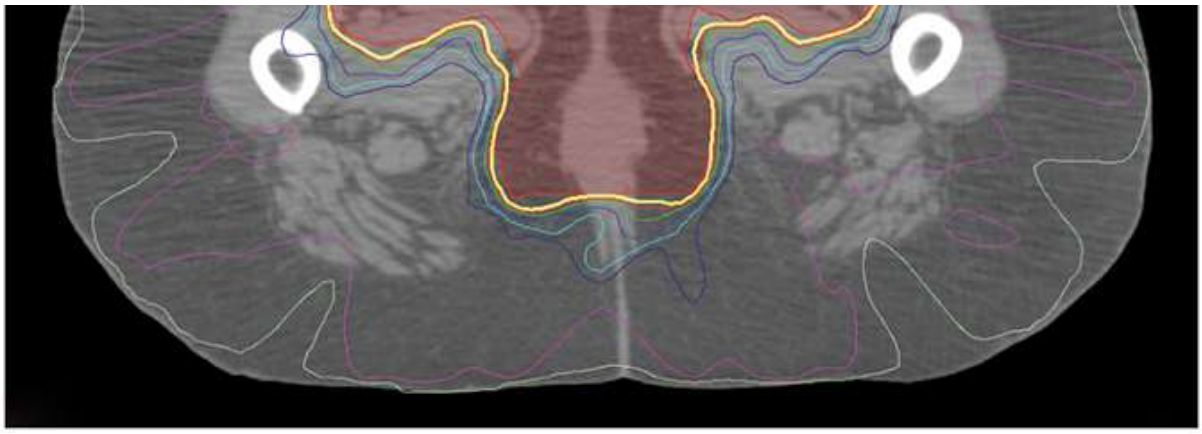


FIGURE 81.7 Intensity-modulated radiation therapy for vulvar cancer. This patient had a lesion of the posterior portion of the labia minora, involving the fourchette and the distal vagina. Three axial views are shown of the conformality of the 100% isodose line (yellow) and the planning treatment volume contour (shaded red volume). The central dose in the middle axial level is the superior margin for the vagina, added in this case due to the distal vaginal involvement.

Border definition is of understandable paramount in either delivery approach, with special attention paid to target delineation given the conformality that IMRT provides. External and internal iliac nodal coverage would correspond to a superior border along the middle of the sacroiliac joints with a 2D technique. However, if the patient has internal or external iliac node involvement, the superior border should be raised to the L3/L4 interspace to provide coverage to the common iliac nodes. Inferior borders should cover the entirety of the vulva and the most superficial inferior inguinal nodes. Laterally, the pelvic field would extend 2 cm laterally using 2D/3D techniques in order to encompass the widest point of the pelvic inlet. Although there are no data regarding scar recurrences, it is common practice to include the inguinal node dissection scars in the radiation field.

CHEMOTHERAPY

The use of chemotherapy alone is usually reserved for patients having advanced, inoperable, or recurrent disease. Even in the setting of advanced distant disease, however, radiation is often recommended for locoregional control and/or palliation of symptoms. With regard to systemic therapy as monotherapy for stage IV disease beyond the pelvis, there are limited data, given the rarity of this tumor type. Many of the recommended treatment regimens are in extrapolation from regimens studied in advanced cervical cancer, and reports of treatment regimens are generally small, single-institution studies. Current common treatment regimens include cisplatin and paclitaxel combination therapies. To date, there is no standard systemic therapy regimen for those with advanced, metastatic, or recurrent disease.

Single-Agent Chemotherapy

There is limited experience with single-agent chemotherapy for the treatment of vulvar cancer (Table 81.5). The single agents cisplatin, piperazinedione, mitoxantrone, and etoposide have all been evaluated prospectively by the GOG with disappointing results.[110-112] In a prospective study of patients with stage III/IV disease, single-agent adjuvant cisplatin resulted in 3-year OS and PFS rates of 86% and 71%, respectively; however, this was in fully resected patients.[113] Paclitaxel has moderate activity, with a 14% response rate described in a phase II trial of the European Organisation for Radiation Therapy and Chemotherapy (EORTC).[53]

TABLE 81.5 CHEMOTHERAPY FOR VULVAR CANCER

Authors	Number of Patients	Regimen	Partial Response (Number of Patients)	Complete Response (Number of Patients)
Geisler et al[120]	9	FP	5	4
	3	P	0	0
Wagenaar et al[116]	25	BMC	12	2
Durrant et al[115]	31	BMC	15	3
Benedetti-Panici et al[117]	21	PBM	Tumor, 2 Node, 3	Tumor, 0 Node, 11
Belinson et al[147]	3	BOMP	0	0

BMC, bleomycin, methotrexate, CCNU; BOMP, bleomycin, vincristine, mitomycin-C, cisplatin; FP, 5-fluorouracil, cisplatin; P, cisplatin; PBM, cisplatin, bleomycin, methotrexate.

Multiagent Regimens

Combination chemotherapy regimens have previously included bleomycin, which is associated with considerable pulmonary toxicity.[114] The Gynecological Cancer Cooperative Group of the EORTC conducted two phase II studies using neoadjuvant regimens of bleomycin, vincristine, mitomycin-C, and cisplatin and bleomycin, methotrexate, and lomustine.[115,116] The overall response rate (ORR) was between 55% and 65%, with a complete response rate of 8% to 11%. Unfortunately, the toxicity was high with treatment-related death in four (7.5%) patients and frequent withdrawals due to toxicity. A group of prospective studies evaluated cisplatin, bleomycin, and methotrexate in the neoadjuvant setting and reported a 10% response rate for the primary tumor but a 67% response rate for nodal disease after two cycles of treatment.[117] A more recent multicenter study evaluated cisplatin-based neoadjuvant chemotherapy in patients with locally advanced vulvar cancer and

reported a 5-year survival rate of 92%.[118] Compared to bleomycin-containing regimens, cisplatin may exhibit improved response rates and reduced toxicity.

In other small series, combinations of cisplatin with a second agent such as vinorelbine or 5-FU showed significant activity.[119,120] In a small report of neoadjuvant chemotherapy with cisplatin and 5-FU, at least a partial response was observed in all 10 patients. Of interest, three patients were treated with cisplatin alone in the same series with no responses.[120]

Biologic Agents

Biomarker-directed therapy has increasingly become an area of focus for the management of vulvar cancers. PD-1 is an immune checkpoint protein that promotes antitumor activity, and many tumors overexpress PD-L1. KEYNOTE-158 was a phase 2 multicenter study of pembrolizumab monotherapy in patients with advanced solid tumors and included 101 patients with heavily pretreated vulvar squamous cell carcinoma.[121] The ORR was 10.9% among all patients with vulvar cancer, 9.5% among those with PD-L1–positive tumors, and 28.6% among those with PD-L1–negative tumors. The median duration of response was 20.4 months. Prospective biomarker analyses of the KETNOTE-158 study found that patients with a high tumor mutational burden or DNA mismatch repair deficiencies/microsatellite instability had a more robust response to pembrolizumab.[122,123] The efficacy of nivolumab, a PD-1 immune checkpoint inhibitor, was evaluated in five patients with recurrent or metastatic vaginal/vulvar cancer in the phase I/II CheckMate 358 trial. The ORR in the vaginal/vulvar cohort was 20.0%, with a median duration of response of 5.0 months.[124] Thus, immunotherapy may be useful for managing vulvar cancer and is subject to ongoing investigation.

The epidermal growth factor receptor (EGFR) is a tyrosine kinase overexpressed in many squamous cell carcinomas of the vulva.[125] Erlotinib, an EGFR inhibitor, was reported to have significant activity in a case report, leading to the development of a phase II trial of this agent for women with lesions amenable to surgery or chemoradiation (cohort 1) or metastatic measurable disease.[126] The overall clinical benefit rate was 67.5%, with 27.5% experiencing partial responses and 40% with stable disease. Responses, however, were of short duration. Rare but significant grade 3 to 4 toxicities included diarrhea/electrolyte abnormalities, ischemic colitis, and renal failure.[127] In one other case report, the EGFR inhibitor cetuximab elicited a partial response when administered in combination with cisplatin.[128] Further studies may elucidate the role of EGRF-targeted agents and other biologics in the treatment of this disease.

Bevacizumab was studied in combination with cisplatin/carboplatin and paclitaxel or topotecan in the GOG 240 study for metastatic and/or recurrent cervical cancer,

resulting in improved OS (HR, 0.77, P = .007).[129] While these regimens have not been studied prospectively in vulvar cancer, they have been incorporated into some vulvar cancer guidelines by analogy.

In conclusion, single-agent cisplatin shows activity against advanced vulvar cancer. Combination chemotherapy regimens, particularly those including cisplatin and 5-FU, yield improved response rates, but they are associated with significant toxicity. In the recurrent or metastatic setting, the choice of regimen requires consideration of single agents with modest activity and low toxicity versus combination regimens that carry both higher response and toxicity rates. Targeted therapies are increasingly being investigated and utilized for the treatment of vulvar cancer and may have a significant effect on the future of vulvar cancer management. They may also have a role in combination with RT in the perioperative or definitive settings; however, this is as of yet unstudied.

TREATMENT SEQUELAE

The adverse effects of treatment can be classified as acute or chronic and depend on the treatment modality or modalities used, as well as the intensity of the treatment. With early-stage disease and more limited surgery to the primary site, the acute surgical complications are often minor, such as the development of wound infection and hematomas. With more extensive surgery, the frequency and degree of the complications can be more significant. With single "longhorn" or "butterfly" incisions for bilateral inguinal lymphadenectomies and for resection of the primary lesions, wound infection, necrosis, and breakdown occurred in 50% to 85% of the cases. Since the use of separate incisions was adopted, the incidence of groin wound infection, necrosis, and breakdown has decreased to nearly 15%.[43,130] Other potential complications or surgery include wound infections, seromas, hemorrhage, deep vein thrombosis, pulmonary embolism, osteitis pubis, and loss of sensory perception in the anterior aspect of the thigh secondary to femoral nerve injury.

The most significant chronic surgical complication is edema of the lower extremities. Lymphedema is related to the extent of the lymphadenectomy, and it is, therefore, more likely to occur with a deep inguinal node dissection, with a risk of approximately 30%.[130,131] Lymphedema can be progressive and very difficult to manage. Early referral for physical therapy is indicated to prevent progression and stimulate regression of symptoms. Other chronic complications reported are chronic cellulitis of the inguinal areas, stenosis of the introitus, femoral hernias, and rectovaginal or rectoperineal fistulas.

The most significant acute morbidity of radiation, either alone or in combination with chemotherapy, is the mucocutaneous reaction in the vulva, perineum, and inguinal folds. The severity of the reaction depends upon the radiation fractionation

schema used and the type of chemotherapy employed. The degree of reaction may result in treatment interruptions; frequent assessments of the treatment area are necessary for early supportive interventions. Topical agents, such as zinc oxide preparations, may be helpful; however, these preparations must be off the skin during radiation treatment because they can exacerbate the skin reaction. Sitz baths with sodium bicarbonate may also aid in the cleansing and soothing of the affected skin. In cases with excessive moist desquamation, astringents such as aluminum acetate solution may be applied. Narcotic pain medications are often required in the final weeks of treatment.

Treatment of candidal infections with appropriate antifungal agents should be provided as required. These can mimic radiation-associated desquamation, and topical or oral agents (such as fluconazole) should be considered if the degree of desquamation is beyond that expected with the current accumulated dose. These may be more frequent in those receiving concurrent chemotherapy or steroids or are otherwise immune suppressed.

Acute hematologic toxicity is common and depends upon the type and intensity of the chemotherapy used. Decreased leukocytes may be managed well with colony-stimulating factors, and blood transfusions may be necessary for anemia. Chemotherapy dose adjustments or interruptions are sometimes required. Severe hematologic toxicity can lead to septicemia, with fatal consequences in some instances.[96,132]

The late complications of radiation include telangiectasias, atrophy of the skin and mucosa of the vulva, dryness of the vaginal/vulvar mucosa, and narrowing of the vaginal introitus. Avascular necrosis of the femoral head is possible, though rare. In the GOG combined-modality study for patients with advanced disease, only one patient developed avascular necrosis of the femoral head, even though the femoral heads were fully treated in the inguinal fields.[96] In this study, there were two instances of injury to the femoral artery. In one patient, necrosis of the femoral artery occurred immediately following surgery and was fatal. The second patient required femoral artery angioplasty.

Besides the generally recognized complications seen with surgery, radiation, and/or chemotherapy, the treatment of carcinoma of the vulva has significant psychosocial and sexual health consequences.[133] In a study by Andersen et al. of 42 patients, most of whom were treated with conservative surgery, with wide local excision in 32 patients and simple vulvectomy in 10, there was a 2- to 3-fold increase in the frequency of sexual dysfunction from the pretreatment level.[134] In this study, 30% of the patients were sexually inactive at follow-up. Andersen and Hacker also reported that vulvar surgery has a significant impact on sexual functioning and body image, even when intercourse remains possible.[135] As might be expected, after pelvic exenteration, patients also experience significant sexual dysfunction, even when a

neovagina is created. Ostomies necessitated by exenteration have a significant detrimental impact on quality of life.[136]

RT is also associated with sexual dysfunction due to narrowing of the introitus, vulvar edema, decreased vaginal lubrication, injury to the bulboclitoris, and premature menopause due to ovarian dose. While data specific to vulvar cancer are sparse, there is growing literature related to dysfunction after radiation for anal canal cancer.[137] The bulboclitoris is an erectile organ, which is a key anatomic structure for arousal and orgasm; proposals for sparing this organ have been proposed for anal canal cancer, though this is not feasible for vulvar cancers.[138] Dilator therapy to limit stenosis is indicated, similar to recommendations in uterine and cervical cancer, as well as early referral to sexual health physical therapy. Hormone replacement should also be offered as it is associated with improved sexual function when hormonal function is compromised by treatment.[139]

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PART J

Adrenal and Retroperitoneal Tumors

CHAPTER 82

Retroperitoneum

Meng Xu-Welliver, Eric D. Miller, Joel L. Mayerson, Brian A. Van Tine, and Jeffrey C. Buchsbaum

Primary tumors of the retroperitoneum are rare and account for 0.1% to 0.2% of all malignancies,[1-3] with up to 80% of lesions being malignant.[4] A retroperitoneal lesion was first reported by Morgagni in 1761 following an autopsy,[5] with additional work by Pack and Tabah demonstrating the variety of histologies that can originate from the retroperitoneum.[3] This chapter focuses on lesions that primarily arise from tissues in the retroperitoneum.

ANATOMY

The anatomy of the retroperitoneum has been described in detail by Burkill and Healy[6] and reviewed by Osman et al[7] and shown in Figure 82.1. In summary, the anterior border of the retroperitoneal compartment is the posterior parietal peritoneum, and the posterior border is the transversalis fascia. Superiorly, it extends to the diaphragm and inferiorly to the superior aspect of the pelvic diaphragm formed by the levator ani and coccygeus muscles. The retroperitoneum can be divided into three compartments: the anterior pararenal, the perirenal, and the posterior pararenal spaces. The anterior pararenal compartment is bordered anteriorly by the posterior parietal peritoneum, posteriorly by the anterior renal fascia, and laterally by the lateroconal fascia and contains the ascending and descending colon, the pancreas, and the second portion of the duodenum. The perirenal compartment is located between the anterior and posterior renal fascia and

contains the kidneys and adrenal glands. It is shaped like an inverted cone and superiorly abuts the bare liver on the right and the subdiaphragmatic space on the left. The posterior pararenal compartment is located between the posterior renal fascia and the transversalis fascia and contains fat without any visceral organs. Below the level of the kidneys, the anterior and posterior pararenal compartments combine to form the infrarenal retroperitoneal space, which communicates with the pelvis inferiorly.[4] The aorta and inferior vena cava are contained within the great vessel space that is a primarily fat-containing region immediately anterior to the vertebral bodies and psoas muscles.[4]

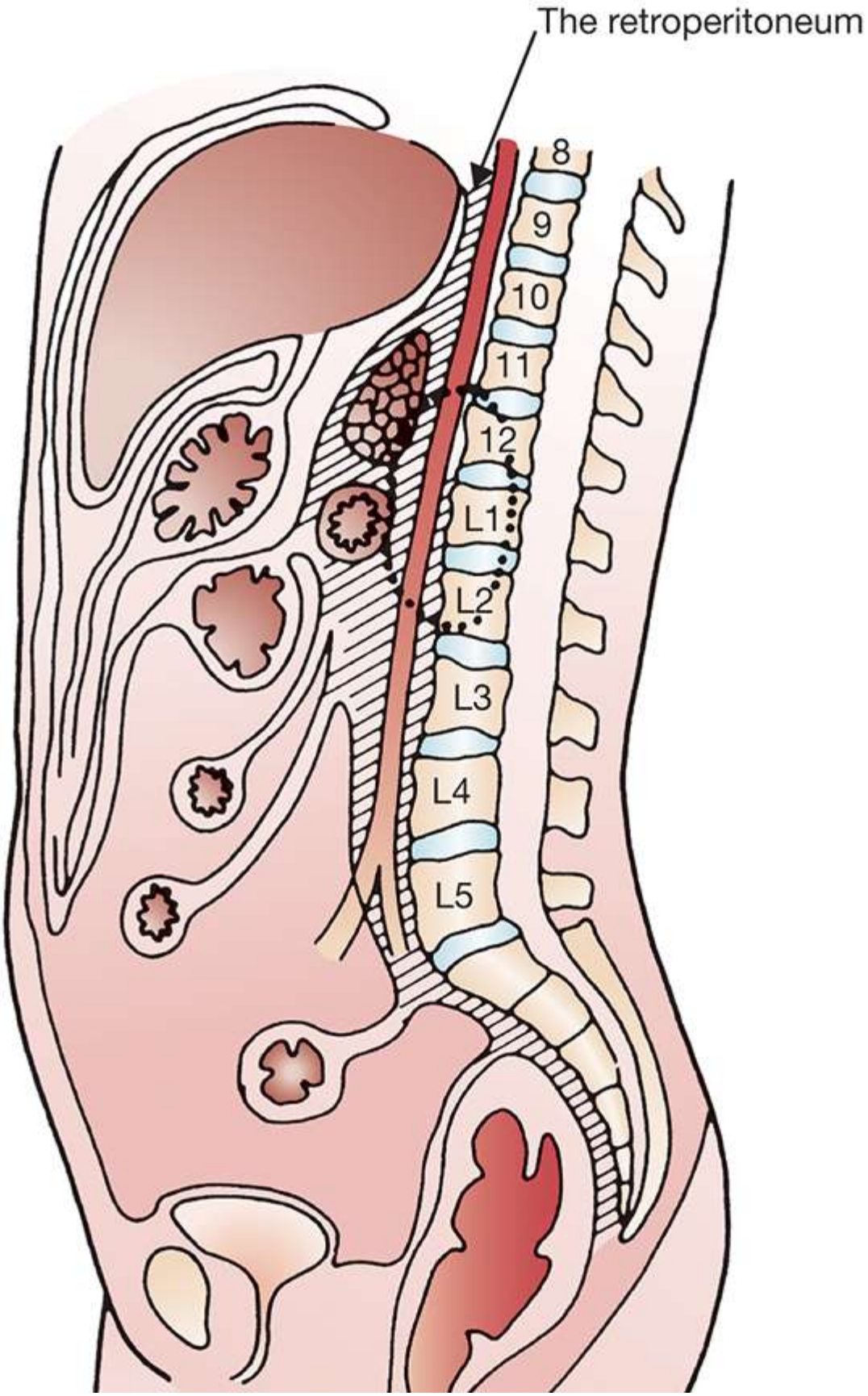
The retroperitoneum
8
9
10
11
12
L1
L2
L3
L4
L5

FIGURE 82.1 Sagittal view of trunk showing the retroperitoneal space (shaded area). The kidney is outlined by dots.

EPIDEMIOLOGY

The population incidence of retroperitoneal tumors is based on two population studies and is estimated to be 3 per million persons.[1,2] The age range of patients varied between 3 and 83 years, with half of the patients diagnosed between the ages of 60 and 80. There was no significant difference in frequency observed between males and females.[2]

The age at diagnosis of several large series of patients with primary retroperitoneal tumors is shown in Figure 82.2.[1-3,8,9] Two peak age periods are seen, with the first peak occurring during the first decade of life generally caused by neuroblastoma or germ cell tumors and a second peak occurring during the sixth decade generally caused by mesenchymal lesions. These histologies are outlined in Figure 82.3. Lawenda and Johnstone performed a comprehensive review of the Surveillance Epidemiology and End Results (SEER) public use registry focusing on retroperitoneal tumors.[10] As seen in the results of this review in Table 82.1, soft tissue sarcomas (STSs) constitute a major portion of retroperitoneal tumors. However, in general, retroperitoneal sarcomas (RPSs) are uncommon representing approximately 15% of all STSs,[11] with an average estimated annual incidence of 2.7 cases per million persons.[12] Most of this chapter is focused on the diagnosis and management of RPSs.

TABLE 82.1 SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS DATA: RETROPERITONEAL MALIGNANCIES, 2002[10]

Patient Data (*n* = 162)	Number	Percent
Patient sex		
Male	78	48

Patient Data (*n* = 162)	Number	Percent
Female	84	52
Patient race		
White	128	79
Black	16	9.9
Other	17	10.5
Unknown	1	0.06
Histologic derivation		
Soft tissue sarcoma	126	77.8
Sympathetic nervous system	14	8.6
Epithelial	7	4.3
Germ cell	5	3
Renal	1	0.06
Other (unspecified)	9	5.6

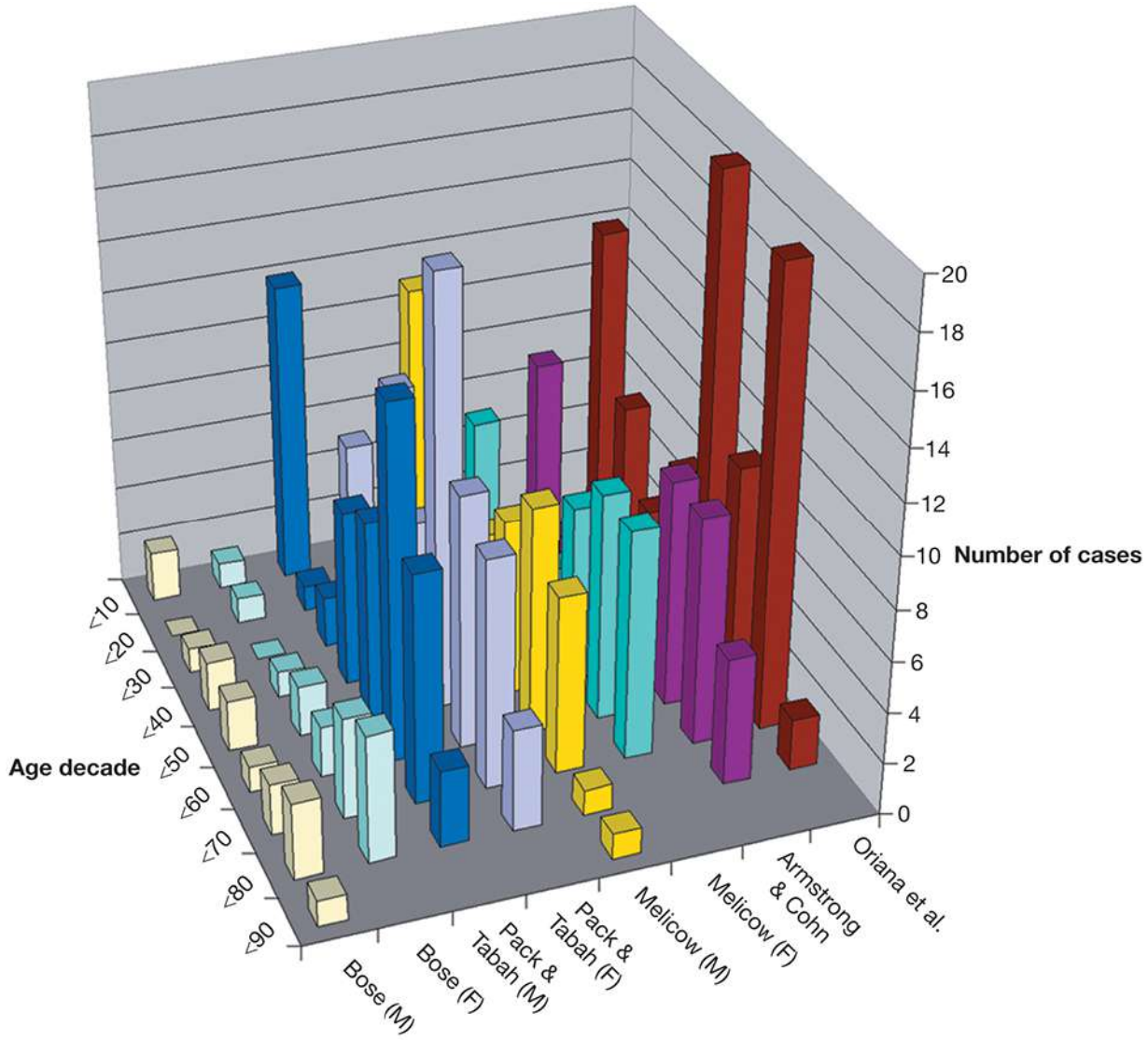

FIGURE 82.2 Age at diagnosis of malignant retroperitoneal tumors (pooled data from multiple series).

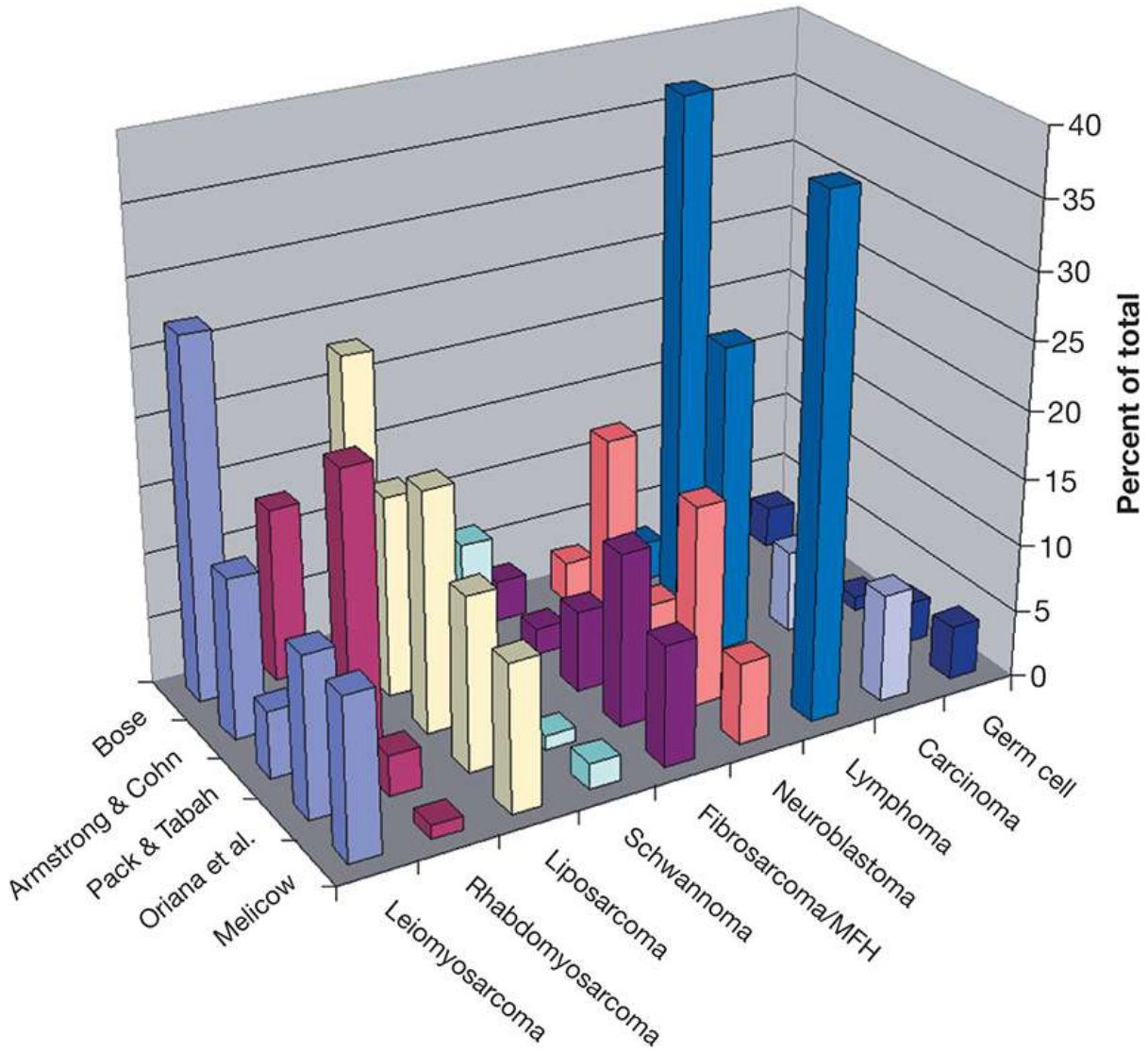

FIGURE 82.3 Percentage of retroperitoneal lesions by histology (pooled data from multiple published series).

NATURAL HISTORY

With such varied neoplasms occurring in the retroperitoneum, the natural history is primarily dependent on histology. As the retroperitoneum is a potential space, neoplasms in this region can become quite large, weigh over 50 kg, and cause displacement or compression of adjacent organs prior to diagnosis.

CLINICAL PRESENTATION

Table 82.2 outlines pooled data regarding signs and symptoms at presentation of retroperitoneal tumors. In general, presentation involves a mass or abdominal pain in most cases.

TABLE 82.2 PRESENTING COMPLAINTS (%) OF PATIENTS WITH RETROPERITONEAL LESIONS

Sign/Symptom	Bose[2] (*n* =30)	Pack and Tabah[3] (*n* =120)	Oriana et al[9] (*n* =56)
Mass	83	31	42
Abdominal pain	60	51	42[a]
Back pain	20	7	
Weight loss	35	3	12
Anorexia	20	NS	9
Nausea/vomiting	20	20	8
Lower extremity edema	17	7	9

NS, not stated.

[a]Indicates all patients with pain as presenting sign.

DIAGNOSTIC WORKUP

Retroperitoneal tumors include a diverse group of both benign and malignant neoplasms that may be primary or secondary in origin.[7] Imaging serves an important role in differentiating retroperitoneal masses, with computed tomography (CT) and magnetic resonance imaging (MRI) serving as the primary imaging modalities. Although the differential diagnosis is broad, certain imaging characteristics such as fat content, necrotic changes, contrast enhancement, presence of calcifications and/or cysts, and appearance on T1- and T2-weighted images all provide clues to narrow the differential diagnosis.[4] For example, in retroperitoneal liposarcoma (LPS), the most common subtype,[13] tumors appear as a hypoattenuating lesion on CT because of the fat content and are indistinguishable from a benign lipoma.[4,7] On MRI, a well-differentiated LPS demonstrates high-signal intensity on T1, intermediate signal on T2, and loss of fat signal intensity on fat-suppressed images and may be contrast enhancing.[4,7] However, in a dedifferentiated LPS, both fat and solid

components are observed with occasional associated calcifications.[4] Leiomyosarcomas (LMSs), the second most common subtype,[13] appear on CT as homogeneously solid, but larger tumors may develop areas of necrosis and hemorrhage.[4] On MRI, these tumors demonstrate low T1 signal intensity and intermediate to high T2 signal intensity depending on the presence of necrosis with peripheral and heterogeneous contrast enhancement.[4,14] In general, retroperitoneal neoplasms can be divided into either solid or cystic tumors based on their imaging appearance.[7] Solid tumors fall into three main categories, including mesodermal, neurogenic, or extragonadal germ cell origin, whereas cystic tumors include cystic changes in solid neoplasms as well as cystic lymphangioma, cystic teratoma, cystadenoma, cystadenocarcinoma, and cystic mesothelioma.[7]

As part of the primary workup, in addition to imaging the primary tumor with a CT of the abdomen/pelvis with intravenous (IV) contrast, a CT of the chest should also be obtained to evaluate for the presence of metastatic disease. Arterial phase CT imaging can be helpful for operative planning. MRI of the abdomen/pelvis with and without IV contrast can also be considered to further classify the lesion and evaluate the extent of disease. Imaging with 18-fluorine-labeled 2-deoxy-2-fluoro-D-glucose ([18]F-FDG-PET) is not routinely performed for RPSs but may be useful for evaluating the extent of distant metastasis during initial staging if the primary lesion is PET avid in the first place.[15]

Functional assessment of the contralateral kidney is necessary if ipsilateral kidney may be removed along with the primary retroperitoneal tumor. This may be achieved using CT with IV contrast or pharmacologic renal scan with radioisotope (differential renal scan).[16]

A definitive diagnosis is obtained with a biopsy and should be performed unless preoperative treatment is not planned. Image-guided core needle biopsy is recommended with multiple cores obtained for histologic and molecular subtyping.[17] Both fine-needle aspiration and laparotomy with open biopsy should be avoided. Ideally, biopsy of a solid, well-perfused portion of the tumor should be performed rather than an area of necrosis.[17]

RETROPERITONEAL SARCOMA GENERAL MANAGEMENT

The first decision point is determining whether the patient is resectable or unresectable.[18] Surgical resection is the primary treatment for RPS and is the only potentially curative option for localized and resectable disease. Criteria for unresectable tumors may include extensive major vessel involvement, including the root of the mesentery, spinal cord involvement, peritoneal implants, and distant metastasis.[18] Achieving an R0 resection of a RPS is often challenging due to the size and anatomic location of the tumor. Based on a review by Mendenhall et al,[13] which includes data from four large institutional series, the rate of complete resection, which includes R0 and R1 resections, was 50% to 67%. Patients who have an R1 resection are at increased risk of local recurrence,[19,20] with recent data from the National Cancer Database (NCDB) suggesting inferior survival as well.[21] Surgical resection often involves resection of adjacent organs to achieve complete extirpation of the tumor. Liberal visceral en bloc resections may increase morbidity but also have been associated with higher rates of local control and potentially an improvement in overall survival based on retrospective data, although this practice has not yet been widely adopted.[21,22]

Because of the rarity of RPS, patients should be evaluated and managed at high-volume centers with expertise in sarcoma by a multidisciplinary team, including surgical oncology, radiation oncology, and medical oncology.[17] Management of this rare disease in high-volume sarcoma centers is strongly recommended: It is associated with reduced early postoperative morbidity, reduced risk of postoperative mortality, reduced risk of relapse, reduced death rates from sarcoma, and, most importantly, improved long-term overall survival.[23-27]

PERIOPERATIVE RADIOTHERAPY

The efficacy of radiotherapy (RT) for RPS has been controversial, substantiated primarily by its well-established role in extremity sarcoma. Local control remains a challenge for RPS, due largely to the anatomic constraints of the retroperitoneum. Incomplete resection (R1 or R2) and subsequent locoregional failure have been reported in up to 50% of patients who undergo surgery with curative intent.[28]

Two cohort studies utilizing publicly available registry data have compared survival outcomes for patients with resectable RPS receiving

surgery alone to outcomes for patients receiving perioperative RT or chemotherapy.[29,30] The first study performed two case-control, propensity score-matched analyses of NCDB, which included adult patients with RPS who were diagnosed from 2003 to 2011. Both preoperative RT (hazard ratio [HR] 0.70, 95% confidence interval [CI] 0.59-0.82; $P < .0001$) and postoperative RT (HR 0.78, 0.71-0.85; $P < .0001$) were significantly associated with improved overall survival compared with surgery alone.[30] The second study compared survival outcomes in patients with primary resectable RPS diagnosed between 2006 and 2015.[29] On multivariable analysis adjusted for facility type, age, sex, income, Charlson-Deyo comorbidity score, histologic characteristics, tumor grade, tumor size, surgical type, surgical margin, and postoperative inpatient duration, addition of preoperative radiation was associated with improved overall survival (HR, 0.88; 95% CI, 0.77-0.99; $P = .03$), while the addition of preoperative chemotherapy was associated with lower overall survival (HR, 1.54; 95% CI, 1.27-1.88; $P < .001$).[29]

Despite the abovementioned NCDB studies as well as several nonrandomized prospective studies, and retrospective studies evaluating the role of perioperative RT in resectable RPS,[31-36] there has been no evidence to support such a treatment approach from any randomized studies. In the United States, the only randomized controlled trial addressing the use of perioperative RT for RPS did not accrue enough patients for completion (ACOSOG Z90312, NCT00091351). The European Organisation for Research and Treatment of Cancer (EORTC) conducted a prospective, randomized phase III study in patients with RPS comparing patients treated with surgery alone to patients treated with preoperative RT followed by surgery (EORTC 62092-22092), known as the STRASS trial.[37] Between January 2012 and April 2017, 266 patients were enrolled in this study and randomized to one of the two arms: preoperative RT plus surgery versus surgery alone. RT was delivered as 50.4 Gy in 28 daily fractions, either with three-dimensional (3D) conformal RT or intensity-modulated radiotherapy (IMRT). Surgery was defined as a macroscopically complete resection of the tumor mass with en bloc organ resection as necessary. Primary end point was abdominal recurrence-free survival (ARFS) as assessed by the investigator. With median follow-up of 43.1 months, median ARFS was not different between the two groups (4.5 years in the RT plus surgery group

and 5.0 years in the surgery-only group [HR 1.01, 95% CI 0.71-1.44; log-rank P = .95]). While no difference in primary end point was observed, twice as many local relapses were observed in the surgery group than in the RT plus surgery group, possibly related to RT, specifically in the LPS cohort. In fact, in the subgroup analyses exploring patients with LPS only, there was a 10% absolute ARFS benefit in favor of the RT plus surgery arm.[37] This is consistent with a prior multicenter study from the Trans-Atlantic Australasian Retroperitoneal Sarcoma Working Group, which showed that intra-abdominal local recurrence was the predominant pattern of failure for LPS, whereas distant metastasis was the principal pattern of failure for LMS.[38]

The STRASS trial was the first successfully completed randomized phase III study comparing preoperative RT plus surgery to surgery alone, and its results suggested that preoperative RT should not be considered as standard-of-care treatment for every patient with RPS; rather, RT should be considered on a case-by-case basis.[37] National guidelines suggest the use of neoadjuvant RT in selected cases, where tumors are at high risk for local recurrence, with or without intraoperative RT (IORT) boost. If neoadjuvant RT is anticipated, IMRT and other advanced image-guided radiation techniques are recommended.

For patients with unresectable or borderline resectable tumors, downstaging can be attempted using preoperative chemotherapy, RT, or chemoradiation. Repeat imaging with CT of the chest/abdomen/pelvis with or without MRI of the abdomen/ pelvis should then be performed to evaluate the treatment response and to verify that the patient has not developed metastasis. If the tumor progresses or the patient develops metastatic disease, palliative care can be considered, which may involve any combination of chemotherapy, RT, surgery to help control symptoms,[39] or other supportive care. In patients with unresectable tumors, particle therapy may provide durable local control.[40]

Following preoperative RT in the definitive setting, surgical resection is typically delayed 3 to 8 weeks with radiographic restaging performed to assess for metastases and treatment response. In the setting of a positive microscopic margin (R1 resection) following preoperative RT, a postoperative external beam RT (EBRT) boost can be considered but is discouraged. In general, postoperative RT is discouraged in favor of

observation following surgical resection with consideration of preoperative EBRT in the event of a local recurrence. However, postoperative EBRT should be considered when a local recurrence would cause significant morbidity because of a critical anatomic location. For patients who undergo a resection where gross residual disease is present (R2 resection), reresection should be discussed, if possible.

Unlike extremity sarcomas, where the most first recurrences are distant, RPSs tend to fail locally with a 5-year local control of approximately 50%.[13] In the setting of recurrent disease, patients who did not receive prior RT can be considered for preoperative radiation. Repeat resection should be offered, if possible, as patients who completed resection for recurrent disease had improved survival based on a large retrospective study from the Trans-Atlantic Retroperitoneal Sarcoma Working Group.[41] IORT can also be considered in an attempt to improve the chances of local control in the recurrent setting.[42-44]

Patients who present with or develop metastatic disease should be managed on a case-by-case basis. Any combination of chemotherapy, RT, surgery to palliate symptoms, and other supportive care is appropriate.[18]

Following definitive treatment, patients should undergo physical examination with imaging every 3 to 6 months for the first 2 to 3 years.[18] For the next 2 years, the patient should undergo physical examination and imaging every 6 months, and then annually after that. Imaging should include CT or MRI of the abdomen/pelvis with a chest x-ray or CT of the chest also included.

A histology-based RPS prognostic system identifies RPS into three prognostic groups, and it can be used in both primary and recurrent RPS. Distinct risk stratification is necessary for specific assessment of prognosis and decision regarding individualized adjuvant therapy.[45] Some authors recommend the formulation of an LPS-specific postoperative nomogram based on histologic subtypes, which provides more accurate survival predictions for patients with primary RPS.[46,47] Well-differentiated and dedifferentiated LPSs differ significantly in their biologic behavior and are treated by different surgical approaches at the MD Anderson.[48] Researchers at the center recommend that the American Joint Committee on Cancer STS staging system needs to incorporate the primary site, histologic subtype, margin status, and recurrence to further shed light on prognosis.[49]

CHEMOTHERAPY

Adjuvant chemotherapy is controversial in the management of adult patients with macroscopically completely resected retroperitoneal STSs. Retrospective analysis of both preoperative[50] or postoperative[18,51-53] chemotherapy has yet to demonstrate overall survival benefit. In a National Cancer Institute trial, patients with STSs were randomized to chemotherapy or observation following resection; some patients had postoperative irradiation.[54] Among patients who were assigned to chemotherapy, survival was favorably affected in those with extremity tumors. However, patients with head and neck and truncal lesions (including RPSs) did not benefit; the 5-year survival rate was approximately 40% in both arms. Similar findings were reported in a large meta-analysis of patients with STS.[55]

The use of neoadjuvant or adjuvant chemotherapy is not standard in the management of nonmetastatic adult retroperitoneal STSs. Neoadjuvant chemotherapy has been primarily studied in the setting of high-grade, extremity STSs. Pisters et al[56] demonstrated feasibility of using preoperative concurrent doxorubicin and EBRT (18-50.4 Gy), followed by resection and IORT (15 Gy) in patients with RPS. An R0 or R1 resection was possible in 90% of the patients who went to surgery (83%). Newer studies have shown that doxorubicin-based adjuvant chemotherapy significantly improves local and distant recurrence in localized resectable STS.[57] Newer agents, such as olaratumab,[58] are currently being tested in the neoadjuvant setting to see if overall survival can be improved.

Overall, treatment with chemotherapy is not recommended outside clinical protocols. Currently, EORTC EA7211/STRASS 2, a randomized study investigating preoperative chemotherapy followed by surgery versus surgery alone in patients with high-risk RPS, is ongoing. Patients will include those with localized resectable high-risk LMS or LPS (NCT04031677).

RADIATION THERAPY TECHNIQUES

External Beam Radiation Therapy

In patients for whom RT is recommended, preoperative RT is the preferred approach. Treatment guidelines based on the consensus of an international expert panel for preoperative RT of RPS have been published by Baldini et

al[59] Suitable candidates for preoperative RT include patients with unifocal or localized tumors that are amenable to an R0 resection and where delivery of 50 to 50.4 Gy to the tumor while meeting the dose objectives for the adjacent normal structures is feasible. Patients with symptoms requiring urgent surgical intervention should not be considered for preoperative RT. Prior to any therapy, the surgical and radiation oncologist should work together to develop a consensus plan. In the setting of kidney or liver involvement where surgical resection may involve either a nephrectomy or partial hepatectomy, or where RT may result in impaired function of one kidney, preliminary studies need to be performed to ensure adequate function in the remaining kidney or liver. Further, in the setting of a nephrectomy or partial hepatectomy, care should be taken to minimize the radiation dose to the remaining kidney and/or liver. Kidney function can be evaluated using a renal perfusion study, whereas the liver can be evaluated using serum liver chemistries.

CT simulation should be performed with the patient in the supine position with suitable custom immobilization device to allow reproducible setup during treatment. Both oral and IV contrast should be considered for the simulation scan to better delineate the tumor and adjacent normal structures including bowel. A 4D CT should be performed to evaluate tumor motion during the respiratory cycle with more motion anticipated in superiorly located tumors in the abdomen.[60] For patients with more than 1 cm of motion, motion management techniques should be considered, such as active breathing control, respiratory gating, or end-expiration breath-hold. To aid with target and organ at risk of delineation, registration of the free-breathing planning CT with diagnostic studies should be performed. Useful diagnostic studies may include a diagnostic CT and/or T1-weighted postcontrast MRI. Data on the use of [18]F-FDG-PET in the staging of RPS and for use in RT treatment planning are currently limited, with more data likely to emerge in the coming years. Proton therapy (especially intensity-modulated proton therapy) may allow dose escalation to the targets while sparing normal tissues, including liver, small bowel, and large bowel.

Target Delineation/Organs at Risk

Target volumes for RPSs are included in the international expert panel consensus guidelines from Baldini et al[59] For upper abdominal tumors where a 4D CT simulation is performed, the gross tumor volume (GTV) is delineated, and an internal gross tumor volume (iGTV) is made based on the motion of the GTV throughout the respiratory cycle. The internal target volume (ITV) is made using a 1.5-cm uniform expansion of the iGTV edited off uninvolved bone, kidney, and liver. The ITV should expand 5 mm into the bowel and any air cavities and should be cropped away from uninvolved skin per institutional guidelines. If the tumor extends into the inguinal canal, the inferior expansion of the iGTV to make the ITV should be 3 cm. For an upper abdominal tumor where a 4D CT simulation is not performed, the GTV should be expanded by 2 to 2.5 cm in the superior-inferior direction and 1.5 to 2 cm radially. The CTV should be edited off the interfaces in the same manner as the ITV in the upper abdomen case where a 4D scan is obtained. For tumors below the level of the iliac crest, the GTV can be expanded 1.5 cm uniformly and edited off the interfaces as mentioned above to create the CTV. In all cases, the planning target volume, which accounts for setup error and patient movement, should be based on imaging frequency and institutional guidelines. The standard preoperative dose is 50.4 Gy in 1.8-Gy fractions or 50 Gy in 25 fractions. The delivery of a boost dose to the areas considered to be at high risk for a positive margin has been reported.[61] However, this approach remains experimental and is the subject of a currently accruing phase I/II trial at Massachusetts General Hospital.[35] In the setting of a positive surgical margin following preoperative EBRT, a postoperative EBRT boost may be considered; however, it is considered controversial.

In the postoperative setting, the treatment volumes are generally larger, with a larger volume of normal tissue in the treatment field as the bowel and other organs initially displaced by the tumor fall into the resection cavity. Temporary tissue expanders have been used in a limited number of studies to displace bowel and other organs at risk out of the treatment volume.[62,63] Target delineation in the postoperative setting is challenging, and no consensus guidelines exist. Therefore, adjuvant RT following surgery is generally discouraged for retroperitoneal/intra-abdominal sarcoma. If RT is not delivered prior to surgical resection, consider follow-up with possible neoadjuvant RT at the time of localized recurrence.

Adjacent organs at risk include liver, stomach, bowel including duodenum, small and large bowel, kidneys, spinal cord, testicles, ovaries, bladder, rectum, and femoral heads. To aid in normal organ contouring, consensus guidelines and an atlas are available from the Radiation Therapy Oncology Group.[63] Again, the consensus guidelines for preoperative RT for RPS include a summary of constraints for organs at risk primarily derived from Quantitative Analysis of Normal Tissue Effects in the Clinic data.[59,64] In brief, no more than 100% of the stomach should receive ≥45 Gy, the mean bilateral kidney dose is 15 to 18 Gy, and no more than 15% of the remaining kidney should receive >18 Gy if one kidney is removed. For the small/large bowel contoured as the peritoneal cavity, no more than 195 cm^3 should receive >45 Gy. The mean residual liver dose should be limited to <26 Gy, and the spinal cord dose should be <50 Gy.

Treatment Planning and Delivery

For RT planning using photons, IMRT is preferred to 3D conformal radiation because of increased conformality with decreased dose to adjacent organs at risk.[65] Swanson et al[65] determined the optimal RT technique for the treatment of RPSs by comparing plans prepared using 3D conformal proton RT, IMRT, and 3D conformal photon RT. The IMRT and conformal proton plans were more conformal than the 3D photon plans. Furthermore, the IMRT and proton plans provided a lower bowel and kidney dose than the 3D photon plans.

Based on the results of Wong et al, which demonstrated volumetric changes and significant interfraction displacement during preoperative RT for RPS, daily image-guided RT should be considered where soft tissue is clearly visible, such as cone-beam CT.[59,60] Prophylactic antiemetics should be considered for the patient depending on the location of the tumor.

Additional Radiation Techniques

IORT refers to the delivery of either brachytherapy or external beam irradiation to a target area, whereas the area is exposed during surgery. IORT is typically used to deliver a focal boost to areas of concern, such as close or positive margins. The advantages of IORT include the ability to directly visualize the area of concern and manually remove normal tissues

from the field or shield them prior to treatment delivery. When electron beams are used (intraoperative electron radiation therapy [IOERT]), typical doses range from 10 Gy for completely resected tumors with negative margins, 12.5 to 15 Gy for positive microscopic margins, and 15 to 20 Gy for gross residual disease.[66] Typical electron energies range from 9 to 15 MeV based on the desired depth of penetration.

IORT can also be delivered using high-dose rate intraoperative irradiation (HDR-IORT) as previously described in detail by Harrison et al.[67,68] For HDR-IORT, following displacement of normal tissue from the field of interest, a Harrison-Anderson- Mick (HAM) applicator (an array of catheters spaced 1 cm apart in a silicone rubber pad) is secured in the target region, and a dose of 10 to 20 Gy at a tissue depth of 5 to 10 mm is typically delivered.[66] Following delivery of IORT, the applicators are removed from the target region, and the surgeon continues with the case. The advantages and disadvantages of each IORT technique have been previously summarized.[66] HDR-IORT allows for delivery of more conformal treatments along curved surfaces secondary to the flexible nature of the HAM applicator, the ability to treat large fields without field matching, and the ability to deliver RT to areas that may not necessarily be accessible with IOERT. HDR-IORT is limited to treating target areas ≤0.5 cm thick. IOERT can treat both superficial and deeper targets by varying the electron energy employed for treatment. Treatment with IOERT is also generally shorter than HDR-IORT, thus decreasing the overall procedure time.

RESULTS OF THERAPY

Surgical resection remains the only curative treatment for patients with RPSs, although local control rates with resection alone remain poor. Because of both the size and proximity of RPSs to critical organs, margin-negative resections are difficult to achieve. Locoregional failure is the predominant pattern of failure,[13,69] and failure to achieve local control is the major cause of death in patients with RPS.[70] A large retrospective series from Memorial Sloan Kettering reported on 231 patients with primary RPS that was resectable.[71] Of the 231 patients, 185 (80%) were able to undergo a gross total resection. Patients with a gross total resection were found to

have a statistically significant increase in survival compared to those who underwent incomplete resection (103 vs 18 months). No difference in survival was observed between patients with unresectable disease and patients who underwent incomplete resection. For patients with localized, completely excised RPS, 5-year overall survival is 49% to 70%, with selected studies summarized in Table 82.3. Preoperative RT potentially could improve local control; however, the STRASS study did not demonstrate this in all comers, but only in patients with LPS. Additional prospective randomized studies with more sophisticated RT techniques and/or biomarker-informed systemic therapies are needed.

TABLE 82.3 COMPLETE RESECTION AND SURVIVAL IN PATIENTS WITH NONMETASTATIC (M0) RETROPERITONEAL SARCOMA (RPS)

Study	Complete Resection	Local Recurrence	Overall Survival	Local Recurrence with Incomplete Excision	Overall Survival With Incomplete Excision
Ferrario and Karakousis[72]	95%	Primary RPS: 41% Recurrent: 61%	Primary RPS: 65% 5 y 56% 10 y Recurrent: 53% 5 y 34% 10 y		
Stoeckle et al[22]	65%	57% 5 y	49% 5 y		
Lewis et al[73]	Primary RPS: 67%		70% 5 y Median 103 mo		Median 18 mo
Catton et al[69]	43%	50% 5 y 82% 10 y	55% 5 y 22% 10 y	86% 5 y 95% 10 y	15% 5 y 10% 10 y
Gronchi et al[74]	88%	Primary RPS: 37% Recurrent: 72%	54% 5 y 27% 10 y		

Patients with positive microscopic margins are at increased risk of local recurrence[75] based on retrospective data, with a recent study from the NCDB demonstrating a survival advantage in patients able to achieve an R0

resection versus R1 resection (92 and 70 months, respectively).[19] As part of the analysis, preoperative RT was associated with an increased probability of R0 resection. A number of retrospective studies demonstrate an improvement in local control with postoperative RT, with select studies summarized in Table 82.4. In the report by Stoeckle et al,[22] patients with complete excision had a significant reduction in local recurrence risk when treated with received postoperative RT (median dose = 50 Gy) compared to those not treated with adjuvant RT (relative risk, 3.36; $P = .0021$). However, no improvement in overall survival on multivariate analysis was observed. Catton et al[69] found that adjuvant RT for patients who had a complete resection increased the time to locoregional relapse, from 30 (no radiation) to 103 months ($P = .06$). Again, radiation did not have an impact on survival.

TABLE 82.4 LOCAL RECURRENCE IN PATIENTS WITH OR WITHOUT POSTOPERATIVE RADIATION THERAPY (PORT) FOLLOWING A COMPLETE RESECTION

Study	Local Recurrence With PORT	Local Recurrence Without PORT	*P* Value
Ferrario and Karakousis[72]	38% 41 mo	53% 41 mo	.16
Stoeckle et al[22]	45% 5 y	77 5 y	.0021
Catton et al[69]	103 mo to LRF	30 mo to LRF	.02

LRF, locoregional failure.

IORT is used by some centers to deliver a boost to the resection cavity to improve local control. A prospective randomized trial was performed by the National Cancer Institute to evaluate the benefit of gross total resection with IORT followed by postoperative EBRT compared to gross total resection and postoperative EBRT alone.[71,76] IORT was delivered with electrons with an energy of 11 to 15 MeV delivered in a single dose of 20 Gy. For patients treated with IORT, the postoperative EBRT dose was 35 to 40 Gy delivered in 1.5 to 1.8 Gy fractions. For patients treated with postoperative EBRT alone, the dose was 50 to 55 Gy delivered in 1.5 to 1.8 Gy fractions. For patients treated in the IORT arm, significantly fewer locoregional

recurrences were observed compared to the postoperative EBRT-alone arm. No difference in survival was observed between the two arms. Additional nonrandomized studies summarized in Table 82.5 have demonstrated excellent local control with the use of IORT and EBRT with acceptable toxicity.

TABLE 82.5 OUTCOMES WITH EXTERNAL BEAM RADIOTHERAPY (EBRT) + INTRAOPERATIVE RADIOTHERAPY (IORT) BOOST FOLLOWING RESECTION OF PRIMARY AND RECURRENT RETROPERITONEAL SARCOMA (RPS)

Study	Median EBRT Dose	Median IORT Dose	Local Recurrence	5-Y Overall Survival	Toxicity
Petersen et al[76]	Primary RPS: 48.6 Gy Recurrent: 45 Gy	Primary RPS: 12.5 Gy Recurrent: 15 Gy	Primary RPS (5-y LC): 0% CE 8% micro 40% gross Recurrent: 0% CE 64% micro 33% gross	Primary RPS: 62% CE 54% micro 29% gross Recurrent: 80% CE 44% micro 45% gross	Chronic enteritis 16% Grade 3-4 GI complications 18% Fistula formation 18% Neuropathy: mild 12%; moderate/severe 21%
Sindelar et al[71]	IORT arm: 35-40 Gy (post-op) EBRT-alone arm: 50-55 Gy (post-op)	20 Gy	IORT arm: time to in-field local recurrence >127 mo EBRT-alone arm: 38 mo (P < .05)	IORT arm: 45% EBRT-alone arm: 52% (P = .39)	IORT arm: Chronic enteritis 13% Neuropathy: mild 13%; moderate/severe 47% EBRT-alone arm: Chronic enteritis 50% Fistula formation 25% Neuropathy: mild, 6%; moderate/severe, 0%
Gieschen et al[44]	45-50.4 Gy (pre-op)	10 Gy CE 12.5-15 Gy micro 15-20 Gy gross	Complete excision (5 y): EBRT + IORT 17% EBRT alone 39%	Complete excision: EBRT + IORT 74% EBRT alone 30%	Neuropathy 19% Hydronephrosis 19% Vaginal fistula 6% Ureteral fistula 6% Small bowel obstruction 6%

Study	Median EBRT Dose	Median IORT Dose	Local Recurrence	5-Y Overall Survival	Toxicity
Alektiar et al[42]	45-50.4 Gy (post-op)	12-15 Gy HDR, Ir-192	Complete excision (5 y): EBRT + IORT: Primary RPS 29% Recurrent 39% Total 44% IORT alone: Primary RPS NR Recurrent 67% Total 50%	Primary RPS: 75% Recurrent: 30%	Bowel obstruction 18% Fistula 9% Neuropathy: mild 6%; moderate/severe 0% Ureteral injury 3%

CE, complete excision; GI, gastrointestinal; gross, gross residual disease; HDR, high-dose rate; LC, local control; micro, microscopic residual disease; NR, not reported; OS, overall survival.

Patients with unresectable disease have a poor prognosis. Surgery may be considered to palliate symptoms. A retrospective study from Memorial Sloan Kettering was performed to evaluate patients with RPS who underwent palliative procedures.[77] Patients most frequently underwent a procedure because of gastrointestinal (GI) symptoms (44% of patients). Overall, about 50% of patients were symptom free at 100 days postprocedure, but only 23% of patients with GI obstructive symptoms were symptom free at 100 days. The postoperative morbidity was 29%, and the postoperative mortality was 12%. Particle therapy can also be considered for patients with unresectable disease. Serizawa reported on a small series of patients with unresectable RPS treated with carbon ion RT.[40] The patient cohort included both primary and recurrent diseases, with doses ranging from 52.8 to 73.6 GyE in 16 fractions. The local control rates at 2 and 5 years were 77% and 69%, respectively, with a 2- and 5-year overall survival of 75% and 50%, respectively. No grade ≥3 toxicities were observed.

Recurrence is common, and there are minimal data to guide management in the recurrent setting.[41] A large retrospective series from the Trans-Atlantic Retroperitoneal Sarcoma Working Group evaluated postrelapse

outcomes in 408 patients.[41] For patients with a local recurrence only, the median time from initial resection to recurrence was 23 months. Repeat resection was performed in 48% of patients with chemotherapy and RT given to 31% and 18% of patients, respectively. Following local recurrence, the median overall survival was 33 months and the 5-year overall survival was 29%, with repeat resection and longer time interval to recurrence found to be significant predictors for survival. Treatment with RT trended for significance. The 5-year overall survival for patients who underwent repeat resection was 43% versus 11% for those not able to undergo repeat resection. The 5-year overall survival for patients with distant metastasis and those with local recurrence and distant metastasis was 20% and 14%, respectively. For patients with distant metastasis only, resection of the distant metastasis was found to be a significant predictor of improved disease-specific survival. For patients with both a local recurrence and distant metastasis, patients who completed resection of the recurrent disease had longer survival than those who did not.

TREATMENT SEQUELAE

Acute symptoms from EBRT of the retroperitoneum include fatigue, radiation dermatitis, nausea, vomiting, and diarrhea. For large radiation fields where the adjacent spine is included, a significant portion of bone marrow may also be included, and anemia, neutropenia, and thrombocytopenia may occur. At minimum, weekly monitoring of vital signs should be performed, and monitoring of blood counts should be considered. Reported postoperative complications include bleeding, impaired wound healing or dehiscence, infection, myocardial infarction, and death.[33,77]

Late toxicities of surgery and radiation include small bowel enteritis, stricture, perforation, fistula, and obstruction. Development of nephritis is possible after radiation doses >30 Gy with resultant hypertension. Late complications are associated with the number of laparotomies to which the patient has been subjected and with the radiation dose and volume.[78,79] A lower incidence of enteritis has been reported with the use of EBRT and an IORT boost compared with EBRT alone, as the bowel is able to be moved from the field, resulting in a lower radiation dose[63] (Table 82.5). Overlap of

adjacent IORT fields can increase the risk of neuropathy and ureteral injury.[33,77] As discussed previously, preoperative RT is the preferred approach to postoperative RT because of a more favorable toxicity profile and ease of target delineation.[59] Proton therapy may also allow a decreased dose to the bowel, resulting in a decrease in acute and late toxicity.[80]

Callegaro et al[80] performed a cross-sectional study to assess the long-term morbidity of patients treated for RPS. Patients were evaluated for lower limb function using the Lower Extremity Functional Scale (LEFS) and pain was assessed using the Brief Pain Inventory—Short Form, both self-report questionnaires. RT and chemotherapy were used in 28.8% and 51.4% of patients, respectively. Overall, sensory impairment of the limbs was reported in 76% of patients with a median LEFS score of 60 out of a maximum of 80 (high function), indicating overall good motor function. Mean pain scores varied from 1.23 to 2.68 out of a maximum of 10 (bad pain), indicating mild pain overall. No difference in median creatinine levels on multivariate analysis was observed in patients requiring nephrectomy compared to those who did not.

LYMPHOMAS

Lymphomas frequently involve the retroperitoneum, with the predominant histologic variant being non-Hodgkin lymphoma. Workup generally includes CT and/or MRI and ^{18}F-FDG-PET. On CT, lymphomas appear as a homogeneous mass that generally spreads between normal structures occasionally causing displacement, but generally not resulting in compression.[4] On MRI, lymphomas are isointense on T1 and iso- to hyperintense on T2-weighted images with patchy contrast enhancement.[4] PET imaging is also generally used with FDG avidity dependent on histologic subtype.[81] A definitive diagnosis requires a tissue biopsy that can be difficult in the retroperitoneum. An image-guided needle biopsy is to be used over fine-needle aspiration for diagnostic purposes if no other superficial lymph nodes are accessible and also because sarcoma is in the differential.[82] Flow cytometry and immunohistochemical stains are used to confirm the diagnosis of lymphoma. The diagnosis, staging, and management of retroperitoneal lymphoma are similar to that of other lymphoma sites and are discussed elsewhere in this text. As with all

retroperitoneal tumors, radiation doses and treatment volumes may be limited by adjacent normal tissues.

OTHER LESIONS

Neuroblastoma is the most common solid extracranial tumor in children and the most common cancer in infants younger than 12 months, though this can occur rarely in adults.[83] In the United States, approximately 650 new cases are diagnosed per year,[84] with a prevalence of 1 case per 7,000 live births and an incidence of 10.54 cases per 1 million per year in children younger than 15 years.[83] Ninety percent of cases are diagnosed in children <5 years of age, with about 37% diagnosed as infants.[83] Neuroblastoma accounts for approximately 15% of all pediatric cancer fatalities. This tumor is extraordinarily uncommon in adults, with an estimated incidence of 0.2 per million population in those aged 30 to 39.[85] The paradigm for the treatment of neuroblastoma includes combination therapy with chemotherapy, surgery, and RT in advanced-stage disease, which is most commonly found in adults.[86]

Wilms tumor (WT) or nephroblastoma is the most common intra-abdominal malignancy of childhood, with an incidence of 7.1 cases per 1 million children younger than age 15 years, with approximately 650 cases diagnosed in the United States each year.[83] It is the second most common extracranial solid neoplasm of childhood and the most common renal malignancy in children.[87] In contrast, it is an uncommon malignancy in patients ≥16 years of age, with an estimated incidence of 0.2 per million population.[88,89] Adults frequently present with flank pain and painless hematuria,[90] whereas children are more likely to present with painless hematuria and/or a palpable abdominal mass.[83] The treatment and outcomes of patients with adult Wilms tumor (AWT) remain controversial, with no standard therapy yet developed.[91] Kalapurakal et al[92] reported the outcomes of 23 adults (>16 years of age) treated on Children Oncology Group (COG) protocols (National Wilms Tumor Study Group; NWTS 4 and NWTS 5) and found no difference between the adults and their pediatric counterparts. Similarly, the International Society of Pediatric Oncology (SIOP) published results from an SIOP retrospective review of 30 patients with AWT >16 years of age with comparable results between adults and children.[90]

Conversely, Izawa et al[93] reported on 128 patients with AWT from SIOP as well as individual institutional reports and concluded that the outcomes in adults were inferior to that of children. A SEER study by Ali et al[94] concluded that the outcome in 152 patients with AWT was worse than in children. Overall survival at 5 years was 69% in AWT versus 88% in children ($P < .001$). On multivariate analysis, adult status (≥16 years), SEER stage, treatment era (before 1990), and lack of surgical staging of lymph nodes were significant prognostic factors in this cohort. A consensus statement by an international group of childhood renal experts was published that recommends adoption of the pediatric paradigm for the treatment of patients with AWT, including surgical resection, chemotherapy agents depending on stage and histologic subtype, and local therapy with irradiation depending on the stage of disease.[91] Furthermore, patients <30 years old are included on the current COG WT studies. The toxicities of treatment (severe acute neuropathy, grade 4 hematologic toxicity) in patients with AWT may be somewhat higher than in the pediatric population but are thought to be reasonable in view of the high response rates.[90]

Retroperitoneal schwannomas are a rare tumor, accounting for approximately 4% of retroperitoneal tumors, but are the most common benign tumor found in this location.[95,96] They belong to the family of peripheral nerve sheath tumors, which, in addition to schwannomas, includes neurofibromas, solitary circumscribed neuromas, and perineuriomas.[97] Schwannomas may occur in any nerve trunk in the body, with the exception of cranial nerves 1 and 2 (which are not covered by Schwann cells), and are most commonly found at peripheral nerve sites of the upper extremities and cranial nerves, with only 0.3% to 3.2% of all schwannomas occurring in the retroperitoneum.[97] Benign schwannomas are associated with neurofibromatosis 2 (NF2) in approximately 5% to 18% of patients with NF2, presenting most commonly between 20 and 50 years of age.[98] They are slow-growing nonaggressive tumors that displace rather than invade normal tissues and often form large, well-circumscribed masses.[96,97] They may display cystic degeneration, calcification, hemorrhage, and hyalinization on imaging studies. In several moderate to large series, there appears to be a slight female patient propensity, and the tumors are often diagnosed incidentally during radiologic examinations for unrelated symptoms.[99,100] Bone changes may occur in tumors adjacent to the

spine with invasion into nerve roots or the spinal canal, which may lead to neurologic symptoms, including paresthesias, weakness, and pain. MRI examinations are the preferred method of imaging these soft tissue neoplasms, although CT scanning may be necessary to better visualize potential bone abnormalities, particularly in the spine. Because these tumors are frequently quite vascular, some investigators do not recommend the use of CT-guided biopsies because of the risk of hemorrhage.[101] Whenever feasible, complete surgical resection with negative margins is the treatment of choice, although adjuvant RT may be necessary for incompletely excised sacral schwannomas.[102] Patients with NF1 have a particularly high risk of developing STS, particularly malignant peripheral nerve sheath tumors, often with an aggressive clinical presentation and poor outcome.[103]

Aggressive fibromatosis, also referred to as desmoid tumors, is a rare fibroblastic neoplasm that arises from deep musculoaponeurotic connective tissue and has an incidence of 2 to 4 cases per million population,[104] occurring either sporadically or associated with familial adenomatous polyposis (FAP).[105-108] Ten to 30% of patients with FAP eventually develop desmoid tumors, with most occurring in either the extremities or abdomen/retroperitoneum.[109-111] They occur slightly more frequently in women than in men.[112] Although benign in nature, they are locally aggressive and may infiltrate critical structures. Complete surgical resection is the mainstay of treatment, but because the local recurrence rate and morbidity from resection can be high, some patients are now managed with observation and close clinical radiologic follow-up per the National Comprehensive Cancer Network guidelines. Local recurrence is common, even in the setting of a wide local resection in up to 40% of patients depending on the series.[113-116] Postoperative RT and/or chemotherapy may be indicated when a complete surgical resection is not achieved or is not feasible or in multiple recurrent disease, though some institutions have been adopting a watch-and-wait approach to the treatment of desmoids as they are an indolent disease. The data are variable regarding the dose and treatment volumes for this disease; however, most reported series suggest that a dose of 50 to 60 Gy with margins of 5 to 7 cm is appropriate.[116,117] Doses >56 Gy may not be necessary to control gross disease.[117] A meta-analysis by Nuyttens et al, which included data from 22 studies, suggested that local control was improved with adjuvant RT compared to surgery

alone; local control after surgery alone was 72% (R0) and 41% (R1 and R2) compared to 94% (R0) and 75% (R1 and R2) after surgery and adjuvant radiation.[116] In patients with unresectable disease, RT alone is effective in providing long-term local control in up to 80% of patients.[116,118] Systemic therapy may also play a role in unresectable, incompletely resected, or recurrent disease. Systemic therapy options include both cytotoxic and noncytotoxic agents, including anthracyclines, hormonal therapy, nonsteroidal anti-inflammatory drugs, imatinib, and clinical trials with agents like sorafinib.[119]

Extragonadal germ cell tumors (EGCTs) account for approximately 1% to 5% of all germ cell tumors and occur in the retroperitoneum as the second most common extragonadal site in adults after the mediastinum.[120] Primary retroperitoneal germ cell tumors account for approximately 5% of all primary malignant retroperitoneal tumors in adults.[121] It is believed that these tumors arise from primordial germ cells, which are displaced during their migration along the urogenital ridge to the gonads.[120] When they occur in the retroperitoneum, they are considered to be metastases from an occult or "burned out" gonadal primary until proven otherwise. EGCTs are most typically found in children or young adults and mostly arise in midline locations. Most of these tumors occur in young men, and most are nonseminomatous germ cell tumors (NSGCTs) rather than seminomatous germ cell tumors (SGCTs).[120] In young women, the histologic varieties are dysgerminomas and nondysgerminomas. NSGCTs include the following histologies: teratoma, embryonal carcinoma, endodermal sinus tumor (yolk sac tumor), choriocarcinoma, and mixed histologies. Any proportion of nonseminomatous component is enough to classify a tumor as an NSGCT. NSGCTs generally have a much more aggressive course than do SGCTs. Serum markers, although nonspecific, may help to categorize the histology and can be useful for following both response to therapy and the presence of recurrence. β-Human chorionic gonadotropin is elevated in choriocarcinoma and embryonal carcinoma and in approximately 10% to 15% of SGCTs.[122] Serum α-fetoprotein is elevated in endodermal sinus tumors and embryonal carcinomas. These tumors often present as large masses in the retroperitoneum and frequently displace, compress, or encase abdominal vessels. There are no distinguishing features by imaging to differentiate germ cell tumors from other retroperitoneal masses; thus,

image-guided biopsy is necessary. Gonadal primaries must be ruled out using high-resolution ultrasound.[123] A biopsy of the gonads appears to be unnecessary in the presence of a negative ultrasound. Common sites of metastases are liver, bone, brain, and lungs. The prognosis of retroperitoneal SGCTs and their mediastinal counterparts is similar; however, retroperitoneal NSGCTs actually have a better prognosis than those occurring in the mediastinum.[120]

The treatment for EGCTs has evolved over past 10 to 15 years from the use of primary RT for SGCTs to the more commonly recommended treatment of platinum-based chemotherapy regimens.[120] Treatment paradigms for early-stage SGCT and NSGCT are covered elsewhere in this book. The International Germ Cell Cancer Collaborative Group established a classification system for assessing prognosis in NSGCT and SGCT[124] (Table 82.6), which is used to guide treatment decisions. For patients with a retroperitoneal SGCT, the preferred treatment approach is systemic chemotherapy using a cisplatin- based regimen similar to a patient with advanced testicular SGCT. In an international retrospective review of EGCTs, patients with retroperitoneal SGCTs had an overall survival of approximately 90%, with most patients treated with chemotherapy alone.[120] Patients treated with primary RT had an inferior progression-free survival compared to patients treated with either chemotherapy alone or chemotherapy plus RT.[120] For retroperitoneal NSGCTs, the preferred treatment is also cisplatin-based chemotherapy as in a testicular NSGCT, with the number of cycles dependent on if the patient is in the good or intermediate/poor prognosis group (Table 82.6). Residual masses should then be resected. In the international retrospective review of EGCTs, patients with retroperitoneal NSGCTs were primarily treated with primary chemotherapy, with 45% of patients undergoing a secondary surgery for residual disease.[120] The 5-year overall survival for patients with retroperitoneal NSGCTs was 62%.[120]

TABLE 82.6 THE INTERNATIONAL GERM CELL CANCER COLLABORATIVE GROUP CLASSIFICATION SYSTEM FOR ASSESSING PROGNOSIS IN NSGCT AND SGCT

Tumor	Good Prognosis	Intermediate Prognosis	Poor Prognosis
NSGCT	• Testis/retroperitoneal primary, no	• Testis/retroperitoneal primary, no	• Indicated by any of the following:

Tumor	Good Prognosis	Intermediate Prognosis	Poor Prognosis
	nonpulmonary visceral metastases, AFP <1,000 ng/mL, β-hCG <1,000 IU/L, and LDH <1.5 × upper limit of normal • 5-y PFS, 89% • 5-y survival rate, 92%	nonpulmonary visceral metastases, AFP >1,000 ng/mL and <10,000 ng/mL and/or β-hCG 5,000-50,000 IU/L and/or LDH > 1.5 × normal to 10 × normal • 5-y PFS, 75% • 5-y survival rate, 92%	mediastinal primary, nonpulmonary visceral metastases or AFP >10,000 ng/mL, β-hCG >50,000 IU/L, or LDH > 10 × normal • 5-y PFS, 41% • 5-y survival rate, 48%
Seminoma	• Any primary site, no nonpulmonary visceral metastases, normal AFP, any β-hCG, any LDH • 5-y PFS, 92% • 5-y survival rate, 88%	• Any primary site, nonpulmonary visceral metastases, normal AFP, any β-hCG, any LDH • 5-y PFS, 67% • 5-y survival rate, 72%	• No patients classified as having poor prognosis

AFP, α-fetoprotein; β-hCG, β-human chorionic gonadotropin; NSGCT, nonseminomatous germ cell tumor; LDH, lactate dehydrogenase; SGCT, seminomatous germ cell tumor.

Adapted with permission from International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. *J Clin Oncol*. 1997;15(2):594-603. Copyright © 1997 by American Society of Clinical Oncology.

CONCLUSION

The retroperitoneum is a challenging space for clinicians with a wide variety of possible histologies and adjacent normal tissues limiting therapeutic options. Advances in imaging have improved the ability to characterize these lesions, although, ultimately, a histologic diagnosis is necessary. In general, treatment is driven by histology. For most neoplasms in the retroperitoneum, evaluation by a multidisciplinary team is necessary. RT technology advances, including the use of IMRT and particle therapy, have improved the ability to deliver a therapeutic radiation dose to the tumor in this challenging space while sparing abutting organs at risk. Although much progress has been made with advances in surgery, systemic

therapy, and RT, patient outcomes remain poor; thus, additional advancements need to be made, including more prospective multi-institutional studies.

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CHAPTER 83

Adrenal Cancer

Filip T. Troicki

ANATOMY

The paired suprarenal (adrenal) glands are located between the superomedial aspects of the kidney and the diaphragmatic crura. They are surrounded by connective tissue containing perinephric fat. The glands are enclosed by renal fascia but separated from the kidneys by fibrous tissue. The triangular right gland relates to the diaphragm posteriorly and the inferior vena cava and liver anteriorly. The semilunar left adrenal gland is positioned in the middle of the left crux of the diaphragm. The omental bursa separates it from the stomach. It is also related to the spleen and pancreas.[1]

The endocrine function of the adrenal glands necessitates an abundant blood supply. The superior suprarenal arteries are derived from the inferior phrenic artery, the middle suprarenal arteries from the abdominal aorta near the origin of the superior mesenteric artery, and the inferior suprarenal arteries from the renal artery. A large central vein leaves the anterior surface of the gland at the hilum. The shorter right suprarenal vein drains into the inferior vena cava, and the longer left suprarenal vein drains into the left renal vein.[1]

The lymphatic drainage follows the arterial supply and is predominantly to lumbar lymph nodes. The superior lymphatic trunks end in aortocaval lymph nodes located near the origin of the celiac plexus. The inferior lymphatic trunks end in lateral aortic nodes above the renal pedicle. Some trunks may pass through the diaphragm, following the splanchnic nerves, ending in retroaortic nodes in the posterior mediastinum. On the right, some lymphatic trunks may penetrate the liver.[2]

The adrenal gland is composed of a central catecholamine-producing medulla enveloped by the steroid-secreting cortex. Although they are in

intimate contact, they represent two functionally separate organs with different embryologic origins.

EPIDEMIOLOGY

Adrenal Cortical Tumors

Adrenocortical carcinomas (ACCs) are rare. Benign tumors are more common, occurring in 1% to 8% of the general population, and are typically discovered incidentally in up to 4% of abdominal imaging studies.[3] The incidence of carcinoma is approximately 1 per million population in the United States.[4,5] There are approximately 75 to 115 new cases per year.[6] Adrenal cortex carcinoma deaths account for 0.2% of all yearly cancer deaths. There is a bimodal age distribution with disease peaks before the age of 5 years and in the fourth to fifth decades of life.

Overall, ACC is slightly more common in women than in men. Nonfunctional carcinomas occur in an older age population (>30 years old) and are more common in men (3:2 male-to-female ratio), although functional tumors are more common in women (7:3 female-to-male ratio) and younger patients. As they frequently present with symptoms related to hormone production, typically symptomatic cortisol hypersecretion, functional tumors are usually detected at an early stage.

Although most cases of ACC are sporadic, it has been described as a component of several hereditary cancer syndromes, including Li-Fraumeni syndrome (breast cancer, soft tissue and bone sarcoma, brain tumors, and ACC), Beckwith- Wiedemann syndrome (Wilms tumor, neuroblastoma, hepatoblastoma, and ACC), multiple endocrine neoplasia type I (MEN-I) (parathyroid, pituitary and pancreatic neuroendocrine tumors, and adrenal adenomas and carcinomas), and sarcoma, breast, lung, ACC, and other tumors.[7-10] A role for p53 mutations in sporadic ACC is suspected.

Adrenal Medulla Tumors

Ganglioneuromas are rare, benign tumors of the adrenal medulla seen in children and young adults.[11,12] Neuroblastoma is the most common malignant tumor of the adrenal gland in children, accounting for 90% of all cases.[4,13]

Pheochromocytomas and functional ganglioneuromas (or extra-adrenal pheochromocytomas) are rare tumors that arise from chromaffin cells in the adrenal medulla and elsewhere. They secrete catecholamines and cause intermittent, episodic, or sustained hypertension. Pheochromocytomas have an estimated prevalence of 0.1% in patients with hypertension.[14] In autopsy series, there is a 0.01% to 0.1% prevalence of unsuspected pheochromocytomas. Extra-adrenal tumors are more commonly malignant.[15] Estimates of the incidence of malignancy in pheochromocytoma range from 5% to 46% in different series.[16,17] Approximately 400 new cases of malignant pheochromocytomas are expected each year in the United States.[18,19]

Pheochromocytomas may be associated with a variety of endocrine and nonendocrine inherited disorders. Bilateral pheochromocytomas are a component of multiple endocrine neoplasia type IIA (MEN-IIA) syndrome (pheochromocytoma, medullary thyroid carcinoma, and parathyroid hyperplasia) or MEN-IIB syndrome in which they are associated with marfanoid habitus, mucosal neuromas, and medullary thyroid carcinoma. Pheochromocytomas occur in 25% of patients with von Hippel-Lindau syndrome and <1% of patients with neurofibromatosis and von Recklinghausen disease.[20,21]

NATURAL HISTORY

Fifty-nine percent of adrenal cortex tumors are functional, the left-to-right ratio is approximately 1:1, and 2.4% are bilateral.[22] Unless bothersome symptoms prompt a rapid workup, diagnosis is frequently delayed because of the rarity of the disease and the deep retroperitoneal location of the adrenal glands.[23]

Nonfunctioning ACCs are typically large, often >6 cm, whereas functioning tumors are smaller because they tend to be discovered at an earlier stage (for tumor, node, metastases [TNM] staging, see Table 83.1). Incidentally discovered adrenal masses <4 cm are rarely malignant. In fact, a study from the National Italian Study Group on Adrenal Tumors found that 90% of adrenal carcinomas found incidentally were >4 cm in diameter.[24] ACC is an aggressive malignancy that frequently violates the tumor capsule and invades surrounding tissues. It metastasizes early to

lungs, liver, brain, and regional lymph nodes. Many patients present with widespread metastasis; most of these patients die within 6 months of diagnosis. This situation is especially common in the pediatric population. For all stages, the 5-year overall survival (OS) is only 20% to 25%.[23]

TABLE 83.1 TNM STAGING FOR ADRENAL CELL CARCINOMA

Tumor (T)
T1: Tumor ≤5 cm in size; invasion absent
T2: Tumor >5 cm in size; invasion absent
T3: Tumor outside adrenal in fat
T4: Tumor invading adjacent organs
Lymph nodes (N)
N0: No positive lymph nodes
N1: Positive lymph nodes
Metastases (M)
M0: No distant metastases
M1: Distant metastases
Stage I—T1, N0, M0
Stage II—T2, N0, M0
Stage III—T1, N1, M0, T2, N1, M0, T3, N1, M0
Stage IV—T3, N1, M0, T4, N1, M0, any T, any N, M1

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Malignant pheochromocytomas not only exhibit a similar pattern of spread but also metastasize to bone. They are equally common in men and women. The average age of presentation is 40 to 50 years old, but these carcinomas may also occur in children.

CLINICAL PRESENTATION

Functional adrenocortical tumors most frequently secrete cortisol and androgens, resulting in Cushing syndrome, virilization, and hypertension. Estrogen or aldosterone production is less common. It is estimated that up to 10% of adult patients with Cushing syndrome have adrenal adenomas. Approximately 60% of ACCs are functional. In a child, virilization is the most common symptom of ACC, and Cushing syndrome is relatively uncommon. By contrast, adults usually present with either Cushing syndrome alone or mixed with virilization. Patients with nonfunctioning

tumors present with nonspecific symptoms related to tumor burden, including abdominal fullness, early satiety, pain, weight loss, weakness, fever, or an abdominal mass. Nonfunctioning ACCs are more common in older patients and tend to progress more rapidly. An increasing number of adrenal tumors are incidentally discovered during abdominal imaging in the absence of any symptoms.

Pheochromocytomas arising in the setting of an inherited disorder occur in the adrenal medulla in 90% of cases, as compared with 75% of sporadic pheochromocytomas. When associated with MEN-II syndromes, 80% are bilateral. A tumor >4 cm more commonly has a malignant course than a smaller lesion. Serum catecholamines and urinary metanephrine and vanillylmandelic acid levels are elevated in 90% of pheochromocytomas. These patients present with a range of symptoms from mild labile hypertension to sudden cardiac death secondary to hypertensive crisis, myocardial infarction, or cerebrovascular accident. The classic triad of symptoms consists of episodic headaches, diaphoresis, and tachycardia.[9,25] About half of patients have paroxysmal hypertension, and others have sustained hypertension. Pheochromocytomas may also present with normal blood pressure in 5% to 15%. Other symptoms may include pallor, palpitations, panic attack symptoms, or generalized weakness. Orthostatic hypertension may occur in association with hypovolemia.

DIAGNOSTIC WORKUP AND STAGING

Patients with adrenal gland tumors should be evaluated for other primary tumors. Metastases to the adrenal gland, typically from lung, breast, skin, kidney, thyroid and colon, are far more common than primary adrenal gland tumors.[26] In metastatic tumors that are not adrenal in origin, a biopsy is recommended. Prior to obtaining a biopsy, however, pheochromocytomas must be ruled out by measuring the fractionated plasma-free metanephrine, as well as the 24-hour urine fractionated metanephrines and catecholamines. Low suspicion for pheochromocytoma either clinically or biochemically should steer providers toward obtaining an adrenal biopsy. Furthermore, any patient with a suspected adrenal tumor should be screened for hormonal hypersecretion, including cortisol, aldosterone, and catecholamine secretion (Table 83.2). As hypercortisolism is the most

frequent abnormality, serum cortisol, a 24-hour urinary cortisol, and an overnight dexamethasone suppression test should be obtained.

TABLE 83.2 DIAGNOSTIC WORKUP FOR ADRENAL TUMORS

General
History
Physical examination
Radiology
Chest CT
Abdominal CT with thin cuts MRI
Ultrasonography
Angiographic studies
Nuclear medicine studies
Fluorodeoxyglucose positron emission tomography
Laboratory studies
Complete blood count, blood chemistry, urinalysis
Serum and urine cortisol (adrenal cortical tumors)
Serum and urine catecholamines (pheochromocytoma)

CT, computed tomography; MRI, magnetic resonance imaging.

Morphologic evaluation of the adrenal glands with computed tomography (CT) of the abdomen should be performed as per adrenal protocol. CT of the abdomen with thin cuts through the adrenal gland is the imaging test of choice for the evaluation of adrenal tumors. Carcinomas can mimic adenomas but are characterized by larger size, irregular margins, and heterogeneous enhancement. They may also demonstrate tumor necrosis and cystic degeneration. Local invasion, tumor extension into the vena cava, as well as lymph node or other metastases are often seen in advanced ACC. Magnetic resonance imaging (MRI) is useful in the evaluation of adrenal tumors (Figure 83.1). ACC and pheochromocytomas are hyperintense on T2-weighted images, and venous invasion is better imaged on MRI. If there is still question of vascular invasion, an angiographic study can be performed preoperatively, either selective arteriography or vena cavography. Fluorodeoxyglucose positron emission tomography may be useful in differentiating benign from malignant lesions. It may also serve as an additional staging study for patients with known ACC. A chest CT should also be obtained.

FIGURE 83.1 T2-weighted magnetic resonance image of a 35-year-old woman with a left adrenal carcinoma.

Evaluation of the patient's adrenal function is indicated if there is no suspicion of adrenal metastasis. Workup for hyperaldosteronism, Cushing syndrome, and pheochromocytoma should be performed when clinically indicated. The diagnosis of pheochromocytoma is confirmed by measurements of urinary and plasma fractionated metanephrines and catecholamines. Medication-induced elevation of metanephrine levels is common and should be evaluated prior to initiating further costly workup. Levels of metanephrine 4 times the normal limit are diagnostic of pheochromocytoma, and biochemical confirmation of disease is followed by imaging to locate the tumor. Other scans, including the OctreoScan

(Mallinckrodt Inc) and a bone scan, may be indicated if metastatic disease is suspected.

Levels of plasma aldosterone (high) and renin (low) activity should be assessed when suspecting primary aldosteronism (hyperaldosteronism). The ratio of aldosterone to renin above 30 is suggestive of hyperaldosteronism and should be confirmed with saline suppression or salt loading tests, and electrolytes should be measured. Although malignant hyperaldosteronism is rare, these patients require an open adrenalectomy (OA) to prevent tumor rupture. In benign cases of hyperaldosteronism, adrenal vein sampling for aldosterone is considered standard of care.

Patients with Cushing syndrome require an evaluation of serum levels of corticotropin, cortisol, as well as the sex steroid dehydroepiandrosterone sulfate. If cortisol levels are elevated, a confirmatory test with dexamethasone suppression is recommended. It is important to remember that elevated corticotropin levels do not indicate adrenal origin, and further workup is necessary to look for primary causes of increased corticotropin. Benign adrenal tumors can be removed laparoscopically. Patients who present with Cushing syndrome in the presence of large (>4 cm), inhomogeneous, or invasive masses should be suspected to have malignant tumors, and imaging of the chest, abdomen, and pelvis is warranted to look for metastasis.

Pathologic Classification

Tumors <6 cm are more likely adenomas, although some smaller tumors may be malignant (Table 83.3). In order to establish stability of an adrenal mass, imaging should be repeated in 6 to 12 months for benign-appearing adenomas measuring <4 cm, and 3 to 6 months for larger lesions up to 6 cm. Hemorrhage and necrosis may be observed macroscopically in carcinomas. Numerous mitotic figures and cellular undifferentiation are common microscopic findings. Larger size, vascular invasion, or invasion of surrounding tissues and numerous mitotic figures are poor prognostic features.[27]

TABLE 83.3 CLASSIFICATION OF ADRENAL TUMORS

Adrenal cortex

Adenoma
Functioning
Nonfunctioning
Carcinoma
Adrenal medulla
Ganglioneuroma
Pheochromocytoma
Neuroblastoma
Mixed type (ganglioneuroblastoma)
Connective tissue tumors
Myelolipomas
Lipomas
Myomas
Angiomas
Fibromas
Fibrosarcoma

Pheochromocytomas have malignant features in <10% of cases. Macroscopically, they tend to be encapsulated with areas of cystic change, hemorrhage, and necrosis. The capsule is frequently invaded, but that does not constitute malignant change. Benign and malignant pheochromocytomas may appear identical histologically. A fine-needle aspiration cannot be utilized to differentiate between a benign or malignant adrenal tumor, but it can be used when a metastatic adrenal lesion is suspected.[10] A pheochromocytoma must be ruled out with biochemical testing before any biopsy is attempted in order to avoid a potentially devastating hemorrhage, hypertensive crisis, or capsular rupture.[28] Histologically, cell size, nuclear size, and arrangement of cells are variable. A twisted cell cord pattern, basophilic or cytophilic staining with fine intracytoplasmic pigment granules, and periodic acid-Schiff staining of secretory droplets aid in the diagnosis.

GENERAL MANAGEMENT

The most important prognostic factors that predict outcomes in patients with ACC are stage and extent of resection. Benign tumors are nonfunctioning and are most often found incidentally. After the benign nature of these tumors is confirmed, small tumors can be left untreated and can be followed up by repeat imaging 6 to 12 months after diagnosis to confirm their stability. Larger tumors (>4 cm) should be followed up with

imaging in 3 to 6 months after diagnosis. A small benign mass that grows at the rate of >1 cm/y can be removed electively, but any significant growth of a larger mass should alert the clinician to a potentially malignant nature of the tumor and adrenalectomy is recommended in that case.

Nonfunctioning adrenal tumors that are >4 cm, are heterogeneous, or have irregular margins are suspicious for adrenal carcinomas. Surgery with removal of adjacent lymph nodes is the primary and only potentially curative treatment for ACC, especially in stage I and II patients.[29] Complete resection is the only treatment that offers long-term disease-free survival, but it is not always feasible.[30] Although minimally invasive adrenalectomy (MIA) has been pursued at some institutions, data regarding the management of MIA are limited, and as of this publication, OA remains the gold standard. For patients with a macroscopically complete resection, a margin-free resection is a strong predictor for survival. Efforts to avoid tumor spillage are warranted, and the tumor capsule should remain intact. Invasion or adherence of adjacent structures often necessitates en bloc resection of the kidney or spleen, partial hepatectomy, or pancreatectomy. The presence of tumor thrombus in the renal vein or vena cava does not preclude resection. A lymphadenectomy is often included. An extensive regional lymph node dissection has not been shown to have any impact on OS or disease-specific survival.[31] For patients with localized disease who have high-risk features, such as positive margins, rupture of capsule, high grade, or large size, postoperative radiation should be considered. The role of tumor debulking in the presence of metastatic disease is not clear. Incomplete resection of the primary tumor or metastatic disease not amenable to surgery is associated with a poor prognosis. Still, tumor debulking may help control hormonal oversecretion or relieve local symptoms in certain cases. Neoadjuvant chemotherapy to facilitate surgery is not a standard approach, although cisplatin-based treatments have been shown to have a cytoreductive effect in some patients.[32] Even with a complete resection, local recurrence and metastatic disease are common. For isolated distant metastases and locally unresectable disease, cytoreductive resection with or without radiation is recommended.

Adjuvant therapies typically depend on factors that affect recurrence risks. Patients with low recurrence risk include those who are early stage and underwent a complete resection of the tumor (R0). Proliferation marker

Ki67 below 10% has been shown to be another favorable feature after an R0 resection of ACC.[33] Low-risk patients can be typically observed postoperatively. High-risk patients have a higher risk of recurrence and typically require some form of adjuvant treatment.

Mitotane, a chemical congener of the insecticide dichlorodiphenyltrichloroethane, is an adrenolytic compound with specific activity on the adrenal cortex. It is the chemotherapeutic agent most commonly used in the management of ACC. In patients with measurable disease, overall response rates of 14% to 36% have been reported, but most studies have reported no significant survival benefit.[34] The largest retrospective study from Italy and Germany that included 177 patients with resected ACC (stages I-III) showed improvements in disease- free survival and OS.[35] Unfortunately, responses are usually partial and transient, with only an occasional complete remission.[22] The role of mitotane as adjuvant therapy after complete surgical resection is questionable. Despite limited supporting data, it is frequently employed in this setting, given the high rates of locoregional and distant recurrence. Serum levels of mitotane are monitored in order to optimize therapy because objective response in the metastatic setting was associated with higher serum levels (>14 mg/L). Unfortunately, increased toxicity is also associated with higher serum levels. Side effects are predominantly gastrointestinal, particularly nausea, but anorexia and diarrhea also occur. Although less common, central nervous system toxicity can include lethargy, somnolence, ataxia, dizziness, or confusion.

Single-agent chemotherapy has proven disappointing in the management of ACC. Doxorubicin and cisplatin have both been evaluated as either single-agent therapy and in combination with mitotane. Neither drug was efficacious.[36] Multiagent chemotherapy has shown more promise. A multicenter phase II study by the Italian Group for the Study of Adrenal Cancer demonstrated 49% overall response rate using a regimen of etoposide, doxorubicin, and cisplatin in combination with mitotane. The regimen was well tolerated. The most common side effects were gastrointestinal. The time to progression in responding patients was 2 years.[7] Inclusion of mitotane in a multidrug regimen is rational as ACCs are prone to multidrug resistance mediated by the multidrug resistance-1/P

glycoprotein drug pump, whose mechanism is inhibited by mitotane. This multidrug regimen is worthy of further study.

The role of radiation in the management of ACC is not well defined. Adjuvant radiation in patients with stages I and II ACC who underwent a complete resection is typically discouraged. Radiation has been proposed as adjuvant therapy in patients with stage III disease, as well as those with high-grade adrenal carcinoma, and those who underwent an R1 or Rx resection or had tumor spillage during surgery. Although the benefits of adjuvant radiation are in local control, one series reported a 10-year crude survival rate of 33% for surgical resection followed by adjuvant radiation.[37] Previous beliefs that ACC is radioresistant have been challenged with a significant response of tumor cells when utilizing modern radiation techniques. External radiation results in good response rates and effective palliation in patients with residual macroscopic disease or bone or nodal metastasis.[19,38]

Surgical resection is the definitive management of pheochromocytoma, but it is a high-risk procedure. Cardiovascular and hemodynamic parameters must be monitored closely. Preoperative medical therapy is aimed at controlling hypertension and expanding intravascular volume. Preoperative pharmacologic preparation typically includes combined α- and β-adrenergic blockade.

In patients with undiagnosed pheochromocytomas who undergo surgery for other reasons, surgical mortality rates are high because of lethal hypertensive crisis and multiorgan failure.[39] In the largest series of 147 patients undergoing surgery for pheochromocytoma, perioperative mortality and morbidity rates were 2.4% and 24%, respectively.[40] Although it results in rapid symptomatic control, surgical removal of a pheochromocytoma does not always lead to a long-time cure. In a large series of 176 patients, pheochromocytoma recurred in 16% of patients. Half of these recurrences were malignant.[41] In patients with bilateral pheochromocytomas, usually in the setting of an inherited syndrome, bilateral adrenalectomy is recommended. Hormone replacement is required in this setting. Although not curative, debulking surgery for control of symptoms is the primary therapy for malignant pheochromocytoma.

The radioisotope iodine-131 metaiodobenzylguanidine (^{131}I-MIBG) has been used as a therapeutic agent in malignant pheochromocytomas that

demonstrate avid uptake of the agent. Investigators have reported partial responses, based on biochemical response as well as decreased tumor volume, ranging from 18% to 82%.[42-44] Symptomatic improvement was observed in responding patients with regard to both painful metastases and manifestations of increased catecholamine levels. Partial remissions are usually temporary, with some patients relapsing between doses of MIBG. In other patients, sustained partial remissions have been noted with durable palliation extending 2 to 3 years.[43,45] Prolonged survival has been associated with measurable responses and higher administered doses of MIBG (>500 mCi).[46] Toxicity includes bone marrow toxicity (particularly thrombocytopenia), nausea, and vomiting.

Combination chemotherapy with cyclophosphamide, vincristine, and dacarbazine has shown efficacy in a small study. In 14 treated patients, the clinical and biochemical response rates were 57% and 79%, respectively. Response was associated with objective improvement in performance status and blood pressure, and treatment was well tolerated.[47]

RADIATION THERAPY TECHNIQUES

The role of radiation in the management of ACC is controversial. Locoregional disease control remains a major problem in this disease, and some reports suggest that external radiation may reduce recurrence rates.

In the primary management of ACC, external radiation may play a role preoperatively for unresectable tumors, postoperatively for patients with residual disease or high risk of local failure, or as definitive therapy for patients who are medically unfit for surgery. In a recent large retrospective review, the time to tumor progression in advanced ACC has been significantly improved with conventional and stereotactic radiation.[48] Radiation is also effective in the palliative setting for bone and nodal metastases.

For patients with macroscopic or unresectable disease, doses of 50 to 60 Gy delivered during 5 to 6 weeks should be considered. Adjuvant radiation should be started within 12 weeks post-op. Initial fields should encompass the gross tumor with adequate margins as well as the regional lymph nodes, which should include the contralateral para-aortic and inter-aortocaval lymph nodes. Dose to regional nodes can be limited to 45 Gy when they are

not macroscopically involved. Care should be taken to limit dose to the spinal cord, kidneys, liver, and small bowel. Avoiding adjacent organs at risk is vital in treating adrenal cancers and intensity-modulated radiation therapy or volumetric modulated arc therapy should be considered standard. For patients receiving postoperative treatment for high-risk or microscopic disease, doses of 45 to 54 Gy are appropriate. The role of stereotactic body radiotherapy (SBRT) for primary adrenal tumors has not been established, although it is now a common practice for oligometastatic disease to the adrenal gland. A handful of case series have shown potential efficacy of SBRT for primary adrenal tumors that are unresectable because of comorbidities or patient preference. The popularity of SBRT for metastatic lesions is mainly based on results of case series and retrospective reviews, which show good local control rates ranging from 60% to 70% at year 1 and between 40% and 50% at year 2.[49] No prospective randomized trials are available to compare the efficacy of SBRT against a surgical resection. SBRT doses typically range from 30 Gy in 3 fractions to 50 Gy over 5 fractions for both primary and oligometastatic adrenal tumors.

In the palliative setting, doses of 30 to 40 Gy given during the course of 2 to 3 weeks are reasonable. In patients with painful bone metastases, hypofractionated regimens should be considered for patients with poor performance status or otherwise limited life expectancy.

External beam radiation is limited to a palliative role in the management of pheochromocytomas.

FOLLOW-UP

Patients with pheochromocytomas should have frequent follow-up that includes a thorough history and physical examination with an evaluation of vital signs and plasma markers. This should be done every 6 months for the first 3 years starting around 3 months postsurgery and annually thereafter. Advanced or persistent disease may require more frequent follow-up and symptom management.

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PART K

Lymphoma and Hematologic Tumors

CHAPTER 84

Hodgkin Lymphoma

Bradford S. Hoppe, Omran Saifi, and Richard T. Hoppe

The management of Hodgkin lymphoma (HL) continues to evolve. Since the last edition of this text, initial treatments have become more refined, relying on interim or end of systemic therapy response assessments to adapt therapies. The role of radiation therapy (RT) for early, intermediate, and advanced stages has become better defined. Targeted systemic therapy (brentuximab vedotin [BV]) has been introduced in all stages of disease, and immunotherapy with nivolumab and pembrolizumab has shown significant benefit in advanced and relapsed disease and is being explored in early stage, as well. Large prospective, randomized clinical trials have allowed us to refine treatments, and data regarding late effects continue to influence the development of management approaches.

ANATOMY

HL almost always begins in the lymph nodes. Over 80% of patients present with cervical lymph node involvement, and over 50% have mediastinal disease. Disease can extend into extralymphatic sites, such as lung, pericardium, and soft tissue, but solitary extralymphatic involvement without nodal disease is rare.

EPIDEMIOLOGY AND RISK FACTORS

The reported incidence of HL is 2.3 per 100,000, with a slight male predominance (1.2:1). It accounts for 0.51% of all cancers diagnosed. The death rate decreased from 0.7 per 100,000 per year to 0.1 per 100,000 per year between 1975 and 2020.[1] Although HL is rare in children older than 10 years, it is the fourth most commonly diagnosed malignancy among individuals younger than 20 years.[1] The median age of patients at the time of diagnosis is 26 years. Its incidence shows a bimodal peak as a function of age.[1] The early peak, from ages 20 to 24 years, shows an incidence

of approximately 4.1 per 100,000 per year. A second peak, from age 80 to 84 years, shows a similar incidence (4.4/100,000 per year).[1]

Geographic clusters of patients with HL have been reported, but these are likely coincidental.[2] Inherited risk has also been reported among first-degree relatives.[3] A relation between HL and previous infection with Epstein-Barr virus (EBV) has been proposed.[4] Components of the EBV genome have been identified in the cellular DNA of Reed-Sternberg (R-S) cells in lymph nodes involved by HL. The risk for the development of HL is 2.55 times higher among individuals with a history of infectious mononucleosis than among noninfected control subjects. Several series have demonstrated an association between EBV infection and mixed cellularity HL (MCHL), especially among children in developing countries. However, the precise relationship between EBV infection and the development of HL remains undefined.[5] The coexistence of EBV and human immunodeficiency virus (HIV) infections may account for the higher risk of HL in the acquired immunodeficiency syndrome population. Studies attempting to link occupational exposures or other etiologic factors with the development of HL have been inconclusive or contradictory.[2]

NATURAL HISTORY AND CLINICAL PRESENTATION

Patients with HL usually present with painless lymphadenopathy. Some note systemic symptoms such as unexplained fevers, drenching night sweats, weight loss, generalized pruritus, fatigue, and alcohol-induced pain in tissues involved by HL. Still, other patients are diagnosed after the detection of a mediastinal mass on a routine chest radiograph.

Sites of involvement are typically contiguous, although occasional skip areas occur.[6,7] The theory of contiguity of spread and the development of treatment programs with radiation that included treatment of uninvolved sites were important conceptual advances in the treatment of HL in the latter half of the 20th century.

HL can extend from the lymph nodes to adjacent organs, as when it spreads from enlarged mediastinal or bronchopulmonary (pulmonary hilar) nodes directly into the pulmonary parenchyma. It can also be hematogenous, as with nodular disease in the liver or multiple bony sites. Involved bones can undergo blastic changes, especially those in the vertebrae (creating the classic “ivory vertebra” on plain radiographs), pelvis, sternum, or ribs.

The likelihood of disseminated disease, including bone marrow and liver involvement, increases with splenic involvement.[8,9] HL rarely involves the Waldeyer lymphoid region or the gut-associated lymphoid tissues, such as Peyer patches. It also rarely involves the upper aerodigestive tract, central nervous system, and skin.[6]

The rapidity of HL’s growth and spread varies. Disease can evolve over several years, as demonstrated on serial radiographs or suspected by clinical history, and it

is uncommon to document progression during evaluation and staging.

Three "B symptoms" are included as part of the staging system for HL (see later discussion): fever, drenching night sweats, and significant weight loss (10% of baseline weight). One-third of patients present with one of these symptoms. Fevers may present in the classic waxing-and-waning Pel-Ebstein pattern. Drenching night sweats may require a change of bedclothes and/or sheets. The B symptoms can occur even in patients with relatively limited disease (stage II), but they are uncommon in stage I disease.

Historically, children fare better with treatment than adults, so different treatment strategies have been developed for children (see Chapters 97).[10,11] Yet, recent pediatric approaches in North America are utilizing adult systemic therapy backbones. Older adults (>60 years) have a worse prognosis, often secondary to intercurrent illness or an inability to tolerate standard therapies, especially bleomycin, anthracyclines, and extended-field RT.[12] The risk of bleomycin lung toxicity is especially increased in older patients.

If HL is diagnosed during pregnancy, special treatment considerations are warranted; however, no evidence exists that pregnancy affects the natural course of the disease. Adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine (ABVD) may be administered safely after the first trimester of pregnancy.[13] Many women become pregnant after successful treatment. Among patients infected with HIV type 1, HL tends to behave differently, with a poorer prognosis.[14]

DIAGNOSTIC WORKUP

Diagnostic and staging procedures commonly used for HL are listed in Table 84.1. Patient age and intercurrent disease may influence the selection of staging studies.[15,16]

TABLE 84.1 DIAGNOSTIC AND STAGING PROCEDURES FOR HODGKIN LYMPHOMA

History
Systemic B symptoms: unexplained fever, drenching night sweats, weight loss >10% of body weight in the last 6 mo
Other symptoms: alcohol intolerance, pruritus, respiratory problems, fatigue
Physical Examination
Palpable nodes (note number, size, location, shape, consistency, mobility)
Palpable liver or spleen
Laboratory Studies
Complete blood count, differential, platelets

ESR
Serum albumin, lactate dehydrogenase, liver function studies
Blood urea nitrogen, creatinine
If indicated:
Pregnancy test in women of childbearing age
Pulmonary function studies
Cardiac ejection fraction
HIV testing
Imaging
Chest radiograph: posterior-anterior and lateral
Integrated PET-CT scan (skull base to midthigh) (or integrated PET-MRI scan)

CT, computed tomography; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; PET, positron emission tomography.

Hematologic evaluation may reveal anemia, leukocytosis, lymphopenia, or thrombocytosis, common paraneoplastic effects stimulated by cytokines. Anemia, lymphopenia, leukocytosis, and hypoalbuminemia are adverse prognostic factors, especially in patients with advanced disease (stages III-IV).[17] The serum alkaline phosphatase level can serve as a nonspecific marker of tumor activity or hepatic, bone marrow, or bone disease. The erythrocyte sedimentation rate (ESR) is a prognostic factor for patients with limited disease (stages I-II).[18] Other useful markers include lactate dehydrogenase and β_2-microglobulin levels.

Radiographic evaluation with posterior-anterior (PA) and lateral chest radiographs is helpful for the stratification of patients in clinical trials. Mediastinal adenopathy can be measured by dividing the maximum width of the mediastinal mass by the maximum intrathoracic diameter (near the level of the diaphragm) on a standing PA chest radiograph. When this ratio exceeds 1:3, the disease is defined as bulky, which affects assignment to many clinical trials. Other definitions of bulky mediastinal adenopathy include a mass greater than 10 cm and a ratio of mediastinal mass to the chest diameter at T5-T6 exceeding 0.35 (employed in European Organisation for the Treatment of Cancer [EORTC] clinical trials). Contrast-enhanced (diagnostic) computed tomography (CT) scans of the chest, abdomen, and pelvis may reveal adenopathy or organ involvement but rarely identify disease beyond that detectable by an integrated positron emission tomography (PET)-CT scan. Lymph nodes larger than 1.5 cm on a CT scan are considered enlarged.[16] Although splenomegaly or hepatomegaly alone do not suggest involvement of HL (in the absence of confirmatory findings on a contrast-enhanced CT scan or 2-

fluoro-2-deoxy-D-glucose [FDG]-PET scan), a spleen over 13-cm long is considered likely involved per the current staging system.[16]

PET using FDG with fused CT images (PET-CT scan, subsequently abbreviated as PET) is essential to staging HL. Omitting PET as part of staging can negatively influence outcomes, especially as they pertain to designing radiation treatment fields.[19] Tissues affected by HL are intensely FDG avid, and FDG-PET is more sensitive than CT for detecting disease. FDG's uptake pattern in bone defines whether bone or bone marrow is involved, obviating the need for a bone marrow biopsy.[20] The overall incidence of bone marrow involvement in HL is only approximately 5%.

PET is also an essential study for response assessment, is particularly useful for evaluating residual masses detected by CT scanning, and can be a useful prognostic indicator when repeated after some chemotherapy (CT) has been administered (vide infra interim PET).[15,16] The 5-point Deauville visual score is used to evaluate the degree of response to therapy, based on the comparison of FDG activity in initial disease sites to background levels in the liver and mediastinal blood pool (Table 84.2).

TABLE 84.2 DEAUVILLE FIVE-POINT SCALE FOR ASSESSING TREATMENT RESPONSE ON PET-CT

Score	PET-CT Scan Result
1	No uptake
2	Uptake # mediastinum
3	Uptake > mediastinum but #liver
4	Uptake moderately higher than liver
5	Uptake markedly higher than liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma

PET-CT, positron emission tomography-computed tomography.

Although not widely used, magnetic resonance imaging (MRI) is an alternative to chest or abdominal-pelvic CT scanning for initial staging. Its main value is in the staging evaluation of children and pregnant women (without contrast). Furthermore, it can be incorporated with FDG-PET to generate fused PET-MRI scans.[21]

Staging

The Ann Arbor staging system for HL, used since 1971, was modified in the Cotswolds, England, in 1989,[22] and in Lugano, Switzerland, in 2014[16] (Table 84.3).[23] The lymphoid regions as defined in the Ann Arbor staging system are shown in

Figure 84.1. Although somewhat arbitrary in their anatomic borders, these definitions reliably describe the extent of disease and help to define clinical risk groups for clinical trial assignment. Defining the "E" lesion has always been a challenge. The Cotswolds system attempts to clarify it as a direct disease extension from any nodal site that can be encompassed by a radiation field; however, some scenarios are more complex.[24] The final stage reflects the distribution of disease as observed on physical examination and imaging studies, with or without B symptoms.

TABLE 84.3 THE ANN ARBOR STAGING CLASSIFICATION FOR HODGKIN DISEASE

Stage I	Involvement of a single lymph node region
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and one or more lymph node regions on the same side of the diaphragm (IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which can be accompanied by involvement of the spleen (IIIS) or by localized involvement of an extralymphatic organ or site (IIIE) or by both (IIISE)
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues, with or without associated lymph node involvement

The absence or presence of fever, night sweats, and/or unexplained loss of 10% or more body weight in the 6 months before diagnosis is denoted by the suffix letter A or B, respectively. The Cotswolds system used X to designate bulky disease, variably defined, but including a mediastinal mass width exceeding one-third of the thoracic ratio at the T5-T6 interspace and any disease >10 cm.[25] The Lugano system recommended deleting X and instead noting the size of the largest node.[26]

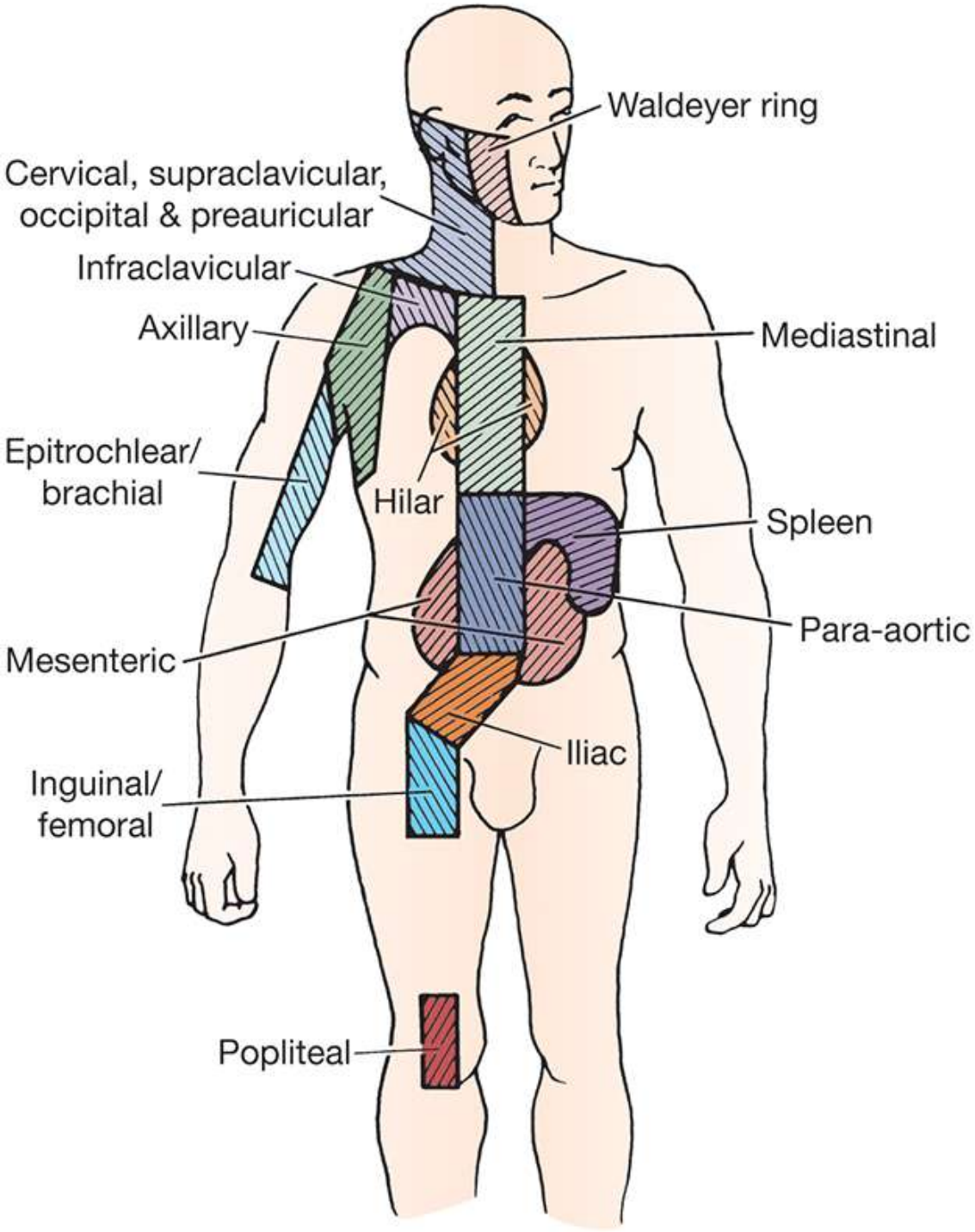

FIGURE 84.1 The lymph node regions are defined in the Ann Arbor staging system. Note that the ipsilateral supraclavicular, cervical, preauricular, and occipital nodes are defined as a single region. The mediastinum and pulmonary hila are defined as separate regions. The infraclavicular region corresponds to the subpectoral nodes. The GHSG and EORTC define the lymph node regions slightly differently. Both combine the hilar and mediastinal regions. The GHSG also combines subpectoral with cervical, whereas the EORTC combines subpectoral with axilla. EORTC, European Organisation for the Treatment of Cancer; GHSG, German Hodgkin Study Group. (Reprinted from Hoppe RT. The

non-Hodgkin's lymphomas: pathology, staging, treatment. *Curr Probl Cancer*. 1987;11[6]:364-434. Copyright © 1987 Elsevier. With permission.)

Pathologic Classification

The World Health Organization (WHO) defines two major categories of HL: classic HL (cHL) and nodular lymphocyte–predominant HL (NLPHL).[27] At the same time, the WHO acknowledges that NLPHL might be more accurately termed "nodular lymphocyte–predominant B-cell lymphoma." The Clinical Advisory Committee prefers the later term, recognizing its origin as a mature B-cell neoplasm.[26]

cHL is characterized by its signature neoplastic cell, the R-S cell. Morphologically, the R-S cell is binucleate with a prominent, centrally located nucleolus in each nucleus, a well-demarcated nuclear membrane, and eosinophilic cytoplasm with a perinuclear halo. R-S cells usually account for less than 1% of the cells in a lymph node involved by HL. The components of the microenvironment include lymphoid cells, eosinophils, plasma cells, and other normal inflammatory cells.[28]

R-S cells likely originate from B-lineage cells at various stages of development, including pre–B-cell and germinal center B-cell origin. Interactions of these cells with the cells of the microenvironment are complex.[5] In most instances, the R-S cells stain positively with the lymphocyte activation marker CD30, with PAX5 (dimly), and with variable expression of the antigranulocyte monoclonal antibody CD15. CD20, a marker of mature B cells, is expressed on some tumor cells with variable intensity in as many as 40% of cases. They stain negatively with CD45, ALK, and J-chain. Nearly all R-S cells express the PD-1 ligand.[29] The expression of CD30 and PD-L1 open opportunities for targeted therapy of cHL.

cHL is divided into four histologic subtypes. *Nodular sclerosis HL* (NSHL) is the most common histologic subtype diagnosed in developed countries. Involved nodes often have a thickened capsule and are traversed by broad bands of birefringent collagen that surround nodules of cells consisting of lymphocytes, eosinophils, plasma cells, and tissue histiocytes intermixed with a variable proportion of atypical mononuclear cells, inflammatory cells, and R-S cells. The syncytial variant of NSHL refers to cases of prominent cellular aggregates of atypical cells and histiocytes. Patients with NSHL typically present in the clinic with mediastinal involvement, and one-third have B symptoms. It is more common among women, especially young ones. The natural history of NSHL is favorable.

MCHL is characterized by lymph nodes that are diffusely effaced by lymphocytes, eosinophils, plasma cells, inflammatory cells, and relatively abundant atypical mononuclear and R-S cells. Adult patients with MCHL usually present with

advanced disease and tend to be slightly older than those with NSHL. The natural history of MCHL in adult patients is less favorable than that of NSHL.

Lymphocyte-rich Hodgkin lymphoma (LRHL)[30] typically has a nodular growth pattern but may be diffuse. In the past, many cases of LRHL were confused with lymphocyte- predominant HL (LPHL); however, the staining characteristics of the malignant cells in LRHL are consistent with those of cHL. The clinical characteristics of patients affected by LRHL resemble those of NLPHL: early stage, absence of B symptoms, and excellent prognosis.

Lymphocyte-depleted Hodgkin lymphoma (LDHL) varies in its microscopic appearance but reveals a paucity of normal-appearing cells and an abundance of abnormal mononuclear cells, R-S cells, and R-S variants. Differentiating LDHL from anaplastic large cell lymphoma is sometimes challenging, especially because both are CD30 positive. It is an exceedingly uncommon subtype of HL. It tends to occur in older patients and is more likely to be associated with advanced disease and B symptoms. It has the worst prognosis of all histologic subtypes of HL.[31]

NLPHL has recently been subdivided into six immunoarchitectural patterns based on morphology and immunohistochemistry characteristics termed *typical and variant histologies*.[32,33] Unlike the other subtypes of HL, the abnormal cells ("L and H cells" or "popcorn cells"), which are few in number, are strongly reactive for CD20, CD45, CD79a, and PAX5 and negative for CD15 and CD30.[27] NLPHL is usually diagnosed in early-stage disease, often in a single peripheral nodal site. Systemic symptoms are uncommon (<10%). The natural history is the most favorable of the histologic subtypes. Some patients demonstrate a pattern of late relapse but good survival, resembling that observed in the follicular (B-cell) lymphomas. In as many as 14% of patients, NLPHL will transform into an aggressive B-cell lymphoma as part of its natural history.[25,34] Patients with a variant histology, versus those with typical NLPHL, are at greater risk for transformation[33,34] and are also more likely to present with advanced disease and experience disease relapse. A reactive process termed *progressive transformation of germinal centers* may be observed either before, with, or after the diagnosis of NLPHL.[35,36]

PROGNOSTIC FACTORS AND THERAPEUTIC IMPLICATIONS

In HL, prognostic factors are important for defining therapy and predicting outcome. Histologic subtypes now have little impact on therapy, except for the identification of NLPHL, for which different treatment algorithms apply. Although large series report a slightly worse outcome for men than women,[1] gender influences treatment selection primarily because of potential reproductive complications (see section "Sequelae of Treatment").

Ann Arbor stage is the primary determinant of therapy. Stage has a marked impact on prognosis, although current management programs blur its influence. For many patients, disease bulk influences treatment selection, especially bulky mediastinal disease. Combined modality therapy historically was the preferred option for patients with bulky disease; however, those with a complete response (CR) by interim PET may do similarly well with CT alone.[37]

An important international study evaluated a series of prognostic factors among 5,141 patients with advanced-stage HL (Table 84.4).[17] Seven factors were identified, each of which had an independent yet similar effect on prognosis. Unfavorable factors included male gender, age greater than 45 years, Ann Arbor stage IV, hemoglobin level less than 10.5 g/dL, white cell count greater than 15,000/mL, lymphocyte count less than 8% or absolute lymphocyte count less than 600, and albumin less than 4 g/dL. Note that neither bulk, ESR level, presence of B symptoms, nor histology was important factor. The International Prognostic Score (IPS) is now used to assign patients to clinical trials. Patients with three or more adverse risk factors are often considered to be in an unfavorable prognostic group for stages III to IV HL. Recently, the HOLISTIC group developed the Advanced-stage classic Hodgkin Lymphoma International Prognostication Index calculator based on greater than 5,000 diagnosed with advanced-stage HL between 1996 and 2014, which includes age, sex, stage, bulky absolute lymphocyte count, hemoglobin, and albumin with Kaplan-Meier estimators of 0.77 for 5-year progression-free survival (PFS) and 0.92 for 5-year overall survival (OS).[38]

TABLE 84.4 INTERNATIONAL PROGNOSTIC SCORE FOR ADVANCED HL[17]

Factor	Unfavorable Covariate
Serum albumin	<4 g/dL
Hemoglobin	<10.5 g/dL
Sex	Male
Age	≥45 y
Stage	IV (Ann Arbor)
Leukocyte count	≥15,000/mm^3
Lymphocyte count	<600/mm^3 or <8% of white count

HL, Hodgkin lymphoma.

Patients with stage I or II diseases often have only one or two adverse factors based on the IPS. Other factors, such as the number of sites of disease, age, ESR, bulky disease, and the presence of B symptoms, can help stratify these patients with

early-stage disease by prognosis and are often used for assignment to clinical trials. Unfortunately, the criteria for defining "unfavorable" presentations of stage I to II diseases vary among clinical trial groups. The German Hodgkin Study Group (GHSG) includes any of the following: ESR 30 mm or higher with any B symptoms or 50 or higher without B symptoms, bulky disease based on mediastinal mass ratio (MMR) greater than 0.33, more than two nodal regions (defined by GHSG), or any E lesion. The EORTC criteria include age 50 or above, ESR 30 mm or higher with any B symptoms or 50 or higher without B symptoms, bulky disease defined by mediastinal thoracic ratio (MTR) 0.35 or greater, or more than three nodal regions (defined by EORTC).

The reliable FDG-avidity of HL has enabled the study of PET metrics as correlates of prognosis. One of these is the baseline metabolic tumor volume (MTV) or total MTV (TMTV). The TMTV is calculated by summing the metabolic volumes of all involved nodal and extranodal tissues, using a maximum standardized uptake value (SUV). A high MTV was shown to be an important prognostic factor in the EORTC H10 trial.[39] Total lesion glycolysis measured by the total body MTV multiplied by the SUV_{mean} of that MTV has been shown to be prognostic in pediatric HL.[40] Another PET metric is the D_{max}, a measure of the distance between the lesions that are the greatest distance apart. The D_{max} has been shown to have prognostic significance in diffuse large B-cell lymphoma but has not yet been tested in HL.[41]

In NLPHL, yet another IPS, the lymphocyte-predominant IPS has been proposed for all stages.[42] This includes the following adverse risk factors: age greater than 45 years, stage III to IV, hemoglobin less than 10.5, and splenic involvement.

GENERAL MANAGEMENT

Radiation Therapy

RT is the most effective therapeutic agent for treating HL and has been used in its management for over a century.[43] The optimal RT technique includes meticulous pretreatment evaluation of disease sites, precise simulation and immobilization, individually contoured treatment volumes according to the location of a patient's tumor configuration, radiation exposure to all adjacent organs at risk (OARs) that is as low as reasonably achievable (ALARA), an adequate target dose, a multifield fractionated regimen, and image guidance during therapy. Outcomes are best maximized and risks minimized through scrupulous attention to every detail of therapy.[44]

Chemotherapy

The standard drug combinations in use worldwide for the primary treatment of HL are ABVD[45,46] and bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP).[47]

Targeted Therapy

New systemic agents have been approved by the Food and Drug Administration for the treatment of HL. These include BV and the checkpoint inhibitors (CPIs) nivolumab[48] and pembrolizumab.[49] BV is an anti-CD30 monoclonal antibody linked to an antitubulin agent. BV has demonstrated efficacy in $CD30^+$ lymphomas, including HL and anaplastic large cell lymphoma. It is approved for pediatric and adult patients with advanced-stage disease and in those in the relapse or refractory settings.[50,51] Because of overlapping pulmonary toxicity, however, bleomycin is removed from any drug combination that includes BV, so trials of primary therapy with an ABVD backbone typically incorporate BV-doxorubicin, vinblastine, and dacarbazine (BV-AVD). Owing to the ETHERA trial, BV has been approved as a maintenance therapy following autologous hematopoietic cell transplant.[52] Pembrolizumab and nivolumab are both approved for patients with disease that is chemoresistant or has relapsed. Based on encouraging results from the S1826 study in pediatric and adult patients with advanced-stage disease, we may see nivolumab in conjunction with AVD (N-AVD) approved in the up-front setting for these high-risk patients.

Combined Modality Therapy

Combined modality therapy has become the most common form of general management for patients with HL. Modern treatment protocols can include RT of all initially involved sites, bulky sites only, slowly responding sites, or sites of incomplete response to CT. In general, RT of all initially involved sites is indicated when combined with abbreviated CT in early-stage HL. Treatment of just high-risk areas, such as bulky disease, slowly responding disease, or incompletely responding disease, is reserved for more advanced-stage disease treated with definitive CT (ie, six cycles of ABVD, BV-AVD, or escalated BEACOPP [eBEACOPP]).

RADIATION THERAPY TECHNIQUES

The principal objective of RT in HL is to treat regions at high risk for containing disease to a dose associated with a high likelihood of tumor eradication, meanwhile keeping the dose to adjacent tissues and organs ALARA. Thoughtful evaluation of all imaging studies, especially diagnostic CT and integrated PET scans; precise simulation with appropriate immobilization and consideration of organ motion;

detailed treatment planning; and effective and conformal treatment delivery, including image guidance, treatment verification, and appropriate quality assurance measures are requisite to achieving the best outcomes.[44]

Simulation

Patient positioning for simulation must allow for patient comfort, daily reproducibility, displacement of OARs (such as breasts) beyond the treatment field, impact of positioning on target delineation, and feasibility of treatment delivery. For patients with low neck and mediastinal involvement, a headrest with a face mask that extends the head can help pull the chin superiorly and beyond the radiation field. However, a headrest and face mask can also introduce uncertainties when fusing with the baseline staging PET scan, which is often done with the head flexed on a pillow for comfort. Arm position, in general, is more comfortable at the patient's side or slightly akimbo and affects whether breast tissue falls inferior/laterally or beyond the field, especially when combined with an inclined board and immobilization bag. Conversely, patients with axillary, infraclavicular, or subpectoral involvement may have smaller target volumes with less uncertainty when their arm position resembles that in the baseline PET scan because defining the target is challenging after systemic therapy. In these circumstances, the best position in which to treat the patient may be with arms above the head in an immobilization bag, which helps with reproducibility and with reducing the dose to the lungs. Occasionally, the prechemotherapy CT imaging is performed with arms up, whereas the PET scan is performed with arms down, providing both options to optimize treatment.

With proton therapy, some immobilization devices can hinder the path of the particle beam and compromise beam selection, a concern that should be evaluated with physics and dosimetry before simulation.

Simulation should be done with intravenous contrast to help define the interface between normal soft tissues and residual disease. Furthermore, it can be helpful in identifying the cardiac substructures.

Motion Management

Patients with mediastinal involvement and certain abdominal locations (eg, spleen) must undergo motion management strategies with the use of a four-dimensional (4D) CT scan or deep inspiration breath-hold (DIBH) technique.

4D CT scans acquire imaging throughout the full 10 phases of the respiratory cycle, allowing us to assess the margin to add to the clinical target volume (CTV) that will account for normal respiratory motion. This internal treatment volume

(ITV) margin can be an expansion of the CTV on the average scan of the 4D CT scan or independently drawn as the ITV, ensuring coverage of all 10 phases of the scan. In some cases, respiratory gating can be used to minimize the ITV margin.

Alternatively, DIBH is a technique that results in reduced doses to the lungs and may also reduce dose to the heart for patients with mediastinal involvement.[53] DIBH can spare additional volume of the lungs when treating superior mediastinal disease. In addition, DIBH pulls the heart medially and down, away from mediastinal disease located above the heart. In most cases, DIBH is likely to reduce the lung and heart doses, but in cases with extensive lower mediastinal involvement including cardiophrenic nodes, the relative benefit of DIBH for sparing the heart may diminish.[54]

Various techniques of DIBH have been described.[55-57] Important concepts to consider with DIBH include breath-hold reproducibility, the patient's ability to maintain the breath-hold or multiple breath-holds during treatment, and the breath-hold's impact on contouring. Our practice is to perform three DIBH scans at the time of simulation to assess reproducibility of the target across the three different breath-holds.

Involved-Node and Involved-Site Radiotherapy

The classic field configurations for HL treatment with RT alone have included the mantle and inverted Y. However, clinical trials have shown the equivalence of "involved-field radiotherapy" (IFRT) treatment with "extended-field" or "subtotal lymphoid" RT as part of combined modality therapy programs; thus, IFRT was adopted as the standard for combined modality therapy in clinical trials.[58-60] Field reductions and 3D target volume definitions comprise the loosely described techniques for "intelligent-field RT" and "modified IFRT." The more clearly defined "involved-node radiotherapy" (INRT)[61] and "involved-site radiotherapy" (ISRT)[44] have become the standard of care (SOC) in clinical practice and more recent clinical trials. INRT, as defined by Girinsky et al for the EORTC-GELA Lymphoma Group, requires baseline diagnostic CT and PET imaging with the patient in the treatment position, postchemotherapy contrast-enhanced CT simulation, and fusion of the baseline and postchemotherapy images.[61-63] The fields are designed to treat only the initially involved nodes with some modifications to avoid OARs. This gross tumor volume (GTV) then becomes the CTV, and a 1-cm expansion of the CTV defines the planning target volume (PTV).

When components of this planning process are missing—perhaps the pretreatment PET scan was not done in the treatment position, there is poor registration between scans, or the CT simulation scan was done without intravenous

contrast—it may be impossible to treat such strictly defined INRT fields. However, field reduction is still possible to what has been termed *involved-site radiotherapy*.[44]

ISRT volumes will vary depending on the clinical situation and treatment protocol. In general, because of the use of abbreviated chemotherapy (ie, 2-4 cycles of ABVD), patients with favorable early-stage HL receive ISRT to all initial sites of disease after completing chemotherapy.

For patients treated with RT alone (ie, NLPHL), the ISRT CTV should be increased to include sites of potential subclinical disease. In practice, this would mean an additional 2- to 5-cm margin within the lymphatic stations superior and inferior to the initially involved disease on PET imaging, taking into account the OARs.[64]

Among patients with unfavorable early-stage HL, ISRT to all sites of disease should be used when abbreviated chemotherapy has been delivered; however, for those who receive more intensive chemotherapy (such as six cycles of ABVD), certain complete responding areas that could result in an unacceptable dose to an OAR if included could be omitted (ie, cardiophrenic nodes or axillary lymph nodes in a young woman could be omitted if they have had a CR by CT scan). Patients with stage III/IV diseases previously received ISRT to sites of initially bulky disease, but recent data have questioned its benefit in the era of PET response assessment.[65,66] PET-directed RT (PD-RT) may still be used in patients with stage III/IV diseases to sites of slow or incomplete response to chemotherapy.

Design of Involved-Site Radiotherapy Fields

Many descriptive guidelines for ISRT and atlases exist.[67,68] The prechemotherapy GTV is based on localizing the initially positive lymph nodes (and extranodal sites) on the staging PET scan fused to the treatment planning CT. The postchemotherapy GTV is based on the anatomic residual disease observed at the time of CT simulation. When RT is the sole treatment modality, it is simple to identify the GTV, especially after PET simulation. This may be the case for treating patients with primary RT for NLPHL.[44]

For the more common situation of combined modality treatment, the CTV includes the postchemotherapy GTV and also the entire initial disease volume but is modified (reduced) to exclude uninvolved normal organs (eg, lungs, bones, muscles, great vessels) and to accommodate shrinking lymph node masses following chemotherapy, especially in the chest. The CTV can be expanded based on the quality of the initial imaging or owing to concerns of subclinical disease. For initially large mediastinal masses, the postchemotherapy treatment fields should conform to the width of only the residual disease (absent any pulmonary parenchymal extension), and the superior and inferior field margins should

encompass the initial extent of disease with the margin previously noted (Figure 84.2).[44] Adjacent organ dose constraints may also mean reducing the CTV. The PTV is an expansion of the CTV based on day-to-day setup uncertainties.

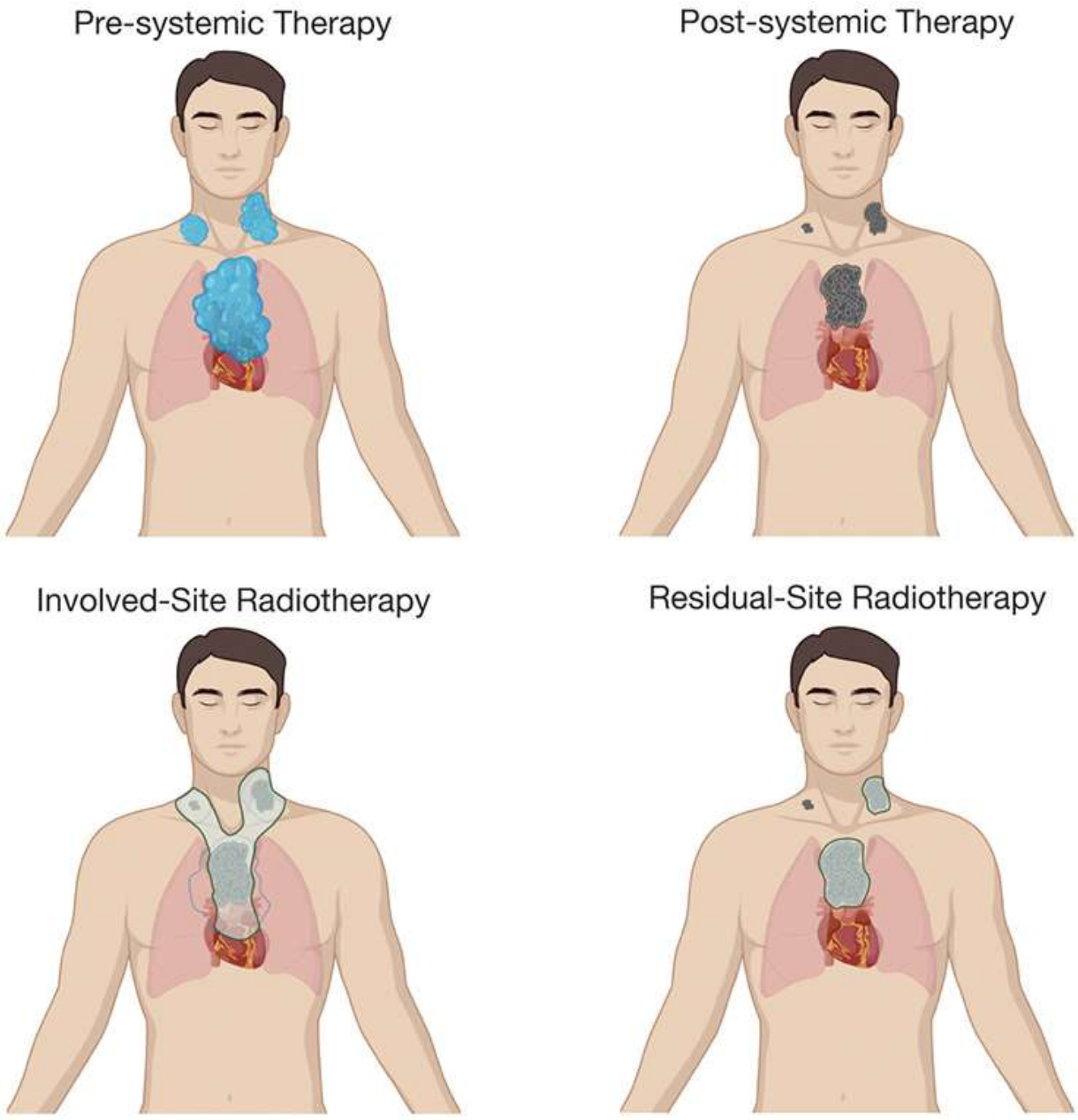

FIGURE 84.2 Involved-site and residual site radiotherapy volumes (green contours) in a patient with Hodgkin lymphoma involving the bilateral neck and mediastinum (blue masses) who achieved partial response following systemic therapy with residual computed tomography anatomic disease (black-gray masses) ≥1 cm in the left neck and mediastinum.

Contemporary Radiation Fields Beyond Involved-Site Radiotherapy

ISRT was developed to replace 2D era IFRT, while providing a more pragmatic field design compared to INRT. Yet, ISRT volumes can be interpreted and translated quite differently depending on the accuracy of pretreatment and simulation scans fusion, suspicion of subclinical disease involvement, and dose constraints of OARs. As such, several groups have begun to research smaller treatment volumes based on the postchemotherapy extent of disease, residual site radiotherapy (RSRT). While ISRT includes the prechemotherapy extent of disease in the cranial-caudal dimension, taking into account the postchemotherapy anatomic changes in the axial dimension, RSRT includes only the postchemotherapy anatomic extent of disease that is greater than a certain size cutoff (per protocol) as visualized on the contrasted CT simulation[69,70] (Figure 84.2). The RSRT volume may be much smaller than the ISRT volume and is very similar to the ISRT postchemotherapy gross tumor volume ($GTV_{postchemo}$) with a PTV margin. For patients with advanced-stage disease, the use of comprehensive RT to all sites of initial involvement is rarely employed, due to the significant amount of tissue irradiation. Instead, for advanced-stage disease, ISRT or RSRT can be restricted to areas at high risk of relapse, such as initially bulky sites, as per AHOD 1331[50] or based on interim or end of systemic therapy PET response as per S1826.

PET imaging is prognostic and can help identify disease sites at high risk of relapse, which may further direct the delivery of RT.[71] Negative interim and end of systemic therapy PET scans yield excellent outcomes regardless of receipt of RT.[65,66,72] This has restricted the use of RT on contemporary HL clinical trials to patients with positive PET/CT imaging. Thus, the NRG Hematologic Malignancies Working Group has provided consensus on the nomenclature of PD-RT that utilizes the interim and/or end of systemic therapy PET scans to better define sites at high risk of relapse, which may benefit from the addition of radiation or escalating the dose. Regardless of the initial presystemic therapy sites of disease, PD-RT would target only sites that are Deauville 4-5 on interim PET (if performed and indicated) and sites with partial or no response on end of systemic therapy PET scan. PD-RT can be used either alone or as a boost in combination with ISRT/RSRT based on patient's disease stage and treatment setting on current National Clinical Trials Network (NCTN) clinical trials (eg, AHOD 2131: NCT05675410).

PD-RT includes PET-directed involved-site radiotherapy (pISRT), PET-directed residual site radiotherapy (pRSRT), and PET-directed residual PET RT (pRPRT) (Table 84.5) (Figure 84.3). pISRT target volume includes the presystemic therapy involved lymph node site(s) that continue(s) to harbor PET-avidity on the interim and/or end of systemic therapy PET scan. pISRT may be used in noncontiguous early-stage or advanced-stage disease to identify areas at highest risk of relapse that warrant local therapy and was used in the AHOD 1331 trial.[50] pRSRT target volume

includes the postsystemic therapy CT anatomic residual mass that contains the PET-avid lesion on the interim and/or end of systemic therapy PET scan without covering/including all the initial extent of involved lymph node site(s). pRSRT can be used as a boost following ISRT as done for patients younger than 15 years on the AHOD 2131 trial, or for consolidation/salvage of residual disease in the up-front setting as per S1826 trial or relapsed/refractory setting. pRPRT target volume includes only the PET-avidity. It is very similar to pRSRT in cases where the residual CT anatomic mass is fully avid. However, it differs from pRSRT in cases where there is a large residual CT anatomic mass (pRSRT volume), with only a small focus of residual PET-avidity (pRPRT volume) as seen in patients with large bulky mediastinal mass who achieve partial response to systemic therapy. pRPRT is mostly used as a boost following ISRT, RSRT, or PD-RT as it is in S1826.

TABLE 84.5 CONTEMPORARY TUMOR VOLUMES AND TARGET DELINEATION DEFINITIONS

Gross Tumor Volumes (GTVs)	Clinical Tumor Volumes (CTVs)
$GTV_{prechemo}$ = Disease prior to any treatment based on the baseline PET/CT or PET/MRI scans	CTV_{ISRT} = lymph nodes/tissues originally involved with lymphoma (ie, $GTV_{prechemo}$) + a margin of 1.0 cm above and below $GTV_{prechemo}$
	CTV_{pISRT} = lymph nodes/tissues originally involved with lymphoma (ie, $GTV_{prechemo}$) that still contain PET-avidity on iPET and/or EST-PET ± a margin of 1.0 cm above and below $GTV_{prechemo}$
$GTV_{postchemo}$ = Residual CT anatomic mass ≥ 1 cm[a] on EST ± interim scans	$CTV_{RSRT} = GTV_{postchemo}$
GTV_{PET+} = PET-avid lesion on iPET and/or EST-PET	CTV_{pRSRT} = CT anatomic mass that contains GTV_{PET+}
	$CTV_{pRPRT} = GTV_{PET+}$

CT, computed tomography; EST-PET, end of systemic therapy positron emission tomography; iPET, interim positron emission tomography; ISRT, involved-site radiotherapy; MRI, magnetic resonance imaging; PET, positron emission tomography; pISRT, PET-directed involved-site radiotherapy; pRPRT, PET-directed residual PET radiotherapy; pRSRT, PET-directed residual site radiotherapy; RSRT, residual site radiotherapy.

[a]$GTV_{postchemo}$ size cutoff might be different based on protocol.

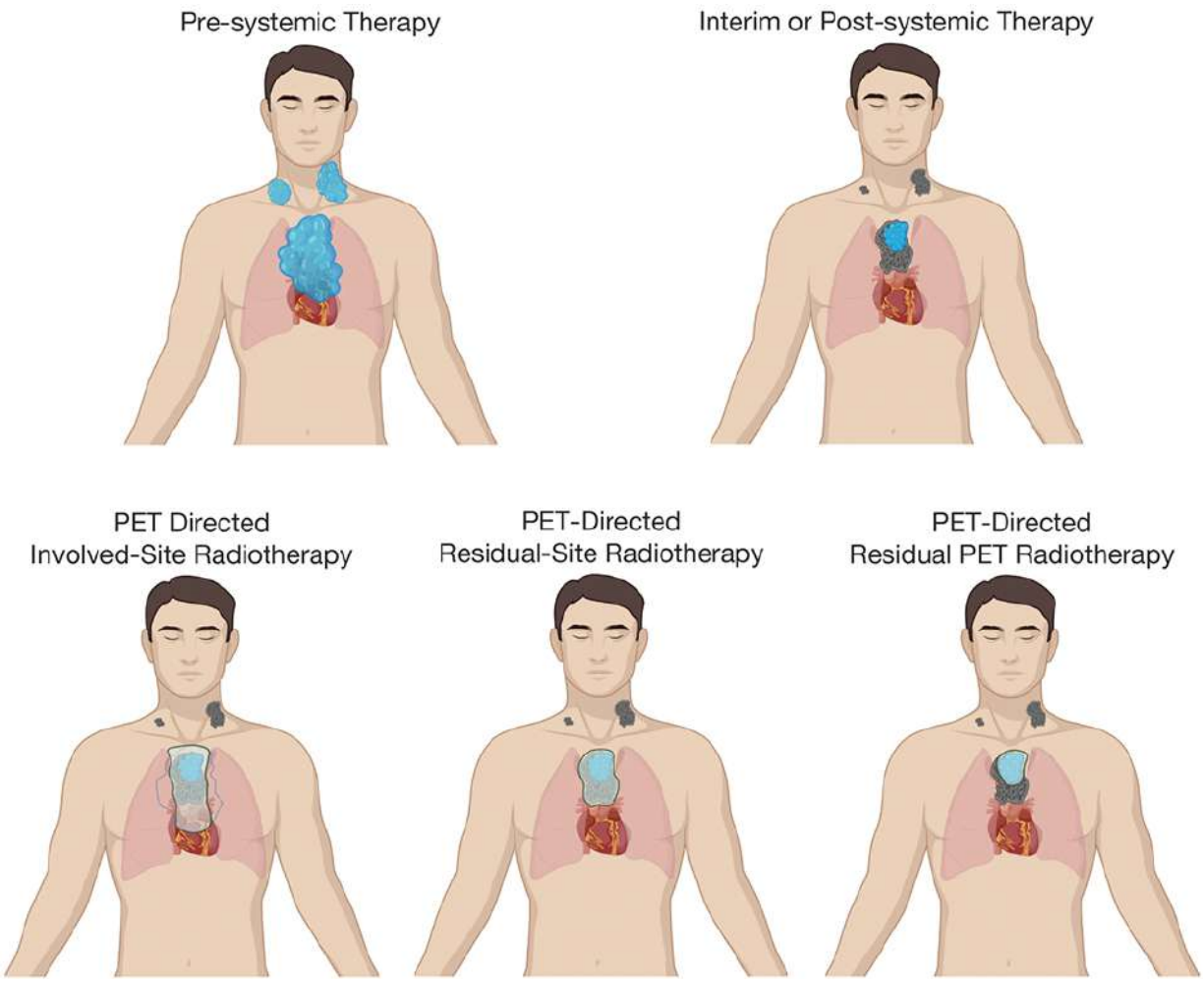

FIGURE 84.3 Positron emission tomography (PET)–directed radiotherapy volumes (green contours) in a patient with Hodgkin lymphoma involving the bilateral neck and mediastinum (blue masses) who achieved partial response following systemic therapy with residual PET-avidity (blue mass) in the mediastinum only, and non–PET-avid lesions (black-gray masses) in the bilateral neck.

Radiation Dose

In the uncommon scenario that RT alone is used for the treatment of HL (most commonly for NLPHL), national consensus guidelines recommend a dose of 30 to 36 Gy to involved sites and 25 to 30 Gy to sites of potential subclinical involvement, delivered in 1.5- to 2-Gy fractions. More commonly, however, RT is as a component of a combined modality approach, with chemotherapy expected to eradicate subclinical disease, and radiation playing a role in eradicating disease in involved sites. Doses vary considerably among trials, depending on the prognostic category of patients, disease bulk, and chemotherapy regimen. The dose ranges considered acceptable per national consensus guidelines are 20 to 30 Gy for nonbulky and 30 to 36 Gy for bulky sites, delivered 1.5 to 2 Gy per fraction.

Patients with incomplete metabolic response (Deauville 4, 5) following chemotherapy can receive higher doses (36-45 Gy).

Radiation Delivery

Historically, RT was delivered after 2D or 3D treatment planning, typically with opposed anterior-posterior (AP)/PA treatment fields. Over the past 20 years, however, with more refined radiation fields and 3D target delineation, modern radiation delivery systems have helped to reduce the radiation dose to the OARs. Such techniques require photon-based systems (intensity-modulated RT [IMRT], volumetric modulated arc therapy [VMAT], tomotherapy) and proton-based systems (3D and intensity-modulated proton therapy [IMPT]) with passive scatter, uniform scanning, and pencil beam scanning. The benefit of each treatment type depends on various factors, including disease distribution relative to the OARs, patient age and comorbidities, and type of prior chemotherapy. An example of the dose distributions achieved with 3D conformal radiotherapy (CRT), IMRT, and proton therapy for a patient is shown in Figure 84.4.[73]

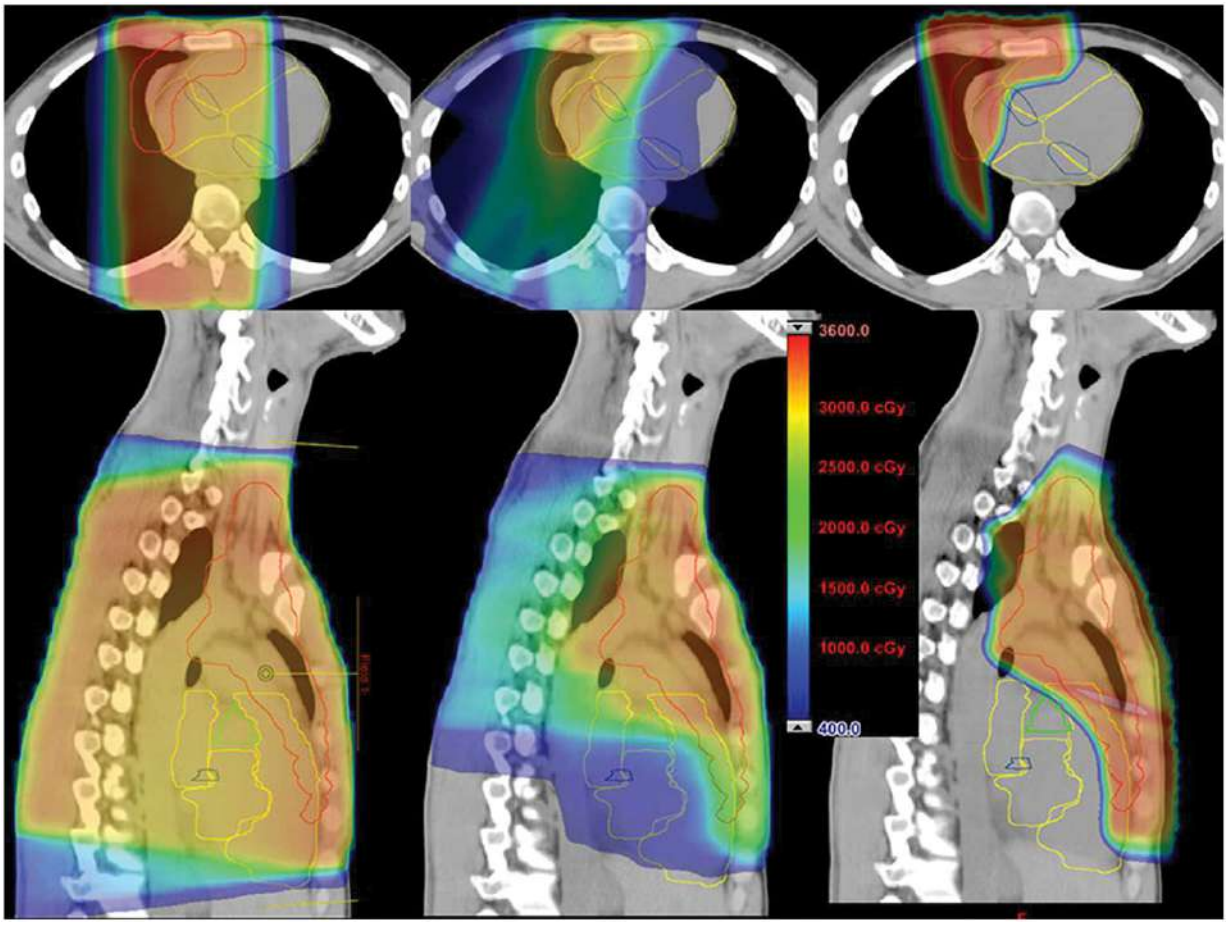

FIGURE 84.4 Involved-site radiotherapy axial and sagittal color wash isodose plans for a Hodgkin lymphoma patient with three-dimensional conformal radiation therapy (left), intensity-modulated radiation therapy (middle), and proton therapy (right). Cardiac chambers are outlined in yellow, cardiac valves are outlined in blue, and the planned target volume is outlined in red. (Reprinted from Hoppe BS, Flampouri S, Su Z, et al. Effective dose reduction to cardiac structures using protons compared with 3DCRT and IMRT in mediastinal Hodgkin lymphoma. *Int J Radiat Oncol Biol Phys*. 2012;84[2]:449-455. Copyright © 2012 Elsevier. With permission.)

In general, when comparing IMRT with 3D CRT plans, IMRT delivers a more conformal dose distribution in the high-dose region, but less conformality in the low-dose region and the creation of a "low-dose bath." Conversely, when comparing proton therapy techniques with 3D CRT, protons deliver a more conformal dose distribution in both the high- and low-dose ranges.

Among patients with high cervical disease, IMRT or protons can be useful in reducing the radiation dose to the parotid glands and oral cavity. But the radiation dose to the thyroid warrants consideration because the low-dose bath of IMRT can increase its exposure to radiation compared with conventional 3D CRT.

For most patients with involvement of the mediastinum and/or axilla, IMRT can improve dose-volume histogram (DVH) criteria for the heart, coronary arteries,

esophagus, and lungs, compared with 3D CRT. Yet, the low-dose bath from IMRT puts larger volumes of normal tissue at risk for the development of secondary cancer,[74,75] such as the breasts or pneumonitis,[76] although this may be overshadowed by the significant sparing of the heart and coronary arteries with the IMRT plan. Proton therapy allows for a reduced dose to the heart, lungs, breast, and body compared with either IMRT or 3D CRT techniques[75,77,78] without generating a low-dose bath.

Infradiaphragmatic radiation may also benefit from the use of IMRT or proton therapy, especially when the spleen is irradiated, to help minimize the radiation dose to the heart, stomach, pancreas, and left kidney.[79,80]

IMRT and proton therapy are also useful in patients reirradiated for relapsed disease close to or within a previously treated area.[81]

Clinical results using these modern radiation technologies are beginning to emerge, but, thus far, they only demonstrate clinical effectiveness in regard to disease control and acceptable rates of acute toxicities. Investigators at three centers have reported their experiences using IMRT for HL (N = 40-60 patients), observing excellent relapse-free survival (~95%).[63,82,83] Similar results have been found by investigators at proton therapy centers, some of whom conducted a small prospective clinical trial. In a combined analysis of academic and community proton centers where patients received consolidative proton therapy, the 3-year event-free survival rate was approximately 95% for patients with a CR before radiation.[84,85] The true benefit of these technologies will not be realized for at least two decades, when late toxicities become apparent. Some data are already emerging from large cancer registries. Xiang et al compared second cancer development among patients within the National Cancer Database receiving 3DCRT, IMRT, and proton therapy and found significantly fewer second cancers among patients receiving proton therapy compared with IMRT.[86] Consequently, radiation oncologists should utilize all tools available to them to minimize the dose to the OARs and, therefore, minimize acute and late toxicities.

Intensity-Modulated Radiation Therapy, Volumetric Modulated Arc Therapy, and Tomotherapy for Mediastinal Disease

Various techniques exist for delivering IMRT, VMAT, and tomotherapy.[82] Cella et al reported comparison planning using forward-planned IMRT wherein the treatment fields were chosen to mimic an AP/PA field arrangement and then compared with a seven-field IMRT plan or tomotherapy. The forward-planned IMRT was better at reducing the radiation dose to the lungs and breast, but the seven-field IMRT plan and the tomotherapy plan were better at sparing the heart. Accordingly, the optimal treatment approach should be individually tailored to address potential toxicities.

Proton Therapy

Several techniques exist for delivering proton therapy, including passive scatter, uniform scanning, and pencil beam scanning with single-field optimization or multifield optimization. Several important factors should be considered when proton therapy is employed.[75] DIBH may be combined with proton therapy to further improve doses to the heart and lung. In addition, DIBH in combination with IMPT can provide meaningful dose reduction to the cardiac substructures, more than what can be achieved with IMRT.[87,88] In general, multiple fields are encouraged to spread out the relative biologic effectiveness uncertainties within the distal edge (2-3 mm) of the spread-out Bragg peak.

Organs at Risk

The dose range used for HL (20-36 Gy) is below the threshold tolerance for most organs; however, intrathoracic structures can be affected by these doses, and careful review of DVHs is warranted to minimize both acute and late effects. ILROG and other consensus guidelines have provided guidance on dose constraints to the OARs.[89]

With respect to carcinogenesis, because data indicate that lung cancer risk increases after doses as low as 5 Gy, it is reasonable to define and minimize the lung V_5 if multiple plans are reviewed, taking into account potential toxicity to other organs.[90] The lung cancer risk is also increased by the use of alkylating agent chemotherapy or procarbazine.[91,92]

In women, given the excess risk of secondary breast cancer for doses as low as 4 Gy, it is reasonable to track the breast V_4 and keep the volume as small as possible, especially for women younger than 30 years.[93] A less rigorous constraint is to keep the mean breast dose less than 4 Gy. When calculating the V_4 and mean breast dose, only the glandular tissue of the breasts should be contoured, not the anatomic structures.

The criteria for cardiac dose tolerance are less well defined. Tolerances are influenced by lifestyle; comorbidities such as diabetes mellitus, hyperlipidemia, and hypertension; family history; and prior treatment with cardiotoxic drugs like doxorubicin. In a large analysis of Dutch patients treated before 1996 (with lymphoma radiation fields and doses that are no longer employed), patients who received mediastinal RT had a 4- to 6-fold increased standardized incidence ratio of cardiovascular disease.[94] In a more detailed comparison of coronary heart disease and mean heart dose (MHD), the excess relative risk (ERR) was 7.4% per Gy of MHD.[95] The ERR was negligible with an MHD less than 5 Gy and was approximately 2 for an MHD of 12 Gy, a dose that should be achievable in most

patients with contemporary treatment techniques. Although the MHD has been used as a surrogate for the likelihood of developing secondary cardiac effects, the dose to individual subunits of the heart is more likely to define the true cardiac risks. Therefore, effort should be made to contour all of the cardiac subunits using one of the standard cardiac atlases as a guide.[96] It is likely the dose to the left anterior descending coronary artery and left ventricle is the most important; however, it is only recently that the dose to these structures has been contoured and measured, so limited retrospective data are available regarding acceptable threshold doses. The best approach is to keep the dose ALARA. With respect to valvular disease, the ERR is increased only minimally for valve doses up to approximately 20 Gy, but with a steep increase in risk thereafter.[97] Congestive heart failure risk is demonstrable when the left ventricular mean dose exceeds 15 Gy, or V_{30} is 50% or greater, but the greatest increase in risk for congestive heart failure is associated with the use of anthracycline-based chemotherapy.[98] Acute pericarditis, an occasional risk following treatment with classic mantle field RT that includes large parts of the pericardium treated to doses greater than 30 Gy, has essentially disappeared with current standard radiation treatment techniques.

Treatment techniques such as IMRT may help reduce the cardiac dose but increase the V_5 to the lungs or V_4 to the breasts, potentially resulting in a higher risk for secondary cancer in those organs. This is not a problem when using proton therapy.[75]

In treating retroperitoneal nodes or the spleen, the organ at greatest risk is the left kidney. QUANTEC data recommend that the mean kidney dose (bilateral) should be less than 18 Gy, which should always be achievable in the context of treating HL.[99] In women who require pelvic nodal RT, the dose to the ovaries must be considered, as they are near the iliac nodes. Occasionally, an oophoropexy is necessary to provide sufficient ovarian protection. If an oophoropexy is performed, the surgeon should clip the superior and inferior poles of the ovary for precise localization on simulation scans. The menopausal effect of RT on the ovaries is dependent upon a woman's age. At age 20, the mean sterilizing dose is 15 Gy, but it drops to 12 Gy at age 30 and 8 Gy at age 40.[100] Alkylator agent chemotherapy, such as is in BEACOPP, will induce menopause in more than 50% of women, also correlating with age.[101] Among men, the possibility of inadvertent testicular RT is most likely to occur when the inguinal-femoral nodes are treated.[102] This dose can be readily reduced 3- to 10-fold by use of a "clamshell" testicular shield.

Hypothyroidism is a common complication following cervical/ supraclavicular node RT, as the thyroid cannot be spared completely because of the involvement of those nodes. Data regarding dose-volume risks are limited. One analysis showed

that the risk of developing hypothyroidism is only 11.5% if the V_{30} is 62.5 or less and 70.8% if the V_{30} is greater than 62.5.[103]

RESULTS OF THERAPY

HL is responsive to both RT and chemotherapy, and a variety of regimens can achieve similar survival rates. However, significant differences in freedom from relapse rates and potential complications of therapy can occur. The results described in the following sections emphasize treatment programs that adhere to national consensus guidelines. Clinical trial results that have helped define the current standards are shown in Tables 84.6 and 84.7.

TABLE 84.6 SELECTED CLINICAL TRIALS IN STAGE I TO II FAVORABLE AND UNFAVORABLE HL

iPET Response	Stage	Study	Response Stratification	Chemotherapy	Radiation	5-y PFS
iPET negative	Early favorable	GHSG HD16	PET2 (DS1-2)	ABVD × 2	20 Gy IFRT	93%[a]
			PET2 (DS1-2)	ABVD × 2	None	86%
		UK Rapid	PET3 (DS1-2)	ABVD × 3	30 Gy IFRT	97% (3 y)[b]
			PET3 (DS1-2)	ABVD × 3	None	91% (3 y)
		EORTC H10F	PET2 (DS1-2)	ABVD × 3	30 Gy INRT	99% (10 y)[c]
			PET2 (DS1-2)	ABVD × 4	None	85% (10 y)
		CALGB 50604	PET2 (DS1-3)	ABVD × 4	None	91% (3 y)[d]
	Early unfavorable	EORTC H10U	PET2 (D1-2)	ABVD × 2; ABVD × 2	30 Gy INRT	91% (10 y)[e]
			PET2 (D1-2)	ABVD × 2; ABVD × 4	None	87% (10 y)

iPET Response	Stage	Study	Response Stratification	Chemotherapy	Radiation	5-y PFS
		UK RATHL (stage II)	PET2 (D1-3)	ABVD × 2; ABVD × 4	None	92% (3 y)[f]
			PET2 (D1-3)	ABVD × 2; AVD × 4	None	92% (3 y)
		CALGB 50801	PET2 (D1-3)	ABVD × 2; ABVD × 4	None	93%
		GHSG HD17	PET4 (D1-2)	eBEACOPP × 2; ABVD × 2	None	95%[g]
				eBEACOPP × 2; ABVD × 2	30 Gy INRT	97%
iPET positive	Early favorable/unfavorable	GHSG HD16	PET2 (D3-4)	ABVD × 2	20 Gy IFRT	88% (80% D4)
		UK Rapid	PET3 (D3-5)	ABVD × 4	30 Gy IFRT	88%
		EORTC H10- F & U	PET2 (D3-5)	ABVD × 2; eBEACOPP × 2	30-36 Gy INRT	85% (10 y)[h]
			PET2 (D3-5)	ABVD × 3-4	30-36 Gy INRT	79% (10 y)
		CALGB 50604	PET2 (D4-5)	ABVD × 2; eBEACOPP × 2	30.6 Gy ISRT	67%
		CALGB 50801 (bulky)	PET2 (D4-5)	ABVD × 2; eBEACOPP × 4	30.6 Gy ISRT	90%

ABVD, Adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine; EORTC, European Organisation for the Treatment of Cancer; GHSG, German Hodgkin Study Group; HL, Hodgkin lymphoma; IFRT, involved-field radiotherapy; NS, nonsignificant; PET, positron emission tomography; PFS, progression-free survival.

[a] $P = .04$

[b] $P = .02$ (per-protocol analysis)

[c] $P < .0001$

[d] 3-year PFS = 77% for patients with interim PET = Deauville 3.

[e] $P = .8$

[f] P = NS

[g] 2 + 2 noninferior to 2 + 2 + INRT

[h] P (noninferiority) = .86.

TABLE 84.7 SELECTED CLINICAL TRIALS IN ADVANCED-STAGE HL

Study	iPET (If Applicable)	Chemotherapy	Radiation	Progression-Free Survival
UK RATHL IIB-IVB (+D4-5)	PET2−	ABVD × 6	None	3-y 92%
	PET2−	ABVD × 2; AVD × 4	None	3-y 92%
	PET2+	ABVD × 2; eBEACOPP × 3	Some	3-y 68%
GITIL/FIL HD0607 IIB-IVB (+D4-5)	PET2−	ABVD × 6	30 Gy >5 cm	6-y 92%[a]
	PET2−	ABVD × 6	None	6-y 90%
FIL HD0801 2B-IVB (+D4-5)	PET2−	ABVD × 6	30 Gy >5 cm	2-y 94%[b]
	PET2−	ABVD × 6	None	2-y 86%
ECHELON-1		ABVD × 6	None	6-y 75%
		BV-AVD × 6	None	6-y 82%
S1826 III-IV		BV-AVD × 6	pRSRT	1-y 86%[c]
		N-AVD × 6	pRSRT	1-y 94%

ABVD, Adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; eBEACOPP, escalated BEACOPP; HL, Hodgkin lymphoma; N-AVD, nivolumab, doxorubicin, vinblastine, and dacarbazine; PET, positron emission tomography; rSRT, stereotactic radiotherapy.

[a] $P = .48$

[b] $P = .5$ (per-protocol analysis)

[c] $P = .005$ (one-sided).

Interim Positron Emission Tomography

The utility of PET imaging as a prognostic indicator after two cycles of chemotherapy was first demonstrated in patients with stages III to IV HL.[104] Patients with a positive interim PET study had a significantly higher risk for relapse than patients with a negative study, regardless of their initial IPS.[105] An interim PET has become standard for all stages of disease in most recent clinical trials, as well as in clinical practice, allowing for potential de-escalation of treatment if the interim PET is negative or escalation of treatment if it is positive. Yet, the value of an interim PET scan among patients receiving CPIs, such as nivolumab or pembrolizumab, is still unclear, due to the phenomena of pseudo-progression with CPIs.

Favorable Prognosis Stage I to IIA Classic Hodgkin Lymphoma

In favorable prognostic groups, patients are treated with either chemotherapy alone or combined modality therapy (Table 84.6). Prospective randomized clinical trials often show a significant advantage for combined modality therapy (2-3 cycles of ABVD followed by 20-30 Gy IFRT/ISRT/INRT) with respect to PFS (absolute differences of 6.3%-11.9% at 3-5 years) but no differences in OS compared to two to four cycles of ABVD alone.[106-108] As a result, treatment selection is often based upon factors including patient age, gender, and sites of disease that would influence the risk for both early and late complications of therapy. This is important, as none of the prospective trials in the modern era have a duration of follow-up that allows for true comparison of late effects. Late effects may be reflective of initial radiation treatment or salvage therapy required for relapse. Nevertheless, the smaller radiation fields and lower doses now used compared to historical experience should result in a lower risk of radiation-related late effects.[109-111] Selecting the right treatment for these patients depends on many variables, and patient education and engagement are encouraged. For example, a young woman with mediastinal and axillary node involvement might choose the greater risk of relapse with ABVD alone over the risk of breast cancer from combined modality therapy. The opposite may be true for a patient with neck and superior mediastinal involvement, for which the heart and breasts would receive little radiation exposure.

According to the GHSG HD10 and HD16 trials, patients with favorable disease (per GHSG criteria) can be treated effectively with just two cycles of ABVD followed by 20-Gy ISRT.[108,112] For patients who do not fit all of these criteria, standard combined modality therapy programs can include four cycles of ABVD followed by 30-Gy ISRT, per the GHSG HD14 trial[113] or, if the interim PET is negative (Deauville 1 or 2), three cycles of ABVD followed by 30-Gy ISRT, per the UK RAPID trial or the EORTC H10F trial.[106,107]

If the interim PET is positive following two cycles of ABVD, and absent progressive disease, additional treatment can include two to four additional cycles of ABVD (total 4-6) plus 30-Gy ISRT or INRT, per the UK RAPID or EORTC H10 trials,[106,107] or treatment escalation to two cycles of eBEACOPP followed by 30-Gy ISRT.[107] Outcomes for any of these approaches are excellent (Table 84.6).

Unfavorable Prognosis Stage I to II Classic Hodgkin Lymphoma

This category includes a diverse patient group (Table 84.6). A commonly used treatment for stage I or II HL with large mediastinal adenopathy is combined modality therapy with four cycles of ABVD plus 30-Gy ISRT. The reported 5-year PFS was 89.1% and 10-year PFS 83.9%.[113,114] Four cycles of ABVD is sufficient in the combined modality setting, as the EORTC H9U study showed no significant benefit to six cycles compared with four cycles of ABVD[115] when given with RT. An

essential concern with this treatment program is the potential for overlapping toxicities of radiation with doxorubicin, bleomycin, and RT (ie, cardiac and pulmonary effects).

The EORTC H10U trial evaluated the use of interim PET to define a group of patients who might be treated effectively with ABVD alone.[107] In this trial, 40% of patients had bulky mediastinal disease (mediastinal-thoracic ratio ≥0.35 at the T5-T6 interspace) and 39% had B symptoms. Patients with a negative interim PET were randomized to four additional cycles of ABVD or two cycles of ABVD plus INRT. Among the patients randomized to treatment with six cycles of ABVD alone, the 10-year PFS rate was 86.5% versus 91.4% with combined modality therapy. No subset analysis was performed to analyze the impact of specific unfavorable characteristics. Although noninferiority of the six cycles of ABVD versus standard combined modality therapy could not be demonstrated, the rather similar 5-year PFS rates (P = .7) justify a consideration of six cycles of chemotherapy alone for these patients.

In the H10 trial, if the interim PET was positive (Deauville 3-5), long-term data demonstrated no benefit to escalating treatment to eBEACOPP followed by INRT.[107] Patients whose treatment was escalated had a similar 10-year PFS compared to those who continued ABVD plus INRT (85.1% vs 79.2%, P = .18). The OS difference (92% vs 90.4%) was also not statistically significant (P = .18).

The RATHL UK trial for advanced disease included 41.6% of patients with stage II disease and unfavorable characteristics, often large mediastinal adenopathy.[116] Following two cycles of ABVD and a negative interim PET (Deauville 1-3), patients were randomized to an additional four cycles of ABVD or four cycles of AVD. The AVD option was noninferior to ABVD, and the deletion of bleomycin led to a lower risk for adverse respiratory events. The 3-year PFS for patients with stage II disease and bulk was 91.5% on this study.

In summary, patients with unfavorable early-stage HL can be successfully treated with ABVD × 4 cycles with 30 Gy of ISRT if they have a negative interim PET (Deauville 1-3). Alternatively, if significant amounts of the heart or breasts (females) are within the RT field, a chemotherapy alone approach with two cycles of ABVD followed by four cycles of AVD could be considered. For patients with a positive interim PET (Deauville 4-5), patients should be treated with another four cycles of ABVD or eBEACOPP followed by ISRT.

Infradiaphragmatic Stage I to II Classic Hodgkin Lymphoma

Infradiaphragmatic involvement is seen in fewer than 10% of patients with stage I or II HL. These patients may have more adverse risk factors such as older age, a greater number of disease sites, male predominance, or worse performance status

and may require more intensive initial therapy.[117-119] Patients with bulky abdominal presentations or those with involvement of the spleen are typically treated according to guidelines for "unfavorable" stage I or II disease or for stage III to IV diseases.

For more favorable patients with infradiaphragmatic disease in whom disease is nonbulky and limited to pelvic lymph nodes with or without extension into the lower para-aortic nodes, the same general treatment principles apply as for supradiaphragmatic disease. In general, the outcome of treatment for these more favorable patients resembles that of patients with supradiaphragmatic disease.

Use of Novel Agents in Stage I to II Classic Hodgkin Lymphoma

Although novel agents such as BV and the CPIs have been incorporated into standard management programs in the primary treatment of advanced disease (vide infra), these agents have been utilized only in phase 2 clinical trials for stage I to II diseases.

Abramson et al have reported two trials utilizing BV in conjunction with other drugs for limited-stage nonbulky HL. One included BV-AVD[120] and the other included just doxorubicin and dacarbazine (BV-AD).[121] In the first study, 34 patients received four to six cycles of BV-AVD, depending upon the results of an interim PET following two cycles of BV-AVD. The 3-year PFS was 94%; however, the toxicity was significant. There was 79% peripheral neuropathy (24% grade 3-4), neutropenia 76% (62% grade 3-4), and 35% febrile neutropenia. In the second study, 34 patients were treated with BV-AD for four to six cycles, depending on the results of the interim PET. The 5-year PFS was 91%. With the deletion of vinblastine, the rate of peripheral neuropathy was reduced to 59%, all grade 1 to 2. There was no grade 4 neutropenia or neutropenic fever.

Kumar et al, treated 117 patients in four cohorts using four cycles of BV-AVD followed by RT.[70] In cohort 1, RT was 30-Gy ISRT, in cohort 2 20-Gy ISRT, in cohort 3 30-Gy RSRT, and in cohort 4 no RT. This series included 86% of patients with bulk and 39% of patients with B symptoms. The combined 2-year PFS was 94%, ranging from 90% to 97%. Adverse events included 54% peripheral neuropathy (3% grade 3-4), 44% neutropenia (39% grade 3-4), and 8% febrile neutropenia.

The LYSA-FIL-EORTC BREACH trial randomized patients to four cycles of BV-ABVD plus 30-Gy INRT versus four cycles of ABVD plus 30-Gy INRT.[122] In all, 55% of patients had bulky mediastinal disease and 39% had B symptoms. The complete metabolic response by interim PET after two cycles of chemotherapy was 82.3% versus 75.4%. The 2-year PFS was 97.3% and 92.6%. Patients with a high TMTV at the outset (30% of the patients) seemed to benefit the most, with 2-year

PFS of 90.9% and 70.7%. This study suggests that just a limited subset of patients with stage I to II diseases may benefit from the inclusion of BV in primary therapy.

The main clinical trial that has incorporated a CPI in the treatment of stage I to II diseases is the GHSG phase 2 NIVAHL trial.[123] This trial for patients with unfavorable disease characteristics compared sequential versus concomitant nivolumab (nivo) combined with AVD. All patients were then treated with 30-Gy ISRT. In all, 21% of patients had B symptoms and 20% of patients had a large mediastinal mass. With a median follow-up of 41 months, the 3-year PFS was 98% and 100% in the two arms of the study.

A multicenter, phase 2 study of sequential pembrolizumab and AVD (4-6 cycles) was studied among 30 patients with unfavorable early-stage or advanced-stage disease without any RT. The 3-year PFS and OS were 100%.[124]

An international study was conducted in patients with early-stage nonbulky disease incorporating both nivo and BV in addition to doxorubicin and dacarbazine.[125] A total of 154 patients were treated with four cycles of systemic therapy. With a median follow-up of 15.2 months, three patients had progressive disease, but there were no deaths.

Stage I to IIA Nodular Lymphocyte–Predominant Hodgkin Lymphoma

In contrast to the standard therapy for cHL, patients with limited presentation of NLPHL can achieve long-term disease-free survival after treatment with limited RT alone.[126-129] The appropriate treatment volume is ISRT, but ISRT is defined somewhat differently than in cHL where typical treatment is with combined modality therapy. The CTV expansion in NLPHL treated with ISRT must account for possible microscopic spread beyond the lymph nodes clinically observed on PET imaging. For example, in a patient who presents with unilateral cervical level I or IIA disease, the CTV should be expanded to include ipsilateral levels IIB, III, and even IV. For a femoral node presentation, the CTV should include an approximately 5-cm extension along the lymphatic chains superiorly and a 2-cm extension inferiorly.[64] The usual dose for NLPHL is 30 to 36 Gy. Doses as low as 4 Gy have been evaluated, but responses have not been as durable as with conventional doses.[130]

Retrospective data from the GHSG show a 4-year PFS rate of 93.2% and an 8-year OS rate of 99% for patients with stage I NLPHL treated with IFRT.[128] There was no benefit from extending the radiation fields or adding chemotherapy. Single-institution results for treatment of stage I to II diseases with RT alone include a 10- to 15-year PFS rate of 75% to 82% and 10-year OS rate of 83% to 100%.[126,127,131,132]

At some treatment centers, management resembling that for cHL is preferred, utilizing combined modality therapy.[132,133] With combined modality therapy, the

chemotherapy delivered can be ABVD (with or without rituximab), but patients may also be treated effectively with alkylator-based chemotherapy.[134]

A recent international multi-institutional analysis included 559 adult patients with stage I to II NLPHL.[34] The 5-year PFS was 91.1% after RT alone treatment (89.8% in stage I and 93.9% in stage II). Adverse risk factors among these patients on a multivariable analysis were a variant immunoarchitectural pattern and more than two nodal sites of disease. In the combined modality treatment group, the only factor impacting PFS was the presence of B symptoms. The overall 5-year survival was 99.4% following either RT alone or combined modality therapy. The absolute risk of transformation to an aggressive B-cell lymphoma was 3.8% (3.3% 5-year actuarial risk). The risk for transformation was also associated with more than two sites of disease and a variant immunoarchitectural pattern.

In the GHSG HD16 trial following ABVD, patients had a PET scan. Those with negative PET imaging were randomized with or without 20-Gy IFRT. Patients with NLPHL treated with chemotherapy alone had an inferior 5-year PFS compared to those treated with combined modality therapy (83% vs 100%, $P = .05$).[133]

Based on these data, European Society for Medical Oncology and other national consensus guidelines reflect a preference for ISRT alone in stage I disease and, per NCCN, contiguous stage II disease.[37] For other patients with stage II disease, combined modality therapy (including rituximab) is preferred. Attention is also brought to the potential importance of a variant immunoarchitectural pattern and the risk for transformation, mandating rebiopsy at the time of relapse.

Stage III to IV Classic Hodgkin Lymphoma

Systemic therapy is the mainstay of treatment for patients with stage III to IV HL (Table 84.7). Six cycles of ABVD was first established as the SOC among patients with advanced-staged disease in the landmark clinical trial conducted by the Cancer and Leukemia Group B.[46]

The value of a PET/CT response-based treatment approach has been evaluated in advanced disease. Both the RATHL study[135] and the SWOG S0816[136] trial used eBEACOPP for patients with PET-positive (Deauville 4-5) disease following two cycles of ABVD. Although eBEACOPP improved patient outcomes, neither trial had a comparison arm for continued treatment with ABVD. An important conclusion of the RATHL study was that patients with a negative interim PET scan could have bleomycin removed from cycles 3 to 6 of ABVD without compromising outcomes.

Based on encouraging results of BV in the relapse and refractory setting, the ECHELON-1 study investigated BV-AVD × 6 cycles versus ABVD × 6 cycles among adults with stage III or IV cHL. This study first demonstrated a significant

improvement in 2-year modified PFS with BV-AVD (82.1% vs 77.2%),[137] which ultimately translated into an improvement in OS at 6 years (93.9% vs 89.4%, P = .009)[51] and established BV-AVD as the new SOC in North America for advanced-stage disease.

Following the success of the ECHELON-1 study, the SWOG S1826 study, an NCTN study that included pediatric and adult patients with cHL, reported early PFS outcomes comparing BV-AVD × 6 cycles with N-AVD × 6 cycles with pRSRT for both groups based on the end of chemotherapy PET scan. The results demonstrated with a median follow-up of 12 months that N-AVD had a superior PFS to BV-AVD (94% vs 86%) without significantly higher rates of toxicity.[138] While these results are encouraging, longer follow-up is needed to confirm the difference in outcomes.

Role of Radiotherapy in Stage III/IV Classic Hodgkin Lymphoma

Bulky disease historically was thought to be a poor prognostic factor for patients with advanced-stage disease and as such was often a target of consolidative RT in this patient cohort. However, two recent studies have demonstrated minimal value to adding RT to sites of bulky disease among patients receiving six cycles of ABVD with a Deauville 1-3 response after two cycles. These studies include the GITIL/FIL HD0607[66] study and FIL HD0801 study.

On the other hand, RT may be valuable for patients with a positive interim PET regardless if they have bulky disease. While the ECHELON-1 study did not incorporate a PET response-based treatment approach, an interim PET was conducted after two cycles of systemic therapy. Patients with a PET2+ (Deauville 4-5) had significantly worse 3-year PFS in both arms than PET2− (Deauville 1-3), including after ABVD (79.5% PET2− vs 51.5% PET2+) and BV-AVD (85.8% PET2− vs 67.7% PET2+). Understanding the pattern of relapse on this study with respect to PET2+ sites of disease could help inform us whether a role of RT to PET2+ sites would be helpful. Nevertheless, trials of systemic therapy for advanced disease continue to include the selective use of consolidative RT.[139-141]

In summary, N-AVD × 6 cycles appears to be the new SOC treatment for patients with stage III/IV disease, while ABVD and BV-AVD could be considered in certain circumstances. The role of RT has diminished in advanced-stage disease and should be reserved for sites of partial response at completion of systemic therapy and also possible to sites of partial response after two cycles of systemic therapy.

Pediatric Patients

The management of pediatric patients with cHL is evolving and synergizing in some regard with adult patients, as seen with inclusion of both pediatric and adult patients

on recent NCTN HL studies (S1826 and AHOD 2131). More discussion can be found in the pediatric HL chapter.

Older Adult Patients

Treating HL in older patients (>60 years) is challenging because they often have less favorable histologies and a worse performance status.[142-144] They are also more likely to have intercurrent disease that compromises the aggressive management programs used for younger patients. Overall outcomes for patients older than 60 years are comparably poor.[142] Chemotherapy programs must often be modified to minimize cardiac or pulmonary toxicity, and the hematologic reserve in older patients requires dose reductions or premature discontinuation.[145] Bleomycin should be avoided, and eBEACOPP should not be used in patients over 60 years old.[146] Drug combinations better tolerated by older adults include ChlVPP;[147] procarbazine, Alkeran, and vinblastine;[148] and vinblastine, bleomycin, and methotrexate (used primarily for stages I-II).[149] More recently combinations of novel therapeutics including BV plus dacarbazine and BV plus nivolumab have demonstrated encouraging results.[150] Patients receiving RT may require slower fractionation programs and must be observed carefully for signs of weight loss or general decline in performance status. Extended fields are more difficult to tolerate than limited ones.[151]

Treatment for Relapse

Treatment for relapse must be individualized. Initial disease characteristics, initial treatment and response duration, relapse sites, and general patient status must be considered in developing an effective secondary treatment program. The conventional salvage therapy for most patients who were treated initially with either chemotherapy alone or combined modality therapy is high-dose chemotherapy followed by autologous hematopoietic cell transplantation, which is effective in approximately 50% of patients.[152,153] Allotransplantation is not used often for relapsed HL but can be considered after an unsuccessful autotransplant or when disease is refractory to both conventional chemotherapy and biologic agents. Reduced-intensity conditioning regimens appear to be safer than myeloablative regimens.[154]

An increasing dilemma is the management of patients who present with stage I to II diseases and are treated with abbreviated chemotherapy only, such as three to four cycles of ABVD. In these patients, relapse may be restricted to initial sites of disease.[155] The Checkmate 744 study recently reported on a small cohort of 28 patients who met a strict criterion for low-risk relapse disease and went on to

receive BV plus nivolumab with additional bendamustine for patients who were only partial responders. All patients were then treated with ISRT to 30 Gy and had a 3-year PFS of 95%.[156] While the study was small, the results are encouraging and could help establish a growing role of using RT in the second-line treatment in place of high-dose chemotherapy and autologous stem cell transplant. Although more evidence is needed to define the best "salvage" regimens for these patients, it has become apparent that autologous transplant can be avoided in many situations.

The Role of Radiation Therapy in Hematopoietic Cell Transplantation

RT can be incorporated into high-dose therapy/hematopoietic cell transplantation programs for relapsed or refractory HL. Fractionated total body irradiation is sometimes used, but its value is debatable. Often, relapse is locoregional rather than systemic. Data suggest that RT doses resembling those used for total body RT (12-15 Gy) are likely to eradicate disease in only approximately 20% of treated sites.[6] Thus, radiation should be limited to sites of failure or sites at high risk for disease, such as initially bulky ones.

Other considerations relevant to the issue of RT are its timing (pretransplant or post-transplant), field design, and dose. The advantages of using RT as cytoreductive treatment before high-dose therapy are that it can effectively reduce the tumor burden before high-dose treatment and the risk of interruption or delay of the locoregional RT is minimal. The primary disadvantages include potential delay of the high-dose therapy and the potential overlapping toxicities of the locoregional RT and high-dose therapy, including mucositis and pneumonitis.[157]

Many published series of high-dose therapy for HL have included locoregional RT in selected patients, usually after transplant.[158] The range of intervals from transplant to RT varies from 1 to 4 months. Often, the fields treated include sites of bulky disease (variably defined) at the time of relapse or sites that remain positive on PET imaging before the transplant. Some fields included all sites involved at the time of relapse.

In these studies, radiation doses ranged from 18 to 40 Gy. In general, lower doses were employed when initially nonbulky disease was included in the treatment or when there was a CR to high-dose therapy.

The use of locoregional RT in high-dose therapy programs can alter disease patterns and reduce the failure risk. At Stanford University, 49 patients with relapsed stage I to III diseases underwent high-dose therapy and received IFRT as a component of their salvage treatment.[159] Investigators observed 3-year freedom from relapse, OS, and event-free survival rates of 100%, 85%, and 85%, respectively, compared with only 67%, 60%, and 54%, respectively, for patients who received high-dose chemotherapy alone. The difference in freedom from

relapse was statistically significant (P = .04). The same was observed in a cohort of patients who received transplants at several centers.[160,161] The International Lymphoma Radiation Oncology Group has developed radiation treatment guidelines for patients undergoing hematopoietic cell transplantation.[162]

FOLLOW-UP

All studies that initially yielded abnormal results (eg, blood work and imaging) should be repeated upon completing therapy to document the patient's response to treatment. The Lugano response criteria mandate PET imaging immediately following therapy for this purpose.[15,16] Earlier challenges with interpreting residual mediastinal abnormality after therapy have been obviated by the adoption of FDG-PET imaging as a post-treatment assessment tool, so concern can be limited to those patients with residual PET activity.[163]

The follow-up interval is typically every 3 to 6 months during the first 2 years and every 6 to 12 months thereafter. The most important component of follow-up is an interim history and physical examination, which help identify two-thirds of relapses.[164] Relapses can be detected by enlarged nodes or when the initial symptoms return, such as night sweats, pruritus, or alcohol intolerance. If ESR, serum albumin, and other serum marker studies were abnormal at presentation, they can be repeated, although they rarely suggest disease recurrence without clinical symptoms or physical findings.[165] Given the effectiveness of primary therapy for HL, the low rate of relapse, the risk for "false-positive" imaging studies, and the expense to the health care enterprise, the value of routine imaging has become debatable and guidelines remain nonspecific.[164,166,167] National consensus guidelines endorse up to three CT scans in the first 2 years after therapy.[168,169] Surveillance PET imaging is not indicated because of the high likelihood of false-positive findings, radiation exposure, and economic costs.[170-172]

In virtually every case, the first episode of relapse should be documented by biopsy. Inflammatory disease, especially following the use of CPIs; progressive transformation of germinal centers; or the rebound growth of the thymus in young patients are other reactive processes that can be confused with recurrent HL. All of these processes can be FDG avid on PET imaging.

Long-term follow-up helps detect late effects and ensures health maintenance. Serum thyroxine (T_4) and sensitive thyroid-stimulating hormone (TSH) levels should be obtained at least annually in patients who received radiation to the neck to detect subclinical hypothyroidism.

Cardiovascular risk factors should be managed aggressively, especially for patients exposed to thoracic radiation or doxorubicin chemotherapy. National consensus guidelines recommend annual fasting blood sugar and biannual lipid

panels and a stress echocardiogram, and carotid ultrasound should be done 10 years after treatment. Women exposed to thoracic radiation should initiate routine mammographic screenings starting at age 25 or 8 years after radiation, whichever occurs first. Also, women treated before 30 years old should undergo both routine mammography and magnetic resonance mammography annually. Surveillance for other malignancies should conform to the American Cancer Society guidelines. Annual immunization against influenza is recommended.

SEQUELAE OF TREATMENT

Depending on the fields treated, the acute side effects of RT can include mild skin reactions, sore throat, an altered sense of taste, dysphagia, reflux symptoms, dry cough, nausea, occasional vomiting, diarrhea, and blood count suppression. Most of these sequelae can be managed symptomatically. Complications that arise in the early phase of the follow-up program can include mild radiation pneumonitis, radiation pericarditis, hypothyroidism, herpes zoster, Lhermitte sign, and xerostomia.

Subclinical hypothyroidism develops in as many as half of patients who receive doses above 30 Gy to the neck.[173] It can be detected by elevated TSH levels even in the presence of a normal T_4 level. Thyroid replacement therapy with L-thyroxine is recommended, with an initial dose of up to 0.1 mg/d. The T_4 and TSH values are monitored regularly to adjust dose. Evidence suggests that thyroid replacement therapy in this setting reduces the risk of developing benign thyroid nodules.[174] It is likely that newer treatment techniques with lower doses and better shielding of the thyroid gland will result in decreased risk.

Herpes zoster can occur either during or within the first few years of HL treatment in 10% to 15% of patients.[175] Acyclovir can limit the duration and intensity of the infection and decrease the likelihood of cutaneous or visceral dissemination. Currently, zoster vaccine immunization is not recommended for patients treated for lymphoma (www.cdc.gov/vaccines).

Significant xerostomia can follow RT of the Waldeyer lymphoid region or the bilateral submandibular regions, which is rarely necessary, and permanent attention to dental care is required for these patients. Frequent dental prophylaxis and use of fluoride supplements are recommended.

An uncommon but potentially serious complication is overwhelming sepsis after splenectomy or splenic RT.[176,177] The most serious infections occur with Gram-positive organisms, including *Streptococcus pneumoniae*, meningococci, and *Haemophilus* strains. Immunizing against these organisms minimizes risk. Patients can be immunized upon diagnosing the HL. Recommendations vary for the immunization of patients who have been previously treated, but not immunized.

Recent data suggest that patients can develop adequate antibody titers to *Haemophilus influenzae* type b-conjugate, four-valent meningococcal polysaccharide vaccine, and 23-valent pneumococcal polysaccharide vaccine 2 after treatment.[178] Reimmunization is recommended for every 5 to 7 years. Fortunately, sepsis has become even more rare with the declining use of staging laparotomy and splenic RT.

An uncommon but significant treatment complication is the "dropped-head syndrome" secondary to cervical muscle atrophy that occurs in just some patients treated with high-dose RT (>36 Gy) to the neck.[179] This is a late risk, not usually apparent until greater than 10 years after therapy. Management of this problem is challenging, with varying responses to physical therapy and use of a "soft collar." Surgical intervention has been attempted in some patients.[180] The use of contemporary therapies should obviate this risk.

Long-term follow-up is essential to identifying significant adverse late treatment complications in all patients.[181-184] The most important long-term concerns are secondary malignancies[92] and cardiovascular disease.[95]

Secondary malignancies include leukemia, lymphoma, and solid tumors. In a large series by Schaapveld et al, the standardized incidence ratio for developing a second malignancy after treatment for HL was 4.6, with 121.8 excess cancer cases per 10,000 patients per year.[92] Breast cancer was the greatest contributor to excess risk, followed by lung cancer, gastrointestinal tract cancers, and non-HLs. The highest (relative) risks were for thyroid cancer, soft tissue sarcoma, mesothelioma, and non-HL. Patients were also at an elevated risk of developing esophageal, gastric, pancreatic, and lung cancers as well as leukemia. These data were gathered in an earlier era of larger radiation fields, higher doses, and alkylating agent chemotherapy; therefore, risks are likely much lower now with the current management programs.[74,185-187] Secondary solid tumors, which have a latency of at least 7 to 10 years, are largely attributable to RT, although chemotherapy plays a part, especially with secondary lung cancers and gastrointestinal tract cancers.[91,92,188]

Secondary lymphomas are usually of the diffuse large cell B-cell type. The latent interval is typically over 5 years. The relative risk is 13.4, and the absolute excess risk is 16.0.[92] The development of secondary lymphomas does not seem to be related to any specific component of therapy but can be related to underlying immunosuppression.

A recent study of more than 1,000 women below age 51 years when treated for HL reported a 5.6-fold increased risk of developing invasive breast cancer compared with the general population of women (absolute excess risk, 57 cases per 10,000 persons per year).[186] The increased risk was primarily among women younger than 40 years at the time they were treated, and the risk was greater for

women treated to a full mantle field compared with mediastinal RT only. The risk can also be related to radiation dose. Travis et al[93] reported that doses exceeding 4 Gy were associated with an increased risk for developing a secondary cancer. Recently, there is reported to be an increased risk of secondary breast cancer following the use of doxorubicin without radiation.

The lung cancer risk after RT exposure is also dose related, with an increased risk for lung cancer following doses as low as 5 Gy.[90] In addition, it has been clearly demonstrated that the lung cancer risk is extraordinarily high among irradiated patients who continue to smoke after treatment.[189] Because of this inordinately high risk for lung cancer, patients who continue to smoke after treatment should be urged to stop and enter smoking cessation programs.

Potential cardiac complications following treatment for HL include pericarditis (which can occur during therapy), valvular dysfunction, conduction abnormalities, coronary artery disease, and ventricular dysfunction.[95] Radiation pericarditis is a potential risk if a large portion of the pericardium is treated, which is uncommon in the current management programs; it presents as an acute febrile syndrome associated with chest pain and friction rub, an asymptomatic pericardial effusion diagnosed by chest radiograph or echocardiogram, or constrictive pericarditis or tamponade. Mild manifestations can be managed with conservative medical treatment, including analgesics and nonsteroidal anti-inflammatory agents; it usually clears within a few weeks. Although rare, tamponade or constrictive pericarditis is the most serious and can require surgical intervention.

Long-term cardiovascular sequelae result in increased morbidity and mortality.[95] Coronary heart disease for patients increases 2.5-fold for those who receive an MHD of 20 Gy. The use of doxorubicin did not increase this risk, although it did increase the risk for congestive heart failure nearly 3-fold.[98] Compared with the general population, the risk for cardiac morbidity requiring hospitalization is 2.77-fold for patients treated with both mediastinal RT and doxorubicin and 1.82-fold following mediastinal RT alone.[190] Screening studies have shown a significant risk of asymptomatic coronary artery disease, although optimal screening guidelines for patients after mediastinal RT have not been clearly defined.[191] Aggressive management of hypertension, diabetes, and serum lipid abnormalities is recommended for all patients.[192]

Another group of sequelae involves psychosocial problems, fatigue, marital difficulties, and employment issues.[193-195] Identifying these problems can promote the development of rehabilitation programs to anticipate and deal with these issues early in the course of treatment.

CURRENT CLINICAL TRIALS

In North America, the NCTN is currently enrolling patients in AHOD 2131 for pediatric and adult patients with early-stage cHL. Following two cycles of ABVD, patients undergo PET response assessment, and patients with a rapid early response, defined as a Deauville 1-3, go on to be randomized between SOC with additional A(B)VD chemotherapy (two more cycles of ABVD if favorable risk per EORTC guidelines; four cycles of AVD if unfavorable risk) versus four cycles of experimental treatment of BV plus nivolumab. Patients with a slow early response, defined as a Deauville 4 to 5, are randomized between SOC with eBEACOPP × 2 cycles followed by ISRT versus experimental treatment with four cycles of BV and nivolumab followed by ISRT.

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CHAPTER 85

Non-Hodgkin Lymphomas

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Non-Hodgkin lymphomas (NHLs) are a heterogeneous group of malignancies of the lymphoid system characterized by an abnormal clonal proliferation of B cells, T cells, or NK (natural killer) cells. Significant molecular and immunobiologic advances over the past several decades have inevitably led to evolving classification systems as well as novel therapies for NHL, with chemotherapy, immunotherapy, cell-based therapy, and radiation therapy (RT) all playing important therapeutic roles.

There are currently approximately 47 distinct mature B-cell entities and approximately 34 mature T-cell and NK cell entities within the 2022 World Health Organization (WHO) classification.[1] A second classification system, the International Consensus Classification (ICC) from the Clinical Advisory Committee, has also been described, which categorizes some entities slightly different than the WHO.[2] A description of all the varieties of NHL is not practical and beyond the scope of this chapter. We focus on the most common diseases encountered by radiation oncologists including diffuse large B-cell lymphoma (DLBCL) along with several other large cell lymphomas, follicular lymphoma (FL), marginal zone lymphomas (MZLs), mantle cell lymphoma (MCL), and various peripheral T-cell lymphomas (PTCLs), including extranodal NK/T-cell lymphoma, nasal type. Other entities less frequently encountered by radiation oncologists are also briefly discussed.

EPIDEMIOLOGY

The U.S. age-adjusted incidence rate for NHL was 19.3 per 100,000 between 2015 and 2019, with a projected 80,550 new cases in 2023 (4.1% of new cancer diagnoses) and 20,180 estimated NHL-associated deaths in

2023.[3] With worldwide incidence rates of NHL totaling only 5.9 per 100,000, the United States, along with Europe and Australia/New Zealand, has the highest rates of NHL, while Asian and African populations are least likely to be diagnosed.[4]

Following a doubling in incidence rates of NHL between 1975 and 2000, a rise thought to be attributable to various factors including advancing molecular diagnostic techniques, immunosuppression from human immunodeficiency virus (HIV), environmental factors, and an aging population, new cases peaked at 21.3 per 100,000 in 2010[5] and have since been relatively stable. The U.S. NHL mortality rate rose from 5.6 per 100,000 to 8.2 per 100,000 between 1975 and 2000. Despite only a slight decrease in incidence rates since 2000, NHL mortality rates have nearly halved from a peak of 8.9 per 100,000 in 1997 to 4.9 per 100,000 in 2020, reflecting advances in NHL therapies.[3]

ETIOLOGY

Several genetic diseases, environmental exposures, and infectious agents have been associated with the development of lymphoma. In addition, a family history of NHL is naturally associated with an increased risk of all forms of NHL, most notably in PTCL, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), and MCL.[6]

Immune Disorders

The frequency of NHL is greatly increased in immunocompromised patients and predominantly manifested in patients who are HIV infected and solid organ transplant recipients.[7,8] Between 1996 and 2009, HIV-infected individuals experienced a 4.5% incidence of NHL (the highest of any malignancy), most commonly DLBCL, Burkitt lymphoma (BL), and primary central nervous system lymphoma (PCNSL).[9] While the introduction of highly active antiretroviral therapy has resulted in the decline in NHL incidence and mortality among those infected with HIV, HIV-associated NHL typically exhibit more aggressive clinical behavior and can be refractory to standard therapeutic regimens.

Immunosuppression caused by organ transplantation and end-stage renal disease is also associated with an increased risk of NHL. A large registry

study of 221,962 American transplant recipients between 1987 and 2014 revealed that NHL incidence increased approximately 8-fold post-transplant and led to 5,430 life-years lost over this time frame, contributing to 15% of all cancer-related deaths among these transplant recipients, second only to lung cancer.[10] In addition, those with rare inherited immunodeficiency disorders such as X-linked lymphoproliferative syndrome, common variable immunodeficiency, Wiskott-Aldrich syndrome, and ataxia-telangiectasia, experience up to a 7% lifetime risk for the development of NHL.[11]

NHL is more common among those with certain autoimmune diseases. Sjögren disease is strongly associated with increased incidence of MZL.[12] Sjögren disease is also associated with DLBCL, as are other B-cell–activating autoimmune diseases such as autoimmune hemolytic anemia, systemic lupus erythematosis, and rheumatoid arthritis.[13-15] T-cell–activating autoimmune disorders such as celiac disease, psoriasis, bullous pemphigoid, and atopic dermatitis are associated with an increased frequency of T-cell lymphomas.

Infectious Agents

Infectious exposures have long been associated with the pathogenesis of several forms of NHL. For example, Epstein-Barr virus (EBV) and human herpes virus 8 are thought to be causal in BL, human T-cell lymphotropic virus type 1 conveys a 5% lifetime risk of developing adult T-cell leukemia/lymphoma, and chronic hepatitis C virus (HCV) is associated with a 2- to 10-fold increased incidence of DLBCL, lymphoplasmacytic lymphoma, and MZL.[16]

Of particular relevance to radiation oncologists is the association of MZL with localized bacterial infections, most notably *Helicobacter pylori* and the development of gastric mucosa-associated lymphoma tissue (MALT). Infection with this organism is found in over 90% of patients with gastric MALT.[17] Successful eradication of *H. pylori* with antibiotic therapy in localized gastric MALT results in complete remission in more than 80% of patients.[18]

The role of other bacterial infections in nongastric MALT is controversial. Several studies document, for example, an association

between *Chlamydia psittaci* and ocular adnexal MALT, *Borrelia burgdorferi* and cutaneous MZL, and *Campylobacter jejuni* with MZL of the small bowel and responses to antibiotics have been reported, particularly for orbital MZL. However, the association with infectious agents varies widely depending on geographic locale. At present, there is no established role for the use of antibiotics in the treatment of nongastric MZL. Antivirals are recommended in patients who are seropositive for the HCV with splenic MZL.

Environmental and Occupational Exposures

Many occupations have been associated with a higher risk of developing NHL. A comprehensive pooled analysis from the InterLymph Consortium demonstrated a 1- to 2-fold increased incidence of NHL in populations exposed to various pesticides and solvents, including farmworkers, women's hairdressers, charworkers/cleaners, spray painters, and carpenters.[19] Despite occupational associations and litiginous pursuits, conclusive evidence establishing a causal relationship between individual pesticides and the development of lymphoma has remained elusive.[20] Ionizing radiation exposure is associated with the development of leukemia and many solid tumors, but the link to the development of NHL is tenuous. Large analyses of atomic bomb survivors, radiologic technologists, and those who have received therapeutic radiation have not detected a definite association with NHL. Other studies, however, have shown an increased risk of developing NHL among those who underwent therapeutic radiation for Hodgkin lymphoma (HL).[21] This is probably related to the increased susceptibility of young patients to the development of radiation-induced second malignancies, compared with an older population.

PATHOLOGY

NHL comprises numerous disease entities with intricate and frequently evolving histopathologic subtleties, which often complicate the process of establishing a specific diagnosis. Over the past two decades, the WHO classification system has stood as the lone international standard for diagnosing and classifying lymphoid neoplasms. A wide array of novel molecular, clinical, and immunophenotypic data have been implemented

into the fifth edition of the WHO classification, released in 2022.[1] The exhaustive nature of the WHO classification system renders a comprehensive discussion of its components beyond the scope of this chapter. Table 85.1 lists the disease entities most commonly encountered by a radiation oncologist and discussed within this chapter. Key updates in the WHO include adherence to a more clearly defined hierarchical classification system extending most broadly from lymphoid neoplasm category (eg, mature B cell), to family/class (eg, large B-cell lymphoma), to entity/type (eg, DLBCL, not otherwise specified [NOS]), to the most granular specification-subtype (eg, DLBCL, NOS, germinal center B cell [GCB] like). Furthermore, molecular diagnostic advances have led to the identification of several entities not previously recognized (eg, B-lymphoblastic leukemia/lymphoma with TCF3.HLF fusion) and have allowed for more diagnostic certainty (eg, removal of "provisional" classifiers).

TABLE 85.1 WHO AND ICC CLASSIFICATION OF LYMPHOID NEOPLASMS

WHO Classification, 5*th* Edition[1]	ICC 2022[2]
Large B-cell lymphomas	
Diffuse large B-cell lymphoma, NOS • Subtypes recommended but not officially included in WHO	Diffuse large B-cell lymphoma, NOS • Germinal center B-cell subtype • Activated B-cell subtype
Diffuse large B-cell lymphoma/high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements	High-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements
	High-grade B-cell lymphoma with *MYC* and *BCL6* rearrangements (provisional)
High-grade B-cell lymphoma, NOS	High-grade B-cell lymphoma, NOS
Primary large B-cell lymphoma of immune-privileged sites • Primary large B-cell lymphoma of CNS	Primary diffuse large B-cell lymphoma of CNS
Primary mediastinal B-cell lymphoma	Primary mediastinal B-cell lymphoma
T-cell/histiocyte-rich large B-cell lymphoma	T-cell/histiocyte-rich large B-cell lymphoma

WHO Classification, 5*th* Edition[1]	ICC 2022[2]
Mediastinal gray-zone lymphoma	Mediastinal gray-zone lymphoma
Primary large B-cell lymphoma of immune-privileged sites	Primary diffuse large B-cell lymphoma of the testis
Follicular lymphoma	
Follicular lymphoma • Duodenal-type follicular lymphoma	Follicular lymphoma • Duodenal-type follicular lymphoma
Marginal zone lymphoma	
Extranodal marginal zone lymphoma of MALT lymphoma	Extranodal marginal zone lymphoma of MALT lymphoma
Nodal marginal zone lymphoma	Nodal marginal zone lymphoma
Splenic marginal zone lymphoma	Splenic marginal zone lymphoma
Primary cutaneous marginal zone lymphoma	Primary cutaneous marginal zone lymphoproliferative disorder
Mantle cell lymphoma	
Mantle cell lymphoma	Mantle cell lymphoma
Transformations of indolent B-cell lymphomas	
Transformations of indolent B-cell lymphomas	
Primary cutaneous T-cell lymphomas	
Primary cutaneous CD30-positive T-cell lymphoproliferative disorder • Primary cutaneous anaplastic large cell lymphoma • Lymphomatoid papulosis	Primary cutaneous CD30-positive T-cell lymphoproliferative disorder • Primary cutaneous anaplastic large cell lymphoma • Lymphomatoid papulosis
Anaplastic large cell lymphomas	
ALK-positive anaplastic large cell lymphoma	Anaplastic large cell lymphoma, ALK positive
ALK-negative anaplastic large cell lymphoma	Anaplastic large cell lymphoma, ALK negative
Breast implant-associated anaplastic large cell lymphoma	Breast implant–associated anaplastic large cell lymphoma
NK/T-cell lymphomas	
Extranodal NK/T-cell lymphoma	Extranodal NK/T-cell lymphoma, nasal type

WHO Classification, 5th Edition[1]	ICC 2022[2]
Peripheral T-cell lymphoma, NOS	Peripheral T-cell lymphoma, NOS
Lymphoid proliferations and lymphomas associated with immune dysregulation	
Polymorphic lymphoproliferative disorders arising in immune deficiency or dysregulation	Post-transplant lymphoproliferative disorders

This table includes only those entities discussed within the text. Refer to individual references for comprehensive classification of all recognized hematolymphoid tumors.
ALK, anaplastic lymphoma kinase; CNS, central nervous system; ICC, International Consensus Classification; MALT, mucosa-associated lymphoid tissue; NOS, not otherwise specified; WHO, World Health Organization;

Notably, the WHO has recently been joined by an influential companion lymphoid neoplasm classification system, the ICC.[2] Finalized in 2022, the ICC closely mirrors the WHO classification yet harbors several subtle distinctions (eg, preservation of "provisional" classifiers in ICC, more granular DLBCL subtype delineation, and substantial genomic refinement of multiple myeloma subtypes), sparking concerns that clinicians and pathologists may no longer have a unifying approach to the diagnosis of lymphoid neoplasms.[22] Nevertheless, the classification of NHL types is generally concordant. Table 85.1 provides specific comparisons between the WHO and ICC classifications for the NHL entities discussed within this chapter.

CLINICAL FEATURES AND EVALUATION

Clinical Presentation, Evaluating, and Staging

NHL has a slight male preponderance (~55% male) and is predominantly a disease of older adults, in contrast to HL, with a median age at presentation of approximately 68 years.[3] Over the past several decades, the ratio of NHL cases to HL has increased from approximately 3:1 to 10:1. The clinical features differ widely depending on the histology and location of disease involvement. NHL may involve lymph nodes in almost any area of the body, but a typical presentation is an asymptomatic lump in the neck or inguinal-femoral region. Most nodal presentations of NHL are asymptomatic as B symptoms are much less frequently encountered than in HL, are not prognostic, and usually do not influence the choice of

treatment. For these reasons, it is unnecessary to add "A" or "B" designation to the numerical stage of a patient with NHL. Extranodal involvement is common in DLBCL (eg, ~50% of patients with early-stage disease and ~70% of all patients)[23] with symptoms related to the organ involved. Extranodal disease is relatively rare with FL.

Initial evaluation includes a complete physical examination with particular attention to node-bearing areas and other sites depending upon the specific disease entity (eg, parotids and orbits in MZL). Positron emission tomography-computed tomography (PET-CT) is now the imaging procedure of choice as the great majority of NHLs are fluorodeoxyglucose (FDG) avid. The Lugano classification is used for staging (Table 85.2). Tumor bulk is no longer considered because of the lack of consensus as to what constitutes bulky disease as well as the uncertain influence of bulk on prognosis in the current therapeutic era. Routine bone marrow biopsy has been standard in lymphoma evaluation for many years, but the high negative predictive value of PET-CT for bone marrow involvement in DLBCL allows for consideration of omitting this procedure in the setting of a negative PET-CT.[24] Similarly, bone marrow biopsy should typically be deferred if PET-CT indicates marrow involvement in DLBCL, given high positive predictive value. There are considerably less data, however, for other histologies, particularly FL where bone marrow biopsy remains standard of practice and is particularly important in patients with ostensible stage I or II disease being considered for definitive RT.

TABLE 85.2 REVISED STAGING SYSTEM: THE LUGANO CLASSIFICATION

Stage[a]	Involvement	Extranodal (E) Status[b]
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesion without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I/II by nodal extent with limited contiguous extranodal involvement
II bulky	II as above with "bulky" disease[c]	NA
Advanced		

Stage[a]	Involvement	Extranodal (E) Status[b]
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	NA
IV	Additional noncontiguous extralymphatic involvement	NA

[a]Note, for non-Hodgkin lymphoma, A and B subtypes have been dropped because of the infrequency of systemic symptomatology, the unclear influence on prognosis, and the usual lack of relevance for management decisions.

[b]Tonsils, Waldeyer ring, and spleen are considered nodal tissue.

[c]Definition of bulky disease in diffuse large B-cell lymphoma is not consistent across studies, most recently considered to be 7 to 7.5 cm, but 6 to 10 cm also generally accepted.

Adapted with permission from Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32(27):3059-3068. Copyright © 2014 by American Society of Clinical Oncology.

As discussed earlier, the initial diagnosis of NHL based on WHO or ICC criteria is dependent on morphology, immunohistochemistry, flow cytometry, and molecular studies. An incisional or excisional biopsy is strongly preferred for diagnosis, though a core-needle biopsy is acceptable in difficult-to-access sites. Fine-needle aspirate rarely provides sufficient tissue to perform the studies necessary for a detailed classification. Additional laboratory procedures include complete blood count (CBC), metabolic panel, lactate dehydrogenase (LDH), β2-microglobulin (B2M), and hepatitis B, C, and HIV antibodies in selected patients.

Response Assessment

Response assessment should include a clinical evaluation with interval history and physical examination, laboratory evaluation (eg, CBC, LDH), and repeating any positive pretreatment imaging studies, most commonly PET-CT, as it is the most accurate imaging modality for response assessment. Responses may be divided into complete, partial, no response or stable disease, and progressive disease. For PET-CT, this is currently based on the five-point scale of the Lugano response criteria.[25,258] A complete response (CR) is defined as a score of 1, 2, or 3; a partial response (PR) is defined as a score of 4 or 5 but with reduced uptake compared with

original scans; no response or stable disease is defined as a score of 4 or 5 with no significant change in FDG uptake from baseline; progressive disease is scored when the intensity of uptake has increased from baseline and/or new lesions have developed. Definitions of PET-CT scores (Deauville criteria) are listed in Table 85.3.

TABLE 85.3 DEAUVILLE CRITERIA (PET-CT 5-POINT SCALE)

Score	Definition
Deauville 1	No uptake above background
Deauville 2	Uptake ≤ mediastinal blood pool
Deauville 3	Uptake > mediastinal blood pool but ≤ liver
Deauville 4	Uptake moderately increased compared to liver
Deauville 5	Uptake markedly increased compared to liver or new sites of disease

PET-CT, positron emission tomography-computed tomography.

Adapted by permission from Springer: Barrington SF, Qian W, Somer EJ, et al. Concordance between four European centres of PET reporting criteria designed for use in multicentre trials in Hodgkin lymphoma. *Eur J Nucl Med Mol Imaging*. 2010;37(10):1824-1833. Copyright © 2010 Springer-Verlag.

A Deauville 4 treatment response can be quite variable ranging from a dramatic decrease in size of a large tumor mass but with a small focus of residual FDG uptake slightly above liver, to a minimal response in size of a mass with intense residual FDG uptake. Clinical judgment is required to determine if the response to systemic therapy was satisfactory in these settings. If so, proceeding with consolidation RT, often to a slightly higher dose, is often justified. The use of RT in the event of PR is discussed in the individual disease sections. If the response to initial therapy is judged inadequate and a major change in therapy is planned, it is often advisable to confirm the persistence of active disease with repeat biopsy.

In some NHL subtypes, imaging response assessment is often carried out midway through the course of therapy, the so-called interim PET-CT imaging. Many studies of interim PET-CT have been carried out, particularly in DLBCL, suggesting that an interim positive PET-CT (Deauville 4 or 5) predicts for a worse outcome. Modifying treatment based

on interim PET-CT in DLBCL and other NHLs requires further studies to understand how this is best accomplished.

Follow-Up and Routine Surveillance

Follow-up procedures and routine surveillance studies have been infrequently addressed in the literature, but consensus guidelines suggest a history and physical and routine laboratory assessment every 3 to 6 months for 5 years and then annually or as clinically indicated thereafter. There is no clear consensus on the role of surveillance imaging in NHL as the great majority of relapses are associated with clinical symptoms or abnormal physical findings and studies have not generally demonstrated a benefit for intense surveillance programs.

Detection of relapse is most relevant for diseases where curative therapy is available, such as chimeric antigen receptor (CAR) T-cell therapy or autologous stem cell transplantation (ASCT). For many histologies, particularly FL, the detection of recurrence is less relevant. Generalized FL is still regarded as incurable (in contrast to localized FL). Relapse after treatment of localized FL is almost always generalized, and because generalized FL is often observed without treatment until specific criteria for initiating therapy are met, there is little rationale for aggressive attempts at early detection of relapse in an asymptomatic patient with a normal examination.

LARGE B-CELL LYMPHOMAS

The fifth edition of the WHO classification lists 18 entities under the category "Large B-cell lymphomas."[1] The most common diseases encountered by radiation oncologists in this category (and reviewed in this chapter) include DLBCL NOS, high-grade B-cell lymphoma, NOS (HGBL NOS), DLBCL/HGBL with *MYC* and *BCL2* rearrangements, primary mediastinal (thymic) large B-cell lymphoma (PMBCL), T-cell/histiocyte-rich large B-cell lymphoma, mediastinal gray zone lymphoma (MGZL), and primary testicular DLBCL (included in the category of primary large B-cell lymphoma of immune-privileged sites by the WHO). PCNSL and primary cutaneous DLBCL, leg type are discussed elsewhere. With minor

exceptions that are noted, RT recommendations are similar across large B-cell lymphoma entities and are discussed under DLBCL NOS.

DIFFUSE LARGE B-CELL LYMPHOMA, NOT OTHERWISE SPECIFIED

Pathology

DLBCL is a neoplasm of large, transformed B cells with a diffuse growth pattern that totally or partially effaces the nodal architecture. The proposed normal counterparts are peripheral B cells of either germinal center or post–germinal center (activated B-cell [ABC]) origin. DNA microarray analyses using fresh frozen tissue show that unique molecular subgroups exist, which include a GCB subgroup and an ABC subgroup.[26,27] Algorithms utilizing immunohistochemistry to identify molecular subgroups, using formalin-fixed, paraffin-embedded tissue, have also been developed.[28] No single algorithm using immunohistochemistry is perfect in regard to predicting gene expression profiling results, though each divides patients into groups with different survival outcomes. Treatment tailored to molecular subclassification of this disease is currently being evaluated in prospective studies and remains investigational.

DLBCLs express one or more pan B-cell markers (CD19, CD20, CD22, and CD79a) and often surface and/or cytoplasmic immunoglobulin.[29] *MYC*, *BCL2*, and/or *BCL6* gene rearrangements are present in a minority of patients with DLBCL. Large cell lymphomas with gene rearrangements of *MYC* (a potent oncogene) together with a translocation of *BCL2* (an antiapoptotic gene) are now referred to by the WHO as DLBCL/HGBL with *MYC* and *BCL2* rearrangements (double-hit lymphoma). Similarly, other patients, typically with an ABC-like subtype, have overexpression by immunohistochemistry of MYC and BCL2 and/or BCL6, without the accompanying gene rearrangements. Such DLBCLs are referred to as double or triple expressors. Such patients also have a worse prognosis, though more favorable than double-hit lymphomas.[30]

Clinical Presentation

DLBCL is primarily a disease of older adults, with a median age of 64 years and a slight preponderance of men (55%). B symptoms are present in approximately one-third of patients but are not prognostic.[25] Just over half of patients (55%) have localized disease (stage I or II). About half of patients with stage I or II DLBCL present with extranodal disease, as opposed to localized FL where nodal presentation predominate. Patients with primary nodal disease most often present with an enlarging peripheral nodal mass.

Prognostic Factors

The International Non-Hodgkin's Lymphoma Prognostic Factors project examined data on 2,031 patients, all with aggressive histology NHL.[31,32] Two indices were developed, the international prognostic index (IPI) and the age-adjusted international prognostic index, because age was found to be a highly significant prognostic variable (>60 vs ≤60 years). For the IPI, five prognostic variables were found to be significant: age, performance status, stage, number of extranodal sites, and LDH (Table 85.4). The relative risks of these factors were low, ranging from 1.47 for stage to 1.96 for age. Five-year survival was 73%, 51%, 43%, and 26% when 0 to 1, 2, 3, and 4 to 5 risk factors were present. When patients were divided by age, three factors remained independently significant: performance status, stage, and LDH.

TABLE 85.4 PROGNOSTIC INDICES: DIFFUSE LARGE B-CELL LYMPHOMA AND FOLLICULAR LYMPHOMA

Prognostic Index	Risk Factors	Score (Number of Factors)	Outcome
Diffuse Large B-cell Lymphoma[a]			
IPI[31]	Age >60 y Performance status ≥2 Stage III-IV Elevated LDH >1 extranodal site	Low (0-1) Low intermediate (2) High intermediate (3) High (4-5)	73% (5-y survival) 51% 43% 26%
Follicular Lymphoma			

Prognostic Index	Risk Factors	Score (Number of Factors)	Outcome
FLIPI[33]	Age ≥60 y >4 nodal sites Elevated LDH Stage III-IV Hemoglobin <12 g/dL	Low (0-1) Intermediate (2) High (≥3)	71% (10-y survival) 51% 36%
FLIPI-2[34]	Age >60 y B2M elevated Hemoglobin <12 g/dL BM involvement Nodal diameter >6 cm	Low (0) Intermediate (1-2) High (≥3)	80% (5-y PFS) 51% 19%

β2M, β2-microglobulin; BM, bone marrow; FLIPI, follicular lymphoma international prognostic index; IPI, international prognostic index; LDH, lactate dehydrogenase; PFS, progression-free survival.

[a]Developed in the pre-rituximab era.

The IPI was designed in the pre-rituximab era. In the past 10 to 15 years, multiple randomized studies have shown that rituximab significantly improves survival when combined with standard combination chemotherapy.[35-37] Using data from three prospective trials, the German High-Grade Non-Hodgkin's Lymphoma Study Group found the IPI to retain prognostic significance in the rituximab era.[38] Adding approximately 10% survival to each IPI subgroup approximates outcomes when rituximab is added to combination chemotherapy.

As mentioned previously, several pathologic factors carry prognostic implications. The GCB subtype has a more favorable prognosis compared with the ABC subtype (defined using gene expression profiling) or non–GCB-like subtype (defined using immunohistochemistry).[26,39] Additional molecular signatures that appear to influence tumor behavior have also been proposed.[27]

Both interim and postchemotherapy PET-CT assessment also carry prognostic importance. At present, the five-point scale (Deauville criteria) should be utilized to interpret interim and post-treatment PET-CTs.[25] In numerous studies, residual PET-positive disease (Deauville 4-5) after the completion of chemotherapy alone in aggressive NHLs (mostly DLBCL) is associated with a high risk of disease progression.[40-43] For example, in the

setting of advanced DLBCL with PET-positive disease after chemotherapy without rituximab, the risk of progression was 100% in a series by Mikhaeel et al (n = 9)[41] and Spaepen et al (n = 26).[40] Similarly, poor outcomes have been noted when a post-treatment PET-CT is still positive after R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone).[44] Outcomes appear to be much better when RT is administered in this clinical setting.[45-47]

Achievement of a negative PET-CT early in the course of therapy (after 2-3 cycles) is generally associated with improved outcomes.[48] For example, in a study by Safar et al, 3-year progression-free survival (PFS) and overall survival (OS) were 84% and 88%, respectively, in patients achieving a negative PET-CT after two cycles of chemotherapy plus rituximab.[49] This compared with 47% and 62%, respectively, in patients who were still PET positive. Although the negative predictive value of interim PET-CT is high, the positive predictive value is relatively low. When compared with interim response assessment, postchemotherapy PET-CT response appears to be more prognostic, particularly in terms of the positive predictive value.[50]

Clinical Management

Chemoimmunotherapy, with or without consolidation RT, is standard in all stages of DLBCL. The most widely used drug combination is R-CHOP. R-CHOP is administered every 3 weeks in the outpatient setting.

DLBCL expresses the B-cell antigen CD20. Rituximab, an anti-CD20 antibody, improves survival in all stages of DLBCL when combined with chemotherapy.[35,36] A recent randomized trial demonstrated that R-CHOP was just as effective as the more aggressive regimen DA-EPOCH-R (dose adjusted, etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, rituximab).[51] Thus, R-CHOP remains the standard regimen for DLBCL NOS.

Stage I and II Diffuse Large B-Cell Lymphoma

Historically, stage I and II DLBCL was often managed with RT alone. This strategy proved successful in approximately 40% to 45% of patients. Outcomes were better for those with stage I, compared with stage II, disease. Though rarely employed today, definitive RT is an appropriate

treatment option for patients with localized disease who are not candidates for, or refuse, chemoimmunotherapy. It can also be considered as an option for select patients with localized disease who do not respond to induction chemoimmunotherapy. A dose of approximately 40 Gy is recommended to the involved site(s) without any elective coverage.

Definitive RT as the preferred treatment for early-stage DLBCL was abandoned in the 1980s after randomized studies demonstrated that RT plus chemotherapy was superior to RT alone.[52-55] Chemotherapy became the foundational treatment, and RT transitioned to a consolidation modality. After improved outcomes were seen with the addition of rituximab to CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), the need for consolidation RT has been called into question. Multiple randomized studies in early-stage DLBCL have been conducted comparing chemotherapy with a combined modality program (Table 85.5).[56-61] Interpretation of the trials can be challenging, given their individual peculiarities. A brief summary of the key trials follows.

TABLE 85.5 SELECT RANDOMIZED TRIALS IN EARLY-STAGE DLBCL

Study	*n*	Disease Characteristics	Randomization	Progression-Free Survival[a]	Comments
Pre-Rituximab/PET-CT era					
SWOG[59,62]	401	I II (nonbulky)	CHOP × 8 CHOP × 3 + RT	64% 77% (*P* = .03)	No difference with long f/u
ECOG[57]	172	I (high risk) II	CHOP × 8 CHOP × 8 + RT	56% 73%[b] (*P* = .05)	Only patients in CR by CT randomized
GELA 93-4[56]	576	I-II (without risk factors)	CHOP × 4 CHOP × 4 + RT	61% 64% (*P* = .6)	Only patients ≥60 y old
Rituximab/PET-CT era					
LYSA/GOELAMS[63]	301	I-II (nonbulky)	R-CHOP × 4-6 R-CHOP × 4-6 + RT	89% 92% (*P* = .18)	In PET-CT CR
FLYER[64]	592	I-II (nonbulky)	R-CHOP × 4 + 2R	96%	No risk factors

Study	*n*	Disease Characteristics	Randomization	Progression-Free Survival[a]	Comments
			R-CHOP × 6	94%[c] (*P* = NS)	

CHOP, cyclophosphamide, Adriamycin, vincristine, prednisone; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; GELA, Groupe d'Étude des Lymphomas de l'Adulte; LYSA/GOELAMS, Lymphoma Study Association/Groupe Ouest-Est des Leucémies et des Autres Maladies du Sang; PET-CT, positron emission tomography-computed tomography; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; SWOG, Southwest Oncology Group; RT, radiation therapy.

[a]5 years, unless otherwise noted.

[b]6 years.

[c]3 years.

Pre-Rituximab/Positron Emission Tomography-Computed Tomography Era: Key Prospective Trials

The SWOG S8736 study evaluated the feasibility of replacing a significant number of chemotherapy cycles with consolidation RT. Three cycles of CHOP chemotherapy plus RT (40-55 Gy) was compared with a more extended CHOP regimen (eight cycles) without RT.[59] Unexpectedly, both PFS (77% vs 64%) and OS (82% vs 72%) at 5 years were improved in the combined modality arm with less toxicity. However, after a median follow-up of almost 18 years, no significant differences were apparent, in part because of a higher risk of late systemic relapses in the arm with only three cycles of CHOP.[62] A follow-up phase II study demonstrated 4-year PFS of 88% with three cycles of R-CHOP plus RT.[65] However, long-term data from both studies demonstrated a continuous risk of relapse over time.[62] Thus, three cycles of CHOP, or even R-CHOP, may provide insufficient systemic treatment for some patients with early-stage DLBCL.

The Eastern Cooperative Oncology Group (ECOG) 1484 study evaluated whether consolidation RT (30 Gy), after achievement of a CR by CT imaging, would reduce the risk of relapse in the setting of extended chemotherapy (eight cycles of CHOP in this case).[57] The primary outcome was PFS, which was significantly improved with the addition of RT (73% with consolidation RT vs 56% with observation at 6 years) (P = .05). No difference in OS was noted, though the study was not powered to evaluate

this. This study suggests that consolidation RT provides benefit even after an extended course of chemotherapy.

The Groupe d'Etudes des Lymphomes de l'Adulte (GELA) 93-4 enrolled older patients (>60 years) with early-stage disease without adverse risk factors.[56] Crude rates of local failure were less with RT (18% vs 7%). However, neither PFS nor OS was improved with consolidation RT (40 Gy) after four cycles of chemotherapy. This study suggests that older patients, especially those with favorable prognostic factors and/or medical comorbidities, may derive less benefit from consolidation RT.

Rituximab/Positron Emission Tomography-Computed Tomography Era: Key Prospective Trials

The Lymphoma Study Association/Groupe Ouest-Est des Leucémies et des Autres Maladies du Sang (LYSA/GOELAMS) trial enrolled 319 patients with nonbulky (<7 cm), stage I and II DLBCL.[63] Patients were randomized to four to six cycles of R-CHOP-14 with or without consolidation RT (40 Gy). Only patients in CR by PET-CT after four cycles (n = 281) proceeded with treatment according to their random assignment. The study was designed as a noninferiority study. By intention-to-treat analysis, 5-year event-free survival (EFS) was 89% with R-CHOP versus 92% with R-CHOP plus RT (P = .18). Crude rates of local failure were 4% (5/137) versus 0% (0/144).

Several nuances of this study deserve attention. First, 62 (~20%) patients had a negative staging PET-CT after diagnostic excisional biopsy. This would significantly dilute the effect of consolidation RT. Further, eight patients randomized to receive consolidation RT arm declined treatment. Since nonadherence to an allocated treatment in noninferiority studies will bias results in favor of the investigational arm, a per-protocol analysis is typically standard with such trial designs. Yet, no per-protocol analysis was reported for this trial. Finally, 94% of patients had a very favorable modified IPI (MIPI) score (0-1).

The FLYER study did not directly examine the role of RT in early-stage DLBCL.[64] Patients (n = 558) aged 60 years or below, with nonbulky (<7.5 cm) DLBCL and HGBL, without risk factors such as elevated LDH or poor performance status, were randomized to four cycles of R-CHOP with two

additional cycles of rituximab or six cycles of R-CHOP. PET-CT imaging was not standardized within the protocol. PFS at 3 years was no different between arms (96% vs 94%) in the intention-to-treat analysis. A per-protocol analysis (n = 482) was performed given the noninferiority study design and showed similar findings (98% vs 94%). The investigators concluded that young patients without risk factors can be successfully treated with four cycles of R-CHOP with two additional cycles of rituximab.

The Intergroup National Clinical Trials Network Study S1001 did not specifically investigate the role of consolidation RT in early-stage DLBCL.[66] In this randomized phase II trial, patients with nonbulky (<10 cm), stage I and II, ECOG performance status 0-2, DLBCL or HGBL with or without gene rearrangements, were eligible. Patients received three cycles of R-CHOP and then underwent an interim PET-CT. Those with a negative PET-CT (Deauville 1-3) received an additional cycle of R-CHOP without consolidation RT. Patients with a positive PET-CT (Deauville 4-5) received both consolidation RT (36-45 Gy) and ibritumomab tiuxetan. In general, patients in the S1001 study had more risk factors than those on the LYSA/GOELAMS or FLYER studies but were still relatively low risk (stage-modified IPI 0-1 in 70%). All gross disease was resected in 10% of patients before initiating systemic therapy. A CR by PET-CT was achieved in 110 (86%) of 128 patients after three cycles of R-CHOP. Among patients with a negative interim PET-CT who received four cycles of R-CHOP, 5-year PFS and OS were 89% and 91%, respectively. Among the 14 patients with a positive interim PET-CT, all but one received consolidation RT. With the addition of RT, 5-year PFS was 86%, similar to that among patients who had a negative interim PET-CT. Only two of these patients relapsed, one of whom refused RT and one received only one cycle of chemotherapy before going off treatment.

In conclusion, for patients with stage I and II nonbulky DLBCL with 0-1 IPI risk factors, four cycles of R-CHOP (FLYER, LYSA/GOELAMS, S1001) or three cycles of R-CHOP plus RT (SWOG S0014) are reasonable options. Patients with early-stage DLBCL with an IPI of 2-3, underrepresented in the modern trials, may be considered for consolidation RT depending upon distribution of disease, response to therapy, and risks of

RT. Consolidation RT is recommended in patients with bulky disease (variably defined in randomized studies, most commonly >7.5 cm).

At present, a dose of 30 Gy is standard. A prospective study by the International Lymphoma Radiation Oncology Group (ILROG) is assessing whether 20 Gy is sufficient in the setting of a CR by PET-CT (Deauville 1-3). In the setting of a PR (Deauville 4), a higher dose of RT would be appropriate (40-44 Gy).

Stage III and IV Diffuse Large B-Cell Lymphoma

The mainstay of treatment of advanced DLBCL is systemic chemoimmunotherapy, typically R-CHOP, with 5-year survival of approximately 60%.[35] Many strategies have been explored to improve upon R-CHOP, including more chemotherapy cycles,[67] dose-dense chemotherapy,[68,69] more intensive chemotherapy regimens,[70,71] maintenance rituximab,[37] and high-dose chemotherapy and ASCT.[72] None have consistently improved survival compared with standard R-CHOP.

Several retrospective studies have suggested a benefit for consolidation RT in advanced DLBCL.[73-75] One rational for the use of consolidation RT is the tendency of patients with advanced lymphoma to relapse at sites of original involvement and, in particular, sites of original bulk.[74,76,77]

The RICOVER-60 and RICOVER-noRTh trials primarily enrolled patients with advanced disease (50% and 60%, respectively).[78] The original RICOVER-60 trial was a randomized study that investigated different chemoimmunotherapy regimens in older adults (ages 61-80) with both early and advanced DLBCL. Those with bulky (≥7.5 cm) or extranodal disease were to receive RT to those areas if a CR or PR was achieved by CT imaging. PET-CT imaging was not utilized in this trial. The treatment arm yielding the best outcomes consisted of six cycles of dose-dense R-CHOP (administered every 2 weeks) with two additional cycles of rituximab and RT to bulky or extranodal sites of disease. The RICOVER-noRTh trial was an amendment to the original trial in which this same regimen was administered but without RT to bulky or extranodal disease. Comparing outcomes from the two studies, the risk of relapse in patients with bulky disease achieving a CR was higher when RT was not administered (22% vs 4%, $P = .007$). A per-protocol analysis of all patients with bulky disease

revealed improved PFS in patients receiving RT (88% vs 62%, $P < .001$). Of course, these were not randomized comparisons but suggest that RT improves outcomes in the setting of bulky disease. A limitation of this study was the lack of PET-CT imaging.

The UNFOLDER trail enrolled younger patients (≤60 years) with high-grade NHLs including DLBCL presenting with an age-adjusted IPI (aaIPI) of 1 or aaIPI of 0 with bulky disease (≥7.5 cm).[79] Patients were randomized to R-CHOP14 or R-CHOP21 with a secondary randomization to consolidation RT or observation. PET-CT imaging was not utilized. A planned interim analysis demonstrated a significantly better 3-year EFS for patients randomized to RT (84% vs 68%, $P = .001$), in part because patients randomized to observation who only achieved a PR (by CT imaging) to chemotherapy proceeded to RT and were scored as an event. This study is still only published in abstract form.

Several retrospective studies have shown that consolidation RT, in the setting of a PR to systemic therapy, provides long-term disease control in a significant proportion of patients.[80-82] A recent retrospective study from British Columbia reporting their institutional experience in advanced DLBCL is illustrative.[47] Patients with advanced DLBCL were initially treated with at least six cycles of R-CHOP. Only patients who were PET positive at the completion of chemoimmunotherapy received consolidation RT. Time to progression at 3 years was 83% in the cohort who achieved a CR by PET-CT to R-CHOP alone. Notably, patients who were PET positive at the completion of chemoimmunotherapy and received consolidation RT had similar outcomes to the PET-negative cohort and far better outcomes than those who were PET positive but did not receive RT.

In addition to bulky disease and PRs, other circumstances that may warrant consideration of consolidation RT include limited skeletal disease[83] and disease in sensitive locations where achievement of local control is critical (eg, spinal canal, cavernous sinus).

Relapsed and Refractory Diffuse Large B-Cell Lymphoma

Until recently, high-dose chemotherapy followed by ASCT was the preferred salvage regimen for patients with relapsed or refractory (R/R) DLBCL. In a phase III trial from the Parma group, patients with DLBCL

who had relapsed following initial CHOP chemotherapy and were responsive to a salvage regimen (dexamethasone, cisplatin, cytarabine-DHAP) were then randomly assigned to receive either four additional cycles of DHAP or high-dose chemotherapy followed by ASCT.[84] Those receiving ASCT had a markedly improved PFS (46% vs 12%) and OS (53% vs 32%), compared with those receiving conventional chemotherapy. Note that in both arms of this trial, RT to original bulky sites of disease (≥5 cm) was utilized (35 Gy in 20 fractions in the conventional chemotherapy arm and 26 Gy in 1.3 Gy fractions bid in the ASCT arm). All patients in the Parma trial were younger than 60 years of age. It is important to recognize that only patients with chemotherapy-sensitive disease (those who achieve a CR or PR by CT imaging to salvage chemotherapy) are candidates for ASCT. More recently, PET-CT imaging is the preferred method to define response. Those with a persistently positive PET-CT after a salvage program (Deauville 4) do poorly with ASCT.[85,86]

The role of RT in patients undergoing ASCT is not well defined due to the lack of prospective studies. The ILROG has published detailed guidelines regarding RT in the setting of ASCT.[87] We generally recommend post-ASCT RT for patients with bulky and/or localized disease at the time of relapse. A dose of 30 Gy is recommended in the setting of a CR with higher doses reserved for PRs.

However, recent randomized studies have shown that CAR T-cell therapy, described later, provides superior outcomes, compared with ASCT, in patients with refractory DLBCL or who relapse within 12 months of completing therapy.[88,89] Thus, ASCT is now primarily pursued for patients with late relapses.

In 2017, the U.S. Food and Drug Administration approved CAR T-cell therapy, a novel treatment for R/R DLCBL. CAR T cells are a type of immunotherapy, consisting of autologous T cells that are harvested from a patient and genetically engineered to express CAR molecules that target a specific antigen of interest on malignant cells. CD19, a transmembrane protein expressed on all B cells, has proved to be an ideal target for DLBCL. In a typical course, patients undergo leukapheresis, wait a minimum of 2 weeks for the CAR T-cell production process, and are then treated with lymphodepleting chemotherapy several days prior to infusion of the autologous CAR T-cell product. This allows for optimal CAR T-cell

survival, expansion, and tumor cell killing upon reinfusion. The genetic engineering breakthrough of CAR T cells, which combine the exquisitely specific antigen-recognition capabilities of antibodies with the downstream cytotoxic effector functions of T cells, has proved to successfully lead to long-term remissions in patients with refractory disease. Three phase II clinical trials (JULIET, ZUMA-1, and TRANSCEND) demonstrated overall response rates between 52% and 82% and CR rates between 40% and 54%, with sustained PFS at approximately 40% following a single infusion of the engineered cellular product.[90-92]

Given the delay between apharesis and infusion of the final CAR T-cell product, bridging RT is often employed. Bridging RT is ideal for patients with symptomatic disease or rapidly progressing disease, to maintain performance status and control pain and other symptoms, which will help the patient better tolerate the CAR T-cell procedure. The optimal RT schedule, timing, and other such issues remain to be clarified. In regard to timing, it seems advisable to delay RT until after apheresis has taken place. Even with low RT doses and minimal bone marrow exposure, circulating lymphocytes within the bloodstream remain susceptible to RT. Prior studies primarily treated patients after apheresis (84% for Moffit, 65% for MDACC, 100% for University of Pennsylvania).[93-95] Such concerns must be counterbalanced against the need to treat patients with symptomatic disease awaiting insurance approval. The optimal dose for bridging RT is also uncertain. In some circumstances, the dose is limited by logistical timing of the CAR T-cell schedule. While many patients have been treated with palliative doses (20-30 Gy), at least one study suggests that “definitive” doses may be ideal. Sim et al demonstrated that local control was 100% in patients who received at least an EQD2 dose of 39 Gy.[96] The utility of higher doses and prolonged fractionation schemes must be weighed against the putative benefits of shorter RT courses, allowing more prompt CAR T-cell infusion.[80]

For patients with localized presentations that can be safely encompassed in RT fields, we recommend comprehensive treatment, ideally to definitive doses (eg, ~40 Gy). This can often be accomplished in a hypofractionated manner (eg, 3 Gy per fraction) to expedite treatment and minimize reinfusion delays. If definitive doses are not feasible or practical given the circumstances, a total dose of 20 to 30 Gy in 2 to 4 Gy fractions could be

pursued. For patients with more extensive disease who present with bulky tumors, symptomatic disease, or lymphoma in sensitive locations (eg, spinal cord, airway), we suggest localized irradiation of select sites to a dose of 20 to 30 Gy. Hypofractionation is often feasible.

Palliation

For patients with relapsed/refractory disease, RT is an effective modality to achieve palliation of symptomatic disease. While doses of 24 to 30 Gy, typically administered in a hypofractionated manner, are most commonly utilized, low-dose RT (2 Gy × 2) may be reasonable in select circumstances. Response rates of 50% to 80% have been reported with 2 Gy × 2, with a median time to progression of about 1 year.[81,97] Larger and more durable responses are likely achieved with more traditional dosing schemes.

Radiation Therapy Dose and Field Design

The dose of RT in a combined modality treatment program depends principally on the response to chemotherapy. For patients with stage I and II diseases, the standard dose is 30 Gy when a CR (Deauville 1-3) has been achieved by PET-CT after chemoimmunotherapy. A British National Lymphoma Investigation randomized study showed no difference in freedom from local progression, PFS, or OS between 30 and 40 to 45 Gy.[98] Local control is approximately 95% if RT is given in the setting of a CR to systemic therapy.

Even smaller doses may suffice with more effective systemic therapy, including rituximab-based regimens. A phase II study from Duke University demonstrated a 98% freedom from local recurrence with R-CHOP or R-EPOCH followed by 20 Gy of RT in DLBCL and PMBCL.[99] A confirmatory study by the ILROG has completed accrual.

For patients who respond favorably but not completely to chemoimmunotherapy (Deauville 4), higher doses of consolidation RT may be required to achieve optimal local control (≥40 Gy)[45,46] (Figure 85.1). In refractory localized DLBCL (Deauville 4-5), primarily those with stage I disease, salvage RT (≥40 Gy) may be a reasonable option, reserving CAR T-cell therapy if RT unsuccessful. In the unusual circumstance when RT

alone is pursued for patients with localized disease, a dose of 40 Gy is recommended. There is little evidence for doses above 40 Gy.

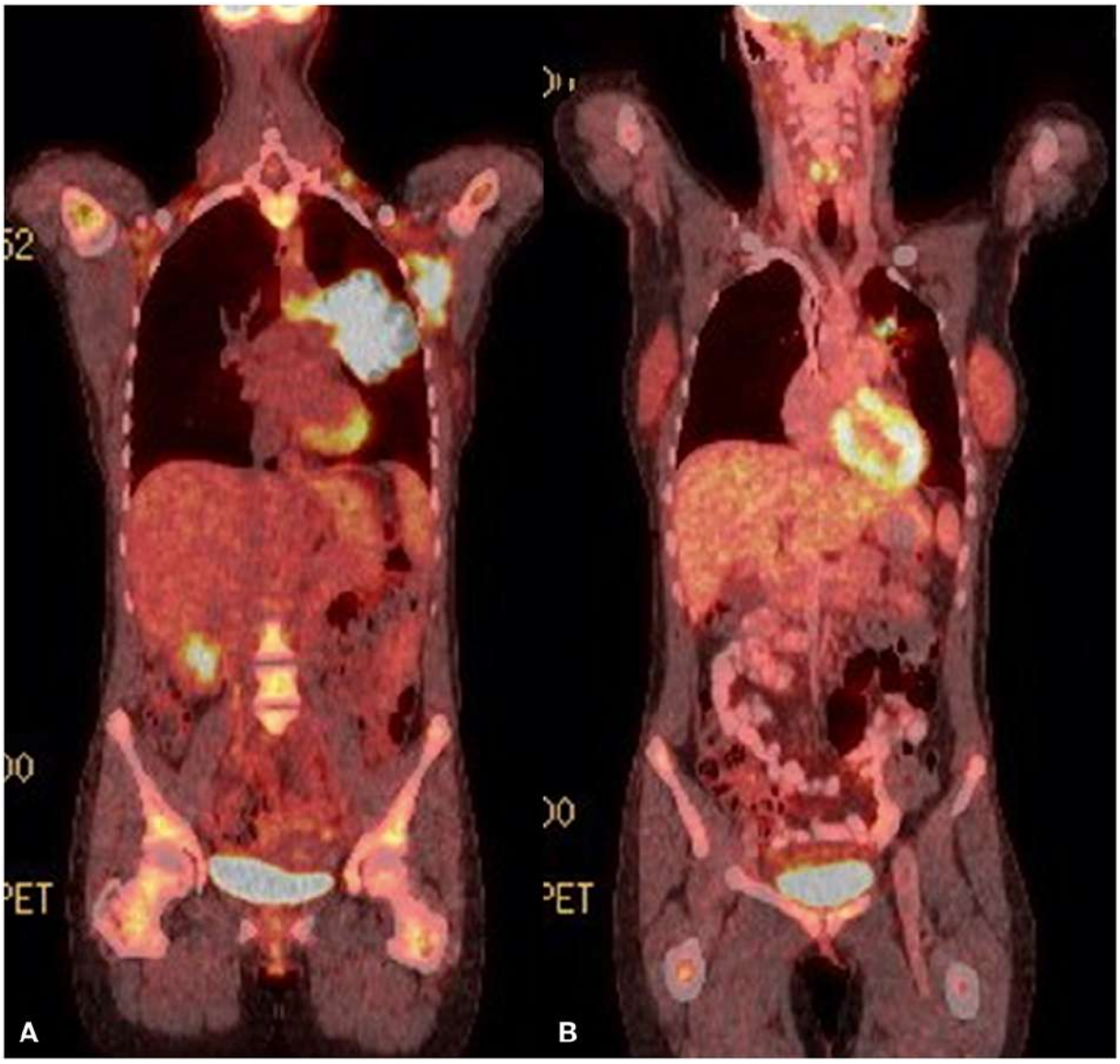

FIGURE 85.1 Fused coronal positron emission tomography-computed tomography (PET-CT) im ages of a patient with diffuse large B-cell lymphoma before (A) and after (B) chemoimmunotherapy. The postchemotherapy PET-CT was scored as a Deauville 4 (uptake above liver) in the left hilum. Biopsy confirmed persistent disease.

In advanced DLBCL, a dose of 20 to 30 Gy is appropriate in the setting of a CR to systemic therapy (Deauville 1-3). We prefer 20 Gy as patients with advanced DLBCL receive a full course of chemoimmunotherapy (six cycles) and are dependent upon an excellent response to such for low-dose

consolidation RT to be of effect. In patients who achieve a good, but not complete (Deauville 4), response to chemoimmunotherapy, with localized persistent FDG-avid disease, consolidation RT to higher doses (≥40 Gy) can be considered.[47]

In regard to field design, detailed guidelines from the ILROG are available.[100,101] These guidelines recommend treatment using "involved-site" principles. Involved-site radiation therapy (ISRT) involves creating a clinical target volume (CTV) that consists of the prechemotherapy extent of disease, adjusted to exclude uninvolved normal tissues after chemotherapy, and expanded to account for uncertainties in recreating the prechemotherapy extent of disease (anatomic changes, patient positioning differences between diagnostic PET-CT and planning CT scan, imaging uncertainties, etc) (Figure 85.2). A planning target volume (PTV) is then created to account for setup variation and potential organ motion.

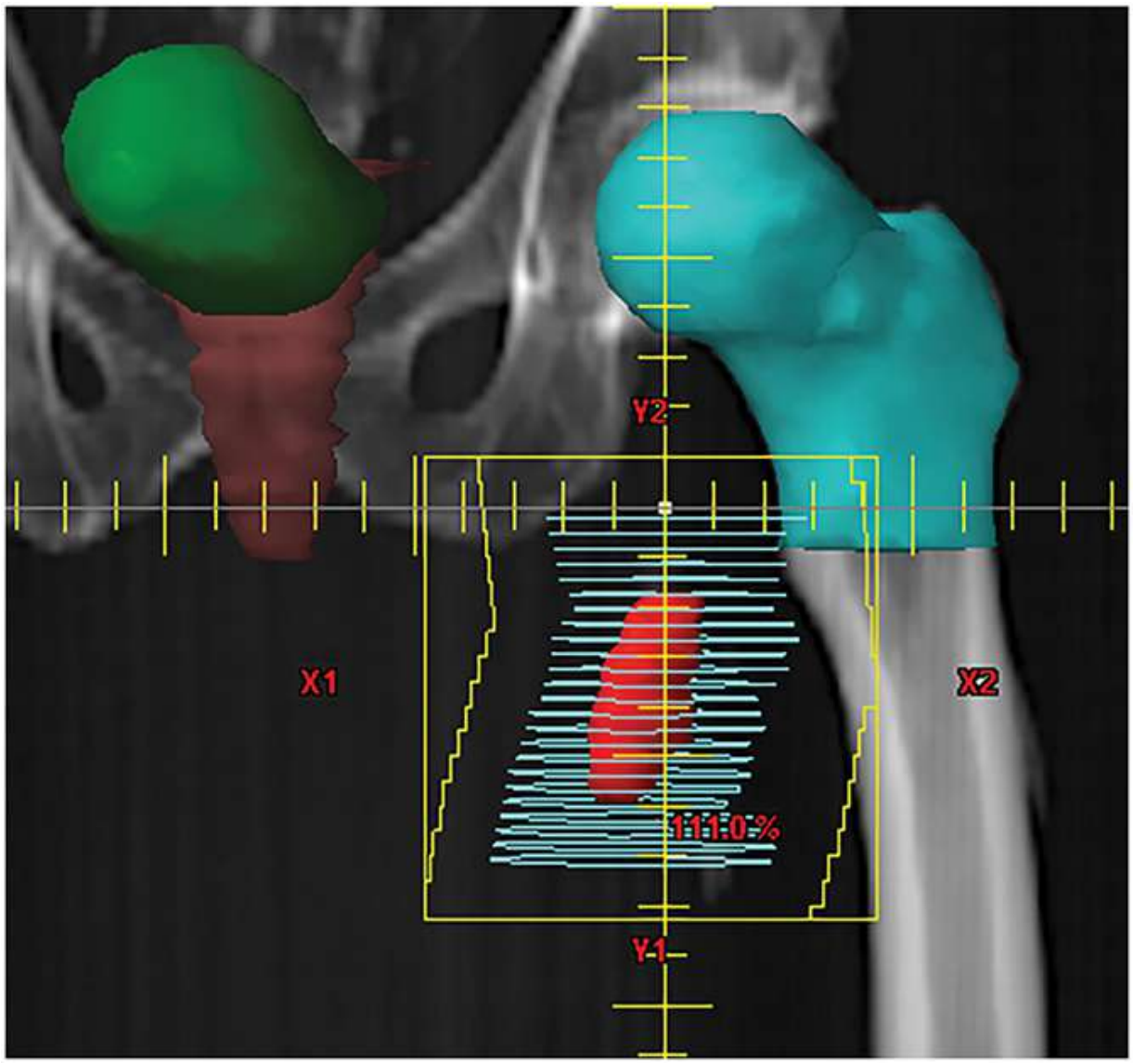

FIGURE 85.2 Stage I diffuse large B-cell lymphoma of the L inguinal region s/p three cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone followed by radiation therapy (30 Gy). The original extent of disease was recreated on the planning computed tomography scan (red structure). The clinical target volume is represented by the aqua contours.

Such recommendations are supported by prior studies, demonstrating that the dominant pattern of failure after combined modality therapy is usually disseminated disease, with a small percentage with local failure.[59] On the other hand, after chemotherapy alone, more local failure occurs.[59,102] Failure in nodal areas adjacent to the original disease is uncommon.

For patients with localized disease (stages I-II), all sites of original involvement should be treated. For patients with advanced disease (stages III-IV), treatment fields should be customized. In those with reasonably limited presentations, consolidation of all sites of original involvement can be considered. When this is not practical, treatment of select sites may be more prudent. This may include original sites of bulk, limited skeletal involvement, or a site that failed to achieve a CR to chemotherapy.

RT delivery techniques should be customized to the site being treated, proximity of critical normal organs, dose of RT being prescribed, and treatment intent. In many cases, three- dimensional conformal RT (3D-CRT) is appropriate. For example, if administering consolidation RT to a CTV within the axilla, anteroposterior/posteroanterior (AP/PA) fields using 3D-CRT techniques to avoid the lung is very reasonable. On the other hand, intensity-modulated RT (IMRT) may be selected to treat CTVs in close proximity to the parotid gland, heart, kidneys, or other critical structures (Figure 85.3). In some cases, protons, if available, may be advantageous over IMRT. Simpler techniques are often sufficient when treating in a palliative fashion. Radiation oncologists should choose the modality that provides clinically meaningful avoidance of critical surrounding structures to limit both acute and long-term toxicity.

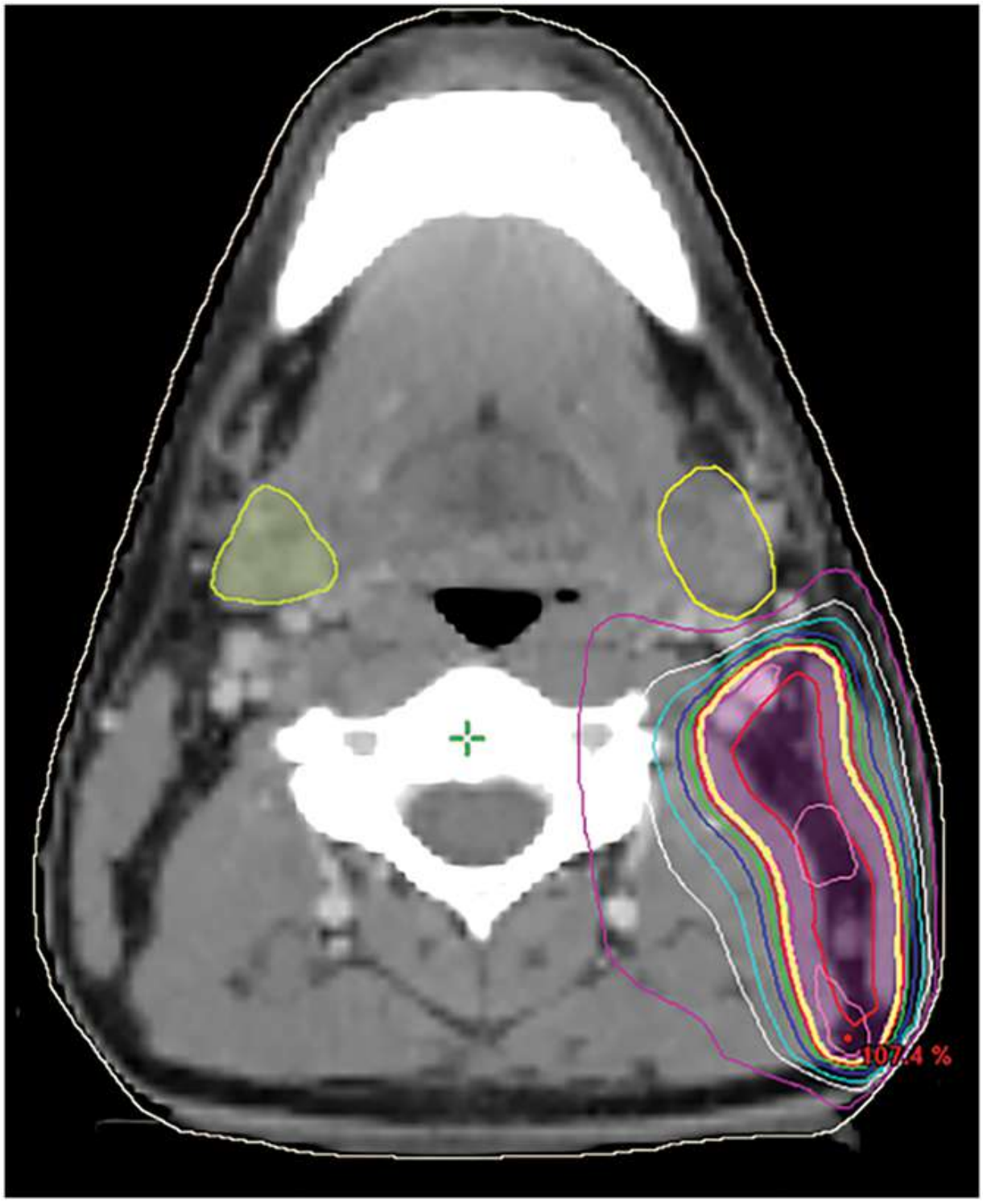

FIGURE 85.3 Stage I diffuse large B-cell lymphoma of the L neck s/p three cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone followed by radiation therapy (30 Gy). Note ability of intensity-modulate radiation therapy to avoid left submandibular gland (yellow contour).

HIGH-GRADE B-CELL LYMPHOMAS

HGBL is a distinct entity within both the WHO and the ICC classification systems and is closely related to DLBCL. HGBL NOS is an aggressive mature B-cell process, typically composed of intermediate-sized or blastoid cells, that does not fit into other well-defined entities, such as DLBCL. HGBL with *MYC* and *BCL2* and/or *BCL6* gene rearrangements, often referred to as "double-hit" or "triple-hit" lymphomas, can also contain large cells. Approximately 5% to 10% of patients with large B-cell lymphoma have double-hit or triple-hit genetics, which carries a particularly poor prognosis, despite the fact that the molecular subgroup is typically GCB like.[103]

These patients generally present with advanced disease with a high IPI score and are at higher risk of central nervous system (CNS) involvement. Given the higher risk of relapse in the setting of *MYC* and *BCL2/BCL6* gene rearrangements, more aggressive chemotherapy regimens are often utilized, such as DA-EPOCH-R.[104] R-CHOP may be suitable for patients presenting with early-stage disease with a low-risk IPI score. Regardless of which chemoimmunotherapy therapy is pursued, consolidation RT is recommended in patients with early-stage double-hit or triple-hit lymphoma.[105] R-CHOP is often recommended for HGBL NOS.

PRIMARY MEDIASTINAL (THYMIC) LARGE B-CELL LYMPHOMA

PMBCL comprises about 10% of all large cell lymphomas and is believed to arise from thymic medullary B cells. Although the histologic appearance can vary, compartmentalizing alveolar fibrosis is a common feature. PMBCL expresses pan B-cell antigens, including CD20, but is negative for surface immunoglobulin. CD30 is present in a majority of patients but stains weaker than classic HL.[106] PMBCL also has a unique molecular signature that closely resembles classic HL.[107] The disease affects primarily young women (median age 37) with prominent anterior mediastinal disease, generally with stage I and II presentations. When grouped according to the IPI, the prognosis is similar to that of DLBCL generally, perhaps a bit more favorable[108,109] with a plateau observed in the PFS curve after 18 to 24 months.[108]

PMBCL is typically managed with more intensive chemotherapy (DA-EPOCH-R) without RT, less commonly standard chemotherapy (R-CHOP), with or without consolidation RT (30 Gy).[110,111] Omission of RT with DA-EPOCH-R is primarily based on phase II[112] and retrospective data,[111,113] and more studies are needed. The failure of DA-EPOCH-R to improve outcomes compared with R-CHOP in DLBCL NOS should temper enthusiasm of this regimen in PMBCL until more data are available.[71] Preliminary results from a randomized trial (IELSG-37, NCT01599559) suggested that RT can be omitted in patients achieving a CR (Deauville 1-3) using more standard regimens such as R-CHOP.[114] In this study, PFS at 30 months was 96% with chemoimmunotherapy alone. Notably, only 50% of patients achieved a CR and were randomized to observation or RT. It should be noted that it is common for patients with PMBCL to have residual FDG uptake (Deauville 4) in the anterior mediastinum after completing chemotherapy. If the residual uptake is mild, albeit above liver background, observation with serial PET-CT studies is appropriate as most patients will not relapse, even without RT.[115] Thymic rebound may be explanatory. When consolidation RT is pursued, dose and field recommendations are the same as DLBCL NOS.

T-CELL/HISTIOCYTE-RICH LARGE B-CELL LYMPHOMA

T-cell/histiocyte-rich B-cell lymphoma consists of large malignant B cells with a florid background of inflammatory T cells, with or without histiocytes. Clinically, it occurs in a younger population compared with DLBCL, generally with a male predominance.[116,117] This entity is also more likely to present with B symptoms and involves the spleen, liver, and bone marrow. Treatment recommendations are similar to DLBCL NOS.

MEDIASTINAL GRAY ZONE LYMPHOMA

MGZL is a B-cell lymphoma with features that overlap classic HL and PMBCL. This disease typically affects young adults, generally with involvement of the anterior mediastinum. The histologic appearance and immunophenotype are aberrant. For example, cases that appear histologically to resemble classic HL may show strong CD20 and CD79a expression. On the other hand, cases that resemble PMBCL histologically

may lack B-cell antigens, such as CD20. MGZL generally exhibits an aggressive course with inferior outcomes compared with classic HL or PMBCL. Combined modality therapy is generally recommended, typically employing B-cell chemotherapy regimens such as R-CHOP or DA-EPOCH-R, with RT for patients with stage I and II presentations or bulky disease.[118]

PRIMARY TESTICULAR DLBCL

Included in the category of primary large B-cell lymphoma of immune-privileged sites, primary testicular DLBCL deserves special attention. Patients typically present with a painless testicular mass with the diagnosis established after orchiectomy. The majority (~80%) of patients have stage I or II disease. Even with chemotherapy, there is a high risk of failing in the contralateral testicle (~40%). Prophylactic scrotal irradiation significantly reduces this risk (<10%) and is associated with improved survival.[119] Patients are also at risk of CNS failure, most commonly in the brain parenchyma necessitating some form of CNS prophylaxis. An international phase II trial demonstrated good outcomes with R-CHOP chemotherapy, intrathecal methotrexate, and prophylactic scrotal irradiation with consolidation RT to regional lymph nodes in the setting of stage II disease.[120] A variety of RT techniques can be employed to treat the testicles (PMID 22836054). We utilize a single superior-anterior-oblique 6X photon field setup clinically using 1.5 cm of bolus. A dose of 26 to 30 Gy in conventional fractionation is recommended.

FOLLICULAR LYMPHOMA

FL is the second most common NHL in the United States and western Europe, comprising approximately 20% of cases. It is the most common “indolent” lymphoma.

Pathology

FL is a tumor of follicle center B cells (centrocytes and centroblasts) with a follicular (nodular) pattern that morphologically is similar to normal germinal centers. The neoplastic follicles may be present in the entire

tumor, or the lymphoma may contain a diffuse component as well. In the WHO classification, the number of large cells per high-power field is used to assign grades (0-5, 5-15, >15 for grades 1-3, respectively). Grade 3 is further subdivided into 3A and 3B, with the latter characterized by an absence of centrocytes and replacement by sheets of centroblasts. Grades 1, 2, and 3A FL are all closely related with similar biologic behavior and response to therapy. FL grade 3B, however, has a clinical course very similar to DLBCL and is usually managed as such.[121] Any area of DLBCL in an FL, irrespective of grade, suggests the disease is DLBCL and should be managed as such.

The tumor cells of FL are usually surface immunoglobulin positive, express pan B-cell–associated antigens (CD19, CD20), CD21, and CD10 (60% of the time), but lack CD5. Most cases are BCL-2 positive; nuclear BCL-6 is expressed by at least some of the neoplastic cells. The (14;18) translocation is characteristic for FL and, together with the *BCL-2* rearrangement, is present in approximately 85% of cases. It is frequently absent, however, in FL grade 3B, further supporting the biologic distinctiveness of this category.

Clinical Presentation

FL primarily affects older adults (median age 65 years). There is a slight female preponderance. Most patients present with painless peripheral lymphadenopathy involving cervical, axillary, or inguinal/femoral regions. There may often be a history of spontaneous waxing and waning of lymph node size. Constitutional B symptoms of fever, sweats, or weight loss are uncommon. In contrast to DLBCL, approximately 80% of patients present with generalized disease, most often with stage IV disease. The bone marrow is the principle extranodal organ involved.

In contrast to DLBCL, localized extranodal presentation of FL is uncommon, reported in only 6% of the International Lymphoma Study Group (ILSG) series.[122] A unique but uncommon variant of FL is extranodal presentation in the intestinal tract, usually the duodenum, usually stage I.[123] Duodenal FL, which generally arises in the second portion of the duodenum and is often not FDG avid, seems to have a lower propensity to fail at systemic sites after definitive local therapy.

The principle indicated imaging study is the PET-CT scan. Although FL is typically less FDG avid than DLBCL, increased uptake is still seen in about 90% to 95% of cases.[124] Bone marrow biopsy should be performed in all patients thought to have early-stage disease, given the high incidence of involvement. PET-CT is less accurate in detecting bone marrow involvement than in DLBCL. For patients with advanced disease, a bone marrow can be pursued if the results will change clinical management.

Large cell transformation to DLBCL occurs in approximately 30% of patients with FL at a rate of approximately 2% per year.[125] This should be suspected if LDH levels are rising, B symptoms develop, extranodal sites become involved, disproportionate growth occurs, or high SUVmax is observed (>10).[126] The prognosis after transformation is generally not good but better in the rituximab era, with a median survival of 50 months following transformation. The outlook is better with an increasing interval between FL diagnosis and the occurrence of transformation.

Prognostic Factors

Subsequent to the development of the widely used IPI for DLBCL, attempts were made to apply it to FL, but here it was less useful because most patients fell into a favorable prognostic category. Additional efforts to address this problem led to the development of the follicular lymphoma international prognostic index (FLIPI)[33] (Table 85.4). The initial database included 4,167 patients with FL diagnosed between the years 1985 and 1992 (the pre-rituximab era). Five adverse prognostic factors were identified on multivariate analysis, age (>60 vs <60 years), stage (I/II vs III/IV), hemoglobin level (<12 vs ≥12 g/dL), number of nodal areas (>4 vs ≤4), and elevated serum LDH. Low-risk patients had 0 to 1 adverse factors, intermediate risk 2 factors, and poor risk 3 or more. Patients were divided approximately equally between the three groups with good separation in terms of OS (Table 85.4).

The FLIPI was subsequently modified to take into account the advent of rituximab leading to the FLIPI-2 categorization.[34] That index identified age, elevated B2M, hemoglobin, bone marrow involvement, and lymph node diameter greater than 6 cm as independent risk factors for PFS (OS data not as yet available) (Table 85.4).

Recently, a third prognostic index is under development utilizing genetic risk factors as well and is known as the M7-FLIPI.[127] This model integrates the mutational status of seven genes known to be important in FL.

As with DLBCL, post-treatment PET-CT response appears to have prognostic significance.[128,129] Limited studies on interim PET scanning have suggested no benefit from this.[129,130]

Clinical Management

The majority of patients with FL present with advanced-stage disease. Advanced FL is still considered incurable despite advances in chemoimmunotherapy in the past several years, with resulting prolongation of both PFS and OS. For the minority (20%-25%) of patients who present with localized disease, local RT has curative potential.

Stage I to II Follicular Lymphoma

A large number of retrospective studies have shown a high rate of local disease control, greater than 90%, with approximately 50% of patients achieving long-term survival without relapse in early-stage FL. Selected series are shown in Table 85.6.

TABLE 85.6 RADIOTHERAPY FOR STAGE I/II FOLLICULAR LYMPHOMA

Study	Year	Number of Patients	Radiation Fields	Radiation Dose (Gy)	Failure-Free Survival % (10 y)	Overall Survival % (10 y)
Vaughan Hudson et al[131]	1996	208	NS	35	47	71-84[a]
Mac Manus and Hoppe[132]	1996	177	IF, EF, TNI	34-55	44	64
Stuschke et al[133]	1997	117	ER, TNI	36	59	86
Wilder et al[134]	2001	80	IF, EF	26-50	57	65
Peterson et al[135]	2004	460	IF	16-47	41	62

Study	Year	Number of Patients	Radiation Fields	Radiation Dose (Gy)	Failure-Free Survival % (10 y)	Overall Survival % (10 y)
Guadagnolo et al[136]	2006	106	IF, EF	30-42	46	75
Pugh et al[137]	2010	2,222	NS	NS	NS	62-79[a]
Campbell et al[138]	2010	237	IN, EF	20-40	49	66-82[a]
Vargo et al[139]	2015	10,613	NS	NS	NS	68%

EF, extended field; IF, involved field; IN, involved nodal; NS, not specified; TNI, total nodal irradiation.

[a]Overall survival and cause-specific survival.

Several comments about the series listed in Table 85.6 are listed in the following in order:

1. Most of the studies shown are older, which gives them the advantage of long follow-up but the disadvantage of lack of modern staging, notably the absence of PET-CT studies. Further, most of the series included some patients with low-grade lymphoma histologies other than FL, although the great majority were FL.
2. The radiation doses used varied widely from 16 to 50 Gy, although most patients received in the neighborhood of 30 Gy. None of the series report detailed dose response data. In general, there appeared to be no dose response demonstrated, with greater than 90% local control with doses in the 30 Gy range.
3. The field sizes also varied considerably with somewhat different definitions than are now used. In brief, involved-field radiation, in which the nodal area in question was treated with a generous margin, appeared to be as effective as larger fields.
4. Ten-year PFS is remarkably close to 50% in all of the series. There was more variation in the OS, which generally ranged from about 60% to 80% depending on whether lymphoma-only deaths were counted or all deaths due to any cause. In general, the risk of a patient with stage I/II

FL treated with radiation alone *dying of lymphoma* at 10 years was approximately 20%.

5. As can be inferred by the high local control rate of approximately 90%, the great majority of relapses were at distant sites from the original disease, not adjacent nodal areas. This has led directly to the practice of irradiating only the involved nodal site with a generous margin. Importantly, few relapses were observed after 10 years with a general flattening of the PFS curve.

The largest series in the literature is the report from Pugh et al[137] The Surveillance, Epidemiology, and End Results (SEER) database forms the basis of this study. In all, 6,558 patients were identified from 1973 to 2004 with localized FL. Of these patients, 2,222 (34%) were treated with initial RT. No details as to radiation fields or dose are available. Compared with patients from the SEER database who received no RT, cause-specific survival was improved in the radiation group at 10 years from 65% to 79%. Survival at 10 years was 60% in the radiated patients and 50% in those not receiving RT.

A recent multi-institutional study from the ILROG addressed the issue of whether the results would be improved in patients with localized disease who underwent modern staging with PET-CT.[140] In all, 512 patients were included, all of whom were staged with PET-CT. The majority (80%) were stage I. Bone marrow biopsies were not done in about one-third of patients. Five-year OS and freedom from progression (FFP) were 96% and 69%, respectively. FFP was 74% for stage I and 49% for stage II. Local control was 97%, with 1.6% true in-field failures and 0.9% marginal recurrences. In the great majority of recurrences, these results suggest a better outcome for the treatment of localized disease when patients have been staged with contemporary techniques outside the radiation field. There was no effect of field size on the outcome, with comparable results achieved with either involved-field radiation therapy (IFRT), ISRT, or involved nodal RT (INRT), with some variation, however, in how these fields were defined. There were several predictors of a worse outcome, including BCL-2 expression and early relapse within 12 months of completion of treatment. FFP at 10 years was approximately 50%, similar to historical series. Compared to historical controls, these results suggest a better outcome for

the treatment of localized disease when patients have been staged with contemporary techniques but longer follow-up is needed.

On the basis of these studies, RT remains the standard of care for early-stage FL. Most of the patients in these series had stage I disease or contiguous stage II disease. For noncontiguous stage II disease, the data are sparse. Many centers individualize the treatment of such patients rather than automatically treating with RT.

Small series of patients with localized disease have been observed without treatment with apparently favorable results.[141] Experience with this approach, however, is quite limited. National consensus guidelines recommend RT as the standard approach for localized disease with observation reserved for selected patients in whom there might be a concern for the ability to tolerate RT.

Despite the abovementioned data and European Society for Medical Oncology[142] and other national consensus guidelines endorsing RT as the preferred initial management, the use of radiation in patients with early-stage FL continues to decline. In the Pugh study, only 24% of patients with localized disease received RT as initial treatment.[137] In the National LymphoCare study, 23% of patients with stage I FL received RT alone.[143] The remainder of the patients were treated in a variety of ways, including rituximab plus chemotherapy (30%), rituximab alone (13%), and observation (29%). OS at 5 years was approximately 90% in all treatment groups.

Adjuvant systemic therapy after definitive RT in early-stage FL has been investigated in an attempt to prolong PFS and ultimately OS. In the pre-rituximab era, four randomized trials (three of which included a small number of patients with FL as part of larger DLBCL trials) showed no benefit for adjuvant systemic therapy.[52,53,144,145]

A recent multicenter prospective phase III trial randomized 150 patients with limited-stage FL to RT alone or with the addition of systemic therapy (cyclophosphamide, vincristine, and prednisone [CVP] ₊/− rituximab [R-CVP]).[82] Of the 75 patients randomized to the latter, only 31 received rituximab with a benefit in PFS seen in this group only. No OS benefits were seen. Given the rapidly evolving area of innovative systemic agents,

this remains under active investigation, but outside of a clinical trial, this approach cannot be recommended.

For patients with localized FL treated with definitive RT (with or without adjuvant systemic therapy), the optimal surveillance approach is not well defined. In the asymptomatic patient with a negative physical examination, PET-CT at regular intervals will lead to early detection of recurrent disease. However, such recurrences are usually disseminated disease, generally considered incurable, with little suggestion of benefit for early initiation of therapy in the absence of symptoms. We recommend focusing subsequent imaging on the symptomatic patient or one with abnormal physical examination findings.

Stage III and IV Follicular Lymphoma

Advanced FL is still considered an incurable disease with survival curves that never become parallel to that of the corresponding normal population. The clinical course, however, is often prolonged with multiple effective therapeutic agents available. Because of the relatively indolent nature of advanced FL, a strategy of initial observation without therapy was introduced first at Stanford University.[146] It was later confirmed in randomized trials that this approach did not adversely affect long-term survival.[147] Note that these trials were performed in the pre-rituximab era. Nonetheless, the strategy of "watchful waiting" has gained widespread acceptance. The decision to pursue treatment is generally based on GELF criteria in which any one of the following may be an indication to begin active therapy: (1) three distinct nodal sites, each ≥3 cm; (2) a single nodal or extranodal site ≥7 cm; (3) splenomegaly; (4) organ compression or compromise; (5) pleural effusions or ascites; (6) B symptoms; (7) leukemia (>5 × 10^9/L malignant cells); or (8) cytopenias.[148]

A recent report from the National LymphoCare Study compared outcomes in 386 patients initially managed with observation, rituximab alone (296 patients), or rituximab combined with chemotherapy (1,072 patients).[149] OS rates were approximately 70% in all three groups.

One recent treatment algorithm divides patients with advanced-stage disease into four categories depending upon symptoms and tumor burden. For asymptomatic patients with a low tumor burden, the proposed

therapeutic strategies are either observation or treatment with single-agent rituximab, with observation being preferred. For asymptomatic patients with a high tumor burden, proposed therapeutic choices are observation or chemotherapy along with rituximab. For symptomatic patients with low tumor burden, treatment choices include single-agent rituximab or in combination with chemotherapy. For high tumor-burden symptomatic patients, the preferred strategy is rituximab-containing chemotherapy with maintenance rituximab. In this decision-making process, there is room for considerable individualization with consideration for the patient's age, comorbidities, predicted life expectancy, and general patient preference.[150] For select patients with generalized disease but with a problematic localized area of lymphoma, ultra-low-dose RT (4 Gy) constitutes very effective palliation with almost no toxicity.

The majority of patients for whom systemic therapy is desirable will receive rituximab in combination with chemotherapy. In the past two decades, the addition of rituximab to chemotherapy constitutes a major therapeutic advance. Its use has been associated with increased response rates, duration of response, and improvement in PFS at a minimum. One recent meta-analysis suggests a benefit in OS as well, although longer follow-up is needed.[151]

Multiple chemotherapy combinations have been studied in combination with rituximab, including CHOP, CVP, and fludarabine. In brief, no one drug program when combined with rituximab has demonstrated superior OS over another. Recently, however, the alkylating agent bendamustine has been introduced for the therapy of FL in combination with rituximab. A phase III trial from the Study Group Indolent Lymphoma compared bendamustine-rituximab (BR) to R-CHOP and demonstrated increased efficacy and reduced toxicity with the BR combination.[152] This improved efficacy was manifested by prolongation of PFS and improved response rates, but, as is so often the case with FL, no differences in survival were found. A second study, a randomized phase III noninferiority trial (BRIGHT study) indicated the equivalence of BR to R-CHOP or R-CVP with, however, somewhat different toxicity profiles.[153] Since the BR combination appears to be generally significantly less toxic, this has led to the rapid adaptation in North America of BR as first-line systemic therapy for patients with advanced-stage FL who require treatment.

Another novel strategy for first-line treatment has involved combining rituximab with the immunomodulatory agent lenalidomide. Among patients with previously untreated advanced FL, rituximab plus lenalidomide was as efficacious as rituximab plus chemotherapy in a randomized trial.[154] This regimen provides a chemotherapy-free treatment option for symptomatic patients with advanced FL.

The use of maintenance rituximab after chemoimmunotherapy has gained widespread acceptance following a large phase III intergroup trial (PRIMA study).[155] In this trial, patients with previously untreated FL who had responded to chemoimmunotherapy were randomly assigned 2 years of maintenance with rituximab or placebo. With short follow-up, the 2-year PFS in the rituximab maintenance arm was 75% compared with 58% in the observation arm. There was a slight increase in adverse events in the maintenance arm. There was no difference in OS. Thus, the benefit of rituximab maintenance is unclear but is being increasingly employed.

Treatment of Relapsed, Refractory, or Transformed Follicular Lymphoma

Patients who relapse after initial therapy of localized FL almost always have generalized disease, even if the area of relapse is ostensibly localized. These patients should be reevaluated in a similar manner to those who present with advanced disease, as has been already discussed. Similarly, patients who presented with advanced disease and relapse after initial therapy should be reevaluated in a similar manner as they were at the time of diagnosis. Are they symptomatic, what is the extent of the tumor burden, do they meet the GELF criteria for treatment, what is the goal of therapy, what are the patient preferences, and, finally, what is the patient's overall medical condition? Answers to these questions will guide the therapeutic choices.

At the time of relapse, biopsy of a new disease site is appropriate to rule out transformation to a more aggressive histology. Restaging is usually appropriate as well with the procedures mentioned earlier, including routine blood studies, LDH, B2M, and PET-CT scan. A bone marrow examination is less important in the presence of known generalized disease.

For patients relapsing with a limited extent of disease, low-dose palliative RT, to 4 Gy total, should be strongly considered. Such low doses have been found to be remarkably effective (see later). Side effects are minimal, with 1% grade III to IV toxicity. Unfortunately, low-dose palliative RT is often overlooked in the management of generalized disease.

For patients with generalized disease who do require systemic therapy, the choice of agents is greatly influenced by what prior therapy the patient has received. For example, if the initial systemic therapy was BR, it would be logical to proceed with R-CHOP or vice versa. A new anti-CD20 antibody, obinutuzumab, may be employed.[156] A number of other agents are also available for relapsed FL.

Finally, stem cell transplantation (SCT) has been extensively studied in FL, both autologous (ASCT) and allogeneic. In the only phase III trial to compare ASCT to conventional chemotherapy in relapsed FL, patients appeared to demonstrate a higher PFS and OS when treated with ASCT.[157] However, the procedure is not believed to be curative for relapsed disease, in contrast to the situation with DLBCL. Allogeneic transplantation may have curative potential, but its use has been hindered by the high treatment-related mortality of approximately 40% at 3 years for a full myeloablative transplant and a treatment-related mortality of up to 20% even for the reduced-intensity conditioning transplant, as well as the logistical difficulties of finding a matched donor. In a recent retrospective analysis, however, 3-year OS for allogeneic SCT versus ASCT was 87% versus 61%.[158] It should be noted that neither ASCT nor allogeneic SCT has any proven role in the initial treatment of generalized FL, such as consolidation therapy for patients in first remission.

Histologic transformation to DLBCL occurs in approximately 2% to 3% of patients per year and historically has been associated with a poor clinical outcome. The prognosis directly relates to the number of prior therapies the patient has received with a much poorer outlook in those with multiple prior therapies. Aggressive chemotherapy has most often been employed in this situation. In selected patients in a Canadian trial, treated after transformation by induction chemotherapy followed by high-dose chemotherapy and ASCT, a 5-year survival of 65% has been reported.[159]

Radiation Dose and Field Size

As can be seen from Table 85.6, the dose of RT employed in older retrospective studies varied widely from approximately 20 to 44 Gy, with local control being achieved in over 90% of patients irrespective of dose. Retrospective dose analyses reported from the Princess Margaret Hospital and the University of Florida suggested local control rates over 90% with doses in the range of 25 to 35 Gy at the Princess Margaret[160] and 30 Gy at the University of Florida.[161]

These discrepancies led to the performance of a large prospective trial by the British National Lymphoma Investigation comparing 24 to 40-45 Gy.[98] This is one of the few prospective phase III trials of different RT doses in any disease. In brief, no differences were observed in any measured outcome, either local control, PFS, or OS between the two different doses employed. This study made no mention of bulk of disease. Such patients appeared to have been included. There is no information as to whether their outcome was any different from those with small-volume disease.

This study has led to the widespread adoption of 24 to 30 Gy as the appropriate dose for curative treatment of FL and other so-called indolent lymphomas. Phase III data suggest 24 Gy is sufficient, but there is a large historical experience with 30 Gy and little increase in toxicity in many instances. Many centers would probably give 30 Gy for bulk disease (variably defined).

Even lower doses (4 Gy) have been found to be quite effective in the palliation of advanced FL. Response rates of 80% to 90% have been reported with a median duration of response ranging from 22 to 45 months.[162-164] These data have led some to propose the use of very low doses of 4 Gy as appropriate for curative treatment of limited-stage FL, leading to a randomized trial involving 548 patients who were prospectively allocated to receive either 4 or 24 Gy.[163] In 40% of these patients, the treatment was curative in intent, 60% palliative. PFS at 2 years was superior in both the curative and palliative cases for the 24 Gy dose. Thus, 24 to 30 Gy remains the standard dose for curative therapy of localized FL, with 4 Gy reserved for palliation of advanced disease. This issue is discussed further in the following section on MZL.

The choice of an appropriate radiation field size for localized FL is more complex. Prospective randomized trials addressing this issue do not exist. The field sizes used in the studies in the table were highly variable, with no suggestion of a different outcome related to field size. Almost none of the studies employed modern imaging techniques in either the initial diagnosis or subsequent therapy. CT-based 3D treatment planning was carried out in almost none of these studies. The only trial that looked at INRT or ISRT and compared it with larger fields was the Campbell trial from British Columbia.[138] This trial had a relatively large number of patients. No difference was observed in the treatment outcome depending on field size. Additional evidence for small fields derives from the patterns of failure in patients with limited-stage FL treated with RT alone. Most recurrence are at distant sites, either nodal, extranodal, or both, very seldom at adjacent nodal areas or within the radiation field.

Extensive guidelines for both radiation field size and target definition as well as radiation doses have been developed by the ILROG[101] (Figure 85.4). Most patients with FL will not have received preradiation systemic therapy, but for those who may have, the target volume is still the initial extent of disease prior to any therapeutic intervention. Modern imaging techniques should be used to define the extent of gross disease (gross tumor volume [GTV]), preferably a PET-CT scan. As stage I FL is generally treated with RT alone, the CTV will consist of the GTV plus lymph nodes in the immediate vicinity at risk of harboring microscopic disease (typically a 3-4 cm expansion along the lymph node chain). The CTV expansion is highly dependent on the clinical situation. For example, the margin may be reduced when the GTV is close to important normal organs or tissues. A final PTV margin will account for day-to-day setup variation.

FIGURE 85.4 Stage I follicular lymphoma of a right inguinal lymph node treated with radiation therapy alone using involved-site principles. The gross tumor volume is contoured in red. The clinical target volume (orange) includes the immediate area at risk of harboring microscopic disease. The planning target volume (purple) includes a small margin to account for daily setup error.

Most patients with localized FL have peripheral nodal areas involved, such as neck or inguinal-femoral regions. Often relatively simple field arrangements such as AP/PA will suffice, but 3D planning or IMRT should be considered depending on individual circumstances.

MARGINAL ZONE LYMPHOMAS

MZL accounts for approximately 8% to 10% of all cases of NHL. MZL entities traditionally included nodal MZL, splenic MZL, and extranodal MZL of MALT. Primary cutaneous MZL was recently added as a distinct entity by the WHO. The classification of pediatric MZL is uncertain and is considered by some to be a subset of pediatric FL. MALT is the most frequent MZL entity encountered in clinical practice and is the focus of the following section. A brief synopsis of the other varieties of MZL is also included (primary cutaneous MZL is reviewed in Chapters 86).

Pathology

MALT lymphoma is characterized by a polymorphous infiltrate of marginal zone (centrocyte-like) B cells, small lymphocytes, monocytoid B cells, and plasma cells, as well as rare large basophilic blast cells (centroblast or immunoblast like). In epithelial tissues, the marginal zone B cells typically infiltrate the epithelium, forming lymphoepithelial lesions defined by invasion and partial obstruction of mucosal glands by tumor cells.[165] Although transformed large cells are typically present, they are in the minority. If present in large numbers, a diagnosis of DLBCL is warranted.

The tumor cells express pan B-cell–associated antigens, including CD19, CD20, CD22, and CD79a, but there is no specific marker for MALT at present. However, lack of CD5 (positive in CLL/SLL and MCL), CD10 (positive in FL), and cyclin D1 (positive in MCL) expression helps distinguish MALT from other small B-cell lymphomas.[166]

Clinical Presentation

Two-thirds to three-fourths of patients have stage I or II diseases, usually stage I. The most common locations for MALT lymphoma are the stomach, orbit, and skin.[167] Other less common anatomic sites include the parotid, breast, thyroid, and lung. Involvement of paired organs simultaneously, or less commonly two distinct extranodal sites, is occasionally encountered. With such scenarios, it best to stage each site separately as opposed to making a stage IV designation. Such patients may be treated with local RT to both extranodal sites with long-term disease control.[168]

The most common site of MALT is the stomach. A unique feature of gastric MALT is the association with *H. pylori* infection. *H. pylori* can be identified in up to 92% of patients.[17] Lymphoid tissue is not normally present in the stomach, but in response to an antigenic stimulus brought about by *H. pylori*, normally present T cells in the gastric mucosa attract a B-cell population, giving rise to lymphoid follicles and, after prolonged antigenic stimulation, lymphomas.[169]

An association with bacterial infection for MALT at sites other than the stomach has been described.[170] *C. psittaci* has been found in some cases of ocular adnexal lymphoma. In addition, *B. burgdorferi* and *C. jejuni* have been associated with MZL arising in the skin and small intestine,

respectively.[170,171] There is a wide geographic variation of these associations, however, which have not generally been observed in cases in the United States. Accordingly, while there are some reports of antibiotic efficacy for MALT at sites other than the stomach, the standard initial treatment remains local RT with very high rates of CR and local control in excess of 90%, similar to what has been reported for gastric MALT.[172,173]

Patients with orbital MALT typically present with mass lesions in the bulbar or palpebral conjunctivae, described in the literature as "salmon pink" in color. Tumors of the retrobulbar region may present with swelling, proptosis, double vision, and/or other associated disturbances in function of the extraocular muscles. Bilaterality is not unusual, occurring in 10% to 15% of cases. Similar to salivary gland and skin tumors, this does not adversely affect prognosis.

Prognostic Factors

The primary prognostic factor is disease site. MALT arising in paired organs (eg, orbit or salivary gland) appears to have a higher risk of relapse compared with that arising in a single organ (eg, stomach or thyroid).[167,172,174] Relapse after RT for cutaneous MZL is also rather frequent.[175] Such relapses, however, are almost always distant from the initial RT field and usually amenable to a second course of RT.

Treatment of gastric MALT with antibiotics is a special consideration. Predictive factors associated with a lower chance of achieving and maintaining a CR after antibiotic therapy include deep gastric wall invasion,[176-178] nodal involvement,[178,179] and the translocation t(11;18).[18,180]

Clinical Management

First-line treatment for localized MZL should be RT, with the exception of *H. pylori*–positive gastric MALT lymphoma. MZL is extremely radiosensitive. CR rates approach 100%, with doses approximately 24 to 30 Gy.[174] Local failure is rare.[167] The overall prognosis of patients with localized MZL treated with RT is generally excellent, with more than 90% 5-year survival and more than 80% 10-year survival, although relapses occur in approximately 25% of patients.[167,173,174] Relapses seldom develop within nodal areas but rather at sites prone to MZL development. Many

such relapses are localized, often in the contralateral paired organ, and after appropriate treatment, often further RT alone, long-term survival is excellent.

For patients with gastric MALT lymphoma, antibiotic treatment is indicated in the presence of *H. pylori* infection. Eradication of *H. pylori* is near universal after antibiotics. A frequently recommended combination is omeprazole, metronidazole, and clarithromycin.[181] A CR is achieved in approximately 80% of patients, though this may take up to 2 years or longer to achieve.[18] As long as the lymphoma is regressing on serial endoscopy, a watch-and-wait policy is appropriate. The t(11;18) translocation, however, is predictive for failure to respond to antibiotics.

Of patients achieving a CR to antibiotics, less than 10% will relapse clinically. Some patients will be found to have microscopic foci of disease on random biopsies performed during upper endoscopy. Continued observation and monitoring is preferred for these patients as many will subsequently revert to a histologic CR.[18,182]

For patients who are *H. pylori* negative and who do not respond to or relapse clinically after antibiotics, the treatment of choice is RT. Long-term PFS and OS exceeds 90%.[174] Interestingly, the original B-cell clone is also detected frequently after RT for gastric MALT lymphoma but without an associated risk of relapse.[183]

Because of the efficacy of RT in controlling MZL locally with minimal side effects, there is little indication for surgical resection, with a few possible exceptions such as involvement of spleen (rituximab-refractory splenic MZL), small intestine, or lung. In particular surgical resection for gastric MALT, although often practiced historically, is to be avoided.

Radiation Dose and Field Design

Detailed radiation field and dose guidelines for extranodal lymphomas, including MALT, have recently been published.[100] For MALT lymphoma, particularly gastric MALT, local control rates of 95% to 100% are achieved with doses of approximately 24 to 30 Gy.[174,184] Similar results, although in smaller numbers, are available for MZL at sites other than the stomach.[172,185] A small number of patients with MALT were included in the randomized British National Lymphoma Investigation demonstrating similar clinical

outcomes with 24 Gy compared to 40-45 Gy.[98] With modern treatment techniques and doses of 24 to 30 Gy, long-term RT complications are very infrequent, with the exception of the eyes where post RT cataracts are common and some degree of dryness may result. Very modest doses of RT (2 Gy × 2) have been demonstrated to be effective palliation for FL and MZL, leading some centers to recommend a 4-Gy dose for curative treatment of orbital MZL.[186,187] Preliminary results are quite encouraging, but follow-up is short. A randomized British trial, however, comparing 24 versus 4 Gy for the treatment of indolent NHL demonstrated superior local control with the higher dose (~90% freedom from local progression at 5 years vs 70%).

Thus, in general, a dose of 24 Gy is recommended for localized MZL. A trial of 4 Gy may be appropriate for select patients with orbital disease (and possibly parotid presentations), given the risk of long-term side effects with 24 Gy. However, this response-adapted approach requires careful monitoring with ophthalmology, including surveillance imaging if appropriate for nonconjunctival presentations, with a plan for salvage therapy (typically a definitive course of RT) should the disease persist or progress after 4 Gy. This approach is not recommended for most other sites, given the limited risk of long-term toxicity.

For disease involving the palpebral and/or bulbar conjunctiva alone, a single en-face electron field is preferred. Given the multifocal nature of extranodal MZL, we prefer treatment of the entire conjunctiva, which is set up clinically with 1 cm of overlying bolus and treated using a 6-MeV beam prescribed to 90%. While some institutions utilize a hanging lens shield, at our institution, we have not pursued this, given the concern for shielding potential disease and the ease in which cataracts can be addressed. For disease confined to the lacrimal gland, a conformal IMRT plan is very reasonable. For patients with disease involving the posterior orbit, where the disease is often not well circumscribed, a wedged-pair photon beam arrangement treating the entire bony orbit is preferred.

For stage IE gastric MALT lymphoma, the entire stomach should be included in the CTV. Both 3D and IMRT can be utilized to minimize dose to the heart, liver, and kidneys. Clinicians must be mindful of several characteristics of the stomach that can make IMRT problematic. First, the shape and position of the stomach in the upper abdomen often changes from

day to day. The patient should fast for 3 to 4 hours before simulation and treatment. Daily cone-beam CTs with soft tissue matching can be helpful in some situations, but in others, the CTV from the planning CT scan simply cannot be matched to the stomach as visualized on the cone-beam CT due to these variations. Second, the stomach typically moves significantly during the respiratory cycle, necessitating some form of active respiratory management, ideally deep-inspiratory breath-hold, especially if IMRT is utilized.

One helpful 3D approach is to use a single isocenter, half-beam block technique with the isocenter position at the top of the kidneys. AP/PA (or slightly oblique) fields are utilized superiorly to treat the upper stomach (while avoiding almost all of the liver), with more oblique fields (sometimes very close to laterals) utilized inferiorly to avoid the posteriorly positioned kidneys. When treating the entire stomach, 1.5-Gy daily fractions with prophylactic antiemetics are helpful to minimize nausea.

For conjunctival MALT, a single en-face electron field provides appropriate coverage of the conjunctiva while minimizing the dose to the lacrimal gland and posterior globe. It is usually appropriate to treat the entire conjunctiva. A lens shield is occasionally used to prevent cataracts but may increase marginal misses. We generally do not use one. Well-circumscribed orbital lesions elsewhere can be managed with either a 3D or IMRT approach. Target volumes are somewhat controversial. Some authors suggest the entire orbit be treated to avoid marginal misses.[188,189] Depending on the size and location, partial orbit coverage may also be reasonable. With doses of 24 Gy, cataract formation is the principle risk, occurring in 20% to 30% of patients,[189] which, however, can be easily corrected surgically. Some dryness may result from inclusion in the field of a portion of the lacrimal gland and meibomian glands. These side effects are avoided with the lower dose of 4 Gy.

As mentioned, orbital MZL may involve both eyes at presentation. Under these circumstances, RT alone remains the treatment of choice, with careful attention to treatment planning and prescribed dose to minimize eye complications. For MALT lymphomas of the thyroid and parotid, treatment of the entire gland is generally advisable, given the multifocality of the disease.

In the unusual circumstance of disseminated MALT lymphoma, treatment generally follows the guidelines for advanced FL. Chemotherapy is palliative and reserved for patients with generalized disease who are symptomatic. MALT lymphomas also respond well to rituximab.[190] Asymptomatic individuals with generalized disease should be considered for observation, similar to patients with generalized FL, since the course is so often indolent. Patients with generalized disease with symptoms due to a localized tumor mass may be easily palliated with modest doses of RT (eg, 2 Gy × 2) to the mass in question. That approach is often superior to systemic chemotherapy. There is no established role for chemotherapy or rituximab in localized disease.

Splenic Marginal Zone Lymphoma

Splenic MZL is a rare subset of MZL constituting less than 10% of all MZL and less than 1% of all NHL. The diagnosis is often difficult since definitive tissue diagnosis requires splenectomy. It is often made by examination of bone marrow histology and correlation with clinical findings. Patients usually present with splenomegaly.[191-193] Almost all have stage IV disease, principally because of bone marrow or blood involvement. The disease is relatively indolent with three-quarters of patients alive at 5 years, but a more aggressive subset does exist. Observation is typically pursued for asymptomatic patients. When symptomatic, splenectomy and rituximab with or without chemotherapy are all options. There is virtually no literature regarding splenic irradiation, but it is a consideration in patients with symptomatic splenomegaly in whom splenectomy is contraindicated and/or does not respond to chemoimmunotherapy. Modest doses should be utilized (4-20 Gy) depending on clinical response. As with other varieties of MZL, an association with an infectious agent (HCV, in this case) has been reported, and clinical responses to antiviral treatment in seropositive patients have been observed.

Nodal Marginal Zone Lymphoma

This entity is rare as well, comprising about 10% of all MZL and less than 2% of all NHL. Patients generally present with disseminated lymphadenopathy. Bone marrow involvement is common, observed in

about one-third of patients. B symptoms are uncommon. The clinical course and outcome are similar to that of other indolent nodal lymphomas, in particular FL. In the uncommon event of localized nodal MZL, RT has curative potential, although clinical data are sparse. For localized disease, we recommend ISRT with doses of 24 to 30 Gy. As with FL, the FLIPI may distinguish patients with different outcomes. Also similar to FL, chemoimmunotherapy has not proven curative. Accordingly, some asymptomatic patients with disseminated disease may be observed without treatment. If HCV is demonstrated, however, antiviral therapy is appropriate and will result in tumor regression in most patients. Overall, 5-year survival ranges from 70% to 90%, higher for cause-specific survival. If systemic therapy is advisable, the choice of agents generally follows the recommendations for FL. Indeed, data for the response of MZL to chemotherapy almost always derive from the inclusion of such patients in a larger series of patients with FL. Patients with disseminated disease with a problematic local lesion may be very effectively palliated with ultra-low-dose RT (4 Gy).

MANTLE CELL LYMPHOMA

MCL was first distinguished in the 1980s by Weisenburger et al,[194] who described a type of FL in which there were wide mantles of malignant cells around apparently benign germinal centers. It was thought to represent a variant of FL and was classified under the Working Formulation as a low-grade lymphoma. Its behavior, however, is more characteristic of aggressive disease.

Pathology

MCL is a neoplasm of small- to medium-sized B cells with irregular nuclei that resemble the cleaved cells (centrocytes) of germinal centers. The morphologic pattern may be diffuse, nodular, a mantle zone, or some combination thereof.[195] Tumor cells are typically CD5 positive, CD23 negative, CD20 positive, and CD10 negative. A characteristic cytogenetic abnormality is t(11;14) involving the *BCL-1* gene and resulting in the overexpression of cyclin D1. The product of the cyclin D1 gene can be detected in paraffin-embedded tissue sections with the immunoperoxidase

technique and is useful in distinguishing MCL from other lymphoma variants.[196,197]

Immunophenotyping studies are useful in confirming malignancy (light-chain restriction) and in excluding other B-cell histologies, such as CLL ($CD5_+$, $CD23_+$, and $CD200_+$) and FLs ($CD10_+$).[166]

Clinical Presentation

MCL accounts for approximately 3% to 7% of patients with NHL, with approximately 70% of all cases in men.[198,199] The median age at diagnosis is 68 years. Stages I and II MCL are rare. Most cases of MCL present with an aggressive natural history. More than 75% of patients have stage III or IV disease at onset. IPI scores are high, with 23% of patients with a score of 4 or 5, 54% 2 or 3, and only 23% 0 or 1. In common with FL, the organ most likely to be involved is the bone marrow, which is positive in two-thirds of patients at the time of diagnosis. Gastrointestinal tract involvement is frequent as well.[200] CNS involvement is occasionally encountered, particularly in those with blastoid histology or elevated LDH.[201]

Prognostic Factors

Although originally classified among the low-grade/indolent lymphomas, the clinical course for MCL is unfavorable in the great majority of patients. The 5-year survival rate in the ILSG project was only 27%, with a PFS rate of 11%.[122] This PFS rate is, in fact, among the worst for virtually any type of lymphoma. The survival pattern of MCL resembles advanced FL in its response to therapy and PFS (ie, no plateauing of the PFS curve and thus no indication of cure), but DLBCL in its OS (ie, much shorter than FL).[202-205] A proportion of patients with MCL have a more indolent course, but identifying these patients prospectively can be challenging. They are usually asymptomatic with small-volume nodal disease.

TP53-mutated MCL is associated with inferior outcomes, and more aggressive regimens, in appropriate patients, are recommended. In addition to TP53, a simple prognostic scoring has continued utility: the MIPI or MCL IPI.[206] This index uses four parameters: age, performance status, LDH, and leukocyte count. The MIPI score allows discrimination into three

prognostic subgroups: low risk (MIPI ≤5.7), intermediate risk (MIPI >5.7 and ≤6.2), and high risk (MIPI >6.2). The MIPI score was created using the data from 455 patients with advanced-stage MCL treated within three clinical trials. The median survival was not reached in the low-risk group (5-year OS of 60%). The intermediate- and high-risk groups had a median OS of 51 and 29 months, respectively. The 5-year OS was approximately 40% and approximately 15% months in the intermediate- and high-risk groups, respectively. The MIPI has been prospectively validated, and multiple reports have shown consistent reliability of the MIPI prognostic scoring that has had independent significance over pathologic, molecular-based, and clinical/therapeutic predictors.[207,208] The Ki-67 index has also been combined with the MIPI to estimate prognosis in trials as a biologic MIPI.[209]

Clinical Management

Chemoimmunotherapy is the standard initial treatment for all stages of MCL. Rituximab is generally combined with chemotherapy regimens as it is CD20+. There is no standard treatment regimen for MCL. The choice of chemotherapy regimen is often guided by age and performance status. There are several options for both “aggressive” and “less aggressive” regimens. High-dose chemotherapy and ASCT are often pursued in patients who achieve a CR to initial therapy. Maintenance rituximab with or without ibrutinib is generally recommended.[210] Patients with MCL seldom achieve a cure.

Patients presenting with localized MCL (stage I or II) are rare. A small series from British Columbia suggested that RT was an integral treatment component in localized disease.[211] Of 26 patients reviewed, 17 received RT with or without chemotherapy and 9 patients received chemotherapy or were observed. RT was associated with improved PFS (68% vs 11%, P = .002). This finding was corroborated by the large National Cancer Database and SEER database analyses.[212,213] Thus, for early-stage disease, we recommend a combined modality approach.

RT should be considered in salvage settings of a localized relapse since MCL is radiosensitive and palliation can resolve symptoms even in patients who have received multiple lines of systemic therapy. RT is also very

effective for palliation for patients with advanced disease.[214] Modest doses (4-10 Gy) are typically sufficient in the palliative setting.

Radiation Dose and Field Design

For patients presenting with localized (stages I-II) disease, we recommend consolidation RT after chemoimmunotherapy. In the setting of a CR by PET-CT, a dose of 30 Gy is appropriate. Treatment of the original site of disease with a margin, following involved-site principles, is recommended.

PERIPHERAL T-CELL LYMPHOMAS

The PTCLs are the group most confusing to clinicians. The term *peripheral T-cell lymphoma* is often misinterpreted. It refers not to the anatomic distribution of the lymphomas but to their origin, from the so-called peripheral or mature T cells outside the thymus, as opposed to thymic (precursor) T lymphocytes. The T-cell and NK lymphomas collectively make up approximately 10% of all NHL.[215] Their frequency is quite different, however, by geographic locale, with a roughly 5% to 10% incidence of PTCL in North America compared with 15% to 20% in Asia.[216] They are a diverse group that includes nearly 30 distinct entities (Table 85.1).[1,2]

Pathology

PTCL NOS typically contains a mixture of small, medium, and/or large cells with many mitotic figures. The architectural pattern is diffuse. T-cell–associated antigens (CD2, CD3, CD4) are variably expressed, and oftentimes the T-cell antigens CD5 and CD7 are lost. A CD4+/CD8− phenotype is typical in nodal cases. B-cell–associated antigens are lacking. The T-cell receptor (*TCR*) genes are usually, but not always, rearranged. TCR β-chain is typically expressed distinguishing PTCL from NK cell lymphomas and γ-Δ T-cell lymphomas.

A special variant of PTCL is anaplastic large cell lymphoma (ALCL).[217,218] In the ILSG project, this comprised 2% of all NHL.[219] The tumor is usually composed of large cells with round, pleomorphic, or horseshoe-shaped nuclei with single or multiple prominent nucleoli and

abundant cytoplasm, giving the cells an epithelial or histiocyte-like appearance. The cells express CD30 (Ki-1) and usually express CD25 and either T-cell or null lineage–specific antigens.[218] CD30 was originally recognized on HL cells. In some cases, there may be confusion between ALCL and HL, but distinction between the two on the basis of immunophenotyping and morphology is usually possible.

The WHO recognizes two distinct entities anaplastic lymphoma kinase (ALK)-positive ALCL and ALK-negative ALCL, with the former characterized by overexpression of ALK-1 protein, typically from a chromosomal translocation [t(2:5)].[220] Approximately 60% of cases overexpress the ALK protein; such cases have a better prognosis than ALK-negative cases (except primary cutaneous ALCL, which is invariably ALK negative but has an excellent prognosis).

Extranodal NK/T-cell lymphomas are characterized by a diffuse lymphomatous infiltrate with an angiocentric pattern. The cells are variable in morphology and can be of any size. Necrosis is common and attributed to vascular obstruction by lymphoma cells, though chemokines and cytokines may also be contributory. CD56, though not specific for NK cells, is generally expressed with extranodal NK/T-cell lymphoma. Cytotoxic molecules including granzyme B and perforin are also positive. EBV analyses, preferably in situ hybridization, are mandatory and should be positive. No specific translocations have been observed for this disease.

Clinical Presentation

The most common T-cell lymphoma in North America is PTCL NOS, accounting for about one-third of cases (vs ~20% in Asia).[221] The median age at diagnosis is 62 years. Both nodal and extranodal diseases are common in a similar manner to B-cell lymphoma. In contrast to DLBCL, however, the great majority of patients (~70%) have stage III or IV disease at diagnosis, and overall, the outlook is considerably worse. The International T-Cell Lymphoma Project reported 10-year survival in the range of 20%.[221]

ALCL consists of both a systemic malignancy, typically presenting with widespread involvement of lymph nodes and extranodal sites, and a type limited to the skin (primary cutaneous ALCL).[218,222-226] The systemic type

may in turn be separated into those patients who are ALK positive and those who do not overexpress this protein. The clinical features and prognosis differ widely among these two categories. Patients with ALK-positive ALCL are predominantly young men and, despite advanced-stage disease, respond well to combination chemotherapy with 10-year survival rates of approximately 70%.[220] ALCL in children/young adults is usually ALK positive.[211] Patients who are ALK negative, in contrast, tend to be older, with a more nearly equal male/female ratio and a long-term OS of approximately 20%.

Cutaneous ALCL constitutes a special situation.[222] It is almost invariably ALK negative but carries an excellent prognosis. It is often difficult to distinguish from benign lymphomatoid papulosis. The latter may spontaneously remit and tends to run a benign clinical course over many years. ALCL of the skin is quite responsive and highly curable with localized RT[227] (see Chapters 86). Chemotherapy generally has no role.

Extranodal NK/T-cell lymphoma is a T-cell lymphoma of special interest. It is much more frequent in Asia (about 22% of T-cell lymphomas) than in the United States and associated with EBV.[228] There is a male-to-female ratio of 2:1. In contrast to most lymphomas, tissue destruction of the nasal, paranasal sinuses, and/or facial area is common. Patients can also present with epistaxis and nasal obstruction. Lymph nodes may also be involved. Extranodal sites outside the head and neck region may be manifest, with or without nasal involvement. The International Peripheral T-Cell Lymphoma Project reported superior OS in nasal type (5-year OS 42% with an apparent plateau) compared to extranasal cases (5-year OS 9%).[221] The response to chemotherapy and RT is variable and slow, in contrast to the usual rapid response observed in most other lymphomas. The disease appears to progress primarily locally with only a small predilection for regional or systemic failure.[229]

A unique entity in the WHO classification is breast implant– associated ALCL. It is thought to develop in the setting of chronic inflammation induced by textured surface implants and often presents as an accumulation of fluid between the implant and the fibrous capsule. Given the rarity and recent identification of this presentation, the optimal management remains largely unknown, though capsulectomy removal of the breast implant and removal of any disease mass appear to be essential.[230] Surgery alone may be

sufficient for those with disease confined within the fibrous capsule.[231] Adjuvant RT to the breast may be appropriate after incomplete resection.

Prognostic Factors

Two prognostic scores are commonly utilized for PTCL NOS—the IPI and the prognostic index for PTCL-unspecified (PIT). The IPI, primarily utilized for DLBCL, has also been shown to be prognostic in PTCL. The PIT identified four factors on multivariate analysis including three that are also contained in the IPI: age 60 years or above, elevated LDH, and ECOG performance 2 or higher. The novel factor was bone marrow involvement.[232] Using this prognostic model, patients with no adverse factors had a 5-year OS rate of approximately 63%. Patients with 1, 2, or 3 to 4 of the adverse prognostic factors had 5-year OS rates of approximately 53%, 33%, and 18%, respectively. Patients with stages I to II disease, although quite uncommon, also appear to have a more favorable prognosis.[233]

In ALCL, the prognosis can vary considerably. Several studies have shown that survival is significantly better with ALK-positive ALCL compared with ALK-negative ALCL.[220,234-236] The International Peripheral T-cell Lymphoma Project demonstrated that ALK-positive ALCL has the most favorable prognosis among all T and NK histologies, followed by ALK-negative ALCL.[221] The heterogeneity and complexity of ALCL well illustrate past difficulties of attempting to group lymphomas in categories of low grade, intermediate, and high grade; indolent or aggressive; and favorable or unfavorable, on the basis of histologic appearance alone, since all ALCL appears aggressive histologically. There remains some uncertainty on whether ALK expression is independently prognostic or simply correlates with other favorable factors (eg, young age). IPI score has also been found to be a predictor of outcome in patients with ALCL. Other factors that have been found prognostic for OS and predictive of inferior outcomes include an elevated B2M and older age (≥40 years).[234]

For extranodal NK/T-cell lymphomas, age 60 years or above, stages III to IV disease, distant lymph node involvement, and non–nasal-type disease have been identified as unfavorable prognostic factors. There are several prognostic models that have been used. The Prognostic Index of Natural Killer Lymphoma (PINK) stratifies patients into low-, intermediate-, and

high-risk cohorts with 0, 1, or 2 or higher risk factors.[237] In an analysis of 527 patients, the low-, intermediate-, and high-risk groups had a 3-year OS of 81%, 62%, and 25%, respectively. Detectable EBV DNA in the circulating blood at diagnosis also appeared to be a negative prognostic factor for OS in the subset of patients who had EBV DNA data. The EBV DNA data are incorporated into the PINK-E prognostic scoring system.

Clinical Management

For PTCL NOS and ALCL, CHOP is probably the most commonly employed regimen in the United States. For younger patients, the addition of etoposide (CHOEP) can be considered.[238] Since this is a T-cell lymphoma, there is no role for rituximab. For the minority of patients who present with stages I to II PTCL[239,240] or ALCL,[241] consolidation RT after chemotherapy is recommended. Three-year PFS and OS were 50% and 33% in early-stage PTCL NOS with combined modality therapy versus 23% and 15% with chemotherapy alone, in one small series.[240]

The optimal treatment of localized NK/T-cell lymphoma, nasal type is not established. Treatment approaches have consisted of RT alone, chemotherapy alone, and the two combined.

The contribution of chemotherapy to the management of NK/T-cell lymphoma is unclear. When treated initially with CHOP-like regimens, CR occurs in only a minority of patients,[242-245] in contrast to the results seen with most other lymphomas. Japanese and Korean investigators have reported the use of concurrent chemotherapy and radiation with encouraging results.[246,247] The Japanese Clinical Oncology Group study (JCOB0211) used concurrent chemoradiation therapy that consisted of dexamethasone, etoposide, carboplatin, and ifosfamide with a dose of 50 Gy of RT. The CR rate was 77% and the 2-year survival was 78% compared with historical controls of 45%.[241] In an updated analysis, the 5-year PFS and OS were 67% and 73%, respectively.[248] The Korean series employed concurrent cisplatin and RT (40-50 Gy), followed by three cycles of cisplatin, dexamethasone, ifosfamide, and etoposide. The CR rate was 83%, and the 3-year survival was 86%.[247] In both series, the number of patients was small (33 and 30 patients, respectively), but the results were quite promising and worthy of further study.

Combined modality therapy options include not only concurrent chemoradiation but also sequential and sandwich approaches. There are a variety of sequential chemoradiation regimens using pegaspargase, which can be considered (eg, dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide, and gemcitabine, dexamethasone, cisplatin). There are no data, particularly from the United States, to recommend one regimen over another at this point.

In a cohort of 240 patients with early-stage extranodal NK/T-cell lymphoma from the China Lymphoma Collaborative Group, the addition of RT to chemotherapy significantly improved OS, disease-free survival (DFS), and local-regional control (LRC), even after achieving a CR after asparaginase-containing chemotherapy.[249] The 5-year OS, DFS, and LRC rates were 85%, 76%, and 85% for RT and chemotherapy, compared to 59%, 44% and 62%, respectively, for chemotherapy alone. In patients with stages I to II disease in the United States, the omission of RT or the use of a suboptimal RT dose has been found to be associated with a worse OS.[250]

In stage III or IV extranodal NK/T-cell lymphoma, nasal type, chemotherapy with or without RT is the primary treatment. Non–anthracycline-based regimens have also been shown in retrospective analyses to have a survival benefit compared to anthracycline-based regimens.[251] In a retrospective study, consolidative RT was found to improve survival among patients with stage III or IV disease who exhibit complete or partial remission after initial chemotherapy.[252] Relapsed and refractory disease management is informed by prior therapy and can include salvage chemotherapy regimens, immunotherapy, reirradiation, and hematopoietic SCT.

Radiation Therapy Dose and Field Design

Doses and field sizes of RT for PTCL NOS and ALCL should approximate those for DLBCL. For extranodal NK/T-cell lymphomas, nasal type, higher doses of RT are generally employed. It has been found that radiation dose and target volume are associated with LRC and OS. For patients with early-stage disease receiving RT, higher doses of RT (≥50 Gy) were associated with significantly better 5-year LRC (85% vs 73%), PFS (61% vs 50%), and OS (70% vs 58%) than lower doses of RT (<50 Gy).[253] With RT alone

as primary treatment, the recommended tumor dose is 50 to 56 Gy. When RT is given with concurrent or sequential chemotherapy, doses of 45 to 56 Gy can be considered due to radiosensitization and/or cytoreduction. In palliative settings, doses of 20 to 36 Gy seem reasonable.

Physical examination and endoscopic examination should be considered in defining radiation target volumes of lesions in aerodigestive tract sites and particularly in lesions that cannot be identified well on imaging. Basic involved-site principles apply for extranodal NK/T-cell lymphomas. However, the CTV may be larger than other more chemosensitive lymphomas due to both the uncertain effect of chemotherapy and the submucosal infiltration of the tumor that is beyond the apparent initial macroscopic disease. The CTV is also dependent on the location of primary tumor, involved lymph nodes, and the pattern of microscopic spread. The value of prophylactic cervical lymph node RT is controversial. IMRT is often, but not always, required, given the proximity of the tumor to critical structures such as the optic apparatus, parotid glands, and brain and brainstem (Figure 85.5). The relevant critical structures are determined mainly by the location of the primary disease.

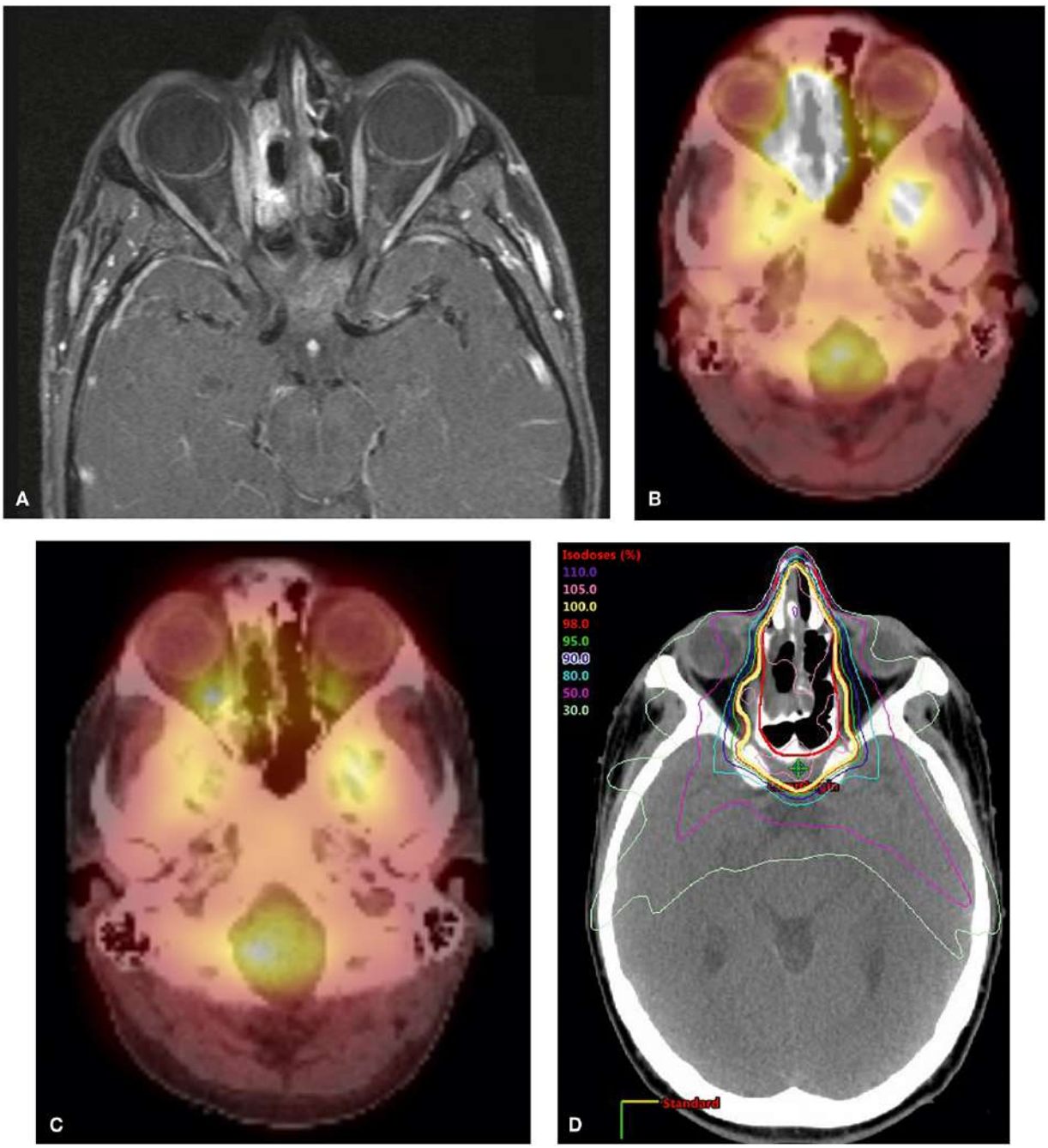

FIGURE 85.5 IE natural killer/T-cell lymphoma of the left nasal cavity and ethmoid sinuses on magnetic resonance imaging (A) and positron emission tomography-computed tomography (PET-CT) (B). The patient achieved a complete response (C) by PET-CT (Deauville 2) after dexamethasone, methotrexate, ifosfamide, pegaspargase, etoposide chemotherapy. He then received consolidation radiation therapy (D) to 50 Gy. The clinical target volume (red contour) included bilateral nasal cavities and ethmoid sinuses.

In general, adhering to published protocols, in relation to both dose and field, is prudent, given the rarity of this disease. More detailed

recommendations have been published by the ILROG.[100]

LYMPHOID PROLIFERATIONS AND LYMPHOMAS ASSOCIATED WITH IMMUNE DEFICIENCY AND DYSREGULATION

The number and success of solid organ transplants have increased substantially over the past several decades. Unfortunately, with long-term immunosuppression, post-transplant lymphoproliferative disorders (PTLDs) are being increasingly diagnosed. The WHO currently describes four distinct entities under the category "Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation" depending upon the pathologic findings and underlying disease. For simplicity, we refer to them collectively as PTLD.

EBV is implicated in the majority of cases (50%-80%), especially if PTLD occurs within 2 years of transplantation. During the diagnostic workup, infection with lymphoplasmacytic infiltrations, graft rejection, graft-versus-host disease, and/or recurrence from a previous lymphoma should be ruled out.

The prognosis of PTLD is poor compared to immunocompetent counterparts with similar histologies. Five-year OS ranges from 40% to 60%. The IPI can be used in patients with PTLD to predict outcomes. Other various prognostic indices have been developed as well but ultimately are fraught with validation inconsistencies. Still, older age, advanced disease, poor Karnofsky Performance Status, elevated LDH, and CNS involvement are consistently associated with inferior outcomes.[254]

Management can be variable depending on clinical presentation and pathology. In solid organ PTLD, reduction of immunosuppression should be considered, which can lead to responses in about 10% of people within a matter of weeks. Caution should be taken to prevent graft rejection or graft-versus-host disease. If no response is achieved with immunosuppression reduction, rituximab can be considered for $CD20_+$ PTLDs. Overall response rates are approximately 40%, and CR rates can be almost 30%, with little risk of treatment-related mortality.[255] Chemotherapy can also provide good responses but is associated with increased toxicity. A phase II study demonstrated that the combination of rituximab and CHOP is an effective,

with up to a 90% response rate and a 68% CR rate.[256] Mortality from chemotherapy remains a significant risk in PTLD.[256,257]

Radiation is reserved for localized disease (consolidation after chemotherapy or as a definitive modality) or in palliative situations. Involved-site radiation principles with appropriate doses depending on the underlying histology are recommended.

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CHAPTER 86

Primary Cutaneous Lymphomas

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Primary cutaneous lymphoma is defined as an accumulation of malignant lymphoid cells in the skin without evidence of extracutaneous disease at the time of diagnosis. The distinction between a primary cutaneous lymphoma and a nodal lymphoma with secondary cutaneous involvement is important and markedly impacts evaluation, staging, prognosis, and therapeutic management. The term *primary cutaneous lymphoma* encompasses a heterogeneous group of extranodal non-Hodgkin lymphomas, and in 2005, the World Health Organization (WHO) and European Organisation for Research and Treatment of Cancer (EORTC) endorsed a consensus classification system that defines three categories of primary cutaneous lymphomas: cutaneous T-cell (CTCL) and natural killer (NK) cell lymphomas, cutaneous B-cell lymphomas, and precursor hematologic neoplasms/immature hematologic malignancies (Table 86.1).[1] This chapter reviews the primary cutaneous lymphomas in the context of this consensus system. A slightly modified classification system was updated by the WHO in 2022.[2]

TABLE 86.1 WHO-EORTC CLASSIFICATION

Cutaneous T-cell and NK/T-cell lymphomas
Mycosis fungoides and variants (folliculotropic mycosis fungoides, pagetoid reticulosis, and granulomatous slack skin)
Sézary syndrome
$CD30^+$ lymphoproliferative disorders (primary cutaneous anaplastic large cell lymphoma and lymphomatoid papulosis)
Extranodal NK/T-cell lymphoma, nasal type
Subcutaneous panniculitis-like T-cell lymphoma
Primary cutaneous peripheral T-cell lymphoma, unspecified
Primary cutaneous aggressive epidermotropic $CD8^+$ T-cell lymphoma (provisional)

Primary cutaneous γ/Δ T-cell lymphoma
Primary cutaneous $CD4^+$ small-/medium-sized pleomorphic T-lymphoproliferative disorder (provisional)
Cutaneous B-cell lymphomas
Primary cutaneous marginal zone lymphoma
Primary cutaneous follicle center lymphoma
Primary cutaneous diffuse large B-cell lymphoma, leg type
Primary cutaneous diffuse large B-cell lymphoma, other
Precursor hematologic neoplasm
$CD4^+/CD56^+$ hematodermic neoplasm (blastic NK cell lymphoma)

EORTC, European Organisation for Research and Treatment of Cancer; WHO, World Health Organization.

Adapted from Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood*. 2005;105(10):3768-3785. Copyright © 2005 American Society of Hematology. With permission.

CUTANEOUS T-CELL AND NK CELL LYMPHOMAS

CTCL is the most common primary cutaneous lymphoma. In the United States, 71% of the 3,884 cases of primary cutaneous lymphoma diagnosed during 2001 to 2005 were CTCLs.[3] Similarly, 78% of primary cutaneous lymphoma diagnoses recorded in the Dutch and Austrian Cutaneous Lymphoma Group registry over 1986 to 2002[1] and 85% of diagnoses in the Central Cutaneous Lymphoma Registry of the German Society of Dermatology over 1999 to 2004 were CTCLs.[4]

CTCL subtypes include mycosis fungoides (MF); $CD30^+$ lymphoproliferative disorders; extranodal NK/T-cell lymphoma, nasal type; subcutaneous panniculitis-like T-cell lymphoma; adult T-cell leukemia/lymphoma; and primary cutaneous peripheral T-cell lymphomas. MF is the most common CTCL, responsible for 54% of CTCL diagnoses in the United States over 2001 to 2005.[3] $CD30^+$ T-cell lymphoproliferative disorders and cutaneous peripheral T-cell lymphomas represent the majority of the remaining cases of CTCL. The remaining CTCL subtypes are extremely rare and represent <1% of primary cutaneous lymphomas.

Mycosis Fungoides

MF is the archetype cutaneous lymphoma. The first case of MF was reported in 1806 by the French dermatologist Jean-Louis-Marc Alibert in his atlas of dermatoses, *Descriptions des maladies de la peau* (Figure 86.1). After Alibert released his depiction of MF, approximately 300 similar cases were reported over the next decade, and in modern times, approximately 1,500 new cases of MF were diagnosed during 2001 to 2005.[3] MF is a disease of skin-homing $CD4^+$ T-helper cells[5] and is more commonly diagnosed in men (male/female ratio of 1.6-2.0:1), with a median age at diagnosis of 55 to 60.[1] Significant advances in MF therapy have been made over the past 200 years, but the precise etiology responsible for the development of MF remains elusive.

FIGURE 86.1 Pian fungoide, from Jean-Louis-Marc Alibert's atlas of dermatoses, *Descriptions des Maladies de la Peau*.

Cutaneous Disease

Pruritus, either diffuse or localized to areas of involved skin, is the most common symptom associated with MF. Ulcerated lesions may also cause patients significant pain. Cutaneous lesions in classic (or Alibert-Bazin) MF follow a predictable evolutionary course, and a consensus statement from the International Society for Cutaneous Lymphomas (ISCL), U.S. Cutaneous Lymphoma Consortium (USCLC), and EORTC defines the lesions found in distinct phases of MF.[6] In the *premycotic phase*, a small number of red, scaled, macular or patch-like lesions develop in sun-shielded

areas of the skin, such as the trunk, pelvis, and extremities. These early lesions are unstable and usually regress, followed by the development of new lesions. Biopsies of premycotic lesions are rarely diagnostic due to a paucity of malignant lymphocytes in the lesion. With an increased deposition of malignant T cells in the skin, the lesions become increasingly durable, and persistent cutaneous patches are characteristic of the *patch phase*. The ISCL/USCLC/EORTC consensus definition of an MF patch is "any size lesion without induration or significant elevation above the surrounding uninvolved skin: poikiloderma may be present."[6] As the lesions become more densely infiltrated by both malignant and reactive lymphocytes, they evolve into plaques with thickened and raised borders in the *plaque phase* of classic MF. Plaques are defined by the ISCL/USCLC/EORTC as "any size lesion that is elevated or indurated: crusting or poikiloderma may be present."[6] Plaques may evolve into cutaneous tumors, which the ISCL/USCLC/EORTC defines as "any solid or nodular lesion ≥1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth." The presence of cutaneous tumors designates the tumor phase of MF. MF may also progress to or present with erythroderma, in which a diffuse erythema involves >80% of the skin surface area.[6] Representative images of patches, plaques, tumors, and erythroderma are shown in Figure 86.2.

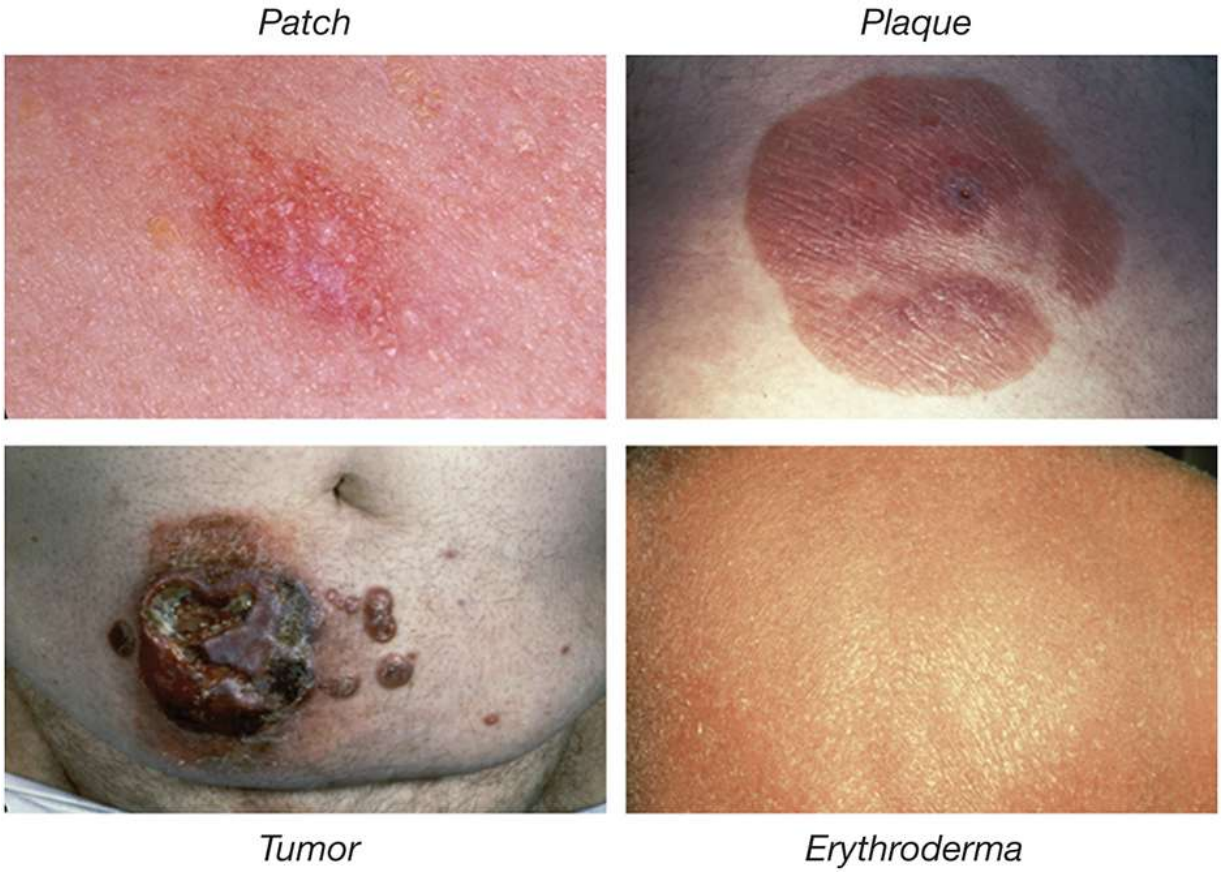

FIGURE 86.2 Representative images of cutaneous lesions in mycosis fungoides. (Used with permission of MJH Life Sciences, LLC from Smith BD, Wilson LD. Management of mycosis fungoides Part 1. Diagnosis, staging, and prognosis. *Oncology (Williston Park)*. 2003;17[9]:1281-1288; permission conveyed through Copyright Clearance Center.)

Leukemic Cutaneous T-Cell Lymphoma and the Sézary Syndrome

In rare CTCL cases, circulating malignant T cells are identified in the peripheral blood. This phenomenon, sometimes referred to as leukemic CTCL or the Sézary syndrome (SS), most commonly occurs in association with erythroderma but may occur in patients with minimal cutaneous disease.[1] The circulating malignant T cells (also called Sézary cells) are atypical T cells with hyperconvoluted nuclei seen at the analysis of peripheral buffy coat smear. The circulating atypical T cells most commonly possess a $CD4^+/CD7^-$ or $CD4^+/CD26^-$ immunophenotype, and flow cytometry allows for quantification of the proportion of circulating malignant T cells. In addition, the presence of a dominant circulating malignant clone may be demonstrated by evaluation of the T-cell receptor

(TCR) by polymerase chain reaction (PCR) or next-generation sequencing (NGS). The degree of tumor burden in the peripheral blood is denoted as B0 (atypical T cells <250 Sézary cells/mm^3 by flow cytometry), B1 (atypical T cells >250 Sézary cells/mm^3 but not meeting B2 criteria), or B2 (combination of the presence of a dominant T-cell clone in the peripheral blood identified by routine PCR or TCR NGS and ≥1,000 Sézary cells/mm^3).[7] If peripheral blood is evaluated for a circulating clone by PCR or Southern blot, B0 or B1 disease may be stratified into B0a or B1a (absence of circulating clone) or B0b or B1b (presence of circulating clone). The mechanism responsible for the development of leukemic disease in MF is unknown and, in some cases, may simply reflect disease progression. In other cases, erythroderma and circulating cell disease develop simultaneously, which has historically been referred to as SS. The distinction between SS and erythrodermic MF with leukemic involvement (or SS syndrome preceded by MF) has been a point of controversy, and it remains unclear whether the two diseases are distinct or merely variants of one another. At present, SS is specifically defined as the combination of erythroderma with B2 disease.[6]

Extracutaneous Disease

In advanced stages of disease, MF may progress to involve regional or distant lymph nodes or extracutaneous organ systems (most commonly the lungs, oral cavity, pharynx, or central nervous system), and these sites may cause patients significant pain or functional impairment.[8] Of note, in advanced cases of MF, the extent of cutaneous or extracutaneous disease may vary significantly in patients of the same clinical stage. Clinical trials that report results by stage alone may, therefore, be difficult to interpret. The ISCL/USCLC/EORTC consensus statement on clinical end points and response criteria should facilitate improved communication of the degree of disease and response to treatment in future clinical trials.[7]

Molecular and Cellular Pathophysiology

Examination of early-phase MF lesions by hematoxylin and eosin staining commonly reveals epidermotropism, a profound infiltration of lymphocytes into the epidermis. As the lesions progress and become thickened,

epidermotropism is gradually lost as the lymphocytes begin to localize more diffusely in the skin. Only a fraction of the skin-homing lymphocytes in MF are malignant, and the malignant T cells may be identified by visualization of their small- to medium-sized hyperconvoluted (or cerebriform) nuclei and surrounding lacunae, which give them the impression of being surrounded by a halo. Pautrier microabscesses (Langerhans cell surrounded by atypical T cells in the epidermis) are less common, but a pathognomonic histologic finding associated with MF is common.[1,5] The malignant cells in MF are $CD4^+$ T-helper cells, which most commonly express a $CD3^+$, $CD4^+$, $CD45RO^+$, CLA^+, and $CCR4^+$ immunophenotype. Evaluation of the TCR profile of malignant T cells in MF reveals a predominant TCR rearrangement, indicative of clonal dominance in a majority of cases.

The specific stimuli and molecular events responsible for the activation and development of clonal dominance of a specific T cell are unknown. Genetic profiling studies have identified a number of chromosomal deletions and duplications associated with MF/SS, and microRNA profiling may reveal distinct molecular profiles associated with different phases of MF. More recently, whole-exome/genome sequencing of leukemic CTCL cells revealed mutations of interest involving 17 genes associated with a range of cellular functions, including TCR and NF-κB signaling and T-cell activation and survival pathways, chromatin remodeling, and DNA repair. In addition to any molecular aberrations intrinsic to the malignant T cells, the cutaneous microenvironment is also likely to play a key role in the development and maintenance of disease.[5,9-14]

Diagnosis and Evaluation

Evaluation of a patient with suspected or recently diagnosed MF should include a comprehensive history/physical examination, biopsy of cutaneous lesion(s) and suspicious lymph nodes, and appropriate laboratory and imaging studies. The ISCL has designed a diagnostic algorithm for early-stage MF (not applicable to MF variants) (Table 86.2),[15] and specific recommendations for patient evaluation have been released by the ISCL/EORTC.[16,17]

TABLE 86.2 DIAGNOSTIC CRITERIA FOR EARLY-STAGE MYCOSIS FUNGOIDES[A]

Clinical

Persistent and/or progressive patches and plaques plus:
Non–sun-exposed location
Size/shape variation
Poikiloderma
Scoring: 2 points if two or more criteria met; 1 point if only one criterion met

Immunopathologic

CD2, 3, 5 <50% of T cells
CD7 <10% of T cells
Epidermal discordance from expression of CD2, CD3, CD5, or CD7 on dermal T cells
Scoring: 1 point if any criterion met

Molecular/biologic

Clonal TCR gene rearrangement
Scoring: 1 point if present

Histopathologic

Epidermotropism without spongiosis
Lymphoid atypia
Scoring: 1 point for each

TCR, T-cell receptor.

[a]Not applicable to mycosis fungoides variants. Diagnosis made with 4 points or more.

Adapted from Pimpinelli N, Olsen EA, Santucci M, et al. Defining early mycosis fungoides. *J Am Acad Dermatol*. 2005;53(6):1053-1063. Copyright © 2005 American Academy of Dermatology, Inc. With permission.

History and Physical Examination

The duration of symptoms, evolutionary course of cutaneous disease, and presence or absence of B symptoms should be determined. The percentage of body surface area involved by disease and the presence or absence of cutaneous tumors should be documented, and a thorough evaluation of the lymphatic system should be performed. Appropriate images of cutaneous lesions should be recorded so that disease progression or response to therapy may be monitored.

Skin Biopsy

Biopsies should be taken from a minimum of two distinct sites of disease. Lesions of the greatest induration will be most likely to yield a diagnosis

due to greater numbers of malignant cells. However, scaled lesions are more likely to show epidermotropism. Tissue should be evaluated with hematoxylin and eosin staining, immunostaining for surface marker expression profiles (including CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, CD26, CD56, TIA1, granzyme B, βF1), and routine PCR or TCR NGS for clonal TCR rearrangement. Slides should be reviewed by a dermatopathologist.

Excisional biopsies of enlarged or otherwise suspicious lymph nodes (fixed or matted lymph nodes, or lymph nodes ≥1.5 cm or ≥1 cm in the head and neck) should be evaluated as described previously. When multiple suspicious lymph nodes are encountered, the choice of lymph node to be excised should be based on size, fluorodeoxyglucose avidity, and location, with priority given to the largest lymph node draining an affected area of skin or the lymph node with the highest standardized uptake value on positron emission tomography (PET) scan. If all other factors are equal, priority should be given first to cervical nodes, followed by axillary and then inguinal nodes.[16,17]

Laboratory and Imaging Studies

Laboratory studies should include a complete blood count, chemistry panel, liver function tests, and lactate dehydrogenase (LDH). Examination of the peripheral blood for circulating disease by PCR and flow cytometry should also be considered, particularly for patients with erythroderma, nodal, or extracutaneous disease. Bone marrow biopsy should be considered if peripheral blood or extracutaneous organs are found to harbor disease.[16,17] Computed tomography (CT) of the chest, abdomen, and pelvis is recommended in the evaluation of all patients with MF, with the exception of patients with patch/plaque disease limited to 10% or less of the body surface area. In these cases, a chest x-ray or nodal ultrasound may suffice. PET scanning was shown to be more sensitive than CT in identifying involved lymph nodes, and the role of PET in MF continues to evolve.[18]

Staging and Prognosis

MF is presently staged using the modified TNMB system proposed by the ISCL/EORTC (Table 86.3).[15] Based on a review of 525 patients with MF

(staged using the previous 1979 TNMB system), the majority of patients present with early-stage disease (30% IA, 25% IB, 11% IIA, 16% IIB, 3% IIIA, 8% IIIB, 6% IVA, and 1% IVB). Only 7% of patients presented with peripheral blood involvement. [8] Similar results were obtained in a validation study of the current staging system.[19] Of note, stage IA MF is not associated with any increase in mortality risk in comparison to an age- and ethnicity-matched control population and is associated with only a 16% rate of disease progression at 20 years of follow-up.[8] Benton et al proposed a cutaneous lymphoma international prognostic index (CLIPi) for both early- and late-stage MF/SS that is based on the presence of certain adverse features identified in a multivariate analysis, including "male gender, age >60, plaques, folliculotropic disease and stage N1/Nx for early-stage disease, and male gender, age >60, stages B1/B2, N2/3 and visceral involvement for late-stage disease."[20] The CLIPi then stratifies patients into low- (0-1 risk factors), intermediate- (2 risk factors), and high- (3-5 risk factors) risk groups.[20] A report from Emory University indicates that the CLIPi successfully stratified patients with early-stage, but not late-stage, MF/SS.[21] The Cutaneous Lymphoma International Consortium conducted a multi- institutional and international study of potential prognostic factors in advanced stage (IIB-IV) MF/SS and has proposed an alternative prognostic index based on the presence of four risk factors (stage IV disease, age>60, elevated LDH, and large cell transformation in the skin). Based on these factors, patients are stratified into low- (0-1 risk factor; 67.8% 5-year survival), intermediate- (2 risk factors; 43.5% 5-year survival), or high- (3-4 risk factors; 27.6% 5-year survival) risk groups.[22] Overall, these studies underscore the complexities and difficulties inherent to developing accurate prognostic indices for such rare disease entities.

TABLE 86.3 ISCL/EORTC REVISIONS TO MYCOSIS FUNGOIDES STAGING

T Stage
T1: Limited patches, papules, and/or plaques covering <10% of the skin surface. May further stratify into T1a (patch only) vs T1b (plaque/patch)
T2: Patches, papules, or plaques covering ≥10% of the skin surface. May further stratify into T2a (patch only) vs T2b (plaque/patch)
T3: One or more tumors (≥1-cm diameter)
T4: Confluence of erythema covering >80% body surface area

M Stage

M0: No visceral organ involvement
M1: Visceral involvement (must have pathology confirmation and organ involved should be specified)

N Stage

N0: No clinically abnormal peripheral lymph nodes; biopsy not required
N1: Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or NCI LN0-2 (N1a: clone negative, N1b: clone positive)
N2: Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN3
N3: Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 3 or 4 or NCI LN4; clone positive or negative
NX: Clinically abnormal peripheral lymph nodes; no histologic confirmation

B Stage

B_0 = <250/μL of $CD4^+/CD26^-$ or $CD4^+/CD7^-$ cells,
B_1 = does not meet criteria for B_0 or B_2, and
B_2 = ≥1,000/μL of $CD4^+/CD26^-$ or $CD4^+/CD7^-$ cells or other aberrant population of lymphocytes identified by flow cytometry.

Staging Groups

IA: T1 N0 M0 B0-1
IB: T2 N0 M0 B0-1
IIA: T1-2 N1-2 M0 B0
IIB: T3 N0-2 M0 B0-1
IIIA: T4 N0-2 M0 B0
IIIB: T4 N0-2 M0 B1
IVA1: T1-4 N0-2 M0 B0-2
IVA2: T1-4 N3 M0 B0-2
IVB: T1-4 N0-3 M1 B0-2

EORTC, European Organisation for Research and Treatment of Cancer; ISCL, International Society for Cutaneous Lymphomas; NCI, National Cancer Institute.

Adapted from Olsen E, Vonderheid E, Pimpinelli N, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood*. 2007;110(6):1713-1722. Copyright © 2007 American Society of Hematology. With permission.

Treatment

Skin-Directed Therapy

MF is not generally considered to be curable, although extended periods of disease-free survival after treatment have been reported. Efforts to treat MF are primarily focused on preventing progression and ameliorating symptoms. In early-stage disease, a number of skin-directed treatments are effective and should be considered as first-line therapy. Topical therapies include corticosteroids (complete response [CR] rates of 63% for T1 and 25% for T2 disease),[23] nitrogen mustard (CR rates of 76%-80% for stage IA and 35%-68% for stage IB),[24] carmustine (CR rates of 86% for T1 and 47% for T2 disease),[25] and bexarotene gel (CR rate of 21% in early-stage MF).[26] Phototherapy with narrow-band ultraviolet B (NB-UVB) (54% CR in stage IA or IB)[27] or psoralen + UVA (PUVA) (CR rate of 65%)[28] is also frequently used. However, the most effective skin-directed therapy for MF is ionizing radiation.

Ionizing radiation is well suited to the treatment of cutaneous lymphoma. Lymphocytes are highly radiosensitive, and radiation doses may be effectively limited to the epidermis and dermis by appropriate selection of photon or electron energies. Options for irradiation include local superficial irradiation or irradiation of the entirety of the skin via total skin electron beam therapy (TSEBT). The International Lymphoma Radiation Oncology Group (ILROG) has suggested guidelines for field and dose selection.[29]

Local Superficial Irradiation

A small portion (5%) of patients with stage IA MF present with “minimal” disease, defined as a solitary lesion or two to three MF lesions clustered sufficiently close to one another that they are amenable to treatment with a single or abutting radiation field.[30] For these patients, treatment with local superficial irradiation may be considered. Treatment fields should be designed to encompass the entirety of the lesion (determined by visual inspection, palpation, and/or appropriate imaging) with a 1- to 2-cm margin, with the use of a lead or Cerrobend cutout to conform field borders to the anatomy of the cutaneous lesion. Skin collimation can also be incorporated. Treatment is most commonly provided with electrons, with energies (usually 6-16 MeV) carefully selected to optimize dose penetration. The EORTC recommends that the 80% isodose line is set at the deep border of the dermis,[31] which is commonly at a depth of approximately 4.5 mm.

Local superficial radiation is very effective in generating a CR for patients with "minimal" stage IA MF. In a review of 21 patients with "minimal" stage IA MF treated with local superficial radiation (superficial or orthovoltage x-rays or megavoltage electrons) to doses ranging from 20 to 40 Gy in four to five or 10 to 15 fractions, Wilson et al[30] found a CR rate of 97%. Importantly, a review of the recurrence rates associated with different total doses of local superficial radiation revealed a 25% local recurrence rate (2/8 fields) with treatment to 20 Gy and an 8% local recurrence rate (2/25 fields) with treatment to 20 to 40 Gy. Similarly, Cotter et al[32] reported a local recurrence rate of 42% for fields treated to 10 Gy or less, but 0% for fields treated to >30 Gy. Based on these studies, it is recommended that "minimal" stage IA (ie, unilesional or up to three closely approximated sites) MF lesions are treated to a dose of at least 24 Gy, With respect to palliative treatment of individual lesions, Patel et al reported on 225 lesions irradiated in 41 patients with 4, 8, or 12 Gy.[33] The response rates ranged from 82.2% to 91.5%. The response rates for 4 versus 8 Gy were 82.2% and 91.5%, respectively (P = .057). The higher dose also achieved more durable control. Treatment with a dose as low as 8 Gy in a single fraction is now considered standard as a palliative treatment. Side effects of local superficial radiation are usually limited to mild dermatitis, local alopecia, and pigmentation changes.

Total Skin Electron Beam Therapy

Technique

TSEBT is technically challenging and should be attempted only in centers with special expertise in its provision, including skilled physics support. EORTC recommendations regarding the technical aspects of TSEBT are presented in Table 86.4. Modern TSEBT is usually accomplished with 6- to 9-MeV electrons generated by a medical linear accelerator directed at a patient standing behind a polycarbonate screen, 3.8 m from the linear accelerator head. The polycarbonate screen scatters the incident electron beam and contributes to an improved surface dose. Treatment is often provided in "cycles," with one cycle composed of treatment of the patient in six different positions (Figure 86.3A) over 2 days (three positions each day). Typically, a dose of 2 to 3 Gy is provided to the entirety of the skin

during one cycle, and two cycles are usually administered per week. Treatment in six positions optimizes dose distribution at the skin surface (Figure 86.3B). At Yale and Stanford, the anterior, right posterior oblique, and left posterior oblique positions are treated on cycle day 1, and the posterior, right anterior oblique, and left anterior oblique positions on cycle day 2.[34,35] When the patient stands in a treatment position, a dual-field technique is used to deliver treatment to a superior and inferior field by angling the gantry 16° to 17.5° above and below horizontal, respectively, with the specific angle dependent upon individual machine characteristics (Figure 86.4). Treatment to the six positions using the dual-field technique, which is in use at Yale and Stanford, delivers maximum dose to a depth of 1 mm, 80% dose to 6 to 7 mm, and 20% dose to 12.5 mm.[34,35]

TABLE 86.4 EORTC TECHNICAL RECOMMENDATIONS FOR TSEBT

The primary target in TSEBT is the epidermis, adnexal structures, and dermis.
The goal of treatment (either by primary or supplemental treatments) is to deliver a dose of 26-28 Gy to a depth of 4 mm below the skin surface, which usually translates to a truncal dose of 31-36 Gy.[a]
Treatment should be provided in 30-36 fractions (1-1.2 Gy/fraction) over 6-10 wks. Fraction sizes should not exceed 2-2.5 Gy due to increased acute and late side effects.
The 80% isodose line should extend to 4 mm below the skin surface, the dose 20 mm deep to the skin must be <20% of the maximum dose at skin, and the dose at curved skin sites must not exceed 120% of the prescribed skin dose.
Patient positioning is critical, and patients must be positioned in a manner to maximize unfolding of the skin. A minimum of six treatment positions is recommended.
The optimal source-to-patient distance is 3-8 m, and dose should be homogeneous to within 10% across the entire vertical and lateral dimensions of the beam at the patient's surface.
The globe of the eye must be limited to <15% of the maximum skin dose, and photon contamination at the bone marrow must be limited to <0.7 Gy.

EORTC, European Organisation for Research and Treatment of Cancer; TSEBT, total skin electron beam therapy.

[a]Lower doses of 10-12 Gy are now most commonly used.

Reprinted from Jones GW, Kacinski BM, Wilson LD, et al. Total skin electron radiation in the management of mycosis fungoides: consensus of the European Organization for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Project Group. *J Am Acad Dermatol*. 2002;47(3):364-370. Copyright © 2002 American Academy of Dermatology, Inc. With permission.

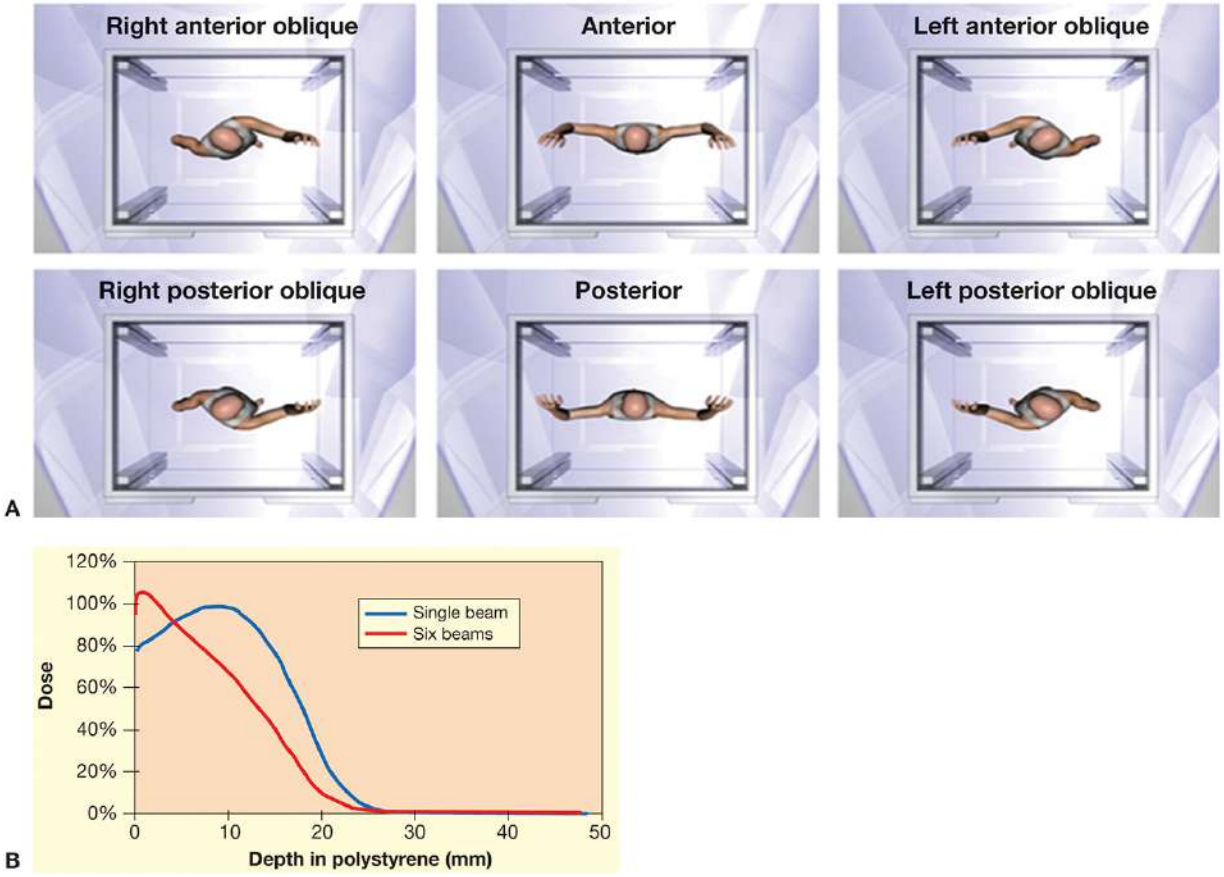

FIGURE 86.3 A. The six total skin electron beam therapy treatment positions as viewed from above. Images not to scale. B. Comparison of depth dose profiles associated with a single-treatment position (blue curve) versus six treatment positions (red curve). (A. courtesy of Christian Chang, www.christianchang.com, printed with permission from the artist. B. Used with permission of MJH Life Sciences, LLC from Smith BD, Wilson LD. Management of mycosis fungoides: part 2. Treatment. *Oncology (Williston Park)*. 2003;17[10]:1419-1433; permission conveyed through Copyright Clearance Center.)

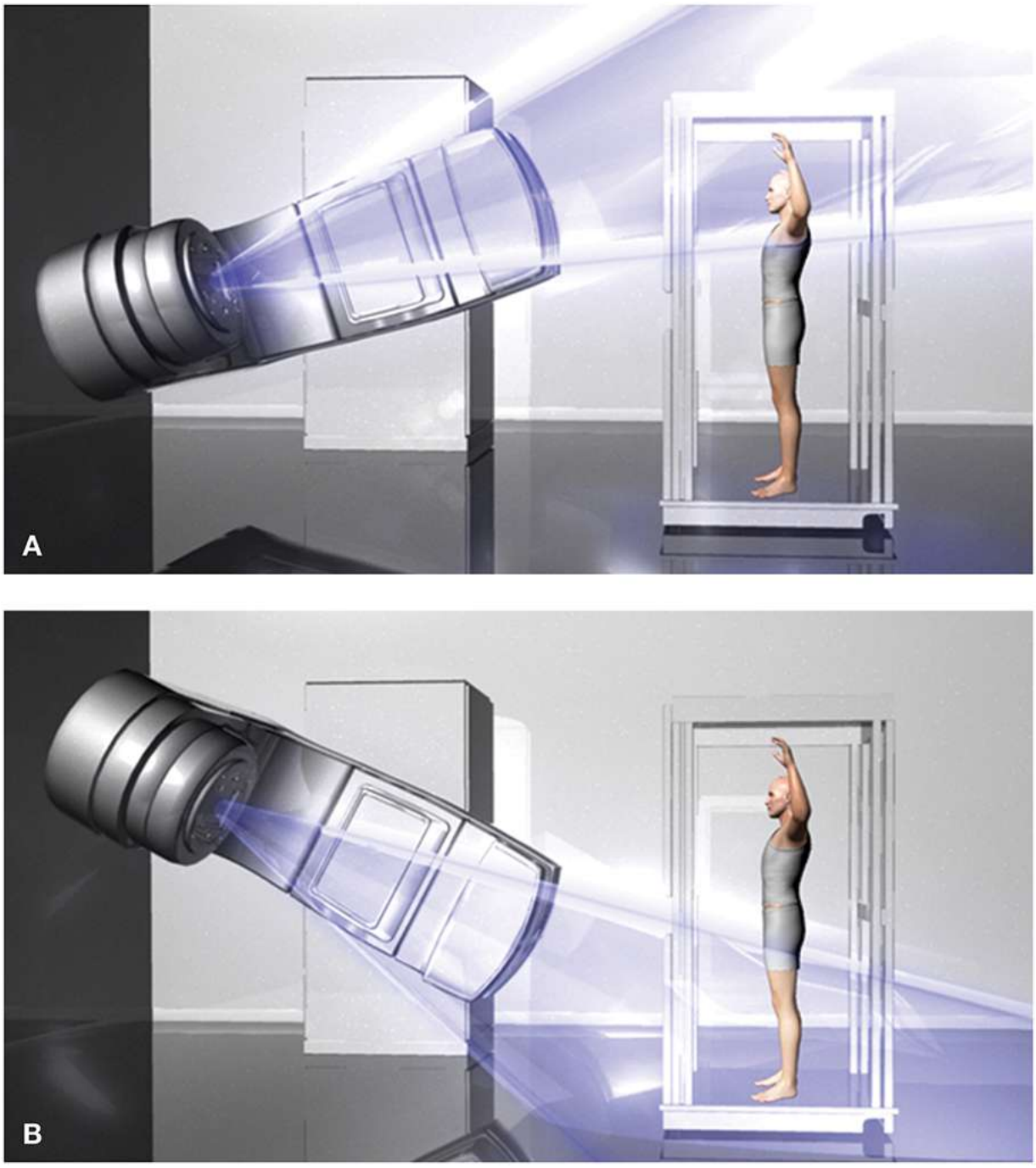

FIGURE 86.4 Dual-field technique for total skin electron beam therapy. A. Treatment of superior field. B. Treatment of inferior field. Images not to scale. (Courtesy of Christian Chang, www.christianchang.com, printed with permission from the artist.)

Dose and Fractionation

Sublethal damage repair does not appear to be a major factor in determining the response of MF to ionizing radiation,[36] and modern TSEBT is provided

with a relatively protracted course. The classic approach delivered 36 Gy to the skin surface in 9 to 10 weeks. The total radiation dose appears to be directly associated with CR rates, with 18% CR with treatment to <10 Gy, 55% CR with treatment to 10 to 20 Gy, 66% CR with treatment to 20 to 25 Gy, 75% CR with treatment to 25 to 30 Gy, and 94% CR with treatment to 30 to 36 Gy.[37] However, lower doses yield impressive rates of overall response (defined as a >50% reduction in cutaneous disease), overall survival, progression-free survival, and relapse-free survival rates. Relapse rates are relatively high even in patients in which a CR is obtained, and the absolute benefit of a CR relative to the increased side effects at higher doses of TSEBT is unclear. This has led to the use of reduced-dose TSEBT (10-20 Gy) in combination with additional therapies and has become preferable to the use of higher doses of TSEBT.[38-40] These studies consistently show overall excellent outcomes with reduced toxicity, allowing TSEBT to be repeated as necessary for a patient's disease.

Supplemental Treatments

The six treatment positions in TSEBT maximize unfolding of the skin and exposure of the skin surface to the incident electron beam, but areas such as the soles of the feet, perineum, and scalp remain obscured and require supplemental doses to ensure that a minimum of 20 Gy is administered to a depth of approximately 4 mm. Supplemental treatment to these areas may be accomplished by the use of 120-kV superficial photons with half-value layer 4.2-mm or low-energy (6 MeV) electrons with 1-cm bolus to treat the soles of the feet (1 Gy per fraction) and the perineum (1 Gy per fraction). In some setups, the scalp is treated by placing an angled electron reflector above the patient,[34] but supplemental boosting is an alternative approach that is incorporated in some centers. Additional areas that may need supplemental dose include thick cutaneous tumors and skin folds secondary to body habitus, and the need for a supplemental dose to such areas is based on the judgment of the radiation oncologist.[34,35]

Side Effects

In a review of perceptions of MF therapy, patients overall considered high-dose TSEBT to be a more difficult treatment to endure as compared to other

treatments,[41] and it is important that patients are advised that symptoms such as pruritus and cutaneous erythema may be exacerbated during therapy. Additional acute side effects that commonly occur after high-dose TSEBT include xerosis, dry desquamation, extremity edema, blister/bullae formation over the lower extremities, alopecia (including hair of the scalp, eyebrows, eyelashes, and body), and nail changes (nails may ultimately be lost but usually regrow). Hypohydrosis secondary to damage to sweat glands may occur. Similarly, dryness and irritation of the nasal mucosa may result in nosebleeds. Gynecomastia is a rare occurrence. Following lower doses of TSEBT (~12 Gy), all of these effects are diminished. Dryness, xerosis, and alopecia (temporary) may still occur, but nail changes and hypohydrosis are notably less. Late/chronic side effects are minimal and dose related but may include cataract formation, chronic xerosis, persistent alopecia, dystrophic nails, telangiectasia, and secondary skin cancers, including squamous and basal cell carcinomas and melanomas. Clinicians should be vigilant for the possibility of active cutaneous infection during the course of therapy.[31,42-46]

In an effort to minimize side effects, areas that are most sensitive to TSEBT such as the eyes, lips, hands, fingernails, feet, and testes may be blocked completely or during certain cycles of treatment. Shielding of the eye and lens may be accomplished by a combination of internal/external shields, selected based upon the proximity of clinical disease. Usually, if internal eye shields are used, they are used for only a portion of the therapy (7-20 Gy). The lips, hands, and fingernails may be blocked by lead mitts or fingernail shields as clinical circumstances warrant. The feet may be blocked by footboards for a portion of the treatment. A testicular shield may be used during TSEBT or perineal boost treatments.[34] The scalp may be shielded if there is no nearby disease.[47]

Clinical Efficacy

TSEBT is very effective, particularly for early-stage disease. TSEBT yields a CR rate of >90% with a 15-year relapse-free survival of 40% in patients with T1 disease, although it is no longer recommended for such limited disease.[37] Of note, patients with recurrent disease after a course of TSEBT most commonly have disease restricted to <5% of the skin surface area, and

these recurrences are, therefore, amenable to local salvage therapy with topical therapy or limited superficial radiation. When successful salvage of such limited recurrences is taken into account, relapse-free survival improves to 70% at 15 years.[48-50]

In T2 disease TSEBT is similarly effective, with a CR rate of 76% to 90% and a 50% relapse-free survival rate at 5 years and 10% at 10 years. Relapse-free survival is significantly improved by the addition of adjuvant PUVA or nitrogen mustard. Specifically, adjuvant PUVA improves 5-year relapse-free survival to 85%, and nitrogen mustard improves 10-year relapse-free survival to 40%.[31,50-52]

When cutaneous tumors are present (T3 disease), TSEBT is less effective but still yields an impressive CR rate of 44% to 54% of patients, much greater than any other single modality. Adjuvant treatment is indicated, and retrospective studies suggest that nitrogen mustard, PUVA, low-dose methotrexate, interferon (IFN), or acitretin may increase the durability of response. Alternatively, a combination of topical therapy and local superficial radiation may be considered for tumors localized to a small percentage of the skin surface.[50,51,53] Supplemental boosts should be considered for patients with tumors, and such boost treatment should be provided concomitantly with the initiation of TSEBT or prior to its initiation. The purpose of the boost is to diminish the thickness of the lesion so that electrons from TSEBT can effectively penetrate the entire depth of the lesion.

In erythrodermic MF (T4 disease), TSEBT yields a 70% to 100% response rate (for patients with T4N0 disease) and 5-year progression-free survival of 25% to 69%. When disease involves the peripheral circulation or extracutaneous sites, TSEBT is less effective and response and progression-free survival rates decrease to 74% and 36%, respectively. TSEBT appears to be synergistic with extracorporeal photopheresis (ECP), and the combination of TSEBT and ECP is associated with improved disease-specific survival and decreased levels of circulating malignant cells.[53-56] Occasional patients with erythroderma have exquisitely sensitive skin, necessitating the use of lower daily doses of TSEBT.

Palliative Radiotherapy

Symptomatic nodal or visceral disease may be effectively palliated by a brief course of localized radiotherapy, usually to a total dose of 12 to 30 Gy. If this treatment is given in conjunction with a course of TSEBT, a similar dose may be used. In the subset of patients who develop extensive recurrence of cutaneous disease after a previous course of TSEBT, additional courses of TSEBT to lower total doses can be considered and have proven effective in studies at Yale and Stanford.[57,58] This is especially appropriate when lower initial doses of TSEBT have been used.

Systemic Therapy

Skin-directed therapy should be attempted first for patients with early-stage disease, but in patients with advanced or refractory disease, systemic therapy should be considered. Common options for systemic therapy have included oral bexarotene (response rate up to 54% in refractory CTCL at a dose of 300 mg/m^2, and bexarotene may be used in combination with other therapies)[59,60] and histone deacetylase inhibitors (such as vorinostat and romidepsin, 30% response rate in refractory CTCL).[61,62] One of the most effective systemic therapies is brentuximab vedotin (BV). In the ALCANZA study, patients with MF were randomized to treatment with BV or physician choice (methotrexate or bexarotene). The global objective response lasting at least 4 months was 56.3% in the BV group and only 12.5% in the control group. The likelihood of grade 3 to 4 events was similar in both groups, but the risk for peripheral neuropathy was much higher in the BV group (67% vs 6%).[63] Another novel effective therapy is mogamulizumab (moga), a monoclonal antibody directed against C–C chemokine receptor 4. In the MAVORIC study, moga was compared to vorinostat in previously treated patients. The progression-free survival was 7.7 months in the moga group versus only 3.1 months for vorinostat.[64] Other systemic options include alemtuzumab (a monoclonal antibody targeted against the CD52 surface marker with a 38% overall response rate in relapsed or refractory CTCL and 86% response rate in SS),[65,66] INF-α2a (a biologic modifier with a response rate of 40%-80% in CTCL as a single agent and with synergistic activity with other MF therapies),[67-69] ECP (associated with improvement in peripheral blood and skin involvement, especially in those with T4 disease),[70] and pembrolizumab (38% overall

response rate in heavily pretreated patients with advanced disease).[71] With respect to cytotoxic chemotherapy, single-agent treatment with agents such as purine or nucleoside analogs, liposomal doxorubicin, and antifolate agents, including methotrexate and pralatrexate, is preferred because no distinct advantages have been identified with the use of multiagent regimens.[72-76]

Autologous or Allogeneic Stem Cell Transplant

Patients with MF/SS refractory to other therapies may be considered for stem cell transplant. Autologous stem cell transplantation is ineffective, but greater success has been achieved with allogeneic stem cell transplants. Additional studies are necessary to fully define the role of allogeneic transplantation, but this approach may prove to be a valuable option for patients with refractory disease.[77-81]

Treatment Recommendations by Stage

Treatment recommendations for MF/SS are presented by stage in Table 86.5.[82]

TABLE 86.5 RECOMMENDATIONS FOR TREATMENT OF MF BY STAGE

Stage	First-Line Therapies	Options for Refractory or Relapsed Disease
"Minimal" IA	Local superficial irradiation Topical corticosteroids	Consider standard-stage IA first-line therapies
IA, IB, IIA	Expectant observation (for stage IA) Topical therapies (corticosteroids, nitrogen mustard, bexarotene) Phototherapy (PUVA, NB-UVB) TSEBT (consider adjuvant PUVA or nitrogen mustard) Oral retinoids Methotrexate	Second-course TSEBT Oral bexarotene (or other retinoids) IFN-α Low-dose MTX Vorinostat Brentuximab vedotin Clinical trials NOTE: Chemotherapy is not Recommended.
IIB	TSEBT (consider boosts to cutaneous tumors and adjuvant	Second-course TSEBT Oral bexarotene

Stage	First-Line Therapies	Options for Refractory or Relapsed Disease
	PUVA IFN-*α* Brentuximab vedotin (esp if LCT)	Vorinostat Romidepsin Pralatrexate Pembrolizumab Clinical trials Chemotherapy Allogeneic stem cell transplant in R/R cases, LCT
IIIA, IIIB, leukemic CTCL or SS	TSEBT + ECP ECP alone IFN-*α* PUVA + IFN-*α* MTX Oral retinoids Mogamulizumab (esp in those with high Sézary burden)	Second-course TSEBT Oral bexarotene Mogamulizumab Vorinostat Romidepsin Pembrolizumab Alemtuzumab Clinical trials Chemotherapy Allogeneic stem cell transplant
IVA (1-2), IVB	Chemotherapy TSEBT for palliation Oral bexarotene IFN-*α* Brentuximab vedotin Pralatrexate Pembrolizumab Vorinostat Romidepsin Clinical trials	Liposomal doxorubicin Gemcitabine Combination chemotherapy (esp if bridging to allogeneic HSCT) Allogeneic stem cell transplant

BCNU, *bis*-chloroethylnitrosourea; CTCL, cutaneous T-cell lymphoma; ECP, extracorporeal photopheresis; IFN-*α*, interferon-alpha; MTX, methotrexate; NB-UVB, narrow-band ultraviolet B; PUVA, psoralen plus ultraviolet A; SS, Sézary syndrome; TSEBT, total skin electron beam therapy.

Transformed Disease

In some cases, large cell transformation of MF may occur, which is identified on biopsy by >25% large cells in the sample. Large cell transformation may be associated with decreased survival rates and occurs in 8% to 39% of cases. Patients with advanced stage or high levels of β_2-microglobulin or LDH are at the greatest risk of large cell transformation.

Treatment options include BV, systemic chemotherapy, stem cell transplant, and consolidative or local radiation for localized disease.[79,63]

Variants of Mycosis Fungoides

Variant forms of MF that share histologic and clinical features with classic MF but exhibit distinct clinical behavior have been recognized and include folliculotropic MF, Woringer-Kolopp disease, granulomatous slack skin (GSS), and hypopigmented MF.

Folliculotropic MF is characterized by a folliculotropic pattern of cutaneous infiltration of malignant T cells. Folliculotropic MF lesions present as patches, plaques, or tumors or may manifest in an acneiform pattern. Lesions primarily develop over the head and neck and are rarely found over the trunk. Localized alopecia secondary to the folliculotropic pattern is common. Folliculotropic MF is associated with a 15-year survival of 41% for early-stage disease. Early-stage disease may be treated with PUVA combined with bexarotene or IFN-α. Local radiation therapy may be advantageous because it can effectively treat to deeper depths of involvement seen in this variant. Advanced-stage disease is minimally responsive to cytotoxic chemotherapy, and alternate options such as irradiation or allogeneic stem cell transplant should be considered.[1,83,84]

Woringer-Kolopp disease (pagetoid reticulosis) is characterized by a solitary erythematous and scaling cutaneous patch on an extremity. Biopsy results are similar to classic MF, and the malignant T cells commonly carry a $CD3^+/CD4^+/CD8^-$ or $CD3^+/CD4^-/CD8^+$ immunophenotype. If $CD8^+$ disease is identified, it is important to consider the alternative diagnosis of $CD8^+$ aggressive peripheral CTCL, and the distinction between these diagnoses is made by the aggressiveness of disease. Specifically, as compared to $CD8^+$ aggressive peripheral CTCL, Woringer-Kolopp disease is very slowly progressive and carries an excellent prognosis. Treatment options include skin-directed therapies, such as corticosteroids, nitrogen mustard, resection, or local irradiation. Local radiation may be very successful in achieving long-term local control, even in locally very advanced disease. In rare cases of diffuse or refractory disease, irradiation is also recommended.[1,85]

GSS is an extremely rare variant of MF, with <100 cases reported in the literature. It is characterized by cutaneous infiltration of a clonal population of malignant T cells coupled with a granulomatous infiltration. The granulomatous infiltrate ultimately causes destruction of local elastin fibers and impairs the structural integrity and elasticity of the skin, which results in loose or "slack" skin. This loosening of the skin is most commonly observed in the axilla, groin, neck, and breast. Although GSS is itself an indolent disease, it is associated with an increased incidence of secondary lymphomas, most commonly Hodgkin lymphoma or MF. Given the rarity of this disease, it is difficult to make definitive recommendations regarding therapy, but surgical resection or local superficial radiation may be effective.[1,86]

Hypopigmented MF presents at an earlier age (childhood or adolescence) than classic MF and is characterized by the development of hypopigmented patches frequently over the trunk or extremities. In contrast to classic MF, the malignant T cells are often $CD8^+$. Treatment and disease course are otherwise similar to classic MF.[87,88]

NON–MYCOSIS FUNGOIDES CUTANEOUS T-CELL LYMPHOMA

Staging

In 2007, the ISCL and EORTC presented a new TNM staging system for non-MF/SS cutaneous lymphomas (Table 86.6).[89]

TABLE 86.6 ISCL/EORTC TNM CLASSIFICATION OF CUTANEOUS LYMPHOMA OTHER THAN MYCOSIS FUNGOIDES/SÉZARY SYNDROME

T Stage

T1: Solitary skin involvement
T1a: A solitary lesion <5 cm in diameter
T1b: A solitary lesion >5 cm in diameter
T2: Regional skin involvement: multiple lesions limited to 1 body region or 2 contiguous body regions
T2a: All disease encompassing in a <15-cm-diameter circular area
T2b: All disease encompassing in a >15- and <30-cm-diameter circular area
T2c: All disease encompassing in a >30-cm-diameter circular area
T3: Generalized skin involvement
T3a: Multiple lesions involving 2 noncontiguous body regions
T3b: Multiple lesions involving and ≥3 body regions

N Stage

N0: No clinical or pathologic lymph node involvement
N1: Involvement of 1 peripheral lymph node region that drains an area of current or prior skin involvement
N2: Involvement of 2 or more peripheral lymph node regions or involvement of any lymph node region that does not drain an area of current or prior skin involvement
N3: Involvement of central lymph nodes

M Stage

M0: No evidence of extracutaneous non–lymph node disease
M1: Extracutaneous non–lymph node disease present

EORTC, European Organisation for Research and Treatment of Cancer; ISCL, International Society for Cutaneous Lymphomas.

Reprinted from Kim YH, Willemze R, Pimpinelli N, et al. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood*. 2007;110(2):479-484. Copyright © 2007 American Society of Hematology. With permission.

CD30-Positive Lymphoproliferative Disorders

A review of the Surveillance, Epidemiology, and End Results registry identified 268 cases of primary cutaneous $CD30^+$ lymphoproliferative disorders recorded between 1974 and 2004 (58% male and 42% female patients). The median age of diagnosis was 61, and population-matched 3-year relative survival was 87%, with 5-year disease-specific survival of 92%. Localization of disease in the head and neck appears to be a negative prognostic factor.[90] The primary cutaneous $CD30^+$ lymphoproliferative disorders recognized by the WHO/EORTC are primary cutaneous anaplastic large cell lymphoma (PC-ALCL) and lymphomatoid papulosis (LyP).[1] These cannot be differentiated histologically. It is essential to take a careful clinical history to document the distribution of lesions and their clinical course (eg, history of spontaneous regression). The diagnosis is clinicopathologic. The EORTC, ISCL, and USCLC have provided consensus recommendations regarding the evaluation and treatment of primary cutaneous $CD30^+$ lymphoproliferative disorders.[91]

Primary Cutaneous Anaplastic Large Cell Lymphoma

PC-ALCL is characterized by the development of cutaneous plaques, nodules, or tumors that are usually solitary or clustered into a localized area. Multifocal disease is uncommon (occurring in only 20% of patients), and lymph nodes are involved in only 10% of cases. Nonnodal extracutaneous disease is rarely found. PC-ALCL is most commonly diagnosed in males, with a male:female ratio of 2 to 3:1. When disease is localized to the skin and regional lymph nodes, prognoses are excellent, with anticipated 5-year overall survival and 10-year disease-specific survival rates of 90%. Progression to extracutaneous disease affects overall survival, and extensive limb disease (defined as "initial presentation or progression to multiple skin tumors in one limb or contiguous body regions")[92] impacts disease-specific survival. Biopsies of PC-ALCL lesions reveal a diffuse infiltration of large anaplastic $CD4^+$ T cells, and at least 75% of these anaplastic T cells express CD30. Similar to MF, clonal dominance is frequently detected by PCR evaluation for TCR rearrangement.[1]

Limited resection or local superficial irradiation is very effective in controlling localized cutaneous disease, and BV or low-dose methotrexate may be considered when widespread cutaneous disease precludes simple resection or irradiation. Local superficial radiation to a dose of 34 to 44 Gy was associated with a 100% CR rate,[93] but more recent data suggest that lower doses such as 20 Gy may be adequate.[94] In rare cases in which extracutaneous disease is found, treatment with BV should be considered in limited regional lymph node involvement with a potential role for local radiation in addition. Anthracycline-based combination chemotherapy is reserved for systemic ALCL. Of note, prior to initiating therapy, it is critically important to verify that PC-ALCL has been correctly distinguished from the more common systemic ALCL. Molecular studies to evaluate the presence of the (2:5) (p23;q35) chromosomal translocation and expression of anaplastic lymphoma kinase (ALK) or epithelial membrane antigen (EMA) are useful in making this distinction, because the (2:5) translocation and expression of ALK and EMA are found in systemic ALCL but rarely found in PC-ALCL.[1,95]

Lymphomatoid Papulosis

LyP carries an excellent prognosis, with a 5-year overall survival rate of 100%. However, 15% to 20% of patients with LyP will develop MF, PC-ALCL, or a Hodgkin lymphoma. LyP is characterized by the development of violaceous papular or papulonodular lesions over the trunk or extremities, which typically regress after 3 to 12 weeks, often leaving a residual scar. Biopsy of LyP cutaneous lesions reveals epidermotropic atypical $CD3^+/CD4^+/CD8^-$ lymphocytes, and clonal TCR rearrangement is identified in 60% to 70% of cases. Three distinct histologic subtypes are recognized: LyP A, LyP B, and LyP C. LyP A (characterized by large multinucleated $CD30^+$ cells intermixed with an inflammatory infiltrate) and LyP C (characterized by large $CD30^+$ cells with minimal inflammatory infiltrate) represent 90% of cases. In contrast to types A and C, atypical lymphocytes in LyP B are $CD3^+/CD4^+/CD30^-$, reminiscent of MF.[1]

Aggressive therapies such as chemotherapy should be avoided in LyP. In the rare patient with a large cutaneous burden of disease, skin-directed therapy with PUVA or a topical chemotherapy agent may be considered. In addition, low-dose oral methotrexate or BV may be effective in suppressing the development of new lesions and may be considered if previous LyP lesions caused significant scarring.[1]

Extranodal NK/T-Cell Lymphoma, Nasal Type

Extranodal NK/T-cell lymphoma, nasal type most commonly arises in the nasal cavity and nasopharynx but, in select cases, may present with cutaneous plaques or tumors over the extremities and trunk and is, therefore, included in the WHO/EORTC classification of cutaneous lymphomas. Biopsy of a cutaneous lesion reveals a dense lymphoid infiltrate, which may exhibit an epidermotropic component. The malignant cells are most commonly NK in origin with a $CD3^-/CD2^+/CD56^+$ immunophenotype, but on occasion, the malignant cells are derived from cytotoxic T cells. Epstein-Barr virus (EBV) is directly associated with disease development, and cutaneous lesions are nearly always EBV^+. Consistent with an EBV-mediated pathophysiology, the disease occurs more commonly in geographic distributions in which EBV is endemic (Central America, South America, South Asia). The TCR usually remains in germline configuration when the malignant cells are of NK cell origin, but

clonal TCR rearrangement may be observed in cases in which the malignant cells are derived from cytotoxic T cells. Optimal treatment regimens for cutaneous extranodal NK/T-cell lymphoma, nasal type have not yet been determined. Treatment with radiotherapy to a median dose of 50 Gy yields a CR rate of 95.4% in early-stage disease, but local or distant recurrences are common and adjuvant therapy with L-asparaginase- based chemotherapy regimens should be considered. Advanced-stage disease is treated primarily with chemotherapy; recently, checkpoint inhibitor pembrolizumab was shown to be active in NK/T-cell lymphoma.[1,96-99]

Subcutaneous Panniculitis-Like T-Cell Lymphoma

Subcutaneous panniculitis-like T-cell lymphoma presents with subcutaneous nodules and/or plaques, which are commonly localized over the legs or trunk. Biopsy reveals a lymphoid infiltrate composed primarily of malignant cytotoxic $CD8^+$ T cells. Prior to the establishment of the WHO/EORTC classification system, α/β and γ/Δ T-cell forms of disease were each recognized as subcutaneous panniculitis-like T-cell lymphoma. However, γ/Δ T-cell lymphoma is now recognized as a distinct, more aggressive disease and is categorized as a primary cutaneous peripheral T-cell lymphoma. The 5-year survival of the less aggressive α/β disease approaches 80%, and treatment involves combinations of corticosteroids and radiation, and potentially chemotherapy for refractory or aggressive disease.[1] The more aggressive γ/Δ type requires intensive therapy that may include allotransplantation with radiation for local control.[100] The presence of the hemophagocytic syndrome predicts a worse prognosis.

Adult T-Cell Leukemia/Lymphoma

Infection with the human T-lymphotropic virus 1 (HTLV-1) may result in adult T-cell leukemia/lymphoma in approximately 1% to 5% of individuals, and patients may develop associated cutaneous disease, characterized by papules, plaques, and tumors. In smoldering disease, cutaneous lesions may be the only sign of pathology. Chemotherapy is often the primary initial therapy for acute adult T-cell leukemia/lymphoma, with recent studies also showing the efficacy of agents such as moga. Smoldering cases may be treated with skin-directed therapies.[1]

Primary Cutaneous Peripheral T-Cell Lymphoma

Additional CTCLs that do not fit into the previously discussed categories are grouped as "primary cutaneous peripheral T-cell lymphomas," and provisional subsets of this category described by the WHO/EORTC include primary cutaneous aggressive epidermotropic $CD8^+$ cytotoxic T-cell lymphoma (characterized by cutaneous papules/plaques, nodules, and tumors with ulceration and a propensity for extracutaneous spread of disease; of note, it has recently been proposed that $CD8^+$ should be removed from the naming of this disease entity in order to allow inclusion of diseases of similar behavior that are $CD8^-$ or have variability in TCR expression status),[101] cutaneous γ/Δ T-cell lymphoma (most commonly characterized by subcutaneous plaques or tumors in the extremities), primary cutaneous $CD4^+$ small-/medium-sized pleomorphic T-cell lymphoma (usually presents as a single cutaneous plaque or tumor on the head and neck or upper trunk and has an indolent clinical behavior), and primary cutaneous peripheral T-cell lymphoma, unspecified (most commonly presents as solitary or generalized nodules). The primary cutaneous peripheral T-cell lymphomas are primarily treated with chemotherapy or allogeneic stem cell transplantation, with the exception of primary cutaneous $CD4^+$ small-/medium-sized pleomorphic T-cell lymphoma, which may be treated with local resection or radiation.[1]

PRIMARY CUTANEOUS B-CELL LYMPHOMAS

Classification

Primary cutaneous B-cell lymphoma (PCBCL) was first recognized as a distinct clinicopathologic entity in 1981 and accounts for 29% of the 3,884 cases of primary cutaneous lymphoma diagnosed in the United States during 2001 to 2005.[3] The WHO/EORTC classification system recognizes three primary categories of CBCL: primary cutaneous marginal zone B-cell lymphoma (PCMZL), primary cutaneous follicle center B-cell lymphoma (PCFCL), and primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT).[1] In a large Dutch series of PCBCL, 57% were PCFCL, 24% were PCMZL, and 19% were PCDLBCL-LT.[102]

Primary Cutaneous Marginal Zone B-Cell Lymphoma

PCMZL commonly presents with isolated or multifocal red or violaceous papules, plaques, and/or nodules on the trunk or extremities. The malignant cells are marginal zone B cells with a $CD20^{+}/CD79a^{+}/CD5^{-}/CD10^{-}$ immunophenotype. Biopsies reveal an infiltrate composed of numerous lymphoid cells, including marginal zone B cells, lymphoplasmacytoid cells, plasma cells, centroblast- and immunoblast-like cells, reactive T cells, and reactive germinal centers. The prognosis for patients with PCMZL is excellent, and extracutaneous disease is rarely seen. Five-year overall survival rates of approximately 99% are expected, and cutaneous disease is very responsive to therapy. Cutaneous relapses are common but do not predict decreased survival.[1]

Primary Cutaneous Follicle Center Lymphoma

In contrast to PCMZL, PCFCL frequently presents with solitary or clustered plaques and tumors on the scalp, forehead, and trunk. Biopsy reveals a nodular or diffuse lymphoid infiltrate containing varying proportions of centrocytes, centroblasts, and reactive T cells growing in patterns ranging from follicular to diffuse. Similar to PCMZL, the malignant cells in PCFCL are of a $CD20^{+}/CD79a^{+}$ immunophenotype. Clonal rearrangement of immunoglobulin genes is usually observed. Importantly, the chromosomal translocation *t*(14:18) is infrequent in PCFCL, and therefore, detection of this translocation should prompt consideration of a nodal or systemic follicular lymphoma. Similar to PCMZL, cutaneous lesions respond well to treatment. Extracutaneous disease is detected in 5% to 10% of patients, and bone marrow biopsy is an important component of evaluation. The 5-year overall survival rate for PCFCL is estimated at 95%.[1]

Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type

PCDLBCL-LT usually presents with violaceous cutaneous tumors over the lower extremities. It is most common in older females. Despite the nomenclature, anatomic restriction to the legs is not a requirement, and in rare cases, PCDLBCL-LT may be found in other cutaneous sites than the leg. The disease is characterized by diffuse lymphoid infiltrates with a predominance of centroblasts and immunoblasts, with the absence of any significant number of centrocytes being a key distinguishing feature from

PCFCL. A $CD20^+$, $CD79a^+$, Bcl-$6^{+/-}$, $CD10^-$, Bcl-2^+, MUM-1^+, $FOXP1^+$, and MYD-88 immunophenotype is usually observed. In contrast to PCMZL and PCFCL, both cutaneous relapses and the development of extracutaneous disease are common, and the 5-year overall survival is only about 50%. A very small subset of PCLBCL (such as intravascular PCLBCL or anaplastic or plasmablastic PCLBCL) is categorized as PCLBCL, other.[1]

Diagnosis and Evaluation

Evaluation of patients with suspected PCBCL should follow the basic protocol recommended by ISCL/USCLC/EORTC previously discussed.[7] A thorough skin and lymph node examination and a PET/CT are warranted.[103] In addition, a bone marrow biopsy is needed for PCBCL-LT and should be strongly considered in PCFCL (rate of bone marrow involvement may be as high as 11%). In other cases, the need for bone marrow biopsy is left to the discretion of the treating physician. A further component for the evaluation of PCBCL in Europe includes evaluation for *Borrelia burgdorferi* infection.[1,104] The *Borrelia* subspecies *Borrelia afzelii* that appears to be the causative organism is not found in the United States.[105]

Staging and Prognosis

PCBCLs should be staged in accordance with the ISCL/EORTC staging system for non-MF/SS cutaneous lymphomas (Table 86.6). In 2011, the International Extranodal Lymphoma Study Group released the CLIPi for indolent CBCL. Independent prognostic factors associated with progression-free survival included serum LDH, morphology (nodule vs other), and number of distinct cutaneous sites of disease (greater than two). One point is scored for each factor, and patients are grouped into low risk (score 0), intermediate risk (score 1), and high risk (score 2 or 3), with associated 5-year progression-free survival rates of 91%, 64%, and 48%, respectively.[106] The clinical utility of this prognostic system in determining risk-adapted therapy remains unclear.

Treatment

No prospective randomized clinical trial data are available to help guide treatment decisions, but the ISCL/EORTC recently performed an extensive survey of the literature pertaining to the treatment of the PCBCLs and published consensus recommendations. The ILROG has also published treatment guidelines for the use of radiation therapy in the B-cell cutaneous lymphomas.[29]

Primary Cutaneous Marginal Zone B-Cell Lymphoma and Primary Cutaneous FollicleCenter B-Cell Lymphoma

PCMZL and PCFCL are not expected to be associated with decreased survival relative to control populations (although PCFCL arising in the leg may have a worsened prognosis under the WHO/EORTC classification), and therefore, side effects of proposed treatments should be carefully considered. Treatment options include local superficial irradiation, surgical excision, intralesional IFN-α, local and systemic rituximab, antibiotics (where *B. burgdorferi* is endemic), and chemotherapy.

Local Superficial Irradiation

In the ISCL/EORTC literature review, 132 patients with PCMZL treated with local superficial irradiation were identified, and a 99% CR rate was observed. Doses ranged from 30 to 45 Gy, and field margins ranged from 1 to 5 cm. Although cutaneous relapse of disease occurred in 46% of patients, extracutaneous progression occurred in only 2% of patients. For PCFCL, 460 patients treated with radiation were reviewed, and the CR rate was 99% with a 30% relapse rate. Doses ranged from 20 to 54 Gy, and margins were 0.5 to 5+ cm. National guidelines recommend a definitive dose of 24 to 30 Gy. Local superficial irradiation to 4 Gy in two fractions has been shown to yield a 72% CR rate for PCMZL and PCFCL and is recommended as a palliative dose.[27,107]

Surgery

Excision is associated with a 99% CR rate and 43% cutaneous relapse rate in PCMZL and a 98% CR rate and 40% cutaneous relapse rate in PCFCL.[107]

Rituximab

Systemic rituximab (monoclonal antibody targeted against CD20) has proven effective as a treatment for non-Hodgkin lymphomas and has been applied to the treatment of PCBCL. In a review of five patients with PCMZL treated with systemic rituximab, the overall response rate was 60%, and in 10 patients with PCFCL treated with systemic rituximab, a 100% overall response rate and 80% CR rate were observed. Intralesional rituximab may also be effective, with a reported CR rate of 89% in nine patients with PCMZL, but with a high relapse rate of 62%. Twelve patients with PCFCL treated with intralesional rituximab had a CR rate of 83% with 40% relapse.[108] In general, rituximab is most useful for a patient who has multiple symptomatic sites of disease.

Chemotherapy

Chemotherapy is appropriate only for patients with symptomatic disease who have failed prior therapy, including rituximab. Single-agent treatment with chlorambucil was evaluated in 14 patients with PCMZL, and a CR rate of 64% with a 33% relapse rate was observed. Multiagent chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) was also evaluated in 33 patients with PCMZL, and an 85% CR rate with a 57% relapse rate was observed. In 104 patients with PCFCL treated with CHOP or CHOP-like regimens, an 85% CR rate with a 48% relapse rate was reported.[107]

International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer Recommendations

For patients who have only one or a few lesions clustered in one region, radiation (30 Gy or more) using a margin of 1 to 1.5 cm is highly effective. Patients presenting with a single small lesion may be treated with resection alone. Scattered lesions that cannot easily be encompassed in one or a few radiation fields may be carefully observed, with treatment reserved for only the most concerning or symptomatic sites. In the setting of diffuse disease, systemic rituximab should be considered. Of note, cutaneous relapses are common, and relapsed disease often responds to retreatment and does not predict for worsened overall survival rate.[107]

Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type

PCDLBCL-LT is a significantly more aggressive entity in comparison to PCMZL and PCFCL. It is managed similarly to systemic DLBCL (R-CHOP), with radiation usually employed for local control.

Local Superficial Irradiation

The ISCL/EORTC literature review found 101 patients with PCDLBCL-LT treated with radiation. In contrast to the more indolent lymphomas in which CR rates were close to 100%, the CR rate for PCDLBCL-LT was lower at 88%. The rate of cutaneous relapse rate was high (58%), and even more concerning, 30% of patients were found to have extracutaneous progression of disease. Generally, higher doses are used for this entity (24-36 Gy), depending upon the response to chemotherapy.

Rituximab

Systemic rituximab in PCDLBCL-LT has been investigated (dose 375 mg/m^2 weekly for 4-8 weeks) and yielded a CR rate of 38%. Relapse rates are as yet unknown, and additional follow-up is necessary.[107] However, single-agent rituximab should only be used with palliative intent. Primary treatment should include a combination of rituximab and chemotherapy.

Chemotherapy

Multiagent chemotherapy regimens have been tested in PCDLBCL-LT, and in 32 patients treated with CHOP or CHOP-like regimens, an 81% CR rate has been observed. However, despite aggressive therapy, relapse rates remain high at 54%.[107]

International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer Recommendations

Based on the aggressive nature of PCDLBCL-LT and its propensity to develop extracutaneous disease, the recommended treatment in patients able to tolerate multiagent chemotherapy is R-CHOP, with the likely addition of local superficial radiation to distinct cutaneous lesions. In the subset of patients unable to tolerate a multiagent course of chemotherapy, systemic

rituximab may be considered. Alternatively, an aggressive course of radiation to all cutaneous sites of disease may be considered, but relapse is likely.[107]

PRECURSOR HEMATOLOGIC NEOPLASMS

The third category of cutaneous lymphomas in the WHO/EORTC system is precursor hematologic neoplasms/immature hematologic malignancies. At present, this category primarily references $CD4^{+}/CD56_{+}$ hematodermic neoplasm (also referred to as blastic NK cell lymphoma or blastic plasmacytoid dendritic cell neoplasm), which is characterized by the development of red or violaceous cutaneous nodules. Biopsy reveals cutaneous infiltration of abnormal cells with an appearance reminiscent of lymphoblasts and myeloblasts. The origin of the tumor cells in $CD4^{+}/CD56^{+}$ hematodermic neoplasm is unclear. Immunohistochemistry indicates that the tumor cells lack CD3 and CD8 and express both CD4 and CD56. The expression of CD56 initially led investigators to believe these cells were of NK origin. However, the concomitant expression of CD4 and CD56 is unusual, and further exploration led to the identification of expression of CD123 and TCL1 in these tumor cells, which suggests a possible origin in plasmacytoid dendritic cells. Examination of TCR status in these cells indicates it remains in germline configuration, providing further support for the notion that these cells are not derived from a B- or T-cell lineage. $CD4^{+}/CD56^{+}$ hematodermic neoplasm is an aggressive malignancy, and it is common for patients to harbor nodal or systemic disease at diagnosis. Due to the propensity for systemic spread of disease, skin-directed therapies are usually unlikely to control disease, and chemotherapy is often necessary. Although chemotherapy may induce remission of disease, the duration of remission is typically relatively brief, and median survival is only 14 months.[1]

SUMMARY

The primary cutaneous lymphomas are a diverse group of extranodal non-Hodgkin lymphomas, each with distinct a biologic activity. A correct histopathologic diagnosis is critical to the determination of appropriate

management. Although significant advances in therapy have been made since the recognition of MF in 1806, numerous questions remain unanswered regarding the pathophysiology and optimal treatment of the cutaneous lymphomas. Advances in genomic profiling of the cutaneous lymphomas may yield greater insight into the molecular bases of these diseases and help identify better and more individualized therapies. Recent efforts to develop improved prognostic indices and uniform criteria for the classification of disease and response to treatment should facilitate ongoing international collaborations. Due to the rarity of these diseases, large multi-institutional collaborative efforts are critical to the advancement of our understanding of primary cutaneous lymphomas.

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CHAPTER 87

Leukemia

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The leukemias are a group of neoplastic disorders of the hematopoietic system, characterized by aberrant or arrested differentiation that results in unlimited proliferative potential of cells within the hematopoietic lineage (Figure 87.1). Leukemias are not only typically highly radiosensitive but also widely disseminated with respect to anatomy (ie, the entire bone marrow and blood compartment), with limited settings in which radiation can be used to help improve outcomes. The role of radiotherapy (RT) in up-front curative treatment is largely to deliver central nervous system (CNS) treatment in combination with systemic therapy for patients with acute lymphocytic leukemia (ALL) with evidence of CNS involvement. While the role of CNS prophylaxis in childhood ALL has declined over the past 15 years because of toxicity concerns, it remains an important component of therapy for high-risk patients. Radiation oncologists must also be familiar with certain palliative situations unique to the leukemias, including myeloid sarcomas (macroscopic tumors composed of leukemic cells also known as extramedullary acute myeloid leukemia [eAML] tumors), splenomegaly (due to direct involvement with leukemic cells or extramedullary hematopoiesis [EMH]), and chemotherapy-refractory CNS recurrence. Lastly, radiation oncologists must be at least peripherally familiar with total body irradiation (TBI) (discussed elsewhere), as the latter is often part of an allogeneic hematopoietic stem cell transplant (allo-HSCT) program.

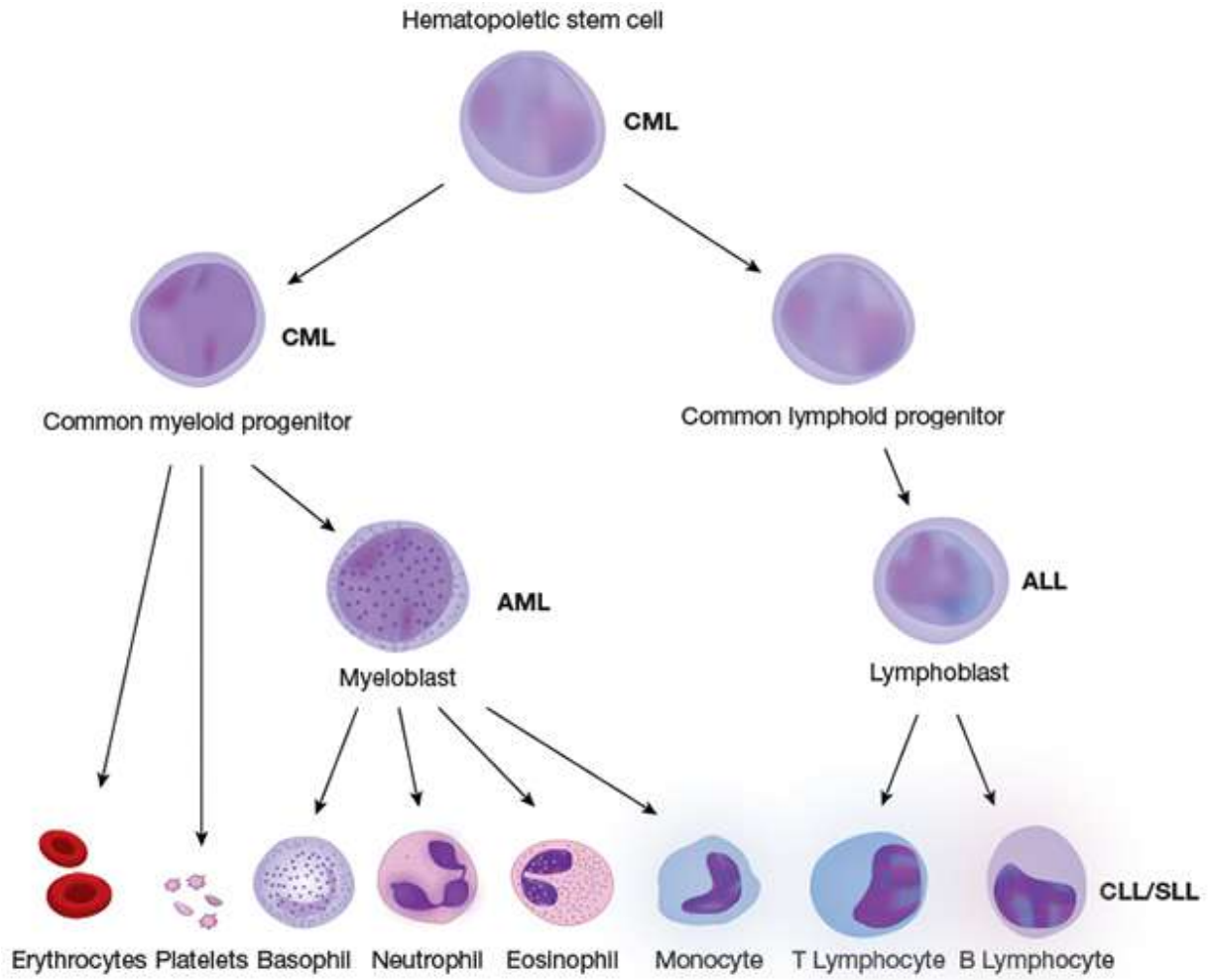


FIGURE 87.1 Hematopoietic stem cells naturally divide into common myeloid (marrow) and lymphoid progenitors. These subsequently differentiate into immature, rapidly growing blast cells, which then undergo additional differentiation into mature, functionally normal components of the blood. Acute myeloid (AML) and acute lymphoid leukemias (ALL) are characterized by an excess of blasts (myeloblasts and lymphoblasts, respectively), reflecting their relatively undifferentiated and rapid disease course. At the other extreme, CLL/SLL reflects mature lymphoid cells. CML can include not only multiple cell histologies ranging from the common myeloid progenitors to differentiated myeloid cells but can also lymphoblasts. Thus, it is shown in both locations on the diagram (common myeloid progenitor as well as hematopoietic stem cell). CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.

Cure rates of childhood ALL have improved from approximately 10% in the 1960s to over 90% with modern treatment,[1] with frontline Children's Oncology Group (COG) trials from 1996 to 2014 reporting 12% relapse rates,[2] improved from the 20% relapse rate reported by COG in 2008.[3] Initial remissions generally occurring in about 90%.[1,4-6] In adults, initial

remission rates are generally equally high, but cure rates are only in the 30% to 45% range.[7] In contrast to the situation in pediatric ALL, pediatric AML generally fairs less well, with 60% cure rates, although this represents a marked improvement since the 1970s when cure rates were roughly 20%.[6] Adult AML cures are less frequent in the overall population, in large part a reflection that this disease principally afflicts older individuals. About 20,000 new cases are diagnosed per year in the United States, with 11,000 patients dying from the disease.[8] Allo-HSCT has specifically targeted refractory/recurrent ALL and AML. Reduced-intensity transplants are being used to address the needs of high-risk older patients with acute leukemia.

A notable recent addition to the armament in systemic therapies for B-cell ALL includes chimeric antigen receptor T-cell (CAR T) therapy. CAR T therapy involves harvesting a patient's T cells (ie, "apheresis"), genetically engineering them to express a recombinant T-cell receptor that targets a protein that is highly expressed on the surface of B-cell malignancies (CD19), and then reinfusing these cells into the patient after lymphodepleting therapy. CAR T therapy in B-cell ALL has been associated with long-term durable remissions,[9] with 55% to 59% of patients remaining disease free a year after treatment.[10] The use of radiation in combination with CAR T therapy has not been reported in patients with leukemia. However, studies of patients receiving CAR T therapy for lymphoma or multiple myeloma suggest no evidence of increased toxicity in patients receiving RT immediately prior to or following CAR T.[11-15]

Chronic myelogenous leukemia (CML) and chronic lymphocytic leukemia (CLL) are primarily diseases of adults and have natural histories measured in years to decades. While both chronic leukemias can transform into more aggressive diseases, CML can progress to a more acute disease or blast crisis in its terminal phase. Allo-HSCT is associated with a high cure rate for patients with CML if conducted early in the chronic phase of the disease. However, due to the widespread use of the BCR-ABL tyrosine kinase inhibitors (TKIs), the use of allo-HSCT for CML has declined dramatically over the past two decades.[16]

CML, ALL, and AML, but not CLL, have all been associated with exposure to ionizing radiation, with at least one study reporting a risk with exposures of even less than 1 Gy in atomic bomb survivors,[17] an estimated 2.5-fold increased risk of following therapeutic thyroid cancer treatment

with I-131,[18] and at least one report observing that radiation-related leukemia may be more resistant to treatment compared with nonradiation cases.[19]

A BRIEF HISTORICAL PERSPECTIVE OF LEUKEMIA CLASSIFICATION

The term *leukemia* comes from the Greek word roots meaning "white blood" with early variants of the term including the more precise *leukocythemia* or "white cell blood" (WBC).[20] All leukemias were initially bundled under this single entity, characterized as a fatal condition in adults who presented with general ill health and a range of potential symptoms that could include frequent hemorrhage, abnormally thickened blood, lymphatic masses, and/or splenomegaly. At this time in the mid-1800s, clinical microscopy was in its infancy and was only able to distinguish normal red blood cells from nonred (clear, ie "white") cells. Leukemia was, therefore, characterized by a reversal of the roughly approximately 300:1 red-to-white cell ratio seen in the blood of healthy patients. During the latter half of the 1800s, it was discovered that blood was formed within the bone marrow from ancestral (ie, stem) cells, that leukemia was in fact a disease of the bone marrow, and that bone marrow biopsies could be used to aid in diagnosis.[21]

The introduction of triacid stains enabled the ability to further distinguish between subtypes of WBCs as granulocytes versus lymphocytes. Granulocytes were known to come from the bone marrow, whereas lymphocytes arose from lymphoid tissues. Leukemias were thus able to be classified into myelogenous (from the Greek for "originating in the bone marrow") versus lymphoid (from the Greek for "resembling lymph tissues") subtypes. By 1900, the primitive precursor myeloblasts and lymphoblasts had been identified as hallmarks of rapidly progressive disease, and the presence of blast cells was used to further distinguish acute (vs chronic) leukemias. Diagnosis of both AML and ALL, for example, to this day in some circumstances requires that 20% or more blast cells (myeloblasts and lymphoblasts, respectively) be present among nucleated cells (ie, not red blood cells) within the bone marrow or peripheral blood.

Further clinical experience and advances in histology led to the French-American-British (FAB) morphologic criteria, which remained in use until the turn of the 21st century. In this system, AML and its subtypes were identified microscopically by morphologic features including the presence of Auer rods, and cytochemistry staining for myeloperoxidase or monocyte-associated esterases, and other markers. Certain genetic abnormalities, particularly translocations, were also found to be common to each AML subtype. The FAB assignment of subtypes was replaced by the World Health Organization (WHO) in 2002[22] and most recently updated in the 2022 classification.[23,24] Most of these entities previously covered by the FAB morphologic criteria, with the exception of Burkitt, which is classified as lymphoma, fall under the category of precursor lymphoid neoplasms.[23]

ACUTE LEUKEMIAS

Current Classification Systems and Risk Stratification

The WHO classification scheme for myeloid neoplasms was most recently updated in 2022 (fifth edition).[24] The competing International Consensus Classification was released in 2022 as well.[25] The new acute leukemia subgroups have been developed to highlight meaningful biologic and genetic differences between disease entities with differing prognoses and clinical behavior. The latest WHO classification creates two key subgroups for AML: AML with defining genetic abnormalities (including with *RUNX1::RUNX1T1* fusion due to t(8;21), *CBFB::MYH11* fusion due to inv(16) and acute promyelocytic leukemia (APML) with *PML::RARA* fusion due to t(15;17), among others); AML defined by differentiation (similar to previous FAB subgroups; Table 87.1). For ALL, the WHO 2022 subcategorizes disease into B-cell lymphoblastic leukemia/lymphoma, not otherwise specified (NOS); B-cell leukemia/lymphoma with recurrent genetic abnormalities; and T-lymphoblastic leukemia/lymphoma, NOS; and early T-precursor lymphoblastic leukemia/lymphoma (ETP-ALL).[23] Acute lymphoblastic leukemia and lymphoblastic lymphoma are considered the same disease with latter predominantly affecting extramedullary sites, including lymph nodes, liver, and spleen. In this chapter, both conditions are abbreviated as ALL (Table 87.2).

TABLE 87.1 2022 WHO CLASSIFICATION OF AML

AML with defining genetic abnormalities
Acute promyelocytic leukemia with *PML::RARA* fusion
AML with *RUNX1::RUNX1T1* fusion
AML with *CBFB::MYH11* fusion
AML with *DEK::NUP214* fusion
AML with *RBM15::MRTFA* fusion
AML with *BCR::ABL1* fusion
AML with *KMT2A* rearrangement
AML with *MECOM* rearrangement
AML with *NUP98* rearrangement
AML with *CEBPA* mutation
AML, myelodysplasia related
AML with other defined genetic abnormalities
AML, defined by differentiation
AML with minimal differentiation
AML without maturation
AML with maturation
Acute basophilic leukemia
Acute myelomonocytic leukemia
Acute monocytic leukemia
Acute erythroid leukemia
Acute megakaryoblastic leukemia

AML, acute myeloid leukemia; WHO, World Health Organization.
Adapted from Arber DA, Orazi A, Hasserjian RP, et al. International consensus classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data. *Blood*. 2022;140(11):1200-1228. Copyright © 2022 American Society of Hematology. With permission.

TABLE 87.2 2022 WHO CLASSIFICATION OF SELECT B- AND T-CELL LYMPHOID MALIGNANCIES

Precursor lymphoid neoplasms
• B-cell lymphoblastic leukemias/lymphomas

- B-lymphoblastic leukemia/lymphoma, not otherwise specified (NOS)
- B-lymphoblastic leukemia/lymphoma with high hyperdiploidy
- B-lymphoblastic leukemia/lymphoma with hypodiploidy
- B-lymphoblastic leukemia/lymphoma with iAMP21
- B-lymphoblastic leukemia/lymphoma with *BCR::ABL1* fusion
- B-lymphoblastic leukemia/lymphoma with *BCR::ABL1*-like features
- B-lymphoblastic leukemia/lymphoma with *KMT2A* rearrangement
- B-lymphoblastic leukemia/lymphoma with *ETV6::RUNX1* fusion
- B-lymphoblastic leukemia/lymphoma with *ETV6::RUNX1*-like features
- B-lymphoblastic leukemia/lymphoma with *TCF3::PBX1* fusion
- B-lymphoblastic leukemia/lymphoma with *IGH::IL3* fusion
- B-lymphoblastic leukemia/lymphoma with *TCF3::HLF* fusion
- B-lymphoblastic leukemia/lymphoma with other defined generic abnormalities

- T-cell lymphoblastic leukemia/lymphoma
  - T-lymphoblastic leukemia/lymphoma, NOS
  - Early T-precursor lymphoblastic leukemia/lymphoma

Mature lymphoid neoplasm

- Mature B-cell neoplasms
  - Chronic lymphocytic leukemia/small lymphocytic lymphoma
  - Splenic B-cell lymphomas and leukemias
  - Lymphoplasmacytic lymphoma
  - Marginal zone lymphoma
  - Cutaneous follicle center lymphoma
  - Mantle cell lymphoma
  - Transformations of indolent B-cell lymphomas
  - Large B-cell lymphomas
  - Burkitt lymphoma
  - KSHV/HHV8-associated B-cell lymphoid proliferations and lymphomas
  - Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation
  - Hodgkin lymphoma
- Mature T-cell neoplasms
  - Mature T-cell and NK cell leukemias
  - Primary cutaneous T-cell lymphomas
  - Intestinal T-cell and NK cell lymphoid proliferations and lymphomas
  - Hepatosplenic T-cell lymphoma
  - Anaplastic large cell lymphoma
- Nodal T-follicular helper cell lymphoma
  - Peripheral T-cell lymphomas
  - EBV-positive NK/T-cell lymphomas

- EBV-positive T- and NK cell lymphoid proliferations and lymphomas of childhood

EBV, Epstein-Barr virus; NK, natural killer; WHO, World Health Organization.

Adpated from Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: lymphoid neoplasms. *Leukemia*. 2022;36(7):1720-1748. http://creativecommons.org/licenses/by/4.0/.

As may be apparent from the previous discussion of the transition from the FAB to the WHO criteria for categorization, immunophenotyping, cytogenetic, and molecular markers have become very important in the classification of leukemia. Flow cytometry with specific monoclonal antibodies can be used to assay for a panel of antigens, often known as *cluster of differentiation (CD) molecules*, that define leukocyte maturation. For instance, CD19 and cytoplasmic CD79a define B-cell lineage, whereas cytoplasmic or surface CD3 defines T-cell lineage. Myeloid cells are correlated with positivity for CD13 and CD33, but cytoplasmic myeloperoxidase is required to definitively assign the cell to myeloid linage. The common ALL antigen (CALLA, CD10) is expressed in about 85% of ALL cases. With other markers defining different degrees of differentiation and maturation, ALL is conventionally divided into T-cell and B-cell lineage. T-cell ALL can be further characterized based on immunophenotype as ETP-ALL, which is associated with a worse prognosis.

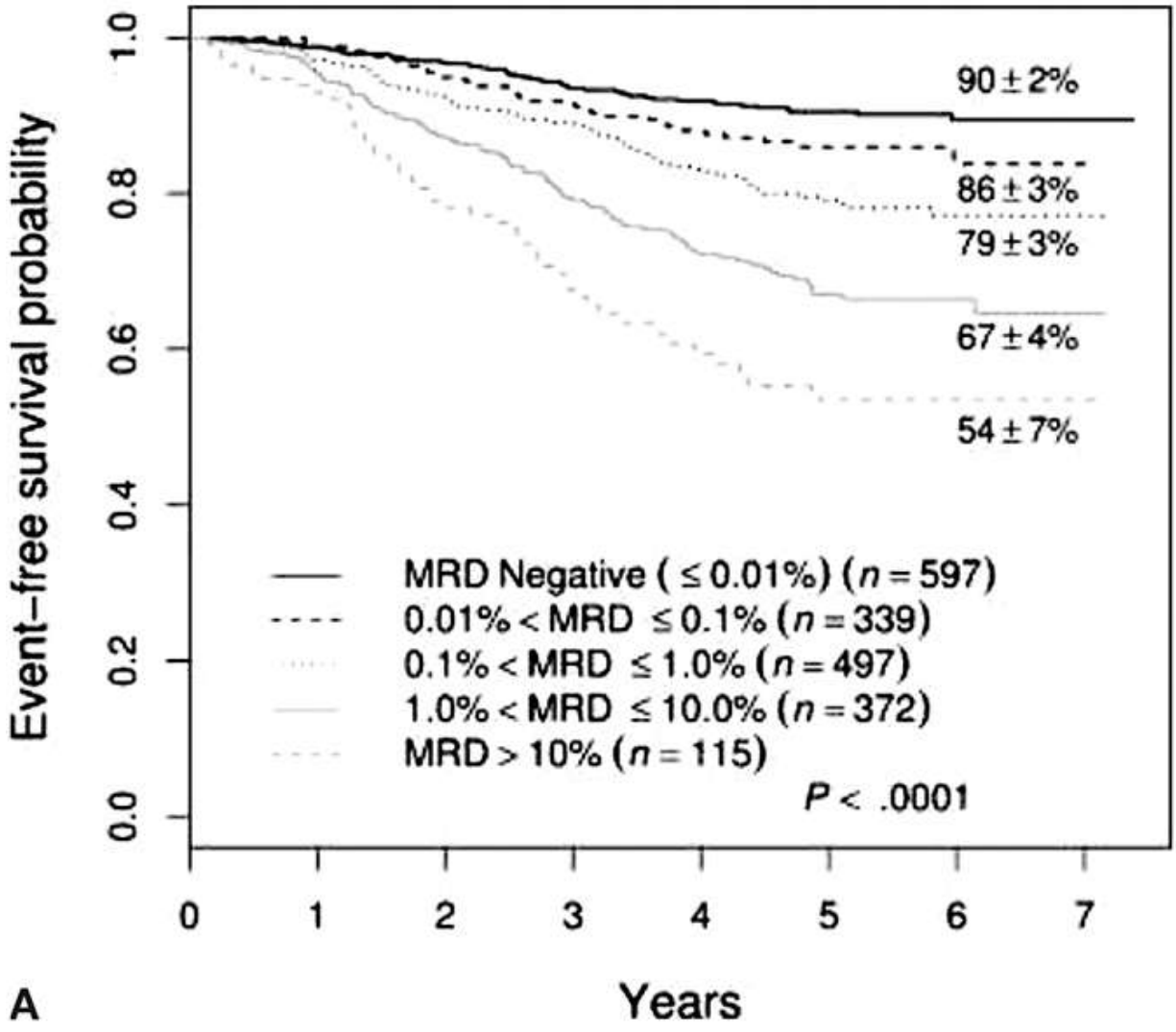
Cytogenetic or chromosomal abnormalities occur in up to 90% of ALL cases. Of these, roughly two-thirds are nonrandom, falling into distinct patterns. Specific cytogenetic abnormalities have important prognostic and therapeutic implications in ALL. Chromosomal translocations occur in approximately 15% of pediatric ALL, and a bit higher in adult cases. The oldest known is the *BCR::ABL1* fusion due to t(9;22), which forms the Philadelphia (Ph) chromosome. This translocation is associated with a higher risk of CNS involvement and overall poorer prognosis. Adult and childhood forms of ALL have distinctly different patterns of genetic abnormalities as well as immunophenotyping. This may partially explain the poorer prognosis in older patients. For example, *BCR::ABL1* fusion occurs in 4% of childhood ALL cases compared to about 25% in adults; moreover, this genetic lesion now represents an important therapeutic target with the development of TKIs, which led to improved outcomes in this

disease. On the other hand, a new subtype of B-cell ALL with *BCR::ABL1*-like features in the setting of multiple genetic aberrations including ABL-class fusions involving *ABL1, ABL2, CSF1R*, and *PDGFRB* that phenocopy *BCR::ABL1* and alterations of *CRLF2, JAK2*, and *EPOR* that activate JAK/STAT signaling are associated with poor prognosis.[26] In addition to specific genomic alterations, abnormal DNA ploidy is extremely common, with two noted patterns that seem to be clinically important. Hyperdiploidy with greater than 51 chromosomes per cell (or DNA index ≥1.6) occurs in 25% of children with ALL. Although there is some association with favorable clinical factors (age >10 years and low presenting leukocyte counts), hyperdiploidy is an independent favorable factor; however, in adults with ALL, outcomes are poor, even in the presence of hyperdiploidy. In childhood ALL, the most common trisomies involve chromosomes 4, 10, and 17 and are associated with a good prognosis. Conversely, hypodiploidy of less than 45 chromosomes is associated with a more unfavorable outcome.

The aforementioned laboratory assessment and clinical disease features have led to distinct risk stratification categories, at least as far as childhood ALL is concerned. Clinical prognostic features of B-cell leukemias have been commonly used to place patients into risk groups. Using the National Cancer Institute's risk classification scheme, standard risk includes patients (two-thirds of pediatric patients with B-cell ALL) whose age at diagnosis is between 1 and 10 years as well as a presenting leukocyte count of less than 50,000/μL, in the absence of CNS involvement, was historically associated with an 80% 4-year disease-free survival (DFS).[27] High-risk patients—defined as a high WBC count, age below 1 year or above 10 years, or CNS involvement at diagnosis—had a corresponding 65% 4-year DFS. T-cell phenotype occurs in 12% to 15% of pediatric ALL cases and is thought to convey a poorer prognosis due to numerous unfavorable clinical correlations, including older age, male sex, elevated WBC count, extensive extramedullary disease including mediastinal and peripheral adenopathy or hepatosplenomegaly, and a higher tendency for relapse in the CNS and testes in males.[28] Current clinical practice is for T-cell leukemias to be treated on different protocols than B-lineage ALL. However, when one factors out unfavorable clinical features, the prognostic difference between T- and B-cell ALL is difficult to discern. In regard to B-cell ALL, current

protocols assign patients to low, standard, and high risk. Low-risk patients are operationally defined by age (1-10 years old) and standard-risk features along with anticipated rapid early response to induction chemotherapy.[29] Apart from this, the intensity of the treatment program is of importance as shown by the fact that adolescents and young adults treated on pediatric leukemia regimens have had better outcomes than those treated on adult programs.[30]

The response to induction chemotherapy has also been proven to be an extremely important prognostic category. In pediatric ALL, the concept of measurable (previously called minimal) residual disease (MRD) detected by flow cytometry or polymerase chain reaction (PCR) of postinduction peripheral blood or marrow aspirates has led to critical prognostic stratification that cannot be underestimated as it is a single most important prognostic factor for patients with ALL (hence the name change from "minimal" to "measurable"). A new method to identify the presence of MRD using next-generation sequencing techniques with the depth of MRD detection at 10^{-6} (superior to PCR and flow cytometry) is increasingly being used.[31] From the assessment of MRD, the concept of risk-adapted therapy has allowed for improved outcomes with the intensification of therapy, including allo-HSCT in those patients who continue to have detectable lymphoblasts after initial chemotherapy (Figure 87.2).


Event–free survival probability
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
6
7
Years
90 ± 2%
86 ± 3%
79 ± 3%
67 ± 4%
54 ± 7%
MRD Negative (≤ 0.01%) (n = 597)
0.01% < MRD ≤ 0.1% (n = 339)
0.1% < MRD ≤ 1.0% (n = 497)
1.0% < MRD ≤ 10.0% (n = 372)
MRD > 10% (n = 115)
P < .0001

A

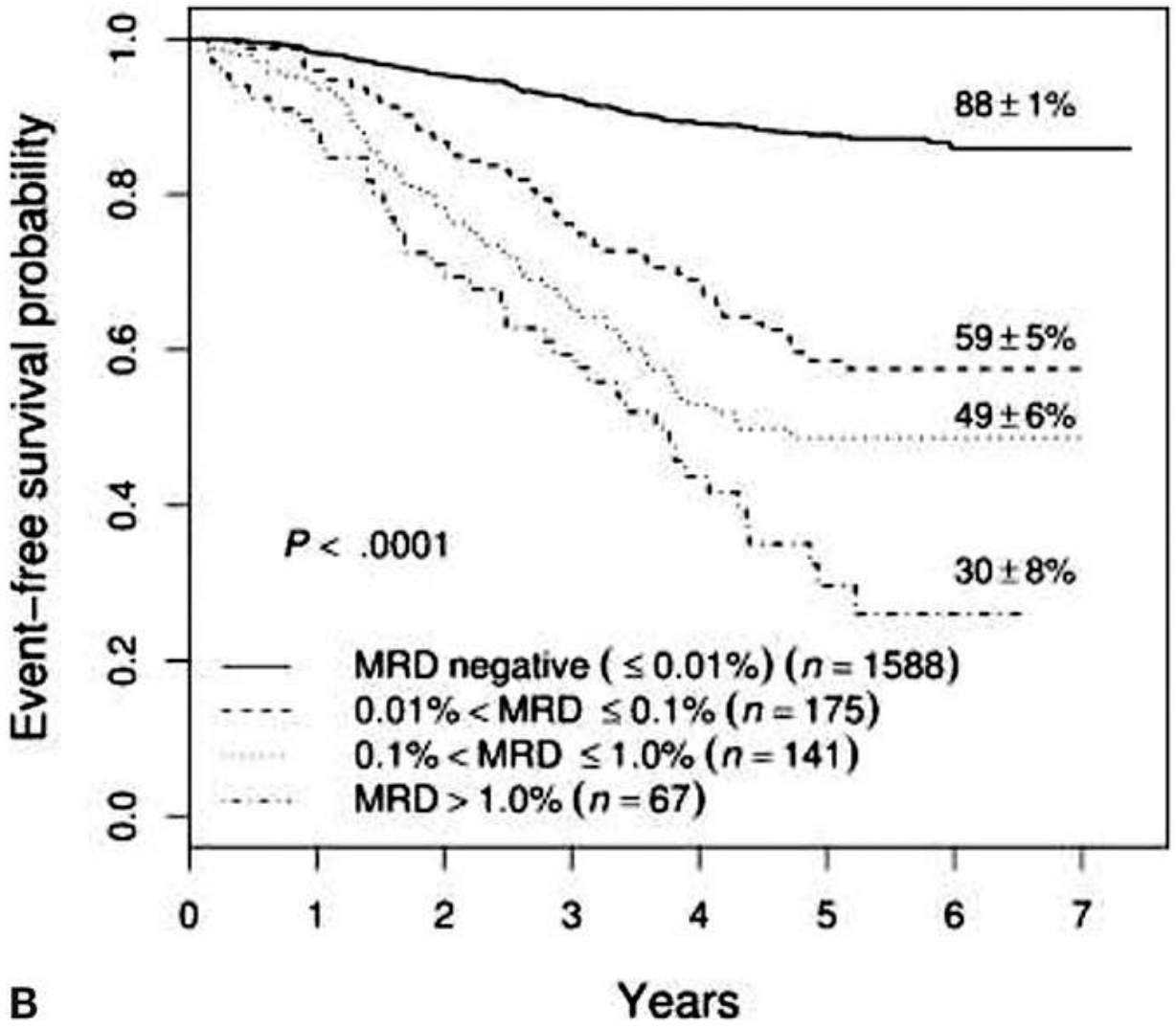


FIGURE 87.2 The prognostic importance of measurable residual disease (MRD) after induction chemotherapy for acute lymphoblastic leukemia (ALL). A. Event-free survival (EFS) of patients with ALL as a function of level of day-8 PB MRD. B. EFS of patients with ALL as a function of level of day-29 marrow MRD. (Reprinted from Borowitz MJ, Devidas M, Hunger SP, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. *Blood*. 2008;111[12]:5477-5485. Copyright © 2008 American Society of Hematology. With permission.)

Assessment of CNS involvement at diagnosis in ALL is critical for risk stratification, which is of particular importance to the radiation oncologist. Unfortunately, despite low sensitivity and specificity, cerebrospinal fluid (CSF) cytospin smear analysis and cytology remain the primary means of determining CNS involvement at diagnosis. In addition to CSF, clinical CNS involvement may be detected clinically through the presence of

neurologic symptoms, magnetic resonance imaging (MRI) findings, or slit-lamp examination (in the setting of visual symptoms). Emerging technologies such as quantitative flow cytometry,[32,33] clone-specific PCR, or other CSF-based cytokines or microRNAs may offer improved detection but are not widely available or routinely used at present.[34] Unequivocal CNS involvement (CNS-3) is defined by a CSF leukocyte count of 5 WBC/μL or greater along with either blast cells on cytospin, the presence of cranial nerve (CN) palsy, gross disease by MRI of the brain or spine, or fundoscopic findings. CNS-1 is defined as no blast cells on CSF cytology, whereas CNS-2 is less than 5 WBC/μL with blast cells present. Clinical data are conflicting as to the prognostic importance of CNS-2, reflecting the fact that CNS involvement is not simply a distinction of being present or absent, but that it has also been associated with improved control with more intensive systemic and intrathecal (IT) therapies.[35,36] Traumatic lumbar puncture at diagnosis has been associated with a worse prognosis.[37] Patients with CNS-3 disease who have more intensive IT chemotherapy along with cranial radiation within the first year of therapy have similar event-free survival (EFS) as patients with CNS-2. COG stratification of CNS involvement has added complexity, taking into account a correction formula for traumatic lumbar punctures (the so-called Steinherz-Bleyer algorithm; Table 87.3).[38-41] CNS-2 and CNS-3 are further subgrouped. Regardless, patients with CNS-3 disease are allocated to high-risk treatment protocols.

TABLE 87.3 ASSIGNMENT OF CNS STATUS AT DIAGNOSIS OF PEDIATRIC ALL[42]

CNS-1	In CSF, absence of blasts on cytospin preparation, regardless of the number of WBCs
CNS-2	In CSF, presence of <5/μL WBCs and cytospin positive for blasts, or ≥5/μL WBCs but negative by Steinherz-Bleyer algorithm[a]
CNS-2a	<10/μL RBCs; <5/μL WBCs and cytospin positive for blasts
CNS-2b[b]	≥10/μL RBCs; <5/μL WBCs and cytospin positive for blasts
CNS-2c[b]	≥10/μL RBCs; ≥5/μL WBCs and cytospin positive for blasts but negative by Steinherz-Bleyer algorithm
CNS-3	In CSF, presence of ≥5/μL WBCs and cytospin positive for blasts and/or clinical

	signs of CNS leukemia
CNS-3a	<10/μL RBCs; ≥5/μL WBCs and cytospin positive for blasts
CNS-3b[b]	≥10/μL RBCs; ≥5/μL WBCs and positive by Steinherz-Bleyer algorithm
CNS-3c	Clinical signs of CNS leukemia (such as facial nerve palsy, brain/eye involvement, or hypothalamic syndrome)

ALL, acute lymphocytic leukemia; CNS, central nervous system; CSF, cerebrospinal fluid; RBC, red blood cell; WBC, white blood cell.

[a]The Steinherz-Bleyer algorithm provides a method of evaluating initial traumatic lumbar punctures (TLPs): If the patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic and contains ≥ 5 WBC/μL and blasts, the following algorithm should be used to distinguish between CNS-2 and CNS-3 disease:

CSF WBCx/CSF RBCx > 2× blood WBCx/blood RBCx.

A patient with CSF WBC ≥ 5/μL blasts, whose CSF WBC/RBC is 2 times greater than the blood WBC/RBC ratio, has CNS disease at diagnosis.

[b]CNS status that can be assigned after a TLP with blasts.

AML patient risk stratification is based on cytogenetic and molecular characteristics, de novo versus secondary nature of the disease (Table 87.4). The presence of complex karyotype abnormalities, FLT3-ITD, and TP53 mutations, among others, may justify a more aggressive treatment approach. In addition, the presence of MRD after induction chemotherapy in certain subtypes of AML including with *NPM1* mutation and with *RUNX1::RUNX1T1*, *CBFB::MYH11* fusion considered a good prognosis based on European Leukemia Net criteria is associated with a significant risk of relapse and may dictate the need for allo-HSCT rather than chemotherapy consolidation.[41] Selecting treatment for older patients with AML should take into consideration not only disease characteristics but also patient's characteristics such as age, comorbidities, and performance status with induction chemotherapy reserved for fit patients and less intense regimens aimed at preserving the quality of life for others.[43]

TABLE 87.4 2022 EUROPEAN LEUKEMIA NET RISK CLASSIFICATION OF AML BY GENETIC ABNORMALITIES IDENTIFIED AT THE TIME OF DIAGNOSIS

Favorable risk

- t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*
- inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*

- Mutated *NPM1* without *FLT3*-ITD
- bZIP in-frame–mutated *CEBPA*

Intermediate risk

- Mutated *NPM1* with *FLT3*-ITD
- Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions)
- t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A*
- Cytogenetic and/or molecular abnormalities not classified as favorable or adverse

Adverse risk

- t(6;9)(p23.3;q34.1)/*DEK::NUP214*
- t(v;11q23.3)/*KMT2A* rearranged
- t(9;22)(q34.1;q11.2)/*BCR::ABLq*
- t(8;16)(p11.2;p13.3)/*KAT6A::CREBBP*
- inv(3)(q21.3;q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)*
- t(3q26.2;v)/*MECOM(EVI1)* rearranged
- −5 or del(5q); −7; −17/abn(17p)
- Complex karyotype; monosomal karyotype
- Mutated *ASXL1*, *BCOR, EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, and/or *ZRSR2*
- Mutated *TP53*

AML, acute myeloid leukemia.

Reprinted from Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood*. 2022;140(12):1345-1377. Copyright © 2022 American Society of Hematology. With permission.

Treatment of Acute Myeloid Leukemias

Classic induction therapy for AML consists of an anthracycline on days 1 to 3 along with cytarabine (cytosine arabinoside, ara-C) for 7 days. APML represents an exception to this rule. In many cases, the coagulopathy predisposing to severe bleeding including intracranial and pulmonary hemorrhage as well as associated *PML::RARA* fusion in APML are best managed with a combination of all-*trans*-retinoic acid and arsenic trioxide, which promote differentiation and apoptosis of malignant promyelocytes.[44,45] Patients with high-risk APML defined by WBC greater than 10,000/μL are treated with the combination of differentiating agents and chemotherapy including CD33 antibody-drug conjugate gemtuzumab ozogamicin and anthracyclines.[46] For the remainder of the AML subtypes, daunorubicin and idarubicin are the anthracyclines most commonly used in

induction chemotherapy regimens. Remission rates vary from 50% to 80% depending on patient age, karyotype, and subtype of AML.

Patients younger than age 60 have complete remission (CR) rates of 70% to 80%, whereas older patients tend to have lower CR rates of 50% to 60%. Patients who develop secondary AML following chemotherapy for other cancers have CR rates in the 40% to 50% range. Some induction regimens in children have added other drugs, such as etoposide. Adding other chemotherapy drugs to anthracycline and cytarabine was evaluated in many studies without convincing survival benefit for AML induction in adults[47] until the addition of midostaurin in patients with previously untreated *FLT3* mutation-positive (FLT3+) AML, for which a randomized trial of 717 patients demonstrated an improvement in overall survival (OS) compared with placebo (hazard ratio [HR] 0.77, $P = .016$).[48] The Food and Drug Administration (FDA) approved midostaurin for the treatment of adult patients with newly diagnosed AML who are *FLT3* mutated in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation (RATIFY). Midostaurin approval in 2017 opened the gate for multiple additional drug approvals by FDA in AML (11 drugs in total between 2017 and 2023) including another FLT3 inhibitor quizartinib in combination with 7+3 based on the results of the QuANTUM-First trial.[49] In addition, multiple other targeted agents were approved including IDH1 and IDH2 inhibitors in the second-line setting.[50]

Adults older than 60 years with AML and intermediate- or adverse-risk disease who are not candidates for allo-HSCT are generally considered suitable for treatment with low-intensity palliative therapies, such as low-dose subcutaneous cytarabine and DNA hypomethylating agents (HMAs) (azacitidine, decitabine).[43] Since FDA approval in 2018, most of these patients received treatment of intermediate intensity with HMAs in combination with bcl-2 inhibitor (venetoclax). VIALE-A randomized placebo-controlled phase 3 trial showed improved survival among older patients “unfit” for induction chemotherapy treated with azacitidine and venetoclax when compared to azacitidine and placebo with a median OS of 14.7 versus 9.6 months. Treatment was complicated with febrile neutropenia in 49% versus 19% of patients.[51]

Once remission is achieved, the need for additional therapy has been well documented in large randomized trials due to high rates of subsequent

relapse in the absence of further treatment. Current data suggest that optimal postremission consolidative therapy begins with high-dose ara-C for up to four cycles.[52] Alternatively, additional cycles of anthracycline for 2 days along with conventional-dose cytarabine for 5 days have been used in both younger and older individuals with AML. With the utilization of new drugs, AML outcomes are improving, but cure rates still remain suboptimal (10%-20%) for older patients with intermediate- and adverse-risk diseases, especially if not treated with allo-HSCT. High-dose ara-C has considerable CNS toxicity in older patients and has also been avoided in pediatric protocols. Other drugs used for consolidative treatment or for second-line induction therapy combinations include anthracyclines mitoxantrone, etoposide, fludarabine, and clofarabine, but no one regimen is clearly advantageous. Lower intensity therapies for older patients include FLT-3 inhibitor gilteritinib, IDH1 inhibitors (ivosidenib, olutasidenib), and IDH2 inhibitor (enasidenib), among others (Table 87.5).[53]

TABLE 87.5 NEW DRUGS FOR AML: 2017-2023

Drug (Brand Name)	FDA Approval	Indication	Schedule
Midostaurin (Rydapt)	4/28/17	New dx FLT3-mut AML with 7+3 induction and HiDAC consolidation	PO BID
Enasidenib (Idhifa)	8/1/17	R/R IDH2-mut AML	PO daily
Liposomal daunorubicin and cytarabine (CPX-351, Vyxeos)	8/3/17	New dx therapy-related AML or AML with MDS-related changes	IV days 1, 3, and 5
Gemtuzumab ozogamicin (Mylotarg)	9/1/17	• CD33+ AML in adults • R/R CD33+ AML in adults and children	IV days 1, 3, and 8
Ivosidenib (Tibsovo)	5/3/18 5/2/19 5/25/22	• R/R IDH1-mut AML • Frontline: ≥75 y or ineligible for intensive chemotherapy • Frontline: combination with azacitidine	PO daily

Drug (Brand Name)	FDA Approval	Indication	Schedule
Venetoclax (Venclexta)	11/21/18	New dx AML > 75 yo or ineligible for chemo with azacitidine, decitabine, or low-dose cytarabine	PO daily
Glasdegib (Daurismo)	11/21/18	New dx AML > 75 yo or ineligible for chemo with low-dose cytarabine	PO daily
Gilteritinib (Xospata)	11/28/18	R/R FLT3-mut AML	PO daily
Oral azacitidine (Onureg)	9/1/20	Maintenance for AML in CR1	PO daily, 2 wk on 2 wk off
Olutasidenib (Rezlidhia)	12/1/22	R/R IDH1-mut AML	PO BID
Quizartinib (Vanflyta)	7/20/23	New dx FLT3-mut AML with 7+3 and as maintenance monotherapy following consolidation chemotherapy	PO daily ×2 wk for induction and consolidation; dose for maintenance based on QTcF

AML, acute myeloid leukemia; BID, twice daily; chemo, chemotherapy; CR, complete remission; dx, diagnosis; FDA, Food and Drug Administration; HiDAC, high-dose ara-C; MDS, myelodysplastic syndrome; mut, mutant; PO, oral; R/R, relapsed/refractory.

The Role of Up-front Radiation in Routine Treatment of Acute Myeloid Leukemias

Historically, prophylactic cranial radiation has been used to decrease the risk of CNS and overall recurrence rates following initial therapy for high-risk AML, particularly with CNS-3 disease. However, CNS prophylaxis is no longer routinely used for AML in the setting of low CNS relapse rates (5%-10%), improved systemic and IT up-front prophylactic regimens, reasonably effective salvage therapy options, and, most importantly, the potential for late effects, particularly in the pediatric population. Patients without neurologic symptoms who have a high WBC count (>40,000/μL) at diagnosis, extramedullary involvement, high-risk APML, mixed phenotype acute leukemia, or monocytic variants of AML are believed to have a higher risk for CNS involvement and screening CSF evaluation with prophylactic IT chemotherapy administration may be considered at the end of induction.

At least one study of childhood AML demonstrated a lower systemic relapse rate after cranial radiation.[54] This observation has been replicated in the Berlin-Frankfurt-Münster (BFM) group, which has studied the role of prophylactic cranial RT in childhood AML in a similar manner to their ALL studies described later. In combination with increasing intensity of induction therapy emphasizing anthracycline chemotherapy and cytarabine IT chemotherapy, cranial irradiation has helped to reduce the risk of CNS relapse, Results from study AML-BFM 87 including nonrandomized patients showed an increased risk of mainly bone marrow relapses in nonirradiated patients. Five-year DFS for patients who received cranial radiotherapy (CRT) was 69% compared to 46% for those not receiving RT. In later studies (AML-BFM 98 and 2004), randomized evidence indicated that 12 Gy resulted in the same relapse rate as 18 Gy.[55] At present, most AML study groups (including BFM-AML 2012)[56] do not include prophylactic CNS-directed RT due to concerns for late effects observed in ALL studies.[57] Although no randomized data have compared the efficacy of radiation versus systemic and IT prophylaxis, triple IT chemotherapy (cytarabine, methotrexate [MTX], and steroids) has demonstrated a lower rate of CNS failures than cytarabine monotherapy and has been a common standard in children in CNS-negative AML.[57]

The radiation oncologist may be called on to treat tissue-based eAML tumor, also known as myeloid or granulocytic sarcoma or chloroma is subtype of AML per WHO, which may predate a diagnosis of leukemia or be a harbinger of systemic relapse, and is typically associated with systemic AML: About 75% to 90% of patients with isolated myeloid sarcoma will develop metachronous intramedullary AML with a median latency period ranging from 4 to 12 months. Myeloid sarcomas may also be seen with other myeloid neoplasms transforming to AML.[58] These solid masses of leukemic infiltrates are responsive to modest doses of RT. The name chloroma derives from the fact that myeloid cells contain myeloperoxidase, which manifests a greenish color on gross inspection. These may occur in all varieties of extramedullary sites, including periosteum, skin, conjunctiva, testicles, soft tissues, gastrointestinal tract, the spine, and epidural spaces or meninges.[58] Pathologic misclassifications are common, as this is a rare clinicopathologic disorder. Based on various case reports in the literature, symptomatic problems from myeloid sarcomas may be

readily relieved with doses of 10 to 24 Gy. The fractionation and total dose need to take into consideration any normal tissue toxicities, and the potential for future TBI should the patient be a potential candidate for an allo-HSCT. Recent reviews and commentary have suggested a prescription dose of 24 Gy in 12 fractions for most patients.[59,60] However, it should be noted that leukemias are at least in principle thought to be more radiosensitive than indolent lymphomas, in which a shift toward ultra-low dose of 4 Gy in two fractions has been adopted, particularly in palliative settings. Anecdotally, ultra-low doses of RT can be highly effective in AML, but little has been published in the way of formal reports. Although OS may be better for isolated myeloid sarcomas as compared with systemic AML, due to high co-incidence of medullary and extramedullary disease, long-term disease control requires similar systemic therapy as is used for systemic AML.[61-64] Outcomes among patients with myeloid sarcomas are defined by cytogenetic and molecular testing results, and selection of systemic treatment strategy should be similar to other patients with AML.[58]

Treatment of Acute Lymphoblastic Leukemia/Lymphoblastic Lymphoma

The approach to the treatment of ALL is based on disease Ph chromosome status (Ph-positive or negative), phenotype (T or B cell), and patient's age (children, adolescents and young adults, adults and older adults). Multiagent regimens are usually used to treat this disease. The four components of ALL therapy are typically (1) induction of remission, (2) intensification and/or consolidation, (3) maintenance therapy, and (4) CNS prophylaxis. Duration of treatment is about 2 to 3 years, including more intense up-front treatment periods and a 2-year period of prolonged low-intensity maintenance at the end. It is significantly longer than chemotherapy for AML, which typically includes induction and up to four cycles of consolidation spanning 6 to 7 months. In the 1960s, the problem of CNS recurrence was addressed with CNS radiation and IT chemotherapy. Subsequent improvements in ALL cure rates over the past two to three decades have resulted from improved risk stratification of patients with more effective, tailored multidrug regimens. As discussed in the following text, the late sequela of 24-Gy cranial irradiation was recognized in the

1980s and 1990s, leading to the elimination of CRT in favor of intermediate- or high-dose MTX in all but high-risk patients or those with CNS-3 disease. While not a standard worldwide, investigators at St Jude Children's Research Hospital (SJCRH) have completely eliminated the use of up-front CRT in their protocols of pediatric ALL, accepting a small incidence of CNS relapse even in their high-risk patients.[65] In addition, with the improvements in systemic therapy, testicular relapse in males has become a rare event.[66] Testicular irradiation is rarely necessary, except in the setting of testicular relapse or bone marrow transplantation.

Current induction therapy for pediatric and young adult patients with ALL as a minimum typically includes a glucocorticoid, anthracycline, vincristine, and L-asparaginase.[67] Other four or greater multidrug regimens have been used, all of which have resulted in initial remission rates of 95% to 99% in children and 75% to 90% in adults. Dexamethasone is now the preferred systemic steroid treatment as suggested in two clinical reports comparing it to prednisone, with dexamethasone reducing both CNS and systemic relapse in pediatric ALL.[68,69] This may be related to dexamethasone's better penetration into the CSF and longer half-life, providing enhanced protection against CNS relapse.[70]

Following induction and achieving CR, patients then receive intensification therapies that have been developed by cooperative groups in the United States and Europe.[71,72] This may consist of high doses of antimetabolites, such as MTX, ara-C, and L-asparaginase. It is believed that high-dose MTX helps control CNS disease, which has allowed for less use of cranial radiation. After intensive therapy, patients undergo a phase of prolonged maintenance treatment with agents such as monthly vincristine, a short course of steroid, weekly low-dose MTX, and daily mercaptopurine, which appear to be quite important, albeit for unclear reasons.

For ALL in adults, patients have experienced improved CR rates (>90%) with multiagent induction regimens similar to pediatric protocols but with decreased exposure to certain medications (eg, steroids, L-asparaginase), which are not well tolerated by this patient population. The issue for these groups is preventing relapse and accomplishing cure, which has been suboptimal among adults at around 30% to 40% but is improving to about 60% to 70% with the use of pediatric- inspired regimens, especially among

adolescents and young adults.[73] Survival of older patients with ALL who are not able to tolerate pediatric-inspired treatment approaches remains poor.

Ph-positive B-cell ALL had been considered prognostically poor with universal indication for allo-HSCT frontline consolidation for fit patients who were able to accomplish remission with a multiagent regimen until the introduction of BCR::ABL1 TKIs. The use of third-generation TKI ponatinib together with a multiagent regimen hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) led to CR in all 68 patients enrolled in a phase 2 trial. Twenty patients (23%) underwent allo-HSCT. With a median follow-up of 80 months (range, 16-129 months), the estimated 6-year EFS rate was 65% and the OS rate was 75%. There was no difference in outcome by the performance of allo-HSCT in the first CR.[74]

Patients with T-cell ALL receive multiagent regimens as patients with B-cell ALL with some modifications based on the recently completed large COG study (AALL0434), which showed that lower dose but more frequent administration of MTX (Capizzi-Style) was superior to high-dose MTX. The 5-year DFS rate was 87.4% and OS 90.5% versus 70% and 79.1%.[75] Introduction of nucleoside analog nelarabine approved in the second-line setting to the frontline led to improved DFS (4-year DFS of 88.9% vs 83.3%, $P = .0332$) with significant reduction of CNS relapse incidence (0.3% vs 4.3%, $P = .0009$) based on the same study.[76] Finally, the study showed similar EFS and OS among patients with ETP and near-ETP versus patients with non-ETP, albeit with decreased CR rate in the ETP-/near ETP-ALL group.[77]

For relapsed ALL, the traditional treatment has included a second induction that generally consists of multiple drugs similar to frontline regimes. If the CNS is involved, IT treatment is given along with RT.[78] If testicular relapse occurs, bilateral testicular irradiation is administered. When isolated CNS or testicular relapse develops, systemic therapy is indicated along with local RT.[79] If a second remission develops, as occurs in 70% to 90% of cases, subsequent treatment includes either allo-HSCT or consolidative chemotherapy.[79,80] There are no randomized trials to indicate which is better, but comparative analysis suggests that survival is improved with allo-HSCT, particularly in patients with ALL who had brief initial remissions.[80,81]

Treatment approaches for relapsed ALL have begun to undergo a paradigm shift in treatment thanks to the recent influx of immune-modulating and other targeted agents in oncology. These include bispecific T-cell engagers (BiTEs), which are monoclonal antibodies designed to link CD3-positive host T cells to leukemic cells (eg, via CD19 expressed in >90% of patients with B-cell ALL). The CD3-CD19 BiTE blinatumomab, for example, has been shown to be safe and effective in the up-front treatment of infant ALL[82] and high-risk relapsed ALL.[83] Blinatumomab was approved for Ph-negative and positive, CD19-positive B-cell ALL in relapse as well as for patients with positive MRD and serves as a bridge for curative allo-HSCT in some patients.[84,85] Antibody-drug conjugate inotuzumab ozogamicin, which targets CD22 expressed in 80% of B-cell ALL, has been approved for the management of relapsed/refractory disease but should be used with caution prior to allo-HSCT due to high incidence of veno-occlusive disease.[86] Both drugs are currently investigated in the frontline setting with successful outcomes already reported in a few studies with the anticipated approval for use in the frontline setting.[87-89] Additional advances in salvage therapies include CD-19–directed CAR T therapy, which has shown remarkable efficacy in multiply relapsed/refractory (third-line or greater) patients with B-cell ALL, with 48% of patients remaining disease free at 3 years.[90] CAR T therapy is associated with unique toxicity profiles, including cytokine release syndrome in most patients and immune effector cell–associated neurotoxicity syndrome in over one-third of patients.[10] There are numerous immune-modulating and targeted agents under active investigation, which will likely continue to impact relapsed management options;[67] however, none of these have yet made it into first-line standard-of-care therapy for childhood ALL.

The Role of Radiation Therapy in Acute Myeloid Leukemia and Acute Lymphoblastic Leukemia

As noted earlier, the use of prophylactic CNS radiation has been largely removed from the up-front treatment of pediatric leukemias due to advances in alternative systemic therapies and an increasing appreciation for the potentially devastating and lifelong consequences of brain radiation in these patients. The data surrounding this evolution are described in the next

sections. However, there still remains a role for RT in patients with highly selected leukemia, particularly adults, in which palliation of local disease or CNS salvage remains important, potentially life-saving treatment options. The local-only progression of leukemias, which was previously a relatively uncommon phenomenon, has become more prevalent as systemic therapies have improved.

Radiotherapeutic Emergencies

The radiation oncologist will be called on to assist with certain emergencies when the patient first presents with leukemia or at the time of relapse. Mediastinal adenopathy causing airway compression or spinal cord compression from epidural disease is clear indication for emergent RT. Generally, only one to three 1.5- to 2.0-Gy fractions are required while the diagnosis is being established and systemic therapy is being initiated (Figure 87.3). Glucocorticoids are an important adjunct to CNS RT but can produce rapid lysis of some lymphoblastic lymphomas/leukemias, which may hamper diagnostic evaluation. In the presence of CN palsies at diagnosis, some radiation oncologists recommend 10 to 15 Gy to the base of skull early in the treatment course to try and reverse the neurologic deficits.[91,92] However, it should be noted that larger retrospective studies of isolated CNS leukemia relapses have observed increased rates of CNS failure with base of skull alone, and therefore, any curative treatment, particularly in adults, should consider larger treatment fields with whole brain or even craniospinal irradiation (CSI) in selected cases (isolated CNS failure with no evidence of marrow disease).[93] CN palsies can improve rapidly after initiation of radiation (within two fractions),[94] but complete neurologic recovery may take weeks or months if it happens at all. Extreme leukocytosis with blast counts over 75,000 to 100,000/μL is a concern with myeloid leukemia, as leukostasis may occur, particularly in the vessels of the brain or lung. Lymphoid blasts are less adhesive to vessel walls, and blast counts of up to 400,000/μL or more are often well tolerated. In decades past, RT directed at the whole brain was employed using low doses on the order of 6 to 10 Gy in various fractionations. However, the role of RT in this setting has been questioned[95-97] but may be considered when leukophoresis is contraindicated or unavailable. Nevertheless, one recent

report suggests reconsideration of the role of CRT for leukostasis. Eighteen patients received whole-brain RT in one to three fractions for a mean total dose of 5.63 Gy (range 2-9 Gy). Thirteen patients were treated to control neurologic symptoms rather than in a preventive manner, resulting in 92% achieving prompt resolution of symptoms during RT or immediately thereafter. There was no toxicity above grade 2. Two (6%) patients developed an intracranial bleed following therapy from underlying leukostasis, while historically, this leukostasis syndrome has been associated with a 20% acute mortality rate from stroke or heart failure.[98]

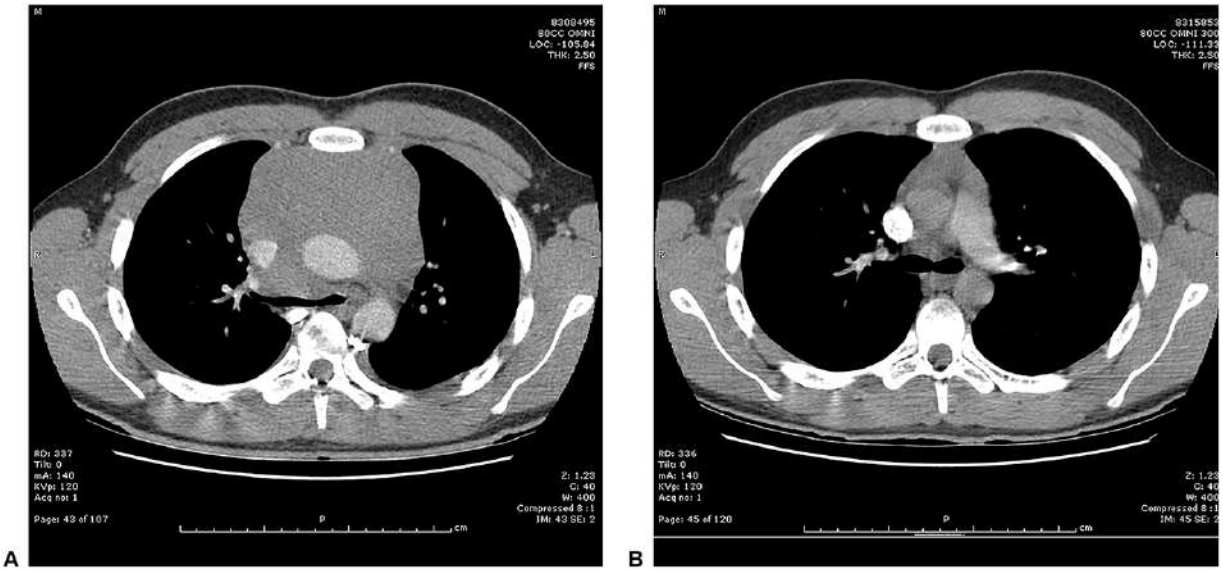


FIGURE 87.3 Computed tomography scans of chest before (A) and after (B) palliative radiotherapy (RT) for mediastinal mass associated with T-cell acute lymphocytic leukemia. A 16-year-old boy presented with dyspnea and chest pain. A chest x-ray showed a mediastinal mass, while blood counts revealed a lymphocytosis. Diagnosis was established by flow cytometry of blood. Initial treatment with steroids, doxorubicin, vincristine, and methotrexate failed to produce immediate response. Megavoltage RT with anterior and posterior opposed beams for 6 Gy in three fractions was administered, subsequently relieving acute symptoms and allowing for general anesthesia to take place without risk for complete airway obstruction in order for central line placement and lumbar puncture to be performed.

Central Nervous System Prophylaxis of Acute Leukemia

Patients with AML, except for specific subtypes such as monocytic variants, are not generally treated with prophylactic cranial radiation at the present as the risk for CNS relapse is less than 5%. The risk of CNS relapse

is dramatically higher for ALL, however, which is the focus of the remainder of this section.

The Historical Role of Prophylactic Central Nervous System–Directed Radiotherapy in Acute Lymphoblastic Leukemia

As investigators in the 1970s began producing remissions in childhood ALL, CNS relapse became the next hurdle to long-term cure, with historical chemotherapy regimens (ie, without CNS prophylaxis associated with rates of up to 67% CNS relapse).[99] The CNS was thus recognized as a sanctuary site, protected from chemotherapy by the blood-brain barrier. In addition, it was observed that CNS recurrences invariably led to systemic recurrence, suggesting that CNS disease was capable of reseeding the blood and marrow.

This observation led to a long series of CNS preventive therapy trials in pediatric ALL, which initially utilized CSI. For instance, studies V and VI in 1962 to 1967 from SJCRH established that CSI to 24 Gy in 15 to 16 fractions reduced the isolated CNS relapse rate from 67% to 4%.[100,101] Concerns that full-dose spinal RT would be associated with more acute myelosuppression, late musculoskeletal hypoplasia, as well as the technical difficulties of CSI led to the subsequent investigation of prophylactic cranial irradiation (PCI) without the treatment of the spine and lower doses of radiation. Important milestones and lessons learned ensued. Early lessons of toxicity came from the SJCRH study VII, in which 24-Gy cranial radiation with concurrent MTX resulted in a 55% rate of leukoencephalopathy, characterized by a disabling syndrome of lethargy, seizures, spasticity, paresis, and ataxia.[102] In contrast, no such toxicity was observed in patients treated sequentially with cranial radiation followed by maintenance oral MTX and mercaptopurine, in which only 1.5% of patients experienced CNS relapse. To this day, intravenous (IV) MTX and cranial radiation in close temporal proximity are avoided, with at least 2 weeks of washout for MTX provided prior to CNS radiation whenever feasible in both periods.

Further cooperative group trials have refined the efficacy of CNS-directed therapies within patient groups stratified by risk. Several trials have compared CRT with intermediate- or high-dose IV MTX along with IT

chemotherapy (some with the addition of IT hydrocortisone and ara-C to MTX known as "triple" IT therapy).[66,103,104] The essential findings have been that in patients with low- or standard-risk ALL (eg, age 3-6 years and WBC count <10,000/μL) who are managed without cranial radiation by substituting IT MTX throughout induction, consolidation, and maintenance therapy, CNS relapse rates have remained at a low level of 5% or less.[105-107] In addition, with triple IT chemotherapy, there was a trend toward fewer systemic failures as well as excellent CNS control when given throughout consolidation and maintenance therapy. This may be at the expense of increased neurotoxicity, however, when given in conjunction with intermediate-dose IV MTX.[107] A meta-analysis of 65 randomized trials of pediatric ALL worldwide initiated prior to 1993 that evaluated the role CRT concluded that in the vast majority of patients, CRT may be avoided with the use of extended IT therapy.[108] One notable exception to the conclusions of aggregated trials of this meta-analysis was the CCG-105 trial of intermediate-risk ALL,[109] in which patients treated with standard (ie, nonintensified) chemotherapy without cranial radiation experienced a CNS recurrence rate of 20%. Thus, more intensive systemic therapy can lower CNS recurrence rates, abrogating any benefit to cranial irradiation. As a result, the vast majority of patients with ALL are treated without RT in the up-front setting.

The Current Role of Prophylactic Central Nervous System–Directed Radiotherapy in Acute Lymphoblastic Leukemia

The use of PCI in pediatric ALL is undergoing continued restriction and even abandonment due to concerns for limited efficacy due to improved alternative systemic and CNS-directed therapies, as well as a growing body of evidence that many CNS relapses are harbingers of systemic relapse. Any benefit of PCI must be weighed against a historical body of evidence for musculoskeletal, neurocognitive, endocrine, and secondary tumor toxicities associated with RT. Conversely, adverse effects of radiation on IQ are known to be particularly pronounced in very young patients (under age 2) and comparisons that exclude these very young patients (as is routinely done in all modern trials) suggest that the neurocognitive impact of CRT compared with non-RT regimens may be far less pronounced than was

previously thought.[110,111] These data support that while the avoidance of RT is preferred wherever possible, RT may not add significant risk of neurotoxicity when therapeutically necessary.

The most sweeping assessment of PCI use came from a group of international investigators in 2016, in which they performed a detailed meta-analysis of PCI use from 10 cooperative groups involving 16,623 patients aged 1 to 18 years with newly diagnosed ALL treated between 1996 and 2007.[112] The proportion of patients eligible for PCI varied from 0% to 33% by trial, unrelated to eligibility for allo-HSCT in the first CR. A meta-analysis using PCI as a dichotomous covariate compared EFS and cumulative incidence of isolated or any CNS relapse and isolated bone marrow relapse in high-risk subgroups of patients who either did or did not receive PCI. Results showed that only a small subgroup of patients with overt CNS disease at diagnosis had a plausible benefit from RT, with a significantly lower risk of isolated CNS relapse of 4% with PCI compared to 17% who did not receive RT (P =.02); moreover, there was a trend toward lower risk of any CNS relapse (7% with PCI vs 17% without, P = .09). These investigators, however, still questioned the role of PCI even in this or other high-risk groups of pediatric ALL receiving contemporary risk-adapted therapy as systemic relapse and death were equally high occurring in roughly one-third of patients, regardless of RT usage.

At present, only patients who are at the highest risk for CNS relapse receive RT as part of their CNS prophylaxis, with some groups such as SJRCH forgoing RT in all up-front cases including those with CNS-3 disease. In all practicality, decisions made regarding CNS prophylaxis and/or TBI in the context of leukemia are typically made by the managing leukemia oncologist or transplant team member within the context of tertiary cancer centers. The role of the radiation oncologist, therefore, is primarily to be (1) familiar with subsets of patients for which CNS prophylaxis may be recommended and is appropriate, (2) understand the appropriate dose of radiation and associated toxicities, and (3) be proficient in the modern technical delivery of CNS-directed therapy. Therefore, in this section, we highlight current practices with a focus on which patients receive prophylactic CNS-directed therapy.

At one extreme is the St Jude's group, which has become particularly concerned about the late effects of 24 Gy to the brain in terms of

neurocognitive disabilities, hypothalamic/pituitary dysfunction, and secondary malignancies. With risk-adapted intensification of chemotherapy, Pui et al have reported favorable results with the complete elimination of CRT in all patients with newly diagnosed ALL.[65] In their St Jude Total XV trial, 498 patients were treated without CRT, yielding an 86.6% 5-year EFS, which was comparable to their prior studies that had included CRT. CNS-directed therapy used five cycles of high-dose MTX including, as part of induction therapy, dexamethasone, and extended IT chemotherapy. High-risk patients with ALL received up to 16 to 25 IT chemotherapy sessions, whereas low-risk patients received 13 to 18 doses of IT chemotherapy. Patients who were at increased risk of CNS relapse were those who had positive CSF cytology (CNS-2 or CNS-3) or T-cell ALL. Moreover, a relatively high 7% of patients in the first remission went on to undergo an allo-HSCT correlating with high-risk features of MRD and adverse cytogenetic markers. An additional 598 patients were treated on Total XVI, which not only randomized the dosage of PEG-asparaginase but also omitted RT, reporting 5-year EFS of 88.2%, with a cumulative risk of any CNS relapse (isolated or combined) of 1.5%. In patients with features associated with CNS relapse (eg, T-cell phenotype), the 5-year rate of any CNS relapse was lower than that seen in Total XV (1.8% vs 5.7%).[113]

Elsewhere worldwide, the philosophy on the use of CRT in pediatric ALL has been to use it judiciously in high-risk patients while also reducing radiation doses to address the concerns about late effects. The European BFM-ALL trials since 1990 have reduced the cranial radiation dose to 12 Gy with their risk-adapted intensification schemes, although those with CNS-3 disease received 24 Gy in their BFM-90 trial and 18 Gy in the more recent BFM-95 trial. The recent Intercontinental BFM 2009 has similarly employed a dose of 12-Gy cranial radiation for high-risk prophylaxis, in which 13% of patients received CRT.[114]

Currently, the COG has followed suit with a reduction in both the utilization and intensity (ie, dose) of cranial radiation in its current ALL trials. One of the largest reductions in utilization has been for T-ALL, where T-cell subtype is a known substantive risk factor for CNS and overall relapse. In the COG ALL1231 trial of patients with T-ALL, RT was given to only 9.5% of patients (very high risk or CNS-3) compared with the precursor ALL0434, in which 90.8% of patients received CRT. No

statistically significant differences in EFS or OS were observed between matched patients who did versus did not receive CRT, suggesting that up to 90% of patients with T-ALL can safely forgo RT.[115]

In the AIEOP-BFM ALL 2009 study, approximately 10% of patients receive PCI. In the current COG studies, prophylactic CRT is given only to the 2% to 3% of patients with CNS-3 status and approximately 10% of patients with T-ALL with high levels of MRD after 3 months of therapy. Bcr-abl mutations and other high-risk molecular markers are no longer an indication for PCI by itself. In the current DFCI Consortium study, approximately 20% of patients (all patients with T-ALL and patients with B-cell precursor ALL with CNS-3, high level of MRD at the end of remission induction, MLL rearrangement, or low hypodiploidy) receive PCI. But, in the upcoming DFCI study, only CNS-3 status will be used as a criterion for PCI for patients with B-cell ALL. In the current Cooperative Acute Lymphoblastic Leukemia 08-09 study, PCI 12 Gy is given to approximately 6% of the patients. Only patients with CNS-3 status receive PCI in the current trial of the Japanese Pediatric Leukemia/Lymphoma Study Group. Of note, several groups have completely omitted PCI, including the Dutch group, the Nordic Society of Hematology and Oncology, the European Organisation for Research and Treatment of Cancer (EORTC), the UK ALL group, and the SJCRH.[112]

Meningeal Leukemia at Diagnosis

At the time of diagnosis of ALL, approximately 3% to 5% of patients will present with clinically detectable CNS involvement (ie, CNS-3 disease). Meningeal leukemia at diagnosis is typically managed as high-risk leukemia with CRT. The St Jude investigators may disagree with the use of RT even here, but their results of the Total XV protocol included nine patients with CNS-3 disease whose 5-year EFS was only 43%.[65] These high-risk patients receive chemotherapy programs that include dose-intensive therapy with agents that penetrate the blood-brain barrier as well as IT therapy. Cranial radiation doses may vary from 18 to 25 Gy. Historically, CSI has been used, but modern practice has dispensed with the spine fields as the IT and systemic chemotherapy programs appear to be effective in assisting with CNS control. In children with ALL, meningeal

involvement no longer carries a dire prognosis, as 5-year DFS rates approaching 70% are commonly seen.[116]

Delay in CRT or craniospinal RT up to 12 months has been found to be safe as long as intensive chemotherapy is being given first.[117,118] This avoids the marrow compromise that could potentially occur with early spine irradiation. In addition, with doses less than 16 Gy to the spine, myelosuppression has not been a major problem. Musculoskeletal hypoplasia would not be expected to be a significant problem for long-term survivors. The sequencing of RT *after* rather than *before* potentially neurotoxic drug therapy such as MTX may theoretically result in a lower incidence of cognitive dysfunction or encephalopathy. Some pediatric protocols will also tailor the dose to the brain based on patient age. For instance, the ALL-BFM 90 protocol, which utilizes cranial rather than CSI, avoids any RT for those younger than 1 year of age, 18 Gy for ages 1 to 2 years, and 24 Gy for older patients. In this large multicenter trial, 54 patients presented with CNS-3 disease and achieved a 48% 6-year EFS.[119] Arguably, this is inferior to protocols that use CSI, such as those reported by the CCG.[116] However, in the ALL-BFM 95, there were 64 patients with CNS-3 disease who had a 6-year EFS of 57.7% in which therapy included cranial radiation to 18 Gy without irradiation of the spine.

Some investigators in addition to those at SJCRH continue to try to avoid CRT in all cases, including those with CNS-3 disease. The Dutch Childhood Oncology Group (DCOG) and the EORTC have omitted cranial radiation by also using more high-dose MTX during postinduction consolidation and by an increased frequency of IT chemotherapy. The SJCRH study also included higher cumulative doses of anthracycline than on COG trials, and frequent vincristine/dexamethasone pulses and intensified dosing of L-asparaginase, while the EORTC trials included multiple doses of high-dose cytarabine, during postinduction treatment phases for patients with CNS-3. On the DCOG-9 trial, 21 patients with CNS-3 treated without cranial radiation had a 5-year EFS of 67% ± 10%. On the EORTC trial, the 8-year EFS of 49 patients with CNS-3 treated without cranial radiation was 68%. The cumulative incidence of isolated CNS relapse for those patients was 9.4%. This CNS-3 subgroup is relatively

uncommon, and further studies will be required to see if CNS irradiation can be safely eliminated.[120,121]

Cranial Radiation Dose

To reduce the toxicity of prophylactic cranial radiation, several investigations have explored a reduction in radiation dose. In earlier, circa 1981 trials, the use of 18 Gy in 9 or 10 fractions along with IT MTX yielded comparable disease control rates as 24 Gy.[122] Although there were some initial reports of reduced cognitive dysfunction even with such a dose reduction,[123] this issue is by no means completely settled.[124-126] The Dana Farber Cancer Institute ALL Consortium has studied the role of hyperfractionated cranial radiation (0.9 Gy twice daily) compared to standard daily fractionated treatments (1.8 Gy daily) to 18 Gy in high-risk patients.[127,128] Results from Dana Farber ALL 87-04 show excellent CNS control rates with both the standard or hyperfractionated treatments. Late neurocognitive sequela has been similar in which systemic therapy emphasizes L-asparaginase and omits high-dose MTX. A follow-up Dana Farber ALL trial 95-01 compared hyperfractionated 18-Gy CRT to extended IT chemotherapy without CRT. The interesting finding here is that quantitative measurements of neurocognitive function were similar in both groups.[111] The German-Austrian-Swiss ALL-BFM Study Group has further reduced the radiation dose to 12 Gy, initially in a selected group of standard-risk pediatric patients.[106] With modern chemotherapy regimens as opposed to the older SJCRH experience, this further reduction in radiation dose was associated with excellent CNS control. Moreover, the ALL-BFM 90 protocol stopped using CRT in low- or standard-risk patients, but both the medium- and high-risk patients received 12-Gy prophylactic cranial radiation, resulting in CNS recurrence rates well below 5%.[119] For the ALL-BFM 95 trial, CRT was deleted for the patients with intermediate-risk B-cell ALL. This has resulted in a small increased risk for CNS relapse, which is considered clinically acceptable in order to avoid the late effects of such RT.[129] Specifically comparing intermediate-risk BFM 90 to BFM 95 patients, the isolated CNS relapse rate at 6 years is 0.5% versus 1.9% ($P <$ .01). The 6-year “any CNS” relapse rate was also statistically different at 2.2% versus 4.4%. Further follow-up and additional experience within the

COG with this lower cranial radiation dose will be of interest in the years to come, hopefully seeing a reduction in late toxicity without compromising efficacy as CRT continues as used in a subset of high-risk pediatric patients with ALL.

For adults with ALL, various protocols have used 24 Gy, whereas others employ 18 Gy.[124,125,130] Recent studies have explored even lower doses, including 6 Gy, with no evidence of neurocognitive toxicity and a suggestion toward improved local control and may warrant future study.[131] Some programs such as hyper-CVAD omit the use of CRT in the face of high-dose MTX and ara-C, which effectively penetrate the blood-brain barrier.

Summary of Cranial Radiotherapy for Initial Acute Lymphoblastic Leukemia Management

In summary, CRT may be used to prevent CNS relapse of leukemia. From a historical perspective that considered the brain as a sanctuary site, CRT has been well documented to improve outcomes for selected patients with pediatric ALL. With concerns about late sequela and improvements in systemic therapy including agents that can better penetrate the blood-brain barrier, CRT is used much less frequently in the up-front management of ALL. Overall, only 15% to 20% of pediatric patients with ALL who have high-risk features require CRT currently. In current practice, cranial radiation is employed selectively in patients with high-risk ALL. Although the definition of high risk has been shifting, one needs to take into account the intensity and specifics of risk-adapted chemotherapy. Nevertheless, patients with ALL who benefit from CRT include older age (eg, older than 10 years of age, and probably increasing benefit at ages older than 13 years); T-cell phenotype, especially in older patients with high presenting WBC over 100,000; and risk groups CNS-2 or CNS-3 by CSF findings. In addition, among B-cell patients, those with MRD and adverse cytogenetics should be strongly considered for CRT. Moreover, a recent meta-analysis supports the concept that a relatively small cohort of high-risk pediatric patients with ALL require CRT as part of initial CNS-directed therapy.[132] All adults with ALL may be considered to be at high risk for CNS relapse, but there are no standard recommendations on CRT. Unless otherwise

indicated, in a specific treatment protocol, the radiation prescription for prophylactic cranial radiation to prevent ALL relapse is 18 Gy in 9 or 10 fractions. When BFM-type chemotherapy programs are used, the radiation dose has been reduced to 12 Gy with favorable outcomes. The spinal region is specifically treated by IT chemotherapy rather than RT, although an open question is whether there would be an incremental benefit to low radiation doses to the spine with meningeal leukemia at diagnosis.

Therapeutic Central Nervous System Irradiation for Meningeal Relapse

With modern chemotherapy programs incorporating CNS-directed treatment, CNS relapse rates are typically less than 10%. As in overt CNS leukemia at diagnosis, RT has a central role. Formally, CNS relapse was thought to have a poor prognosis. Studies in the 1970s and 1980s describe disease control rates of 25% to 50%.[133-139] More recent trials, however, utilizing more intensive chemotherapy as well as RT, have reported ALL 5-year survivals of 50% to 70%.[118,140-143] Almost all trials have employed RT; the debate has been between CRT alone or CSI. Doses used have generally been approximately 24 Gy to the brain and 10 to 15 Gy to the spine. Most comparisons have not been randomized, but superior outcomes seem to be achieved with CSI.[119,118,140-143] One small phase III trial did show superiority for CSI compared to CRT.[140]

Although CNS relapse may ostensibly occur without overt systemic disease, the latter is viewed as inevitable without additional systemic therapy. Therefore, intensive chemotherapy is an essential component of the treatment of meningeal relapse.[120,144]

Several prognostic factors have been found to be of importance in the setting of CNS relapse.[145-147] Patients who were originally deemed at diagnosis to be at low risk for CNS relapse by virtue of a low initial leukocyte count (<20,000/μL), who originally did not receive cranial irradiation, or whose CNS relapse occurred at a relatively long period after the original diagnosis have a better prognosis after CNS recurrence. An isolated CNS relapse has generally been more prognostically favorable compared to combined CNS and systemic relapse. After completing chemotherapy, those children with CNS relapse have better outcomes with

longer disease-free intervals. For instance, experience within the Pediatric Oncology Group (POG) with isolated CNS relapse of ALL in which RT used a cranial dose of 24 Gy and a spine dose of 15 Gy. The 4-year EFS was 71%. Those patients who presented with greater than an 18-month disease-free interval prior to CNS relapse had a 4-year EFS of 83% compared to 46% for those with shorter initial remission durations.[118] This has led subsequent POG and COG trials that omit RT to the spine if there is a long disease-free interval, but if the disease-free interval is less than 18 months, 24 Gy is given to brain while 15 Gy is delivered to the spine. Whether the omission of spinal RT in this favorable subgroup is detrimental is unclear. However, high-dose ara-C has generally been added to the management of CNS relapse of ALL. With this agent, Morra et al[148] reported a favorable 63% complete response rate. These concepts have been maintained with current COG trials for CNS relapse of ALL, but with intensification of systemic therapy, spinal RT has been proposed to be dropped even for short disease-free intervals, while the brain is treated to 18 Gy. As for adults with CNS leukemia, most of the published experience and commentary from medical oncologists has been opposed to the use of CSI mainly for fear of excessive myelosuppression.[124] Cranial irradiation is relatively standard, however. Quite possibly, the avoidance in treating the entire CNS is detrimental, although admittedly this is not a settled issue. Modern CSI techniques using either protons or photon-based approaches that spare the vertebral bodies may be able to reduce the risk of myelosuppression compared with historical three-dimensional (3D)-based approaches.[149]

Selected high-risk patients with CNS relapse may be candidates for allo-HSCT. TBI is often a component of the preparative regimen. One function of the TBI is to specifically treat the CNS burden of disease. Because doses on the order of 12 to 15 Gy are employed here, it makes sense to boost the head prior to TBI to bring total doses to the cranium to 18 to 25 Gy. Investigators at Stanford have evaluated the neurocognitive effects of this practice of boosting the CNS in conjunction with TBI. Forty-one pediatric patients with relapsed ALL undergoing TBI-based allo-HSCT had the brain boosted to a total mean dose of 24 Gy. In 18 patients, the spine was also boost to a total cumulative dose of 18 Gy. Five-year DFS for all patients was 67% for this high-risk group. Patients with isolated CNS disease before

transplant had a trend toward superior DFS (HR 3.64, $P = .11$, 5-year DFS 74%) compared with those with combined CNS and bone marrow disease (5-year DFS 59%). Neurocognitive testing revealed a mean post-SCT overall intelligence quotient of 103.7 at 4.4 years. While relative deficiencies in processing speed and/or working memory were noted in 6 (38%) of 16 tested patients, the pre- and post-transplant neurocognitive testing revealed no significant change in intelligence quotient. At a mean of 12.5 years after transplant, 11 (85%) of 13 long-term survivors had completed some college-level coursework.[150]

Considerations for Adult Central Nervous System Leukemia Salvage

Adult patients with CNS relapse leukemia, particularly those with isolated CNS failure after prolonged disease-free intervals, may benefit from consideration of comprehensive CSI and do not face the same concerns as pediatric populations regarding developmental delays and secondary radiation-induced malignancies. Secondary therapeutic cranial radiation-induced CNS malignancies are strongly age dependent, are difficult to detect at the population level after age 18, and may take 20 to 25 years to manifest in adults, assuming there is any increased risk at all.[151] Current International Lymphoma Radiation Oncology Group guidelines recommend doses of 18 to 24 Gy.[152] These data stem from evidence of long-term disease control in some adult patients with CSI, which is highly effective at eliminating CNS disease. One retrospective review of 16 patients (ages 16-58) described a mix of CNS leukemia recurrences from AML, ALL, and one patient in CML blast crisis.[153] A median dose of 24 Gy to cranium and 18 Gy to the spine was used with median fraction sizes of 1.8 and 1.5 Gy, respectively, and 15 also received IT chemotherapy. CNS clearance was shown to be effective, with 13 of 16 patients achieving clearance of CNS disease with no evidence of disease at the time of death or last follow-up, with two patients experiencing greater than 5-year DFS. Eleven patients experienced bone marrow failure, which continued to drive overall outcomes.

A second, larger series of 163 adults treated between 1996 and 2012 examined patients with CNS leukemia treated with base of skull (29%), whole brain (41%), and CSI (29%). Common symptoms included headache

and CN deficits (ie, facial, optic, oculomotor, or abducens). Among patients with neurologic deficits, two-thirds experienced improvement or resolution with RT. Base of skull radiation, as opposed to whole brain or spine radiation, was associated with worse 12-month CNS progression-free survival (51% vs 77%). Patients with isolated CNS involvement benefited the most from comprehensive radiation fields, suggesting that "aggressive" comprehensive CSI may be capable of achieving cure in these cases. Although not formally examined in these studies, patients with a longer bone marrow–free disease interval (ie, at least 6 months) who present with isolated CNS leukemia are thought to stand the most to benefit from curative-intent CSI.[93] Technical considerations related to CSI delivery are discussed later in this chapter.

Testicular Relapse

In boys with ALL, particularly those with T-cell subtype, testicular involvement was once a common problem. Overt testicular involvement by leukemia at diagnosis occurs in approximately 2% of males with ALL and is a particularly poor prognostic situation. Microscopic burden in the testes is estimated to be higher at 5% to 15% based on biopsy data and the historic risk for testicular relapse. With modern chemotherapy, especially the use of intermediate- to high-dose MTX, testicular relapse is now rare. Similar to the experience with CNS relapse, there once was speculation as to whether the testes acted as a sanctuary site due to a physiologic blood-testes barrier. In 1980, a trial of prophylactic testicular irradiation significantly reduced the risk of testicular relapse but did not improve survival.[154] Modern risk-adapted chemotherapies as promulgated by SJCRH investigators no longer require testicular RT in the up-front management of patients presenting with testicular involvement as there is no reduction in relapses nor improvement in OS or EFS.[155]

In cases of testicular relapse, systemic and/or CNS relapse usually follows.[156] Both intensive systemic therapy and local RT are indicated. Doses less than 12 Gy are generally thought to be suboptimal, whereas doses of 24 to 26 Gy over 2.5 to 3.5 weeks are considered standard. Case reports of local recurrences despite adequate RT have led some to suggest higher doses. When only one testis is clinically involved, imaging or biopsy

of the contralateral testes frequently reveals bilateral disease. Similarly, unilateral irradiation or orchiectomy as local management is felt to be associated with a significant risk of contralateral testicular relapse, justifying treatment directed at both testes for leukemia management, despite the expectation of infertility from RT. Data from CCG and POG studies suggest that local irradiation and intensive systemic therapy result in prolonged EFS in roughly 50% to 65% of patients.[79,157] Where allo-HSCT is indicated, TBI is often part of the conditioning regimen. One retrospective series from the Memorial Sloan-Kettering Cancer Center suggests that for TBI/cyclophosphamide preparative regimens, the risk of testicular relapse is significantly reduced with a local boost to the scrotum of 4 Gy to bring the total testicular dose to 16 to 20 Gy.[158] However, a retrospective study from Stanford did not observe any improvement associated with testicular boost with respect to leukemia control and was associated with worse gonadal function.[159] There is not universal agreement about the need for a testicular boost in this setting, and most transplant programs have stopped the practice of prophylactic testicular boost with TBI.

Ocular Relapse

Historically, choroidal recurrence of leukemia was sometimes associated with inadequate coverage of the optic nerve and posterior globe with CRT. This has led to practice patterns in which the posterior eye is included in standard cranial fields. Even so, isolated relapse in the eye is rarely seen and may even occur in the anterior chamber. RT is often used as part of retrieval therapy analogous to relapse in the brain or testes. The best report of the incidence and management of this situation comes from the United Kingdom Medical Research Council leukemia clinical trial experience.[160] Investigators found a 2.2% incidence of eye relapse in their Leukaemia XI and ALL97 trials between 1991 and 2001. There were 17 patients who had ocular leukemia as a first relapse, either in isolation or combined with relapse at another site, and three occurred as a poor prognosis second relapse event. Among the patients with ocular relapse as a first site of recurrence, 11 patients were long-term survivors with disease control who were treated with a full chemotherapy relapse protocol along with local RT. Disease tended to not be controlled when chemotherapy was of reduced

intensity; again, a lesson that isolated leukemia recurrences is a harbinger of systemic relapse. From this limited experience and from other cooperative groups, there is a sense that posterior eye relapse should direct the RT volume to include not just the eye but also the CNS comprehensively. Radiation doses to the eye ranged from 10 to 24 Gy, mostly using 24 Gy as a cumulative dose that might have also entailed TBI or CRT/craniospinal RT volumes with differential dosing. An isolated relapse in the anterior chamber is felt to have less risk for occult CNS involvement and may be managed with electron beam RT rather than photons just to the eye along with intensive chemotherapy.

THE CHRONIC LEUKEMIAS

Chronic Myelogenous Leukemia

CML is a chronic myeloproliferative disorder arising from clonal expansion of the hematopoietic stem cell. CML involves both mature and precursor myeloid, erythroid, megakaryocytic, and, sometimes, lymphoid elements. It is the first neoplastic process to be characterized by a specific cytogenetic marker, the Ph chromosome, t(9;22) described in 1960.[161] This is detectable by cytogenetics in 90% to 95% of patients and by molecular analysis in most other patients.[162] This translocation results in a BCR::ABL1 fusion protein that has tyrosine kinase activity critical for leukemic transformation. CML, the subject of this chapter, is not to be confused with chronic myelomonocytic leukemia (CMML) or atypical CML (myelodysplastic syndrome/myeloproliferative neoplasm [MDS/MPN] with neutrophilia per WHO 2022 classification). These latter two entities are both classified under MDS/MPNs, characterized by defective bone marrow hematopoiesis, and are not associated with the Ph chromosome that is characteristic of CML. CMML is associated with excess monocyte production and atypical CML with excess neutrophil proliferation and myeloid left shift. CMML, atypical CML, and other myeloid disorders beyond AML and CML are not separately covered in this text, as RT is not a direct component of their treatment. However, MDs/MPNs and MPNs are still relevant to radiation oncologists in that any form of aberrant hematopoiesis can also result in splenomegaly and other foci of aberrant hematopoiesis (discussed more in the splenomegaly section), which can be palliated with RT. Any myeloid

malignancy can be complicated by the development of myeloid sarcoma, which has been previously discussed.[58]

Clinically, CML can manifest several phases: If untreated, an initial chronic indolent phase of 3 to 4 years will progress to an accelerated phase for about 6 months and finally will transform into blast phase with a survival of 3 to 6 months. As the disease advances, the accelerated phase is characterized by increasing difficulty in controlling the peripheral WBC count, increasing splenomegaly, increasing blasts in the peripheral blood and bone marrow, and increasing basophilia and eosinophilia. The blast crisis resembles acute leukemia with more than 20% blasts in blood or bone marrow with symptoms such as bone pain, sweats, fever, anorexia, or weight loss. Anemia, thrombocytopenia, and extramedullary disease involving bones, skin, CNS, and lymph nodes are common. In about 20% of cases, blasts are lymphoid by phenotype. Historically, prognostic factors for CML have included age, splenic size, platelet count, percent of basophils in blood, and marrow. Factors associated with a poor prognosis include age greater than 60 years, spleen greater than l0 cm below the left costal margin, more than 3% blasts in blood or marrow, basophilia more than 7% in blood or marrow, and platelets greater than 700,000/μL.[163] More recently, the prognostic scoring system has been updated (European Treatment and Outcome Study (EUTOS) Long-term Survival score) but still uses the same parameters, including age, spleen size by palpation below the costal margin, and blast and platelet count in peripheral blood.[164] High-risk patients are usually managed with second-generation TKIs rather than imatinib as discussed in the following section.

Therapy of Chronic Myelogenous Leukemia

The first effective therapy for chronic leukemias was RT to the spleen and sometimes the liver, initiated in 1902 by Pusey[165] and assessed in 1924 by Minot et al.[166] Today, RT is primarily used in a palliative setting to relieve painful splenomegaly or other extramedullary sites when indicated. In some centers, TBI plays an important role in allo-HSCT. The use of the latter is now quite limited in CML management due to successful management with TKIs.

There is a long history of treating CML in the chronic phase with alkylating agents, hydroxyurea, cytarabine, and interferon-α, which is beyond the scope of this chapter. Since the approval of the first-generation TKI, imatinib, in 2001, such therapies, as well as allo-HSCT, have largely been relegated to the salvage setting. Multiple ABL TKIs effective in inducing and maintaining long-term remissions in CML without cumulative toxicities have been approved for use in first-, second-, and third-line settings in the past 20 years.[167,168] Imatinib is a relatively well-tolerated oral medication that has been shown to be effective in CML in both chronic and accelerated phases.[169,170] This agent has been a paradigm for molecularly targeted therapies and is now used as up-front therapy for CML.[171] Second-generation TKIs such as dasatinib, nilotinib, and bosutinib may be used for patients with resistance to imatinib or with poor prognostic features.[172,167] The potent third-generation TKIs ponatinib and asciminib are available for use in the relapsed and/or refractory setting, as well as for patients with a T315I *ABL1* gatekeeper mutation, which confers resistance to earlier generation TKIs.[167] Approximately one-third of patients with chronic-phase CML who have been treated with TKIs for over 3 years and achieved a deep molecular response for over 2 years may be eligible for treatment discontinuation. Roughly half of those patients can successfully maintain treatment-free remission with close monitoring of the BCR::ABL1 transcript level in blood, which is essential for the successful management of CML. For a minority of patients who do not respond adequately to the TKIs or who lose response, allo-HSCT remains an important option.[173,174] About 70% of favorable-risk patients achieve long-term DFS.[175] Allo-HSCT and TBI are further discussed in Chapters 15.

Palliative RT may be of benefit in those patients with massive splenomegaly with responses seen with low doses (<20 Gy) and is discussed further in the splenomegaly treatment section.

Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

CLL/SLL (small lymphocytic lymphoma) is an indolent leukemia of B-cell origin and is characterized by the accumulation of clonal, functionally incompetent mature B lymphocytes. It is the most common leukemia in the

Western world, and the course of the disease demonstrates marked variability. While some patients live a normal lifespan and never require therapy, others progress rapidly despite treatment. The usual course is characterized by gradual progression from incidentally found lymphocytosis to lymphadenopathy, splenomegaly, to anemia and thrombocytopenia due to progressive bone marrow involvement and/or autoimmune phenomena. Nonlymphoid organ involvement may occur with advanced stage of disease. CLL/SLL is often diagnosed following an elevated WBC discovered during a routine office visit. In symptomatic patients, 80% present with lymphadenopathy and 60% with splenomegaly. Other signs and symptoms include "B" symptoms of lymphoma, hepatomegaly, or skin lesions. Patients may also present with complications associated with CLL/SLL, including thrombocytopenia, anemia, and infections, which are usually indicative of advanced disease. Workup for CLL/SLL should include history (with specific inquiry into the presence of B symptoms) and physical examination (with focus on node-bearing areas, liver, and spleen). Imaging with a computed tomography (CT) of the chest/abdomen/pelvis may be helpful to characterize the extent of disease, but positron emission tomography (PET)/CT is typically not recommended in CLL unless Richter transformation is suspected.

It should be noted that *CLL and SLL* are terms used to describe different patterns of gross anatomic behavior of the same underlying pathology, in which CLL refers to a predominantly leukemic process (ie, high blood lymphocyte counts), and SLL refers to a predominantly lymphatic process (ie, lymphadenopathy or splenomegaly). A diagnosis of CLL requires the presence of greater than 5.0×10^9/L monoclonal B cells in the peripheral blood with or without lymph node/splenic involvement, while a diagnosis of SLL is made when lymph nodes and/or spleen are infiltrated with mature B cells in the absence of a lymphocytosis greater than 5.0×10^9/L.[176] Diagnosis of CLL is made by flow cytometry of peripheral blood, which should confirm a monoclonal B-cell population. A typical immunophenotype of CLL is $CD5^+$, $CD10^-$, CD20 dim, and $CD23^+$. Fluorescence in situ hybridization analysis for t(11:14) is helpful to distinguish it from mantle cell lymphoma, which is included in the differential diagnosis of $CD5^+$ B-cell neoplasms. If analysis of peripheral blood confirms CLL, a bone marrow biopsy is typically not required. A

diagnosis of SLL can similarly be made with flow cytometry of a biopsied lymph node or with immunohistochemistry for the abovementioned cell surface markers. Histologically, CLL cells have a similar appearance to mature lymphocytes with scant cytoplasm, a dense nucleus, and no discernable nucleoli.[177] Although there are likely underlying additional clinical nuances and genomic or molecular features that vary between CLL and SLL, they remain somewhat interchangeable terms that reflect the same basic underlying pathology, often referred to as CLL/SLL.

Occasionally, patients with CLL/SLL develop transformation to an aggressive large B-cell lymphoma referred to as *Richter syndrome*.[178] Its incidence ranges from 3% to 5% of CLL cases.[179] It may arise in the setting of active disease or during a remission. It is characterized by an abrupt onset of asymmetric adenopathy, splenomegaly, B symptoms, and elevated lactate dehydrogenase. Other transformations include evolution to prolymphocytic leukemia with the development of progressive refractory disease and a majority of prolymphocytes in the blood. Rarely, ALL or myeloma develops in the course of CLL.[180,181] The fundamental process of transformation can occur because CLL/SLL reflects a more mature cell type. When additional genomic alterations occur, the differentiation can be blocked and the disease phenotype can suddenly revert to an earlier precursor, characterized by a more primitive (de-differentiated) and rapidly growing entity with aggressive clinical behavior.

There have been many staging systems proposed, but the most widely used are those modified by Rai et al[182] and Binet et al,[183] the former used in the United States and the latter in Europe (Table 87.6). Clinical stage is the most important predictor of survival in patients with CLL. Numerous other factors have been reported to have an impact on survival and include age, sex, lymphocyte doubling time, pattern of marrow involvement, β-2 microglobulin levels, and immunophenotype of malignant cells.[184] Cytogenetic and molecular abnormalities have more recently emerged as powerful predictors of outcome and may impact treatment decisions.[185] For example, deletion of chromosome 17p or p53 mutation confers both an inferior OS and resistance to purine analog and alkylator-based therapy.

TABLE 87.6 CHRONIC LYMPHOCYTIC LEUKEMIA STAGING SYSTEMS

Staging System	Clinical Features	Median Survival (y)
Rai staging		
Low risk		>10
0	Lymphocytosis of blood and marrow	
Intermediate risk		7
I	Lymphadenopathy	
II	Splenomegaly	
High risk		2-4
III	Anemia, Hgb <10 g/dL (unrelated to hemolysis)	
IV	Thrombocytopenia <100,000 platelets/μL	
Binet staging		
A	<3 Areas of lymphadenopathy	12
B	≥3 Involved nodal areas	7
C	Anemia and/or thrombocytopenia	2

Hgb, hemoglobin.

Asymptomatic early-stage patients are typically followed without therapy ("watch-and-wait" or "active surveillance" approach). About 20% of such patients will continue to have an indolent course and never require therapy. Of the remaining patients, the decision to intervene therapeutically is often challenging. The International Workshop on CLL has established guidelines for the initiation of treatment, which include constitutional symptoms ("B symptoms") due to CLL, symptomatic lymphadenopathy and/or hepatosplenomegaly, anemia (hemoglobin <10 g/dL), thrombocytopenia (platelets <100,000/μL), and refractory autoimmune disease.[186] The absolute lymphocyte count should not be used as an indication for treatment, as symptoms associated with marked lymphocytosis due to leukocyte aggregation do not typically occur in patients with CLL.

For many years, the standard treatment for CLL included single-agent chlorambucil with or without prednisone.[187] The newer purine analogs, 2-deoxycoformycin, fludarabine, and 2-chloro-2′-deoxy-*b*-D-adenosine (cladribine or 2-CDA), have been tested in CLL, and, of these, fludarabine has shown a high response rate in combination with the anti-CD20

antibody, rituximab.[188] In a phase III trial comparing fludarabine to chlorambucil, the complete response rate with chlorambucil was 4% and with fludarabine 20%.[189] Overall response rates (ORRs) were 37% with chlorambucil and 63% with fludarabine. The median survival was 66 months (fludarabine) versus 56 months. For these reasons, fludarabine was a standard backbone of therapy for CLL for much of the late 20th century. More recently, a combination of fludarabine, cyclophosphamide, and rituximab, has resulted in a very high CR rate of 70% in patients with CLL, with a median time to progression of 80 months.[190] Moreover, when compared to fludarabine and cyclophosphamide, the addition of rituximab led to a survival benefit, which made this the regimen of choice in the up-front treatment of the young and fit.[191]

For patients who are older than 65 years, have comorbidities, and/or decreased renal function, bendamustine plus rituximab has been used traditionally, given the increased risk for adverse events including infectious complications.[192] This regimen has a relatively low toxicity mainly confined to a mild to moderate degree of reversible myelosuppression.[193]

However, the past decade has been revolutionized with the advent of targeted therapies, which have demonstrated superior efficacy and safety compared to chemoimmunotherapy in CLL. Ibrutinib—a selective irreversible inhibitor of Bruton tyrosine kinase, part of the B-cell receptor signaling cascade—was the first FDA-approved novel orally administered agent for the up-front treatment of older patient with CLL based on the results of the RESONATE-2 trial.[194] This was an open-label, randomized phase 3 trial, which compared ibrutinib and chlorambucil, in previously untreated older patients with CLL or SLL, and resulted in a higher ORR (86% vs 35%, $P < .001$), longer progression-free survival (median, not reached vs 18.9 months), and OS, with a relative risk of death that was 84% lower in the ibrutinib group than in the chlorambucil group (HR 0.16; $P = .001$). Ibrutinib has also been FDA approved for patients with relapsed/refractory CLL and for the up-front treatment of patients with CLL harboring a deletion in chromosome 17p or a deletion on p53 who have historically a poor response to traditional chemoimmunotherapy.[195,196]

More recently, ibrutinib with or without rituximab was found to have improved clinical outcomes and favorable safety when compared in large,

randomized trials to either standard chemotherapy with R-bendamustine or fludarabine, cyclophosphamide, and rituximab (FCR).[197,198] The role of targeted Bruton tyrosine kinase inhibitors (BTKi) was further advanced with the development of second-generation molecules with fewer off-target inhibition, including the approval of zanubrutinib and acalabrutinib for the treatment of CLL following head-to-head trials against ibrutinib that showed at least equivalent efficacy, but more favorable safety profile compared to ibrutinib.[199,200]

While BTKi have remarkable activity against CLL/SLL, they typically require continuous therapy for years until toxicity or intolerance. Acute toxicities may be less when compared to chemoimmunotherapy; however, cumulative toxicities such as cardiovascular, bleeding, and myalgias/arthralgias can limit long-term administration.[201] Fortunately, a second class of targeted orally administered medications targeting BCL2 have been shown to be highly efficacious against CLL/SLL and allow for a time-limited treatment over 12 to 24 months. Here, venetoclax was first shown to have efficacy in relapsed CLL, including with 17p deletion, and has a low toxicity profile, except for a propensity to cause tumor lysis syndrome due to its high response rate.[202] Impressively, it has led to an ORR of 79%, with a 20% CR, which is highly unusual in this heavily pretreated patient population. Based on these results, it had an initial FDA approval for patients with CLL with 17p deletion after at least one prior line of therapy. Subsequent large-scale randomized trials have established that venetoclax combined with anti-CD20 therapy (obinutuzumab in first line or rituximab in relapsed/refractory) has superior efficacy over prior standard chemoimmunotherapy.[203,204]

Modern CLL/SLL management in both the first-line and relapsed settings is typically without any chemotherapy, instead relying on sequential use of BTKi followed by venetoclax-based therapies or vice versa. However, recent trials that combine orally administered BTKi with venetoclax has also been shown to be safe and may provide durable remissions following time-limited therapy.[205]

Given the availability of highly active orally administered targeted therapies for CLL/SLL, there has been a dramatic shift away from traditional chemoimmunotherapy in the past decade. However, for younger patients with high-risk CLL, refractory disease may still occur. Here, allo-

HSCT has been employed with the recognition of graft-versus-leukemia effects and the advent of reduced-intensity conditioning. Earlier studies of allografting showed promising results in young patients with regard to disease control at the expense of significant treatment-related toxicity.[206,207] Several groups have reported favorable disease control and survival in high-risk patients with reduced-intensity conditioning regimens that are fludarabine or low-dose TBI based. Of note, patients with chromosome 17p deletion appear to respond as well to allografting as those without 17p deletion.[208,209] Indications for consideration of allografting have been proposed by the European Group for Blood and Marrow Transplantation and include early relapse following chemoimmunotherapy, resistance to fludarabine, chromosome 17p deletion, and Richter transformation.[209] The use of CAR T therapy may also be a viable option in the near future for multiply relapsed CLL/SLL refractory to BTKi and BCL2-based therapy.[210]

The Role of Radiotherapy in Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

RT was historically a very effective initial therapy for CLL. Prior to the plethora of modern chemotherapeutics, ultra-low-dose TBI was used without stem cell support decades ago for CLL, given its extraordinary radiosensitivity. This historical use of TBI used roughly 3 to 12 rad or 0.03 to 0.12 Gy per fraction several times a week titrated to response, but total doses in the range of 1 to 4 Gy,[211-214] But, RT is now almost entirely relegated to a palliative role for CLL, for instance, used in the management of painful splenomegaly or occasionally for cytopenias associated with splenomegaly when splenectomy is not an option. It is also indicated in instances of unresponsive disease to alleviate symptomatic adenopathy or nonlymphoid organ involvement. Remarkably, low doses on the order of 4 Gy in one to two fractions can be effective for palliation as used with low-grade B-cell lymphomas, although fractionated doses up to 20 Gy are also reasonable for more definitive local control.[215-217]

Localized SLL (stage I) is seldom encountered, but when it is, RT is the treatment of choice. In a series of 54 patients with SLL, including 14 patients with stage I or II disease who were treated with RT alone (40-44 Gy), the 10-year freedom from relapse for the patients with stage I and II

diseases treated with RT was 80% and 62%, respectively.[218] Radiation dose and field size are similar to that of other indolent non-Hodgkin lymphomas. The recommended total dose is 24 to 30 Gy; treatment volumes should follow involved-site principles similar to follicular lymphoma (FL). Like FL, RT can be used to palliate symptomatic lymphadenopathy in CLL/SLL. A small series of 14 patients with symptomatic SLL were treated with 2 Gy × 2 with involved-field radiation, resulting in an ORR of 85% with a median time to local progression of 14 months.[219] The regimen can be safely repeated if symptoms recur.

IRRADIATION TECHNIQUES

Anatomic Considerations

The radiation oncologist must be knowledgeable about the anatomy of the CNS, particularly the meninges (Gk. "membranes," ie, dura mater, arachnoid, and pia mater) and subarachnoid space for the proper design of CNS-directed radiation treatments. The epidural space lies between the periosteum and the dura, whereas the potential space between the dura and the arachnoid is called the *subdural space*. The pia and arachnoid are often described as a combined membrane called the *leptomeninges* (Gk. lepto, "thin" or "peel"). Between the arachnoid and pia is the subarachnoid space, which is filled with CSF. The pia hugs the surface of the brain, extending into sulci, fissures, and the internal cavities or ventricles, while the bulk of the arachnoid follows along the dura, except for the fine trabeculations, and into some of the major fissures of the brain. Arachnoid sheathes both nerves and blood vessels penetrating the pia and exiting the CNS, creating relatively short segments of subarachnoid space, which is of particular anatomic importance in the vertebral column. In the design of the inferior aspect of craniospinal radiation fields, the subarachnoid space extends laterally to the spinal ganglia, which are located within the intervertebral foramina.[220,221] Thus, coverage of the entire sacroiliac joints in such spinal field design is excessive. The caudad extent of the subarachnoid space is variable within the sacrum.[222] Clinically, the end of the thecal sac is now routinely determined on MRI scanning. A large retrospective study of 502 children (ages 1 month to 19 years) with nonpathologic MRI of the spine demonstrated that the mean level of thecal sac termination lies around the

level of mid-S2, with 90% ending at S2 or higher. All patients terminated between S1 and S3. For this reason, if MRI is not available, coverage through S3 can be used to ensure the entire sac is covered.[223] Pathologically, CNS leukemia originates as a perivascular infiltrate along the subpial blood vessels. As this progresses, the leukemia infiltrates preferentially into the subarachnoid space as well as into the brain parenchyma.[224]

Base of skull anatomy is also of importance to the radiation oncologist in the design of lateral cranial fields. The middle cranial fossa and temporal lobe project over the sphenoid sinuses on lateral radiographs. The cribriform plate projects along the roof of the orbit along an imaginary line that connects to the inferior aspect of the frontal sinuses. Several radiologic-anatomic studies have pointed out how the eye's lens in this "beam's-eye view" is less than 1 cm away from the cribriform plate, having implications in field design. Insuring coverage of the entire subarachnoid space should supersede the concerns of radiation-induced cataracts as this is a readily manageable complication.[225,226] Moreover, because subarachnoid space extends as a sheath along the optic nerve, it is standard to include the posterior half of the eye globes within cranial radiation fields by using the anterolateral aspect of the bony orbit as an anatomic landmark, as it typically lies along a line that roughly bisects the eye[226] (Figures 87.4 and 87.5).

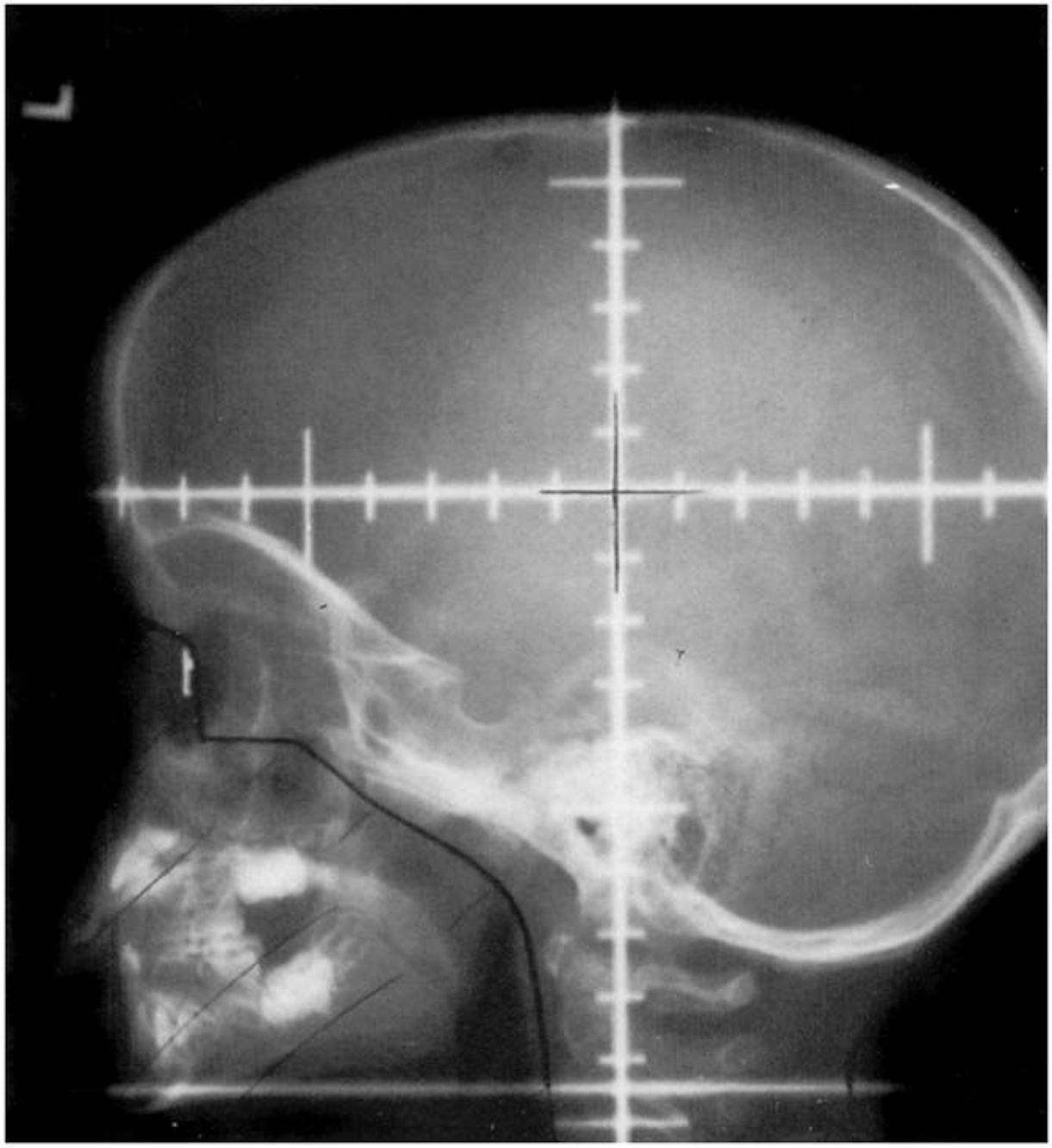
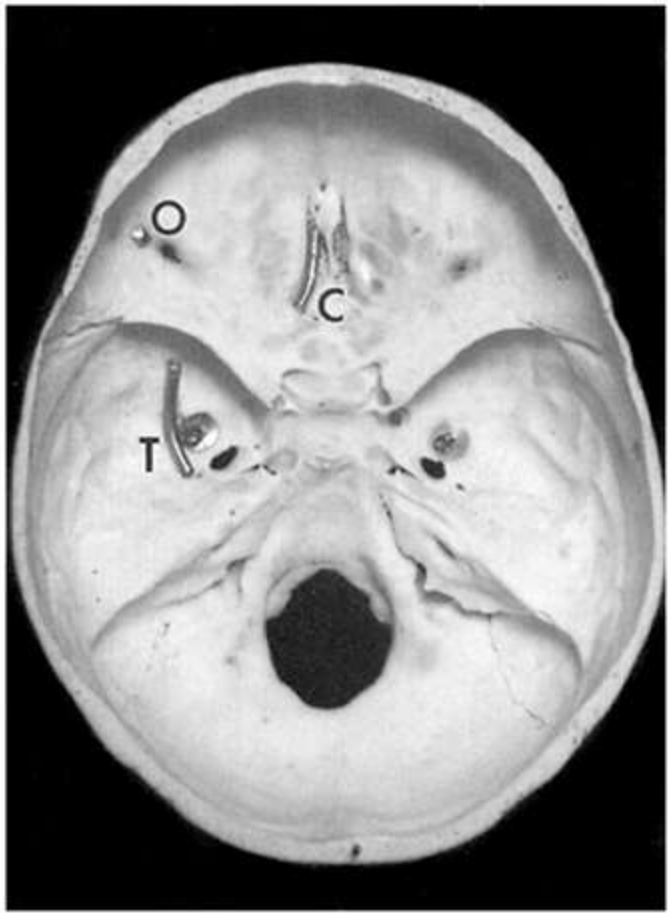


FIGURE 87.4 Cranial irradiation field outlining treatment that encompasses the entire cranial subarachnoid space. The radio-opaque markers outline the anterior aspect of the bony orbit to demarcate inclusion of the posterior aspect of the eye within the treatment fields.



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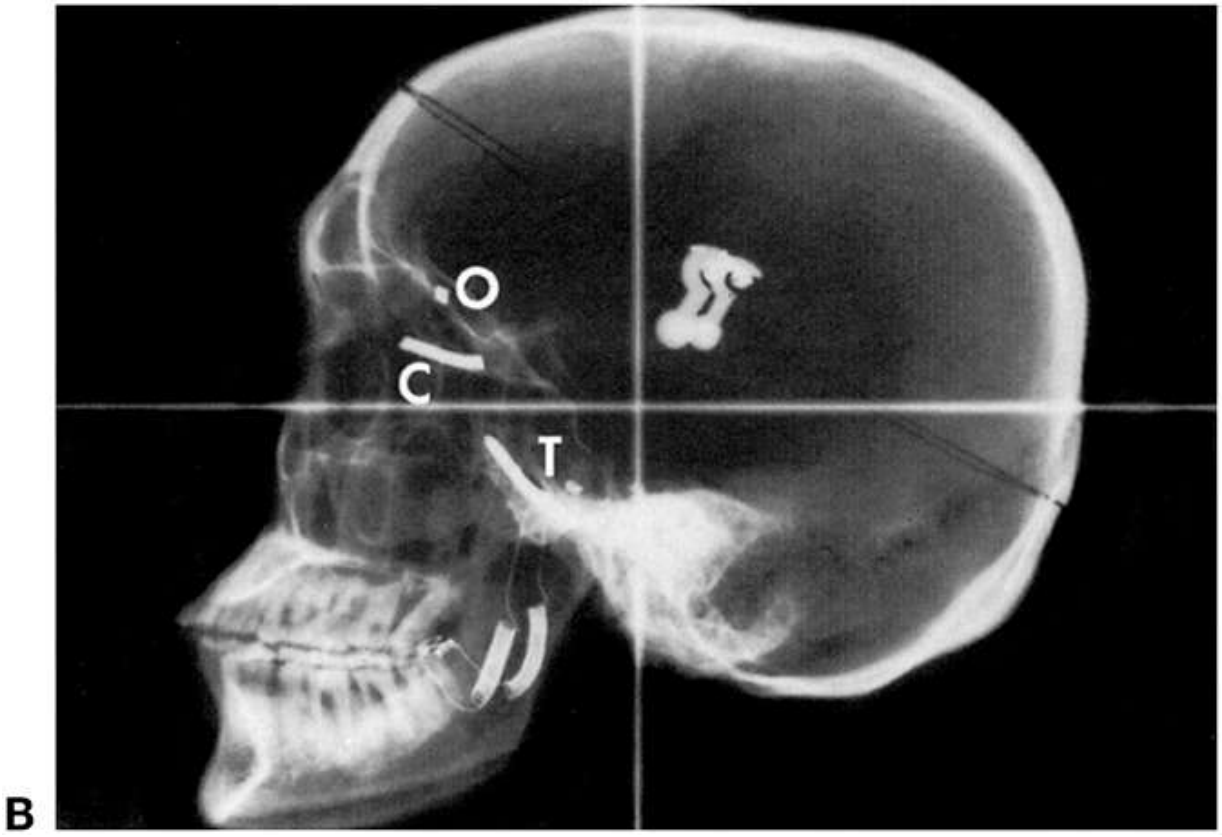

FIGURE 87.5 Skull views outlining anatomic limits of the base of skull for inclusion of the cranial subarachnoid space. A. Radio-opaque markers have been placed at the cribriform plate (C), roof of the orbit (O), and the temporal fossa (T). B. Plain lateral radiograph shows the projection of the cribriform plate, orbital roof, and temporal fossa.

To compensate for the blood-brain barrier, certain drugs are administered directly into the subarachnoid space either via lumbar puncture or via an intraventricular reservoir (eg, an Ommaya reservoir). IT drugs distribute unevenly, however, throughout the subarachnoid space.[227,228] This is not surprising, given the knowledge of brain anatomy and CSF circulation. CSF is mainly formed in the brain ventricles by the choroid plexuses, which are specialized capillary-rich tufted structures. This fluid then flows through the intraventricular foramina and the cerebral aqueduct of the midbrain into the fourth ventricle, from where it communicates with the rest of the subarachnoid space. CSF is resorbed principally in the dural sinuses via button-like projections called *arachnoid villi*. Thus, IT therapy theoretically undertreats the ventricular spaces and cerebral/cerebellar sulci as well as any gross disease extending into the brain substance. This concern has led

to the concept of combining CRT with IT chemotherapy; the latter to cover the spinal subarachnoid space. Similarly, when CSI is needed to treat a higher burden of CNS leukemia, IT therapy allows the spine to be treated at a lower dose than the brain.

Cranial Radiation

The volume of treatment must include the subarachnoid space within the cranial vault. The inferior margin has by historical convention extended to the bottom of the second cervical vertebra and includes the whole vertebral body. This may facilitate the matching of potential future treatment fields to the spine but is less of a practical concern with modern RT techniques. Limiting inferior coverage to C1 may better reduce incidental parotid irradiation,[229,230] while extending to C2 may offer a theoretical benefit of fully covering the inferior aspect of the dura within the brain as is used for primary CNS lymphoma and leptomeningeal disease. The inferior most point of the fourth ventricle, the obex, should be included in the field. Regardless, current COG protocols and practice have consistently used C2 as the inferior border for cranial fields.[231] Traditional field boundaries typically involve "flashing" over the scalp. However, it should be noted that this flashing also results in a hot spot of radiation dose within the vertex scalp using legacy 2D treatment planning techniques, responsible for much of the permanent alopecia seen in this location following cranial radiation at doses exceeding 20 to 24 Gy. Modern "scalp-sparing" techniques using nonflashed block edges or even modern conformal ("field-in-field" compensation) techniques. Higher energy radiation (10-15 MV) can be used to reduce scalp and follicle doses without underdosing the brain itself and has been described in adult patients with brain metastases from solid tumors.[232,233] However, these matters are largely cosmetic and should be placed in the context of the patient's clinical situation. Therefore, these approaches may not be appropriate for urgent cases of relapsed/refractory CNS leukemia or for patients for which on-treatment setup may be challenging due to altered mental status or young age may far outweigh long-term cosmetic outcomes. With regard to blocking the anterior facial structures, attention must be given to the base of skull anatomy to adequately cover the cribriform plate and the middle cranial fossa. The

cribriform plate is somewhat variable as a function of the age of the patient but is generally in line with the bottom of the frontal sinuses extending posteriorly for several centimeters and can also be identified via the use of standard CT simulation. The middle cranial or temporal fossa projects on lateral radiographs over the sphenoid sinuses. Figure 87.5 shows plain radiographs of an adult skull with radio-opaque markers at various anatomic landmarks. The posterior globe of the eye is included, given concerns of leukemic relapse in the posterior retina near where there is subarachnoid space extending along the optic nerves. Radio-opaque markers on the anterior aspect of the bony orbit are generally a good anatomic landmark that bifurcates the globe.

Figure 87.3 shows an example of conventional lateral fields used to treat a patient with ALL. Head immobilization with Aquaplast or similar thermoplastic material facilitates a high degree of treatment position reproducibility. Accounting for setup variation and beam penumbra leads to field design that clearly must encroach on the eye. With a forward gaze of the eyes, this would imply that the superior half of the lens is within the dose build-up region of the treatment fields. With the exception of very young children who cannot cooperate, voluntary rotation of the eye downward ("looking toward one's toes") would theoretically reduce the risk of cataracts. It should be noted that cataract repair surgery has become a commonplace safe and effective outpatient procedure, making cataracts a far less concerning potential side effect than it has been historically. However, it should be noted that the lens dose and downward rotation may also protect the central cornea and eyelid margins. Decreased dose to the cornea may reduce corneal irritation and sensitivity. Decreased dose to the Meibomian glands and accessory lacrimal glands located within the eyelids themselves is critical for preventing dry eye.[234] The Meibomian glands are critical in this respect, as they secret a lipid-based additive to tears that reduces tear evaporation,[235] in addition to other properties that help promote a functional tear film.[236] Contrary to common teachings in radiation oncology, the major lacrimal gland's primary role is largely for bolus tear secretion in response to emotional responses (ie, crying) or flushing out foreign bodies from the eye. and its role in basal eye lubrication, critical for maintaining quality of life, is a matter of debate.[237] Another important caveat in the treatment technique to minimize dose to the anterior portion of

the eyes is the alignment of the anterior beam edge divergence. Figure 87.6 depicts this concept of angling the gantry 3° to 5° to achieve a parallel anterior beam margin behind the lens, bisecting the eye and producing a relatively tight radiation dose gradient.

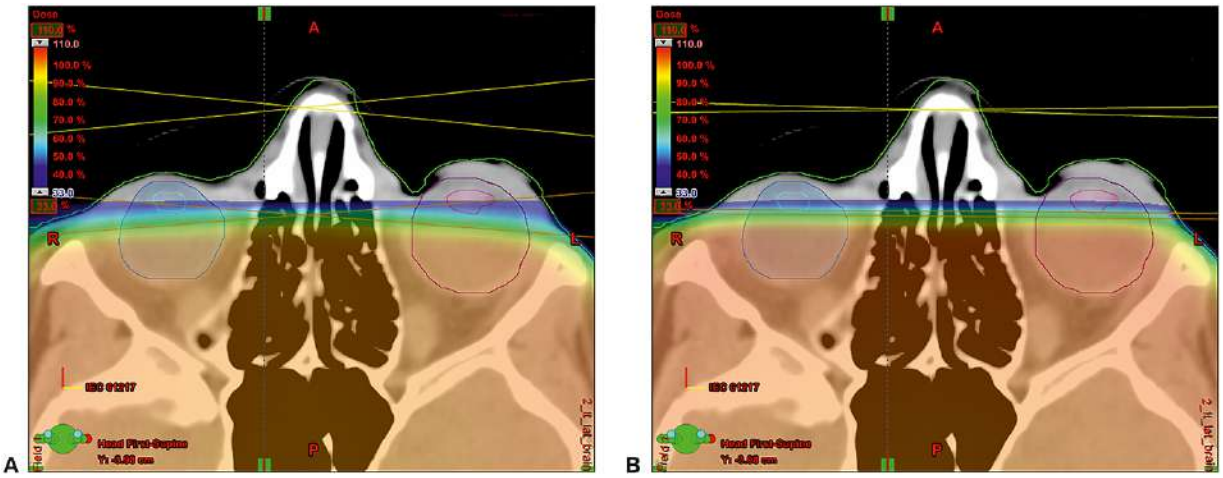

FIGURE 87.6 An 8-year-old boy with T-cell acute lymphoblastic leukemia, central nervous system type 3 at diagnosis, requiring cranial radiotherapy to 18 Gy in 12 fractions after remission from systemic therapy. Alignment of anterior divergence of lateral cranial fields showing beam edge and color wash of radiation dose superimposed on axial computed tomography scan at level of eyes. A. Parallel opposed fields result in widened dose gradient within anterior aspect of eyes. B. Gantry angle of 3° to 5° results in alignment of anterior margin beam divergence from lateral fields and tighter dose gradient.

Some radiation oncologists prefer to simply place the isocenter of the treatment beam just posterior to the lens so that the anterior eye is protected by a modified "half-beam block." With the advent of CT simulators, alignment of beam divergence can be performed graphically, also correcting for any head rotation with immobilization without the need for trigonometric calculations. The standard radiation dose for prophylactic cranial radiation in pediatric ALL is 18 Gy in 9 to 10 fractions, but protocol-driven use of 12 to 15 Gy in 8 to 10 fractions is based on evolving experience, with selected patients being treated with BFM-type ALL programs. Although this is a reasonable dose for adults, some protocols still continue to utilize 24 Gy in 12 fractions or even 23.4 Gy in 13 fractions.

Craniospinal Radiation and Therapeutic Cranial Radiation for Central Nervous System Leukemia

Historical, photon-based 3D techniques of cranial spinal radiation involved precise matching of beam divergence between a PA spine field and lateral parallel opposed cranial fields. Additional details of this technique are discussed in detail in the previous edition of this textbook in the chapter on medulloblastoma (see Chapters 90). Limitations of 3D craniospinal, photon-based radiation include the creation of hot- and cold-matched spots, limited forgiveness at the matched junction of each field, and the need to shift or "feather" the match junction by 1 to 2 cm once or twice during the treatment course (resulting in essentially two additional plans). When CSI is indicated, referral to a proton center may be considered if it is logistically feasible in order to decrease anterior structure (lungs, heart, liver, abdomen, kidneys, bowel, etc). However, given the current and likely ongoing scarcity and cost associated with proton beam centers in many areas, volumetric modulated arc radiotherapy (VMAT)-based approaches may offer a feasible and acceptable alternative.[238] VMAT-based treatment planning uses two to three isocenters (based on patient height), one for the brain and then one to two for the upper and lower spine. Gradients or "auto-feathering" is used to create gradual gradients of several centimeters (eg 6-8 cm) to minimize the impact of minor daily variations in setup. However, robust coordination of isocenters in CSI remains critical and is required for proper dosimetry for both photon and proton-based CSI treatment. Critically, VMAT-based CSI can be used to spare anterior structures, dramatically reducing the radiation dose to the heart, lungs, liver, bowel, and esophagus. Recent "vertebral body–sparing" approaches, in which the vertebral bodies themselves are spared, have been reported and found to be associated with marked reductions in cytopenias.[149] This is particularly critical in relapsed and/or refractory adult CNS leukemia cases, where severe or persistent life-threatening cytopenias caused by disease and prior chemotherapy can be exacerbated by large-volume CSI and lead to life-threatening complications. Acute drops in platelet counts at 7 to 10 days following initiation of CSI of approximately 75% are common and correlate roughly with the anatomic distribution of bone marrow residing in the adjacent cervical spine (~4%), thoracic spine (~18%), lumbar spine (~15%),

sacrum (~8%), and partial pelvis (~23%).[239] In patients without preexisting cytopenias, marrow recovery is typically rapid and complete following CSI. However, in patients with previously existing severe cytopenias, CSI can exacerbate these further and contribute to mortality from complications related to profound persistent cytopenias.

Radiation doses for overt CNS leukemia are 16 to 30 Gy to the cranium in 1.5- to 1.8-Gy fractions. The authors recognize that it is increasingly rare that overt CNS leukemia for children or adults be treated with craniospinal fields, but there can be clinical circumstances where this may still be rational. In such cases, along with the administration of IT chemotherapy, the spine may be treated to lower doses than the brain to total doses of 6 to 15 Gy depending on individual circumstances. However, salvage CSI for patients with isolated CNS relapse with a long (>6 months) disease-free interval may be curable with definitive intent CSI as mentioned earlier (Figure 87.7). Plans for possible TBI must be taken into account. This part of the preparative regimen for an allogeneic transplant can be conceptualized as being in part CNS therapy.

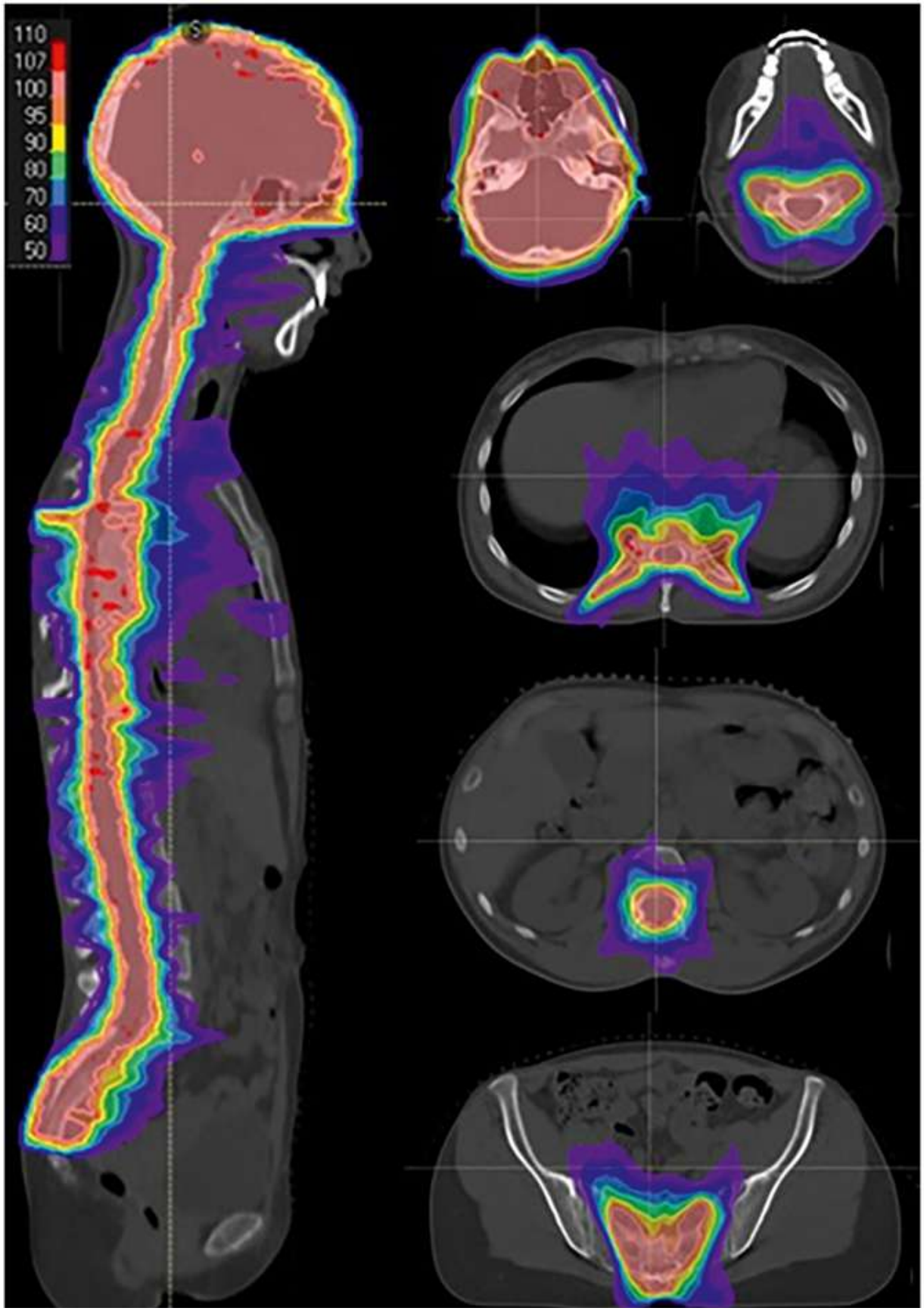
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FIGURE 87.7 Example of salvage VMAT CSI case. Sagittal and selected axial views are shown with percent doses (50%-110%) of the prescribed 21 Gy in 1.5-Gy fractions. The patient was a 39-year-old female with acute myelogenous leukemia who completed fludarabine/busulfan induction therapy followed by allogeneic hematopoietic stem cell transplant. One year later, she developed midback pain with magnetic resonance imaging evidence of bulky recurrent disease at T6-7 with enhancement of the right-sided nerve roots and deformation of the spinal canal. Cerebrospinal fluid was positive for malignant cells, which progressed on intrathecal therapy after a brief initial response. She completed urgent radiotherapy to T5-7 paraspinal nerve roots to 4 Gy over two fractions treated with anteroposterior/posteroanterior fields. She then underwent CSI with curative intent to a dose of 21 Gy in 1.5 Gy per fraction to the entire neuroaxis with coverage of adjacent peripheral nerve roots with the involved thoracic paraspinal nerve roots (second axial image from the top right). CSI was accomplished using a VMAT approach using a multiple isocenter "auto-feathering" (ie, gradient match) technique with an overlap of 3 cm. Acutely, she developed G2 oral mucositis and G2 nausea. Long-term toxicities included generalized fatigue, which ultimately resolved, and dry eyes. Her malignancy-related back pain completely resolved. She was in remission without evidence of disease at her last follow-up 2.6 years after CSI. CSI, craniospinal irradiation; VMAT, volumetric modulated arc radiotherapy.

Testicular Irradiation

For the management of leukemic infiltration of the testes, both gonads and the scrotum can be irradiated with either electrons or photons. With the patient in a "frog-leg" position and the penile shaft taped onto the abdomen, an anterior inferior oblique photon field works well. Attention to the cremaster reflex and potential ascent of the testes into the inguinal canal is important so as to avoid a geographic miss. For megavoltage photon beams, bolus is often required to avoid superficial underdosing. An anterior wedged pair beam arrangement often works well. In young boys where the scrotum/testes thickness is under 2 cm, 250-kV orthovoltage x-rays may also be used. Alternatively, direct en face electron beams of appropriate energy work adequately. Though there are considerable dose inhomogeneities in treating such a curved surface with electrons, the relatively low doses employed in this setting translate into relatively low risks related to skin and subcutaneous soft tissue reactions. Radiation doses typically used are 24 to 26 Gy in 1.5- to 2.0-Gy fractions. When a testicular boost is given in conjunction with TBI for an HSCT, the dose is either 4 Gy × 1 fraction or 2 Gy × 2 fractions.

Splenic Irradiation

Massive splenomegaly may be seen with CML, CLL, hairy cell leukemia, and splenic marginal zone lymphomas where the spleen can extend into the pelvis. Significant splenomegaly may also occur with prolymphocytic leukemia, myeloproliferative disorders such as CMML, polycythemia vera or essential thrombocytosis, or myelofibrosis. One type of myelofibrosis called *agnogenic myeloid metaplasia* is characterized by progressive bone marrow failure, splenomegaly, and EMH. It is therapeutically important to recognize which conditions of splenomegaly are due to EMH rather than leukemic infiltration as whole-spleen RT with modest radiation doses can result in severe, long-lasting pancytopenia when the spleen is the primary hematopoiesis site.[240] Splenic hematopoiesis can also occur with late stages of CML, myeloproliferative disorders, and hairy cell leukemia. Extreme care is required to proceed slowly with RT in these circumstances.

Historically, splenic RT was commonly employed for palliation, but it is now uncommon, as more effective systemic treatments have been developed. Nevertheless, the radiation oncologist is called on to assist with the management of symptomatic splenomegaly from these hematologic disorders from time to time, often with excellent results.[241] Symptomatic problems include pain, early satiety, diaphragmatic irritation, and bleeding risk related to sequestration of platelets. Leukemic infiltration of the spleen responds to relatively low doses of radiation.[242] Particularly in an older patient with other comorbidities, palliative splenic RT can offer significantly less risk than splenectomy.[243] Splenic irradiation has been reviewed by Weinmann et al.[244]

Anterior and posterior opposed portals for photon treatments are generally employed. In cases of leukemic infiltration, standard practice is to treat the whole spleen in 0.25- to 1.0-Gy fractions either daily or once to 3 times a week with doses titrated to response and hematologic tolerance.[245] As the spleen responds, one may progressively shrink the treatment fields accordingly. Generally, it is prudent to start treatment very conservatively. Blood counts may need to be monitored several times a week. Total radiation dose delivered is determined clinically by when palliation is achieved. Total doses are typically in the range of 4 to 10 Gy with usually no more than 20 Gy required. Occasionally, a large spleen that is

extensively fibrotic will not respond to RT. CLL and prolymphocytic leukemia are particularly radiosensitive, with occasional abscopal effects seen with splenic irradiation. One trial of CLL and splenomegaly successfully used 1.0 Gy a fraction once a week for an average of seven treatments, yielding good palliation including complete normalization of blood counts in 44% of patients.[246]

In patients with EMH, the potential for severe neutropenia or thrombocytopenia is very high with even modest radiation doses. Dose per fraction may need to be as low as 0.1 to 0.5 Gy treating several times a week to avoid severe and protracted myelosuppression. Another strategy in this situation is to treat only half of the spleen. For myelodysplastic conditions or EMH/intrasplenic hematopoiesis, total doses of 1 to 9 Gy are usually adequate.

With splenic irradiation, nausea is uncommon with these low-dose fractions but can be readily managed with antiemetics if necessary. As there can be rapid cell lysis, allopurinol to prevent uric acid nephropathy is advised. Cumulative dose to the left kidney should be monitored, especially as retreatment in the future may be required, but it is rare for doses beyond 20 Gy to be required.

SEQUELAE OF THERAPY IN PEDIATRIC PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

Somnolence Syndrome

Approximately 1 month following cranial radiation, up to 40% to 50% of patients may develop lethargy, irritability, anorexia, and even fevers. This has been termed *somnolence syndrome*. It has been associated with electroencephalographic abnormalities and CSF pleocytosis.[247,248] This syndrome is self-limited and typically reverses within 1 to 3 weeks. Glucocorticoids in acute management may be helpful. Two reports suggest that the incidence of this syndrome is reduced if patients receive steroids during CRT.[117,249]

Pituitary Dysfunction

Hypothalamic-pituitary irradiation can impact endocrine function in a dose- and age-dependent manner. For the doses used in leukemia management, growth hormone (GH) deficiency is the most common abnormality observed. Age younger than 5 years at the time of RT is associated with particular susceptibility to the development of GH deficiency. Higher radiation doses as well as younger age correlate with an increased incidence of GH deficiency and a shorter time period for its clinical manifestations.[250] It is more common after 24 Gy than 18 Gy.[251,252] Up to 22% of adult survivors of pediatric ALL who have received CRT may have diminished GH responses to provocative testing.[253] Precocious puberty has been reported with radiation doses to the hypothalamic-pituitary region as low as 18 Gy, although it seems to be more prevalent in females who receive doses of 24 Gy or higher.[254] Doses less than 35 to 40 Gy are rarely associated with other pituitary hormone deficiencies or abnormalities. Thus, patients receiving CRT for leukemia, particularly in childhood, require regular follow-up of their linear growth and sexual development. Abnormalities should then lead to appropriate endocrinologic evaluation so as to determine the need for therapy with either GH replacement or gonadotropin-releasing hormone agonists.

Cognitive Dysfunction

Intellectual and psychological impairments from the treatment of leukemia have received wide attention. Evidence that RT is to blame has been a major impetus in investigations aimed at lowering the dose delivered to the brain or eliminating it completely. Increasingly, however, there is evidence that chemotherapy may also be causing similar detriments. Objective measures of cognitive function and social functioning are inherently difficult. Nevertheless, a variety of assessment tools, intelligence quotients, or scales have been verified as useful measures of language, reasoning, and performance skills. Other descriptive measures of lowered school achievement have also been reported. Cognitive dysfunction is thought to be the result of white matter injury causing deficits in the speed of information processing.[255] These effects are most pronounced in children younger than age 5 years and probably most pronounced in those younger

than 3 years of age when the brain is still undergoing growth and development, especially with myelinization.

Some reports have suggested a gender difference in susceptibility to radiation injury, with females more likely than males to develop intellectual impairments, although this has not been consistently reported.[256,257] The Dana Farber group has suggested that the reduction in IQ seen in girls was the result of an interaction between high-dose MTX and cranial radiation.[258] Moreover, an impairment in verbal memory observed in both boys and girls was independent of cranial radiation, suggesting toxicity from systemic therapy.[258]

A reduction in radiation dose from 24 to 18 Gy has not consistently been reported to result in lower cognitive difficulties.[123,124,126] Further reduction to 12 Gy is under study. Overall, for these radiation doses, the cognitive deficits have been arguably small, with average full-scale IQ measures decreasing by no more than 10%, while other studies fail to show measurable changes. Perhaps a more important statistic is the proportion of patients with significant reductions, say greater than 15 points in IQ scales; the SJCRH group has reported that up to 22% to 30% of children have such deficits after 18 Gy, 24 Gy, or no CRT.[257] One hypothesis is that a component of cognitive difficulties is related to chemotherapy rather than RT. Regardless, a recent report from the Dana Farber group suggests that in patients with high-risk ALL receiving 18-Gy cranial radiation, neurocognitive function many years after therapy is not significantly different from that of the general population.[127] Importantly, this was a group of patients who experienced a favorable 5-year DFS of 75% with a 1% CNS relapse rate. The Dana Farber group has been investigating hyperfractionated cranial radiation for CNS prophylaxis (0.9 Gy twice daily vs 1.8 Gy daily to a total dose of 18 Gy). There are no obvious differences between standard or hyperfractionated RT in terms of late neurotoxicity reported thus far, although there are numerous methodological problems inherent in such a comparison.[111,127,128] An emerging experience suggests that stimulants such as methylphenidate may be of help in managing treatment-related cognitive problems, particularly some attentional or social deficits.[259]

Leukoencephalopathy

Some early prophylactic cranial radiation studies for childhood ALL showed a significant incidence of profound encephalopathy occurring months after irradiation.[144,260] The highest incidence was seen when cranial radiation with doses as low as 24 Gy were combined with IV MTX. Leukoencephalopathy is thought to represent a demyelinating condition that may be initiated by endothelial damage and a subsequent cytokine cascade with ischemic microinfarcts.[261] While concomitant IV MTX seems to be a significant synergistic factor, leukoencephalopathy has been observed at low incidence rates with RT alone at doses greater than 30 to 35 Gy, with IT MTX, or in conjunction with other chemotherapy agents. High-dose chemotherapy alone is becoming increasingly recognized as causing similar dementia-like syndromes. One should also remember that after CRT, the blood-brain barrier is thought to be more permeable, which may contribute to chemotherapy effects on cognitive function.[262] Regardless, the risk of leukoencephalopathy is decidedly rare after doses of less than 20 Gy.

Secondary Malignancies

One of the larger single-institution series of pediatric ALL with extended follow-up of 2,169 patients from SJCRH treated between 1962 and 1998 reported that the cumulative incidence of secondary cancers was 4.2% and 10.9% at 15 and 30 years, respectively.[263] The incidence does not appear to plateau, although second malignancies occurring after 20 years tend to be lower grade malignancies that include meningiomas and basal cell skin cancers. The Childhood Cancer Survivor Study (CCSG) has also documented an elevated risk for nonmelanoma skin cancers in pediatric ALL survivors, with a cumulative incidence of 10% at 30 years.[264] Cranial MRI surveillance may also increase the detection of asymptomatic radiation–associated meningiomas, estimated to have an incidence of 15% at 20 years and which may sometimes be multifocal.[265] Other secondary cancers attributable to RT include gliomas, parotid gland tumors, thyroid cancers, and sarcomas (bone and soft tissue).[263,266-268] The types of secondary brain tumors from RT tend to be evenly split between meningiomas and high-grade gliomas.[263] In an earlier report from the CCSG of 9,720 patients treated for ALL, 43 secondary cancers were observed after a mean follow-

up of 6 years.[268] Of these, 24 were CNS tumors in patients who had previously received 24-Gy CRT. All but one of these patients with CNS tumors had been younger than 5 years of age at diagnosis of their acute leukemia, suggesting an age-related susceptibility. Additional data from the CCSG suggest that the risk of gliomas and meningiomas both have a linear radiation dose-response relationship.[268,269] The CCSG has now extended additional long-term follow-up of patients with ALL in different treatment eras using various radiation dose prescriptions to more definitely observe that lower doses of cranial irradiation correlate with lower risk for meningiomas.[270] Age of exposure to radiation is also a significant determinant of meningioma risk as lower aged patients have higher risk. On multivariable modeling, there is an increase in HR of 1.12 per 5 Gy of CRT exposure. While there is hope that a reduction in cranial radiation doses to as low as 12 Gy may reduce the incidence of secondary tumors, the German BFM group has observed in the long-term follow-up of their ALL-BFM 90 trial a 3.4% actuarial incidence of secondary brain tumors at 16 years of follow-up.[129] In comparison, for those children with ALL not receiving CRT, the incidence of subsequent brain tumors was 1.2% at 15 years.[266] In a review of 3,182 children treated by an allogeneic bone marrow transplant, 25 solid tumors were observed compared to an expected incidence of one case.[271] Most of these cancers originated in the CNS or thyroid gland. Moreover, most of these patients had received TBI as part of their preparative regimen before transplant.

Testicular Effects From Radiotherapy

Gonadal dysfunction is quite rare from CRT for leukemia management unless patients undergo retreatment that results in high cumulative doses. Direct effects from testicular irradiation, however, are very common. Doses as low as 1 Gy, even from scattered dose from adjacent external beam fields, will cause transient oligospermia or azoospermia. Higher doses, particularly those used in TBI or therapeutic testicular radiation, would be expected to cause permanent infertility. Leydig cell function, on the other hand, is more radioresistent.[272] Low serum testosterone levels or delayed puberty is unusual with doses less than 29 Gy to the testes. One report of 60 male survivors of ALL showed significant germ cell dysfunction as

manifested by increased follicle-stimulating hormone levels and testicular atrophy in 55% of patients treated with testicular RT and in 17% treated with craniospinal RT. The incidence of Leydig cell dysfunction was very low.[272]

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CHAPTER 88

Plasma Cell Neoplasms: Multiple Myeloma and Solitary Plasmacytomas

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EPIDEMIOLOGY AND ETIOLOGY

Plasma cell neoplasms are a rare and heterogeneous group of diseases, usually associated with the presence of a monoclonal (or myeloma) protein (M protein) or free light chain. The majority of plasma cell neoplasms are multiple myeloma (approximately 95%), with solitary plasmacytoma (SP) and plasma cell leukemia occurring less commonly.[1] Myeloma, the second most common hematologic malignancy, currently accounts for approximately 14% of hematologic malignancies.[2]

The incidence of myeloma varies significantly across the world. Reported by the International Agency for Research on Cancer, an estimated 176,404 people worldwide were diagnosed with myeloma in 2020, with age-standardized (world) incidence rate (ASR) of 1.8 per 100,000 and a worldwide annual mortality rate of 1.1 per 100,000.[3] Per 100,000, the ASRs vary: from 1.1 in Asia, to 2.9 in Europe, to 4.7 in North America.[3] Data from the Surveillance, Epidemiology, and End Results database indicates the rate of new myeloma diagnoses in the United States was 7.1 per 100,000 per year during the period 2016 to 2020, with a lifetime risk of 0.9%.[4] For 2023, it is estimated that there will have been 35,730 new cases (constituting 1.8% of all new cancer diagnoses) and 12,590 deaths (representing 2.1% of all cancer deaths) due to multiple myeloma in the United States.[4] Internationally, cancer registry data suggest that the incidence of multiple myeloma is gradually increasing.[1,2,4]

The incidence rises with advancing age, with a median age at diagnosis of 69 years, and only 3% of all cases diagnosed in those younger than 45 years.[4] There is a male predominance, with a male:female ratio of

approximately 1.5:1.[3] For African Americans, the incidence and mortality rates are approximately double that of Hispanic and White people.[4] An increase in prevalence is also contributed to by the availability of effective treatment options. The observed 5-year relative survival rates of patients with multiple myeloma have increased over time, from 26% in 1975 to 34% in 2000, and rising more steeply to 62% in 2015.[4]

There is limited information about the cause of multiple myeloma; however, environmental exposures and genetic events may be the risk factors. There are studies reporting an association with certain chemicals, such as petroleum products.[5,6] Familial clustering has been observed; however, consistent predisposing germline mutations have not yet been uncovered.[7]

It is clear that multiple myeloma evolves from precursor conditions of smoldering myeloma and monoclonal gammopathy of unknown significance (MGUS). A recent large population-based study reports a prevalence of smoldering myeloma of 0.53% in individuals aged 40 years or above.[8] Comparatively, MGUS is a more common condition, with incidence increasing from <2% below the age of 50 to >10% in the ninth decade of life.[9] Annual risks of progression from smoldering myeloma and MGUS are 10% and 1%, respectively.[7,10-12] Further risk stratification is possible on the basis of clinical and genetic criteria,[7] but the precise mechanisms for progression to symptomatic myeloma are not presently clear.

PATHOPHYSIOLOGY

Myeloma arises from malignant transformation of post–germinal center B cells, which are committed to terminal differentiation to plasma cells. One of the earliest genetic events is the illegitimate switch recombination of partner oncogenes into the immunoglobulin heavy chain (IgH).[13] The result of these genetic abnormalities is the development and propagation of a clonal population of B cells within the bone marrow; this, however, is common and can be seen in up to 5% of the general population over the age of 70 (MGUS).[14] However, the vast majority of those with MGUS will not go on to develop myeloma. The subsequent pathogenesis of multiple myeloma is complex with high heterogeneity, and the development of the

disease is a multistep process requiring the activation of oncogenes or mutations in tumor suppressor genes. These secondary events may include *RAS* mutations, chromosome 13 deletions, *MYC* translocations, and increasing genomic instability.[13] This progression results in the proliferation of the malignant plasma cells in the bone marrow microenvironment, which provides a protective niche for myeloma cells and is responsible for many of the unique features of the disease. The contribution of the bone marrow microenvironment to the pathogenesis is a focal area of research, resulting in current and potential future therapeutic targets. Established myeloma is sustained by a number of microenvironment features, including the bone marrow stroma itself and the cytokines interleukin-6, vascular endothelial growth factor, and insulin-like growth factor-1.[13] The slow accumulation of these malignant cells gradually results in the characteristic clinical features of myeloma: anemia, bone resorption, hypercalcemia, renal failure, and immunodeficiency. Myeloma-induced bone destruction is a result of the imbalance between osteoblast and osteoclast activation, leading to osteoporosis and osteolytic bone lesions, primarily by amplification of the RANK pathway and the inhibition of the Wnt signaling pathway.[13]

CLINICAL PRESENTATION

Plasma cell neoplasms have a wide clinical spectrum, ranging from asymptomatic MGUS and smoldering myeloma, to SP, symptomatic slowly progressive myeloma or Ig light chain amyloidosis, and aggressive plasmablastic disease and plasma cell leukemia (Table 88.1).[14,15,41] In all cases, the existing plasma cell clone usually secretes either a monoclonal IgG/IgA paraprotein or κ/λ free light chains (light chain myeloma). The interaction of the malignant plasma cells with the bone marrow environment or the monoclonal light chains with other organs is the source of organ damage in patients with this illness.[13] Significant interpatient and intrapatient heterogeneity in clinical presentations is demonstrated by these disorders, which raises many challenges in diagnosis and patient management. These concepts have become particularly important, as the molecular mechanisms by which the disease progresses through these "stages" provide essential information that may help us to better understand the disease and its potential therapies.

TABLE 88.1 THE SPECTRUM OF MYELOMA[14,41]

	MGUS	Smoldering Multiple Myeloma	Multiple Myeloma[a]	Plasma Cell Leukemia
Clinical	No organ damage	No myeloma-defining events[b] or amyloidosis	One or more myeloma-defining events[b]	Organ damage, leukocytosis, high tumor burden, and high proliferation rate
Marrow disease/M protein features	<10% clonal plasma cells	10%-60% clonal plasma cells and/or M protein ≥30 g/L (or urinary M = protein ≥500 mg per 24 h)	≥10% clonal plasma cells or biopsy-proven plasmacytoma[a]	Plasma cells in peripheral blood ≥2 × 10^9/L or ≥20%. Immature plasma cells in bone marrow
Management	Monitor	Close follow-up	Chemotherapy	High-dose chemotherapy
Transformation rate	0.5%-1% per year	10% per year	—	—

CT, computed tomography; MGUS, monoclonal gammopathy of unknown significance; MRI, magnetic resonance imaging; PET, positron emission tomography.

[a]Multiple myeloma can be diagnosed when (a) clonal bone marrow plasma cells ≥10% or biopsy-proven bone or extramedullary plasmacytoma is present, plus (b) any one or more myeloma-defining events as outlined below.[b] Alternatively, without the presence of myeloma-defining events, the presence of (a) any one or more of the following biomarkers of malignancy also satisfies the diagnosis of multiple myeloma: clonal bone marrow plasma cell percentage ≥60%, involved:uninvolved serum light chain ratio ≥100, or >1 focal lesions on MRI (each focal lesion must be 5 mm or more in size).[13] This is also known as the SLiM (Sixty percent, Light chains, MRI) criteria.

[b]Myeloma-defining events: end-organ damage attributed to myeloma: hypercalcemia (calcium >2.75 mmol/L); renal insufficiency (creatinine >177 μmol/L or creatinine clearance <40 mL/min); anemia (hemoglobin <10 g/dL or >20 g/L below the lower limit of normal); and bone lesions (one or more osteolytic lesions on x-rays, CT, or PET scan).

Monoclonal Gammopathy of Unknown Significance

MGUS has traditionally been considered a benign or a premalignant condition, in which a small proportion of patients will ultimately progress to multiple myeloma or related diseases (Table 88.1). There are three distinct clinical types of MGUS: light chain MGUS, IgM MGUS (rarest

subtype, subdivided into plasma cell type and not otherwise specified type), and non-IgM MGUS (IgG, IgA, or IgD MGUS).[16] Non-IgM MGUS is the commonest subtype; light chain Ig MGUS represents 20% of cases.[12,15] Diagnostic criteria for MGUS include all of the monoclonal proteins <3 g/dL, bone marrow clonal plasmacytosis <10%, and no related organ damage. This condition is likely much more common than initially thought, as it has been documented in 3% of the population and 5% in those over the age of 70 and 7.5% of those over the age of 85.[17] The risk of transformation to myeloma and related diseases (such as amyloidosis, indolent lymphoproliferative disorders, or Waldenström macroglobulinemia) has been estimated at 1% per year, based on a 30-year follow-up of 1,384 patients at the Mayo Clinic.[12] Further risk stratification based on the level and subtype of the paraprotein and alteration of the free light chain ratio can be used to determine the risk of progression.[18] Most individuals present to attention when an M protein is detected as an incidental finding on protein electrophoresis performed as part of an evaluation for one of a wide variety of clinical symptoms and disorders. By definition, individuals with MGUS have no symptoms of myeloma; surveillance, based on the risk of progression, is the only management required.

Smoldering Myeloma

Smoldering myeloma represents an intermediate stage between MGUS and symptomatic multiple myeloma. In this precursor form of myeloma, patients meet serologic monoclonal IgA/IgG protein levels ≥3 g/dL or urinary protein >500 mg per 24 hours and/or bone marrow clonal plasma cell infiltration of 10% to 60%,[14] with the absence of myeloma-defining events or amyloidosis (Table 88.1). These patients are not significantly anemic, do not have hypercalcemia or renal insufficiency, and do not have bony disease. The risk of transformation to multiple myeloma is high: approximately 10-fold higher than in MGUS (approximately 10% per year).[15] However, 30% of patients will remain asymptomatic without significant progression to multiple myeloma at 10 years.[15] Further stratification based on clinical and biochemical parameters segregates groups into those with the highest risk (50%) of progression over 2 years.[19,20] This group is the subject of previous and ongoing trials for early

intervention, which have demonstrated a benefit for progression-free survival (PFS) from immunomodulatory- based treatment. Most patients with smoldering myeloma are managed by close surveillance and do not require active treatment; however, some guidelines recommend that established risk models are used to identify those who may benefit from early implementation of therapy despite not yet fulfilling the criteria for symptomatic myeloma.[19-21]

Solitary Plasmacytomas

Two forms of SP are recognized according to the site of origin: SP of bone (SBP) and solitary extraosseous/extramedullary plasmacytoma (SEP).[16] SPs are rare, with SBP accounting for 4% to 5% of all plasma cell neoplasms and SEP accounting for 1% to 3% of all plasma cell neoplasms.[15] The median age at diagnosis of SP is 55 to 65 years, on average about 10 years younger than patients with multiple myeloma.[22-25] Males are affected predominately (male-to-female ratio 2:1).[22,23] A diagnosis of SP is made if all the following criteria are satisfied at presentation: a histologically confirmed single lesion (arising in bone or extramedullary tissue) with negative skeletal imaging outside the primary site, normal bone marrow biopsy (<10% monoclonal plasma cells), and no myeloma-related organ dysfunction.[14] A monoclonal protein is present in 30% to 75% of cases (particularly for an osseous presentation), and the level is usually minimally elevated (IgG < 3.5 g/dL, IgA < 2.0 g/dL, and urine monoclonal κ or λ < 1.0 g per 24 hours).[26-28]

SPB are more common, constituting 70% to 80% of SP.[23] Such cases are considered stage I multiple myeloma according to the original Durie Salmon staging system.[29] The most common location is the vertebra.[22,23] Most patients present with skeletal pain or a pathologic fracture of the affected bone. On imaging, a lytic lesion is typical, with or without adjacent soft tissue mass. SEPs are less common (20%-30% of all SPs) and commonly present with local compressive symptoms, for example, a mass in the upper aerorespiratory passages may present with dyspnea and cough.[22-24,30]

Histologically, both SBP and SEP are characterized by monotonous proliferations of mostly mature plasma cells with light chain restriction.[15]

The histologic diagnosis of SEP can be difficult in the presence of an accompanying neoplastic B-cell population, with the main differential diagnosis being extranodal marginal zone lymphoma (mucosa-associated lymphoid tissue type), where there can be extensive infiltration by plasmacytoid cells.[31,32] Anaplastic SEPs may show plasmablastic cytology, raising the differential diagnosis of an aggressive B-cell lymphoma with plasmablastic differentiation, and can arise in the context of immunosuppression and Epstein-Barr virus infection.[33,34]

Multiple Myeloma

By definition, a diagnosis of multiple myeloma involves end-organ damage or imminently anticipated damage. These myeloma-defining events are described by the mnemonic CRAB (*C*alcium elevation, *R*enal insufficiency, *A*nemia, and *B*one disease).[13,14] Recent modification added additional features when CRAB findings are absent, to include the SLiM criteria of 60% or more clonal plasma cells in bone marrow (*S*), light chains (*Li*) involved:uninvolved ratio >100, or magnetic resonance imaging or MRI (*M*) detected number of bone lesions >1, measuring at least 5 mm in size for the diagnosis of multiple myeloma.[35]

Patients with multiple myeloma usually present with signs or symptoms related to the infiltration of plasma cells into the bone or other organs, or secondary to kidney damage from Ig deposition. Bone pain and symptoms of anemia, such as easy fatigability, are the most common.[36] Because of the myriad effects of the disease, other insidious symptoms can result from a combination of hypercalcemia, renal impairment, infection, neurologic compression, and, occasionally, hyperviscosity. Bone disease manifesting as generalized osteopenia and multiple lytic bone lesions can frequently lead to pathologic fractures. In the vertebral column, this may often result in diminished height. Sclerotic lesions at presentation are rare and can be a manifestation of a related disorder, POEMS syndrome. Amyloidosis, a disorder related to the deposition of misfolded light chains in various organs, can occur as a secondary manifestation in some cases of multiple myeloma. Another important manifestation of the disease can be major or recurrent infection due to hypogammaglobulinemia, which is especially prominent in patients with relapsed and refractory disease.

Laboratory evaluation generally confirms anemia, high erythrocyte sedimentation rate, and a variable degree of granulocytopenia and thrombocytopenia. An abnormal monoclonal Ig (M protein) in the blood or urine is characteristic,[13,36] most commonly IgG or IgA. Biclonal disease is also recognized, and, rarely, nonsecretory disease in approximately 3% of cases. In up to 20% of cases, only monoclonal light chains are detected. It is important to assess for hypercalcemia, renal dysfunction, and integrity of the skeleton because these complications require appropriate management. A constellation of polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes characterizes a rare plasma cell dyscrasia known as POEMS syndrome.[37,38]

Plasma Cell Leukemia

Plasma cell leukemia is a relatively rare variant of multiple myeloma, where the proliferation of plasma cells is not confined to the bone marrow but may be detected in the peripheral blood. Plasma cell leukemia is defined as ≥5% circulating plasma cells in the peripheral blood smears of patients with symptomatic myeloma.[39] Although recent studies suggest that even 1% to 2% circulating plasma cells confer a prognosis similar to plasma cell leukemia,[40] presenting signs and symptoms can include those seen in multiple myeloma and other leukemias such as anemia, thrombocytopenia and infections. It carries a very poor prognosis, with a median survival of <1 year, and shorter when occurring as secondary plasma cell leukemia.[41-43] There is currently no standard therapy for this condition, but patients are usually treated with high-dose, multiagent chemotherapeutic regimens or with experimental therapies, followed by autologous stem cell transplant (ASCT).[41]

DIAGNOSTIC WORKUP AND STAGING

The recommended tests for the diagnosis of plasma cell neoplasms are outlined in Table 88.2. The most important components relate to the measurement and quantification of the M protein on serum electrophoresis, bone marrow examination with flow cytometry and cytogenetic studies, serum β_2 microglobulin and albumin, and diagnostic imaging.[44]

Quantification of the monoclonal Ig with immunofixation techniques is also acceptable and especially useful if the M component is at a low level. Assays for free light chains should be performed in the serum and the urine (Bence Jones proteinuria).

TABLE 88.2 DIAGNOSTIC WORKUP FOR PLASMA CELL NEOPLASMS

General

History and physical examination
Complete blood count and blood smear, chemistry panel including calcium and creatinine

Standard Laboratory Tests

Bone marrow aspirate and trephine biopsy or biopsy of mass if solitary lesion (clonality, immunophenotype, and cytogenetic studies [both conventional cytogenetics and fluorescence in situ hybridization], and plasma cell labeling index)
Serum β_2 microglobulin, albumin, C-reactive protein, and lactate dehydrogenase
M component measurement:

- Serum protein electrophoresis and immunofixation for quantification of immunoglobulins
- Urine protein electrophoresis
- Serum-free light chain measurements

Imaging Studies

Skeletal survey
Computed tomography and magnetic resonance imaging (eg, detailed assessment of local disease extent and bulk, visualize soft tissue tumor, and assess vertebral column for occult disease, compression fractures, or spinal cord compression)
Fluorine-18-fluorodeoxyglucose positron emission tomography or magnetic resonance imaging to detect and quantify occult disease

Imaging is essential for diagnosis, staging, and treatment planning. The traditional imaging modality is the plain x-ray skeletal survey. However, this lacks the sensitivity of more modern imaging modalities.[45] Radionuclide bone scan has limited value in myeloma due to low sensitivity.[19] For structural assessment, both computed tomography (CT) and MRI are useful. CT is a fast and convenient modality for the detection and assessment of lytic bone lesions and extramedullary disease in three dimensions but lacks the sensitivity of MRI. MRI has higher sensitivity for earlier detection of marrow infiltration by direct visualization of the disease within the bone marrow, rather than the myeloma-related secondary effects on cortical bone that are seen on CT.[46] MRI of the axial skeleton is

recommended as a sensitive screening tool to rule out occult vertebral lesions (eg, for patients with SP) and to evaluate for the presence of spinal cord or nerve root compression.[46] MRI is also useful to assess the extent of infiltration of SP (eg, in the head and neck region), providing valuable information to guide radiotherapy (RT) planning.[25] 18-Fluorine (^{18}F)-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT combines the complementary information of the metabolic activity of the disease with the spatial resolution of CT. FDG-PET/CT has recognized the value in the detection of additional plasmacytomas as well as diffuse and variegated marrow infiltration that cannot be appreciated on other imaging modalities; however, false positives can occur secondary to infection or inflammation (eg, postsurgery, post-RT), and false negatives may occur in patients with diabetes or receiving steroid therapy.

For patients with presumed SP or smoldering myeloma, the use of more sensitive studies (flow cytometry of the bone marrow, cytogenetics, and sensitive whole-body imaging such as MRI and PET/CT) as part of the diagnostic workup is strongly recommended to rule out subclinical multiple myeloma.[47] In a consensus statement from the International Myeloma Working Group (IMWG), whole-body MRI or FDG-PET/CT is mandatory for patients with suspected SP.[48] Similarly, whole-body MRI or FDG-PET/CT is also strongly recommended to distinguish between smoldering myeloma and active multiple myeloma.[48]

The staging criteria for the historical Durie Salmon staging system are detailed in Table 88.3.[29] The newer revised International Myeloma Staging System (R-ISS) is simple, validated, and of importance particularly for present and future clinical trials (Table 88.4).[49] It incorporated important cytogenetic abnormalities (eg, del[17p], t[4;14], and t[14;16]) into the staging system. Criteria for the diagnosis of MGUS and smoldering myeloma have been recently updated by the World Health Organization and the IMWG.[16,21]

TABLE 88.3 DURIE AND SALMON SYSTEM FOR STAGING OF MULTIPLE MYELOMA

Clinical Stage	Description
Stage I	All of the following: • Hemoglobin >10 g/dL

Clinical Stage	Description
	• Serum calcium normal • Normal bone structure or solitary plasmacytoma only • Low M component (IgG < 5 g/dL, IgA < 3 g/dL, and urine light chains <4 g/24 h)[a]
Stage II	Fitting neither stage I nor stage III
Stage III	One or more of the following: • Hemoglobin <8.5 g/dL • Serum calcium >12 mg/dL • Advanced lytic bone lesions • High M component (IgG > 7 g/dL, IgA > 3 g/dL, and urine light chains >12 g/24 h)
Subclassified	
A	Relatively normal renal function (serum creatinine <2 mg/dL)
B	Abnormal renal function (serum creatinine ≥2 mg/dL)

IgG, immunoglobulin G.

[a]For solitary plasmacytoma: IgG < 3.5 g/dL and IgA < 2 g/dL.

From Durie BG, Salmon SE. A clinical staging system for multiple myeloma correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer. 1975;36(3):842-854. Copyright © 1975 American Cancer Society. Reprinted by permission of John Wiley & Sons, Inc.

TABLE 88.4 ISS AND R-ISS STAGING OF MULTIPLE MYELOMA

Stage	Description	Median Survival
International Staging System (ISS)[72]		
ISS stage I	Serum β_2 microglobulin <3.5 mg/L and serum albumin ≥35 g/L	62 mo
ISS stage II	Neither I nor III ie, β_2 microglobulin <3.5 mg/L, with albumin <35 g/L, or β_2 microglobulin 3.5-5.5 mg/L	44 mo
ISS stage III	Serum β_2 microglobulin ≥5.5 mg/L	29 mo
Revised International Staging System (R-ISS)[49]		

Stage	Description	Median Survival
R-ISS stage I	ISS stage I and standard risk chromosomal abnormalities[a] (by iFISH) and normal LDH	Not reached[b]
R-ISS stage II	Neither R-ISS stage I nor III	83 mo
R-ISS stage III	ISS stage III and either high-risk chromosomal abnormality[a] (by iFISH) or high LDH	43 mo

iFISH, interphase fluorescent in situ hybridization; LDH, lactate dehydrogenase.

[a]High-risk chromosomal abnormalities are any one of Del(17p), translocation t(4;14), or translocation t(14;16).

[b]Median follow-up 46 months.

PROGNOSTIC FACTORS

Solitary Plasmacytoma

For patients with SP, several factors have been associated with the risk of progression from SP to myeloma. Many of these factors reflect the presence of subclinical myeloma and were derived from early patient cohorts that predate the highly sensitive staging investigations that are mandated in modern practice. Bony presentation has been consistently demonstrated to have a significantly higher risk of progression to myeloma, with a 10-year rate of 76% observed in earlier cohorts, compared with an extramedullary presentation that has a 10-year rate of 36%[23,50] (Figure 88.1). Subclinical bone disease that may be detected radiographically as generalized osteopenia[51] or abnormal MRI scan of the spine[46,52-54] predicts for rapid progression to symptomatic multiple myeloma. Therefore, in the updated IMWG criteria for the diagnosis of multiple myeloma, MRI detection of more than one focal lesion in bone, of 5 mm or more in size, is recognized as multiple myeloma.[14] Furthermore, careful evaluation of the bone marrow using flow cytometry identifies clonally related plasma cells in some patients treated for presumed SBP, and this occult bone marrow disease is highly predictive of progression to myeloma and of major prognostic value.[15,47,55,56] In addition, suppression of the normal Ig classes correlates with a higher risk of progressing to myeloma.[51,57] The presence of low-level M protein prior to RT is extremely common and is not associated with a

higher risk of progression to multiple myeloma; however, its persistence following RT is highly predictive of subsequent systemic failure.[28,47,58-60] In addition, the presence of anaplasia (ie, a higher histologic grade)[61] or high-grade angiogenesis[62] in the tumor sample is associated with a poor outcome. The prognostic value of age remains uncertain; older age has been identified as a risk factor for progression to myeloma and poor prognosis in some series,[58,63-66] but not in others.[23,67-71]

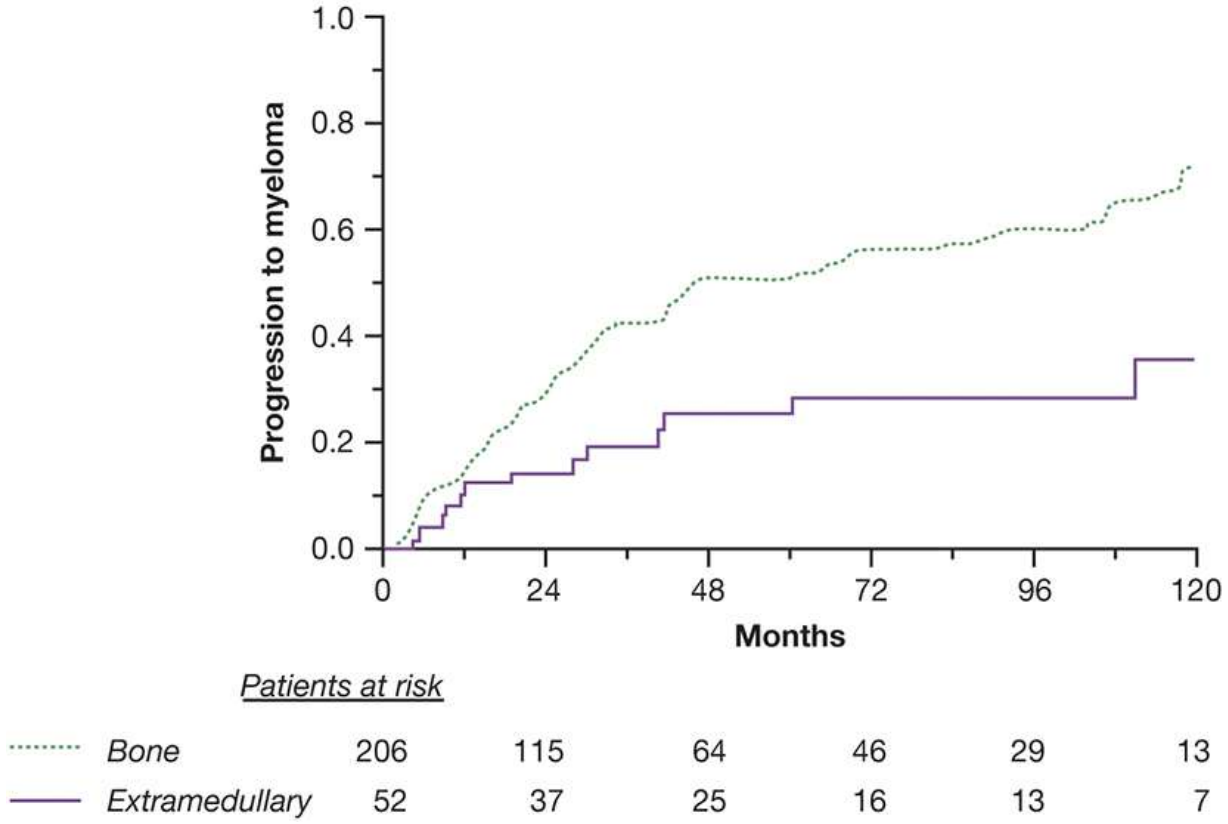

FIGURE 88.1 Probability of progression to multiple myeloma according to bone (dotted line) versus extramedullary (solid line) solitary plasmacytoma in 258 patients (P = .0009). (Reprinted from Ozsahin M, Tsang RW, Poortmans P, et al. Outcomes and patterns of failure in solitary plasmacytoma: a multicenter Rare Cancer Network study of 258 patients. *Int J Radiat Oncol Biol Phys*. 2006;64[1]: 210-217. Copyright © 2006 Elsevier. With permission.)

Multiple Myeloma

Analysis of over 1,000 patients evaluated at the Mayo Clinic revealed the following adverse prognostic risk factors: Eastern Cooperative Oncology Group performance status 3 or 4, serum albumin <3 g/dL, serum creatinine

≥2 mg/dL, platelet count <150,000/μL, age ≥70 years, β_2 microglobulin >4 mg/L, plasma cell labeling index ≥1%, serum calcium ≥11 mg/dL, hemoglobin <10 g/dL, and bone marrow plasma cell percentage ≥50%.[36] The International Staging System (ISS)[72] and the R-ISS[49] have been validated to assist in prognostication. For the original ISS, over 10,000 patients were evaluated, and the three-stage system was developed based on two variables: serum albumin and β_2 microglobulin. In the R-ISS, cytogenetic abnormalities associated with a worse prognosis were also incorporated[68] (Table 88.4). The definition of high-risk disease continues to evolve. To risk-stratify patients with myeloma at initial diagnosis, fluorescence in situ hybridization studies are performed on the bone marrow for t(4;14), t(14;16), t(14;20), gain/ amp 1q, del 1p32, and del 17p13 with biallelic TP53 inactivation and/or multiple cytogenetic aberrations.[73] The presence of certain clinical features such as extramedullary disease, plasma cell leukemia, primary refractoriness to treatment, or early relapse within 18 months is also classified as high-risk disease.[74]

MANAGEMENT OF SOLITARY PLASMACYTOMA

Confirming the true solitary nature is critical for accurate diagnosis of SP. For all patients with presumed or suspected SP, full evaluation is mandatory to exclude occult myeloma (see section “Diagnostic Workup and Staging”).

Solitary Bone Plasmacytoma

Radiotherapy

Localized RT is the standard of care for SBP, achieving long-term remissions and potential for cure. Early patient data demonstrate high rates of local control following RT for SBP; however, long-term overall survival (OS) rates were more modest due to the high risk of progression to multiple myeloma[23,28,51,57,59,63-65,67,75-78] (Table 88.5). As shown in Table 88.5, rates of progression to myeloma vary across the published literature, likely reflecting the less sensitive staging investigations used in earlier patient cohorts to exclude sites of subclinical involvement. In the largest series of 206 patients with SBP diagnosed from 1977 to 2001, the multicenter Rare

Cancer Network reported the 10-year rate of progression to myeloma to be 72%, with higher annual risk occurring within the first 3 years of diagnosis.[23] This finding suggests that subclinical myeloma may have existed in a proportion of patients at the time of initial diagnosis with SBP. However, in modern practice, the use of more sensitive imaging and bone marrow evaluations upfront are more likely to identify patients with occult myeloma.[56] For example, studies have documented that 29% to 50% of patients with apparent SP had multiple asymptomatic lesions detected in the spine on MRI.[44,46,52,54,79] With increasing availability of whole-body MRI and FDG-PET/CT, "stage migration" is a likely phenomenon, with a proportion of patients with presumed SP being upstaged following the detection of additional sites of disease by MRI or FDG-PET/CT.[80-82] This "Will Rogers phenomenon"[83] is likely to contribute to an observed increase in myeloma-free survival rates for patients with SP in studies where more sensitive staging investigations are employed. A recent multicenter study of 54 patients diagnosed with SBP from 2000 to 2019, and in whom 55% had either staging MRI or FDG-PET/CT, revealed a relatively lower risk of progression to myeloma and excellent survival, with myeloma-free survival rate of 69% and OS rate of 95%, at 5 years.[84] Details regarding RT dose and technique are discussed later in this chapter.

TABLE 88.5 SOLITARY PLASMACYTOMA OF BONE: REPRESENTATIVE TREATMENT RESULTS (SERIES INCLUDING MORE THAN 30 PATIENTS)

Reference	Number of Patients (Median f/u)	Local Control (%)	Progression to Myeloma (10-y Rate %)	Overall Survival (10-y Rate %)
Bataille and Sany[64]	114 (>10 y)	88	58	68[a]
Chak et al[65]	65[b] (87 mo)	95	77	52
Frassica et al[75]	46 (90 mo)	89	54[a]	45
Jackson and Scarffe[57]	32 (101 mo)	97[a]	~76	~45
Holland et al[67]	32 (66 mo)	94	53[a]	—
Galieni et al[51]	32[b] (69 mo)	91[a]	~68	49

Reference	Number of Patients (Median f/u)	Local Control (%)	Progression to Myeloma (10-y Rate %)	Overall Survival (10-y Rate %)
Liebross et al[59]	57	96[a]	51[a]	~55
Tsang et al[63]	32 (95 mo)	78 (8-y rate)	64 (8-y rate)	65 (8-y rate)
Wilder et al[28]	60 (94 mo)	90	62	59
Ozsahin et al[23]	206[b] (56 mo)	79 (10-y rate)	72	52
Kilciksiz et al[94]	57[b] (29 mo)	94	37[a]	68
Reed et al[58]	59 (64 mo)	97	56 (5-y rate)	76 (5-y rate)
Katodritou et al[96]	65[b] (60 mo)	—	—	69
Finsinger et al[76]	35 (107 mo)	94	57[a]	51
Barzenje et al[77]	49 (152 mo)	100	59[a]	60
Sharpley et al[78]	53[b] (54 mo)	89	47 (3-y rate)	
Elsayad et al[84]	54[b] (42 mo)	91	31 (5-y rate in living patients)	95 (5-y rate)

[a]Crude rate.

[b]Multiple institutions.

Surgery

For patients with mechanical bone instability or rapidly progressive neurologic compromise such as spinal cord compression, urgent surgery should be considered.[26] For those with gross tumor resection of SBP, postoperative RT is indicated because of a high likelihood of residual microscopic disease.[47] Surgery alone, without RT, leads to an unacceptably high local recurrence rate[23] and is generally not recommended.

Adjuvant Systemic Therapy

Arguably, for patients at high risk of occult systemic disease, management approaches that incorporate systemic therapy may be of theoretical appeal to eradicate subclinical disease and prevent the development of myeloma.[85] However, the role of adjuvant systemic therapy in accurately staged SBP is a highly contentious area of debate.[47] By definition, true SBP represents localized disease with the absence of occult systemic disease on highly sensitive staging modalities, in which case the addition of adjuvant systemic therapy may be of questionable value and remains to be proven in the modern era. Published in 1996, one randomized trial suggested a benefit from adjuvant melphalan and prednisone (MP) given for 3 years after RT: With median follow-up of 8.9 years, patients treated with adjuvant chemotherapy had a myeloma progression rate of 12%, compared to 54% in those treated with RT alone.[86] However, this was a small study that used less sensitive staging investigations coupled with outdated systemic therapies and RT techniques; furthermore, the risk of diminishing stem cell reserve and/or inducing leukemia makes the prolonged use of alkylating agents an undesirable treatment option for most patients. The use of adjuvant novel agents, such as proteasome inhibitors (PIs) (eg, bortezomib) or immunomodulatory drugs (IMIDs, eg, lenalidomide), may be more theoretically attractive. Pilot data indicate feasibility of combining novel agents with RT,[87] and this approach is under active investigation. In the United Kingdom, a multicenter, phase III clinical trial is underway to examine the potential role of adding lenalidomide and dexamethasone (LD) to definitive RT (NCT02544308). A phase III study is underway in China to compare RT alone to RT combined with bortezomib, lenalidomide, and dexamethasone for SP (NCT05248633). In Alaska, USA, a phase III study is investigating the addition of adjuvant ixazomib, lenalidomide, dexamethasone, and zoledronic acid, to adjuvant zoledronic acid alone, after definitive RT for patients with SBP (NCT02516423). And, a single-arm pilot study from Memorial Sloan Kettering in the United States is investigating checkpoint blockade therapy (durvalumab, anti–PD-L1 [Programmed Cell Death Ligand 1]) plus definitive RT on the development of multiple myeloma in patients with SBP with limited clonal bone marrow plasmacytosis (NCT03196401).

Solitary Extramedullary Plasmacytoma

Radiotherapy

Localized RT is associated with high rates of long-term disease control and is the standard of care for patients with SEP.[47] In contrast to SBP, SEP is generally associated with a lower risk of progression to myeloma and improved prognosis.[47] In the reported literature, the long-term outcomes for patients with SEP vary widely, with 10-year OS rates ranging from 43% to 89% and progression to myeloma rates ranging from 7% to 44%[23,24,58,61,69,77,84,88-97] (Table 88.6). Older studies utilizing less sensitive staging modalities should be interpreted judiciously. Two of the more recently published series, with patients diagnosed no earlier than 2000, report myeloma-free survival rates of 76% to 88% and OS rates of 81% to 88% at 5-years.[84,97] Details regarding RT dose and technique are discussed later in this chapter.

TABLE 88.6 SOLITARY EXTRAMEDULLARY PLASMACYTOMA: REPRESENTATIVE TREATMENT RESULTS (SERIES INCLUDING MORE THAN 20 PATIENTS)

Reference	Number of Patients (Median f/u)	Local Control (%)	Progression to Myeloma (10-y Rate %)	Overall Survival (10-y Rate %)
Knowling et al[89]	25 (71 mo)	88	28	43
Soesan et al[90]	25 (44 mo)	88	—	~50
Susnerwala et al[61]	25 (73 mo)	79	8[a]	59 (5-year rate)
Liebross et al[91]	22 (44 mo)	95[a]	44 (5-year rate)	50
Galieni et al[92]	46[b] (118 mo)	92	15[a]	78 (15-year rate)
Strojan et al[24]	26 (61 mo)	87	8	61
Ozsahin et al[23]	52[b] (56 mo)	74 (10-y rate)	36	72
Bachar et al[93]	56 (96 mo)	88 (10-y rate)	28	56

Reference	Number of Patients (Median f/u)	Local Control (%)	Progression to Myeloma (10-y Rate %)	Overall Survival (10-y Rate %)
Kilciksiz et al[94]	23[b] (29 mo)	95	17[a]	89
Reed et al[58]	25 (64 mo)	80	30 (5-y rate)	85 (5-y rate)
Sasaki et al[95]	67 (63 mo)	87	30	56
Katodritou et al[96]	32[b] (60 mo)	—	—	89
Zhu et al[69]	48 (45 mo)	86	—	60
Barzenje et al[77]	28 (172 mo)	96	7[a]	67
Elsayad et al[84]	30[b] (42 mo)	90	24 (5-y rate)	88 (5-y rate)
Nakaya et al[97]	24[b]	—	—	81 (5-y rate)

[a]Crude rate.

[b]Multiple institutions.

Surgery

Although complete surgical excision may have curative potential for small SEP,[98] most patients present with larger lesions or with tumors that are not amenable to complete excision. Postoperative RT is indicated for all incompletely excised lesions due to unacceptably high rates of local recurrence from surgery alone.[25,47]

MANAGEMENT OF MULTIPLE MYELOMA

For patients with myeloma of all ages, survival outcomes have continued to improve over recent decades following the development of effective chemotherapy combinations, including PIs, IMIDs, monoclonal antibodies (MoAbs), and high-dose chemotherapy with ASCT.[7,99-101] These agents have been used sequentially in induction, consolidation, and maintenance strategies, resulting in the majority of patients achieving minimal residual disease (MRD)-negative status with a resultant PFS of >60 months in both

transplant eligible and nontransplant eligible patients.[102,103] In the past decade, advances in immunotherapy including T-cell redirecting therapies such as bispecific antibodies (BsAbs) and chimeric antigen receptor T-cell (CAR-T) therapy have shown high levels of efficacy in relapsed/refractory multiple myeloma with deep and durable responses.[35] A list of approved agents is summarized in Table 88.7. Choice of therapy is significantly determined by access to treatments in different geographical, regulatory, and resource-limited environments; these are major considerations for decision-making in addition to routine clinical factors.[104-110] Despite these therapeutic advances, disease progression presently remains the most common cause of death, highlighting the ongoing need for more effective and more accessible treatment strategies for patients with multiple myeloma.[111]

TABLE 88.7 SYSTEMIC TREATMENT OPTIONS FOR RELAPSED/REFRACTORY MULTIPLE MYELOMA

Conventional therapy	Low-dose alkylators: melphalan, cyclophosphamide Corticosteroids: dexamethasone, prednisolone
Combination chemotherapy	DTPACE (dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide)/DCEP High-dose cyclophosphamide
Autologous stem cell transplantation	High-dose melphalan 140-200 mg/sqm conditioning
Novel agents	Proteasome inhibitors: bortezomib, carfilzomib, ixazomib Immunomodulatory agents (IMIDs): thalidomide lenalidomide, pomalidomide Monoclonal antibodies: anti-CS1—elotuzumab; anti-CD38—daratumumab, isatuximab Histone deacetylase (HDAC) inhibitors: panobinostat XPO1 inhibitor: selinexor Bispecific antibodies: CD3 B-cell maturation antigen (BCMA)—teclistamab, elranatamab; CD3/GPRC5D—talquetamab Chimeric antigen receptor T (CAR-T) cell therapies: anti-BCMA—idecabtagene vicleucel, ciltacabtagene autoleucel
Agents targeting bone disease	Bisphosphonates: pamidronate, zoledronic acid Anti-RANKL: denosumab

DCEP, dexamethasone, cyclophosphamide, etoposide, and cisplatin.

Initial Treatment of Symptomatic Multiple Myeloma

Patients who have symptomatic multiple myeloma require treatment of the malignant plasma cell clone. Once the decision is made to treat, however, the first step is to determine eligibility for high-dose chemotherapy and ASCT.[13] This modality has become the standard of care for patients <65 years of age, with fit patients up to 75 years also being considered for transplant in many treating centers. It is necessary to stratify patients early so that the ability to collect stem cells is not compromised by some types of induction therapy.[112]

Patients Eligible for Autologous Stem Cell Transplantation

In patients who are candidates for ASCT, various regimens can be used to induce response prior to stem cell collection. Historical regimens included combinations of chemotherapeutic agents, such as alkylators, anthracyclines (vincristine, adriamycin, dexamethasone or VAD), and corticosteroids.[113,114] Since the turn of the century novel agents, IMIDs, PIs, and MoAbs have been used in combination for induction therapy, with significantly superior results for depth of response and PFS and OS.[102,115]

Bortezomib

Bortezomib was the first PI to be used in clinical trials and has demonstrated efficacy and safety in frontline therapy, when used in combination with alkylators, anthracyclines, or IMID. Indeed, response rates have dramatically improved when compared with VAD or dexamethasone alone. A randomized comparison of bortezomib plus dexamethasone (BD) versus VAD as induction therapy before ASCT showed that BD produced superior complete response (CR) or near-CR rate (14.8% vs 6.4%), at least very good partial response (PR) rate (37.7% vs 15.1%), and overall response rate (ORR) (78.5% vs 62.8%), as compared to VAD. Median PFS was 36.0 months (BD) versus 29.7 months (VAD; P = .064).[116] Even as a single agent, with dexamethasone or doxorubicin, bortezomib has remarkable efficacy and safety in initial therapy.[117] Bortezomib is often the preferred agent in patients with renal insufficiency and high-risk disease. The greatest challenge, however, remains neuropathy, occurring in 9% to 13% of patients at ≥grade 3 in initial trials[118]; this may

be mitigated by early recognition and dose reduction strategies and by using weekly dosing schedules[119] or subcutaneous route of delivery.[120]

Lenalidomide

Lenalidomide is an IMID derived from thalidomide that has also been shown to be effective, both as upfront therapy and in relapsed disease. It is most commonly used in combination with low-dose dexamethasone. A phase III trial of lenalidomide with low-dose dexamethasone versus lenalidomide with high-dose dexamethasone found that despite a higher rate of CR or PR with high-dose therapy, 1-year OS was 87% in the high-dose group versus 96% in the low-dose group ($P = .0002$), largely because of the significant toxicity of the former.[121] As a result, the trial was stopped and patients on high-dose therapy were crossed over to low-dose therapy. Three-year OS rates in both arms were 75%.[122] This has resulted in the extensive use of this combination in upfront myeloma.

Lenalidomide has also been used in combination with conventional chemotherapy and most recently with bortezomib. This has resulted in even higher ORRs of >90% and near-CR rates of >50%.[115,123] The combination of lenalidomide, bortezomib, and dexamethasone (RVD) gave a CR/very good PR rate of 77% and is considered to be the current standard of care for induction.[115] The post-transplant MRD-negative rate for this combination is 54%, which translates to a median PFS of 67 months.[102]

Thalidomide

Early reports indicate that thalidomide and dexamethasone yield a response rate of 64% (similar to VAD), without compromising the ability to collect stem cells, but with a rate of deep vein thrombosis of 12%.[124] The Medical Research Council Myeloma IX trial compared cyclophosphamide-thalidomide-dexamethasone (CTD) with cyclophosphamide-VAD as induction before ASCT: The CR rate was 20.3% after CTD and 11.7% after cyclophosphamide-VAD,[124] lower than other regimens cited above. Thus, preferred initial regimens include bortezomib- and/or lenalidomide-based combinations, whereas thalidomide or doxorubicin is very infrequently used in current practice.

Daratumumab

The addition of anti–CD38-directed antibody therapy with daratumumab to the standard of care of bortezomib, lenalidomide, and dexamethasone (D-RVD) has been demonstrated to further improve the depth of response for transplant-eligible, newly diagnosed patients with myeloma. In the phase III GRIFFIN study, stringent complete response (sCR) rates and PFS were greater for D-RVD than RVD: sCR 62% versus 45%, and 2-year PFS 96% versus 90%.[125] In the recently published phase III PERSEUS study, CR rates were 88% versus 70% and 4-year PFS rates were 84% versus 68% for D-RVD versus RVD groups.[126] Quadruplet therapy is likely to be the new induction therapy of choice.

Patients Not Eligible for Autologous Stem Cell Transplantation

In patients who will not be undergoing a transplant, often because of a combination of advanced age, comorbidities, and unfit health status, there are various options available for initial therapy.[13,127] Treatment decision-making is based on frailty assessment and ability to tolerate triplet versus doublet therapy. Geriatric assessment with a recognized scoring system is an important part of patient evaluation for those over the age of 65 and with comorbidities or physical and/or cognitive impairment, as patients who are frail have lower tolerance of treatment and poorer prognosis.[128]

Historically, most transplant-ineligible patients received MP, which produced partial remissions in approximately 55% of patients, with the occasional CR.[129] Several therapy options have been shown to improve outcomes for patients who will not proceed to ASCT. In a phase III study, 682 patients were randomized to receive either nine 6-week cycles of MP or the same chemotherapy with bortezomib: The addition of bortezomib increased the proportion of patients achieving CR (30% and 4%, $P < .001$) and improved median duration of response (19.9 vs 13.1 months), time to progression (24 vs 17 months; hazard ratio 0.48, $P < .001$), and the risk of death (hazard ratio 0.61, $P = .008$).[130] The addition of thalidomide to MP (MPT) also improves outcome compared with MP alone: The median PFS was 21.8 months for MPT and 14.5 months for MP ($P = .004$); however, thromboses were more common with thalidomide (12% vs 2% in the MP group).[131,132] A meta-analysis of MP versus MPT concluded that MPT

increases response rates and OS but with increased toxicity, such as thrombosis and somnolence.[133] In the FIRST randomized trial, LD when used continuously (until disease progression) gave a better median PFS (25.5 months) when compared with MPT (median PFS 21.2 months, $P <$ .001), and 4-year OS was also improved (LD regimen 59%, MPT regimen 51%, $P = .02$).[134] A randomized phase III study demonstrated the benefit of adding bortezomib to LD (median PFS, 41 vs 29 months, hazard ratio 0.74, $P = .003$).[135] The addition of the anti-CD38 MoAb daratumumab to IMID and PI backbones provides further benefit in this patient cohort: This was demonstrated in the phase III MAIA study, in which the triplet combination of daratumumab, lenalidomide, and dexamethasone (D-Rd) was associated with a median PFS of 62 months (vs 34 months for LD doublet therapy, hazard ratio 0.55, $P <$ .00001), which is close to expected outcomes in the transplant-eligible cohort of patients.[136] Presently, several treatment strategies exist for the initial therapy of patients who will not proceed to ASCT, with preference for a lenalidomide-based regimen approach and elimination of alkylator (melphalan) therapy altogether.[134,137]

Autologous Stem Cell Transplantation

ASCT has become the standard of care for eligible patients, as it has been demonstrated in multiple trials to improve the likelihood of CR, prolong disease-free survival, and extend OS.[13,62,115,138] ASCT is still important even with highly effective induction therapy consisting of RVD regimen, as shown in a phase III trial of comparing RVD (eight cycles) with RVD (three cycles) followed by ASCT and then two further cycles of RVD.[115] Treatment-related mortality rates are now standardly <2%, and often, the transplant can be performed entirely as an outpatient.[115,139] Melphalan 200 mg/m^2 is the most commonly used conditioning regimen; doses may be reduced in older/less fit patients or patients with renal insufficiency.

Tandem Transplantation

Tandem or double transplantation refers to a planned second ASCT after the patient has recovered from the first. A phase III trial in France evaluated tandem transplant versus single ASCT and demonstrated superior OS in the tandem ASCT group.[140] On further analysis, the patients who benefited most

from the second transplant were those who did not achieve a very good PR after the first ASCT;[140] therefore, it may be more prudent to consider tandem transplantation only in patients whose response to the first ASCT is suboptimal. Also, the results of the phase 3 EMN02/HO95 study suggest that tandem ASCT may be beneficial in the cohort of patients with high-risk cytogenetics.[141]

Allogeneic Stem Cell Transplantation

Myeloablative allogeneic stem cell transplant was previously considered the only current potential curative option for patients with myeloma, as the graft is not contaminated with tumor cells and may produce a graft versus myeloma effect.[142] However, its use is very limited because of the lack of donors, age restriction, high treatment-related mortality, and graft versus host disease. Reduced intensity nonmyeloablative allogeneic transplant following ASCT has also been investigated as a means of inducing a graft versus myeloma effect. In one study of 102 patients undergoing nonmyeloablative transplant, 5-year OS and PFS were 64% and 36%, respectively, although the 5-year rate of nonmyeloma mortality was 18%.[143] Recent pooled and retrospective data suggest that the long-term potential for cure of myeloma following allogeneic stem cell transplant is low, with 8- to 10-year PFS of around 10% to 18%.[144,145]

Maintenance Therapy

The use of maintenance therapy post-ASCT to prolong remission and survival has been extensively investigated. Two large randomized trials used maintenance lenalidomide versus placebo, with prolongation of PFS by approximately 20 months.[146,147] OS was similar in the European trial,[146] whereas the U.S. trial showed a statistically improved survival with lenalidomide maintenance (3-year survival 85% vs 77% with placebo).[147] Post- autograft maintenance therapy with low-dose lenalidomide is now considered to be current standard of care, with a meta-analysis of three large randomized phase 3 trials demonstrating a consistent benefit for improvement in median PFS of >50 months.[148] Further trials are now exploring the benefit of adding other agents to lenalidomide, especially in high-risk patients.

Treatment of Relapsed/Refractory Multiple Myeloma

The general approach to myeloma after failure of frontline therapy is influenced by a number of factors, including patient fitness, agents used in initial therapy, prior toxicities, duration of prior response, treatment goals, and patient priorities regarding quality of life. The plethora of complex factors, which influence decision-making in this setting, means that a one-size-fits-all approach is not feasible.[104]

Patients generally receive sequential lines of treatment of combination regimens and monotherapies, balancing the needs for improving depth of response to prolong the period of disease control against tolerability and quality of life. The armamentarium of effective therapies available has expanded considerably over the past 10 years, contributing to a significant prolongation of the median survival of patients with myeloma (Table 88.7). These include PI (carfilzomib and ixazomib), IMID (pomalidomide), and MoAb (elotuzumab, daratumumab, and isatuximab), which can be used in doublet or triplet combination regimens. Carfilzomib is an irreversible PI with significant activity in relapsed myeloma. Pomalidomide is an IMID that has demonstrated efficacy in relapsed myeloma, in patients who are refractory to both bortezomib and lenalidomide.[149,150] Elotuzumab and daratumumab/isatuximab are MoAbs targeting a glycoprotein SLAMF-7[151] and CD38,[152,153], respectively, both showing activity as single agents and in combination with IMIDs/PIs and dexamethasone.[154] Another novel agent recently approved for the management of heavily pretreated myeloma is the selective inhibitor of nuclear export XPO1 inhibitor, selinexor, which is used in combination with corticosteroids and bortezomib.[155]

Bispecific Antibody and Chimeric Antigen Receptor T-Cell Immunotherapies

The single biggest recent advance in the management of myeloma is the development of immunotherapeutic options of highly effective T-cell redirecting therapy with BsAbs and CAR-T cells. These agents have demonstrated unprecedented efficacy in patients with heavily pretreated myeloma.

BsAbs are engineered antibodies designed to simultaneously bind to two antigens, CD3 on T cells and a target moiety on myeloma cells, for

example, B-cell maturation antigen (BCMA), G-protein coupled receptor family C group 5 member D (GPRC5D), and Fc receptor homolog 5 (FcRH5). The resulting immune synapse causes T-cell activation and proliferation and leads to tumor cell lysis. Teclistamab and elranatamab, which target BCMA, have been approved for the treatment of myeloma with four prior lines of therapy on the basis of the phase 1/2 MajesTEC-1 (ORR 61%) and MagnetisMM-3 (ORR 57%) studies, along with talquetamab, which targets GPRC5D on the basis of the MonumenTAL-1 (ORR 73%) study.[156-158] There are significant risks for infections during treatment for this class of agents, along with early risks for cytokine release syndrome (CRS).[156-158]

CAR-T cells are genetically modified, most commonly using lentiviral or retroviral vectors, autologous or allogeneic cells, with a specific tumor-targeted receptor against antigens, such as BCMA, GPRC5D, and FcRH5. The CAR consists of a single chain variable fragment (scFv) with specificity for the target antigen, a transmembrane domain CD8α and an intracellular co-stimulatory domain, 4-1BB or CD28, co-stimulatory domain linked to the T-cell activation domain CD3ζ. The currently approved CAR-T cells are generated from autologous mononuclear cells collected from the patient by a steady-state apheresis procedure. These are enriched for T cells that undergo modification to express the desired scFv, which recognizes BCMA, by viral transduction. These cells are then expanded before reinfusion into the patient, after prior lymphodepletion chemotherapy. Two agents are currently approved for the treatment of relapsed and refractory myeloma after four prior lines of therapy, idecabtagene vicleucel and ciltacabtagene autoleucel, on the basis of the phase 1/2 trials, KarMMa (ORR 72%, CR 33%)[159] and CARTITUDE-1 (ORR 97%, sCR 67%),[160] respectively. Important adverse events noted included CRS, immune effector cell–associated neurotoxicity syndrome, macrophage activation syndrome, myelosuppression, and infections.

While the response rates to these therapies are high, disease progression continues to be a significant issue; hence, future areas for research include combinations with established antimyeloma therapies and concurrent or sequential targeting of different antigens.

Supportive Care

A description of therapy for multiple myeloma would not be complete without addressing the need to treat not only the disease itself but also the complications of this disease. Many of these complications are treatable, allowing an improved quality of life for patients with myeloma. Patients with symptomatic hypercalcemia require immediate treatment with hydration, glucocorticoids, bisphosphonates, and/or hemodialysis/calcitonin. Red blood cell transfusion should be considered for patients with significant symptoms of anemia. Erythropoietic agents may assist in the management of chemotherapy-induced anemia, leading to reduced transfusion requirements. Osteoclast inhibitor with bisphosphonate or denosumab therapy is critical to the optimal therapy of bone disease and has been demonstrated to improve OS in patients with the initial diagnosis of myeloma, with the benefit being seen irrespective of overt bone lesions.[161-163] In patients with skeletal lesions, osteoclast inhibitors reduce vertebral fractures, skeletal-related events, and associated pain,[164] with an observed reduction of the use of RT from 50% to 34% in one study.[165] Local RT remains a highly effective, local therapy for painful bone lesions and for debulking of symptomatic or threatening plasmacytomas. Surgical pinning of high-risk long bones may avoid the morbidity of pathologic fracture. Surgical techniques such as vertebroplasty and kyphoplasty may be beneficial in improving back pain and spinal symptoms in patients with vertebral disease.[166]

RADIATION THERAPY OF MULTIPLE MYELOMA

Local External Beam for Palliation

The most common use of RT in the management of multiple myeloma is for palliative treatment of bony disease and relief of compression of the spinal cord, cranial nerves, or peripheral nerves. The proportion of patients with myeloma in whom RT would be recommended at some time point during the course of their disease has been estimated to be 45%.[167] In practice, however, the actual RT utilization rate is lower, varying from 11% to 34% of patients with myeloma in cancer registry data.[168-171] A recently published review from the prospective Connect Multiple Myeloma Registry in the United States of 3,011 patients with myeloma demonstrated an RT

utilization rate of 30%.[168] Taken together, these data suggest that RT is underutilized in the management of myeloma, with a gradual decline in utilization rates observed over time.[169]

Palliative RT is highly effective in patients with myeloma, with high rates of local symptom relief reported[67,172-175] (Figure 88.2). In a recently published, retrospective study of 312 patients with myeloma with 577 lesions, 206 lesions were treated with RT alone and achieved a pain control rate of 83% at the end of treatment, which increased to 98% at 1 month, 99% at 3 months, and 94% at 6 months; the radiologic response rate following RT alone was 90% (CR 12%, PR 63%, stable disease 15%) at 6 months.[175] Patient-reported outcome data have shown that delivery of palliative RT in patients with myeloma is associated with approximately 5-fold lower total symptom scores compared to patients who did not receive RT.[176] Significant improvements were seen in pain (odds ratio [OR] 1.6, P = .031), breathing (OR 4.47, P = .022), depression (OR 17.4, P < .001), anxiety (OR 19.0, P < .001), overall well-being (OR 3.6, P = .24), spiritual well-being (OR 10.4, P = .008), and constipation (OR 4.14, P = .024).[176]

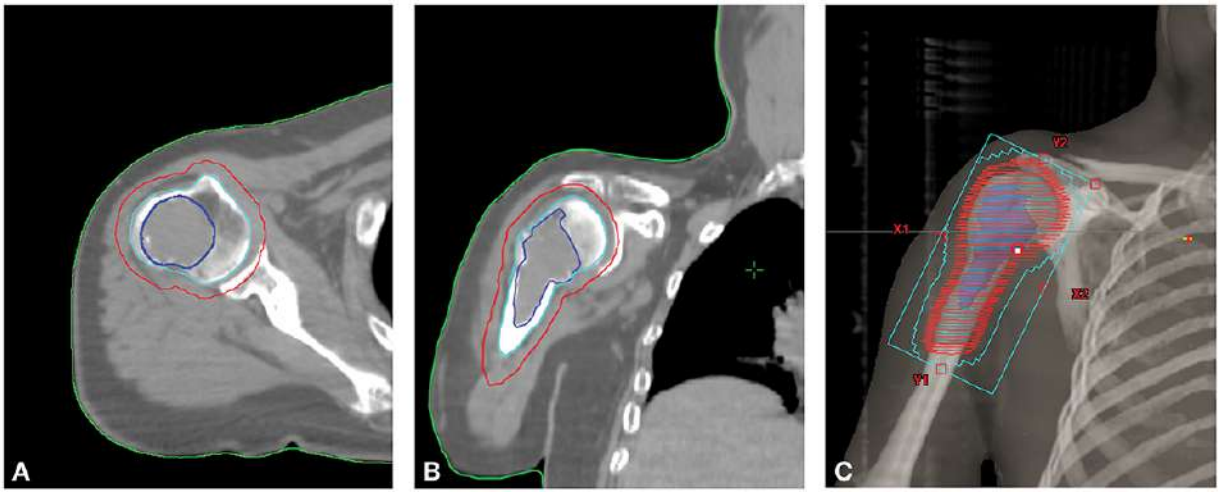

FIGURE 88.2 Radiotherapy treatment plan for a patient with multiple myeloma, presenting with severe pain in the right shoulder. The patient was treated with palliative radiotherapy to the symptomatic lytic lesion in the proximal right humerus, with 8 Gy in one fraction. Gross tumor volume (blue), clinical target volume (aqua), and planning target volume (red) are displayed on an axial slice (A) and a sagittal slice (B) of the computed tomography simulation scan, with beam's-eye view (C) of the right anterior oblique field from a parallel-opposed beam arrangement. Excellent symptomatic relief was achieved, allowing for complete cessation of opioid medications.

For patients with malignant spinal cord compression, RT is an effective, noninvasive treatment modality. In a large retrospective series of 238 patients with multiple myeloma with malignant spinal cord compression, excellent outcomes were observed after RT alone, with an overall high response rate of 97% (53% motor improvement, 44% no further progression); following RT, 88% of patients were able to walk, including the 64% of nonambulatory patients who regained the ability to ambulate.[177] In a second retrospective series of 172 patients with myeloma receiving RT for malignant spinal cord compression, improvement in motor function was experienced in 52% of patients overall, but with significantly greater frequency in patients receiving longer courses (10 × 3 Gy, 15 × 2.5 Gy, 20 × 2 Gy) of RT than shorter courses (1 × 8 Gy, 5 × 4 Gy) from 1 to 18 months following RT.[178] A dose-response was also seen in a retrospective series of 162 patients with myeloma with severe spinal cord compression, with the highest rate of good outcomes (defined as American Spinal Injury Association [ASIA] score E or improvement to ASIA score D) observed in patients who received doses ≥30 Gy.[179] Published in 2018, the International Lymphoma Radiation Oncology Group (ILROG) guidelines for RT for myeloma recommend 30 Gy in 10 to 15 fractions for patients with malignant spinal cord compression.[25] Glucocorticoids are also recommended for patients with nerve root or spinal cord compression (eg, dexamethasone 4 mg qid, prednisone 50-75 mg bid, or equivalent).[25] Upfront decompressive surgery may also be considered for malignant spinal cord compression, extrapolating from randomized evidence in nonhematologic malignancies showing a higher chance of ambulation after surgery plus RT compared to RT alone.[180]

Palliative RT to the spine may also reduce the incidence of future vertebral fractures or the appearance of new lesions. In a small study of patients with myeloma prospectively followed with MRI following localized spinal RT, low rates of fracture (5% vs 20%) and new focal lesions (4% vs 27%) revealed in the irradiated vertebrae compared to nonirradiated vertebrae.[181] However, the role of RT in preventing impending pathologic fracture is unclear; in general, lesions at high risk for pathologic fracture should be referred for surgical stabilization, with RT administered after surgery for control of residual disease at the local site. Similarly, surgical intervention (decompression with or without stabilization) is

indicated in patients who have structural compromise because of vertebral disease, for example, a bone fragment displaced into the spinal canal and/or vertebral instability. Surgery is usually performed first, with RT considered in the postoperative period usually 4 to 6 weeks after surgery to allow for adequate healing.

It is unclear if pain relief is improved if RT is given concurrently with systemic therapy. An earlier retrospective study of 70 patients with myeloma reported complete pain relief in 80% of patients receiving RT with chemotherapy (melphalan and prednisolone), compared to only 40% among those who received RT prior to chemotherapy, with an association seen between RT dose and the duration of pain control.[182] In contrast, other studies have not found an impact on pain control from the delivery of concurrent systemic therapy.[172,175].

With the increasing availability of novel systemic therapies, the effects of drug-radiation combinations are a topical concern in current clinical practice. To date, most series demonstrate that RT with concurrent systemic therapy (either chemotherapy or biologic agents) is well tolerated with low rates of high-grade toxicity.[175,183-185] In a study of 312 patients treated with a mix of RT alone (38%), RT with concurrent chemotherapy (13%), or RT with concurrent biologic treatment (48%), concurrent systemic therapy was associated with increased toxicity; however, high-grade (grades 3-4) toxicities were rare (<4%) across every subgroup.[175] In a study of 55 patients, 64 sites were irradiated within 3 weeks of receiving dexamethasone, cyclophosphamide, etoposide, and cisplatin +/− other agents (35% PI, 18% additional cytotoxic chemotherapy, and 5% immune checkpoint inhibitors): Overall, concurrent therapy was well tolerated, with a nonsignificant increase in grade ≥ 3 hematologic toxicity observed from 21% prior to RT to 35% during RT (P = .13), which subsequently decreased to 12% at 3 to 6 months after RT (P = .02).[183] In a study of 130 patients treated with RT to a median dose of 20 Gy in 10 fractions +/− concurrent biologic agents (42% bortezomib, 23% carfilzomib, 15% daratumumab, and 20% other), no grade ≥ 3 toxicity was noted in the entire cohort, and no significant difference in toxicity was observed between patients who received versus who did not receive biologic agents concurrently with RT.[184] On the other hand, other reports suggest a significant risk of high-grade toxicity after RT plus concurrent PI, especially with higher radiation

doses.[186-188] In a report of 82 patients with myeloma treated with RT with a median dose of 40 Gy +/− concurrent systemic therapy (with 68% including a PI), 45% of patients experienced at least one high-grade (grade III/IV) toxicity; after RT, a significant increase in the rate of high-grade toxicities was observed in the group who received combined modality therapy (49% vs 17%, $P = .018$).[186] Furthermore, case reports of bortezomib and spinal radiation (30 Gy in 10 fractions and 20 Gy in 8 fractions) given concurrently have been reported to result in severe enteritis.[187,188]

Hemibody Radiotherapy

Diffuse bone pain involving wide areas of the skeleton can be effectively palliated by half-body RT with single doses of 5 to 8 Gy.[189-193] However, this technique is rarely used now due to the ready availability of other effective systemic therapy options. The main toxicity risk is myelosuppression; growth factor support may be helpful, and transfusions of blood products should be given as needed. In hemibody RT, the bone marrow in the unirradiated half body serves as a stem cell reserve and will slowly repopulate the irradiated marrow after treatment. The use of hemibody RT must be carefully considered in patients heavily pretreated with chemotherapy who may have lesser marrow reserve. For the upper half body, the hemibody RT dose should not exceed 6 to 8 Gy because of the risk of radiation pneumonitis following larger single doses to lung.[191]

The sequential hemibody RT technique has also been investigated as a consolidation treatment to control myeloma.[194] In the South West Oncology Group phase III trial, patients were first treated with combination chemotherapy with complete responders randomized to consolidation with sequential hemibody RT (7.5 Gy in five fractions, upper hemibody, followed 6 weeks later by lower hemibody) or a further 12 months of chemotherapy; however, relapse-free survival and OS were significantly inferior in those receiving RT and with significantly worse myelosuppression compared to those receiving chemotherapy.[194] For patients with myeloma, there is presently no standard role for sequential or concurrent combination therapy with hemibody RT outside a clinical trial.

Total Body Irradiation and Total Marrow Irradiation

Some high-dose chemotherapy protocols for multiple myeloma incorporate total body irradiation (TBI) into the conditioning regimen. Because of toxicity concerns (mucosal and hematologic) with TBI, many programs use chemotherapy alone, most commonly melphalan. A phase III French study (Intergroupe Francophone du Mye'lome trial 9502) examined melphalan 200 mg/m^2 alone (M200) versus melphalan 140 mg/m^2 with TBI, 8 Gy in four fractions (M140/TBI), and found that patients in the M140/TBI-containing arm suffered more grade 3 or 4 mucosal toxicity, heavier transfusion requirement, longer hospitalization stay, and higher toxic death rate (3.6% vs 0% for the M200 arm).[195] Although the event-free survival was no different between the two treatments, the 45-month OS favored the M200 arm (M200: 65.8%; M140/TBI: 45.5%; $P = .05$).[195] TBI is now rarely used in conditioning regimens for ASCT, unless in the context of a clinical trial.

Emerging prospective studies suggest that total marrow irradiation (TMI) may be a feasible alternative to TBI associated with lesser toxicity.[196-202] A phase I trial was designed to determine the maximum tolerated dose (MTD) of TMI in 13 patients with myeloma treated with melphalan 140 mg/m^2 combined with TMI followed by ASCT as consolidation: Four TMI dose levels were investigated (8, 10, 12, and 14 Gy), with only one dose-limiting toxic event observed at 12 Gy, while the one patient treated at 14 Gy had no adverse events.[196] The CR and very good PR rates were 30.8% and 38.5%, respectively, and acute toxicity rates were low, with only 38% experiencing grade 3 and 4 diarrhea, mucositis, or unexplained fever.[196] In a phase I-II trial of 54 patients, TMI was investigated as the sole ablative modality during the second cycle of tandem ASCT: TMI doses were escalated from 10 to 18 Gy in 2-Gy increments, and 55.6% received the MTD of 16 Gy.[198] Very good PR and CR were achieved in 48.1% and 22.2% of patients, respectively, after ASCT and maintenance, and the treatment was well tolerated.[198] Further research is needed to investigate incorporating TMI as a conditioning regimen in the context of modern induction and maintenance therapies.

Radioimmunotherapy Approaches

Bone-seeking radiopharmaceuticals targeting the bone marrow have been studied as an alternative to TBI. Typically, a β-emitting isotope is conjugated to a phosphonate complex, such as samarium-153-ethylene diamine tetramethylene phosphonate (^{153}Sm-EDTMP or Quadramet). The isotope also emits a γ-ray, permitting scanning to locate areas of uptake, and for use in the palliation of bone metastasis.[203] Other bone-seeking pharmaceuticals include holmium-166-DOTMP (^{166}Ho-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene- phosphonic acid) and rhenium-118-labeled anti-CD66 antibodies. Compared to ^{153}Sm, holmium-166-DOTMP and Re-188-anti-CD66 have higher energy β emission (maximum energy 1.85 and 2.12 MeV, respectively) and shorter $T_{1/2}$ (26.8 and 16.9 hours, respectively).[204,205] ^{153}Sm-EDTMP, holmium-166-DOTMP, and Re-188-anti-CD66 all have a γ emission (81-155 keV) suitable for imaging. With the ability to deliver much higher doses to the bone marrow than TBI, in the range of 30 to 60 Gy, yet sparing the dose-limiting normal tissues such as the lung, mucosa, and kidneys, the concept of targeted radiation therapy is tantalizing. Small series investigating radiopharmaceuticals prior to stem cell transplantation have reported on the feasibility, tolerability, and promising outcomes of this approach.[206,207] However, there remains a problem of heterogeneity of uptake in the skeleton, and the dosimetric variation may be even larger at a microscopic level because of the limited range of the β particle. Whether this approach will have a more favorable therapeutic ratio than standard conditioning regimens in the transplant setting awaits larger scale phase II and phase III trials.

Bridging Radiotherapy to Chimeric Antigen Receptor T-Cell Therapy

CAR-T therapies are promising new therapies for patients with relapsed/refractory hematologic malignancies. Current research is investigating the potentiation effects of bridging RT before CAR-T infusion. Early data suggest that bridging RT prior to B-cell maturation (BCMA)-targeted CAR-T is safe and feasible in patients with myeloma.[208,209] In a report of 25 patients undergoing CAR-T BCMA for relapsed/refractory myeloma, those who received bridging RT after

apheresis and ≤35 days before CAR-T infusion (N = 4) had qualitatively lower rates of hematologic toxicities and neurotoxicity, compared to those who received RT within 1 year before apheresis (N = 18) and those with no RT within 1 year before apheresis (N = 13).[209] Interestingly, RT administered within 1 year (P = .002) and within 100 days (P = .069) before apheresis was associated with lower in vitro proliferation during manufacturing; however, in vivo CAR-T BCMA expansion appeared similar across the patient groups.[209] Further clinical research is required to investigate the safety and optimal timing of bridging RT prior to CAR-T therapy for patients with multiple myeloma. Presently, equitable access to CAR-T therapy is challenged by geographic, socioeconomic, and racial factors, with opportunities for health services research and implementation science to reduce this disparity.[210,211]

RADIATION THERAPY TECHNIQUES

Delineation of Target Volumes

There are few data to support specific guidelines regarding RT treatment volumes. To improve uniformity of practice, ILROG published contouring guidelines specific to myeloma and SP, in 2018.[25] Accurate delineation of tumor extent is important for the irradiation of plasma cell neoplasms, especially for the radical treatment of SP. MRI is useful to evaluate the extent of disease infiltration. This is particularly true for the paranasal sinuses, where inflammatory changes may be difficult to distinguish from tumor on CT imaging. FDG-PET/CT provides complimentary detail, distinguishing between active and inactive disease (Figures 88.3A and 88.4A).

FIGURE 88.3 Radiotherapy treatment plan for a patient with solitary plasmacytoma of the sternum who presented with a 1-year history of a painless, enlarging chest wall mass. The patient was treated with definitive radiotherapy, 45 Gy in 25 fractions. (A) Staging positron emission tomography/computed tomography (CT) scan demonstrated a single plasmacytoma arising in the manubrium. (B) Gross tumor volume (blue), clinical target volume (aqua), and planning target volume (red) on a sagittal slice of the CT simulation scan. (C) Dosimetry from a conformal volumetric modulated arc therapy plan with isodose lines displaying 50%, 80%, 90%, 95%, 100%, and 110% of the prescription dose. (D) Dose-volume histogram of heart (green) and bilateral lungs (purple).

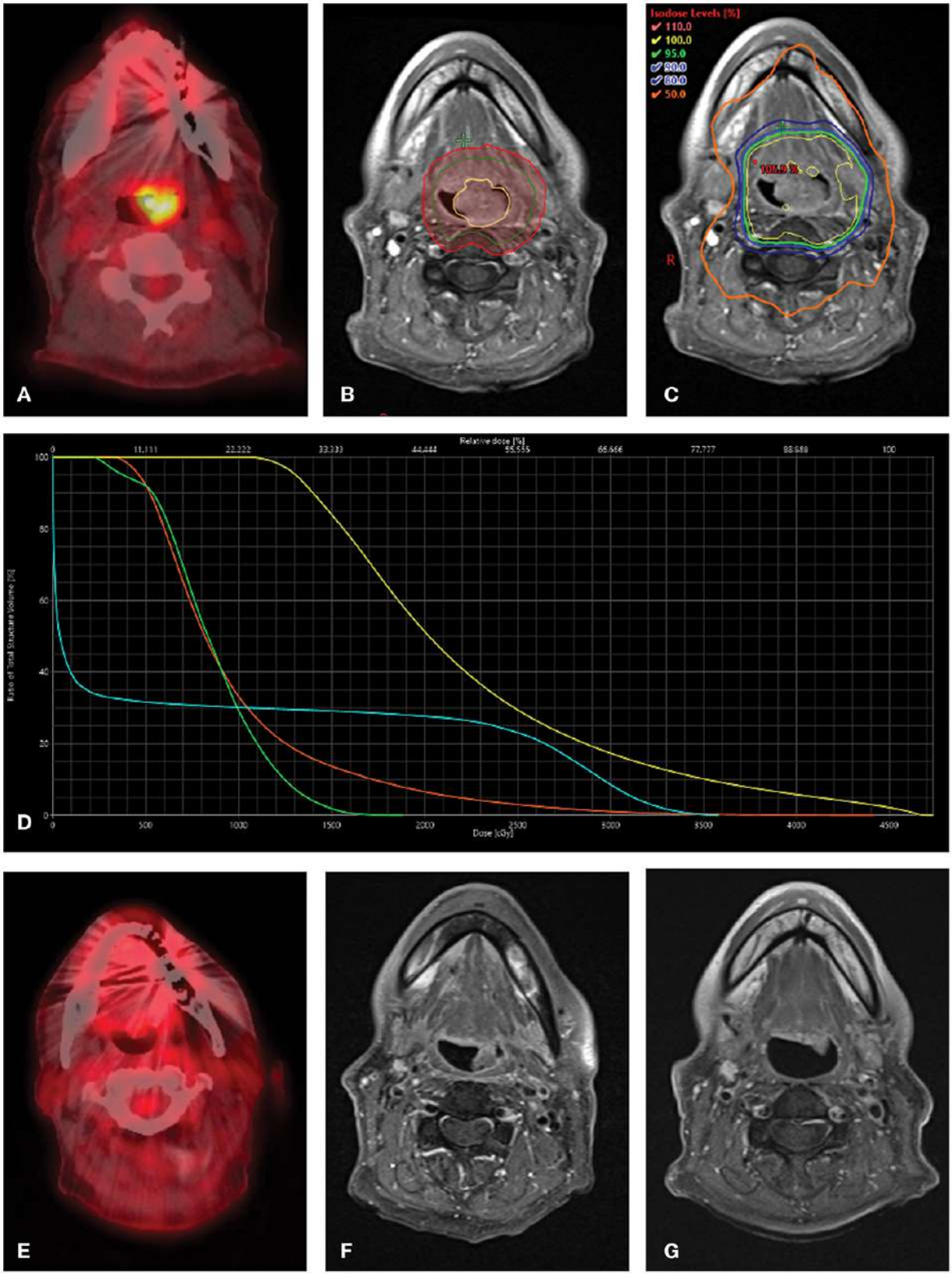

FIGURE 88.4 Radiotherapy treatment plan for a patient with solitary extramedullary plasmacytoma of the base of tongue who presented with 6-month history of dysphagia and

hoarseness. The patient was treated with definitive radiotherapy, 45 Gy in 25 fractions. (A) Axial image from Staging positron emission tomography (PET) scan. (B) Magnetic resonance imaging (MRI) fused to the computed tomography simulation scan to aid contouring of gross tumor volume (yellow), clinical target volume (green), and planning target volume (red), as depicted on this axial slice. (C) Dosimetry from a conformal volumetric modulated arc therapy plan with isodose lines displaying 50%, 80%, 90%, 95%, 100%, and 110% of the prescription dose. (D) Dose-volume histogram of the right parotid gland (green), left parotid gland (orange), oral cavity (yellow), and spinal cord (aqua). (E) PET to assess metabolic response approximately 3 months after radiotherapy showing a partial metabolic response. (F) MRI to assess structural response at 3.5 months postradiotherapy showing partial response. (G) Follow-up MRI 24 months postradiotherapy showing further interval improvement. The patient remains disease free.

In modern RT, "involved field RT" is no longer the preferred terminology, and the "involved site RT" concept should be adopted, as described in the ILROG guidelines.[25] Three- dimensional (3D) planning should always be used (except for a small skin lesion that can be treated with superficial x-rays or high-energy electrons guided by clinical examination). Field placement based on anatomic landmarks should no longer be used and should be replaced by volumetric delineation;[25] for example, the historical practice of inclusion of two vertebral bodies above and below the grossly involved vertebra(e) should be abandoned.

For defining gross tumor volume (GTV), the primary imaging (ie, CT, MRI, and PET) of the untreated lesion should be outlined on the simulation scan, with fusion of the primary imaging to the simulation scan if helpful (Figures 88.2A-B, 88.3B, and 88.4B). Clinical target volume (CTV) should encompass probable routes of microscopic spread, recognizing that barriers to the extension of local disease will vary according to anatomic location, as will the morbidity of treating adjacent normal tissues. In determining the CTV, using the GTV plus a margin of 0.5 to 3 cm is reasonable (depending on the site) respecting anatomic boundaries (Figures 88.2A-B, 88.3B, and 88.4B). In soft tissues, GTV to CTV expansion of 0.5 to 1 cm in the axial plane may be appropriate for covering potential microscopic extension, for example, in the head and neck area (Figure 88.4B). For a long bone site (eg, the humerus), the proximal and distant expansion should be increased to 2 to 3 cm (Figure 88.2B).[25] Coverage of the entirety of an involved long bone is no longer considered necessary as smaller, localized RT fields are associated with good palliation of symptoms and allow for greater marrow

sparing[212] (Figure 88.2C). Adjacent normal structures that are clearly uninvolved or at low risk of microscopic disease should not be included in the CTV.

Elective regional lymph node RT for SBP or SEP is generally not recommended by ILROG, with the exception being in the situation of convincing clinical evidence of a high risk of nodal involvement (eg, bulky primary disease in proximity to the drainage lymph node station where nodal coverage will not increase the treatment toxicity in a significant way).[25]

When physiologic movement could affect the CTV, an additional margin, ideally based on 4D CT simulation, should be added to the CTV to create an internal target volume (ITV). Planning target volumes (PTV) account for day-to-day setup variation and will typically add 5 to 10 mm around CTV volumes depending on the immobilization technique employed (Figures 88.2A-B, 88.3B, and 88.4B).

Radiation Therapy Techniques

In current practice, CT-based planning and conformal RT techniques are essential to reduce toxicity risks and improve the therapeutic ratio for patients with SP. The steeper dose gradients of intensity-modulated RT and volumetric modulated arc RT are especially useful when the PTV is adjacent to critical structures, for example, for SP of the head and neck, conformal techniques are important to reduce dose to the adjacent organs at risk, including optic structures and salivary glands (Figures 88.3C-D and 88.4C-D). Other highly conformal techniques, including stereotactic body radiation therapy (SBRT) and proton therapy, are presently investigational. A preliminary, prospective report of five patients with SBP treated with hypofractionated SBRT suggests the technique is safe and feasible[213]; however, further robust data are required. To date, the published experience of proton therapy for SP is limited to case reports only, but the sharp dose fall-off profile of proton therapy is attractive in the treatment of SP with proximity to dose-limiting critical organs (eg, an SP in the base of skull).[214]

Radiation Therapy Dose

Solitary Plasmacytoma

Studies evaluating RT dose-response in SP have produced differing results. However, these published data are largely limited to retrospective series, which may be confounded by selection bias (eg, higher doses prescribed to bulkier tumors) or limitations in surveillance imaging. For SP treated with RT, durable local control has been demonstrated from RT doses of 35 to 50 Gy.[30,63,75,215] For SP measuring <5 cm in size, data suggest excellent local control can be achieved by 35 Gy.[63] However, SP ≥5 cm is associated with inferior local control and may benefit from higher RT doses.[23,63,69,216] For SEP, some published studies report greater local control following doses of ≥40 Gy.[24,30,78] The current ILROG guidelines for clinical practice recommend doses of 35 to 40 Gy for SBP <5 cm and 40 to 50 Gy for SBP ≥5 cm or SEP.[25] However, one should be reminded that the quality of evidence supporting the use of higher RT doses is limited and that local failures are occasionally observed even after doses of 50 Gy or higher.[23,58,63]

Multiple Myeloma

For multiple myeloma, the most commonly used doses range from 8 to 30 Gy, resulting in excellent ORRs, although the pain relief is often partial.[172,174,175,217] Response rates exceed 80%, with complete pain relief in approximately 30%.[59,172,174] In a large study of 772 patients with myeloma and 1,513 irradiated sites (the most common biologic equivalent dose [BED] was 20-25 Gy in 43%), only 2.6% of sites required reirradiation, with the most common indications being persistent pain and radiographic progression.[217] Higher rates of pain control have been demonstrated from BED_{10} >38 Gy and lower rates associated with BED_{10} <15 Gy.[101] However, the cost of increased toxicity from higher doses is important to consider, as BED_{10} >38 Gy is associated with higher rates of grade 1 toxicity[207] and BED_{10} >36 Gy is associated with scarce bone marrow recovery.[218] Published in 2018, the ILROG guidelines recommend a hypofractionated regimen to a total dose of 8 to 30 Gy, with a single 8 Gy fraction preferred for bone disease in patients with poor prognosis.[25] However, more recent studies suggest that low-dose RT regimens are a feasible alternative. In a retrospective study of dose-response from palliative RT for uncomplicated myeloma osseous lesions (ie, without impending risk of pathologic fracture, prior orthopedic fixation, or spinal lesions with malignant epidural

involvement), there was no significant difference in duration of pain response after an equivalent dose in 2 Gy fractions <12 Gy versus ≥ 12 Gy.[219] An ongoing prospective multi-institutional study is investigating the use of a 2 × 2 Gy for painful myeloma lesions, including quality of life assessment (NCT03858205).[220] Recent publications suggest that RT regimens involving fewer fractions are being increasingly favored over time in the treatment of multiple myeloma. A population-based analysis in Australia found that the proportion of RT courses given over 2 to 5 fractions increased from 48% in 2012 to 60% in 2017, with a corresponding decrease in the use of 6 to 10 fractions from 26% in 2012 to 20% in 2017 (*P*-trend = .003).[221]

Assessment of Response and Follow-Up

Response assessment is indicated following RT for SP, with re-imaging best performed 3 to 6 months after therapy, as recommended by ILROG.[25] Following RT, bony destruction caused by the tumor can produce persistent abnormalities on CT and x-ray; and it is common for a residual soft tissue abnormality to persist on follow-up imaging (Figure 88.4F, G). Periodic reimaging may be required every 4 to 6 months until any residual mass disappears or remains stable on consecutive scans. For patients with persistent structural abnormalities seen on CT or MRI, FDG-PET/CT is a powerful tool to distinguish between active and nonactive sites of disease and to assess response to treatment.[47] FDG-PET/CT is the preferred functional imaging modality of the IMWG for evaluation of response to treatment.[48] As metabolic changes precede structural changes, FDG-PET/CT may also allow for earlier response assessment.[45,48] Repeated surveillance imaging is not considered beneficial in the context of a stable radiologic abnormality; however, reimaging should be considered in the context of persistent, deteriorating, or new symptomatology.

Follow-up procedures include clinical assessment plus serum and urine testing for any persistent M protein on a regular basis (eg, every 6 months).[29] Repeat measurement of the M protein often detects the onset of systemic disease prior to the development of symptoms and may be used as an indicator of disease burden.[28,222] A complete blood count, serum chemistry (calcium and creatinine), and episodic skeletal survey are

common practices for surveillance of myeloma. The development of new symptomatology necessitates further investigation and workup, including imaging as appropriate.

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PART L

Soft Tissue

CHAPTER 89

Soft Tissue Sarcoma (Excluding Retroperitoneum)

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INCIDENCE

Soft tissue sarcomas (STSs) comprise a heterogeneous group of rare malignancies that vary extensively by anatomic location, histology, and biologic behavior. They can occur at any anatomic site and may arise from many soft tissues including connective tissues, fat, muscle, vascular tissue, peripheral neural tissue, or visceral tissue. Annually, there are about 13,400 expected new cases of STS in the United States, and this accounts for approximately 0.7% of all new cancer diagnoses.[1] The median age at diagnosis for all STSs is 65 years, but incidence varies by histologic subtype.[2] For example, embryonal rhabdomyosarcoma is common in children; synovial sarcoma occurs mostly in young adults; and undifferentiated pleomorphic sarcoma, liposarcoma, and leiomyosarcoma are seen mostly in older adults.

ETIOLOGY AND GENETICS

For the great majority of STS, there is no known etiology. A minority of cases can be attributed to environmental or genetic factors.[2] Associated environmental factors include radiation exposure; chemical exposures, such as vinyl chloride, dioxin, arsenical pesticides, and phenoxy herbicides; immunosuppression; lymphedema (Stewart-Treves syndrome); and viruses (human immunodeficiency virus, human herpes virus type 8). Certain

clinical syndromes are associated with a genetic predisposition for the development of sarcoma. A few examples include Li-Fraumeni syndrome and Werner syndrome, which are associated with the development of STS as well as other malignancies; neurofibromatosis type 1, which is associated with the development of malignant peripheral nerve sheath tumors (MPNSTs); and familial adenomatous polyposis (Gardner syndrome), which is associated with the development of abdominal desmoid tumors.

HISTOLOGIC CLASSIFICATION

The World Health Organization divides soft tissue tumors into four categories reflecting biologic potential: benign; intermediate, locally aggressive (eg, desmoid fibromatosis); intermediate, rarely metastasizing (eg, plexiform fibrohistiocytic tumor); and malignant. These include adipocytic, fibroblastic/myofibroblastic, so-called fibrohistiocytic, vascular, pericytic (perivascular), smooth muscle, skeletal muscle, chondro- osseous, peripheral nerve sheath tumors, and those of uncertain differentiation. There are more than 50 histologic subtypes of STS. The most common subtypes include undifferentiated pleomorphic sarcoma, liposarcoma, leiomyosarcoma, myxofibrosarcoma, synovial sarcoma, and MPNST. Together, these account for about 75% of STS cases.[2] Histologic diagnosis is determined largely by tumor cell morphology. Immunohistochemical staining, cytogenetics, and molecular genetic testing can help refine the diagnosis in many cases. Increasingly, several of the histologic subtypes have characteristic chromosome translocations and gene rearrangements. Some of these characteristic translocations include Ewing sarcoma, t(11,22); synovial sarcoma, t(X,18); myxoid liposarcoma, t(12,16); and clear cell sarcoma, t(12,22).[2]

There are several grading systems. The two most widely used are the U.S. National Cancer Institute (NCI) and the French Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading systems, both of which employ a three-tiered system of low, intermediate, and high grade based on mitotic activity, necrosis, and differentiation.[3,4] The College of American Pathologists prefers the FNCLCC system as it is easier to use, more reproducible, and may be a better predictor of prognosis.[5] Lastly, there are certain STS subtypes for which grading is not applicable and less

informative than histopathologic subtypes, including rhabdomyosarcoma, alveolar soft part sarcoma, clear cell sarcoma, Ewing sarcoma, and epithelioid sarcoma.[2]

Given the rarity of STS as well as the numerous histologic subtypes, it is very important to submit diagnostic slides for review by an experienced sarcoma pathologist for confirmation of diagnosis and grade prior to embarking on treatment.[6-8]

NATURAL HISTORY

STS can occur anywhere in the body. The most common site of presentation is an extremity, specifically, the thigh. The approximate distribution of STS sites at presentation is extremity, 50% to 60% (lower extremity, 40%-45%, upper extremity, 10%-15%); trunk, 15% to 20%; retroperitoneum, 10% to 15%; and head and neck, 5% to 10%.[9,10] This chapter will primarily address truncal and extremity STS. Retroperitoneal sarcoma is covered in Chapters 82. STSs arising from other anatomic sites (eg, head and neck, breast, thorax, abdomen) are less common and not directly addressed here.

Interestingly, certain histologic subtypes have predilections for specific sites. For example, angiosarcoma commonly occurs in the head and neck, desmoid tumors frequently occur in the abdomen associated with Gardner syndrome, and epithelioid carcinoma often involves the hand or forearm.[11-13]

In the classic reports by Simon and Enneking and Enneking et al, the local behavior of STS is well described.[14,15] STS tends to spread longitudinally along musculoaponeurotic planes. Depending on the location, these planes may be diagonal as in the gluteal or superficial truncal musculature, rather than craniocaudal. These tumors infrequently transgress fascial boundaries and rarely invade bone. As the sarcoma grows, it compresses surrounding normal tissue to form a pseudocapsule, which contains a compression zone and a reactive zone. The latter comprises edema, inflammatory cells, and tumor cells. Furthermore, Simon and Enneking have shown that microscopic tumor cells perforate through and extend beyond the pseudocapsule.[14]

Unlike most solid tumors, STSs rarely spread to lymph nodes. Three series, each with more than 1,000 consecutive patients with STS, cited only 1.8% to 3.7% lymph node involvement at the time of initial presentation.[16-

[18] However, there are a few histologic subtypes for which lymph node involvement is more common. Notable lymph node involvement rates have been demonstrated for *C*lear cell sarcoma (10%-18%), cutaneous *A*ngiosarcoma (10%-15%), *R*habdomyosarcoma (20%-25%), and *E*pithelioid sarcoma (20%-35%); these histologic subtypes can be remembered by the mnemonic "*CARE*."[13,17-21] Synovial sarcoma is no longer considered to have a greater propensity for lymph node involvement.[22-24]

The American College of Surgeons' Patterns of Care Study for adult STS showed that 23% of patients had metastatic disease at presentation.[9] The single most frequent site of distant metastasis (34%) was the lung; bone, liver, and brain involvement were less common. Furthermore, as was the case for lymph node spread, certain histologic subtypes exhibit distinct patterns of recurrence and distant metastatic spread. Knowledge of these unique natural histories informs the appropriate imaging that should be done for staging evaluation. For example, myxoid liposarcoma has a predilection for spread to the retroperitoneum, other extrapulmonary soft tissue sites, and bone, including the spine. Among reported recurrences, about 50% occur in the retroperitoneum, 20% in other extrapulmonary soft tissue, and 15% to 17% in bone.[25,26] For retroperitoneal STS, the most common site of recurrence is locally in the retroperitoneum.[27] These tumors also have a predilection for spreading to the liver as well as the lung.[27] Epithelioid sarcoma can present with skip metastases involving discontiguous locations in a limb as well as lymph node involvement.[2,13,19] Lastly, myxofibrosarcoma exhibits an infiltrative growth pattern and is associated with higher rates of positive resection margins and local recurrence (LR) compared to other STS histologic subtypes; conversely, the rate of distant recurrence to the lung is lower than for other STS types.[2,28-31]

INITIAL EVALUATION

Most STS cases present as a painless mass. When taking a history, one should ask how long the mass has been present, if it has changed in size and at what rate, and if there are any associated local or systemic symptoms. It is also important to ask about potential risk factors for STS, including a history of radiation exposure or a family history of malignancies including STS. On physical examination, one should assess the mass for

characteristics such as size, depth, fixation to underlying structures, the presence of overlying skin changes, and potential evidence of neurovascular compromise. On the general examination, one should also note if there are any stigmata of neurofibromatosis, such as neurofibromas or café au lait spots (as there is an association between neurofibromatosis type I and MPNST).[2]

When STS is suspected, evaluation should include imaging of the primary site prior to biopsy or surgical resection. For STS of the extremity, trunk, or head and neck, evaluation of the primary tumor with a magnetic resonance imaging (MRI) scan is generally preferred to computed tomography (CT) scanning.[32,33] The T1-weighted images of the MRI scan provide an excellent definition of the anatomic relation between the tumor and adjacent structures. T2-weighted images demonstrate the tumor and any associated edema. As peritumoral edema can contain malignant cells, it is important to identify this for both radiation and surgical planning.[34]

Figure 89.1 depicts a case of synovial sarcoma of the left gluteus medius muscle. The mass is difficult to discern on CT imaging (Figure 89.1A) but very clearly delineated on MRI (Figure 89.1B). Figure 89.2 is a second comparative example of CT and MRI and shows a leiomyosarcoma of the proximal anterior thigh. Although the differences between the imaging modalities are not as pronounced as in Figure 89.1, the MRI again provides superior information compared to the CT scan. The MRI demonstrates probable arterial wall invasion, fascial enhancement of the vastus medialis muscle, and definition of tumor spiculations into the adjacent fat and along the biopsy tract.

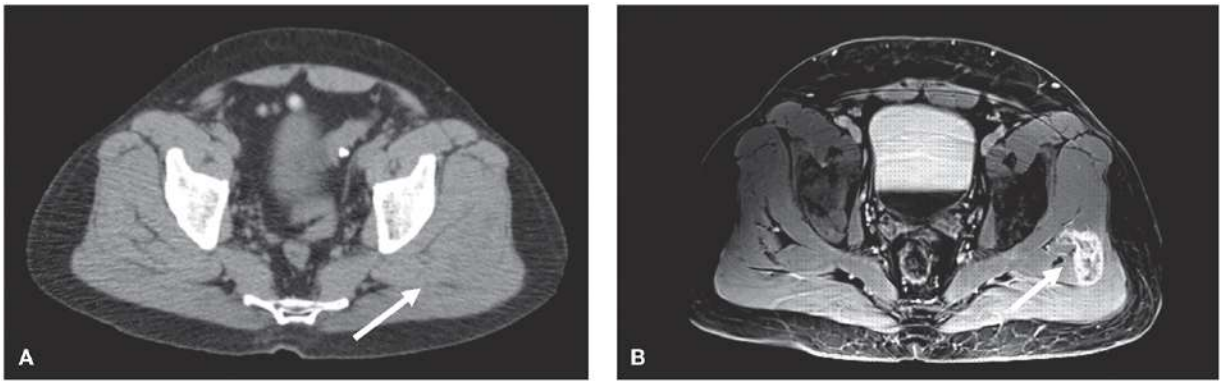

FIGURE 89.1 Comparison of computed tomography (CT) and magnetic resonance imaging (MRI) axial slices for a synovial sarcoma of the left gluteus medius muscle in a 56-year-old man. A. The CT axial slice shows a vaguely defined soft tissue mass in the left gluteus medius muscle. B. The anatomic definition of the soft tissue sarcoma is seen much more clearly on the corresponding T1 post-gadolinium axial slice of the MRI.

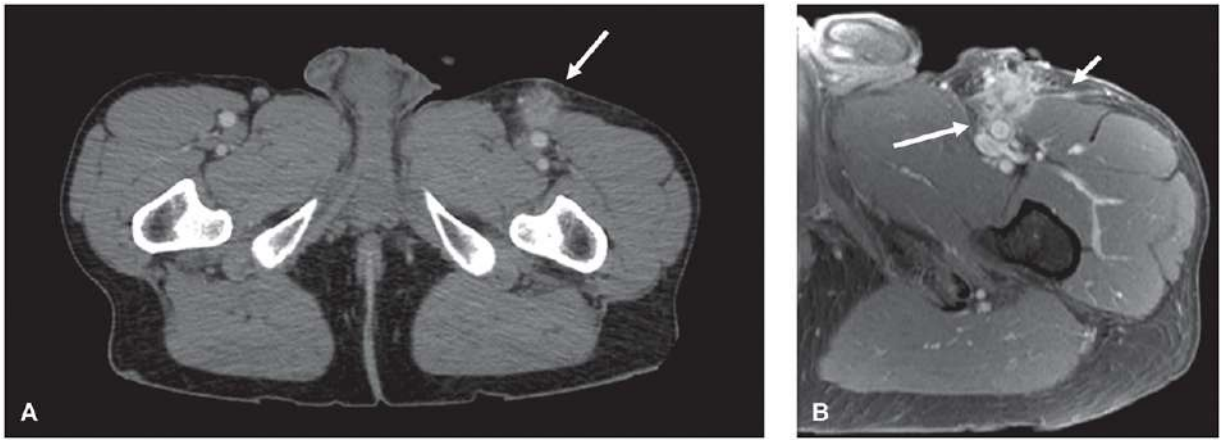

FIGURE 89.2 Comparison of computed tomography (CT) and magnetic resonance imaging (MRI) axial slices for a high-grade leiomyosarcoma of the proximal anterior thigh in a 53-year-old man. A. The CT axial slice shows a soft tissue mass in the left anterior upper thigh anterior to the superficial femoral artery and vein. B. The T1 post-gadolinium image of the MRI at the same level provides superior resolution compared to the CT. It shows a loss of fat plane between the mass and the superficial femoral artery suggestive of arterial invasion (long arrow), linear fascial enhancement overlying the vastus medialis muscle (short arrow), and tumor spiculations into adjacent subcutaneous fat and to the skin along the biopsy tract.

Diagnosis of STSs requires pathologic confirmation. Image-guided core biopsy is the preferred diagnostic approach as it is accurate, safe, and allows for directed sampling of multiple sites within the mass. Image-guided core biopsies are expeditious and do not cause a delay in time to initiation of the next therapy.[35] Incisional biopsies are accurate and

acceptable, but more invasive than core biopsy and often no longer necessary. If utilized, incisional biopsies must be appropriately oriented and should ideally be performed by the surgical or orthopedic oncologist who will be involved in the subsequent oncologic resection.[36] Tumor cells can potentially seed an incision, thereby necessitating the removal of skin incisions at the time of surgical resection. It is important that the biopsy approach does not transgress an uninvolved compartment or joint, as this would create a situation where a much more radical resection would need to be performed. Consequences of inappropriately placed incisional biopsies can be significant and include the need to perform more complex operations, with the potential for subsequent loss of function, LR, and death[36] (Figure 89.3). Excisional biopsies and marginal excisions are not recommended, as they do not provide adequate sarcoma margins and may similarly complicate subsequent oncologic resection. Fine needle aspirations can confirm malignancy for recurrent disease but typically do not yield enough tissue to establish an initial diagnosis.

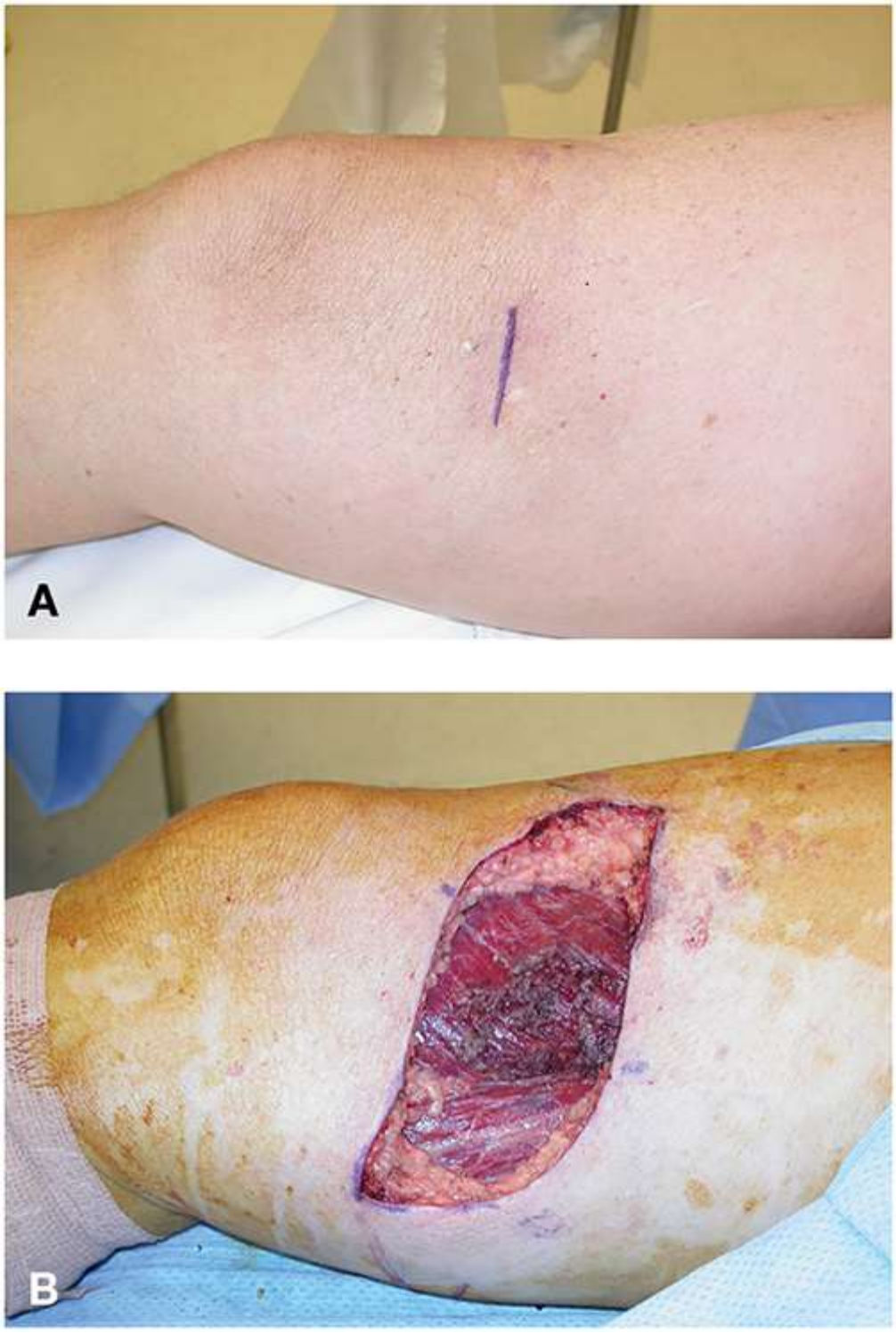

FIGURE 89.3 Images demonstrating consequences of a maloriented transverse incision from an unplanned excision. A. The purple marker overlies the prior incision. B. Extent of subsequent oncologic resection necessary to excise the prior incision. Had the initial incision been oriented longitudinally, the subsequent resection would have been smaller and less complex.

After pathologic confirmation of STS and determination of histopathologic subtype and grade, additional staging evaluation and appropriate imaging can be performed based on the risks for local, regional, and distant metastatic spread. Given the general predilection of STS for hematogenous spread to the lungs, chest imaging is most commonly performed. Chest CT scan is recommended to rule out pulmonary metastases for all cases except low-grade tumors or small (<5 cm) high-grade lesions, and even in these latter cases, it can be helpful to obtain a baseline chest CT at diagnosis. Additional site-directed staging imaging should be tailored to the unique natural history of the specific subtype. For example, given that myxoid liposarcoma has a predilection for spread to bone and soft tissue, MRI of the spine and CT of the abdomen and pelvis are recommended as part of the initial evaluation for high-risk patients with this histologic subtype.[25,26,37] Currently, there is no clearly defined role for the routine use of positron emission tomography (PET) as part of the diagnostic evaluation.[38] However, PET scanning may have potential utility to help distinguish MPNSTs from benign neurofibromas in patients with neurofibromatosis.[39,40] PET can be used to assess response to neoadjuvant chemotherapy and selectively in the evaluation of histopathologic subtypes with increased propensity for lymph node involvement (eg, epithelioid sarcoma).[41]

STAGING

In 2017, the American Joint Committee on Cancer (AJCC) published the 8th edition of the TNMG (tumor, node, metastasis, grade) staging system for STS.[37] There are several changes compared to the prior edition. Given the importance of the anatomic site, there are separate staging systems for STS involving the extremity and trunk, retroperitoneum, head and neck, and visceral sites.

In the staging system for STS of the extremity and trunk, grade, tumor size, lymph node, and distant organ involvement all remain important elements. There are now four T size categories: T1 less than or equal to 5 cm, T2 greater than 5 to 10 cm, T3 greater than 10 to 15 cm, and T4 greater than 15 cm, and tumor depth (superficial or deep to fascia) has been removed. Regional nodal involvement (N1) has moved and is now

considered stage IV. Histologic subtype is still not included as a category. The 8th edition AJCC extremity and trunk STS stage groupings are shown in Table 89.1.

TABLE 89.1 AMERICAN JOINT COMMITTEE ON CANCER TNMG STAGE GROUPINGS FOR EXTREMITY AND TRUNK SOFT TISSUE SARCOMA, 8*T*H EDITION

Stage IA	**G1,X**	**T1**	**N0**	**M0**	**Low grade, small**
Stage IB	G1,X	T2-4	N0	M0	Low grade, large
Stage II	G2,3	T1	N0	M0	Moderate/high grade, small
Stage IIIA	G2,3	T2	N0	M0	Moderate/high grade, intermediate
Stage IIIB	G2,3	T3-4	N0	M0	Moderate/high grade, large
Stage IV	Any grade	Any T	N1	M0	Nodal involvement
	Any grade	Any T	Any N	M1	Metastatic

G, grade; GX, grade cannot be assessed; M0, no distant metastasis; M1, distant metastasis; LN, lymph node; N0, no regional LN metastasis; N1, regional LN metastasis; T1, tumor ≤5 cm; T2, tumor >5-10 cm; T3, tumor >10-15 cm; T4, tumor >15 cm.

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PROGNOSTIC FACTORS FOR SURVIVAL AND LOCAL RECURRENCE

Many reports have evaluated patient and tumor characteristics to determine prognostic factors for disease-free survival (DFS) or overall survival (OS) and LR. The most powerful predictor for DFS and OS is the AJCC TNMG stage of the tumor. The staging system incorporates most of the relevant prognostic variables. It is also valuable to consider predictive factors individually. The single most important individual prognostic factor for distant metastatic risk and lower survival rates is high grade.[42-47] Five-year DFS rates range from 44% to 67% for high-grade tumors compared to 90% to 100% for low-grade tumors.[42-44] Other significant predictors for DFS include tumor size and anatomic site.[37,42,44-47] For a series of 1,091 patients from MD Anderson Cancer Center, 5-year OS rates were 85% for tumors less than or equal to 5 cm, 68% for tumors greater than 5 to 15 cm, and 52% for tumors greater than 15 cm.[46] Furthermore, patients with tumors located

in the head and neck or retroperitoneum had lower survival rates than those with tumors located in the extremity or superficial trunk.[43,47,48] Histologic subtype is predictive of both OS and DFS in several reports.[42,45,46,48,49] Callegaro et al developed two robust nomograms to predict OS and DFS for extremity STS and demonstrated adverse survivals for vascular tumors, leiomyosarcoma, synovial sarcoma, and MPNST compared to all liposarcoma subtypes, myxofibrosarcoma, and undifferentiated pleomorphic sarcoma.[45] It now appears that tumor depth (superficial or deep to fascia) is not a prognostic factor, and accordingly, depth has been removed from the staging system.[37,45,47,50] Older age at presentation, positive resection margins, bone or neurovascular invasion, gender, and race all show mixed results regarding their predictive value for DFS.[42-48] Lymph node involvement for STS is rare; but if present, it is an adverse prognostic factor.[16-18]

Margin status is the most significant predictor for LR.[42,43] Other predictors for LR include presentation with locally recurrent disease, older age, tumor size, and head and neck or retroperitoneal location. Rates of LR for tumors resected with positive margins range from 28% to 56% compared to 0% to 20% for those with negative margins.[31,42,43,51-56] Patients who present with locally recurrent disease are at higher risk for subsequent LR (25%-47%) than those who present with primary disease (11%-21%).[42,52] Age has been analyzed with varying cut-off values including older than 50 years, older than 64 years, and as a continuous variable. Repeatedly, older age has been associated with higher LR rates.[42,43,57] The influence of tumor size and anatomic site on LR risk may reflect challenges in obtaining widely negative margins.[43,58]

MANAGEMENT AND OUTCOMES OF SOFT TISSUE SARCOMAS OF EXTREMITY AND TRUNK

Because of the rarity of STS and the numerous forms in which it can present with respect to tumor histology, anatomic site, and size, there are many nuances related to optimal management. Furthermore, delivery of treatment requires a multimodality team that includes experienced pathologists; radiologists; surgeons from the disciplines of surgical oncology, orthopedics, and reconstructive surgery; radiation oncologists;

medical oncologists; nurses; physical therapists; and social workers. Treatment goals include complete eradication of tumor with optimal function preservation and minimal treatment-related toxicities. Execution of these goals is complex, and, for this reason, STS is best treated by experienced multidisciplinary teams at specialized sarcoma centers.[10,59,60] Reports from Sweden, the United Kingdom, the United States, and Canada have shown superior outcomes, including higher rates of limb-sparing resections and survival, for STS treated at specialized centers and those with higher volumes of patients.[61-66]

SURGERY

In almost all cases, appropriate surgical resection is a prerequisite for curative treatment of STS. A range of surgical procedures has been employed for the treatment of STS with varying levels of success. These procedures include marginal resection or excisional biopsy, wide resection, and radical resection or amputation. A marginal resection refers to the simple removal of the tumor with its pseudocapsule. This is also often described as a "shell-out" or "whoops" procedure and is commonly performed when the diagnosis of STS is not suspected. LR rates after marginal resection range from 50% to 93%.[15,67,68] This is not surprising, as it is known that microscopic tumor cells can extend beyond the pseudocapsule and up to several centimeters beyond the palpable gross tumor.[14,34] Marginal resection is not an appropriate oncologic treatment for STS.

At the other end of the spectrum is radical resection, which involves removal of all of the muscles and neurovascular structures within the compartment where the tumor resides, or amputation. Reported LR rates after radical resection are much lower, ranging from 0% to 18%, but come at the cost of significant functional loss.[15,53,67,68] Historically, amputation was a common procedure for STS of the extremities; however, it is rarely required for local management of STS in the modern era. In approximately 5% of patients, amputation may still be indicated for appropriate oncologic management, including in those for whom no limb-sparing approach is feasible. This may be due to patient-related comorbidities or disease extent

including involvement of bone, joint, multiple compartments, or major arteries or nerves.[69]

The intermediate procedure is a wide resection. Wide resection is also described as conservative surgery, limb-sparing surgery, or function-sparing surgery. It involves *en bloc* removal of tumor with a desired rim of normal tissue varying in width from about 1 cm to several centimeters depending on anatomic constraints. Wide resection preserves good function (limb-sparing) but as a treatment by itself is usually associated with moderately high LR rates, ranging from 25% to 60%.[15,67,68,70] Radiation therapy (RT) is combined with wide resection for most patients with STS to improve local control. Surgeons should attempt to obtain oncologically appropriate negative margins at the time of definitive resection. The presence of positive margins is consistently associated with increased LR rates, even when RT is used.[42,43,51-56,71] The appropriate margin attained should be tailored to both the anatomic site and surrounding tissues and the histopathologic subtype. For example, myxofibrosarcoma and MPNST are highly infiltrative, often extending beyond the imaging-visible tumor, and associated with increased risk for LR.[29,72,73]

Although the goal of resection is to attain wide negative margins, if this would require debilitating surgery, such as resection of a nerve, vessel, or bone, a function-sparing approach with a planned positive margin is acceptable.[54] These decisions are best handled by experienced sarcoma surgeons with input from radiation oncologists regarding the addition of RT. Gerrand et al evaluated LR rates in patients who had positive margins after limb-sparing surgeries and received RT. Those with planned positive margins (abutting critical structures) had a 4% LR rate compared to a 32% to 38% rate of LR in those with unplanned (unexpected) positive margins.[54] Given the increased risk for LR in the setting of unplanned or grossly positive margins, re-resection should be considered to obtain negative margins if feasible.[74,75]

In contrast, there are some exceptions for the general indication for re-resection to obtain wide negative margins. These include following microscopic positive margin resection of atypical lipomatous tumors (formerly well-differentiated liposarcoma) involving the extremity and desmoid tumors for which observation may be appropriate in selected

patients when salvage surgical options are available for recurrence if needed.[76-82]

Because STS is rare in comparison to benign soft tissue lesions, the initial procedure performed for an unsuspected is often an unplanned excision. Close or positive margins are frequent, as these procedures do not attempt to obtain wide margins. As these unplanned excisions continue to occur frequently, it is important to have a level of suspicion for STS when evaluating soft tissue masses, particularly those that are new and growing. Following an unplanned excision, definitive oncologic re-excision is recommended, if possible, as the likelihood of finding residual disease is significant, on the order of 24% to 83%.[75,83-90] As part of the re-resection, incisions, biopsy tracts, drain sites, and any tissues contaminated by the first surgery need to be removed *en bloc* along with appropriate tumor-bed margins. Unfortunately, re-resection often results in a greater scope of surgery and increased functional deficit than would otherwise have been required had the diagnosis of STS been anticipated and the initial planned excision had been performed by an experienced oncologic surgeon.[36] When there are indications for RT, it may be delivered "preoperatively" prior to the definitive oncologic resection, and when re-resection is not feasible, "postoperatively" following the unplanned excision.[75] Although RT is typically recommended for most large and high-grade STS of the extremity, superficial trunk, and head and neck locations in the setting of unplanned excision with gross macroscopic negative margins, some centers have selectively considered observation with the use of RT and delayed resection at recurrence, particularly when there would be an increased risk for morbidity with reexcision.[91]

Conservative Surgery and Radiation Therapy

Three sentinel randomized trials have been performed and established RT combined with conservative surgery as the standard management for most (high grade) STS of the extremities and trunk (Table 89.2). The first of these trials was conducted at the NCI.[53] Patients with high-grade STS of the extremity were randomized to amputation or wide resection and postoperative external-beam RT (60-70 Gy). Patients in both treatment arms received chemotherapy. LR rates were 0% (0 of 16) and 15% (4 of 27) for

patients treated with amputation and with wide resection and RT, respectively ($P = .06$). There was no significant difference in survival rates. The NCI I trial was instrumental in establishing the new standard for limb-sparing local management of STS. Amputations are now performed sparingly and in less than 15% of cases.[69,92,93]

TABLE 89.2 RANDOMIZED CONTROLLED TRIALS INCLUDING RADIATION THERAPY FOR SOFT TISSUE SARCOMAS OF THE EXTREMITIES AND TRUNK

Study	Treatment Arms	Local Recurrence	OS or DFS
Rosenberg et al[53] NCI 1982 *N* = 43 (Extremity)	Amputation vs CS + EBRT (60-70 Gy) (both arms received doxorubicin, cyclophosphamide, and methotrexate)	0% (0/16) 15% (4/27) *P* = .06	88% 83% *P* = .99 (5-y OS)
Pisters et al[71] MSKCC 1996 *N* = 164 (Extremity + trunk)	High grade (*n* = 119) CS vs CS + BRT (42-45 Gy) Low grade (*n* = 45) CS vs CS + BRT (42-45 Gy)	30% (19/63) 9% (5/56) *P* = .0025 26% (6/23) 36% (8/22) *P* = .49	All patients 81% 84% *P* = .65 (5-y DFS)
Yang et al[70] NCI 1998 *N* = 141 (Extremity)	High grade (*n* = 91) CS vs CS + EBRT (63 Gy) (both arms received doxorubicin, and cyclophosphamide) Low grade (*n* = 50) CS vs CS + EBRT (63 Gy)	19% (9/47) 0% (0/44) *P* = .003 33% (8/24) 4% (1/26) *P* = .016	74% 75% *P* = .71 (10-y OS) 92% (22/24) 92% (24/26) (no. alive)
O'Sullivan et al[96,105] NCIC 2004 *N* = 190 (Extremity)	Preop RT (50 Gy) + CS CS + postop RT (66 Gy)	7% 8% *P* = NS (5-y LR)	73% 67% *P* = .48 (5-y OS)

BRT, brachytherapy; CS, conservative (limb-sparing) surgery; DFS, disease-free survival; EBRT, external-beam radiation therapy; MSKCC, Memorial Sloan-Kettering Cancer Center; NCI, National Cancer Institute; NCIC, National Cancer Institute Canada; OS, overall survival; postop, postoperative; preop, preoperative.

With the role of wide resection instead of amputation established, the next question posed was whether adjuvant RT is necessary following conservative surgery. The NCI II study randomized patients with low- and high-grade STS of the extremity to conservative surgery with or without postoperative external-beam RT (63 Gy).[70] Patients with high-grade STS also received adjuvant chemotherapy. LR rates for the high-grade tumors were 20% (9 of 44) for wide resection with chemotherapy compared to 0% (0 of 47) for wide resection, chemotherapy, and RT (P = .003). For the low-grade tumors, LR rates were 33% (8 of 24) for wide resection alone and 4% (1 of 26) for wide resection and RT (P = .016). There were no significant differences in survival rates between the two groups. An update of this trial confirmed the lack of survival difference with a 20-year OS of 64% for wide resection alone and 71% for wide resection and RT (P = .22).[94]

The other hallmark trial showing improved local control with the addition of RT to conservative surgery was conducted at Memorial Sloan-Kettering Cancer Center (MSKCC).[71] Similar to NCI II, this trial randomized patients between wide resection alone and wide resection plus RT; however, the RT was adjuvant brachytherapy (BRT) rather than external-beam RT. BRT was delivered using an Iridium-192 implant via catheters placed in the tumor bed in a parallel array. A dose of 42 to 45 Gy was delivered over 4 to 6 days. LR rates for high-grade tumors were 30% (19 of 63) for wide resection alone compared with 9% (5 of 56) for wide resection plus BRT (P = .0025). No difference in LR rates by treatment was seen for low-grade tumors; rates were 26% (6 of 23) and 36% (8 of 22) for patients treated with wide resection alone and wide resection plus BRT, respectively. As in the NCI trials, there were no significant differences in survival outcomes.

These randomized trials established the role of RT combined with conservative surgery for the management of high-grade (and, in select cases, low-grade) STS.[53,70,71] In modern series, local control following wide resection and RT is excellent, with most reported LR rates being less than 15%.[52,56,95-99] Current treatment recommendations for the use of RT with conservative surgery require an assessment of risk for LR.[75] For STS at increased risk for recurrence (eg, tumors that are large, high grade, or associated with expected close or positive resection margins), combined

modality therapy with wide resection and RT is recommended for local control.[75]

Conservative Surgery Alone

Although conservative surgery and RT is the standard treatment for most STS of the extremity and trunk, there are several reports that demonstrate excellent outcomes following treatment with surgery alone. It is important to acknowledge that these are single-institution or large population-based series, all but one are retrospective, and patients were highly selected for treatment. LR rates in these studies range from 0% to 20%, most are 10% or lower.[100-104] In the prospective trial of surgery alone, negative resection margins were a required criterion and LR was 10.6% at 10 years.[101] In another series of patients treated with surgery alone, the overall 10-year actuarial LR rate was 7%. No LRs were seen with resection margins greater than or equal to 1 cm compared to an LR rate of 13% for those with margins less than 1 cm ($P = .04$).[100]

Other than for low-grade tumors resected with negative margins, treatment with surgery alone should be employed cautiously. Additional characteristics of tumors considered for treatment with surgery alone often include primary presentation of disease (not locally recurrent), low-grade, small, subcutaneous, superficial to fascia, or completely intramuscular that can be resected with wide margins, tumor locations amenable to limb-sparing salvage surgery for recurrence, and patient willingness to comply with appropriate follow-up.[100,101,104] Relative indications for RT in the setting of low-grade tumors include positive margins, locally recurrent disease following prior wide excision, and tumor location that would not be amenable to subsequent salvage surgery.

In sum, for select patients with STS of the extremity or trunk at low risk for recurrence, omission of RT and management with wide resection alone is reasonable.[75] A postoperative nomogram can be used to help predict the risk for LR following wide excision without RT.[103] Risk factors for LR included in the nomogram were age, tumor size, grade, histology, and margin status.

RADIATION THERAPY

Radiation Timing: Preoperative Versus Postoperative

The foundational studies that established the role of RT in addition to conservative surgery to improve local control, RT (either external-beam or BRT) was delivered postoperatively.[53,70,71] The role of preoperative RT was investigated in the National Cancer Institute Canada (NCIC) SR2 trial.[96,105] Patients were randomized to receive either preoperative RT (50 Gy preoperative ± 16 to 20 Gy postoperative boost) or postoperative RT (50 Gy + 16 to 20 Gy boost to the tumor bed) with limb-sparing resection. Local control at 5 years was the same with either sequence of therapies, 93% and 92% for the preoperative and postoperative groups, respectively, with no difference in survival.[96] The primary endpoint of the NCIC SR2 trial was major wound complication within 120 days of resection, defined as secondary operation for wound repair or other wound management, including readmission for care, antibiotics, or deep packing. With a median follow-up time of 3.3 years, the study met early stopping rules and closed. Wound complication rates were 35% for patients treated with preoperative RT compared to 17% for those treated with postoperative RT ($P = .01$). On multivariate analysis, other predictors for increased risk of wound complications included lower-extremity site and large tumor size (>10 cm). Although wound complications adversely affected functional outcome for patients in the early postoperative period (6 weeks after surgery), this toxicity was largely reversible, as evidenced by the fact that function was equivalent between the treatment arms 1 year after resection.[106,107] The Musculoskeletal Tumor Society Rating Scale (MSTS) and the Toronto Extremity Salvage Score (TESS) were used to assess late toxicity and functional status. Rates of greater than or equal to grade 2 late toxicity were higher for the postoperative RT group than the preoperative group: subcutaneous fibrosis, 48% versus 31.5%; joint stiffness, 23% versus 18%; and edema, 23% versus 15.5%. These differences were not statistically significant, but the study was not powered to detect these differences. The presence of late toxicities predicted lower functional status ($P < .01$). Statistically significant associations were seen between field size (greater with postoperative RT) and rates of fibrosis, joint stiffness, and edema ($P = .002$, $P = .006$, and $P = .06$, respectively).[106]

Although the efficacy of these approaches seems to be similar, the toxicity profiles are clearly different. Preoperative RT is associated with a well-established increased risk of acute wound complications.[105] On the other hand, patients treated with postoperative RT have a higher rate of chronic and generally irreversible toxicities, which include subcutaneous fibrosis, joint stiffness, and edema.[106] An additional late toxicity of significant concern is the risk of radiation-associated pathologic fracture. This occurs more commonly in weight-bearing long bones of the lower extremity and can lead to nonunion and significant morbidity.[94,108,109] Many series have reported increased rates of bone fracture for patients treated postoperatively (60-66 Gy) compared to those treated preoperatively (50 Gy).[94,108-113] Other risk factors for fracture include total RT dose, circumferential bone dose and other dose-volume parameters, RT treatment technique, age, female sex, receipt of chemotherapy, tumor anatomic site and size, and extent of periosteal stripping at time of resection.[108,109,112,113]

Advantages of preoperative RT include the ability to treat with smaller RT fields and lower doses, both of which are associated with reduced permanent long-term toxicities. Lower RT doses are also associated with reduced treatment time, lower costs, and a hypothetical possibility of lower second-malignancy risks. Other potential advantages of preoperative RT include the ability to render unresectable or marginally resectable tumors operable, the potential to prevent tumor seeding of the operative bed or systemic circulation, and an increased efficacy of RT from good oxygenation of tissues due to unperturbed tumor vasculature. Furthermore, in most cases, defining the tumor volume for RT planning is relatively straightforward, given that it is in situ. The main disadvantage of preoperative RT is the higher risk of major wound complications and its concomitant increased morbidity and cost. However, most major wound complications are treatable and, therefore, this toxicity is generally considered reversible. Another disadvantage of preoperative RT is that the resected specimen is potentially less informative on pathology review due to the prior treatment.

Postoperative RT has the advantage that the complete tumor specimen is available for pathology review for determination of histology and margin status. Another important advantage is the lower risk of major wound complications. The main disadvantages of postoperative RT are the

necessity for larger treatment volumes and higher doses, which are associated with higher long-term toxicities such as subcutaneous fibrosis, joint stiffness, edema, pain, and bone fracture. For the most part, these toxicities are irreversible. In theory, the interrupted vasculature related to surgery may create a hypoxic environment, rendering RT less effective (this is a potential explanation for the need for higher doses compared to the preoperative setting). Lastly, determining an RT target definition is more complex in the postoperative setting, as it requires reconstruction of where the tumor resided as well as the definition of the entire operative field.

In conclusion, pre- and postoperative RT are associated with equivalent efficacies but different toxicity profiles, the most salient of which are increased (reversible) wound complications for preoperative RT and increased (irreversible) long-term toxicities of fibrosis, edema, joint stiffness, and fracture for postoperative RT. The sequence of RT and conservative surgery for an individual patient should be determined with multidisciplinary input and coordination, considering the risks for acute and late toxicities. In general, when RT is indicated for local control in combination with wide resection, preoperative RT is preferred over postoperative RT for STS of the extremities or trunk.[75] In select patient circumstances, the risks for major acute wound complications may supersede those of late effects and postoperative RT may be appropriate.[75] Even when a patient is at high risk of developing a wound complication, one could argue for preoperative RT, as most wound problems are highly treatable with eventual recovery of good function. In cases where there was no clear initial indication for RT and upfront surgery was performed, postoperative RT is indicated for adverse pathologic features associated with increased risk for recurrence (eg, unanticipated close or positive margins, higher grade, nodal involvement, or discontinuous spread).[75]

Radiation Therapy Dose and Fractionation

Preoperative Dose

The foundational randomized clinical trials defining the role of external-beam RT with conservative surgery for extremity and truncal STS have used conventional fractionation, which remains the standard at this time.[53,70,105] The preferred dose for preoperative external-beam RT is 50 Gy

delivered in 2 Gy fractions.[75,114] Although concurrent or interdigitated sensitizing chemotherapy combined with preoperative RT is not considered standard of care, if utilized, the RT total dose and dose per fraction may be reduced (44-50.4 Gy in 22-28 fractions).[115,116]

Postoperative Boost for Positive Margins

When positive margins occur following preoperative RT and conservative surgery, the site and type of margin (anticipated or unplanned) and options for subsequent management should be discussed in a multidisciplinary setting. If feasible without significant morbidity, re-resection to achieve negative margins should be performed. If further resection is not feasible, the potential role of a postoperative external-beam RT boost of 16 to 20 Gy (delivered in 1.8-2 Gy fractions) may be considered. However, the efficacy of such a boost dose has not been proven and, as it may be associated with increased toxicity, it is not routinely recommended.[117,118] Selective situations where a postoperative RT boost may be reasonable include those with positive margins at high risk for recurrence, where the site of the positive margin can be clearly delineated for treatment planning, and the additional dose would not confer untoward morbidity.[58,75,105,119] Other techniques to deliver an additional boost dose include BRT and intraoperative RT.

Postoperative Dose

For postoperative external-beam RT, treatment usually commences about 4 to 6 weeks following surgery and once the wound is fully healed. Recommended total doses are 60 to 66 Gy for negative margins and 66 Gy for microscopic positive margins.[43,58,75,105,119,120] Higher total doses may be considered selectively for gross residual disease. Postoperative RT is usually delivered with a dose of 50 Gy to a larger volume, and the balance of the dose is given to a reduced field. Traditionally, these doses were delivered sequentially, but they can also be given using a simultaneous integrated boost.

Alternative Dose and Fractionation Regimens

Based on the observed clinical behavior and relative radioresponsiveness of myxoid liposarcoma, the Dose Reduction of Preoperative Radiotherapy in

Myxoid Liposarcoma (DOREMY) study was designed to evaluate whether preoperative RT dose reduction to 36 Gy could result in comparable local control to conventional 50 Gy and minimize wound complications and late morbidity.[25,121,122] The primary endpoint of this prospective multicenter phase II single-arm study was extensive histologic treatment response. With a median follow-up of 25 months, local control was 100%, regardless of treatment response. Wound complications occurred in 22% of patients, with 17% requiring intervention. Grade 2 or higher late effects were less than 10% for fibrosis, edema, and joint stiffness. Although the results from this trial are appealing, further follow-up data are needed prior to incorporating dose reduction into routine clinical practice. Ongoing registry data with the use of 36 Gy in this setting are being collected to confirm the DOREMY study results (NCT04699292).

Although the current standard for preoperative external-beam RT remains conventional fractionation to 50 Gy, there is an active investigation into the use of moderate hypofractionated and ultrahypofractionated regimens. Interest in hypofractionated regimens for STS is not new, and early studies often included concurrent systemic therapy.[123-130] More recent evaluations have primarily investigated various dose regimens for preoperative RT without chemotherapy.[131-139] These studies differ significantly in the dose fractionation schema used, the timing of treatment delivery (daily or every other day), target volumes, timing to resection, length of follow-up, and toxicity assessment and reporting. Among the recently studied ultrahypofractionated regimens, 5 Gy × 5 fractions resulted in local control on the lower end of acceptable.[131-134] Regimens of 6 Gy and 7 Gy × 5 fractions appear to result in excellent local control comparable to conventional fractionation, but further study and follow-up are needed to adequately assess wound complications and late toxicity rates (fibrosis, edema, joint stiffness, fracture).[135-137] The regimen of 8 Gy × 5 fractions resulted in an unacceptable rate of amputation for complications of therapy.[138] The HYPORT-STS study used moderate hypofractionation (2.85 Gy × 15 fractions) with resulting excellent local control, but this regimen also requires further study with respect to late effects.[139] The hypofractionated regimens most radiobiologically equivalent to 2 Gy × 25 fractions are 2.85 × 15 fractions and 6 Gy × 5 fractions (using an α/β of 3-5 for STS).[140] As such, one would anticipate that the local control would be

comparable to conventional fractionation; however, given that normal connective tissues have lower α/β ratios, the question remains whether they will be comparable for toxicity. Ongoing follow-up and reporting on toxicities of wound healing, edema, fibrosis, joint stiffness, and fracture are necessary to determine the role of any of these hypofractionated regimens in routine clinical practice. No regimen can be considered an established alternative to conventional fractionation at this time; ideally, these appealing hypofractionation regimens will be tested against conventional fractionation in a randomized controlled trial.

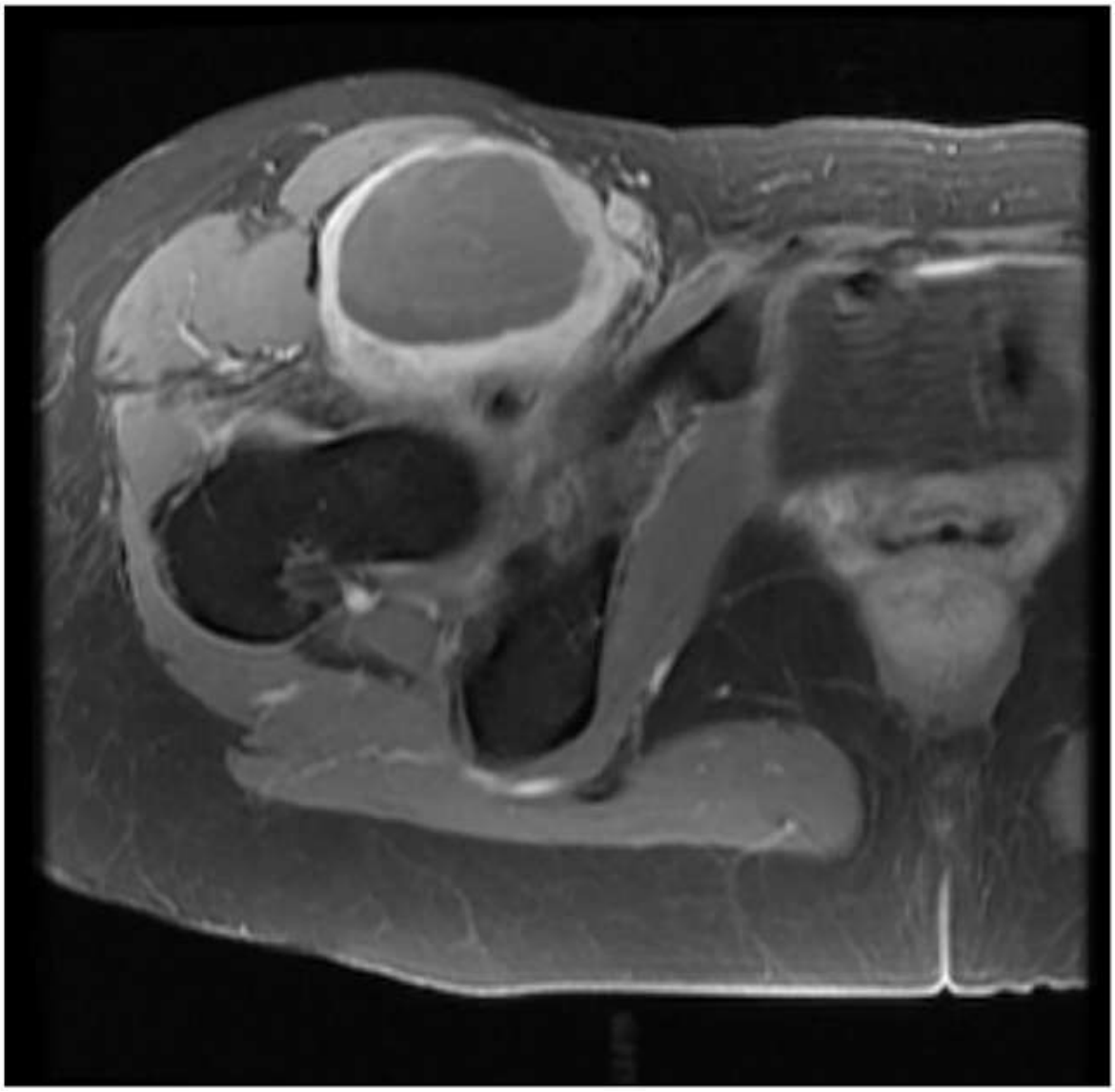
Radiation Target Volumes

Preoperative Radiation Therapy

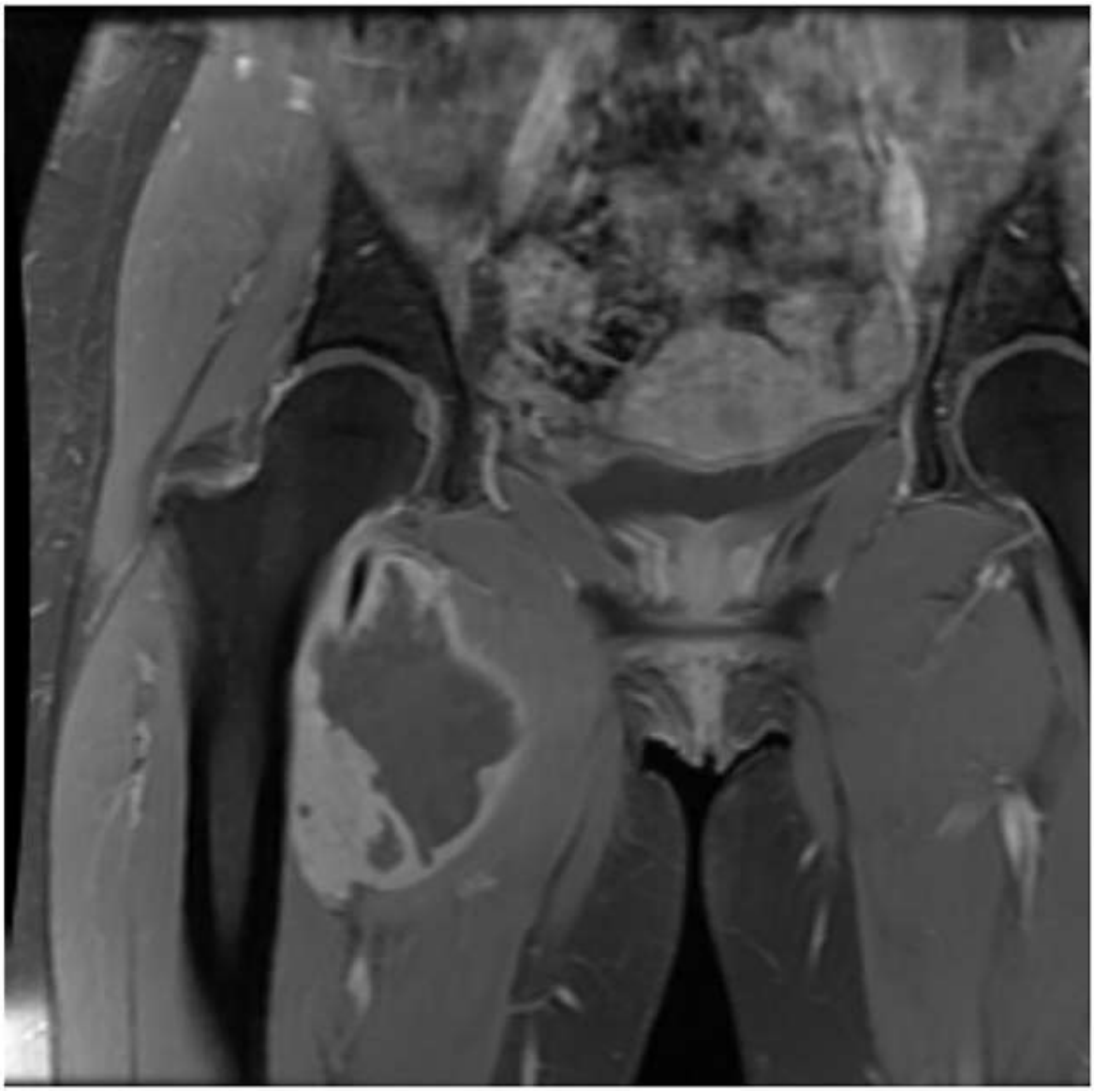
Historically, treatment volumes for STS of the extremities and trunk were comprised of large longitudinal margins of at least 5 cm, and sometimes greater than 10 cm, often covering the full compartment. With improved preoperative imaging modalities, treatment delivery techniques, setup reproducibility, and supportive data from studies, these margins have been reduced. Current standard target volumes for preoperative RT include the gross tumor volume (GTV), defined as the tumor delineated on T1 post-gadolinium MRI.[75,114] Fusion of the diagnostic MRI, and/or other staging imaging, with the planning CT for optimal target definition is strongly encouraged. For extremity and truncal STS, the clinical target volume (CTV) is defined as the GTV plus 3 to 4 cm margin in the longitudinal directions (along the plane of the musculature) and 1.5 cm margins radially.[75,114] These margins are anatomically constrained to not extend into bone or beyond the compartment or skin. CTV margins may also be constrained such that they only extend about 0.5 to 1 cm across intact fascial planes. For subcutaneous STS, as there are no longitudinal or radial muscle planes, the CTV is a 3- to 4-cm circumferential margin on the GTV, with an expansion of 0.5 to 1 cm into uninvolved underlying muscle. Target volumes are edited 0.5 cm beneath the skin surface in most scenarios to attain superficial dose avoidance and minimize the risk of wound complications (Figure 89.5). When this is done, the plan for resection of subcutaneous tissue and overlying skin should be confirmed with the surgeon. The biopsy tract and peritumoral edema on T2 MRI are included

within the CTV when feasible. For cases where peritumoral edema is extensive, greater clarity is needed to determine how much should be included in the CTV. One report showed the presence of sarcoma cells beyond the gross tumor in 10 of 15 patients. The location of the cells varied from 1 to 4 cm beyond the tumor but did not correlate with the location or extent of peritumoral edema on MRI.[34] It is reasonable to try to include the edema in the CTV unless doing so would require a significant increase in the treatment field. As lymph nodes are not frequently involved in STS, there is no elective inclusion of nodal basins within the CTV. The planning target volume (PTV) is defined as the CTV plus 0.5 to 1 cm or greater based on institution setup uncertainty and image guidance practices.

Figure 89.4 depicts MRI images and target volumes for a patient with STS of the right proximal medial thigh treated with preoperative intensity-modulated RT (IMRT). Figure 89.5 shows the preoperative RT treatment volumes for a patient with a subcutaneous STS involving the superficial tissues of the thigh.



A



B

FIGURE 89.4 An undifferentiated pleomorphic high-grade sarcoma of the medial proximal right thigh in a 30-year-woman treated with preoperative intensity-modulated radiation therapy (IMRT) to 50 Gy. A. Axial T1 post-gadolinium image of the magnetic resonance imaging (MRI) scan. B. Coronal T1 post-gadolinium image of the magnetic resonance imaging (MRI) scan. C. Axial slice of the planning computed tomography (CT) scan showing the gross tumor volume (GTV, cyan), clinical target volume (CTV, dark blue), and planning target volume (PTV, red).

A
P
- C1_final
F

FIGURE 89.5 Representative preoperative radiation treatment planning volumes for a patient with subcutaneous soft tissue sarcoma (STS) involving the superficial tissues of the thigh. A. Axial and (B) sagittal slices from the planning computed tomography (CT) showing the gross tumor volume (GTV, orange), clinical target volume (CTV, green), and planning target volume (PTV, red). The CTV is a 3- to 4-cm circumferential margin on the GTV with an expansion of 0.5 to 1 cm into the uninvolved underlying muscle. Target volumes are edited 0.5 cm beneath the skin surface in most scenarios to attain superficial dose avoidance and minimize the risk of wound complications. When this is done, the plan for resection of subcutaneous tissue and overlying skin should be confirmed with the surgeon.

Postoperative Radiation Therapy

For postoperative treatment, the nomenclature for "GTV" and CTV is variably described and is partly a matter of semantics, given that there is no actual "gross tumor." It can be helpful to recreate a "GTV" in the location where the gross tumor was preoperatively, as sometimes this volume is used for cone-down volumes. For extremity and truncal STS, the CTV1 includes the tumor bed (defined by surgical clips and preoperative imaging) plus 3 to 4 cm margin in the longitudinal directions and 1.5 cm margins radially that are anatomically constrained. For subcutaneous STS, as there are no longitudinal or radial muscle planes, the CTV1 is a 3- to 4-cm circumferential margin on the tumor bed (defined by surgical clips and preoperative imaging) with an expansion of 0.5 to 1 cm into uninvolved underlying muscle. CTV1 should encompass all the tissues within the operative field including postoperative changes, the incision, and any drain sites, when feasible.[75,114] The same principles apply as for preoperative RT target volumes in terms of using the T1 post-gadolinium images for "GTV" definition, fusing the planning CT and MRI when possible, and editing the CTV to exclude bone, intact fascial planes, skin, or extension beyond an uncontaminated compartment. As lymph nodes are not frequently involved in STS, there is no elective inclusion of nodal basins within the CTV. The PTV is typically CTV plus 0.5 to 1 cm, per institutional standard for setup uncertainty and image guidance practices. Typically, a CTV2 is used for field reduction (cone down) in the postoperative setting. For extremity and truncal STS, CTV2 includes the tumor bed with approximately 2 cm longitudinal and 1.5 cm radial margins. For subcutaneous STS, CTV2 includes the tumor bed with a 1.5- to 2-cm circumferential margin and 0.5 cm expansion into the uninvolved underlying muscle. The PTV expansion

is the same as above. CTV2 can be treated sequentially to CTV1 or delivered as a simultaneous integrated boost during the same course.

Series using treatment volumes similar to those described above have reported excellent local control rates on the order of 85% to 90%.[96-99,141] Furthermore, using these standard volumes, most LRs that occur are located within treatment fields rather than marginal to the fields, indicating that the fields are not too small.[97,98]

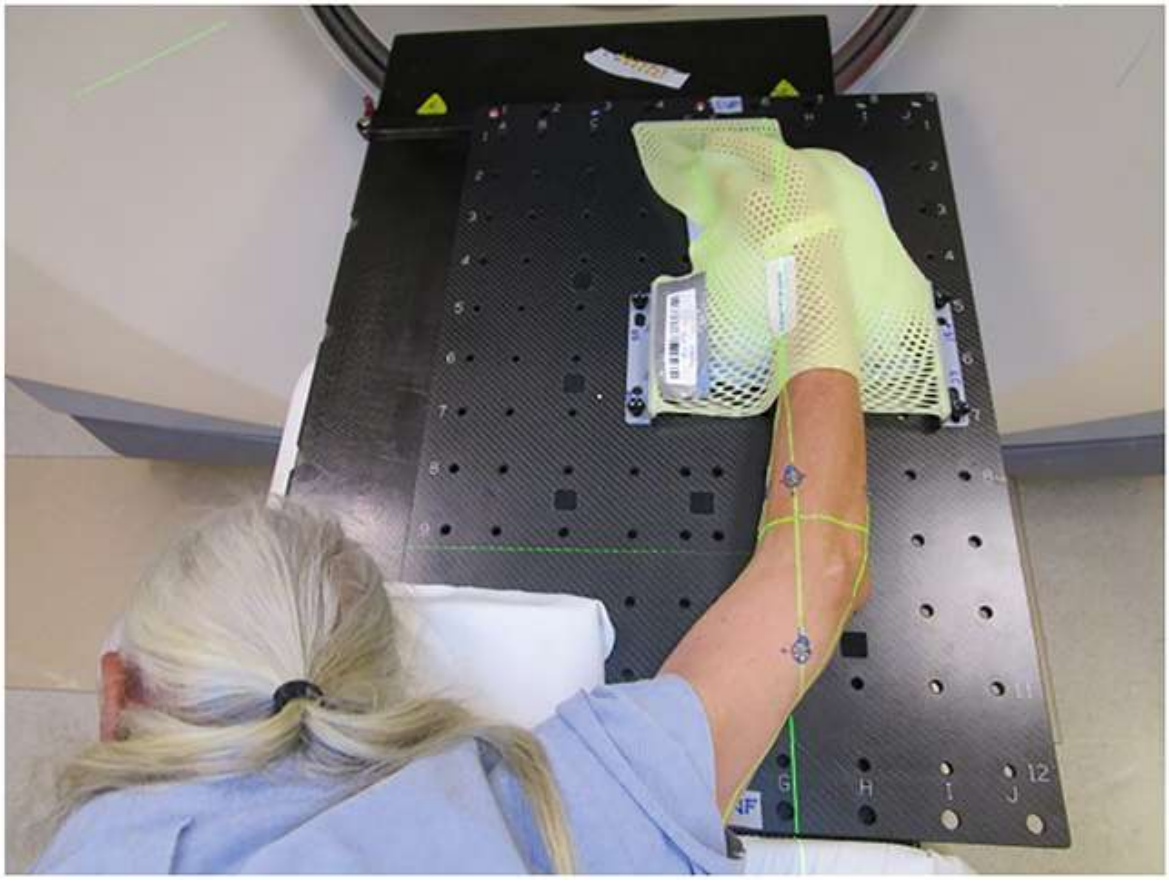
The excellent local control rates resulting from the use of standard preoperative and postoperative treatment fields establish that these fields are adequately large, but they do not address the question of whether these field sizes could be reduced. The initial design of these large fields predated the CT and MRI era, when imaging modalities to define STS were suboptimal. Moreover, the BRT experience at MSKCC produced excellent local control rates using treatment volumes that extended only 1.5 to 2 cm beyond the tumor bed.[71] Based on these observations, the RTOG 0630 and VORTEX (Randomised Trial of Volume of Post-operative Radiotherapy Given to Adult Patients with eXtremity Soft Tissue Sarcoma) trials evaluated whether treatment field sizes could be reduced.[119,142] The RTOG 0630 study was a phase II study investigating the, then novel, use of daily image-guided RT (IGRT) and (somewhat) reduced fields for preoperative RT for extremity STS. For tumors that were intermediate to high grade and greater than or equal to 8 cm, the CTV was defined as GTV plus 3 cm longitudinal and 1.5 cm radial margins; for tumors that were low-grade or less than 8 cm, the CTV was defined as GTV plus 2 cm longitudinal and 1 cm radial margins. The CTV also included suspicious edema on MRI T2 images. For a cohort of 79 patients, 2-year local control was 11%, and all five LRs occurred within the treatment fields.[119] The authors concluded that due to the absence of marginal field recurrences and reduction in reported late toxicities, the reduced volumes were appropriate. Importantly, daily image guidance is now the standard of care at most institutions. Whereas the RTOG 0630 trial evaluated margin reduction (with IGRT) in the preoperative setting, the VORTEX trial investigated CTV margin reduction for postoperative RT. Patients in this trial were randomized to standard fields with GTV plus 5 cm longitudinal and 2 cm radial margins or to tailored fields of GTV plus 2 cm in all directions. Preliminary results presented in abstract form did not show an improvement in limb function at

2 years, and there were too few events to evaluate noninferiority.[142] The study question is intriguing, but it is not appropriate to adopt reduced postoperative volumes at this time.

Radiation Therapy Planning

Positioning the Patient and Simulation

The first step of RT planning is to determine the appropriate positioning of the patient. It is important for the patient to be comfortable to ensure setup reproducibility. The multiple beam angles employed with IMRT techniques enable more positioning options than would be the case for 3D-CRT techniques.[143] As STS can occur throughout the body, there is no one typical STS simulation setup. In general, patients with extremity or truncal STS should be simulated in a comfortable, neutral, and reproducible position. This is generally in the supine position unless this places pressure on and deforms the tumor, in which case the prone position may be used. Suitable positions for upper-extremity lesions include supine with abduction of the arm away from the body with supination or pronation of the arm determined by the location of the tumor. Another good approach for upper-extremity lesions is the "swimmer position," whereby the patient is prone with the arm extended above the head (Figure 89.6A). For the treatment of a leg, the ipsilateral leg should be straight, and the contralateral leg separated to create a gap (Figure 89.6B). If the target is in the proximal thigh, the contralateral leg can be in a frog-leg position with support under the knee. For men with proximal thigh tumors, the genitalia should be displaced to the contralateral side (using mesh or other techniques). Men with treatment fields close to the genitalia should consider sperm banking if they wish to preserve fertility. Similarly, for cases with treatment fields close to the ovaries (eg, tumors of the proximal thigh, buttock, abdominal wall), women interested in fertility preservation should be referred for reproductive counseling prior to starting RT.[144]



A

B

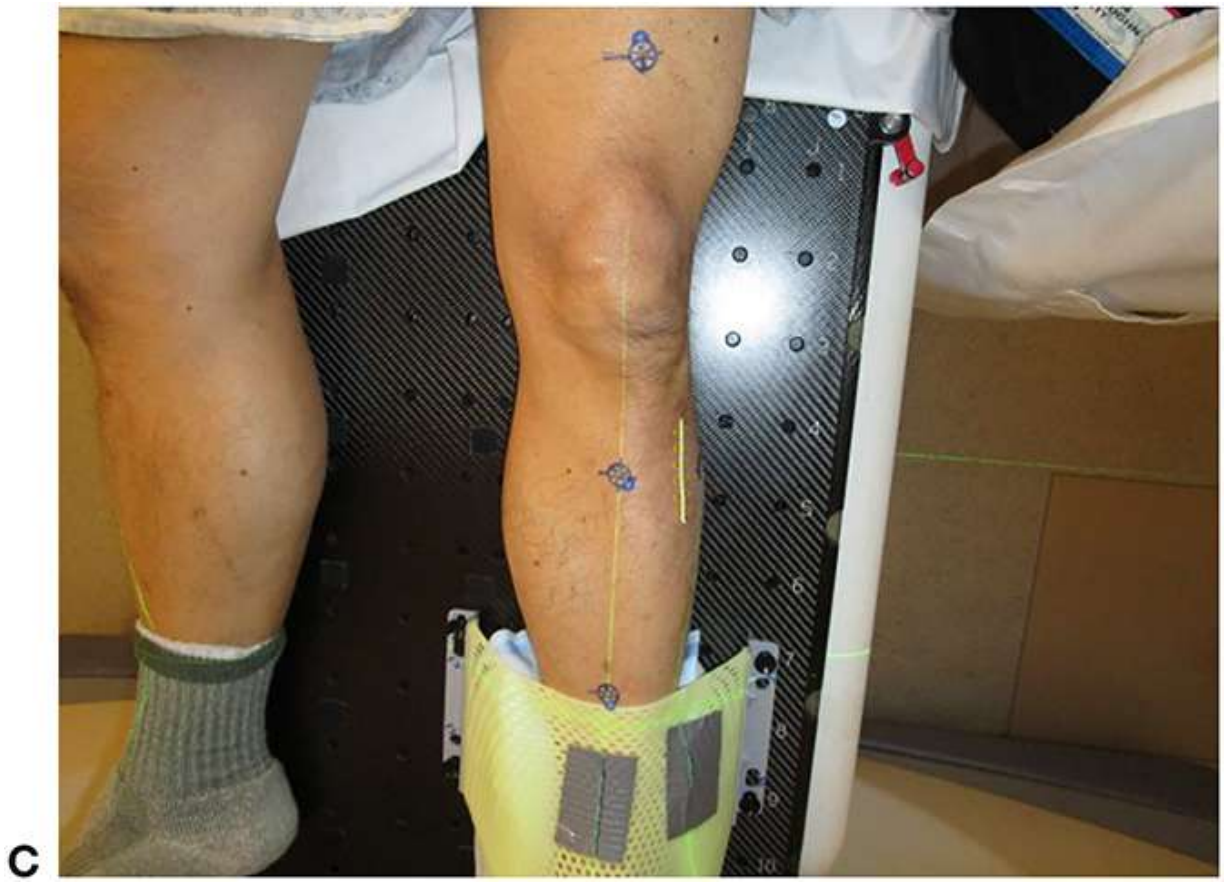


FIGURE 89.6 Examples of patient positions, immobilization, and tattoo placement for treatment of upper- and lower-extremity soft tissue sarcoma (STS). Patients are immobilized in custom casts which are indexed to the tabletop. A. The "swimmer position" is often an ideal position for treating STS of the hand, forearm, or distal upper arm. The hand is immobilized with a custom cast for all upper-extremity tumors. Anterior tattoos are placed approximately 15 to 20 cm apart along the same sagittal plane. B. For treatment of a lower leg tumor, the patient is supine with the ipsilateral leg neutral and straight, and the contralateral leg is separated to create a gap. The foot is immobilized with a custom cast for all lower-extremity tumors. Lateral tattoos are placed along the same axial plane as the anterior tattoos. C. Anterior view of the lower leg tumor showing placement of tattoos at the isocenter and approximately 15 to 20 cm apart along the same sagittal plane.

Once the position is determined, the patient must be immobilized in a reproducible fashion. A custom cast indexed to the tabletop is highly recommended for almost all scenarios; it is important to immobilize the foot with a custom mold for all lower-extremity tumors and to immobilize the hand for all upper-extremity tumors (Figure 89.6A,B). With respect to tattoo placement, a helpful protocol for extremities is to use three anterior tattoos and three lateral tattoos. The three anterior tattoos are placed

approximately 15 to 20 cm apart along the same sagittal plane (Figure 89.6A,C), and at each point, an additional lateral mark is placed in the same axial plane (Figure 89.6B). The six tattoo points are all placed in a stable anatomic location for the primary purpose of reproducing the position of the entire length of the extremity and the secondary purpose of creating a reference point for aligning the isocenter.

CT simulation with slice thickness less than or equal to 3 mm is recommended for conformal treatment planning. Biopsy sites, incisions from prior excisions, and drain sites (if present) should be marked with radioopaque wires or BBs to help define targets and sites at risk for seeding of the tumor. Relevant diagnostic imaging should be fused to the planning CT to assist with target delineation.

Radiation Treatment Planning and Delivery

As for any other malignancy, the basic principles of RT planning for STS are to achieve good coverage of the PTV with maximal sparing of adjacent normal structures. For extremity lesions, the important normal structures are the limb itself, skin and subcutaneous tissues, soft tissues, bones, and joints. For proximal thigh lesions, the perineum, external genitalia, and testes or ovaries are also relevant (Figure 89.7A). It is not always possible to preserve fertility, and patients desiring fertility preservation should be referred for consultation prior to treatment for discussion of sperm banking, oocyte cryopreservation, or other options. Every effort should be made to place the testicles as far out of the field as possible to avoid direct treatment and to minimize the contribution from internal scatter. For truncal STS, adjacent organs at risk (OARs) can include the small bowel, kidneys, spinal cord, stomach, liver, heart, and lung.

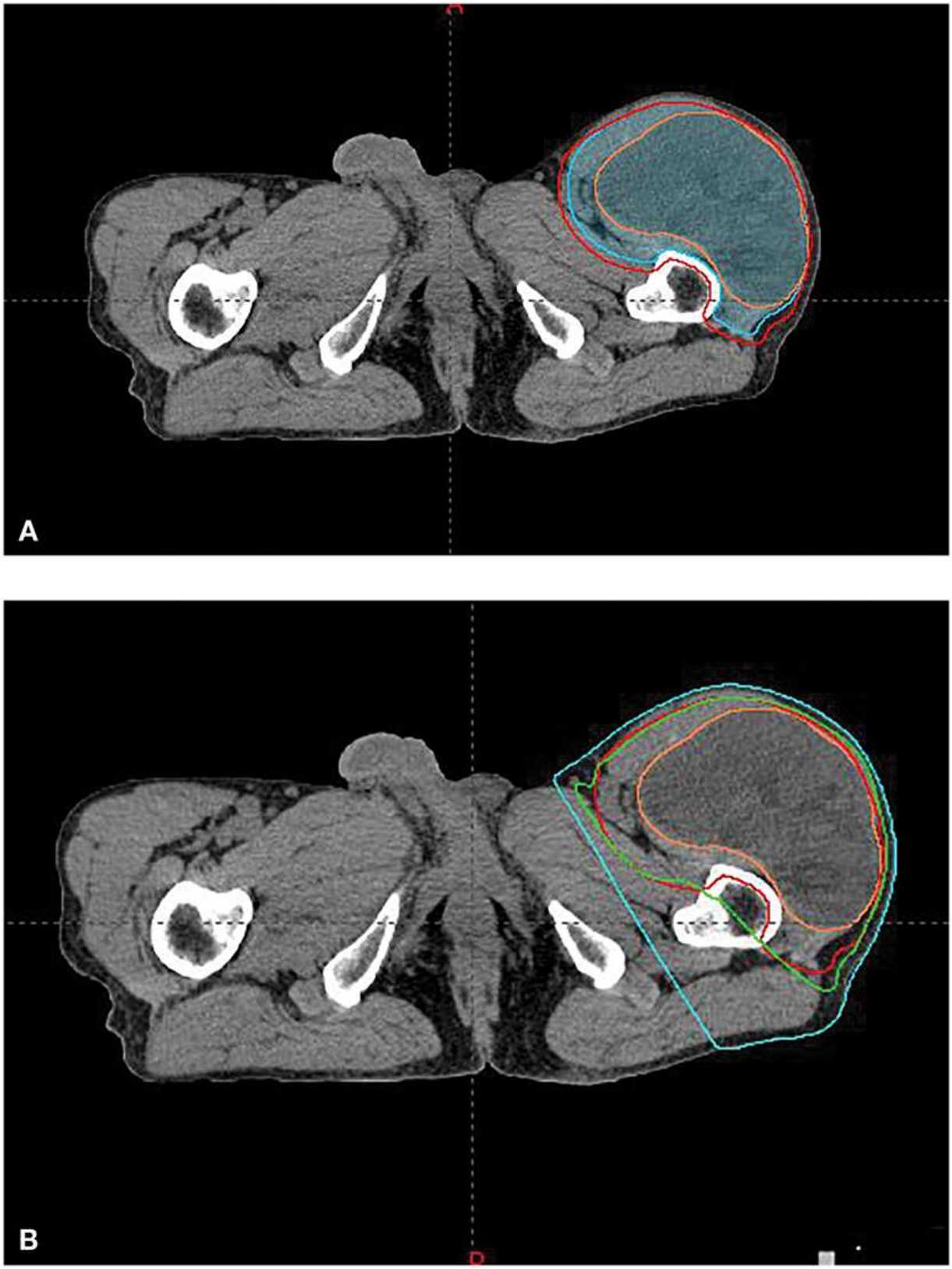


FIGURE 89.7 A myxoid liposarcoma of the proximal thigh in a 32-year-old man treated with preoperative intensity-modulated radiation therapy (IMRT) to 50 Gy. A. Axial slice of the

planning computed tomography (CT) scan showing the gross tumor volume (GTV, orange), clinical target volume (CTV, light blue), and planning target volume (PTV, red). The CTV does not extend into bone. Organs at risk (OARs) include the skin and subcutaneous tissues, soft tissues, the femur, hip, perineum, external genitalia, and testes. The external genitalia have been displaced to the contralateral side. Patients desiring fertility preservation should be referred for reproductive consultation prior to treatment. B. Axial slice from the planning CT showing the GTV (orange), PTV (red), 50 Gy isodose line (green), and the 20 Gy isodose line (cyan). The 50 Gy isodose line covers the PTV while avoiding a full circumferential dose to the femur. High dose is pulled back from the overlying skin and subcutaneous tissues. The 20 Gy isodose line shows the sparing of a strip of skin and subcutaneous tissue and avoidance of dose to the perineum, external genitalia, and contralateral limb.

Basic tenets for treating the extremity are to “spare a strip” of the limb circumference (to prevent subsequent lymphedema and pain), to avoid treating the whole thickness of bone to high doses (to diminish the risk of fracture), and to avoid treating an entire joint to high doses (to decrease joint stiffness). In the preoperative treatment setting, it is also necessary to pay attention to the dose received by skin and subcutaneous tissues comprising the future surgical resection flaps (to minimize wound complications) (Figure 89.7B).

For extremity STS, recommended OAR constraints are as follows.[75] Spare as much as possible of the limb circumference from receiving any dose, and limit the dose to a longitudinal strip of skin and subcutaneous tissue so that no more than 50% receives 20 Gy. Minimize skin dose overlying joints or sites of frequent trauma (eg, anterior leg) and hot spots within superficial tissues. For patients receiving preoperative RT, discussion with the surgeon regarding the anticipated operative plan can facilitate dose sparing of skin and subcutaneous tissue at the site of the anticipated incision and if resection of skin is planned, the PTV may be cropped 0.5 cm from the skin surface to reduce the risk for wound healing complications. Avoid entrance or exit dose through the contralateral extremity. For proximal tumors, limit the dose to the perineum, external genitalia, and testes or ovaries. Full circumferential bone irradiation should be avoided if possible, and the mean and maximum doses to the whole bone should also be kept to a minimum.[108] For planning, the weight-bearing bone OAR is defined as the extent of the long bone from 2 cm above and below the PTV.[108] The suggested dose constraints to minimize risk for fracture are volume of bone

receiving greater than or equal to 40 Gy (V40) less than 64%, mean dose to bone less than 37 Gy, maximum dose to bone less than 59 Gy and to try to limit no more than 50% of the bone within the field from receiving 50 Gy.[108,109] For select patients at high risk for fracture, when achieving these weight-bearing bone constraints is not possible and when resection will include periosteal stripping, discussion with an orthopedic oncologist regarding consideration for prophylactic fixation may be warranted.[109] Additionally, planning should minimize the dose to any joint as much as possible, avoid treating the entirety of the joint, and keep less than 50% of the joint from receiving 50 Gy.

For STS involving the trunk or other anatomic sites, dose constraints for underlying OARs should follow established tolerances. Normal-tissue complication probabilities for organs that may be affected by treatment are listed in the Quantitative Analysis of Normal Tissue Effects in the Clinic document.[145] If RT treatment of a trunk lesion may potentially significantly reduce or ablate ipsilateral kidney function, an assessment of adequate contralateral kidney function should be performed.

Use of tissue-equivalent bolus material is discouraged in the preoperative setting and infrequently necessary in the postoperative setting, with the exception of skin or subcutaneous tissue involvement.[75,119,146] In the preoperative setting, a paddle of skin is typically removed along with a superficial tumor obviating the need for bolus; furthermore, increased surface dose appears to increase wound complication risk.[99,146] In the postoperative setting, the BRT experience showed that failure to treat incision or drain sites was not associated with scar or drain site recurrences.[71]

Three-dimensional-conformal RT (3D-CRT) and IMRT, including volumetric modulated arc therapy (VMAT) are acceptable external-beam treatment techniques, but IMRT has several advantages over 3D-CRT and is generally preferred.[75] The principal dosimetric differences between these two techniques are that IMRT typically achieves comparable or improved target coverage, improved conformality of the dose distribution around the target volume, and reduced volumes of high doses to normal tissues, compared with 3D-CRT, but the volume of tissue receiving low dose is increased with IMRT.[147,148] Several studies show similarly excellent local control rates with IMRT compared to 3D-CRT, and some show superior

local control for IMRT.[96,99,119,141,146] Importantly, IMRT is associated with a more favorable late toxicity profile compared to 3D-CRT including a superior ability to spare dose to weight-bearing bone minimizing risk for fracture.[113,149] In select situations, such as STS involving the distal extremities, a carefully designed 3D-CRT approach may be helpful, as part of the limb can usually be excluded entirely from the treatment fields. However, if using 3D-CRT for preoperative RT, it is important to minimize dosimetric hotspots in the skin and subcutaneous tissues to reduce the risk of wound complications. On balance, given the dosimetric advantages and favorable toxicity profile, IMRT is the preferred technique for most STS of the extremity and trunk.

Even with custom immobilization, reproducible setup for extremity STS can be challenging. With the increased use of highly conformal techniques for treatment delivery, setup verification is necessary to ensure accurate positioning. IGRT refers to serial imaging of patient setup prior to treatment so that appropriate positional adjustments can be made before treatment delivery. Various imaging modalities, including kV orthogonal images and cone beam CT, can be used for alignment. Because the use of IGRT increases the certainty of treatment accuracy, in many cases, the added margins for “setup error” can be reduced, which allows for smaller treatment fields and potential dose escalation without undue normal tissue toxicity. Daily IGRT and reduced treatment fields were used in the phase II RTOG-0630 trial.[119] An analysis of the daily positioning variation on this trial suggested that in the absence of daily IGRT, a CTV to PTV expansion of 1.5 cm would have been required to account for all setup uncertainty.[150] The appropriate PTV margin used for planning should reflect this uncertainty, frequency of imaging, and institutional practices to address such setup errors. Another benefit of IGRT is that imaging during a course of treatment can show changes in patient anatomy (eg, due to weight loss) or changes in tumor shape. This allows for adaptive RT and the generation of an updated treatment plan. This is relevant for preoperative treatment of histologies that respond dramatically to RT, such as myxoid liposarcoma.[151,152] Daily image guidance is recommended for setup verification throughout treatment, with the inclusion of at least weekly (if not daily) volumetric imaging.[75]

Radiation Therapy Toxicities

Acute Toxicities

Acute toxicities following RT to the extremities include skin erythema, dermatitis, and possible desquamation in high-dose areas, skin folds, or when the tumor involves the skin or subcutaneous tissues, problems with wound healing, localized alopecia, and fatigue. Moist desquamation can be quite uncomfortable, but this typically heals quickly after completion of RT. Depending on tumor location, treatment of STS of the trunk can be associated with additional toxicities such as nausea, esophagitis, or bowel irritability.

The most significant of these acute sequelae is problems with wound healing. Rates of reported wound complication rates following preoperative RT were 35% on the NCIC SR2 trial and 37% on the RTOG 0630 study.[105,119] Rates following postoperative RT are lower and were 17% on the NCIC SR2 trial.[105] In addition to preoperative RT, other predictors for wound complications include lower-extremity site, tumor size greater than 10 cm, tumor proximity to skin surface less than 0.3 cm, vascularized flap closure, and diabetes mellitus.[99,105] In an attempt to decrease wound complications following preoperative RT, a phase II prospective study of image-guided IMRT was conducted for patients with lower-extremity STS.[146] Together with the surgeon, the radiation oncologist contoured the area of the subsequent surgical flaps and designated it as an avoidance structure for treatment planning. Although the resulting rate of wound complications (30.5%) was not statistically significant, rates of primary closure were higher and the need for reoperations was lower. For patients with minimal (<1%) overlap of the flap and PTV, the wound complication rate was 14.3% compared to 39.5% for those with flap and PTV overlap (P = .04). The association of higher wound complications with higher flap doses is consistent with the report showing increased complications for tumors within 0.3 cm of the skin surface.[99] Efforts continue to try to minimize postoperative wound complications, for example, the use of enhanced recovery programs employing preoperative, intraoperative, and postoperative interventions.[153]

Chronic Toxicities

The most significant chronic toxicities following RT to the extremities include edema, subcutaneous fibrosis, decreased muscle strength, decreased range of motion, pain, and, less frequently, bone fractures. Published rates of these toxicities vary, as series have different patient inclusion criteria (with respect to tumor site and treatment) and some report only moderate or severe complications, while others report any degree of complication. For series primarily comprised of patients treated with 2D or 3D-CRT, reported rates for edema are 10% to 20%, for fibrosis they are 30% to 60%, and for bone fracture, they are 0.04% to 7%.[106,108-157] Furthermore, several of these studies correlated higher complication rates with higher doses and larger field sizes. Doses greater than 60 or 63 Gy and large field sizes, as used for postoperative RT, have been associated with higher rates of fibrosis, edema, bone fracture, pain, decreased muscle strength, joint stiffness, and decreased range of motion.[106,108,110,154] There have been no randomized trials comparing chronic toxicities for patients treated with 3D-CRT versus IMRT, but series comprised primarily of patients treated with IMRT report lower chronic toxicities with rates greater than or equal to grade 2 edema of 5.3% to 11.1%, fibrosis of 5.3% to 9.3%, and joint stiffness of 3.5% to 5.6%.[146,119] The risk of bone fracture has been clearly correlated with bone doses, and IMRT enables better bone avoidance than 3D-CRT.[113]

OTHER TREATMENT MODALITIES AND TECHNIQUES

Brachytherapy

BRT can be used as monotherapy or in combination with external-beam RT depending on the clinical and pathologic features (eg, grade, size, and margins) and setting, either as primary treatment or for recurrence. A comprehensive description of BRT modalities, techniques, and indications is beyond the scope of this chapter. The American Brachytherapy Society consensus statement provides a detailed review.[158]

Particle Beams

Particle beams such as protons and heavier ions (eg, carbon ions) have favorable physical and biologic characteristics, which make them appealing for clinical use. Because of the Bragg peak dose distribution property,

treatment plans can be created with steep dose falloff at field borders.[159] This may allow for the sparing of adjacent critical normal structures, lower integral dose, smaller treatment volumes, and potential for dose escalation. Much of the data for the use of protons and heavy ions arise from the treatment of primary bone sarcomas. Most data for the use of protons specifically for STS are from the treatment of pediatric patients.[160] There have been no randomized studies comparing photons and protons for STS. Potential indications for the use of protons in the treatment of STS include young patients, clinical circumstances in which the rapid dose falloff may provide greater OAR sparing than IMRT (eg, young adults with pelvic sarcoma for sparing of reproductive organs), treatment of unresectable disease, and reirradiation.

Stereotactic Body Radiation Therapy

Stereotactic body radiation therapy (SBRT) is a technique that delivers highly focused photon radiation doses to extracranial lesions. It is also referred to as stereotactic ablative radiotherapy (SABR). The dose schedules are hypofractionated, with large ablative fractions, typically delivered in a course of one to five treatments. With respect to sarcoma, SBRT is increasingly being used in the treatment of oligometastatic disease. The lung is the most common site of metastatic spread of STS. Historically, lung metastasectomy had been the standard approach for limited pulmonary disease in selected patients. Now there are multiple options for local therapy in the setting of oligometastatic disease, including SBRT.[161] Patient and disease characteristics considered when selecting treatment intent for metastatic disease include performance status, disease-free interval, location and extent of disease, histology, response to systemic therapy, and potential morbidity.

Although most SBRT reports are in the setting of oligometas tatic lung disease, SBRT has also been reported for nonpulmonary sites, including the spine, liver, soft tissue, and lymph nodes.[162-168] Published series show that SBRT is a feasible treatment option and provides excellent 1- and 2-year local control (>90%-95%) with minimal toxicity.[162-166] Various dose fractionation regimens have been used. Figure 89.8 shows a representative SBRT plan for the treatment of pulmonary oligometastasis.

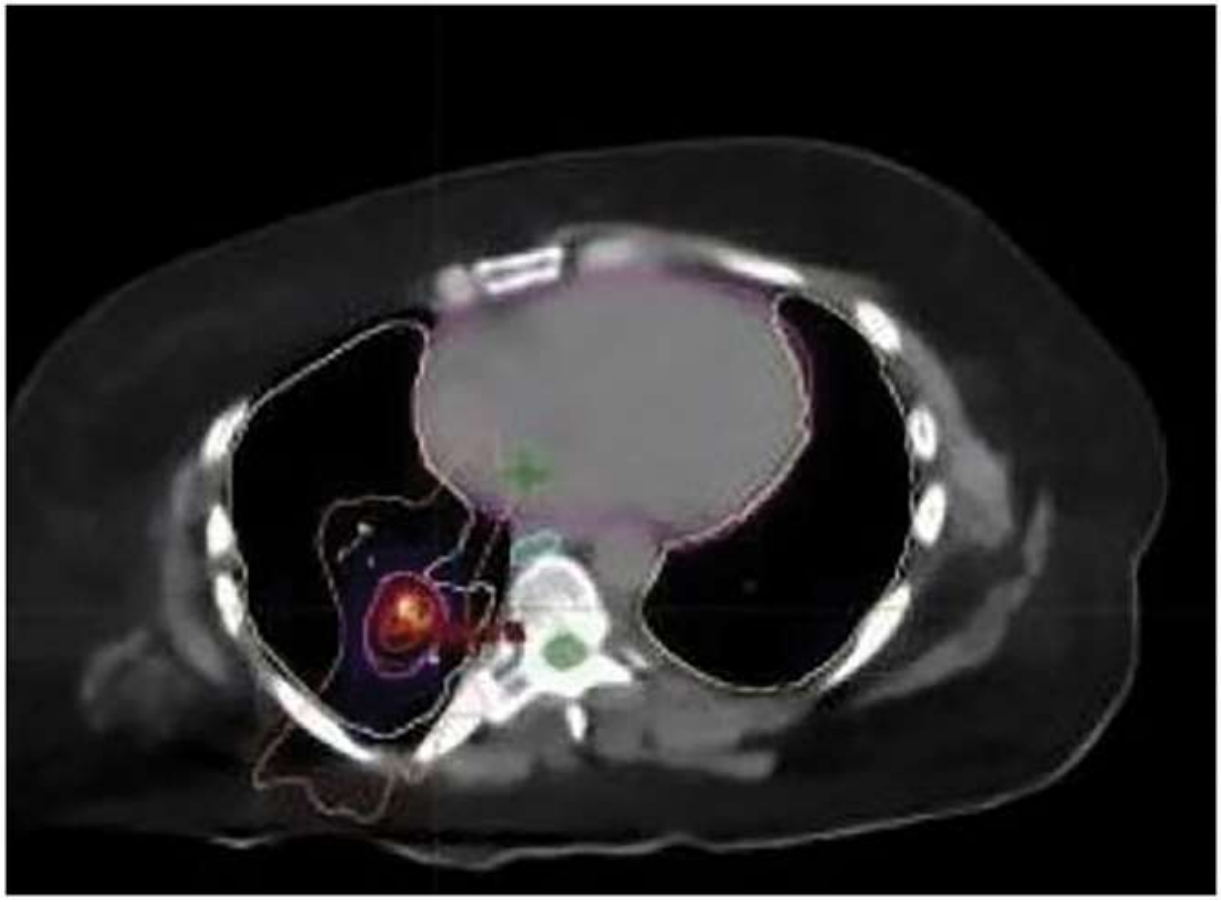


FIGURE 89.8 Axial computed tomography (CT) image showing a representative stereotactic body radiation therapy (SBRT) plan for treatment of a pulmonary oligometastasis.

There are less data regarding the role of SBRT in definitive treatment of primary sarcomas, but there may be a role in select patients with tumors located in or adjacent to sensitive normal structures. In contrast to the planning recommendations for resectable STS treated with wide resection and pre- or postoperative RT, the target volume for SBRT is a gross disease (GTV) with a PTV expansion. There is no CTV. Referral to expert centers is recommended. Figure 89.9 shows an MRI and dosimetry for an unresectable leiomyosarcoma of the inferior vena cava treated with definitive intent SBRT at Brigham and Women's Hospital.

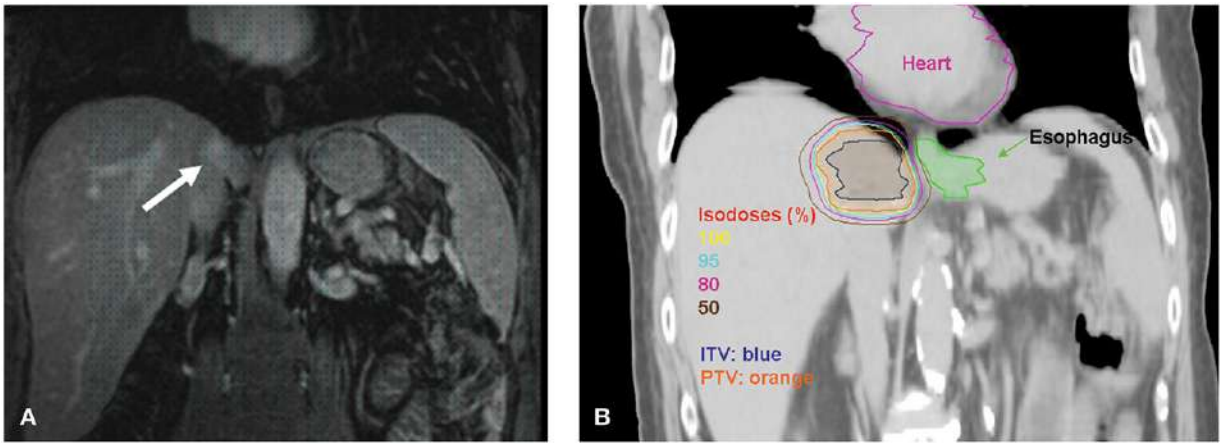


FIGURE 89.9 A 72-year-old man with a 1.8 × 1.8 cm unresectable leiomyosarcoma of the intrahepatic inferior vena cava close to the liver, esophagus, and heart treated with stereotactic body radiation therapy (SBRT) to 60 Gy in five fractions. A. Coronal T1-weighted magnetic resonance image (MRI) slice showing the tumor. B. Coronal slice of the SBRT plan showing the internal target volume (ITV, blue), planning target volume (PTV, orange), and covering isodose lines.

OTHER ROLES FOR RADIATION THERAPY

Reirradiation for Local Recurrence

When LR occurs in a previously irradiated field, management is complex. Resection with wide negative margins is the goal; however, it is not always feasible in this setting. At times, amputation may be required. The addition of reirradiation to resection may be considered in select cases, for example, when there is significant risk for subsequent recurrence and such a recurrence would be associated with significant morbidity. Additionally, reirradiation may be considered when radical resection is not feasible or declined. Multidisciplinary input and shared decision-making with the patient are necessary when reirradiation is considered, given that its use has been associated with significant wound and other complications.[169-171] BRT, particle therapy, and advanced RT planning techniques have been used for reirradiation to try to spare normal tissues and minimize toxicity.[158,172]

Radiation Therapy for Unresectable Disease

For patients with unresectable or medically inoperable disease or those who decline radical resection or amputation, the use of RT for local control may be considered, recognizing that control rates will be lower than with the use

of resection. In these circumstances, goals of care are important to define when determining the treatment intent and approach, and multidisciplinary evaluation for management is essential.

Durable control of gross disease using RT alone is best achieved for smaller tumors.[173,174] Dose escalation (>63 Gy) has been used, yet higher doses are associated with increased toxicity (particularly with doses >68 Gy).[173,174] Use of modern RT planning techniques and modalities, including SBRT and protons, has improved the therapeutic ratio, and a recent series reported less toxicity.[175,176] Hypofractionated RT can also confer durable local control and relief of symptoms.[177] The target volumes for planning in these circumstances are the gross disease (GTV), a smaller CTV expansion (~1.5 cm), and standard PTV. Systemic therapy, concurrent chemoradiation, isolated limb perfusion (ILP), isolated limb infusion (ILI), and hyperthermia are other potential approaches in the armamentarium for locally advanced and unresectable STS.

NEOADJUVANT, CONCURRENT, OR ADJUVANT CHEMOTHERAPY

Patients with STS of the extremities and trunk with high-risk features (eg, high grade, large tumors, specific histologies) have distant metastatic spread and mortality rates greater than 50%. A nomogram can be used to help predict survival and risk for distant disease in patients with extremity STS after resection.[45] The rationale for the addition of systemic therapy in patients with localized disease is to reduce distant recurrence risk and improve survival. To this end, there is an established role for chemotherapy as part of the treatment for rhabdomyosarcoma and Ewing sarcoma.[178,179] Unlike its established role in the treatment of various histologies for pediatric, adolescent, and young adults, the benefit of chemotherapy in adults with localized STS remains unproven.

Informative data are scarce regarding the use of concurrent preoperative chemotherapy and radiotherapy in adults with STS. Studies have shown that treatment with interdigitated chemotherapy and split-course RT or concurrent chemoradiotherapy is feasible but with increased rates of toxicity. Neither approach is commonly used for adults with localized

STS.[116,125,180-183] There is a selective role for use in patients with locally advanced and unresectable disease.[82]

The two most standardly used chemotherapies in the treatment of STS are doxorubicin and ifosfamide.[82,184] As STS is comprised of many heterogeneous histopathologic subtypes with unique natural histories, there are ongoing efforts to try to tailor systemic regimens to histology. Although there have been encouraging response rates noted in some trials, a phase III randomized trial did not show improved disease free or OS with histology-tailored neoadjuvant chemotherapy over anthracycline and ifosfamide-based standard therapy.[185] This remains an area of active investigation, and going forward, trials should include centralized pathology review and stratification by histology.

In totality, although there are hints of efficacy for certain subgroups, the available data do not support the routine use of chemotherapy in adults for locally advanced resectable STS (excluding Ewing sarcoma). However, for select high-risk patients with high-grade and large tumors (>8 to 10 cm), it is reasonable to address the pros and cons of neoadjuvant, concurrent or interdigitated, or adjuvant chemotherapy on an individual patient basis. Choices to proceed with chemotherapy should be a result of shared decision-making with the patient and multidisciplinary discussion.[82] Appropriate indications for the addition of systemic therapy, either neoadjuvant or adjuvant, include borderline resectable tumors, chemosensitive histologies, and patients at high risk for distant metastases with excellent performance status.[82] As toxicity can be significant, concurrent approaches are best undertaken at experienced centers.

ISOLATED LIMB PERFUSION, ISOLATED LIMB INFUSION, AND CHEMOTHERAPY WITH REGIONAL HYPERTHERMIA

ILP is a complicated technique that has been used in Europe for the treatment of locally advanced STS that would otherwise require amputation.[82,186] This procedure involves isolating the arterial and venous circulation of the limb by connecting it to an extracorporeal circulation, where it is oxygenated and instilled with systemic agents, most commonly, melphalan and tumor necrosis factor. A tourniquet is applied to the limb to prevent leakage into the systemic circulation, and the limb is often treated

with hyperthermia as well. The treatment can have significant morbidity, but reported limb salvage success rates are quite high.[186-191] ILI employs low-flow ILP without oxygenation and has been developed as a simpler alternative to ILP.[192] Available data suggest comparable efficacy and less toxicity for ILI compared to ILP.[193-196] Lastly, chemotherapy with regional hyperthermia (delivered via an external electromagnetic field) is another approach for locally advanced disease.[197] A randomized trial of doxorubicin, ifosfamide, and etoposide, with or without regional hyperthermia delivered before and after local therapy, has shown superior DFS and progression-free survival rates for the regional hyperthermia group.[198] All of these techniques are complicated to deliver and associated with significant risk for toxicity. However, they represent valuable potential alternatives to amputation in such settings as extensive LRs after prior surgery and RT, unresectable disease, or in transit metastases of epithelioid or clear cell sarcoma.

CONCLUSION AND FUTURE DIRECTIONS

STSs are rare malignancies comprised of multiple heterogeneous histopathologic subtypes with unique behaviors. The primary treatment approach for STS of extremity and trunk remains oncologic resection with RT added to improve local control in patients at increased risk for LR. The treatment plan and sequences of modalities should be determined by a multidisciplinary team with sarcoma expertise prior to the initiation of therapy. Tumor control outcomes are the same with either preoperative or postoperative RT; however, toxicities differ. Preoperative RT is associated with an increased risk of wound healing complications, which are generally temporary and reversible, whereas postoperative RT has a greater risk for late toxicities, which are permanent and can impact long-term function. In general, preoperative RT followed by resection is preferred. Advances in treatment planning and delivery, including the use of IMRT and daily IGRT, have improved outcomes for patients with STS. The role of chemotherapy for localized STS remains unproven, but it is a reasonable option for patients at very high risk for recurrence and with shared decision-making.

Future investigations and further refinements of STS treatments are needed to continue to improve cancer control and functional outcomes and to mitigate acute and late toxicities. These include innovative techniques to

reduce postoperative wound complications and late toxicities, efforts to reduce RT margins or doses, risk-adapted and histology-tailored approaches for both local and systemic therapies, and improved response assessments for neoadjuvant the rapies. Preliminary reports suggest likely similar efficacy of moderately hypofractionated and some ultrahypofractionated regimens for preoperative RT, but with concern for wound complications, including the necessity of amputation, and long-term toxicities, including fracture risk. Additional moderately hypofractionation studies are ongoing, including a single-arm phase II study of 2.85 Gy × 15 fractions (NCT04562480), and a randomized study of 3 Gy × 14 fractions versus standard 2 Gy × 25 fractions (NCT04425967), and their results are eagerly anticipated. A randomized clinical trial comparing moderate and ultra-hypofractionation to conventional fractionation for preoperative RT is greatly needed. Efforts for treatment de-escalation include better definition of patient subsets at lower risk for recurrence that can be effectively treated with surgery alone, reduced-dose preoperative RT for myxoid liposarcoma (NCT02565498 and NCT04699292), and an ongoing study of lower postoperative RT dose for patients resected with negative margins (NCT02565498). Conversely, for situations in which it is difficult to achieve local control and in the setting of recurrent or unresectable disease, more aggressive local treatment is needed; this could include the use of RT dose escalation, heavy particles, SBRT, or concurrent chemoradiation strategies. For patients with a high risk of distant relapse and death, novel systemic therapies are needed to improve outcomes.

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PART M

Pediatric

CHAPTER 90

Central Nervous System Tumors in Children

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Central nervous system (CNS) tumors account for 20% to 25% of all malignancies that occur in childhood. The incidence of brain tumors in pediatric and young adult patients varies around the world from 1.12 to 5.26 cases per 100,000.[1] The incidence was highest among children younger than 4 years.[2] Since 2011, brain cancer is the leading cause of cancer-related death in pediatric patients, having surpassed leukemia.[3]

The etiology of pediatric CNS tumors remains largely unknown. Only 2% to 5% can be ascribed to a known genetic predisposition. Included in this category are those seen in patients with neurofibromatosis types 1 (NF-1) and 2 (NF-2), tuberous sclerosis, nevoid basal cell (Gorlin) syndrome, familial adenomatous polyposis, and Li-Fraumeni syndrome. An even smaller percentage can be attributed to ionizing radiation used for diagnostic or therapeutic purposes. For the majority of patients, no predisposing factors can be identified.

The management of children with CNS tumors has changed substantially over recent decades. Routine use of magnetic resonance imaging (MRI), now frequently including functional imaging, and improved neuropathologic examination and molecular diagnostics have contributed to better characterization of different tumor types. Improved neurosurgical techniques and perioperative care permit greater degrees of surgical resection even for tumors previously considered inoperable because of their location in eloquent areas of the brain. All of these, together with improved

radiotherapy (RT) techniques, newer chemotherapy agents and regimens, and national and international clinical trials, have contributed to improved outcomes for children and adolescents with CNS tumors. Five-year survival has increased from 59% for patients diagnosed in 1975 to 1979 to 75% for those diagnosed in 2003 to 2009.[2]

RADIOTHERAPY FOR PEDIATRIC CENTRAL NERVOUS SYSTEM TUMORS: GENERAL ISSUES

RT is an essential component of treatment for many children with CNS tumors. However, survivors are at significant risk for the development of long-term sequelae.[4,5] While many of the long-term toxicities post-RT are multifactorial, radiation treatment is an important contributing factor. Thus, studies in the past three decades have explored novel regimens or techniques seeking to reduce risks associated with treatment. Recent developments in RT including improved targeting, new technologies and modalities, and novel techniques for treatment offer important opportunities for therapeutic gain that are discussed later and in each section of this chapter.

Long-Term Effects of Radiotherapy

Quality of life of children with brain tumors may be compromised by long-term sequelae. Although some patients (eg, patients with NF-1) may be at particular risk and some sequelae (eg, neurologic deficits) are more often due to tumor and/or surgery, it is clear that RT is directly, either alone or modulated by other factors, responsible for many late effects. A review by Kortmann et al[6] provides an excellent account of radiation-related sequelae in children treated for low-grade glioma, including effects on brain parenchyma, neurologic deficits, neurocognitive and behavioral effects, endocrine dysfunction, vasculopathy, and second tumors.

The neurocognitive sequelae of RT have become much better characterized over recent years. It is now known that myelinization and functional maturation of the CNS continue until well into adolescence and even into young adulthood. Through its effect on the microvasculature as well as on the oligodendrocyte precursor cells that produce myelin, RT causes disrupted neurogenesis and cortical atrophy. Patients fail to acquire

new knowledge and skills at an age-appropriate rate and show a progressive decline in IQ over time.[7] The magnitude of the deficit depends most importantly on age at treatment, but many other host (eg, NF-1), tumor (eg, location, hydrocephalus), and treatment factors (eg, RT volume and dose,[8-10] use of chemotherapy[11,12]) play a role. Moreover, the development of other deficits such as behavioral difficulties related to the location of the tumor and/or surgery or hearing impairment because of cisplatin may have a modulating effect. The result for many patients is impaired school and social performance that deteriorates over time. There is increasing evidence that intervention using cognitive or behavioral therapy or pharmacotherapy and even exercise may be useful and that this should start soon after treatment for best results.[7,13,14]

Endocrine deficits are very common after RT.[15] Even though a substantial proportion of patients may have had deficits prior to RT because of the tumor or to surgery,[16,17] and even though there may be modulating factors such as chemotherapy that affect the frequency of deficits, RT is primarily responsible for the growth hormone deficiency that correlates with the dose of RT to the hypothalamic-pituitary axis[18-20] and the primary hypothyroidism seen after craniospinal irradiation (CSI). There may be direct and indirect effects on musculoskeletal development. Osteopenia is a rather common finding that may put patients, particularly those with residual neurologic deficits, at significant risk for fracture.

RT has been implicated as well in the development of cardiovascular complications, including cerebrovascular events and coronary heart disease.[16,21] Although again the etiology is likely multifactorial, it is important to be cognizant of the risks and to minimize the dose to vascular structures and the heart.

Strategies that have been used to avoid or minimize the long-term effects of treatment for pediatric brain tumors include the following:

- Avoidance of RT altogether (eg, in patients with low-grade astrocytoma [LGA] for whom surgery alone may be a good option)
- Delay of RT for young children (ie, those younger than age 3-8) using chemotherapy
- Use of daily anesthesia, improved immobilization techniques (eg, rigid casts or a stereotactic frame), and/or daily pretreatment image

verification, all of which allow the use of reduced safety margins

- Use of image-based treatment planning using computed tomography (CT)-MRI or CT-MRI–functional imaging co-registration and better treatment planning and delivery techniques that result in greater sparing of normal brain and organs at risk (OARs)
- Use of new radiation modalities (particularly proton therapy that provides even greater sparing of the surrounding normal brain and OARs). Over the past 5 to 10 years, there has been a significant increase in the proportion of children with CNS tumors treated with proton therapy.
- Use of reduced RT target volumes when it is shown safe to do so (eg, involved field boost rather than whole posterior fossa boost for standard-risk medulloblastoma [MB])
- Reduction of RT dose (eg, in young patients with standard-risk MB for whom in the North American studies dose for craniospinal irradiation [CSI] has been reduced progressively from 36 to 23.4 Gy and, in current studies, examining decreasing CSI dose for patients with WNT-driven MB)
- Use of smaller fraction sizes where appropriate (eg, 1.5 Gy/day for patients with radiosensitive tumors such as germinoma)
- Use of hyperfractionated radiotherapy (HFRT) (eg, as in the current European studies for standard-risk MB)

These are discussed later in each relevant clinical situation.

Preparation for Radiotherapy

The planning and delivery of RT for children with CNS tumors are technically challenging and labor-intensive for the entire interprofessional team. The expertise of specialist personnel such as pediatric nurses and child life specialists can be pivotal in supporting a young child through making an immobilization device, RT planning procedures, and treatment itself. For children younger than age 4 or 5 years, daily anesthesia will almost always be necessary, and this will require a skilled pediatric

anesthesiologist because anesthesia will be administered in an environment without all the support available in an operating room.

Radiotherapy Target Volumes and Treatment Techniques

Focal, Tumor, or Tumor Bed Radiotherapy

For most tumor types, target volume definition is best accomplished using CT simulation with CT-MRI co-registration. For patients who have undergone cerebrospinal fluid (CSF) diversion or surgical resection or in whom tumor shrinkage has occurred with chemotherapy, it will be important to consider any anatomic shifts that may have taken place. This will be more of an issue for tumors arising in some areas than others and often adds significantly to the time required for contouring. The clinical target volume (CTV) will be tumor type specific, whereas the planning target volume (PTV) will be technique specific, ranging from 1 to 5 mm depending on the type of immobilization device used and whether daily pretreatment image verification is to be performed.

Modern RT treatment planning and delivery techniques make it easier to achieve conformity of the treated volume to the target and sparing of uninvolved normal structures than in the past. The choice of technique in an individual patient will require careful analysis of the dosimetry in the context of available options. A review by Beltran et al[22] provides an excellent example of the issues to be considered when weighing alternatives.

Other options for focal treatment include brachytherapy and intracystic injection of radioactive colloids. These are discussed in the context of the relevant clinical situation.

Whole-Ventricular Radiotherapy

Whole-ventricular irradiation is used most frequently in patients with CNS germ cell tumors. Because subependymal spread is common, the target volume logically would include the lateral, third, and fourth ventricles with a margin of 0.5 to 1 cm. If lateral-opposed fields are used, the volume of brain spared will be small.[23] Better sparing can be achieved using intensity-modulated image-guided RT[24-26] or, more recently, the use of proton therapy is advocated.

Craniospinal Radiotherapy

The CTV for CSI has an irregular shape that consists of the whole brain and spinal cord and their overlying meninges. In standard techniques, the lower borders of lateral whole-brain fields are matched to the cephalad border of a posterior spine field, usually with a moving junction between the brain and the spine fields to minimize the risk of underdose or overdose in the cervical spinal cord. With conventional techniques, compensators may be needed to achieve dose homogeneity throughout the target volume. In recent years, when possible, intensity-modulated radiotherapy (IMRT) or proton RT, particularly pencil beam scanning, has been utilized for CSI to provide more conformal treatment and decrease dose to normal organs and toxicity.[27-30]

Patient Positioning and Immobilization

Patients have traditionally received CSI in the prone position, but modern technology allows safe treatment in the supine position that in general is more comfortable and, if anesthesia is required, allowing better control of the airway. In either case, immobilization is essential and involves the use of a head shell or full-body immobilization. Careful attention to positioning at the time of simulation is critical to minimize or even eliminate the risk of certain long-term effects. For example, using neck extension together with careful selection of the level for the junction of the brain and spine fields, it is possible to avoid including the dentition in the exit from the superior aspect of the spinal field and thus damage to developing dentition. When modern techniques are employed, it is essential to apply the relevant dose constraints to avoid excessive or unnecessary dose to OARs.

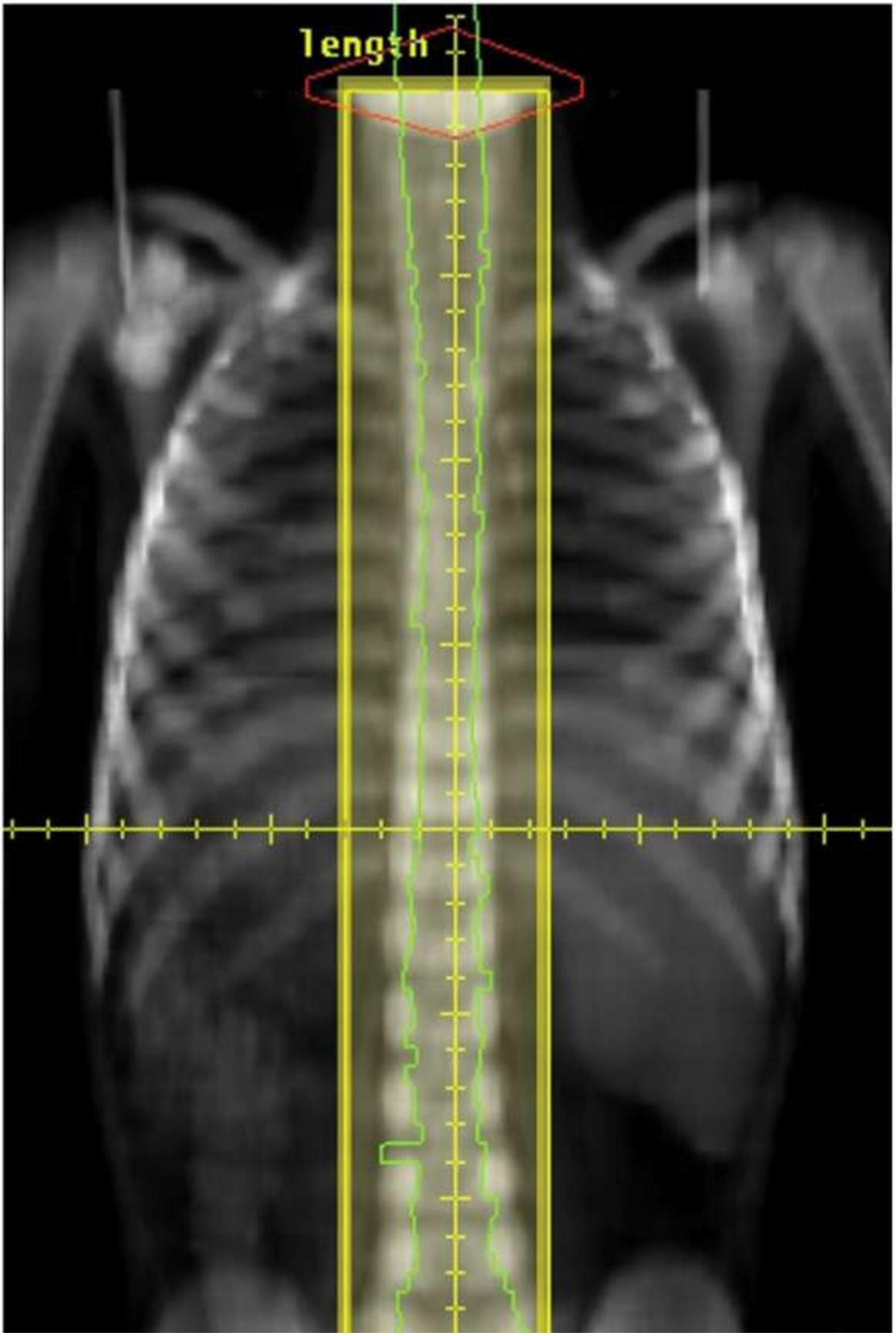
Target Volume Definition

CT simulation is necessary to ensure adequate coverage of the CTV in the subfrontal region at the cribriform plate. Traditionally, blocks have been used in the lateral fields to shield not only the facial structures but also the lenses. However, in most children, it is impossible to adequately irradiate the cribriform plate and entirely shield the lenses (Figure 90.1), and adequate PTV coverage should take precedence.

FIGURE 90.1 The use of computed tomography simulation is superior to conventional radiographs for determination of the clinical target volume for craniospinal irradiation and ensures coverage of the meninges in the subfrontal region. In most children, adequate coverage of the planning target volume precludes significant sparing of the lens.

CT simulation is also helpful in identifying the lateral aspect of CTV for the spine field that includes the extensions of the meninges along the nerve roots to the lateral aspects of the spinal ganglia (Figure 90.2). The field will be narrower in the thoracic region to avoid unnecessary irradiation of the heart and lungs and wider in the lumbar region, although here it is

important to avoid an excessively wide field that will result in unnecessary irradiation of the bone marrow and gonads. The lower limit of the CTV for the spine field should be determined using MRI. The lower border of the spinal CTV should include the lower border of the thecal sac, which can be as high as L5 or as low as S3. In the interest of both CTV coverage and normal tissue sparing, it is important that the lower border be individualized according to the MRI findings.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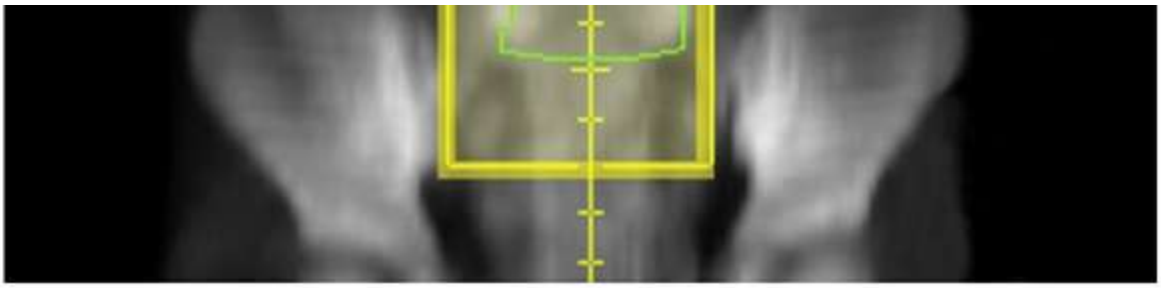


FIGURE 90.2 The use of computed tomography simulation with contouring of the cord and overlying meninges that extend laterally to the lateral aspect of the spinal ganglia results in a field width that is narrower than one based on bony anatomy. The addition of shielding further reduces the volume of normal tissues included in the treated volume.

Treatment Planning and Delivery

There are many issues that need to be addressed in designing a CSI technique. Many of the different solutions add further complexity.[31] Using modern tools for treatment planning and delivery, it is possible to greatly simplify the technique and substantially reduce planning and delivery times. One such technique is shown in Figure 90.3.[32] In general, photons in the 6- to 10-MV range provide satisfactory coverage of the PTV. A variation of dose along the spinal axis of more than 10% will require the use of dose compensation that can be achieved using multileaf collimation.

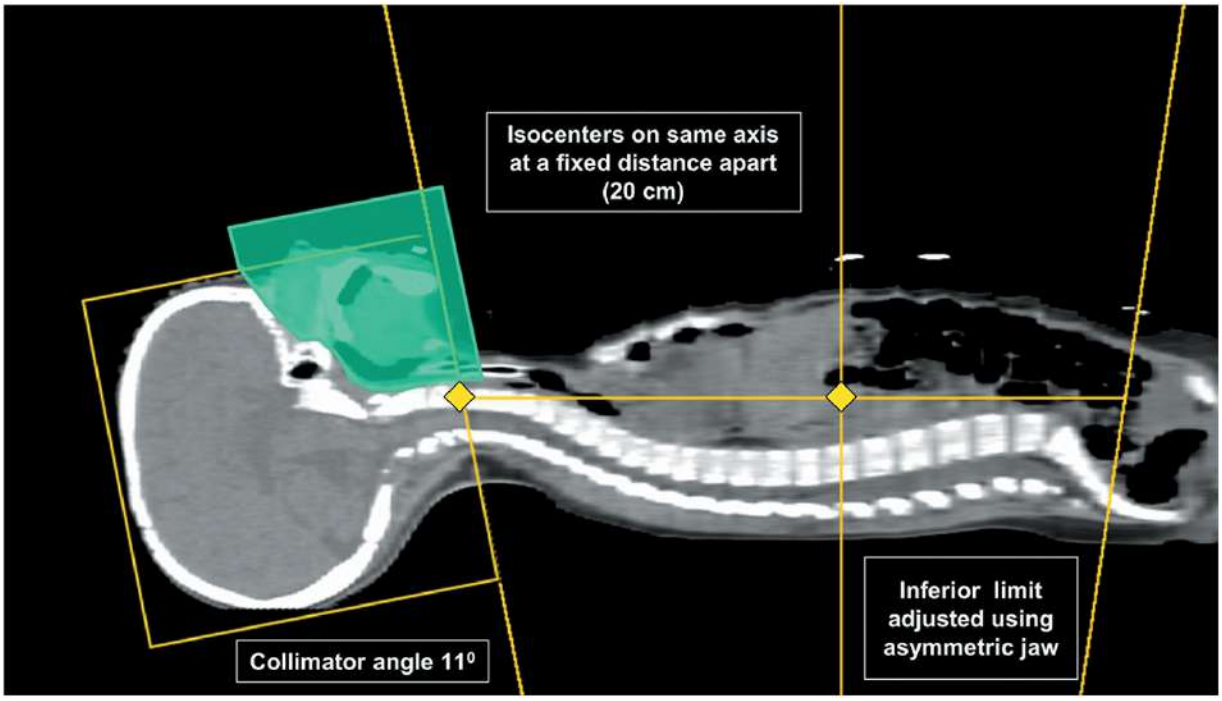


FIGURE 90.3 To cover the clinical target volume for craniospinal irradiation, lateral-opposed fields are used to treat the brain and a direct posterior field is used to cover the spinal axis. Magnetic resonance imaging is used to identify the caudal extent of the thecal sac. The field junction over the cervical cord should be at a level that avoids the inclusion of the teeth in the exit of the spinal field and is usually moved weekly ("feathered") to avoid over- or underdosage. The supine position is more comfortable for the patient and safer if sedation or anesthesia is required. In the technique shown, fixed-field parameters are used, which greatly facilitates treatment planning and delivery. (Reprinted from Parker WA, Freeman CR. A simple technique for craniospinal radiotherapy in the supine position. *Radiother Oncol*. 2006;78[2]:217-222. Copyright © 2005 Elsevier Ireland Ltd. With permission.)

Electrons are used in some centers to treat the spinal axis and in fact may be of greater interest now than in the past because of improved dose calculation algorithms and even electron dose modulation techniques.[33] However, at the same time, newer treatment planning and delivery methods such as IMRT together with daily image verification allow for improved dosimetry with photons with clinically relevant dose reductions to structures anterior to the target volume, such as the heart, gastrointestinal (GI) tract, and gonads.[34] The use of IMRT and smaller PTV margins raises new issues that are not as relevant as when lateral-opposed fields were used, such as the need to ensure adequate coverage of all CSF extensions

including those along the optic nerves and other cranial nerves (Figure 90.4).

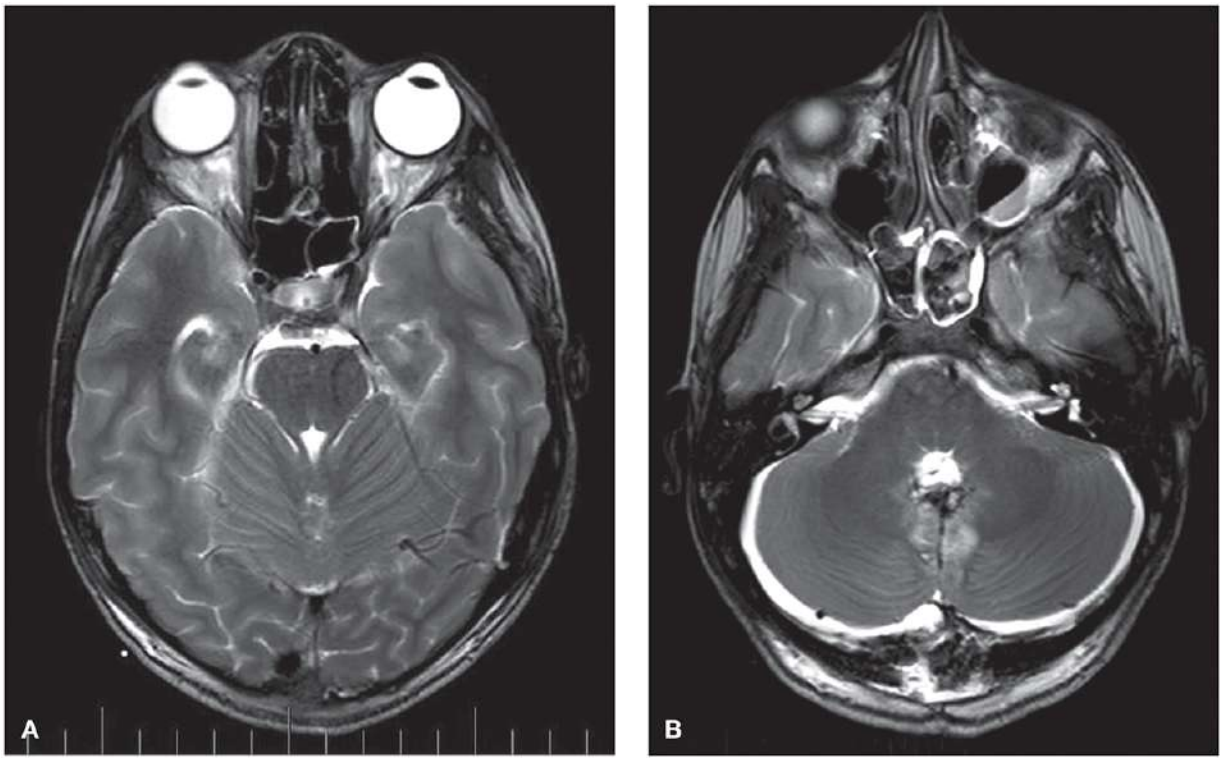


FIGURE 90.4 Postoperative axial T2-weighted magnetic resonance imaging for a patient receiving craniospinal irradiation (CSI) for medulloblastoma showing extension of cerebrospinal fluid along the optic nerves to the lamina cribrosa (A) and into the internal auditory canals (B). Care is necessary to identify all such extensions when using intensity-modulated radiation therapy for CSI, given that the margins are much tighter than when using conventional lateral-opposed fields.

New Treatment Modalities for Craniospinal Irradiation

Protons provide a dose distribution for CSI that cannot be achieved by even the most sophisticated photon beam treatment planning, with a significant reduction in low-dose exposure outside the target volume.[35] There may be significant benefits from reduced irradiation of the heart and organs anterior to the spine.[36] Currently, an increasing number of children requiring RT for CNS malignancies are treated by proton beam RT.[37]

Radiation Dose and Dose Fractionation Regimens

The conventional daily fraction size for the treatment of most pediatric CNS tumors is 1.8 Gy and the total dose typically on the order of 54 to 55.8 Gy. When treating primary tumors of the spinal cord, it is conventional to use lower total doses (eg, 50.4 Gy). Lower doses are also used for children younger than age 3 years to reduce the risk of neurocognitive deficits. When treating radiosensitive tumors such as intracranial germinoma, RT may be delivered using a lower dose per fraction (eg, 1.5 Gy) and lower total doses of 30 to 45 Gy.

Many pediatric brain tumors exhibit a dose-response relationship for tumor control, and in some cases, local progression is not prevented using a conventional "CNS tolerance" radiation dose. When the target contains only a small volume of normal brain tissue, dose escalation may be possible using newer treatment planning and delivery techniques. HFRT may be a useful strategy in situations where dose escalation cannot be achieved safely using conventional fractionation.

Follow-Up During and After Radiotherapy

An excellent review by Donahue[38] describes the acute reactions seen during treatment with RT and provides guidelines for their management. These days nausea and vomiting almost always can be prevented using the 5-hydroxytryptamine type 3 antagonists. Headache is not an expected side effect and should be investigated by physical examination for signs of raised intracranial pressure and by imaging as appropriate. Steroids, if used, usually can be tapered by the second or third week of treatment. Fatigue is a rather common symptom and is cumulative. The neurologic status of the patient, especially coordination and gait, may appear to worsen during the last weeks of treatment. Children usually recover relatively quickly and often can get back to their usual routines quite soon after completion of treatment.

Predictable effects of treatment include hormonal deficits, especially primary hypothyroidism when CSI is delivered using photons and growth hormone deficit secondary to the inclusion of the hypothalamic-pituitary axis. Patients should be monitored closely in follow-up and treatment instituted as appropriate. Many will also need regular follow-up in ophthalmology and audiology.

Extra pedagogic support may be necessary. Patients should have ready access to a neuropsychologist for evaluation of any special needs and in the longer term to vocational assessment and counseling.

RADIOTHERAPY FOR SPECIFIC TUMOR TYPES

The World Health Organization (WHO) classification of tumors of the nervous system was updated in 2021,[39] and the distribution by tumor type and location is given in Figure 90.5. The 2021 classification considers molecular characteristics of CNS tumors. There are important differences between tumors seen in childhood and those occurring in adults. In children, almost half of all tumors arise in the infratentorial compartment. Low-grade astrocytic tumors as a group account for approximately one-third to half of all CNS tumors, but MB is the most common distinct entity. High-grade gliomas, which account for most primary brain tumors seen in adults, are less common in children.

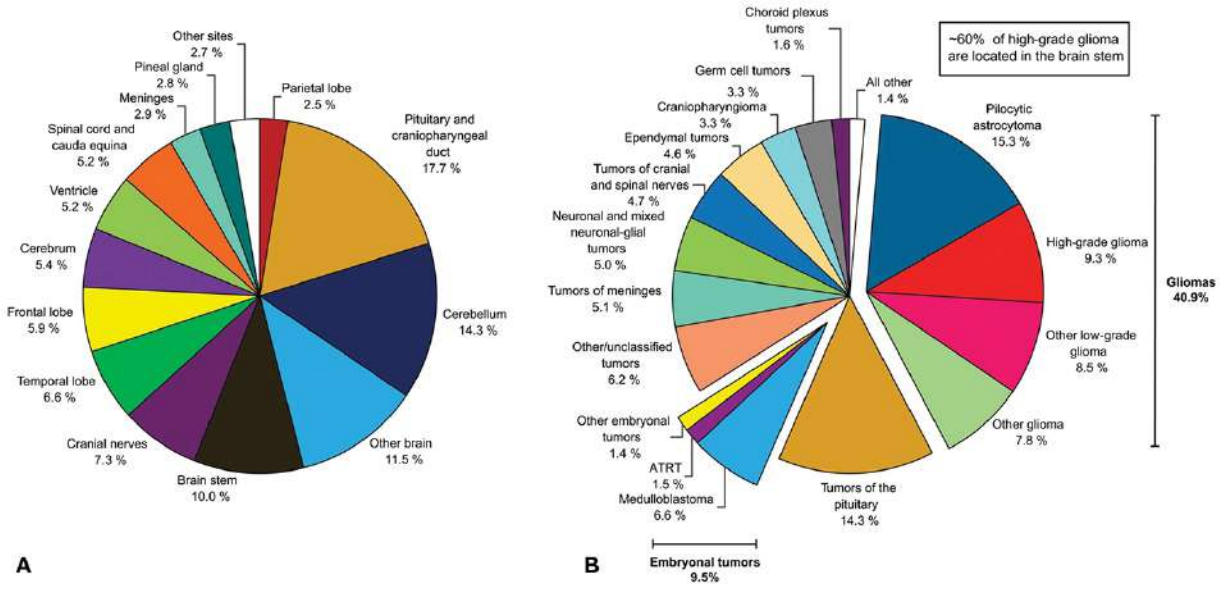


FIGURE 90.5 Distribution in children and adolescents ages 0 to 19 years of all primary malignant and nonmalignant brain and other central nervous system tumors (5-year total = 25,497; annual average cases = 5,099) by site (A) and histopathology (B). ATRT, atypical teratoid/rhabdoid tumor. CBTRUS Childhood and Adolescent Report: U.S. Cancer Statistics—NPCR and SEER, 2014-2018. (From Ostrom QT, Price M, Ryan K, et al. CBTRUS statistical report: Pediatric Brain Tumor Foundation childhood and adolescent primary brain and other central nervous system tumors diagnosed in the United States in 2014-2018. *Neuro Oncol*. 2022;24[suppl 3]:iii1-iii38. Reproduced by permission of Society for Neuro-Oncology.)

This chapter follows the order of the fifth edition of the WHO CNS tumors classification, or CNS5, published in 2021. Although tumors arising in infants and very young children were grouped together in the past and all managed similarly with chemotherapy in order to delay or if possible avoid RT, they are now managed according to the specific tumor type and so are discussed here in each relevant section.

- Pediatric-type diffuse low-grade gliomas
  - Diffuse astrocytoma, MYB or MYBL1 altered
  - Angiocentric glioma
  - Polymorphous low-grade neuroepithelial tumor of the young
  - Diffuse low-grade glioma, MAPK pathway altered
- Pediatric-type diffuse high-grade gliomas
  - Diffuse midline glioma (DMG), H3 K27 altered

    - Diffuse hemispheric glioma, H3 G34 mutant
    - Diffuse pediatric-type high-grade glioma, H3 wild type and IDH wild type
    - Infant-type hemispheric glioma
- Circumscribed astrocytic gliomas
    - Pilocytic astrocytoma (PA)
    - High-grade astrocytoma (HGA) with piloid features
    - Pleomorphic xanthoastrocytoma
    - Subependymal giant cell astrocytoma
    - Chordoid glioma

These astrocytic tumors are heterogeneous with respect to clinical presentation (age, gender, location in the CNS, imaging findings) as well as growth potential and rate of progression. Two types, pleomorphic xanthoastrocytoma and subependymal giant cell astrocytoma, are rare tumors. Their clinical presentations and imaging findings are quite characteristic, and surgery is usually curative.[39] They are not discussed further here.

Low-Grade Astrocytoma (World Health Organization Grades I and II)

So-called benign or low-grade astrocytomas (LGAs) comprise a heterogeneous group of tumors with behavior patterns in accordance with location and pathologic type. Generally, in children, they follow an indolent clinical course with overall survival (OS) rates at 10 and 15 years as high as 80% to 100%. LGAs can be grouped according to their anatomic location:

- Cerebellar astrocytomas (15%-20% of all CNS tumors)
- Hemispheric astrocytomas (10%-15% of all CNS tumors)
- Midline supratentorial tumors, including the corpus callosum, lateral and third ventricles, and hypothalamus and thalamus (10%-15% of all CNS tumors)
- Optic pathway tumors (~5% of all CNS tumors)

- Brainstem LGAs (brainstem tumors account for 10%-15% of all CNS tumors; 20%-30% of these are LGAs)
- LGAs of the spinal cord (spinal cord tumors account for 3%-6% of all CNS tumors; ~60% of these are LGAs)

PAs are the most common type in the pediatric age group, accounting for almost all LGAs at certain sites (eg, the cerebellum and the anterior optic pathway). They account for a smaller proportion of LGAs arising in the deep midline structures and in the cerebral hemispheres. Macroscopically, PAs appear well circumscribed and frequently have an associated cystic component. PAs are characterized histologically by a biphasic pattern with a varying proportion of compacted bipolar cells with Rosenthal fibers and loose-textured multipolar cells with microcysts and granular bodies. Rare mitoses, occasional hyperchromatic nuclei, microvascular proliferation, and even infiltration of the meninges are compatible with a diagnosis of PA and not a sign of malignancy. *KIAA1549-BRAF* fusions have been identified in 75% of patients with PA using a reverse transcriptase-polymerase chain reaction assay from formalin-fixed paraffin-embedded tissue.[40] A variant, pilomyxoid astrocytoma, first described in infants and young children with chiasmatic/hypothalamic tumors, appears to be associated with more aggressive behavior that may include leptomeningeal seeding.[41]

Diffuse astrocytomas account for only 10% to 15% of all LGAs in children but for a relatively higher proportion of those seen in infants and adolescents. Most intrinsic pontine tumors and a large proportion of astrocytomas arising in the cerebral hemispheres are diffuse astrocytomas. Diffuse astrocytomas grow by infiltration rather than destruction of anatomic structures and are usually not well circumscribed. Microscopically, they are composed of well-differentiated fibrillary or gemistocytic neoplastic astrocytes on a background of loosely structured, often microcystic, tumor matrix. Cellularity is moderately increased. The presence of nuclear atypia is a diagnostic criterion, but mitotic activity, necrosis, and microvascular proliferation are absent. The growth fraction as determined by Ki-67 and MIB-1 labeling indices is usually low. Diffuse astrocytomas may undergo malignant progression, although this is not common in the pediatric age group with the notable exception of tumors arising in the pons.

Patients with LGAs typically present with a long history of nonspecific and nonlocalizing symptoms. Symptoms and signs of raised intracranial pressure may be seen in patients with midline and cerebellar tumors. Patients with posterior fossa tumors may present with neck stiffness and a head tilt as a manifestation of raised intracranial pressure, causing tonsillar herniation, altitudinal diplopia, or spinal accessory nerve irritation. Seizures are present in as many as three-quarters of patients with hemispheric lesions. Other symptoms relatively less frequent and usually of more recent onset relate to the location of the tumor. These may include, for example, focal motor deficits with hemispheric tumors, visual field deficits with tumors compressing or involving the optic pathway, neuroendocrine deficits with hypothalamic tumors, and diencephalic syndrome (consisting of emaciation with loss of subcutaneous fat despite normal or increased appetite, alert appearance, increased vigor and euphoria, pallor without anemia, and nystagmoid movements of the eyes) in young children with chiasmatic/hypothalamic tumors.

Neuroimaging findings are usually quite characteristic. PAs are well circumscribed, often with a cystic component that may be large relative to the size of the solid component. There is usually little edema or mass effect. The solid component enhances brightly and uniformly with contrast material. Diffuse or fibrillary astrocytomas are usually not well seen on nonenhanced CT or MRI and usually show little enhancement with contrast material. T2-weighted or fluid-attenuated inversion recovery (FLAIR) MRI sequences usually best demonstrate the extent of disease.

Management of Low-Grade Astrocytomas: General Principles

Some children with LGAs may not require any tumor-specific treatment. These include, for example, patients with NF-1, as many as 15% of whom have optic pathway tumors.[42] Patients with NF-1 also may have astrocytic tumors in other parts of the CNS as well as hamartomatous lesions, typically in the brainstem. These lesions may be detected on routine imaging, but even tumors that are symptomatic may remain stable over long periods so that surveillance may be an appropriate initial management.[43-45] A number of clinical and imaging characteristics have been correlated with a more aggressive course, but even for these patients, active intervention

will usually be undertaken only at the time of progressive disease that is symptomatic.

Progression-free survival (PFS) without treatment may also be very good for patients with tectal plate lesions who present with hydrocephalus without localizing brainstem signs. LGA in this region may be very indolent, showing either no progression (the majority) or only very slow progression over the course of many years following CSF diversion alone. The common characteristics of these very indolent tumors are their small size (,1.5 or 2 cm) and the fact that on imaging they are hypodense/hypointense and nonenhancing. Follow-up with MRI is essential to identify patients with progressive lesions as manifested by increasing size and/or enhancement with gadolinium. Treatment at the time of progression is associated with a high probability of long-term tumor control. Treatment options can include surgery, RT, and chemotherapy.[46,47] Patients who undergo RT have an excellent prognosis with a 10-year PFS of 82%.[47] For many pediatric patients, chemotherapy may be favored in efforts to avoid brain RT and excellent prognosis.[46,47]

These special situations underscore the need for careful evaluation and individualization of the management of patients with LGAs depending on the specific clinical situation and tumor type. If in doubt, a period of surveillance generally will be an acceptable initial approach, reserving nonsurgical treatment for symptomatic progression.

Surgery is the mainstay of treatment for LGAs. Complete resection is more likely to be accomplished in patients with smaller tumors and those arising in noneloquent parts of the brain as well as in patients with the generally well-circumscribed pilocytic tumors. Modern surgical techniques that include, for example, computer-assisted resections (“neuronavigation”) aided by preoperative functional MRI, MR tractography, and intraoperative mapping of eloquent areas (Figure 90.6) together with intraoperative MRI permit greater degrees of resection in larger proportions of patients, including many who in the past would have been considered to have inoperable lesions. Complete resection is now achieved in more than 80% of cerebral, cerebellar, and spinal cord tumors and about 50% of diencephalic tumors.

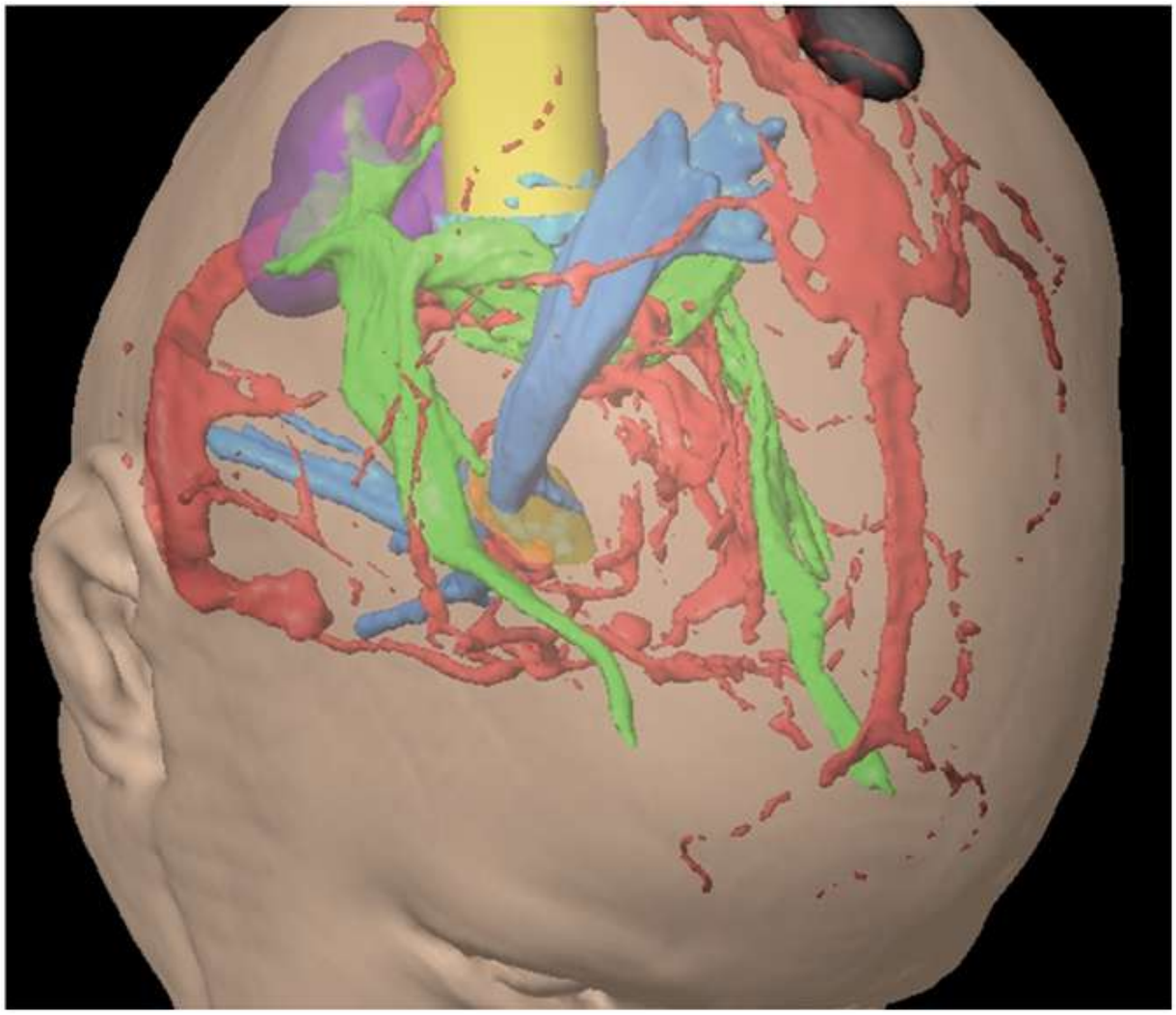


FIGURE 90.6 Surgical planning for a dysembryoplastic neuroepithelial tumor (light blue) in the right occipital lobe presenting with seizures. Functional magnetic resonance imaging data are used to identify the 1-degree visual cortex (purple). Fiber tracking identifies the optic radiations (green) and the corticospinal tract (darker blue). These data are then used to plan the trajectory (yellow). By identifying regions to be selectively avoided, similar information could be helpful in radiotherapy treatment planning.

Children with LGAs who undergo complete resection fare very well, with long-term disease-free survival and OS rates of 80% to 100%, respectively.[48-53] In most series, results are better (close to 100%) for patients with PAs than for those with diffuse or fibrillary LGAs, although some have disputed this, showing equally satisfactory results for both. In either type, postoperative adjuvant therapy is not indicated.

For children who undergo less than complete resection, the PFS rate after surgery alone is less satisfactory. In a joint Children's Cancer Group (CCG)-Pediatric Oncology Group (POG) study in which such patients were observed without adjuvant treatment, any residual tumor was associated with an inferior PFS rate: The 8-year PFS rate was 56% for patients with less than 1.5 cm^3 residual tumor and 45% for those with greater than 1.5 cm^3. However, most patients can be salvaged with a second surgical resection and/or RT. In the CCG-POG study, OS at 8 years was 95% and 90% for patients with less than 1.5 and greater than 1.5 cm^3 residual tumor, respectively.[54]

The role of postoperative RT following less than complete resection remains unclear. In most series, the use of RT in this situation results in improved disease-free survival without any benefit in terms of OS. Because only approximately half of all patients will develop PFS, the usual recommendation for a patient who is neurologically stable will be surveillance, with MRI performed at least every 6 months for the first 3 years, the period during which the risk of progression is greatest.[55] A second surgical procedure would usually be considered at the time of progression, and other treatment, either RT, chemotherapy, or targeted systemic therapies, reserved for patients with progressive, inoperable disease (Figure 90.7).

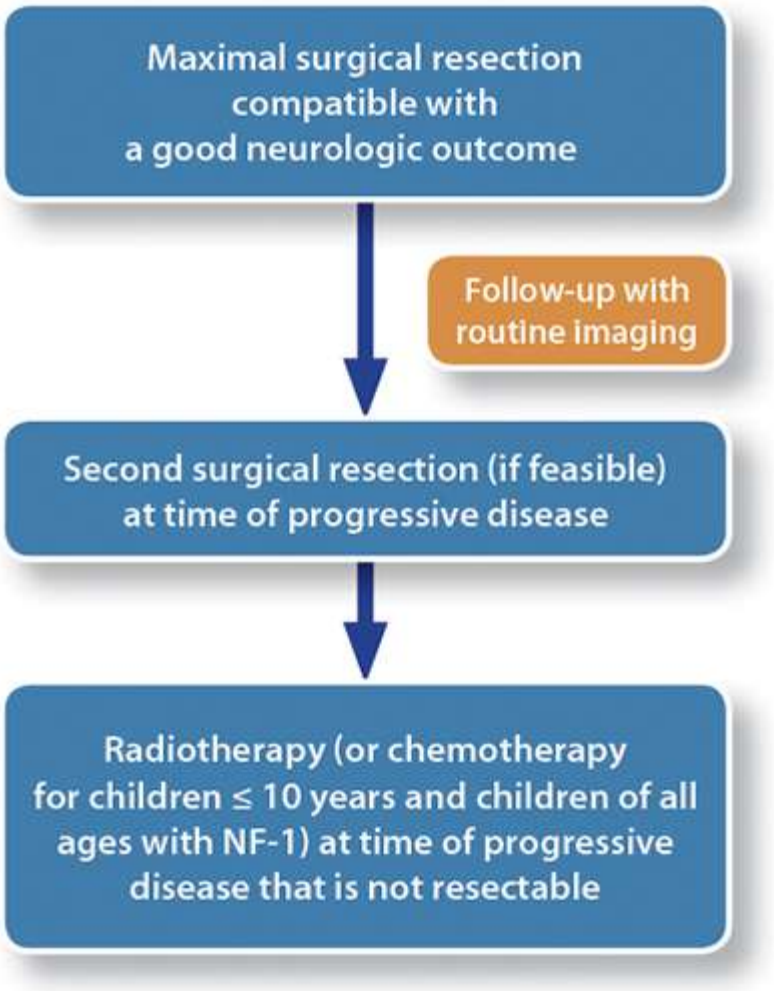


FIGURE 90.7 An algorithm for the management of patients with low-grade astrocytoma. NF-1, neurofibromatosis type 1.

In the past, patients with deep midline and other tumors considered surgically inaccessible were treated with RT, often even without histologic confirmation of diagnosis. However, using modern neurosurgical techniques, it is feasible to resect surgically about half of these lesions (Figure 90.8), and the overall strategy for these patients should now be as for patients with LGAs at other locations, albeit with the understanding that outcome is not as satisfactory. The 8-year PFS and OS rates in the CCG-POG study for patients with midline chiasmatic tumors were 25% and 84%, respectively.[55]

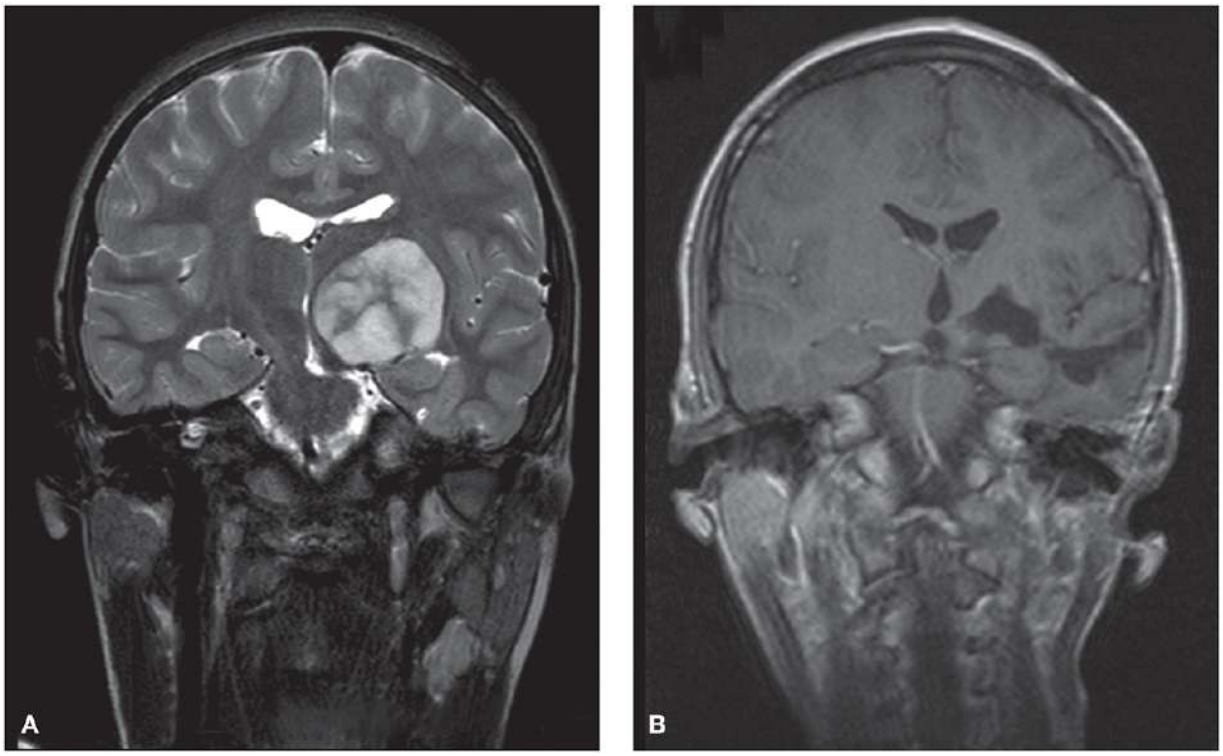


FIGURE 90.8 A 12-year-old boy referred to the radiation oncology department 3 years after diagnosis of a biopsy-proven juvenile pilocytic astrocytoma of the left thalamus at another institution. He had been deemed inoperable at diagnosis and had received chemotherapy first with vincristine and carboplatin and then with weekly vinblastine. A. At the time of referral, he was having more frequent choreoathetotic movements of his right hand, and there was evidence of progressive disease on magnetic resonance imaging (MRI). B. He underwent complete resection without complications and has no evidence of residual disease on his most recent MRI. This was a far better approach than radiotherapy, avoiding the neurocognitive, endocrine, and vascular complications associated with radiotherapy for tumors in this region, and with a greater probability of long-term tumor control.

When adjuvant therapy is indicated, the options include chemotherapy or targeted therapies, particularly for infants and young children and for patients of all ages with NF-1 who are at greatest risk of developing neurocognitive, vaso-occlusive, and neuroendocrine sequelae of treatment.[56,57] There is a trend over time for chemotherapy to be employed as the initial treatment with 5-year PFS rates at approximately 50%.[58-63] Complete responses to chemotherapy are not common, but overall response rates that include stable disease range can be up to 85% and the use of chemotherapy has been shown to allow many patients to omit RT altogether or permit the delay of RT by many years without an impact on survival.[58-62] A recent study found that pediatric patients with BRAF V600E–mutant

pediatric glioma had longer PFS compared with those receiving chemotherapy.[64] Furthermore, at the time of progression, patients often have additional systemic therapy options, including additional chemotherapy or targeted therapy.[56,65-68] It is likely that most patients will not need RT, but patients at risk of neurologic compromise from tumor progression continue to benefit from RT.[69]

Radiotherapy in Low-Grade Astrocytomas

Due largely to improvements in surgery and, to a lesser extent, to successful treatment of younger children with chemotherapy, there has been a substantial decrease in the use of RT over recent years. Currently, only approximately 10% of all children with LGAs receive RT.

Indications for Radiotherapy

- RT is not indicated after complete resection.
- RT may be indicated following incomplete resection in situations when tumor progression would compromise neurologic function (eg, "threat to vision").
- The clearest indication for RT is in patients with progressive and/or symptomatic disease (especially in settings of neurologic deficits) despite multiple lines of systemic therapy and is unresectable.

Radiotherapy Target Volume

The RT target volume (the gross tumor volume or GTV) consists of all diseases seen on MRI performed just prior to treatment (Figure 90.9). The resulting treatment volume usually will be considerably smaller than one based on preoperative imaging, which until recently would have constituted standard practice. Similarly, margins that were considered standard (and still are in adult practice) are unnecessary, particularly for the well-circumscribed pilocytic tumor for which a CTV margin of 1 cm[51] or even 0 cm (ie, CTV = GTV)[70] around the GTV as seen on T1-weighted gadolinium-enhanced images has been shown to result in excellent local control. More generous margins of 1 to 1.5 cm around the GTV as seen on T2-weighted or FLAIR images may be more appropriate for the more

infiltrative diffuse fibrillary tumors. RT planning will also consider OARs, including the hippocampus. Future protocols will specify hippocampal dose constraints.

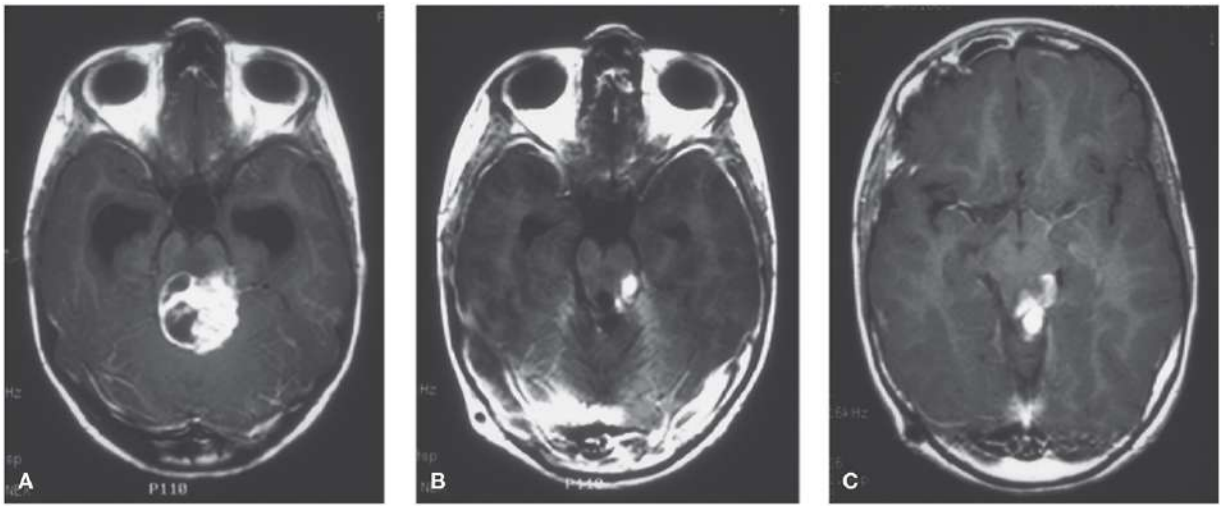


FIGURE 90.9 A patient underwent subtotal resection of a low-grade astrocytoma of the left cerebellar peduncle at age 8. A. Preoperative. B. Postoperative. C. Three years later, routine imaging showed evidence of progressive disease. The gross tumor volume for radiotherapy consists of the tumor as seen on magnetic resonance imaging at the time of treatment.

Radiotherapy Dose

Evidence for a dose-response correlation in LGAs in children is scant. Although the European and North American studies that randomized adult patients with LGAs between low-dose (45 and 50.4 Gy, respectively) and high-dose (59.4 and 64.8 Gy, respectively) RT failed to demonstrate any advantage for the higher dose,[71,72] it may be unwise to extrapolate that in children doses of 45 to 50 Gy are as effective as the higher doses of 54 to 55 Gy that until now have constituted standard practice. There are biologic differences between LGAs in children and adults. As well, children who have progressed on chemotherapy may have tumors that are less sensitive. For now, the recommendation for children with LGAs would be a "standard" dose of 50.4 to 54 Gy depending on the age of the child and the location of the tumor and its relationship to critical normal structures, such as the optic chiasm.[73,74]

Radiotherapy Technique

External beam RT using a conventional dose fractionation schedule should be considered the standard of care in LGAs and the technique to be used that provides homogeneous irradiation of the CTV and best spares surrounding normal tissues. Increasingly proton therapy is being employed for the treatment of LGAs as a means of minimizing nontarget dose and hopefully late neurocognitive effects.

Other approaches that have been used in LGAs include radiosurgery using gamma knife or linear accelerator–based techniques.[75] Although the use of a single fraction, typically of 10 to 20 Gy, to the periphery of the lesion or a small number of large fractions may not be optimal for diffuse or fibrillary LGAs with tumor cells embedded in rather than displacing normal brain, such treatment may be of interest for part or even all of the treatment for the less invasive PAs that are often small at the time of progression.

Another option for treatment is brachytherapy, which has been used with some success, particularly in European centers.[76-80] As for radiosurgery, the principal limitation with respect to the use of brachytherapy is the size of the target volume. Brachytherapy series necessarily select for smaller tumors, and there is no evidence that brachytherapy is a better treatment option than external beam RT. Radioactive solutions such as ^{33}P, ^{91}Y, ^{199}Au, and ^{187}Re may be useful in cystic LGAs, particularly for patients with recurrent disease after RT in whom symptoms not infrequently relate more to the cyst than to the solid component of tumor. Simple aspiration with or without placement of an internal shunt usually will alleviate symptoms for protracted periods, but in some cases, particularly those in which the cyst wall enhances and is felt to be biologically active, control of the cyst may be difficult, and the use of radioactive solutions could be considered. However, this is not a procedure without risks, and care must be taken to avoid leakage.

Follow-Up After Radiotherapy

Tumor regression after RT is typically slow, and patients and their families need to be warned that the tumor may remain stable or sometimes even increase in size in the first months after completion of treatment. It is important not to assume that changes seen on MRI represent progressive

disease. Close follow-up with early repeat imaging usually will be the best approach in this situation.

High-Grade Astrocytoma (World Health Organization Grades III and IV)

Anaplastic astrocytoma (AA) is a diffusely infiltrating malignant astrocytoma characterized by nuclear atypia, increased cellularity, and significant proliferative activity. Glioblastoma (GBM) is the most malignant astrocytic tumor. Histopathologic features include nuclear atypia, cellular pleomorphism, mitotic activity, vascular thrombosis, microvascular proliferation, and necrosis. Both AA and GBM may develop from WHO grade II astrocytomas. However, except for tumors that arise in the pons, they arise almost always in the pediatric age group de novo without evidence of a less malignant precursor lesion.

HGAs account for 5% of all CNS tumors in the pediatric age group. They are the most common tumor type in older adolescents. Two-thirds of HGAs are located in the cerebral hemispheres and the remainder approximately equally divided between the deep midline structures (thalamus and basal ganglia) and cerebellum. Patients with HGAs usually present with symptoms of short duration that relate to the location of the lesion.

Surgery is an important component of treatment. Because most studies show a survival advantage for patients who have undergone complete resection,[81-85] maximal surgical resection compatible with a good neurologic outcome should be the goal for all patients and a second surgical procedure should be considered if there is significant residual tumor after the first. Postoperative RT is always indicated. Although leptomeningeal seeding is seen in a substantial minority (10%-30%) of patients, the predominant failure pattern is local and the RT target volume is local, with GTV that consists of tumor bed and any residual enhancing or nonenhancing residual tumor plus any abnormality seen on T2-weighted MRI with a margin for the CTV of 1.5 cm. Because these are often large tumors and doses beyond tolerance levels for structures such as the optic chiasm are required, it is usual to consider a volume reduction at 50 to 54 Gy to a CTV that consists of the tumor bed and any residual tumor plus a reduced margin of 1 cm. The dose to the CTV should be at least 54 Gy given over 6 weeks, but a dose of

59.4 to 60 Gy is more typical when feasible. There is no evidence that higher doses delivered using radiosurgery or stereotactic boosts, boosts with brachytherapy, or HFRT result in improved outcome, but IMRT delivering accelerated treatment to a component of the target volume (such as the GTV) may be of interest, if only to decrease the overall treatment duration.

The role of chemotherapy remains to be defined. Although responses are seen to many different agents and regimens, results have often been difficult to interpret because of small patient numbers, inconsistent inclusion criteria with respect to pathology, and confounding variables such as tumor location and extent of surgical resection.[86-88] The cooperative groups in North America and Europe are investigating several approaches that include newer chemotherapeutic and biologic agents, some of which have radiosensitizing properties. Whenever possible, patients should be treated on such protocols. Off study, it may be difficult to make a recommendation with respect to adjuvant chemotherapy, although the poor prognosis, particularly for patients with macroscopic residual disease following surgery, is usually given as an argument for the use of the "current best" regimen, most often now temozolomide as in adults.[86-88]

The prognosis for children with HGAs is poor, with a median time to progression of 10 to 11 months and an OS at 5 years of only approximately 20%. Several factors correlate with outcome. Patients with lesions in the cerebral hemispheres fare better than those with tumors in other locations, apparently independent of the extent of surgical resection. The prognosis for children with thalamic lesions appears to be particularly poor.[89] Age also may be an important factor. In contrast to most other tumor types, children younger than age 3 with HGAs fare better than older children, with OS at 3 to 5 years in the 33% to 50% range in the North American and United Kingdom Children's Cancer Study Group/International Paediatric Oncology Society (SIOP) baby studies.[90-93] The prognosis may be even better for children younger than age 1.[94] Prior studies have not consistently found that histologic grade (AA vs GBM) impacts outcome, but p53 overexpression and a high MIB-1 labeling index appear to identify patients with a particularly adverse prognosis.[95]

Management of Astrocytic Tumors in Specific Locations

Optic Pathway Gliomas

Optic pathway gliomas collectively account for approximately 5% of all CNS tumors in the pediatric age group. These are tumors of young children: The peak age incidence is between 2 and 6 years, and 75% of all patients are younger than 10 years. One-third of patients have NF-1. They may be divided into three clinicopathologic entities: tumors confined to the optic nerve(s), tumors of the optic chiasm with or without optic nerve involvement (collectively "anterior" tumors), and tumors that involve the hypothalamus or adjacent structures ("chiasmatic/hypothalamic" or "posterior" tumors). Management of patients with optic pathway gliomas is often said to be controversial but is really not when differences in behavior between the different tumor types and between patients with and without NF-1 are taken into consideration.

Optic nerve gliomas may involve one or both optic nerves. Bilateral involvement is pathognomonic of NF-1. In a substantial proportion of cases, the optic nerve tumors are incidental findings on routine imaging, and patients may remain asymptomatic with nonprogressive lesions over long periods; even spontaneous regression is well documented. The frequency of progression is difficult to establish, ranging from lows of less than 10% among patients followed in NF-1 clinics to 40% to 50% in series reported by oncology centers. Even in patients with symptomatic tumors, the course can be quite variable: Only 30% to 60% of such patients will develop progressive disease that requires treatment.[44,96] Thus, management of patients with optic nerve tumors will usually consist initially of close follow-up with regular ophthalmologic examinations and MRI, with active intervention, usually chemotherapy, reserved for patients with clear evidence of progression that is symptomatic.[96-98]

Patients with unilateral optic nerve involvement may not have NF-1. They present most frequently with proptosis that may be relatively long-standing. Findings on examination may include optic atrophy and impaired visual acuity. On MRI, optic nerve tumors are usually relatively small and well circumscribed, with bright enhancement typical for PA. Biopsy is not necessary to make a diagnosis. Treatment usually, although not always, will be necessary, and the approach will depend on whether there is useful vision. If not, then surgical resection will be the treatment of choice. If

useful vision is preserved, chemotherapy would be the preferred option for infants and very young children up to age 5 years and for patients of all ages with NF-1. RT could be considered for older children. Overall, the prognosis is very good. Visual acuity remains stable or improves in most cases following chemotherapy or RT. Long-term tumor control approaches 100% with either modality.[99]

Chiasmatic gliomas are tumors that involve the optic chiasm and sometimes one or both optic nerves as well. Patients typically present with loss of visual acuity and temporal field defects. On imaging, the tumors are usually relatively small and well circumscribed and enhance uniformly and brightly with contrast material, suggestive of pilocytic histology. Biopsy is usually not necessary.

A period of surveillance is appropriate as initial management, particularly for patients with NF-1. For patients without NF-1, especially those who present before age 5 years, there is a high probability of early progression, and the majority of patients will require nonsurgical treatment within a few months following diagnosis. Surgery is rarely an option for tumors in this location. As for optic nerve tumors, chemotherapy usually will be the treatment of choice for infants and young children and for patients with NF-1. RT is reserved for salvage after chemotherapy and can be considered for definitive treatment of older children without NF-1 and visual decline despite systemic therapy, providing a reasonable expectation that vision will not deteriorate further and a probability of long-term PFS in the 60% to 90% range.[98,100-104] OS for patients with chiasmatic tumors is in the 90% to 100% range.

Posterior, or chiasmatic/hypothalamic, gliomas account for approximately 70% of all optic pathway gliomas in children. They are typically rather large lesions that probably arise in the optic chiasm and extend to involve the hypothalamus. They may extend posteriorly along the optic tracts as well. They often fill the third ventricle, eventually causing hydrocephalus. Early findings consist of nystagmus, impaired visual acuity, and visual field deficits; only later do patients present increasing head circumference and/or symptoms and signs of raised intracranial pressure.

Treatment consists of CSF diversion, if necessary, and surgical resection, particularly if tumor is growing exophytically into the basal cistern because this may provide rapid relief of symptoms. In most patients, however,

resection will be incomplete. As for LGAs at other locations, a period of surveillance following surgery is reasonable, although most patients will require adjuvant therapy.[58,99] The treatment of choice for children younger than 5 and those with NF-1 usually will be chemotherapy. PFS at 3 to 5 years is rather low at 20% to at best 60%.[58,59,61,105] However, some patients will never need further treatment, and the vast majority do not need RT with RT-free survival at 5 years of 83%.

The indications for RT are progressive disease after multiple lines of systemic therapy or growth may jeopardize important neurologic function, such as vision. RT in this situation, given to local fields to a dose of 45 to 50 Gy for younger children and of 50 to 54 Gy for those older than 5, results in local tumor control in 70% to 80% of cases.[58,99,101,106,107] Overall, however, outcomes are less satisfactory for this group of patients than for those with anterior tumors. Long-term survival is in the 50% to 80% range, and many patients will be left with significant neuroendocrine and neuropsychological sequelae. Patients with NF-1 are particularly at risk. They may have subnormal IQ even without chemotherapy and/or RT.[108] They are also at greater risk for moyamoya syndrome, a progressive vaso-occlusive process involving the circle of Willis. This may be seen without RT, but when RT is used in patients with NF-1, it is important to include MR angiography as part of the regular follow-up imaging protocol and intervene surgically if necessary to avoid a cerebrovascular accident.

Brainstem Gliomas

Tumors arising in the midbrain, pons, and medulla oblongata account for 10% to 15% of all CNS tumors in the pediatric age group. They are of several distinct types that can be broadly grouped as the more favorable low-grade focal, dorsal exophytic, and cervicomedullary tumors and the much more aggressive DMGs, formerly known as diffuse intrinsic pontine gliomas.[109-111]

Focal tumors are tumors of limited size (,2 cm) that on MRI are well circumscribed, without evidence of infiltration, and without edema. They may be cystic, and, as with cystic tumors at other sites, the cystic component may be large relative to the solid, biologically active, component. Focal tumors may occur at any level in the brainstem but most

frequently are seen in the midbrain and medulla. They usually present with a long history of localizing findings, such as an isolated cranial nerve deficit and contralateral hemiparesis. Signs and symptoms of raised intracranial pressure are uncommon, except in patients with tumors arising in the tectal region that may cause aqueduct stenosis while still small.

The management depends on the location of the tumor in the brainstem and the specific imaging characteristics of the tumor. As noted previously, patients with nonenhancing focal tumors in the tectal region who present with only hydrocephalus may do well without any treatment other than CSF diversionary procedures, usually endoscopic third ventriculostomy. Active intervention, including biopsy, is reserved for patients with clinical and radiologic evidence of progressive tumor. This is important because surgery for tumors in this location is associated with a substantial risk of morbidity, even with modern techniques.

Surgery is the treatment of choice for focal tumors at other locations that are surgically accessible (meaning that they extend either toward the surface of the brainstem laterally or at the floor of the fourth ventricle) and have imaging characteristics suggestive of low-grade histology. In this regard, uniform bright enhancement with contrast material, which correlates with pilocytic histology, and the absence of peritumoral hypodensity are of particular importance. In experienced hands, the risk of morbidity for well-selected patients is low and, as with completely or subtotally resected LGAs at other sites, results may be excellent with freedom from progression in a majority of cases.[112,113] Outcomes are less satisfactory for patients with bulky tumors and for patients with tumors in the medulla with lower cranial nerve deficits who are at risk of developing postoperative feeding and/or breathing difficulties.

There are several treatment options for patients with surgically inaccessible focal lesions. By extrapolation from series reporting results of treatment using conventional RT in brainstem tumors in which outcome correlates with location (pons vs other), imaging appearance (tumor volume, density on CT, enhancement pattern), and histology (malignant vs benign), it is reasonable to assume that 50% to 70% of focal lesions may be permanently controlled with such treatment. Similar results have been obtained in small numbers of patients treated with HFRT and with interstitial irradiation using ^{126}I.[77-79] There is also some experience with the

use of radiosurgery. However, standard treatment is as for LGAs at other locations, that is, external beam RT using a margin for the CTV of 0.5 cm, to a total dose on the order of 54 Gy given over 6 weeks. The risks of HFRT, radiosurgery, or stereotactic irradiation with large fraction sizes, or interstitial irradiation in inexperienced hands cannot be justified in the absence of any established superiority.

Dorsal exophytic tumors arise from the floor of the fourth ventricle. They are usually large, filling the fourth ventricle, but do not invade the brainstem to any significant extent. They present insidiously with failure to thrive in younger children and symptoms and signs of raised intracranial pressure in older patients. Cranial nerve deficits are seen in about half of the patients. On MRI, they are sharply delineated from surrounding structures. They are hypointense on T1-weighted images, are hyperintense on T2-weighted images, and enhance uniformly and brightly after gadolinium injection. Most are PAs.

Surgery is the treatment of choice for dorsal exophytic tumors. Intraoperative image guidance is essential to achieve a maximal degree of tumor resection. However, because there is usually no definite tumor-brainstem interface, even an optimal resection will leave a thin layer of tumor on the floor of the fourth ventricle. Nonetheless, most children do well following surgery, and routine postoperative adjuvant therapy is not indicated. RT may be considered for the rare patient who is found to have a high-grade lesion or for patients with low-grade tumors who develop progressive disease in the early (<9 months) postoperative period. For patients whose tumors recur later, further surgery should be considered, and RT reserved for those with inoperable disease. The RT volume and dose should be similar to those used for LGAs in other locations. The literature suggests that salvage is possible in most cases, and overall, the prognosis for patients with dorsal exophytic tumors is excellent.[114-116]

Cervicomedullary tumors arise in the upper cervical cord and grow rostrally beyond the foramen magnum. Most are low-grade lesions whose axial growth is limited by the pyramidal decussations located ventrally at the junction of the cervical cord and medulla. At this point, the tumor grows posteriorly, causing a bulge in the dorsal aspect of the medulla, toward the fourth ventricle.[109] These tumors typically present with lower cranial nerve

deficits, sleep apnea and feeding difficulties in younger children, long tract signs, and, sometimes, torticollis. Hydrocephalus is unusual.

Surgery is the treatment of choice. Gross total resection may be achieved in 70% to 80% of cases and subtotal removal in most of the remainder. The probability of long-term tumor control after such treatment appears to be excellent for the typical low-grade lesion. There is, therefore, no indication for routine postoperative RT for these patients.

DMGs account for 70% to 80% of all brainstem tumors. They arise in the pons and cause diffuse enlargement of the brainstem. Extension to the midbrain and medulla and/or exophytic growth are seen in at least two-thirds of cases. These tumors are defined by their H3 K27 alteration, including H3.3 K27 mutations, H3.1/H3.2 K27 mutations, and EZHIP overexpression.[117]

DMGs typically present with a short duration of symptoms consisting of multiple, bilateral, cranial nerve deficits (especially VI and VII) as well as long tract signs and ataxia. About 10% of patients have hydrocephalus at diagnosis. On CT, DMGs are isodense or hypodense, with little enhancement after contrast injection, similar to diffuse fibrillary astrocytomas at other sites. They are best seen on T2-weighted or FLAIR MRI. The presence of ring enhancement is suggestive of high-grade histology.

Surgery has no role in the management of patients with DMGs. Biopsies are now increasingly common and carry relatively low risk of morbidity, and some have advocated for biopsies as the standard of care.[118-120] Nonetheless, the MRI findings are characteristic, and for families who do not want to pursue biopsy, treatment can commence based on radiographic diagnosis alone.[121,122] Treated with conventional RT, the majority (≥70%) of patients with DMGs will improve clinically. However, the progression-free interval is short (median <6 months) and survival is poor, with a median survival of less than 1 year and survival rates at 2 years less than 20%.

Unfortunately, alternative dose or fractionation regimens have not improved outcomes for children with DMGs. HFRT was tested in a series of phase I/II studies using doses ranging from 64.8 to 78 Gy. Time to progression and OS were not improved in comparison with conventional RT.[123,124] Moreover, at the higher doses of HFRT of 75.6 and 78 Gy, morbidity was considerable. This included steroid dependency, vascular

events, and white matter changes outside the radiation field, as well as hearing loss, hormone deficiencies, and late-developing seizure disorders in the small number of long-term survivors.[123,125-127] Accelerated and hypofractionated RT regimens have also been tested in single-institution studies using, respectively, a total dose of 50.4 Gy given in 28 twice-daily fractions of 1.8 Gy over 3 weeks[128] and 39 Gy in 13 daily fractions and 45 Gy in 15 daily fractions.[129-132] PFS and OS rates were similar to those seen in the HFRT studies. However, there are potential benefits to the reduced duration of the RT course to help facilitate rehabilitation.

Alternative approaches that use chemotherapy in combination with RT also have been disappointing. Many single-agent and multiagent regimens have been tested in this patient population without providing a survival advantage compared with RT alone.[133] New agents and novel chemotherapy-RT combinations are under investigation by the pediatric cooperative groups in North America and Europe. Recent clinical studies suggest that ONC201, a novel dopamine receptor D2 antagonist,[134] and GD2-directed chimeric antigen receptor T-cell therapy[135] may be efficacious in patients with DMGs.

Currently, standard treatment for DMGs consists of RT given to the GTV as usually best demonstrated on T2-weighted or FLAIR MRI with a margin for the CTV of 1 to 1.5 cm to a dose of 54 Gy given in 30 daily fractions over 6 weeks. For tumors with supratentorial components, radiation doses up to 59.4 Gy can be considered. Because the initial progression of neurologic deficits can be rapid, treatment often needs to be started on a semi-urgent basis. Because no unexpected toxicity was seen with the hypofractionated regimens, these regimens could be considered an alternative to conventional RT in some patients if reducing the burden of treatment for the child and family is preferred.

Improvement in clinical status is usually evident as early as 2 to 3 weeks into treatment, and steroids, if used, usually can be discontinued at that point. This improvement is often impressive and well appreciated by the family, despite being of only short duration. Treatment at the time of progression may include experimental chemotherapy regimens or supportive care or even retreatment with RT in selected cases.[136-138] Of note, there is no consensus regarding the dose of reirradiation at the time of progression.[139]

Astrocytoma of the Spinal Cord

Intramedullary spinal cord tumors account for 3% to 6% of all CNS tumors in the pediatric age group. About 60% are astrocytomas, the majority of which are LGAs, 30% are ependymomas, and the remainder are gangliogliomas and developmental tumors, such as teratomas, lipomas, and dermoid and epidermoid cysts.

Patients typically present with pain and motor deficits, often of long duration. Rapid progression of symptoms and signs is suggestive of high-grade histology. On imaging, astrocytomas most often are seen to comprise a solid component and one or more cysts that may be intratumoral and/or extend rostrally and caudally beyond the solid component. Most enhance heterogeneously with the use of contrast material. Ependymomas, in contrast, only rarely harbor intratumoral cysts (although they may have an associated syrinx) and usually enhance homogeneously.

The management of spinal cord tumors has changed over recent years.[140] In the past, patients were typically treated with biopsy followed by RT, and there is evidence to suggest that this is effective treatment in more than half of children with LGAs.[141] However, improvements in surgery and the routine use of surgical adjuncts such as ultrasonic aspiration and support systems such as intraoperative ultrasonography and sensory and, more recently, motor-evoked potential monitoring improve the safety and completeness of resection so that complete or subtotal resection (STR) is now possible in approximately 80% of children with PA (the majority), especially those with a syrinx. Resection is more difficult and less likely to be complete in patients with grade II astrocytoma because of the more infiltrative nature of these tumors and the absence of a clear interface.[140] Because outcome following complete resection or STR for LGAs is very good, with long-term PFS in the 70% to 90% range,[142-144] routine postoperative adjuvant therapy is not indicated. For children in whom complete resection or STR is not possible, the options will be as for patients with LGAs in other locations, that is, early second surgery if feasible, or close follow-up with second surgery and/or RT at the time of progression. As for LGAs in other locations, chemotherapy may be an alternative to RT for young children.[145,146] The benefit of surgical resection in HGAs is less

clear, and the more usual approach is biopsy followed by postoperative RT.[147]

The RT target volume for LGAs consists of the solid portion of the tumor (including intratumoral cysts) with a margin for the CTV of 1 to 1.5 cm. The usual dose is 50.4 Gy given in 28 daily fractions over approximately 6 weeks. The CTV should be larger for patients with HGAs for whom a margin beyond the entire lesion of at least 1.5 cm (or one vertebral body) would be more appropriate. The dose usually will be as for LGA because of the substantial risk of morbidity at higher doses, but often chemotherapy will be given as well. Although older studies[141,142] and data from the Surveillance, Epidemiology, and End Results registry[148] and from the German cooperative group[149] all suggest that 20% to 35% of children with high-grade gliomas will survive following such treatment, a study from St Jude Children's Research Hospital presents an even bleaker picture with a very high rate of both local progression and leptomeningeal spread and no long-term survivors among patients with GBM.[147]

EPENDYMAL TUMORS

The following types of ependymal tumors are seen in children:

- Myxopapillary ependymoma (WHO grade II)
- Ependymoma (WHO grade II)
- Ependymoma (WHO grade III)

Myxopapillary Ependymoma

Myxopapillary ependymomas are slowly growing lesions almost always located in the conus filum terminale region of the spinal cord. They are the most common spinal cord tumor in this location. They usually present with back pain. On imaging, myxopapillary ependymomas are well circumscribed and usually enhance brightly after contrast injection. Despite their lower-grade histology, leptomeningeal spread is not uncommon even at diagnosis, and all patients should have an MRI of the whole spine and brain as part of their initial workup. In fact, myxopapillary ependymoma is now considered CNS WHO grade 2 rather than grade 1, by the 2021 WHO

CNS5 classification, in contrast to previous versions, given its relatively high likelihood of recurrence akin to conventional spinal ependymoma.[39]

Surgical resection is the treatment of choice. If the tumor is contained within the filum, complete resection may be possible after mobilization of the filum. The role of adjuvant RT remains poorly understood for pediatric myxopapillary ependymoma, but most patients may not need adjuvant RT, particularly after a complete resection.[150] A significant proportion of tumors recur locally, in multifocal locations, and/or with leptomeningeal metastases, but salvage with further surgery and/or with RT is possible in most.[151-153] If the tumor is in continuity with the conus, resection is more difficult and more likely to result in significant sequelae necessitating frequent residual tumor. If the tumor is not resected en bloc or if there is macroscopic residual tumor, the risk of recurrence is high. Postoperative RT in this setting results in improved local control.[144,154,155] Furthermore, radiation treatment provides excellent local control within the radiation field, but pediatric patients continue to be at risk of relapse outside the radiation field, including intracranial relapse.[156] The RT target volume is local (macroscopic disease plus a margin cephalad and caudad of 1.5 cm [or one vertebral body]) for the CTV, and the dose can range from 50.4 to 54 Gy depending on the location of the disease.[154-157] If focal radiation is planned to the lumbar spine and/or sacrum, the entire thecal sac inferior to the focal radiation should be considered within the field, given the propensity of myxopapillary ependymoma to relapse with drop metastases inferiorly.[156] Data also suggest that doses as low as 36 Gy may be adequate for uninvolved levels of the spinal canal.[156] The role of CSI for patients with leptomeningeal seeding at diagnosis or at relapse remains controversial, and because this disease's natural history, the long-term morbidity of treatment must also be considered when weighing treatment options.[156,158]

Ependymoma

Ependymoma is the third most common CNS tumor in children, with 5-year OS increasing from 65.4% in 1990 to 1999 to 91.4% in 2010 to 2016.[159] However, late relapses are common.[160] About half of all cases arise in children younger than 5 years.[161] Ependymoma can occur at any site in the ventricular system or in the spinal canal, but in children, approximately

two-thirds arise in the ependymal lining of the fourth ventricle. Tumors in this location typically present with symptoms and signs of raised intracranial pressure. On imaging, the tumor is usually large but relatively well circumscribed, with displacement rather than invasion of adjacent structures. Extension through the foramen magnum into the upper cervical region is not uncommon (Figure 90.10). Tumors that arise in the supratentorial compartment, some of which arise outside the ventricular system, present with focal neurologic deficits. Intramedullary ependymomas, which account for approximately 30% of all spinal cord tumors arising in childhood, usually present initially with dysesthesia and sensory deficits because of their central location in the cord and only later with pain and motor deficits.[162] Recently, the updated WHO-CNS5 classification outlined distinct groups that are defined by histopathologic, molecular, and anatomic features. These include posterior fossa A and posterior fossa B tumors in the posterior fossa; zinc finger translocation–associated (formerly RELA) fusion–positive and yes-associated protein 1 fusion–positive supratentorial tumors; and MYCN-amplified spinal ependymoma usually in the context of NF-2. Moreover, myxopapillary ependymoma is now considered CNS WHO grade 2 rather than 1, given its conventional spinal ependymoma–like odds of recurrence.[39]

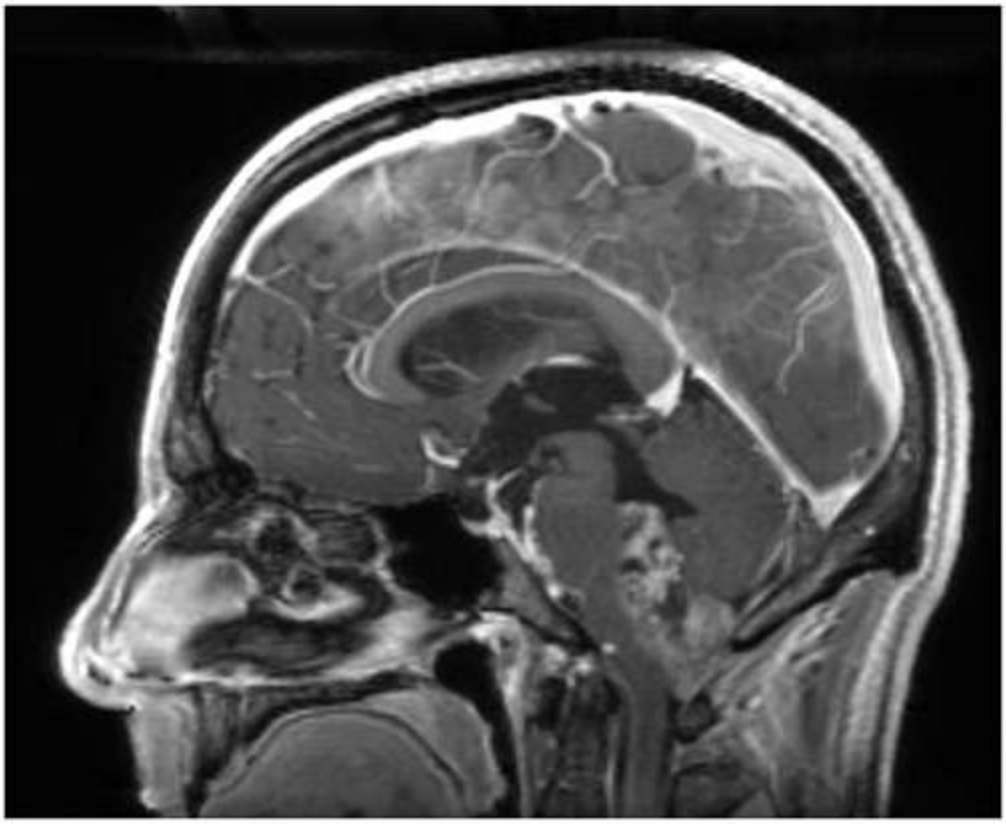


FIGURE 90.10 Typical appearance of an ependymoma that fills the fourth ventricle and extends inferiorly below the foramen magnum over the dorsal aspect of the spinal cord.

Spread of ependymoma is primarily local. However, 5% to 10% of patients have leptomeningeal seeding at diagnosis, and gadolinium-enhanced MRI of the whole CNS and CSF cytology are essential components of the workup for all patients.[163,164]

Management of Ependymoma

The completeness of the surgical resection is the factor that has the greatest impact on outcomes of patients with ependymoma.[165-171] Currently, it is estimated that complete resection is achieved in 70% to 90% of supratentorial ependymomas and in a similar percentage of spinal ependymomas. Complete resection is less frequently possible in patients with infratentorial ependymomas. Most commonly, residual tumor is left behind on the floor of the fourth ventricle or laterally at the cerebellopontine angle where tumor protruding through the foramen of Luschka encircles lower cranial nerves and vessels. “Second-look” surgery

may be considered, if feasible, either after the realignment of structures that takes place following resection of an initially bulky tumor in an often-unstable young child or after chemotherapy.[172]

Postoperative RT is the standard of care for children with ependymoma. Some have questioned the need for such treatment for patients who have undergone complete resection.[173-175] However, a number of studies including studies in young children in which the goal was to delay or avoid altogether RT suggest that such a strategy results in worse disease-free survival and OS and in the long-term greater morbidity[176-180] and, therefore, can be considered acceptable only for (a) patients with ependymoma of the spinal cord who have undergone complete resection for whom disease-free survival in contemporary series approaches 100%[181-184] and (b) select patients with supratentorial ependymoma that are solid and located in noneloquent areas and can be completely resected with a wider margin.[175] Moreover, children with grade 2 supratentorial tumors could be observed safely following complete resection as suggested by ACNS0121 (NCT01407744) phase 2 trial that reported 100% 5-year OS with the caveat of significantly lower 5-year event-free survival (EFS) of 61%.[172] A more recent phase 3 randomized trial, ACNS0831 (NCT01096368), concluded there is no survival benefit to giving maintenance chemotherapy even in patients with STR, irrespective of the extent of second-look resection after induction chemotherapy.[185] CSI was previously the standard of care for anaplastic ependymoma, but several institutional studies, a careful retrospective review, and prospective studies by the POG all suggest that there is no survival advantage for CSI.[171,186-190] Patients with leptomeningeal dissemination at diagnosis fare poorly despite intensive treatment that includes CSI and chemotherapy.

Radiotherapy Target Volume

Focal RT is the standard of care.[167,172,191] The GTV is a composite of the tumor bed, including any extension caudal to the foramen magnum and taking into account any anatomic shifts because of surgery plus any residual tumor. For several prospective studies, the margin for the CTV was 1 cm.[167,172] In patients who received immediate postoperative RT, local control was excellent (cumulative incidence of local failure 7.8%) for patients who

had undergone gross total resection, whereas patients who had undergone near-total resection or STR fared less well.[167] All failures were reported to be within the 95% isodose. The current Children's Oncology Group (COG) study uses an even smaller margin for the CTV of 0.5 cm.

Radiotherapy Dose

There is evidence for a dose-response in ependymoma, with improved tumor control using doses greater than 45 to 50 and even 54 Gy.[191] Although the lower doses may be the maximum possible for spinal ependymomas, the current standard is a dose of 54 to 59.4 Gy for children older than 18 months with infra- or supratentorial tumors.[167,172] Moreover, because failure most often occurs at the site of macroscopic residual disease, even higher doses may be desirable and most would reduce the CTV at 54 Gy to respect the tolerance of the spinal cord and/or other structures, for example, optic chiasm, and continue to a total dose of 59.4 Gy (Figure 90.11). Studies such as ACNS0831 assigned more conservative brainstem dose constraints to patients receiving proton therapy given proton's higher relative biologic effectiveness and end-of-range uncertainties, and a few unexpected brainstem-related adverse events. Goal dose constraints include brainstem D50 61 Gy or less and D10 63 Gy or less (photons) versus D50 52.4 Gy or less and D0.1 cc 56.6 Gy or less (protons); and maximum constraints of brainstem D50 62 Gy or less and D10 64 Gy or less (photons) versus D50 54 Gy or less and D0.1 cc 58 Gy or less (protons).[192]

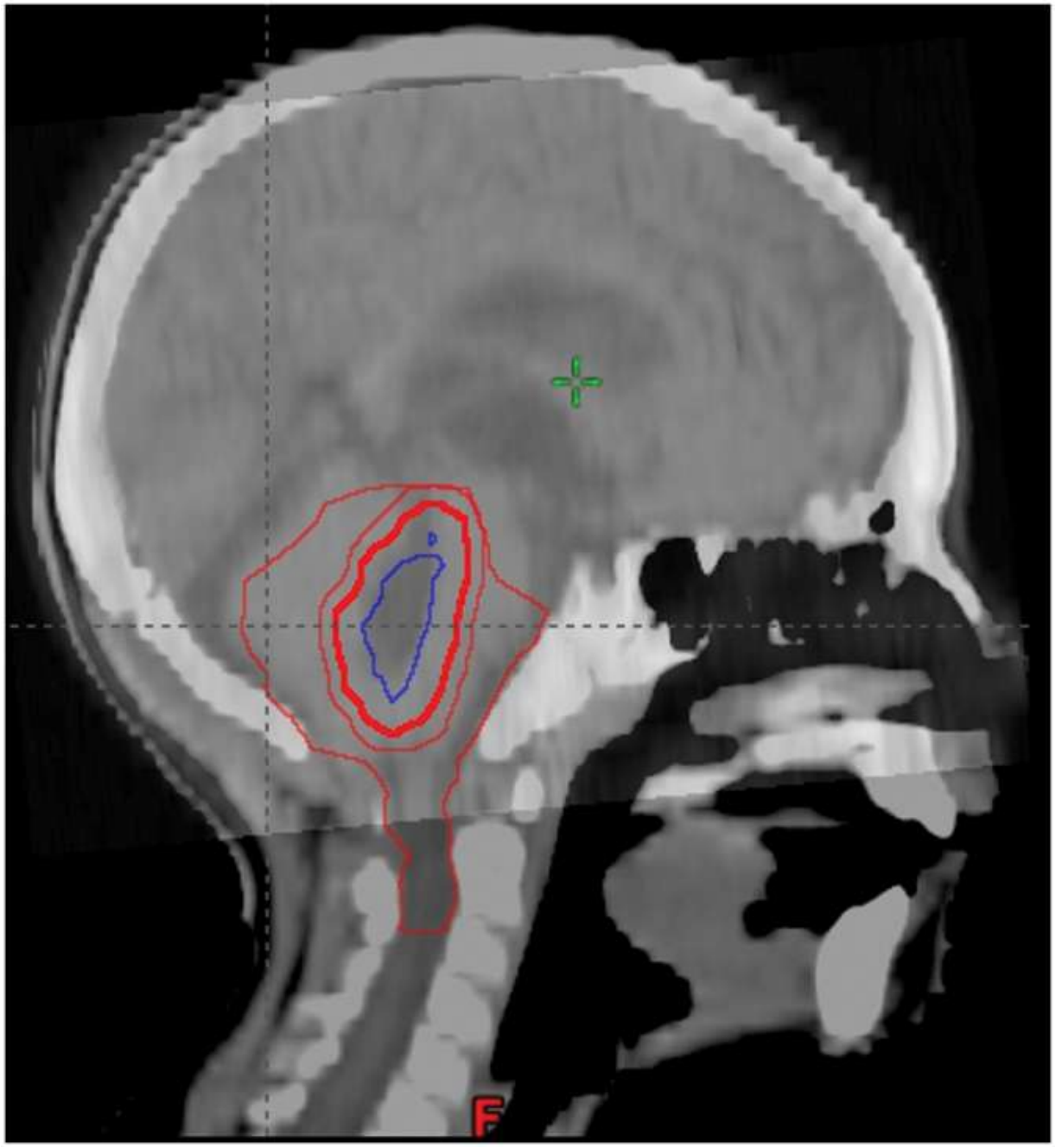


FIGURE 90.11 Care is necessary to ensure that the inferior extent of disease is included in the radiotherapy target volume. Volume reduction at 54 Gy is necessary to respect the tolerance of the spinal cord.

HFRT has been explored in ependymoma as a strategy to more safely deliver these higher RT doses. Studies from the Children's Hospital of Philadelphia in which the majority of patients received HFRT to a mean dose of 70.7 Gy,[193] from the Italian pediatric oncology group that used a

dose of 70.4 Gy,[194] and from the French pediatric oncology group that used a lower total dose of 60 Gy in 60 fractions,[195] all reported HFRT to be feasible. However, in none of these studies was there any clear evidence of benefit, particularly in the context of improved surgery and modern RT.

Reirradiation for Ependymoma

For patients who fail standard treatment with either local recurrence or, less frequently, leptomeningeal dissemination, retreatment with RT is an option that may result in durable control in a proportion of patients.[196-199] A subset of locally recurrent tumors can be managed with potentially curative intent using salvage surgery and focal RT. For children over 3 years old with local recurrence, the St Jude Phase II trial RERTEP allowed the use of photon or proton CSI to reduce the risk of metastatic tumor progression (NCT02125786). This was justified by higher risk of metastatic tumor progression in patients receiving focal reirradiation, especially those with chromosome 1q gain,[200] and backed by data from Canada and France.[198,201]

CHOROID PLEXUS TUMORS

Choroid plexus tumors arise from the epithelium of the choroid plexus of the cerebral ventricles. They include the following:

- Choroid plexus papilloma (CPP) (WHO grade I)
- Atypical CPP (WHO grade II)
- Choroid plexus carcinoma (CPC) (WHO grade III)

Choroid plexus tumors account for only 2% to 4% of all brain tumors that occur in children but as many as 10% to 20% of those seen in the first year of life. CPPs, which account for more than half of choroid plexus tumors in children, are composed of delicate fibrovascular connective tissue fronds covered by a single layer of uniform cuboidal columnar epithelial cells with round or oval basally situated monomorphic nuclei. Mitotic activity is low, and increased mitotic activity in a CPP defines an atypical CPP. In contrast to both, CPCs are solid tumors that tend to transgress the ventricular wall and invade the brain. Histologically, CPCs show frank evidence of malignancy, including frequent mitoses (>5%/10 high-power fields), increased cellular density, nuclear pleomorphism, blurring of the

papillary pattern with poorly structured sheets of tumor cells, and necrotic areas.

In children, most choroid plexus tumors arise in the lateral ventricles, causing obstruction to CSF flow. Infants commonly present with increasing head circumference and older children with symptoms and signs of raised intracranial pressure. On neuroimaging, choroid plexus tumors are usually hyperdense, contrast-enhancing masses. Even papillomas seed into the CSF space, and workup for both benign and malignant lesions should include a gadolinium-enhanced MRI of the spinal axis and CSF cytology.

Management of Choroid Plexus Tumors

Surgery is the treatment of choice for CPPs both for the primary lesion and for metastatic deposits, if feasible. Complete resection is achieved in a high percentage of cases now, and outcome in this situation is excellent. Less than 10% of tumors recur, and OS is close to 100%.[202-205] The role of RT following incomplete resection is unclear, but because not all patients will progress, follow-up without adjuvant treatment would be the usual strategy, with consideration of further surgery, if feasible, and/or RT only at the time of progression.

Results are less satisfactory for patients with CPCs. Surgery is an important component of treatment but often difficult. Blood loss may be considerable, and staged procedures may be necessary to obtain maximal resection. In most series, results are better for patients who have undergone complete resection,[205-215] and the need for adjuvant therapy in this situation is not clearly established. In one series of pooled data, survival was significantly better when RT had been given postoperatively despite a probable bias toward the use of RT in patients considered to have more unfavorable disease.[209,210] Others have reported excellent results following complete resection, in some cases with chemotherapy but without RT.[206,207,212,213] In contrast, patients who have residual disease fare very poorly. Postoperative RT appears to be useful,[215] but the desire to avoid RT in infants and very young children may mean that chemotherapy is used instead. Evidence suggests that a subset of patients can be cured without RT.[216] When both are used, RT is usually delivered early (following two cycles of chemotherapy), with the exception of infants and very young

children in whom RT is delayed until age 3 years. Genetic and genomic analyses may in the future help guide therapy. A substantial percentage of patients with CPCs have TP53 mutations, and patients without such mutations are reported to have a more favorable prognosis and be successfully treated without RT.[217,218] It is possible that radiation may have a deleterious effect in patients with Li-Fraumeni syndrome and CPCs, though selection bias with more aggressive disease undergoing RT cannot be excluded.[219]

The RT target volume is also controversial. CSI was traditionally used in patients with CPCs, and a recent literature review showed that the use of CSI was associated with improved PFS as compared with RT to the whole brain or tumor bed only.[215] Importantly, more than half of all failures occurred outside the treatment field. This is problematic given the young age of the patients, and a pragmatic approach in which local fields are used for patients with CPPs with postoperative residual (including metastatic sites) as well as for patients with atypical CPPs or CPCs without evidence of leptomeningeal seeding and only patients with atypical CPPs or CPCs with leptomeningeal seeding receive CSI would seem reasonable for now.

NEURONAL AND MIXED NEURONAL-GLIAL TUMORS

These are uncommon tumors that are characterized by the presence of both neuronal and glial elements in variable amounts. They include entities such as desmoplastic infantile astrocytoma and dysembryoplastic neuroepithelial tumor. Most will be cured by surgery, but RT may be indicated in two tumor types:

- Ganglioglioma and anaplastic ganglioglioma
- Central neurocytoma

Ganglioglioma and Anaplastic Ganglioglioma

Gangliogliomas are well-differentiated slowly growing tumors composed of mature ganglion cells in combination with neoplastic glial cells (WHO grade I or II). Tumors in which the glial component shows anaplastic features (WHO grade III) are called anaplastic gangliogliomas.

Although these tumors can arise anywhere within the CNS, most in children arise in the temporal region and typically present with seizures. Surgery is the treatment of choice. When resection is complete, the probability of long-term tumor control in patients with ganglioglioma is excellent.[220-222] Indications for adjuvant RT are WHO grade III tumors and progressive or recurrent WHO grade II tumors that are unresectable, symptomatic, and have recurred despite multiple courses of systemic therapy. The RT target volume is the postoperative cavity and residual disease with the CTV being a 1 to 1.5 cm expansion and doses can range from 54 to 59.4 Gy with standard fractionation. The significance of a high proliferation index or of the presence of anaplasia in patients with ganglioglioma is controversial. Although it seems clear that the risk of recurrence is higher in patients with these features,[220,221,223-225] the indications for postoperative RT remain undefined, except for patients with anaplastic gangliogliomas who have undergone less than complete resection in whom the use of RT has been shown to result in improved PFS.[222,226]

Central Neurocytoma

This is a neoplasm composed of uniform round cells with neuronal differentiation that arises in the lateral or third ventricles, typically the former, that is seen predominantly in adolescents and young adults. Patients usually present with symptoms and signs of raised intracranial pressure. Surgery is the treatment of choice, and when complete resection is achieved, long-term tumor control is excellent without adjuvant treatment.[227] Patients in whom complete resection cannot be achieved as well as those with tumors with atypical histology or a high mitotic rate fare less well,[227,228] and postoperative RT should be considered in these situations. Although a dose of 50 Gy appears adequate for patients with typical neurocytomas,[229] there is evidence of improved tumor control at doses of at least 54 Gy in patients with atypical neurocytoma.[230]

PINEAL PARENCHYMAL TUMORS

Pineal region tumors account for 2% to 8% of intracranial tumors in children. Approximately half are germ cell tumors, one-fourth to one-third are pineal parenchymal tumors, and most of the remainder are astrocytic

tumors. Pineal parenchymal tumors are derived from pineocytoma, which are cells with photosensory and neuroendocrine functions, or their embryonal precursors. According to the WHO classification, the following entities can be distinguished:

- Pineocytoma (WHO grade I)
- Pineal parenchymal tumor of intermediate differentiation
- Pineoblastoma (WHO grade IV)

Pineocytoma

Pineocytoma is a slow-growing tumor composed of small uniform mature cells resembling pineocytes, with occasional large pineocytomatous rosettes, that accounts for approximately half of pineal parenchymal tumors and in childhood most commonly occurs in the teenage years. Patients typically present with symptoms and signs of raised intracranial pressure. Some will have symptoms of upper mesencephalic tegmental dysfunction (Parinaud syndrome), consisting of limitation of upward gaze, lid retraction, retraction nystagmus, and pupils that react more poorly to light than to accommodation. On MRI, pineocytomas are usually spherical, well-circumscribed masses, hypointense on T1- and hyperintense on T2-weighted images, with homogeneous contrast enhancement. Leptomeningeal spread has been described in pineocytoma,[176] but it is probable that the explanation for this lies in sampling error. With better imaging and more extensive surgery with more complete histologic evaluation of the tumor, it seems that leptomeningeal spread can be considered an uncommon event.[231]

Treatment consists of surgical resection via an occipital transtentorial or an infratentorial supracerebellar approach using modern operative adjuncts such as functional MRI and MR tractography in relation to the location of the primary visual cortex and deep MR venography. If complete resection or STR is accomplished, PFS is in the 90% to 100% range.[232,233] Patients who undergo lesser degrees of resection or only biopsy fare less well, and although some have questioned its usefulness based on the results of a systematic review,[232] postoperative RT may be offered after multidisciplinary discussion.[234] The target volume is local, consisting of

macroscopic residual disease with a margin for the CTV of 1 cm, and the dose, 50 to 55 Gy over 6 weeks.

Pineal Parenchymal Tumor of Intermediate Differentiation

Pineal parenchymal tumors of intermediate differentiation are composed of diffuse sheets or large lobules of uniform cells with mild-to-moderate nuclear atypia and low-to-moderate mitotic activity. They are rare tumors, accounting for only 10% of pineal parenchymal tumors, and optimal management remains to be defined.[235,236] Some patients treated with surgery alone have survived free of disease.[233,236,237] Disseminated disease is frequent at the time of recurrence; thus, some providers recommend postoperative treatment with CSI as for pineoblastoma,[231,238] while other series have reported favorable results after focal RT.[239,240]

Pineoblastoma

Pineoblastoma is a highly malignant tumor composed of patternless sheets of densely packed small cells with round to irregular nuclei and scant cytoplasm.

Pineoblastomas most frequently affect infants and very young children, who typically present with an enlarged head circumference or symptoms and signs of short duration of raised intracranial pressure. On MRI, pineoblastomas are usually multilobulated and often enhance heterogeneously, with areas of necrosis and/or hemorrhage. Infiltration of surrounding structures is common. Leptomeningeal spread is seen in as many as 50% of patients at diagnosis.

Surgery for lesions in the pineal region is difficult, and complete resection is often not possible. Postoperatively, children older than 3 years are treated with CSI and chemotherapy as for high-risk MB (see later). Five-year survival in this age group is in the 50% to 70% range.[231,241-243] Although the standard of care remains 36 Gy CSI with a tumor bed boost to 54 Gy, there is evidence to suggest a risk-adapted approach may identify patients who may benefit from reduced dose CSI (23.4 Gy compared to 36 Gy).[244] However, infants treated with chemotherapy without RT fare extremely poorly: In prospective studies of the POG and CCG, all tumors recurred within the first 11 months (POG) and 1.2 years (CCG) and all

patients died of disease.[243,245,246] Thus, more aggressive treatment that includes chemotherapy dose intensification is necessary. Patients with familial bilateral retinoblastoma with pineoblastoma ("trilateral retinoblastoma") also have an extremely poor prognosis, most dying within a year following diagnosis.

EMBRYONAL TUMORS

Embryonal tumors as a group are the second most common type of CNS tumor in the pediatric age group. They include MB and atypical teratoid/rhabdoid tumor (ATRT):

- MB
  i. MB, WNT activated
  ii. MB, sonic hedgehog (SHH) activated, TP53 mutant versus TP53 wild type
  iii. MB, non-WNT/non-SHH, group 3
  iv. MB, non-WNT/non-SHH, group 4

These MB subgroups refer to the use of conventional histopathologic features together with molecular biologic parameters in classification. Conventional histologic varieties are also recognized and are associated with particular clinical characteristics. Desmoplastic MB is associated with a better prognosis, particularly in very young children.[247] Anaplastic/large cell MBs appear to be adverse prognostic factors.[248]

Medulloblastoma

MB accounts for 15% to 20% of all CNS tumors in children, with a median age at presentation of 6 years. It is a malignant invasive embryonal tumor of the cerebellum or posterior fossa with predominantly neuronal differentiation and an inherent tendency to metastasize via CSF pathways.

It is accepted that MBs are defined according to four subgroups based on a combination of histopathology and molecular biology.

The WNT subgroup is associated with a very good prognosis, with long-term survival greater than 90%. The majority of WNT subgroup MBs have classic histology, and a particular feature is that these tumors demonstrate

β-catenin nucleopositivity, *CTNNB1* gene mutations, and monosomy-6. Rarely, the WNT subgroup may include large cell/anaplastic cases. WNT MB can arise at all ages but is infrequent in infants. Although overall MB is more common in males, the male-to-female (M:F) ratio for the WNT subgroup is approximately 1:1. Germline mutations of the WNT pathway inhibitor APC predispose to Turcot syndrome, which includes a predisposition to MB.

The SHH MB subgroups include *TP53* mutant and *TP53* wild-type subgroups. They are named after the SHH signaling pathway, which is considered to drive tumor initiation in the majority of cases. The age incidence of SHH subgroups of MB is bimodal and is frequent in both infants aged less than 3 years and adults. The M:F ratio is approximately 1:1. The majority of nodular/desmoplastic MBs are included within the SHH subgroup. However, around 50% of SHH subgroup MB have other histologic subtypes, including classic and large cell/anaplastic varieties. The prognosis for SHH appears to be similar to group 4 (see later) and intermediate between WNT and group 3. Individuals with germline mutations of the SHH receptor PTCH have Gorlin syndrome, which, for several decades, has been recognized as carrying a predisposition to the development of MB. Preliminary clinical trials are being designed to target the SHH pathway to improve outcome for this subgroup.

Group 3 MB represents the subgroup of MB with the poorest prognosis. The majority of MBs in group 3 are classic MB and include most large cell/anaplastic tumors. They are more frequent in males than females. They arise in infants and older children, but only rarely in adults and frequently present with metastases. Group 3 MB is typically characterized by high-level amplification of the *MYC* proto-oncogene, and almost all cases exhibit aberrant *MYC* expression.

Patients with group 4 MB have an intermediate to good prognosis similar to patients with SHH tumors. They include classic and large cell/anaplastic histologies and account for approximately 30% to 40% of cases. This subgroup represents the archetypal MB, exemplified by a 7-year-old boy with a classic histology MB who has an isochromosome 17q. The M:F ratio is approximately 3:1. The molecular pathogenesis of group 4 MB is not currently clear.

Improvements in the understanding of the molecular mechanisms of MB tumorigenesis are emerging as important factors in clinical trial design, leading to a tailored approach for different histologic and molecular biologic subtypes. Collaborative clinical trial groups are developing studies that will investigate prospectively the stratification of therapy according to pathologic, biologic, as well as the more traditional clinical parameters. In particular, clinical studies are beginning to involve a cautious lowering of the treatment intensity for patients with WNT MB and maintaining intensity for those in group 3. This approach requires a timely and well-coordinated approach to tumor sample collection and analysis of biologic parameters prior to treatment decisions.[249]

In most cases of MB, the tumor arises in the cerebellar vermis and projects into the fourth ventricle. Patients typically present with symptoms and signs of raised intracranial pressure (ie, headache and morning vomiting). On MRI, MBs appear as solid masses that generally enhance homogeneously with contrast material (Figure 90.12). The frequency of leptomeningeal seeding at diagnosis is approximately 30% to 35%, and investigation at diagnosis must include a gadolinium-enhanced MRI of the spinal axis and CSF cytology. The former should be obtained whenever possible preoperatively or else at least 2 weeks postoperatively because of the artifactual changes that may be seen in the early postoperative period. CSF cytology, which should be obtained by lumbar puncture, usually cannot be obtained safely preoperatively because of the presence of raised intracranial pressure and more commonly is obtained at least 2 weeks postoperatively to avoid false positives that may be seen in the early postoperative period. MB is one of the few CNS tumors to spread outside the CNS (to lymph nodes, bone), but this is a very uncommon event at diagnosis, and other studies such as a bone scan or bone marrow aspiration or biopsy are not justified as a routine.

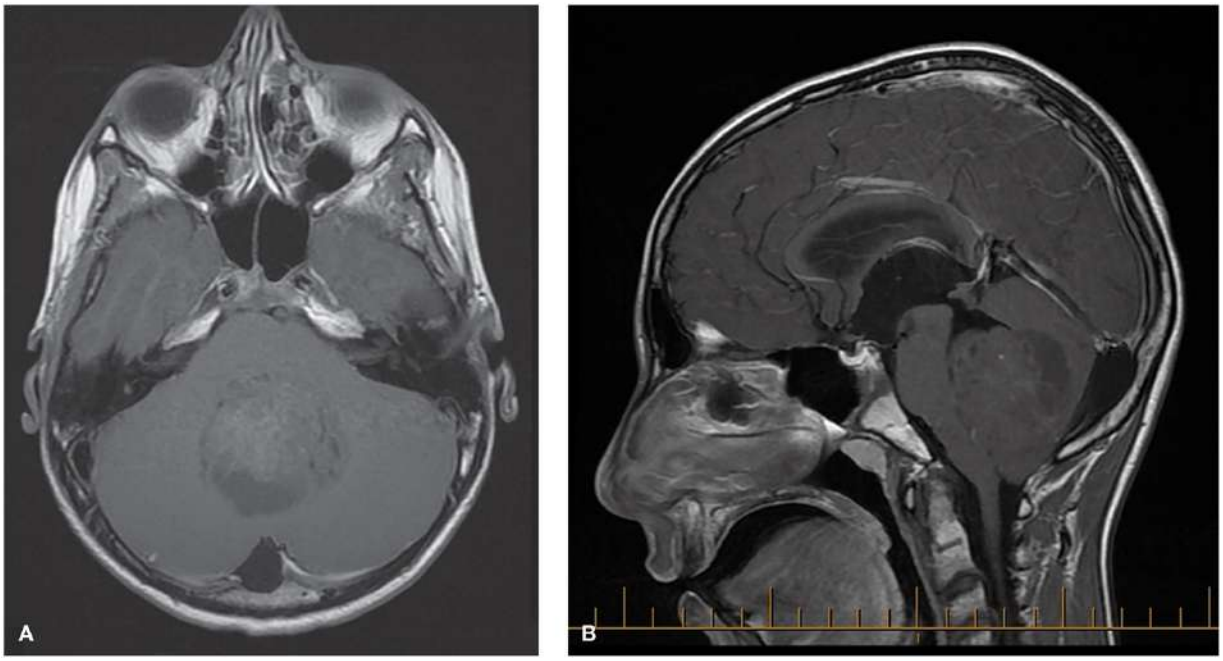


FIGURE 90.12 T1 axial (A) and T1 gadolinium-enhanced sagittal (B) magnetic resonance images of a medulloblastoma in an 11-year-old boy. Note the typical midline location of the tumor that is causing ventricular outlet obstruction with dilatation of the third and lateral ventricles.

In addition to molecular biologic parameters, conventional factors that correlate with outcome include age at diagnosis, the presence or absence of leptomeningeal spread at diagnosis, and the completeness of the surgical resection. Patients are allocated to one of two overall risk categories: standard and high risk. Those who have undergone complete resection or STR with less than 1.5 cm^2 of residual tumor on postoperative MRI performed within 48 to 72 hours of surgery, and no evidence of CSF dissemination (M0) are considered to have standard-risk disease, whereas patients who have larger volume residual tumor and those with evidence of CSF dissemination at diagnosis are characterized as high risk. With contemporary neurosurgical techniques, complete or near-total resection is accomplished in approximately 80% of cases. Overall, approximately two-thirds of patients will be standard risk and one-third will be high risk.

Management of Standard-Risk Medulloblastoma

Until the 1990s, the standard of care for patients older than 3 years with standard-risk disease consisted of postoperative RT to the craniospinal axis

to a dose of 35 to 36 Gy followed by a boost to the whole posterior fossa to a total dose of 54 to 55.8 Gy. In multi-institutional studies, such treatment results in long-term EFS in 60% to 65% of patients.[12,250,251] Sequelae of treatment include hormonal deficits, decreased bone growth, and neurocognitive deficits that correlate with the age of the child and the radiation dose.[10]

Several treatment strategies designed to reduce the morbidity associated with the use of RT have been tested. An attempt by the French Cooperative Group (SFOP) to reduce the RT target volume to avoid supratentorial radiation produced disastrous results,[252] and studies have shown that omission of RT or CSI (in favor of focal RT) leads to unacceptably poor outcomes for the WNT subgroup.[253,254] Thus, CSI remains the standard of care. The use of reduced-dose CSI (23.4 Gy) alone (without chemotherapy) in the North American intergroup study (CCG-923/POG#8631) resulted in a significantly increased risk of isolated neuroaxis failure and an EFS at 5 and 8 years of only 52%.[251] HFRT may be a more promising strategy. In an SFOP pilot study that tested HFRT to a CSI dose of 36 Gy without chemotherapy, early toxicity was reduced and PFS at 3 years was 81%.[255] The results of the European SIOP PNET-4 study in which patients were randomized to HFRT or conventional RT found no significant benefit to HFRT; thus, conventional RT remains the standard.[256]

An alternative strategy consists of reduced-dose CSI followed by a boost to the posterior fossa to a total dose of 55.8 Gy in combination with systemic chemotherapy. PFS was 79% at 5 years in a CCG pilot study that used CSI to a dose of 23.4 Gy in combination with weekly vincristine followed by adjuvant systemic chemotherapy consisting of vincristine 1.5 mg/m^2, lomustine (CCNU) 75 mg/m^2, and cisplatin 75 mg/m^2.[257] In the joint CCG/POG phase III randomized study (A9961) that followed, this regimen was compared to a regimen in which the CCNU was replaced by cyclophosphamide. EFS at 4 years was approximately 85% in both arms,[258] and such an approach is now considered the standard of care for children with standard-risk MB in North America. The recently presented COG ACNS0331 trial evaluated the safety of an even lower dose of CSI (18 Gy) in children aged 3 to 8 years and of a reduced-volume posterior fossa boost in children of all ages. There was no significant difference in EFS for patients treated with a tumor/surgical bed plus margin boost compared with

those treated with a whole posterior fossa boost.[259] However, patients treated with 18 Gy CSI had significantly inferior 5-year EFS of 71.4% compared with 82.9% for those treated with 23.4 Gy CSI.[259] Currently, the standard of care for children with standard-risk MB is with CSRT 23.4 Gy with a boost to the tumor bed to a total dose of 54.0 Gy, followed by eight cycles of chemotherapy with vincristine, CCNU, and cisplatin.

In the latest generation of trials in MB such as the open European PNET-trial, risk stratification is based on biologic parameters in addition to clinical and pathologic features.[260] Patients with anaplastic/large cell histology are no longer included in the standard-risk group, given their poorer outcome. Furthermore, evidence suggests that WNT MB with β-catenin nucleopositivity is associated with better prognosis and MYC gene amplification with worse prognosis, raising the possibility of reduced-intensity RT and chemotherapy for patients with WNT MB (NCT01878617, NCT02724579, and NCT02066220), and the evaluation of additional treatment intensity for patients with less favorable prognosis.

Management of High-Risk Medulloblastoma

Patients with residual disease greater than 1.5 cm^2 and/or those with leptomeningeal seeding are considered to have high-risk disease. This is the group of patients in which the use of chemotherapy was shown in the prospective randomized phase III studies conducted in the 1970s to result in significant improvement in disease-free survival. Research since then has largely focused on the chemotherapy regimens, including changes in scheduling in relation to RT and in doses and routes of delivery of chemotherapy. Some have used higher dose CSI or altered RT fractionation schedules. An overview of studies performed by the North American and European cooperative groups up until the early 2000s is given in Freeman et al.[261]

It is important to note that the definition of risk factors has evolved considerably over the past two decades, making comparison of published data quite problematic. Better postoperative imaging and more complete staging as well as identification of unfavorable pathologic features (eg, large cell and anaplastic histology) have led to transfer of patients from the standard-risk to the high-risk category, which may partly explain the

improving results for both standard-risk and high-risk diseases. The category of high-risk disease is heterogeneous and includes more favorable subsets such as patients with postoperative residual disease without leptomeningeal spread, and even those with M1 (cytology-positive) disease, for whom it may be appropriate to consider a treatment approach different from that for patients with M2/3 disease with nodular seeding. For example, for patients with residual disease, M0, it would be logical to consider using a boost to residual disease in the posterior fossa to a dose higher than the standard 55.8 Gy. Management of patients with M1 disease remains controversial, but the weight of evidence suggests that they should be treated similarly to those with M2/3 disease.[262] Results for patients with M2/3 disease remain quite poor, although an impressive 82% 4-year OS was reported for patients treated on a COG pilot study using carboplatin daily during RT as a radiosensitizer.[263] The most recent COG ACNS0332 study did not show a benefit to isotretinoin during maintenance chemotherapy, and only patients with group 3 MB benefited from daily carboplatin (73% vs 54%).[264] Many centers in Europe use a hyperfractionated accelerated RT regimen, given in combination with pre- and post-RT chemotherapy.[265-268]

Management of Medulloblastoma in Infants

MB accounts for 20% to 40% of all CNS tumors in infants. Although up to half of infants have more favorable histologic types (desmoplastic/nodular or MB with extensive nodularity), the prognosis overall is worse than in older children. The explanation for this is likely multifactorial. In addition to biology, the rate of complete resection is lower in this age group, and the frequency of leptomeningeal seeding at diagnosis is higher (as much as 50%), but also, many patients do not receive optimal treatment.[269] Because of the significant risks with respect to neurocognitive function associated with the use of RT in infants and very young children,[270] chemotherapy has been used in an attempt to either delay or avoid RT altogether. Infants with M0 disease who have undergone total resection may do well with chemotherapy alone, with a 5-year OS of 69% in the first POG infant study[271] and of 93% in the German study,[272] although it is noteworthy that treatment in the latter included intraventricular methotrexate for which there

are also concerns about the risk of neurocognitive sequelae. The use of high-dose chemotherapy (HDCT) followed by autologous stem cell transplant leads to similar efficacy with 5-year OS of 70% for patients who underwent a gross total resection.[273] In other studies, results were less satisfactory, in some because of the need for aggressive salvage regimens that were associated with significant long-term sequelae.[274] In fact, with the possible exception of very young children with desmoplastic/nodular MB without residual disease, evidence suggests that RT is an important component of treatment,[92] and because recurrences are generally early (6-12 months) and local,[92,270,274] the recently completed North American study used early RT to a limited treatment volume consisting of the tumor bed plus an anatomically confined margin for the CTV of 1 cm for patients without leptomeningeal seeding. Infants with M2/3 disease are generally treated with intensive chemotherapy regimens. Although patients with desmoplastic/nodular histology may do quite well, with an OS at 5 years of 52.9% to 89%,[93,275,276] the prognosis for those with other subtypes is much less satisfactory. Further studies have found that infant and very young children with SHH subtype may have better prognosis.[277] Despite this, the goal of treatment generally will still be to avoid RT (especially CSI) and the decision to use it in highly individualized based on the clinical situation and the wishes of the parents. Of note, a substantial proportion of children who relapse despite an initial CSI-sparing approach can be salvaged with RT, generally using CSI.[278]

Radiotherapy for Medulloblastoma

CSI is the standard of care, and careful attention to coverage of the entire target volume that includes the meninges overlying the brain and spine including extensions along nerve roots is critical. In the SFOP M-7 protocol, 50% of relapses could be correlated with targeting deviations. In the subsequent studies (MSFOP-93 and MSFOP-98), the relapse rate was 17% in patients who had inadequate coverage of only one part of the CTV (a typical example being the cribriform plate), 28% for patients who had inadequate coverage at two sites, and 67% for patients who had inadequate coverage at three or more sites.[279,280] In an SFOP pilot study that tested reduced-dose CSI for standard-risk disease, OS at 5 years was significantly

worse for patients with inadequate coverage at two or more sites as compared with no or only one major deviation (54.4% vs 79.3%).[281]

CSI is followed by a boost to the tumor bed or posterior fossa. For standard-risk disease, involved-field boost is appropriate. The optimal CTV for a reduced-volume posterior fossa boost remains to be defined, although an anatomically confined expansion of 1 to 1.5 cm around the GTV (any macroscopic residual tumor and the surgical bed) until recently has been regarded as reasonable. Patients with high-risk MB often receive posterior fossa boost. While no prospective study has examined the role of involved-field boost for high-risk MB, the involved field can also be considered for patients with high-risk MB. The total dose is typically 54 to 55.8 Gy. Using conformal treatment techniques, it is possible to reduce the dose to the cochlea, which is important in children who will also be receiving cisplatin-based chemotherapy. Better sparing of the cochlea,[282] pituitary, and hypothalamus, and the temporal lobes can be achieved using a reduced target volume for the boost (Figure 90.13). Fukunaga-Johnson et al[283] found a low risk of isolated failure outside the tumor bed in the posterior fossa in a cohort of 114 patients, and data from several other centers as well as an SFOP pilot study that used a conformal boost limited to the tumor bed similarly support such an approach.[255,259,284-286]

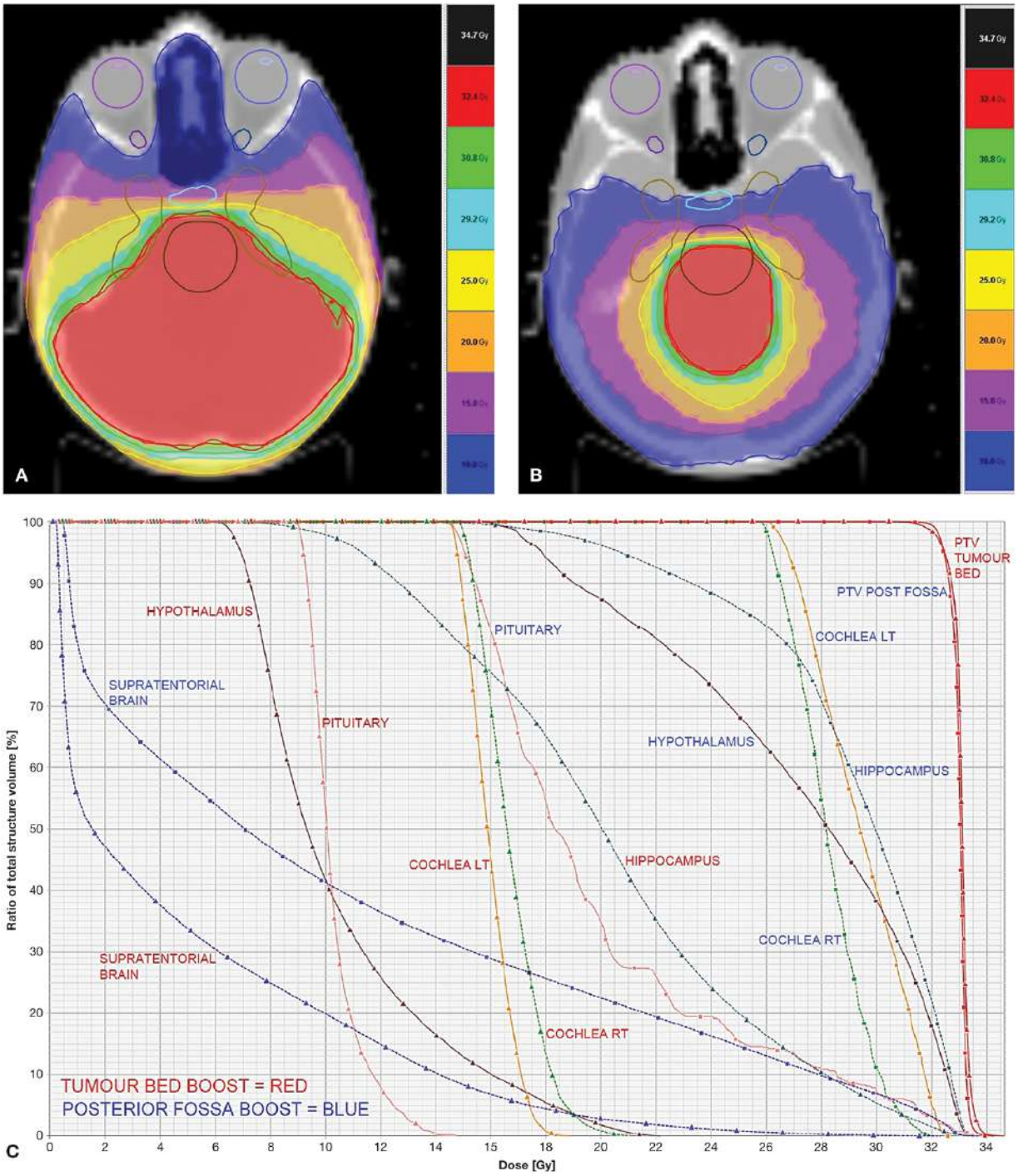


FIGURE 90.13 Axial images of an intensity-modulated radiation therapy/image-guide radiation therapy plan for a whole posterior fossa (A) and a reduced-volume posterior fossa boost (B) for a patient with medulloblastoma. C. Dose-volume histograms show significant sparing of organs at risk with the reduced-volume boost. LT, left; PTV, planning target volume; RT, right.

Further data suggest that IMRT can further spare normal OARs in the brain, and proton RT can further decrease integral low dose and acute and long-term toxicity.[36,287,288] Recent studies also suggest that the use of proton RT may improve long-term neurocognitive outcomes.[289-291]

Delay to RT may be associated with poorer outcomes, and CSI should ideally start within 28 to 40 days following surgical resection. There is also evidence that it is important to deliver RT in a timely manner, avoiding unnecessary gaps in treatment resulting from machine servicing, holidays, and the like. In the SIOP PNET-3 and PNET-4 studies, EFS and OS were significantly worse when the duration of treatment exceeded 50 days.[256,292] When CSI has to be interrupted, for example, because of hematologic toxicity, treatment should continue to the posterior fossa boost volume while waiting for the blood counts to recover. Granulocyte colony-stimulating factor may be used to hasten recovery of the counts.

Supratentorial Primitive Neuroectodermal Tumor

Recent molecular analysis of case series has established that the group of tumors previously referred to as supratentorial primitive neuroectodermal tumor (stPNET) are now more correctly allocated to various different histologic groups, including other embryonal tumors such as ATRT (see later) or sometimes those of astrocytic lineage.[293] This has led to confusion over how best to manage these patients.

Traditionally, the conventional usual approach for a child older than 3 years with an stPNET without leptomeningeal spread consisted of maximal surgical resection followed by postoperative RT (CSI followed by a boost) and chemotherapy. Experimental regimens such as HDCT with stem cell rescue (SCR) are used in infants and young children and in patients with M+ disease. In view of current knowledge, patients who would previously have been diagnosed as having stPNET require multidisciplinary discussion including detailed expert review of pathology to determine optimum management of the individual case.

Atypical Teratoid/Rhabdoid Tumor

ATRT is a highly malignant embryonal tumor seen in very young children with a peak incidence in the birth to 2-year age group, at which age in one

population-based study ATRT was as common as PNET and MB.[294] Composed of rhabdoid cells with or without fields resembling a classic PNET, ATRT is diagnosed on the basis of the characteristic molecular findings, namely, deletion and/or mutation of the INI1 locus (also known as *SMARCB1* gene) on chromosome 22 or less frequently mutations in *SMARCA4* gene on chromosome 22. ATRT can arise at any location within the CNS, including the spine. Leptomeningeal seeding is seen at diagnosis in a quarter to one-third of patients.[295] Staging workup includes renal imaging, given the high prevalence of rhabdoid tumor predisposition syndrome in 35% of patients with ATRT.[296]

Since the recognition of ATRT as a separate entity with a high frequency of early relapse and a very poor prognosis, patients have been treated with increasingly intensive chemotherapy regimens. RT appears to be an important component of treatment.[297-303] In a series of 37 patients treated at St Jude, early use of RT and the use of CSI were found to be associated with improved outcomes,[302] and it has been suggested that the worse survival reported for children younger than age 3 may be due, in part, to the less frequent use of RT and, when used, to the use of local RT rather than CSI in this age group. However, in a recent update limited to patients who received age- and risk-stratified RT, delay to RT was found to be the important factor.[304] The current treatment paradigm includes surgery, two courses of chemotherapy, followed by three courses of HDCT with peripheral blood SCR and RT: involved field with or without CSI for localized and disseminated disease, respectively. This ACNS0333 study–based treatment resulted in superior 4-year EFS and OS of 37% and 42%, respectively, compared to less than 10% in historical trials, where the protocol calls for early RT (after completion of at least two cycles of induction chemotherapy).[301] However, the use and timing of RT depend on the age of the child, the location (infratentorial or supratentorial), and the extent of disease at diagnosis (M0 or M+). Thus, children younger than 6 months at completion of chemotherapy with an infratentorial tumor and those younger than 12 months with a supratentorial tumor receive RT later, upon completion of both induction and consolidation chemotherapy with or without HDCT and autologous stem cell transplant. The RT target volume is local (tumor bed and any macroscopic residual disease plus a margin for the CTV of 1 cm) for children with localized disease and CSI followed by a

boost for those with leptomeningeal spread. Doses are age dependent for both local RT and CSI (50.4 vs 54 Gy and 23.4 vs 36 Gy for children younger and older than 3 years, respectively).[301] In Europe, patients with nonmetastatic ATRT receive doxorubicin-based chemotherapy and local RT to a dose of 54 Gy, whereas those with metastatic disease receive CSI. An ATRT registry (EURHAB) has been established to collect multi-institutional and multinational data on patient management and outcome.[305] Recently, a phase 1 study (NCT02601937) showed promising efficacy of a single-agent tazemetostat, Enhancer Of Zeste 2 Polycomb Repressive Complex 2 Subunit inhibitor, in the management of refractory or relapsed ATRT.[306]

Embryonal Tumors With Multilayer Rosettes

In 2000, Eberhart et al[307] described a variant of stPNET, the embryonal tumor with abundant neuropil and true rosettes (ETANTR) as a tumor exhibiting prominent ependymoblastic rosettes, neuronal differentiation, and a neuropil background. This tumor was predominantly recognized in young children and was associated with a very poor prognosis. More recently, in 2014, it has been recognized that there is a group of tumors that are distinct from other embryonal tumors and are referred to as embryonal tumors with multilayer rosettes (ETMRs). ETMR is now recognized as containing the three histologic variants ETANTR, ependymoblastoma, and medulloepithelioma.[220] These newly recognized tumors are yet to have a universally accepted mode of management. Given ETMR's rarity, there is no standard treatment paradigm. Current management is largely adapted from other embryonal tumor treatment strategies including surgery, age- and risk-adapted RT, HDCT with autologous SCR, and/or intrathecal therapy with relatively improved outcomes according to some case series despite an overall dismal prognosis.[308,309]

GERM CELL TUMORS

Germ cell tumors of the CNS constitute a group of rare tumors that are morphologic homologs of germinal neoplasms arising in the gonads and at other extragonadal sites. They include the following entities, although, in many cases, more than one tumor type is present:

- Germinoma
- Embryonal carcinoma
- Yolk-sac tumor (endodermal sinus tumor)
- Choriocarcinoma
- Teratoma
  - Mature
  - Immature
  - Teratoma with malignant transformation
- Mixed germ cell tumor

A teratoma is a tumor composed of an admixture of different tissue types that are representative of ectoderm, endoderm, and mesoderm. A mature teratoma is composed exclusively of fully differentiated tissues, sometimes arranged in such a manner as to resemble normal tissue relationships. Mitoses are absent or rare. An immature teratoma is composed of incompletely differentiated tissues resembling those of the fetus. Mitoses are typically present.

In the West, CNS germ cell tumors are relatively rare, accounting for 3% to 5% of all CNS tumors in the pediatric age group. They are more common in Asia, where they account for as many as 15% to 18% of all CNS tumors occurring in childhood. The peak age incidence is 10 to 12 years. Boys are affected more frequently than girls, with a ratio of approximately 3:1. CNS germ cell tumors arise from primordial germ cells in structures about the third ventricle, with the region of the pineal gland being the most common site of origin followed by the suprasellar region. Nongerminomatous germ cell tumors (NGGCTs) are the most common tumor type in the former area and germinomas in the latter.

The presenting symptoms and signs depend on the tumor type and the location of the tumor. Tumors in the pineal region cause obstruction to CSF flow at the aqueduct of Sylvius resulting in hydrocephalus, and most patients with tumors in this region present with a relatively short history with symptoms and signs of raised intracranial pressure. Another characteristic presentation of tumors in this region is Parinaud syndrome as a result of dorsal midbrain compression. In contrast, patients with tumors in

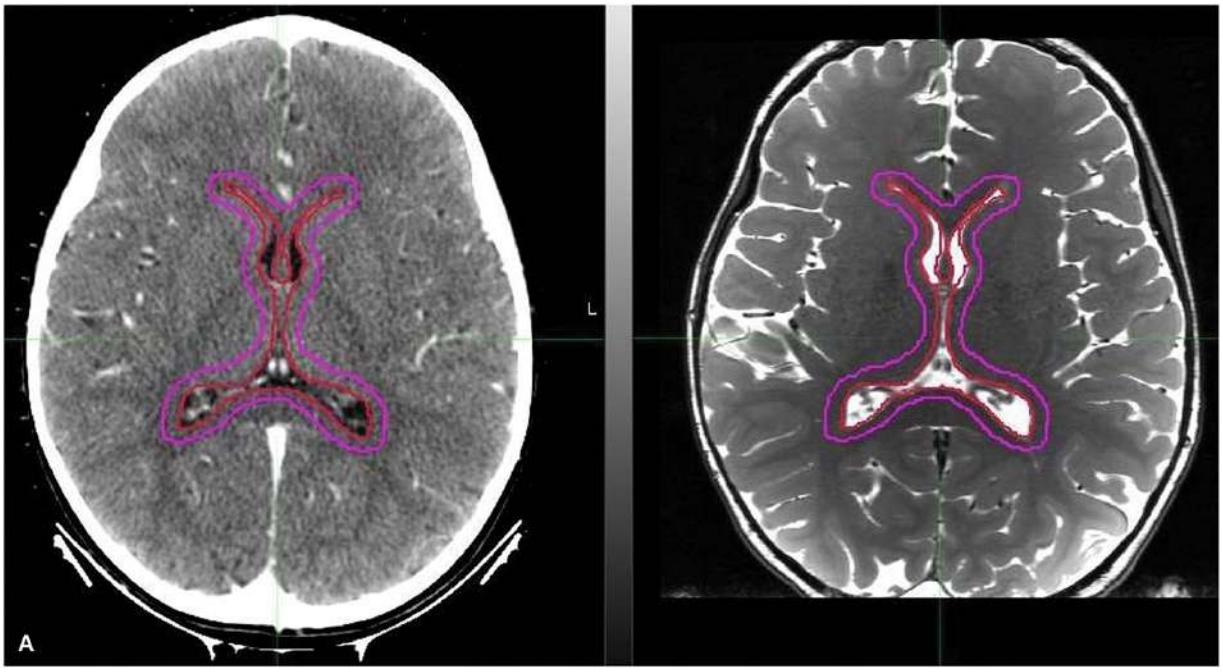
the suprasellar region usually present with a longer history initially of neuroendocrine deficits, especially diabetes insipidus, growth failure, and precocious puberty, and only later of visual field deficits and, later still, of symptoms and signs of raised intracranial pressure. On imaging, most germ cell tumors appear as solid masses. Teratomas are more heterogeneous with cysts, areas of calcification, and, sometimes, fat, whereas choriocarcinomas often contain areas of hemorrhage. Bifocal or multifocal disease around the third ventricle is seen in approximately 10% of patients with germinomas. Gadolinium-enhanced MRI of the spinal axis is an essential part of the workup to exclude leptomeningeal dissemination, which is found at diagnosis in approximately 10% of patients with germinomas and 10% to 15% of patients with NGGCTs. Measurement of serum and CSF tumor markers is another essential part of the initial workup. Modest elevation of β-human chorionic gonadotropin (β-hCG) (,100 IU/mL) may be seen with pure germinomas that may contain syncytiotrophoblastic cells. Higher levels of β-hCG are more suggestive of a choriocarcinoma. An elevated α-fetoprotein (α-FP) is diagnostic of a yolk-sac tumor.

In the past, many lesions arising in or about the third ventricle were treated without histologic confirmation of diagnosis. This is no longer considered acceptable practice because the differential diagnosis includes many disparate entities (such as Langerhans cell histiocytosis, astrocytoma, and ependymoma), and all patients should undergo biopsy unless CSF and/or serum markers confirm the presence of an NGGCT (elevated α-FP and/or β-hCG .100 IU/mL) or unless a histologic diagnosis is made by other means (eg, CSF cytology). For tumors in the pineal region with hydrocephalus, the usual surgical approach is an endoscopic third ventriculostomy, which allows access to the lesion for biopsy purposes. Intraventricular lesions have to be biopsied with care because hemorrhage, which is not infrequent, may be difficult to manage endoscopically. A stereotactic approach is also possible, but this may be quite challenging because of the proximity of deep cerebral veins and, moreover, may be suboptimal for diagnosis because of the potential for sampling error. Occasionally, complete resection will be possible; this would be a reasonable strategy for patients with NGGCTs if it can be accomplished without major morbidity because it would ensure complete characterization of the pathology and may even obviate the need for further therapy.

Germinoma

In the past, standard treatment for patients with germinoma, whether localized or disseminated, was RT alone. Results of treatment using CSI followed by a boost to the primary site are excellent, with long-term disease-free survival rates of 100% in some series.[310-313] For patients with unifocal disease without leptomeningeal spread, RT alone to limited volumes, that is, whole brain[314,315] or whole ventricle,[316] results in a high probability of local control and a low (0%-5%) risk of failure in the spinal axis. Experience with local RT (tumor plus a margin) alone generally has been less satisfactory.[317-320] To reduce the risk of morbidity associated with RT, chemotherapy has been considered another option, either alone or in combination with reduced-volume and/or reduced-dose RT. Several studies have shown clearly that the former, that is, the use of chemotherapy alone, is not acceptable: Only 40% to 50% of patients remain disease free, and although salvage using further chemotherapy together with RT is possible in most cases and OS is high, this is achieved at the cost of considerable toxicity.[321-323]

In contrast, a combined approach using platinum-based chemotherapy followed by reduced-volume, reduced-dose RT is an attractive option that results in disease-free survival rates in the 90% to 96% range.[316,324-326] Local failures were seen in 10 of 60 patients treated in the SFOP TGM-TC-90 study with chemotherapy followed by local RT and primarily located along the ventricles.[320] Local failure appears to be less frequent after whole-ventricular RT, and the recent COG ACNS1123 showed excellent outcomes (Figure 90.14).[316,317,327]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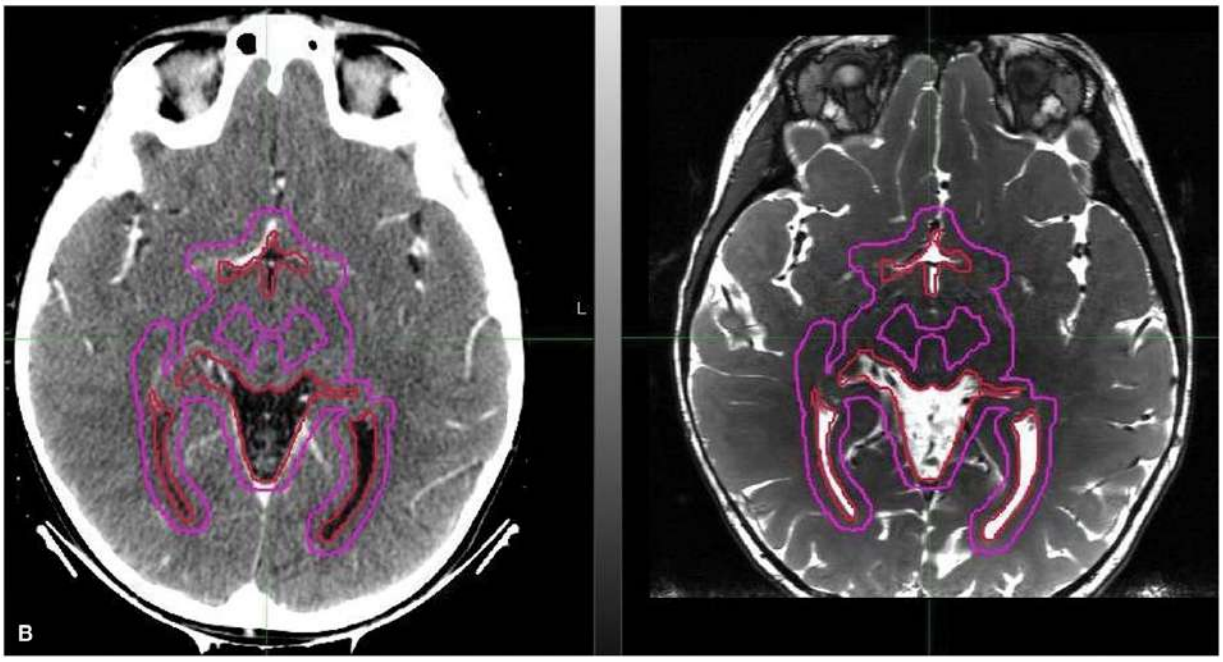
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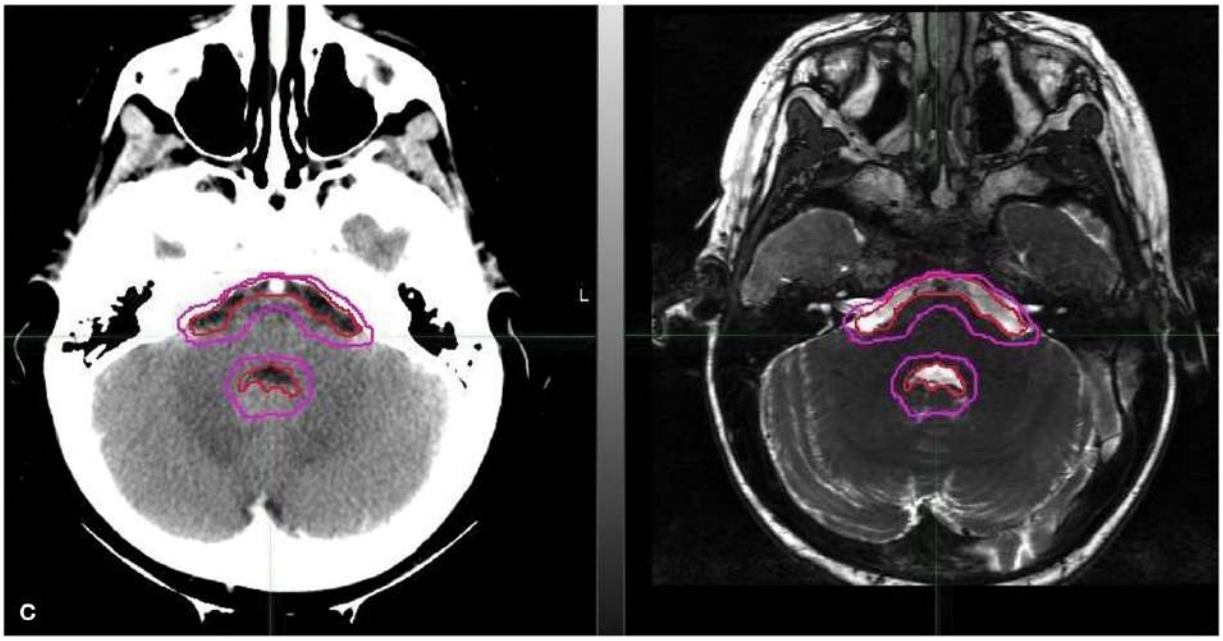

FIGURE 90.14 Target volume definition for whole-ventricular irradiation as per the guidelines for the current Children's Oncology Group study for central nervous system germ cell tumors. Planning computed tomography and T2-weighted magnetic resonance images at the level of lateral ventricles (A), hypothalamus and pineal cistern (B), and fourth ventricle and prepontine cistern (C). Note that this volume needs to be expanded to include the primary tumor and any other sites of involvement. Whether the suprasellar, basal, and prepontine cisterns need to be included is controversial for now. Better sparing of nontarget tissues will be achieved with the use of a four-field technique or intensity-modulated radiation therapy than with lateral-opposed fields. (Courtesy of Dr Shannon MacDonald.)

For patients with leptomeningeal spread at diagnosis, RT alone using CSI with boosts to macroscopic disease is certainly an option, although, in North America and Europe, chemotherapy followed by CSI followed by a boost to all sites of involvement would now be the more usual approach. Management of patients with bifocal or multifocal midline tumors is controversial. In the past, these patients were treated as having disseminated disease, but at least some, that is, those with bifocal disease by imaging or by inference (eg, in a patient with a pineal region primary who has diabetes insipidus), are now more usually treated with chemotherapy and whole-ventricular RT.

There is less controversy now with regard to the RT dose and dose fractionation schedule for germinoma. For localized (unifocal or bifocal) pure germinoma, the current standard in North America is induction chemotherapy followed by whole-ventricular RT to 18-24 Gy with an

involved-field boost to 30-36 Gy. Given recurrences can happen after biopsy through the endoscopic third ventriculostomy tract, it is important to include the tract within the radiation field. Results are excellent for those patients with metastatic disease, with a CSI dose as low as 21 Gy even in patients with leptomeningeal spread. The total dose to the primary site has typically been 40 to 45 Gy, but probably can be safely reduced to 36 Gy or even to 30 Gy[316,317] in patients treated with a combined chemotherapy-RT regimen who have had a complete response to chemotherapy. Finally, because germinoma is a very radiosensitive tumor, a fraction size of 1.5 Gy can be used, which, in theory, further reduces the risk of injury to normal structures.

Nongerminomatous Germ Cell Tumors

For NGGCTs, the diagnosis can be made in as many as one-third of all patients on the basis of imaging findings (location and appearance) plus tumor markers. NGGCTs are of several different histopathologic types that carry different prognoses. Patients with mature teratomas without any associated malignant elements can be managed with surgery alone, whereas those with mature teratoma with germinomatous elements will be treated as germinomas. All other patients with intermediate and poor prognosis tumor types[328] require more aggressive treatment. The results of treatment using RT alone are very poor, with OS in the 10% to 30% range. Results are better with chemotherapy alone, although 40% to 60% of patients relapse following chemotherapy and will be subjected to aggressive salvage regimens.[329,330] A multimodality approach that includes both chemotherapy and RT appears to be associated with the best outcome, with 5-year OS more than 80%.[331,332] The most recent COG ACNS1123 study found that omitting CSI led to increased failures in the spine, suggesting that spine irradiation is needed for patients with NGGCT.[332,333] The current standard of care, therefore, consists of platinum-based chemotherapy followed by RT.

There is controversy with respect to the RT target volume for NGGCT. Although good results have been reported by some groups using chemotherapy followed by local RT,[331] others show a high rate of failure outside the primary site.[332-335] Thus, CSI remains the standard of care for patients with NGGCT using a dose of 30 to 36 Gy, with a boost to the

primary site for a total dose of 54 Gy. There may be a subset of patients who may have favorable outcomes without CSI, but this remains to be determined. The ongoing COG ACNS2021 study will explore the role for whole ventricular and spine irradiation for patients with NGGCT.

Patients who have less than a complete response to chemotherapy fare poorly. Second-look surgery may be useful to both exclude the possibility that the residual imaging abnormality represents mature teratoma and/or resect residual viable tumor. This would be followed by CSI and more intensive chemotherapy, such as HDCT/SCR.[331]

TUMORS OF THE SELLAR REGION

Tumors arising in the sellar region in children include the following:

- Craniopharyngioma
- Adamantinomatous
- Papillary
- Pituitary adenomas

Craniopharyngioma

Craniopharyngiomas are benign partly cystic epithelial tumors that arise in the sellar region from remnants of Rathke pouch. In children, almost all are of the adamantinomatous type. They account for approximately 5% of intracranial tumors in the pediatric age group, with a peak incidence between the ages of 5 and 14 years.[336]

In most patients, craniopharyngiomas have both suprasellar and intrasellar components. Children typically present with neuroendocrine deficits, especially diabetes insipidus and growth failure. Visual field deficits often go unnoticed initially. Cognitive and behavioral changes are not uncommon. Compression of or tumor growth within the third ventricle may lead to hydrocephalus and symptoms and signs of raised intracranial pressure. On neuroimaging, the findings are very typical, with solid and cystic areas in varying proportions. Calcification is seen in the majority of cases. The solid portion(s) and the cyst capsule usually enhance with the use of contrast material.[337]

Treatment of craniopharyngiomas, although long considered a controversial issue,[338] in practice depends on the characteristics of the tumor and the availability of the surgical expertise required. Many patients have long-term tumor control after complete resection[339]; however, many patients suffer recurrence, with a prospective study finding EFS at 3 years of 64%.[340] Moreover, although visual deficits, if present, improve after surgery in the majority of cases, new neuroendocrine deficits are very common and hypothalamic damage is a major concern, particularly in patients with tumors that have grown retro-chiasmatically into the floor of the third ventricle.[341-343] Devastating sequelae that include rage, aggressivity, and hyperphagia permanently compromise the quality of life of the patient and their family. The transsphenoidal approach that has been used more frequently in recent years, even in younger children and even in patients with tumors with a supradiaphragmatic component, is associated with fewer complications. In general, therefore, tumors that are smaller and/or subdiaphragmatic in location and without hypothalamic involvement would be managed surgically. Patients who have residual tumor following surgery are at high risk for progressive disease within the first 2 to 3 years following surgery,[344-347] mandating close follow-up with MRI performed at 3-month intervals during that time period. Patients at greater risk for complications secondary to surgery would be managed with biopsy, cyst decompression, if necessary, and RT.[348-353]

RT may, therefore, be given as the sole therapy after biopsy, after incomplete surgery, or at the time of progression/recurrence after surgery. A retrospective study found that delaying radiation until recurrence can lead to worse endocrine and visual outcomes.[354] Given the heterogeneity of tumor types and situations, many treatment options have been used and explored. For example, a lesion with a small solid component and a simple cyst may be well treated with intracavitary injection of liquid radioactive material. Most contemporary experience is with β emitters such as ^{33}P and ^{91}Y delivering a high dose (ie, 200 Gy) to the cyst wall. Intracavitary injection of radioactive material is not always easy.[355] Sometimes, the cyst fluid is very thick in consistency, and there may be little or no communication between multiple cysts. It is essential to use contrast material to ensure that the catheter is well placed in the cavity and that there is no leakage of material outside the cyst before injecting radioactive

material. This could be combined with radiosurgery or fractionated stereotactic irradiation to the associated solid component, although it may be reasonable to do so only later and only if there is evidence of progressive disease. Special care is needed if, as is usually the case, the tumor is near the optic chiasm or optic nerves.[356] Tumor control rates using this approach are good for carefully selected patients.[357] However, conventionally fractionated external beam RT with photon or proton RT may be a better option for all except very small tumors, with a lower risk of morbidity.[358-362]

The target volume for external beam RT consists of the entire lesion (ie, both the solid and cystic components) as demonstrated on postcontrast T1- and T2-weighted MRI sequences for better visualization of the solid and cystic components, respectively, ideally with a 1- to 2-mm slice thickness, performed just prior to treatment. Although some have used a margin for the CTV of 1 to 2 cm,[360,361] a smaller margin of 0.5 cm or even 0 cm (ie, CTV = GTV) can be justified based on excellent tumor control using such margins.[359,363-365] However, the use of reduced margins should be paired up with close in-treatment surveillance, given the potential for cystic growth.[366] A dose of 50.4 to 55.8 Gy given in 1.8 Gy daily fractions over 6 weeks appears to be necessary to achieve a high probability of tumor control. Cyst enlargement during treatment or within the first 2 to 3 months after completion of RT is common. Early recognition and appropriate management consisting usually of cyst decompression is essential to avoid further neurologic compromise or even death.[354,367] The long-term prognosis is good, with EFS more than 80% in most series.[359-362] Patients may have long-term sequelae after RT, including vasculopathy; however, many of these toxicities are present prior to radiation.[361,368]

There is increasing interest in the use of proton therapy to reduce nontarget dose, which would be predicted to minimize late endocrine and neurocognitive effects (Figure 90.15).[359,362]

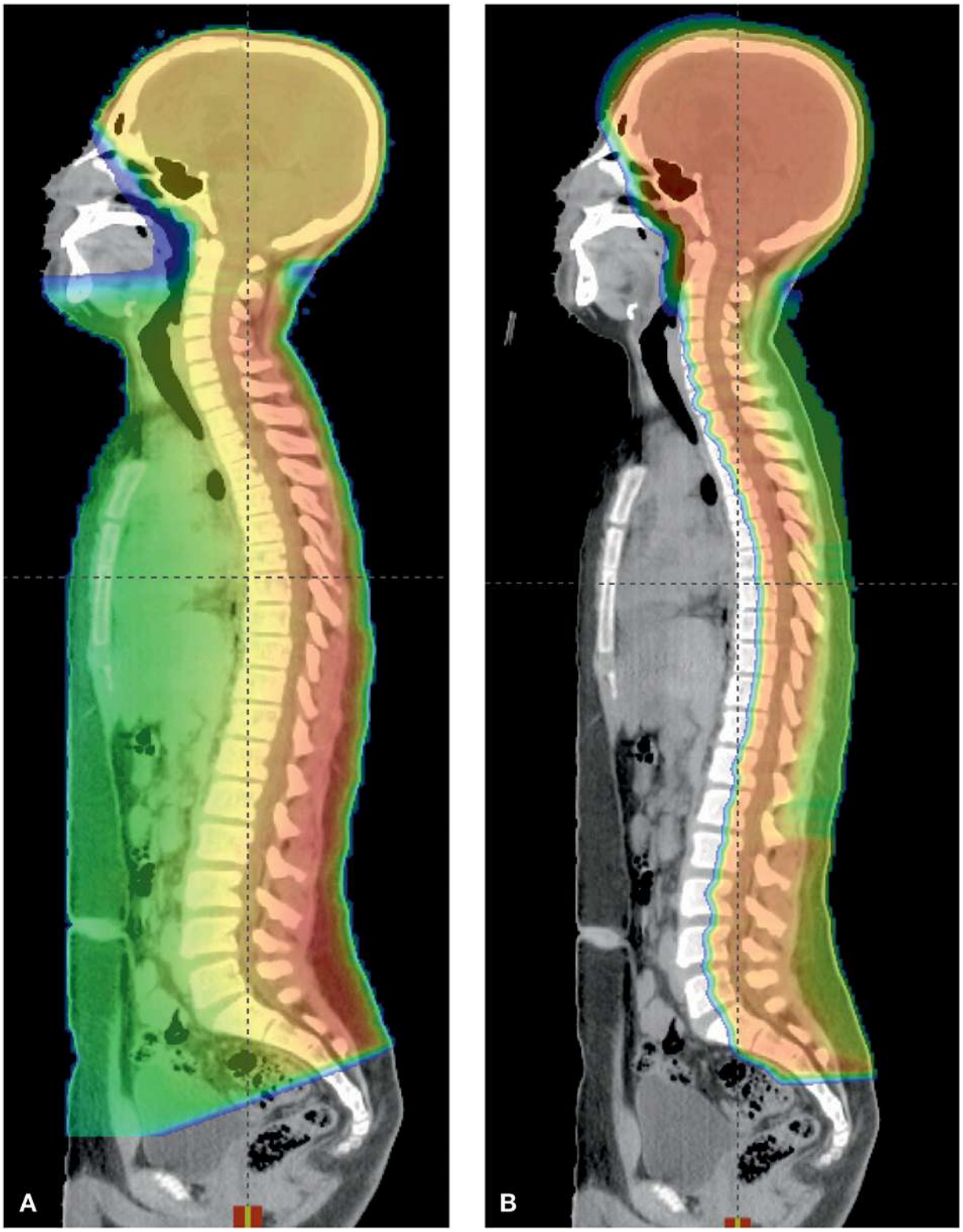

FIGURE 90.15 A. Craniospinal radiotherapy for young adult with conventional photon radiotherapy—exit from spinal field delivers low to intermediate dose to structures anterior to spine. B. Craniospinal radiotherapy for young adult with proton therapy—no exit dose

beyond Bragg peak avoiding dose to structures anterior to spine. (Figure courtesy of Dr D. Indelicato, University of Florida, Jacksonville.)

Pituitary Adenomas

Pituitary adenomas are rare in childhood. Almost all cases arise in adolescence. Most are functioning adenomas that present with endocrine dysfunction, most often menstrual irregularities and galactorrhea in girls and delayed puberty in boys. They may be quite large, with extrasellar extension, and appear to be more invasive than those seen in adults.[369-371] Visual loss, when present, may be more severe and more likely to be associated with optic atrophy.[371]

Management will, in general, parallel that for adult patients. Prolactin- and growth hormone–secreting adenomas are managed medically as in adults. When surgery is necessary, a transsphenoidal approach using neuronavigation appears to be feasible and safe in children, even in those with poor pneumatization of the sphenoid sinus.[369,370] RT is indicated if surgical resection is not possible or in cases of unresectable recurrence or intractable hormone elevation following surgery. GTV delineation should be performed using pre- and postcontrast-enhanced T1-weighted MRI, ideally with fat suppression and 1-mm slice thickness, and using preoperative imaging, if applicable.[366] Highly conformal treatment with a margin for the CTV of 0.5 cm beyond macroscopic disease is appropriate in most cases, especially in case of invasive and aggressive pituitary tumors, to encompass all potential areas of microscopic tumor infiltration while sparing adjacent critical structures, including major vessels. The usual dose, as in adults, will be 45 to 50.4 Gy and up to 54 Gy over 5 to 6 weeks for nonsecretory, secretory, and larger more aggressive pituitary tumors, respectively. Single-fraction and fractionated stereotactic radiosurgery have become increasingly adopted in clinics following comparable efficacy and safety for smaller pituitary tumors located at a safe distance from critical structures like the optic apparatus. Common dose fractionation regimens include 13 to 16 and 16 to 25 Gy in one fraction for nonfunctioning and secreting pituitary adenomas, respectively, as well as 21 Gy in three fractions and 25 Gy in five fractions for larger and/or closer tumors to the optic chiasm.[372,373] Close follow-up by an endocrinologist is essential to ensure appropriate management of hormone deficits.[374]

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CHAPTER 91

Wilms Tumor

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Wilms tumor (WT), or nephroblastoma, is a highly curable childhood neoplasm. The prognosis of children with WT has improved considerably from a very high mortality rate at the beginning of the 20th century to the current cure rate of >90%.[1] The management of WT is a paradigm for successful interdisciplinary treatment of solid tumors of childhood to maximize cure rates and minimize treatment-related complications.

EPIDEMIOLOGY

WT is the most common malignant renal tumor of childhood. The incidence of WT is 10.4 cases for every 1 million children younger than 15 years. Approximately 650 cases of WT are diagnosed in the United States each year.[2,3] The peak incidence is between 3 and 4 years of age. WT may arise as sporadic or hereditary tumors or in the setting of specific genetic disorders.[4] Most WTs are solitary lesions within a kidney, multifocal within a single kidney in 12% and bilateral in 7%.[5] The clinical syndromes associated with WT include WAGR syndrome (*WT*, *A*niridia, *G*enitourinary malformations, mental *R*etardation), Denys-Drash syndrome (pseudohermaphroditism, mesangial sclerosis, renal failure, and WT), and overgrowth syndromes like Beckwith-Wiedemann syndrome (somatic gigantism, omphalocele, macroglossia, genitourinary abnormalities, ear creases, hypoglycemia, hemihypertrophy, and a predisposition to WT and other malignancies), and Simpson-Golabi-Behmel syndrome.[4,6]

BIOLOGY

Among the various genetic changes implicated in the development of WT, the most widely studied involves *WT1*, which is a tumor suppressor gene at chromosome 11p13 that was isolated from a child with WAGR syndrome.[7]

WT1 is likely to play a specific role in glomerular and gonadal development.[8] *WT1* can also act as a dominant negative oncogene, resulting in abnormal cell growth such as in Denys-Drash syndrome.[9] Germline *WT1* mutations are observed in approximately 82% of patients with WT who have genitourinary anomalies or renal failure. The frequency of *WT1* mutations in sporadic and familial WT is much lower at 20% and 4%, respectively.[10] Beckwith-Wiedemann syndrome maps to chromosome 11p15.5; this locus is also referred to as *WT2*.[11]

Patients with loss of heterozygosity (LOH) at 16q and 1p have higher relapse and mortality rates.[12] The National Wilms Tumor Study-5 (NWTS-5) prospectively evaluated the prognostic significance of LOH on 16q and 1p. When the effects of LOH for both 1p and 16q were considered jointly, the relative risk (RR) for relapse in stage I and II familial hypercholesterolemia (FH) diseases was 2.9 ($P = .001$) and for stage III and IV FH diseases was 2.4 ($P = .01$). The RR for death for patients with stage I and II FH diseases with LOH for both regions was 4.3 ($P = .01$) and for stages III and IV was 2.7 ($P = .04$).[13]

A novel WT suppressor gene on the X chromosome, *WTX (AMER1)* is inactivated in approximately one-third of sporadic WT cases.[14] Anaplastic tumors have shown changes on 17p consistent with *TP53* deletion and specific genomic loss or underexpression on 4q and 14q and focal gain of *MYCN*.[15] Rhabdoid tumors are characterized by the genetic loss of the *SMARCB1/hSNF5/INI-1* gene located at chromosome 22q11. Global gene expression studies have shown that loss of *SMARCB1* results in repression of neural crest development and loss of cyclin-dependent kinase inhibition.[16] The rhabdoid tumor predisposition syndrome is an autosomal dominant condition observed in 30% to 35% of patients with rhabdoid tumors due to germline mutations in SMARCB1 or SMARCA4.[17] In children with very low-risk WT treated with just surgery alone, the presence of *WT1* mutation and 11p15 loss has been prospectively validated to be an important predictor of relapse.[18,19] Another Children's Oncology Group (COG) study demonstrated that gain of 1q is a promising biomarker for patients with favorable histology WT. In a report of 1,114 patients on NWTS-5, 317 (28%) patients displayed 1q gain. The 8-year event-free survival (EFS) with and without 1q gain was 77% and 90%, respectively ($P < .001$). The 8-year overall survival (OS) with and without 1q gain was

88% and 96%, respectively ($P < .001$). 1q gain was associated with a higher RR of relapse (2.4, $P < .001$).[20] In the International Society of Pediatric Oncology (SIOP) WT2001 study after preoperative chemotherapy and nephrectomy, among 586 patients, 28% had 1q gain. The 5-year EFS was 75% and 88% ($P < .001$) and OS was 88% and 94% ($P = .01$), with and without 1q gain, respectively. Other molecular aberrations associated with poorer outcomes included *MYCN* gain and *TP53* loss.[21]

PATHOLOGIC CLASSIFICATION

The first acceptable pathologic classification was reported by Beckwith and Palmer from the NWTS-1.[22] The NWTS classifies all tumors as having either FH or unfavorable histology (UH). The UH tumors include anaplastic tumors, clear cell sarcoma of the kidney (CCSK), and rhabdoid tumor of the kidney (RTK). Of 1,465 patients randomly assigned on NWTS-3, 163 (11.1%) had UH.[23] WTs are usually sharply demarcated, spherical masses with a "pushing" border and a surrounding distinct intrarenal pseudocapsule. Histologically, WT reflects the development of the normal kidney, consisting of three components, blastemal, epithelial (tubules), and stromal elements, in varying proportions.[22] The proportion of the different components has prognostic significance.[24] Nephrogenic rests consist of embryonal nephroblastic tissue and are found in 35% of kidneys with unilateral WT and in nearly 100% of kidneys with bilateral WT (BWT).[25] Nephrogenic rests may be intralobar or perilobar based on their location within the kidney.[26] Most nephrogenic rests undergo spontaneous regression, and only a small proportion (1%-5%) transform into WT.[27] The histologic feature of greatest clinical significance in WT is anaplasia.[28] Anaplasia may be focal (FA) or diffuse (DA). The definitions of FA and DA have been revised to reflect the distribution of anaplastic cells in the tumor rather than their quantitative density. These revised definitions are of prognostic significance. The 4-year survival rates for patients with stage II, III, and IV FA were 90%, 100%, and 100%, compared with 55%, 45%, and 4%, respectively, for patients with similar stage DAWT.[29]

CCSK and malignant RTK are no longer considered true WT, but they have been included in NWTS protocols.[22] CCSK has a propensity to metastasize to bone and lymph nodes (LNs), and a skeletal survey and bone

scan should be performed. RTK is commonly seen in very young children and is the most lethal renal neoplasm in children. Primitive neuroepithelial tumors of the cerebellum or pineal region may be seen in 10% to 15% of patients with RTK.[30]

CLINICAL PRESENTATION

The classic presentation for WT is that of a healthy child in whom abdominal swelling is discovered by the child's parent or by a physician during a routine physical examination. A smooth, firm, nontender mass on one side of the abdomen is felt. Gross hematuria occurs in as many as 25% of these cases.[31] The child may be hypertensive or have nonspecific symptoms, such as malaise or fever.[32] Only rarely does a patient present with symptomatic metastases.

DIAGNOSTIC WORKUP

The differential diagnosis of WT includes other malignant childhood lesions of the kidney, neuroblastoma, and benign conditions, such as hydronephrosis, polycystic disease, and splenomegaly in left-sided tumors. Plain films of the abdomen may demonstrate calcifications, which occur in 60% to 70% of neuroblastomas but in only 5% to 10% of WT. Excretory urography (intravenous pyelography) was once the mainstay of imaging in WT and now has largely been replaced by ultrasonography and computed tomography (CT) scanning. Ultrasonography is very useful because it is readily available and is cost-effective.[33] A specific advantage of ultrasonography is its ability to assess vessels for flow and tumor thrombus with duplex and color Doppler.[34] Routine use of Doppler sonography after abdominal CT scans was not found to be useful in detecting cavoatrial thrombus in a COG study.[35] Abdominal CT scans can demonstrate gross extrarenal spread, LN involvement, liver metastases, and the status of the opposite kidney (Figure 91.1).[36] Magnetic resonance imaging (MRI) has several advantages over CT scans, especially in identifying renal origin and vascular extension of the tumor.[37] CT and MRI are useful in the detection and follow-up of patients with nephrogenic rests.[38] Clinical and imaging impressions do not, however, obviate the need for inspection at laparotomy.[39] Chest CT scans are also essential because asymptomatic

pulmonary metastases are common.[40] A complete blood cell count and urinalysis should be performed. Patients with WT can be anemic from hematuria. Serum blood urea nitrogen and creatinine levels and liver function tests are routine. If neuroblastoma is not ruled out, a test for urinary catecholamines should be performed. Table 91.1 outlines the pretreatment investigations recommended by the COG.

TABLE 91.1 PRETREATMENT WORKUP

History	Record preexisting conditions, family history of cancer, or congenital defects
Physical examination	Blood pressure, weight, height, presence of abdominal masses, congenital anomalies particularly genitourinary, hemihypertrophy, and aniridia
Laboratory	Hemoglobin, white cell, differential counts, platelets, urinalysis, serum blood urea nitrogen, creatinine, protein, alanine, aspartate aminotransferases, alkaline phosphatase, bilirubin
Radiology	CT or MRI scan of the abdomen and pelvis, abdominal ultrasonography, chest CT scan Bone scan and MRI of the brain (CCSK, RTK, and renal cell carcinoma)

CCSK, clear cell sarcoma of the kidney; CT, computed tomography; MRI, magnetic resonance imaging; RTK, rhabdoid tumor of the kidney.

FIGURE 91.1 Computed tomography scan of a 4-year-old girl with a large right-sided Wilms tumor measuring 10.5 cm × 8.4 cm × 13.5 cm. The left kidney did not show any lesions. At laparotomy, the tumor was found to invade the diaphragm. She underwent a right radical nephrectomy. Surgical margins of resection were positive, and she had metastases in the para-aortic lymph nodes. The tumor was classified as stage III favorable histology and received 10.8 Gy to the right flank and chemotherapy with vincristine, dactinomycin, and doxorubicin.

NATURAL HISTORY

The disease is often localized at diagnosis, as evidenced by the fact that surgery and radiation therapy (RT) are curative in almost 50% of cases.[41] The first signs of local tumor spread beyond the pseudocapsule are invasion into the renal sinus or the intrarenal blood and lymphatic vessels. Spread throughout the peritoneal cavity may also occur, especially if there has been preoperative rupture or the disease has been spilled at surgery.[42,43] The most common sites of metastases of WT are in the lungs, LNs, and liver. Among patients with stage IV disease, lungs were the only metastatic site in

approximately 80% and 15% had liver metastases.[44] The NWTS and COG studies have clearly demonstrated the prognostic importance of LN involvement. Among children with stage III FHWT in AREN0532, those with LN-positive disease and either LOH at 1p or 16q had worse EFS compared to LN-negative disease, regardless of LOH status and node positive with no LOH at 1p or 16q.[45,46]

STAGING

Tumor staging is performed after examining the radiologic, operative, and histopathologic findings.[43,44] In NWTS-1 and NWTS-2, a tumor grouping system was used for staging and treatment stratification. After analyzing the prognostic significance of several clinical-pathologic factors in NWTS-1 and NWTS-2, a new staging system was adopted in NWTS-3. The presence of LN involvement was upstaged to stage III instead of group II, and local tumor spill was downstaged from group III to stage II.[43] In NWTS-5, the most significant change was the distinction between stages I and II. The criteria for stage I were revised to accommodate an important subset of WT that is being managed by nephrectomy alone. Before NWTS-5, the distinction between stages I and II in the renal sinus was established by the hilar plane that was difficult to apply due to tumor distortion, and thus, the hilar plane criterion has been replaced with renal sinus vascular or lymphatic invasion. This definition includes not only the involvement of vessels within the hilar soft tissue but also the vessels located in the radial extensions of the renal sinus into the renal parenchyma.[45,47] The COG staging guidelines for WT are shown in Table 91.2. The major change from NWTS-5 is that children with tumor spillage are upstaged from stage II to stage III because of the higher risk for relapse with two-drug chemotherapy alone.[48] The COG risk group classification for treatment assignment in the first generation of WT protocols is shown in Table 91.3. In addition to tumor stage, this classification will also consider the patient's age, tumor weight, presence or absence of LOH at 1p and 16q, and response to chemotherapy in children with FH tumors and lung metastases.

TABLE 91.2 CHILDREN'S ONCOLOGY GROUP STAGING OF WILMS TUMOR, RHABDOID TUMOR, AND CLEAR CELL SARCOMA OF THE KIDNEY

Stage I	Tumor limited to the kidney, completely resected. The renal capsule is intact. The tumor was not ruptured or biopsied prior to removal. The vessels of the renal sinus are not involved. There is no evidence of tumor at or beyond the margins of resection. *Note*: For a tumor to qualify for certain therapeutic protocols as stage I, regional lymph nodes must be examined microscopically.
Stage II	The tumor is completely resected, and there is no evidence of tumor at or beyond the margins of resection. The tumor extends beyond the kidney, as is evidenced by any one of the following criteria[a]: • There is regional extension of the tumor (ie, penetration of the renal capsule or extensive invasion of the soft tissue of the renal sinus). • Blood vessels within the nephrectomy specimen outside the renal parenchyma, including those of the renal sinus, contain tumor.
Stage III	Residual nonhematogenous tumor present following surgery and confined to the abdomen. Any one of the following may occur: • Lymph nodes within the abdomen or pelvis are involved by tumor (lymph node involvement in the thorax or other extra-abdominal sites is a criterion for stage IV). • The tumor has penetrated through the peritoneal surface. • Tumor implants are found on the peritoneal surface. • Gross or microscopic tumor remains postoperatively (eg, tumor cells are found at the margin of surgical resection on microscopic examination). • The tumor is not completely resectable because of local infiltration into vital structures. • Tumor spillage occurring either before or during surgery. • The tumor was biopsied (whether Tru-Cut, open, or fine-needle aspiration) before removal. • Tumor is removed in more than one piece (eg, tumor cells are found in a separately excised adrenal gland; a tumor thrombus within the renal vein is removed separately from the nephrectomy specimen).
Stage IV	Hematogenous metastases (ie, lung, liver, bone, brain) or lymph node metastases outside the abdominal-pelvic region are present (the presence of tumor within the adrenal gland is not interpreted as metastasis and staging depend on all other staging parameters present).
Stage V	Bilateral renal involvement by tumor is present at diagnosis. An attempt should be made to stage each side according to the criteria here on the basis of the extent of disease.

[a]Rupture or spillage confined to the flank, including biopsy of the tumor, is no longer included in stage II and is now included in stage III.

TABLE 91.3 CHILDREN'S ONCOLOGY GROUP RISK GROUP CLASSIFICATION FOR FAVORABLE HISTOLOGY WILMS TUMORS

Age	Tumor Weight	Stage	LOH	Rapid Response	Risk Group	COG Study	Treatment
<2 y	<550 g	I	Any	NA	Very low	AREN0532	Surgery only
Any	≥550 g	I	None	NA	Low	AREN0532	EE4A
≥2 y	Any	I	None	NA	Low	AREN0532	EE4A
Any	Any	II	None	NA	Low	AREN0532	EE4A
≥2 y	Any	I	Yes	NA	Standard	AREN0532	DD4A
Any	≥550 g	I	Yes	NA	Standard	AREN0532	DD4A
Any	Any	II	Yes	NA	Standard	AREN0532	DD4A
Any	Any	III	None	Any	Standard	AREN0532	DD4A
Any	Any	III	Yes	Any	Higher	AREN0533	M
Any	Any	IV	Yes	Any	Higher	AREN0533	M
Any	Any	IV	None	Yes	Standard	AREN0533	DD4A
Any	Any	IV	None	No	Higher	AREN0533	M

DD4A, V (vincristine), A (dactinomycin), D (doxorubicin); EE4A, VA; LOH, loss of heterozygosity at both 1p and 16q; M, VAD/Cy (cyclophosphamide), E (etoposide); NA, not applicable.

GENERAL MANAGEMENT

The diagnosis of WT is usually made before surgery and confirmed at surgery. A generous transabdominal or thoracoabdominal incision is recommended for adequate exposure. Flank or retroperitoneal approaches are strongly discouraged due to an increased rate of rupture and the inability to adequately assess the peritoneal cavity for intraperitoneal spread. Complete exploration of the abdomen should be performed. A radical nephrectomy is performed with the ureter divided as distally as possible.[49] The surgeon must excise all tumors without spillage, if possible. The presence of positive LNs is a significant prognostic factor. For the current study (AREN2231), the presence of a positive LN will affect the treatment stratum for which the patient may be eligible. Surgical sampling of LNs in the renal hilum, aortocaval window, and along the vena cava (for right-sided tumors) or aorta (for left-sided tumors) is critical for adequate staging (Figure 91.1). Even in children with stage IV disease, local staging is vital

because it will determine the need for local RT. For example, while a child with lung metastases may require pulmonary radiation, if the primary tumor is stage I or II, flank radiation could be avoided. Similarly, in cases where there is preoperative tumor rupture or intraoperative tumor spill, the local stage may be set, but the LN status will affect the protocol treatment stratum; thus, ALL cases require surgical LN sampling and pathologic confirmation.

The chemotherapy and RT regimens for WT in the first generation of COG protocols are outlined in Tables 91.4 and 91.5.

TABLE 91.4 OUTLINE OF CHILDREN'S ONCOLOGY GROUP RENAL TUMOR STUDY

Tumor Risk Classification	Multimodality Treatment
Very Low-Risk FH Wilms Tumor	
<2 y, stage I, tumor weight <550 g	Nephrectomy without adjuvant therapy, if node sampling and central pathology review have been performed
Low-Risk FH Wilms Tumor	
≥2 y, stage I, tumor weight ≥550 g, stage II without LOH	Nephrectomy, no RT, regimen EE4A
Standard-Risk FH Wilms Tumor	
Stage I and II with LOH	Nephrectomy, no RT, regimen DD4A
Stage III without LOH	Nephrectomy, RT, regimen DD4A
Stage IV FH: rapid responders of lung metastases at week 6 with regimen DD4A, without LOH	Nephrectomy, RT, regimen DD4A; no WLI
Higher-Risk FH Wilms Tumor	
Stage III with LOH	Nephrectomy, RT, regimen M
Stage IV slow responders (lung) and nonpulmonary metastases, with LOH	Nephrectomy, RT, regimen M, WLI and RT to metastases
High-Risk UH Renal Tumors	
Stage I-IV focal anaplasia	Nephrectomy, RT, regimen DD4A
Stage I diffuse anaplasia	Nephrectomy, RT, regimen DD4A
Stage I-III CCSK	Nephrectomy, RT, regimen I

Tumor Risk Classification	Multimodality Treatment
Stage II-IV diffuse anaplasia	Nephrectomy, RT, regimen UH1, RT to all metastatic sites
Stage IV CCSK	Nephrectomy, RT, regimen UH1, RT to all metastatic sites
Stage I-IV RTK	Nephrectomy, RT, regimen UH1, RT to all metastatic sites

CCSK, clear cell sarcoma of the kidney; FH, favorable histology; LOH, loss of heterozygosity at 1p and 16q; regimen DD4A, V (vincristine), A (dactinomycin), D (doxorubicin); regimen EE4A, VA; regimen I, alternating VDCy/CyE; regimen M, VAD/Cy (cyclophosphamide), E (etoposide); regimen UH1, alternating VDCy/CyC (carboplatin) E; RT, flank or abdominal irradiation; RTK, rhabdoid tumor of the kidney; UH, unfavorable histology; WLI, whole-lung irradiation.

TABLE 91.5 CHILDREN'S ONCOLOGY GROUP RENAL TUMOR PROTOCOL RADIATION THERAPY GUIDELINES

Abdominal Tumor Stage and Histology	RT Dose/RT Field[a]
Stage I and II FH Wilms tumor	None
Stage III FH, stage I-III focal anaplasia	10.8 Gy to the flank[b]
Stage I-II DA, stage I-III CCSK[c]	10.8 Gy to the flank[b]
Stage III DA, stage I-III RTK	19.8 Gy flank[b] RT, infants ≤12 mo 10.8 Gy
Recurrent abdominal Wilms tumor	12.6-18 Gy (<12 mo)[b]
	21.6 Gy (older children, previous RT ≤ 10.8 Gy)
	Boost dose of 9 Gy to gross residual tumor
Lung metastases (favorable histology)	12 Gy WLI in eight fractions[d]
Lung metastases (unfavorable histology)	12 Gy WLI in eight fractions
Brain metastases	30.6 Gy whole brain in 17 fractions
	21.6 Gy whole brain + 10.8 Gy IMRT or stereotactic boost
Liver metastases	19.8 Gy whole liver in 11 fractions
Bone metastases	25.2 Gy to the lesion plus 3-cm margin

Abdominal Tumor Stage and Histology	RT Dose/RT Field[a]
Unresected lymph node metastases	19.8 Gy

CCSK, clear cell sarcoma of the kidney; DA, diffuse anaplasia; FH, favorable histology; IMRT, intensity-modulated RT; RT, radiation therapy; RTK, rhabdoid tumor of the kidney; WLI, whole-lung irradiation.

[a]Timing of RT (RT delay): RT should begin as close to the beginning of chemotherapy as possible, preferably by day 9 (surgery is day 0), but no later than day 14, unless medically contraindicated or when there is a delay in central pathology review.

[b]Whole-abdomen irradiation (WAI) is indicated when there is diffuse tumor spillage, preoperative or intraperitoneal tumor rupture, peritoneal tumor seeding, or hemorrhagic or cytology-positive ascites. When WAI dose is >10 Gy, renal shielding is required to limit the dose to the remaining kidney to <14.4 Gy. Gross residual disease after surgery should receive a boost of 10 Gy. WAI dose is not to exceed 10 Gy in infants ≤12 months.

[c]COG protocol (AREN0321) is studying the possibility of eliminating RT in children with stage I CCSK tumors who have lymph node sampling and central pathology review.

[d]COG protocol (AREN0533) is studying the possibility of eliminating WLI in children with lung metastases who are rapid responders (complete response of lung metastasis after three-drug chemotherapy on central review of computed tomography [CT] scans at week 6). Tumor size, number of lesions, and CT or x-ray detectability are not considered indications for WLI in FH tumors.

RADIATION THERAPY TECHNIQUES

RT guidelines used for primary and recurrent WT in the COG protocols are shown in Table 91.5.

Timing of Radiation Therapy

The NWTS has shown that although RT does not need to be given immediately after surgery,[41] a delay of ≥10 days after surgery was associated with a significantly higher abdominal relapse rate, particularly among patients with UH tumors.[50-53] The influence of RT delay on abdominal tumor recurrence in patients with FH tumors treated on NWTS-3 and NWTS-4 has been reported. The mean RT delay was 10.9 days. Although univariate and multivariate analyses did not reveal RT delay of ≥10 days to adversely influence flank and abdominal recurrence, it is important to note that in 59% of children, the RT delay ranged from 8 to 12 days.[54] For the first generation of COG protocols, it was recommended that RT be given preferably by day 9 but no later than day 14 after surgery. In

the second generation of COG trials, flank/abdomen RT will be delayed until week 6 for stage IV patients with lung metastases so that both sites can be treated simultaneously if indicated, in order to avoid higher radiation doses to organs such as heart, lungs, and liver at overlapping field edges. SIOP recommends starting RT in nonmetastatic patients within 2 to 4 weeks after abdominal surgery. In non–high-risk patients with local stage III, metastatic disease, delayed RT can be considered to avoid overlapping fields.[55]

Radiation Therapy Dose

In NWTS-1 and NWTS-2, RT dosages to the operative bed were given according to the age of the patient; however, no significant dose-response association was detected.[50,51,53] In NWTS-3, there was a randomization for patients with FH tumors that resulted in elimination of RT for stage II FH and a reduction of dose from 20 to 10 Gy for stage III patients.[52] NWTS-3 and NWTS-4 data showed no RT dose response for CCSK and anaplastic tumors.[56] Therefore, it was decided to treat all abdominal disease (FH and UH) with 10 Gy in NWTS-5. In the COG protocols, the dose is 10 Gy for most indications, except for stage III DA and stage I to III RTK, where a higher dose of 19.8 Gy is recommended (Table 91.5).[57,58]

Radiation Therapy Volume

For flank and abdomen RT fields, parallel-opposed fields using 4- or 6-MV photons are preferred. The flank RT field is determined by the CT or MRI scan performed at diagnosis before any chemotherapy is administered. The planning target volume (PTV) is the tumor bed (outline of the kidney and associated tumor on the initial CT or MRI) with a 1-cm margin. The medial border must cross the midline to include the entire width of the vertebrae so as to minimize growth disturbances. An example of a flank RT portal is shown in Figure 91.2. In the UMBRELLA Renal Tumor Study Group of the International Society of Pediatric Oncology (SIOP-RTSG) protocol, for flank RT, investigators will explore the feasibility of target volume reduction to include only the posterior abdominal wall in contact with the preoperative tumor and the para-aortic nodes, while excluding noninfiltrated anterior organs, using intensity-modulated radiation therapy

(IMRT) with central quality assurance (QA) preapproval.[59] When whole-abdomen RT is administered, the femoral heads and acetabulum must be shielded (Figure 91.3). Whole-lung irradiation (WLI) anteroposterior-posteroanterior (AP-PA) portals are shown in Figure 91.4. If the lungs and either the flank or the whole abdomen have to be treated simultaneously, it is preferable to include them in one treatment portal.

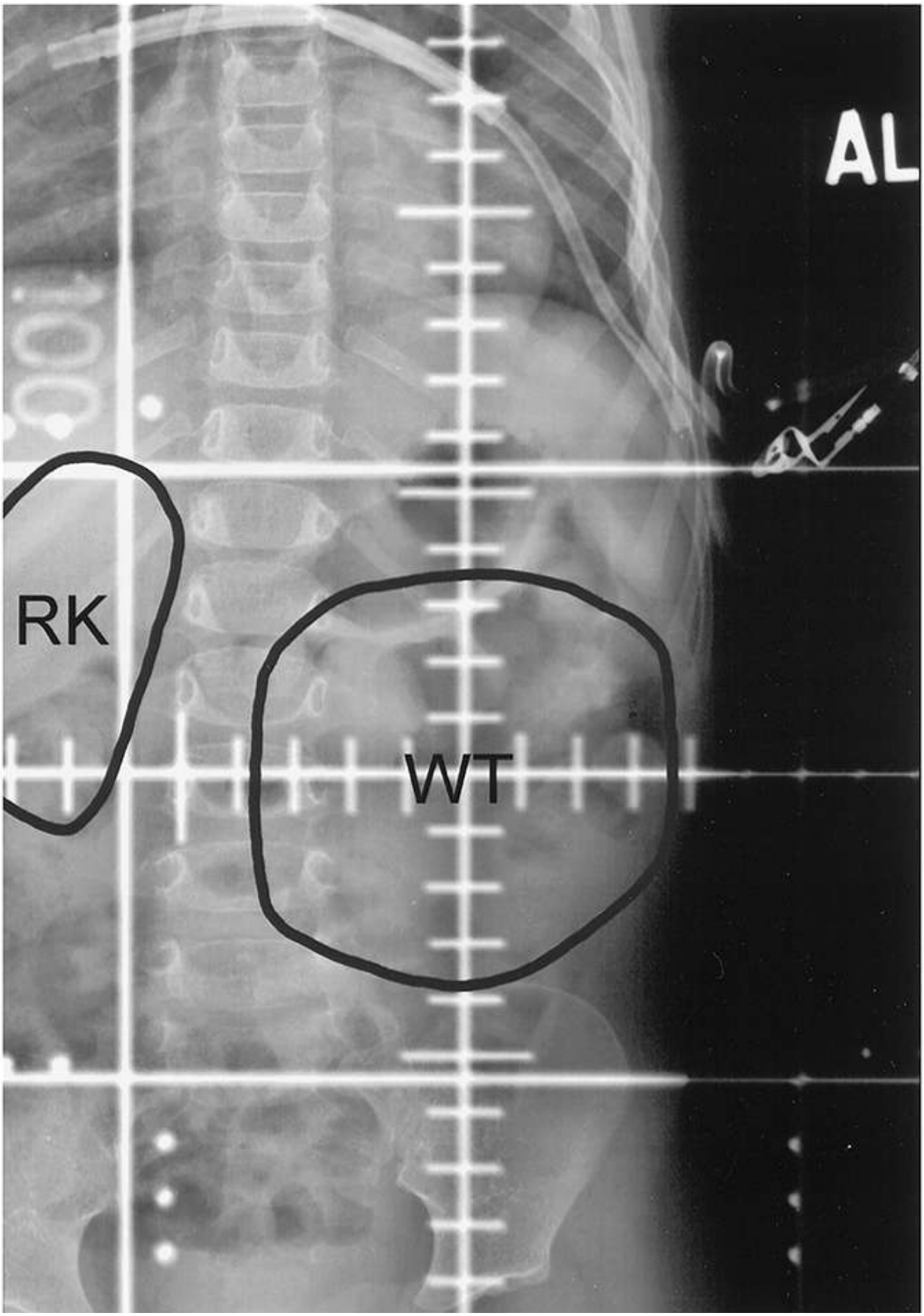
AL
RK
WT

FIGURE 91.2 Anteroposterior flank irradiation portal in a 2-year-old child with a left-sided stage III favorable histology Wilms tumor (WT) showing inclusion of the entire width of the vertebral body in the irradiated volume. The outline of the right kidney and the WT from the preoperative computed tomography scan is shown.

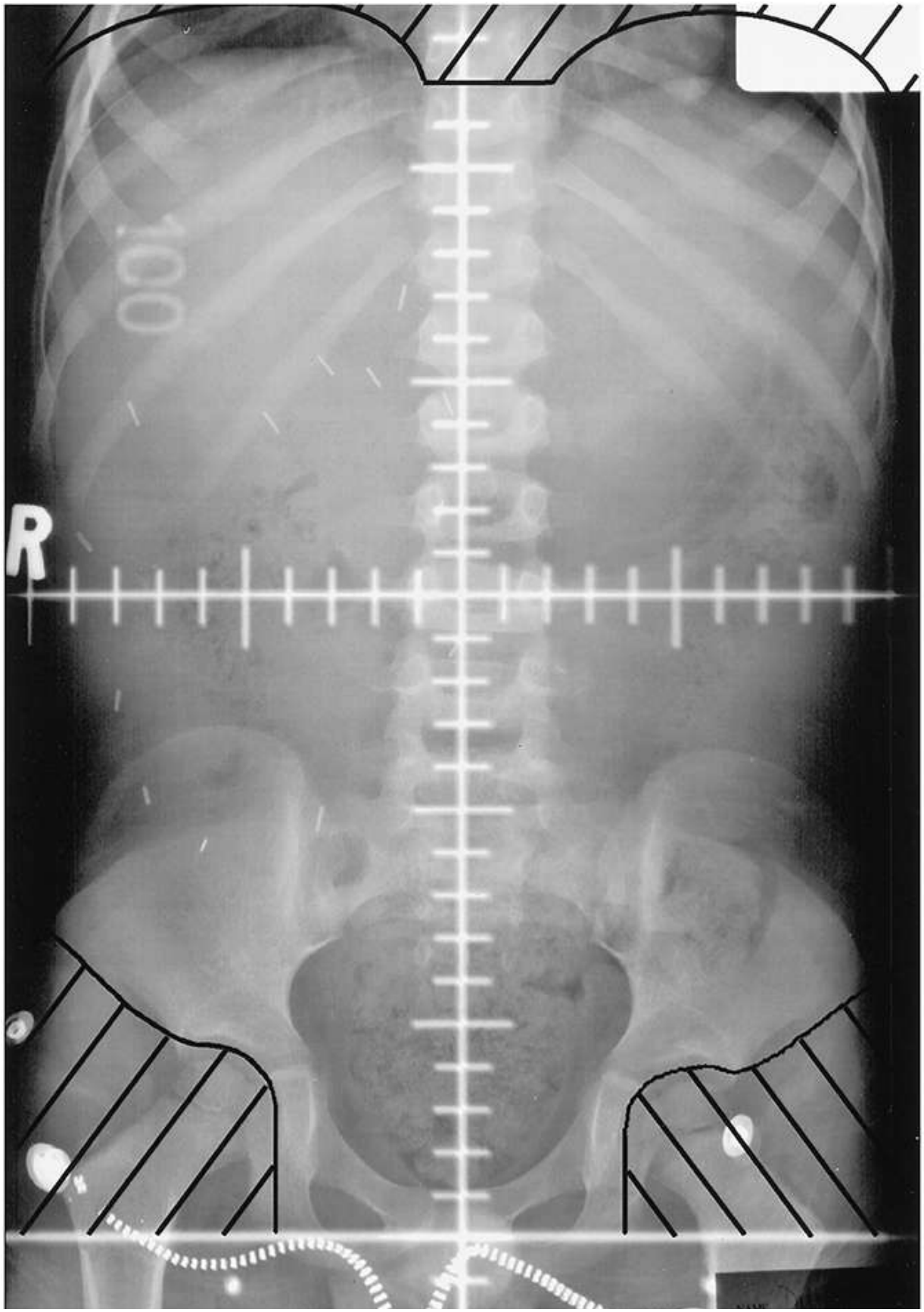
100
R

FIGURE 91.3 Anteroposterior whole-abdomen irradiation portal in a patient with stage III Wilms tumor and diffuse peritoneal tumor spillage. The upper margin of the abdominal field must include the diaphragm. The acetabulum and femoral head should be excluded from the irradiated volume to decrease the probability of slipped femoral capital epiphysis. The pants zipper can be seen low on the hips. In general, it is advisable to remove the trousers completely to ensure a reproducible setup.

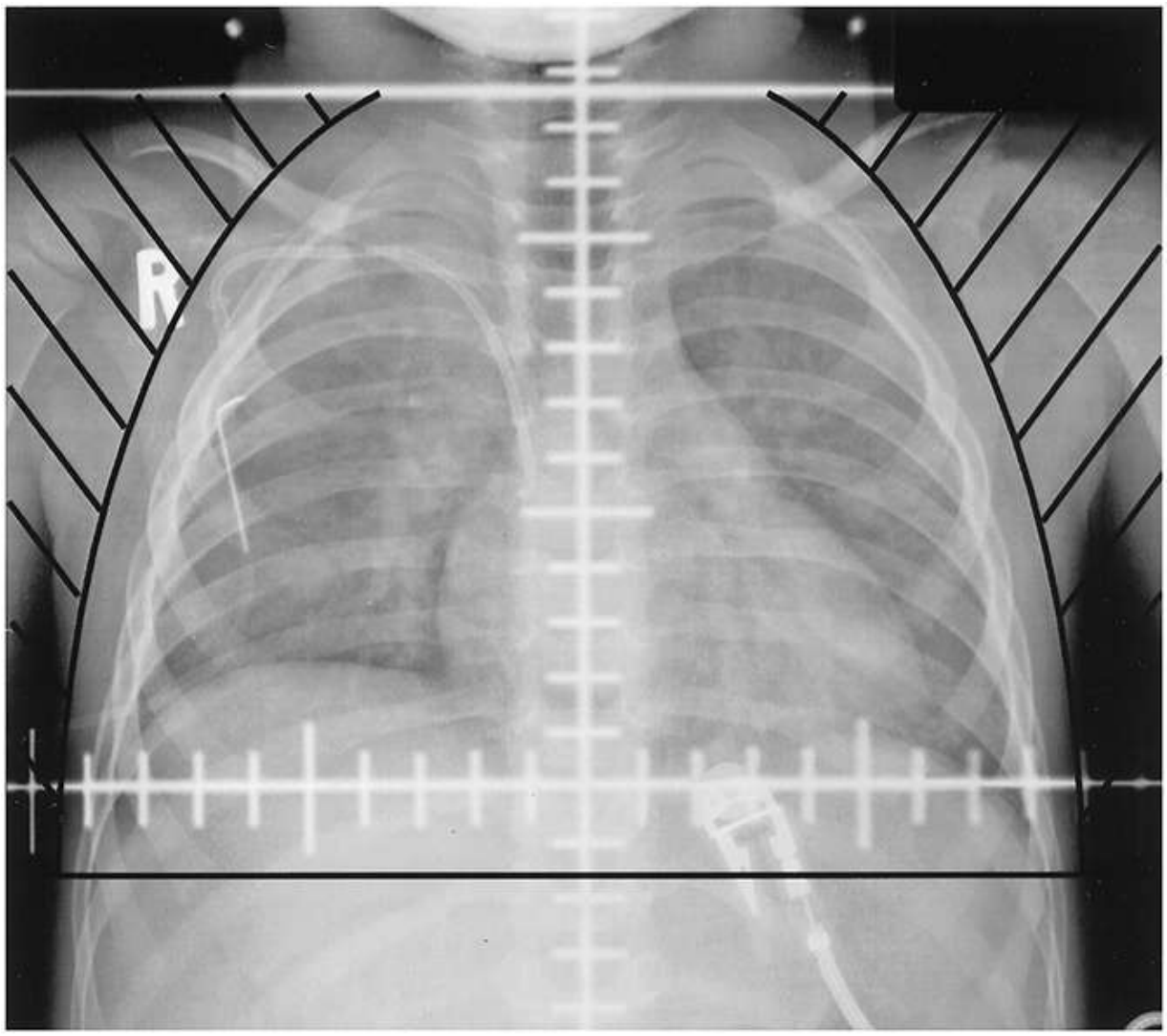

FIGURE 91.4 Anteroposterior whole-lung irradiation portal in a patient with stage IV favorable histology Wilms tumor. The axial, coronal, and sagittal chest computed tomography simulation scans should be carefully reviewed to ascertain inclusion of the anterior and posterior costophrenic angles at the inferior edge of the treatment volume with a 1-cm margin.

Intensity-Modulated Radiation Therapy for Lung and Liver Irradiation

A multi-institutional prospective clinical trial was conducted to determine the feasibility of cardiac-sparing lung IMRT. All centers were credentialed. The IMRT PTV was the four- dimensional (4D) minimum intensity projection total lung volume plus 1 cm. All target volumes, cardiac contours, and treatment plans were centrally reviewed Quality Assurance Review Center (QARC) for preapproval prior to treatment. Twenty patients were accrued. The majority had pediatric sarcomas or WTs. Lung IMRT was feasible in all patients. The median RT dose was 15 Gy (12-15 Gy). Pretreatment review resulted in target contour changes in seven, replanning in three, and minor dose deviations in two patients. There were no major deviations. The mean cardiac (whole heart, ventricles, atria, coronary arteries, myocardium) volume doses were significantly lower after IMRT compared to AP-PA techniques. The 4D lung volumes were significantly larger than 3D volumes ($P < .0001$), and thus, standard AP-PA RT would have significantly underdosed 4D lung volumes ($P = .008$). IMRT was well tolerated. No patient had radiation pneumonitis, pulmonary consolidation, or fibrosis after a minimum 2-year follow-up. The 2- and 3-year OS was 90% and 90% and lung metastasis progression-free survival was 65% and 52%, respectively. This trial demonstrated the feasibility, dosimetric advantages, safety, and efficacy of lung IMRT with chemotherapy.[60,61] The dosimetric advantages of whole-liver IMRT compared to AP-PA techniques have also been reported (Figure 91.5).[62] In all second-generation COG WT protocols (AREN1921 and AREN223), IMRT targeting 4D lung and liver volumes with Imaging and Radiation Oncology Core (IROC) central preapproval will be utilized for all stage IV patients with lung and liver metastases.

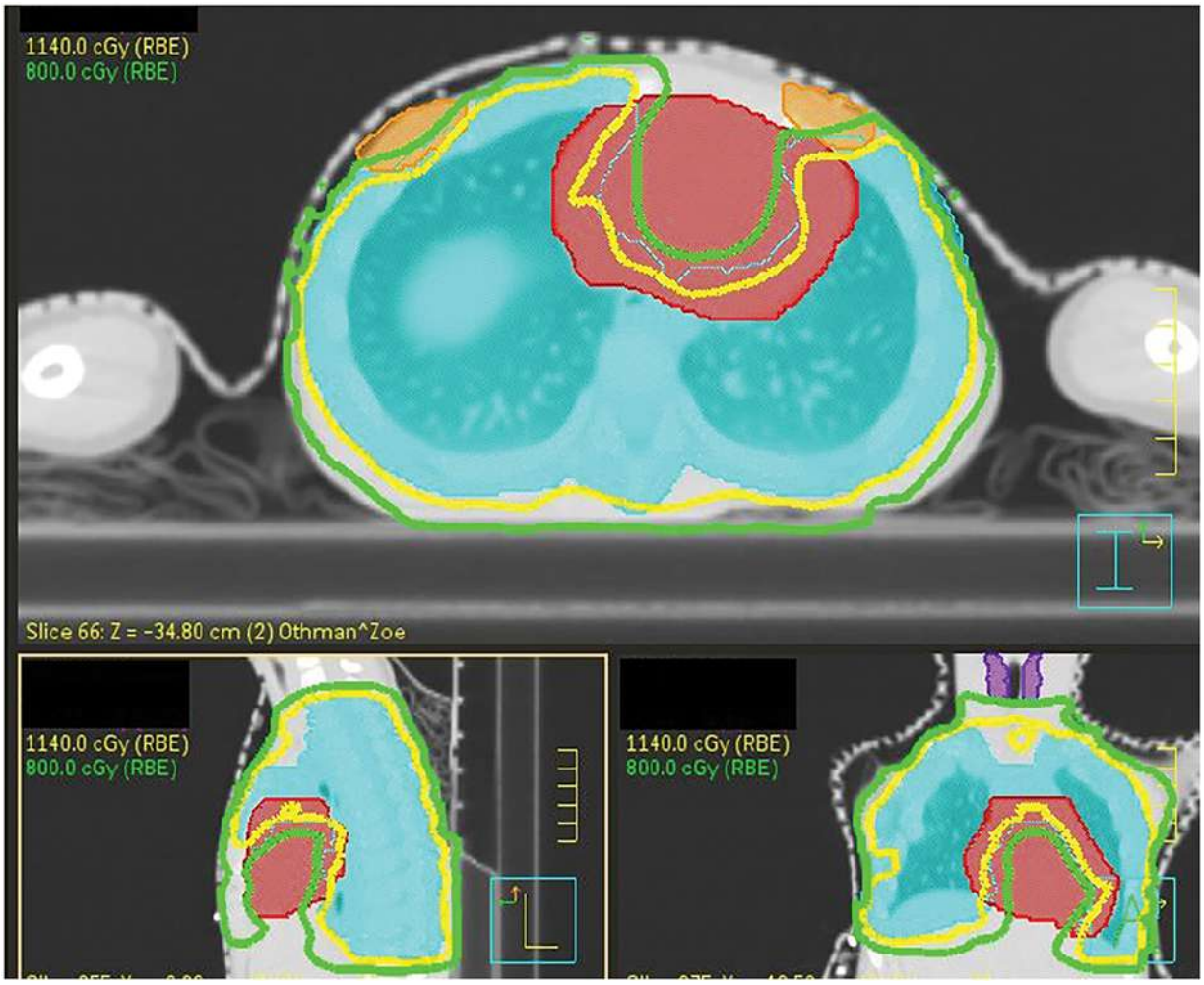

FIGURE 91.5 Cardiac-sparing whole lung intensity-modulated radiation therapy plan (12 Gy in eight fractions) showing the 11.4 Gy (yellow) and 8 Gy (green) on computed tomography images of the whole lung planning target volume (blue), heart (red), breast bud planning risk volumes (brown), and thyroid gland (purple). Axial, sagittal, and coronal images showing adequate dose coverage of planning target volume (95%, 11.4 Gy) and sparing of the heart, breast, and thyroid gland.

SUMMARY OF CLINICAL TRIALS

No tumor has been studied by clinical trials as thoroughly and effectively as WT. The NWTS conducted all WT trials in North America from 1969 to 2001. There have also been successful studies run by the SIOP. The long-term results of NWTS-3 and NWTS-4 are shown in Table 91.6.

TABLE 91.6 LONG-TERM RESULTS OF NATIONAL WILMS TUMOR STUDIES 3 AND 4

Category	Number of Patients	10-Year RFS (%)	10-Year OS (%)
Stage I FH	1,582	91.4	96.6
Stage II FH	1,006	85.5	93.4
Stage III FH	1,038	84.2	89.5
Stage IV FH	592	75.2	80.7
Stage V FH	344	65.1	77.9
All FH	4,562	84.4	90.8
Clear cell sarcoma	170	67.1	77.1
Stage II-III anaplasia	128	43.0	49.2
Stage IV anaplasia	55	18.2	18.2
Rhabdoid tumor	88	27.3	28.4

FH, favorable histology; OS, overall survival; RFS, relapse-free survival.
National Wilms Tumor Study unpublished data.

First National Wilms Tumor Study (1969-1974)

NWTS-1 showed that postoperative RT was not necessary for children younger than 2 years of age with group I tumors and that combined dactinomycin and vincristine for irradiated patients with group II and III tumors was better than therapy with either agent alone. The relapse-free survival (RFS) with and without RT among patients with group I tumors younger than 2 years of age was 90% and 88%, respectively.[50]

Second National Wilms Tumor Study (1974-1979)

NWTS-2 showed that in patients with group I tumors, there was no survival difference between 6 and 15 months of dactinomycin plus vincristine. Patients with group II to IV tumors had a superior 2-year RFS of 77% with doxorubicin, dactinomycin, and vincristine compared with 63% with dactinomycin and vincristine alone.[51]

Third National Wilms Tumor Study (1979-1985)

The overall objective of NWTS-3 was to reduce therapy for low-risk patients (stage I-III FH) and to intensify treatment by adding a fourth drug,

cyclophosphamide, for stage IV tumors with FH and all UH tumors. The results of this study demonstrated that RT and doxorubicin could be eliminated in children with stage II FH tumors. Patients with stage III FH tumors who received doxorubicin or 20 Gy had fewer abdominal relapses than those receiving 10 Gy without doxorubicin. This study provided the basis for the safe reduction of RT dose from 20 to 10 Gy in stage III FH. The addition of cyclophosphamide in high-risk patients did not improve outcomes.[52]

Fourth National Wilms Tumor Study (1986-1994)

By the conclusion of NWTS-3, it was clear that the treatment of WT had been refined for the majority of patients; 62% of patients with WT have stage I or II FH disease and, therefore, require neither flank RT nor the potentially cardiotoxic doxorubicin. NWTS-4 was designed with cost containment in mind. The results proved that the survival was similar among patients who received standard course (5 days) or single-dose, pulse-intensive (PI) dactinomycin chemotherapy. Further, PI therapy was associated with less hematologic toxicity and marked reduction of treatment costs.[63,64]

Fifth National Wilms Tumor Study (1995-2001)

One of the major goals of the NWTS-5 trial was to prospectively analyze the prognostic significance of LOH at chromosomes 1p and 16q. These results have been discussed above.[13] Patients with stage I FH and anaplastic histology and stage II FH tumors were treated with 18 weeks of dactinomycin and vincristine without RT. Stage I FH tumors in children younger than 24 months of age and with tumor weight <550 g were treated with surgery alone without chemotherapy. This treatment arm was stopped early because the number of relapses observed exceeded the predefined stopping rule. However, nearly all patients with relapse were successfully treated, leading to 5-year EFS and OS rates of 84% and 98%, respectively.[65] Stage III and IV FH and stage II to IV focal anaplastic tumors were treated with 24 weeks of dactinomycin, vincristine, doxorubicin, and irradiation. Stage II to IV diffuse anaplastic tumors and stage I to IV CCSK were treated with cyclophosphamide, vincristine, doxorubicin, and etoposide

along with irradiation.[57] Stage I to IV RTK was treated with carboplatin, etoposide, cyclophosphamide, and irradiation.[58] The RT guidelines in NWTS-5 were similar to those used in NWTS-4, except for anaplastic tumors, where a dose of 10.8 Gy to the flank and abdomen was recommended compared to an age-adjusted schedule used in NWTS-1 to NWTS-4.[57]

National Wilms Tumor Study-5 Relapsed Wilms Tumor Study

Children with relapsed FHWT have a variable prognosis depending on the site of relapse, the time from initial diagnosis to relapse, and their previous therapy. The favorable prognostic factors include no previous treatment with doxorubicin, relapse more than 12 months after diagnosis, and intra-abdominal relapse in a patient not previously treated with abdominal RT.[66] In NWTS-5 relapse protocol, patients who relapsed after initial treatment with vincristine and dactinomycin only without RT were treated on stratum "B" with regimen "I" chemotherapy, surgery, and RT. The 4-year RFS and OS were 71% and 81% for all patients, 68% and 81% for those who relapsed in the lung only, and 78% and 83% for those who relapsed in the operative bed, respectively.[67] Patients who relapsed after treatment with vincristine, dactinomycin, doxorubicin, and RT were treated on stratum "C" of NWTS-5 protocol, with alternating courses of drug pairs, cyclophosphamide/etoposide and carboplatin/etoposide, surgery, and RT. The 4-year RFS and OS were 42% and 48% for all patients and 49% and 53% for those who relapsed in the lung only, respectively.[68] The COG protocol (Table 91.5) recommends postoperative RT for all children with abdominal relapse because these tumors are generally large and infiltrative and surgical resection with negative margins is unlikely.

Clear Cell Sarcoma of the Kidney

Data from NWTS-1 to NWTS-4 suggested that the addition of doxorubicin to vincristine and dactinomycin improved RFS rates of patients with CCSK.[69] NWTS-3 demonstrated no improvement in outcomes of patients with CCSK with the addition of cyclophosphamide. In NWTS-4, patients with CCSK showed no significant difference in outcome between the standard and PI chemotherapy regimens. However, there was a trend toward

improved RFS with long-duration therapy.[70] An analysis of patients enrolled on NWTS 1-5 with stage I CCSK based on the updated NWTS-5 definition of stage I disease showed that regardless of the treatment regimen, the EFS and OS rates were 100%.[71] NWTS-5 studied regimen I (vincristine, doxorubicin, cyclophosphamide, and etoposide) for patients with CCSK, yielding 5-year EFS of 100%, 88%, 73%, and 29% for stage I, II, III, and IV, respectively.[72] Based on these results, COG study AREN0321 used the same regimen as in NWTS-5 for stages I to III disease, except that RT was omitted for patients with stage I. Patients with stage IV CCSK were treated with cyclophosphamide, carboplatin, and etoposide alternating with vincristine, doxorubicin, and cyclophosphamide, similar to patients with diffuse anaplastic WT (AWT).

Rhabdoid Tumor of the Kidney

Patients with RTK have been treated on NWTS trials with agents such as vincristine, dactinomycin, and doxorubicin with or without cyclophosphamide. The outcomes attained with these agents have been consistently very poor.[58,73,74] To try to improve on these results, NWTS-5 adopted a different treatment strategy consisting of carboplatin and etoposide alternating with cyclophosphamide. Preliminary analysis of patients treated with this regimen revealed an OS of 26%, not an improvement compared with previous studies, and thus the treatment arm was closed.[58] The COG AREN0321 protocol evaluated whether a treatment regimen containing cyclophosphamide, carboplatin, and etoposide alternating with vincristine, doxorubicin, and cyclophosphamide improves the EFS and OS in these patients.

Children's Oncology Group Studies

The COG renal tumor committee is the successor of the NWTS. The COG staging and risk group classification for treatment assignment in the first generation of WT protocols are shown in Tables 91.2 and 91.3. This classification will, in addition to tumor stage, also consider the patient's age, tumor weight, presence or absence of LOH at 1p and 16q, and response to chemotherapy in children with FH tumors and lung metastases. The objectives and results of the first generation of COG protocols are described

below. The COG chemotherapy regimens and RT guidelines are outlined in Tables 91.4 and 91.5, respectively.

AREN03B2 (2006-2023)

The AREN03B2 Renal Tumor Biology and Risk Stratification Protocol opened in 2006 with a primary goal to provide real-time risk stratification to enable appropriate enrollment of patients onto COG renal tumor trials and to build a well- annotated tumor bank to enable basic and translational research.

AREN0321 (2006-2012)

In NWTS-5, the 4-year EFS and OS were 70% and 83%, respectively, for patients with stage I focal or diffuse AWT treated with vincristine and dactinomycin without flank RT.[57] In AREN0321, 18 patients with stage I AWT (8 focal and 10 diffuse) treated with doxorubicin, vincristine, dactinomycin, and RT (10.8 Gy) had a 4-year EFS and OS of 100%.[75] For stage II to IV diffuse AWT in NWTS-3 and NWTS-4, the addition of cyclophosphamide to vincristine, dactinomycin, and doxorubicin (regimen "J") improved the 4-year RFS to 55% compared to 27% for regimen DD-RT.[56] In NWTS-5, further augmentation using a regimen of vincristine, doxorubicin, cyclophosphamide alternating with cyclophosphamide, and etoposide for 24 weeks plus RT (regimen "I") resulted in additional improvement in patient outcomes.[57] However, the survival outcomes were still unsatisfactory, and 46% of the recurrences were local. AREN0321 evaluated an intensive regimen that used carboplatin in addition to the regimen "I" agents (regimen UH-1) for stages II to IV diffuse AWT and with the incorporation of vincristine/irinotecan window upfront in patients with stage IV diffuse AWT with measurable disease (regimen UH-2). The combination of vincristine and irinotecan was well tolerated and highly active, with a response rate of 79% in 14 patients. Patients with stage III DAWT received a higher flank RT dose (19.8 Gy) than NWTS-5. Compared to NWTS-5, this intensified treatment improved RFS (73% compared to 58%) for stage II to IV DAWT. The local relapse rate among patients with local stage III DAWT in AREN0321 was 6.4% compared to 14.8% on NWTS-5. However, this intensive treatment regimen in

AREN0321 was associated with increased toxicity, necessitating modification of the regimen part way through the study to reduce the doxorubicin, cyclophosphamide, and etoposide exposure. Overall, four (6%) patients died of cardiac and pulmonary toxicity.[76]

AREN0532 (2006-2013)

AREN0532 included patients with very low-risk FHWT, stage I/II FHWT with LOH at chromosomes 1p and 16q, and stage III FHWT. AREN0532 showed a 4-year EFS and OS of 89.7% and 100%, respectively, for 116 patients with very low-risk WT (stage I FH, age < 24 months, and tumor weight < 550 g, with LN sampling and no predisposition syndromes) treated with nephrectomy alone, showing excellent outcomes with a high salvage rate for relapses using DD4A and RT.[77] Molecular analysis demonstrated the association of LOH at 11p15 and loss of imprinting at 11p15, which occurs much less commonly than LOH, with an increased risk of relapse.[18] Patients with stage I or II FH tumors with LOH at 1p and 16q treated with regimen DD4A without RT had a 4-year EFS and OS of 87% and 100%, respectively. Patients with stage III FH without LOH at 1p/16q treated with regimen DD4A and RT had a 4-year EFS and OS of 88% and 97%, respectively. Positive or unknown LN status, positive LOH at 1p or 16q, and blastemal predominant histology at delayed nephrectomy were identified as adverse prognostic factors. Patients with both positive LNs and LOH at either 1p or 16q had 4-year EFS of only 73.8%.[78] A report on the prognostic impact of positive LNs and/or LOH of 1p or 16q was assessed in children with stage III FHWT enrolled on AREN0532 and AREN03B2. Lack of LN sampling, LN positivity, and LOH 1p and LOH 16q were associated with worse EFS. Patients positive for both LN and LOH had the worst EFS.[46]

AREN0533 (2007-2013)

AREN0533 included patients with stage IV FHWT and stage III FHWT with LOH at chromosomes 1p and 16q. A subanalysis of the SIOP 93-01 and SIOP-2001 populations found that lung nodule incomplete response (CR) after 6 weeks of chemotherapy was an adverse prognostic indicator.[79] Based on these observations, in AREN0533, patients with isolated lung

metastases defined by the presence of nodules on centrally reviewed CT scans, who achieved lung nodule CR after 6 weeks of DD4A continued the same chemotherapy without lung RT. Patients with lung nodule incomplete response or the presence of LOH 1p/16q received lung RT and switched to regimen M, which added 4 cycles of cyclophosphamide and etoposide in addition to DD4A. The 4-year EFS and OS for patients with isolated lung metastases was 85.4% and 95.6%, respectively, compared with 72.5% and 84.0% for patients on NWTS-5. The CR rate of lung nodule after 6 weeks of DD4A chemotherapy was 46%, and 54% had incomplete response. For patients with incomplete response, the 4-year EFS and OS were 88.5% and 95.4%, respectively, with regimen M and WLI. For those with CR, the 4-year EFS and OS were 79.5% and 96.1%, respectively, with regimen DD4A and no lung RT.[80] Patients with extrapulmonary metastases (EPMs) also received regimen M and RT to all metastatic sites, regardless of chemotherapy response. For these patients, the 4-year EFS and OS were 76% and 89.1%, respectively, compared to the 4-year EFS and OS was 64.9% and 86.5% after DD4A chemotherapy and RT in NWTS-5. Liver metastases remained the most common site of EPM. There was no difference in clinical outcomes between liver and non-liver EPM.[81] AREN0532 and AREN0533 were the first studies to describe the effect of augmentation of therapy for patients with combined LOH at chromosomes 1p and 16q. AREN0532 added doxorubicin to the standard vincristine/dactinomycin for stages I/II FHWT, and AREN0533 added cyclophosphamide and etoposide to the standard DD4A regimen for stage III/IV FHWT. The 4-year EFS and OS for patients with stage I or II FH with LOH 1p/16q were 87.3% and 100% after DD4A and no RT in AREN0532, compared to 68.8% and 91.6%, respectively, in NWTS-5. The 4-year EFS and OS for patients with stage III or IV FH with LOH 1p/16q was 90.2% and 96.1% after regimen M and RT in AREN0533, compared to 61.3% and 86% in NWTS-5.[82]

AREN0534 (2009-2015)

AREN0534 was the first prospective study for patients with bilateral, multicentric, or bilaterally predisposed unilateral WT. The primary aims for BWT were to improve 4-year EFS to 73%; to prevent complete removal of

at least one kidney in 50% of patients by using prenephrectomy chemotherapy with vincristine, dactinomycin, and doxorubicin; and to have at least 75% of children undergo definitive surgical treatment by 12 weeks after initiation of chemotherapy. Postsurgical chemotherapy was based on histology and postsurgical stage according to SIOP and COG staging systems. The 4-year EFS and OS for 189 patients with BWT were 82.1% and 94.9% respectively. A total of 39% of patients were able to undergo bilateral nephron-sparing surgery and 84% underwent definitive surgical treatment by 12 weeks after initiation of chemotherapy.[83] Among seven patients with completely necrotic tumors, the 4-year EFS rate of 100%. Among patients with intermediate-risk pathology, the 4-year EFS and OS rates were 82% and 97% respectively. Fourteen patients with blastemal-type tumors had 4-year EFS and OS rates of 79% and 93% respectively. Eighteen patients with DA had 4-year EFS and OS rates of 61% and 72%, respectively. The 4-year EFS and OS rates of seven patients who had FA were 71% and 100%, respectively.[84] In 34 children with bilaterally predisposed (syndromic features, multicentric tumors) unilateral WT, the aim of this protocol was to facilitate partial nephrectomy in lieu of nephrectomy in 25% by using prenephrectomy chemotherapy with vincristine and dactinomycin. Among the 34 patients evaluable in this stratum, 4-year EFS and OS were 94% and 100%, respectively; prenephrectomy chemotherapy facilitated renal preservation in 65% of patients.[85]

International Society of Pediatric Oncology Trials

SIOP studies have primarily used preoperative therapy with the goals of facilitating surgical removal of the tumor without rupture, allowing for early treatment of micrometastases, and stratifying patients for postoperative therapy based on pathologic tumor response at the time of surgery. The first SIOP trial found that preoperative RT reduced the incidence of tumor spillage but did not increase survival.[86] SIOP-5, reported in 1983, showed that preoperative chemotherapy with vincristine and dactinomycin was as effective as preoperative RT plus dactinomycin in preventing tumor rupture.[87] In SIOP-6, patients with stage I disease were randomly assigned to either 17 or 38 weeks of vincristine and dactinomycin

and showed no difference in survival.[88] In SIOP-9, there was a randomization of the duration of prenephrectomy therapy with vincristine and dactinomycin (4 vs 8 weeks). No advantage was noted for 8 weeks of therapy.[89] SIOP 93-01 further stratified treatment according to the pathologic response to preoperative chemotherapy. The recommended dose of RT in SIOP-9 and SIOP 93-01 was 15 Gy in patients with low- and intermediate-risk stage III disease and 30 Gy in high-risk patients.[74] SIOP 93-01 showed that the amount of postoperative chemotherapy of stage I patients with either intermediate-risk histology or anaplasia could be reduced to four doses of vincristine and one course of dactinomycin with 5-year RFS and OS rates of 87% and 95%, respectively.[90] Among 1,090 patients in SIOP 93-01, 5% had tumor progression during preoperative chemotherapy. These tumors were generally smaller at diagnosis, more often stage III after surgery, and associated with higher grade histology and had poorer outcomes.[91] A pathologic review of stage II tumors in SIOP 93-01 revealed that there was a significantly higher survival among patients who were stage II because of nonviable tumor in the renal sinus or perirenal fat compared to those with viable tumor in these sites (100% vs 91%). It was proposed that the definition of stage II be revised.[92] In a report from SIOP WT2001 trial, after preoperative chemotherapy VA (vincristine, actinomycin D) and surgery, patients with stage II to III intermediate-risk tumors were randomized to receive AVD (actinomycin D, vincristine, doxorubicin) versus AV (actinomycin D and vincristine) without doxorubicin. Stage III patients received 14.4-Gy flank RT and 10-Gy boost to positive LNs or macroscopic residual tumor. The 2-year EFS was 93% and 88%; and the 5-year OS was 97% and 96%, with no statistically significant difference between these two regimens. They concluded that doxorubicin was not required for these patients.[93] In another WT2001 report for blastemal-type WTs after VA chemotherapy and surgery, stage I patients received AVD for 26 weeks, and stage II to III patients received etoposide, carboplatin, doxorubicin, and cyclophosphamide for 26 weeks. Local RT was recommended only for stage III patients. The 5-year EFS and OS were 80% and 88%, respectively, in WT2001 compared to 67% (P = .006) and 84% (P = .4), respectively, in SIOP 93-01 trials.[94] The local control rates for intermediate-risk WT treated with SIOP multimodality regimens were excellent, with <12% overall failure and 1% to 3% local-only recurrence.[55]

LATE EFFECTS OF TREATMENT

The study of late effects is of paramount importance to prevent survivors of childhood cancer from becoming chronically sick adults. The COG long-term follow-up guidelines, version 5.0, provide extensive recommendations for the appropriate surveillance and management of childhood cancer survivors for common RT-induced toxicities observed in WT survivors (http://survivorshipguidelines.org).

Musculoskeletal Effects

Musculoskeletal toxicity may occur from RT in young children, the severity of which depends on the patient's age at treatment, RT dose, fractionation, and RT fields. Growth of normal tissues can be impaired, resulting in reduced spinal growth and sitting height after RT for WT.[95] Scoliosis and kyphosis are other possible complications of WT therapy. At a median follow-up of 12 to 13 years, WT survivors have reported scoliosis in 54% to 67% and kyphosis in 14%, with 10% to 20% experiencing symptoms or requiring intervention.[96,97] A higher scoliosis rate of 88% was observed in one report with a longer median follow-up of 19 years and more complete radiologic follow-up. However, in the vast majority of patients, the scoliosis was mild and asymptomatic.[98] In another report, the incidence of scoliosis after 10 to 12 Gy, 12.1 to 23.9 Gy, and 24 to 40 Gy was 8%, 46%, and 63%, respectively.[99] Thus, at present, with the use of megavoltage x-rays, lower doses, and coverage of the entire width of the vertebra, the incidence of scoliosis should be low.

Congestive Heart Failure

The cumulative frequency of congestive heart failure among patients on NWTS-1 through NWTS-4 was 4.4% at 20 years among patients treated initially with doxorubicin and 17.4% among patients treated with doxorubicin for their first or subsequent relapse. The factors that were significantly associated with the incidence of heart failure were female sex, cumulative doxorubicin dose, standard AP-PA WLI, and left abdominal RT.[100]

Pregnancy Outcomes

The NWTS Long-Term Follow-Up Study analyzed pregnancy outcomes among WT survivors. Malposition of the fetus and premature labor were significantly more frequent among previously irradiated women. The offspring of female patients who received flank RT were more likely to be of low birth weight (<2,500 g), premature (<36 weeks of gestation), and to have congenital malformations. A flank RT dose response was identified with higher complication rates at doses >25 Gy. A number of radiation-induced side effects involving the spine, uterus, and ovaries may all have been responsible.[101-103] The pregnancy outcomes in survivors who received abdominal RT on NWTS protocols were also analyzed. Fertility could be preserved in children with upper abdominal RT that did not include the pelvis. In rare instances, fertility could be preserved after whole-abdominal RT to 10.5 Gy. However, higher doses to the abdomen and pelvis resulted in miscarriages and fetal deaths.[104]

End-Stage Renal Disease

The 20-year cumulative incidence of end-stage renal disease among WT survivors after unilateral nephrectomy on NWTS protocols was 74% for children with Denys-Drash syndrome, 36% for children with WAGR syndrome, 7% for children with genitourinary anomalies, and 0.6% for patients with none of these conditions. Long-term follow-up guidelines emphasize the importance of long-term screening for high-risk children to facilitate early detection and treatment of impaired renal function.[105]

Second Malignant Neoplasm

Among patients with NWTS, the 15-year cumulative risk of second malignant neoplasm (SMN) was 1.6%. The risk of developing a lymphoma or leukemia was 0.4% at 8 years, after which no cases occurred. However, the risk of developing a solid tumor continued to rise sharply with time. The use of RT and doxorubicin has been clearly associated with higher risk of SMNs.[106] In the British Childhood Cancer Survivor Study, the majority of solid tumors (89.7%) of the thorax, abdomen, or pelvis developed within RT fields.[107] In the NWTS report, RT increased the risk of an SMN

(Standardized Incidence Ratio (SIR), 1.43/10 Gy) and doxorubicin potentiated the RT effect. Among 234 patients who received doxorubicin and >35 Gy of abdominal RT, the SIR was 36. The changes in RT doses in NWTS protocols from 40 Gy in the 1960s to 10 Gy in the 1990s was also associated with a decrease in time-specific incidence rates of SMNs.[106] In another NWTS report, the standardized mortality ratio was 24.3 within 5 years of diagnosis, 12.6 for the next 5 years, and >3.0 thereafter. The main cause of mortality within the first 5 years was the original disease (91%). However, beyond 5 years, the two important causes of mortality were the original disease (40%) and late effects of treatment (39%). The three common treatment- related late effects that contributed to mortality were SMNs, congestive heart failure, and end-stage renal disease. The risk of death, particularly from treatment-related late effects, remained elevated even 20 years after diagnosis.[108] Similar results have been shown recently by the Childhood Cancer Survivor Study after a follow- up of 25 years.[109] In the British Cancer Survivor Study, the cumulative incidence of a second primary neoplasm at 30, 40, and 50 years of age was 2%, 7%, and 12%, respectively.[107] In another NWTS report, female survivors who received WLI had nearly a 15% risk of developing invasive breast cancer by age 40 years.[110]

Update on 35-Year Incidence of Chronic Health Conditions Among Unilateral Wilms Tumor Survivors

An update from the Childhood Cancer Survivor Study showed that the 35-year cumulative incidence of late toxicities was as follows: 34.1% for any grade 3 to 5 chronic health condition (CHC); 6.1% for a secondary malignant neoplasm (breast, thyroid, and colorectal were most frequent); 8.1% for intestinal obstruction; 7.3% for premature ovarian insufficiency (POI); 4.0% for heart failure; and 2.4% for kidney failure. WLI was associated with an increased risk of SMN, heart failure, and intestinal obstruction. Whole Abdomen Radiation Therapy (WART) was associated with an increased risk of SMN, heart failure, intestinal obstruction, and POI, and the magnitudes of risk increased with RT dose (>20 Gy). The RR of POI after WART ≤20 Gy was 13.1, compared to 36.5 for >20 Gy. Flank RT >20 Gy was associated only with an increased risk of intestinal

obstruction compared with no RT, whereas flank RT <20 Gy was not associated with SMN or any other CHC. High-dose doxorubicin (>250 mg/m^2) was associated with a nearly 5-fold rate of the development of heart failure.[111]

Next Generation of Wilms Tumor Protocols

UMBRELLA Protocol

The SIOP-RTSG has developed a new protocol for childhood renal tumors, UMBRELLA SIOP-RTSG 2016. Histologic classification after preoperative chemotherapy defines three major subgroups of WT: low-risk (completely necrotic WT), high-risk (blastemal type and DA), and intermediate-risk tumors (all other types). The molecular biology aim is to validate the prognostic value of 1q gain and other copy number alterations (1p/16q, *MYCN*, and *TP53*). For localized WT, after preoperative AV postoperative treatment will be delivered according to tumor stage and histologic risk group as in SIOP-2001. Low-risk tumors will get no therapy (stage I), and stage II and III tumors will receive AV for 27 weeks. All intermediate-risk tumors (<500 mL) and intermediate-risk stromal or epithelial-type tumors (≥500 mL) will get AV for 4 weeks (stage I), AV for 27 weeks (stage II), and AV for 27 weeks plus flank RT (stage III). Intermediate-risk nonstromal or non–epithelial-type tumors (≥500 mL) will get AV for 4 weeks (stage I), doxorubicin added to AV (AVD) for 27 weeks (stage II), and AVD for 27 weeks plus flank RT (stage III). High-risk blastemal-type tumors will get AVD for 27 weeks (stage I); etoposide, carboplatin, cyclophosphamide, and doxorubicin (HR-1) for 34 weeks (stage II), and HR-1 plus flank RT (stage III). High-risk diffuse anaplastic tumors will receive similar chemotherapy as blastemal-type tumors, and flank RT will be given for both stage II and stage III tumors.

Stage IV low- and intermediate-risk tumors with a complete or very good partial remission and complete surgical resection of primary and metastatic tumors will receive AVD150 (150 mg/m^2 of doxorubicin) for lung nodules 3 to 5 mm and AVD250 (250 mg/m^2 of doxorubicin) for lung nodules >5 mm. Lung RT will be given only if complete resection of visible metastasis is not performed. Stage IV tumors with a partial response or stable disease will receive chemotherapy regimen AVD250 (low risk, unresectable, or resected

with viable metastasis) and CDCV regimen (cyclophosphamide, doxorubicin, carboplatin, and etoposide) for intermediate-risk tumors (unresectable, or resected with viable metastasis). Regarding RT recommendations, patients with intermediate- and high-risk stage III and stage II high risk (DA but not blastema type) will receive flank RT to 14.4 Gy for intermediate-risk and 25.2 Gy for high-risk tumors. Macroscopic residual disease in high-risk tumors will get an additional 10.8 Gy boost. Completely resected nodes are no longer irradiated with a boost since no local control or survival benefit was observed. If diffuse intraperitoneal spillage is present, whole abdominopelvic RT to 12 Gy in infants <2 years (intermediate and high risk), 15 Gy (intermediate risk), or 19.5 Gy (high risk) will be given. Intermediate-risk patients with macroscopic peritoneal deposits after surgery receive 19.5 Gy. Patients with lung metastasis will receive WLI 12 Gy in 8 fractions (intermediate-risk tumors with incomplete remission after chemotherapy or persistent viable tumor) and 15 Gy in 10 fractions (all high-risk tumors). For flank RT, this trial will explore the feasibility of target volume reduction to include only the posterior abdominal wall in contact with the preoperative tumor and the para-aortic nodes, while excluding noninfiltrated anterior organs, using IMRT with central QA preapproval.[112,113]

Children's Oncology Group Protocols

AREN2231 will be the new COG FHWT study that will open to accrual in 2024. The risk stratification will include patient age, chromosome 1q gain, LOH of 1p, LOH of 16q, LOH of 11p15, clinical response after two initial cycles of three-drug chemotherapy, postchemotherapy stage and histology of patients with delayed nephrectomy, LN metastasis, EPM, and epithelial histology. LN sampling will be required for all children in this trial. The trial will include six chemotherapy treatment regimens: EE4A (vincristine, actinomycin), DD4A (vincristine, actinomycin, doxorubicin), VIVA (vincristine, actinomycin, irinotecan), M (vincristine, actinomycin, doxorubicin, cyclophosphamide, and etoposide), MVI (vincristine, actinomycin, doxorubicin, cyclophosphamide, etoposide, and irinotecan), and UH-3 (vincristine, doxorubicin, cyclophosphamide, etoposide, carboplatin, and irinotecan). The overarching aim of the trial is to improve

outcomes within cohorts of patients with FHWT with current long-term EFS rates at or below 80% and to maintain outcomes despite therapy reduction within cohorts of patients with FHWT with current long-term EFS rates at or above 84%.

Stage I patients who will receive nephrectomy only will be expanded to include those without adverse biology and who are 2 to <4 years of age, or <2 years with tumor weight ≥550 g or those who are over 4 years of age with epithelial histology subtype. Stage I patients with adverse biology will receive regimen EE4A. Stage II patients with adverse biology will be randomized to regimen VIVA versus DD4A to determine if VIVA is noninferior to DD4A and doxorubicin can be eliminated. Stage III patients without adverse biology will receive regimen EE4A. Stage III and IV patients with adverse biology, slow incomplete lung response, or EPMs will be randomized to regimen MVI versus M, to demonstrate the noninferiority of regimen MVI to regimen M. Regimen MVI is a variation of regimen M studied on AREN0533. Regimen M includes four cycles of cyclophosphamide (cumulative dose 8.8 g/m^2) and etoposide (cumulative dose 2 g/m^2), with consequent risk of second malignancy and infertility, particularly for males. Regimen MVI will reduce alkylator exposure below the threshold for decreased fertility (cumulative dose of 4.4 g/m^2) and add known active agents (vincristine/irinotecan) to the regimen, with a goal to preserve excellent clinical outcome and potentially decrease infertility and secondary malignancy risk. Stage III and IV patients with blastemal predominance will be treated with regimen UH-3. The RT indications and doses will remain the same as in AREN0532 and AREN0533. This protocol will also determine the feasibility of IMRT with IROC preapproval required for all patients, to reduce radiation-induced toxicity to the heart, thyroid, breast, and solitary kidney for children with lung and liver metastases. This study will also encourage resection of residual pulmonary nodules for stage IV patients with standard biology and who have 1 to 3 residual pulmonary nodules on imaging after cycle 2. Lung RT will be omitted for those patients who are found to have no viable tumor in resected nodules.

AREN1921 is currently open and aims to increase the survival rates of children with stage II to IV diffuse AWT and standard-risk relapsed FHWT by the addition of vincristine and irinotecan to cyclophosphamide, carboplatin, and etoposide alternating with

vincristine/doxorubicin/cyclophosphamide (regimen UH3). Patients with high-risk and very high-risk relapsed FHWT will be treated with ifosfamide/carboplatin/etoposide alternating with cyclophosphamide/topotecan. The RT indications and doses will remain the same as in AREN0321 and NWTS-5 relapsed Wilms protocol. This protocol will also determine the feasibility of IMRT with IROC preapproval required for children with lung and liver metastases.

In AREN2231 and AREN1921 protocols, flank/abdomen RT will be delayed until week 6 for stage IV patients with lung metastases so that both sites can be treated simultaneously in case lung RT is needed to avoid higher radiation doses to organs such as the heart, liver, and lungs at overlapping field edges.

FUTURE DIRECTIONS

The cure rates of patients with WT following multimodality therapy including RT are excellent. The next generation of COG and SIOP protocols described above seeks to further refine the treatment of low-risk patients to decrease treatment-related toxicity and intensify the treatment of high-risk tumors to improve outcomes. These protocols examine the value of novel molecular biomarkers such as 1q gain, LOH of 1p and 16q, and LOH of 11p15 to further improve the WT risk stratification system and refine treatment. Novel RT techniques such as IMRT and proton therapy are also being studied to reduce normal tissue toxicity. Novel chemotherapy regimens eliminating doxorubicin and reducing the doses of alkylators and etoposide are being evaluated to safely reduce the risks of cardiotoxicity, infertility, and secondary malignancies. The biologic sample banks of COG will continue to be a valuable source of tissue for studies aimed at identifying new biologic markers that may be of prognostic significance. However, RT is an important cause of late toxicity. Currently, WT biomarkers are only utilized for defining high-risk tumors to be treated with chemotherapy. Their utilization for potentially refining indications for RT in certain risk groups remains to be studied. Detailed studies of late toxicities specifically by analyzing the effects of RT doses to target organs are critical to improve our understanding of the relationship between RT and a variety of toxicities, such as infertility, hypogonadism, congestive heart failure, and

secondary malignancies in WT survivors.[114,115] The use of novel biomarkers that could detect RT injury earlier in various organs, and genomic studies to assess individualized genetic susceptibility for late toxicities, can improve our understanding of the risks of RT and refine treatment and surveillance guidelines for high-risk survivors to mitigate late toxicity.[116-120] The National Cancer Institute is promoting the adoption of novel clinical protocols aimed at studying the mechanistic interactions and biologic consequences of RT, prioritizing a comprehensive study of patient (genomic and epigenomics), tumor, and treatment (chemotherapy, RT, dosimetry) factors, together with longitudinal multiomics (pre- and post-therapy) (RFA-CA-21-040). We hope that these innovations in radiation oncology and biology can be harnessed for the benefit of children with WT and long-term WT survivors.

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CHAPTER 92

Neuroblastoma

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HISTORY

Neuroblastoma is an embryonal cancer of the sympathetic nervous system, first described by the pioneering German physician Rudolf Virchow in 1864.[1] In 1901, William Pepper from the University of Pennsylvania reported a series of infants with a phenotype of the disease we now call stage MS neuroblastoma—extensive hepatic metastases in a young baby with a small primary adrenal tumor.[2] In 1907, Sir Robert Hutchison, a pediatrician at Great Ormond Street in London, published a series of older children with extensive osseous metastases most obviously affecting the skull—the phenotype we now refer to as stage M neuroblastoma.[3] These apparently disparate conditions were brought together as a single diagnosis by the Massachusetts General Hospital pathologist James Homer Wright, who described the characteristic rosette of cells around a central tangle of neuropil, and gave the disease the name "neuroblastoma".[4,5]

In the modern era, two exceptional individuals working together at the Children's Hospital of Philadelphia can be regarded as the parents of contemporary neuroblastoma science and practice. Giulio D'Angio,[6] a pediatric radiation oncologist, and Audrey Evans, a pediatric oncologist,[7] published in 1971 both the first staging system for neuroblastoma[8] and an analysis of stage MS neuroblastoma.[9] They established the series of *Advances in Neuroblastoma Research* meetings, initially in Philadelphia, but subsequently throughout the world, which brought together scientists and clinicians to work together to improve the understanding and treatment of this enigmatic cancer type. They worked together and published many other papers on neuroblastoma over a period of about 50 years.

DIVERSITY

Neuroblastoma is incredibly varied in its characteristics and natural history. It may be asymptomatic and discovered incidentally[10] or through screening.[11] The primary tumor is typically situated along the sympathetic chain, most commonly in the adrenal gland[12] or elsewhere in the abdominal retroperitoneum, less commonly in the thorax,[13] and occasionally in the neck[14] or pelvis.[15] Sometimes, bilateral, independent primary tumors are present.[16] Occasionally, there is widespread metastatic disease with no discernible primary tumor.[17] It may present with symptoms due to the local tumor, including spinal cord compression as a result of invasion of neural foramina,[18] metastatic disease, or the effects of hormone production or other paraneoplastic phenomena.[19-21] Pathologically, it sits on a spectrum with ganglioglioma at the benign end, then various forms of ganglioneuroblastoma through to differentiating and undifferentiated neuroblastoma, which is definitely malignant.[22] There is now a growing understanding of the molecular pathology features that govern the biologic behavior of the tumor,[23] and these are used for risk stratification[24] and, in some cases, are targets for treatment.[25] While the disease may be congenital and even diagnosed antenatally,[26] and most cases occur in the first 5 years of life, there is a tail in older children, adolescents, and even young adults.[27,28] Age at diagnosis is an important prognostic factor, with those under 18 months faring better.[29]

Once diagnosed, it is important to ensure a comprehensive assessment of the disease, including staging[30] and molecular biology.[31] These features, taken into account with age, determine the risk stratification, which guides the choice of treatment and gives an indication of the chances of survival.[32,33] Complex algorithms are used to determine the intensity of treatment based on the risk group and may involve induction chemotherapy,[34] surgery to remove the primary tumor,[35,36] one or two courses of high-dose myeloablative chemotherapy,[37,38] radiotherapy,[39,40] molecular radiotherapy,[41] and a range of biologic treatments, including differentiation therapy,[42] immunotherapy,[43,44] and anaplastic lymphoma kinase (ALK) inhibitors.[45] Different protocols are used in the main cooperative oncology groups in North America and Europe, and different questions are asked in the trials, but in general, the principles are similar.[46]

Outcomes range from spontaneous regression without treatment,[47] through babies with an excellent prognosis despite minimal treatment,

intermediate-risk patients who are likely to do well with more intensive treatment,[48] and high-risk patients who have an approximately equal chance of being cured with very aggressive treatment,[31] or having primary progressive, refractory, or relapsing disease that, despite innovative approaches, is unlikely to be cured.[49,50] For some, symptom control and palliative care are important consideration.[51] For the optimal outcome, patients are best managed in specialist centers where enrollment into cooperative pediatric oncology research group clinical trials is offered. Modified treatment protocols[52] and international tumor boards[53] are available for use in resource-challenged settings where not all components of treatment may be readily available or affordable and outcomes are recognized to be worse.[54,55]

In summary, neuroblastoma should not be considered a single entity requiring a one-size-fits-all treatment approach. Patients should be considered individually in tumor boards where all relevant specialties, including pediatric radiation oncology, are represented.[56,57] As the results of treatment are far from satisfactory, basic and clinical research should ideally be embedded into the standard of care pathway, in an attempt to improve survival rates and lessen treatment-related morbidity.[58]

ROLE OF RADIOTHERAPY

Radiation treatment has a number of distinct roles as part of the multimodality treatment for neuroblastoma, which is considered in this chapter. Arguably, the most important is the use of external beam radiotherapy to the primary site after surgery to achieve local control, or radical irradiation of the primary tumor if surgery is not considered to be safely possible.[39] Traditionally, photon techniques have been used,[59] but with increasing availability worldwide, proton beam therapy techniques are being increasingly frequently employed.[60] This is considered for almost all patients with high-risk disease and for a subgroup of harder-to-treat intermediate-risk patients. Intraoperative radiotherapy has been explored in the past but is not regarded as a universal standard of care.[61]

Metastatic site irradiation is given as the standard of care alongside primary-site radiotherapy in some, but not all, protocols—practice varies across the world.[62] Molecular radiotherapy with iodine-131 *meta*-

iodobenzylguanidine (^{131}I-mIBG), which has the advantage of biologically targeting disseminated disease, has been used for around 40 years but has yet to find an established place and remains the subject of a number of clinical trials.[63] Other forms of molecular radiotherapy including lutetium-177 DOTATATE[64] and radiolabeled monoclonal antibodies directed against the cell surface di-sialo-ganglioside GD2[65] are being evaluated in clinical trials but cannot yet be considered as standard therapy.

In patients who relapsed, radiotherapy may sometimes be used as part of potentially curative treatment, for example, following local recurrence,[66] or central nervous system (CNS) relapse,[67] but more often, this is not considered feasible, and radiotherapy is reserved for palliation of, for example, bone pain.[68]

EPIDEMIOLOGY

Incidence

Population-based cancer registry data give the most accurate idea of frequency of diseases. A report on the incidence and outcome of all malignant diseases in babies, children, teenagers, and young adults up to the age of 25 from the four nations of the United Kingdom over a 20-year period 1997 to 2016 presents interesting insights.[69] Among 42,205 registrations in total, neuroblastoma and other peripheral nervous cell tumors accounted for 1,956 (4.6%) cases; however, there was a striking difference in the various age groups. Neuroblastic tumors accounted for 11% of all malignancies in the 0- to 4-, 2.8% in the 5- to 9-, 0.75% in the 10- to 14-, 0.48% in the 15- to 19-, and 0.22% in the 20- to 24-year-old age groups. Of all neuroblastic tumors, 79% occurred in the 0- to 4-year-old cohort, 12% in the 5- to 9-year-old cohort, and just 9% in those aged 10 to 24 years. The sex ratio is broadly equal (53% male, 47% female).

Similar data have been published from the United States using the Surveillance, Epidemiology, and End Results (SEER) program database.[70] From 1975 to 2013, 3,998 (93%) cases were recorded in children aged up to 15 years and 282 (7%) cases in adolescents and adults aged 15 years or above.

A comparison of data from Southeastern European registries with U.S. SEER data shows some differences.[71] The overall age-adjusted incidence

rate was significantly lower in Southeastern Europe (10.1 per million) compared with the United States (11.7 per million); the difference was maximum during infancy (43.7 vs 53.3 per million). Incidence in babies and younger children was positively associated with the Human Development Index, whereas a lower median age at diagnosis was correlated with higher overall incidence. These findings may indicate greater case ascertainment of those young patients with disease, which might spontaneously regress if never diagnosed.

Etiology

In most cases, the cause of neuroblastoma is unknown, but as with other embryonal tumors in young children where exposure to environmental carcinogens cannot be causal, a genetic predisposition may be relevant. There are family pedigrees that display an autosomal dominance of neuroblastoma susceptibility, but these account for only approximately 1% to 2% of neuroblastoma cases.[72] Mutations in the paired-like homeobox 2B (*PHOX2B*) gene may lead to families where neuroblastoma is associated with Hirschsprung disease and congenital central hypoventilation syndrome.[73] *ALK* germline mutations have also been identified as a cause of familial neuroblastoma.[74] The identification of *ALK* mutations is important, as it may allow the use of an ALK inhibitor as a therapeutic option. In nonfamilial, or sporadic, neuroblastoma, which constitutes the majority of cases, genome-wide association studies have identified an increasing number of neuroblastoma susceptibility loci and candidate genes as independent drivers of neuroblastoma predisposition.[75]

ASSESSMENT

Presentation

Neuroblastoma may present in a variety of ways: with symptoms from the primary tumor, with symptoms from metastases, with generalized and nonspecific symptoms of advanced malignancy, or with symptoms from paraneoplastic phenomena. In addition, asymptomatic disease may be discovered as an incidental finding, for example, on a routine antenatal ultrasound scan or on a healthy baby check.

As the primary tumor is most commonly situated in the suprarenal region or elsewhere in the retroperitoneum, presentation with pain or swelling due to an abdominal mass is common. Lower limb weakness due to spinal cord compression caused by extension of the tumor through the neural foramina, referred to as a "dumbbell tumor," is not unusual.[76] It is more frequently seen in babies and younger children and may be present at birth.[77] Less commonly, the primary tumor may present as a thoracic mass, with a posterior mediastinal location.[13] Rarely, the primary tumor may be in the neck, perhaps associated with Horner syndrome and anisocoria if it arises from the stellate ganglion.[78] Sometimes, bilateral or multiple primary tumors may be found.[79] Examples of various primary tumors are shown in Figure 92.1.

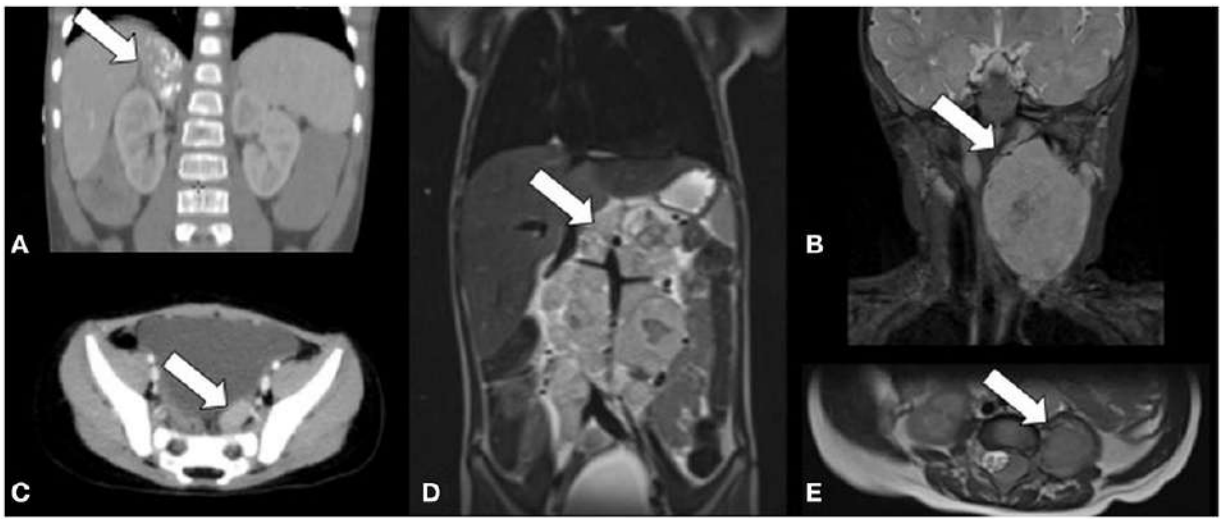

FIGURE 92.1 Examples of different primary neuroblastoma tumors. A. Coronal computed tomography (CT) scan of the upper abdomen showing a relatively small right suprarenal tumor (*arrow*) with extensive calcification. B. Coronal magnetic resonance imaging (MRI) scan showing a large localized left cervical tumor (*arrow*) stage L2 displacing the carotid vessels and airway. C. Axial CT scan through the pelvis showing a small, localized stage L1 left presacral tumor (*arrow*) behind the bladder, which presented with opsoclonus-myoclonus. D. Coronal MRI scan showing a large central abdominal mass encasing the abdominal aorta, renal arteries bilaterally and other branches, and extending below the aortic bifurcation. E. MRI scan demonstrating left-sided paravertebral mass entering the spinal canal through the neural foramen and displacing the thecal sac.

In very young children, rapidly progressive hepatomegaly due to metastatic disease in the liver, which may cause respiratory distress, may be

the presenting feature.[80] This can be associated with the “blueberry muffin” appearance of multiple cutaneous metastases. These are features of stage MS disease.

In older children, symptoms of metastatic disease may dev elop more slowly. Bone metastases are common, and so pain in the back or limbs, sometimes associated with limping, and occasionally resulting in a pathologic fracture, is nonspecific, and diagnosis of the underlying cancer may be delayed. Swelling arising from the bones of the skull may lead to proptosis and orbital ecchymoses. These are classic characteristics of stage M disease. Rarely, base of skull disease may cause visual compromise.[81] Sometimes, metastatic lymphadenopathy may be palpable, most often in the left supraclavicular fossa.[82] Lung and parenchymal cerebral metastases are unusual at diagnosis. Examples of metastatic spread are shown in Figure 92.2.

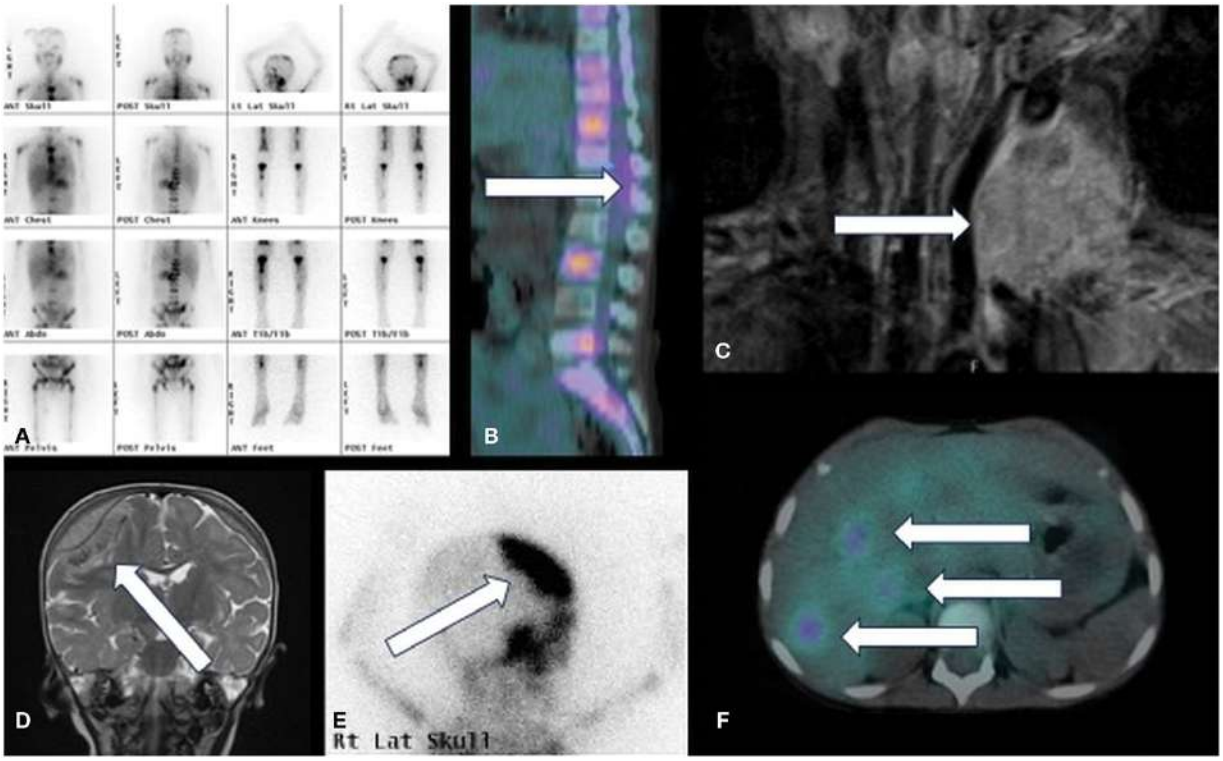

FIGURE 92.2 Examples of metastatic spread of neuroblastoma. A. Planar spot view ^{123}I-mIBG scans of a patient with extensive avid pathologic uptake throughout the skeleton. B. Sagittal ^{123}I-mIBG single-photon emission computed tomography (SPECT) computed tomography (CT) scan through the lower thoracic and lumbar spine of the same patient showing multiple vertebral metastases and disease within the spinal canal at T12/L1 (*arrow*). C. Coronal magnetic resonance imaging (MRI) scan of the neck showing a left supraclavicular lymph node metastasis (*arrow*). D. Coronal MRI scan of the brain showing a large right parietal bone metastasis with soft tissue extension internal and external to the skull (*arrow*). E. Right lateral skull ^{123}I-mIBG spot view planar scan of the same patient showing avid uptake in the large right parietal bone metastasis (*arrow*). F. Axial ^{123}I-mIBG SPECT/CT scan through the liver showing several hepatic metastases (*arrow*). ^{123}I-mIBG, iodine-123 *meta*-iodobenzylguanidine.

Other general and nonspecific symptoms, which may be present alongside the symptoms of the primary tumor and metastases, are lethargy, tiredness, weight loss, anorexia, fever, anemia, and petechiae due to thrombocytopenia.

Sometimes, an autoimmune (paraneoplastic) phenomenon can result in the opsoclonus-myoclonus-ataxia, or "dancing eyes," syndrome.[21] This is not always caused by neuroblastoma, but if it is, the tumor is often low risk.

The neurologic symptoms may persist after successful treatment of the cancer.

The wide variety of symptoms means that there is a broad differential diagnosis. If neuroblastoma is not borne in mind as a possibility, it is likely that there may be a delay in diagnosis. There is evidence that diagnostic delay leads to worse clinical outcomes.[83] Increased symptom duration before diagnosis is also associated with an increased risk of early death.[84] Public awareness of cancer in children and young people and its presenting symptoms is low.[85] Even knowledge of childhood cancers among junior doctors is suboptimal.[86] It is impor tant, therefore, for these reasons, that there is at least an awareness of cancer, including neuroblastoma, in children and young people among primary care doctors and general pediatricians, even if it is highly unlikely that the patient in front of them has this disease. National guidelines aimed at reducing diagnostic delay indicate symptoms that merit urgent referral for further investigation.[87]

Previously, cases of neuroblastoma without symptoms were diagnosed on screening by the testing of babies' urine for catecholamine metabolites. This approach resulted in an increased incidence, but the mortality rate remained stubbornly unchanged. Many of the additional cases diagnosed by screening were good prognosis tumors destined to regress spontaneously had they not been identified. As a number of studies failed to show a population benefit for this approach, population-based screening is no longer a standard practice.[88-90]

Imaging

There are several roles for imaging in a newly presenting pati ent suspected to have neuroblastoma: to provide supportive evidence for that disease or another alternative diagnosis, to guide a biopsy, and to define precisely the anatomic location of the tumor, the presence or absence of imaging-defined risk factors, and metastatic staging to indicate and quantify the presence of nodal and distant metastatic disease.

Following a definitive diagnosis of neuroblastoma, repeat imaging is required to assess the response to systemic therapy in terms of both distant disease and the suitability of the primary tumor for surgical removal. Postoperatively, completeness of excision can be determined. Repeat

imaging may be required for surveillance and to investigate symptoms of possible relapse.

Ultrasound is the initial imaging modality for the investigation of a child with a suspected abdominal mass. It will confirm whether a mass is present and indicate its location in relation to organs such as the kidneys, the presence of nodal or hepatic metastases, and displacement and encasement of great vessels, which is typical for neuroblastoma. Endovascular extension is more likely to be seen with primary renal tumors than neuroblastoma. Ultrasound may also be useful in evaluating abnormalities at other sites, such as supraclavicular fossa nodes.

Following the demonstration of an abdominal abnormality, a computed tomography (CT) scan and/or magnetic resonance imaging (MRI) are required. Both modalities have advantages and disadvantages. CT is often more widely available and faster to perform, with, therefore, less need for anesthesia in younger children. It is better at showing calcification, which is often a feature of neuroblastoma. MRI shows greater soft tissue detail, particularly invasion into the spinal canal and bone marrow involvement, and does not utilize ionizing radiation.[91] The accurate identification of imaging-defined risk factors is key to the accurate local staging of neuroblastoma.[30] In essence, these risk factors include encasement of critical structures, such as major blood vessels and nerves, and invasion of the spinal canal (Figure 92.3).

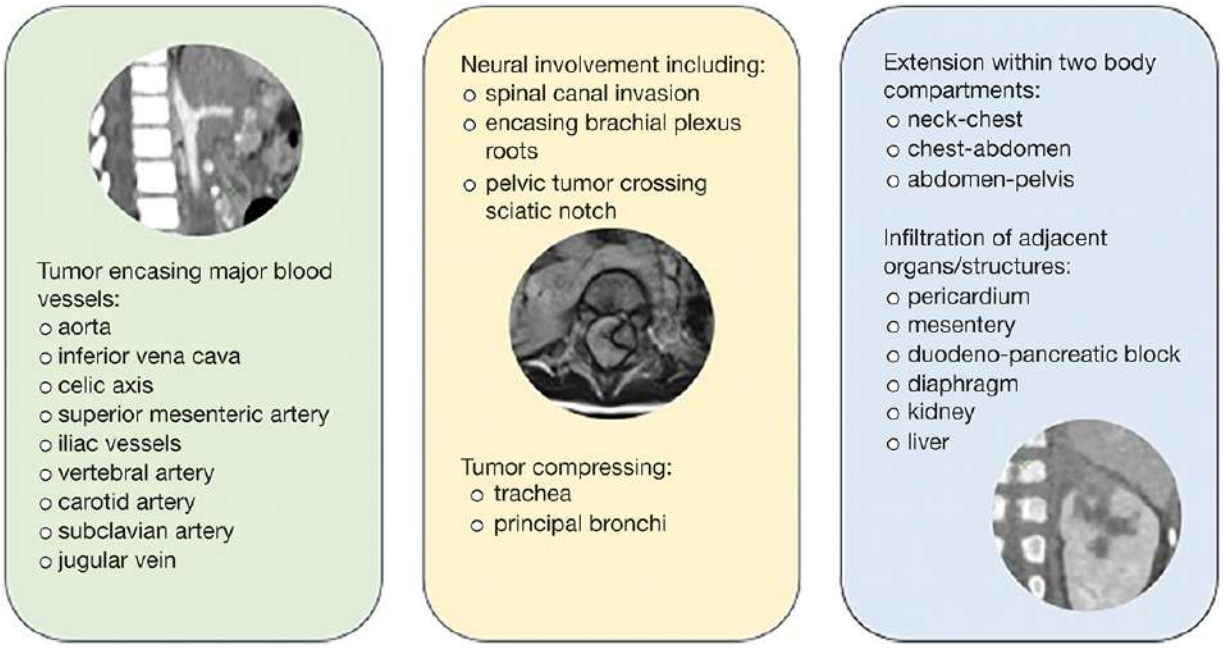

FIGURE 92.3 Infographic to indicate some of the imaging-defined risk factors used in the staging of neuroblastoma in the International Neuroblastoma Risk Group Staging System.

Biopsy is essential for the diagnosis of neuroblastoma, as well as characterization of its molecular biology. Interventional radiology core needle biopsies have largely replaced open surgical biopsies.[92] These may be performed at the same time as bone marrow aspirates and trephines, and insertion of a central venous catheter, thereby reducing the number of general anesthetics the child requires.

The standard of care for the assessment of distant metastatic disease, in addition to bone marrow examination, is ^{123}I-mIBG planar scintigraphy and single-photon emission computed tomography CT (SPECT/CT). In some countries, ^{123}I-mIBG is not available, and ^{131}I-mIBG is used, although the radiation exposure is greater and the image quality is infe rior.[93] Semiquantitative scoring of ^{123}I-mIBG scans allows for estimation of the disease burden, which correlates with prognosis, and a more objective assessment of response. Two systems are in current use, both divide the planar scan into a number of segments, and a numerical score is assigned to each segment. In the United States, the Children's Oncology Group (COG)[94] protocols use the Curie score, where 10 body segments are given a score of 0 to 3, making a maximum possible score of 30.[95] In Europe, the International Society of Paediatric Oncology European Neuroblastoma

group (SIOPEN)[96] system is used, where 12 body segments are given a score of 0 to 6, making a maximum possible score of 72.[97] Both systems appear equally useful, with the SIOPEN score having been cross-validated in COG trial patients, and the Curie score similarly assessed in SIOPEN patients.[98,99]

While over 90% of neuroblastoma tumors take up ^{123}I-mIBG, and so are amenable to this form of scoring, a small number do not. In this patient group, ^{18}F-fluorodeoxyglucose positron emission tomography (FDG PET) scanning is preferred to demonstrate the presence or absence of distant metastatic disease.[100] FDG PET may also be used in countries where ^{123}I-mIBG is not readily available.

A variety of other positron-emitting radiotracers may also be used for PET scanning in neuroblastoma, including somatostatin receptor imaging with ^{68}Ga-DOTA-peptide PET radiopharmaceuticals (^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, and ^{68}Ga-DOTANOC) and catecholaminergic PET tracers (^{11}C-meta-mydroxyephedrine, ^{18}F-dihydroxyphenylalanine ^{124}I-mIBG, and ^{18}F-meta-fluorobenzylguanidine).[101,102] However, while there is considerable interest in the evaluation of these alternative forms of imaging, none has yet become the standard of care in neuroblastoma management.

There is a strong research interest in radiomic evaluation of imaging data in neuroblastoma, and while this may be demonstrated to be of clinical value in the future, at present, it has no clearly established place in neuroblastoma care.[103]

Pathology

Primary surgery is not often undertaken for neuroblastoma, and so most often the tissue diagnosis is based on core bio psies. Neuroblastoma is one of the embryonal malignancies collectively referred to as “small, round, blue cell tumors of childhood.” Conventional light microscopy may show such cells forming rosettes around neuropil, and Schwannian stroma and larger ganglion cells may also be apparent in varying proportions. Immunohistochemical staining adds infor mation and allows the differential diagnosis between neuroblastic tumors and “small round blue cell tumors” of other types to be reliably distinguished.[104,105]

Depending on the level of differentiation and the balance bet ween stroma, mature cells, and neuroblasts, peripheral neuroblastic tumors are grouped into (1) ganglioneuroma, which is benign and is mostly mature Schwannian stroma and ganglion cells with no neuroblastoma; (2) ganglioneuroblastoma where stroma predominates, but with a neuroblastic component where immature cells may be scattered widely (ganglioneuroblastoma intermixed) or focally concentrated (nodular ganglioneuroblastoma); and (3) neuroblastoma, which has a limited stromal component and may be subcategorized as undifferentiated, poorly differentiated, or differentiating.[106] The International Neuroblastoma Pathology Classification (INPC) separates neuroblastic tumors into two categories: favorable histology and unfavorable histology.[22] This is based on a number of factors including grade, mitosis-karyorrhexis index, and age—which, although important, is not a histopathologic feature and may lead to confounding.

Molecular Biology

Molecular biology is a fast-moving area of scientific endeavor and is increasingly valuable in the management of neuroblastoma. It is a complex field, and a detailed review is beyond the scope of this chapter; however, the importance of sending tumor tissue, bone marrow, and blood for detailed analysis in a specialist laboratory at the time of diagnosis and in the case of subsequent relapse cannot be overstated.

One of the earliest findings of prognostic importance was that amplification of the oncogene *MYCN* was associated with advanced disease stage[107] and rapid disease progression.[108] Following these discoveries, *MYCN* has been an important factor in risk stratification.[24]

The presence or absence of numerical (eg, hyperdiploidy) and segmental (eg, 1p deletion, 11p deletion, and 17q gain) chromosomal abnormalities is another fundamental finding of significance.[109,110]

Disruptions in telomere maintenance caused by *ATRX* mutation and *TERT* rearrangement resulting in alternative lengthening of telomeres are indicators of poor prognosis, especially in older children.[111]

ALK mutations are important to identify, as they are of therapeutic value as well as prognostic significance.[112,113]

In addition to assessing tumor tissue for these abnormalities, repeated bone marrow and blood tests assaying messenger RNA and cell-free DNA, sometimes called "liquid biopsies," are becoming increasingly important to identify complete response, minimal residual disease, and early rela pse, especially in high-risk disease.[114,115]

Staging and Risk Group Assignment

The three factors most important for risk group assignment, which guide the treatment schedule used and prognosis, are stage, age, and molecular biology characteristics.

Over the years, the staging classifications used for neuroblastoma have evolved from the original Evans system[8] through the International Neuroblastoma Staging System (INSS)[116] to the International Neuroblastoma Risk Group Staging System (INRG SS).[30] The INRG SS is the most commonly used classification currently, which will likely be subject to revision in keeping with future data. In essence, patients are divided into two groups, depending on whether tumors are localized or metastatic. Localized tumors are further subdivided into two categories depending on the absence (stage L1) or presence (stage L2) of imaging-defined risk factors. Metastatic tumors are classed as stage M, except when metastases are confined to the liver, skin, and/or bone marrow in babies and children less than 18 months of age, and stage MS—broadly equivalent to Evans stage IVS.[9] The fundamental difference between the INRG SS and the earlier INSS is that the previous classification was a postsurgical system, where the stage is depended on the completeness of excision of the primary tumor, whereas currently, surgery is rarely the first treatment for neuroblastoma of any stage, and the classification relies predominantly on anatomic relations as demonstrated by radiologists. Imaging-defined risk factors indicate a higher probability of complications when surgery is performed.

Age has long been recognized as an important prognostic factor in neuroblastoma, with babies faring much better than older children. Previously, patients were separated into those aged less than or more than 1 year at diagnosis; however, analyses performed in very large numbers of patients have shifted the cutoff point to 18 months.[29,117] A large retrospective

study has demonstrated no detriment to children between 12 and 18 months of age as a result of deintensification of therapy as a result of this change.[118]

The key biologic factors used in risk stratification are amplification of *MYCN* and, in the absence of that, the presence of segmental chromosomal abnormalities. Ploidy and the INPC category add further value.

Broadly speaking, risk classification schemes divide cases into low-, intermediate-, and high-risk cases, where there is a strong association with prognosis. However, this field is complex and evolving as new data emerge, for example, from the INRG Data Commons.[119,120] Examples of the complexity include the addition of a very low-risk category in the INRG classification.[24] Different cooperative clinical trial groups use similar, but slightly different, risk classification systems.

The European group SIOPEN defines high risk in its High-risk 2 Trial (clinicaltrials.gov ID NCT04221035) as stage M disease in children over the age of 12 months, with any *MYCN* status or stage L2, M, or MS neuroblastoma with *MYCN* amplification, at any age. SIOPEN had one trial for low- and intermediate-risk patients (clinicaltrials.gov ID NCT01728155). The low-risk group included patients without *MYCN* amplification and either aged less than 18 months with stage L2 or aged less than 12 months with stage MS. The intermediate-risk group included patients with stage L2 aged less than 18 months without MYCN amplification; those aged less than 12 months with stage M, without MYCN amplification; and those with stage L1 disease and MYCN amplification.

The COG has used a similar, but slightly more complex classification with age, *MYCN* status, INSS stage, ploidy, and INPC histology criteria. While this has been functionally valuable, the use of age, when age is already a criterion in the INPC system, may lead to a degree of bias.[121] The relative contributions of the different elements to risk have been teased out, and a refined classification system has been developed.[31]

Even within established risk groups, subgroups of patients can be identified who have a greater risk; for example, att empts have been made to define an ultra-high-risk subgroup of patients,[122] and a nomogram has been devised to subdivide high-risk patients into groups with better (about 58% 3-year overall survival) and worse (about 30% 3-year overall survival) prognosis.[123]

TREATMENT STRATEGIES

Low Risk

Patients with low-risk neuroblastoma—babies with localized or stage MS disease with no adverse biologic features (*MYCN* nonamplified tumors without segmental chromosomal abnormalities)—have an excellent prognosis, with reported 5-year event-free survival of 90.7% and overall survival of 97.9%.[31] In the absence of life-threatening symptoms, a watch-and-wait policy may be justified, as a proportion of patients may experience spontaneous regression of their tumors. Otherwise, relatively simple chemotherapy schedules may be used, sometimes, but not always, in association with surgery. Primary-site radiotherapy is not indicated.

Intermediate Risk

Intermediate-risk neuroblastoma characterizes disease with a range of different characteristics. Overall, the prognosis is good: A 5-year event-free survival of 85.1% and overall survival of 95.8% has been reported.[31] However, more intensive chemotherapy is required for this to be achieved, compared with low-risk patients. Primary-site radiotherapy is indicated for those older than 18 months at diagnosis with poorly differentiated or undifferentiated MYCN nonamplified tumors. Of note, this latter category of patients is considered intermediate risk on European protocols but is included on high risk in U.S. protocols.

High Risk

High-risk disease requires intensive multimodality therapy. Outcomes have improved significantly over the years as a result of sequential clinical trials refining our understanding of biology, evaluating innovative treatment strategies, and better supportive care. For example, patients with metastatic high-risk neuroblastoma treated between 1990 and 1999 in the ENSG5 trial had a 5-year overall survival of 21.2% or 31.5% depending on which treatment arm they were allocated to, or about 26% overall.[124] In contrast, high-risk patients enrolled from 2007 to 2017 in ANBL00B1 had 5-year event-free survival of 51.2% and a 5-year overall survival of 62.5%.[31]

Current high-risk neuroblastoma treatment protocols vary in detail, but in general have the same concept, which includes a series of systemic therapies designed to treat metastatic disease as well as to shrink the primary tumor, interlaced by local treatments aimed at removing the primary tumor and reducing the chance of local recurrence. Typically, induction schedules are based on chemotherapy,[34] although molecular radiotherapy in addition has been explored.[125] Following several cycles of systemic therapy, maximal safe resection of the primary tumor is undertaken if feasible.[35,36] This is normally followed by intensification with one (or two) high-dose chemotherapy administrations, supported by peripheral blood stem cell reinfusion.[37,38] Historically, total body irradiation (TBI) was used as part of intensification but is no longer used because of the associated long-term toxicity.[126] Radiotherapy is then given to the primary tumor bed as described later,[39] and sometimes to sites of residual metastatic disease.[62] Following this, minimal residual disease-directed therapy follows, with the differentiating agent 13 *cis*-retinoic acid[42] and immu notherapy.[43,44] Each of these steps has evidence-based support; however, as there is still substantial mortality and treatment-related morbidity in high-risk neuroblastoma, further research is needed in order to determine which patients may require escalated therapies versus those who may need less intensive therapy. The paradigm in well-resourced countries is for children to be offered treatment within clinical trials wherever possible. The main cooperative groups running front-line trials are COG and SIOPEN. Early-phase clinical trials are also run by cooperative groups including the New Approaches to Neuroblastoma Therapy (NANT) consortium[127] and the Innovative Therapies for Children with Cancer in Europe (ITCC) consortium,[128] as well as individual institutions, for children with refractory or relapsed high-risk neuroblastoma. It is beyond the scope of this chapter to provide a very detailed review of the nonradiotherapeutic aspects of treatment, but some key references have been given.

EXTERNAL BEAM RADIOTHERAPY

Primary Tumor Treatment

Photon Techniques

Radiotherapy for children should only be given in departments that have appropriately trained staff for this highly specialist area of practice.[57] A broadly based multiprofessional team including pediatric anesthesiologists is required.[129]

Following a multidisciplinary discussion in a pediatric oncology tumor board and agreement that radiotherapy is appropriate, the pediatric radiation oncologist, possibly accompanied by other team members, should meet with the patient and family to explain what is proposed, and why. An assessment is to whether general anesthesia is required. Support and preparation for radiotherapy from a child life and health specialist (hospital play specialist) with experience in radiotherapy may help children to receive radiotherapy without the need for anesthesia. The principles and practicalities of the planning and treatment procedures should be explained, along with the likely short-term and possible longer term side effects. This discussion should be supplemented by the provision of written information. There should be an opportunity for reflection and time to ask questions. Informed consent will then be received from the parent or guardian, or the patient in the exceptional case of adult neuroblastoma.

Specific immobilization is not normally required for the treatment of abdominal neuroblastoma, but a vacuum bag may help with reliable repositioning. The patient will be positioned supine, with the arms either over the chest or above the head. In the rare case of a cervical primary tumor, a head and neck shell with five-point fixation may be required. A planning CT scan with contrast will be performed, under general anesthesia if necessary. Typically, the region scanned will encompass the thorax, abdomen, and pelvis, to enable dosimetry of organs at risk, as well as the tumor to be outlined. Consideration may be given to performing four-dimensional (4D) CT to assess diaphragmatic and upper abdominal movement with respiration. However, this can be difficult to achieve in very young children under general anesthesia, and probably not necessary as respiratory excursions are small and regular.[130] Most radiotherapy centers utilize tattoos to allow accurate and reproducible positioning for treatment.

Fusion of the planning CT scan to prior diagnostic imaging is required. As a minimum, this will be the postinduction chemotherapy, presurgery CT scan, and/or MRI scan used for surgical planning, but other imaging including other time points or types such as mIBG SPECT/CT scans may be

of value. As the extent of tumor found at surgery is sometimes more exten sive than was indicated by the imaging, the operation note from definitive surgery is required, and it can be helpful if this includes the International Neuroblastoma Surgical Report Form.[131] The histopathology report should also be available.

The preoperative gross tumor volume (GTV) should be carefully delineated on the presurgical scan(s). This should be extended, if necessary, in light of information from the surgical and histopathology reports. Care should be taken to include extension retrocrurally, and inferiorly along the vasculature, if necessary. The GTV can then be cut back on the planning CT scan where previously displaced organs, for example, the liver and kidneys, have returned to a more normal position following resection of the tumor mass.

The clinical target volume is then formed by an isotropic expansion, typically 5 to 10 mm, and cut back to normal barriers of spread such as the vertebrae, unless there was evidence of extension into spinal foramina at the time of surgery. A narrower margin may be used over uninvolved organs such as the liver or kidneys to spare function. However, care should be taken to include all surfaces that were in contact with the tumor before surgery. It is important to ensure that coverage in areas where tumor abutted or encompassed vascular structures such as the aorta and its branches, including the celiac axis and superior and inferior mesenteric arteries, the renal vessels, the inferior vena cava, and the hepatic portal vein, are not compromised.

The planning target volume (PTV) is formed by an isotropic expansion of typically 5 mm, or slightly greater or smaller than this depending on institutional standards and the results of departmental audits of motion, to ensure robust coverage (Figure 92.4).

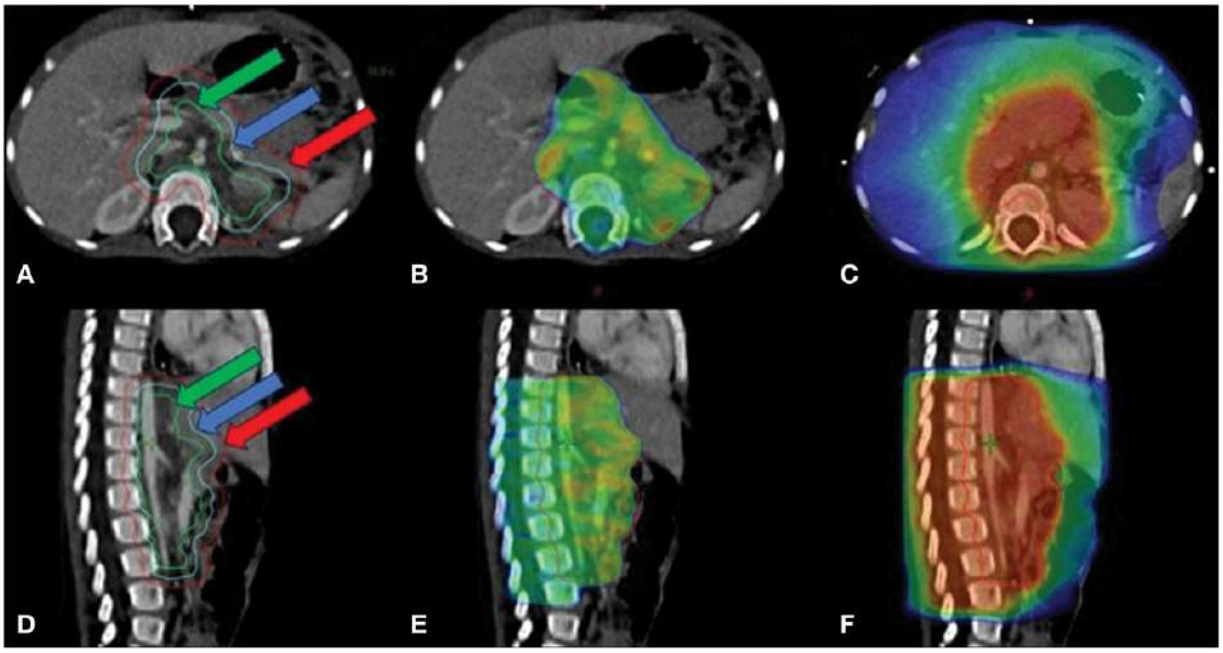

FIGURE 92.4 Intensity-modulated arc photon radiotherapy of a left suprarenal neuroblastoma with extensive nodal disease around the great vessels. A. Axial contrast-enhanced computed tomography scan to show target volumes: gross tumor volume (GTV) (*green arrow*), clinical target volume (CTV) (*blue arrow*), and planning target volume (PTV) (*red arrow*). B. Axial scan showing volume receiving 95% or more of the prescribed dose (21.6 Gy). C. Axial scan showing volume receiving a dose of 5 Gy or more, indicating the "low-dose bath" with photon treatment. D. Sagittal scan of the same patient showing GTV (*green arrow*), CTV (*blue arrow*), and PTV (*red arrow*). E. Sagittal scan showing volume receiving 95% or more. F. Sagittal scan showing volume receiving 5 Gy or more, demonstrating low dose outside the target volume.

All relevant organs at risk should be delineated to allow the dosimetrist to keep doses outside the target volume as low as reasonably achievable and within generally accepted tolerance doses.[132] International Consensus guidelines to support consistent practice are available.[133] Some organs deserve special mention.

The kidneys are radiosensitive organs[134] and are often intimately related to the location of neuroblastoma tumors. As renal function may be impaired by chemotherapy and surgical trauma, it is sensible to have an up-to-date assessment (including glomerular filtration rate measurement and a technetium-99m dimercaptosuccinic acid scan to show the contribution of each kidney separately) to guide preservation of kidney function during radiotherapy planning.

Splenic function is also affected by radiation, and the spleen is often incidentally irradiated to some extent during upper abdominal radiotherapy, especially if the tumor is lateralized to the left. High-quality volumetric evidence on splenic tolerance is limited, but it has been suggested that, if possible without compromising target volume coverage, the mean spleen dose should be kept below 10 Gy.[135]

Radiotherapy affects vertebral growth in young children, and a significant radiation dose gradient, especially laterally, across the vertebral column may lead to scoliosis. Care must, therefore, be taken to outline vertebrae adjacent to or overlapped by the PTV and to ensure symmetrical coverage.[136] The spinal cord, of course, runs through the vertebrae in the spinal canal. While the standard neuroblastoma dose of 21.6 Gy is well tolerated without adverse effects, a higher dose may result in myelopathy, especially following high-dose chemotherapy containing busulfan. It may be necessary to constrain the maximum cord dose to a lower level, such as 30 Gy, than the standardly recognized tolerance.[137]

It is considered good practice for volumes to be peer- reviewed internally by colleagues before they are accepted, as even experienced radiation oncologists may make errors that can be detected and corrected.[138] For some patients in clinical trials, external prospective peer review by radiation oncologists from the trial team is also required.[139]

The dosimetrists will then produce a plan for review. While previously parallel-opposed techniques were usually used, organ at risk tolerance frequently limited delivery of the prescribed dose to the PTV.[140] The widespread introduction of rotational intensity-modulated radiotherapy, or intensity-modulated arc therapy, has allowed better delivery of the prescribed dose to the PTV and also permits safe dose escalation if required.[141]

The standard-dose fractionation schedule prescribed in both North America and Europe is 21.6 Gy in 12 fractions, 5 days per week over 16 days. Some controversy still remains surrounding radiation dose for patients with significant residual disease following induction chemotherapy, surgical resection, and consolidation with high-dose chemotherapy. On the COG protocol ANBL0532, patients with incompletely resected primary neuroblastoma received an additional 14.4 Gy boost to areas of gross residual disease, for a total dose of 36 Gy; however, analysis of local

control rates compared to historical controls suggested no benefit of this escalated dose, resulting in removal of the "boost" from current COG protocols.[142] Arguments for both higher and lower doses exist for the cone-down/boost phase of therapy when residual disease is present,[143,144] but randomized data are not yet available. A randomized SIOPEN trial will provide evidence. Photons with an energy of 6 MV are most commonly used.

Image guidance with kilovoltage (kV) imaging and cone-beam CT (CBCT) will be used to ensure accuracy of treatment delivery. Typically, kV imaging will be used daily, and CBCT for the first 3 days, then weekly.[145]

Care of the patient on treatment will include regular review of the complete blood count as anemia should be avoided and irradiation of a significant number of vertebrae, especially after intensive chemotherapy, may lead to myelosuppression. Antiemetics should be provided. Acute side effects may include anorexia, nausea and vomiting, and tiredness. Supplementary feeding may be needed. Diarrhea can occur, but is not frequent. Patients are at risk of general complications, not specifically related to radiotherapy, such as central venous catheter infections, while receiving radiotherapy, and access to urgent pediatric care may be needed. Families may require social support, especially if treatment requires staying at a long distance away from home to receive the treatment, or help with psychological issues such as anxiety.

Following completion of treatment, a discharge summary detailing the radiotherapy delivered, including doses to organs at risk, should be sent to the referring pediatric oncologist and other relevant health care professionals involved in the child's care, to guide follow-up, especially with regard to late effects and the possible requirement for organ function monitoring or prophylactic care against overwhelming infections.

Proton Techniques

Proton therapy is a radiation modality that has been used to treat malignancies for over 40 years[146] and has become more widely available in the United States, Europe, and Asia over the past decade. Proton therapy may allow improved normal tissue sparing compared to x-ray therapy due to the abrupt dose falloff of the proton beam, an appealing quality

considering the vulnerability of growing tissues to radiation damage.[147,148] Local control is an important part of treatment for high-risk neuroblastoma, but, as described earlier, neuroblastoma tumors are often in close proximity to vital structures and organs at risk, including kidneys, liver, spleen, spinal cord, and lungs. Patients with high-risk neuroblastoma are also subjected to myriad lifesaving systemic therapies, requiring intact organ function; it is essential to avoid toxicity that could compromise delivery of other essential components of therapy required to cure the disease. In addition, as the number of long-term survivors of neuroblastoma grows, survivors who have received abdominopelvic radiation are increasingly recognized to be at risk for a wide range of late toxicities, including bowel obstruction, hepatotoxicity, diabetes, infertility, cardiac toxicity, kidney hypoplasia, and second malignancy.[149-154] Proton therapy is an appealing method for radiation delivery while potentially decreasing the risk to normal tissues (Figure 92.5). Concerns regarding increased relapse risk related to the precise nature of proton therapy have not been validated, with excellent outcomes in patients with neuroblastoma treated with proton therapy having been documented at the institutional and cooperative group levels.[60,155,156]

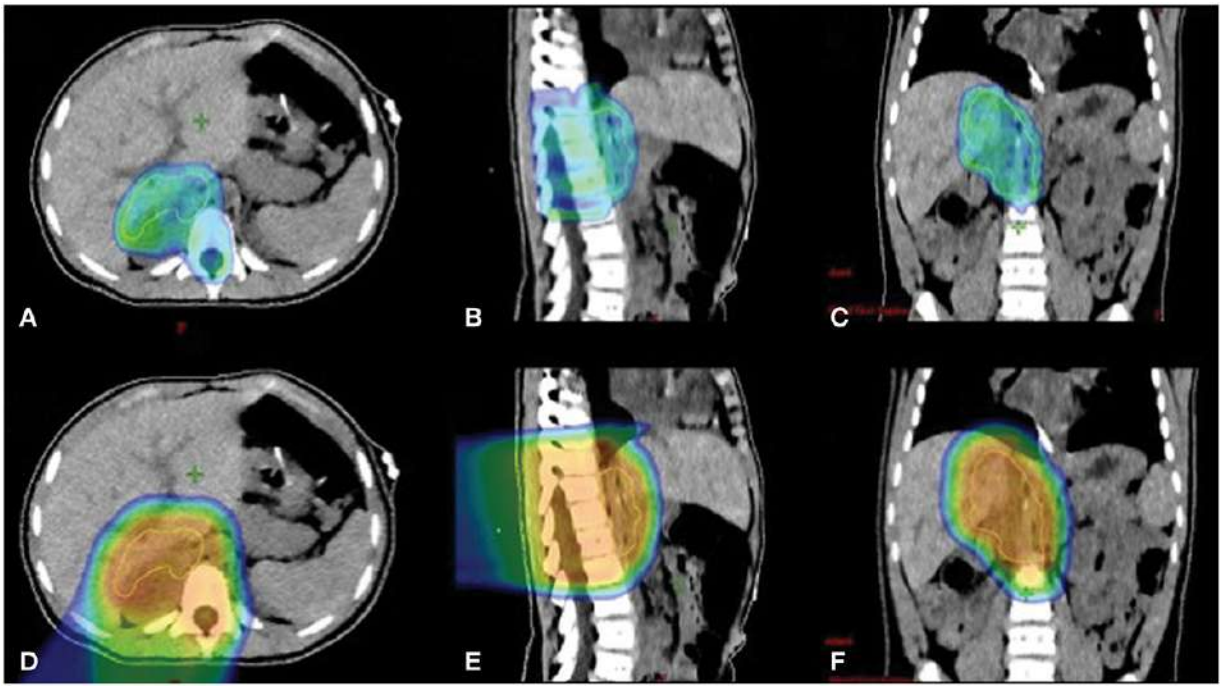

FIGURE 92.5 Pencil-beam scanning proton therapy for a small localized right suprarenal neuroblastoma. Axial (A), sagittal (B), and coronal (C) computed tomography (CT) scans through the upper abdomen showing volume treated with 95% or more of the prescribed dose of 21.6 Gy. Axial (D), sagittal (E), and coronal (F) CT scans showing volume receiving 5 Gy or greater, indicating the lack of an extensive "low-dose bath," in contrast to photon treatment (see Figure 92.4).

As is true with any treatment modality, nuances in delivery of proton therapy are numerous. A major distinction must be made with regard to delivery of the proton beam—namely, the use of a double scattered versus a pencil beam. Double-scattered technology has been available for clinical use for more years than has been pencil beam; it involves the use of a scattering foil to broaden a narrow proton team. This broad beam is directed through custom-milled compensators to sculpt its distal edge, and through apertures or a multileaf collimator to modify its lateral edges in accordance with the target. Collimators and apertures must be custom milled for each beam used to treat a patient, which is expensive and labo rious, and may also increase the risk of quality concerns.[157] Radiation planning with double-scattered beams is analogous to 3D planning with x-rays, including limited conformality. Because neuroblastoma target volumes are complex and in proximity to other normal structures, they may not be suitable for all patients with neuroblastoma. In some circumstances, in particular large and

centrally located tumors, rotational arc x-ray therapy may prove to provide optimal dosimetry compared to double-scattered proton beams.[158]

In contrast, pencil beam scanning beams utilize a single narrow beam to "paint" across a target, reducing dose to adjacent tissues and allowing sculpting to accommodate concave targets. It requires less planning time and has many fewer mechanical parts compared to double-scattered proton therapy[60] and is rapidly becoming a standard of care for delivery of proton therapy.

Target volumes for the treatment of neuroblastoma with proton therapy versus photon therapy are identical (as described earlier), with the exception of the PTV, which may be different for each beam as compared to an isotropic expansion used for photon planning; planning expansions include beam-specific planning targets based on range to target and width of the spread-out Bragg peak. Even so, a classic PTV should be created to allow plan comparison to other modalities. 4D planning may have increased utility in proton planning because understanding normal organ motion can improve robustness of proton planning.[130] The longer nature of daily treatments and the sensitivity of proton beams to motion may result in more patients requiring anesthesia compared to those being treated with photons, and this should be taken into account during decision regarding treatment modality. In general, posterior beams (posterior and posterior-oblique) should be used to avoid traversing bowel, minimizing positional uncertainty from varied bowel filling and breathing. Daily image guidance for delivery of proton beam radiotherapy is usually performed using kilovoltage x-ray image pairs or CBCT; image guidance should be performed with the lowest radiation dose possible during the treatment of pediatric patients.[159]

Metastatic Site Treatment

Radiotherapy to metastatic sites remains a topic of uncertainty, with practices varying widely. The presence of continued mIBG-avid metastatic disease on end-induction scans is associated with poorer prognosis[98,160,161]; the potential benefit of radiotherapy to address these disease sites is not definitively known.[62] COG protocols include radiotherapy (21.6 Gy) to sites of disease that persist at end-induction; however, when the number of sites is five or greater, radiation is not mandated and may be adjusted to be

directed only at sites still avid after high-dose chemotherapy. This stands in contrast to the SIOPEN approach, which does not include radiotherapy to metastatic sites due to the lack of evidence of benefit.

The role of metastatic site irradiation has been evaluated in several retrospective studies, with several institutional and multi-institutional author groups finding decreased risk of relapse at irradiated metastatic sites,[162-164] and retrospective data from Memorial Sloan Kettering Cancer Center finding improved overall survival after metastatic site radiation.[161] These data are intriguing, but the question of utility of metastatic site irradiation remains unanswered in a randomized manner.

A retrospective review of three COG high-risk neuroblastoma trials suggested that patients who had undergone TBI during consolidation had fewer metastatic relapses in sites with prior mIBG avidity.[165] As noted earlier, TBI is no longer utilized due to its very high toxicity profile in very young children, but the authors suggest that systemic radiotherapy in the form of ^{131}I-mIBG might have utility in the management of metastatic sites. This concept remains under investigation.

Low-dose radiotherapy can be effective for extensive metastatic disease in the liver in stage 4S disease,[166] but is less commonly used now, as other treatments are often effective.[167]

Palliation

For patients, especially when relapse has occurred after high-dose chemotherapy, where cure seems a very unlikely outcome, external beam radiotherapy can be used for palliation of symptoms. While often effective and widely used, there is a significant diversity of practice.[68] The most common indication is bone pain from skeletal metastases.[168] Short courses of treatment result in high rates of pain control with limited toxicity.[169] Craniospinal radiotherapy may be effective for CNS metastatic relapse, particularly when no extra-CNS disease is identified.[170]

MOLECULAR RADIOTHERAPY

Meta-iodobenzylguanidine Therapy

The catecholamine analog, mIBG, is taken up by the majority of neuroblastoma cells, and some normal tissues, though an active transport process. This has enabled the use of ^{123}I-mIBG to become the standard of care for imaging and staging of neuroblastoma, as discussed earlier. The use of higher activities of ^{131}I-mIBG can be cytotoxic when localized in neuroblastoma cells. First used as a palliative treatment in the 1980s, ^{131}I-mIBG therapy has gradually moved to an earlier stage in the management of metastatic neuroblastoma.[171] Reported response rates vary widely, depending on the schedule used, the position of the patient in the disease trajectory, and the definition of response.[172] The majority of reports of ^{131}I-mIBG therapy are case series in patients with relapsed or refractory disease, and despite evidence of effectiveness, it is difficult to ensure which schedules are best. To date, only one phase II randomized trial has been published, comparing either ^{131}I-mIBG therapy alone or in combination with irinotecan, vincristine, or vorinostat.[173] The response rate reported in the vorinostat arm was higher than that in the other two. The results of the COG ANBL1531 trial, which incorporated mIBG therapy into front-line therapy, are awaited.

Other Therapy Radiopharmaceuticals

Several other radiopharmaceuticals are being investigated in metastatic neuroblastoma, but all must be considered experimental rather than established therapy of proven benefit. ^{177}Lu-DOTATATE, which targets the somatostatin receptor and is an established form of peptide receptor radionuclide therapy for gastro-entero-pancreatic neuroendocrine tumors, has been assessed for the treatment of metastatic neuroblastoma. One study showed some transient responses, but no patient achieved the end point of a partial response after completion of therapy.[64] A further study with increased dose intensity is in progress.[174]

An alternative approach is the compartmental use of radiolabeled monoclonal antibodies to treat meningeal dissemination of neuroblastoma. Rather than intravenously, the radiopharmaceutical is delivered directly into the cerebrospinal fluid.[175]

RADIOTHERAPY SIDE EFFECTS

Acute Toxicity

Primary-site radiotherapy is generally well tolerated. Children having abdominopelvic treatment may experience gastrointestinal side effects, which should be managed with antiemetic and antidiarrheal medications, and stool softeners, as needed. Persistent nausea and/or vomiting can often be addressed with antiemetics given approximately an hour prior to radiotherapy. Symptoms of gastrointestinal reflux are rare due to low radiation dose but can be managed with H_2-blockers or proton pump inhibitors.

Children receiving radiation to the chest or neck may experience odynophagia from esophagitis; this is generally not severe, again due to low dose. Radiation to the head may cause fatigue, corneal irritation, or mucositis, which should be managed supportively. Skin toxicity is rarely more than grade 1 and can be managed with emollients.

Long-Term Effects

Long-term radiation toxicities are unfortunately common in young children and are based on the location of the radiation delivered. Toxicities from primary-site radiotherapy can include bowel obstruction, hepatotoxicity, diabetes, acute ovarian insufficiency/premature ovarian failure, cardiac toxicity, kidney hypoplasia, and second malignancy.[149-153] Short stature and/or scoliosis from vertebral body irradiation are also risks.[176] Patients who have undergone such radiotherapy should undergo screening tests for liver/kidney function annually, as well as hemoglobin A1c to screen for endocrine pancreatic insufficiency. Survivors should also consider screening for colorectal cancers and breast cancers in adulthood, as breast tissue may be part of an abdominal radiation field in small children.[177] Survivors may benefit from consultation with a reproductive endocrinologist if parenting is desired.

When radiotherapy is delivered to the thorax, cardiopulmonary toxicity is a long-term risk, and patients should undergo regular screening with pulmonary function testing and echocardiogram. Patients who have undergone head/neck radiation may develop dental anomalies, including missing teeth, caries, and/or malformed teeth, as well as cataract deve

lopment and orbital hypoplasia.[178,179] Those treated with skeletal metastases may be at risk for limb-length discrepancy and/or arthritis.[176]

Survivor education including abstaining from tobacco use, use of sun protection, recommended screening tests, healthy diet, and symptoms of bowel obstruction is essential to healthy survivorship, particularly as children develop and transition away from parental management of their medical care.[180]

OUTCOMES

The overwhelming majority of patients with low- and intermediate-risk neuroblastoma are survivors. Although for high-risk disease, prognosis has improved in recent decades as a result of better understanding of biology, improved supportive care, and additional therapeutic options, the mortality rate is still substantial, with only about half of those treated becoming long-term survivors. There is also a significant treatment-related long-term morbidity among those who do not die from disease. Therefore, for high-risk disease, although the landscape is gradually changing, efforts must continue to refine present treatments and find new treatments, with the twin aims of improving the probability of cure and diminishing late treatment-related complications.

FUTURE PRIORITIES

In the relatively resource-rich developed world, large cooperative clinical research groups such as COG and SIOPEN are running trials to refine and optimize care, and early-phase consortia such as NANT and ITCC are piloting new approaches. However, it must be remembered that most of the world's children live in less privileged environments, where access to cutting-edge treatment may not be available, and even the more standard approaches of chemotherapy, surgery, and radiotherapy may be hard to access.

Therefore, the priority for the future must not be restricted to basic science and clinical research aimed at improving outcomes and diminishing morbidity, but we must work toward making the best quality of evidence-based established treatment as widely available as possible.

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CHAPTER 93

Rhabdomyosarcoma

Michael D. Young and Dana L. Casey

ANATOMY

Rhabdomyosarcoma (RMS) is a highly malignant soft tissue sarcoma that arises from unsegmented, undifferentiated mesoderm or myotome-derived skeletal muscle. It may occur at any site in the body, but the most frequently involved sites are the orbit (9%), head and neck (excluding parameningeal tumors) (7%), parameningeal (25%), genitourinary (31%), extremity (13%), trunk (5%), retroperitoneum (7%), and other sites (3%).[1]

EPIDEMIOLOGY AND RISK FACTORS

RMS is the most common of the childhood soft tissue sarcomas, with an annual incidence of 4.4 per 1 million White people and 1.3 per 1 million Black people. The male-to-female ratio is approximately 1.5 to 1.0.[2]

The great majority of patients are less than 10 years of age at the time of diagnosis, and approximately 5% are less than 1 year of age. There are two peak age frequencies, at ages 2 to 6 and in adolescence. Tumors in the younger age group are likely to be of embryonal histology. About 25% of patients are 10 years or above at diagnosis, and their tumors are often of alveolar histology. Age has been identified as an independent predictor of prognosis, with children below 1 and above 10 years having inferior survival.[3] Adults with RMS have been reported to have poor outcomes, although there is evidence that when they are treated aggressively using pediatric-type protocols, the prognosis may be similar to that of younger patients.[4-6]

Although 5% to 10% of cases are associated with cancer predisposition syndromes, most cases of RMS are sporadic and the cause is unknown; however, it is associated with disorders in development, including central nervous system, genitourinary, gastrointestinal, and cardiovascular

anomalies, and with congenital disorders including congenital pulmonary cysts, Gorlin basal cell nevus syndrome, and neurofibromatosis. In addition, RMS is the most frequently occurring childhood cancer in families with Li-Fraumeni syndrome, and its incidence is increased in children with neurofibromatosis type 1, Beckwith-Wiedemann syndrome, and Costello syndrome.

Recent developments in cytogenetics and molecular genetics now provide a more comprehensive understanding of the origin and biologic behavior of RMS. The classic distinction of embryonal versus alveolar histology has been largely replaced by the PAX/FOXO1 fusion status (fusion negative vs fusion positive) for both prognostic and therapeutic decision-making. These details are discussed in more detail later.

NATURAL HISTORY AND PATTERNS OF SPREAD

There are unexplained associations of site of primary tumor with age at diagnosis and tumor histology. For example, tumors arising in the urinary bladder and vagina occur primarily in infants and are often of the embryonal or botryoid histologic type. Tumors arising in the trunk and extremity occur in adolescents and are often alveolar. Tumors of the head and neck area occur throughout childhood and are commonly of the embryonal type.

RMS, a locally invasive tumor often with a pseudocapsule, has the potential for local spread along fascial or muscle planes, lymphatic extension, and hematogenous dissemination. The overall risk of regional lymphatic spread is approximately 15% but varies with the site of the primary lesion. Lymph node metastases are rare in orbital tumors, but they occur in approximately 15% of tumors at other head and neck sites, most commonly the nasopharynx. Accounting for staging inaccuracies, regional lymph node extension occurs in approximately 25% of children with paratesticular, extremity, and truncal tumors and in approximately 50% of children with perineal and perianal tumors.[7,8] The risk for lymph node involvement also correlates with primary tumor invasiveness and large tumor size.

Hematogenous metastases are detected at the time of presentation in approximately 15% of patients, particularly those with truncal and

extremity primary tumors. The most common sites of hematogenous dissemination are lungs, bone marrow, and bone. Malignant pleural and peritoneal effusions may also accompany tumors primarily to the chest and abdomen or pelvis, respectively.[9]

CLINICAL PRESENTATION

Because RMS occurs in multiple primary sites, there are many site-specific clinical signs and symptoms. It usually presents, however, as an asymptomatic mass. When symptoms are present, they relate to the mass effect on associated organs and tissues. Tumors in the orbital area may cause proptosis and ophthalmoplegia. Patients with parameningeal tumors often present with nasal, aural, or sinus obstruction; cranial nerve palsy; and headache. Genitourinary tumors may cause hematuria, urinary obstruction, or constipation.

DIAGNOSTIC WORKUP

Determination of tumor extent is best done with a multidisciplinary approach by a radiation oncologist, pediatric oncologist, and appropriate subspecialty surgeon. An expeditious local and systemic workup is essential because these tumors have the potential to grow rapidly. The initial assessment by all members of the team permits accurate staging and the formation of a uniform treatment plan. Table 93.1 provides recommendation for diagnostic workup at various sites. Experience with combined positron emission tomography (PET) and computed tomography (CT) scanning indicates this modality may be a valuable component of staging[10] and may in fact provide more accurate staging than conventional imaging.[11] PET-CT may be especially valuable in assessing response to therapy and in predicting outcomes, as conventional imaging has not shown a good correlation of tumor response to long-term clinical outcome.[12-14] Some children whose tumors exhibit characteristic fusion transcripts can be shown to have micrometastatic disease using reverse transcriptase polymerase chain reaction techniques, even when there is no evidence of metastases from routine diagnostic procedures. The clinical significance of this is, however, unknown.[15] For imaging of the primary tumor, magnetic resonance imaging (MRI) is often indicated and provides superior soft

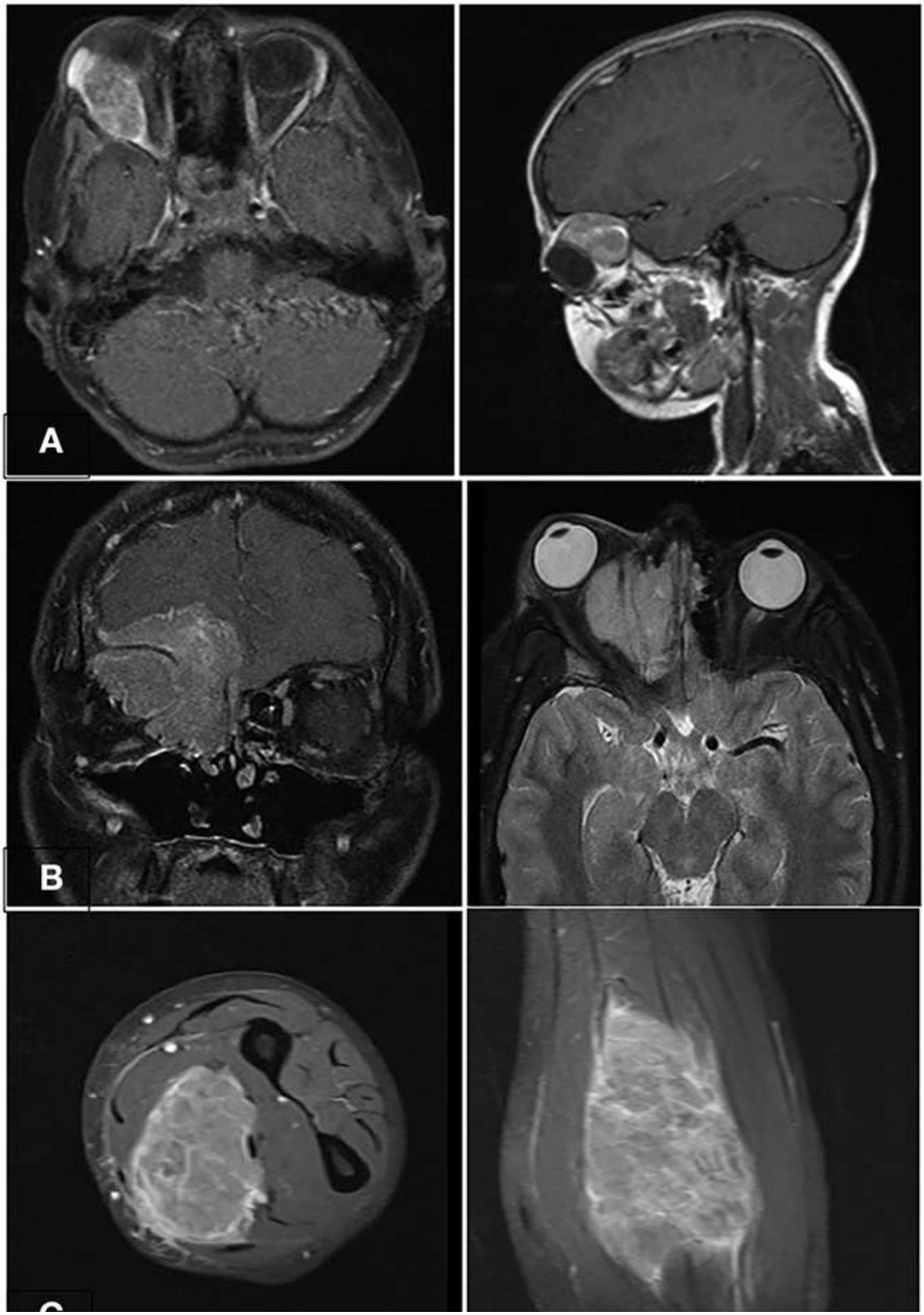
tissue contrast when compared with CT imaging. For radiation planning, preferred sequences include morphologic sequences (T1-, T2-weighted sequences with fat-suppressed T2 sequences) and postcontrast T1 sequences (Figure 93.1). In addition, diffusion-weighted sequences can help distinguish reactive edema from residual tumor and aid in tumor response and radiation planning.

TABLE 93.1 RECOMMENDED WORKUP FOR TUMORS AT VARIOUS SITES

All Patients	Optional
All sites	
History	
Physical examination by several observers (including a pediatric oncologist, surgical oncologist, and radiation oncologist)	Examination under anesthesia for infants and youngsters
Laboratory studies Complete blood count Liver function tests Renal function tests Urinalysis	Plain films of bones abnormal on scans Abdomen/pelvis CT, MRI, or ultrasound
Imaging studies	
PET-CT (this study can likely replace chest/abdomen/pelvis CT and bone scan studies)	
MRI or CT of primary tumor	
Bone marrow biopsy and aspirate	
Head and neck	
MRI or CT of primary tumor (with contrast)	Plain films of area
Lumbar puncture with cytologic examination of fluid (in parameningeal primary tumors)	Dental evaluation and x-rays Paranasal sinus and skull films MRI of the spine if cerebrospinal fluid is positive or patient is symptomatic
Genitourinary	
CT of MRI of the abdomen/pelvis (with contrast)	Ultrasound of the pelvis
Pelvic examination under anesthesia	Cystoscopy
Extremity and truncal lesions	

All Patients	Optional
MRI or CT of primary lesion (with contrast)	Plain films of primary site
	Ultrasound
	Barium gastrointestinal contrast studies

CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.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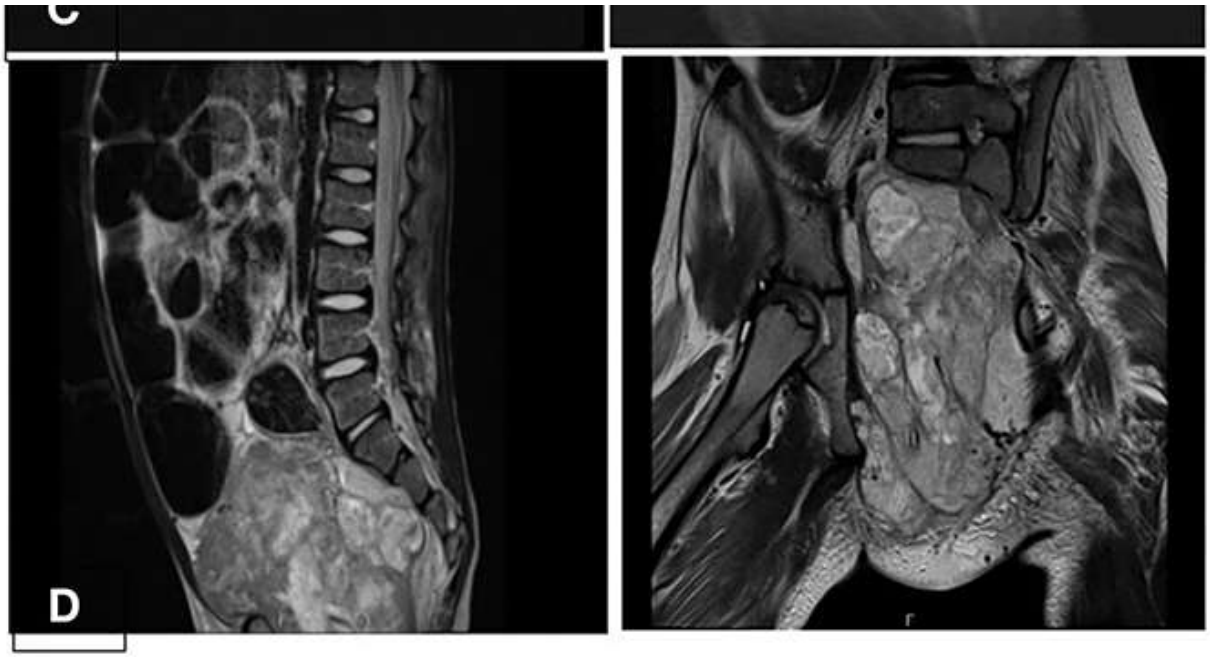

FIGURE 93.1 Magnetic resonance images with T1 postcontrast and T2 sequences with and without fat suppression depicting orbital rhabdomyosarcoma (A), parameningeal rhabdomyosarcoma with intracranial extension appreciated on coronal views (B), extremity rhabdomyosarcoma (C), and pelvic rhabdomyosarcoma (D).

STAGING SYSTEMS

The clinical grouping classification used extensively by the Intergroup Rhabdomyosarcoma Study (IRS) Group (now known as the Children's Oncology Group Soft Tissue Sarcoma [COG STS] committee) investigators is somewhat of a misnomer because it actually requires surgical pathologic evaluation (Table 93.2). It is not a staging system and does not accurately reflect the biology of the disease; rather, it reflects the surgical procedure selected for an individual patient. It is, however, useful for guiding decisions for radiotherapy, based on the amount of residual tumor after the initial surgical procedure. A more valid pretreatment staging system uses a tumor, node, metastasis (TNM) approach, which emphasizes characteristics of the primary tumor, size and invasiveness, nodal status, and systemic spread. Noninvasiveness, small size, and an absence of metastases have been shown to influence prognosis.[16] The site of primary tumor also has a significant impact on local control and survival.[17,18] The Intergroup Rhabdomyosarcoma Study-IV (IRS-IV) prospectively demonstrated the validity of a staging system incorporating TNM classification along with

primary tumor site (Table 93.3). Three-year failure-free survival was 86% for stage 1 tumors, 80% for stage 2, 68% for stage 3, and 25% for stage 4.[1,9] Of note, the clinical grouping did not correlate as well with survival. In fact, failure-free survival for clinical group II patients in the IRS-IV study was superior to that for clinical group I patients (86% vs 83%), probably reflecting the routine use of radiotherapy for group II patients.

TABLE 93.2 INTERGROUP RHABDOMYOSARCOMA STUDY CLINICAL GROUPING CLASSIFICATION

Group I	Localized disease, completely resected
A	Confined to organ or muscle of origin
B	Infiltration outside organ or muscle of origin; regional nodes not involved
Group II	Compromised or regional resection
A	Grossly resected tumor with microscopic residual disease
B	Regional disease, completely resected, in which nodes may be involved or extension of tumor into adjacent organ may exist
C	Regional disease with involved nodes, grossly resected, but with evidence of microscopic residual disease
Group III	Incomplete resection or biopsy with gross residual disease
Group IV	Distant metastases at diagnosis

Adapted from Maurer HM. The intergroup rhabdomyosarcoma study II: objectives and study design. *J Pediatr Surg*. 1980;15(3):371-372. Copyright © 1980 Elsevier. With permission.

TABLE 93.3 INTERGROUP RHABDOMYOSARCOMA STUDY PRETREATMENT STAGING SYSTEM

Stage	Site[a]	Invasiveness	Size	Nodal Status	Metastases
I	Favorable	T1 or T2	a or b	N0 or N1	M0
II	Unfavorable	T1 or T2	A	N0	M0
III	Unfavorable	T1 or T2	B	N0	M0
			a or b	N1	M0
IV	Any site		T1 or T2	N0 or N1	M1

a, ≤5 cm; b, >5 cm; M0, no distant metastasis; M1, evidence of distant metastasis; N0, no evidence of regional node involvement; N1, evidence of regional node involvement (enlargement of nodes on radiographic imaging is considered evidence of involvement, although histologic confirmation is recommended when possible); T1, tumor confined to site or organ of origin; T2, regional extension beyond the site or organ of origin.

[a]Favorable sites: orbit, head and neck (nonparameningeal), and genitourinary (non–bladder-prostate); unfavorable sites: genitourinary (bladder-prostate), extremity, and parameningeal, other.

PATHOLOGIC CLASSIFICATION

The histogenesis of RMS can be traced from mesoderm to mesenchyme and ultimately to striated muscle tissue. The classification of RMS initially used by the IRS investigators consisted of four histologic subtypes: embryonal, botryoid subtype of embryonal, alveolar, and pleomorphic. Embryonal histologies constitute approximately two-thirds of all cases, with most of the rest having alveolar histology.[19] Other variants including a "solid" alveolar pattern, considered a subtype of alveolar RMS, a spindle cell subtype of embryonal RMS, and a diffuse anaplastic variant have also been described.[20]

To improve reproducibility of pathologic subtyping and prognostic utility, pediatric pathologists developed an updated classification system: the International Classification of Rhabdomyosarcoma. This system is based on a review of the second IRS (IRS-II) data, and it groups pathologic subtypes into distinct prognostic groups. The International Classification of Rhabdomyosarcoma system appears to be predictive of outcome and has been reproduced by several reference pediatric pathologists.[20,21] The superior prognosis group, consisting of two subsets (botryoid and spindle cell), carries a projected 5-year survival rate of 88% to 95%.[21] The botryoid subtype, a polypoid variant of embryonal RMS, has a grapelike appearance. The stroma consists of loose cellular tissue with a myxoid appearance. Under the superficial stroma is a hypercellular zone of tumor cells called the cambium layer of Nicholson. Botryoid tumors are usually noninvasive and localized and occur in mucosal-lined organs, such as the vagina, urinary bladder, middle ear, biliary tree, and nasopharynx. The spindle cell subtype of embryonal RMS has a spindled appearance, often with a storiform pattern. It is frequently found in paratesticular sites.

Patients with embryonal RMS have an intermediate prognosis, with an 83% failure-free survival at 3 years.[17] The embryonal type consists of blastemal mesenchymal cells that tend to differentiate into cross-striated muscle cells. There is often a considerable variation in the degree of cytoplasmic development, ranging from primitive mesenchymal to highly differentiated muscle tumor cells. Most of the tumor cells have eosinophilic cytoplasm, which is positive by periodic acid-Schiff staining. Immunohistochemistry may demonstrate actin- or desmin-positive reactions. Ultrastructural studies exhibit evidence of myogenesis with the presence of thick and thin cytoplasmic intermediate filaments or Z-band material. Ribbon or strap-shaped cells and tadpole cells are characteristic. The presence of cross-striations confirms the diagnosis. The embryonal form may be distinguished from the other subtypes by specific structural abnormalities. A consistent loss of heterozygosity at the chromosome 11p15.5 locus suggests that this site is specific for the embryonal subtype,[22] although, unlike alveolar histology, no characteristic translocation has been identified. Immunohistochemical presence of epidermal growth factor receptor and fibrillin-2 appears to be highly specific for embryonal histology and is predictive of a favorable outcome.[23,24] Dysregulation of the renin-angiotensin system (RAS) pathway has also been found in some patients and may be involved in the pathogenesis of this subtype.[25] The embryonal histology is found most commonly in the orbit, head and neck, and genitourinary sites.

The group with poor prognosis includes alveolar, diffuse anaplastic, and undifferentiated sarcomas. With routine use of immunohistochemistry and molecular genetic analysis, about one-third of RMSs are classified as alveolar; it is most commonly found in adolescents with truncal, retroperitoneal, and extremity tumors. The alveolar subtype is characterized by a pseudoalveolar pattern of connective tissue trabeculae, lined by large rhabdomyoblasts and multinucleated giant cells. The “solid” variant of alveolar RMS grows as solid nests of closely aggregated tumor cells with less alveolar pattern. Alveolar histology is strongly associated with hyperdiploid content.[26] Approximately 75% of children with alveolar RMS exhibit a characteristic translocation involving chromosomes 2 and 13, t(2;13)(q35;q14), and, occasionally, a 1;13 translocation.[22,27] These translocations correspond to abnormal fusion genes involving *PAX3-FKHR*

and *PAX7-FKHR*, respectively, and are probably the initial oncogenic events in these tumors.[28,29] Immunohistochemical presence of AP2-β and P-cadherin is also highly specific for alveolar histology.[23,24] The projected 3-year failure-free survival for children with the alveolar subtype is 66%.[1]

Undifferentiated sarcoma is largely a diagnosis of exclusion; it consists of a diffuse cell population of primitive, noncommitted mesenchymal cells. The 3-year failure-free survival rate of patients with undifferentiated sarcoma is 55%.[1] Today, sarcomas that lack characteristics of differentiation are most appropriately managed as non-RMS soft tissue sarcomas, though their outcomes have been similar to alveolar RMS.

The pleomorphic type is extremely rare; many cases formerly classified as pleomorphic RMS are currently considered to be malignant fibrous histiocytoma. Previously, tumors classified as extraosseous Ewing sarcoma were treated using guidelines for RMS. These are more appropriately considered in the Ewing family of tumors and are managed as such.

As more is learned about the molecular biology of RMS, fusion status rather than histology seems to be the more important driver of clinical outcomes. Recent data suggest that fusion-negative alveolar RMS is more similar to embryonal histology both clinically and molecularly.[30] On COG D9803, there was a trend toward improved event-free survival (EFS) among patients with fusion-negative alveolar RMS when compared to those with embryonal RMS (EFS 90% vs 77%).[31] Other studies have confirmed that fusion status may be more important prognostically than histology.[30,32] As such, modern COG clinical trials account for fusion status in addition to histology for risk stratification.

PROGNOSTIC FACTORS AND THERAPEUTIC CONSIDERATIONS

Because RMS is protean in presentation, factors such as age, site, stage, extent of disease, and pathologic characteristics of the tumor influence therapeutic decisions. These prognostic factors are interrelated and are best discussed as a function of the specific site (Figure 93.2). Although most treatment failures occur within 3 years of diagnosis, about 10% of children who are free of disease at 5 years will subsequently experience disease recurrence.[33]

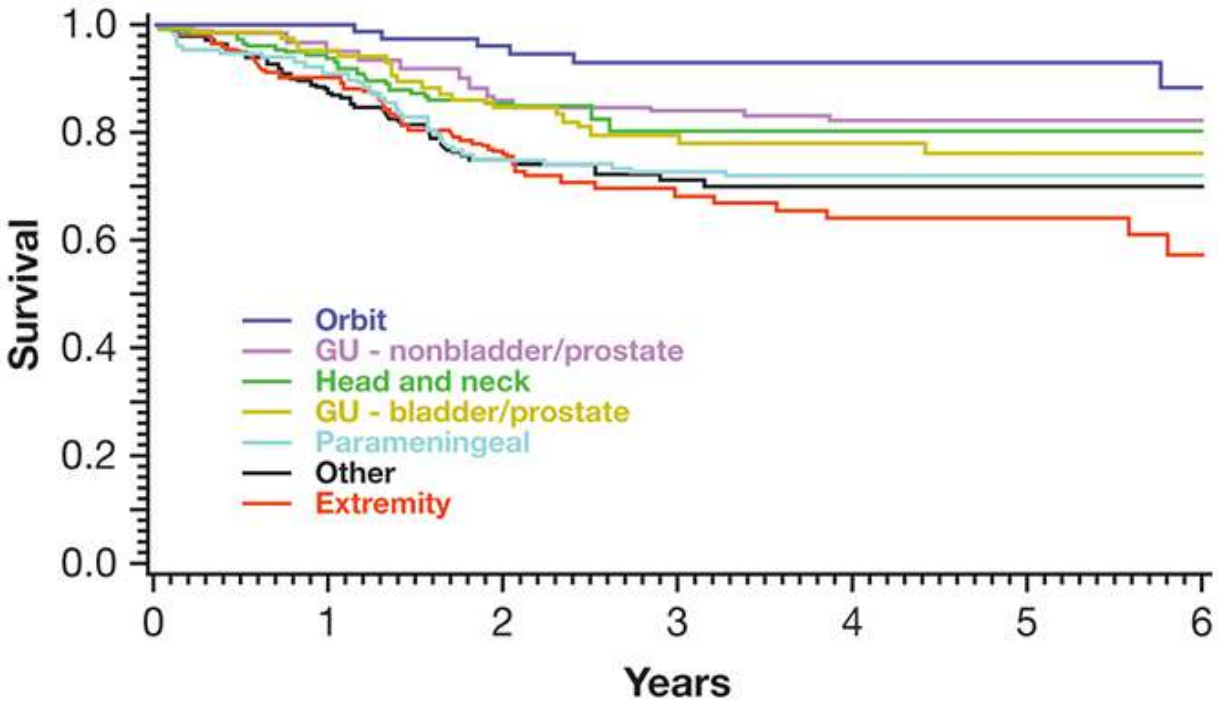

FIGURE 93.2 Survival curves for 883 children with nonmetastatic disease entered into the fourth Intergroup Rhabdomyosarcoma Study are shown by anatomic site of the primary tumor. GU, genitourinary. (Adapted with permission from Crist WM, Anderson JR, Meza JL, et al. Intergroup rhabdomyosarcoma study-IV: results for patients with nonmetastatic disease. *J Clin Oncol*. 2001;19[12]:3091-3102. Copyright © 2001 by American Society of Clinical Oncology.)

Orbit

The orbit has long been recognized as a favorable prognostic site (see Figure 93.1A). In addition to prompt recognition of the tumor, the paucity of lymphatics in this area means that lymphatic extension is rare. Most tumors in this site have embryonal histology and are fusion negative, and hematogenous metastasis at the time of diagnosis is uncommon. Approximately 10% are alveolar histology, however, and the prognosis for these children is more guarded.[34]

When treatment for orbital tumors is individualized, it is generally agreed that no surgical procedure should be used that may compromise vision or loss of function. In most patients, this means that biopsy only should be performed to provide the diagnosis. Primary treatment typically consists of vincristine, actinomycin-D, and cyclophosphamide (VAC) or vincristine and actinomycin-D (VA) chemotherapy with local radiotherapy beginning

after the 12th week of treatment. Radiation doses of approximately 50 Gy are often used. Dose reduction to 45 Gy was tested on D9602, resulting in a local failure rate of 14% (compared to 5% seen on IRS-IV).[35,36] A dose of 45 Gy was shown to result in unacceptable rates of local control for orbital RMS again on ARST0331 in those without a complete response to chemotherapy. As discussed later, orbital tumors should be treated with similar doses as other primary sites.

Chemotherapy without irradiation has resulted in local relapse and inferior EFS.[37] Although salvage radiotherapy for these patients can still be curative, functional vision in this setting is often poor.[38] Orbital exenteration should be reserved for salvage treatment and enucleation for the management of post-treatment ocular complications.

With a combined modality approach, radiotherapy can be directed to the tumor plus a margin without necessarily irradiating the entire orbit. Technique is very important for minimizing corneal and lacrimal gland dose and for preserving useful vision, ocular function, and appearance. Photon irradiation with the eyelid open can minimize the corneal dose when an anterior field is used and may be associated with improved long-term functional outcome.[39] Intensity-modulated radiotherapy techniques or proton therapy when available are optimal for treating the target volume and sparing normal structures.[40]

Head and Neck: Parameningeal Sites

Nonorbital RMS of the head and neck is grouped into parameningeal sites (nasopharynx, nasal cavity, paranasal sinuses, middle ear, pterygopalatine fossa, and infratemporal fossa; see Figure 93.1B) and nonparameningeal sites based on differences in natural history, treatment, and prognosis. Parameningeal RMS represents the majority of nonorbital head and neck RMS, and radiotherapy is essential for maximizing the probability of cure.[17,41] These tumors have a propensity for invading the base of the skull, creating a potential for cranial nerve palsy and direct extension into the central nervous system, a pattern of spread that is seen in as many as 41% of these patients.[42] Historically, as many as 35% of children with tumor arising in a parameningeal site would later have meningeal extension, and previous irradiation regimens called for whole-brain irradiation as part of

central nervous system prophylaxis.[43] However, the prognosis of these patients is markedly improved with appropriate imaging, multiagent chemotherapy, and adequate irradiation of the primary tumor and adjacent meninges, and studies demonstrate that whole-brain irradiation is not necessary, even in the presence of direct intracranial tumor extension.[44] However, patients with known meningeal dissemination (as determined via cerebrospinal fluid analysis and/or imaging) may receive craniospinal irradiation. A radiation dose of 50.4 Gy in 28 fractions to the primary site is commonly used. Data from the IRS studies show improved local control in patients with intracranial tumor extension when radiotherapy is started within 2 weeks of diagnosis,[42] although other reports show no disadvantage with delayed radiotherapy.[45]

Aggressive surgery is rarely indicated because complete resection is usually not possible, does not obviate the need for high-dose radiation therapy, and often results in a delay of systemic chemotherapy because of postoperative complications. Surgical approaches to these tumors have been described by proponents of multispecialty skull base surgery, but the efficacy of these approaches has not been firmly established.[46] Delayed surgical resection has been proposed as beneficial for children with residual tumor after completing chemotherapy and radiotherapy but is not considered standard of care and has not been shown to improve oncologic outcomes.[47-49]

Five-year survival for patients with parameningeal RMS is approximately 75% with adequate radiotherapy.[50] For the subset of parameningeal tumors arising in the nasopharynx or nasal cavity, middle ear, and parapharyngeal locations, survival may be even higher,[44] and functional and cosmetic outcomes can be good with conformal radiation techniques in spite of an aggressive treatment regimen (Figures 93.3 and 93.4).

FIGURE 93.3 A 12-year-old girl treated at age 3 years for an embryonal rhabdomyosarcoma of the nasal cavity. Her treatment consisted of excisional biopsy, followed by vincristine, actinomycin-D, and cyclophosphamide chemotherapy and 41.4-Gy radiotherapy. Slight hypoplasia of the midface is evident, but overall cosmesis is excellent.

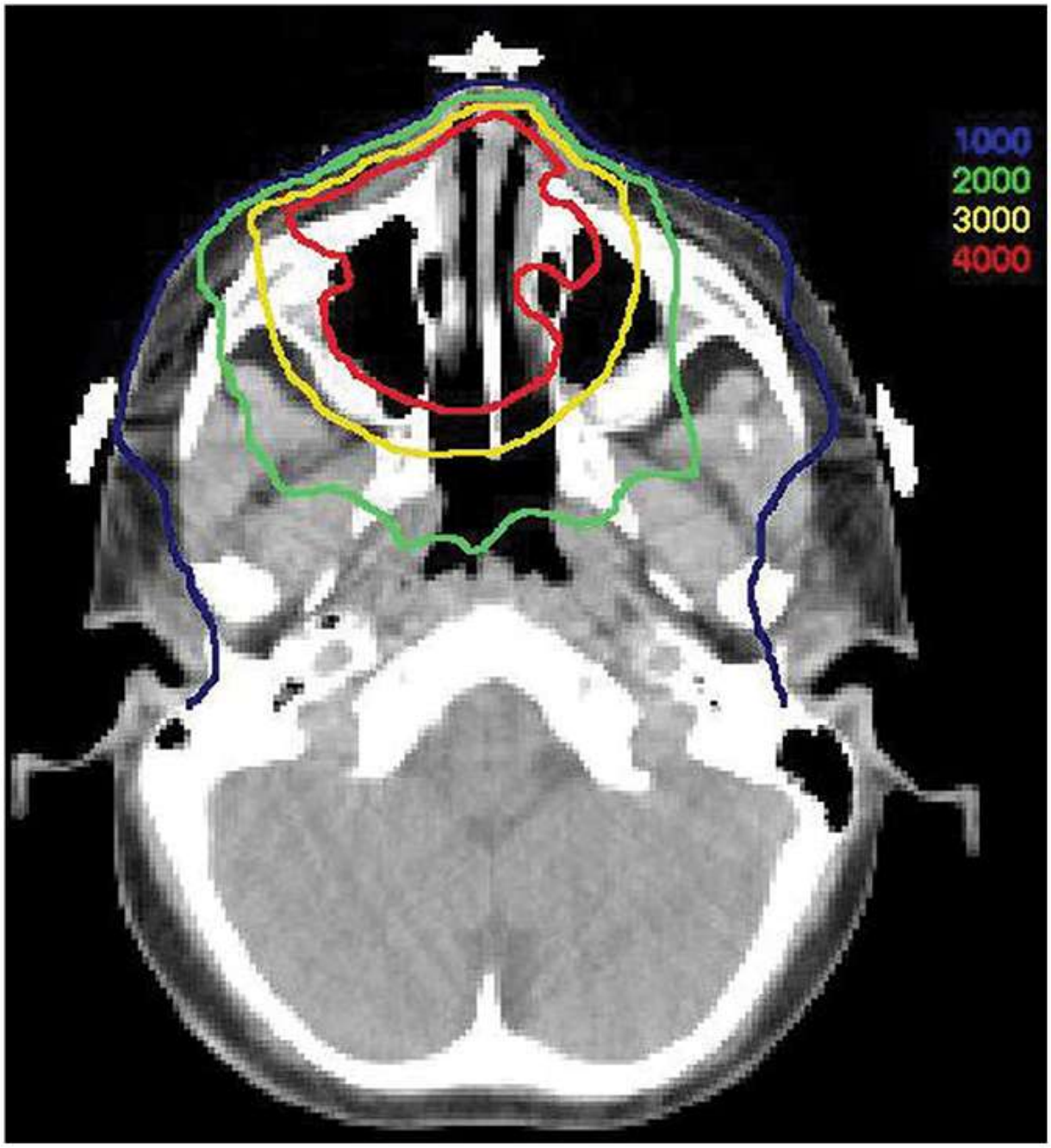

FIGURE 93.4 Isodose distribution from the treatment of the child in Figure 93.3 (doses in cGy).

Head and Neck: Nonparameningeal Sites

Children with tumors in nonparameningeal head and neck sites tend to have a better outcome than their parameningeal counterparts (80% 5-year failure-free survival in IRS-IV) and may require less intensive chemotherapy.[1,17]

These sites include the scalp, parotid, oral cavity, larynx, oropharynx, and cheek (see Figure 93.1C). These tumors may be more amenable to complete gross surgical excision compared with their parameningeal counterparts. Approximately 15% of these patients present with regional lymph node metastases. Radiotherapeutic management is based on the extent of resection, if performed. Draining regional lymph nodes are not routinely irradiated unless they are considered to be involved with tumor by clinical or pathologic assessment.

Pelvis

Pelvic tumors are usually divided into anatomic subgroups because the natural history, treatment, and prognosis are different for each site (see Figure 93.1D). Some children present with locally advanced pelvic tumors for which an exact site of origin cannot be determined. These large tumors are associated with an unfavorable prognosis.

Bladder and Prostate Tumors

Bladder and prostate primary tumors account for about half of all pelvic RMS[41]; 75% of patients are aged less than 5 years at presentation, and more than 90% of these tumors are of the embryonal histologic subtype, with approximately one-third having a botryoid morphology. In boys, it is often difficult to differentiate a tumor of prostatic origin from one of bladder origin because the disease usually involves both structures. However, patients with tumors arising in the prostate have significantly inferior survival compared with those with tumors confined to the bladder.[51]

Historically, anterior pelvic exenteration (or partial cystectomy for small tumors arising from the dome of the bladder) combined with chemotherapy and irradiation for microscopic or gross residual disease has been associated with a survival rate of approximately 70%.[18] This strategy evolved to one with limited surgery to preserve bladder function. The IRS-II study treated these patients primarily with chemotherapy followed by delayed surgery or radiation therapy when there was residual or recurrent disease. This approach resulted in an inferior 3-year disease-free survival rate of 52%, compared with 80% for a primary radical surgical approach, and only 22% of patients survived with intact bladders.[52] Subsequently, IRS-III intensified

the therapy with systematic use of planned irradiation 6 weeks after the start of treatment and added cisplatin and doxorubicin (Adriamycin) chemotherapy.[53] The 5-year survival rate for patients with locoregional disease was 82%, with 64% of surviving patients retaining functional bladders, demonstrating the necessity of routine radiation therapy early in treatment.[54] Survival of patients with locoregional bladder or prostate tumors treated on IRS-IV was similar, with 40% of all enrolled patients reporting normal bladder function at follow-up.[55] A more recent analysis showed maintenance of continence in 69% treated with conservative surgery in a multimodality treatment program.[56]

The German Cooperative Weichteilsarkom Studiengruppe CWS-96 protocol treated children with bladder or prostate RMS using multiagent chemotherapy followed by response-adapted radiotherapy and surgery. Children with complete resection did not have radiotherapy, whereas others received 32 to 44.8 Gy using 1.6 Gy twice a day, depending on the tumor's IRS group and response to chemotherapy. Five-year EFS was 70%.[57]

A pooled analysis of patients treated prospectively on several cooperative group trials from North America and Europe showed improved local control for those who received radiotherapy as part of their initial treatment, but this did not translate into improvement in overall survival.[58]

Paratesticular Tumors

Paratesticular tumors represent approximately 7% of all RMS and may arise anywhere along the spermatic cord, from the intrascrotal area through the inguinal canal.[59] At presentation, the tumor is usually a painless scrotal or inguinal mass that does not transilluminate. Most boys with paratesticular RMS present with early-stage disease that is amenable to complete resection and is associated with cure rates approaching 90%. As with prostatic primary tumors, the lymphatic network is rich, draining directly to the retroperitoneal nodes along the external iliac and spermatic vessels, the aorta, and the vena cava. The incidence of retroperitoneal lymph node involvement varies with the age of the patient and the method of staging (surgical vs nonsurgical). In the IRS-III study, retroperitoneal lymph node sampling was done in most patients, showing a 14% incidence of node involvement for children less than 10 years of age and a 47% incidence for

those 10 years or above. In IRS-IV, thin-cut CT without surgical sampling was used for staging, and the incidence of detected nodes dropped to 4% and 13% for the two age groups, respectively.[59]

The recommended surgical procedure for the primary tumor is inguinal orchiectomy. If there is no evidence of invasion into the scrotum and the proximal spermatic cord is free of tumor, this procedure is considered equivalent to an amputation, and no further local therapy is necessary. In the IRS, the high risk of nodal involvement in certain subsets of these patients has led to the recommendation for ipsilateral retroperitoneal nerve–sparing node dissection for staging of all children 10 years of age or above.[59] In the absence of histologic documentation, enlargement of retroperitoneal lymph nodes on thin-section CT imaging is considered evidence of tumor involvement.

Patients with nodal disease have a 5-year survival rate of 69%, compared with 96% for those without regional nodal disease ($P < .001$). Regional lymph node irradiation to the periaortic and ipsilateral iliac nodes is recommended when there is nodal involvement.[60] Surgical violation of the scrotum or tumor extension to the structure is an indication for hemiscrotectomy or, less commonly, scrotal irradiation. If scrotal irradiation is used, orchiopexy should be considered prior to treatment to protect the remaining testes. Treatment programs must be planned to reduce morbidity, particularly among this group with a high likelihood of cure.

Gynecologic Tumors

Tumors arising in the vulva, vagina, cervix, and uterus are about one-third as common as bladder and prostate primary tumors and account for 4% of all RMS.[61] Within this group, the vagina is the most common site of origin.

Patients with vaginal tumors are often much younger than those with other pelvic RMS, with most girls diagnosed before the age of 3 years. Most present with a vaginal mass or discharge; botryoid morphology is common. Initial surgery is used primarily for diagnosis, although gross tumor resection is occasionally possible without cosmetic or functional deformity. These tumors are often quite sensitive to chemotherapy, and treatment regimens had previously used a strategy of chemotherapy only, reserving surgery and radiotherapy for persistent or recurrent tumor.[61-63]

However, analysis of data from the IRS-IV and IRS-V studies has revealed high rates of local failure for vaginal tumors when local control with surgery or radiotherapy is omitted.[36,64] Current guidelines from the COG STS committee call for radiotherapy, often with intravaginal brachytherapy to limit dose to surrounding normal tissues such as ovaries, in all patients with postsurgical microscopic or macroscopic tumor.

Uterine, cervical, and vulvar tumors receive chemotherapy and radiotherapy based on the amount of tumor present after initial surgery. Intracavitary and interstitial brachytherapy are useful irradiation techniques in some of these patients.[65] Data are limited, but with proper patient selection, disease control is excellent and late normal tissue effects may be significantly less with brachytherapy than is seen with external beam techniques.[66] Permanent implants with iodine-125 and temporary low-dose rate and high-dose rate brachytherapy have all been used, and there are no clear differences among these techniques in terms of disease control or late effects. When temporary implants are used, high-dose rate brachytherapy has the practical advantage of minimizing radiation exposure to the family and medical personnel caring for the child.

Survival after treatment is excellent. Children aged 1 to 9 years have a 98% 5-year survival. Survival for infants and adolescents approaches 90%, although these patients may require more intensive systemic therapy for cure.[61]

Other Pelvic Sites

These tumors include perianal, perirectal, and perineal primary sites. The location of these primary tumors creates surgical and irradiation challenges. Combined chemotherapy and radiation therapy programs are favored over primary surgical procedures if excision requires exenteration with urinary and fecal diversion procedures or is associated with organ or sphincter dysfunction. In general, tumors in these locations are associated with poor prognostic features, high rates of regional nodal involvement, and dismal outcomes, especially in children above 10 years of age.[8]

Extremity

Tumors arising in the extremity are often of the alveolar or undifferentiated subtypes, large, deeply invasive, and associated with a high probability of lymphatic and hematogenous metastasis (Figure 93.1).[67] Complete surgical resection is difficult to achieve, usually requires extensive dissection, and is associated with a high risk of residual disease. Because radiation therapy and multiagent chemotherapy have been shown to provide excellent local control, it is advisable to avoid disfiguring and mutilating surgical procedures, with their attendant functional disabilities, and to recommend limb-salvage procedures, including irradiation and chemotherapy.

Regional lymph node involvement is present in approximately 24% of patients and confers a more guarded prognosis.[67] Aggressive surgical staging of draining lymph node basins is important to define the extent of involvement, although if lymph node dissection is performed, it is for the purpose of staging, not for treatment. Sentinel lymph node mapping and biopsy provide diagnostic and prognostic value for extremity tumors.[68,69] Radiotherapy of involved regional lymphatics is mandatory, and aggressive treatment of involved in-transit nodal sites may improve overall local control.[7]

Radiation therapy for extremity primary tumors requires careful immobilization techniques, sparing of nonirradiated skin for lymphatic drainage, and use of shrinking fields. Routine physical therapy during and after radiation therapy is important for obtaining an optimal functional result. Overall survival at 3 years for these patients is about 70%, although failure-free survival is only 55%.[70]

Other Sites

Patients with tumors arising in sites such as a paraspinal, retroperitoneal, or intrathoracic location have a poor outcome compared with other patients.[17] Most patients with tumors in these locations are unable to undergo complete resection of the tumor. Both local and distant relapse are common. These patients should be treated aggressively with high-dose radiation therapy and multiagent chemotherapy.

Metastatic Disease

Hematogenous or distant lymph node metastasis at the time of diagnosis is an ominous finding, although not all these children do poorly. The subset of patients who are less than 10 years of age, fusion negative, and have only one or two sites of metastatic disease may have long-term survival chances of more than 50%.[9] Intensive multiagent chemotherapy plays a major role in the treatment of these patients, although marrow ablative techniques have not improved efficacy compared with conventional chemotherapy approaches.[71,72] Local control of the primary tumor is site specific, as previously described. Metastatic sites should be treated with comprehensive radiotherapy whenever feasible for optimal oncologic outcomes, and control rates after radiation are similar to local control rates at the primary site.[73] The role of stereotactic body radiotherapy (SBRT) for bony sites of metastatic disease is currently being explored. Whole-lung irradiation for lung metastases is currently the standard of care, although SBRT for residual lung metastases is also an area of active investigation.[74,75]

RESULTS OF THERAPY: SUMMARY OF CLINICAL TRIALS

Because of the low incidence of RMS, much of what has been learned about its treatment has come from cooperative group trials performed in North America and Europe. Various cooperative groups have used different philosophies of treatment. In general, the North American IRS and COG studies have emphasized the role of local control measures, and European studies have focused more on chemotherapeutic approaches.

Intergroup Rhabdomyosarcoma Studies

The IRS began intergroup clinical trials for RMS in 1972 and has enrolled several thousand children with this disease since then. A primary goal has been to test the efficacy of chemotherapy and radiation therapy as a function of surgical stage. In the IRS-I study, radiation therapy was given initially for patients with group I and II disease and was delayed until week 6 for those with group III and IV disease. All patients received multiagent chemotherapy for 2 years. This study made several important observations[76]:

1. For localized tumors amenable to complete resection (IRS group I), postoperative radiation therapy is unnecessary if the patient is given 2 years of VAC. For these patients, the relapse-free survival rate in IRS-I at 5 years was 80%, and the 5-year survival rate was 81% to 93%. Subsequent analysis has shown a benefit to postoperative radiation therapy for patients with group I tumors of alveolar or undifferentiated histology.[119]
2. VAC failed to improve results obtained with intensive VA for patients with group II disease if postoperative radiation therapy was given. For these patients, the relapse-free survival rate at 5 years was 65% to 72%, and the overall 5-year survival rate was 72%.
3. VAC + Adriamycin provided no advantage over VAC for patients with group III disease (gross residual) or group IV disease (metastasis) if routine radiation therapy was used in addition. The complete remission rate for group III patients was 69%, and for group IV patients, it was 50%. Those who achieved complete remission had a 60% chance of staying in remission for 5 years in group III and a 30% chance in group IV. The survival rate at 5 years was 52% for group III and 20% for group IV patients.
4. The 5-year survival rate for the entire group was 55%.
5. Survival after relapse was poor—32% at 1 year and 17% at 2 years.
6. The risk of distant metastasis was much greater than the risk of local recurrence.
7. Primary tumors of the orbit and genitourinary tract carried the best prognoses, and tumors of the retroperitoneum had the worst.
8. The alveolar histologic subset had a poor prognosis, especially in extremity lesions.

IRS-II was built on the findings of IRS-I.[41] The results from this study include the following:

1. The 5-year survival rate for the IRS-II group was 62%, with a 7% improvement over the IRS-I rate.
2. Patients in group I (excluding patients with alveolar extremity) had better disease-free status with VAC (82%) than those who received only

VA (68%), but they had similar survival rates (82% and 88%) at 5 years. Cyclophosphamide could not be withdrawn safely from the standard VAC regimen if irradiation was omitted from patients with group I disease.

3. Intensive (cyclic-sequential) VA therapy was as effective as repetitive pulse VAC therapy for patients with group II disease, if all patients received postoperative irradiation. At 5 years, 68% to 75% remained disease free and 77% to 90% were alive, with no differences between the two therapy groups.
4. Repetitive pulse chemotherapy for 2 years increased survival in children with group III disease, but not in those with group IV disease; doxorubicin and dactinomycin had comparable efficacy in the pulse regimens used. The complete remission rates were 72%. At 5 years, 70% remained in complete remission and 64% were surviving.
5. In IRS-I, patients having tumors in parameningeal sites with high-risk factors (cranial nerve palsy, erosion of the base of the skull, or intracranial extension) had a high incidence of central nervous system relapse. In IRS-II, whole-brain radiotherapy irradiation, with or without intrathecal chemotherapy, was introduced. This prevented meningeal recurrence and increased survival in these patients with high-risk parameningeal primary tumors.
6. Primary repetitive pulse VAC for patients with special pelvic primary tumors (ie, bladder, prostate, uterus, vagina) did not reduce the frequency of total cystectomy or produce durable bladder salvage, although survival was not compromised.
7. Survival after relapse was only 17% at 5 years.

The IRS-III study covered the period 1984 to 1991. This study revealed the following[17]:

1. The 5-year survival rate for the IRS-III group was 71%, with an 8% improvement over the IRS-II rate. The 5-year progression-free survival rate was 65%, with a 10% improvement over IRS-II.
2. Patients with group I favorable-histology tumors fared as well on a 1-year regimen of VA as did a comparable group treated with VA plus

cyclophosphamide. The 5-year progression-free survival rates were 83% and 76%, respectively ($P = .18$).

3. Results for patients with group II favorable-histology tumors, excluding orbit, head, and paratesticular sites, were not improved with the addition of doxorubicin over VA chemotherapy × 1 year and radiation therapy.
4. Patients with group III tumors, excluding those in special pelvic, orbit, and other selected head sites (scalp, parotid, oral cavity, larynx, oropharynx, and cheek), fared better on the more intensive regimens of IRS-III than on pulsed VAC or VAC vincristine and doxorubicin (VADR) in IRS-II; the 5-year progression-free survival rates were 62% and 52%, respectively. The intensive regimen from IRS-III included multiple agents (VAC + doxorubicin + cisplatin + etoposide) plus radiation therapy plus second-look surgery. There were no differences in outcome among the three chemotherapy programs on IRS-III.
5. Patients with group IV tumors did not benefit from the aggressive therapy of IRS-III.
6. Patients with tumors in the bladder, vagina, and central pelvis in clinical group III had significantly improved outcome as compared with those with IRS-II, primarily because of the routine administration of early radiation therapy, which improved the bladder salvage rate from 25% in IRS-II to 60% in IRS-III.
7. Patients with unfavorable histology, in clinical groups I and II, who received VADR-VAC + cisplatin and radiation therapy had improved outcome over patients in IRS-II receiving VA or VAC and irradiation.
8. Patients with favorable-histology group II paratesticular tumors and those with favorable-histology orbit and head tumors in groups II and III do not require cyclophosphamide when VA × 1 year plus radiation therapy is used.
9. Whole-brain radiotherapy was omitted for patients with parameningeal primary tumors and cranial nerve palsy or base of skull erosion (although patients with intracranial extension of tumor still received this treatment). Risk of central nervous system relapse and survival was not compromised by this change if adequate local fields were used.

The IRS-IV study was conducted from 1991 to 1997 (Figure 93.5).[1] The results from this study are as follows:

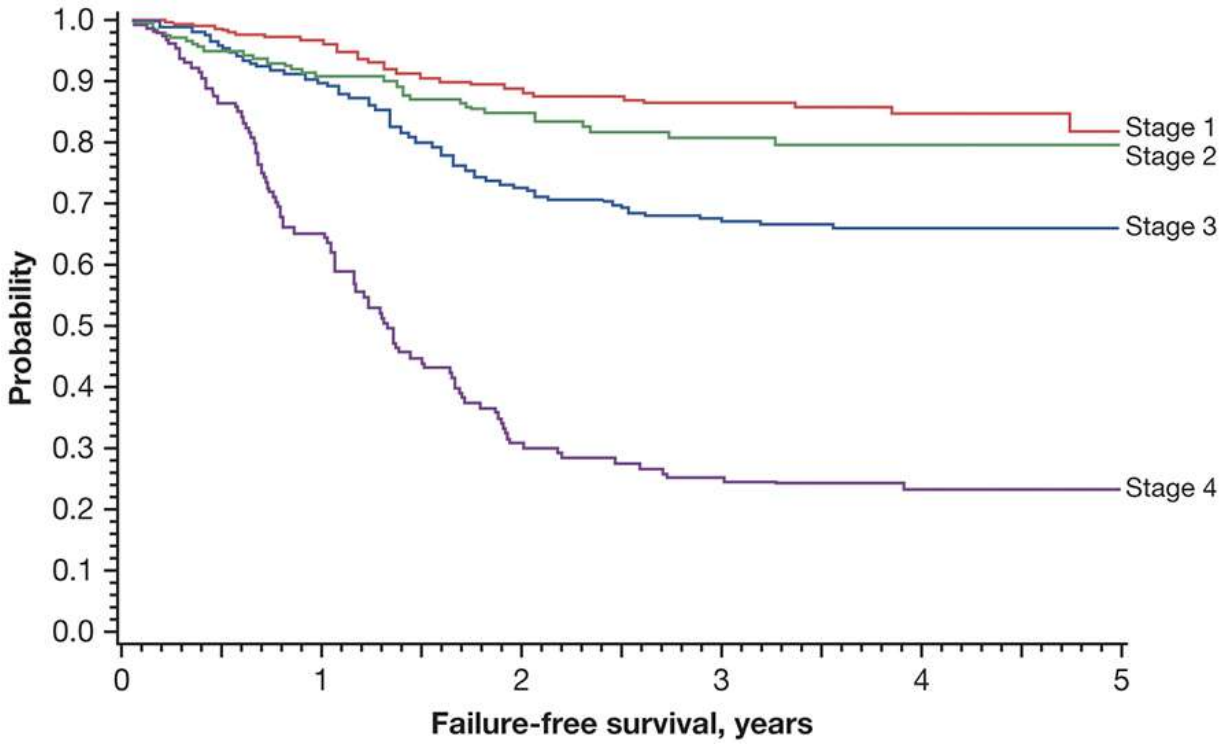

FIGURE 93.5 Survival curves of 1,010 children with rhabdomyosarcoma entered into the fourth Intergroup Rhabdomyosarcoma Study are shown by stage. (From Crist WM, Anderson JR, Meza JL, et al. The Intergroup Rhabdomyosarcoma Study-IV: results for patients with non-metastatic disease. *J Clin Oncol*. 2001;19[12]:3091-3102; Breneman JC, Lyden E, Pappo AS, et al. Prognostic factors and clinical outcomes in children and adolescents with metastatic rhabdomyosarcoma—a report from the Intergroup Rhabdomyosarcoma Study IV. J Clin Oncol. 2003;21:78-84.)

1. For patients with group III tumors, hyperfractionated radiotherapy was no more effective than conventional radiotherapy for tumor control and survival. Local control at 5 years was 87% for all patients with group III tumors (98% orbit, 88% head/neck, 84% parameningeal, 81% bladder/prostate, 93% extremity, 86% other).[115]
2. There was no difference in survival between VAC and vincristine/actinomycin/ifosfamide and vincristine/ifosfamide/etoposide in children with nonmetastatic disease.

3. Failure-free survival at 3 years for patients with embryonal histology was superior to results seen in IRS-III (83% vs 74%), but no difference was seen for alveolar or undifferentiated subtypes.
4. Survival for patients with group I or II orbit or eyelid tumors was excellent when treated with VA and radiotherapy for group II disease.
5. Prognostic subsets of patients based on histologic subtype, stage, and group could be identified as follows: Low-risk patients had embryonal histology and were stage 1 (all groups), or stage 2 or 3 and group I or II. All other patients with locoregional disease were at intermediate risk.
6. Survival for patients with metastatic disease was superior with the drug pair ifosfamide/etoposide when compared with vincristine/melphalan.[100]
7. Whole-brain radiotherapy was omitted for all patients with parameningeal primary tumors, except when there was cytologic evidence of cerebrospinal fluid involvement. Survival was not compromised by this approach.

The fifth IRS (IRS-V) studies consisting of COG D9602, COG D9803, and COG D9802 were conducted from 1997 to 2005. The results from these studies are as follows:

1. Failure-free survival for low-risk patients (treated without cyclophosphamide and given decreased radiation doses with 36 Gy for microscopic disease) was similar to results seen in IRS-III, which also did not use cyclophosphamide, but was inferior to results from IRS-IV where cyclophosphamide or ifosfamide was given. The conclusion of this study was that reduced radiotherapy doses with 36 Gy for microscopic disease did not appear to compromise local control, but the inclusion of an alkylating chemotherapy agent in the treatment regimen may be important for maximizing outcomes in these patients.
2. For group III orbital tumors specifically, dose reduction to 45 Gy resulted in an unacceptably high rate of local failure rate at 14% (compared to 5% seen on IRS-IV). As such, 50.4 Gy remains the standard of care for orbital tumors without a complete response to induction chemotherapy.[35,36]

3. For vaginal tumors treated without radiation, local failure rates were also unacceptably high (26% on D9602 and 43% on the subsequent trial ARST0031).[64] Omission of radiation therapy for these children is not advisable, and intravaginal brachytherapy may be the preferred modality of treatment, given the high-dose gradient and subsequent sparing of surrounding normal tissue.
4. For patients who undergo second-look surgery or delayed primary excision (DPE) after induction chemotherapy, radiation dose can be successfully reduced to 36 Gy for negative margins and 41.4 Gy for microscopically positive margins without compromising local control.[77] However, an oncologic benefit to DPE (compared to radiotherapy alone) was not observed.
5. For patients with intermediate-risk disease treated on D9803, the addition of topotecan to the standard VAC regimen did not improve failure-free survival.[78]

Following IRS-V, the COG conducted separate protocols by risk group from 2004 to 2013: ARST0331 for low-risk patients,[79] ARST0531 for intermediate-risk patients,[80] and ARST0431 for high-risk patients.[81] The results from these studies are as follows:

1. On ARST0331, unacceptable local control rates were again seen for orbital tumors treated to 45 Gy with reduced-dose cyclophosphamide and incomplete response to chemotherapy, as well as for vaginal tumors not treated with radiotherapy, confirming results from D9602.[82]
2. A reduction in cyclophosphamide dose from prior trials appeared to result in inferior survival outcomes for subset 2 low-risk patients treated on ARST0331[83] and intermediate-risk patients treated on ARST0531.[97]
3. For patients with intermediate-risk disease treated on ARST0531, the addition of irinotecan to the standard VAC regimen did not improve survival outcomes.[80]
4. On both D9803 and ARST0531, tumor size 5 cm or more at diagnosis was associated with significantly increased local failure after radiotherapy.[84,97]

5. For patients with high-risk disease treated on ARST0431, those with embryonal histology 10 years of age or less had a superior prognosis compared to other high-risk patients, leading to reclassification of this subset of patients as intermediate risk for subsequent trials. [81] In distinction, those with metastatic fusion-positive disease experienced long-term survival outcomes of less than 20%.

GENERAL MANAGEMENT

A multidisciplinary approach using surgery, irradiation, and chemotherapy is important in the management of RMS; however, the optimal sequence and specific application of each modality continue to be investigated. Although the primary goal remains long-term cure, improvement in therapeutic results necessitates considerations of quality of life, with particular attention to maximization of functional and cosmetic results.

Surgery

Before the era of multidisciplinary therapy, surgical ablation resulted in a long-term survival rate of approximately 20% of those patients able to undergo resection.[85] Certain primary sites represented exceptions to these data; for example, approximately 50% of those with localized disease of the orbit survived after orbital exenteration.[86] However, with the introduction of effective adjunctive treatment, preservation of function and appearance became major goals. The concept of reasonable surgery has evolved. It involves maximal conservation of anatomic structures, including preservation of bladder, bowel, and sexual function in patients with tumors of genitourinary origin; limb function in patients with extremity tumors; and vision, voice, deglutition, and appearance in patients with head and neck tumors.

Resection of RMS from normal surrounding tissues is often technically challenging. Only 20% of tumors are located in sites where complete excision can readily be accomplished without an undesirable loss of function or cosmesis.[17] An additional 20% of patients have compromised surgical procedures, leaving microscopic residual disease. Sixty percent of patients have tumors amenable to biopsy only or present with metastatic disease and are not candidates for primary resection. When the IRS surgical

grouping system is used, patients with tumor amenable to complete excision fare better than those who have subtotal resection or biopsy alone. However, the tumors that are most accessible to surgical excision are small and noninvasive and are confined to the organ or structure of origin. Assessment using a TNM system demonstrates that prognosis is dictated by tumor size and invasiveness rather than by the initial surgical approach.[87] Furthermore, combined modality therapy provides good local control of the primary tumor, even after subtotal excision.[88] For these reasons, local control most often consists of less aggressive surgical resection, with more reliance on radiation therapy and chemotherapy to provide control of local-regional disease.[17]

In cases of suspected RMS, the initial surgical procedure should be an incisional biopsy. Surgical excision is indicated if it can be done without compromise of function or cosmesis. Normal tissue margins of at least 5 mm around the tumor are usually required to consider the resection complete (IRS group I), although this is sometimes not feasible in some anatomic sites and smaller margins may suffice. If microscopic disease remains after initial resection, a primary reexcision can be considered prior to begin chemotherapy. Those children who can be rendered microscopically free of disease by this procedure have an improved outcome, compared with children who remain in clinical group II following initial surgery.[89,90] Amputation of an extremity, orbital exenteration, mutilating surgery of the head and neck area, therapeutic lymphadenectomy, and radical neck dissection are not routinely performed upfront and are instead reserved in case initial therapy fails.

Second-look operations (also termed *delayed primary excisions* [DPEs]) may be useful for converting partial responses after chemotherapy into complete responses, and there is conflicting evidence regarding whether these procedures affect oncologic outcomes.[12,48,85,91] The IRS-V study evaluated whether DPE might allow a reduction in the amount of radiotherapy that is necessary to provide local tumor control; local control following DPE and reduced-dose radiation for bladder dome, extremity, and trunk tumors was similar to historic results after higher doses of definitive radiation. Some investigators have used second-look operations in an attempt to eliminate radiotherapy, although this approach of radiation omission has resulted in inferior local control and survival and has not been

recommended on previous COG trials.[92] Second-look operations may be used to evaluate therapeutic response after chemotherapy or radiation therapy. In the IRS-III study, 28% of patients categorized as having clinical partial response and 43% of those scored as having no response to induction chemotherapy were reclassified as having pathologic complete response after second-look operation.[93] These children enjoyed a survival rate similar to that of children who were able to undergo complete surgical excision at the time of initial diagnosis. Therefore, a clinical or radiographic evaluation indicating residual tumor after initial therapy may be misleading and is not associated with worse outcomes. Further investigation of the role of DPE and potential oncologic benefit (or lack thereof) on ARST1431 is being evaluated.

Chemotherapy

Chemotherapy is necessary in all cases. Several drugs have demonstrated single-agent activity measured as a percentage response rate, including vincristine (59%), dactinomycin (24%), cyclophosphamide (54%), cisplatin (15%-21%), dacarbazine (11%), mitomycin-C (36%), etoposide (15%-21%), ifosfamide (86%), irinotecan (23%), and topotecan (46%).[94-96] Agents with known activity against central nervous system tumors, such as nitrosoureas and methotrexate, have not shown activity against RMS.

The most extensive experience in combination chemotherapy is with VAC. Some studies have suggested that patients with embryonal histology tumors in favorable sites who have no gross residual disease or lymph node involvement after the initial surgical resection may be adequately treated with VA for 1 year, provided that irradiation is given for microscopic residual disease.[17] However, data from the IRS-V study and ARST0531 suggest that local control for low- and intermediate-risk RMS may be compromised when alkylating agents are omitted or reduced in dose.[35,36,97] Patients with unresectable pelvic tumors may benefit from the addition of doxorubicin and cisplatin to VAC, but tumors in other sites do not seem to benefit from the addition of these drugs compared with an intensive regimen of VAC alone.

Some subsets of patients, such as those with tumors of unfavorable histology or unfavorable site and those with extensive tumor burden,

continue to fare poorly. Some of these patients with embryonal histology may benefit from intensification of the cyclophosphamide or ifosfamide component of their chemotherapy, although there are conflicting data regarding this.[98,99] Patients with metastatic RMS may benefit from the addition of ifosfamide and etoposide to the standard VAC regimen,[100] and the role of upfront vinorelbine for the treatment of metastatic RMS is currently being explored on ARST2031. High-dose chemotherapy with total-body irradiation and autologous bone marrow transplantation has not improved the outcome in these high-risk patients.[71,72]

Initial intensive chemotherapy has been used as a means of pharmacologic debulking, potentially allowing for a more conservative surgical approach or less aggressive radiation therapy.[52,101,102] However, data consistently fail to show that response to induction chemotherapy predicts the ultimate outcome.[14,103] When chemotherapy alone is used for tumors in sites such as the head and neck or pelvis, most children require radiation therapy.[18,37,104,105] Omission of radiotherapy in these patients may result in inferior survival.[92,106] Even patients with only microscopic disease after initial resection (group II) require radiotherapy to achieve optimal local control.[107] In patients with group II disease who routinely receive radiotherapy, local control is 92%.[108] The approach of initial chemotherapy followed by limited irradiation or less radical surgery may be appropriate in the management of infants and very young children, in whom late effects of aggressive surgery or high-dose, large-volume irradiation are particularly severe, although this may lead to inferior local control and survival.

Radiation Therapy

Adequate irradiation implies careful attention to volume and dose. It is essential to evaluate the soft tissue extent of the primary lesion with cross-sectional imaging by CT scan and often MRI. Because RMS tends to infiltrate tissue planes widely, tumors often extend beyond a fascial compartment and beyond the obvious visible margins. Careful examination by a radiation oncologist at the time of initial diagnosis, even if the treatment plan calls for neoadjuvant chemotherapy, is essential to establish the appropriate tumor volume.

Treatment portals are designed to encompass the involved region at the time of presentation (before chemotherapy) with margins that encompass surgical sites and biopsy tracts. A biopsy should be performed of clinically suspicious lymph nodes, or they should be included in the radiation therapy portal. Prophylactic lymph node irradiation is not necessary for children with clinically negative findings who will be receiving combination chemotherapy. The gross tumor volume is defined as the tumor as seen at the time of initial diagnosis. A clinical target volume of 1 cm is added and can be modified to account for anatomic barriers to tumor spread (such as the bony orbit in primary orbital tumors) or to account for regression of "pushing" the tumor border after chemotherapy, such as may occur in large pelvic tumors that initially displace contents of the peritoneal cavity. The planning target volume adds a patient-specific margin, which is typically about 5 mm, although varies by setup and radiation technique (protons vs photons). Many current treatment protocols use a cone-down boost or simultaneous integrated boost to any gross post-treatment tumor volume after a microscopic tumor dose has been delivered. Patients with tumors at parameningeal sites (middle ear, paranasal sinuses, nasopharynx, nasal cavity, infratemporal fossa, and parapharyngeal area) have developed meningeal extension of tumor when inadequate irradiation portals were used.[44] With improved imaging modalities, intracranial extension may be more accurately delineated, and radiation therapy volumes that cover any involved adjacent meninges are necessary.[17,42]

Intensity-modulated radiotherapy treatment planning techniques are valuable for ensuring adequate treatment of the tumor volume and minimizing acute and chronic toxicity from the irradiation of uninvolved, adjacent structures.[42,109-111] Proton-beam radiotherapy is being increasingly utilized as access to this form of therapy increases,[40] and dosimetric studies consistently demonstrate decreases of integral dose to normal structures compared to photon-based techniques for many children with RMS (Figures 93.6 and 93.7).[112,113] Local control and survival outcomes appear similar after proton radiation compared to historical cohorts treated with photon radiation. In addition, acute and early late toxicity rates with protons appear quite promising, especially for tumors in the head and neck region.[114] Follow-up is limited, though, and long-term toxicity data are necessary to follow up for adverse events that may take many years to develop.

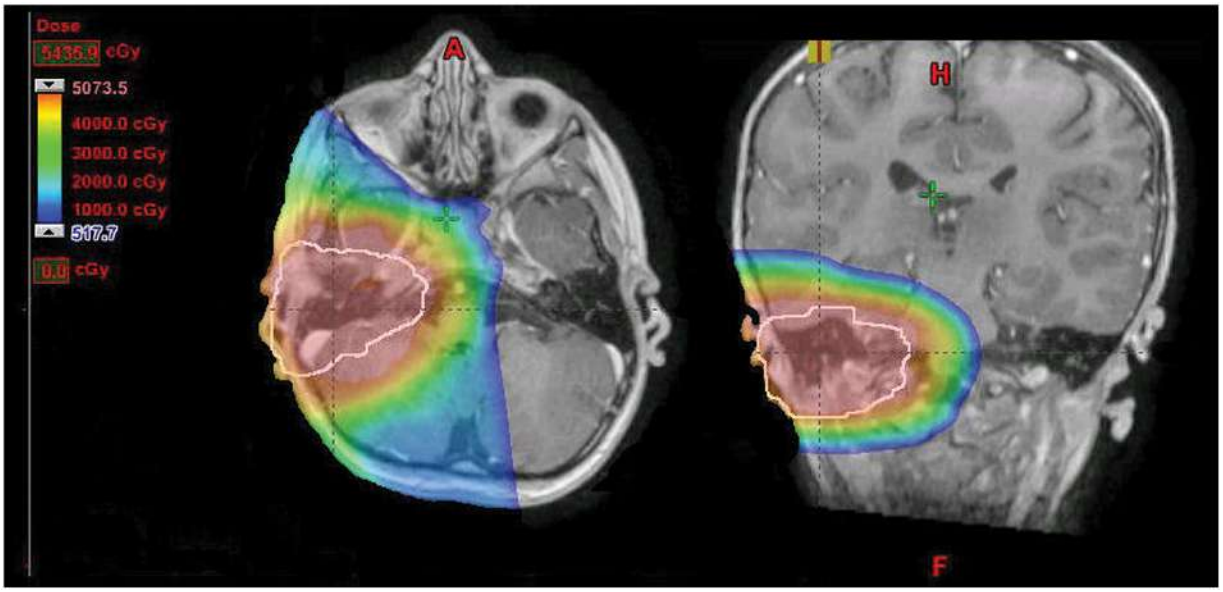

FIGURE 93.6 Isodose distribution in the axial and coronal planes for treatment of a middle ear rhabdomyosarcoma using protons. The physical properties of protons permit complete sparing of the contralateral structures and ipsilateral eye. 3D-CRT, three-dimensional conformal radiation therapy; VMAT, volumetric arc–based therapy. (Courtesy of Danny Indelicato, MD.)

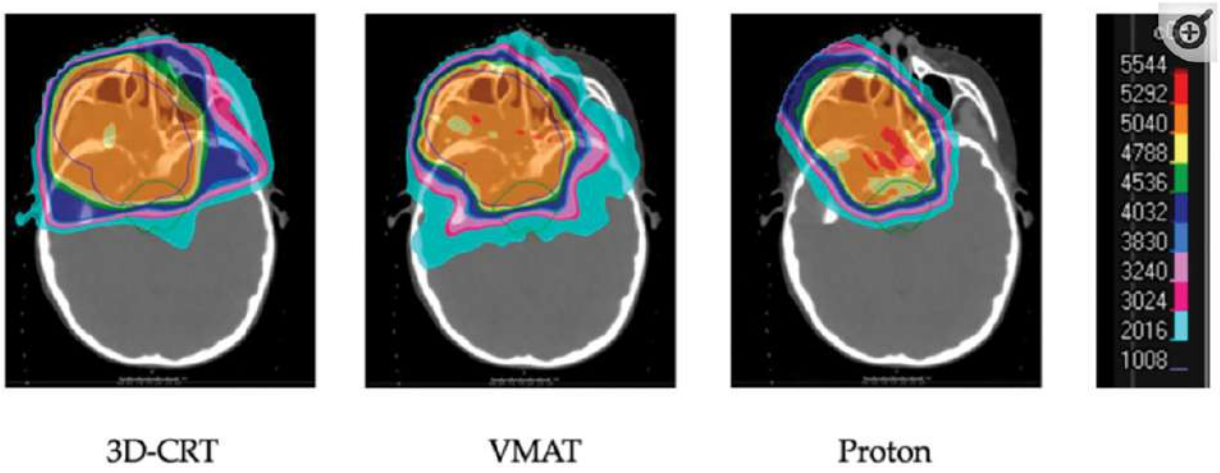

FIGURE 93.7 Comparison of isodose distribution in the axial planes for treatment of parameningeal rhabdomyosarcoma using three-dimensional conformal radiation therapy, volumetric arc–based therapy, and proton therapy, highlighting the reduction in dose to normal tissue with proton therapy. (Courtesy of Andrew Frankart, MD.)

Immobilization techniques that ensure reproducibility are essential. Sedation or anesthesia may be necessary to ensure adequate implementation of the treatment plan in young children. These complex programs are best

conducted in regional centers by an experienced team of physicians, including a pediatric surgeon, pediatric anesthesiologist, pediatric oncologist, and radiation oncologist.

Local control of gross disease in most anatomic sites requires doses of 50 to 55 Gy. In the IRS-IV study, investigators studied the efficacy of a higher radiation dose (59.4 Gy), given in 1.1-Gy fractions twice daily at 6-hour intervals for children with gross residual disease.[115] This hyperfractionated regimen was compared in a prospective, randomized manner to a standard radiotherapy regimen consisting of 50.4 Gy given as 1.8 Gy once daily. There was no difference in locoregional disease control, failure-free survival, or overall survival between the two groups. Therefore, the standard of care for group III RMS continues to be conventionally fractionated radiation (50.4 Gy) with chemotherapy. The value of a boost to 59.4 Gy delivered with daily fractionation for group III tumors measuring 5 cm or more in size at diagnosis is being investigated in the recently closed ARST1431 trial for intermediate-risk patients.

Ninety percent of patients with microscopic residual tumor achieve local control with 41.4 Gy, and the D9602 study results suggest that 36 Gy may be adequate for microscopically positive margins that are not associated with lymph node involvement as described in more detail later. Investigators have been unable to generate a strict dose-response curve but have observed an association with age that suggests that lower doses, often given to infants and youngsters, are associated with higher relapse rates.[116] They also suggest that local tumor control is greater for tumors less than 5 cm in diameter than for larger lesions, supporting the adult experience with soft tissue sarcomas and the investigation of a radiation boost for these larger tumors.[84,117,118]

The results of the IRS-I study had indicated that radiotherapy was not needed for patients whose tumors were completely resected at diagnosis (group I). Subsequently, a reanalysis of data from the IRS-I to IRS-III studies suggested that the subset of group I patients with alveolar or undifferentiated histology had improved overall and failure-free survival when radiotherapy was given to the primary tumor site.[119] A more recent analysis using data from IRS-IV did not, however, show a significant advantage for radiotherapy in group I alveolar tumors. This practice is

currently under review for the next generation of RMS protocols, with fusion status playing a critical role in risk stratification.[120]

Interstitial radiation therapy may play a role as primary treatment or as a boost after external beam therapy for selected sites at specialized centers.[46,66] The advantages of precise shaping of the dose distribution, sharp falloff of radiation dose, and shortening of overall treatment time are especially attractive in dealing with infants and young children. Some investigators report a decrease in late normal tissue effects when compared with external beam techniques.[121] There are no data regarding comparative efficacy or toxicity between high-dose rate and low-dose rate techniques. However, high-dose rate remote brachytherapy may be particularly attractive in this patient population for logistical reasons. These children often require extensive care from family members and medical personnel during their treatment, and high-dose rate techniques can eliminate radiation exposure to these caregivers.

The timing of radiation therapy must be carefully coordinated with planned surgical intervention and combination chemotherapy scheduling to optimize local control and ensure optimization of drug doses and unimpaired postoperative healing. Although radiation therapy is often delayed for several weeks (approximately weeks 12-13) to allow administration of neoadjuvant chemotherapy, some data suggest that earlier irradiation, particularly in high-risk parameningeal patients with intracranial extension, may provide better local tumor control.[42,122,123] Interaction between radiation and some of the commonly used chemotherapeutic drugs can produce undesirable early and late effects. This is particularly true of dactinomycin and doxorubicin. Radiation therapy given concurrently with these agents is usually avoided. In contrast, systemic treatment with drugs such as vincristine and cyclophosphamide can usually be continued concurrently with the administration of irradiation.

Retrieval Therapy

Salvage after recurrence of RMS is difficult, which probably accounts for the inferior survival seen with treatment approaches that do not maximize therapy at the time of initial diagnosis.[106,124] Because local recurrence is the most common pattern of failure, surgery, and radiotherapy play especially

important roles in the treatment of these children. Aggressive treatment programs utilizing radical resection and brachytherapy have had success in selected patients with head and neck RMS.[46] Care must be taken when evaluating patients for local recurrence. Residual masses can be seen in as many as 40% of children who are shown to be pathologically free of tumor.[125]

SEQUELAE OF TREATMENT

Acute Effects

Acute side effects from surgery are primarily postoperative complications that are usually reversible and not serious. The acute toxicity from chemotherapy includes nausea, vomiting, mucositis, alopecia, and hematopoietic suppression. Drug-induced granulocytopenia significantly increases the risk of fever and infection, although the routine use of granulocyte colony–stimulating factor has lessened these risks. Protocols using more aggressive therapy, including topoisomerase inhibitors, ifosfamide, etoposide, and other agents, have other acute side effects, including renal and electrolyte imbalance, which demand close monitoring.

Acute radiation toxicity is related to the regions irradiated and the dose administered. It can be especially pronounced for tumors of the head and neck, abdomen, and pelvis. The synergistic effect of chemotherapeutic drugs such as dactinomycin and doxorubicin can be severe and may require modification of the treatment plan. Both dactinomycin and doxorubicin are known to accentuate a “recall” of radiation injury if given during or immediately after the course of radiation therapy.

Prompt attention to skin care is important. Moisturizers and steroid creams are effective symptomatic treatments for erythema and dry desquamation. Moist desquamation may be treated with aluminum acetate soaks or hydrocolloid dressings. Occasionally, a delay in radiation therapy is necessary to permit healing.

After orbital irradiation, an acute inflammatory reaction of the cornea and conjunctiva may be seen within weeks of completion of treatment. This can result in pain and photophobia. Topical steroids should be administered under the direction of an ophthalmologist for these symptoms.

Acute otitis externa or media with hyperemia and swelling of the membranes of the eustachian tube is common during or soon after treatment of head and neck areas. Decongestants are helpful in reducing the swelling. Erythematous mucositis, leading to a patchy, fibrinous exudate, is seen after head and neck irradiation, after drug therapy, and almost universally if the two are used simultaneously. Mouthwashes such as baking soda, 1% hydrogen peroxide, or combinations of diphenhydramine elixir, hydrocortisone, and antibiotics partially alleviate the reaction. Bacterial or fungal superinfection requires specific drug management. Pretreatment evaluation by a dentist is important to correct preexisting problems and help guide preventive therapy, such as dental hygiene and fluoride applications.

Acute gastrointestinal sequelae, such as vomiting and diarrhea, are usually managed by supportive care. Parenteral nutritional support may be necessary to prevent protein or calorie malnutrition.

Late Effects

Life-threatening late events occur in approximately 9% of survivors after treatment.[33] A higher percentage experience lesser degrees of late morbidity, with the risks dependent on factors such as primary tumor site, disease stage, and the treatment modalities employed.

Long-term sequelae related to specific chemotherapy drugs are usually organ specific, and the morbidity may be accentuated by radiation therapy. Cyclophosphamide may induce hemorrhagic cystitis, and doxorubicin is implicated in late myocardiopathies.[126] Cisplatin carries a high incidence of hearing impairment. Alkylating agents and topoisomerase inhibitors are associated with the development of secondary neoplasms, particularly acute myeloid leukemia.[127,128]

Late radiation effects are related to the irradiated site, the dose of radiation, and the age of the child at the time of treatment. Effects include bone and soft tissue growth disturbances, dental abnormalities, cataract, hypopituitarism, gonadal dysfunction, induction of second malignant tumors (particularly bone sarcomas), and chronic organ dysfunction.[56,127,129-131] Long-term follow-up and treatment are important to minimize the impact of these, particularly for endocrine and dental complications.[132] Combined modality treatment programs are significantly implicated in many of these

complications. Long-term follow-up and data are needed to determine whether proton therapy can reduce the incidence of the abovementioned late radiation effects compared to photon-based techniques.

Late surgical complications depend mainly on the choice of surgical procedure for the primary treatment of the tumor. They include disfigurement and loss of function. Serious late effects of surgical treatment include the consequences of fecal and urinary diversion as well as ejaculatory impotence after retroperitoneal lymph node dissection. Long-term complications from initial surgical resections or DPE have not been reported.

FUTURE DIRECTIONS AND RESEARCH

Advances in molecular biology are providing a more comprehensive understanding of the biologic behavior of RMS and directing new research initiatives. Although the PAX3-FOXO1 fusion gene plays a key role in the oncogenesis of fusion-positive RMS, its targeting for therapeutic purposes has thus far been unsuccessful due to its nuclear localization, lack of catalytic activity, and disordered state. Attempts to target its co-regulators and other chromatin-remodeling proteins are currently underway, as well as investigation of histone deacetylase inhibitors, drugs that target the RAS pathway, and drugs that can take advantage of the dysregulated DNA damage response that is sometimes observed.[133] The utility of circulating tumor DNA to inform management is also under current investigation.

With advances in molecular characterization of RMS, fusion-negative RMS has been found to have recurrent point mutations in genes, such as *TP53*, *NRAS*, *KRAS*, *HRAS*, *MYOD1*, *FGFR4*, and *PIK3CA*. Among these, *TP53* and *MYOD1* have been associated with significantly worse survival outcomes.[134,135] As a result, these alterations are now incorporated into risk classification in the ongoing COG trials, and patients who harbor these mutations are treated with more intensive systemic therapy.

The recently closed ARST1431 trial did not show a clear benefit of adding temsirolimus for intermediate-risk patients in initial results, although final publication is pending. The current generation of COG STS studies tests a number of clinical hypotheses, including testing the ability to reduce the duration of chemotherapy for molecularly favorable low-risk tumors,

boosting tumors initially measuring more than 5 cm to 59.4 Gy total, evaluating the prognostic value of early treatment response as assessed by PET imaging, exploring the utility of circulating tumor DNA, investigating the ideal dose of cyclophosphamide for optimal local control and survival outcomes, and testing the value of SBRT and comprehensive radiation to metastatic sites for those with high-risk disease. Future directions and research in RMS are being driven by many exciting molecular biologic and technological advances.

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CHAPTER 94

Nonrhabdomyosarcoma Soft Tissue Sarcoma in Children

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EPIDEMIOLOGY

Soft tissue sarcomas (STS) are a group of rare tumors that arise primarily from mesenchymal cells in connective tissues. Approximately 900 pediatric patients a year are diagnosed with STS, amounting to about 7% of all pediatric malignancies.[1] STS in pediatric patients is classified into two groups: rhabdomyosarcoma (RMS) and nonrhabdomyosarcoma soft tissue sarcoma (NRSTS). NRSTS accounts for approximately 60% of pediatric STS diagnoses annually,[2] with incidence highest in adolescence from 10 to 19 years of age.[1] The incidence of STS subtypes varies with age; in infancy, infantile fibrosarcoma, malignant rhabdoid tumor, and RMS are the most common histologies, whereas synovial sarcoma and malignant peripheral nerve sheath tumor (MPNST) are observed more frequently in the adolescent population.[1] Although the etiology of NRSTS is unclear in the majority of patients, there are several genetic predisposing conditions associated with the development of NRSTS: Neurofibromatosis 1 (NF1) is associated with MPNST, Li-Fraumeni germline P53 mutation leads to increased risk of NRSTS and retinoblastoma, DICER1 and APC mutations can lead to desmoid fibromatosis, and IN1 deficiency can lead to malignant rhabdoid tumor. In addition, the risk of secondary sarcoma is increased after exposure to radiation and anthracyclines.[1]

PATHOLOGY

The classification of soft tissue tumors is based on the World Health Organization (WHO) Classification of Tumors of Soft Tissue and Bone, with the fifth edition published in 2020,[3] as well as within the WHO Classification of Paediatric Tumors, published in 2022. Histologic classification is determined by cellular differentiation and molecular drivers. Each tumor entity is then grouped according to biologic behavior: benign, intermediate locally recurrent or rarely metastasizing, and malignant locally aggressive with a risk of distant metastasis. Table 94.1 includes the most common intermediate and malignant NRSTS histologies in pediatric patients, which require more aggressive treatment based on their pathologic and clinical risk factors. Although benign neoplasms are not discussed in this chapter, they comprise a large proportion of histologic entities and may still have rapid growth or local recurrence, despite not being locally destructive or metastatic.

TABLE 94.1 WHO CLASSIFICATION OF TUMORS OF SOFT TISSUE

Classification	Intermediate Entities: Locally aggressive or Rarely Metastasizing	Variants	Malignant Entities	Variants
Adipocytic	Atypical lipomatous tumor		Liposarcoma, well differentiated, NOS	Lipoma-like liposarcoma Inflammatory liposarcoma Sclerosing liposarcoma
			Dedifferentiated liposarcoma	
			Myxoid liposarcoma	
			Pleomorphic liposarcoma	Epithelioid liposarcoma

Classification	Intermediate Entities: Locally aggressive or Rarely Metastasizing	Variants	Malignant Entities	Variants
			Myxoid pleomorphic liposarcoma	
Fibroblastic and myofibroblastic	Solitary fibrous tumor, benign		Solitary fibrous tumor, malignant	
	Palmar/plantar-type fibromatosis		Fibrosarcoma, NOS	
	Desmoid-type fibromatosis	Extra-abdominal desmoid Abdominal fibromatosis	Myxofibrosarcoma	Epithelioid myxofibrosarcoma
			Low-grade fibromyxoid sarcoma	
	Lipofibromatosis		Sclerosing epithelioid fibrosarcoma	
	Giant cell fibroblastoma			
	Dermatofibrosarcoma protuberans, NOS	Pigmented dermatofibrosarcoma protuberans Dermatofibrosarcoma protuberans, fibrosarcomatous Myxoid dermatofibrosarcoma protuberans Plaque-like dermatofibrosarcoma protuberans		
	Solitary fibrous tumor, NOS	Fat-forming solitary fibrous tumor Giant cell–rich solitary fibrous tumor		
	Inflammatory myofibroblastic tumor	Epithelioid inflammatory myofibroblastic sarcoma		
	Myofibroblastic sarcoma			
	Superficial CD34-positive fibroblastic tumor			
	Myxoinflammatory fibroblastic sarcoma			
	Infantile fibrosarcoma			
Fibrohistiocytic tumors	Plexiform fibrohistiocytic tumor		Malignant tenosynovial giant cell tumor	
	Giant cell tumor of soft parts, NOS			
Vascular	Kaposiform hemangioendothelioma		Epithelioid hemangioendothelioma, NOS	Epithelioid hemangioendothelioma with WWTR1-CAMTA1 fusion Epithelioid hemangioendothelioma with YAP1-TFE3 fusion
	Retiform hemangioendothelioma			
	Papillary intralymphatic angioendothelioma		Angiosarcoma	
	Composite hemangioendothelioma	Neuroendocrine composite		

Classification	Intermediate Entities: Locally aggressive or Rarely Metastasizing	Variants	Malignant Entities	Variants
		hemangioendothelioma		
	Kaposi sarcoma	Classic indolent Kaposi sarcoma Endemic African Kaposi sarcoma AIDS-associated Kaposi sarcoma Iatrogenic Kaposi sarcoma		
	Pseudomyogenic (epithelioid sarcoma–like) hemangioendothelioma			
Perivascular	Glomus tumor, NOS	Glomangioma Glomangiomyoma Glomangiomatosis Glomus tumor of uncertain malignant potential	Glomus tumor, malignant	
	Myopericytoma	Myofibromatosis Myofibroma Infantile myofibromatosis		
	Angioleiomyoma			
Smooth muscle	Leiomyoma, NOS		Leiomyosarcoma, NOS	
	EBV-associated smooth muscle tumor/smooth muscle tumor of uncertain malignant potential		Inflammatory leiomyosarcoma	
Gastrointestinal stromal tumors			Gastrointestinal stromal tumor	
Peripheral nerve sheath tumor			Malignant peripheral nerve sheath tumor, NOS	Malignant peripheral nerve sheath tumor, epithelioid
			Melanotic malignant peripheral nerve sheath tumor	
			Granular cell tumor, malignant	
			Perineurioma, malignant	
Tumors of uncertain differentiation	Hemosiderotic fibrolipomatous tumor		Phosphaturic mesenchymal tumor, malignant	NTRK-rearranged spindle cell neoplasm (emerging)
	Angiomyolipoma, epithelioid		Synovial sarcoma	Synovial sarcoma, spindle cell Synovial sarcoma, biphasic Synovial sarcoma, poorly differentiated
	Atypical fibroxanthoma			
	Angiomatoid fibrous histiocytoma			
	Ossifying fibromyxoid tumor, NOS		Epithelioid sarcoma	Proximal or large cell epithelioid sarcoma Classic epithelioid sarcoma
	Mixed tumor, NOS			

Classification	Intermediate Entities: Locally aggressive or Rarely Metastasizing	Variants	Malignant Entities	Variants
	Mixed tumor, malignant, NOS		Alveolar soft-part sarcoma	
	Myoepithelioma, NOS		Clear cell sarcoma, NOS	
			Extraskeletal myxoid chondrosarcoma	
			Desmoplastic small round cell tumor	
			Rhabdoid tumor, NOS	
			Perivascular epithelioid tumor, malignant	
			Intimal sarcoma	
			Myoepithelial carcinoma	
			Undifferentiated sarcoma	Spindle cell sarcoma, undifferentiated Pleomorphic sarcoma, undifferentiated Round cell sarcoma, undifferentiated

AIDS, acquired immunodeficiency syndrome; EBV, Epstein-Barr virus; NOS, not otherwise specified; NTRK, neurotrophic tyrosine receptor kinase; WHO, World Health Organization.
Data from Sbaraglia M, Bellan E, Dei Tos AP. The 2020 WHO classification of soft tissue tumours: news and perspectives. *Pathologica*. 2021;113(2):70-84.

There are significant differences in the prevalence, biology, prognostic factors, response to therapy, and outcomes of STS histologic subtypes in pediatric versus adult patients.[4] This chapter first discusses the pathophysiology and management considerations according to specific tumor subtypes and then describes the overall approach to treatment for NRSTS.

Adipocytic

Of the adipocytic class of tumors, there are few that occur in pediatric patients. Myxoid liposarcoma and myxoid pleomorphic liposarcoma are the most common adipocytic subtypes in young patients; myxoid pleomorphic liposarcoma frequently occurs in the mediastinum.[5] The most common adipocytic tumor in all patients is the atypical lipomatous tumor or well-differentiated liposarcoma, which is very rare in children, but can be associated with Li-Fraumeni syndrome.[6]

Fibroblastic and Myofibroblastic

There are several locally aggressive entities within the fibroblastic and myofibroblastic classification that occur in pediatric patients. Desmoid fibromatosis is a locally aggressive tumor that can be associated with familial adenomatous polyposis and is usually located in the abdomen but can occur in the head and neck.[7] The majority of desmoid tumors result from a gain-of-function mutation in beta-catenin (CTNNB1) with constitutive activation of the Wnt pathway.[8] Notably the primary approach to treatment is active surveillance, with surgery reserved for patients who fail observation.[9] Lipofibromatosis, or infantile fibromatosis, is a locally aggressive entity that can be congenital with a median age of presentation of 1 year, occurring most commonly on the extremities, hands, or feet.[10] Giant cell fibroblastoma is another locally aggressive entity in childhood that can evolve into dermatofibrosarcoma protuberans (DFSP); both entities can bear a (17;22)(q22;q13) translocation, resulting in a *COL1A1::PDGFB* gene fusion.[11] DFSP is typically well localized and most frequently identified in

childhood or early adulthood. It has been described as slow growing before a more rapid period of growth.[12]

The fibroblastic and myofibroblastic entities with metastatic potential are few. DFSP can transform into a fibrosarcomatous variant with an increased risk of recurrence and metastasis.[13] Inflammatory myofibroblastic tumor has a predilection for children and can present with elevated inflammatory markers and systemic symptoms thought to be related to cytokine release.[14] Infantile fibrosarcoma presents before age 2 with rapid growth, with most cases harboring a (12;15)(p13;q26) translocation, in contrast to adult-type fibrosarcoma, which occurs after age 10 and is not associated with translocation.[15] Low-grade fibromyxoid sarcoma is occurring with increasing frequency in pediatric patients, is located most commonly in the thigh and trunk, and has the potential to metastasize.[16]

Fibrohistiocytic

The fibrohistiocytic class of tumors includes only a few entities. Within this group, the most common entity in the pediatric population is plexiform fibrohistiocytic tumor. Plexiform fibrohistiocytic tumor presents on average at age 14, with female predominance; it typically occurs on the extremities, with a tendency to recur locally rather than metastasize.[17]

Vascular

Within the vascular classification of STS, there are a number of entities that are locally aggressive and occur in pediatric populations. Kaposiform hemangioendothelioma (KHE) is a solitary tumor that presents at birth or during infancy.[18] Tufted angioma, a precursor to KHE, is superficial and likely to regress, while KHE is locally aggressive, presenting as a violaceous plaque within the trunk or extremities, often associated with a thrombocytopenic coagulopathy known as Kasabach-Merritt phenomenon.[18] Retiform hemangioendothelioma typically pres ents after age 10 as a violaceous plaque on the skin of the extremities and is locally aggressive.[19] The papillary intralymphatic angioendothelioma, Dabska tumor, occurs on the skin of children and rarely metastasizes to nodes.[20] The composite hemangioendothelioma occurs across the pediatric age spectrum, is located on the hands and feet, and is locally aggressive with low metastatic potential.[21] Kaposi sarcoma related to human herpesvirus 8 can be found in children; the variant that is endemic to Sub-Saharan Africa can present in the viscera or lymph nodes, while Kaposi sarcoma associated with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome occurs on mucosa, skin, and viscera.[22] Lastly, pseudomyogenic hemangioendothelioma occurs typically as a nodule of the lower limbs of young male patients and is locally aggressive, but rarely metastatic.[23]

Of the malignant entities within the vascular class of tumors, epithelioid hemangioendothelioma and angiosarcoma occur rarely in pediatric patients. Epithelioid hemangioendothelioma occurs mostly in females on any body location and is often multifocal and infiltrative.[24] Angiosarcoma in the first two decades of life is exceedingly rare; when it occurs, it is aggressive, typically occurring in the head, neck, or mediastinum.[25]

Perivascular

There are two main types of perivascular tumors that can be found in pediatric patients: glomus tumor and myopericytoma. The glomus tumor occurs primarily in the extremities.[26] Myopericytoma is also most common in the extremities and has a male predominance.[27] Both tumors are typically benign but can be locally aggressive or malignant depending upon the level of nuclear atypia, infiltrative growth, and mitotic figures.

Smooth Muscle

Several tumors that arise from smooth muscle can occur in young patients. The Epstein-Barr virus–associated smooth muscle tumor occurs in the setting of immunodeficiency. In adults, it is found in association with HIV or post-transplant. In pediatric patients, it is seen in association with primary immunodeficiency disorders like GATA2 and CARMIL2 deficiency.[28] These tumors occur anywhere in the body, are unlikely to metastasize, and often require stem cell transplant as part of the treatment regimen.[28] Leiomyosarcoma is rare in pediatric patients. When it occurs, it is typically low grade and can be associated with hereditary retinoblastoma, Li-Fraumeni syndrome, and radiation exposure.[29] It can occur in any body location, but in children, it is more common in the gastrointestinal tract.[30] Childhood leiomyosarcoma is similar to gastrointestinal stromal tumor but can be distinguished on the basis of CD117 (KIT) staining patterns, which helps guide treatment options.[31]

Peripheral Nerve Sheath Tumors

As previously mentioned, the peripheral nerve sheath tumors are seen in children and young adults. MPNST commonly occurs in the trunk and extremities; the risk of MPNST in the setting of NF1 is around 10%.[32] MPNST has a high propensity for local relapse without complete surgical resection; however, large tumor size and extensive nerve involvement often impede negative margin resection.[33] Distant metastatic progression is also common, with up to 40% of patients developing metastases during their disease course. Malignant melanotic nerve sheath tumor or melanotic schwannoma is a very rare type of nerve sheath tumor that commonly involves the paravertebral nerve roots and can be associated with the multiple neoplasia syndrome Carney complex.[34] Granular cell tumors are typically solitary slow-growing lesions that occur sporadically in all body sites; they have been observed in the setting of NF, Noonan syndrome, and LEOPARD syndrome.[35,36] Finally, intraneural and soft tissue perineurioma occur in the arms and legs, while intraneural perineurioma can present with weakness, muscle atrophy, and sensory disturbances, soft tissue perineurioma typically presents with a painless mass.[37]

Tumors of Uncertain Differentiation

The last class of tumors to be discussed encompasses all NRSTS of uncertain differentiation. Angiomatoid fibrous histiocytoma is locally aggressive, occurring on the superficial extremities of children and young adults, and has a small risk of metastasis; it is associated with fusion of EWSR1/ATF1 as well as EWSR1/CREB1.[38] Ossifying fibromyxoid tumor can be seen in young adults, most commonly in the lower extremities, and presents as a slow-growing, painless mass.[39] Mixed tumor, myoepithelioma, and, the more aggressive entity, myoepithelial carcinoma arise as a nodule with progressive growth on the trunk and extremities and can be seen in newborns throughout teenage years.[40]

There are numerous malignant tumors of uncertain differentiation that occur in pediatric patients. In all, 17% of synovial sarcoma occurs in pediatric patients.[41] Synovial sarcoma can occur anywhere in the body but is most common in the extremities; it has characteristic fusion (X;18)(p11;q11), resulting in impaired tumor suppressor function.[42] Clear cell sarcoma infrequently occurs in teens and young adults, is most common in the lower extremities, and, like angiomatoid fibrous histiocytoma, can result from fusion of EWSR1/ATF1 or EWSR1/CREB1.[38] Malignant epithelioid tumor comprises 4% to 8% of NRSTS in pediatric populations, can be associated with trauma at the site of tumor development, and occurs in the extremities or trunk.[43] Alveolar soft-part sarcoma has a tendency to metastasize and occurs first in the deep soft tissues of extremities of young adults or in the head and neck of children; it is associated with (X;17)(p11;q25) translocation.[44] Desmoplastic small round cell tumor primarily occurs in the abdomen of children and young adults with male predominance; the (11;22)(p13;q12) translocation has been observed in these tumors.[45] Rhabdoid tumor occurs in infants and young children and arises primarily in the brain and kidney, but has been described in other body sites; it can develop sporadically or in association with SMARCB1 mutation.[46] The perivascular epithelial cell tumor is rare in pediatric patients, with reports of occurrence starting after age 5, and can be associated with tuberous sclerosis.[47]

Last of all, undifferentiated sarcoma, a diagnosis of exclusion, includes spindle cell, pleomorphic (UPS), and round cell types; it is typically high grade and occurs in the extremities.[48] It is common in older adults, with a median age of 52, but can also occur in young adults.[49]

CLINICAL PRESENTATION

Clinical presentation varies depending upon the particular entity of NRSTS. Most commonly, NRSTS presents as a painless mass located in the trunk or extremities. Displacement of local structures can lead to symptoms, including numbness, weakness, pain, and swelling; systemic symptoms are uncommon with nonmetastatic disease.[50] Approximately 15% of patients present with distant metastatic disease at diagnosis. The most common site of metastatic disease involves the lung, and other less frequent sites of metastasis include bone, liver, and peritoneum. Involvement of the regional lymphatics is also rare, with the exception of clear cell sarcoma, angiosarcoma, and epithelioid sarcoma histologic subtypes.[51]

DIAGNOSTIC WORKUP

Ultrasound can be utilized for an initial evaluation to identify size, extent, homogeneity, and solid versus cystic components and to justify subsequent imaging. Following the ARST0332 protocol,[52] computed tomography (CT) and magnetic resonance imaging are then utilized in further evaluation of NRSTS primary lesions to provide soft tissue definition and define the extent of disease or invasion into the nearby structures. Biopsy, either core needle or incisional, is needed for diagnosis and should be carefully planned to be surgically excised or included within the radiation field during definitive management. For staging of high-grade/unresectable tumors, CT of the chest is required and CT of the abdomen and pelvis is often obtained. Fluorodeoxyglucose-positron emission tomography imaging is optional but encouraged particularly if patients undergo neoadjuvant chemoradiation for assessment of tumor response.

STAGING

Grade can be determined by two methods: Pediatric Oncology Group (POG) and French Federation of Cancer Centers Sarcoma Group (FNCLCC) grading systems. The POG system, a prospectively validated variation of the National Cancer Institute grading, defines tumor grade using the propensity for malignancy based on histologic subtype, percent necrosis, and mitotic count (Table 94.2).[53] In comparison, FNCLCC assigns a score for each of three categories: tumor differentiation, mitotic index, and tumor necrosis.[54] A sum equaling 2 or 3 is grade 1, 4 or 5 is grade 2, and 6 to 8 is grade 3 (Table 94.3).[55] Both the FNCLCC and POG systems provide adequate prognostic measures in NRSTS, with the mitotic index being a key parameter in grading pediatric NRSTS.[53] Comparing the POG and FNCLCC grading systems, the FNCLCC system was found to be a better predictor of tumor mortality and distant metastasis; this system may be favored in determining the aggressiveness of STS but may also lead to overtreatment.[56] Currently, the FNCLCC system is more widespread due to its use in adult STS. Prognosis including the risk of metastasis may be better evaluated by genetic signatures using tools such as CINSARC, which quantifies chromosomal complexity[54]; Genomic Grade Index[57]; and Immunologic Constant of Rejection gene signature[58]; importantly, the majority of this type of analysis has been based on adult tumor samples.

TABLE 94.2 PEDIATRIC ONCOLOGY GROUP GRADING SYSTEM

Grade	Description
1	Liposarcoma: myxoid and well differentiated Deep-seated dermatofibrosarcoma protuberans Fibrosarcoma: well differentiated or infantile (<5 y) Hemangiopericytoma: well differentiated or infantile (<5 y) Well-differentiated malignant peripheral nerve sheath tumor

Grade	Description
	Angiomatoid malignant fibrous histiocytoma
2	All NRSTS not in grades 1 or 3; <15% of tumors with geographic necrosis, or mitotic index <5 mitoses/10 HPFs
3	Fibrosarcoma with >15% of tumor with geographic necrosis or mitotic index >5 mitoses/10 HPFs Liposarcoma: pleomorphic, round cell Mesenchymal chondrosarcoma Extraskeletal osteosarcoma Malignant triton tumor

HPF, high-power field; NRSTS, nonrhabdomyosarcoma soft tissue sarcoma.

Used with permission of Elsevier Science & Technology Journals from Parham DM, Webber BL, Jenkins JJ III, Cantor AB, Maurer HM. Nonrhabdomyosarcomatous soft tissue sarcomas of childhood: formulation of a simplified system for grading. *Mod Pathol*. 1995;8(7):705-710; permission conveyed through Copyright Clearance Center.

TABLE 94.3 FRENCH FEDERATION OF CANCER CENTERS SARCOMA GROUP GRADING SYSTEM

Parameter	Score
Tumor differentiation	
Closely resembling normal tissue	1
Histologic typing certain	2
Embryonal or undifferentiated sarcomas	3
Mitotic count (per 1.7 mm^2)	
0-9	1
10-19	2
>19	3
Tumor necrosis	
No necrosis	1
<50% necrosis	2
≥50% necrosis	3
Total score	**Grade**
2 or 3	1
4 or 5	2
6-9	3

From Obeidin F. Soft tissue: grading. PathologyOutlines.com. Accessed February 6, 2024. https://www.pathologyoutlines.com/topic/softtissuegrading.html. Table provided by PathologyOutlines.com.

Prognostication requires stratification of several key factors, including the presence of distant and nodal metastases, histologic grade, size of the primary tumor (≤5 cm vs >5 cm), and extent of surgical resection.[52,59]

Per the North American Children's Oncology Group (COG) ARST0332, tumors are divided into three tiers of risk: low, intermediate, and high. Any nonmetastatic tumor is either low or intermediate risk. Low-risk tumors are resectable and low grade of any size or high grade with a maximal diameter of 5 cm or less. Intermediate-risk tumors are resectable, high grade, and larger than 5 cm or nonmetastatic, but unresectable. Finally, high-risk tumors are metastatic to lymph nodes and/or distant sites.[52] This risk group system was highly predictive of survival when tested in this prospective trial.

GENERAL TREATMENT PARADIGMS

Treatment decision-making is often complex, and patients should be treated using a multidisciplinary approach and enrolled in prospective clinical trials whenever possible. Two large multinational

prospective studies (ARST0332 and EpSSG NRSTS 2005) currently define the management for NRSTS.[52,59] Patients undergo a risk-stratified treatment paradigm based on initial clinicopathologic factors that include histologic grade, size of primary tumor, extent of surgery, and involvement of nodal or metastatic sites (Table 94.4).

TABLE 94.4 RISK STRATIFICATION AND TREATMENT

Staging	Treatment
Grade 1, R0-1 resection	Initial resection only, no adjuvant treatment
Grade 2-3, R0 resection, tumor size ≤5 cm	
Grade 2-3, R1 resection, tumor size ≤5 cm	Adjuvant radiation
Grade 2-3, R0-1 resection, tumor size >5 cm	Adjuvant chemotherapy +/− radiation
Grade 2-3, delayed surgery planned or unresectable, tumor size >5 cm	Neoadjuvant chemotherapy and radiation
Grade 2-3, metastatic NRSTS	

NRSTS, nonrhabdomyosarcoma soft tissue sarcoma.

Reprinted from Ferrari A, Orbach D, Sparber-Sauer M, et al. The treatment approach to pediatric non-rhabdomyosarcoma soft tissue sarcomas: a critical review from the INternational Soft Tissue SaRcoma ConsorTium. *Eur J Cancer*. 2022;169:10-19. Copyright © 2022 Elsevier. With permission.

Low Risk

Low-risk patients encompass those with low histologic grade (POG grade 1-2 or FNCLCC grade 1) with an R0 or R1 resection or a high-grade tumor (POG grade 3 or FNCLCC grade 2-3) 5 cm or smaller with R0 resection. These patients are treated with surgery alone as the risk of metastatic recurrence is extremely low. For patients who have a high-grade tumor with an R1 resection, they should receive adjuvant radiation to 54 to 55.8 Gy. Five-year event-free survival (EFS) was 89% to 91% and 5-year overall survival (OS) was greater than 90% in both ARST0332 and EpSSG NRSTS 2005.[52,59] There was a statistical difference in 5-year OS between low-grade histologies (>99%) and high-grade histologies (93%-96%) in both studies.

Intermediate Risk

Intermediate-risk patients require adjuvant therapy due to concern for local control or distant metastatic progression. These patients include high-grade tumors greater than 5 cm who receive neoadjuvant or adjuvant chemotherapy and radiation based on planned surgical resection. Chemotherapy is delivered using ifosfamide and doxorubicin, with timing dependent on the sequence of surgery and radiation. Preoperative radiation is delivered using 45 Gy in 1.8 Gy fractions. An additional boost of 9.0 to 10.8 Gy in 1.8 Gy fractions is delivered for R1 resection and 14.4 to 19.8 Gy for gross residual disease following surgical resection. In this cohort, the estimated 5-year OS was 79.2% in ARST0332 and 5-year EFS was 65.0%, with the majority of progressions being metastatic recurrence.[52] Comparatively, in the EpSSG NRSTS 2005 study, estimated 5-year EFS and OS for patients receiving chemotherapy were 66% and 76% for the adjuvant arm and 56% and 70% for the neoadjuvant arm, respectively.[59]

High-Risk/Metastatic Disease

The high-risk cohort is composed of patients with disease involving the lymph nodes or metastatic sites. If the tumor is low grade, surgical resection of the primary and all metastatic sites is recommended if feasible and no further adjuvant therapy is necessary. If the tumor is high grade, neoadjuvant chemotherapy with doxorubicin and ifosfamide is initiated, and patients with resectable disease may receive adjuvant chemotherapy and radiation. Unresectable metastatic sites should be evaluated for focal radiation treatment. Whole-lung or liver radiation is generally not recommended for diffuse metastases,

except in the setting of synovial sarcoma where whole-lung radiation is considered.[60] Estimated 5-year EFS for the high-risk cohort was 21% and OS was 36% in ARST0332.[52]

GENERAL MANAGEMENT

Surgery

En bloc surgical resection with R0 margins remains the mainstay of treatment for NRSTS. If there is concern for residual microscopic disease after initial resection, a primary reexcision should be performed to achieve a negative surgical margin. Extent of surgical resection is significantly associated with survival outcomes. Pediatric patients who received a gross total resection or microscopic residual disease had an estimated 5-year OS of 90%, which was significantly higher than patients who had macroscopic residual disease with an estimated 5-year survival of 63%.[52] Estimated 5-year OS was also significantly improved in patients who had negative margins as compared to those with microscopic residual disease (93% vs 80%). Although margin adequacy is still an ongoing question, particularly as wide margins are not feasible in a small child or in various anatomic locations, ARST0332 defined negative microscopic margins as 5 mm or larger[52]; however, more recent international consensus guidelines define a negative margin as greater than 1 mm.[61] For high-risk patients, neoadjuvant therapy and delayed resection were very successful in achieving local control, with up to 94% of patients achieving an R0/R1 resection.[62] Systematic lymph node sampling should be considered in certain histologic subtypes as the overall incidence of regional nodal dissemination is less than 10%. Lymph node sampling should be considered in pediatric patients with histologic subtypes with the highest incidence of lymph node metastases, which include epithelioid sarcoma (18%), angiosarcoma (17%), and clear cell sarcoma (14%),[51] with the caveat that many of these patients will have radiographic evidence of lymph node involvement.

Chemotherapy

The role of systemic therapy is largely derived from data on adult STS. In the two large prospective clinical trials on pediatric NRSTS, both the ARST0332 and EpSSG NRSTS 2005 trials utilized ifosfamide/doxorubicin-based chemotherapy, although the regimens were not identical. ARST0332 assigned (ifosfamide 9 g/m^2/cycle × 6 cycles and doxorubicin 75 mg/m^2/cycle × 5 cycles) to all patients treated with adjuvant or neoadjuvant chemotherapy.[62] EpSSG NRSTS 2005 utilized (ifosfamide 9 g/m^2/cycle × 3-7 cycles, doxorubicin 75 mg/m^2/cycle × 3-5 cycles), with cycles of chemotherapy dependent on histology (synovial sarcoma vs other histologies), tumor size, lymph node involvement, extent of resection, and margin status.[59] ARST1321 investigated the efficacy of neoadjuvant chemotherapy with the addition of a targeted tyrosine kinase inhibitor, pazopanib, which acts on the vascular endothelial growth factor receptor (VEGF-R), PDGF-R, and cKit pathways in STS.[63] Although the addition of pazopanib improved the rate of pathologic near-complete response (≥90% nonviable tumor) from 22% to 58%,[63] long-term outcomes did not find a difference in 3-year EFS (76% vs 65%, P = .19),[64] indicating pathologic near-complete response may not be a good surrogate marker for survival outcomes.

RADIATION THERAPY

Indications for radiation are based on the risk for disease progression and potential side effects. Postoperative radiation is recommended for high-grade tumors 5 cm or smaller with positive surgical margins and high-grade tumors greater than 5 cm, regardless of margin status due to the risk of local recurrence. Low-grade tumors do not need adjuvant radiation when gross total resection is completed unless there is a particular individual concern. Omission of radiation can also be considered in low-grade tumors with a positive microscopic surgical margin, as ARST0332 demonstrated 18% local recurrence without adjuvant radiation in low-grade tumors,[52] although further surgical resection for negative margins is often pursued. When the patient has unresectable primary disease or delayed resection is planned,

patients should receive preoperative chemoradiation to improve the extent of resection. This is recommended as compared to postoperative adjuvant radiation, as much of the irradiated tissue is resected and there is a higher likelihood of negative margins[65] as well as a less than 15% rate of wound complication.[52] Relative to historical neoadjuvant chemoradiation with wound complication rates near 35%,[66] the use of modern techniques has significantly decreased this rate; these data mirror wound complication rates in modern adult STS neoadjuvant paradigms.[67] In addition, volumes for preoperative radiation are often smaller than those utilized for postoperative radiation, which can, in turn, lead to less late morbidity such as fibrosis.

Radiation Dose and Volumes

Radiation volumes in the pediatric population are smaller than in adults in effort to decrease long-term toxicity. With this approach, prospective studies have demonstrated low rates of local failure. For unresected tumors, preoperative radiation (45-50.4 Gy) is delivered to the initial target volume (gross tumor volume [GTV]) as defined by preoperative imaging (Figure 94.1). The full list of dose fractionation schema for preoperative and postoperative volumes is given in Table 94.5. Clinical target volume (CTV) should include at least a 1.5-cm expansion, with consideration of areas with potential occult tumor involvement, adjacent lymph nodes for sites with clinical or pathologic involvement, and modified to account for anatomic barriers. CTV expansion for extremity tumors is defined by skeletal maturity with different margins for patients older than 18 years (skeletally mature). CTV expansion for patients older than 18 years with intermediate- to high-grade tumors 5 cm or larger includes a 3-cm longitudinal margin and 1.5-cm radial margin. For patients older than 18 years with all other tumors, CTV should include a 2-cm longitudinal margin and 1-cm radial margin. The planning target volume (PTV) includes a setup margin, typically 5 mm, although it can vary depending on the institution and immobilization methods. Proton PTV varies with each individual field and should account for range and setup uncertainty. The postoperative radiation field (PTV1) is defined by the initial tumor location on preoperative imaging excluding the volume that extends into cavities that have returned to normal anatomic position (Figure 94.2). A boost (PTV2) should be delivered to gross residual disease and the operative tumor bed determined by the operative note, pathology report, and surgical clips. Dose is prescribed where at least 95% of the specified dose encompasses 100% of the PTV. No more than 10% of the PTV should receive greater than 110% of the prescription dose. Organs at risk dose guidelines are shown in Table 94.6.

TABLE 94.5 PRESCRIBED DOSE AND FRACTIONATION

	Total Dose (Gy)	CTV1 (Gy)	CTV2 (Gy)
Postoperative Radiation			
Negative margins (R0)	54.0-55.8	45.0	9.0-10.8
Microscopic margins (R1)	54.0-55.8	45.0	9.0-10.8
Macroscopic margins (R2)	59.4-64.8	45.0	14.4-19.8
Preoperative Radiation			
Negative margins (R0)	45.0-50.4[a]	45.0-50.4	0
Microscopic margin (R1)	54.0-55.8	45.0	9.0-10.8
Macroscopic margins (R2)	59.4-64.8	45.0	14.4-19.8

All treatment given in 1.8 Gy per fraction.
CTV, clinical target volume.
[a]45 Gy recommended for concurrent preoperative chemoradiation.

TABLE 94.6 ORGANS AT RISK DOSE GUIDELINES

Organ	Volume (%)	Dose (Gy)
Single Organ		
Bladder	100	45.0
Esophagus	50	40.0
Heart	100	30.0
Liver	100	23.4
Liver	50	30.0
Rectum	100	45.0
Optic chiasm	100	54.0
Small bowel	75	45.0
Spinal cord	Any volume	50.4
Paired Organs[a]		
Kidney (bilateral)	50	24.0
Kidney (bilateral)	100	14.4
Lung (bilateral)	20	20.0
Lung (bilateral)	35	20.0
Optic nerve	100	54.0
Eye	100	45.0
Lens	100	6.0
Cochlea	100	40.0

[a]Paired organs volume refers to one of the paired organs unless specified as bilateral (kidney, lung) in which both of the paired organs are included in the percentage.

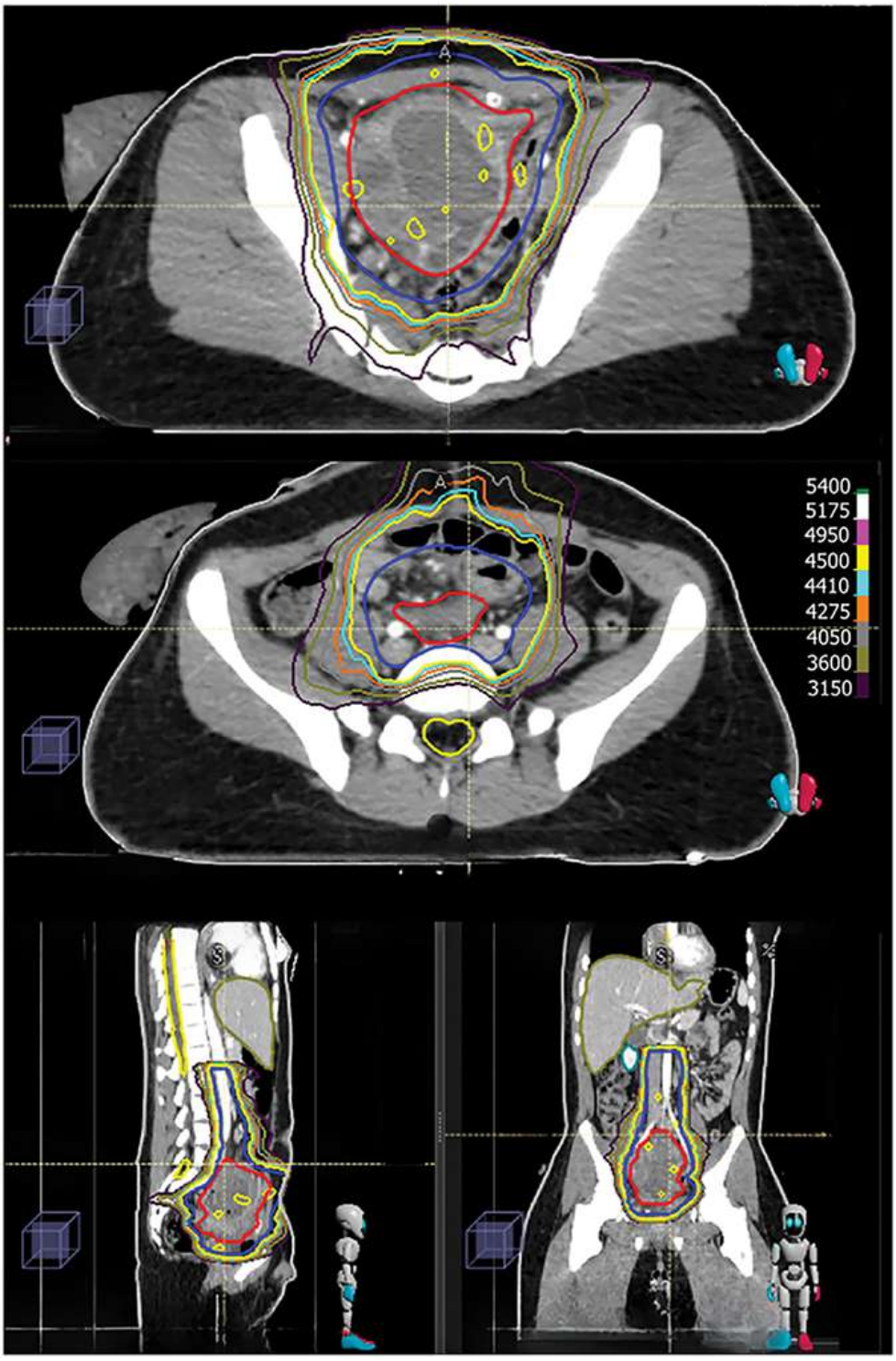


FIGURE 94.1 Preoperative radiation plan for abdominal nonrhabdomyosarcoma soft tissue sarcoma. Contouring the gross tumor volume (red) and regional involved retroperitoneal and pelvic lymph nodes in the clinical target volume (blue).

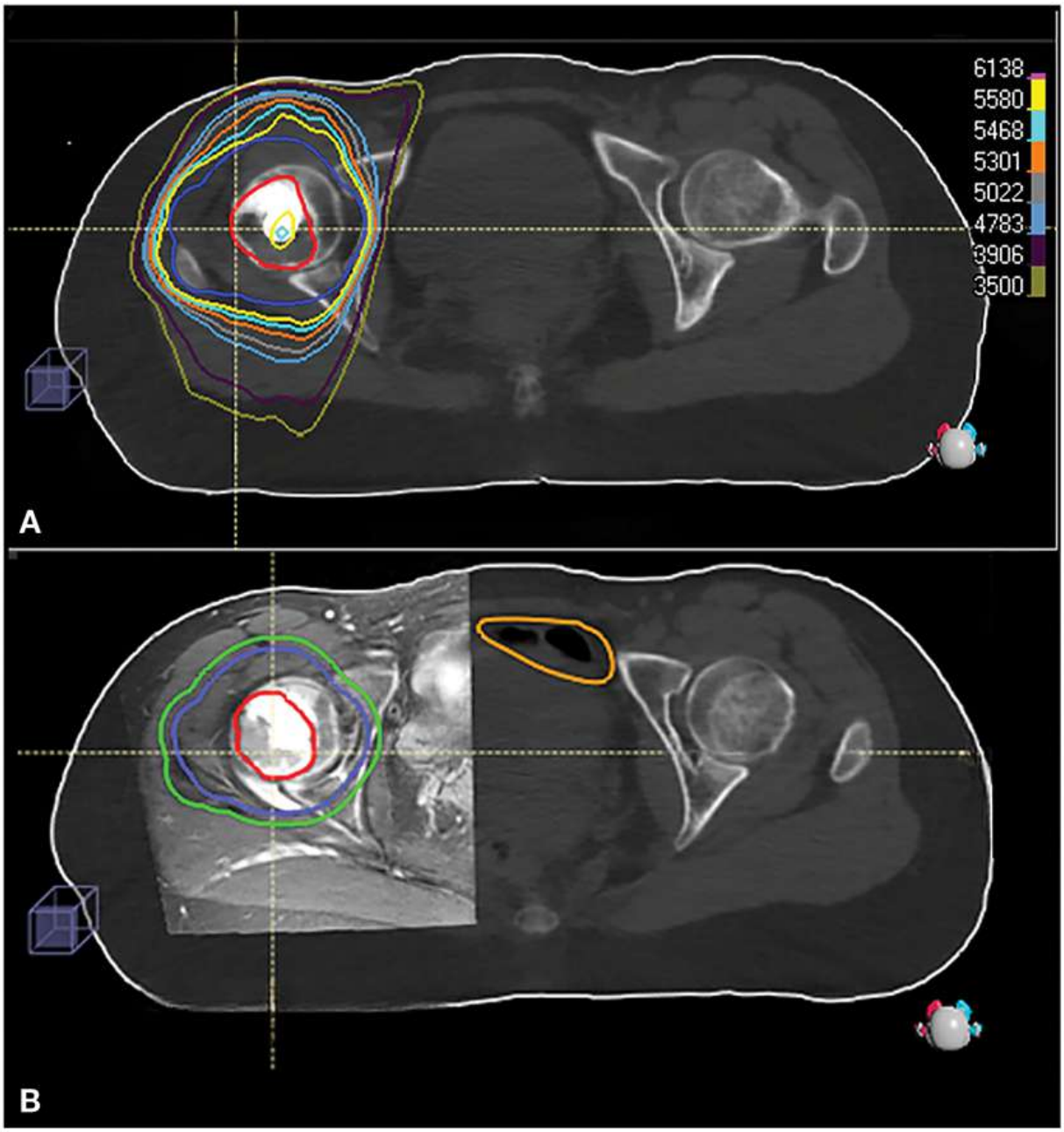


FIGURE 94.2 Postoperative radiation plan for a femoral head nonrhabdomyosarcoma soft tissue sarcoma. A. postoperative plan with the preoperative gross tumor volume (red) and postoperative hardware covered in the clinical target volume (blue). B. preoperative and magnetic resonance imaging with superimposed volumes.

Radiation Technique

Treatment planning techniques to treat the target volume and spare normal structures include three-dimensional conformal radiation therapy (3DCRT), intensity-modulated radiation therapy (IMRT), and proton radiation. Secondary analysis of ARST0332 preoperative radiation planning found that IMRT plans significantly improved CTV coverage and reduced the volume of skin and adjacent joint coverage receiving 45 Gy (V45 Gy) as compared to 3DCRT, which may reduce clinical and toxicity outcomes.[68] Proton beam radiotherapy (RT) is also being increasingly used as dosimetric studies demonstrate a decrease in integral dose to normal structures and, therefore, reduce the risk for radiation-related adverse

events as compared to photon-based techniques.[69] However, the potential benefit of proton therapy over IMRT is dependent on site; for many extremity tumors, photon-based techniques achieve comparable plans.

Site-Specific Considerations

Extremity Tumors

Whenever possible, the CTV should be modified to avoid circumferential irradiation of extremity lymphatics by sparing at least a 1- to 2-cm strip of tissue to prevent lymphedema. If there is no extension across the joint space, a smaller margin may be considered so the adjacent epiphysis can be excluded. The most active epiphyses for growth include the knee, shoulder, and wrist.

Head and Neck Tumors

Many of these tumors may be considered unresectable due to proximity to critical structures. Dose limitations to the brain, cochlea, optic chiasm, orbit including the eye, lacrimal gland, and optic nerve should be attempted. Conformal techniques such as IMRT or proton therapy should be utilized.

Chest Wall/Intrathoracic Tumors

GTV will be defined as the pretreatment tumor volume, excluding the component that has decreased in size or has been removed in tumors where lung parenchyma has returned to normal anatomic position after surgery or chemotherapy. All areas of pleural involvement will be included in the GTV.

Intra-Abdominal/Retroperitoneal Tumors

GTV will be defined as pretreatment tumor volume, excluding the component that has decreased in size or has been removed in tumors where bowel parenchyma has returned to normal anatomic position after surgery or chemotherapy. All areas of peritoneal or mesenteric involvement will be included in the GTV. Whole-abdomen radiation is typically not indicated in patients with diffuse peritoneal involvement or malignant ascites, with the exception of desmoplastic small round cell tumor.

Radiation Boost for Postoperative Margin Status

Postoperative radiation boost included 10.8 Gy in six fractions for R0 with less than 5-mm margins/R1 resection and 19.8 Gy in 11 fractions for R2 or unresected tumors in ARST0332.[52] However, in patients who received a boost after R1 resection, many were found to recur locally within the 100% isodose distribution,[62] providing little evidence to support a postoperative radiation boost for close margins. In ARST1321, boost was only delivered to gross disease using 19.8 Gy in high-grade extremity and trunk primary sites. Similarly, in adults with STS, postoperative boost after preoperative radiation and a margin-positive excision did not provide an advantage in preventing local recurrence.[70]

Radiation Therapy for Metastases

Consideration of radiation for metastatic disease depends on resectability, symptomatic metastases, and feasibility of radiation due to the number and location of metastatic sites. Patients with oligometastatic disease may benefit from dose-escalated radiation using conformal techniques like stereotactic ablative radiation to provide durable local control and provide a potential progression-free survival benefit.[71,72] Whole-lung or liver radiation is generally not recommended for diffuse metastases, although whole-lung irradiation has been evaluated in a single-institution series from Memorial Sloan Kettering Cancer Center for patients with synovial sarcoma and lung metastases.[60] Most of the patients (13/14) had gross residual disease in the lungs for which whole-lung irradiation was delivered via IMRT 15 Gy in 10 fractions. Although this was well tolerated with limited toxicity, durable pulmonary control was not achieved, as

pulmonary failure-free survival was 14% at 18 months. However, two of three patients who received a stereotactic body radiotherapy (SBRT) boost (25-30 Gy in five fractions) to gross disease experienced improved local control, which suggests that boost should be considered for gross disease. Treatment of malignant pleural or peritoneal effusions or intracavitary tumor spill with radiation is generally not recommended. Palliative radiation for symptomatic metastases should be considered for quality-of-life improvement.

Long-Term Toxicity

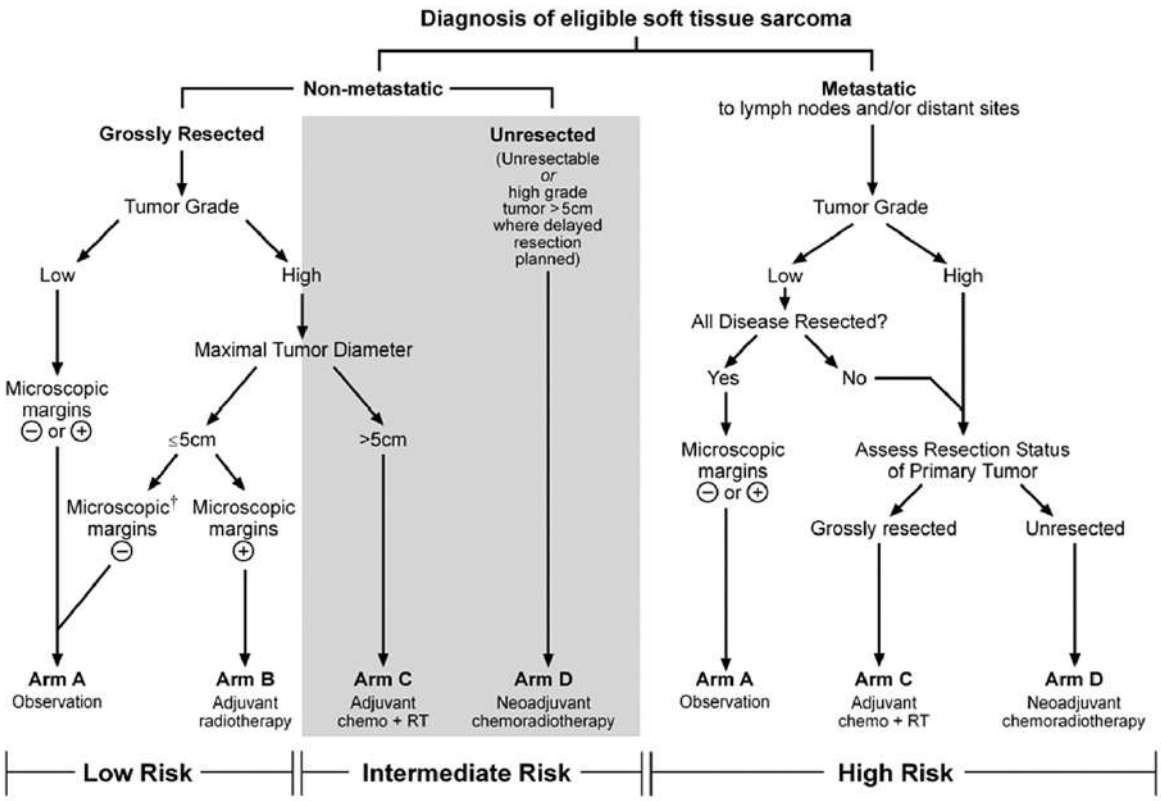
Late effects of therapy depend on the site of disease treated and the treatment modalities used. Late adverse effects can include psychosocial changes and decrements in quality of life. Importantly, patients should continue to be followed by supportive services, including physical and occupational therapies and nutrition and psychosocial services. These measures aim to mitigate long-term risk of lower education achievement, disability due to chronic pain, financial hardship, and development of mental health disorders and anxiety. Radiation to the extremity may lead to fibrosis, impaired bone growth, edema, nerve injury, and bone fracture. Progressive organ dysfunction can also occur due to radiation treatment, including pulmonary fibrosis, radiation nephropathy, and gonadal hormonal failure.[73,74] In addition, secondary malignancies may emerge several years after the completion of radiation and chemotherapy treatments.[75]

Chemotherapy can also cause long-term organ dysfunction. Specific agents including doxorubicin and other anthracyclines may result in a dose-dependent cardiomyopathy. Both ARST0332 and EpSSG NRSTS 2005 restricted cumulative dose of doxorubicin to 375 mg/m^2 as incidence of cardiotoxicity is significantly higher with a cumulative dose of doxorubicin above 500 mg/m^2.[76] Alkylating agents can contribute to oligospermia/azoospermia,[77] loss of oocytes, and gonadal hormonal insufficiency, potentially causing delayed or arrested puberty, premature menopause, infertility, and other complications.[78,79] Although advancements in supportive care have reduced the risk of hemorrhagic cystitis, alkylating agents still pose the possibility of chronic or recurrent cystitis, leading to bladder fibrosis and dysfunctional voiding.[80] Ifosfamide may cause glomerular and tubular nephrotoxicity, coupled with associated metabolic bone disease, though permanent and clinically significant renal impairment is relatively rare. Regular monitoring and ongoing support services are essential components of comprehensive care to address and mitigate these late effects.

SUMMARY OF CLINICAL TRIALS

ARST0332

ARST0332 is the first large-scale clinical trial for pediatric NRSTS in the United States, which enrolled patients less than 30 years of age with NRSTS of all stages. The primary objective was to use a risk-stratified treatment strategy and assess clinical outcomes and patterns of failure in treated patients (Figure 94.3). Patients were stratified based on metastatic status, extent of primary tumor resection, tumor size (≤5 cm vs >5 cm), and POG histologic grade (see Table 94.2). All patients had a gross total resection of their tumor prior to enrollment, unless they had a high-grade tumor greater than 5 cm and there was anticipated residual disease after resection, unresectable disease, or high-grade metastatic disease. Low-risk patients received surgery alone. Patients received adjuvant or neoadjuvant chemotherapy and radiation based on their risk group and the extent of resection of the primary tumor at study entry. All patients received the same ifosfamide/doxorubicin chemotherapy regimen (ifosfamide 9 g/m^2/cycle × 6 cycles and doxorubicin 75 mg/m^2/cycle × 5 cycles), with the timing of each cycle dependent on the sequence of surgery and RT. A radiation dose of 45 Gy was given neoadjuvantly with a boost of 10.8 Gy for R1 resection and 19.8 Gy for R2 or unresectable disease. Despite the lower radiation dose with neoadjuvant therapy, there was a high rate of local control, with 94% of eligible patients with high-grade tumors greater than 5 cm achieving an R0/R1 resection.



† Negative microscopic margins defined as the presence of a cuff of non-malignant tissue measuring at least 5mm in all directions surrounding the tumor in the operative specimen. When the tumor abuts fascia or periosteum and the fascia or periosteum is removed in continuity with the tumor specimen, this margin will also be considered negative.

FIGURE 94.3 ARST0332 treatment schema. RT, radiation therapy. (Reprinted from Spunt SL, Million L, Chi YY, et al. A risk-based treatment strategy for non-rhabdomyosarcoma soft-tissue sarcomas in patients younger than 30 years (ARST0332): a Children's Oncology Group prospective study. *Lancet Oncol*. 2020;21[1]:145-161. Copyright © 2019 Elsevier. With permission.)

The study outcomes demonstrate that risk stratification was able to separate patients into prognostic subgroups with significantly different 5-year EFS and OS (Figure 94.4). Clinical factors prognostic for OS include patient age, tumor size, tumor depth, tumor invasiveness, POG and FNCLCC grade, presence of metastases, extent of resection, and risk group. In patients who received neoadjuvant chemoradiation, response at week 13 was also prognostic for 5-year OS and EFS. Histologic subtype was found as a predictor for local control, with synovial sarcoma having a low rate of local recurrence (2.7%), whereas MPNST had a higher rate of recurrence (27.9%) likely also related to their propensity to involve the brachial/lumbosacral plexus, which is a challenging location for surgical resection. Secondary analysis of patients with lymph node involvement found that overall lymph node metastases are rare in this population, approximately 4% of the entire cohort, and limited to specific subtypes, including epithelioid sarcoma, undifferentiated sarcoma, clear cell sarcoma, and angiosarcoma. Pediatric patients with isolated lymph node metastases have a high 5-year OS of 86% and should be treated with curative intent. This risk stratification system was able to successfully separate patients into low-risk, intermediate-risk, and high-risk prognostic subgroups and risk-adapted treatment paradigms.[52]

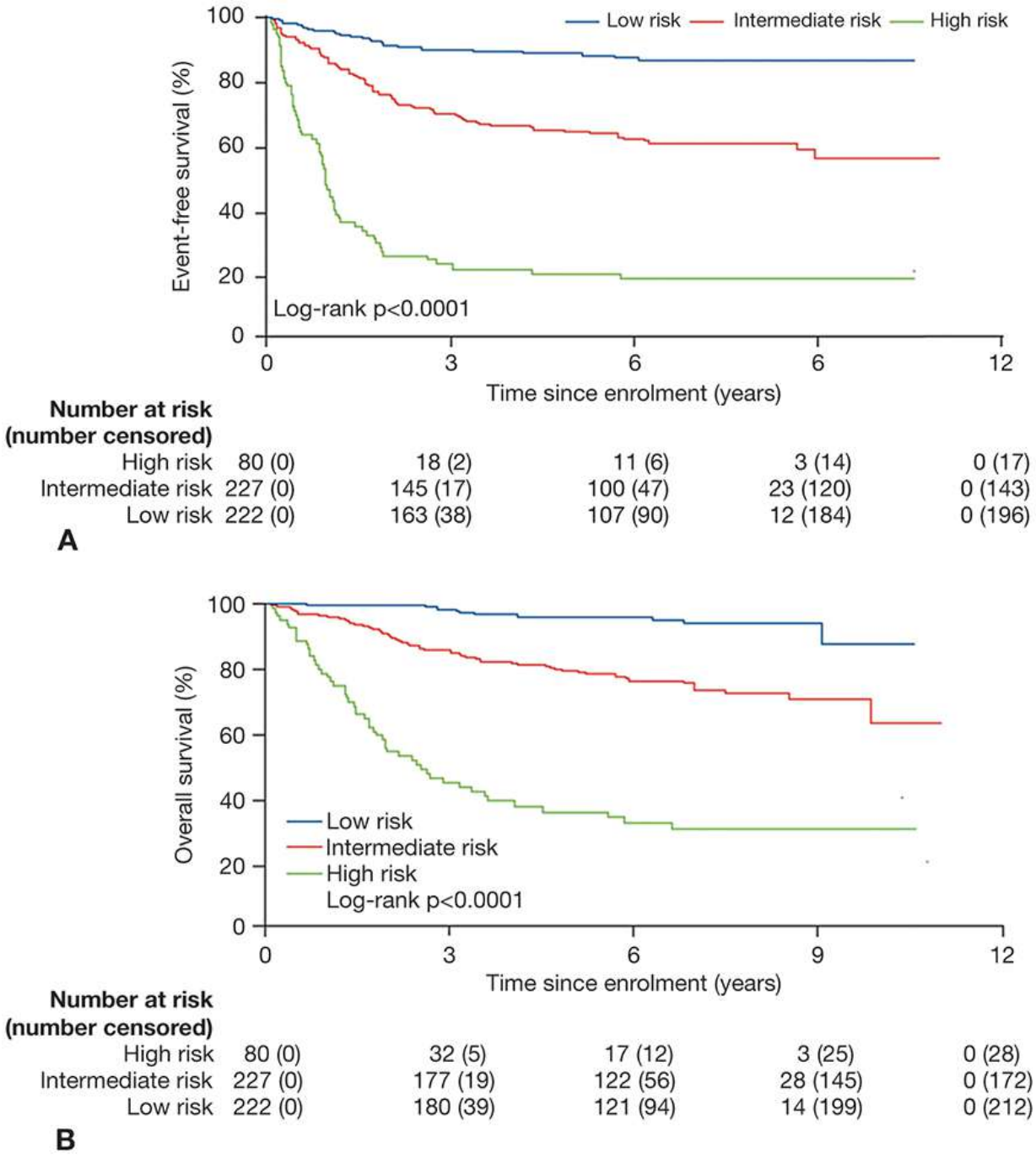


FIGURE 94.4 Estimated 5-year event-free (A) and overall (B) survival by risk group. (Reprinted from Spunt SL, Million L, Chi YY, et al. A risk-based treatment strategy for non-rhabdomyosarcoma soft-tissue sarcomas in patients younger than 30 years (ARST0332): a Children's Oncology Group prospective study. *Lancet Oncol*. 2020;21[1]:145-161. Copyright © 2019 Elsevier. With permission.)

EpSSG NRSTS 2005

In Europe, the EpSSG cooperative group enrolled patients with nonmetastatic NRSTS under 21 years of age in EpSSG NRSTS 2005.[59] These patients were assigned to different treatment groups depending on the extent of primary tumor resection, tumor size (≤5 cm vs >5 cm), nodal involvement, and FNCLCC histologic grade ("adult-type" NRSTS only) (see Table 94.3). Patients with synovial sarcoma were

further stratified by tumor site. Treatment groups included surgery alone, adjuvant radiation, adjuvant chemotherapy (with or without radiation), and neoadjuvant chemotherapy (with or without radiation) (Table 94.7). All patients with synovial sarcoma received chemotherapy, except those with a 5 cm or less tumor that had undergone R0 resection. Chemotherapy administration was limited to "adult-type NRSTS" histologies with unresectable disease, greater than 5 cm FNCLCC grade 3 with R0 or R1 margins, or involved lymph nodes. Chemotherapy regimen utilized ifosfamide 9 g/m^2/cycle × 3 to 7 cycles and doxorubicin 75 mg/m^2/cycle × 3 to 5 cycles, with the number of cycles dependent on the stage of disease. RT dose ranged from 50.4 to 59.4 Gy depending on the extent of primary resection and could be given preoperatively or postoperatively.

TABLE 94.7 TREATMENT GROUPS FOR NONRHABDOMYOSARCOMA SOFT TISSUE SARCOMAS IN THE 2005 EUROPEAN PEDIATRIC SOFT TISSUE SARCOMA STUDY GROUP

Treatment	Stage	Radiation Dose (Gy)
Surgery alone		
Synovial sarcoma	R1 resection, tumor size ≤5 cm	
Adult-type NRSTS	R0 resection, tumor size ≤5 cm, any grade	
Adjuvant radiation		
Adult-type NRSTS	R0 resection, tumor size >5 cm, grade 2	Dose 50.4
Adult-type NRSTS	R1 resection, tumor size ≤5 cm, grade 2-3	Dose 54
Adjuvant chemotherapy +/− Radiation		
Synovial sarcoma	R0 resection, tumor size >5 cm	
Synovial sarcoma	R1 resection, tumor size ≤5 cm	Dose 50.4
	R1 resection, tumor size >5 cm	Dose 54
No Adjuvant Radiation		
Adult-type NRSTS	R0-1 resection, tumor size >5 cm, grade 3 or N1	Dose 54
Neoadjuvant chemotherapy		
Synovial sarcoma and adult-type NRSTS	Unresected primary or unresected N1	Dose 50.4-59.4

NRSTS, nonrhabdomyosarcoma soft tissue sarcoma.

Reprinted from Ferrari A, van Noesel MM, Brennan B, et al. Paediatric non-rhabdomyosarcoma soft tissue sarcomas: the prospective NRSTS 2005 study by the European Pediatric Soft Tissue Sarcoma Study Group (EpSSG). *Lancet Child Adolesc Health*. 2021;5(8):546-558. Copyright © 2021 Elsevier. With permission.

The primary end points were EFS and OS, which were evaluated per treatment group. The highest estimated 5-year EFS was 91% and OS was 98% in the surgery-alone group. In the adjuvant RT group, 5-year EFS was 76% and 5-year OS was 88%. For patients receiving chemotherapy, 5-year EFS and OS were 66% and 76% for the adjuvant arm and 56% and 70% for the neoadjuvant arm, respectively. On multivariable analysis, the variables prognostic for OS included histology, tumor grade, extent of surgical resection, and tumor site, with intra-abdominal primary having the worst prognosis. In patients who received neoadjuvant chemotherapy, receipt of RT and delayed surgery was shown to significantly improve 5-year OS; however, pathologic response to chemotherapy was not found to be prognostic.

Secondary analysis of 60 patients enrolled in ARST0332 and EpSSG NRSTS 2005 with low-risk synovial sarcoma found that adequately resected synovial sarcoma 5 cm or less could be safely treated with surgery alone, with 3-year EFS of 90%. In addition, EpSSG NRSTS 2005 found differences in both 5-year OS and EFS outcomes based on histology. MPNST had the worst outcomes (5-year OS 58% and 5-year EFS 43%), whereas patients with "adult-type" NRSTS (5-year OS 86% and 5-year EFS 80%) and synovial sarcoma (5-year OS 89% and 5-year EFS 76%) had improved outcomes. Similar to ARST0332, this study demonstrated the ability to use risk-adapted multimodal treatment, with results suggesting low-

risk patients can be successfully treated with surgery alone. In patients with locally advanced or unresectable disease treated with neoadjuvant chemoradiation, this study illustrated improved outcomes in comparison to historical cohorts, with 5-year EFS increasing from 48.2% to 56.4%.[81]

BERNIE Study

EpSSG patients with metastatic NRSTS and RMS were enrolled in BERNIE, a phase II randomized study to evaluate the addition of bevacizumab, a monoclonal antibody inhibitor of VEGF, to the standard RMS induction chemotherapy with ifosfamide, vincristine, actinomycin D, doxorubicin, and maintenance low-dose cyclophosphamide and vinorelbine for 1 year. The addition of bevacizumab did not improve EFS as compared to historical controls, with an estimated 2-year EFS of 41% in both arms.[82]

ARST1321

Following ARST0332, ARST1321 was the first jointly conducted pediatric/adult sarcoma trial developed by COG and NRG oncology. This is a randomized phase II study for patients with intermediate- or high-grade NRSTS greater than 5 cm in the trunk/extremity. This study was conducted to evaluate the benefit of adding pazopanib, an oral tyrosine kinase inhibitor, to neoadjuvant radiation alone or chemoradiation with concurrent ifosfamide and doxorubicin with the primary end point of improvement of pathologic response, a known predictor for outcomes in adult STS. This study enrolled patients in a concurrent chemotherapy cohort for chemosensitive WHO intermediate or malignant tumors, including liposarcoma, undifferentiated STS, synovial sarcoma, angiosarcoma of soft tissue, adult fibrosarcoma, mesenchymal chondrosarcoma, leiomyosarcoma, liposarcoma (excluding myxoid liposarcoma), UPS, and embryonal sarcoma of the liver. Patients were enrolled in nonchemotherapy cohort and treated with radiation and pazopanib alone for the following histologies: fibrohistiocytic tumors, fibroblastic/myofibroblastic tumors, tumors of uncertain differentiation, chondro-osseous tumors, perivascular tumors, nerve sheath tumors, and undifferentiated sarcomas. Interim analysis determined that the pathologic near-complete response (≥90%) was significantly improved with the addition of pazopanib (58.3% as compared to 22.2%), and the study was terminated early. Despite the high pathologic response rate, there was not an associated improvement in the estimated 3-year EFS or OS, though these data need to be interpreted within the context of the primary study design to assess pathologic response. Secondary analysis also found significantly increased rates of wound complications among patients randomized to receive pazopanib as compared to induction chemoradiation alone (50% vs 22%).[63]

FUTURE DIRECTIONS

Future multi-institutional collaborative trials play a crucial role in advancing the care for pediatric patients diagnosed with NRSTS. The INSTRuCT consortium was created by three large cooperative groups (EpSSG, CWS, and COG) to collaborate and pool resources and expertise of major pediatric STS groups.[83] This subgroup of experts defined a common approach concerning the treatment of pediatric NRSTS with recommendations for a multidisciplinary approach at experienced centers where patients can enroll in prospective clinical trials in national and international sarcoma networks. Future integration between the histologic diagnosis and molecular characterization is being studied to improve diagnosis and genetic drivers of NRSTS as well as molecular targets for novel therapies.[58] Larger collaborative efforts for this translational research include the European MYKIDS project (Molecular Identification and Characterization of non-Rhabdomyosarcoma Soft Tissue Sarcoma in Kids, Adolescent and Young Adults),[84] HEROES-AYA (Heterogeneity, evolution and resistance of sarcomas driven by fusion genes in adolescents and young adults) project, and the COG's 2023 blueprint for research[85] to better study the epidemiology and molecular characterization of childhood cancers. Within the COG blueprint for STS, future trials will explore immune checkpoint inhibitors and genomic alteration-specific novel agents, including multi–tyrosine kinase inhibitors. For example, COG is currently investigating the potential to

develop a trial investigating novel agents in combination with SBRT for relapsed/refractory pediatric NRSTS. In addition, continued collaboration with adult cooperative groups in the National Clinical Trials Network is planned, with an umbrella trial utilizing comprehensive genomic screening and circulating tumor DNA for prognostic and response assessment.

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CHAPTER 95

Osteosarcoma and Other Primary Tumors of Bone

Safia K. Ahmed and Nadia N. I. Laack

Primary bone tumors are rare, accounting for approximately 0.2% of all malignancies. Osteosarcoma, Ewing sarcoma, and chondrosarcoma account for the majority of primary bone tumors. Other rarer histologies include chordoma, fibrosarcoma, and fibrous histiocytoma. This chapter discusses osteo sarcoma for the younger age group, chondrosarcoma, and chordoma in detail. Ewing sarcoma is discussed separately in Chapters 96. Chordoma and chondrosarcoma in skull-base loca tion in adults are discussed in Chapters 42.

OSTEOSARCOMA

Epidemiology

Approximately 1,000 new osteosarcoma cases are diagnosed annually in the United States. Osteosarcoma has a bimodal age distribution. Most cases occur in children and adolescents, with a smaller peak seen in adults over 65 years of age. Most childhood and adolescent cases occur sporadically, whereas cases in adulthood are more commonly associated with sarcomatous degeneration of Paget disease or other benign bone lesions. Osteosarcoma is also associated with retinoblastoma gene mutations and a history of radiation therapy (RT), especially in patients with genetic abnormalities such as retinoblastoma.

Pathogenesis and Risk Factors

Osteosarcoma is derived from bone-forming mesenchyme and is described as a malignant sarcomatous stroma associated with the production of osteoid bone.[1] The peak incidence coincides with a period of rapid bone growth. The most common osteosarcoma type in pediatric patients is conventional osteosarcoma, including osteoblastic, chondroblastic, and fibroblastic types. Each subgroup has varied amounts of osteoid formation and a different predominant component. Conventional osteosarcoma accounts for 90% of cases and are mostly high-grade tumors. There is no difference in outcome or treatment recommendations based on osteosarcoma subtypes. Other less common subtypes include telangiectatic, small cell, juxtacortical, periosteal, paraosteal, and high-grade surface osteosarcomas.

Approximately one-third of osteosarcoma cases are associated with inactivation of the retinoblastoma tumor suppressor gene (13q14).[2] Other genetic abnormalities include abnormal TP53 function, gene amplification, and translocations.[3,4] Prior history of RT is associated with the risk of secondary osteosarcoma. Overall, the rate of secondary osteosarcoma has dec reased in patients with retinoblastoma, given the declining use of RT in this population. Some data suggest limiting dose to less than 60 Gy in patients with Ewing sarcoma treated with RT can reduce the risk of secondary osteosarcoma.[5] Benign bone lesions, such as Paget disease, chronic osteomyelitis, fibrous dysplasia, and multiple hereditary exostoses, have also been associated with osteosarcoma. Malignant transformation is generally observed in long-standing Paget disease and occurs in 0.7% to 1.0% of cases.[6]

Clinical Manifestations, Diagnostic Evaluation, and Staging

In general, patients with osteosarcoma present with localized pain, swelling, and a palpable mass. The most common primary tumor sites are femur (49%), tibia (26%), and humerus (10%). Approximately 90% of patients present with localized disease. Lung is the most common site of metastases followed by bone.

A complete history and physical examination are performed, with particular attention to the duration of symptoms, the presence of pain, difficulty of function, and the location and size of the mass. Studies commonly obtained to evaluate the extent of disease include routine blood work, plain radiographs, a computed tomography (CT) scan to assess bone involvement and integrity, and magnetic resonance imaging (MRI) to assess soft tissue extent. CT and MRI are both required (Figure 95.1) of the primary region and should encompass the entire bone to evaluate for skip metastases (<5% incidence). Plain radiographs typically show sclerotic or lytic lesions of the metaphysis. A bony sunburst pattern is often seen as a result of the periosteal new bone formation. The elevated periosteal reaction may generate a Codman triangle. ^{18} fluorodeoxyglucose-positron emission tomography (^{18}FDG- PET) is obtained to evaluate for metastatic disease. PET is also helpful in assessing response to neoadjuvant chemotherapy. Tumors that are not particularly ^{18}FDG avid should undergo a bone scan. In addition, if high-resolution CT is not performed with PET, a diagnostic chest CT scan should be obtained to rule out lung metastases. In general, lung nodules are considered to be metastatic if the lesion size is 5 mm or larger or there is calcification. Nodules 3 mm or larger are highly suspicious for metastatic disease if they have at least two of the following features: occurrence in the context of two or more nodules, nonsubpleural location, documented growth, or solid density.

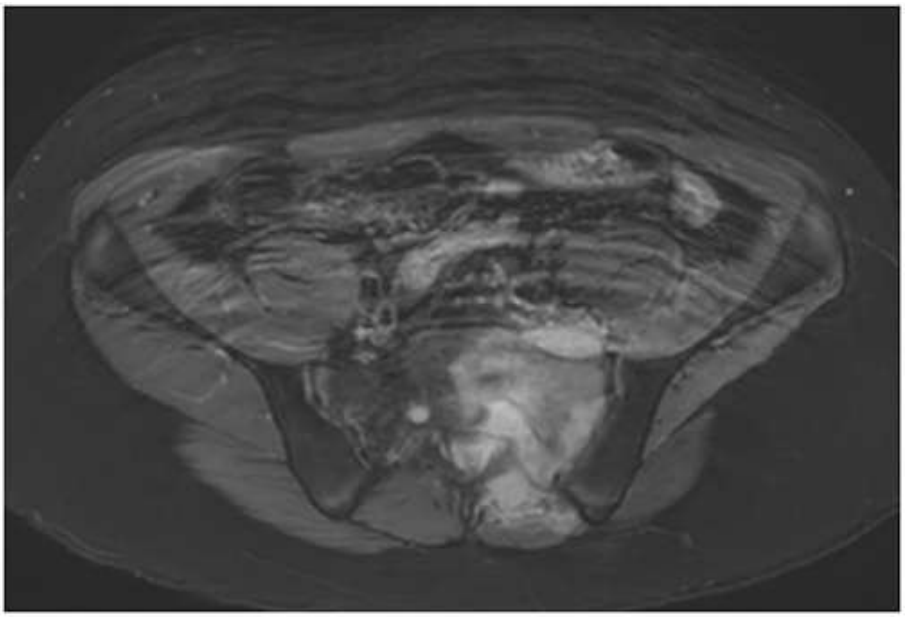

FIGURE 95.1 Magnetic resonance imaging demonstrating a primary pelvic osteosarcoma involving the left sacrum, adjacent soft tissue/muscles, left sacroiliac joint, left iliac bone, left L5-S1 and S1-S2 neuroforamen, and spinal canal.

A biopsy of the primary tumor should be obtained after complete evaluation, ideally by the surgeon who will perform the definitive resection. The biopsy should be placed carefully to avoid contamination of uninvolved areas, vital structures, and hematoma development. It must not increase the extent of surgery, especially jeopardize the possibility of a limb-preserving procedure. Staging systems include those from the Musculoskeletal Tumor Society (MSTS) and the American Joint Committee on Cancer (AJCC).[7,8] The MSTS staging system is a surgical staging system stratifying tumors by grade and subdividing by local extent (Table 95.1).[8] The AJCC system is less routinely used (Table 95.1). Prognostic features include the presence or absence of metastatic disease, tumor location, and size, whether complete resection of the primary tumor is possible, and response to chemotherapy.[9] Retrospective analysis suggests circulating tumor DNA levels correlate with the risk of recurrence and death.[10]

TABLE 95.1 MSTS AND AJCC STAGING OF OSTEOSARCOMA

MSTS Staging System

Stage	Grade	Site	Metastases
IA	Low	Intracompartmental	None
IB	Low	Extracompartmental	None
IIA	High	Intracompartmental	None

MSTS Staging System

Stage	Grade	Site	Metastases
IIB	High	Extracompartmental	None
III	Any	Any	Present

AJCC Staging System

Stage	T	G	N	M
IA	T1	G1, GX	N0	M0
IB	T2	G1, GX	N0	M0
	T3	G1, GX	N0	M0
IIA	T1	G2, G3	N0	M0
IIB	T2	G2, G3	N0	M0
III	T3	G2, G3	N0	M0
IVA	Any T	Any G	N0	M1a
IVB	Any T	Any G	N1	Any M
	Any T	Any G	Any N	M1b

AJCC, American Joint Committee on Cancer; MSTS, Musculoskeletal Tumor Society.

Treatment

Treatment involves multiagent chemotherapy and local therapy. If only the primary tumor site is treated, about 90% of patients will experience metastatic disease.[1] Surgical resection is the preferred local treatment and consists of amputation or a limb-sparing procedure. RT has a limited role in osteosarcoma because of the radioresistant nature of the tumor. Currently, between 60% and 70% of patients with localized osteosarcoma are cured. Survival is superior in cases of less common low-grade tumors, such as parosteal osteosarcoma. Oftentimes, surgery alone is sufficient for these cases and is associated with survival rates of 80% to 90%.[11]

Chemotherapy

Chemotherapy is given prior to and after surgical resection. The concept of neoadjuvant chemotherapy arose in combination with evolving surgical techniques striving for limb-preserving surgeries and improved functional outcomes. The Pediatric Oncology Group (POG) study randomized 8,651 patients with nonmetastatic, high-grade osteosarcoma to neoadjuvant chemotherapy followed by surgery versus surgery followed by chemotherapy.[12] The rate of limb salvage was not statistically significant between the two groups (55% vs 50%).[12] There was also no difference in 5-year relapse-free survival between both groups (65% vs 61%).[12] This trial demonstrated equivalence for both approaches and established a benchmark for

comparison with future studies. Most centers favor neoadjuvant chemotherapy with the notion that the likelihood of limb-salvage surgery can be higher with improved functional outcomes. Prospective randomized studies have also demonstrated an improvement in overall survival outcomes for patients treated with adjuvant chemotherapy.[1,13-16] Currently, the initial chemotherapeutic agents used include methotrexate, doxorubicin, and cisplatin (MAP). Pathologic response (tumor necrosis >90%) is associated with improved survival in osteosarcoma.[13,17] Patients with minimal response to neoadjuvant chemotherapy can be considered for alternative adjuvant therapy regimens, but this approach has not been proven.[18] Recent prospective studies have evaluated the efficacy of additional systemic therapy agents to the MAP regimen. The international collaborative study EURAMOS-1 evaluated the addition of pegylated interferon α-2b following completion of MAP chemotherapy in good (>90% histologic response to preoperative chemotherapy) responders. High-dose ifosfamide and etoposide were added to MAP chemotherapy in poor (≤90% histologic response to preoperative chemotherapy) responders. The results did not demonstrate an improvement in outcomes with either approach.[18,19]

The ongoing Children's Oncology Group (COG) study AOST2032 is evaluating the feasibility and efficacy of adding the VEGFR2/MET inhibitor, cabozantinib, in a randomized manner to the MAP regimen. The rationale for this approach is to target signaling pathways known to be altered in osteosarcoma. There is clinical evidence of activity with cabozantinib in prospective studies for pediatric and adult patients with advanced osteosarcoma. Neoadjuvant MAP with or without cabozantinib is given for two cycles prior to primary tumor surgery and for four cycles following primary tumor surgery in the study. Patients randomized to the cabozantinib arm will receive six additional cycles of maintenance cabozantinib.

Local Therapy

Surgery is the mainstay of local treatment of osteosarcoma. Surgical resection is performed by either amputation or a limb-sparing approach and is associated with a less than 10% local failure rate. For extremity tumors, limb preservation is preferred and can be accomplished in most cases. Retrospective series have demonstrated equivalent outcomes between amputation and limb-sparing approaches as long as adequate margins are achieved.[20-22] Contraindications to limb-preserving surgery are pathologic fracture, nerve or vascular encasement, or large biopsy-related hematoma. Reconstructive options include endoprostheses, allografts, and rotationplasty. Axial tumors pose a greater challenge with surgical resection, though these primary tumor sites are less common. Pelvic tumors typically require a hemipelvectomy in order to obtain an en bloc resection. An internal hemipelvectomy (resection of hemipelvis

with preservation of the extremity) is associated with better functional outcomes compared to an external hemipelvectomy, which involves a hindquarter amputation in addition to resection of the hemipelvis. Spine tumors are often resected with vertebrectomy for an en bloc resection combined with mechanical stabilization.

Osteosarcoma is usually considered to be a radioresistant tumor. However, in vitro studies demonstrate osteosarcoma has a radiosensitivity similar to that of other human tumor cell lines.[23] In addition, case reports document that patients with inoperable or residual tumor treated with RT doses ranging between 50 and 70 Gy have remained in continuous remission.[24] As such, RT can be used for unresectable and metastatic cases as well as for cases with residual disease postresection. For example, postoperative RT can also be added for axial tumors when negative margins cannot be obtained, such as microscopic dural involvement with a spine tumor.

Research studies suggest RT is most effective with de novo cases, when the tumor burden is small, when patients have had a good response to chemotherapy, and/or with cases that have undergone a gross total or subtotal resection. Machak et al reported a 5-year progression-free survival rate of 56% in a series of patients with osteosarcoma who refused surgery but received systemic therapy and local RT.[25] Moreover, the survival rate was approximately 90% at 5 years in the subgroup of patients who responded to chemotherapy and received RT. Schwarz et al reported local control was higher for primary tumors at 40% versus 17% for recurrent tumors in a series of 100 patients with osteosarcoma treated with RT.[26] DeLaney et al[27] reported outcomes in a series of 41 patients with osteosarcoma treated with definitive RT or adjuvant RT for surgical cases with close or positive margins at the time of resection. The 5-year local control rate was 40% for patients treated with definitive RT, 78% for postoperative RT with a close surgical margin, and 78% for postoperative RT with positive surgical margins.[27] The median dose was 66 Gy, with doses as high as 80 Gy for gross disease. Over half of patients received some or all of their treatment with proton RT, given the unfavorable tumor locations often seen with definitive or postoperative RT cases as well as the high treatment doses needed. Carbon therapy may be beneficial for unresectable osteosarcoma. A retrospective review of 78 patients with unresectable axial osteosarcoma treated with carbon ion RT demonstrated local control was 62% at 5 years for all patients and 88% for tumors less than 500 mL. Patients received a median of 70.4 CGE (cobalt gray equivalent) in 16 fractions over 4 weeks.[28] Other series have also reported acceptable local control outcomes with particle therapy.[29,30]

To summarize, although surgery is the local treatment of choice, RT is an acceptable treatment option in inoperable tumors or patients refusing surgery. RT should also be administered in R1 and R2 resections. The current recommended doses per AOST2032 are 73.8 Gy for gross disease and 66.6 Gy for resected tumors

with microscopic residual disease, both in 1.8 Gy per fraction. RT is given after completion of consolidation chemotherapy.

Radiation Therapy Volumes and Techniques

Current COG recommendations are outlined in this section. The prechemotherapy/presurgery gross tumor volume (GTV) includes all T1 gadolinium-enhancing tumor, all T2 signal abnormalities, and all CT and MRI bone abnormalities. This volume is then expanded by 1.5 to 2 cm (up to 3 cm craniocaudally for extremities) to create the prechemotherapy/presurgery clinical target volume (CTV). The prechemotherapy GTV and CTV can be modified for pushing, noninfiltrative borders. These volumes are treated to 50.4 Gy in 28 fractions. The postchemotherapy GTV includes the residual soft tissue mass after induction chemotherapy and all bone abnormalities evident prior to chemotherapy. For tumors with microscopic residual disease following surgery, the postchemotherapy GTV is the postinduction chemotherapy target volumes determined on preoperative imaging. For partially resected tumors, the volume also includes the tumor bed. The postchemotherapy CTV is generated with a 1-cm expansion of the GTV, anatomically modified to barriers of tumor spread. These volumes are treated to 66.6 Gy in 37 fractions. The final boost volume is treated to 73.8 Gy for definitive RT cases or for gross residual disease postsurgery. This volume encompasses the residual tumor following induction chemotherapy without margin (ie, GTV = CTV). Planning target volumes are a 0.5 to 1-cm expansion on the CTVs, depending on tumor location and daily image-guidance available.

Circumferential irradiation of the extremities should be avoided to reduce the risk of lymphedema. In growing children, growth plates must be factored into RT planning. Growth plates should either be fully included in the high-dose RT field or not included at all (no portion of the growth plate receiving >30 Gy). A dose gradient through the epiphysis can result in asymmetric growth and lead to functional deficits. Similarly, vertebral bodies should be either fully included or spared (no portion of the vertebral body receives >20 Gy). Given the high dose needed for RT, advanced planning techniques, such as intensity-modulated RT or proton therapy, are recommended.

Metastatic Disease

The overall approach to metastatic disease with osteosarcoma is surgical resection and multiagent chemotherapy. The overall prognosis depends on the location and number of metastases, response to chemotherapy, and whether complete surgical resection of all tumors is possible.[31,32] Patients with metastasis only in the lung or a limited number of metastases who can undergo complete surgical resection are

associated with slightly improved outcomes. The 3-year survival rate in this population is approximately 50%, compared with 20% to 30% for more advanced disease. The currently open COG study AOST2031 is a randomized trial comparing open versus thoracoscopic management of pulmonary metastases. The primary aim of the trial is to determine if open surgical resection is superior to thoracoscopic resection for thoracic event-free survival in patients with resectable oligometastatic pulmonary osteosarcoma.

The use of whole-lung RT in the setting of metastatic disease or as prophylaxis for metastatic disease is controversial. Randomized trials from the European Organization for Research and Treatment of Cancer demonstrated prophylactic whole-lung RT with or without chemotherapy did not result in a statistically significant difference in outcomes.[33] As such, whole-lung RT is currently not recommended for patients with osteosarcoma.[34] The currently open COG study AOST2032 recommends definitive local therapy (surgery, conventionally fractionated RT, hypofractionated RT, or stereotactic body radiation therapy [SBRT]) to all metastatic sites documented at diagnosis. The study will evaluate the feasibility and efficacy of metastatic site–directed local therapy for osteosarcoma. The recommended RT dose for pulmonary metastatic sites is 50 Gy in 5 fractions for unresected pulmonary metastases measuring less than <5 cm, 60 Gy in 8 fractions for unresected pulmonary metastases measuring 5 cm or more but 8 cm or less, and 70 Gy in 10 fractions for unresected pulmonary metastases measuring greater than 8 cm.

RT may be utilized to treat osseous metastatic sites not amenable to surgical resection. The Cooperative Osteosarcoma Study Group demonstrated improved outcomes when metastases were surgically excised in a cohort that analyzed prognosis of relapsing patients. In addition, RT of inoperable sites was associated with improved survival compared to patients who received no local therapy.[35] AOST2032 recommends SBRT 50 Gy in 5 fractions for bone metastatic sites amenable to SBRT and 73.8 Gy in 41 fractions for metastatic sites not amenable to SBRT.

CHONDROSARCOMA

Epidemiology

Chondrosarcomas are a group of primary bone malignancies that produce chondroid (cartilaginous) matrix. They are completely devoid of osteoid, which is characteristic of osteosarcoma. Chondrosarcomas account for approximately 30% of primary bone tumors.[36] Chondrosarcomas can occur at any age but most commonly occur in middle-aged and older adults.[37]

Pathogenesis and Risk Factors

Chondrosarcomas can occur sporadically or with malignant transformation of benign cartilaginous lesions, including enchondromas or osteochondromas. Enchondromas develop in the bone marrow cavity. Enchondromatosis, or Ollier disease, is a condition characterized by the presence of multiple enchondromas causing a deformity. Malignant transformation of solitary enchondromas is extremely rare, but the risk is as high as 30% with enchondromatosis.[38,39] Osteochondromas are cartilage-capped bony projections arising on the external surface of bone. They contain marrow cavities that are continuous with the underlying bone. Most osteochondromas are located on long bones, especially around the knee. Multiple osteochondromas are associated with hereditary multiple exostoses. Malignant transformation occurs in 5% of patients with either solitary or multiple osteochondromas.[38,40]

Conventional chondrosarcomas account for about 90% of cases.[41] Conventional chondrosarcoma is further subdivided into central, peripheral, and periosteal. Central chondrosarcoma is the most common type, accounting for 75% of all chondrosarcoma cases. Forty percent of cases may arise from underlying enchondromas. The proximal femur, proximal humerus, and pelvis are commonly involved. Peripheral chondrosarcomas arise from a preexisting osteochondroma. The long bones, pelvis, and shoulder girdle are most commonly affected. Periosteal chondrosarcomas arise from the surface of bone, are rare, and usually affect young adults in their 20s and 30s. These malignancies tend to have a better prognosis.[36] High-grade chondrosarcomas account for the remaining 10% of cases and include dedifferentiated, mesenchymal, myxoid, and clear cell chondrosarcoma.[41] Clinical behavior of chondrosarcoma is highly dependent on histologic grade.[42,43]

Clinical Presentation, Diagnostic Evaluation, and Staging

Patients often present with localized pain involving the affected bone. There may or may not be a palpable mass and associated soft tissue swelling. Plain radiographs, CT, and MRI are obtained to characterize the lesion and evaluate the full extent of disease. Pathologic confirmation of chondrosarcoma is obtained via biopsy aimed at the most aggressive portion seen on imaging. This approach avoids potential biopsy of an associated benign precursor lesion and also guides the optimal surgical approach if a high-grade component is present. CT of the chest should also be obtained to evaluate for metastatic disease. The risk of lung metastases is less than 10% for low-grade lesions and 30% to 70% for intermediate- and high-grade lesions.[44,45] Similar to osteosarcoma, both the MSTS and AJCC staging systems can be used to stage chondrosarcoma.

Treatment

The primary treatment for chondrosarcomas is surgical resection. Histologic grade and tumor location are key factors in determining surgical extent, associated morbidity, and need for adjuvant treatments. For low-grade tumors, surgical resection alone is sufficient to achieve a high rate of disease control. For low-grade central tumors, intralesional excision or curettage is the preferred method of resection. This can be combined with local adjuvant chemical treatment or cryotherapy. These approaches result in good local control rates and minimize the morbidity of more extensive surgical resection.[46-49] Larger tumors, tumors with intra-articular or soft tissue involvement, and axial or pelvic tumors have higher local recurrence rates with these more conservative treatments. As such, these tumors are best treated with wide excision.[50] For the less common intermediate- and high-grade tumors, wide en bloc excision is the optimal surgical approach.[43,51] RT is indicated for incompletely resected high-grade or locally recurrent tumors, as well as for tumors that are unresectable. Chondrosarcomas are believed to be more radiosensitive than chordomas and can be treated with high-dose RT only in the setting of a highly morbid surgery. If a tumor is incompletely resected, reresection is generally only recommended if a separation surgery between residual disease and critical organs at risk is needed to safely deliver high-dose RT. Chemotherapy is not very effective for chondrosarcoma, especially for conventional chondrosarcoma. There is no established adjuvant chemotherapy regimen. There is some suggestion that dedifferentiated and mesenchymal chondrosarcomas may potentially benefit from chemotherapy, but phase III randomized data are lacking in these rare tumors.[52-54]

Radiation Therapy

RT principles for chondrosarcoma are similar to that for osteosarcoma. Definitive RT is recommended for inoperable tumors or for patients refusing surgery. Adjuvant RT is indicated after incomplete resection of tumors at high risk for local recurrence. Goda et al reported outcomes in 60 patients with high-risk extracranial chondrosarcoma treated with surgery and RT. With a median follow-up of 75 months, the local control rates were 100%, 94%, and 42% for R0, R1, and R2 resected patients, respectively. Overall survival at 10 years was 86%.[55] Definitive RT has also been used for chondrosarcomas of the spine and skull base, where an R0 resection is difficult to achieve.[56,57] Similar to osteosarcoma, particle therapy is often advantageous in terms of permitting dose escalation while sparing adjacent critical normal tissues. Rosenberg et al reported on a series of 200 patients with skull-base tumors treated to a median dose of 72 Gy CGE with a combination of photon and proton RT. They reported a 10-year local control rate of 98%.[58] Similar local control

rates have been reported by other institutions with particle therapy.[59-61] Table 95.2 summarizes the results of select particle therapy studies for bone sarcomas involving the pelvis. RT doses, volumes, and planning approaches are similar to that of osteosarcoma.

TABLE 95.2 SELECT PARTICLE THERAPY STUDIES FOR PELVIC BONE SARCOMAS

Series	Histology	Pelvic Patients/Total Patients	Modality	Median Dose (GyRBE)	Local Control	Survival	Toxicities
Aibe et al[84]	Chondrosarcoma	33/33	Proton	70.4	89.6% @ 3 y	92.7% @ 3 y	Grade 3: dermatitis (1), ileus (1), sacral fracture (2)
DeLaney et al[85]	Chondrosarcoma	52/67	Proton	78.6	75.1% @ 5 y	83.5% @ 5 y	Sacral fracture (15), sacral neuropathy (5), proctitis (4), fibrosis (1), infection (1)
Imai et al[86]	Chondrosarcoma	188/188	Carbon	70.4	77.2% @ 5 y	81.1% @ 5 y	Grade 3 nerve toxicity (6)Grade 4 skin toxicity (2)
Bostel et al[87]	Chordoma	68/68	Carbon	66	53% @ 5 y	74% @ 5 y	Grade 3 toxicity, 21% (sacral fracture; nerve, intestinal, and skin damage)
Bhatt et al[88]	Osteosarcoma	6/44	Proton	70.2	57% @ 5 y	68% @ 5 y	Grade 3: neuropathy, fracture, bowel dysfunction, chronic pain
Snider et al[89]	Chondrosarcoma	5/33	Proton	68.4	58% @ 5 y	68% @ 5 y	Grade 3: 3% acute, 9% late

Series	Histology	Pelvic Patients/Total Patients	Modality	Median Dose (GyRBE)	Local Control	Survival	Toxicities
Imai et al[90]	Chondrosarcoma	38/75	Carbon	70.4	53% @ 5 y	53% @ 5 y	Grade 3: fracture (5), skin (3)
Mohamad et al[30]	Osteosarcoma	24/26	Carbon	70.4	62.9% @ 5 y	41.7% @ 5 y	Grade 3: fracture (1), nerve (2), skin (1)

CHORDOMA

Epidemiology

Chordomas are slow-growing, locally aggressive neoplasms that arise from embryonic remnants of the notochord. They account for 1% to 4% of primary bone tumors. The median age at presentation is 60 years, but skull-base tumors typically present in the third or fourth decade of life.

Pathogenesis and Risk Factors

During normal embryologic development, the notochord regresses. Notochord remnants, however, can be found along the tract anywhere from the skull base to the sacrum, with the largest foci of remnants located at the cranial and caudal ends. This pattern corresponds with the anatomic distribution of chordomas. Approximately half of chordoma cases arise in the sacrococcygeal region and one-third of cases at the skull base, usually the clivus. The remainder of cases involve the cervical, thoracic, and lumbar spine.[62]

Chordomas are histologically classified as conventional/classic, chondroid, and dedifferentiated. Most cases are conventional chordomas. Chondroid chordoma accounts for 5% to 15% of cases and is typically associated with a superior prognosis. Dedifferentiated chordoma accounts for less than 5% of cases and is more aggressive, faster growing, and more likely to metastasize.[63] Brachyury, a transcription factor required for notochord development during embryogenesis, is often used as a diagnostic marker for chordoma.[64] Molecular characterization of chordomas is evolving. Zenonos et al demonstrated homozygous 9p21 deletions and 1p36 deletions are independent prognostic factors in clival chordoma and likely correlated with progression-free survival after local therapy.[65] This suggests that a continued molecular characterization of these tumors may help guide management.

Clinical Presentation, Diagnostic Evaluation, and Staging

Patients with chordoma often present with pain of the affected area that may be long-standing in nature. Associated neurologic symptoms are frequent. Skull-base tumors can present with cranial nerve deficits, especially cranial nerve 3 or 6 palsies. Sacral tumors can present with bowel or bladder dysfunction secondary to sacral nerve root involvement. Sensory motor deficits are also seen.

Diagnostic evaluation includes CT and MRI to characterize the extent of the primary tumor and involvement of adjacent neurological structures (Figure 95.2). Biopsy is needed to confirm the pathologic diagnosis. Metastases can occur in 10% to 40% of patients.[66-69] Metastatic spread typically occurs late in the disease course and can involve lung, bone, liver, lymph nodes, or soft tissues. Similar to the primary site, metastatic sites tend to be slow growing.

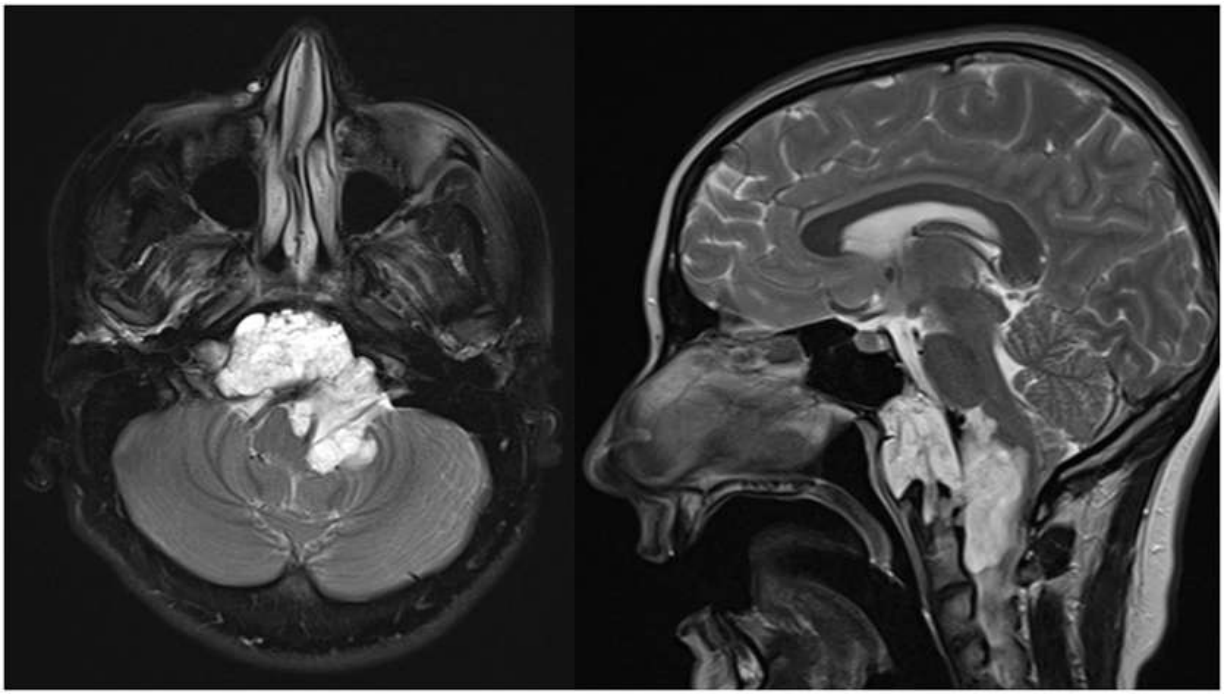

FIGURE 95.2 Magnetic resonance imaging demonstrating a skull-base chordoma. Given the compression of the brainstem and spinal cord, the patient underwent a maximum safe resection followed by postoperative radiation therapy.

Treatment

Given the locally aggressive nature of chordoma, aggressive upfront local therapy is needed for cure. The standard of care is surgery with an en bloc resection if possible. This approach is associated with local control in 70% to 80% of patients.[70] En bloc resection, however, is challenging for most tumors, given the proximity to critical adjacent tissues. Less than half of sacral tumors and even fewer skull-base tumors are amenable to complete resection. In addition, aggressive surgery can result in

significant morbidity. This includes cranial nerve deficits for skull-base tumors and bowel and bladder dysfunction when S2 or S3 nerves are injured or sacrificed for sacral tumors.[71-73] As such, surgery in combination with RT is often used.[74] An analysis of the Surveillance, Epidemiology, and End Results program of the National Cancer Institute consisting of 345 patients treated from 1974 to 2011 showed that 5-year overall survival of 78% to 80% was achieved with treatment using surgery with or without RT.[75] Chordomas, however, are considered to be quite "radioresistant," with studies demonstrating the volume of disease as well as proximity to critical structures associated with suboptimal oncologic outcomes.[76-78] As such, repeat surgery is often considered in the event of an incomplete resection prior to administering RT in order to optimize oncologic outcomes. Chemotherapy does not play a role in the definitive management of patients with chordoma, given the absence of active and effective agents.

Radiation Therapy

RT principles for chordoma are similar to that for osteosarcoma and chondrosarcoma. Definitive RT is recommended for inoperable tumors or for patients refusing surgery. Adjuvant RT is indicated after incomplete resection of tumors at high risk for local recurrence. Chordomas are considered "radioresistant" tumors, and as such, doses greater than 70 Gy are required. Given the high RT doses and adjacent critical normal tissues, advanced planning techniques, such as particle therapy, are favored. Local control rates ranging from 54% to 90% have been reported with definitive RT.[57,59,79,80] Figure 95.3 illustrates treatment volumes and proton treatment plan for a sacral chordoma treated with definitive RT. When treating pelvic bone tumors to high doses, it is essential to be mindful of dose constraints for the cauda equina, sacral plexus, bowel, and rectum. DeLaney et al provide guidance on dose constraints for these organs at risk based on treatment-associated toxicities with their phase II study of high-dose radiation for bone sarcomas.[80] Skull-base tumors also require particular attention to organs at risk during treatment planning, including brainstem, optic structures, spinal cord, cochlea, and temporal lobes.[81-83] In general, we accept higher dose constraints (and consequently higher risk of toxicities) when treating bone sarcomas compared to nonradioresistant tumors to enhance local control. Careful review of dose distribution to the treatment volumes and organs at risk during treatment plan review is essential to ensure the optimal therapeutic ratio has been achieved. Oftentimes, target volumes are undercovered near critical organs at risk. In addition, it is important to consent patients appropriately to the higher risk of toxicities.

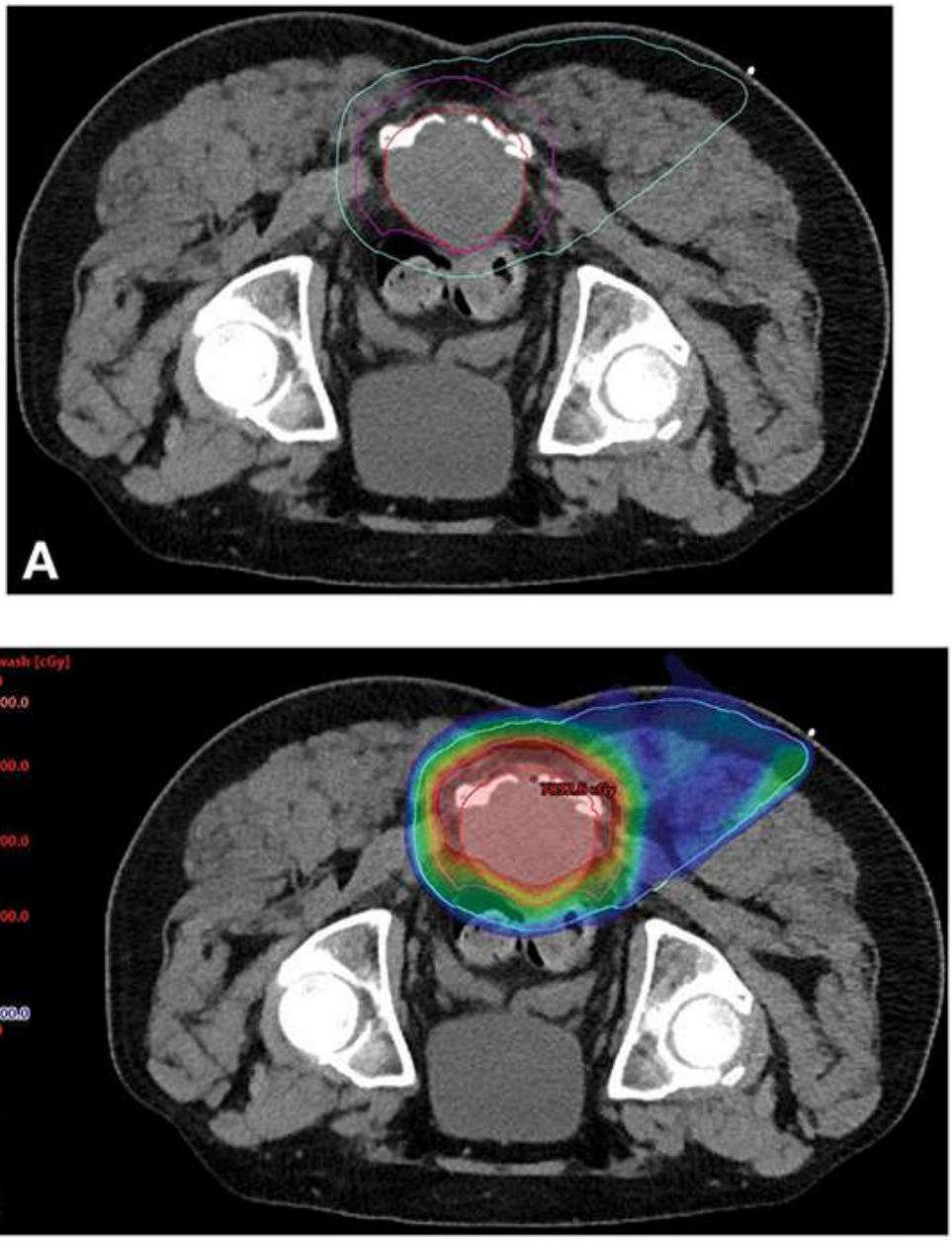

FIGURE 95.3 A. Treatment volumes for a patient with sacral chordoma. The patient was simulated and treated in the prone position. Gross tumor volume (GTV) is represented in red. The high-dose clinical target volume (CTV) is represented in magenta. The low-dose CTV includes the biopsy tract and is represented in cyan. B. Proton treatment plan. The GTV was treated to 73.5 Gy in 30 fractions (equivalent to 83 Gy in 1.8 Gy per fraction), the high-dose CTV was treated to 69 Gy in 30 fractions (equivalent to 77.4 in 1.8 Gy per fraction), and the low-dose CTV was treated to 54 Gy in 30 fractions.

TREATMENT-ASSOCIATED TOXICITIES

Given the aggressive approaches needed for the treatment of bone sarcomas, it is important to be mindful of the treatment-associated toxicities. For tumors treated with surgery, late complications are largely related to surgical interventions. Limb

functional outcomes are associated with the location of the primary tumor along with the type of resection and reconstruction performed. Radiation-associated complications depend on tumor location as well. For pelvic tumors, treatment-associated toxicities can include joint fibrosis, decreased range of motion, bone fracture, limb-length discrepancy, weakness, neuropathy, fertility issues, sexual dysfunction, bowel toxicity, rectal bleeding, lymphedema, osteonecrosis, and risk of secondary malignancy. For extremity tumors, radiation can be associated with joint fibrosis, decreased range of motion, bone fracture, limb-length discrepancy, weakness, gait changes, lymphedema, osteonecrosis, and risk of secondary malignancy. For spine tumors, key treatment-associated toxicities include spinal cord damage, bone fracture, osteonecrosis, and risk of secondary malignancy. For skull-base tumors, there is a risk of blindness, cranial nerve dysfunction, pituitary dysfunction, stroke, brain necrosis, osteonecrosis, hearing loss, and secondary malignancy. Physical rehabilitative therapy should be considered for all cases to help minimize late functional impairment.

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CHAPTER 96

Ewing Sarcoma

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EPIDEMIOLOGY

Ewing sarcoma family of tumor (EWS) accounts for about 2% of cancers in children and is the second most common primary tumor of the bone in childhood. EWS primarily affects adolescents/young adults, with a median age of 15 years and rarely occurring in children younger than 8 years or adults older than 25 years.[1] The incidence is estimated to be 3 in 1,000,000 per year in White population[2] but is rarer in African and Asian people.[3]

Overall survival (OS) has improved mainly in localized disease since a few decades, thanks to a multimodal treatment approach. Five-year OS in localized EWS increased from approximately 45% to 70% after the 1990s.[4] Five-year OS in metastatic disease has also increased but remains quite poor (30%-40%),[3] especially for patients with metastasis beyond isolated lung lesions.

PATHOLOGY AND CYTOGENETICS

Light microscopy shows a tumor of small, round blue cells that lack markers for lymphoma, neuroblastoma, or rhabdomyosarcoma. Cytogenetics has shown that EWSs of the bone and soft tissue are undifferentiated members of a tumor family that shares a common neuroectodermal precursor cell, arrested at different stages of differentiation.[5] Cells are periodic acid-Schiff positive, vimentin positive, and often cytokeratin positive. Approximately 95% of EWSs have a translocation between the *EWS* gene on chromosome 22 and the *FLI1* gene on chromosome 11 (t[11;22][q24;q12]) or the *ERG* gene on chromosome 21 (t[21;22][q22;q12]).[6] The translocations are present only in tumor cells and occur in bone and soft tissue EWS, primitive neuroectodermal tumors of the

bone and soft tissue, peripheral primitive neuroectodermal tumors, Askin tumors, some esthesioneuroblastomas in children, and some central nervous system (CNS) tumors.[7]

The t(11;22) juxtaposes the *EWS* gene with the *FLI* gene (*EWS/FLI* gene), which seems to act as an aberrant transcription factor, resulting in tumorigenesis.[8] The t(11;22) breakpoint location has been reported as prognostic factor in some publications,[9] but both recent reports from EURO-EWING 99 (EE99) study and Children's Oncology Group (COG) study have not confirmed this impact.[10,11]

Since 2020, the World Health Organization (WHO) has recognized three other small round cell tumors previously classified as EWS but now distinctly recognized as separate, both pathologically and molecularly. This includes translocations involving the *EWS* gene and non-ETS genes (*NFATc2*, *SMARCA5*, *PATZ1*, *SP3*), CIC-rearranged sarcomas (eg, CIC-DUX4 fusion), and BCOR-rearranged sarcomas (eg, BCOR-CCNB3 fusion). These translocations are associated with different mechanisms of oncogenesis and have different clinical impacts and, therefore, are now classified as undifferentiated small round cell sarcomas of bone and soft tissues along with EWS by WHO.[12-14]

CLINICAL PRESENTATION

Locoregional pain is the most common presenting symptom in patients with EWS, reported in about 90% of cases. Pain can be intermittent and variable in intensity, often not completely disappearing during the night.[15] As the majority of patients with EWS are in their second decades of life and physically active, pain is often mistaken for "bone growth" or injuries. Tumor growth eventually leads to a visible or palpable swelling of the affected site. The tumor bulk, however, may be indiscernible for a long time in patients with pelvic, chest wall, or femoral tumors. Significant limitation of movement has been described in 25% of presentations, and a pathologic fracture is reported in 10% to 15% of cases.[15]

As EWS may arise in virtually any bone and in soft tissue, additional symptoms, depending on the affected site, may vary considerably. Patients with chest wall or pelvic primaries may experience significant complaints only at a very late stage. Neurologic symptoms or signs occur in 15% of

children, either as spinal cord compression or as peripheral nerve compression.

Unlike other bone sarcomas, constitutional symptoms such as fever, weight loss, and fatigue can be noted at presentation, mostly in advanced and/or metastatic stages, affecting about one-third of patients.[16] The duration of symptoms prior to the definitive diagnosis can be weeks to months, with a median of 3 to 9 months.[17]

DIAGNOSTIC WORKUP: LOCAL AND SYSTEMIC

Local Workup

The initial imaging investigation when an osseous lesion is suspected is usually a simple radiograph. EWSs are defined as a destructive lesion of the bone. Tumor-related osteolysis, detachments of the periosteum from the bone (Codman triangle), and spiculae of calcification in soft tissue tumor masses suggest the diagnosis of a malignant bone tumor. Diaphyseal location suggests an EWS, as compared with the metaphyseal location more common in osteosarcoma.[18]

Local computed tomography (CT) and magnetic resonance imaging (MRI) are needed, and complementary CT outlines better the bone extent of central EWS. The most precise definition of the local extent of disease, including tissue extension, the intramedullary portion, and the relation of the lesion to adjacent blood vessels and nerves, is provided by MRI[19] (Figure 96.1).

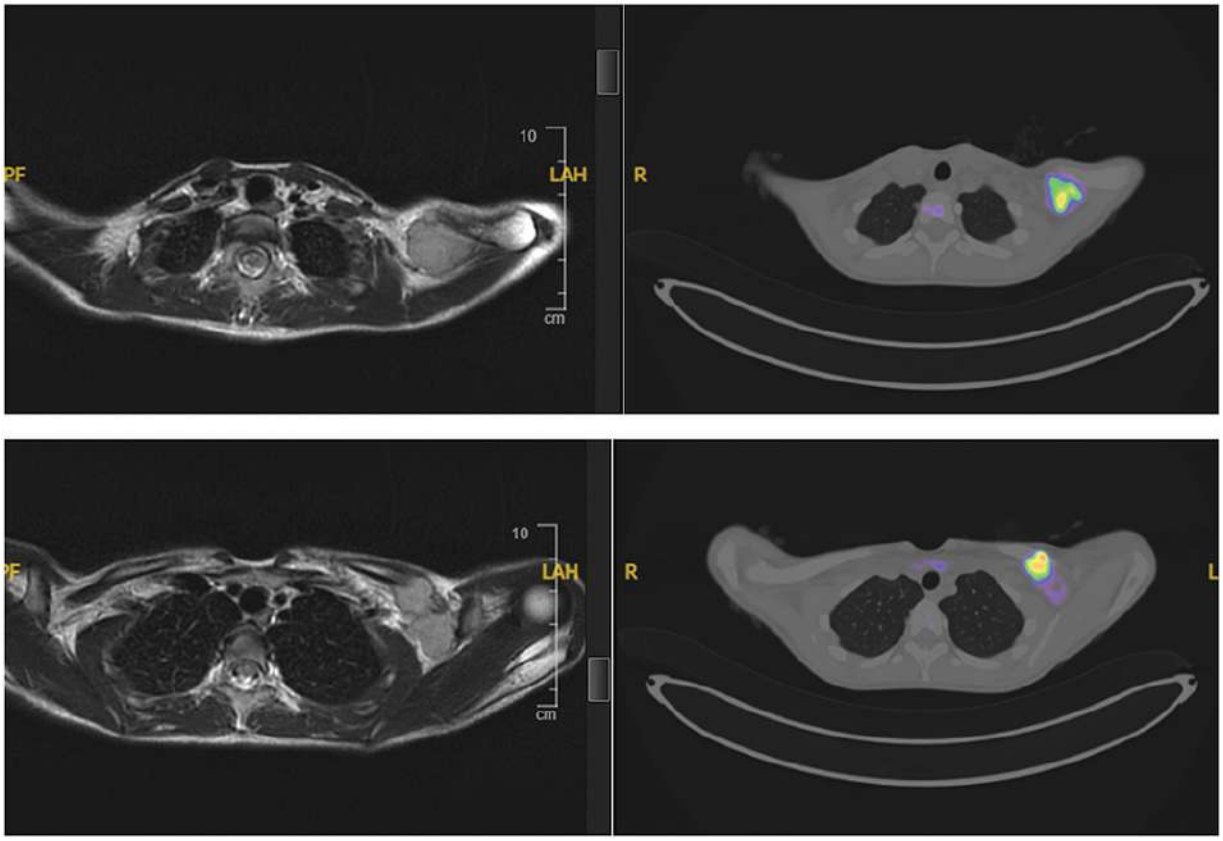

FIGURE 96.1 Example of a localized Ewing sarcoma from the left clavicle in a 14-year-old girl. Magnetic resonance images are shown on the left and fluorodeoxyglucose positron emission tomography/computed tomography on the right.

Systemic Workup

Nonspecific signs of tumor or inflammation may be noted, such as an elevated erythrocyte sedimentation rate, moderate anemia, or leukocytosis. The pretreatment serum lactate dehydrogenase rate may be a prognostic factor.[20]

Currently, fluorodeoxyglucose positron emission tomography (FDG-PET/CT) is recommended in the systemic staging; it is sensitive and accurate in staging EWS compared with non-PET imaging.[21] FDG-PET/CT has been shown to detect more bone metastases than traditional bone scans do, both at diagnosis and at recurrence.[22]

The gold standard diagnosis for bone marrow (BM) involvement has long been made by cytologic and pathologic analysis through BM aspiration and biopsy. Several recent studies suggest that invasive BM biopsy should no longer be systematically performed for the staging at the

diagnosis of EWS if FDG-PET/CT shows no sign of distant BM involvement.[23,24]

CT remains a superior diagnostic method for detecting lung metastasis as lesions less than 8 mm are not always detectable using plain film or FDG-PET/CT imaging.[21,22] Whole-body MRI has also been reported to be superior to bone scan in detecting bone metastases in patients with EWS, particularly diffusion-weighted images or short-time inversion recovery images.[19] It also involves substantially less radiation than at FDG-PET/CT. The whole-body MRI availability is still a limiting point, and the question whether whole-body MRI or FDG-PET/CT has a better diagnosis ability still has to be confirmed on large studies.[25]

The potential utility of integrated PET/MRI for the primary diagnostic workup in patients with EWS has also to be confirmed in the future, but preliminary results are positive.[26]

Results of Workup

EWS can occur in any part of the body but most commonly involves the pelvis and proximal long bones. EWS can be extraosseous (20%) and can arise in numerous organs (kidney, liver, brain, etc) and are more frequent in adults.[27,28]

Approximately 53% of EWS have a primary site in an extremity, and 47% have central primaries.[2,29] EWS can be localized everywhere, but the most frequent sites are the pelvis (23%-25%), femur (16%-18%), below the knee (10%-16%), ribs (12%-13%), spine (8%), and humerus (5%).[30] On the whole, the proportion of metastatic patients at diagnosis is about 25% in large prospective studies. Metastasis is more frequent in pelvic primaries as compared with tumors of the extremities or ribs.[2,31,32]

Metastatic extent can vary from solitary lesion in a lung or a bone to systemic disease with extensive affection of multiple organs, including BM. Most frequent metastatic sites are the lungs (40%) and bones (40%), with less common disease involving the BM, lymph nodes, soft tissue, and visceral sites. Rarely, the CNS is involved.[2,20]

PROGNOSTIC FEATURES

Metastatic status at diagnosis is the strongest prognostic factor across different treatment strategies, whereas the 5-year progression-free survival (PFS) remains less than 30% for metastatic patients.[31] However, patients with only lung metastasis have a better clinical outcome than those with metastases in other sites. Three-year PFS is about 50% to 55% in recent studies.[4]

The most important risk factors in both localized disease and metastatic disease are reported in Table 96.1.

TABLE 96.1 POOR-RISK FACTORS IN EWING SARCOMAS AT DIAGNOSIS

Poor-Risk Factors in Localized Disease	Poor-Risk Factors in Metastatic Disease
Axial tumor (pelvis ++, spine) vs extremities[2,29,33,99,125-131]	Metastasis other than in lung[4,31,132]
Large volume > 200 mL or size > 8 cm	Large volume > 200 mL or size > 8 cm[31]
Poor histologic response[133-136]	
Age > 14 y[2,29,33,127-130,133,137]	Age > 14 y[2,29,31,33,127-130,133,137]
Inflammatory disease at diagnosis (fever, LDH, CRP, anemia)[138,139]	Inflammatory disease at diagnosis (fever, LDH, CRP, anemia)[138-140]
	>5 extralung metastases and/or bone marrow involvement and/or uncommon sites[31,61]

CRP, C-reactive protein; LDH, lactate dehydrogenase.

RESULTS OF THERAPY

Results of Clinical Trials for Patients With Localized Disease at Diagnosis

Local controls (LCs) and survival rates are shown in Table 96.2 for patients treated with different local treatment strategies in recent cooperative group trials that reported appropriate data. LC after surgery (or surgery and radiotherapy [RT]) is over 90% in recent trials. Historically, LC after definitive RT was reported close to 75%, but nonoperated tumors were usually much bigger, in poorer sites (pelvis especially) than tumors treated by surgery. In recent international studies using "modern" RT and local strategy optimized to the situation (site, tumor volume, and expected local

treatment sequelae), the LC after surgery, definitive radiation, and combined modality local therapy is the same (over 90%), regardless of approach.[33,34]

TABLE 96.2 SURVIVAL AND LOCAL CONTROL BY METHOD OF TREATMENT TO PRIMARY LESIONS IN MAJOR COOPERATIVE GROUP TRIALS (LOCALIZED LESIONS ONLY)

Trial	Years Open	Local Control (%)			5-Y Survival (%)			
		RT	Surgery	Both	RT	Surgery	Both	Overall
CCG/POG Intergroup II[a,141]	1995-1998	75	75	89.5	52	41.7	47.4	49
Scandinavian and Italian group phase III[50]	1999-2006	–	–	–	–	–	–	75
INT 0054[142]	1995-1998	91.8	94.9	98	–	–	–	78
Pilot COG[143]	2008-2015	–	–	–	–	–	–	88
INT 0091 POG 8850 VACA-IE[30] INT 0091 POG 8850 VACA	1988-1992	–	–	–	–	–	–	72 61
EURO-EWING 99-R1[39]	2000-2010	–	–	–	–	–	–	3 y: 86
EURO-EWING 99-R2 HDCT vs VAI[52]	2000 2015							3 y: 69 3 y: 57
COG AEWS0031[84] VDC-IE/2 wk vs VDC-IE/3 wk	2001-2005	–	–	–	–	–	–	3 y: 83 3 y: 77
COG AEWS1031[33]	2010 2016	92.2	95	93.5	82[b]	79[b]	74[b]	5 y: 87
EURO-EWING 2012[49] VIDE vs VDC-IE	2014 2019							3 y: 61[c] 3 y: 67[c]

CCG/POG, Children's Cancer Group and Pediatric Oncology Group; COG, Children's Oncology Group; EFS, event-free survival; ET, Ewing tumor; HDCT: high-dose chemotherapy; RT, radiotherapy; CNR, Italian Cooperative Study of Ewing Sarcoma; VACA-IE, vincristine, actinomycin D, cyclophosphamide, and doxorubicin and ifosfamide-etoposide; VDC-IE, vincristine, doxorubicin, cyclophosphamide, and ifosfamide-etoposide;

VTC, vincristine, topotecan, cyclophosphamide; VIDE, vincristine, ifosfamide, doxorubicin, and etoposide.

[a]Pelvic primaries only.

[b]5-year EFS on 594 patients.

[c]Both localized and metastatic patients.

Results After Definitive Radiotherapy

The question whether RT dose escalation in nonoperated patients can increase the LC as well as the survival is pending and was suggested in four studies.[34-37] Ongoing studies, such as the International Clinical Research Programme to Improve Outcomes in Newly Diagnosed Ewing Sarcoma–Trial 1 (INTER-EWING-1, EudraCT number: 2021-005061-41) and the iEuroEwing trial (EudraCT number 2019-004153-93), investigate the role of a boost delivered on the postinduction chemotherapy residual volume, in a randomized manner. The COG is likewise investigating the indications for, and benefits of, dose escalation for large tumors. This will be paired with necessary data collection on toxicity and functional consequence.

EWS of the pelvis is historically associated with a worse prognosis when compared to nonpelvic tumors. Patients with pelvic tumors often present with larger tumor volumes compared with extremity sites and more often have metastatic disease at diagnosis. The 5-year-PFS is between 41% and 66%[38] as compared with 5-year PFS over 75% in patients with nonpelvic localized tumors using recent strategies.[39] However, in the last COG AEWS1031 trial using optimized local and systemic strategies, results were better with a 5-year event-free survival (EFS) of 75%.[33] In this study, the pelvis location was not a risk factor for inferior LC or EFS. Encouraging results with 3-year PFS of 83% have also been obtained after high-dose proton therapy (+/− surgery) in a retrospective study on selected patients with pelvic localized EWS.[37] These results support the question of dose-escalation strategies addressed in current trials in patients with pelvic EWS to optimize the outcome.

Impact of Postoperative Radiotherapy

Different factors have traditionally served as indicators for postoperative RT, that is, histopathology, response to induction chemotherapy, site of primary tumor, quality and size of the resection margins, and whether the

prechemotherapy tumor volume extension and/or the originally contaminated tissue were completely removed. In general, tumors located in the pelvis and paraspinal tumors are very likely to benefit from RT.[40-42] The indication for RT and its benefits should be carefully balanced in very young children, as well as in the situations where radiosensitivity genetic predisposition is present.

Jereb et al[43] found that the local recurrence rate after conservative surgery was high without RT. Ozaki et al[44] also reported a slight advantage for adding postoperative RT for patients with inadequate margins. Dunst and Schuck[45] reported that patients with a wide resection alone but a poor histologic response had a local failure rate of 12%, in comparison with 6% for similar patients who received postoperative RT.

In addition, taking into account competing events, a recent analysis of the EE99 trial showed that adjuvant RT improves LC for all the patients, even after good response to induction chemotherapy.[40] With a median follow-up of 6 years, 8-year local relapse incidence was 12%. A statistically significant reduction of local relapse was shown in patients treated with surgery and RT compared to surgery alone ($P = .02$). The benefit of RT was particularly marked for tumors larger than 200 mL at diagnosis and less than 100% necrosis. A nonsignificant trend for benefit associated with postoperative RT for PFS, EFS, and OS was reported.

As a consequence, in the EE2012 protocol, postoperative RT was discussed for all patients, except for those who have had a wide local excision, defined as negative resection margins of at least 1 mm, and a good histologic response (>90% necrosis) to preoperative chemotherapy and with removal of all tissues originally involved by the prechemotherapy tumor volume. Results are pending.

Prospective studies with quality control on radiation are, however, highly required to assess the balance between adjuvant RT benefit and risks, especially in patients with complete R0 resection and good histologic response.

Within the INTER-EWING-1 trial, as well as in the iEuroEwing trial, randomizations are proposed in order to attain evidence as to the optimal dose in postoperative setting. A dose escalation of 9 Gy with prescriptions ranging between 45 versus 54 Gy (or 50.4 vs 59.4 Gy, depending on the anticipated risk for local recurrence) is used in the iEuroEwing trial.

The INTER-EWING-1 trial will randomize 45 versus 54 Gy in postoperative situations. In the trial, a prospective quality control is mandatory for all the randomized patients to ensure the homogeneity of the treatment (delineation and planning treatment).

In the COG trials, a dose of 50.4 Gy (1.8 Gy once a day) is given if postoperative RT is indicated, mainly in case of microscopic positive margins. The most recent COG study (AEWS1031) did not consider histologic response as an indication for radiation, but it did inform the size of the RT treatment margins.[33]

Doses in the range of 30 to 44.8 Gy at 1.8 Gy a day have also been reported to be effective for subclinical disease.[44,46]

In a review of 153 patients treated with surgery followed by postoperative RT from Cooperative Ewing Sarcoma Study (CESS) 86 and EICESS 92, Schuck et al showed that the interval between surgery and RT did not influence survival, although there was a slight trend for improved LC in patients receiving RT less than 90 days postoperatively.[47]

Systemic therapy does also influence the rate of local relapse and ultimately survival. The first Intergroup Ewing's Sarcoma Study reported that the addition of doxorubicin improved LC.[48] The first Children's Cancer Group/Pediatric Oncology Group (CCG/POG) intergroup study showed an improvement in survival in the intensified arm for patients with localized disease and large primary or pelvic tumors. The improvement with the more intensive regimen resulted from a decrease in the rate of local relapse; the rate of distant metastases was similar in both arms.[30]

Impact of the Systemic Treatment

The dose intensity of the induction chemotherapy is also important. In a randomized trial for patients younger than 50 years with localized EWS (*n* = 568), Womer et al. reported that vincristine, actinomycin D, cyclophosphamide, and doxorubicin and ifosfamide-etoposide (VAC-IE) given on an every-2-week schedule was found to be more effective (median 5-year EFS 73%) than VAC-IE given on an every-3-week schedule (median 5-year EFS 65%), with no increase in toxicity.[39]

The compressed vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide (VDC-IE) scheme was confirmed as the best induction

treatment (as compared with the vincristine, ifosfamide, doxorubicin, and etoposide [VIDE] induction) in the international randomized European trial for both patients with localized disease and metastatic patients. The 3-year PFS was over 80% in patients treated with surgery with or without RT compared with patients with good histologic response.[49]

The time interval between initiation of chemotherapy and start of RT has also been reported to influence survival (LC was not evaluated), with early RT preferable to late RT.[45]

In addition, few institutions have used a single transplant to treat high-risk patients with localized disease (large primary tumors or tumors of the pelvis/trunk), while both LC and survival are poorer in these patients. Two cooperative groups used high-dose chemotherapy busulfan-melphalan (HDCT-BuMel) as consolidation treatment for high-risk localized EWS, defined by poor histologic response to induction chemotherapy.[50,51] They have reported encouraging results (5-year EFS between 49% and 72% in high-risk patients), which were the basis of EE99-R2 trial for high-risk localized disease. Between 2000 and 2013, from 477 patients classified as "high-risk patients," 216 were randomized to vincristine, actinomycin D, and ifosfamide (VAI) or HDCT-BuMel. Some patients requiring RT to the primary site were excluded to avoid excess organ toxicity from interaction between axial RT (high dose to digestive tract, spinal cord, or lung) and busulfan. In an intention-to-treat analysis, the risk of an event was significantly decreased by HDCT-BuMel compared to VAI: 3-year EFS was 67% using BuMel versus 53% after VAI (P = .023). OS was also significantly better after HDCT-BuMel.[52]

As a consequence, HDCT-BuMel can be considered an option for adjuvant therapy in poor responder patients with high-risk localized disease, instead of conventional adjuvant chemotherapy.

Results of Clinical Trials for Patients With Metastatic Disease at Diagnosis

Patients With Lung Metastasis Only

The 5-year EFS for patients with lung metastases ranges is about 50% to 55% in the most recent studies.[53-55]

The phase III EURO-EWING 2012 (EE2012) trial established the VDC-IE chemotherapy to be the new standard induction therapy for EWS, including patients with lung metastasis at diagnosis.[49]

Whole-lung irradiation (WLI) has been shown to improve survival in the CESS 81, CESS 86, and EICESS 92 trials for patients with lung metastases as the only site of metastatic disease at diagnosis.[55],[56] The CESS 81 and CESS 86 studies also showed increasing survival rates with an increasing RT dose to the lung fields, particularly with a dose of greater than 18 Gy (corrected for lung transmission) at either 1.5 Gy once a day or 1.25 Gy twice a day.

The Italian Sarcoma Group and the Scandinavian Sarcoma Group designed a joint prospective study for 102 patients with metastatic EWS (lungs, pleura, or single bone).[53] Intensive combination chemotherapy, surgery, and/or RT and consolidation treatment with HCDT-BuMel and WLI were planned. Only 71 patients of 102 received the whole therapeutic program, mostly because of disease progression. With a median follow-up of 62 months, 5-year OS and PFS for the whole group were 52% and 43%, respectively. However, for the patients with only lung metastases who completed the therapeutic program, 5-year OS and PFS were 66% and 53%, respectively.[53]

The EE99-R2Pulm and subsequent EWING 2008 trials thus evaluated in a randomized way the question of the best consolidation treatment after initial chemotherapy with VIDE, comparing WLI with conventional VAI chemotherapy versus HDCT-BuMel in patient with lung metastasis. Two hundred and eighty seven patients were randomized: 143 received VAI-RT and 144 received HDCT. The 3 and 8-year EFS of the randomly assigned patients was 56.6% and 52.9%, respectively, after HDCT versus 50.3% and 43.1% for the conventional arm patients (P = .16). No benefit of BuMel compared with VAI plus WLI in terms of OS was observed. Significantly, more patients in HDCT experienced severe acute toxicities than in the standard arm. The authors concluded that in EWS with lung metastases, there is no clear benefit associated with HDCT-BuMel compared to conventional chemotherapy combined with WLI.[54]

The question whether local treatment (surgery or stereotactic body radiotherapy [SBRT]) in addition to WLI should be done on residual lung metastasis after induction chemotherapy remains under debate, but several

nonrandomized studies encourage to develop and test this strategy.[57,58] As an example, in a study from MD Anderson, pulmonary metastasectomy with or without WLI significantly improved survival, compared to those not having metastasectomy (80% vs 0% at 5 years). Despite a clear selection bias in this study, it shows potential for improved survival among patients who undergo metastasectomy.[58]

Results in Patients With Metastasis Other Than Lung

Patients with de novo bone metastasis fare poorly compared to patients presenting with pulmonary-only metastasis.[59,60] Moreover, solitary bone metastasis has superior outcomes compared to those with more than one bony metastasis.[31]

In patients with disseminated disease, results are better with adequate treatment of the primary as well as all the metastases whenever feasible. EE99 showed that the 3-year EFS was better (47%) for patients receiving both surgery and radiation to the primary lesion versus either surgery alone (25%) or RT alone (23%). Without local therapy, the EFS was 13%.[59]

Paulino et al showed similar results with local therapy to all sites of metastatic disease in a pediatric series, with disease control rate at 3 years of 94% versus 32% when no local treatment was performed on mets.[61] Similarly, an American retrospective study on adults showed a survival benefit after local treatment of all the extrapulmonary metastasis when feasible.[62]

These analyses are subject to selection bias and need to be confirmed with addition data. If pursued, it is acceptable to delay the RT to metastatic sites until close to the end of chemotherapy if a significant amount of BM would be treated.

Further intensification of this strategy through adding ganitumab (a monoclonal antibody against the insulin-like growth factor-1 receptor) was tested in a phase III trial of pediatric patients with newly diagnosed metastatic EWS (AEWS1221 COG protocol). In the experimental arm, ganitumab was added to the standard VDC-IE treatment. No difference in EFS or OS between the two arms was shown.[63] Despite the increased toxicities in the ganitumab arm, the study has shown the feasibility of using targeted therapy in addition to intensive chemotherapy in this clinical

situation. Other targeted therapy may prove more effective in the future. For example, a phase Ib study using the combination of regorafenib with conventional chemotherapy for the treatment of newly diagnosed patients with multimetastatic EWS was recently opened to assess the feasibility of the combination (NCT05830084). If the safety is established, regorafenib will be randomized in addition to VDC-IE in the INTER-EWING-1 trial for patients with other than lung metastatic EWS.

Many institutions have investigated end intensification with HDCT and stem cell rescue with and without total-body irradiation (TBI), for patients with metastatic disease. TBI has been largely abandoned as part of the conditioning regimen. Many different regimens have been used, mostly a combination of melphalan with etoposide, busulfan, carboplatin, and thiotepa.[64]

Table 96.3 presents results of the most recent studies with HDCT in metastatic situations.

TABLE 96.3 SURVIVAL IN METASTATIC EWING SARCOMA: MOST RECENT STUDIES

Study	Induction Chemotherapy	Local Treatment +/− WLI	HDCT or Adjuvant Chemotherapy	PFS (%)	OS (%)
Loschi et al[144] *n* = 18 PDMES 2002-2013	VIDE × 6 HDCT Thiotepa	Surgery +/− RT or RT on primary tumor	BuMel	3 y: 11	3 y: 22
Paulussen et al[60] *n* = 171 1981-1997	VAIA × 6-10	Surgery +/− RT or RT on primary tumor WLI 15-18 Gy (*n* = 57)	HDCT (with or without TBI)	4 y: 27	4 y: 32
Ladenstein et al[31] *n* = 281 1999-2005	VIDE × 6 + VAI × 1	Surgery +/− RT or RT on primary tumor	HDCT-(BuMel or others)	3 y: 27	3 y: 34
Oberlin et al[68] *n* = 97 1991-1999	VA × 5 + IE × 2		HDCT-BuMel	5 y: 38	5 y: 37

Study	Induction Chemotherapy	Local Treatment +/− WLI	HDCT or Adjuvant Chemotherapy	PFS (%)	OS (%)
Grier et al[30] *n* = 120 1988-1992	VACA × 17 VACA + IE × 17	Surgery +/− RT or RT on primary tumor	VIDE, VACA VACA + IE	5 y: 22 5 y: 22	5 y: 35 5 y: 34
Koch et al[72] 2009-2018	VIDE × 6	Surgery +/− RT or RT on primary tumor	8 VAC vs 8 VAC + Treo-Mel	3-y 19 vs 3-y 21	

BuMel, busulfan/melphalan; HDCT, high-dose chemotherapy; IE, ifosfamide-etoposide; N, number of patients; OS, overall survival; PFS, progression-free survival; TBI, total-body irradiation; VAC, vincristine, dactinomycin, and cyclophosphamide; VACA, vincristine, actinomycin D, cyclophosphamide, doxorubicin; VAI, vincristine, dactinomycin, ifosfamide; VAIA, vincristine, dactinomycin, ifosfamide, and doxorubicin; VDC-IE, vincristine, doxorubicin, cyclophosphamide, ifosfamide-etoposide; VIDE, vincristine, ifosfamide, doxorubicin, etoposide; WLI, whole-lung irradiation.

Patients with metastatic disease treated on EICESS studies between 1990 and 1995 had a superior 4-year EFS when HDCT was added to the end of therapy, but CCG-7951 showed no improvement with this approach over a matched cohort from other Ewing tumor studies for patients with bone or BM metastases.[60,65] Some institutional pilot studies without strict selection criteria show promising, but not conclusive results.[66-71] The EURO-EWING 99-R3 study evaluated the efficacy of induction chemotherapy (six courses of VIDE), local treatment (surgery and/or RT), and HDCT in 281 patients with EWS with primary disseminated disease. After a median follow-up of 3.8 years, the 3-year EFS for the entire study cohort was disappointing (27%), but the EFS rates were 57% and 25% for patients with complete and partial response after HDCT, respectively. The comparison of the outcome of patients with and without HDCT was not possible because of the bias introduced in the nontransplant group: 82% of patients without HDCT died after a median time of 1 year.[31]

More recently, 109 patients with metastasis other than lung were randomized in the Ewing 2008 trial, between adjuvant HDCT (treosulfan/melphalan) versus conventional adjuvant chemotherapy. No

difference in survival was shown, and results were still disappointing with 3-year EFS about 20%.[72]

The benefit of HDCT in patients with nonpulmonary metastatic disease remains under debate in Europe. It is generally avoided in North America. The question whether patients with highly chemosensitive disease benefit from HDCT will be hopefully answered by the French trial CombinaiR3 (NCT03011528). These results are forthcoming.

GENERAL MANAGEMENT

Biopsy

The biopsy should be performed at the same institution where the treatment will be performed, ideally by a sarcoma specialist. Tissue has to be collected for microscopy as well as cytogenetics. Image-guided core-needle biopsy has been reported as safe and efficient and is now the first-line method for establishing a definitive diagnosis in EWS.[73] As often as possible, extraosseous soft tissue alone is sampled.

Induction Chemotherapy

Effective local *and* systemic therapy is necessary for the cure of EWS. Induction chemotherapy is preferred to starting the systemic therapy and local therapy concomitantly, in both localized and metastatic EWS. There are several advantages to this approach: Administering the chemotherapy first allows an evaluation of the effectiveness of the regimen. Response rates to induction chemotherapy are high, with radiologic complete response and partial response rates of up to 90% reported.[66,74,75] Good histologic response (>90% have been reported in >60% in recent studies).[49] Dose-intensive chemotherapy with VDC-IE has been reported as the most effective, less toxic, and shorter in duration and is now the standard of induction chemotherapy in all stages of newly diagnosed EWS.[49] Induction chemotherapy also allows local treatment to adapt to the postchemotherapy tumor volume. For example, shrinkage of the soft tissue mass may help the surgeon or radiation oncologist decrease the volume of the local therapy. Shrinkage of the soft tissue mass may also allow the surgeon to achieve better margins.

Primary Tumor Local Treatment

Retrospective studies demonstrate better LC and EFS after complete surgery (+/− followed by RT) as compared with RT alone.[61,76,77] However, patients treated with exclusive RT often come from older protocols and generally have a lower prognosis: larger tumors, more pejorative sites, and poor response to chemotherapy.[77-79] Modern prospective cooperative group studies tend to demonstrate that LC, EFS, and OS are similar following definitive surgery, definitive radiation, or surgery plus radiation.[33,80] Thus, the decision regarding local therapy is based on a multidisciplinary discussion of expected side effects and toxicity of each approach.

North American Versus European Strategies

In North America, the use of surgery (vs RT or surgery + RT) as part of local therapy is guided by the results of COG study AEWS1031, which had a cumulative incidence of local failure of 6%, the lowest reported to date in prospective trials of EWS.[33,80] There were no statistically significant difference in outcomes by LC modality, tumor site, or patient age. Thus, determination of RT versus surgery versus surgery and RT is based on a multidisciplinary discussion of side effects and toxicity of local therapy for each given situation. Generally speaking, surgery alone is often the choice for extremity tumors while definitive radiation is utilized for axial tumors. If surgical margins are unexpectedly positive following an attempt at definitive surgery, postoperative radiation is indicated. The role of preoperative radiation remains undefined in North America but may have a role in selected cases of borderline resectability because the preoperative radiation dose is less than the definitive or postoperative radiation dose.

In Europe, the strategy has gradually moved from exclusive RT to surgery with or without RT. Surgery of the primary tumor is nowadays considered as the standard of treatment, providing a complete resection is expected. In case of either incomplete surgical resection or inacceptable surgical toxicity is expected, definitive RT is the alternative, representing 23% to 30% of the EWS local treatment in the recent trials.[49,66,81] Intralesional resection or debulking procedures followed by RT do not offer increased LC or PFS compared with definitive RT and should be avoided.[77]

After surgery, different factors have traditionally served as indicators for postoperative RT, that is, histopathology, response to induction chemotherapy, site of primary tumor, quality and size of the resection margins, and whether the prechemotherapy tumor volume extension and/or the originally contaminated tissue were completely removed. In general, tumors located in the pelvis and paraspinal tumors are very likely to benefit from RT.[40-42] The indication for RT and its benefits should be carefully balanced in very young children, as well as in the situations where radiosensitivity genetic predisposition is present.

The indications, technical details, and value of preoperative RT for EWS are still being defined. Good results have been reported with preoperative RT for patients with a poor response (<50% reduction of the evaluable soft tissue mass) after two cycles of chemotherapy.[44,82,83] Situations where preoperative radiation can be considered include the following:

- RT is thought to be definitely required.
- Technical advantages to delivering RT prior to surgery (eg, dosimetry, limiting dose to organs at risk)
- Higher risk of microscopic positive margins for resectable tumors in selected sites (eg, pelvis, chest wall)
- The information on the histologic response after induction chemotherapy is not relevant for the further management of the patient.

Consolidation Chemotherapy

Consolidation chemotherapy is indicated in all patients. Consolidation using vincristine, cyclophosphamide, etoposide, and ifosfamide is the standard of care.

For poor-risk localized disease (histologic response >10% viable tumor in resected tumors, or tumor volume >200 mL for nonoperated tumors), EE99 and Ewing 2008 trials conducted randomized studies comparing high-dose therapy using BuMel against standard chemotherapy (VAI, seven courses), demonstrating that BuMel significantly reduces events and deaths compared to standard chemotherapy arm. A 10% difference in both EFS and OS (60% and 64%, respectively) in the BuMel arm was reported. The

BuMel strategy can thus be discussed in poor responding patients with localized disease.[52]

Local Therapy for Metastases

Patients with only lung metastasis have a better outcome than patients with metastasis in other sites.[56] The standard of treatment for patients with only lung metastasis is conventional chemotherapy followed by WLI, while no clear benefit from HDCT (BuMel) was reported. Three-year EFS is around 55% and 50% to 53% at 8 years.[54] Surgical resection or radiation boost using SBRT before WLI can be discussed in case of postchemotherapy-limited residual lung metastasis, as suggested in the current European trials INTER-EWING-1 (EudraCT number: 2021-005061-41) and iEuroEwing trial (EudraCT number: 2019-004153-93).

Local therapy to nonlung metastatic sites is believed to improve survival outcome and is, therefore, recommended whenever feasible.[60,61] Three-year EFS after local therapy of both primary and metastatic sites was reported to be 39% compared to 17% when local therapy is only given to either the primary or the metastatic sites.[60] Local therapy of metastatic sites can be given together with the local therapy of primary site or delayed until the end of the adjuvant chemotherapy, particularly if it involves irradiation of a large volume of the patient's BM.

The option of locally treating all metastatic sites is not feasible in all cases, and the criteria with which to choose patients for this approach (eg, number, site, size) are not clearly defined.

RADIOTHERAPY TECHNIQUES

All patients should be discussed in a multidisciplinary team meeting to decide on the indication for RT of the primary and metastatic sites.

Radiation of the Primary Tumor

Table 96.4 shows the RT dose for primary tumor.

TABLE 96.4 RECOMMENDATIONS FOR RADIATION THERAPY ON PRIMARY TUMOR VOLUMES AND DOSES

Clinical Situation	Total Dose (Gy)	Dose Per Fraction (Gy)[a]	Volume
Definitive radiotherapy	45-50.4	1.8-2	Original bone and soft tissue mass + margin
	5.4-14.4[b] (total dose 54-59.4 to GTV)	1.8-2	Original bone and *residual* soft tissue mass + margin
Postoperative radiotherapy (especially after marginal resection and/or poor histologic response at surgery)	45-54	1.8-2	Original bone and soft tissue mass plus surgical scars and drains (if no increased toxicity deemed) + margins
Preoperative radiotherapy	45-50.4	1.8-2	Original bone and soft tissue mass + margins

CTV, clinical target volume; GTV, gross target volume.

[a]Equivalent doses in the context of the use of simultaneous integrated boost are allowed.

[b]Depending on initial dose.

Exclusive Radiotherapy

Patients not undergoing surgery for the primary tumor or those in whom macroscopic disease is present after resection (R2) will receive definitive RT.

For gross disease, standard treatment is a total dose of 55.8 at 1.8 Gy/day. Prospective studies suggest that doses ranging from 59.4 to 70.2 Gy may enhance LC for large tumors.[34-36]

A dose of 45 to 54 Gy is usually recommended to the initial prechemotherapy target for the initial tumor site (PTVp_Pre), including the initial bone and soft tissue involvement. A boost to a total dose greater than 54 Gy should be directed to the initial bone and the postchemotherapy soft tissue residue (PTVp_Post). Unresectable EWS of the spine and paraspinal region may be treated to 50.4 Gy without compromising LC. LC at doses less than 40 Gy is significantly worse, even for small lesions[84] (Figures 96.2 and 96.3).

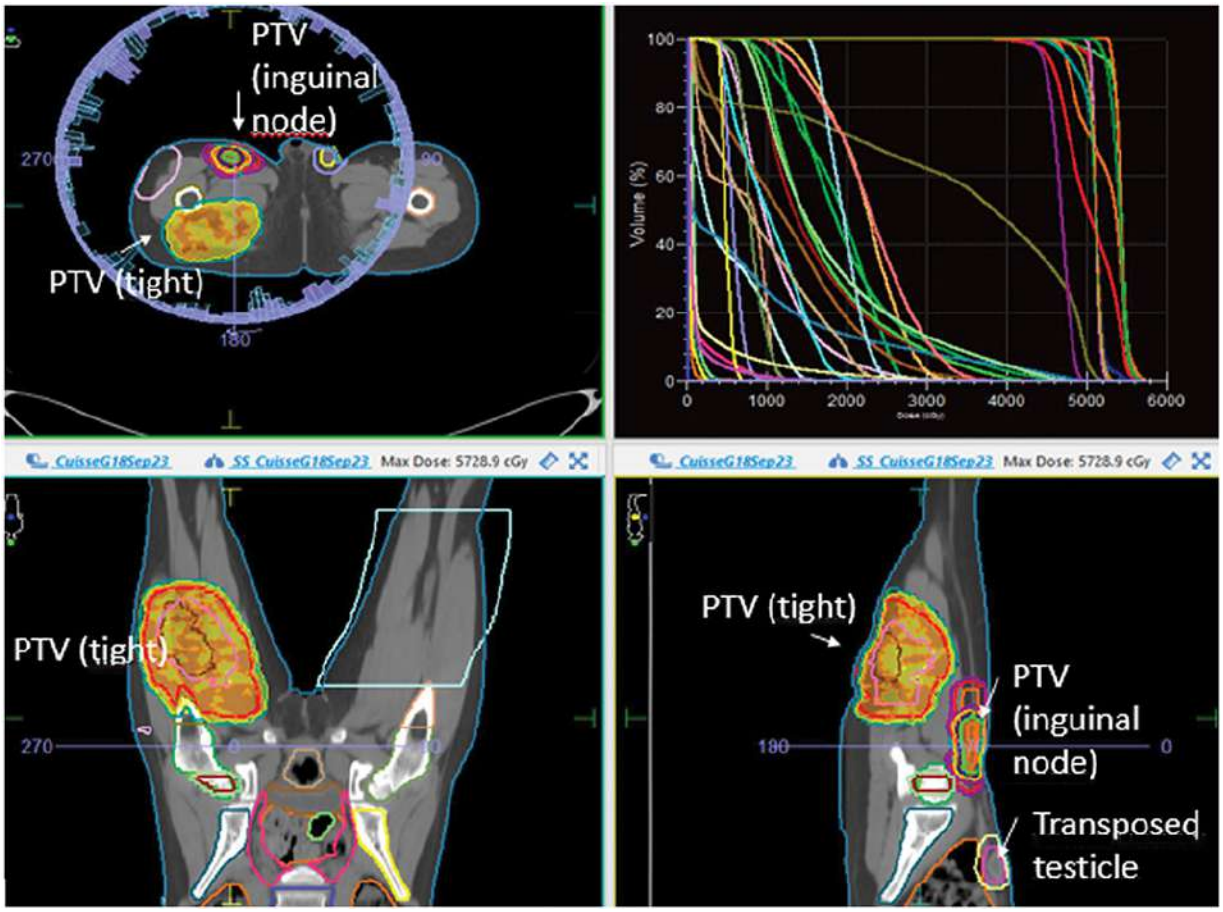

FIGURE 96.2 A 5-year-old boy was treated using preoperative radiotherapy (photons) for Ewing sarcoma of the tight and ipsilateral inguinal proven node involvement. Both primary planning tumor volume (PTV_tight) and PTV_inguinal nodes are represented. Testicles were transposed before radiotherapy to avoid radiation late toxicity.

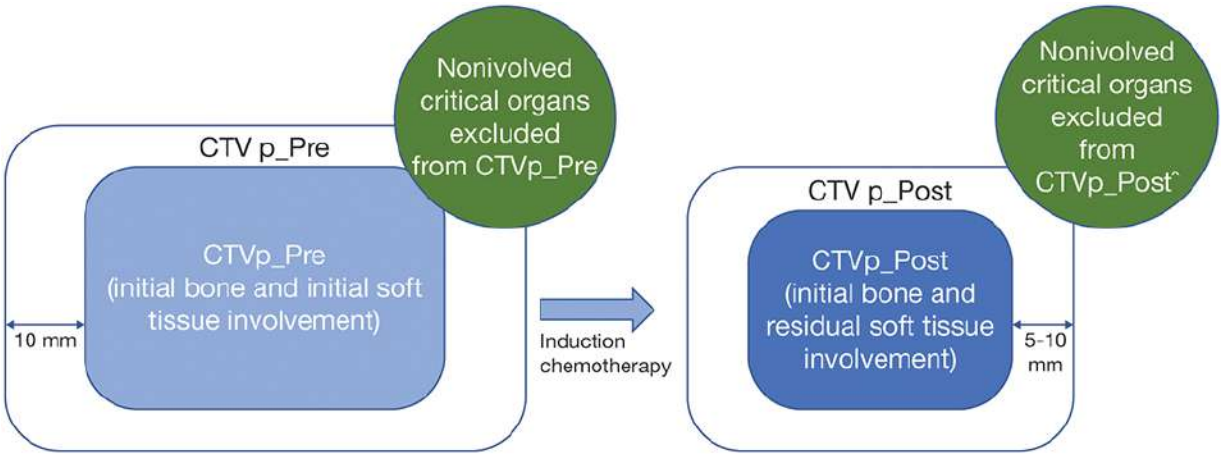

FIGURE 96.3 The concept of volume delineations. Gross tumor volume (GTVp_Pre) is defined as the visible tumor on imaging at its maximal extent (using computed tomography [CT], fluorodeoxyglucose positron emission tomography/CT, bone and magnetic resonance imaging scans, as available) prior to any chemotherapy or surgery. Clinical target volume (CTVp_Pre) should encompass any sites of potential microscopic extension of GTVp_Pre, or of contamination by GTVp_Pre. Margin to CTVp_Pre should be GTVp_Pre + 1 cm isotropic (except in limbs: proximal and distal margin of 15 mm), respecting unviolated anatomic margins to tumor spread. "Pushing borders" within body cavities are not included in the CTV.

Adjuvant Radiotherapy

A total dose between 45 versus 54 Gy depending on the anticipated risk for local recurrence is usually delivered (ie, INTER-EWING trial).

In the COG trials, a dose of 50.4 Gy (1.8 Gy once a day) is given if postoperative RT is indicated, mainly in case of microscopic positive margins. The most recent COG study (AEWS1031) did not consider histologic response as an indication for radiation, but it did inform the size of the RT treatment margins.[33]

Doses in the range of 30 to 44.8 Gy at 1.8 Gy a day have also been reported to be effective for subclinical disease.[44,46]

Preoperative Radiotherapy

The total dose for preoperative RT is usually ranging between 50.4 and 54 Gy (1.80/fr) in a single phase. If there are concerns about organ tolerance or wound healing, a reduction of dose to 36 to 45 Gy can be considered.

Radiation on Metastatic Sites

Local Therapy of Lung Metastasis

WLI is given independent of metastatic response to induction chemotherapy. The recommended WLI total dose is usually 12 to 15 Gy in young children or 15 to 18 Gy in older patients (>14 years). This is usually delivered at 1.5 Gy per fraction daily.

Residual metastasis after chemotherapy is often considered for metastasectomy or extra boost using stereotactic technique, particularly if the number of metastasis is less than 3.

SBRT can be used instead of surgery to treat inoperable or nonresectable residual lung mets after chemotherapy. Doses for SBRT boost are typically 30 to 35 Gy in five fractions, depending on the number and sites of lung metastasis.

Poor responders to induction chemotherapy whose lung metastasis cannot be removed probably still benefit from WLI.[85]

Local Therapy of Bone Metastasis

A dose of around 50 Gy to the metastatic bone site can lead to 91% LC rates at 3 years, as seen in an MSKCC study.[86] The same study concluded that this benefit declines with a number of metastasis more than five. SBRT to metastatic sites less than 5 cm is effective, well tolerated, with the advantage of a short treatment time. A retrospective study of 14 pediatric patients with 27 EWS or osteosarcoma lesions were treated with 40 Gy using SBRT in five fractions reported a 2-year LC rate of 85% and a low toxicity rate.[87] A Swedish study in patients with adult sarcoma reported also excellent results after SBRT in 46 patients with 136 metastatic sarcoma lesions. Overall response rate was 88% with a median follow-up of 21 months. The LC rate for the 14 EWS cases was 75%.[88] Several ongoing trials recommend the use of SBRT on EWS metastasis.[89] The St Jude EWS trial (NCT01946529) recommends RT to metastatic sites at week 19 and allows to use SBRT with 30 Gy in six fractions. The COG AEWS1221 (NCT02306161) recommended local therapy for metastasis after the completion of consolidation chemotherapy and allows for the use of SBRT with 40 Gy in five fractions.

Both INTER-EWING-1 trial and iEuroEwing trial also recommend a systematic treatment of extrapulmonary mets providing a limited number of

lesions, including SBRT when feasible.

Radiotherapy After High-Dose Chemotherapy With Busulfan

Because of the high risk of toxicity of the association of RT and HDCT including busulfan (BuMel), both indications should be early discussed in multidisciplinary meetings.

In case of patients receiving BuMel before RT, the total dose can be limited (generally at 45 Gy), whereas the dose constraints to major critical organs have to be strictly respected to avoid severe toxicity. Using conventional fractions, RT doses will not exceed 30 Gy to the spinal cord[90] and 45 Gy on a small volume of the gastrointestinal tract, including the bowel, colon, rectum, stomach, and duodenum.[91] Large irradiated lung volumes should be also avoided. Hemithoracic lung or whole-lung RT is not recommended in first-line treatment after HDCT-BuMel, because of the risk of respiratory toxicity. Spacer devices can be discussed in the pelvis to displace the bowel away from treatment volumes.

Modern external beam radiation techniques, such as intensity-modulated radiotherapy (IMRT) techniques, volumetric modulated arc therapy (VMAT), or proton therapy should be used to spare critical organs as much as possible in this situation. For patients who receive HDCT-BuMel, RT should begin later; especially when organs such as spinal cord, lung, or bowel need to be exposed to RT. In general, RT should commence at least 10 weeks after BuMel-HDCT delivery.[53,92,93]

Fractionation

Standard fractionation delivers 1.8 to 2 Gy per fraction, 5 days a week.

Twice-a-day RT has been used in several trials. To treat EWS, radiation oncologists at the University of Florida used 1.2 Gy twice a day to a total dose of 50.4, 55.2, or 60 Gy, depending on the tumor response to induction chemotherapy, and showed that late effects could be decreased while maintaining good LC, even for large primary tumors.[94,95] In CESS 86, doses of 1.6 Gy twice a day to a total of 60 Gy were given, although not in a continuous course. The Italian SE-91 trial also used 1.6 Gy twice a day to a total of 60.8 Gy, but in a continuous course. The CESS 86 trial showed no advantage for the accelerated hyperfractionated approach, but the early

results of SE-91 were promising with regard to LC.[45,96] Both of the latter regimens would be theoretically expected to increase late effects, but this remains unproven.

Radiation Volumes

The POG 8346 trial showed, in a randomized manner, that the traditional approach of irradiating the entire marrow cavity was not necessary.[76] Although "tailored" fields are the standard of care today, attention to the requisite volume is critical to obtaining maximal control rates; geographic miss has been a frequent source of failure in cooperative group studies.[76,97] Three-dimensional treatment planning, an appropriate immobilization, and cone-beam CT guidance are essential.

Gross tumor volume (GTV1/GTVp_Pre) is defined as the visible tumor on imaging at its maximal extent (using CT, FDG-PET/CT, bone and MRI scans, as available) prior to any chemotherapy or surgery.

Clinical target volume (CTV1, or CTVp_Pre) should encompass any sites of potential microscopic extension of GTV1/GTVp_Pre, or of contamination by GTV. The inclusion of metallic prostheses, drain sites, and surgical scars (if feasible and no extra toxicity is anticipated) are discussed, but the benefit is unclear. Margin to CTV should be GTV + 1 cm isotropic, respecting unviolated anatomic margins to tumor spread. "Pushing borders" within body cavities should not be included in the CTV.

The concept of internal target volume should be implemented when applicable (mobile targets), especially in thoracic or abdominal sites.

Planning target volume (PTV1, or PTVp_Pre) is defined from CTV1/CTVp_Pre, with a margin to account for day-to-day setup variation. This will vary according to tumor location in the body and the used immobilization and is specific to individual institutions. PTV1/PTVp_Pre will be typically CTV1 + 0.3 to 1.0 cm.

The boost is delivered to the residual tumor volume (GTV2/GTVp_Post) at the time of RT plus a 0.5 to 1 cm margin to CTV2/CTVp_Post. Any initial bone or BM abnormalities in the primary bone should be included in GTV2/GTVp_Post. CTV2/CTVp_Post does not need to include scars and drain sites. It should take into account anatomic barriers to tumor spread,

such as facial boundaries and bone. PTV2/PTVp_Post will be typically CTV + 0.3 to 1.0 cm.

The use of MRI is essential to identify the tumor extent, at the diagnosis and after the induction chemotherapy. PET-CT may be helpful for planning.

Extremity tumors may require sparing of at least a 1- to 1.5-cm strip of normal tissue to prevent lymphedema (corridor), aiming for a V20 50% or more constraint (D1.0 mL ≤ 50 Gy). An effort ought to be made in order to spare adjacent growth plates and joints without compromising adequate target coverage.[36]

With the high doses of cyclophosphamide or ifosfamide given in consolidation chemotherapy regimens for Ewing tumor, it is important to minimize the dose to the bladder.

Radiotherapy in Special Sites

Ribs

Rib lesions should be treated conformally with a minimum of lung and heart in the high-dose field. However, rib primary tumors often present with pleural effusion.

In the EICESS 92 trial, the 7-year rate of EFS was 63% with hemithorax RT versus 46% without.[47] Claren et al. recently confirmed that pleural effusion at diagnosis and incomplete resection were both independent risk factors for survival in localized tumor of the rib. Eighty-two French patients, with median age 13.6 years and median follow-up 8.4 years, were treated in EE99 protocol and reviewed. Five-year PFS was 69%. Pleural effusion and incomplete surgical resection (R1 or R2) were independent prognostic factors for PFS and OS. In case of initial pleural effusion, documented or not, OS was 27% without RT versus 68% after RT (P = .01).[98]

For very small pleural effusions that are considered to be reactive, ipsilateral hemithorax RT may be judged not to be necessary, particularly in young children. Doses between 12 to 15 (young children) and 15 to 18 Gy (older patients) are typically prescribed.

Spine

The type of local treatment remains a pending question in this site.

The standard dose for vertebral lesions used to be 45 Gy due to the limited dose to spinal cord and led historically to limited LC. As an example, a French cohort of 75 patients with localized spinal EWS treated between 1988 and 2009 was reported. Local treatment modality was surgery and RT in 50 patients, RT alone in 19, and surgery alone in 6. After a 7-year median follow-up, the 5-year LC, EFS, and OS were 78.0%, 57.0%, and 70.0% (95% confidence interval: 59.1-81.0), respectively.[99]

Modern techniques including VMAT or protons allow nowadays to increase the dose of RT beyond 50.4 Gy for tumors adjacent to the spinal cord to standard doses of 55.8 Gy for tumors below the spinal cord. In a large retrospective American study including 59 patients with spine EWS, the 5-year estimate of local failure by tumor site was low (3.6%), with no statistically significant difference in local failure incidence by local treatment modality (surgery vs definitive RT).[100]

HDCT-BuMel should not be given before RT for spinal lesions if RT dose to the spinal cord is expected to be over 30 Gy, because of the increased risk of myelitis.[90]

Treatment for Relapses

The prognosis after relapse is poor, with a 5-year OS of only 13% for patients recurring after treatment in the CESS 81, CESS 86, and EICESS 92 studies. Patients experiencing either late (>2 years) or isolated localized relapses fared slightly better, with 5-year OS 24% to 30%.[2,101] Relapse occurring only at the local site warrants aggressive attempts at salvage.[101] To date, no standard treatment has been defined in relapsed EWS. Patients who relapse only with lung metastases can sometimes be salvaged with additional chemotherapy and WLI. Resecting or treating the lung metastases with SBRT, if there are fewer than four lesions, may also be beneficial.[102] Patients with late pulmonary relapses fare better than those with early relapses.[103] Patients who relapse with bone metastases, however, are essentially incurable with current available therapies.

Positive response rates have been reported in retrospective studies and/or phase II trials, including topotecan-cyclophosphamide,[104] temozolomide-irinotecan,[105] gemcitabine-docetaxel,[106] and high-dose ifosfamide.[107] A recent international multiarm “rEEcur” trial (multistage randomized phase

II/phase III trial) comparing these four regimens was recently reported. High-dose ifosfamide was shown to be more effective in prolonging survival than the other combinations.[108]

The role of HDCT for relapsed tumors, which respond to second-line therapy, is controversial, with both positive and negative results reported in retrospective and single-arm studies.[92] A systematic review on the role of HDCT for children and young adults with relapsed EWS concluded that most studies using HDCT/autologous stem cell transplantation (aSCT) as consolidation regimen showed improved survival benefits compared to conventional chemotherapy.[109] Randomized controlled studies are highly needed to determine the true clinical benefit of HDCT followed by aSCT in patients with relapsed EW.

SEQUELAE OF TREATMENT

Treatment for EWS has been reported to have an actuarial complication rate of 70% at 35 years.[110] Paulino et al reported that 10 (53%) of 19 patients receiving RT alone, 4 (25%) of 16 receiving surgery alone, and 2 (40%) of 5 undergoing combined surgery and RT therapy had significant late effects.[111]

More recently, a retrospective chart review of 101 pediatric patients reported the most common complications were musculoskeletal abnormalities (50%) and cardiac toxicity (28%).[112] Neither study included loss of function related to planned surgical resection as a complication.

The most common skeletal complication of RT is abnormal growth and development of the irradiated tissues. RT can cause premature closure of active epiphyses, producing growth deficits and limb-length discrepancies. The degree of discrepancy depends on the RT dose, patient's age, and epiphysis radiated. Because 65% of leg growth is from the distal femoral (37%) and proximal tibial (28%) epiphyses, typical RT doses to the knee in boys younger than 14 years of age and girls younger than 12 years of age will usually cause a severe enough leg-length discrepancy to require intervention.[113] Deficits of 2 to 6 cm can usually be managed by a shoe lift; larger deficits require surgical treatment.

Approximately 15% of long bone lesions develop pathologic fractures at some time in their course, 5% at diagnosis, and 10% after RT, although

approximately one-third of the latter are caused by tumor recurrence or occasionally a secondary malignant neoplasm (SMN).[114] Whether the fracture is disease or treatment related, the most common site is the femur, particularly the proximal femur. RT-related fractures usually occur within 24 months after treatment but can be much later. Doses below 40 Gy using once-a-day doses of 1.8 to 2.0 Gy appear to have a very low risk, as does a hyperfractionated approach using 1.2 Gy twice a day from 50.4 to 55.2 Gy.[114,115] Extremity weakness, decreased range of motion secondary to fibrosis, pain in the extremity (particularly in the early morning), discoloration of the skin, and lymphedema can also occur after RT, even with careful planning and sparing of an adequate strip of tissue. Sarcomas, often osteosarcoma, are the most common second tumor, and the risk for increased dose therapy has been reported as 1% to 5% at 20 years.[112,116-118]

The Italian Sarcoma Group Experience followed 543 patients with EWS, treated between 1983 and 2006. Fifteen patients (2.8%) experienced secondary cancer. The cumulative 10- and 20-year incidence was 3.4% ± 0.9% and 4.7% ± 1.6%, respectively. The most common SMN in the EWS group was RT-induced osteosarcoma ($n = 6$).[119]

The British Childhood Cancer Survivor Study reported cause-specific mortality and risk of secondary neoplasms for 664 bone sarcoma survivors.[120] Beyond 25 years of follow-up, the risk of dying from all causes was comparable to the general population. In contrast, before 25 years, the risk was 12.7-fold than expected. Survivors were 4 times more likely to develop a secondary cancer than expected (bone and breast mainly), but the excess was restricted to 5 to 24 years postdiagnosis.

Retrospectively analyzed data from 4,518 patients with EWS treated in five consecutive trials from the CESS group were also reported.

The latency period between EWS and the secondary cancer was 8.4 years for solid tumor and 2.4 years for hematologic secondary malignancy ($P < .001$). The cumulative incidence of SMNs increased over time from 4% at 10 years to 14% at 30 years. An increased risk at radiation doses greater than 60 Gy was reported.[121]

The quality of life of 618 long-term survivors of EWS was reported by Ranft et al. Median observation time was 12.9 years from primary diagnosis. Survivors were less active than control subjects; however, the recommended level for an active lifestyle was achieved. This study

demonstrated that overall survivors of EWS were able to return to normal activity levels with minor limitations. Pelvic tumor location was the major inferior disease-specific prognostic factor as well as older age at diagnosis and female sex.[122] About 10% patients develop significant pulmonary dysfunction after WLI.[123,124]

FUTURE CONSIDERATIONS

Although the 5-year survival rate of patients with EWS appears to have improved since 1970, almost half of all patients diagnosed with Ewing tumor die of it within 10 years.[3] Outcomes for patients with metastatic disease other than lung and recurrent EWS especially remain poor with current strategies.[112]

Recent international trials have defined the better induction chemotherapy regimen for all the patients, but the limits of intensification have probably been reached with the presently available drugs.

For patients with localized disease receiving modern chemotherapy, more information is needed to estimate the probability of local progression. Traditional factors (eg, primary tumor site, modality of local therapy, patient age, histologic response) may no longer apply, and thus local disease risk stratification is a challenge. Accurate risk stratification is critical to identify which patients would benefit from treatment intensification (eg, radiation dose escalation) and de-escalation (radiation avoidance). Moreover, comparative data on toxicity and function following LC with radiation, surgery, or a combination thereof are largely absent. Within each group, subtypes of local therapy are unexplored: Outcomes based on specific surgical technique and radiation modality, such as IMRT and proton therapy, are important topics for future investigation. Future studies should prospectively collect these data to aid individualized decisions surrounding local therapy. The question whether treatments other than chemotherapy (ie, immunotherapy, targeted treatments) could be safe and efficient is crucial for high-risk patients (metastatic situations and recurrences); several trials will evaluate them in the next future (NCT05830084). The most promising targeted therapies are those acting on the microenvironment and are under research.[4] In addition, the question of maintenance treatment is also under debate and will be also randomized in two next trials (INTER-EWING 1

[EudraCT number 2021-005061-41], and iEuroEwing trial [EudraCT number 2019-004153-93]).

Future COG LC efforts are focused on risk stratification to help guide local therapy de-intensification and intensification. Future European LC efforts are also focused on practice homogenization and prospective quality control to improve local treatment data.

In patient with metastases at diagnosis, treating all metastases with RT or surgery appears to be promising for these high-risk patients. SBRT is promising, particularly in patients with oligometastatic disease. Feasibility and toxicity have to be prospectively evaluated to assess the benefits of such strategies.

International harmonization efforts are also ongoing (ie, Harmonization International Bone Sarcoma Consortium (HIBiSCus), Euro-Ewing consortium) to pool our strengths in these rare tumors, both in systemic treatments and in local strategies.

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CHAPTER 97

Lymphomas in Children, Adolescents, and Young Adults

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Childhood lymphomas comprise a broad spectrum of cancers with a range of prognoses. A challenge in management is to optimally balance treatment intensity with its attendant toxicity. Historic treatment with large radiation fields and high radiation doses, although effective, caused unacceptable morbidities in children, such as impaired musculoskeletal development, increased risks of secondary benign and malignant neoplasms, and cardiopulmonary and other organ toxicities. The introduction and refinement of effective systemic therapies enabled reductions in radiation field sizes and doses. In addition, modern radiation techniques have been incorporated into standard management, further reducing the radiation dose to normal tissues.

Modern research aims to tailor therapy to maximize efficacy and minimize treatment-related toxicity. There is a focus on risk and response adaptation to intensify therapy in children with an unfavorable prognosis and de-escalate treatment in those with a favorable prognosis. Thoughtful application of radiation therapy (RT) maintains a critical role in risk- and response-adapted treatment algorithms for pediatric lymphomas, given its efficacy.

HODGKIN LYMPHOMA

Hodgkin lymphoma (HL) constitutes a class of diseases that arise in both children and adults. Although histologic similarities between adult and pediatric subtypes exist, there are differences to suggest that the biology is only partially shared. For example, the clinical presentations vary in terms of gender ratio, distribution of histologic subtypes, hypotheses of etiology, role of Epstein-Barr virus (EBV), and prognosis.[1] Historic therapies, though effective for disease control, caused substantial cumulative morbidity in children.[2,3] Since patients were often cured, survivors of pediatric HL who were treated with historic approaches have served as models for understanding the long-term toxicity of RT and chemotherapy. A strong desire to avoid the toxicities associated with high-dose, extended-field RT prompted the first generation of studies examining combined modality therapy using lower radiation doses and/or smaller fields with the expectation that multiagent chemotherapy could eradicate microscopic disease.[4-9] The elevated rates of secondary malignancies attributed to alkylating agents led to the second generation of investigations using doxorubicin-containing chemotherapy regimens to reduce doses of alkylating agents.

Outcomes of children and adolescents with HL have improved over time, and 5-year survival rates now exceed 90%.[10] Today's treatment of children with HL employs multiagent chemotherapy regimens and nuanced RT approaches to mitigate long-term toxicity. Risk- and response-adapted treatment approaches are now widely employed: Patients receive varying intensities of chemotherapy with or without low-dose RT, with many contemporary studies using treatment response to guide elimination of RT in appropriately selected patients.[11-17] Future directions will aim to identify and subsequently integrate biologic markers to tailor therapy in patients with either very good or very poor outcomes.

Epidemiology

In the United States, childhood HL is the eighth most common cancer in children (ages 0-14) and the most common malignancy of adolescence (ages 15-16).[10] Although non-Hodgkin lymphoma (NHL) is slightly

more common than HL in children younger than 14, comprising 6% versus 4% of all cancer diagnoses, HL is more common than NHL in adolescents, constituting 15% of new cancer diagnoses compared to 8%.

There is marked variation in the international incidence of HL, with an inverse relationship between the occurrence of the childhood and young adult forms of the disease.[18,19] Countries with a high incidence of childhood HL generally demonstrate a low incidence of young adult HL and vice versa. Early and intense exposure to infectious agents has been speculated to increase the risk for the childhood form of HL.[20,21]

The childhood form of classic HL (cHL) usually occurs in children older than 10 years and is rare in children younger than 4 years. The incidence is associated with male gender, increasing family size, and decreasing socioeconomic status.[22-25] In the United States, Caucasians have the highest overall incidence rates for both males and females, but the male gender association of childhood HL is strongest in Black and Hispanic patients.

In contrast to childhood HL, adolescent and young adult cHL is associated with a higher socioeconomic status, smaller family size, and later birth order.[21-23] There is a roughly equal incidence between adolescent males and females.[26] Similarities between HL and paralytic poliomyelitis suggest that delayed exposure to an infectious agent may be a risk factor for the development of young adult HL, with the risk of oncogenesis increasing with later age of infectious exposure.[23] Interestingly, there also seems to be an association between exposure to children at nursery school and daycare and decreasing risk of young adult HL, most likely by facilitating early childhood exposure to common infections and promoting maturation of cellular immunity.[21]

Nodular lymphocyte–predominant HL (NLPHL) is a less common subtype compared to cHL, representing approximately 5% of pediatric HL diagnoses. It is associated with a much higher incidence in males, Caucasians, and younger children (<10 years), and it does not have a strong association with income or birth order.[27]

Pathologic Classification

As in adults, pediatric HL follows the World Health Organization (WHO) classification into two major groups of HL: cHL and NLPHL. Distinctions between groups are made according to their biologic and clinical features.[28,29] cHL is further subclassified into nodular sclerosing (NS), mixed cellularity (MC), lymphocyte-rich (LR), and lymphocyte-depleted (LD) histologies based on their unique morphologies. The most prevalent subtype in North America is NS cHL. NLPHL has a better outcome, and treatment typically varies from that of cHL. Of note, this category of lymphoma is called NLPHL in the WHO,[28] but it is labeled nodular lymphocyte–predominant B-cell lymphoma (NLPBL) by the 2022 International Consensus Classification.[29]

The relative distribution of the subtypes differs in younger children compared with adolescents and adults.[25,30] Although NS is the most common subtype in all age groups, it constitutes a significantly larger proportion of cases of adolescents (77%) and adults (72%) than in children younger than age 10 (44%). Conversely, MC subtype is more common in younger children (33%) than in adolescents (11%) or adults (17%). Similarly, NLPHL is more common in children younger than 10 years (13%) than in adolescents (8%) and adults (5%). LD subtype is rare in all age groups.[25]

Biology

Pediatric HL and NHL arise from the germinal center of lymph nodes. HL is unique among the lymphomas because the malignant Reed-Sternberg (RS) cells in cHL and lymphocytic-and-histiocytic (L-and-H) cells in NLPHL account for less than 1% of the tumor cell population. Identical immunologic gene rearrangements in RS and L-and-H cells support their origin from a single transformed B cell that subsequently undergoes monoclonal expansion.[31-33] There are two distinct immunophenotypes of HL, which distinguish the differentiation of HL into WHO's classifications of cHL and NLPHL.[28] The first immunophenotype associated with cHL is characteristic of RS cells that consistently express CD30 and often express CD15 with weak PAX5 expression.[28] The second immunophenotype associated with NLPHL

is characteristic of L-and-H cells that consistently express CD20 and J chain and do not express CD30 or CD15.[33,34]

Considerable evidence suggests an etiologic role of EBV in the pathogenesis of both childhood and young adult HL.[35,36] Early serologic studies linked EBV to HL.[35,36] Delayed early adolescent exposure to EBV is frequently associated with the development of infectious mononucleosis, and studies show an increased risk of HL in patients diagnosed with infectious mononucleosis.[37-42] In addition, increased EBV antibody titers have been observed in patients with HL several years prior to their HL diagnosis.[43] The incidence of EBV-associated HL varies by age, gender, ethnicity, histologic subtype, geography, and regional economic level.[36] EBV-positive tumor genomes are more frequent in children younger than 10 years and in those who live in low-income countries.[36] EBV positivity is most common in MC and LD cHL and is observed in approximately 80% of children aged 0 to 14 years with these subtypes. Tumors of children with NS HL were found to be EBV positive in nearly 40% (childhood HL) and 20% (young adult HL) of cases.[36]

The association of lymphoma with inborn errors of immunity is increasingly recognized. HL is also associated with inherited (eg, ataxia-telangiectasia)[44] and acquired (eg, human immunodeficiency virus [HIV]) immunodeficiencies, and EBV appears to be an important cofactor in the development of HL in these patients.[45] There is familial clustering of HL with concordance in siblings who have an over 4-fold increased risk of developing HL.[46] As high as a 99-fold increased risk in monozygotic twins of patients with HL has been reported, with no increased risk in dizygotic twins.[47] These familial cases of HL suggest a genetic predisposition to the disease.[48]

Clinical Presentation

Most pediatric patients with HL present with cervical lymphadenopathy.[49] The typical clinical presentation includes the indolent onset of lymphadenopathy, compressive symptoms due to a mediastinal mass, and/or systemic (“B”) symptoms. The lymph nodes are often fixed, firm, and painless. Mediastinal involvement is present in 76% of adolescents but in only 33% of children aged 1 to 10 years.[49] If mediastinal lymphadenopathy is present, it may be associated with a nonproductive cough, respiratory distress, or other symptoms of tracheal or bronchial obstruction or with superior vena cava (SVC) syndrome, but patients have relative clinical stability due to the slow growth and ability to accommodate compromise with collaterals. While disease may spread below the diaphragm, isolated infradiaphragmatic HL is rare, occurring in less than 5% of patients. Central nervous system (CNS) involvement is extremely rare.[50]

As a result of cytokine production by the RS cells, one-third of patients have one or more B symptoms at diagnosis. These include recurrent unexplained fevers greater than 38.3 °C during the previous month, drenching night sweats, or weight loss of more than 10% of body weight in the 6 months preceding diagnosis.[49,51] Other cytokine-mediated systemic symptoms may include anorexia, pruritus, fibrosis, eosinophilia, thrombocytosis, plasmacytosis, and immunodeficiency.[52]

Diagnostic Workup

The investigations required for accurate staging and diagnosis of childhood lymphomas are summarized in Table 97.1. The diagnosis of HL is made based on morphology, immunohistochemistry, and flow cytometry reviewed by experienced lymphoma pathologists. When appropriate, molecular studies may be needed for further characterization. The diagnosis is facilitated through an excisional lymph node biopsy to provide adequate tissue for evaluation of the malignant RS and L-and-H cells and of the characteristic architectural changes associated with the specific histologic subtypes. Although less desirable, core-needle biopsy can be considered when excisional biopsy is not possible; however, lack of adequate tissue may result in failure to obtain the diagnosis from a core- needle biopsy specimen.[53]

TABLE 97.1 INVESTIGATIONS REQUIRED FOR ACCURATE STAGING AND DIAGNOSIS OF CHILDHOOD LYMPHOMAS

History and Physical Examination

B symptoms (unexplained recurrent fever, drenching night sweats, weight loss >10% body weight within 6 mo)
Examination of lymph node regions, liver, spleen
Blood Work
Complete blood count with differential
Liver and renal function panels
Erythrocyte sedimentation rate (ESR)
Lactate dehydrogenase (LDH)[a]
C-reactive protein (CRP)
Imaging Studies
Chest radiograph[b]
Neck, chest, abdominal, and pelvis CT scan
Fluorine-18 FDG-PET imaging
Excisional or Incisional Biopsy
Morphology (fixed)
Immunohistochemistry
Immunophenotypic analysis (fresh or fixed)[a]
Cytogenetics (fresh)[a]
Molecular analysis (fresh or fixed)[a]
FISH for specific translocation (fresh or fixed)[a]
Immunoglobulin gene rearrangements (fresh or fixed)[a]
Bone Marrow Examination (Bilateral Aspirates and Biopsies) in Some Cases[a]
Cerebrospinal Fluid Examination (Cell Counts and Cytology) in Some Cases

CT, computed tomography; FDG-PET, fluorodeoxyglucose positron emission tomography; FISH, fluorescence in situ hybridization; NHL, non-Hodgkin lymphoma.

[a]NHL only.

[b]Chest x-ray is necessary if cross-sectional imaging is unavailable, or if needed to assess for mediastinal bulk according to a clinical trial's definition.

Adapted from Shad A, Magrath I. Non-Hodgkin's lymphoma. *Pediatr Clin North Am*. 1997;44(4):863-890. Copyright © 1997 Elsevier. With permission; Gross TG, Perkins SL. Malignant non-Hodgkin lymphomas in children. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 6th ed. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2011:663-682.

A detailed history should evaluate the age, sex, and presence or absence of B symptoms, each of which may alter the management of a child with HL. Fatigue, pruritus, and alcohol- induced pain should be noted. Although these symptoms do not direct treatment, their recurrence may be an early indication of disease relapse. Physical examination involves a detailed lymph node evaluation, including assessment of Waldeyer ring, as well as assessment for splenomegaly and/or hepatomegaly. Laboratory evaluation should include a complete blood count with white blood cell differential and platelet count, erythrocyte sedimentation rate (ESR), albumin, renal and liver function tests, and lactate dehydrogenase (LDH). Evaluation for risk of HIV should be considered, as should a more detailed immunologic profile in younger children.

Imaging of the chest is required to assess for sites of thoracic involvement and for mediastinal bulk. Many protocols, including those run by the Children's Oncology Group (COG), define mediastinal bulk as a mass measuring 33% or more of the maximum intrathoracic cavity on an upright posterior-anterior chest radiograph (CXR). CXR is highly concordant with chest computed tomography (CT) for the detection of mediastinal bulk.[54,55] It is possible that CT-based definitions of mediastinal bulk are stronger predictors of relapse than CXR-based definitions.[55] CT, rather than CXR, is increasingly used to define bulk, with

common definitions including mediastinal masses larger than 10 cm and nonmediastinal masses larger than 6 cm. Even if a CXR is used to assess for mediastinal bulk, a contrast-enhanced CT is necessary in all patients to assess for subcarinal, hilar, and cardiophrenic lymphadenopathy, as well as extranodal disease sites including the pleura, chest wall, or pericardium, which may influence management.[56]

Infradiaphragmatic disease is assessed by a CT scan of the abdomen and pelvis with oral and intravenous contrast to distinguish lymphadenopathy from other structures. CT evaluation of the abdomen and pelvis may be limited, however, with suboptimal contrast administration or in children who lack retroperitoneal fat. In such cases, magnetic resonance imaging (MRI) may provide better assessment of disease involvement in the retroperitoneal lymph nodes.

Essentially all cases of HL demonstrate ^{18}fluorine-fluorodeoxyglucose ([18]F-FDG) avidity, and thus [18]F-FDG positron emission tomography (PET) is required as standard staging for HL.[57,58] The use of PET in addition to CT scans results in a change in disease stage in 10% to 30% of patients, more often upstaging.[59] In addition, PET-CT is critical for monitoring treatment response,[57,58] particularly in cases with persistent radiographic abnormalities[60] or "rebound" thymic growth after completion of therapy.[61] Splenic and hepatic involvement by HL is suggested by the presence of enlarged organs with areas of abnormal density on CT or MRI scans, as well as increased [18]F-FDG uptake on PET scans. Splenic enlargement alone, without nodular densities, does not necessarily indicate splenic involvement.

Traditionally, bone marrow biopsy (BMB) was standard in lymphoma staging; however, PET-CT has a high negative predictive value to exclude marrow involvement in HL.[62] Therefore, in the setting of PET-CT, BMB can be restricted to patients with unexplained cytopenias and a PET that is negative for marrow involvement.[57]

Staging Systems

Children and adults with HL are staged according to the system devised at the Ann Arbor Staging Conference in 1970 and revised at the Cotswolds meeting, as summarized in Table 97.2.[63] Patients are typically treated based on limited (stages I and II, nonbulky) or advanced (stage III or IV) disease, with stage II bulky classified as limited or advanced based on other prognostic factors. Stratification into prognostic groups has varied across and within pediatric consortia by study.[64]

TABLE 97.2 COTSWALDS MODIFIED ANN ARBOR STAGING SYSTEM

Stage	Definition
I	One nodal group or lymphoid organ (eg, spleen, thymus)
IE	Local extension from one nodal group to an extranodal site
II	Two or more nodal groups, same side of diaphragm
IIE	Two or more nodal groups, extension from a nodal group to an extranodal site, same side of diaphragm
III	Nodal groups on both sides of the diaphragm
IIIS	Nodal groups on both sides of the diaphragm, splenic involvement
IIIE	Nodal groups on both sides of the diaphragm, localized extension from a nodal group to an extranodal site
IIISE	IIIS and IIIE criteria
IV	Disseminated involvement of one more extranodal organs (eg, lung, bone, bone marrow, liver) with or without nodal involvement
Modifications	
A	Absence of B symptoms
B	Presence of B symptoms
X	Bulky disease[a]
E	Extranodal extension
S	Splenic involvement

Positron emission tomography-computed tomography used to define extent of disease in Hodgkin lymphoma. Tonsils, Waldeyer ring, and spleen are considered nodal tissue.

[a]Bulky definition varies across protocols but most commonly as a mass of more than one-third of the maximum intrathoracic diameter or extramediastinal mass greater than 6 to 10 cm.

Derived from Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *J Clin Oncol*. 1989;7(11):1630-1636.

Prognostic Factors

A discussion of prognostic factors in pediatric HL is complicated for several reasons. First, prognostic factors such as disease stage, bulk, and biologic aggressiveness are frequently codependent.[65] Second, identification of baseline prognostic factors is confounded by the impact of therapy, with higher intensity therapies negating previously determined adverse risk factors, and the changing climate of novel therapies.[66] Third, different institutions and cooperative groups have employed various risk stratification schemes within pediatric HL protocols, and within these determinations, patients with early-stage disease have different prognosticators than patients with advanced-stage disease.[65]

The following are some generalizations regarding prognostic variables derived from both adult and pediatric data:

- *Stage of disease* is the most significant prognosticator of treatment outcome. Advanced-stage disease, particularly stage IV disease with multiple organ involvement, confers an inferior prognosis with conventional therapy.[67,68]
- *Bulk of disease* reflects the volume of involvement at each site. Bulky mediastinal adenopathy has historically been associated with an increased risk of disease recurrence, particularly when disease is managed with RT alone.[69-72] Bulky mediastinal adenopathy has been defined using a variety of definitions, most commonly as a mass of more than one-third of the maximum intrathoracic diameter on a posteroanterior CXR.[72-75] Other common definitions include a ratio of the mediastinal mass to the intrathoracic width at T5-6 measuring greater than 1/3,[76] or transverse diameter of greater than 10 cm,[77] 5 cm,[78] or 6 cm[79,80] depending on the protocol. In Europe, bulk is defined as a tumor volume of at least 200 mL estimated using an ellipsoid formula ($V = (xyz)/2$, where x, y, and z are the diameters of the mass in three dimensions).[11,12,17]
- *Systemic or B symptoms*, defined as unexplained fever, drenching night sweats, or unintentional weight loss, result from cytokine secretion. These reflect biologically more aggressive disease and are associated with an increased risk of relapse compared with the absence of such symptoms.[51,68]
- *Abnormal levels of serum markers*, including ESR, hemoglobin, serum albumin, and white blood cell count, are negative prognostic factors.[65,68] These are confounded by increased tumor volume, so it is unclear if elevated serum markers are independently prognostic for more malignant biology of disease.[65,68]
- *Histologic subtype* may correlate with prognosis. Patients with NLPHL have superior outcomes compared to cHL histologies. LD histology confers a worse outcome than the other cHL subtypes, but it is rare.[72] MC has a favorable prognosis when early stage, but a higher relapse risk when advanced stage.
- *Patient age* is a determinant of outcome with children younger than 10 to 15 years of age experiencing superior event-free (EFS) and overall survival (OS) compared to adolescents.[25,30,81]
- *Response to initial therapy* is a prognostic factor,[82] with a rapid early response (RER) associated with superior disease control. Early treatment response was the foundation for trials of response-based conventional therapy that are discussed later. Methods used for response assessment have varied across studies. A five-point score known as the Deauville criteria is a reproducible approach to evaluate response by PET-CT and is now being applied as a standard reporting criterion in both pediatric and adult HLs.[57,83] The Deauville score is defined as follows:
  - 1: No FDG-avidity

- 2: FDG-avidity ≤ mediastinal blood pool
- 3: FDG-avidity > mediastinal blood pool but ≤ liver
- 4: FDG-avidity moderately > liver
- 5: FDG-avidity markedly > liver or new site(s) of disease
- X: New lesion that is not attributable to lymphoma

*Note that the growth of disease or new lesions seen on imaging during therapy are rare, and other reasons for their development should be considered. A biopsy is not needed prior to continuation of prescribed therapy.

There is a prognostic risk scoring system for pediatric HL that is treated with modern era combined modality therapy. This system was defined based on a retrospective analysis of the COG study AHOD0031 that analyzed response-based therapy in intermediate-risk patients. The Childhood Hodgkin International Prognostic Score (CHIPS) allocates one point each for fever, stage IV disease, albumin less than 3.5 g/dL, and large mediastinal adenopathy (defined as mass of more than one-third of the maximum intrathoracic diameter on CXR). CHIPS was highly predictive of EFS, and it identified a subset (CHIPS 2 or 3) that comprised 27% of intermediate-risk patients with inferior outcomes (EFS <80%) with conventional ABVE-PC (doxorubicin, bleomycin, vinblastine, etoposide, prednisone, cyclophosphamide) who may benefit from early intensification of therapy.[84]

General Management

Given the high cure rates and lifespan of pediatric HL survivors, individualized risk for treatment-related late morbidity must be considered when selecting therapies. Historically, extended-field RT to curative doses that could exceed 40 Gy produced the first cures in patients with HL. In children with early-stage disease confirmed by surgical staging, 5-year disease-free survival (DFS) rates following extended-field RT ranged from 60% to 80% when treated with RT alone.[6,85,86] For patients with advanced-stage disease, the development of non–cross-resistant chemotherapy combinations provided the first effective therapy; however, the specific chemotherapeutic combinations have changed as their gonadotoxic and leukemogenic properties have become better understood. Treatment approaches of the past involving large radiation fields and toxic alkylating chemotherapy are no longer used; the observed late morbidity and mortality caused by these treatments have steered the management of pediatric HL to balance the efficacy and toxicity of contemporary combined modality regimens.

Modern trials for the treatment of pediatric HL are summarized in Tables 97.3 and 97.4 and reflected in national guidelines specific to pediatric HL. Current management paradigms involve a risk- and response-adapted approach. Therapy typically involves multiagent chemotherapy followed by low-dose RT for bulky, slowly responding, or residual disease, as summarized in Table 97.5. The development of this treatment approach is discussed later.

TABLE 97.3 SUMMARY OF CONTEMPORARY LOW-RISK PEDIATRIC HODGKIN LYMPHOMA TRIALS

					Percent Outcome (Years)	
Reference	Patients (*n*)	Stage	Chemotherapy	Radiation (Gy), Field	DFS, EFS, or RFS	Overall Survival
Euronet-PHL-C1[11]	440	IA, IB, IIA	2 OEPA	CR, no RT	86 (5)	99 (5)
	273			<CR, 19.8 IF ± 10.8 boost	87 (5)	98 (5)
COG AHOD0431[87]	175	IA, IIA	3 AV-PC	CR, no RT	80 (2)	100 (2)
	100			<CR, 21 IF	88 (2)	
SJCRH HOD05[88,89]	49	I, II	4 VAMP	CR, 15 IF	95.2 (10)	100 (10)
	61			<CR, 25.5 IF	84.5 (10)	93 (10)

Reference	Patients (*n*)	Stage	Chemotherapy	Radiation (Gy), Field	Percent Outcome (Years)	
					DFS, EFS, or RFS	Overall Survival
GOPH-HD-2002[17]	62	IA, IB, IIA	2 OEPA (boys) or 2 OPPA (girls)	CR, no RT	93 (5)	100 (5)
	126			<CR, 19.8-35 IF	92 (5)	100 (5)

AV-PC, Adriamycin, vincristine, prednisone, cyclophosphamide; CR, complete response; DFS, disease-free survival; EFS, event-free survival; IF, involved field; OEPA, Oncovin, etoposide, prednisone, Adriamycin; OPPA, Oncovin, procarbazine, prednisolone and Adriamycin; RFS, recurrence-free survival; RT, radiation therapy; VAMP, vincristine, amethopterin, mercaptopurine, prednisone.

TABLE 97.4 SUMMARY OF CONTEMPORARY INTERMEDIATE- AND HIGH-RISK PEDIATRIC HODGKIN LYMPHOMA TRIALS

Reference	Patients (*n*)	Stage	Chemotherapy	Radiation (Gy), Field	Percent Outcome (Years)	
					DFS, EFS, or RFS	Overall
EuroNet-PHL-C1[12]	514	IIE, IIB, I III, IV	2 OEPA + COPP vs COPDAC (2 for IR, 4 for HR)	AR at ERA, no RT	90 (5)	99 (5)
	773			<AR at ERA, 19.8 modified IFRT +/− 10.8 boost	87 (5)	98 (5)
COG-AHOD1331[13]	289	IIIB, IVA, IVB	5 ABVE-PC vs	LMA or SRL, 21 Gy ISRT	82 (3)	99 (3)
	298		5 BV-AVE-PC		92 (3)	98 (3)
SJCRH HLHR13[14]	77	IIB, IIIB, IV	2 AEPA + 4 COPDAC	<AR at ERA, 25.5 RNRT	97 (3)	99 (3)
COG-AHOD0831[15]	165	IIIB, IVB	5 ABVE-PC	21 risk-adapted ISRT (initial bulk, slow response)	80 (4)	96 (4)
COG-AHOD0031[16]	361	I/IIA with bulk, I/IIB, IIIA, IVA	RER: 4 ABVE-PC	No RT	84 (4)	99 (4)
	355			21 IFRT	88 (4)	99 (4)
	151		SER: 4 ABVE	21 IFRT	75 (4)	94 (4)
	153		SER: 4 ABVE + 2 DECA	21 IFRT	79 (4)	96 (4)
GPOH-HD-2002[17]	139	IE, IIB, IIEA/B,	2 OEPA/OPPA + 2 or 4 COPP/COPDAC	19.8 IFRT ±15.2 boost	88 (5)	100 (5)
	239	IIIEA/B, IIIB, IV			87 (5)	95 (5)

ABVE-PC, Adriamycin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide; AEPA, Adcetris (brentuximab vedotin), etoposide, prednisone, Adriamycin; AR, adequate response; COPDAC, cyclophosphamide, Oncovin, prednisone and dacarbazine; COPP, cyclophosphamide, Oncovin, prednisone and procarbazine; CR, complete response; DFS, disease-free survival; EFS, event-free survival; ERA, early response assessment; IFRT, involved field; ISRT, involved-site radiation therapy; LMA, large mediastinal adenopathy; OEPA, Oncovin, etoposide, prednisone, Adriamycin; OPPA, Oncovin, procarbazine, prednisolone and Adriamycin; RFS, recurrence-free survival; RNRT, residual node radiation therapy; RT, radiation therapy; SRL, slowly responding lesion.

TABLE 97.5 RECOMMENDED TREATMENT APPROACH IN CLASSIC PEDIATRIC HODGKIN LYMPHOMA

Clinical Presentation	Stage[a]	Recommended Treatment Approach
Low risk Localized disease and absence of "B" symptoms, bulk, or extranodal extension	IA, IIA	**Recommended therapy** 2-4 cycles non–cross-resistant chemotherapy (OEPA, VAMP, COPP-ABV, AV-PC) Response-based low-dose ISRT (1,500-2,550 cGy) **Other considerations** If complete response after 2 cycles of OEPA and absence of bulk or elevated ESR, RT

Clinical Presentation	Stage[a]	Recommended Treatment Approach
		may be omitted[11]
Intermediate risk Localized disease with bulk (mediastinal ratio ≥33%; lymph node mass ≥6-10 cm), B symptoms, and/or extranodal extension. Advanced stage without B symptoms or extranodal disease	I/IIA with bulk, IB, IIB, IE, IIE, IIB[a], IIIA	**Recommended therapy** 3-6 cycles dose-intensive, non–cross-resistant chemotherapy (OEPA/COPDAC, ABVE-PC) Response-based low-dose ISRT (1,500-2,550 cGy) **Other considerations** If rapid early response after 2 cycles and complete response after 4 cycles of ABVE-PC, RT may be omitted[16]
High risk Stage II with B symptoms and bulk. Advanced stage with B symptoms and/or extranodal disease	IIB[a], IIIB, IV	**Recommended therapy** 4-6 cycles of dose-intensive, non–cross-resistant chemotherapy (OEPA/COPDAC/, ABVE-PC, BV-AVE-PC) Response-based low-dose ISRT (1,500-2,550 cGy) **Other considerations** If rapid early response after 2 cycles and absence of mediastinal bulk, RT may be omitted after 5 cycles Bv-AVE-PC[13] Immunotherapy may be considered based on emerging data.

Involved-site radiation therapy (ISRT) is the recommended RT technique. In treatment centers where prechemotherapy, postchemotherapy, and radiation simulation imaging are all obtained in the same position with the radiation simulation immobilization device, then involved-node radiation therapy (INRT) can be used instead of ISRT.

ABV, doxorubicin, bleomycin, and vinblastine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ABVE-PC, doxorubicin, bleomycin, vinblastine, etoposide, prednisone, cyclophosphamide; AEPA, brentuximab vedotin, etoposide, prednisone, and doxorubicin; AV-PC, doxorubicin, vincristine, prednisone, and cyclophosphamide; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; Bv-AVE-PC, brentuximab vedotin, doxorubicin, vinblastine, etoposide, prednisone, cyclophosphamide; CAPDAC, cyclophosphamide, brentuximab vedotin, prednisone, dacarbazine; COPDAC, cyclophosphamide, vincristine, prednisone, dacarbazine; ISRT, involved-site radiation therapy; OEPA, vincristine, etoposide, prednisone, and doxorubicin; VAMP, vinblastine, doxorubicin, methotrexate, and prednisone.

[a]Different studies and cooperative groups have used various risk stratification schemes. When recommending therapy according to a particular protocol, reviewing the inclusion criteria for that study is recommended. For example, patients with stage IIB disease have been variably treated as intermediate or high risk. Some studies use associated risk factors, such as weight loss, bulk disease, and extranodal extension, for further risk stratification.

Combination Chemotherapy

The first effective systemic therapy for HL was MOPP (mechlorethamine, vincristine, procarbazine, prednisone).[90-92] This regimen was associated with ovarian failure in women, infertility in both sexes, and a high rate of secondary acute myeloid leukemia (s-AML).[93,94] The cumulative risk of secondary malignancy is 4% to 8% after MOPP-based therapy,[95] with the incidence peaking 5 to 10 years after treatment.[96] A regimen substituting cyclophosphamide for mechlorethamine (COPP) was associated with a lower incidence of s-AML.[95]

Subsequently, an alternative regimen using ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) was shown to result in superior disease control compared to MOPP.[97,98] This change shifted the toxicity pattern, because the side effects of bleomycin and doxorubicin are pulmonary and cardiovascular injury, respectively, and the risk increases when these agents are combined with RT that delivers dose to the lungs and heart.[71,99,100] Anthracycline exposure confers a dose-dependent risk of cardiotoxicity[101]; therefore, one approach to reduce the risk of cardiomyopathy is to limit the anthracyclines for pediatric HL to a cumulative dose of 250 mg/m^2, particularly in the case of favorable-risk disease. Bleomycin- induced pulmonary toxicity is manifested as a chronic pneumonitis or pulmonary fibrosis and typically occurs at doses exceeding 400 U/m^2.[102] Most modern pediatric HL regimens use doses in the range of 60 to 100 U/m^2. Such doses may result in subclinical pulmonary restriction and

diffusion defects, but toxicity can be exacerbated by thoracic RT. Serial pulmonary function tests including diffusing capacity for carbon monoxide are recommended, and if a significant decline from baseline is observed, bleomycin may be held.[103]

To reduce the treatment-related toxicities associated with six cycles of either MOPP or ABVD, strategies alternating the two regimens, and using fewer cycles of each, were developed. The combined ABVD and MOPP regimens used for children produced excellent disease control with diminished toxicity.[104,105]

Etoposide, a topoisomerase II inhibitor, was incorporated into treatment regimens to intensify therapy for unfavorable HL and serve as an alternative to alkylating agents to reduce the risk of gonadal toxicity.[106-109] There is a risk of secondary leukemia with topoisomerase II inhibitors due to a different pathogenesis than alkylator-related s-AML,[110] and the risk is compounded by the use of multiple topoisomerase II inhibitors. For example, in one POG trial that used dexrazoxane (a topoisomerase II inhibitor) as a cardiac protectant during treatment with ABVE or ABVE-PC, there was an unacceptably high rate of s-AML attributed to the use of multiple topoisomerase II inhibitors.[111] Risk of s-AML is low when the etoposide dose is limited to 5.0 g/m^2 or less.

Using a different multiagent chemotherapy regimen, gender- adapted therapy has been considered, given the differing susceptibility to infertility caused by procarbazine in boys compared to girls. The German Society for Paediatric Oncology and Haematology (GPOH) evaluated a gender-adapted approach according to which boys received OEPA (vincristine, etoposide, prednisone, doxorubicin) to limit alkylator exposure, whereas girls received OPPA (vincristine, procarbazine, prednisone, doxorubicin) substituting procarbazine for etoposide.[17,112,113]

Therapy for children, adolescents, and young adults with HL continues to be refined. Newer systemic agents are emerging, such as brentuximab vedotin (Bv), an antibody-drug conjugate that combines an anti-CD30 antibody with a synthetic tubulin disruptor and thereby targets CD30, which is ubiquitous in cHL. The anti-programmed death-ligand 1 (PD-L1) and anti-PD-L2 drugs exploit the abundance of programmed cell death protein 1 ligands associated with alterations in chromosome 9p24.1 in HL that allows immune evasion of the tumor.

Frontline regimens that are used for pediatric HL today include the following:

- AV-PC (doxorubicin, vincristine, prednisone, cyclophosphamide)[87]
- ABVE-PC[15,16]
- Bv-AVE-PC (brentuximab vedotin, doxorubicin, vincristine, etoposide, prednisone, cyclophosphamide)[13]
- OEPA[11,17]
- OEPA/COPDAC (cyclophosphamide, vincristine, prednisone, dacarbazine)[12,17]
- AEPA/CAPDAC (brentuximab vedotin, etoposide, prednisone, doxorubicin/cyclophosphamide, brentuximab vedotin, prednisone, dacarbazine)[14]
- N-AVD (nivolumab, doxorubicin, vinblastine, dacarbazine)[114,115]
- Bv-AVD (brentuximab vedotin, doxorubicin, vinblastine, dacarbazine)[114,115]

Modern Techniques of Radiation Therapy

Commensurate with the use of increasingly effective chemotherapy, there has been a more tailored approach to RT, with significant reductions in prescription doses and irradiated volumes, as shown in Figure 97.1. The RT technique progressed from extended fields, which included total lymphoid, mantle field, and pelvic radiation, to involved-field (IFRT) volumes, which encompassed involved lymph node regions or compartments based on bony anatomic landmarks. IFRT included not just the involved lymph nodes but also the entire lymph node region including adjacent uninvolved lymph nodes.[116] Today, involved-site radiation therapy (ISRT) or involved-node RT (INRT) is the standard, accepted approach for

defining treatment volumes. This modern, highly individualized approach targets only the lymph nodes or tissues that were initially involved by lymphoma. It takes into consideration imaging advances, including high-quality PET-CT scans, three-dimensional (3D) and 4D treatment planning with CT scanning, conformal radiation techniques, and image guidance, dramatically improving upon IFRT that was based on 2D treatment planning.

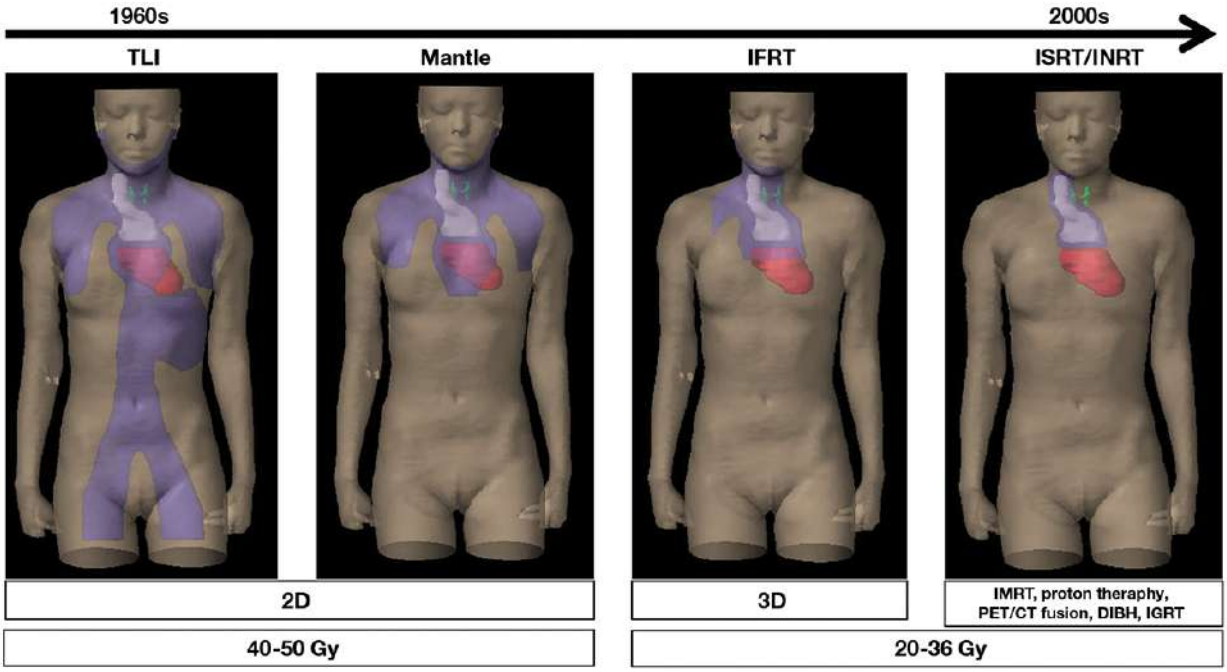

FIGURE 97.1 Evolution of the radiation therapy fields, doses, and techniques that have been used for lymphomas. Purple: irradiated volume; white: site of involvement by lymphoma; red: heart; green: thyroid. 2D, two-dimensional radiation planning; 3D, three-dimensional radiation planning; DIBH, deep inspiration breath-hold; IFRT, involved-field radiation therapy; IGRT, image-guided radiation therapy; IMRT, intensity-modulated radiation therapy; ISRT/INRT, involved-site radiation therapy/involved-node radiation therapy; PET/CT, positron emission tomography/computed tomography; TLI, total lymphoid irradiation. (Reprinted from Milgrom SA, Bakst RL, Campbell BA. Clinical outcomes confirm conjecture: modern radiation therapy reduces the risk of late toxicity in survivors of Hodgkin lymphoma. *Int J Radiat Oncol Biol Phys*. 2021;111[4]:841-850. Copyright © 2021 Elsevier. With permission.)

A review of relapse patterns after chemotherapy in patients with HL supported the reduction in radiation field sizes. The observation that recurrence occurs most often in initially involved sites[117] suggests that chemotherapy is sufficient to treat microscopic disease, so RT can be limited to sites of initial gross involvement. Thus, with sophisticated imaging techniques, a concerted effort to scan patients in the radiation treatment position, and more accurate RT delivery, the practice of INRT emerged as an effort by the European Organisation for Research and Treatment of Cancer and Group d'Etude des Lymphomes de l'Adulte (EORTC-GELA) investigators to customize delivery of RT to the radiographically involved regions.[118,119] Such reduction in treatment volumes is feasible largely because of PET scanning. FDG-PET identifies involved lymph nodes that were radiographically occult on CT scans. As such, prechemotherapy PET is necessary to delineate the full extent of disease.[120]

The efficacy of the smaller INRT target volumes was first demonstrated in retrospective studies and then in a large, prospective cooperative group trial by the EORTC-GELA.[121-123] Thus, RT fields that target only the nodes and tissues of initial gross disease involvement have become the accepted standard-of-care RT technique for HL. Paramount to successful INRT is the acquisition of pre- and postchemotherapy CT and PET scans with the patient in the treatment position for RT. In North America, ISRT, in contrast to INRT, is accepted as the standard conformal therapy. ISRT is an extension of INRT that provides greater flexibility

for patients without prechemotherapy imaging performed in the RT treatment position,[124] as is common in North America.

Radiation Simulation

When possible, CT simulation for the treatment of children with HL should be carried out with intravenous contrast to best delineate nodal stations and differentiate nodes and masses from vessels. Oral contrast may be helpful for the treatment of abdominal and pelvic tumors. 4D CT can assess for target motion and aid in the selection of appropriate margins to account for respiratory movement. If the patient is able to participate with breath-hold techniques, deep inspiration breath-hold at the time of simulation and treatment can allow for significant sparing of the heart and lung.[124] In older children, techniques such as respiratory gating may also be useful to minimize the impact of respiratory motion.

Careful consideration of immobilization can offer significant advantages by increasing setup reproducibility, translating into smaller margins needed for setup uncertainty with the planning target volume (PTV). In addition, thoughtful patient positioning may aid in reducing the dose to normal tissues. For example, when treating the axillae, positioning the arms above the head can reduce dose to the lungs. However, positioning of the arms above the head may not be recommended in patients who are still growing because the axillary lymph nodes then move into the vicinity of the humeral heads, which should be blocked in growing children. Also, breast doses in female pediatric patients may be lower with akimbo, rather than raised, arm positioning.[125] Thus, the position chosen involves weighing concerns regarding tumor volume coverage and dose delivered to adjacent organs at risk.

Radiation Therapy Target Delineation

Guidelines for INRT and ISRT have been published to aid the radiation oncologist in defining treatment volumes.[124] The principles of target volume delineation for INRT and ISRT are largely the same, with differences in the quality and accuracy of prechemotherapy imaging. The margins for ISRT are larger to allow for uncertainties in contouring the clinical target volume (CTV) when prechemotherapy imaging is not performed in the RT treatment position. For both approaches, the pre- and postchemotherapy PET and CT, ideally obtained in the treatment position using the planned immobilization devices, should be fused with the simulation CT in the RT planning system. The gross tumor volume (GTV), CTV, internal target volume (ITV) when relevant, and PTV should be delineated using all available imaging information on contrast-enhanced CT and PET-CT as shown in Figure 97.2 and described as follows:

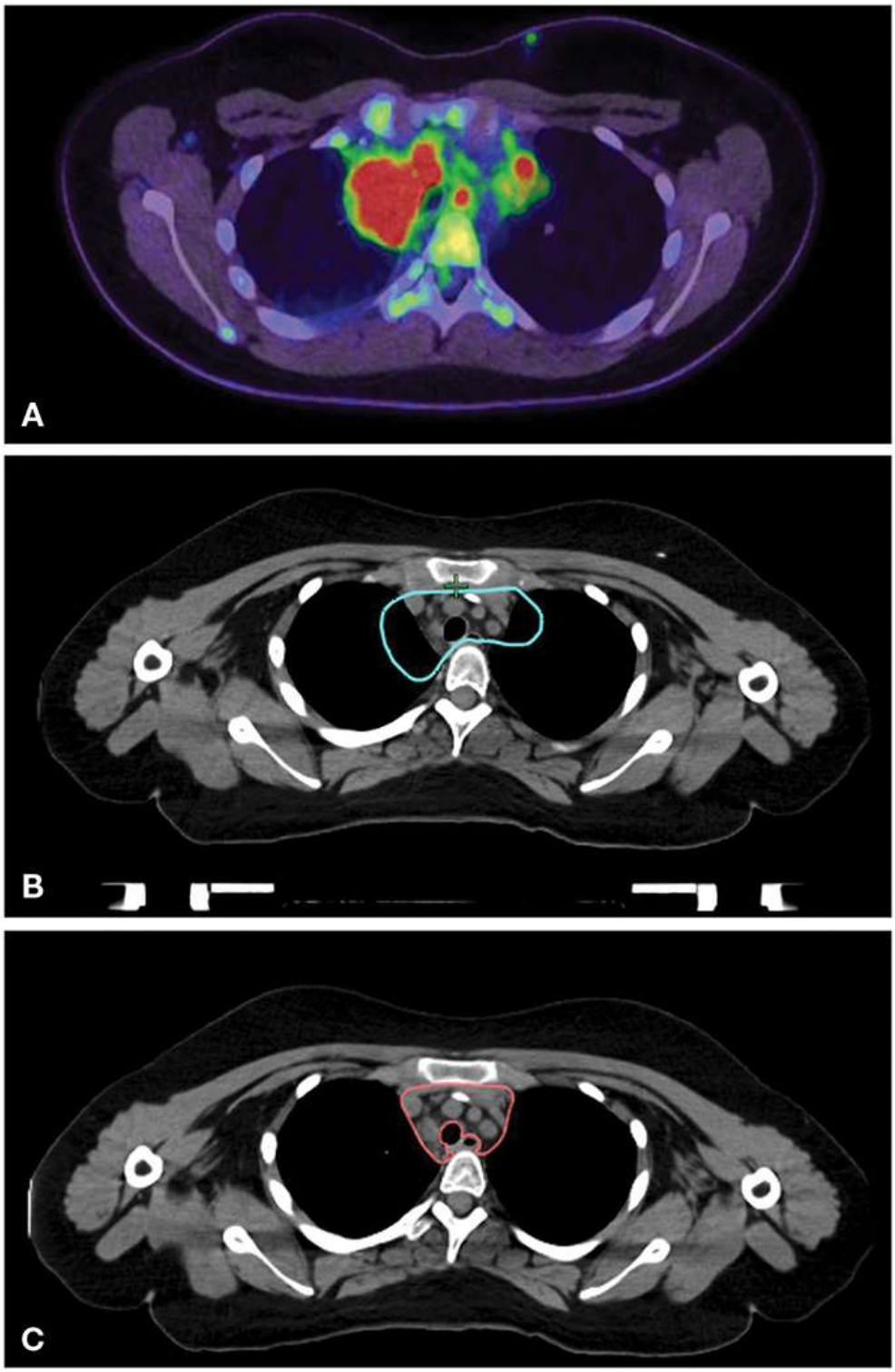

FIGURE 97.2 Illustration of involved-site radiation therapy target volumes informed by the prechemotherapy positron emission tomography (PET)/computed tomography (CT) scan. A. The prechemotherapy PET/CT scan demonstrates fluorodeoxyglucose-avid superior mediastinal disease. B. The prechemotherapy gross tumor volume (blue) encompasses the site of disease at diagnosis. C. The clinical target volume (CTV) contour (pink) encompasses the site of disease at diagnosis, accounting for anatomic changes that occurred with chemotherapy; for example, the CTV does not include lung tissue that was displaced by, but not invaded by, the mediastinal mass initially.

- Prechemotherapy GTV: GTV contoured on prechemotherapy CT and PET scans.
- Postchemotherapy GTV: GTV contoured on postchemotherapy CT and PET scans.
- CTV: A volume encompassing the superior and inferior extent of the prechemotherapy GTV with the radial extent respecting overtly uninvolved, normal structures (ie, lungs, kidneys, muscles) based on clinical judgment. The CTV should also take into account the quality and accuracy of imaging, pattern or spread of disease, changes in the volume of disease since imaging, risk of subclinical involvement, and nearby structures. Nodal volumes that are more than 5 cm apart can be treated as separate fields and do not need to be connected volumes. The CTV for ISRT will generally be larger than that for INRT because of the lack of optimal imaging information. If RT is used as the sole treatment modality, as in NLPHL, the CTV should be more generous because microscopic disease is likely more extensive in the absence of treatment with chemotherapy.
- ITV: Target motion should be accounted for using an ITV as defined by the International Commission on Radiation Units and Measurements as the CTV with a margin to consider organ motion for an individual patient.[126] A 4D CT simulation can be useful to obtain the ITV margins. With free breathing, respiratory motion may be significant in the chest or upper abdomen, so margins of up to 1.5- to 2-cm may be necessary.
- PTV: This margin should account for uncertainty in setup based on patient factors or immobilization that varies across institutions.

Radiation Therapy Dose

The dose of RT prescribed is guided by the intensity of the chemotherapy regimen used in combined modality approaches. Typical doses in the current era of low-dose RT are 15 to 30 Gy.[2,11-17,88] In North America, the COG has used a dose of 21 Gy in 14 fractions. Sites of partial response after completion of chemotherapy may receive an additional boost of 9 to 19 Gy (total 30-40 Gy).[13,15,16] On the current COG study for early-stage disease, AHOD2131, a slightly higher ISRT dose of 30 Gy is recommended, since RT is reserved for patients with less chemosensitive disease based on a slow early response (SER) to two cycles of ABVD chemotherapy (NCT05675410).

Radiation Therapy Planning

Given the risk of late effects in this patient population, children should be treated with the most conformal radiation approach that is reasonably available to them, typically either advanced photon-based techniques, such as intensity-modulated RT (IMRT) and volumetric modulated arc therapy, or proton therapy. While concerns existed previously that the "low-dose bath" with IMRT plans may increase the risk of second cancers in survivors, this is not borne out in data from 300 children treated at Memorial Sloan Kettering Cancer Center with a median follow-up of 11.2 years. The solid second malignant neoplasms that developed in these children were predominantly within the high-dose regions.[127] Before proton therapy was widely used, concerns were raised regarding potential increased second cancer risk due to neutron contamination, but no clinical evidence has arisen to date to support this possibility. For example, data from the University of Florida regarding 1,713 children treated with double- scattered proton therapy allay some of those fears. In their series, the absolute excess risk for a second cancer was 1.5 per 1,000 person-years, and all second tumors in children without genetic predisposition syndromes occurred in the high-dose region.[128] Proton therapy may offer the advantage of reduced doses to normal surrounding tissues and reduced integral dose.[129] Therefore, proton therapy may be particularly useful in cases where the target volume extensively contacts the heart or lungs, given the potentially additive effect between chemotherapy- and RT-related late toxicity to those tissues. Proton therapy may also be favored in the setting of prior RT targeting an adjacent area.

As always, we should strive to limit normal tissue doses to levels that are as low as reasonably achievable. Data suggest that the volume of tissue exposed even to low-dose radiation may be associated with the risk of toxicity in this population. For example, a radiation dose of 4 Gy or more to the breast

tissue has been associated with an increased risk of secondary breast cancer in survivors of HL.[130] Similarly, the volume of normal tissue receiving a dose of 5 Gy has been associated with the risk of pneumonitis[131] and late cardiac disease.[132]

Complications of Radiation Therapy

Acute Effects

The side effects of RT are related to the treated site and dose. Because doses used in pediatric HL are low, acute toxicities are typically limited. For supradiaphragmatic sites, the most common toxicities include temporary altered sense of taste, xerostomia, esophagitis, low posterior scalp epilation, skin erythema, and, occasionally, dyspepsia, nausea, and vomiting, depending on the anatomic location treated. Acute effects of para-aortic irradiation may include nausea, vomiting, and abdominal cramping. Fatigue is also reported by some patients, independent of anemia. Patients treated with larger fields may be subject to bone marrow suppression, the severity of which may be influenced by the systemic regimen preceding radiation.

Late Effects

Patients with HL have excellent prognoses, so the late effects of therapy are a critical concern. Studies of survivors who were treated for HL as children with historic, extended radiation fields have shed light on the potential late effects of RT.

Musculoskeletal

Impaired growth of bones and muscles is a potential long-term consequence of RT. The impact on growth is most severe with doses greater than 20 Gy, large fields, and prepubertal age at the time of RT. For example, decreased height was observed in young children who were treated with high doses and large fields (eg, total lymphoid irradiation that included most of the spine), and interclavicular shortening and hypoplasia of the neck muscles occurred when prepubertal children were irradiated to the neck.[133] Impaired musculoskeletal growth and development is modest with the low doses used in modern pediatric HL treatment strategies.[134] Avascular necrosis of the femoral or humeral heads is possible, but rare if appropriate shielding is employed. Radiation to the mandible in young children may result in dental abnormalities, such as stunted tooth development, incomplete calcification, premature apical closure or eruption, and root tapering with apical constriction.[135]

Cardiovascular

Cardiac sequelae, including pericarditis, pericardial effusion, valvular thickening, biventricular dysfunction, diastolic dysfunction, and coronary artery disease, may be observed after irradiation of the heart.[136,137] Increased mortality risk because of premature coronary artery disease and acute myocardial infarction has been demonstrated in patients who received mediastinal radiation doses greater than 30 Gy with historic RT treatments before 20 years of age.[119] Radiation-specific factors that influence the risk of cardiotoxicity include the total radiation dose to the heart, the volume of the heart exposed, and the dose per fraction.[138-144] In addition, other treatment and patient-specific factors contribute to the risk of radiation-associated cardiotoxicity. For example, the incidence of cardiotoxicity is higher in patients who received both anthracyclines and RT compared to RT alone.[137,141] In a recent review, every 100 mg/m^2 of anthracycline exposure was equivalent to a 10.5 Gy increase in mean heart dose with respect to late cardiac risk.[145] In addition, conventional cardiac risk factors, such as dyslipidemia, hypertension, and smoking, are independently associated with late cardiotoxicity in survivors.[138-141]

The risk of late cardiac toxicity is lower in survivors treated for HL in more recent decades compared to those treated with historic approaches, and a reduction in radiation dose to the heart has contributed significantly to the decline in cardiac toxicity incidence.[139] Using modern, conformal techniques, dose to the heart can be calculated and constrained in order to minimize the risk of long-term cardiac injury. Modern techniques enable radiation oncologists to consider more modern and aggressive dose constraints.

Recently, it has been shown that mean doses to individual cardiac substructures may better predict the risk of specific late cardiac diseases than mean dose to the entire heart[146]—work is ongoing to identify the best dose constraints to minimize cardiac risk in this patient population.

Pulmonary

The incidence of acute and subacute radiation-associated pneumonitis and late pulmonary fibrosis is low; however, the use of bleomycin can increase the risk.[147,148] It is manifest clinically in restriction defects and reduced diffusion capacity on pulmonary function tests. With advanced radiation planning, dose to the lungs should be limited, using constraints specific to the lymphoma population.[131] These low lung doses, in combination with contemporary regimens that eliminate or reduce the dose of bleomycin, result in a low risk of pulmonary toxicity.

Thyroid

Thyroid dysfunction may result from neck or upper mediastinal irradiation and most often is manifested by an elevated serum concentration of thyroid-stimulating hormone (TSH) indicative of primary thyroid failure. Constine et al noted an increased serum TSH in 4 (17%) of 24 children who received mantle doses of 26 Gy or less and in 74 (78%) of 95 who received higher than 26 Gy. Approximately one-fourth of these children had a concomitant low thyroxine level. In this series, 36% of children experienced spontaneous improvement in thyroid function.[149]

In a Childhood Cancer Survivor Study (CCSS), thyroid abnormalities were self-reported by 34% of patients in an era of extended-field RT. Hypothyroidism was the most common thyroid disturbance, with a relative risk of 17.1 ($P < .0001$) compared with sibling controls. Risk factors for hypothyroidism include increased dose of radiation, older age at diagnosis of HL, female sex, and Caucasian race.[150] However, work from the CCSS has also demonstrated a lower risk of hypothyroidism with lower radiation doses that are typical of modern HL treatment.[151,152]

The incidence of hypothyroidism varies, but it is directly related to radiation dose. No threshold radiation dose has been observed that is associated without a risk of hypothyroidism.[153] Therefore, thyroid exposure should be minimized when feasible to reduce the risk of hypothyroidism, and dose constraints specific to the lymphoma population should be used.[154,155]

Pelvis

Gonadal toxicity, including infertility and impaired secretion of sex hormones, is a potential complication of pelvic RT. In women, irradiation of the pelvis can affect the ovaries, resulting in premature menopause or impaired fertility. In a report by the Late Effects Study Group, 42% of female survivors of HL treated with alkylating agent chemotherapy and subdiaphragmatic radiation had experienced menopause by 31 years of age, compared with 5% of control subjects.[156] In childhood cancer survivors who continued to have spontaneous menses more than 5 years after their cancer diagnosis, the cumulative incidence of nonsurgical menopause was 8% by 40 years of age, representing a 13-fold higher risk compared with a sibling control group. Risk factors for premature menopause included exposure to increasing doses of ovarian radiation, increasing exposure to alkylating agents (based on the number of agents and cumulative dose), and diagnosis of HL.[157] In an effort to preserve ovarian function, the ovaries can be transposed via oophoropexy to increase their distance from the site to be irradiated. Normal pregnancies, without increased risk of fetal spontaneous abortion or birth defects, have been reported after pelvic irradiation.[158]

In boys irradiated to the pelvis, oligospermia is common, but it is reversible in most cases if the radiation dose scattered to the testes is low.[159] Permanent oligospermia may occur, however, after higher dose testicular irradiation.[159] Alkylating agent chemotherapy may also impact fertility. Several investigations have demonstrated that fertility is compromised in boys treated with gonadotoxic chemotherapy combinations like COPP, even when the cycles of alkylating agent chemotherapy are limited.[112,160] Anthracycline-based regimens such as ABVD (or a similar hybrid) are associated with

recovery of spermatogenesis after a temporary period of azoospermia.[161,162] In the modern treatment era, risk-adapted strategies seek to reduce or eliminate gonadotoxic treatments, resulting in excellent potential to preserve fertility in boys.[17] For male patients at risk of infertility, early oncofertility counseling and discussion of sperm banking are recommended.

Secondary Malignant Neoplasms

Survivors of HL are at risk for developing secondary malignancies including leukemias and solid tumors, most commonly breast, thyroid, bone, and soft tissue cancers. The risk of leukemia, which exhibits a peak frequency in the first 5 to 10 years after treatment, is associated primarily with the use of alkylating agents and etoposide.[163,164] In contrast, the risk of developing a second solid tumor increases with time after therapy, with a latency usually exceeding 10 years from diagnosis, and the risk is associated with radiation dose and field size.[165] In survivors treated with historical radiation approaches, the 15-year actuarial risk of second malignant neoplasms ranged from 8% to 15%.[96,103,130,163,164,166-169]

Several studies revealed an increased ratio of observed to expected second tumors for female survivors compared with males.[170-172] A large portion of this risk in females results from breast cancer. This increased risk of breast cancer is related to the patient's pubertal status at the time of RT and to the radiation dose and field size.[173,174] Historical extended fields included a substantial amount of breast tissue that was exposed to full-dose RT. Based on data from survivors who were treated with historic radiation techniques, a female survivor of HL who was treated at 25 years of age with thoracic RT of 40 Gy or greater, without alkylating agents, had an estimated cumulative risk of breast cancer of 1.4%, 11.1%, and 29.0% by 35, 45, and 55 years of age, respectively.[173] Breast tissue exposure was most significant when the axillae were irradiated in a typical mantle field, as opposed to the mediastinal and hilar region.

With modern RT, breast exposure is lower, translating into a reduced risk of secondary breast cancer. The practice of prophylactically irradiating the axillae is no longer performed, and, thus, the volume of breast tissue exposed to RT using ISRT or INRT approaches is substantially less. Using CT-based planning, the breast tissue can be contoured as an avoidance structure and dose to the breasts can be minimized, a practice that was not used with older radiation approaches. The risk of secondary breast cancer is lower in survivors who receive RT using modern techniques. In a population-based study of female survivors of HL who received treatment before 50 years of age, the risk of secondary breast cancer was significantly elevated after historic mantle RT; however, after modern "small field" RT, the risk was no greater than after chemotherapy alone.[175] Similarly, several other studies have demonstrated that smaller RT field sizes are associated with a lower risk of secondary breast cancer in survivors.[175-177]

As described earlier, historic, high-dose, large-field RT was associated with an elevated risk of serious, late adverse events.[3,96,130,137,140,141,177-183] This risk has declined significantly with temporal changes in the therapeutic management of HL.[184] Evolution in the use of RT has contributed, and decreased risks of late effects have been associated with reductions in RT dose and field size.[184] These findings support the use of the contemporary risk- and response-adapted treatment algorithms that are described later.

Modern Risk- and Response-Adapted Therapy for Classic Hodgkin Lymphoma

Contemporary therapy for pediatric HL using either chemotherapy alone or combined modality therapy produces long-term DFS in 85% to 100% of patients.[11-17,88,89] Multiagent chemotherapy alone is an effective treatment approach for many patients with pediatric HL[8,9,99,185-187] A chemotherapy alone paradigm eliminates the risk of radiation-specific toxicities; however, regimens may require more cycles and/or higher doses of chemotherapy, placing patients at an increased risk of chemotherapy-related toxicity. Furthermore, chemotherapy alone may be less effective than combined modality therapy for the treatment of higher risk disease.[9,188]

The sequence of therapy in the setting of combined chemotherapy and RT generally utilizes chemotherapy as the first modality. This allows assessment of chemotherapy response, maximization of the amount of systemic treatment, and shrinkage of disease, enabling more limited radiation fields. Rarely,

focal RT prior to chemotherapy is necessary because of significant symptoms, such as airway compression or symptomatic SVC syndrome. Typically in this setting, a low dose of radiation is used to palliate symptoms while maintaining the ability to deliver RT with curative intent later, if needed.

Current recommendations for therapy follow a risk- and response-adapted approach. Risk factors at presentation include B symptoms, mediastinal and peripheral lymph node bulk, extranodal extension of disease, and higher Ann Arbor stage. The most recent COG risk stratification defines patients into risk groups as follows:

- Favorable risk: stages IA and IIA without bulk
- Intermediate risk: stages I to IIA with bulk, I to IIAE, I to IIB, and IIIA
- High risk: stages IIB with bulk, IIIB, and IV

In Europe, the EuroNet cooperative group most recently has categorized patients into treatment groups (TGs) as follows[108]:

- TG-1: stages IA/B and IIA, without bulk 200 mL or higher or ESR 30 mm/h or greater
- TG-2: stages IEA/B, IIEA, IIB, IIIA, and IA/B and IIA with bulk 200 mL or higher or ESR 30 mm/h or greater
- TG-3: stages IIEB, IIIEA/B, IIIB, or IVA/B

The response to chemotherapy as assessed on CT and FDG-PET after two cycles of therapy is a significant prognostic factor.[189] As a result, a series of trials have explored if early response during conventional chemotherapy can be used to guide a reduction or intensification of therapy, as described later and summarized in Table 97.5. In addition, imaging at interim time points or at the end of planned chemotherapy can be used to direct the use of consolidative RT in disease that is less sensitive to chemotherapy alone.

Low-Risk Classic Hodgkin Lymphoma

Low-risk disease is defined differently by various clinical trial groups,[64] but it generally comprises patients with localized stages I and II disease without adverse prognostic features like bulk or B symptoms. Treatment typically involves two to four cycles of chemotherapy with or without low-dose ISRT. Patients with low-risk disease are the natural group in which to consider de-escalation of therapy because of their excellent outcomes.

In some regimens, RT has been dose reduced or eliminated based on a favorable response to chemotherapy. Early investigations of response-based therapy in the French Society of Pediatric Oncology MDH90 trial included 202 children with stage I/II HL.[106] Patients were treated with four cycles of vinblastine, bleomycin, etoposide, and prednisone and then a CT was obtained to assess response to therapy. A good response was defined as at least a 70% reduction in tumor size. Good responders received 20 Gy RT to initially involved fields. The remaining patients (poor responders) were given one or two more cycles of chemotherapy and were evaluated after each cycle. If they remained poor responders, then RT was administered to 40 Gy. If the response after additional chemotherapy exceeded 70%, then they received 20 Gy to involved fields. Eighty-five percent of patients were good responders, and the overall 5-year OS and EFS of the entire cohort were 97.5% and 91.1%, respectively. These results were comparable to the prior French Society of Pediatric Oncology (MDH82) in which all patients received chemotherapy consisting of alkylating agents and anthracyclines followed by RT.[190]

The GPOH successfully omitted RT in patients with early-stage disease who achieved a complete response (CR) to chemotherapy. This group pioneered the use of risk- and gender-adapted chemotherapy, according to which males received OEPA to limit alkylator exposure, and females received OPPA. After two cycles, a CR was defined as a volume reduction of 95% or more and 2 mL or less residual volume. In the GPOH-HD 95 trial, 20% of patients in TG-1 fell into this category of complete responders and were assigned to receive no RT. There was no difference in outcome between favorable-risk patients treated

with chemotherapy alone and those treated with combined modality therapy. Notably, the cohort consisted of cHL and NLPHL.[188] These outcomes were confirmed in the GPOH-HD 2002 study that excluded patients with NLPHL. In this study, for patients in TG-1, RT was omitted if they achieved a CR after two cycles of OEPA or OPPA, as defined in the prior GPOH-HD 95 study. All other patients were treated with IFRT to 19.8 Gy. A boost was given if less than 75% tumor reduction was noted (total 30 Gy) or residual disease measured greater than 100 mL (total 35 Gy). In TG-1, 5-year EFS was 92% and was similar in patients who did not receive RT (93%) and those who did receive RT (92%).[17]

The subsequent EuroNet-PHL-C1 incorporated PET for response assessment. The study investigated whether RT can be omitted in patients with an adequate anatomic and metabolic response to OEPA. Patients with newly diagnosed stage IA, IB, and IIA cHL were assigned to TG-1. They received two cycles of OEPA. Then, patients with an inadequate response by PET/CT received IFRT to a total dose of 19.8 Gy, whereas patients with an adequate response were observed. An adequate response was defined as at least 50% reduction in tumor volume and FDG-avidity that did not exceed mediastinal blood pool uptake (for residual volumes ≥2 cm in maximum diameter) or background uptake (for residual volumes <2 cm in largest diameter). The primary objective of the study was to maintain a 5-year EFS rate of 90% with omission of RT in patients with an adequate response to OEPA. In an intention-to-treat analysis of the 440 patients who achieved an adequate response, 5-year EFS was 86.5% (95% confidence interval [CI]: 83.3-89.8), which was just below the 90% target rate. In a per- protocol analysis of patients with an adequate response, 5-year EFS was 87.1% (95% CI: 83.9-90.3), which met the 90% target rate. In the 273 patients with an inadequate response who received RT, 5-year EFS was 88.6% (95% CI: 84.8-92.5), for which the 95% CI included the 90% target rate. Patients with risk factors, defined as ESR 30 or greater or bulky mass 200 mL or greater, were found to have an increased risk of disease relapse. Based on this finding, the protocol was amended so patients with these adverse features were assigned to TG-2. The authors concluded that RT could be omitted in patients with early-stage cHL and an adequate response to OEPA, but patients with risk factors might need more intensive treatment.[11]

In addition, several North American studies have demonstrated excellent results using response-adapted combined modality therapy for favorable-risk HL. Investigators from Stanford University Medical Center, St Jude Children's Research Hospital, and Dana-Farber Cancer Institute reported results using a nonalkylator regimen, VAMP (vinblastine, doxorubicin, methotrexate, and prednisone), for children with clinical stage I/II, nonbulky HL, including cHL and NLPHL.[89] Following four cycles of VAMP, patients were treated with 15 Gy IFRT if they achieved a CR or 25.5 Gy if they had a partial response after two cycles of VAMP. At a median follow-up of 9.6 years, 5- and 10-year EFS rates were 92.7% and 89.4%, respectively.

The POG evaluated the feasibility of combined modality therapy using four courses of DBVE (doxorubicin, bleomycin, vincristine, and etoposide) followed by IFRT to 25.5 Gy to treat stages IA, IIA, and IIIA HL.[136] At a median follow-up of 8.4 years, nearly all patients (98%) achieved a complete remission, and 6-year OS and EFS rates were 98% and 91%, respectively. This DBVE regimen was used by the POG and the COG to support reduction of chemotherapy via an early response-based treatment algorithm evaluated on P9426.[191] Patients received only two courses of DBVE if they achieved an early CR (45% of all patients) versus four courses of DBVE if they were slower responders. All patients were treated with IFRT to 25.5 Gy. Five-year OS and EFS were 98% and 88%, respectively.

The CCG trial 5942 compared a chemotherapy-alone regimen to a risk-adapted combined modality treatment approach with low-dose IFRT in low-risk disease achieving a CR. Patients were treated with COPP/ABV. Those achieving a CR to chemotherapy were randomized to receive low-dose IFRT or no further therapy. Given a significantly higher number of relapses in patients who were treated with chemotherapy alone, the trial was terminated early.[192] Of note, this trial used less intensive chemotherapy compared to most contemporary trials.

To better select low-risk patients with cHL who may benefit from the omission of RT, the COG AHOD0431 single-arm study incorporated interim PET-CT when possible to assess disease response and identified a group of very early responders (negative PET scan after one cycle, PET1) who may have

favorable outcomes even without adjuvant RT. Two hundred and eighty-seven stage IA/IIA patients were treated with three cycles of AV-PC. Those who achieved a CR after three cycles received no further therapy, whereas partial responders received 21 Gy IFRT. In the initially reported results, 2-year OS was 100%; however, 2-year EFS for those with CR to chemotherapy and no RT was 80% compared to 88% in those with partial response who received IFRT ($P = .11$). A subset analysis suggested the utility of PET1 in identifying patients who may be treated without RT after three cycles of AV-PC. Of the patients with a CR who did not receive RT, the 2-year EFS rate for those with a positive/equivocal PET1 versus those with a negative PET1 was 65% compared to 87% ($P = .005$). Similarly, 2-year EFS in partially responding patients with a positive/equivocal PET1 versus a negative PET1 was 82% versus 96% ($P = .047$).[193] The 4-year EFS rate was 79.9% overall, with superior EFS in those with a partial response or stable disease who received RT (82.8%) compared to those with a CR who did not receive RT (77.5%), although this difference was not statistically significant. The 4-year OS rate was 99.6%, emphasizing the efficacy of salvage therapy in this patient population. The value of PET1 persisted with longer follow-up. Patients with a negative PET1 had a significantly improved 4-year EFS (88.2% vs 68.5%).[87] These data highlight the importance of the interim FDG-PET scans when evaluating early-stage, low-risk patients for response-adapted therapy.

Intermediate-Risk Classic Hodgkin Lymphoma

Patients with stages IA and IIA disease with unfavorable features, including bulk and extranodal extension, and with stage IIIA disease are grouped into an intermediate-risk category. Treatment typically involves four cycles of chemotherapy and possible low-dose ISRT based on the risk factors and response to chemotherapy. As in low-risk disease, RT is generally dose reduced or eliminated based on a favorable response to chemotherapy.

In the GPOH-HD 2002 study, all patients received two cycles of chemotherapy (OEPA for males and OPPA for females), then intermediate-risk patients (TG-2) received two cycles of COPP for females and COPDAC for males. Subsequently, patients in TG-2 were treated with IFRT to 19.8 Gy with possible boosts as described earlier. In TG-2, 5-year progression-free survival (PFS) was 93%.[17]

In the EuroNet-PHL-C1 study, patients in TG-2 received two cycles of OEPA, then two cycles of COPP or COPDAC. RT was omitted for patients with an adequate response at early response assessment after two cycles of OEPA, with an adequate response defined as at least 50% reduction in tumor volume and PET negativity. All other patients received RT to 19.8 Gy targeting all initially involved sites of disease, with possible boosts as described earlier. In both adequate responders who did not receive RT and inadequate responders who were scheduled for RT, 5-year EFS was approximately 90%. The authors concluded that RT can be omitted in patients with an adequate early response to therapy, when consolidated with COPP or COPDAC.[12]

North American cooperative groups have completed two trials to evaluate a response-based approach. The first, POG9425, evaluated the prospect of reducing the number of chemotherapy cycles based on response to therapy.[107] The second, AHOD0031, evaluated a regimen to omit RT in patients with a RER and CR to chemotherapy and to intensify therapy for those with an SER.[16]

In POG9425, intermediate- and high-risk patients received three or five cycles of ABVE-PC followed by 21 Gy regional (mantle, para-aortic, or pelvic) RT for RER and SER, respectively. There was no difference in EFS between the two groups, demonstrating the efficacy of a response-based approach.[107]

The COG study AHOD0031 was a randomized trial comparing standard and response-based treatment for omission of RT or augmentation of systemic therapy in intermediate-risk cHL and NLPHL. Early response to therapy was assessed by CT scan, and CR status was determined by CT and gallium or FDG-PET scan. All 1,712 patients received two cycles of ABVE-PC followed by early response assessment. At this time point, an RER was defined as a reduction in tumor size by at least 60% in the product of the perpendicular diameters or return to normal size. Patients with an RER received two additional cycles of ABVE-PC followed by a second response assessment. At this point, a CR was defined as at least 80% reduction in the product of the perpendicular diameters, no extramediastinal mass larger than 2 cm in

maximum diameter, and PET or gallium negativity. Patients with an RER and subsequent CR were randomized to receive 21-Gy IFRT or no further therapy. Patients with an RER who did not have a CR were nonrandomly assigned to receive IFRT. Patients with an SER were randomized to either two additional cycles of ABVE-PC or intensified therapy with dexamethasone, etoposide, cisplatin, and cytarabine (DECA) followed by an additional two cycles of ABVE-PC. All patients with an SER received 21-Gy IFRT after chemotherapy. Four-year EFS rates were 85% overall, and 86.9% for patients with an RER versus 77.4% for those with an SER ($P < .001$). The 4-year OS for the entire cohort was 97.8%, and 98.5% for patients with an RER versus 95.3% for those with an SER ($P < .001$). The 4-year EFS rate was 87.9% for patients with an RER/CR randomized to receive IFRT versus 84.3% for those randomized to no IFRT ($P = .11$).[16] Thus, the results of AHOD0031 suggest that early response to chemotherapy is a powerful predictor of outcome that can help optimize subsequent treatment and that RT may be omitted for patients with an RER and CR after four cycles of ABVE-PC.

As PET was emerging at the time of the AHOD0031, FDG-PET was not required, but an interim PET after two cycles of ABVE-PC (PET2) was obtained in 1,135 (66%) patients, of whom 746 were eligible for the two random assignments in the study. Of the 550 patients with available PET2 imaging who had an RER/CR, there was no difference in EFS with versus without IFRT in those with a negative PET2 (86.7% vs 87.3%; $P = .87$) or a positive PET2 (83.1% vs 78.1%; $P = .80$). Of the 196 patients with SER with available PET2 results, there was no difference in EFS in patients treated with versus without DECA when PET2 was negative (90.1% vs 85.6%; $P = .54$). However, among patients with SER and PET2-positive results, EFS was marginally superior with DECA versus without DECA (70.7% vs 54.6%; $P = .05$).[16] A secondary analysis of PET response after two cycles of ABVE-PC demonstrated that PET may further assist with treatment optimization.

In a secondary analysis of the patterns of failure of AHOD0031, relapses commonly occurred in previously involved disease sites (94% of relapses) and within the irradiated fields, suggesting that INRT or ISRT target volumes may be sufficient and that larger IFRT volumes might not be necessary. In addition, recurrences occurred in both bulky and nonbulky initial sites of disease, suggesting that in intermediate- risk HL, irradiation of bulky sites alone may not be the optimal treatment strategy.[194]

High-Risk Classic Hodgkin Lymphoma

The criteria for high-risk HL are typically restricted to stage III or IV disease, often with “B” symptoms and/or extranodal extension to contiguous structures. Historically, chemotherapy was administered over the course of 6 to 8 months on a twice-monthly schedule.[7,8,107,195,196] An alternative strategy condenses the chemotherapy component of treatment into 3 to 5 months to enhance dose intensity and reduce the risk of developing resistant disease. RT for high-risk HL is variable and protocol dependent.

As in the cases of other risk groups, there is increasing interest in developing a response-adapted treatment approach for children with high-risk HL. In the GPOH-HD 95 trial outlined previously, RT was omitted in patients achieving a CR after OEPA-COPP chemotherapy.[197] PFS for high-risk patients who experienced a CR and did not receive RT was significantly lower than in patients without a CR who received RT ($P = .01$). This study highlighted the need for more refined criteria and modalities for response assessment than those used on GPOH-HD 95 to successfully identify patients for whom treatment RT may be omitted.[197]

The subsequent GPOH-HD 2002 and EuroNet-PHL-C1 studies, described earlier, established less gonadotoxic chemotherapy regimens and omission of RT in patients with an adequate early response to therapy.[12,17] In the most recent trial, EuroNet-PHL-C1, described earlier, patients in TG-3 received two cycles of OEPA, then four cycles of COPP or COPDAC. RT was omitted for patients with an adequate response after two cycles of OEPA; patient with an inadequate early response received RT to 19.8 Gy targeting all initially involved sites of disease, with possible boosts as described earlier. In both adequate responders who did not receive RT and inadequate responders who were scheduled for RT, 5-year EFS was approximated 90%.

An assessment of a dose-intense, response-based regimen using BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) in children with high-risk disease was evaluated in the COG 59704 trial. Females with a rapid response received four cycles of COPP/ABV following BEACOPP without IFRT, and males received two cycles of ABVD and IFRT. All patients with a slow response received four additional cycles of BEACOPP and IFRT. A high 5-year EFS rate of 94% was achieved, and the 5-year OS rate was 97%. However, significant acute hematologic toxicity was observed, and two patients developed secondary leukemia.[195]

The COG AHOD0831 trial evaluated a risk- and response-adapted approach for high-risk disease. Patients were treated with two cycles of dose-dense ABVE-PC and then assigned to one of two consolidation therapy regimens based on response to induction therapy. Patients with an RER received two more courses of ABVE-PC. Those with an SER received intensification of therapy with the addition of two cycles of ifosfamide/vinorelbine followed by two courses of ABVE-PC. Patients with a continued response after completion of chemotherapy proceeded to risk-adapted RT (21 Gy in 14 fractions IFRT) delivered only to sites of initially bulky disease or SER. With this approach, 4-year EFS was 91.9%, below the ambitious, projected rate of 95%. Five-year OS was 95%. Of particular note, 8 of the 11 SER patients with persistent PET-positive lesions at the end of chemotherapy had clinical evidence of active disease by either biopsy or further progression at that site, emphasizing the value of PET-CT scans in this patient population.[15] With this treatment strategy, most relapses occurred in initially involved sites that were neither bulky nor FDG avid after two cycles of chemotherapy and, therefore, were not treated with RT.[198] These findings suggest a role for refinement of strategies to optimally identify which patients and disease sites may benefit from RT.

To examine the efficacy of the antibody-drug conjugate Bv, AHOD1331 randomized children with stage IIIB, IVA, or IVB disease to ABVE-PC or Bv-AVE-PC for five cycles. All children were evaluated by a PET-CT scan after two cycles of therapy, and disease sites with a Deauville score of 4 or 5 were deemed "slowly responding lesions." Children received 21-Gy ISRT targeting initially bulky mediastinal disease, regardless of early response, and targeting slowly responding lesions. An additional 9-Gy boost was given if the final PET after all five cycles of systemic therapy had a Deauville score of 3 to 5. Children receiving Bv experienced significantly improved 3-year EFS (92.1% vs 82.5%, $P < .001$). However, driven by protocol-specified RT to all large mediastinal adenopathy, there was no difference in utilization of RT by study arm (53.4% vs 56.8%). There was also no difference in OS at 3 years (99.3% vs 98.5%).[13]

A similar open-label single-arm study was completed at St Jude (SJCRH HLHR13). In this study, pediatric patients with stage IIB, IIIB, or IV disease were treated with AEPA/CAPDAC, with the vincristine of OEPA/COPDAC replaced with Bv or "Adcetris." RT, using limited "residual node RT," was given at the end of chemotherapy only to nodal sites that did not achieve a CR after two cycles of therapy. A CR at early response assessment was defined as a Deauville score of 1 to 3 and 75% or more reduction in the product of the perpendicular diameters. In this cohort, 35% of patients achieved a CR after two cycles and avoided RT. For the total cohort, the 3-year EFS was 97.4% and 3-year OS was 98.7%.[14]

The ongoing EuroNet-PHL-C2 trial (NCT01026220) is also evaluating a risk-stratified and response-adapted approach in children with high-risk HL. Using the Deauville score for PET response assessment, patients with an adequate response after two cycles of initial OEPA chemotherapy will not receive RT and those with an inadequate response at this time point (Deauville ≥4 or <50% volume reduction in a bulky site) will receive modified (smaller field) IFRT to 19.8 Gy with a 10-Gy boost to sites with Deauville 3 or higher at the end of all chemotherapy. All intermediate- and high-risk disease will be treated with consolidation chemotherapy based on randomization between two and four cycles of standard COPDAC-28 (cyclophosphamide, vincristine, prednisone, dacarbazine) or intensified DECOPDAC-21 (doxorubicin, etoposide, cyclophosphamide, vincristine, prednisone, dacarbazine). This study will evaluate (a) whether intensified DECOPDAC-21 consolidation chemotherapy improves EFS as compared to standard COPDAC-28 in early responders and (b) if DECOPDAC-21 combined with RT restricted to sites that remain FDG-PET positive at the end of all chemotherapy has comparable EFS compared to COPDAC-28 plus RT as in the EuroNet-PHL-C1 trial.

Nodular Lymphocyte–Predominant Hodgkin Lymphoma

NLPHL is typically indolent, with a favorable prognosis and OS rates of close to 100%. It typically presents as localized, early-stage disease. Relapses can occur many years after the end of therapy, with 10- and 15-year cumulative relapse rates of 4.8% and 8.3%, respectively. Relapsed disease is curable, and OS rates are near 100% in patients with or without relapsed disease.[199] Historically, patients with NLPHL have been treated on protocols for patients with cHL; however, there are several reports in the adult and pediatric literature suggesting that they can be cured with less aggressive therapies. Adult patients with localized disease are typically treated with RT alone to 30 to 40 Gy.[200,201] However, given the concern for late toxicity of RT in children, alternative strategies are typically used in the pediatric population.

Surgery has been considered a treatment approach for localized pediatric NLPHL that is amenable to complete resection without the need for radical lymph node dissection. Removal of just a focal lymph node(s) is sufficient. A meta-analysis of French, United Kingdom, and German trial series showed that surgery alone was a feasible option for localized disease and yielded a long-term relapse-free survival rate of 67%.[202] The COG AHOD03P1 study prospectively evaluated 52 stage IA patients who were observed after surgery only.[203] Five-year EFS was 77%, with 13 patients experiencing relapse. Twelve of these relapses were stage IA, occurring at the initially involved site or in adjacent nodes or nodal regions; one relapse was stage IIA. Nine of these patients received salvage chemotherapy with AV-PC, all achieving a CR.[203]

In patients whose disease is not amenable to complete resection, low-dose chemotherapy is an effective treatment option. On the COG study AHOD03P1, patients with unresected stage IA or IIA NLPHL were treated with three cycles of AV-PC. Patients with less than a CR received 21 Gy IFRT. Of 135 patients treated with AV-PC, only 11 had less than a CR and received IFRT. Five-year EFS was 88.8% and OS was 100%.[203]

The EuroNet conducted a clinical trial to prospectively validate a “watch-and-wait” approach for children with completely resected disease and low-dose chemotherapy for patients with residual disease after resection, and the results are pending publication (EuroNet-PHL-LP1, NCT01088750).

Refractory or Relapsed Hodgkin Lymphoma

Treatment failures in pediatric cHL typically develop within the first 3 years; however, late relapses have been reported, particularly in patients with NLPHL. The most common site of relapse following risk-adapted therapies remains an initially involved site of disease.[194,198] Generally, positive prognostic factors include a nodal site of relapse (rather than extranodal), early stage at relapse (rather than advanced), longer duration from initial treatment until relapse, favorable histology, and robust response to first-line salvage chemotherapy. The selection of the most appropriate salvage regimen is based on whether a complete remission was achieved, the durability of the remission, the extent of disease at relapse, and the intensity of the frontline therapy given. Treatment options include standard-dose chemotherapy, high-dose chemotherapy followed by autologous stem cell transplantation, clinical trials, or palliative therapy. In addition, newer agents such as Bv and nivolumab are reinduction therapy options for relapsed/refractory cHL.[204,205] RT may be incorporated into any of these strategies. When pursuing autologous stem cell transplantation, RT may also be used pre- or post-transplant depending on the clinical scenario.[206]

Because of the excellent outcome for most children and adolescents with HL, investigations regarding salvage strategy have been limited. For high-risk relapses, a combination of ifosfamide and vinorelbine for pediatric patients in first relapse was studied by the COG on the AHOD00P1 study. This regimen showed a very good overall response rate of 72% and allowed for good stem cell mobilization for future autologous stem cell transplantation once remission was achieved.[207] Similarly, ifosfamide, gemcitabine, and vinorelbine was shown to be an effective salvage regimen with an overall response rate of 100% and excellent stem cell mobilization in relapsed/refractory pediatric HL.[208] In addition, Bv and gemcitabine is a highly active combination for pediatric patients with primary refractory or high-risk relapsed HL, with a CR rate of 67% based on modern response criteria.[205]

A risk-based approach for relapsed pediatric HL was recently proposed and evaluated.[209] CheckMate 744 was a phase II trial of children, adolescents, and young adults with relapsed/refractory HL that explored a risk-stratified, response- adapted strategy. Patients with a late recurrence and limited-stage relapsed disease were stratified into the low-risk group, whereas patients with an early recurrence or extranodal disease or B symptoms at relapse were classified as standard-risk group. All patients received nivolumab plus Bv; those without a complete metabolic response then received Bv plus bendamustine intensification. Patients in the standard-risk cohort who achieved a CR proceeded to consolidation with high-dose chemotherapy and autologous stem cell transplantation. In the standard-risk cohort, a complete metabolic response was achieved in 94% of subjects, 1-year PFS was 91%, and toxicities were limited.[204] Patients in the low-risk cohort were eligible for transplant-free consolidation with RT alone. Early results for the low-risk cohort demonstrated 3-year EFS and PFS rates of 87% and 95%, respectively, suggesting that these patients may be effectively salvaged without the need for high-dose chemotherapy with autologous stem cell transplant.[210]

Future Investigations

To build on the current era of risk- and response-adapted trials in pediatric HL, future studies will focus on refining baseline and longitudinal prognostic factors. Novel features that may improve risk stratification include PET volumetric parameters[211-213] and circulating tumor DNA burden.[214] In addition, accurate identification of patients at high risk of treatment-related toxicity may one day influence tailored treatment recommendations. For example, preliminary data suggest genetic risk factors for the development of radiation-associated breast cancer[215] and anthracycline-induced cardiotoxicity.[216] Such research will enable future clinicians to develop personalized treatment recommendations that are informed by both disease and host factors. Newer drugs may offer great efficacy with less toxicity. Current studies are moving novel agents, such as Bv and checkpoint inhibitors, into upfront treatment. With future study, these agents, as well as patient stratification using recently identified disease and host risk factors, will contribute to the decades-old goal of maintaining outstanding disease control while minimizing treatment-associated toxicity for children with HL.

NON-HODGKIN LYMPHOMA

Childhood NHLs are a heterogeneous group of malignancies with variable histopathology, sites of origin, and clinical manifestations. In contrast to HL, childhood NHLs are rapidly growing, diffuse, high grade, and poorly differentiated. Extranodal involvement is common, and dissemination occurs early and often.[217] This is in striking contrast to adult NHL, in which low- and intermediate-grade nodal disease predominates.[218] The common low-grade lymphomas seen in adults, such as follicular lymphomas (FLs) and marginal zone lymphomas, are extremely rare in children. These differences in pathology and clinical behavior between children and adults explain the markedly different clinical presentations, staging practices, and treatment strategies between age groups.

Epidemiology

In the United States, approximately 800 children and adolescents younger than 20 years of age are diagnosed with NHL every year, compared to 60,000 adult cases. According to the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute, NHL accounts for about 8% of all cases of childhood cancer.[219] Compared to HL, NHL is more common in very young children and less common in adolescents. The incidence of NHL is higher in males than in females (ratio of 3-1) and in Caucasians than in African Americans (ratio of 1.5-1).

Although NHL is associated with several genetic and environmental factors, its cause and pathogenesis remain unclear. A small proportion of cases are seen in association with inherited immunodeficiencies (eg, Wiskott-Aldrich syndrome, X-linked lymphoproliferative disease [XLP], ataxia-telangiectasia, and

common variable immunodeficiency) or acquired immunodeficiencies (eg, HIV infection or immunosuppressive therapy in patients receiving solid organ or bone marrow transplants).[217] Given these associations, a comprehensive medical and family history should be obtained at diagnosis with referral to a geneticist for any concerns; treatment is influenced by certain syndromes, such as XLP in which allogeneic bone marrow transplantation is needed, and implications for testing siblings should be considered.

Geographic variation exists in the incidence and pathogenesis of NHL. For example, EBV infection is present in the majority of endemic Burkitt tumors in equatorial Africa, but it occurs in only 10% to 15% of sporadic cases outside Africa. Data suggest a significant role for EBV in lymphomagenesis leading to the development of the same oncogenic chromosomal translocations as those observed in non–EBV-associated sporadic cases of Burkitt lymphoma (BL).[220-222] EBV infection is also associated with the development of post-transplant lymphoproliferative disease, a B-cell disorder seen in patients after solid organ or hematopoietic stem cell transplantation.[223,224]

Pathologic Classification

Pediatric NHL cases are divided into four major histopathologic subtypes based on morphology and immunophenotype: (a) Burkitt leukemia or lymphoma; (b) lymphoblastic lymphoma (LL), including B-cell LL (B-LL) and T-cell LL (T-LL); (c) large B-cell lymphoma, including diffuse large B-cell lymphoma (DLBCL) and primary mediastinal (thymic) large B-cell lymphoma (PMBCL); and (d) anaplastic large cell lymphoma (ALCL).[217] The distribution of histologies is shown in Table 97.6.

TABLE 97.6 CLINICAL CHARACTERISTICS OF CHILDHOOD NON-HODGKIN LYMPHOMA

Histologic Subtype	Proportion of Cases (%)	Most Common Sites of Presentation
Burkitt lymphoma	35-40	Abdomen or head and neck
T-lymphoblastic lymphoma	15-20	Mediastinum
B-lymphoblastic lymphoma	3	Cutaneous masses, isolated nodes, and bone
Diffuse large B-cell lymphoma	15-20	Nodes, abdomen, and bone
Primary mediastinal B-cell lymphoma	1-2	Mediastinum
Anaplastic large cell lymphoma	15-20	Skin, nodes, and bone

Adapted from Sandlund JT. Childhood lymphoma. In: Abeloff MD, Armitage JO, Lichter AS, et al, eds. *Clinical Oncology*. 2nd ed. Churchill Livingstone; 2000:2438. Copyright © 2000 Elsevier. With permission.

The classification of NHL by the WHO was updated in 2016[225] and increasingly incorporates immunophenotype and cytogenetics into diagnostic, prognostic, and therapeutic decision-making. Several noteworthy changes with respect to pediatric NHL exist in the updated WHO classification. Pediatric-type FL became a distinct subtype from adult variants.[217,225,226] It is characterized by large, expansile, highly proliferative follicles that often have prominent blastoid follicular center cells, rather than classic centroblasts, and lack MYC, BCL6, and BCL2 rearrangements; however, BCL2 protein may be expressed. Large B-cell lymphoma with IRF4 rearrangement, which commonly occurs in children and young adults, was added as a new provisional entity. Most of these cases have IG/IRF4 rearrangements, some with BCL6 rearrangements, but they uniformly lack BCL2 rearrangements. These lymphomas typically occur in Waldeyer ring and/or cervical lymph nodes and are more aggressive than other pediatric-type FL. Burkitt-like lymphoma with 11q aberration was added as a provisional entity to distinguish a subset of lymphomas that have more complex karyotypes, lack MYC rearrangements, and have lower levels of MYC expression than BLs. Instead, this subtype is notable for chromosome 11q changes with proximal gains and telomeric losses, but the clinical course appears similar to BL.[227,228]

The identification of large numbers of monoclonal antibodies directed against surface antigens permitted subclassification of many NHL subtypes according to immunophenotype, as summarized in Table 97.7.[229] Thorough evaluation of histology and immunophenotype is critical to the diagnosis,

prognosis, and selection of therapy. Cytogenetic analysis and identification of molecular markers provide a more precise means to characterize these tumors and will likely provide insights into pathogenesis and potential novel therapeutic approaches.

TABLE 97.7 IMMUNOPHENOTYPIC, CYTOGENETIC, AND MOLECULAR MARKERS OF PEDIATRIC NHL

Histology and Frequency						
		LBCL (10%-15%)		LL (20%-25%)		
Marker	BL (50%-60%)	DLBCL	PMBCL	B-LL	T-LL	ALCL (10%-12%)
Immunohistochemistry[a]						
MIB1	~100%	40%-90%	30%-90%	Not informative	Not informative	Not informative
CD10	+	+/−	−/+	+/−	+/−	−
CD19	+	+	+	+	−	−
CD20	+	+	+	+/−	−	−
CD79a	+	+	+	+	−	−
sig	+	+/−	−	−	−	−
Bci-6	+	+/−	+/−	−	−	+/−
MUM1	−	−/+	+	−	−	−
MAL	−	−/+	+	−	−	−
TdT	−	−	−	+	+	−
cCD3	−	−	−	−	+	−/+
CD4	−	−	−	−	+/−	−/+
CD8	−	−	−	−	+/−	−/+
CD7	−	−	−	−	+	−/+
CD5	−	−/+	−	−	+/−	+/−
CD30	−	[b]	+/−	−	−	+
ALK	−	[c]	−	−	−	+
Cytogenetic	*t*(8;14)(q24;q32)*t*(2;8)(p12;q24)*t*(8;22)(q24;q11)	R8q24 (~30%)	Few data	Few data	Translocations involving 14q11-13; few other data	*t*(2;5)(p23;q35) > 90% or variants involving 2p23
Molecular biology	*MYC/IGH IGK/MYC MYC/IGL*		Nuclear factor-κB pathway dysregulation	*IGH/TCR* rearrangements	*NOTCH/FBXW7, PTEN IGH/TCR* rearrangements	*NPM/ALK* > 90% or variants

Other NHLs, such as peripheral T-cell lymphoma, extranodal natural killer/T-cell lymphoma, nasal type, and pediatric follicular lymphoma, represent less than 5% of pediatric NHLs and are not indicated in the table.

ALCL, anaplastic large cell lymphoma, ALK positive; BL, Burkitt lymphoma; B-LL, B-cell lymphoblastic lymphoma; DLBCL, diffuse large B-cell lymphoma; LBCL, large B-cell lymphoma; NHL, non-Hodgkin lymphoma; PMBCL, primary mediastinal (thymic) large B-cell lymphoma; T-LL, T-cell lymphoblastic lymphoma.

[a]+, more than 90% of patients; +/−, more than 50% of patients; −/+, less than 50% of patients; −, less than 10% of patients.

[b]Positive especially in the rare anaplastic variant.

[c]Positive in the ALK-positive LBCL.

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Clinical Presentation

The clinical presentation of NHL varies according to the site of involvement, but often children present in distress. A mediastinal mass is present in 25% of children with NHL and is commonly associated with T-LL, DLBCL, and PMBCL.[230] Due to the rapid onset of the mediastinal masses, they often cause respiratory symptoms (eg, cough, wheezing, shortness of breath, and orthopnea) due to airway compression and can cause neck, face, and upper extremity swelling due to obstruction of the SVC. Hemodynamic compromise may also occur because of pericardial effusions. Due to rapid tumor growth, patients may experience an acute decline in 12 to 24 hours without initiation of therapy.

The NHL subtypes have typical presentations. For example, the majority (50%-70%) of children with precursor T-LL present with rapidly enlarging neck and large mediastinal lymphadenopathy and pleural effusions.[231,232] However, children and adolescents with precursor B-LL tend to have limited disease in sites such as skin, bone, and peripheral lymph nodes.[233] DLBCL frequently presents with nodal disease, although bone involvement is also relatively common.[231,234] PMBCL typically presents with signs and symptoms related to a large mediastinal mass and, often, pleural effusions.

Sites of involvement differ in sporadic compared to endemic BL. In sporadic BL, the abdomen is the most common site of disease involvement, and patients often present with abdominal pain, distension, a palpable mass, nausea, vomiting, and gastrointestinal bleeding. Bone marrow involvement is seen in about 20% of patients with sporadic BL.[235] However, in endemic BL, jaw involvement is most common, and bone marrow involvement is rare.[236]

ALCL may be systemic or cutaneous. In systemic disease, peripheral, mediastinal, and intra-abdominal nodal involvement, extranodal disease, and B symptoms are common. A translocation resulting in the fusion of the anaplastic lymphoma kinase (*ALK*) gene to one of several partners occurs in more than 90% of patients. Conversely, primary cutaneous ALCLs usually lack the ALK translocation, remain confined to the skin, and follow a more indolent course.[217]

Diagnostic Evaluation

Tissue diagnosis, imaging, and often BMB should be completed expeditiously to determine the extent of disease. Histology, immunophenotype, karyotype, and molecular studies are vital to identifying the optimal treatment plan, which should be initiated urgently due to the rapid growth rate of most pediatric NHL.[217] It is, therefore, critical that an adequate quantity of tissue be obtained at biopsy by performing an excisional biopsy, ideally, or a core-needle biopsy, if an excisional biopsy is not possible. Steroid use before a biopsy may be necessary in the case of a symptomatic mass to achieve clinical stability, but it may result in rapid shrinkage and necrosis, complicating the establishment of a tissue diagnosis.[237,238] Therefore, every attempt should be made to obtain a biopsy before steroids are administered. If steroids must be started emergently, then a biopsy should be obtained as soon as possible to have the greatest chance at making a diagnosis.

BMB has been a standard component of NHL staging and diagnosis (ie, Burkitt leukemia vs lymphoma or T-LL and B-LL vs acute lymphoblastic leukemia [ALL]). In DLBCL, FDG-PET-CT has been shown to be more sensitive for detecting marrow involvement than BMB, but PET may miss low-volume disease when less than 10% to 20% of the marrow is involved.[239,240] Therefore, in pediatric patients with DLBCL, FDG-PET-CT indicating bone marrow involvement is typically sufficient for diagnosis, and BMB may not be required. If the PET is negative for bone marrow involvement in DLBCL, however, a BMB should be recommended, particularly if the presence of bone marrow disease would influence management. For all other NHL histologies, a 2.5-cm unilateral BMB, along with immunohistochemistry and flow cytometry, is still considered standard practice because there are not conclusive data guiding the utility of PET.[57,58]

PET-CT is strongly encouraged for staging FDG-avid NHL.[57,58] Contrast-enhanced CT is indicated for all non–FDG-avid histologies. The FDG-avidity of the different NHL subtypes is summarized in Table 97.8.

TABLE 97.8 FDG-AVIDITY OF NHL ACCORDING TO WHO CLASSIFICATION

Histology	Number of Patients	FDG Avid (%)
HL	489	97-100
DLBCL	446	97-100
FL	622	91-100
Mantle cell lymphoma	83	100
Burkitt lymphoma	24	100
Marginal zone lymphoma, nodal	14	100
Lymphoblastic lymphoma	6	100
Anaplastic large T-cell lymphoma	37	94-100[a]
NK/T-cell lymphoma	80	83-100
Angioimmunoblastic T-cell lymphoma	31	78-100
Peripheral T-cell lymphoma	93	86-98
MALT marginal zone lymphoma	227	54-81
Small lymphocytic lymphoma	49	47-83
Enteropathy-type T-cell lymphoma	20	67-100
Marginal zone lymphoma, splenic	13	53-67
Marginal zone lymphoma, unspecified	12	67
Mycosis fungoides	24	83-100
Sézary syndrome	8	100[b]
Primary cutaneous anaplastic large T-cell lymphoma	14	40-60
Lymphomatoid papulosis	2	50
Subcutaneous panniculitis-like T-cell lymphoma	7	71
Cutaneous B-cell lymphoma	2	0

DLBCL, diffuse large B-cell lymphoma; FDG, [^{18}F]fluorodeoxyglucose; FL, follicular lymphoma; HL, Hodgkin lymphoma; MALT, mucosa-associated lymphoid tissue; NK, natural killer.

[a]Only 27% of cutaneous sites.

[b]Only 62% of cutaneous sites.

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Laparotomy is no longer indicated for staging of lymphomas. MRI may be helpful in detecting disease at specific sites, particularly the CNS, and should be considered in appropriate cases.

Staging Systems

The Ann Arbor staging system,[63] commonly used in adult NHL, has limited prognostic value in pediatric NHL because of the often-disparate clinical presentation and disease course in children, the higher incidence of extranodal primary sites and CNS involvement, and the infrequent evolution into frank leukemia. The Lugano lymphoma staging classification similarly focuses on adult lymphomas.[57] In the 1980s, the Murphy/St Jude Children's Research Hospital staging system was introduced specifically for pediatric NHL. This system incorporates the extent of disease and clinical patterns.[217] Since the introduction of the Murphy/St Jude staging system, the pathologic classification of NHL has changed significantly. New subtypes of pediatric NHL have been identified, some of which display unique patterns of organ involvement, including the mucosa, skin, bone, ovary, and kidney. Therefore, a Revised International Pediatric NHL Staging System Classification was developed by a multidisciplinary,

international consortium that incorporates new histologic entities, extent of extranodal dissemination, and modern diagnostic methods and imaging techniques, as shown in Table 97.9. This revised staging system will enable more precise, reproducible comparisons of treatment efficacy across cooperative groups.[241]

TABLE 97.9 STAGING AND GROUPING SYSTEM FOR CHILDHOOD NON-HODGKIN LYMPHOMA

Stage	Murphy Staging System[218]	International Pediatric Non-Hodgkin Lymphoma Staging System[241]
I	Single EN tumor or single anatomic N area, excluding the mediastinum or abdomen	Single tumor excluding the mediastinum or abdomen (N; EN; B or S: EN-B, EN-S)
II	Single EN tumor with regional lymph node involvement Two or more N areas on the same side of the diaphragm Two single EN tumors + regional node involvement on the same side of the diaphragm Primary GI tract tumor (usually in ileocecal area), + involvement of associated mesenteric nodes only	Single EN tumor with regional node involvement Two or more N areas on the same side of the diaphragm Primary GI tract tumor (usually in ileocecal area), + involvement of associated mesenteric nodes, that is completely resectable (if malignant ascites or extension of tumor to adjacent organs, it should be regarded as stage III)
III	Two single EN tumors on opposite sides of the diaphragm Two or more N areas above and below the diaphragm All primary intrathoracic tumor (mediastinal, pleural, thymic) All extensive primary intra-abdominal disease including disease with spread via lymphatics to para-aortic and retroperitoneal nodes via intraperitoneal dissemination to form implants and plaques along the mesentery or peritoneum, or by direct infiltration of structures adjacent to primary tumor. Ascites may be present, and complete resection of all gross tumor is not possible. All paraspinal or epidural tumors, regardless of other tumor sites	Two or more EN tumors (including EN-B or EN-S) above and/or below the diaphragm Two or more N areas above and below the diaphragm Any intrathoracic tumor (mediastinal, hilar, pulmonary, pleural, or thymic) Intra-abdominal and retroperitoneal disease, including liver, spleen, kidney, and/or ovary localizations, regardless of degree of resection (except primary GI tract tumor [usually in ileocecal region] involvement of associated mesenteric nodes that is completely resectable) Any paraspinal or epidural tumor, regardless of whether other sites are involved Single B lesion with concomitant involvement of EN and/or nonregional N sites
IV	Any of the above with initial CNS or BM involvement (<25% blasts)	Any of the above findings with initial CNS involvement (stage IV CNS), BM (stage IV BM), or both (stage IV combined) based on conventional methods
Group Classification in the B-Cell Lymphomas[242]		
A	Completely resected stage I or completely resected abdominal stage II lesions	
B	All cases not eligible for group A or group C (Murphy stage III and non-CNS stage IV)	
C	Any CNS involvement and/or bone marrow involvement ≥25% blasts. For CNS involvement, one or more of the following applies: 1. Any L3 blasts in CSF 2. Cranial nerve palsy (if not explained by extracranial tumor) 3. Clinical spinal cord compression 4. Isolated intracerebral mass 5. Parameningeal extension: cranial and/or spinal	

B, bone; BM, bone marrow; CNS, central nervous system; CSF, cerebrospinal fluid; EN, extranodal; N, nodal; S, skin.

Prognostic Factors

Stage is the most important prognostic factor in childhood NHL and accounts for other known prognostic variables, including tumor burden and site of involvement.[241] Other important prognostic factors in NHL include LDH level at diagnosis and CNS involvement. Biologic characteristics including the presence of 13q abnormalities, MYC/8q24 rearrangement in DLBCL, and minimal disseminated disease and minimal residual disease in BL may also be prognostic.[243,244] As most pediatric NHL subtypes are high grade and

aggressive, few reports support the role of histologic subtype as a prognostic factor. Response to therapy is also being investigated,[245] and attempts are being made to standardize pediatric NHL response criteria.[246]

Treatment of Non-Hodgkin Lymphoma

OS of children with NHL was poor before the advent of multiagent chemotherapy in the mid-1970s.[247] Even in cases with localized disease based on the optimal staging of the time, cure rates as low as 20% were reported. In most cases, early systemic dissemination of disease already occurred. In modern regimens, chemotherapy is the primary therapeutic modality for all histologies and stages of childhood NHL. The dramatic improvement in the overall rate of survival in childhood NHL can be attributed not only to the development of highly effective, multiagent chemotherapy regimens, but also to the systematic evaluation of these diseases and their treatment by pediatric cooperative group clinical trials. EFS rates exceeding 90% in patients with limited disease (Table 97.10) and 70% in those with extensive involvement (Table 97.11) are now reported.[242,248-276]

TABLE 97.10 MODERN TREATMENT OUTCOMES FOR LIMITED-STAGE NON-HODGKIN LYMPHOMA BASED ON RECENT TRIALS

Histology (# Patients)	Protocol	Stage/Group	Event-Free Survival
BL (40) B-like L (15) DLBCL (43) Total = 132	FAB/LMB96[248]	A	4 y = 98%
BL (148) DLBCL (60) NOS (21) Total = 229	NHL-BFM 95[249]	I/II, III (LDH < 500)	3 y = 94%
ALCL (82)	HM 89 and HM 91[250]	I-IV (I/II, *n* = 23)	3 y = 94% (stage I/II)
T-cell and B-cell LL (55)	AIEOP LNH 92[277]	I-IV (I/II, *n* = 5)	3 y = 100% (stage I/II)
B-NHL (119, subtypes unspecified)	SFOP LMB 89[242]	I II	5 y = 93% 5 y = 99%

AIEOP, Italian Association of Pediatric Hematology and Oncology; ALCL, anaplastic large cell lymphoma; BFM, Berlin-Frankfurt-Muenster Study Group; BL, Burkitt lymphoma; B-like L, Burkitt-like lymphoma; DLBCL, diffuse large B-cell lymphoma; FAB, French-American-British Study Group; HM, French protocols for pediatric ALCL; LL, lymphoblastic lymphoma; LMB, protocol for mature B-cell lymphomas; LNH, protocol for childhood lymphoblastic lymphomas; NHL, non-Hodgkin lymphomas; NOS, not otherwise specified; SFOP, Societe Francaise d'oncologie Pediatrique.

TABLE 97.11 MODERN TREATMENT OUTCOMES FOR ADVANCED-STAGE NON-HODGKIN LYMPHOMA BASED ON RECENT TRIALS

Histology (*N*)	Protocol	Stage/Group	Event-Free Survival
BL (25) DLBL (10) PMBCL (4) Other B-NHL (6) Total = 45	ANHL01P1 pilot[251]	III/IV	3 y = 95%
BL (67) DLBL (15) Other B-NHL (5) Total = 87	R + B-NHL-BFM 04[278]	I/II/IV/IV	3 y = 94%
BL (450) DLBL (151) PMLBL (32) Other B-NHL (4) Total = 637	FAB/LMB 96[245,248,252]	Intermediate risk (nonresected stage II/I and CNS-negative advanced stage III/IV)	4 y = 92%

Histology (*N*)	Protocol	Stage/Group	Event-Free Survival
BL/BLL/B-ALL (168) DLBL/TCRLCL (13) Other B-NHL (9) Total = 190		High risk (CNS or BM positive)	Full intensity arm: 4 y = 90% Reduced intensity arm: 4 y = 80%
BL (108) DLBL (11) B-cell ALL (80) Other B-NHL (16) Total = 215	NHL-BFM 95[249,253]	III (LDH 500-1,000) IV (CNS−) III (LDH >1,000) IV (CNS+)	3 y = 85% 3 y = 81%
LL Total = 156		III/IV[a]	5 y = 82%
B-NHL (340, subtypes unspecified)	SFOP LMB 89[242]	III IV	5 y = 91% 5 y = 87%
T-cell and B-cell LL (55)	AIEOP LNH 92[277]	III-IV (I/II, *n* = 50)	3 y = 62% (stage III) 3 y = 75% (stage IV)
T-cell LL Total = 137	POG 9404[254] With HD-MTX Without HD-MTX	III/IV	5 y with HD-MTX = 82% 5 y without HD-MTX = 88%
ALCL Total = 217	ALCL99[255]	High risk (mediastinal, lung, liver, or spleen involvement or biopsy-proven skin lesion)	2 y = 71%
ALCL Total = 352	EICNHL[256]	All	2 y = 74%
ALCL (144) PTCL (28) LCL[b] (75) LCL NOS (9) Total = 175	POG 9315-APO vs IDM/HiDAC[257]	III/IV	4 y = 67%
ALCL (82)	HM89 and HM91[250]	I-IV (III/IV = 59)	3 y = 55% (stage III/IV)
DLBL Total = 120	POG 8615-APO vs ACOP+[258]	III/IV	8 y (III) = 68% 8 y (IV) = 59%
BL (281) DLBCL (31) High-grade BCL NOS (13) PMBCL (2) Precursor B-cell acute lymphoblastic leukemia (1) Total = 328	ANHL1131[279]	III with elevated LDH or IV	3 y = 94% (rituximab); 82% (no rituximab)

ALCL, anaplastic large cell lymphoma; ALL, acute lymphoblastic leukemia; BFM, Berlin-Frankfurt-Muenster Study Group; BL, Burkitt lymphoma; BM, bone marrow; B-NHL, B-cell non-Hodgkin lymphoma; CNS, central nervous system; DLBL, diffuse large B-cell lymphoma; EICNHL, European Inter-group Cooperation on Childhood and Adolescent Non-Hodgkin Lymphoma; FAB, French-American-British Study Group; HD-MTX, high-dose methotrexate; HM, French protocols for pediatric ALCL; LCL, large cell lymphoma; LDH, lactate dehydrogenase; LL, lymphoblastic lymphoma; LMB, protocol for mature B-cell lymphomas; NOS, not otherwise specified; PMBCL, primary mediastinal B-cell lymphoma; POG, Pediatric Oncology Group; PTCL, primary T-cell lymphoma; SFOP, Societe Francaise d'oncologie Pediatrique; TCRLCL, T-cell–rich large-cell lymphoma.

[a]Excludes patients with CNS-positive disease and those who had insufficient response on day 33.

[b]Includes DLBL, follicular lymphoma, and mucosal-associated lymphoid tissue lymphoma.

Burkitt Leukemia or Lymphoma

As a result of several consecutive prospective trials, outcomes for BL have dramatically improved.[242,245,248,249,252,263,266,275,276] Treatment consists of 2 to 6 months of multiagent, cyclophosphamide-based chemotherapy. The current paradigm has been established through collaborative efforts across consortiums such as the French Society of Pediatric Oncology and French-American-British (FAB), Lymphomes Malins B (LMB), and the Berlin-Frankfurt-Munster studies.[242,245,248,249,252,263,266,275,276] Since BL

frequently occurs in lower income countries, treatments have been adapted to balance toxicity, efficacy, and cost. OS rates are now greater than 90% in the developed world for advanced BL, and more than half of patients can be cured using resource-adapted protocols in low- and middle-income countries.[280,281] Relapses most commonly occur within the first year of therapy.

In non–resource-constrained health systems, standard frontline therapy for advanced BL is based on the FAB/LMB96 regimen[245] with cyclophosphamide, vincristine, prednisone, high-dose methotrexate, doxorubicin, and cytarabine. Although 20% to 25% of patients present with advanced-stage disease involving the bone marrow and/or CNS, this treatment approach results in EFS of approximately 90%. Of note, involvement of more than 25% of the marrow by Burkitt is classified as Burkitt leukemia, which is treated using a high-risk BL treatment paradigm. High-dose methotrexate with or without high-dose cytarabine and intrathecal methotrexate with or without cytarabine provide effective CNS prophylaxis and treatment for high-risk and CNS-positive disease, eliminating the need for CNS irradiation.[242,245,248,249,252,263,266,275,276] Testicular involvement at diagnosis is uncommon but may occur in about 5% of children with disseminated BL and Burkitt-like NHL.[282] Testicular disease does not confer an inferior prognosis, and disease is still curable with intensive combination chemotherapy alone. Local surgery or radiation is not needed.

BL, like DLBCL, expresses CD20. As such, recent studies added the anti-CD20 monoclonal antibody, rituximab, into multiagent chemotherapy. In 2004, the COG implemented ANHL01P1, a pilot study evaluating the toxicity of adding rituximab to standard therapy for patients with newly diagnosed, pediatric BL and DLBCL.[283] Survival rates were similar to the 4-year reported EFS in patients treated with FAB/LMB96 therapy.[245] In a multicenter European phase II study, 136 pediatric patients with newly diagnosed B-cell NHL received one dose of rituximab in an upfront window prior to starting standard chemotherapy to assess the possibility of a future phase II trial to test if rituximab could substitute for chemotherapy. A response rate of higher than 65% was set for the classification of favorable activity of rituximab; although this ambitious rate was not met, 41% of patients experienced disease improvement after a single dose of rituximab.[278] The International B-NHL ritux 2010 trial randomized patients with stage III disease and elevated LDH or stage IV disease to intensive LMB/FAB chemotherapy with or without six doses of rituximab. The authors identified a significant improvement in EFS with rituximab (3-year EFS 94% vs 82%, $P = .00096$). Thus, the addition of rituximab to intensive chemotherapy should be considered the current standard of care for these patients.[279]

Diffuse Large B-Cell Lymphoma

The treatment of DLBCL follows the same protocols as BL in pediatric and young adult patients. Follow-up for patients with DLBCL, however, should be focused on the possibility of comparatively later relapses, which may occur up to 3 years after treatment.[242,263,276] Rituximab combined with intensive chemotherapy is considered standard of care in DLBCL as in BL based on ANHL1131.[279]

Primary Mediastinal B-Cell Lymphoma

PMBCL most commonly occurs in adolescents and young adults. Since the disease biology appears similar across age groups, the common adult treatment regimens are used in pediatric patients, including rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHOP) and dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, and rituximab (DA-EPOCH-R). Of note, treatment with DA-EPOCH-R obviated the need for RT in adult patients with PMBCL.[284] DA-EPOCH-R was evaluated in an intergroup trial of children and adolescents with newly diagnosed PMBCL, but the 4-year EFS in 46 patients was only 69.6% (95% CI 55.2-80.9),[285] which is lower than the EFS observed in adults.[284] Treatment of PMBCL with FAB/LMB96 chemotherapy resulted in an EFS of 70%.[286] The current intergroup study ANHL1931 (NCT04759586) is exploring whether the addition of nivolumab will improve cure rates when compared to chemo-immunotherapy alone. On ANHL1931, ISRT is used for (1) patients enrolled on the R-CHOP plus RT arm and (2) patients with a Deauville 4 or 5 response at the

completion of systemic therapy, with the presence of disease confirmed by biopsy. The ISRT dose is 30 Gy, with a possible boost of 9 to 15 Gy to residual FDG-avid sites.

Lymphoblastic Lymphoma

LL consists of both precursor T-LL and B-LL NHLs, with the majority (80%-90%) being T-LL. A BMB is required to distinguish between ALL and LL by the extent of bone marrow involvement. T-LL generally presents at an advanced stage with a mediastinal mass and occasionally bone marrow involvement. B-LL is more commonly localized and presents in various locations, including the bones, skin, soft tissues, and peripheral nodes.[287] Treatment follows an ALL-based paradigm with the addition of high-dose methotrexate and/or intrathecal injections for CNS prophylaxis,[254,288,289] rather than CNS RT.[253,290] These regimens include early intensified multiagent chemotherapy consisting of vincristine, prednisone, L-asparaginase, doxorubicin, cytarabine, cyclophosphamide, and high-dose methotrexate, followed by maintenance chemotherapy for 2 years.[253,254,269,270,277,288,289,291-294] In localized B-LL and T-LL treated with such intensive therapy, OS rates are 90% or better. In AALL1231, receipt of bortezomib significantly improved both 4-year EFS and OS in patients with T-LL, although no significant difference was observed in ALL.[295] Following relapse, the outcomes of patients with B-LL and T-LL remain mediocre. Novel agents, such as daratumumab, have demonstrated activity in T-LL and may be promising to consider as first-line therapy for T-LL and T-ALL in the future.[296]

Anaplastic Large Cell Lymphoma

ALCL presents in either a systemic or primary cutaneous form. Systemic ALCL is frequently associated with “B” symptoms and extranodal disease. Advanced systemic ALCL has been treated with short-pulse chemotherapy, proven effective in B-cell lymphomas, or with modifications of high-risk ALL protocols.[256,257,274] Long-term EFS ranges from 65% to 75%[250,255-257,297,298]; however, recurrences are comparatively more responsive to salvage therapies than relapsed disease in other NHL subtypes.[217] Treatment of recurrent ALCL involves chemotherapy followed by hematopoietic stem cell transplantation or weekly vincristine and yields survival rates of more than 90%.[255,256,299-301]

Role of Radiation Therapy

With the development of the current multiagent chemotherapy regimens in many NHL subtypes, the role of RT for local control of primary tumors and CNS prophylaxis is limited. At present, cranial irradiation is generally only indicated in patients with symptomatic CNS lymphoma, particularly if unresponsive to frontline chemotherapy, or in the event of CNS relapse.[302]

The role of consolidative RT for PMBCL is often considered. Adult data suggest that consolidative RT should be recommended in PMBCL after R-CHOP, but that it is generally not indicated following a complete metabolic response to DA-EPOCH-R. Given the poorer outcomes of PMBCL treated with DA-EPOCH-R in children compared to adults, the role of consolidative RT is less clear. At present, the authors recommend that consolidative RT to a minimum of 30 Gy be strongly considered in patients with PMBCL if they are treated with R-CHOP chemotherapy or if they have an incomplete response following any induction chemotherapy regimen.[284,303,304]

Historically, consolidative RT was included in the treatment of primary lymphomas of the bone.[259] An early trial randomized children and young adult patients with limited-stage NHL to receive RT or no consolidation after chemotherapy and demonstrated that consolidative RT was not needed in many patients with early-stage NHL. In this trial, however, all patients with primary lymphoma of the bone received 37.5 Gy and were not included in the randomization.[259] Given the rarity of these entities, the patterns of failure of all early-stage primary lymphomas of the bone treated on three consecutive POG studies were examined to determine the impact of RT on outcomes. Across the three studies, a total of 31 patients with primary bone lymphomas were analyzed, with 7 receiving combined modality therapy and 24 receiving

chemotherapy alone. In this analysis, no patient developed a local relapse, suggesting that NHL of the bone may be treated with chemotherapy alone.[305]

RT should be considered for relapsed or refractory disease, either as part of combined modality therapy with definitive intent or as palliation when appropriate. Selected patients with NHL may benefit from urgent RT for symptomatic mediastinal disease, spinal cord compression, pain, and symptomatic CNS lymphoma.

Pediatric patients with relapsed or refractory disease following frontline chemotherapy often receive high-dose chemotherapy and stem cell rescue as part of salvage therapy.[306] RT to limited site(s) of residual or relapsed disease may be beneficial in combination with hematopoietic cell transplantation and generally should use a dose of 30 to 36 Gy. Emergent palliative radiation to control symptoms of SVC syndrome, airway impingement, spinal cord compression, and orbital proptosis can produce dramatic and rapid responses, typically within 48 hours of treatment. In general, these regimens using daily fractions of 2 to 3 Gy or twice-daily treatments of 1.2 to 1.5 Gy are efficacious. For symptom control, total doses as low as 4 Gy can lead to relief.[307,308] Higher doses to 20 to 30 Gy may be more appropriate for cranial nerve deficits and other situations in which durable disease control is important.[308,309] Corticosteroids, ideally after the diagnosis is confirmed by biopsy, can also lead to dramatic tumor responses in NHL.

Future Investigations

Future pediatric NHL trials will aim to identify and incorporate novel therapies into frontline and salvage regimens, including targeted agents, monoclonal antibodies, and immunotherapies. Small patient numbers for individual NHL histologies and the rarity of patients developing relapsed/refractory disease are the most daunting obstacles to clinical trial design and implementation. Despite these limitations, considerable progress has been achieved in identifying potential targets and utilizing novel therapies in pediatric NHL. For example, ALCL arises from T cells but strongly expresses CD30, leading to the evaluation of Bv in a phase II study of adults and pediatric patients with relapsed or refractory ALCL with promising response rates.[310] Given that most pediatric patients have ALK-positive disease, ALK inhibitors may also be promising agents in ALCL.[311] CD20 is commonly expressed in DLBCL and BL, and rituximab is now employed during frontline therapy; next-generation anti-CD20 monoclonal antibodies may be reasonable to evaluate in DLBCL and BL, as well.[312] Immunotherapy will also be further explored in NHL and is part of the current COG study in PMBCL. Ultimately, these therapies may reduce treatment intensity and chemotherapy-related toxicities and may improve efficacy.

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CHAPTER 98

Retinoblastoma

Beate Timmermann and John T. Lucas, Jr

Retinoblastoma is a malignant embryonal tumor of the eye that exclusively occurs during childhood. It originates from the retina in the early years of life. Various treatment modalities are available depending on the degree of spread and other factors. In general, eye-preserving therapies or surgery (enucleation), if necessary, are combined with adjuvant therapies.

EPIDEMIOLOGY

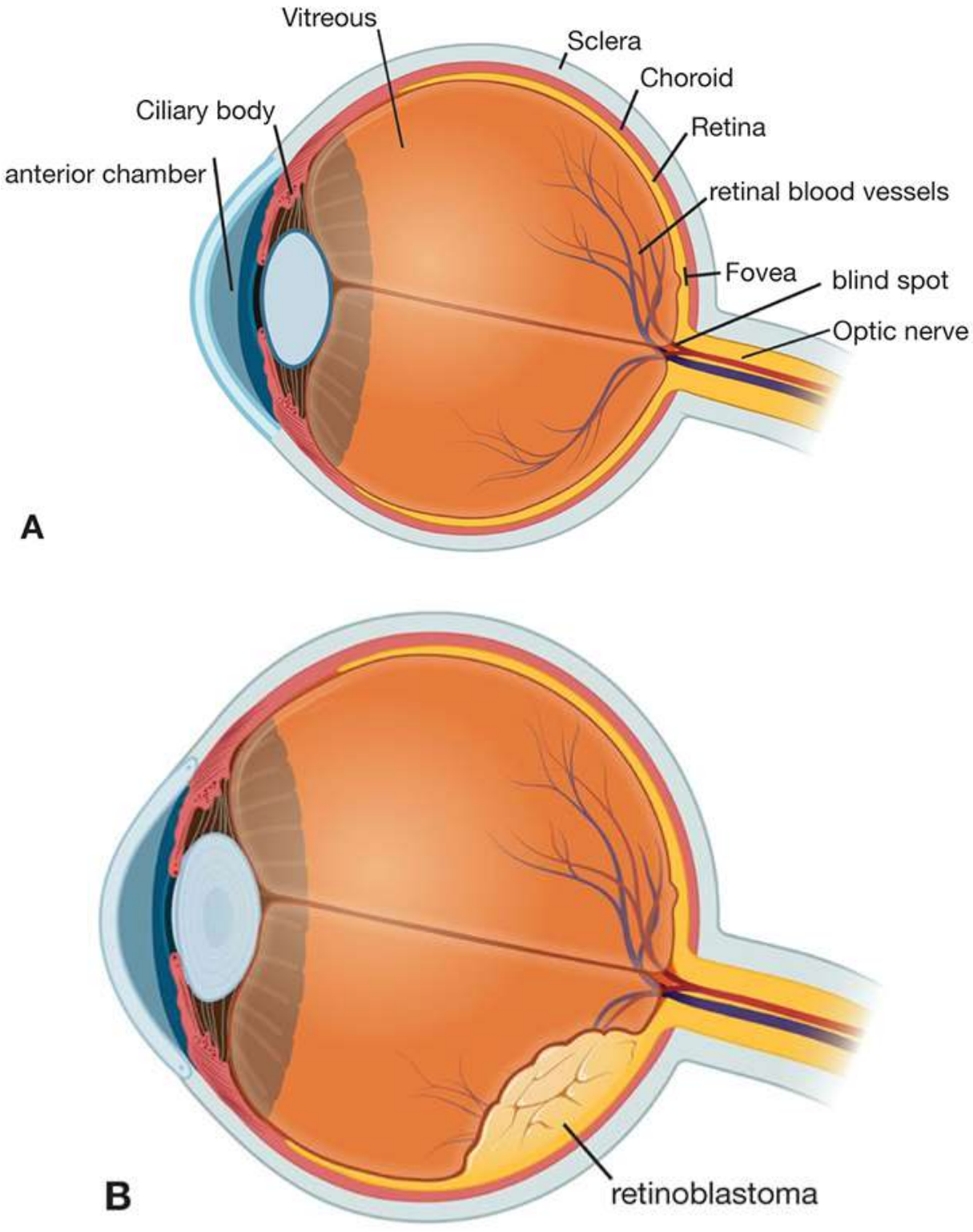
With an incidence of 1 in 15,000 to 20,000 live births worldwide, retinoblastoma is the most common eye tumor in children.[1] Approximately 8,000 new cases are diagnosed worldwide each year,[2,3] primarily in children aged under 5 years. The median age at diagnosis is 2 years.[1] Incidence is higher in low- and middle-income countries (LMICs) with an estimated 1,300 to 4,000 cases annually, compared to approximately 200 to 300 cases in the United States and around 500 cases in Europe.[4]

Retinoblastoma can present as unifocal (single tumor) or multifocal (many tumors). Approximately 60% of all retinoblastomas affect one eye (unilateral disease), while 40% affect both eyes (bilateral disease). All bilateral and multifocal forms are hereditary.

Survival rates for retinoblastoma vary greatly such that in high-income countries (HICs), almost all retinoblastoma cases survive, whereas in LMICs, the mortality rate can reach up to 70%.[4] The discrepancy is primarily due to differences in the time of diagnosis. In HICs, the tumor is often detected before critical structures of the eye are affected. In LMICs, diagnosis frequently occurs when there are signs of invasive disease, leading to a higher risk of local and distant metastasis.[5] While some patients with metastatic disease are still curative, those with involvement of the central nervous system (CNS) are rarely curable.

PATHOGENESIS

Retinoblastoma is a cancer characterized by small, round cells. These cells have large, deeply stained nuclei and minimal cytoplasm. Although retinoblastoma arises from retina cells and the retina is part of the CNS, retinoblastomas are not assigned to the CNS tumors.[6] Tumor cells grow around feeding blood vessels, forming a cuff-like structure. As they extend beyond the vascular supply, they become necrotic and calcified.[7] Retinoblastoma is a fast-growing eye cancer that can spread within and outside the eye (Figure 98.1). Intraocular retinoblastomas can affect only the retina or spread to structures such as the choroid, ciliary body, anterior chamber of the eye, and/or the optic nerve head. The tumor can grow into the vitreous (endophytic) or develop into the subretinal space while growing toward the choroid (exophytic).[8] The extent of disease, including seeding, is crucial for treatment decisions. Seeding can be localized, limited, or massive and nondiscrete and either described as subretinal or within the vitreous cavity. Diffuse infiltrating growth has also been described.[8] Retinoblastoma may extend beyond the eye into the bulb wall and spread to the tissue around the eye, referred to as an orbital retinoblastoma. In addition, the tumor can spread locally and regionally along the optic nerve, via the cerebrospinal fluid (CSF) space into the CNS, or through the bloodstream to the bone marrow, lymph nodes, or other parts of the body.[7,9]


Vitreous
Sclera
Choroid
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Retina
anterior chamber
retinal blood vessels
Fovea
blind spot
Optic nerve
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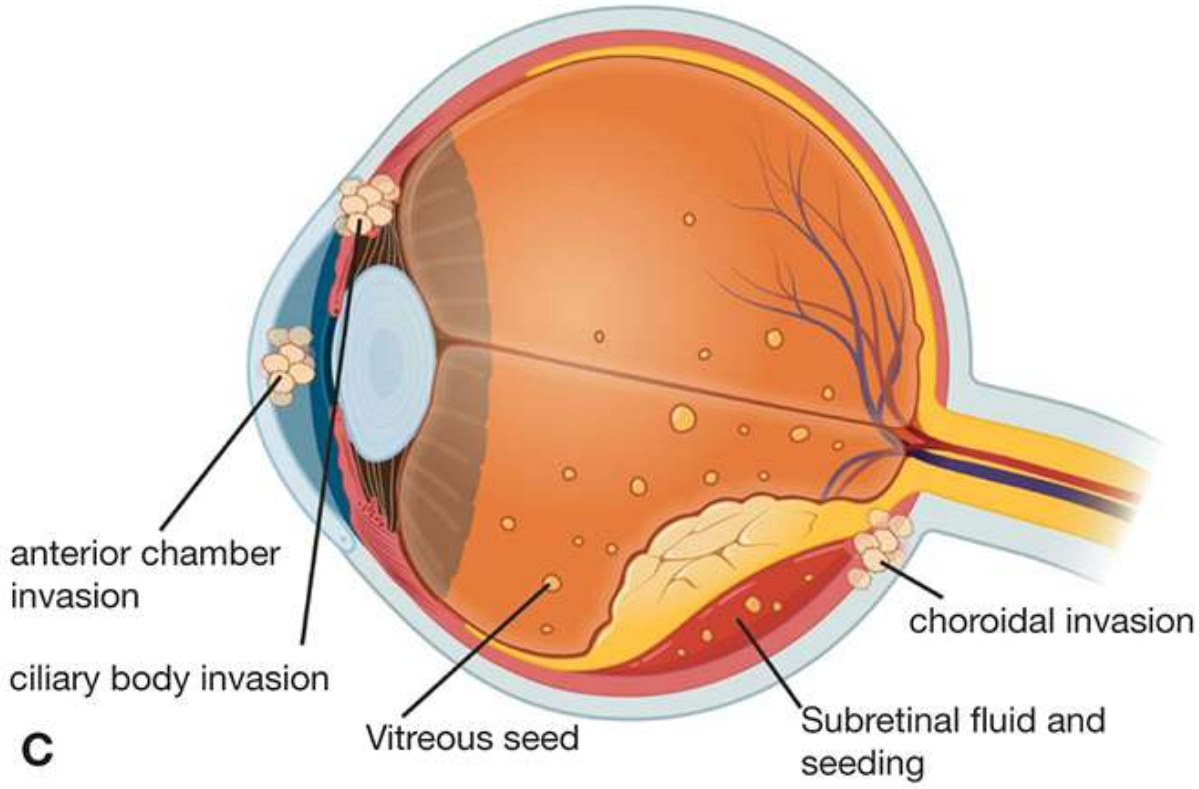
retinoblastoma


anterior chamber invasion
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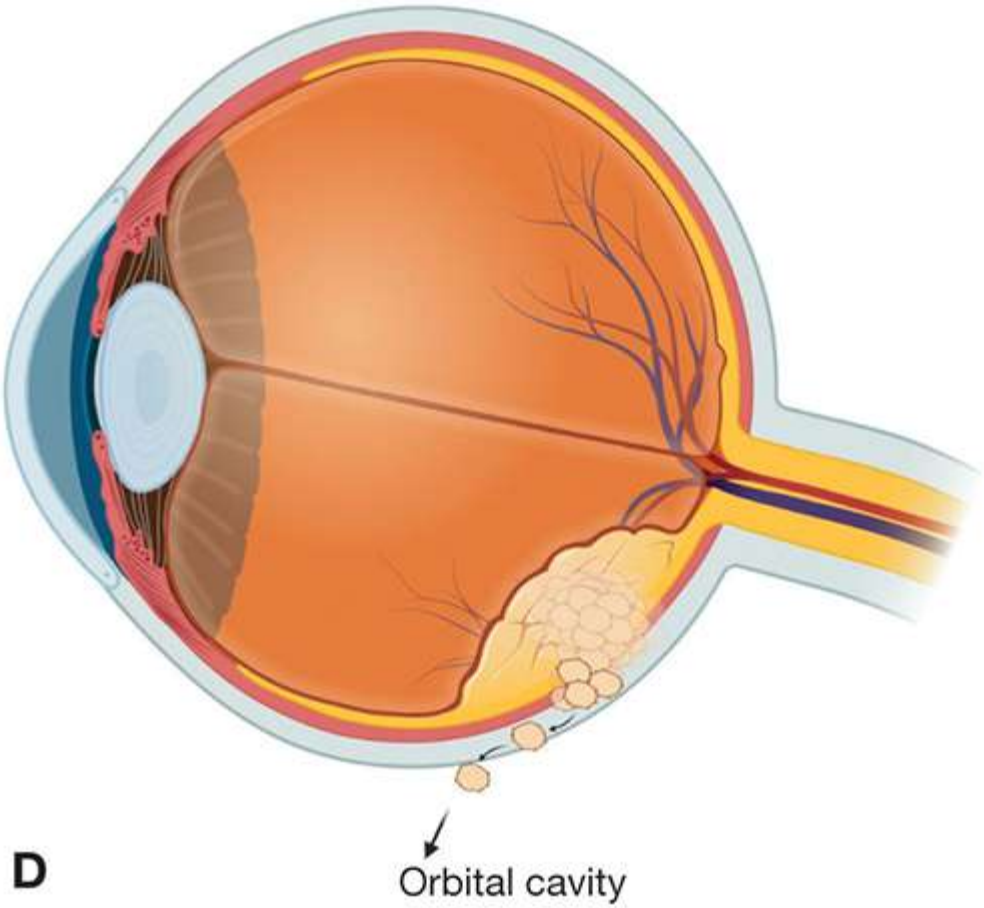

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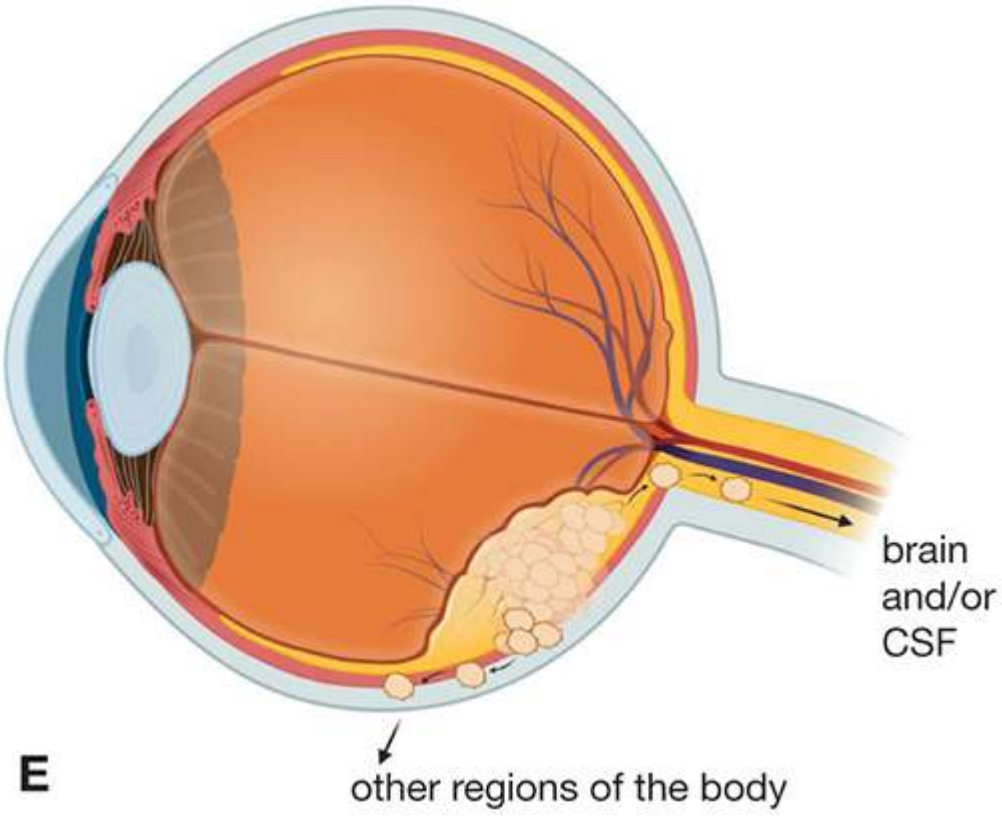


FIGURE 98.1 Patterns of spread in retinoblastoma. A. Healthy eye and relevant anatomic structures. B. Intraocular retinoblastoma: tumor limited to retina. C. Intraocular retinoblastoma: pathways of intraocular extent (vitreous seeding, anterior chamber invasion, choroidal invasion, ciliary body invasion). D. Extraocular retinoblastoma with extension into the orbital cavity. E. Extraocular retinoblastoma with metastatic dissemination—extension along the optic nerve via cerebrospinal fluid (CSF) into the central nervous system, hematogenous/bone marrow, or lymphatic seeding. (A. Created in BioRender. Thomas H. BioRender. 2025. https://BioRender.com/9c3mu9h. B. Created in BioRender. Thomas H. BioRender. 2025. https://BioRender.com/plyzauq. C. Created in BioRender. Thomas H. BioRender. 2025. https://BioRender.com/6wdyy4j. D. Created in BioRender. Thomas H. BioRender. 2025. https://BioRender.com/i2f9i67. E. Created in BioRender. Thomas H. BioRender. 2025. https://BioRender.com/8boxqsq.)

Typically, undifferentiated tumor cells are more prevalent in retinoblastoma, and differentiation does not significantly impact the prognosis. However, tumors can exhibit varying levels of photoreceptor differentiation, resulting in the formation of rosettes at the cellular level. Flexner- Wintersteiner rosettes comprise a circular arrangement of columnar cells with eosinophilic cytoplasm and nuclei located peripherally around a central lumen. This lumen is lined by a refractile membranous structure corresponding to the outer limiting membrane of the retina. The

lumen is lined by a refractile membranous structure that corresponds to the outer limiting membrane of the retina. Homer-Wright rosettes are formed by cells surrounding a central structure known as the fibril tangle, which consists of their own projections. While these two types of rosettes can also be found in other neural tumors, their simultaneous occurrence is specific to retinoblastoma.[7,9] Fleurettes are curved cell accumulations composed of inner rod and cone segments. They are notably associated with the benign precursor of retinoblastoma, known as retinoma.[7]

GENETICS

Retinoblastoma arises from retinal progenitor cells carrying biallelic mutations of the retinoblastoma tumor suppressor gene *RB1*. Gene inactivation occurs according to the two-hit model, which was first described by Knudson in 1971.[10] To date, more than 2,500 *RB1* gene mutations are known. Most of these mutations are in the 180 kb of the coding region of the gene, but they can also affect the promoter and intron regions.[11] No clear hot spots exist. The mutations are distributed over the entire gene, which is localized on chromosome 13q14.2.[8] The *RB1* gene encodes the retinoblastoma protein (pRB), a phosphoprotein expressed in all human tissues. In the cell cycle, pRB regulates the transition from G1 to S phase by blocking the interaction of the transcription factors E2F and DP with DNA. In response to mitogenic stimuli, pRB becomes hyperphosphorylated, removing the blockade and enabling active transcription by E2F and DP. Mutations that impair pRB function lead to uncontrolled entry into the S phase, resulting in increased cell cycle activity and uncontrolled cell growth, which, in turn, leads to tumorigenesis. In addition, pRB function is associated with differentiation, chromatin remodeling, genomic stability, apoptosis, and epigenetic processes.[7,12,13-23] pRB dysfunction causes dysregulation of many tumor suppressor pathways.

Retinoblastoma exists in two forms: hereditary and nonhereditary. The hereditary form accounts for 30% to 40% of retinoblastoma cases. It is characterized by a germline mutation in one allele of the *RB1* gene, which is present in all cells of the child's body at birth. Prior to tumorigenesis, this germline mutation is followed by a somatic mutation in the second *RB1* allele in a retinal progenitor cell, leading to gene inactivation. In 25% of

patients, the germline mutation is inherited autosomal dominantly from one parent; otherwise, it arises during germ cell development.[8] If the mutation occurs later in development, postconception, it may lead to mosaicism, indicating that only some of the body cells carry the mutation.[24] Hereditary retinoblastoma typically presents early, with a median age of 15 months, and often manifests multifocally and bilaterally. However, 10% to 20% of unilateral cases are also based on a germline mutation.[25] Hereditary retinoblastoma is associated with an increased risk of developing second primary cancer, such as osteosarcoma, soft tissue sarcoma, malignant melanoma of the skin, or neuroectodermal tumors.[26,27] External beam radiotherapy (EBRT) further elevates this risk both inside and outside the radiation field.[28-30]

Nonhereditary retinoblastoma is the more common variant and develops as a result of random somatic mutations in both *RB1* alleles of a single retinal progenitor cell. It usually occurs as a solitary focus in one eye. The median age for nonhereditary retinoblastoma is 24 months.[4,31] In rare cases, patients with unilateral retinoblastoma develop new intraocular tumor foci in the opposite eye 2 to 18 months after diagnosis, a condition termed *metachronous retinoblastoma*. This phenomenon is suggested to be associated with family history, early age at diagnosis, tumor multifocality, and oncogenic mutations in the tumor.[32,33] Trilateral retinoblastoma describes a situation where bilateral retinoblastoma coexists with a third, intracranial tumor (Figure 98.2). The reported incidence is 5% to 15% of bilateral cases, although a recent analysis excluding studies with small cohorts estimates a lower incidence.[34] Importantly, this scenario does not represent CNS metastatic disease. The intracranial component is most commonly located in the pineal region, and less frequently in the suprasellar region. Extremely rare cases with both pineal and suprasellar locations are termed *quadrilateral retinoblastoma*.[8]

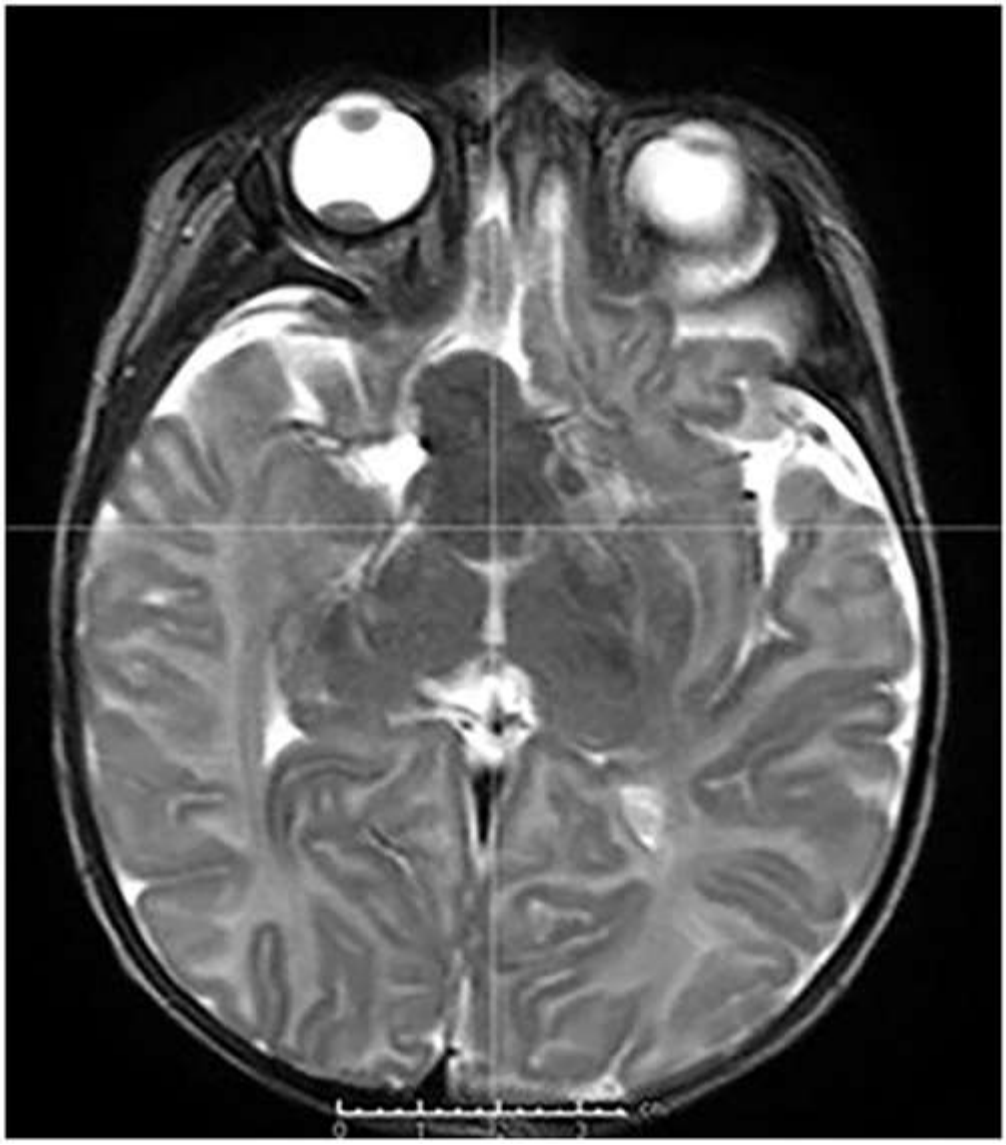


FIGURE 98.2 Transversal view of a T2-weighted magnetic resonance imaging of a trilateral retinoblastoma in suprasellar region.

Beyond *RB1* Gene Mutation

Tumorigenesis involves several stages. In addition to *RB1* gene inactivation, other genetic and epigenetic changes contribute to the development and progression of retinoblastoma. Recurring genetic changes in the epigenetic modifier genes *BCOR* (BCL6 corepressor) and *OTX2* (orthodenticle homeobox 2) have been identified.[35,36] A distinct pattern of genomic gains on chromosomes 1q, 2p, and 6p and loss on 13q and 16q has also been detected in retinoblastoma. Oncogenes and tumor suppressor

genes such as *KIF14* (kinesin family member 14, 1q), *MDM4* (murine double minute 4, 1q), *MYCN* (2q), *DEK* (6p), *E2F3* (E2F transcription factor 3, 6p), *CDH11* (cadherin 11, 16q), and *RBL2* (RB transcriptional corepressor like 2, 16q) are located in these regions.[36-39] Epigenetic dysregulation, including DNA methylation, histone modifications, and noncoding RNAs, also plays a significant role in retinoblastoma tumor formation and metastasis.[35,39] For instance, aberrant methylation of certain promoters, such as *MGMT* (methylguanine methyltransferase), *RASSF1A* (Ras association domain family member 1), *CASP8* (caspase 8), and *MLH1* (MutL homolog 1), contributes to the disease.[39-41] Dysregulation of microRNAs, including *let-7*, *miR-24a*, and the *miR17-92* cluster, is also observed in retinoblastoma.[39] In addition, long noncoding RNAs may act as potential modulators in retinoblastoma progression and metastasis.[42]

CLINICAL PRESENTATION AND DIAGNOSIS

The most common early symptoms of retinoblastoma are leukocoria (also known as "cat's-eye reflex") and strabismus (Figure 98.3A). However, this is not usually an abnormality at birth; rather, the signs develop between 6 months and 2 years of age. Other, less common signs of retinoblastoma include inflammation in various areas of the eye and orbit, mydriasis, microphthalmia, buphthalmos, neovascular glaucoma, uveitis, hyphema, and iris heterochromia. Proptosis (bulging of the eye) and periorbital swelling are symptoms of advanced retinoblastoma.[7,8,43-45]

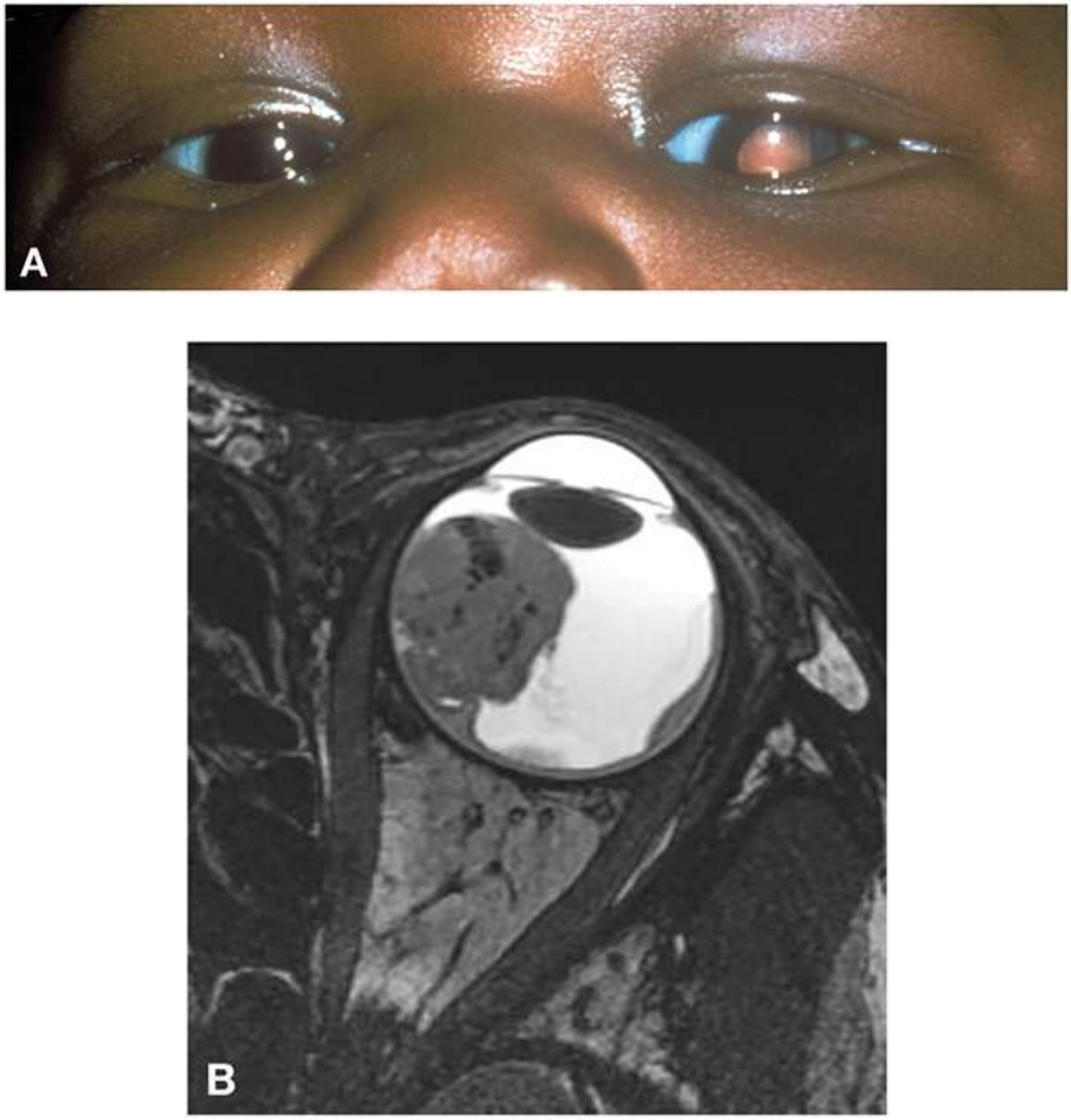


FIGURE 98.3 Diagnosis of retinoblastoma. A. Leukocoria flash-lit photographs ("cat's-eye"). B. T2-weighted magnetic resonance image showing the nasally located retinoblastoma with discrete vitreous seeding and contralateral retinal detachment.

Diagnosis of retinoblastoma is based on clinical features and not on histopathology. A biopsy is obsolete as it can lead to seeding and extraocular spread along the needle tract. Molecular testing of tumor tissue is only performed after enucleation.[46] It is crucial that tumors are diagnosed as early as possible, as this maximizes the prognosis for survival as well as

the chance of preserving vision and reduces the need for chemotherapy, radiotherapy, or enucleation.

The diagnosis of retinoblastoma requires several examinations. If retinoblastoma is suspected, a detailed medical history of the patient and their family is first taken to enable a focused examination. This is followed by clinical examinations under anesthesia (EUA) with a fully dilated pupil and mechanical dilation of the sclera for complete visualization of the entire retinal surface. The use of imaging techniques plays an important role here. Wide-angle retinal images and ultrasound examinations, as well as magnetic resonance imaging (MRI) examinations of the orbit and brain, are performed. Ophthalmoscopy, sonography, and orbital MRI are used to assess intraocular masses, retinal detachment, and calcification (see Figure 98.3B). The cranial MRI provides information on extrascleral extension, infiltration of the optic nerve, metastasis, and the presence of a pineoblastoma. In some cases, a computed tomography (CT) scan may also be conducted, but usually, efforts are made to avoid this radiation exposure, especially in hereditary forms. In the case of an extraocular retinoblastoma, a bone marrow aspiration and a lumbar puncture are also performed to rule out systemic metastasis.[9,44] Once the diagnosis has been confirmed, the parents receive detailed counseling on treatment options, followed by genetic counseling and diagnostics for all family members.[47]

Staging and Risk Classification

Retinoblastoma is classified based on several factors, including tumor size, location within the eye, extent of seeding, severity of retinal detachment, signs of increased intraocular pressure, neovascularization, and hemorrhage. Various classification systems exist for both intraocular and extraocular retinoblastoma (Figure 98.4, Tables 98.1 and 98.2). The historically first grouping system, known as the Reese-Ellsworth classification,[48] was initially designed to predict the outcome of radiotherapy (see Table 98.2). However, with the shift in therapeutic approaches from radiotherapy to chemotherapy, other staging systems have emerged.

TABLE 98.1 COMPARISON OF RETINOBLASTOMA STAGING SYSTEMS

AJCC Clinical and Pathologic Staging Eighth Edition[49]		IIRC[50]	ICRB[51]	IRSS[52]	SJCRH[53]
cT1	Intraretinal tumor(s) with subretinal fluid ≤5 mm[a]				
cT1a	Size ≤3 mm and distance to disc and fovea >1.5 mm	A, >3 mm to fovea OR B, 1.5-3 mm	A, >3 mm to fovea OR B, 1.5-3 mm	—	I
cT1b	Size >3 mm or distance to disc and fovea ≤1.5 mm	B	B, ≤3 mm OR C, 3-5 mm	—	I
pT1	Intraocular tumor(s) without any local invasion, focal choroidal invasion, or pre- or intralaminar involvement of the optic nerve head	—	—		I
cT2	Intraocular tumor(s) with retinal detachment, vitreous seeding, or subretinal seeding				
cT2a	Subretinal fluid >5 mm[a]	C, >5 mm OR D, >1 quadrant	C, OR E, tumor >50% eye volume	—	II
cT2b	Vitreous seeding and/or subretinal seeding	C, “local” OR D, “diffuse”	C, ≤3 mm OR D, >3 mm OR E, tumor >50% eye volume	—	II
pT2	Intraocular tumor(s) with local invasion				II or III
pT2a	Concomitant focal choroidal invasion and pre- or	—	—	—	II or III

AJCC Clinical and Pathologic Staging Eighth Edition[49]		IIRC[50]	ICRB[51]	IRSS[52]	SJCRH[53]
	intralaminar involvement of the optic nerve head				
pT2b	Tumor invasion of stroma of iris and/or trabecular meshwork and/or Schlemm canal	—	—	—	III
cT3	Advanced intraocular tumor(s)				
cT3a	Phthisis or prephthisis bulbi	E	E	I or II	III
cT3b	Tumor invasion of choroid, pars plana, ciliary body, lens, zonules, iris, or anterior chamber	E	E	I or II	III
cT3c	Raised intraocular pressure with neovascularization and/or buphthalmos	E	E	I or II	III
cT3d	Hyphema and/or massive vitreous hemorrhage	E	E	I or II	III
cT3e	Aseptic orbital cellulitis	E	E	I or II	III
pT3	Intraocular tumor(s) with significant local invasion				III
pT3a	Massive choroidal invasion (>3 mm in largest diameter, or multiple foci of focal choroidal involvement totaling >3 mm, or any full-thickness choroidal involvement)	E	E	I or II	III
pT3b	Retrolaminar invasion of the optic nerve head, not involving the transected end of the optic nerve	E	E	I or II	III
pT3c	Any partial-thickness involvement of the sclera within the inner two-thirds	E	E	I or II	III
pT3d	Full-thickness invasion into the outer third of the sclera	E	E	I or II	III

AJCC Clinical and Pathologic Staging Eighth Edition[49]		IIRC[50]	ICRB[51]	IRSS[52]	SJCRH[53]
	and/or invasion into or around emissary channels				
pT4	Evidence of extraocular tumor: tumor at the transected end of the optic nerve, tumor in the meningeal spaces around the optic nerve, full-thickness invasion of the sclera with invasion of the episclera, adjacent adipose tissue, extraocular muscle, bone, conjunctiva, or eyelids	E	E	I or II	IVA
cT4	Extraocular tumor(s) involving the orbit, including the optic nerve				
cT4a	Extraocular tumor(s) involving orbit, including optic nerve	—	E	I or II	IVA
cT4b	Extraocular tumor clinically evident with proptosis and/or an orbital mass	—	E	IIIa	IVA
cN1	Evidence of preauricular, submandibular, and cervical lymph node involvement	—	—	IIIb	IVB
pN1	Pathologically proven regional lymph node involvement	—	—	IIIb	IVB
cM1	Clinical signs of distant metastasis				IVB or IVC
cM1a	Tumor(s) involving any distant site (eg, bone marrow, liver) on clinical or radiologic tests	—	—	IVa1: Single lesion IVa2: Multiple lesions	IVB or IVC
cM1b	Tumor involving the CNS on radiologic imaging (not including trilateral RB)	—	—	IVb1: Prechiasmatic lesion	IVA

AJCC Clinical and Pathologic Staging Eighth Edition[49]		IIRC[50]	ICRB[51]	IRSS[52]	SJCRH[53]
				IVb2: CNS mass	
pM1	Pathologic confirmation of distant metastasis				
pM1a	Histopathologic confirmation of tumor at any distant site (eg, bone marrow, liver, or other)	—	—	IVa1: Single lesion IVa2: Multiple lesions	IVB or IVC
pM1b	Histopathologic confirmation of tumor in the CSF or CNS parenchyma	—	—	IVb1: Prechiasmatic lesion IVb2: CNS mass	IVA
H	Hereditary trait				
HX	Unknown or insufficient evidence of a constitutional *RB1* gene mutation				
H0	Normal *RB1* alleles in blood tested with demonstrated high-sensitivity assays				
H1	Bilateral RB, RB with an intracranial primitive neuroectodermal tumor (ie, trilateral RB), patient with family history of RB, or molecular definition of a constitutional *RB1* gene mutation				

AJCC, American Joint Committee on Cancer; CNS, central nervous system; CSF, cerebrospinal fluid; d, distance; SJCRH, St Jude Children's Research Hospital; ICRB, International Classification of Retinoblastoma; IIRC, International Intraocular Retinoblastoma Classification; IRSS, International Retinoblastoma Staging System; RB, retinoblastoma.

[a]From base of any tumor.

TABLE 98.2 RETINOBLASTOMA GROUPING SYSTEM ACCORDING TO REESE AND ELLSWORTH

Group	Subgroup	Characteristics	Prognosis
I	A	Solitary tumor, less than 4 disc diameters in size, at or behind the equator	Very favorable
	B	Multiple tumors, none more than 4 disc diameters in size, all at or behind the equator	
II	A	Solitary tumor, 4-10 disc diameter in size, at or behind the equator	Favorable
	B	Multiple tumors, 4-10 disc diameters in size, at or behind the equator	
III	A	Any lesion anterior to the equator	Doubtful
	B	Solitary lesion larger than 10 disc diameters behind the equator	
IV	A	Multiple tumors, some larger than 10 disc diameters in size	Unfavorable
	B	Any lesion extending anterior to the ora serrata	
V	A	Massive tumors involving over half of the retina	Very unfavorable
	B	Vitreous seeding	

Reproduced with permission from Reese AB, Ellsworth RM. The evaluation and current concept of retinoblastoma therapy. *Trans Am Acad Ophthalmol Otolaryngol*. 1963;67:164-172.

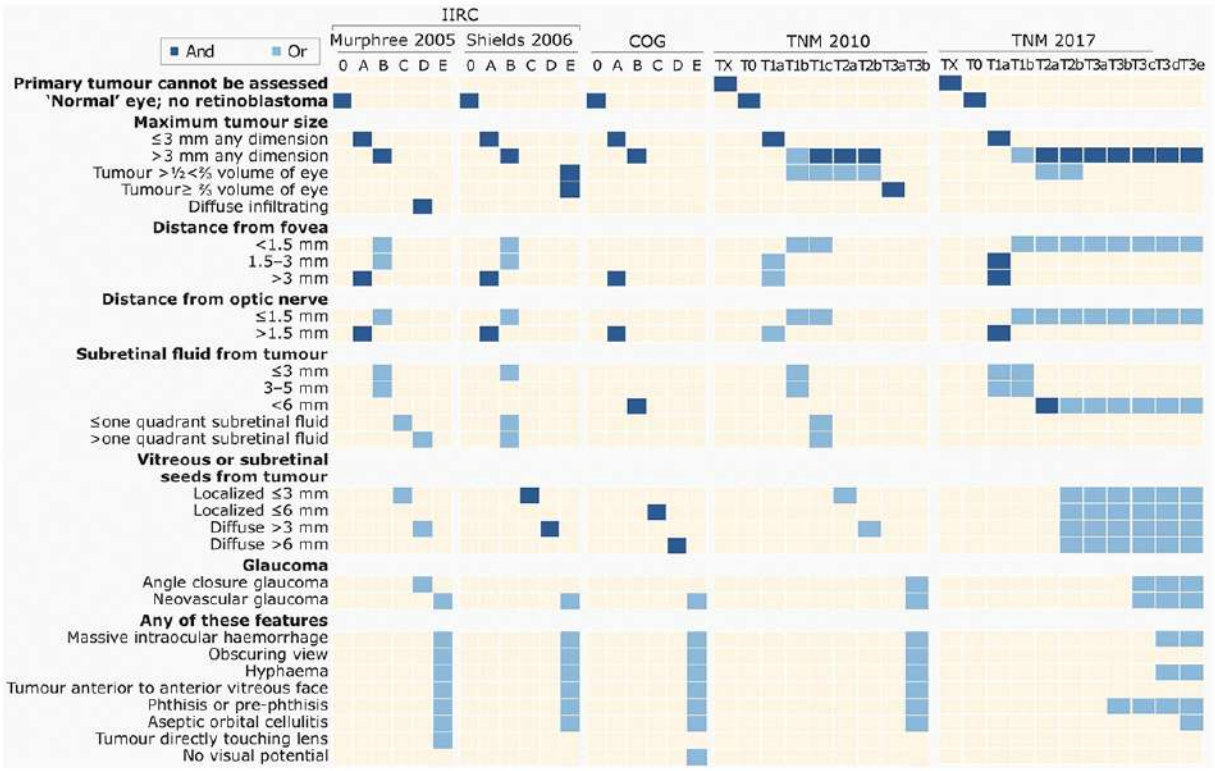


FIGURE 98.4 Comparison of retinoblastoma staging systems. COG, Children's Oncology Group; IIRC, International Intraocular Retinoblastoma Classification; TNM, tumor node metastasis. (Adapted by permission from Nature: Dimaras H, Corson TW, Cobrinik D, et al. Retinoblastoma. *Nat Rev Dis Primers*. 2015;1:15021. Copyright © 2015 Springer Nature.)

Currently, intraocular retinoblastomas are categorized into subgroups A to E according to the International Intraocular Retinoblastoma Classification system[50] and its modified version, the International Classification of Retinoblastoma.[51]

For extraocular retinoblastoma, extensive staging procedures are necessary to determine the appropriate treatment approach. These cases are classified according to the International Retinoblastoma Staging System developed by Chantada et al.[52] Enucleated retinoblastomas are divided into four stages (I-IV), while stage 0 includes all cases treated conservatively without enucleation. In addition, a staging system for vitreous seeding has been developed.[54-56]

Analogous to other types of cancer, retinoblastomas are also classified using the tumor node metastasis (TNM) system of the American Joint Commission on Cancer, currently in its eigh[th] edition.[49] The TNM system combines information on both intraocular and extraocular diseases. Based

on clinical characteristics, the tumor stage is initially determined for each eye, and subsequently, the patient is assessed with regard to the most advanced eye. Radiology plays an important role in this process.

Differential Diagnosis

The diagnosis of retinoblastoma is challenging, with a misdiagnosis rate of 10% to 40% based on histopathologic analysis after enucleation and 16% to 53% based on clinical examination.[44,57] The most common differential diagnosis is Coat disease. Other simulating lesions include congenital cataract, choroiditis, persistent fetal vasculature, astrocytic hamartoma, intraretinal hemorrhage, retinal detachment, retinopathy of prematurity, retinal astrocytoma, retinoma, toxocariasis, Bloch-Sulzberger disease, retinal dysplasia, and Patau syndrome.[9,44,45,58]

Risk Factors

Early diagnosis of retinoblastoma is an important prognostic factor, as the stage of the tumor is predictive for survival and preservation of vision (Figure 98.5). Socioeconomic differences in individual countries significantly impact prognostic outcomes. In HICs, retinoblastoma is considered a curable tumor, with a survival rate of more than 90%. In LMICs, the prognosis for retinoblastoma is significantly worse, with survival rates of approximately 70% and 40%, respectively.[43,59] Histopathologic risk factors are invasion of the choroid, the anterior chamber, the sclera, and infiltration of the optic nerve to varying degrees. Invasion of the choroid and sclera favors hematogenous spread, while infiltration of the optic nerve increases the risk of CNS metastases. Extraocular extension significantly reduces the chance of cure and increases mortality rates.[60-62] Furthermore, genetic predisposition increases the risk of developing multifocal bilateral and trilateral retinoblastoma in the first years of life. The risk of second primary cancers later in life is elevated with hereditary retinoblastoma, especially if EBRT has been performed.[63]

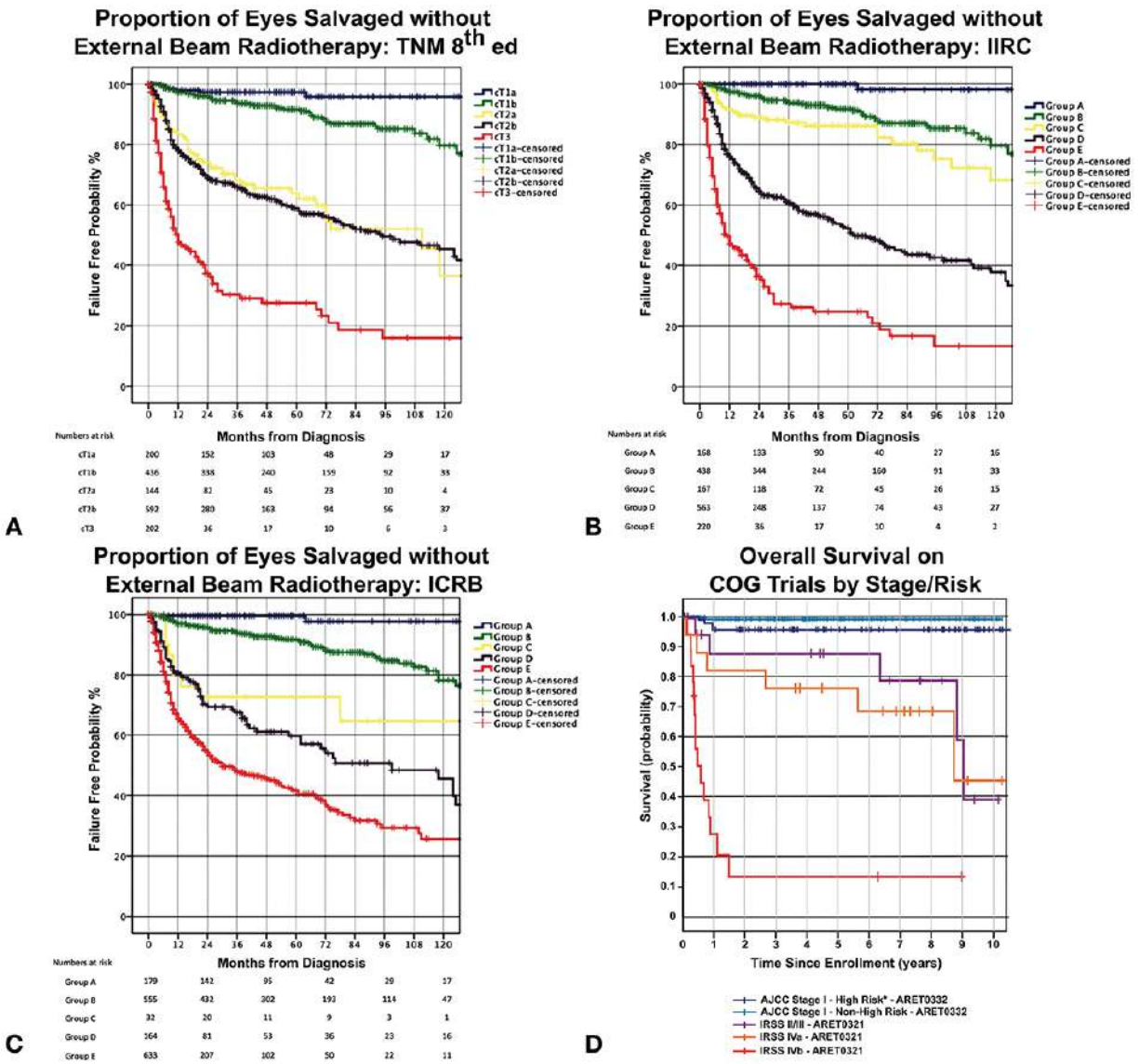


FIGURE 98.5 Outcomes by staging system and treatment approach on recent Children's Oncology Group (COG) trials. Proportion of eyes salvaged without external beam radiotherapy stratified by (A) TNM 8th edition T stage, (B) IIRC stage, and (C) ICRB stage. D. Overall Survival on Children's Oncology Group Trials stratified by stage, risk and treatment approach. AJCC, American Joint Committee on Cancer; ICRB, International Classification of Retinoblastoma; IIRC, International Intraocular Retinoblastoma Classification; TNM, tumor node metastasis.[64-66]

GENERAL MANAGEMENT

Retinoblastoma is a fast-growing tumor with a risk of extraocular spread to the orbit cavity, into the CNS, and other organs. Untreated, retinoblastoma disease is usually fatal. However, with a proper approach, it is curable.

When the diagnosis is made early enough, that is, when the disease is still limited to the eye (intraocular retinoblastoma), the survival probability is 99.2%.[67] In recent decades, even in cases of extraocular retinoblastoma without metastases, curative treatment with acceptable sequelae has been provided. However, metastatic disease has an unfavorable prognosis, particularly in CNS dissemination.[64]

For retinoblastoma treatment, various treatment options or their combination are available, such as surgery (enucleation), focal nonradiation therapies (laser photocoagulation, cryotherapy, hyperthermia), focal radiation therapy (plaque brachytherapy), chemotherapy, and EBRT.[68] Systemic chemotherapy administers vincristine, etoposide, and carboplatin.[69] Targeted chemotherapies (intra-arterial or intravitreal) administer agents directly to the eye. During enucleation surgery, an artificial eye is implemented, aiming to improve quality of life of the affected children.[70,71]

The overall treatment approach for retinoblastoma is complex. Fortunately, retinoblastoma cells are sensitive to chemotherapy and radiation. In cases of advanced extraocular disease, the approach is similar to multidisciplinary approaches used for pediatric brain tumors. However, traditionally, ophthalmologists primarily manage patients with retinoblastoma, rather than pediatric oncologists. To achieve the best possible outcomes, close communication and interdisciplinary review of findings are mandatory. Thorough documentation of the disease extent at diagnosis, response during therapy (Figure 98.6), and prior to other local treatments is of utmost importance. Treatment should occur in specialized centers. The typically young age of the child must be considered within diagnostic and therapeutic treatment. Ophthalmologic examinations and treatments are performed under anesthesia, requiring an experienced anesthesia team.

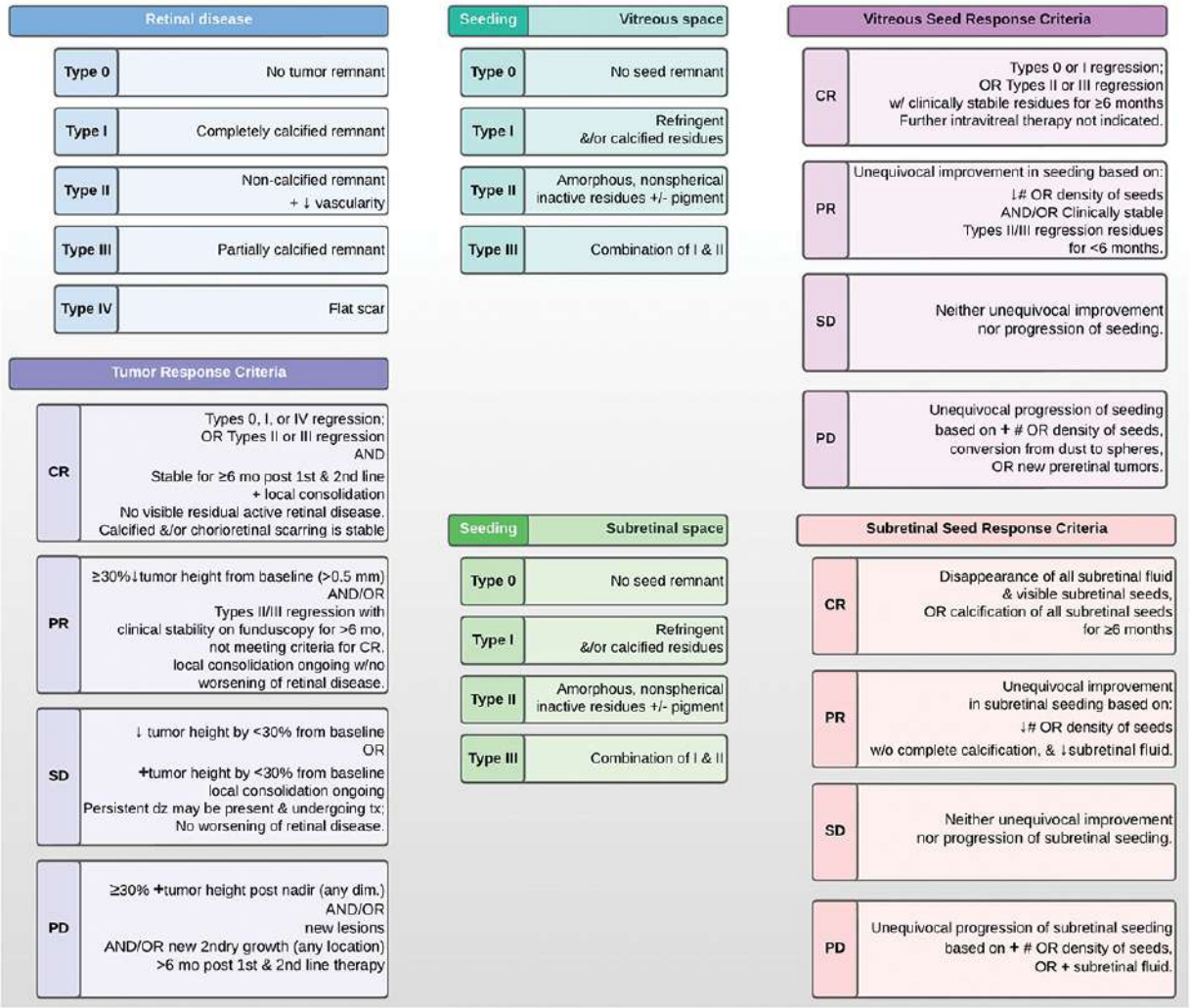


FIGURE 98.6 RB-RECIST criteria and response type for retinal tumors, and vitreous and subretinal seeds.[72] +, plus; ↓, decrease; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

The primary goal of treatment is to achieve a cure, that is, to save the patient's life, and the secondary goal is to preserve the eye and vision. Furthermore, preventing second primary cancer is a crucial objective, especially in hereditary diseases. Therefore, the risk of second primary cancer must be considered when planning comprehensive treatment, particularly in the context of radiation therapy. Decisions regarding the extent of treatment depend significantly on staging and laterality.

The intensity of treatment varies based on the extent of the disease, histopathologic features, genetics, and the patient's age. Treatment decisions also consider factors such as the availability of treatment options,

medications, specialists, and other resources, which can vary depending on a population's income level.[2] For developing countries, evidence-based treatment guidelines from various cooperative groups exist.[73-76] Currently, a collaboration between St Jude Global and the International Society of Pediatric Oncology (SIOP) is developing an adapted resource and implementation application guideline[77] with recommendations for the global management of unilateral retinoblastoma across all resource settings.[77]

General Approach in Intraocular Retinoblastoma

In the context of intraocular retinoblastoma, first-line therapy offers several treatment options, including focal therapy, chemotherapy, and surgery (Table 98.3). EBRT no longer plays a significant role in first-line treatment for intraocular retinoblastoma due to concerns about ionizing radiation exposure in patients with retinoblastoma (see Chapters 1).

TABLE 98.3 INDICATIONS FOR RADIATION THERAPY IN RETINOBLASTOMA

	Brachytherapy	External Beam Radiation Therapy
Intraocular RB	**Plaque Brachytherapy**	**Highly Conformal Radiation Therapy**
First-line treatment	*Not routine, rare indication* • Unsuitable for other focal therapies • Incomplete response with other local therapy • Eligibility criteria (tumor size and localization)	*No role* —
Second-line treatment	*Routine indication* • Unilateral RB after local treatment failure • PR to CTx and nonirradiative focal therapies	*Not routine, rare indication* • Globe preservation of remaining eye in bilateral RB ("last" eye) after prior contralateral eye enucleation • Select high-risk RB (eg, diffuse vitreous seeding)
Contraindications	• Vitreous seeding (>2 mm of tumor surface) • Dimensions unsuitable (depth, width)	• Lack of useful vision

	Brachytherapy	External Beam Radiation Therapy
Intraocular RB	**Plaque Brachytherapy**	**Highly Conformal Radiation Therapy**
	• Involvement of anterior chamber	
Extraocular RB	**Orbital Brachytherapy**	**Highly Conformal Radiation Therapy**
First-line treatment	*No role* —	*Common indication* • Part of multimodality approach as adjuvant therapy • Regional spread: lymphatic involvement • Intracranial metastatic disease (CSI, trilateral disease) • Extracranial metastatic disease (bone, soft tissue)
Second-line treatment	*Rare indication* • Recurrence in the bony orbit after prior EBRT	*Rare indication* • Palliation
Contraindications	• Gross orbital extension • Positive optic nerve margin	—

ant., anterior; CSF, cerebrospinal fluid; CSI, craniospinal irradiation; CTx, chemotherapy; EBRT, external beam radiation therapy; RB, retinoblastoma.

Whenever feasible, patients receive conservative treatment without the need for enucleation. Over the past decade, chemoreduction strategies have emerged to initially reduce extensive tumor volume before implementing focal therapy in children with residual useful vision.[68,69] Intra-arterial chemotherapy or intravenously (IV) administered chemotherapy is now considered the first-line therapy for early-stage retinoblastoma. In addition, nonirradiative focal therapies such as laser photocoagulation, cryopexy, and hyperthermia have demonstrated promising disease control rates, favorable vision preservation, and an acceptable toxicity profile. For small tumors, focal therapies alone may suffice. In selected cases (eg, small, isolated tumors distant from critical structures), plaque brachytherapy is a viable treatment option.[68,78]

Enucleation, while resulting in a cure for unilateral intraocular disease, comes at the cost of complete vision loss. Therefore, enucleation is reserved as salvage treatment when initial focal therapy failed. However, specific clinical features, such as neovascular glaucoma, nonfunctional eyes, and anterior disease, may necessitate primary enucleation.[68] Enucleation allows for histopathologic evaluation of the tumor, revealing features such as massive choroidal invasion, focal choroidal invasion, and/or optic nerve invasion.[79] This assessment informs decisions regarding adjuvant therapy in advanced retinoblastoma, with the goal of preventing further spread and metastasis.

Surgery remains the primary treatment worldwide for retinoblastoma.[68] However, in LMICs, conservative treatment for unilateral disease has been relatively infrequent until now. This is partly because retinoblastoma tends to be diagnosed at an advanced stage in these countries. Consequently, the affected eye is often enucleated in developing nations.[80] Nevertheless, even in low-income settings, there is an increasing trend toward using intense chemotherapy and focal therapies to avoid enucleation. In specific situations, such as buphthalmos, neoadjuvant therapy becomes necessary to facilitate subsequent surgery.[80] In resource-limited countries, the absence of pathologic review may influence treatment decisions, which are then based on clinical investigations.[80]

Apart from enucleation, plaque brachytherapy serves as an option for residual tumors located near the optic nerve and macula, potentially as a second-line treatment.[81] While EBRT is typically avoided, proton beam therapy (PBT) may hold promise even as a first-line therapy for highly selected patients with advanced disease.[82]

For children with retinoblastoma in both eyes (bilateral disease), doctors consider the severity of the tumors in each eye to decide on the best treatment, along with the factors mentioned earlier.[68] If other treatments are not effective or are not possible, EBRT can be used as a last resort to avoid removing the eye (enucleation) in cases where the cancer inside the eye is getting worse, coming back, or resisting other treatments.

This consideration is particularly relevant in bilateral disease scenarios where only one eye remains after enucleation of the other eye.

General Approach in Extraocular Retinoblastoma

When retinoblastoma spreads beyond the eye, it can affect various areas. This includes the outer layer of the eye (sclera), surrounding tissues, the optic nerve, and even distant sites like the CSF, bloodstream (hematogenous spread), and lymphatic system. Fortunately, due to early detection, this spread of retinoblastoma is uncommon in developed countries.

Orbital Disease

Achieving a cure for children with isolated orbital disease is feasible through conventional therapies, including enucleation. In cases of unilateral orbital retinoblastoma, enucleation serves as the preferred first-line treatment. However, due to the risk of metachronous contralateral disease, enucleation is often delayed in unilateral cases, especially among very young children.

The approach to extraocular disease involves starting multiagent systemic chemotherapy to address CNS invasion, when necessary. This is followed by enucleation and subsequent chemotherapy. Orbital EBRT completes the local treatment. It is administered either after enucleation or delayed until the completion of systemic therapy (see Table 98.3). Historically, brachytherapy implants have been used in collaboration with ophthalmologic oncology surgeons following enucleation.[83] However, EBRT is now more commonly employed to prevent recurrence. In cases of subsequent recurrence within the bony orbit after prior EBRT, orbital brachytherapy may be considered. When the optic nerve and locoregional lymph nodes are involved, EBRT is indicated to prevent further spread via the CSF and lymphatic system.

Metastatic Disease

Patients with extraocular metastatic retinoblastoma require intensive multimodality therapy, including high-dose chemotherapy, stem cell rescue, and EBRT to metastatic sites. In addition to orbital radiation therapy, radiation therapy of other sites may be indicated in cases of disseminated disease. The prognosis for patients with CNS metastases is extremely poor, while those with non-CNS metastases have a potential for cure, with an

approximate 80% survival rate.[64] In cases of CNS dissemination, craniospinal axis irradiation (CSI) is the typical approach.[64] Patients with limited CNS extension along the optic nerve and/or chiasm without leptomeningeal disease may represent a potentially curable subset of CNS metastatic disease (stage IVb).[84] If a patient does not respond to standard chemotherapy, palliative radiotherapy can be offered to preserve function and improve quality of life.

Trilateral Disease

Trilateral retinoblastoma is a rare condition in patients with heritable retinoblastoma characterized by the presence of unilateral or bilateral intraocular retinoblastoma and an intracranial primitive neuroectodermal tumor, most frequently located in the pineal gland but can also occur in the suprasellar region.[85,86] This advanced stage of retinoblastoma necessitates a multimodality treatment approach, including intensive chemotherapy, with or without stem cell rescue, and radiation therapy.[87] In cases of localized intracranial disease without CSF spread, local EBRT is recommended. However, trilateral retinoblastoma often presents with leptomeningeal involvement. Therefore, CSI with a sequential local boost is the recommended approach.

HISTORY OF RADIATION THERAPY FOR RETINOBLASTOMA

While enucleation has always been considered the gold standard for disease control, the adverse impact on vision, cosmesis, and quality of life prompted providers to consider EBRT. In fact, the first examples of the use of EBRT date back to Hilgartner in 1903[88] and Verhoeff in 1921.[89,90] EBRT became the preferred means of preserving vision and preserving the globe, and in fact, early staging systems such as the Reese-Ellsworth staging system[48] were used to assess the probability of vision preservation following radiotherapy. While even its first applications were associated with vision preservation, the late effects of therapy were becoming readily apparent as even Verhoeff's patient developed a lid basal cell carcinoma. These early experiences and our mounting knowledge of the late effects of radiotherapy resulted in providers shifting preference for nonirradiative local therapies, which had the potential to offer disease control and preserve

the globe and vision. As early as the 1930s, Moore and colleagues utilized radioactive seeds to treat patients with retinoblastoma.[91] This offered substantially less exposure, similar disease control, and a comparably less morbid late effect profile. This approach matured to the Stallard method in the mid-1960s[92] such that intervening nonirradiative methods such as diathermy went by the wayside due to their excessive complications. As systemic therapy approaches became available, chemoreduction techniques were pioneered by Kupfer and colleagues[93] and were increasingly used to facilitate less extensive local therapy procedures and vision preservation. Chemoreduction cleared the path for both nonirradiative and irradiative focal therapies. Irradiative techniques such as episcleral plaque brachytherapy were heavily utilized to either consolidate or definitively treat small foci of retinoblastoma tumors in the absence of vitreous seeding. Other nonirradiative techniques soon emerged like Xenon arc photocoagulation, which was first used in the late 1950s by Schwickerath.

Alternative means of administering chemotherapy have also had a substantial impact on the need for radiotherapy. Intravitreal chemotherapy has been used as early as the 1990s for heavily pretreated eyes as a means of avoiding enucleation.[94] Periocular injections for advanced eyes were used in combination with other local therapies to facilitate globe preservation as early as 2004.[95] Meanwhile, EBRT application for RB significantly decreased from 30.5% to 2.6% between 1980 and 2000.[96] Still, other providers explored more directed approaches to deliver systemic therapy with the selective ophthalmic infusion of chemotherapy.[97] Recent clinical trials illustrate the potential for topotecan plaques to potentially supplant the use of episcleral plaque radiotherapy. While the clinical experience is early, the first results have been presented by Morganstern and Gallie at SIOP 2023.[98] Topotecan is also being explored for administration for the control of CNS disease with intrathecal (IT) administration as this is an unmet need for patients with stage IVb who almost uniformly succumb to their disease.

In the late 1940s, Robert R. Wilson, a physicist postulated the idea of using protons for clinical applications,[99] although its use was only for limited areas/body sites at select locations in the use throughout the 1950s. As proton therapy technology has evolved, it is increasingly applied for the treatment of childhood cancers. Today, proton therapy is generally accepted

as the preferred means of EBRT in retinoblastoma, when required in cases of either globe preservation or in cases of extraocular spread.

RADIATION THERAPY TECHNIQUES

Choice of radiotherapy technique for retinoblastoma varies by setting, indication, and resources.

Intact Globe: Vision Preservation

Delayed, Consolidative, or Salvage Episcleral Plaque Brachytherapy

While episcleral plaque brachytherapy utilization of either incompletely responding (non–type 1 and non–type 4 regression patterns[100]) lesions or as consolidation for high-risk localized disease,[101] its utilization has been and will continue to be reduced secondary to the evolution of other nonirradiative local therapies (cryotherapy, thermotherapy, laser, etc) and alternative means of administering systemic therapy (topotecan plaque, periocular injection chemotherapy, intra-arterial chemotherapy) (see Figure 98.6). Regardless, there will likely continue to be select circumstances where episcleral plaque brachytherapy is the only remaining potential option that preserves vision and offers favorable disease control.

Typically, episcleral plaque brachytherapy is used for tumors ≤15 mm at the base and ≤10 mm in thickness. EUA performed by an oncologic ophthalmologist is needed for determining the proper dimensions and location for treatment planning. Typically, the thickness is estimated using a B- ultrasound scan, although CT and/or MRI can be complementary and aid three-dimensional (3D) planning. RetCam images obtained at the time of EUA can be co-registered with CT and/or MRI by specialty planning groups like EyePhysics to ease improved localization and improved organ sparing (optic nerve, macula, lens, etc). 3D planned cases can also facilitate calculation of approximate suture coordinates for plaque placement by the ophthalmologist in lieu of difficult transillumination at the time of the brachytherapy procedure for smaller tumors. The treating radiation oncologist and oncologic ophthalmologist should review serial fundus

diagrams to ensure that the appropriate lesion is targeted when 3D approaches are utilized.

The choice of the plaque type/model will depend on the availability and preferred supplier of the treatment radiation oncologist. While historically Collaborative Ocular Melanoma Study (COMS) plaques standardized the application of episcleral plaque brachytherapy for small retinal/choroidal tumors, their dimensions and dosimetry are not optimal for application in children.[102] More recent designs have been shown to reduce integral dose, provide improved organ at risk sparing, and target coverage. When choosing the plaque size/dimensions, the treating provider should ensure that the entirety of the tumor base is covered entirely with a tumor-free margin of 1 to 2 mm on all sides (Figure 98.7). When the relationship between the chosen plaque and tumor does not meet the prior criteria, the next largest plaque template should be chosen. One exception to the prior statement is when the tumor closely approximates the optic nerve (ie, juxtapapillary tumors). In these situations, the plaque may be trimmed or notched around the optic nerve so that the posterior edge of the plaque lies between the optic nerve and the posterior edge of the tumor.

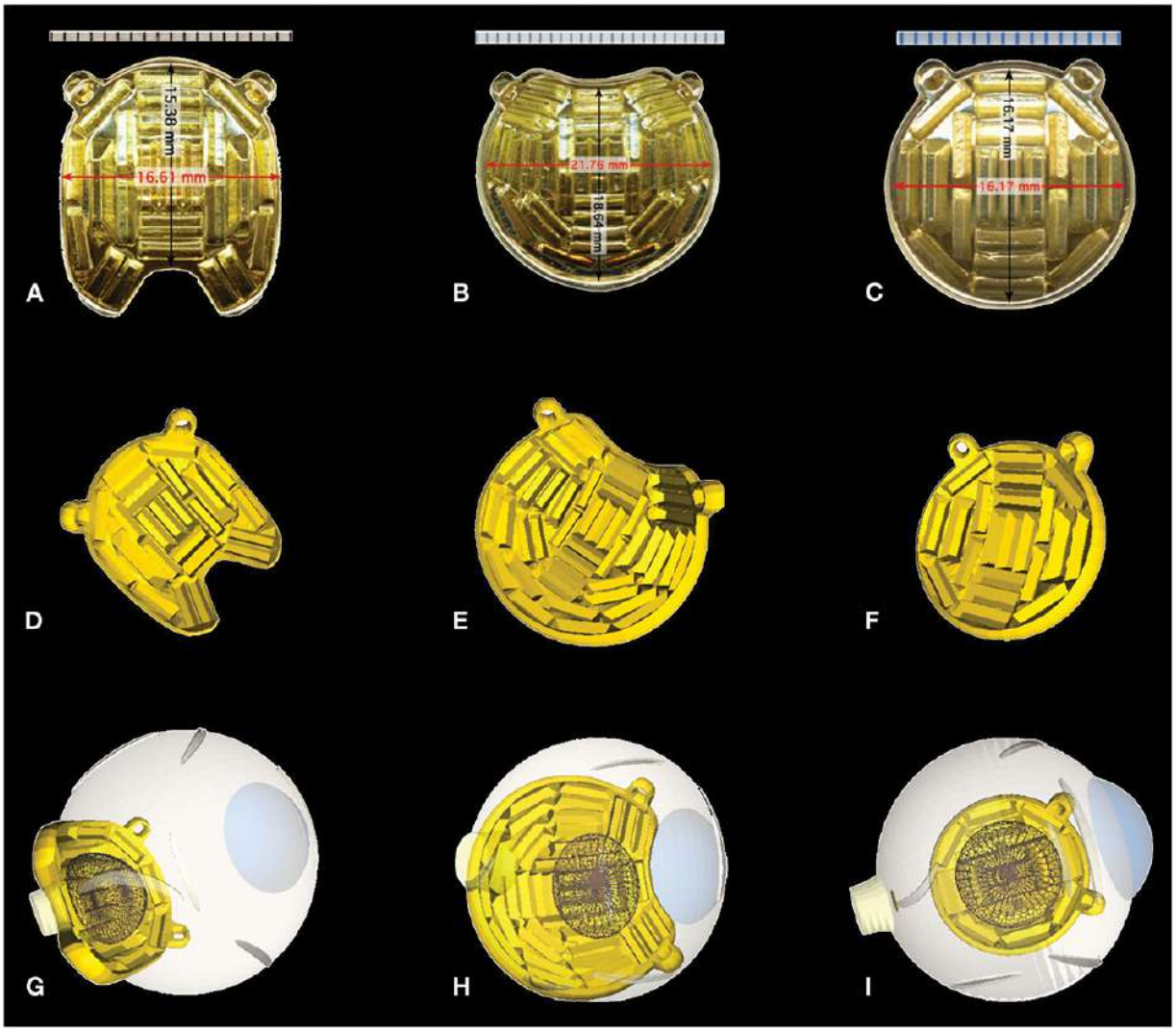


FIGURE 98.7 Representative episcleral plaque designs. A-C. Notched, limbus, and circular plaques respectively. D-F. Three-dimensional reconstructions of the plaque used in plaque simulator planning software. G-I. Representative placement of each plaque adjacent to the optic nerve (G), lens (H), and typical unobstructed globe location (I). (Adapted with permission from Melvin Astrahan, PhD, Eye Physics LLC. Available from https://www.eyephysics.com/)

Prescribing radiotherapy with episcleral plaque radiotherapy requires knowledge regarding the aforementioned dimensions, radionuclide choice, tumor location, and planned treatment dates/duration. Radiation is prescribed to the apex of the tumor, regardless of whether TG-43U or model-based dose calculation methods are utilized.[103] When tumors are thinner than 5 mm, the prescription depth is 5 mm. The sclera is assumed to be 1 mm thick, so this is added to the prescription depth. When the plaque

design requires a seed carrier that adds to the distance between the seeds and the tumor, this thickness should be added to the prescription depth (ie, silastic carrier in COMS plaques). While vitreous seeds are a contraindication for successful episcleral plaque radiotherapy, approximating seeds are not, and these should be added to the prescription depth when present. The total tumor dose ranges from 36 to 45 Gy, with 40 Gy being the most commonly used dose. A representative plan is shown in Figure 98.8. The dose rate at the prescription point should be ≥35 cGy/h but <65 cGy/h. Generally, tumors are treated over 3 to 5 days to facilitate placement removal at the beginning and end of a week, although it is frequent that providers will place a plaque to facilitate treatment over the weekend. The choice of radionuclide will depend on isotope availability and tumor characteristics. Iodine-125 (^{125}I) is the most commonly utilized isotope and, in general, is favored for thicker tumors over palladium-103 (^{103}Pd) and ruthenium-106 (^{106}Ru), which are preferred for thinner tumors (Figure 98.9). Prior treatment planning calculations used for COMS plaques have ignored the effect of the gold backing on scatter, attenuation, and shielding effects of the collimating lip. Recent analyses indicated that these should be taken into account as they may facilitate clinically significant reduction of doses to eye structures of interest.[104] As such, some providers have recommended that these adaptations be incorporated in future versions of the existing American Association of Physicists in Medicine TG43 brachytherapy formalism.[105]

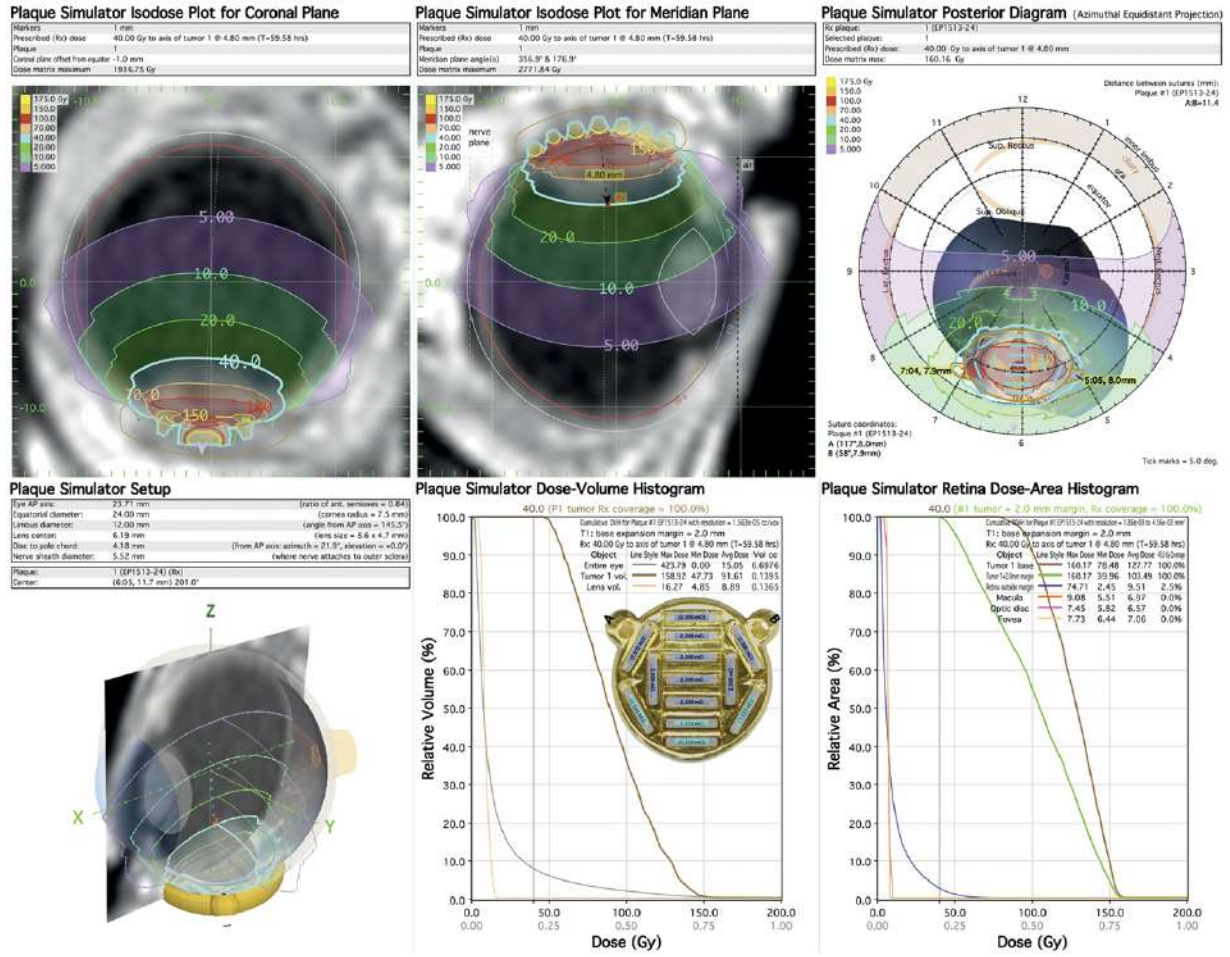
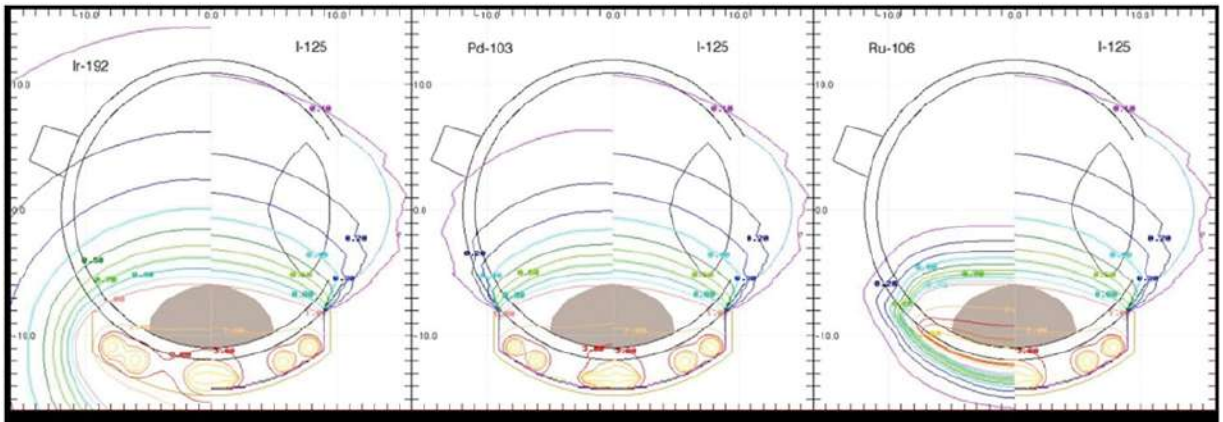


FIGURE 98.8 Representative episcleral plaque brachytherapy plan. The two top left panels are representative coronal and meridian plane depictions of the plaque with adjacent tumor with corresponding isodose lines. An azimuthal equidistant projection is shown in the top right adjacent with the optic nerve sheath represented centrally. A three-dimensional depiction of the plaque localized on the globe is shown in the bottom left. The bottom right two figures depict coverage of the tumor and organs at risk for the represented case. Finally, in the middle bottom portion of the figure is the representative plaque with ^{125}I seeds of varying strengths. (Reprinted with permission from Melvin Astrahan, PhD, Eye Physics LLC. Available from https://www.eyephysics.com/.)



Radionuclide	Half-life	Energy	HVL(mm lead)
^{60}Co	5.26 yr	1.17 & 1.33 MeV	11
^{192}Ir	73.8 d	0.136-1.06 MeV	2.5
^{125}I	**59.4 d**	**~28 keV**	**0.025**
^{103}Pd	17 d	~21 keV	0.008
^{106}Ru	368 d	~1.4 MeV	12

FIGURE 98.9 Plaque radionuclide comparison. Comparison of commonly used radioisotopes in brachytherapy planning including ^{192}Ir (left), ^{103}Pd (middle), and ^{106}Ru all relative to ^{125}I. The table depicts the half-life, energy, and half-value layer (HVL) (mm lead) for each radioisotope.

While treatment volumes and organ at risk definitions are not needed for 1D planning, these may be incorporated into 3D plans to facilitate improved tumor coverage, and visual structure dose sparing (see Figure 98.8). When 1D methods are utilized, dose reporting should be completed according to Krintz et al.[104] When 3D methods are used, target coverage, organ at risk doses, and plan quality should be assessed according to Fili et al.[106]

Several locations may be challenging for plaque placement (see Figure 98.7). When the application of plaque brachytherapy is the last line of salvage, anterior hemispheric plaques may be preferable for iris or ciliary body lesions as these may limit lens dose. Given that this may result in an increased dose to the trabecular meshwork of the eye, any signs of increased intraocular pressure should be promptly evaluated clinically. Juxtapapillary tumors are also challenging, and in these cases, a notched plaque is preferred. In these applications, seeds are inserted into notched plaque sites such that the posterior edge of the plaque lies between the optic

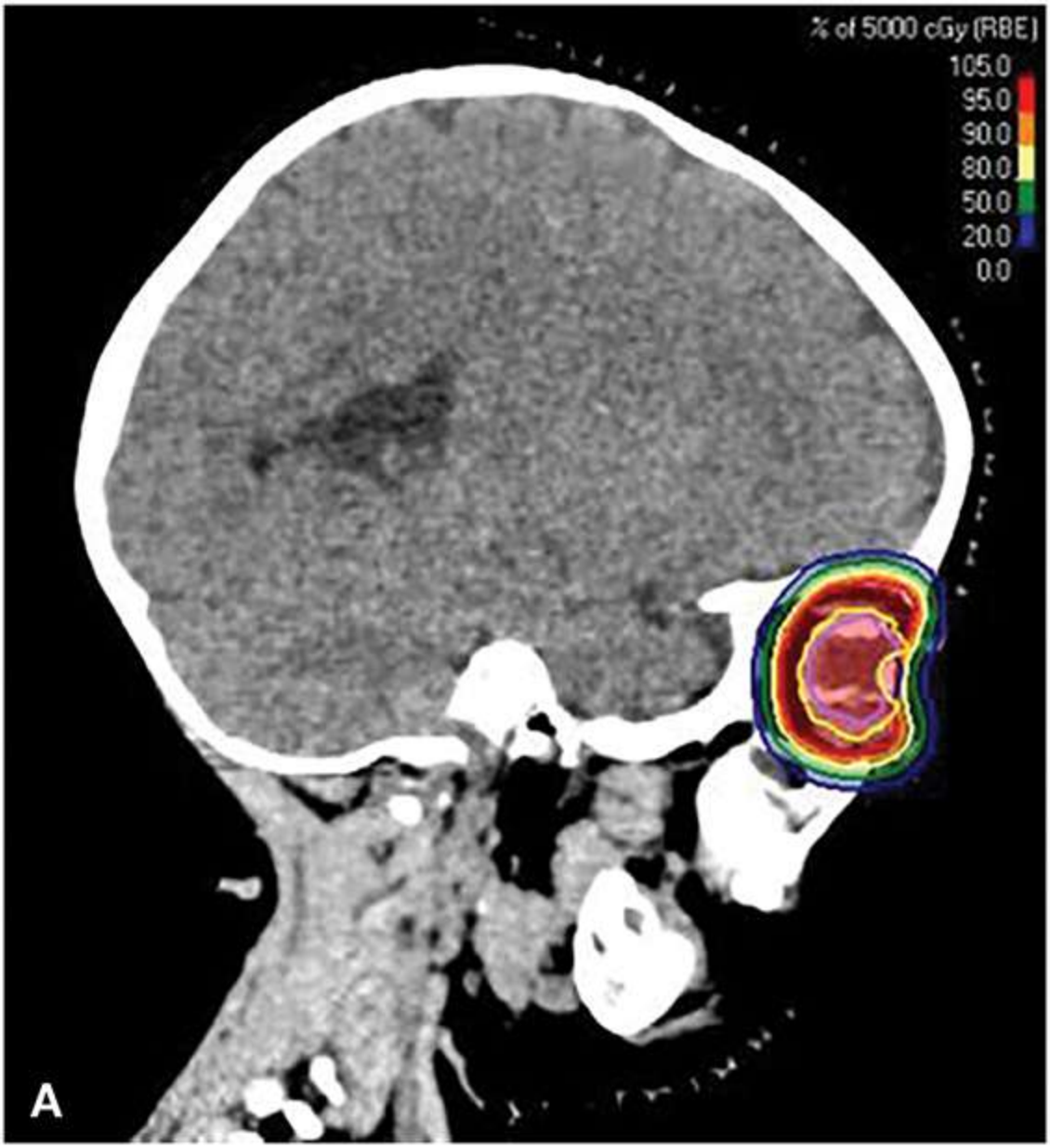
nerve and the posterior edge of the tumor. Varying source strengths may allow for some dose modulation across critical structures such that maximal vision preservation may occur.

Plaque placement takes place in an operating room under the direction of an ophthalmologic oncologist under general anesthesia. The procedure typically consists of lesion visualization, transillumination for localization, tumor margin marking, occasional muscle release (if necessary), plaque application, and stitching (two-three) followed by 3 to 5 days of treatment. Immediately following the procedure, plaque placement safety procedures should be tightly adhered to. This includes careful confirmation of the directive, activity calculations, proper shielding, and subsequent survey of the room and patient to account for all sources of radioactivity. Generally, one-two excess seeds are ordered to be assayed locally prior to implantation. Outpatient care is typically recommended unless the child is expected to encounter pregnant women or persons less than 18 years of age. Lead shielding is typically placed over the treated eye and should be worn at all times. The patient should sleep in their own bed when the plaque is in place and avoid touching the eye (aided by the shield). As long as the guidelines are followed, caregivers can stay with their child for as long as needed. However, they will usually be given a radiation badge as a precaution. The patient's family should be provided with the contact information for the treating radiation oncologist in case of a medical emergency or if the plaque becomes dislodged.

External Beam Radiotherapy

EBRT to the retina and vitreous cavity is infrequently provided for patients with an intact globe. The most common indication is in a patient with bilateral disease with prior enucleation and one remaining eye with useful vision (see Table 98.3, Figure 98.10). In these cases, the optimal vision preservation outweighs the potential late effects concerns associated with treating a patient with a germline *RB1* mutation. The choice of modality and technique for these cases is predicated on minimizing treatment exposure to any uninvolved tissue to limit the potential for out-of-field complications. Total dose is usually 40 to 50 Gy, given with a 1.8 or 2 Gy single dose. Typically, proton therapy is preferred, and a single lateral field may offer

the best balance between vision preservation, disease control, and limited late effects. Unless extrascleral extension is documented, the radiation target is either the posterior aspect of, or the entirety of the globe and should be defined as the clinical target volume (CTV). The gross tumor volume (GTV) is defined as the visible imaging defining the extent of the retinal tumor. The anterior chamber may be excluded from the CTV if no anterior disease is present and sufficient immobilization is available. The setup/immobilization appropriate planning target volume (PTV) should be defined by the treating institutional physics team.


% of 5000 cGy (RBE)
105.0
95.0
90.0
80.0
50.0
20.0
0.0
A

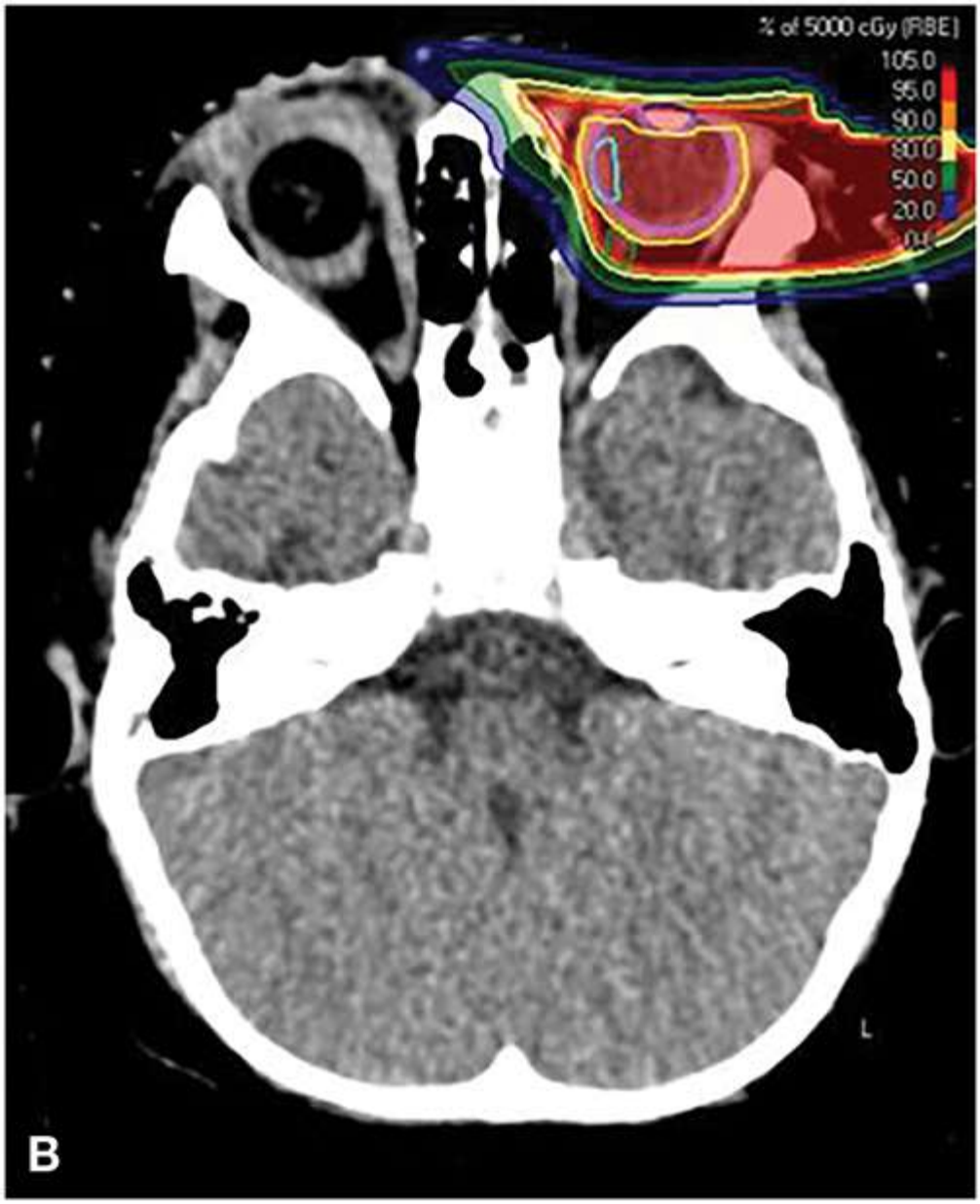


FIGURE 98.10 Dose plan for proton beam therapy (PBT) in intraocular bilateral retinoblastoma. Treatment with chemotherapy, focal laser, enucleation of the right eye, and intravitreal chemotherapy and radiation therapy to the remaining eye (as the last possible treatment option before enucleation of the second eye). PBT to the bulb dorsal of the ora serrata to a total dose of 50 Gy (RBE1.1). A. Sagittal view. B. Transversal view with delineated optical nerve (green line). Colored lines represent respective isodoses. Plans are generated using the treatment planning system RayStation.

Extraocular Disease

A range of indications for radiotherapy are possible for extraocular disease (see Table 98.3). In cases of extrascleral spread, the entirety of the bony

orbit should be targeted at the CTV and either a wedged pair or single lateral proton therapy field should be used for treatment (Figure 98.11). Total dose of orbital EBRT is usually 40 to 50 Gy in conventional fractionation. If protons are not available, a volumetric arc therapy (VMAT)/intensity-modulated radiation therapy (IMRT)/arc therapy plan is preferred and should have objectives set to minimize the integral dose, approximating brain, contralateral face, and eye. In cases of positive optic nerve cut margins, a similar volume is treated with the exception that the CTV should extend beyond the apex of the orbit to the chiasm. A similar beam arrangement for proton and photon therapy is appropriate to that of the prior example. Lymph node spread is rare but may require treatment of the perifacial and/or neck nodes. In these cases, treatment targets may need to be split into two different regions, which are adequately targeted by different beam arrangements that minimize radiation exposure. Recent trials target the entirety of the lymph node station as the CTV in case of positive lymph nodes while the GTV is defined as any pathologic unresected lymph nodes within that region. Again, proton therapy is preferred, but when not available, IMRT/VMAT/arc therapy are reasonable alternatives.

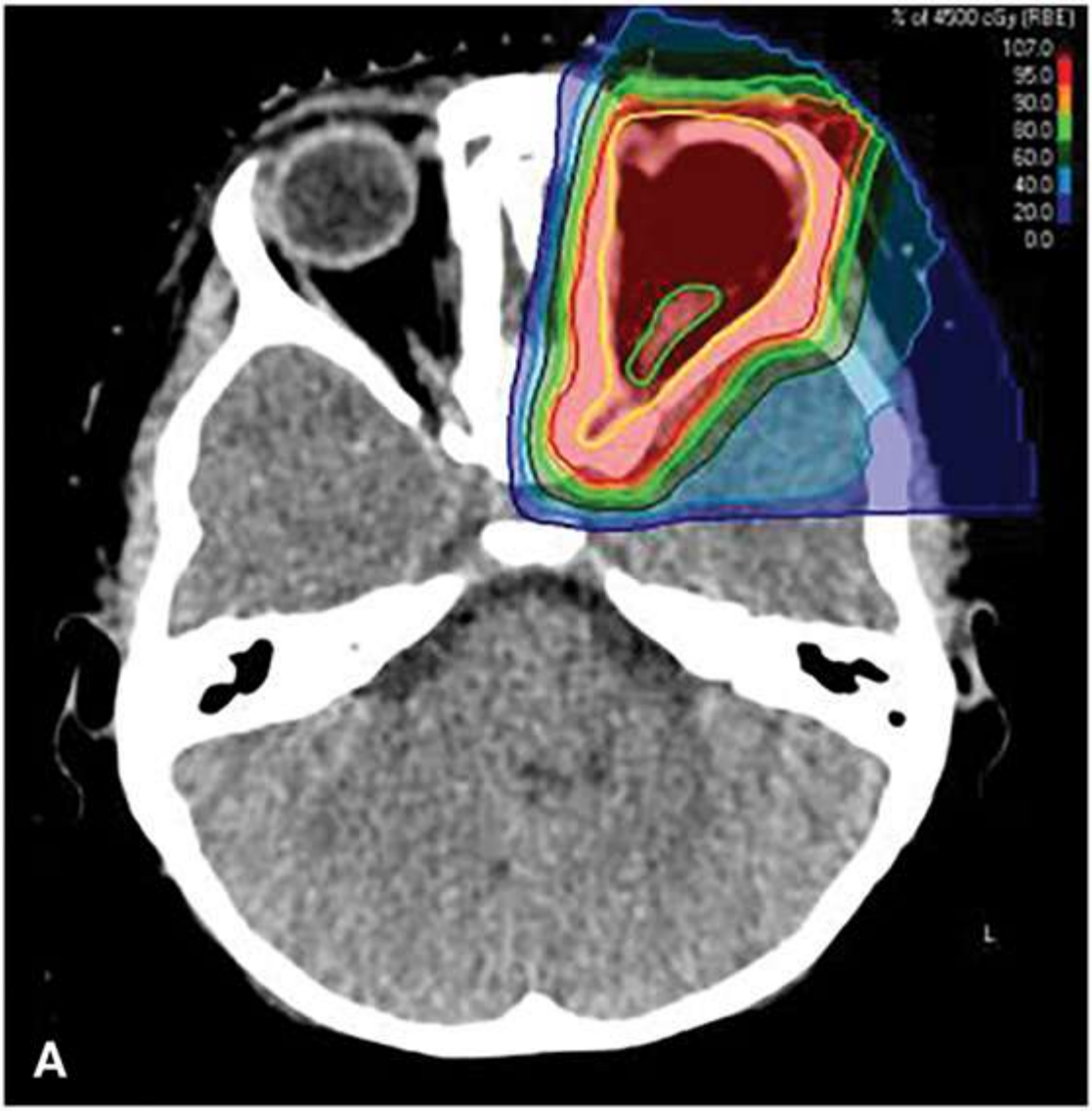

% of 4500 cGy (RBE)
107.0
95.0
90.0
80.0
60.0
40.0
20.0
0.0
L
A

FIGURE 98.11 Dose plan for orbital proton radiation therapy in a unilateral advanced retinoblastoma. Extraocular tumor growth with massive choroidal and postlaminar invasion, positive resection margin at optical nerve, and tumor cells in subarachnoid space. Treatment with primary enucleation, chemotherapy and high-dose chemotherapy with autologous stem cell transplantation, and external beam radiation therapy with a total dose of 45 Gy (RBE1.1). A. Transversal view. B. Sagittal view. Colored lines represent respective isodoses. Plans are generated using the treatment planning system RayStation.

Metastatic Disease

Intracranial Metastatic Disease

CSI is infrequently used in retinoblastoma unless the patient has stage IVb disease and has completed their systemic therapy without evidence of progression. Typically, response-adapted dosing has been used, but the

existing treatment paradigms are arranged such that CSI is delayed. As a result, most patients progress prior to the application of CSI. While ARET0321 allowed for patients in complete response to abstain from CNS-directed radiotherapy, the high failure rate and progression prior to EBRT preclude this approach from being used in routine practice as active systemic therapy approaches are not adequate to address intracranial disease. This is an unmet need in stage IVb retinoblastoma, and while some groups are evaluating the use of IT topotecan to maximize disease control, their efficacy is unknown, and as such, this approach is not considered standard. While target volume delineation and treatment technique for CSI are beyond the scope of the present chapter, general principles in CSI volume delineation were published by the SIOP-Europe brain tumor group.[107] CSI doses between 23.4 and 36 Gy are typically recommended depending on age. CSI can be followed by a local boost to the primary or spinal and intracranial metastases (total dose 36-49.6 Gy to focal spinal sites; 45-49.6 Gy to focal intracranial sites). A CSI plan using protons irradiation in a patient with metastatic trilateral retinoblastoma is presented in Figure 98.12. Multiphase treatment plans are needed when there is contemporaneous high-risk orbital disease following enucleation, trilateral disease, and/or extracranial metastatic sites.

% of 5500 cGy (RBE)
107.0
95.0
70.0
50.0
20.0
0.0
P

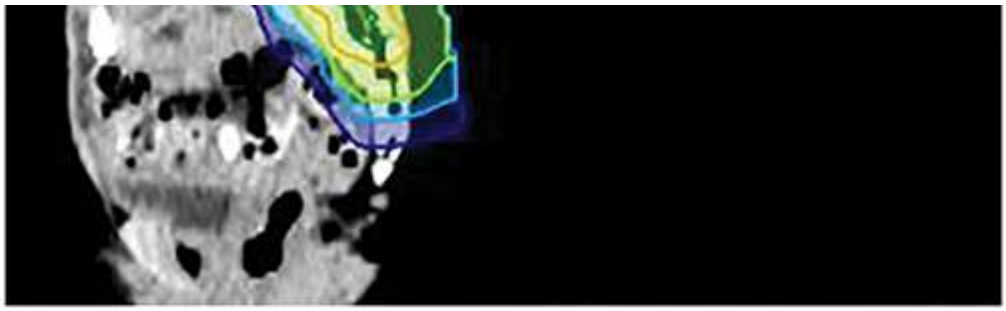


FIGURE 98.12 Composite plan of proton craniospinal irradiation (CSI) in a 3-year-old child with metastatic trilateral retinoblastoma. CSI volume (total dose 35.2 Gy [RBE1.1]) with a sequential boost to the intracranial tumor bed including residual tumor (cumulative dose 55 Gy [RBE1.1]; PTV in dark blue), and boost to metastatic sites (up to 49.6 Gy [RBE1.1]; PTVs in pink and orange). Plans are generated using the treatment planning system RayStation. PTV, planning target volume.

Extracranial Metastatic Disease

Consolidative extracranial metastatic site–directed radiotherapy was the response adapted on the last clinical trial. While patterns of failure analysis of these data have not been completed, patients in complete response were permitted to omit radiotherapy to metastatic sites. Of those who had metastatic site EBRT omitted following complete response, 14.3% experienced treatment failure, while no patients in partial response (PR) who received consolidative radiotherapy failed.[64] At present, the lack of detailed patterns of failure analysis precludes the omission of metastatic site EBRT for complete response. As such any patients with a PR at a metastatic site should undergo 36 Gy of radiotherapy at 1.8 Gy per fraction to the lesion with a 5-mm expansion to CTV and expanded setup/imaging appropriate PTV.

RESULTS OF THERAPY

Reporting of individual patient outcomes is confounded by the evolution of staging and risk stratification schemes (see Figure 98.4, Tables 98.1 and 98.2). Treatment outcomes according to several staging systems are shown in Figure 98.5. Outcomes following therapy for retinoblastoma by stage and treatment approach for high-risk stage 1, non–high-risk stage 1, and various stages of retinoblastoma with extraocular spread are shown in Figure 98.5D. Outcomes in LMICs show profound inequality relative to HIC

counterparts.[108] While death due to disease in lower stages is rare in HICs, LMIC 3-year overall survival is just 50%, and improving access to care and aiding infrastructure for early diagnosis are key to improving outcomes in this setting and as such remote screening and diagnostic approaches are being piloted.[47]

SEQUELAE OF RADIATION THERAPY

Episcleral Plaque Brachytherapy

The short-term side effects of episcleral plaque brachytherapy are largely related to the placement and removal of the plaque and include soreness, swelling, and bruising. The long-term side effects of brachytherapy potentially include blurry vision, dry eye, cataracts, retinal detachment, glaucoma, loss of eyelashes, tear duct problems, and bleeding into the eye — although the probability of many of these potential side effects will vary heavily and depend on the location of the tumor and preceding therapy.

Orbital Brachytherapy

The acute and late side effects of orbital brachytherapy are poorly characterized, given the rarity of the application. Given that brachytherapy is the most conformal radiotherapy delivery option, it is anticipated that dose to the surrounding bony orbit is reduced, which may have implications for bony symmetry and reduced risk for second primary cancer (Table 98.4), although proximal seed/catheter doses may be increased such that acute effects may be more pronounced. Dissecting the contribution of orbital brachytherapy-related side effects from preceding insult (surgical or external beam related) may also be challenging.

TABLE 98.4 SUBSEQUENT CANCERS FOLLOWING MULTIMODALITY FOR RETINOBLASTOMA AMONG HERITABLE AND NONHERITABLE PATIENTS

	Heritable Retinoblastoma Survivors						Nonheritable Retinoblastoma		
Reference	Total *N*	*N*	SBCs	SBC SIR	AER	Cumulative Incidence (95% CI)	N	SBCs	SBC SIR
Dutch[27]	668	298	62	20.4 (15.6-26.1)	86.1	28% (21-35)[a]	370	12	1.85 (0.96-3.24)
The United States[109]	1601	963	260	19 (16-21)	97.2	32.9% (27-38.9)[a]	638	17	1.2 (0.7-2.0)
British[110,111]	1927	806	146	13.7 (11.3-16.5)	57.9	68.8% (48-87.4)[b]	1121	23	1.5 (0.9-2.3)
Danish[112]	323	133	25	11.39 (7.4-16.8)	70.3	51% (NA)[c]	190	13	1.52 (0.81-2.6)

AER, absolute excess risk; CI, confidence interval; NA, not available; SBC, subsequent cancer; SIR, standard incidence ratio (observed/expected) per 10,000 person-years.

[a]Reported at 40 years of follow-up.

[b]At the end of surveillance interval for the population (range 25-84 years).

[c]Reported at 60 years of follow-up.

Adpated from Fabius AWM, van Hoefen Wijsard M, van Leeuwen FE, Moll AC. Subsequent malignant neoplasms in retinoblastoma survivors. *Cancers (Basel)*. 2021;13(6):1200. http://creativecommons.org/licenses/by/4.0/.

Orbit/Eye External Beam Radiotherapy

Short-term complications are more prominent with the use of EBRT and typically more protracted compared to episcleral plaque brachytherapy. Acute side effects may include radiation dermatitis, tearing, local swelling, flushing, and eye irritation. While symptoms may persist for several weeks following therapy, generally, these resolve within a month of completion. Long-term side effects may include dryness and inflammation in and around the cornea, changes in vision secondary to swelling under the retina with associated detachment, poor eye alignment, bleeding into the vitreous space, cataracts, and increased intraocular pressure. Given the young age at treatment, anatomic developmental issues are also possible and include underdevelopment of the socket and surrounding bony ridges and can be

exacerbated by EBRT.[113,114] While hypoplasia of the orbit is frequently attributed to radiotherapy, it is well recognized that enucleation alone can result in a similar extent of orbital hypoplasia due to the lack of mass effect exerting pressure on the surrounding bony socket.[115] In fact, post–enucleation socket syndrome may become more pronounced as the child ages and additional procedures may be required to attain favorable cosmesis.[115,116] The most feared complication is that of second primary cancer, which can occur anywhere in the treated field and is more common in patients with known germline predisposition. While formal comparisons between photon and PBT are limited, the reduced integral dose is presupposed to result in a decline in the incidence and potential severity of some complications, although the extent of this reduction will be heavily dependent on patient and disease-related factors.

Regional/Nodal External Beam Radiotherapy

Short-term side effects are expected to be comparable to other EBRT applications regarding radiation dermatitis and local swelling with a few exceptions. Parotitis, mucositis, esophagitis, and cheilitis are possible, which may lead to anorexia, nausea, weight loss, and vomiting. Long-term side effects associated with neck radiotherapy include thinning skin, reduced subcutaneous tissue thickness, shoulder/neck asymmetry, hypothyroidism, xerostomia, dental complications, and second primary cancers.

Craniospinal Radiotherapy

CSI side effects are numerous and typically associated with significant morbidity in young patients.[117] However, the prognosis associated with stage IVb is poor, and disease control without CSI is rare.

FUTURE THERAPEUTIC APPROACHES AND RECENT CLINICAL TRIALS

Retinoblastomas are the most common intraocular tumors arising in early childhood and represent a particular challenge for optimal treatment.

Future therapeutic improvements require close collaboration of all involved disciplines. Apart from the young age of the patient, multiple classification systems, various complex clinical situations in difficult local therapy locations (anterior segment or link to CNS via optic nerve, etc), limited evidence for multiple treatment approaches as well as substantial differences concerning incidences and treatment availability worldwide, make therapy very challenging. In developing countries, national health care systems have limited financial resources and infrastructure. Currently, cross-border cooperative groups are developing evidence-based treatment guidelines to address these obstacles. Various existing classification systems impede the comparison of previous results. Therefore, harmonization regarding the use of one uniform system will be crucial. Further adaptations regarding more detailed subgroup classification are proposed to improve prognostic value.[118] In future, noninvasive prognostic biomarkers like circulating tumor DNA will complement staging examinations early (ie, prior enucleation).[119] After enucleation, prognostic biomarkers will also supplement histopathologic analysis.

Contemporary high conformal techniques, such as PBT, may enable limiting radiation fields, potentially decreasing the risk of second primary cancer, even in hereditary retinoblastoma. Regarding radiotherapy doses and volumes, there are still many open questions to be addressed in the future. Only international studies will be able to generate sufficient data due to the rarity of disease. Regarding systemic therapy, targeted therapies or new drug discoveries in immunotherapy or gene therapy may add to the treatment efficacy for patients with retinoblastoma. When establishing any innovative therapy, outcomes must be evaluated in interdisciplinary clinical trials.

Current and future approaches to retinoblastoma therapy will likely continue to optimize the route and means of administration of chemotherapy in place of other local therapies. Current therapeutic approaches being investigated in both institutional and cooperative group trials are testing a range of means of administering local chemotherapy, including, but not limited to, selective ophthalmic intra-arterial chemotherapy, periocular injection chemotherapy (subtenon or subconjunctival), chemotherapy-impregnated episcleral plaques, intravitreal chemotherapy, and IT chemotherapy (for advanced disease).

Routes of administration like intravitreal chemotherapy will be essential for evaluating whether cytotoxic chemotherapy such as melphalan or topotecan can successfully clear vitreous seeding without compromising vision in advanced eyes. Ongoing trials are evaluating either intravitreal chemotherapy alone or in combination with systemic and local therapies (ClinicalTrials.gov identifiers NCT04681417, NCT04455139, NCT02866136, NCT01899066, NCT05504291, NCT01558960, NCT02792036, and NCT04990271). If successful, this could reduce the already small number of patients with bilateral retinoblastoma who have had prior enucleation requiring globe-directed radiotherapy for their remaining functional eye and has the potential to further improve the globe salvage rate.

Intra-arterial chemotherapy can be administered using a broad range of methods. The first example likely dates back to 1954 when Algernon B. Reese injected the alkylating agent, triethylene melamine, into the internal carotid artery for treatment of retinoblastoma.[120] This concept was improved upon by Yaman and Kaneko who introduced selective ophthalmic artery infusion.[97] In this technique, a micro-balloon catheter is positioned in the ophthalmic artery, allowing targeted drug delivery.[121] Currently, three principal chemotherapies are being evaluated—melphalan, topotecan, and carboplatin (ClinicalTrials.gov identifiers NCT04564521, NCT04342572, NCT03935074, NCT01393769, NCT01293539, NCT01151748, and NCT00901238). This technique has shown significant promise in reducing the systemic toxicity (ie, myelosuppression) of cytotoxic chemotherapy in very young children, and recently published trials such as that published by Wen et al demonstrated that in advanced unilateral disease, intra-arterial chemotherapy resulted in a dramatic increase in the progression-free globe salvage rate relative to conventional IV systemic chemotherapy.[122] The use of intra-arterial chemotherapy was associated with a ~20% increase in the overall globe salvage rate and had comparable overall survival to conventional chemotherapy. While intra-arterial chemotherapy rates of ophthalmic artery occlusion are rare (<5%), as many as one in five patients will develop ophthalmic artery stenosis. Extended reports of these outcomes are needed to evaluate the long-term impact on vision and globe salvage.

However, others are evaluating whether active systemic therapy agents such as topotecan can be impregnated in a carrier for local episcleral

delivery akin to what is done with episcleral plaque brachytherapy. Early results indicate that penetration into the vitreous is within a therapeutic range and has low systemic toxicity with favorable overall response rates.[123] Whether this will supplant the episcleral plaque brachytherapy remains unclear.

Finally, recent results of studies in patients with extraocular retinoblastoma demonstrate that there are unmet needs for patients with stage IVb disease. Given the early age at presentation, many providers are reluctant to provide even dose-reduced CSI for disease within the CNS. Furthermore, existing paradigms such as ARET0321 have shifted the application of radiotherapy to the completion of all other therapies such that most patients with CNS disease have progressed prior to the appropriate timepoint for administration.[50] As such, novel approaches are needed. At least three ongoing studies are evaluating the use of IT chemotherapy to mitigate the risk of CNS failure and hopefully at least stabilize the disease until the child is both a little older and has completed the rest of their systemic therapy (ClinicalTrials.gov identifiers NCT04903678, NCT03475121, and NCT02870907).

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CHAPTER 99

Rare Tumors in Children

Cheng-Chia Wu and Matthew Krasin

Many rare childhood tumors are comparable to those that occur in the adult population and require a similar therapeutic strategy, with particular attention given to late sequelae. There are groups of rare tumors, however, diagnosed predominantly in children and require specific treatment strategies including radiotherapy.

NASOPHARYNGEAL CARCINOMA IN CHILDHOOD

Nasopharyngeal carcinoma (NPC) is a rare malignant tumor in childhood and adolescence (<1% of pediatric malignancies). The frequency differs greatly by geographic area: 1 case per 100,000 in Europe, the United States, and Australia; 10 per 100,000 in North Africa; and 80 per 100,000 in South China, Malaysia, and Greenland. Interestingly, although the absolute numbers are lower in nonendemic countries (the United States, Turkey, and Israel), childhood NPC is 6% to 18% of all cases of NPC (childhood and adult) compared to less than 1% to 2% in endemic countries/regions (southern China, Southeast Asia, and the Mediterranean basin).[1] A study from 2016 found that NPC in children has a different demographic distribution relative to adults and is associated with low socioeconomic status, rural location, and more advanced disease at presentation.[2] The fifth edition of the World Health Organization divided NPC into three distinct classification groups: nonkeratinizing squamous cell carcinoma (NK-NPC); keratinizing squamous cell carcinoma (K-NPC); and basaloid squamous cell carcinoma. NK-NPC is further subdivided into two categories, undifferentiated or differentiated.[3]

Most pediatric NPC cases are undifferentiated. As in older patients, Epstein-Barr virus is associated with this type of NPC in addition to certain human leukocyte antigen haplotypes/alleles (A2 Bsin2, Aw19, Bw46, and

B17). The virus is found in the tumor cells and not in the surrounding lymphocytes. Antibody and antigen titers are useful for both diagnosis and follow-up (Table 99.1).[4] The association between dietary factors and NPC has been suspected in China and seems to be confirmed in a case-control study published by Jia et al.[5]

TABLE 99.1 ANTIGEN AND ANTIBODY EPSTEIN-BARR VIRUS (EBV) TITERS

	IgG VCA	Ig EA	IgM VCA	IgA VCA	IgA EA	EBNA
Naive patient	0	0	0	0	0	0
Immune patient	Mild	0	0	0	0	Mild
Burkitt lymphoma	Raised	Raised	0	0	0	Raised
AIDS	Very raised	Raised	0	0	0	0
NC	Very raised	Very raised	Mild	Raised	Raised	Very raised

AIDS, acquired immunodeficiency syndrome; EA, early antigen (active disease); EBNA, EBV-associated nuclear antigen (cellular immunity); Ig, immunoglobulin; NC, nasopharynx carcinoma; VCA, vision capsid antigen (immune status).

Clinical Presentation

The incidence of NPC is bimodal. First occurrences are seen in late adolescence/early adulthood (ages 15-24) with a second peak later in life (ages 65-79),[6] with a higher incidence in males (2.75:1). The disease is in part associated with EBV infection, and there is a significantly higher incidence in endemic regions including Southwest Asia, Mediterranean region, North Africa, Greenland, and Alaska. Typically, the initial presentation can range from painless mass in the upper neck, nasal obstruction, epistaxis, otitis, cranial nerve palsy, and neck and facial pain. The tumor usually originates in the fossa of Rosenmüller, followed early on by locoregional extension, including extensive pharyngeal involvement and often bone, lung, and cervical lymph node metastases.

On clinical examination, bilateral lymphadenopathy and cranial nerve palsies are found; a nasopharyngeal mass can be seen by direct or indirect nasopharyngoscopy, and sometimes, a protruding mass can be seen in the oral cavity.

The diagnostic workup must include a cranial and neck computed tomography (CT) scan with contrast, magnetic resonance imaging (MRI), and positron emission tomography- computed tomography or chest CT. Pathologic confirmation is obtained by biopsy. More recently, EBV DNA load has been tested. Commonly used staging systems are the tumor-node-metastasis (TNM)/American Joint Committee on Cancer (AJCC), Kyoto, and Ho classifications. The Ho and Kyoto systems are based on topographic extension; the more commonly used TNM/AJCC classification is based on tumor volume and CT information.[7]

Treatment

In adult NPC, T1N0M0 disease is treated with radiotherapy (RT) alone. For locally advanced NPC, concomitant RT and chemotherapy with cisplatin followed by adjuvant (cisplatin and 5-fluorouracil) is the standard of care.[8,9] More recently, phase III clinical trial showed survival benefits with neoadjuvant induction gemcitabine and cisplatin and has been accepted as the standard of care for locally advanced disease.[10] Because of the scarcity of pediatric NPC cases, it is difficult to perform randomized studies in the pediatric age group. Based on adult trials, multimodality treatment is generally accepted as the standard of care for children for Stage II or greater with potentially RT alone for Stage I.[11] Children's Oncology Group (COG) study ARAR0331 treated pediatric patients with NPC with induction chemotherapy with cisplatin and 5-fluorouracil followed by concurrent chemoradiation with cisplatin. Radiation planning was response based with dose de-escalation depending on outcome. The single-arm phase II study enrolled 111 patients. The study had a 5-year event-free survival (EFS) of 84.3% and overall survival (OS) of 89.2%. When divided by stage, patients with Stage IIb, III, and IV disease had EFS of 100%, 82.8%, and 82.7%, respectively. The cumulative incidence estimates of local, distant, and combined relapse in 5 years were 3.7%, 8.7%, and 1.8%, respectively. This has largely been the US standard approach for treating pediatric NPC.[12] Interestingly, there is much interest in further decreasing the radiation dose with the addition of immunotherapy. In Germany, pediatric patients with NPC are treated with induction chemotherapy and concurrent chemoradiation followed by a year of interferon-β. All patients received 45

Gy to the primary tumor, involved node, and the subclinical regions. Patients with complete response received a boost to 54 Gy, whereas patients with incomplete response received a boost to 59.4 Gy.[13] The EFS and OS for these pediatric and young adult patients with locoregionally advanced NPC were 93.6% and 96.7%, respectively, after a median follow-up of 73 months. This has since led to the design of two clinical trials exploring the use of immune checkpoint inhibitors in the setting for NPC.[14]

Radiation Therapy

Adult patients with NPC are typically treated to 70 Gy in the setting of gross disease. A dose-response relationship for local control with a threshold of 60 Gy has been reported in a number of series.[15-17] However, Habrand et al[18] reported interesting results with lower doses of radiation therapy (50 Gy) in patients with a good response to chemotherapy. With the results from ARAR0331 and the German study, there is evidence that dose de-escalation is feasible in pediatric patients with induction and concurrent systemic therapies. Following the COG induction therapy schema, patients are treated with 45 Gy to the high-risk nodal stations, the nasopharynx and high-risk regions, and the primary tumor. In the setting of complete or partial response, 61.2 Gy is delivered to the entire nasopharynx and residual enhancing tumor and residual lymph node. For patients with stable disease, they receive 70.2 Gy using the same approach.

Late Effects

Given the rarity of pediatric NPC, many reported patient side effects are based on historic radiation techniques. With modern- day techniques including proton therapy and intensity- modulated radiation therapy (IMRT), the true incidence is likely lower. Similarly, with a reduction in radiation dose due to induction chemotherapy response, the anticipated radiation-induced side effects are likely lower. Xerostomia is the main side effect of treatment, followed by dental caries, trismus, muscular atrophy and fibrosis, nerve palsies, and endocrine dysfunction resulting from pituitary irradiation. Significant auditory late toxicity and sporadic cases of visual morbidity, secondary to RT with or without cisplatin-based chemotherapy, have been reported.[19] The St. Jude retrospective analysis

reported a rate of 8.5% of subsequent malignancies 8.6 to 27 years after treatment.[20]

OTHER HEAD AND NECK TUMORS

Carcinoma of the Oropharynx and Salivary Glands

Schwaab et al[21] reported the largest pediatric series, with only 2% squamous cell carcinoma among 380 head and neck tumors. The more frequent sites of disease are the tongue, lip, tonsil, palate, and salivary glands. Cigarette smoking or use of smokeless tobacco has been shown to be an etiologic factor for adolescent tongue carcinoma.[22] For other sites, passive smoking, poor oral hygiene, or genetic predispositions (xeroderma pigmentosum [XP] or retinoblastoma) have been suggested.

Special attention must be paid to laryngeal carcinoma because some of the cases may develop from juvenile papillomatosis, a benign condition of the aerodigestive tract that may undergo malignant degeneration. Guidelines for surgery and radiation therapy are the same as those for adults. Combined chemotherapy and radiation can be attempted for organ conservation.[23] The node area to treat does not differ from adults and must follow the Gregoire definition.[24] Psychological support and rehabilitation programs are an essential part of the comprehensive treatment for children who undergo major surgical resection.

Human papillomavirus (HPV)-positive oropharyngeal cancer is not a significant problem in this age group, as HPV exposure is associated with sexual activity. However, in one series, the HPV prevalence in the oral cavity/oropharynx of children was 1.9%.[25] This should help guide vaccine recommendations that may help reduce the incidence of HPV-positive disease in the future.

Esthesioneuroblastoma

Esthesioneuroblastoma is a malignant tumor arising from the olfactory nerve in the upper nasal cavity. Intracranial extension is common at the time of diagnosis. Esthesioneuroblastoma is mostly seen in patients in their 20s or 60s. Positive S100 and neuron-specific enolase stains combined with negative epithelial markers strongly suggest a neurogenic origin.[26] The

clinical presentation includes nasal obstruction, loss of smell, epistaxis, and, sometimes, enlarged cervical lymph nodes. Bony structures are often involved, as well as the ethmoid and maxillary sinuses. The most commonly used staging/grouping system is by Kadish et al[26] and is based on the degree of local tumor extension. Tumors are also graded according to the Hyams system.[27]

There is no universally agreed-upon standard of care. For localized disease, tumors are resected, if possible. Because of the high risk of recurrence, postoperative RT is usually offered and has been shown to reduce recurrence risk. Earlier studies have shown local control can be obtained in more than 75% of cases.[28] Eich et al[29] and Broich et al[30] recommend combined surgery and RT in all stages. Demiroz et al[31] reviewed 26 patients treated between 1995 and 2007. The relapse rate for patients treated with surgery alone was 29% versus 0% for those treated by surgery and postoperative radiotherapy. The recommended dose is 50 to 60 Gy.

More recently, for previously untreated disease, Hollen et al showed local control rates at 5 years of 79%. The age range for these 26 patients was 3 to 82 years.[32] One large retrospective study from China examined long-term outcomes for 113 patients from 1979 to 2014. The majority of patients were Kadish stage C, and they were treated with multimodality therapy and different sequencing including 51 who received preoperative radiotherapy. The local control for preoperative RT followed by surgery was 91% at 5 years.[33]

Elective neck irradiation or dissection is not typically advocated because less than 10% of early-stage cases exhibit nodal involvement. However, node metastases are frequent if the tumor extends beyond the paranasal sinuses, and Hollen et al[32] show that elective nodal irradiation reduces the risk of regional relapse for stage B and C disease. Therefore, lymph node dissection or prophylactic irradiation may be considered under certain clinical circumstances. Chemotherapy has yet to be accepted as part of routine first-line treatment for early-stage disease, although responses to chemotherapy have been reported.[34] It can reduce tumor volume prior to surgery or RT and can be used for palliative purposes in advanced cases. Promising results with cyclophosphamide, doxorubicin, vincristine, *cis*-platinum, and etoposide, combined with RT and stem cell support, have

been reported by Mishima et al.[35] They obtained eight complete responses in 12 Kadish stage C and D patients. Neoadjuvant concurrent chemoradiotherapy as preoperative treatment for locally advanced esthesioneuroblastoma has been reported by Sohrabi et al[36] with very promising results.

Recently, data evaluating the role of proton therapy have begun to accumulate. Lucas et al retrospectively evaluated eight patients (4-21 years old), most of whom were treated with different surgery, chemotherapy, and RT sequencing; however, all received proton treatment (59.4-70 GyE). The results are encouraging with a 5-year OS of 87.5% and local control of 100% with acceptable toxicities.[37] Drescher et al[38] reported similar rates of disease-free survival (86%) with doses in the 54 Gy (microscopic) and 66 Gy (gross disease) range. They did note a spectrum of local regional effects that were identified during long-term follow-up.

Juvenile Nasopharyngeal Angiofibroma

Juvenile nasopharyngeal angiofibroma (JNA) is a malignant vascular tumor most often arising from the posterior lateral wall of the nasopharynx in adolescent males. The lesion tends to extend into the nasal cavities, maxillary and sphenoid sinuses, orbit, and infratemporal fossa. Several classifications have been proposed, but the classification of Radkowski et al[39] appears to be the most appropriate, at least for surgical purposes (Table 99.2). Common symptoms are epistaxis, cheek swelling, a visible orbital tumor, and cranial nerve palsies. JNA is more frequent in patients with familial adenomatous polyposis. A mutation in the cluster region of the APC gene was reported in several studies, suggesting that JNA is perhaps a familial adenomatous polyposis tumor.[40,41]

TABLE 99.2 STAGING CLASSIFICATION FOR JUVENILE NASOPHARYNGEAL ANGIOFIBROMA

Stage	Description
Ia	Limited to the nose and/or nasopharynx
Ib	Same as Ia, but with an extension into one or more paranasal sinuses
IIa	Minimal extension through the sphenopalatine foramen, into and including a minimal part of the medial most part of the pterygomaxillary fossa

Stage	Description
IIb	Full occupation of the pterygomaxillary fossa, displacing the posterior wall of the maxillary antrum forward; lateral and/or anterior displacement of branches of the maxillary artery; superior extension may occur, eroding orbital bones.
IIc	Extension through the pterygomaxillary fossa into the cheek and temporal fossa or posterior to the pterygoid plates
IIIa	Erosion of the skull base with minimal intracranial extension
IIIb	Erosion of the skull base with extensive intracranial extension with or without cavernous sinus invasion

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Treatment consists of surgery for small lesions, often with preoperative embolization or hormone therapy. Surgery carries a risk of significant operative blood loss. For localized JNA, the cure rate obtained by surgery alone can be as high as 90%. Resection with negative margins is required because inadequate margins will result in a high local failure rate.[42] Minimally invasive endoscopic resection has been proposed for early-stage JNA. Lesions limited to the nasal cavity and/or nasopharynx or lesions with minimal extension through the sphenopalatine foramen are suitable for this procedure. A craniofacial approach is recommended for lesions extending into the pterygoid plates.[43,44] For tumors with intracranial extension, there are recent data demonstrating near-total tumor resections with good outcomes.[45] Radiation therapy is used either as adjuvant treatment or as sole treatment in locally advanced lesions extending into unresectable areas. IMRT has been successfully applied in unresectable and recurrent tumors.[46] A wide range of doses has been used, but there is no evidence that doses of greater than 36 Gy are advantageous. Chakraborty et al[47] treated eight patients with IMRT with a median dose of 39 Gy. The local control rate was 87% with a mean follow-up of 2 years. Mallick et al[48] looked at long-term outcomes for patients treated with RT for refractory residual or unresectable disease from 1990 to 2012, with a median dose of 30 Gy and showed a 10-year progression-free survival of 70.7%. Cataract and growth retardation have been reported.[49] There is no role for cytotoxic chemotherapy in JNA. The role of antiangiogenic agents is speculative, although a recent complete molecular profile suggests other potential targets.[50]

LUNG CANCER

Bronchogenic Carcinoma

Pediatric bronchogenic carcinoma is extremely rare, and its management does not differ from that of adults. Most of the tumors occur during adolescence. Histology is more frequently undifferentiated adenocarcinoma or carcinoid tumors rather than squamous cell carcinoma.

Of 230 cases of primary pulmonary neoplasms of childhood reviewed by Hartman and Shochat,[51] less than 25% were bronchogenic carcinoma. The survival rate was very similar to that of adults, stage for stage. Treatment strategies of these patients should be similar to adults.

Pleuropulmonary Blastoma

Pleuropulmonary blastoma (PPB) is the most common malignant lung tumor in children. Up to 90% of type I, II, and III are diagnosed in children 7 years of age or younger.[52] PPB was often mixed with pulmonary blastoma until it was accepted that PPB is purely a pediatric tumor. The main histologic difference between pulmonary blastoma and PPB is the absence of epithelial carcinomatous components in PPB; PPB consists of mesenchymal stroma only. The tumor usually begins in pulmonary tissue, but it can also originate in the pleura or mediastinum.[53] According to the Dehner et al[54] classification, three pathologic features can occur: cystic (type I), mixed cystic and solid (type II), and solid (type III). According to the International Pleuropulmonary Blastoma Registry (IPPBR), the 5-year OS rates are 91%, 71%, and 53% for types I, II, and III, respectively, with the PPB type shown to be the strongest predictor of outcome.[55,56] A germ line mutation in DICER1, leading to a loss of function, is the known cause of the majority of PPB cases.[57] Messinger et al concluded that surveillance of DICER1 carriers may be reasonable to detect PPB before it progresses. Patients with DICER1 pathogenic variants are associated with other malignancies as well.[52] Some reports described PPB association with a preexisting pulmonary cyst.[58] It is unclear whether PPB arises in preexisting malformation or whether PPB induces cystic lesion formation. The report from the IPPBR showed that great vessel or cardiac extension is present at diagnosis in 3% of cases.[59]

Clinically, PPB exhibits no specific symptoms. The usual presentation is cough, thoracic pain, and fever. Respiratory impairment is unusual. Radiologic findings depend on the extent of the cystic component (Figure 99.1). The standard treatment is surgery alone with chemotherapy included, and RT is used in a minority of cases.

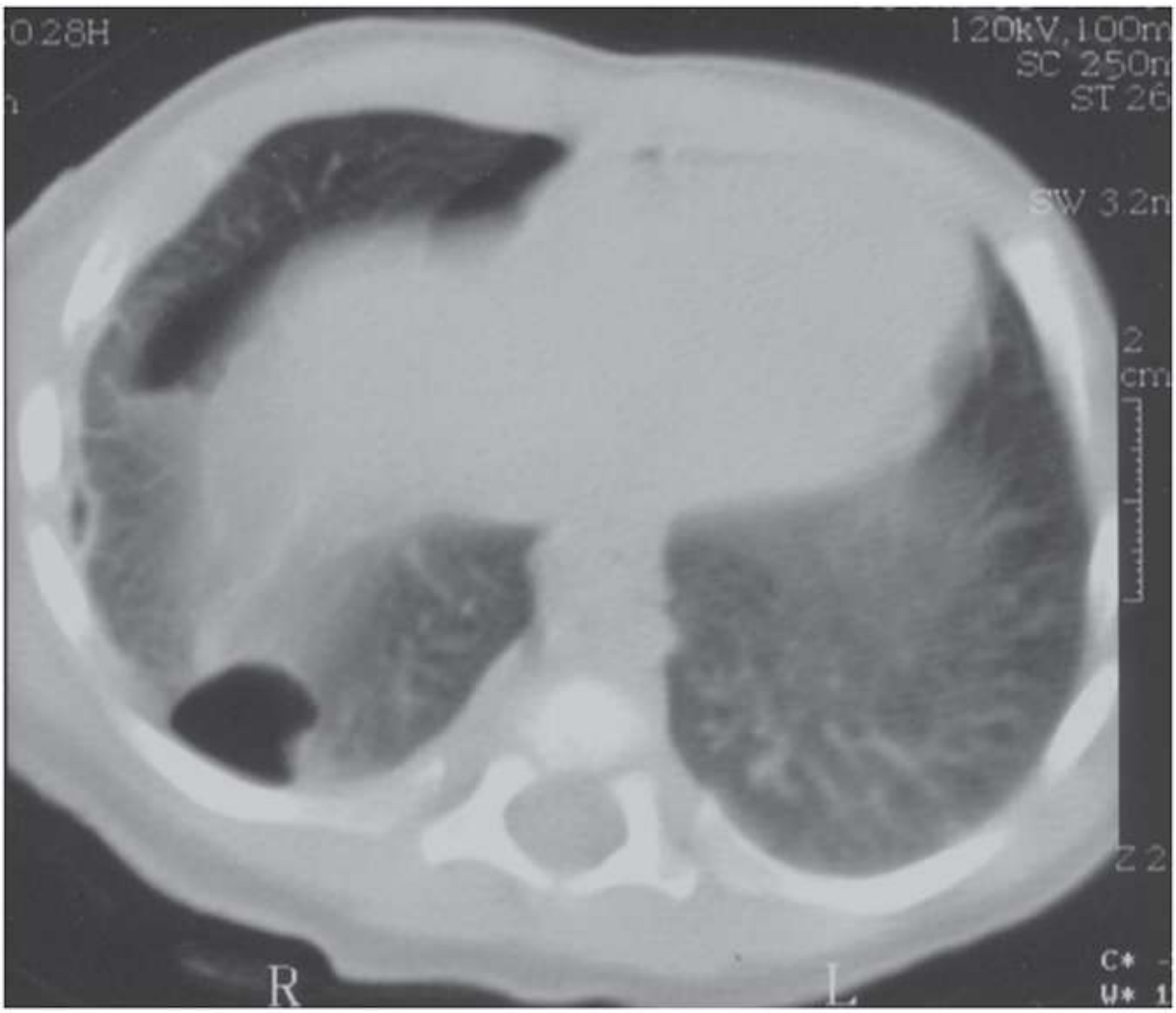

FIGURE 99.1 Pleuropneumoblastoma in a 1-year-old girl.

Priest et al reported an only 8% survival rate at 5 years among 50 patients[60]; however, large cohorts described earlier showed superior outcomes. Multimodal therapy with surgery followed by chemotherapy and RT (10.5 Gy) has been reported[61]; however, the IPPBR study examining the largest patient cohort demonstrated no benefit from adjuvant radiotherapy.[56]

The value of chemotherapy is somewhat controversial for type I PPB. Because of higher metastatic potential, multiagent combinations such as actinomycin D, cyclophosphamide, cisplatin, etoposide, doxorubicin, and vincristine have been used in type II and III PPB.[53,62-65] Long-term survival can be achieved for patients treated with surgery and chemotherapy; however, the optimal combination of chemotherapy drugs or their direct impact on outcomes is less clear. Current plans by the COG include the proposed study, ARAR2331, that will explore the use of camptothecins as window therapy and during consolidation and maintenance. This is in hopes of reducing local relapse and central nervous system (CNS) metastatic spread. Furthermore, this study will help standardize the approach to types I and Ir PPB. Lastly, it will also explore the use of circulating tumor DNA as a prognostic biomarker for Types I, II, and III PPB.[52]

BREAST TUMORS

Malignant breast tumors account for less than 1% of all childhood cancers and less than 0.1% of all breast cancers.[66-68]

A review of adolescents seen at the MD Anderson Cancer Center during a 40-year period identified breast cancer in 16 patients younger than 20 years of age.[69] Ten patients had primary adenocarcinoma of the breast, four had cystosarcoma phyllodes, and two had breast metastases from other primary tumors. Four of the 16 patients had a family history of breast disease. Roisman et al[70] reported seven female patients, ages 14 to 17 years, who were treated in various hospitals in Israel for malignancy of the breast between 1967 and 1989. There were two cases of undifferentiated carcinoma with positive axillary lymph nodes, two cases of cystosarcoma phyllodes, one case of rhabdomyosarcoma, and two cases of malignant lymphoma, one of them Burkitt type. Umanah et al[71] reported 1 case (1.2%) of an invasive ductal carcinoma among 84 breast tumor materials from patients aged 10 to 19 years in a Nigerian city.

Ultrasonography is the most appropriate initial investigation in any adolescent patient with a breast mass because dense breast tissue adversely affects the quality of mammography.[72] MRI is recommended for diagnosing breast cancer when conventional imaging is complex and indeterminate, especially in young patients with dense mammographies.

Juvenile secretory carcinoma of the breast is rare and was first described by McDivitt and Stewart[73] in 1966 in seven girls ages 3 to 15 years, all of whom had a benign clinical course. The tumor cells are characterized by abundant mucin- and mucopolysaccharide-containing materials.[74] Hormonal receptors are generally negative.[75] Local tumor excision alone may be adequate therapy, although simple and radical mastectomies have also been used.

The histology and patterns of the spread of adenocarcinoma of the breast in children and adolescents are similar to those in adults. Because most publications refer to isolated cases, neither a consensus of opinion nor specific guidelines exist with regard to treatment. In general, principles of clinical management established for adults should be adopted. Because recurrences were found in 25% of patients treated with excisional biopsy alone, this seems inadequate, and a simple mastectomy with axillary lymph node dissection should probably be performed.[76] Sentinel lymph node biopsy offers an approach to stage the axillary lymphatic drainage, with a lower complication rate than formal dissection.[77] On the other hand, McDivitt and Stewart[73] believed that the disease tends to run a relatively favorable course and that radical therapy is therefore unnecessary. Hartman and Magrish[78] considered it important to avoid RT in young children, and instead, they recommended radical mastectomy. A multidisciplinary approach is necessary to review the risks, benefits, and long-term toxicities associated with treatment decisions.

Inflammatory carcinoma of the breast is extremely rare in children. There have been case reports of primary lymphoma, rhabdomyosarcoma, adenoid cystic carcinoma, radiation- induced sarcoma, and cystosarcoma phyllodes of the breast in children.

Cystosarcoma phyllodes appears as a large breast mass; in 25% of cases, it is bilateral. Norris and Taylor[79] were the first to separate benign from malignant lesions in this disorder. The distinction is based on tumor size, stromal invasion, cellular atypia, degree of mitotic activity, focal calcification, and/or patterns of infiltration. Metastases occur in the lungs and bones. Lymph node metastases are extremely rare. Simple or wide local excision or simple mastectomy, with rare local recurrences, may adequately treat histologically benign lesions. In malignant cystosarcoma phyllodes, some authors recommend radical mastectomy with or without axillary

lymph node dissection, and others are in favor of simple mastectomy.[80,81] The use of RT and postoperative chemotherapy in cystosarcoma phyllodes is controversial. These modalities should be reserved for locally advanced, palliative, and disseminated cases.

Rhabdomyosarcoma of the breast, either primary or metastatic, is rare. Billroth reported the first case of primary rhabdomyosarcoma in a 16-year-old girl in 1860.[82] In a series of 108 patients younger than 20 years of age with this malignancy, Howarth et al[83] reported seven patients who had metastatic tumors to the breast with primary rhabdomyosarcoma located on an extremity or buttock. Six of the seven patients had alveolar histology. Rhabdomyosarcoma of the breast and other sarcomas of the breast are treated primarily by surgery followed, in most cases, by adjuvant radiation and chemotherapy.

Breast metastases in the pediatric age group include hepatocarcinoma, non-Hodgkin lymphoma, rhabdomyosarcoma, Hodgkin disease, neuroblastoma, and adenocarcinoma.[84]

GASTROINTESTINAL TUMORS OF CHILDHOOD

Gastrointestinal tract malignant tumors are relatively rare in children. Carcinoid and hepatobiliary tumors are the most common.[85] Others are adenocarcinoma, lymphoma, and leiomyosarcoma. More common are benign tumors such as hamartoma, leiomyoma, neurofibroma, and hemangioma.

Esophagus

In most cases, an esophageal tumor is of epithelial origin, either squamous cell carcinoma or adenocarcinoma. Rarely, sarcomas may develop in the esophagus (leiomyosarcoma, carcinosarcoma, and malignant schwannoma). Malignization of a chemical injury to the esophagus has been described.[86] Carcinoma of the esophagus may develop in association with Barrett esophagus and Cornelia de Lange syndrome.[87,88] McGill et al[89] reported on a 16-year-old 3-year survivor of gastroesophageal junction cancer following resection and chemotherapy. The most common benign tumor of the esophagus in the pediatric age group is leiomyoma; desmoid and teratoma

may also occur. The management of esophageal cancer in the pediatric age group follows the same guidelines of treatment as in adults.[90]

Stomach

Adenocarcinoma is extremely rare, representing less than 0.05% of pediatric gastrointestinal malignancies; it may arise in association with Peutz-Jeghers syndrome.[91] *Helicobacter pylori* infection also appears to be a risk factor.[92] In children, the prognosis is exceedingly poor with a median survival of 5 months.[93] A report from 2015 described an *H. pylori*– positive antral tumor in a 16-year-old boy.[94]

Non-Hodgkin lymphoma is the most frequent gastric malignancy in the pediatric age group, followed by leiomyosarcoma and leiomyoblastoma.[95] The management of non-Hodgkin lymphoma follows the treatment guidelines of non-Hodgkin lymphoma in adults. There is also some evidence that primary gastric Burkitt lymphoma may also be associated with *H. pylori*.[96]

Leiomyosarcoma of the stomach is treated primarily with surgery. Postoperative irradiation is given to patients with a high risk of local recurrence (such as positive surgical margins or extension into the retroperitoneum).

As in the adult age group, subtotal gastrectomy with resection of associated lymph nodes is the treatment of choice for children with gastric carcinoma. No data are available on adjuvant radiation-chemotherapy in the pediatric age group. In adults, multiple randomized studies have shown a benefit to adjuvant chemoradiotherapy compared to chemotherapy alone if the patient has a D2 dissection with positive lymph nodes.[97] A sandwich regimen of chemo, surgery, and chemotherapy has also demonstrated a progression-free and OS benefit.[98] More recent studies with modern chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel (FLOT) have shown better outcomes.[99]

Radiotherapy guidelines are similar to those for the adult age group. At the time of RT planning, attention should be given to vital structures such as the spinal cord, kidneys, small bowel, and liver. During treatment, acute side effects may occur, such as nausea, weight loss, and fatigue.

Several combination chemotherapy regimens have been used in the adjuvant setting and for locally advanced or metastatic gastric carcinoma. Over 20% of gastric cancers and up to 33% of gastroesophageal junction tumors show HER2 overexpression.[100] There is interest in exploring the role of trastuzumab.[101]

Small Bowel

According to the Surveillance, Epidemiology, and End Results (SEER) data, the incidence of malignant small intestine tumors is low in patients younger than 30 years of age.[102] The most common malignancy of the small intestine in children is non-Hodgkin lymphoma. Sarcomas of the small bowel and carcinoids may also develop in children. Small intestine adenocarcinoma may develop spontaneously or in association with Peutz-Jeghers syndrome.[103]

Treatment guidelines are similar to those of the adult age group. Adjuvant radiation can be given after surgery for duodenal sarcomas or adenocarcinomas arising in the segment fixed to the retroperitoneum or for palliative purposes such as for pain or bleeding.

Colorectal Cancer

Carcinoma of the rectum and the large bowel is rare in children and adolescents. Recent SEER data for 2014 record a rate of around 0.4 per 100,000 for patients younger than 20 years of age.[104] Young patients with long-standing ulcerative colitis have an increased risk of developing colorectal cancer.[105] Several genetic conditions may also be associated with colorectal carcinoma in childhood and adolescence. These include familial polyposis, Turcot syndrome, Oldfield syndrome, and Gardner syndrome.[100,102-104,106-110] The genetic events associated with the development of colorectal carcinoma in familial adenomatous polyposis syndrome, from epithelial proliferation, through the formation of adenomas, to the sequential development of colorectal malignancy, have been described by Vogelstein et al,[111] and more recently, the associated mutations have been well characterized.[112]

Similar to the adult age group, signs and symptoms of colorectal cancer are related to the segment of the large bowel where the tumor is located.

Because of its rarity in the pediatric and adolescent age groups, diagnosis of colorectal carcinoma is often delayed, and patients usually present with acute symptoms that necessitate urgent laparotomy. Colorectal cancer in the young is usually diagnosed at an advanced stage, with metastases involving the omentum, peritoneum, mesenteric lymph nodes, liver, ovaries, and sometimes lungs, brain, and bones, and therefore, it carries a poor prognosis.[113]

Colorectal carcinoma is diagnosed by direct fiberoptic colonoscopy. Radiographic studies include barium enema with air contrast, CT scan, and radioisotope studies (fluorodeoxyglucose– positron emission tomography [FDG-PET]) to determine metastatic spread. Preoperative carcinoembryonic antigen (CEA) level is important both as a prognosticator and for follow-up purposes. CA19-9 has been less valuable, although some tumors produce CA19-9 without CEA production.

Adenocarcinoma of the colorectum may be well, moderately, or poorly differentiated. The mucinous variety and signet cell types are associated with an extremely poor prognosis. Mucinous adenocarcinoma is the most common histotype in the pediatric age group.[114] Unlike adult patients, in whom 60% of colonic cancers are located within 25 cm of the anus and in whom the rectum and sigmoid are also common sites for mucinous adenocarcinoma, tumors in children are probably more evenly distributed in all parts of the colon.[115] In a series reported by Andersson and Bergdahl,[116] the most common area was the transverse colon (39%). In a series of 20 patients reported by Karnak et al[117] from Turkey, the rectosigmoid area was the most frequent site of location of the primary tumor (65%, the same as in adults). Another series from St. Jude's evaluated 24 adolescents with colorectal, 21 of whom had poorly differentiated mucin-producing adenocarcinoma.[118] The disease-free survival reported was extremely poor.

Surgery alone is the primary and most effective treatment for early-stage colorectal carcinoma. Because of late diagnosis, the rate of complete resection has been less than optimal in children. In the series of Karnak et al,[117] complete resection was possible in only 6 of 20 patients. The surgical guidelines are similar to those of adult patients. Similarly, the use of chemotherapy and RT follows the guidelines of the adult age group with Sauer et al,[119] demonstrating superiority for preoperative chemoradiotherapy for T3, T4, or node-positive rectal cancer. Special attention should be given

to radiochemotherapy sequelae on the reproductive system, as both the ovaries and testes are exquisitely radiosensitive.

More recently, there have been emerging data demonstrating that adult patients with deficient DNA mismatch repair or microsatellite instability respond to immunotherapy targeting the PD1/PD-L1 immune checkpoint axis.[120] COG, in cooperation with Alliance, is exploring the role of chemotherapy alone versus chemotherapy and anti-PD-L1 immune checkpoint inhibitor for patients with Stage III colon cancer with deficient DNA mismatch repair or microsatellite instability.[121]

Appendix

The most frequent malignant tumors of the appendix in the pediatric age group are carcinoids. These tumors are usually diagnosed incidentally during surgery for acute appendicitis or during other abdominal surgery. Complete surgical removal is the treatment of choice.[122]

Pancreas

Pancreatic tumors are rare in children. The most important types are functional tumors, pancreatoblastomas, and solid papillary epithelial neoplasms.[123,124] The adult form of pancreatic adenocarcinoma rarely occurs in children.

Functional islet cell tumors are characterized by their hormonal activity. The diagnostic procedures and management follow the same guidelines set for adults.

Pancreatoblastoma, a rare tumor, accounting for 25% of pancreatic cancer in children younger than 10 years old, has an annual incidence of 0.004 per 100,000 persons.[125] The mean age of diagnosis is 5.[126] The European Cooperative Study Group for Pediatric Rare Tumors analyzed 20 patients diagnosed between 2000 and 2009.[127] The tumor is characterized by adenocarcinomatous tissue with ductal cells, acinar cells, squamoid corpuscles, and sometimes islet cell differentiation. These tumors stain positively by periodic acid–Schiff, α-trypsin, and α-keratin and in many cases can be associated with increased levels of α-fetoprotein (AFP).[128-130] Familial adenomatous polyposis and Beckwith-Wiedemann syndrome are associated with neonatal cases.[126] The SEER database from 1973 to 2004

reports 10 cases, and the United Kingdom National Registry of Childhood Tumors reports 11 cases.[131]

In most cases, the tumor is located in the head of the pancreas. In patients with a solitary noninfiltrative tumor, complete local resection without radical pancreatoduodenectomy is recommended. Unlike patients with local disease, in whom local resection can be curative, in many other cases, the tumor is clearly malignant, with porta hepatis or vascular invasion, local recurrences, and nodal and disseminated metastases. The prognosis for these patients is very poor. For unresectable diseases, neoadjuvant chemotherapy may be recommended with adjuvant chemotherapy to follow resection.

Radiation therapy is used in the postoperative setting, in locoregional recurrences, and in the neoadjuvant setting. A dose of 40 to 50 Gy is recommended.[130,132] Technical guidelines of RT planning are similar to those of the adults. Intraoperative RT for recurrent disease has also been used.

Chemotherapy has been used for unresectable tumors, to treat metastatic disease, or in the adjuvant setting.[126,133,134] Because the disease is so rare, it is impossible to set firm guidelines and treatment policies for chemotherapy in pediatric pancreatoblastoma; however, there are case reports of long-term survival and tolerance of aggressive surgical and chemotherapy regimens for locally advanced disease.[135] There is also evidence that a combination of vinorelbine and oral cyclophosphamide may be effective for relapsed disease.[136]

Papillary cystic tumors of the pancreas, also known as Frantz tumors or solid pseudopapillary tumors, are usually encapsulated lesions that can develop throughout the pancreas. They are characterized by cystic or pseudocystic spaces surrounded by residual solid tissue. Only 15% of these tumors are malignant, and they usually occur in female patients at a mean age of 24 years at diagnosis.[137]

These tumors usually present as an upper abdominal mass. Unlike other malignant pancreatic tumors, their prognosis is excellent after complete surgical excision.[138] In a retrospective analysis, Hwang et al showed that CT scan findings of an increased solid component indicated the disease was more likely to be malignant and a more radical resection should be recommended.[139]

The adult type of pancreatic adenocarcinoma is extremely rare in the pediatric and adolescent age groups. Signs and symptoms are similar to those of adult carcinoma of the pancreas.[132] These tumors are managed according to guidelines of treatment set for adult patients with surgery for resectable disease.

Hepatobiliary Tumors

Hepatobiliary tumors are the most common neoplasms of the gastrointestinal tract to occur in children. They constitute 0.5% to 2% of pediatric cancer in Europe and in the United States. Hepatocellular carcinoma (HCC) occurs more frequently in Saharan Africa and Asia.[71,140,141] This geographic clustering may be explained by the high rates of hepatitis B infection and hepatitis B serum antigen positivity.[142] This is supported by the dramatic decrease in the rate of HCC in Taiwan from 10% to 1% 10 years after a nationwide hepatitis B vaccination program was launched.[143]

Benign hepatic tumors are more frequent than malignant tumors in young children. In older children, malignant tumors become more common. Benign tumors are classified according to the cell of origin: mesenchymal (hemangioma, hemangioendothelioma, hamartoma, peliosis hepatis) or epithelial (cysts, focal nodal hyperplasia, adenoma).[144] On rare occasions, radiation therapy may be used for the treatment of hemangiomas.

Malignant tumors of the liver are classified according to the tissue of origin, with hepatocellular tumors (hepatoblastoma [HBL] and HCC) most common, constituting 75% to 90% of primary hepatic malignant tumors of childhood. Other tumors include malignant mesenchymoma, undifferentiated embryonal sarcoma, primary hepatic malignant tumors with rhabdoid features, leiomyosarcoma, angiosarcoma, hepatic sinusoid tumors, carcinoid, and non-Hodgkin lymphoma.

Bile duct adenocarcinoma (cholangiocarcinoma) is extremely rare before the age of 30. This tumor has been associated with certain rare congenital biliary anomalies, ulcerated colitis, cystic fibrosis, and sclerosing cholangitis.[144] The liver is also a common site for metastatic disease.

Of the malignant tumors of the liver in childhood, HBL is the most common. HBL occurs almost exclusively in small infants, although isolated

instances in older children and in young adolescents have been reported. These tumors occur more frequently among males.

HBL is associated with Beckwith-Wiedemann syndrome, familial adenomatous polyposis, and congenital anomalies like hemihypertrophy and cleft palate, Wilms tumor, and glycogen storage diseases.[145-147] Although the association between HBL and Beckwith-Wiedemann syndrome indicates abnormalities on chromosome 11 and loss of heterozygosity of 11p, increased incidence of HBL in families with familial adenomatous polyposis indicates abnormalities of chromosome 5q.[147,148] More recently, it has been shown that familial adenomatous polyposis cases with HBL are associated with germ line mutations of APC, located on 5q. However, the sporadic cases of HBL instead demonstrate mutations in the Wnt-β-catenin pathway.[149] Others have shown that activation of the telomerase gene, TERT, and MYC expression are associated with the more aggressive HBL phenotypes.[150]

The presenting signs and symptoms are distension of the abdomen, anorexia, vomiting, anemia, fever, and jaundice. Isosexual precocity secondary to human chorionic gonadotropin (HCG) secretion or testosterone production by the tumor can be seen in some cases.[151]

Serum AFP produced by the embryonal endoderm is increased in 84% to 90% of patients with HBL.[152] HCG and cystathionase may also serve as tumor markers.[153] Histologically, HBLs (Figure 99.2) are frequently composed of combinations of epithelial, mesenchymal, poorly differentiated, cholangioblastic and other cell types (Table 99.3). Over the years, through the collaboration of multiple cooperative groups—including COG, International Childhood Liver Tumors Strategy Group (SIOPEL), Gesellschaft fur Padiatrische Onkologie undHamatologie (GPOH), and Japanese Study Group for Pediatric Liver Tumors (JPLT)—new prognostic definitions have been created. In the United States, COG AHEP0731 is a multicenter phase 3 trial, in which patients are stratified into four risk groups: very low risk, low risk, intermediate risk, and high risk. The risk stratification is based on Evans surgical stage, Histology, and AFP level at diagnosis. Patients received risk-adaptive therapy: very low risk will be treated with surgery only, low risk will be treated with surgery and regimen T (two adjuvant cycles of cisplatin, 5-FU, and vincristine), intermediate risk will be treated with surgery and regimen F (perioperative doxorubicin in

addition to cisplatin, 5-FU, and vincristine), and high risk will receive regimen H (vincristine, irinotecan, and temsirolimus in an upfront window to assess for response rate followed by perioperative doxorubicin, cisplatin, 5-FU, and vincristine).[154] Recent results for the Low-Risk stratum showed that two cycles of adjuvant chemotherapy resulted in a 4-year EFS of 92% and a 5-year EFS of 88%. In the setting of High-Risk HBL, the addition of temsirolimus did not improve the response rate in patients treated with vincristine and irinotecan alone.[155] Further results are pending. The role of radiation for HBL is not clearly defined at this time. Radiation treatment has been used in the inoperable or metastatic setting with various degrees of success.[156]

TABLE 99.3 HISTOLOGIC CLASSIFICATION OF HEPATOBLASTOMA[323]

Classification	Microscopic Features	Clinical Features
Epithelial		
Fetal		
Pure Fetal	Well differentiated and uniform	More favorable
Crowded	Mitotically active	Often mixed with other subtypes
Pleomorphic	Nuclear pleomorphism	Seen post therapy
Embyronal	Angulated nuclei	Mixed with other subtypes
Macrotrabecular	Cells growing in trabeculae	Unclear prognosis
Small-cell	Small cells with no architecture	Aggressive, low to normal alpha fetoprotein levels
Cholangioblastic	Small duct formation	Differentiate from other cholangioblastic tumors
Mixed epithelial and mesenchymal	Blastoma, osteoid, muscle sometimes mixed with neuroectoderm and endoderm	20-30% of cases, prognosis unclear

Modified from López-Terrada D, Alaggio R, de Dávila MT, et al. Towards an international pediatric liver tumor consensus classification: proceedings of the Los Angeles COG liver tumors symposium. *Mod Pathol*. 2014;27(3):472-491. Copyright ©© 2014 United States & Canadian Academy of Pathology. With permission.

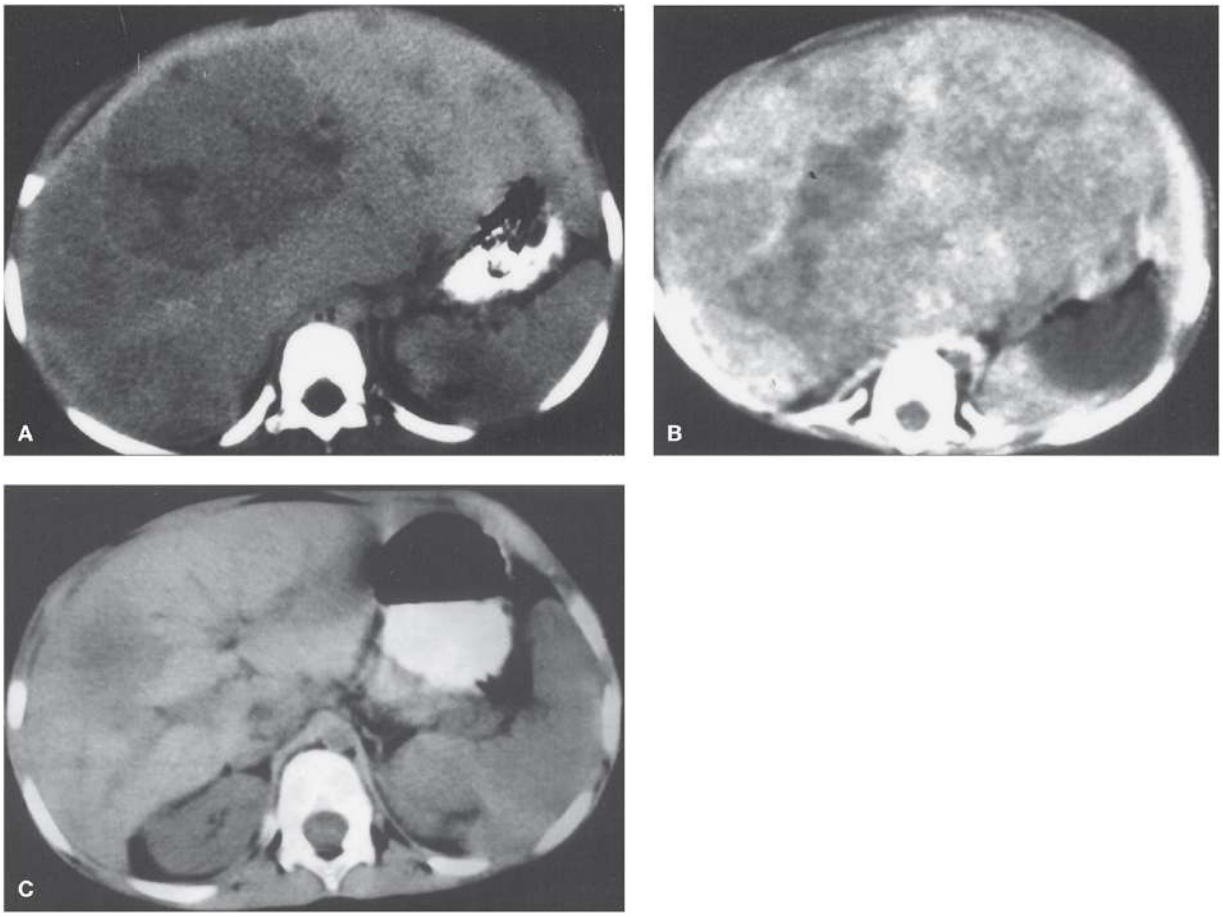

FIGURE 99.2 A 7-year-old girl with hepatoblastoma at diagnosis (A), after one cycle of chemotherapy (B), and after four cycles of chemotherapy before right hepatic lobectomy (C).

HCC is the second most common primary malignant liver tumor in the pediatric age group and accounts for about one-fourth to one-third of hepatic malignancies. Although reported in children as young as 21 months, most reports indicate that HCC usually develops in early adolescence.[157,158] This is in contrast to HBL, which occurs primarily in infancy and is seldom seen in children older than 3 years. Similar to HBL, HCC occurs mainly in males.[159,160] The fibrolamellar carcinoma variant of HCC occurs mainly in young adults around the age of 20 years but has also been reported in childhood.[161,162]

Approximately 25% of HCC cases in childhood are associated with cirrhosis secondary to biliary atresia, Fanconi anemia, glucose-6-phosphatase deficiency, and hereditary tyrosinemia.[163] The most important known etiologic factor for HCC is the high incidence of maternal

transmission of the hepatitis B surface antigen in Africa and Asia.[164,165] Other etiologic factors include exposure to aflatoxins, hepatic fibrosis, anabolic steroids, inherited disorders of metabolism, membranous obstruction of the inferior vena cava, and possibly ethanol abuse.[141,160] However, these etiologic factors apply mostly to HCC in the adult age group. In adult Black South African patients, deletions of alleles on chromosome 17p and P53 (codon 249) have been identified[166,167]; the exact molecular mechanisms responsible for the development of HCC are not known.

Similar to HBL, two-thirds of children with HCC have an elevated AFP.[168] AFP levels are high in healthy newborns and drop rapidly by the age of 1 month and should not be detectable by age 2 years.[169] Initial AFP level is a significant prognostic factor: In a study performed by the Radiation Therapy Oncology Group,[170] the mortality in HCC was 1.8 times higher in patients with strongly positive AFP. AFP is an indicator of tumor growth and can serve as a valuable marker of response to therapy. After complete tumor resection, the AFP level should return to normal within 2 months.[171] Increasing levels of AFP during the follow-up period after surgery indicate local recurrence or metastatic disease.[168]

The Children's Cancer Study Group intergroup and Pediatric Oncology Group (POG) staging systems for primary malignant liver tumors are based on resectability and on the histologic subtype (Tables 99.4[172] and 99.5[173]).

TABLE 99.4 INTERGROUP STAGING SYSTEM FOR LIVER TUMORS

Stage	Description
I	Complete resection
IA	Favorable histologic features
IB	Unfavorable histologic features
II	Microscopic residual, negative nodal involvement, and no spilled tumor
IIA	Residual in liver
IIB	Extrahepatic residual
III	Gross residual, nodal involvement, or spilled tumor
IIIA	Nodal involvement or tumor spill but tumor completely resected
IIIB	Gross tumor not completely resected

Stage	Description
IV	Metastatic disease (as per evaluation immediately before first cycle of chemotherapy)
IVA	Primary tumor completely resected
IVB	Primary tumor not completely resected

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TABLE 99.5 PEDIATRIC ONCOLOGY GROUP STAGING SYSTEM FOR PRIMARY MALIGNANT LIVER TUMORS

Stage	Description
I	Complete resection achieved
II	Microscopic residual tumor remaining
III	Gross residual tumor remaining
IV	Metastatic disease present at diagnosis

Modified from Bowman LC, Riely CA. Management of pediatric liver tumors. *Surg Oncol Clin N Am*. 1996;5(2):451-459. Copyright © 1996 Elsevier. With permission.

Successful therapy of localized HBL or HCC depends mainly on the feasibility of complete surgical excision.[174] Up to two-thirds of patients with HBL have resectable tumors at presentation because these tumors are usually unifocal and encapsulated. Cure can be achieved in one-third of the successfully operated patients, typically those with fetal HBL.[145,175]

In contrast, only 30% of the cases of HCC are suitable for complete resection at the time of diagnosis because of the multifocal involvement or size. From 50% to 75% of the fibrolamellar variant of HCC is amenable to complete resection at the time of presentation.[156,176] In principle, tumor resectability is determined by the tumor size, the existence of bilobar involvement necessitating the resection of more than three liver segments, vascular invasion, or metastatic spread. Patients with advanced disease who are not suitable for primary surgery may be considered for neoadjuvant preoperative cytoreductive chemotherapy. In these cases, the diagnosis can be based on clinical presentation; on imaging findings, including FDG-PET

scan[177] and tumor markers; or on tissue diagnosis obtained via open biopsy or CT/ultrasound-guided needle biopsy, although there are some concerns that a needle biopsy may cause a significant hemorrhage. Preoperative cytoreductive chemotherapy can reduce the size of the tumor in the majority of patients with HBL and in a significant percentage of patients with HCC, rendering them resectable. A variety of chemo regimens exist, including cisplatin, vincristine, and 5-fluorouracil,[178] the camptothecin analogues topotecan and irinotecan; oxaliplatin; and liposomal doxorubicin (Doxil).[174] Sorafenib, a tyrosine kinase inhibitor, is available for unresectable HCC. In animal models of pediatric HCC, sorafenib has shown promising efficacy.[179] A phase II trial also demonstrated a good toxicity profile for sorafenib in children.[180] Bevacizumab has shown a survival benefit in a phase II trial.[181,182] In one center's experience, bevacizumab plus conventional platinum-based chemotherapy was effective and safe.[183] If resectability cannot be achieved using chemotherapy, there is still a chance to render unresectable tumors resectable by radiotherapy.[156] The perioperative mortality of hepatic lobectomy is on the order of 5% to 10% in specialized centers applying improved surgical techniques, modern methods of anesthesia, and state-of-the-art postoperative intensive care.[184]

Surgical resection of pulmonary metastases can be attempted if they persist after chemotherapy and if the primary tumor can be completely resected. Patients who are successfully operated on for Stage I disease and later develop a solitary lung metastasis are also suitable for metastasectomy.

Total hepatectomy and liver transplantation can be attempted in unresectable HBL (about 10% after chemotherapy) and HCC (>50% are unresectable at diagnosis), with the tumor confined to the liver without penetration of the capsule and in the absence of lymph node and distant metastases. The OS is between 50% and 83%, with a minimum follow-up of 2 years. The best outcome was achieved in patients with a good response to chemotherapy who had a "first-line transplant" (ie, not after an unsuccessful attempt at resection).[174,185-187]

Although it has been used preoperatively and postoperatively in children with HBL and HCC, radiation therapy has a limited role in curative management. Transarterial radioembolization (TARE) has been used in adult patients with HCC to offer tumor local control. TARE usually requires a mapping process and a treatment process. ^{99m}Technetium-labeled

macroaggregate albumin is used to map the liver prior to treatment to assess for possible deposition of the microsphere in extrahepatic regions.[188] More recently, the use of TARE as a bridging therapy to help reach surgical resection has been explored.[189,190] Historically, standard fractionated radiation schemes have been tested, but with the usage of stereotactic body irradiation (SBRT) for adult HCC, the role of SBRT for HCC in pediatric patients has been explored. This includes utilizing SBRT as a bridging therapy for diseases with central biliary obstruction or nodal involvement.[191,192] More data are needed at this time.

LANGERHANS CELL HISTIOCYTOSIS

Langerhans cell histiocytosis (LCH), a dendritic disorder, is believed to affect fewer than 1 in 200,000 children; however, any age group can be affected.[193]

Other terms for LCH include histiocytosis X, eosinophilic granuloma, Letterer-Siwe disease, and Hand-Schüller- Christian disease; however, the preferred term is LCH.

The pathogenesis is not completely understood, but excessive production of interleukin-1, interleukin-17a, prostaglandin, and metalloproteases MMP9 and MMP12,[194] as well as of prostaglandin E_2, has been demonstrated in the affected bone. These factors can play a major role in osteoclast activation. Controversy exists regarding whether the clonal proliferation of LCH cells results from a malignant transformation or is the result of an immunologic stimulus. Regardless of the mechanism responsible for the clonal proliferation, the primary treatment, if necessary, involves chemotherapeutic agents. Select chemotherapeutic drugs also have immunomodulatory activity. The diagnosis of LCH is based on a histologic and immunophenotypical examination of tissue. The main feature is the morphologic identification of the characteristic Langerhans cells. In addition, LCH stains positive for CD1a, langerin (CD207), and S100.[195] The expression of langerin confirms the presence of Birbeck granules, the cytoplasmic organelles typically found in Langerhans cells.[196]

In children older than 2 years, the disease is less aggressive, with widespread bone granulomas causing pain, otitis, diabetes insipidus (42%), and exophthalmos. Eosinophilic granuloma is characterized by bone

involvement only and with symptoms related to the location of the granuloma. CNS involvement is possible; most frequently, meningeal and pituitary lesions occur, but intraparenchymal lesions, especially hypothalamic and cerebellar, can also be encountered.

Staging procedures include a skeletal survey (rather than an isotopic bone scan). Many prognostic scores have been proposed, all based on the extent of disease, age at diagnosis, and demonstrable organ dysfunction. Cases are classified into the following groups[197]:

- **Single system**
  - Unifocal or multifocal organ system involvement
  - Unifocal or multifocal bone involvement
  - Skin
  - Lymph node
  - Hypothalamic/pituitary/CNS
  - Other (eg, thyroid)
- **Multisystem**
  - Involvement of greater than or equal to two organs or systems

Treatment decisions are based on whether the high- or low-risk organs are involved and whether the disease is a single system or multisystem. Many cases of LCH are indolent or resolve spontaneously. Aggressive treatment therefore should not be given if there is no organ dysfunction. International efforts during the last 20 years have shown that combination therapy with vinblastine/prednisone is an effective therapy for multisystem LCH. There is the potential of adding mercaptopurine for high-risk LCH.[195] Trials conducted by the Histiocyte Society confirmed this regimen as standard therapy for multisystem LCH with and without risk organ involvement.[198,199]

Risk organs and their involvement were defined according to modified Lahey criteria as follows[200]:

- Hematopoietic: Anemia and/or leukopenia and/or thrombocytopenia
- Liver: Enlargement greater than 3 cm below the costal margin, dysfunction, or both

- Spleen: Enlargement greater than 2 cm below the costal margin
- Lung: Typical changes via high-resolution CT, histopathologic diagnosis, or both

Local Therapy

Various local therapies have been explored. Those include local steroid injection, various forms of surgical intervention, and radiotherapy.[201] The POG 8047 study demonstrated that a similar control rate can be achieved (70%-90%) with biopsy, curettage, or tumor excision.[202] Wide excision is recommended for expendable bones (clavicle, ribs) and biopsy for other sites. Curettage is not indicated if there is a risk of instability (cervical vertebra, femoral neck) or if a poor cosmetic or orthopedic outcome is likely.

Radiation therapy was widely used in the 1960s but is no longer indicated in the large majority of cases. Radiation therapy could be discussed in a case of resistant cerebral location. Tumors are very radiosensitive; however, a wide range of doses has been reported for the treatment of LCH (2.5-50 Gy).[203-206]

It appears that 9 Gy for bone lesions and 15 Gy for soft tissues will result in very high response and local control rates; however, they may still be consequential for children and should be only considered in selected cases. Typically, for pediatric cases, radiation is avoided; however, in the setting in which RT is needed, a low dose of 6 to 10 Gy is preferred to limit secondary malignancy.[201,207]

ENDOCRINE TUMORS

Adrenocortical Carcinoma

Adrenocortical carcinoma (ACC) accounts for 0.2% of childhood cancer, and in 75% of the cases, it occurs in children younger than 5 years, more commonly in females.[208-212] Half of ACCs are associated with Li-Fraumeni syndrome.[121] ACC is sometimes associated with Beckwith-Wiedemann syndrome and hemihypertrophy.[213]

Children with ACC may present with abdominal pain and a palpable mass. More than 75% of the tumors are functional, secreting one or more

hormones: androgens, cortisol, aldosterone, or estrogens. The most common presenting sign is virilization, with deepening of the voice, hirsutism, premature pubic hair, clitoromegaly, phallumegaly, excessive muscular development, and advanced bone age. Pure Cushing syndrome (moon face, plethora, hypertension, striae, weight gain, acne, and "buffalo hump") is rare in children. Feminization or aldosterone- secreting tumors are also rare.[211]

Urinary 17-ketocorticosteroids and 17-hydroxycorticosteroids are usually elevated, with steroid production not influenced by adrenocorticotropic hormone suppression.

Diagnostic imaging studies include CT and/or MRI. It is sometimes difficult to separate ACC from adenoma. However, at presentation, most carcinomas are greater than 6 cm and calcified, whereas benign adenomas are small and nonfunctional. A characteristic echogenic star pattern can be seen on ultrasonography, and a CT scan shows an inhomogeneous tumor with irregular contrast material. Recently, the use of 18-FDG-PET has been shown to be effective in discriminating between benign and malignant adrenal lesions.[214,215] Because both benign adenomas and ACC may exhibit abnormal mitoses and cellular and nuclear pleomorphism, malignancy is determined by the finding of capsular penetration, invasion of the inferior vena cava up to the right atrium, lymph node, and distant metastases.[208]

Generally, the prognosis of ACC depends on disease presentation and can range from 30% to 70% 5-year survival.[216-219] In COG ARAR0332, a single-arm risk-stratified study was performed. Patients with Stage I ACC were treated with surgery alone. Stage II patients were treated with adrenalectomy and retroperitoneal lymph node dissection. Stage III or IV patients were treated with mitotane and chemotherapy. Rodriguez- Galindo et al reported their results, and the 5-year EFS for Stages I, II, III, and IV disease were 86.2%, 53.3%, 81%, and 7.1%, respectively. The 5-year OS rates were 95.2%, 78.8%, 94.7%, and 15.6%.[220] Repeat complete resection of local recurrences and discrete metastatic lesions can improve survival.[221]

The literature on adjuvant radiation therapy after resection of ACC is scarce and relatively old and consists of a small series or case reports.[222] There is no standardized role for RT for pediatric ACC; however, there is interest to utilize RT for local therapy in the setting of advanced ACC.[222]

PHEOCHROMOCYTOMA AND PARAGANGLIOMA

Pheochromocytoma and paraganglioma are rare tumors of childhood and adolescence.[223-227] Pediatric pheochromocytoma occurs usually between 8 and 14 years of age, more frequently in males. More than 90% of all pheochromocytomas in adults, and 70% of pheochromocytomas in children, originate in the adrenal gland, but the tumor can occur at any site in the sympathetic chain, most commonly below the diaphragm. The most common sites of occurrence of extra-adrenal pheochromocytoma are the superior para-aortic region, between the diaphragm and the lower renal poles, in the paraganglia, the organs of Zuckerkandl, and the bladder. Extra-abdominal tumors may develop in the brain, thorax, and the bladder.[223,226,228,229] Approximately 10% of all patients with pheochromocytoma are children, but several characteristics distinguish them from their adult counterparts. Unlike pheochromocytomas of the adult age group, children with pheochromocytoma have a higher incidence of bilaterality, a higher association with the multiple endocrine neoplasia (MEN) syndromes, and a lower incidence of malignant neoplasms.[223,228,230,231]

Familial pheochromocytoma is associated with other endocrine tumors in the MEN IIA and IIB syndromes.[228,232-234]

In addition to the familial syndrome of isolated pheochromocytomas, pheochromocytomas in the pediatric age group can be associated with other inherited diseases, such as von Hippel-Lindau disease (retinocerebral angiomatosis), tuberous sclerosis, and von Recklinghausen neurofibromatosis.

Malignant pheochromocytomas occur in 10% of the pediatric cases of pheochromocytoma. The definition of malignancy is based on biologic and clinical behavior and not on histologic features alone.

Pheochromocytoma is responsible for 1% of cases of childhood hypertension, which, unlike the situation in adults, is sustained and not paroxysmal. Other signs and symptoms include diaphoresis, flushing, fatigue, headache, and convulsions.[235]

Adrenal pheochromocytomas produce epinephrine and norepinephrine, but most extra-adrenal pheochromocytomas produce only norepinephrine.

Urinary epinephrine, norepinephrine, metanephrine, and vanillylmandelic acid values remain the gold standard for biochemical screening of pheochromocytoma. On some occasions, urinary catecholamine levels may be normal, whereas serum levels are elevated. Imaging studies include ultrasonography, CT scan, and/or MRI. Iodine-131 metaiodobenzylguanidine (MIBG) scan provides the most accurate and direct method of diagnosing adrenal, extra-adrenal, or metastatic pheochromocytoma because MIBG, which has a molecular structure similar to that of norepinephrine, is actively concentrated and stored in catecholamine storage vesicles of pheochromocytoma cells.[223,228,236-238]

Surgery is the definitive therapy. The most significant reduction in preoperative and postoperative mortality has come from the control of perioperative hypertension using α- and β-blockers.[28,239]

External-beam irradiation is used for palliation of lymph nodes, bone, brain, and spinal cord metastases. High-dose iodine-131 MIBG has been used with modest results in metastatic disease. Streptozotocin or cyclophosphamide, vincristine, and dacarbazine may produce modest decreases in catecholamine secretion in patients with malignant pheochromocytoma. Patients with malignant pheochromocytoma require chronic medical control of their elevated blood pressure by α and β blockade or inhibition of catecholamine synthesis with α-methyl-para-tyrosine.[240-242]

THYROID CARCINOMA

Thyroid carcinoma accounts for 1% to 1.5% of all cases of cancer in the pediatric and adolescent age groups, with between 0.4 and 1.5 cases per million, 2 to 3 times as frequent in girls as in boys.[243] After the April 26, 1986, Chernobyl nuclear reactor accident, a remarkable incidence increase was observed in children exposed to radioactive iodine (RAI) fallout.[244,245] The incidence of thyroid cancer in Belarus and Ukraine began to rise sharply from 1989 to 1990: in adults, the number of new cases increased 2- to 3-fold; and in children younger than 20 years of age, and particularly during the first 5 years of life, the number of new cases increased 20- to 30-fold.[244] Almost all new pediatric cases were papillary tumors (94%-98%), with a relatively high incidence of lymph node (65%) and lung (5%)

metastases at presentation (Table 99.6). Lubin et al[246] reported pooled data from nine cohort studies of childhood external radiation exposure and thyroid cancer with individualized dose estimates, more than 1,000 irradiated subjects, or more than 10 thyroid cancer cases, with data limited to individuals receiving doses less than 0.2 gray.

TABLE 99.6 HISTOLOGIC TYPES OF CHILDHOOD THYROID CANCER

Type	Frequency (%)	Characteristics
1. Differentiated carcinoma		
a. Papillary carcinoma	70-80	Infiltrative and multicentric; lymph node metastases in 70%-90% of cases; hematogenous spread (mainly lung) in 5%-10% of cases
b. Follicular carcinoma	16-20	Vascular invasion
2. Medullary carcinoma	Rare	Occurs in isolation, but more frequently associated with one of the MEN syndromes; usually aggressive and can be fatal
3. Undifferentiated carcinoma	Rare	Aggressive, usually fatal within 6 months of diagnosis
4. Insular carcinoma	Very rare	A variant of the poorly differentiated carcinoma; aggressive, poor prognosis

MEN, multiple endocrine neoplasia.

Estimates of threshold dose ranged from 0.0 to 0.03 gray, with an upper 95% confidence bound of 0.04 gray. The increasing dose-response trend persisted for more than 45 years after exposure, was greater at younger age at exposure and younger attained age, and was similar by sex and number of treatments.

For pediatric patients, 85% of childhood thyroid cancers are papillary thyroid cancers (PTCs), with the remainder divided between follicular thyroid cancer (FTC) and medullary thyroid cancer. PTC is a tumor named for its papillary growth pattern, although the defining diagnostic criteria are actually the nuclear features of neoplastic cells. In addition to enhanced screening, the important factor contributing to the increased incidence of

PTC is the increase in diagnosis of a variant of PTC known as the follicular variant of PTC (FVPTC). Among the two main subtypes, infiltrative (or nonencapsulated) and encapsulated, encapsulated FVPTC (EFVPTC) has increased in incidence by an estimated 2- to 3-fold over the past two to three decades and makes up 10% to 20% of all thyroid cancers currently diagnosed in Europe and North America.[247,248] A recent international, multidisciplinary, retrospective study of patients with thyroid nodules diagnosed as EFVPTC, including 109 patients with noninvasive EFVPTC observed for 10 to 26 years and 101 patients with invasive EFVPTC observed for 1 to 18 years, found that thyroid tumors currently diagnosed as noninvasive EFVPTC have a very low risk of adverse outcome and should be termed as noninvasive follicular thyroid neoplasm with papillary-like nuclear features.[249] This reclassification will affect a large population of patients worldwide and result in a significant reduction in psychological and clinical consequences associated with the diagnosis of cancer.[250]

FTC are typically unifocal and have a risk for hematogenous spread. They are subdivided into microscopic or no capsular invasion versus widely invasive FTC.[251] Medullary carcinomas are rare, tend to be more aggressive than the differentiated carcinomas, and can be fatal. They are associated with the immunoreactive thyrocalcitonin marker. Because of the aggressive clinical course, experts advocate genetic testing to identify affected individuals with specific mutations in the ret oncogene that predict MEN syndromes. Those individuals could be candidates for prophylactic thyroidectomy at an earlier age than if the increase in serum calcitonin was used to identify C-cell hyperplasia or early carcinoma. At present, genetic testing should be performed at birth in children suspected of having the MEN IIA syndrome and no later than 1 year of age for those with possible MEN IIB.[252-254]

Children with thyroid cancer are commonly euthyroid and usually present with a thyroid nodule or palpable cervical lymph node. Conventional radiographs may show calcifications in the region of the thyroid gland (psammoma bodies). An iodine radionuclide scan may show a cold nodule.

Paradoxically, despite the fact that 70% to 80% of patients present with regional lymph node involvement and approximately 20% have distant

metastases at diagnosis, the prognosis of differentiated thyroid cancer (DTC) in children and adolescents is excellent.[254-256]

Thyroid carcinoma is treated primarily by surgery. The extent of surgery for the primary tumor (subtotal lobectomy, lobectomy, total thyroidectomy) and involved lymph nodes (node picking, modified or radical neck dissection) is controversial.[257]

The arguments in favor of total thyroidectomy include the multifocality of the tumor, decrease in neck recurrences, the ability to use serum thyroglobulin as a tumor marker after radical surgery, and the ability to detect pulmonary metastases by RAI scan earlier. The arguments for more limited surgery are mainly the increased complication rate of radical surgery, with apparently no clear survival advantage.[253-255,258-260]

The use of RAI for routine ablation of remaining thyroid tissue after surgery in patients without any known metastatic disease is another area of controversy. However, many support the administration of RAI in this setting because of the high incidence of nodal and systemic metastases of thyroid cancer in the young.[261] Unlike adult thyroid cancer where RAI is routinely used, RAI in pediatric patients has risks for developing secondary malignancies. The American Thyroid Association (ATA) guideline for pediatric DTC stratifies patients by risk. ATA pediatric low-risk patients are initially treated with thyroid-stimulating hormone (TSH)-suppressed thyroglobulin. For ATA pediatric intermediate and high-risk patients, a postoperative TSH-simulated thyroglobulin and diagnostic whole-body (DxWBS) scan are recommended. ^{123}I should be used for DxWBS when possible. RAI is recommended for pediatric patients with iodine-avid persistent locoregional or nodal disease that cannot be resected or with known or presumed iodine-avid distant metastatic disease.[262,263]

Side effects of RAI include nausea, xerostomia, taste alterations, increases in caries, stomatitis, candidiasis, glossalgia, hypogeusia, thyroiditis, and gastrointestinal discomfort.[264,265] Potential and rare long-term complications include myelosuppression, leukemia, bladder cancer, salivary cancer, gastric cancer, breast cancer, and infertility. These complications occur rarely with today's treatment doses and protocols.[261]

Exogenous thyroid hormone is given to suppress TSH production and to decrease the probability of tumor recurrence. Exogenous thyroid hormone

is also given as replacement therapy to keep the patients euthyroid despite thyroidectomy.[258,266,267]

External-beam irradiation in children with DTC is indicated for unresectable primary tumor or cervical or mediastinal lymph nodes that do not take up RAI. It also has a role in advanced locoregional disease, with extensive extrathyroid extension, or where there is gross residual tumor after attempted surgical excision, or when definitive resection has not been possible. Although external-beam irradiation is useful for palliative therapy of advanced or metastatic disease, the lack of randomized controlled studies makes its role as part of initial adjuvant treatment controversial, and it is rarely indicated for microscopic residual disease. Radiotherapy, with or without chemotherapy, can be administered in children with anaplastic thyroid carcinoma.[256]

The volume of irradiation is designed according to operative and pathologic findings and can range from whole-neck and upper mediastinal irradiation to just treating the thyroid gland or thyroid bed. CT-based planning, with proton therapy or IMRT, is advocated to allow the administration of curative doses (in the range of 55-70 Gy) to the target volume without compromising spinal cord tolerance. This can be achieved by a variety of techniques.[268]

In the Mayo Clinic series, survival rates for children did not differ significantly from those of matched controls at 20 to 30 years.[269] In the Royal Marsden series,[258] the median OS was 53 years, and the median survival for patients who developed recurrence was 30 years. The only presenting feature predictive of poorer survival was the presence of metastases at diagnosis. According to a study reported by the Surgical Discipline Committee of the Children's Cancer Group, the OS for children presenting with distant metastases was 100% at 10 years. The progression-free survival rate was 76% at 5 years and 66% at 10 years. In a series of 14 children with PTC and pulmonary metastases treated at the Mayo Clinic[267] by various surgical procedures, RAI, external-beam irradiation (one patient), and suppressive hormone therapy, at a mean follow-up time of 19.3 years, 50% were alive completely free of disease and 50% were alive and asymptomatic with residual pulmonary disease.

GERM CELL TUMORS

Gonadal or extragonadal germ cell tumors (GCTs) represent less than 2% of pediatric cancer. The tumor is the result of neoplastic transformation of primitive germ cells or totipotent embryonal cells (Figure 99.3).[270] The GCTs can arise from the brain to the sacrococcygeal region, with the most common site presentation in the testis, ovary, sacrococcygeal region, retroperitoneum, and mediastinum. Aberrant migration can explain unusual tumor sites.[271] The Children's Oncology Group evaluated the link between a family history of cancer and pediatric GCT in a case-control study of 274 cases. The risk of GCT decreased among female cases with a family history with onset before 40 years but increased for boys, especially for those with a family history of melanoma.[272] The most frequent cytogenetic abnormality is the isochromosome 12p for both gonadal and extragonadal GCT, except for children younger than 3 years of age at diagnosis. Klinefelter syndrome can be associated with GCT in boys.[244] Intracranial GCTs are discussed in Chapters 90.

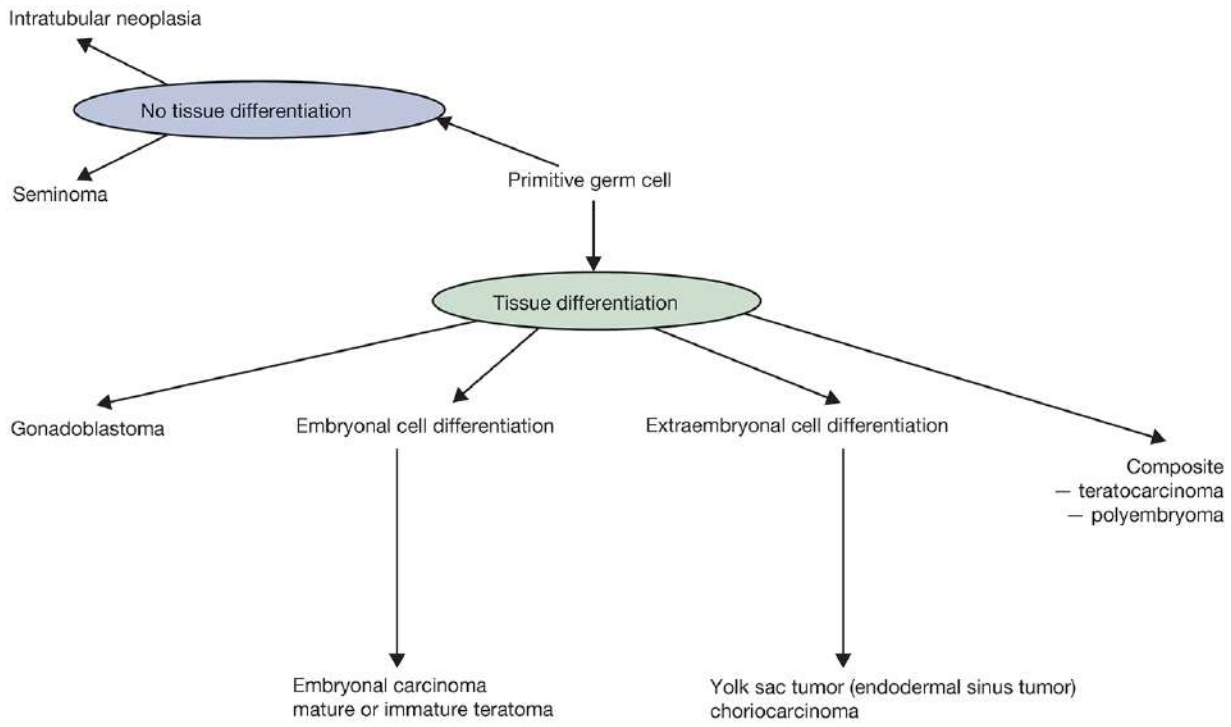

FIGURE 99.3 Classification of germ cell tumors.

Clinical Presentation

Abdominal pain, abdominal distension, and sacrococcygeal or buttock swelling are the frequent presenting signs.[273] Staging includes imaging both the primary tumor and the most frequent sites of metastatic dissemination (lungs, liver, brain, and bone). Serum AFP, *β*-HCG, lactate dehydrogenase, CEA, and placental alkaline phosphatase levels are mandatory prior to the initiation of any treatment. Serum AFP level must be interpreted according to patient age (level >1,000 mg/mL is normal until the age of 1 month). Clinical markers are strongly correlated with some histologic features (Table 99.7); however, high AFP levels can be detected in infectious diseases of the liver, and increased *β*-HCG levels can be associated with malignancies other than choriocarcinoma. The half-life time of AFP is 5 to 7 days and that of *β*-HCG is 24 to 36 hours. Both are very useful tools for predicting and monitoring treatment response, progression of disease, and relapse.[274]

TABLE 99.7 GERM CELL TUMOR AND CLINICAL MARKERS

Tumor Type	*β*-HCG	AFP	LDH	CEA	PLAP
Embryonal carcinoma	+	+		+	
Mature teratoma					
Immature teratoma	+	+	+	+	
Yolk sac tumor		+++	+	+	
Choriocarcinoma	+++		+		
Germinoma	+		+	+	+++

AFP, *α*-fetoprotein; *β*-HCG, beta-human chorionic gonadotropin; CEA, carcinoembryonic antigen; LDH, lactate dehydrogenase; PLAP, placental alkaline phosphatase.

Treatment

Their cure rate is high and strongly correlated with adherence to strict treatment guidelines.

Surgery is the standard treatment for mature teratomas and sacrococcygeal tumors (with complete removal of the tumor and the coccyx), but it may be combined with chemotherapy to limit the extent of irradiation. Surgery is often the first treatment for malignant gonadal GCT: orchiectomy with high inguinal ligation or ovariectomy with careful

peritoneal cavity exploration. Lymph node dissection is not recommended in early-stage GCT, especially in germinomas. Second-look surgery can be indicated in cases of residual disease (clinical or biochemical) after chemotherapy.

Since the introduction of cisplatin-based chemotherapy, the survival rate of GCT has risen from 60% to 90%,[275] and regimens used are similar to those used in the adult age group. Carboplatin is often used to reduce late toxicities.[276] The rate of decline of serum tumor markers has demonstrated prognostic significance and must be used in the management of poor-risk patients.[277] Although GCTs are in general sensitive to radiation and are used in the adult setting, RT is rarely indicated for pediatric patients due to known late effects. Even in advanced cases of ovarian dysgerminoma, careful surgical staging followed by conservative resection and chemotherapy without RT results in an OS rate as high as 85% without compromising the possibility of future pregnancy.[60] There is no indication for RT after complete response in extragonadal GCT. For Stage IA ovarian dysgerminoma, conservative surgery is the gold standard, even in a case of incomplete staging, and chemotherapy is given only in the event of relapse, according to the last Italian group report.[278]

BENIGN VASCULAR TUMORS

Hemangiomas

Infantile hemangiomas, congenital hemangiomas, and Kaposiform hemangioendotheliomas constitute vasculoproliferative tumors. They are subdivided based on the presence or absence of endothelial cell glucose transporter 1 (GLUT1) isoform protein. Infantile hemangioma is the most common benign vascular tumor in children and affects approximately 40% of all infants. The skin, subcutaneous, and soft tissue of the head and neck are the site of origin in 60% of patients, followed by the trunk, extremities, and viscera (eg, liver, lung, gastrointestinal tract).

In some cases, their development can be associated with adverse cosmetic effects, unacceptable symptoms, and organ compression that, in certain cases, could be life threatening. Such cases require therapy. There are two distinct types of hemangiomas: dynamic lesions, which include cellular hemangiomas, capillary hemangiomas, and cavernous

hemangiomas; and adynamic lesions, which include port-wine stains, telangiectasias, and venous lakes. Vascular malformations are subdivided into two major groups, low or slow flow and high or fast flow.[279]

Treatment of infantile hemangiomas depends on the location and number of lesions as well as associated symptoms. Laser therapy is available for skin ulceration, the most frequent complication. For hemangiomas with symptoms, including thrombocytopenia or hypothyroidism, as well as heart failure caused by numerous hepatic hemangiomas, treatment is typically started with antiangiogenic drugs (propranolol, steroids, and less often vincristine) followed by gradually more aggressive treatments, such as embolization and rarely surgery. External-beam RT was used in the past for patients not responding to steroids or interferon. Total doses of 300 to 750 cGy, and rarely exceeding 1,000 cGy, at 10 to 20 cGy per fraction could achieve good local control.[280] Higher doses (30-40 Gy) are used in older patients for large and progressive lesions to achieve lasting local control.[281] However, radiation therapy in the treatment of hemangiomas has fallen out of favor because of concerns for potential late effects, like scarring, bone growth abnormalities, dental and periodontal problems, and secondary neoplasms, and is rarely used anymore.

Special attention must be given to the Kasabach-Merritt syndrome (KMS) (Figure 99.4), which is defined as a combination of cutaneous vascular abnormalities with or without visceral involvement and thrombopenia because of intravascular coagulopathy. KMS is associated only with Kaposi-like hemangioendothelioma or tufted angioma. Kaposi-like hemangioendothelioma must be distinguished from infantile hemangioma, which disappears spontaneously.[282,283] These are alarming hemangiomas with life-threatening lesions (mediastinum, lower extremities, abdomen), either because of compression or secondary to a thrombocytic coagulopathy or high-output cardiac failure. Cavernous hemangiomas can be located in the epidural space and cause spinal cord compression. Surgical resection is the standard treatment.[284]

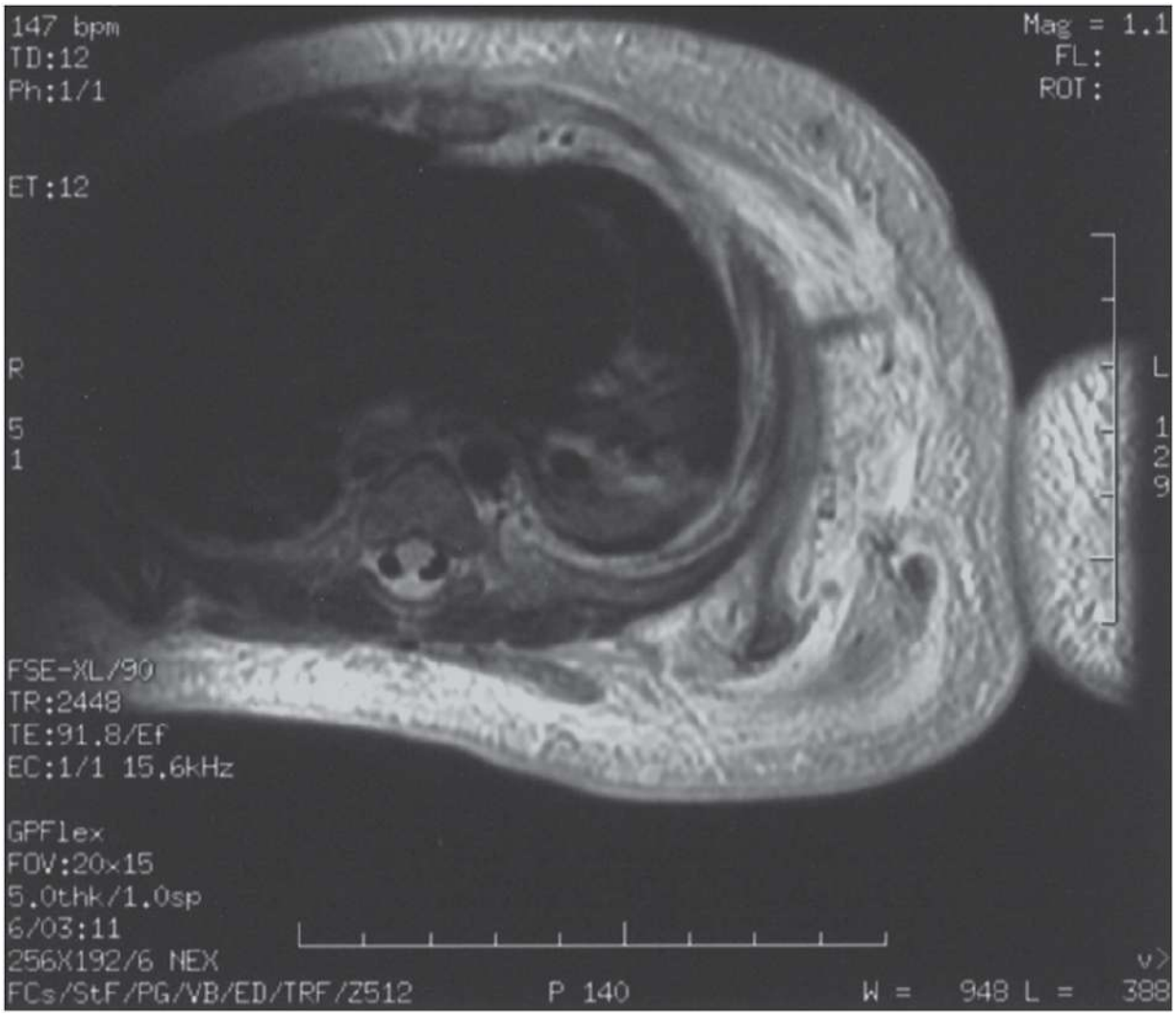

FIGURE 99.4 Kasabach-Merritt syndrome. Massive left hemithorax infiltration and involvement of the left arm.

Radiotherapy is used in a rare setting for unresectable cases and should be considered very cautiously because of its late effects. A dose of 10 Gy in 10 fractions can be given; it is not mandatory to encompass the whole hemangioma in the target volume.[285,286]

Lymphangiomas

Histologically, lymphangiomas are a benign proliferation of lymph vessels. Four types are recognized: capillary lymphangiomas, cavernous lymphangiomas, cystic hygromas, and hemangiolymphangioma. Surgery is the treatment of choice.

Special attention must be given to the Gorham syndrome, also known as the bone-vanishing syndrome or massive osteolysis of bone.[287] Gorham syndrome is a bone hamartoma with various percentages of lymphangioma and hemangioma, characterized by well-margined osteolytic scattered lesions that progressively affect the cortex, with no respect for joint boundaries (Figure 99.5). All bones can be affected (vertebrae, ribs, scapula). Progression is unpredictable, from spontaneous remission to bone absorption and sometimes even death. The prognosis is very poor when pleural or visceral involvement develops. Some encouraging results have been reported using antiresorptive therapy such as calcitonin or biphosphonates.[288] Although RT is the last resort for the patient, encouraging results have been reported for patients with chylothorax and in patients with rib, thorax, and vertebral body involvement. The usual dose is approximately 18 Gy to the hemithorax. Affected bones have been treated to approximately 40 Gy with good response.[289]

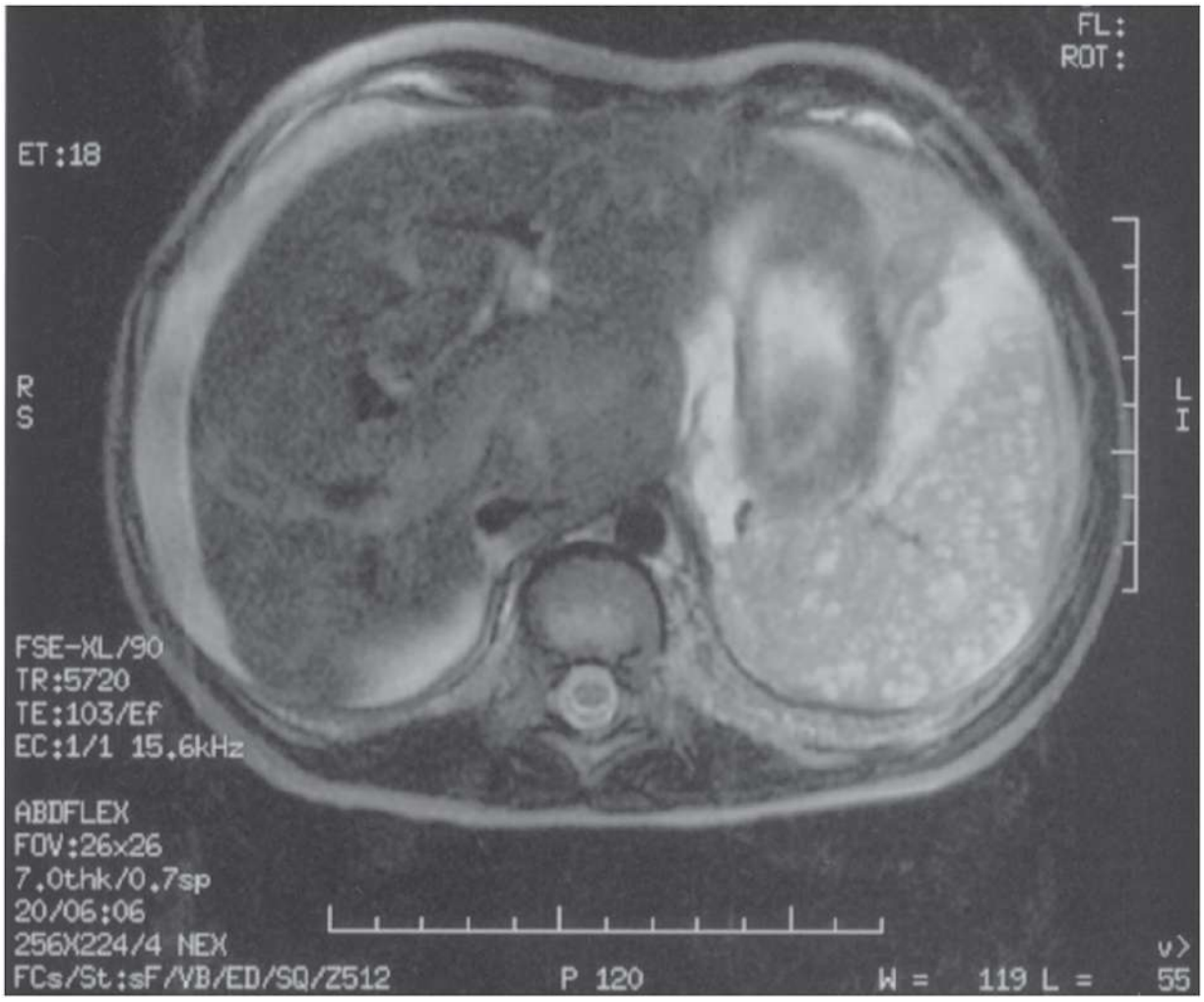

FIGURE 99.5 Gorham disease in a 3-year-old girl. Diffuse lymphangiomatosis affecting pelvic bones, ribs, spleen, and liver.

DESMOPLASTIC SMALL ROUND CELL TUMOR

Desmoplastic small round cell tumor (DSRCT) was first described in 1989.[290] It is a rare aggressive neoplasm with typical clinical, histologic, karyotypic, and biologic characteristics. DSRCT mainly affects male adolescents and young adults, but it sometimes occurs in young females. Clinically, patients present with a bulky abdominal or pelvic mass, but intracranial, testicular, renal soft tissue, and bone DSRCTs have also been described.[291-294]

The tumor is characterized by a desmoplastic stroma with circumscribed tumor cells and encased nests of primitive undifferentiated cells. The

tumoral cells express epithelial (keratin, EMA), conjunctival (vimentin), muscular (desmin), and neuroendocrinal markers.

Reciprocal translocation (11:22) (p13:q12) has been described, which results from a fusion between the terminal part of the Ewing sarcoma gene and the carboxy terminus part of the Wilms tumor gene (WT1).[295]

The DSRCTs are highly chemosensitive, but the prognosis is still poor. Kretschmar et al[296] reviewed 101 cases of DSRCT: after 2 years, only two patients were still alive, and the median survival was 17 months. Newer agents including tyrosine kinase inhibitors, mTOR inhibitors, immune checkpoint inhibitors, and others are being explored.

The treatment approach for DSRCT is largely multimodality therapy including intensive chemotherapy even including high-dose chemotherapy with stem cell transplant, debulking surgery, and adjuvant radiotherapy. This disease often presents with intraperitoneal implants, and imaging studies, whether CT or MRI, typically underestimate the extent of disease found during surgery.[297] Patients are treated with upfront chemotherapy followed by aggressive surgical excision. Following maximal excision, patients are then treated with adjuvant whole abdominal irradiation to 30 Gy and treatment to 54 to 55.8 Gy for residual gross disease. One alternative to the use of whole abdominal irradiation is the use of hyperthermic intraperitoneal chemotherapy, and some studies have tried to combine the two therapies.[297]

NONMELANOMA SKIN CANCER

Basal and squamous cell carcinomas are rare in children and adolescents. When they occur in the pediatric and adolescent age groups, there is usually an underlying predisposing genetic disorder, such as basal cell nevus syndrome (BCNS) or Gorlin-Goltz syndrome and XP. Basal and squamous carcinomas have also been reported to arise in nevus sebaceous[298] and after radiation for benign or malignant conditions.[299,300]

BCNS or Gorlin-Goltz syndrome[301] is an autosomal dominant disorder with variable penetrance characterized by a “coarse face” with hypertelorism and frontal bossing, multiple basal cell carcinomas presenting at a young age, pits on the palms and soles, skeletal abnormalities (eg, bifid ribs, hemivertebrae, fusion of vertebral bodies), jaw cysts, epidermic cysts

and hamartomas, oculoneurologic abnormalities, and ectopic calcification of the falx cerebri and other structures. Skin lesions located in the head and neck tend to invade the deep structures. Several patients with BCNS were reported to have developed medulloblastoma at early childhood and ovarian fibromas.[138,301-305]

Mutation of the human homologue of the *Drosophila*-patched (PTC) gene is considered the molecular defect in BCNS.[306] The Gorlin-Goltz syndrome is a unique example of the genetic-environmental interaction for the production of malignancies: children treated for medulloblastoma by craniospinal irradiation developed multiple skin cancers in the irradiated area, an unusual and special illustration of multihit mutagenesis, suggesting that RT should probably be omitted or limited in children with BCNS.[307]

XP is an extremely rare, autosomal recessive inherited disease characterized by abnormal pigmentation and a greater than 1,000-fold increase in nonmelanoma skin cancer (basal cell carcinoma and squamous cell carcinoma) on sun-exposed skin. Patients with XP are also at a significant risk of developing melanoma.[307,308] Neurologic abnormalities such as areflexia and mental retardation are sometimes associated with XP.

The genetic abnormality underlying XP leads to defects in nucleotide excision repair of ultraviolet-induced DNA damage.[307,309,310]

Skin cancer in affected children is treated by standard techniques (such as surgery, cryosurgery, and chemosurgery). There should not be any contraindication to using RT to treat skin cancer or any other malignancy in patients with XP because ionizing radiation damage is normally repaired in these patients.[311]

MALIGNANT MELANOMA

Childhood melanoma can present in an atypical manner that does not fit the traditional clinical findings for adult melanoma: **a**symmetry, irregular **b**orders, **c**olor variation, **d**iameter greater than 6 mm, and lesion evolution. For these reasons, it can sometimes delay diagnosis. Sometimes childhood melanoma is associated with large congenital nevocytic nevi, dysplastic nevus syndrome, immunosuppression, transplacental malignant melanoma, and XP. Pediatric malignant melanoma should be distinguished from

juvenile melanoma or Spitz nevus characterized by a relatively benign course and long-term survival.[312-314]

The management of childhood melanoma follows the guidelines set for adult patients.[315] The prognosis is related to the Breslow or Clark thickness of the primary lesion and nodal status. Chemotherapy regimens usually have poor activity against melanoma in adults. However, St. Jude Children's Research Hospital (SJCRH) reported a complete or partial response in 8 of 18 (44%) pediatric patients receiving cyclophosphamide, vincristine, and dacarbazine.[316] Immunotherapy has been explored with promising results. Given the favorable results with the use of interferon α-2b in adults, 15 patients younger than 18 years of age with Stage III melanoma, defined as having a primary tumor thickness greater than 4 mm or having lymph node or in-transit metastases, were included in an SJCRH feasibility study.[317] Another group from Toronto used the high-dose interferon in children with metastatic disease.[318] Most of the patients in both studies did complete their therapy with some alterations in dosage because of toxicity. Intergroup Study of Cancer and Leukemia Group B, Children's Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group (S0008) studied the role of biochemotherapy, which provided statistically significant improvement in recurrence-free survival (RFS) but no difference in patients with OS with high-risk melanoma.[319] Targeted therapies, such as BRAF and MEK inhibitors that are approved for the treatment of patients with advanced melanoma who harbor *BRAF* V600E mutation–positive tumors, result in a significant survival advantage compared to chemotherapy.[320]

Drugs blocking immune checkpoints, such as cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and the programmed cell death protein 1 (PD-1), have been used to enhance antitumor immunity and have become the standard of care.[321,322] Overall, the pediatric age group represented a very small proportion of patients studied for systemic therapy. Therefore, treatment plans for children are mainly extrapolated from adult studies.

Radiotherapy has a role mainly in the palliation of metastatic disease or in locally advanced lesions. Again, data here should extrapolate from the adult literature; however, high-dose per fraction regimens will need to be evaluated with caution because of toxicity concerns.

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PART N

Benign Diseases

CHAPTER 100

Nonmalignant Diseases

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Benign diseases generally include a class of localized tumors or growths that have a low potential for progression and do not invade surrounding tissue or metastasize to distant sites. Pathologically, they are composed of well-differentiated cells that are considered nonmalignant and usually do not require any treatment. However, clinically, not all benign diseases have benign consequences. Some untreated benign diseases can produce bothersome mass or secretory effects. Others can be locally aggressive and cause secondary debilitating symptoms. For example, Graves ophthalmopathy (GO) can lead to local pain and visual impairment without therapeutic intervention,[1] a hormonally active pituitary adenoma may cause growth abnormality in addition to blindness,[2] and desmoid tumors can be locally persistent after surgical resection and grow uncontrollably similar to their malignant counterparts.[3]

Documented empirical use of radiation in imaging and the treatment of benign diseases or conditions occurred soon after the discovery of x-rays by Wilhelm Röntgen in 1895.[4] Between 1920 and 1960, over a million Americans, mostly young adults and children, received x-ray treatments to the head and neck region for benign conditions.[5] The efficacy of painless x-ray treatment led to the treatment of many benign conditions with radiation: acne, body hair, scalp ringworm, enlarged tonsils, enlarged thymus, enlarged neck lymph nodes, whooping cough, and others. Radiation therapy

(RT) was used in some instances due to a lack of effective alternative therapies.

Over the past decades, advances in medical and surgical therapies have provided new treatment options for many diseases. With improved awareness of late radiation sequelae on normal tissue, particularly radiation carcinogenesis, the use of RT for the treatment of benign conditions has gradually declined. However, with modern RT techniques and a better understanding of radiobiology, judicial use of radiation provides good local control with minimal toxicity and relief of associated symptoms.

THE HISTORIOGRAPHY OF THE RADIATION THERAPY OF NONMALIGNANT DISEASES

From the dawn of RT, in the late 19th and early 20th centuries, ionizing radiation was used in all manner of malignant and nonmalignant diseases. The early textbooks of RT are filled with case descriptions and photographs of these attempts.

In the English-language literature, three textbooks of the past 60 years are particularly deserving of note in this field. The first was by a radiologist practicing at the Hunterdon Regional Medical Center in Flemington, Stephen B. Dewing. His textbook, *Radiotherapy of Benign Disease* (Charles C. Thomas, Publisher; 1965), is beautifully written with clear and thoughtful prose and is awash with commonsense advice. As a largely single-author book, Dr Dewing's voice is clearly present.

Twenty-five years later, a book of tabulations of the use of RT for benign disease with brief summary paragraphs was published. Stanley E. Order and Sarah S. Donaldson's *Radiation Therapy of Benign Diseases*: *A Clinical Guide* (Springer-Verlag; 1990) explained to its readers what was available from single case reports and small clinical series to inform practice.

Eighteen years later, the magisterial book edited by M.H. Seegenschmiedt, H.-B. Makoski, K.-R. Trott, and L.W. Brady was published. *Radiotherapy for Non-Malignant Disorders; Contemporary Concepts and Clinical Results* (Springer; 2008) comprehensively reviewed the available literature, compared and contrasted experiences from different countries, and put in perspective what was known and what was not known and the state-of-knowledge of mechanisms of actions.

If available from used booksellers, all three books merit a place on the bookshelf of interested radiation oncologists. The Order and Donaldson book has appeared in a subsequent edition.

THE INFLUENCE OF NATIONAL CONTEXT ON PATTERNS OF PRACTICE

A distinctive feature of RT use for nonmalignant disease is the substantial influence of the country of practice on treatment patterns. If one reviews the literature for the treatment of adult bronchogenic carcinoma or childhood medulloblastoma, one may find differences in the nuances of RT dose or the sequencing of surgery, RT, and chemotherapy, but the basic principles of treatment remain broadly consistent across economically developed nations.

In contrast, the willingness to employ RT for nonmalignant disease varies significantly depending on national context. Utilization is more common in Eastern and Central Europe, declines in Western Europe (including the United Kingdom and Ireland), and is used sparingly in North America.

In the United States, although some practitioners advocate for an expanded role of RT in nonmalignant disease—and occasionally frame this as a "resurgence"—this overlooks the long history of such applications, which extends over a century. Hesitancy among American and Canadian radiation oncologists is shaped by concerns regarding the strength of supporting evidence, reliance on retrospective clinical series rather than prospective randomized trials, and the potential for late toxicities, including secondary malignancies. As Leer and colleagues noted in their international survey, concerns have also been raised that efforts to secure reimbursement may, in some cases, have outpaced the generation of rigorous clinical data evaluating safety and efficacy.[6]

RADIOBIOLOGIC EFFECTS ON BENIGN DISEASES

The precise radiobiologic mechanisms of radiation effects on benign diseases are not well defined. Radiation is believed to work through complex multicellular interactions that affect different cell types in our body system.[7,8] Specific cellular and functional mechanisms depend on the specific disease and site. Although most benign lesions have no known stimuli or causes, some benign lesions may be triggered by trauma, as seen

in keloid formation after body piercing or heterotopic bone formation after surgery. In conditions that arise following trauma, local inflammation and repair occur, often characterized by excess stimulation of growth factors and accelerated cellular proliferation. For example, in the development of keloids, fibroblast proliferation is responsible for most of the hyperproliferative process. Even with the lower doses commonly used in benign diseases, RT is clinically effective in inhibiting cell proliferation and suppressing cell differentiation without inducing cell death as is typically seen with tumoricidal doses of radiation. Yet, radiation can induce apoptosis in selected target cells by influencing the expression of cytokines in macrophages, leukocytes, endothelial cells, and other cells, thereby modulating the inflammatory cascade.

Among the major sites of radiation effects are the blood vessels; vascular endothelial cells respond rapidly to radiation damage by upregulating the cytokine-mediated cellular reactions responsible for inflammatory tissue response. Low-dose irradiation (total dose <12 Gy using #1.0 Gy per fraction) exerts anti-inflammatory effects on the endothelial cells of capillaries and mononuclear cells of the immune system.[9]

Cell adhesion molecules, including selectins, are mobilized to the cell membrane and disrupt capillary permeability, allowing the inflammatory cells (lymphocytes, macrophages, monocytes) to migrate into the interstitial space. The anti-inflammatory effect is attributed to the modulation of cytokine and adhesion molecule expression on the activated endothelial cells and leukocytes. These cells are known to be radiosensitive. They express pro-inflammatory cytokines (eg, interleukin-1 [IL-1], IL-6) or necrosis factors (eg, tumor necrosis factor-α [TNF-α]) that influence the complement cascade and inflammatory reaction. IL-1 stimulates the production and release of pro-inflammatory prostaglandins, leading to a change in the synthesis of inducible nitric oxide synthetase.

The radiation-induced modulation of nitric oxide production and oxidative burst in activated macrophages and native granulocytes leads to modification of the immune response, inflammatory process, and clinical analgesic effects.[10] Although endothelial cells possess a high proliferative potential and are sensitive to radiation damage at high doses, they are not prone to rapid mitotic radiation death at low doses.

Chronic inflammatory processes are triggered by antigen-antibody reactions and mediated by mononuclear peripheral blood cells in the immune system. Ionizing radiation helps suppress some of the cell populations, such as T lymphocytes, in the inflammation process or modulate their effects. While low doses of radiation can exert an anti-inflammatory response, high doses of radiation as used in malignant tumors can elicit pro-inflammatory effects and fibrotic change in normal tissue.[11] At higher single or total doses, endothelial cell damage can lead to sclerosis and obliteration of blood vessels. In vascular disorders such as hemangiomas or arteriovenous malformations (AVMs), high radiation doses may induce occlusion of pathologic vessels. In addition to inhibition of cell proliferation, cell killing may play a part in the management of benign meningiomas, pituitary adenomas, or neuromas where higher, tumoricidal doses of radiation may be required. In summary, the normal balance within the inflammatory and proliferative milieu, when altered, can result in the growth of benign lesions, which may or may not become clinical entities that require intervention.

RISK OF SECOND MALIGNANCIES

The induction of cancer or genetic defects by radiation exposure is attributed to stochastic effects where there is no absolute threshold level of radiation exposure below which cancer induction or genetic effects will not occur. Increasing the radiation dose or the volume of exposure will increase the probability that a cancer or genetic effect may eventually occur with long enough follow-up. Sometimes, the effects of radiation are difficult to separate from the inherent genetic effects. For example, in patients with retinoblastoma, the *Rb1* gene plays an important role in developing radiation-induced sarcomas.[12,13] In a study of 384 patients with retinoblastoma treated with radiation, the actuarial risk for developing sarcoma in the treatment field 18 years after treatment was 6.6%.[12] In another study of 693 patients, the cumulative risk for any sarcoma 50 years after RT was 13.1%.[13] Although most sarcomas were within the irradiated fields, 18 out of 69 sarcomas developed outside the treatment fields. Rb1 mutations appear to confer a genetic predisposition to developing sarcomas, especially after radiation exposure.

The risk of the induction of secondary tumors was overestimated in the past.[14] More recently, Trott and Kamprad used the epidemiologic data from long-term follow-up studies on patients treated with RT for benign diseases to estimate the risk of cancer induction.[15] Taking all known modifying and organ-specific factors into account, including radiation doses and volume irradiation, the estimated absolute lifetime risk for sarcoma induction was less than 0.0001% for 1 Gy and a 100-cm^2 field. Table 100.1 lists the absolute lifetime risk for other malignancies.

TABLE 100.1 THE ESTIMATED ABSOLUTE LIFETIME RISK FOR MALIGNANCIES AFTER RADIATION THERAPY FOR BENIGN DISEASES

Types	Absolute Lifetime Risk
Skin (basal cell carcinoma)	0.1% for 100-cm^2 field
Osteosarcoma	< 0.0001% for 1 Gy and a 100-cm^2 field
Leukemia	1% for 1 Gy TBI
Brain tumor	0.2% after 20 Gy for endocrine orbitopathy
Thyroid carcinoma	1% per Gy for children < 10 y
Breast carcinoma	5% for one breast, 1 Gy, age < 35 (<3% for age 35-45)
Lung carcinoma	1%. within 25 y after a mean lung dose of 1 Gy

TBI, total body irradiation.

Jansen et al applied the effective dose concept and estimated the carcinogenic risk in patients after RT of benign diseases (heterotopic ossification [HO], omarthritis, gonarthrosis, heel spurs, and hidradenitis suppurativa).[16] Special risk-modifying factors, including age at exposure and gender, were taken into account. For an average-aged population, the estimated number of radiation-induced fatal tumors was between 0.5 and 40 persons per 1,000 patients treated. The range of effective doses was also found to be large (5-400 mSv). In addition to age and gender, the individual risk also depended on individual inherent sensitivity, anatomic site, type of disease, and treatment technique, such as dose and fractionation. The International Commission on Radiological Protection estimates that cancer incidence due to ionizing radiation increases linearly and is about 5.5% per Sv.[17] Thus, for a patient exposed to 20 mSv—the typical limit for radiation

workers per year—irradiation increases the lifetime cancer risk by about $0.020 \times 5.5\ Sv^{-1} = 0.1\%$.[8]

INDICATIONS FOR RADIOTHERAPY

Most benign diseases can be classified as inflammatory, degenerative, hyperproliferative, or functional. Therefore, therapeutic approaches vary widely due to the paucity of well-controlled prospective therapeutic clinical trials. Radiation treatment of benign diseases is less commonly used in the United States than in some other parts of the world, where variation in indications and treatment schedules is institutionally based.[18] Within Germany, a pattern of care study revealed significant geographic and institutional differences.[19] Most radiation treatments for benign diseases are delivered in the low-dose range (<10-15 Gy).

Degenerative processes in tendons, ligaments, and joints can cause pain by chronic inflammation and trigger secondary functional impairment of the involved musculoskeletal system. Although radiation does not halt the degenerative process, it may reduce inflammation and provide partial or complete pain relief. This clinical effect is well established in reports of osteoarthritis (OA), synovitis, and bursitis, where low-dose RT has improved the function of affected joints.[19,20]

Benign diseases may have a significant effect on self-image and self-esteem because of cosmetic appearance (eg, facial keloids, juvenile angiofibroma) or a lasting impact on quality of life (QoL) because of chronic pain or other secondary symptoms (eg, heterotopic bone, macular degeneration). When benign diseases become locally invasive with aggressive growth, therapeutic intervention can prevent or limit functional loss of organs. In rare cases of large hemangiomas with associated thrombocytopenia and consumption coagulopathy (Kasabach-Merritt syndrome), potentially fatal complications can occur, and timely therapeutic intervention can be lifesaving.[21]

Although there is a lack of an international consensus, the German Working Group on Radiotherapy of Benign Diseases published its consensus guidelines for RT of nonmalignant diseases. The guidelines were to serve as a starting point for quality assessment, prospective clinical trials, and outcomes research.[8,20,22-24] In brief, treatment is indicated when benign

diseases are symptomatic or potentially symptomatic. When other methods are unavailable or have failed, RT should be considered. As medical professionals, we remain mindful of therapeutic gain and potential treatment side effects and complications. A thorough risk-benefit analysis is always pertinent. Organ-specific acute and chronic toxicities, including potential effects on fertility and induction of secondary tumors in the future, must be explained to and discussed with patients, especially those who are young and have a long life expectancy. Informed consent that is required for all medical interventions is certainly required for the treatment of benign diseases and should be obtained prior to the delivery of RT.

The current chapter covers some of the more common benign conditions that we encounter in the practice of radiation oncology. Details on the therapeutic approaches and data on radiation dose regimens for different benign diseases are summarized in the individual corresponding sections.

BENIGN NEOPLASMS OF THE BRAIN, HEAD, AND NECK

Nonmalignant tumors of the central nervous system and neck can lead to severe, life-threatening symptoms due to pressure and mass effect on critical structures from tumor growth. However, depending on growth rate and location, the surrounding tissue may adapt leading to a delay in the clinical diagnosis.

The role of RT in the following nonmalignant tumors of the brain, head, and neck is addressed in the following chapters:

Meningioma: Chapters 40

Pituitary adenoma: Chapters 41

Craniopharyngioma: Chapters 40 and, briefly, in Chapters 41

Vestibular schwannoma (acoustic neuroma): Chapters 16 and 40

Chordoma: Chapters 54

Glomus tumor/chemodectoma/paraganglioma: Chapters 54

Juvenile nasopharyngeal angiofibroma: Chapters 54

Langerhans Cell Histiocytosis (Histiocytosis-X)

Background and Clinical Aspects

Langerhans cell histiocytosis (LCH) is a rare disorder that affects approximately 300 individuals with a higher incidence in children (3-5 per million) than adults (1-2 per million). Age is an important prognostic factor, with children having better outcomes than adults. In the past, it was felt that children younger than 2 years were felt to have a poor prognosis, but recent data from the LCH-II study now refute that point.[25]

The disease is due to an accumulation and/or proliferation of cells that phenotypically resemble the Langerhans skin cell and can cause tissue damage by the production of cytokines and infiltration. The actual Langerhans cell is a myeloid dendritic cell that expresses the same antigens (CD1a and CD207) as the Langerhans skin cell.[26] On electron microscopy, Birbeck granules are the classic finding.

LCH encompasses a spectrum of diseases with varying clinical presentations. The most common form is called eosinophilic granuloma, which typically affects bones, most commonly the skull, long bones, and spine. Other forms include Hand-Schüller-Christian disease (involving multiple organs) and Letterer-Siwe disease (a severe multisystem form that is more common in infants). Patients are typically stratified into groups based on the extent of disease: single-system disease at a single site, single-system disease involving multiple sites, or multisystem disease. The clinical presentation is dependent upon the sites of the disease. Involvement of the skeletal system is the most common site for children and may manifest as pain, palpable mass, motion deficit, or chronic otitis in the case of mastoid or middle ear involvement. Bony lesions from LCH are predominantly lytic in appearance, and the skull is the most frequently involved bony structure.

Cutaneous involvement affects primarily the skin of the scalp and groin and resembles a seborrheic dermatitis. Patients with cranial involvement (posterior pituitary or hypothalamus) may present with diabetes insipidus (DI). The disease may also involve the cervical lymph nodes. Pulmonary involvement is more typically seen in adults. Hepatomegaly, splenomegaly, bone marrow infiltration, and involvement of the gastrointestinal tract are further potential sites of disease.

Evaluation of a patient suspected of having LCH involves a complete history and physical examination, including routine laboratory work such as complete blood count with differential. The biopsy of affected tissues, such as bone, skin, or lymph nodes, is often necessary to identify the

characteristic Langerhans cells and confirm the diagnosis, including determination of druggable mutations. In addition, imaging studies like x-rays, computed tomography (CT) scans, or magnetic resonance imaging (MRI) are performed to assess the extent and location of the disease (Figure 100.1). Patients with symptoms of DI should undergo a water restriction test, while a skeletal survey with or without a bone scan is useful for assessing potential lytic lesions. For patients with skull, orbital, or mastoid involvement, CT of the head is recommended, and MRI of the head is indicated for those with DI or suspected brain parenchymal disease involvement. In cases of pulmonary involvement, a CT of the chest is performed, and an MRI of the abdomen is conducted for patients with palpable hepatomegaly or splenomegaly. Overall, the diagnosis of LCH relies on a combination of clinical, radiologic, and pathologic findings to accurately identify and characterize the disease.

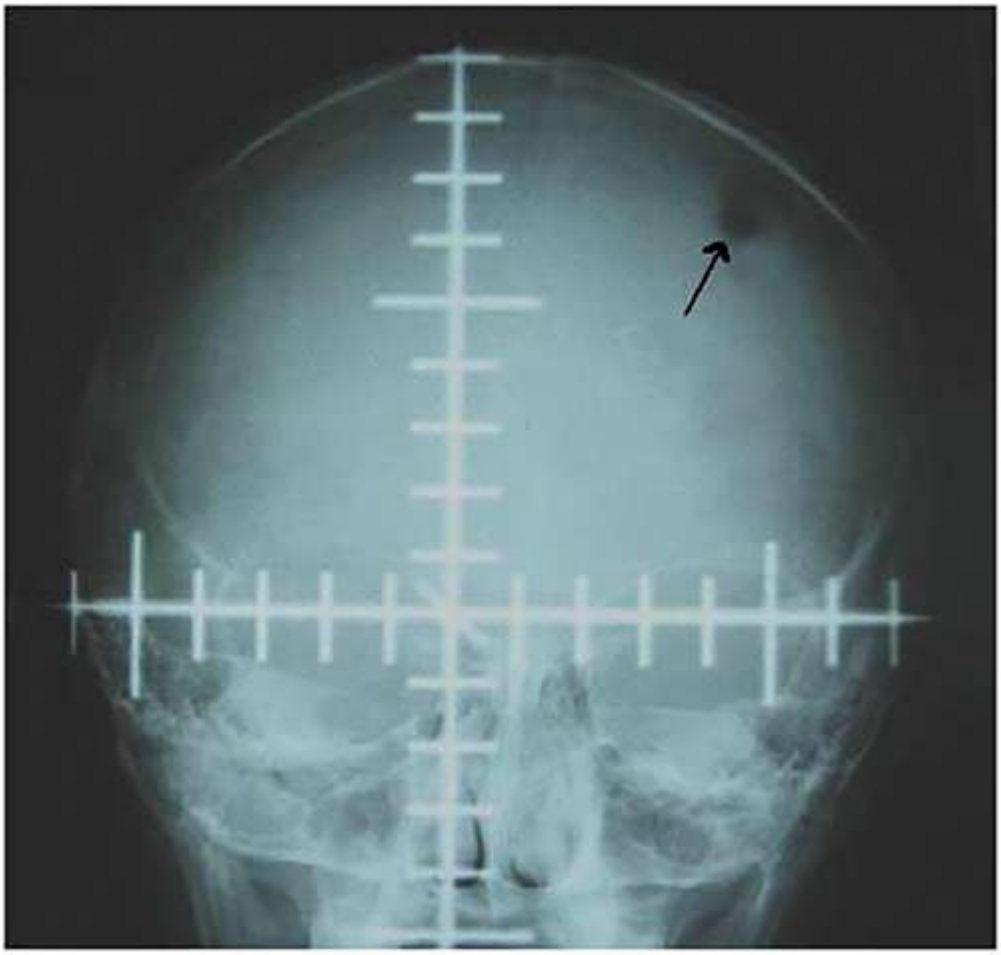

FIGURE 100.1 A typical punched-out skull lesion in a 10-year-old boy with histiocytosis. (Reprinted from Eng TY, Abugideiri M, Chen TW, et al. Radiation therapy for benign disease: arteriovenous malformations, desmoid tumor, dupuytren contracture, graves ophthalmopathy, gynecomastia, heterotopic ossification, histiocytosis. *Hematol Oncol Clin North Am*. 2020;34[1]:205-227. Copyright © 2019 Elsevier. With permission.)

Surgery

Surgery plays a limited role in the treatment of LCH. It is primarily used in specific situations where there is a localized and accessible lesion that can be surgically removed. Asymptomatic lesions may be observed. Treatment options include curettage, excision, or intralesional steroid injection for patients with a single bone lesion or a soft tissue mass that can be excised without causing significant functional or cosmetic impairment. The goal is to completely remove the affected tissue to achieve local disease control. Response rates with curettage or excision alone range from 70% to 90%.[27] It is important to note that surgery alone is not considered curative for LCH.

Due to the systemic nature of the disease and the potential for involvement of multiple organs, a comprehensive treatment approach is necessary.

Systemic Therapy

Single-system multifocal bone disease may be effectively treated with corticosteroids or chemotherapy, such as vinblastine. For skin-only disease, topical nitrogen mustard and methotrexate are considered effective treatments. For patients with multisystem disease with symptoms (fever, pain, failure to thrive) or organ dysfunction, treatment with systemic therapy is indicated. In LCH-II, a study conducted on patients with LCH, all participants initially received treatment with prednisone and vinblastine. They were then randomly assigned to receive additional intensification with or without etoposide. The group that received intensification showed superior rapid response rates and decreased mortality rates compared to the standard arm.[25,28]

For children with DI, exogenous antidiuretic hormone (ADH) (vasopressin) is used as a treatment. Overall, the treatment approach for LCH involves a combination of therapies tailored to the individual patient, which may include chemotherapy (such as vinblastine and steroids), targeted therapies (such as BRAF inhibitors for patients with specific mutations), and immunotherapy.

Radiation Therapy

RT is a safe and effective measure for providing symptom palliation and local control of LCH involving the bone.[29] However, due to the excellent response rates to nonradiotherapeutic measures, the role of RT in the treatment of LCH bony lesions has decreased. Indications for RT to bony sites include relapse after surgery, no signs of clinical healing after other interventions, pain relief, potential compromise of critical structures from an expansile lesion (ie, cord compression), or if the bony site is not amenable to other local therapies. Collapsed vertebral lesions should not be irradiated unless they are painful. Controversy still remains regarding the role of RT in the management of DI. In a retrospective series from MGH, 14 of 17 patients with DI received irradiation to the hypothalamic-pituitary axis.[30] Only two of these patients had a complete response (cessation of

ADH therapy), and no patients had a partial response. When the decision is made to treat, three-dimensional (3D) RT should be the technique of choice.

The target volume for patients with bony disease should encompass the abnormality seen on imaging with a small margin. For children, low doses on the order of 5 to 10 Gy given in 1.5 to 2 Gy daily fractions should be sufficient to control most bony lesions. Higher doses can be used in adults. In a study of 80 patients irradiated up-front or as salvage therapy with a median total dose of 15 Gy, 77% achieved a complete remission and 12.5% achieved a partial remission. The long-term control rate was 80%.[31] The University of California, Los Angeles found local control rates of 88%, with doses ranging from 6 to 15 Gy for previously untreated lesions and 8 to 15 Gy for recurrent lesions.[32]

The target volume for patients receiving treatment for DI should encompass the hypothalamus and pituitary gland. The recommended prescribed dose is 15 Gy in 1.5-Gy daily fractions. In a report from the Mayo Clinic, 36% of 28 evaluable patients responded to RT.[33] The response rates were 60% (3/5 patients) in those treated with more than 15 Gy compared to 30% (7/23 patients) treated with doses of less than 15 Gy. Six patients had a complete response to therapy, five of whom received treatment within 14 days from diagnosis of DI.

VASCULAR DISORDERS

Vascular disorders are broadly categorized into vascular tumors, most commonly benign hemangiomas, and vascular malformations, including AVMs and cavernous hemangiomas. Radiosurgery has emerged as an important and common treatment option for AVMs. While radiation was used commonly in the past to treat hemangiomas in children, the recognition of late effects associated with RT, especially secondary malignancies, has rendered this practice less common.

AVMs are covered later, and hemangioma/Kasabach- Merritt syndrome is addressed in Chapters 99.

Arteriovenous Malformations

Background and Clinical Aspects

Intracranial AVMs are congenital vessel abnormalities consisting of conglomerations of dilated arteries and veins with a resultant lack of a normal capillary bed. The nidus is a tangle of vessels connected by one to several fistulas with a risk of rupture. The overall prevalence is low, affecting approximately 18 in 100,000 individuals, with the age at presentation typically between 20 and 40 years.

Clinical concern comes from the high risk of bleeding, estimated to be 2% to 4% per year. Approximately 50% of patients present with hemorrhage and 50% present with nonfocal (headache, nausea) symptoms or incidentally found focal neurologic deficits. The risk of death per bleed is up to 10%, and approximately 30% have serious morbidity associated with each bleed.

Diagnostic imaging includes angiography, which is invasive but allows for full grading of the AVM according to the Spetzler-Martin scale,[34] which is predictive of hemorrhage risk. MRI, MR angiography, and CT angiography are noninvasive, and complementary studies may be used to visualize the AVM.[34]

Surveillance

A randomized trial of unruptured brain AVMs entitled the ARUBA trial was performed to help determine the role of surgical intervention versus medical management. Two hundred twenty-three patients were available for outcome analysis at the time the cohort reached 33 months of follow-up. The risk of death and stroke was significantly lower in the medical management group (hazard ratio [HR]: 0.27, confidence interval [CI], 0.14-0.54).[35] The findings have been controversial, as there have been concerns about halting of the trial early, small patient numbers, and nonstandard treatment approaches. However, it stands as the largest trial of its kind in this space.

Surgical Management

The goal of any therapy for AVM is to completely obliterate the nidus to decrease the cumulative bleeding risk. Complete microsurgical excision provides immediate cure but carries a risk of intraoperative bleeding, ischemic cerebrovascular accident, infection, and death. Surgery is

particularly indicated for AVMs in superficial, noneloquent regions of the brain. Endovascular therapy (embolization) is typically not curative but is frequently used to decrease the risk of intraoperative bleeding.[36] The best success of monotherapy with embolization is in small AVMs with a single draining vein.[37] There is a theoretically increased risk of hemorrhage or neurologic complication postembolization, and increasingly very selective embolizations are being performed to mitigate risk. Historically, embolization has been performed to decrease the size of the nidus before planned RT, but there have been data suggesting that preradiosurgery embolization negatively impacts the obliteration rate.[38,39]

Radiation Therapy

Stereotactic radiosurgery (SRS) is the radiation modality of choice for the treatment of AVMs. SRS is indicated mostly for lesions in deep or eloquent regions of the brain and is particularly safe and successful for lesions that are less than 3 cm. Unlike surgery, the time to obliteration ranges from 1 to 4 years after SRS, so the patient remains at a continued bleeding risk. Even with time, Maruyama et al demonstrated that the bleeding risk is not completely eliminated but reduced by approximately 88%.[40] Overall, the obliteration rate is 80% by 3 years for lesions that are 3 cm or smaller. For larger lesions, the angiographic obliteration for large AVMs is significantly reduced, with a mean approximating 66%.[41]

Based on the Flickinger dose-response data, typical prescriptions for the treatment of AVM are 21 to 22 Gy prescribed to the 50% isodose line (IDL) for frame-based radiosurgery (Table 100.2).[42] The prescription should be lowered for AVMs near the brain stem or larger lesions (> 3 cm). For Linac-based SRS, prescriptions generally range from 16 to 24 Gy in a single fraction to 20 to 22 Gy in two fractions for spinal AVMs (Figure 100.2).[43]

TABLE 100.2 FLICKINGER PREDICTED RATES OF IN-FIELD AVM OBLITERATION BASED ON THE MINIMUM DOSE WITHIN THE TARGET VOLUME

Minimum Dose to Target (Gy)	Predicted AVM Obliteration Rate (%)
27	99
25	98
22	95

Minimum Dose to Target (Gy)	Predicted AVM Obliteration Rate (%)
20	90
17	80
16	70
13	50

AVM, arteriovenous malformation.

Adapted from Flickinger JC, Pollock BE, Kondziolka D, Lunsford LD. A dose-response analysis of arteriovenous malformation obliteration after radiosurgery. *Int J Radiat Oncol Biol Phys*. 1996;36(4):873-879. Copyright © 1996 Elsevier. With permission.

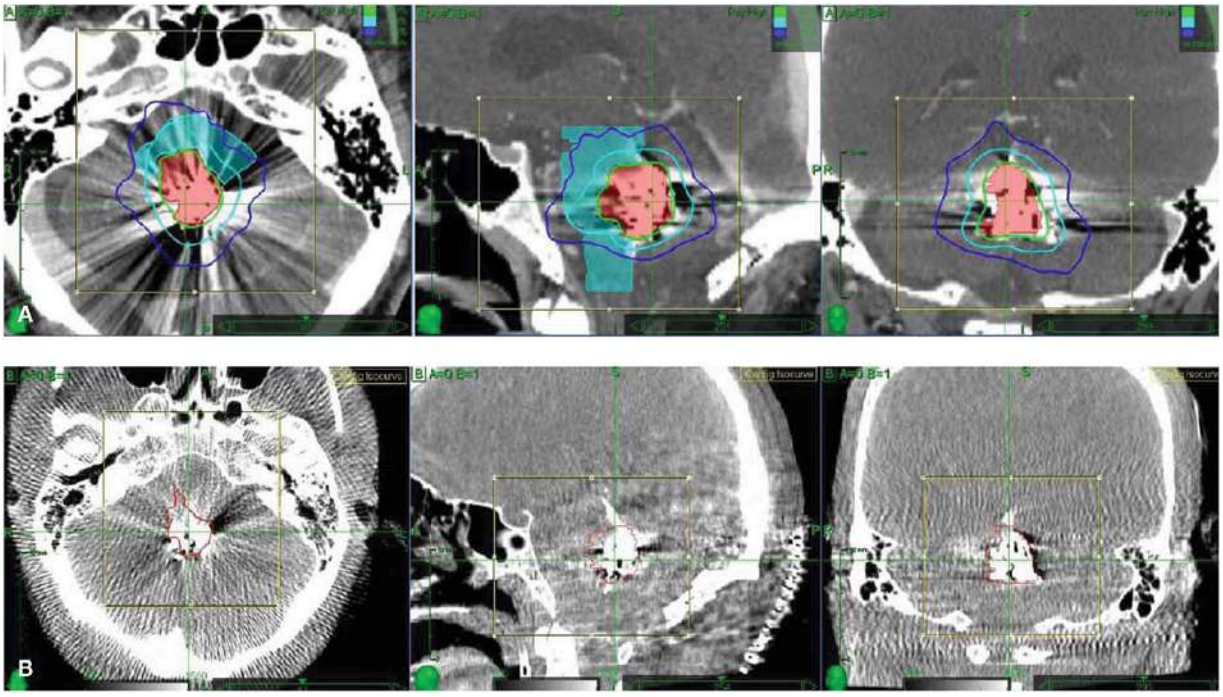

FIGURE 100.2 A. Stereotactic radiosurgery plan for an arteriovenous malformation (AVM) (red) in the dorsal pons treated with 22 Gy in two fractions. The prominent streak artifacts are present because of embolization 1 year prior to treatment. B. Computed tomographic angiogram of the same patient used to assist in defining the AVM nidus (red contour).

Finding the best approach for the management of large AVMs is ongoing. Over the past decade, hypofractionated, dose-staging, and volume-staging treatment schemas have all been attempted, and there are data suggesting that volume-staging approaches can yield the highest obliteration rates among these approaches. Treatment of less than 10-mL sections of the nidus volumes in 3- to 6-month periods has shown 5-year obliteration rates

between 35% and 58% and 10-year rates between 75% and 80% far outpacing the obliteration rates of the other two approaches.[44,45]

FUNCTIONAL DISORDERS

SRS is widely used for the treatment of benign tumors. However, a significant number of patients benefit from the use of SRS to treat functional disorders, such as trigeminal neuralgia (TN), tremors, and epilepsy. Over the past several years, there have been increasing reports of the use of SRS for the treatment of refractory psychiatric disorders, including obsessive-compulsive disorder (OCD) and major depressive disorder.

Trigeminal Neuralgia (Tic Douloureux)

Background and Clinical Aspects

TN is a common problem that affects approximately 15,000 patients each year in the United States, with a slight female predominance (1.5:1). The disorder is currently classified into type I and type II TN, which is based on pain characteristics, as opposed to the traditional classification system that divided patients into idiopathic TN versus secondary TN.[46-48] The classic form of the disease, type I TN, is described as sudden shocks of sharp, lancinating facial pain lasting anywhere from a few seconds to minutes with pain-free intervals. Patients with type II TN predominantly experience constant burning, aching, or throbbing pain, generally of lower intensity.[49] This system also carries prognostic significance, with patients with type I TN more likely to be pain free and have longer disease control than patients with type II TN after decompression.[46] Compression of the TN by an artery or vein within a few millimeters from the root entry zone is believed to account for more than 80% of cases, while the remainder can include benign tumors, cysts, or, rarely, a vascular malformation.[50-52] In addition, multiple sclerosis has also been associated with TN, though demyelination, plaques, and even vascular compression have been observed in these patients.[53,54]

The classic clinical feature is recurrent episodes of sudden, brief, severe, stabbing, or lancinating pain in the area of the trigeminal nerve sensory

distribution. It is most commonly unilateral, but some cases are bilateral. Common triggers for attacks include talking, chewing, brushing teeth, and cold air. The diagnosis is often suspected on the basis of the abovementioned clinical symptoms, but an MRI of the brain should be performed to rule out structural abnormalities that may be causing secondary TN.

Systemic Therapy

TN is first treated with pharmacotherapy, with carbamazepine being the most common and extensively studied agent. Oxcarbazepine is an option for patients who are unable to tolerate carbamazepine. Numerous other agents have been used to treat carbamazepine-refractory patients, including lamotrigine, neurontin, pimozide, tizanidine, and topiramate. Carbamazepine has been demonstrated to have complete or near-complete pain relief in 58% to 100% of patients in early clinical trials, and a more than 50% decrease in attacks achieved by more than 88% of patients. Those of East Asian and South Asian descent should be tested for the *HLA-B*15:02* allele as both carbamazepine and oxcarbazepine should be avoided unless benefits clearly outweigh the increased risk of developing Stevens-Johnson and/or toxic epidermal necrolysis.

Surgical Management

In patients who have medically refractory disease, microvascular decompression is the treatment of choice for immediate relief of symptoms. Pain relief is attained in 90% of patients and declines to 80%, 75%, and 73% by years 1, 2, and 5, respectively. This has the longest duration of pain control in surgical procedures.[51] Other options include rhizotomy with either radiofrequency ablation, glycerol injection, or balloon compression.

Radiation Therapy

SRS has emerged as a successful and minimally invasive procedure to treat classic TN. Treatment planning involves the fusion of a contrast-enhanced MRI with less than 1-mm axial sequences to the treatment planning CT scan. The target for SRS varies along the track of the trigeminal nerve. Potential targets described in the literature include the anatomic emergence

of the trigeminal nerve from the pons—proximal dorsal root entry zone (DREZ), the prepontine cistern slightly anterior of the DREZ—retrogasserian target, and the semilunar ganglion.[55-63] Typical doses using a frame-based radiosurgery platform range from 70 to 90 Gy prescribed to an isodose range from 50% to 100%, with prioritization of low doses to the brainstem for minimal toxicity. This dose range is largely based on a composite of trials originating from Kondziolka et al who prospectively assigned patients to low-dose (60-65 Gy) or high-dose (70-90 Gy) SRS and demonstrated higher rates of pain relief in the high-dose arm (72% vs 9% for patients treated with ≥70 vs <70 Gy).[57,63]

The durability of treatment and time to response depend on the dose distribution. The median time to treatment response varies from 2 to 4 months, with higher doses yielding better treatment response but increased chances of sensory neuropathy (facial numbness).[49,64-66] Flickinger et al prospectively randomized patients to 75 Gy targeted to a shorter (one isocenter) or longer (two isocenters) segment of the trigeminal nerve, demonstrating that treating larger segments of the nerve with higher doses is associated with delayed onset of facial numbness.[67] Although the rates of pain relief were surprisingly identical between the two groups, there was a trend toward a higher incidence of numbness or paresthesias in the two-isocenter patients, and overall, the nerve length irradiated was significantly correlated with the development of numbness and paresthesias. However, in a report by Adler et al, 46 patients received treatment with a frameless robotic radiosurgery platform to a 6-mm segment of the trigeminal nerve, with a mean marginal prescription dose of 58.3 Gy and mean maximal dose of 73.5 Gy.[68] In this cohort of patients, 85% experienced a complete response; and at a mean follow-up of 15 months, 96% reported excellent or good outcomes. Only 15% of patients experienced ipsilateral facial numbness.[69]

Epilepsy

Background and Clinical Aspects

Epilepsy is a disorder characterized by recurring seizures. It affects 0.5% to 1% of the population, and its etiology is unknown in most cases. The clinical presentation of patients with seizures is broad, depending on the

type of seizure and the area of the brain involved. Seizures are generally classified into simple versus complex (loss of consciousness) and generalized versus partial (affecting only one focus in the brain).

Systemic Therapy

Antiepileptic drugs are the treatment of choice for patients with epilepsy, and about half of those with a new diagnosis will become seizure free with their first prescription.[70] Therapy is typically not given until patients have had two or more unprovoked seizures, and generally, treatment is begun as monotherapy at lower doses that are slowly titrated up to a level of seizure freedom. Drug choice is based on several factors, including, not limited to, tolerability, comorbid conditions, factors affecting drug clearance or metabolism, cost/availability, and age. Furthermore, combination therapy for the management of intractable seizure activity is often employed when seizure freedom has not been achieved.

Surgical Management

Surgery is an option for patients who develop medically refractory disease.[71,72] Candidates for surgical management of seizure activity require delineation of a focal epileptogenic zone in which surgery can be performed that will not injure an eloquent brain region. Mesial temporal lobe epilepsy is generally the most common remediable and generally involves resection of the anterior temporal lobe (ATL) or selective amygdalohippocampectomy (SAH). There are no high-quality data comparing SAH and ATL, but they seem to have similar seizure control outcomes, approximating 50% to 60% 1 year rare to seizure-free outcomes.[73]

Radiation Therapy

SRS may be an alternative to surgery in medically refractory epilepsy for patients who are not surgical candidates. In a multi-institutional study, Regis et al treated 20 patients with SRS for intractable mesial temporal lobe epilepsy.[74] The mesial temporal lobe was treated to a dose of 24 to 25 Gy in a single fraction with Gamma Knife. At a follow-up of 2 years, 65% of the patients were seizure free. However, there was a 1-year lag between

treatment and maximal effect, and there was a transient increase in seizures before the seizures started to diminish. In a study by Barbaro et al, 30 patients were randomized to low-dose (20 Gy) or high-dose (24 Gy) radiosurgery targeting the amygdala, hippocampus, and parahippocampal gyrus.[75] At 3 years, the seizure-free rate was 67% among all patients, with a trend toward a higher response rate (77% vs 59%) and earlier response in the high-dose group. No serious toxicity was reported in the study.

The randomized controlled ROSE trial was a multi- national, randomized, single-blinded, controlled trial comparing radiosurgery (SRS, 24 Gy to the 50% IDL) versus open surgery (ATL) for mesial temporal epilepsy. The findings suggested that ATL had an advantage over SRS in 3-year seizure remission (78% vs 58%), with seizure remission taking 1 to 2 years and with a similar impact on memory and language outcomes. Unfortunately, the study was severely limited by patient numbers, only accruing 58 of the 234 cases needed to determine noninferiority.[76] In evaluating these outcomes in the context of the data, radiosurgery is a reasonable tool in the armamentarium for drug-resistant epilepsy.

Parkinson Disease

Background and Clinical Aspects

Parkinson disease (PD) results from the loss of dopaminergic neurons in the substantia nigra. It is a debilitating and progressive neurodegenerative disorder that affects approximately 1 million people in the United States. The hallmark clinical symptoms include masked facies, resting tremor, slow movements, shuffling gait, and muscle rigidity. Some patients also develop dementia as part of the disorder.

Systemic Therapy

Pharmacotherapy with dopamine agonists and other compounds is the treatment of choice for patients with PD. Most patients use levodopa (usually in the form of carbidopa-levodopa [Sinemet]) as initial therapy and with high efficacy and the lowest need to add on a secondary therapy as compared to other drugs.[77-79] Device-assisted therapies are available for continuous infusion approaches for medically refractory cases. The best studied are the continuous levodopa-carbidopa intestinal gel and the

continuous subcutaneous apomorphine infusion. These are not widely available currently. In addition, there is a positive clinical trial supporting the use of continuous subcutaneous foslevodopa-foscarbidopa.[79]

Surgical Management

Once refractory to medical therapy, surgery may be used to remove the overactive brain nuclei. Ideally, MRI-guided focused ultrasound (FUS) pallidotomy for those with motor fluctuations or dyskinesias favoring one side. For medication-refractory tremors, MRI-guided FUS thalamotomy is used.

Deep brain stimulation (DBS) is the most common invasive procedure used in medically refractory PD. The primary targets for DBS are the subthalamic nucleus, the internal globus pallidus (GPi), and the ventral intermedius nucleus (VIM). DBS of the VIM is only effective for tremor, while the other targets can impact bradykinesia and motor fluctuations as well. DBS has been effective in providing an improvement in motor movement and QoL as compared to the best medical therapy with 4 to 5 hours per day mean improvement in time without troubling dyskinesia.[80]

Radiation Therapy

Patients who are poor candidates for surgery may receive SRS for the treatment of medically refractory PD. To relieve tremor, the target is the nucleus intermedius (thalamotomy) with a dose in the range of 120 to 180 Gy. Evidence demonstrates long-term success rates of 80% to 90% in relieving symptoms from PD tremor, as well as essential and other types of tremors with a very low rate of permanent complications.[81-86]

Although radiosurgery has proven beneficial for tremors, mixed results have been found with regard to the treatment of PD-related akinesia/dyskinesia/rigidity. Treatment entails targeting the GPi (pallidotomy) with doses in the range of 120 to 180 Gy. Rand et al reported that four of eight patients received relief in rigidity with no serious complications.[87] However, Friedman et al achieved a response in only one of four patients, and dementia and psychosis developed in the only patient responder.[88] Young et al[89] treated 29 patients with SRS pallidotomy, with an

80% success rate at a mean follow-up of 2 years and only one (3.4%) complication at 9 months (homonymous hemianopia).

Psychiatric Disorders

Background and Clinical Aspects

Psychiatric disorders such as OCD, bipolar disorder, major depressive disorder, and subgroups of autism with pathologic aggression are debilitating illnesses. Radiosurgery has been used for the treatment of some of these psychiatric illnesses, with the majority of experience in patients with OCD. OCD is characterized by intrusive thoughts (obsessions) that lead to repetitive behaviors (compulsions).

Systemic Therapy

The combination of pharmacotherapy (ie, selective serotonin reuptake inhibitors) and behavioral therapy is the treatment of choice for patients with mood disorders and OCD. Surgical management and DBS are used for extreme and severe cases.

Radiation Therapy

Patient selection for the use of SRS to treat psychiatric disorders is complex. Friehs et al recommend that such patients must be enrolled on an institutional protocol after careful evaluation by a multidisciplinary team.[90] Similar strict criteria were used by Kondziolka et al.[91]

The treatment of OCD involves targeting the bilateral anterior capsules to a total dose of 120 to 140 Gy (Figure 100.3). Kondziolka et al delivered a maximum dose of 140 or 150 Gy to the anterior limb of the internal capsule in three patients.[91] At a minimum follow-up of 28 months, all patients noted significant functional improvements with no treatment-related complications. In a pilot study by Lopes et al, five patients were treated with SRS to a maximum dose of 180 Gy to the anterior limb of the internal capsule.[92] At 3 years, three patients had a complete response to treatment and one patient had a partial response based on changes in scores on an OCD assessment tool. Based on these findings, the group has opened a double-blind, randomized controlled study on the use of SRS to treat refractory OCD.[92]

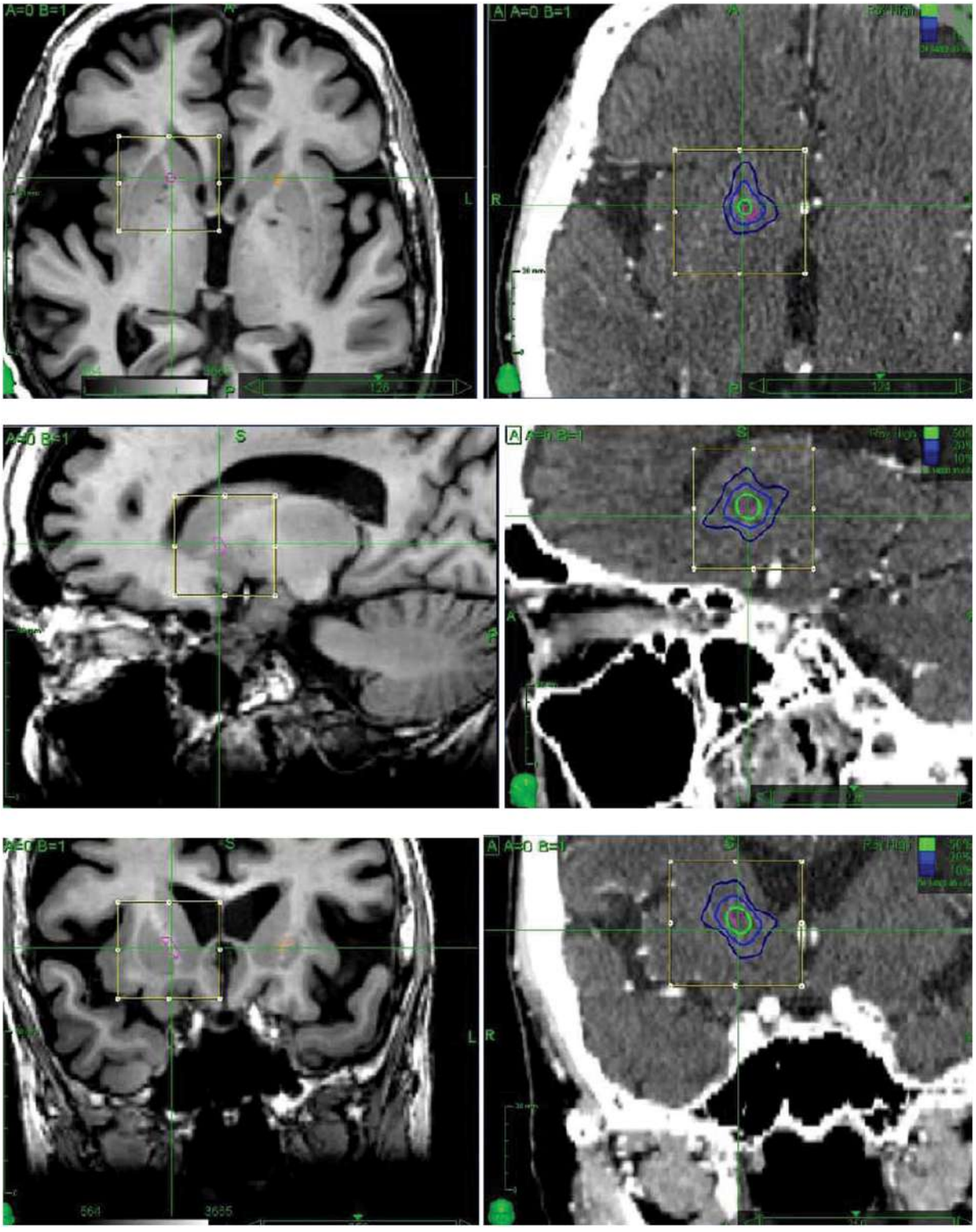

FIGURE 100.3 Stereotactic magnetic resonance imaging sequences (left) demonstrating the contoured anterior limbs of the internal capsule bilaterally and the corresponding treatment plan (right) for the right internal capsule for a patient with refractory obsessive-

compulsive disorder. The right internal capsule was prescribed 70 Gy to the 50% isodose line (140 Gy maximum dose) in a single fraction.

Radiosurgical capsulotomy in the same manner has been used to treat refractory depression (Figure 100.3). Findings include significant improvement in depression burden, decreased need for electroconvulsive therapy, decreased need for ketamine therapy, and decreased suicidal ideation with no reported neurologic decline or toxicity.[93,94]

In a small series from the Hospital Ruber in Spain, 10 patients with autism spectrum disorder with either pathologic aggression, dyscontrol, or activity of daily living–limiting OCD underwent SRS, with a significant improvement in behavior, symptoms, and QoL, though in 8 of 10 patients, there was a need for repeat treatment.[95]

While the efficacy of radiosurgery for movement disorders or severe pain has a reasonably clearly defined end point, radiosurgery for psychiatric disorders often does not, and there is, of course, a very troublesome history of the use of surgical interventions for psychiatric disease, particularly the use of frontal lobotomies. Before this area of clinical practice would be considered within the standard of care, rigorous investigations of the highest standards are called for at selected academic centers by multidisciplinary teams capable of conducting such work.

Cardiac Arrhythmias

Over the past 10 years, there has been an increasing interest in the use of RT for patients with refractory cardiac arrhythmias, now commonly known as stereotactic arrhythmia radioablation (STAR). There have now been several prospective clinical trials evaluating the use of STAR for patients with refractory ventricular arrhythmias, including ventricular tachycardia (VT) and ventricular fibrillation (VF). There are limited human studies regarding the role of STAR for atrial fibrillation (AF) perhaps in large part due to the fact that AF is a benign arrhythmia whereas refractory VT/VF are life-threatening.[96] In this regard, any studies of STAR for AF need to primarily focus on safety, both short term and long term, while efficacy end points are appropriate for patients with VT/VF as these patients have

limited treatment options and life expectancy. Herein, we focus on the use of STAR for ventricular arrhythmias.

VT is a life-threatening form of structural heart disease that occurs when there is electric reentry in areas of myocardial fibrosis, and the main treatment is with invasive catheter procedural techniques to find the areas of fibrosis with abnormal electrical activity and then apply thermal-ablative energy to these areas.[97,98] Since these invasive procedures may take several hours and require anesthesia often in patients with numerous comorbidities, STAR emerged as a potential noninvasive alternative. While the goal of STAR is similar to that of catheter ablation procedures in that the goal is to target surviving myocytes within the areas of myocardial fibrosis, the exact mechanism of action of STAR is not yet known.

To date, numerous small prospective studies and/or case series have evaluated the use of STAR for VT, with sample sizes ranging from 5 to 19 patients.[99-105] The largest series by Robinson et al. evaluated the safety and efficacy of STAR in 19 patients with refractory VT and found a reduction in VT or premature ventricular contractions in 94% of the evaluable patients (17/18).[104] A 2023 study from the Netherlands, termed the *STAR-NL1 study*, was the first prospective trial evaluating the use of STAR for VT in Europe.[105] In this study of six patients, STAR resulted in a 50% or more reduction in VT episodes in four of the six patients with a simultaneous tapering off of antiarrhythmic medications. The Europeans have formed a consortium of 31 clinical and research institutions as a large research network to systemically investigate the use of STAR for VT, with a goal of enrolling over 300 patients into the STAR treatment registry over the study period.[106]

The most common dose and fractionation is 25 Gy in a single fraction to the well-defined target. The definition of the target requires close collaboration with cardiology and requires various imaging studies as described by Robinson et al., including a cardiac CT scan, cardiac MRI, cardiac single-photon emission CT, 12-lead electrocardiogram during VT, and electrocardiographic imaging.[104] While the treatment appears to be well tolerated, several complications of STAR have been published, including one case of worsening mitral regurgitation,[103] one case of acute pericarditis,[104] two cases of delayed pericardial effusions,[104] one case of fatal gastropericardial fistula,[104] and two cases of radiation pneumonitis.[102] These

potential complications underscore the importance of selecting patients who have no or few alternatives for the treatment of recurrent VT and also emphasize why the use of STAR for benign arrhythmias, such as AF, should be limited to prospective protocols.

In summary, STAR is emerging as a potential noninvasive alternative to catheter ablation in select patients with refractory VT supported by a small, but growing body of literature. Well-designed, careful randomized trials are needed to help determine the true efficacy and toxicity of STAR.

Sialorrhea

Background and Clinical Aspects

Sialorrhea, from excess saliva production or inadequate saliva clearance, affects up to 80% of patients with PD and approximately 30% of patients with amyotrophic lateral sclerosis (ALS). The neurodegenerative process of ALS affects upper motor neurons of the anterior horn of the spinal cord with bulbar involvement seen in the later stages of the disease. A pseudobulbar palsy resulting in dysphagia and inability to control swallowing causes drooling and subsequent facial and skin irritation. Furthermore, the use of noninvasive ventilation, which has been shown to increase life expectancy and QoL for patients with ALS, is limited due to the risk of choking and pulmonary aspiration.[107]

Systemic Therapy

Medical management is not always effective and can come with side effects that have the potential to further complicate an already progressively debilitating disease state. Treatment consists of postural changes, repetitive swallowing, suctioning, botulism injections, surgery, and/or radiation.[108]

Anticholinergic drugs are the primary medications deployed in the management of sialorrhea. Scopolamine patches are thought to be the most effective and well-tolerated anticholinergic drugs in the management of sialorrhea. Oral anticholinergics are often discontinued due to systemic side effects, such as sedation and delirium. Glycopyrrolate has been shown to have a more favorable toxicity profile regarding central side effects and can also be administered subcutaneously.[107,109]

Botulism can be injected into the submandibular or parotid glands under ultrasound guidance. Because the duration of effect can range from 3 to 7 months, repeat injections are often necessary.[109]

Radiation Therapy

Electron-based and photon therapy are both techniques employed in delivering RT for sialorrhea. Photon therapy is typically delivered with parallel-opposed radiation targeting the inferior two-thirds of the bilateral parotids and the entire bilateral submandibular glands. Most common electron field arrangements target the entire bilateral submandibular and parotid glands. The durability of the treatment effect is variable, but the side effects of treatment are characteristic of patients receiving head and neck radiation. Guy et al compared the two treatment techniques and demonstrated longer durability and less acute toxicity (oral pain and mucositis) among patients treated with electron therapy.[110] A systematic review demonstrated median time to symptomatic improvement was 2 months, with efficacy ranging from 3 months to over 5 years.[108] Optimal treatment is likely a 3D conformal plan with a combination of mixed photon-electron beams using an oral cavity avoidance to minimize toxicity. Assouline et al treated 50 patients with a regimen of 20 Gy in four fractions or 10 Gy in two fractions, with 92% of patients achieving a complete response with no difference in toxicity.[111] In this cohort of patients, eight of nine patients treated with the lower dose regimen required a second RT course.

DISEASES OF THE EYE AND ORBIT

Ptyergium is addressed in Chapters 22 and 44.

Choroidal hemangioma is addressed in Chapters 44.

Reactive lymphoid hyperplasia/orbital pseudotumor is addressed in Chapters 44.

Age-Related Macular Degeneration

Background and Clinical Aspects

Age-related macular degeneration (AMD) is a progressive eye condition that affects the macula and is the leading cause of blindness in the developed world.[112] The development of AMD is dependent on age, with a prevalence of up to 35% in the eighth decade of life. AMD can be classified into two main types. The more common form is dry AMD, which accounts for about 80% to 90% of cases. It is characterized by the gradual thinning and breakdown of the macula over time. In this type, small yellow deposits called drusen may accumulate in the macula, affecting its function (Figure 100.4). On the other hand, wet AMD, although less common, is more severe and accounts for about 10% to 20% of cases. It involves the growth of abnormal blood vessels beneath the macula, which can leak fluid and blood, resulting in rapid and significant vision loss. AMD risk factors include age, genetics, smoking, race (more common in Caucasians), cardiovascular disease, and unhealthy lifestyle factors, such as obesity and poor diet. In the early stages, AMD may not exhibit noticeable symptoms. However, as the condition advances, individuals may experience distorted or impaired central vision. Reading and tasks requiring fine vision may become challenging. Color perception may decrease, and sensitivity to glare can increase. In addition, dark or empty areas may appear in the central vision.

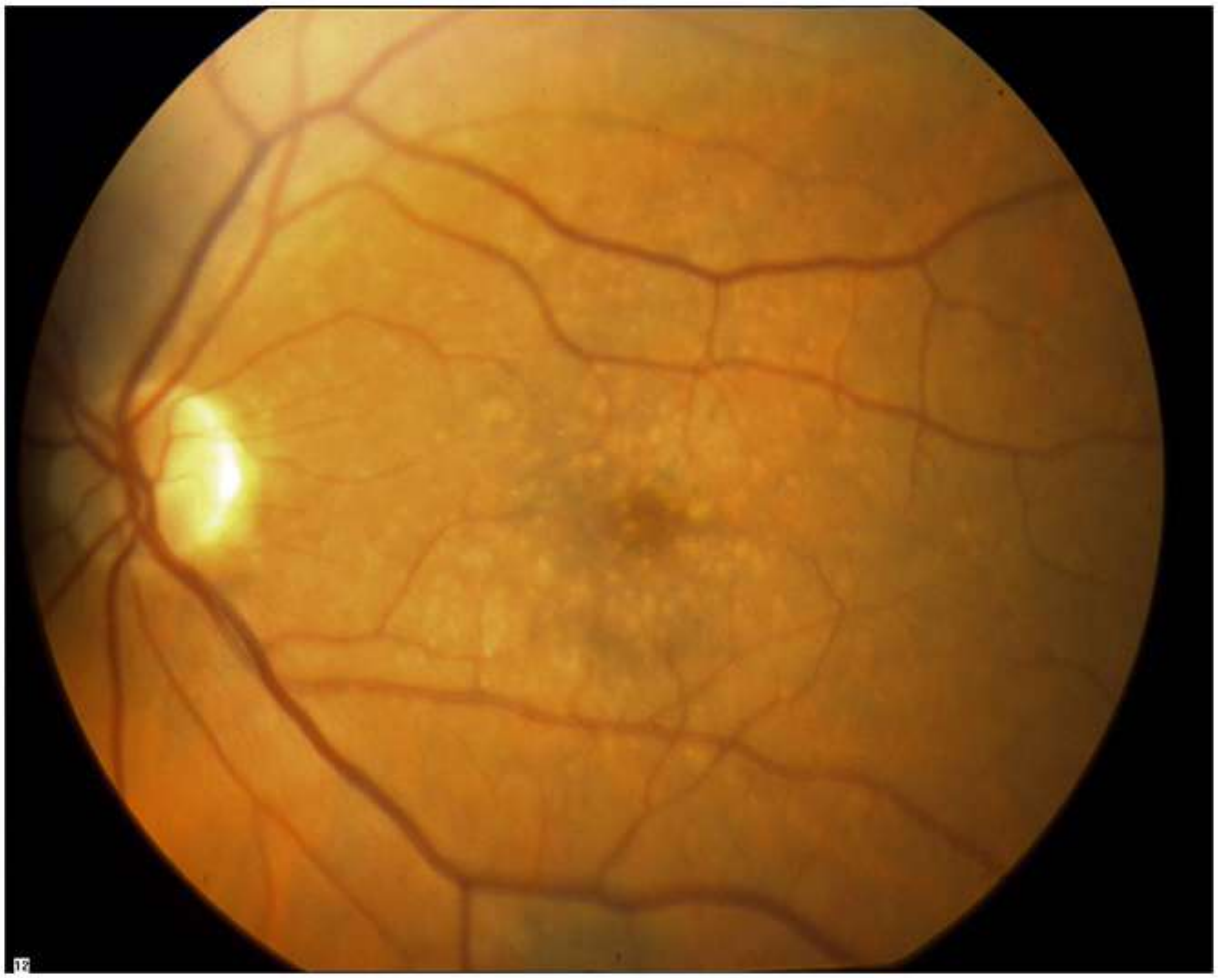

FIGURE 100.4 Macular degeneration with atrophic-appearing macula and surrounding drusen. (Reprinted from Eng TY, Abugideiri M, Chen TW, et al. Radiation therapy for benign disease: keloids, macular degeneration, orbital pseudotumor, pterygium, Peyronie disease, trigeminal neuralgia. *Hematol Oncol Clin North Am*. 2020;34[1]:229-251. Copyright © 2019 Elsevier. With permission.)

Management Overview

While there is currently no cure for AMD, treatment options are available to slow its progression and manage its effects, particularly for wet AMD. Intravitreal injections of anti-vascular endothelial growth factor (VEGF) medications can reduce abnormal blood vessel growth and leakage in wet AMD, stabilizing or improving vision.[113] In certain cases of wet AMD, vascular-targeted photodynamic therapy can selectively destroy abnormal blood vessels using a light-activated drug combined with laser therapy.[114]

External beam RT (EBRT) with photons or protons and brachytherapy have been used in the past to treat macular degeneration. Overall, the results

of RT in the management of this disease have been mixed. Most studies took place before the routine use of anti-VEGF and before the development of modern RT techniques, such as stereotactic radiation therapy (SRT).[115] A Cochrane meta-analysis in 2010 analyzed 14 randomized trials utilizing RT as a treatment for AMD and concluded that the review "does not provide convincing evidence that RT is an effective treatment for neovascular AMD."[116]

However, there is renewed interest in RT for AMD based on the results of the RT in Conjunction with Anti-VEGF Treatment for Patients with Wet AMD trial.[117] In this study, 230 participants who had received at least three injections with anti-VEGF therapy were randomized to 16 Gy, 24 Gy, or sham SRT. The primary end point was the mean number of pro re nata (PRN) intravitreal ranibizumab injections over 52 weeks. With 2 years of follow-up, patients who received 16 or 24 Gy had fewer PRN treatments compared to the sham SRT group. SRT was found to induce microvascular change, but this affected vision in only 1% of patients.[118] This trial supports SRT as a potential method to stop or slow down the visual loss associated with continued intravitreal injections of anti-VEGF therapy.

Graves Ophthalmopathy

Background and Clinical Aspects

GO (also referred to as Graves orbitopathy, thyroid eye disease, Basedow disease, or Parry disease) is an autoimmune disorder affecting the musculature of the orbits. It is commonly associated with an overactive thyroid (hyperthyroidism). The presence of activated T lymphocytes leads to an inflammatory reaction secondary to the release of cytokines. It is estimated that up to 50% of patients with Graves disease will develop orbitopathy, but 10% of patients are euthyroid and some are hypothyroid at presentation.[1] Smoking is the greatest risk factor for the development of GO and also predicts a poorer response to therapy.

A multidisciplinary team including an ophthalmologist, endocrinologist, and radiation oncologist should be involved in the evaluation of the patient with GO. Clinical features of patients with GO include proptosis (measured by the Hertel exophthalmometer on physical examination), photophobia, upper eyelid retraction, periorbital edema (due to the accumulation of

collagen and hyaluronin, which attract water), conjunctival erythema, tearing, and visual impairment (Figure 100.5). Patients may complain of a "gritty" sensation in their eyes. Several classification systems are available to document the extent of disease, including SPECS Ophthalmic Index (Table 100.3), which assigns a score of 1 to 3 on the basis of six categories: ***S***oft tissue involvement, ***P***roptosis, ***E***xtraocular movements, ***C***orneal involvement, and ***S***ight (visual acuity).

TABLE 100.3 SPECS CLASSIFICATION SYSTEM FOR GRAVES OPHTHALMOPATHY

Clinical Feature	Grade 1 (1 Point)	Grade 2 (2 Points)	Grade 3 (3 Points)
S (soft tissue involvement)	Minimal objective symptoms: redness, chemosis, slight periorbital edema	Moderate objective symptoms: redness, chemosis; moderate periorbital edema	Severe objective symptoms: conjunctival exposition, prominent periorbital edema
P (proptosis)	>20-23 mm	24-27 mm	>27 mm
E (eye muscle dysfunction)	Rare diplopia; none in primary position	Frequent diplopia; moderate mobility impairment	Severe constant muscular dysfunction
C (corneal involvement)	Slight corneal changes and no symptoms	Prominent corneal changes and moderate symptoms	Keratitis or other severe eye symptoms
S (sight loss)	20/25-20/40	20/45-20/100	>20/100

SPECS, ***S***oft tissue involvement, ***P***roptosis, ***E***xtraocular movements, ***C***orneal involvement, and ***S***ight (visual acuity).

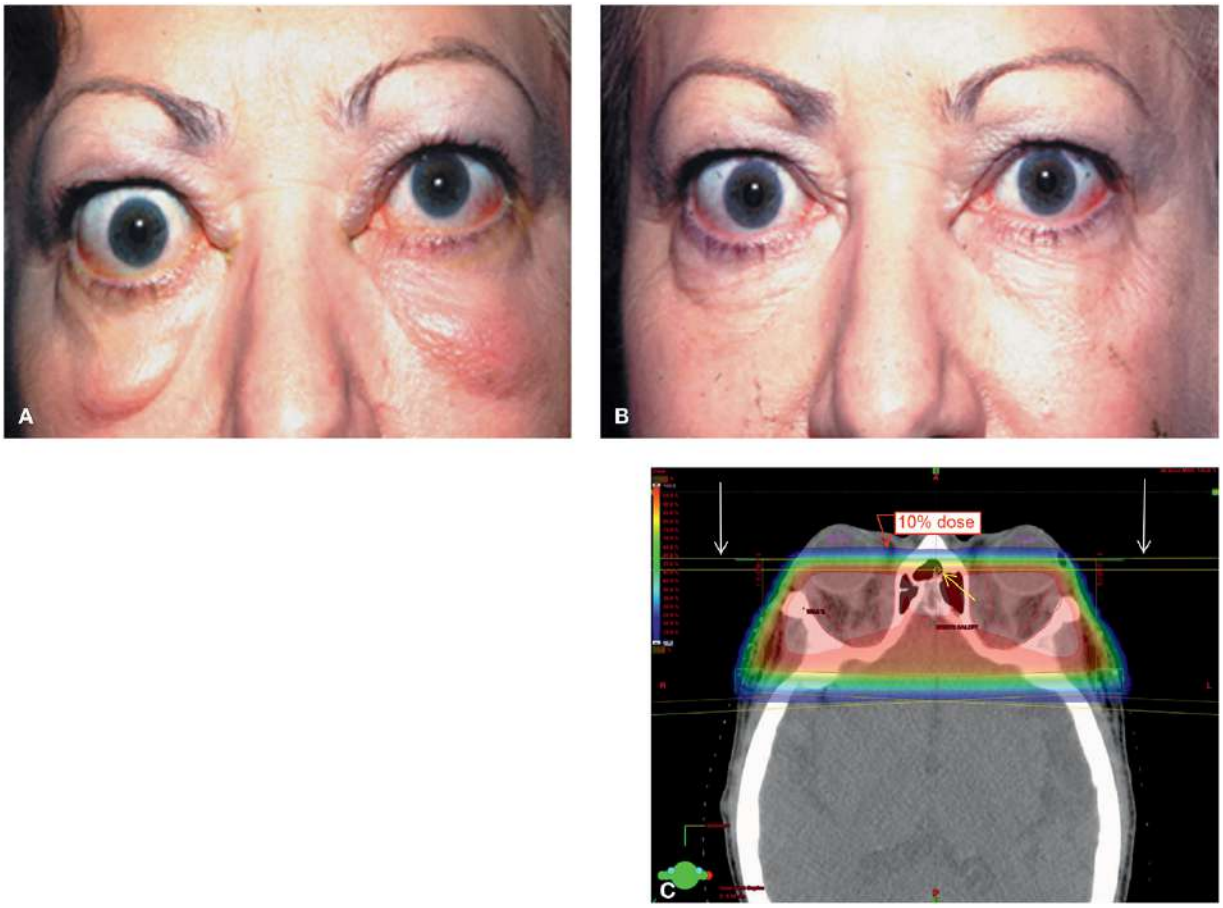

FIGURE 100.5 A 50-year-old woman with Graves ophthalmopathy before (A) and after (B) treatment with corticosteroids and radiotherapy for prominent eyelid edema and strabismus. C. Three-dimensional conformal radiotherapy treatment plan for a patient with Graves ophthalmopathy. The isocenter (yellow arrow) is placed a few mm posterior to the lenses (magenta), and the opposing fields are beam split anteriorly (white arrows). The extraocular muscles are contoured in red. The color wash display demonstrates that <10% of the dose reaches the lens.

Imaging studies, such as CT or MRI, will demonstrate abnormalities, including enlargement of the extraocular muscles and fatty infiltration, in 70% to 80% of cases.[1] The most commonly involved muscles include the inferior and medial rectus muscles.[118]

Management Overview

Treatment options for GO include glucocorticoids (GCs), orbital RT, and surgery (orbital decompression, eye muscle surgery, eyelid surgery). Smokers should be encouraged to quit. Prior to the initiation of treatment, the patient's thyroid function should be normalized. Radioiodine therapy,

but not antithyroid drugs, may cause worsening of GO, especially in smokers.[119,120] Once thyroid function is stabilized, the treatment of GO depends upon the severity of the disease.

Systemic Therapy

GCs are a mainstay of treatment for GO. Immediate treatment with high-dose steroids (intravenous [IV] or oral) is required for patients whose vision is threatened by optic neuropathy.[121] GCs may also be used to treat patients with moderate-to-severe active ophthalmopathy.[121] In a double-blind randomized trial, 28 patients with moderately severe GO were treated with a 3-month course of oral prednisone and sham irradiation, and 28 received retrobulbar irradiation (20 Gy) and placebo capsules, oral prednisone, and RT appeared to be equally effective as initial treatment in patients with moderately severe GO.[66]

Surgery

In the event that GCs fail to improve optic neuropathy, urgent orbital decompression is necessary.[122,123] Another indication for urgent orbital decompression is exposure keratopathy not relieved by local measures.[122]To improve extraocular muscle function and cosmesis, other procedures such as strabismus surgery and lid surgery may be performed. It is recommended that the GO be inactive for at least 6 months before pursuing these procedures.[122]

Radiation Therapy

RT has shown to be an effective treatment option for palliating clinical symptoms in GO, although some conflicting data on the efficacy of RT for GO exist.[66,123-126] Indications for RT in the management of GO have been outlined by Donaldson and McDougall and include (Table 100.4) inducing clinical regression, improving functional deficits, improving cosmesis, and avoiding side effects of other treatments.[127]

TABLE 100.4 CLINICAL GUIDELINES FOR USE OF RADIOTHERAPY IN GRAVES OPHTHALMOPATHY (GO)

Radiotherapy Goal	Precondition/Indications	Contraindications
Induce clinical regression	*Pretherapeutic diagnostics*: evidence of autoimmune thyroid disease; CT/MRI	Stable GO without clinical progression
Reduce/eliminate functional deficits	*Ophthalmologic diagnostics*: documented progressive disease	Lack of euthyroid
Improve cosmetics/aesthetics	*Subjective/objective findings*: evidence of functional deficits and disorders	"Cosmetic" indication alone without functional impairment
Avoid/decrease undesired effects of other measures	*Exclusion of risk factors*: no other eye disease (ie, diabetic retinopathy)	No consent to planned therapy

CT, computed tomography; MRI, magnetic resonance imaging.

Adapted by permission from Springer: Donaldson SS, McDougall IR. Graves' disease. In: Sagerman RH, Alberti WE, eds. *Radiotherapy of Intraocular and Orbital Tumors*. Springer; 2003. Copyright © 2003 Springer-Verlag Berlin Heidelberg.

RT is generally administered with 3DRT. Both orbits, including the entire length of the extraocular muscles, are treated to a total dose of 20 Gy in 2-Gy fractions using opposed lateral fields with the isocenter placed a few millimeters posterior to the lenses using a beam-split technique (see Figure 100.3).

For patients with progressive GO, retrospective data suggest that orbital RT is an effective treatment modality. Marquez et al reviewed the records of 197 patients treated at Stanford, all of whom received 20 to 30 Gy to the bilateral retrobulbar region.[128] Outcomes assessed included SPECS score and patient satisfaction. There was a 96% overall response rate and 98% patient satisfaction rate, with the largest improvements in soft tissue findings (89%), extraocular muscle dysfunction (85%), and corneal abnormalities (96%). In a later study, Matthiesen et al. reported on 211 patients who received orbital RT between 2000 and 2010 for GO.[129] Overall, 97% of patients had stabilization of disease and 84% reported symptomatic improvement. Steroids were discontinued in 98% of patients who received them as initial therapy. A subset of 14 patients received orbital reirradiation for persistent symptoms, with 5 achieving a complete response

and 9 having disease stabilization. These 14 patients did not experience increased toxicity compared to the rest of the cohort.[129]

There have been limited data comparing the effectiveness of low-dose versus high-dose RT. In a recent study of 127 patients with stage III/IV GO who received 20 Gy in 2-Gy fractions versus 4.8 Gy in 0.8-Gy fractions, with a median follow-up of 9.0 years, 63.8% of the patients experienced an improvement in symptoms after RT, irrespective of the use of low dose or high dose. However, low-dose RT required retreatment more frequently (13.1% vs 1.7%).[130]

BENIGN DISEASES OF SOFT TISSUE AND BONES

General Overview of Inflammatory Conditions of Joints and Tendons

The role of RT in the treatment of benign inflammatory conditions involving the joints and/or tendons is controversial. OA, tendonitis, bursitis, rotator's cuff syndrome, and tennis elbow are examples of inflammatory conditions for which RT has been used in the past. These soft tissue syndromes may result from repetitive activities that cause overuse or injury to the joint areas, incorrect posture, stress on the soft tissues due to an abnormal or poorly positioned joint or bone, or other conditions such as autoimmune diseases or infection.

Although the cause of each disorder may be different, the clinical presentation and general treatment plan are frequently similar. Symptoms include pain, swelling, or inflammation in the tissues and structures around a joint, such as the tendons, ligaments, bursae, and muscles. Treatment generally involves a combination of exercise, lifestyle modification, and analgesics. If pain becomes debilitating, joint replacement surgery may be used to improve the QoL. In rare instances, low-dose RT (<10-15 Gy) can be employed. The low dose required to improve symptoms suggests the possible mechanism of action for RT, as shown in Table 100.5.

TABLE 100.5 RADIATION THERAPY MECHANISM OF ACTION DOSE CONCEPTS

Mechanisms of Action	Single Dose (Gy)	Total Dose (Gy)
Cellular gene and protein expression (eg, eczemas)	<2.0	<2

Mechanisms of Action	Single Dose (Gy)	Total Dose (Gy)
Inhibition of inflammation in lymphocytes (eg, in orbital pseudotumor)	0.3-1.0	2-6
Inhibition of fibroblast proliferation (eg, in keloids)	1.5-3.0	8-12
Inhibition of proliferation in benign tumors (eg, in desmoids)	1.8-3.0	45-60

Osteoarthritis

OA, the most common joint disorder, is a chronically debilitating musculoskeletal disorder, which predominately affects older people. It presents with pain associated with cartilage destruction, bone modification, and structural changes of the capsule and synovia. Symptoms are caused by reactive inflammation of the joint surface and joint capsule lining (synovia). Risk factors include age; genetic predisposition; bone fracture or joint injury, whether by an accident of overuse from work or sports; and increased body mass index.[131] The incidence of OA is expected to rise worldwide due to an aging population and the increasing prevalence of obesity compared to previous decades.

Systemic Therapy

Hunter and Lo provide a general overview of the diagnosis, investigation, and treatment of OA.[69] The treatment of early OA is intended to reduce the primary symptoms of joint pain and stiffness, with the goal of maintaining and improving the functional capacity of the affected joint(s).[132] Exercise, weight reduction, and joint braces have shown some success at unloading damaged joints and improving symptoms.[133] For OA of the hip and knee, exercises that strengthen muscles and improve aerobic condition are most effective.[134]

Oral analgesics are the mainstay of treatment for OA. While acetaminophen is frequently offered due to its relative safety and efficacy, a nonsteroidal anti-inflammatory drug (NSAID) may be added or substituted.[135] NSAIDs can be used in patients with symptomatic OA of the hand, hip, or knee. The goal is to administer the lowest effective dose for the shortest duration. The use of stronger analgesics, such as weak opioids

and narcotics, may be considered when other methods have been ineffective or if certain drugs are contraindicated.[133] Glucosamine and chondroitin sulfate are over-the-counter remedies that are frequently used to reduce pain, but their efficacy has not been proven.[136] Corticosteroids and other analgesics may be injected directly into the joint; injections may temporarily reduce swelling and pain. Acupuncture and other complementary and alternative treatment modalities have been used, but their efficacy is unproven.[84]

Surgery is reserved for patients with severe OA and those who have not responded to noninvasive therapies. Total or partial joint replacement is most commonly used for OA involving the knee, hip, and shoulder and is considered when structural damage is visible on x-rays. However, there are modern surgical procedures that can obviate or delay the need for joint replacement, including osteotomies and joint resurfacing.[85] Joint fusion or arthrodesis may be used to treat arthritis of the spine, ankles, hands, and feet. Arthroscopy, or arthroscopic surgery, is a minimally invasive surgical procedure that can be used to examine and treat the interior surface of a damaged joint. Arthroscopic procedures can help relieve pain for a short time and allow the joints to move better. While arthroscopy may delay the need for joint replacement surgery, it does not improve the arthritis itself.[86]

Radiation Therapy

In nonsurgical candidates, low-dose RT may be considered if pharmacotherapy has failed. RT can lead to freedom from pain and improved joint function.[137] Several single-institution studies have been published that report long-term pain relief and functional gain in 50% to 75% of patients. In Germany, a pattern of care study investigated the use of RT for the treatment of OA of the knee (gonarthrosis) from the years 2006 to 2008.[138] Almost 80% of institutions in Germany used RT to treat OA in the 2-year period analyzed. Treatment of 4,544 patients was performed annually at 188 institutions. The median total dose was 6 Gy (range 3-12 Gy), with a median single dose of 1 Gy (0.25-3 Gy). Long-term clinical outcomes were available in 5,069 cases. The majority of patients experienced pain reduction for at least 3 months, but pain management for up to 12 months was reported. In 30% of patients, a second course of RT

was used for inadequate pain response or early pain recurrence.[138] Micke et al published a prospective study on older patients with gonarthrosis using a similar RT regimen, demonstrating a good analgesic effect of low-dose RT with minimal side effects.[139]

As with arthroscopy, radiation may reduce pain and pain-related dysfunction, but it does not improve the arthritis itself. Due to its efficacy and relative safety, RT may provide an alternative to conventional conservative treatment for patients who are not surgical candidates.

Gorham-Stout Syndrome

Gorham-Stout syndrome, also known as disappearing bone disease or massive osteolysis, is a rare bone disorder of unknown etiology. It is characterized by progressive proliferation of small blood or lymph vessels, resulting in destruction and resorption of the bone matrix. The symptoms are nonspecific but include muscular weakness, limb tenderness, and pathologic fracture occurring with minimal trauma. Involvement of the cervical spine or skull base could be fatal. Case reports indicate limited efficacy of systemic therapies, such as zoledronic acid and interferon-alpha.[140,141] RT has also been used.[142] Heyd et al completed a national patterns-of-care study and literature review that summarized the scant data available for this rare disorder.[143] The 38 articles listed therein provide evidence from the treatment of 44 patients and show that conventionally fractionated EBRT (total dose of 36-45 Gy) may prevent disease progression in 75% to 80% of cases.

Pigmented Villonodular Synovitis

Pigmented villonodular synovitis or tenosynovial giant cell tumor is a rare proliferative disorder of synovial tissue. Symptoms include sudden onset, unexplained joint swelling, and pain that frequently involves a single joint. The knee and foot are most commonly affected, but there are reports of shoulder, hand, and hip involvement.[144] Decreased motion, joint stiffness, and increased pain occur as the disorder progresses. Surgical resection with either synovectomy or joint replacement is the treatment of choice.[145]

RT is indicated in cases of diffuse, bulky disease resulting in bone destruction or in the rare instance of multiple recurrences after resection.

Although intrasynovial injection of radioactive isotopes postoperatively has been used in the past for high-risk patients,[146] most institutions use EBRT. RT to a dose of 36 to 50 Gy has been effective.[23,147,148] MRI is essential for delineating disease pre- and postoperatively. The final dose of RT should be tailored to the amount of residual disease.[149]

Vertebral Hemangiomas

Hemangiomas are benign proliferations of blood vessels that can affect any tissue and are typically asymptomatic. About 50% of hemangiomas involving the vertebral body are associated with pain and, therefore, may require treatment. Treatment options include surgical resection or more conservative interventions such as transarterial embolization, vetebroplasty, or intralesional injections.[150] RT either alone or postoperatively has been successful in reducing pain caused by vertebral hemangiomas.[151] In a German multicenter trial, a total of 84 patients with 96 symptomatic lesions were irradiated for symptomatic vertebral hemangioma. At a median 68-month follow-up, 90% of patients had either complete or partial pain relief. Radiation doses 34 Gy or greater resulted in significantly improved pain relief. A total radiation dose of 36 to 40 Gy delivered in 2 Gy per fraction was recommended.[152]

DISEASES OF CONNECTIVE TISSUE AND SKIN

Desmoid Tumors

Background and Clinical Aspects

Desmoid tumors (also called aggressive fibromatosis or deep musculoaponeurotic fibromatosis) are benign tumors of connective tissue that arise from muscle fascia, aponeuroses, tendons, and scar tissue. They are slightly more predominant in females and tend to occur during the third and fourth decades of life, although children and the older patients can be affected. In the general population, desmoids are rare; the estimated incidence is 2 to 4 per million per year. Genetic factors, trauma, and/or surgery predispose to the development of desmoids. Most desmoids arise sporadically, with 85% of cases associated with *CTNNB1* gene mutation in the Wnt/β-catenin signaling pathway. Mutation in the *APC* genes results in

desmoid tumors affecting 10% to 20% of patients with familial adenomatous polyposis (FAP) and is a manifestation of Gardner syndrome.[153,154]

Tumors can develop anywhere in the body, but most commonly involve the trunk/extremity, abdominal wall, and intra-abdominal sites, including the bowel and mesentery. Approximately 30% of patients with desmoid tumors have a history of prior desmoid tumors.[155,156] Sporadic cases commonly involve the extremities, the shoulder girdle, and the buttock.[157] In patients with FAP, intra-abdominal desmoids predominate and tend to be associated with surgical sites and anastomoses following colectomy.[158] Desmoid tumors in women can occur during or after pregnancy; they may be associated with high estrogen states. Women who have been pregnant are more likely to have abdominal desmoid tumors that develop within 10 years of the last pregnancy.[159]

Desmoids are locally aggressive and commonly have a high rate of recurrence, even after complete resection. Diagnostics workup with MRI helps to estimate size and infiltration into other organs and should be obtained prior to incisional biopsy for diagnostic confirmation.

Systemic Therapy

Observation is a viable option for stable, asymptomatic desmoids. Treatment is indicated for symptomatic patients, if there is a risk to adjacent structures, or to improve cosmesis. Complete surgical resection of the tumor with negative microscopic margins is the treatment of choice for most desmoid tumors. Due to the size and infiltrative nature of extra-abdominal desmoids, resection may result in significant morbidity, requiring skin grafting or flap reconstruction. Desmoid tumors have a high rate of recurrence following even complete surgical removal. A recent meta-analysis of 1,295 patients demonstrated that the risk of recurrence in patients with positive surgical margins was almost 2-fold higher.[160] While resection does not alter survival in most patients, given the histologically benign nature of desmoids, the overall surgical strategy should still be an attempt at complete removal using function-preserving surgical approaches to minimize major morbidity (functional and/or cosmetic).[161]

While extra-abdominal desmoid tumors can generally be treated effectively with local therapy, surgical intervention tends to be counterproductive in intra-abdominal variants, especially the ones associated with FAP. In some instances, systemic therapy may achieve significant and durable cytoreduction, obviating the need for resection. Patients with desmoid tumors have been treated with NSAIDs. The most widely used NSAID for the treatment of desmoid tumors is sulindac. Hormonal agents such as tamoxifen, raloxifene, and progesterone have been used, often in combination with NSAIDs. Tamoxifen has been used most widely and is typically prescribed at doses similar to those used for breast cancer (10 mg daily). Much higher doses (120 mg daily) have been recommended,[162] but high-dose tamoxifen is difficult to tolerate, and there is no evidence to suggest that higher doses of tamoxifen are better than lower doses.

A variety of palliative chemotherapeutic regimens have been used.[163-165] With the waxing and waning natural history of desmoids, it is difficult to say whether systemic therapy provides much benefit over observation. In one series, 142 patients presented with either a primary (n = 74) or recurrent (n = 68) desmoid tumor. Eighty-three patients were treated with observation alone, and 59 received either hormone therapy or chemotherapy. There was no statistically significant difference in progression-free rates between the two groups.

Desmoid tumors also respond to the tyrosine kinase inhibitor imatinib.[166,167] The response is thought to be due to the expression of one of Gleevec molecular targets, platelet-derived growth factor receptor, on desmoid tumors.[168] Phase II clinical trials have demonstrated the efficacy of imatinib in the treatment of progressive and recurrent aggressive fibromatosis. While response rates are low, the 2-year progression-free rate in responders is about 50% with a favorable toxicity profile.[167,169] Kasper et al prospectively administered imatinib (800 mg/daily) to patients with desmoid tumors not amenable to R0 resection without significant function loss and demonstrated a 2-year progression arrest rate of 45%.[169]

Intralesional injections[170] and radiofrequency ablation[171] have also been used. Although the techniques led to some tumor shrinkage, the experience to date is limited, and the long-term results are not yet known.

Radiation Therapy

RT is a viable option for inoperable patients and may also be used in combination with surgery or chemotherapy. Spear et al retrospectively compared the efficacy of surgery alone, radiation alone, and combined modality therapy (radiation and surgery) in the treatment of desmoid tumors.[172] Five-year local control rates among surgery, RT, and combined modality groups were 69%, 93%, and 72%, respectively. More recently, Janssen et al performed a meta-analysis on the influence of surgical margin and adjuvant RT on local recurrence and found that RT reduces the risk of recurrence in patients with microscopically positive resection margins.[159] The association of adjuvant RT benefit was even stronger for resection of recurrent tumors with positive margins. Of note, adjuvant RT for patients with negative margins did not affect recurrence rates.

The general recommended radiation dose for inoperable or recurrent desmoids is 60 to 65 Gy.[23] However, long-term results at another institution show increased post-treatment toxicity in patients who receive RT doses greater than 56 Gy.[160]

Young age (# 30 years) was also associated with increased late toxicity. In a retrospective study of 30 patients under the age of 30, younger age (<18) was associated with inferior local-regional control following RT. Although actuarial control rates were better with RT doses of 55 Gy or higher, almost 50% of patients experienced grade 3 to 4 complications, including pathologic fractures, impaired range of motion, pain, and in-field skin cancers.[173,174] Since long-term results suggest that unresectable tumors respond to 56 Gy with a 75% expectation of local control, the lower dose may be more appropriate in this population.

When an R0 resection is not possible, doses of 50 to 60 Gy postoperatively should be given to improve local control. RT is often not considered for intra-abdominal tumors because the dose and increased field size increase the risk of bowel injury. Due to the complexities involved in managing the disease, a multidisciplinary approach must be taken.[175]

Peyronie Disease

Background and Clinical Aspects

Peyronie disease (PYD) (also known as “induratio penis plastica”) is a chronic inflammatory connective tissue disorder involving the penile tunica albuginea that results in tissue proliferation and the development of hard plaques, most commonly on the dorsal surface of the penis. These may cause a curvature, indentation, and changes in the length or circumference of the penis while erect. Symptoms may lead to difficult intercourse, penile pain, and erectile dysfunction.

PYD affects up to 10% of men, although a recent population-based study suggests the condition may be underreported in the United States.[176] While PYD can affect teenagers, men between the ages of 40 and 70 are mostly affected, with a peak incidence at 50 years of age. The cause is unknown but is often associated with prior penile trauma. Diabetes mellitus and arterial and venous vascular disease are risk factors, along with an assumed genetic predisposition. Slow progression over several months is typical, with spontaneous remission occurring in less than 15% of men.[177]

Systemic Therapy

Results of nonsurgical treatment of PYD are mixed and controversial.[178,179] Some success has been reported with vitamin E supplementation, but results have not been confirmed in larger studies.[180] A combination of vitamin E and colchicine may delay disease progression.[181] Other agents that specifically target inflammatory pathways have also shown mixed benefit, including tumor growth factor-β1 inhibitors,[182] coenzyme Q10,[183] and sildenafil, among others.[184] Topical therapies have largely been ineffective, but penile injection with verapamil or collagenase, intended to break up scar tissue formed by the inflammation, has shown some efficacy.[185] Physical therapy and extracorporeal shock treatments have also had limited benefit.

Surgical options for PYD are complex procedures that should only be performed by experienced urologists and are reserved for patients not responding to other therapies.[186] Although the nonsurgical treatments discussed may not reliably treat the disease, they can be used to stabilize the scarring process and may result in some reduction of deformity. A combination of nonsurgical techniques may have even more efficacy.[187]

Radiation Therapy

The largest experience with the use of RT in the treatment of PYD has been in Europe. Retrospective studies report varied symptom improvement with the use of RT in terms of pain, curvature reduction, plaque volume, and sexual functioning.[189] These data also suggest that any benefit of RT is best in the treatment of early stages of disease, when radio-responsive inflammatory cells and fibroblasts are still active. RT in later stages of PYD once the plaques have fully formed is thought to yield worse outcomes.

The current recommendation for RT in PYD is a total dose of 10 to 20 Gy in daily single fractions of 2 to 3 Gy using a direct ventral field. The penis lays on the scrotum, and a lead or polyethylene layer is placed between the scrotum and penis to shield the testes. Orthovoltage, low-energy photons and/or electrons may be used. One retrospective study from the Netherlands indicated that low-dose RT, either 13.5 Gy (9 × 1.5 Gy, three fractions per week) or 12 Gy (6 × 2 Gy, daily fractions), resulted in pain relief in the majority of the 179 patients evaluated.[189] Sexual dysfunction was a reported side effect, although this is confounded by the underlying disease.

As experimental models improve our understanding of the pathogenesis of PYD, the use of RT for plaque development in this highly complex vascular organ may further decline, given concerns regarding radiation-induced vascular fibrosis and the development of more effective therapies.[190,191]

Dupuytren Contracture

Background and Clinical Aspects

Dupuytren contracture, also known as Morbus Dupuytren (MD) and Morbus Ledderhose (ML) depending on the involvement of the hands or feet respectively, is a connective tissue disorder that affects the palmar or plantar fascia. Some authors estimate the global prevalence of Dupuytren disease to be between 3% and 6%. Incidence increases after the age of 40, and the condition affects men more often than women. A genetic predisposition along with a number of environmental factors (smoking, alcohol use) can lead to local ischemia and free radical release, which

stimulates fibroblast proliferation and cytokine production, particularly IL-1.

In the early stage, subcutaneous nodules appear, which may be fixed to the overlying skin. As the disease progresses, cords develop and become visibly predominant. With further progression, the cords reach the periosteum of the bones and lead to the characteristic appearance of palmar or plantar contraction. The fourth/fifth phalanges of the hand (MD) or the first/second toes of the foot (ML) are the most commonly affected digits (Figure 100.6). With increased thickening of the fascia and progressive contracture, the fingers and toes begin to curl, resulting in significant functional deficits, for example, difficulty grabbing (MD) or walking (ML).

FIGURE 100.6 Dupuytren contracture of both hands and the left foot.

Surgical management

Excision of diseased cords and fascia via limited or selective fasciectomy is widely considered the gold standard treatment for Dupuytren

contracture.[192,193] A 20-year review of open surgery for Dupuytren contracture showed that major complications occurred in 15.7% of cases and that wound complications were seen in 22% of cases.[194] Even with excellent surgical resection, relapse is common, with a 30% to 50% recurrence rate at 3 years.

Modern minimally invasive techniques have substantially reduced the complication rates. Percutaneous needle fasciotomy is a technique where cords are weakened through the insertion and manipulation of a small 25-gauge needle mounted on a 10-mL syringe.[195] The procedure is performed under local anesthesia, and patients may return to full usage of the affected limb within 24 hours. Since the cords and nodules are not fully excised, minimally invasive surgery has an even higher recurrence rate that surgical excision. A randomized study comparing percutaneous needle fasciotomy with limited fasciectomy showed an 85% recurrence rate after 5 years with the minimally invasive procedure.[196]

During the early stage of Dupuytren, medication (steroids, allopurinol, nonsteroidal vitamin E) may provide benefit, but the effects are temporary. Collagenase *Clostridium histolyticum* injections (CCH) are the Food and Drug Administration–approved nonsurgical treatment option for adult patients with Dupuytren contracture with a palpable cord. Injections of this collagenase enzyme weaken the cords through the breakdown of the peptide bonds in collagen, which subsequently allows for finger manipulation and release of contractures.[197-199] While CCH has proven to be a useful minimally invasive technique for patients with later stage DC, recurrence rates of 35% at 3 years of follow-up have been reported.[199,200]

Radiation Therapy

RT is currently used in the treatment of Dupuytren exclusively for early-stage patients (who have a <10-degree deformity) and is considered standard of care for the prevention of Dupuytren progression. Low-dose RT hinders fibroblast proliferation and the cascade of inflammatory markers that induce collagen formation and fibroblast differentiation into fibronectin. Many studies have demonstrated patient-reported effectiveness of radiation, preventing further Dupuytren progression with minimal toxicity.[201-204] Adamietz et al reviewed 176 hands treated with low-dose RT.

Of those patients with less than 5-degree deformity, 82% had a patient-hand reported disease progression-free survival at the 10-year follow-up. Betz et al retrospectively reviewed 208 hands treated with low-dose radiation and found that patients with less than 5-degree deformity had an 87% patient-hand reported disease progression-free survival at the 13-year follow-up. Most recently in 2015, a prospective study by Schuster et al published the largest U.S. patient-reported outcomes after low-dose radiation for early-stage Dupuytren.[205] In this study, 45 patient-hands received low-dose radiation via electrons directed en face. After 31 months, 94% of surveyed patients reported the RT was successful with minimal toxicity.

Seegenschmiedt et al performed a randomized clinical trial comparing the safety and efficacy of two different dose regimens and an untreated control group.[201] Group A received 10 × 3 Gy (30 Gy) via a split course (5 × 3 Gy) repeated at intervals of 12 weeks; in group B, patients were treated with 7 × 3 Gy (21 Gy) delivered over 2 weeks. Regardless of the dose regimen, approximately 90% of treated patients had stable or improved disease. After a mean follow-up of 8 years, the extension deficit increased in 35% of the control group, in 7% of the 21 Gy group, and in only 4% of the 30 Gy group. Acute toxicity was more pronounced in group B, but long-term toxicity was comparable and included dryness, desquamation, skin atrophy, and altered sensation. The results of this study indicate that prophylactic RT is well tolerated by patients and effective at preventing disease progression. The 30-Gy regimen may be superior.[23] Irrespective of the dose regimen, the target volume should include palpable or detectable nodules and cords surrounded by a 3- to 5-mm margin; appropriate immobilization and shielding of unaffected joints are required (Figure 100.7).

A

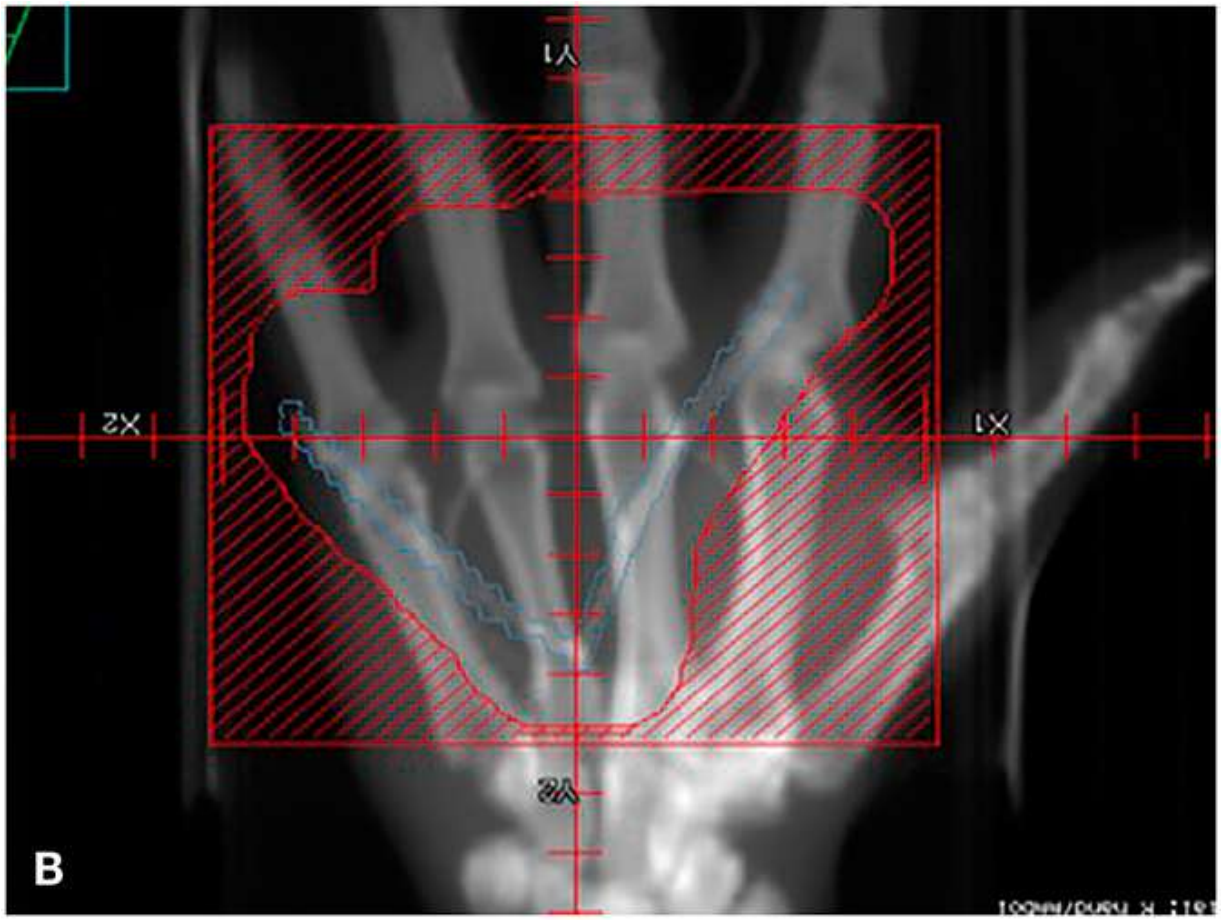

FIGURE 100.7 A. Immobilization for the treatment of Dupuytren contracture with electrons. B. Block formation with clinical margin. (Courtesy of Barbara Agrimson CMD, RT, Oregon Health and Science University.)

Keloids and Hypertrophic Scars

Background and Clinical Aspects

Keloids are excessive tissue proliferation around scars after skin injury from surgery, heat, chemical burns, inflammation (eg, acne), or even spontaneous proliferation. They differ from hypertrophic scars by their typical infiltrative growth pattern, causing local pain and inflammatory reactions, and sometimes long-term progression; hypertrophic scars show thickening without surrounding reaction and can flatten spontaneously. Keloids appear mainly in the upper body and in regions with high skin tension (eg, sternum, earlobes). The cause is still unknown, although there is a genetic and race-specific predisposition that can already be noted during adolescence. Keloids at the earlobe after piercing are typical. In

some patients, the resulting lesions are severely disfiguring and painful (Figure 100.8). Recurrence is common after treatment.

FIGURE 100.8 A. Keloid behind left earlobe. B. Status of keloid following resection plus 4 × 4 Gy radiotherapy.

Systemic Therapy

Silicone bandages, pressure dressings, and cryosurgery have all been used to treat keloids with varying efficacy.[206,207] Intralesional injections remain the first-line therapy for most keloids. Corticosteroids, 5-fluorouracil, and verapamil have all been directly injected into keloid lesions with symptom improvement. Up to 70% of patients respond to intralesional corticosteroid injection with flattening of keloids, although the recurrence rate is high in some studies (up to 50% at 5 years).[208]

Surgical excision may be indicated if injection therapy alone does not result in improvement. In patients treated with excision alone, recurrence rates range from 45% to 100%[209]; therefore, excision is typically combined

with perioperative or postoperative injections of either triamcinolone or interferon.[208]

Radiation Therapy

RT should be considered in cases of repeat recurrences postoperatively or where there is a high risk of recurrence (eg, marginal resection, large lesion, unfavorable location). Primary RT can be considered in instances where resection would result in functional impairment and in actively proliferating disorders within about 6 months after the triggering trauma. Because proliferating fibroblasts and mesenchymal and inflammatory cells are the target cells for RT, fully matured keloids have minimal response to RT alone. Prophylactic RT immediately following excision (within the first 24 hours) is most effective and reduces the risk of recurrence to 15% to 25% in most series.

Among different modalities for postexcisional RT, brachytherapy was found to have a lower recurrence rate when compared to electron and x-ray therapy by meta-analysis.[210] The target volume is limited to the scar plus a 1-cm margin; lead shielding can be constructed to protect normal tissue. An analysis of multicenter data on the use of postoperative RT for earlobe keloids showed that a higher dose per fraction and the use of deeper penetrating electrons were preferable to standard 2-Gy fractionation schemes.[211] A retrospective review of 124 patients with 250 keloids treated with postoperative RT to a biologically equivalent $dose_2$ of 35 to 36 Gy_2, 48 to 52.5 Gy_2, and 60 to 72 Gy_2 demonstrated a recurrence rate of 10% (P = .007), 8.9% (P = .16), and 1.6% (P = .02), respectively.[212] Common side effects include erythema and changes in skin pigmentation.

Heterotopic Ossification

Background and Clinical Aspects

HO is a common complication of total hip arthroplasty, hip trauma, or acetabular fracture. HO occurs when the soft tissues around the bone become ossified. Following trauma, primitive mesenchymal cells in the surrounding soft tissues are transformed into osteoblastic tissue that then forms mature bone. The hip is the most common joint affected; HO

typically occurs around the femoral neck and adjacent to the greater trochanter. The risk factors for the development of HO are unknown. The incidence is greater in men, and HO occurs in more than 80% of patients who have a history of ipsilateral or contralateral HO. It is also more common in patients with a known history of OA, ankylosing spondylitis, and Paget disease.[213] Hip stiffness is the primary symptom, and the diagnosis is made radiographically. Pain is typically not associated with HO.

Systemic Therapy

The treatment for HO is surgical excision followed by some form of HO prophylaxis. Prophylaxis is only applied to patients at high risk for developing HO. A meta-analysis showed that NSAIDs are effective in reducing the risk of postoperative HO.[214] Indomethacin is the most commonly used nonselective NSAID for HO prophylaxis. Indomethacin is a prostaglandin synthase inhibitor that also suppresses mesenchymal cells. The limited data available have not shown a clear benefit to the use of selective cyclooxygenase-2 (COX-2) inhibitors in HO prophylaxis.[215,216] Kan et al performed a meta-analysis comparing selective NSAIDs (COX-2 inhibitors) and nonselective NSAIDs versus placebo in HO prevention. Efficacy was the same among the two classes with similar rates of discontinuation from gastrointestinal side effects.[217] Bisphosphonates have been used for prophylaxis because they delay the mineralization of osteoid and appear to have some efficacy in preventing HO if used at the appropriate time. In one study, the cost of bisphosphonate use was prohibitive for routine use when compared to indomethacin.[218]

Radiation Therapy

External beam radiation is an effective method for the prevention of HO after total hip arthroplasty. Prophylactic RT for the prevention of HO has been used since the 1970s. A single fraction of 700 or 800 cGy to the at-risk region (Figure 100.9) is recommended and should be delivered in the perioperative period, either preoperatively (within 4 hours) or postoperatively (within 72 hours).[24] Typically, an anteroposterior/posteroanterior field size measures 14 × 14 cm^2, with the

cranial field border approximately 3 cm above the acetabulum and the caudal field border encompassing two-thirds of the proximal implant. The dose is prescribed to the body midplane.[24]

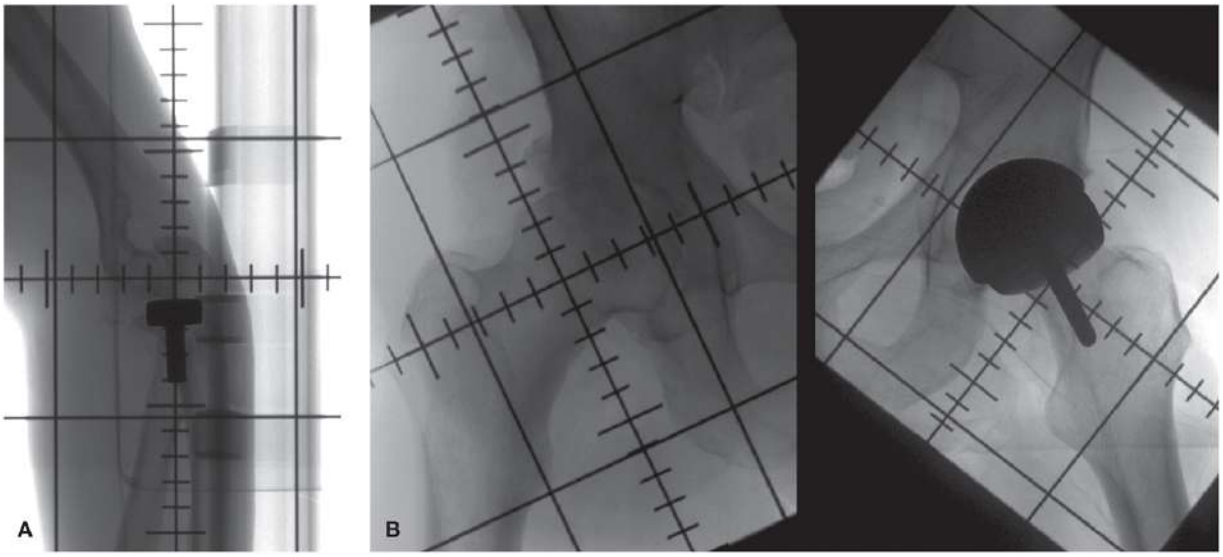

FIGURE 100.9 Typical treatment field for heterotopic ossification (HO). A. Field setup for elbow after radial head replacement. B. Field setup of acetabulum with active HO and after hip arthroplasty.

When comparing RT and NSAIDs, there is no clear benefit for the use of one modality over another. A prospective, randomized study demonstrated that RT and indomethacin are both effective in the prevention of postoperative HO.[219] Although one meta-analysis of seven randomized studies concluded that RT is more effective compared to NSAIDs for HO prophylaxis,[220] a separate analysis of nine studies involving 1,295 patients found no statistically significant difference between the two.[221] An economic analysis using the same nine studies and the meta-analysis suggest that RT is not cost-effective when compared to the use of NSAIDs.[222] This analysis has yet to be validated. Further data suggest the cost of NSAIDs approaches the cost of administering RT when considering costs of treatment failure and treatment-induced morbidity.[223]

Plantar Fasciitis

Plantar fasciitis is characterized by pain in the heel and the bottom of the foot. Typically, the pain is most severe with the first steps of the day or following rest. The pain is often exacerbated by bending the foot and toes up toward the shin.

This disease has acquired an impressive number of names in addition to plantar fasciitis. Alternative names include painful heel spur, Kalkaneussporn (calcaneal spur), policeman's heel, heel spur syndrome, plantar or dorsal heel spur, Haglund exostosis, achillodynia or calcaneodynia, jogger's heel, tennis heel, and subcalcaneus bursitis.[224]

The plantar fascia is a thick, broad, inelastic band of fibrous tissue on the plantar surface of the foot. It is attached to the calcaneus and then fans out to attach to the metatarsal bones in the area of the ball of the foot. The anatomy of the plantar fascia, along with a possible explanation for plantar fasciitis, has been artfully described by Micke et al[224]:

> Because the normal foot has an arch, this tight band of tissue (plantar fascia) is at the base of the arch. In this position, the plantar fascia acts like a bowstring to maintain the arch of the foot…. Pathophysiologically, excessive stretch of the plantar fascia can result in microtrauma…. This microtrauma, if repetitive, can result in chronic inflammation and degeneration of the plantar fascia. (Reprinted by permission from Springer: Micke O, Ernst-Stecken A, Mücke R, Seegenschmiedt MH. Calcaneodynia: plantar and dorsal heel spur/heel spur syndrome. In: Seegenschmiedt MH, Makoski HB, Trott KR, Brady LW, eds. *Radiotherapy for Non-Malignant Disorders*. Springer; 2008:296-297. Copyright © 2008 Springer-Verlag Berlin Heidelberg.)

Indeed, the use of the word *fasciitis* implies that the core issue in this disease is inflammation. That is far from clear. This has led some writers to propose yet another name for the disease, *plantar fasciosis*, an agnostic term that does not imply that the crux of the problem is inflammation.

The most commonly invoked alleged mechanism of action of RT in the treatment of plantar fasciitis is that it damps down the local inflammatory process. This mechanism is, of course, a hollow explanation if, indeed, inflammation does not play an important role in many cases. Furthermore, as with many nonmalignant diseases in which local RT is asserted to be useful in treating inflammation, proponents are left with having to explain why inflammatory cells outside the field of radiation do not pour into the treated area after each fraction of radiation. They usually respond by

making claims that the inflammatory cascade and/or antigen presentation are disrupted by ionizing radiation.

In his 1965 textbook *Radiotherapy of Benign Disease*, Dewing classified "calcaneal spurs" as a "sterile inflammatory condition."[225] He wrote,[225]

> Whether the lesion is primarily a plantar fasciitis or is combined with a periostitis can probably never be determined in a given case. The title "painful calcaneal spur" is certainly a misnomer, for the bony spur itself is not primarily the seat of the disorder (or the pain). Many such spurs are seen in asymptomatic persons, and surgical resection of a spur is often quite ineffective in relieving the symptom. The practical problem, however, is pain, and there is no adequate specific therapy.

Many patients get better with supportive care. Among the long list of therapies are various forms of physical therapy, oral and locally injected drugs, extracorporeal shock wave therapy, and a wide variety of types of surgery.

The end point of the clinical studies on RT relies on patient-reported symptoms. The possibility of a placebo effect is real. About 25 papers, dating from the 1950s forward, have been invoked to allege that RT at a total dose of 90 to 150 cGy in three to five treatments, or 5 Gy in 5 weeks, or 7 to 7.5 Gy in one to five treatments, or 3 to 6 Gy fractionated over 2 weeks is helpful with response rates of 65% to 100%. Patients are typically irradiated 2 to 3 times per week. The largest volume of data is from Germany.[224-227]

The subject cries out for rigorous clinical investigation driven by science rather than an urge to find another billable procedure for RT. Reporting that "I treated a patient and he got better" or, even worse, "I treated a celebrity patient and he got better" brings to mind the old clinical adage that "In medicine, the pleural of clinical anecdote is not data."

OTHER CONDITIONS IN WHICH RADIATION THERAPY HAS BEEN EMPLOYED

Solid Organ Transplantation

The first human-to-human heart transplant, performed by Dr Christiaan Barnard in South Africa in 1967, included local field irradiation of the transplanted donor heart as part of the immunosuppressive program.[228] Low-dose fractionated RT was used at many centers in the 1960s to 1980s

in an attempt to forestall rejection of cardiac and renal allografts. Total lymphoid irradiation was investigated for a potential role in creating a sustained immunosuppressive state for heart, liver, and kidney allografts and xenografts. There were some notable successes in experimental models of xenografts.[229-232]

The evaluation of more powerful and less toxic chemical immunosuppressives and the development of genetically engineered pigs have made the use of EBRT for human solid organ allografting and xenografting largely of historical interest, but it remains possible that as xenografting evolves, there may once again be an impetus to investigate RT's usefulness in certain situations.

Alzheimer Disease

Because of the aging population in the economically developed world, societies face the growing effect on morbidity, mortality, economic costs, and social stress of a rising incidence of Alzheimer disease. In view of the largely unsatisfactory attempts to reach a consensus on the pathophysiology of this disease and the lack of efficacy of therapy, it is not surprising that some investigators have turned to EBRT in experimental animal models and clinical studies. For example, in a clinical investigation of five patients with Alzheimer dementia irradiated with 2 Gy/fraction of whole-brain irradiation for five fractions, Rogers et al reported results with a positive safety profile and suggested cognition was stabilized or improved by the treatment.[233] The authors offer, as mechanisms of action for this possible benefit of RT, the reduction of amyloid and tau burden, as well as decreased neuroinflammation.[233-236]

One can expect, in the coming years, further laboratory and clinical studies in this disease regarding the use of RT.

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SECTION V

Palliative and Supportive Care

CHAPTER 101

Palliation of Brain Metastases

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BRAIN METASTASIS

Brain metastasis is a very common diagnosis, with an annual incidence of approximately 170,000 to 300,000 cases. Brain metastasis represents the most common intracranial lesion in adults, occurring at a median time of 8.5 to 12 months from primary diagnosis. The rising incidence of brain metastasis is likely in part from a combination of increasing survival from recent advances in therapy and a greater availability and use of magnetic resonance imaging (MRI). The most common primary site is the lung followed by the breast (Table 101.1).[1-4]

TABLE 101.1 EPIDEMIOLOGY OF BRAIN METASTASIS

Primary Site	
Lung	20%-50%
Breast	5%-20%
Small cell lung cancer	15%
Melanoma	7%-10%
Renal cell carcinoma	4%-6%
Colon	2%-5%
Relevant Facts	
Median survival	<1 y
Mean age	60 y
Annual U.S. incidence	>170,000
Clinical incidence	30%

From Lagerwaard FJ, Levendag PC, Nowak PJ, Eijkenboom WM, Hanssens PE, Schmitz PI. Identification of prognostic factors in patients with brain metastases: a review of 1292 patients. *Int J Radiat Oncol Biol Phys*. 1999;43(4):795-803; Suh JH, Chao ST, Peereboom DM, Barnett GH. *Metastatic Cancer to the Brain in Cancer—Principles & Practice of Oncology*. 10th ed. Lippincott Williams & Wilkins, 2015; Nussbaum ES, Djalilian HR, Cho KH, Hall WA. Brain metastases. Histology, multiplicity, surgery, and survival. *Cancer*. 1996;78(8):1781-1788; and Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P, Sawaya RE. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. *J Clin Oncol*. 2004;22(14):2865-2872.

Clinical Presentation, Diagnosis, and Prognosis

The majority of patients present with neurologic signs and symptoms (Table 101.2).[1,5] Although differential diagnoses such as an abscess or a stroke must be considered, new-onset neurologic symptoms in a patient with known cancer should always be presumed to be from brain metastasis until proven otherwise.

TABLE 101.2 CLINICAL PRESENTATION OF BRAIN METASTASIS

Symptom	Percentage of Patients
Headache	24-53
Mental Disturbance	14-32
Motor weakness	20-40
Cerebellar Dysfunction	7-26
Seizures	12-22
Speech problems	14

From Lagerwaard FJ, Levendag PC, Nowak PJ, Eijkenboom WM, Hanssens PE, Schmitz PI. Identification of prognostic factors in patients with brain metastases: a review of 1292 patients. *Int J Radiat Oncol Biol Phys*. 1999;43(4):795-803; and Posner JB. Brain metastases: 1995. A brief review. *J Neurooncol*. 1996;27(3):287-293.

Patients presenting with acute neurologic signs and symptoms will likely undergo an initial noncontrast computed tomography (CT) due to its ease of completion and ability to rule out life-threatening etiologies. However, contrast-enhanced MRI represents the most sensitive imaging modality to detect brain metastases, especially for identifying small lesions, which can have a significant effect on the patient's prognosis and treatment course.

Most brain metastases are located in the cerebral hemisphere (80%) at the junction of gray-white matter. While there are no pathognomic MRI characteristics of brain metastases, they generally tend to be T1 iso- or hypointense and T2 hyperintense and enhance with contrast administration.[6,7] Full systemic workup (eg, positron emission tomography and CT) should be promptly initiated if brain metastasis is the presenting event.

Performance status and extracranial disease status have consistently been shown to impact prognosis. Gaspar et al[8] reported on the Radiation Therapy Oncology Group (RTOG) experience of 1,200 patients. This analysis revealed three recursive partitioning analysis (RPA) classes, with the RPA class I (Karnofsky performance score [KPS] ≥70, controlled primary, age <65 years, no extracranial metastases), class II (not meeting requirements of class I or III), and class III (KPS <70) having median survivals of 7.1, 4.2, and 2.3 months, respectively. This class scheme has subsequently been validated using the patient cohort from RTOG 91-04.[9] Contemporary series have further refined the class division by incorporating disease-specific prognostic factors, thereby creating and validating a diagnosis-specific graded prognostic assessment (DS-GPA) index to estimate survival outcomes with brain metastases.[10]

Corticosteroids

Initial therapy for suspected or confirmed brain metastases should promptly start with corticosteroids (eg, dexamethasone or methylprednisolone), which effectively improve edema and neurologic deficits in approximately two-thirds of patients within 24 to 48 hours.[11] The only randomized trial evaluating steroid dosage was reported by Vecht et al.[12] This trial included two successive groups of patients. The first group (n = 47) evaluated 8 versus 16 mg/day initial dexamethasone doses, with tapering schedules over 4 weeks. The second group (n = 49) evaluated 4 versus 16 mg/day of initial dexamethasone, with continuation of these doses for 28 days before tapering. The patients were scheduled for whole brain radiotherapy (WBRT) and concurrent ranitidine. All arms had similar KPS improvements at 7 days (54%-70%) and 28 days (50%-81%). The study concludes that 4 mg/day of dexamethasone (with a taper over 4 weeks) is the preferable

regimen. One should be cautious, however, in interpreting the results of this study. Patients in the 4 mg/day arm had to have the medication be reinstituted at a higher rate than the patients in the 8 or 16 mg/day arms. Furthermore, the arm with the greatest improvement in the KPS was the 16 mg/day arm when this was tapered over 4 weeks, compared with any of the other arms. It can be argued that higher KPS improvement arose from the maximal anti-inflammatory effects of the initial higher doses, with the 4-week taper minimizing the late toxicity associated with corticosteroids.

A reasonable corticosteroid regimen in patients with brain metastases is a 10-mg intravenous (IV) or oral bolus, followed by a 4 to 6 mg every 6 to 8 hours of dexamethasone equivalent dose (with a concurrent proton-pump inhibitor; PPI), before this is tapered in a clinically cautious manner. The trial by Vecht et al, however, did demonstrate that 4 mg/day (eg, 2 mg twice daily) of dexamethasone is probably acceptable in select, symptomatic patients with minimal mass effect. In asymptomatic patients with little peritumoral edema or mass effect, initial corticosteroids may be reserved until the first sign of neurologic symptoms.

Anticonvulsants

Patients may present to the radiation oncologist already started on prophylactic anticonvulsants. This represents one of the most preventable causes of neurocognitive decline in patients with brain tumor, given the known negative impact on quality of life and neurocognition with anticonvulsants. In a study of 156 patients with low-grade glioma (85% experiencing a seizure), Klein et al[13,14] analyzed the impact of antiepileptic treatment on quality of life and neurocognitive function. This study convincingly demonstrates the significant correlation between the use of anticonvulsants (even with the lack of seizures) and a decrease in quality of life and neurocognitive function.

Based on four negative randomized trials, the American Academy of Neurology in 2000 recommended that prophylactic anticonvulsants not be initiated in patients with newly diagnosed brain tumor who have not experienced a seizure.[15] This recommendation continues to be relevant as there has now been a fifth randomized trial that has shown no benefit in newly diagnosed brain tumors.[16]

Whole Brain Radiotherapy

WBRT continues to be a standard of care in select patients with diffuse brain metastasis (≥5 brain metastases). WBRT is well known to provide improvement in neurologic symptoms with overall response rates of 70% to 93%.[17] Unfortunately, there exists no agreement on the optimal dose and fractionation schedule for WBRT, despite numerous studies designed to determine the optimal delivery. Table 101.3 summarizes selected randomized fractionation studies.[18-22] A total of 30 Gy in 10 fractions or 37.5 Gy in 15 fractions continue to remain the standard for a vast majority of patients receiving WBRT.[2] As reported by Nieder et al, the radiographic overall response rate with this fractionation scheme is 59% (24% complete response [CR] and 35% partial response [PR]).[23]

TABLE 101.3 SELECTED RANDOMIZED TRIALS EXAMINING VARIOUS FRACTIONATION SCHEDULES FOR BRAIN METASTASIS

Author/Study Group (Reference)	Dose/Fractions	*N*	Median Survival	*P*
Borgelt et al/RTOG[22]				
1st study (1971-1973)	30 Gy/10	233	21 wk	NS
	30 Gy/15	217	18 wk	
	40 Gy/15	233	18 wk	
	40 Gy/20	227	16 wk	
2nd study (1973-1976)	20 Gy/5	447	15 wk	NS
	30 Gy/10	228	15 wk	
	40 Gy/15	227	18 wk	
Haie-Meder et al/French (1986-1989)[20]	25 Gy/10	110	4.2 mo	NS
	36 Gy/6[a]	106	5.3 mo	
Priestman et al/Royal College of Radiology (1990-1993)[18]	30 Gy/10	263	84 d	.04
	12 Gy/2	270	77 d	
Murray et al/RTOG-91-04 (1991-1995)[19]	30 Gy/10	213	4.5 mo	NS
	54.4 Gy/34[b]	216	4.5 mo	

Author/Study Group (Reference)	Dose/Fractions	*N*	Median Survival	*P*
Graham et al/Australia (1996-2006)[21]	40 Gy/20[c]	57	6.1 mo	NS
	20 Gy/4	56	6.6 mo	

NS, not significant; RTOG, Radiation Therapy Oncology Group.

[a]18 Gy/3 split course with another 18 Gy/3 within 1 month.

[b]32 Gy in 1.6Gy twice-daily hyperfractionation to the whole brain followed by boost of 22.4 Gy in 1.6 twice-daily hyperfractionation to visible lesions with a 2-cm margin.

[c]40 Gy in 1.0 Gy twice-daily hyperfractionation for the entire course of therapy.

For patients with poor performance status and/or uncontrolled extracranial disease burden, a shorter fractionation scheme (eg, 20 Gy in 5 fractions) can be considered. For this patient cohort, a supportive care–alone strategy may also be considered. The phase III randomized, noninferiority QUARTZ (Quality of Life after Treatment of Brain Metastases) trial compared the quality-adjusted life years (QALY) between optimal supportive care (OSC) alone and OSC plus WBRT (20 Gy in 5 daily fractions) for patients with non–small cell lung cancer (NSCLC) with brain metastases unsuitable for resection or stereotactic radiotherapy (SRT). OSC consisted of dexamethasone titrated based on patient's symptoms as well as patient access to palliative care clinicians and nurses. The results revealed a difference in mean QALY of 4.7 days (46.4 QALY days for OSC + WBRT vs 41.7 QALY days for OSC), which was within the prespecified noninferiority margin of 7 days. Overall survival (OS) was not significantly different between randomization arms (OSC + WBRT: 9.2 weeks vs OSC alone: 8.5 weeks). Subgroup analysis suggested a survival benefit in favor of OSC plus WBRT for patients younger than 60 years, KPS 70 or higher, and controlled extracranial primary.[24] However, serious concerns about patient selection, methodology, and trial design have been pointed out.[25,26] Therefore, while WBRT may be omitted in select patients with very poor prognosis, it still remains an important therapeutic strategy.

Historically, WBRT has been frequently cited as the major cause of neurocognitive decline in patients with cancer. One of the most misinterpreted studies on this subject is the Memorial Sloan-Kettering Cancer Center experience reported by DeAngelis et al[27,28] who reported an

11% risk of radiation-induced dementia in patients undergoing WBRT for brain metastasis. The 11% figure is very misleading. Of the 47 patients who survived 1 year after WBRT, 5 (11%) patients developed severe dementia. When these five patients were examined, all were treated in a way that would significantly increase the risk of late radiation toxicity (ie, large daily fractions and concurrent radiosensitizer). Three patients received 5- and 6-Gy daily fractions, while the fourth patient received 6-Gy fractions with concurrent Adriamycin. Only one patient received what is considered a standard radiation fractionation scheme (ie, 30 Gy in 10 fractions), but this patient received a concurrent radiosensitizer (lonidamine). *No* patient who received the standard 30 Gy in 10 fractions WBRT alone experienced dementia.

In addition, this trial did not address the potential neurocognitive changes in patients who received WBRT resulting from any underlying disease progression.[29,30] Li et al have attempted to further elucidate the true incidence of WBRT-related neurocognitive changes while controlling for brain metastasis response. All patients received WBRT in 30 Gy in 10 fractions and were subjected to a battery of neurocognitive tests monthly for 6 months and then every 3 months thereafter until death. The neurocognitive tests covered domains of memory, verbal fluency, and executive function. In addition, patients underwent serial MRI with the summed volume of up to 6 brain metastases used for assessment of good or poor response. Good or poor response was defined as reduction of the summed volume at 2 months being more than 45% or less than 45%, respectively. The results revealed that volume regression was associated with the preservation of neurocognitive function, primarily in the domains of executive function and fine motor coordination. Tumor volume changes, however, had a weaker association with preservation of memory function (recall and delayed recall), which were domains most susceptible to changes from WBRT use.[31]

The RTOG subsequently completed RTOG 0933 and RTOG 0614, evaluating the role of hippocampal avoidance WBRT (HA-WBRT) and use of WBRT plus memantine, respectively, in an effort to preserve memory-related dysfunction as was identified by Li et al.[31] RTOG 0933 was a phase II trial comparing the 4-month decline in Hopkins verbal learning test (HVLT)-DR (delayed recall) scores with HA-WBRT (30 Gy in 10 fractions)

relative to a historical control group receiving standard WBRT (30 Gy in 10 fractions). HA-WBRT resulted in a mean decline of 7% in HVLT-DR scores from baseline to 4 months, which was significantly lower than the mean decline of 30% for historical controls.[32] RTOG 0614 was a phase III placebo-controlled trial randomizing patients to WBRT (37.5 Gy in 15 fractions) with or without 24 weeks of memantine administration. The primary end point was the effect of memantine use on DR at 24 weeks, which trended in favor of memantine use, though was not statistically significant (P = .059). The use of memantine, nonetheless, resulted in superior results in various other domains, including delayed recognition, executive function, and processing speed.[33] These results prompted the trial NRG Oncology CC001, which evaluated the role of WBRT with or without HA in patients all of whom receive memantine.

Hippocampal Avoidance Whole Brain Radiotherapy

Based on preclinical and clinical studies including RTOG 0933, NRG Oncology CC001 was developed to investigate the role of HA-WBRT in a phase III trial. This trial assessed the impact of WBRT with HA and memantine on reducing the risk of cognitive failure, defined as decline using the reliable change index on at least one of the cognitive tests (HVLT-R [total recall, DR, delayed recognition], Controlled Oral Word Association [COWA], Trail-Making Test [TMT] Parts A and B), after brain irradiation. HA-WBRT plus memantine significantly lowered the risk of cognitive failure (hazard ratio [HR] 0.74, P = .02) compared to WBRT with memantine, and this effect was sustained on longer term follow-up (HR 0.74, P = .016).[34,35] Importantly, there were no significant differences in OS, intracranial progression-free survival (PFS), toxicity, or perihippocampal failures. There was less deterioration in executive function at 4 months and learning and memory at 6 months. Patient-reported outcomes including symptom burden and symptom interference also favored the WBRT with HA arm. Confirmatory results of the neuroprotective benefits of HA were demonstrated in two additional smaller phase II trials: Yang et al compared HA-WBRT and conformal WBRT and found that memory decline at 6 months was improved with hippocampal techniques.[36] Westover et al evaluated hippocampal-sparing whole brain irradiation with simultaneous

integrated boost and found a 10.6% mean decline in HVLT-R DR at 3 months, which was significantly improved compared to historical outcomes.[37] Given these neuroprotective data, WBRT with HA is the new standard of care for patients with diffuse brain metastases and no lesions within a 5-mm margin around the bilateral hippocampi.

Targeted Agents as an Alternative to Whole Brain Radiotherapy in Non–Small Cell Lung Cancer

Historically, the use of systemic chemotherapy for control of NSCLC brain metastasis has been limited by the poor penetration of these agents through the blood-brain barrier (BBB). However, with a greater understanding of the BBB and the many oncogenic drivers present in NSCLC, contemporary targeted therapies have begun to play a larger role in the management of brain metastases. Epidermal growth factor receptor (EGFR) mutations as well as anaplastic lymphoma kinase (ALK) rearrangements, which occur in 15% to 20% of advanced NSCLC cases,[38] represent two commonly targeted mutations. Zimmerman et al, identified a brain metastasis response rate of 74% to 89% with the use of EGFR tyrosine kinase inhibitors (TKIs).[39] Similarly, Rusthoven and Doebele noted response rates of 36% to 67% with next-generation TKIs, such as alectinib, in ALK-positive NSCLC brain metastases.[40] Magnuson et al have reported the largest pooled multi-institutional analysis to date evaluating the optimal sequencing of EGFR-TKIs and radiation therapy in patients with EGFR-mutant NSCLC brain metastases. TKI-naïve patients who had developed brain metastases underwent one of three treatment regimens: stereotactic radiosurgery (SRS) followed by EGFR-TKI, WBRT followed by EGFR-TKI or EGFR-TKI followed by SRS, or WBRT at the time of intracranial progression. At baseline, patients receiving up-front EGFR-TKI had smaller (<1 cm) and less symptomatic intracranial disease. Median OS for the up-front SRS, WBRT, and EGFR-TKI arms was 46, 30, and 25 months, respectively ($P <$ .001). Both up-front SRS and WBRT use were independently associated with improved OS relative to up-front EGFR-TKI. The use of up-front SRS or WBRT was also associated with a trend toward lower risk of intracranial progression, highlighting the potential for inferior outcomes with deferral of early radiotherapy.[41] On the contrary, Gerber et al found equivalent survival

outcomes with the use of up-front EGFR-TKI or WBRT in patients with EGFR-mutant brain metastases.[42]

More recently, osimertinib, a third-generation EGFR-TKI, was shown to have high intracranial penetration and efficacy as demonstrated in a subset analysis of the FLAURA trial.[43,44] Patients in this trial were randomly assigned to osimertinib or standard EGFR-TKIs (gefitinib or erlotinib). A preplanned central nervous system (CNS) PFS primary objective was performed, which demonstrated a significant improvement in CNS PFS (HR 0.48, $P = .014$). CNS objective response rates were 91% and 68% in patients with CNS lesions in the osimertinib and standard EGFR-TKI groups, respectively (odds ratio [OR] 4.6, $P = .066$). In patients with measurable and/or nonmeasurable CNS lesions, response rates for the same groups were 66% and 43%, respectively (OR 2.5, $P = .011$). A phase III randomized clinical trial is currently open to accrual (NCT05236946), in which patients with oncogene-mutated NSCLC and asymptomatic brain metastases are randomized to up-front cranial radiation and TKI versus TKI and observation/delayed cranial radiotherapy to assess the superiority of early versus delayed brain radiation in these patients.

Similarly, the ADAURA trial randomized patients with resected EGFR-mutated NSCLC to receive osimertinib or placebo and demonstrated significant improvements in disease-free survival (HR 0.20, $P < .001$) and CNS disease–free survival consisting of CNS disease recurrence or death (HR 0.18, $P < .0001$) with osimertinib on initial primary analysis at 24 months.[45] CNS recurrences were rare in the osimertinib-treated patients (1%) versus 10% in the placebo arm. In the updated analysis by Herbst et al, the estimated probability of observing CNS recurrence at 36 months was 2% in the osimertinib arm and 13% in the placebo arm; CNS DFS continued to be significantly improved with osimertinib at 48 months (HR 0.24).[46]

There have also been multiple studies examining ALK-positive targeted therapies in NSCLC. The ALEX trial randomized patients with previously untreated advanced ALK-positive NSCLC to receive alectinib or crizotinib. The primary end point was investigator-assessed PFS; time to CNS progression was a secondary end point. Time to CNS progression was significantly longer with alectinib (HR 0.16, $P < .001$), and the cumulative incidence rate of CNS progression was 9.4% at 12 months (compared to

41.4% for crizotinib).[47] In the CROWN phase III study, patients were randomly assigned to lorlatinib or crizotinib in patients with ALK-positive NSCLC. Lorlatinib substantially reduced the 12-month cumulative incidence of CNS progression in patients with (7% vs 72%) and without (1% vs 18%) brain metastases at the time of enrollment, as compared to crizotinib.[48]

Immunotherapy in the Treatment of Brain Metastases

The use of immunotherapy for brain metastases has also increased over the past several years. Goldberg et al ran a phase II trial in which patients with NSCLC and at least one brain metastasis that was not previously treated (≥5 mm, <2 cm) or was progressing after prior RT received pembrolizumab 10 mg/kg every 2 weeks.[49] Patients were divided into two cohorts (cohort 1 for those with programmed cell death ligand 1 [PD-L1]) ≥ 1%; cohort 2 for those with PD-L1 <1% or unevaluable. The primary end point of the trial was the proportion of patients achieving response (either PR or CR) in the CNS. In all, 29.7% of patients in cohort 1 had brain metastasis response, which met the trial's prespecified success criteria; 10.8% of patients had stable disease, while 43% had CNS progression. The median duration of response in the patients who achieved response was 5.7 months. The authors commented that the extracranial response rates to programmed cell death protein 1 axis inhibitors in other studies were comparable to the CNS response rate in this study. Similarly, a pooled analysis of KEYNOTE-001, KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042 demonstrated in patients with PD-L1 tumor proportion score (TPS) 1% or higher and TPS 50% or higher, the overall response rate was 33.9% with pembrolizumab compared to 14.6% in the chemotherapy arm.[50]

Surgical Resection

Surgical resection can aid in obtaining a pathologic diagnosis of intracranial lesions, provide immediate relief of tumor mass effect (Figure 101.1), and may cure a small percentage of patients with single or solitary lesions. On the other hand, radiation typically takes several days to work. Radiobiologically, 30 Gy in 10 fractions to a solid tumor (excluding radiosensitive tumors) is not adequate to achieve long-term tumor control.

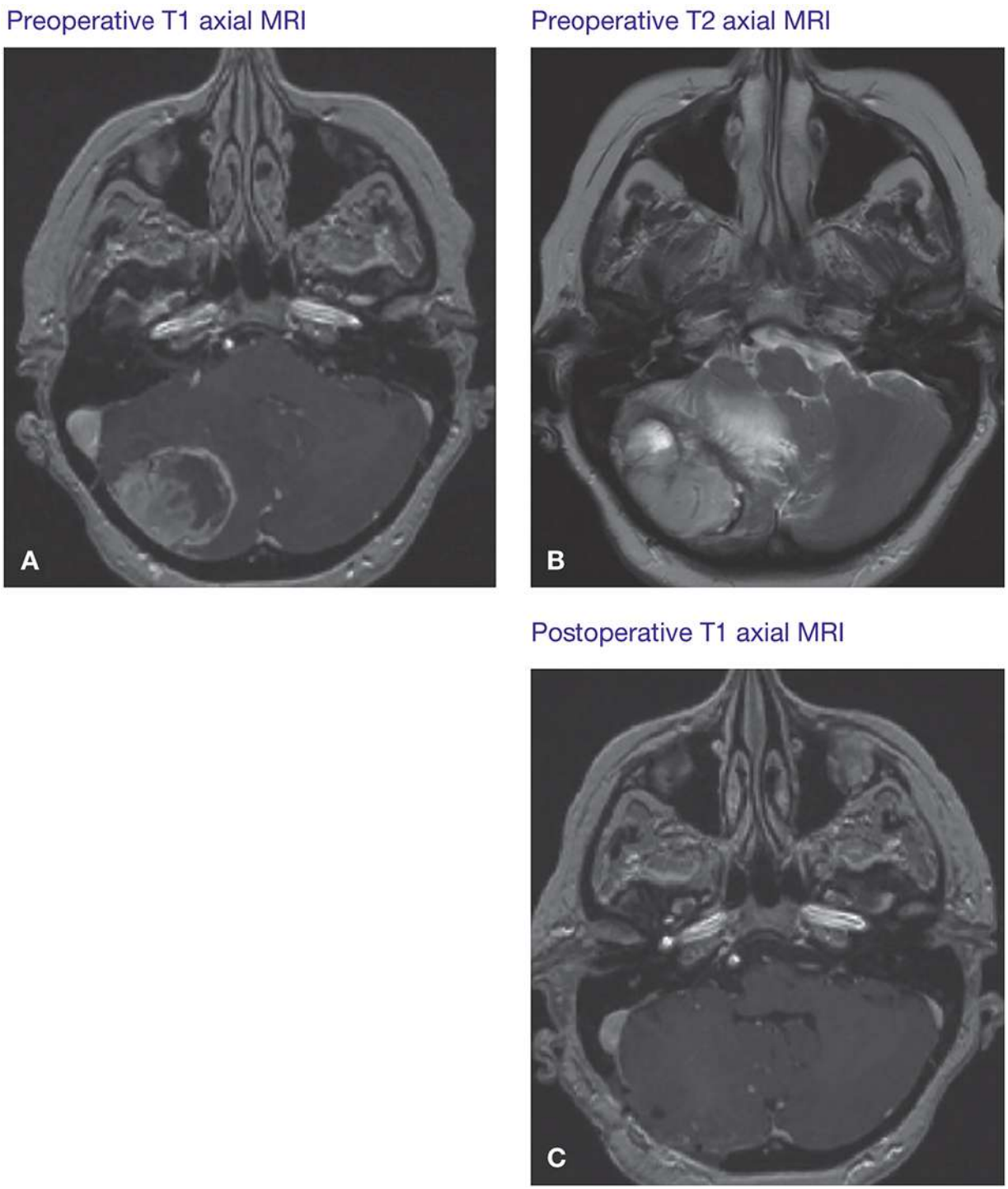

FIGURE 101.1 A. Six months after definitive therapy for stage IIIB non–small cell lung carcinoma (NSCLC), a patient presented with progressively worsening headache, nausea, vomiting, and coordination difficulties. Preoperative T1 gadolinium-enhanced axial magnetic resonance imaging (MRI) demonstrates a large, necrotic right cerebellar mass. B. Preoperative T2 axial MRI reveals large area of vasogenic edema, with resultant mass effect causing fourth ventricular compression and hydrocephalus (not shown). C. Patient was taken immediately for a craniotomy, and a gross total resection was achieved.

Pathology revealed metastatic NSCLC. Postoperative T1 gadolinium-enhanced axial MRI reveals no residual tumor, decompression of the mass effect, and reexpansion of the fourth ventricle.

Given that up to 50% of brain metastases can present as a single lesion, there has been historical interest in evaluating the role of surgery in the management of brain metastases.[51] There have now been three phase III trials testing the hypothesis that surgical resection of single-brain metastasis is potentially beneficial. All three trials included patients with either a single lesion, defined as the presence of only one intracranial lesion regardless of the extracranial disease status, or a solitary lesion, defined as the intracranial lesion being the only site of metastatic disease. Table 101.4 summarizes the three trials.[52-54] The studies by Patchell et al[53] (KPS ≥70) and Noordijk et al[54] (World Health Organization grade #2) included better performance status patients compared with the Mintz et al[52] study (KPS ≥50), which may have contributed to the differences in the outcomes between these studies. In addition, 45% of patients in the study by Mintz et al had extracranial metastases, as compared to 37.5% and 31.7% in the studies by Patchell et al and Noordijk et al, respectively. Similarly, as highlighted by Noordijk et al, the survival benefit to the addition of surgery to WBRT was most pronounced in patients with inactive or stable extracranial disease, with no survival benefit present for patients with active or progressive extracranial disease. The results of these studies suggest that surgical resection should be reserved for lesions causing life-threatening complications, requiring pathologic confirmation, or in patients with good performance status (ie, KPS ≥70) and controlled extracranial disease burden.

TABLE 101.4 RANDOMIZED TRIALS OF SURGICAL RESECTION OF SINGLE-BRAIN METASTASIS

Study			*P*
Patchell et al[53]; Univ. Kentucky (*n* = 48)	**Surgery + WBRT** 36 Gy/12 fx	**WBRT alone** 36 Gy/12 fx	
Primary end point: OS	40 wk	15 wk	<.01
Secondary end points			

Study			*P*
Local control			
Local failure	20%	52%	<.02
Time to local failure	>59 wk	21 wk	<.0001
Time to neurologic death	62 wk	26 wk	<.0009
KPS ≥70 maintenance	38 wk	8 wk	<.005
Noordijk et al[54]; Dutch (*n* = 63)	**Surgery + WBRT** 40 Gy/20 fx[a]	**WBRT alone** 40 Gy/20 fx[a]	
Primary end points			
OS	10 mo	6 mo	.04
FIS[b]	7.5 mo	3.5 mo	.06
Mintz et al[52]; Canadian (*n* = 84)	**Surgery + WBRT** 30 Gy/10 fx	**WBRT alone** 30 Gy/10 fx	
Primary end point: OS	5.6 mo	6.3 mo	NS
Secondary end points			
FIS[c] (proportion of days, mean)	32%	32%	NS
Quality of life (Spitzer score)			
1-3 mo (mean)	6.38	5.36	NS
4-6 mo (mean)	6.32	6.15	NS

FIS, functionally independent survival; fx, fractions, KPS, Karnofsky performance score; OS, overall survival; WBRT, whole brain radiotherapy; WHO, World Health Organization.

[a]40 Gy total in 2 Gy twice-daily hyperfractionation for the entire course of therapy.

[b]As defined by WHO performance status #1 and neurologic condition #1.

[c]As defined by KPS ≥70. Functionally independent survival.

Radiosurgery Boost Trials

Radiosurgery provides a suitable alternative to conventional surgery. The three aforementioned randomized trials of surgical resection were all performed before the widespread availability of SRS. Although no randomized trials have been performed comparing surgery with SRS, SRS boost appears to provide at least comparable, if not improved, local control rates (80%-90% when combined with WBRT). Therefore, in the setting of

limited intracranial disease burden, unless emergent surgery is warranted, SRS alone or as a boost can serve as a noninvasive alternative. In addition, while two of the three aforementioned surgery trials have shown a survival benefit in single-brain metastasis, there have been no randomized trials addressing the role of surgery for multiple lesions. In contrast, three randomized trials have assessed the efficacy of SRS boost in the treatment of multiple metastases (Table 101.5).

TABLE 101.5 RANDOMIZED TRIALS OF STEREOTACTIC RADIOSURGERY BOOST IN BRAIN METASTASES

Study			*P*
Andrews et al[55]; RTOG 95-08 (*n* = 333; 1-3 lesions)	**WBRT 37.5 Gy/10 fx**	**WBRT alone 37.5 Gy/10 fx**	
Primary end point: OS			
1-3 lesions	5.7 mo	6.5 mo	NS
Single-brain metastasis (planned subgroup analysis)	6.5 mo	4.9 mo	.04
Secondary end points			
Local control (1 y)	82%	71%	.01
Neurologic death rate	28%	31%	NS
Performance outcome			
KPS stable/improve			
At 3 mo	50%	33%	.02
At 6 mo	43%	27%	.03
Mental status			NS
Unplanned subgroup analysis (OS)			
Largest tumor >2 cm	6.5 mo	5.3 mo	.04
RPA class I	11.6 mo	9.6 mo	.05
Squamous/NSCLC	5.9 mo	3.9 mo	.05
Response rate (3 mo)			
Tumor	73%	62%	.04
Edema	70%	47%	.002

Study				*P*
Kondziolka et al[56]; University of Pittsburgh (*n* = 27; 2-4 lesions)	**WBRT 30 Gy/12 fx**	**WBRT alone 30 Gy/12 fx**		
Primary end point: local control (1 y)	92%	0%		.0016
Time to local failure	36 mo	6 mo		.005
Time to any brain failure	34 mo	5 mo		.002
Secondary end points				
OS	11 mo	7.5 mo		NS
Treatment morbidity	0	0		
Progression-free survival	NR			
Need for retreatment	NR			
Chougule et al[57]; Brown University (*n* = 109; 1-3 lesions)	**WBRT + SRS 30 Gy/10 fx + 20 Gy**	**WBRT alone 30 Gy/10 fx**	**SRS alone 30 Gy**	
End points (abstract only)				
OS	5 mo	9 mo	7 mo	NR
Local control	91%	62%	87%	NR
New brain lesions	19%	23%	43%	NR

fx, fractions; KPS, Karnofsky performance score; NR, not reported; NS, not significant; NSCLC, non–small cell lung cancer; OS, overall survival; RPA, recursive partitioning analysis; SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy.

The first randomized trial was reported by Kondziolka et al[56] from the University of Pittsburgh. This small study was stopped early at a planned interim analysis of 60% patient accrual because the authors reported having found a large difference in the primary end point of 1-year local control in favor of SRS (92% vs 0%; $P = .0016$). Unfortunately, the study used nonstandard end points to measure recurrence, defining it as *any* increase in the lesion size on MRI. Furthermore, no attempt was made to control for steroid use, radiation changes, or other factors that might produce small fluctuations in the lesion size on MRI. Median OS was not significantly different between arms (WBRT alone: 7.5 months vs WBRT + SRS: 11 months, $P = .22$). Therefore, this study is difficult to interpret.

Chougule et al[57] from Brown University reported the second trial, although this has to date only been published in abstract form. This trial had three treatment arms and randomized patients to treatment with SRS alone, SRS plus WBRT, or WBRT alone. This trial suffers from several methodological problems. Although the authors conclude that the survival times among the treatment arms were similar and that patients treated with SRS experienced superior local control, no probability values are given. Furthermore, 51 patients had surgical resection for at least one symptomatic brain metastasis prior to entry into the study, and no attempt was made to stratify for previous surgery. The inclusion of the surgically resected patients effectively made this a six-arm trial and, therefore, the size of this trial was not large enough to support a meaningful analysis. Finally, the radiation doses used in the SRS arms cannot be considered conventional because the peripheral dose was not individualized based on the tumor size or volume.

In the third study, RTOG-95-08, inclusion was limited to 1 to 3 metastases, with a maximum diameter of 4 cm for the largest lesion with additional lesions not exceeding 3 cm. WBRT dose was 37.5 Gy in 15 fractions, whereas SRS boost dose was lesion size based in accordance with the results of RTOG 90-05. The primary end point was OS, which was not statistically different between the WBRT plus SRS and WBRT-alone arms (6.5 months and 5.7 months, respectively; $P = .1356$), although the SRS boost improved the survival in the subgroup (planned analysis) of patients with single metastasis.[55] For secondary end points, the local control and performance measures were higher in the SRS boost arm, but this did not translate into a lower death rate from neurologic progression. Multiple unplanned subgroup analyses were completed, and an OS benefit with SRS boost was found in several subgroups that included patients with RPA class 1, tumor size 2 cm or larger, and NSCLC or metastatic squamous histology from any site. Unfortunately, these subset analyses were not planned or prespecified, and the probability values needed for significance should have been adjusted for inflation of the type I error. When this was done, none of these subgroup analyses showed a positive benefit for SRS. On the other hand, this trial did demonstrate that SRS boost is associated with lower edema and corticosteroid use, countering a commonly held notion that SRS

actually increases the edema risk. However, regarding the major end points for multiple metastases, this study should be considered a negative trial.

More recently, Sperduto et al completed a secondary analysis of RTOG 95-08 to determine the efficacy of SRS boost with patients restratified by DS-GPA scores. Their secondary analysis predominantly included lung cancer primaries (84%). The results revealed an OS benefit to SRS boost in patients with DS-GPA scores of 3.5 to 4, irrespective of the number of metastases (WBRT alone: 10.3 months vs WBRT + SRS: 21 months, P = .05). No survival benefit for SRS boost was observed with DS-GPA scores less than 3.5. These results should be interpreted with caution, however, given the small sample size and potential nonrandom selection of patients in the secondary analysis.[58]

In conclusion, although it would seem SRS boost WBRT is indicated (from RTOG-95-08 and from the extrapolation of surgical resection data) in patients with a single metastasis, it is difficult to justify its use (ie, WBRT + SRS boost) when multiple trials have failed to demonstrate the benefit of WBRT after local therapies like surgery or SRS.

Postoperative or Postradiosurgery Radiotherapy

A historic controversy in the treatment of brain metastasis has been the role of WBRT postoperatively or post-SRS. In a multi-institutional retrospective SRS study, Sneed et al argued for the omission of up-front WBRT because this does not compromise OS.[59,60] Regine et al reported on 36 patients with planned observation after initial SRS alone. Even with close follow-up with examinations and high-resolution MRIs, 47% of patients experienced brain failure, with 71% and 59% experiencing symptomatic relapse and neurologic deficits, respectively.[61] It was also felt that the omission of up-front WBRT may have even more serious consequences for patients with more radioresistant tumors, such as renal cell carcinoma (RCC). The Eastern Cooperative Oncology Group protocol E6397 was a phase II trial that evaluated SRS alone in radioresistant tumors (RCC, melanoma, sarcoma). Manon et al[62] reported a 6-month total brain failure rate of 48.3% with 6-month local failure within the SRS volume of 32.2%. The authors concluded that routine avoidance of WBRT should be approached judiciously.[62] Unfortunately, none of this previous generation of studies

analyzed the consequences of recurrences and WBRT with modern neurocognitive testing.

There have been now multiple phase III trials that have assessed the use of postoperative or postradiosurgery radiation (Table 101.6). Patchell et al[63] evaluated up-front WBRT (50.4 Gy in 28 fractions) versus observation in resected metastatic lesions with a primary end point comparing local and distant intracranial control rates. The results demonstrated that surgical resection without WBRT led to a failure rate at the original site and distant brain/leptomeningeal recurrence of 46% and 37%, respectively. In comparison, surgical resection with up-front WBRT led to a significantly lower failure rate at the original site and distant brain/leptomeningeal recurrence of 10% and 14%, respectively. More importantly, 44% of the patients in the surgery-alone arm died as a result of neurologic sequelae from brain failure as compared to 14% of patients receiving up-front WBRT ($P = .003$). OS was not significantly different between arms (surgery alone: 43 weeks vs surgery + WBRT: 48 weeks, $P = .39$). The results of this study have been frequently misinterpreted in the literature. Some have justified the withholding of up-front WBRT based on the fact that this study demonstrated equivalent survivals. In fact, this study was designed with brain tumor recurrence rate as the primary end point and not OS. To show an OS difference, this trial needed to enroll over 2,000 patients. This study met its primary end point and confirmed the importance of postoperative WBRT in preventing brain failure and death from neurologic causes.

TABLE 101.6 RANDOMIZED TRIALS OF POSTOPERATIVE/POSTRADIOSURGERY WHOLE BRAIN RADIOTHERAPY

Study			*P*
Patchell et al[63]; University of Kentucky (*n* = 95; single lesion)	**Surgery 1 WBRT** 50.4 Gy/28 fx	**Surgery only**	
Primary end point: Brain tumor recurrence			
Total brain recurrence	18%	70%	<.001
Original site only	4%	33%	
Distant site only	8%	24%	
Original and distant	6%	13%	

Study			*P*
Distant site total	14%	37%	<.01
Original site total	10%	46%	<.001
Secondary end points			
Cause of death			
Neurologic	14%	44%	.003
Systemic	84%	46%	<.001
Functional independence[a]	37 wk	35 wk	NS
OS	48 wk	43 wk	NS
Aoyama et al[64]; Japanese JROSG-99-1 (*n* = 132; 1-4 lesions)	**SRS 1 WBRT** 30 Gy/10 fx	**SRS alone**	
Primary end point: OS			
1 y[b]	39%	28%	NS
Median	7.5 mo	8.0 mo	NS
Secondary end points			
Brain recurrence (total)[b]	47%	76%	<.001
Functional preservation[a,b]	34%	27%	NS
Neurologic death	23%	19%	NS
Need for salvage therapy	10 patients	29 patients	<.001
Radiation morbidity			
Acute	4 patients	8 patients	NS
Late	7 patients	3 patients	NS
Muacevic et al[65]; German (*n* = 70; 1 lesion)[c]	**Microsurgery 1 WBRT** 40 Gy/20 fx	**SRS alone**	
Primary end point: OS	9.5 mo	10.3 mo	NS
Secondary end point: Brain recurrence			
Local (1 y)	18%	3.2%	.06
Distant (1 y)	3%	25.8%	.04

Study			*P*
Kocher et al[66]; EORTC-22952-26001 (*n* = 359; 1-3 lesions)	**SRS or surgery 1 WBRT** 30 Gy/10 fx	**SRS or surgery alone**	
Primary end point: Functional independence	9.5 mo	10 mo	NS
Secondary end points			
Brain tumor recurrence			
Original site: SRS	19%	31%	.040
Distant site: SRS	33%	48%	.023
Original site: surgery	27%	59%	<.001
Distant site: surgery	23%	42%	.008
Progression-free survival	4.6 mo	3.4 mo	NS
OS	10.7 mo	10.9 mo	NS
Brown et al[67]; NCCTG N0574 Alliance Study (*n* = 213; 1-3 lesions)	**SRS 1 WBRT** 30 Gy/12 fx	**SRS alone**	
Primary end point: Cognitive deterioration[d]	91.7%	63.5%	<.001
Secondary end points			
Local control (1 y)	90.1%	72.8%	.003
Distant brain control (1 y)	92.3%	69.9%	<.001
OS	7.4 mo	10.4 mo	.92
Chang et al[68]; MDACC (*n* = 58; 1-3 lesions)	**SRS 1 WBRT** 30 Gy/12 fx	**SRS alone**	
Primary end point: Neurocognitive function[e]	52%	24%	Significant
Secondary end points			
Local control (1 y)	100%	67%	.012
Distant brain control (1 y)	73%	45%	.02
OS	5.7 mo	15.2 mo	.003

fx, fractions; JROSG, Japanese Radiation Oncology Study Group; KPS, Karnofsky performance score; NS, not significant; OS, overall survival; SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy.

[a]As defined by KPS ≥70 maintenance.

[b]1-y actuarial rates.

[c]SRS alone versus microsurgery plus WBRT.

[d]Decline >1 SD from baseline on at least 1 of 7 cognitive tests at 3 months.

[e]Drop in Hopkins Verbal Learning Test–Revised score at 4 months.

Given the long-term cognitive impact attributed to WBRT, however, contemporary series have evaluated the efficacy of postoperative SRS as an alternative to up-front WBRT. Brown et al reported the results of the phase III NCCTG N107C/CEC.3 trial, which randomized patients to postoperative SRS versus postoperative WBRT.[69] Patients with one resected metastatic brain lesion and a resection cavity 5.0 cm or less in maximal extent as well as up to 3 unresected metastases were included in this trial. They were then randomly assigned to postoperative single-fraction SRS (12-20 Gy, dose determined by surgical cavity volume) or WBRT (30 Gy in 10 fractions or 37.5 Gy in 15 fractions). The remaining unresected lesions also received SRS. The coprimary end points of this trial were cognitive deterioration–free survival and OS. Cognitive deterioration–free survival was defined as a drop of greater than 1 standard deviation (SD) from baseline in at least one of the six cognitive tests. Cognitive deterioration–free survival was significantly longer after SRS to the surgical cavity compared to WBRT (median 3.7 vs 3.0 months, HR 0.47, $P < .0001$). At 6 months, cognitive deterioration in patients who had cognitive evaluation was statistically more frequent ($P = .00031$) in the WBRT arm (85%) versus the SRS arm (52%); this held true for all cognitive domains. OS was similar in both arms (median OS 12.2 months in WBRT arm vs 11.6 months in SRS arm, HR 1.07, $P = .70$). However, SRS was associated with a quicker time to intracranial progression as compared to WBRT (median 6.4 vs 27.5 months, HR 2.45, $P < .0001$). In addition, 6-month surgical bed control was significantly lower with SRS (80.4% vs 87.1% with WBRT, $P = .00068$); this difference was even more pronounced at 12 months (60.5% vs 80.6%).

In addition, Mahajan et al prospectively evaluated local tumor control rates of resected metastases receiving postoperative cavity SRS versus

observation in 1 to 3 brain metastases.[70] All lesions not resected received definitive SRS. Secondary objectives included distant brain control and OS. The results revealed 1-year local control rates for observation and postoperative SRS of 43% and 72%, respectively (P = .015). Smaller tumors demonstrated greater 12-month local control (91% for tumors #2.5 cm, 40% for tumors >2.5 and #3.5 cm, and 46% for tumors >3.5 cm, P = .0002). One-year freedom from distant brain failure with observation and postoperative SRS was 33% and 42%, respectively (P = .35). Similarly, OS did not differ with the use of postoperative cavity SRS (observation: 18 months vs postoperative SRS 17 months, P = .24).

Therefore, these data strongly suggest that postoperative SRS should be done over WBRT.

There have now been multiple phase III trials that have evaluated the role of SRS alone versus the addition of WBRT. In the Japanese Radiation Oncology Study Group JROSG-99-1 phase III trial of one to four lesions, the SRS-only arm experienced increased 1-year total brain recurrence rate (46.8% in WBRT + SRS cohort vs 76.4% in the SRS-alone cohort; P < .001), increased 1-year rate of distant brain relapse (P = .003), and increased 1-year local tumor failure (P = .002). This resulted in more frequent use of salvage therapy (P < .001) in the SRS-alone arm.[64] Furthermore, the average time until Mini-Mental State Examination (MMSE) deterioration was significantly longer for the combined arm (16.5 vs 7.6 months; P = .05).[71] Median OS did not differ between groups (WBRT + SRS: 7.5 months vs SRS alone: 8 months, P = .42). Despite no OS benefit for the entire group, this study demonstrates the importance of WBRT in decreasing brain failure, corroborating the findings of the Patchell et al[63] study.

Subsequently, this group has performed a secondary analysis evaluating the outcomes of post-SRS WBRT in non–small cell lung primaries restratified by DS-GPA. Significantly increased median OS was observed with DS-GPA score of 2.5 to 4 (WBRT + SRS: 16.7 months vs SRS alone: 10.6 months, P = .04), whereas no survival differential was observed with DS-GPA scores less than 2.5. No significant difference in neurocognitive function, as assessed by the MMSE, was observed at baseline or during follow-up for WBRT plus SRS or SRS-alone arms for DS-GPA scores of either less than 2.5 or greater than 2.5.[72] The results of the secondary

analyses of the RTOG 95-08 and JROSG-99-1 trials, therefore, indicate that patients with brain metastases from NSCLC primary with favorable DS-GPA scores may benefit more from combined treatment (WBRT + SRS) than either treatment alone. Future prospective examination of this conclusion is warranted.

Muacevic et al[65] randomized patients with single-brain metastasis patients (KPS ≥70, size #3 cm, stable systemic disease) to SRS alone versus resection plus WBRT. While this trial is not exactly an SRS with or without WBRT trial, it addresses the benefit of WBRT to local therapies. Those randomized to SRS alone experienced worse distant (P = .04) recurrences, but there were no differences in neurologic death rates or OS.

The results of EORTC-22952-26001 have been reported with the primary end point of evaluating duration of functional independence.[66] In this study, patients with 1 to 3 brain metastases underwent local therapy with either surgery or SRS and were then randomized to the addition of WBRT versus observation. WBRT did not improve the duration of functional independence or OS but was associated with a significant decrease in 2-year local and distant brain relapse rate versus observation with either surgery or SRS. This resulted in a 16% decrease in the risk of neurologic death. Although there was no difference in the duration of functional independence between the two arms, the authors conclude that this is likely due to a variety of factors, including the subjective definition of functional independence, the routine use of MRI rendering the majority of recurrences as asymptomatic, and the potential impact of systemic progression on performance status.

Brown et al randomized patients with 1 to 3 brain metastases less than 3 cm to SRS alone or SRS and WBRT in the NCCTG N0574 Alliance Study.[67] The primary end point of this trial was cognitive deterioration, defined as a decline in greater than 1 SD from baseline on at least one of seven cognitive tests at 3 months. Secondary end points included tie to intracranial failure, quality of life, functional independence, long-term cognitive status, and OS. Data revealed that there was less cognitive deterioration at 3 months with SRS alone as compared to SRS plus WBRT (63.5% vs 91.7%, respectively, $P < 0.001$). Quality of life was also higher at 3 months with SRS alone ($P = 0.002$). Local control was improved with the addition of WBRT (90.1% vs 72.8% in SRS-alone arm at 1 year, P = .003)

as was 1-year distant brain control (92.3% vs 69.9.%, $P < .001$). Time to intracranial failure was significantly shorter for SRS alone compared with SRS plus WBRT ($P < .001$), though there was no difference in OS (10.4 months for SRS-alone patients vs 7.4 months for SRS + WBRT patients, $P = .92$).

Chang et al[68] reported on a series of 58 patients with 1 to 3 brain metastases randomized to SRS with or without WBRT. The primary end point of the study was neurocognitive function, which was assessed using the Hopkins Verbal Learning Test–Revised at 4 months after therapy. They found that patients receiving combined therapy were more likely to have a decline in learning and memory function at 4 months compared with patients who did not receive WBRT. The median survival was 15.2 months for the SRS-alone group and 5.7 months for the WBRT/SRS group ($P = .003$). However, the local (100% vs 67%; $P = .012$) and distant (73% vs 45%; $P = .02$) brain control rates were worse in the SRS-alone group compared with the WBRT/SRS group. There are multiple criticisms of this study worth noting.[73] First, because the primary end point was neurocognitive function, the authors did not stratify by baseline neurocognitive function or other factors known to impact neurocognition. Second, the authors chose a single test at a single time point. Ideally, a whole battery of tests should be performed at multiple time points to adequately assess the trend of something as complex as neurocognition. Most importantly, the combined arm inexplicably had a shorter survival, contrary to the four previously mentioned trials that demonstrated equivalent survivals. The median survival of 5.7 months was within 2 months of the primary end point mark, which classically falls within the time point of progressively worsening cognition seen in patients who are terminally ill [74,75] The superior survival in spite of inferior local and distant brain control is unprecedented and can possibly be explained by an improper randomization that is possible in a small study.

In summary, four of the five phase III local with or without WBRT trials unequivocally show a meaningful benefit of WBRT in terms of preventing neurologic deaths or brain failure. However, there has been no demonstrated OS benefit with the addition of WBRT. In light of the potential added neurotoxicity of WBRT, it is critical for radiation

oncologists to help patients navigate through the risks and benefits of additional WBRT after local therapy with surgical resection or SRS.

Radiosurgery for Multiple Brain Lesions

The Japanese Leksell Gamma Knife Society designed a prospective observational study (JKGK0901) to assess SRS treatment for 5 to 10 brain metastases.[76] At the time of initiation of this trial, major guidelines suggested that two to four metastases were the ideal number for SRS. This was a noninferiority prospective observational cohort study; 1,195 patients with 1 to 10 brain metastases were assigned to groups 1 (1 brain metastasis), 2 (2-4 brain metastases), and 3 (5-10 brain metastases). The primary end point was OS, with secondary end points of neurologic death, neurologic deterioration, local recurrence, distant brain failure, and maintenance of neurocognitive function, among others. Data revealed that patients with 1 brain metastasis (13.9 months) had significantly longer OS compared to those with 2 to 4 (10.8 months, $P = .0004$) or 5 to 10 (10.8 months, $P = .019$). However, the median OS was not statistically different in patients with 2 to 4 versus 5 to 10 metastases treated with SRS ($P = .78$, $P_{\text{noninferiority}} < .0001$), thereby meeting the primary end point of the study. There were no differences in preservation of neurocognitive function (defined as MMSE score decrease of <3 points from baseline) between the groups of patients with more than 1 brain metastasis. Other secondary end points were also not different between these same groups (local recurrence cumulative incidence, distant brain failure, and leukoencephalopathy). At longer term follow-up of 4 years, maintenance of cognitive function and post-SRS complication incidence did not differ among the aforementioned groups, thus supporting the noninferiority of SRS alone for patients with 5 to 10 brain metastases.[77]

The results of a randomized phase III trial of SRS versus WBRT for patients with 4 to 15 brain metastases were also recently presented.[78] Patients with 4 to 15 untreated brain metastases (up to 20 lesions allowed at time of treatment) were randomized to receive SRS (dosing per RTOG 9005) or WBRT (memantine strongly encouraged). The coprimary end points were memory function assessed by HVLT-R total recall at 4 months and local control. At 4 months, the SRS arm had increased Z-score in

HVLT-R total recall by 0.21 compared to a decreased of 0.74 Z-score in the WBRT arm (P = .041). Similarly, a statistically significant benefit with SRS was also seen at 1 (P = .033) and 6 months (P = .012). Significant improvements in composite neuropsychiatric scores were seen in the SRS arm at 1, 4, and 6 months. There were no differences in OS (median 7.8 months in SRS vs 8.9 months in WBRT arms, P = .59) nor in local control at 4 months (95% in SRS vs 87% in WBRT arms, P = .79). Notably, there was a significant shortening (P = .001) in time to initiation of systemic therapy favoring the SRS arm (1.7 weeks) versus the WBRT arm (4.1 weeks). The trial was terminated early due to the results of NRG CC001 (benefit of HA), but the authors concluded that SRS was associated with reduced neurocognitive decline and shorter time to systemic therapy, without any detriment in OS or local recurrence risks.

These data have laid the foundation for a currently-accruing phase III trial (CCTG CE.7) comparing HA-WBRT + memantine and SRS for patients with 5 to 15 brain metastases.

In summary, SRS can be considered a standard of care for patients with 4 to 15 brain metastases as opposed to up-front WBRT, but we await definitive results from the aforementioned trials, and especially the ongoing HA-WBRT versus SRS trial.

Treatment of Distant Brain Recurrences After Initial Radiosurgery

Modern series have demonstrated that rates of distant brain recurrences following SRS alone at 12 months can be as high as 40% to 60%. Many SRS trials to date have been focused on patients with newly diagnosed brain metastases, so the impact of multiple serial salvage SRS procedures on neurocognitive cognition or OS remains unknown. Brain metastasis velocity (BMV) defined as cumulative number of new brain metastases since up-front SRS/total time interval since up-front SRS at the time of distant brain relapse after up-front SRS has been shown to predict the risk of developing serial distant brain relapse after salvage SRS and has been corelated with survival and neurologic death.[79] Patients were classified by BMV into low (<4 new metastases since first SRS per year), intermediate (4-13 new metastases since first SRS per year), and high risk groups (>13

new metastases since first SRS per year). The use of BMV was subsequently validated in a multi-institutional dataset as a predictor of OS following initial SRS.[80] Median OS in this validation dataset was 12.5 months for BMV <4, 7.0 months for BMV 4 to 13, and 4.6 months for BMV >13 ($P < .0001$).

NRG BN009 is an ongoing phase III trial that is open to accrual. Patients with distant failure after initial SRS (either first or second relapse) will be randomized to receive SRS + HA-WBRT + memantine or SRS alone. The primary end point of the phase IIR will be time to neurologic death, and the end point of the phase III component is OS.

Preoperative Stereotactic Radiosurgery

Postoperative SRS/SRT has several potential drawbacks, including need for expansion of cavity in addition to occasional need for coverage of meninges and surgical tract. These can substantially increase the volume of normal brain that is irradiated. Preoperative SRS delivers radiation to intact brain metastases prior to planned resection. This often means that margin expansion is not required given these intact brain metastases are easily identifiable on preoperative imaging. Dose can often times be decreased with this approach. Preoperative SRS is also not contingent on clinical course after surgery, which may ultimately increase compliance rates. Finally, preoperative SRS can potentially reduce the likelihood of leptomeningeal disease associated with surgical spillage and perturbation, described as nodular meningeal disease, as opposed to classical leptomeningeal disease.

The PROPS-BM multicenter cohort study compiled patients from five institutions with brain metastases who had at least one lesion treated with preoperative SRS.[81] Most patients (98.8%) were treated with single-fraction SRS to a median dose of 15 Gy. Cavity local recurrence rates at 1 and 2 years were 15% and 17.9%, respectively while 1 and 2-year rates of meningeal disease were 6.1% and 7.6%, respectively. Only 10 out of 242 (4.1%) patients experienced grade 3 or higher postoperative surgical complications.

With the challenges of postoperative cavity SRS target delineation, need for larger treatment volumes, and concerns of meningeal disease in mind,

NRG opened the phase III trial (NRG BN012) which is comparing preoperative to postoperative SRS in patients with resectable brain metastases. The primary objective is time to composite adverse end point (defined as either local tumor progression in the surgical cavity, adverse radiation event, or nodular meningeal disease). Patients can have up to 4 brain metastases, one of which requires resection. This lesion must measure between 2 cm and 5 cm.

Small Cell Lung Cancer

Patients with small cell lung cancer were excluded from the landmark clinical trials that established SRS as the preferred treatment for limited brain metastases, and thus WBRT has remained the standard of care for these patients. However, there remain many patients who may be candidates for SRS especially when considering the quality of life and long-term neurocognitive advantages of avoiding WBRT.

The First-line Radiosurgery for Small-Cell Lung Cancer (FIRE-SCLC) cohort study has now been published.[82] This was a multicenter retrospective analysis of patients with small cell lung cancer brain metastases treated with SRS without prior WBRT or prophylactic cranial irradiation (PCI). 710 patients were included in the study; the median OS was 8.5 months and the median time to CNS progression was 8.1 months. Twelve-month competing risk estimate for local failure was 7.0% and for distant CNS failure was 41.6%. Propensity score-matched analyses comparing SRS with WBRT demonstrated that WBRT was associated with improved time to CNS progression (HR 0.38, $P < .001$) but not OS (median 6.5 months for SRS vs 5.2 months for WBRT, $P = .003$) or CNS PFS (median 4.0 months for SRS vs 3.8 months for WBRT, $P = .79$). These data are similar to the other SRS versus WBRT trial data that established SRS as a standard of care.

NRG CC009 is an ongoing phase III trial comparing SRS versus HA-WBRT for patients with 10 or fewer brain metastases from small cell lung cancer. The primary objective of this trial is to assess whether SRS relative to HA-WBRT + memantine prevents cognitive function failure as measured by cognitive decline on a battery of tests. OS and cumulative incidence of intracranial disease progression, neurologic death, and number of salvage procedures used to manage recurrent intracranial disease are secondary end

points. Until these data mature, selected patients with small number of metastases may be candidates for SRS.

For patients receiving PCI for small cell lung cancer, there have now been three phase III randomized studies assessing HA for neurocognitive protection. The PREMER study randomized 150 patients to standard PCI (25 Gy in 10 fractions) or to HA-PCI.[83] The primary objective was decline (defined as a decrease of ≥3 points from baseline) on the delayed free recall (DFR) on the Free and Cued Selective Reminding Test at 3 months. Decline on DFR was significantly lower (P = .003) in the HA-PCI arm (5.8%) compared with the PCI arm (23.5%). Incidence of brain metastases, OS, and quality of life were not significantly different between the arms. In contrast, in the multicenter NCT01780675 trial in the Netherlands, HA-PCI was not associated with a lower probability of cognitive decline.[84] This trial randomized 168 patients to standard PCI or HA-PCI with the same dosing fractionation. The primary end point of this trial was failure in total recall on the HVLT-R at 4 months, defined as a decline of at least five points from baseline. 29% and 28% of patients in the PCI and HA-PCI arms, respectively, showed decline on total recall on the HVLT-R at 4 months (P = 1.000). OS was not different between arms, nor was the cumulative incidence of new brain metastases at 2 years.

NRG CC003 was a phase IIR/III trial that was recently reported in an oral presentation form.[85] Patients were again randomized to PCI or HA-PCI. HVLT-R, TMT, and COWA tests were performed. The primary end points were noninferiority of 12-month intracranial relapse rate (phase II) and 6-month HVLT-R delayed recall failure, defined as using the reliable change index (phase III). For the phase IIR primary end point, HA-PCI had noninferior 12-month intracranial relapse rate (14.8% for PCI arm vs 14.2% for HA-PCI arm, P < .0001 to rule out inferiority). For the phase III primary end point, HA-PCI was not associated with a significant reduction in 6-month HVLT-R delayed recall deterioration (PCI 30.0% vs HA-PCI 26.0%, P = .31). However, HA-PCI did prevent neurocognitive function failure in any neuropsychiatric test (HR 0.77, P = .03). Again, there were no differences in OS (P = .19). Though the study did not meet its primary end point, the authors concluded that HA-PCI did significantly reduce the likelihood of neurocognitive function failure with noninferior intracranial relapse risk and similar OS. The final results and publication are pending.

Therefore, HA-PCI may be a reasonable treatment option especially if patients are concerned about neurocognitive toxicities of PCI, though the data remain mixed.

Repeat Whole Brain Radiotherapy

Occasionally, patients will fail in the brain after initial WBRT. Salvage surgery, SRS, or repeat WBRT should strongly be considered. Wong et al[86] reported on a series of 86 patients who underwent repeat WBRT. The median dose for the first course was 30 Gy in 10 fractions, while the median dose for the second course was 20 Gy. A total of 70% experienced neurologic improvement, with 27% experiencing complete neurologic resolution, while 43% had partial improvement after repeat WBRT. Median survival was 4 months after the second course of WBRT, with a retreatment dose of greater than 20 Gy associated with a significantly longer survival. Clinically significant radiation-related complications were rare.

Son et al[87] similarly reported on a series of 17 patients who underwent whole brain reirradiation. The median RT dose for the first course of treatment was 35 Gy in 14 fractions and for the second course 21.6 Gy in 1.8 Gy per fraction. The median survival time for all patients after retreatment WBRT was 5.2 months. In patients with stable extracranial disease, the median survival time after retreatment was 19.8 months compared with 2.5 months in patients with progressive extracranial disease. Eighty percent of patients experienced improved symptoms, with acute mild to moderate adverse reactions seen in 70.5% of patients.

Therefore, repeat WBRT is relatively safe and highly effective for recurrent or progressive brain metastases after initial WBRT. A minimum of 20 Gy in 1.8 to 2 Gy fractions should be given.

Concurrent Radiosensitizers

Although most patients with brain metastases ultimately succumb to systemic progression, a significant percentage will die from neurologic progression. Multiple randomized trials of concomitant radiosensitizers have been performed in an attempt to optimize brain control (Table 101.7).[88-97] No trial has demonstrated a survival advantage, although a few have demonstrated an increased response rate. The trials with temozolomide

show promise. Temozolomide is an oral alkylating agent with excellent CNS penetration. However, the findings of these relatively small trials need to be confirmed in a larger trial. Otherwise, a patient should be treated with a concomitant radiosensitizer only on a prospective trial.

TABLE 101.7 SELECTED RANDOMIZED TRIALS OF RADIOSENSITIZERS IN BRAIN METASTASIS

Study	*n*	Arms	Response Rate (%)	*P*	Median Survival	*P*
Komarnicky et al[93]; RTOG 79-16	859	RT (30 Gy/10 fx) RT + misonidazole RT (30 Gy/6 fx) RT + misonidazole	45[a] 42[a] 42[a] 45[a]	NS NS	4.5 mo 3.9 mo 4.1 mo 3.1 mo	NS NS
Ushio et al[89]; Japan[b]	88	RT (40 Gy/20 fx) RT + nitrosurea RT + nitrosurea + tegafur	36 69 74	<.05	27 wk 29 wk 30.5 wk	NS
Phillips et al[91]; RTOG-89-05	72	RT (37.5 Gy /15 fx) RT + BrdUrd	50[c] 63[c]	NS	6.1 mo 4.3 mo	NS
Guerrieri et al[95]; Australia[b]	42	RT (20 Gy/5 fx) RT + carboplatin	10 29	NS	4.4 mo 3.7 mo	NS
Antonadou et al[96]; Greece	52	RT (40 Gy/20 fx) RT + temozolomide	67 96	.017	7.0 mo 8.6 mo	NS
Verger et al[88]; Spain	82	RT (30 Gy/10 fx) RT + temozolomide	54[d] 72[d]	.03	3.1 mo 4.5 mo	NS
Mehta et al[92]; SMART Trial	401	RT (30 Gy/10 fx) RT + MGd	51 46	NS	4.9 mo 5.2 mo	NS
Suh et al[90]; REACH Trial	515	RT (30 Gy/10 fx) RT + efaproxiral	38 46	NS	4.4 mo 5.4 mo	NS
Knisely et al[94]; RTOG-01-18	175	RT (37.5 Gy/15 fx) RT + thalidomide			3.9 mo 3.9 mo	NS

BrdUrd, bromodeoxyuridine; fx, fractions; KPS, Karnofsky performance score; MGd, motexafin gadolinium; NS, not significant; RT, radiotherapy; RTOG, Radiation Therapy and Oncology Group; SWOG, South West Oncology Group.

[a]Percentage of survival time in KPS 90 to 100 range.

[b]Only patients with lung cancer.

[c]Overall complete and partial response rate.
[d]Ninety-day freedom from brain metastasis.

Leptomeningeal Carcinomatosis

Leptomeningeal carcinomatosis (LCM) is a rare complication of multiple cancers, occurring in approximately 5% of metastatic cancer. A diagnosis of LCM portends a poor prognosis, with a medial survival of 2.3 to 4.7 months in modern series.[98] The most frequent cancers associated with LCM are lung and breast. In breast cancer, it is often seen in patients who have *HER2-neu* overexpression or infiltrating lobular histology.[99] In lung cancer, it is most commonly involved by NSCLC, with adenocarcinoma histology accounting for 50% to 78% of cases.[100]

The majority of patients present with signs and symptoms. According to the review by Gleissner and Chamberlain,[101] spinal symptoms (>60%) are the most common, followed by cerebral (50%) and cranial nerve symptoms (40%). Contrast-enhanced MRI is the radiographic modality of choice. The entire neuroaxis must be imaged if LCM is clinically suspected in a patient with a known malignancy as multifocal involvement is common. In most patients, the MRI will reveal leptomeningeal enhancement that is frequently associated with cranial nerve enhancement and gross tumor deposits. MRI can provide a diagnosis of LCM, with a sensitivity and specificity of 76% and 77%, respectively.[102] A radiographic diagnosis of LCM may be limited, however, in the setting of hematopoietic tumors as the rate of positive neuroimaging is approximately 50%, thereby requiring cerebrospinal fluid (CSF) cytology for confirmation.[98]

CSF cytology is also warranted in a setting when suspicion for LCM is high but MRI is equivocal. Multiple samples may need to be obtained because the initial yield of a lumbar tap may be only 50%.[101] Neurosurgery must be consulted to evaluate the need for (a) shunting if hydrocephalus is suspected and (b) placement of Rickham or Ommaya reservoir for possible intrathecal (IT) chemotherapy. Gleissner and Chamberlain[101] argue that CSF flow studies should be performed with indium-111 or technetium-99, because up to 40% of patients have abnormal CSF flow from gross tumor deposits that may disrupt adequate IT chemotherapy delivery. However, flow studies are not performed by many centers because gross tumor

nodules, most likely to cause flow disruption and not effectively treated by IT chemotherapy, are treated with radiation anyway. Thus, CSF flow studies typically do not change the overall management of patients with LCM who require treatment decisions to be made in an expedient manner.

There is no consensus on the optimal management of patients with LCM. This is mainly because of the lack of large published experiences, limited number of randomized trials, nonuniform treatment regimens in single-institution experiences, and inclusion of various primary tumor histologies in the clinical trials. However, most would agree that an aggressive treatment with radiation and appropriate chemotherapy are indicated in patients with good performance status. The optimal dose and fractionation schedule of radiation therapy delivered in the setting of LCM remains unknown; however, similar to WBRT and MSCC, 30 Gy in 10 fractions is the most typical scheduled used. In a large published experience on LCM from small cell lung cancer (n = 36), the dismal median survival of 1.3 months is a direct result of only 14 patients being offered some kind of therapy (n = 9 for radiation, n = 5 for chemotherapy).[103] In contrast, Chamberlain and Kormanik[104] in a series of patients with LCM from NSCLC (n = 32) treated patients prospectively with radiotherapy followed by IT chemotherapy. The median survival for the entire cohort was 5 months, while patients with normal CSF flow had a significantly longer median survival compared with patients with interrupted CSF flow (6 vs 4 months; $P < .05$). This suggests that an aggressive multimodality approach can produce survival times that are comparable to patients with multiple brain parenchymal metastases.

A phase II randomized trial assessing proton therapy and craniospinal irradiation (CSI) was recently published. Patients with NSCLC and breast cancers with leptomeningeal disease were randomized to proton CSI or photon involved-field radiotherapy (IFRT), which included WBRT and/or focal spine RT.[105] All patients received memantine. There was also an exploratory proton CSI cohort that enrolled patients with other solid tumors. At interim analysis, CNS PFS was significantly improved ($P < .001$) with proton CSI (median 7.5 months) compared to the photon IFRT arm (2.3 months); this led to early discontinuation of the trial. Moreover, there was a statistically significant ($P = .029$) OS benefit with proton CSI (9.9 months) versus photon IFRT (6.0 months), with no difference in the rates of grade 3

or 4 treatment-related adverse events. On multivariable analysis, proton CSI remained significantly associated with CNS PFS (HR 0.15, $P < .001$) and OS (HR 0.43, $P = .025$) improvements. The trial was not powered to evaluate differences in OS, and as such, a phase III randomized trial is in the works to validate these findings.

Most of the historic randomized clinical trials on patients with LCM from solid tumors have included IT methotrexate (MTX)-based regimens (Table 101.8).[106-110] The only trial that compared IT versus non-IT (ie, systemic) chemotherapy was reported by Boogerd et al[110] However, this negative trial only included patients with breast primaries. Glantz et al[109] reported that IT DepoCyt (cytarabine liposome injection) led to a greater median time to neurologic progression (8 vs 4 weeks; $P = .007$), although the OS was not statistically different. The only positive trial reported to date has been by Kim et al[106] from Seoul National University. Patients randomized to IT MTX, arabinofuranosyl cytidine, and hydrocortisone had a significantly longer survival than those randomized to IT MTX alone (18.2 vs 10.4 weeks; $P = .029$). Patients with adenocarcinoma of the lung in the multiagent arm had a significant, longer survival (23.9 vs 10.4 weeks; $P = .038$). Multiple other agents have been studied, but none have demonstrated significant responses. Targeted agents that cross the BBB should be used when appropriate.

TABLE 101.8 RANDOMIZED TRIALS OF SOLID TUMOR PATIENTS WITH LEPTOMENINGEAL CARCINOMATOSIS

Study	*N*	Histology	Arms[a]	RR[b] (%)	Median Survival	Survival (*P*-value)
Hitchins et al[107]	44	Solid tumors	IT MTX 15 mg	61	12 wk	.08
			IT MTX + Ara-C 50 mg/m^2	45	7 wk	
			Concurrent RT (not randomized)	75		
			No concurrent RT	35		<.05
Grossman et al[108]	52	Nonleukemic[c]	IT MTX 10 mg	0	16 wk	NS

Study	*N*	Histology	Arms[a]	RR[b] (%)	Median Survival	Survival (*P*-value)
			IT thiotepa 10 mg	0	14 wk	
Glantz et al[109]	61	Solid tumors	IT MTX 10 mg	20	2.6 wk	.15
			IT DepoCyt 50 mg	26	3.5 wk	
Kim et al[106]	55	Solid tumors	IT MTX 15 mg	14	10 wk	.03
			IT MTX + Ara-C 30 mg/m^2 + Hydrocortisone 15 mg/m^2	39	19 wk	
			Concurrent RT (not randomized)	82	19 wk	
			No concurrent RT	50	11 wks	.47
Boogerd et al[110]	35	Breast	IT chemotherapy[d]	41	18 wk	.32
			Non-IT chemotherapy	39	30 wk	

Ara-C, arabinofuranosyl cytidine; CSF, cerebrospinal fluid; DepoCyt, sustained-release cytarabine; IT, intrathecal; MTX, methotrexate; NS, not significant; RR, response rate; RT, radiotherapy.

[a]All studies allowed palliative radiation when necessary.

[b]RR determination by neurologic and CSF improvements as predefined by each study.

[c]Fourteen patients (19%) had lymphoma, the rest had solid tumors.

[d]All patients started with MTX and switched to Ara-C if no response.

There is ample evidence that focal radiation, such as WBRT or spinal radiation, provides added benefit to IT chemotherapy. This is particularly true in patients with bulky meningeal disease because IT chemotherapy only penetrates 2 to 3 mm. In the randomized IT chemotherapy trial reported by Hitchins et al[107] patients who received concurrent CNS radiation had a higher response rate compared with those who did not (73% vs 35% $P < .05$). Likewise, in the randomized trial reported by Kim et al[106] those who received concurrent CNS radiation had a significant higher neurologic response rate (81.5% vs 50.0% $P = .014$). There is a concern that concurrent radiation and IT chemotherapy could potentially increase toxicity. The vast

majority of patients, however, do not survive long enough to see the late neurologic toxicity manifest.

With the recent findings of the first prospective trial of RT for solid tumor leptomeningeal disease, there is now evidence of the potential benefits of proton CSI in terms of improved CNS PFS and potentially OS. It is premature to say that proton CSI should be a standard of care for patients with leptomeningeal disease at this time, but discussion with patients about the benefits and risks of this more aggressive treatment, as opposed to focal radiation, is warranted. Logistical considerations regarding proton CSI planning are also very important, especially since these patients are often symptomatic and need more urgent initiation of treatment. Phase III results are still awaited to more definitively define the role of radiation in the setting of leptomeningeal disease.

CONCLUSION

A significant percentage of patients with cancer will require palliative radiation therapy at some point during their natural history. On the basis of randomized data, patients with a limited number of brain metastases should be treated with local therapy such as surgery or SRS with or without whole brain irradiation, while those with numerous brain metastases should be treated, with whole brain irradiation alone. LCM continues to have an unfavorable prognosis, and the use of radiation therapy should be based on the palliation of individual signs and symptoms.

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CHAPTER 102

Palliation of Vertebral and Spinal Cord Metastases

Emily MacDuffie and Joshua Jones

METASTASES TO THE SPINE

Metastatic tumors are the most common malignancy in the spine, with an estimated 30% of patients with solid cancer harboring spinal metastasis at the time of death and over 15% receiving a clinical diagnosis of spinal metastasis at some point after their cancer diagnosis.[1] Spinal metastases deserve special consideration as progression of spinal tumors can lead to pain, significant morbidity including numbness, weakness, loss of bowel and bladder continence, and the potential for the development of metastatic spinal cord compression (MSCC) in the future. Spinal metastases in about 10% of patients will progress to cause MSCC, resulting in symptoms that range from paresthesias to paralysis. Given the risk of permanent disability, MSCC is considered an oncologic emergency that warrants expedited treatment. Even in the absence of frank MSCC, spinal metastases should be evaluated by a multidisciplinary team due to the risk of spinal instability, including from pathologic compression fractures, which can be associated with significant pain and limited mobility. This chapter will discuss the epidemiology, pathology, evaluation, and treatment options for spinal metastases and their associated complications.

Spinal Cord Compression

In the United States, more than 20,000 cases of MSCC are diagnosed annually, and it is estimated to develop in approximately 5% to 10% of all patients with cancer.[2,3] MSCC is a devastating complication of cancer associated with complete loss of function below the level of the injury. It is considered a true medical emergency with immediate intervention required. Even with aggressive therapy, results can often be unsatisfactory. Although

most patients with MSCC have limited survival, up to one-third will survive beyond 1 year.[4] As such, and in the context of ever-evolving systemic therapies that are leading to lover survival for patients with metastatic disease, evaluation of prognosis is critical in determining appropriate treatment for patients with MSCC.

Pathophysiology

MSCC develops primarily in one of four ways: (a) continued growth and expansion of vertebral bone metastasis into the epidural space; (b) neural foramina extension by a paraspinal mass; (c) destruction of vertebral cortical bone, causing vertebral body collapse with displacement of bony fragments into the epidural space; or (d) rarely primary hematogenous seeding to the epidural space. Although complex, the most significant damage caused by MSCC appears to be vascular in nature as opposed to mechanical. Epidural tumor extension causes epidural venous plexus compression, which leads to intramedullary edema. This increase in vascular permeability and edema causes increased pressure on the small arterioles. Capillary blood flow diminishes as the disease progresses, leading to white matter ischemia. Prolonged ischemia eventually results in white matter infarction and permanent cord damage.[5] When symptoms are rapid and develop over hours to days, the likelihood of response decreases with time and urgent/emergent intervention is indicated. When symptoms develop more slowly over days or weeks, the injury is more likely related to direct compression and recovery is more likely.[6]

Clinical Presentation and Evaluation

Most patients with MSCC have a history of prior cancer diagnosis. Around two-thirds of MSCC cases have a diagnosis of breast cancer, lung cancer, or prostate cancer, each histology accounting for 15% to 20% of all cases.[7] This reflects the high natural incidence of these tumors and their propensity for osseous metastasis. Back pain is the most common presenting symptom (70%-94%), followed by weakness (61%-91%), sensory deficits (46%-90%), and autonomic dysfunction (40%-57%).[7] Presentation of new-onset back pain in patients with cancer should raise suspicion of vertebral involvement and prompt thorough physical exam and imaging workup.

Even without a prior cancer diagnosis, MSCC should be suspected in patients who present with progressively worsening back pain, incontinence, or paraplegia, especially in the high-risk population such as long-time smokers. Those presenting with MSCC at initial diagnosis are more likely to be subsequently diagnosed with cancers such as lung cancer, non-Hodgkin lymphoma, myeloma, or unknown primary origin.[7] The most common level of the MSCC involvement is in the thoracic spine (60%-80%), followed by lumbar (15%-30%) and cervical spine (<10%); however, multilevel involvement can be identified in 20% to 30% of patients, with the second site often asymptomatic. Providers should be aware that location of pain as described by patients does not reliably correlate to tumor location on imaging, further underscoring the need for accurate imaging.[8]

At initial presentation, computed tomography (CT) is often the first imaging study ordered to identify the etiology of symptoms, and it has a relatively high sensitivity and specificity for the detection of spinal cord compression (SCC).[9-11] However, full spine magnetic resonance imaging (MRI) is the gold standard to best delineate the extent and severity of compression[12] and should be ordered in conjunction with CT for patients with moderate to high suspicion of SCC. Because patients can have synchronous, multifocal MSCC, an MRI of the entire spine with and without contrast should be promptly performed in anyone suspected of having MSCC. High-resolution CT scan or CT myelogram of the spine should be performed for those with contraindications to MRI.

After images are obtained, scoring tools such as the Bilsky epidural spinal cord compression scale[13] can be used to estimate the severity of SCC and the Spinal Instability Neoplastic Score (SINS)[14] can be used to assess the stability of the bony spine (Figure 102.1; Table 102.1).

TABLE 102.1 SPINAL INSTABILITY NEOPLASTIC SCORE (SINS) SYSTEM

Component	Score
Location	
Junctional (O-C2; C7-T2; T11-L1; L5-S1)	3
Mobile spine (C3-6; L2-4)	2

Component	Score
Semirigid (T3-10)	1
Rigid (S2-S5)	0
Pain[a]	
Yes	3
Occasional pain but not mechanical	1
Pain-free lesion	0
Bone lesion	
Lytic	2
Mixed (lytic/blastic)	1
Blastic	0
Radiographic spinal alignment	
Subluxation/translation present	4
Deformity (kyphosis/scoliosis)	2
Normal	0
Vertebral body collapse	
>50% collapse	3
<50% collapse	2
No collapse with >50% body involved	1
None of the above	0
Posterolateral involvement of spinal elements[b]	
Bilateral	3
Unilateral	1
None of the above	0

The SINS represents a validated measurement of spine stability that requires clinical (pain scores) and imaging input (magnetic resonance imaging as well as evaluation of lytic vs blastic tumors). Scores of 0 to 6 indicate a mechanically stable spine, while scores of 7 to 12 represent a potentially unstable spine and scores of 13 to 18 represent unstable spinal pathology.

[a]Pain improvement with recumbency and/or pain with movement/loading of spine.

[b]Facet, pedicle of costovertebral joint fracture or replacement with tumor.

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approach and expert consensus from the Spine Oncology Study Group. *Spine (Phila Pa 1976)*. 2010;35(22):E1221-E1229.

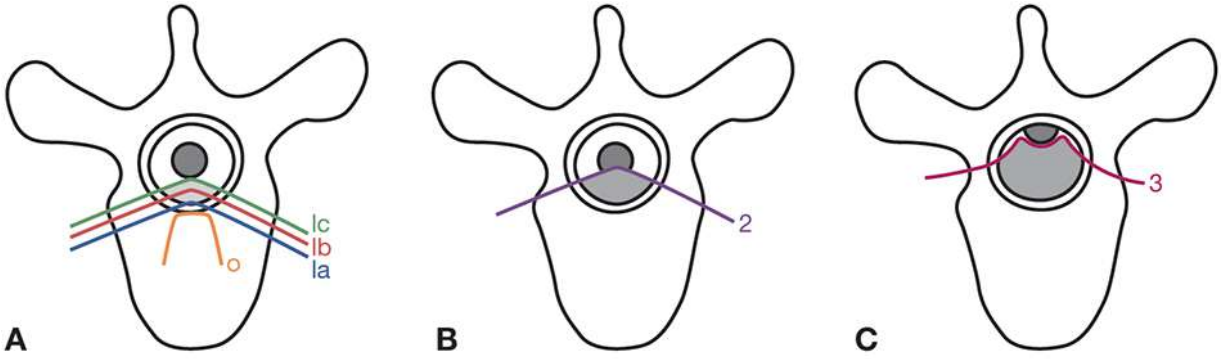


FIGURE 102.1 Epidural spinal cord compression grade. The "Bilsky" score or epidural spinal cord compression grade details extent of epidural tumor in patients with spinal metastases. T2-weighted axial magnetic resonance imaging represents the gold standard for evaluation of epidural tumor. A score of 0 represents no epidural tumor extension (bone-only disease). Score 1a represents epidural tumor extension without deformation of the thecal sac. Score 1b represents epidural tumor with deformation of the thecal sac, but without spinal cord abutment. Score 1c represents epidural tumor with defamation of the thecal sac and with spinal cord abutment. Score 2 represents epidural tumor with mass effect on the spinal cord (spinal cord compression), but with cerebrospinal fluid (CSF) visible around the spinal cord. Score 3 represents epidural tumor with complete spinal cord compression with no CSF visible around the spinal cord. (Reproduced with permission from Bilsky MH, Laufer I, Fourney DR, et al. Reliability analysis of the epidural spinal cord compression scale. *J Neurosurg Spine*. 2010;13[3]:324-328. An Open Access or Creative Commons publishing model conveys no rights to use this material in any format without written permission from the JNS Publishing Group.)

Treatment Algorithms

Options for the management of spinal metastases have expanded dramatically in recent years and include surgical decompression, minimally invasive separation surgery, external beam radiotherapy (conventionally fractionated radiotherapy or stereotactic radiotherapy), interventional spine techniques including kyphoplasty/vertebroplasty and ablative spine interventional techniques such as microwave ablation or cryoablation, systemic therapies such as chemotherapy, targeted therapies or immunotherapy, corticosteroids such as dexamethasone and bone-modifying agents such as bisphosphonates or RANK-L inhibitors. Given the potential high levels of morbidity when patients develop spinal cord compression, multiple treatment algorithms have been developed to guide

management of patients with spinal metastases. The Neurologic, Oncologic, Mechanical, Systemic (NOMS) framework incorporates neurologic, oncologic, mechanical, and systemic factors into clinical decision-making.[15] This score evaluates the neurologic tumor impact, including Bilsky epidural spinal cord compression grade and resulting neurologic symptoms, the oncologic factors of tumor radiosensitivity (eg, lymphoma, myeloma, small cell carcinoma are highly "radiosensitive," while melanoma and renal cell carcinoma are "radio-resistant"; Figure 102.2), mechanical stability as assessed by the SINS, and the patient's overall ability to tolerate surgical intervention or other treatments. These factors can be used to guide decision-making regarding the need for surgery, conventional or stereotactic radiotherapy. An alternative framework for the management of spinal metastases created by the International Spine Oncology Consortium is the LMNOP framework.[16-18] This framework evaluates the number and site of spinal levels involved by tumor (L), the mechanical stability (now incorporating SINS: M), the neurologic deficits and epidural extent of tumor (N), the oncologic parameters including radiosensitivity (O) and patient prognosis, preferences and response to prior treatment (P) (Table 102.2). While clinical decisions must be nuanced based on each patient's individual case, generally patients who have asymptomatic low-grade SCC or highly radiosensitive tumors can undergo radiotherapy alone, whereas those with high-grade SCC or spinal instability who can tolerate surgery should first undergo decompressive surgery, separation surgery, and/or stabilization surgery followed by postoperative radiation to optimize ambulatory and neurologic outcomes.

TABLE 102.2 LMNOP FRAMEWORK FOR THE MANAGEMENT OF SPINAL METASTASES

L: Number of spinal levels involved and location of disease in the spine
M: Mechanical instability, subsequently incorporating SINS
N: Neurology (including epidural tumor extension and neurologic deficits)
O: Oncology, incorporating tumor radiosensitivity
P: Patient fitness, prognosis, and response to prior therapy

SINS, Spinal Instability Neoplastic Score.

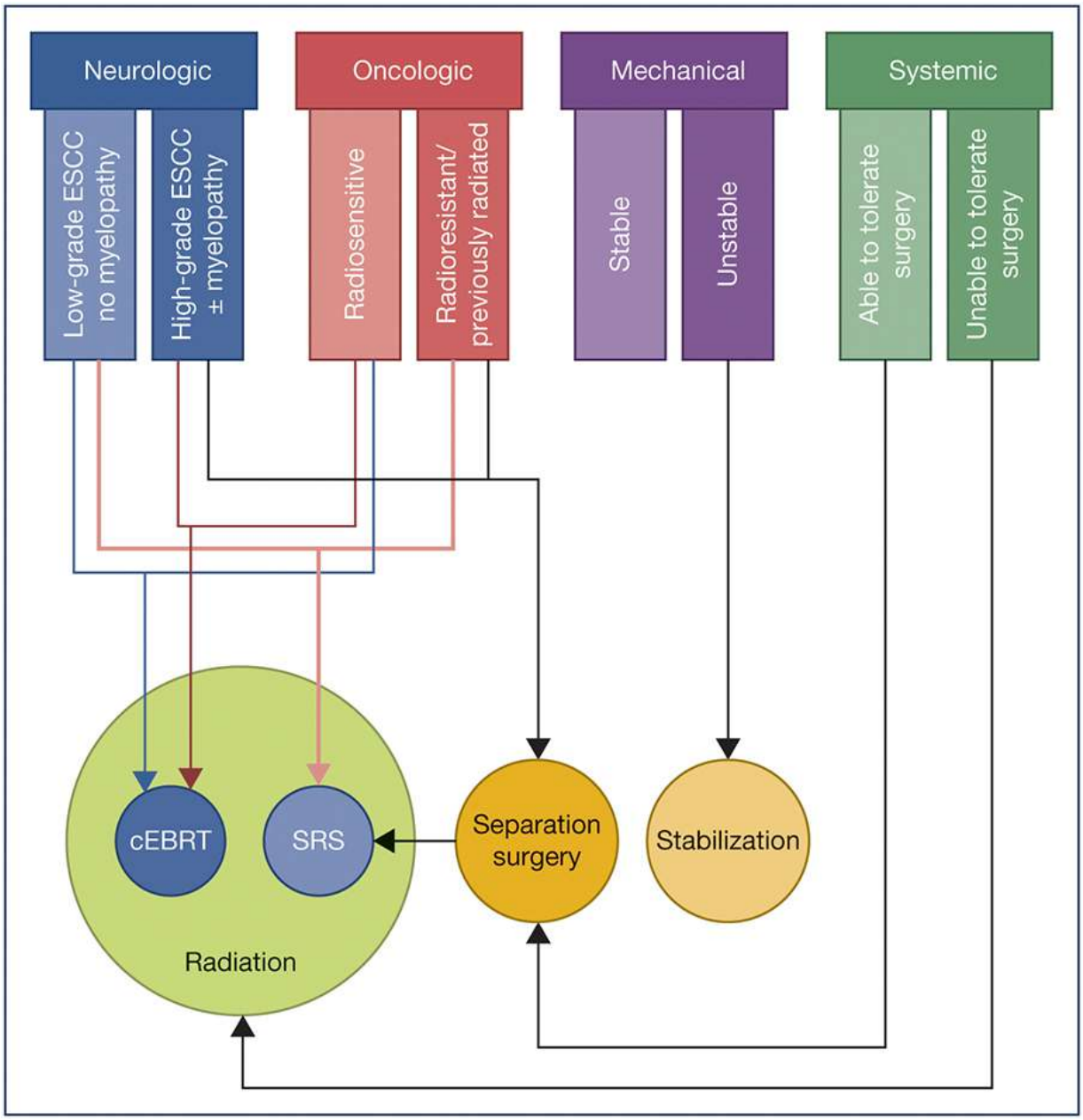


FIGURE 102.2 Neurologic, Oncologic, Mechanical, Systemic (NOMS) approach. The NOMS approach incorporates degree of spinal canal compression and degree of myelopathy (epidural spinal cord compression score) with the radiosensitivity of the tumor, the mechanical stability of the spine (SINS), and the patient's overall ability to tolerate surgery in an approach for evaluating optimal management of spine tumors. For the purposes of this approach, the following tumors were defined as radiosensitive: seminoma, lymphomas (all), myeloma and breast, prostate, ovarian and neuroendocrine carcinomas. The following tumors were defined as radioresistant: renal cell carcinoma, thyroid cancers, hepatocellular carcinoma, colon cancer, non–small cell lung carcinomas, sarcomas, and melanoma. cEBRT, conventional external beam radiotherapy; ESCC, epidural spinal cord compression; SRS, stereotactic radiosurgery. (From Laufer I, Rubin DG, Lis E, et al. The

NOMS framework: approach to the treatment of spinal metastatic tumors. *Oncologist*. 2013;18[6]:744-751. Reproduced by permission of Oxford University Press.)

Estimating Survival for Patients With Metastatic Spinal Cord Compression

Patients with spinal metastases and spinal cord compression can present with symptoms at any time point in the cancer trajectory, from initial diagnosis with a long anticipated survival to near end of life with days or weeks to live. As such, accurate prediction of survival is critical to determining the optimal treatment approach for patients with spinal metastases. Traditional scores predicting ambulatory status, neurologic outcomes, and survival have been developed to help with clinical decision-making for patients with spinal metastases including the Tokuhashi score, revised Tokuhashi score, the Tomita index, the Baur score, modified Baur score, Katagiri score, and van der Linden score.[19,20] In addition, multiple scores from Rades, both general scores for all histologies and various histology-specific scores, have been used to predict outcomes including survival-based retrospective evaluation of thousands of patients. Rades et al validated the use of a scoring system for patients treated with radiation alone by assigning 2 to 8 points for six prognostic factors: tumor type, interval between tumor diagnosis and MSCC, other bone or visceral metastases, ambulatory status, and duration of motor deficits.[21] The 6-month survival rates were 14% for those with 20 to 30 points, 56% for those with 31 to 35 points, and 80% for those with 36 to 45 points. Use of these tools may help guide physicians in selecting the appropriate intervention and length of a radiation course based on a patient's prognosis and potential for recurrence over their remaining lifetime.

More recently, machine learning algorithms have been utilized to predict 90-day and 1-year survival for patients with spinal metastases undergoing surgery. The Skeletal Oncology Research Group (SORG) has developed a machine learning algorithm that has been externally validated by multiple groups and predicts 90-day and 1-year survival for patients undergoing surgery for spinal metastases.[22-24] The group created a classic scoring algorithm, nomogram, and boosted algorithm with machine learning to evaluate survival for patients with spinal metastases. Factors that impact survival include age, performance status, primary cancer type, more than

one spinal metastasis, lung and/or liver metastasis, brain metastasis, any systemic therapy prior to surgery, white blood cell count, and hemoglobin levels. Regardless of which system is utilized, validated prognostic models should be incorporated into clinical decision-making for patients with spinal metastases.

Corticosteroids

Corticosteroids are a critical component of the management of MSCC. Administration is often indicated even prior to radiographic diagnosis if there is any suspicion of MSCC, as medications can be rapidly discontinued if a negative diagnosis is obtained. Corticosteroids effectively decrease cord edema and serve as an effective bridge to definitive treatment. In addition to multiple retrospective studies that have demonstrated their clinical efficacy, Sorensen et al[25] reported a randomized controlled study (n = 57) on the utility of high-dose corticosteroids before definitive radiotherapy in MSCC from solid tumors. The treatment arm consisted of 96 mg of intravenous (IV) bolus of dexamethasone followed by 96 mg oral per day for 3 days and a 10-day taper versus no corticosteroid therapy. This study demonstrated 3-month and 6-month ambulatory rates of 81% versus 63% and 59% versus 33% ($P < .05$), respectively, in favor of high-dose dexamethasone.

The optimal maintenance dose of corticosteroids has not been firmly established, but historical trials have shown little benefit to very high doses of dexamethasone as compared to moderate doses. An early trial by Vecht et al[26] comparing an IV loading dose of 10 to 100 mg followed by 16 mg daily showed equal efficacy in pain reduction. However, very high doses of corticosteroids are associated with significant side effects. The Sorensen et al[25] phase III study reported an 11% incidence of serious side effects for patients in the treatment arm. Heimdal et al[27] reported a 14.3% incidence of serious gastrointestinal (GI) side effects in patients treated with 96 mg of IV dexamethasone per day, including a fatal ulcer hemorrhage, rectal bleeding, and bowel perforations. No additional events were recorded after the dose was decreased to 16 mg/d for the remainder of the study, yet ambulatory rates did not decline on the lower dose. Other known side effects of corticosteroids include opportunistic infections, hyperglycemia, and neuropsychiatric disturbances, all of which may disrupt delivery of

oncologic care if severe.[28] Thus, appropriate dosing is important when balancing the benefits and risks of steroid administration.

In clinical practice, a loading dose of 10 mg of IV dexamethasone followed by a maintenance dose ranging from 8 mg every 12 hours to 4 mg every 6 hours is reasonable for patients presenting with MSCC. In clinical practice, it is reasonable to time dosing with diurnal cortisol releases (morning and early to late afternoon) to decrease side effects. Every 6-hour dosing should be reserved only for patients with severe myelopathic symptoms. Patients who can tolerate PO intake can be safely switched to an oral regimen after their initial IV loading dose due to the high oral bioavailability of corticosteroids. Although there are no strict recommendations regarding steroid tapers, after definitive treatment is underway (eg, decompressive surgery has been performed or radiotherapy has been initiated), it is reasonable to reduce by 2 to 4 mg every 3 to 6 days and discontinue within 2 weeks.

Patients initiated on steroids should also be considered for GI prophylaxis with a proton pump inhibitor (PPI) if they are anticipated to have a prolonged steroid course, taking nonsteroidal anti-inflammatory drugs (NSAIDs) concomitantly, or are hospitalized. No randomized trials utilizing PPIs in patients receiving corticosteroids exist, but extrapolations have been made from literature on chronic NSAID use, which mirrors steroid use in the similar disruption of mucosal-protective prostaglandins, and show that PPIs reduce the risk of peptic ulcer development.[29] Use of oral antacids is not recommended as they have not been shown to protect against injury. For patients who are anticipated to remain on 20 mg or more of daily prednisone equivalent dose (ie, 3.2 mg dexamethasone) for 4 weeks or more, prophylaxis for *Pneumocystis jiroveci* pneumonia (PJP) with trimethoprim/sulfamethoxazole or equivalent should be considered.[28,30] Patients with comorbid diabetes should monitor their blood sugar closely and be counseled that they may need to initiate or increase subcutaneous insulin administration while on steroids.

Surgery

Under the NOMS framework, patients who present with symptomatic cord compression, radiographic evidence of Bilsky grade 1a cord compression or

greater, a SINS suggesting spinal instability, radioresistant tumor histology, and fitness for surgery should be considered for surgical intervention and evaluated by a surgeon. In these patients, surgery has the potential benefit of immediate decompression of neurovascular structures and allowing for collection of tissue for pathologic examination. Consultation with a radiation oncologist is always warranted as patients will require radiotherapy as a component of their treatment regardless of surgical candidacy. Effective multidisciplinary teamwork is critical for the rapid evaluation and management of patients with MSCC.

The seminal phase III randomized trial from Patchell et al[31] that established the benefit of surgical intervention over radiation alone reported the efficacy of direct decompressive surgery in patients with MSCC (Table 102.3). The study compared radiation alone (standard 30 Gy in 10 fractions) versus circumferential decompressive and stabilization surgery within 24 hours of diagnosis followed by the same radiotherapy (within 2 weeks of surgery). The trial was prematurely terminated due to statistical improvement in ambulation outcomes in the surgical group. This trial demonstrated a statistically significant advantage to surgery for outcomes including regaining ambulatory function, maintenance of continence, maintenance of American Spinal Cord Injury Association (ASIA) scale and Frankel score (measures of spinal function after injury), median overall survival, and median mean daily dexamethasone and morphine equivalent doses.

TABLE 102.3 KEY FINDINGS OF A PHASE III STUDY OF PATIENTS WITH METASTATIC SPINAL CORD COMPRESSION[31]

	Surgery + Radiation (*n* = 50)	Radiation Alone (*n* = 51)	*P*
Primary endpoint			
Ability to walk posttreatment			
Rate	84% (42/50)	57% (29/51)	.001
Time[a]	122 d	13 d	.003
Secondary endpoints[a]			
Maintenance of continence	156 d	17 d	.016

	Surgery + Radiation (*n* = 50)	Radiation Alone (*n* = 51)	*P*
Maintenance of ASIA score[b]	566 d	72 d	.001
Maintenance of Frankel score[b]	566 d	72 d	.0006
Overall survival	126 d	100 d	.033
Other endpoints			
Mean daily morphine[c]	0.4 mg	4.8 mg	.002
Mean daily dexamethasone[c]	1.6 mg	4.2 mg	.0093
In patients ambulatory at study entry			
Ability to walk (maintaining)			
Rate	94% (32/34)	74% (26/34)	.024
Time[a]	153 d	54 d	.024
In patients nonambulatory at study entry			
Ability to walk (regaining)			
Rate	62% (10/16)	19% (3/16)	.012
Time[a]	59 d	0 d	.04

ASIA, American Spinal Injury Association.

[a]Reported time (days) are median values.

[b]Measures of spinal function after injury.

[c]Converted into equivalent doses.

Critics have noted that patients in this trial were highly selected, and a matched pair analysis of patients with symptomatic MSCC by Rades et al[21] suggested that endpoints such as posttreatment motor function, ambulatory status, regaining ambulatory status, local control, and survival evaluated after radiotherapy alone appeared similar to those of surgery plus radiotherapy. However, further matched pair analysis of patients with radioresistant histologies did demonstrate superior outcomes for those who received surgical decompression prior to radiation compared to those who received radiation alone.[32] Notably, consistent with prior studies,[33] laminectomy did not demonstrate benefit in this study.

While surgical decompression has traditionally been the preferred surgical approach, new surgical approaches combined with stereotactic ablative radiotherapy may allow similar outcomes with a less invasive approach. Minimally invasive surgical (MIS) separation of tumor and spinal cord can allow for high-dose stereotactic body radiation therapy (SBRT) to be delivered while limiting the dose to the spinal cord. Recently, MIS techniques have been implemented in separation surgery and may show promise for patients who would otherwise not tolerate decompression. Echt et al[34] reported on a single-institution, retrospective comparative study of MIS versus open approach for separation surgery in patients with MSCC. They found that despite having a significantly older population, the MIS group had significantly reduced blood loss during surgery and there was a nonsignificant trend toward reduced time to starting radiation treatment. There were similar rates of local recurrence and hardware failure. In the future, this technique may allow for a broader inclusion of candidates for surgical intervention. Other types of MIS interventions include percutaneous cement augmentation (eg, kyphoplasty or vertebroplasty) or pedicle screw fixation, which can allow for stabilization of the spine followed by oncologic treatment with radiation, with reduced time required for postoperative healing.[35,36]

In summary, for appropriate patients with MSCC, direct surgical decompression, tumor debulking, and spinal stabilization can improve clinical outcomes compared to radiation alone. While there are no randomized phase III data comparing MIS to direct decompressive surgery, outcomes with MIS followed by SBRT may allow faster recovery and less disruption of systemic therapy. All patients should undergo postoperative radiation to prevent local recurrence and the subsequent risk of recompression or disruption of surgical hardware.

Radiotherapy

Palliative radiotherapy has been the standard of care in the treatment of patients with MSCC for many decades. Historically, 30 Gy in 10 fractions has been the most frequently employed fractionation schedule; however, a number of modern studies have suggested that shorter fractionation schemes can be equally effective in many scenarios.[4,37] In one of the largest

studies to date, Rades et al[38] reported a retrospective series of 1,304 patients with MSCC. The patients were separated into five schedules: 8 Gy × 1 in 1 day (n = 261, group 1), 4 Gy × 5 in 1 week (n = 279, group 2), 3 Gy × 10 in 2 weeks (n = 274, group 3), 2.5 Gy × 15 in 3 weeks (n = 233, group 4), and 2 Gy × 20 in 4 weeks (n = 257, group 5). All of the groups had similar posttreatment ambulatory rates (63%-74%) and motor function improvements (26%-31%). However, in-field recurrence rates were much lower for the protracted schedules. The 2-year in-field recurrence rates for groups 1, 2, 3, 4, and 5 were 24%, 26%, 14%, 9%, and 7% (P < .001), respectively. They recommend that a single fraction of 8 Gy should be used in patients with MSCC with limited survival expectations and that 30 Gy in 10 fractions should be used for all other patients.

Rades et al[39] followed up with a randomized trial comparing a short-course regimen (4 Gy × 5) to 30 Gy × 10 in patients with poor to intermediate survival prognosis, defined as having an estimated 6-month survival of 14% to 56% based on a validated scoring system. Primary endpoint was motor function response rate showing improvement or no progression of motor deficits at 1 month. Seventy-five percent of patients survived more than 1 month. One-month response rates were similar for both radiation regimens (87.2%-89.6%, P = .73). Both regimens also had similar effects on motor function at 3 and 6 months posttreatment. Ambulatory status at 1, 3, and 6 months was not significantly different between regimens. Local progression-free survival and overall survival (median: 3.2 months) were also similar for both arms. Based on the trial results, 4 Gy × 5 was deemed noninferior to 30 Gy × 10 and should be strongly considered for patients with poor prognosis in whom limiting treatment time and discomfort should be a high priority.

The SCORAD randomized trial reported by Hoskin et al[40] compared a single dose of 8 Gy radiotherapy with 20 Gy in five fractions with a primary endpoint of ambulatory response (grades 1 and 2, ie, able to ambulate with or without assistance) at 8 weeks posttreatment. While the primary endpoint did not meet the criterion for noninferiority for achieving ambulatory response status at 8 weeks (grade 1 or 2; P = .06), for all other time points of 1, 4, and 12 weeks, the threshold for noninferiority was met. Overall survival was not different between groups. This trial suggests that the use of single-fraction radiation for MSCC may be appropriate in a wider

variety of clinical scenarios than only for patients with very poor performance status.

Table 102.4 compares outcomes of the SCORE 2 and SCORAD randomized studies of radiotherapy alone for patients with MSCC.

TABLE 102.4 COMPARISON OF SCORE-2 AND SCORAD RANDOMIZED STUDIES OF DIFFERENT RADIOTHERAPY DOSE-FRACTIONATION SCHEDULES FOR PATIENTS WITH EPIDURAL SPINAL CORD COMPRESSION

Trial	Score-2, Rades et al[39]		Patchell et al[31]	
Treatment arm	400 cGy × 5	300 cGy × 10	300 cGy × 10 alone	Surgery + 300 cGy × 10
Ambulatory pretreatment	58 of 101 (57.4%) (w/ and w/o aid)	57 of 102 (55.9%) (w/ and w/o aid)	35 of 51 (68.6%) (aid not specified)	34 of 50 (64%) (aid not specified)
Median time, diagnosis to MESCC	>5 mo = 45.5% (46 of 101)	>5 mo = 50% (51 of 102)	7 mo	3 mo
Time motor symptoms to treatment	1-7 d: 45.5% 8-14 d: 25.7% >14 d: 28.7%	1-7 d: 45.1% 8-14 d: 26.5% >14 d: 28.4%	12 d	10 d
Ambulatory status posttreatment	61 of 96 (63.5%)	62 of 96 (64.6%)	57%	84%
Duration of ambulatory status after treatment	71.8% ambulatory, 44.9% with aid at 1 mo	72.0% ambulatory, 42.9% with aid at 1 mo	13 d (median)	122 d (median)
Overall survival (OS)	Median OS 3.0 mo	Median OS 3.7 mo	100 d	126 d

MESCC, metastatic epidural spinal cord compression; SCORAD, Spinal Cord Outcomes Research Consortium.

Multiple alternative approaches for patients with longer anticipated survival have been published, demonstrating potential benefit of dose escalation for patients with spinal cord compression and longer anticipated survival. In the RAMSES 01 phase II study, 22 patients were treated with dose-escalated intensity-modulated radiation therapy (IMRT) with either 15

× 2.633 Gy (41.6 Gy_{10}) or 18 × 2.33 Gy (43.2 Gy_{10}) and compared with a propensity-matched historical control group of 266 patients treated with 10 × 3 Gy.[41] The 15-fraction alternative was introduced during the COVID-19 pandemic. Spinal cord maximum dose was 101.5% of the prescription. The dose-escalated population had improved rates of local progression-free survival at 12 months compared with historical controls, a trend toward improved motor functions and similar overall survival and ambulatory rates. Two patients died during radiotherapy and, per protocol, were not included in the analysis. Twenty percent of patients had grade 2 toxicity and 4% had grade 3 toxicity (mostly diarrhea, esophagitis).[42]

The PRE-MODE trial examined 40 patients with spinal cord compression treated with 5 × 5 Gy (biologically effective dose [BED] equivalent to 10 × 3 Gy) using IMRT and compared them to propensity-matched historical controls treated with 5 × 4 Gy. Spinal cord maximum dose was kept to 101.5% of the prescription dose. The 6-month rate of local progression-free survival was 95.0% with improvement in local progression-free survival compared with the historical control. A total of 82.5% of patients were ambulatory after survival. Rates of motor function and overall survival were similar between the 5 × 5 Gy group and historical controls.[42]

SBRT is not usually offered in the setting of spinal cord compression given proximity of tumor to spinal cord and need to "underdose" the tumor to spare the spinal cord. However, a prospective study of 62 patients treated for 85 lesions with spinal cord compression and neurologic power scores of 4 or 5 showed improvement in neurologic function in 81% of patients. Patients were treated with doses ranging from 12 to 20 Gy in a single fraction and the maximum dose of the spinal cord was kept to 14 Gy. There was evidence of tumor regression with thecal sac patency improving from 55% to 76%.[43]

Stereotactic Body Radiation Therapy Versus Conventional Radiotherapy for Spine Metastases

Numerous prospective and retrospective single-arm studies suggest high rates of pain control and local control for patients treated with SBRT.[44] However, only three randomized studies have prospectively randomized patients to SBRT versus conventional palliative radiotherapy in the

management of patients with spine metastases. The SC.24 phase II/III study randomized 229 patients with spinal metastases who did not need surgical decompression to 24 Gy in two fractions SBRT versus 20 Gy in five fractions conventional palliative radiotherapy. Patients were included with SINS less than 12, Eastern Cooperative Oncology Group performance status 0-2, pain score more than 2 and 3, or fewer contiguous spinal segments. The primary endpoint showed improved complete pain response at 3 months (35% vs 14%) with persistence of improved pain control at 6 months. There was no difference in rates of compression fractures and no spinal cord toxicity through the course of the study.[45] Local control rates were higher with SBRT versus conventional palliative radiotherapy (2.8% vs 11.2% at 6 months, 6.1% vs 28.4% at 12 months, and 14.8% vs 35.6% at 24 months) and rates of reirradiation were higher at 1 year for conventional palliative radiotherapy (2.2% vs 15.8%).[46]

A phase II study randomized 55 patients to 24 Gy in 1 fraction SBRT versus 30 Gy in 10 fractions with the primary endpoint pain control at 3 months after radiotherapy. There was a trend toward improved pain control at 3 months and statistically significant improvement in pain control at 6 months and beyond. Compression fracture rates were 27% in the SBRT arm versus 5% in the conventional radiation arm.[47]

The NRG Oncology/RTOG 0631 study randomized 339 patients with painful spinal metastases to 16 to 18 Gy single-fraction stereotactic radiotherapy versus palliative radiotherapy of 8 Gy in a single fraction. Patients were not stratified by SINS. The primary endpoint of pain response at 3 months favored conventional external beam radiotherapy with 60.5% of patients achieving a pain response with cEBRT compared with 41.3% pain response with SRS. Performance status was the most significant factor influencing pain response. Compression fracture rates were 19.5% with SRS and 21.6% with cEBRT.[48]

A meta-analysis of these studies showed improved complete pain response with SBRT without improvement in overall response rates. There were no differences in overall survival or local progression according to the meta-analysis,[49] though the SC.24 study supplemental analysis showed improvement in local control and reirradiation for SBRT compared with cEBRT.[46]

There is no standardized response assessment for clinical evaluation of patients who have been treated with spine SBRT for spinal metastases. The Spine Response Assessment in Neuro-Oncology (SPINO) group has published two reports on the challenges in assessing clinical outcomes after treatment of spinal metastatic disease based on imaging, clinical outcomes, and patient-reported outcomes. Imaging responses can be difficult to interpret due to overlap between tumor and treatment effect signal on MRI. Pain relief can be difficult to assess—what is residual pain from tumor versus spinal stability? In this context, the first SPINO report evaluated the response outcomes used in various retrospective and prospective trials of spine SBRT.[50] The second report created recommendations for clinical evaluation of patients treated with SBRT for spinal metastases, both imaging and clinical responses[51] (Table 102.5).

TABLE 102.5 SPINO RESPONSE ASSESSMENT GUIDELINES FOR EVALUATION OF CLINICAL RESPONSE TO SPINE SBRT

Clinician-based measures	
Spinal stability	SINS
Epidural tumor extension	Bilsky grade
Neurologic assessment	AIS, MRC, 10-m walk test
Functional assessment	KPS, ECOG
Patient-reported outcomes	
Generic	EQ-5D or SF-36
Pain	BPI
Spine tumor specific	SOSGOQ or MDASI-SP

AIS, ASIA impairment scale; BPI, Brief Pain Inventory; ECOG, Eastern Cooperative Oncology Group; EQ-5D, EuroQol-5D; KPS, Karnofsky Performance Status; MDASI-SP, MD Anderson Symptom Inventory for spine tumors; MRC, Medical Research Council; SBRT, stereotactic body radiation therapy; SF-36, 36-Item Short Form Survey; SINS, Spinal Instability Neoplastic Score; SOSGOQ, Spine Oncology Study Group Outcomes Questionnaire; SPINO, Spine Response Assessment in Neuro-Oncology.

From Laufer I, Lo SS, Chang EL, et al. Population description and clinical response assessment for spinal metastases: part 2 of the SPIne response assessment in Neuro-Oncology (SPINO) group report. *Neuro Oncol*. 2018;20(9):1215-1224. Reproduced by permission of Society for Neuro-Oncology.

The American Society of Radiation Oncology (ASTRO) and the European Society of Radiation Oncology (ESTRO) have each published updated guidelines on the management of bone and spinal metastases. Based on the available data, ASTRO conditionally recommends surgery followed by radiotherapy for patients with spinal cord compression. ASTRO recommends 8 Gy in 1 fraction, 20 Gy in 5 fractions, 24 Gy in 6 fractions, or 30 Gy in 10 fractions for patients with spinal cord compression based on overall clinical status. ASTRO conditionally recommends 24 Gy in two fractions with SBRT rather than conventional palliative radiotherapy for patients with spinal metastases, no neurologic deficits, and who are eligible for SBRT, noting that other dose-fractionation schemes may be reasonable.[52]

ESTRO has published a systematic review and meta-analysis for patients treated with de novo spine SBRT. Sixty-nine studies demonstrated outcomes of 5,736 patients treated for 7,236 metastases with overall pain response rates of 83%, 1-year local control rate of 94%, but with high heterogeneity among studies. Pooled vertebral fracture rate was 9%, myelopathy rate was 0%, and pain flare rate was 6%, again with high heterogeneity among studies.[53]

Technical Considerations for Spine Stereotactic Body Radiation Therapy

The American Association of Physicists in Medicine (AAPM) has outlined safe practices for delivery of SBRT.[54] Specific technical expertise is required for safe delivery of stereotactic radiotherapy to the spine, including optimizing patient immobilization, definition of targets and organs at risk, managing patient setup, patient-specific quality assurance, and intrafraction motion. Consensus guidelines for contouring for spine SBRT have been published in the intact (Figure 102.3), postoperative (Figure 102.4), and sacrum SBRT settings (Figure 102.5).[55-57]

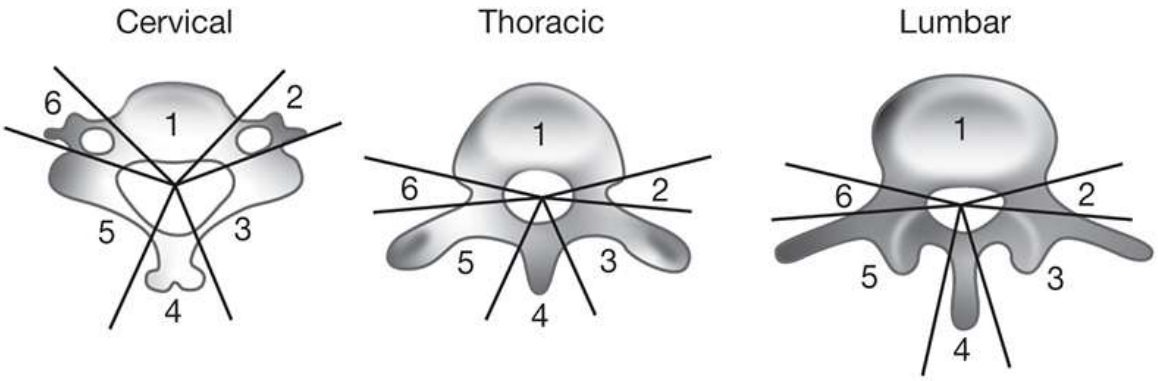
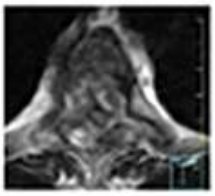
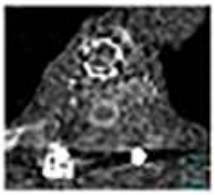
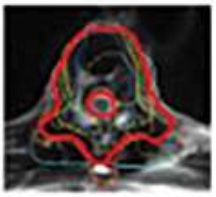
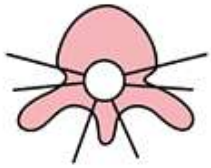
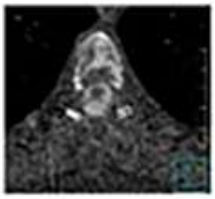
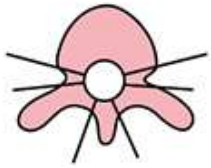
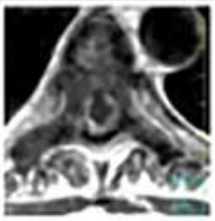
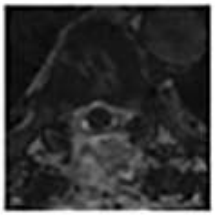
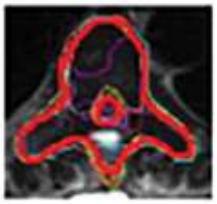
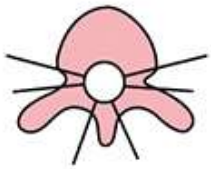
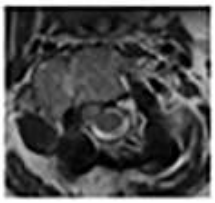
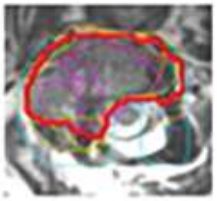
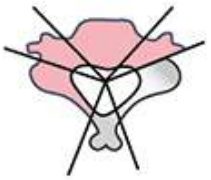
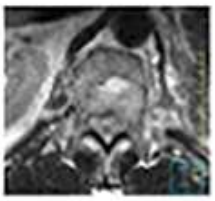
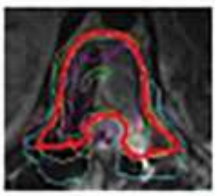
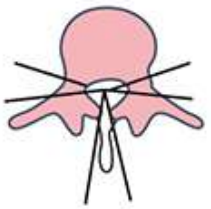
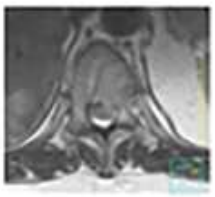
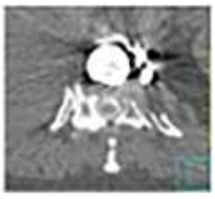
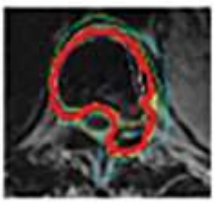
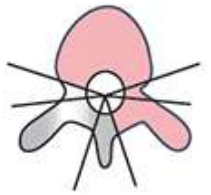


FIGURE 102.3 Consensus contouring guidelines demonstrate the need to cover adjacent spine segments. If a tumor is in a specific spinal segment, the immediately adjacent segment should be included in the target volume. (Reprinted from Cox BW, Spratt DE, Lovelock M, et al. International Spine Radiosurgery Consortium consensus guidelines for target volume definition in spinal stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys*. 2012;83[5]:e597-e605. Copyright © 2012 Elsevier. With permission.)

Level	Preop Axial MRI	Postop Axial CT Myelogram of T2MRI	MRI with Individual and Consensus CTV Contour	Schematic Diagram
T5				
T4				
T6				
C2				
L1				
T11				

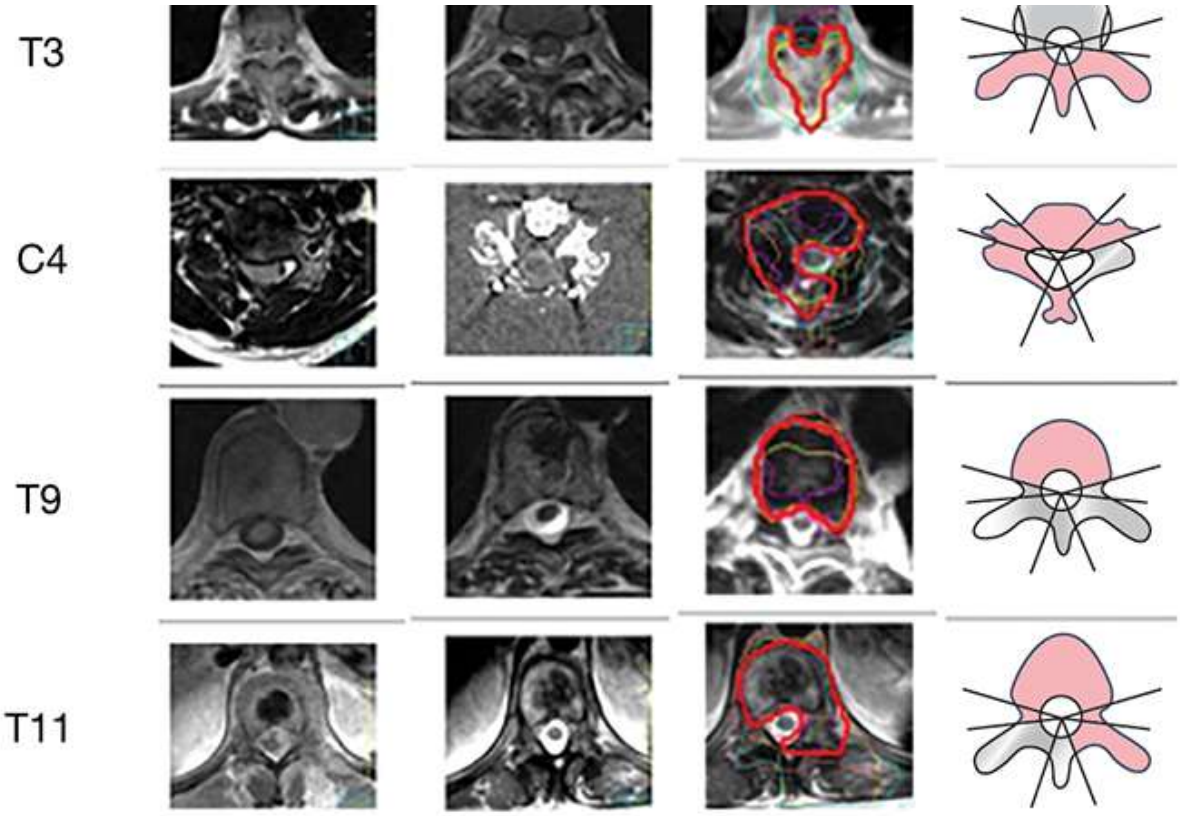


FIGURE 102.4 Consensus guidelines for contouring spine stereotactic body radiation therapy in the postoperative setting. CT, computed tomography; CTV, clinical target volume; MRI, magnetic resonance imaging. (Reprinted from Redmond KJ, Robertson S, Lo SS, et al. Consensus contouring guidelines for postoperative stereotactic body radiation therapy for metastatic solid tumor malignancies to the Spine. *Int J Radiat Oncol Biol Phys*. 2017;97[1]:64-74. Copyright © 2016 Elsevier. With permission.)

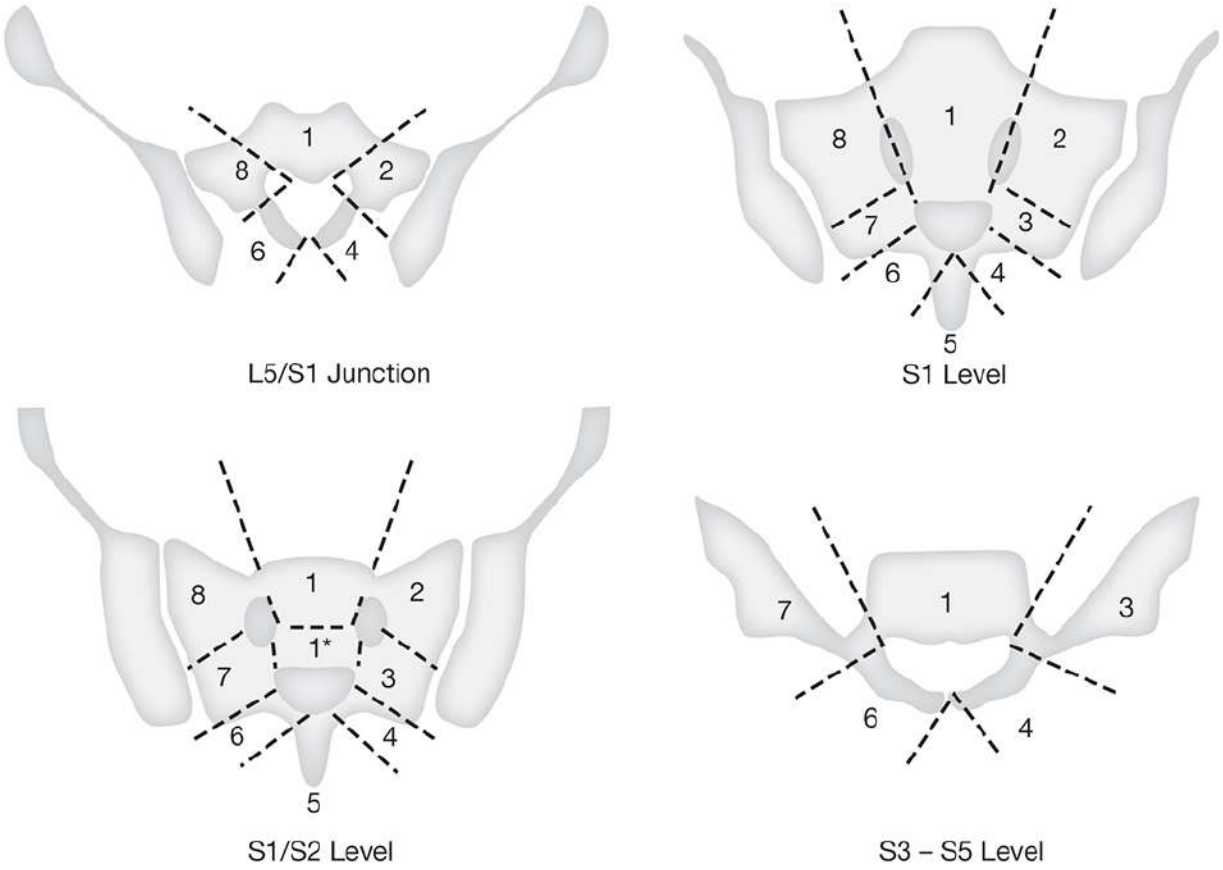


FIGURE 102.5 The consensus contouring guidelines for sacral SBRT demonstrate adjacent segments that should be covered when treating with SBRT to the sacrum. SBRT, stereotactic body radiation therapy. (Reprinted from Dunne EM, Sahgal A, Lo SS, et al. International consensus recommendations for target volume delineation specific to sacral metastases and spinal stereotactic body radiation therapy (SBRT). *Radiother Oncol*. 2020;145:21-29. Copyright © 2019 Elsevier. With permission.)

ESTRO guidelines further outline the specifics required for appropriate treatment with spine stereotactic radiotherapy. Essential to a spine SBRT program is collaboration between physicians, medical physicists, dosimetrists, radiation therapists, spine surgeons, neuroradiologists; use of adequate patient immobilization; MR simulation or fusion of a diagnostic MRI to evaluate target volumes and organs at risk including spinal cord and thecal sac; use of pretreatment imaging; and intrafraction patient analysis. Ideally, a six-degrees-of-freedom treatment couch should be utilized to account for pitch and role in patient daily setup.[58]

There are multiple references for tolerances of organs at risk in the management of patients undergoing spine SBRT. Mutually agreed upon

constraints should be established up-front prior to treatment planning; priority should be given to spinal cord/thecal sac constraints over tumor coverage to decrease the risk of myelopathy. The ASTRO guidelines have published sample single- and two-fraction constraints for patients undergoing spine SBRT (Table 102.6).

TABLE 102.6 SAMPLE CONSTRAINTS FROM THE ASTRO BONE METASTASIS GUIDELINES FOR ONE- AND TWO-FRACTION SPINE SBRT

	1 Fraction			
Organs at Risk	**Volume**	**Volume Max (cGy)**	**2 Fractions**	**Endpoint**
Spinal cord[a]	≤0.35 mL ≤10% of partial spinal cord ≤0.03 mL	1,000 1,000 1,400	N/R	Myelopathy
Spinal cord PRV/thecal sac	N/R		Max point dose ≤1,700 cGy	Myelopathy
Cauda equina	<0.03 mL ,5 mL	1,600 1,400	Max point dose ≤1,700 cGy	Neuropathy
Sacral plexus	<0.03 mL ,5 mL	1,800 1,440	Max point dose ≤2,600 cGy	Plexopathy
Esophagus[b]	<0.03 mL ,5 mL	1,600 1,190	Max point dose ≤2,000 cGy	Stenosis/fistula
Ipsilateral brachial plexus	<0.93 mL ,3 mL	1,750 1,400	N/R	Plexopathy
Heart/pericardium	<0.03 mL ,15 mL	2,200 1,600	N/R	Pericarditis
Great vessels[b]	<0.03 mL 10 mL	3,700 3,100	N/R	Aneurysm
Trachea[b] and larynx	<0.03 mL ,4 mL	2,020 1,050	Max point dose ≤2,000 cGy Larynx: Mean ≤900 cGy	Stenosis/fistula
Skin	<0.03 mL ,10 mL	2,600 2,300	N/R	Ulceration

	1 Fraction			
Organs at Risk	Volume	Volume Max (cGy)	2 Fractions	Endpoint
Stomach	<0.03 mL ,10 mL	1,600 1,120	Max point dose ≤2,000 cGy	Ulceration/fistula
Duodenum[b]	<0.03 mL ,5 mL	1,600 1,120	Max point dose ≤2,000 cGy	Ulceration
Jejunum/ileum[b]	<0.03 mL ,5 mL	1,540 1,190	Max point dose ≤2,000 cGy	Enteritis/obstruction
Colon[b]	<0.03 mL ,20 mL	1,840 1,430	Max point dose ≤2,000 cGy	Colitis/fistula
Rectum[b]	<0.03 mL ,20 mL	1,840 1,430	Max point dose ≤2,000 cGy	Proctitis/fistula
Renal hilum/vascular trunk	<2/3	1,060	N/R	Malignant hypertension
Lungs (right and left)	Spare 1,000 mL	740	V10 <10%, V5 <35%, and V20 <3% and a mean dose of ≤500 cGy for each lung	Pneumonitis
Renal cortex (right and left)	Spare 200 mL	840	Max point dose ≤2,600 cGy Mean dose for each kidney ≤600 cGy	Basic renal function
Liver	N/R		Max point dose ≤2,600 cGy Mean dose ≤800 cGy	Liver dysfunction
Pharynx	N/R		Max point dose ≤2,000 cGy Mean ≤900 cGy	Stenosis/fistula
Parotids	N/R		Mean dose ≤700 cGy for each parotid	Xerostomia

ASTRO, American Society of Radiation Oncology; Max, maximum; N/R, not reported; PRV, planning organ at risk volume; SBRT, stereotactic body radiation therapy.

[a]The partial spinal cord should be contoured starting from 5 to 6 mm above the superior extent of the target volume to 5 to 6 mm below the inferior.

[b]Avoid circumferential irradiation.

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Pediatric Spinal Cord Compression

MSCC in the pediatric population differs from adult MSCC. Histologic subtypes commonly encountered in children (eg, neuroblastoma, Wilms tumor, and Ewing sarcoma) rarely occur in adults. In adults, most cases of MSCC are caused by direct invasion into the epidural space by metastatic vertebral body tumors, although, in children, most are caused by direct neural foraminal invasion, causing the characteristic "dumbbell" tumor. Chemotherapy plays a central role in the treatment of pediatric MSCC.[59]

Neuroblastoma is the most common histology of pediatric MSCC. Hayes et al[60] (nine cases of neuroblastoma and five cases of Ewing sarcoma) and Sanderson et al[61] (four cases of neuroblastoma) demonstrated that chemotherapy alone allowed complete recovery of spinal cord function in all cases. The French Society of Pediatric Oncology protocol NBL-90 included 42 nonmetastatic neuroblastoma patients with intraspinal extension and consequent MSCC.[62] All were treated with initial chemotherapy, and this resulted in intraspinal tumor shrinkage, avoidance of surgery, and neurologic deficit improvement in 58%, 60%, and 92% of the patients, respectively. Severe neurologic sequelae occurred in only six patients (15%).

Emergent surgery should be offered to any pediatric patient with rapid neurologic progression at initial presentation or while on chemotherapy. In most circumstances, this should be followed by definitive chemotherapy. In stable or mildly symptomatic patients, chemotherapy can obviate the need for surgery, which is often associated with long-term skeletal deformities. Radiation should be reserved only for those who require palliation for progressive disease after failure of multiple systemic regimens, those who progress neurologically despite the initial treatment with chemotherapy or surgery, and those who present with primary vertebral tumors (eg, primary vertebral Ewing sarcoma) in which definitive surgery is rarely feasible.

Intramedullary Spinal Cord Metastasis

Intramedullary spinal cord metastasis (ISCM) is rare, representing only 1% of all intramedullary tumors but being more greatly recognized as an entity given enhanced radiographic techniques. According to a review by Kalayci et al,[63] ISCM is most commonly secondary to a lung primary (54%), followed by breast cancer (11%). Although back pain is common in more than 90% of patients with MSCC, back or neck pain was seen in only 38% of patients with ISCM. However, high sensory deficits (79%), sphincter dysfunction (60%), and weakness (91%) are more common in ISCM. The most striking difference between ISCM and MSCC is the high incidence of synchronous brain metastasis (41%) in patients presenting with ISCM. This is not surprising when one considers the route of spread and the high incidence of lung primaries in patients with ISCM. An MRI of the brain should be obtained.

The treatment of ISCM should be approached very similarly to MSCC, except for the role of surgery. Most surgeons are reluctant to operate in ISCM because surgery carries a high morbidity rate. Corticosteroids as well as radiation therapy should be promptly initiated. Unfortunately, a diagnosis of ISCM portends a poor prognosis, with median survival of 1 to 5.5 months.[64]

Reirradiation

As patients with metastatic cancer live longer, more patients are developing symptomatic progression in previously irradiated fields. Similar algorithms for patient management to de novo radiotherapy are applicable, but special attention must be paid to spinal cord tolerance. Patients should be evaluated for prognosis, spine stability, degree of spinal cord compression, and prior dose of radiotherapy to the spinal canal.

A phase III randomized trial of patients requiring reirradiation for bone metastases included randomization for patients with spinal metastases to 8 Gy in one fraction or 20 Gy in eight fractions reirradiation. About 45% (single fraction) versus 51% (multifraction) of patients who underwent repeat irradiation had pain response, including patients with spine and non-spine bone metastases.[65] Thus, for patients with short anticipated survival, reirradiation with 8 Gy in one fraction or 20 Gy in eight fractions is reasonable for palliation of pain in patients with spinal metastases.

A retrospective review of patients receiving reirradiation who developed and did not develop radiation myelopathy was conducted to evaluate spinal cord tolerance to reirradiation. The authors used BED calculations with an α/β ratio of 2 and found that the risk of myelopathy is low (<3%) if the following factors are utilized: time between radiotherapy courses more than 6 months, cumulative effective dose to spinal canal less than 135.5 Gy (BED2), and neither course to spinal exceeding 98 Gy (BED2).[66]

Patients who have better anticipated survival may be candidates for SBRT in the reirradiation setting. No randomized comparisons of conventional palliative reirradiation versus SBRT have been conducted, but if a patient has a good anticipated survival, it is reasonable to consider dose escalation with SBRT. One retrospective study analyzed 60 patients treated with 24 Gy in three fractions versus 25 to 30 Gy in five fractions depending on tumor proximity to spinal cord. A total of 65% of patients had at least some pain relief and 93% of patients had stable disease at 9 months.[67] Thecal sac constraints have been evaluated in the spine SBRT reirradiation setting and are listed in Table 102.7.

TABLE 102.7 ASTRO BONE METASTASES GUIDELINE SUGGESTED THECAL SAC CONSTRAINTS FROM AN ANALYSIS OF SPINE SBRT REIRRADIATION

Prior Radiation Details		SBRT Reirradiation Dose Recommendations		
Prior Spinal Cord Total Dose	**Prior EQD2-2**	**Planned Number of Fractions**	**Acceptable Range of Reirradiation Total Dose**	**Recommended Thecal Sac Constraint (Dmax)**
2,000 cGy/5 fx-3,000 cGy/10 fx	3,000-3,750 cGy	1	1,600-1,800 cGy	900 cGy
4,000 cGy/20 fx-5,000 cGy/25 fx	4,000-5,000 cGy	1	Not recommended	Not recommended
2,000 cGy/5 fx-4,500 cGy/25 fx	3,000-43,000 cGy	2	1,600-2,400 cGy	1,220 cGy
5,000 cGy/25 fx	5,000 cGy	2	1,600-2,000 cGy	1,100 cGy
2,000 cGy/5 fx-4,500	3,000-4,300	3	1,800-2,700 cGy	1,450 cGy

Prior Radiation Details		SBRT Reirradiation Dose Recommendations		
Prior Spinal Cord Total Dose	Prior EQD2-2	Planned Number of Fractions	Acceptable Range of Reirradiation Total Dose	Recommended Thecal Sac Constraint (Dmax)
cGy/25 fx	cGy			
5,000 cGy/25 fx	5,000 cGy	3	1,500-2,400 cGy	1,250 cGy
2,000 cGy/5 fx-4,500 cGy/25 fx	3,000-4,300 cGy	4	2,400-3,600 cGy	1,620 cGy
5,000 cGy/25 fx	5,000 cGy	4	2,000-2,600 cGy	1,400 cGy
2,000 cGy/5-4,500/25 fx	3,000-4,300 cGy	5	2,500-3,000 cGy	1,800 cGy
5,000 cGy/25 fx	5,000 cGy	5	2,000-2,500 cGy	1,550 cGy

ASTRO, American Society of Radiation Oncology; Dmax, maximum point dose to an organ or tumor target; EQD2-2, dose calculation to an equivalent dose of 2 Gy with α-to-β ratio of 2; SBRT, stereotactic body radiation therapy.

Adapted from Sahgal A, Chang JH, Ma L, et al. Spinal cord dose tolerance to stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys*. 2021;110(1):124-136. Copyright © 2021 Elsevier. With permission.

CONCLUSION

Metastases to the spine require special care and consideration given the possibility of significant morbidity including loss of function from spinal cord compression. Prognostic algorithms should be utilized to assess anticipated overall survival and neurologic outcomes for patients with spinal metastases with promise from machine learning algorithms to help predict survival. The degree of epidural spinal cord compression and spine stability can be utilized in conjunction with the NOMS framework. Prognostic models should be used to assess likelihood of overall survival and neurologic outcomes. Surgical decompression should be considered for patients with an unstable spine or for patients with spinal cord compression and neurologic deficits. Dexamethasone should be utilized for patients with neurologic deficits and can help with pain control. Conventional palliative

radiotherapy with doses of 8 Gy in 1 fraction, 20 Gy in 5 fractions, 24 Gy in 6 fractions, and 30 Gy in 10 fractions can be utilized for pain control and to improve neurologic function. SBRT, particularly 24 Gy in two fractions, has shown improved complete pain responses compared to 20 Gy in five fractions. Care must be taken when using spine SBRT to ensure adequate patient setup, reproducibility, and adequate patient-specific quality assurance. In the reirradiation setting, conventional palliative radiotherapy can be utilized for pain control with respect to spinal cord tolerance. BED2 should be limited to 135.5 Gy_2 cumulative, 98 Gy_2 with each course and at least 6 months between courses. SBRT reirradiation should be considered for patients with recurrent/progressive spinal metastases with a good prognosis.

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CHAPTER 103

Palliation of Bone Metastases

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BACKGROUND AND INCIDENCE

Metastatic disease to the bone is a common cause of pain and other significant symptoms that are detrimental to quality of life. The exact incidence of bone metastases is difficult to determine, but estimates are that >100,000 people in the United States will develop osseous metastatic disease annually, with a prevalence of more than 300,000 patients living with bone metastases.[1-3] The incidence of bone metastases varies significantly, depending on the primary site, with prostate, lung, renal, and breast cancers having the highest incidence.[4] Bone metastases may be found in up to 85% of patients dying from breast, prostate, or lung cancer. Other primary sites with a propensity for bone metastases include thyroid, melanoma, and kidney. On the other hand, primary gastrointestinal malignancy gives rise to bone metastasis in only 3% to 24% of patients with metastatic disease.[5,6] Some hematologic malignancies, including myeloma and lymphoma, can also cause significant pain and bone destruction.

The ultimate prognosis for patients with bone metastases is poor, with a median survival typically measured in months rather than years, although there may have been some changes in the recent past that will change these timelines. Overall survival depends on the primary site and the presence or absence of visceral metastases. Patients with bone metastases from lung cancer have short median survival durations of 6 months. However, patients with bone metastases from breast or prostate cancer may have significantly longer survival times. In patients with bone-only metastatic prostate or breast cancer, median survivals of 2 to 4 years have been reported.[7-9] Whether the survival time is only a few months or extends to multiple years, these patients will often require active treatment because of pain, difficulty with ambulation and immobility, hypercalcemia, pathologic fractures, neurologic deficits, anxiety, depression, spinal cord or nerve root compression, fatigue, insomnia or sleep disturbances, and general deterioration of quality of life.[5,10,11]

The axial skeleton is the most common site of bone metastasis, with metastasis most frequently occurring in the spine, pelvis, and ribs. The lumbar spine is the most frequent site of bone metastasis.[12-15] In the appendicular skeleton, the proximal femurs are the most common site of metastatic disease. The acral sites (feet and hands) are rarely involved. Certain skeletal sites are associated with specific types of metastatic cancer. For example, scapular metastases are seen more frequently from renal primaries.[16] Involvement of the skull is more common with breast primaries. The distal appendicular skeleton (tibia, fibula) and acral sites (especially the hands) are more common with lung primaries, and involvement of the toes is seen more commonly with genitourinary primaries.

The most common symptom of bone metastases is progressive pain that is well localized. Pain from the femur or acetabulum may worsen with weight bearing or ambulation. In contrast, pain from the inferior ischium or sacrum may be worse with sitting but less bothersome with ambulation. Although the pain is frequently localized, pain may radiate to other areas. This is most frequently seen with pain in the lower back, pelvis, or hips that may radiate down the legs. Pain that radiates does not necessarily indicate nerve impingement because radicular pain can also be caused by spasm of muscles that originate or insert near the area of disease (eg, pain in the hip radiating to the knee).

Bone metastases can present a risk to health and quality of life even if they do not initially present with symptoms. Locally destructive bone metastases can increase the risk of bone fracture. Fracture of certain bones can lead to significant sequelae and potentially shorten a patient's survival. Treatment of these

lesions, either with prophylactic surgical repair or prophylactic palliative radiation therapy (RT) can improve a patient functional status, improve patient mobility, and potentially improve overall survival.[17,18]

The concept of "oligometastases" was proposed by Hellman and Weichselbaum[19] in 1995. In brief, it describes how the clinical outcomes of patients with a small burden of metastatic disease may differ from the patients with a higher volume of metastatic disease. It then follows that these patients may benefit from different treatment paradigms. In these cases, the goals of treating with a limited number and low burden of bone metastases may shift away from the palliation of pain to improving cancer control.[20-23]

PATHOPHYSIOLOGY

There are primarily three types of cells within mature bone: osteocytes, osteoblasts, and osteoclasts. Osteoblasts originate from osteogenic cells, found in the periosteum or endosteum. The osteogenic cells differentiate into osteoblasts when there is a mechanical or chemical stimulus for remodeling or repair. The osteoblasts build bone by depositing collagen type I into the extracellular space. An inorganic complex of calcium and phosphate (hydroxyapatite) is laid down within this organic matrix to provide the strength and density of the bone. The osteoblasts then mature into osteocytes, which maintain the bone structure. Osteoclasts are multinucleated giant cells that originate from pluripotent hematopoietic bone marrow cells and adhere to the bone surface.[24] These cells create an acidophilic environment that causes dissolution of the hydroxyapatite crystals and proteolysis of the bone matrix.

The differentiation and activation of osteoclasts occur because of the effects of a group of proteins that are related to tumor necrosis factor, including osteoprotegerin, receptor activator of nuclear factor-κB (RANK), and the RANK ligand (RANKL). Osteoblasts, stromal cells, and activated T cells express and release RANKL. The RANKL binds to the RANK receptor on osteoclast precursors, which then induces the formation of mature osteoclasts. The destruction of bone by osteolytic metastases is mediated by the osteoclasts, not by the tumor cells. However, the factors that activate the osteoclasts are likely produced by the tumor cells, including RANKL, interleukin-1, interleukin-6, parathyroid hormone–related peptide, transforming growth factor β (TGF-β), and macrophage inflammatory protein 1α.[25-27]

Normal bone is constantly being remodeled in a cycle lasting about 120 to 200 days (3-6 months). For the first 20 to 40 days of the cycle, the bone is resorbed by osteoclasts. The bone is then rebuilt by osteoblasts during the next 100 to 150 days.[28]

The structure of the bone changes during growth and development. At the time of birth, all bones are immature, woven bone. Woven bone is more cellular, with no organized orientation to the collagen fibers of the bone. As bones age, the woven bone is absorbed and is replaced by lamellar bone. The lamellar bone is organized circumferentially around neurovascular canals. This cylindrical structure provides much more strength than the haphazard orientation of woven bone. Most adult bone is lamellar.

Adult bone has three distinct layers: cortical, cancellous, and bone marrow. The cortical bone is the dense, compact exterior portion of the bone. This portion of the bone comprises most of the mass and strength of the skeleton. Internal to the cortical bone is the porous, haphazard network of bone tissue known as cancellous bone, which is also known as trabecular or spongy bone. Inside the porous cancellous bone is the bone marrow. There are two different types of bone marrow, red marrow and yellow marrow. Red marrow produces red blood cells, white blood cells, and platelets. Red marrow is highly vascular. Yellow marrow produces fat, cartilage, and bone. Yellow marrow is scantly vascular. At birth, all marrow is red marrow, but as bone ages, red marrow is slowly replaced by yellow marrow.

In the adult body, there are five different types of bone: long, short, flat, sesamoid, and irregular bone. Long bones consist of the epiphyses, metaphyses, and a diaphysis. The diaphysis is the long shaft of the bone, consisting of a hard cortical exterior encapsulating a central cavity consisting of cancellous bone and bone marrow, known as the medullary cavity. The epiphyses are at the ends of the bone. These are composed of hyaline cartilage initially, which becomes ossified during puberty. The metaphysis is the area between the epiphysis and the diaphysis. Most of the bones of the limbs are made of long bones. Short bones are cuboid in shape and make up the bones of the wrist and ankle. Flat bones are thin and

curved bones. They make up the skull and sternum. Sesamoid bones are found suspended in tendons, such as the patella. Irregular bones are oddly shaped bones that contain a thin layer of cortical tissue surrounding an interior of active cancellous and bone marrow. The majority of the axial skeleton, including the spine and pelvis, is made up of irregular bones.

Metastases to the bone most often occur in the red marrow, which is found in highest concentration in the skull, irregular bones of the axial skeleton, and the medullary portion of the appendicular skeleton. This most often occurs by hematogenous spread but may occur by direct extension as well. Involvement of adjacent bone by direct extension (eg, mandibular involvement from an oral cavity cancer) does not necessarily imply that there is a higher likelihood of distant bone metastases and that its management is very different from that of bone metastases from hematogenous spread.

The relatively high proportion of hematogenous metastasis to bone compared with other sites in the body cannot simply be explained by blood flow, which is >30 times greater in the lung than in red bone marrow.[29] The predilection of certain tumor sites to metastasize to bone may be related to local growth factors in the bone, such as TGF-β, insulin-like growth factors I and II, fibroblastic growth factors, platelet-derived growth factors, preferential adherence to endothelial surfaces in certain bones by cell adhesion molecules, or chemotactic attraction from bone cells by osteocalcin or type I collagen.[5,24,30]

Bone metastases are often described as either osteolytic or osteoblastic. However, these are different representations of abnormalities in the normal bone remodeling process. Breast and lung cancers more commonly cause osteolytic-appearing lesions. Prostate and thyroid cancers more often have osteoblastic-appearing lesions. Only myeloma is associated with purely osteolytic lesions.[24] Most other tumors have a combination of osteolytic and osteoblastic components.

The mechanism of pain from bone metastases is not clearly understood. Possible mechanisms include mechanical instability, irritation of periosteal stretch receptors, tumor-directed osteoclast-mediated osteolysis, tumor cells themselves, tumor-induced nerve injury, production of nerve growth factor, or stimulation of other cytokine receptors.[2,7,31,32] Because the mechanisms of pain may be multifactorial, a combination of therapies may be superior to any one therapy alone.[31]

EVALUATION

The most common symptom associated with bone metastasis is pain. Therefore, the physical examination is an important step in evaluating a patient with bone metastases. The physical examination may help make decisions regarding appropriate subsequent imaging studies. Firm palpation will often elicit the specific area of pain, with “point tenderness” often pointing directly to the affected area in the bone. It is important to carefully evaluate the entire skeletal system with examination because intense pain at one site often masks subjective reports of pain at other sites. A careful physical examination may reveal hidden pain in other locations. A thorough neurologic examination is also important, especially in patients with spinal metastases, to carefully evaluate for the possibility of spinal cord, cauda equina, or nerve root compression.

Technetium-99m (Tc-99m) bone scintigraphy (nuclear medicine bone scan) is the best method for screening patients at risk for bone metastasis who may not present with bone pain. It is also useful to evaluate the extent of metastatic disease in the bone (Figure 103.1). Bone scintigraphy is an indicator of osteoblastic activity. Because multiple myeloma is frequently purely osteolytic, bone scans are less useful for evaluating the extent of disease in myeloma. Bone scintigraphy is not specific for metastatic disease, and positive findings must often be confirmed using other imaging studies. A confirmatory study is especially important in a weight-bearing bone, such as the proximal femur. False-positive readings may be seen in areas of arthritis, trauma, prior fractures, or Paget disease. In addition, the osteoblastic activity in healing bone after treatment may give the appearance of progressive disease. False-negative readings may occur in fast-growing, highly aggressive tumors, especially if these are mainly osteolytic.

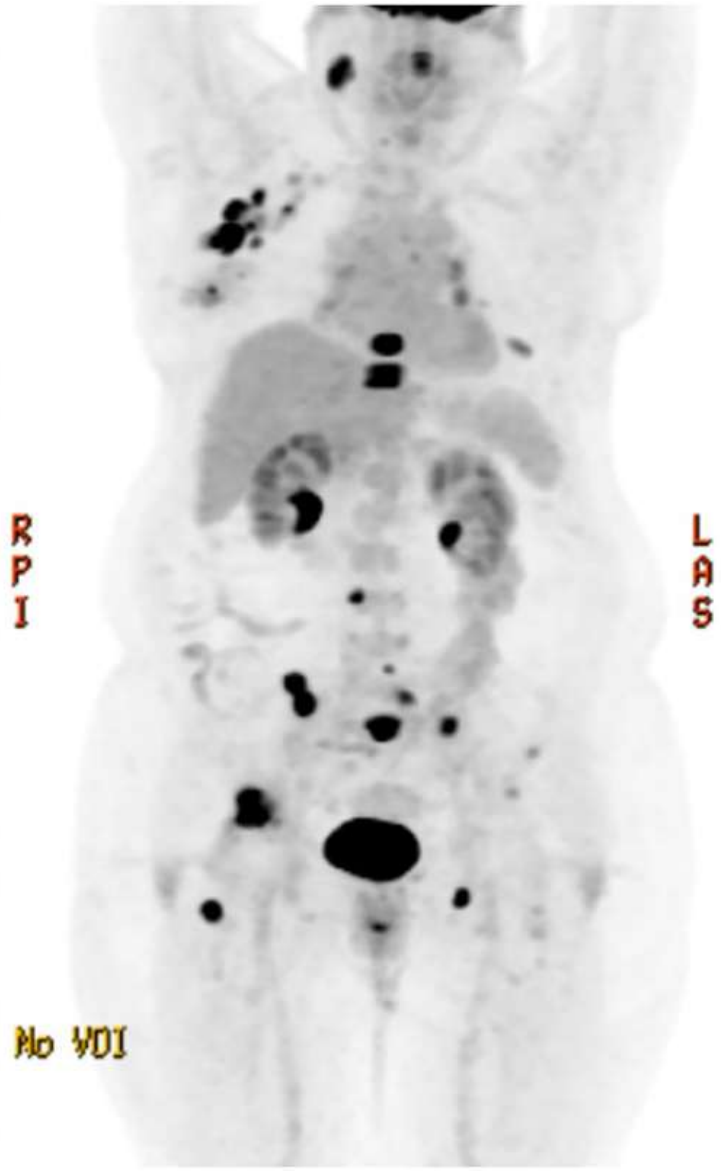
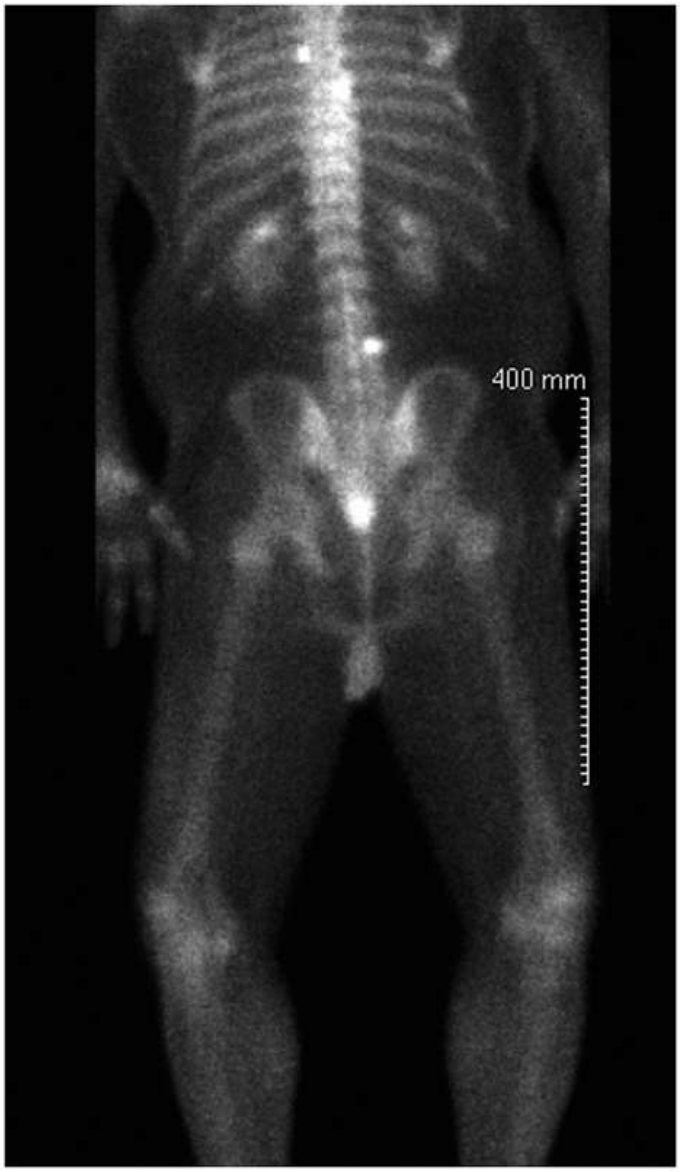


FIGURE 103.1 Nuclear medicine bone scan from a woman with metastatic breast cancer. The bone scan shows the abnormality in multiple osseous sites, as well as in the right breast and axilla.

For symptomatic patients with point tenderness or for patients with an abnormal bone scan, plain radiographs are typically the most appropriate first or next imaging study.[33] Radiographs are easy to obtain and inexpensive. The appearance of bone metastases on x-rays varies depending on the primary site and histology, with some appearing osteolytic and some osteoblastic. However, nearly all bone metastases have components of both osteolytic and osteoblastic processes. The primary disadvantage of plain radiographs is that small lesions are rarely seen. Approximately 30% to 50% of the bone mineral content must be lost before the lesion will be apparent on x-rays.

Computed tomography (CT) scans are more sensitive than plain radiographs and may be better able to localize the lesion within the bone. However, CT scans are more expensive and more time-consuming and may not be useful as a screening tool for skeletal metastasis. The CT may be useful in defining the extent of cortical destruction and helping to assess the risk of a pathologic fracture.[34] In addition, the CT scan may be used to guide needle biopsies to obtain a tissue diagnosis (Figure 103.2A, B). CT scans have

limited usefulness in detecting marrow involvement but are much better than plain radiographs at evaluating soft tissue extension of disease.



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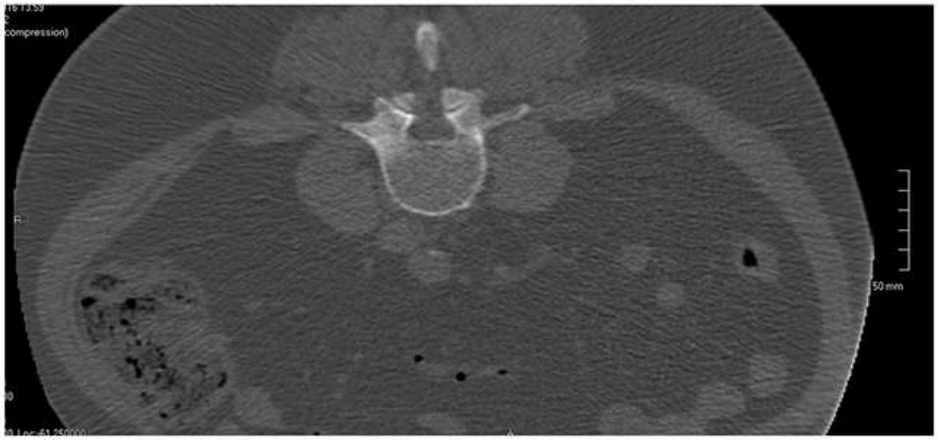

B

C

FIGURE 103.2 Images from a patient with metastatic prostate cancer. Nuclear medicine bone scan (A) shows uptake in the right pedicle of L4, seen as an osteoblastic lesion on axial computed tomography (B). This biopsy confirmed metastatic prostate cancer. The bone scan does not demonstrate the lesion in the L2 vertebral body, which is demonstrated on the sagittal (C) and axial (D) magnetic resonance images.

Magnetic resonance imaging (MRI) is better than plain radiography or nuclear medicine bone scintigraphy at assessing the involvement of trabecular bone and bone marrow, especially in the vertebral bodies (Figure 103.2C, D). The findings are typically best seen on T1 contrast-enhanced images and short-tau inversion recovery (STIR) images. Metastatic prostate cancer is visible as high-intensity lesions on the STIR images and is visible prior to its appearance on bone scintigraphy.[35] In addition, MRI scans are useful in determining the involvement of neurovascular structures. MRI scans are not useful as a screening tool for bone metastases because of the high cost and lengthy time of the examination. However, MRI scans may be more sensitive than bone scintigraphy in the vertebral body region. The sensitivity of MRI scanning has been reported as 91% to 100%, compared with 62% to 85% for bone scintigraphy.[35,36] In addition, MRI can help distinguish whether a vertebral body compression fracture is from malignancy or osteoporosis.

Positron emission tomography (PET) scanning evaluates areas of increased metabolic activity, most commonly using the 18-fluorodeoxyglucose (FDG) isotope. These scans are useful in detecting highly metabolic osteolytic bone metastases but are less sensitive for the less metabolically active osteoblastic metastases. In addition, precise determination of the location of lesions is difficult with PET scans, but the use of simultaneous CT scans allows for much better localization of the abnormal FDG uptake.[37] PET scans may be useful as a whole-body screening tool.[37,38] Comparative studies have shown PET scans to

be more sensitive than Tc-99m scintigraphy or whole-body MRI scans in detecting bone metastases.[39,40] There may be limitations in the sensitivity of PET scanning in certain areas such as the skull, where the intense physiologic metabolic uptake from the adjacent brain parenchyma may obscure small skull metastases. 18-FDG-PET scans have been used for many epithelial tumor types, but less frequently for prostate cancers. There are multiple new PET scan isotopes, which may be more sensitive and more specific for metastatic prostate cancer, including ^{18}F-NaF, ^{11}C-choline, ^{11}C-acetate, and ^{18}F-fluciclovine.[41] Cancer-specific PET scans, such as prostate-specific membrane antigen (PSMA) and Axumin PET scans for prostate cancer and Dotatate PET scans for neuroendocrine tumors, can identify bone metastases from these primaries with improved sensitivity and specificity.[42,43] These novel PET tracers have begun to be incorporated into randomized trials with encouraging results for the improvement of target delineation and patient outcomes.[22,44]

PAIN MANAGEMENT

The majority of patients with bone metastases will experience pain during their disease course. Controlling pain for a patient with cancer can significantly improve their quality of life. Pain management may be achieved either by debulking disease using cytotoxic therapy, modifying the bone/tumor microenvironment, or by symptomatic control with pharmacologic interventions.

Despite increasing understanding about the effective treatment of pain, patients with pain from bone metastases frequently have inadequate pain management. Barriers to pain treatment include physician underestimation of the patient's pain as well as reluctance by the patient to report the true level of pain.[45] In addition, concerns about opioid abuse and dependence may lead to undertreatment of cancer pain, either or both by the patient or by the physician. There is a significant discrepancy between the physician's estimate of pain and the pain level reported by the patient.[46] The use of a validated pain scale, such as the Brief Pain Inventory, gives the patient an opportunity to describe both the severity of pain and the interference it has with daily functioning in a manner that can be understood by both the patient and the physician.[45] This also allows for distinguishable comparisons of pain levels over time, to better assess the effectiveness of treatments.

Pain control can be achieved in the majority of patients using the World Health Organization analgesic ladder. Step I uses nonopioid analgesics, such as acetaminophen or nonsteroidal anti-inflammatory drugs; step II uses weak opioids, such as codeine; and step III uses strong opioids, such as morphine or oxycodone. These medications are increased as necessary until the patient is free of pain. Typically, the medications are given on a schedule ("by the clock") rather than waiting until a certain level of pain is reached ("on demand"). Using a scheduled approach, 70% to 76% of patients will have good pain relief.[47,48] Alternative, nonopioid medications such as gabapentin, pregabalin, or amitriptyline may be used for neuropathic pain. Antianxiety or antidepressant medications may also be of benefit in selected patients.

The opioid-based pain medications frequently cause constipation and may cause nausea. Patients using opioid medications should routinely be administered a fiber supplementation with or without a stool softener or osmotic laxative to minimize constipation. Other side effects of the opioid analgesics may include sedation, mental status changes, and mood changes.

SURGICAL MANAGEMENT

Surgical management of bone metastases is performed primarily to prevent or treat pathologic fractures. The goals of surgical intervention are to prevent or relieve pain, improve motor function, and improve overall quality of life. Treatment techniques are simpler and more effective when the procedure is performed prophylactically for an impending fracture rather than after the occurrence of a pathologic fracture. The risk of pathologic fracture depends on multiple factors, including the location and extent of the lesion; whether the lesion is osteolytic, osteoblastic, or mixed; and the primary cancer site.

Fractures of the weight-bearing bones are the most likely to cause significant functional deficits. The proximal femur may have a higher propensity for fracture than other sites, but some authors have suggested that the fracture risk in upper limbs is similar to the risk in the femur. Whether there is a difference in the risk of fracture, the peritrochanteric femur is the site most likely to cause serious morbidity, and therefore, the threshold for prophylactic intervention should be relatively low. The femur accounts for 65% of pathologic fractures requiring surgical intervention.[49] The humerus and vertebral bodies are also sites that require special attention because of the potential functional deficits from pathologic fractures.

The size of the bone metastasis is an important predictor of risk of fracture, especially with regard to the extent of cortical destruction. Various models have been used to predict the risk of pathologic fracture based on the size of the lesion. In series using plain radiographs, lesions ≥2.5 cm in the cortex of the femur were significantly more likely to fracture.[50] The proportion of cortical destruction is important as well. The risk of pathologic fracture of the femur begins to significantly increase when there is destruction of >50% of the cortex; the risk of fracture is 80% when >75% of the cortex is destroyed.[51] Femoral lesions with axial cortical destruction >30 mm had a 23% risk of pathologic fracture, compared with 3% risk of fracture for cortical destruction ≤30 mm.[52] The location within the bone is important as well. An experimental model has shown that the greatest reduction in strength of the femur occurs with lesions in the inferior and medial aspects of the femoral neck, and posterior lesions have the least impact (Figure 103.3).[53]

A

FIGURE 103.3 Anteroposterior (A) and oblique (B) radiographs of the right femur in a patient with metastatic breast cancer. Note the significant destruction of the posterior cortex from the proximal to mid-diaphysis of the femur, in a "moth-eaten" appearance.

A scoring system proposed by Mirels[54] has a 12-point scale based on the location of the lesion, pain, extent of cortical destruction, and radiographic appearance (Table 103.1). The risk of fracture is 15% for a score of 8 and 33% for a score of 9. He proposed that prophylactic fixation is indicated for a score of ≥9.

TABLE 103.1 MIRELS SCORING SYSTEM OF PREDICTION OF PATHOLOGIC FRACTURE RISK

Score	Pain	Location	Cortical Destruction	Radiographic Appearance
1	Mild	Upper limb	<1/3	Blastic
2	Moderate	Lower limb	1/3-2/3	Mixed
3	Severe	Peritrochanteric	>2/3	Lytic

A score is assigned for each of the four categories, and the sum of those scores is used to estimate the risk of pathologic fracture.
Adapted with permission from Mirels H. Metastatic disease in long bones: a proposed scoring system for diagnosing impending pathologic fractures. *Clin Orthop Relat Res*. 1989;(249):256-264.

The decision to proceed with surgery should be based on a number of factors, which include, but are not limited to, the estimated risk of pathologic fracture and overall life expectancy. For patients with a very limited life expectancy, surgery may not be indicated even if the risk of pathologic fracture is relatively high.[49] An approach utilizing clinical assessment, patient, and cancer-specific parameters, along with evidence-based prognostic models can be used to aid in identifying which patients are best served for surgical resection versus less or noninvasive approaches.[55-58]

Femoral fractures are the most common site of surgical correction. Fractures of the femoral neck can be managed by either total hip arthroplasty (which replaces both the femoral head and the acetabulum) or a proximal femoral endoprosthesis alone.[49] Fractures of the intertrochanteric area may be managed by open reduction and internal fixation without the use of a prosthesis. This may allow for better long-term gait because of the preservation of the hip flexor and adductor strength.[49] Lytic disease that extends below the intertrochanteric area is treated with a long intramedullary rod that provides stability throughout the length of the femur. If there is significant destruction of the greater trochanter and femoral neck or head in addition to subtrochanteric involvement, a prosthetic replacement would be more appropriate than a reconstruction nail.[59] Fractures of the distal femur may be managed either with a plate and compression screw or with an intracondylar nail and screws augmented by intramedullary methyl methacrylate cement. The latter method may reduce the risk of late failure of the repair, especially in patients receiving postoperative RT.[49]

Repair of pathologic fractures of the humerus may be more problematic because of the small intramedullary canal and because of the proximity of the radial nerve, which may require extensive dissection.[49] Pathologic fractures of the proximal humerus will frequently require prosthetic replacement.[49] Fractures in the diaphysis may be repaired with a compression plate and screws. An alternative is to use a segmental diaphyseal replacement prosthetic device, which involves a prosthetic device that can be cemented into an allograft.[59] Supracondylar fractures are difficult to manage because the shape of the bone is not conducive to a plate and screws; these lesions may require intramedullary rods inserted in a retrograde manner through both the medial and lateral condyles, supplemented by intramedullary cement.[49]

Most pathologic fractures of the pelvis do not require surgical intervention, except for those involving the acetabulum.[49] Repair of acetabular fractures may involve the use of a total hip acetabular prosthesis, but more extensive lesions may require reconstruction that transfers the load-bearing stresses into more structurally intact bone in the iliac bone or sacroiliac joint.[49]

Surgical intervention for bone metastasis typically does not address the underlying oncologic issue that initially put the patient at risk for fracture. If the underlying cancer is not addressed, there is a risk of worse functional outcomes as well as fixation failure. One study from the University of Kansas found that patients who received adjuvant RT to the site of surgical fixation were found to have improved function status and lower rates of repeat surgical interventions at the site, as well as longer overall survival, as compared to patients who received surgery alone.[17]

INTERVENTIONAL TECHNIQUES

Vertebroplasty is an effective method of palliating pain from vertebral body metastases, even in patients who have received prior RT.[60] Most patients experience pain relief within 48 hours. The procedure involves percutaneous injection of methyl methacrylate under CT or fluoroscopic guidance. Retropulsion of bone, epidural tumor, and collapse of the bone to less than one-third of its original height are relative contraindications to percutaneous vertebroplasty because of the risk of extrusion of the cement into the spinal canal, potentially causing neurologic complications. In some patients with epidural tumor,

percutaneous vertebroplasty can be performed safely and effectively with a relatively low risk of serious complications.[61,62] However, the procedure should be considered with some caution; in a systematic review of 987 patients, there were 5 deaths and 19 other serious complications.[63]

Kyphoplasty involves the percutaneous placement of a balloon-like device into a symptomatic spinal metastasis (most commonly into a fractured or compressed vertebral body).[64] The balloon is then inflated to restore the height of the vertebral body, and methyl methacrylate is subsequently injected into this cavity. This procedure may provide significant relief of pain and improve overall functioning, especially in patients with mechanical instability of the vertebral body.[65,66] Kyphoplasty may be a better option than vertebroplasty in patients with vertebral wall deficiency.[65]

An ablative procedure is frequently coupled with vertebroplasty or kyphoplasty.[67] Radiofrequency ablation (RFA) may be used to ablate the tumor but is most effective for tumors that are osteolytic or mixed osteolytic and osteoblastic. The RFA may not be as effective in tumors that are primarily sclerotic. Cryoablation may be used for larger lesions or those that are sclerotic. For both of these procedures, special attention to cord and nerve temperatures is required to minimize the risk of complications.

These interventional procedures are often paired with RT to ensure that the underlying malignancy is addressed. An evidence-based review of the literature leads to ASTRO guidelines noting that, "… vertebroplasty and kyphoplasty for the treatment or prevention of cancer related symptoms does not obviate the need for EBRT in appropriate patients."[68]

SYSTEMIC TREATMENT

The rationale for using systemic therapy in the management of bone metastasis is compelling. The pathophysiology of bone metastasis involves hematogenous dissemination, and most patients with bone metastasis suffer from multiple synchronous sites of disease. In theory, administering systemic cytotoxic therapy should deliver palliative benefit by simultaneously addressing all sites of bone metastasis. A localized therapy such as external beam radiation may be most appropriate for palliation if symptoms are localized. On the other hand, systemic chemotherapy may offer palliative benefit if symptoms are diffuse or constitutional and the disease is widespread. The chemotherapy drugs are frequently given with bisphosphonates and corticosteroids, which may affect the response rates.

Measurement of response to systemic therapy has generally been with the same criteria used for solid metastatic tumors: a measurable radiographic change. This works well for lung and liver metastasis, but not as well for bone metastasis. For bone metastases, the definition of a complete response is complete disappearance of all lesions on radiographs for at least 4 weeks. This is unlikely to occur even if all tumor cells are eradicated. A partial response requires some recalcification of lytic lesions, which may not be evident for 6 months or more.[69] PET scans may be more accurate at assessing response in a timely manner but are too expensive to be used as a routine follow-up evaluation for bone metastases. Response to therapy for other modalities (ie, RT, bisphosphonates) is measured in terms of pain relief and quality-of-life measures. Unfortunately, there is not much literature on accurate and reliable response criteria to palliative systemic therapy for bone metastasis. Most of the studies of chemotherapy for metastatic disease involve patients with visceral as well as osseous metastases. The responses in terms of pain are typically reported for all patients, not just those with bone metastases, so pure bone metastatic pain is difficult to ascertain.

Tannock et al[70] recommended using more relevant end points of palliation. They performed a randomized trial of mitoxantrone plus prednisone versus prednisone alone for patients with hormone-refractory prostate cancer and pain. Improvement in pain was seen in 29% of patients receiving the chemotherapy, compared with 12% of those who received prednisone alone. In a subsequent study, they compared mitoxantrone and prednisone plus or minus clodronate for a similar group of patients. Most had mild pain at study entry (160/209; 77%), and the remainder had moderate pain scores. The patients with moderate pain who received chemotherapy and clodronate had a 58% response rate (≥2-point improvement in pain score) compared with 26% for those who received chemotherapy alone. The median

duration of pain response was 6 months. The TAX327 phase III trial was conducted in 1,006 men with hormone-resistant metastatic prostate cancer and randomized patients to receive prednisone combined with either docetaxel or mitoxantrone. The docetaxel arm showed an improvement in overall survival, lower cancer-induced bone pain, and better objective tumor response.[71]

In patients with bone metastasis, there is seldom reason to combine chemotherapy with concurrent RT because of the potential for increased toxicity when both modalities are delivered concurrently.

A number of hormonal therapies are available in the management of metastatic prostate and breast cancer. In properly selected patients, hormonal therapy has the potential for providing excellent palliation of metastatic disease with limited morbidity. In 1984, the Medical Research Council started a prospective, randomized trial in which 938 patients who either had asymptomatic metastatic prostate cancer or were not medical candidates for definitive therapy were randomized to immediate versus delayed hormone ablation therapy. Hormone ablation was achieved using either a luteinizing hormone–releasing hormone agonist or orchiectomy. This study showed that immediate versus delayed initiation of hormone ablation therapy in the subset of patients with metastatic prostate cancer helped to prevent serious complications from metastatic disease. Serious complications including pathologic fracture, spinal cord compression, development of extraskeletal metastases, and ureteral obstruction were 2-fold more frequent in patients whose hormonal therapy was deferred compared with patients who received immediate hormone ablation therapy.[72]

Osteoclast inhibitors are also often used in conjunction with other systemic treatments. The bisphosphonates are pyrophosphate analogs that bind to calcium phosphate with high affinity and are potent agents affecting bone resorption through osteoclast inhibition.[73] The nitrogen-containing bisphosphonates inhibit the key enzyme farnesyl diphosphate synthase in the mevalonate pathway.[74] This prevents the action of several additional enzymes required for bone resorption. The bisphosphonates include pamidronate, alendronate, ibandronate, risedronate, and zoledronic acid. Zoledronic acid is much more potent than the other bisphosphonates, in part because it also inhibits tumor cell adhesion to the extracellular matrix. There is evidence that the bisphosphonates also induce apoptosis in cancer cells.[75]

The initial studies of bisphosphonate usage were primarily in women with metastatic breast cancer. Pamidronate was evaluated in multiple randomized, prospective studies of women with osteolytic bone metastases from breast cancer. The Aredia Breast Cancer Study Group Protocols 18 and 19 enrolled women receiving either chemotherapy (P19) or hormonal therapy (P18). In the P18 study, 372 women were randomized to receive either placebo or pamidronate.[76] The primary end point was the prevention of "skeletal-related complications" (pathologic fractures, spinal cord compression, hypercalcemia, or the requirement for surgery or RT on bone). There were fewer skeletal-related complications in the pamidronate arm, but the benefit in reducing pathologic fractures and hypercalcemia was not significant until 18 to 24 months of treatment. The primary difference was that twice as many placebo patients required RT for palliation of pain, most often in the first 6 to 12 months. There was no difference in survival, although pain levels and serum markers of bone resorption were significantly lower in the group receiving pamidronate. In the P19 study, women with stage IV breast cancer who were receiving chemotherapy and had lytic bone metastasis were given placebo or pamidronate for 12 monthly cycles.[77] Patients in the pamidronate arm suffered fewer overall skeletal complications and had a greater median time to first skeletal complication when compared with patients in the placebo arm of the study. Women treated with pamidronate maintained better performance status and had less bone pain secondary to metastasis.

Rosen et al[78] evaluated 773 patients with bone metastases from solid tumors, including lung cancer, renal cell carcinoma, head and neck cancers, thyroid, and other primary sites (excluding breast and prostate cancer). They compared placebo with zoledronic acid in doses of either 4 or 8 mg given every 3 weeks for 9 months. The primary end point was the proportion of patients developing a skeletal-related event (SRE), including pathologic fracture, spinal cord compression, or the need for surgery or RT. The proportion of patients developing an SRE was 44% in the placebo group compared with 38% in the 4-mg

zoledronic acid group (P = .127) and 35% in the 8-mg group (P = .023). The time to the development of an SRE was significantly longer with zoledronic acid compared with placebo (230 vs 163 days; P = .017).

The Medical Research Council PRO4 and PRO5 were two prospective, randomized trials conducted to evaluate sodium clodronate in men with prostate cancer. Long-term data showed that sodium clodronate improved overall survival in men with metastatic prostate cancer who were starting hormone therapy, but there was no improvement in overall survival for men with nonmetastatic disease.[79]

Complications of supportive therapy with bisphosphonates include osteoradionecrosis (particularly of the jaw) and renal insufficiency.[80] The mechanism of bisphosphonate-induced osteoradionecrosis is not known. Risk factors include the intravenous use of pamidronate and zoledronic acid, duration of treatment of 36 months or longer, older age in patients with multiple myeloma, and need for periodontal procedures.[81] Bisphosphonates are not metabolized by the body and are excreted by the kidneys. Bisphosphonate therapy can lead to renal toxicity. The incidence of renal toxicity is 9% to 15% in trials when 4 mg of zoledronic acid is delivered intravenously for 15 minutes.[80] Moreover, the rate of renal toxicity depends on underlying renal disease, dose of bisphosphonate used, and duration of the infusion.

Another form of systemic therapy is the use of agents that target the RANK pathway. Denosumab is a human monoclonal antibody specific for the RANKL. The antibody binds to RANKL and thus inhibits the formation, activation, maturation, and survival of osteoclasts.[82] In randomized, prospective comparisons of denosumab with zoledronic acid in patients with metastatic breast or prostate cancer, denosumab was superior to zoledronic acid in delaying or preventing the time to SREs.[83,84]

RADIATION THERAPY

RT has been reported to be effective in palliating painful bone metastases, with partial pain relief seen in 60% to 90% of patients and complete pain relief in 30% to 50% of patients. These data are primarily from meta-analyses of studies using physician evaluation of pain. When patient evaluation of pain is used, pain improvement is seen in 60% to 80% of patients and complete pain relief is seen in 15% to 40% of patients.[85] The response to treatment depends on a large number of factors, including sex, primary site and histology, performance status, type of lesion (osteolytic vs osteoblastic), location of the metastases, weight-bearing versus non–weight-bearing site, extent of disease, number of painful sites, marital status, and level of pain prior to treatment. The effectiveness of the treatment also depends on the goal: palliation of pain, prevention of pathologic fracture, avoidance of future treatments, or local control of the disease. The doses required and volumes treated may be quite different for each of these goals. In addition to pain relief, other symptoms may also be relieved by RT. Patients who have improvement in pain after RT may also have improvement in emotional functioning, decreased insomnia, decreased constipation, and overall improvement in quality-of-life scores.[86] RT should be an integral part of palliative treatment for bone metastases to treat pain and prevent other symptoms.[68]

Local-field external beam RT is typically used for palliation of a few discrete areas of painful metastases (Figure 103.4). The first large randomized study evaluating different dose and fractionation schemes was the Radiation Therapy Oncology Group (RTOG) 74-02 trial.[87] Patients with solitary bone metastases were randomized to 40.5 Gy in 15 fractions versus 20 Gy in 5 fractions. Patients with multiple painful metastases were allocated to one of four treatment schedules: 30 Gy in 10 fractions, 15 Gy in 5 fractions, 20 Gy in 5 fractions, or 25 Gy in 5 fractions. The initial analysis by Tong et al[87] in 1982 showed no statistically significant difference in response rates between any of the treatment arms, with complete responses in 49% to 61% of patients. These results were questioned by Blitzer,[88] who reanalyzed the data using different criteria for complete response, which excluded patients who received repeat treatment, and defined complete response as no pain and no analgesic usage. With this adjustment in response definition, there was a significant difference in response favoring the longer treatment courses: 40.5 Gy in 15 fractions for the solitary metastases and 30 Gy in 10 fractions for multiple metastases. This was offered as evidence that higher doses were necessary for optimal palliation, even though one of the

highest biologic doses for multiple fractions (25 Gy in five fractions) had one of the lower response rates. This reanalysis highlighted the importance of retreatment in this group of patients, especially in those given lower total doses during the initial course of RT.

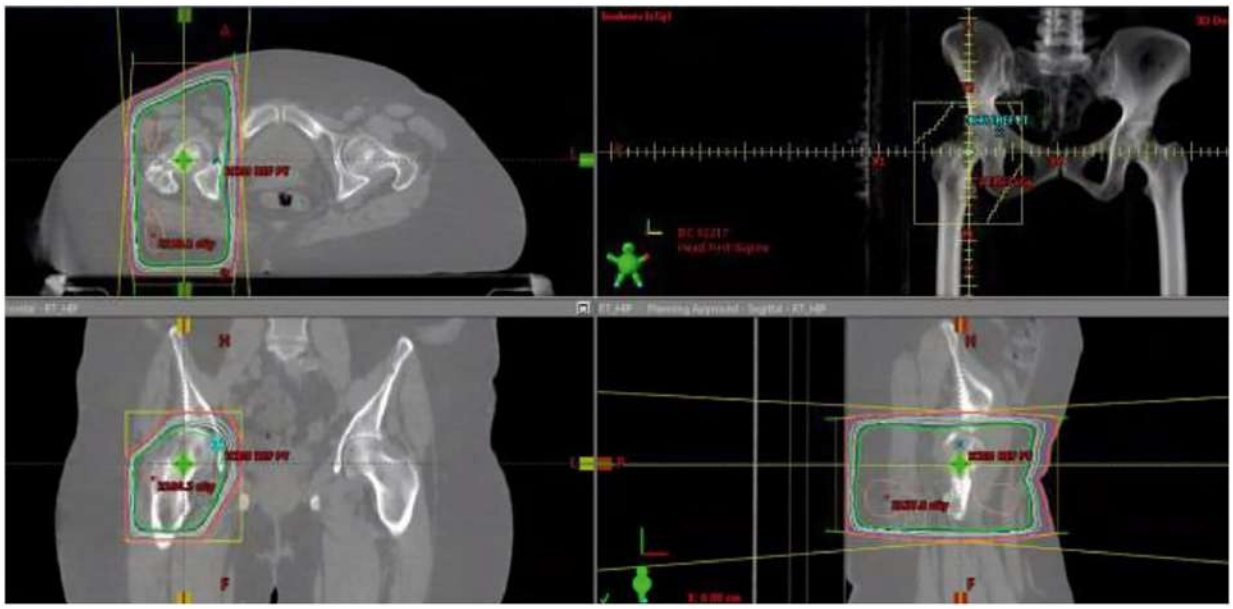

FIGURE 103.4 Isodose plan for a patient receiving radiation therapy to the right hip showing axial and coronal projections of the doses as well as a digitally reconstructed radiograph of the treatment fields.

There have been multiple randomized, prospective trials evaluating different dose and fractionation schemes.[87,89-101] Most of the earlier studies evaluated different multifraction treatment regimens (Table 103.2). No significant difference was seen between longer course treatments and the shorter duration, lower total dose treatment courses. Two randomized studies evaluated single doses of RT for palliation of bone metastases. Hoskin et al[102] randomized patients to 4 versus 8 Gy, and Jeremic et al[103] randomized patients to one of three dose levels, 4 versus 6 versus 8 Gy. In both of these studies, the 8-Gy arm was superior to 4 Gy, indicating that there is a threshold dose necessary to achieve adequate palliation. Most of the randomized trials during the past 15 years used a multiple-fraction treatment scheme as the control arm and a single dose of 8 to 10 Gy as the study arm (Tables 103.3 and 103.4).

TABLE 103.2 RANDOMIZED TRIALS WITH ≥100 EVALUABLE PATIENTS COMPARING MULTIPLE-FRACTION TREATMENTS FOR PALLIATION OF BONE METASTASES

Study	Number of Patients (Number Evaluable)	Dose (Gy)/Number of Fractions	Complete Response[a] (%)	Overall Response[a] (%)	Pathologic Fractures (%)
Tong et al,[87] 1982, the United States (solitary treatment site)	266 (146)	20/5 40/15	53 61	82 85	4 18
Tong et al,[87] 1982, the United States (multiple sites)	750 (613)	15/5 20/5 25/5 30/10	49 56 49 57	87 85 83 78	5 7 9 8
Hirokawa et al,[93] 1988, Japan	128 (128)	25/5 30/10	NA	75 75	NA
Rasmusson et al,[100] 1995,	217 (127)	15/3 30/10	NA	69 66	NA

Study	Number of Patients (Number Evaluable)	Dose (Gy)/Number of Fractions	Complete Response[a] (%)	Overall Response[a] (%)	Pathologic Fractures (%)
Denmark					
Niewald et al,[99] 1996, Germany	100 (100)	20/5 30/15	33 31	77 86	8 13

Number of patients entered on study and number of patients evaluable for response; dosage schedule; complete and overall responses; and proportion of patients with pathologic fractures after treatment.

NA, not available.

[a]Response rates listed are for pain relief.

TABLE 103.3 RANDOMIZED TRIALS OF SINGLE VERSUS MULTIPLE FRACTIONS WITH ≥100 EVALUABLE PATIENTS: DEMOGRAPHICS AND STUDY DESIGN

Study	Primary End Point	Secondary End Point(s)	Primary Site	Treatment Site	Response Evaluation Time[a]	Percentage Severe Pain Pretreatment[b]
Foro Arnalot et al,[90] 2008, Spain 160	Pain and relief analgesics	—	Breast 27%, lung 26%, prostate 25%, pelvis 39%, spine 36%, long bones 14%	—		50 (median pain score of 7)
Kaasa et al,[94] 2006, Norway/Sweden	376	Pain relief	Fatigue, quality of life	Prostate 38%, breast 30%, lung 11%, spine 38%, pelvis 35%, extremities 20%	—	35-41
Hartsell et al,[92] 2005, the United States/Canada	949 (898)	Pain relief	Analgesic use, toxicity, path, fracture rate, retreatment rate	Breast 50%, prostate 50%, C spine 5%, T spine 19%, L spine 27%	3 mo	72-73
Kirkbride et al,[95] 2000, Canada	398 (287)	Pain relief and analgesics	—	Breast 40%, lung 26%, prostate 23%, spine 30%, pelvis 29%	3 mo	—
Steenland et al,[101] 1999, the Netherlands	1,171 (1,073)	Pain relief	Quality of life	Breast 39%, lung, 25%, prostate 23%, TL spine 30%, pelvis 36%, femur 10%, ribs 8%, humerus 6%	During first year	Mean pain score: 6.3 (moderate)
Bone Pain Trial Working Party,[89] 1999, the United Kingdom/New Zealand	765	Pain relief	Nausea and vomiting	Breast 36%, prostate 34%, lung 12%, pelvis/hip 28%, L spine 20%, ribs 11%, T spine 9%, femur 6%	—	22-23
Koswig and Budach,[96] 1999, Germany	107	Pain relief	Recalcification	Breast 58%, lung 24%, prostate 10%, kidney	6 wk	—

Study	Primary End Point	Secondary End Point(s)	Primary Site	Treatment Site	Response Evaluation Time[a]	Percentage Severe Pain Pretreatment[b]
				7%, spine 81%, extremities 13%		
Nielsen et al,[98] 1998, Denmark	241 (239)	Pain relief	Quality of life, analgesic use	Breast 39%, prostate 34%, lung 13%, TL spine 42%, pelvis 21%, hips/femur 18%, other 19%	12 wk	—
Gaze et al,[91] 1997, the United Kingdom	265 (240)	Pain relief	Side effects, quality of life	Any epithelial tumor		

C, cervical; L, lumbar; NA, not available; T, thoracic.

[a]Time from study entry to assessment of response.

[b]Proportion of patients with severe pain scores at the time of study entry.

TABLE 103.4 RANDOMIZED TRIALS OF SINGLE VERSUS MULTIPLE FRACTIONS: RESULTS

Study	Number of patients (Number Evaluable)	Dose (Gy)/Fractions	Median Survival (mo)	Complete Response[a]	Overall Response[a]	Retreatment Rate (%)	Pathologic Fractures[b] (%)	Toxicity
Foro Arnalot et al,[90] 2008, Spain	160	8/1 vs 30/10	6.5 7.6	15 13	75 86	2 28	NA	12% 18%
Kaasa et al,[94] 2006, Norway/Sweden	376	8/1 vs 30/10	9.6 7.9	NA	No difference	16 4	4 11	NA
Hartsell et al,[92] 2005, the United States/Canada	949 (898)	8/1 vs 30/10	9.1 9.3	15 18	65 66	18 9	5 4	10% grade 2-4 17% *P* = .002
Kirkbride et al,[95] 2000, Canada	398 (287)	8/1 vs 20/5	NA	22 29	51 48	NA	NA	NA
Steenland et al,[101] 1999, Netherlands	1,171 (1,073)	8/1 vs 20/5	?	37 33	72 69	25 7	4 2	No difference
Bone Pain Trial Working Party,[89] 1999, the United Kingdom/New Zealand	761 (681)	8/1 vs 20/5[c]	NA	57 58	78 78	23 10	2 <1	No difference
Koswig and Budach,[96] 1999, Germany	107 (107)	8/1 vs 30/10	NA	33 31	81 78	NA	NA	NA
Nielsen et al,[98] 1998, Denmark	241 (239)	8/1 vs 20/5	NA	15 15	73 76	21 12	NA	No difference
Gaze et al,[91] 1997, the United Kingdom	265 (240)	10/1 vs 22.5/5	NA	37 47	81 76	NA	NA	21% *P* = NS 26% emesis

NA, not available; NS, not statistically significant.

[a]Proportion of patients with pathologic fractures after treatment.

[b]Response rates listed are for pain relief.

[c]A regimen of 30 Gy/10 was also allowed; 98% of patients received 20 Gy/5.

Two large studies compared single-dose treatment to longer courses of RT. The Dutch trial evaluated patients with bone metastases from solid tumors, primarily breast (39%), prostate (23%), and lung (25%); patients with metastatic melanoma and renal cell carcinomas were excluded.[101] The primary end point was patient-assessed pain relief, evaluated on an 11-point scale (0 = no pain, 10 = worst imaginable pain). A total of 1,171 patients were randomized to either 8 Gy in a single fraction or 24 Gy in six fractions. The painful areas had to be included in a single-treatment volume. The spine (36%) and pelvis (30%) were the two most common sites of treatment. The median pain score was 6.3, with a minimum score of 2. About half of the patients were receiving narcotic pain medications prior to randomization, and slightly more than half (53%) were receiving systemic therapy. The median survival after treatment was 30 weeks, with no difference between the two treatment groups. There was no difference in overall or complete response rates between the single-dose versus longer course treatment arms. Overall, 71% of patients achieved a response to therapy during follow-up, with 35% achieving a complete response. Most of the responses occurred within the first 4 to 6 weeks after treatment. Complete response rates were higher for patients with breast and prostate primaries than with lung or other primary sites (44% and 41% vs 21% and 16%).

There were two significant differences between the two treatment groups: retreatment rates and pathologic fracture rates. The rate of pathologic fracture in the treated area was 4% for the 8-Gy single-treatment arm compared with 2% for the 24 Gy/six fraction group. The median time to fracture was similar for the two groups at 21 and 17 weeks. Although there was a significant difference in pathologic fracture between the two groups, these rates are still relatively low. There was also a significant difference in retreatment rates between the two arms of the study, with a much higher likelihood of a second course of treatment in the single-treatment group. The group of patients receiving 24 Gy in six fractions initially was given a second course of treatment 7% of the time, whereas 25% of the 8-Gy single-fraction group was given retreatment. Retreatment occurred more commonly with lung/other tumors than with breast/prostate primaries. In addition, the retreatment was given at a lower pain score (median 6.8 for 8-Gy single-fraction compared with 7.5 for the multiple-fraction group) and at an earlier time (14 weeks after initial treatment compared with 23 weeks). This may indicate a greater willingness to reirradiate after a single dose of 8 Gy or more reluctance to give retreatment after a higher initial dose of RT.

The second large study of single-dose versus longer course treatment for palliation of bone metastases was RTOG study 9714, which was conducted in the United States and Canada.[92] This was limited to patients with painful bone metastases from breast or prostate primaries, with up to three painful sites allowed. Pain was evaluated using the Brief Pain Inventory, an 11-point scale. At the time of randomization, the patient was required to have a minimum pain score of 5 or a high narcotic pain medication requirement of the equivalent of >60 mg of morphine per day. More than 70% of the patients had severe pain at study entry (pain scores of 7-10). Patients were randomized to 8 Gy in a single fraction versus 30 Gy in 10 treatments. The median survival was 9.3 months. Overall toxicity rates were low, with fewer patients in the 8-Gy treatment group experiencing acute toxicity. There were no significant differences in complete (17%) and partial pain response rates (49%) between the two treatment groups. Complete pain and narcotic response (0 pain score and no narcotic pain medication use) were seen in 11%; these responses were all determined at the 3-month post-treatment evaluation. As in the Dutch trial, the rate of retreatment was higher in the 8-Gy treatment group, with 18% in that group receiving retreatment compared with 9% in the 30-Gy group. This disparity in the rate of retreatment occurred despite nearly identical rates of stable (26% vs 24%) or progressive pain scores (9% vs 10%) and similar rates of narcotic use between the two groups.

In contrast to the Dutch trial, there was no difference in the rate of pathologic fractures between the two groups (5% for 8 Gy vs 4% for 30 Gy). Further analysis of this study has shown that certain subgroups may benefit from the longer course of palliative RT. Konski et al[104] showed that although married men and both single and married women were more likely to receive retreatment after receiving 8 versus 30 Gy of palliative RT, there was no difference in retreatment rates among single men. The authors suggest that social support factors may significantly affect the ability of some patients to access repeat therapies for painful bone metastasis, especially as their health declines. Such subgroups of patients may benefit from the longer 10-fraction course of therapy.

These two large prospective, randomized trials comparing single-fraction to multiple-fraction palliative RT have similar results and help to clarify the role of palliative RT for bone metastases. The assessment of pain was performed by the patients rather than by physicians or other health care providers. The studies with the highest response rates generally used physician assessment of pain response. Even with patient assessment of response, the single-fraction treatment yields similar response rates to the longer course treatment. The patients in the Dutch trial were treated when their pain was in the moderate range, with only half on narcotic pain medications, compared with severe pain and high-dose narcotic pain medication for most of the patients entered on the RTOG trial. This may account for the higher rates of complete response on the Dutch trial. In the RTOG trial, the group of patients with a single area of pain or with moderate pain scores at the time of study entry had higher complete response rates. Thus, it appears that the outcome is much better if patients are treated with palliative RT earlier in the course of their bone metastases rather than waiting until pain is severe or narcotic pain medication requirements are significant. There was no difference in pain response whether the treated bone metastases were in the spine or in extremity sites. The rates of pathologic fracture after treatment are relatively low, but it is not clear whether higher doses provide greater protection from fractures. The rates of retreatment are significantly higher with the single-dose schedules, but there may be some physician bias partially accounting for this difference because the retreatment tends to be offered at an earlier time and at lower levels of pain following the single-dose treatment.

There have been multiple randomized, prospective trials in the past 40 years comparing shorter course, lower total dose treatment to the more “standard” longer course, higher dose treatment. Several conclusions are clear from these studies:

1. Single-dose treatments of 8 Gy provide similar pain relief to longer treatment regimens (30 Gy in 10 fractions or 20 to 24 Gy in five to eight treatments).
2. The retreatment rates are higher after short-course treatment by a factor of 2 to 3.
3. Response rates are lower when scored by the patient instead of by the treating physician.
4. Response rates are better when the initial pain scores are lower, that is, when the patients are treated for moderate pain rather than severe pain.
5. There is no consistent dose-response relationship for palliation of bone metastases.

The lack of a dose-response relationship suggests that the mechanism of initial pain relief is not a reduction in tumor burden but more likely a change in the local environment that has caused activation of bone resorption by osteoclasts.[2] This helps to explain the seeming paradox of similar pain improvement with single-dose treatment compared with higher total dose, longer course treatment. The treatment paradigm for bone metastases may be more analogous to treatments for certain benign conditions, such as prevention of heterotopic ossification or keloid formation. In those conditions, a single or few treatments are given to diminish the activation of osteoblasts or fibroblasts.

This mechanism of pain relief may also help to explain the higher rates of retreatment after single-dose 8-Gy treatment because there will be less cell kill with this dose compared with 30 Gy in 10 fractions. Thus, for patients with a longer lifespan, there is a greater opportunity for regrowth of the tumor, which may again affect the local milieu, causing osteoclast activation.

For patients with a poor performance status, difficulty making multiple trips for treatment, extensive nonosseous metastases, and/or a short life expectancy, the most appropriate treatment is a single fraction of 8 Gy. Even with a limited expectancy (<3 months), the majority of patients experience pain relief, and palliative RT should still be considered for those patients.[105,106] For patients with a longer life expectancy, bone-only metastases, and good performance status, a longer course of treatment (30 Gy in 10 fractions) may be more appropriate to minimize the risk of retreatment. For selected patients with a solitary bone metastasis ("oligometastasis"), an even higher dose of treatment may be indicated, although this must be tempered by potential weakening of surrounding normal bone.

The single large-fraction treatment may be more likely to cause a "flare" reaction, with a temporary increase in pain at the site of the metastases.[107] The risk of this side effect may be diminished by the use of anti-inflammatory medications, either corticosteroids or nonsteroidal anti-inflammatory medications. Although the risk of significant acute toxicity has been low in the randomized trials, another potential concern is the risk of nausea or emesis if a significant portion of the stomach is within the treatment field (eg, with a field covering the lower thoracic spine). It may be beneficial to give prophylactic antiemetics 1 to 2 hours before the treatment to minimize the possibility of this side effect.

For select patients who do not respond to the initial treatment course or for those with pain recurrence after an initial successful treatment, reirradiation to the painful metastatic sites can be administered.[108] Approximately 60% of retreated patients experienced an improvement of their pain, with 16% to 28% of patients experiencing a complete resolution of pain.[109] Patients also experienced an improved overall quality of life and decrease in pain associated functional limitations after retreatment of a painful bone metastasis.[110] A randomized, controlled, noninferiority study compared single-dose treatment to longer courses of RT for the retreatment of previously irradiated painful metastatic bone cancer. Four hundred and twenty-five patients were randomized to receive either 20 Gy over multiple fractions or 8 Gy over one fraction. The single-fraction course was found to be noninferior to the multiple-fraction course and resulted in a lower frequency of acute toxicity. There was no difference in pathologic fracture or spinal cord compression between these two groups.[108]

STEREOTACTIC RADIOSURGERY OR STEREOTACTIC BODY RADIATION THERAPY FOR BONE METASTASES

Stereotactic radiosurgery (SRS) has been evaluated for the treatment of bone metastasis, particularly in the spinal region. Indications for the use of SRS in treating vertebral body metastases vary, but the use of SRS is often considered in cases of pain, reirradiation, and ablation of oligometastatic or oligoprogressive disease.

A prospective, nonrandomized cohort study conducted at the University of Pittsburgh in 500 cases of spinal metastasis treated with single-fraction radiosurgery to a maximum intratumor dose of 12.5 to 25 Gy demonstrated long-term pain level improvement in 86% of cases. Long-term tumor control was demonstrated in 90% of cases when radiosurgery was used as the primary treatment modality.[111]

The RTOG 0631 is a phase II/III study evaluating the role of SRS for patients with spine metastasis. Patients on this trial were randomized to either single-fraction external beam radiation to 8 Gy or to single-fraction image-guided SRS to 16 Gy. The primary end point of this study was assessment of pain control at the treated site(s). The phase II portion of this study demonstrated the feasibility and accurate use of SRS to treat spinal metastases.[112] The primary end point of the phase III portion of the study compared the pain relief at the treated site(s) and improvement in quality of life between the two groups. The results demonstrated no difference in pain control at 3 months due to the lower pain control rate at 3 months.[113]

Another prospective phase 3 randomized trial compared 24 Gy in 1 fraction to 9 Gy × 3 stereotactic body radiation therapy (SBRT) to evaluate local control of oligometastatic disease.[114] One hundred and seventeen patients with 154 oligometastatic lesions (osseous or lymph node metastases) were randomized between the two groups with a median follow-up of 52 months. The cumulative incidence of local

recurrence for 24 Gy × 1 was 2.7% and that for 9 Gy × 3 was 9.1%. No differences in toxicity were observed, with the authors concluding the 24 Gy × 1 to be a superior ablative treatment.

In another regimen, Sahgal et al[115] compared 24 Gy in two fractions using SBRT compared to 20 Gy in five fractions using standard techniques. In the randomized controlled phase II/III trial, 229 patients with spinal metastases were treated with a median follow-up of 6.7 months. At 3 months, 35% of patients in the SBRT group versus 14% of patients in the conventional group had a complete response to pain (P = .0002). The SBRT dose was shown to be superior in improving the complete response to pain, and the authors suggested the dose-escalated RT to be appropriate in the palliative setting for symptom control.

In a prospective randomized phase II trial by Nguyen et al,[116] 160 patients with mostly non–spine bone metastases were randomized to receive single-fraction SBRT (12 Gy for lesions ≥4 cm and 16 Gy for lesions <4 cm) versus standard palliative RT (30 Gy in 10 fractions). SBRT resulted in a higher proportion of patients experiencing complete or partial pain response at 3 months (73% vs 49%, P = .04). The results of this trial suggest that SBRT should be considered for patients expected to have a relatively long survival.

There have been multiple contouring guidelines published for the use of SBRT in spinal metastases. The International Spine Radiosurgery Consortium developed guidelines for target volume delineation in the intact setting based on the extent of disease.[117] In the postoperative setting, Redmond et al[118] created consensus guidelines for common scenarios.

RADIATION, BONE PROTECTION, AND OSSEOUS REPAIR

External beam radiation has become standard of care for pain relief of symptomatic bone metastases, but it has been shown to impart benefits in select asymptomatic patient. One multicenter randomized trial by Gillespie et al[18] assigned patients to receive prophylactic RT to asymptomatic high-risk bone metastases and compared outcomes to patients receiving standard care. The primary outcome was SREs. In this trial, 78 patients with 122 high-risk bone metastases were enrolled with different primary malignancies. At 1 year, SREs occurred in 1.6% in the RT arm versus 29% in the standard care of arm (P < .001). In the RT arm, the results demonstrated significantly fewer hospitalized patients. At 2.5 years median follow-up, the RT arm also demonstrated a significant increase in overall survival.

The use of bisphosphonates with external beam RT may further improve the outcome in terms of bone repair and pain relief. A prospective trial by Vassiliou et al[119] evaluated 45 patients who received both external beam irradiation and monthly ibandronate for painful bone metastases from solid tumors. All of the patients had improvement in pain, with 57% complete responses and 43% partial responses when using the same response criteria as RTOG 9714. The average pain score decreased from 6.3 to 0.8, and opioid pain medication use decreased from 84% of the patients before treatment to 24% after treatment. Bone density in the area of the metastases increased by 73% by 10 months after treatment. A similar study using pamidronate and 30 Gy of external beam RT in women with painful bone metastases from breast cancer found that 88% of patients had complete radiographic response by International Union Against Cancer criteria.[120]

The majority of patients with osseous metastases have multiple lesions. Although focal RT is effective at palliating pain in a few sites, it cannot be used to treat widespread disease. Two techniques have been used to treat more diffuse metastases: hemibody irradiation and intravenous radiopharmaceuticals. Hemibody irradiation was used before there were effective targeted radiopharmaceuticals but is used much less commonly now. Systemic agents capable of treating the entire skeletal system, such as radiopharmaceuticals, may be a better option in treating patients with a high burden of osseous metastatic disease.

Radiopharmaceuticals

The concept of radiopharmaceutical treatment is compelling.[121] Calcium (and to a lesser extent phosphorous) analogs will preferentially accumulate in bone, especially in areas of active bone turnover. A radioactive isotope that is a β-emitter or low-energy γ source will allow localized treatment in the areas in which the radiopharmaceutical accumulates, thus minimizing side effects and giving an excellent therapeutic ratio. The radiopharmaceuticals are given in a single injection that is easily administered. The treatment can be combined with other modalities, including chemotherapy or external beam RT.

The first radiopharmaceutical used for the treatment of bone metastases was phosphorous-32 (P-32). Treatment with P-32 for diffuse bone metastases was successful in giving subjective pain relief but with unacceptable bone marrow toxicity. Other radioisotopes have been used for the palliation of diffuse osseous metastases with a better therapeutic ratio than P-32. Strontium-89 (Sr-89) is chemically similar to calcium and is deposited in the bone matrix, preferentially in sites of active osteogenesis. Sr-89 is a pure β-emitter with an energy of 1.4 MeV and a half-life of 50.6 days.[122] Samarium-153 (Sm-153) is primarily a β-emitter but also has a component of γ-emission, which is useful for imaging purposes. The Sm-153 ethylenediamine tetra-methylenephosphonic acid is concentrated in areas of high bone turnover, accumulating in areas of hydroxyapatite. The physical half-life of Sr-153 is 46.3 hours, but the biologic half-life is much shorter because about half of the compound is excreted in the urine within 8 hours of injection.[123] These isotopes accumulate in areas of osteoblastic activity, especially in areas of increased uptake on bone scintigraphy; for this reason, most of the patients entered on prospective trials have metastatic prostate cancer. Sr-89 and Sm-153 are used infrequently now and are becoming more difficult to obtain. There are multiple new radiopharmaceutical agents being investigated for the treatment of metastatic disease, which are increasingly better targeted, such as radium-223 (Ra-223) and lutetium-177 PSMA.

Radium-223

Ra-223 dichloride is a pharmaceutical that emits α-particles and selectivity targets bone metastases. The ALSYMPCA trial was a phase III, prospective randomized study of men with castrate-resistant prostate cancer with bone metastases. Patients were randomized to receive six injections every 4 weeks of either Ra-223 or placebo. The randomization was 2:1, with 614 patients receiving Ra-223 and 307 patients receiving placebo. The primary end point of the study was survival, which was significantly greater in the patients treated with Ra-223 (14.9 months) compared to placebo (11.3 months).[124] Multiple secondary end points were improved with the Ra-223 compared to placebo: (1) time to first symptomatic skeletal event (15.6 vs 9.8 months), (2) decreased risk of spinal cord compression, (3) lower use of external RT for bone pain, and (4) decrease in certain biomarkers (total alkaline phosphatase and lactic dehydrogenase, although there was not a statistically significant difference in prostate-specific antigen).[124,125] There was no difference between the groups in pathologic bone fractures or the need for orthopedic intervention. The rates of significant adverse events were low, as was the risk of myelosuppression, in the patients receiving Ra-223.[125] Ra-223 has been used concomitantly with abiraterone, enzalutamide, and denosumab in an open-label prospective but nonrandomized study, with relatively low significant toxicity rates (grade ≥ 3 hematologic toxicity was <10%).[126] The use of Ra-223 in combination with abiraterone resulted in excess toxicity in a randomized trial and is discouraged.[127] Ra-223 is the only bone-directed radionuclide, which has shown improvement not only in pain and quality of life but also in overall survival.

Lutetium-177

The VISION trial evaluated lutetium-177 (Lu-177)-PSMA-617 for the treatment of metastatic castration-resistant prostate cancer.[128] These were heavily pretreated patients (at least one androgen pathway inhibitor and at least one taxane regimen) who had PSMA-gallium-68 scans, which were positive for metastatic disease. Over 90% of the patients in the study had bone metastases. The patients were randomized in a 2:1 manner to either Lu-177-PSMA-617 at 7.4 GBq every 6 weeks for 4-6 cycles or to

standard care. Standard care, however, excluded Ra-223, chemotherapy, immunotherapy, or other investigational drugs. Patients on the Lu-177-PSMA-617 arm had significantly better overall survival, progression-free survival, objective response rates, and disease control compared to standard therapy, although with a higher risk of grade >3 adverse events (52.7% vs 38.0%). Several studies using Lu-177 in combination with immunotherapy or in lieu of more traditional therapies for metastatic prostate cancer have been initiated and initial results are promising, suggesting that its use may become increasingly more common.[129,130]

Patient Selection

Radiopharmaceuticals, specifically Ra-223, Sr-89, and Sm-153, are effective in providing pain relief for patients with diffuse osseous metastases. This is primarily true for metastases that have an osteoblastic component. In general, if a Tc-99m nuclear medicine bone scan shows localized areas of increased uptake, then radiopharmaceutical treatment is likely to be of benefit. An advantage of radioisotope treatment is that it can be combined with other modalities, such as external beam RT or chemotherapy. Because the targets of treatment are similar, treatment with bisphosphonates should not be given simultaneously with radioisotopes because this may reduce the efficacy of both medications. However, there is evidence that the Ra-223 can be given concomitantly with denosumab. Relative contraindications to therapy would be impaired renal or hepatic function or inadequate hematologic reserve.

Radiopharmaceuticals: Summary

Both Sr-89 and Sm-153 radiopharmaceuticals appear equally effective at palliating pain from bone metastasis; however, these radioisotopes are becoming increasingly difficult to obtain. Ra-223 offers not only palliation of pain but also the possibility of improved overall survival, at least in patients with castrate-resistant metastatic prostate cancer. Radiopharmaceuticals, not only in bone metastases, but in the management of visceral disease are continuing to grow. Newer radiopharmaceutical agents that have more specificity to bind to specific tumor parkers are continuing to be developed. These newer agents not only can palliate painful bone metastases but have the ability to provide more targeted RT to nodal and visceral metastases as well.[128] These radiopharmaceuticals add to the growing armamentarium of therapies designed to palliate pain and improve the quality of life of patients with bone metastasis from cancer.

CONCLUSION

Palliative RT is of significant benefit to patients with painful bone metastasis, with most patients experiencing relief in the magnitude of pain following treatment. Response rates to palliative RT for localized sites of pain are consistently higher than response rates from palliative systemic therapy, and palliative external beam RT remains the mainstay of treatment for clinically localized painful bone metastasis. Providing shorter, single-fraction palliative treatment schedules (ie, 8 Gy in a single fraction) for properly selected patients with bone metastasis can help better integrate palliative RT into the multidisciplinary management of patients with metastatic cancer and offer equivalent palliation compared with longer courses of palliative RT. Meanwhile, SRS can be used in treating challenging bone metastases when standard palliative doses may not be enough. Systemic targeted therapies offer yet another means to target painful sites of bone metastasis without limiting the ability to use localized external beam RT and systemic chemotherapy. The role of radiation in treating bone metastases will continue to grow as newer data are highlighting the benefits in treating select patients who have asymptotic bone metastasis.

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CHAPTER 104

Palliation of Visceral Recurrences and Metastases and Treatment of Oligometastatic Disease

Alexander A. Harris, Michael Kharouta, Chirag Modi, and William F. Hartsell

The 5-year survival and overall cure rates for many cancers have significantly improved over the past 40 years. Unfortunately, there is still a large number of patients who develop recurrent or metastatic disease. The most common sites of metastatic disease are bones, brain, lungs, and liver. In addition, there are other visceral sites of recurrence or metastatic disease that may cause significant symptoms. Palliative radiation therapy (RT) for the treatment of bone and brain metastases is well established, with multiple randomized prospective trials evaluating best treatment practices. However, there is less information on the treatment of palliative radiation in treating visceral metastases and recurrences, although radiation oncologists recognize that RT is frequently effective at palliating symptoms in these settings.

The specific goals of treatment will depend on the symptoms, treatment site, functional status of the patient, and other patient-specific factors. The indications for treatment may include pain, visceral obstruction, bleeding, or other symptoms that negatively impact the quality of life. In general, this treatment is given with the goal of improving the quality of life, not the quantity of life. For some disease sites, this can be done with a very low-dose, short course of treatment. For other sites, this will require higher doses given to control the local disease.

Some visceral metastases will cause pain. For example, liver or adrenal metastases may cause significant pain. Splenic metastases from hematologic metastases may cause abdominal pain, early satiety, and abdominal distention. In contrast, pulmonary metastases rarely cause pain. Instead, these lesions may cause airway obstruction or hemoptysis.

Metastatic lesions in the gastrointestinal system may cause bleeding or obstructive symptoms (esophageal obstruction, gastric outlet obstruction, gastric bleeding, biliary obstruction, rectal obstruction). In addition to rectal obstruction, pelvic masses may cause ureteral obstruction, bleeding (vaginal, bladder, or rectal), or pain from involvement of the sacrum or sacral nerves.

There has been a revolution in the understanding of the metastatic process in the past decade. Traditionally, in solid tumor biology, cancer cells are thought to undergo some genetic change that potentiates them to grow into tumors and cause daughter cells to spread through the lymphatic or circulatory system to lymph nodes and distant sites. However, recent understanding of the epithelial-mesenchymal transition demonstrates that cancer cells develop embryonic stem cell–like properties that allow them to disseminate to distant sites. The microenvironment surrounding the primary tumor and metastatic sites can regulate the metastatic process. In addition, metastasis occurs much earlier than clinical detection of lymphadenopathy and radiographic or symptomatic evidence of the development of distant visceral disease.[1] Treatment of visceral metastases in the oligometastatic setting may allow for improved palliation and may also improve the overall survival (OS) in carefully selected patients.

PALLIATION OF HEAD AND NECK CANCER

Palliative RT for head and neck cancers is an essential treatment approach for patients who have locoregional disease recurrence or who are not candidates for curative therapy. The primary objective of palliative RT is to relieve debilitating symptoms, such as pain, dysphagia, and tumor ulceration, with minimal side effects, thereby improving the patient's quality of life.

The first and most important decision in treating these patients is to decide if treatment should be definitive or palliative. Candidates who may be best treated with palliative radiation over a definitive approach are often those with poor performance status, advanced age, uncontrolled medical comorbidities, recent prior radiation, organ dysfunction, and bulky tumors. Various nomograms can be used to help aid in the decision-making process.[2,3]

For patients who are best served with palliative RT, short courses of palliative radiation can be effective at reducing the tumor and associated pain, with objective response rates ranging from 40% to 80%.[4,5]

The QUAD shot regimen involves delivering 350 to 370 cGy twice daily (BID) for 2 consecutive days, repeated every 3 to 4 weeks. Studies have shown significant improvement in symptoms with minimal toxicities using this approach. In a study by Paris et al, the QUAD shot regimen demonstrated a 77% objective response rate, with most patients reporting subjective improvement in symptoms without major toxicities.[4] Corry et al reported a 50% objective response rate and a median OS of 5.7 months using a similar approach.[5] In another study by Lok et al, a higher number of QUAD shot cycles correlated with increased palliative response.[6]

Other fractionation schedules have also been explored and can provide a balance between high response rates with short, convenient treatment courses. The Hypo Trial treated patients deemed unsuitable for curative treatment to 30 Gy in five fractions, administering two treatments per week (at least 3 days apart). They found an objective response rate of 80%.[7] A regimen of 32 Gy delivered at 4 Gy per fraction biweekly in 126 patients with mostly stage IVB cancers showed a 74% treatment completion rate, a 42% response rate at the primary site of disease, and 55% at the site of nodal disease.[8] A retrospective study involving 21 patients used a 24 Gy in three-fraction regimen, delivering one fraction per week. This approach was effective in managing symptoms with a reasonable safety profile.[9] Another study of 32 patients deemed unfit for radical treatment due to poor performance status or advanced stage treated patients with 25 Gy in five fractions in 1 week. A significant portion of these patients had T4, N3, or M1 stage, and efficacy and tolerability were high, with only 13% of patients experiencing any grade 3 toxicities, no grade 4 or 5, and patients reporting equal or lower than baseline symptoms at up to 6 months post-treatment.[10] Another retrospective analysis with 65 patients used a higher dose regimen of 60 Gy in 20 fractions or 72 Gy in 24 fractions for a more aggressive approach in patients unable to tolerate continuous-course definitive chemoradiation, incorporating a mid-treatment break to manage toxicity, though feeding tube rates still reached 42%.[11] Several retrospective studies on the use of palliative stereotactic body radiotherapy (SBRT) have also been reported with good local control and toxicity rates. Siddiqui et al

reported a retrospective study of the treatment of 55 lesions in 44 patients with primary, recurrent, and metastatic tumors using either 13 to 18 Gy in a single fraction or 36 to 48 Gy in five to eight fractions, showing a 77% overall response rate.[12] Khan et al reported a similar study of 24 sites treated in 21 patients with de novo and recurrent head and neck cancers with SBRT using 35 to 48 Gy in five to six fractions with an overall response rate exceeding 90%.[13]

Proton therapy may be appropriate for some patients, especially since it limits dose to other normal tissues, which may have been previously irradiated. A single-institution study evaluated 242 patients with head and neck cancers in previously irradiated fields, who were treated with proton therapy for reirradiation. A significant proportion had salvage surgery before irradiation (40.5%), and 57% received concurrent chemotherapy. Approximately one-third were treated with "QUAD shot" treatment of 14.7 Gy_{RBE} in four fractions over 2 days, repeated every 2 to 4 weeks for a total of up to four cycles (median was three cycles, total dose of 44.4 Gy_{RBE}). The remainder of the patients were treated with more standard fractionation; the median dose of proton reirradiation in those patients was 70 Gy_{RBE}. Control rates and survival rates were significantly better in the fractionated arm, with 63% local control at 2 years, and a 1-year survival rate of 66.6%.[14]

These regimens showcase the diverse approaches in palliative RT, each with its specific benefits and considerations. Each regimen can be tailored to individual patient needs and treatment objectives. The choice of a specific regimen depends on various factors, including the patient's overall health status, the extent of the disease, and the primary symptoms to be alleviated. Though no consensus guidelines exist on optimal treatment volumes, it is generally recommended to select volumes that minimize toxicity from treatment while balancing the risk of untreated or undertreated disease causing symptoms in the future. While simpler techniques may minimize the time to treatment, intensity-modulated radiation therapy (IMRT) or protons should be considered in situations where it may otherwise be difficult to minimize treatment toxicity.

MALIGNANT LOWER AIRWAY OBSTRUCTION

The lower airway is generally defined as being below the first tracheal ring. Upper airway obstructions can be emergently treated with a tracheostomy. The lower airway can become compromised from either primary or metastatic malignancy. Patients may have intrinsic compression caused by an endobronchial tumor or extrinsic airway compression by a tumor mass in the lung parenchyma or bulky lymphadenopathy during the course of their illness. Clinical symptoms, bronchoscopy, and radiographic imaging are used to determine the extent of luminal obstruction. It is important to determine whether the airway obstruction is endobronchial or from external compression of the airway in order to select the most appropriate treatment. For intrinsic compression of a tumor mass growing inside the bronchial lumen, interventional bronchoscopy techniques offer immediate benefit in many patients. These interventional techniques can result in relief of dyspnea, decreased risk of postobstructive pneumonia, and improved functional status.[15-17] Either laser resection of tumor or endobronchial stent placement, along with RT, is effective in maintaining the patency of the lower airway.[18,19] The additional treatment of the airway can be given with either external-beam RT, endobronchial brachytherapy, or photodynamic therapy. Brachytherapy is typically the best option in patients who have recurred after prior external-beam RT. For endobronchial therapy, the recommended doses are 7.5 Gy × 3 or 10 Gy × 2.[20] In a prospective observational study, de Aquino Gorayeb et al utilized high-dose-rate endobronchial brachytherapy for palliation of malignant airway obstruction. The study protocol consisted of three fractions of 7.5 Gy weekly or biweekly, with over half of the patients having been previously treated with external-beam radiation. Of the 78 patients treated, 70% reported an improvement in performance status and 87% noted improvement of one or more of their presenting complaints (dyspnea, cough, infection, and/or hemoptysis). Of the patients who presented with one or more of the abovementioned symptoms, 57% noted improvement in their dyspnea, 34% noted improvement in their cough, 80% noted improvement in their infection symptoms, and 100% noted improvement in their hemoptysis.[21]

External-beam RT is typically used for the treatment of airway compromise caused by extrinsic compression of a bronchus. Endobronchial brachytherapy typically does not improve symptoms when there is external compression of the airways.[22,23] The highest doses from brachytherapy will

be given to the (relatively) normal mucosa of the airway, with a much lower dose to the extrinsic tumor that is causing the compression.

There is no standard fractionation scheme or total dose for palliative external-beam treatment for lung cancer. A review by Fairchild et al found the best results, in terms of palliation of symptoms, are achieved with relatively high doses of RT: 3 Gy per fraction to a total of 30 to 45 Gy, or 2 Gy per fraction to 50 to 60 Gy.[24] The trade-off is that there is a higher rate of acute esophagitis with these higher doses. The American Society for Radiation Oncology clinical practice guideline consensus statement recommends doses equivalent to 30 Gy in 10 fractions or greater.[25] For patients with a poor performance status or who have difficulty traveling for multiple treatments, shorter fractionation schemes such as 20 Gy in five fractions can be used. Very short regimens (17 Gy in two fractions or 10 Gy in one fraction) may be useful in certain situations; however, there are reports of radiation myelopathy with these regimens (17 Gy in two fractions).[25]

In most patients who receive RT for palliation of pulmonary symptoms, there is no benefit to the addition of chemotherapy. Combined chemotherapy and RT may improve response rates slightly, but with significantly greater acute toxicity.[25]

LIVER METASTASES

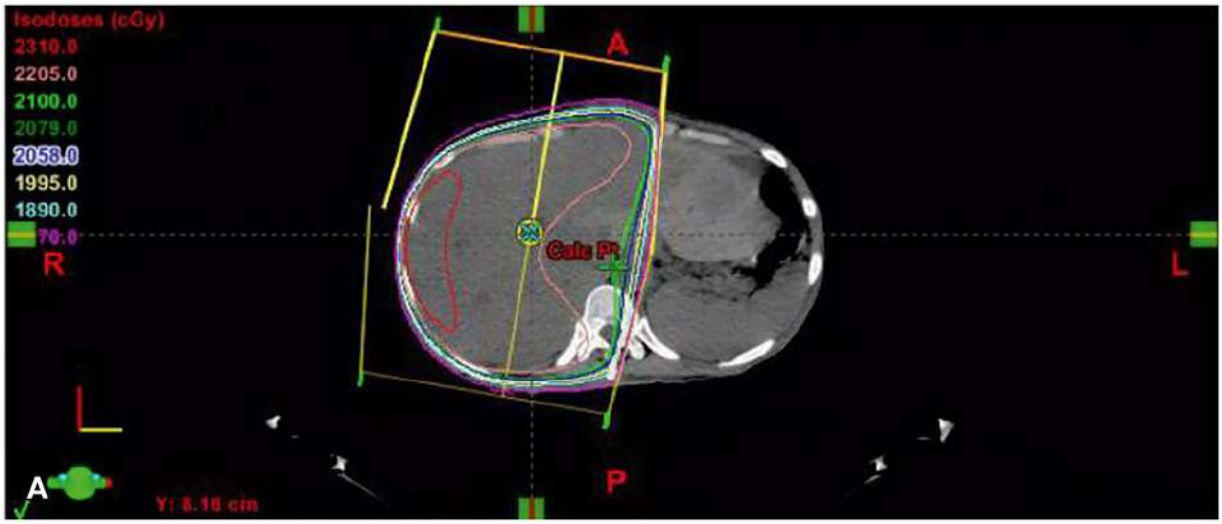
The liver is the most frequent site of distant metastatic disease from gastrointestinal tumors, especially colorectal, but also esophageal, stomach, and pancreatic cancers. The liver is also a frequent site of metastases from lung cancer, breast cancer, and melanoma. A patient with liver metastases may have symptoms of anorexia or early satiety, weight loss, nausea, right upper quadrant or epigastric pain, pruritis, jaundice, and fever.

For patients with few metastatic lesions in the liver and no evidence of extrahepatic metastases, 12% to 36% may be cured with surgical resection.[26] The risk factors associated with the best outcome are clear resection margins, low levels of carcinoembroyonic antigen, a single metastatic deposit, metachronous presentation of the liver metastasis, and node-negative disease (with the original primary).[26] Other liver-directed therapies can be used for patients with one or a few hepatic metastases,

including radiofrequency ablation, microwave coagulation therapy, transarterial chemoembolization, transarterial radioembolization, hypofractionated external-beam RT, and SBRT.[27]

Most patients with liver metastases are found to have multiple lesions, extrahepatic disease, or other risk factors that make them unsuitable for these surgical or ablative procedures. It is common for these patients to undergo multiple courses of systemic therapy prior to being seen and evaluated by a radiation oncologist. For many years, the only viable chemotherapy option for metastatic gastrointestinal tumors was 5-fluorouracil, often given in combination with leucovorin. More recently, multiple drug regimens including oxaliplatin or irinotecan have significantly improved the response rates and increased the median duration of survival. Targeted agents such as cetuximab or bevacizumab may improve the response rates even further. These new combinations have changed the goal of treatment from palliation to prolonging survival; with this new paradigm, the multiple drug regimens are given as neoadjuvant therapy with the goal of downsizing tumor bulk in order to facilitate a resection.[28] Hepatic arterial infusion of chemotherapy gives higher local concentrations of the chemotherapy agents and also gives higher response rates. A meta-analysis of hepatic arterial infusion chemotherapy for liver metastases demonstrated a significantly higher response rate but showed no improvement in survival duration.[29] Increasingly, these targeted agents are being paired with ablative radiation-based treatment to with a goal of improving outcomes.

The group of patients who are referred to a radiation oncologist for palliation of liver metastases tend to be the patients who have more medical comorbidities, a greater tumor burden, and who have been previously treated with multiple other therapies. Despite these poor prognostic factors, RT can be effective in palliating symptoms (Figure 104.1).[30]


Isodoses (cGy)
2310.0
2205.0
2100.0
2079.0
2058.0
1995.0
1890.0
70.0
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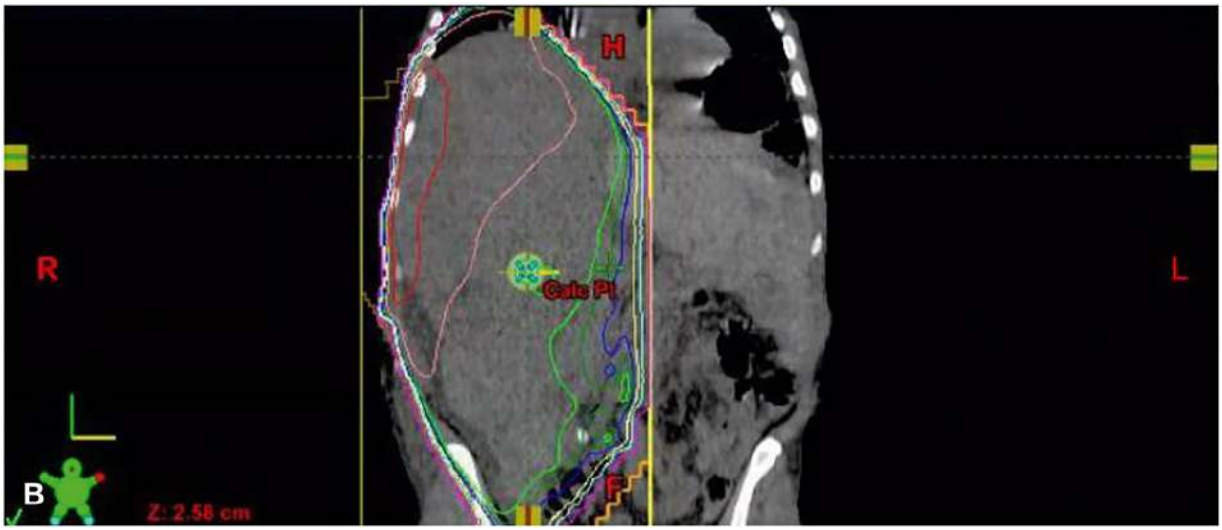
Y: 8.16 cm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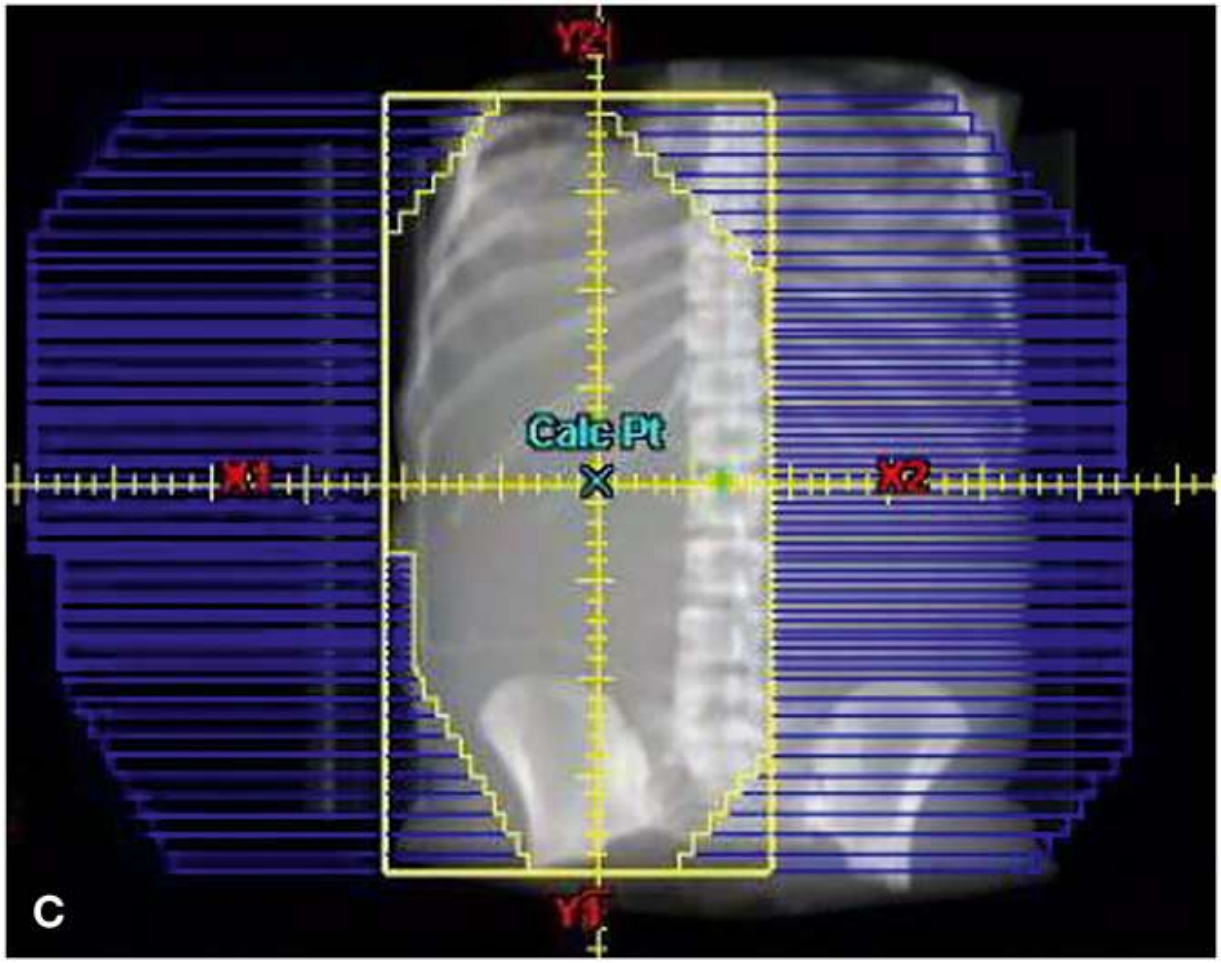


FIGURE 104.1 Axial (A) and coronal (B) isodose plots in a patient with diffuse metastases in an enlarged liver, causing significant pain. Treatment field is shown in (C). This patient was given 21 Gy in seven fractions and had significant improvement in pain within 4 weeks.

Palliative treatment of the liver is limited by radiation- induced liver disease (RILD). This toxicity becomes apparent 1 week to 3 months after treatment and may result in liver failure and death.[31] Both dose and volume of liver irradiated are important in avoiding RILD. For treatment of the whole liver, the threshold for RILD is approximately 30 Gy in 2 Gy fractions or 33 Gy in 1.5 Gy BID fractions.[32,33] The Radiation Therapy Oncology Group's trial RTOG-7605 evaluated multiple regimens in patients with multiple liver metastases: 30 Gy in 15 fractions, 25.6 Gy in 16 fractions, 20 Gy in 10 fractions, and 21 Gy in 7 fractions.[34] Improvement in symptoms was seen in 55% of the patients, with no difference among the four treatment regimens. A subsequent RTOG trial evaluated whole-liver RT with a dose of 21 Gy in seven fractions; patients were randomized to

receive either the radiation alone or the addition of misonidazole to the radiation.[35] There was minimal toxicity and a rapid symptomatic response in the majority of patients. Complete pain relief was reported in 54% of the patients, and 80% of the patients noted an improvement in pain following treatment. Overall, there was no significant benefit with the addition of misonidazole. The best response rates were seen in patients with colorectal primaries. Bydder et al[36] reported on a series of 28 patients treated with a hypofractionated regimen of 10 Gy in two fractions to the whole liver. The overall response rate was 54%, with two patients experiencing grade 3 toxicity (emesis and diarrhea). For patients where a shorter course of treatment may be best, a phase II trial showed that approximately half of patients treated with a single fraction of 8 Gy will experience measurable improvements in symptoms with a low rate of treatment-related toxicities.[37]

If a smaller portion of the liver is irradiated, higher doses can be given with low risk for RILD. A 5% risk of RILD is associated with 90, 47, and 31 Gy with uniform irradiation of one-third, two-thirds, and the whole liver, respectively. If the effective liver volume irradiated is less than 25%, doses greater than 100 Gy can be given with little risk of RILD.[38,39]

SBRT has been shown to be an effective and well-tolerated way to treat patients with a limited number of liver metastases. In one retrospective review of patients treated with a single fraction of SBRT (median dose 24 Gy) showed a high rate of local control, with 6- and 12-month control rates of 87% and 70%, respectively.[40] However, these control rates are likely improved with increasing doses and fractionation. In a dose-escalation study of UT Southwestern, Rule et al found that 2-year local control rates increased from 56% to 89% to 100% as treated dose increased from 30 Gy in three fractions to 50 Gy in five fractions to 60 Gy in five fractions. This was done with a low rate of toxicity in all arms, with no treatment-related grade 3+ toxicities reported.[41] These findings were further supported in a phase I/II study of SBRT in patient with limited number of liver metastases (one to three). Ablative radiation provided an in-field local control rate of 95% at 1 year and 92% at 2 years. The 2-year local control rate was noted to be higher (at 100%) in the treated tumors that were smaller than 3 cm in diameter. This was done with a low rate of grade 3 toxicities (2%).[42]

Selective internal radiation therapy (SIRT) is another option for patients with diffuse liver metastases. This technique involves the use of yttrium-90

(^{90}Y) glass or resin microspheres that are given through intra-arterial infusions into the liver. A phase III trial of patients with liver metastases from colorectal cancer evaluated intra-arterial floxuridine alone compared to intra-arterial floxuridine plus SIRT with ^{90}Y resin microspheres.[43] The patients who received SIRT had a significantly better overall response rate, time-to-tumor progression, and OS. The addition of SIRT did not increase grade 3 or 4 toxicity. SIRT can also be used to debulk liver metastases in an effort to later resect. One study showed that the addition of SIRT to chemotherapy in patients with liver metastases from colorectal primaries improved the rate of resectability of liver metastases over chemotherapy alone.[44]

In summary, patients with multiple symptomatic liver metastases may be palliated by whole-liver RT. Relatively low doses of 21 Gy in 7 fractions or 30 Gy in 15 fractions are generally well tolerated and provide symptomatic relief for the majority of patients. Treatment to high doses can be done, often with improved control or to convert an unresectable patient into a resectable one, if a smaller percentage of the liver is radiated.

BILIARY OBSTRUCTION

Malignant biliary obstruction may be caused by a tumor mass causing either extrinsic compression onto the bile duct or intrinsic compression from tumor progression within the bile duct lumen. This obstruction can lead to hyperbilirubinemia and jaundice, which can cause pruritus, anorexia, and weight loss. The biliary obstruction may be a life-threatening emergency. Emergent drainage of the bile duct is achieved initially by external stent or percutaneous drain placement. The stents are later converted to internal endoprostheses; however, these catheters typically only remain patent for 4 to 8 months.[45] The patency of these stents can be extended with the use of intraluminal brachytherapy, photodynamic therapy, or external-beam RT. Intraluminal brachytherapy extends stent patency and lengthens survival duration in patients with inoperable cholangiocarcinoma.[46,47] Although there are few data specifically for the use of external-beam RT for palliative treatment of recurrent, metastatic, or inoperable biliary disease causing obstruction, it may be of benefit especially for the treatment of extrinsic bile duct compression by a tumor mass.[48] One retrospective study showed that in

patients with metastatic cholangiocarcinoma, treating the primary tumor with high doses of RT along with chemotherapy not only improved symptoms of biliary obstruction but also prolonged OS (21 vs 9 months) as compared to a propensity score–matched cohort of patients from the same institution that received chemotherapy alone.[49]

PAINFUL ADRENAL METASTASES

The adrenal glands are a common site of metastatic disease from many types of cancer, primarily due to the rich blood supply of the adrenal gland. Lung cancer is the most common source of adrenal metastases. These metastases are frequently asymptomatic, but occasionally may cause pain. For patients with a good performance status and few sites of metastatic disease, surgical management may be appropriate. RT is also appropriate for palliative treatment.

Palliative RT typically has been given with conventional external-beam techniques. Soffen et al[50] reported the results in 16 patients with painful adrenal metastases treated with palliative RT. The majority of the patients received 30 Gy in 10 to 12 treatments. A response was seen in 12 (75%) of 16 patients, with 6 of those patients having complete response for the duration of their survival. Nearly half of the patients (44%) experienced nausea, which may have been related to the technique of treatment with anterior and posterior fields. No late toxicity was seen, but the median survival was only 3 months. A multicenter retrospective study assessed results from 134 patients treated with three-dimensional (3D) conformal (88%), IMRT (6%), or SBRT (6%) for adrenal metastasis from hepatocellular carcinoma. Treatment regimens ranged from 20 to 60 Gy (median of 45 Gy) with dose per fraction of 1.8 to 15 Gy (median 2.5 Gy). A complete response was seen in 6 patients, and a partial response was seen in 48 patients, for an objective response rate of 39%. Seventy-eight patients (55%) were noted to have stable disease.[51]

There are multiple reports evaluating the use of IMRT techniques or SBRT techniques for the treatment of adrenal metastases. Most of these patients were treated for asymptomatic adrenal metastases, rather than for palliation of symptoms. These treatments appear to provide a high rate of local control. SBRT studies have shown local control rates ranging from

73% to 100% after 1 year, with minimal toxicity.[52-54] These RT treatments may be appropriate for patients with limited volume disease (oligometastases) (Figure 104.2). In the palliative setting, there is a benefit with a dose of 30 Gy in 10 treatments using conventional techniques.

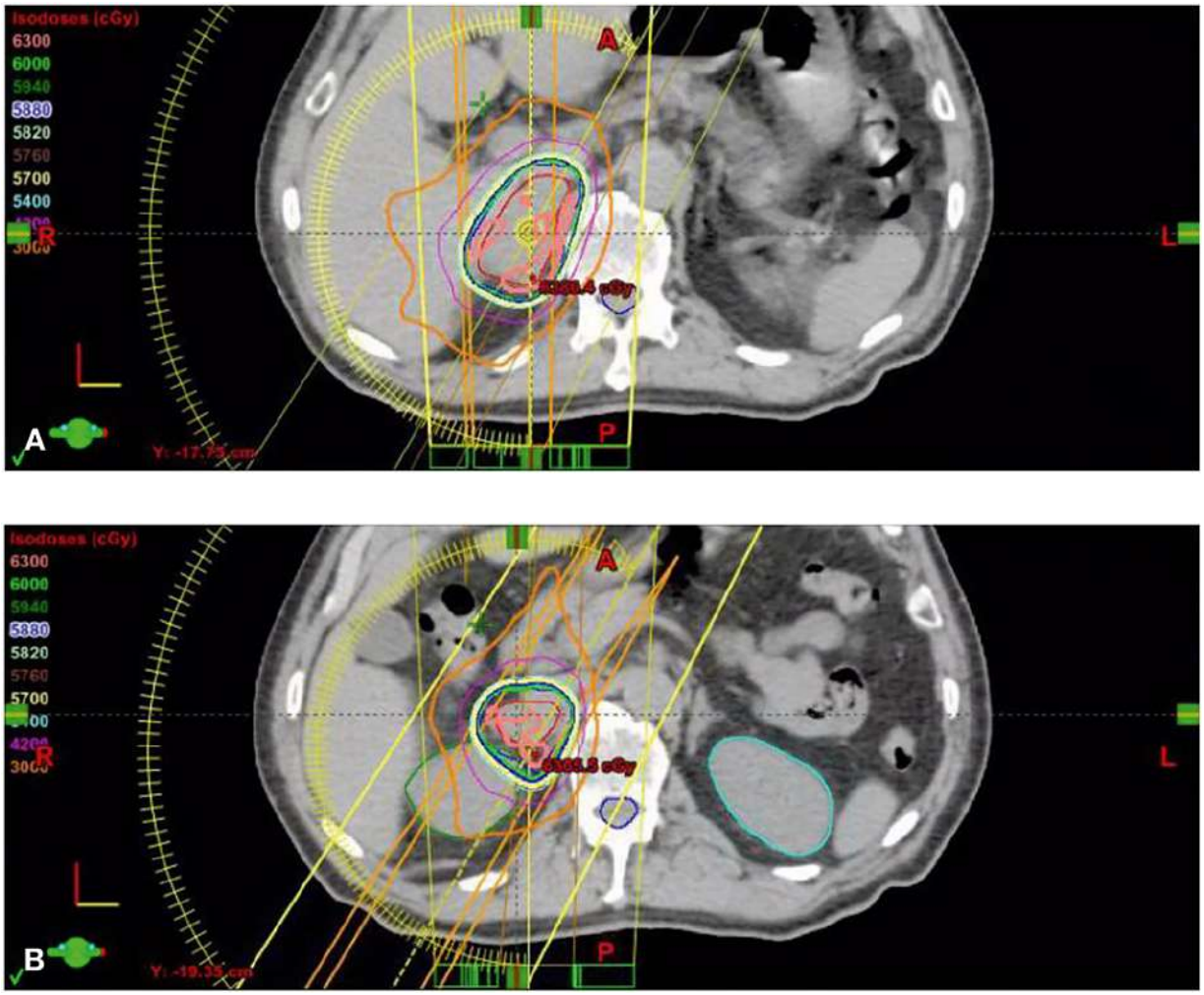


FIGURE 104.2 Axial isodose plots from superior (A) and inferior (B) aspect of stereotactic body radiotherapy fields for an adrenal metastasis. This patient was given 50 Gy in five fractions.

SPLENIC METASTASES

It is relatively uncommon for solid tumors to metastasize to the spleen. Splenomegaly is more often associated with hematologic malignancies and disorders, such as leukemia or myeloproliferative diseases. The spleen can become massively enlarged, causing pain, early satiety, nausea, or emesis.

These symptoms may also occur when the spleen is enlarged because of extramedullary hematopoiesis due to marrow failure.[55]

Treatment with RT can be very effective at reducing the size of the spleen and palliating the other symptoms associated with splenomegaly. The doses required for palliation of symptoms are much lower than the doses typically used for palliation of other visceral metastases. The response may be quite rapid as well, which necessitates evaluation of the field sizes on a frequent basis. The regimens frequently used include doses of 0.25 to 1 Gy given 2 to 3 times per week. It is important to evaluate blood counts on a frequent basis, since anemia and thrombocytopenia may occur rapidly with precipitous drops in the counts over a very short period. A typical regimen is the one reported by McFarland et al.[56] Their patients were treated twice weekly beginning at 0.5 Gy per fraction the first week, increasing to 0.75 Gy per fraction in the second week and 1 Gy per fraction on the third week. A complete blood count was obtained prior to each treatment. The total dose was typically less than 5 Gy. Even with these low doses, 14 of 16 patients had subjective improvement in their symptoms, and 12 of 16 patients had objective decrease in the splenomegaly.

A recent systemic review of palliative splenic radiation for the treatment of splenomegaly in the setting of hematologic malignancy showed that the treatment was effective at reducing splenic size, splenic pain, and improving cytopenias. Over the 27 articles reviewed, the average partial response rate was 85%, with 72% of the treatment courses resulting in splenic size reduction, 59% resulting in pain relief, and 78% resulting in improvement in cytopenia. Of the total of 766 treatment courses assessed, 33% resulted in acute toxicities, with the most common being a grade 3 to 4 leukopenia/neutropenia or thrombocytopenia. No long-term toxicities were noted.[57] Treatment of the spleen may cause an abscopal effect as well, with decrease in the size of involved lymph nodes distant to the treated spleen.[56]

VAGINAL BLEEDING OR DISCHARGE

Vaginal bleeding is a common symptom at diagnosis in several gynecologic tumors, especially cervical, uterine, and vaginal tumors.[58] The initial treatment should be with vaginal packing, but this often does not treat the underlying issue.[59] RT is also effective at controlling this type of vaginal

bleeding. A hypofractionated treatment course is typically used, usually with 2.5 to 4 Gy per fraction. A typical course of treatment would be 30 Gy in 10 fractions. Often, the bleeding will slow or stop after three to five treatments. The treatment can be continued to definitive doses at that point, using more standard fractionation of 1.8 to 2.0 Gy per fraction (Figure 104.3). An alternative method of palliating bleeding and vaginal discharge is to use a single large fraction of 10 Gy.[60-62] This will result in a high likelihood of reducing or stopping the bleeding, often within 24 to 48 hours of the first dose. This dose of 10 Gy can be repeated at 1-month intervals. The risk of complications increases when this dose is repeated a third or fourth time, so this should be limited to one to two fractions.[63]

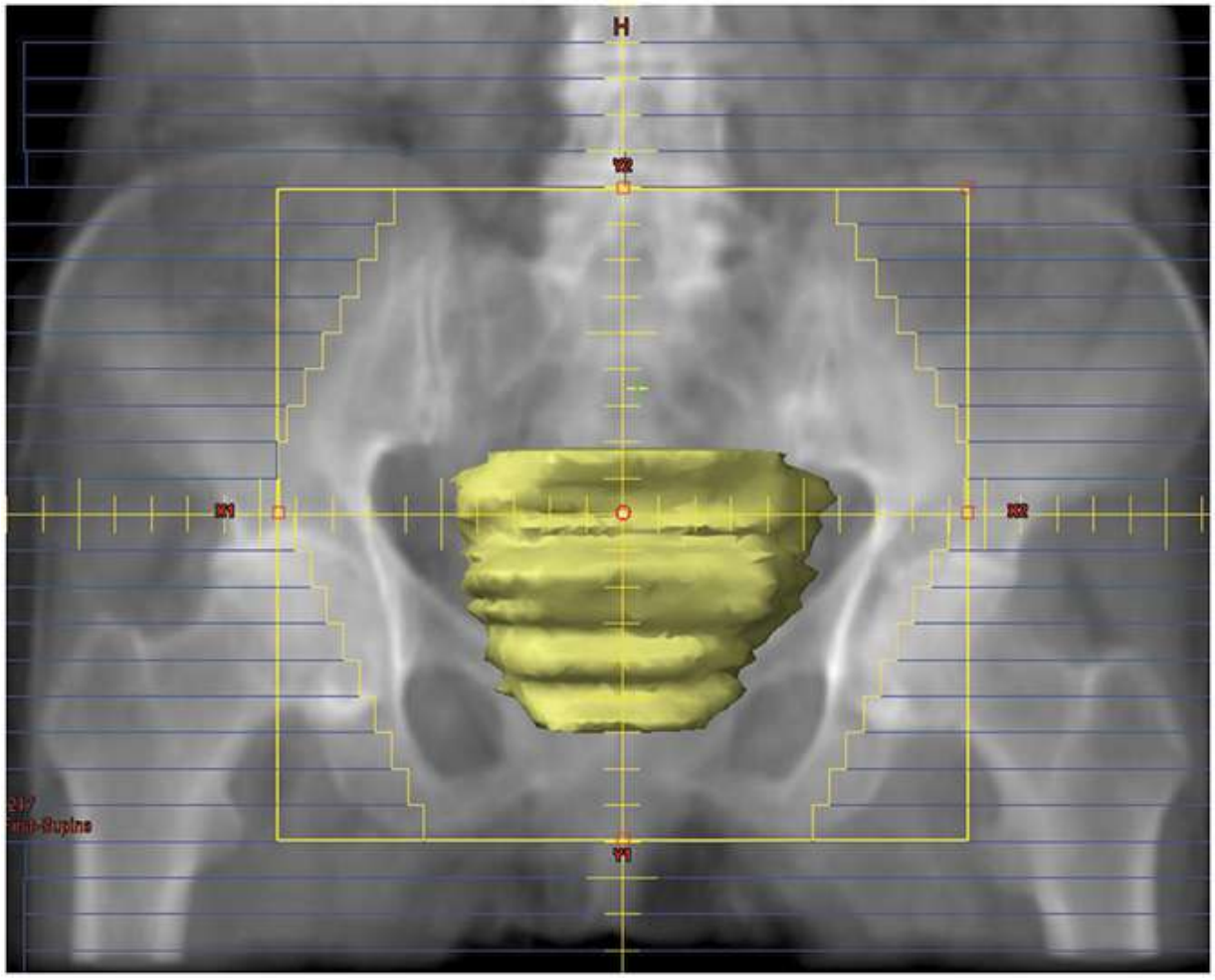


FIGURE 104.3 Digitally reconstructed anterior-posterior radiograph of a palliative pelvic field. This palliative field arrangement would be appropriate to treat a patient with hemorrhage from a cervical or bladder cancer.

PELVIC RECURRENCE

Recurrent pelvic malignancies may cause significant symptoms, including pain, bleeding, or obstruction. The choice of the appropriate palliative treatment depends on multiple factors, including the type and amount of prior treatment. In contrast to palliative treatment of other sites of recurrent disease, aggressive combined-modality treatment may provide the best chance of palliation of symptoms for recurrent pelvic malignancies.

Recurrent colorectal cancer may cause life-threatening problems from bowel obstruction. For most patients in this circumstance, surgical intervention is the most appropriate treatment. This may involve complete surgical removal of the disease, if possible, or a diverting colostomy to alleviate the symptoms of obstruction.[64] There is a high risk of perioperative complications in this group of patients, primarily because it is frequently difficult to perform an adequate bowel preparation prior to surgery.

Hydronephrosis and severe pain may be signs of a more advanced tumor and are relative contraindications to surgical resection.[65] The majority of patients with recurrent rectal cancers have posterior or posterolateral involvement of the pelvis, which makes surgery more difficult.[66] The presence of severe pain may indicate invasion of the sacrum or sacral nerve roots. Tumors that invade these structures are more difficult to resect completely. Melton et al[67] and Wells et al[68] reported that patients who underwent an aggressive surgical resection of locally recurrent rectal cancers had a high risk of significant complications. Patients who had sacral resection as part of the surgical treatment had a 42% risk of significant complications.[68]

Patients with bulky pelvic recurrences who have not previously received RT are appropriate candidates for combined chemotherapy and RT. A prospective randomized Danish trial evaluated RT alone (50 Gy in 25 fractions, with a boost of 10-20 Gy in 5-10 fractions) compared with the same RT with concomitant weekly bolus dose of 5-fluorouracil.[69] This treatment was given to patients with locally recurrent or inoperable rectal cancers. There was no improvement in survival with the addition of chemotherapy, but there was a higher rate of acute complications (33% with chemotherapy vs 13% with radiation alone). In several retrospective studies, the addition of chemotherapy was beneficial. Ito et al[70] reported on

30 patients with symptomatic intrapelvic recurrent rectal cancers. They noted a higher pain relief rate in the patients receiving chemotherapy (100% vs 77% for radiation alone) and a near doubling of the median survival time (7.8 vs 4 months). For these patients with locally recurrent rectal cancers, combined-modality therapy is usually recommended to improve the likelihood of local control.

Relatively high doses of RT are required for palliation of symptoms. A review by Wong et al[71] showed that total dose was important in achieving a response, with the highest responses seen in patients receiving 50 Gy or more. In their series, the patients with the best prognostic factors received higher doses, but the dose-response relationship was still predictive of local control and survival in a multivariate analysis. Bae et al[72] also found improvement in the rate and duration of symptom control in patients who received higher doses. They recommended a biologic effective dose greater of than 40 Gy_{10} when possible.

Patients who have received prior irradiation and subsequently develop locally recurrent rectal cancer are frequently treated with either surgery, chemotherapy, or a combination of the two. However, there are circumstances in which additional RT may be beneficial. The RT may be given as hyperfractionated external-beam radiation, intraoperative radiation therapy (IORT), or brachytherapy. Lingareddy et al[73] utilized hyperfractionation with 1.2 Gy BID to a median dose of 30.6 Gy for reirradiation of patients with locally recurrent rectal cancer; these patients had received full-dose pelvic RT as part of their initial treatment. They used limited fields for the reirradiation, excluding the bladder and small bowels. Most of the patients (90%) received concurrent 5-fluorouracil chemotherapy. There was improvement in pain in 65% of these patients and cessation of bleeding in 100%. The late toxicity of treatment was significantly lower in patients who received hyperfractionated treatment compared to single daily treatments (18% vs 47%). The most frequent late toxicities were small bowel obstruction (17%) and fistula formation (8%). An Italian prospective study evaluated patients with recurrent rectal cancer who had previously received RT.[74] Patients with biopsy-proven recurrent disease were given preoperative combined-modality treatment, with hyperfractionated RT (30.6 Gy using 1.2 Gy BID, followed by a 10.8-Gy

boost also with 1.2 Gy BID) and continuous infusion 5-fluorouracil. The patients were then evaluated for resection, and surgery was performed at 4 to 6 weeks following the chemoradiotherapy, when feasible. Fifty-one (86%) of the patients completed the preoperative treatment as planned, and 30 (50.8%) underwent resection. The overall median survival was 42 months, and the 5-year survival was 39%. Seven patients had late grade 3 toxicity, and there were no grade 4 toxicities.

An alternative treatment paradigm for patients with advanced pelvic malignancies mirrors the QUAD shot technique utilized in head and neck palliative RT. RTOG 8502 utilized a BID treatment technique to deliver four fractions of 14.8 Gy in 3.7 Gy per fraction over 2 days. This regimen was repeated every 3 to 6 weeks for a total of three cycles for a total dose of 44.4 Gy. Utilizing this technique, the authors found a 45% response rate for individuals who finished the recommended three courses of RT.[75]

SBRT has shown promising results for treating previously irradiated pelvic cancers; however, the majority of the literature is limited to small, single-institution studies.[76,77] Dewas et al[77] reviewed 16 patients with lateral pelvic recurrences of anal, rectal, endometrial, or bladder cancer. The patients received reirradiation of 36 Gy over six treatments to the lateral pelvic recurrence. The 1-year local control rate was approximately 50%, with a median disease-free survival of 8 months, with toxicities limited to grade 2 or below. Defoe et al[78] repor ted on 14 patients with presacral tumors from rectal cancer who received SBRT treatment after prior RT. The patients were retreated to a dose of 36 Gy over three fractions. Local control rates were 91% at 1 year and 68% at 2 years, with OS of 90% and 79%, respectively. Toxicities were limited to grade 2 or below. Jereczek-Fossa et al treated 34 patients with recurrent prostate cancer, localized to pelvic lymph nodes. The patients were retreated on average to 30 Gy over 4.5 fractions. About half of the treated patients received androgen deprivation therapy.[79] Biochemical response was noted in 84% of cases. In patients who received SBRT without androgen deprivation therapy, the biochemical response rate was 81%, with a complete prostate-specific antigen (PSA) response rate of 56%. Most toxicity was acute, with 18% of treated patients experiencing acute urinary toxicity and 3% experiencing acute rectal toxicity. Late urinary toxicity occurred in 20% of patients, and late rectal toxicity in 6%.

IORT may be useful in some patients with locally recurrent rectal cancer. The patients who may benefit from this treatment are those with locally advanced recurrent rectal cancer who have no evidence of metastatic disease. Haddock et al[80] reported on a series of 51 previously irradiated patients with recurrent rectal cancer who underwent maximal resection followed by IORT using electrons. The dose given was 10 to 30 Gy, with a median of 20 Gy. Thirty-seven patients received additional external-beam RT (median 25.2 Gy) following the surgery and IORT. The 2-year survival rate was 48%, but the 5-year survival rate was only 12%. The local control rate was 60% at 2 years, with a trend toward better local control in patients who received 30 Gy or more external-beam treatment in addition to the IORT (81% local control vs 54% for those who received no external-beam treatment or doses <30 Gy). The toxicity included peripheral neuropathy in 32% of patients and ureteral narrowing or obstruction in 14%.

Brachytherapy is another alternative method to deliver radiation dose to a relatively limited volume. Alektiar et al[81] reported on 74 patients with locally recurrent colorectal cancers. The patients underwent surgical resection of the recurrence, followed by high-dose rate intraoperative brachytherapy, with doses of 10 to 18 Gy. The 5-year OS rate was 23%, with a 5-year local control rate of 39%. The primary toxicity was peripheral neuropathy, which occurred in 16% of the patients. Patients with negative margins of resection had a higher likelihood of local control compared to those who had positive margins (43% vs 28%). Kolotas et al[82] evaluated palliative interstitial high-dose rate brachytherapy in a group of 38 patients. Only four of the patients had the catheters implanted intraoperatively; most were placed using computed tomography guidance, with the catheters implanted through the perineum or sacrum. This group of patients had bulky disease at the time of implant. The median survival was 15 months following brachytherapy, with most deaths caused by distant metastases. There was stable disease in 28 of 38 patients, with pain relief in 89.5% of patients.

In summary, palliative RT is effective in reducing pain or bleeding from recurrent pelvic malignancies. Because of the location and nature of pelvic recurrences, combined-modality treatment with chemotherapy, RT, and surgery may be needed. Relatively high doses of radiation may also be needed to provide the palliative benefits of treatment.

RADIATION THERAPY IN THE SETTING OF OLIGOMETASTATIC DISEASE

As reviewed in the preceding sections, the radiotherapeutic management of metastatic disease has historically been limited to palliation, typically utilizing relatively low overall doses and abbreviated treatment schedules. The goal of this approach has been to provide short- to moderate-term palliation, while limiting treatment-related toxicity and minimizing duration of therapy. Until recently, this paradigm has been generalized to nearly all patients staged as metastatic, with an essentially uniform treatment strategy applied to a widely heterogeneous group of patients, presentations, and disease biology. The paradigm shift of "curative" local therapy, including RT, for select presentations of "oligometastatic" disease, was first proposed by Weichselbaum and Hellman in a 1995 editorial.[83] According to this concept, select patients with controlled locoregional disease and a limited number of metastatic sites may theoretically be cured with definitive local therapy, especially in the setting of effective systemic therapy. During the era of Weichselbaum and Hellman's writing, limitations in RT technique precluded effective ablation of most sites of oligometastatic disease without significant toxicity. Furthermore, available systemic therapy was largely ineffective in eliminating microscopic systemic disease. Interval advances in highly conformal image-guided RT and the increased efficacy of systemic and molecular therapies have allowed for the translation of this theoretical concept into clinical investigation and practice.

Early investigations of definitive RT for metastatic disease included isolated metastatic liver disease.[84] Investigators at the University of Michigan first pioneered the paradigm of high-dose 3D conformal RT in a cohort of patients that included both primary hepatocellular carcinoma and hepatic metastasis, achieving acceptable local control and toxicity (Figure 104.4). With the advent of image-guided SBRT, the definitive treatment of isolated hepatic metastasis has been the focus of intense clinical investigation and practice.[85] A multi-institutional phase I and II trial of 47 patients with one to three liver lesions (each <6 cm in size) tested dose-escalated SBRT of 36 to 60 Gy in three fractions, reporting a 2-year local control of 92% for all lesions. Local control rates of 100% for lesions 3 cm or less and 77% for lesions greater than 3 cm were also achieved in the 60-

Gy cohort. With a median follow-up of 16 months, an OS of 20.5 months was reported, with no documented RILD and grade 3 toxicity or higher of 2%.[42] A pooled analysis of 65 patients from three institutions has also demonstrated an excellent efficacy and toxicity profile for SBRT in the definitive treatment of colorectal liver metastasis, recommending a prescription dose of at least 48 Gy for a three-fraction regiment for optimal local control.[86] More recently, Goodman et al evaluated the long-term safety and efficacy of SBRT treatment for oligometastatic liver disease. Eighty-one patients, with one to three liver metastases were treated with a median dose of 54 Gy in three to five fractions.[52] They found that local control was 94% after 33 months, and a partial or complete response was observed in 69% of lesions treated. Grade 3 liver toxicity occurred in 5% of the cases.[33] In a study conducted by Scorsetti et al, the long-term efficacy and safety of SBRT for unresectable liver metastases were evaluated. The trial involved 61 patients with 76 lesions, treated with a high dose of 75 Gy in three consecutive fractions. Key findings included a median OS of 27.6 months and local control rates of 94%, 78%, and 78% at 1, 3, and 5 years, respectively. The study concluded that SBRT is both effective and safe for treating unresectable liver metastases, highlighting the importance of patient selection and the timing of SBRT in the treatment pathway.[87]

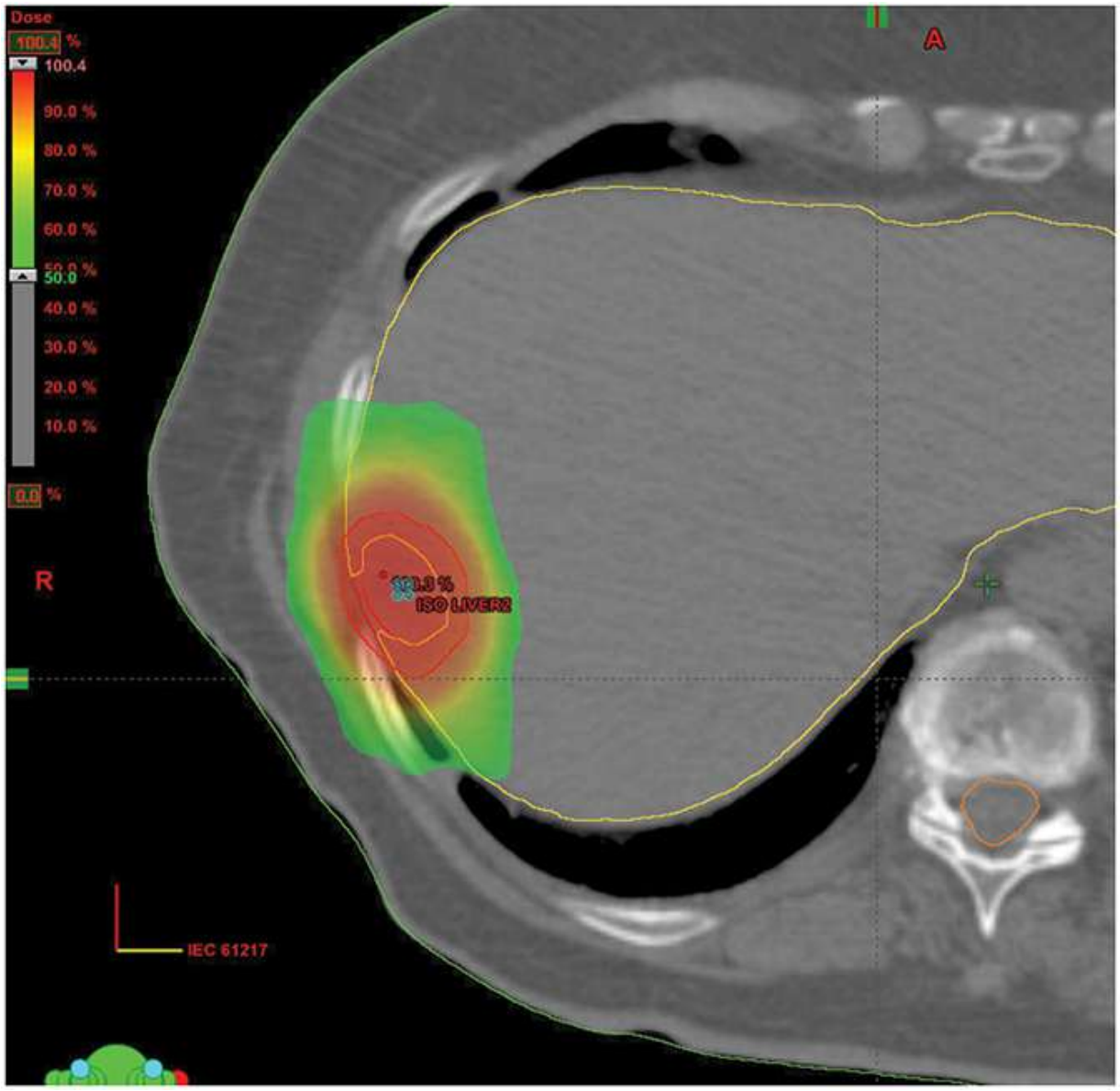


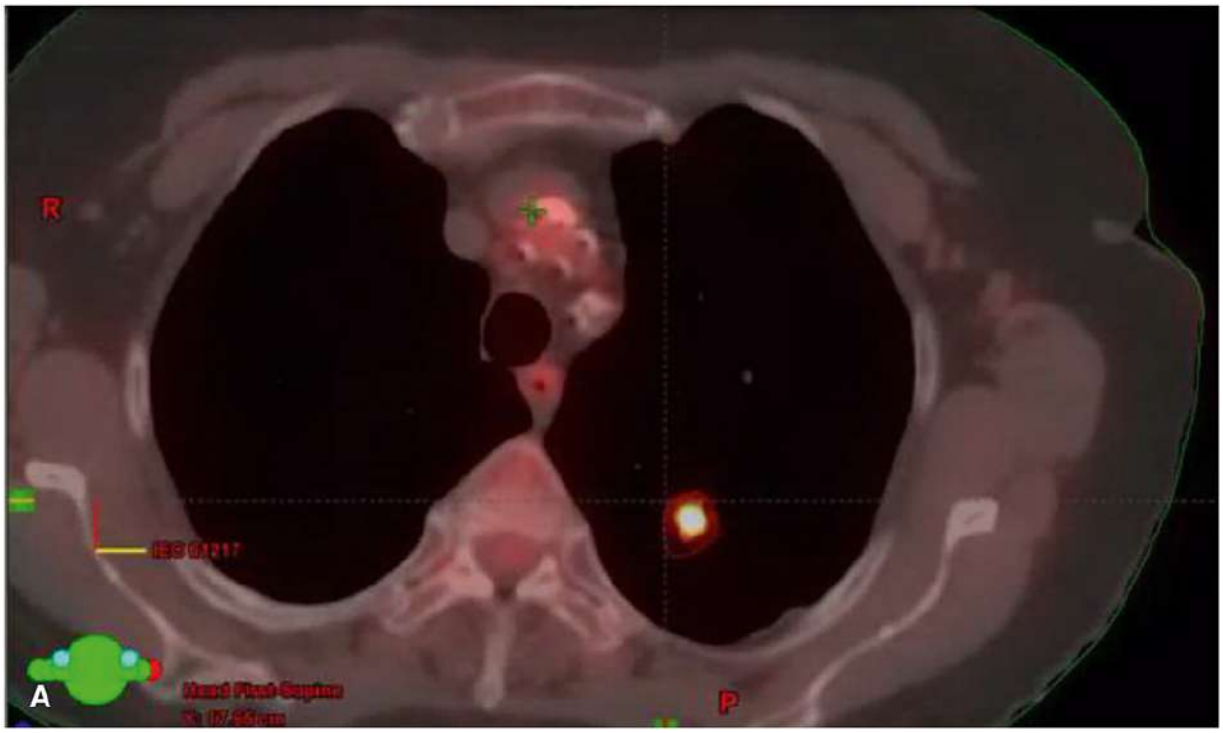
FIGURE 104.4 Axial computed tomography images showing the dose distribution from stereotactic body radiotherapy treatment of a liver metastasis.

With rapid advances in SBRT technique and experience, a number of modern trials on the treatment of oligometastatic disease have been initiated and reported. The phase II Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastases (SABR-COMET) trial, with its extended long-term outcomes, compared the outcomes of patients receiving standard palliative care (control arm) with those receiving SABR in addition to standard care (SABR arm), specifically targeting patients with one to five metastases and a controlled primary tumor. The 8-year follow-up

data revealed that the SABR arm exhibited significant improvements in OS and progression-free survival (PFS). Notably, the 8-year OS rate in the SABR arm was 27.2%, compared to 13.6% in the control arm. Moreover, 21.3% of patients in the SABR arm achieved survival beyond 5 years without recurrence, suggesting a potential shift toward a curative paradigm in select patient populations. In addition, the extended follow-up period reported no new major late toxicities, affirming the safety profile of SABR. Another noteworthy finding was the reduced utilization of cytotoxic chemotherapy in the SABR arm, indicating a potential for SABR in decreasing the need for more aggressive treatments in the long term.[88] Two phase III follow-up studies, SABR-COMET-3 and SABR-COMET-10, have been initiated to further explore the question of patient selection for metastasis-directed therapy using SABR, particularly by number of metastatic lesions.[89,90] Complementing these studies, the SABR-5 trial focused on the PFS and local control achievable with SABR in patients with up to five oligometastases.[91] This trial reported a median PFS of 15 months and local control rates of 93% and 87% at 1 and 3 years, respectively. Key prognostic factors influencing PFS included tumor diameter, performance status, and the number of metastases at the time of SABR. These findings, demonstrating notable outcomes in both PFS and local control, further reinforce the significant role of SABR in managing oligometastatic disease. The outcomes of these studies underscore the significant role of SABR in the management of oligometastatic disease, reinforcing its value in extending survival and maintaining quality of life.

The definitive SBRT treatment of oligometastatic disease involving the lung has also been the subject of numerous clinical reports.[92,93] A multi-institutional phase I and II trial of SBRT for lung metastases dose-escalated 38 patients with one to three lesions and cumulative maximal tumor diameters of less than 7 cm from 48 to 60 Gy in three fractions. A median survival of 19 months and local control rate of 96% at 2 years were achieved, while symptomatic radiation pneumonitis was uncommon (2.6%) and grade 3 toxicity or higher was reported as 8%.[94] A German multi-institutional pooled database of 700 patients with oligometastatic lung cancer treated with SBRT showed a 2-year local control rate of 81.2% and OS rate of 54.4%. Radiation-induced pneumonitis grade 2 or higher was observed in 6.5% of patients.[95]

The curative treatment of oligometastatic sites in addition to lung and liver has also shown promise in published clinical reports. In most series, the oligometastatic state has been defined as one to five sites of metastatic disease, with inconsistent application of primary disease status, overall disease volume, or maximal lesion size as constraints for oligometastatic disease (Figure 104.5). Investigators from the University of Chicago have reported a dose-escalation trial of 29 patients with one to five sites of metastatic disease, concluding that there was minimal toxicity and potential clinical benefit from this approach.[96] Another prospective study of 121 curative-intent SBRT with five or fewer oligometastatic lesions yielded 4-year survival rates of 28%, PFS of 20%, and local control of 60%.[97] Twenty-nine patients were alive and with no evidence of disease at last follow-up, leading the authors to conclude that "oligometastatic disease is a potentially curable state of distant cancer spread."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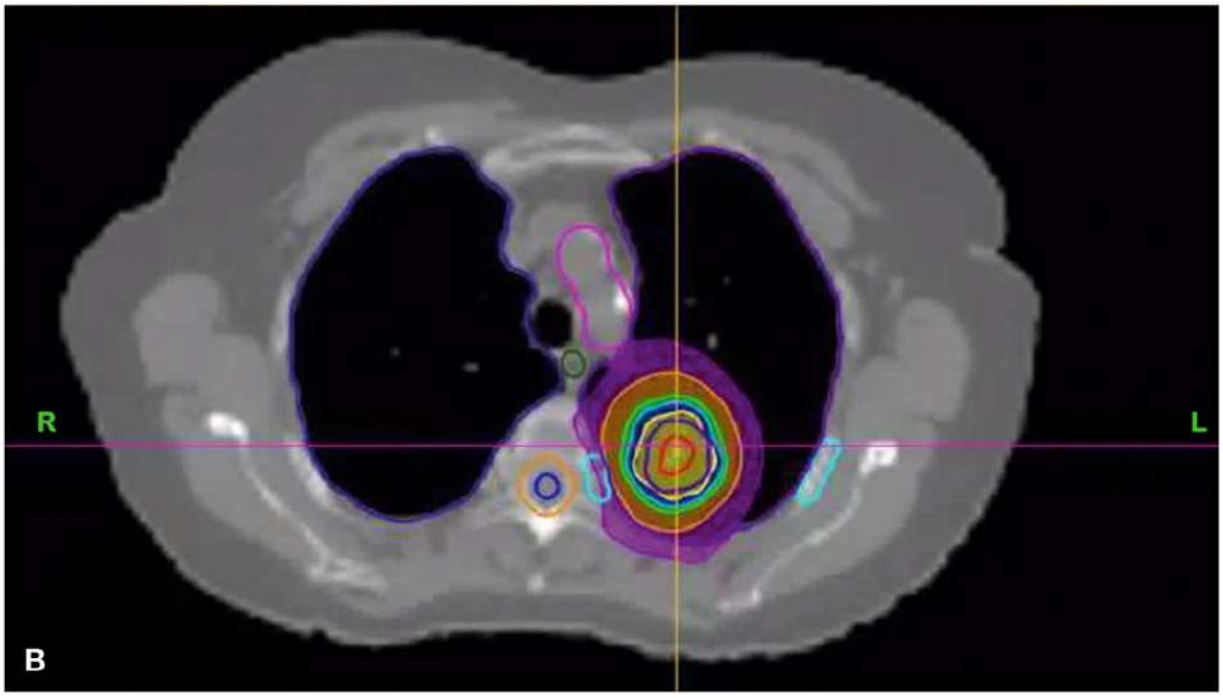
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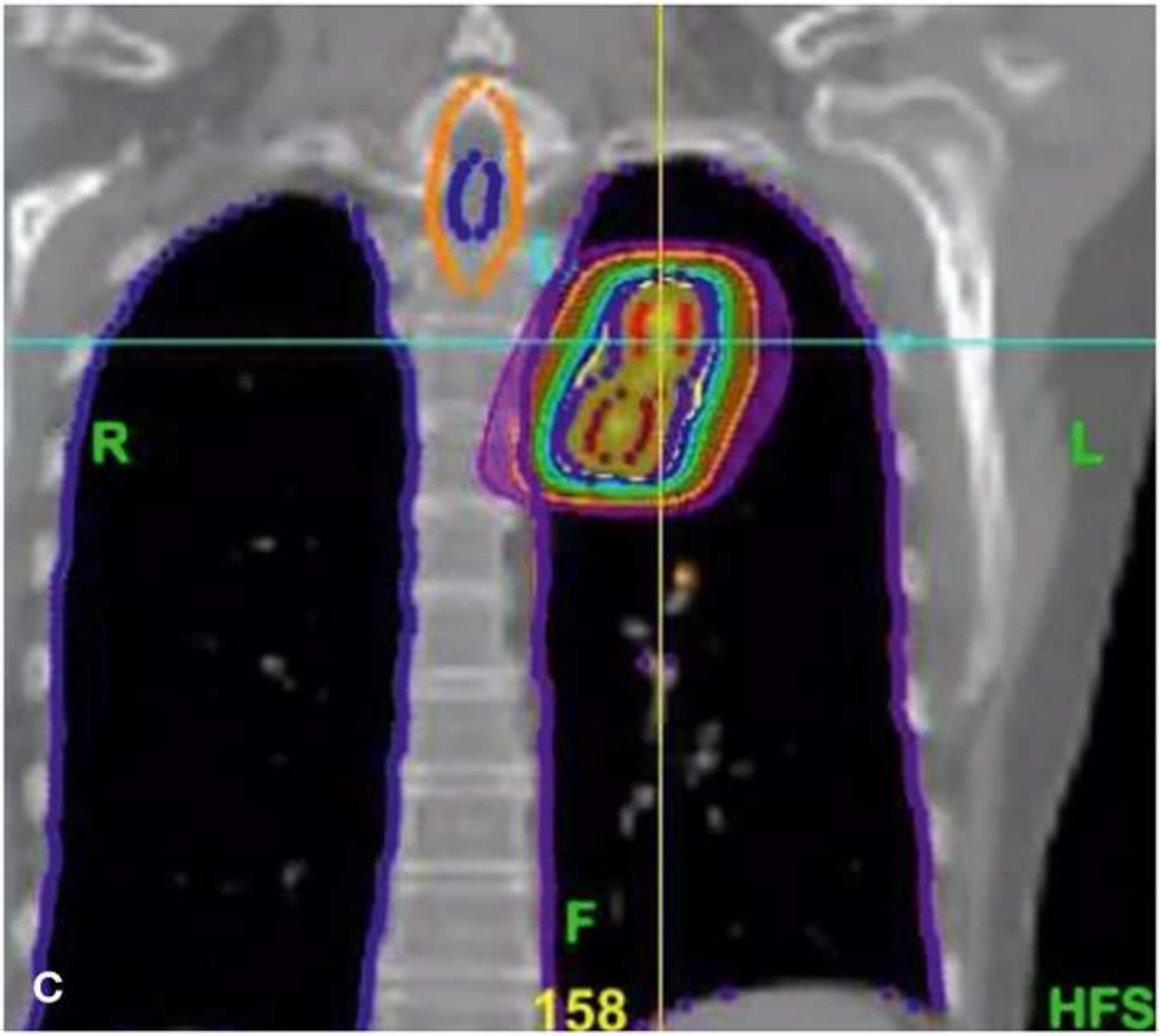

FIGURE 104.5 Positron emission tomography scan showing a solitary lung metastasis from a patient with a renal cell carcinoma (A), with axial (B) and coronal (C) isodose images.

Other investigators have also examined the curative role of oligometastatic disease for specific primary sites of disease. Milano et al[98] examined the role of curative SBRT for 51 patients with metastatic breast cancer, concluding prolonged survival and possible cure for select patients with limited metastatic disease, as well as the utility of palliative-intent SBRT for symptomatic or potentially symptomatic sites. International guideline statements have also addressed the management of select patients with oligometastatic breast cancer in consensus recommendations, stating "a small but very important subset of metastatic breast cancer patients, for

example those with a solitary metastatic lesion, can achieve complete remission and a long survival."[99]

Similarly, the role of curative SBRT for the treatment of limited metastatic prostate cancer shows promise. Prospective studies have shown good rates of local and PSA control in limited boney and nodal metastatic disease.[100,101] The ORIOLE trial further substantiates this, demonstrating that SBRT significantly reduces disease progression at 6 months in patients with oligometastatic prostate cancer compared to observation alone (19% vs 61%).[102] This trial, which randomized patients in a 2:1 ratio to receive SBRT or observation, also indicated that SBRT improved median PFS and that complete consolidation of prostate-specific membrane antigen (PSMA) radiotracer-avid disease with SBRT decreased the risk of new lesions. Importantly, SBRT was found to induce a systemic immune response, suggesting its potential for enhancing disease control beyond the treated lesions.

In addition to metastasis-directed therapy, the HORRAD and STAMPEDE trials in patients with limited metastatic disease to the bones and lymph nodes investigated the benefit of treatment of the primary site.[103,104] A meta-analysis including these trials showed that for patients with less than five metastases, there was a 7% improvement in 3-year survival with the addition of prostate RT, and for all patients, there was approximately 11% biochemical PFS benefit, though no OS benefit.[105]

While initial studies of the treatment of oligometastatic disease show promising results, safety of these treatments has been a concern since inception of this concept. Several studies have now demonstrated the safety of this approach. The NRG-BR001 phase 1 trial was a critical study evaluating the safety of SBRT in patients with oligometastatic disease.[106] The trial focused on patients either with three or four metastases or with two metastases in close proximity in patients with non–small cell lung, breast, and prostate cancer, utilizing SBRT to target these lesions. The findings demonstrated the safety of this approach, with no incidents of treatment-related deaths. However, the occurrence of late grade 3 adverse events emphasized the importance of prolonged follow-up for patients with oligometastatic disease. These promising results led to the initiation of a successor phase II study, NRG BR-002. This randomized phase II/III study investigated the role of metastases-directed treatment (MDT) with SBRT or

surgical resection alongside standard of care systemic therapy (SOC ST) in newly diagnosed oligometastatic breast cancer. The trial enrolled patients with four or less extracranial metastases, who were randomized to receive either SOC ST alone or in combination with MDT.[107] The results indicated no significant improvement in PFS or OS with the addition of MDT. While there were fewer new metastases within the treated/index areas in the MDT arm, the overall outcomes did not support a substantial benefit of adding MDT to SOC ST in patients with oligometastatic breast cancer, and the trial did not proceed to phase III.[78]

Early reports have also documented the potential utility of curative SBRT for oligometastatic disease from gynecologic and non–small cell lung primary sites, as well as involved oligometastatic sites such abdominal nodal metastases and adrenal gland metastasis.[87,108-112] For additional information on the treatment of oligometastases for specific sites, refer to the specific disease site chapter for each site.

The abscopal effect is a phenomenon where local RT leads to regression of distant, nonirradiated tumors. This concept has garnered renewed interest in the context of modern immunotherapy and the oligometastatic paradigm. This effect is thought to be underpinned by the immunomodulatory impact of radiation, which can stimulate a systemic antitumor immune response. Historically considered too rare and unpredictable for therapeutic goals, the abscopal effect is now increasingly observed in conjunction with immune checkpoint inhibitors (ICIs). The integration of RT with ICIs has been demonstrated to enhance the abscopal response, suggesting a potential new avenue for treating metastatic disease. Originally identified in the early 1950s, this effect encapsulates the regression of nonirradiated distant tumors following RT to a specific site.[113] The synergy between RT and ICIs, such as antibodies against cytotoxic T-cell antigen 4, programmed cell death protein 1, and programmed death ligand 1, has been a focal point of recent research.[114] The underlying mechanism, though not fully elucidated, seems to involve the optimal induction of DNA double-stranded breaks by specific radiation doses, triggering an antitumor immune response through the cGAS-STING pathway.[115]

Clinical and preclinical studies have reported systemic abscopal effects when combining immunotherapy with RT.[116] Golden et al showed that concurrent treatment with RT and ipilimumab in a patient with metastatic

lung adenocarcinoma showed regression of disease at distant sites, with a post-treatment increase in tumor-infiltrating cytotoxic lymphocytes observed.[117] Preclinical studies have highlighted the variety of factors that can influence this phenomenon, mostly associated with modulation of cytotoxic T-cell behavior, and emphasize the importance of dosage and timing of both RT and immunomodulatory drugs in its promotion.[118] While the abscopal effect offers a promising avenue in cancer treatment, its rarity and unpredictability remain challenges. Ongoing research aims to understand the mechanisms driving this effect, and many modern trials exploring the treatment of oligometastatic disease include biomarkers with the hope of improving patient stratification and treatment planning.

In summary, local therapy, particularly using advanced techniques such as SBRT, may be beneficial in selected patients with a small number of metastatic sites; these patients should be treated on prospective trials in order to obtain a better understanding of the appropriate use of this technology.

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CHAPTER 105

Cancer Pain: Assessment and Management

Ellen Kim and Tracy A. Balboni

The most common cancer-related symptom that radiation oncologists are called upon to assess and manage is cancer-related pain. More than half of patients undergoing radiotherapy (RT) experience pain.[1] Notably, majorities of patients and physicians feel that patients' pain is suboptimally controlled,[2] highlighting the need for oncologists to have a comprehensive understanding of and facility with cancer pain assessment and management.

PAIN AS A MULTIDIMENSIONAL CONSTRUCT

Pain is a complex symptom that is dynamically related to physical, emotional, social, and spiritual aspects of illness and quality of life. For example, the young parent with metastatic cancer who is struggling emotionally with concerns of how this will impact young children may experience bone pain heralding progressive disease with much greater intensity than a patient who has experienced acceptance of illness. Dame Cicely Saunders, founder of the modern hospice movement, termed this comprehensive concept, "total pain" (Figure 105.1).[3] Such an approach is critical to holistic pain assessment and management, addressing the multidimensionality of pain and drawing upon multidimensional resources for its mitigation. In the patient example above, physical strategies to address pain, such as pharmacologic agents and palliative RT, should be considered together with psychosocial/spiritual assessment and care as part of a comprehensive approach to pain management, an approach discussed further in Chapters 106. Such an approach is fostered by multidisciplinary management of patients with cancer pain, including palliative and psychosocial specialists, social work, and chaplaincy.

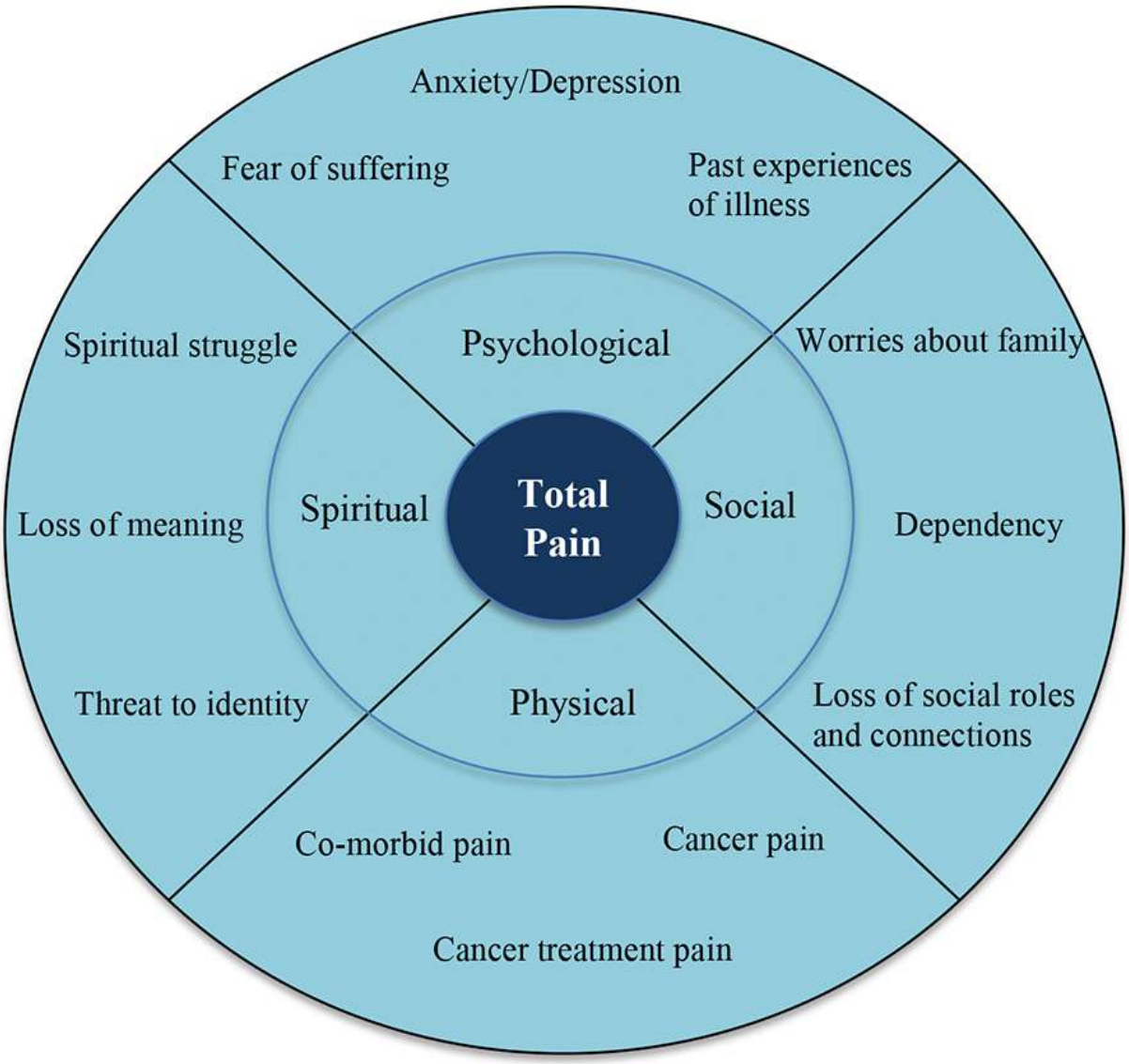

FIGURE 105.1 Dame Cicely Saunders conceptual model of total pain, with examples of factors contributing to the physical, psychological, social, and spiritual pain domains. (Derived from Saunders C. The treatment of intractable pain in terminal cancer. *Proc R Soc Med*. 1963;56[3]:195-197.)

PHYSICAL ETIOLOGIES OF CANCER-RELATED PAIN

Though cancer can be asymptomatic within the normal tissues, symptoms arise once sufficient disruption of normal tissues has occurred, with pain being the most common manifestation. Cancer pain has been hypothesized to be multifactorial in its etiology (Figure 105.2).[4] It is hypothesized to arise from induction of local inflammatory cytokines within the microenvironment with recruitment of inflammatory cells. These, in turn,

promote sensitization and activation of primary afferent neurons. In addition, cancer pain can arise from mechanical disruption and/or mass effect on normal tissues. This includes normal tissue destruction resulting in pain, such as lytic disease causing bone instability as well as local tissue compression or expansion resulting in pain, such as back pain from malignant spinal cord compression or capsular stretch pain from extensive liver metastases.

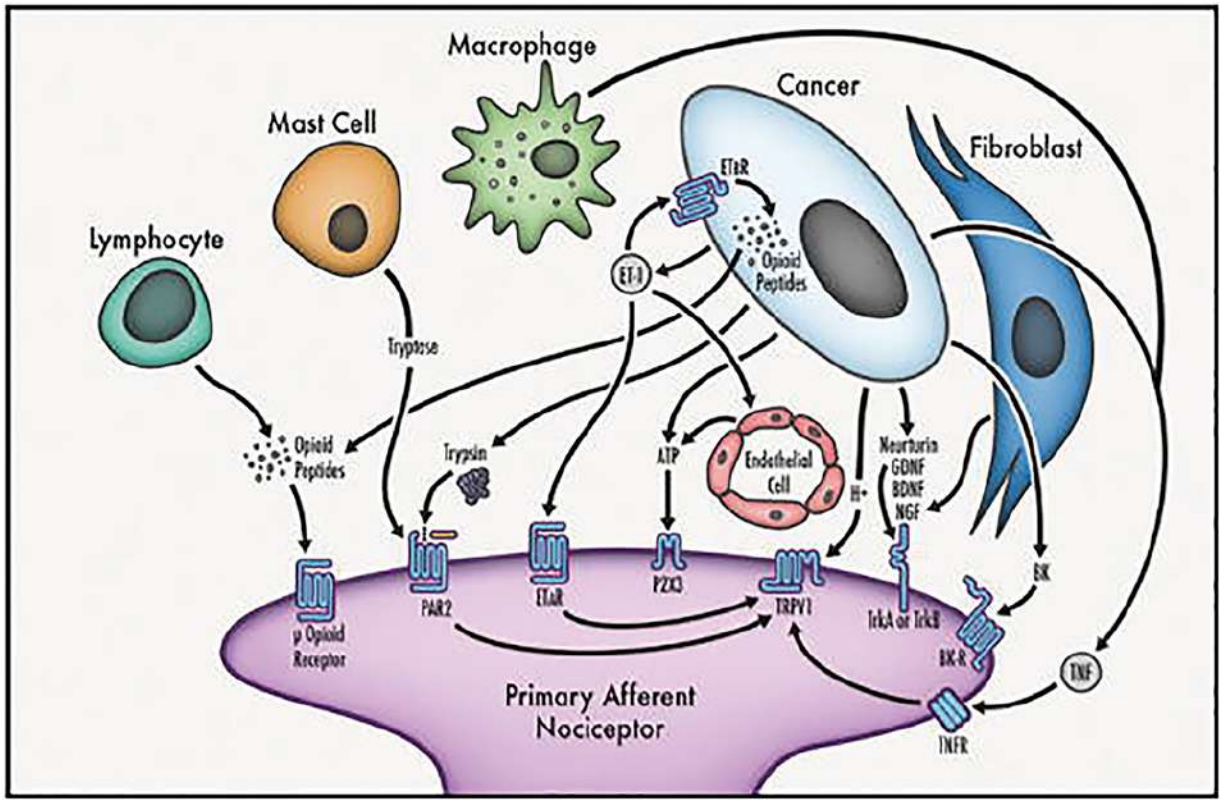

FIGURE 105.2 Schmidt model of the mechanisms of cancer pain. Cancer cells are hypothesized to secrete mediators that sensitize and/or activate primary afferent neurons within the local microenvironment. Cancer cells are posited to secrete chemoattractants that recruit lymphocytes, mast cells, macrophages, and fibroblasts that secrete mediators modulating cancer pain. BDNF, brain-derived neurotrophic factor; BK, bradykinin; BK-R, bradykinin receptor; ET-1, endothelin-1; ET_AR, endothelin A receptor; ET_BR, endothelin B receptor; GDNF, glial-derived neurotrophic factor; NGF, nerve growth factor; PAR2, protease-activated receptor 2; TrkA, tyrosine kinase receptor A; TrkB, tyrosine kinase receptor B; TRPV1, transient receptor potential vanilloid 1. (From Schmidt BL. The neurobiology of cancer pain. *Neuroscientist*. 2014;20[5]:546-562. Copyright © 2014 SAGE Publications. Reprinted by permission of SAGE Publications.)

Cancer-related pain can also result from the delivery of RT and subsequent complications to normal tissues. Acutely, irradiation of normal tissues with a rapid growth rate causes cell death and triggers a cascade of cytokines and thrombotic and growth factors, propagating local painful reactions.[5,6] Examples include RT-related mucositis and dermatitis. RT can also cause pain because of late or chronic tissue damage such as fibrosis and damage to local microvasculature. Pain management in the setting of acute RT toxicities typically requires a strategy conducive to dynamic pain management needs, including rapid uptitration with gradual downtitration of pain interventions, as symptoms resolve. In the setting of pain related to the long-term effects of RT, pain management strategies should reflect the frequent long-term nature of these pain syndromes, given that they often are caused by permanent damage to normal tissues.

This chapter provides an overview of cancer pain assessment, management, and guidelines critical to the practice of radiation oncology. RT is often a valuable component of a treatment plan for cancer-related pain, given its efficacy in palliating symptomatic cancers involving bone, nerves, and other soft tissues.[7] The application of RT for the palliation of cancer-related pain and other symptoms is covered in their respective chapters elsewhere in this book.

Types of Cancer-Related Pain

Pain is generally classified as nociceptive or neuropathic or can present as a combination of these pain types. For example, lumbar vertebral body involvement at L1 with tumor compressing the L1 exiting nerve root can cause both local somatic pain (eg, mid to lower back pain) because of bone involvement by tumor as well as referred neuropathic pain down the L1 dermatomal distribution to the lateral hip. Nociceptive pain refers to the nervous system response that is proportional to the tissue damage initiating the response. Nociceptive pain is subcategorized into somatic pain and visceral pain depending on the location and symptoms of the painful stimulus. Somatic pain generally is a local response to damage to normal tissues, such as skin, muscle, or connective tissue. It often presents as a dull or achy pain that is localizable to its source. Conversely, visceral pain is typically due to irritation of viscera (eg, colic from gallstones) and may be

difficult to localize, though it can also have a somatic component. Visceral pain often is characterized as a dull, sharp, and/or cramping pain.

Neuropathic pain results from irritation and activation of peripheral or central nerves. Patients may complain of burning, shooting, tingling, or numbness, which generally occurs along a nerve distribution.[8] Neuropathic pain can result in pain out of proportion to the pain stimulus where there is abnormal pain processing by the peripheral or central nervous system.

Cancer Pain Assessment

All patients should be screened for pain at each point of clinical contact. Typically, screening is performed with the 0 to 10 pain intensity scale. A comprehensive pain assessment should be performed at initial consultation and at each subsequent evaluation of their ongoing pain management. A comprehensive pain assessment is critical for determining the etiology of pain and for informing strategies for symptom management, both pharmacologically and with local interventions such as RT. Each type of pain syndrome is amenable to treatment with different modalities. For example, localized, somatic pain may be better treated with nonsteroidal anti-inflammatory drugs (NSAIDs) and/or with opioid medications, whereas neuropathic pain may be more effectively managed with anticonvulsants or antidepressants with or without opiates.

Comprehensive pain assessment should include assessment of the following factors, captured in the acronym “PAINED” to aid in application to clinical practice. Place (P) is assessment of the location of pain, including any pain radiation. Activators (A) are determining factors that make the pain worse, such as positions (eg, lying down), actions (eg, walking), or time of day. Intensity and interval (I) are assessment of the intensity of the pain, typically assessed with the 0 to 10 pain scale from 0 (none) to 10 (worst possible pain) together with the interval of time the pain has been present; this includes assessment of changes in pain intensity over time. Asking about the range of pain intensity and intensity changes with aggravating factors can also be informative. Nullifier (N) is assessment of those factors that reduce pain, including analgesics (with full assessment of analgesic types used and quantity), positions and activities reducing pain, or other practices (eg, meditation). Effect (E) is assessment of the effect of

pain on daily activities, including activities of daily living and additional activities important to the patient (eg, being able to pick up a grandchild). Finally, description (D) is assessment of the quality of the pain in the patient's own words (eg, dull, stabbing, aching, burning).

Assessment of the patient goals for pain management (eg, activity goals) and evaluation of risk factors for opioid misuse and diversion are also important to determine an optimal strategy for pain management. Risk factors include a prior history of drug or alcohol abuse, family history of substance abuse, history of psychiatric disorders (eg, anxiety, depression, post-traumatic stress disorder), history of legal problems or incarceration, and age <45 years. In patients with risk factors, referrals to clinicians with experience in managing pain in high-risk patients, such as palliative medicine specialists, should be considered. All patients given opiates should be educated regarding safe use, storage, and disposal of opiates. Furthermore, opioid contracts—statements signed by the patient regarding the appropriate use of opioids, commitment to opioid safety, and nonmisconduct—are often performed at the time when long-acting opioids are required. Finally, opioid prescribing should include review of the patient's prescription history with the local state prescription monitoring program.

Cancer Pain Management

A comprehensive pain assessment guides the application of workup and treatment strategies. For example, a patient with metastatic cancer and low back pain radiating to the lower extremities should have a magnetic resonance imaging (MRI) of the spine to assess for possible etiology of cord/cauda compression, with the treatment strategy based on the etiology. Wherever possible, the etiology of the pain should be addressed (eg, RT for bone metastasis–related pain) in addition to pharmacologic intervention. The roles of RT in alleviating cancer-related pain are addressed elsewhere. Herein, guidelines to approach pharmacologic and other non–cancer-directed therapies to alleviate pain are outlined.

GUIDELINES FOR PAIN MANAGEMENT

Many national and international organizations have developed guidelines for pain management. Despite variations in the details, the principles and approaches are consistent across guidelines. The World Health Organization (WHO), American Pain Society (APS), and other national consensus guidelines are discussed here.

WHO pain ladder. The WHO guidelines for analgesic management of cancer pain, first described in the early 1980s,[9,10] consist of a three-step approach that has been validated in clinical trials.[11] Despite some debate on its effectiveness,[12] it establishes a widely practiced, stepwise approach in the treatment of various levels of pain severity.

The first tier involves the use of nonopiate medications, primarily NSAIDs (Table 105.1). These medications include acetaminophen, nonspecific cyclooxygenase inhibitors (including ibuprofen, diclofenac, and aspirin), and cyclooxygenase-2 inhibitors (celecoxib).[13] NSAIDs are considered the first group of medications to administer. If the patient's pain persists or worsens, the second tier adds a weak opioid in addition to the nonopiate. Finally, continued treatment for worsening pain includes the addition of a strong opioid to replace the weak opiate, the third tier (Table 105.2).

TABLE 105.1 GUIDE TO COMMON NONOPIATE MEDICATIONS AND STARTING DOSES FOR ADULTS

Medication	Starting Dose (Maximum Daily Dose in mg)
Acetaminophen	500, 3-4 × day (4,000)
Nonsteroidal anti-inflammatory drugs	
Aspirin	325, 3-4 × day (4,000)
Ibuprofen	200, 3 × day (2,400)
Naproxen	250, 2 × day (1,250)
Ketorolac	IV 15-30 up to 4 doses
Diclofenac	50, 3 × day (150 mg)
Specific COX-2 inhibitors	
Celecoxib	100, 2 × day (400-800)

COX-2, cyclooxygenase-2; IV, intravenous.

TABLE 105.2 GUIDE TO COMMON WEAK AND STRONG OPIOID MEDICATIONS AND POTENTIAL STARTING DOSES

Opioid	Starting Dose	PO Conversion (mg)	IV Conversion (mg)
Weak			
Tramadol	50 mg PO 2-3 × day	—	—
Codeine	30 mg PO 4-6 × day	—	—
Hydrocodone	5 mg PO 4-6 × day	—	—
Strong			
Morphine	15 mg PO 4-6 × day	30	10
Hydromorphone	2-4 mg PO 4-6 × day	8	2
Methadone	2.5-5 mg PO 2-3 × day	2	1
Fentanyl	Transdermal 25 μg/d	NA	0.2
Oxycodone	5-15 mg PO 4-6 × day	20	NA

Opiate medication must be titrated for adequate pain relief and minimal side effects. For the strong opiates, equivalent doses for conversion are given, with methadone IV as the base dose of 1 mg. The conversion factors can be used to change PO or IV doses among the different opiates (ie, 2 mg of PO methadone is roughly equivalent to 30 mg of PO morphine). Similarly, 2 mg of PO methadone is equivalent to 1 mg of IV methadone. When changing from one opiate to another, a reduction factor is sometimes applied (usually 25%-50% of the original medication's dose) because of less tolerance to the new medication. For example, if a patient is using 60 mg of PO morphine every 4 hours, an equivalent oxycodone dose may be 40 mg × a 50% reduction, leading to 20 mg every 4 hours.

IV, intravenous; NA, not applicable; PO, by mouth.

Five simple principles are recommended to make the pharmacologic treatments effective: (a) Oral administration of analgesics should be used whenever possible; (b) analgesics should be given at regular intervals; (c) analgesics should be prescribed according to pain intensity as evaluated with a pain scale; (d) dosing of analgesics should be adapted to the individual; and (e) analgesics should be prescribed with a constant concern for detail.[14]

Over time, adaptations of the WHO ladder have been proposed. In refractory pain or crises of chronic pain, a fourth step may be considered. This fourth step includes invasive techniques such as nerve blocks, neurolysis, or surgical or other interventions.[9,15] Adjuvant medications

including steroids, anxiolytics, antidepressants, hypnotics, anticonvulsants, antiepileptic-like gabapentinoids (gabapentin and pregabalin), membrane stabilizers, sodium channel blockers, *N*-methyl-D-aspartate receptor antagonists, and cannabinoids may be used in the treatment of neuropathic pain.[16,17]

APS and other national consensus guidelines. Although the WHO guidelines are a good initial step in pain management, other organizations have expanded these strategies to improve treatment for cancer pain. These guides provide initial medication dosages, the addition of adjuvant medications, and information on appropriate dose increases, allowing the radiation oncologist to further develop pain management skills.

The 2005 APS *Guideline for the Management of Cancer Pain in Adults and Children* contains detailed discussions of cancer pain management algorithms, pharmacologic strategies, co-analgesics, psychological strategies, supportive therapy, integration of nonpharmacologic and pharmacologic treatments, physical strategies, nerve blocks, surgical strategies, RT, chemotherapy, and pain management in special populations. It also discusses patient education and the importance of patients' adherence to the pain management plan as well as how to improve quality of care in pain management.[18]

The latest national consensus guidelines for adult cancer pain outline the following principles: (a) Patients should be screened for pain at each point of contact; (b) pain intensity must be quantified and quality described by the patient whenever possible; (c) a formal comprehensive pain assessment must be performed for new or worsening pain; (d) pain management plans should employ optimized disease-specific therapies, rely on multidisciplinary input as appropriate, anticipate and minimize pain management side effects (eg, opioid-related side effects), involve patients in the development of treatment plans and goals, and address the multidimensional impacts of pain on patients and families; (e) reassessment of pain intensity must be performed at specified intervals to ensure that the therapy selected is having the desired effect; (f) education must be provided to the patient to ensure understanding of anticipated side effects and of safe use and disposal of opiates and other analgesics; and (g) all patients should be screened for potential opiate misuse, abuse, or diversion and include the

use of prescription monitoring programs as directed by state government requirements. The guidelines provide specific suggestions for dosing of NSAIDs, opioids, and co-analgesics, as well as titrating and rotating of opioids, escalating opioid dosage, managing opioid adverse effects, and deciding when and how to proceed to other techniques/interventions for the management of cancer pain.

Role of Oncologists and Pain Specialists in Managing Cancer-Related Pain

Radiation oncologists, together with other oncology clinical practitioners, are responsible for assessing and managing pain for their patients by utilizing the guidelines as noted above. However, this raises the question of when to call upon palliative medicine or acute pain specialists in pain management. Randomized trials have shown a quality of life benefit of early involvement of palliative medicine clinicians in the care of cancer patients, and hence, the American Society of Clinical Oncology recommendations call for the early integration of palliative care into standard oncology care.[19] Oncologists should have a low threshold to call upon palliative care providers to guide pain management strategies, particularly in the setting of refractory pain, complex pain syndromes, and/or difficult-to-manage side effects. Integration of palliative medicine into oncology care, and when to refer patients to palliative medicine specialists, is discussed in more detail in Chapters 106.

Routes of Administration

Chemotherapy, surgery, and RT often produce significant side effects that can limit oral administration of pain medications. Furthermore, cancer-related pain can be so severe that acute pain management requires hospital admission and intravenous (IV) pain medication administration. Both opiate and nonopiate pain medications come in formulations that can be delivered via nonoral routes, such as transdermal, IV, or rectal. When changing from oral to another delivery mode, care must be taken to give equipotent analgesic doses. Conversion charts for opioids are readily available in the literature.[20] When switching opiate agents, a 25% to 50% dose reduction should be applied to account for incomplete cross-tolerance between

distinct opioid agents. Such complicated pain management scenarios may require an inpatient stay and/or the assistance of pain management specialists.

Opiate Side Effects

Treating a patient's pain is a balance of maximizing analgesic effects and minimizing side effects.[21] Common opioid side effects include gastrointestinal (constipation, nausea, and emesis), respiratory (decreased respiratory rate), dermatologic (pruritus and dry mouth), and peripheral/central nervous system (myoclonus, sedation, hallucinations, and seizures) effects.

General management strategies include the pharmacologic treatment of the side effects. These include the standard inclusion of strategies to mitigate constipation, such as high water intake, dietary fiber, and a daily regimen of stool softeners and laxatives. Consideration of peripherally acting opioid antagonist methylnaltrexone is made in the case of constipation refractory to these measures. Nausea can be mitigated through the use of antiemetics, though care must be taken in the use of antiemetics that can cause constipation, such as ondansetron. Another important opiate side-effect mitigation strategy is to reduce the dose of opiates required to achieve analgesia through the use of adjunctive medications for pain management, including agents such as glucocorticoids, anticonvulsants, and antidepressants. These medications are discussed further in the next section. A third strategy is opioid rotation as some opiate side effects such as pruritis and myoclonus can be mitigated by rotating to another opioid agent. Opioid rotation should follow the principles of an approximate 25% to 50% dose reduction based on an equianalgesic table, given incomplete cross-tolerance of different opiate agents.

Adjuvant Therapies and Interventions for Pain Management

Using the WHO ladder, pain related to cancer can be managed with oral medications in 70% to 85% of patients.[11,22] At any point on the WHO analgesic ladder, adjuvant therapy can be initiated to supplement NSAIDs and opioid treatment. Benefits of adjuvant therapy include the use of

medications tailored to specific causes of nociceptive responses (ie, neuropathic pain) and reduction of opiate side effects.

Adjuvant Therapies in Neuropathic Pain

Because neuropathic pain is often not responsive to opioid medications unless high doses are applied, other classes of medications are often prescribed.[23] Glucocorticoids (eg, dexamethasone) are effective for the short-term management of tumor-related neuropathic pain and are often the initial agent of choice when managing neuropathic pain while awaiting an anticipated response to palliative RT. Dexamethasone is usually preferred in oncology due to its favorable balance of glucocorticoid (anti-inflammatory and analgesic) to mineralocorticoid properties (eg, fluid retention), longer half-life allowing for less frequent dosing, and availability in both oral and IV formulations.[24] If glucocorticoids are insufficient to control neuropathic pain, and/or palliative RT does not sufficiently resolve neuropathic pain symptoms, typically anticonvulsants or antidepressants are considered.

Anticonvulsants such as gabapentin, carbamazepine, and pregabalin are effective in managing neuropathic symptoms.[8] Both gabapentin and pregabalin are renally excreted and have minimal drug-drug interactions, which renders these medications effective first-line treatments for neuropathic pain.[8] Like anticonvulsants, antidepressants are a broad category of medications that stabilize neurons involved in neuropathic pain. Tricyclic antidepressants in low doses, such as amitriptyline, have been well studied and can be effective for pain relief.[25] Serotonin reuptake inhibitors and newer classes of antidepressants, including selective serotonin and norepinephrine reuptake inhibitors (milnacipran, duloxetine, and venlafaxine), are less well studied but are often prescribed for neuropathic pain. Because many patients with neuropathic pain experience depression or anxiety, antidepressants may play a dual treatment role and improve the efficacy of pain control.[26]

Topical agents can also be effective in the management of neuropathic pain and often have minimal side effects. These include capsaicin cream and transdermal lidocaine, both found to be effective in the management of neuropathic pain.[26-28]

Muscle relaxants are another class of agents that can be used in both neuropathic pain and other pain syndromes. Because painful muscle spasm can add to the pain etiology in both neuropathic and other pain syndromes (eg, somatic pain from vertebral body fracture), muscle relaxants can have a role in mitigating pain in this setting. Agents typically used include baclofen and cyclobenzaprine.

Finally, agents that antagonize the NMDA (*N*-methyl-D-aspartate) receptor are also considered in the management of neuropathic pain; however, prescription of these medications is typically limited to pain specialists. The NMDA receptor has a role in modulating pain signals throughout the nervous system. Methadone is a long-acting opioid receptor antagonist, which is hypothesized to also act as an NMDA receptor antagonist, preventing morphine tolerance and NMDA hyperalgesia effects.[29] Ketamine, a specific NMDA receptor antagonist, is also employed by pain management specialists to relieve cancer and neuropathic pain, especially refractory pain.[30]

Other adjuvant analgesic drug classes used in cancer therapy include local anesthetics, steroids, muscle relaxants, benzodiazepines, α-adrenergic agonists, and bisphosphonates.[30] In recent years, there has been a resurgence in clinical trials of cannabis extracts and analogs in the treatment of refractory cancer pain.[31] Many of these medications are used in specific pain syndromes, which may be useful for the radiation oncologist (Table 105.3).

TABLE 105.3 COMMON ADJUVANT MEDICATIONS WITH STARTING DOSAGES AND COMMON SIDE EFFECTS

Medication	Starting Dose (PO Unless Otherwise Specified; mg)	Significant Side Effects
Antidepressants		
Amitriptyline	10-25 at night	Cardiac, CNS
Nortriptyline	10-25 at night	Cardiac, CNS
Venlafaxine	37.5 every day	CNS
Duloxetine	60 every day	Nausea, somnolence
Anticonvulsants		

Medication	Starting Dose (PO Unless Otherwise Specified; mg)	Significant Side Effects
Gabapentin	100, 3 × day	CNS, sedation
Carbamazepine	100, 2 × day	Bone marrow, liver, CNS
Pregabalin	75, 2 × day	CNS, sedation
Topicals		
Lidocaine 5%	1-3 patches for 12 h	CNS, cardiac
Capsaicin	0.025% cream	Burning
Muscle relaxants		
Baclofen	5, 3 × day	CNS
Cyclobenzaprine	5, 3 × day	Drowsiness, dry mouth
Tizanidine	2 every night (4 mg tid)	Weakness, dry mouth
***N*-Methyl-D-aspartate antagonist**		
Ketamine	Intravenous infusion	Hallucinations, CNS

CNS, central nervous system; PO, by mouth; tid, three times a day.

INTERVENTIONAL PAIN MANAGEMENT STRATEGIES

Although most cancer pain can be managed medically, some patients require interventional procedures to achieve pain relief. Such interventions include neuroablative techniques and implantable neuroaxial drug delivery devices. These strategies should be considered in patients with refractory pain despite pharmacologic management via traditional administration routes (eg, oral) escalated according to WHO guidelines or among patients with severe side effects despite optimization of pharmacologic agents.

Neuroablative Techniques

Neuroablative techniques can be excellent options for patients who have pain along discrete nerve distributions when chronic and/or insufficiently controlled by conventional systemic pharmacologic management. Interventional pain management specialists offer a myriad of neurolytic

procedures that can be highly efficacious and can reduce or even obviate the need for systemic pharmacologic pain medications.

Common nerves targeted include intercostal nerves for thoracic chest wall or abdominal wall pain, maxillary and mandibular nerves for facial pain, and median branch nerves for facet arthropathy.[32] Cryoanalgesia techniques apply subzero temperatures to induce Wallerian degeneration of neurons while allowing normal regrowth of axons. Radiofrequency techniques use heat to induce nerve damage. Chemical neurolysis can be achieved with phenol or alcohol preparations.

Pain signals initiating from the perineal, pelvic, and abdominal regions may be transmitted via visceral afferents following the sympathetic nervous system. Along with these fibers, the sympathetic nerves coalesce at specific ganglia (impar, superior and inferior hypogastric, and celiac plexus). At these sites, image-guided neurolytic procedures can be performed.[33] When pain fibers are destroyed in this process, the associated region is also sympathetically denervated.

Implantable Neuroaxial Drug Delivery Devices

Implantable neuroaxial drug delivery devices are indicated when oral opioid doses are escalated without sufficient pain relief and/or when side effects are intolerable.[34] Either semipermanent epidural systems or permanent intrathecal delivery systems can be used to deliver local anesthetic and opiate medications in low concentrations to appropriate spinal cord root levels.[35] The benefits of these methods include decreased side effects than systemic pain pharmacologic agents and often superior pain control.[36]

Electrostimulation techniques may also be applied to disrupt the flow of pain signals in the spinal cord. Transcutaneous electrical nerve stimulation (TENS), spinal cord stimulation at thoracic and lumbar regions, and deep brain stimulation at the thalamus or motor cortex can interfere with the conduction of pain signals.[37] The stimulation of large motor fibers inhibits the conduction of pain signals by small nerve fibers and has shown efficacy for various pain syndromes.[38]

Neurosurgical techniques are generally reserved for refractory pain and specific indications. Plexus root avulsions may be responsive to dorsal root entry zone lesioning, but the indications and success rates are limited.[39]

More specific lesions at the spinal cord and central nervous system (eg, thalamotomy and deep brain stimulation) have also been used with variable success and significant side effects.[40] Finally, various chemoneurolytic medications can be delivered intrathecally for the destruction of specific nerve roots or parts of the spinal cord for the treatment of refractory cancer pain.[41]

Finally, electroanalgesia involves a noninvasive strategy of electrical disruption of pain signals from a locus of pain to reduce pain perception. The most common types include TENS and scrambler therapy. A recent review[42] suggests some potential for benefit in chronic pain management, including in cancer-related pain,[43] though further research is required.

COMPLEMENTARY THERAPIES

Conventional medical regimens may not satisfactorily treat cancer-related pain syndromes. Several complementary modalities such as hypnosis, biofeedback, massage, music therapy, mind-body exercises, and dietary supplementation have been shown to reduce anxiety and chronic pain,[44] yet more multi-institutional, randomized controlled trials are needed to confirm their efficacy in this setting.[45]

Acupuncture is perhaps the most extensively studied alternative method for pain control.[46] Acupuncture can relieve both acute pain (eg, postoperative dental pain) and chronic pain (eg, headache, osteoarthritis).[47-49] Acupuncture also appears effective against cancer-related pain. A randomized, placebo-controlled trial tested auricular acupuncture for patients with cancer pain despite medication. Pain intensity decreased by 36% at 2 months from baseline in the treatment group, a statistically significant difference compared with the two control groups for whom little pain reduction was seen.[50] Most patients in this study had neuropathic pain, which is often refractory to conventional treatment. Neurophysiologic studies show that acupuncture-induced analgesia appears to be mediated by endogenous opioids and other neurotransmitters.[51] Functional brain imaging studies suggest that acupuncture also modulates the affective-cognitive aspect of pain perception.[52] Correlations between functional MRI signal intensities and analgesic effects induced by acupuncture have been reported.[53]

SPECIFIC SCENARIOS FOR THE RADIATION ONCOLOGIST

The following section identifies some common pain scenarios and syndromes specific to the setting of radiation oncology and proposes strategies for their management. As previously noted, radiation oncologists are generalist palliative care providers who should readily reach out for the expertise of pain specialists (eg, palliative medicine and anesthesia pain services) to ensure optimal pain control and quality of life for their patients.

Pain During Radiotherapy Planning and Treatment

Radiation oncologists regularly encounter patients who cannot tolerate RT positioning secondary to pain. The first goal should be to optimize treatment positioning and to decrease time on the treatment table to minimize pain. Often, simple modifications in treatment setup (eg, cushion under the knees and/or neck), where feasible without compromising radiation delivery, can greatly mitigate incident pain. Next, overall pain management using the aforementioned guidelines should be optimized. Premedication with additional dosing of the breakthrough pain agent such as short-acting opiates approximately 1 hour prior to the simulation or treatment should be performed to anticipate incident pain. Not infrequently, patients will require IV pharmacologic management as an inpatient and hence IV premedication can be given. For such inpatients with severe pain, pain specialists should be involved to optimize pain management using specialized strategies. Among patients with pain that is severe only with the positioning and who may become overmedicated with traditional short-acting opiates, fast-acting opiates can also be considered. For example, transmucosal preparations of fentanyl are optimal because of their pharmacologic properties of fast onset and resolution of effect.

Mucositis and Proctitis

Pain associated with mucositis (up to 75% of patients treated with radiation) can be debilitating and, if not sufficiently controlled, may result in treatment delays and/or dose limitations of RT.[54] Pain control strategies for patients with mucositis follow the aforementioned pain management guidelines but with some adaptations, given the particular needs of this

patient population. Topical analgesics, such as viscous lidocaine preparations (eg, 1:1:1 solution of magnesium and aluminum hydroxide, diphenhydramine, and lidocaine), can provide relief from incident pain when swallowing.[55] When systemic pain management is required, often, liquid short-acting opiate preparations and transdermal long-acting agents (eg, fentanyl patch) are required, given difficulty swallowing pills. Mucositis prevention and management will be discussed in greater detail in Chapters 106.

Similar to oral mucosa, the rectum is susceptible to acute and chronic proctitis, with patients typically presenting with tenesmus and rectal pain. In addition to systemic pain control, topical-directed therapies are often used in this setting, including hydrocortisone topical preparations and the use of sucralfate.[56] Management of constipation and diarrhea is also critical in these patients as either can worsen local irritation. Acute proctitis in the setting of RT most often heals within several weeks of RT completion without clinical sequelae, but particularly among patients receiving high-dose RT to the rectum, chronic proctitis can occur. These patients have chronic mucosal irritation that can be painful with rectal mucosal thinning and aberrant blood vessel formation that can result in rectal bleeding. Novel therapies, including hyperbaric oxygen and laser therapy, have been used successfully to heal rectal mucosa and reduce associated symptoms.[57-59]

Plexopathy

Nerve plexopathies are a frequent problem encountered by radiation oncologists, often because of tumor involving the nerve plexus. This scenario is typically managed with RT directed at the culprit tumor site for palliation together with the aforementioned pharmacologic processes for managing neuropathic pain. Though less common, RT can also cause plexopathies. Similar to muscle fibers, nerve bundles exposed to dose equivalents of more than approximately 60 Gy in 2 Gy fractions undergo significant decreases in large nerve fiber density.[60] Significant pain may ensue months to years after RT, especially in the brachial plexus distribution.[61] Rates of radiation-induced plexopathy range from 1% to 5% in selected patient populations. Among these patients, 10% will have complicated pain syndromes.[62] Treatments involve physical and

occupational therapy, together with pain management strategies, generally overseen by a pain specialist. Typical strategies include multimodality pain regimens (opioid and neuropathic pain medications as previously discussed), with consideration of interventional pain procedures and other novel interventions.[63]

Radiation-Related Muscle Spasm

Muscle fibers, once thought to be radioresistant, may undergo significant change, especially months to years after radiation exposure.[64] One-time muscle exposures to 10 to 20 Gy or fractionated doses >55 Gy are associated with myokymia, pain, and decreased muscle strength and range of motion.[65] Specific cancer locations susceptible to muscle complications include head and neck cancers and soft tissue cancers (eg, Ewing sarcoma).[65] Treatment regimen includes early physical therapy and orthopedic exercises and pharmacologic therapy such as muscle relaxants, such as baclofen or cyclobenzaprine. Novel treatments involve the use of botulinum toxin injected in small doses (15-25 units) into the muscle to relieve contracture or spasm.[65,66]

SUMMARY

Pain is a common problem in patients with advanced cancer. RT is frequently utilized to treat pain caused by the underlying cancer. A multimodal management approach should be applied, starting with oral analgesics administered according to clinical practice guidelines, with simultaneous attention to the psychosocial and spiritual aspects of pain and illness. For patients who experience refractory pain despite medical management according to pain management guidelines, pain specialists (eg, palliative medicine and/or anesthesia pain services) should be involved and specialty pain interventions (eg, interventional procedures) considered, where applicable. Complementary therapies may be helpful in some patients, although their efficacy has not been definitively established.

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CHAPTER 106

Palliative and Supportive Care

Ellen Kim and Tracy A. Balboni

DEFINITIONS

The National Consensus Project defines *palliative care* as "beneficial at any stage of a serious illness, palliative care is an interdisciplinary care delivery system designed to anticipate, prevent, and manage physical, psychological, social, and spiritual suffering to optimize quality of life for patients, their families and caregivers."[1] Palliative care may be delivered in a variety of settings including inpatient and outpatient care as well as throughout the patient's disease course, from the initial diagnosis to the end of life. The National Consensus Project has defined eight domains of palliative care (Table 106.1) critical to quality palliative care provision.

TABLE 106.1 DOMAINS FROM THE NATIONAL CONSENSUS PROJECT GUIDELINES

NCP Domain	Domain Description
Domain 1: Structure and Processes of Care	This domain addresses interdisciplinary team engagement and collaboration with patients and families, with an emphasis on developing a comprehensive palliative care assessment and plan, ensuring continuity of care across healthcare settings, and planning for care coordination. Clarity and specificity of interdisciplinary composition, team member qualifications, necessary education, training, and support are described. This section includes quality assessment process and parameters for continuous quality improvement. Emotional support for the interdisciplinary team is also defined as part of a goal of building resilient teams. Finally, palliative care model sustainability and growth are also addressed.
Domain 2: Physical Aspects of Care	This domain addresses the assessment of physical symptoms with appropriate, validated tools and the multidimensional management of symptoms with pharmacological, interventional, behavioral, and complementary interventions. Explicit policies for the treatment of pain and symptom management and safe prescribing of controlled medications are recommended.
Domain 3: Psychological and Psychiatric Aspects of Care	This domain addresses the collaborative assessment process for psychological concerns and psychiatric diagnoses. Essential elements are described and include patient–family communication on assessment, diagnosis, and treatment options for common conditions in context of respect for goals of care of the patient and family. The domain also includes description and required elements of a bereavement program.

NCP Domain	Domain Description
Domain 4: Social Aspects of Care	This domain addresses interdisciplinary engagement and collaboration with patients and families to identify, support, and capitalize on patient and family strengths. The essential elements of a palliative care social assessment are defined. The role of the professional social worker is described.
Domain 5: Spiritual, Religious, and Existential Aspects of Care	This domain defines spirituality and describes assessment, access, and staff collaboration in attending to spiritual concerns throughout the illness trajectory. Requirements for staff training and education are set forth, and responsibility of the interdisciplinary team—including a chaplain—to explore, assess, and attend to spiritual issues of patients and families are discussed. Spiritual and religious rituals and practices to promote comfort are promoted.
Domain 6: Cultural Aspects of Care	This domain sets forth how the interdisciplinary team can deliver care that is respectful of patient and family cultural beliefs, values, language, and communication preferences. This domain aims to ensure care that is culturally respectful in terms of the care environment, care policies and procedures, and care practices.
Domain 7: Care of the Patient at the End of Life	This domain highlights communication and documentation of signs and symptoms of the dying process for the patient, the family, and involved health providers. Meticulous assessment and management of patient pain and other symptoms and attention to family guidance as to what to expect in the dying process and post death period are emphasized. Bereavement support, beginning with anticipatory grief, is emphasized, together with social, spiritual, and cultural aspects of care throughout the dying process.
Domain 8: Ethical and Legal Aspects of Care	This domain addresses global ethics, legal considerations, screening and assessment, and treatment decision making. Global ethical principles (e.g., autonomy, beneficence) are set out. Team competencies in identifying and resolving commonly encountered ethical issues are described. The importance of seeking guidance from ethical committees is also emphasized. Within legal considerations, the complex legal and regulatory issues in palliative care are acknowledged. There is also an emphasis on the necessity of and access to expert legal counsel when navigating intricate and sensitive legal and regulatory issues in palliative care. Guidelines for screening and assessment for patient preferences and goals are set forth, including advance care planning. Finally, for treatment and ongoing decision-making, the interdisciplinary team is to follow patient-centered goals within the applicable laws and standards of practice.

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Of note, until a paradigm shift in the late 2000s, palliative care was often considered synonymous with hospice and end-of-life care.[2] Lingering misunderstandings from both patients and providers can interfere with palliative care engagement.[2]

Palliative care delivered in definitive cancer care settings is at times separately referred to as "supportive care." Furthermore, in some cancer care settings, regardless of the treatment intent, the term "supportive care" is used. To ensure clarity and comprehensiveness, this chapter defines "palliative and supportive care" as care that addresses the biopsychosocial and spiritual dimensions of patient quality of life throughout the cancer care continuum.

EVIDENCE AND CLINICAL GUIDELINES

In the oncology setting, there is a strong body of evidence supporting the integration of specialty palliative care into oncology care. The American Society of Clinical Oncology (ASCO) set forth the 2012 ASCO Provisional Clinical Opinion based on the randomized controlled trial (RCT) by Temel et al.[3] This study of 151 patients with advanced lung cancer randomized to receive either concurrent palliative care at the time of diagnosis or usual care showed that integration of palliative care into oncology care resulted in better quality of life and fewer depressive symptoms. In addition, despite receiving less aggressive medical interventions, patients randomized to early palliative care had longer median survival.[3] A survival benefit was also seen in the ENABLE III trial, which randomized patients to early or delayed palliative care. Survival at 1 year was 63% for patients who enrolled early versus 48% for those who enrolled 3 months later.[4] Subsequent RCT, meta-analysis, and systematic reviews have suggested that palliative care interventions either improve or have no effect on survival[5]; reassuringly, they have not suggested a negative effect on survival.[6] Caregivers may also experience lower levels of depression and stress burden with early enrollment.[7] In the realm of everyday life, early consultation can improve symptom severity and ongoing quality of life for patients.[8] These studies clearly demonstrate that early initiation of palliative care has wide-ranging benefits for both patients and caregivers.

Multiple models have been proposed to strategize effective palliative care using health care ecosystem resources efficiently, though each country faces different challenges due to different resources, needs, and financial structures of health care systems.[9-11] Multiple studies have demonstrated the value of palliative care interventions by reducing patient and hospital costs while improving care quality.[12]

Based on these findings and others, ASCO, the American Cancer Society, the Institute of Medicine, the European Society for Medical Oncology (ESMO), and the World Health Organization have all called for the early integration of palliative care in the treatment of patients with cancer.[2,13] Providing palliative care is not limited to one clinical specialty; multidisciplinary care is optimal for addressing all

domains of palliative care.[14] The 2017 ASCO Clinical Practice Guidelines call for oncologists to act as generalist providers of palliative and supportive care.[15] Specific to radiation oncology, radiation oncologists provide specialty expertise in the use of radiation therapy (RT) for the management of cancers, both definitively and palliatively. Together with this specialist role, radiation oncologists must have a basic competency in addressing the aforementioned domains of palliative and supportive care that can arise at all phases of cancer treatment.[2] Palliative medicine teams may then be viewed as corresponding specialist providers working in tandem with the oncology team. Notably, some cancer care centers do not have ready access to palliative care teams. Telemedicine has the potential to help reduce the impact of the limited access to palliative care specialists[16,17] but may worsen health inequities,[17] and the unmet need has been predicted to worsen.[18] In this setting, the oncology care team is called upon to gain more in-depth facility in providing palliative and supportive care. Though advocacy for the establishment of palliative medicine resources is needed, care teams in those settings are encouraged to seek out continuing medical education experiences that deepen palliative and supportive care knowledge. Organizations such as the American Society for Radiation Oncology, the ASCO, and the American Academy of Hospice and Palliative Medicine sponsor educational opportunities for oncology clinicians using a variety of formats, such as online or conferences. Leaders in U.S. residency education are discussing how to train residents to provide palliative and supportive care beyond simply delivering palliative radiation.[19,20] As demonstrated in the other chapters in this section (Section IV), palliative radiation is becoming more sophisticated and more integral to symptom management in patients with cancer.

As generalist providers of palliative care, oncologists have a role in the initial screening, assessment, and management of several palliative care domains, including physical, psychological, social, and spiritual aspects of quality of life. To this end, patient-reported outcome measures (PROMs) are surveys that allow patients to comprehensively and systematically report and rate their symptoms and psychosocial/spiritual distress. PROMs aid in informing when clinicians are needed to provide additional supportive care and interventions to improve symptom control and overall patient well-being.[21] A trial of electronic integration of PROMs in patients with metastatic cancer demonstrated improved measures of quality of life[22] and a significant survival benefit with the addition of PROMs, with results guiding supportive care intervention.[22] These findings point to the need for the standard integration of PROMs in oncology settings as a means of screening patients for palliative and supportive care needs.

In the ensuing sections, we review common palliative and supportive care issues that arise in the radiation oncology setting and strategies for their management. These include fatigue (both cancer and radiation related), weight loss and cachexia, radiation-induced salivary gland injury, radiation-related mucosal injury, radiation-induced nausea and vomiting, radiation-related diarrhea and other intestinal injury, radiation-induced skin injury, and radiation-related genitourinary injury, including male and female sexual function. Given its frequency and complexity, cancer pain management is addressed with a dedicated chapter (see Chapters 105). Radiation oncology clinicians can be expected to provide more in-depth expertise and management for common palliative supportive care issues that arise among their patients. Palliative and supportive care issues with which radiation oncologists have less familiarity (eg, psychosocial and spiritual issues) should be addressed with established screening tools such as PROMs that provide thresholds to prompt referrals to specialty providers for intervention.

CONSTITUTIONAL SYMPTOMS

Cancer-Related Fatigue

Cancer-related fatigue (CRF) affects a majority of patients with a cancer diagnosis including those receiving active treatment as well as cancer survivors.[23] CRF is generally defined as tiredness due to cancer or cancer treatment that interferes with normal functioning. The national consensus guidelines recommend screening for CRF in all patients undergoing treatment for cancer at regular intervals with simple age-appropriate measures, such as rating their degree of fatigue in the past 7 days on a 0 to 10 rating scale. CRF is often multifactorial and can be related to the cancer treatments themselves (including RT and chemotherapy), tumor burden, and upregulation pro-inflammatory cytokines, including interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α).[24,25]

Screening for CRF in all patients undergoing treatment for cancer is recommended at regular intervals with simple age-appropriate measures, for example, asking adults, “How would you rate your fatigue on a scale of 0 to 10 over the past 7 days?” For those with fatigue score of 4 or greater, a more focused history should be obtained with an emphasis on possible contributing or related factors, including disease status, pain, medication side effects, emotional distress, sleep disturbances, hypothyroidism, anemia, nutritional deficits, and comorbidities.[26]

Primary management of CRF should be focused on correcting any of these contributing factors. Nutrition deficits and imbalance often occur and may be overlooked in these patients. Weight, caloric intake, fluid intake, electrolyte

abnormalities, and micronutrient deficiency from an imbalanced diet should be identified and nutritional counseling provided. One of the most common causes of fatigue is inadequate and/or poor-quality sleep. Control of stimulus, optimization of sleep environment, control of symptoms (pain, fever, dyspnea) and side effects, treatment of sleep-related breathing disorders such as sleep apnea, and promotion of sleep hygiene are all important. Massage therapy to reduce tension and stress is often helpful. The patient should be counseled on self-monitoring of fatigue levels, energy conservation techniques, and the use of distraction. Simple behavioral changes in daily life, such as setting priorities, pacing daily activities, delegating as much as possible, scheduling activities at times of peak energy, and structuring a daily routine to promote quality of sleep, can go a long way to reduce fatigue. Emotional and psychosocial support should also be provided.

Many nonpharmacologic interventions have proven successful in managing CRF. A meta-analysis of 113 studies examined the effect of exercise, psychological interventions, and pharmacologic interventions for CRF.[27] This analysis showed a significant reduction in fatigue scores in patients with cancer with both exercise and psychological interventions but not with pharmacologic interventions. Specifically, there is randomized evidence in support of the use of yoga in reduction of CRF in patients being treated for breast and colorectal cancer.[28,29] Massage therapy by a therapist or a lay person may improve CRF, with the strongest evidence among patients with breast cancer.[30] Cognitive behavioral therapy has been found to be effective in the treatment of CRF in a randomized trial of cancer survivors,[31] and other psychosocial interventions such as mindfulness-based stress reduction and supportive-expressive therapies have also been shown to be beneficial after treatment.

Pharmacologic interventions can also be implemented in carefully selected patients for whom nonpharmacologic interventions are not effective.[32] Short-term uses of glucocorticoids such as dexamethasone and methylprednisolone have been evaluated in several randomized trials. Dexamethasone 4 mg twice daily for 14 days was compared to placebo in 84 patients with advanced cancer showed short-term improvement in fatigue scores, quality of life, and physical well-being.[33] A separate randomized trial of methylprednisolone 32 mg daily for 14 days was also compared to placebo, again showing short-term improvement in fatigue.[34] However, long-term use of glucocorticoids is limited by their significant side-effect profile including hyperglycemia, psychological symptoms including anxiety and agitation, insomnia, gastrointestinal (GI) bleeding, and adrenal insufficiency upon withdrawal.[35,36]

Psychostimulants such as methylphenidate and modafinil have also been evaluated in CRF with conflicting results. A meta-analysis of five RCTs (298

patients) in the treatment of CRF showed improvement in fatigue scores with methylphenidate over placebo but not in cognition or quality of life and with increased rates of vertigo, anxiety, nausea, and anorexia.[37] Modafinil was compared to placebo in 208 patients with advanced lung cancer showing no difference in fatigue, depression, sleepiness, or quality of life.[38] In general, these medications should only be considered in patients refractory to more established treatment modalities, and a referral to palliative care should be strongly considered in these cases.

Radiotherapy-Associated Fatigue

RT can also be directly responsible for worsening fatigue in patients with cancer. Radiation-related fatigue is often difficult to distinguish from generalized CRF resulting from multiple aforementioned etiologies. A review of CRF showed prevalence was 50% to 75% at cancer diagnosis, 80% to 96% during chemotherapy, and 60% to 93% during radiation treatments.[23] RT fatigue has been demonstrated in patients treated to multiple different body sites, including treatment for prostate, breast, and head and neck cancer. Radiation-associated fatigue typically is shorter in duration and less severe than chemotherapy-generated fatigue. Compared with women who received adjuvant radiation, women receiving adjuvant chemotherapy were more than twice as likely to develop fatigue during the course of therapy.[39] In a prospective study of 28 men receiving radical external beam radiation with androgen deprivation therapy (ADT) for prostate cancer, the prevalence of moderate-to-severe fatigue increased from 7% at baseline to 32% at completion of radiation. Fatigue significantly interfered with walking ability, normal work, daily chores, and enjoyment of life, but only at the end of radiation. Improvement occurred after completion of treatment but remained higher than baseline at 6.5 weeks of follow-up.[40] Similar results are seen in studies of patients with breast cancer. In 38 women alive with no evidence of disease 2.5 years after adjuvant radiation for localized breast cancer, there was no significant difference between chronic fatigue levels after radiation and pretreatment values.[41] In another cohort of patients with breast cancer, during and for 3 months after adjuvant radiation for breast cancer, fatigue increased from 33% to 93% and gradually improved during the following 3 months.[42] In patients with advanced cancer, fatigue levels initially worsened with radiation, stabilized at week 8, and returned to baseline by week 27.[43]

The size of the RT field also relates to the likelihood of developing fatigue. For example, patients treated with whole-breast RT are more likely to experience fatigue compared to those treated with partial-breast RT.[41] In addition, in a survey

of patients with brain metastases treated with whole-brain radiation or radiosurgery, 69% of patients receiving whole-brain radiation experienced severe fatigue and problems with cognition. Only 5% of radiosurgery patients reported fatigue.[44] Furthermore, the degree of radiation-associated fatigue may depend not only on the cumulative whole-body dose/volume but also on which organs at risk (OARs) are exposed, such as the brainstem/cerebellum.[45,46]

Cancer-Related Weight Loss and Cachexia

Weight loss and anorexia are a commonly encountered problem among patients with cancer and have been associated with poor overall survival.[47] Cancer-related cachexia is a distinct category within weight loss and anorexia categorized by a metabolic syndrome associated with a pro-inflammatory state resulting in loss of muscle with or without associated loss of fat. This syndrome can occur even in the absence of decreased caloric intake or malabsorption.[48] Increases in IL-1, IL-6, and TNF-α have all been associated with increased protein catabolism, resulting in skeletal muscle breakdown and a worsening cachexia syndrome.[49] The exact definition and diagnostic criteria for cancer-related cachexia have been previously ill-defined. An international panel of experts published a definition and classification of cancer-related cachexia in 2011, defining *cachexia* as "patients who have more than 5% loss of stable body weight over the past 6 months, or a body mass index less than 20 kg/m^2 and ongoing weight loss of more than 2%, or sarcopenia and ongoing weight loss of more than 2%."[50]

The data regarding the optimum treatment of cancer- related cachexia are limited. Patients with cachexia should be managed by a multimodality approach with an emphasis on identifying potentially reversible factors. Although there is mixed evidence on intensive nutritional intervention, all patients with cancer-related cachexia should be evaluated by a nutritionist for advice on diet modification and liquid meal supplementation.[50,51] Dietary counseling has been shown to improve outcomes in selected populations.[52] Patients should be encouraged to take in multiple smaller, calorie-dense meals throughout the day.[51] Liquid meal supplements seem to have the greatest impact if they are taken in between, rather than with meals, with a reduction in early satiety and improved overall caloric intake.[53]

Patients with cancer tend to have a higher protein turnover. Adequate protein intake is critical in patients undergoing cancer treatment. Daily intake of 1.5 to 2.0 g of protein per kilogram of ideal body weight generally maintains a positive nitrogen balance. Caloric intake helps maintain the weight. Between 30% and 90% of total calories can come from carbohydrates. Fat provides energy, serves as a

vehicle for other nutrients, and performs other important biologic functions. It usually makes up around 30% of the content in enteral formulas. Vitamins, minerals, and other micronutrients should be included. Sufficient water intake is required to offset the 2.5-L daily fluid loss. Body weight and serum markers (albumin, transferrin, and prealbumin) can be monitored to assess whether the nutritional support is adequate.[54,55] In patients with moderate-to-severe radiation-induced oral mucositis or esophagitis, oral nutritional support can be challenging. Tube feeding bypasses the injured tissues and provides direct access to the absorption surface. Nasogastric or nasojejunal tubes enable short-term access. For longer term access (>30 days), gastrostomy, gastrojejunostomy, and jejunostomy tubes can be placed endoscopically, radiologically, or surgically. Percutaneous endoscopic gastrostomy is increasingly the method of choice, often placed prophylactically when severe upper GI toxicity is anticipated.[56-59] Gastrostomy tube placement is not without risk. Some series suggest a 17% morbidity rate. In 3% of patients, serious complications such as peritonitis, sepsis, perforation, and dislodgement were reported.[60,61] For patients with reflux esophagitis, gastroparesis, aspiration pneumonia, or limited stomach volume, a jejunostomy tube may be placed instead. The feeding tube should be cared for properly to prevent displacement or malfunctioning, such as clogging.

When adequate nutrition intake can be achieved, enteral intake is preferred to parenteral support because it uses and helps maintain the existing alimentary functions. It is less expensive, safer, and associated with fewer side effects. However, in patients without a functioning GI tract because of obstruction, poor GI motility, intractable vomiting, severe diarrhea, short bowel syndrome, or severe pancreatitis, total parenteral nutrition may be appropriate. Implementation of total parenteral nutrition requires special expertise and is done in a concerted manner between the cancer-treating team and the nutrition support team.[62,63]

Pharmacologic interventions have also been studied to improve appetite, weight gain, and quality of life in patients with cancer-related cachexia, particularly those who have failed intensive nutritional support. Short-term uses of glucocorticoids (such as prednisone and dexamethasone) have shown modest benefits in improving appetite and weight gain but do not seem to improve quality of life and can result in significant side effects such as hyperglycemia, psychological side effects such as anxiety and agitation, insomnia, adrenal insufficiency, and GI bleeding.[35,36] Megestrol acetate, a progestin with antiandrogen activity, has also been shown to modestly improve appetite compared to placebo in randomized trials at a dose of 800 mg/daily.[64] A head-to-head comparison of megestrol acetate and dexamethasone showed them to be equivalent in the induction of weight gain.[36] Dronabinol, a cannabinoid, which has been examined for the treatment of nausea

and anorexia, has not been shown to be superior to placebo in inducing weight gain in patients with cancer and has been shown to be inferior to megestrol acetate.[65] In general, short-term use of glucocorticoids and more sustained use of megestrol acetate can be considered for the management of cachexia in patients who have failed conservative nutritional management.

SALIVARY GLAND INJURY: XEROSTOMIA

Xerostomia, the subjective experience of dry mouth, is among the most common complaints experienced by patients with cancer treated with RT to the head and neck area. It is caused by salivary gland dysfunction as a result of damage in the field of radiation. Histologically, irradiated salivary glands demonstrate acinar atrophy and chronic inflammation. Inflammatory changes and fibrosis are observed in periductal and intralobular areas, whereas the ductal system remains relatively intact.[66,67]

Salivary dysfunction develops immediately and predictably. A 50% to 60% decrease in salivary flow occurs during the first week. As RT continues and the total radiation dose increases, salivary function decreases accordingly in a dose-dependent manner. After initial deterioration, a recovery phase may be seen, with patients reporting reduced xerostomia even though salivary flow remains depressed. This may result from adaptation to the sensation of xerostomia and compensatory response from surviving functional glandular tissues. However, salivary function usually continues to decline for 6 to 8 months after therapy, and many patients show no recovery even at 12 months.[68,69] In some patients, xerostomia may be permanent.

In addition to oral discomfort, radiation-induced salivary gland injury contributes to systemic problems, including loss of appetite, chronic esophagitis, gastroesophageal reflux, and sleep disruption because of the need for frequent mouth moistening and subsequent polyuria.[70] The lubricating, buffering, and antimicrobial effects of saliva maintain the integrity of oral tissue (dental and mucosal). Saliva also assists in speech, taste perception, mastication, bolus formation, and swallowing.[71] Decreased salivation can lead to dental caries, periodontal diseases, a shift of oral flora, poor tolerability to dental prosthesis and inflammation, and atrophy and ulceration of mucosa. As a result, radiation-induced xerostomia has a debilitating impact on health and overall quality of life in patients and survivors with head and neck cancer.[72]

Xerostomia Prevention

The extent of radiation-induced salivary dysfunction is influenced by radiation field, radiation dose, and initial volume and function of the salivary gland. Several approaches have been developed to prevent or minimize injury to salivary glands. They include salivary gland transplantation, intensity-modulated radiation therapy (IMRT), and amifostine therapy.[73] In several earlier studies, surgical transfer of submandibular glands into the submental space prior to RT resulted in the prevention of xerostomia.[74-77] A 2-year follow-up showed that 83% to 92% of patients reported no or minimal xerostomia.[77,78] Advances in three-dimensional (3D) conformal RT and IMRT make it possible to conduct gland-sparing RT. Several studies showed that both subjective and objective measures of salivatory function are preserved. Limiting the mean dose of the parotid glands to 26 Gy or less decreases the risk of long-term xerostomia. Local treatment failure rates do not appear to be compromised by the use of salivary gland-sparing IMRT.[79-84]

Intravenous (IV) amifostine, a thiol-containing radioprotectant, administered at 200 mg/m^2 daily 15 to 30 minutes before irradiation, reduced acute and chronic xerostomia in an open-label phase III study.[85] Antitumor treatment efficacy was preserved; however, oral mucositis was not reduced. Nausea, vomiting, hypotension, and allergic reactions were the most common side effects.[86] Subcutaneous administration of amifostine has been explored for reduced side effects.[87-89] A multicentered phase III randomized trial failed to show that subcutaneous amifostine is superior to IV amifostine in terms of patient compliance or efficacy.[90] Other agents are less promising. Pilocarpine during RT was compared to salivary gland transfer in the prevention of xerostomia and found to be inferior.[91,92] Cevimeline, a muscarinic agonist, was evaluated in RCT with conflicting results.[93,94]

Management of Radiation-Induced Xerostomia

Current treatment of radiation-induced xerostomia includes dietary and oral hygiene, saliva substitution, or stimulation of salivation by moistening agents or medications.[73,95,96] Cold, tepid, soft food and beverages are preferred. Hard, spicy foods should be avoided. In patients without residual salivary function, saliva substitutes are used to relieve xerostomia. Water is commonly used and preferred by patients. Other types of mouthwash such as saline, bicarbonate, glycerol, or commercial formulations are available. Artificial saliva has been designed to mimic natural saliva. It may contain carboxymethylcellulose, porcine and bovine mucin, or xanthan gum. In patients with residual salivary function, increased flow of natural saliva can be achieved by stimulation with chewing gum, sugarless

candies, menthol, acid, vitamin C, or lozenges developed to provide antimicrobial enzymes.

Several sialagogues, defined as systemic salivary gland stimulants, have been tested with mixed results. They are typically muscarinic agonists, such as pilocarpine, bethanechol, carbachol, or cevimeline. Other classes of agents include neostigmine, physostigmine, nicotinic acid, potassium iodide, bromhexine (a mucolytic), and anethole trithione.[67] Current data support the use of pilocarpine. Further studies are needed to determine the long-term efficacy and safety of cevimeline and bethanechol.[73]

The most extensively studied pharmacologic treatment for xerostomia is pilocarpine. Oral administration at 5 to 10 mg, 3 times daily, is the standard regimen. Several randomized, double- blind, placebo-controlled trials have shown the clinical efficacy and safety of pilocarpine in treating radiation-induced xerostomia.[97,98] In a multicenter study, 54% of the 207 study subjects reported a reduction in the overall severity of xerostomia. Only 25% of those receiving a placebo reported improvement. Speaking ability improved in 33% of patients receiving pilocarpine versus 18% of those receiving placebo. Saliva production also improved, but this did not correlate with subjective symptom relief.[97] In another multicenter trial that involved 162 patients, both subjective symptom and objective measurement of saliva flow improved significantly in those receiving pilocarpine versus placebo. Best results were obtained with continuous treatment for 8 to 12 weeks.[99]

Some patients require pilocarpine treatment for 2 months or longer to achieve maximum effect. Sweating, the most common side effect, is experienced by 37% to 65% of patients. In one study, 6% and 29% of patients in the 5- and 10-mg groups, respectively, dropped out because of the adverse effects.[97] Because of the cholinergic activity of pilocarpine, it is not recommended for patients with cardiovascular disease, and it is contraindicated in patients with narrow-angle glaucoma and uncontrolled asthma.[100]

Acupuncture has been shown to stimulate saliva production.[101-103] It even has shown benefit in pilocarpine-resistant xerostomia.[104] Patients with more severe symptoms appear to benefit more from acupuncture treatment.[105] Acupuncture given concurrently with RT was shown to significantly reduce xerostomia and improve quality of life.[106] Yet, an acupuncture-like transcutaneous electrical nerve stimulation given concomitantly with radiation failed to do the same.[107] Acupuncture appears to modulate the function of the autonomic nervous system, which may stimulate salivary gland function and induce salivary flow.[108-111] Functional magnetic resonance imaging (MRI) changes in the brain were associated with acupuncture treatment.[112] In summary, acupuncture appears to be a

low-risk intervention that offers a potential future treatment for radiation-induced xerostomia.[73,113]

MUCOSAL INJURY: ORAL MUCOSITIS, NAUSEA AND VOMITING, DIARRHEA, AND OTHER GASTROINTESTINAL TOXICITY

RT causes mucosal injury. When such injury occurs in the oral cavity, as commonly seen in patients irradiated at the head and neck area, it is called *stomatitis* or *oral mucositis*. When the injury occurs in nonoral alimentary tract mucosa, it presents as esophagitis, gastritis, enteritis, colitis, or proctitis. These injuries manifest as pain, dysphagia, odynophagia, nausea, vomiting, and diarrhea, typically described as GI toxicity. Mucosal injuries by radiation appear to share the same underlying molecular pathogenesis, regardless of anatomic location.[114-116] Some favor the terminology of *alimentary mucositis* to describe the hierarchy and constellation of toxicity to the oral and GI mucosa.[117] Depending on the site of irradiation, dosage, and fractionation, patients' risks of mucositis vary. More than 50% of patients receiving radiation to the head and neck, abdomen, or the pelvis will experience moderate-to-severe mucositis. Stem cell transplant recipients who received total-body irradiation have more severe and prolonged symptoms.[118] Finally, medical judgment is also necessary to consider a differential including the development of a new condition with symptoms similar to radiation-induced mucosal toxicity, such as ulcers, gastroesophageal reflux disease, irritable bowel disease, or irritable bowel syndrome.

Recent research indicates that the pathogenesis of mucositis is not simply the result of nonspecific epithelial cell death. Rather, it may involve a more complex pan-tissue process.[119-121] The complexity of the pathogenesis of mucositis reflects the dynamic interactions of all of the cell and tissue types that comprise the epithelium and submucosa. Genetic predisposition, circadian variables, epithelial type and characteristics, and local microbial environment all play a role in determining the risk of mucosal injury.[122-124] Novel therapies are being developed based on these new findings.[123,125]

A practice guideline developed in 2004 by the Multinational Association of Supportive Care in Cancer (MASCC) and International Society of Oral Oncology (ISOO) was most recently updated in 2020.[120,126] These guidelines provide an excellent and evidence-based reference in the prevention and management of chemotherapy and RT-related mucositis.

Oral Mucositis Prevention

Basic oral care is the foundation of care for oral mucositis. There is a lack of evidence supporting one protocol over another. Therefore, feasibility, adherence, performance, and outcomes are more important than the use of specific agents. Three randomized and three nonrandomized trials showed that implementation of a systematic protocol improved outcome.[127-132] Protocols consisting of brushing, flossing, bland rinses, and moisturizers should be implemented for all patients. An interdisciplinary approach to oral care (nurse, physician, dentist, dental hygienist, dietician, pharmacist, and others as relevant) is preferred. Dental examinations and treatment are important prior to the start of cancer therapy, especially for those with head and neck cancer, and should continue throughout active treatment and follow-up.[133]

Radiation treatment techniques to minimize radiation dose to the mucosa, though trade-offs between target coverage and acute and late side effects, must be considered.[46] Beyond avoidance of the mucosa with radiation fields, various pharmacologic agents have been tested. Topical benzydamine, a drug with anti-inflammatory, analgesic, and antimicrobial effects, has been shown to reduce the frequency and severity of oral ulcers and pain in an RCT.[134] It inhibits the production of pro-inflammatory cytokines, including TNF-α.[134,135] Chlorhexidine failed to prevent radiation-induced oral mucositis (Figure 106.1).[136-138]

FIGURE 106.1 A, B. Radiotherapy-induced oral mucositis.

Studies testing amifostine for oral mucositis have been disappointing. Although it appeared useful in the prevention of xerostomia, inconsistent results have been reported for its use for oral symptoms.[139] New classes of agents are being investigated. A commercially available oral lozenge of probiotic *Streptococcus salivarius* K12 colonized the oral cavity and produced bacteriocin-like inhibitor substance to significantly reduce grade 3 to 4 mucositis in a prospective randomized trial, though it may cause flatulence or dyspepsia.[140] Recombinant

human keratinocyte growth factor-1 (palifermin) was shown to reduce mucositis in patients with hematologic malignancies receiving high-dose chemotherapy and total-body irradiation with autologous stem cell transplantation.[141] Palifermin reduces the incidence of severe oral mucositis in patients with head and neck cancer receiving definitive chemoradiotherapy and delays the onset of severe symptoms when compared to placebo. Yet, the differences are not significant after multivariate analysis.[142] Its use in non–stem cell transplantation settings is not recommended based on current data.

Multiple other agents for oral mucositis prevention are in various phases of development and testing. These include epidermal growth factor, transforming growth factor-β, glucagonlike peptide-2, lactoferrin, anti-inflammatory amino acid decapeptide, recombinant human interleukin 11, and insulin-like growth factor-1.[143] Others include natural product and dietary supplements such as glutamine, PV701 (milk- derived protein extract), several vitamins (A, B_{12}, E), folate, aloe vera (a plant extract), probiotics, and curcumin, an extract from turmeric. Thus far, studies of these agents are not of sufficient quality to support a recommendation regarding their use.

Oral Mucositis Treatment

Pain management is an important component of the management of oral mucositis. Most studies were done in the setting of chemotherapy-induced mucositis, instead of radiation-induced oral mucositis. Systemic and topical analgesics are used, as are coating agents. The use of opioids, nonopioids, and adjuvant medications is covered in more detail in Chapters 105. These agents can be given via oral, transmucosal, transdermal, or IV routes. The use of topical agents is widespread in practice, with practices and institutions using their own favorite formulation. Typically, these are compounded mixtures with nicknames such as “magic mouthwash.” Common ingredients include viscous lidocaine, diphenhydramine, and Maalox. Despite their popularity, there is little evidence supporting their effectiveness.[138,144-149] Doxepin rinses have also been evaluated for the treatment of oral mucositis and were recommended in the MASCC/ISOO 2014 guideline.[150] However, the MASCC/ISOO 2020 guideline currently suggests benzydamine mouthwash for the treatment of RT-associated oral mucositis.[150]

Gastrointestinal Mucositis Prevention

Several medications have been shown to significantly reduce the frequency and severity of radiation-induced GI mucositis, which usually presents as diarrhea and pain. Depending on the location, the GI mucositis may be termed *esophagitis*,

enteritis, *colitis*, *proctosigmoiditis*, or *proctitis*. External beam irradiation to the pelvis as part of treatment for prostate, rectal, or cervical cancer produces lower GI injury in the majority of patients. Acute side effects include pain, melena or hematochezia, diarrhea, and rectal urgency during or shortly after the radiation course.[151] Chronic side effects months to years later can lead to strictures, ulcerations, or fistulas.[151]

Radiation modality, planning, and delivery should try to minimize the dose to GI structures. The transition from 3D to IMRT treatments improved late GI toxicity in patients with prostate and gynecologic cancer.[152-154] Proton therapy seems to have similar or worse GI toxicity than IMRT, at least among patients with prostate cancer.[155,156] Studies of prostate cancer treatments have demonstrated consistent dose-volume relationships with grade 2 or higher rectal toxicity with dose 60 Gy or greater.[157] Improvements in immobilization, simulation (eg, 4D, breath hold, gating), placement of devices (fiducials, hydrogel spacers),[158-160] patient instruction (eg, NPO or dietary modification, visualization of respiratory guidance, bowel and bladder preparation), and daily image guidance (computed tomography, MRI, intrafractional imaging)[161,162] can all contribute to improved dosimetry and potentially reduce GI toxicity, through smaller margins on both targets (planning target volume) and OAR (planning risk volume). However, these changes must be made cautiously in a scientific manner to avoid compromising tumor control.[163]

In an RCT of pelvic irradiation, sulfasalazine 1 g orally twice daily reduces GI toxicity from 93% to 80% and diarrhea from 86% to 55% when compared with placebo. Grade 4 diarrhea was reduced from 16% of the patients to none.[164] Amifostine is an antioxidant that appears to protect normal cells from radiation injury preferentially to cancer cells.[165] But the evidence of amifostine's efficacy seems mixed.[123,131-133,139,166-168] Furthermore, IV amifostine is not without side effects. A small randomized phase 3 trial has suggested selenium supplementation during pelvic radiation for uterine/cervical cancer can reduce moderate-to-severe diarrhea.[169]

Other agents that did not show significant benefit include glutamine,[167] oral sucralfate,[170,171] rectal administration of sucralfate,[172] and other anti-inflammatories commonly used in ulcerative colitis, such as 5-aminosalicylates,[173] mesalazine,[174] and olsalazine.[175] They should not be used to prevent radiation GI toxicity.

Gastrointestinal Mucositis Treatment

Nausea and Vomiting

In addition to measures discussed here that aim to treat the underlying pathology of radiation-induced mucosal injury, symptomatic treatment should also be provided.

Radiation-induced nausea and emesis tend to be undertreated. Factors that influence radiation-induced emesis include single and total dose rate, fractionation, field size and irradiated volume, site of irradiation and organs included in the radiation field, patient positioning, radiation technique, energy and beam quality, previous or simultaneous influencing therapy, and general health status of the patient.[176] Evidence-based practice guidelines developed by national organizations differ in specific recommendations and in, when recommendations apply, reflecting the limited amount of high-level evidence available to date. The updated guidelines from the MASCC and ESMO[177] and ASCO[178] are summarized in Table 106.2.

TABLE 106.2 GUIDELINES FOR PREVENTION AND TREATMENT OF RADIATION-INDUCED NAUSEA AND VOMITING

	Risk			
	High	**Moderate**	**Low**	**Minimal**
MASCC/ESMO risk category	Total body	Upper abdomen, craniospinal	Brain, H&N, thorax, pelvis	Breast, extremities
MASCC/ESMO recommendation	Prophylaxis with 5-HT_3 receptor antagonists + dexamethasone	Prophylaxis with 5-HT_3 receptor antagonists + optional dexamethasone	Rescue with dexamethasone, a dopamine receptor antagonists, or 5HT_3 receptor antagonists	Rescue with dexamethasone, dopamine receptor antagonists, or 5-HT_3 receptor antagonists
ASCO risk category	Total body	Upper abdomen, craniospinal	Brain, H&N, thorax, pelvis	Breast, extremities
ASCO recommendation	Ondansetron 8 mg oral or 0.15 mg/kg IV once or twice a day on days of radiation with first dose daily before radiation and every 1 d after radiation, or granisetron 1-2 mg oral or 0.01 mg/kg IV once daily on days of radiation before radiation and every 1 d after	Ondansetron 8 mg oral or 0.15 mg/kg IV once or twice a day on days of radiation with first dose daily before radiation, or granisetron 1-2 mg oral or 0.01 mg/kg IV or tropisetron 5 mg oral or IV once daily on days of radiation before radiation; and	Ondansetron 8 mg oral or 0.15 mg/kg IV as breakthrough, or granisetron 1-2 mg oral or 0.01 mg/kg IV as breakthrough; or dexamethasone 4 mg oral or IV as breakthrough (titrate up as needed to a maximum of 16 g oral of IV daily); prochlorperazine 5-10 mg oral or	Ondansetron 8 mg oral or 0.15 mg/kg IV as breakthrough, or granisetron 1-2 mg oral or 0.01 mg/kg IV as breakthrough; or dexamethasone 4 mg oral or IV as breakthrough; or prochlorperazine 5-10 mg oral or IV or metoclopramide 5-20 mg oral or

	Risk			
	High	Moderate	Low	Minimal
	radiation; and dexamethasone 4 mg oral or IV once daily on days of radiation before radiation and every 1 d after radiation	dexamethasone 4 mg oral or IV once daily before radiation for the first 5 d of	IV or metoclopramide 5-20 mg oral or IV as breakthrough (titrate up as needed to maximum 3-4 administrations daily)	IV as breakthrough

5-HT_3, 5-hydroxytryptamine 3; ASCO, American Society of Clinical Oncology; H&N, head and neck; MASCC, Multinational Association of Supportive Care in Cancer; RT, radiotherapy.

Diarrhea

Symptomatic management of radiation-induced diarrhea is similar to that of chemotherapy-induced diarrhea.[179,180] Diarrhea usually occurs during the third week of fractionated abdomen or pelvic RT. Guidelines were developed by an expert panel and updated in 2004.[181]

For mild-to-moderate diarrhea, the initial management should include dietary modifications.[182] Patients should eat small, frequent, protein-rich meals. Adequate fluid intake (35 mL/kg/day) is necessary. Liquids should be taken primarily between meals. Soluble fibers such as oats, pectin, guar, and psyllium help retain stool consistency. Spices, alcohol, caffeine, high-osmolar beverages, and high-lactose food should be avoided.[182]

Loperamide remains the mainstay of pharmacologic treatment. It should be started at 4 mg followed by 2 mg every 4 hours or after every unformed stool (maximum 16 mg/day). Unlike in chemotherapy, where loperamide may be discontinued after initial response, standard doses of loperamide should be continued for the duration of radiation. This is because the long duration of fractionated radiation may cause repeated injury to the intestinal mucosa. The dose is increased to 2 mg every 2 hours if the diarrhea persists for more than 24 hours.

If diarrhea has not resolved after another 24 hours on the higher dose of loperamide, the drug should be continued and a second-line agent, such as tincture of opium (paregoric), an antimotility agent, can be added. Diphenoxylate and atropine can also be used, although they do not have as favorable a side-effect profile as loperamide. Mesalamine or corticosteroid enemas can help reduce the frequency of bowel movement and discomfort.[151] Sodium butyrate enemas can also effectively treat acute radiation proctitis.[183] For chronic proctitis, patients can

consider sucralfate enemas, formalin, mesalamine or glucocorticoid suppositories, short-chain fatty acid enemas, or hyperbaric oxygen therapy.[151,184] For rectal bleeding, argon beam plasma coagulation is very effective, but complications can include rectal ulcerations or fistula formation.[151] Surgery should be reserved for very severe complications. There is no evidence to support ozone therapy, metronidazole, or other endoscopic treatments, such as bipolar electrocoagulation, radiofrequency ablation, or Nd-YAG laser.[151]

Patients with diarrhea may require outpatient evaluation and IV fluid. Antibiotics and complete stool and blood workup are usually not necessary in the absence of signs of dehydration or infection. Octreotide and glutamine have been studied and found of no benefit.[185,186] Probiotic supplementation showed beneficial effect in the prevention and treatment of radiation-induced diarrhea in animal studies, but high-quality clinical studies are lacking. If diarrhea is severe, persistent, or complicated, hospitalization may be considered.[181]

SKIN INJURY: ACUTE DERMATITIS AND CHRONIC SKIN CHANGES

Radiation-induced skin injury can lead to acute dermatitis or chronic skin changes.[187,188] These changes can occur at both the entrance and exit sites of the irradiation beam. Severity is determined by the dose, fractionation, beam, volume, and surface area. Patient-specific factors such as poor nutrition status, preexisting vascular condition or connective tissue disease, excessive skin folds, and genetics also play a role.[189] The pathophysiology is a combination of direct radiation injury and a subsequent inflammatory response. Free radicals from ionizing radiation cause alteration of DNA, proteins, lipids, and carbohydrates. Epithelial basal cells, vascular endothelial cells, and Langerhans cells are damaged. A cascade of pro-inflammatory cytokines, thrombotic factors, growth factors, and other molecules is activated.[190]

Acute skin changes may become visible after 10 to 14 hours. Grade 1 changes include mild generalized erythema and dry desquamation, pruritus, scaling, dyspigmentation, and hair loss. After 4 or 5 weeks of RT and radiation doses to the skin of 40 Gy or greater, grade 2 dermatitis may develop, with tender or edematous erythema, moist desquamation in skin folds, and considerable pain. They tend to peak 1 to 2 weeks after the last treatment and start healing 3 to 5 weeks after radiation. Complete healing may take 1 to 3 months. Occasionally, dermatitis may progress to grade 3, characterized by confluent moist desquamation, or even grade 4, with ulcers, hemorrhage, and necrosis.[187,191] Chronic changes may develop months or years after the initial exposure. Postinflammatory hypopigmentation or hyperpigmentation, textural changes (xerosis and hyperkeratosis), loss of hair

follicles and sebaceous glands, atrophy, telangiectasia, or subcutaneous fibrosis are among the manifestations. Fibrosis can result in tissue retraction, pain, and limitation of movement. The scalp appears more tolerant to radiation injury than the skin of the face, neck, trunk, and extremities. The affected skin can be predisposed to ulcers and skin breakdown.[192,193] In some patients, radiation recall dermatitis may occur. This happens when a patient who has completed radiation encounters a drug and develops skin reaction similar to an acute radiation dermatitis. The offending drugs are usually cytotoxic agents. Radiation recall dermatitis is probably due to local cutaneous immunologic responses to the challenging agent.[194]

Mild acute dermatitis is treated symptomatically. Washing with water, gentle cleansing with a mild agent, wearing loose, nonbinding clothing, and avoidance of irritants, antiperspirants, and ultraviolet exposure all help. When erythema and dry desquamation occur, creams or ointments (petrolatum-based, castor oil, balsam of Peru, trypsin, trolamine) can be used. Topical sucralfate or hyaluronic acid was shown to be efficacious in some controlled studies.[195,196] In a phase III study in patients with breast cancer receiving postoperative RT, an extract from the calendula plant significantly reduced the occurrence of moderate-to-severe acute dermatitis from 63% to 41% when compared with trolamine, a nonsteroidal agent.[197] Other topical agents containing aloe vera, D-panthenol, almond, or chamomile can also be tried. The use of these agents is supported only by uncontrolled studies or anecdotal evidence.[198,199]

The value of topical antioxidants has not been established, and topical steroids are controversial, with research producing conflicting results. There are concerns of infection and skin atrophy, known side effects of topical steroids. At best, steroids may ameliorate the symptoms, but they do not prevent the dermatitis.[200] Topical ascorbic acid lotion (vitamin C) did not show discernible benefit for the prevention of radiation dermatitis.[201]

When acute dermatitis becomes severe, usual wound care should be applied to the erosions and ulcerations. Key measures are keeping the site clean and moist, pain management, protection from contamination, debridement, and infection control.[193,202] During radiation treatment, hydrogel dressings, hydrocolloid dressing, burn pads, or foam dressings can be applied. If the wound is infected, ionic silver powder, topical antibiotics, cadexomer iodine, or maltodextrin powder can be added. Referral to wound care specialists should be made in these cases.[198] In recent years, more specific agents have been investigated, such as topical granulocyte-macrophage colony–stimulating factor, tacrolimus, pimecrolimus, and platelet-derived growth factor, though these are not included in the standard of care.[187]

Chronic skin changes from radiation injury are more challenging to treat. Chronic fibrosis is associated with a high incidence of skin breakdown and infection. A team approach should be adopted that includes wound care, physical therapy, deep massage, and pain management to address cosmetic and quality-of-life issues. Pentoxifylline appears to have an antifibrotic effect. Oral pentoxifylline (800 mg/day) and vitamin E (1,000 IU/day) for 6 months significantly reduce radiation-induced fibrosis.[203] Prophylactic use of pentoxifylline significantly reduces late skin changes, fibrosis, and soft tissue necrosis in a randomized controlled study, possibly through its protective effect against vascular pathology.[204] Intramuscular liposomal copper or zinc superoxide dismutase, subcutaneous interferon-γ, or hyperbaric oxygen therapy has also been used. Persistent radiation-induced alopecia may occur particularly after greater scalp radiation dose or proton therapy and may be improved with topical minoxidil or surgical procedures.[205]

GENITOURINARY TRACT INJURY

Urinary Symptoms

Irradiation to the pelvic region as part of treatment for cancer of the prostate, uterus, ovary, cervix, rectum, or urinary bladder can cause urinary problems because of injury to the mucosa, vasculature, and smooth muscles.[206,207] Acute reactions occur within 3 to 6 months of treatment. Chronic changes occur later. Acute reactions present as dysuria, frequency, and urgency. Strictures or fistula can develop during the years following RT.[208,209]

Once infection is ruled out, symptomatic relief with phenazopyridine is usually the first-line treatment for acute symptoms. It is given at 200 mg orally, 3 times a day. Phenazopyridine accumulates in the urine essentially unchanged and acts as a topical analgesic within the bladder. Patients should be warned that phenazopyridine turns the urine into a bright orange color and can stain clothing. If the symptoms are not adequately relieved, antispasmodics can be added. Oxybutynin or flavoxate helps relax the smooth muscles and reduces urinary urgency and frequency.[210] Tolterodine is a cholinergic antagonist that is also effective for overactive bladder. It causes less dry mouth, but its response rate is lower.[211] Trospium was documented to improve symptoms in radiation-induced cystitis and is significantly better tolerated than immediate-release oxybutynin.[212]

Intravesical infusion of hyaluronic acid or chondroitin sulfate, injection of botulinum toxin A into bladder wall, and hyperbaric oxygen therapy have shown benefit.[213-216] IV WF10 (tetrachlorodecaoxide), an immunomodulator, was reported

to be beneficial.[217,218] In patients with severe pain, aggressive pain control with opioids may be needed.

Symptomatic management of chronic changes is similar to that of acute reactions. Dilatation or placement of a permanent catheter may be required for significant obstruction. Patients not responding to less aggressive treatment may be candidates for reconstructive surgery to repair the stricture, sphincter failure, or fistula.

Female Sexuality

High-dose radiation to the pelvis causes varying degrees of sexual dysfunction related to injury to the ovaries and vagina.[219,220] Ovarian failure as a result of pelvis irradiation leads to postmenopausal changes. Acute injury occurs during the course of RT and the following few months. It usually presents as vaginal and vulvar mucositis, pain, and ulceration. Chronic changes develop more than 3 months after the completion of treatment and include fibrosis, loss of elasticity and sensation, susceptibility to trauma and infection, postcoital bleeding, and dyspareunia.[221-224]

Maintenance of local hygiene, aggressive treatment of infection, and regular dilatation of the vaginal canal help reduce the acute reaction. Hormone replacement therapy and application of lubricants for mucosal dryness can be used to treat acute injury. To prevent chronic changes, the use of vaginal dilators, lubricants, and supplemental estrogen was shown to be helpful. When fibrosis is established, treatment may require more drastic measures, such as hyperbaric oxygen therapy or surgical reconstruction. Although these are common options in clinical practice, the level of evidence supporting their use varies.[219]

Most studies of the use of topical estrogen showed benefit.[225,226] Radiation causes damage to the epithelium, which may persist for another 3 to 6 months after therapy. Topical estrogen promotes epithelial regeneration. Benzydamine is an anti-inflammatory that also has analgesic, local anesthetic, and antimicrobial effects. It can be applied topically to achieve a higher local tissue concentration. It reduced both subjective symptoms and objective observation of vaginal mucositis.[227,228] There have been several uncontrolled studies of hyperbaric oxygen therapy in the treatment of established necrotic wound resulting from perineal and vaginal radiation; the strength of evidence is modest.[229,230] In women with severe radiation damage, such as perineal defect or obliteration of the vagina, reconstructive surgery may be considered.[219]

Male Sexuality

When planning radiation for prostate cancer, its effect on male sexual function must be considered and discussed with the patient. Although the rate of erectile dysfunction (ED) is lower in patients receiving RT versus radical prostatectomy, sexual dysfunctions remain one of the most important post-treatment quality of life issues.[231,232] A survey showed that 68% of men aged 45 to 70 years were willing to trade off a 10% or greater advantage in 5-year survival to maintain sexual potency.[233] Onset of ED is gradual, usually beginning about 6 months post-treatment and continuing to deteriorate for 4 years.[234]

Radiation does not appear to reduce testosterone production or cause pelvic nerve injury.[235] In addition to psychological reasons, vascular changes after radiation appear to be the predominant cause of postradiation male sexual dysfunction. As such, smoking and hypertension are risk factors.[236,237] With external beam radiation, the rates of ED vary from 7% to 72%, a wide range attributed to the differing study populations. Brachytherapy is associated with 2% to 89% of ED.[238] Diminished sexual desire, decreased orgasmic pleasure, and a reduced ejaculation volume are other problems reported by patients.[239]

The rising use of ADT for the treatment of intermediate-risk, high-risk, and metastatic prostate cancer has also had a dramatic impact on male sexuality. Rapid drops in testosterone brought on by the initiation of ADT can cause decrease or result in the complete loss of libido and sexual desire in up to 90% of men being treated for prostate cancer as well as physical and emotional changes such as weight gain, gynecomastia, genital shrinkage, depression, and emotional lability.[240] Sexual side effects related to ADT can begin almost immediately and can last for several years after completion of therapy. A quality-of-life analysis of a prospective, definitive prostate cancer trial demonstrated that at 2 years after completion of the therapy, 75.4% patients receiving 4 to 8 months of ADT in conjunction with definitive RT stated that their ability to function sexually was poor or very poor versus only 44.0% treated with RT alone.[241] Patients and their partners are often unprepared for the profound side effects related to ADT. In a survey of 79 patients and their partners recently prescribed ADT, 30% to 50% were unaware that low of libido, ED, and genital shrinkage were possible side effects of ADT. Care should be taken by physicians to communicate all of these side effects to both patients and their partners and to facilitate consultation with couple counseling, sex therapy, and men's health clinics when appropriate.

Treatment of postradiotherapy sexual dysfunction should take a multidisciplinary approach, including psychosocial evaluation and counseling, pharmacologic intervention, and exploration of the use of mechanical devices.[238,242] The mainstay of pharmacologic treatment is phosphodiesterase inhibitors in patients with arteriogenic ED. A randomized double-blinded, placebo-controlled,

crossover trial suggests a positive response to sildenafil. Yet, the overall response rate is low. Only 21% of patients improved during sildenafil treatment, but not during placebo treatment.[243] Tadalafil has also been found to be beneficial in this patient population.[244,245]

Intracavernosal injection of prostaglandins or phentolamine papaverine is also effective. For patients who are refractory to pharmacologic intervention, implantation of a penile prosthesis can be considered. Minimal intraoperative and postoperative complications and an excellent patient satisfaction rate were reported.[246] Vacuum devices are another option.

SUMMARY

Palliative and supportive care is an integral component of cancer care, as reflected in national and international cancer care guidelines. Palliative and supportive care includes the role of oncologists, including radiation oncologists, as generalist palliative care providers who assess and initially address patient physical and psychosocial-spiritual issues. Specialty palliative care and other practitioners (eg, social work, psychiatry, chaplains) are regularly integrated for specialized palliative and supportive care needs. In addition to cancer-related pain (addressed in Chapters 105), patients with cancer frequently present to radiation oncologists with CRF, weight loss and cachexia, xerostomia, oral mucositis, nausea and vomiting, diarrhea and other intestinal injury, dermatitis, and genitourinary toxicities. Hence, radiation oncologists must be equipped to mitigate these issues with strategies, such as radiation planning techniques, and be facile with their assessment and management.

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CHAPTER 107

Management of Radiation Side Effects

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This chapter is organized by organ system affected rather than by cancer site treated. For example, lymphedema from breast cancer radiation is listed under the lymphatic system, and osteoradionecrosis (ORN) of the mandible is listed under the skeletal system. The text outlines the presentation, symptoms, referrals, and interventions with existing supporting data, and the tables summarize medication management. Secondary malignancies and side effects unique to the pediatric population are beyond the scope of this chapter.

NERVOUS SYSTEM

See Table 107.1 for an overview of the medical management of radiation toxicity to the nervous system.

TABLE 107.1 MEDICAL MANAGEMENT OF RADIATION TOXICITY OF THE NERVOUS SYSTEM

Radiation Toxicity	Timing	Medical Management

Neurocognitive decline	Late	• Memantine (Namenda) 10 mg bid for 24 wk (memantine is titrated upward as tolerated by 5 mg/d per wk to the maximum dose of 20 mg/d)[16]
		  • Advise tapering dose by 50% q2-4 wk until 5 mg daily and then discontinue.
		  • Dose modifications required for patients with renal insufficiency

Fatigue and somnolence syndrome	Acute or late	• Methylphenidate (Ritalin, Class II) 10-20 mg PO bid-tid • Ritalin LA 20 mg PO q am; increase 10 mg q wk to 60 mg qd max • Armodafinil (Nuvigil, Class IV) 50-150 mg (older) or 250 mg q am (non-older)

Radiation Toxicity	Timing	Medical Management
		• Modafinil (Provigil, Class IV) 100 mg (older) or 200 mg PO q am (non-older)
Edema	Acute or late	• Dexamethasone (Decadron) 4-8 mg PO qd (morning dosing preferred to reduce insomnia with a gradual taper as tolerated monitoring for symptoms)[424]
Radiation brain necrosis	Late	• Dexamethasone (Decadron) 4-8 mg PO qd (morning dosing preferred to reduce insomnia; titrate and taper as tolerated monitoring for new/recurrent symptoms)[424] • Bevacizumab 1-15 mg/kg q2-3wk[425] • 5-Loxin 150 mg PO bid[42]
Seizure	Acute or late	Newer antiepileptics • Levetiracetam (Keppra) 500-750 mg bid; max 3,000 mg qd • Pregabalin (Lyrica) 50 mg tid; increase to 200 mg tid max • Topiramate (Topamax) 200 mg bid; weekly increase 50 mg bid to 800 mg bid max Older antiepileptics • Divalproex (Depakote ER) initial 10-15 mg/kg/d. Titrate upward 5-10 mg/kg/d in weekly intervals for optimal response; max 60 mg/kg/d. • Phenytoin (Dilantin) 100 mg tid initially, increase 100 mg q2wk to desired response (usually 300-600 mg); once stabilized, change to extended-release daily. • Carbamazepine (Tegretol) 200-600 mg bid

Nausea	Acute	Antiemetics
		• 5-HT3 receptor antagonists
		  • Ondansetron (Zofran) 8 mg PO q8h
		  • Also available as Zofran ODT (orally disintegrating tablet)
		  • Granisetron (Kytril) 2 mg tablet PO 1 h within XRT
		• Phenothiazine
		  • Prochlorperazine (Compazine) 5-10 mg PO q6-8h
		  • Promethazine (Phenergan) 12.5-25 mg PO/PR q4-6h
		Benzodiazepine

Radiation Toxicity	Timing	Medical Management
		• Lorazepam (Ativan) anticipatory 1-2 mg PO 45 min prior to XRT, adjunct to antinausea medications 0.5-1 mg PO tid Anti-inflammatory • Glucocorticoids, eg, dexamethasone (Decadron) 2-4 mg PO q8h Appetite stimulation: • Dronabinol (Marinol) 2.5-10 mg PO q6-8h
Myelitis	Subacute to late	• Dexamethasone (Decadron) 4-8 mg PO q am (with gradual taper) • Lowest effective dose should be used to minimize side effects. Patients who do not respond within days should be tapered off.[424]
Brachial plexopathy	Late	• NSAIDs • Gabapentin (Neurontin) 300-600 mg qd to tid • Pregabalin (Lyrica) 50 mg tid; increase to 200 mg tid max

bid, 2 times daily; NSAIDs, nonsteroidal anti-inflammatory drugs; PO, oral; PR, by rectum; q, every; qd, everyday; tid, 3 times daily; XRT, radiotherapy.
Dziuk T. *Commonly Prescribed Medications in Radiation Oncology*. 11th ed. https://www.texasoncology.com/getmedia/ddb81e5b-0532-4200-b25e-20a538cd9221/Commonly-Prescribed-Medications-in-Radiation-Oncology.pdf

Fatigue, Radiation-Induced Cognitive Decline

Radiation-induced cognitive decline (RICD) is a multifactorial toxicity, with a number of external confounding variables that make precise identification and qualification challenging. These include, but are not limited to, completion of accurate baseline neurocognitive testing, tumor-related deficits, concurrent medications, and comorbid neuropsychiatric conditions (such as dementia, depression, and anxiety), all of which independently and collectively contribute to cognitive functioning. Moreover, many patients with primary or secondary central nervous system malignancies have historically experienced limited long-term survival, restricting the capacity to observe and study post-treatment cognitive functioning over an extended time frame.

RICD may evolve in a “biphasic” pattern, with subacute transient decline peaking at the 4-month post-treatment interval, followed by a late, irreversible phase of impairment that is apparent anywhere from months to years later. Notably, approximately 50% of patients who receive partial- or whole-brain radiation experience RICD within 6 months of completion of radiotherapy (RT).[1,2] The pathophysiology of RICD appears to involve microvascular damage, neuronal loss, and demyelination/white matter changes, which may manifest as fatigue, diminished attention, working verbal and spatial memory, attentive capacity, informational processing speed, and novel problem-solving abilities.[3,4]

Physicians should refer all patients suspected of having RICD to certified neuropsychologists for formal evaluation. While the Mini-Mental Status Examination has been used historically for this purpose, this tool—which was developed to screen for dementia—has largely been supplanted by more sophisticated methodologies.[5-7] Patient compliance with such intense neurocognitive assessment may be challenging, especially in the setting of clinical deterioration. To help overcome this, the RTOG has formulated neurocognitive tests and a quality-of-life instrument with an estimated completion time of 30 minutes.[3,8]

Radiographic imaging is largely corroborative for RICD. Whole-brain and partial-brain radiation is associated with reductions in hippocampal volume, dose-dependent temporal-limbic cortical atrophy, and white matter T2 and fluid attenuated inversion recovery changes on magnetic resonance imaging (MRI), findings that are not uniformly apparent and oftentimes do not correlate to neurocognitive function.[9-12] Although functional MRI and positron emission tomography (PET)-based imaging are evolving for neurocognitive disorders, their utility in assessing RICD has not been established.

Various treatment strategies exist to help mitigate the risk of RICD, particularly in the setting of intracranial metastatic disease. The adoption of stereotactic radiosurgery (SRS), in which a number of selected brain lesions could be effectively targeted in a single treatment with preferential sparing of intervening healthy brain tissue, has been shown in multiple trials to more effectively preserve normal neurocognition without apparent decrement in overall survival.[13-15] For this reason, SRS has largely supplanted whole-brain RT (WBRT) as the first preferred first-line

treatment of patients with a limited number of brain metastases, even though rates of regional intracranial recurrence are higher with SRS than with WBRT.

When WBRT is necessary, the addition of memantine, *N*-methyl-D-aspartate receptor antagonist delays time to cognitive decline when taken both concurrently and as maintenance.[16] The mechanism may be similar to that of dementia. Hippocampal avoidance WBRT (HA-WBRT) in appropriate patients also appears to be associated with less cognitive decline when compared to WBRT alone.[17] The use of these two modalities together—HA-WBRT and memantine—has been investigated in a phase III randomized trial, with improvement in time to cognitive failure and fewer associated cognitive symptoms, memory complaints, and symptom interference as compared to the WBRT with memantine arm.[18] Both HA-WBRT and memantine are considered standard practice for the treatment of brain metastasis per ASCO-SNO-ASTRO guidelines published in 2021.[19]

The acetylcholinesterase inhibitor donepezil prescribed for mild-to-moderate Alzheimer dementia may be of some utility in patients with notable memory deficits, although data supporting its use in this setting are somewhat mixed.[20,21] Care should be maintained in prescribing this medication, given its common associated gastrointestinal side effects (nausea, vomiting, diarrhea) and contraindications (eg, QT-interval prolongation, bradycardia, asthma, or pulmonary disease).[22,23] Methylphenidate has also been suggested for patients with diminished attentive capacity as their predominant RICD- associated symptom, although phase III data supporting its use in the adult population are lacking, and the medication also carries with it many associated side effects and contraindications (cancer-related anorexia, monoamine oxidase inhibitor use, prior seizure disorder among others) limiting its broad applicability in this setting.[24]

Neurocognitive rehabilitation represents an alternative or complementary approach in which patients undergo cognitive and/or compensation training to help recuperate certain mental capacities and/or better accommodate to new functional deficits.[25]

Cerebral Edema

Patients undergoing intracranial irradiation for primary brain tumors, benign lesions, or metastasis may experience acute side effects of headache, nausea, vomiting, and temporary worsening of preexisting neurologic deficits. These symptoms are often indicative of worsening peritumoral vasogenic edema.

Patients without evidence of significant mass effect or herniation on imaging may be managed conservatively with low-dose dexamethasone or prednisone.[26] The starting dose and taper regimen should be individualized based upon the severity of the patient's symptoms, clinical response, and physician discretion. Treatment goal is to provide symptomatic relief with a quick taper if achievable to minimize unwanted effects of high-dose steroids. If unable to taper successfully, the lowest effective dose should be used. Potential side effects associated with glucocorticoid therapy include mood changes, agitation, sleep disturbance, myopathy, hyperglycemia, and gastrointestinal upset. All patients with prior diagnosis of diabetes mellitus should have their blood glucose levels routinely monitored. Gastric prophylaxis with proton pump inhibitors (PPIs) or additional form of antisecretory therapy should be provided.

Radionecrosis

Cerebral radiation necrosis (RN) is a late side effect of RT, presenting after 6 months and frequently 1 to 2 years following completion of treatment and —in keeping with the so-called "vascular injury" versus "glial injury" theory of RN—is presumed to result from direct injury to surrounding cerebral vessels. Radiation-induced damage to local arterioles and venules proceeds through a complex biologic process that culminates in luminal narrowing and occlusion by which local tissue ischemia, edema, and parenchymal cell death result.[27,28] Nevertheless, the precise mechanisms and pathophysiology underlying RN have not been entirely elucidated, and some controversy exists over the role of additional immunologic and pro-inflammatory mediators.

Estimates of the natural incidence of RN have ranged from 5% to 50%, contingent upon multiple treatment parameters, including total radiation dose, dose/fractionation, volume, and use of radiosensitizing agents.[29-32]

Although most patients with RN are asymptomatic, some may present with signs and symptoms associated with increased intracranial pressure (headaches, lethargy, nausea/vomiting, and seizures) with or without additional anatomically correspondent focal neurologic deficits.[27,33]

Differentiating post-treatment brain tissue necrosis from tumor progression based upon computed tomography (CT) or conventional MRI of the brain alone is challenging. Radiographically, RN has an anatomic predilection to form within periventricular white matter or deep-seated brain regions. Nevertheless, supposedly characteristic, visually descriptive findings of perilesional edema and contrast enhancement have a low positive predictive value for RN, frequently necessitating the use of more sophisticated tools for clarification.[34] Diffusion-weighted imaging may be helpful, though has similar limitations.[35]

MR spectroscopy can be used to evaluate the metabolic composition of lesions, with increased choline-creatinine and choline-*N*-acetyl aspartate ratios suggestive of tumor recurrence and elevated lipid lactate peaks that are more characteristic of RN.[36] MR perfusion studies can better characterize the relative cerebral blood volume and hemodynamics in areas of concern.[37] PET with carbon-11 methionine, fluoro-1 thymidine, and fluoroethyltyrosine exploit the differential uptake of amino acid by tumor when compared with normal brain parenchyma.[38-40] Each of these imaging modalities is beset by inherent limitations.[41] Unfortunately, the accuracy for imaging to confirm whether the changes reflect necrosis or recurrent tumor remains quite poor and often requires symptom management with follow-up imaging to ultimately define the process.

Surgical exploration with biopsy represents the “gold standard” for confirmation of RN versus tumor progression and may be therapeutic in patients with significant associated edema. Nevertheless, this approach has obvious limitations, the most obvious being that many intracranial lesions that are treated with SRS are deemed surgically inaccessible ab initio, such that excision may render the patient neurologically impaired or incapacitated. Moreover, histopathology from surgically resected lesions post-RT often reveals an admixture of residual viable/nonviable tumor cells and necrotic tissue, for which unequivocal classification is problematic.

The management of RN is largely dependent on the presence of associated symptoms. For patients with radiographic evidence of RN alone,

the condition may self-resolve without the need for additional intervention, and continued surveillance is considered appropriate.[41] For others with mild-to-moderate symptoms, initiation of low-dose oral corticosteroids with gradual taper may result in improvement. Nonsteroid conservative management can include pentoxifylline and vitamin E. When these fail, recent studies suggest a benefit to 5-Loxin (*Boswellia serrata*), an inhibitor of vascular endothelial growth factor (VEGF) expression.[42] Patients with steroid-refractory symptomatic RN may be considered appropriate candidates for antiangiogenic therapy with the VEGF inhibitor bevacizumab. The precise mechanism by which bevacizumab helps reduce RN is unknown, but its efficacy as a form of RN treatment has been corroborated by a number of different studies.

For patients who remain symptomatic with RN in spite of conservative management, surgical resection may be indicated, although initial concerns regarding operative morbidity remain. Laser interstitial thermal therapy (LITT) is an emerging novel technique of some promise; LITT treatment involves stereotactic placement of a laser fiber and generation of elevated temperatures with MR thermometry to effectively "ablate" both necrotic or viable tumor tissues and can hasten steroid taper.[43-45] Additional treatment with heparin, warfarin, oral pentoxifylline, vitamin E, and hyperbaric oxygen (HBO) have all shown benefit in small case series but remain investigational at present as evidence to support their broad applicability in the management of RN is limited.[46-48] In addition, one should be hesitant to recommend HBO if there is any concern for a viable tumor.

Myelitis

Acute radiation myelopathy (Lhermitte syndrome [LS]) describes a descending electric shock–like sensation radiating from the nape of the neck to the distal limbs that is often precipitated by neck flexion.[49] LS is believed to be secondary to axonal denudation of the ascending sensory neurons of the spinal cord. LS most frequently presents from 3 to 6 months following spinal irradiation. The development of LS has been associated with higher spinal cord V40 and mean doses, although additional evidence has accrued that inhomogeneous dose gradients along the axial plane of the spinal cord may contribute to its development.[50,51] However, dose and

volume metrics do not fully explain the phenomenon since LS can develop with low-dose radiation for pediatric lymphoma or ipsilateral neck treatment with conformal avoidance of the spinal cord.

LS is generally transient, self-resolving, and does not reliably progress to chronic radiation myelopathy; patients with persistent or progressive symptoms merit additional workup to rule out neoplasm or other neurologic or structural etiologies (eg, multiple sclerosis, subacute combined degeneration, cervical spondylosis).[52-54]

Chronic radiation myelopathy is a far more serious, typically irreversible neurologic sequela of prior spinal irradiation, which presents months to years following completion of RT.[55,56] The pathophysiology of chronic radiation myelopathy is complex and poorly understood but is believed to implicate direct glial cell injury and vascular damage, resulting in small vessel ischemia.[57,58] Symptoms of chronic radiation myelopathy vary in both extent and severity depending on the region of the spinal cord that is affected. These range from mild peripheral sensory paresthesias or motor weakness, to upper motor neuron signs (eg, spasticity, clonus, hyperreflexia), Brown-Sequard syndrome, fecal and urinary incontinence, and complete paraparesis or paraplegia below the distal to the designated compromised spinal level.

Chronic radiation myelopathy remains a diagnosis of exclusion with requisite clinical correlation, and competing demyelination, rheumatologic, infectious, and paraneoplastic etiologies must be considered to be ruled out per clinical judgment.[58] MRI may be helpful in corroboration and can demonstrate supporting characteristics of spinal cord atrophy, T2 hyperintensity, and focal contrast enhancement, but these findings remain nonspecific. Primary prevention of chronic radiation myelopathy is paramount; care should be exercised to minimize therapeutic radiation maxima within the treatment field and respective appropriate spinal cord dosimetric constraints, which are dose and fractionation dependent. While some series suggest interval symptomatic improvement over extended longitudinal follow-up, the condition is typically considered permanent.[55,58]

The management of chronic radiation myelopathy is largely supportive, and limited evidentiary data exist to support improvements associated with any particular therapy. Treatment parallels that of brain radionecrosis—oral corticosteroid therapy. Anti-VEGF therapy with bevacizumab and HBO

have also been suggested to support tissue recovery, but all such therapies remain under investigation at this time.[59,60]

Brachial plexopathy is rare, with a reported incidence between 1% and 4%, and typically manifests 1 to 4 years following completion of RT.[61] Radiation-induced brachial plexopathy is presumed secondary to direct radiation-induced damage to the nerves via a mechanism of glial cell injury, Schwann cell demyelination and ischemia, and/or as a result of extrinsic compression from supraclavicular and axillary fibrosis.[62] Patients may experience neurogenic upper extremity and axillary pain as well as progressive sensory and motor deficits of the affected limb.

The diagnosis of radiation-induced brachial plexopathy remains a diagnosis of exclusion, with primary concern for disease recurrence in the neck and/or axilla. CT and MRI may be useful to assess the anatomy of the brachial plexus and correlate the presence or absence of a distinct mass.[63,64] MRI findings of radiation-induced plexus changes have been described in conflicting terms of both T2 sequence hypointensity relative to surrounding muscle and T2 hyperintensity with infiltration and swelling.[63,65] Electromyography can be used to assess nerve conduction with myokymia and is strongly associated with radiation-induced brachial plexopathy, but not diagnostically sufficient without other supportive findings.

As with most other radiation-induced neurologic toxicity, primary prevention through appropriate treatment planning and delivery is paramount. Radiation-induced brachial plexopathy is a dose-dependent toxicity, which varies with fractionation. Care should be exercised to minimize therapeutic radiation hot spots within the structure and utilizing various fractionation schema to encourage sublethal repair as a means to reduce risk when necessary.

Management of radiation-induced brachial plexopathy is largely supportive and consists of physical therapy, and medical management with nonnarcotic analgesics, neuropathic pain medications, anticonvulsants, tricyclic antidepressants, gabapentinoids, and selective serotonin-norepinephrine reuptake inhibitors may be of utility.[66] More severe cases may be appropriate candidates for narcotic pain medication and surgical exploration with neurolysis to release the plexus and associated vasculature from perineural scar tissue and fibrosis.[67] Additional investigational management techniques include the use of pulsed radiofrequency ablation

and hyperbaric oxygen therapy (HBOT).[66,68] Unfortunately, and importantly, once symptomatic brachial plexopathy develops, medical management has limited effectiveness to control symptoms that dramatically alter patient lifestyles.

VISUAL SYSTEM

See Table 107.2 for an overview of the medical management of radiation toxicity to the visual system.

TABLE 107.2 MEDICAL MANAGEMENT OF RADIATION TOXICITY OF THE VISUAL SYSTEM

Radiation Toxicity	Timing	Medical Management
Ocular inflammation	Acute	Cortisporin ophthalmic (combination steroid and antimicrobial): Apply ointment or 1-2 gtts q3-4h. • Note: Do not use >5-10 d.
Dry eye	Late	Tear replacement agents • Refresh (OTC) 1-2 gtts to affected eye qid • Tears Naturale (OTC) 1-2 gtts prn • Visine (OTC) usually 1-2 gtts to affected eye qid • Lacrisert insert as directed qd, box of 60 unit doses, plus applicators • Note: Consider for severe dryness. Cyclosporine emulsion (Restasis) 1 gtt q12h
Optic neuropathy	Late	Triamcinolone 4-mg intravitreal injection Bevacizumab 1.25-mg injection q6-8wk[426]

gtts, drops; OTC, over the counter; prn, as needed; q, every; qd, everyday; qid, 4 times daily.

Dziuk T. *Commonly Prescribed Medications in Radiation Oncology*. 11th ed. https://www.texasoncology.com/getmedia/ddb81e5b-0532-4200-b25e-20a538cd9221/Commonly-Prescribed-Medications-in-Radiation-Oncology.pdf

Xerophthalmia

Radiation-related damage to the lacrimal and/or meibomian glands can result in xerophthalmia. Patients with radiation-related xerophthalmia may

present with a subjective "dry eye" sensation, in addition to conjunctival irritation and chemosis.

Lacrimal shielding or avoidance should be offered to all patients when appropriate as a form of primary prevention, and the lacrimal glands may be contoured as organs at risk (OARs) to minimize integral radiation dose. Preservative-free artificial tears or ocular lubricants may be administered to help supplant diminished lacrimal and mucus production. Ophthalmologic interventions include temporary or permanent surgical punctal occlusion and tarsorrhaphy.[69,70]

Cataracts

The lens remains the most radiosensitive structure of the eye due to the high mitotic rate, and cataracts—a disease of progressive clouding of the lens—is a well-recognized late effect of RT. The development and latency of radiation-induced cataracts appear to be dose dependent, and most patients who develop radiation-induced cataracts will present with impaired vision 2 to 3 years following RT.[71] Treatment is concordant with non–radiation-induced cataracts, with extracapsular cataract extraction followed by prosthetic lens replacement.

Retinopathy and Maculopathy

Radiation retinopathy (RR) and radiation maculopathy (RM) are additional dose-dependent late sequelae of prior RT to the orbit, which typically present 6 months to 3 years following treatment.[72] Patient-related risk factors include prior diabetes, hypertension, coronary artery disease (CAD), pregnancy, concurrent chemotherapy, pretreatment tumor size, and larger irradiated retinal area in the posterior ocular fundus.[73]

Clinical features of RR and RM may be occult in the early stages of the disease requiring testing with measures such as dilated fundoscopic examination to identify characteristic changes.[73,74]

Currently, there is no well-defined treatment for RR and RM, and therapy is largely directed at visual stabilization and prevention of progressive future vision loss. All such patients should be referred to ophthalmology for definitive assessment and management: Therapeutic interventions have

included laser photocoagulation, local injections of anti-VEGF agents, intravitreal triamcinolone acetonide, and dexamethasone implants.[73]

Optic Neuropathy

Radiation optic neuropathy (RON) is a severe late complication of radiation to the optic apparatus (left and right optic nerves, optic chiasm), which results in acute, painless typically monocular visual impairment and/or blindness. The pathogenesis of RON is believed to be similar to that of cerebral RN, such that delayed ischemia and neuronal injury result from radiation-induced vasculopathy and local inflammation (RN).[75] The diagnosis of RON remains a diagnosis of exclusion; primary suspicion for recurrent or residual neoplasm should be considered first and foremost.

Damage to the optic apparatus is a function of the total dose received, dose/fractionation regimen, and volume of optic nerve/chiasm irradiated. Symptoms of RON usually manifest within months to years upon completion of RT, with an average onset of 18 months after treatment.[76] Patients may report sudden changes in visual acuity, loss of normal color perception, or other more specific patterns of optic or chiasmatic visual defects, including, but not limited to, central scotoma or bitemporal hemianopia.[77]

The prognosis of RON is relatively poor, and the majority of affected patients will have a final visual acuity of 20/200; radiation treatment planning, which preferentially avoids excess radiation dose or therapeutic radiation maxima (hot spots) within the optic nerves and optic chiasm, is prudent to reduce the risk of RON.[78] The optimal management of RON is controversial and limited by the paucity of randomized data to guide recommendations but parallels that of RN. Oral corticosteroid therapy with low-dose dexamethasone has been recommended and is generally worth consideration for patients with mild-to-moderate symptoms. Anti-VEGF therapy with bevacizumab, therapeutic oral anticoagulation, angiotensin-converting enzyme inhibitor (ACEI), and HBO have also been suggested, but all such therapies remain under investigation.[75,77]

AUDITORY SYSTEM

See Table 107.3 for an overview of the medical management of radiation toxicity to the auditory system.

TABLE 107.3 MEDICAL MANAGEMENT OF RADIATION TOXICITY OF THE AUDITORY SYSTEM

Radiation Toxicity	Timing	Medical Management
Eustachian tube edema	Acute or subacute	Decongestant • Pseudoephedrine (available *behind* the counter without a prescription) 1 PO q6h Short-course steroids • Methylprednisolone (Medrol Dosepak) 4 mg tablets PO as directed over a 6-d taper • Dexamethasone (DexPax) 1.5 mg PO as directed, 6-, 10-, and 13-d tapering dose packs
External otitis	Acute	Tympagesic otic solution: Fill canal q4h, place stopper.

PO, oral; q, every.

Dziuk T. *Commonly Prescribed Medications in Radiation Oncology*. 11th ed. https://www.texasoncology.com/getmedia/ddb81e5b-0532-4200-b25e-20a538cd9221/Commonly-Prescribed-Medications-in-Radiation-Oncology.pdf

Ototoxicity

Radiation-related hearing loss may proceed via two primary mechanisms: disruption in normal mechanical propagation of sound from the external auditory canal to the cochlea, resulting in "conductive hearing loss," or direct damage to the cochlea and/or acoustic nerve itself, resulting in "sensorineural hearing loss" (SNHL). These two forms of radiation-induced ototoxicity are not mutually exclusive, and patients who receive cranial or head and neck irradiation are at risk.

Radiation-induced conductive hearing loss may derive from any process extending from the pinna to the ossicles. Radiation-induced otitis media with effusion (OME) is the most common culprit, but additional processes include, but are not limited to, external auditory canal stenosis, middle ear fibrosis, tympanic membrane sclerosis, and ossicular necrosis.[79-81] These findings are best appreciated on direct otoscopic examination, or through dedicated CT or MRI.

Many cases of OME resolve over time and can be managed conservatively.[82] Apart from this self-limiting condition, the evaluation of conductive hearing abnormalities and consideration of therapy for radiation-induced conductive hearing loss is highly nuanced and complex; all patients should be referred to a dedicated otolaryngologist or neuro-otologist for diagnosis and management. Additional interventions such as tympanocentesis, myringotomy, tympanostomy tube insertion, intratympanic steroid injections, and implantation of osseointegrated hearing aids—in addition to other sophisticated forms of functional middle ear surgery—may be necessary.[81]

SNHL is a dose-dependent toxicity, occurring in approximately one-third of patients who receive significant radiation dose to the middle ear. Patients may present with deficits in sound discrimination, volume, and tinnitus; Radiation-related SNHL often affects higher frequency hearing and is typically progressive over time.[81]

Treatment for SNHL is limited. Prevention remains the most effective management. The use of concurrent or adjuvant cisplatin should be judiciously limited to patients for whom chemotherapy is clearly indicated, as this chemotherapy regimen may further contribute to ototoxicity. Conventional hearing aids may be employed, with cochlear implant reserved for those patients with profound deficits or total deafness.[79]

VOCAL SYSTEM

Dysphonia

Vocalization is a complex process involving not only the generation of intermittent airflow pulses by the glottic larynx but also proper articulation and resonance through the oropharynx, oral, and nasal cavities.[83] Radiation-induced changes to any of these structures may affect a patient's phonation, including vocal strain, diminished vocal projection and volume, diminished pitch variability, and increased hoarseness or "breathiness."[84]

Any patient presenting with dysphonia should be evaluated for residual, recurrent, or secondary primary neoplasm. In addition, as these patients may have a history of tobacco use, a lung tumor should also be considered with hoarseness developing from external compression of the recurrent laryngeal nerve.

Visualization of the larynx may reveal vocal fold lesions, paresis, or cord paralysis but has relatively poor sensitivity to detect more subtle vibratory glottic abnormalities.[84] Videostroboscopy, videokymography, and high-speed videolaryngoscopy allow for more detailed evaluation of the mucosal wave of glottic vibration.[85,86]

Speech therapy remains the primary treatment modality for voice rehabilitation and has been associated with beneficial effects on communication function and quality-of-life domains.[87,88] Symptoms of vocal cord paralysis can be improved with local injections or procedures that medialize the cord.

DIGESTIVE SYSTEM

See Table 107.4 for an overview of the medical management of radiation toxicity to the digestive system.

TABLE 107.4 MEDICAL MANAGEMENT OF RADIATION TOXICITY OF THE DIGESTIVE SYSTEM

Radiation Toxicity	Timing	Management
Oral, pharyngeal, or esophageal mucositis	Acute	Baking soda mouthwash: 1-3 tsp gargle and spit, >4 to 6 qd • Mix 1 tbsp baking soda, 1 tbsp salt, 1 quart water Cepacol lozenges prn, max 12 per d Orabase paste (20% Benzocaine, OTC): Apply prn. Ulcerease (OTC topical anesthetic): 2 tsp swish and swallow or spit prn • Mix with ice chips for posterior pharyngitis. Triple mix 1:1:1: Benadryl elixir, Maalox: viscous, Xylocaine 2%, 2 tsp PO 10 min qac and qhs Sucralfate solution (Carafate): 2 tsp swish and swallow qid Gelclair swish in oral cavity 1 min, spit; avoid eating or drinking for 1 h, use up to tid Lidocaine • Xylocaine oral spray 10% PO prn (10 mg per dose) • Xylocaine viscous 2% 2 tsp PO swish and swallow/spit prn • Note: may mix 2% viscous lidocaine 1:1 with liquid antacid (Maalox or Mylanta) to improve coating Miracle mouthwash 2 tsp PO swish and spit/swallow qid

Radiation Toxicity	Timing	Management
		• Mix 60 mL tetracycline oral suspension (125 mg/5 mL), 30 mL Mycostatin oral suspension (100,000 U/mL), 30 mL hydrocortisone oral suspension (10 mg/5 mL), and 240 mL Benadryl syrup (12.5 mg/5 mL) RadiCare oral wound rinse 15 mL swish/gargle qid Doxepin hydrochloride 0.5% mouthwash (or 25 mg/5 mL water solution) swish for 30-60 sec, then spit within 1 h of radiation[427]
Thrush	Acute	Mycelex troche: Dissolve lozenge in mouth, 5 per d × 14 d. Nystatin suspension 5 mL swish well for 2 min and swallow qid; or dissolve 2 lozenges orally bid; through 2 d postclinical resolution. fluconazole (Diflucan) 200 mg PO day 1, then 100 mg PO qd × 7 d (if candida recurs, repeat for 21 d)
Sialadenitis	Acute	NSAIDs • Ibuprofen 200-800 mg PO q6h • Naproxen (Naprosyn) 500-750 mg PO initially, then 250-500 mg PO q6-12h If associated with temp >101°F, add antibiotics.
Xerostomia	Acute to late	Saliva substitutes • Artificial saliva (OTC): Apply to oral mucosa prn. • Aquoral 2 sprays PO tid-qid prn • Moi-Stir (OTC) spray prn • Mouth Kote 1% (OTC) 5 mL PO gargle, swish, hold for 1 min, then spit • Note: combination moisturizer/lubricant Salivary stimulants • Pilocarpine (Salagen) 5 mg PO tid initially; consider 10 mg PO tid prn (12 wk required to assess efficacy) • Cevimeline (Evoxac) 30 mg PO tid Xerostomia can be exacerbated by candidiasis, anticholinergic drugs, opioids, decongestants, antidepressants, anxiolytics, and antidiarrheals.
Thickened saliva/gag response	Acute to late	Guaifenesin (Mucinex) 600-1,200 mg PO bid Baking soda mouthwash 1-3 tsp gargle and spit, >4 to 6 qd • Mix 1 tbsp baking soda, 1 tbsp salt, 1 quart water Scopolamine patches (Transderm Scop): Apply to skin behind ear, 2-3 d per patch.

Radiation Toxicity	Timing	Management
		Lorazepam (Ativan) 0.5-2 mg 3 times daily
Dental prophylaxis	Late	Fluoride toothpastes • Biotene dry mouth toothpaste bid-tid brushing • Note: contains antibacterial enzymes, fluoride, natural Xylitol • GelKam fluoride toothpaste, brush 10 min bid Provident fluoride toothpaste, brush 10 min bid

Esophagitis	Acute	Topical
		• 2% viscous lidocaine by itself or in suspension with antiacids and mucosal protective agents (sucralfate) administered qac for temporary relief
		  • Triple mix 2 tsp PO 10 min qac and qhs, 1:1:1 Benadryl elixir, Maalox: viscous, Xylocaine 2%
		  • Note: Anesthetic lasts ~20 min; may repeat once during meal.
		• Sucralfate (Carafate) 2 tsp swish and swallow qid
		Antisecretory medications: proton pump inhibitors:
		• Omeprazole (Prilosec) 20 mg PO qd
		• Pantoprazole (Protonix) 40 mg PO qd
		• Esomeprazole (Nexium) 20-40 mg PO qd
		Antifungals if suspect component of candidiasis (especially with steroid therapy):
		• Nystatin suspension 5 mL swish well for 2 min and swallow qid
		• Fluconazole (Diflucan) 200 mg PO day 1, then 100 mg PO qd, × 7 d; if candida recurs, repeat for 21 d

Gastritis and duodenitis	Acute	Topical
		• 2% viscous lidocaine by itself or in suspension with antiacids and mucosal protective agents (sucralfate) administered prior to meals for temporary relief. See esophagitis section for dose information.
		Antisecretory medications
		• Proton pump inhibitors. See esophagitis section for dose information. Consider doubling the recommended doses for erosive gastritis.
		• H_2-receptor blockers
		  • Ranitidine (Zantac) 50 mg PO bid or 300 mg PO qhs
		  • famotidine (Pepcid) 10-20 mg PO bid

Radiation Toxicity	Timing	Management
		Non-NSAID analgesic • Hydrocodone/acetaminophen elixir 15 mL PO q4h Promotility agent • Metoclopramide (Reglan, generic) 10-20 mg PO q4h Antispasmodic • Hyoscyamine (Levsin) 0.125-0.25 mg PO/SL tid-qid

Nausea/vomiting	Acute (within hours)	Antiemetics
		• 5-HT3 receptor antagonists
		  • Ondansetron (Zofran) 8 mg PO q8h
		  • Also available Zofran ODT (PO disintegrating tablet) and Zuplenz (PO dissolving film)
		  • Granisetron (Kytril) 2 mg tablet PO 1 h within XRT
		• Phenothiazine:
		  • Prochlorperazine (Compazine) 5-10 mg PO q6-8h
		  • Promethazine (Phenergan) 12.5-25 mg PO/PR q4-6h
		• Benzodiazepine: lorazepam (Ativan) anticipatory 1-2 mg PO 45 min prior to XRT, adjunct to antinausea medications 0.5-1 mg PO tid
		Anti-inflammatory
		• Glucocorticoids, eg, dexamethasone (Decadron) 2-4 mg PO q8h
		Appetite stimulation: dronabinol (Marinol) 2.5-10 mg PO q6-8h
		Promotility: metoclopramide (Reglan) 10-20 mg PO q4h

Anorexia	Acute	• Dronabinol (Marinol) 2.5-10 mg PO q6-8h
		• Mirtazapine (Remeron) 7.5-15 mg nightly
		• Megesterol (Megace) 800 mg qd
		  • Contraindicated in older patients
		• Prednisone 10-40 mg qd
		  • Contraindicated in older patients
		• Zinc—may improve taste

Enteritis	Acute	Antidiarrheal medications • Loperamide (Imodium A-D) 1-4 mg PO q am, then 2 mg PO prn, 1-4 mg qd-bid as prophylaxis prn; max 16 mg/d • Diphenoxylate/atropine (Lomotil) ½-2 tablets or 10 mL PO initially or q am, then 1 after each loose stool prn,

Radiation Toxicity	Timing	Management
		diphenoxylate 2.5 mg/atropine 0.025 mg per tablet or per 5 mL; max 8 tablets or 40 mL/d Bile acid sequestrants • Cholestyramine (Questran) 1 packet or 1 scoopful mixed per directions PO qd initially; may increase to 1-2 packets or scoopfuls PO bid, 1 scoop (9 g) or 1-g packets contain 4 g cholestyramine (mix dose with at least 2 oz water)
Pancreatic exocrine insufficiency	Chronic	Pancrelipase (Pancrease) 400-2,500 units/kg/meal
Hemorrhoidal inflammation	Acute	Topical analgesic • ELA-Max 5 Anorectal Cream (5% lidocaine): Apply to intact skin. Topical anti-inflammatory treatment: creams and ointments for external hemorrhoids; suppositories for internal hemorrhoids • Hydrocortisone rectal suppository (Anusol-HC) 1 PR bid-tid • Hydrocortisone (Proctocort) 30 mg suppository 1-2 bid PR or 1% cream apply bid-qid PR • Hydrocortisone 10% (Cortifoam) 1 PR qd-bid • Rectal Rocket 1 PR qhs × 5 d (custom formulation or hydrocortisone 5%, lidocaine 2.5% [or 5%], nifedipine 0.3% [to 0.4%]) Mesalamine (Canasa) rectal suppository 1 PR bid-tid

Proctitis	Acute	Antidiarrheal: See enteritis section for medications and dose information.
		Stool softeners
		• Docusate sodium (Colace) 1-3 capsules daily prn
		Anti-inflammatory topical treatments: See hemorrhoidal section for medication and dose information.
		Antiflatulents
		• α-Galactosidase enzyme (Bean-O) 5 drops or 3 tablets q 3 servings
		• Simethicone variable dosing, see individual products:
		  • Gas-X (regular, extra strength, max strength)
		  • Maalox (regular and max strength)
		  • Phazyme

bid, 2 times daily; NSAIDs, nonsteroidal anti-inflammatory drugs; OTC, over the counter; PO, oral; PR, by rectum; PRN, as needed; tbsp, tablespoon; tsp, teaspoon; q, every; qac,

before meals; qd, everyday; qhs, every night; qid, 4 times a day; SL, sublingual; tid, 3 times daily; XRT, radiotherapy.

Dziuk T. *Commonly Prescribed Medications in Radiation Oncology*. 11th ed. https://www.texasoncology.com/getmedia/ddb81e5b-0532-4200-b25e-20a538cd9221/Commonly-Prescribed-Medications-in-Radiation-Oncology.pdf

Xerostomia

Xerostomia refers to the subjective sense of dry mouth from the lack of adequate saliva production. Major salivary glands, which include the parotid, submandibular, and sublingual glands, ordinarily produce approximately 90% of normal salivary output in both a stimulated (parotid) and unstimulated (submandibular, sublingual) capacity. Due to their location, these structures often receive a collateral radiation dose in head and neck cancer treatment, from which decreased salivary production and altered salivary composition may result. The constituent aspects of saliva are varied: While the liquidity of saliva helps with lubrication to facilitate normal food bolus formation and articulation of speech, additional components (enzymes, bicarbonates, macromolecule proteins and mucins, calcium ions, phosphates, and immunoglobulins) confer additional benefits, including control of dental plaque formation, bone mineralization, and antimicrobial function. As such, sequelae of xerostomia include dysphagia, dysarthria, inadequate enteral intake, predisposition to dental caries, and oral cavity infection.[89]

Xerostomia may affect upward of 60% of patients who receive external beam treatment to the head and neck.[89,90] Temporary xerostomia may be appreciated within 1 week of initiation of RT, often peaking within 6 to 7 weeks of conventionally fractionated treatment, with gradual recovery over a 2- to 3-year time frame.[91,92] Typical manifestations of xerostomia include subjective sense of oral dryness, the presence of viscous and ropy secretions, tacky appearance of the gingiva and buccal mucous membranes, oral cheilitis, and intolerance to oral appliances/prostheses.[89] Given the frequency with which xerostomia is seen in patients with head and neck cancer, the clinical threshold for diagnosis should remain low, and additional testing beyond patient report and visual examination of the oral cavity and oropharynx is rarely necessary.

Preventive measures include conformal avoidance during planning as well as the use of the radioprotector amifostine and, in selected patients, submandibular gland transfer. The various preclinical data regarding the use of amifostine are conflicting, and concerns regarding amifostine utility in the modern era of intensity-modulated RT (IMRT)- or volumetric modulated arc therapy (VMAT)-based treatment delivery, the inconvenience associated with its intravenous administration, and related side effects (hypotension, nausea, vomiting, allergic reaction) have limited its clinical use.[93-96] Submandibular gland transfer has shown benefit over pilocarpine in preventing xerostomia in a prospective trial, but as a technique is limited to patients who are appropriate surgical candidates, for whom neoplastic involvement of the prospectively transposed gland is minimal and can have the submental region safely omitted from radiation fields.[97-100] Additional studies have analyzed transfer of the submandibular to the parotid region, or temporary relocation to the forearm prior to native reimplantation.[101,102]

Patients who develop xerostomia during treatment should be encouraged to maintain adequate oral hydration, as baseline dehydration may exacerbate symptoms. Frequent small sips of water or the use of ice chips may help mitigate the subjective sense of xerostomia and help prevent associated dysphagia and odynophagia with oral intake of food. Additional lifestyle modifications may include the use of humidifiers and avoidance of consuming dry, highly absorbent foods (crackers, breads, meats) without supplementary liquid to accompany them.

Prompt initiation of an oral rinsing and gargling regimen with either a dilute solution of saline and sodium bicarbonate or dilute 25% hydrogen peroxide 4 times daily is suggested. Each of these rinse solutions provides exogenous hydration of the oral cavity and oropharyngeal mucosa and aids in the maintenance of oral hygiene with certain antimicrobial properties. In particular, the effervescence of both the baking soda and peroxide components of these rinses assists in manual mucus clearance, which may be particularly helpful in patients with tenacious secretions.[92] Additional mucolysis may be achieved with the expectorant, guaifenesin. Over-the-counter alcohol-based mouthwashes should be avoided.

Sialagogues such as pilocarpine, cevimeline, and bethanechol are muscarinic-cholinergic agonist parasympathomimetic agents that stimulate salivary tissue; prior series suggests that approximately 50% of patients

experience some degree of postradiation xerostomia relief with the use of pilocarpine, although other studies suggest more modest overall benefit.[96,103-108] Nevertheless, this class of medication is associated with traditional anticholinergic side effects, such as sweating, tachycardia, flushing, lacrimation, and dizziness, and are contraindicated in patients with prior diagnoses of asthma, acute iritis, or glaucoma.[96] Caution should also be exercised for those with chronic obstructive pulmonary disease and/or prior cardiovascular disease. Moreover, their functional gains cease if treatment is discontinued, necessitating lifelong therapy for effect.[96,109] Nonpharmacologic stimulation of salivary production with the use of sugar-free candy, lozenges, or chewing gum may provide some relief to patients with reserve levels of parotid function. Extraoral and intraoral electrostimulation to the parotid gland (via transcutaneous electrical nerve stimulation) and to the buccal mucosa are newer techniques of salivary induction but remain investigational.[110,111] Acupuncture has also shown utility in alleviating postradiation xerostomia in selected studies, although robust evidentiary support of this technique is limited, and the lack of randomized trial data—coupled with the profound heterogeneity of its delivery—limits acceptance of acupuncture as a primary form of treatment.[96,112,113]

Lastly, mucosal lubricants and artificial salivary substitutes may be offered to patients for whom stimulation of salivary secretion is ineffective. These substances—which typically consist of minerals, preservatives, flavorings, and methylcellulose or methacrylate viscous base agents—come in a wide variety of formulations; application of one product over another may be based on patient preference.[103] These substances do not replace the antimicrobial and immunogenic function of native saliva. Specialized toothpastes/dentifrices and/or fluoride- or chlorhexidine-based mouthwashes may be prescribed by the dental provider.[89]

Dysgeusia and Ageusia

RT to the head and neck region may result in alteration of taste perception (dysgeusia) or loss of taste (ageusia) in upward of 80% of patients. Dysgeusia and ageusia appear to be a dose-dependent toxicities; of the various taste perceptions (sweetness, bitterness, saltiness, sourness, and

savoriness, aka "*umami*"), umami appreciation has a lower dose threshold of loss than the remaining four tastes.[114] Nevertheless, this does not appear to be borne out clinically, as alterations in or loss of bitter and salty discrimination are the most commonly reported symptoms following head and neck RT.[115] All five taste types typically decline by the fifth week of conventionally fractionated radiation, with maximum impairments seen in the fourth to fifth weeks, and gradual improvement 11 weeks following initiation of RT and substantial recovery by 3 to 9 months thereafter.[116]

Attempts to minimize excess radiation dose to the nasal mucosa and oral tongue should be attempted in the radiation treatment planning process, as preferential sparing of these tissues can preserve normal gustatory function.[117] Unfortunately, pharmacologic interventions directed at restoring normal gustation and olfaction in the post-RT setting have been disappointing.[118,119] Trials of amifostine have also proven underwhelming, with one study suggesting that dysgeusia is actually *more* frequent among patients who receive this cytoprotective agent.[120,121]

For any given patient presenting with taste disturbance, evidence of oropharyngeal infection (ie, candidiasis), which can often confound a diagnosis of dysgeusia, should be ruled out or if present, treated appropriately. Patients with dysgeusia and ageusia are at elevated risk for poor oral intake and malnutrition. Comprehensive evaluation and management under the care of a registered dietician are suggested. In severe cases, nutritional supplementation and enteral feeding with gastrostomy or jejunostomy tube may ultimately still be required.

Oropharyngeal Mucositis/Oral Infection

Oral mucositis represents one of the most common and prominent side effects of head and neck RT, affecting upward of 90% of patients who receive radiation treatment for this indication, with frequency and severity increased by the use of concurrent chemotherapy or altered fractionation schemes.[122,123] The rapid rate of cellular turnover of the mucosal basal epithelial layer makes it particularly susceptible to radiation-induced damage. Additional patient-related risk factors that appear to contribute to the development of mucositis include advanced age, poor oral hygiene, preexisting xerostomia, and baseline malnutrition.[124]

Symptoms of mucositis most often present in the third week of RT and may be associated with early discontinuation and suboptimal treatment-related survival outcomes. As mucositis develops and progresses, patients often develop significant pain and dysphagia that limit appropriate oral intake. Mucositis can also contribute to symptoms of dysgeusia and dysphagia, further compounding challenges with feeding and speech production.

Primary prevention of mucositis largely consists of appropriate treatment planning and delivery in which the regions of high dose within the oral and oropharyngeal mucosa are avoided or minimized as feasible.[125] The use of intraoral positioning systems (colloquially referred to as "bite blocks"), in addition to dental rolls and/or wax bolus, may effectively increase the effective oral cavity surface area spared, provide a greater degree of anatomic separation between tissues, and help absorb backscatter radiation dose generated by metallic dental implants or fillings.[126]

Optimization of oral hygiene prior to RT is similarly important, and we encourage all patients to initiate an oral rinsing and gargling regimen with a dilute solution of saline and sodium bicarbonate (one tablespoon salt, one tablespoon baking soda, mixed in one quart of water) with the start of radiation treatment (see section "Xerostomia"). Alcohol-based, over-the-counter mouthwashes should be avoided, and chlorhexidine mouth gargles —which are often recommended as the prevention of chemotherapy-induced mucositis—are not suggested in the setting of RT.[127] Pretreatment dental evaluation and extraction with a formal dental provider should be a standard part of care.

In spite of prophylactic measures, comorbid fungal, viral, and bacterial oral infections due to epithelial mucosal barrier breakdown are common. Oral and oropharyngeal *Candida* infections are optimally managed first via the use of topical antifungal solutions (nystatin swish and swallow, clotrimazole troches dissolved, or miconazole mucoadhesive buccal tablets).[128,129] Caution should be maintained as certain nystatin suspensions contain supplementary sugars that can contribute to the formation of dental caries and appear to be associated with poor taste and gastrointestinal upset.[130] Patients with moderate or severe disease, or candidiasis refractory to these first-line oral solutions, should be treated with oral fluconazole. Herpetic vesicular eruption and ulceration may arise especially in the

setting of immunosuppression and should be managed with oral acyclovir or valacyclovir.[131]

Once radiation-related mucositis is apparent, certain dietary and behavioral modifications should be undertaken to help minimize discomfort. Patients should be counseled to avoid smoking, caffeine, or alcohol consumption and to adopt a diet devoid of spicy, acidic, temperature extreme, and texturally sharp or rough food items. Softened toothbrushes and specialized dentifrices may be used to help minimize abrasion.

Topical anesthetics including lidocaine, benzocaine paste, and 2% viscous xylocaine may be strategically used prior to meals to alleviate discomfort. These anesthetics may be used in isolation or, in the case of lidocaine, as part of a "Miracle," "Magic," or "Triple-Mix" mouthwash elixirs; such solutions often contain diphenhydramine and aluminum hydroxide/magnesium hydroxide antacid, with or without the addition of oral tetracycline, mycostatin, and hydrocortisone components. Doxepin mouth rinses can be used to accomplish the same effect, although this may be associated with stinging, burning, unpleasant taste, and drowsiness due to a certain degree of systemic absorption and antihistaminergic action.[132] Various mucoadhesive hydrogels are available and function to form a synthetic, palliative, and protective barrier to damaged oral and oropharyngeal mucosa that ameliorates both the onset and course of symptomatic mucositis, although honey—which also has inherent antimicrobial properties lacking in synthetic products—has been investigated for the same indication with encouraging results.[133,134]

Even with the utilization of any of these mixtures, additional pain control is often required in the form of oral narcotic medication or 0.2% morphine mouthwashes, and patients with severe symptoms may require temporary radiation treatment breaks to allow for appropriate healing.[135,136] Nutritional support of patients with mucositis is paramount, and many patients will require gastrostomy or jejunostomy tube placement to help prevent significant malnutrition and weight loss, even with appropriate mucositis management.

Dysphagia

Radiation-associated dysphagia refers to impaired swallowing efficiency and safety following RT.[137] The physiologic process of swallowing includes four distinct phases: an oral preparatory phase, an oral phase, a pharyngeal phase, and an esophageal phase. As such, radiation-related dysphagia is multifactorial, with many potential mechanical-structural, anatomic sources, neurologic mediators, and disparate contributing toxicities being involved.[138]

Patients who are expected to proceed with head and neck radiation should undergo formal evaluation with a dedicated speech and language pathologist (SLP) prior to initiation of treatment, even in the absence of swallow-related symptoms. Pretreatment baseline levels of subclinical (silent) aspiration are common and are often exacerbated by radiation treatment.[139]

Primary prevention of radiation-associated dysphagia requires treatment planning that minimizes radiation dose to susceptible structures—such as the oral cavity, larynx, pharyngeal wall/pharyngeal constrictor muscles, and esophagus.[140] Implementation of proactive swallowing therapy—that commences prior or concurrent to the advent of RT—is associated with improved rates of functional swallowing, mouth opening, and dysphagia-related quality of life in multiple series.[141-143]

Appropriate management of additional contributing toxicities (eg, fluids, oral hydration for patients with xerostomia) may further reduce apparent swallowing impairment. Nutritional support in the form of altered food textures, thickened liquids, and purees tailored to the nature of underlying dysphagia should be provided under the guidance and supervision of both a registered dietician and SLP. Prophylactic gastrostomy tube placement in the head and neck population continues to remain controversial; certain data are suggestive of benefit, and other studies show prolonged rates of percutaneous endoscopic gastrostomy-tube dependence and delay in resumption of normal oral-enteral alimentation.[144-146]

Referral to a registered dietician early in the course of treatment is paramount for guidance regarding nutritional needs. There are a variety of oral supplement nutritional drinks available that can support appropriate caloric and macro- and micronutrient needs. Typically, feeding tubes (gastric tube, jejunostomy feeding tube, gastrojejunostomy feeding tube) are recommended for patients receiving RT who are malnourished and who

are expected to be unable to ingest or absorb adequate nutrition over for more than 7 to 14 days. Fluid and electrolyte supplementation may be necessary in patients with vomiting, diarrhea, or ostomy drainage.

Radiation Esophagitis

Acute symptoms of radiation esophagitis often present 2 to 3 weeks following initiation of conventionally fractionated radiation and may include globus sensation, dysphagia, odynophagia, or substernal discomfort. Additional symptoms, such as hematemesis from esophageal bleeding, perforation, fistula, or esophageal obstruction in the setting of acute radiation esophagitis, are comparatively less common.[147,148]

Management of acute radiation esophagitis includes behavioral and dietary modifications, as well as utilization of topical anesthetics for relief. Patients should be counseled to avoid smoking or alcohol consumption and to adopt a relatively bland diet devoid of spicy, acidic, excessively dry, fatty, and temperature extreme hot or cold foods that may aggravate odynophagia or gastroesophageal reflux.[149] Multiple small-volume semisolid meals spaced throughout the day are preferable to the consumption of large meals, with further caloric supplementation as needed to meet daily requirements. Topical 2% viscous lidocaine, either by itself or in suspension with additional antacid (magnesium aluminum hydroxide) and mucosal coating protective (sucralfate) agents, is the common formulation that may be swallowed by the patient for symptomatic relief[150]; such elixirs may be strategically administered prior to meals. Additional therapies include anti-inflammatory and narcotic agents for analgesia, antisecretory agents such as PPIs (omeprazole, pantoprazole) and H_2-blockers (ranitidine) to mitigate underlying gastroesophageal reflux, and antifungal therapy (nystatin suspension, fluconazole) for those patients with esophageal candidiasis. Feeding tube placement and intravenous hydration may be required for those unable to maintain food and fluid intake per os. Symptoms of acute radiation esophagitis are usually self-limiting and resolve within 2 to 4 weeks after completion of therapy.

Chronic radiation esophagitis may present as early as 3 months following completion of radiation, with a median onset of 6 months following treatment.[151,152] Progressive fibroblast and inflammatory infiltration of the

irradiated esophageal mucosa may result in progressive dysmotility, stricture, and/or fistula. Esophageal strictures are typically managed with endoscopic dilation combined with acid suppression therapy.[153] Development of symptomatic esophageal fistula can be a life-threatening complication with a poor prognosis, one requiring expedient evaluation and potential surgical correction if feasible.[154]

Gastritis/Duodenitis

Radiation gastritis commonly includes symptoms such as nausea, vomiting, dyspepsia, epigastric discomfort, abdominal pain, and/or cramping and may present both during an active course of radiation or up to 1 year after completion of therapy.[152] As with radiation esophagitis, upper endoscopy is the diagnostic modality of choice for radiation gastritis.

Nausea and vomiting are frequent side effects of RT to the abdomen both as a component of radiation gastritis and as a distinct clinical entity in isolation; moreover, radiation-induced nausea and vomiting (RINV) and can manifest in the immediate hour(s) following completion of a given radiation fraction.[155] It is suggested that patients fast or consume minimal amounts of food or drink at least 2 hours prior to receipt of RT targeting the stomach, as the presence of gastric contents and active digestion may predispose to RINV. Common antiemetics used to prevent or mediate nausea and vomiting include 5-HT3 receptor antagonists such as ondansetron, followed secondarily by phenothiazine-class medications such as prochlorperazine or chlorpromazine. Additional glucocorticoids, such as dexamethasone, may also have an antiemetic role in more refractory cases of RINV.[156] Lorazepam or dronabinol may also help with nausea and/or appetite stimulation.

Further management of the symptoms of radiation gastritis includes the use of antisecretory therapies (PPIs omeprazole, pantoprazole; H_2-receptor blocker ranitidine) and gastric mucosal protective agents (sucralfate), with consideration of non–nonsteroidal anti-inflammatory drug (NSAID)-based analgesics, promotility agents (metoclopramide), and antispasmodics (hyoscyamine) for those with abdominal pain and/or cramping. Patients with hemorrhagic gastritis require comprehensive assessment by gastroenterology and medical stabilization in the setting of acute upper

gastrointestinal bleeding and ultimately may submit to similar endoscopic therapies for hemostasis (eg, argon plasma coagulation [APC]) as those patients with radiation esophagitis.[157] Gastric outlet obstruction is often treated with serial endoscopic balloon dilation, similar to esophageal stricture.

Radiation duodenitis presents with similar symptoms as radiation gastritis, although additional symptoms such as loose stools and diarrhea may be present. Suggested medical management of mild-to-moderate acute radiation duodenitis consists of antisecretory therapies (H_2-blockers, PPIs) and non–NSAID-based analgesics for pain. Agents such as sucralfate appear to have less demonstrable benefit for patients with radiation-induced small bowel toxicity than those with gastritis.[158] Patients with concern for duodenal ulceration or bleeding require upper endoscopy.

Radiation Enteritis

Radiation enteritis is a comprehensive term that describes secondary damage to the small and/or large intestines resulting from prior abdominopelvic irradiation, with symptoms including, but not limited to, nausea and vomiting, abdominal bloating, abdominal pain, excessive flatus, diarrhea or loose stools, and malabsorption. Additional symptoms, such as hematochezia or melena due to intestinal bleeding, partial or complete bowel obstruction from the development of adhesive disease, sepsis from perforation, or enteric fistula, may also be present but are more rare.

The temporal development of radiation enteritis can be both acute (#3 months after RT) and chronic (>3 months after RT). In concert with the aforementioned symptoms, the diagnosis of radiation enteritis can be corroborated by abdominal CT or MR enterography. These studies typically show bowel wall thickening or mucosal hyperenhancement. Direct visualization with upper endoscopy and/or colonoscopy with biopsy may provide macroscopic and microscopic confirmation of postradiation changes and absence of other factors.

Initial management of acute radiation enteritis includes behavioral and dietary modifications. Patients who develop mild-to-moderate diarrhea are suggested to adopt a low-fiber, low-fat diet.[159,160] Any offending medications with laxative effects should be discontinued and appropriate hydration

maintained. The antidiarrheal agent loperamide is a preferred first-line therapy for those without signs or symptoms of bowel obstruction.[161] Additional antidiarrheal therapies include diphenoxylate/atropine and bile acid sequestrants (cholestyramine, colestipol, colesevelam), which effectively chelate elevated intraluminal levels of bile salts that are not absorbed by the affected bowel mucosa. For patients with small intestinal bacterial overgrowth, tailored antibiotic therapy and correction of micronutrient (vitamin B_{12}, fat-soluble vitamins, iron, thiamine) deficiency should be completed.[162]

Chronic radiation enteritis may present as early as 3 months following completion of radiation, with a median onset of 8 to 12 months following treatment.[152] In addition to the aforementioned symptoms, progressive fibrosis and ischemia of the irradiated bowel may result in intestinal dysmotility, fibrosis, adhesions, ulceration, stricture, and/or fistula development. Patients with small or large intestinal bleeding require endoscopic intervention for hemostasis. For those presenting with evidence of bowel obstruction, nonoperative management with nasogastric decompression, intravenous hydration with electrolyte replacement, and parenteral nutrition are preferred.[163] Surgical approaches for chronic radiation enteritis should be reserved for cases that are severe and refractory to medical treatment.

Pancreatitis/Pancreatic Insufficiency

Radiation-induced acute pancreatitis is an exceptionally rare toxicity of upper abdominal radiation, although this clinical entity has been described in select case reports.[164] Management of radiation-related acute pancreatitis should follow the typical paradigm of supportive therapy with goal-directed fluid resuscitation, analgesia, and temporary bowel rest until enteral nutrition can be resumed and a normal diet advanced.

Chronic radiation pancreatitis resulting from prior abdominal RT has also been described, with endocrine and exocrine pancreatic insufficiency resulting in varying degrees of steatorrhea, macronutrient and micronutrient deficiency, unintentional weight loss, and/or glucose intolerance.[165-169] Any clinical suspicion of chronic pancreatic insufficiency in patients with prior

abdominal radiation should prompt referral to gastroenterology and/or endocrinology for further workup and management.[170]

Radiation-Induced Liver Disease

Radiation-induced liver disease (RILD) is a significant and potentially life-threatening complication of RT to the abdomen. RILD typically occurs 4 to 8 weeks following completion of radiation, with an incidence that appears dependent on cumulative radiation dose, volume of irradiated liver, and baseline hepatic function, among other factors.

Patients who develop classic RILD present with fatigue, abdominal pain, and distension due to hepatomegaly and anicteric ascites. Serum alkaline phosphatase levels are elevated, while bilirubin and transaminases are normal. The current model of pathogenesis suggests classic RILD is caused by veno-occlusive disease and retrograde congestion resulting from radiation-induced fibrosis of the central vein lumina.[171] Nonclassic RILD arises in patients with baseline underlying liver disease. Patients with nonclassic RILD often present with signs of jaundice, and laboratory values often show markedly elevated alanine and aspartate aminotransferase levels.[172] Unfortunately, while the pathophysiologic characteristics of RILD are well described, the mechanisms involved with the development and evolution of RILD remain unknown.

Mild elevations in transaminases or alkaline phosphatase can be transient and self-limiting and should be periodically reevaluated for resolution. For patients with persistent elevation in alkaline phosphatase or transaminases beyond 6 months, referral to a hepatologist is prudent. The only treatments for RILD are supportive and include diuretics for edema, therapeutic paracentesis for ascites, and steroids for hepatic congestion.

Biliary Stricture

A rare but potentially severe late effect after treatment to the liver and biliary system is radiation-induced stricture of the bile duct. Affected patients may present with symptoms of obstructive jaundice, and findings are corroborated on laboratory workup with conjugated hyperbilirubinemia. Management of radiation-induced biliary stricture is similar to that of any nonmalignant biliary stricture: Balloon dilation, stenting, or surgical bypass

is indicated to relieve symptoms of cholestasis and prevent the development of ascending cholangitis, Gram-negative septicemia, and hepatic abscesses.[173-175]

Radiation Proctitis

Radiation proctitis (RPr) is a comprehensive term that describes the development of rectal symptoms secondary to radiation damage to the sigmoid colon and rectum, including, but not limited to, diarrhea, fecal urgency, fecal incontinence, rectal pain, excess flatus, fecal mucus, tenesmus, and/or hematochezia. The temporal development of RPr can be both acute (#3 months after RT) and chronic (>3 months after RT). Given that the term "proctitis" is felt by some to be a misnomer that inaccurately suggests the condition is one of chronic inflammation, chronic radiation proctitis (CRP) is alternatively referred to as "rectal proctopathy" or "pelvic radiation disease."[176] In addition, "radiation-associated vascular ectasias" has been proposed for those patients whose postradiation rectal pathology consists primarily of bleeding from affected vasculature.[177] In concert with the aforementioned symptoms, the diagnosis of RPr is established with direct visualization of the rectal mucosa—often demonstrating telltale changes of telangiectasias, fibrosis, and pallor. Biopsy is typically not recommended in cases of acute radiation proctitis (ARP) due to concern for increased risk of bleeding and subsequent fistula formation.[178]

ARP is typically self-limiting, with symptoms of ARP resolving after discontinuation of radiation. Supportive measures with appropriate hydration, antidiarrheal (loperamide), and/or antigas (simethicone) medication may be used as needed.

CRP is a far more consequential sequela of pelvic irradiation and is associated with significant morbidity. The median onset of CRP is 8 to 12 months postradiation but can occur as late as 30 years after treatment. Three types of CRP exist: inflammation predominant, bleeding predominant, and mixed, which represents a combination of the former two types in varying degrees. Bleeding predominant is not only the most common form but also the most likely to resolve over time. Optimization of bowel function and fecal consistency with dietary modification, fiber supplementation, or laxative use is suggested as a first step to help prevent traumatic bleeding

associated with the passage of indurated stool. Additional noninvasive therapies include the use of antioxidant vitamin A/E/C or metronidazole 400 mg 3 times daily for 30 days.[179,180] Sucralfate enemas are the most well-accepted medical option for CRP and appear to provide cytoprotection to the rectal mucosa by stimulating local prostaglandin production. Their use for patients with CRP has been associated with a 77% improvement rate in bleeding grade in one series.[181,182]

Endoscopic therapies may be reserved for patients with bleeding-predominant CRP with severe or recalcitrant symptoms. APC is a commonly employed technique to ablate superficial hemorrhagic vasculature within the rectum and remains the best studied technique in the treatment of bleeding CRP.[183] Nevertheless, the widespread use of APC may be limited by its cost and availability. APC treatment requires antecedent colonic lavage, and the treatment itself can be associated with rectal side effects, such as pain, ulceration, and stricture.[184,185]

Topical formalin, which functions as a local sclerosant and chemical cauterizing agent, is sometimes used as an alternative to APC in CRP management. As compared to APC, formalin therapy is comparatively inexpensive and widely available. The success rate of formalin in the long-term management of CRP appears highly variable, ranging from 27% to 100%, a fact likely attributable to differences in technique of application and chemical concentration. Much like APC, however, concerns about severe formalin-related toxicity, such as fistula and necrosis, remain.[182,186,187]

HBOT to increase neovascularization and facilitate mucosal healing remains an option for patients with persistent symptoms after ablation, although data from only one randomized clinical trial support its use in CRP.[188,189] However, HBOT should only be used in patients with no evidence of active malignancy. Lastly, surgical treatments such as local excision, urinary and fecal diversion, and coloanal J-reservoir construction are considered last resorts for patients with CRP, due to concern for poorly vascularized tissues and low healing rates in patients with prior pelvic irradiation.

Inflammation-predominant RPr may be managed with loperamide, fiber supplementation, and stool-bulking agents. Rectal betamethasone or rectal hydrocortisone may also be of additional utility.[190]

Anal Toxicity

Patients undergoing pelvic irradiation for lower gastrointestinal malignancies or gynecologic malignancies may experience additional anal toxicity. Symptoms often overlap with those of rectal toxicity and may include diarrhea, tenesmus, fecal incontinence, and/or hematochezia. Additional symptoms specific to anal toxicity in particular include anal pain and perianal skin reaction with pruritus, erythema, and variable extent of desquamation.[191,192]

Management of acute anal toxicity consists of supportive care with dietary modification and antidiarrheal agents as needed. Patients with perianal pain and radiation skin reaction (see section "Integumentary") traditionally benefit from the use of barrier creams and frequent sitz baths, either with lukewarm water alone or with dilute solutions of baking soda or astringent aluminum acetate. Sitz baths accomplish mutual goals of both improved anal hygiene and direct analgesic effect on the irritated anal and perianal epithelium. Additional pain control may be achieved with narcotic pain medication; corticosteroid and lidocaine suppositories have also been trialed for local analgesia but remain investigational.[193]

Additional late anal toxicity includes the development of chronic fecal incontinence, anal ulceration, anal stricturing/ stenosis, and fistula formation.[194] Chronic fecal incontinence may be managed with a mixture of antidiarrheals and stool bulking agents, as well as pelvic floor strengthening exercises and biofeedback techniques carried out by specialist practitioners or community teams.[195]

Mild-to-moderate cases of anal stricture are managed conservatively with the regulation of stool transit by dietary fiber supplementation and manual dilation, while more severe cases of anal stenosis merit surgical correction with sphincterotomy or anoplasty.[196] The feasibility of complex anorectal fistula repair is highly variable and patient dependent, as surgical concerns exist regarding appropriate postsurgical healing.[197,198] As such, diverting colostomy may represent a final but necessary resort for refractory cases of anal sphincter dysfunction, fistulae, or stricture otherwise not amenable to other forms of amelioration.[199]

RESPIRATORY SYSTEM

See Table 107.5 for an overview of the medical management of radiation toxicity to the respiratory system.

TABLE 107.5 MEDICAL MANAGEMENT OF RADIATION TOXICITY OF THE RESPIRATORY SYSTEM

Radiation Toxicity	Timing	Medication Management
Pneumonitis	Subacute	NSAIDs • Ibuprofen 200-800 mg PO q6h • Naproxen 500-750 mg PO initially, then 250-500 mg PO q6-12h • Indomethacin 25 mg bid-tid initially; max 200 mg/d Advance to prednisone with a gradual taper • Prednisone 40-60 mg/d (or 1 mg/kg/d) with slow taper over 4-8 wk with close monitoring of symptoms[424]
Bacterial pneumonia	Acute or late	Outpatient pneumonia with immune compromise or comorbidities: moxifloxacin or combination of azithromycin and amoxicillin/clavulanate • Moxifloxacin (Avelox) 400 mg PO qd • Azithromycin (Z-Pak) 500 mg PO qd day 1, then 250 mg PO qd × 4 d • Amoxicillin/clavulanate (Augmentin) 250-500 mg PO tid or 875 mg PO bid If aspiration suspected Clindamycin 150-450 mg PO tid-qid
Cough	Acute or late	• Guaifenesin (Mucinex DM) 600-1,200 mg PO bid • Benzonatate (Tessalon) 100-200 mg PO q8h
Hiccups	Acute or late	• Baclofen 5-20 mg PO tid; titrating up at 2-d intervals • Note: antispastic muscle relaxant • Metoclopramide (Reglan) 10-20 mg PO q4h • Chlorpromazine (Thorazine) 25 mg IV or IM, or 50 mg PO tid (range 25 mg PO tid to 50 mg PO qid); maintenance 10 mg 50 mg PO tid
Sinusitis	Acute	To promote sinus drainage • Guaifenesin (Mucinex) 600-1,200 mg PO bid • Pseudoephedrine (available “behind” the counter without a prescription) 1 PO q6h For infection

Radiation Toxicity	Timing	Medication Management
		• Amoxicillin/clavulanate (Augmentin) 250-500 mg PO tid or 875 mg PO bid • Levofloxacin (Levaquin) 500-750 mg qd • Ciprofloxacin (Cipro) IR 250-750 mg q 12 h or XR 500-1,000 mg qd

bid, 2 times daily; IM, intramuscular; IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs; PO, oral; q, every; qd, everyday; qid, 4 times a day; tid, 3 times daily.
Dziuk T. *Commonly Prescribed Medications in Radiation Oncology*. 11th ed. https://www.texasoncology.com/getmedia/ddb81e5b-0532-4200-b25e-20a538cd9221/Commonly-Prescribed-Medications-in-Radiation-Oncology.pdf

Radiation-Induced Lung Injury

Radiation-induced lung injury (RILI) is a comprehensive term that refers to any damage to lung parenchyma as a result of therapeutic irradiation and is most often defined in terms of its acute (radiation pneumonitis: RPn) and chronic (radiation fibrosis [RF]) manifestations. Although described separately, both RPn and RF arise from the same underlying physiologic process, often evolving as a stepwise series of five clinicopathologic phases: early phase, latent phase, exudative phase, intermediate phase, and fibrotic phase.[200] The pathologic changes underlying the RILI are characterized by progressive alveolar epithelial and endothelial degeneration, culminating in fibroblast infiltration and collagen deposition within the pulmonary interstitium.[201]

Traditionally, RPn occurs anywhere from 4 to 12 weeks after radiation, although its origin as an "acute" phase of RILI suggests that the development of any radiation-induced pulmonary toxicity within a 6-month time frame following RT constitutes RPn.[202,203] In cases of acute RILI, patients may present with exacerbation of preexisting respiratory symptoms or new-onset dyspnea, cough, chest pain, low-grade fevers, and/or malaise. Less common, more severe signs include tachypnea, labored respirations with evident hypoxemia, and abnormal findings on pulmonary auscultation (eg, pulmonary friction rub, rales).[200]

Initial workup of RILI consists of direct patient evaluation followed by dedicated chest imaging with plain film chest radiograph and/or chest CT.

Chest radiographs may show hazy opacification and infiltrates in the distribution of the prior radiation portal, although, in the modern era of IMRT and VMAT delivery, the "straight line" test in which abnormal pulmonary densities conform to the confines of a distinct geometric border is no longer as valid an indicator of RPn as previously.[204] Furthermore, changes outside the prior radiation field—potentially due to infection, atelectasis, obstruction, or additional immune-mediated hypersensitivity reaction—may also be apparent, further confounding the diagnosis.[205]

Ideally, RPn risk should be minimized through diligent radiation planning by limiting normal irradiated lung tissue volume and dose according to established metrics (such as lung V20 and mean lung dose). Nevertheless, once present, the mainstay of treatment for RPn consists of supportive therapy and corticosteroids. Patients with mild symptoms can be treated with NSAIDs (ibuprofen, naproxen, indomethacin) and antitussives (dextromethorphan, codeine), as needed.[92] For other individuals presenting with moderate-to-severe symptoms, glucocorticoid therapy is suggested; oral prednisone (ideally 1 mg/kg/day, often suggested at a maximum dose of 60 mg/day) is considered a reasonable starting dose, with slow taper over a period of 3 to 12 weeks based on symptomatic reassessment and improvement. Starting dose and taper schedule needs to balance the needs of the individual patient with regard to respiratory symptoms as well as unwanted effects attributed to high-dose and long-term steroid use. Reinitiation or change in taper regimen may be necessary for patients with recurrent or recalcitrant symptoms. *Pneumocystis jirovecii* prophylaxis with trimethoprim-sulfamethoxazole or inhaled pentamidine may be considered when prednisone is administered.[200,201] Patients who present with severe symptoms or hypoxemia often require more aggressive management and should be evaluated for hospitalization, intravenous methylprednisolone 2 to 4 mg/kg/day, supplemental oxygen therapy, and other forms of respiratory support as needed. Patients who are diagnosed and managed appropriately with RPn generally have favorable outcomes, and pulmonary function may be expected to recover within an 18-month time frame from completion of therapy.[206]

RF represents the end stage of RPn, and while certain medications such as ambroxol, pentoxifylline, amifostine, and ACEIs have been suggested as potential mediators and attenuators of the progression of RPn to RF,

radiation-induced lung fibrosis is currently resistant to all known pharmacologic interventions.[207-210] Pirfenidone, a medication used to treat idiopathic pulmonary fibrosis, has also been suggested as a potential prophylactic therapy to prevent RF, although its use for this indication remains completely investigational at present.[211] Patients with established RF should be managed supportively under the supervision of a dedicated pulmonologist.

As immune checkpoint inhibitor use increases in patients who have previously received thoracic radiation, it will be a challenge to differentiate checkpoint inhibitor–mediated pneumonitis from radiation-related pneumonitis.[212] The pathways involved in this process are under current investigation, although both seem to mediate damage through cytokine secretion (interleukin-1β, interleukin-6, interleukin-17, and interferon-γ) promoting the process of lung inflammation.[213] Initial management depends on the severity of symptoms and findings but includes considering discontinuing immune checkpoint inhibitor followed by a similar steroid regimen and supportive care.

Radiation Recall Pneumonitis

Recall radiation pneumonitis (RRP) is an acute inflammatory response seen in previously irradiated but otherwise quiescent lung tissue that typically occurs with the advent of new antineoplastic systemic therapy (most notably taxane and anthracycline chemotherapeutics).[201,214] Confounding direct cause and effect in these cases lies in that many of these agents have an inherent risk for pneumonitis even when patients have no history of radiation treatment to the lungs. In addition, RRP has been described in patients with a prior history of thoracic RT who suddenly discontinue steroids prescribed for an alternative medical indication, unmasking latent RPn in the process.[215] The onset of RRP can occur anywhere from hours to days following initiation of the offending agent, and the intervening time between receipt of RT and development of RRP can be years in duration.[216] Management of symptomatic RRP generally consists of discontinuation of the inciting therapy in question, with additional treatment per standard RPn paradigms as earlier.

Bronchial Stenosis/Obstruction/Fistulae

Symptomatic narrowing of the tracheobronchial tree has been reported in patients treated with conventionally fractionated radiation, endobronchial high-dose rate (HDR) brachytherapy, a combination of external beam RT (EBRT) and HDR brachytherapy, and, more recently, stereotactic body radiation therapy (SBRT).[217-221] Lobar bronchi appear more susceptible to bronchial stenosis as compared to mainstem and intermediate bronchi, although these findings do not necessarily correspond to clinically apparent pulmonary toxicity.[222]

Patients with symptomatic manifestations of bronchial stenosis may present with new-onset or progressive dyspnea, cough, and/or wheezing. CT imaging of the chest may reveal radiation-induced changes in major, lobar, segmental, and/or subsegmental bronchial caliber, but direct visualization of the tracheobronchial tree with diagnostic bronchoscopy is gold standard. Patients may benefit from therapeutic bronchoscopy with endobronchial balloon dilation and/or endobronchial stenting.[223,224]

Radiation-induced bronchial fistulae are rare and, depending on the anatomic location of the sinus tract in question (eg, bronchopleural, bronchomediastinal, broncho- esophageal), may result in severe sequelae, such as empyema and mediastinitis. As with bronchial stenosis, CT imaging of the chest and direct bronchoscopic evaluation are indicated. Management is difficult, with mortality rates associated with pulmonary fistulae being very high. Management is not standardized but typically consists of appropriate antimicrobial therapy and attempted closure of the fistulizing tract. Smaller fistulas (<3-8 mm in size) may be amenable to seal with various occlusive materials.[225-228] Larger fistulae may require placement of coils, Amplatzer devices, or endobronchial stents.[229-231] Surgical intervention includes attempted closure with pedicled muscle flaps or free flaps, although the risk of an operation in previously irradiated and poorly vascularized tissue must be considered.[232,233]

CARDIOVASCULAR SYSTEM

Cardiovascular toxicity resulting from radiation treatment may manifest in a variety of ways, as radiation may induce changes in the different tissues and

structural components of the heart. See Table 107.6 for an overview of the medical management of radiation toxicity to the cardiovascular system.

TABLE 107.6 MEDICAL MANAGEMENT OF RADIATION TOXICITY OF THE CARDIOVASCULAR SYSTEM

Radiation Toxicity	Timing	Medication Management
Pericarditis	Acute	NSAIDs • Ibuprofen 200-800 mg q4-6h, 3,200 mg/d max • Naproxen 250-500 mg q12h, 2,500 mg/d max • Indomethacin 25-50 mg q8-24h

NSAIDs, nonsteroidal anti-inflammatory drugs; q, every.
Dziuk T. *Commonly Prescribed Medications in Radiation Oncology*. 11th ed. https://www.texasoncology.com/getmedia/ddb81e5b-0532-4200-b25e-20a538cd9221/Commonly-Prescribed-Medications-in-Radiation-Oncology.pdf

Pericarditis

Radiation-induced pericardial disease has a temporal development that includes both acute and chronic manifestations.[234] Symptoms of acute pericarditis, such as chest pain and fever, may result within days of radiation exposure, and pericardial effusions, either developing during acute pericarditis or in isolation, can present weeks to months following initial treatment.[235-238] Further workup of presumed pericardial toxicity may consist of electrocardiogram (ECG), transthoracic echocardiogram, and/or cardiac markers; classic findings such as diffuse ST elevation on ECG may help secure a diagnosis of pericarditis when clinical suspicion is present. Most cases of acute pericarditis secondary to radiation treatment are self-limiting with supportive therapy and the use of NSAID as well as colchicine providing relief of pain and resolution of inflammation, with steroids reserved as second-line agents in refractory cases.[239-242] Patients who have a pericardial effusion resulting in hemodynamic compromise may require pericardiocentesis.[243] With a latency period of 10 years, constrictive pericarditis represents the most severe, chronic form of radiation-induced pericardial disease. Pericardiectomy serves as the definitive therapy for this condition.[244]

Coronary Artery Disease

CAD may represent the most common radiation-induced cardiovascular toxicity, with clinical manifestations typically present 10 to 30 years after initial radiation exposure.[245] Radiation-induced injury to the intima of the coronary arteries can initiate an inflammatory cascade leading to atheromatous plaque formation. The extent of CAD in affected patients can manifest across a spectrum of severity and presentation, ranging from asymptomatic, incidentally noted instances of coronary stenosis, to life-threatening cases of acute coronary syndromes.[246,247] Examining the effect of radiation dose to independent cardiac substructures on the development of CAD remains an active area of interest within the field of radiation oncology; while mean heart dose has been associated with a proportional increase in the risk of ischemic heart disease, certain series have correlated the risk of major cardiovascular events (unstable angina, heart failure, myocardial infarction, coronary revascularization, and cardiac death) to radiation dose received by the left anterior descending artery.[248,249] The presence of additional comorbid conditions and factors, including preexisting hypertension, hyperlipidemia, and active smoking history, increases the risk of developing CAD.[250]

Valvulopathy

Valvulopathy and valvular dysfunction represent an additional chronic complication of radiation, with a median interval incidence of approximately 20 years following initial exposure. The left-sided mitral and aortic valves are most frequently affected, and progressive fibrosis, thickening, and calcifications of the valvular apparatus may result in structural incompetence with stenosis and/or regurgitation.[251] Similar interstitial fibrotic changes within the myocardium result in ventricular wall stiffening with systolic and diastolic dysfunction, cardiomyopathy, and/or heart failure. Cardiac arrhythmias, such as bundle branch block, may result when electrical signal propagation through the cardiac conduction system is similarly affected by radiation-induced fibrosis.[252,253]

In general, although no specific cardiovascular screening guidelines exist for patients with prior receipt of RT, echocardiography is largely considered a first-line imaging modality for radiation-induced cardiovascular toxicity

due to its noninvasive nature and widespread utility in the assessment of multiple aspects of cardiac anatomy and physiology. Further assessment with ECG, cardiovascular CT, CT coronary angiography, cardiac stress testing, cardiac MRI, and measurement of serum biomarkers such as brain natriuretic peptide may also play a role in the diagnosis of these patients.[254,255]

The management of these and other radiation-related cardiovascular toxicities is largely in keeping with non–radiation- related cases of the same clinical entities, the details of which are beyond the scope of this text. All patients, following radiation that involves the heart and major vasculature, should be well informed regarding late risks of CAD with recommendations for a heart-healthy diet, regular exercise, appropriate primary care follow-up and as-needed blood pressure control, diabetes management as well as the addition of lipid-lowering agents, such as statins as necessary. Smoking cessation should be encouraged. For more complicated management, it is recommended that a cardiologist be intricately involved in post-treatment care.

Vascular Effects

Similar to breast and thoracic treatment, RT that targets disease in the brain and head and neck has the potential to affect local vasculature with the carotid arteries, most commonly described as at risk for stenosis and an antecedent to cerebrovascular accident (CVA).[256] Dose-dependent inflammatory effects within the vessel substructure result in atheroma development following the same cascade of events previously described for CAD.[257] The effect is stochastic without a threshold dose and becomes more probable when patients are greater than 5 years from treatment completion.[258] A large cohort study with post-treatment ultrasound analysis showed 2-, 5-, and 10-year asymptomatic stenosis rates to be 8.9%, 17%, and 29.6%, respectively.[259] Symptomatic stenosis rates for patients in this same study were reported as 1.8%, 5.1%, and 10.1%. Although a “no radiation” control was not included, longitudinal studies have reported rates of 1% to 5% (age 70-79) for asymptomatic stenosis in the general population.[260] Even high-risk populations (those with reported cardiovascular risk factors) have less than 5% prevalence of asymptomatic

stenosis.[261] The time frame for the event is unfortunately well beyond most typical cancer-specific follow-up schemes; therefore, vascular effects are likely under-identified with delayed management in the community. We typically follow up patients with a 2-year post-treatment carotid ultrasound and 5-year interval imaging from that point. However, current guidelines do not include a history of head and neck radiation as a factor to support asymptomatic screening.[262] Cardiovascular risk reduction as previously described for CAD represents current management to reduce risk. When significant or symptomatic stenosis develops, invasive procedures need to be considered, which include carotid endarterectomy and stenting. In certain situations, procedural intervention for asymptomatic stenosis may reduce the risk for CVA and transient ischemic attack.

URINARY SYSTEM

See Table 107.7 for an overview of the medical management of radiation toxicity to the urinary system.

TABLE 107.7 MEDICAL MANAGEMENT OF RADIATION TOXICITY OF THE URINARY SYSTEM

Radiation Toxicity	Timing	Pharmaceutical Management

Cystitis	Acute and late	If UA negative for infection: Treat with analgesics or antispasmodics.
		Analgesics
		• Phenazopyridine (Pyridium, or OTC Azo-Standard) 200 mg PO tid
		• If insufficient advance to
		  • Prosed DS (combination of local analgesic, antiseptic, and parasympatholytic) 1 tab qid
		  • Note: Contraindicated in glaucoma, urinary bladder neck obstruction, pyloric or duodenal obstruction, or cardiospasm; do not use with sulfonamides; formulation includes atropine.
		  • Pentosan (Elmiron) 100 mg PO qd-tid
		Antispasmodics
		• Oxybutynin (Ditropan XL) 5-10 mg qd; increase 5 mg qd weekly to 30 qd max
		• Darifenacin (Enablex) 7.5 mg, advancing to 15 mg PO qd

Radiation Toxicity	Timing	Pharmaceutical Management

		• Solifenacin (VESIcare) 5 mg, advancing to 10 mg PO qd
		• Tolterodine (Detrol LA) 4 mg PO qd
		• Flavoxate (Urispas) 100-200 mg PO tid-qid
		• If symptoms persist, consider:
		  • Hyoscyamine (Levsin) 0.125-0.25 mg PO/SL tid-qid
		  • Levsinex TIMECAPS 0.375-0.75 mg PO bid-tid
		  • Hyoscyamine, phenobarbital, atropine, scopolamine (Donnatal Extentabs) 1 PO bid (to tid) belladonna/opium (B&O Supprettes, Class II) 1 supprette PR qd-qid, 15A: 30 mg opium, 16.2 mg belladonna, 16A: 60 mg opium, 16.2 mg belladonna
		If UA and culture reveal infection: 7-14 d course of antibiotics based on culture sensitivity analysis
		• 1st line
		  • Trimethoprim/sulfamethoxazole (Bactrim, Bactrim DS): 2 regular or 1 DS tablet PO bid, regular 80 mg/400 mg; DS 160 mg/800 mg
		• 2nd line
		  • Amoxicillin/clavulanate (Augmentin) 500/125 mg tid
		  • Cephalexin (Keflex) 500 mg qid
		  • Ciprofloxacin (Cipro) 250-750 mg PO bid; Cipro XR 500-1,000 mg PO qd
		  • Levofloxacin (Levaquin) 500-750 mg qd
		  • Nitrofurantoin (Macrobid) 50-100 mg qid

Hemorrhagic cystitis	Late	For pain: pentosan (Elmiron) 100 mg PO qd-tid Consider radiation fibrosis protocol with pentoxifylline and vitamin E for 3-6 mo: • Pentoxifylline (Trental) 400 mg PO tid with meals • Note: Do not use if history or cerebral or retinal bleeding. • Vitamin E (tocopherol) 1,000 IU PO qd

Prostatitis	Acute	Treat with urinary obstruction modifier.
		• For BPH or radiation edema: α-1 blockers: Note Flomax, Rapaflo, and Uroxatral carry less potential for hypotension compared to Hytrin and Cardura.
		  • tamsulosin (Flomax) 0.4-0.8 mg 30 min after same meal qd
		  • Note: may be tapered to a prn schedule
		  • Silodosin (Rapaflo) 4-8 mg PO with same meal qd
		  • Alfuzosin (Uroxatral) 10 mg PO following same meal qd

Radiation Toxicity	Timing	Pharmaceutical Management

		• Doxazosin (Cardura XL) 4 mg qd; increase to 8 qd after 3-4 wk
		• Terazosin (Hytrin) 1 mg qhs initially; increase stepwise to 2 mg, 5 mg, 10 mg (the target dose) qhs
		  • Note: may cause significant hypotension at the beginning of treatment; initiate at bedtime checking blood pressure routinely.
		• For BPH alone: 5α reductase inhibitor (antiandrogen therapy)
		  • Dutasteride (Avodart) 0.5 mg qd
		  • Finasteride (Proscar) 5 mg qd
		For severe symptoms, use a combination of α-1 blocker and 5α reductase inhibitor.
		• Dutasteride/tamsulosin (Jalyn) 1 tab post same meal qd
		For bacterial prostatitis, treat with 28 d of levofloxacin or 3 mo of Bactrim (refer to cystitis section above for dosing).

BPH, benign prostatic hyperplasia, OTC, over the counter; PO, oral; PR, by rectum; PRN, as needed; qd, everyday; qid, 4 times a day; qhs, every night; tid, 3 times daily; UA, urinalysis.

Dziuk T. *Commonly Prescribed Medications in Radiation Oncology*. 11th ed. https://www.texasoncology.com/getmedia/ddb81e5b-0532-4200-b25e-20a538cd9221/Commonly-Prescribed-Medications-in-Radiation-Oncology.pdf

Radiation Nephropathy

The kidneys are inherently radiosensitive organs, with EBRT and radionuclide therapies shown to result in radiation damage causing progressive loss of renal function.[263,264] Radiation is also known to contribute to renal artery stenosis, independent of its effect on renal parenchyma.[265]

Acute radiation nephropathy presents with an onset of 6 to 12 months following radiation exposure, while chronic renal failure resulting from chronic radiation nephropathy takes years to develop. Patients with radiation nephropathy may experience hypertension as well as symptoms consistent with advanced renal failure (lethargy, edema, headaches, and dyspnea).[266] Imaging with a technetium-labeled diethylene triamine penta-acetic acid scan can detect a decrease in glomerular filtration rate, and

dimercaptosuccinic acid scintigraphy can show a decline in renal tubular function following RT.[267]

Renal protection with appropriate shielding, and/or radiation planning with dedicated renal dose constraints, is paramount and can reduce the incidence of radiation nephropathy. As with any patient with kidney disease, all patients presumed to have radiation nephropathy should be evaluated and followed by a dedicated nephrologist. Once present, treatment of radiation nephropathy consists primarily of the management of hypertension with ACEIs or angiotensin II receptor antagonists.[266] Patients with anemia may also respond to human recombinant erythropoietin.[268] Additional medication to manage fluid overload and hyperkalemia may be utilized as needed.

Radiation Cystitis

Radiation cystitis is a comprehensive term that describes the development of "irritative" bladder symptoms associated with receipt of pelvic irradiation, such as increased frequency of urination (polyuria, nocturia), increased urgency, incontinence, and/or discomfort with urination (dysuria). In clinical instances where significant blood is present in the urine (hematuria), the term "hemorrhagic cystitis" (HC) may be used. Much like RPn, the temporal development of radiation cystitis can be both acute (#3 months after RT) and chronic (>3 months after RT). Acute radiation cystitis is more common, with a reported incidence of up to 50% in one selected series, while chronic radiation cystitis is thought to affect approximately 5% to 10% of patients, with an event-free interval ranging anywhere from months to years after completion of treatment.[269,270]

As with most radiation-associated side effects, radiation cystitis remains a diagnosis of exclusion and can be easily mislabeled or conflated with alternative etiologies. Chemical exposure can also result in cystitis, and for those patients currently receiving or having received chemotherapy in the past, it is nearly impossible to accurately discern whether radiation or these other systemic chemotherapeutics (eg, oxazaphosphorines [ifosfamide, cyclophosphamide], doxorubicin, busulfan) serve as the primary inciting culprit. Given such a broad differential, any patient either receiving pelvic radiation or with a prior history of pelvic radiation presenting with new or

worsening “irritative” urinary symptoms should undergo workup with urinalysis and urine culture. A more thorough evaluation with urine cytology, dedicated upper tract imaging (CT urogram, retrograde pyelogram), and cystoscopy may also be indicated.[271]

Most mild-to-moderate cases of acute radiation cystitis can be sufficiently managed with anticholinergic medication, such as oxybutynin chloride. Mirabegron represents a potential second-line option. Patients presenting predominately with bladder spasms may benefit from the use of hyoscyamine or flavoxate hydrochloride. Dysuria may be alleviated with phenazopyridine hydrochloride, although patients should be cognizant that this medication results in orange discoloration of the urine and ideally should be used 2 to 3 times per week at maximum. Blood in the urine in the acute setting is typically mild and self-limiting, but significant, worsening, or persistent hematuria beyond a 6-week timeframe warrants further urologic workup and dedicated cystoscopy.

Patients presenting with mild-to-moderate symptoms of chronic radiation cystitis often also respond to these above-mentioned measures, although the total duration of medication use in the long-term merits further consideration, and periodic reassessment of symptoms without medication is prudent. It is our opinion that any patient presenting with severe urinary symptoms greater than 3 months following completion of pelvic RT should undergo prompt evaluation by urology to rule out other abnormalities, such as stricture, ulcer, vesicular fistula (discussed later), and/or secondary malignancy.

HC represents the most concerning and potentially severe form of chronic radiation cystitis. Initial conservative management of HC usually consists of hydration, continuous bladder irrigation, and blood transfusion as indicated with additional supportive and corrective measures (eg, reversal of coagulopathy) that address factors potentially contributing to the bleeding. Additional intravesical and extravesical therapies such as alum, silver nitrate, aminocaproic acid (Amicar), prostaglandins, or formalin may be administered. If hematuria continues despite this, patients may require cystoscopy with clot evacuation and/or fulguration of hemorrhagic sites within the bladder. Lastly, in patients with refractory and intractable cases of HC, HBO, vesical artery embolization, or urinary diversion with or without cystectomy may be necessary.[271] Diversion of urine from the

bladder—that is defunctionalizing the bladder—can serve as an effective treatment for refractory bleeding. In patients who are not suitable candidates for ileal conduit diversion, bilateral nephrostomy tubes can be placed to divert urine.

Prostatitis

Lower urinary tract symptoms, such as polyuria, dysuria, urinary hesitancy, weak urinary stream, or urinary straining, resulting from prostate-only irradiation are often a consequence of inflammation of the prostatic stroma rather than of the entirety of the bladder mucosa. Such instances of "benign prostate obstruction" may be managed with α-adrenergic receptor antagonists so as to allow for more facile passage of urine.[272] While first-generation selective α-1 adrenergic receptor antagonists (prazosin, alfuzosin) are effective for this purpose, they require twice-daily dosing. As such, prostate-selective second-generation agents, such as tamsulosin 0.4 mg, are preferable and can be used up to twice daily if needed.[273] Silodosin 8 mg daily remains an additional option if a patient's polyuria is otherwise refractory to tamsulosin. While effective, terazosin and doxazosin are associated with a more significant risk of hypotension, a side effect that may be potentiated by concurrent use of phosphodiesterase type 5 inhibitors (PDE5-I) (sildenafil, vardenafil) used for erectile dysfunction (ED).[272,274]

Urethritis, Stenosis

Urethral strictures resulting from prior pelvic irradiation are relatively infrequent, occurring in approximately 3% of patients with prostate radiation,[275,276] and appear to be most common in the setting of prior HDR brachytherapy or in patients treated with combined modalities of brachytherapy and external beam radiation.[277,278] Symptoms can often mimic benign prostatic hypertrophy symptoms, including decreased urinary stream, acute urinary retention, split urinary stream, and increased postvoid residual. Flexible cystoscopy is diagnostic. Usually, additional characteristics of the stricture are needed to plan treatment, and a retrograde urethrogram can help delineate the length and location of the stricture. Urethral stricture can be seen in the postprostatectomy salvage radiation setting, with the combination of tissue ischemia from both the surgery itself

and the radiation serving as contributing factors. Treatment options for urethral stricture are largely interventional, including minimally invasive dilation and endoscopic urethrotomy with or without drug eluting balloon placement. Urethral reconstruction (urethroplasty) or urinary diversion may be appropriate for more severe cases.[279] Postradiation strictures tend to be more challenging to treat, often with the need for tissue transfer, due to the loss of healthy vascularized tissue.

FEMALE REPRODUCTIVE SYSTEM

See Table 107.8 for an overview of the medical management of radiation toxicity to the female reproductive system.

TABLE 107.8 MEDICAL MANAGEMENT OF RADIATION TOXICITY OF THE FEMALE REPRODUCTIVE SYSTEM

Radiation Toxicity	Timing	Medication Management
Vulvar and vaginal mucositis	Acute	• Betadine-medicated douche (povidone-iodine 10%; OTC): 2 tbsp concentrate to 1-quart warm water qd • Betadine-medicated gel (povidone-iodine 10%, OTC): 1 applicator full qhs; may apply externally as well • Betadine-medicated vaginal suppositories (povidone-iodine 10%, OTC): insert intravaginally qhs • Replens vaginal moisturizer (OTC): one applicator q2-3d prn • Lidocaine: Apply to affected area prn for topical anesthesia, 2.5% ointment, 4% and 5% cream. • EMLA cream (lidocaine 2.5%, prilocaine 2.5%): Apply topically prn.
Bacterial vaginosis	Acute or chronic	Topical antibiotics • Metrogel vaginal (0.75%) 1 applicator qd-bid × 5 d • Cleocin vaginal ovules (clindamycin) 1 ovule intravaginally qhs × 3 d Oral antibiotics • Metronidazole (Flagyl) 375-500 mg PO bid • Flagyl ER 750 mg PO qd × 7 d

Radiation Toxicity	Timing	Medication Management
Vaginal candidiasis	Acute or chronic	Topical antifungals • Miconazole (Monistat) 100 mg intravaginally qd × 7 d or 200 mg qd × 3 d • Clotrimazole (Mycelex) cream or vaginal tablets qd × 1, 3, or 7 d • Butoconazole (Femstat-3) qd-q3d, cream (× 3 d) or extended-release cream (× 1 d) If refractory to topical, try oral antifungal medication: • Fluconazole (Diflucan) 150 mg PO × 1 d; if refractory, 100 mg qd × 14 d
Premature menopause	Subacute	In patients with cancer who are ER-negative, consider hormone replacement therapy[428]
Hot flashes	Subacute	For mild symptoms: vitamin E 800-1,000 IU qd For severe symptoms • Paroxetine (Paxil CR) 12.5 + mg PO qd • Venlafaxine (Effexor XR) 75 mg PO qhs (titrate upward from 37.5 mg) • Clonidine patch (Catapress TTS) 0.1 mg patch q week • Methyldopa (Aldomet) 250 mg PO bid If refractory to above • Gabapentin (Neurontin) 300 mg qd × 3 d, then 300 mg tid or titrate down to effective level • Medroxyprogesterone (Depo Provera) 150 mg IM q 3 mo • Megesterol (eg, Megace) 20 mg PO bid initially; 10 mg qd or qod once responsive
Vaginal atrophy, dryness, dyspareunia	Late	Vaginal moisturizers can be used several times a week to maintain vaginal health. • Replens vaginal moisturizer (OTC): 1 applicator q2-3d prn • Hyaluronic acid vaginal lubricants should be applied prior to penetration/intercourse. • Water- or silicone-based lubricants are recommended. • Petroleum-based lubricants are not recommended (increase the risk of infection and can damage latex condoms). • Avoid lubricants with perfumes or flavors as these can be irritating.

Radiation Toxicity	Timing	Medication Management
		Low-dose vaginal estrogen is available in creams (Estrace, Premarin), tablets, and rings (Estring, Femring).[429] • Associated with minimal serum estrogen elevation Selective estrogen reuptake inhibitor: • Ospemifene (Osphena)[430]
Hypoactive sexual desire disorder	Late	Flibanserin 100 mg PO qhs[430]

OTC, over the counter; PO, oral; PRN, as needed; tbsp, tablespoon; q, every; qd, everyday; qhs, every night; tid, 3 times daily.

Dziuk T. *Commonly Prescribed Medications in Radiation Oncology*. 11th ed. https://www.texasoncology.com/getmedia/ddb81e5b-0532-4200-b25e-20a538cd9221/Commonly-Prescribed-Medications-in-Radiation-Oncology.pdf

Vaginal Mucositis

Vaginal toxicity and sexual dysfunction are common for women undergoing radiation treatment of gynecologic malignancies. Selected series suggest that the highest incidence of postradiation sexual dysfunction may be seen in women undergoing multimodal treatment for cervix cancer.[280-282]

Acute vaginal mucositis is a presumptively underreported toxicity of radiation, and as such, estimates of its true incidence are difficult to ascertain. Affected patients may present with symptoms of vaginal burning, pruritus, pain, dyspareunia, and/or variable degrees of bleeding.[283] Speculum examination may reveal erythematous vaginal mucosa with variable extent of edema, ulceration, and overlying exudate; serosanguinous discharge with pooling in the posterior aspect of the vaginal canal may also be present. Clinicians should maintain a low threshold of suspicion for infectious candidal vaginitis in patients with thick, adherent white vaginal discharge, or bacterial vaginosis in patients with copious gray, thin malodorous vaginal discharge. Either of these clinical entities may develop secondarily in patients undergoing active radiation treatment and are typically treated with topical antifungals (clotrimazole, miconazole) or antibiotics (metronidazole, clindamycin), respectively.[92]

Management of noninfectious causes of vaginal mucositis is largely in keeping with the management of vulvar mucositis, and the two conditions

are often comorbid. Patients are suggested to maintain appropriate hygiene of the genitalia and perineum through frequent use of lukewarm water sitz baths. Additional cleansing of the vaginal canal directly with medicated douching of dilute hydrogen peroxide, or povidone-iodine 10% solution, also has therapeutic utility.[92,284,285] Glycerin and mineral oil–based moisturizers (Remedy cream) and topical lidocaine and/or prilocaine ointments may be applied to provide more focal relief in bothersome and symptomatic areas.[92]

Vaginal Ulceration, Necrosis, Fistula

More rarely, patients may develop more chronic sequelae of vaginal ulceration, necrosis, and/or fistula formation after completion of RT. Vaginal necrosis may appear as a small region of mucosal whitening and hypopigmentation, progressing to diffuse, "glassy" edema of the affected mucosa with exudate.[286] This often results within 15 months after completion of treatment and, if limited in extent, may resolve spontaneously or after conservative management with hydrogen peroxide vaginal douching and/or antimicrobial therapy.[287] Biopsy should be completed in equivocal cases to rule out residual disease or recurrence, although this must be weighed against concern for delayed vaginal wound healing and further tissue injury. For more severe cases, pentoxifylline, HBO, or surgical intervention with debridement may be required.[286]

Rectovaginal fistula or vesicovaginal fistula development is an additional chronic complication that may present with the passage of urine, flatus, or feces from the vaginal canal, among other locoregional symptoms such as incontinence, pain, burning, and/or bleeding. The diagnosis and treatment of vaginal fistulae is complex, and any patient suspected to have vaginal fistula should be promptly referred for surgical assessment.[288,289] Careful consideration is made of the extent of fistula and its anatomic location; conservative, nonsurgical management in patients with small or asymptomatic fistula may be attempted, while more severe but appropriately operable cases may require surgical closure of the fistula with interposition of a pedicled tissue flap.[290]

Vaginal Stenosis

Vaginal stenosis is a well-recognized late side effect of pelvic irradiation. Affected patients may present with symptoms of sexual dysfunction, including dyspareunia, vaginismus, and postcoital bleeding as early as 3 to 6 months following completion of therapy. Pelvic examination may demonstrate progressive loss of elasticity of the vaginal mucosa with the variable extent of intracavitary adhesions and occlusion, and the act of gynecologic examination itself may be prohibitively uncomfortable for affected patients.[291]

Although limited primary data support its use, management of vaginal stenosis generally consists of insertional vaginal dilator use, both for prophylaxis and as an active treatment.[292] The principle of dilation, either through regular penetrative coitus or with an appropriately sized physical dilator, is to maintain patency of the vaginal canal through manual expansion of surrounding tissues and lysis of adhesions.[293] Despite its commonplace adoption and ubiquity, no consensus exists on the frequency and overall duration of dilator use, and care must be taken in select patients to avoid the potential adverse psychological impact associated with manual dilation.[292] Many suggest utilization of vaginal dilators 3 to 5 times weekly, followed by a progressive tapering schedule with continual assessment of patient tolerance and compliance. Discontinuation of dilation may be considered when patients are no longer experiencing discomfort during vaginal examination at follow-up 1 to 2 years post-treatment, although some practitioners suggest continual dilation indefinitely.[92,293]

Sexual Interest/Arousal Disorder

Some patients who received pelvic radiation may develop sexual interest/arousal disorder. Diagnosis involves meeting any three of the following criteria: reduced interest in sexual activity, reduced sexual/erotic thoughts or fantasies, reduced initiation of sexual activity and typically unreceptive to a partner's attempts to initiate, reduced sexual excitement/pleasure during sexual activity in 75% to 100% of sexual encounters, reduced sexual interest or arousal in response to any internal or external sexual cues, or reduced genital or nongenital sensations during sexual activity in 75% to 100% of sexual encounters.[294] Referral to a

psychotherapist, or a provider who specializes in cognitive behavioral therapy or sexual psychoeducation is recommended.

Ovarian Failure and Infertility

RT is a well-known cause of premature ovarian failure (POF), early-onset menopause, and infertility. The degree of ovarian impairment subsequent to radiation is multifactorial and dependent on a number of separate variables, including total dose received by the ovaries, the dose and, fractionation regimen employed, the total pelvic irradiation volume, and uniquely, the patient's age at the time of treatment.[295-298] Of the various cell types (eg, theca, granulosa, oocyte) that are found within the ovary, germ cells appear to be the most inherently radiosensitive; the apparent dose required to kill half of all human oocytes (LD_{50}) is 2 Gy or less.[299] Since the number of ovarian primordial follicles decreases with age, older women are more susceptible to radiation-induced POF than younger women, such that the effective sterilizing dose associated with radiation at birth is 20.3 Gy, while at 30 years, the value is 14.3 Gy.[300]

All patients who desire to preserve fertility through cancer treatment should be referred to fertility specialists, and it is recommended that any patient who has a greater than 30% chance of losing fertility from subsequent cancer therapy should receive some form of fertility preservation counseling.[301]

Oophoropexy is a well-established surgical procedure that manually relocates the ovaries outside the prospective radiation field in an attempt to preserve gonadal function and potential fertility in premenopausal patients. In oophoropexy, both ovaries are laparoscopically transposed from the prospective radiation field without compromising the blood supply to the ovary or torsing the infundibulopelvic ligament.[302-305] Once transposed, the placement of radiopaque clips intraoperatively may allow for facile identification of the ovaries as OARs during CT simulation and treatment planning. Importantly, oophoropexy should only be considered in patients for whom the risk of occult ovarian metastasis is low. While oophoropexy may help maintain normal ovarian endocrine function, it is also important to recognize that transposition does not obviate the potential deleterious impact of radiation on the uterus and cervix—consequences that might

otherwise preclude normal fertilization and pregnancy in and of themselves, separately.

Additional modern techniques, such as embryo cryopreservation, immature or mature oocyte preservation, and ovarian tissue cryopreservation, also exist for patients who wish to preserve their fertility prior to RT. A detailed explanation of these techniques is outside the scope of this text. Nevertheless, as mentioned previously, each of these procedures carries with it unique requirements, benefits, and limitations that merit nuanced assessment and understanding prior to recommendation for a given individual who will undergo RT. Other newer investigation techniques, such as in vitro follicle culture, appear promising, although further research is required prior to their widespread adoption.[306]

For patients who do subsequently develop radiation-induced ovarian failure, significant vasomotor symptoms (VMS) and genitourinary symptoms of menopause (GSM) may ensue and confer a negative impact on quality of life.[307]

Hot flashes are the most frequently reported VMS of menopause, occurring in upward of 80% of women. While lifestyle modifications may be adequate to mitigate mild VMSs, patients with moderate-to-severe hot flashes often benefit from estrogen replacement therapy; this may be delivered via oral, transdermal, and cutaneous formulations.[308,309] For those who are not appropriate candidates for hormonal replacement, additional medications such as selective serotonin uptake inhibitors (SSRIs: paroxetine, citalopram, escitalopram) and selective norepinephrine uptake inhibitors (SNRIs: venlafaxine, desvenlafaxine) may be used to help mitigate VMSs. For patients who cannot tolerate SSRI or SNRI therapy, further consideration may be made for other tertiary pharmacologic agents, including gabapentin, pregabalin, clonidine, and fezolinetant, a novel neurokinin-3 receptor antagonist.[310,311]

Initial lines of therapy for GSM consist of local, nonhormonal vaginal moisturizer creams and lubricants, which can help mitigate dryness associated with mucosal atrophy. Vaginal moisturizers are recommended to be used routinely, while lubricants are generally reserved for sexual activity. For those patients with moderate GSM or symptoms otherwise refractory to moisturizers and lubricant therapy alone, additional vaginal estrogen applications may be of utility. Although levels of systemic estrogen

absorption from these local therapies are generally felt to be minimal, some caution may be warranted in patients with hormone-dependent malignancies, and an individualized discussion regarding the risks and benefits of topical estrogen for these women, based on their disease pathology and symptom severity, is suggested.[312,313] The use of vaginal estrogen therapy may be employed for patients also receiving concurrent systemic hormone replacement therapy, but with persistent atrophic vaginal symptoms.

MALE REPRODUCTIVE SYSTEM

See Table 107.9 for an overview of the medical management of radiation toxicity to the male reproductive system.

TABLE 107.9 MEDICAL MANAGEMENT OF RADIATION TOXICITY OF THE MALE REPRODUCTIVE SYSTEM

Radiation Toxicity	Timing	Medication Management
Erectile dysfunction	Late	Phosphodiesterase-5 inhibitors • Tadalafil (Cialis) 10 mg qd prn (range 5-20 mg) as single dose or 2.5 mg qd (up to 5 mg qd) for continuous dosing • Vardenafil (Levitra) 10 mg PO prn (range 5-20 mg) • Avanafil (Stendra) 100 mg qd prn (range 50-200 mg) • Sildenafil (Viagra) 50 mg qd prn (range 25-100 mg)
Male hot flashes	Late	Antidepressant • Venlafaxine (Effexor XR) 75 mg PO qhs Progestional agents • Medroxyprogesterone (Depo-Provera) 150 mg IM q 3 mo • Megestrol (Megace) 20 mg PO bid, 10 mg qd or qod once responsive

IM, intramuscular; PO, oral; PRN, as needed; qd, everyday; qhs, every night; qod, every other day.

Dziuk T. *Commonly Prescribed Medications in Radiation Oncology*. 11th ed. https://www.texasoncology.com/getmedia/ddb81e5b-0532-4200-b25e-20a538cd9221/Commonly-Prescribed-Medications-in-Radiation-Oncology.pdf

Erectile Dysfunction

ED is a well-recognized toxicity associated with pelvic irradiation, particularly following definitive radiation for prostate cancer. Impotence may develop anywhere from 8 to 16 months following completion of treatment, with an estimated prevalence of around 34% at 1 year that approaches 50% at 5 years.[92,314] Clinical evaluation of patients with suspected RIED generally consists of comprehensive history and physical, with particular attention to a detailed sexual history that appropriately addresses the severity, timing, and duration of sexual dysfunction as it pertains to receipt of radiation treatment.[315] Additional offending medications contributing to impotence should be discontinued and potential psychological contributors elucidated. PDE5-Is (tadalafil, vardenafil, avanafil, sildenafil) represent the general first-line treatment for radiation-induced ED. This class of medications work by inhibiting the PDE5 enzyme found within the smooth muscle of corporal penile tissue and thereby enhance the erectile, vasodilatory effects of endogenous nitric oxide.[316] PDE5-Is are generally safe, well tolerated, and efficacious.[317] Importantly, however, cavernosal nerve activation is required to initiate the physiologic cascade that mediates the effect of this medication class, and therefore, PDE5-I use is most effective in those individuals with some preexisting level of neurovascular preservation and prior capacity for sexual stimulation. In addition, PDE5-Is are contraindicated with the concurrent use of α-adrenergic and nitrate medications; the combination of both classes of medication may result in significant vasodilation and hypotension and should, therefore, be avoided whenever possible.[316]

Vacuum erection devices (VEDs) may also be employed in the management of RIED. These instruments function by exerting negative external pressure on the penile tissue, allowing for passive engorgement of blood that is maintained through the presence of external constriction ring that prevents blood outflow.[318,319] While VEDs are associated with high rates efficacy in instantiating on-demand erections, long-term compliance of this therapy may be limited by the mechanical procedure required for its use and unnatural feeling.[320,321]

Patients with persistent RIED refractory to the above- mentioned interventions should be referred to urology for further evaluation and management. In addition, second- and third-line therapies for RIED may

include intracavernosal injections, transurethral suppositories, and penile prosthesis.[320]

Oligospermia, Azoospermia, and Infertility

The development of radiation-induced male gonadal toxicity is similarly multifactorial and dependent on a number of separate variables, including total dose, dose and fractionation regimen employed, patient age, and target cell population. Of the various cell types (eg, Sertoli, Leydig, germ) that are found within the testis, germ cells also appear to be the most inherently radiosensitive. Significantly, the process of spermatogenesis is such that developing germ cells become progressively more resistant to single doses of radiation with increasing degree of maturation: that is, single doses as low as 0.1 Gy may temporarily compromise spermatogenesis via damage to spermatogonia, 2 to 3 Gy can damage the more mature spermatocytes, and doses in excess of 6 Gy may be necessary to deplete spermatids and incite permanent azoospermia.[322-325] This graded radioresistance, coupled with the prolonged time of the germ cell maturation process itself, explains the relatively unique, temporally dependent process of both radiation-induced male infertility and recovery by which lower, but increasingly fractionated doses can have a more deleterious effect on sperm production than higher, single doses of radiation. Leydig cells of the testis are otherwise less sensitive to the damaging effects of irradiation, and doses of 12 to 20 Gy are typically required for clinically relevant impairments in testosterone production.[326-329] See the endocrine section for information regarding testosterone replacement therapy.

Again, we suggest that all patients who desire to preserve fertility through cancer treatment should be referred to fertility specialists. Sperm cryopreservation—in which a semen sample is collected from a patient prior to receipt of RT and frozen in preservation—represents one of the most common methods of fertility preservation. The freezing process allows for up to 15 years of storage, with success rates of up to 40% in the use of subsequent in vitro fertilization.[330,331]

SKELETAL SYSTEM

Trismus

Trismus refers to restriction in range of motion of the jaw. The condition of trismus is thought to result from progressive radiation-induced fibrosis of the pterygoid muscles, masseter, and temporomandibular joint, leading to involuntary muscular fiber contracture and ankylosis. Patients may present with subjective sense of "lockjaw," jaw pain, jaw clicking, muscle spasm, difficulty chewing, and/or dysarthria.

Patients with radiation-induced trismus may benefit from intensive physiotherapy in which regular opening, closing, and lateral movement of the mouth are completed at regular intervals via an exercise protocol.[332] Numerous trismus appliances exist for this purpose, including externally or internally activated devices such as threaded tapered screws, tongue spatulas, and/or dynamic bite openers.[333,334] In spite of the many different appliances and techniques that exist, no clearly superior strategy for conservative management of trismus exists; most exercise regimens and rehabilitation devices appear to have similar effectiveness, and more importance remains with patient adherence to the utilized therapy.[335] Physical therapy can also help lessen edema, soften fibrous tissue, improve range of motion and muscle strength, and restore circulatory efficiency.[336]

More severe and extreme cases of trismus may require surgical intervention with coronoidectomy, myotomy tissue release, or scar tissue resection followed by free flap reconstruction.[337]

Osteoradionecrosis of the Mandible

ORN of the mandible is a sequela in which hypovascular, devitalized bone is openly exposed for a minimum of 3 months.[338] Radiation to the head and neck region is believed to induce an obliterative endarteritis of osseous and overlying soft tissue that results in progressive hypoxia and eventual necrosis; the otherwise limited, tenuous blood supply to the mandible and relatively high collateral doses to this region—particular in the primary treatment of oral cavity cancer—make it particularly susceptible to radionecrosis as compared to other at-risk adjacent bone (eg, maxilla).[339] Moreover, the phenomenon of ORN is frequently heralded by mechanical insult or traumatic injury (ill-fitting dentures, dental extractions), in which appropriate wound healing is impaired.[340] ORN is a dose-dependent toxicity in which total dose, maximum dose, and volume of mandibular irradiation

are important; smoking, preexisting poor dentition and oral hygiene, and the use of bisphosphonates represent additional identifiable patient-related risk factors.[341-346]

The incidence of ORN following RT to the head and neck approaches 3% to 8% and often develops anywhere from 2 to 4 years following treatment.[343,347,348] Patients with mandibular ORN traditionally present with a painful, nonhealing lesion or ulcer of the oral cavity. Additional ancillary symptoms may include expectoration of bone fragments, tooth luxation, periodontal disease, halitosis, trismus, dysarthria, dysesthesia, or anesthesia in the distribution of the inferior alveolar nerve. Depending on the severity of the condition, secondary osteomyelitis of adjacent bone, pathologic mandibular fracture, and/or osseous fistula may also ensue.[349] Biopsy of the wound in question is important to definitely rule out recurrent or residual malignancy.[350] Additional imaging studies may aid in diagnosis, including panoramic mandibular radiograph and CT of the head and neck, demonstrating radiolucencies and cortical bone disruption, respectively.

The risk of ORN is best mitigated through appropriate radiation treatment planning that minimizes excess radiation dose to the mandible, and avoidance of unnecessary oral trauma. Preradiation dental extractions are preferred to postradiation dental extraction, and for this reason, any patient who is anticipated to undergo head and neck radiation should have formal dental evaluation prior to initiation of RT.[340] Once present, asymptomatic or mildly symptomatic cases of ORN may be managed conservatively with appropriate pain control, good oral hygiene (frequent saline irrigation), antimicrobial therapy, and/or minimal dental interventions as needed; filing, smoothening, and debridement of sharp, exposed bone and bony fragments can be performed to prevent aggravation and injury of adjacent buccal, gingival, and lingual tissue.[351,352] Patients with more significant symptoms, symptoms refractory to first-line conservative therapies, or with substantial evidence of necrosis merit formal evaluation by otolaryngology and are instead treated via invasive surgical approaches (wound debridement, sequestrectomy, decortication, or radical mandibular surgical resection and microvascular reconstruction).[353]

The role of HBOT in mandibular ORN is conflicting and controversial. Conclusive data supporting HBO's benefit in this setting are lacking. HBO treatments are time-consuming, often consisting of 30 consecutive daily

sessions, each of which is approximately 90 minutes in duration.[354] As such, many refrain from routine HBO use in the modern era, recommending therapy on a case-by-case basis for those with persistent ORN in spite of conservative management and/or more aggressive surgical approaches as earlier.[355] Pentoxifylline and tocopherol (vitamin E) therapy has shown therapeutic promise as synergistic antifibrotic agents to help treat refractory ORN, although adoption of this regimen awaits further prospective randomized data.[356]

Osteoradionecrosis of the Femur (Aka Avascular Necrosis)

ORN of the femur may result from prior pelvic irradiation via a mechanism that is presumed commensurate with that of both mandibular ORN and pelvic insufficiency fracture (PIF): namely, progressive vascular obliteration that results in local ischemia, bony matrix remodeling, and structural weakening that predisposes to fracture or collapse. Patients with ORN of the femur may, therefore, present with more overt symptoms of hip, groin, thigh, and/or buttock pain and limited mobility than other patients with occult, asymptomatic PIF.[357]

Initial, conservative therapeutic management may consist of analgesia with nonsteroidal anti-inflammatory agents, limitation or avoidance of weight bearing, and biophysical therapy to improve motion and gait.[358] Surgical interventions for cases of hip ORN are based on preoperative staging criteria and may include femoral core decompression or bone grafting for early stages versus total hip arthroplasty for more advanced stages.[359] ORN of the humeral head has also been reported in the breast radiation literature, and workup/management is similar.

Costochondritis

RT to the breast, chest wall, lung, or mediastinum may also precipitate costochondritis, as evidenced by tenderness of the costochondral junctions in anatomic areas corresponding to prior treatment fields. A paucity of data exists regarding the frequency and management of this toxicity in the setting of RT, although treatment is generally supportive: simple analgesia with NSAIDs, and topical heat or ice application for similar purposes when the overlaying skin is otherwise intact, is usually sufficient. Rarely,

escalation to additional narcotic pain medication, use of local anesthetic injections, or corticosteroids may be necessary.[360] Some case series have reported instances of necrotic, secondarily infected radiation-related costochondritis in patients with postoperative breast cancer requiring surgical debridement.[361] See Table 107.10 for an overview of the medical management of costochondritis.

TABLE 107.10 MEDICAL MANAGEMENT OF RADIATION-INDUCED COSTOCHONDRITIS

Radiation Toxicity	Timing	Medication Management
Costochondritis	Acute	NSAIDs • Ibuprofen 200-800 mg q4-6h, 3,200 mg/d max • Naproxen 250-500 mg q12h, 2,500 mg/d max

NSAIDs, nonsteroidal anti-inflammatory drugs; q, every.
Dziuk T. *Commonly Prescribed Medications in Radiation Oncology*. 11th ed. https://www.texasoncology.com/getmedia/ddb81e5b-0532-4200-b25e-20a538cd9221/Commonly-Prescribed-Medications-in-Radiation-Oncology.pdf

Pelvic Insufficiency Fracture

PIFs are a well-recognized late side effect of pelvic RT. The process of pelvic irradiation is believed to cause progressive osteoblast reduction in the bone matrix, fatty marrow replacement, and obliterative ischemia of osseous tissue, and PIFs are believed to occur when normal biomechanical stresses overwhelm the compromised integrity of this structurally weakened, inelastic bone.[362,363] The reported rates of insufficiency fracture incidence vary widely in the historic literature—from levels less than 1% to as high as 89%—and are most frequently associated with RT for gynecologic malignancies. More modern estimates place the crude incidence of PIFs around 15%, with a median time to diagnosis between 8 and 39 months.[364]

Patients with PIFs will most often present with complaints of intractable pain in the region of the lumbar spine, sacrum, hips, groin, or pelvis, which may or may not radiate distally to the legs. These symptoms may be exacerbated by weight bearing.[365] Other patients may remain entirely asymptomatic, such that the diagnosis of PIFs is made on the basis of

radiologic imaging alone. The sacrum and pubis are the most common sites of PIFs.[364]

Prevention of PIFs is largely directed at modification and mediation of risk factors; individuals with osteoporosis should undergo appropriate screening, evaluation, and management with reversal of secondary causes of osteoporosis when indicated. Vitamin D and calcium supplementation may be necessary.

Currently, there is little consensus regarding the treatment of radiation-induced PIFs, and these patients are best managed in a multidisciplinary setting including orthopedic surgeon and endocrinology. Conservative approaches are typically suggested initially, through the use of analgesics and appropriate mobilization, with assisted ambulation, transfers, and weight bearing as tolerated. The role of bone-directed antiresorptive agents, such as bisphosphonates, in the setting of acute fracture remains unclear. Operative intervention with sacroplasty or internal fixation may be considered for those who fail medical and nonoperative therapies.[365]

Another common location for radiation-related insufficiency fractures includes ribs in the setting of thoracic SBRT and breast irradiation and is typically managed conservatively with pain management and rest.

INTEGUMENTARY SYSTEM

See Table 107.11 for an overview of the medical management of radiation toxicity to the integumentary system.

TABLE 107.11 MEDICAL MANAGEMENT OF RADIATION TOXICITY OF THE INTEGUMENTARY SYSTEM

Radiation Toxicity	Timing	Medication Management
Dermatitis	Acute	Moisturizers used to prevent and treat: Aquaphor, Calendula, Calmoseptine, Miaderm, etc Domeboro compresses: Dissolve 1 tablet or packet in 1-pint water and apply moist (not wet) soak 20 min tid-qid. Topical analgesics: Aquaphor/Xylocaine 5% ointment, topical lidocaine 2.5% ointment and 4% or 5% cream, EMLA (lidocaine 2.5%, prilocaine 2.5%)
Pruritus	Acute	Topical steroids: hydrocortisone 1% (OTC), betamethasone 0.05%, desoximetasone cream

Radiation Toxicity	Timing	Medication Management
		0.25%, 0.05%, ointment 0.25% Sarna sensitive (OTC, 1% hydrocortisone; 1% pramoxine)
Miliaria rubra aka inflammation of sweat glands	Acute	Topical steroids: hydrocortisone 1% (OTC), betamethasone 0.05%, desoximetasone cream 0.25%, 0.05%, ointment 0.25%
Moist desquamation	Acute	Silvadene cream 1% or SilverMed (OTC): Apply to affected area tid. Mupirocin applied 3 times daily. Domeboro compresses: Dissolve 1 tablet or packet in 1-pint water and apply moist (not wet) soak 20 min tid-qid prior to topical ointments/creams. Nonstick adhesive pads (eg, Tefla) or hydrocolloid and hydrogel wound dressings
Ulceration/slow healing	Subacute or late	In addition to the above-mentioned skin care, consider debridement with saline or MPM wound and skin cleanser. Capillary bed stimulant: Xenaderm (Balsam of Peru, trypsin, and castor oil) applied bid-tid. Pentoxifylline 400 mg PO tid with vitamin E 1,000 IU PO qd
Wound infection		For minor/superficial open wound infections • OTC Bacitracin or Polysporin • Advance to Silvadene 1% or mupirocin For uncomplicated subcutaneous involvement • Trimethoprim/sulfamethoxazole (Bactrim DS) 1 PO bid • Cephalexin (Keflex) 250-500 mg PO q6h For patients who are diabetic or infections of the groin and perineum, add • Clindamycin 150-450 mg PO q6h If pseudomonas is suspected • Ciprofloxacin 250-750 mg PO bid or XR 500-1,000 mg PO qd • Levofloxacin 500-750 mg qd
Fungal/yeast infection		OTC: Terbinafine (Lamisil) applied bid or Lotrimin antifungal applied bid if refractory try naftifine 1% applied qd or fluconazole 200 mg day 1, then 100 mg qd.
Herpetic infections		For herpes simplex

Radiation Toxicity	Timing	Medication Management
		• Valacyclovir 1 g bid × 7 d • Acyclovir 200 mg PO 5 times daily × 10 d For herpes zoster • Valacyclovir 1 g tid × 7 d • 800 mg PO 5 times daily × 7-10 d
Capsular contracture around breast prostheses	Late	Leukotriene antagonist Singulair 10 mg qd for 3 mo Trental 400 mg tid with vitamin E 1,000 mg qd for 6 mo
Fibrosis	Late	Trental 400 mg tid with vitamin E 1,000 mg qd for 6 mo Pravastatin 40 mg daily

bid, 2 times daily; OTC, over the counter; PO, oral; q, every; qd, everyday; qid, 4 times a day; tid, 3 times daily; XE, extended release.

Dziuk T. *Commonly Prescribed Medications in Radiation Oncology*. 11th ed. https://www.texasoncology.com/getmedia/ddb81e5b-0532-4200-b25e-20a538cd9221/Commonly-Prescribed-Medications-in-Radiation-Oncology.pdf

Radiation Dermatitis

Radiation dermatitis is one of the most common and conspicuous side effects of RT, such that 90% or more of patients will experience some extent of radiation-related skin reaction.[366] Acute radiation changes include erythema, dry desquamation, moist desquamation, poor wound healing, skin necrosis, and/or ulceration. Chronic radiation dermatitis may arise from months to several years after treatment and may present as hypo- or hyperpigmentation, skin fibrosis/scarring, skin atrophy, and telangiectasias.

The recommendations for the management of radiation dermatitis are somewhat discordant across multiple series of national and international guidelines, as there is a relatively narrow window of medications or interventions that can be strongly supported on the basis of level 1 evidence; some paradigms of approaches to therapy are based on clinical practice.[367] Topical steroids such as beclomethasone, hydrocortisone 1%, or mometasone furoate 0.1% appear to decrease the risk of patient-reported symptoms and moist desquamation.[368] A number of additional topical agents have been investigated as prophylaxis for radiation dermatitis, all with either weak or contradictory data to support their use: petroleum-based ointments, ascorbic acid, almond oil or olive oil, triethanolamine, silver

sulfadiazine, calendula cream, barrier films, silver nylon dressing, and sucralfate.[369]

Patients with common terminology criteria for adverse effects (CTCAE) grade 1 radiation dermatitis are characterized as having faint skin erythema and peeling.[370] Such patients can be managed with general precautionary advice, with maintenance of appropriate skin hygiene and moisturization with hydrophilic ointments. Patients with notable irritation and pain may benefit from the use of Aquaphor/xylocaine ointment 5% mixture for soothing.[92]

Grade 2 and 3 radiation dermatitis includes those with moderate redness and swelling with thinning of skin folds, or skin thinning more than 1.5 cm across not limited to folds, with severe swelling.[370] Treatment generally consists of focal dressings—usually silicone foam bandage, hydrogel, or hydrocolloid—over areas of exposed skin to help minimize insensible fluid loss, prevent secondary superinfection, and accelerate normal skin repopulation and reepithelialization. Additional use of Silvadene cream and Burow solution soaks (aluminum sulfate tetradecahydrate/calcium acetate monohydrate astringent) may be helpful.[92]

Any patient with evidence of skin infection or cellulitis should begin topical (mupirocin) and/or systemic therapy with antibiotics. Patients with grade 3 dermatitis may require treatment breaks to allow for appropriate healing. Grade 4 radiation dermatitis is defined by skin necrosis or ulceration of the full thickness of the dermis, from which spontaneous bleeding may occur.[370] Skin necrosis is typically described as leathery in texture, yellow in appearance, and adherent.[371] Patients who develop ulceration should have appropriate wound debridement and irrigation to keep the skin and soft tissue clean and free of debris.[92] Grade 4 radiation dermatitis is relatively rare and should be treated on a case-by-case basis; more conservative management may consist of silver sulfadiazine cream, capillary stimulation with Balsam of Peru/trypsin/castor oil, and covering with a hydrocolloid or hydrogel, although most patients require specialized wound care. More severe and refractory cases may merit surgical intervention, with methods including advanced reconstructions with skin flaps or artificial skin.[372,373] HBO has been used for chronic nonhealing skin ulceration or necrosis, although well-designed clinical trial data to substantiate the efficacy of HBO in this setting have not been completed.[374]

The therapies for chronic radiation dermatitis are more limited, and we suggest a formal evaluation by dermatology and/or plastic surgery for patients with persistent, bothersome sequelae. Again, the use of rehabilitative care and deep friction manual massage has been suggested to help manually dissipate scar tissue and fibrosis with softening over time. Trials of pentoxifylline and vitamin E have shown promise in managing cutaneous radiation-related fibrosis and scarring, although the therapeutic effect required prolonged administration over years, which may limit patient adherence.[375] Additional options for skin or soft tissue fibrosis that have been suggested include liposomal-encapsulated superoxide dismutase injections and fractional laser therapy, both of which also remain investigational at present.[376,377] Patients with breast cancer with post-treatment telangiectasias have been treated with multiple pulsed dye-laser treatments with satisfactory cosmetic results.[378,379]

Mastalgia, Post-Breast Surgery Pain Syndrome

Patients who are receiving whole- or partial-breast RT may experience worsening mastalgia, often experienced as the onset of sharp, shooting, shock-like sensations, referred to as “zinger pains” or “zingers.” Radiation may also increase the frequency or conspicuity of such pain, which may otherwise normally be present in the postoperative period.

Little randomized data exist to guide a formalized process of workup or management of such patients, given the ubiquity, and generally self-limiting nature of this form of mastalgia. All such patients should have additional competing etiologies of breast pain—including mastitis, cellulitis, seroma, or hematoma formation—ruled out through physical examination and dedicated imaging as necessary, per clinical judgment. Analgesia with NSAIDs is typically a sufficient treatment for zinger pain, with escalation to additional opioid medication or neuropathic pain medications if relief is not achieved by more conservative regimens.

Patients may also experience “post-breast surgery pain syndrome” (PBSPS), a more chronic form of neuropathic pain in the absence of disease recurrence, which persists for greater than 3 to 6 months. PBSPS, previously referred to as postmastectomy pain syndrome—is a comprehensive diagnosis that includes a variety of conditions including

phantom breast pain, pain resulting from intercostobrachial nerve injury, or neuroma formation, all of which may be exacerbated by prior breast or chest wall RT, likely through mechanisms of perineural and intraneural fibrosis. Younger patient age at the time of surgery appears to be associated with this syndrome, which is often accompanied by symptoms of persistent hyperesthesia, hypoesthesias, and numbness of the affected breast or chest wall.[380,381] Given the wide variety and potentially multifactorial causes of PBSPS, these patients often require multidisciplinary evaluation between surgical oncology, plastic surgery, and pain management specialists. Identification of the underlying etiology of pain is paramount for appropriate treatment, which may include neurolysis, autologous fat grafting, topical capsaicin cream, tricyclic antidepressant, and/or antiepileptic neuropathic pain medications.[380-382]

Breast Fibrosis/Contracture

Radiation-induced breast or chest wall fibrosis typically presents 4 to 12 months following completion of RT, and affected patients may experience symptoms, such as breast shrinkage and induration, breast contraction, delayed wound healing, and/or diminished range of motion of the upper extremity.

The risk of radiation-induced breast or chest wall fibrosis does appear to be impacted by the nature of prior breast oncologic surgery and reconstruction. Immediate, rather than delayed, breast reconstruction may be preferred by patients and surgeons alike in its ability to lessen the psychological impact of mastectomy, better concord to preoperative quality of life, eliminate need for second operation and anesthesia, and obviate risks associated with resection of irradiated tissue. Unfortunately, this approach of immediate reconstruction is also associated with increased risk of complications. Irradiation of a foreign body, whether a tissue expander or breast implant—is associated with increased rates of toxicity and cosmetic side effects, including fat necrosis, breast volume loss, and capsular contracture. These side effects exist irrespective of impact on postmastectomy radiation techniques. Unfortunately, such toxicity does not appear to be avoided with the use of retropectoral implants or when the prosthesis is covered by a tissue flap.[383-388] This recommendation also exists

for transverse rectus abdominis muscle flap reconstruction, where higher incidences of complication are noted with immediate versus delayed reconstruction.[389] As such, increasing consensus exists for delayed reconstructive techniques in which breast reconstruction is performed several months following completion of postmastectomy radiation.[390] Delayed-immediate reconstruction also exists, by which the mastectomy skin envelope is preserved with a tissue expander that is deflated during RT and later inflated and replaced by a tissue flap.[386]

Additional preventive efforts include the use of prophylactic oral pentoxifylline and vitamin E for at least 6 months in selected high-risk patients (ie, those undergoing reconstruction). Multiple trials have demonstrated significant benefits in various fibrosis-related end points associated with this form of medical management, including direct measurement of tissue compliance of the irradiated breast or chest wall.[391-393] Additional isolated randomized trials have investigated reducing RF with the use of deep friction massage/endermotherapy and kinesiotherapy, which have the ability to manually break down fibrotic tissue, improve muscular elasticity, and conserve a functional range of motion.[393-395]

LYMPHATIC SYSTEM

Lymphedema of the Extremities

RT-related peripheral lymphedema may affect both the upper and lower extremities, although is most frequently associated with upper extremity lymphedema in the setting of prior breast RT, and lower extremity edema in the setting of prior gynecologic RT.

The risk of radiation-related upper and lower extremity edema is compounded by prior surgery; the extent of axillary surgery is a known risk factor of breast cancer–related lymphedema (BCRL), such that axillary lymph node dissection may quadruple the risk of BCRL than sentinel lymph node biopsy.[396] Similarly, the extent of pelvic lymph node dissection appears to increase the risk of lower extremity lymphedema in endometrial cancer.[397] The greater extent of prior radiation fields (supraclavicular, posterior axillary, internal mammary nodal coverage) also increases the risk of BCRL, with additional independent risk factors including elevated body mass index (BMI) at the time of cancer diagnosis, and preexisting cellulitis.

Symptoms of radiation-related extremity lymphedema typically present months to years following surgery and may include notable extremity edema with restriction of clothing in the affected leg or arm, subjective sense of heaviness of the affected extremity, and/or pain. Screening for population at risk is suggested, which requires objective limb measurements both at baseline and regular intervals over time—potentially as often as every 6 to 12 months for up to 3 years. BCRL is typically defined as a relative volume change of 10% or more, or weight-adjusted change of 10% or more, greater than 3 months after surgery.

Preventive measures include judicious use of radiation, management of obesity and maintenance of a healthy BMI, and exercise of the affected limb. Any potential soft tissue infection should be addressed before radiation treatment. Additional precautionary actions include preferential avoidance of blood pressure cuffs or venipuncture and the use of compression hosiery during air travel: nevertheless, some feel that these risk-reducing recommendations were initially adopted based on the preponderance of precaution and that there is a lack of robust data to support their widespread adoption or efficacy.[398]

Once peripheral lymphedema is present, all patients are recommended to meet with a certified lymphedema therapist for evaluation and treatment. Again, these licensed professionals may assist patients with complete decongestive therapy with serial bandaging and manual lymphatic drainage and can provide instruction on appropriate home exercises to increase range of motion and mobility. Once patients have experienced adequate lymphedema reduction, a “maintenance phase” of therapy may be ensured with the use of additional compression garments and self-directed manual lymphatic drainage.[396,399,400]

Lymphedema of the Head and Neck

Lymphedema of the head and neck is well-established but likely underreported late toxicity; it is believed that upward of 75% of patients who receive prior head and neck irradiation will experience some form of local lymphedema and that many patients have some preexisting form of lymphedema even prior to treatment due to local tumor involvement and inherent lymphatic disruption.[401]

External lymphedema may be appreciated by visual examination of the head and neck showing visible swelling of the skin and soft tissue, and the patient may report notable cosmetic changes in the face, submental, submandibular, neck, and shoulder regions, as well as a subjective sense of tightness and limited cervical range of motion. Internal lymphedema requires direct examination and/or flexible endoscopy of the upper aerodigestive tract and is evinced by turgidity of the mucosa and underlying soft tissue of the oral cavity, pharynx, and/or larynx. Depending on its anatomic location, internal lymphedema may result in dysphagia, dysarthria, dysphonia, and wheezing with concern for potential airway compromise and need for tracheostomy.[402,403]

Most patients with lymphedema can be managed through approaches of education, complete decongestive therapy, stretching exercises, and appropriate skin care. Minimizing select postures and body positions, for instance, may help mitigate gravity-dependent reducible edema in certain locations. Manual lymph drainage and compression therapy may help return lymph back into the circulatory system, facilitating the regression of soft tissue swelling and preventing the deposition of fibrofatty scar tissue that results in permanent neck fibrosis.[404] Various pneumatic compression devices may also aid in this purpose.[405] Qualified physical and occupational therapists trained in lymphedema management may assist patients with decongestive therapy and can provide instruction on appropriate home exercises to increase range of motion and mobility. Surgical revascularization attempts via lymphaticovenous anastomosis appear promising, but remain investigational in this setting.[406,407] Patients with overt neck fibrosis may benefit from the use of pentoxifylline.[408]

ENDOCRINE SYSTEM

See Table 107.12 for an overview of the medical management of radiation toxicity to the endocrine system.

TABLE 107.12 MEDICAL MANAGEMENT OF RADIATION TOXICITY OF THE ENDOCRINE SYSTEM

Radiation Toxicity	Timing	Medical Management
Hypopituitarism	Late	Endocrine supplementation
Hypothyroidism	Late	Levothyroxine supplementation titrated based on TSH level
Premature menopause	Subacute	In patients with ER-negative cancer, consider hormone replacement therapy.[428]
Testosterone deficiency	Late	Testosterone replacement therapy • Testosterone gel (Androgel) 1.62% 40.5 mg (2 pumps or 1 packet) applied to shoulders and upper arms daily (dose adjusted to maintain testosterone levels between 350 and 750 ng/dL)[423] Lack of evidence for use in patients with prostate cancer[421]

ER, estrogen receptor; TSH, thyroid-stimulating hormone.
Dziuk T. *Commonly Prescribed Medications in Radiation Oncology*. 11th ed. https://www.texasoncology.com/getmedia/ddb81e5b-0532-4200-b25e-20a538cd9221/Commonly-Prescribed-Medications-in-Radiation-Oncology.pdf

Hypopituitarism

Patients who receive cranial irradiation, total body irradiation, and radiation to the nasopharynx or skull base are at risk for hormone deficiency secondary to hypothalamic and pituitary injury, with decreased production of growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), and gonadotropins (luteinizing hormone and follicle-stimulating hormone). Central obesity due to hypothalamic damage, in which patients experience appetite dysregulation and significant weight gain, may also result, presumably through a mechanism of impaired leptin and insulin homeostasis.[409,410]

Early detection and treatment of radiation-induced endocrinopathy are particularly important in the pediatric population, where appropriate hypothalamic-pituitary axis function is implicated in meeting age-appropriate milestones of growth, physical and mental development, and psychosocial attainment.[411] Radiation dose, age at treatment, and length of time from irradiation are independent predictors of endocrinopathy within this cohort.[411]

The diagnostic criteria for classification of radiation-induced endocrinopathy are distinct for each hormone and may take both laboratory

values and clinical factors into account. GH appears to be the most sensitive of the anterior pituitary hormones to the effects of radiation, such that GH deficiencies following RT are most common. The incidence of radiation-induced ACTH and TSH deficiencies is much lower, although discrepancies exist in the literature regarding the exact descending sequence of hormones that are most-to-least commonly affected and may in fact be distinct between pediatric and adult populations.[412]

Strategies that help minimize radiation dose to the hypothalamus and pituitary gland, such as proton beam therapy, may be employed to help mitigate the risk of radiation-induced endocrinopathy. Once present, hypopituitarism is generally irreversible and progressive; all patients at risk for hypopituitarism should be evaluated by a dedicated endocrinologist prior to initiation of RT, where pretreatment levels of key hormones and implicated hormone mediators may be obtained and followed longitudinally over time. Requisite long-term hormone replacement is the primary form of treatment, and patients may also require stress doses of steroids in instances of acute insult or illness.[413]

Hypothyroidism

Primary radiation-induced hypothyroidism is defined as low level of blood thyroid hormone due to direct insult to the thyroid gland, often as a result of head and neck irradiation. This is important to distinguish from *secondary* radiation-induced hypothyroidism, which occurs after hypothalamic or pituitary damage precludes the normal production of TSH (see section "Hypopituitarism"). Thyroid hormone deficiency in primary hypothyroidism is indicated by a serum level of TSH (thyrotropin) elevated above the upper limit of normal: 4 mU/L is a typical reference value.[414]

The presentation of hypothyroidism is quite variable. Patients with clinically overt hypothyroidism may develop symptoms such as fatigue, cognitive slowing, weight gain, cold intolerance, brittle hair or hair loss, xerosis, decreased wound healing, constipation, myalgias, and/or soft tissue edema. Pediatric hypothyroidism can also result in significant growth retardation and developmental delay. Subclinical hypothyroidism, however, is generally symptomatically occult and suggested only by elevated serum TSH values with normal serum T4 (thyroxine).[414]

More modern, comprehensive estimates suggest a higher incidence of radiation-induced hypothyroidism in the range of 40% to 50%, which is likely owing to improved routine modern screening practices; the incidence of hypothyroidism based solely upon the presence of clinical symptoms is low, with a mean value of approximately 5%.[415] Radiation-induced hypothyroidism typically manifests months to years after RT, with a median onset of 1 year.[416] Female sex, decreased thyroid volume, and receipt of multimodal therapy (surgery, chemotherapy) have been associated with increased risk of radiation-related hypothyroidism.[415]

Radiation-induced hypothyroidism is treated with synthetic T4 (levothyroxine), which represents standard replacement therapy. A few different formulations of synthetic T4 exist, including liquids, tablets, and gel capsules that are taken without food.[417] All patients with hypothyroidism merit evaluation by a dedicated endocrinologist or other appropriate medical practitioner, as management will require continual monitoring and potential dose adjustment every 8 to 12 weeks based on serum TSH concentration and amelioration of preexisting symptoms.[418,419]

Radiation-Induced Premature Menopause

Protecting the ovaries from off-target collateral radiation with the use of appropriate treatment planning and delivery techniques is ideal. Nevertheless, in most cases of pelvic malignancies requiring RT, the natural anatomic proximity (and inherent mobility) of the ovaries to the uterus, cervix, bladder, and rectum makes achieving this goal challenging, even with modern OAR-sparing IMRT. To this end, oophoropexy is a well-established surgical procedure that manually relocates the ovaries outside the prospective radiation field in an attempt to preserve gonadal function and potential fertility in premenopausal patients.

For patients who do subsequently develop radiation-induced ovarian failure and premature menopause, significant VMSs and GSM may ensue and confer a negative impact on quality of life.[307]

Hot flashes are the most frequently reported VMS of menopause, occurring in upward of 80% of women. They are characterized by a sudden flush of warmth that envelops the torso and face before radiating to the remainder of the body and often last for only a few seconds or minutes

before self-resolving. While lifestyle modifications may be adequate to mitigate mild VMSs, patients with moderate-to-severe hot flashes often benefit from estrogen replacement therapy; this may be delivered via oral, transdermal, and cutaneous formulations.[308,309] Importantly, estrogen replacement should not be administered to those with a history of estrogen-based, hormone-dependent malignancies (eg, estrogen receptor–positive breast cancer), and individuals with an intact uterus will require coadministration of progestins to decrease the risk of endometrial proliferation and neoplasia. Additional hormone replacement contraindications include use in patients with a prior history of deep venous thrombosis and/or clotting disorder, CAD, and chronic liver disease, among other factors and comorbidities.[420] As such, it should be mentioned that a particular patient's candidacy for and selection of hormone replacement therapy should only be determined by a dedicated medical practitioner who specializes in reproductive medicine (obstetrician/gynecologist, reproductive endocrinologist) and is well acquainted with the patient's prior cancer history.

GSM vulvovaginal atrophy may manifest with symptoms such as vulvar burning, pain, dryness, and concomitant dyspareunia.[309] Refer to the female reproductive section for more details on the management of these symptoms.

Patients treated with pelvic radiation may develop low testosterone levels. Typical presentation may include reduced libido, decreased spontaneous erections, testicular atrophy, loss of body hair, low bone mineral density, gynecomastia or breast discomfort, and hot flashes. Less specific symptoms include fatigue, depression, and muscle atrophy. Chemical confirmation with serum morning total testosterone levels is the initial diagnostic test. If total testosterone is near the lower limit of normal, an additional test of free or bioavailable testosterone level is recommended. Referral to an endocrinologist is advised. Androgen replacement therapy may be subsequently recommended for men with symptoms to improve sexual function, maintain secondary sex characteristics, improve muscle mass and strength, elevate bone mineral density, and enhance general well-being.

Although there is a lack of data on the safety of androgen replacement therapy in patients with previously treated prostate cancer, it is generally

not advised out of a principle of caution.[421] Androgen replacement therapy is also not advised in patients with a history of breast cancer, palpable prostate nodules, prostate-specific antigen levels greater than 4 ng/mL, men at high risk for prostate cancer, hematocrit more than 50%, severe sleep apnea, severe lower tract urinary symptoms with an International Prostate Symptom Score of greater than 19, or poorly controlled heart failure.[422] Treatment consists of testosterone gel applied to the shoulder and upper arms (locations that will not be direct contact with other people) daily with dose adjustments to maintain testosterone levels between 350 and 750 ng/dL.[423]

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Index

Note: Page numbers followed by "*f*" indicate figure, page numbers followed by "*t*" indicate table, and page numbers followed by "*b*" indicate box.

A

AAPM. *See* American Association of Physicists in Medicine (AAPM)
Abdomen
  oncologic anatomy, 701–703
  proton therapy, 308–309
Abdominal compression method, 33
Abdominoperineal resection (APR), 1579
Abducens nerve (CN VI)
  nasopharyngeal cancer and, 693
Ablative radiation therapy, 645
Ablative therapy, for VAIN, 1881
ABMT. *See* Autologous bone marrow transplantation (ABMT)
Abnormal squamous cells of undetermined significance (ASCUS), 1766
Abortion, cervical cancer and, 1798–1799
Abraxane (nab-paclitaxel, ABI-007), 719
Abscopal effects, 54–55
Absorbed doses
  calculation of, 190–192
  definition, 189
  determination of, 189–192
Absorption edges, 174, 174*f*
ABVD regimen
  components of, 2180
  for Hodgkin lymphoma, 1957, 1959, 1965
  for Hodgkin lymphoma, 2181
  late effects of, 1969
AC regimen, 1458
Accelerated oropharyngeal cancer, 1130, 1131
Accelerated partial-breast irradiation (APBI), 1438*f*, 1439–1441, 1439*t*, 1440*f*
  clinical trials, 1443*t*
  intraoperative, 1441–1442
Accelerated repopulation, 38, 39–40*f*, 715
Accelerator structure, 179
Acceptability, radiation therapy, 758
Accountability, QA and, 297*t*

Accountable care organizations (ACOs), 827
Accreditation, 367
  conformal radiation therapy, 297*t*
ACE (angiotensin-converting enzyme) inhibitors, 154
Achalasia, 1318
Acinic cell carcinoma
  derivation of, 1072
  imaging, 1065*f*
  outcomes, 1082
  salivary gland cancer and, 1062*f*
ACKD. *See* Acquired cystic kidney disease (ACKD)
ACOs (accountable care organizations), 827
Acoustic nerve (CN VIII)
  late effects of RT, 327
  vestibular schwannomas, 692
Acoustic neuromas. *See* Vestibular schwannomas
Acoustic schwannomas, 428
Acquired cystic kidney disease (ACKD), 1611
Acquired immunodeficiency syndrome (AIDS)
  anal cancer and, 1596, 1598–1599
  EBV antibody titers and, 2218*t*
ACR. *See* American College of Radiology (ACR)
Acromegaly, 916, 917*t*
Actinium series, 173
Actinomycin-D
  for solitary fibrous tumors, 1188
Acupuncture
  pain management using, 2319
  saliva production and, 2326
Acute lymphoblastic leukemia (ALL)
  B-cell
    age at diagnosis, 2015
    high risk, 2018
    prognosis, 2015
  in children, 2016*t*
  classification, 2013–2016
  CNS involvement
    high risk, 2018
    palliative RT, 2019*f*
    prognosis, 2015
  natural history, 2012
  radiotherapeutic emergencies, 2019, 2019*f*
  T-cell
    age at diagnosis, 2015
  treatment of, 2018
Acute lymphocytic leukemia (ALL), 405. *See* Acute lymphoblastic leukemia (ALL)
  classification, 2013, 2014*t*
  conditioning regimens, 407–408, 408*t*

induction chemotherapy, 2015
natural history, 2012
secondary tumors, 419
single-fraction TBI for, 418
TBI dose and fractionation, 406
Acute promyelocytic leukemia (APL), 2013
Acute radiation syndrome (ARS), 156, 158
Acute urinary retention (AUR), 1693–1694
Adaptive immunity, 699
Adaptive radiation therapy (ART)
online, 183, 296, 297, 298
Adaptive radiotherapy, 738
ADC (apparent diffusion coefficient), 689
Addiction
non-oncogene, 152
oncogene, 152
Adenocystic carcinomas, 1398
Adenoid basal carcinoma, cervical, 1771
Adenoid cystic carcinoma
cervical cancer and, 1771
esophageal, 1327
incidence, 1063
perineural invasion, 1081
prostate, 1680
radiation therapy, 1079–1080
salivary gland cancer and, 1065*t*
submandibular gland, 1081*f*
Adenoma malignum, cervical, 1771
Adenomatous polyposis coli (APC), 106
Adenosquamous carcinomas, 1327
Adipose tissue tumors, mediastinal, 1296
Adjuvant chemotherapy, 62, 715, 1572, 1864, 1864*t*, 2067
Adjuvant immunotherapy, 1634
Adjuvant radiation therapy (ART), 1930
Adjuvant radiotherapy
for bladder cancer, 1629
clinical studies, 1629
identifying patients, 1630–1631
latest studies, 1633–1634
ongoing studies, 1635–1636
radiation planning and delivery techniques, 1631–1633, 1633–1634*t*
rationale, 1629
Adnexal/serosal involvement, 1837
Adoption, of cancer screening, 758
Adrenal cancer, 1951–1955
classification, 1953, 1953*t*
diagnosis, 1952–1953, 1952*t*, 1953*f*
epidemiology, 1951

management
follow-up, 1955
radiation therapy, 1954–1955
surgical, 1953
natural history, 1951–1952
palliative therapy, 1954
presentation, 1952
staging, 1952–1953, 1952*t*
Adrenal gland
anatomy, 1951
metastatic disease, 2305–2306
pain management, 2305–2306
Adrenal medulla tumors, 1951
Adrenocortical carcinoma (ACC), 1951
Adriamycin. *See* Doxorubicin (Adriamycin)
ADT (androgen deprivation therapy), 1703, 1719–1721, 1721–1722, 1721*t*, 2330
Adult brainstem glioma, 894–896
Adult T-cell leukemia/lymphoma, 2006
Advanced model-based dose calculation algorithms, 522–524
Adventitia, esophageal, 1316
Adverse events
clinical trial reporting of, 384–385
radiation oncology trials, 378
Advertising, radiation oncology, 818
Advisory Committee on Human Radiation Experiments (ACHRE), 815
Aerobic glycolysis, 99
Affordability, radiation therapy, 758
Aflatoxins, liver cancers and, 1545
Age-related macular degeneration (AMD), 2246, 2246*f*
Age/aging
breast cancer
prognosis and, 1402
risk and, 1388
endometrial cancer and, 1836
at menarche, 1828
prognosis and
in cervical cancer, 1772
in vaginal cancer, 1886
Ageusia, 2342
Aggressive fibromatosis. *See* Desmoid tumors
AIDS. *See* Acquired immunodeficiency syndrome (AIDS)
AIN (anal intraepithelial neoplasia), 1595–1596
Air cavities
correction for, 229–231
dose algorithm accuracy and, 264*f*
dose distribution and, 261*f*
isodose contours, 259
patient topography and, 230

source-to-surface distance and, 263*f*
tissue interface dosimetry and, 236–237
Air-kerma strength, 513–514
Airway obstruction, malignant, 2303
ALA. *See* Aminolevulinic acid (ALA)
Alanine aminotransferase (ALT) levels, 341
Alcohol consumption
breast cancer and, 1390
colorectal cancer and, 1568
esophageal cancer and, 1318
hepatocellular cancer and, 1541
hypopharynx cancer and, 1144
nasal cancer and, 1040
nasopharyngeal cancer and, 1003
oral cavity cancer and, 1092
Aldosteronism, 1953
Alibert, Jean-Louis-Marc, 1998, 1998*f*
Alimentary mucositis, 2326
ALK (anaplastic lymphoma kinase), 1269, 1990
ALK gene, 386
Alkeran, for HL, 1968
Alkylating agents, radiation response and, 718
ALL (acute lymphocytic leukemia), 405
All-*trans* retinoic acid (ATRA), 2016
Allogeneic stem cell transplantation, 2044
Alopecia
acute toxicity
chemoradiotherapy, 1131
cisplatin-based chemotherapy with, 1743
oropharyngeal carcinoma, 481
reversible, 418
rhabdomyosarcoma, 2140
Alpha-fetoprotein
ovarian cancer and, 1862
Altered fractionation, 37–38, 38*f*
Alveolar ridge
anatomy of, 1095
subsite-specific treatment, 1116–1117
tumors of, 1097–1098, 1116–1117
Alzheimer disease, 2255
AMA. *See* American Medical Association (AMA)
AMD3100 inhibitors, 154
Amenorrhea, after RT, 1033
American Association of Physicists in Medicine (AAPM)
Task Group 101, 441
Task Group 105, 231, 232
Task Group 132, 286
Task Group 21, 410

Task Group 29, 410, 412
Task Group 51, 410
TG-21 protocol, 192
American College of Radiology (ACR), 59
American Medical Association (AMA)
code of ethics, 814
pericardial neoplasms, incidence of, 1361
American Society for Radiation Oncology (ASTRO), 778
on dose reporting, 291
American Society for Radiation Oncology Accreditation Program for Excellence (ASTRO APEx), 364
American Society of Clinical Oncology (ASCO), 2322–2323
Amifostine (WR-2721, Ethyol)
function of, 681
for GI mucositis, 2327
protective use of, 1156
toxicity of, 681
Amitriptyline, 2318*t*
Anal canal
adenocarcinomas, 1604
anatomy, 1595, 1595*f*
lymphatics, 1595
radiation therapy, doses, 1604
squamous cell carcinoma, 1595
Anal cancer, 1595–1607
clinical trials, 1600*t*
diagnosis, 1597
epidemiology, 1596
extrapelvic, 1603
lymphatic invasion, 1596–1597
management
RT, 1602
RT with CT, 1601
sequelae of treatment, 1607–1608
surgery, 1602–1603
metastatic, 1597
natural history, 1596–1597
presentation, 1597
prognostic factors, 1597–1599
biochemical, 1599
molecular, 1599
patient-related, 1598–1599
tumor-related, 1597–1598
risk factors, 1596
Anal intraepithelial neoplasia (AIN), 1595–1596
Anal margin, 1595
Anal toxicity, 2345–2346
Anaplastic astrocytoma, 889–890

pediatric, 2080
Anaplastic large cell lymphoma (ALCL)
classification, 2194
CNS involvement, 2194
cutaneous, 2006
presentation, 2189–2190
Anaplastic lymphoma kinase (ALK), 1990
Anaplastic oligodendroglioma, 888–889
Anaplastic thyroid carcinoma (ATC), 1238, 1240*f*, 1248–1249
Anastrozole, neoadjuvant, 1459
Anatomy-based optimization, 531–532
Androgen deprivation therapy (ADT), 1703, 1719–1721, 1721–1722, 1721*t*, 2330
Androgen suppression therapy (AST), 1724
Anemia
in cervical cancer, 1772–1773
prognostic value of, 1772–1773
Angiofibromas
juvenile, 2239
Angiogenesis, 137. *See* Tumor angiogenesis
microenviroment and, 153–154
sprouting, 137
Angiography
fundus fluorescein, 963*f*
magnification, 1183
solitary fibrous tumors, 1187
Angiosarcomas
breast, 1447
pericardial, 1362
postirradiation, 1447
Angiostatin, 99
Angiotensin-converting enzyme (ACE) inhibitors, 154
Angiotensin-II (Ang-II), 154
Angle of rotation, 250
Anisotropy, 506
Anorexia
chronic myelogenous leukemia, 2024
during gastric radiation therapy, 1518
hypercalcemia, 1252
liver metastases, 2303
neuroblastoma, 2117
somnolence syndrome, 2030
stomach cancer, 1493
weight loss and, 2305, 2324
Anterior (distal) urethral cancer, 1914
Anthracycline chemotherapy
for AMLs, 2017
for breast cancer, 1458
radiation-related cardiac toxicity and, 338

for salivary gland cancer therapy, 1086
Anti-early antigen (EA), 1008–1009
Anti-Kickback Statute, 816
Anti-VEGF agents, 14*b*
Anti-VEGFR agents, 14*b*
Anti-viral capsid antigen (VCA), 1008–1009
Antiangiogenesis
for ovarian cancer, 1867
therapy, 14*b*
Antiangiogenic therapy, 153–154
Anticholinergic medications, 1902
Anticonvulsants
pain management using, 2318
quality of life and, 2263
Antidepressants, pain management using, 2318, 2318*t*
Antidiarrheal medications, 1902
Antigen-presenting cells (APCs), 406
Antimetabolites, radiation response and, 717–718
Antispasmodic medications, 1902
Antivascular therapy, 154
Anus, 574. *See also* Anal canal
APBI. *See* Accelerated partial-breast irradiation (APBI)
APCs (antigen-presenting cells), 406
Apoptosis, 9–10
p53 dependent, 101
radiation-induced, 99*t*, 101
resistance to, 1751
Apparent diffusion coefficient (ADC), 689
Appendix cancer, pediatric, 2222
Applications, 726–731, 729*f*, 730*f*
APR (abdominoperineal resection), 1579
APS Guideline for the Management of Cancer Pain in Adults and Children, 2317
Ara-C, for ALL, 2018
Arachnoid mater, 692
Arc therapy techniques, 242–243, 242*f*
AREN clinical trials, 2109–2110
Argyrophilia, 1896
ARID1A mutations, 1856
Aristolochic acid, 1637
Aromatase inhibitors, 1460
ARS (acute radiation syndrome), 156, 158
Arsenic
bladder cancer and, 1637
drinking water with, 1637
lung cancer and, 1251
Artemis, in DSB repair, 104
Arteriovenous malformations (AVMs), 2240–2241
radiosurgery for, 427, 429, 429*f*

stereotactic radiosurgery (SRS), 2241, 2242*f*
Artificial intelligence (AI), 58, 58*b*, 350, 726–731, 726*t*, 727–728*t*, 730*f*, 763–764
delivery, in, 295
planning, in, 295
as quality and safety tool, 371
treatment verification, in, 295
Aryepiglottic folds, 333, 1162–1163
Arylamine, bladder cancer and, 1638
As Low as reasonably achievable (ALARA) standard, 1246
Asbestos exposure
lung cancer and, 1251
ovarian cancer and, 1858
Ascorbic acid lotion, 2329
ASCUS (abnormal squamous cells of undetermined significance), 1766
Aspartate aminotransferase (AST), 341
Aspergillus spp.
A. flavus, HCC and, 1545
A. parasiticus, HCC and, 1545
liver cancer and, 753
Assault, 67
Assessment biases, 384
Assignment of CNS status, 2016*t*
Association for Medical Education in Europe (AMEE), 779
AST (aspartate aminotransferase), 341
ASTRO. *See* American Society for Radiation Oncology (ASTRO)
Astrocytoma anaplastic. *See* Anaplastic astrocytoma
Astrocytic tumors, pediatric, 2076
Astrocytoma
diffuse, 2076
high-grade, 2080
low-grade
management of, 2077–2078, 2078*f*
pediatric, 2077–2080
radiotherapy, 2078–2080
treatment planning, 2077, 2078*f*
pediatric, 2077–2080
spinal cord, 949–951
treatment planning, 240
Asymmetric collimator jaws, 243, 243*f*
Asymmetric X-ray collimators, 233
Ataxia
definition of, 692
Ataxia telangiectasia (ATM)
mutations in, 101, 117
NHL and, 1974
oral cavity cancer and, 1092
ATC (anaplastic thyroid carcinoma), 1238, 1240*f*, 1248–1249
ATM. *See* Ataxia telangiectasia (ATM)

ATM mutations, 101
Atomic mass units, 169
Atomic numbers (Z), 170
Atomism, structure of, 169–171
Atoms, structure of, 169*f*
Atrial myxomas, 1361
Attenuation coefficients, 174, 174*f*
Atypical teratoid/rhabdoid tumors (ATRTs), 2090–2091
Auditory apparatus, effects of RT, 327–329
Auditory canal tumors
  management, 978, 980
Auditory system
  radiation side effect management
    ototoxicity, 2339
Auger electrons, 172
AUR (acute urinary retention), 1693–1694
Auricle
  anatomy of, 973, 974*f*
  malignant disease of, 973
Autologous stem cell transplantation, 2044
  patients eligible for, 2043–2044
Autologous transplantation, 405
Autophagy, 99*t*, 102, 119
Availability, radiation therapy, 756–758
Avastin (bevacizumab). *See* Bevacizumab (Avastin)
Average lives (Ta), radionucleotide, 173
AVMs. *See* Arteriovenous malformations (AVMs)
Awareness, of cancer screening, 758
Axillary lymph nodes
  breast cancer prognosis and, 1400
  dissection of, 1404, 1405*t*
  irradiation of, 1432–1433*f*, 1433
  metastases, unknown primary site, 1483
  RT *vs.* surgery, 1417–1419, 1418*t*
Azoospermia, 2353
Azoospermia, after RT, 2184

B

B-cell acute lymphocytic leukemia, 2013
B-cell lymphomas
  CNS involvement, 2194
  cutaneous, 2007
Bacillus Calmette-Guéin (BCG), 1642
Back pain, metastatic disease and, 1252
Backscatter, 191, 269
BAF250a mutations, 1856
Barrett esophagus (BE)

development of, 2221
esophageal cancer and, 1319
Bartholin glands, 1924–1926
Basal cell carcinomas (BCCs)
ear, 974
parotid, 1073
periorbital, 969
vulvar carcinoma and, 1925
Basal cell nevus syndrome (BCNS)
pediatric, 1771
Basaloid carcinoma, cervical, 1771
Basaloid squamous carcinomas (BSCs), 1923
Base excision repair (BER), 103–104, 116
Base of skull. *See also* Chordomas
proton therapy, 307, 308*f*
Basedow disease. *See* Graves ophthalmopathy
Batson venous plexus, 707
BCCs. *See* Basal cell carcinomas (BCCs)
BCG (Bacille Calmette-Guéin), 1642
BCL-2 gene, 1983, 1984, 1989
BCL-6 gene, 1983
BCNU. *See* Carmustine
BCON regimen, components, 1554, 1655
BCS. *See* Breast-conserving surgery (BCS)
BCT. *See* Breast conservation therapy (BCT)
bDFS (biochemical disease-free survival), 1716*f*
BE. *See* Barrett esophagus (BE)
BEACOPP regimen
components of, 2187
for HL, 1959, 1965, 1966
for HL, 2187
Beam arrangements
3DCRT, 288
quality assurance, 298
Beam dose rates, megavoltage, 232
Beam hardening, 197
Beam transport systems, 179
Beam's-eye views (BEV), 281, 289*f*
Beckwith-Wiedeman syndrome, 1951, 2103, 2223
Becquerel, Antoine Henri, 75–76, 75*f*
Becquerel, Henri, 172, 616
Becquerels (Bq), 173
BED. *See* Biologically effective dose (BED)
Beeswax bolus, 260*f*
Belmont Report, 815
Bendamustine, 2025
Benign diseases
soft tissue and bones

joints and tendons, inflammatory conditions of, 2248
osteoarthritis, 2248–2249
pigmented villonodular synovitis, 2249
vertebral hemangiomas, 2249
Benign hypertension, risk of, 342
Benign notochordal cell tumors(BNCTs)/rests, 924
Benign ocular diseases, management of, 961–963
Benign prostatic hypertrophy (BPH), 1666
Bentel, Gunilla, 86, 86*f*
Benzydamine, 2329
BEP regimen
components, 1741
for testicular cancer, 1741, 1743
BET (bromodomain and extra-terminal) inhibitors, 108
Betel nut leaves, 1092, 1098
Bethanechol, 2325–2326
Bethe equation, 303
Bevacizumab (Avastin), 669, 1867, 1868
for cervical cancer, 1794
for colorectal cancer, 1572, 1574
for nasopharyngeal cancer, 1024
for ovarian cancer, 1866–1867
for pancreatic cancer, 1537
for RCC, 1621
for solitary fibrous tumors, 1188
toxicity of, 154
Biases, clinical trial design and, 384
BIBF 1120, 1867
Bile duct
cancer, pediatric, 2223
imaging, 703
Bilharzia, bladder cancer and, 1637, 1638
Biliary atresia, 2224
Biliary obstruction
metastatic, 2305
palliative therapy, 2305
presentation, 2305
Biliary stricture, 2345
Biliary tract, 574
Biliary tract cancers, 1556. *See also* Cholangiocarcinomas
Biliary tree, oncologic anatomy, 702–703
Billing practices, ethical issues, 817
Bilsky epidural spinal cord compression grade, 2277, 2278*f*
Binding energies, 171
Biochemical disease-free survival (bDFS), 1716*f*
Bioethics, definition of, 812
Biofeedback, pain management using, 2319
Biologic modifiers, of radiation response, 680–681

Biologically effective dose (BED)
radiation fractionation and, 991
Biology, Physics vs., 49–51
Biomarkers
radiation injury, 159
trial inclusion and, 386
Biophysical modeling, 541–542
BIRADS system, 1392, 1394*t*
Birt-Hogg-Dubé (BHD) syndrome, 1611–1612
Bisphosphonates
for bone metastases, 2293–2294
radiolabeled, 691
renal toxicity of, 2294
Bite blocks
as alternative to masks, 204
immobilization, 247*f*
registration, 247*f*
treatment planning and, 246, 247*f*
BL. *See* Burkitt lymphoma (BL)
Blackstock, A. William, 89, 89*f*
Bladder, 564
Bladder cancer, 1637–1660. *See also* Urinary bladder
adjuvant radiotherapy, 1629
bladder tumors
small cell carcinoma, 1659
squamous cell carcinoma, 1659
urachal adenocarcinomas, 1659
development of, 1640*f*
diagnosis, 1640
epidemiology, 1537–1538
etiology, 1638
external beam radiation
role of, 1656
histologic of
trimodality, 1659*f*
incidence, 1637
invasive
factor, 1647
management, 1642
natural history, 1638
nonmetastatic, 1642–1646
predictive and, 1645–1646
prognosis, 1643
prognostic, 1645–1646
surgical management, 1646–1647
maintenance therapy, 1658
management
failures after CT, 1655–1656

late toxicities, 1654*f*
metastatic UC, 1657–1659
outcomes, 1659
RT after TURBT, 1649–1650
synchronous CT, 1654
metastatic disese, 1638
neoadjuvant
adjuvant systemic therapy, role of, 1648–1649
neoadjuvant/adjuvant therapy
role of, 1656
node negative, 1647–1648
node positive, 1648
non-muscle-invasive, 1638, 1639
palliative, 1656
palliative therapy, 1656
pathology, 1641
presentation, 1638
radiation therapy
palliative, 1656
rhabdomyosarcoma, 2133–2134
second-line therapy, 1658–1660
staging, 1640, 1641*t*
surgical therapy
summary of, 1649
urothelial carcinoma
histologic with, 1659–1660
trimodality therapy, 1659–1660
Bleomycin, 1934. *See also* ABVD regimen; BEACOPP regimen; BEP regimen; COPP/ABV regimen; CVB regimen; MACOP-B regimen
for cervical cancer, 1792
for penile cancer, 1753*t*
RT with, 985
for vaginal cancer, 1888
for vulvar cancer, 134
Blood vessels
normal tissue tolerances, 467
Bloom syndrome, 1092
BMI. *See* Body mass index (BMI)
BMT. *See* Bone marrow transplantation (BMT)
BNCT. *See* Boron neutron capture therapy (BNCT)
Body mass index (BMI)
breast cancer prognosis and, 1402
breast cancer risk and, 1390
endometrial cancer and, 1828
prostate cancer and, 1667
RT toxicity and, 1815
Body weight, nutritional support and. *See* Weight loss
Bohr, Niels, 169

Boluses
electron beam therapy and, 266–268
patient topography and, 246
rigidity of, 266
Bone
dose distribution and, 263*f*
necrosis, 1087
Bone cancer. *See also* Chondrosarcomas; Osteosarcomas
extranodal lymphomas, 1987–1988
fibrosarcomas, 2157
lung cancer and, 1252
metastatic
diagnosis, 2290*f*
evaluation, 2289–2291
imaging of, 691–692, 2289–2290
incidence of, 2288
pain management, 2291
palliation, 2288–2299
pathophysiology, 2288–2289
radiation therapy, 2294–2298
radiopharmaceuticals in, 2298–2299
retreatment rates, 2295
surgical management, 2291–2293
systemic treatment, 2293–2294
radiation-related injury, 1818
remodeling of, 691
resection, 2158
resorption markers, 2294
strength of, 2289
Bone marrow
metastatic disease of, 2289
radiation damage, 409
red, 261
stromal cells, 409
Bone marrow transplantation (BMT)
allogenic, 405
late complications of, 418–419
pneumonitis in setting of, 418
Bone scan
diagnostic, 1395
low-risk prostate cancer, 1674–1675
Bone scintigraphy, 691–692
Bone-soft tissue interfaces
dose distribution issues, 261
tissue interface dosimetry and, 237
Boost techniques, 1715
Boron neutron capture therapy (BNCT), 53–54, 53*b*, 146
Borrelia burgdorferi, 1974

Borrowed-servant doctrine, 68
Bortezomib, 2043
Botulinum A toxin, 2329
Boveri, Theodor, 5
Bowel obstruction, risk factors, 342
Bowen disease, 1749, 1923
Brachial plexopathy
  lung cancer and, 1252
  after RT, 1443–1444
Brachial plexus, 697, 698*f*
Brachytherapy, 29–30, 43–47, 672, 1047
  applicators
    for cervical cancer, 1800–1801, 1801*f*
    imaging, 1801–1802
    insertion, 1801, 1801*f*, 1802*f*
    positioning, 1801
    selection of, 1800–1801
  basic terminology, 504
  for bladder cancer, 1657
  boosts, nasopharygeal carcinoma, 920*t*
  brachytherapy dose, measurement of, 557–558
  brachytherapy isotopes, clinical uses of, 556
    permanent implants, 556
    temporary implants, 556
  brachytherapy source strength specification and dosimetry, 513–524
    advanced model-based dose calculation algorithms, 522–524
    classic dose calculation formalism: isotropic point source, 515–517, 515–517*f*
    Medicine Task Group 43 Table-Based Dose Calculation Formalism, American Association of Physicists in, 520–521, 521*t*, 521*f*, 522*f*, 523*t*
    source-specific dosimetric characterization, 518–520, 519*f*
    source strength specification quantities and units, 513–515, 514*f*
  brachytherapy sources and radionuclides, properties of, 504–513, 505*t*
    high-dose rate brachytherapy, sources for, 512*f*, 512–513, 512*t*
    low-dose rate gynecologic brachytherapy, intracavitary sources for, 508–509
    low-dose rate temporary interstitial brachytherapy, sources for, 509
    permanent interstitial brachytherapy, sources for, 509–512, 509*f*, 510*t*, 511*f*
    photon spectrum and dosimetric characteristics, 504–508, 506*f*, 507*f*
  for cervical cancer, 1799–1811
    clinical outcomes, 1807–1808
    preparation, 1800
    pulsed-dose rates, 1805
    shielding, 1784
    timing of, 1800
  for choroidal hemangiomas, 962
  clinical sites, 558–575
    anus, 574
    biliary tract, 574
    bladder, 564

breast, 569–570, 570–572*f*
central nervous system, 574–575, 575*f*
cervix, 558–559, 558*f*, 559*f*
endometrium, 559–560, 560*f*, 561*f*
esophagus, 574
eye, 573–574, 573*f*
head and neck, 564–568, 565–567*f*
penis, 562, 563*f*
prostate, 560–562, 561–563*t*, 562*t*
rectum, 574
sarcoma, 570, 572*f*, 572*t*
superficial sites, 570–573, 573*f*
thorax, 568–569, 568*f*, 569*f*
urethra, 564, 564*f*
clinical suitability for, 556
dose rate definitions, 555, 556*t*
EBRT *vs.*, 1902
electromagnetic tracking, 220
endobronchial, 1270
for esophageal cancer, 1342, 1351–1353
high-dose rate, 760
disease sites commonly treated with, 594–595
dosimetry/treatment planning, 589–593, 592*f*, 593*f*
intraoperative, 461
nature of, 581–584, 583*f*
operation, 584–586
remote afterloading unit, quality assurance of, 586–589, 587*f*
high-dose rate
for cervical cancer, 1799–1800, 1800*f*
dose fractionation in, 1805, 1807*t*
pelvis, 1787*f*
for urethral cancer, 1913, 1915, 1916*f*, 1919*f*
for vaginal cancer, 1898
for vaginal intraepithelial neoplasia, 1881
history, 555
image-guided, 1899–1900
immobilization, 216–217
new technologies, 219–220
workflow, in, 218–219
interstitial brachytherapy, 524–535
classic implant systems for temporary implants, 524–530, 525*f*, 526–527*t*, 528*f*, 529*t*, 530*f*
dose specification in interstitial brachytherapy, 533–535, 535*f*
modern approaches for temporary implantation, 530–532
permanent implantation, 532–533, 532*f*
interstitial
HDR, for breast cancer, 1439–1440
lip implants, 1113*f*
multicatheter technique, 1439–1440

postimplantation dosimetry, 1688
prostate gland, 1688
template-based, 1810–1811, 1810*f*
for vaginal cancer, 1898–1902
intracavitary brachytherapy, 535–541
image-guided intracavitary brachytherapy, 540–541
intracavitary brachytherapy, dose specification in, 536–540, 537–539*f*, 540*t*
intracavitary therapy systems, manchester family of, 535–536, 536*f*
intracavitary
for cervical cancer, 1787
cervical stump, 1796–1797
isodose charts, 1806
for vaginal cancer, 1898
intraoperative, 1944
low-dose rate, 760
low-dose rate
erectile function, 1694
rectal tolerance, 1694
urinary toxicity, 1693–1694
for vaginal cancer, 1898
nasal cavity, 1047
for nasopharyngeal cancer, 1019–1021, 1021*f*, 1022*t*, 1026*t*
older patients, 1811
for oral cavity cancer, 1112–1113
palliative, 2303
for penile cancer, 1755, 1756*f*
plaque, for ocular melanomas, 966–967, 966*f*
for prostate cancer, 1687, 1687*f*, 1715–1717
outcomes, 1691, 1691*t*
for prostate cancer
erectile dysfunction and, 345
rectal toxicity and, 344
pulsed-dose rates
for cervical cancer, 1807–1808
quality assurance, 62
radiobiologic considerations, 557
reassortment, 557
reoxygenation, 557
repair, 557
repopulation, 557
radiobiology of, 541–548
biophysical modeling, 541–542
linear-quadratic model, 542–543
radiobiologic features, 543–548, 543*f*, 544*f*
use of biophysical models in, 548
shielding, 1784
for soft-tissue sarcomas, 2058
target definition, 557

three-dimensional printing in, 219–220
timing, for cervical cancer, 1800
toxicities related to, 1808–1809, 1818–1819
for urethral cancer, 1919*f*
for vaginal cancer, 1888–1891, 1889*t*
vaginal cuff brachytherapy, complications, 1848
for vulvar cancer, 1931
Brady, Luther W., 85
BRAF mutations, 1856
Bragg peak, 53
Bragg peak effect, 53
Bragg peaks
description of, 176
electrons and photons, 472, 472*f*
spread-out, 176, 177*f*
Bragg–Gray cavity theory, 191
Brain
benign diseases, 2239–2240
collimator rotation, 250–251
dose–volume limits, 323
late effects of RT, 320
oncologic anatomy, 692–694
proton therapy, 307, 308*f*
radiation necrosis, 321*f*
Brain cancer
intraoperative radiotherapy, 464–465
Brain metastasis velocity (BMV), 2271
Brain tumors
craniospinal axis, 486
management of, 422
metastatic disease, 2262–2274
corticosteroids, 2262–2263
diagnosis, 2262
distant brain recurrences, 2271
epidemiology of, 2262*t*
immunotherapy, 2265
multiple brain lesions, radiosurgery for, 2270–2271
postoperative RT trials, 2268*t*
preoperative stereotactic radiosurgery, 2271
presentation, 2262, 2262*t*
prognosis, 2262
radiation boost trials, 2266–2267, 2267*t*
radiosurgery for, 426*f*
radiotherapy for, 433–434
small cell lung cancer, 2271–2272
surgical resection, 2265–2266, 2266*t*
whole-brain radiotherapy, 2263–2264, 2268–2269*t*, 2272
metastatic disease

lung cancer and, 1252
presentation, 1252
neurocognitive decline and, 2271
pediatric
benign and, 485–486, 485*f*
distribution by histology, 2076*f*
distribution by site, 2076*f*
RT effects in, 2072–2073
primary, imaging of, 694
reirradiation, 668*t*
whole-brain radiotherapy
for metastatic disease, 2263–2264, 2268–2269*t*
pediatric patients, 320
portals, 251
BrainLabExacTrac Dynamic system, 214
Brainstem, dose-volume recommendations, 326–327
Brainstem tumors
gliomas
cervicomedullarytumors, 2082
diffuse intrinsic pontine tumors, 2081
dorsal exophytic tumors, 2082
focal tumors, 2081
late effects of radiation, 325, 326*t*
BRCA1 mutations, 1389, 1421–1422, 1422*f*, 1423*f*, 1857–1858
BRCA1 protein, 1377
BRCA2 gene, 101, 1525
BRCA2 mutations, 1389, 1421–1422, 1421*t*, 1422*f*, 1423*f*, 1857–1858
BRCA2 protein, 1377
Breast, 569–570, 570–572*f*
anatomy, 1386–1387
ductal branches, 1377*f*
internal mammary vessels, 1387*f*
lymphatic drainage, 1432–1433
oncologic, 700–701
augmentation, breast cancer after, 1425–1426
lymphatic drainage, 1386, 1386*f*, 1432–1434
mammographic density, 1390
oncologic imaging of, 701
proton therapy, 308, 309*f*
Breast boards, 1426*f*
Breast brachytherapy, 595
Breast cancer, 606–608, 662–663
axillary metastases, 1483
biopsies, benign, 1389
BRCA1/2 mutation carriers, 1421–1422, 1421*t*, 1422*f*, 1423*f*
cancer-related fatigue (CRF), 2324
cardiac mortality after RT, 337, 337*f*
classification, 1396, 1398–1399, 1399*t*

clinical indications, 606, 606*t*
complications after RT, 1443
contralateral
  irradiation dose to, 1437
  risk factors, 1421–1422
  after RT, 1446
diagnosis, 1392–1399
  Breast Imaging Reporting and Data System, 1392, 1394*t*
  imaging in, 1392–1396
  pathologic studies, 1396
ductal carcinoma in situ, 701, 701*f*, 1374–1382
early stage, 1386–1449
  familial, 1421–1422
  follow-up, 1449
  radiation therapy, 1405–1407
  RT technical issues, 1426–1439
edema after RT, 1442–1443
elderly women, 1312–1314
epidemiology, 1387–1388
extranodal lymphomas, 1987–1988
familial, 101
familial, 1421–1422
follow-up, 608
after HL treatment, 1966
imaging of, 701
in-breast tumor recurrence, 1372
inflammatory
  diagnosis, 1462
  epidemiology of, 1461–1462
  management, 1462–1463
  natural history of, 1462
  outcomes, 1463
intracranial metastases, 694
intraoperative radiotherapy, 464
invasive ductal carcinoma, 195*f*
lobular carcinoma in situ, 1372–1373
local relapse
  age and, 1407, 1409*f*
  extensive intraductal carcinoma and, 1410
  histology and, 1410
  margin status and, 1407–1408
  risk factors, 1408*t*
  systemic management and, 1409–1410, 1410*t*
  tumor size and, 1410
locally advanced, 1455–1484
  combined modality therapy, 1457–1460
  diagnosis, 1456–1457, 1456*f*
  histopathology and clinical, 1455–1456

lymph node involvement, 1456*f*
management, 1480
mastectomy, 1455, 1458, 1463
natural history of, 1455
neoadjuvant chemotherapy, 1458–1459
neoadjuvant endocrine therapy, 1459–1560
outcomes, 1461, 1463
patient selection, 1460
presentation of, 1455–1456
staging, 1457
systemic therapy, 1360
treatment, 1461
lymph node involvement, 700*t*
lymphatic drainage, 770
male, management of, 1483–1484
management of, 1405–1407
BCS without RT, 1413*f*, 1421–1426
boost techniques, 1432
chemoradiation, 1419–1421
clinical trials, 1414–1415*f*, 1415*t*
cosmetic and follow-up, 1448–1449
cosmetic outcomes, 1448*f*
cost *vs.* benefits, 1447–1448
intraoperative RT, 1442*f*
lymphatics and RT, 1417–1419, 1418*t*
during pregnancy, 1424
radiation therapy, 1405–1407
randomized trials, 1412–1413
RT technical issues, 1426–1439
sequelae of RT, 1442–1448
sequencing CRT, 1419–1421, 1419*f*
sequencing hormone therapy, 1419–1421
surgical, 1404
systemic, 1405, 1409–1410
metastatic
bone metastases, 2292*f*
predictors of, 1400
microinvasive, 1377
multicentric disease, 1425
natural history and origins
axillary spread, 1391–1392
internal mammary spread, 1392
local control and systemic metastasis, 1392
supraclavicular spread, 1392
outcomes, 607, 607*t*
pediatrictumors, 2221
prevention
prophylactic surgery, 1391

tamoxifen, 1390–1391
prognostic factors, 1399–1402
age, 1401–1402
axillary nodal status, 1400
body mass index, 1402
DNA ploidy index, 1401
estrogen receptor status, 1400
genetic profiling, 1401, 1402*f*
lymphatic invasion, 1401
micrometastasis, 1400
obesity, 1402
p53 expression and, 1401
parity, 1402
pregnancy, 1402
progesterone receptor status, 1400
race, 1402
S-phase, 1401
smoking, 1402
thymidine labeling index, 1401
tumor-related, 1400, 1400*f*
vascular invasion, 1401
proton therapy, 491–492, 493*f*
radiotherpay-associated fatigue, 2324
recurrent, 1480–1482
after breast conservation therapy, 1480–1482
management of, 1480–1482
after mastectomy, 1482
molecular factors in, 1411
nodal status and, 1411
postmastectomy and RT, 1480
after surgery and RT, 1406
reirradiation
BCS for IBTR, 670–672
isolated supraclavicular/axillary recurrence, 672–673
management after mastectomy and PMRT, 672
outcomes, 672*t*
rhabdomyosarcoma, 2221
risk factors, 1388–1390, 1388*t*
salivary gland cancers and, 1063
secondary after BMT, 419
stage Tis, 1373–1382
staging, 1396, 1397*t*, 1398*f*
technique, 607
treatment planning, 607, 608*t*
Breast-conserving surgery (BCS)
controversies, 1421–1426
mastectomy or, 1403
after neoadjuvant CT, 1482

with or without RT, 1414–1415*f*, 1415*t*, 1421–1426
patient selection, 1405–1406
radiographic findings after, 1449
recurrence after, 1480–1482
RT with
mastectomy compared with, 1405*t*, 1406–1407
outcomes, 1406
special circumstances, 1421–1426
Breast-conserving surgery (BCS), 670–672
Breast fibrosis/contracture, 2356
Breastfeeding, breast cancer risk and, 1388
Breath hold (BH), 215
Breath hold techniques, 1330, 1502
Breathing-related motion, 441–442
Bremsstrahlung spectrum, 172, 172*f*
Brenner tumors, 1861
Bromodomain and extra-terminal (BET) inhibitors, 108
Bronchial stenosis/obstruction/fistulae, 2347
Bronchiolitis obliterans syndrome (BOS), 406
Bronchogenic carcinoma, 2220
Bronchoscopy, for lung cancer, 1253
Brown-Séquard syndrome, 948
Buccal mucosa
anatomy of, 1095
carcinomas of, 1098, 1117
subsite-specific treatment, 1117
tumors of, 1098
Buccogingival space, SCC, 1099*f*
BuCy regimen. *See* Busulfan-cyclophosphamide (BuCy) regimen
Bunchers, linear accelerator, 179
Burkitt lymphoma (BL)
CNS involvement, 2191
EBV antibody titers, 1974, 2218*t*
presentation, 2189
Burnout, 364
Buschke, Franz J., 2
Busulfan-cyclophosphamide (BuCy) regimen
chemotherapy-alone conditioning regimens, 407
vs. TBI-Cy, 407–408
BV (brentuximab vedotin), 1970
Bystander effect, 54–55, 362

C

CA 125, 1774, 1830, 1858–1859, 1861, 1863, 1868, 1873
CA-19-9, 1774
Cabozantinib, 1869
Cachexia, 1536

CAF regimen
for breast cancer, 1420
components of, 1420
Calcifications
ductal carcinoma in situ, 1374
fibromas and, 1364
mammographic imaging, 1396*f*
Calcitriol secretion, 1252
Calcium levels. *See also* Hypercalcemia
Call-Exner body, 1861
Campylobacter jejuni, 1974–1975
Cancer stem cells (CSCs), 97, 98, 107–108
targeting of, 155
Cancer. *See also particular type of cancer*
angiogenesis and tumor cell invasion, 13, 13*f*, 14*b*
antiangiogenesis therapy of, 14*b*
causes of, 16*t*
cell proliferation, 99
chemoprevention, 17
childhood, 15*t*
components of definition of, 3*f*
defined, 3–4
energy metabolism, 99
estimated cases and deaths, 14*t*
estimates of avoidable risks of, 16*t*
financial burden of care, 832
forms of, 14–15
genes and biology of, 4–10, 4*f*, 5*f*, 7*f*
global radiation oncology
age-standardized incidence, 755*f*
burden of, 753
epidemiology, 753–756
and megavoltage machine supply, 757
mortality, 754*f*
hallmarks of, 97–100, 98*f*, 99*t*
immune destruction, 99
incidence and mortality, 15*f*
management, 62
metastasis, 10–12, 10*f*, 12*f*
metastatic phenotype and angiogenesis, 12–13
molecular biology of, 97–110
pain
assessment, 2315–2316
complementary therapies, 2319
guidelines, 2316–2318, 2318*t*
management, 2316, 2318
multidimensional construct, 2314, 2314*f*
physical etiologies, 2314–2316, 2315*f*

radiation oncologist, 2319
types, 2315
prevention, 15–17, 16*t*, 17*t*
replication potential, 98–99
risk factors, 108, 753
screening, 16
tissue invasion and, 98
vasculature in, 99
Cancer-related fatigue (CRF), 2323–2324
Cannabinoids, pain management, 2316
Capecitabine. *See also* XP regimen
Capecitabine
for colorectal cancer, 1572
for pancreatic cancer, 1534
radiation response and, 717
Capillary hemangiomas, 962
Capsaicin
pain assessment and managment using, 2318, 2318*t*
routes of administration, 2318*t*
Captain of the ship doctrine, 68
Carbamazepine
pain assessment and management using, 2317–2318, 2318*t*
Carbogen, 677–678. *See also* BCON regimen
Carbon dioxide laser, 1150
Carbon ion therapy
chordomas, 1194
Carbonic anhydrase-9 (CA-9), 320
Carboplatin, 1866–1867, 1868
for liver cancer, 2229
radiation response and, 716
for cervical cancer, 1794
for endometrial cancer, 1844
for nasopharyngeal cancer, 1024
for ovarian cancer, 1864
for spinal cord tumors, 952
for testicular cancer, 1736, 1738
Carcinoembryonic antigen (CEA), 1557, 1571, 1774, 2222
Carcinogenesis, 36–37
Carcinogens, 5, 5*f*
Carcinosarcomas, 1894
prostate, 1680
uterine, 1849–1850
Cardiac arrhythmias, RT for, 2244
Cardiac pacemakers, 251, 251*t*
Cardiac sarcomas, 1361*t*
Cardiac toxicity, radiation-related, 338
Cardiovascular system
radiation side effect management

coronary artery disease, 2347–2348
pericarditis, 2347
valvulopathy, 2348
vascular effects, 2348
Care and protection, in radiation therapy
artificial intelligence, 58, 58*b*
follow-up care, 57
patient evaluation, 56
preparing for treatment, 56–57
process of care in, 55–56
radiation oncology team, 58–59
staffing requirements, 59, 59*t*
telemedicine and remote practice, 57–58
treatment delivery, 57
treatment management, 57
Carina, location of, 698
Carmustine
for mycosis fungoides, 2001
Caroli disease, 1557
Carotid artery stenosis, 1033
Carotid blowout syndrome (CBOS), 667
Caspases, apoptosis and, 101
Casuistry theory, 812
Cataracts, 2338
induction of
steroid use and, 418
TBI and, 418
after RT, 2140, 1087
Cauda equina nerve root compression syndrome, 948
Cavity-gas calibration factor (Ngas), 191
CBA (cost-benefits analyses), 1447–1448
CBCT. *See* Cone beam computed tomography (CBCT)
CBT (cognitive behavioral therapy), 2324
CD11b, 154
CD13, 2013
CD19, 2013
CD30, 1958
$CD30^{+}$lymphoproliferative disorders, 1998
CD33, 2013
CD79a, 2013
CDC genes, 8–9
CDC2 gene, 9
CDDP (cisplatin), for salivary gland cancer, 1086
CDKN2 mutation, 1639
CEA. *See* Cost-effectiveness analyses (CEA)
Cediranib (AZD2171), 154
Cell adhesion molecules, 2238

Cell biology, radiobiology and, 97
Cell cycle, 8–9, 98
  checkpoints, 98
  delays, 104–105
  radiation-induced blocks
    G1 phase, 105
    G2 phase, 105
    S phase, 105
  redistribution
    chemoradiation therapy and, 714
Cell death mechanism, 118–119
Cell death, 320
  loss of tumor suppressor proteins, 98–99
  radiation-induced, 99*t*, 101–102
  resistance to, 98, 99
Cell loss factor (f), 123
Cell repopulation, 542
Cell survival curve, 47–48, 47*f*
  chemoradiation therapy, 713
Cellular damage repair, 542
Centers for Medicare & Medicaid Services (CMS), 822
Central lung distance (CLD), 1429*f*
Central nervous system (CNS) tumors
  brain, metastatic disease of, 2262–2274
  pediatric patients, 2072–2076
    RT planning, 2073
    tumor distribution by histology, 2076*f*
    tumor distribution by site, 2076*f*
  prophylactic radiotherapy, 2019–2021
  spinal cord, metastatic disease of, 2262–2274
Central nervous system (CNS). *See also* Brain; Spinal cord
  benign diseases, 2239
  late effects of RT, 320–332
  leukemias and, 2012, 2012*f*
  malignancies, intraoperative radiotherapy, 466–467
  prophylactic radiotherapy, 2019–2021
  total-body irradiation, 414
Central nervous system, 574–575, 575*f*
Central neurocytomas, 433
  pediatric, 2086
Central vein thrombosis, 340
Central-field depth dose, 256
CER (comparative effectiveness research), 387
c-erb-B-2/neu proto-oncogene, 6–7
Cerebral edema, 875, 2336
Cerebrospinal fluid (CSF)
  analysis of, 949
  leptomeningeal carcinomatosis and, 2273

Cerenkov radiation camera systems, 215–216
Cerivcal stump, carcinoma of, 1796–1797
Cerrobend blocks, 186, 244, 244*f*
Cerrobend stents, 999
Cervical cancer brachytherapy, 594
Cervical cancer, 597–599, 663
  adenocarcinomas, 1770–1771
  carcinoma in situ, 1787
  in cervical cancer, 1702
  chemoradiotherapy trials, 1791–1793
  classification, 1770–1772
  clinical biomarkers, 1774–1775
    carcinoembryonic antigen, 1774–1775
    cytokeratin, 1774
    cytokeratin markers, 1774
    epidermal growth factor receptor pathway, 1774
    HPV DNA, 1775
    PD-L1, 1775
    squamous cell carcinoma antigen, 1774–1775
  clinical target volumes, 1804*f*
  diagnosis, 1766–1769, 1767*t*
  epidemiology, 1764–, 1765
  gross tumor volumes, 1804*f*
  invasive disease, 1775–1778, 1788–1794
    chemoradiotherapy, 1794
    early local disease, 1789–1791
    locally advanced disease, 1791–1794
    microinvasive disease, 1788–1789
  isodose curves, 1806
  management of
    duration of, 1774
    failure rates, 1774*f*
    follow-up, 1812–1814
    radiation therapy, 1778–1787
    RT/CRT trials, 1792*t*
    sequalae of, 1815–1818, 1815*f*
    side effects, 1814–1819
    surgical, 1774
  metastatic disease
    to para-aortic nodes, 1795
  natural history of, 1765
  nodal assessment, 1777
  palliative care, 1814
  patterns of spread, 1765
  pelvic examination, 1775–1777
  pregnancy and, 1798–1799
  preinvasive disease, 1775
  presentation, 1766

prognostic factors, 1772–1775
age, 1772
histology, 1773
margin status, 1773–1774
patient-related, 1772
treatment duration, 1774
tumor-related, 1773
recurrent, 1812–1814
stage IA, management of, 1788
staging, 1770, 1770*t*, 1771
laparotomy, 1777
U.S. deaths, 1764*f*
U.S. incidence of, 1764*f*
vaginal cancer and, 1885
anatomy, 705–706
clinical indications, 597–598, 598*t*
follow-up, 599
imaging, 706–707, 707*f*
incidence worldwide, 753, 755*f*
outcomes, 598
rhabdomyosarcoma, 2134
secondary, after BMT, 419
technique, 598–599
treatment planning, 599, 599*t*, 599*f*
Cervical intraepithelial neoplasia (CIN), 1765
Cervical lymph nodes
metastatic disease of unknown primary tumor, 1229–1232, 1230*t*
portals, 1230*f*
RT of, 1220, 1222–1226
Cervical lymphadenopathy, 1008*f*
Cervix, 558–559, 558*f*, 559*f*, 705–706
Cesium-137 sources, 508
Cesium-137, 1881
Cetuximab (C225), cell sentization by, 680
Cetuximab (C225, Erbitux)
for anal cancer, 1602
for colorectal cancer, 1572
for nasopharyngeal cancer, 1024
for NSCLC, 1263
for oropharyngeal cancer, 1130, 1132–1133, 1135, 1138
for pancreatic cancer, 1537
Cevimeline, 2325
CFs (correction factors), 229–230
Chamomile, 2329
Charge (e), definition of, 169
CHECKMATE trial, 996
Checkpoints, 8–9
Chemodectoma, 1181

carotid body, 1181
Chemodectomas/glomus tumors, 922
Chemoembolization. *See* Transcatheter arterial chemoembolization
Chemokine receptors, 154
Chemoprevention, 17
Chemoradiation therapy
acute toxicity of, 1131
adjuvant, 1129–1130
late toxicities, 1131–1132
for nasopharyngeal cancer, 1022–1024, 1023*t*, 1025*f*
for oral cavity cancer, 999, 1104–1105, 1114, 1116
toxicity mitigation, 1262
vs. chemotherapy trial, 1844–1845
vs. RT trials, 1843–1844
basic concepts, 712–721
in cancer, 720–721
disease sites and, 721*t*
drug-radiation interactions, 713–715
improvement of, 719–720
sequencing issues, 715*t*
spatial cooperation in, 712
strategies, 712–713
toxicity, 712–713
Chemoradiometer, 17
Chemotherapy, 1866–1867, 1868–1869, 62–63, 658, 2006–2007
adjuvant, 715, 1024
cancer risk and, 1611
cholangiocarcinoma, 1558
concurrent, 1131
hepatocellular cancer, 1555
induction, 992–994, 1025*f*, 1132, 1154–1155, 1257–1258
intraperitoneal, 1867
neoadjuvant, 1024
palliative, 1155
concurrent, 716
induction, 715, 2168
limb perfusion, 2067
radiation response, 680
and TBI, 407
Chemotherapy/targeted agents, 878–881
conventional chemotherapy, 879
direct delivery of therapeutic agents, 879–880
targeted agents, 880
tumor-treating fields therapy, 881
Chest wall
dose homogeneity, 270*f*
electron arc therapy, 277
reirradiation, 671*t*, 672

Chest X-rays
cervical cancer patients, 1812
diagnostic, 1252
Chest, late effects of radiation, 334–339
Chiasmatic gliomas, pediatric, 2081
Child bearing, 1388
Child-Pugh score, 1550*t*
Children. *See* Pediatric patients
Chimeric antigen receptor T-cell therapy, 2047
Chlamydia psittaci, 1975
Chlorambucil, 2025
Chlorinated hydrocarbons, 1637
Cholangiocarcinoma,
Cholangiocarcinomas, 703
acute and late complications, 1562
anatomy of, 1556–1557
diagnosis, 1557, 1557*t*
distal bile duct, 1559
epidemiology, 1556–1557
intrahepatic, 1558–1559
management
chemotherapy, 1560
radiation therapy, 1561–1562
target therapy, 1561
pathology, 1557–1558
pathways of spread, 1558
perihilar, 1559
risk factors, 1556–1557
staging, 1558
palliative care, 2305
Chondritis, acute, 1178
Chondrosarcoma, 931–934. *See also* Bone cancer
clinical presentation, 932
diagnostic workup, 932
epidemiology and risk factors, 931
general management, 932, 932*f*
imaging, 932
natural history, 932
pathology, 931
principles of radiation therapy, 933
radiation techniques, 933, 934*f*
staging, 932
surgery, 933
systemic therapy, 934
spinal cord, 950
uterine, 1849
diagnosis, 2160
epidemiology, 2159

pathogenesis, 2159
pathology, 2159–2160
presentation, 2160
risk factors, 2159–2160
sacral/spine, 2160*t*
skull, 2160*t*
staging, 2160
treatment
outcomes, 2160
radiation, 2160
CHOP regimen, 1978
for NHLs, 1978
for PTCLs, 1991
Chordoma, 924–931
clinical presentation, 927
diagnostic workup, 927
epidemiology and risk factors, 925, 927
general management, 928, 929*f*
imaging, 927, 928*f*
natural history, 927
pathology, 924–925
principles of radiation therapy, 928–929
radiation techniques, 929–930, 930*t*, 931*f*
staging, 928
surgery, 928
systemic therapy, 930–931
Chordomas
anatomy, 1188
clinical presentation, 1189
clivus, RT, 1191–1192, 1191*f*
diagnosis, 1189–1190, 1189*t*, 1190*f*, 2161, 2161*f*
epidemiology, 1188, 2160–2161
natural history, 1188–1189
pathology, 1189
photon irradiation, 1191–1192
radiation therapy, 1190–1191, 1194
spinal cord, 950
surgical options, 1190
pathogenesis, 2161
pathology, 2161
presentation, 2161
treatment
radiation, 2161–2162
surgical, 2162
Choriocarcinomas
testicular, 1731–1732
Choroid plexus
tumors, pediatric patients, 2085

Choroidal hemangiomas, 961–962
Choroidal melanomas, 964
Choroidectomy, 966
Chromogranin A, 1896
Chronic lymphocytic leukemia (CLL), 2013, 2025, 2025*t*
  natural history, 2013
  total-body irradiation for, 405
Chronic myelogenous leukemia (CML), 2013, 2024
  natural history, 2013
  therapy of, 2024
Cilengitide, 155
Ciliary body melanoma, 963, 964–965
CIN (cervical intraepithelial neoplasia), 1765
Circular anatomy, 274*f*
Circulating tumor cells (CTCs), 107
Circulating tumor DNA (ctDNA) analysis, 159
Circumscribed precancerous melanosis of Dubreuilh. *See* Lentigo malignamelamonas
Cirrhosis, grading system for, 1550*t*
Cisplatin (CDDP), 1842–1844, 1866, 1934. *See also* BEP regimen; CMV regimen; DHAP regimen; ECF regimen; EP regimen; IPA regimen; MVAC regimen; PLADO regimen; TPF regimen; XP regimen
  for adrenal tumors, 1954
  adverse effects of, 1744
  alternatives to, 1792–1793
  for anal cancer, 1601
  for endometrial cancer, 1844
  for esophageal cancer, 1345–1346, 1346–1347
  esthesioneuroblastoma (ENB) management using, 1198
  for germ cell tumors, 1295
  for HNC SCC, 987
  hypoxic cell targeting by, 679
  for hypopharyngeal cancer, 1154, 1154–1155
  induction chemotherapy, 1154, 1154–1155
  late effects of, 2140
  for lung cancer, 1261
  for nasopharyngeal cancer, 1024, 1025*f*
  nephrotoxicity, 1743
  for osteosarcoma, 2158
  for ovarian cancer, 1866
  for penile cancer, 1753
  radiation response and, 716
  radiosensitization, 987
  for rhabdomyosarcoma, 2137
  for salivary gland cancer, 1086
  for spinal cord tumors, 952
  tirapazamine with, 679
  for urethral cancer, 1753, 1758
  for vaginal cancer, 1888–1891

for vocal cord cancer, 1167
for vulvar cancer, 1934, 1954
Cisplatin, vincristine, and cyclophosphamide (PVC), 1872
Cisplatin-free radical–mediated sensitization, 716
CKC (cold knife conization), 1775
Cladribine, 2025
Classic dose calculation formalism: isotropic point source, 515–517, 515–517*f*
Classic manchester system, 535–536, 536*f*
Classical scattering. *See* Coherent scattering
CLD (central lung distance), 1429*f*
Clear-cell adenocarcinomas, 1894–1895
Clear-cell carcinomas
cervical cancer and, 1770–1771
endometrial, 1832
ovarian, 1860–1861
Clinical informatics, 731–732
Clinical photon beam dosimetry, 234–239
Clinical research nurses, 384
Clinical target volume (CTV), 30
in esophageal cancer, 1330
in gastric cancer, 1502
in lung cancer, 1264–1265
in nasal fossa tumors, 1047–1049, 1049*t*
in nasopharyngeal cancer, 1015, 1016*t*
in oral cavity cancer, 1106–1107
in oropharyngeal cancer, 1133
in paranasal sinus tumors, 1049–1050
in prostate cancer, 1684, 1711, 1719, 1725
in retroperitoneal sarcomas, 1943
in spinal canal tumors, 953
in testicular cancer, 1741
for three-dimensional RT, 1897
treatment planning, 1330
in vulvar cancer, 1933
in CNS tumors, 2073–2074, 2074*f*
craniospinal irradiation, 2074*f*
definitions, 282, 282*f*
delineation of
conformal radiation therapy, 285–288
therapeutic ratio and, 687
in prostate cancer, 287*f*
in soft-tissue sarcomas, 2061, 2061*f*
Clinical trials, 64. *See also* Study design
categorical data analysis, 394–396, 395*f*
comparative effectiveness research, 398
conduct of, 384–385
conflict of interest, 396
data committees, 385, 396

definitive analysis, 384
design of, 379–384
endpoints, 381–384
ethical issues, 377, 817
inclusion criteria, 386
independent monitors, 384
Institutional Review Board, 396
interim analyses, 383–384
interim analysis, 394
Kaplan-Meier plot, 394–395, 395*f*
meta-analyses, 398–399
methodology of, 375–400
monitoring committees, 385
next-generation radiation oncology trials, 398–399*f*, 399
patient population, 391
phase 0, 379
phase I
  alternative designs, 385–386
  design, 389
  end points, 389–390
  investigators, 375
  objectives of, 378
  for radiation oncology, 385–386
  radioresistant phenotypes, 390*f*
  RT-drug trials, 388
  SEARS, 397, 397*f*
phase II
  efficacy and toxicity, 397
phase III
  design, 390
  equivalence design, 390
  investigators, 375
  limitations of, 386
  noninferiority design, 391
  objectives of, 378–379
  quality assurance/contouring, 391
  randomization, 390–391
  superiority design, 391
phase IV, 379
practical issues in, 384–385, 396
pragmatic, 398
principal investigator responsibilities, 376–377, 377*t*
radiation oncology, 375
randomization, 379–380
  covariate-adaptive, 392
  permuted block, 392
  response-adaptive, 393
  simple, 392

stratified, 392
redefining approach, 397–398
reporting of, 385
of rhabdomyosarcoma, 2135–2137
safety monitoring committees, 396
sample sizes, 382–383, 393–394, 393*f*
secondary analyses, 384
statistical issues, 379–384, 391–394
statistical power in, 382–383, 393–394
stopping rules, 383–384, 394
subject eligibility, 391–392
survival analysis, 394–396, 395*f*
trial reporting, 385
ClinicalTrials.gov, 375, 385, 397
Clinton, William J., 815
Clivus
chordoma of, 1191–1192, 1191*f*
CLL. *See* Chronic lymphocytic leukemia (CLL)
Clodronate, 2294
Clonogenic cells, 21
Clonorchis sinensis, 1557
Cloquet node, 1922
C-MET proto-oncogene, 1497
CMF regimen
for breast cancer, 1420, 1458
CML. *See* Chronic myeloid leukemia (CML)
CMOS (complementary metal oxide semiconductor) circuitry, 251
CMS (Centers for Medicare and Medicaid Services), 822
CNS. *See* Central nervous system (CNS)
Cobalt-60, 178, 424, 425, 763
Cochlea, late effects of RT, 327–329
Code of ethics
AMA, 814, 818
National Electrical Manufacturers Association, 815–816
Cognitive behavioral therapy (CBT), 2324
Cognitive bias, 365
Cognitive dysfunction, 2030
Coherent scattering, 174
Cohort studies, 387
COI (conflict of interest), 376, 396
Cold knife conization (CKC), 1775
Cold knife treatment, 1881
Cold spots. *See* Geographic underdosage
Coleman, C. Norman, 88, 88*f*
Colitis. *See* Mucositis, gastrointestinal
Collagen vascular disease, 1422–1424, 1423*t*
Collagens, deposit of, 141, 154
Collimator scatter factor (Sc), 229

Collimators. *See also* Multileaf collimation (MLC) systems
  jaws
    asymmetric, 243, 243*f*
    X type, 243
    Y type, 243
  multileaf, linear accelerator, 181*f*
  primary, linear accelerator, 179–180
  rotation, whole-brain portals, 251
Colon cancers, 1568–1576
  anatomy, 1568
  concurrent chemotherapy, 1573–1574
  extrapelvic, 1575*f*
  locally advanced
    palliative care, 1574
  neoadjuvant treatment, 1574
  radiation therapy, 1573–1574
  sigmoid, 1576*f*
  staging, 1571*t*
  surgical management, 1572
  treatment, 1572–1574
Colonoscopy guidelines, 1572
Color Doppler ultrasound, 690
Colorectal cancers, 1568–1576. *See also* Colon cancers; Rectal cancers
  intraoperative radiotherapy, 466
  palliative care, 2307–2308
  pediatric, 2222
  recurrent, 2307–2308
  epidemiology, 1569
  management
    adjuvant chemotherapy, 1572–1573
    adjuvant RT, 1572–1574
    surgical, 1572
  metastatic, 1574
  pathology, 1569–1570
  pathways of spread, 1569–1570
  patient evaluation, 1569–1570
  patterns of spread, 1569
  presentation, 1570–1571
  risk factors, 1569
  screening for, 1570
  staging, 1571–1572
  TNM staging of, 1571*t*
Colorectum, 1568
Common bile duct, 703
Common hepatic duct, 703
Common Rule, 815
Common Terminology Criteria for Adverse Events (CTCAE), 747
Common variable immunodeficiency, 1974

Comparative effectiveness research (CER), 387, 749–750
Compensating filters, 246, 246*f*
Complementary metal oxide semiconductor (CMOS) circuitry, 251
Complete responses (CRs), 382
Complex decongestive physiotherapy, 1443
Compliance issues, 993
Complications. *See also* Normal tissue complication probability (NTCP) models; specific adverse effects
  hemibody irradiation, 420
Compton scattering, 175, 175*f*, 288
Computed tomography (CT)
  brachytherapy contouring, 1802
  for cervical cancer, 1767
  diagnostic
    for adrenal tumors, 1952
    for breast cancer, 1395
    for cervical cancer, 1768*t*
    for Hodgkin lymphoma, 1957
    for lung cancer, 1253
    for oropharyngeal cancer, 1125–1126
    for pancreatic cancer, 1524
    for prostate cancer, 1674, 1685*f*
    for testicular carcinoma, 1734
    for vaginal cancer, 1884–1885
    for vulvar cancer, 1927
    for osteosarcomas, 2157
    for prostate cancer, 287*f*
    for soft-tissue sarcomas, 2055*f*
  for endometrial cancer on, 1829–1830
  pelvic, 1829
  spinal canal tumor, 948
  clinical target volumes, 287*f*
  contrast-enhanced, 688
  gross tumor volumes, 286*f*
  imaging using, 688
  multidetector systems, 688
  planning protocols, 284
  planning target volumes, 287*f*
    prostate cancer patient, 287*f*
  proton therapy, 309
  QA programs and, 297*t*
  simulations, 297*t*
  simulators, 186, 188*f*
  topograms, 284
Computed tomography simulator, 201
Computer vision model development, current challenges in, 734–735
Concurrent chemotherapy regimens, 991–992
Concurrent chemotherapy, 716, 2067

Cone beam computed tomography (CBCT), 178, 187
  proton therapy, 310, 310*f*
  prostate cancer, 1718
Conflict of interest (COI), 376, 396
Conformal electron therapy, bolus construction, 267*f*
Conformal planning, 288
Conformal radiation therapy (CRT), 280–299
  data management, 295–296
  dose reporting, 292–293
  dose-volume histograms, 293, 294*f*
  historical development of, 281
  plan implementation, 291
  planning process, 283–295, 294*t*
  quality assurance, 299
  treatment verification, 291
  volume specification for, 282–283, 282*f*
Congestive heart failure (CHF), post-RT, 338, 2111
Conization, 1767, 1775
Conjunctiva
  radiation tolerance of, 960
  tumors of, 968
Connective tissue and skin diseases
  desmoid tumors, 2249–2250
  dupuytren contracture, 2251–2252, 2251–2252*f*
  heterotopic ossification, 2253–2254, 2254*f*
  hypertrophic scars, 2252–2253
  keloids, 2252–2253, 2253*f*
  Peyronie disease (PYD), 2250–2251
  plantar fasciitis, 2254–2255
CONsolidated Standards of Reporting Trials (CONSORT), 385, 396
Contact units, treatment machines, 177
Continence, anorectal, 1595
Continuing education
  QA programs and, 297*t*
Contrast agents, 688
Conus medullaris, 694
Conventional chemotherapy, 879
Conventional external radiation (cERT), 455
Conventional fractionated external beam radiotherapy, 914
Conventional radiotherapy vs. stereotactic body radiation therapy, 2282
  spinal instability neoplastic score (SINS) system, 2277, 2278*t*
Convolution/superposition algorithm, 231
Convolutional neural networks, 58*b*
COPP/ABV regimen, 2184
Cordectomy, 1167, 1177
Cornea
  anatomy of, 960
  radiation tolerance of, 960

Coronary artery disease, 1970
Coronary artery disease, 2183, 2347–2348
Coronary stenosis, after RT, 1445
Corpus Hippocraticum, 813
Correction factors (CFs), 229–230
Corticosteroids
  for metastatic spinal cord compression, 2279–2280
  for mycosis fungoides, 2001
Cost analysis, process flow and, 1816
Cost-benefits analyses (CBA), 1447–1448
Cost-effectiveness research, 748
Costochondritis, 2354, 2354*t*
Costodiaphragmatic recess, 698, 698*f*
Costs, 837–838
Coulomb forces, 171, 172
Coulomb scattering, 303
COVID-19 global pandemic/global oncology, 764–765
COVID-19 pandemic, 790–791, 800, 822
Cox model, 395
CQI. *See* Continuous quality improvement (CQI), error avoidance
Cranial irradiation
  prophylactic, 1273
  for leukemias, 2031
  prophylactic, 2020
  radiation therapy, 2194
  sequelae, 2030–2031
Cranial nerve deficits, 918, 919*t*
Cranial nerves. *See also specific nerves*
  neuropathies, 1032
  relative positions of, 1003, 1003*f*
  examination of, 692
  oncologic anatomy, 692–694
  radiosensitivity, 428
Cranial neuropathy, 1032
Craniopharyngioma, 903
Craniopharyngiomas
  IMRT/SRT and proton plans, 485*f*
  pediatric, 2092–2095, 2095*f*
  proton therapy, 485–486, 485*f*
Craniospinal axis irradiation, 486, 487*f*
Craniospinal irradiation (CSI)
  clinical target volumes, 2074*f*
  for CNS tumors, 2073
  pediatric patients, 2076
    CNS tumors, 2073
  proton beam, 2074
  therapeutic, 2029
Craniospinal irradiation, 876–877

CRC. *See* Colorectal cancers
Cribriform adenocarcinoma, 1073
Critical element models, 295
Critical volume models, 295
Crizotinib, 1269–1270
CRs (complete responses), 382
CRT. *See* Conformal radiation therapy (CRT)
Cryoablation, palliative therapy with, 2293
CSCs. *See* Cancer stem cells (CSCs)
CSF. *See* Cerebrospinal fluid (CSF)
CSI. *See* Craniospinal irradiation (CSI)
CTCL (cutaneous T-cell lymphomas), 1998–1999
CTCs (circulating tumor cells), 107
CTNNB1 (*β* catenin) mutations, 1837
CTVs. *See* Clinical target volumes (CTVs)
Culture of safety, 363–364, 364*t*
Curative radiation therapy, 29
Curcumin, for mucositis, 2326
Curie, Marie Sklodowska, 76, 76*f*, 172, 616
Curie, Pierre, 76, 172, 616
Current practices, RO, 789
  areas for further scholarship in, 804
  continuing medical education in radiation oncology, 802–803
  equity, diversity, and inclusion in, 804–805, 805*t*
  graduate medical education, 792–802, 793–794*t*, 793*f*, 795*f*, 799–802*t*
  undergraduate medical education, 789–792, 791*f*
Curriculum development, 774–789, 776*t*
  curriculum development models, 776–777
  dissemination, 788
  systematic curriculum development, 777–788, 777*f*, 778*t*, 779*t*, 780*f*, 781*f*, 781*t*, 783*t*, 784*f*, 785*t*, 786*t*, 786*f*, 788*t*
Curriculum maintenance, renewal, and reform, 788–789
Cushing disease, 916, 917*t*, 918
Cushing syndrome
  adrenal tumors and, 1953
  lung cancer and, 1252, 1271
Cutaneous angiosarcomas, 2055
Cutaneous B-cell lymphomas, 2007
Cutaneous lymphomas
  classification, 1998*t*
  primary, 1998–2009
Cutaneous T-cell lymphomas (CTCL), 1998–1999
CyberKnife radiosurgery system
  spinal canal tumors, 954, 955*f*
CyberKnife radiosurgery system
  techniques, 424–425
Cyclin D1, 1319
Cyclin dependent kinase (CDK), 8

Cyclin, 8, 9
Cyclochoroidectomy, 966
Cyclooxygenase inhibitors, 2316
Cyclophosphamide, 1866. *See also* AC regimen; BEACOPP regimen; CAF regimen; CHOP regimen; CMF regimen; CNF regimen; COP regimen; COPP/ABV regimen; CVB regimen; FAC regimen; FEC regimen; MACOP-B regimen; ProMACE/MOPP regimen; TC regimen
  for adrenal tumors, 1954
  for ALL, 2018
  and antithymocyte globulin, 407
  for bladder cancer, 1637
  busulfan with, 407
  for CLL, 2025
  cystitis prevention, 2169
  ENB management using, 1198, 1201
  for endometrial cancer, 1843–1844
  for ovarian cancer, 1866
  for rhabdomyosarcoma, 2137
  for solitary fibrous tumors, 1188
  for spinal cord tumors, 952
  late effects of, 2140
  TBI-based, 407
Cyclophosphamide, vincristine, and bleomycin (CVB), 1872
Cyclosporine
  post-grafting, 406
Cyclotrons, 185, 473
Cystectomy
  bladder preservation and, 1642–1644
  cystectomy versus bladder preservation, 1642–1644
  radical, 1647
    outcomes, 1647
    recovery program, 1648*f*
Cystic atrioventricular node tumor, 1361
Cystosarcoma phylloides, 1399, 2221
Cystoscopy, cancer diagnosis, 1884
Cystourethritis, radiation-related, 1818
CYT-6091, 163
Cytarabine, 1980, 2021. *See also* DHAP regimen
Cytokines
  secretion of, 1252
  phases of, 98
Cytotoxic agents, 20. *See also specific agents*
  tumor microenvironment and, 153
Cytotoxic T-lymphocyte–associated protein 4 (CTL4), 106
Cytoxan
  endometrial cancer, 1845
  complications of, 344

D

Dacarbazine. *See also* ABVD regimen
  for adrenal tumors, 1954
  for rhabdomyosarcoma, 2137
  for solitary fibrous tumors, 1188
Daidzein, protective action, 1668
Daily quality assurance, 584
Danger-associated molecular patterns, 54–55
Dasatinib, 2024
Data management, conformal radiation therapy, 295–296
Daughter nuclides, 173, 174*f*
Daunorubicin, 2016
Death, trial endpoints, 382
Decay constants, 172
Decision analysis, of mathematical tools, 834
Decision trees
  ductal carcinoma in situ, 1382
  mastectomy or BCS, 1403
Decisional regret, 833–834
Declaration of Geneva, 814–815
Deep inspiration breath hold (DIBH), 215
Deep musculoaponeurotic fibromatosis. *See* Desmoid tumors
Deep therapy units, 177
Deep vein thrombosis, prophylaxis, 1900
Definitive radiation therapy
  for oropharyngeal cancer
    treatment planning, 1133–1135
Dehydration, after RT, 1518
Dehydroepiandrosterone sulfate (DHEA-S), 1953
Delivery of treatment, 585
Dementia, after WBRT, 2263
Denosumab, 2294
Dental abnormalities, after RT, 2183
Dental decay, after RT, 1033
Denys-Drash syndrome, 2103
Deontology theory, 812
Deoxyribonucleic acid (DNA)
  aneuploidy in tumors, 1074
  damage recognition, radiation-induced, 103
  double-strand breaks, 718
  ligases, 104
  methylation, 108
  mismatch repair genes, 101
  ploidy index, 1401
  repair after ionizing radiation, 101, 103
  repair of, 714
  single-strand breaks, 116

Depth dose, 256, 259*f*
Depth-dose buildup regions, 235–236
Dermatitis, radiation-induced, 2329
Dermis. *See also* Skin cancers
Dermoid tumors
  spinal canal, 2083
  spinal cord, 950
Desmoid tumors, 2249–2250
Desmoplastic small round-cell tumors (DSRCT), 2230–2231
Desquamation, after TSEBT, 2003
Dexamethasone (Decadron), 1991. *See also* DHAP
  for metastatic spinal cord compression, 2263
  regimen for ALL, 2021
  for RT-induced edema, 1178
DHAP regimen, 1980
Diabetes
  cancer risk and, 1611
  endometrial cancer and, 1828
Diagnostic whole-body scan (DxWBS), 1239–1240, 1240*t*
Diaphysis, long bone, 2289
Diarrhea, radiation-induced, 343, 1818, 2140, 2327–2328
Diet. *See also* Nutrition
  cancer risk and, 1611
  prostate cancer risk and, 1667–1668
Diethylstilbesterol (DES)
  cervical cancer and, 1765
  clear-cell adenocarcinomas, 1894
  vaginal cancers, 1894
Differential pencil beams, 231
Differentiated thyroid carcinomas (DTC), 1237
  chemotherapy, 1248
  imaging studies, 1240*t*
  management, 1244–1246
  neck dissection in, 1244
  radioactive iodine for, 1245
  targeted agents, 1248
  TSH suppression therapy, 1248
Differentiated vulvar intraepithelial neoplasia (dVIN), 1923
Diffuse intrinsic pontine tumors, 2081
Diffuse large B-cell lymphoma (DLBCL)
  characteristics, 1977
  classification, 2192
  clinical management, 1978–1982
  clinical presentation, 1977
  palliation, 1980
  pathology, 1977
  PET image, 1981*f*
  presentation, 2189

primary cutaneous diffuse large, 2007
prognostic indexes, 1977–1978, 1977*t*
refractory, 1980
relapsed, 1980
RT dose and field design, 1980–1982, 1981*f*
stage I, 1977, 1978*t*
stage II, 1978, 1978*t*
stage III, 1979–1980
stage IV, 1983
Diffusion-weighted imaging (DW/DWI), 689
Digestive system, 2341–2342*t*
radiation side effect management
ageusia, 2342
anal toxicity, 2345–2346
biliary stricture, 2345
dysgeusia, 2342
dysphagia, 2343
gastritis/duodenitis, 2344
oropharyngeal mucositis/oral infection, 2342–2343
pancreatitis/pancreatic insufficiency, 2344
radiation enteritis, 2344
radiation esophagitis, 2343–2344
radiation-induced liver disease, 2344–2345
radiation proctitis, 2345
xerostomia, 2339, 2341–2342
Digital rectal exams (DREs), 1571
Digitally reconstructed radiographs (DRRs), 281, 288, 289*f*, 297
Diode detectors
in total-body irradiation, 414
Dioxin, soft-tissue sarcomas and, 2054
Diphenoxylate, atropine and, 2328
Direct delivery of therapeutic agents, 879–880
Disease-free survival (DFS), 378
Distant metastasis, nasopharyngeal cancer, 1005
DLBCL. *See* Diffuse large B-cell lymphoma (DLBCL)
DNA damage
by ionizing radiation, 18
oxygen and severity, of, 118
DNA damage responses (DDRs), 117
DNA-PK, radiation-induced, 99*t*
DNA-PKCS, 103, 104
Docetaxel (Taxotere), 1868. *See also* TC regimen; TPF regimen
for NSCLC, 1261
radiation response and, 717
Documentation. *See also* Policies and procedures; Protocol documents
Dorsal exophytic tumors, 2082
Dosages
absorbed doses, 189–192

dosimetry profiles, 196
homogeneity, 293
linear accelerator profiles, 197*f*
Dose calculations
algorithms, 232
convolution/superposition algorithm, 231
methods, 229–234
model-based, 231
monitor unit methods, 232–234
Monte Carlo method, 232
patient-related, 262–264
tissue heterogeneities and, 232
Dose clouds, display of, 291
Dose depth, 255–256, 256*f*, 472*f*, 475
Dose distributions
brain sparing, 274*f*
calculations, 288–289
conformal radiation therapy, 288–289
imaging, 290*f*
intraoperative, 273*f*
protein therapy, 471
radiosurgery treatment, 425
surface irregularities and, 260*f*
therapeutic ratio and, 471
in water, 255–258
Dose fractionation. *See also* Fractionated radiation
historical background, 129
hyperfractionation, 130–131
hypofractionation, 130
modification, of, 129–131
patterns of, 129–131
Dose fractionation patterns, modification of, 129–130
hyperfractionation, 130–131
Dose in free space (Dfs), 190
Dose prescriptions
conformal radiation therapy, 284*t*, 288
monitor unit calculations and, 261–262
Dose reporting, 292–293
Dose-response curves
chemoradiation therapy, 713*f*
Dose spread arrays, dose calculations, 231
Dose statistics, 293
Dose-time factors, 37, 38*f*, 42*b*
Dose-time parameters. *See* Time-dose parameters
Dose to air (Dair), 190
Dose-volume data
clinical guidelines and, 316–317
outcomes and, 317

tissue toxicity and, 316*f*
Dose-volume effects
in children, 318
HyTEC review, 318
QUANTEC review, 316–350
Dose-volume histograms (DVHs)
brachytherapy, 1803–1805
breast cancer, 1430*f*
external beam radiation, 1430*f*
Dose-volume histograms (DVHs), 281
conformal radiation therapy, 293
cumulative, 293
differential, 293, 294*f*
figures of merit, 317
rectal toxicity and, 343*f*
treatment plan evaluation, 293
types of, 293
Dose-volume responses, 294
Dose voxels, 293, 294*f*
Dose/volume/outcome data, 345, 346–349*t*
Dosimetric effects, 209
Dosimetry, 1900, 1900*t*
brachytherapy
HDR vs LDR, 1807
charaterization of TBI, 410
clinical photon beam, 234–239
conformal radiation therapy, 299
diode type, 192
incident electron energy and, 256
methods
diode type, 192
film dosimetry, 192
metal oxide semiconductor-field effect transistor, 193
polymer gel, 193
radiochromic film dosimetry, 192
thermoluminescence, 192
parameters for
dose profiles, 196, 197*f*
isodose curves, 195–196, 196*f*
output factors, 194–195, 195*f*
percentage depth doses, 193, 194*f*
scatter-air ratios, 194
tissue-air ratios, 193–194, 194*f*
tissue-maximum ratios, 194, 195*f*
tissue-phantom ratios, 194, 195*f*
wedge filters, 196–197, 197*f*
photon external-beam, 229–252
principles of, 169–197

proton therapy, 304–305
quality assurance, 299
systems for iodine-131, 1244*t*
tissue interface, 236–237
total-body irradiation, 410
wedge filter, 237–239, 238–239*f*
Dosiomics, 733
Double helix, 9
Double-strand breaks (DSBs)
DNA
repair, 714
repair pathways, 104, 117
sensing of, 103
Doxorubicin (Adriamycin), 1868, 1842–1843, 1866. *See also* ABVD regimen; AC regimen; BEACOPP regimen; CAF regimen; CHOP regimen; COPP/ABV regimen; FAC regimen; MACOP-B regimen; OEPA regimen; OPPA regimen; PLADO regimen; ProMACE/MOPP regimen; VACA regimen
for adrenal tumors, 1954
adverse effects, 2167
for breast cancer, 1458
for DTC, 1188
for endometrial cancer, 1842–1843
for osteosarcoma, 2158
RT and, 2167
for soft-tissue sarcomas, 2067
for Solitary fibrous tumors, 1188
for urethral cancer, 1754, 1758
DRRs (digitally reconstructed radiographs), 281, 288, 289*f*, 297
Drug-radiation interactions
additive effects, 713
assessment of, 713
mechanistic issues, 713–715
Drug resistance, 715
Drug therapy, 62–63, 64*f*
Dry-eye syndrome, 960, 1058, 1087
DSB repair, nonhomologous end joining, 116
DTC. *See* Differentiated thyroid carcinomas
Ductal adenocarcinoma, 1679
Ductal carcinoma in situ (DCIS)
breast, 1374–1382
epidemiology, 1374
imaging, 1374
calcifications, 1375*f*
management
breast conservation, 1379–1381
decision tree, 1382
lumpectomy, 1379*t*
mastectomy, 1378–1379, 1378*f*

radiation therapy, 1379
tamoxifen, 1380*t*, 1381
natural history, 1377–1378
pathology, 1374–1377
Comedo, 1376*f*
cribiform, 1376*f*
micropapillary, 1376*f*
papillary, 1376*f*
solid, 1376*f*
presentation, 1374
prognostic factors, 1378
recurrence
clinical trials, 1379, 1379*t*
ipsilateral breast, 1379, 1379*t*
management of, 1381
predictive factors, 1380
Duloxetine, 2318*t*
Dupuytren contracture, 2251–2252, 2251–2252*f*
Dural tail, 694
DVHs (dose-volume histograms)
breast cancer, 1430*f*
external beam radiation, 1430*f*
Dysgerminomas, 1858, 1861, 1871, 1947
Dysgeusia, 2342
Dysparenuria, radiation-related, 1818
Dysphagia, 2343
cranial nerve involvement and, 693
esophageal cancer and, 1328–1330
IMRT and, 1134
laryngeal dose and, 333*f*
oropharyngeal cancer and, 1134
radiation-induced injury, 333, 1352
Dysphonia, 2339
Dyspnea
lung cancer and, 1252
Dysregulation, 1991–1992
Dysuria, post-RT, 344

E

E-Cadherin
loss of, 1372
nasopharynx, 1014
E-Cadherin
familial diffuse gastric carcinoma and, 101
E2F transcription factor, 109
E5 gene, HPV, 1764
E6 gene, HPV, 1764

E7 gene, HPV, 1764
EA (anti-early antigen), 1008–1009
Ear
  anatomy of, 973, 973*f*, 975*f*
    blood supply, 973
    innervation, 973
  clinical presentation, 974
  coronal anatomy of pathways, 974*f*
  epidemiology, 973–974
Ear cancer
  clinical presentation, 974
  diagnosis of, 974*t*
  diagnostic workup, 974–976, 974*t*
  management, 976–977
  normal-tissue complications, 980, 981*t*
  palliative RT, 978–980
  pathology, 976, 977*t*
  prognostic factors, 976
  radiation therapy, 977–980
  sequelae of treatment, 981
  staging, 976, 976–977*t*
Early Breast Cancer Trialists' Collaborative Group (EBCTCG), 672
EBRT. *See* External-beam radiotherapy (EBRT)
Ecchordosisphysaliphora, 924
ECF regimen, 1516
Echogenicity, 690
Edema
  extremity, 2003
  after RT, 2066
  after TSEBT, 2003
Eelectronic brachytherapy, 463–464
EGFR, 20
EIC (extensive intraductal carcinoma), 1410
Elastic interactions, 176
Elderly patients
  Hodgkin lymphoma, 1968
Elective nodal irradiation (ENI), prostate cancer, 1725
Electrocoagulation, 1880
Electromagnetic radiation (EM)
  description of, 171
  noise interference, 251
  pacemakers and, 251
Electromagnetic spectra, 171*f*
Electromagnetic tracking, 220
Electrometers, 189, 192–193
Electron applicator mounting, 181
Electron arc therapy, 265
Electron beam therapy

bolus use, 266–268
dose distribution in water, 255–258
depth dose, 255–256, 256*f*
isodose plots, 258
off-axis dose, 257–258
dosimetry, 255–278
field abutment, 269, 269–270*f*
internal shielding, 268–269
intraooperative accelerator, 272*f*
mixed beam therapy, 269–271, 271*f*
for mycosis fungoides, 2001–2004, 2002*f*, 2003*f*
photon beam therapy with, 271
specialized techniques, 271–278
electron arc therapy, 275–278, 276*f*, 277*f*
intracavitary irradiation, 271–272
total-limb irradiation, 272–273, 274*f*
total-scalp irradiation, 272, 273*f*, 274*f*
total-skin irradiation, 275, 275*f*
total skin, 2001–2004, 2002*f*, 2003*f*
treatment planning, 264–271
Electron beam units
treatment machines, 178–185
very-high energy, 186
Electron beams, modulation of265
Electron capture, 173
Electron guns, 179
Electron-scattering foils, 179
Electron volts (eVs), 169
Electronic brachytherapy/low-kilovoltage x-ray IORT (KV-IORT)
description of, 461
physics of, 463–464
technical applications of, 463–464
Electronic equilibrium, 189, 190*f*
Electronic hospital records (EHRs), 296
Electronic medical records (EMRs)
conformal radiation therapy, 296
data management, 296
dose reporting, 292–293
ethical issues, 817
Electronic view box, 281
Electrons
backscatter, 269
interactions with matter, 176
Electrostatic forces, 171, 172
Electrostimulation techniques, 2318
Electrosurgical loop excision, 1881
Elekta Gamma Knife, 178, 178*f*
Elekta-Impac MOSAIQ, 296

Elekta MLC systems, 244
Elekta Synergy IGRT system (XVI), 181, 182*f*
Embryonal carcinoma, 1731
Embryonal tumor with abundant neuropil and true rosettes (ETANTR), 2091
Empiricism
  vs. research-based radiation oncology, 49
Employees. *See also* Staff
Emulsions, film dosimetry and, 192
ENB. *See* Esthesioneuroblastoma (ENB)
End points, clinical trials, 381–384
End-stage renal disease (ESRD), 2111
Endocrine dysfunction, after RT, 1033, 2072
Endocrine system, 2357*t*
  radiation side effect management
    hypopituitarism, 2357
    hypothyroidism, 2358
    radiation-induced premature menopause, 2358
Endocurietherapy, 44
Endodermal sinus tumors, 1947
Endometrial cancer, 599–601
  adjuvant vaginal cuff brachytherapy, 599–600, 600*t*
  inoperable endometrial carcinoma, 601
  vaginal cuff recurrences, 600–601, 601*f*
Endometrial cancers, 1828–1850
  cervical, 1771, 1842
  classification, 1830–1832, 1831*f*, 1831*t*
  diagnosis, 1829–1833
  early, RT recommendations, 1841–1842
  epidemiology of, 1828–1829
  management
    chemotherapy and immunotherapy trials, 1845
    CRT *vs.* RT trials, 1843–1844
    CT *vs.* RT trials, 1843
    observation *vs.* RT, 1839–1840
    pelvic *vs.* vaginal cuff brachytherapy, 1841
    radiotherapy, 1839–1841
    RT complications, 1848
    RT techniques, 1846–1848, 1847*f*
    surgical, 1838–1839
    surgical complications, 1848
    systemic therapy, 1845–1846
  molecular biology of, 1832–1833
  natural history, 1829
  presentation, 1829
  prognostic factors
    adnexal/serosal involvement, 1837
    age, 1836
    cervical involvement, 1837

grade, 1836
histologic subtype, 1836
lower uterine segment involvement, 1837
lymphovascular invasion, 1837
molecular prognostic factorst, 1837
myometrial invasion, 1837
pelvic and para-aortic lymph node involvement, 1837
peritoneal cytology, 1837
race, 1836
recurrent, 1849
risk factors, 1828–1829
stage I, 1839
stage II, 1839
stage III, 1845–1846
staging, 1833–1837
Endometrial hyperplasia, 1830–1831
Endometrial stromal sarcomas, 1850
Endometrioid adenocarcinomas, 1895
Endometrioid tumors, 1831–1832, 1831*f*, 1860
prostate, 1680
Endometriosis, 1857
Endometrium, 559–560, 560*f*, 561*f*
Endoscopic retrograde cholangiopancreatography (ERCP), 703
Endoscopic ultrasound (EUS)
diagnostic
for colorectal cancer, 1571
for gastric cancer, 1494
for pancreatic cancer, 1524
Endoscopic ultrasound (EUS)
description of, 690, 690*f*, 690*t*
Endostatin, 99
Endothelial cells (ECs)
migration, 137
radiation responses, 319
Endothelial precursor cells (EPCs), 137
endothelial vasculogenesis
precursor cells and, 137
Energy bands
allowed, 192
forbidden, 192
Energy deposition kernals, 231
Energy selection systems (ESSs), 474
Enteritis. *See* Mucositis, gastrointestinal
Enucleation
guidelines, 965
Environmental exposures
hepatocellular cancer and, 1443
NHL and, 1974

EP regimen, for NSCLC, 1261
Ependymoma, 896–897
Ependymomas
  anaplastic, 953
  chemotherapy, 952
  fourth-ventricle, 2084*f*
  myxopapillary, 2083
  myxopapillary, 953
  pediatric, 2083–2085
  spinal canal, 2083
  spinal canal, 950–951
  spinal cord, 949–950
Epic system, 296
Epidemiology of cancer. *See specific cancers*
Epidermal growth factor receptors (EGFRs)
  activation of, 78
  clinical trials, 1794
  family members, 78
  inhibition, 106
  inhibitors of, 1794
  lung cancer and, 1258
, overexpression, 680
  overexpression, 680
  targeted therapy using, 994
  in thymomas, 1289
  treatment selection and, 1268–1269
Epidermoid cysts, spinal, 2083
Epidermoid tumors, 950
EPIDs. *See* Electronic portal imaging devices (EPIDs)
Epigenetics, 108
Epiglottis, infrahyoid, 1162
Epilepsy, RT for, 2242–2243
Epinephrine, glomus tumors and, 1183
Epiphysis, long bone, 2289
Epirubicin, 1844. *See also* ECF regimen; FEC regimen
  for salivary gland cancer, 1086
Epithelial-myoepithelial carcinomas, 1073, 1074*f*, 1083
Epithelial tumors
  consolidative intraperitoneal phosphorus 32, 1868
  consolidative whole-abdomen irradiation, 1868
  management of, 1863*t*
    adjuvant chemotherapy, 1864, 1864*t*
    adjuvant whole-abdomen irradiation, 1864–1865
    advanced-stage disease, 1865–1867, 1866*t*
    early-stage disease, 1864–1865
    postoperative management, 1864
  palliative radiation treatment, 1869–1870
  palliative surgery, 1869

recurrent ovarian cancer, 1868
Epitheloidhemangioendothelioma, 1368*f*
Epstein-Barr virus (EBV)
antibody titers
AIDS, 2218*t*
Burkitt lymphoma and, 2218*t*
nasopharyngeal cancer and, 2218*t*
Hodgkin lymphoma and, 1956
Hodgkin lymphoma and, 2176
nasopharyngeal cancer and, 1003, 1013–1014
NHL and, 1974, 2192
PC-ALCL and, 2006
Equilibrium, electronic, 189, 190*f*
Equivalent uniform dose (EUD)
calculation of, 295
ErbB1. *See* Epidermal growth factor receptors (EGFRs)
ErbB2 gene expression, 1375–1376
Erectile dysfunction (ED), 2329
after EBRT, 1693–1694
penile bulb irradiation and, 345
Erectile dysfunction, 2352–2353
Erlotinib (Tarceva)
for lung cancer, 1268
for NSCLC, 1262
for vulvar cancer, 1935
Error, definition of, 359, 361–362
Erythema, after TSEBT, 2005
Erythrocyte sedimentation rate (ESR), 1957
Erythroplakia, 1097
Erythroplasia of Queyrat, 1749, 1923
Esophageal cancer, 663
classification of, 1327, 1327*t*
diagnosis, 1213*t*, 1321–1324
epidemiology of, 1317–1319
imaging of, 698, 699*f*
local failure, 1321
management
brachytherapy, 1342, 1351–1353
BT or EBRT, 1351–1353
chemoradiation therapy, 1345–1351
chemotherapy, 1345–1346
clinical trials, 1348*t*, 1351, 1352
combination therapy, 1328
nodal basins included, 1334*f*, 1335*f*, 1336*f*, 1337*f*
outcomes, 1342–1343
palliative treatment, 1328–1330, 1353
radiation therapy, 1330–1342, 1344*t*
RT dose constraints, 1340–1341

sequelae of treatment, 1353–1355
surgical, 1328, 1342, 1343*t*
metastatic, 1319–1321*f*, 1323*f*
natural history of, 1319–1321
patterns of failure, 1323*t*
pattrns of spread, 1319–1321
pediatric, 2221
presentation, 1321
prognostic factors, 1327–1328
proton therapy, 490, 491*f*
risk factors, 1317–1319
staging, 1324, 1324–1325*t*
treatment algorithm, 1329*f*
Esophagectomy, 1033
Ivor-Lewis type, 1328
use of, 1328
Esophagitis. *See also* Mucositis, gastrointestinal
acute, 339*f*
radiation-induced, 1354
risk factors, 339
Esophagus
anatomy of, 1316–1317, 1317*f*
lymphatic drainage, 1317, 1317*f*
RT dosage constraints, 1291*t*
Esophagus, 574
anatomy of, 698
dose-volume limits, 339
dose/volume/toxicity data, 339
endoscopic US layers, 690*t*
late effects of radiation, 338–339
Esthesioneuroblastoma (ENB), 1054–1056, 1055*t*, 1056*t*
chemoradiation therapy, 1201
clinical presentation, 1196
diagnostic workup, 1196–1197, 1197*f*
epidemiology, 1196
management, 1198–1199
outcomes, 1200–1201
sequelae of treatment, 1201–1202
natural history of, 1196
pathologic features of, 1197–1198
pediatric, 2219
prognostic factors, 1197–1198
radiation therapy
IMRT, 1201*f*
techniques, 1200
staging, 1196–1197
Estrogen receptor (ER) status
breast cancer and, 1413

breast cancer prognosis and, 1401
tamoxifen trials, 1413
Estrogens, topical, 2329
Etanidazole (SR2508), 678
Ethics
clinical trial issues, 377
codes of, 813–816
committees, 818
conceptual approaches to, 812
consultants, 818
error disclosure, 371
formal oaths, 813–816
principles of, 812–813
Ethmoid sinus cancers
adenoid cystic, 1047, 1048*f*
carcinomas, 1041
clinical presentation, 1043
hematogenous dissemination, 1041
lymphatic spread, 1041
perineural extension, 1041
staging of, 1043
Ethnicity. *See* Race/ethnicity
Etoposide (MP-16)
ENB management using, 1198
for esophageal cancer, 1345
for spinal cord tumors, 952
for vulvar cancer, 1934
Etoposide (MP-16), 1934, 1978. *See also* BEACOPP regimen; BEP regimen; CDE regimen; OEPA regimen; ProMACE/MOPP regimen
for AML, 2016
for osteosarcoma, 2158
for rhabdomyosarcoma, 2137
for soft-tissue sarcomas, 2067
European Organisation for Radiation Therapy and Chemotherapy (EORTC), 1934
clinical trials, 375
EUS. *See* Endoscopic ultrasound (EUS)
Eustachian tube anatomy, 1001
Event, definition of, 359
Evidence-based medicine (EBM), 750–751
Ewing, James, 3, 76–78, 77*f*
Ewing sarcoma family of tumor (EWS), 2164–2173
cytogenetics of, 2164
diagnostic workup, 2164–2165
epidemiology, 2164
management, 2168–2169, 2168*t*, 2170*f*
chemotherapy, 2168
clinical trials, 2168*t*
fractionation, 2171

high-dose therapy with SCR, 2169
outcomes, 2173
radiotherapy, 2169–2172, 2169*t*
radiotherapy recommendations, 2169*t*
after relapse, 2172
sequelae of, 2172–2173
metastatic disease, 2169
pathology of, 2164
presentation, 2164
prognostic features, 2165
Excitation
of atoms, 171, 176
description of, 171, 172
Exenteration, 1929
Exit doses, photon beam dosimetry, 236, 236*f*
Experimental intracavitary brachytherapy radionuclides, 508–509
Exposure calibration factors (Nx), 189, 191
Exposures, definition of, 189
Extended field RT, 1756
Extensive intraductal carcinoma (EIC), 1410
External auditory canal, clinical presentation, 974
External-beam conformal radiation
3D-CRT and, 1440–1441
in breast cancer, 1440–1441, 1441*f*
External beam quality assurance, 61–62
External beam radiation therapy (EBRT), 597
for bladder cancer, 1649–1653
brachytherapy and, 1902
for breast cancer, 1430*f*
breast reirradiation, 671–672
for cervical cancer, 1778
for cholangiocarcinoma, 1559
complications of, 1562
dose escalation, 1534–1536
dose-volume histograms, 1430*f*
for endometrial cancer, 1846–1848
IORT combined with, 461, 468
for oral cavity cancer, 1104–1105, 1110
for oropharyngeal cancer, 1016–1018
ipsilateral treatment, 1134
for pancreatic cancer, 1532
for penile cancer, 1754–1755, 1755*f*
prospective trials, 1532–1534
for prostate cancer, 1681
prostate cancer, 1703, 1717–1718
in retroperitoneal sarcomas, 1945, 1945*t*
for thyroid cancer
dose and target guidelines, 1246*t*, 1247

indications, 1246, 1246*t*
management, 1246–1247
sequencing, 1247
for vaginal cancer, 1888–1891, 1896–1897
External ear
clinical presentation, 974
management, 976–977
External ear canal, management, 976–977
Extracellular matrix (ECM), 134, 134*f*
latent TGF-β, 109
mitogenic signals, 97
proteins, 106
tumor, 154–155
Extradural tumors, 946*f*
Extramedullary plasmacytomas
clinical presentation, 1202
diagnostic workup, 1202
epidemiology of, 1202
management, 1205
diagnostic workup, 1205
mucosal melanomas, 1205
RT, 1203–1206
sequelae of therapy, 1204–1205
surgical, 1203
therapy, result of, 1204
therapy, result of, 1205
heavy particles, 1205–1206
immunotherapy, 1205
Extranodal NK-/T-cell lymphoma, 2006
Extremities
rhabdomyosarcoma, 2134
Eye, 573–574, 573*f*
anatomy of, 959–960, 959*f*, 966*f*
orbital lymphomas, 1988
Eye and orbit diseases
age-related macular degeneration (AMD), 2246, 2246*f*
Graves ophthalmopathy, 2246–2248, 2247*f*, 2247*t*
Eye lens, TBI toxicity, 418
Eye malignancies
proton therapy, 489*f*
Eye shields
electron, 269*f*
Eyelids
radiation tolerance of, 960
sebaceous carcinoma of, 968–969

F

Feminism, 812
F-box/WD repeat-containing protein7 isoform 1 (FBXW7), 1849
FAC regimen
during pregnancy, 1424
Facial nerve (CN VII)
function impairment, 1074
grafting, 1087
invasion of, 1075
palsy, 1064
paralysis, 1087
paresis, 1077
Factor (*f*med), 190
Failure modes and effects analysis (FMEA), 297*t*
Fallopian tube cancer, 1861–1862
Fallopian tubes, anatomy, 1854–1855, 1854*f*
False cord, laryngeal cancer, 1162
Familial adenomatous polyposis (FAP), 2223
agressive fibromatosis and, 1947
colorectal cancer risk and, 1569
soft-tissue sarcomas and, 2054
Familial diffuse gastric carcinomas, 101
Familial medullary thyroid carcinomas (MTCs), 1238
Familial polyposis, 2222
Family history, cancer risk and, 1389
Fanconi anemia
HCC and, 2224
oral cavity cancer and, 1092
Farnesyltransferase inhibitors (FTIs), 106
Fast electron, 18*f*
Fat, dietary, 1667–1668
Fatigue, after RT, 1518–1519
Favorable disease, 602
Fecal incontinence, post-RT, 343
Fee-for-service system, 827
Fee-for-service–based system, 824, 832
Female reproductive system, 2351*t*
radiation side effect management
fistula, 2351
infertility, 2352
necrosis, 2351
ovarian failure, 2352
sexual interest/arousal disorder, 2351–2352
vaginal mucositis, 2351
vaginal stenosis, 2351
vaginal ulceration, 2351
Femoral neck fractures, 1818, 2292
Femur, metastatic bone disease, 2292*f*
Ferchuck, Sylvia, 84, 84f

Fetal doses, treatment planning and, 251–252, 252*t*
Few leaf-electron collimator (FLEC), 277
FFF therapy. *See* Flattening filter free (FFF) therapy
Fibroelastoma, papillary, 1361
Fibrohistocytoma, malignant, 1206
Fibromas, calcifications, 1364
Fibromatosis, retroperitoneal, 1947
Fibromyxosarcoma, cardiac, 1368
Fibronectin
  receptor for, 106
Fibrosarcomas, 2157
  pericardial, 1361–1362
Fibrosis, after hysterectomy, 1814
Fibrous dysplasia, 922–923
Fibrous histiocytoma, malignant, 2157
Fiducials
  gold seed markers, 1718
Field abutment, geometries of, 269, 269–270*f*
Field blocking, 1435*f*
Field junctions
  axillary, 1434–1437
  internal mammary, 1435–1437
  supraclavicular
    isocenter technique, 1435, 1436*f*
    tangential fields and, 1435–1437
  tangential fields and, 1435, 1436*f*, 1437*f*
  x-ray fields, 248–249, 248–250*f*
Field shaping, 243–245, 243–245*f*
Field sizes
  definition, 180, 235
  depth dose and, 257*f*
  dose/monitor units and, 263*f*
  linear accelerator, 181*f*
  monitor unit calculations, 232–233
  surface doses *vs.*, 235
Film dosimetry
  film emulsion and, 192
  radiochromic, 192
Financial toxicity, 832–833
Fine needle aspiration (FNA)
  EBUS-TBNA, 1253
  percutaneous, 1253
Fischer, James J., 86–87
Fistula, 2351
Fistulas
  radiation-induced injury, 1903
  rectal, post-RT, 343
5-Aminosalicylates, 2327

5-Fluorouracil (5-FU). *See also* CAF regimen; CMF regimen; ECF regimen; FAC regimen; FEC regimen; FOLFIRI regimen; FOLFOX regimen; TPF regimen
5-Fluorouracil (5-FU)
for anal cancer, 1601
for bladder cancer, 1642
for cervical cancer, 1791
for esophageal cancer, 1345–1348
for HNC SCC, 983, 989
for hypopharyngeal cancer, 1154
induction chemotherapy, 1154
for nasopharyngeal cancer, 1024
for oesophageal cancer, 1345–1346
postoperative, 1580
postoperative *vs.* preoperative, 1583
radiation therapy and, 986
topical, for vaginal intraepithelial neoplasia, 1880–1881, 1890–1891
for urethral cancer, 1752, 1753–1754
for vaginal cancer, 1880–1881, 1890–1891
vaginal intraepithelial neoplasia, 1880–1881
for vocal cord cancer, 1167
for vulvar cancer, 1934
5-Fluorouracil (5-FU)
radiation response and, 717
5-FU (5-Fluorouracil)
for esophageal cancer, 1345–1346, 1347–1348
for vocal cord cancer, 1167
5α-reductase, 1667
^{18}Fluorodeoxyglucose-PET (^{18}F-FDG-PET)
target delineation and, 691
^{18}Fluoromisonidazole positron emission tomography imaging, 760
Fixed fields, monitor unit calculations, 232–233
FLASH radiation therapy (FLASH-RT), 646–647
FLASH radiotherapy, 30, 155–156
FLASH therapy, 20, 55
Flattening filter free (FFF) therapy, 243. *See also* Rotational (arc) therapy
Flattening filters, linear accelerator, 180
Flavoxate (Urispas), 1818, 2329
Fletcher, G. H., 255
Fletcher, Gilbert H., 83
Fletcher-Suit applicator system, 1801
Flint, Austin, 375
Fludarabine
for CLL, 2025
TBI and, 407
Fluorescence, description of, 192
Fluoride carrier trays, 1111*f*
FNA (fine needle aspiration)

EBUS-TBNA, 1253
Foam dressings, 2329
Focal ablative therapies, prostate cancer, 1695–1696
FOLFIRI regimen
for colorectal cancer, 1574
components of, 1574
FOLFOX regimen
in colorectal cancer, 1572
components, 1572, 1574
Folkman, Judah, 13, 153
Follicle center lymphomas, 2007
Follicular carcinomas, thyroid, 1237
Follicular lymphomas
characteristics, 1983
clinical management, 1984–1987
clinical presentation, 1983
pathology, 1983
prognstic indexes, 1977*t*
radiation dose and field size, 1986–1987, 1986*f*
refractory, 1985–1986
relapsed, 1985–1986
stage I, 1984–1985, 1984*t*
stage II, 1984–1985, 1984*t*
stage III, 1985
stage IV, 1985
transformed, 1985–1986
Folliculotropic mycosis fungoides, 2004–2005
Follow-up care, 57
Fontaine sign, 935
Foramen lacerum, 693
Foramen ovale, 693
Foramen rotundum, 693
Forward planning approaches, 280, 284*t*, 288
Fossa of Rosenmüller, 1001
Fovea ethmoidalis, 1040
Fractionated radiation. *See also* Dose fractionation; Hyperfractionation
adjuvant, 1105
biologically equivalent doses, 991
brainstem toxicity, 326*t*
for breast cancer, 1429–1430
for cervical cancer, 1806–1807
chemoradiation therapy and, 720
fraction size, 320
HDR brachytherapy and, 1806–1807
for HNCs, 988
for nasopharyngeal cancer, 1014, 1021–1022
Fractionated stereotactic radiotherapy (FSRT), 878
definition of, 424

Fractures, pathologic
bone metastases and, 2293
femoral neck, 1818, 2292
hip, 1818
prediction scoring, 2292*t*
radiation-related, 1818, 2065, 2172
vertebral, 445
Frantz tumors, 2223
Free radicals, 118, 319
Frequency, definition of, 171
Frey syndrome, 1087
Fricke dosimetry, 190
Frontal sinuses, anatomy of, 1040
Functional subunits (FSUs), 120, 294–295
Functioning pituitary neuroendocrine tumors, 916–918
acromegaly, 916, 917*t*
Cushing disease, 916, 917*t*, 918
pituitary adenoma suppressive medications, temporary cessation of, 918
prolactinoma, 918
whole-sellar treatment, 918

G

G1/S transition, loss of pRB function and, 105
Gabapentin, 2291, 2317, 2318*t*
Gadolinium chelates, 689
Gag reflex, 693
Galactorrhea, after RT, 1033
Gallbladder adenocarcinoma. *See also* Biliary tract cancers
incidence, 1562
presentation, 1562
risk factors, 1562
Gallbladder cancer, 1563
adjuvant RT, 1563
Gamma decay, 173
Gamma Knife radiosurgery, 967
Gamma knife units
components, 178
description, 178, 178*f*
radiosurgery, 1621
radiosurgery, 425
Ganglioglioma
pediatric, 2086
spinal canal, 2083
Ganglioneuromas
adrenal cancer and, 1951
mediastinal, 1298
Gardner-Robertson hearing grade, 327

Gardner syndrome, 2054, 2222
Gastrectomy
  late effects of RT, 1519*t*
  risk of malignancies and, 1491
Gastric cancer. *See also* Stomach cancer
  adenocarcinomas, 1491
  chemoradiation therapy, 1514–1515
  chemotherapy
    adjuvant, 1516–1517
    perioperative, 1517–1518
    preoperative, 1515–1516
  diagnosis, 1495*t*
  epidemiology, 1489–1492
  intraoperative radiotherapy, 465–466
  lymphatic spread, 1503*f*
  lymphatic spread, 701–702
  pathology, 1495–1497
  patterns of failure, 1493*f*
  positive margins, 1499
  prognostic factors, 1497
  radiation therapy
    adjuvant, 1512–1513, 1513*t*
    dose constraints, 1511
    fields, 1505*f*, 1510*f*
    indications for, 1501
    intraoperative, 1513–1514
    lymph node coverage, 1503*f*, 1507*t*
    neoadjuvant, 1513
    nodal stations, 1506*f*
    palliative, 1518
    sequelae of, 1518–1519
    stage and, 1435*t*, 1508*t*
    techniques, 1502–1512
  resectable, outcomes, 1512
  staging, 1494–1495, 1495–1496*t*
  surgical management, 1497–1500
    palliative, 1501
    patterns of failure, 1499*t*, 1500–1501
    subtotally resected, outcomes, 1512
  survival rates and, 1497
  treatment planning, 1494
  unresectable
    clinical trials, 1512*t*
    outcomes, 1512
  worldwide incidence, 755*f*
  worldwide mortality rates, 753
Gastric ulcers, cancer and, 1490
Gastritis/duodenitis, 2344

Gastroesophageal reflux disease (GERD), 1319
Gastrointestinal cancer
  intraoperative radiotherapy, 465–466
  lymphomas, 1989
  pediatric, 2221–2225
Gastrostomy tubes, 1178
Gefitinib (Iressa)
  for NSCLC, 1262, 1268
Gel dosimetry, 193
Gemcitabine, 1868
  for bladder cancer, 1638
  for lung cancer, 1268
  for pancreatic cancer, 1532–1534
  radiation response and, 717–718
  for salivary gland cancer, 1086
Gender, 846–847
  cancer care, disparities in, 846
  definition, 846
  sexual and gender minorities, cancer disparities in, 846–847
Gene amplification, 1073
Gene expression
  profiling, 1401, 1402*f*
  RT-induced, 109
General adversarial networks, 58*b*
Generalized linear-quadratic model (LQM), 461–462
Genetically significant doses (GSDs), 252
Genetics, ethical issues, 817–818
Genistein, protective action, 1668
Genitourinary diaphragm (GUD), 1665
Genitourinary malignancies. *See Specific malignancies*
Genitourinary tract injury, 2329–2330
Genitourinary tract, RT-induced injury, 2329–2330
Genomic instability, mutation and, 99, 109
Genomic Prostate Score (GPS), 1677
Geographic overdosage. *See* Hot spots
GERD (gastroesophageal reflux disease), 1319
Germ cell neoplasia in situ (GCNIS), 1731, 1732*t*
Germ cell tumors (GTCs)
  extragonadal, 1947
  management of, 1871–1872
  mediastinal
    diagnosis, 1295
    epidemiology of, 1294
    management, 1295–1296
    natural history, 1294
    presentation, 1294–1295
    prognostic factors, 1295
    seminomatoustumors, 1295

nongerminomatous, 2092
nonseminomatous, 1295–1296, 1947
ovarian, 1861
markers, 1871*t*
pediatric, 2091–2092, 2228–2229
clinical markers, 2229*t*
presentation, 2228
treatment, 2228–2229
retroperitoneal lesions, 1948*t*
seminomatous, 1947
testicular, 1732, 1732*t*
Germinomas, pediatric, 2092, 2093–2094*f*
Glasscock-Jackson classification, 1184
Glassy-cell carcinomas, 1771
Glatstein, Eli, 2, 2*f*
Gleason scores, 703
Glioblastoma (GBM)
imaging of, 694
Glioblastoma, 663, 882–885, 882*t*
MRI of, 669*f*
Glioblastoma multiformae (GBM)
pediatric, 2080
recurrent, 154
spinal cord, 952
Glioma
brainstem, 326
grade II, 952
high-grade, 434–435
low-grade
pediatric, 2072
Gliomatosis cerebri, 894
Glioneuromas, mediastinal, 1298
Global radiation oncology, 753–765
cancer
burden of, 753
epidemiology, 753–756, 754–756*f*
definition, 753
in low- and middle-income countries
economics, 760–761
quality, 758–760
Globe, perforated, 1087
Globus pallidus, radiosurgery, 429
Glomus bodies, 1181
Glomus jugulare
anatomy, 1181*f*
tumor, 1183*f*
Glomus tumors, 432
Glossectomy, 1104, 1107*f*

partial, 1115
total, 1116
Glossopharyngeal nerve (CN IX), 1001
Glottic larynx cancer, 1163
radiation therapy, 1169*f*, 1173–1174*t*
treatment outcomes, 1174–1175*t*
Glottis, verrucous carcinoma of, 1166
Glucose-6-phosphatase deficiency, 2224
Glutamine, for GI mucositis, 2328
Glutathione, ionizing radiation therapy, 116
Glycogen storage diseases, 1545
GOG 88 protocol, 1929
Gold-198
implants, 1899
Gold nanoparticles, 162–163
Goldblatt kidney, 342
Gonadal doses, treatment planning and, 252
Gonadal dysfunction, after RT, 2031, 2140
Good clinical practice (GCP), 376
Gorham syndrome, 2230, 2231*f*
Gorlin-Goltz syndrome, 2231
Gradient-recalled echo (GRE) pulse sequences, 689
Graft versus host disease (GVHD)
acute, 406
allo-SCT limitation, 406
chronic, 406
kidney complications, 419
lung injury, 418
squamous cell cancers, 419
Graft-*versus*-tumor effect, 405, 409
Graham Bell, Alexander, 43–44, 43*f*
Granulocyte colony-stimulating factor (G-CSF), 405
Granulocytic sarcoma. *See* Chloromas
Granulomatous slack skin (GSS), 2004–2005
Granulosa cell tumors
adult, 1872
juvenile, 1872
Graves ophthalmopathy, 2246–2248, 2247*f*, 2247*t*, 2248*t*
Graves orbitopathy. *See* Graves ophthalmopathy
Grays (Gy), 190
Great vessel tumors, 1361–1370
GRID therapy, 54–55, 455
Grievances, 69–70
Gross tumor volume (GTV), 30, 286*f*. *See also* Treatment planning
auditory canal tumor, 978, 980*f*
bladder cancer, 1652
cervical cancer, 1804*f*
cholangiocarcinomas, 1561

definition of, 282, 282*f*, 2138
delineation of, 285–288
esophageal cancer, 1330
gastric cancer, 1502
lung cancer, 1264–1265
middle ear cancer, 978, 979–980*f*
nasal fossa tumor, 1049*t*
nasopharyngeal cancer, 1013, 1014
oropharyngeal cancer, 1133
retroperitoneal sarcoma, 1943
soft-tissue sarcomas, 2061
spinal canal tumor, 953
for three-dimensional RT, 1896–1897
Grounded theory, 773
Growth factors, 9
cell death from withdrawal, 102
mitogenic signals from, 97
molecular mechanisms, 97
vasculature and, 99
withdrawal of, 102
Growth hormone
deficiency, 418
Growth suppressors, 97–98
GTCs. *See* Germ cell tumors (GTCs)
GTV. *See* Gross tumor volume (GTV)
Gynecologic cancers. *See also Specific cancers*
intraoperative radiotherapy, 466
radiation therapy, 344
rhabdomyosarcoma, 2134
Gynecomastia, 1734, 2003

H

Hair, depigmentation of. *See* Alopecia
Half-lives (T1/2), radionucleotide, 173
Half-value layers (HVLs), 174
Halofuginone, 154
Hamartomas, hypothalamic, 429
Hard palate
anatomy of, 1094–1095
subsite-specific treatment, 1116–1117
tumors of, 1116–1117
Harm, definition of, 359
Harrison-Anderson-Mick applicators, 1944
Hartwell, Lee, 8–9
HCC. *See* Hepatocellular cancer (HCC)
HDR. *See* Brachytherapy, high-dose rate
HDR-IORT. *See* High-dose-rate brachytherapy IORT (HDR-IORT)

Head and neck
lymphatic drainage, 1216*f*
Head and neck, 564–568, 565–567*f*
benign diseases, 2239–2240
lymphatic drainage, 695–696
oncologic anatomy, 695
reirradiation, 668*t*
Head and neck cancers (HNCs)
advanced
combined-modality therapies, 995–996
human papillomavirus-positive disease, de-escalation in, 995–996
immunotherapy, 996–997
postoperative irradiation, 989–990
treatment selection, 990–995
imaging, 696–697, 697*f*
intraoperative radiotherapy, 467
late effects of RT, 327–329
mucosal sites, 1145*f*, 1230*f*, 1231*f*
palliation of, 2302–2303
paraganglioma distribution, 1182*f*
pediatric, 2219–2220
PET/CT scans, 1101
proton therapy, 307–308
radiation response, 677–678
radiation therapy
anatomical landmarks, 1151–1152
complications, 1155–1156
hearing preservation in, 327*t*
reirradiation
clinical data on, 667
median overall survival, 671, 671*f*
postoperative regimen, 670
rhabdomyosarcoma, 2132, 2133*f*
sarcomas
chemotherapy, 1210–1211
clinical presentation, 1206–1207
diagnostic workup, 1206–1207
natural history, 1206
prognostic factors, 1207
radiation therapy, 1207–1209
surgical management, 1207
treatment results, 1210*t*
tumor characteristics, 1210
squamous cell carcinomas
chemoradiotherapy, 985–988
locally advanced, 983–997
Headaches, after RT, 418
Health economics and policy

gross domestic product percentage, 822*f*
health care costs, 822
ideal, 823
value
components, 824*f*
definition, 823
equation, 824–831
Health Insurance Portability and Accountability Act (HIPAA), 70, 817
Health-related quality of life (HRQoL), 1818
Health services research, 834, 839
Hearing loss
cisplatin and, 1744
cisplatin and, 2140
after RT, 1033, 1087
Hearing, preservation of, 327–329
Heart. *See also* Cardiac entries
blocks, 1430*f*
calcifications, 1363
dose-volume limits, 338
late effect of radiation, 337
radiation-induced injuries, 1367
breast cancer patients, 1445
esophageal cancer and, 1355
RT dosage constraints, 1291*t*
tumors, benign, 1366
tumors, malignant, 1361–1370, 1364*t*
classification, 1364, 1365*t*
diagnosis, 1362*t*, 1363–1364
epidemiology, 1361–1362
incidence, 1361–1362
management, 1365–1366
metastatic, 1361*t*, 1366
natural history, 1362–1363
outcomes, 1368–1370
presentation, 1362*t*
prognostic factors, 1364
staging, 1364
Heart disease
cisplatin and, 1744
RT-related, 1970, 2072
Heart, oncologic anatomy, 699
Heavy charged particles, 878–879
Heavy-ion radiation therapy, 176, 185–186
Heavy ions, 185
Heavy particle beams, 53
chordoma therapy, 1194
non-small cell lung cancer, 1194
Hedgehog pathway signaling, 155

Helicobacter bilis, 1562
Helicobacter pylori, 753, 1489, 1974
Heller, Jean, 815
Helsinki, Declaration of, 375
Hemangioblastoma, 432–433, 905
  spinal cord, 950
Hemangioendotheliomas, 1298
  mediastinal, 1297*f*, 1298
Hemangiomas, 2249
  cardiac, 1361
  imaging of, 703
  pediatric, 2229–2230
Hemangiopericytoma, 905
Hemangiopericytomas, 1298
Hematologic syndrome, 156
Hematopoietic stem cell transplantation (HSCT), 405
  engraftment, 409
  for Hodgkin lymphoma, 1968
  RT and, 1969–1970
Hematopoietic system, normal, 409
Hematuria
  bladder cancer and, 1640
  radiation-related, 1817
  renal cell carcinoma and, 1612
Hemibody irradiation (HBI)
  application, 419
  complications, 420
  pain management using, 2298
  technique, 419–420
Hemoglobin
  modified structure of, 677
  prognostic value of, 1886
Hemorrhage, after hysterectomy, 1814
Hemorrhagic cystitis, 344
Hepatic cirrhosis, 1551
Hepatic veno-occlusive disease. *See* Sinusoidal obstructive syndrome (SOS)
Hepatitis B, 1543, 2224
Hepatitis C, 1543, 1611
Hepatitis, radiation-induced, 1625–1626
Hepatobiliary tumors, 2223–2225
Hepatoblastomas, 2224*f*, 2224*t*
Hepatocellular cancer (HCC), 1542–1556
  aflatoxin and, 753
  anatomy, 1541–1542
  BCLC staging system for, 1550*t*
  clinical presentation, 1541–1542
  diagnosis, 1557
  epidemiology, 1541

hepatitis B and, 1543
imaging of, 703
inoperable, 442–443
management
SBRT, 442–443
management
acute and late complications, 1553
chemotherapy, 1555
conventional radiotherapy, 1551
liver transplantation, 1548
percutaneous ablation, 1548
planning and prescription, 1553
radiotherapy, 1551, 1551*t*
surgical resection, 1550
TACE with RT, 1551–1552, 1554*t*
treatment volumes, 1551–1552
tumor contouring, 1552
pediatric patients, 2223–2225
prevention, 1546–1547
risk factors, 1543
staging, 1548
surveillance, 1546–1547
worldwide incidence of, 753
Hepatolithiasis, 1557
HER2/neu mutations, 1411
HER2/*neu* protein, 1073
HER2/neu proto-oncogene
assays for, 1396
breast cancer and, 1376
Herbicides, 2054
Hereditary nonpolyposis colorectal cancer (HNPCC)
colorectal cancer risk and, 1569
endometrial cancer and, 1829
mismatch repair genes in, 101
ovarian cancer and, 1765
Hereditary papillary renal cancer (HPRC), 1611–1622
Heregulin-α, 1373
Herpes zoster, 1969
Hertz (Hz), 171
Heterotopic ossification, 2253–2254, 2254*f*
Hierarchy of interventions, 363*t*, 367
High dose rate (HDR) brachytherapy, 44
advantages, 581–582
applicators, 583–584, 584*f*
breast cancer, 606–608
clinical indications, 606, 606*t*
follow-up, 608
outcomes, 607, 607*t*

technique, 607
treatment planning, 607, 608*t*
cervical cancer, 597–599
clinical indications, 597–598, 598*t*
follow-up, 599
outcomes, 598
technique, 598–599
treatment planning, 599, 599*t*, 599*f*
disadvantages, 582
disease sites commonly treated with
breast brachytherapy, 595
cervical cancer brachytherapy, 594
prostate brachytherapy, 594–595
dosimetry and treatment planning
differences between low- and high-dose rate brachytherapy treatment planning, 589
evaluation of dose distributions, 592
optimization, 589–592, 592*f*, 593*f*
quality control of treatment plan, 593
time course of procedures, 589
endometrial cancer, 599–601
adjuvant vaginal cuff brachytherapy, 599–600, 600*t*
inoperable endometrial carcinoma, 601
vaginal cuff recurrences, 600–601, 601*f*
facility design, 586
fractionation, 582
operation
emergency procedures, 585–586
normal procedures, 585
personnel roles, 584–585
other cancers, 609–610
practical aspects of, 610–612
prostate cancer, 601–606
clinical indications, 601–602, 602*t*
follow-up, 605, 606*f*
outcomes, 602–605, 603–604*t*
technique, 605
treatment planning, 605, 605*t*
quality management program, 610–612
rectal cancer, 608
clinical indications, 608
follow-up, 608
technique, 608
treatment planning, 608
remote afterloaders, 582–583, 583*f*
remote afterloading unit, quality assurance of
checks after treatment, 589
checks preceding treatment, 588–589
daily quality assurance checks, 586–588, 587*f*

initial checks, 588
skin cancer, 608
clinical indications, 608–609
follow-up, 609
technique, 609
treatment planning, 609, 609*f*
sources, 583
High-dose-rate brachytherapy IORT (HDR-IORT), 461, 463. *See also* Brachytherapy, HDR
High-dose rate brachytherapy, sources for, 512*f*, 512–513, 512*t*
High-risk clinical target volume (HR-CTV), 599
High-Z elements, 163
Hinge angles, 239
Hip fractures, radiation-related, 1818
Hippocratic oath, 813*f*
Hiroshima, salivary gland cancers and, 1062
Histones, H2AX, 117
HMB-45 protein, 1891
HMLH mutations, 1829
HNCs. *See* Head and neck cancers (HNCs)
HNPCC syndrome, 1569
Hoarseness, oral cavity cancer and, 1100
Hodgkin lymphoma (HL), 1956–1970
cardiac mortality after RT, 337*f*, 338
classic, 1958
prognosis, 1959
classification, 1958–1959
diagnosis, 1957–1959, 1957*t*
epidemiology, 1956
imaging of, 708, 709*f*
lymphocyte-depleted classic, 1958
lymphocyte-rich classic, 1958
management
complications of, 2183–2185
radiation therapy, 2181–2185
management
breast cancer after RT, 1425
combined modality, 1960
CT, 1959
follow-up, 1969
infradiaphragmatic involvement, 1966
organs at risk, 1964–1965
proton beam therapy, 1964
RT techniques, 1960–1965
sequelae of, 1969–1970
mixed-cellularity classic, 1958
natural history, 1956–1957
nodular lymphocytic predominant, 1958–1959
nodular sclerosis classical, 1958

pediatric, 2176–2188
classification, 2176–2177
diagnosis, 2177–2178
epidemiology of, 2176
presentation, 2176
prognostic factors, 2178–2179
radiation therapy, 2181–2185
staging, 2178
presentation, 1956–1957
prognosis, 1965–1966, 1967*t*
prognostic factors, 1959, 1959*t*
relapsed, 1969
relapsed, 2188
risk factors, 1956
staging, 1957*t*, 1958*f*, 1958*t*
VMAT/IMRT and proton plans, 487*f*
Holliday junctions, 104
Holthusen, Herman, 23, 24–26*f*
Holznecht Radiometer, 18, 18*f*
Homogeneity coefficients, 188
Homologous recombination (HR), 103*f*, 104
Hormonal therapy
sequencing with RT, 1420–1421
Hormone
abnormalities after RT, 2220
Hormone receptor
for breast cancer, 1460–1461
Hormone replacement therapy (HRT), 2329
breast cancer risk and, 1389
after cervical cancer treatment, 1819
estrogen-only, endometrial cancer and, 1828
Hormone therapy
during pregnancy, 1424
prostate cancer, 344
Horner syndrome, 1252, 1263, 1263*f*
Hot spots, 271*f*, 282
Hounsfield unit (HU), 688
HOXB13, 1668
HSP. *See* Heat shock proteins (HSPs)
Human chorionic gonadotropin (HGC), 1732, 1734, 1862
Human glandular kallikrein 2, 1712
Human immunodeficiency virus (HIV)
anal cancer and, 1596
Hodgkin lymphoma and, 2177
NHL and, 1974
soft-tissue sarcomas and, 2054
vaginal intraepithelial neoplasia and, 1886
Human papillomavirus (HPV), 753

anal cancer and, 1596
cervical cancer, 100, 108–109
cervical cancer and, 1764–1765
prognosis, 1772–1773
E7 oncoprotein, 109
genome, 109
head and neck cancers and, 1144
infection status, 110
nasopharyngeal cancer, 1014
oral cavity cancer and, 1092, 1117
oropharyngeal cancer and, 1123–1124, 1135–1137
penile cancer and, 1747, 1751
transmission of, 1764
vaccination against, 1765
vaginal cancer and, , 1879–1882
vaginal intraepithelial neoplasia and, , 1879–1882
vulvar intraepithelial neoplasia and, 1923
Human T-cell lymphotropic virus type 1, 1974
Hunt, Tim, 9
Hunter–Driffield (H-D) curve, 192
Hürthle cell (Oncocytic) carcinoma, 1237
Hürthle cell carcinoma, 1243
Hutchinson melanotic freckle. *See* Lentigo malignamelamonas
Hydronephros
intravenous pyelograms for, 1767
palliative treatment, 2307
presentation, 2307
Hydroxyurea, for cervical cancer, 1787
Hyperbaric oxygen (HBO)
trials of, 677
toxicities related to, 1819
Hyperbaric oxygen/tourniquet techniques, 20
Hypercalcemia, 1252
Hyperfractionation. *See also* Fractionated radiation
brainstem toxicity, 326*t*
chemoradiation therapy and, 720
clinical trials, 1787
effects of, 130–131
oropharyngeal cancer, 1130–1131
for recurrent rectal cancer, 2307
Hyperreninemic hypertension, 342
Hypertension
benign, risk of, 342
cisplatin and, 1744
endometrial cancer and, 1828
malignant, 342
post-RT, 342
Hyperthermia (HT), 20

biology of, 656–659
blood flow manipulation, 658
cell survival, effects of, 656, 657*f*
chemotherapy, 658
definition of, 656
heat shock response, immunologic implications of, 657
hyperthermic cytotoxicity, mechanisms of, 656
key biologic effects of, 659*f*
physiologic approaches to enhance thermal cytotoxicity: pH modification, 658
physiology, 657–658
radiation, 658
thermal isoeffect dose: the arrhenius relationship, 656
thermotolerance/clinical trial design, 656–657
clinical studies, 661–664, 662*f*
chemotherapy and hyperthermia: key randomized trials, 663–664
notable studies, 664
radiation and hyperthermia: key randomized trials, 661–663
physics and application, 659–661, 659*f*
capacitive electromagnetic heating, 660
conductive heating, 660–661
hyperthermia treatment planning, 661
local/locoregional hyperthermia approaches, 659–660
monitoring temperature/thermal dose, 661
radiative electromagnetic heating, 660
summary of, 661
ultrasound heating, 660
radiation response, 156, 679–680
for recurrent cervical cancer, 1814
regional, 2067
for soft-tissue sarcomas, 2067
Hyperthermia treatment planning (HTP), 651
Hypertrophic osteoarthropathy (HPO), 1252
Hypertrophic scars, 2252–2253
Hypoadrenalism, 1033
Hypoesthesia, 1100
Hypofractionated radiation therapy, 645
Hypofractionated stereotactic radiotherapy (HFSRT)
brainstem toxicity, 326
hearing loss after, 327
for vestibular schwannomas, 329
Hypofractionation, 130. *See also* Fractionated radiation; Hyperfractionation
for cervical cancer, 760
effects of, 130
for lung cancer, 760
relative, 130
stereotactic radiotherapy, 428*t*
whole breast irradiation, 1416–1417
Hypogastric chain, 704

Hypohydrosis, after TSEBT, 2003
Hypopharyngeal cancer
  advanced, 1154*t*
  classification, 1149
  clinical presentation, 1146–1149
  complications
    radiation therapy, 1156
    surgery, 1155–1156
  epidemiology, 1144–1145
  etiology, 1144–1145
  follow-up, 1156
  patterns of spread, 1146, 1147*f*
  prognostic factors, 1145
  quality of life, 1157
  recurrence, 1156–1157
  staging, 1146, 1146*t*, 1147*f*, 1148*t*
  treatment
    curative radiation therapy, 1151
    definitive radiation therapy, 1151–1154
    induction chemotherapy and sequential (chemo)radiation, 1154–1155
    palliative chemotherapy, 1155
    palliative radiotherapy, 1155
    palliative surgery, 1151
    postoperative radiation therapy, 1151
    postradiotherapy neck dissection, 1155
    primary surgery, 1149–1151
    surgical management, 1149, 1149*t*
Hypopharynx, 1143–1157
  anatomy of, 696, 1143–1144, 1143*f*, 1144*f*
Hypophysis cerebri. *See* Pituitary gland
Hypopituitarism, 918, 2140, 2357
Hypothalamic glioma, 2081
Hypothalamic–pituitary dysfunction, 1033
Hypothyroidism, 2358
  after RT, 1033
  after RT, 2184
  subclinical, 1969
Hypoxia, 20–21
  diffusion-limited, 49
  key determinants, of, 135–137
  microenvironment normalization alleviates, of, 137–144
  perfusion-limited, 49
  permanent, 49
  production of, 319
  radiation response and, 677
  tissue injury and, 319
  transient, 49
  tumor microenvironment and, 153

Hypoxia-inducible factors (HIFs)
heterodimer formation, 319
production of, 319
Hypoxic cells
pharmacologic targeting of, 678
sensitization of, 678
sensitizers, 153, 719
Hypoxic tumors, and cytotoxins and, 153
Hysterectomy
abdominal radical, 1776
cervical stump carcinoma, 1796–1797
for endometrial cancer, 1838
laparoscopic vaginal, 1838
radical, 1775–1776
margin status after, 1773–1774
during pregnancy, 1798–1799
side effects of, 1814
simple, 1788
total, 1776
total abdominal, 1838
types of, 1775–1776, 1776*t*
vaginal cancer prognosis and, 1886
Hysteroscopy, 1829
HyTEC (high dose per fraction, hypofractionated treatment effects in the clinic), 350
HyTEC review, 318IFN-α, 2008

I

Ifosfamide, 1991. *See also* IPA regimen; VAIA regimen
for osteosarcoma, 2158
radiation response and, 2171
for rhabdomyosarcoma, 2138
for soft-tissue sarcomas, 2067
IGRT. *See* Image-guided radiation therapy (IGRT)
Iliac lymph nodes, 1763*f*
Image guidance radiation therapy (IGRT), 57
Image-guided IMRT, prostate cancer, 1718
Image-guided intracavitary brachytherapy, 540–541
Image-guided radiation therapy (IGRT), 178, 442
for cervical cancer, 1781
chemoradiation therapy and, 720
concepts of, 280
linacs, 179
for soft-tissue sarcomas, 2065
stereotactic, 425
Image-segmentation software, 285*f*
Imaging
modalities of, 688–692

oncologic, 688–692
planning of, 284–285
Imaging biomarkers,146
Imatinib, 2024
Imiquimod cream, 1881
Immobilization
conformal radiation therapy, 284*f*, 284–285, 284*t*
importance of, 2138
mechanical, 32–33, 32–33*t*
pediatric patients, 2073
quality assurance, 297–298
treatment planning, 246–247, 247*f*
Immobilization devices
body conformal, 204–208
prone positioning for pelvic and breast treatments, 208–209
space considerations, 209
dosimetric effects of, 209
head and neck
bite blocks as an alternative to masks, 204
thermoplastic masks, 201–204
stereotactic
extracranial immobilization devices, 211–212
immobilization and internal motion management, 212
intracranial immobilization devices, 210–211
Immune checkpoints, 106
Immune deficiency, 1991–1992
Immune disorders, 1974
Immune responses. *See also* Radioimmunology
radiation therapy and, 440
Immune surveillance, 635, 636
Immuno-oncology, 635–640
current directions in, 639–640
escaping immune surveillance, mechanisms of, 636
decreased tumor immunogenicity, 636
exclusion of immune cells, 636
metabolic immune suppression, 636
poor priming of T-cell responses, 636
upregulation of immune-suppressive cells and molecules, 636
immune recognition of tumors, 635–636
modern immunotherapy approaches, 636–639
antibody therapies, 638
cellular therapies, 637
cytokine immunotherapy, 639
immune-modulating antibodies (checkpoint inhibitors), 638–639
innate immunotherapy, 639
vaccines, 637–638
Immunohistochemical (IHC), 1645
Immunosuppression

soft-tissue sarcomas and, 2054
stem cell transplantation and, 406
TBI, 409
Immunotherapy (IT), 139–141
areas of failure and cause of death, 1556
hepatocellular cancer, 1555–1556
radiation, 399, 399*f*
Immunotherapy-Induced Vascular Normalization, 141–144
IMN. *See* Internal mammary nodes (IMN)
Implantable cardioverter-defibrillators (ICD), 251
Implantable neuroaxial drug delivery devices, 2318
In-breast tumor recurrence (IBTR), 670–672, 1372, 1379
Incident learning systems (ILS), 370
Incident reporting, 297*t*
Inclusion criteria, clinical trials, 386
Incontinence
after cytoxan, 344
gross fecal, 1597
radiation-related, 1816
Indigenous populations, in high-income countries, 762
Indocyanine green (ICG) retention, 1550, 1552
Induction chemotherapy, 1132
Induratio penis plastic. *See* Peyronie disease (PYD)
Inelastic interactions, 176
Infants. *See also* Pediatric patients
medulloblastoma in, 2087–2089
Infections, after HL treatment, 1969
Infertility, 2184, 2352, 2353. *See also* Azoospermia, after RT; Erectile dysfunction (ED)
Infiltrating lobular carcinoma, 1411, 1411*t*
Inflammation, 119–120, 643
bladder cancer and, 1639
radiation responses, 319, 2238
Inflammatory bowel disease (IBD)
radiation-related, 1816
risk of cancer and, 1556–1557
Informed consent, 71–72, 71*t*
for radiation therapy, 2239
Infrahyoid epiglottis, 1162
Inguinal lymph nodes
evaluation, 1753
involvement of, 1922, 1922*f*
whole-pelvis RT field, 1916*f*
Inguinofemoral lymph nodes, 1929
Inherent radiosensitivity, 21
Inherited cancer syndromes, 101
Inhibin, total, 1862
Inner ear, anatomy of, 973, 973*f*, 974*f*
Institute of Medicine (IOM), 819

Insular carcinoma, thyroid, 1237
Insurance companies. *See* Centers for Medicare and Medicaid Services (CMS)
Insurance disputes, 69–70
Integrated boost technique, 289
Integrated multimodality cancer management and organ preservation, 63–64
Integrins
  signaling mediated by, 106
  tumor vascular morphology and, 154
Integumentary system, 2355*t*
  radiation side effect management
    breast fibrosis/contracture, 2356
    mastalgia, 2356
    post-breast surgery pain syndrome, 2356
    radiation dermatitis, 2354–2356
Intensity-modulated arc therapy (IMAT)
  rotational therapy and, 234
Intensity-modulated proton therapy (IMPT), 51–52, 1695
Intensity-modulated radiation therapy (IMRT), 51–52, 1847–1848, 1933, 1934*f*, 2106
  beam energies, pelvic, 1786–1787
  for breast cancer, 1437–1439
  for cervical cancer, 1781–1784
  chemoradiation therapy and, 720
  craniospinal irradiation, 2073
  with CT image guidance, 1915, 1918*f*
  dose-volume histograms, 1964
  on dysphagia, 1134
  extended-field, 1785*f*, 1847
  for endometrial cancer, 1847–1848, 1847*f*
    complications, 1848, 1849
  for gastric cancer, 1511
  for Hodgkin lymphoma, 1964
  head and neck, 1105–1106
  inverse planning approach, 280, 281*f*
  LINAC, 425
  multileaf collimation systems, 181
  for nasal cavity tumors, 1047
  nasopharyngeal cancer, 1016–1018, 1018*t*, 1020–1021*f*, 1022*t*
  for oropharyngeal cancer, 1134–1135
  for ovarian cancer, 1870
  for paranasal sinus tumors, 1049
  pediatric patients, 2073
  pelvic fields, 1933, 1934*f*
  phase III clinical trial, 397
  prostate cancer, 1681, 1711, 1718–1719, 1720*f*
  for soft-tissue sarcomas, 2065
  sliding window, 181
  step-and-shoot, 181
  stereotactic (SIMRT), 424

for thyroid cancer, 1247
for urethral cancer, 1915
for vaginal cancer, 1897
vulvar cancer, 1933
of xerostomia, 1134
Intentional tort, 67
Intergroup Rhabdomyosarcoma Studies (IRS), 2135–2137, 2136*f*
Interleukin 1 (IL-1), 109
Intermediate-risk CTV (IR-CTV), 599
Intermittent HDR brachytherapy, 44
Internal conversion, 173
Internal jugular chain (IJC) nodes, 1216
Internal mammary nodes (IMN), 1455
electron therapy, 249*f*, 277, 277*f*
irradiation of, 1418–1419, 1433–1434, 1434*f*, 1435*f*
radiation fields
tangential, 1347*f*, 1436*f*, 1437, 1438*f*
Internal margins, 283
Internal target volumes (ITVs)
definitions of, 283
International Atomic Energy Agency (IAEA), 758–761, 763, 765
International Commission on Radiation Units and Measurements (ICRU)
report definition, 282–283, 282*f*
volume nomenclature, 283, 283*t*
International Committee of Medical Journal Editors (ICMJE), 385
International Society of Pediatric Oncology (SIOP), 2108
International System of Units (SI units), 173, 189*t*
Intersectionality, 849–850
Interstitial brachytherapy, 29, 44, 524–535
classic implant systems for temporary implants, 524–530, 525*f*, 526–527*t*, 528*f*, 529*t*, 530*f*
dose specification in interstitial brachytherapy, 533–535, 535*f*
modern approaches for temporary implantation, 530–532
permanent implantation, 532–533, 532*f*
Interstitial fluid pressure (IFP), outcomes and, 154
Interstitial pneumonitis, 418
Intracavitary brachytherapy, 29, 44, 535–541
dose specification in, 536–540, 537–539*f*, 540*t*
image-guided intracavitary brachytherapy, 540–541
intracavitary brachytherapy, dose specification in, 536–540, 537–539*f*, 540*t*
intracavitary therapy systems, manchester family of, 535–536, 536*f*
Intracavitary therapy systems, manchester family of, 535–536, 536*f*
Intracavitary treatment systems. *See also* Brachytherapy
electron beam, 272
Intracranial malignancies. *See also* Brain tumors; Central nervous system (CNS) tumors
Intracranial stereotactic radiosurgery, 215
Intracranial tumors, benign, 429
Intraluminal radiotherapy, 1559
Intramedullary spinal cord metastasis (ISCM), 2285

Intraocular lymphoma, 968
Intraoperative dose distributions, 273*f*
Intraoperative electron radiation therapy (IOERT)
  case study, 467–468
  description of, 461
  normal tissue tolerances, 467
  physics of, 462–463
  technical applications, 462–463
Intraoperative radiotherapy (IORT), 223, 461–468
  brachytherapy, 1944
  for cervical cancer recurrences, 1814
  dose escalation, 1534
  electronic brachytherapy, 463–464
  evidence by disease site, 464–467
  for gastric cancer, 1513–1514
  and global health, 468
  history of, 461
  for ovarian cancer, 1870
  for pancreatic cancer, 1532, 1534
  for rectal cancer, 1588
  intraoperative electron radiation, 462–463, 463*f*
  and novel therapies, 468
  radiobiologic rationale, 461–462
  single fraction doses, 468
Intraoral cone, 1105, 1110, 1111*f*, 1113
Intraperitoneal chemotherapy, 1867
Intratubular germ cell neoplasia, 1732, 1732*t*
Intravenous pyelograms (IVP), 1767, 1884
Invasion-metastasis cascade, 11
Invasive ductal carcinomas, breast, 1398
Invasive micropapillary carcinomas, 1398
Inverse planning
  IMRT and, 1511
  conformal radiation therapy, 284*t*, 288
  conformal therapy and, 280
Inversion recovery (IR) pulse sequences, 689
Involved-node/involved site radiotherapy (INRT), 1960–1961
Iodine-131
  adverse effects of treatment, 1246, 1246*t*
  biological half-times, 1244*t*
  dosimetry systems, 1244*t*
  goals, 1244
  outpatient management, 1246
  patient preparation for, 1243*t*, 1245, 1245–1246*t*
  radioactive decay of, 1244
  sequencing, 1247
Iodine, thyroid hormone and, 1236
IOERT. *See* Intraoperative electron radiation therapy (IOERT)

Ionization
of atoms, 171, 176
chambers
free-air, 189, 190*f*
thimble chambers, 189
kinetic energy and, 176
Ionizing radiation (IR)
cellular effects of, 101, 101*f*
reactive oxygen species (ROS), 116
tumor cell killing and, 677
Ionizing radiation-induced foci (IRIF), 117
Ionizing radiation therapy (IR)
high-energy electromagnetic, 116
IORT. *See* Intraoperative radiotherapy
Irene, 79–80, 79*f*
Irinotecan. *See also* FOLFIRI regimen
cisplatin with, 952
for colorectal cancer, 1572, 1574
for lung cancer, 1261
for rectal cancer, 1584
for rhabdomyosarcoma, 2137
for spinal cord tumors, 952
Iris
anatomy of, 959
melanoma of, 966*f*
radiation tolerance of, 960
after RT, 1058
Iron deficiency anemia, 1318
Irradiated volumes, definitions of, 282, 282*f*
Irradiation
and drug therapy, 62–63, 64*f*
effects on cells, 18–20, 18–19*f*
and surgery, 62
Isobolograms, 713, 713*f*
Isocenter distances, 230. *See also* Source-to-axis distances (SADs)
Isodose charts
abutting fields, 270*f*
beam's-eye view, 244*f*
cervical cancer, 1806
distribution, 196*f*
dosimetry, 195–196
photon beam dosimetry, 235
single field, 234–235
wedge, 237, 238*f*, 239
wedge filter, 196, 197*f*
Isodose distributions
treatment planning, 1431*f*
Isodose plots

bone, 261
electron beam therapy, 258
lung, 271*f*
Isoeffect graphs, 38–40, 41*f*
Isoflavones, 1668
Isolated limb infusion (ILI), 2067
Isolated limb perfusion (ILP), 2067
Isotones, 170
Isotopes, definition of, 170
IT. *See* Immunotherapy (IT)
Ivor-Lewis esophagogastrectomy, 1328

J

Jaundice, pancreatic cancer and, 1524
Jejunostomy, nutritional support and, 2324
Johns, N. Harold E., 84, 84*f*
Joints and tendons
inflammatory conditions of, 2248
Joliot-Curie, Frederic, 79–80, 79*f*
Jun gene, induction of, 109
Juvenile nasopharyngeal angiofibromas (JNA)
pediatric, 2219–2220, 2220*t*
staging, 2220*t*
Juvenile pilocytic astrocytoma, 949
Juvenile secretory carcinoma of the breast, 2221
Juxtopapillarytumors, 965

K

K-*sam*proto-oncogene, 1497
Kadish staging system, 1197–1198, 1197*t*
Kaplan, Henry S., 84–85
Kaplan-Meier plot, 394–395, 395*f*
Kaposi sarcoma, oral, 1099
Kasabach-Merritt syndrome, 2230, 2230*f*
Keloids, 2252–2253, 2253*f*
Kennedy Paterson, James Ralston, 82
Keratinizing squamous carcinomas (KSCs), 1923
Keratinocyte growth factors (KGF)
human recombinant, 682
use of, 683
Keratitis, after RT, 1058
Kerma (kinetic energy released in the medium)
absorbed dose and, 190*f*
definition of, 189–190
Ketamine, pain management using, 2318*t*
KEYNOTE trial, 996
Kidney. *See also* Renal entries

anatomy, 1611
hydronephrosis, 2307
late effects of radiation, 342–343
RT dosage constraints, 1291*t*
scarred encapsulated, 342
TBI toxicity, 419
Kilovoltage units, 177, 177*f*
Kinetic energy, ionizations and, 176
Kligerman, Morton, 2
Klinefelter syndrome, 1294
Klinefelter syndrome, 2228
Knowledge-based planning (KBP) approach, 291
Knudson, Alfred, 7–8, 7*f*
Knudson two-hit hypothesis, 8
Kolb's experiential learning model, 770*f*
KRAS mutations, 1525, 1856
Kraske approach, 1579
Krukenbergtumors, 1854
Kutcher-Burman DVH reduction scheme, 295
KV-IORT. *See* Electronic brachytherapy/lowkilovoltage x-ray IORT (KV-IORT)
Kyphoplasty, 2293

L

L-asparaginase, 2018, 2194
induction therapy using in ALL, 2018
lymphoblastic lymphoma, 2194
Lacrimal acinar cell dysfunction, 960
Lacrimal system, radiation tolerance of, 960
Lactate dehydrogenase (LDH), 1734, 1862
Lactation, after breast conserving therapy, 1425
LAMB gene, 1361
Lambert-Eaton myasthenic syndrome (LEMS), 1252
Lamina papyracea, 1040
Langerhans cell histiocytosis (LCH)
radiation therapy, 2240
Laparoscopy, diagnostic, 1524
Laparotomy, 1328
Large B-cell lymphomas, 2193–2194. *See also* Diffuse large B-cell lymphoma (DLBCL)
Large language model applications, 731–732, 731*f*
Laryngeal cancer, 1160–1178
classification, 1165–1166
clinical presentation, 1163–1164
diagnosis, 1164–1165, 1165*t*
epidemiology, 1162
follow-up, 1177
pathologic classification, 1165–1166
patterns of spread, 1162–1163

prognostic factors, 1166
risk factors, 1162
sequelae of treatment, 1177–1178
staging, 1165, 1165*t*
supraglottic larynx, 1162
vocal cord carcinoma, treatment of, 1166–1170
Laryngeal edema, 333
Laryngectomy
partial, 1166
patient refusal, 1150
supracricoid, 1166
supraglottic, 1171
supraglottic larynx, 1176*t*
total, 1166
wide-field total, 1171
Laryngopharyngectomy, 1150
Laryngopharynx. *See* Hypopharynx
Larynx
anatomy, 1160–1162, 1160*f*, 1161*f*
edema of, 1177–1178
dose/volume/toxicity data, 333
late effects of radiation, 333
oncologic anatomy, 696
Laser photocoagulation, 1914
Laser vaporization, 1880
Late toxicity, 1902–1903
Latent conditions, definition of, 359–360
Latent errors, definition of, 359
Lateral retropharyngeal lymph nodes, 1216
Lattice therapy, 451, 455, 458
Lawrence, Ernest, 185
LCIS (lobular carcinoma in situ), 1372–1373
LDR. *See* Brachytherapy, low-dose rate
Learning Theory, 770–772, 770*f*, 771*f*
Leg-length discrepancies, 2172
Leiomyoblastomas, 2222
Leiomyomatosis, 1611
Leiomyosarcomas, 1327, 1850, 1926
Leksell Gamma Knife surgery, 967
Leksell, Lars, 178
Lens
anatomy of, 960
radiation tolerance of, 960
Leonard, Charles L., 24
Leptomeningeal carcinomatosis (LCM), 2273, 2274*t*
Leptomeninges, 692
Leucovorin. *See* FOLFIRI regimen; MACOP-B regimen
Leukemias, 2013–2031

anatomic considerations, 923–1922
after radiation therapy, 1446
CNS involvement, 2014–2015
lymphomas and, 2190
meningeal, 2021
radiobiologic effects on, 409
Leukoencephalopathy, 2030–2031
Leukoplakia, 1097
Levamisole, 1573
Levitt MD, Seymour H., 85
Leydig cell dysfunction, 418
Leydig cell tumors, 1872
Lhermitte syndrome, 1969
Li Fraumeni syndrome
adrenocortical carcinoma and, 1951
oral cavity cancer and, 1092
soft-tissue sarcomas and, 2054
TP53 mutations and, 101
LIAC linear accelerators, 462
Lichen sclerosus (LS), 1923
Lidocaine, 2318, 2319
LINACs. *See* Linear accelerators
Lind, James, 375
Linear accelerators
components of, 179–181, 180*f*, 181*f*
radiosurgery techniques, 425
treatment machines, 179–181
Linear energy transfer (LET), 19–20, 36, 36*f*, 176
stopping power and, 476
Linear no-threshold (LNT) model, 156
Linear quadratic equation, 40–43, 41*f*, 42*t*
Linear-quadratic model (LQM), 461, 462
Linear-quadratic model, 542–543
Lip
anatomy of, 1093
carcinomas of, 1097–1098, 1115
subsite-specific treatment, 1115
Lip cancer
brachytherapy, 1113*f*
outcomes and, 1115
squamous cell carcinoma, 1112–1113*f*
Lipomas
cardiac, 1361
spinal cord, 950
spinal canal, 2083
Liposarcomas
mediastinal, 1296–1298, 1297*f*
retroperitoneal, 1941, 1942–1943

Liposomes, 162*f*, 163
Lipowitz metal, 265
Lipowitz metal shielding block system, 244–245, 245*f*
Liver
  anatomy, 1542*f*
  cirrhosis, 1552
  imaging, 703
  impact of SBRT, 442–443, 443*f*
  late effects of radiation, 340–341
Liver cancers, 1541
  metastatic
    case study, 443–444
    dose distribution, 2308*f*
    lung cancer and, 1252
    management of, 2303–2305, 2304*f*
  pediatric, 2223–2225
    chemotherapy, 2225
    RT, 2225
    staging, 2225*t*
    surgical management, 2225
  transarterial radioembolization, 2225
  radiation-induced injury, 1625–1626
Liver flukes, 1557
Liver transplantation, 1541, 1548
Liver transplantation, 2225
Lobectomy, lung, 1255
Lobular carcinoma in situ (LCIS), 132–1373, 1411
Lobular invasive carcinomas, breast, 1398
Local tumor control, 22–23
Locality rule, 66
Locoregional failures, incidence of, 1629
Loeffler, Jay S., 88, 88*f*
Log-rank test, 395
Logarithmic cell kill, 22*b*
Logistic regression model, 395
Lomustine (CCNU), 952, 1934
Long bones, anatomy of, 2289
Long-term tumor occurrence, 918
Loop electrosurgical excision procedures (LEEP), 1775
Loperamide, 1902
Loss of chance, 67
Loss of function mutations, 100
Loss of heterozygosity (LOH), 8, 2103
Low anterior resection (LAR), 1579
Low-dose radiation therapy, 644–645
Low dose rate (LDR) brachytherapy, 44
Low-dose rate gynecologic brachytherapy, intracavitary sources for, 508–509
  cesium-137 sources, 508

experimental intracavitary brachytherapy radionuclides, 508–509
radium-226 sources, 508
Low-dose rate temporary interstitial brachytherapy, sources for, 509
Low-grade glioma, 890–894, 892*t*
Low-income and middle-income countries (LMIC), radiation oncology in, 753–765
Low malignant potential (LMP) tumors, 1854
Lower airway obstruction, malignant, 2303
Lower uterine segment involvement (LUSI), 1837
Lumbosacral plexopathy, RT-related, 1817
Lumpectomy
breast cancer recurrence after, 1409*f*
description of, 1403
Lung
anatomy of, 1251
dose distribution issues, 259–261, 262*f*
dose/volume/toxicity data, 336–337
lymph nodes, 1252
metastatic disease of, 2304*f*
palliative treatment, 2304*f*
radiation-induced injury, 335*t*, 1354, 1444, 1444*f*
reirradiation, 667, 668*t*
RT dosage constraints, 1291*t*
TBI toxicity, 418
tissue interface dosimetry and, 236–237, 238*f*
volume changes, 335
Lung cancer, 1251–1274. *See also specific types of cancer*
after HL treatment, 237, 1970
after radiation therapy, 1446
classification, 1254
diagnosis, 1253
epidemiology of, 1251
extranodal lymphomas, 1987–1988
gross tumor volume, 286*f*
IMPT/IMRT and proton plans, 489*f*
inoperable, 444, 445*f*
intracranial metastases, 694
late effects of radiation, 334–337
management, radiotherapy, 1264–1267
metastatic, RT for, 964–965*f*
palliative radiotherapy, 1270–1271
paraneoplastic syndromes, 1252
patterns of spread, 1251–1252
pediatric, 2220–2221
presentation of, 1251–1252
proton therapy, 487–489, 489*f*
screening for, 1252–1253
staging, 1253, 1253*t*, 1254*t*
Luteinizing hormone–releasing hormone (LHRH) agonists, 1721

Lutetium-177, 2299
Lycopene, 1668
Lyman-Kutcher-Burman model, 294–295, 325, 339
Lymph nodes
  para-aortic, 1784–1786, 1785*f*
  pelvic, 704
Lymphadenectomy, 1443, 1647, 1838
Lymphadenopathy, 1956
Lymphangiomas, 1296, 2230
Lymphangiomatosis, 1296
Lymphangiosarcomas, 1296
Lymphatic drainage, 1922
Lymphatic metastases, 1098, 1098*t*
Lymphatic system. *See also* Lymph nodes
  oncologic anatomy, 708–709
  radiation side effect management
    lymphedema of extremities, 2356–2357
    lymphedema of head and neck, 2357
Lymphedema, 1443, 2171
  of extremities, 2356–2357
  of head and neck, 2357
Lymphoblastic leukemia (LL), 2194
  presentation, 2190
Lymphomas. *See also Specific Lymphomas*
  CNS, 323
  after HL treatment, 1970
  imaging of, 708–709
  leukemias and, 2190
  pediatric, 2176–2194
  penile, 1750
  primary, 1680, 1750
  prostate, 1680
  proton therapy, 486–487
  retroperitoneal, 1946
  spinal cord, 950
  vaginal, 1896
Lymphomatoid papulosis (LyP), 2006
Lymphoproliferative disorders, 1998
Lymphotropic superparamagnetic nanoparticles, 1711
Lymphovascular invasion (LVI), 1837
Lynch syndrome, 1569, 1829
Lysyl oxidase-like-2 (LOXL-2), 155

M

Machine learning(ML), 58*b*, 750
  techniques, 726–731, 726*t*, 727–728*t*, 729*f*, 730*f*
Macrophages, accumulation of, 319

Maculopathy, 2338
Magnetic resonance cholangiopancreatography (MRCP), 704
Magnetic resonance imaging (MRI). *See also* Treatment planning
  brachytherapy contouring, 1802–1803, 1804*f*
  description of, 688–689
  diagnostic
    for adrenal tumors, 1952
    breast cancer, 1395
    cervical cancer, 1768, 1769*f*
    colorectal cancer, 1571
    endometrial cancer, 1829–1830
    oropharyngeal cancer, 1126
    for osteosarcomas, 2157, 2157*f*
    pancreatic cancer, 1524
    prostate cancer, 1685*f*
    for soft-tissue sarcomas, 2055*f*
    testicular carcinoma, 1734
    vaginal cancer, 1884
    vulvar cancer, 1927
  gradient-recalled echo pulse sequences, 689
  inversion recovery pulse sequences, 689
  multiple spin-echo, 689
  prostate cancer, 1711
  signal intensities, 689
  spin echo, 689
  spinal canal tumor, 948–949, 949*f*, 950*f*
Magnetic resonance linear accelerator, 224
Magnetic resonance spectroscopy (MRS), 1676
Magnetrons, linear accelerator, 179
Magnification angiography, 1183
Male reproductive system, 2352*t*
  radiation side effect management
    azoospermia, 2353
    erectile dysfunction, 2352–2353
    infertility, 2353
    oligospermia, 2353
Malignant brain tumors, 485–486
Malignant central nervous system tumors, 433
Malignant glioma, 882
Malignant hypertension, 342
Malignant melanoma, 2231–2232
Malignant oncocytoma, 1073
Malignant peripheral nerve sheath tumors (MPNSTs), 1298
Malpractice
  and radiation oncology, 65–69
    establishment of duty, breach, causation, and damages, 65
    grievances, malpractice claims, and insurance disputes, 69–70
    Health Insurance Portability and Accountability Act, 70

informed consent, 71–72, 71*t*
RAGE campaign, 70*b*
risk management, 70–71
Maltodextrin powder, 2329
Mammary analog secretory carcinoma, 1073
Mammography
assessment categories, 701*t*
breast cancer, diagnosis, 1392–1396
microcalcifications on, 1396*f*
pleomorphic calcifications on, 701*f*
postlumpectomy, 1394
during pregnancy, 1424
Mammoplasty, 1331
MammoSite system, 1440, 1440*f*
Manchester system, 525–528, 526–527*t*, 528*f*
Mandibular alveolus, 1097*f*, 1099*f*
Mandibulectomy, marginal, 1103, 1116
Mansfield, Carl, 85
Mantle cell lymphomas
clinical management, 1989
clinical presentation, 1989
pathology, 1989
prognostic factors, 1989
Marfanoid habitus, 1951
Marginal mandibulectomy, 1103, 1116
Marginal zone B-cell lymphomas, 2007–2008
Marginal zone lymphomas, 1987–1989
Markov models, 836–837, 836*f*
MART-1 protein, 1891
Martinez applicator, 1899
Masaoka staging system, 1292
Masks
plastic, 247, 247*f*
rigidity of, 246
Mass attenuation, water *vs.* lead, 174*f*
Mass numbers (A), 170
Massage therapy, 2323
Mastalgia, 2356
Mastectomy
breast cancer recurrence, 1421
after breast-conserving surgery, 1480–1482
breast-conserving surgery or, 1403, 1406–1407
locoregional recurrence after, 1482
nipple-sparing, 1403
skin-sparing, 1403
Maxillary nerve (CN V_2), 693
Maxillary osteosarcoma, 1033

Maxillary sinus cancer
clinical presentation, 1043
patterns of spread, 1042, 1042*f*
squamous cell carcinoma, 1050*f*
staging of, 1043
target volumes, 1047–1049
Maxillary sinuses, anatomy of, 1040
Maximum doses, definition of, 292–293
MCC. *See* Merkel cell carcinoma (MCC)
McCabe and Fletcher classification, 1184*t*
McKeown esophagogastrectomy, 1328
MCM7 protein, 1599
Meat, prostate cancer and, 1667
Mechlorethamine. *See* MOPP regimen
Meckel cave, 693
Median doses, definition of, 293
Mediastinal mass ratio (MMR), 1957
Mediastinal tumors, 1279–1297
histology of, 1280*t*
incidence of, 1279
mesenchymal, 1296–1298
neurogenic, 1298–1302
epidemiology, 1298
management, 1298–1302
natural history, 1298–1302
presentation, 1298
Mediastinoscopy, 1253
Mediastinotomy, 1253
Mediastinum, anatomy of, 1279, 1279*f*
Medicaid programs. *See* Centers for Medicare and Medicaid Services (CMS)
Medical countermeasures (MCMs), 156, 158, 159, 160
Medical errors, ethical issues, 819–820
Medical Ethics (Percival), 813–814
Medical oncology, economics of, 823
Medicare Chronic Conditions Warehouse (CCW), 398
Medicare programs, Anti-Kickback Statute, 816
Medicine Task Group 43 Table-Based Dose Calculation Formalism, American Association of Physicists in, 520–521, 521*t*, 521*f*, 522*f*, 523*t*
Medullary carcinomas, breast, 1398
Medullary thyroid carcinoma (MTC), 1248, 1951
Medulloblastomas, 897–898
pediatric, 2087–2090, 2088*f*
management, 2087–2089, 2088*f*
post-RT intelligence, 320
radiotherapy for, 2089, 2090*f*
Megavoltage radiation therapy, 757
Megavoltage units, 178–185
Megestrol (Megace), 1842

Meibonian glands, 960
Melanomas
  acral lentiginous, 1923
  cardiac, 1361
  cervical, 1772
  choroidal
    enucleation for, 965
    photocoagulation, 965
  intracranial metastases, 694
  metastatic, 694, 1361
  nodular, 1923
  secondary, 419
  superficial spreading, 1923
  uveal, 964–968
  vaginal, 1891–1893
  vulvar, 1923, 1924*f*
Meningeal leukemia, 2021
Meninges, layers of, 692
Meningioma, 900–903, 901*t*
Meningiomas
  atypical, 432
  benign, 2238
  cerebellar pontine angle, 430
  malignant, 432
  origins of, 692
  skull-base, 325
  spinal cord, 950
Menopause, age at, 1388–1389
Menstrual history, 1388
Merkel cell carcinoma (MCC)
  periorbital, 969
  vulvar carcinoma and, 1831
MERT, uses of, 276–277
Mesalazine, 2327
Mesenchymal tumors, 1296–1298
Mesenchymal–epithelial transition (MET), 98
Mesorectum, 704
Mesothelioma
  imaging of, 699–700
  IMRT for, 336
  pericardial, 1361
Meta-analysis, 387
Metal-oxide-semiconductor field-effect transistor
  detectors, 299
  dosimetry, 193
Metal prostheses, 237
Metalodobenzylguanidine I-131, 1954
Metaphysis, long bone, 2289

Metaplastic carcinomas, breast, 1398
Metastatic disease. *See specific cancers and specific organs*
  biology of, 10–12, 10*f*
  defined, 10
  development of, 12*f*
  pathways of, 11
  tissue invasion and, 98
  tumor, 11
Metastatic phenotype and angiogenesis, 12–13
Metastatic spinal cord compression (MSCC), 2273, 2280*t*
Metastatic tropism, 10
Metastectomy, 1617
Methadone, 2318
Methotrexate (MTX). *See also* CMF regimen; CMV regimen; COMP regimen; MACOP-B regimen; MVAC regimen; ProMACE/MOPP regimen
  for ALL, 2017
  for AML, 2017
  for HNC SCC, 986
  for Hodgkin lymphoma, 1968
  for NHLs, 2186, 2191
  for osteosarcoma, 2158
  for PCNSL, 1991
  for penile cancer, 1754
  for rhabdomyosarcoma, 2137
  for urethral cancer, 1753*t*, 1758
  for vulvar cancer, 1934
Methotrexate, 1991
Methylselenocysteine, 154
MEVION S250 Proton Therapy System, 185
Microbeam/minibeam radiation therapy (MRT), 451
Microenvironments, tumor, 153–155
Microinvasive carcinoma, breast, 1396
Microsatellite instability, 1832
Microtron machines, 271
Microwave linear accelerator, 179
Microwaves
  propagation of, 179
  sources of, 179
Middle ear
  anatomy of, 973, 973*f*, 974*f*
  computerized isodose distribution, 979*f*
  data from patients with tumors, 980*f*
  gross tumor volumes, 978
  malignant disease of, 977
  management, 977, 977*t*
  and temporal bone, 977
  tumor management, 977
Mild acute dermatitis, 2329

Minimal residual disease (MRD), 2015*f*
Minimum doses, 292–293
Minority practice doctrine, 66
Misonidazole, 20, 678
Mistake, definition of, 360
Mitochondria, ROS/RNS links, 319
Mitogen-activated protein kinases (MAPKs), 106
Mitogenesis, phases of, 98
Mitomycin-C (MMC)
  for advanced HNCs, 986, 989
  adverse effects of, 986
  for anal cancer, 1601
  for bladder cancer, 1641
  for cervical cancer, 1793
  hypoxic cell targeting by, 679
  for pancreatic cancer, 1532
  for penile cancer, 1753–1754
  radiation response and, 719
  for urethral cancer, 1753–1754, 1758
  for vaginal cancer, 1891
  for vulvar cancer, 1923
Mitotane, 1954
Mitotic catastrophe, 99*t*, 101
Mitoxantrone, 1934, 2293. *See also* CNF regimen
  for salivary gland cancer, 1086
Mixed beam therapy, 269–271
Mixed cell–type endometrial cancer, 1832
Mixed Müllerian tumors (MMT), 1771, 1894
MLH1 mutations, 1857–1858
Mobeltron self-shielded unit, 272*f*
Mobetron system, 462
Modafinil, 2324
Modern fletcher-suit applicator systems, 536
Modern immunotherapy approaches, 636–639
  antibody therapies, 638
  cellular therapies, 637
  cytokine immunotherapy, 639
  immune-modulating antibodies (checkpoint inhibitors), 638–639
  innate immunotherapy, 639
  vaccines, 637–638
Modern linear accelerators (MLC), 451
Modified radical nodal dissection (MRND), 1219
Modulation factors, 182
Mohs microsurgery, 1913
Mold brachytherapy, 29–30, 44
Molecular cancer biology, 100–101
Molecular forensics, 36
Molecular pathophysiology, tumors, 144–146

chemotherapy, 145
immunotherapy, 145–146
nano-radiosensitizers, combination with, 144–145
three or four modalities, with, 146
tumor microenvironment normalization, combination with, 145
Molecular target therapy, hepatocellular cancer, 1555
Monitor ionization chambers, 180
Monitor unit (MU) calculations, 232–234
asymmetric X-ray collimators, 233
dose prescriptions and, 261–262
fixed fields, 232–233
irregular fields, 233–234
multileaf collimation systems, 233
rotation therapy, 234
Monte Carlo method
in commercial platforms, 255
dose calculations, 232
patient dose calculations, 263
MOPP regimen
components of, 2179–2181
for Hodgkin lymphoma, 2179–2181
Morbus Dupuytren (MD). *See* Dupuytren contracture
Morbus Dupuytren. *See* Dupuytren contracture
Morbus Ledderhose (ML). *See* Dupuytren contracture
Morphine, administration of, 2318
Motion management. *See also* Patient motion
four dimensional imaging and, 1265*f*
Mouth, anatomy of, 696
Mouth, floor of
anatomy, 1093*f*, 1094
carcinomas of, 1097–1098, 1108*f*
subsite-specific treatment, 1116
Mouthpieces, lucite, 1110*f*
MSH2 mutations, 1857–1858
MSH6 mutations, 1857–1858
MTC (medullary thyroid carcinoma), 1248
Mucinous (secretory) myoepithelioma, 1074
Mucinous adenocarcinomas
locations, 1073
ovarian, 1860–1861, 1860*f*
Mucinous carcinomas, 1398
endometrial, 1832
prostate, 1680
Mucoepidermoid carcinoma (MEC), 1062, 1072, 1080
Mucosa-associated lymphoid tissue (MALT), 1987
Mucosal neuromas, 1951
Mucositis, 418, 2329
confluent, 679, 683*f*

erythematous, 2140
focal, 1112*f*, 1113*f*
gastrointestinal, 2327–2328
mitigation of, 682–683
nutritional support in, 2324
oral, 2326, 2327*f*
pain management in, 2319
pallative and supportive care, 2326–2328, 2328*t*
prevention of, 2326–2327
radiation-induced, 1112*f*
reduced severity of, 683*f*
supportive care in, 418
treatment of, 2327
Muir-Torre syndrome, 968
Multicriteria optimization (MCO), 592
Multidetector computed tomography (MDCT), 688
Multidisciplinary, cancer care, 758
Multileaf collimation (MLC) systems
bolus use, 266–268
breast cancer management, 1430
electron beam modulation, 265–266
leaf settings, 180
monitor unit calculations, 233
segmental, 181
treatment planning, 243–244
Multileaf collimator (MLC)-based GRID therapy, 455
Multiple brain lesions, radiosurgery for, 2270–2271
Multiple Coulomb scattering (MCS), 303–304
Multiple endocrine neoplasia type 1 (MEN 1), 1951
Multiple-hit/multiple-target model, 47
Multiple myeloma (MM), 2038*t*, 2039
hemibody irradiation for, 419
management, 2042–2045
radiation therapy, 2045–2050, 2048–2049*f*
relapsed/refractory, 2044–2045
Muscle-invasive bladder cancer (MIBC). *See* Bladder cancer, invasive
Muscle relaxants, 2320
Muscle spasms, 2319–2320
Muscle weakness, 1817
Music therapy, 2319
Mustargen. *See* ProMACE/MOPP regimen
Mutagenesis, 108
Mutagesis, genomic instability and, 109
Mutations
and genome instability, 99*t*, 109
loss of function, 100
MUTYH-associated polyposis, 1569
MVAC regimen

for bladder cancer, 1638
components, 1638
for urethral TCCs, 1758
Myasthenia gravis, 1280
Mycophenolate, 406
Mycosis fungoides, 1998*f*
cutaneous disease, 1998
diagnosis, 2000, 2000*t*
electron beam therapy, 272
evaluation, 2000
extracutaneous, 1999
folliculotropic, 2004–2005
hypopigmented, 2005
local superficial irradiation, 2001
pathophysiology, 1999–2000
prognosis, 2000–2001
skin-directed therapy, 2001
staging, 2000–2001, 2001*t*
total-skin irradiation in, 275
transformed disease, 2004
treatment, 2001–2004
side effects, 2003*f*, 2003–2004
by stage, 2004–2005, 2005*t*
stem cell transplants, 2004
systemic therapy, 2004
variants, 2004–2005
Myelitis, 2337–2338
Myelitis, hyperthermia and, 122
Myeloablative conditioning regimens
allo-SCT, 406, 407
long-term effects of, 406
non-TBI, 407
TBI toxicity, 418–419
vs. nonmyeloablative, 406
Myeloblastomas. *See* Chloromas
Myelodysplastic syndrome, 419
Myelography, 948
Myeloid sarcomas, 2017
Myelopathy, 329
Myelosuppression
cisplatin and, 1743
after RT, 1518
total-body irradiation and, 409
Myocardial infarction, 338. *See also* Heart disease
Myocardium, tumors, 1362
Myoepithelial carcinomas, 1072–1073
Myometrial inclusions, 1830*f*
Myometrial invasion, 1837, 1841

Myxomas, atrial, 161
Myxomas, myocardial, 1362
Myxopapillary ependymomas, 2083

N

N-acetyltransferase-2, bladder cancer and, 1638
N-butyl-cyanoacrylate, 1184
N-methyl-D-aspartate antagonists, 2318, 2318*t*
N-*myc*, 7
Nagasaki, salivary gland cancers and, 1062
NAME gene, 1361
Nanometers, 169
Nanoparticles
  combination therapies, 161–162, 162*f*
  of radiation response, 681
Nanotechnology, 162–164
Naphthylamine, 1638
Narcotics, mucositis care and, 418
Nasal cavity
  anatomy of, 1040
  synechiae, 1058
Nasal cavity cancers, 1040–1058
  chemotherapy, neoadjuvant and concomitant, 1045
  classification, 1043
  clinical presentation, 1042–1043
  diagnostic workup, 1042
  epidemiology of, 1040
  esthesioneuroblastoma, 1196–1202
  follow-up, 1052
  management, 1044–1045, 1057*t*
  neck irradiation and, 1052
  outcomes, 1052–1058, 1055*t*
  patient-specific factors, 1044
  pretreatment evaluation, 1043*t*
  prognostic factors, 1044
  solitary fibrous tumors, 1187
  spread of, 1041
  staging, 1043, 1044*t*
Nasal fossa tumors
  management, 1045
  outcomes, 1052–1056
  RT trials, 1054*t*
  target volumes, 1047–1049
Nasal vestibule, anatomy of, 1040
Nasal vestibule cancers
  clinical presentation, 1042–1043
  management, 1044–1045

natural history of, 1040–1042
RT trials, 1054*t*
squamous cell carcinoma, 1041*f*, 1046*f*
Nasolacrimal duct complications, 1087
Nasopharyngeal cancers (NPCs), 1001–1002
biomarkers, 1013–1014
brachytherapy, 1019–1021, 1021*f*, 1022*t*
cavernous sinus invasion, 1005*f*
chemoradiotherapy, 988, 1018*t*
chemotherapy, 1022–1024, 1023*t*, 1025*f*
classification of, 1011, 1011*t*
clinical presentation, 1005, 1007*t*
cranial nerves and, 692–693
diagnostic workup, 1006–1009, 1007*t*
distant metastasis, 1005
EBV antibody titers, 2218*t*
epidemiology, 1001, 1003
Epstein-Barr virus and, 1013–1014
etiology, 1001, 1003
IMRT, 1016–1018, 1018*t*, 1019–1020*f*, 1021*t*
local extension of, 1003, 1003*t*
locally recurrent, 1026–1027*t*
lymphatic spread, 1004, 1006*f*
MRI, 1004*f*
natural history of, 1003–1005
outcomes, 1030, 1030*t*
patient examination in, 692
pediatric, 2218–2219
prognostic factors, 1012–1014
radiation therapy, 1014–1022
3-D treatment plans, 1015–1016
conventional two-dimensional, 1015, 1017*f*
dose-response, 1014
regimens, 1028*t*
sequelae of, 1030–1033, 1052*t*
stereotactic radiosurgery, 1021
recurrent/metastatic, 1024–1030
staging, 1006–1009, 1010
surgical treatment, 1029–1030, 1029*f*
Nasopharynx
anatomy of, 1001, 1001*f*, 1002*f*, 1002*t*
blood supply, 1001
innervation of, 1001
oncologic anatomy, 693, 696
National Cancer Database (NCDB), 398
National Electrical Manufacturers Association (NEMA), 815–816
National Institute of Allergy and Infectious Diseases (NIAID), 158
National Library of Medicine (NLM), ClinicalTrials.gov and, 385

National Lung Screening Trial (NLST), 1252
National Wilms Tumor Studies (NWTSs), 2103
Natural killer cell lymphomas, 1998–2005
Natural language processing, 731–732
Nausea and vomiting
  cisplatin and, 1743
  management of, 2297
  radiation-therapy related, 1518
Nausea, control of, 418
Nausea, radiation-induced, 2327
NCDs (noncommunicable diseases), 753, 760*f*, 761
Near-minimum doses, definition of, 293
Neck
  anatomy of, 1216
  dissection of, 1219–1220, 1219*t*, 1220*f*, 1244
  dissection post RT, 1155
  dose distributions, 1224*f*, 1225*f*
  irradiation of, 1052, 1225
  late effects of radiation, 332–334
  lymph nodes
    radiographic boundaries, 1125*t*
  radiation field design, 1106*f*
  surgical management, 1103–1104
Neck cancer, 1216–1232. *See also* Head and neck cancers (HNCs)
  biopsy, 1225–1226, 1226*t*
  diagnostic workup, 1217–1218
  imaging, 1218
  management, 1220–1225, 1226*t*
  metastatic, 1218*t*
  natural history of, 1217
  positive nodes, 1227–1228, 1228*f*
  prognostic factors, 1229*t*
  risk groups, 1217*t*
  staging, 1218, 1219*t*, 1227*t*
  treatment outcomes, 1226–1229
Necrosis, 2351
  radiation-induced, 99*t*, 101
Negligence, 65
Neighborhood effect, 45
Neoadjuvant chemotherapy, 1458–1459, 1888, 62–63, 715, 2067. *See also* chemotherapy; *specific regimens*
  HER2-positive disease, 1458
  HER2-negative disease, 1458
Neoadjuvant immunotherapy, 1114–1115
Neoantigen, 108
Neoantigens, 635
Neostigmine, 2325
Neovagina, carcinoma of, 1903–1904

Neovascular glaucoma, 967
Neovascularization, 137
Nephrectomy, 1615, 1617*t*, 2104, 2110
Nephritis, transplant-relate, 419
Nephrogenic rests, 2103
Nephropathy, 342
Nerve sheath tumors, 950
Nervous system, 2325*t*
  radiation side effect management
    cerebral edema, 2336
    fatigue, 2335–2336
    myelitis, 2337–2338
    radiation-induced cognitive decline, 2335–2336
    radionecrosis, 2336–2337
Neurilemonas. *See* Schwannomas
Neuroablative techniques, 2318
Neuroblastoma
  adrenal cancer and, 1951
  classification of, 2120
  clinical presentation, 2017
  diversity, 2116
  epidemiology, 2017
  imaging, 2119*f*
  management
    chemotherapy, 2121
    late effects of, 2124–2125
    outcomes, 2125
    RT, 2121–2124
    surgical, 2119
  mediastinal, 1298
  mortality rates, 2017
  natural history, 2116
  pediatric, 2116–2125, 2283
  prognostic factors, 2120
  retroperitoneal, 1939, 1946
  spinal cord compression and, 2283
  staging, 2120–2121
Neurocognitive effects
  intracranial irradiation, 320–321
  radiation-related, 2072
Neuroendocrine tumors, 1679–1680
Neurofibroma, 904–905, 950, 1301*f*
Neurofibromatosis
  adrenal cancer and, 1951
  intracranial irradiation, 323
  NF1 gene in, 101
  retroperitoneal lesions, 1947
  soft-tissue sarcomas and, 2054

spinal cord tumors and, 950
Neurologic deficits, radiation-related, 1817
Neurologic, Oncologic, Mechanical, Systemic (NOMS) approach, 2278, 2279*f*
Neuromas, spinal cord, 950
Neuron-specific enolases, 1896
Neuropathic pain, adjuvant therapies in, 2317–2318
Neuropathies, optic, 1058
Neurosurgical techniques, 2318–2319
Neutrons
attractive force of, 172–173
beam therapy, 186
capture therapy, 53–54, 53*b*
definition of, 169
interactions with matter, 176
therapy, 1084
New York Times, 65*b*
NF1 gene, 101
NGGCTs (nongerminomatous germ cell tumors), 2092
NHEJ (nonhomologous end joining), 103*f*, 104
NHL. *See* Non-Hodgkin lymphoma (NHL)
Nicotinamide, 677–678
Nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, ROS source, 318–319
Nilotinib, 2024
Nimorazole, 678, 719
Nitric oxide, production of, 2238
Nitric oxide synthase (NOS)
gradient around tumor vessels, 154
Nitrogen mustard, 2001, 2004. *See also* MOPP regimen
Nitrosamides, 1318
Nitrosamines, 1318
Nocturia, radiation-related, 1818
Nominal standard dose, 42*b*
Non-Hodgkin lymphoma (NHL), 1974–11992
advanced, 2193*t*
classification, 1975*t*
clinical presentation, 1976
epidemiology, 1974
etiology, 1974–1975
evaluation, 1976, 1976*t*
event-free survival, 2192*t*
extranodal, 1976, 1985, 1991
follow-up and routine surveillance, 1976–1977
management
chemotherapy, 1978
combined modality treatment, 1978, 1978*t*
immunotherapy, 1974
palliative RT, 1980
nodal *vs.* extranodal, 1976

pathology, 1975, 1975*t*
pediatric, 2188–2194
classification, 2189, 2190*t*
diagnosis, 2190–2191, 2191*t*
epidemiology, 2189
outcomes, 2192*t*
presentation, 2189–2190
prognostic factors, 2191
staging, 2191, 2192*t*
treatment, 2191–2194
treatment selection, 2192*t*, 2193*t*, 2194
primary cutaneous lymphomas, 1998–2009
radiation therapy, 2194
response assessment, 1976
retroperitoneal, 1946
staging, 1976, 1976*t*
stomach, 2221–2222
Non-insulin-dependent diabetes mellitus, 1828
Non-small cell lung cancer (NSCLC), 715
brain metastases, 2264–2265, 2266*f*
case study, 444
imaging, 699
inoperable
EBRT, 1260–1263
management
chemotherapy, 1257, 1261*t*
induction chemotherapy, 1260–1263
postoperative systemic therapy, 1258–1260
radiotherapy, 1260, 1261*t*
surgical, 1254–1255
targeted therapy, 1262
metastatic, 1267–1270
patterns of spread, 1251–1252
PET-CT in detecting mediastinal lymph node involvement, 699
Noncommunicable diseases (NCDs), 753, 760*f*, 761
Nonfunctioning PitNETs (NFPitNETs), 914–916
repeat stereotactic radiosurgery, 916
timing of radiation therapy and stereotactic radiosurgery, 915
tumor control, 914–915, 915*t*
upfront stereotactic radiosurgery, 916
Nongerminomatous germ cell tumors (NGGCTs), 2092
Nonhomologous end joining (NHEJ), 103*f*, 104, 117
Nonmalignant diseases
benign diseases of soft tissue and bones
inflammatory conditions of joints and tendons, 2248
osteoarthritis, 2248–2249
pigmented villonodular synovitis, 2249
vertebral hemangiomas, 2249

connective tissue and skin diseases
desmoid tumors, 2249–2250
dupuytren contracture, 2251–2252, 2251–2252*f*
heterotopic ossification, 2253–2254, 2254*f*
hypertrophic scars, 2252–2253
keloids, 2252–2253, 2253*f*
Peyronie disease (PYD), 2250–2251
plantar fasciitis, 2254–2255
eye and orbit diseases
age-related macular degeneration (AMD), 2246, 2246*f*
Graves ophthalmopathy, 2246–2248, 2247*f*, 2247*t*
functional disorders, 2241
cardiac arrhythmias, 2244
epilepsy, 2242–2243
Parkinson disease (PD), 2243
psychiatric disorders, 2243–2244
sialorrhea, 2244, 2246
trigeminal neuralgia (tic douloureux), 2241–2242
patterns of practice, 2237–2238
radiation therapy, 2237
risk of second malignancies, 2238–2239
vascular disorders, 2240
arteriovenous malformations, 2240–2241
Non–mycosis fungoides cutaneous T-cell lymphoma, 2005–2007
Nonneoplastic diseases, TBI for, 414
Nonrhabdomyosarcoma soft tissue sarcoma, 2144–2154
adipocytic, 2144
classification, 2144, 2145–2146*t*
clinical presentation, 2147
clinical trials, 2152–2154
diagnostic workup, 2147
epidemiology, 2144
fibroblastic, 2144
fibrohistiocytic, 2144
future directions, 2154
management, 2149
myofibroblastic, 2144
pathology, 2144–2147
peripheral nerve sheath tumors, 2147
perivascular, 2146
radiation therapy, 2149–2151
dose, 2149, 2150*t*, 2151*t*
long-term toxicity, 2151
metastases, 2150–2151
site-specific considerations, 2150
smooth muscle, 2147
staging, 2147–2148
treatment, 2148–2149

tumors of uncertain differentiation, 2147
vascular, 2144, 2146
Nonseminomatous germ cell tumors (NSGCTs)
embryonal carcinoma, 1731
germ cell neoplasia *in situ, 1732*
spermatocytic seminoma, 1732
yolk sac tumor and teratoma, prepubertal type, 1733
Nonsteroidal anti-inflammatory drugs (NSAIDs), 2316, 2317
Norepinephrine, 1183
Normal tissue complication probability (NTCP) models
calculation of, 294–295
dose-volume information and, 294
QUANTEC review and, 345, 349*f*
therapeutic index and, 677, 677*f*
Normal tissue, radiation injury to
functional subunits, 120
radiation tolerance, 120
regeneration, 120
retreatment, tissue tolerance, 122
therapeutic use, of, 123
tissue effect from radiation, latency of, 121–122
toxicities, prediction of, 122–123
volume effect, 120–121
Normal tissue, radiation therapy
adverse effects of
radiation fibrosis, 35–36, 35*f*
radiation-induced second primary malignant tumors, 36–37, 36*f*
risk of injury to, 23–24, 24–27*f*
treatment toxicity, 33–35, 33–34*f*
Normal tissues
apoptosis in, 118
contouring, 1684–1686
dose constraints, 1624
modifiers, 158
protection, 720
radiation injury
volume effects, 120–121, 121*f*
radiation tolerance, 120
tolerance, 452, 467, 467*t*
tolerance doses, 426
toxicity, 713
turnover kinetics, 121
Nortriptyline, 2318*t*
NOS. *See* Nitric oxide synthase (NOS)
Nosocomial infections, 407
Notch1 mutations, 1096
Novac 7 linear accelerators, 462
NPCs. *See* Nasopharyngeal cancers (NPCs)

NSCLC. *See* Non-small cell lung cancer (NSCLC)
NSGCTs. *See* Nonseminomatous germ cell tumors (NSGCTs)
NTCP models. *See* Normal tissue complication probability (NTCP) models
Nuclear factor kappa B (NF-κB), 106, 109, 119
Nuclear imaging, 691–692
Nuclear structure, 169–170
Nucleons, 169
Nuclides, daughter, 173–174, 174*f*
Nuremberg Code, 377, 814–815
Nurse, Paul, 9
Nutrition. *See also* Diet
  deficits, 2323
  parenteral, 418
  salivary gland cancers and, 1062
  supportive, 2325

O

OARs. *See* Organs at risk (OARs)
Obesity. *See also* Body mass index (BMI)
  breast cancer prognosis and, 1402
  endometrial cancer and, 1828
Objective outcomes, 830
Oblique filtration, 506
Obsessive-compulsive disorder (OCD), 2243–2244, 2245*f*
Occupational exposures, cancer and, 1063, 1638, 1975
OctreoScan, 1952
Octreotide scintography, 1197
Ocular metastases, 963–964
Ocular reticulum cell sarcoma. *See* Primary intraocular lymphomas (PIOL)
Ocular tracking, 215
Oculomotor nerve (CN III), 693
OEPA regimen
  components of, 2186
  for Hodgkin lymphoma, 2186
Off-axis doses, 257–258
Off-axis factors, 196
Off-center ratios, 196
Olaparib maintenance therapy, 1869
Older patients, brachytherapy in, 1811
Oldfield syndrome, 2222
Olfactory neuroblastoma, 1198
Oligometastases, 441, 2306
Oligometastatic disease, radiation therapy, 2308–2311, 2310*f*
Oligospermia, 2353
  after RT, 2184
Olsalazine, 2327
Omega-3 fatty acids, 1668

Oncocytic carcinoma. *See* Hürthle cell carcinoma
Oncocytoma, malignant, 1073
Oncogene addiction, 152
Oncogenes, 5–7
  activation of, 100
Ontario (Canada) Technology Assessment, 1678
Oophorectomy, 1819
Oophoropexy, 2184
Opiate side effects, 2317
Opioid medications, 2316, 2316*t*
Opisthorchis viverrini, 1557
OPPA regimen
  components of, 2186
  for Hodgkin lymphoma, 2186
Optic disc, anatomy of, 959
Optic nerve (CN II)
  anatomy of, 323
  dose-volume limits, 325
  meningioma, 694
  radiation tolerance of, 961
  radiosensitivity, 427–428
Optic nerve glioma, 2081
Optic neuropathy, 1058, 2338–2339
Optic pathway glioma, 2080–2081
Optical density, definition of, 192
Optical imaging systems, 213–214, 213*f*
Optimizing radiation therapy variables, 644–647
  field size/irradiated target, 645–646
  FLASH radiation therapy, 646–647
  radiation therapy dose/fractionation, 644–645
    ablative radiation therapy, 645
    hypofractionated radiation therapy, 645
    low-dose radiation therapy, 644–645
    standard fractionated radiation therapy, 645
  radiation therapy quality, 647
  sequencing, 646
  spatially fractionated radiation therapy, 646
Optional lymphadenectomy, 1839
Oral cavity, 1092–1118
  anatomy of, 696, 1092–1096, 1093–1095*f*
  nodal levels, 1095–1096
  palpation of, 983
  radiation effects, 1114–1115
  retropharyngeal nodes, 1096
  surgical approaches, 1101, 1115
Oral cavity cancer, 1092–1118
  classification, 1099
  clinical presentation, 1099–1100

diagnostic evaluation, 1100–1101
epidemiology of, 1092
etiology, 1092
follow-up recommendations, 1115
general management, 1101
incidence, 1092
metastatic, 1098
molecular biology of, 1096–1097
natural history, 1097–1099
neck irradiation in, 1220
patterns of spread, 1098–1099
predictive factors, 1115
prognostic factors, 1115
radiation therapy, 1104–1113
recurrent disease, 1117–1118
relative distribution, 1097–1098
simulation and treatment, 1110–1111
staging, 1101, 1102*t*
surgical management, 1101–1104
surveillance, 1115
Oral cavity mouthpiece, 1112*f*
Oral contraception, 1389, 1857
Oral etoposide, 1868
Oral mucositis. *See* Mucositis
Oral shields, 1115
Oral submucous fibrosis, 1097
Orbit
irradiation of, 2132
metastatic, 2117
rhabdomyosarcoma, 2132
tumors of, 959, 968–969
Orbital pseudotumor, management of, 962
Orbital tumors, 968
adult optic pathway glioma, 968
conjunctival tumors, 968
eyelid, sebaceous carcinoma of, 968–969
primary orbital lymphoma, 968
Orchiectomy, inguinal, 2134
Organ transplantation, 1974
Organs at risk (OARs)
conformal radiation therapy, 284*t*
definitions of, 282
delineation of, 285–288
Hodgkin lymphoma RT, 1964–1965
proton therapy, 305
thymic irradiation and, 1291
Oropharyngeal cancer, 481, 483, 484*f*, 485, 1123–1139
adjuvant therapy, 1129–1130

anatomy, 1124
chemoradiation therapy, 988–990, 988*f*, 1131–1132
classification, 1126–1128
clinical presentation, 1125
diagnostic evaluation, 1125–1126
epidemiology, 1123
HPV-associated, 1123–1124, 1135
incidence, 1123
management strategies, 1128
metastatic, 1138–1139
molecularly targeted therapy, 994–995
neck irradiation in, 1220
pediatric, 2219
posttreatment management and surveillance, 1137–1138
radiation therapy, 1130–1131
radiation therapy simulation, 1133–1135
recurrent, 1138–1139
routes of spread, 1124
staging, 1126–1128, 1126–1127*t*
surgical techniques, 1128–1129
targeted agents, 1133
treatment planning, 1133–1135
Oropharyngeal mucositis/oral infection, 2342–2343
Oropharynx, 1123–1139
anatomy, 696, 1124
Orthogonal field junctions, 250–251, 250*f*
Orthovoltage units, 177
Osteoarthritis, 2248–2249
Osteoblasts, 2288
Osteoclasts, 2288
activating factors, 1252
Osteogenic sarcoma, 1849
Osteomyelitis, skull, 923–924
Osteoprotegerin, 2288
Osteoradionecrosis, 1033, 2294
of femur (avascular necrosis), 2354
of mandible, 2353–2354
Osteosarcomas. *See also* Bone cancer
chemotherapy, 2158
diagnosis, 2157–2158
epidemiology, 2157
maxillary, 1033
metastatic disease, 2159
pathogenesis, 2157
presentation, 2157
radiation therapy, 2159
risk factors, 2157
spinal cord, 950

staging, 2157–2158, 2158*t*
treatment, 2158
Otalgia, 1100
Otitis media, 1087
Ototoxicity, 2339
Outcomes
hierarchy measures, 830, 831*f*
objective, 830
patient-reported outcomes, 830–831
subjective, 830, 833
values, 835, 836*f*
Outpatient management, 1246
Output factors
dosimetry, 194–195, 195*f*
field size and, 262, 263*f*
source-to-surface distance, 261, 263*f*
Ovarian cancer, 1854–1873
advanced
chemotherapy for, 1866–1867, 1866*t*
surgical treatment, 1865–1866
anatomy, 705–706
classification, 1859–1861, 1859*t*, 1860*f*
consoidatitive therapies, 1867–1870
diagnosis, 1862
early, 1864–1865, 1864*t*
epidemiology, 1855, 1855*f*
imaging, 706–707
intraoperative RT, 1870
management, 1870
palliative treatment, 1869–1870
pathogenesis, 1855–1856, 1856*t*
patterns of spread, 1861
presentation, 1861–1862
prognosis, 1863
recurrent, 1868
risk factors, 1856–1858, 1857*t*
screening tests, 1858–1859, 1858*t*
serous, 1859, 1860*f*
staging, 1858*t*, 1862–1863, 1862*t*, 1863*t*
Ovarian failure, 2352
radiation-related, 1778*f*
Ovarian function, 1388–1389
Ovarian surface epithelium (OSE), 1855
Ovarian transposition, 1777–1778
Ovaries
anatomy, 705–706, 1854–1855, 1854*f*
genetically significant doses, 252
imaging, 706–707

Oxaliplatin
for colorectal cancer, 1572, 1574
for nasopharyngeal cancer, 1024
radiation response and, 716
for rectal cancer, 1584
Oxybutynin (Ditropan), 1818, 2329
urinary tract injury, 2329
Oxygen (O_2), radiation response, 677

P

P*16* genes, 1525
P21 protein, 105, 109
p27 protein, 109
p53 gene, 8
p53 protein, 99, 119
in DSB repair, 105
loss of function, 105
prognostic value of, 1833
in tumors, 1074
p53 tumor suppressor genes
bladder cancer and, 1639
breast cancer
prognosis and, 1401
endometrial cancer and, 1833
esophageal cancer and, 1319
inactivation of, 1497, 1764
Pacemakers, cardiac, 251, 251*t*
Paclitaxel (Taxol), 1868, 1934
for NSCLC, 1261–1262
for ovarian cancer, 1866–1867
for pancreatic cancer, 1534
radiation pneumonitis and, 1444–1445
radiation response and, 717
for salivary gland cancer, 1086
for vaginal cancer, 1888
Paget disease, 1373–1374, 1398, 1749, 1925, 1925*f*
Paget, James, 10
Paget, Stephen, 10–11, 10*f*
Pagetoid reticulosis, 2005
Pain
cancer
assessment, 2315–2316
complementary therapies, 2319
guidelines, 2316–2318, 2316*t*, 2318*t*
management, 2316, 2318
multidimensional construct, 2314, 2314*f*
physical etiologies, 2314–2316, 2315*f*

radiation oncologist, 2319
types, 2315
causes of, 2315
nociceptive, 2315
nonnociceptive, 2315
screening for, 2315
Pain management
adjuvant therapies, 2317–2318, 2318*t*
bone metastases, 2291
hemibody radiation therapy, 2298
narcotic medications, 2295
stereotactic radiosurgery, 2298
complementary therapies, 2319
electrostimulation, 2318
interventional management, 2318–2319
narcotic medications, 2295, 2297
neuroablative techniques, 2318
neuroaxial techniques, 2318–2319
nonopiate medications, 2316*t*
opioid medications, 2316*t*
radiotherapy procedures, 2319
routes of administration, 2317
WHO pain ladder, 2316
Pair production, 175, 176*f*
Palifermin. *See* Keratinocyte growth factors (KGF)
Palliative and supportive care, 978–980, 1904. *See also specific cancers* and specific techniques
Accountable Care Organizations and, 827
ASCO, 2322–2323
cancer-related fatigue, 2323–2324
cancer-related weight loss and cachexia, 2324–2325
definition, 2322
for metastatic disease, 2288–2299, 2306*f*
PROMs survey report, 2323
radiotherapy-associated fatigue, 2324
Palliative medicine, ethical issues, 818–819
Palliative radiation therapy, 29
Pamidronate, 2293
Pan masala, 1097
Pancoast, Henry, 1263
Pancoast syndrome, 1252, 1263–1264
Pancreas, anatomy, 702, 1523, 1523*f*
Pancreatic cancer, 1523–1537
adenocarcinoma, 703
borderline resectable, 1534
classification, 1524–1525
clinical presentation, 1524
clinical trials, 1528*t*, 1533*t*
epidemiology, 1523

evaluation, 1524
imaging, 703–704
IMRT and VMAT plans, 490*f*
intraoperative radiotherapy, 466
locally advanced, 1532
management
causes of death, 1526
chemoradiation, 1530–1531
patterns of failure, 1526, 1526*t*
RT outcomes, 1526
RT techniques, 1526, 1527*f*
surgical, 1525
pathways of spread, 1523
pediatric, 2222–2223
proton therapy, 489–490, 490*f*
risk factors, 1523–1524
SBRT for, 446–447
staging, 1524, 1526*t*
targeted therapy, 1536–1537
Pancreatitis/pancreatic insufficiency, 2344
Pancreatoblastoma, 2222–2223
Papanicolaou smears, 1765–1766
Papillary fibroelastoma, 1361
Papillary thyroid cancer (PTC), 1237, 1239*f*, 1243
Para-aortic lymph nodes
elective irradiation, 1795
involvement of, 1837
irradiation of, 1784–1786, 1786*f*
metastatic, 1795
sampling, 1838
Paraganglioma, 621, 934–939, 1181
clinical presentation, 935
diagnostic workup, 935
epidemiology and risk factors, 934–935
general management, 936
head and neck, 1182*f*
imaging, 935–936
mediastinal, 1298
natural history, 935
pathology, 934
pediatric, 2226–2227
principles of radiation therapy, 937–938, 938*t*
radiation techniques, 939
staging, 936, 936*t*, 936*f*
surgery, 936–937, 937*f*
systemic therapy, 939
Paragangliomas tumors, 1181–1187
clinical presentation, 1182

diagnostic workup, 1182–1184, 1182*t*
embolization, 1184
epidemiology, 1181–1182
radiation therapy, 1184–1185, 1187*t*
staging, 1184, 1184*t*
surgical management, 1184, 1187*t*
Paralysis, radiation-related, 1817
Paranasal sinus tumors, 1040–1953
chemotherapy, neoadjuvant and concomitant, 1045
epidemiology of, 1040
IMRT and proton plans, 482*f*, 484*f*
management, 1045, 1057*t*, 1058
neck irradiation and, 1052
outcomes, 1052–1058
proton therapy, 481
solitary fibrous tumors, 1187
staging, 1044*t*
target volumes, 1049–1050
Paranasal sinuses
anatomy of, 1040
pretreatment evaluation, 1043*t*
Paraneoplastic syndromes (PNS), 1026, 1252, 1271, 1613
Paratesticulartumors, 2134
Parathyroid hormone-related protein (PTHrP), 1252
Parent nuclides, 173, 174*f*
Parenteral nutrition, 418
Paris system, 529–530, 529*t*, 530*f*
Parity, breast cancer risk and, 1388
Parker, Herbert, 525
Parkinson disease (PD), 428
radiation therapy, 2243
Parotid gland
anatomy, 1061–1062
irradiation volume, 1077–1079
lymph node distribution, 1062*f*
RT effects on, 334
Parotid gland cancer
clinical presentation, 1064
nerve involvement, 1080*f*
prognosis, 1074–1075
radiation therapy, 1077–1079, 1078*f*, 1079*f*
recurrent adenocarcinoma, 1080*f*
SCC, recurrent, 1088*f*
solitary fibrous tumors, 1187
tumors of, 694
Parry disease. *See* Graves ophthalmopathy
Partial responses (PRs), 382
Partially wide tangentials, 1434*f*

Particle therapy, 160, 471–498, 1084–1086
applications and outcomes, 478–496
challenges, 497
comparative effectiveness, 495–497
cost-effectiveness, 496–497
emerging technologies, 497–498
potential applications, 478–481
rationale for, 471–473
therapeutic ratio and, 471
toxicity, 498
treatment planning, 476
x-rays compared with, 471–473
Paterson, Ralston, 525
Pathologic fractures
bone metastases and, 2291–2292
prediction scoring, 2291
radiation-related injury, 1818
Patient-centered cancer care, 831–832
Patient-derived xenograft (PDX), 399
Patient dose calculations, 262–264
Patient evaluation, 56
Patient immobilization and stabilization
body conformal devices, 204–208
prone positioning for pelvic and breast treatments, 208–209
space considerations, 209
brachytherapy. *See* Brachytherapy
computed tomography simulator, 201
dosimetric effects of devices, 209
evolution of, 226
head and neck devices
bite blocks as an alternative to masks, 204
thermoplastic masks, 201–204
intraoperative radiotherapy, 223, 224*f*
magnetic resonance linear accelerator, 224
patient positioning
clinical applications, 214–215
emerging technology for monitoring, 215–216
intrafraction monitoring with surface-guided radiation therapy, 212–213
optical surface-guided radiation therapy systems, 213–214
real-time monitoring, of, 212–216
rationale for, 200
simple immobilization devices, 200–201
stereotactic
extracranial immobilization devices, 211–212
immobilization and internal motion management, 212
intracranial immobilization devices, 210–211
total body irradiation immobilization, 220–222
total skin electron irradiation immobilization, 222–223

upright radiation therapy, 224–225
Patient journey, 735–739
automation of contouring, 736–737
automation of treatment planning, 737
peer review, 737
postsimulation image processing, 735–736
preradiation treatment verification/quality assurance, 737–738
radiation treatment prescription, 735
radiotherapy simulation, 735
treatment setup/delivery, 738–739
workup and treatment decision-making, 735
Patient motion. *See also* Motion management
breathing-related, 441–442
Patient-physician relationships, 818, 819
Patient positioning
cervical cancer patients, 1778
clinical applications, 214–215
conformal radiation therapy, 284–285, 284*t*
emerging technology for monitoring, 215–216
intrafraction monitoring with surface-guided radiation therapy, 212–213
optical surface-guided radiation therapy systems, 213–214
pediatric patients, CNS tumors, 2073
quality assurance, 297–298
real-time monitoring, of, 212–216
for RT
beam alignment, 1428–1429
in breast cancer, 1426, 1426*f*, 1427*f*
target localization and, 441
treatment planning, 246–247
Patient-related quality management, 61
Patient-reported outcome measures (PROMs), 2323
Patient topography
bolus design, 267*f*
circular anatomy, 230*f*
dose calculations and, 230
heterogenous dose, 259–261
varying, 230
Pauli exclusion principle, 170
Pautriermicroabscesses, 2000
PAX3 gene, 2140
Pazopanib, 1867, 1869
PBRT. *See* Proton beam radiation therapy (PBRT)
PCFCL (primary cutaneous follicle center B-cell lymphoma), 2007
PCLBCL, Leg Type (PCBCL-LT), 2007
PCMZL (primary cutaneous marginal zone B-cell lymphoma), 2007
PDDs (percent depth doses), 193, 194*f*, 229
PDT. *See* Photodynamic therapy (PDT)
Peakscatter factor (PSF), 191, 194, 194*f*

Pearson Chi-square test, 395
Pediatric patients
  acute lymphocytic leukemia, 2013
  anaplastic ganglioglioma, 2086
  breast tumors, 2221
  central neurocytomas, 2086
  chordomas in, 1194
  choroid plexus tumors, 2085
  CNS tumors, 2072–2076
  cranial irradiation, 2194
  craniopharyngiomas, 2092–2095, 2095*f*
  craniospinal irradiation, 2076
  CSI treatment, 309*f*
  decreased growth velocity, 418
  desmoplastic small round-cell tumors, 2230–2231
  ependymomas, 2083–2085
  esthesioneuroblastoma, 2219
  ethical issues, 818
  Ewing sarcoma family of tumors, 2164–2173
  fetal radiation doses, 251–252
  ganglioglioma, 2086
  gastrointestinal cancer, 2221–2225
  germ cell tumors, 2091–2092, 2228–2229
  head and neck cancers, 2219–2220
  hemangiomas, 2229–2230
  hepatobiliary tumors, 2223–2225
  high-grade astrocytoma, 2080
  Hodgkin lymphoma, 1968
  juvenile nasopharyngeal angiofibromas, 2219–2220
  leukemias, 2014
  lung cancer, 2220–2221
  lymphangiomas, 2230
  malignant melanoma, 2231–2232
  medulloblastomas, 2087–2090, 2088*f*
  nasopharyngeal carcinoma, 2218–2219
  neuroblastoma, 2116–2125
  non-Hodgkin lymphoma, 2188–2194
  nonrhabdomyosarcoma soft tissue sarcoma, 2144–2154
  optic pathway glioma, 2080–2081
  oropharyngeal cancer, 2219
  pancreatic cancer, 2222–2223
  pineal parenchymal tumors, 2086
  pineocytoma, 2086
  pituitary adenomas, 2095–2096
  pleuropulmonary blastomas, 2220–2221
  proton therapy, 309
  radiation-induced myelopathy in, 330
  radiotherapy

long-term effects, 2072–2073
preparation for, 2073
retinoblastoma, 2201–2216
rhabdomyosarcoma, 2129–2140, 2221
salivary gland cancer, 1086
spinal canal tumors, 952
spinal cord compression, 2283–2285
thyroid cancer in, 1242–1243
thyroid dysfunction, 418
whole brain radiotherapy, 320
Wilms tumor, 2103–2113
Peer review, QA programs and, 297*t*
Pegylated liposomal doxorubicin, 1868
Pel-Ebstein pattern, 1956
Pelvic insufficiency fracture, 2354
Pelvic lymph nodal disease
involvement, 1837
management of, 1711–1715
rationale, 1711–1715
whole-pelvic radiation therapy, 1713*f*, 1715*t*
Pelvic radiation, 1848
Pelvis
anatomy, female, 1762*f*, 1879*f*, 1880*f*
EBRT portals, 1779*f*
extended-field IMRT, 1785*f*
lymph nodes
anatomy, 704
endometrial cancer and, 1838–1839, 1839*f*
field design, 1780*f*
imaging, 704
occult involvement, 1570–1671
sampling, 1838
in vulvar cancer, 1930
pathologic fractures of, 2292
pattern of recurrence, 1631
recurrent malignancies
palliative treatment, 2307–2308
rhabdomyosarcoma, 2133
RT fields, 1934*f*
Pemetrexed, radiation response and, 718
Pencil-beam algorithms (PBAs), 255, 264
Pencil-beam redefinition algorithms (PBRAs), 264
Penile bulb, 345
Penile cancers, 1747–1759
classification of, 1749–1751
diagnosis, 1749, 1749*t*
epidemiology, 1748
lymph nodes, occult positive, 1753*t*

management
brachytherapy, 1755
chemotherapy, 1753, 1753*t*
conservative therapies, 1752
external beam therapy, 1754–1755
outcomes, 1755–1757
radiation therapy, 1753
surgical, 1752–1753, 1757*t*
targeted therapy, 1753–1754
treatment approach, 1752
metastatic, 1750, 1751*t*
natural history, 1748
presentation, 1748, 1748*f*
prognostic factors, 1751
risk factors, 1748
SCC, 1758*f*
secondary cancers and, 1751*t*
staging, 1749, 1750*t*
Penis, 562, 563*f*
Penis, anatomy of, 1747
Pentoxifylline (Trental), 2329
Perceived radiation therapy, 62
Percent depth doses (PDDs), 193, 193*f*, 229, 234–235, 235*f*
Percival, Thomas, 813–814, 814*f*
Percutaneous ablation, 1548
Perez, Carlos, 87, 87*f*
Perfluorocarbons, 20
Performance management guide, 367*f*
Perianal cancer, 1603–1604
Perianal skin, 1595
Pericardial effusion, 337–338
Pericarditis, 2347
Pericardium
radiation-induced injury, 1970, 2178
tumors of, 1361–1370, 1363–1364*t*
classification, 1364, 1365*t*
diagnosis, 1362*t*, 1363–1364
epidemiology, 1361–1362
incidence, 1361–1362
management, 1365–1366
metastatic, 1362*t*, 1366
natural history, 1362–1363
outcomes, 1368–1370
presentation, 1362*t*
prognostic factors, 1364
staging, 1364
Pericytes, 155
Periorbital skin cancers, 969

Peripheral nerve sheath tumors, 1298
Peripheral T-cell lymphomas (PTCL)
  clinical management, 1990, 1992*f*
  clinical presentation, 1990
  pathology, 1989–1990
  prognostic factors, 1990–1991
Peripheral vascular disease, 345
Peritoneal cytology, 1837
Periurethral duct carcinoma, 1679
Permanent brachytherapy, 44
Permanent implants, 556
Permanent interstitial brachytherapy, sources for, 509–512, 509*f*, 510*t*, 511*f*
Peroxynitrite, 319
Personalized ultrafractionated stereotactic adaptive radiotherapy (PULSAR), 454
Pertuzumab, 1462
Pesticide exposures, 1543, 1975
PET. *See* Positron emission tomography (PET)
Peters, M. Vera, 83–84, 84*f*
Peutz-Jeghers syndrome, 1771, 1858, 2221
Peyronie disease (PYD), 2250–2251
Peyton Rous, Francis, 4, 4*f*
pH modification, 658
Phantom scatter factor (Sp), 229–230
Pharmacokinetics, 619, 620
Pharyngotympanic tube, 1001
Pharynx, 332–333
PHD-2, 153, 154
Phenazopyridine (Pyridium), 2329
Phenazopyridine, urinary tract injury, 2329
Phenoxy herbicides, 2054
Pheochromocytomas, 621, 1298, 1951, 2226–2227
Philadelphia chromosome, 2014
Phimosis, 1747, 1748
Phoenix definition, 445, 1696, 1703
Phonation, post-RT, 333
Phosphorescence, 192
Phosphorus-32, 1865, 1868
Photodisintegrqation, 175
Photodynamic therapy (PDT)
  light interaction, 161
  radiation-activated, 163–164
Photoelectric effects, 174–175, 175*f*
Photofrin (porfimer sodium), 163
Photon beam dosimetry, 234–239, 235–236*f*, 235*t*, 238*f*
Photon beam radiotherapy, 1191–1192, 1935
Photon external-beam dosimetry, 229–252
Photon radiation therapy, for spinal canal tumors, 954
Photon spectrum and dosimetric characteristics, 504–508, 506*f*, 507*f*

Photons
attenuation, 173–174
beam energies, 235*t*
definition, 173–174
interaction with matter
coherent scattering, 174
compton effect, 175, 175*f*
pair production, 175, 176*f*
photodisintegration, 175
photoelectric effect, 174–175, 175*f*
relative importance, 175–176, 176*f*
mass attenuation coefficient, 174, 174*f*
treatment machines
cobalt-60 teletherapy, 178–179
Gamma Knife, 178, 178*f*
Halcyon machine, 182, 183*f*
linear accelerator, 179–181, 180*f*, 181*f*
VHE electron beams, 186
ViewRay system, 183*f*
x-ray, 173
Phototherapy, for mycosis fungoides, 2001
Physical therapy, 1444
Physician expertise, 829
Physician-patient relationships, 813
Physics vs. biology, 49–51
Pia mater, 692
Pian fungoide, 1998*f*
Pigmented villonodular synovitis, 2249
PIK3CA mutations, 1833, 1849, 1856
Pineal parenchymal tumors, 2086
Pineoblastomas, 2086–2087
Pineocytoma, 2086–2087
Pinna, 976–977
Pipelle devices, 1829
Piperazinedione, 1934
Pituitary adenomas
anatomy, 912–913
function and blood supply, 912–913
gross anatomy and embryology, 912, 912*f*
benign, 2238
disorders, 913
functioning pituitary neuroendocrine tumors, 916–918
acromegaly, 916, 917*t*
Cushing disease, 916, 917*t*, 918
pituitary adenoma suppressive medications, temporary cessation of, 918
prolactinoma, 918
whole-sellar treatment, 918
histopathology and grading, 913

ionizing radiation techniques, 914
conventional fractionated external beam radiotherapy, 914
proton beam/particle therapy, 914
stereotactic radiosurgery, 914
management, 432
nonfunctioning pituitary neuroendocrine tumors, 914–916
repeat stereotactic radiosurgery, 916
timing of radiation therapy and stereotactic radiosurgery, 915
tumor control, 914–915, 915*t*
upfront stereotactic radiosurgery, 916
pediatric, 2095–2096
pituitary neuroendocrine tumors clinical presentation and treatment, 913–914
suppressive medications, temporary cessation of, 918
toxicity, 918–919
cranial nerve deficits, 918, 919*t*
hypopituitarism, 918
long-term tumor occurrence, 918
vascular stenosis and stroke after prior ionizing radiation, 919
Pituitary dysfunction, 2030
Placental alkaline phosphatase (PLAP), 1732
Planck constant (h), 171
Planning conferences, 298–299
Planning organ at risk volumes (PRVs), 283
Planning target volumes (PTVs), 30
definitions, 282, 282*f*, 2138
low dose regions, 287
in lung cancer, 1265–1266
margins, 287*f*
in nasopharyngeal cancer, 1015
in paranasal sinus tumors, 1049
in prostate cancer, 1684
in testicular cancer, 1741–1742
in urethral cancer, 1917
Planning treatment volumes (PTVs)
in oral cavity cancer, 1110, 1111
in spinal canal tumors, 953
Plantar fasciitis, 2254–2255
PLAP (placental alkaline phosphatase), 1732
Plaque brachytherapy, 964, 966–967, 966*f*
Plasma cell leukemia, 2039
Plasma cell neoplasms, 2037–2050
clinical presentation, 2037–2039
diagnosis, 2039–2040
epidemiology, 2037
etiology, 2037
multiple myeloma, 2038*t*, 2039
management, 2042–2045
relapsed/refractory, 2044–2045

pathophysiology, 2037
plasma cell leukemia, 2039
prognostic factors, 2040
smoldering myeloma, 2038
solitary plasmacytomas, 2038
management of, 2040–2042, 2041*t*, 2041*f*
radiotherapy, 2041
staging, 2039–2040, 2040*t*
Plastic masks, 246
Platelet-derived growth factor receptor (PDGFR), 105
Platinum-based drugs, 716–717
Pleomorphic adenoma, 1077, 1077*f*
Pleomorphic sarcoma, 1369*f*
Pleura, oncologic anatomy, 698, 698*f*
Pleuropulmonary blastomas, 2220–2221, 2220*f*
Plexopathy, 1817, 2319
Plummer-Vinson syndrome, 1145, 1318
Pneumonectomy, 336
Pneumonitis, 1252, 418. *See also* Radiation pneumonitis
Point spread function, 231
Poisson distribution, 48*b*
Policies and procedures, 385. *See also* Documentation; Protocol documents
Policy and procedures (P&Ps), 299
Polycyclic aromatic hydrocarbons, 1251, 1637
Polycystic ovarian disease, 1857
Polymer-gel dosimetry, 193
Polymethylmethacrylate (PMMA), 266
Polyurethane molds, 246
Popcorn cells, 1959
Populations, clinical trials, 379
Porfiromycin, 679
PORTEC trials, 1837
Positive surgical margins (PSM), 1722
Positron decay, 173
Positron emission tomography (PET)
description of, 691
diagnostic
for breast cancer, 1396
for cervical cancer, 1767, 1768–1769, 1768*t*, 1769*f*
for colorectal cancer, 1571
for endometrial cancer, 1830
for gastric cancer, 1494
for Hodgkin lymphoma, 1957
for lung cancer, 1253
for oropharyngeal cancer, 1126
for osteosarcomas, 2157
for pancreatic cancer, 1524
testicular carcinoma, 1734

for vaginal cancer, 1884–1885
for vulvar cancer, 1927
during HL treatment, 1970
post-treatment, 1771
prostate cancer, 1711
proton beam irradiation, 311*f*
simulations, 1960
Post-breast surgery pain syndrome, 2356
Posterior (proximal) urethral cancer, 1914
Posterior glioma, 2081
Postmarketing surveillance trials, 379
Postmastectomy radiation therapy (PMRT)
prostate cancer, 1724
Postmastectomy radiation therapy, 672
Postoperative irradiation, 62
Post-treatment whole-body scans (RxWBS), 1239–1240, 1240*t*
Postvoid residuals, 344
Potentially lethal damage repair (PLDR), 714
Power, statistical, 382–383
PRECIST (Positron Emission Tomography Response Criteria in Solid Tumors) criteria, 389
Precursor hematologic neoplasms, 2008
Prednisone. *See also* BEACOPP regimen; COMP regimen; COP regimen; COPP/ABV regimen; MACOP-B regimen; MOPP regimen; OEPA regimen; OPPA regimen; ProMACE/MOPP regimen
for ALL, 2018
for bone metastases, 2293
for Hodgkin lymphoma, 1959
Pregabalin, pain management using, 2316*t*, 2317
Pregnancy
after breast cancer, 1424–1425
breast cancer prognosis and, 1402
cervical cancer and, 1798–1799
fetal doses in, 251–252
radiation therapy and, 1424
after RT, 2111
Preoperative radiation therapy, 62, 1634
Prescriptions. *See* Dose prescriptions
Primary central nervous system lymphoma, 898–900
Primary chemotherapy, 62
Primary cutaneous anaplastic large cell lymphoma (PC-ALCL), 2006
Primary cutaneous diffuse large B-cell lymphoma, leg type, 2007
Primary cutaneous follicle center B-cell lymphoma (PCFCL), 2007
Primary cutaneous lymphomas, 1998–2009
Primary cutaneous marginal zone B-cell lymphomas (PAMZL), 1917
Primary cutaneous peripheral T-cell lymphoma, 2007
Primary intracranial neoplasms
anatomy, 868–870, 868–870*f*
chemotherapy/targeted agents, 878–881

conventional chemotherapy, 879
direct delivery of therapeutic agents, 879–880
targeted agents, 880
tumor-treating fields therapy, 881
clinical presentation, 871, 871*t*, 872*f*
diagnostic workup, 872–873
cerebrospinal fluid cytology, 872–873
differential diagnosis, 873, 873*t*
histologic confirmation of diagnosis, 872
imaging studies, 872, 873*f*
epidemiology, 870–871
follow-up, 881
general management, 873–875
cerebral edema, 875
seizures, 875
individual tumors, management of, 882
adult brainstem glioma, 894–896
anaplastic astrocytoma, 889–890
anaplastic oligodendroglioma, 888–889
craniopharyngioma, 903
ependymoma, 896–897
glioblastoma, 882–885, 882*t*
gliomatosis cerebri, 894
hemangioblastoma, 905
hemangiopericytoma, 905
low-grade glioma, 890–894, 892*t*
malignant glioma, 882
medulloblastoma, 897–898
meningioma, 900–903, 901*t*
neurofibroma, 904–905
primary central nervous system lymphoma, 898–900
tumor-treating fields, 885–888
vestibular schwannoma, 904
World Health Organization grade 3 gliomas, 888
natural history, 871
pathology, 873, 874*t*
radiotherapy, 875–879
radiobiologic considerations underlying tissue injury, 875–876, 876*f*
radiotherapy techniques, 876–879, 877*f*, 878*t*, 878*f*
sequelae of treatment, 881–882
radiotherapy, 881–882
surgery, 881
surgery, 875
operative technique, 875
Primary lymphomas, prostate, 1680
Primary mammary lymphomas, 1399
Primary mediastinal (thymic) large B-cell lymphoma, 1982
Primary mediastinal B-cell lymphoma (PMBL), 2193–2194

Primary orbital lymphoma, 968, 969*f*
Primary prevention strategies, 15
Primary sclerosing cholangitis, 1557
Primitive neuroectodermal tumors (PNET), 2089
Principal quantum numbers, 169
Principlism, 812
Prior ionizing radiation, vascular stenosis and stroke after, 919
PRKAR1 gene, 1361
Probiotics, 2326
Procarbazine, 1968. *See also* ProMACE/MOPP regimen
Procarbazine hydrochloride, 952, 1968. *See also* BEACOPP regimen; COPP/ABV regimen; MOPP regimen; OPPA regimen
Process, 829–830
Proctitis, 1816, 1902, 2326. *See also* Mucositis, gastrointestinal
  pain management in, 2319
Proctosigmoiditis. *See* Mucositis, gastrointestinal
Proctosigmoidoscopy, 1884
Progesterone receptor status, 1400
Prognostic value of, 1772–1773
Programmed cell death protein 1 (PD1), 108
Programmed death ligand 1 (PD-L1), 1775
Progression, trial endpoints, 382
Progressive transformation of germinal centers, 1959
Prolactinoma, 918
Prolaris, 1677–1678
ProMACE/MOPP regimen, 341
Prosnitz, Leonard, 2
Prostate, 560–562, 561–563*t*, 562*t*
Prostate brachytherapy, 594–595
Prostate cancer, 601–606
  active surveillance, 1681–1682
  anatomy of, 707
  clinical indications, 601–602, 602*t*
  clinical presentation, 1703
  clinical target volume, 287*f*
  detection of, 1672, 1672*t*
  diagnosis, 1673–1674, 1674*t*
  dose distribution displays, 289, 290*f*, 291
  epidemiology, 1667–1669
  focal ablative therapies, 1695–1696
  follow-up, 605, 606*f*
  genomic testing and molecular biomarkers, 1677–1678
  high risk, 1677
  histology, 1679–1680
  hormone-refractory, 2293
  imaging, 707–708
  IMRT, 495*f*
  incidence, 1695

intermediate- and high-risk disease, definitions of
androgen deprivation therapy and RT, 1719–1722, 1721*t*
boost techniques, 1715, 1716*f*, 1717*f*
brachytherapy boost, 1715–1717
external beam radiation therapy, 1717–1718
image-guided IMRT, 1718
IMRT, 1718–1719, 1720*f*
long-term ADT, optimal duration of, 1721–1722
nodal imaging for radiation therapy, implications of, 1710–1711
pelvic lymph nodal disease, management of, 1711–1715
phase III randomized prostate cancer trials, cautionary notes on, 1707–1710
risk group classifications, limitations of, 1703–1707
risk stratification groups, 1703
SBRT boost, 1717
sequence-dependent interactions between ADT and EBRT, 1721
short-term ADT, optimal duration of, 1721
toxicities associated with androgen deprivation therapy, 1722
volumes and setup variation, 1718
whole-pelvic radiation therapy, 1713*f*, 1715*t*
intermediate risk, 1695
low-risk, 1665–1696
lymph node involvement, 1670–1671
natural history of, 1669–1671
outcomes, 602–605, 603–604*t*, 1688–1689
pathology, 1678–1680
penile bulb irradiation in, 345
physiology, 1666–1667
postoperative radiation therapy
androgen suppression therapy, 1724
local *vs.* distant recurrence, 1722–1723
postoperative radiation therapy dose, 1724–1725
postoperative radiation therapy volume, 1725
salvage radiation therapy, 1724
prognosis, 1679
proton therapy, 492–495, 494*t*, 495*f*
proton/heavy ion particle therapy, 1695
radiation therapy techniques, 1683–1687
radical prostatectomy, 1682–1683
rectal toxicity and, 344
rhabdomyosarcoma, 2133–2134
risk factors, 1667–1669, 1668*t*
risk stratification systems, 1676–1678, 1677*t*
SBRT for, 445–446
screening for, 1671–1676
staging, 1673, 1676–1678
technique, 605
treatment planning, 290*f*, 605, 605*t*
U.S., 1680–1681

Prostate gland
anatomy of, 707–708, 707*f*, 1665–1666, 1665*f*, 1666*f*
carcinomas, 1669
imaging, 707
motion of, 1684
Prostate-only radiation therapy (PORT), 1712
Prostate-specific antigen (PSA)
density of, 1672
doubling time, 1695
free, 1673
postirradiation, 1694–1696
RT-PCR assay, 1673
screening for, 1671–1676
secretion of, 1666–1667
velocity of, 1673
Prostate-specific membrane antigen (PSMA), 1673
Prostatectomy, 1682–1683, 1688, 1691–1692
Prostatic acid phosphatase (PAP), 1671
Prostatitis, 2350
Prostheses, metal, 237
Protein kinase C (PKC), 105
Proteins, turnover of, 2324
Proto-oncogenes, 6
Protocol documents, 384. *See also* Policies and procedures
Proton beam radiation therapy (PBRT), 304
craniospinal, 2074*f*
development of, 185
for paranasal sinus tumors, 1049
for uveal melanoma, 967
Proton beam radiation therapy, 1135
for prostate cancer, 1695
Proton beam/particle therapy, 914
Proton beams
delivery of, 475–476
production of, 473–475
radiosurgery techniques, 425
transport of, 473–475
Proton energy, 304*f*
Proton radiosurgery, 425
Proton therapy
biologic dose of, 305
dosimetry, 304–305
image guidance in, 310, 311*f*
physics of, 303–304, 303–304*f*
quality assurance, 309–310
thoracic and abdominal, 308–309
treatment planning
base of skull, 307, 308*f*

brain, 307, 308*f*
breast, 308, 309*f*
head and neck cancer, 307–308
pediatric patient, 309, 309*f*
sarcomas, 309
scanned beams, 306, 306*f*
scattered beams, 306, 306*f*
site-specific proton, 307–309
uncertainties, 305–306, 305*t*
Proton/heavy ion particle therapy, 1695
Protons
definition of, 169
heavy-ion treatment machines, 185–186
interactions with matter, 176
linear energy transfer, 305
Pseudosarcomas, esophageal, 1327
PSF (peakscatter factor), 191, 194, 194*f*
Psychiatric disorders, 2243–2244
Psychosocial problems, 1970
PTC (papillary thyroid cancer), 1237, 1239*f*, 1243
PTCL. *See* Peripheral T-cell lymphomas (PTCL)
PTEN gene
function of, 106
loss of function, 1833
ovarian cancer and, 1856
Pterygium
management of, 961
Puberty, delayed, 2013, 2095
Pulmonary fibrosis, 1743, 2184
Pulmonary function tests (PFTs), 334
Pulsed-dose rate brachytherapy, 44
Pupil, anatomy of, 959
PV701, 2326
PVC regimen, 1872
Pyriform sinus cancer, 1144*f*, 1147*f*, 1148*f*

Q

Qualifications of an expert, 66
Qualified experts, 66
Qualitative versus quantitative research, 773–774, 773*t*, 774*t*
Quality-adjusted life year(QALY), 748, 835
Quality assurance (QA)
AAPM Task Group (TG)-100 FMEA, 360, 361*t*
artificial intelligence, 371
beam arrangement, 298
brachytherapy, 62
conformal radiation therapy, 296–299, 297*t*, 298–299

contributory influencing factors, 360, 360*t*
error contributors, 363
  burnout, 364
  cognitive bias, 365, 365*t*
  culture of safety, 363–364, 364*t*
  hierarchy and fear of reprisal, 364–365
  hierarchy of interventions, 363*t*
  human beings, 363
  mistake-prone design, 365–366
  technological advancement, 365
error etiology, 359–361
error monitoring challenges, 362–363
error prevention
  accreditation, 367
  building and maintaining strong safety culture, 366, 366*f*
  hierarchy of interventions, 367
  performance management guide, 367*f*
  work environment and leadership, 366
ethics of error disclosure, 371
external beam, 61–62
feedback, 362
future directions, 372
hazard and risk analysis, 369
IAEA role in, 761
imaging data acquisition, 297–298
immobilization, 297–298
impaired colleague, 371
key goal, 359–360
mobile IEORT linear accelerators, 463
patient positioning, 297–298
peer review
  chart rounds, 368
  limitations of, 368
  physicist plan and chart review, 368
  prospective review, 369
  standardization, 369
physical dosimetry, 368
plan implementation, 299
planning conferences, 298–299
policy and procedures, 299
prospective risk analysis, 369
proton therapy, 309–310
quality gap, 361–362
Radiation Oncology Health Advisory Committee (ROHAC) score, 360, 360*t*
retrospective risk analysis, 370
  incident learning systems, 370
  London Protocol, 370–371
  root cause analysis, 370–371

second victim phenomenon, 371–372
tools to reduce error, 368
total-body irradiation, 414
treatment plans review, 362
treatment verification, 291, 299
volume delineation, 298
Quality assurance on treatment plan, 585
Quality management (QM)
defined, 61
equipment and device, 61
management program, 610–612
patient-related, 61
Quality of life (QOL)
chemoradiation and, 1536
hypopharyngeal cancer and, 1157
pain management and, 2293
Quality of radiation oncology, LMIC, 758–760, 762
QUANTEC review, 316–350, 346–349*t*
Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC), 35
Quantum physics, 171
Quimby, Edith Hinkley, 80–81, 80*f*
Quimby system, 528–529

R

Race and ethnicity, 847–849
breast cancer prognosis and, 1402
cancer pain management, racial disparities in, 848
cancer survival, racial disparities in, 848–849, 849*f*
definitions, 847
endometrial cancer and, 1836
ovarian cancer and, 1855
prognosis and, 1772
radiation oncology treatment, racial disparities in, 847–848, 848*f*
thyroid cancer and, 1238
vaginal SCC risk and, 1885–1886
vulvar melanomas and, 1923
Racetrack microtrons, 178
Radiation, 119–120
absorbed doses, 17, 189–193
as drug, 152
exposures, 188–189
breast cancer risk and, 1389
salivary gland cancers and, 1063
principles of, 172–173
quality of, 188
radiation-induced normal tissue injury, 139*f*
Radiation addiction, 152

Radiation biology, 97–110
Radiation cystitis, 2348–2350
Radiation dermatitis, 2354–2356
Radiation dose constraints, 939, 940*t*
Radiation-enhanced antigen presentation, 54–55
Radiation enteritis, 2344
Radiation esophagitis, 2343–2344
Radiation fibrosis, 35–36, 35*f*
Radiation immune modulation, 640–643
  effector cells, 642–643
  immunogenic cell death/radiation-induced danger-associated molecular patterns, 640–642
  radiation-induced cytokines/chemokines, 642
  in situ vaccination, 640, 641*f*
  stroma and vascular changes, 640
  surviving tumor cells, radiation effects on, 642
Radiation immune suppression, 643–644
  radiation therapy–induced immune cell cytotoxicity, 643–644
  rebound immune suppression, 644
Radiation-induced heart disease (RIHD), 1367
Radiation-induced liver disease (RILD), 340, 340*t*, 340*f*, 2308, 2344–2345
Radiation-induced lung injury, 2346–2347
Radiation-induced malignancy, 427
Radiation-induced myelopathy, 330
Radiation-induced optic neuropathy (RION), 324, 324*f*, 961
Radiation-induced premature menopause, 2358
Radiation-induced second primary malignant tumors, 36–37, 36*f*
Radiation-induced skin injury, 2328
Radiation necrosis, 320, 321*f*, 426–427
Radiation nephropathy, 342, 2348
Radiation oncologist
  defined, 2–3, 2*f*
  three A's of successful consulting, 64
Radiation oncology (RO)
  applications, 726–731, 729*f*, 730*f*
  artificial intelligence, 726–731, 726*t*, 727–728*t*, 730*f*
  artificial intelligence, assessing role of, 750
  assessment of technology, 746–748
    governmental assessment, 746–747
    insurance company assessment, 747
    outcomes assessment, 747–748, 749*f*
  call for increased diversity/inclusion in the field, 850
  challenges, 740–741
    clinical implementation, 741
    clinical relevance, 741
    data availability and quality, 740
    proprietary software limitations, 741
    transparency/ethics, 741
  clinical informatics, 731–732

comparative effectiveness research, 749–750
computer vision model development, current challenges in, 734–735
current practices, 789
  areas for further scholarship in, 804
  continuing medical education in radiation oncology, 802–803
  equity, diversity, and inclusion in, 804–805, 805*t*
  graduate medical education, 792–802, 793–794*t*, 793*f*, 795*f*, 799–802*t*
  undergraduate medical education, 789–792, 791*f*
curriculum development, 774–789, 776*t*
  curriculum development models, 776–777
  dissemination, 788
  systematic curriculum development, 777–788, 777*f*, 778*t*, 779*t*, 780*f*, 781*f*, 781*t*, 783*t*, 784*f*, 785*t*, 786*t*, 786*f*, 788*t*
curriculum maintenance, renewal, and reform, 788–789
toward evidence-based radiation oncology, 750–751
future directions, 740
  foundation/generalist medical artificial intelligence models, 740
  generative artificial intelligence, 740
  multimodal models, 740
gender, 846–847
  cancer care, disparities in, 846
  definition, 846
  sexual and gender minorities, cancer disparities in, 846–847
generation of evidence, 748–749, 749*f*
intersectionality, 849–850
large language model applications, 731–732, 731*f*
learning Theory, 770–772, 770*f*, 771*f*
machine learning techniques, 726–731, 726*t*, 727–728*t*, 729*f*, 730*f*
natural language processing, 731–732
patient, interprofessional care of, 769*f*
patient journey, 735–739
  automation of contouring, 736–737
  automation of treatment planning, 737
  peer review, 737
  postsimulation image processing, 735–736
  preradiation treatment verification/quality assurance, 737–738
  radiation treatment prescription, 735
  radiotherapy simulation, 735
  treatment setup/delivery, 738–739
  workup and treatment decision-making, 735
pediatric cancers, special considerations for, 850
race and ethnicity, 847–849
  cancer pain management, racial disparities in, 848
  cancer survival, racial disparities in, 848–849, 849*f*
  definitions, 847
  radiation oncology treatment, racial disparities in, 847–848, 848*f*
radiomics/imaging-based risk predictions, 732–734, 733*f*
regulatory/ethics, 739–740

research, AI, 740
scholarship, 772–774
conceptual frameworks, 774, 774*t*, 775*t*
medical education, 772–773, 772*f*
qualitative versus quantitative research, 773–774, 773*t*, 774*t*
socioeconomic status, 843–846
access to care, 845–846, 846*f*
cancer disparities according to, 843–844, 844*f*
definition of, 843
insurance status influencing radiation oncology disparities, 844–845
Radiation oncology (RT)
abscopal effects, 54–55
artificial intelligence, 763–764
low- and middle-income country, challenges of, 764
biographical sketches. *See specific names*
biological basis of, 116–130
boron neutron capture therapy, 53–54, 53*b*
bystander effects, 54–55
cancer. *See* Cancer
care and protection of
artificial intelligence, 58, 58*b*
follow-up care, 57
patient evaluation, 56
preparing for treatment, 56–57
process of care in, 55–56
radiation oncology team, 58–59
staffing requirements, 59, 59*t*
telemedicine and remote practice, 57–58
treatment delivery, 57
treatment management, 57
combined therapeutic modalities
cancer management, 62
clinical trials, 64
integrated multimodality cancer management and organ preservation, 63–64
irradiation and drug therapy, 62–63, 64*f*
irradiation and surgery, 62
perceived radiation therapy, 62
common ethical issues in, 816–818
COVID-19 global pandemic/global oncology, 764–765
danger-associated molecular patterns, 54–55
defined, 2, 2*b*
etymology of radiate, 2*b*
FLASH therapy, 55
GRID therapy, 54–55
heavy particle beams, 53
in LMIC
access to radiation therapy, 756–758, 757*f*
advocacy, 761

burden of disease, 753
developing curricula and educational programs, 761
economics of, 760–761
epidemiology, 753–756
innovation, 762–763
planning, 761
quality of, 758–760, 762
malpractice and, 65–69
grievances, malpractice claims, and insurance disputes, 69–70
Health Insurance Portability and Accountability Act, 70
informed consent, 71–72, 71*t*
RAGE campaign, 70*b*
risk management in radiation oncology, 70–71
practice of
Rosen's rules, 65
three A's, 64
principles of, 50*t*
quality and safety, 59–60, 61*f*
brachytherapy quality assurance, 62
equipment and device quality management, 61
external beam quality assurance, 61–62
patient-related quality management, 61
radiation-enhanced antigen presentation, 54–55
radiation oncologist
defined, 2–3, 2*f*
three A's of successful consulting, 64
radiation therapy. *See* Radiation therapy
toxicity, 33–35, 33–34*f*
Radiation Oncology Practice Accreditation (ROPA), 367
Radiation optic neuropathy (RON), 2338–2339
Radiation physics, principles of, 169–197
Radiation pneumonitis, 1354, 1444, 1444*f*
dosage and, 335*f*, 336
fatal, 410
incidence of, 410
interstitial, 418
non-TBI, 407
risk factors, 336
risk reduction, 414, 418
TGF-β and, 109
Radiation proctitis, 2345
Radiation recall pneumonitis, 2347
Radiation responses, modifiers of, 677–683
Radiation retinopathy, 1058
Radiation side effect management
auditory system, ototoxicity, 2339
cardiovascular system
coronary artery disease, 2347–2348

pericarditis, 2347
valvulopathy, 2348
vascular effects, 2348
digestive system, 2341–2342*t*
ageusia, 2342
anal toxicity, 2345–2346
biliary stricture, 2345
dysgeusia, 2342
dysphagia, 2343
gastritis/duodenitis, 2344
oropharyngeal mucositis/oral infection, 2342–2343
pancreatitis/pancreatic insufficiency, 2344
radiation enteritis, 2344
radiation esophagitis, 2343–2344
radiation-induced liver disease, 2344–2345
radiation proctitis, 2345
xerostomia, 2339, 2341–2342
endocrine system, 2357*t*
hypopituitarism, 2357
hypothyroidism, 2358
radiation-induced premature menopause, 2358
female reproductive system, 2351*t*
fistula, 2351
infertility, 2352
necrosis, 2351
ovarian failure, 2352
sexual interest/arousal disorder, 2351–2352
vaginal mucositis, 2351
vaginal stenosis, 2351
vaginal ulceration, 2351
integumentary system, 2355*t*
breast fibrosis/contracture, 2356
mastalgia, 2356
post-breast surgery pain syndrome, 2356
radiation dermatitis, 2354–2356
lymphatic system
lymphedema of extremities, 2356–2357
lymphedema of head and neck, 2357
male reproductive system, 2352*t*
azoospermia, 2353
erectile dysfunction, 2352–2353
infertility, 2353
oligospermia, 2353
nervous system, 2325*t*
cerebral edema, 2336
fatigue, 2335–2336
myelitis, 2337–2338
radiation-induced cognitive decline, 2335–2336

radionecrosis, 2336–2337
respiratory system, 2346*t*
bronchial stenosis/obstruction/fistulae, 2347
radiation-induced lung injury, 2346–2347
radiation recall pneumonitis, 2347
skeletal system
costochondritis, 2354, 2354*t*
osteoradionecrosis of femur (avascular necrosis), 2354
osteoradionecrosis of mandible, 2353–2354
pelvic insufficiency fracture, 2354
trismus, 2353
urinary system, 2349*t*
prostatitis, 2350
radiation cystitis, 2348–2350
radiation nephropathy, 2348
stenosis, 2350
urethritis, 2350
visual system
cataracts, 2338
maculopathy, 2338
optic neuropathy, 2338–2339
retinopathy, 2338
xerophthalmia, 2338
vocal system, dysphonia, 2339
Radiation therapy (RT)/immune system, 712
acceptability, 758
adversenormaltissueeffectsof, 35–37
arteriovenous malformations, 2240–2241
availability, 756–758
awareness, 758
basic concepts of
accelerated repopulation, 38, 39–40*f*
altered fractionation, 37–38, 38*f*
brachytherapy and radiobiologic dose rate effect, 43–47, 44–45*f*
cell survival curve, 47–48, 47*f*
dose-time factors, 37, 38*f*, 42*b*
isoeffect graphs, 38–40, 41*f*
linear quadratic equation, 40–43, 41*f*, 42*t*
nominal standard dose, 42*b*
target theory of radiobiology, 47–48, 47*f*
for benign diseases, 2238
cellular effects, 318
cholangiocarcinoma, 1561–1562
courseof, 28–30, 29*f*
curative, 29
defined, 2
DNAdamagebyionizing, 18
dosage constraints, 1291*t*

dosein, 17–18, 18*f*
drug administration in, 715–716
ear cancer, 977–980
economics of, 760–761
effectsofirradiationoncells, 18–20, 18–19*f*
field design, 1331–1340
function of, 633–635
heavierions, 176
hyperthermia, 679, 680
for hypopharynx cancer, 1152
  targeted therapy using, 994
  for vulvar cancer, 1934
immuno-oncology, 635–640
  current directions in, 639–640
  escaping immune surveillance, mechanisms of, 636
  immune recognition of tumors, 635–636
  modern immunotherapy approaches, 636–639
indications, 29, 29*f*, 2239
late effects of, 316–350, 1519*t*
localtumorcontrolonsurvival, 22–23
long-term effects, 2072–2073
*NewYorkTimes*investigation, 65*b*
nodal imaging for, 1710–1711
nonmalignant diseases, 2237
optimizing radiation therapy variables, 644–647
  field size/irradiated target, 645–646
  FLASH radiation therapy, 646–647
  radiation therapy dose/fractionation, 644–645
  radiation therapy quality, 647
  sequencing, 646
  spatially fractionated radiation therapy, 646
originsof, 24, 27–30, 28*f*, 29*f*
overdoseandunderdose, 69*b*
palliative, 1151
  chemotherapy, 1155
  radiotherapy, 1155
palliative, 29
physicalfactors, 17
radiation immune modulation, 640–643
  effector cells, 642–643
  immunogenic cell death/radiation-induced danger-associated molecular patterns, 640–642
  radiation-induced cytokines/chemokines, 642
  in situ vaccination, 640, 641*f*
  stroma and vascular changes, 640
  surviving tumor cells, radiation effects on, 642
radiation immune suppression, 643–644
  radiation therapy–induced immune cell cytotoxicity, 643–644
  rebound immune suppression, 644

radiobiologic concepts in, 48–51
to clinical practice of radiation oncology, 48
empiricism *vs.* research-based radiation oncology, 49
physics *vs.* biology, 49–51
radiosensitivityandradiocurability, 20–21
radiotherapy plus immunotherapy, 647–650
antibody therapies, 647–648
cellular therapies, 647
cytokines, 649–650
innate agonists, 649
vaccines, 650
reimbursement, 816
response, modifiersof, 19–20
andriskofinjurytonormaltissue, 23–24, 24–27*f*
SIunitsused, 173, 189*t*
small-cell carcinoma, 1888–1890
SMART, 152–164
spatial accessibility, 758
temporal accessibility, 758
treatmentmachines, 177–186
treatmentplanningin
fourtruisms, 52–53
immobilizationandspacing, 32–33, 32–33*t*
intensity-modulatedprotontherapy, 51–52
intensity-modulatedradiationtherapy, 51–52
respiratory-dampened, respiratory-gated, andrespiration-synchronized, 33, 33*t*
three-dimensionaltreatmentplanning, 51
treatmentvolume, 30
uncertainties, 30–32, 31*f*
tumorcontrolprobability, 21–22, 22*t*, 22*b*, 23–24*f*
tumorradiosensitivityandpredictiveassays, 21
vaginal intraepithelial neoplasia, 1881–1883
vascular changes, 319
volumesin, 24*f*
worldwide access to, 756–758
Radiation Therapy Oncology Group (RTOG), 344, 375, 379, 426, 669
Radiation therapy, tumor response
cell killing, random nature of, 124–127
Mammalian survival curves, 124–127
probability, 127
radiobiology, Rs of, 127–129
Radiation tolerance
functional subunits, 120
normal tissue, 120
Radiation, toxicities of, 939–941
acute toxicity, 939–940
late sequelae, 940–941
Radiation units, nomenclature for, 283*t*

Radical vulvectomy, 1927
Radicular pain, 948
Radioactive decay, process of, 172–173
Radioactive iodine (RAI), 1236. *See also* Iodine-125; Iodine-131
  for DTC management, 1244, 1244*t*, 1245–1246*t*
  for thyroid cancer, 2227
    classification, 1238, 1238*t*
Radioactive iodine uptake (RAIU), 1239, 1240*t*
Radiobiologic considerations, 557
  reassortment, 557
  reoxygenation, 557
  repair, 557
  repopulation, 557
Radiobiologic dose rate effect, and brachytherapy, 43–47, 44–45*f*
Radiobiologic features, 543–548, 543*f*, 544*f*
Radiobiology, 47–48, 47*f*, 616–618
  dose rate/absorbed dose distribution considerations, 616, 618
  immune effects, 618
  low dose-rate effects: hypersensitivity, cell cycle, and cell death, 618, 619*f*
Radiochromic dyes, 192
Radiochromic film dosimetry, 192
Radiocurability, 20–21
Radiofrequency ablation (RFA), 1617, 2293
Radiogenomics, 110
Radiography, 688
  digitally-reconstructed, 281, 288, 289*f*, 297
Radiomics/imaging-based risk predictions, 732–734, 733*f*
Radionecrosis, 2336–2337
Radionucleotides
  average life of, 173
  half-lives, 173
Radiopaque markers, 284, 1800, 1802
Radiopharmaceutical therapy (RPT)
  biomolecular scaffolds/pharmacokinetic implications, 618–620, 620*f*
  birth of radiation medicine, 616, 617*t*
  clinically approved radiopharmaceutical therapy agents, 620–622
  emerging targets/applications, 629
  existing agents, optimization of, 626–629
    αversus β, 628
    combination therapy, 628
    methods for radiopharmaceutical therapy dosimetry, 626–627, 627*f*
    new agents, same targets, 628–629
    new indications, 627–628
    personalized dosimetry, 626
    same agents, different diseases, 628
  nuts and bolts of, 622–626
    implementation, 622–623
    workforce, 623–626, 623–625*f*

radiobiology, 616–618
dose rate/absorbed dose distribution considerations, 616, 618
immune effects, 618
low dose-rate effects: hypersensitivity, cell cycle, and cell death, 618, 619*f*
types of radiation/radiobiologic implications, 616, 617*f*
Radiopharmaceuticals
metastatic disease of bone, 2298–2299
nuclear imaging use of, 691
Radioprotectors, 20
chemical, 681–683
chemoradiation therapy and, 720
toxicity of, 677
Radiorecurrent disease, 605
Radioresistance, 128, 130, 714–715
Radiosensitivity, 20–21
of cardiac pacemakers, 251
chemotherapy-induced, 716*t*
cytotoxins, 153
inherent, 21
normal tissue, 426
and predictive assays, 21
Radiosensitization
chemical, 677–681
hypoxic, 714–715
metastatic brain cancer, 2272, 2272*t*
Radiosensitizers, 20
Radiotherapy, 97, 875–879
effect of, 101
hepatocellular cancer, 1552, 1552*t*
personalized, 110
radiobiologic considerations underlying tissue injury, 875–876, 876*f*
radiotherapy techniques, 876–879, 877*f*, 878*t*, 878*f*
rectal cancers, 1589
Radiotherapy-associated fatigue, 2324
Radiotherapy plus immunotherapy, 647–650
antibody therapies, 647–649
co-stimulatory molecules, 648
immune checkpoint inhibitors, 648
cellular therapies, 647
cytokines, 649–650
innate agonists, 649
vaccines, 650
Radium-223, 2299
Radium-226 sources, 508
Radon, lung cancer and, 1251
Rads, definition of, 189
RAGE campaign, 70*b*
RAI. *See* Radioactive iodine (RAI)

Randomization issues, 379–380
Randomized trials, breast cancer recurrence after, 1412–1413
Range of motion, decreased, 2065
Range straggling, 176
Ras mutations, 106
Ras oncogene, 6, 12, 101
RAS proteins, 106
Ras/RAF/mitogen-activated protein kinase pathway, 106
Rayleigh scattering, 174
Raynaud phenomenon, 1744
RB genes. *See also* Retinoblastoma
RCC. *See* Renal cell carcinoma (RCC)
Reactive nitrogen species (RNSs), 319
Reactive oxygen species (ROS), 99, 102*f*, 116, 319
Reassortment, 45, 557
Receptor activator of nuclear factor-kB (RANK), 2288
Receptor activator of nuclear factor-kB ligand (RANKL), 2288
Receptor tyrosine kinase inhibitors, 14*b*
Receptor tyrosine kinases (RTKs), 105
Rectal bleeding, 343
Rectal cancer, 608, 663, 1576–1577. *See also* Colorectal cancers
  abdominoperineal resection, 1579
  adjuvant therapy, 1580–1581
  clinical indications, 608
  follow-up, 608
  late effects of radiation, 343–344
  lateral treatment, 1590*f*
  local excision, 1587–1588
  locally advanced, 1588
  low anterior resection, 1579
  management, 1589–1590
  margins, 1576–1577
  neoadjuvant therapy, 1581–1582
  oncologic anatomy, 704
  palliative care, 2307
  preoperative *vs.* postoperative therapy, 1583
  prognostic factors, 1578
  radial margin, 1580
  radiation-induced injury, 1902
  radiotherapy, 1589
  recurrent, 1588–1589
  staging, 1571*t*
  surgery, 1578–1580
  technique, 608
  transanal local excision, 1579
  treatment planning, 608
  tumor location in, 1577–1588
Rectal dysfunction, hysterectomy-related, 1814

Rectovaginal fistulae, 1816
Rectum, 574
  anatomy of, 1576, 1577*f*
  imaging, 704–705
Recurrence, visceral, 2302–2311
Recurrent urethral cancer, 1914
Redistribution, 542
Reed-Sternberg cells, 1956
Referrals
  ethical issues, 816
  Stark Law, 816
Regaud, Claudius, 78
Registration, treatment planning, 246–247
Regulatory/ethics, 739–740
Reimbursement, ethical issues, 816
Reinforcement machine learning, 58*b*
Reirradiation, 2285, 2286*t*
  brain, 668–670, 669*f*
  heart, 670
  kidney and bladder, 670
  large arteries, 667
  lung/thorax, 667
  non–small cell lung cancer, 673
  spinal cord, 667–668
  tolerance of heart, 670
Relative biologic effectiveness (RBE), 176, 471
Remote afterloader (RAL), 582–583, 583*f*
Renal cancer. *See also* Kidney
  epidemiology of, 1611–1612
  management, 1624
  rhabdoid tumor of kidney, 2109
  risk factors, 1611–1612
  staging, 1614*t*
Renal cell carcinoma (RCC). *See also* Kidney
  classification, 1614–1615
  diagnosis, 1613, 1613*t*
  dose distribution histogram, 1624*f*
  epidemiology, 1611–1612
  follow-up, 1625
  management
    adjuvant RT, 1617–1619
    neoadjuvant RT, 1617, 1617*t*
    radiation therapy, 1624–1625
    SBRT, 1618–1619
    sequelae of RT, 1625–1626
    surgical, 1616–1617, 1617*t*
    systemic therapy, 1617
    thermal ablation, 1617

metastatic, 1615
dose distribution histogram, 1624*f*
RT for, 1621, 1621*f*
spinal cord compression and, 2279*f*
systemic therapy, 1617
natural history, 1612–1613
presentation, 1613
prognostic factors, 1615–1616
risk factors, 1611–1612
RT for, 1621*f*
staging, 1613–1614
systemic therapy, 1617
Renal dysfunction
cisplatin and, 1744
TBI toxicity, 419
Renal pelvis cancer, 1613–1614
classification, 1614–1615
diagnosis, 1613, 1613*t*
dose distribution, 1623*f*
follow-up, 1625
management
chemotherapy, 1622
radiation therapy, 1625–1626
sequelae of RT, 1625–1626
surgical, 1621
natural history, 1612–1613
presentation, 1613
prognostic factors, 1615–1616
staging, 1614*t*
Reoxygenation, 45, 128, 542, 557
Repair, 557
Replication, potential in cancer, 98–99
Replication protein A, 104
Repopulation, 557
inhibition of, 715
Reprisal, hierarchy and fear of, 364–365
Res ipsa loquitur malpractice law, 66–67
Research, AI, 740
Research-based radiation oncology, 49
Resensitization, 43
Residual Gross Tumor Volume (GTV), 599
Respectable minority rule, 66
Respiration-synchronized radiotherapy, 33, 33*t*
Respiratory-dampened radiotherapy, 33, 33*t*
Respiratory-gated radiotherapy, 33, 33*t*
Respiratory system, 2346*t*
radiation side effect management
bronchial stenosis/obstruction/fistulae, 2347

radiation-induced lung injury, 2346–2347
radiation recall pneumonitis, 2347
Respondent superior, 68
Response Evaluation Criteria in Solid Tumors (RECIST), 692
Restraints, patient positioning and, 246
Retina, radiation tolerance of, 960–961
Retinoblastoma (Rb), 7–8, 7*f*, 2201–2216. *See also* RB genes
classification, 2203, 2206
clinical presentation, 2203
clinical trials, 2215–2216
diagnosis, 2203
differential diagnosis, 2206
epidemiology, 2201
future therapeutic approaches, 2215–2216
genetics, 2201
RB1 gene mutation, 2202–2203
management, 2206–2209
pathogenesis, 2201
radiation therapy, 2209–2214, 2210–2212*f*
risk factors, 2206
sequelae, 2214–2215
staging, 2203, 2204–2205*t*, 2206
Retinoblastoma protein (pRB), 98, 105
Retinopathy, 2338
Retromolar trigone, 1095, 1109*f*, 1117
Retroperitoneal cancers, 1939–1948
diagnosis, 1941
epidemiology, 1939–1940, 1940*f*, 1941*t*
lymphomas, 1946
management, 1941–1942, 1944*t*, 1945*t*
natural history, 1940–1941
outcomes, 1945*t*
presentation, 1941, 1941*t*
sarcomas, 1941–1942
Retroperitoneum, anatomy of, 1939, 1939*f*
Retropharyngeal lymph nodes, 1218*t*
Reverse-transcriptase polymerase chain reaction (RT-PCR) assay, prostate cancer, 1712
RFA (radiofrequency ablation), 1617
Rhabdoid tumor of kidney (RTK), 2109
Rhabdomyomas, cardiac, 1361
Rhabdomyosarcoma (RMS), 1926
alveolar, 2129
anatomy, 2129
breast, 2221
chemotherapy, 2137–2138
classification, 2130–2131, 2130*t*
clinical presentation, 2129
clinical trials, 2135–2137, 2136*f*

diagnostic workup, 2129–2130
diffuse anaplastic, 2131
embryonal, 2131
epidemiology, 2129
extremities, 2134
future directions, 2140
gynecologic, 2134
head and neck, 2132, 2133*f*
lymph node involvement, 2054
management, 2137
metastatic, 2135
natural history, 2129
orbital, 2132
patterns of spread, 2129
pediatric, 2129–2140
retrieval therapy, 2140
risk factors, 2129
staging, 2130, 2130*t*
undifferentiated sarcoma, 2131
uterine, 1849
Richter syndrome, 2025
Rigorous preclinical models, 146
RIHD (radiation-induced heart disease), 1367
RION. *See* Radiation-induced optic neuropathy (RION)
Risk analysis
hazard and, 369
prospective, 369
retrospective, 370
incident learning systems, 370
London Protocol, 370–371
root cause analysis, 370–371
Risk management, QA programs and, 297*t*
Rituximab (anti-CD20), 1991, 2008
for CLL, 2025
for DLBCL, 1977–1978
for follicular lymphomas, 1984–1987
for NHL, 1991–1992
RNS. *See* Reactive nitrogen species (RNSs)
Robotic-assisted hysterectomy, 1838
Roentgen (R) units, 17, 189
Röentgen rays. *See* X-rays
Roentgen-to-rad conversion factor, 190
Röntgen, Wilhelm Conrad, 72–74, 72–75*f*, 172, 616
Room's-eye-view (REV)
plan evaluation, 291
planning target volume, 292*f*
ROS. *See* Reactive oxygen species (ROS)
Rosen's rules, 65

Rotating gamma systems (RGS), 426
Rotation therapy, 234
Rotational (arc) therapy, 242–243, 242*f*
Routes of administration, pain management, 2317
RT. *See* Radiation therapy (RT)
Rubeosis iridis, 967
Rutherford, Ernest, 78–79, 78*f*

S

S-100 protein, 1891
Sacral chordoma, 2161*f*
Sacral insufficiency fractures (SIFs), 1848
Safety. *See also* Quality assurance (QA)
  postmarketing surveillance trials, 379
  SBRT, 441–442
Safety and quality, 59–62, 61*f*
Safety culture assessment survey, 366, 366*f*
Saline-infusion sonography, 1829
Saliva
  artificial, 2325
  function of, 2326
  production of, 333
Salivary duct carcinoma, 1074, 1074*f*
Salivary gland
  dose-volume limits, 334
  dose/volume/toxicity data, 334
  injury, 2325–2326
  late effects of radiation, 333–334
Salivary gland, 1061–1088
  anatomy, 1061–1062, 1061*f*
  cystadenocarcinoma, 1073
  recovery after RT, 1032
Salivary gland cancer, 1061–1062
  in children, 1080
  classification, 1072–1074, 1073*t*
  clinical presentation, 1064, 1064*t*
  diagnostic workup, 1064–1072
  epidemiology, 1062–1063
  general management, 1075–1077, 1086–1087
  lymph node positive, 1063*t*
  minor glands, 1083*t*
  natural history, 1063
  outcomes, 1074*f*
  pediatric, 2219
  prognostic factors, 1074–1075, 1075*t*
  radiation-related injury, 2325–2326
  radiation therapy, 1077–1080

staging, 1064–1072, 1072*t*
systemic therapy, 1086–1087
Salmonella typhi, 1562
Salpingo-oophorectomy, 1859
Salvage radiation therapy (SRT), prostate cancer, 1724
Samarium-153, 2299
Sample sizes, trials and, 382–383
Sarcoma, 570, 572*f*, 572*t*. *See also specific cancers and specific organs*
cardiac, 1361*t*
intraoperative radiotherapy, 465
proton therapy, 309
radiation-induced, 1446–1447
Sarcomatoid carcinomas, 1680
SBRT. *See* Stereotactic body radiation therapy (SBRT)
Scatter-air ratios (SARs), 194
Scatter-maximum ratios, 194
Scattering, coherent, 174
Scattering techniques, 475
SCC. *See* Squamous cell carcinoma (SCC)
Schistosoma haematobium, 1637, 1639
Schmidt-Ullrich, Rupert, 87–88
Scholarship, 772–774
conceptual frameworks, 774, 774*t*, 775*t*
medical education, 772–773, 772*f*
qualitative versus quantitative research, 773–774, 773*t*, 774*t*
School of practice, 66
Schwannomas. *See also* Vestibular schwannomas
histology, 1301*f*
mediastinal, 1298, 1299–1300*f*
nonacoustic, 431
retroperitoneal, 1947
spinal cord, 949–950
SCLC. *See* Small cell lung cancer (SCLC)
Sclera, anatomy of, 959
Sclerosing polycystic adenosis adenoma, 1073
Scoliosis, radiation-related, 2111
SCR. *See* Stem cell rescue (SCR)
Screening tests
for cervical cancer, 1764
for colorectal cancer, 1570
for lung cancer, 1252–1253
for ovarian cancer, 1858–1859
Papanicolaou smears, 1765–1766
for prostate cancer, 1671–1672
Scrotal varicoceles, 1613
Scrotum, rhabdomyosarcoma, 2134
Seamless dose escalationexpansion with adaptive randomization scheme (SEARS), 397, 397*f*
Sebaceous carcinoma, 1073

of eyelid, 968–969
Second victim phenomenon, 371–372
Secondary cancers
after BMT, 419
breast cancer patients, 1446–1447
after cranial irradiation, 2031
Hodgkin lymphoma and, 1425
after proton therapy, 494
radiation-induced, 1033, 1819, 1969, 2111, 2172
TBI toxicity, 419
Secondary prevention strategies, 15
Secular equilibria, 173, 174*f*
Seed and soil hypothesis, 11
Seizures, 875
Selectins, 2238
Selective internal radiation therapy (SIRT), 2305
Selenium, 1668
Self-assessment, 367
Seminomas
management, 1736–1741, 1737*t*, 1738*t*, 1739*t*, 1742–1743
outcomes, 1742–1743
testicular, 1732
Senescence, radiation-induced, 99*t*, 101, 119
Sensitivity analysis, 835–836, 836*f*
Sensitometric curves, 192
Sensorineural hearing loss (SNHL), 327, 328*f*
Sentinel lymph node (SLN)
dissection, 1929
mapping approach, 1839, 1839*f*
Sentinel lymph node biopsy (SLNB)
in breast cancer, 1404–1405, 1405*t*
in cervical cancer, 1777
in endometrial cancer, 1839, 1839*f*
in oral cavity cancer, 1103–1104
Sequential chemoradiation, 992–994
Serotonin, 1183
Serotonin receptor-3 antagonists, 418
Serous carcinoma, 1832, 1856
Sertoli cell tumors, 1872
Set-up margins, definitions of, 283
Sex cord-stromal tumors, 1861, 1872
Sexual dysfunctions, 1818, 2329
Sexual interest/arousal disorder, 2351–2352
Sézary syndrome (SS), 1999
Shellfish allergies, 688
Shielding, oral, 1115
Shot, definition, 178
Shrinking-field technique, 22, 30

Sialorrhea, RT for, 2244, 2246
Sigmoidoscopy guidelines, 1570
Signal transducation
  RTK-initiated
    integrin-mediated signaling, 106–107
    VEGFR-mediated signaling, 106
    Wntsignaling, 106
Signal transduction, 9
Silicone-soft tissue interfaces, 237
Simpson-Golabi-Behmel syndrome, 2103
Simpson Paradox, 350
Simulations
  brachytherapy, 1916*f*
  in cervical cancer, 1778–1779, 1780*f*
  in esophageal cancer, 1330
  in gastric cancer, 1502, 1510*f*
  for Hodgkin lymphoma, 1960
  in testicular cancer, 1742
Simulators
  conventional, 186–187
  CT, 186, 188*f*
  treatment machines, 186–187
Simultaneous tumors, 1832
Single-agent chemotherapy, 1934, 1934*t*
Single-hit/single-target model, 47
Single photon emission computed tomography (SPECT), 1711
Sinonasal undifferentiated carcinoma (SNUC), 1198
Sinus of Morgagni, 1001
Sinusoidal obstructive syndrome (SOS), 418
Skeletal system
  radiation side effect management
    costochondritis, 2354, 2354*t*
    osteoradionecrosis of femur (avascular necrosis), 2354
    osteoradionecrosis of mandible, 2353–2354
    pelvic insufficiency fracture, 2354
    trismus, 2353
Skin
  anatomy, 854
    dermis, 854
    epidermis, 854
    lymphatics, 854
  clinical picture, 856–857
    physical examination, 857
    presenting symptoms, 856–857
  complications after RT, 1443
  diagnosis and staging, methods of, 857–859
    diagnostic imaging, 859
    staging, 857–859, 857–859*t*

electron beam therapy, 255
irregular surface of, 259, 266
pathology, 855
adnexal carcinoma, 855
basal cell carcinoma, 855
keratoacanthoma, 855
melanoma, 855
merkel cell carcinoma, 855
squamous cell carcinoma, 855
patterns of spread, 855–856
basal cell and squamous cell carcinomas, 855
basal cell nevus syndrome, 856
carcinoma of the sweat gland, 855–856
keratoacanthoma, 856
lymphatic metastasis, 856
melanoma, 856, 856*t*
merkel cell carcinoma, 856
sebaceous gland carcinoma, 856
radiation-induced injury, 2328
recurrence, follow-up and management of, 863
results, 864–866
basal cell and squamous cell carcinomas, 864
melanoma, 865, 865*t*, 866*t*
merkel cell carcinoma, 865, 865*t*
primary lesion, 864–865, 864*t*, 865*t*
regional nodes, 865
surface doses, 266*t*
total-skin irradiation, 275
treatment modality, selection of, 859–860
basal cell and squamous cell carcinomas, 859–860
melanoma, 860
merkel cell carcinoma, 860
regional lymph node metastases, 860
treatment techniques, 860–863
axillary metastases, 863
ilioinguinal lymph node metastases, 863
parotid area lymph node metastases, 863, 863*f*
primary lesion, 860–863, 861*f*, 862*f*, 862*t*, 863*t*
Skin biopsy, 2000
Skin cancer, 608, 663
clinical indications, 608–609
cutaneous B-cell lymphomas, 2007
follow-up, 609
pediatric, 2231
periorbital, 969
primary cutaneous lymphomas, 1998–2009
secondary, 2005
technique, 609

treatment planning, 609, 609*f*
Skin collumination, 265, 266*f*
Skin injury, 2328–2329
Skin-vermilion junction, 1092
Skin view, plan evaluation, 291
Sklodowska, Marya. *See* Curie, Marie Sklodowska
Skull base
anatomy of, 1002*f*, 1002*t*
foramina, 1002*f*, 1002*t*
invasion of, 1008*f*
Skull base sarcomas, 479, 480*f*
Skull, chordoma, 2161*f*
Skull tumors
anatomy, 922, 923*f*, 924*t*, 925*f*, 926*f*
chondrosarcoma, 931–934
clinical presentation, 932
diagnostic workup, 932
epidemiology and risk factors, 931
general management, 932, 932*f*
imaging, 932
natural history, 932
pathology, 931
principles of radiation therapy, 933
radiation techniques, 933, 934*f*
staging, 932
surgery, 933
systemic therapy, 934
chordoma, 924–931
clinical presentation, 927
diagnostic workup, 927
epidemiology and risk factors, 925, 927
general management, 928, 929*f*
imaging, 927, 928*f*
natural history, 927
pathology, 924–925
principles of radiation therapy, 928–929
radiation techniques, 929–930, 930*t*, 931*f*
staging, 928
surgery, 928
systemic therapy, 930–931
general pathology, 922–924
paraganglioma, 934–939
clinical presentation, 935
diagnostic workup, 935
epidemiology and risk factors, 934–935
general management, 936
imaging, 935–936
natural history, 935

pathology, 934
principles of radiation therapy, 937–938, 938*t*
radiation techniques, 939
staging, 936, 936*t*, 936*f*
surgery, 936–937, 937*f*
systemic therapy, 939
radiation dose constraints, 939, 940*t*
toxicities of radiation, 939–941
acute toxicity, 939–940
late sequelae, 940–941
Sleep hygiene, 2323
Slips, definition of, 360
SLNB. *See* Sentinel lymph node biopsy (SLNB)
Small bowel
bleeding, 1625
late effects of radiation, 341–342
radiation-induced injury, 1903
stenosis, 1625
Small bowel cancer, 2222
Small cell carcinoma
cervical, 1771
vaginal, 1896
Small cell lung cancer (SCLC), 1271–1274, 2271–2272
management, 1271–1274
paraneoplastic syndromes, 1271
pathology, 1271
patterns of spread, 1251–1252
prognostic factors, 1271
staging, 1271
Small intestine, complications of RT, 1816
Small lymphocytic lymphoma, 1974, 2024–2026
SMARCB1/jSMF5/INI-1 gene, 2103
SMART radiotherapy, 154–164
Smoking
anal cancer and, 1596
bladder cancer and, 1638
breast cancer prognosis and, 1402
cancer rates and, 1611
carcinogenesis and, 1765
esophageal cancer and, 1318
lung cancer and, 1251
nasal cancer and, 1040
nasopharyngeal cancer and, 1003
oral cavity cancer and, 1092, 1096
ovarian cancer and, 1858
Smoldering myeloma, 2038
Socioeconomic status (SES), 843–846
access to care, 845–846, 846*f*

cancer disparities according to, 843–844, 844*f*
definition of, 843
insurance status influencing radiation oncology disparities, 844–845
Sodium iodine symporter (NaIS), 1236
Soft palate cancers, 1128
Soft tissue sarcoma (STS), 570, 2054–2068, 2144–2154
adipocytic, 2144
classification, 2054
classification, 2144, 2145–2146*t*
clinical presentation, 2147
clinical trials, 2152–2154
diagnostic workup, 2147
epidemiology, 2144
etiology, 2054
evaluation, 2055–2056, 2055*f*
extremity, 2057, 2057*t*, 2058*t*
fibroblastic, 2144
fibrohistiocytic, 2144
future directions, 2154
genetics, 2054
incidence, 2054
intraoperative radiotherapy, 465
management, 2149
management
chemotherapy, 2067
isolated limb infusion, 2067
isolated limb perfusion, 2067
radiation therapy, 2059–2066
regional hyperthermia, 2067
surgical, 2057–2059
surgical, 2058*t*
surgical, 2065
myofibroblastic, 2144
natural history, 2054–2055
pathology, 2144–2147
peripheral nerve sheath tumors, 2147
perivascular, 2146
prognostic factors, 2057
radiation-related, 1033
radiation therapy, 2149–2151
dose, 2149, 2150*t*, 2151*t*
long-term toxicity, 2151
metastases, 2150–2151
site-specific considerations, 2150
smooth muscle, 2147
staging, 2056–2057, 2057*t*
staging, 2147–2148
treatment, 2148–2149

trunk, 2057, 2058*t*
tumors of uncertain differentiation, 2147
vascular, 2144, 2146
Solid organ transplantation, 2255
Solitary fibrous tumors
chemotherapy, 1188
clinical presentation, 1187–1188
epidemiology, 1187
incidence, 1187
meningeal, 1187
outcomes, 1188
pathology, 1187
radiation therapy, 1188
recurrent, 1188
surgical management, 1188
vagal, 1187
Solitary plasmacytomas, 2038
Somatostatin receptors (SSTR), 1183
Somatostatin type-2 receptor, 1197
Somnolence syndrome, 2030
Sorafenib, 1869
Source skin ratio method, 230
Source-specific dosimetric characterization, 518–520, 519*f*
Source strength specification quantities and units, 513–515, 514*f*
Source-to-axis distances (SADs), 178, 229
vs. backscatter depth, 236
Source-to-calibration point distance (SCD), 229
Source-to-surface distances (SSDs), 255, 257*f*, 263*f*
Soy protein, 1668
Spatial accessibility, radiation therapy, 758
Spatial cooperation, 712
Spatially fractionated radiation therapy (SFRT)
advantages, 458*t*
conventional external radiation (cERT), 455
disadvantages, 458*t*
GRID therapy, 455
history, 450–451
lattice therapy, 455, 458
mechanisms of action, 452–454, 452–453*f*
multileaf collimator (MLC)-based GRID therapy, 455
normal tissue tolerance, 452
personalized ultrafractionated stereotactic adaptive radiotherapy (PULSAR), 454
preclinical research, 452–454
primary tumor site clinical series, 456–457*t*
risk reduction, 454
temporal fractionation, 454
tumor control, 452
Sperm count, 1743

Spermatic cord, 2134
Spermatocytic seminoma, 1732
Spermatogenesis, 2184
Sphenoid sinuses, 1040
Spin-echo imaging, 689, 689*t*. *See also* Magnetic resonance imaging (MRI)
Spinal accessory chain (SAC) nodes, 1216
Spinal canal anatomy, 946–947
Spinal canal tumors, 946–956
  clinical presentation, 948
  diagnostic workup, 948–949
  epidemiology, 947, 947*t*
  imaging, 948, 949*f*, 950*f*
  management, 951–952, 955*f*
  natural history, 947–948
  pathologic classification of, 949–950
  prognosis, 951
  radiation dose, 953–954
Spinal cord
  anatomy of, 946–947, 947*f*
  astrocytoma of, 2083
  compression
    imaging of, 695
  CT simulation, 2074*f*
  dose-volume limits, 332
  late effects of RT, 329–332
  metastatic disease of, 695, 2262–2274, 2277–2286
    clinical presentation, 2277
    corticosteroids, 2279–2280
    evaluation, 2277
    intramedullary, 2285
    pathophysiology, 2277
    radiotherapy, 2281–2282
    reirradiation, 2285, 2286*t*
    spinal cord compression, 2277, 2278*f*
    stereotactic body radiation therapy vs. conventional radiotherapy, 2282
    surgery, 2280–2281
    treatment algorithms, 2277–2278
  pediatric, 2283–2285
  radiation tolerance of, 954–956, 1224
  reirradiation dose, 667–668
  tumors of, 946, 946*f*
Spinal instability neoplastic score (SINS) system, 2277, 2278*t*
Spinal lesions, 330, 2172
Spine
  chondrosarcoma, 2160*t*
  impacts of SBRT, 445
  metastatic disease of, 695
  oncologic anatomy, 694

Splenectomy, 1969
Splenic irradiation, 2030
Splenomegaly, 2306
Spoliation, 69
Sponsorships, ethical issues, 818
Spread-out Bragg peak (SOBP), 176, 177*f*
Sprouting angiogenesis, 137
Squamous cell carcinoma (SCC)
  anal, 1596
  axial CT scan, 697*f*
  bladder, 1639
  buccogingival tissues, 1099*f*
  cervical, 1798
  endometrial, 1832
  esophageal, 1327
  head and neck, 983–997
  keratinizing, 1011, 1012*f*
  lip, 1098
  mandibular alveolus, 1099*f*
  nasal cavity, 1040
  nasal vestibule, 1041*f*, 1046*f*
  nonkeratinizing, 1011, 1012*f*
  periorbital, 968
  secondary, 419
  vaginal
    chemoradiation, 1890–1891
    chemoradiation, 1890*t*
    clinical presentation, 1883
    diagnosis, 1884–1885
    outcomes, 1891
    patterns of lymphatic drainage, 1883
    prognostic factors, 1888–1891
    radiation, 1888–1890
    risk factors, 1885–1886
    staging, 1883–1884
    staging, 1884*t*
    staging, 1884*t*
    surgery, 1887–1888
    surgery, 1887*t*
Squamous cell carcinomna antigen (SCC-Ag), 1774–1775
Squamous hyperplasia, 1923
SRS. *See* Stereotactic radiosurgery (SRS)
Staff training, QA programs and, 297*t*
Standard fractionated radiation therapy, 645
Standard gamble technique, 748
Standard of care, 65
Stark laws, 816
Stark, Pete, 816

Steatorrhea, 1524
Stem cell rescue (SCR), 2168
Stem cell transplantation (SCT)
  allogeneic, 405–406
    myeloablative, 406
    nonmyeloablative, 406
  autologous, 405
  conditioning regimen
    for acute myelogenous leukemia, 408, 408*t*
    advantage, 409
    BuCy*vs.* TBI-Cy, 407–408
    chemotherapy-alone, 407
    side effect, 409
    single fraction *vs.* fractionated TBI, 407
    TBI-based, 407
  for follicular lymphomas, 1986
  graft failure, 409
  hematopoietic system, 409
  myeloablative allogeneic, 406
  for NHL, 1986
  rationale for, 405–406
  and total body irradiation, 409
Stenosis, 2350
Stenosis, radiation-induced injury, 1354
Stereotactic body radiation therapy (SBRT), 440–447, 823, 2283. *See also* Image-guided radiation therapy (IGRT)
  for cervical cancer, 1784
  guidelines, 441–442
  for intrahepatic lesions, 1552
  liver, 442–443
  lung, 444–445
  for pancreatic cancer, 446–447
  phase III clinical trial, 397
  prostate cancer, 1715–1717
  for prostate cancer, 445–446
  rationale for, 440
  for renal cell carcinoma, 1618–1619
  safety, 441–442
  for soft-tissue sarcomas, 2066
  spine, 445
  technical considerations, 2283
  for vaginal cancer, 1902
  vs. conventional radiotherapy, 2282
Stereotactic, definition of, 424, 442
Stereotactic immobilization and stabilization
  extracranial immobilization devices, 211–212
  immobilization and internal motion management, 212
  intracranial immobilization devices, 210–211

Stereotactic radiosurgery (SRS)
for metastatic RCC, 1621
for nasopharyngeal cancer, 1021
for spinal canal tumors, 954, 955*f*
for uveal melanoma, 967–968
Stereotactic radiosurgery (SRS), 130, 877–878, 914, 2241, 2242*f*. *See also specific techniques*
arteriovenous malformations, 427
for brain metastases, 2266
clinical uses for, 428–435
definition, 424
normal tissue tolerance doses, 426–428
optic nerve tolerance for, 427–428
radiobiologic issues, 424–425
requirements for, 424*t*
uses of, 424–435
Stereotactic radiotherapy (SRT), 178
brain, 322
clinical uses for, 428–435
definition of, 424
hearing preservation, 327*t*
hypofractionated, 428*t*
normal tissue tolerance doses, 426–428
radiobiologic issues, 424–425
radionecrosis and, 322, 322*t*
radiosurgery and, 424–425
requirements for, 424*t*
spinal, 331*t*
uses of, 424–435
Sternocleidomastoid, 693
Stewart-Treves syndrome, 2054
Stomach
anatomy, 1489, 1490*f*, 1491*f*, 1502*f*
late effects of radiation, 341–342
Stomach cancer, 1489–1519. *See also* Gastric cancer
diagnosis, 1493–1494
epidemiology, 1489–1492
intraoperative radiotherapy, 465–466
oncologic anatomy, 701–702
patterns of spread, 1492–1493
pediatric, 2221–2222
presentation, 1493
staging, 1494–1495
treatment planning, 1494
Stomatitis. *See* Mucositis
Stopping power, 53, 472, 476
Stricture formation, 1354
Stroke, 1445–1446
Stroma, tumor, 154–155

Stromal derived factor-1 (SDF-1), 154
Stromal normalization, 139
  vascular, and, 139
Strong nuclear forces, 173
Strontium-89, 2299
Structure
  alternative payment models, 826–829, 827*f*
  definition, 824–829
  integration of care, 826
Study design. *See also* Clinical trials
  cohort studies, 387
  comparative effectiveness research, 387
  meta-analysis, 387
  sample sizes, 382–383
  statistical issues, 379–384
  statistical power in, 382–383
Subadditive effect, 713
Subcutaneous fibrosis, 2065
Subcutaneous panniculitis-like T-cell lymphoma, 2006
Subglottic larynx cancer, 1163
Subjective outcomes, 830
Sublethal damage repair (SLDR), 714
Sublethal damage repair, 21
Sublingual gland, 1062, 1080
Submandibular gland cancer, 1083*t*
  prognosis, 1074–1075
  radiation therapy, 1079–1080
Submandibular glands, 1079–1080
  anatomy, 1062
  RT effects on, 334
  sparing of, 334
Submandibular lymph nodes, 1216
Submucous fibrosis, 1097
Suit, Herman D., 85–86, 86*f*
Sulfasalazine, 2327
Sunitinib (SU11248), 1839
Superficial sites, 570–573, 573*f*
Superficial units, 177
Superior sulcus
  imaging of, 700
  oncologic anatomy, 698
Superior sulcus tumors
  diagnosis, 1264
  management, 1264
  presentation, 1263–1264
Superior vena cava obstruction, 1252, 1270
Superoxide anion, 319
Superoxide dismutase (SOD), 682

Supervised machine learning, 58*b*
Supportive care, 2322–2323
Supra-additive effect, 717, 718
Supraclavicular lymph nodes
  irradiation of, 1432, 1433*f*
  stroke after radiation therapy, 1445–1446
Supraglottic larynx cancer, 1165
  complications of treatment, 1176*t*
  laryngeal cancer, 1162
  laryngectomy outcomes, 1175*t*, 1176*t*
  laser excision outcomes, 1174–1175*t*
  nodal distribution, 1163*f*
  recurrence, 1172
  RT outcomes, 1175*t*
  treatment, of, 1170–1172
  treatment results, 1172, 1173
  treatment selection, 1175*t*
Supratentorial primitive neuroectodermal tumors (stPNET), 2089
Surface doses, 266*t*
Surface-guided radiation therapy, 212–213
Surveillance, Epidemiology, and End Results (SEER) Program, 398
Surveillance trials, postmarketing, 379
survival curves
  mammalian, 124–127
Swallowing
  post-RT, 333
  pre-therapy assessments, 333
  salivary gland function and, 333
SWOG S0713, 391
Syed-Neblett applicators, 1899
Synchrocyclotrons, 185
Synchrotrons, 185, 474–476, 474*f*
Syndrome of inappropriate antidiuretic hormone (SIADH) secretion, 1026, 1252, 1271
Synergy IGRT system (XVI), 181
Systemic therapy. *See* Chemotherapy

T

T cell leukemia/lymphoma, 2006
T-cell lymphomas, 2006
T-cell/histiocyte-rich large B-cell lymphoma, 1982–1983
T cells, antibody-mediated activity, 440
Talc products, 1858
Tamoxifen, 1373
  clinical trials, 1379*t*, 1381
  endometrial cancer and, 1828
  neoadjuvant, 1459
  Neoadjuvant endocrine therapy, 1459

randomized trials, 1413
Tandem transplantation, 2044
Target theory of radiobiology, 47–48, 47*f*
Target volumes
conformal radiation therapy, 283*t*
delineation of, 285–288
Targeted agents, 880
TASTE trial, 398
Taxanes, 1458, 1461, 717. *See also specific drugs*
Taxol, 1864
TBI. *See* Total-body irradiation (TBI)
TBI toxicity, 418–419
TC regimen, 1458
Tear formation, 418
Technology
ethical issues, 817
TEE (transesophageal echocardiography), 1364
Teeth, examination of, 1100
Telangiectasia, 960, 1758–1759*f*, 1759
Telemedicine and remote practice, 57–58
Teletherapy, 29
Telomeres, 9, 99
Temozolomide (TMZ)
for ependymomas, 952
for metastatic brain cancer, 2272
radiation response and, 718
for Solitary fibrous tumors, 1188
Temporal accessibility, of cancer screening, 758
Temporal bone paraganglioma, 1187*t*
temporal bone, 1186*t*, 1187*t*
Temporal bone tumor, 977
Temporal lobe necrosis (TLN), 1031
Temporary brachytherapy, 44
Temporary implants, 556
Temsirolimus, 1625
Tenesmus, 343
Tenosynovial giant cell tumor. *See* Pigmented villonodular synovitis
Teratomas, 1361–1362
TERMA (T*E*), 231
Testes
anatomy, 1733
genetically significant doses, 252
irradiation, 2031
natural history, 1733
Testicular cancer, 1631–1644
bilateral, 1741
classification, 1732
diagnosis, 1734–1735, 1734*t*

epidemiology, 1631–1644
lymphatics, 1733*f*
lymphomas, 2192
management, 1735–1736, 1742–1744, 1742*f*
natural history, 1733
nonseminomatous germ cell tumors, 1732–1733
pathology, 1731
presentation, 1733–1734
prognostic factors, 1735, 1735*t*
seminoma, 1732
staging, 1735, 1735*t*
Testicular irradiation, 2029
Testicular shielding, 1742
Tetracycline, 1178
TGF-α. *See* Tumor necrosis factor-α (TGF-α)
TGF-β. *See* Tumor necrosis factor-β (TGF-β)
TGF-β1 gene expression, 109
Thalidomide
for HCC, 1555
The Office of Management and Budget (OMB), 847
The Response Evaluation Criteria in Solid Tumors (RECIST), 738–739
Thecal cell tumors, 1872
Thecomas, 1861
Therapeutic agents, 161
Therapeutic doses, 259
Therapeutic index (TI)
definition of, 712
tumor control probability and, 677*f*
Therapeutic ratio (gain), 471
Thermal enhancement ratios (TERs), 679
Thermal plastic masks, 247*f*
Thermoluminescence, 192
Thermoluminescent dosimeters (TLDs), 299, 759
Thermoplastic masks, 201–204
frame-based, 425
frameless, 425
Thermotherapy
transpupillary, 966
Thermotolerance, 656–657
Thimble chambers, 189
Thomson scattering, 174
Thoracoscopy, 1253
Thorax, 568–569, 568*f*, 569*f*
lymphatic drainage, 697
oncologic anatomy, 697–700
proton therapy, 308–309
Thorium dioxide, 1611
Thorium series, 173

Thorotrast, 1040
Three-dimensional imaging/dosimetry, 531
Three-dimensional printing, 219–220
Three-dimensional treatment planning systems (3DTPS), 51
  complexity, 296
  CT data transformation, 285
  display feature, 291
  historical development of, 281
Three-dimentional conformal radiation therapy (3DCRT)
  for anal cancer, 1602*t*
  for breast cancer, 1437–1439
  forward planning approach, 280, 280*f*
  historical development of, 281
  for Hodgkin lymphoma, 1964
  multibeam treatment in, 242
  plan evaluation/improvement process, 289–291
  for prostate cancer, 1684, 1686
  treatment planning, 1266
  for vaginal cancer, 1896–1897
Thrombocytopenia, 1518
Thrombocytopenia, 2030, 2239, 2306
Thromboembolism, 1818
Thrombospondins (TSP), 99, 137
Thymic carcinoid tumors, 1293
  associated disorders, 1294
  cellular origin of, 1293
  management, 1293–1294
  staging, 1294
Thymic carcinoma, 1291–1293
Thymidine labeling index, 1401
Thymidylate synthase, 717, 718
Thymoliposarcomas, 1294
Thymomas, 1279–1291
  classification of, 699, 1282–1284, 1282*t*
  diagnosis, 1281–1282, 1282*f*
  epidemiology of, 1280
  management
    chemotherapy, 1289
    combined modality therapy, 1290, 1290*t*
    radiation therapy, 1287–1289
    radiation therapy, 1291*t*
    surgical, 1286–1287
    treatment selection, 1292*f*
  natural history, 1280–1281
  outcomes, 1285*t*
  patterns of failure, 1287
  presentation, 1280
  prognostic factors, 1285–1286, 1286*t*

recurrence rates, 1285*t*
staging, 1284–1285
Thymus. *See also* Thymomas
anatomy of, 699
imaging of, 699
Thyroid cancer, 1235–1249
age, 1242–1243
anaplastic carcinoma, 1238, 1240*f*, 1248–1249
bilaterality, 1235, 1238
classification of, 1237–1238, 1238*t*
clinical manifestations of, 1239
diagnosis, 1239–1241
differentiated carcinomas
imaging studies, 1240*t*
neck dissection in, 1244
prognostic factors, 1241–1243
radioactive iodine treatment, 1244, 1244*t*, 1245–1246*t*
EBRT, 1246–1247
epidemiology of, 1238
extranodal extension, 1243
management, 1243–1246
medullary carcinoma, 1238
mortality rates, 1243*f*
multifocality, 1238
patient follow-up, 1239
positive lymph nodes, 4243
positive surgical margins, 1243, 1243*t*
prognostic factors, 1241–1243
radiation-induced, 1238
recurrence *vs.* survival, 1241–1242
target volumes, 1247
unfavorable variants, 1243
Thyroid cancer, pediatric, 2227–2228
Thyroid dysfunction, 418, 2184
Thyroid eye disease (TEI), 962–963. *See also* Graves ophthalmopathy
Thyroid gland
anatomy, 1235–1237, 1235*f*
dysfunction after BMT, 418–419
physiology, 1236–1237
Thyroid hormone, forms of, 1236
Thyroid nodules, 1239
Thyroid-stimulating hormone (TSH), 1248
Thyroid transcription factor-1, 1896
Thyroidectomy, 1243–1244, 1248
Thyroxine, secretion of, 1236
Time to death (DFS), 382
Time to disease progression (PFS), 382
Time-to-event, 382

Time-to-event continual reassessment method (TiTE-CRM), 388
Tirapazamine (TPZ, SR-4233, WIN 59075-3)
  cytotoxic activity, 153
  hypoxic cell targeting by, 679
  radiation response and, 719
Tissue-air ratios (TARs), 191, 193–194, 229–230
Tissue heterogeneities
  air cavities and, 259, 261*f*
  lung, 308–309
  tissue interface dosimetry and, 236–237
Tissue interface dosimetry, 236–237
Tissue-maximum ratios (TMRs), 194, 195*f*
Tissue-phantom radios (TPRs), 194, 195*f*
Tissues, heterogeneities, 229
Tolterodine (Detrol), 1818, 2329
Tolterodine, urinary tract injury, 2329
Tomatoes, 1668
Tomotherapy
  HI-ART systems, 181, 183*f*
  radiotherapy techniques, 425
Tongue
  anatomy, 1093–1094
  carcinoma of, 1097–1098, 1110*f*, 1223*f*
  oncologic anatomy, 696
  squamous cell carcinoma, 1097–1098, 1112*f*
  subsite-specific treatment, 1115–1116
  tumors, 1128–1129
Tonsillar cancers, 1128, 1222*f*
Topical treatments, vaginal intraepithelial neoplasia, 1881
Topoisomerase I inhibitors, 718
Topotecan, 2137
Total-body irradiation (TBI), 2046
  acute and late toxicities
    myeloablative regimens, 418–419
    nonmyeloablative regimens, 418
  basic requirements, 409–410
  boosting of selected organs, 414–415, 416–417*t*, 418
  chemotherapy with, 407
  CNS, 414
  dose description, 412, 414
  dose-limiting structure, 412
  dose rates, 411
  dose reporting, 412, 414
  dosimetric characterization, 410
  high dose, 418–419
  late effects of, 418–419
  low dose rate, 411, 418
  lung dose attenuation, 414

patient positioning, 412, 413*f*
quality assurance, 414
radiobiologic effects on
hematopoietic system, 409
leukemia, 409
renal toxicity and, 342, 419
skin surface dose, 410–411
stem cell transplantation and, 405–420
techniques, 410, 411*f*
treatment planning, 412
Total body irradiation immobilization, 220–222
Total-limb irradiation, 272–273, 274*f*, 275
Total lymphoid irradiation (TLI), 1965
Total marrow irradiation (TMI), 2046–2047
Total-scalp irradiation, 272, 273*f*, 274*f*
Total skin electron beam therapy (TSEBT), 2001–2004, 2002*f*, 2003*f*
Total skin electron irradiation immobilization, 222–223
Total-skin irradiation (TSI), 275
Town hall meetings, 297*t*
Toxicity, 33–35, 33–34*f*, 918–919
acute, 1902
cranial nerve deficits, 918, 919*t*
hypopituitarism, 918
long-term tumor occurrence, 918
radiation therapy, 2065
vascular stenosis and stroke after prior ionizing radiation, 919
TP53 oncogene, 98, 101, 1096, 1525, 2103
TPF regimen, 1154–1155
Trachea, anatomy of, 1280*f*, 1302
Tracheal cancer, 1303*t*, 1304*t*
anatomy, 1302
demographics, 1302
management, 1303
natural history, 1302
outcomes, 1304*t*
prognostic factors, 1302–1303
radiation techniques, 1304*t*, 1305
staging, 1302–1303, 1303*t*
treatment approaches, 1303–1304, 1304*t*
Trachelectomy, radical, 1775
Trans-Tasman group (TROG 02.02), 719
Transaminases, liver, 340
Transanal local excision (TME), 1479
Transcatheter arterial chemoembolization (TACE), 1550–1551, 1554*t*
Transesophageal echocardiography (TEE), 1364
Transforming growth factor β (TGFβ)
activation of, 109
expression of, 154–155

latent, 109
Transient equilibria, 173, 174*f*
Transition energy, 173
Transitional cell carcinomas (TCCs), 1679, 1747, 1926
Transoral laser excision, 1175*t*
Transoral laser microsurgery, 1129
Transoral laser surgery, 1166, 1172*t*
Transoral robotic surgery, 1129
Transplantation, 1974
Transpupillary thermotherapy (TTT), 966
Transrectal ultrasonography (TRUS), 1671, 1674, 1768
Transthoracic echocardiography (TTE), 1364
Transurethral resection of the bladder (TURBT), 1638, 1643, 1649
Transvaginal ultrasound (TVUS), 1829, 1830*f*, 1858
Transverse myelopathy, 329–330, 330*f*, 331*t*, 332*t*
Trapezius, 693
Trastuzumab, 1420, 1458, 1461, 1462, 1463
Treated volumes (TVs), 282, 282*f*
Treatment planning
beam arrangements, 288
calculation, 584–585
combination fields and, 240–243
conformal radiation therapy, 283–295, 283*t*, 284*t*, 297*t*
electron arc therapy, 275–278
electron beam therapy, 264–271
fetal doses, 251–252
field design, 1331–1340, 1332*f*
forward planning, 280
gastric cancer, 1502
gonadal doses, 252
image-segmentation software, 285*f*
inverse planning, 280
isodose distributions, 1431*f*
lung cancer, 1266
motion control in, 442
multiple beam arrangements
four-field, 240–242, 241*f*
six-field, 242
three-field, 240, 241*f*
nodal volumes, 1428*f*
for oropharyngeal cancer, 1133–1135
pain management, 2319
parallel-opposed fields, 240, 240*f*
patient immobilization, 246–247
patient positioning, 246–247
patient registration, 246–247
patient topography and, 230
pediatric patients, 2074

photon external-beam dosimetry, 229–252
proton therapy, 476
base of skull, 307, 308*f*
brain, 307, 308*f*
breast, 308, 309*f*
head and neck cancer, 307–308
pediatric patient, 309, 309*f*
sarcomas, 309
scanned beams, 306, 306*f*
scattered beams, 306, 306*f*
site-specific proton, 307–309
thoracic and abdominal, 308–309
QA programs and, 297*t*
quality assurance, 296–297
radiation therapy process, 1426–1427*f*, 1430*f*
radiation therapy process, 1778–1787
review process, 298
rotational (arc) therapy, 242–243, 242*f*
for soft-tissue sarcomas, 2063
target design, 1330–1331
target volume definition, 2073–2074
testicular cancer, 1742, 1742*f*
total-body irradiation, 412
treatment delivery and, 2074, 2075*f*
two dimensional, 1901
in vulvar cancer, 1932–1933
Treatment planning system (TPS), 360
Treatment verification
conformal radiation therapy, 291
QA programs and, 297*t*
quality assurance, 299
Treatment volumes, definitions, 282, 282*f*
Treatment windows, 146
Trebananib, 1869
Tremor, medically-refractory, 428
Triiodothyronine, 1236
Trial Assigning IndividuaLized Options for Treatment (Rx) (TAILORx) trial, 387
Tricyclic antidepressants, 2318
Trigeminal ganglion anatomy, 693
Trigeminal nerve (CN V)
innervation by, 1001
invasion of, 1005*f*
nasopharyngeal cancer and, 692
Trigeminal neuralgia (tic douloureux), 2241–2242
Trigeminal neuralgia (TN), 428, 428*f*, 428*t*
Trimodality therapy
description of, 1282
treated with, 1659–1660

Trismus, 1097, 1100, 1125
Trismus, 2353
Truisms, 52–53
TRUS. *See* Transrectal ultrasonography (TRUS)
TSEBT. *See* Total skin electron beam therapy
Tubal intraepithelial carcinomas (TICs), 1855
Tubiana, Maurice, 85
Tubular carcinomas, 1398, 1410
Tumor angiogenesis
  metastatic phenotype and, 12–13
  and tumor cell invasion, 13, 13*f*, 14*b*
Tumor burden, trial endpoints, 381
Tumor cell invasion, 13, 13*f*, 14*b*
Tumor cells, repopulation, inhibition of, 715
Tumor contact length (TCL), 1675
Tumor control probability (TCP), 281
  calculation of, 294
  dose-volume information and, 294
  therapeutic index and, 677, 677*f*
Tumor control probability, 21–22, 22*t*, 22*b*, 23–24*f*
Tumor metastasis, 11
Tumor microenvironment normalization, 139
Tumor necrosis factor (TGF)
  radiation-induced normal tissue damage, 109
  TGF-α, 319
  TGF-β, 319
Tumor necrosis factor receptors (TNFRs), 118
Tumor necrosis factor-β (TGF-β), 319
Tumor neovascularization. *See* Tumor angiogenesis
Tumor-promoting inflammation, 99
Tumor radiosensitivity and predictive assays, 21
Tumor suppressor gene *TP53*, 5, 7–8, 1096. *See also specific genes*
  loss of function mutations, 100
Tumor-treating fields, 881, 885–888
Tumorectomy. *See* Lumpectomy
Tumorigenesis, angiogenesis and, 98
Tumor/normal tissue enhancement, 62
Tumors
  challenges, 146
  contouring, 1552
  disclosures, 147
  genomic studies of, 1872
  hypoxia, 134–144
  microenvironments of, 153–155
  molecular pathophysiology of, 134–147, 144–146
  oxygen level of, 677–678
  perspectives, 147
  slow-growing, 424

volumes, 283*t*
Tungsten atom, 171*f*
Turbo spin echo, 689
Turcot syndrome, 2222
Tylosis, 1318
Tyrosinemia, hereditary, 1545
Tyrosinemia, hereditary, 2224

U

Ulceration, radiation-induced injury, 343, 1903
Ulcerative colitis, 1557
Ultra HDR radiation therapy, 20
Ultra-high dose rate (FLASH) radiation therapy
advantages, 458*t*
disadvantages, 458*t*
history, 451+–152
mechanisms of action, 452–454, 452–453*f*
preclinical research, 454
treatment planning, 450*f*
Ultra-high dose rates (UHDRs), 451
Ultrasonic surgical aspiration, 1881
Ultrasound (US)
cervical cancer patients, 1768
description of, 689–691
diagnostic, 1295
diagnostic, 1734–1735
intraoperative, 951–952
quality of imaging, 690
transvaginal, 1829, 1830*f*
Uncertainties in treatment planning, 30
mechanical, 31
patient-related, 31–32
Undifferentiated carcinoma, 1832
Unfavorable disease, 602, 605
Unit center point (UCP), 178
Universal wedges, 237
Unsupervised machine learning, 58*b*
Upright radiation therapy, 224–226
Uranium series, 173
Ureter carcinoma
diagnosis, 1613, 1613*t*
follow-up, 1625
management, 1625
natural history, 1613
presentation, 1613
prognostic factors, 1615–1616
staging, 1614*t*

treated with, 1659–1660
Ureteral strictures, 1817
Ureterovaginal fistulas, 1814
Urethra, 564, 564*f*
female, 1910, 1910*f*
imaging, 705
male, 1747
oncologic anatomy, 705
Urethral cancer
female, 1910–1920, 1910*f*
anterior, 1914
brachytherapy, 1919*f*
classification, 1912
CT outcomes, 1919
diagnosis, 1911–1912, 1911*f*, 1912*t*
epidemiology, 1910, 1911*f*
etiology, 1910, 1911*f*
imaging, 1913*f*
management, 1914
multimodality therapy, 1919
natural history, 1910–1911
posterior, 1914
presentation, 1911
prognostic factors, 1912, 1913*f*
recurrent, 1914
RT techniques, 1914–1915
sequelae of therapy, 1919–1920
staging, 1912
staging, 1913*t*
surgical outcomes, 1917
treatment outcomes, 1917
trial outcomes, 1920*t*
male, 1747–1759
chemotherapy, 1754
classification of, 1751
diagnosis, 1749, 1749*t*
epidemiology, 1747–1748
natural history of, 1748
presentation, 1748
prognostic factors, 1751
radiation therapy, 1755, 1758*t*
recurrence, 1754
risk factors, 1747–1748
staging, 1750*t*
staging, 1751
surgical excision, 1754
Urethral strictures, 1693–1694, 1748, 1759, 1920
Urethrectomy, 1814

Urethritis, 2350
Urinary bladder. *See also* Bladder cancer
  anatomy, 1637
  dose-volume limits, 344–345
  dose/volume/toxicity data, 344
  imaging, 705
  late effects of radiation, 344–345
  oncologic anatomy, 704
  postvoid residuals, 344
  preservation, 1642–1644
  transurethral resection of, 1638
Urinary system, 2349*t*
  radiation side effect management
    prostatitis, 2350
    radiation cystitis, 2348–2350
    radiation nephropathy, 2348
    stenosis, 2350
    urethritis, 2350
Urological cancer. *See* Bladder cancer
U.S outcomes, 1145, 1154*f*
Uterine cancer, sarcomas, 1850
Uterine sarcoma, 1850
Uterus. *See also* Endometrial cancers
  anatomy, 705–706, 1828
  distensibility, 1818
  imaging, 1830*f*
  imaging, 706–707
  perforations, 1818
Utilitarianism, basis of, 812
Uvea
  bilateral radiation therapy, 964*f*
  endoresection, 965–966
  enucleation, 965
  melanoma, 964–968
  observation, 965
  transscleral resection, 966

V

VAC regimen, 1872, 2137
Vagina
  anatomy, 1878, 1879*f*, 1880*f*
  bleeding, 2306
  rhabdomyosarcoma, 2134
  stenosis, 1902
Vaginal cancer, 1878–1904
  carcinoma of the neovagina, 1811
  clear-cell adenocarcinomas, 1894–1895

epidemiology, 1878–1896
extranodal lymphomas, 1895
follow-up, 1904
lymphomas, 1895–1896
melanomas, 1891–1893
palliative therapy, 1904
patterns of failure, 1903
posthysterectomy, 1903
prior gynecologic cancer and, 1883
prior pelvic radiation, 1903
salvage therapy, recurrent/persistent disease, 1904
sarcomas, 1893–1894
SCC
chemoradiation, 1890–1891
chemoradiation, 1890*t*
clinical presentation, 1883
diagnosis, 1884–1885
outcomes, 1891
patterns of lymphatic drainage, 1883
prognostic factors, 1888–1891
radiation, 1888–1890
risk factors, 1885–1886
staging, 1883–1884, 1884*t*
surgery, 1887–1888, 1887*t*
small cell carcinomas, 1896
treatment
complications of, 1881, 1888, 1898
CRT, 1890–1891, 1890*t*
neoadjuvant CT and, 1888
outcomes, 1891
radiation therapy, 1888–1890, 1889*t*
radiotherapy techniques, 1896–1903
surgical, 187–188
Vaginal cuff brachytherapy, 1846
Vaginal intraepithelial neoplasia (VAIN)
cervical cancer and, 1903
epidemiology, 1878–1883
natural history of, 1880
pathology, 1881
presentation, 1878–1883
prognostic factors, 1886
radiation-related, 1880–1881, 1882*t*
risk factors, 1879–1880
treatment options, 1880, 1882*t*
Vaginal mucositis, 2351
Vaginal stenosis, 2351
Vaginal ulceration, 2351
Vaginectomy, 1880–1881, 1887

Vaginitis, radiation-related, 1818
Vagus nerve (CN X) hemangiopericytoma, 1187
Value
  definition, 823
  equation, 824–831
  patient-centered approach, 831–832, 832*f*
Valvular disease, post-RT, 338
Valvulopathy, 2348
Varian linear accelerators, 181*f*, 244
Varian Medical Systems, 182, 183*f*
Varian MLC system, 244
Varian RapidArc system, 234
Varian Trilogy system, 256*f*, 256*t*
Varian TrueBeam, 255
Vascular disrupting agents (VDAs), 154
Vascular endothelial growth factor (VEGF), 99, 154
Vascular endothelial growth factor receptor (VEGFR), 106
Vascular malformations, 429
Vascular normalization, 137–139, 154
Vasculature
  in cancer, 99
  establishment of, 99
  inducing or accessing, 99
Vasculogenesis
  inhibition of, 154
Vasculopathy, after RT, 2072
Venetoclax, 2026
Venlafaxine, 2318
Veno-occlusive disease of the liver. *See* Sinusoidal obstructive syndrome (SOS)
Ventricular dysfunction, 1970
Verrucous carcinoma, 1883
  cervical, 1770–1771
  esophageal, 1327
  vaginal SCC and, 1883
  vulvar, 1925
Vertebral fractures, 445
Vertebral hemangiomas, 2249
Vertebroplasty, 2293
Vesicoureteral reflux, 344
Vesicovaginal fistulae, 1817
Vestibular schwannoma, 904
Vestibular schwannomas
  cranial nerve involvement, 692
  fractionation schemas, 430
  HFSRT for, 329
  radiosurgery for, 430–431
Vicarious liability, 68
ViewRay system, 183, 183*f*

Villoglandular carcinoma, 1832
Villous adenomas, 1570
Vinblastine. *See also* ABVD regimen; CMV regimen; COPP/ABV regimen; MOPP regimen; MVAC regimen
  for esophageal cancer, 1346
  for lung cancer, 1261
Vincristine (Oncovin)
  for adrenal cancer, 1954
  for adrenal tumors, 1954
  ENB management using, 1198, 1199, 1201
  for Solitary fibrous tumors, 1188
  for spinal cord tumors, 952
Vincristine (Oncovin). *See also* BEACOPP regimen; CHOP regimen; COMP regimen; COP regimen; COPP/ABV regimen; CVB regimen; MACOP-B regimen; MOPP regimen; OEPA regimen; OPPA regimen; ProMACE/MOPP regimen; VAC regimen; VACA regimen
Vincristine (Oncovin), 1978, 1985
  induction therapy using, 2018
Vincristine, dactinomycin, and cyclophosphamide (VAC), 1872
Vinorelbine, 1934
  for salivary gland cancer, 1086
Vinyl chloride, 2054
Virtual University for Cancer Control and Regional Training Network (VUCCnet), 762
Virtue theory, 812
Viruses, oncogenic, 100
Visceral recurrence, 2302–2311
Visual system
  radiation side effect management
    cataracts, 2338
    maculopathy, 2338
    optic neuropathy, 2338–2339
    retinopathy, 2338
    xerophthalmia, 2338
Vitamins, 2326
VMAT. *See* Volumetric modulated arc therapy (VMAT)
Vocal cord anatomy, 1164*f*
Vocal cord cancer, 1163–1170
  advanced, 1167
  early, 1166
  treatment results, 1172–1173, 1172–1173*t*, 1173–1174*t*
Vocal dysfunction, 333
Vocal function assessments, 333
Vocal system
  radiation side effect management
    dysphonia, 2339
Volume delineation, 298
Volumes
  nomenclature for, 283*t*
Volumetric modulated arc therapies (VMATs)

in paranasal sinus tumors, 1049
Volumetric modulated arc therapy (VMAT), 365
Vomiting, after RT. *See also* Nausea and vomitinga
Vomiting, after RT, 2140
Vomiting, radiation-induced, 2327
Von Hippel-Lindau (VHL) disease, 1611, 1951
Von Recklinghausen disease, 1951
Vulva, anatomy of, 1922, 1922*f*
Vulvar cancer
adenocarcinomas, 1924–1925
adjuvant radiation therapy, 1930
diagnosis, 1925
distant metastases, 1926
epidemiology, 1923
management, 1927–1928
2-D and 3-D conformal treatment, 1933
2-D and 3-D conformal treatment, 1934*f*
algorithm, 1928*f*
biologic agents, 1934–1935
chemotherapy, 1933–1934
chemotherapy, 1934*t*
concurrent chemotherapy, preoperative radiation therapy with, 1930–1931
concurrent chemotherapy, preoperative radiation therapy with, 1932*t*
CRT, 1931–1932
CRT, 1932*t*
definitive radiation therapy, 1931
intensity-modulated radiotherapy, 1933
RT, 1930–1931
RT, 1931
simulation and target delineation, 1932
simulation and target delineation, 1933*f*
surgical, 1929–1930
timing of RT, 1837–1838
treatment sequelae, 1935
melanoma, 1923–1924, 1924*f*
patterns of spread, 1926, 1926*t*
presentation, 1926
prognostic factors, 1926–1927
SCC, 1923, 1924*f*
verrucous carcinomas, 1925
Vulvar dystrophy, 1923

W

WAGR syndrome, 2103, 2111
Waldeyer ring, 1976
Warburg effect, 99
Warren, Shields, 83

Warthin tumor, 1062
Water
  intake, 2317, 2324
Waveguide, 179
Wavelength (λ, 171
Wave–particle duality of nature, 171
Wedge filter dosimetry, 237–239, 238–239*f*
Wedge filters, 196–197, 197*f*
Weibel-Palade bodies, 1298
Weight loss
  diagnostic value of, 1251
  pancreatic cancer and, 1524
  after RT, 1518
Werner syndrome, 2054
WF10 (tetrachlorodecaoxide), 2329
WHO (World Health Organization) pain ladder, 2316
Whole-abdomen irradiation (WAI), 1854
Whole-abdomen radiotherapy, 1843, 1864–1865, 1867–1868
Whole-brain radiotherapy, 1621
Whole-brain radiotherapy, 320, 433–434, 876, 2132, 2263–2264, 2268–2269*t*
Whole-breast radiation therapy (WBRT), 1429
Whole-breast radiation therapy (WBRT), 464, 670–672
Whole-lung irradiation (WLI), 2106, 2159, 2167
Whole-pelvic radiation therapy (WPRT), 1710, 1712–1715, 1713*f*, 1715*t*
Whole-pelvis field, 1916*f*
Whole-sellar treatment, 918
Wilms tumor, 2103–2113
  adrenocortical carcinoma and, 1951
  anaplastic, 2109
  bilateral, 2110
  biology of, 2103
  classification of, 2103–2104
  clinical presentation, 2104
  diagnostic workup, 2104, 2104*f*
  epidemiology of, 2103
  management, 2105, 2106*t*
    clinical trials, 2108–2111
    late effects of, 2111–2113
    radiation therapy, 2105–2108
    radiation therapy, 2106*t*
    radiation therapy, 2107*f*
    surgical, 2105
    surgical, 2105*t*
    surgical, 2110
  natural history, 2104
  recurrent, 2105, 2106
  retroperitoneal, 1946
  staging, 2104–2105, 2105*t*

tumor spillage, 2105
Wilson disease, 1545
Wiskott-Aldrich syndrome, 1974
Wnt proteins, 106
Woringer-Kolopp disease, 2005
Working environments, 297*t*
World Health Organization (WHO) pain ladder, 2316
World Health Organization grade 3 gliomas, 888
Wound healing, 2065
WR1065, 681
WR2721 (amifostine, Ethyol), 681
WT, Aniridia, Genitourinary malformations, mental Retardation (WAGR) syndrome, 2103
WTX gene, 2103

X

X-band linear accelerators, 183
X-ray films, diagnostic, 1734
X-rays
adjacent fields, 248–251, 248–250*f*
beams
hardening of, 188
multiple beam arrangements, 240–242
parallel-opposed, 240, 240*f*
penetrability of, 188
Bremsstrahlung spectrum, 172, 172*f*
emission of, 173
linear accelerators, 181–183, 183*f*
principles of, 172
problems with, 471–473
production of, 172*f*
repair cross-complementing protein (XRCC), 104
Xanthochromia, 949
XELOX regimen, 1572
Xeroderma pigmentosum (XP), 1092, 2231
Xerophthalmia, 960, 2338
Xerostomia, 2339, 2341–2342
dosimetric predictors for, 334*t*
after high-dose TBI, 418
after HL treatment, 1969
IMRT, 1134*f*
management, 2325–2326
post-RT, 333
prevention, 2325
reduction of, 681
risk factors for, 334
after RT, 1032–1033, 1104, 1111*f*
XoftAxxent System, 463, 464

XP regimen components, 1513
X–Rays, 176

Y

Yolk sac tumors, 1947
  and teratoma, 1733
York-Mason technique, 1579

Z

Zeiss Intrabeam, 463, 464